Light-induced chemistry of oximes and derivatives

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I. INTRODUCTION

The use of oximes as an important organic feedstock for the synthesis of ε-caprolactam[1], as pesticides[2], as photo-initiators[3] and as drugs, e.g. as NO-donors or antidotes for organophosphorus poisoning[4,5], has increased significantly in recent decades. As a result the presence of oximes in the environment has seen major increases. Because oximes may form a range of reactive intermediates, which have the potential to cause cell and tissue damage, their impact on human life, their metabolism, their effect on enzymes and, coincidentally, their photochemistry, direct or sensitized, by energy or electron transfer, has attracted ever-growing interest.

Oximes undergo a wide variety of photoreactions ranging from the ubiquitous $E-Z$ isomerization, the intriguing photo-Beckmann rearrangement generating amides, the regeneration of the parent ketones with loss of the hydroxylamine function, the formation of nitriles by net elimination of water, the abstraction of a hydrogen atom forming iminoxyl radicals, to cleavage of the nitrogen–oxygen bond, yielding iminyl radicals. Oximes bearing alkene functions may undergo the aza-di-π-methane rearrangement or generate a variety of alicyclic and heterocyclic systems. The photoreactions of some substrates containing an oxime group do not involve this moiety directly.

We will begin with brief comments on the absorption and on the photoexcited states, proceed to the typical reaction types of oximes following light excitation, and review several classes of substrates that have received particular attention. Although electron transfer initiated reactions proceed via different types of intermediates, they are treated along with singlet or triplet excited state oxime reactions, not in a separate section. Finally, we mention some reactions in which the oxime function is not directly involved and several photoreactions involving major changes of the substrate structure where the role of the oxime function has not been elucidated in detail.

II. OXIME ABSORPTION SPECTRA AND EXCITED STATES

The C=N–OH moiety, like the much studied C=O moiety, has two possible absorptions, $n\pi^*$ and $\pi\pi^*$. The isolated C=N–OH group in a non-polar hydrocarbon solvent has a band at 190–200 nm, assigned to the $\pi\pi^*$ transition; the extinction coefficients ($7800 < \varepsilon < 9400$) are much too large for the (forbidden) $n\pi^*$ transition[6,7]. No distinct $n\pi^*$ transition has been observed; they must be submerged under the much stronger $\pi\pi^*$ band. The major fate of the $\pi\pi^*$ excited singlet state is energy dissipation by intersystem crossing to the ($\pi\pi^*$) triplet state, followed by return to the ground state with E,Z-photoisomerization.

Conjugation of the oxime moiety with a C=C bond shifts the absorption to $235 < \lambda < 260$ nm; once again the high extinction coefficients ($11\,000 < \varepsilon < 26\,000$) are compatible only with a $\pi\pi^*$ transition[8]. In case of conjugation with an aromatic ring the key absorption moves further to longer wavelengths.

Conjugation of the oxime moiety with a C=O bond, as in α-ethoxyiminoketones, leads to two well-separated bands at $230\,\text{nm} < \lambda < 245\,\text{nm}$ and at *ca* 325 nm. The high extinction coefficients of the lower wavelength bands, $\varepsilon = 11\,000$ and 3500, respectively, clearly identifies them as due to $\pi\pi^*$ transitions whereas the higher wavelength bands have much lower extinction coefficients, $\varepsilon = 28$ and 62, respectively, values that are characteristic for $n\pi^*$ transitions[9a]. Details will be presented in Section IX, dealing with the photochemistry of α-oxo-oximes.

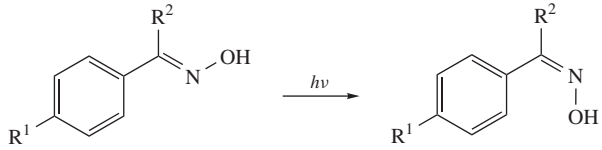
Conjugation of two oxime moieties, as in α-bis(methoxyimino)alkanes, moves the $\pi\pi^*$ absorption band to $216 < \lambda < 268$ nm. The differences in $\boldsymbol{\lambda}_{max}$ vary with the degree of inter-iminyl conjugation as a result of variations in the inter-iminyl dihedral angle and/or the dipolar repulsion of the adjacent methoxyimino moieties. The energy of the

$\pi\pi^*$ absorption maxima of the (*E*,*E*)-α-bis(methoxyimino)alkanes appears to be linearly related to that of the corresponding (*E*)-α-oxo oxime ethers[9c].

For selected conjugated oximes the (*Z*)-isomers undergo only $E-Z$ isomerization whereas the (*E*)-isomers, in addition, suffer photodecomposition (Section IX). The failure of the (*Z*)-isomers to undergo fragmentation was ascribed to the presence of a relatively low-lying doubly excited ($n\pi^*$)($n\pi^*$) state, causing these isomers to decay via $E-Z$ isomerization[9b]. The involvement of a low-lying doubly excited state is somewhat unusual, but is supported in this particular case by an *ab initio* study, using *s-cis*-ethanedial monooxime as model compound (Section IX)[9d].

III. *E–Z* ISOMERIZATION

The prototypical photoreaction of oximes, i.e. the main route for deactivation of the photo-generated excited state, is $E-Z$ (*syn–anti*) isomerization. This type of conversion occurs readily for essentially all oximes. As early as 1890, Hantzsch reported the $E-Z$ isomerization of *p*-tolyl- or *p*-anisylphenyl ketone oxime, (*E*)-**1** to (*Z*)-**1**[10]. In 1903, Ciamician and Silber observed the isomerization of *o*- and *p*-nitrobenzaldehyde oxime[11]. Stoermer included several oximes in his studies of photo-induced isomerizations[12], while Brady and Dunn probed a large number of oximes and extended the work of Ciamician and Silber to the corresponding oxime ethers (Scheme 1)[13].

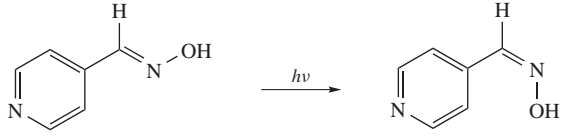


(*E*)-(**1**) $R^1 = CH_3, OCH_3; R^2 = C_6H_5$ (*Z*)-(**1**)

$R^1 = NO_2; R^2 = H$

SCHEME 1

In 1941 Grammaticakis described the 'photochemical stereomutation' of *o*-methylpropiophenone oxime upon prolonged irradiation[14]. In 1965, Poziomek reported the preparation of the pharmacologically active (*Z*)-isonicotinaldehyde oxime, ***Z*-2**, from the (*E*)-oxime, ***E*-2**, by irradiation with a 254-nm quartz lamp at $0-5\,^{\circ}C$ in acetone (Scheme 2)[15].



(*E*)-(**2**) (*Z*)-(**2**)

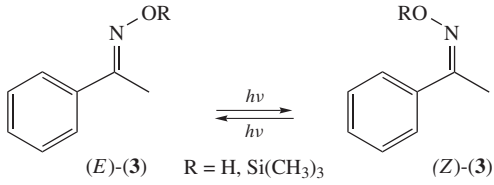
SCHEME 2

Several features of this reaction are of special interest, the mechanism, the quantum efficiency and the photostationary state of the *E*,*Z* equilibrium. Possible mechanistic pathways include rotation around the C=N bond and linear inversion. This is a subtle mechanistic difference that has been addressed only in a few specific cases. On the other hand, the photostationary states for oximes or oxime ethers have been studied in detail, beginning with the pioneering studies of De Mayo and coworkers[7].

For example, the direct irradiation of (*E*)- and (*Z*)-benzaldoxime leads to isomerization with comparable quantum yields, $\Phi\alpha\beta = 0.40$ and $\Phi\beta\alpha = 0.38$, respectively, from the two isomers[7a]. The isomerization can also be induced by triplet-sensitized irradiation and a comparison of the stationary states led to the conclusion that the isomerization following direct irradiation also involves a triplet process[7a].

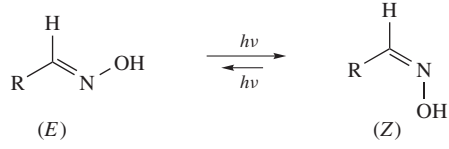
Determining the photostationary state often presents problems because, for many oximes, the thermal barrier between the isomers is quite low; all too often a photochemically induced shift in the equilibrium reverts readily to the initial thermal ratio. To avoid the thermal reversal the irradiations have to be carried out, and the equilibria characterized, at low temperatures. On the other hand, *O*-substituted oximes, even the methyl ethers, have significantly higher barriers and significantly reduced rates of thermal isomerization; *O*-substituted derivatives of oximes offer attractive targets for the study of the *E*,*Z* isomerization.

This thought was not lost on Guillot-Edelheit and Beugelmans who prepared the trimethylsilyl ether, (*E*)-**3**, R = $Si(CH_3)_3$, of (*E*)-acetophenone oxime by silylation. Upon irradiation they obtained predominantly the (*Z*)-isomer, (*Z*)-**3**, R = $Si(CH_3)_3$; the (*Z*)-trimethylsilyl ether could be isolated and its hydrolysis yielded pure (*Z*)-acetophenone oxime, (*Z*)-**3**, R = H (Scheme 3)[16].



SCHEME 3

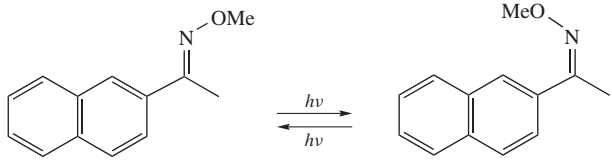
The photostationary states of the *E*,*Z* equilibria of oximes and their ethers and esters can be influenced by steric and mechanistic factors. The intermediate from which the isomers are regenerated after photo-excitation can play a significant role, as illustrated below. Steric factors can be predicted by considering simply the bulk of the interacting groups. Thus, for any aldoxime the *E*-isomer is expected to be favored (Scheme 4).



SCHEME 4

Among mechanistic factors, the involvement of different intermediates may affect *E*,*Z* equilibria significantly. *E*,*Z* isomerization can be induced by triplet sensitizers of a wide range of triplet energies; it is likely to involve the oxime triplet state. In other cases excimers, exciplexes or radical ions have been invoked as intermediates affecting the photostationary state.

Padwa and Albrecht elucidated several facets of oxime photoisomerization. Irradiation of (*E*)- or (*Z*)-2-acetonaphthone oxime *O*-Me ether, **4**, in pentane or benzene caused ready isomerization of (*E*)-**4** to (*Z*)-**4** or *vice versa*. The composition of the photostationary state varied with temperature, oxime ether concentration and solvent[17]. Fluorescence quenching studies (high concentrations of piperylene) and photosensitized isomerization experiments support the involvement of the singlet state, or perhaps a short-lived triplet (Scheme 5).

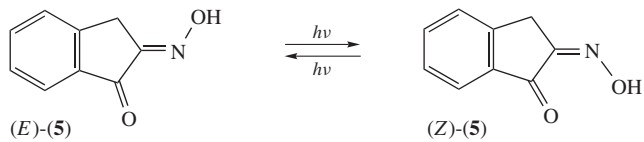


(*E*)-(**4**) (*Z*)-(**4**)

SCHEME 5

The concentration dependence of this reaction is interesting; at low substrate concentrations the (*Z*)-**4** isomer predominates in the photostationary state whereas higher oxime ether concentrations enhance the fraction of the (*E*)-**4** isomer. These findings are consistent with the involvement of an excimer, which is capable of inducing efficient $E-Z$ isomerization with a decay ratio different from the monomer excited state[17].

Cerfontain and coworkers observed a similar concentration-dependent photostationary state upon direct irradiation of the isomeric 2-(methoxyimino)-1-indanone oximes, **5**, or of their 7-methyl derivatives. At low substrate concentrations the (*Z*)-**5** isomer reaches concentrations of up to 35% (an E/Z ratio of *ca* 2). At high oxime or oxime ether concentrations, the *E*-isomers dominate strongly (>90%). The authors ascribed this change to the involvement of an excimer between a $\pi\pi^*$ (S_2) state and a ground state molecule. It is reasonable that an excimer should have a different E/Z partition coefficient, leading to a different E/Z ratio, than the triplet state of the monomer (Scheme 6)[18].



(*E*)-(**5**) (*Z*)-(**5**)

SCHEME 6

For oxime isomerizations sensitized by triplet energy transfer the photostationary state may be affected dramatically by the sensitizer triplet energy (E_T). Padwa and Albrecht illustrated this dependence using (*E*)- and (*Z*)-acetophenone oxime *O*-methyl ether, **3**, R = CH_3, with sensitizers of triplet energies in the range $54 < E_T < 74\,\text{kcal mol}^{-1}$. Direct irradiation of (*E*)- and (*Z*)-**3**, R = CH_3, resulted in a photostationary state with a Z/E ratio of 2.2; the triplet sensitizers produced widely divergent ratios[19]. A plot of photostationary

state vs. sensitizer triplet energy shows three distinct regions: at high sensitizer energies ($E_T > 72\,kcal\,mol^{-1}$) the stationary state ratio is approximately 1.5; in the range $72 > E_T > 59\,kcal\,mol^{-1}$ the Z/E ratio shows a gradual to steep increase; at triplet energies of $59 > E_T > 54\,kcal\,mol^{-1}$ the Z/E ratio showed a sharp decrease.

The steep rise and steep decrease were explained by non-vertical excitation of the acceptor, generating a twisted imine triplet[19]. The difference in the triplet photostationary state values from that obtained by direct irradiation implies that oxime excited singlet states also decay by pathways other than intersystem crossing.

The photosensitized $E-Z$ isomerization of the oxime ether was analyzed by a kinetic scheme involving competing as well as consecutive processes following excitation of the sensitizer to the excited-singlet state, $^1D^*$ (equation 1). $^1D^*$ can decay to the ground state (equation 2) or to the triplet state, ^3D (intersystem crossing, equation 3). ^3D can decay to the ground state (equation 4) or react with the oxime ether isomers by energy transfer, populating a twisted triplet state, ^3X (equations 5 and 6), which decays to the (E)- and (Z)-oximes, O_E and O_Z, respectively (equations 7 and 8).

$$D \xrightarrow{h\nu} {}^1D^* \tag{1}$$

$${}^1D^* \longrightarrow D \tag{2}$$

$${}^1D^* \longrightarrow {}^3D \tag{3}$$

$${}^3D \longrightarrow D \tag{4}$$

$${}^3D + O_E \longrightarrow D + {}^3X \tag{5}$$

$${}^3D + O_Z \longrightarrow D + {}^3X \tag{6}$$

$${}^3X \longrightarrow O_E \tag{7}$$

$${}^3X \longrightarrow O_Z \tag{8}$$

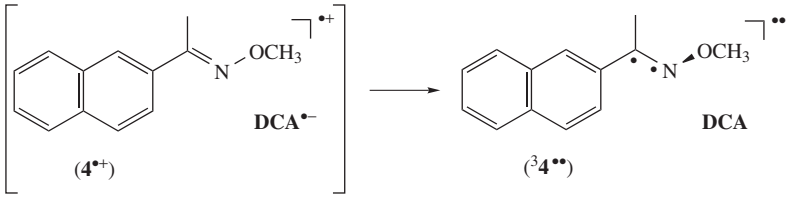
Based on this scheme the quantum efficiencies of pure E- and Z-isomers can be formulated as the products of the efficiencies of intersystem crossing, $[k_3/(k_2 + k_3)]$, and energy transfer, e.g. $\{k_5[O_E]/(k_4 + k_5[O_E])\}$, and the decay ratio, as follows:

$$\Phi_{E,Z} = \frac{k_3}{k_2 + k_3} \frac{k_5[O_E]}{k_4 + k_5[O_E]} \frac{k_8}{k_7 + k_8} \tag{9}$$

$$\Phi_{Z,E} = \frac{k_3}{k_2 + k_3} \frac{k_6[O_Z]}{k_4 + k_6[O_Z]} \frac{k_7}{k_7 + k_8} \tag{10}$$

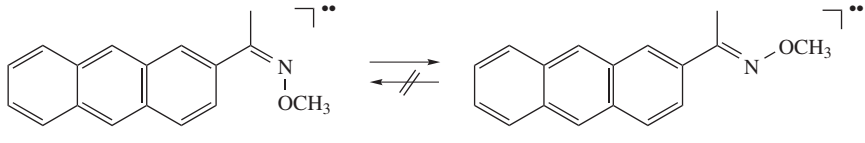
For (E)- and (Z)-**3**, R = CH_3, energy transfer to the oxime ethers does not proceed with identical rates; the (E)-isomer is the better triplet acceptor. On the other hand, the decay ratios, k_7 and k_8, are equivalent. The inefficiency found with some sensitizers suggests that not all triplet sensitizers are effective in generating the twisted imine triplet.

Tokumaru and coworkers approached the E/Z photostationary state of (E)- and (Z)-2-acetonaphthone oxime, **4**, by irradiation of an electron acceptor/sensitizer, 9,10-dicyanoanthracene (DCA). Direct irradiation of (E)- or (Z)-**4** resulted in an E/Z ratio of 60:40 whereas DCA photosensitized irradiation gave an E/Z ratio of 40:60. Oxime **4** quenched the ^{1}DCA* fluorescence efficiently; the interaction produced a weak exciplex emission. Transient absorption spectra compatible with the radical anion, $DCA^{\bullet-}$, and radical cation, $\mathbf{4}^{\bullet+}$, also support an exciplex. Decay of the exciplex populates the triplet states of either sensitizer or oxime; the triplet state of the oxime, $^3\mathbf{4}^{\bullet\bullet}$, generates the altered photostationary state (Scheme 7)[20].



SCHEME 7

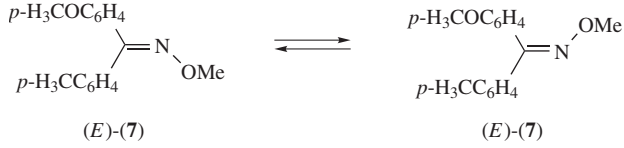
With 2-acetylanthracene oxime *O*-methyl ether, **6**, as substrate the same authors observed 'one-way' *Z*/*E* isomerization via a quantum chain mechanism involving the triplet state, ^{3}**6**••. Quantum yields as high as 22 were observed at substrate concentrations of $1.35 \times 10^{-3} M$. The unpaired electrons of the triplet species are located mostly on the anthracene moiety with limited delocalization onto the C=N bond. Accordingly, both (*E*)- and (*Z*)-**6**•• are local minima, allowing the conversion of the (*Z*)-**6**•• to (*E*)-**6**•• to be followed spectroscopically (Scheme 8)[21].



SCHEME 8

Theoretical calculations were carried out on the T_1 potential energy surface to evaluate whether the isomerization proceeds by double bond twisting or by N atom in-plane inversion. The results suggest that the isomerization occurs by rotation (twisting) and not by linear inversion[22].

An interesting variation of the electron transfer induced *E*/*Z* isomerization was observed by Kawamura and coworkers. The presence of molecular oxygen caused a dramatic change in the *E*–*Z* equilibrium for unsymmetrical diarylketone oxime ethers, (*E*)- and (*Z*)-**7**, upon 9,10-dicyanoanthracene sensitized irradiation[23]. Irradiation under nitrogen resulted in an *E*–*Z* equilibrium of 48:52; under oxygen this value changed to 4:96 (Scheme 9).



SCHEME 9

The reaction proceeds via a radical ion pair, formed by electron transfer from the oxime to excited-singlet DCA (equation 11); in the absence of oxygen the triplet state, ^{3}**7**, is

populated and determines the photostationary state. In the presence of oxygen $DCA^{\bullet-}$ reduces molecular oxygen to superoxide anion (equation 12), which couples to the oxime radical cation at the imine carbon, forming a zwitterion (equation 13). MP3 calculations suggested that this zwitterion favors a conformer, whose heterolytic cleavage forms the *Z*-isomer (equation 14)[23].

$$(E)\text{-}\mathbf{7} + {}^1\mathrm{DCA}^* \longrightarrow (E)\text{-}\mathbf{7}^{\bullet+} + \mathrm{DCA}^{\bullet-} \quad (11)$$

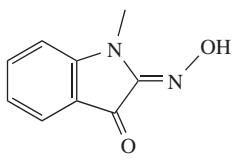
$$\mathrm{DCA}^{\bullet-} + {}^3O_2 \longrightarrow \mathrm{DCA} + {O_2}^{\bullet-} \quad (12)$$

$$(E)\text{-}\mathbf{7}^{\bullet+} + {O_2}^{\bullet-} \longrightarrow (E)\text{-}\mathbf{7}^{+}\text{–}{O_2}^{-} \quad (13)$$

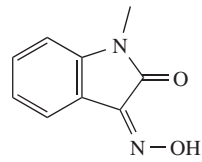
$$(E)\text{-}\mathbf{7}^{+}\text{–}{O_2}^{-} \longrightarrow (Z)\text{-}\mathbf{7} + {}^3O_2 \quad (14)$$

This mechanism is supported by the observation of small amounts of diarylketone in addition to methyl nitrite; these are logical cleavage products of an azadioxetane intermediate.[23]

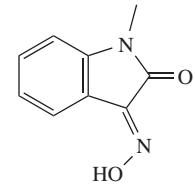
In a few special cases an *E*–*Z* isomerization is suppressed without an obvious reason. For example, only one of the *N*-methyl isatin oxime isomers undergoes photoisomerization: the β-isomer, **9**, irradiated with a 100-W high-pressure Hg lamp in methanol at room temperature under a nitrogen stream, undergoes 35% isomerization. In contrast, the α-isomer, **8**, remains unchanged under similar reaction conditions (Scheme 10)[24].



(**8**)



(*Z*)-(**9**)



(*E*)-(**9**)

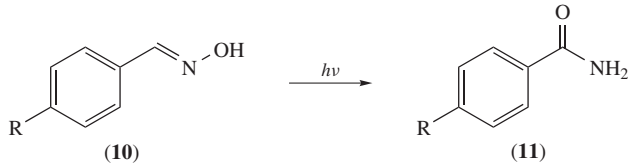
SCHEME 10

IV. THE PHOTO-BECKMANN REARRANGEMENT

The Beckmann rearrangement is an acid-catalyzed reaction converting oximes to amides[25]; the same type of rearrangement also occurs upon irradiation of oximes. The photo-Beckmann rearrangement was discovered by Amin and deMayo in 1963[7a]. Irradiation of the (*E*)-aryl aldoxime, **10**, led, aside from the ubiquitous geometrical isomerization, to formation of the corresponding amides, **11**. In a typical experiment, irradiation of 0.5% solutions of α-(*Z*)-benzaldoxime at 10 °C with an 80-W mercury lamp through quartz formed benzamide, **11**, R = H. This reorganization suggests a migration of O from N to C along with movement of two H atoms (Scheme 11)[7].

The authors showed that the rearrangement is intramolecular because irradiation of ^{18}O-labeled benzaldoxime in the presence of *p*-tolualdoxime failed to scramble the ^{18}O-label. The quantum yield upon direct irradiation (0.034) is more than an order of magnitude larger than that upon triplet sensitization (0.002), suggesting an excited-singlet state reaction[7b].

Yields were highest in acetic acid (*ca* 40% after three hours); addition of 0.5 equivalents of acetic or trifluoroacetic acid to non-acidic solvents increased the

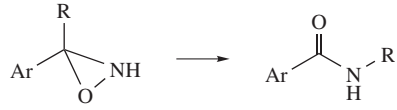


(**10**) (**11**)

SCHEME 11

yield of the amide whereas triethylamine retarded its formation. Benzaldoximes with electron-donating groups gave good yields of the corresponding amides whereas those with electron-withdrawing substituents gave negligible yields of amide.

The solvent effects suggest significant charge separation in the course of amide formation; the substituent effects could indicate a change in the nature of the excited state or in the stability of an intermediate. These observations led the authors to postulate an oxazirane, **12**, as the key intermediate in the rearrangement (Scheme 12)[7b].

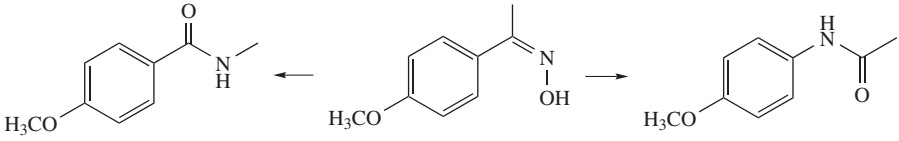


(**12**) (**13**)

R = H, alkyl

SCHEME 12

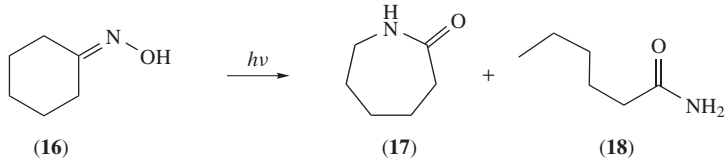
For ketoximes, the rearrangement involves the migration of O from N to C and the migration of one α-substituent to N. In most cases the alkyl group migrates, giving rise to an amide, e.g. **13**; however, *p*-anisylmethyl ketoxime, **14**, yielded products of both alkyl and aryl migration, forming the amide, **13**, and the anilide, **15** (Scheme 13)[7b].



(**13**) (**14**) (**15**)

SCHEME 13

The pioneering work of Amin and de Mayo opened a new chapter in oxime photochemistry that attracted the attention of the photochemical community. The groups of Just and Mukai joined de Mayo's in the pursuit of the putative oxazirane intermediate. Just and coworkers studied oximes ranging from cyclohexanone oxime to steroidal oximes. Irradiation of cyclohexanone oxime, **16** (1% in MeOH, 253 nm, through quartz, under nitrogen, two hours), yielded caprolactam, **17** (46%), cyclohexanone (23%) and caproamide, **18** (5%)[26]. Cyclohexanone is generated formally by hydrolysis of the oxime, whereas caproic acid amide (hexaneamide), **18**, is formed by α-cleavage with rearrangement (Scheme 14).



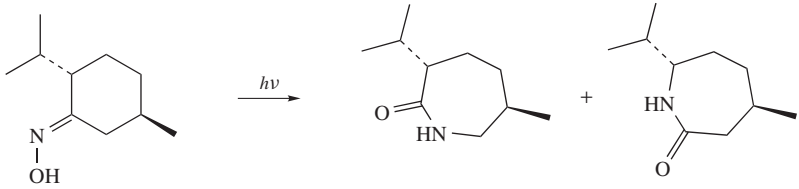
(**16**) (**17**) (**18**)

SCHEME 14

The relative yields of the products varied with reaction conditions. Under oxygen the photo-Beckmann product, **17**, was reduced (to 23%) and the cleavage product, **18**, was suppressed entirely. On the other hand, irradiation in isopropanol under nitrogen favored the cleavage product, **18** (52%), and suppressed the photo-Beckmann product completely. The effect of molecular oxygen suggests a triplet intermediate; however, all attempts to photosensitize the reaction failed. The increased yield of **18** in isopropanol suggests an intermediate that abstracts H selectively, most likely a biradical[26].

A series of cyclic oximes, cyclobutanone oxime to cyclopentadecanone oxime, yields lactams upon irradiation in methanol. Reactions carried out in methanol and isopropanol, respectively, led to significantly different results: irradiation in methanol converted the cycloalkanone oximes to lactams, e.g. **17**, whereas in isopropanol, the ring-opened alkanoic acid amides, e.g. **18**, were obtained. Isopropanol transfers two hydrogen atoms to the oxime molecule and is oxidized to acetone[27].

Just and coworkers recognized two important features of the photo-Beckmann rearrangement: (a) unlike the thermal analog, the photoreaction of unsymmetrical α-substituted cyclohexanone oximes, e.g. **19**, gives mixtures of nearly equal parts of the possible lactams, **20** and **21**; (b) oximes epimeric at an α-carbon form products in which the α-center retained its configuration, suggesting a concerted breakdown of the oxazirane intermediate (Scheme 15)[27].

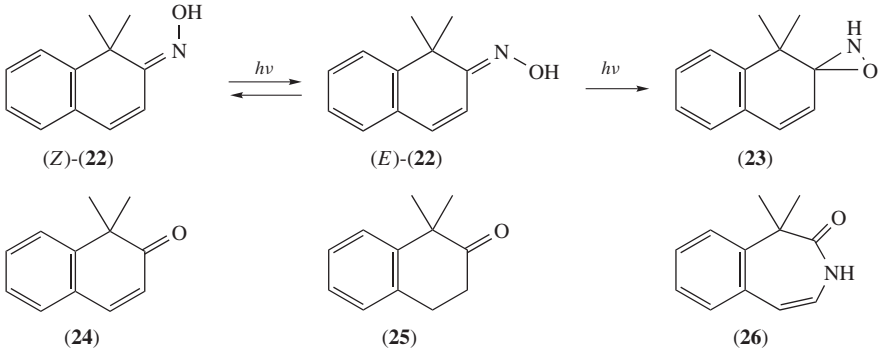


(**19**) (**20**) (**21**)

SCHEME 15

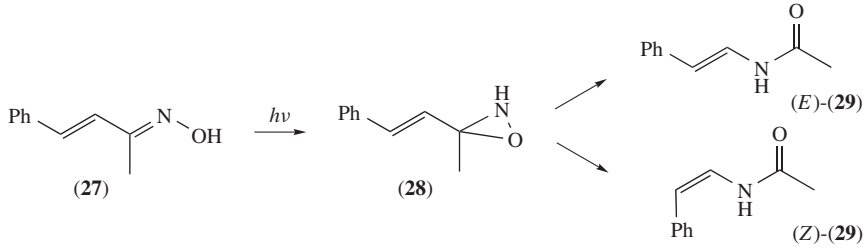
Oine and Mukai found spectroscopic evidence for the putative oxazirane intermediate. A β,γ-unsaturated oxime, '*syn*-'1,1-dimethyl-2-(1*H*)-naphthalenone oxime, (*Z*)-**22**, was readily converted to the (*E*)-isomer (high pressure Hg lamp, Pyrex); both isomers are stable as crystalline solids[28].

After prolonged irradiation, the oxime absorption was replaced by a new band at λ 274 nm, which the authors assigned to the oxazirane, **23**. Stable in dilute solutions, **23** decomposed upon attempts to isolate it with formation of an unsaturated ketone, **24** (54%), a saturated ketone, **25** (6%), and a carboxamide, **26** (4%). The nature of the putative oxazirane, **23**, was further supported by the observation that its solutions reduced iodine and converted a Schiff base to a diazirane; both reactions are characteristic for oxaziranes (Scheme 16)[28].



SCHEME 16

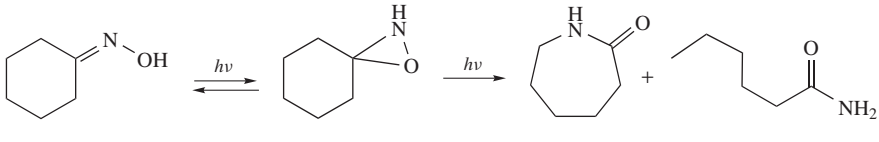
Oine and Mukai also studied several other unsaturated oximes derived from styryl ketones, e.g. 4-phenyl-3-buten-2-one oxime (benzalacetone oxime), **27**, and 4,4-diphenyl-3-buten-2-one oxime, as well as several oximes not conjugated with alkene functions. Benzalacetone oxime, **27**, yielded an intermediate, **28**, and upon its decomposition, amides (*E*)- and *Z*-**29**. The yield of **29** increased threefold (from 14 to 40%) when the solvent was changed from methanol to acetic acid, supporting either 'a protonation' or 'a polarized excited state' (Scheme 17)[28].



SCHEME 17

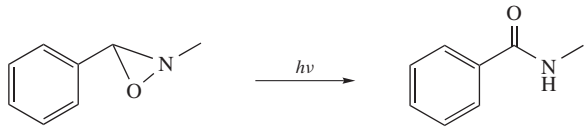
Several groups synthesized oxiranes and studied their photolysis[7b, 29]. Just and coworkers irradiated the oxazirane, **30**, of cyclohexanone in methanol and isopropanol[29]. Photolysis of **30** gave the same products as **16**, i.e. caprolactam, **17**, and hexanamide, **18**; however, the relative yields differed significantly. The oxazirane gave product ratios, **17:18**, of 2:1 in methanol and 1:4 in isopropanol, compared to ratios of 9:1 and 1:50, respectively, from the oxime, **16**. These results do not rule out oxaziranes as intermediates in oxime photolysis, but they require significant contributions from one or more additional mechanisms. Just and Ng also noted that oxime **16** was formed as a product in the photolysis of oxazirane, **32**, indicating that the photoconversion is reversible (Scheme 18)[30].

de Mayo and coworkers noted a further complication: the quantum yield of amide, **32**, formation from phenyl-*N*-methyloxazirane, **31**, depended on irradiation time. The authors concluded that decomposition of **31** is induced via abstraction of the benzylic H by thermally generated minor amounts of benzaldehyde; the required build-up of this



(**16**) (**30**) (**17**) (**18**)

SCHEME 18



(**31**) (**32**)

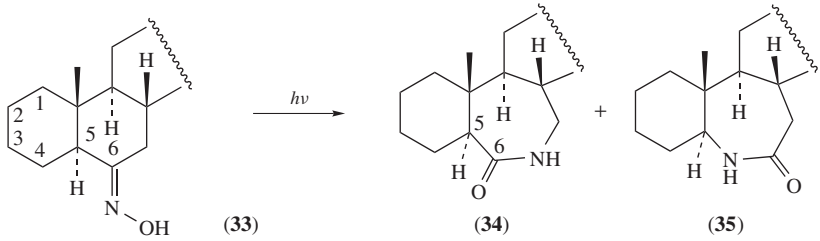
SCHEME 19

product may explain the time-dependent quantum yield[7b] (Scheme 19). Of course, this cannot be a general mechanism as oxaziranes from ketoximes lack a H that could be abstracted.

The sum of these results suggests a complicated mechanism for oxime photolysis in general and for the photo-Beckmann rearrangement in particular, although the oxazirane surely is the key intermediate. There must be several competing pathways, and changes in the reaction conditions may favor one pathway or the other.

With the principal features of the photo-Beckmann rearrangement established, the general scope of the reaction and additional features received increasing attention. Beginning in 1972 Suginome and his group began to provide significant insights into oxime photoreactivity and specifically into the photo-Beckmann rearrangement, specifically the fate of stereochemistry at the migrating carbon center.

For example, the photo-Beckmann rearrangement of 5α-cholestan-6-one oxime, **33**, generated a pair of lactams, **34** and **35**; in both products the original configurations of Cα with respect to the oximino group of **33** were retained. The lactam, **35**, due to the migration of the more substituted carbon was produced in slightly higher yield than that due to the migration of the less substituted carbon. These results indicate a concerted reorganization of an excited-singlet oxazirane intermediate (Scheme 20)[6b].



(**33**) (**34**) (**35**)

SCHEME 20

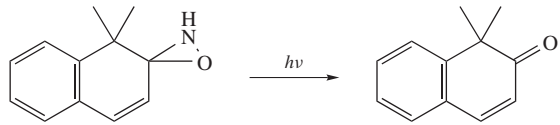
The majority of Suginome's work and additional facets of the photo-Beckmann rearrangement will be discussed in the section dealing with steroidal oximes.

V. COMPETING PHOTOREACTIONS OF OXIMES

While discussing the photo-Beckmann rearrangement we mentioned repeatedly products formed by competing photoreactions. Here we briefly summarize the types of these reactions without going into any detail.

A. Formation of Ketones

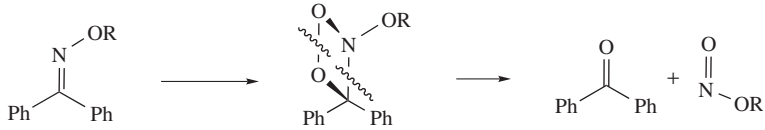
Irradiation of scores of oximes converts them to the parent ketone with loss of the nitrogen atom and the substituent on oxygen. The net result of this reaction is equivalent to hydrolysis of the oxime C=N bond. Just was an early protagonist for this reaction type[26, 30]. Since oximes are prepared typically from ketones or aldehydes, this photoreaction isn't necessarily a useful synthetic tool. In view of this it is hardly surprising that the underlying mechanism has not been studied in much detail. Mukai provided evidence that a ketone, **24**, is a decomposition product of an oxazirane, **23** (Scheme 21)[28].



(**23**) (**24**)

SCHEME 21

The reaction of benzophenone oxime, **36a**, or its methyl ether, **36b**, with singlet oxygen, $^1O_2$, generated by irradiating Rose Bengal, formed benzophenone and nitric acid or methyl nitrite. Although the authors did not find any evidence for an intermediate, the analogy with the reaction of $^1O_2$ with alkenes suggests a four-membered ring intermediate, the azadioxetane, **37**, as a short-lived intermediate (Scheme 22)[31].



(**36**) (**a**) R = H (**b**) R = CH_3 (**37**)

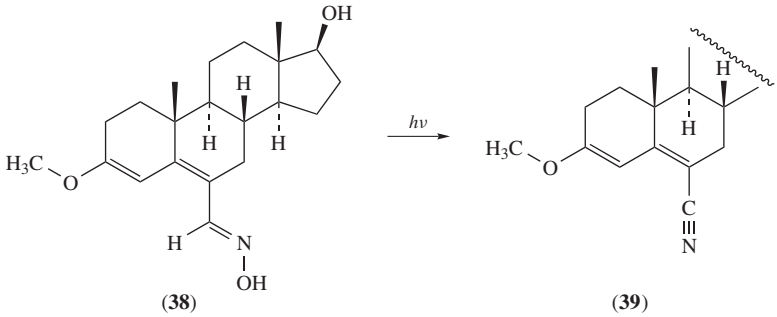
SCHEME 22

This finding is reminiscent of the results of Kawamura and coworkers who identified small amounts of diaryl ketone and methyl nitrite upon 9,10-dicyanoanthracene sensitized irradiation of unsymmetrical diarylmethane oximes in the presence of molecular oxygen (*vide supra*). In this reaction, superoxide ion, $O_2^{\bullet -}$, was assigned as the key intermediate and the reaction conditions support that assignment[23].

As early as 1987 Haley and Yates had considered the photochemical deprotection of oximes to aldehydes and ketones; however, the quantum yields were too low (*ca* 0.01)[32]. Fifteen years later, de Lijser and coworkers succeeded in the deprotection of oxime ethers by electron transfer photosensitized reactions in reasonable to good yields ($\leq$65%); better yields were obtained in non-polar solvents and with triplet sensitizers (*vide infra*)[33].

B. Dehydration of Oximes with Formation of Nitriles

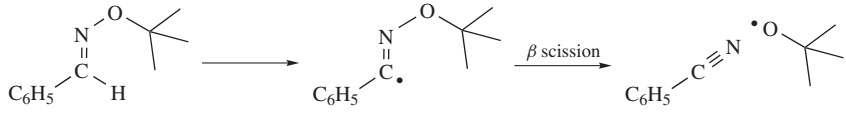
Just and coworkers may have been the first to isolate a nitrile, **39**, as a product of an aldoxime photolysis, viz. irradiation of 17β-hydroxy-3-methoxyandrosta-3,5-diene-6-carboxaldehyde oxime, **38** (Scheme 23)[26, 34].



(**38**) (**39**)

SCHEME 23

Since then nitriles have been observed as products of many oxime photolyses. For aldoximes, e.g. **38**, a simple dehydration may appear plausible. In at least one case, nitrile formation is initiated by abstraction of the imidoyl H atom from the oxime ether **40** by a photo-excited quinone (chloranil); the imidoyl radical, **41**, generates nitrile **42** by β-scission (Scheme 24)[35].



(**40**) (**41**) (**42**)

SCHEME 24

However, the fact that nitrile formation is not limited to aldoximes requires at least one different mechanism for nitrile formation from ketoximes. Indeed, depending on the reaction conditions there may be multiple mechanisms.

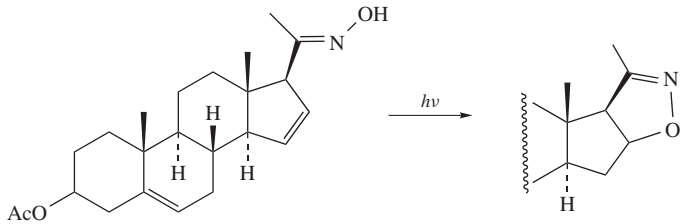
C. Photochemical α-Cleavage of Oximes

Because α-cleavage is one of the principal photoreactions of carbonyl compounds, one might have expected a similar reaction for the related imine compounds. However, this type of reaction has not been observed. The α-cleavage, **16** $\rightarrow$ **18**, reported by Just and coworkers (*vide supra*)[26, 30] is of a different type. It has some characteristics of the photo-Beckmann rearrangement: the C=N−O moiety is converted to an N−C=O function; it may involve an oxazirane whose Beckmann rearrangement is 'diverted' at the stage of the alkyl migration. Because of the strong solvent effect (*vide supra*), one might envision that isopropanol intercepts the oxazirane transferring one H each to the alkyl group about to migrate and to the terminus to which it was to migrate.

A heterolytic α-cleavage of an $\alpha,\beta,\gamma,\delta$-unsaturated oxime is discussed in the Section on unsaturated oximes (see Section VIII.B).

D. Formation of Isoxazolines

The final photoreaction of oximes to be mentioned here is the formation of isoxazolines first observed by Gandhi and Chadha: irradiation of (*E*)-16-dehydropregnenolone oxime 3-acetate, *E*-**43**, with unfiltered UV light in benzene formed the isoxazoline, **44**[36]. The regiochemistry of the cyclization is determined by the stereochemical set-up of the rigid steroid (Scheme 25). This reaction is related to the formation of oxazolidines upon photolysis of β,γ-unsaturated acyclic oximes (see Section VIII.B), but the underlying mechanism is quite different from that delineated by Suginome and coworkers for steroidal α,β-unsaturated oximes, to be discussed in Section VIII.A.



(*E*)-(**43**) (**44**)

SCHEME 25

VI. UNSATURATED OXIMES

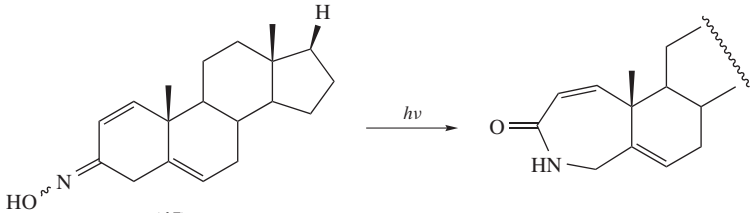
The earliest oximes subjected to photolysis were substituted benzaldehyde oximes[9–15], no doubt due to the availability of these compounds and their relative stability. More recently, unsaturated oximes have been included in the investigations, including 1,1-dimethyl-2-(1*H*)-naphthalenone oxime, (*Z*)-**22**, 4-phenyl-3-buten-2-one oxime (benzalacetone oxime), **27**, and 4,4-diphenyl-3-buten-2-one oxime[28, 29] or the 6-formyltestosterone oxime derivative, **38**[26].

A. α,β-Unsaturated Oximes

Among the unsaturated oximes the α,β-unsaturated ones are special because the two functions are conjugated and offer the possibility of geometric isomerization around either double bond. Apparently, benzalacetone oxime, **27**, and its methyl ether were the targets of choice, presumably because they were readily accessible. Oine and Mukai observed the photo-Beckmann rearrangement of **27** and provided evidence for the corresponding oxazirane, elucidating one facet of the rearrangement[28]. Bonet and coworkers found that an α,β-unsaturated steroid oxime, 17β-hydroxyandost-1,5-dien-3-one oxime, **45**, undergoes the photo-Beckmann rearrangement to **46** with migration of C-4 (Scheme 26)[37].

The photochemistry of additional α,β-unsaturated steroid oximes will be discussed in a separate section (*vide infra*) with other steroid oximes. This research, performed mostly in the laboratory of Suginome, constitutes a major body of work and has contributed much to the understanding of oxime photochemistry.

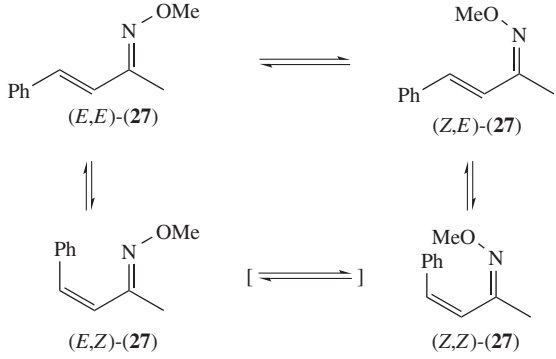
Sato and coworkers were the first to focus on the photoisomerization of **27**, concluding that isomerization occurred only about the C=C double bond[38]. Two decades later Pratt and Abdul-Majid questioned this result in view of the accumulating evidence for ready isomerization of oxime ethers.



(**45**) (**46**)

SCHEME 26

They prepared (*E*,*E*)- and (*Z*,*E*)-**27** and studied their photochemistry. They found rapid isomerization around the C=N double bond and somewhat slower isomerization around the C=C bond. The (*E*,*Z*)- and (*Z*,*Z*)-isomers were not studied in detail because they were isolated only in small amounts (Scheme 27)[39].



(*E*,*E*)-(**27**) (*Z*,*E*)-(**27**)

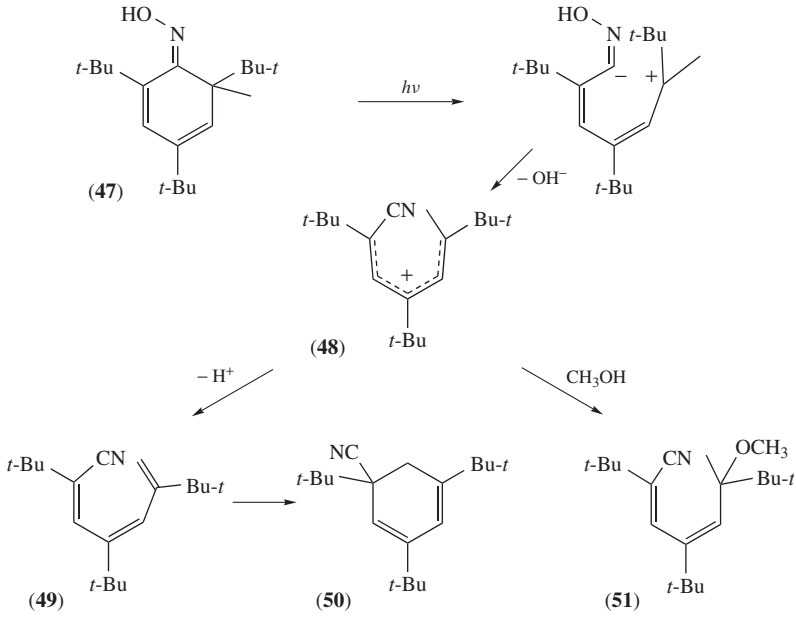
(*E*,*Z*)-(**27**) (*Z*,*Z*)-(**27**)

SCHEME 27

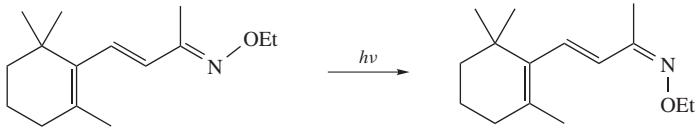
Okazaki and coworkers studied the photochemistry of an $\alpha,\beta,\gamma,\delta$-unsaturated oxime, 2,4,6-tri-*t*-butyl-6-methylcyclohexa-2,4-dienone oxime, **47**. They observed products compatible with heterolytic α-cleavage[40]. The carbocation, **48**, is the key intermediate, formed either by concerted fragmentation of N−O and C−C bonds or by a stepwise equivalent. The major products can be explained by deprotonation of carbocation, **48**, generating trienes, such as **49** (11% yield); electrocyclic ring closure of **49** affords **50**, the major product (19% yield); capture of **48** by methanol gives rise to the methyl ether, **51** (16% yield; Scheme 28).

Another $\alpha,\beta,\gamma,\delta$-unsaturated oxime undergoes an altogether different reaction. The photochemistry of (*E*)-β-ionone oxime ethyl ether (**52**) is an example of two chromophores reacting independently. Direct irradiation of (*E*,*E*)-**52** ($\lambda = 254$ or 313 nm) resulted in the formation of two primary products, the isomer (*E*,*Z*)-**52** and (*Z*)-retro-γ-ionone oxime ethyl ether, (*Z*,*E*)-**53**. The first product indicates the unexceptional geometric isomerization (Scheme 29) whereas the second requires a 1,5-sigmatropic shift (Scheme 30). Both reactions were ascribed to the excited singlet state[41].

Prolonged irradiation of (*E*,*E*)-**52** at λ = 313 nm gave (*Z*,*E*)- and (*Z*,*Z*)-**53**, whereas with λ 254 nm the products are (*E*,*E*)- and (*Z*,*E*)- and/or (*E*,*Z*)-**53**[41].

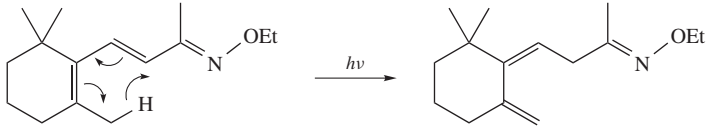


SCHEME 28



(*E*,*E*)-(**52**) (*E*,*Z*)-(**52**)

SCHEME 29



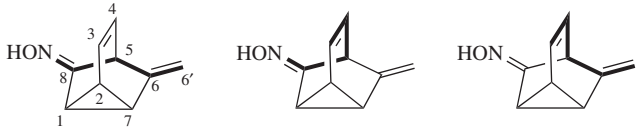
(*E*,*E*)-(**52**) (*Z*,*E*)-(**53**)

SCHEME 30

Upon triplet photosensitization, (*E*,*E*)-**52** undergoes only (*E*,*Z*) isomerization, giving a mixture of all four geometrical isomers. From the dependence of the isomer distribution in the photostationary state on the triplet energy of the sensitizer, the triplet energies of (*E*,*E*)-, (*E*,*Z*)-, (*Z*,*E*)- and (*Z*,*Z*)-**52** were assigned as *ca* 55, <55, 57 and 57 kcal mol^{-1}, respectively[41].

B. β,γ-Unsaturated Oximes

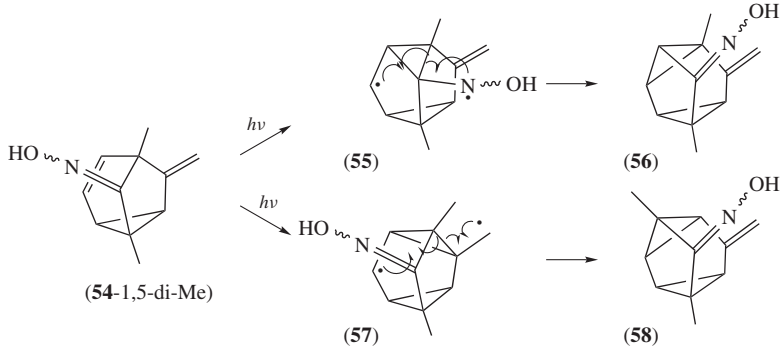
The photoreactions of β,γ-unsaturated oximes have attracted attention because of their potential to undergo an aza-analog of the di-π-methane rearrangement[42]. The first example of such a rearrangement was reported by Nitta and coworkers for a rigid tricyclic system, 6-methylenetricyclo[3.2.1.0^{2,7}]oct-3-en-8-one oxime, **54**. This interesting molecule offers the intriguing possibility of three different di-π-methane systems, viz. C6′C6C5C8N (**54a**), C3C4C5C8N (**54b**) and C3C4C5C6C6′ (**54c**), which might undergo competing isomerizations (Scheme 31).



(**54a**) (**54b**) (**54c**)

SCHEME 31

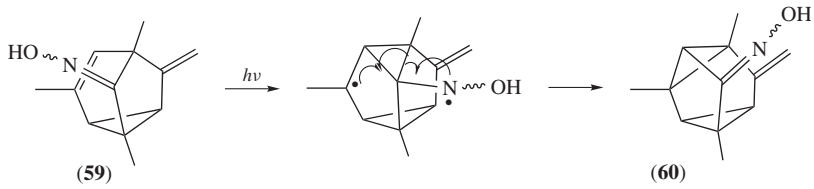
Irradiation of a 1,5-dimethyl-derivative of **54** gave rise to two 3-methylenetetracyclo [3.3.0.0^{2,8}.0^{4,6}]octan-7-one oxime derivatives, **56** (55%) and **58** (24%), supporting two different di-π-methane rearrangements. The major product can be formulated via an aza-di-π-methane rearrangement via biradical **55**; the lesser one requires a competing rearrangement via a carbon biradical, **57** (Scheme 32)[43a].



(**54**-1,5-di-Me) (**55**) (**56**) (**57**) (**58**)

SCHEME 32

A related compound, **59**, bearing a methyl group at the intracyclic alkene function forms only one 3-methylenetetracyclo[3.3.0.0^{2,8}.0^{4,6}]octan-7-one oxime, **60** (54% yield). It is not obvious which feature governs this change in reactivity: the additional methyl group would stabilize diradicals of both type **55** and **57** (Scheme 33)[43a].

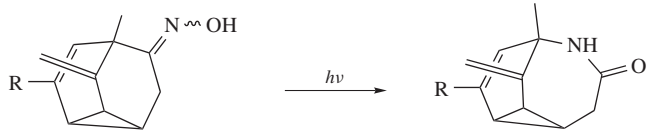


(**59**) (**60**)

SCHEME 33

This reaction most likely proceeds via an excited singlet state, because irradiation in acetone or sensitized irradiation (e.g. benzophenone) in acetonitrile failed to result in any conversion[43a].

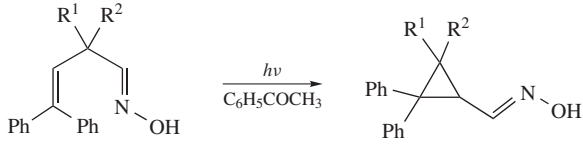
A less constrained tricyclo[3.3.1.$0^{2,8}$]nona-3-en-6-one oxime with the oxime function in a larger ring failed to undergo the aza-di-π-methane rearrangement; instead, **61** reverted to the photo-Beckmann rearrangement, giving rise to **62** (Scheme 34)[43b].



(**61**) (**62**)

SCHEME 34

Armesto and coworkers investigated a selection of acyclic β,γ-unsaturated oximes, frequently in collaboration with Horspool and his group[44–51]. They established a range of isomerizations for these substrates, including aza-di-π-methane rearrangements as well as various cyclization reactions. They applied either triplet or electron transfer sensitization. For example, several β,γ-unsaturated oximes undergo useful photochemical reactions when photosensitized with acetophenone. For example, aldoximes of the type **63** undergo efficient aza-di-π-methane rearrangement, yielding cyclopropanes of type **64**, upon acetophenone-sensitized irradiation (Scheme 35)[44, 45].

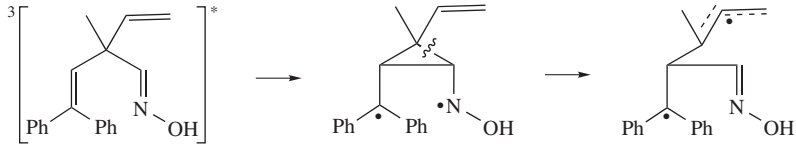


(**63**) $R^1 = R^2 = Ph$
$R^1 = Me$; $R^2 = vinyl$

(**64**)

SCHEME 35

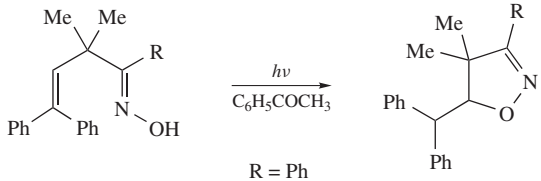
Because the reaction requires triplet sensitization, the triplet state, ^{3}**63**$^{\bullet\bullet}$, and subsequent biradicals, ^{3}**65**$^{\bullet\bullet}$ and ^{3}**66**$^{\bullet\bullet}$, are key intermediates in this conversion. Because these biradicals are stabilized by vinyl or aryl groups in the 2- and 4-positions, their formation diverts the reaction from non-productive deactivation pathways (Scheme 36)[44, 45].



(^{3}**63**$^{\bullet\bullet}$) (^{3}**65**$^{\bullet\bullet}$) (^{3}**66**$^{\bullet\bullet}$)

SCHEME 36

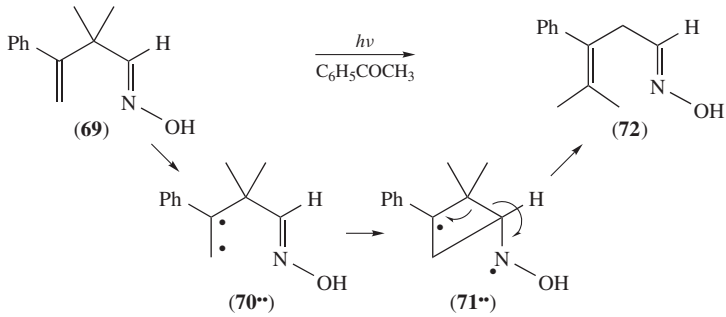
Ketoximes, e.g. **67**, on the other hand, undergo a different cyclization upon acetophenone-sensitized irradiation: they form the corresponding 4,5-dihydroisoxazoles, **68**, providing ready access to that ring system (Scheme 37)[46, 47]. Of course, the cyclization requires a prior geometric isomerization, a reaction that occurs most readily. The authors considered the triplet state the key intermediate in this conversion. Isoxazolines were observed previously upon irradiation of (*E*)-16-dehydropregnenolone oxime 3-acetate, (*E*)-**43**[36]. The formation of isoxazolines by a different mechanism involving a ring contraction is discussed in Section VIII on Steroidal Oximes.



(**67**) R = Ph, R = Me (**68**)

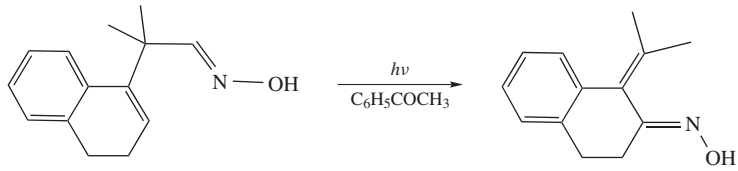
SCHEME 37

β,γ-Unsaturated oximes carrying an aryl group on the β-carbon, e.g. **69**, undergo a photochemical 1,3-migration of the oximino group, generating **72** (Scheme 38) and **74** (Scheme 39) from **69** and **73**, respectively. The likely mechanism involves a 1,4-cyclization of the styrene triplet/biradical, **70**$^{\bullet\bullet}$, followed by ring opening of the aminyl-cyclobutyl biradical, **71**$^{\bullet\bullet}$ (Scheme 38)[48, 49].



(**69**) (**72**) (**70**$^{\bullet\bullet}$) (**71**$^{\bullet\bullet}$)

SCHEME 38

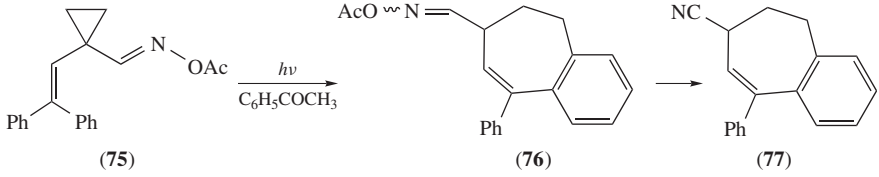


(**73**) (**74**)

SCHEME 39

According to the proposed mechanism, the oxime carbon is actively involved in the rearrangement, yet the oxime function remains unchanged in the product.

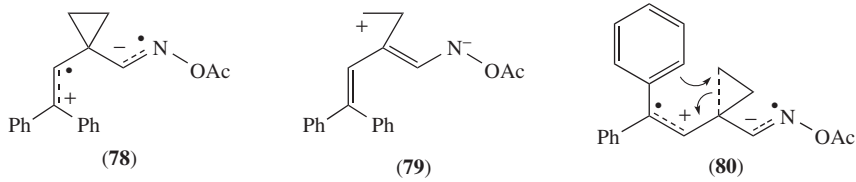
Structural variations in the substrate give rise to interesting modifications of the reaction. For example, introduction of a cyclopropane ring between the two π bonds of a β,γ-unsaturated oxime ester led to the formation of benzocycloheptene derivatives. Thus, acetophenone-sensitized irradiation of oxime ester **75** gave a complex product mixture; when heated under reflux in toluene to promote the conversion of oxime acetates to nitriles, the 6,7-dihydro-5*H*-benzocycloheptene derivative, **77**, was isolated in 12% yield, indicating the formation of oxime ester **76**. The major nitrile isolated corresponds to thermally converted starting material (Scheme 40)[50].



(**75**) (**76**) (**77**)

SCHEME 40

The authors formulated the reaction via intramolecular electron transfer from the alkene to the oxime function, generating a biradical zwitterion, **78** (Scheme 41)[50]. Proceeding from that intermediate, the rearrangement need not involve a zwitterion with a primary carbocation fragment, **79**. Rather, the cyclopropane bond, weakened by delocalization of spin and charge onto the ring, can be captured by the phenyl group, as shown in **80**.



(**78**) (**79**) (**80**)

SCHEME 41

In pursuit of extending the scope of the aza-di-π-methane rearrangement, Armesto and coworkers encountered many substrates that failed to undergo noticeable conversion

upon either direct or acetophenone-sensitized reactions. In an attempt to improve the reactivity of oximes, they probed the electron transfer sensitized reactions and evaluated the reactivity of the corresponding radical cations[51].

Electron transfer sensitization is based on a well-established photochemical reaction sequence[52]. Irradiation of an electron acceptor/sensitizer in the presence of a co-sensitizer and a suitable donor (D) generates a donor radical cation paired with a sensitizer/acceptor radical anion (equation 15). During its (limited) lifetime the radical cation may rearrange (equation 16) or eliminate a suitable group (equation 17). The reaction is terminated when radical cations ($D^{\bullet+}$), rearranged radical cations ($D_r^{\bullet+}$), or those formed by eliminating a group ($D_{el}^{\bullet+}$) regenerate starting material (equation 18) or form products by electron return from the sensitizer anion (equations 19 and 20). With 9,10-dicyanoanthracene (DCA) as sensitizer, biphenyl (BPh) as co-sensitizer and a molecule containing an oxime function as donor, the reaction sequence can be formulated in equations 15–20.

$$\mathrm{BPh} + \mathrm{DCA} + \mathrm{D} \xrightarrow{h\nu} \mathrm{BPh} + [\mathrm{DCA}^{\bullet-} + \mathrm{D}^{\bullet+}] \tag{15}$$

$$\mathrm{D}^{\bullet+} \longrightarrow \mathrm{D_r}^{\bullet+} \tag{16}$$

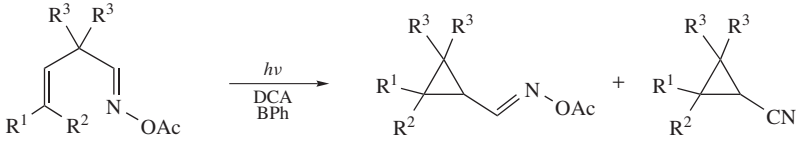
$$\mathrm{D}^{\bullet+} \longrightarrow \mathrm{D_{el}}^{\bullet+} \tag{17}$$

$$\mathrm{D}^{\bullet+} + \mathrm{DCA}^{\bullet-} \longrightarrow \mathrm{D} + \mathrm{DCA} \tag{18}$$

$$\mathrm{D_r}^{\bullet+} + \mathrm{DCA}^{\bullet-} \longrightarrow \mathrm{D_r} + \mathrm{DCA} \tag{19}$$

$$\mathrm{D_{el}}^{\bullet+} + \mathrm{DCA}^{\bullet-} \longrightarrow \mathrm{D_{el}} + \mathrm{DCA} \tag{20}$$

In applying electron transfer sensitization, using 9,10-dicyanoanthracene with biphenyl as a co-sensitizer, to otherwise unreactive oximes or oxime esters, Armesto and coworkers extended the scope of oxime reactivity significantly. A series of β,γ-unsaturated oxime acetates of structure **81** undergo efficient aza-di-π-methane rearrangement via radical cations, yielding cyclopropanes, **82** (Scheme 42). The oxime function participates in the reaction but remains unchanged in the product.



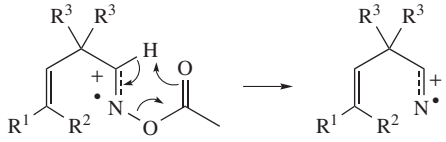
(**81**) R^1 = Ph; R^2 = H; R^3 = Me (**82**) (**83**)

$R^1 = R^2$ = Ph; R^3 = Me

SCHEME 42

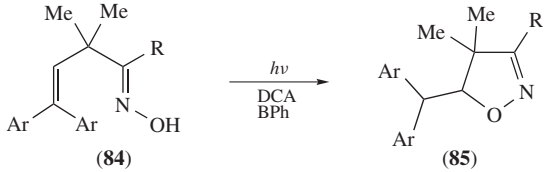
In addition to the cyclopropyl oximes, **82**, the nitriles, **83**, are generated by net loss of acetic acid (*ca* 10% yield; cf. Scheme 43). In this reaction the oxime acetate function is the reactive fragment[53].

A range of ketoximes, e.g. **84**, undergo an electron-transfer sensitized cyclization to 4,5-dihydroisoxazoles, **85** (Scheme 44)[53]. The cyclization is similar to the acetophenone—sensitized reaction (*vide supra*), but the yields of the 4,5-dihydroisoxazoles, **85**, are higher, providing ready access to that ring system[53]. The authors formulated the reaction via an oxime radical cation. For oximes without an



SCHEME 43

aromatic group at the oxime carbon, i.e. R = H, CH_3, one might also consider that the diarylethene moiety serves as the electron donor and that the resulting radical cation is captured by the oxime O−H function. There is ample precedent for the intramolecular capture of a radical cation by a tethered hydroxy group[54].



(**84**) (**85**)

R = H, Me, Ph; Ar = C_6H_5, *p*-$MeOC_6H_4$, *p*-*t*-BuC_6H_4

SCHEME 44

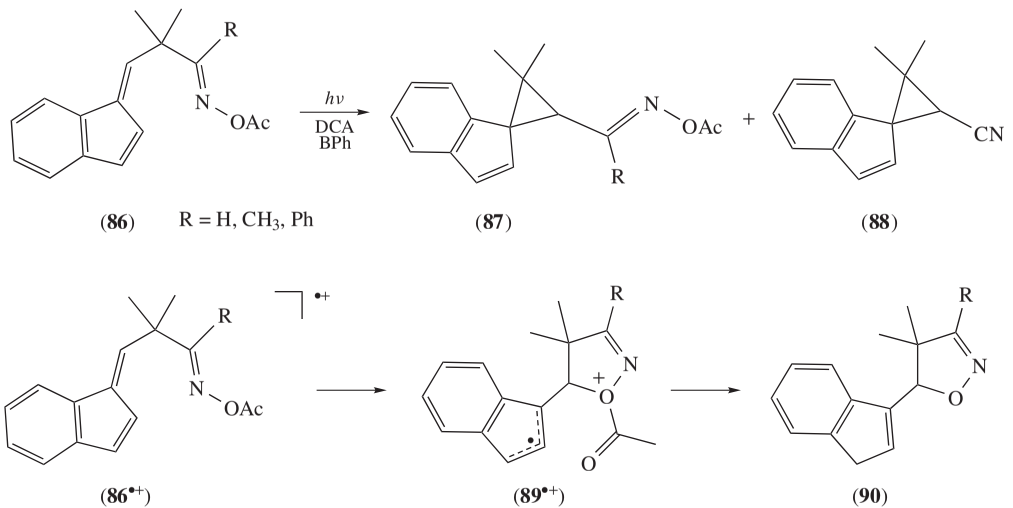
The indenylidene derivative, **86**, yields the cyclopropane **87**, the corresponding nitrile, **88**, and the dihydroisoxazole, **90**, in 18% yield (Scheme 45). Cyclization of the radical cation, **86**$^{\bullet+}$, forms the bifunctional radical cation, **89**$^{\bullet+}$; subsequently, loss of acetyl ion, return electron transfer and protonation could account for the product[54].

The corresponding oxime methyl ethers give results unlike the oxime esters. The monophenyl system, **91a**, forms the aza-di-π-methane product, **92a** (Scheme 46); however, the yield is poor (10% after 14 h) and the reaction mixture is complex. The diphenyl system, **91b**, yields a complex reaction mixture without any aza-di-π-methane product[53].

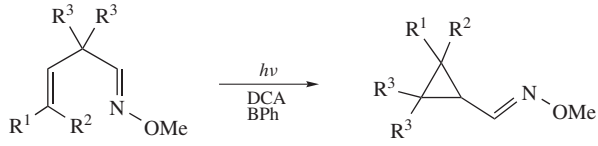
The indenylidene derivative, **93**, generates the interesting adduct, **95**, formally a [4+4] addition product of two bifunctional radical ions, the six-membered cyclized radical cation, **94**$^{\bullet+}$, and the dicyanoanthracene radical anion (Scheme 47)[53].

In an attempt to improve the yields of some of the unusual products obtained in the ET sensitized reactions, Armesto and coworkers used 1,4-dicyanodurene (DCD) as sensitizer. This sensitizer has the disadvantage that it absorbs at shorter wavelength so that its use is limited to oximes that do not absorb strongly above 300 nm. The approach proved successful for several substrates, leading to significantly improved yields. Interestingly, the nitriles obtained in DCA sensitization were not formed with DCD[53].

DCD sensitized irradiation of the monophenyl substrate, **96**, gave rise to the [4+2] adduct, **98** (23% yield), in addition to the aza-di-π-methane product, **97** (7%; Scheme 48). The authors did not comment on the stereochemistry at carbons 7 and 8; presumably, the *trans* arrangement around the double bond of **96** is retained in product **98**[53].

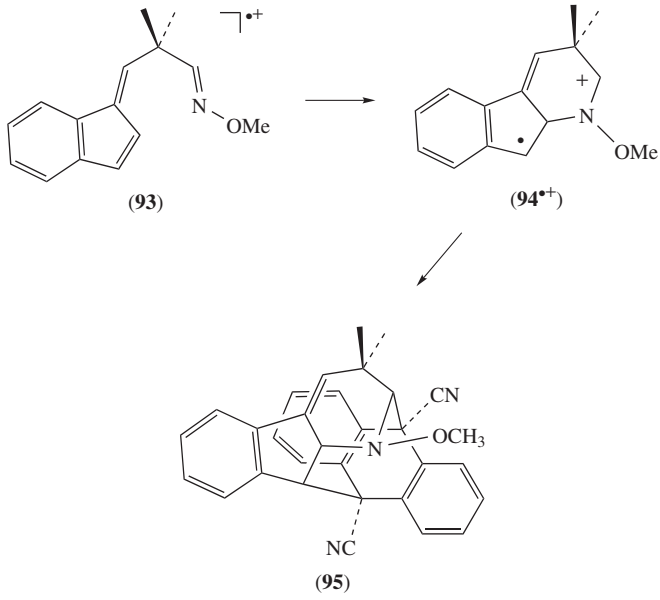

R
N
OAc
hν
DCA
BPh
N
OAc
R
+
CN
(86) R = H, CH3, Ph
(87)
(88)
•+
R
N
OAc
R
N
+
O
O
R
N
O
(86•+)
(89•+)
(90)

SCHEME 45



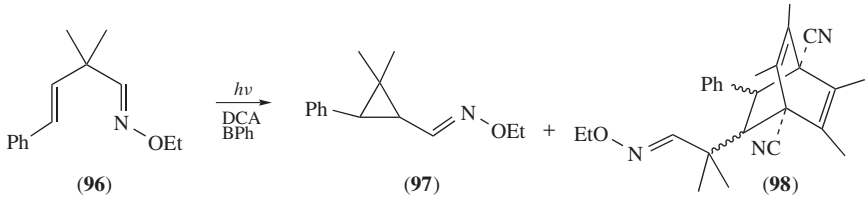
(**91**) (**a**) R^1 = Ph; R^2 = H; R^3 = Me (**92**)
(**b**) R^1 = R^2 = Ph; R^3 = Me

SCHEME 46



(**93**) (**94**$^{\bullet+}$) (**95**)

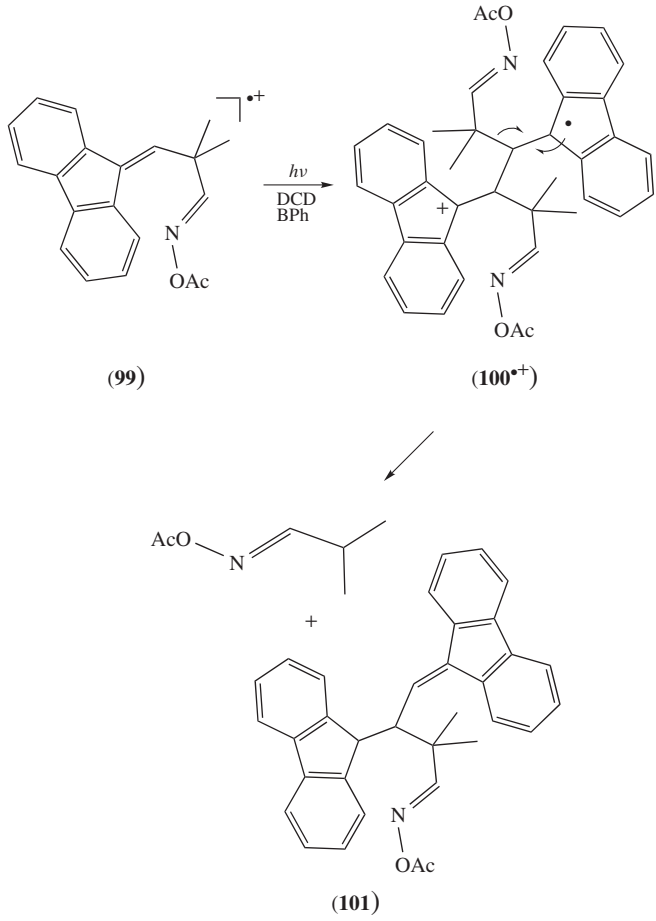
SCHEME 47



(**96**) (**97**) (**98**)

SCHEME 48

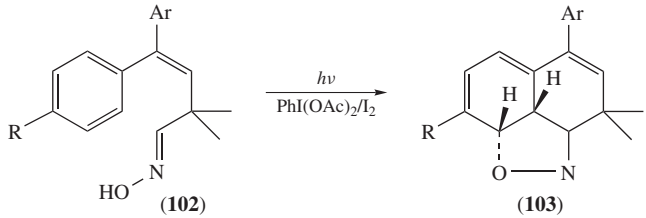
Lastly, Martinez-Alcázar and coworkers obtained the unexpected product, **101**, in the DCA/BPh sensitized reaction of 3-(9-fluorenylidene)-2,2-dimethylpropenal oxime acetate, **99**. This unusual product was rationalized to arise via a dimer radical cation, **100**, and loss of a tertiary free radical bearing an oxime acetate function (Scheme 49)[55].



(**99**) (**100**$^{\bullet+}$) (**101**)

SCHEME 49

An unprecedented photochemical cyclization of a β,γ-unsaturated oxime was observed by Horspool and coworkers in the presence of somewhat uncommon oxidants. Irradiation of the diaryl species, **102**, in the presence of either phenyliodine diacetate and molecular iodine or mercuric oxide/iodine resulted in an oxidative intramolecular cycloaddition to an aryl group, generating peri-naphthisoxazoles, **103**, in good yields (Scheme 50)[56].

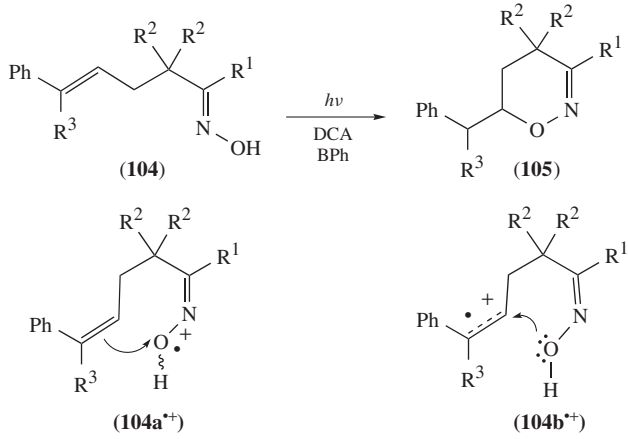


Ar = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-MeC_6H_4
R = H, Br, Cl

SCHEME 50

C. γ,δ-Unsaturated Oximes

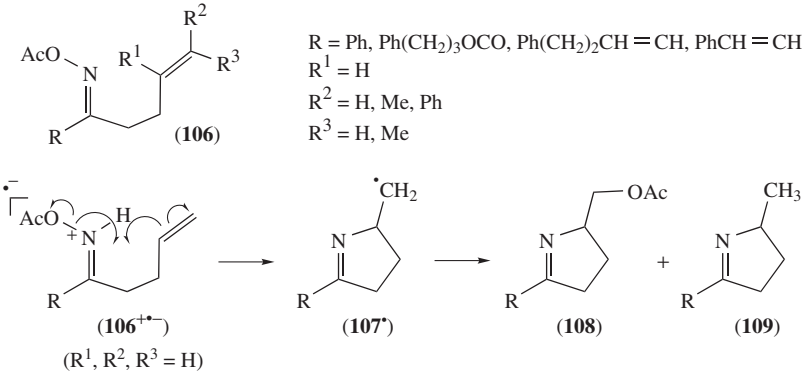
The electron-transfer sensitized reaction of γ,δ-unsaturated oximes, **104**, forms 1,2-oxazines, **105**, as the only products in over 50% yield (Scheme 51). The reaction works well for aldoximes ($R^1 = H$) and ketoximes ($R^1 = CH_3$); it succeeds as long as the C=C bond is substituted with at least one phenyl group; it fails with alkyl substituents[57].



SCHEME 51

The authors proposed a mechanism featuring oxidation of the oxime function and electrophilic capture by the alkene group (viz. **104a**$^{\bullet+}$; cf. Scheme 51). Given the ready oxidation of styrene or diphenylethylene and the ample precedent for nucleophilic capture of alkene radical cations by tethered OH groups[54], we propose a modified explanation: an arylethylene radical cation (**104b**$^{\bullet+}$) that is captured by the oxime OH function. The formation of a six-membered ring falls into the favorable range of intramolecular ring closures. This assignment readily explains why the substrate in which the alkene bond is substituted with two methyl groups fails to react appreciably: the oxidation potential of the isobutylene moiety is too high to be oxidized by excited-singlet 9,10-DCA ($^*E_{A/A^-} = 2.0$ V vs SCE).

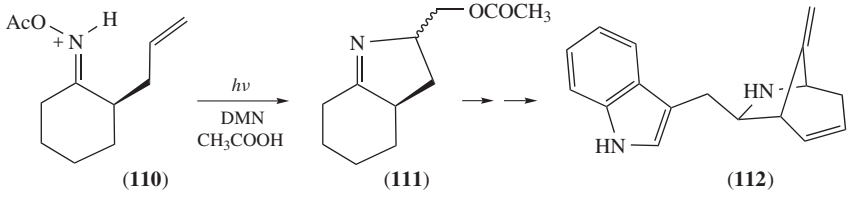
A different mode of cyclization of γ,δ-unsaturated alkyl ketone *O*-acetyloximes, e.g. **106**, was observed by Kitamura and coworkers. Using 1,5-dimethoxynaphthalene (DMN) as the sensitizer they obtained 3,4-dihydro-2*H*-pyrroles, e.g. **108** or **109** (Scheme 52)[58].



SCHEME 52

DMN is an electron donor, which transfers an electron to the oxime, generating the corresponding oxime radical anion. The yields are poor, because the *O*-acetyloxime moiety is a poor electron acceptor; the yields are improved significantly in the presence of acetic acid: the protonated acetyloxime is a much better acceptor. The cyclization proceeds via photosensitized electron transfer from ^{1}DMN*, generating a radical zwitterion, e.g. **106**$^{+\bullet-}$; loss of acetic acid forms free radical, **107**$^{\bullet}$, which is converted to the acetate, **108**, or, by hydrogen abstraction from added cyclohexa-1,4-diene, to **109**[58].

The reaction has synthetic utility; chiral centers adjacent to the oxime acetate are not altered during the reaction, e.g. in the conversion of **110** to **111**. The total synthesis of peduncularine, **112**, was achieved by applying the catalytic radical cyclization of an oxime as a key step (Scheme 53)[59].



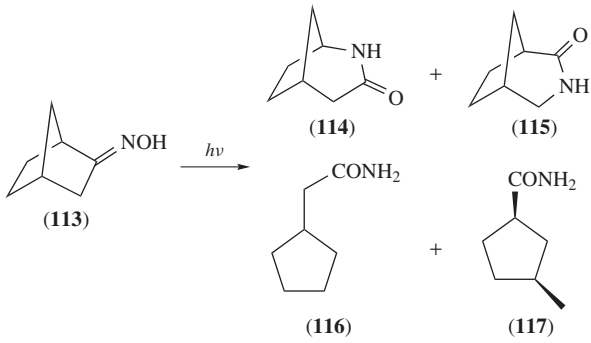
SCHEME 53

VII. BICYCLIC OXIMES AND RELATED SYSTEMS

Given the plethora of terpenes it is not surprising that several oximes derived from these structures have been studied, among them three oximes derived from bicyclo[2.2.1]heptanone. The authors who first studied the photolysis of camphor oxime

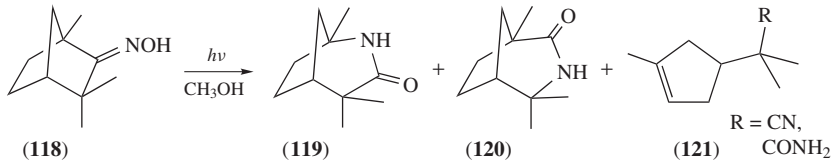
reported only the parent ketone and various nitriles as irradiation products; this report caused some concern because it was at variance with the accepted photoreaction of oximes to form amides[60].

The photolysis of norcamphor oxime, **113**, in anhydrous methanol solution (254 nm) gave rise to two isomeric lactams, **114** and **115**, the expected products of a photo-Beckmann rearrangement, and formed two cleavage products, **116** and **117**, in lesser yields. The *cis* stereochemistry of **117** was assigned on the basis of the mode of formation (Scheme 54)[61].



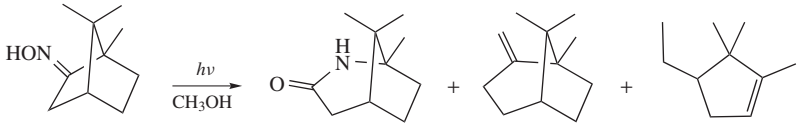
SCHEME 54

Two decades later, Suginome and coworkers studied the photolysis of the oximes of (+)-fenchone and (+)-camphor. The photolysis of (+)-fenchone oxime, **118**, in MeOH produced a 1:1 ratio of two isomeric lactams, 1,4,4-trimethyl-2-azabicyclo[3.2.1]octan-3-one (**119**; 13%) and 1,4,4-trimethyl-3-azabicyclo[3.2.1]octan-2-one (**120**; 13%), an isomer not previously described (Scheme 55). In addition, several nitriles and cycloalkenoic acid amides arising from ring cleavage at the bridgehead, e.g. **121**, were isolated in 11 and 10% yield, respectively[62].



SCHEME 55

Photolysis of (+)-camphor oxime, **122**, in MeOH similarly gave two isomeric lactams, 1,8,8-trimethyl-2-azabicyclo[3.2.1]octan-3-one (α-camphidone; 12%), **123**, and 1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (12%), **124**, as well as a ring-opened amide, α-campholenic amide (32%), **125**, as the major product (Scheme 56). The isolation of **123** and **124** removes any notion that camphor oxime may be a special structure type[62]. Perhaps the earlier authors lost the lactams in the work-up or had 'special' reaction conditions.

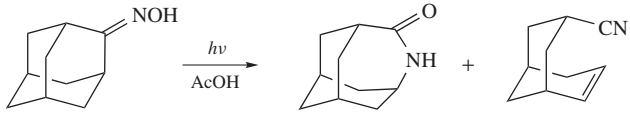


(**122**) (**123**) (**124**) (**125**)

SCHEME 56

Both (+)-fenchone oxime, **118**, and (+)-camphor oxime, **122**, produce nitriles arising from photochemical α-fission, in 11 (from fenchone) and 6% (from camphor) yield. Accordingly, the methyl groups attached to the α-carbons had little effect on the direction of the photoreaction of bicyclo[2.2.1]heptanone oximes. From a synthetic point of view, 2- and 3-azabicyclo[3.2.1]octanones are accessible from the photoreaction of bicyclo[2.2.1]heptanone oximes, although in moderate yields[62].

The photolysis of adamantanone oxime, **126**, in acetic acid under nitrogen produced high yields of the ring-expanded amide, **127** (89% after six hours), and 8% of adamantanone but no fragmentation. The symmetry of the substrate allows only a single lactam. On the other hand, irradiation in methanol or isopropanol diverted the course of the reaction; it produced low yields of adamantanone and nitrile **128**, but no **127** (Scheme 57)[63].



(**126**) (**127**) (**128**)

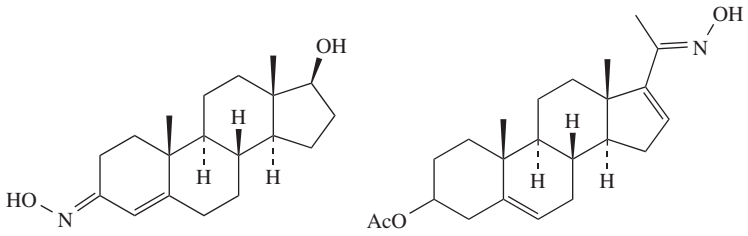
SCHEME 57

The photolysis of 3-ethoxyimino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, another derivative of bicyclo[2.2.1]heptane, is discussed in Section IX dealing with oxo-oximes.

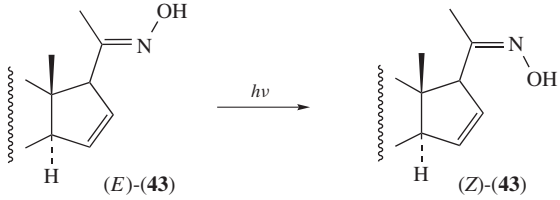
VIII. PHOTOREACTIONS OF STEROIDAL OXIMES

Oximes derived from steroid systems have played a prominent role in the investigation of oxime photochemistry. Just and coworkers studied several steroid oximes as early as 1966[26, 34]. In addition to the common $E-Z$ isomerization, they observed Beckmann-type rearrangement products, cleavage products such as amides, and ketones. They were the first to isolate a nitrile, **39**, in the photolysis of 17β-hydroxy-3-methoxyandrosta-3,5-diene-6-carboxaldehyde oxime, **38** (*vide supra*)[34]. Two α,β-unsaturated ketoximes, testosterone oxime, **129**, and pregna-5,16-dien-3β-ol-20-one acetate oxime, **130** (Scheme 58), with oxime moieties in rings A and D, respectively, showed rapid E,Z-isomerization in methanol followed by slow and extensive decomposition. No rearrangement or cleavage products were isolated[26].

Gandhi and Chadha irradiated *anti*-16-dehydropregnenolone oxime 3-acetate, (*E*)-**43**; we have mentioned the isoxazoline, **44**, as the product obtained upon irradiation of **43** in benzene. In a more polar solvent, tetrahydrofuran, (*E*)-**43** underwent E,Z-isomerization to (*Z*)-**43** (Scheme 59)[36].

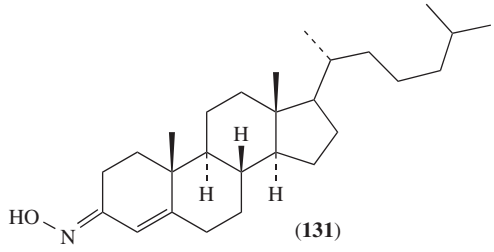


SCHEME 58



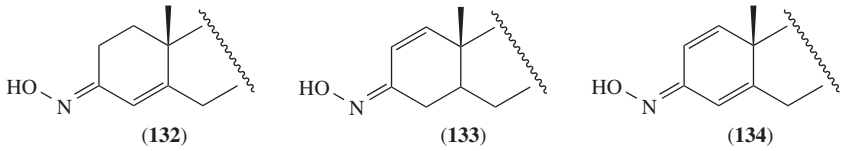
SCHEME 59

Irradiation of cholestanone oxime, **131** (Scheme 60), in benzene or toluene (high pressure lamp) yielded mainly cholestan-3-one (50% yield) and some cholestane (5%). No lactam or amide expected for a photo-Beckmann rearrangement was noted. Irradiation of the oxime acetate of **131** yielded the oxime, **131**, and cholestanone[64].



SCHEME 60

The unsaturated cholestanone oximes, **132** and **133** (Scheme 61), and their acetates, when irradiated in alcoholic solvents, undergo ready *E*,*Z*-isomerization and produce the corresponding ketones in good yields. Similar irradiation of 3-oxo-17β-acetoxy-1,4-androstadiene, **134**, only gave a minimal yield (5–10%) of the dienone together with secondary photoproducts of the ketone. Irradiation of the oxime acetates in benzene gave the corresponding oximes and ketones. Traces of the corresponding cholestane azines support the involvement of small amounts of iminyl radicals from the oxime acetates. No azines were formed from the oximes[65].



(**132**) (**133**) (**134**)

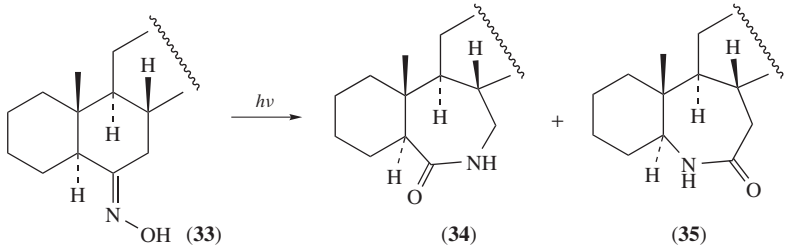
SCHEME 61

In 1972 Suginome and collaborators entered the field of steroidal oxime photochemistry. Over a period of three decades this group carried out a systematic investigation of saturated as well as α,β-unsaturated ketoximes[66]. Their work provided significant insights into oxime reactivity and specifically into the photo-Beckmann rearrangement; they evaluated the migratory aptitude of secondary vs. tertiary vs. quaternary carbons with special attention to the stereochemistry at the migrating carbon center.

A. Saturated Steroidal Oximes

Concerning saturated oximes, Suginome selected a variety of systems bearing oxime functions in rings A, B and D. Most of these underwent the photo-Beckmann rearrangement with retention of stereochemistry at the migrating center. Selected systems reacted by α-fission and by non-concerted photo-Beckmann rearrangement.

The photo-Beckmann rearrangement of (*E*)- or (*Z*)-5β-cholestan-6-one oxime (**33**) generated a pair of lactams, **34** and **35**, both with retention of configurations of the migrating Cα (Scheme 62). These results provided major support for the concept of a concerted reorganization of the excited singlet oxazirane intermediate (see Section IV)[6b].

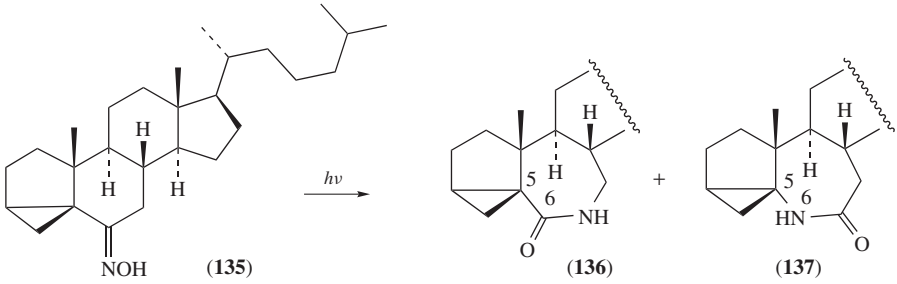


(**33**) (**34**) (**35**)

SCHEME 62

Analogous results were observed for 5α- and 5β-cholestan-1-one oximes, for the corresponding -4-one oximes[67] and for A-nor-5β-cholestan-3-one oxime[68]. In each case, two structurally isomeric lactams were obtained in combined yields of 25–53%; in addition, the parent ketones were isolated in low yields[67, 68].

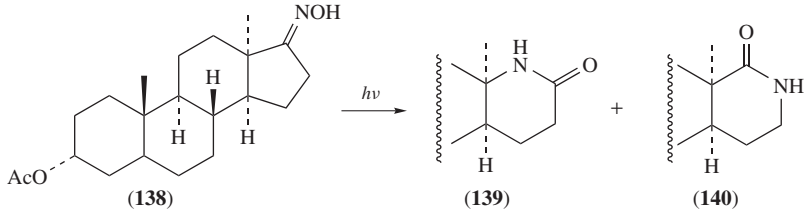
3α,5-Cyclo-5α-cholestan-6-one oxime, **135**, in which the oxime function is conjugated with a cyclopropane ring, also generated two isomeric lactams, **136** and **137**, though in poor yields (Scheme 63). The fact that the cyclopropane ring remains intact further supports the concept of a concerted C $\rightarrow$ N migration in the photo-Beckmann rearrangement[6b]. The major product of the reaction was the parent ketone accompanied by several of its photoproducts. The analogous -6-one oxime with a cyclopropane ring in the β-position gave the corresponding pair of lactams in a combined yield of 45%[69].



(**135**) (**136**) (**137**)

SCHEME 63

Photolysis of *O*-acetyl-13α-androsterone oxime, **138**, gave **139** (1% yield) and **140** (3% yield), both with retention of stereochemistry at the epimeric center (Scheme 64)[70].

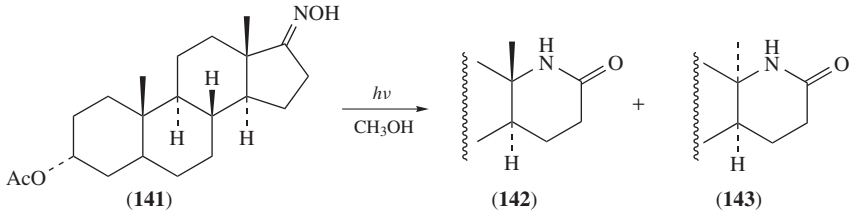


(**138**) (**139**) (**140**)

SCHEME 64

The photorearrangement of a pair of cholestanone oximes bearing a hydroxy function in the 5-position gave rise to two α-hydroxy lactams in 15 and 21% yield, respectively, providing access to these compounds[71].

There are few exceptions to the concept of a concerted C $\rightarrow$ N migration in the oxime to oxazirane to amide conversion. One of these was observed in the photolysis of *O*-acetylandrosterone oxime, **141**, in methanol. This reaction gave *O*-acetyl-D-homo-5α-17a-azaandrosterone, **142** (3% after 30 h), and its 13**α** isomer, **143** (1%; Scheme 65). Product **143** requires epimerization at C-13, a result that is incompatible with a concerted mechanism[70]. In this system, the rearrangement has to proceed via a radical or ionic intermediate; however, the yield of these lactams is low[70].

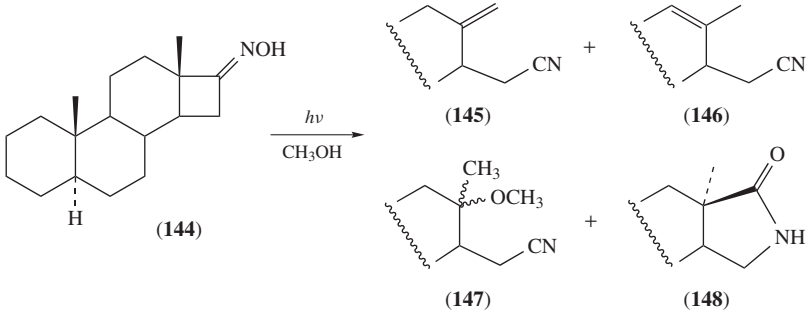


(**141**) (**142**) (**143**)

SCHEME 65

Another case of non-concerted photo-Beckmann rearrangement is that of D-nor-5α-androstan-16-one oxime, **144**, a steroidal cyclobutanone oxime.

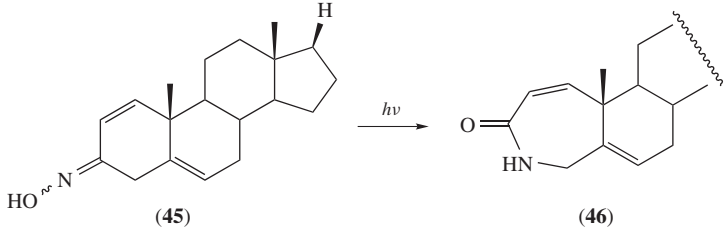
Products **145**–**147** are formed by ionic α-cleavage at the quaternary center, yielding a tertiary carbocation; a nitrile resulting from cleavage at the secondary carbon was also obtained (Scheme 66). In addition, three lactams were obtained in low yields. Significantly, one of these, 17-aza-5$\boldsymbol{\alpha}$,13$\boldsymbol{\alpha}$-androstan-16-one, **148**, is incompatible with a concerted rearrangement[72].



SCHEME 66

B. Unsaturated Steroidal Oximes

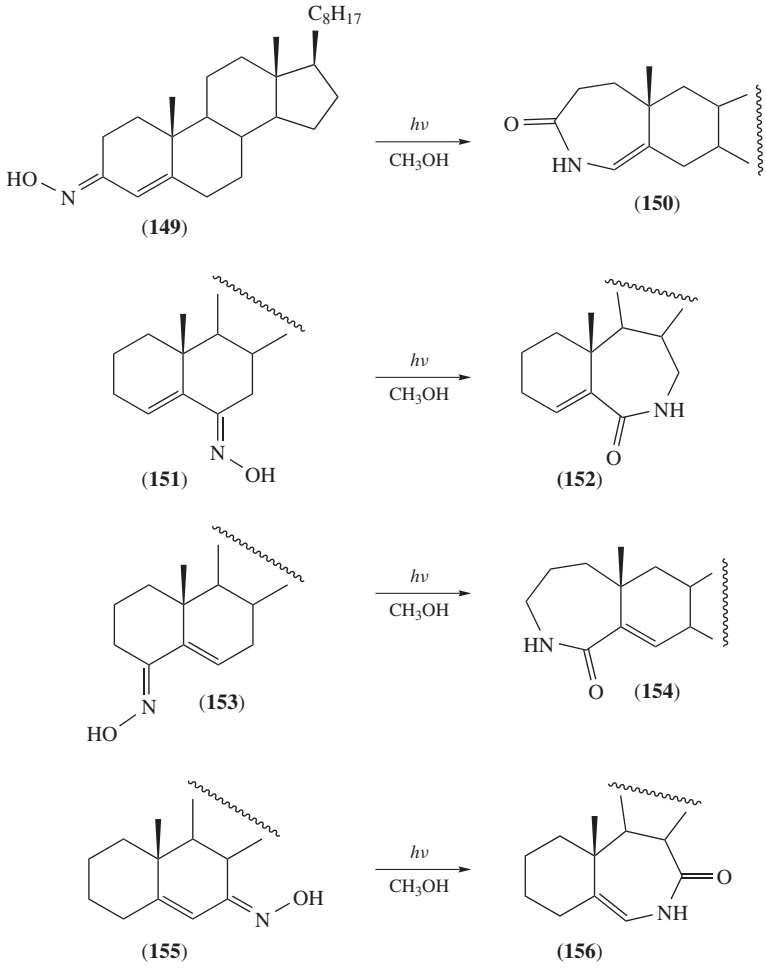
Bonet and coworkers were the first to study the photochemistry of an α,β-unsaturated steroid oxime: 17β-hydroxyandost-1,5-dien-3-one oxime, **45**, undergoes the photo-Beckmann rearrangement with migration of C-4, generating **46** (Scheme 67)[37].



SCHEME 67

Following this isolated result, Suginome and his group elaborated the photochemistry of unsaturated steroidal oximes in significant detail, providing the most coherent study of any oxime series[66]. They selected a variety of steroid systems bearing oxime functions in rings A and B, including the oximes derived from the 1-en-3-one, 2-en-1-one, 2-en-4-one, 3-en-2-one, 4-en-3-one, 5-en-4-one and 5-en-6-one. These oximes underwent four types of reactions in protic solvents: (a) *E*,*Z*-isomerization; (b) photo-Beckmann rearrangement to lactams; (c) additions to the α,β-C=C bond; and (d) rearrangement to an isoxazoline derivative, of a type different from that of Gandhi and Chadha[36] and Armesto, Horspool and coworkers[46] discussed earlier.

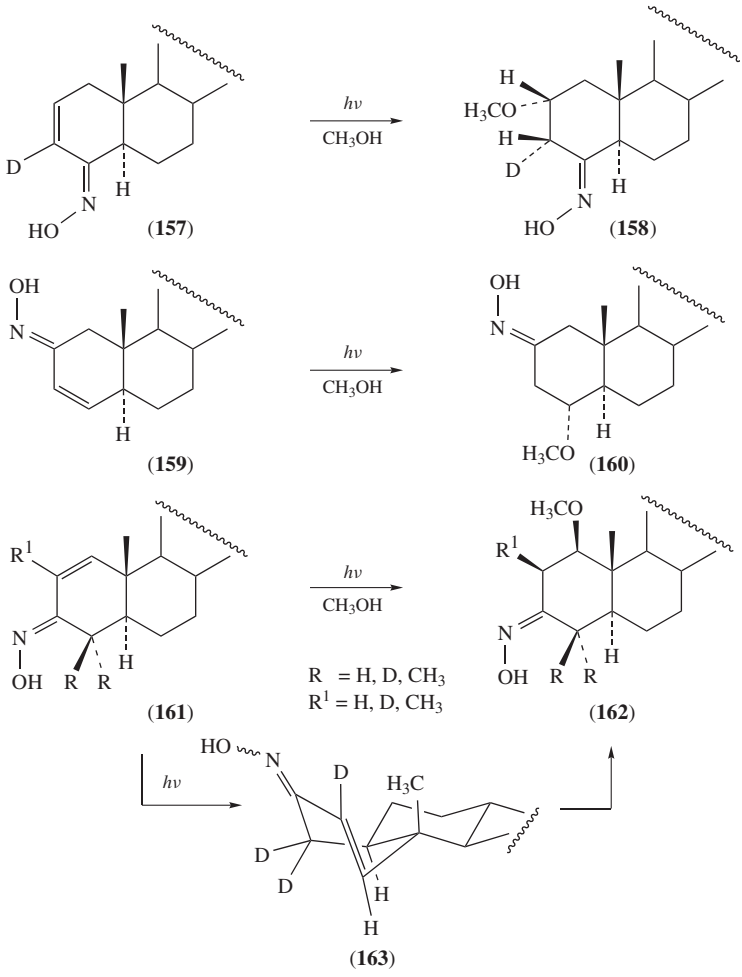
A series of steroidal oximes having a relatively rigid C=C bond at a ring junction undergoes the photo-Beckmann rearrangement, generating either enamine or enamide type lactams. For example, the steroidal 4-en-3-one, **149**, and 5-en-7-one oximes, **155**, give rise to enamines, **150** and **156**, respectively, whereas the 4-en-6-one, **151**, and 5-en-4-one oximes, **153**, produce enamides, **152** and **154**, respectively (Scheme 68)[73]. The factors governing the observed regioselectivity are not fully understood; it is reasonable to assume that the regioselectivity may have its origin in a stereoelectronic effect, such as the three-dimensional arrangement of the nitrogen lone pair relative to the migrating C−C bond in the excited-state oxazirane.



SCHEME 68

Steroidal oximes whose C=C bonds are not at a ring junction are more flexible; they undergo *E*,*Z*-isomerization of the C=C bond, producing transient (*E*)-isomers. These

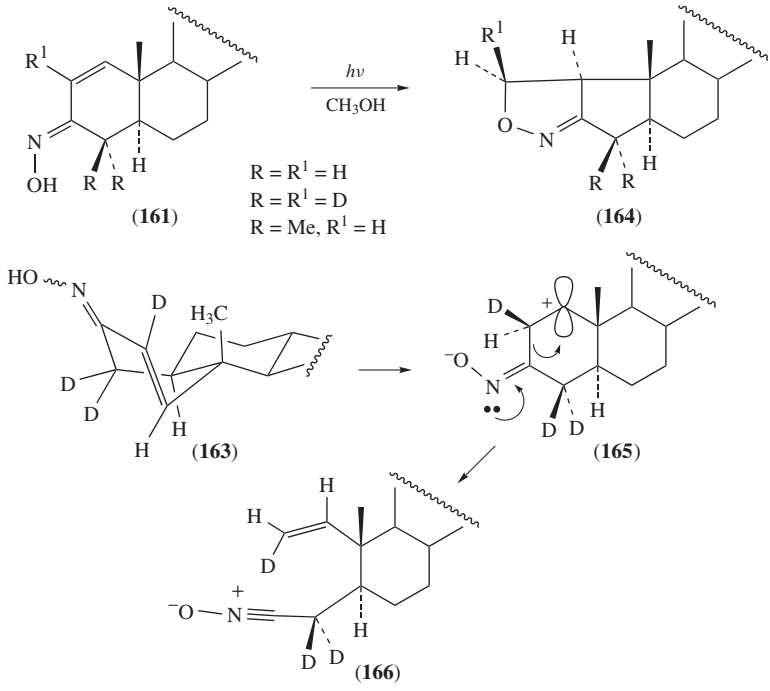
species react by stereospecific addition of H^+ or methanol. 5α-Cholest-2-en-3-one, **157**, 5α-cholest-3-en-2-one, **159**, or **161** form the oxime methyl ethers, **158** and **160**, and the 1β-methoxy oxime, **162**, respectively, by stereospecific addition of methanol. The stereochemistry of the addition was assured by D-labeling (Scheme 69)[73].



SCHEME 69

5α-Cholest-1-en-3-one oxime and 4,4-dimethyl-5α-cholest-1-en-3-one oxime, **161**, undergo, in addition, an interesting rearrangement to isoxazole derivatives, **164**. The structures of these products rest unambiguously on X-ray structure determinations; the mechanism was elucidated by D labeling[74].

The authors identified **163** as key intermediate on the path to the oxazoline. The twisted cyclohexene fragment of **163** is protonated, most likely by the oxime moiety, generating the 'homoallylic' carbocation, **165**; fragmentation yields the nitrile oxide, **166**, which forms two five-membered rings by [3+2] cycloaddition (Scheme 70)[74].



SCHEME 70

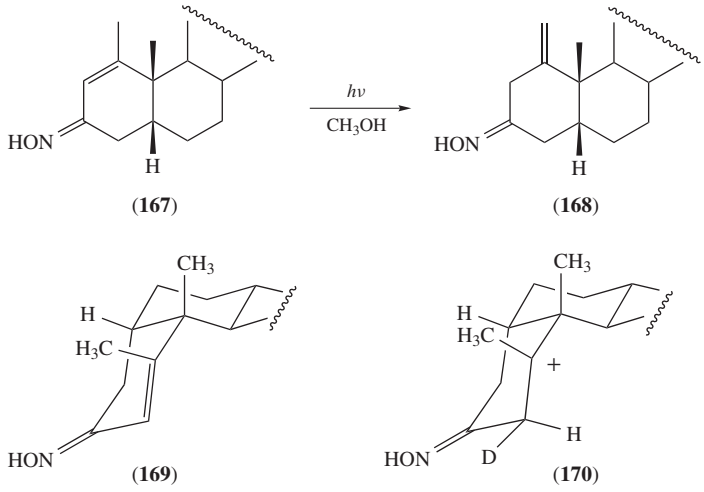
Introducing a methyl group in the 1-position of 5α-cholest-1-en-3-one oxime has a profound effect on the course of the reaction. Irradiation of 1-methyl-5α-cholest-1-en-3-one oxime, **167**, results in an unprecedented deconjugation with formation of the β,γ-isomer, **168**, in protic or aprotic solvents. Deuterium labeling studies showed that D is introduced stereospecifically in the 2α-position, most likely in the twisted (*E*)-cycloalkene, **169**; loss of a proton from the 1-methyl group of the resulting carbocation, **170**, then forms **168** (Scheme 71)[75].

Lastly, β,γ-unsaturated steroidal oximes, such as 4,4-dimethylcholest-5-en-3-one, **171**, undergo the photo-Beckmann rearrangement analogous to those of saturated steroidal ketoximes, giving rise to lactams, such as **172** and **173** (Scheme 72)[76].

IX. OXO-OXIMES

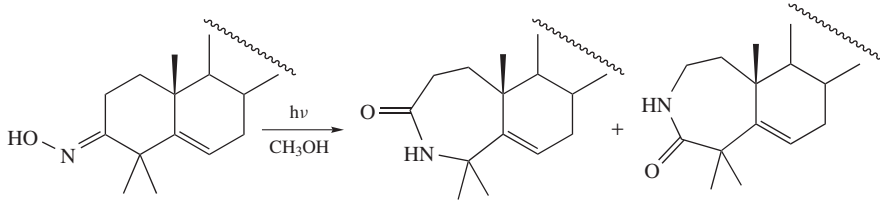
Of special interest are substrates that, in addition to the oxime group, contain a second chromophore, either in conjugation with the oxime moiety, e.g. α-oxo-oximes, or separate from the oxime group. Such systems are exemplified here with linear alkane derivatives, as well as mono- and bicyclic systems.

The products obtained in the photochemistry depend on the wavelength of the irradiation. Irradiation with light of 366 nm causes mainly $E-Z$ isomerization. Cerfontain and his coworkers have studied a large number of α-oxo-oxime ethers, carried out a detailed structural analysis utilizing IR, UV and ^{1}H NMR spectra, assigning configurations and conformations, and measured the photostationary states[9, 18, 77–85].



(**167**) (**168**) (**169**) (**170**)

SCHEME 71

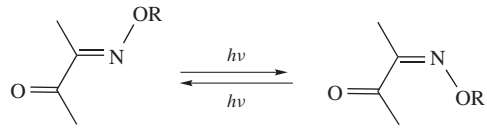


(**171**) (**172**) (**173**)

SCHEME 72

For example, simple alkane derivatives, such as (*E*)-3-ethoxyiminobutan-2-one (biacetyl monoxime ethyl ether), (*E*)-**174**, undergo *E*–*Z* isomerization as the predominant reaction upon 366 nm irradiation. The irradiation resulted in a photostationary state of 6:1 in favor of (*E*)-**174**; the identical ratio was reached from both (*E*)- and (*Z*)-**174** (Scheme 73). The isomerization was not affected by (*Z*)-1,3-pentadiene, suggesting that the isomerization proceeds either from the excited singlet state or from a very short-lived triplet state. The UV spectra of the two isomers are significantly different: the (*E*)-isomer has maxima at 230 nm ($\varepsilon = 11\,000$) and 320 nm ($\varepsilon = 28$) whereas the (*Z*)-isomer has maxima at 245 nm ($\varepsilon = 3500$) and 325 nm ($\varepsilon = 62$)[9a].

The photostationary state obtained upon triplet-photosensitized irradiation showed an interesting dependence on the sensitizer energy not unlike that discussed earlier for acetophenone oxime *O*-methyl ether, **3**, with three distinct regions. At sensitizer energies $E_T \geq 69\,\text{kcal mol}^{-1}$ the isomer ratio is constant, 1.1:1, and the energy transfer to either isomer is diffusion-controlled; in the range $57 < E_T < 69\,\text{kcal mol}^{-1}$ the energy transfer to the *E*-isomer becomes 'non-vertical'[86]; finally, at $E_T < 57\,\text{kcal mol}^{-1}$ the rate of energy transfer is slower than the decay rate of the sensitizer. These results led to estimated triplet energies of $69\,\text{kcal mol}^{-1}$ for the *E*- and $57\,\text{kcal mol}^{-1}$ for the *Z*-isomer. The 0,0 band



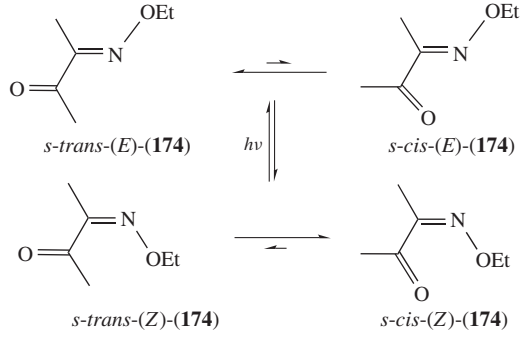
(*E*)-(**174**) R = C_2H_5 (*Z*)-(**174**)

SCHEME 73

of the *E*-isomer corresponds to a singlet energy of 78 kcal mol^{-1}. The authors invoked a triplet state common to both *Z*- and *E*-isomers, very likely a nearly perpendicular one[9a].

Based on a detailed kinetic analysis, the authors concluded that the direct photoisomerization involves the same common triplet state as the triplet-sensitized isomerization; this requires that the decay to the *Z*- and *E*-isomers is faster than diffusion-controlled[9a].

The oxo-oximes offer a more subtle stereochemical problem that hadn't been raised for the α,β-unsaturated oximes, that of the relative orientation of the two π-bonds. Dipole moment measurements had shown that (*E*)-**174** exists in the *s-trans* conformation[87]. Baas and Cerfontain[9a] elucidated the oxo-oxime conformation by applying the aromatic solvent induced shift method (ASIS)[88]. They measured the ^{1}H NMR shift difference, Δ, between carbon tetrachloride [$\delta(CCl_4)$] and benzene [$\delta(C_6H_6)$]. For (*E*)-**174**, a negative Δ for the imine methyl group and a positive Δ for the OCH_2 group confirmed the *s-trans* conformation[9a]. The photochemically generated isomer, on the other hand, has a positive value of Δ for the imine methyl group and a smaller positive value for the OCH_2 group, suggesting the *s-cis* conformation for (*Z*)-**174** (Scheme 74)[9a].

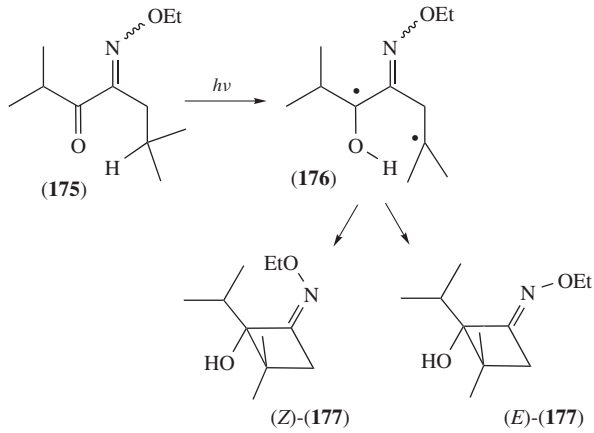


s-trans-(*E*)-(**174**) *s-cis*-(*E*)-(**174**)

s-trans-(*Z*)-(**174**) *s-cis*-(*Z*)-(**174**)

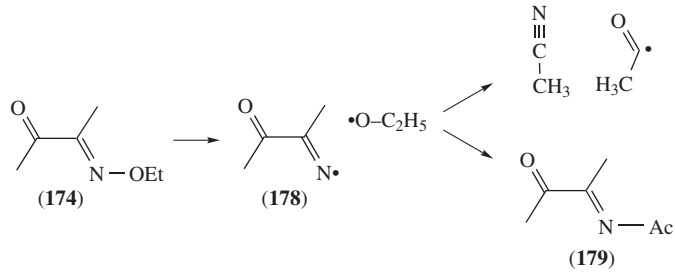
SCHEME 74

For oxo oximes containing longer alkyl chains, e.g. 4-ethoxyimino-2,6-dimethylheptan-3-one, **175**, a Norrish type II reaction of the carbonyl group was observed, generating two isomeric cyclobutanols, (*E*)- and (*Z*)-**177**, though in very low quantum yield (*ca* 0.02; Scheme 75). Obviously the γ-hydrogen abstraction forming biradical **176** can occur only from an *s-trans* conformer. The photostationary ratio of (*E*)- to (*Z*)-**175** was 2.3; the cyclobutanols were formed in a ratio (*E*)-**177**:(*Z*)-**177** of *ca* 7[77].



SCHEME 75

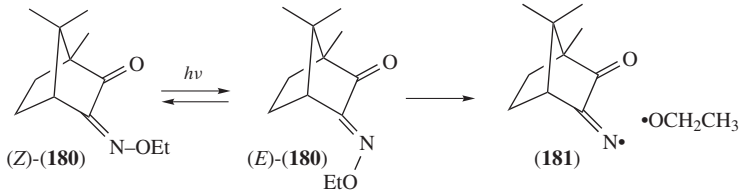
Photolysis of (*E*)-**174** at 254 nm was studied in non-polar (cyclohexane) and polar solvents (acetonitrile). Photo-excited (*E*)-**174*** undergoes N−O bond homolysis with formation of α-oxo-iminyl, **178**, and ethoxyl radical. The α-oxo-iminyl radical undergoes β-scission forming acetonitrile and acetyl radical, or recombines with an acetyl radical to yield the *N*-acetyl-α-oxo-imine (**179**; Scheme 76). Ethoxyl and acetyl radicals undergo a series of reactions not of interest in the context of this chapter[78]. The *N*-acetyl oxo-imine **179** undergoes a series of secondary photochemical reactions, including hydrogen abstraction from cyclohexanone, leading to a series of secondary amides[78].



SCHEME 76

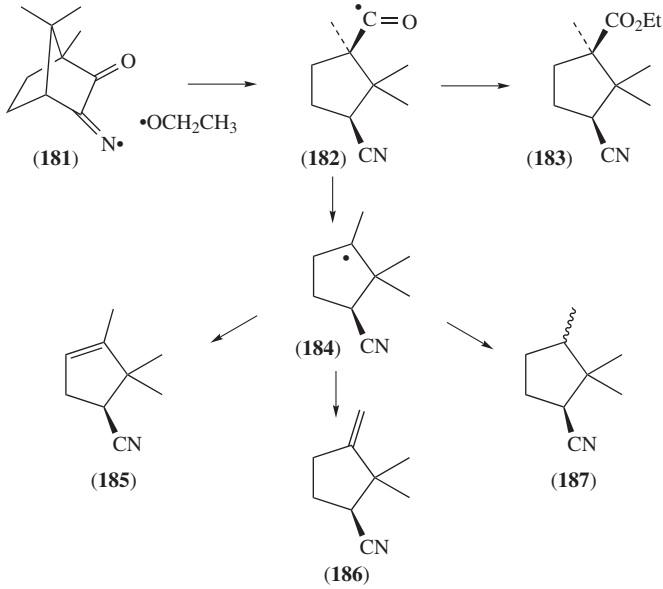
Irradiation of the bicyclic camphor derivative 3-ethoxyimino-1,7,7-trimethylbicyclo [2.2.1]heptan-2-one, **180**, at 254 nm in acetonitrile caused ready *E*,*Z*-isomerization (Scheme 77) and gave rise to several products, **184**–**187**, that require N−O bond homolysis, forming a (short-lived) bicyclic α-oxoiminyl, **181**, paired with an ethoxyl radical, and a subsequent β-scission of **181**, generating **182**[79].

The resulting radical, **182**, may couple with the ethoxyl radical forming the cyclopentane nitrile ester, **183**, or undergo decarbonylation to generate a cyclopentyl radical, **184**. The intermediacy of free radicals **181, 182** and **184** is supported by the ESR spectra



SCHEME 77

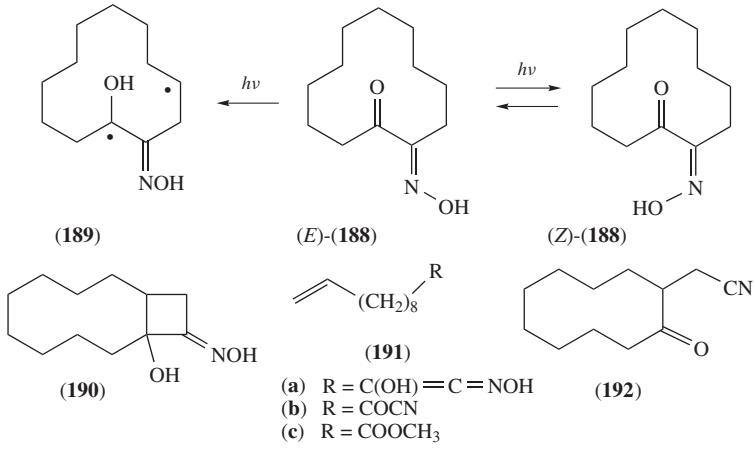
obtained when the photolysis was carried out in the presence of the free radical scavenger *tert*-butyl nitroxide[79]. The formation of products **185**–**187** is readily explained by disproportionation of **184** or hydrogen transfer between **184** and the ethoxyl radical (Scheme 78)[79].



SCHEME 78

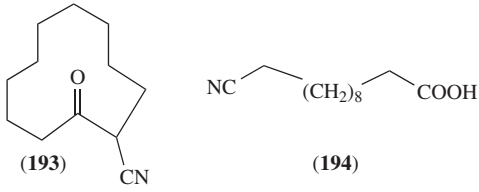
The first α-oxo-oxime whose photochemistry was studied was (*E*)-2-hydroxyiminocyclododecanone, (*E*)-**188**[89, 90]. It is of interest because, in contrast to **180**, the two π bonds of **188** are oriented in *anti* fashion. Irradiation of (*E*)-**188** in methanol results in $E-Z$ isomerization, to (*Z*)-**188**. Additional products arise by Norrish type II processes involving the carbonyl group. The key intermediate, the biradical, **189**, is formed by intramolecular hydrogen abstraction. Coupling of **189** leads to 1-bicyclo[8.2.0]dodecanol-12-oxime, **190** (40% yield after six hours). β-Cleavage of **190** generates the hydroxyketene oxime, **191a**, and two products derived from it, **191b** and **191c** (13% yield after 12 hours). An additional product, 2-cyanomethylcyclodecanone,

192 (5% yield after 12 hours), was identified as a secondary photoproduct of initially formed **190**. This product has only one chromophore, the oxime moiety; N−O scission of **190** followed by C−C cleavage and loss of a hydrogen atom produce **192** (Scheme 79)[90].



SCHEME 79

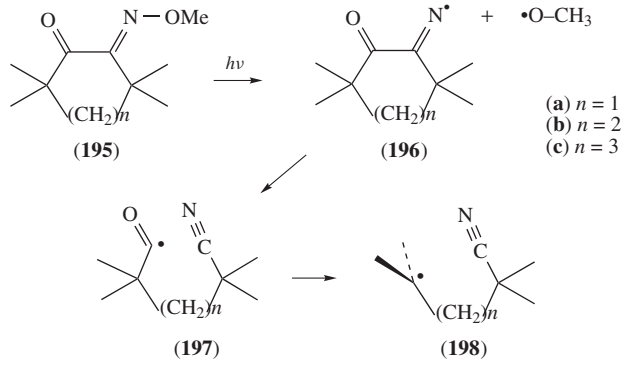
Two interesting photoproducts reported earlier by Stojilkovic and Tasovac[89], the cycloundecanone nitrile, **193**, and the α,ω-nitrile carboxylic acid, **194** (Scheme 80), were not confirmed.



SCHEME 80

A series of 'sterically congested' cyclic 2-methoxyimino-1-cycloalkanones ($n = 1-3$), **195a–c**, and an acyclic analog (*Z*)-4-(methoxyimino)-2,2,5,5-tetramethyl-3-hexanone (**200**) were irradiated at λ 254 nm in acetonitrile. The (*Z*)-isomers undergo only *Z*-*E* isomerization whereas the (*E*)-isomers also undergo photodecomposition. The failure of the (*Z*)-isomers to undergo fragmentation was ascribed to the presence of a relatively low-lying doubly excited ($n\pi^*$)($n\pi^*$) state, causing these isomers to decay via *Z*-*E* isomerization[9b].

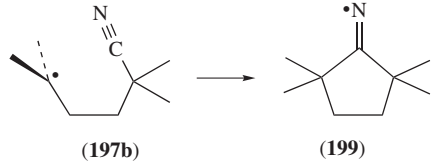
The primary step in the photodecomposition of **195** is homolysis of the N−O bond, forming a cyclic iminyl (**196**)–methoxyl radical pair. The iminyl radicals undergo β-cleavage to cyanoacyl radicals (**197**), followed by decarbonylation to cyanoalkyl radicals (**198**; Scheme 81). Decarbonylation is facilitated by the stability of the resulting tertiary radical[9b].



SCHEME 81

This aspect was further elucidated by an *ab initio* study, using *s-cis*-ethanedial mono-oxime as model compound. The calculations showed that the initial step in the photodissociation is N−O homolysis; N−O scission occurs only from the (*E*) but not from the (*Z*) isomer. The presence of the low-lying doubly excited (nπ^*)(nπ^*) state for the (*Z*) isomer was confirmed[9d].

Ring size has an interesting effect on the product distribution of the cyclic 2-methoxyimino-1-cycloalkanones. Thus, photolysis of **195b** ($n = 2$) gave rise to products formed by cyclization of the 5-cyano-2-hexyl radical, **197b**, generating **199** (Scheme 82)[9b]. The fact that only one of the cyanoalkyl radicals undergoes cyclization reflects the preference for the formation of five-membered rings that is documented also in intramolecular substitutions and in radical cation cyclizations, among others[54].

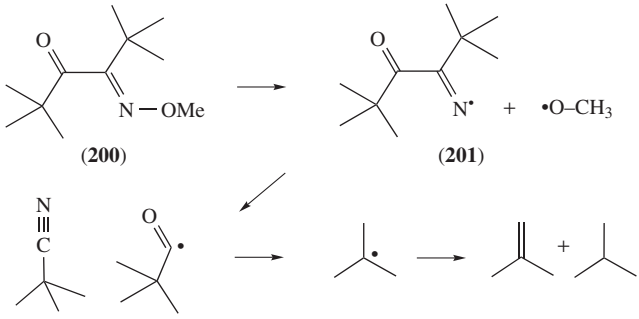


SCHEME 82

Irradiation of the acyclic analog **200** at λ 254 nm follows a similar reaction path. Irradiation leads to homolysis of the N−O bond, forming an iminyl (**201**)−methoxyl radical pair (Scheme 83). β-Scission forms 2,2-dimethylpropionitrile as a major product and, in addition, generates 2-dimethylpropionyl radical; decarbonylation of the latter yields isobutane and isobutene by disproportionation of the *t*-butyl radical[9b].

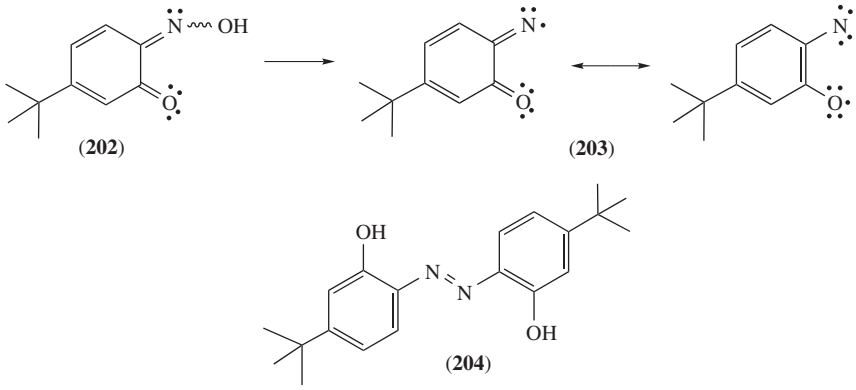
The isomerization of another pair of cyclic α-oxo-oximes, the (*E*)- and (*Z*)-isomers of 2-(methoxyimino)-1-indanone, **6**, and the involvement of an excimer between the $\pi\pi^*$ (S_2) state and a ground state molecule have been discussed in Section III[19].

Lastly, Cerfontain and coworkers also studied a series of *o*- and *p*-benzoquinone mono-oximes and oxime ethers[81]. Direct irradiation of several *tert*-butyl-substituted *o*-benzoquinone mono-oxime methyl ethers, (*E*)-**202**, in acetonitrile at λ 350 nm leads to $E-Z$ isomerization and, in addition, to the formation of (*E*)-azobenzenes, e.g. **204**. This



SCHEME 83

interesting reaction can be explained by N—O bond scission; the resulting iminylcyclohexadienone, **203**, has an *o*-phenoxylnitrene resonance contributor (Scheme 84); after the phenoxyl function abstracts a hydrogen atom (from the methoxyl radical?) the resulting phenylnitrene dimerizes to the azo compound[81]. Alternatively, **203** could dimerize before hydrogen abstraction.

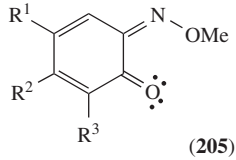


SCHEME 84

Of the 2,4-di-*tert*-butyl-*o*-benzoquinone mono-oxime *O*-methyl ethers, (*E*)- and (*Z*)-**205**, the *Z*-isomer (Scheme 85) undergoes only $Z-E$ isomerization upon direct irradiation (λ 350 nm) in acetonitrile. In contrast, (*E*)-**205** undergoes mainly γ-hydrogen abstraction, most likely from an 'enone' $S_1(n\pi^*)$ state[80].

Cyclization of the resulting biradical, **206**, leads to a relatively stable dienol, **207**, which eventually tautomerizes thermally to the enone **208** (Scheme 86)[80].

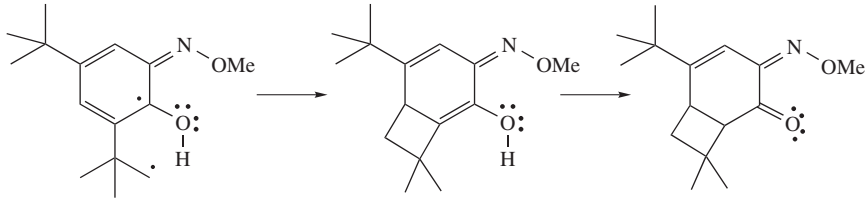
The *p*-benzoquinone mono-oxime methyl ether, **209** (R = H), and the di-*tert*-butyl derivative, **209** (R = *t*-Bu; Scheme 87), appear to be photostable against 254, 300 and 350 nm irradiation; of course, the molecular symmetry renders any $E-Z$ isomerization degenerate so that it could not be detected. These compounds have an ene-oxime $n\pi^*$ absorption at relatively long wavelength[80].



(**a**) $R^1 = C(CH_3)_3$; R^2, $R^3 = H$
(**b**) R^1, $R^3 = H$; $R^2 = C(CH_3)_3$
(**c**) R^1, $R^3 = C(CH_3)_3$; $R^3 = H$

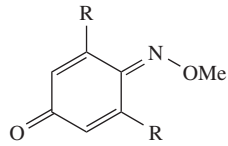
(**205**)

SCHEME 85



(**206**) (**207**) (**208**)

SCHEME 86



(**209**) R = H, $C(CH_3)_3$

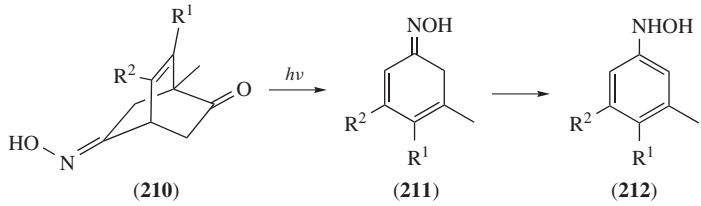
SCHEME 87

Sensitized irradiation of 2,4-di-*tert*-butyl-*p*-benzoquinone mono-oxime *O*-methyl ether (*E*)-**209**, using 1-acetylnaphthalene or 1-fluorenone as triplet sensitizers in acetonitrile, causes only *E*,*Z*-isomerization with photostationary states of [*E*]/[*Z*] ratios 0.78 and 0.88, respectively[80].

A bicyclic non-conjugated γ-oxo-oxime, **210**, chosen as a potential test for the competition between oxy- and aza-di-π-methane rearrangement, failed to undergo either. Acetophenone or acetone sensitization resulted only in $E-Z$ rearrangement. In contrast, direct irradiation led to the extrusion of dimethylketene by a formal retro-Diels–Alder reaction, generating arylhydroxylamines, **212**, presumably via the oxime **211** (Scheme 88). The reaction proceeds in several solvents, the yields being particularly high in acetonitrile[91].

X. PHOTOCHEMICAL CLEAVAGE OF THE OXIME N–O BOND: IMINYL RADICALS

In the preceding section we have discussed the cleavage of the N—O bond of α-oxo-oximes, generating iminyl radicals. N—O scission has been observed also for some oximes not containing the α-oxo function. In fact, it is the predominant primary photoreaction of simple oximes. For example, the flash photolysis of formaldoxime and acetaldoxime yielded iminyl (RCH=N•) and hydroxy (OH•) free radicals under isothermal and adiabatic



(**210**) (**211**) (**212**)

SCHEME 88

conditions (equation 21). Under isothermal conditions iminyl radicals are not very reactive but hydroxyl radicals rapidly abstract hydrogen atoms (eqation 22).

$$RCH{=}NOH \longrightarrow RCH{=}N^{\bullet} + {}^{\bullet}OH \quad (21)$$

$${}^{\bullet}OH + RCH{=}NOH \longrightarrow R^{\bullet}C{=}NOH + H_2O \quad (22)$$

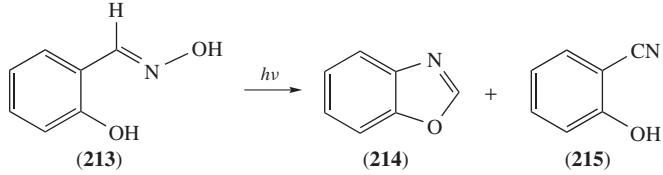
Under adiabatic conditions, formaldoxime decomposes by a short free radical chain mechanism, with hydroxyl and formimidoxyl as the chain-propagating radicals (eqations 23–25). Nitric oxide accelerates the decomposition of the oximes by sensitizing the formation of hydroxyl radicals[92].

$$\text{Initiation} \quad CH_2{=}NOH \longrightarrow CH_2{=}N^{\bullet} + {}^{\bullet}OH \quad (23)$$

$$\text{Propagation1} \quad {}^{\bullet}OH + CH_2{=}NOH \longrightarrow {}^{\bullet}CH{=}NOH \quad (24)$$

$$\text{Propagation2} \quad {}^{\bullet}CH{=}NOH \longrightarrow {}^{\bullet}OH + HCN \quad (25)$$

In series of photochemical experiments aimed to elucidate chemical evolution, Ferris and Antonucci observed the conversion of salicylaldoxime, **213**, to benzoxazole, **214**, and 2-cyanophenol, **215** (Scheme 89)[93]. The latter is an unexceptional product of an oxime photolysis, but the formation of **214** requires an additional reorganization (scrambling) within the five-membered ring. The authors have observed several analogous light-induced rearrangements.

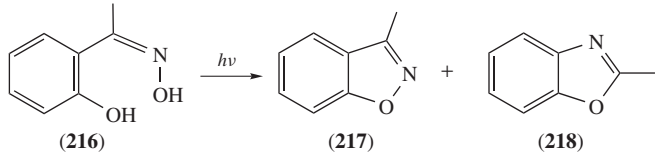


(**213**) (**214**) (**215**)

SCHEME 89

In a related reaction, 2-hydroxyacetophenone oxime, **216**, was converted to 3-methylindoxazene, **217**, and 2-methylbenzoxazole, **218** (Scheme 90). The indoxazene appears to be a logical photoproduct of the oxime; the benzoxazole again requires an additional reorganization[93].

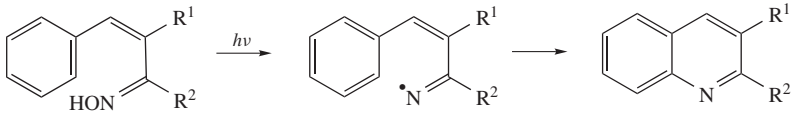
Irradiation of α-phenylbenzylideneacetone oxime, **219**, was reported to give 2-methyl-3-phenylquinoline, **221**, in varying yields, depending on the reaction conditions



(**216**) (**217**) (**218**)

SCHEME 90

(Scheme 91)[94]. Although the *Z*-isomer of **219** may not be favored, the required *E*–*Z* isomerization should occur readily. The product, **221**, might arise via N–O cleavage and ring closure of the tethered iminyl radical, **220**, but alternative mechanisms cannot be excluded.



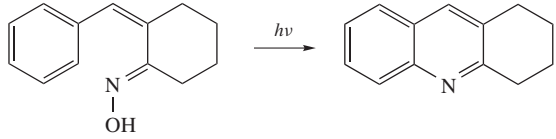
(*Z*)-(**219**) (**220**) (**221**)

(**a**) R^1 = Ph, R^2 = Me

(**b**) R^1, R^2 = $CH_2(CH_2)_nCH_2$; *n* = 1, 2, 3, 4

SCHEME 91

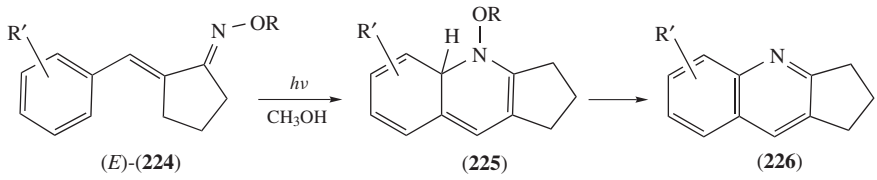
In a study of the photochemistry of (*E*,*E*)- and (*E*,*Z*)-2-benzylidenecyclohexanone oxime, **222**, Olsen observed an electrocyclization with loss of the hydroxyl group to produce tetrahydroacridine, **223** (Scheme 92). The yield of the ring-closed product was enhanced under acidic conditions[95].



(E,*Z*)-(**222**) (**223**)

SCHEME 92

Pratt and coworkers[96] reported a convenient synthesis of substituted annulated quinolines, **226**, by direct irradiation of (*E*)-2-benzylidenecyclopentanone *O*-alkyl and *O*-acetyloximes, **224**, in methanol. These products are analogous to those of Glinka[94] and Olsen[95]. The authors formulated the key reaction (after the *E*- to *Z*-isomerization of the benzylidene C=C bond) as a six π-electron electrocyclic reaction, resulting in a short-lived dihydroquinoline intermediate, **225**. Elimination of an alcohol or acetic acid then yields the aromatic products, **226** (Scheme 93)[96]. The reactions of *meta*-substituted precursors are highly regioselective: alkyl substituents lead to 5-substituted 2,3-dihydro-1*H*-cyclopenta[*b*]quinolines whereas more strongly electron-donating substituents result in 7-substituted 2,3-dihydro-1*H*-cyclopenta[*b*]quinolines[96].

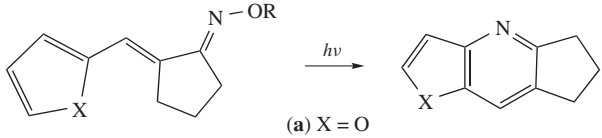


(*E*)-(**224**) (**225**) (**226**)

R = Me, Ac
R′ = alkyl, OR″, OAc, NH_2, $N(CH_3)_2$, benzo
R″ = alkyl

SCHEME 93

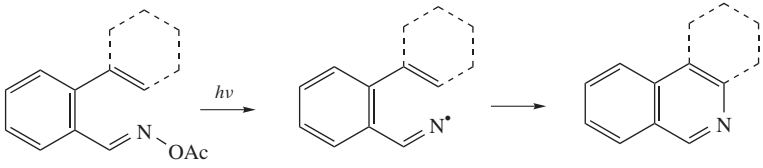
2-Furylmethylene, **227a**, and 2-thienylmethylene analogues, **227b**, of **224** yield annulated furo-, **228a**, and thieno[2,3*e*]pyridines, **228b**, respectively, making these annulated ring systems readily available (Scheme 94)[96].



(*E*)-(**227**) (**a**) X = O (**b**) X = S (**228**)

SCHEME 94

Rodriguez and coworkers reported an 'efficient photochemical approach' for the generation of six-membered heterocyclic rings, viz. isoquinolines and phenanthridines (**231**) from oxime esters, such as **229**[97]. They considered iminyl radicals, **230**, as the key intermediates in the intramolecular cyclizations as well as in intermolecular addition–cyclization sequences (Scheme 95). In contrast to the work of Glinka or Olsen the iminyl radical, **230**, captures a tethered alkene[97].



(**229**) (**230**) (**231**)

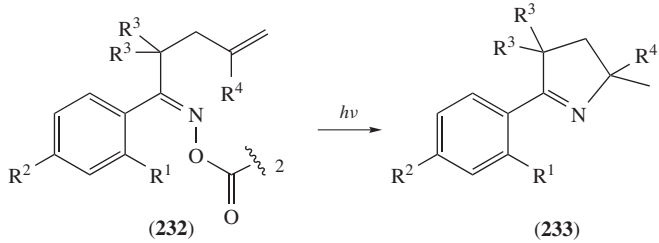
SCHEME 95

This reaction is related to the conversion of γ,δ-unsaturated alkyl ketone *O*-acetyloximes, **106**, to 3,4-dihydro-2*H*-pyrroles, **108** or **109**, with 1,5-dimethoxynaphthalene as electron sensitizer (*vide supra*)[58,59].

The authors carried out illuminating theoretical calculations [CASPT2/6-31G*//CASSCF/6-31G*; active space of 14 electrons in 11 orbitals]. The results identified

S_2 as the spectroscopic state; its relaxation leads directly to N−O bond scission due to coupling between the imine π^* and the σ^* N−O orbitals. The calculations confirmed that the iminyl radicals are able to cyclize to either five- or six-membered rings[98].

4-Methoxyacetophenone-sensitized photolysis of appropriate dioxime oxalates, **232**, is a useful method for the generation of iminyl radicals[99]. This method was applied for the preparations of 3,4-dihydro-2*H*-pyrroles, e.g. **233**, (Scheme 96) and phenanthridines, e.g. **231**[100].

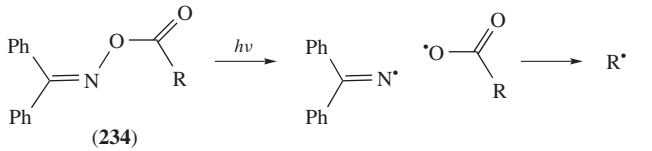


(**232**) (**233**)

(**a**) R^1 = H; R^2 = MeO; R^3 = H; R^4 = H
(**b**) R^1 = MeO; R^2 = MeO; R^3 = H; R^4 = H
(**c**) R^1 = H; R^2 = H; R^3 = Me; R^4 = H
(**d**) R^1 = H; R^2 = H; R^3 = H; R^4 = Me

SCHEME 96

The photolysis of benzophenone oxime esters, **234**, of aromatic or aliphatic acids in benzene or pyridine gave rise to free radical substitution products in up to 70% yield. Scission of the N−O bond followed by decarboxylation generates various aryl and alkyl radicals (Scheme 97); reaction with benzene or pyridine forms biaryls, alkylbenzenes or alkylpyridines[101].



(**234**)

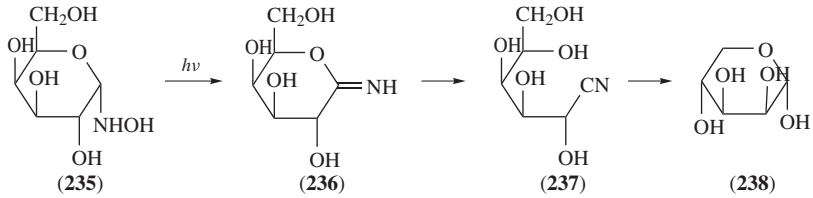
R = *n*-C_7H_{15}, $CH_3CO(CH_2)_2$, $Ph(CH_2)_2$, cyclopentyl, Ph, *p*-NCC_6H_4, 2-, 3-, 4-pyridyl, pyrazinyl

SCHEME 97

Sugar oximes undergo a photochemical equivalent of the Wohl degradation. The Wohl degradation is a chain-contracting reaction that converts a linear sugar to one with one fewer carbon atom[102]. The photochemical equivalent of this reaction is exemplified here by the photolysis of D-galactose oxime or of its methyl ether. These compounds actually exist as D-galactopyranosylhydroxylamine, **235**, and as its methyl ether. Photolysis of **235** gave rise to a mixture of D-galactoimino-1,5-lactone, **236**, and D-lyxose, **238** (Scheme 98). The formation of **236** supports cleavage of the N−O bond in the key step. Upon standing,

the imine **236** decomposes to **238**, most likely via the cyanohydrin, **237**, as a short-lived intermediate[103a].

The UV photolysis of a wide range of sugar oximes, including those of D-mannose, D-glucose, D-ribose, D-arabinose, D-xylose and D-lyxose, was also studied. These reactions gave rise to iminolactones or a sugar with one fewer carbon. Irradiation of the oximes of D-ribose and D-arabinose gave the corresponding iminolactones only; D-xylose oxime gave rise to D-xylonoiminolactone and D-threose; for example, D-threose was obtained in 18% yield from D-lyxose oxime[103b].



(**235**) (**236**) (**237**) (**238**)

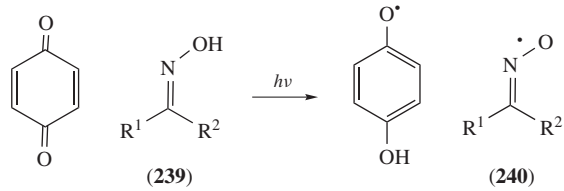
SCHEME 98

In summary, cleavage of the N−O bond, upon direct or electron donor sensitized irradiation, has the potential to be synthetically useful, as shown especially by the various cyclizations [58, 59, 94–98, 100]. The divergent mechanisms proposed make this an interesting area for mechanistic studies. The electron transfer induced cyclizations of Narasaka clearly involve iminyl radicals; the involvement of these radicals is also supported by the calculations of Rodriguez, Sampedro and coworkers[98]. The electrocyclic mechanism offers an interesting alternative. Perhaps the crucial difference between Pratt's substrates, on the one hand, and those of Narasaka and Rodriguez, on the other, is the use of the oxime vs. an oxime ester.

XI. PHOTOCHEMICAL CLEAVAGE OF THE OXIME O–H BOND: IMINOXYL RADICALS

Similar to the oxime N−O bond, the O−H bond can also be cleaved upon direct or sensitized irradiation. The photoreactions of triplet sensitizers with oximes were probed first in an EPR experiment. The reaction of photo-excited quinones with oximes, **239**, gave rise to iminoxy radicals, **240** (Scheme 99), which were detected and characterized by their EPR spectra[104]. The iminoxy radicals are produced by hydrogen abstraction via the $^3n\pi^*$ state of the quinone. This reaction proceeds particularly well for ketoximes, giving rise to isotropic EPR spectra. Aldoximes ($R^2 = H$), on the other hand, undergo a competing abstraction of the aldehydic hydrogen. The competing reaction can be suppressed by using sterically hindered quinones, e.g. 2,5-di-*t*-butylbenzoquinone. The iminoxy radicals decay with pseudo first-order kinetics; the decay has been assigned to radical addition to a quinone molecule[104].

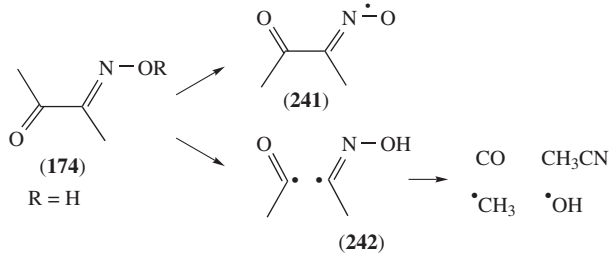
Irradiation of oximes in solid matrices also generates iminoxyl radicals. For example, ESR spectra recorded after irradiation of 3-hydroxyiminobutan-2-one, **174** (R = H), at 77 K generated typical powder patterns with splittings characteristic for an iminoxyl radical, **241** (Scheme 100). These species showed orthorhombic symmetry; for example, acetylmethyliminoxyl had hyperfine tensors, $A_1 = 45.3$ G, $A_2 = 25.2$ G and $A_3 = 26.4$ G[105a]. The same species, generated in a pentasil zeolite, showed axially symmetric *g* and hyperfine tensors, i.e. $A_{||} = 45.7$ G, $A_{\perp} = 26.7$ G[105b]. When **174** (R = H) was irradiated



(**239**) (**240**)

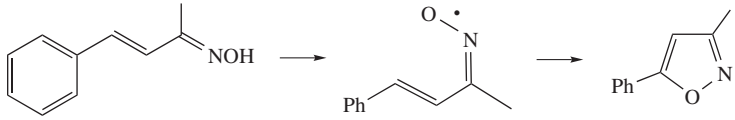
SCHEME 99

at 8 K in a solid matrix, a more complex spectrum with several additional lines was observed. The difference spectrum is an isotropic spectrum of methyl radical. Apparently, loss of a hydrogen atom is not the only photoreaction of **174** (R = H) in the matrix. An alternative reaction involves cleavage of the $sp^2 - sp^2$ C–C bond, generating oximyl, **242**, and acetyl radicals (Scheme 100); the acetyl radical undergoes facile decarbonylation, even at 8 K, whereas the oximyl radical decays to acetonitrile and hydroxyl radical. The fact that an isotropic spectrum is observed indicates that the methyl radical rotates freely in the matrix, even at 8 K. Upon warming to 77 K, as the matrix softens, the methyl radicals begin to migrate and dimerize[105a].



SCHEME 100

Talapatra and coworkers utilized iminoxyl radicals, e.g. **243**, generated by photolysis of *N*-iodosuccinimide in the presence of oximes, for the synthesis of various ring systems, including isoxazole, **244**, from benzalacetone oxime, **27** (Scheme 101)[106]. Obviously, this conversion can occur only from the *s-cis* conformer, but this should be readily accessible.

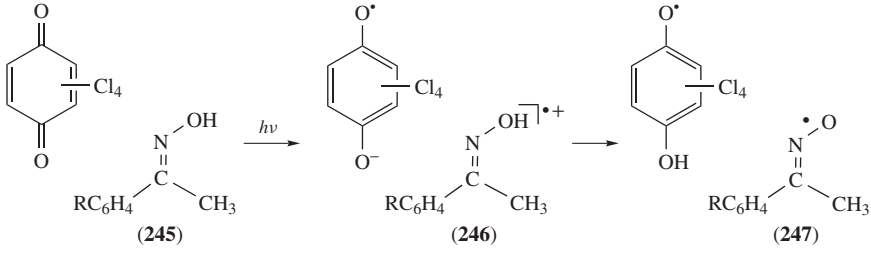


(**27**) (**243**) (**244**)

SCHEME 101

More recently, De Lijser and colleagues introduced modern time-resolved photolysis techniques to the study of electron transfer induced reactions of oximes and oxime

ethers. They carried out detailed mechanistic studies on a series of *o*-, *m*- and *p*-substituted acetophenone oximes, **245**, typically in polar solvents, such as acetonitrile[107]. With chloranil (tetrachlorobenzoquinone) as acceptor/sensitizer the reactions proceed via a two-step sequence: electron transfer generates a sensitizer radical anion paired with an oxime radical cation, **246**; subsequently, a rapid proton transfer generates the iminoxyl, **247**, and the corresponding semiquinone radical (Scheme 102)[107].



(**245**) (**246**) (**247**)

R = H, F, Cl, CF_3, CN, CH_3, OCH_3, NO_2

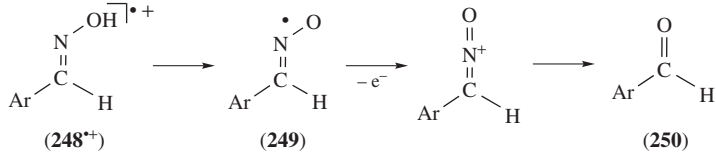
SCHEME 102

Both chloranil radical anion and the semiquinone radical were detected by laser flash photolysis. This implicates the iminoxyl radical, **247**, the type of species previously observed and characterized by ESR[104, 105]. The results were analyzed in terms of the electrochemical peak potentials of the oximes, the rates of triplet chloranil quenching and the degree of conversion of the oximes[108]. The quenching rates correlate well with oxime ionization potentials, supporting electron transfer as the initial step. The calculated charge densities suggest that the substituent effects stabilize/destabilize the transition state rather than the ground state. The efficiency of iminoxyl formation is controlled by (a) the oxidation of the oxime, favored by electron-donating substituents, and (b) deprotonation of the oxime radical cation, favored by electron-withdrawing substituents. The overall reaction shows negligible substituent effects because the two effects counteract each other[33, 108]. The electron transfer reaction yields mainly the parent acetophenones[109].

In trying to characterize the nature of the quenching reaction the authors noted that the relative rates of conversion for *meta*-substituted acetophenone oximes correlate better with Hammett parameters for a radical reaction (ρ_{rad}; $\rho_{rad}/\rho_{pol} = 5.4$), whereas the *para*-substituted oximes are influenced nearly equally by radical and ionic effects ($\rho_{rad}/\rho_{pol} = -1.1$). The follow-up reactions proceed through a number of intermediates with either radical or ionic character[109].

The chloranil(CA)-photosensitized reactions of benzaldehyde oximes, **248**, generate the corresponding aldehydes, **250**, and/or nitriles, **252**[108]. For oximes with oxidation potentials, $E_{ox} < 2.0$ V, the quenching rates vary linearly with E_{ox}; these oximes give rise to radical cations, **248**$^{\bullet+}$, by electron transfer to triplet chloranil, ^{3}CA*. Proton transfer to the choranil radical anion converts the radical cations to iminoxyl radicals, **249**$^{\bullet}$, and these are converted to aldehydes, **250** (Scheme 103).

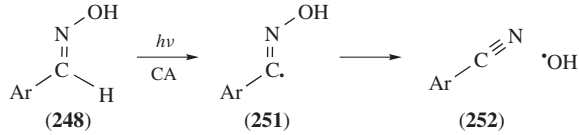
Oximes with $E_{ox} > 2.0$ V quench triplet chloranil at rates independent of E_{ox}. For these oximes, electron transfer is no longer viable; instead, triplet chloranil generates imidoxyl radicals, **251**, by abstracting a hydrogen atom from the oxime carbon; the imidoxyl radicals, **251**, form nitriles, **252**, by β-scission with loss of hydroxyl radical (Scheme 104)[108]. The rates of imidoxyl formation are independent of structure because the C−H bond strength is essentially identical for structurally related oximes. The different quenching



(**248**$^{\bullet+}$) (**249**) (**250**)

SCHEME 103

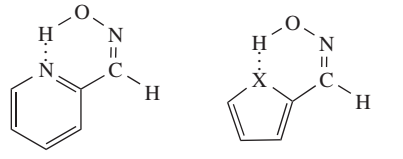
behavior of the two groups of oximes supports different mechanisms for aldehyde and nitrile formation[108].



(**248**) (**251**) (**252**)

SCHEME 104

The formation of nitriles, **252**, is favored for benzaldehyde oximes with electron-accepting substituents, which are less efficient quenchers. Some oximes whose hydroxyl hydrogen atom is shielded from abstraction by intramolecular H-bonding also give rise to nitriles. For example, pyridine-2-carboxaldoxime, **253**, which forms a strong intramolecular hydrogen bond, produces the corresponding nitrile exclusively. Molecules with weaker intramolecular hydrogen bonds, viz. 2-furaldehyde oxime, **254a**, or thiophene-2-carboxaldoxime, **254b**, give rise to increasing yields of the corresponding aldehydes (Scheme 105)[108].

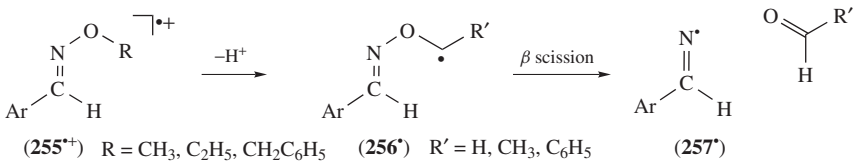


(**253**) (**254**) (**a**) X = O
(**b**) X = S

SCHEME 105

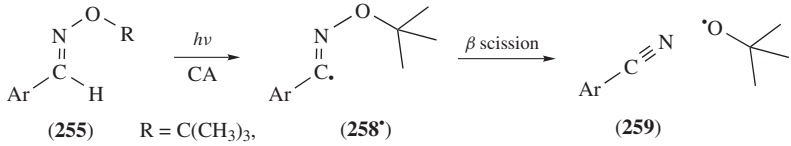
The radical cations generated by photosensitized reactions of aldoxime ethers with chloranil react with nucleophiles (methanol) by second-order kinetics (*k ca* 10^7 M^{-1} s^{-1}). Oxime ether radical cations, **255**$^{\bullet+}$, bearing α-protons, i.e. the alkyl or benzyl ethers, give rise to benzaldehyde plus an aldehyde derived from the *O*-alkyl group. Deprotonation in the α-position of the alkyl or benzyl group generates free radicals, **256**$^{\bullet}$, which undergo β-cleavage forming iminyl radicals, **257**$^{\bullet}$, and these radicals are converted to benzaldehydes (Scheme 106)[108].

In contrast, the chloranil photosensitized reactions of *O-tert*-butylacetophenone oxime, **256** [R = $C(CH_3)_3$], whose alkyl group lacks an α-proton, produced benzonitrile, **42**.



SCHEME 106

For substrate **255** [R = $C(CH_3)_3$] electron transfer is favorable, but it provides no pathway to product formation. As a result, hydrogen abstraction from the oxime carbon [more likely than deprotonation of **256**$^{\bullet+}$, R = $C(CH_3)_3$, from the imine carbon] becomes competitive, forming the imidoyl radical, **258**$^{\bullet}$; subsequent β-cleavage gives rise to **259** (Scheme 107)[35, 110].

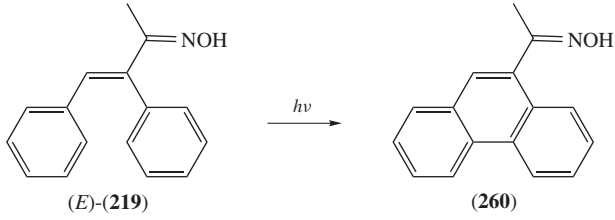


SCHEME 107

The cleavage of the oxime O−H bond has allowed access to a wide range of iminoxyl radicals. On the other hand, only one synthetically useful application has been reported, the cyclization of benzylideneacetone iminoxyl radical to an isoxazole[106]. Perhaps the generation of iminoxyl radicals initiated by electron transfer might lend itself to a range of applications, including cyclizations onto tethered alkene functions.

XII. MISCELLANEOUS PHOTOREACTIONS OF OXIMES

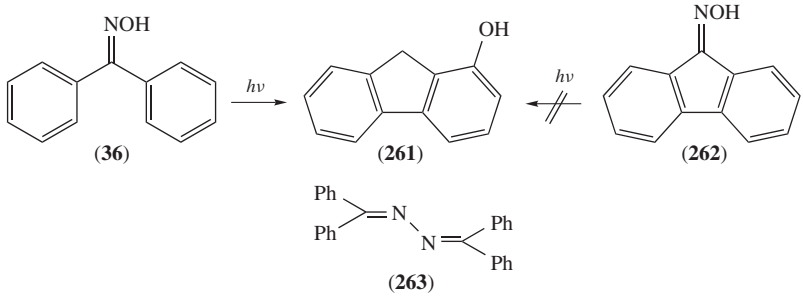
In the long history of oxime photochemistry, a few intriguing reactions have been reported that require multiple steps; the oxime moiety may or may not be involved in the conversion. For example, the photolysis of α-phenylbenzylideneacetone oxime, **219**, results in the formation of acetophenanthrone oxime, **260** (Scheme 108; in addition to 2-methyl-3-phenylquinoline, **221**, discussed above)[94].



SCHEME 108

This product requires formation of a C−C bond between the *o*,*o*′-carbons of the two benzene rings, most likely from a $\pi\pi^*$-state, and subsequent dehydrogenation; the oxime function is not involved directly. The formation of this product is one of many such reactions: systems containing adjacent phenyl groups, e.g. *cis*-stilbene, *cis*-azobenzene, diphenylamine or *cis*-diphenylcyclopropane may undergo an *o*,*o*′-coupling, forming phenanthrene[111], cinnoline[112], pyrrole[113] or 9-methyl phenanthrene[114] systems. Reactions of this type have been observed for excited singlet or triplet states, anions, molecular ions or free radicals.

A related *o*,*o*′-cyclization with dehydrogenation was observed in the photolysis of benzophenone oxime, **36** (R = H), generating 1-hydroxyfluorene, **261** (30–35% yield in methanol). The authors could show that fluorenone oxime, **262**, does not form **261** upon photolysis, so it cannot be an intermediate; the oxime function must be actively involved in the conversion (Scheme 109). The observation of benzophenone azine, **263**, suggests that an iminyl radical is involved, but this intermediate cannot explain the hydroxy function in the 1-position[115]. Electron-donating substituents in the *p*-position favor the *o*,*o*′-cyclization, whereas electron-withdrawing substituents suppress it[115].

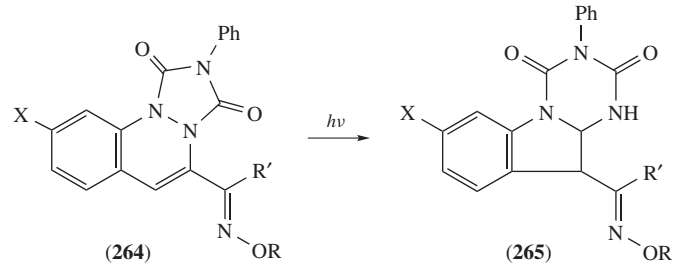


SCHEME 109

An intriguing rearrangement was reported for an oxime, **264**, in which the imine function is conjugated with a 1,2-dihydrocinnoline moiety: photolysis of **264** generates **265** (Scheme 110)[116]. The rearrangement requires cleavage of the dihydrocinnoline N−N bond with ring contraction, ring expansion of the 1,2-dihydro-1,2,4-triazole-3,5-dione system and migration of the oxime moiety. A mechanism accounting for these changes was proposed (Scheme 111)[116a, b]. The oxime function may be involved in stabilizing the carbocation site in the zwitterion intermediate, **266**.

When the photoreaction of 3-acyl-1,2-dihydrocinnoline-1,2-dicarboximide oxime methyl ether, **264**, was carried out in the presence of a β-keto ester in acetonitrile, the authors obtained the interesting heterodiquinane-type tricycles, **267**, in yields of up to 65%. The carbocation site of the zwitterionic intermediate, **266a** (R = Me), is captured by an enolate anion (Scheme 112). Very likely, the oxime ether function does not rise above the status of a spectator function in this intriguing conversion[116c].

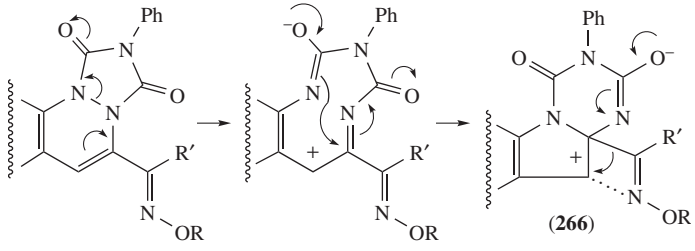
The bastadin class of bromotyrosine derivatives, e.g. the dioxepine bastadin 3, **268**, is a naturally occurring class of dioximes (Scheme 113). Bastadins possessing (*E*,*Z*)-, (*Z*,*E*)- or (*E*,*E*)-dioxime configurations are known, but their existence might very well be an artifact of their isolation or storage. Therefore, their photochemical isomerization was explored[117].



(**264**) (**265**)

X = H, Cl, NO_2, OMe, H, H, H, H, H, H, OMe
R = Me, Me, Me, Me, Me, Me, Me, Me, Me, *n*-Pr, Me
R′ = Me, Me, Me, Me, Et, *n*-Bu, Bz, Ac, H, Me, Bz

SCHEME 110



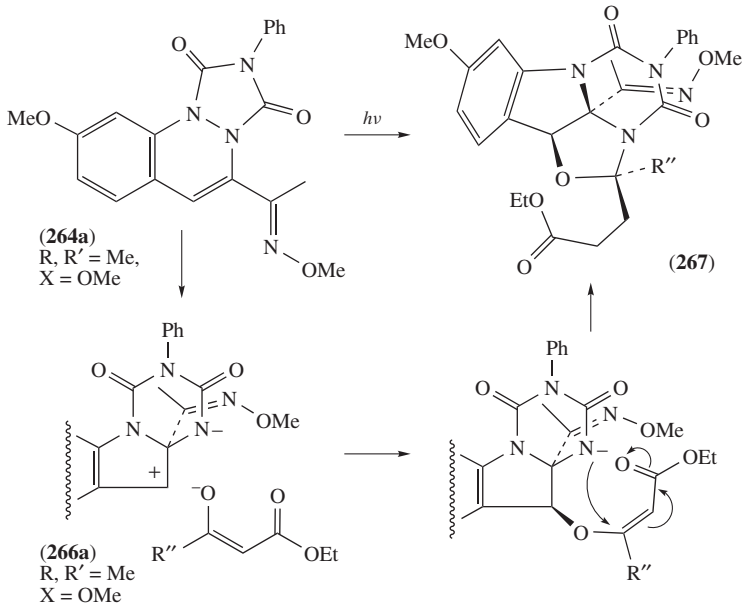
(**266**)

SCHEME 111

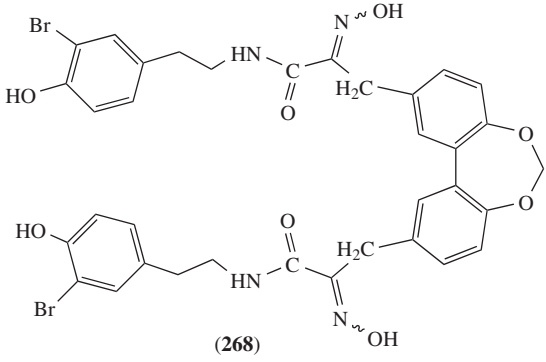
A combination of a photochemical and a thermal reaction converted the morphine derivative, cyclodihydrocodeinone oxime, **269**, to the lactam **271**[118]. Irradiation of **269** in methanol or ethanol generated the secomorphinans, **270** (R = Me, Et), and these produced the lactam upon heating (Scheme 114). The formation of nitrile **270** is unusual as it arises from a ketoxime: nitriles usually are formed from aldoximes (cf. Section V.B). The overall conversion is equivalent to a Beckmann rearrangement (see Section IV); the authors referred to the reaction as a 'second-order' Beckmann rearrangement[118].

Irradiation of tris(trimethylsilyl)silane in the presence of the acetylene substituted cyclobutanone oxime benzyl ether, **272**, leads to the bicyclic oxime ether, **273**, in 70% yield[119]. The conversion was rationalized as a radical cascade reaction: photochemically generated tris(trimethylsilyl)silyl radical initiates the reaction by addition to the alkyne function (Scheme 115); in the course of the reaction, the oxime moiety twice suffers a radical attack (**274** → **275**; **277** → **278**) and is converted to an aminyl radical; both times the oxime function is regenerated by ring-opening (**275** → **276**; **278** → **279**; Scheme 115). The overall reaction amounts to two consecutive ring expansion–cyclizations[119]. The oxime moiety is not involved in the photochemical step.

The final topic to be touched on in this review is the photochemistry of the alkylcobalt^{III}dimethylglyoximates, the so-called alkylcobaloximes, **280** (Scheme 116). Cobalt complexes of dimethylglyoxime form alkyl derivatives with unusually stable cobalt-carbon bonds[120]. Cobaloximes are regarded as 'model' compounds for the biological alkylating agent, vitamin B_{12}[121]. In recent years cobaloximes have been used to catalyze the reduction of protons to molecular hydrogen[122].

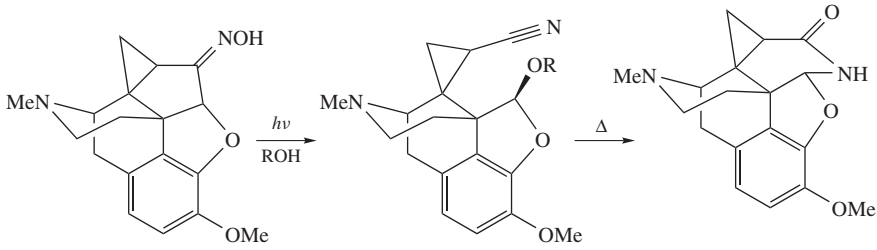


SCHEME 112



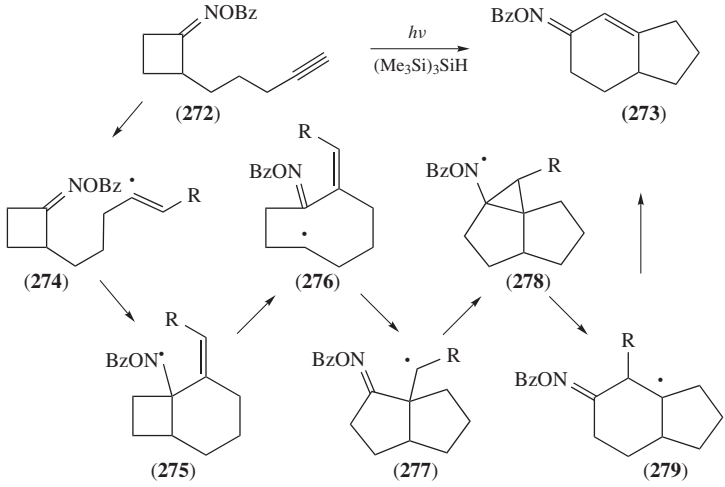
SCHEME 113

Photolysis of a Co^{II}-diglyoxime leads to its reduction, generating a Co^{I} species that reacts, in turn, with a proton source to produce a Co^{III}-hydride. Subsequently, two Co^{III}-hydrides react in a bimolecular step to eliminate molecular hydrogen homolytically. A thermodynamic analysis of hydrogen evolution elucidated barriers and driving forces of the elementary reaction steps involved in proton reduction by Co^{I}-diglyoximes. The rate-limiting step in this hydrogen evolution is associated with formation of the hydride. Of course the dioxime (dimethylglyoxime) serves as a chelating agent and the photochemistry of the chelated metal ion proceeds via a ligand-to-metal charge-transfer state. The nature of the dioxime influences the rate of the photochemical reactions as well as their course[123].



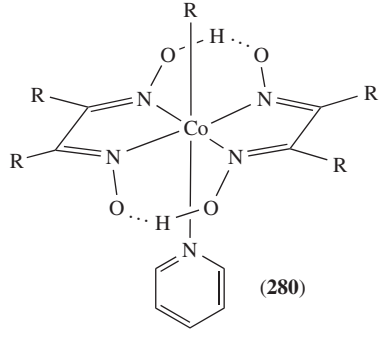
(**269**) (**270**) R = Me, Et (**271**)

SCHEME 114



R = $[(CH_3)_3Si]_3Si$

SCHEME 115



SCHEME 116

XIII. PERSPECTIVE

For more than a century oximes have provided a fruitful target of interest for photochemists offering many interesting facets. From the relatively simple geometric isomerization to the multitude of more complex rearrangements, from their use as precursors for iminyl and iminoxyl radicals to their use in photoresists and as photochemical acid generators, oximes have shown a fascinating palette of reactions. There is little doubt that oximes, and their ethers and esters, will continue to be at the focus of much interest. The electron transfer photochemistry of oximes has been applied in photoresists and for various synthetically promising cyclizations; still, the systematic study of these reactions with modern time-resolved spectroscopic methods has only begun relatively recently. New applications will be explored and some of the remaining mechanistic problems will be probed in more detail. There is still much to be learned about oximes and their photochemistry.

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Conjugate addition of hydroxylamines, oximes and hydroxamic acids

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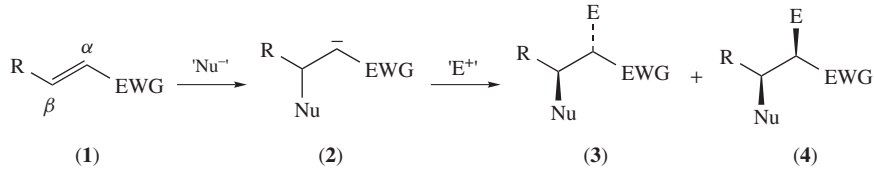
I. LIST OF ABBREVIATIONS

BINOL	1,1′-bi-2,2′-naphthol
Bn	benzyl
BNP	1,1′-binaphthyl-2,2′-diyl phosphate
Boc	*t*-butoxycarbonyl
DBFOX	4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)
DCE	1,2-dichloroethane
Fu	furyl
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilyl
MS	molecular sieves
NOE	nuclear Overhauser effect
PMB	*p*-methoxybenzyl
PTC	phase transfer catalyst
Salen	*N*,*N*′-ethylenebis(salicylideneiminato)bis(salicylidene) ethylenediamine
TADDOL	2,2-dimethyl-α,α, α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol

Tf	trifluoromethanesulfonyl
Ts	tosyl (*p*-toluenesulfonyl)
Vi	vinyl

II. GENERAL INTRODUCTION

Conjugate addition reactions involve the addition of nucleophiles (also referred to as donors) to the β-carbon of alkenes **1** or alkynes attached to an electron-withdrawing group (EWG) (also referred to as acceptors), followed by the trapping of the anionic intermediate **2** with an electrophile E (Scheme 1). The diversity of both the donors and the acceptors makes this class of reaction one of the most important bond-forming strategies, as the donors can be carbon nucleophiles (Michael addition) as well as heteroatom-based (N, O, S, P etc.) nucleophiles, and the acceptors may include a variety of activating electron-withdrawing groups, e.g. carbonyls in aldehydes and ketones, acids, esters, nitro, nitriles, amides, sulfoxides, sulfonates, phosphates and phosphonates. When the acceptor has prochiral centers at the α and/or β positions of the activating group, there is potential for creating new chiral centers. In principle, this stereochemistry can be efficiently controlled by the use of various Lewis acids and chiral auxiliaries in the starting material; often there is a strong preference for formation of the *anti* addition product **3** over the *syn* addition product **4** (Scheme 1). The conjugate addition of nitrogen or oxygen nucleophiles (aza-Michael or oxa-Michael addition, respectively) provides an efficient method for rapid formation of a carbon–nitrogen or carbon–oxygen bond. This chapter reviews the experimental work on the formation of carbon–nitrogen and carbon–oxygen bonds via conjugate addition of hydroxylamines, oximes and hydroxamic acids to alkenes or alkynes attached to one or more electron-withdrawing groups.



(**1**) (**2**) (**3**) (**4**)

SCHEME 1

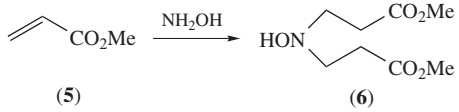
III. CONJUGATE ADDITION OF HYDROXYLAMINE AND ITS DERIVATIVES

The use of hydroxylamine and its derivatives as nitrogen nucleophiles in the conjugate addition is of particular interest due to their high reactivity and the possibility of derivatizing the formed 1,4-adducts. For example, it has been demonstrated that the reactivity of *N*-hydroxylamine derivatives (RNHOH) toward sp^2 centers is much higher than that of the corresponding amines, while the opposite is true toward sp^3 centers such as in reactions with alkyl halides[1]. Furthermore, the resulting β-hydroxylamino derivatives are useful precursors for the preparation of important *N*-containing compounds such as isoxazolidinones, aziridines, β-amino acids and β-lactams, after reductive cleavage of the N–O bond. The conjugate addition of hydroxylamine and its derivatives will be discussed according to the substitution pattern of the nucleophile, namely the non-substituted hydroxylamine (NH_2OH), the *N*-substituted hydroxylamines (RNHOH), the *O*-substituted hydroxylamines ($RONH_2$), the *N*,*O*-disubstituted hydroxylamines (RNHOR′) and the *N*,*N*-disubstituted hydroxylamines (RR′NOH).

A. Conjugate Addition of Hydroxylamine (NH_2OH)

1. Bis-conjugate addition of NH_2OH

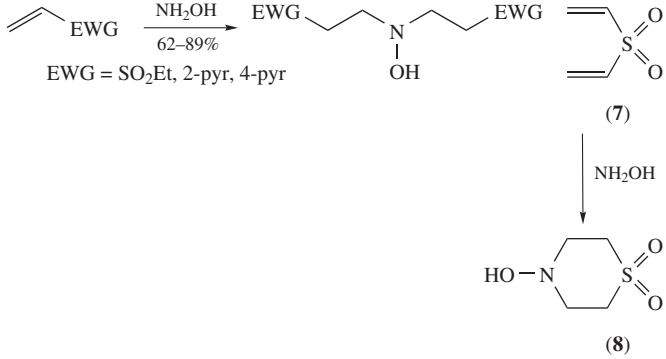
Due to the high nucleophilicity of the nitrogen atom, conjugate addition of NH_2OH usually proceeds without the need of any external catalyst. Since the initial mono-adduct obtained in the first conjugate addition is more nucleophilic than NH_2OH, attack on a Michael acceptor which results in a bis-adduct may take place. For example, the addition of NH_2OH to methyl acrylate **5** leads to the formation of the bis-adduct **6** even under the conditions of inversed addition of methyl acrylate **5** to a large excess of NH_2OH (Scheme 2)[2].



(**5**) (**6**)

SCHEME 2

Similar results were obtained when NH_2OH was added to other activated double bonds with sulfone or pyridine as electron-withdrawing groups. Double conjugate additions occurred and the dialkylated hydroxylamines were produced in good yields; no monosubstituted product was isolated. In the reaction of divinyl sulfone **7** with NH_2OH, a cyclic product **8** was obtained in nearly quantitative yield (Scheme 3)[3].

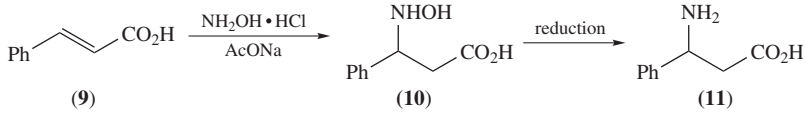


SCHEME 3

2. Mono-conjugate addition of NH_2OH

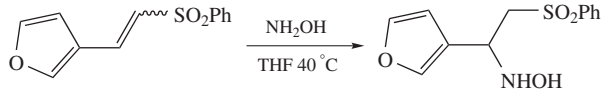
In some cases, the conjugate addition of NH_2OH can stop at the first stage to give the mono-adduct as the sole product. For example, when NH_2OH•HCl reacted with cinnamic acid **9** in the presence of NaOAc, 1,4-conjugate addition took place and gave racemic β-hydroxylaminated β-phenylpropionic acid **10**. Catalytic hydrogenation (H_2, Pd/C) of **10** or other reductive reactions yielded racemic β-amino-β-phenylpropionic acid **11** (Scheme 4)[4]. In 1953, the conjugate additions of NH_2OH to α,β-unsaturated nitro compounds were also reported to give solely mono-adducts similar to **10**[5].

When the Michael acceptor bears a bulky terminal substituent at β-position of the electron-withdrawing group, the conjugate addition of NH_2OH may occur only once.



(**9**) (**10**) (**11**)

SCHEME 4



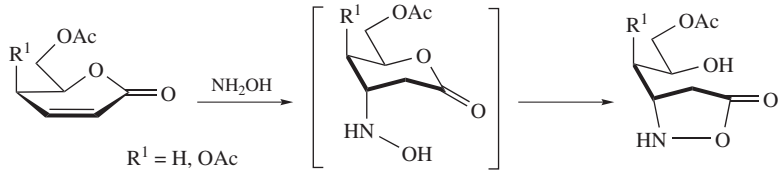
(**12**) (**13**)

SCHEME 5

Ku and coworkers reported that conjugate addition of NH_2OH to the vinylsulfone derivative **12** afforded mono-adduct **13** in 82% yield (Scheme 5)[6].

3. Participation of OH in conjugate addition of NH_2OH

When NH_2OH is added to α,β-unsaturated sugar δ-lactone **14**, the NH_2OH molecule enters the lactone molecule exclusively *anti* to the terminal C-6 carbon atom[7]. The conjugate addition was succeeded immediately by a ring-opening step of lactone **15** via a nucleophilic substitution reaction initiated by the *N*-hydroxyl group which resulted in the isoxazolidin-5-one ring **16** (Scheme 6). Interestingly, this process realized the transformation of a 6-membered ring compound, normally with less strain, into a 5-membered ring compound. Addition of *N*-alkylated hydroxylamines (RNHOH) follows the same addition–rearrangement pathway[8].

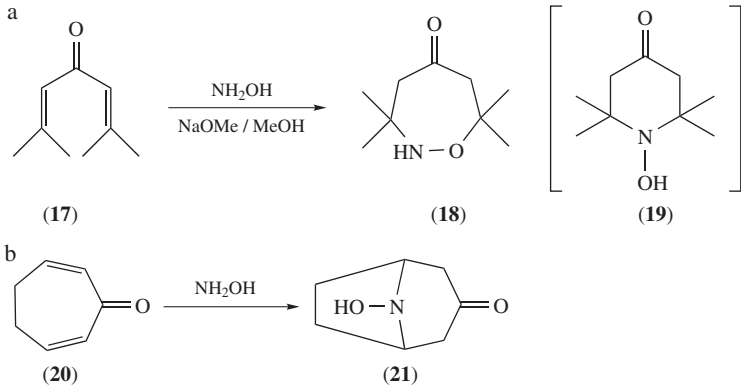


R^1 = H, OAc

(**14**) (**15**) (**16**)

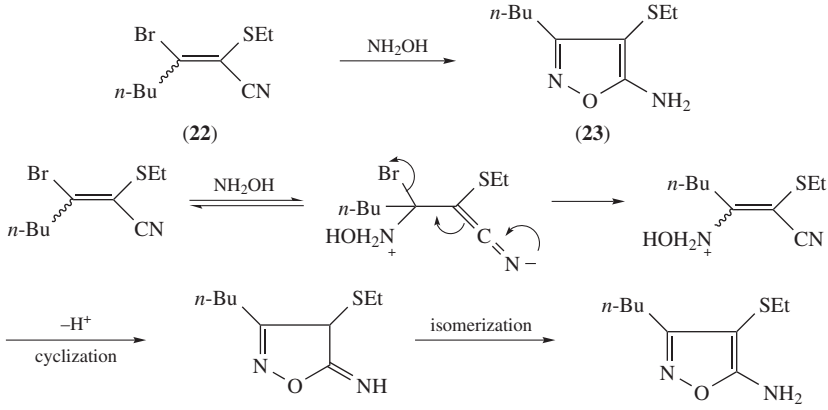
SCHEME 6

Both the NH_2 and the OH moieties of the NH_2OH can undergo conjugate addition to the Michael acceptor, especially when the OH proton is abstracted by a base, as the nucleophilicity is greatly enhanced due to the oxygen anion generated. For example, treatment of phorone **17**, bearing two α,β-unsaturated double bonds, with NH_2OH in methanolic sodium methoxide results in a 14% yield of cyclic hexahydro-3,3,7,7-tetramethyl-1,2-oxazepine-5-one **18**[9]. However, this structure was previously assigned in 1897[10] as 1-hydroxyl-2,2,6,6-tetramethyl-4-piperidone **19** (Scheme 7a). In contrast, sequential conjugate addition of NH_2OH to a cyclic cyclohepta-2,6-dienone **20** leads to the formation of a bridged tropinone analogue **21** (Scheme 7b)[11].



SCHEME 7

When NH_2OH is added to an α,β-unsaturated system with an active functionality, the OH moiety may participate and further promote an intramolecular cyclization reaction. For example, when β-brominated acrylonitrile derivative **22** reacted with NH_2OH, a 5-isoxazoleamine **23** was achieved in good yields. The process was proposed to start with a 1,4-conjugate addition and subsequently followed by the elimination, intramolecular cyclization and isomerization steps (Scheme 8)[12].

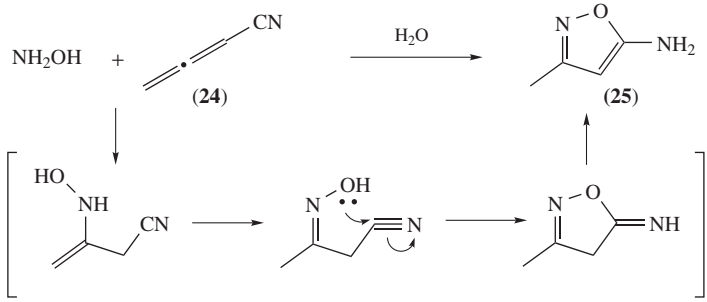


SCHEME 8

In another example, NH_2OH can react with a cyano-substituted allene **24** to furnish a 5-isoxazoleamine **25**[13]. The process can be proposed to be a Michael addition of NH_2OH to the allene central carbon followed by the tautomerization, intramolecular cyclization and isomerization steps (Scheme 9).

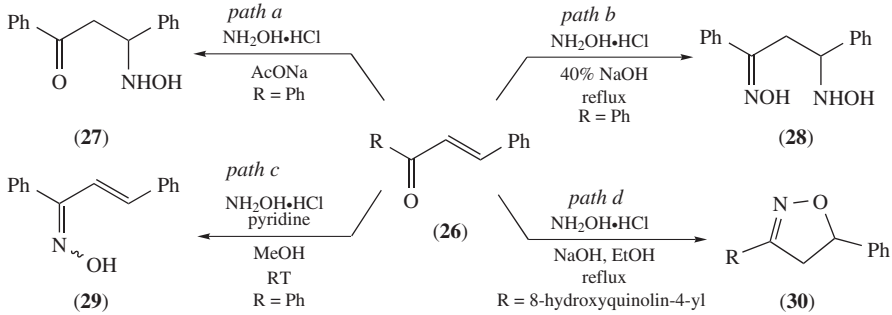
4. Addition reactions of NH_2OH to chalcones

The addition of NH_2OH to chalcones yielded the 1,4-adduct, 1,2-adduct or even the cyclized isoxazoline, depending on the specific reaction conditions. It has been reported



SCHEME 9

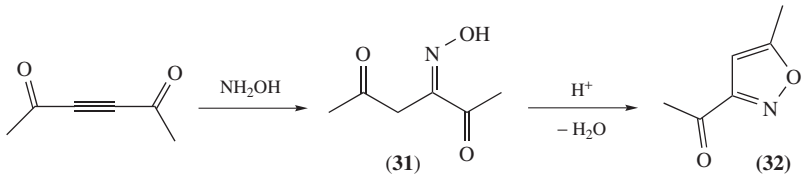
that the reaction of chalcone **26** with NH_2OH•HCl in the presence of NaOAc in EtOH/H_2O gives the 1,4-adduct **27** in 55% yield (Scheme 10, *path a*)[14]. However, treatment of the same chalcone **26** with an excess of NH_2OH•HCl in the presence of NaOH brings about a double addition and produces concurrently both the 1,4- and the 1,2-adduct **28** (Scheme 10, *path b*) under either heat[15] or ultrasonic irradiation[16]. (The reaction of acrolein with an excess of NH_2OH also furnished a bis-adduct similar to **28**[17].) Interestingly, when the same reaction was conducted in the presence of pyridine in MeOH at room temperature, 1,2-adduct **29** was obtained as the predominant product (Scheme 10, *path c*)[18] (both NaOAc and pyridine are weak bases and it should be interesting to know why *paths a* and *c* diverge in terms of the addition pattern). It is also worth noting that the isoxazoline ring **30** was formed when reaction of the analog of **26** carrying a 8-hydroxylquinoline moiety instead of phenyl was conducted with NH_2OH•HCl in the presence of NaOH by heating in EtOH at 80 °C for 12 h (Scheme 10, *path d*)[19].



SCHEME 10

5. Conjugate addition of NH_2OH to activated alkynes

1,4-Conjugate addition/isomerization reaction of NH_2OH with diacetylacetylene affords an oxime product **31**, which conveniently forms 3-acetyl-5-methylisoxazole **32** upon acid-catalyzed cyclization (Scheme 11)[20].

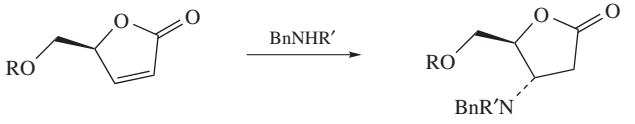


SCHEME 11

B. Conjugate Addition of *N*-Substituted Hydroxylamine Derivatives (RNHOH)

1. General introduction

In general, alkylhydroxylamines react slower than the corresponding alkylamines toward sp^3 centers in the substitution reactions. However, it has been found that *N*-benzylhydroxylamine is more nucleophilic toward sp^2 centers than benzylamine in conjugate addition reactions. For example, reaction of benzylamine with α,β-unsaturated lactones **33a**,**b** in MeOH gives respectively products **34a**,**b** in moderate yields while no reaction was observed in the solvents DMSO or DCE. In contrast, addition of benzylhydroxylamine to **33c** gave **34c** in high yield under a variety of reaction conditions (Scheme 12)[1]. These results cannot be sufficiently explained by the α-effect of N−O moieties, which generally account for the enhanced nucleophilicity toward sp^3 centers on the basis of pKa[21, 22].



(**33a**) R = $BuPh_2Si$
(**33b**) R = H
(**33c**) R = TBS

(**34a**) R′ = H 21%
(**34b**) R′ = H 43%
(**34c**) R′ = OH 95%

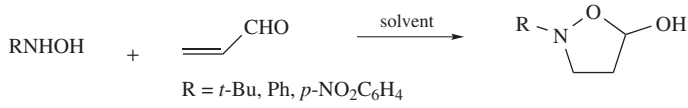
SCHEME 12

The conjugate addition reactions of *N*-substituted hydroxylamines to α,β-unsaturated ketones[23], esters[24, 25], phosphonates[3, 26], sulfones[27], nitriles[28], amides[3], nitro compounds[24] and vinylpyridines[3] are well documented in the literature. Generally, these conjugate addition reactions give mono-adducts (Scheme 13). Both *N*-alkyl and *N*-phenyl hydroxylamines[29] are applicable nucleophiles in this category of reactions. Exceptionally, it was reported that addition of *N*-alkyl or *N*-phenyl hydroxylamines to α,β-unsaturated

R = Alk or Ph

EWG = RCO, COOR′, SO_2R'', CN, $CONH_2$, NO_2, 2-pyr, 4-pyr

SCHEME 13

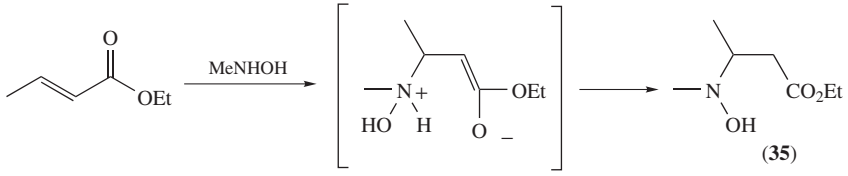


SCHEME 14

aldehyde produced an isoxazolidin-5-ol, possibly via the hemiacetalation of the 1,4-adduct (Scheme 14)[30–32].

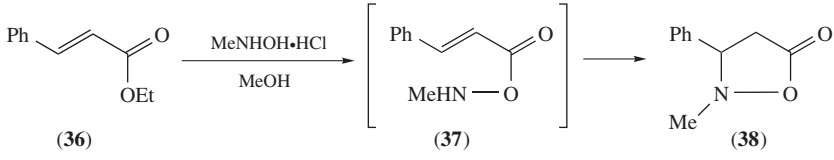
2. Conjugate addition of N-substituted hydroxylamines to α,β-unsaturated esters

In 1976, Stamm and Steudle reported the reaction of *N*-methylhydroxylamine with ethyl crotonate and demonstrated for the first time that the process took place through the 1,4-conjugate addition to afford a *β*-hydroxyamino ester **35** (Scheme 15), which was spectroscopically characterized immediately after the reaction, but was observed to spontaneously cyclize on standing for several days in chloroform solution[33]. On the basis of the acidity of *N*-methylhydroxylamine (pKa 4.6), the authors proposed that the initial addition was assisted by the coordination of the hydroxyl proton to the carbonyl group.



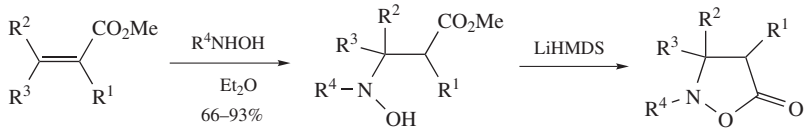
SCHEME 15

Fountain and coworkers reported in 1975 that *N*-methylhydroxylamine hydrochloride reacted with ethyl cinnamate **36** to give an isoxazolidinone (Scheme 16)[34]. However, it was found that *O*-methylhydroxylamine, which should show a similar steric influence, did not produce any of the desired conjugate addition products under identical conditions. Based on these results, the authors proposed that the OH group of the *N*-alkylated hydroxylamine play an important role and the process involve a substitution giving the hydroxamic ester intermediate **37**, which underwent an intramolecular conjugate addition step to further produce the cyclic product **38**.



SCHEME 16

Baldwin and coworkers reported in 1984 that the conjugate additions of *N*-substituted hydroxylamines to *α*,*β*-unsaturated ester **39** followed by cyclization of the 1,4-adducts **40**



(**39**) (**40**) (**41**)

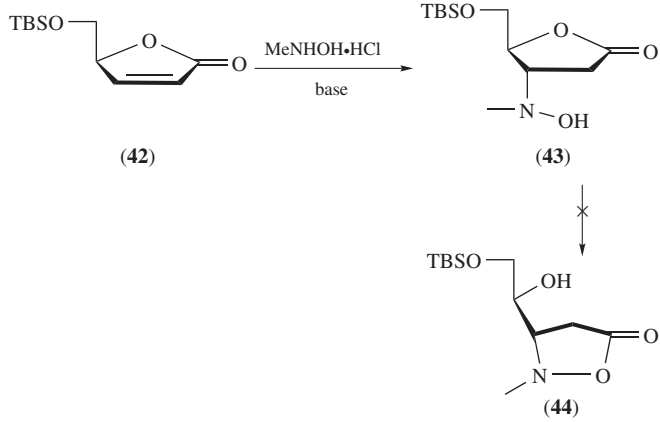
R^1 = H, Me; R^2 = H, Me, CO_2Me; R^3 = H, Me
R^4 = Me, Bn, *i*-Pr, *t*-Bu, *c*-Pen, Ph, (*S*)-PhCHMe, etc

SCHEME 17

with basic LiHMDS provided the first general procedure for the synthesis of isoxazolidin-5-ones **41** (Scheme 17)[2]. The yields of the 1,4-adducts **40** were uniformly good (66–93%), except for those with 2,3-disubstituted-α,β-unsaturated esters as substrates when no addition reaction was observed. The *N*-benzylated derivatives may be hydrogenolized to give β-amino acid. The authors included one example using α-methylbenzylhydroxylamine, but with limited discussion of the stereochemical aspects of the reaction.

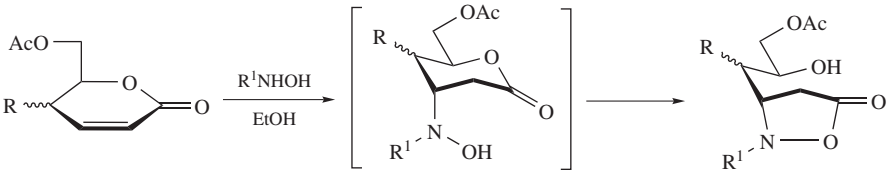
3. Conjugate addition of N-substituted hydroxylamines to lactones

Zhao and coworkers found that reaction of *N*-methylhydroxylamine with a five-membered α,β-unsaturated cyclic lactone, such as **42**, gave stereospecifically the corresponding *trans* 1,4-adduct **43**, which did not rearrange to form the isoxazolidin-5-one ring **44** even under mild basic condition (Scheme 18)[35, 36]. In contrast, Chmielewski and coworkers reported that the reaction of *N*-alkylhyroxylamines with the six-membered α,β-unsaturated lactones **45** underwent a two-step conjugate addition–rearrangement reaction to give isoxazolidin-5-ones **47**. The formation of the conjugate adduct **46** was never observed and the rearrangement process needs neither any basic catalyst nor heating (Scheme 19)[37]. The conjugate addition of *N*-alkylhydroxylamines to enelactone proceeded exclusively *anti* to the terminal acetoxymethyl group. It was thought that



(**42**) (**43**) (**44**)

SCHEME 18



(**45**) (**46**) (**47**)

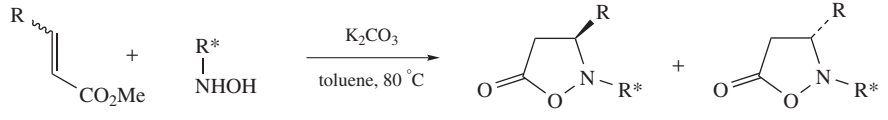
R = H, OAc; R^1 = Me, PMB, Bn *not observed*

SCHEME 19

the axial location of the entering hydroxylamine caused a rapid ring-opening of the six-membered lactone[38].

4. Diastereoselective conjugate addition of N-alkylhydroxylamines to chiral Michael acceptors

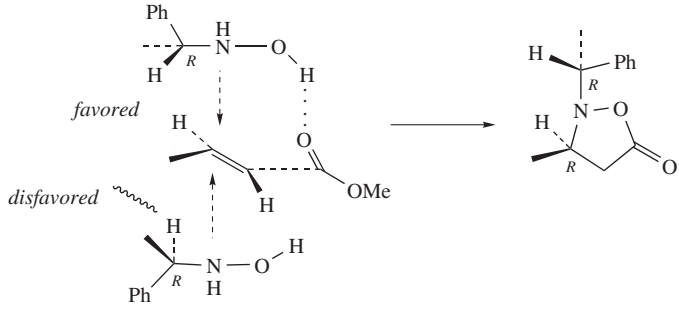
The use of nucleophiles bearing chiral centers provides additional pathways for the stereoselective conjugate addition reactions. Baldwin and Aubé reported in 1987 that the conjugate addition–lactonization reaction between β-substituted acrylate esters **48** and α-methylbenzylhydroxylamine **49** afforded diastereomeric 5-isoxazolidinones **50** (Scheme 20), which were proven to be convenient precursors for optically pure 2-azetidinones[39]. It was found that when (*R*)-α-methylbenzylhydroxylamine was employed, the configuration of the newly formed chiral center of the product is predominantly *R*. Opposite results were obtained from (*S*)-α-methylbenzylhydroxylamine, in which the predominant diastereomer possesses the *S* configuration. The conjugate addition intermediates can be isolated in pure form if the initial reaction is conducted at room temperature. Moreover, the purified uncyclized conjugate addition products also lead to the corresponding single isoxazolidinones under the reaction conditions (toluene/MeOH, K_2CO_3, reflux). Neither the double bond geometry nor the size of the β-substituent seemed to influence the diastereoselectivity of the overall process. Based on the fact that the addition of the parent α-methylbenzylamine to crotonic acid gave a 1:1 mixture of the conjugate addition isomers, the authors suggested that the OH group of the *N*-substituted hydroxylamine play a pivotal role, possibly by coordinating with the carbonyl oxygen in the ester (Scheme 21). This mechanism is similar to that proposed by Stamm and Steudle (Scheme 15)[40]. Bew and coworkers also studied the conjugate addition reactions



(**48**) (**49**) R* = α-methylbenzyl (**50a**) (**50b**)

R = Me (*trans*)	(*R*)-R*NHOH	91%	**50a**:**50b** = 80: 20
R = Me (*trans*)	(*S*)-R*NHOH	84%	**50a**:**50b** = 19: 81
R = Me (*cis*)	(*R*)-R*NHOH	22%	**50a**:**50b** = 86: 14

SCHEME 20

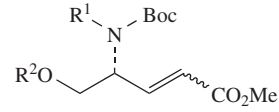


SCHEME 21

of (*S*)-α-methylbenzylhydroxylamine to α,β-unsaturated esters, sulfone, nitrile and nitro species, in which high yields (91–100%) and moderate diastereoselectivity were achieved. They also found that (*S*)-α-methylbenzylhydroxylamine failed to react with the alkyl (Me, Et and *t*-Bu) esters of cinnamic acid, ethyl tiglate or (2*E*,4*E*)-ethylhexa-2,4-dienoate, but could undergo conjugate addition with phenyl cinnamate and phenyl acrylate followed by cyclization[40].

When the double bond is located in conformationally constrained cyclic lactones or lactams, it is easy to rationalize that the stereochemistry of the predominant product should result from the *anti* attack with respect to the substituent attached to the stereogenic centers already present in the substrates. In contrast, it would be difficult to predict the diastereochemistry with flexible open-chained molecules as the reactants. For example, Merino and coworkers reported that in the conjugate addition of *N*-benzylhydroxylamine to L-serine-derived alkenes **51**, there is a substantial degree of substrate-controlled asymmetric induction: (1) for the cyclic ester **51a** with *Z* configuration, the addition predominantly gives the *syn* isomer **52a** (*syn:anti* = 90:10), while for *E*- **51a**, a close to 1:1 ratio of the *syn* and *anti* products were formed. (2) for the open-chained ester **51b**, with R^1 being H and R^2 a bulkier group, an inverse of the diastereoselectivity was observed in the addition process, i.e. the *anti* isomer **52b** was collected as the major isomer from both (*Z*)- and (*E*)-**51b**, and the selectivity was slightly improved when the configuration of the double bond changed from *Z* to *E* (Scheme 22)[41, 42]. Reetz and coworkers also discovered the reversal of diastereoselectivity between the conjugate addition of *N*-methylhydroxylamine to chiral γ-*N*,*N*-dibenzylamino-substituted α,β-unsaturated carboxylic acid esters and dicarboxylic acid esters[43]. For example, the conjugate addition of *N*-methylhydroxylamine to **53** produced isoxazolidin-5-one **54** in 62% yield, with the *syn* isomer **54a** being the predominant product (Scheme 23). These results indicate that both the type of the protecting group and the double bond configuration in the substrates contribute to control the stereochemical outcome of the reaction.

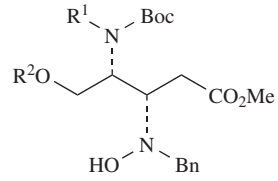
The stereoselective conjugate addition reaction of *N*-alkylhydroxylamine may also be realized by using α,β-unsaturated lactam bearing chiral substituents. Langlois and coworkers reported that the conjugate addition of *N*-benzylhydroxylamine to an optically active α,β-unsaturated γ-lactam **55** gave 1,4-adduct **56** with high diastereoselectivity (Scheme 24), which provided an efficient entry to enantiopure (4*S*,5*S*)-4-amino-5-(hydroxymethyl)pyrrolidin-2-ones[44]. The asymmetric induction in the substrate led to the assignment of a *trans* relationship between the two substituents of the lactam ring and the *S* configuration at the newly created asymmetric center. This assignment was confirmed by a strong NOE observed between the C-6 proton and one of the protons at C-4.



(**51a**) $R^1R^2 = CMe_2$
(**51b**) $R^1 = H$; $R^2 = t\text{-}BuPh_2Si$

BnNHOH

Alkene	*syn* : *anti*	Yield (%)
E-**52a**	53 : 47	78
Z-**52a**	90 : 10	90
E-**52b**	20 : 80	92
Z-**52b**	30 : 70	86



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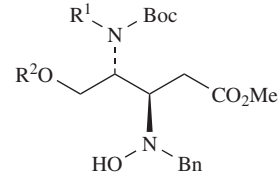
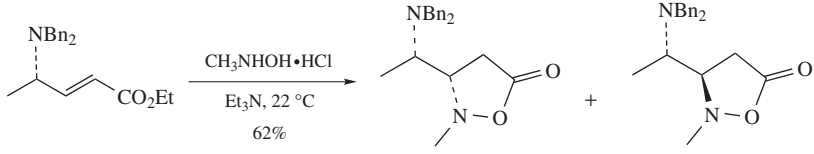


syn-(**52a**) $R^1R^2 = CMe_2$
syn-(**52b**) $R^1 = H$; $R^2 = t\text{-}BuPh_2Si$

anti-(**52a**) $R^1R^2 = CMe_2$
anti-(**52b**) $R^1 = H$; $R^2 = t\text{-}BuPh_2Si$

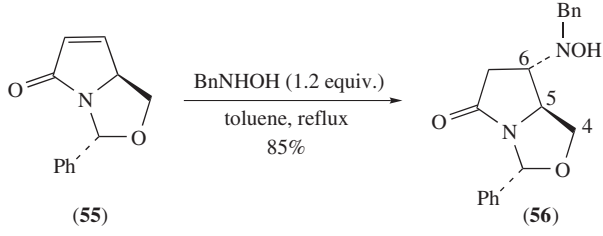
SCHEME 22



(**53**) (**54a**) (**54b**)

54a / **54b** = 9:1

SCHEME 23

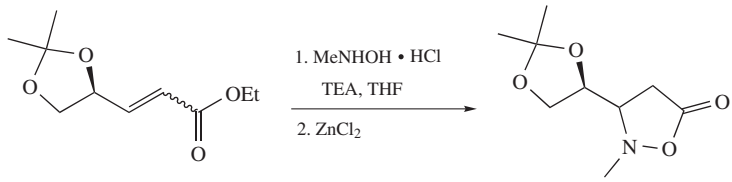


(**55**) (**56**)

SCHEME 24

5. Concerted cycloaddition mechanism for the addition of N-alkylhydroxylamines to Michael acceptors

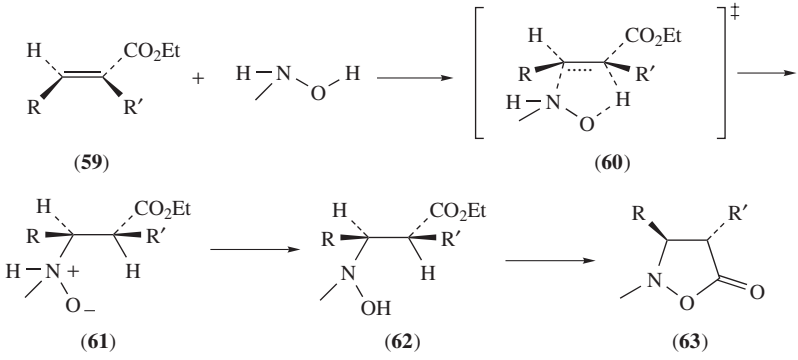
During the course of the synthesis of β-D-isoxazolidinyl pyrimidine and purine nucleosides, Zhao and coworkers investigated the preparation of isoxazolidin-5-one **58** from acyclic ester **57** via the 1,4-conjugate addition and the subsequent metal-catalyzed



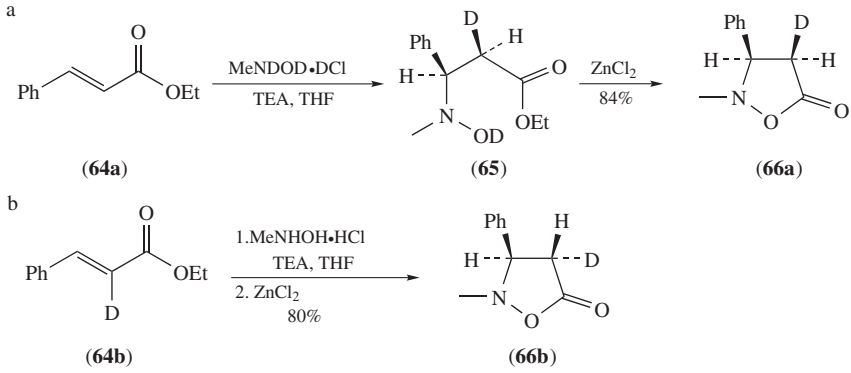
(**57a**) *E*; (**57b**) *Z* (**58a**) *syn*; (**58b**) *anti*

SCHEME 25

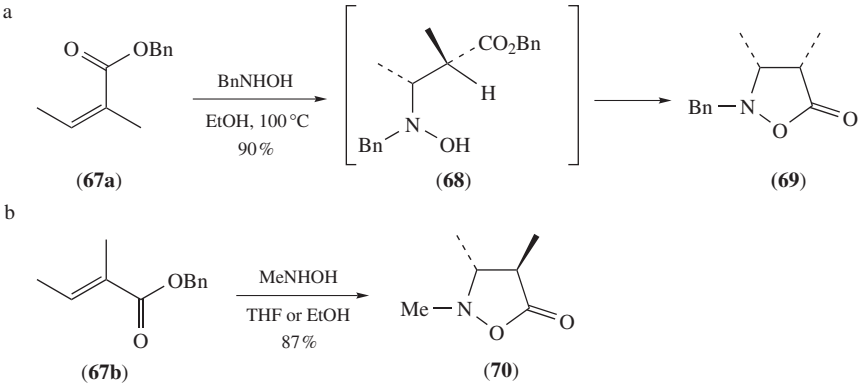
cyclization (Scheme 25)[45]. It was hoped that the *Z*- and *E*-olefins **57** would produce the two isomeric products **58a**,**b** in different ratios. Nonetheless, both **57a** and **57b** gave, in similar ratios (10–14:1), a mixture of compounds in favor of the *cis*-isoxazolidinone **58**, which indicated that the geometry of the olefins **57** has a minimal influence on the outcome of the stereochemistry of **58**, and that the carbonyl oxygen atom is not essential in the transition state of the conjugate addition process. Zhao thus postulated a concerted cycloaddition mechanism involving a cyclic transition state (Scheme 26)[1], where the nitrogen nucleophile initially approaches the alkenoates **59** in a concerted fashion and forms a cyclic five-membered ring transition state **60**; the OH proton is then intramolecularly transferred to the α-carbonyl carbon to give **61**, which tautomerizes rapidly to the corresponding β-hydroxyamino ester **62** with retention of the Z/E configuration of the starting olefin. Compound **62** can either be isolated or further cyclizes to form the five-membered ring compound **63**. The result of two elegant deuteration experiments clearly supported this hypothesis: (1) Treatment of ethyl cinnamate **64a** with deuteriated *N*-methylhydroxylamine gave the expected intermediate **65**, which cyclized to **66a** as a single isomer (Scheme 27a). (2) The deuteriated ester **64b** with *E* configuration reacted cleanly with *N*-methylhydroxylamine to give the expected *trans* isomer **66b** (Scheme 27b). Furthermore, the conjugate addition of *N*-alkylhydroxylamine to trisubstituted alkenoate also proceeded in a *syn* cycloaddition: (1) the conjugate addition of *N*-benzylhydroxylamine to (*Z*)-alkenoate **67a** predominantly gave, via intermediate **68**, *cis* isoxazolidinones **69** (*cis*:*trans* = 12–15:1) (Scheme 28a); (2) the conjugate addition of *N*-methylhydroxylamine to *E*-alkenoate **67b** gave the *trans* compound **70** as the major product (*trans*:*cis* = 25–30:1) (Scheme 28b). This concerted



SCHEME 26



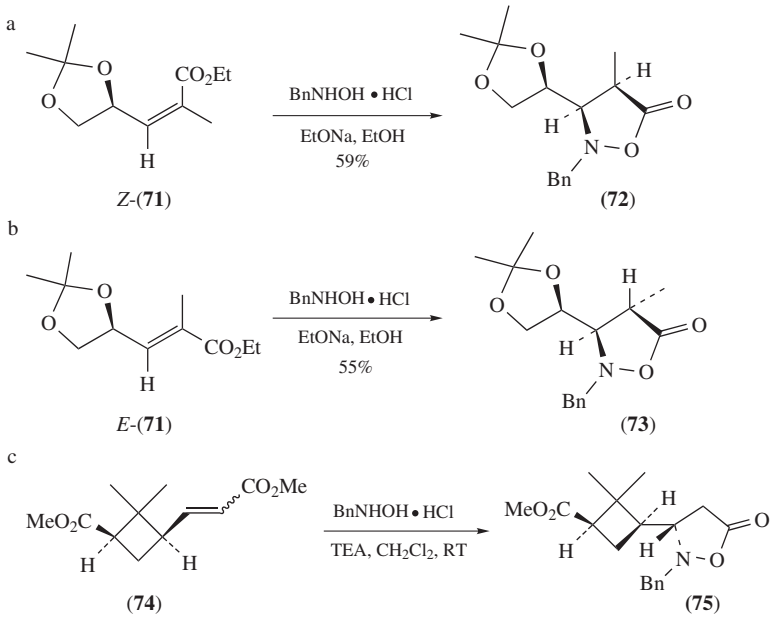
SCHEME 27



SCHEME 28

cycloaddition mechanism can explain the following facts: (1) *N*-alkylhydroxylamines undergo conjugate addition to alkenoates while *O*-alkylhydroxylamine is not reactive toward alkenoates due to the lack of a stabilized transition state; (2) the cyclic state limits the rotational freedom of both starting materials and thus the conjugate addition of *N*-alkylhydroxylamines to optically active ester **57** takes place with a high level of diastereoselectivity; (3) minimal solvent effects have been observed (THF or EtOH has little influence), which are very well ascribed to the formation of a neutral transition state.

Ortuño and coworkers found more evidence for a cycloaddition-like process in reactions between *N*-alkylhydroxylamines and a chiral trisubstituted enoate[46]. It was found that treating trisubstituted olefin (*Z*)- **71** bearing a chiral dioxolane moiety with *N*-benzylhydroxylamine hydrochloride in the presence of excess sodium ethoxide in boiling ethanol for 15 h afforded the *syn* isomeric isoxazolidinone **72** in 59% yield (Scheme 29a). Similarly, the diastereomeric compound **73** was synthesized from (*E*)- **69** in 55% yield (Scheme 29b). These results serve as excellent examples of stereocontrol in the creation of new stereogenic centers in the addition process. Furthermore, they investigated the reactions between *N*-benzylhydoxylamine and the disubstituted



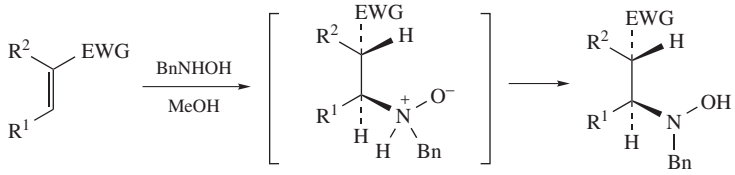
SCHEME 29

(*Z*)- and (*E*)-alkenoate **74** in dichloromethane at room temperature, in which exclusively the isoxazolidinone **75** is achieved in 65% yield (Scheme 29c). It was also found that *E* isomers reacted faster than the *Z* ones and no addition intermediate was detected. The stereoselectivity in the addition process was rationalized as the result of a preferential orientation in the attack on the (C_2-*re*)-face of the double bond induced by the *gem*-dimethyl substitution of the cyclobutane. Finally, they also stated that the concerted reaction mechanism of the conjugate addition process is also supported by a theoretical calculation, which predicts that the *syn* attack is kinetically more favorable and that the *E* isomer is slightly more reactive than the *Z* isomer.

Conjugate additions of *N*-alkylhydroxylamines to α,β-unsaturated sulfones, nitriles and nitro compounds have also been shown to follow the concerted mechanism mentioned above and to proceed with highly stereospecific *cis* addition[47]. The reactivities of the three α,β-unsaturated compounds observed are different: (1) the conjugate addition of *N*-benzylhydroxylamine to nitrostyrene was finished within 1 h at room temperature; (2) the addition of *N*-benzylhydroxylamine to the α,β-unsaturated sulfone was completed in 12 h; (3) it took 7 days for the addition of *N*-benzylhydroxylamine to the α,β-unsaturated nitrile to reach completion (Scheme 30).

6. Asymmetric conjugate addition of N-benzylhydroxylamines using chiral Lewis acid or ligands

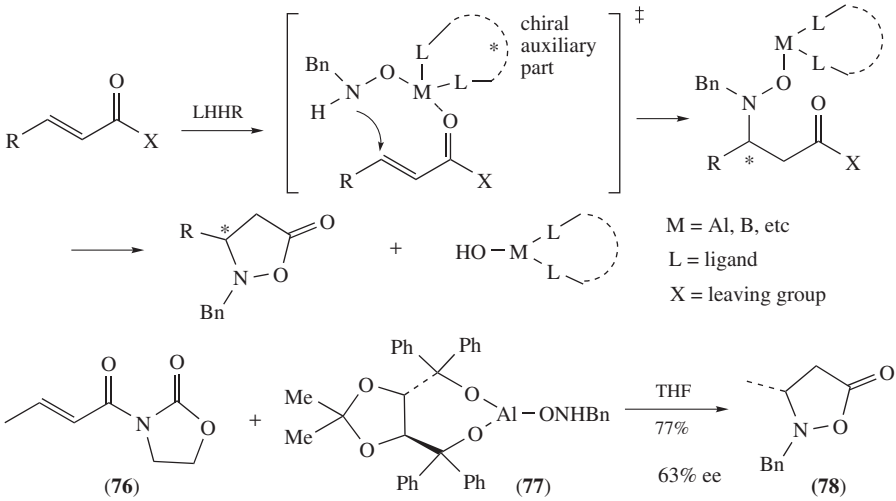
Saito's group utilized both chiral nucleophile and chiral acceptor to study the conjugate addition and found that the reaction of (*S*)-(*N*-α-methylbenzyl)hydroxylamine with diisopropyl (*R*, *R*)-(*O*-crotonoyl)tartrate gave the corresponding isoxazolidinone product



R^1 = Alk, Ar; R^2 = Alk, Br; EWG = SO_2Ph, CN, NO_2

SCHEME 30

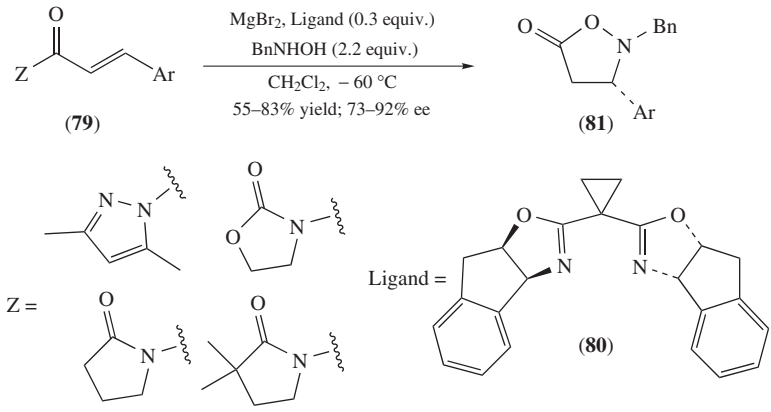
in 70% yield with a de value of 80% as a result of double stereo differentiation[48]. They also introduced the LHHR concept (Lewis acid–hydroxylamine hybrid reagent), which includes inserting a chiral auxiliary with an appropriate metal atom into the OH group of the *N*-benzylhydroxylamine, in order to realize an enantioselective conjugate addition process. The application of chiral LHHR **77** in conjugate addition to α,β-unsaturated imide **76** afforded preferentially (*R*)-isoxazolidinone **78** in 77% yield with 63% ee (Scheme 31)[49].



SCHEME 31

Sibi and Liu conducted the conjugate addition of *N*-benzylhydroxylamine to pyrrolidinone-derived enoates **79** in the presence of chiral Lewis acid ($MgBr_2$ + chiral ligand **80**), and reported that β-aryl-β-amino acid derivatives **81** were obtained in high enantiomeric purity with moderate to good chemical efficiency (Scheme 32)[50]. This reaction represents the first examples of highly enantioselective conjugate additions to cinnamates by using catalytic amounts of a chiral Lewis acid. Their control experiments are analogous to those reported by Zhao while using BnNDOD as the nucleophile, the results of which suggested that the process proceeds via a concerted addition mechanism.

Sibi and Liu utilized a chiral relay strategy to amplify the stereoselectivity in the conjugate addition of 4-$MeOC_6H_4CH_2NHOH$ to pyrazolidinone acrylamide **82**. Two catalytic



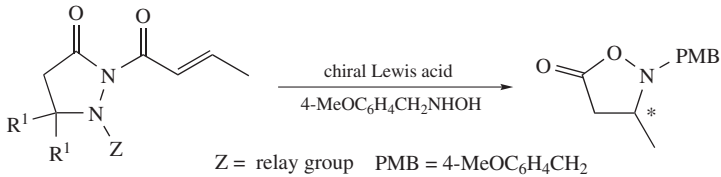
SCHEME 32

systems, i.e. magnesium perchlorate with ligand **83** (catalyst A) and zinc triflate with ligand **84** (catalyst B), were tested, and it was found that a simple change in the Lewis acid reversed the enantioselectivity, allowing either the *R* or the *S* enantiomer to be formed with similarly high selectivities. A bulkier relay group is expected to increase the enantioselectivity in the conjugate reactions with either catalyst system (Scheme 33)[51].

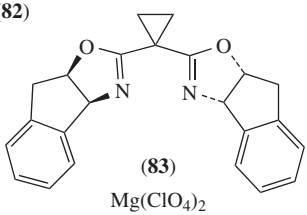
Sibi and coworkers ascribed the poor reactivity experienced in traditional templates such as oxazolidinones to the problematic A interactions in either rotamer **85** or **86**[52]. To relieve the strain in the C−C bond, the enoyl groups would need to twist, which would consequently break the conjugation and result in diminished reactivity at the β-carbon. Therefore, the use of an imide **87** with an N−H group ($R^3 = H$) was envisaged to eliminate the A strain present in **85** and **86** and thus allow for planar enoyl groups with normal reactivity (Figure 1). They surmised that the introduction of rotamer control elements ($R^3 = H$, $R^4 =$ alkyl, aryl) combined with the established concerted addition of *N*-benzylhydroxylamine catalyzed by chiral Lewis acid may provide access to 5-isoxazolidinone products with good relative as well as absolute stereocontrol. They finally discovered that the combination of $Mg(NTf_2)_2$ with ligand **83** could mediate the conjugate addition of *N*-benzylhydroxylamine to α,β-unsaturated imide derivative **88** with outstanding levels of selectivity (60–96% ee and 93–99% de) achieved for **89** (Scheme 34)[52], which indicated that a highly enantioselective synthesis of disubstituted-β-amino acids could be achieved by the method.

7. Conjugate addition of N-hydroxy-4-toluenesulfonamide (N-tosylhydroxylamines)

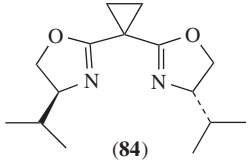
N-Hydroxy-4-toluenesulfonamide (*N*-tosylhydroxylamine) **90** can also be applied in conjugate addition reactions. Recently, an efficient one-pot synthesis of 3,5-disubstitued isoxazoles **93** via the reaction of *N*-hydroxy-4-toluenesulfonamide **90** with α,β-unsaturated aldehydes or ketones **91** was reported[53]. The reactions were shown to be highly regioselective and no regioisomers were formed in any of the cases. The excellent regioselectivity is attributed to the tosyl moiety, which renders the nitrogen atom in the hydroxylamine more nucleophilic in the first conjugate addition step. β-Hydroxyimino ketone intermediate **92** was proposed to be formed after the elimination of the tosyl



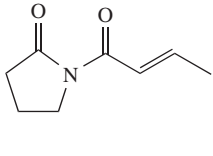
(**82**)



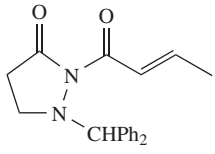
(**83**)
$Mg(ClO_4)_2$
Catalyst A



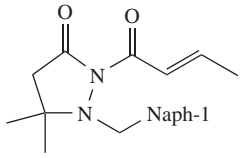
(**84**)
$Zn(OTf)_2$
Catalyst B



non-relay template



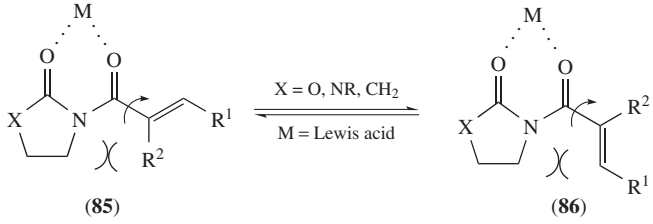
relay template



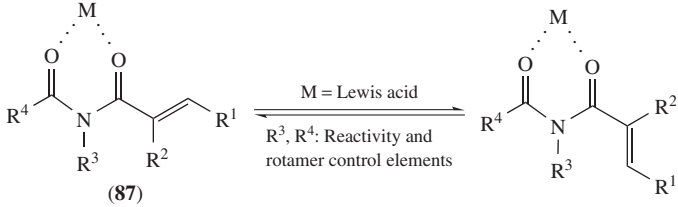
relay template

	non-relay template	relay template	relay template
Catalyst A:	0 °C, 55% ee (*R*)	0 °C, 84% ee (*R*)	0 °C, 81% ee (*R*)
Catalyst B:	0 °C, 29% ee (*S*)	0 °C, 57% ee (*S*)	0 °C, 75% ee (*S*)

SCHEME 33

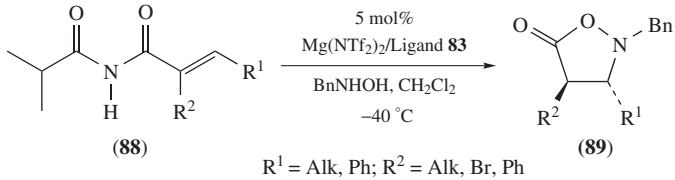


(**85**) (**86**)



(**87**)

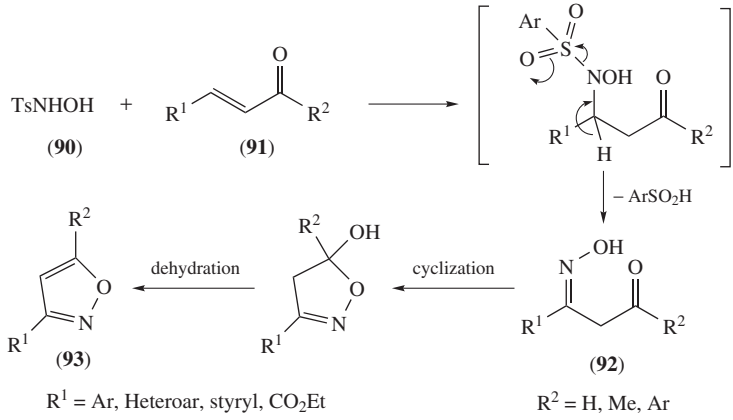
FIGURE 1



(**88**) (**89**)

R^1 = Alk, Ph; R^2 = Alk, Br, Ph

SCHEME 34



R^1 = Ar, Heteroar, styryl, CO_2Et R^2 = H, Me, Ar

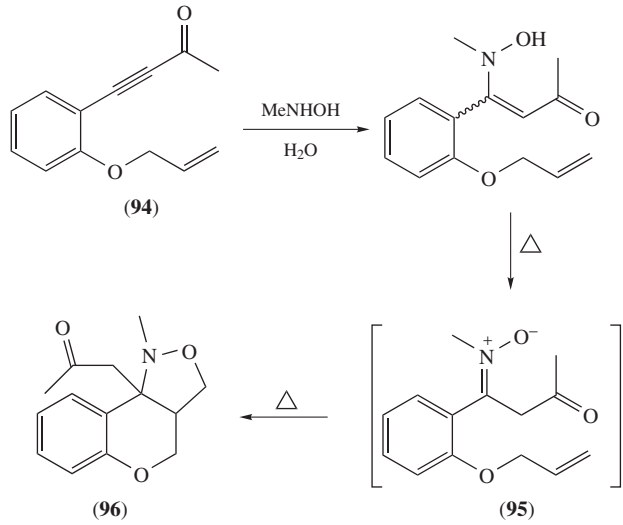
SCHEME 35

moiety, and 3,5-disubstitued isoxazole products **93** were obtained after the subsequent cyclization and dehydration steps (Scheme 35).

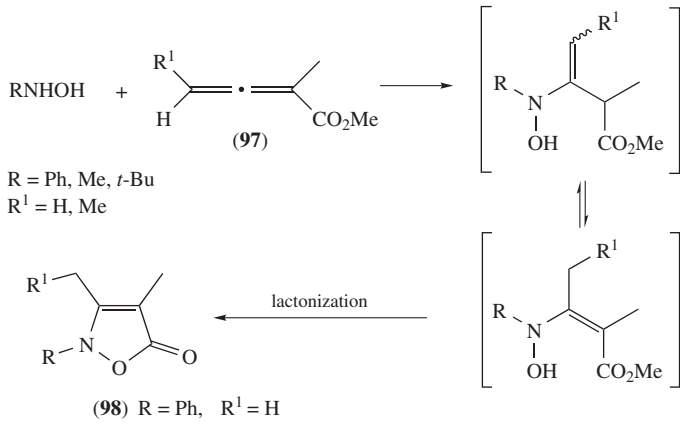
8. Conjugate addition of N-substituted hydroxylamines to activated alkynes or allenes

Padwa and coworkers reported the water-mediated addition of *N*-methylhydroxylamine to the activated triple bond of **94**, followed by a proton shift to give a nitrone intermediate **95**, which undergoes an intramolecular 1,3-dipolar cycloaddition to give the isoxazolidine product **96** (Scheme 36)[54]. However, attempts to isolate both the *cis*–*trans* mixture of the 1,4-adduct and the nitrone intermediate **95** failed.

Padwa and coworkers also studied the reaction of *N*-substituted hydroxylamines with activated allenes[55]. They reported that the reaction of *N*-phenylhydroxylamine and methyl 2-methylbuta-2,3-dienoate **97** gave *N*-phenyl-3,4-dimethylisoxazolin-5-one **98** in 98% yield. Similar results were also obtained with methyl- and *tert*-butylhydroxylamine as well as methyl 2-methylpenta-2,3-dienoate as the allene. The formation of isoxazolin-5-one **98** can be explained in terms of addition of the nitrogen atoms of the hydroxylamine onto the central carbon of the allene followed by a subsequent lactonization (Scheme 37). Interestingly, they found a different pattern of reactivity in the reaction of these *N*-substituted hydroxylamine with methyl or ethyl 2,3-butadienoate **99**, in which 2,3-dihydroisoxazoles

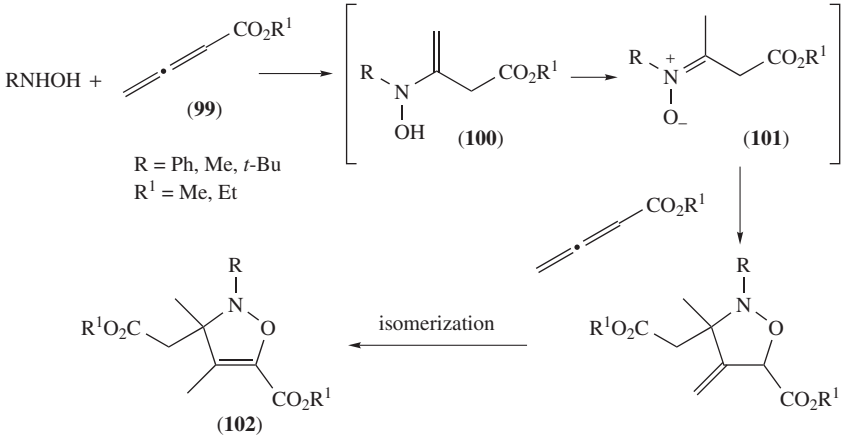


SCHEME 36



SCHEME 37

102 were formed as the products. The authors proposed that the addition of the hydroxylamine across the activated allenyl π-bond followed by a subsequent tautomerization of the resulting vinylhydroxylamine **100** gave a nitrone intermediate **101**. This species undergoes 1,3-dipolar cycloaddition across the allene, and the ensuing cycloadduct rapidly rearranges to the observed product (Scheme 38). These results clearly indicate that the reaction of hydroxylamines with carboalkoxy-substituted allenes is markedly dependent on the nature of the substituent present on the 1-position of the allene.

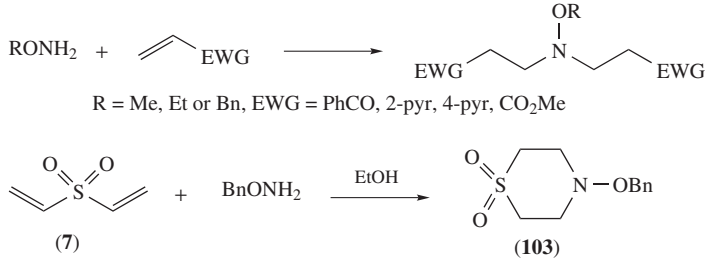


SCHEME 38

C. Conjugate Addition of *O*-Substituted Hydroxylamines (NH_2OR)

1. General introduction

Casey and Marvel reported in 1959 that the reaction of methoxyamine hydrochloride with phenyl vinyl ketone in the presence of NaOAc at 0 °C produced bis(β-benzoylethyl)methoxyamine in 53% yield[56]. Bauer and coworkers also found that during the reaction of *O*-benzylhydroxylamine with either 2- or 4-vinylpyridines, an excellent yield of the dipyridylethyl derivatives was formed[57]. The reaction of methoxyamine or ethoxyamine with methyl acrylate in MeOH under heat provided the bis-adduct in good yield[58], while under almost identical reaction conditions the reaction of methoxyamine with methyl methacrylate yielded just the mono-adduct, which underwent further conjugate addition with methyl acrylate to give the corresponding bis-adduct in 92% yield[59]. In a reaction of divinyl sulfone **7** with *N*-benzylhydroxylamine, a cyclic product **103** was obtained via double conjugate addition[60]. These results indicate that, similarly to hydroxylamine, *O*-substituted hydroxylamine can undergo double conjugate addition to an alkene bearing electron-withdrawing groups such as carbonyls, pyridines or sulfones (Scheme 39). In contrast, for the substituted α,β-unsaturated esters or ketones, the conjugate addition tends to occur only once due to the steric hindrance.



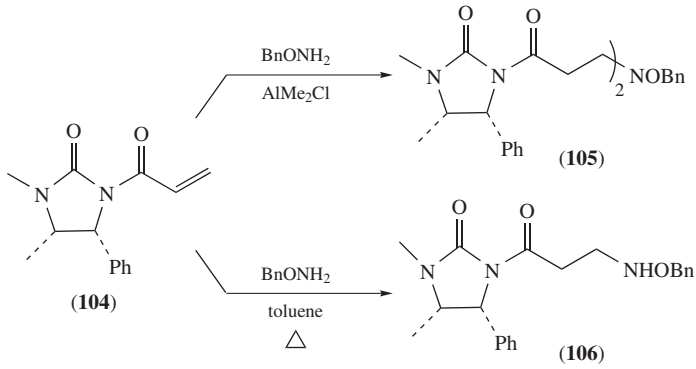
SCHEME 39

Generally, when the alkene bears a relatively weak electron-withdrawing group such as an ester[61–69], phosphonate[70, 71], sulfone[72] or amide[73–76], the conjugate addition provides mono-adduct under mild conditions (Scheme 40). However, Cardillo and coworkers found that in the presence of $AlMe_2Cl$, the conjugate addition of *O*-benzylhydroxylamine to acryloylimidazolidin-2-one **104** at 0 °C occurred and proceeded smoothly to afford the bis-adduct **105**. Mono-adduct **106** was obtained when the addition reaction took place in toluene at 50 °C in the absence of Lewis acid (Scheme 41)[77]. The formation of the bis-adduct in the former case suggests the participation of $AlMe_2Cl$, a Lewis acid, in activating the acrylamide.

R = Me, Bn, TMS

EWG = CO_2Bu-*t*, CO_2Bn, $PO(OEt)_2$, SO_2Ph, CONRR′

SCHEME 40



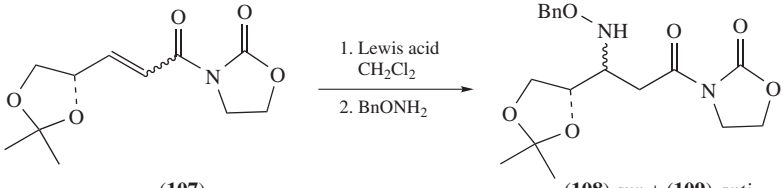
SCHEME 41

It has been known that *N*-alkylhydroxylamines undergo stereospecific *cis* addition to an α,β-unsaturated system with high diastereoselectivity. However, it has been found that similar *O*-alkylhydroxylamines give no stereoselectivity in the conjugate addition to α,β-unsaturated nitro compounds due to the inability to generate a cyclic transition state. Furthermore, under the same reaction conditions, the additions of *N*-alkylhydroxylamines proceeded much faster than those of *O*-alkylhydroxylamines[78].

2. Diastereoselective conjugate addition of O-alkylhydroxylamines to chiral Michael acceptors

Cardillo and coworkers studied the conjugate addition of *O*-benzylhydroxylamine to chiral α,β-unsaturated imides **107** of both *Z* and *E* configurations, promoted by a catalytic amount (0.05 equivalents) of a Lewis acid (no reaction occurred without a Lewis acid catalyst)[79]. As to the conjugate addition of *O*-benzylhydroxylamine to *trans*-**107**, moderate diastereoselectivity was found with the various Lewis acids: the conjugate *syn*-adduct

108 predominated with boron (Bu_2BOTf) and ytterbium ($Yb(OTf)_3$) as Lewis acids, while *anti*-adduct **109** was obtained as the major product with the aluminum salt ($AlMe_2Cl$) and cerium salt hydrate ($CeCl_3{\bullet}7H_2O$) as the catalyst. Under the same reaction conditions, the reaction rate of *O*-benzylhydroxylamine with *cis*-**108** was notably slower than that with *trans*-**108**, but with high yields and almost exclusive stereoselectivity of *syn* over *anti*. From this study, the most appropriate Lewis acids that minimized *cis*–*trans* isomerization and thus gave excellent diastereoselectivity are $CeCl_3{\bullet}7H_2O$, $Cu(OTf)_2$ and $MgBr_2{\bullet}Et_2O$ (Scheme 42).

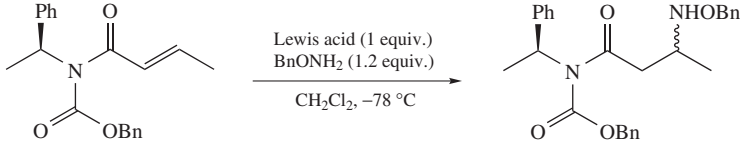


(**107**) (**108**) *syn* + (**109**) *anti*

Alkene	Lewis acid	Temp (°C)	Time (h)	**108**+**109** (%)	**108**/**109** (%)
E-**107**	Bu_2BOTf	−10	12	20	67/33
E-**107**	$Yb(OTf)_3$	−10	4	>98	60/40
E-**107**	$AlMe_2Cl$	−60	1	60	39/61
E-**107**	$CeCl_3{\bullet}7H_2O$	−10	6	90	32/68
Z-**107**	$CeCl_3{\bullet}7H_2O$	−10	18	95	91/9
Z-**107**	$Cu(OTf)_2$	−10	24	75	>99/<1
Z-**107**	$MgBr_2{\bullet}Et_2O$	−10	24	>98	>99/<1

SCHEME 42

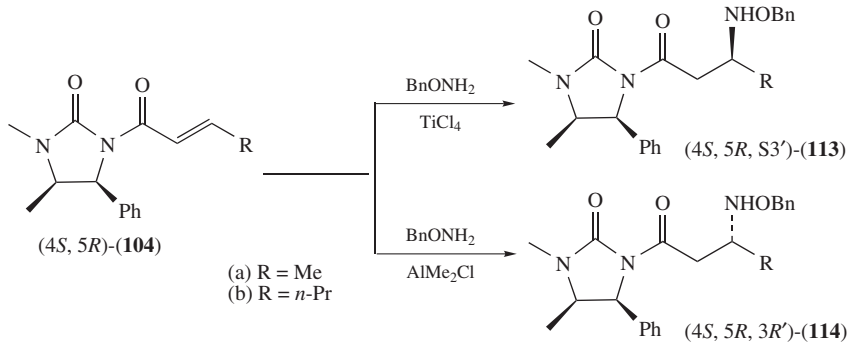
In the conjugate addition reactions, the reactivity of the electrophilic substrates can be enhanced by using a Lewis acid as an activating agent. Cardillo and coworkers studied the conjugate addition reaction of *O*-benzylhydroxylamine to the crotonimide **110** of (*S*)-phenylethylamine and found that reaction occurred smoothly and in good yield in CH_2Cl_2 at −78 °C, while no addition reaction took place in the absence of a Lewis acid. A 1:1 diastereomeric mixture of (*S*,*S*)- and (*S*,*R*)-derivatives **111** was always obtained with the various Lewis acids studied (Scheme 43)[74, 80]. An electrophilic substrate bearing a chiral heterocyclic substrate was applied for improving the asymmetric induction. Treatment of



(**110**) (**111**)

60–80% yield; 1:1 diastereomers
Lewis acid: $TiCl_4$, $AlClMe_2$

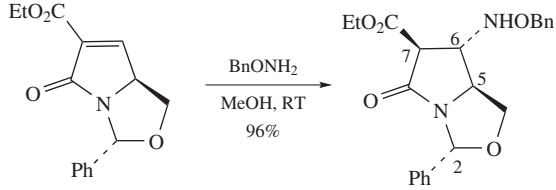
SCHEME 43



SCHEME 44

(4*S*,5*R*)-3-alkenylimidazolidin- 2-one **112** with *O*-benzylhydroxylamine in dry CH_2Cl_2 in the presence of $TiCl_4$ (1 equivalent) afforded an 80:20 ratio of **113a/ 114a** and a 77:23 ratio of **113b/ 114b** (Scheme 44). In contrast, when $AlMe_2Cl$ was used as the Lewis acid, the opposite diastereoselectivities were observed. On increasing the amount of $AlMe_2Cl$ from 1 equivalent to 1.4 equivalents, the diastereoselectivity increased from 26:74 to 19:81 for **113a/ 114a**. The use of 2 equivalents of the Lewis acid $AlMe_2Cl$ produced a 11:89 ratio of **113b/ 114b**. Cardillo and coworkers also found that when BF_3•Et_2O was used as catalyst, the diastereomer **114** was formed as the major isomer[81], similar to the case when $AlMe_2Cl$ was applied as the Lewis acid catalyst. The fascinating aspect of this addition reaction lies in the fact that the predominant *S* or *R* configuration of the newly introduced stereogenic center depends on the particular Lewis acid applied.

The conjugate addition of *O*-benzylhydroxylamine to the α,β-unsaturated lactam **115** gives the corresponding β-amino products **116** in good yield with high diastereoselectivity. The major product (up to four diastereomers were detected by ^{13}C NMR analysis) was determined to have the (2*R*, 5*S*, 6*S*, 7*R*) configuration which was supported by a series of NOE experiments. This configuration corresponded to the expected less-hindered *exo*-approach of the nucleophile followed by *exo*-protonation to give C6–C7 *trans*-product **116** (Scheme 45)[82].

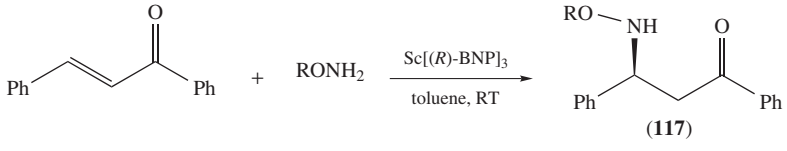


(**115**) diastereomer ratios: 20:2:2:1 (**116**)

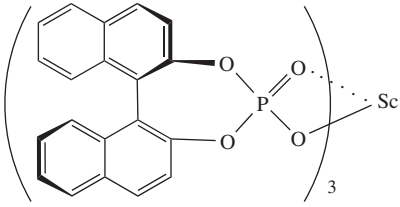
SCHEME 45

3. Asymmetric conjugate addition of O-alkylhydroxylamines using chiral Lewis acids or ligands

Inanaga and coworkers reported that the conjugate addition of *O*-diphenylhydroxylamines to (*E*)-chalcone can be effectively catalyzed by chiral compounds containing



(**117**)

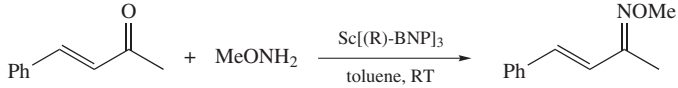


Sc[(*R*)-BNP]$_3$

$RONH_2$	Yield (%)	ee (%)
$MeONH_2$	81	57
$BnONH_2$	94	91
Ph_2CHONH_2	94	99

SCHEME 46

a rare earth metal, e.g. Sc[(*R*)-BNP]$_3$, to afford the corresponding β-amino ketones **117** with high enantioselectivity in nearly quantitative yield[83]. For the less bulky *O*-benzylhydroxylamine and *O*-methylhydroxylamine, both the yield and the ee value decreased (Scheme 46). However, this method is only applicable to the conjugated enones bearing an aryl ketone. In the case of the alkyl ketone **118**, the desired conjugate adduct was hardly obtained under the described conditions and the reaction mainly afforded the oxime product **119** (Scheme 47).

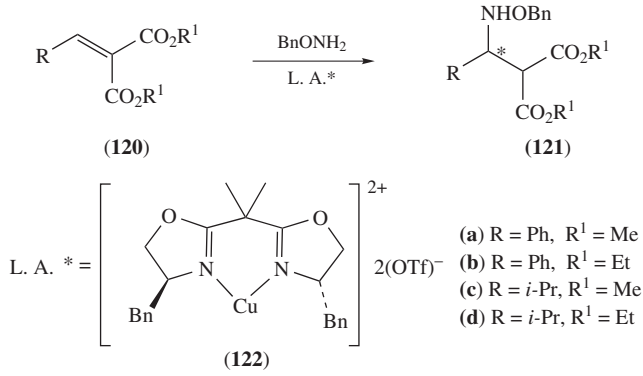


(**118**) (**119**)

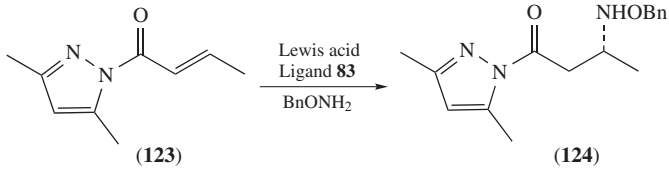
SCHEME 47

Cardillo and coworkers reported in 2001 that the conjugate addition of *O*-benzylhydroxylamine to doubly activated acceptors, i.e. alkylidene and arylidene malonates **120** catalyzed by $Cu(OTf)_2$ in the presence of chiral bisoxazoline ligands **122**, afforded the 1,4-adducts **121** in good yields (Scheme 48)[84]. However, only low to moderate ee values (up to 29%) were obtained for these conjugate addition processes.

Falborg and Jørgensen reported in 1996 a titanium-catalyzed conjugate addition of *O*-benzylhydroxylamine to α,β-unsaturated *N*-acylated 1,3-oxazolidinones. The conjugate adducts were obtained on application of 10 mol% of the catalyst TiX_2-TADDOL (X = Cl or OTf) or $TiCl_2$-BINOL. However, only modest enantioselectivity (up to 42%) was obtained[85]. In 1998, Sibi and coworkers reported that the addition of *O*-benzylhydroxylamine to crotonylpyrazole **123** catalyzed by chiral Lewis acid afforded the conjugate adducts **124** with high enantioselectivity (Scheme 49). In the presence of stoichiometric amounts of the chiral Lewis acid prepared from $MgBr_2 \bullet OEt_2$ and bisoxazoline **83**, an excellent ee (96%) was obtained after 21 h at $-60\,^{\circ}C$. Increasing the reaction temperature to $0\,^{\circ}C$ led to faster reaction but was accompanied by a sharp decrease of the ee value to 61%. A catalytic amount (30%) of the chiral Lewis acid was also effective



SCHEME 48

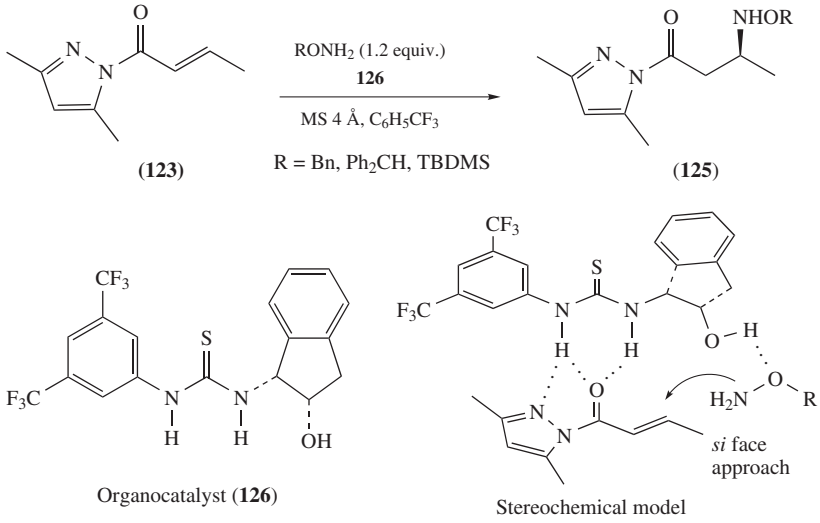


SCHEME 49

for the addition process. Interestingly, the use of $Y(OTf)_3$ (1 equivalent) as the Lewis acid (−60 °C, 22 h) provided the addition product with opposite stereoselectivity to the one obtained by the use of $MgBr_2$ as the Lewis acid, namely *S* over *R* with an ee value being 41–59%[73].

The use of organocatalyst to prepare chiral building blocks has also received intensive attention. In 2007, Sibi and Itoh reported a highly efficient conjugate *O*-alkylhydroxylamines addition to crotonylpyrazole **123** that proceeded with high levels of enantioselectivity by using a bifunctional organocatalyst **126**[86]. The reaction in non-hydrogen bonding solvent, e.g. trifluorotoluene gave the highest ee value. Changing the *O*-substituent on the hydroxylamine from benzyl to benzhydryl to *tert*-butyldimethylsilyl gives the conjugate adducts **125** in good selectivity (ee increased from 71 to 89 to 94%) (Scheme 50). A further study of the substrate effect showed that substrates with alkyl substituents on the β-carbon react with higher enantioselectivity. However, reactions are much slower with pyrazole cinnamate being the Michael acceptor, and products are formed in low yield with low steroselectivity. An applicable model consistent with the observed stereochemistry indicates that the pyrazole template plays a crucial role in providing H-bond sites in the acceptor for better organization to realize the higher levels of selectivity (Scheme 50). Ricci and coworkers also reported an organocatalytic approach for conjugate addition of *O*-benzylhydroxylamine to chalcones utilizing a thiourea derivative bearing quinuclidinic moiety, which gave the β-keto hydroxylamines in up to 60% ee[87].

Shibasaki and coworkers applied heterobimetallic multifunctional catalysis in asymmetric 1,4-addition of *O*-alkylhydroxylamine to (*E*)-chalcone, with high ee and yield

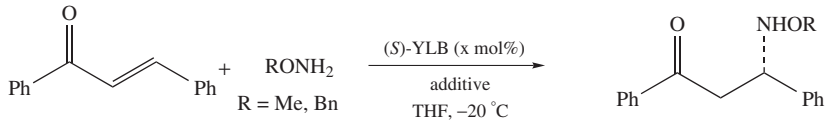


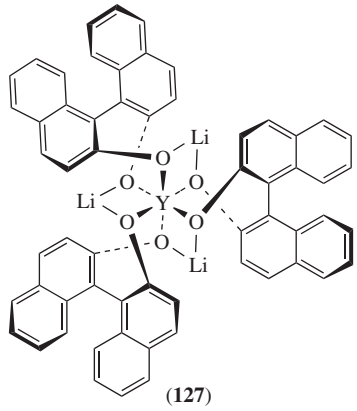
SCHEME 50

achieved using as little as 0.5–3 mol % of a YLi_3tris(binaphthoxide) **127** (Scheme 51)[88]. The inhibition of the Lewis acid catalyst by the nucleophile or product was negligible in such a system, unlike the standard Lewis acid catalysts. The cooperative function of Y and Li metals, which is referred to as heterobimetallic catalysis, was important for achieving high catalyst turnover in the process. It was proposed that the Y metal functions as the Lewis acid activate the enone and the Li metal coordinates to the oxygen atom of *O*-alkylhydroxylamine. The extremely high yield as well as the ee value, together with the low catalyst loading, highlights this process as one of the most promising methodologies in the conjugate addition reactions of *O*-alkylhydroxylamines.

4. Intramolecular conjugate addition of O-alkylhydroxylamines

An intramolecular conjugate addition involving *O*-alkylhydroxylamines can also be achieved under certain circumstances. For example, Bates and coworkers reported in 2008 that treatment of enoate **128** with hydrazine resulted in a tandem deprotection–intramolecular conjugate addition process to construct cyclic hydroxylamine derivatives. In the case of $n = 1$, the isoxazolidine **129** was obtained as an inseparable 1:2 mixture of the stereoisomers; in contrast, only the *trans* isomers of the tetrahydro-1,2-oxazines **130** were formed for $n = 2$ (Scheme 52a). When dienoate **131** was applied under the same reaction conditions, only the deprotection product was achieved as in the first step. However, under heating in THF, cyclization occurred and gave oxazine **132** as the *trans* isomer with the remaining double bond in the β,γ-position (Scheme 52b). The product is clearly formed by kinetic protonation of the intermediate enolate produced by the intramolecular Michael addition. No corresponding α,β-unsaturated isomer was detected since the double bond migration is not likely to occur in the absence of any acid or base. Furthermore, treating the ene-yne substrate **133** with hydrazine afforded isoxazine **134** in 89% yield, with the double bond shown to be α,β to the imine (rather than to the ester) by an HMBC experiment (Scheme 52c)[72].



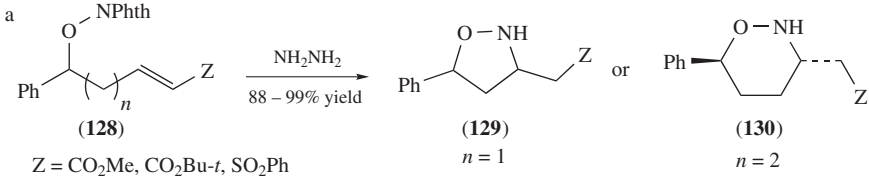


(**127**)

YLi_3tris(binaphthoxide) (YLB)

$RONH_2$	Catalyst (mol%)	Yield (%)	ee (%)
$MeONH_2$	10	94	97
$MeONH_2$	10	94	97
$BnONH_2$	10	91	91
$BnONH_2$	5	94	96
$BnONH_2$	3	97	95
$BnONH_2$	1	95	96
$BnONH_2$	0.5	96	96

SCHEME 51

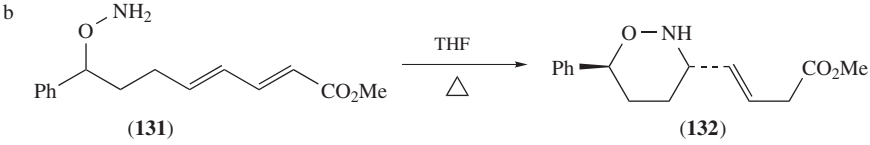


(**128**)

Z = CO_2Me, CO_2Bu-*t*, SO_2Ph

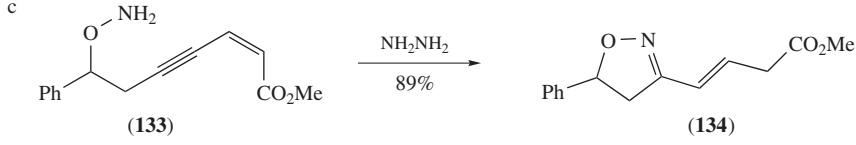
(**129**)
n = 1

(**130**)
n = 2



(**131**)

(**132**)



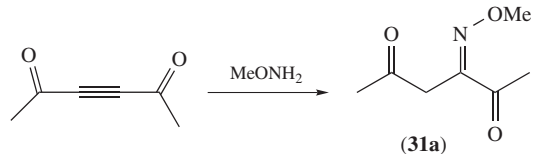
(**133**)

(**134**)

SCHEME 52

5. Conjugate addition of O-alkylhydroxylamines to activated alkynes

The addition of methoxyamine to diacetylacetylene, following the same pattern of conjugate addition/isomerization processes of the reaction between NH_2OH with diacetylacetylene shown in Scheme 10, provides the oxime product **31a** in a 89% yield (Scheme 53). There was no evidence for any addition product to a carbonyl group in either the starting material or the product[89].

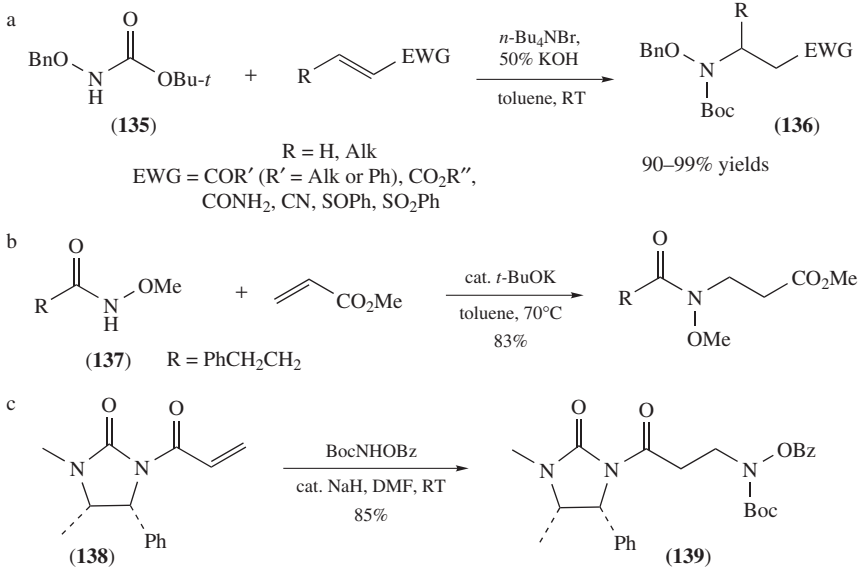


SCHEME 53

D. Conjugate Addition of *N*,*O*-Disubstituted Hydroxylamines (RNHOR′)

1. General introduction

It was reported that *N*,*O*-dimethylhydroxylamine underwent conjugate addition to ethyl acrylate under reflux in acetonitrile for 50 h[90]. Park, Jeong and coworkers reported that *tert*-butyl benzyloxycarbamate **135**, an *N*,*O*-disubstituted hydroxylamine, could undergo smooth aza-Michael addition to form a wide range of **136** in the presence of catalytic phase transfer catalyst under basic conditions. The electron-withdrawing groups attached to the olefins include carbonyl, ester, amide, nitrile, sulfoxide and sulfone (Scheme 54a)[91]. It has been reported that *N*-methoxyamide **137** also underwent conjugate addition to

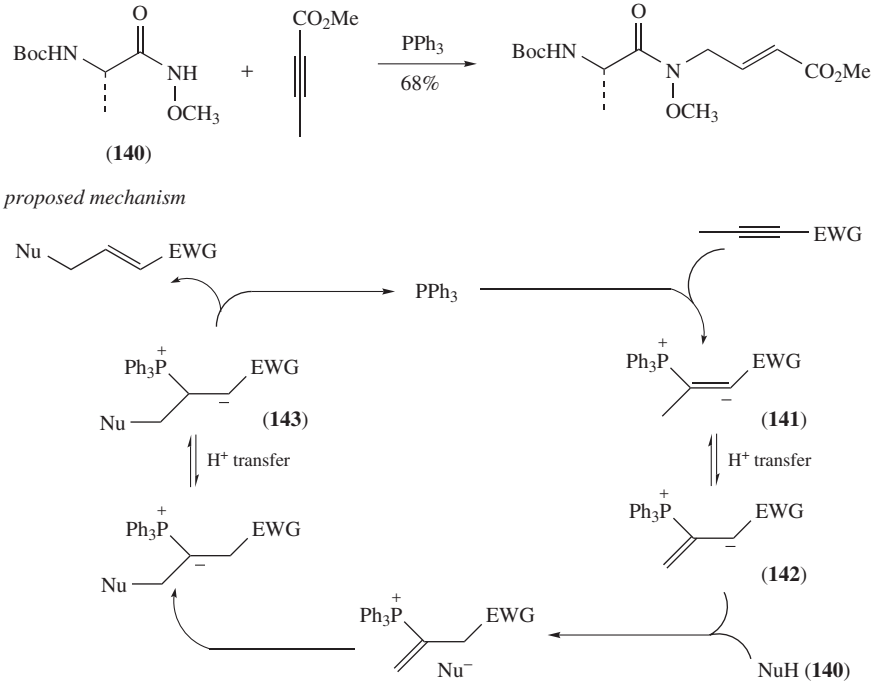


SCHEME 54

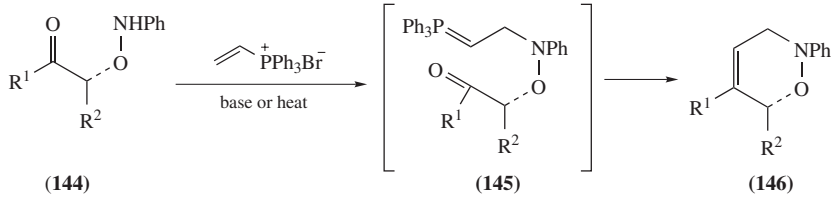
methyl acrylate in the presence of catalytic amount of *t*-BuOK (Scheme 54b)[92]. *N*-Acetyl-*N*-benzyloxyamine may also add to *tert*-butyl acrylate under solvent-free PTC conditions mediated by K_2CO_3[93]. Furthermore, Cardillo and coworkers also reported in 1998 that *N*-Boc-*O*-benzoylhydroxylamine could undergo conjugate addition to a chiral α,β-unsaturated imide **138** catalyzed by sodium hydride to give the 1,4-adduct **139** in high yield (Scheme 54c)[94]. The bases in these reactions are thought to play a role of abstracting the acidic proton on the nitrogen atom, thus enhancing its nucleophilicity.

Trost and Dake reported in 1997 that *N*-methoxyamide derivative **140** underwent a phosphine-catalyzed γ-addition reaction to methyl 2-butynoate, during which process the Michael addition process was entirely suppressed[95]. However, a conjugate addition process can be seen in its mechanistic pathway. First, the triphenylphosphine acts as a 'nucleophilic trigger' and attacks the activated alkyne to give a vinylphosphonium zwitterionic intermediate **141**, which is then converted into a thermodynamically more stable vinylphosphonium **142**. The final γ-adduct **143** is generated after the conjugate addition of the nitrogen nucleophile followed by the proton transfer and the final elimination processes, and the catalytic cycle starts over again (Scheme 55).

Ley and coworkers devised a highly selective, organocatalytic route to 1,2-oxazines derivatives **146** from both aldehydes and ketones by using a chiral *N*-phenyl-*O*-alkylhydroxylamine intermediate **144**, which undergoes conjugate addition to a vinylphosphonium salt. The resulting intermediate ylide **145** cyclizes to form the 1,2-oxazines products via an intramolecular Wittig reaction (Scheme 56)[96].



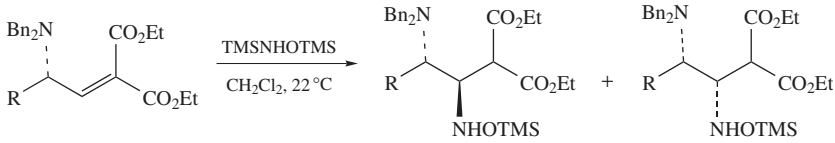
SCHEME 55



SCHEME 56

2. Diastereoselective conjugate addition of N,O-alkylhydroxylamines to chiral Michael acceptors

Reetz and coworkers reported in 1994 that enantiomerically pure γ-*N*,*N*-dibenzylamino-substituted α,β-unsaturated dicarboxylic acid esters **147** underwent smooth diastereoselective conjugate addition with *N*,*O*-bis(trimethylsilyl) hydroxylamine simply by stirring the reactants in dichloromethane at room temperature in the absence of any catalyst. The *anti*-adducts **148** were found to be predominant over the *syn*-adducts **149** (Scheme 57)[43].



(a) R = CH_3	60% yield	**148a/149a** = 95:5
(b) R = Bn	76% yield	**148b/149b** = 94:6
(c) R = *i*-Bu	65% yield	**148c/149c** = 91:9

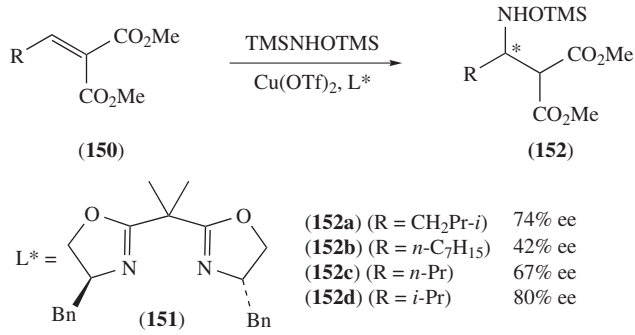
SCHEME 57

3. Asymmetric conjugate addition of N,O-disubstituted hydroxylamines using chiral Lewis acids or ligands

In 2002, Cardillo and coworkers reported the 1,4-addition of *N*,*O*-bis(trimethylsilyl) hydroxylamine to α,β-unsaturated malonates **150** in the presence of chiral Lewis acid to give 1,4-adduct **152**[97]. Good enantioselectivity was observed when the conjugate additions to isobutylidene and 3-methylbutylidene malonates were catalysed by [Cu (*S*,*S*)-Bn-(box), **151**](OTf)$_2$ [box = bis(oxazolinyl)] (Scheme 58). In comparison to *O*-benzylhydroxylamine used as the nucleophile, the bulkier *N*,*O*-bis(trimethylsilyl)hydroxylamine in the conjugate addition to α,β-unsaturated malonates gave better selectivity under the same reaction conditions.

E. Conjugate Addition of *N*,*N*′- Disubstituted Hydroxylamines (RR′NOH)

When the NH_2 group of hydroxylamine is disubstituted, the OH moiety may act as the nucleophilic site in conjugate addition. In 1959, Zinner reported that *N*,*N*′-dialkylhydroxylamines **153** underwent conjugate addition to α,β-unsaturated ketone,



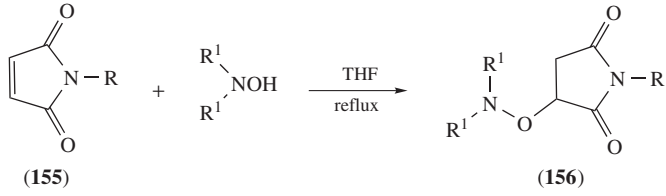
SCHEME 58

nitrile or ester to afford the corresponding *O*-alkylated products **154** (Scheme 59)[98]. Pastor and Hessell also reported in 1988 that conjugate addition of *N*,*N*′-dialkylhydroxylamines to maleimides **155** in THF under reflux gave the *O*-alkylated 1*H*-pyrrole-2,5-dione derivatives **156** (Scheme 60)[99]. The results of this study, together with those of Zinner, suggest that *O*-alkylation of *N*,*N*-dialkylhydroxylamines by an activated double bond is a general reaction and the *N*-alkylation is a fast reversible process.

$R^1R^2 = (CH_2)_5$; $R^1 = R^2 =$ Et

EWG = $COCH_3$, CN, CO_2Me, CO_2Et

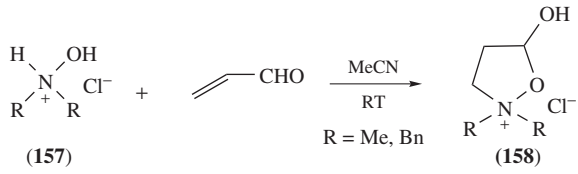
SCHEME 59



R = Ph, H, Me, *c*-hex, 1-octadecyl; R^1 = Bn, Et

SCHEME 60

In contrast, it has been reported that when the salts of *N*,*N*-dialkylhydroxylamine **157** reacted with acrolein in acetonitrile, 3-hydroxylpyrazolidinium salts **158** were obtained in good yields (Scheme 61)[100, 101]. The ^1H and ^{13}C NMR spectral data indicated that the products existed in the cyclic form. This process is likely to involve an initial conjugate addition of the nitrogen center of *N*,*N*-dialkylhydroxylamine to the α,β-unsaturated aldehyde, with a subsequent hemiacetalation.

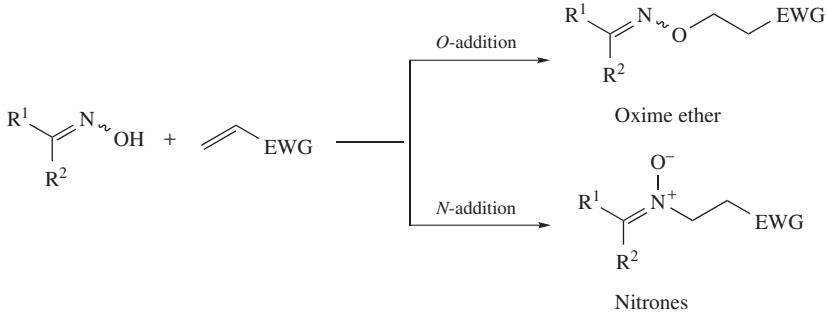


(**157**) (**158**)

SCHEME 61

IV. CONJUGATE ADDITION OF OXIMES

When ambient nucleophilic oximes are applied as donors in the conjugate addition reactions, both nitrogen and oxygen atoms can act as nucleophiles to afford the corresponding nitrones and oxime ethers, respectively, with the outcome products being controlled by the reaction conditions (Scheme 62). The nitrones can be applied in many 1,3-dipolar cycloaddition reactions, and the oxime ether obtained can be used in generating functionalized alcohols via reductive cleavage of the N−O bond.

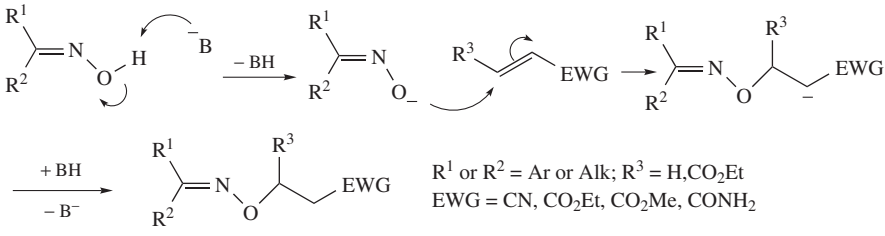


SCHEME 62

A. *O*-Centered Conjugate Addition of Oximes

1. General introduction

The conjugate addition of *O*-centered nucleophiles to electron-deficient olefins has proven a challenging problem in organic synthesis owing to the reversible addition process due to the weak oxygen nucleophiles. However, oximes offer a class of oxygen-containing nucleophiles that partially circumvent this problem. In the presence of a base, the hydroxyl group of an oxime can be deprotonated to give the corresponding oxime anion, which becomes a strong enough nucleophile and allows the conjugate addition reaction to the activated alkenes (Scheme 63) or alkynes. In the presence of NaOH or KOH[102–106], Et_3N[107] or *t*-BuOK[108], ketoximes or benzaldoxime could react with an acrylate to afford a series of β-aminoxypropanoates. For example, the conjugate addition of benzaldoxime to acrylonitrile can be realized with catalysis by KOH, $BnNMe_2OH$, NaOEt or NaOH under heating[109, 110] or microwave irradiation[111]. Bruson and Riener found that ketoximes such as acetone oxime, acetophenone oxime, benzoin oxime, dimethylglyoxime and furfuraldoxime can react with acrylonitrile to form oximino-*O*-cyanoethyl ethers in the presence of MeONa, Triton B or NaOH solution[112]. Newman and Junjappa reported

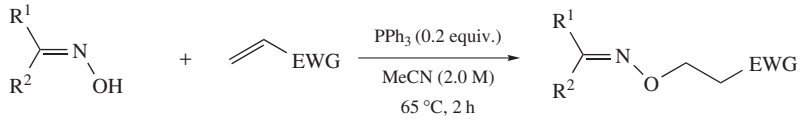


SCHEME 63

that the MeONa-catalyzed reaction of acetone oxime with dimethyl maleate produced dimethyl isopropylideneamine oxysuccinate in 50% yield[113]. The conjugate addition of octan-2-one oxime to acrylamide is also applicable upon treatment with methanolic KOH at 30–35 °C[114].

Bhuniya and coworkers reported in 2003 that triphenylphosphine could be applied as a milder base in a catalytic conjugate addition of oximes to activated olefins[115]. Various aldoximes and ketoximes react with different Michael acceptors such as ethyl acrylate, acrylonitrile, phenyl vinyl sulfone, methyl vinyl ketone, and 1-nitrocyclohex-1-ene, in the presence of 0.2 equivalents of triphenylphosphine in MeCN to obtain the corresponding Michael adducts (Scheme 64a). Phenyl vinyl sulfone was found to be the most reactive Michael acceptor. Interestingly, the conjugate addition of aldoxime **159** to 1-nitrocyclohex-1-ene gave the desired 1,4-adduct **160** in 72% as a mixture of *cis* and *trans* (70:30) isomers based on NMR analysis. However, under heating conditions, a lower yield (25%) of the desired 1,4-adduct **160** was obtained but with higher selectivity for the *trans* geometry (*cis:trans* = 10:90) (Scheme 64b). No reaction occurred in the absence of triphenylphosphine, which is understood to be crucial in the catalytic cycle to generate the oxime anion. They also found that catalyzed by triphenylphosphine, a variety of arylaldoximes and acetophenone oximes underwent conjugate addition to Baylis–Hillman

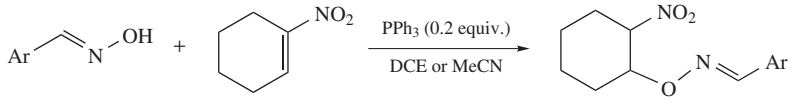
a



R^1 = Ar, Alk; R^2 =Me, H

EWG = CO_2Et, CN, SO_2Ph

b



(**159**)

Ar = 3-nitrophenyl

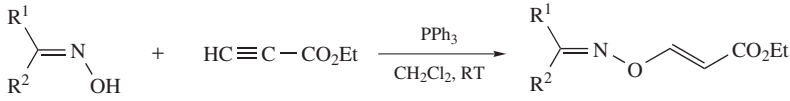
(**160**)

Conditions	Isolated yield	*cis* : *trans*
RT, 24 h	72%	70 : 30
65 °C, 1.5 h	25%	10 : 90

SCHEME 64

adducts, without touching any other functional groups. Unfortunately, many attempts of Michael addition to Baylis–Hillman adducts have led to destruction of the hydroxyl functionality via an elimination or dehydration process[116].

Yavari and Ramazani also used a catalytic amount of triphenylphosphine to realize the conjugate addition of ketoximes **161** to ethyl propiolate, which stereoselectively gave the corresponding *O*-vinyloximes **162** in good yields (70–73%) (Scheme 65)[117].

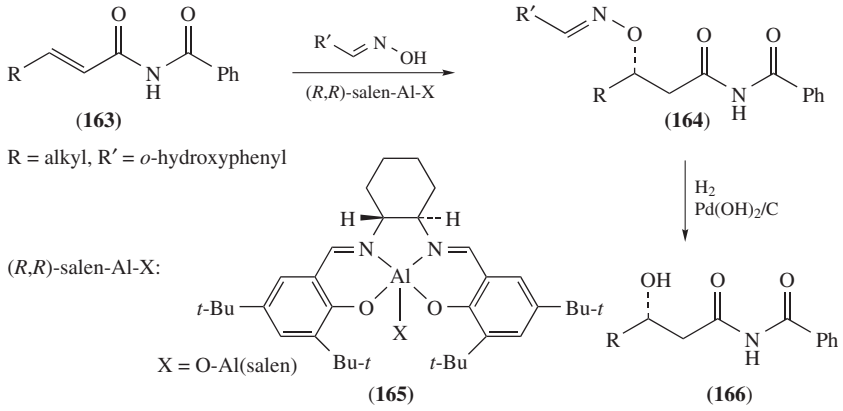


SCHEME 65

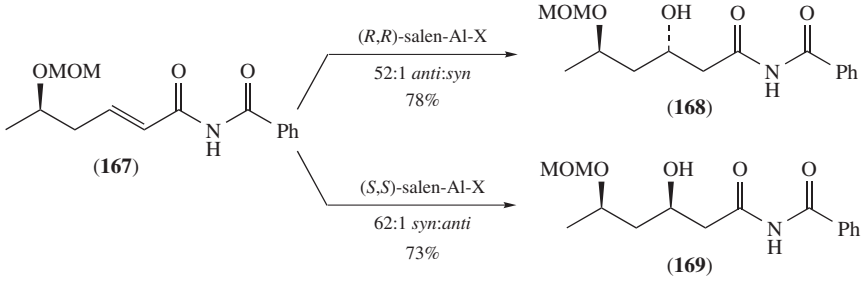
2. Asymmetric O-centered conjugate addition of oximes

In 2004, Vanderwal and Jacobsen reported a (salen)aluminum-catalyzed asymmetric conjugate addition of salicylaldoxime to α,β-unsaturated imide **163**, a process that enabled the synthesis of β-hydroxycarboxylic acid derivatives **164** with high levels of enantioselectivity. The application of 5 mol% μ-oxo dimmer catalyst [(*R*,*R*)-(salen)Al]$_2$O (**165**) effected the addition process with efficient conversion (up to 90%) and excellent enantioselectivity (up to 90% ee), with the ester, acetal and silyl ether functionalities being tolerated. Reductive cleavage of the oxime N−O bond affords the hydrogenation products **166** in high overall yields without affecting the optical purity (Scheme 66)[118]. A high level of diastereoselectivity can be achieved via a catalyst-controlled, two-step hydrogenation of the chiral α,β-unsaturated imide. For example, reaction of ethyl (*R*)-3-hydroxybutyrate-derived **167** in the presence of (*R*,*R*)- **165** led to highly selective formation of the 1,3-*anti* addition product **168**, and (*S*,*S*)- **165** delivered the 1,3-*syn* product **169** (Scheme 67).

Oximes can also undergo selective conjugate addition to α,β-unsaturated aldehyde, with no acetal formation. Jørgensen and coworkers reported a highly enantioselective

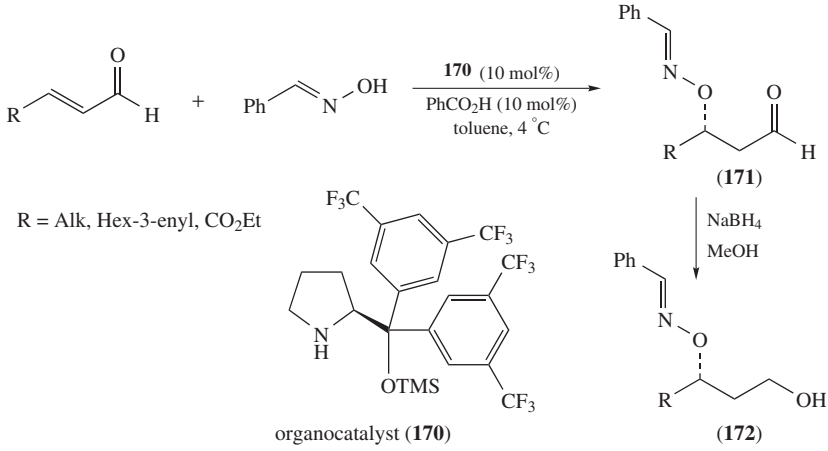


SCHEME 66



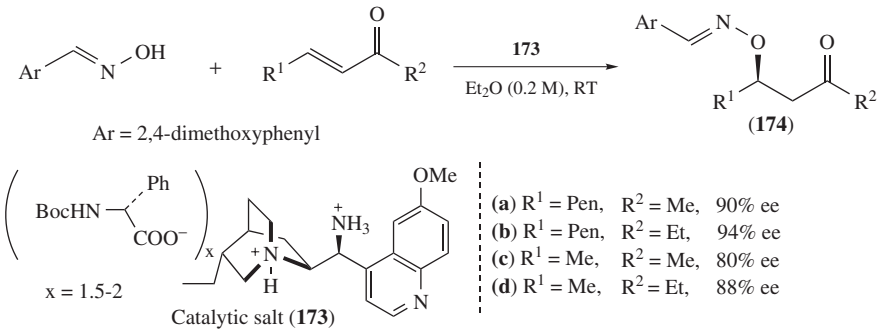
SCHEME 67

β-hydroxylation of α,β-unsaturated aldehyde via an organocatalytic conjugate addition of aromatic oximes and the subsequent reduction. In the presence of 10 mol% 2-[bis(3,5-bis(trifluoromethylphenyl))trimethylsilyloxymethyl]pyrrolidine **170** and 10 mol% $PhCO_2H$, the reaction of (*E*)-benzaldoxime with a series of α,β-unsaturated aldehydes in toluene at 4 °C conveniently afforded the 1,4-adducts **171** which, upon treatment with $NaBH_4$, gave optically active *O*-protected **172** in high yields (up to 75%) and excellent enantioselectivity (up to 95% ee) (Scheme 68)[119]. Feng and coworkers reported a similar oxa-Michael addition of 1-(4-methoxyphenyl) ethanone oxime to various α,β-unsaturated aldehydes by using chiral *N*,*N*′-dioxide–$FeSO_4 \bullet 7H_2O$ (1:1) complex in the presence of aromatic acid in toluene at 0 °C. The corresponding adducts were obtained in moderate yields with up to 76% ee[120].



SCHEME 68

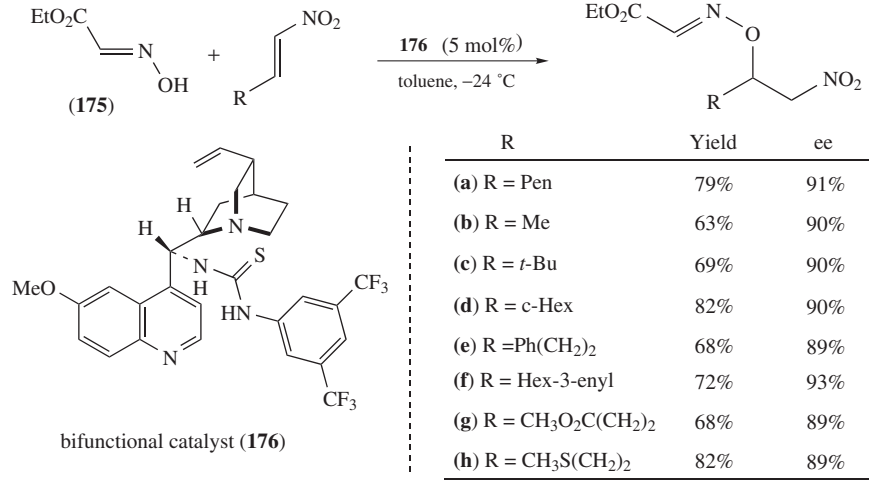
Melchiorre and coworkers reported an enantioselective organocatalytic conjugate addition of aromatic oximes to α,β-unsaturated ketones catalyzed by the primary salt **173**, in which both the cation and the anion are chiral. A survey of the catalytic salt composition revealed that a 1:1.5 ratio of 9-amino(9-deoxy)epihydroquinine to D-*N*-Boc-phenylglycine represented the best compromise between catalyst loading and catalytic efficiency. By this method, the optically active oxime addition products **174** were achieved in moderate-to-good yields with high enantioselectivities (up to 94% ee) (Scheme 69)[121].



SCHEME 69

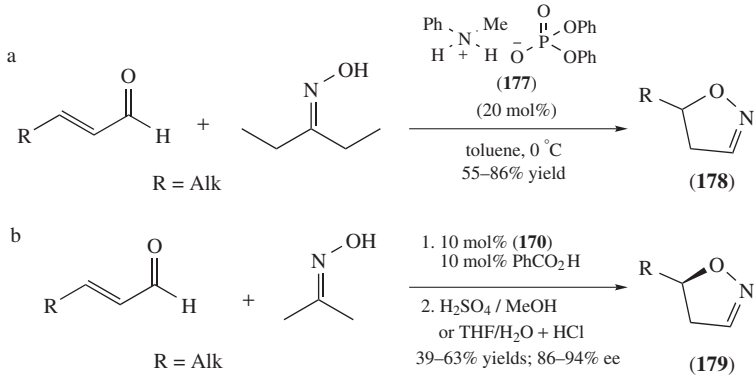
Oximes can be used as oxygen donors for the conjugate additions to nitroalkenes. Jørgensen and coworkers reported in 2007 a highly enantioselective addition of ethyl glyoxylate oxime **175** to various aliphatic nitroalkenes catalyzed by the bifunctional thiourea-cinchona alkaloids **176** in toluene at −24 °C (Scheme 70)[122]. The bifunctional catalyst **176** was expected to have the potential to activate both the oxime, by hydrogen bonding to the basic quinuclidine nitrogen atom, and the nitroalkene via the thiourea moiety as a Lewis acid. However, no reaction was observed under the same reaction conditions between (*E*)-benzaldoxime or acetone oxime with the aliphatic nitroalkene, (*E*)-1-nitrohept-1-ene.

Pohjakallio and Pihko reported in 2008 that 5-substituted-2-isoxazolines **178** could be prepared from aliphatic α,β-unsaturated aldehydes and uncrowded oximes in the presence of an anilinium salt catalyst **177** in toluene at 0 °C (Scheme 71a)[123]. One proposed reaction mechanism involves an initial iminium-catalyzed conjugate addition of oxime to the α,β-unsaturated aldehyde followed by cyclization which proceeds through hydrolysis



R	Yield	ee
(a) R = Pen	79%	91%
(b) R = Me	63%	90%
(c) R = *t*-Bu	69%	90%
(d) R = c-Hex	82%	90%
(e) R =Ph$(CH_2)_2$	68%	89%
(f) R = Hex-3-enyl	72%	93%
(g) R = $CH_3O_2C(CH_2)_2$	68%	89%
(h) R = $CH_3S(CH_2)_2$	82%	89%

SCHEME 70



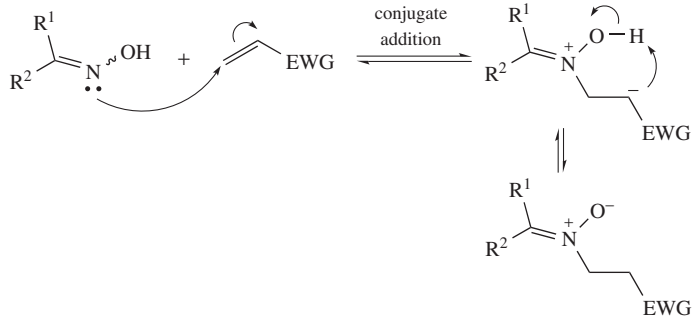
SCHEME 71

of the formed *O*-alkyloxime. In another study, the same group strongly suggested such a two-stage approach based on some delicately designed control experiments. Adopting a modified Jørgensen oxime conjugate addition protocol, they realized an asymmetric synthesis of 2-isoxazolines **179** by an enantioselective conjugate addition and a rapid subsequent quench reaction with a strong acid (Scheme 71b)[124]. The process provides the desired products in moderate yields but high enantioselectivities with catalytic amounts of **170** and $PhCO_2H$ in toluene at 0 °C for 3.5 h.

B. *N*-Centered Conjugate Addition of Oximes

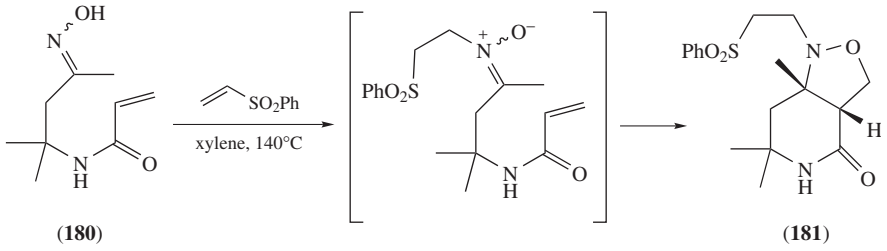
1. General introduction

In the absence of a base catalyst, the *N*-center in an oxime is, as expected, of higher nucleophilicity than the *O*-center. Thus the *N*-centered conjugate additions of oximes, via the nitrogen lone pair to a suitable Michael acceptor, proceed to produce nitrones (now known as Grigg's nitrone generation) (Scheme 72)[125, 126], which undergo further inter- or intramolecular 1,3-dipolar cycloaddition reactions. The Michael acceptors include α,β-unsaturated aldehyde[16], ketones[16, 127], carboxylic esters, sulfones[128], sulfoxide[129],



SCHEME 72

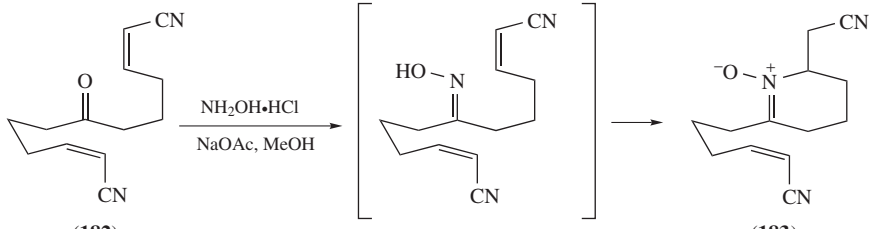
amides[130], imides[127], phosphine oxide[131] and acrylonitrile[130]. Generally, such nitrone formation/1,3-dipolar cycloaddition reaction can occur under reflux conditions in toluene, xylene or benzene in the absence of any catalyst. For example, a 65:35 mixture of stereoisomers of oxime **180** reacts with phenyl vinyl sulfone on reflux in xylene (140 °C) to give the bicyclic compound **181** in quantitative yield (Scheme 73)[125].



(**180**) (**181**)

SCHEME 73

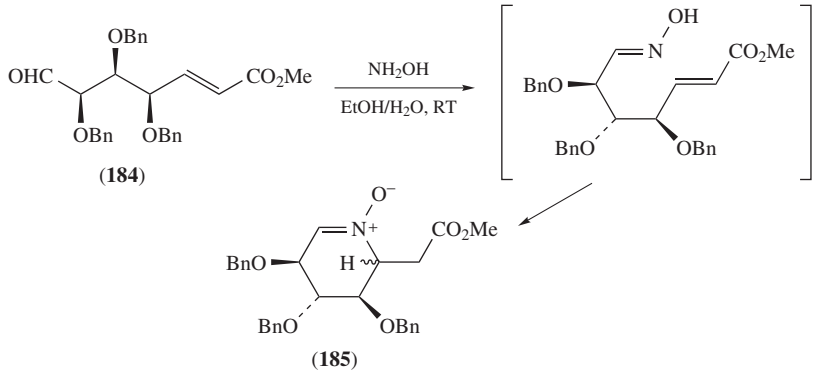
An intramolecular *N*-centered conjugate addition of oxime produces cyclized nitrones. For example, treating ketone **182** with 1.2 equivalents of NH_2OH•HCl in the presence of 2 equivalents of NaOAc in MeOH produced cyclized nitrone **183**, which is presumably formed by oxime formation and subsequently followed by an intramolecular conjugate addition to one of the α,β-unsaturated nitriles, and finished up with a 1,4-proton shift (Scheme 74)[132–134]. Heating the crude nitrone **183** led to the formation of interesting tricyclic compounds via intramolecular [3+2] cycloaddition. In another example, when NH_2OH was added to an α,β-unsaturated ester bearing a terminal aldehyde group **184** in ethanol–water mixture at room temperature, a diastereomeric mixture of the nitrone **185** was formed (Scheme 75)[135].



(**182**) (**183**)

SCHEME 74

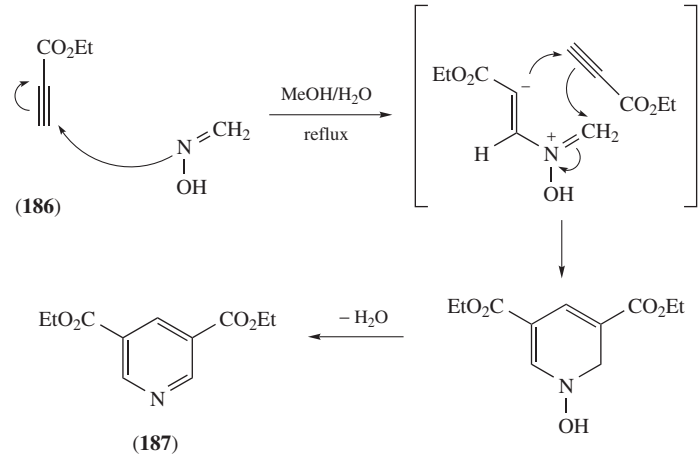
Examples of *N*-centered conjugate addition of oximes to electronegative alkynes are found in previous literature. Ochiai and coworkers reported that heating a mixture containing overdosed ethyl propiolate **186** and trimeric formaldoxime in MeOH/H_2O (1:1) for 4 h gave 3,5-diethoxycarbonylpyridine compounds **187**. This process can be understood as an initial *N*-centered conjugate addition of the oxime, succeeded by an intermolecular 1,4-dipolar cycloaddition and a final dehydration step (Scheme 76)[136].



(**184**)

(**185**)

SCHEME 75

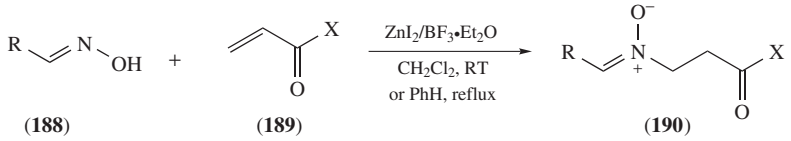


(**186**)

(**187**)

SCHEME 76

The *N*-centered conjugate additions of oximes to α,β-unsaturated carbonyl compounds can be carried out at much lower temperature if the reaction is conducted in the presence of a Lewis or Brønsted acid, since the electrophilicity of the Michael acceptors is to be greatly enhanced via coordination under such conditions. Kanemasa and coworkers reported that the combination of two Lewis acid catalysts, $ZnI_2/BF_3{\bullet}Et_2O$ (50 mol%/50 mol%), conveniently catalyzed the conjugate addition of aldoximes **188** to α,β-unsaturated carbonyl compounds **189** at room temperature to form *N*-alkylnitrones **190** in good yields (79–100%) (Scheme 77)[137]. Not only the bidentate acceptor 3-acryloyl-2-oxazolidinone, but also the monodentate acceptors such as 3-buten-2-one, methyl acrylate and acrolein, can be successfully employed. 3-Acryloyl-2-oxazolidinone was found to be the most reactive acceptor and 3-buten-2-one highly reactive under the catalyzed conditions. On the other hand, methyl acrylate is among the least reactive acceptors such that heating under reflux is necessary to complete the reaction. As for aldoximes, the heteroaromatic



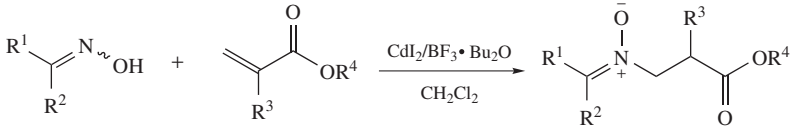
(**188**) (**189**) (**190**)

R = Ph, *p*-MeOC$_6$H$_4$, *p*-MeC$_6$H$_4$, 2-thienyl, 2-Fu, (*E*)-PhCH=CH
(*E*)-MeCH=CH, *n*-C$_7$H$_{15}$, *t*-Bu; X = Me, OMe, H, 2-oxo-3-oxazolidinyl

SCHEME 77

aldoximes are more reactive than benzaldoxime and its *p*-substituted derivatives. However, reactions involving ketoximes such as benzophenone oxime and fluorenone oxime were totally sluggish, and are therefore not considered applicable to the method.

Kurbanli and coworkers reported that the conjugate addition of pyridinecarboxaldehyde oximes, methyl pyridyl ketone oximes, furfural oximes, cinnamaldehyde oxime and crotonaldehyde oxime to acrylate and methacrylate in the presence of a 1:1 mixture of CdI_2 and BF_3•Bu_2O as Lewis catalyst at room temperature gave the corresponding alkyl nitrones in good yields (62–100%) (Scheme 78)[138]. It was found that methyl acrylate was the most reactive acceptor among those including methyl methacrylate, ethyl acrylate, ethyl methacrylate and isopropyl acrylate.

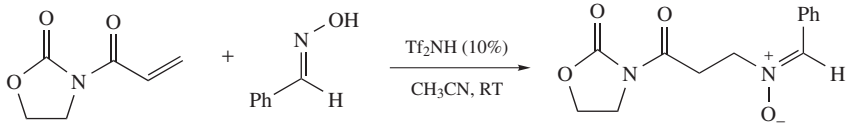


R^1 = R^3 = H or Me; R^2 = Pyr, Fu, PhCH=CH, MeCH=CH

R^4 = Me, Et, *i*-Pr

SCHEME 78

Spencer and coworkers found that a Brønsted acid such as Tf_2NH could also be an active catalyst in the conjugate addition of benzaldehyde oxime to α,β-unsaturated imide **191**. The reaction was conducted in 10% Tf_2NH in acetonitrile for 10 h at room temperature to give the nitrone product **192** in 87% yield (Scheme 79)[139]. In another study, they reported that the conjugate addition of benzaldehyde oxime to (*E*)-1-phenylpent-2-en-1-one catalyzed by $Cu(OTf)_2$ (10 mol%) in acetonitrile at room temperature conveniently generated the nitrone product in 70% yield[140].

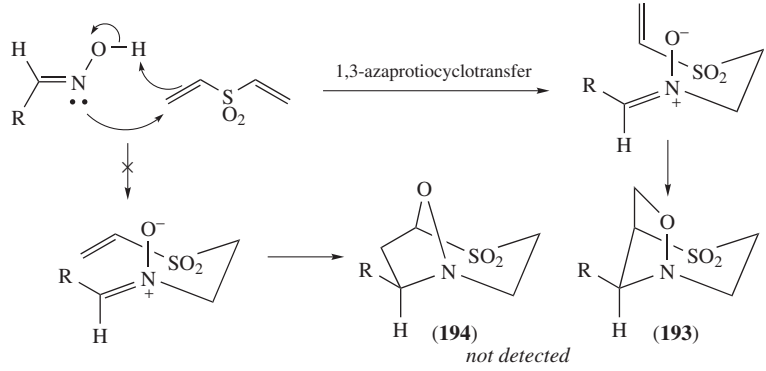


(**191**) (**192**)

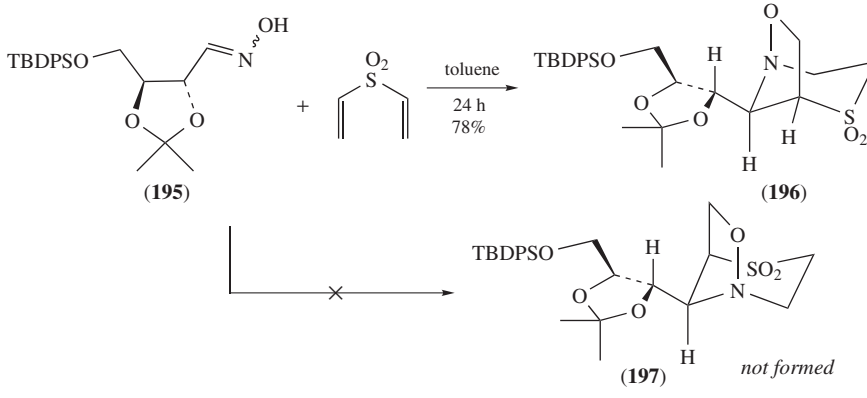
SCHEME 79

2. Regioselective and stereoselective N-centered conjugate addition/ cycloaddition of oximes

Grigg and coworkers found that oximes could react both regio- and stereo-specifically with various dienes bearing electronegative substituents via a tandem Michael addition/1,3-dipolar cycloaddition process to give bridged ring cycloadducts[141]. For example, they discovered that the reaction sequence of various oxygenated aldoximes with divinyl sulfone involves a tandem nitrone formation/1,3-cycloaddition reaction, which regiospecifically affords the 1-aza-7-oxa-4-thiadioxybicyclo[3.2.1]octane rings **193**, without the detection of any other isomeric bicyclic compounds such as **194** (Scheme 80)[142, 143]. The nitrone formation was denoted by Grigg to be a 1,3-azaprotiocyclotransfer (APT) process, but was also apprehended by others as a sequence of conjugate additions of oxime to the diene sulfone with the subsequent proton shift[144]. The application of chiral oxygenated aldoxime with a stereogenic center located α- to the oxime moiety produces the cycloadduct with high diastereoselectivity. For example, L-threose derived aldoxime **195** reacted cleanly with divinyl sulfone over 24 h at 110 °C in toluene to afford a single cycloadduct **196** (de 100%) with none of the isomeric cycloadduct **197** being formed (Scheme 81)[143].

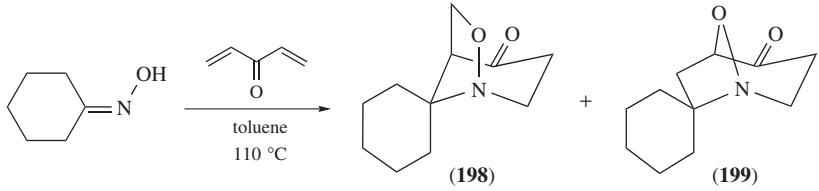


SCHEME 80



SCHEME 81

The reaction between a ketoxime and divinyl ketone follows a similar nitrone formation/1,3-cycloaddition process. However, both 1-aza-7-oxabicyclo[3.2.1]octan-4-one and its isomeric 1-aza-8-oxabicyclo[3.2.1]octan-4-ones were produced. For example, the reaction between cyclohexanone oxime and divinyl ketone (toluene, 110 °C, 16 h) afforded a 1:2 mixture of cycloadducts **198** and **199** in a total of 72% yield. Interestingly, treatment of the same two reactants in the presence of anhydrous zinc bromide (1.5 equivalents) in boiling THF predominantly gave **198** (97% yield, **198**:**199** = 97:3) (Scheme 82)[145].

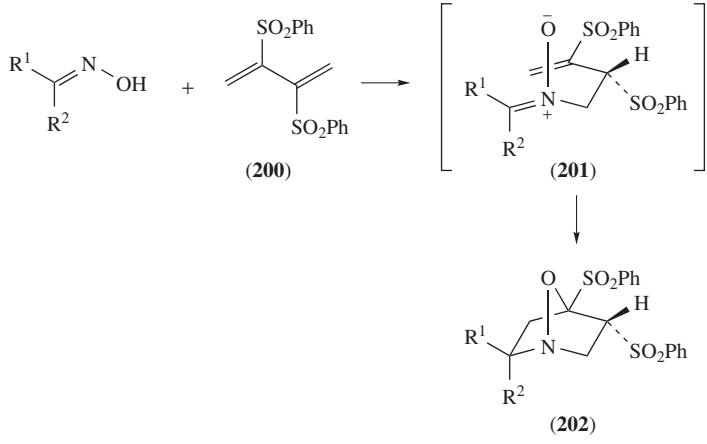


SCHEME 82

The reaction of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene **200** stereoselectively affords 7-oxa-1-azanorbornanes **202** in high yields. The first step in the cascade sequence was shown to involve conjugate addition to the diene, followed by proton transfer to create a transient nitrone **201**, which undergoes a subsequent intramolecular 1,3-dipolar cycloaddition with the tethered vinyl sulfone (Scheme 83)[146]. Such transformation has been applied in several total syntheses of natural products[147–149].

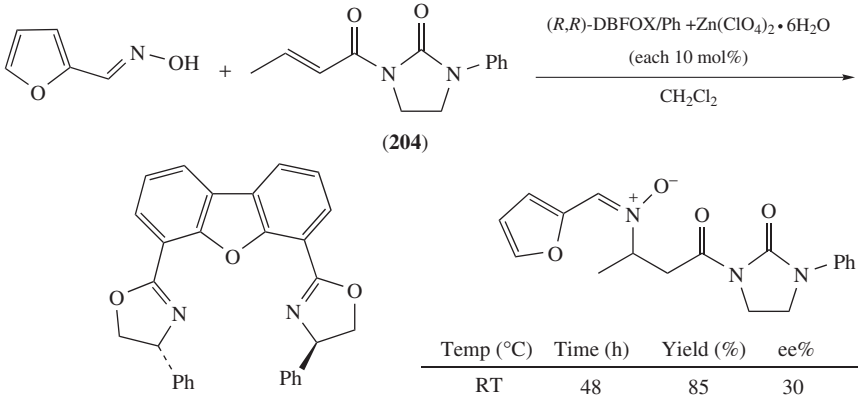
3. Asymmetric N-centered conjugate addition of oximes

The asymmetric formation of nitrones via the conjugate addition of oximes to α,β-unsaturated carbonyl compounds is also operative. Kanemasa and coworkers reported



SCHEME 83

that the aqua complex, derived from (*R*,*R*)-DBFOX/Ph **203** and zinc(II) perchlorate hexahydrate, is an active chiral catalyst for the enantioselective conjugate addition reactions of aldoximes with acceptor substrates containing β-substituents **204** (Scheme 84)[150]. However, the enantioselectivities are only modest in most cases, with the best results reaching up to 64–67% ee.



Temp (°C)	Time (h)	Yield (%)	ee%
RT	48	85	30
0	72	65	64
–40	72	4	67

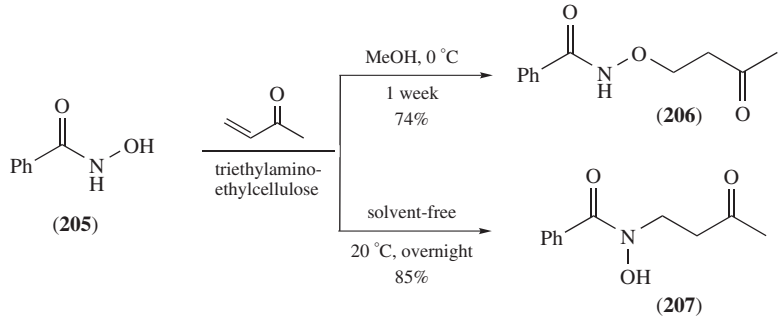
SCHEME 84

V. CONJUGATE ADDITION OF HYDROXAMIC ACIDS

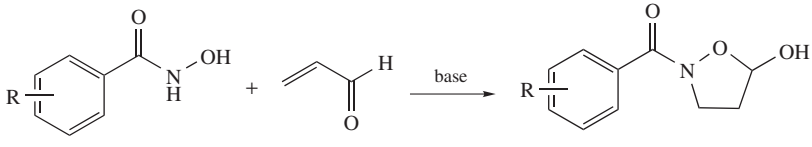
Hydroxamic acids are compounds in which a hydroxylamine replaces the OH group in a carboxylic acid. Literature survey indicates that the conjugate addition of hydroxamic acids has not yet been widely studied. Bezhan and coworkers studied the reaction of benzohydroxamic acid **205** with methyl vinyl ketone and found that both *O*-centered and *N*-centered conjugate additions of benzohydroxamic acid may occur, the preference of which depends on the reaction conditions. The reaction of **205** with methyl vinyl ketone in the presence of basic triethylaminoethylcellulose in MeOH, after standing at 0 °C for a week, gave the *O*-adduct, i.e. 4-(benzamidoxy)-2-butanone **206**, in 74% yield. However, if the same reaction was carried out without a solvent (both reagents were applied to a larger amount of diethylaminoethylcellulose) at 20 °C overnight, the *N*-isomer **207** was achieved in 85% yield (Scheme 85)[151].

The reaction of substituted benzohydroxamic acids **208** with acrolein was reported to give isoxazolidin-5-ols **209** in the presence of triethylaminoethylcellulose or diethylaminoethylcellulose, possibly via a hemiacetalation of the 1,4-adduct (Scheme 86)[30].

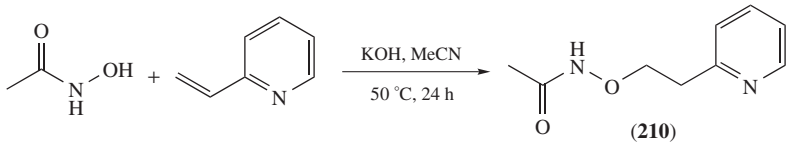
Alunni and Busti reported that the reaction of acetohydroxamic acid (3 equivalents) with 2-vinylpyridine in the presence of KOH in acetonitrile gave *N*-(2-(pyridin-2-yl)ethoxy)acetamide **210** in *ca* 9% yield (Scheme 87)[152]. This process can be perceived as conjugate addition of a hydroxamic acid to an alkene attached to an electron-withdrawing pyridinyl group.



SCHEME 85



SCHEME 86



SCHEME 87

VI. CONCLUSIONS

To summarize, conjugate addition of hydroxylamine and its derivatives, oximes and hydroxamic acids is a convenient way to incorporate an N−O moiety into various Michael acceptors. Hydroxylamine derivatives predominantly undergo *N*-centered conjugate addition, while for the ambient nucleophilic oximes and hydroxamic acids, both *N*-centered and *O*-centered conjugate addition are operative by control of the reaction conditions. A concerted cycloaddition mechanism has been established for the conjugate addition of *N*-substituted hydroxylamines. The last decade has witnessed enormous growth in enantioselective conjugate addition of hydroxylamine derivatives and the *O*-centered oximes. Seeking efficient catalysts that are more reactive, highly enantioselective and more economic is seen to be an ongoing research interest for organic chemists. Furthermore, additional studies are necessary for the asymmetric *N*-centered conjugate addition of oximes, as well as for the chemoselectivity and enantioselectivity of hydroxamic acid derivatives.

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Heterocycles from hydroxylamines and hydroxamic acids

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I. INTRODUCTION

Hydroxylamines and the related hydroxamic acids **1** are polyfunctional organic molecules and several reactive intermediates can be generated from them (Scheme 1). Therefore,

[†]Edmunds Lukevics passed away on November 21, 2009.

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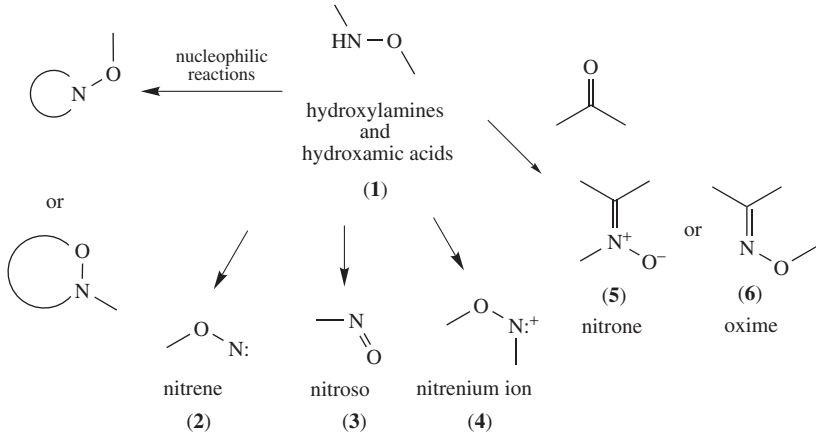
they are versatile substances for application in synthesis of diverse types of heterocycles. Firstly, hydroxylamine moiety is an N and O nucleophile, so it can serve as a starting material for the introduction of an N−O fragment in heterocycles by means of intra- or intermolecular nucleophilic substitution or addition reactions. Oxidation of hydroxylamines and hydroxamic acids **1**, depending on the procedure and the substitution pattern, generates nitrene **2**, nitroso **3** or nitrenium ion **4** species that can undergo different kinds of addition reactions with formation of heterocycles. Reactions of the title molecules with carbonyl compounds generate nitrones **5** or oximes **6**. The synthesis of heterocycles from oximes was recently reviewed[1]. Finally, the presence of a relatively lower energy N−O bond gives the ability of compounds **1** to rearrange to heterocyclic products via cleavage of the N−O bond and formation of new, stronger bonds[2].



SCHEME 1

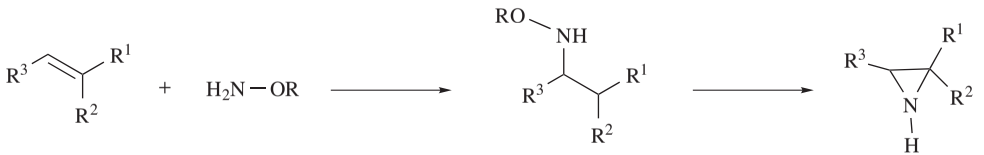
Since the formation of heterocycles can involve several intermediates and processes mentioned above, the present review was arranged according to the size and type of heterocycles.

The aim of this review is to demonstrate applications of hydroxylamines and hydroxamic acids for syntheses of different heterocyclic compounds, rather than to present an exhaustive coverage of the subject. Therefore, the syntheses where the formed heterocycle does not include an N or O atom from the starting hydroxylamine function (for example, the use of Weinreb amides as a carbonyl source) as well as processes with isolation of intermediates such as **3**, **5** or **6** are beyond the scope of this account.

II. THREE-MEMBERED RINGS

Hydroxylamine derivatives having an electron-withdrawing group at the β-position are versatile starting materials for aziridine synthesis (Scheme 2)[3–20]. Compounds **9** are easily available from the electrophilic alkenes **7** by addition reaction of hydroxylamines **8** and can be obtained also in highly optically pure form if chiral auxiliaries[3–7] or chiral Lewis acids[8–11] are applied.

The base-induced cyclization of hydroxylamine derivatives **9** provides aziridines **10** generally in high yields. *t*-BuONa[9–11,17], *t*-BuOK[12,13,16], MeONa[15,17–20], NEt_3 alone[14]



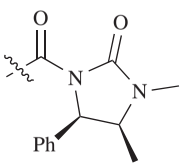
(**7**) (**8**) (**9**) (**10**)

R = Bn;
R^2 = H; R^3 = Me, Et, Pr, $CH_2CH(CH_3)_2$, $(CH_2)_5Ph$, Ph, 4-$PhOC_6H_4O$

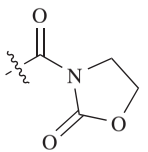
R = Bn; R^2 = H

R = Me, Bn; R^2 = H;
R^3 = $CH_2CH_2CH{=}CH_2$, *t*-Bu, *i*-Pr, $CH_2CH(CH_3)_2$, CH_2CH_2Ph, Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-NCC_6H_4, 4-$O_2NC_6H_4$

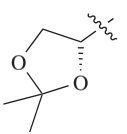
R^1 =



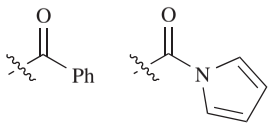
R^1 =



R^3 =

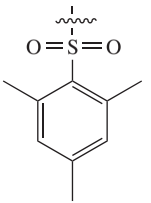


R^1 =



R = Mst
R^1, R^2, R^3= CO_2Me or CN

Mst =

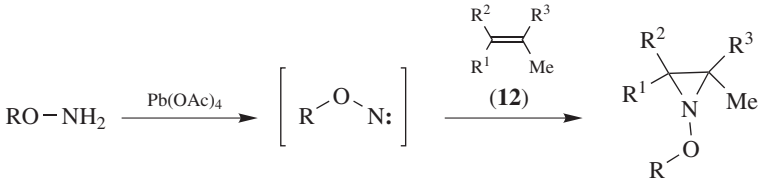


R = TMS; R^1, R^2 = CO_2Me;
R^3 = *n*-Pr, *n*-Hex, *i*-Pr, $CH_2CH(CH_3)_2$

SCHEME 2

(R = Mst) or in combination with $AlMe_2Cl$[5, 7] or $TiCl_4$ [3, 4, 6, 7, 11] and La(OPr-*i*)$_3$ [8, 9, 17] are used for this transformation. Since cyclization proceeds with *trans* selectivity, configuration of the newly created stereogenic center at α-position to the electron-accepting group is determined by the absolute configuration of hydroxylamine **9**. If enantiopure starting materials **9** were used, aziridines **10** were obtained in excellent diastereoselectivity. Such optical active aziridines are useful precursors for various amino acid or β-lactam derivatives with medical or biological importance.

Two methods are reported for the synthesis of *N*-oxyaziridines from hydroxylamines **8**. One of them involves formation of nitrene species **11** by oxidation with $Pb(OAc)_4$ in the presence of alkenes **12** (equation 1)[21–23]. The yields of *N*-oxyaziridines **13** are in range 9–35%. Analytically pure products **13** were obtained by preparative gas chromatography. The stereoisomers of 1-alkoxy-2,2,3-trimethylaziridines (**13**, $R^1 = R^2 = Me$, $R^3 = H$) that possess stable pyramidal configuration at nitrogen atom were separated by the same method[22, 23].



(1)

(**8**) (**11**) (**13**)

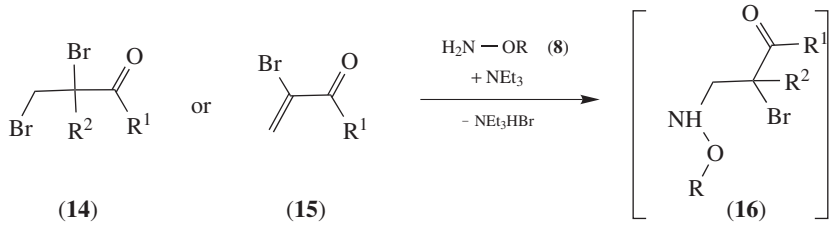
R = Me, Et, *i*-Pr; R^1, R^2, R^3 = H or Me 9–35%

The other method is based on the so-called Gabriel–Cromwell reaction of 2,3-dihalopropionic or 2-bromoacrylic acid derivatives with amines[24]. For example, a series of *N*-oxyaziridines **17** were obtained by treatment of dibromo derivatives **14** or 2-bromoacrylates **15** with hydroxylamines **8** in the presence of triethylamine in refluxing acetonitrile (equation 2)[25–27]. Intermediates like **16** were isolated if the reactions were performed at room temperature. Therefore it can be assumed, at least for bromides **14** bearing an electron-withdrawing group and an α-hydrogen atom ($R^2 = H$), that the first step of the process is elimination of the β-bromine atom following by 1,2-addition of hydroxylamine to the formed double bond.

Derivatives of β-bromo- or β-chlorohydroxylamine **18**, available from the corresponding α-haloalcohols[28] or ketones[29], were also successfully cyclized to *N*-oxyaziridines **19** under phase-transfer catalysis[28] or in the presence of sodium hydride in DMF[29] (equation 3).

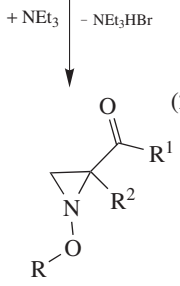
Generally, oxaziridines are synthesized from the corresponding imines by oxidation or electrophilic amination of carbonyl compounds by treatment with *N*-chloroalkylamines[30, 31]. However, some examples of the direct synthesis of oxaziridines from hydroxylamines and hydroxamic acids are reported[32–36].

It seems that the reaction between hydroxamic acids **20** and methyl propiolate in the presence of a catalytic amount of 4-methylmorpholine is most suitable for a preparative purpose (equation 4)[36]. The authors claimed that *N*-acyloxaziridines **21** were formed in good to excellent yields. However, formation of dioxazole from the same starting materials under the same reaction conditions was also reported[37].



(**14**) (**15**) (**16**)

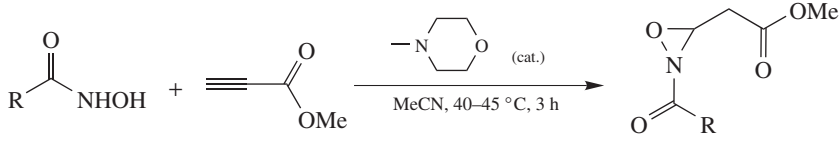
R = Et, Me, *i*-Pr, Bn;
R^1 = Alk, NH_2, NHAlk, SMe;
R^2 = H, CO_2Alk



(**17**) (2)

(**18**) (**19**) (3)

X = Cl, Br; R = H, Me, Ph, Bn; R^1 = Me, CO_2Alk; R^2 = H, CN; R^3 = Me, Ar



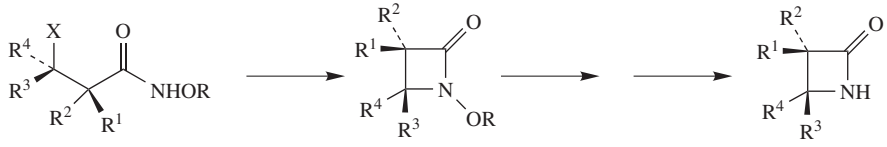
(**20**) (**21**) (4)

R = Alk, Ar, vinyl 86–95%

III. FOUR-MEMBERED RINGS

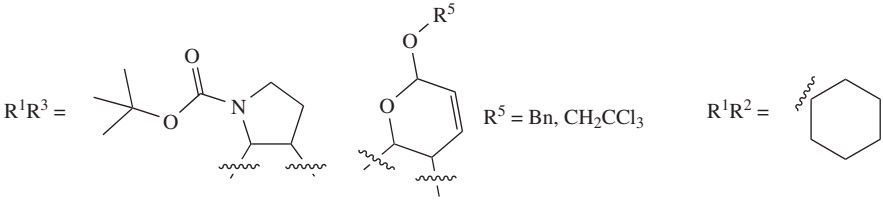
A. Azetidines

The hydroxamate approach for the synthesis of β-lactams **24** (Scheme 3), developed by M. J. Miller's[38–64] and the Squibb[65, 66] groups, is now widely used for the preparation of a broad scope of antibiotics[39, 43, 45, 46, 56–61, 65–81] and amino acid derivatives[63, 64, 81–86]. Since the NH bonds of *O*-alkyl- or acylhydroxamic acids **22** have pKa values of 6–10[87], they can be alkylated under mild conditions in the presence of other amide or carbamate functions. On the other hand, *O*-alkyl or *O*-acyl moieties serve as protecting group of the β-lactam NH and can be easily removed by hydrogenolysis[42, 44, 68, 76, 79, 88–90] on Pd/C, followed by treatment with $TiCl_3$ (**23**, R = Bn) or by alkali metal (Li, Na, Ca) reduction[66, 70, 71, 73, 74, 80, 82, 91] (**23**, R = Me).



(**22**) (**23**) (**24**)

X = OH, Cl, Br, SEt, SPh, SBn;
R = Me, Bn, All, Ac, Cbz, CH_2COAlk;
R^1 = H, Alk, F, acylamino, oxycarbonylamino, 2-oxo-4, 5-diphenyloxazol-3-yl;
R^2 = H, Alk, F, siloxy;
R^3 = H, Alk, cycloalkyl, Ph, $ArCH_2$, All, ethynyl, CO_2Alk, $CONH_2$;
R^4 = H, CO_2Alk

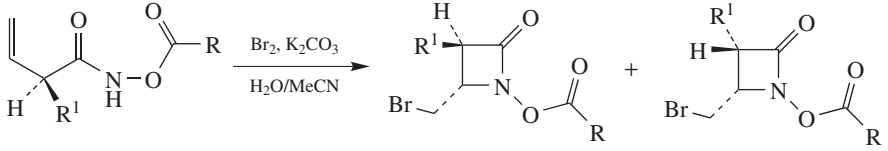


Cbz = benzyloxycarbonyl

SCHEME 3

β-Hydroxyhydroxamates **22** (X = OH) were cyclized to azetidin-2-ones **23** under Mitsunobu reaction conditions (PPh_3, with combination of diazocarboxylates [39, 40, 42, 43, 45–48, 51, 53–56, 58–62, 69, 72, 76, 77, 79–85, 88, 89, 92–94, 96] or CCl_4/NEt_3 [39, 43, 45, 57, 63, 64, 67 84, 95, 96, 99]) or by conversion of the hydroxyl group to mesylate[44, 46, 52, 65, 66, 68, 70, 71, 73, 74, 82 91, 92, 97] or triflate[86] followed by ring closure in the presence of K_2CO_3 [46, 65, 66, 68, 70, 71, 73 74, 82, 91], *t*-BuOK[44], NEt_3 [52] or NaH[92, 97]. β-Chloro[39, 41, 90, 98, 99] and β-bromo[97, 98] derivatives of hydroxamates **22** (X = Cl or Br) yielded azetidin-2-ones **23** in the presence of NaH[39, 41, 97, 98], DBU[90] or CsF/$BnEt_3NCl$[99]. *S*-Alkylation of sulfides **22** (X = SEt, SPh, SBn) with methyl iodide in the presence of $AgClO_4$ followed by treatment of the resulting sulfonium salts with K_2CO_3 afforded β-lactams **23** with high stereoselectivity[75, 78, 100, 101].

β,γ-Unsaturated acylhydroxamates **25** were converted to 4-bromomethylazetidin-2-ones **26** by treatment with Br_2/K_2CO_3 under carefully controlled condition (equation 5)[49, 50]. Alkyl-substituted hydroxamates **25** favored the formation of *trans* β-lactams, benzyl derivative **26** (R = BnO, R^2 = Bz) was obtained as a single enantiomer and a *trans*-**26**/*cis*-**26** ratio for R^1 = Me was 77 to 23. In contrast, cyclization of the 2-benzyloxycarbonylamino derivative (**25**, R^1 = CbzNH) proceeded with a reversed selectivity (*trans*-**26**/*cis*-**26** = 30/70)[50].

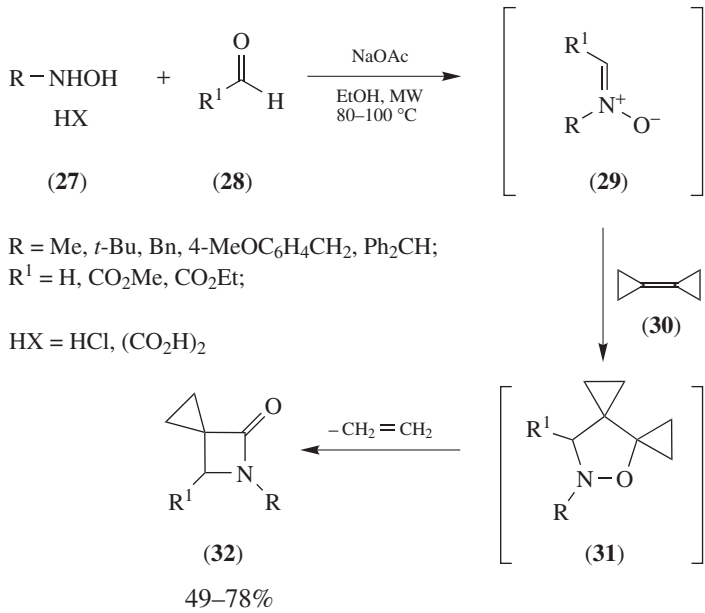


(**25**) *trans*-(**26**) *cis*-(**26**)

75–90%

R = Me, *i*-Pr, *t*-Bu, OBn;
R^1 = H, Me, Bn, CbzNH (5)

A one-pot three-component reaction for the direct conversion of certain alkylhydroxylamines **27**, formaldehyde (**28**, R^1 = H) or alkyl glyoxalates (**28**, $R^1 = CO_2Me$ or CO_2Et) and bicyclopropylidene (**30**) to 3-spirocyclopropanated azetidinones **32** was reported (equation 6)[102]. Presumably, the nitrones **29** initially formed from compounds **27** and **28** had undergone 1,3-dipolar cycloaddition to cyclopropylidene **30**. The resulting isoxazolidines **31** rearranged to β-lactams **32** through homolytical N−O bond cleavage and elimination of ethylene.

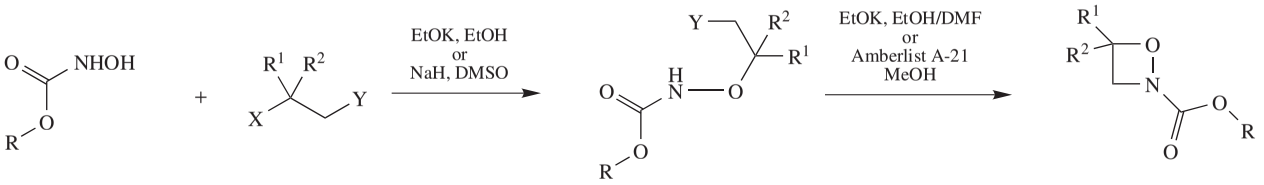


(**27**) (**28**) (**29**) (**30**) (**31**) (**32**)

R = Me, *t*-Bu, Bn, 4-$MeOC_6H_4CH_2$, Ph_2CH;
R^1 = H, CO_2Me, CO_2Et;

HX = HCl, $(CO_2H)_2$ (6)

49–78%



(**33**) (**34**) (**35**) (**36**)

X = Br; R = Et; R^1, R^2 = H; Y = OH 28%
X = I; R = *t*-Bu; R^1 = Me; R^2 = CO_2Me;
Y = 1-ethoxyethyl 61%

38%

Y = Br; R = Et; R^1, R^2 = H 47%
Y = MsO; R = *t*-Bu; R^1 = Me;
R^2 = CO_2Me 53%

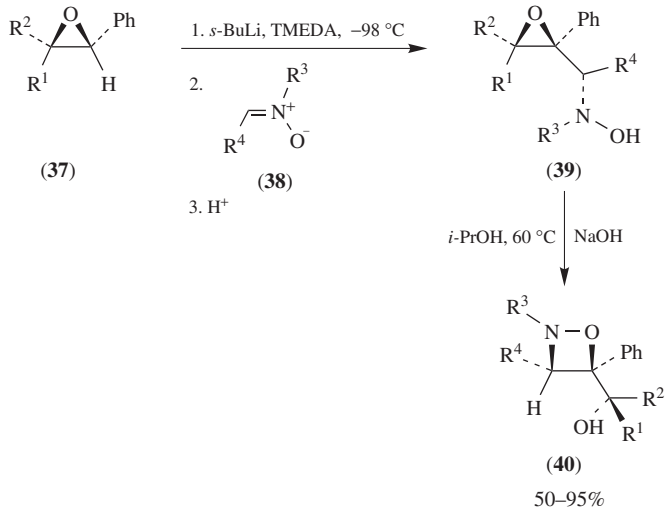
Ms = methanesulfonyl

SCHEME 4

B. Oxazetidines

1,2-Oxazetidines **36** can be obtained in the 'double alkylation' procedure from the hydroxylamine carbamate derivatives **33** (Scheme 4)[103, 104]. Initially, potassium (R = Et) or sodium (R = *t*-Bu) salts of hydroxycarbamates (**33**) were treated with substituted bromo- (R^1, R^2 = H) or iodo- (R^1, R^2 = Me) ethanes (**34**) bearing hydroxyl or 1-ethoxyethyl groups. Thereafter, the hydroxyl functions of the intermediates **35** were converted to bromide or mesylate followed by an intramolecular cyclization to the target 1,2-oxazetidines **36**.

Recently the stereoselective synthesis of 4-hydroxyalkyl-1,2-oxazetidines **40** was reported (Scheme 5)[105]. The precursor β,γ-epoxyhydroxylamines **39** were obtained with an excellent diastereoselectivity from the enantiopure epoxides **37** in a one-pot procedure by lithiation followed by the reaction with the nitrones **38**. Subsequent treatment with NaOH in *i*-PrOH led to the formation of oxazetidine **40**, which is the result of 4-*exo-tet* intramolecular cyclization promoted by oxirane ring opening[105].

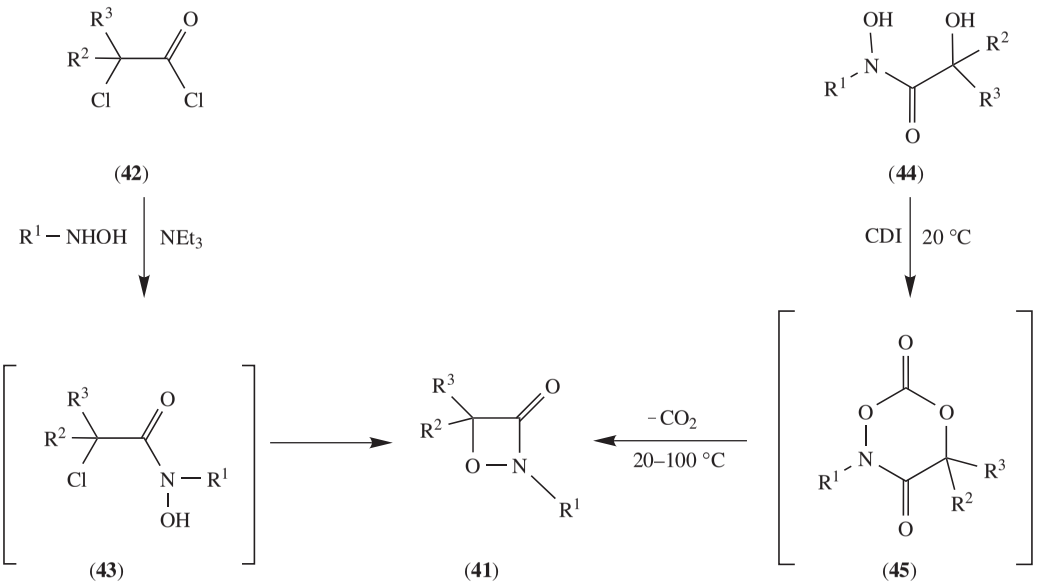


R^1 = H, Me; R^2 = H, Ph; R^3 = cumyl, *t*-Bu; R^4 = Ar, furan-2-yl

SCHEME 5

Oxazetidin-3-ones **41** were obtained either from 2-chloroacyl chlorides **42** and *N*-substituted hydroxylamines via **43** in the presence of triethylamine[106, 107] or by the reaction of glycolohydroxamic acids **44** with 1,1′-carbonyldiimidazole (CDI) (Scheme 6)[108, 109].

Diphenyl hydroxamic acids **43** ($R^2 = R^3$ = Ph) could not be isolated and the oxazetidinones **41** were obtained directly from chloride **42** ($R^2 = R^3$ = Ph) and hydroxylamine derivatives[106]. However, in the case of chloroacetyl chloride (**42**, $R^2 = R^3$ = H) the intermediate **43** was isolated and cyclized in the presence of NaOH[107]. The method is limited to starting materials that do not have hydrogen at the β-position to carbonyl group and therefore are not capable of undergoing β-elimination. For example, the reaction of α-bromoisobutyryl chloride with *N*-phenylhydroxylamine in the presence of a base led to *N*-phenylmethacroylhydroxamic acid[106]. The CDI method does not possess such a drawback. Several 4-thienyloxazetidinones **41** having methyl or even benzyl group at the 3rd



R^1 = Me, *c*-Hex, Ph, 4-MeC_6H_4, 4-ClC_6H_4;
$R^2 = R^3$ = Ph
30–90%

R^1 = $PhC(N{=}OH)CMe_2$;
R^2, R^3 = H
24%

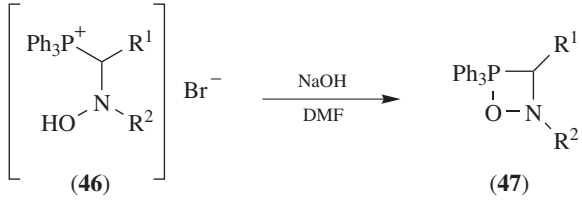
R^1 = Me, *c*-Hex, *i*-Pr, *t*-Bu, Ph, Ar, 2-thienyl;
R^2, R^3 = Ph, Ar, 2-thienyl
80–98%

R^1 = Me, Et, Bn;
R^2 = 2-thienyl;
R^3 = Me, *c*-Hex, Ph, Bn, 2-thienyl
79–97%

SCHEME 6

position were successfully made[108]. The efficiency of the dioxazinane ring **45** contraction also depends on the substitution pattern of starting hydroxamic acid **44**. In some cases, addition of molecular sieves or an increase of the temperature is necessary for formation of the oxazetidinone ring[109].

Unique derivatives of 1,2,4-oxazaphosphetidine **47** were isolated from the reaction of the corresponding phosphonium salts **46** bearing a hydroxylamine group with sodium hydroxide (equation 7)[110]. However, the products **47** were identified only by element analysis and IR spectra.



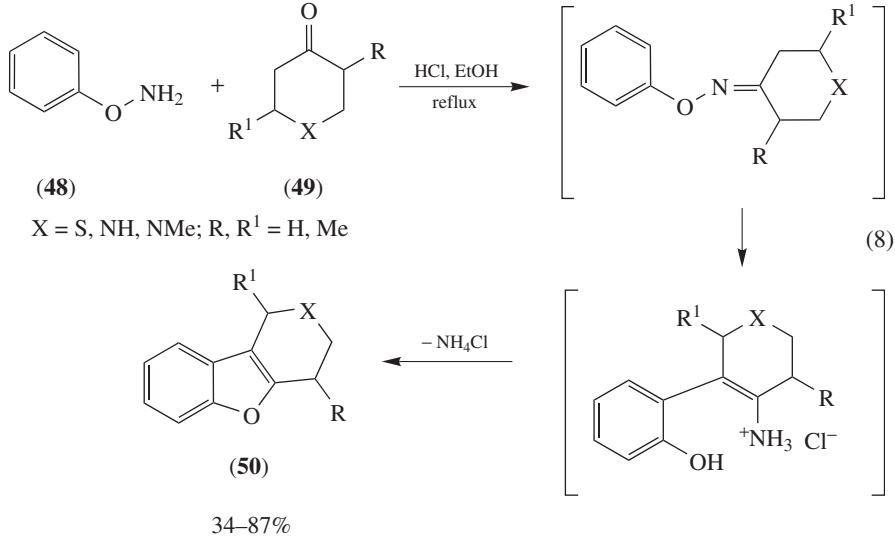
(**46**) (**47**) (7)

R^1 = Bz; R^2 = 4-$Me_2NC_6H_4$, 70%
R^2 = Me; R^2 = 2-hydroxynaphthyl, 54%

IV. FIVE-MEMBERED RINGS

A. Benzofurans

Synthesis of the benzofuran ring from *O*-aryloximes (the oxygen version of the Fischer indole synthesis) was recently reviewed[1, 2]. This transformation can be realized without isolation of the corresponding oximes. For example, treatment of *O*-phenylhydroxylamine **48** and cyclic ketones **49** with hydrogen chloride in dry ethanol gave benzofurans **50** in acceptable yields (equation 8)[111, 112].



(**48**) (**49**)

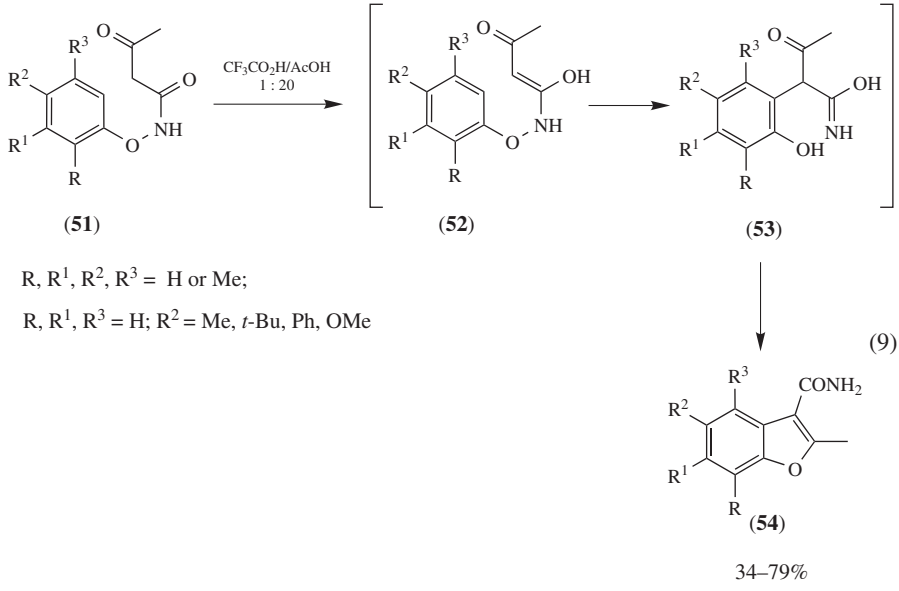
X = S, NH, NMe; R, R^1 = H, Me

(8)

(**50**)

34–87%

The benzofuran derivatives **54** can also be obtained in acid-catalyzed rearrangement of *O*-aryl-*N*-acetoacetylhydroxylamines (**51**) (equation 9)[113]. The initial step of a plausible mechanism for this reaction, similar to indole synthesis from hydrazones, involves [3,3]-sigmatropic rearrangement of enolized species such as structure **52**. Further cyclization occurs between the phenol and ketone functions of intermediate **53**, yielding 3-carbamoylbenzofurans **54**[113].



R, R^1, R^2, R^3 = H or Me;

R, R^1, R^3 = H; R^2 = Me, *t*-Bu, Ph, OMe

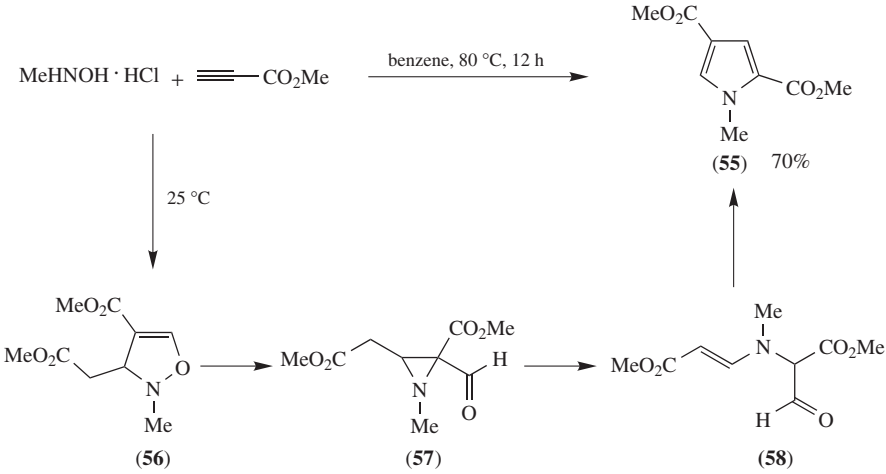
(9)

B. Pyrroles, Dihydropyrroles and Pyrrolidines

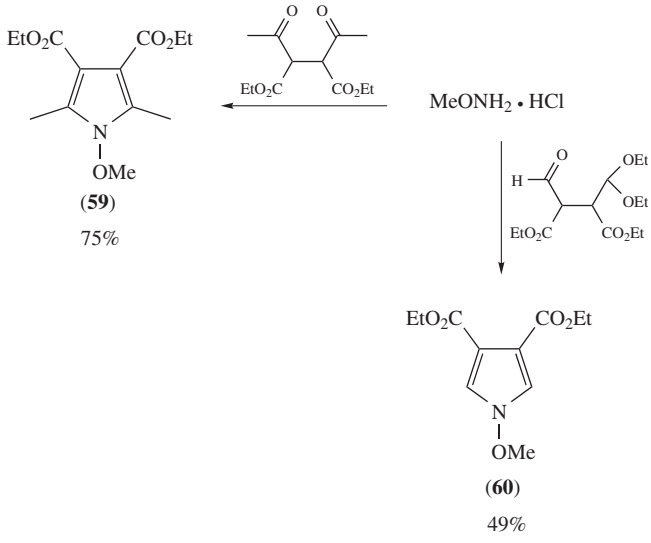
The pyrrole ring has been prepared by cyclization of hydroxylamines with substituted acetylenes[114] or carbonyl compounds[115–117].

Alkyl-substituted 1-alkynes did not react with hydroxylamines even after prolonged heating, but phenylacetylene and methylhydroxylamine yielded only 29% of *N*-methyl-2,4-diphenylpyrrole[114]. *N*-Methyl-2,4-dimethoxycarbonylpyrrole (**55**) was obtained by the reaction of methylhydroxylamine with excess of methyl propiolate (Scheme 7)[114]. The reaction intermediate observed was the corresponding isoxazoline **56**. The formation of the isoxazoline ring was suggested to proceed by addition of the hydroxylamine to the triple bond followed by a proton shift to give a nitrone, which underwent 1,3-dipolar cycloaddition with the second equivalent of propiolate. The thermal conversion of 4-isoxazolines into pyrrole derivatives has been previously postulated[118, 119]. Thus, the reaction mechanism involved homolytical cleavage of the relatively weak O–N linkage to generate a diradical intermediate, which recyclized to give the aziridine **57**. The intermediate **57** underwent cleavage of the C–C bond to form the aminoketone **58**, the dehydrative ring closure of which gave the pyrrole **55**.

N-Methoxy-substituted pyrroles **59** and **60** were synthesized by the reaction of methoxyamine hydrochloride with carbonyl compounds (Scheme 8)[115].

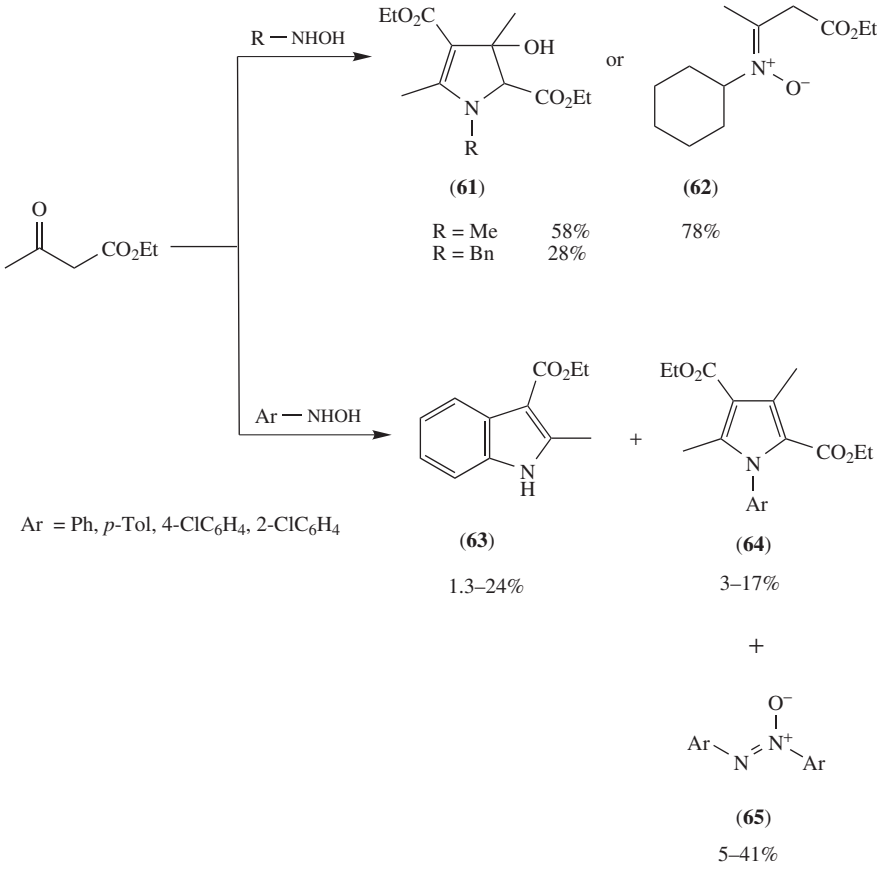


SCHEME 7



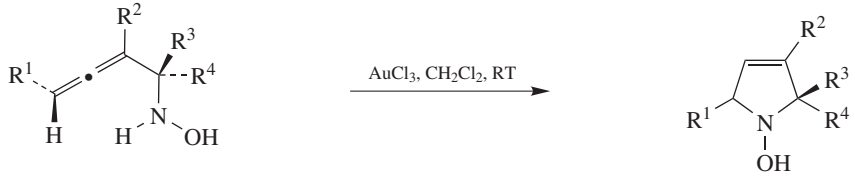
SCHEME 8

Formation of pyrrole derivatives was observed in the treatment of *N*-alkyl- and *N*-arylhydroxylamines with ethyl acetoacetate (Scheme 9)[116, 117]. Thus, the dihydropyrroles **61** were obtained from *N*-methyl- and *N*-benzylhydroxylamines, but *N*-cyclohexylhydroxylamine gave the nitrone **62**[117]. The reaction of ethyl acetoacetate with *N*-arylhydroxylamines led to a mixture of three products: the pyrrole derivatives **64**, as well as the indole **63** and the diaryldiazene-*N*-oxide **65**[116].



SCHEME 9

Recently, synthesis of *N*-hydroxydihydropyrroles **67** from allenic hydroxylamines **66** by gold-catalyzed 5-*endo*-cyclization reaction was described (equation 10)[120].

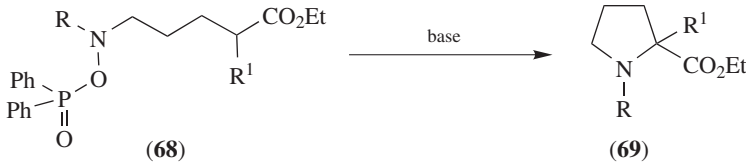


(**66**) (**67**) (10)

R^1 = Me, *i*-Pr, *n*-Bu, Ph; R^2 = H, Me; R^3 = H, CH_2OBn, CH_2OH; R^4 = H, CH_2OBn, $(CH_2)_2Ph$, $(CH_2)_2CO_2Et$

67–80%

Cyclization of 5-(diphenylphosphinyloxyamino)valeric acid derivatives **68** to pyrrolidines **69** was achieved by treatment with appropriate bases (equation 11)[121]. This method is effective for the synthesis of *N*-methyl or *N*-benzyl pyrrolidines **69**. *N*-α-Methylbenzyl- and *N*-allylpyrrolidines **69** were obtained in a low yield (10 and 20%, respectively), but the dimethylbenzyl-substituted esters **68** did not form the product **69** at all.

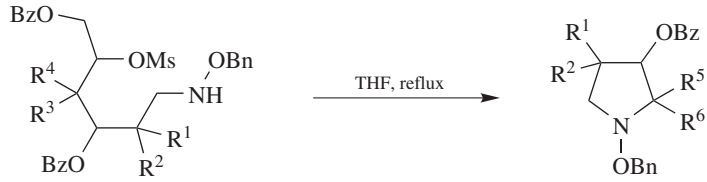


(**68**) (**69**) (11)

10–95%

R = Me, Bn, $CH(CH_3)Ph$, $CH_2CH{=}CH_2$, $C(CH_3)_2Ph$; R^1 = H, CO_2Et

N-Benzyloxypyrrolidines **71** were prepared by cyclization of the 5-*O*-mesyl derivatives of the hexose **70** (equation 12). The mechanism involves a cascade of neighboring group participation steps involving the *O*-benzoyl-protecting groups[122].



(**70**) (**71**) (12)

78–88%

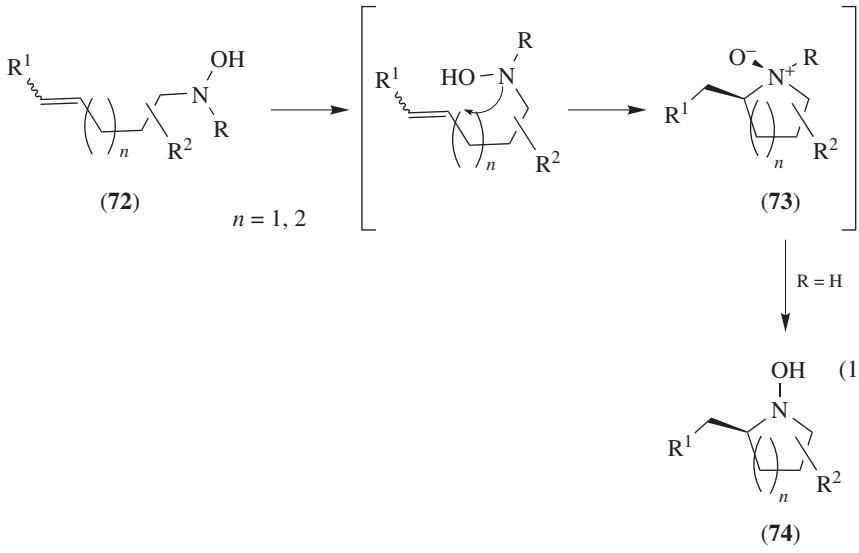
R^1, R^2, R^3, R^4 = H, OBz; R^5, R^6 = H, (*R*)-$HCOBzCH_2OBz$

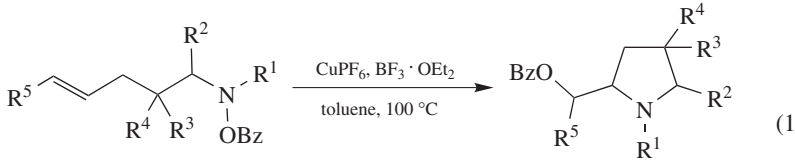
Synthesis of pyrrolidine derivatives has been achieved from unsaturated hydroxylamines[123–136]. A general method for preparation of pyrrolidine- or piperidine-*N*-oxides **73** and *N*-hydroxy-pyrrolidines or piperidines **74** is the Cope–House cyclization (which has also been termed 'retro- or reverse-Cope elimination') of unsaturated hydroxylamines **72** (equation 13). This transformation was discovered in 1976 by House and coworkers[125, 126] and has been described[127–133] and reviewed[134–136] in recent years. As a consequence, the cyclization proceeded highly stereoselectively with respect to the mutual *cis* orientation of the *N*-oxide function and the newly formed alkyl group. Alkyne–hydroxylamine cyclizations strongly favor the formation of six-membered cyclic nitrones at the expense of comparable five-membered rings.

The radical aminohydroxylation of double bonds of *N*-benzoyloxyamines **75** gives pyrrolidines **76** in moderate to good yields (equation 14)[123]. The authors assumed that a copper(I) salt reduced the N–O bond to aminyl radical that can be added to the double bond efficiently when activated by a Lewis acid. The carbon radical thus generated is quickly oxidized by copper(II) via a ligand transfer, regenerating the catalyst and leading to the product.

Iodine-induced cyclization of bis(homoallylic) *N*-alkoxyamines was found to be particularly effective for the preparation of *trans*-2,3- and 2,5-disubstituted pyrrolidylalkyl

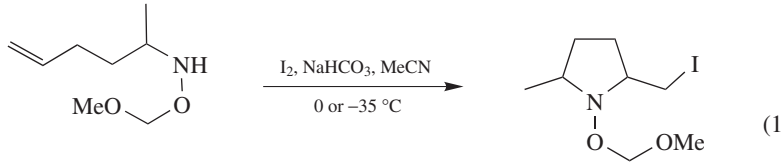
iodides[124]. For example, hydroxylamine **77** was transformed to *N*-alkoxypyrrolidine **78** by treatment with iodine in the presence of sodium bicarbonate (equation 15).





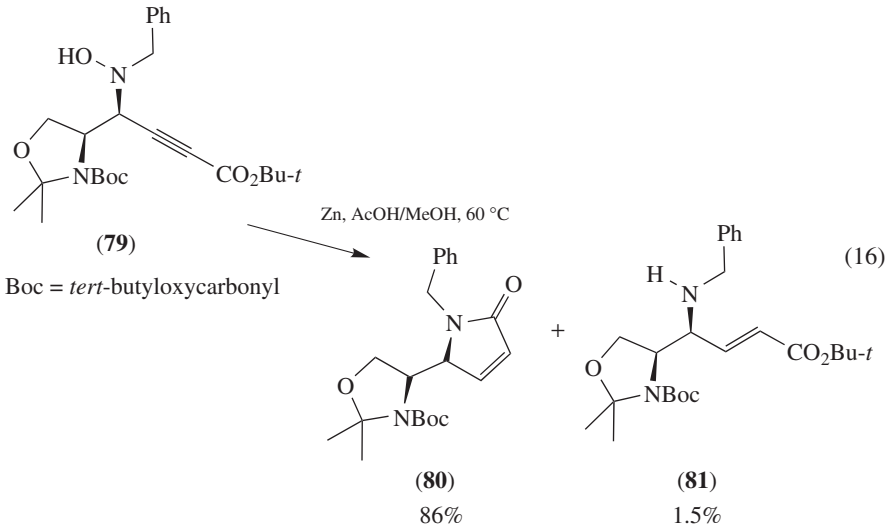
R^1 = Bu, All; R^2, R^4, R^5 = H, Me; R^3 = H, Me, Ph

39–79%



81–87%

Reduction of acetylenic *N*-hydroxylamines with Zn and an acid leads to the 1,5-dihydropyrrol-2-one derivatives[137, 138]. Thus, reduction of compound **79** by Zn in an AcOH/MeOH (1/9) mixture proceeded with high *cis*-selectivity and following *in situ* cyclization gave pyrrolidinone **80** in 86% yield (equation 16)[137]. The corresponding *trans*-α,β-unsaturated ester **81** was isolated in only 1.5% yield.



(**79**)

Boc = *tert*-butyloxycarbonyl

(**80**) 86%

(**81**) 1.5%

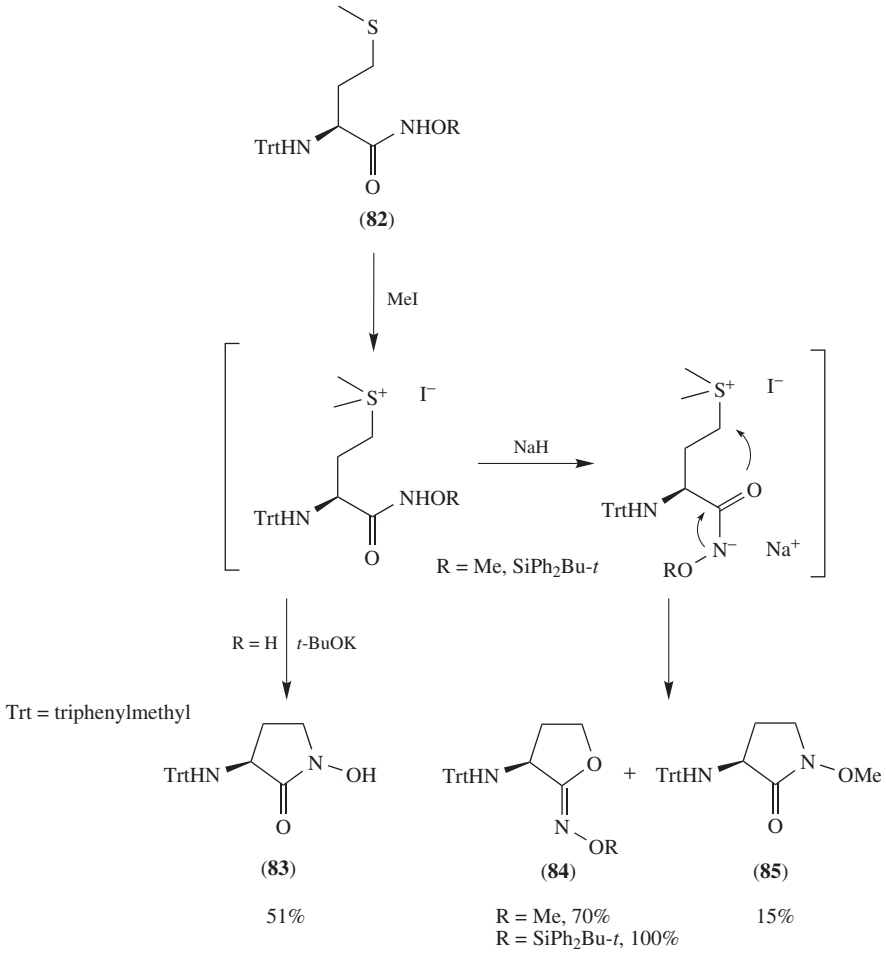
(16)

Synthesis of pyrrolidin-2-ones from hydroxamic acid derivatives by base-induced ring closure reaction has been described[139–143]. Thus, 4-chlorobutyro-*O*-benzylhydroxamate was cyclized with NaH in dichloromethane to provide *N*-benzyloxypyrrolidin-2-one in 65% yield[139]. Sequential treatment of the corresponding hydroxamate derivatives of *N*-trityl-(*S*)-methionine **82** with MeI followed with *t*-BuOK[140] or NaH[141] provides the pyrrolidin-2-ones **83** and **85** or the dihydrofuran-2-one oximes **84** resulting from nucleophilic displacement of the Me_2S group by either the O- or N-atom of the amide function (Scheme 10). Similar cyclization of (*R*)-*N*-benzyloxycarnitine amide in the presence of $NaHCO_3$ led to (*R*)-*N*-benzyloxy-4-hydroxypyrrolidin-2-one (11%) and 4-hydroxydihydrofuran-2-one *O*-benzyloxime (50%)[142].

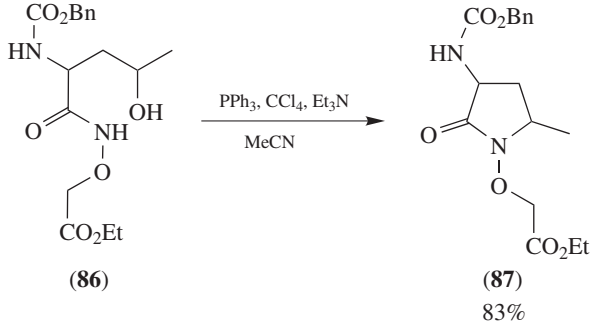
Intramolecular cyclization of hydroxamate **86**, by treatment with triphenylphosphine, carbon tetrachloride and triethylamine in acetonitrile, afforded the *N*-alkoxypyrrolidin-2-one **87** in a good yield (equation 17)[143].

Cyclization of the hydroxamic acid derivative **88** was applied in synthesis of the new α-amino acid dealanylalahopcin (**90**) (Scheme 11)[144, 145]. Thus, oxidative cleavage (catalytic OsO_4, $NaIO_4$) of the alkene **88** gave an aldehyde in equilibrium with the ring closed form, which was converted to methoxylactam **89** without isolation by treatment with MeOH and a catalytic amount of trifluoroacetic acid. A two-stage deprotection procedure lead to the target aminopyrrolidine acetic acid (**90**).

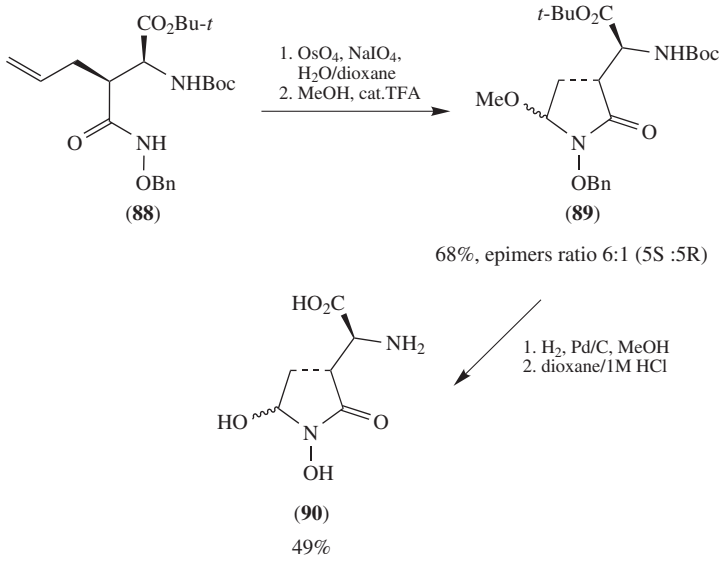
Effective synthesis of spirolactams and *N*-aryl-*N*-alkoxyamide derivatives through a formation of *N*-alkoxy-*N*-acylnitrenium ions was reviewed[146]. Therefore, in the present work this reaction will be described very briefly. Hypervalent iodine reagents, silver carbonate in trifluoroacetic acid, anhydrous zinc acetate in nitromethane and anhydrous ferric chloride with an equimolar amount of acetic acid are used for this transformation. Thus, the stereoselective azaspirocyclization of *N*-acyl-*N*-alkoxynitrenium ions **93** generated by the treatment of *N*-methoxyamides (**91**, R = H, R^1 = Me, Bn, R^4 = OMe) with phenyliodine(III)-bis(trifluoroacetate) (PIFA) gave the spirolactam **92** in a good to excellent yield (Scheme 12A)[147]. Spirocyclization provides the *anti* spirolactam diastereomers with reasonable selectivity. Different cyclohexa-2,5-dienones **92** spiro-derivatives with azetidinone ($n = 0$), pyrrolidinone ($n = 1$) and piperidinone ($n = 2$) rings were prepared using this method.


S
TrtHN
NHOR
O
(82)
MeI
S+ I−
NaH
R = Me, SiPh2Bu-t
RO
N−
Na+
R = H
t-BuOK
Trt = triphenylmethyl
N
OH
OMe
OR
(83)
(84)
(85)
51%
R = Me, 70%
R = SiPh2Bu-t, 100%
15%

SCHEME 10


CO2Bn
HN
OH
O
NH
CO2Et
PPh3, CCl4, Et3N
MeCN
(86)
(87)
83%

(17)



(**88**)

(**89**)

68%, epimers ratio 6:1 (5S :5R)

(**90**)

49%

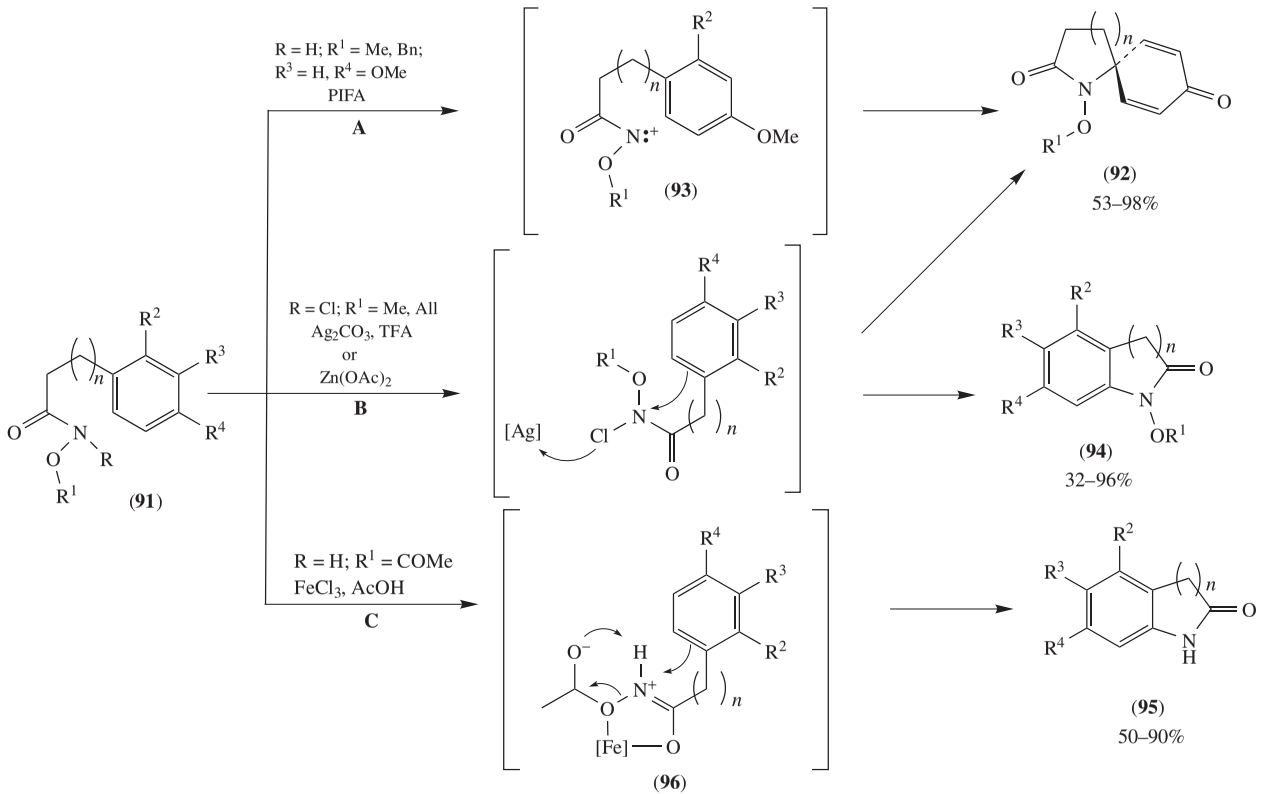
SCHEME 11

Electrophilic intramolecular aromatic substitution with an *N*-methoxy-*N*-acylnitrenium ion, generated from *N*-methoxy-*N*-chloroamides (**91**, R = Cl, R^1 = Me, All) by treatment with Ag_2CO_3/TFA or $Zn(OAc)_2$, resulted in the formation of *N*-methoxy-2-oxindoles **94** ($n = 1$) or *N*-methoxy-3,4-dihydro-2-quinolones **94** ($n = 2$) in a good yield (Scheme 12B). The *N*-allyloxy derivatives of **91** are also suitable substrates for this transformation. A nitrenium ion attacked the *ipso* position when the electron density of the position was increased by an *ortho*- or *para*-substituent. Thus, spirolactams **92** were obtained from *o*- or *p*-methoxybenzene derivatives of **91**.

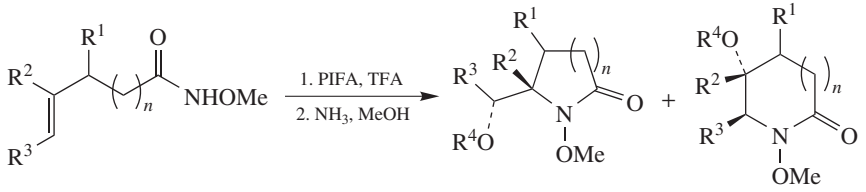
Reaction of *N*-acetyloxyamides (**91**, R = H, R^1 = COMe) with $FeCl_3$ leads to 2-oxindoles (**95**, $n = 1$) or 3,4-dihydro-2-quinolones (**95**, $n = 2$) (Scheme 12C)[148]. The authors assumed that the reaction proceeds through the transition state **96**.

Recently, intramolecular oxamidation of unsaturated *O*-alkyl hydroxamates via *N*-acylnitrenium ions was reported (equation 18)[149]. Thus, lactams **98** were obtained from 1,2-substituted alkenes **97** ($n = 1, 2$; R^2 = H) by treatment with PIFA. In the case of pent-3-enoic hydroxamate (**97**, $n = 0$; $R^1 = R^2$ = H; R^3 = Me) and 1,1-disubstituted alkenes **97** (R^3 = H), cyclization resulted in formation of 'ring expanded' regioisomers **99**. Therefore, the isomer outcome of this process was predictable and reaction proceeded with high stereo- and regioselectivity in most cases. Lower yields and selectivities were observed, if aryl-substituted ($n = 1$, R^2 = H, R^3 = Ar) and trisubstituted ($n = 1$, $R^2 = R^3$ = Me) unsaturated hydroxamates **97** were used as starting materials. Lactams **98** and **99** can be isolated as trifluoroacetic acid esters ($R^4 = CF_3CO$), but in light of the lability of these esters, a methanol/ammonia quench was employed to remove the trifluoroacetate group, providing better total yields of products **98** and **99**.

The hydroxamic acids having alkene substituents were converted into the corresponding pyrrolidinones by intramolecular ene reaction[150, 151], phenylselenium-induced cyclization[152] and radical cyclization[153–160].


R = H; R1 = Me, Bn;
R3 = H, R4 = OMe
PIFA
A
R = Cl; R1 = Me, All
Ag2CO3, TFA
or
Zn(OAc)2
B
R = H; R1 = COMe
FeCl3, AcOH
C
(91)
(93)
(92)
53–98%
(94)
32–96%
(95)
50–90%
(96)
n = 0, 1, 2
R2 = H, Me, i-Pr, OMe; R3 = H, OMe; R4 = H, Me, OMe, Ph, Br, Cl, NO2, AcNH

SCHEME 12



(**97**) (**98**) (**99**) (18)

24–98%

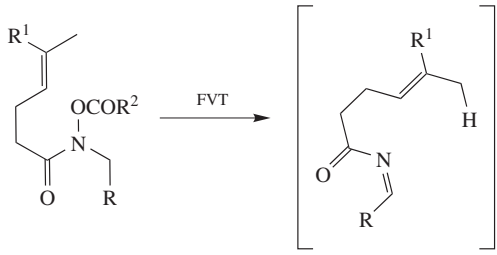
n = 0–3; R^1 = H; R^2 = H, Me; R^3 = H, Me, Et, Ar;
n = 1; R^1R^3 = CH_2CH_2; R^2 = H;
R^4 = H, CF_3CO

Intramolecular ene reaction of *N*-acylimines **101**, produced by the flash vacuum thermolysis of hydroxamic acid derivatives **100**, afforded the corresponding pyrrolidin-2-ones **102** in a moderate yield (equation 19)[150, 151]. *N*-Methylhydroxamic acid (**100**, R = R^1 = H, R^2 = Me) gave the pyrrolidinone **102** as the major product (40%) in addition to 1-methyl-1,4-dihydro-2-pyridone (**103**) and 1,5-dimethyl-2-pyrrolidone (**104**)[150]. The yield of the desired product depended on the substituents at the nitrogen atom of the starting material[151]. Thus, phenyl substitution of the hydroxamic acid (**100**, R = Ph, R^1 = H, R^2 = OMe) suppressed the enophilicity of the *N*-acylimine and only 9% of pyrrolidinone **102** were observed. Another restriction on this ene reaction is that it generally will not be successful if the *N*-acylimine contains a β-hydrogen. In this case a hydrogen shift gave the more stable enamide (**105**, R = Me, R^1 = H, R^2 = OMe). The electron-withdrawing group on the enophile (R = CO_2Et) accelerated the reaction which leads to the pyrrolidinone **102** formation.

Organoselenium-induced cyclizations of γ-substituted β,γ-unsaturated hydroxamic acids **106** gave either the five-membered cyclic *N*-hydroxypyrrolidinone **107** or the *N*-hydroxyimidates **108** (Scheme 13)[152].

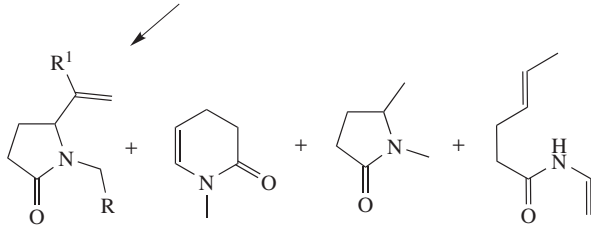
The *O*-benzoyl derivatives of olefinic hydroxamic acids were cyclized to the corresponding pyrrolidin-2-ones by treatment with Bu_3SnH in the presence of AIBN[153–156]. Thus, slow addition of tributylstannane and AIBN to a refluxing solution of benzoate **109** in toluene gave a mixture of *cis* and *trans* pyrrolidinones **110** in a moderate yield through capture of the intermediate amidyl radical by the internal olefin (equation 20)[155].

Treatment of hydroxamic acids having alkene substituents with *tert*-butylsulfinyl chloride and Hunig's base from $-50\,^{\circ}C$ to room temperature in the presence of a radical trap such as diphenyl diselenide, diphenyl disulfide or TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) affords functionalized pyrrolidinones derived from an amidyl radical cyclization[157]. In a more convenient procedure, cyclization can be initiated using diethyl chlorophosphite (equation 21)[158, 159], which generally provided similar (with diphenyl disulfide or TEMPO) or significantly higher (with diphenyl diselenide) yields of product[158]. Thus, hydroxamic acids **111** underwent amidyl radical-olefin cyclization to produce β-tosylethyl-protected lactams **112**, which can be deprotected under mild basic conditions[159].

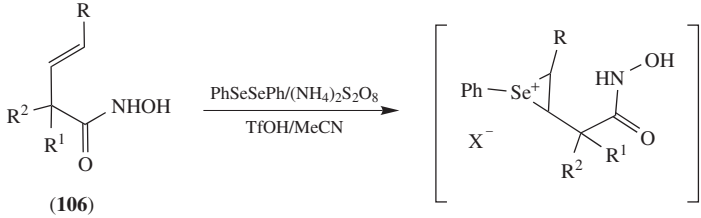


(**100**) (**101**)

R = H, Me, Ph, CO_2Et; R^1 = H, CO_2Et; R^2 = Me, OMe (19)

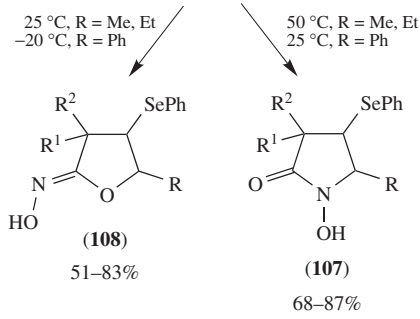


(**102**) 9–54% (**103**) 15% (**104**) 15% (**105**) 85%



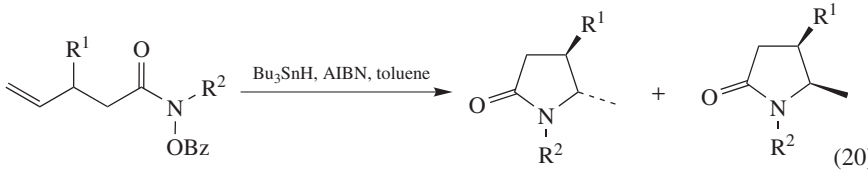
(**106**)

R = Me, Et, Ph; R^1 = H, Me; R^2 = H, Me



(**108**) 51–83% (**107**) 68–87%

SCHEME 13

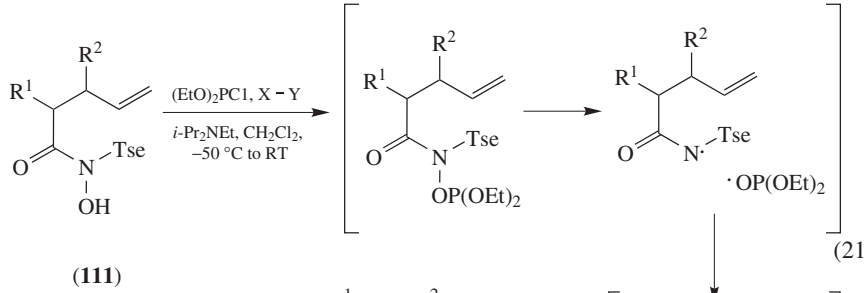


(20)

(**109**) *trans*-(**110**) *cis*-(**110**)

R^1 = Me, Ph; R^2 = Me, Bu, *i*-Pr, Bn

22–82% (*trans* + *cis*)
diastereomeric excess (*de*) 11–43%



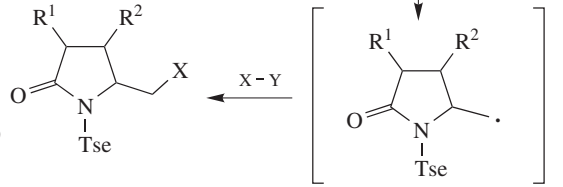
(21)

(**111**)

R^1, R^2 = H, Alk, cycloalkyl
R^1R^2 = cycloalkyl

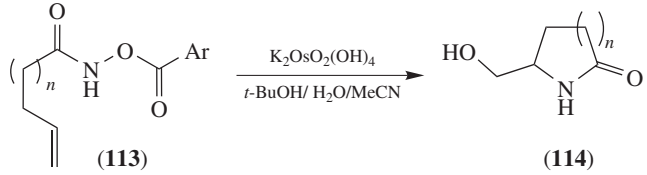
X-Y = Ph_2Se_2, Ph_2S_2, TEMPO

Tse = *p*-toluenesulfonylethyl



(**112**)
62–89%

Synthesis of lactams **114** from olefinic hydroxamic acids **113** by osmium-catalyzed amide-tethered aminohydroxylation reaction was achieved[160]. The reaction conditions are compatible with a variety of different alkene substitution patterns and ring sizes (4, 5 and 6) and works in both cyclic and acyclic systems. For example, *O*-aryloxyhydroxamic acids (**113**) gave β-lactams **114** ($n = 0$), pyrrolidinones **114** ($n = 1$) and piperidinones **114** ($n = 2$) in good yields (equation 22). The reaction mechanism for this transformation is similar to Sharpless aminohydroxylation reaction. In this case the *N*-aroyloxy moiety acts as a reoxidant for Os(VI) to Os(VIII).



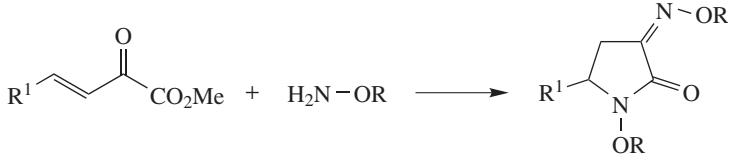
(22)

(**113**) (**114**)

n = 0, 1, 2
Ar = 2,5,6-trimethylphenyl

n = 0, 60%
n = 1, 85%
n = 2, 83%

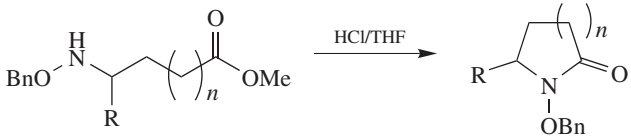
1-Hydroxy- and 1-alkoxy-3-oxime-2-pyrrolidinones (**116**) have been synthesized by the interaction of hydroxylamines **8** (R = H, Bn) with the methyl esters of 2-oxo-3-butenoic acid derivatives **115** (equation 23)[161]. Isolation of several intermediates suggests that formation of products **116** occurs by consecutive oxime formation, addition of hydroxylamine to the double bond and final cyclization by intramolecular acylation of the hydroxylamine nitrogen by the ester group.



(**115**) (**8**) (**116**) (23)

R = H, Bn; R = Ar, hetaryl 31–98%

Synthesis of the 2-pyrrolidinone or 2-piperidinone ring was successfully realized from the *O*-benzylhydroxylamine derivatives in the presence of an acidic catalyst[162–165]. For example, *O*-benzylhydroxylamino esters **117** were easily converted into the corresponding lactams **118** in the presence of a catalytic amount of HCl (equation 24)[163].



(**117**) (**118**) (24)

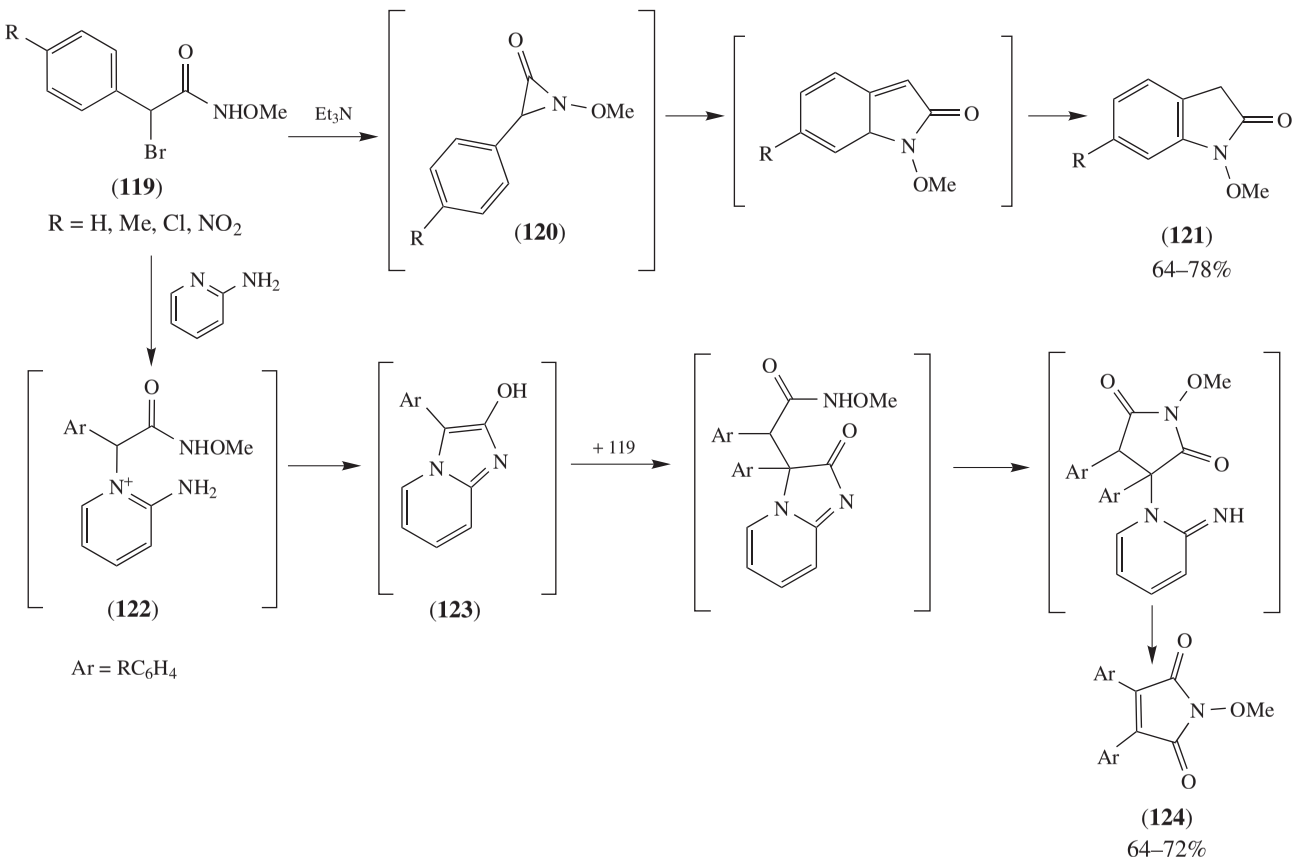
n = 1, 2
R = Alk, cycloalkyl, 1-Ad

n = 1, 65–95%
n = 2, 70–85%

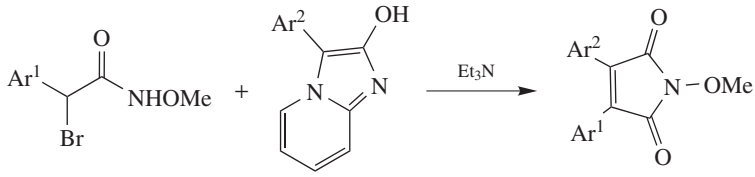
N-Methoxyindolinones and *N*-methoxymaleimides were synthesized from α-halohydroxamic acids in the presence of triethylamine or 2-aminopyridine (Scheme 14)[166].

Thus, treatment of α-bromohydroxamic acids **119** with Et_3N afforded the indolinones **121** in a moderate yield. The cyclization occurred through aziridinone derivatives **120**. *N*-Methoxymaleimides **124** were derived from reaction of the corresponding hydroxamic acids **119** with 2-aminopyridine. The formation of the products **124** proceeded through the intermediate pyridinium salt **122**, which underwent intramolecular cycloaddition to form 4-hydroxyimidazopyridine (**123**). If the latter derivatives were not isolated and excess of hydroxamate **119** was used, symmetric *N*-methoxymaleimides were obtained. Compounds **123** can be isolated and coupled with other hydroxamic acids **119** to produce *N*-methoxymaleimides **124** having different aryl substituents (equation 25).

Several pyrrolidinone derivatives **126** were obtained via palladium-catalyzed C–H activation reactions[99]. Thus, hydroxamic acids **125** in the presence of catalytic amounts of $Pd(OAc)_2$, $CuCl_2$ and 2 equivalents of AgOAc in dichloroethane afforded the lactams **126** in a good yield (equation 26).

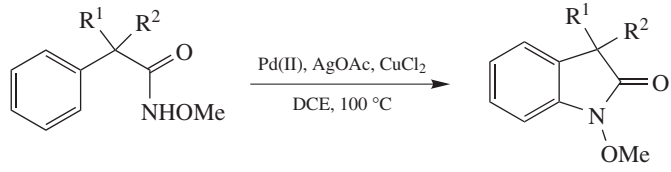

R
O
NHOMe
Br
(119)
R = H, Me, Cl, NO2
Et3N
N
OMe
R
(120)
O
N
OMe
R
(121)
64–78%
N
NH2
Ar
O
NHOMe
N+
NH2
(122)
Ar = RC6H4
Ar
OH
N
N
(123)
+ 119
O
NHOMe
Ar
Ar
O
N
N
O
OMe
Ar
Ar
N
NH
O
Ar
N
OMe
Ar
O
(124)
64–72%

SCHEME 14



(**119**) (**123**) (**124**) (25)

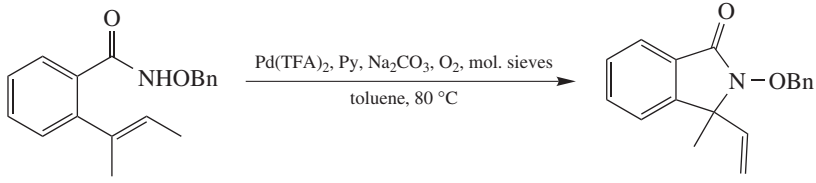
65–72%



(**125**) (**126**) (26)

$R^1 = R^2 = Me$; $R^1R^2 = (CH_2)_2, (CH_2)_4$ 84–96%

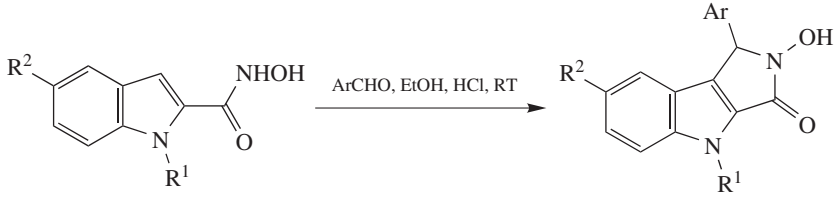
Hydroxamic acids can also be used for the isoindolinone synthesis[167, 168]. For example, Pd-catalyzed oxidative heterocyclizations of *O*-benzylhydroxamic acid **127** gave the isoindolinone **128** (equation 27).



(**127**) (**128**) (27)

82%

Reaction of indole-2-hydroxamic acids (**129**) with substituted benzaldehydes afforded 1,4-dihydro-2*H*-pyrrolo[3,4-*b*]indol-3-ones (**130**) in moderate yields (equation 28)[169].



(**129**) (**130**) (28)

40–70%

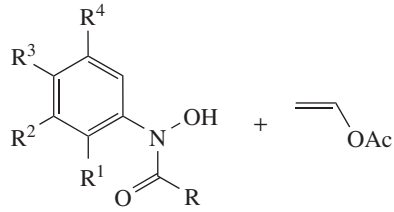
R^1 = H, Me;

R^2 = H, OMe; Ar = Ph, 4-$MeOC_6H_4$, 2-ClC_6H_4, 2-HOC_6H_4

C. Indoles

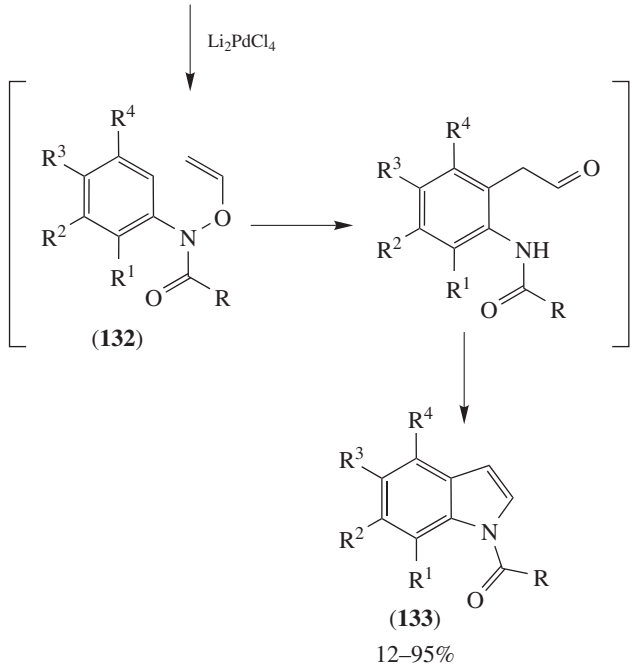
The majority of methods for synthesis of indoles from arylhydroxylamines and hydroxamic acids involve hetero-Cope rearrangement of *in situ* generated *O*- or *N*-vinyl derivatives. Vinyl acetate[170–172], activated alkynes[173–175] and allenes[176–180] were reported as suitable reagents for such a type of indole synthesis.

For example, 2,3-unsubstituted indoles **133** can be obtained in the reaction of *N*-arylhydroxamic acids **131** with vinyl acetate in the presence of Li_2PdCl_4 (2–5 mol%) at 50 °C via [3,3]-sigmatropic rearrangement of the *O*-vinylhydroxylamine derivatives **132** (equation 29)[170–172].



(**131**)

R = H, Me, Ph, CH=CH_2, $ClCH_2$, $ClCH_2CH_2$, OEt;
R^1 = H, Me, Cl; R^2 = H, Me, Cl, Br;
R^3 = H, Me, Cl; R^4 = Br, OMe



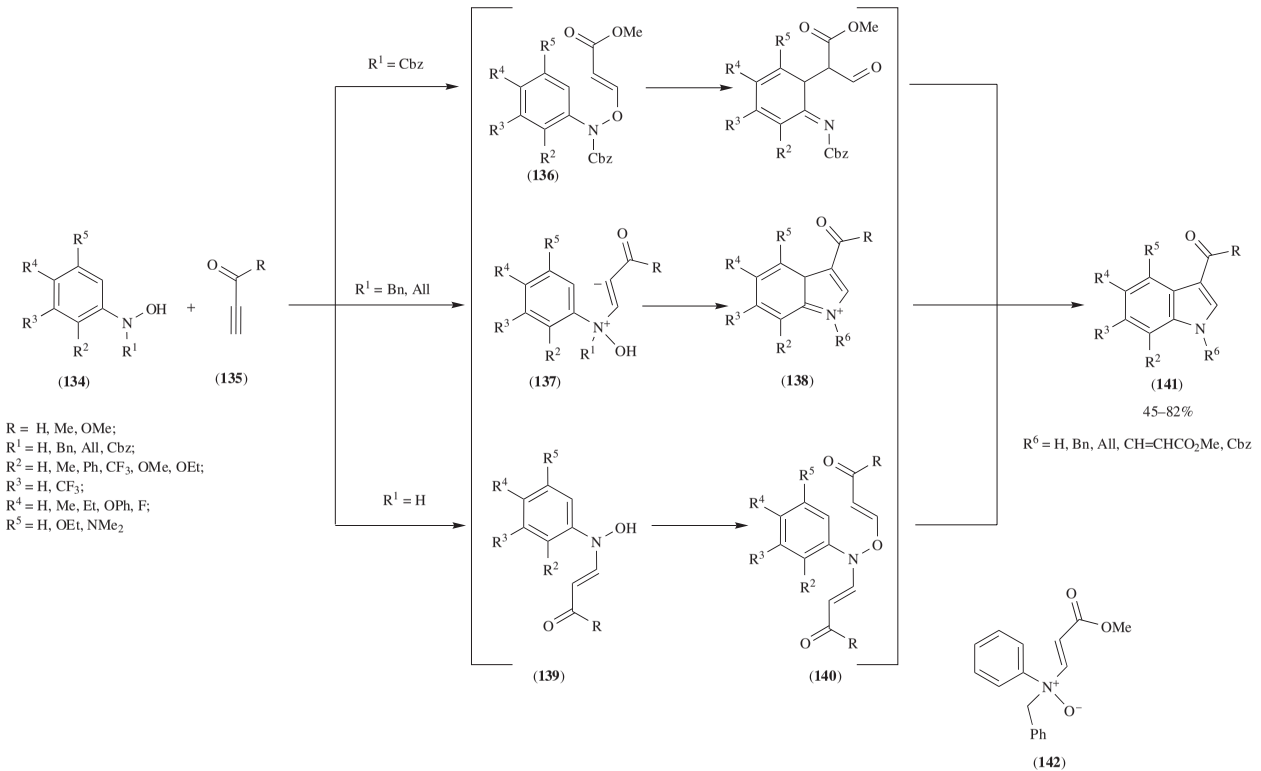
(**132**)

(**133**)

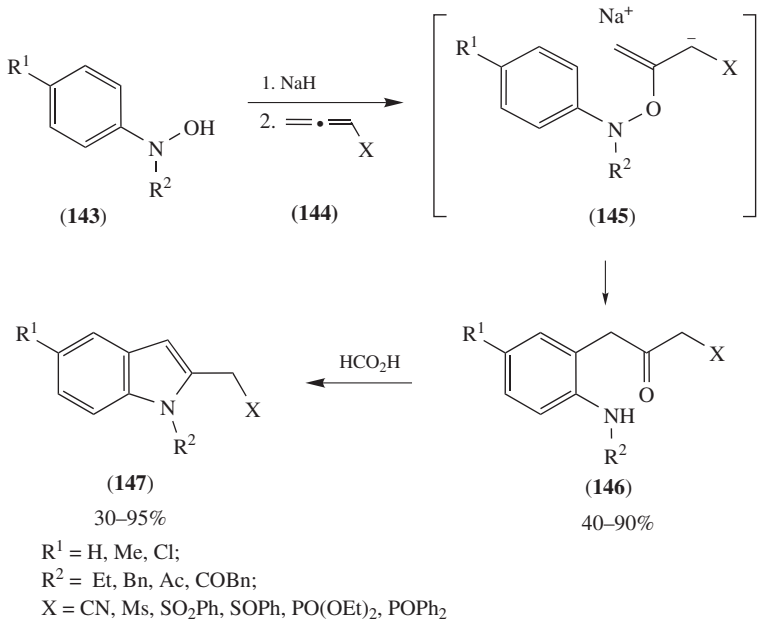
12–95%

(29)

If hydroxamic acid **131** has a 3-methylphenyl group ($R^1 = R^3 = R^4 = H$, $R^2 = Me$), a mixture of 4- and 6-methylindole **133** isomers in ratio 1:1 was obtained[170]. In the case


R1 = Cbz
R1 = Bn, All
R1 = H
(134)
(135)
(136)
(137)
(138)
(139)
(140)
(141)
45–82%
(142)
R = H, Me, OMe;
R1 = H, Bn, All, Cbz;
R2 = H, Me, Ph, CF3, OMe, OEt;
R3 = H, CF3;
R4 = H, Me, Et, OPh, F;
R5 = H, OEt, NMe2
R6 = H, Bn, All, CH=CHCO2Me, Cbz

SCHEME 15



SCHEME 16

of the 3-chloro-5-methoxyphenylhydroxamic acid derivative, the cyclization proceeds in favor (2:1 ratio) of 1-acetyl-6-chloro-4-methoxyindole[172].

The 3-carbonylindole derivatives **141** were obtained from arylhydroxylamines **134** and activated alkynes **135** at room temperature in the presence of Hunnig's base in nitromethane[173], *N*-methylmorpholine in dichloromethane[174] and, more generally, in the presence of 4-(dimethylamino)pyridine (DMAP) and 4A molecular sieves in THF[175] (Scheme 15). The reaction pathway depends on the substituent in the hydroxylamine moiety. The formation of indoles (**141**, R = Cbz, $R^2 = R^3 = R^4 = R^5 = H$ or $R^2 = R^4 = R^5 = H$, R^3 = OMe) proceeds through *O*-substituted hydroxamic acid derivative **136**, if *N*-benzyloxycarbonylphenyl- or 3-methoxyphenylhydroxylamines (**134**) were treated with methyl propiolate (**135**, R = OMe)[173, 174]. In the case of the methoxy derivative (**134**, R^3 = OMe) a single regioisomer was isolated in 66% yield[174].

In the case of *N*-benzyl- or *N*-allylhydroxylamines (**134**) the nitrogen atom preferentially added to the Michael acceptors **135** to give the intermediates **137**, which underwent an intramolecular cyclization to form the pyrrole nucleus of the indole derivatives **141** via isomerization of structure **138**[175]. The enamine oxide **142** that was formed from compound **137** by a proton exchange between a hydroxyl group and the vinyl carbanion moiety was isolated and fully characterized by the ^{1}H NMR and mass spectroscopy, thereby supporting this hypothesis[175]. If unsubstituted arylhydroxylamines (**134**, $R^1 = H$) were used, one equivalent of the acetylene derivative **135** was added to nitrogen atom

to give the intermediates **139**. The oxygen atom of the *N*-vinyl derivative **139** added to the second equivalent of alkyne **135** to produce trisubstituted hydroxylamine **140** that underwent the [3,3]-sigmatropic rearrangement and resulted in the indoles **141** with the carboxyvinyl moiety at 1st position ($R^6 = CH{=}CHCO_2Me$). It is noteworthy that under the same reaction conditions but in the absence of DMAP, isoxazolidines are formed[114].

Blechert[176–180] developed a method for the synthesis of 2-substituted indoles from the *N*-arylhydroxylamine derivatives and allenes. Initially he reported[176, 177] the synthesis of the 2-methyleneindole derivatives **147** (Scheme 16). The activated allenes **144** were added to the sodium salts of hydroxylamines **143** to form intermediate **145** that underwent a rearrangement and the keto derivatives **146** were isolated after quenching reaction with water. The treatment of ketones **146** with formic acid at 80°C produced the indoles **147**. This reaction can be realized also as a one-pot procedure without isolation of the intermediates **146**.

Later, Blechert and his coworkers[178–180] published a three-component reaction that produces substituted 2-vinylindoles **150** from *N*-arylhydroxylamines, allenes and aldehydes (equation 30). The process starts with formation of the nitrone derivatives **148**, which can be isolated or used directly in the next step. A 1,3-dipolar cycloaddition of the nitrones **148** to the activated double bond of the allene initiates the 'domino process'. The formed isoxazoline derivatives **149** underwent a hetero-Cope rearrangement followed by retro-Michael reaction and subsequent irreversible condensation in a highly stereoselective manner to the *Z*-vinylindoles **150**.

Besides processes involving hetero-Cope rearrangement, some other transformations yielding indoles from arylhydroxylamines are reported.

A formation of the indole **154** was observed in the treatment of the arylhydroxylamine di(2-furyl) derivative **151** with $FeCl_3$. In the presence of other acid catalysts (HCl, $BF_3{\bullet}OEt_2$, $HClO_4$, Me_3SiCl and Amberlist 15) the reaction did not proceed. It was assumed[181] that the iron(III) salt oxidized the hydroxylamine group to nitroso compound **152**, that underwent intramolecular Diels–Alder reaction, isomerization and was then reduced by iron(II) to the corresponding indole **154** (equation 31). They also isolated the oxazine derivative **153** from the decomposition products of hydroxylamine **151** and transformed it to the indole **154** by treatment with $SnCl_2$.

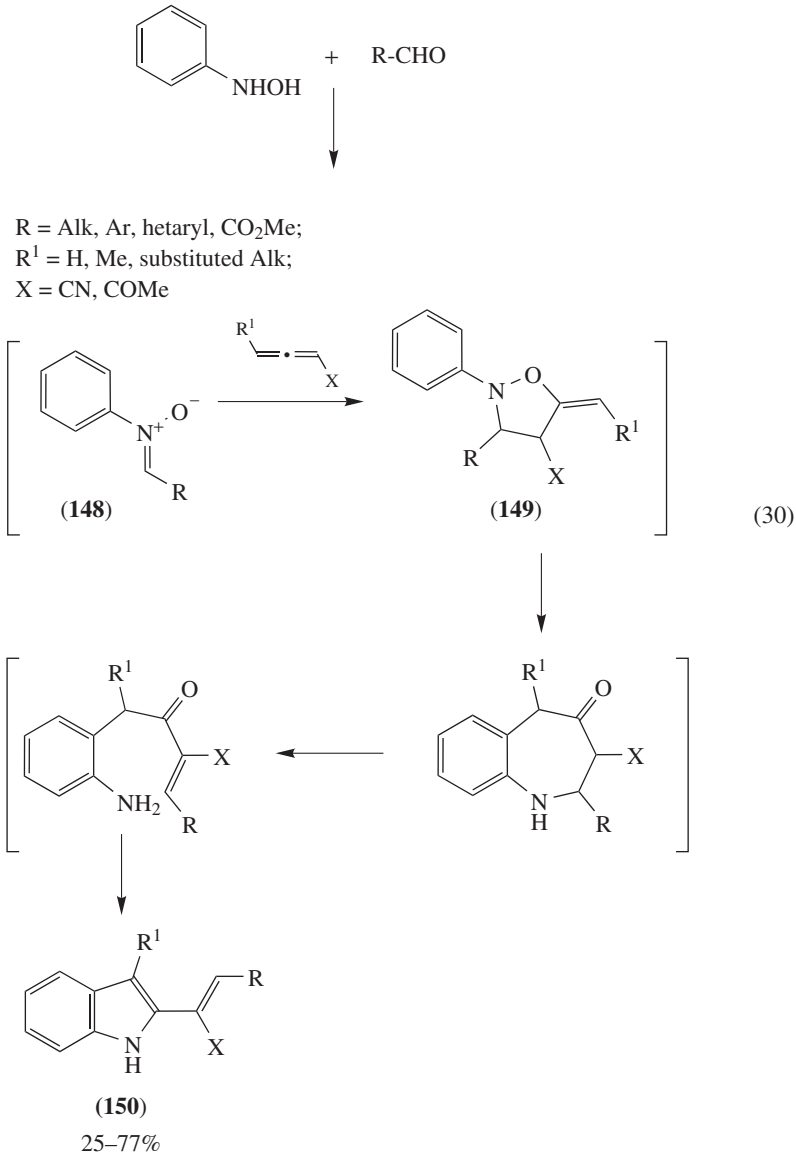
Recently, a more general method for the synthesis of 3-arylindoles from *N*-arylhydroxylamines via annulations with alkynes catalyzed by iron(II) phthalocyanine [Fe(Pc)] was published[182]. The hydroxylamine **155** was slowly added to a solution of alkyne **156** in refluxing toluene or dioxane in the presence of 10% of catalyst (equation 32).

Yields of indoles **157** were in the range from 41 to 61% if terminal acetylenes **156** were used ($R^4 = H$). From prop-1-ynylbenzene (**156**, $R^3 = Ph$, $R^4 = Me$) the indole was obtained only in 25% yield. Mixtures of 4- and 6-substituted indoles were obtained if *meta*-substituted *N*-arylhydroxylamine substrates (**155**) were used, with the 4-substituted indole slightly favored in each case. It was proposed that the catalytic reaction pathway proceeds via ArNHOH oxidation by a $Fe^{III}(Pc)$ species to ArNO, nitroso-alkyne cyclocondensation to the *N*-hydroxyindole, and reduction of the latter to the indole by $Fe^{II}(Pc)$. $Fe^{III}(Pc)$ could form initially from $Fe^{II}(Pc)$ by oxidation with some amount of starting hydroxylamine.

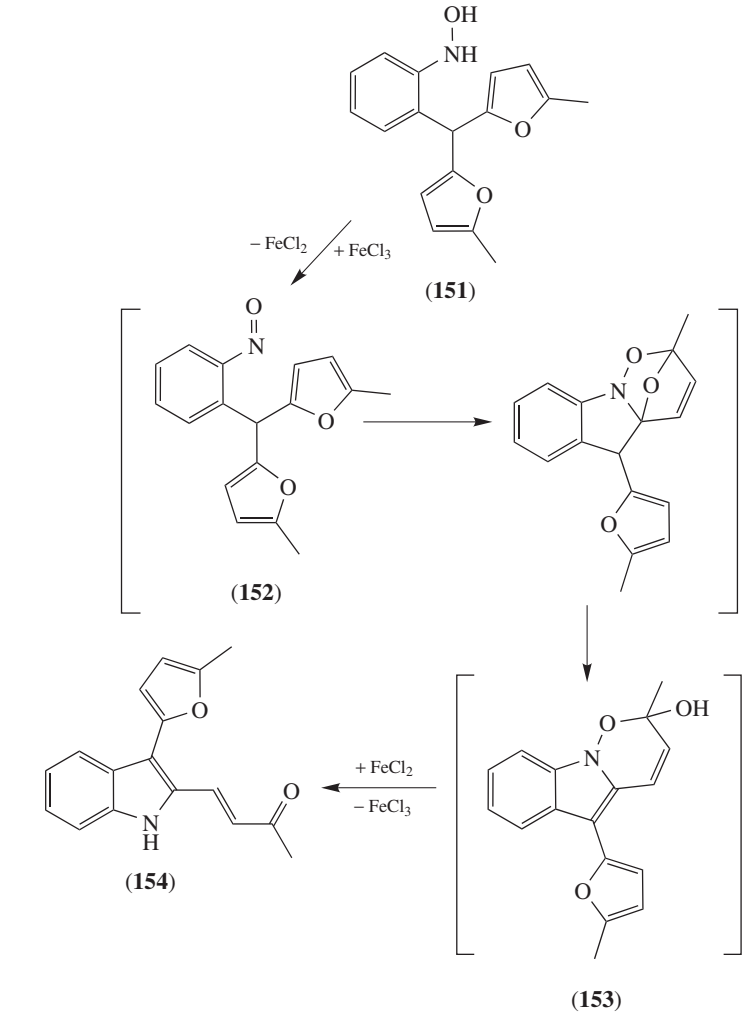
Belleys group[183, 184] in their studies of synthesis of indoles from 2-(2-nitroaryl)acetonitriles (**158**) found that in the presence of $Pd(PPh_3)_4$ the reaction proceeded through the hydroxylamine derivatives **159**. In some cases intermediates **159** could be isolated (for example, when $R = CF_3$, $R^1 = 4\text{-}MeOC_6H_4$) and treated with $Pd(PPh_3)_4$ to obtain 2-amino-1-hydroxyindoles (**160**) (equation 33). In the absence of $Pd(PPh_3)_4$ indole formation was not observed[183].

Treatment of *N*-benzoyl- or *N*-tosyl-*N*-biphenylhydroxylamines (**161**) with P_4O_{10} in refluxing benzene produces the carbazoles **162** in 70% and 55% yields, respectively

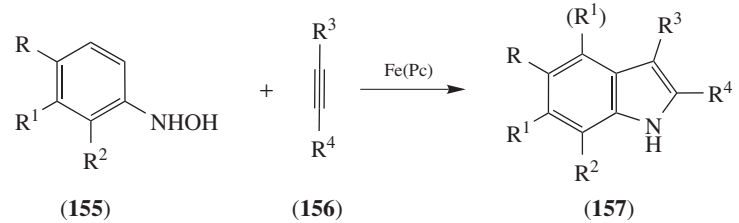
(equation 34)[185]. The initial step of the reaction is most likely the formation of a polyphosphate ester from the hydroxylamine. Then the reaction proceeds either by displacement of the polyphosphate ion by the phenyl ring or, in case of R = H, by loss of the polyphosphate ion and formation of a nitrenium ion. However, the yield of unsubstituted carbazole **162** (R = H) never exceeded 20%[185–187].



(30)

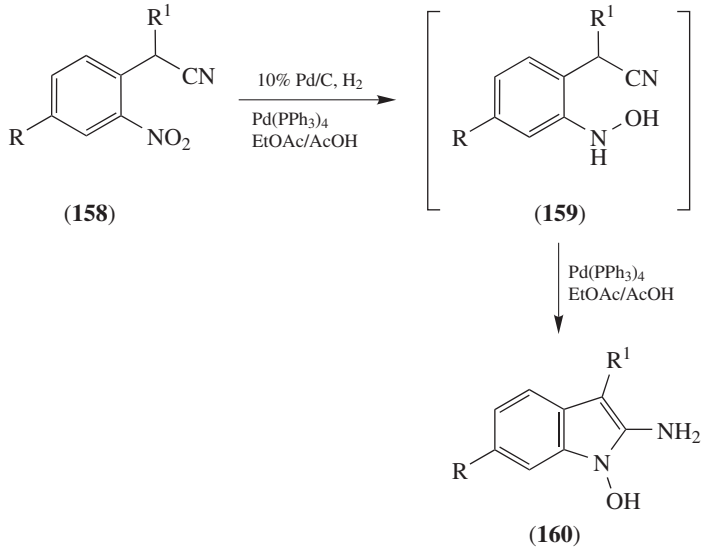


(31)



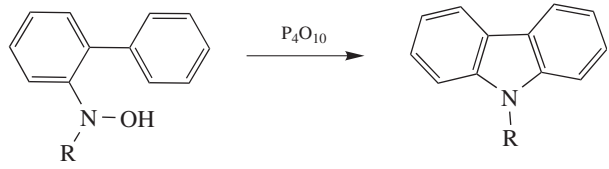
(32)

R = H, Me, CN, Cl; R^1 = H, Me, CF_3, Cl; R^2 = H, Me; R^3 = Ar, Py; R^4 = H, Me



(**158**) (**159**) (**160**) (33)

R = H, CF_3, F, Cl, MeO, Ms; R^1 = Ar, CN, CO_2Et, Ms



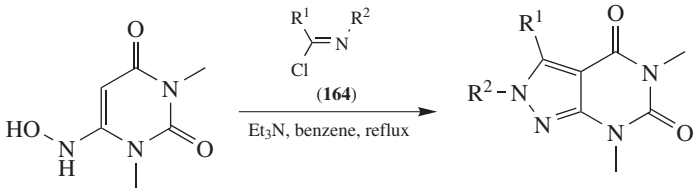
(**161**) (**162**) (34)

R = H, 0–20%
R = Bz, 70%
R = Tos, 55%

D. Pyrazoles and Imidazoles

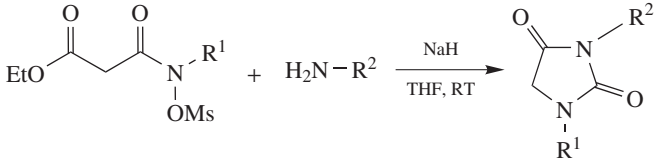
Hydroxylamines and hydroxamic acids often serve as a source of nitrogen atom with attached exocyclic oxygen in formation of pyrazole and imidazole derivatives. However, some cases wherein cleavage of the N−O bond was employed were reported. For example, reaction of hydroxylamine **163** having a pyrimidine moiety with α-chloroimine derivatives **164** in the presence of triethylamine afforded pyrazolo[3,4-*d*]pyrimidines **165** in a good yield (equation 35)[188], and *N*-mesyloxyhydroxamic acids (**166**) were converted to 2,4-imidazolidinones **167** upon treatment with a mixture of benzylamine or hydrazines and sodium hydride (equation 36)[189].

Treatment of (4-oximino-2-methyl-2-pentyl)hydroxylamine with sodium hypobromite leads to 3-bromo-3,5,5-trimethyl-1-pyrazoline-1,2-dioxide in a moderate yield[190]. The reaction of 3-substituted methyl 3-bromo-2-isocyanoacrylates (**168**), which were derived from the corresponding 3-substituted methyl 2-(formylamino)acrylates, with benzyloxyamine allows the synthesis of the 1-benzyloxyimidazoles **169** (equation 37)[191].



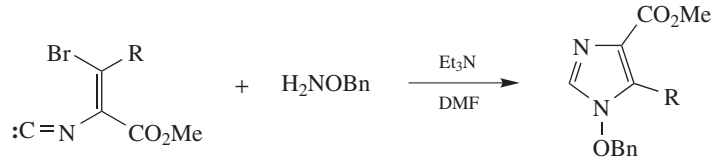
(163) (165) (35)

R^1 = Ph; R^2 = Ph, 4-$EtOC_6H_4$, 4-MeC_6H_4, 3-ClC_6H_4



(166) (167) (36)

$R^1 = C_6H_{11}$; R^2 = Bn, 65%
R^1 = Me; PhNH, BocNH, CO_2All, 60–70%

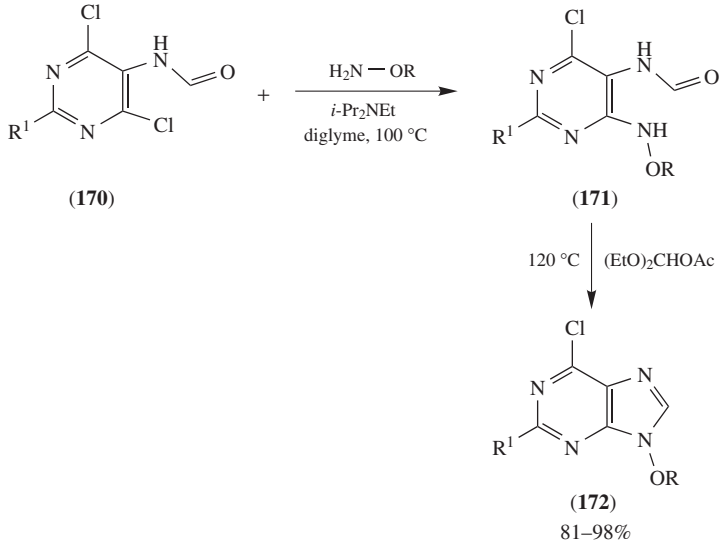


(168) (169) (37)

R = *i*-Bu, Ph, Tol 72–82%

1-Alkoxyimidazole was prepared from alkoxyamine and ethyl *N*-(carbamoylcyano) methylformidate[192]. Synthesis of 9-alkoxypurines as potential antiviral agents from the corresponding 4,6-dichloropyrimidines and alkoxyamines was described[193–197]. For example, reaction of *O*-protected hydroxylamines with derivatives of either 4,6-dichloro-2,5-pyrimidine or 4,6-dichloro-5-pyrimidine **170** and subsequent cyclization of the resultant 6-(alkoxyamino)pyrimidines **171** by heating with diethoxymethyl acetate afforded the 9-alkoxy-6-chloropurines **172** (Scheme 17)[194].

The 1-hydroxy-3-imidazolines[198–204] and the 4*H*-imidazo[2,1-*b*]isoxazole derivatives[201] were obtained from α-hydroxylaminoketones. Thus, condensation of hydroxylaminoketone (**173**, R^1 = Me; $R^2 = R^3$ = Et) with propanal or pentan-3-one in the presence of ammonium acetate or aqueous ammonia gave the imidazolines **174** or **175**, respectively (Scheme 18)[203]. The reaction of **173** with acetylacetone or ethyl acetoacetate gave the hemiacetals **176** or the imidazoisoxazol-6-ones **177**[201]. In the case of the cyclic derivative **173** (R^1R^2 = $(CH_2)_4$), the condensation reaction with acetylacetone was also accompanied by the formation of a considerable amount of pyrazine **178**.



R = 2,2-dimethyl-1, 3-dioxan-5-yl, $(CH_2)_2OBn$, $(CH_2)_2OTBDMS$; R^1 = H, NHCHO

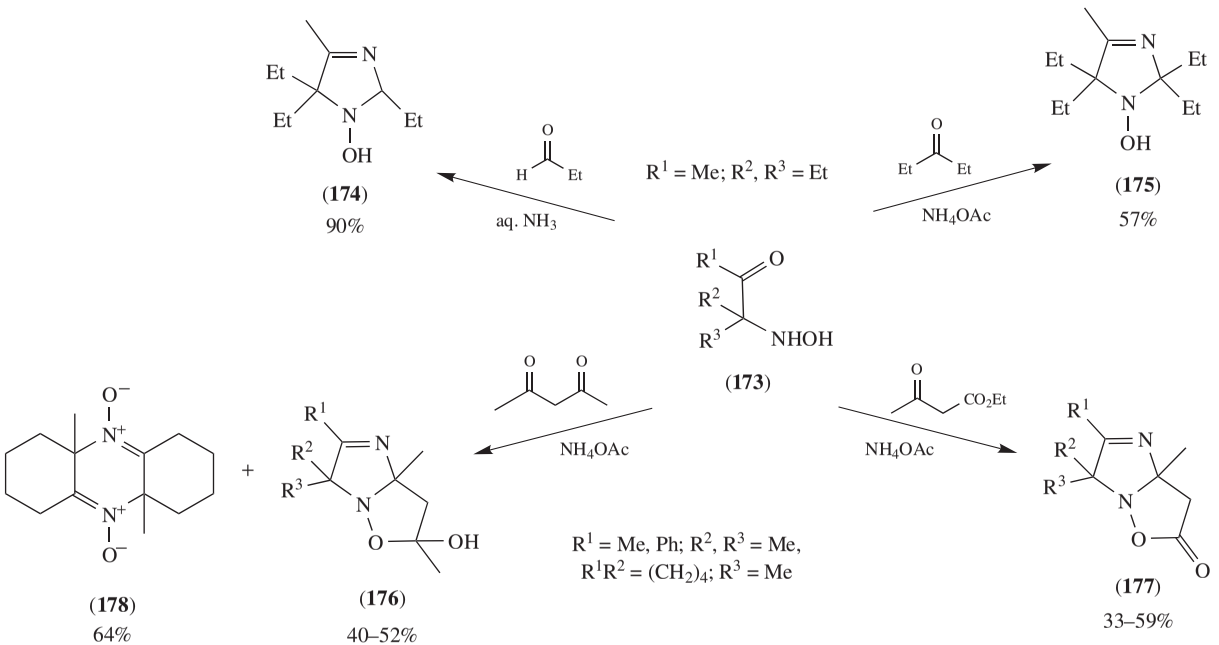
TBDMS = *tert*-butyldimethylsilyl

SCHEME 17

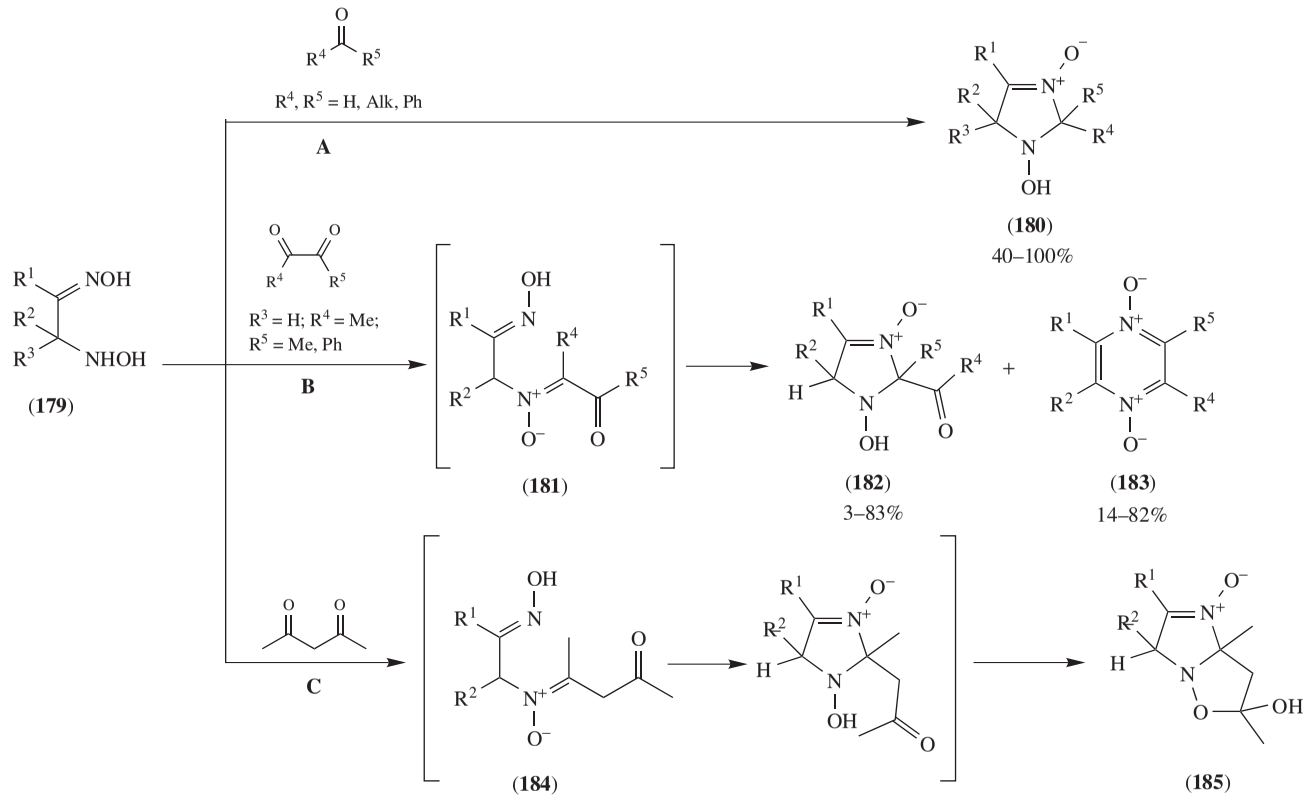
Condensation of the α-hydroxylaminooximes with carbonyl compounds to form 3-oxyimidazoline derivatives was reviewed[205], therefore only several examples will be presented to illustrate this approach.

The 1-hydroxy-3-oxyimidazolines **180** were prepared by the reaction of α-hydroxylaminooximes with aldehydes or ketones (Scheme 19A)[205]. The reaction of 1,2-hydroxylaminooximes with the 1,2-dicarbonyl compounds, depending on the reagents and reaction conditions, gave the 2-acyl-1-hydroxy-3-imidazolin-3-oxides (**182**) and the pyrazine derivatives **183** (Scheme 19B)[206–208]. The formation of the mixture of 1-hydroxyimidazole and pyrazine-1,4-dioxide derivatives proceeded through an initially formed nitrone **181**, which underwent cyclization at both the carbon atom of the nitrone group and the carbon atom of the carbonyl group to form the final products **182** and **183**[206]. The condensation of 1,2-hydroxylaminooximes **179** (R^3 = H) with acetylacetone forms tetrahydroimidazo[1,2-*b*]isoxazoles (**185**) (Scheme 19C)[209]. The formation of imidazoisoxazoles **185** apparently started with condensation of the hydroxylamino group of compounds **179** with the carbonyl group of acetylacetone to give β-oxonitrones **184**. Intramolecular addition of the nitrogen atom of the oxime group to the C atom of the nitrone followed by a second intramolecular addition of the hydroxyl group to the carbonyl formed the final products **185**.

A formation of imidazolidinone **191** from Weinreb amide **186** by treatment with potassium hexamethyldisilazide was observed (Scheme 20)[210]. A possible reaction mechanism involves formation of the enolate **187**, which undergoes a cascade of intramolecular cyclization and ring opening reactions through anions **188**, **189** and **190** that result in product **191** upon protonation.


(174)
90%
aq. NH3
R1 = Me; R2, R3 = Et
NH4OAc
(175)
57%
(173)
NH4OAc
NH4OAc
CO2Et
(178)
64%
(176)
40–52%
R1 = Me, Ph; R2, R3 = Me,
R1R2 = (CH2)4; R3 = Me
(177)
33–59%

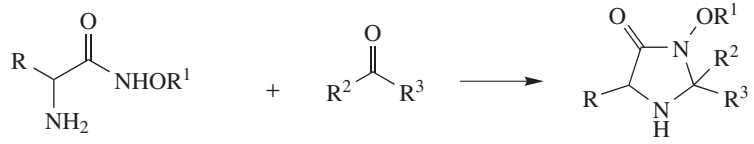
SCHEME 18



R^1 = Me, Ph, furan-2-yl, 5-nitrofuran-2-yl, 2-thienyl; R^1R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$; R^2 = H, Me; R^3 = H, Me

SCHEME 19

A general method for synthesis of imidazolidin-4-one derivatives **193** is the reaction of α-aminohydroxamic acids **192** with a variety of ketones[211–213] or aldehydes[214–217] (equation 38).



(38)

(**192**)

R = H, Alk, CH_2OH, Ar, hetaryl;
R^1 = H, Bn, 2,4-dimethoxybenzyl

$R^2 = R^3$ = H, Me;
$R^1R^2 = (CH_2)_4$, $(CH_2)_5$;
R^2 = Me; R^3 = Et, *t*-Bu, Ph;
R^2 = H; R^3 = Alk, cycloalkyl, Ar, hetaryl

(**193**)

27–90%

E. Isoxazoles, Dihydroisoxazoles and Isoxazolidines

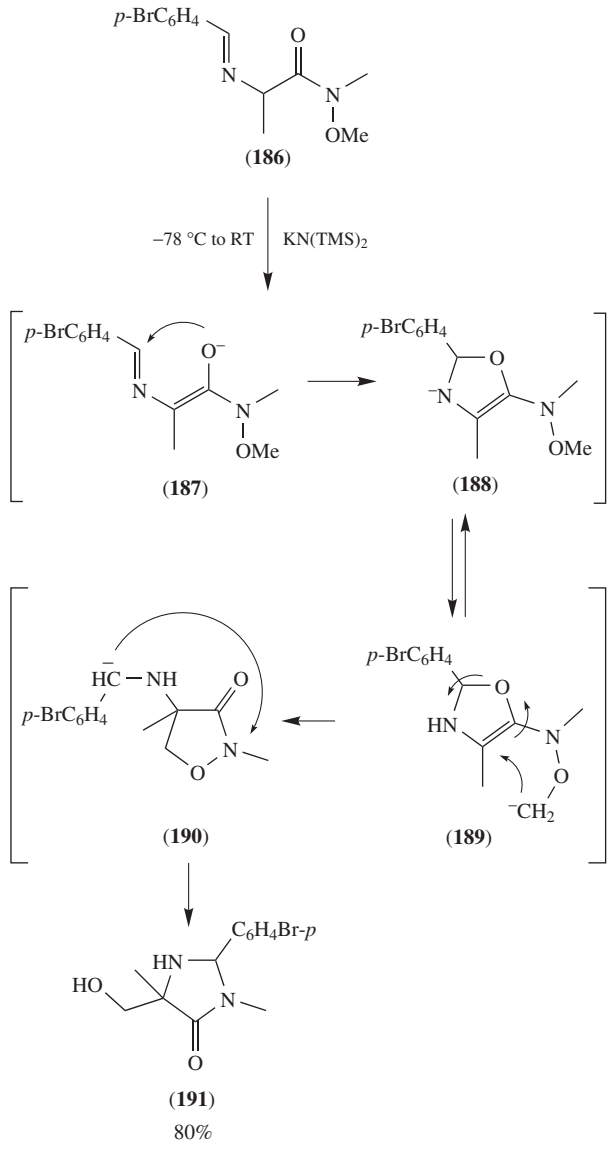
The majority of methods for the construction of an isoxazole ring involves a reaction of a hydroxylamine derivative, as a source of an N–O fragment, with a three-carbon atom component, such as 1,3-diketones, β-keto esters, α,β-unsaturated carbonyl compounds bearing leaving groups, β-ketonitriles and enaminoketones. The syntheses of isoxazoles from hydroxylamines and other approaches were reviewed[218, 219]. Therefore, only examples from the last decade were surveyed along with some experimental details and reaction mechanism consideration.

Derivatives of 3,5-diarylisoxazole **196** were prepared and tested as antihyperglycemic and lipid lowering agents. The key step of the synthesis was the isoxazole ring **195** formation in the reaction of diarylketone **194** with hydroxylamine (Scheme 21)[220].

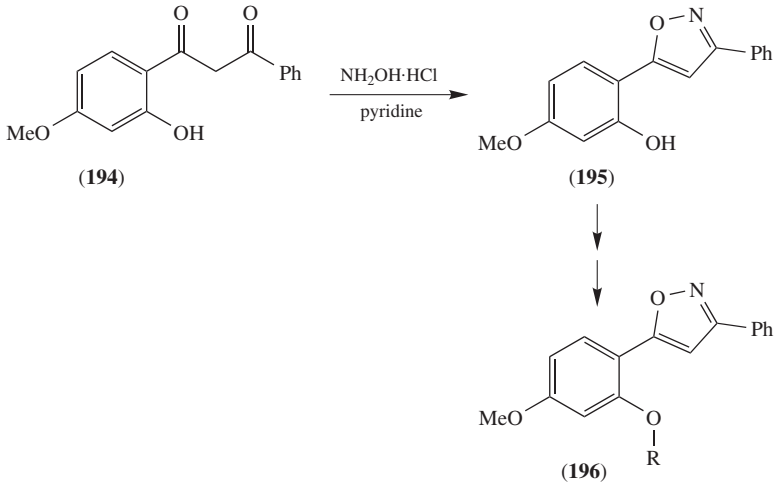
A series of 3-substituted and 3,5-disubstituted isoxazoles **201** have been synthesized in moderate to excellent yields and high regioselectivity by the reaction of *N*-hydroxy-4-toluenesulfonamide (**198**) with α,β-unsaturated aldehydes or ketones **197** (Scheme 22)[221]. It was proposed that the reaction proceeds through conjugate addition of hydroxylamine **198** to the double bond of the enone **197**, elimination of the tosyl moiety from the adduct **199** and a cyclization–dehydratation process of β-ketooximes **200**.

Diarylisoxazoles were also synthesized regioselectively by the reaction of 1,3-diarylpropenones with hydroxylamine hydrochloride using K_2CO_3 as a solid support under microwave conditions[222]. The aryl group from the 3rd position of the propionate always incorporates in the 3rd position of the formed isoxazole and the aryl group from the 1st position is incorporated in the 5th position. 3-Methyl-5-(methylthio)isoxazole-4-carboxamides were prepared in excellent yields by cyclization of various α-acylketene dithioacetals with hydroxylamine hydrochloride in aqueous medium[223].

The reaction of 3-acylchromones **202** with hydroxylamine occurred via nucleophilic 1,4-addition followed by opening of the pyrone ring and subsequent cyclization to 4-(haloalkyl)-4*H*-chromeno[3,4-*d*]isoxazol-4-ols (**204**) (Scheme 23)[224]. Chromone **202** ($R^1 = NO_2$, R^2 = H, $R^3 = CF_3$) with hydroxylamine under the same reaction conditions afforded a mixture of two (*syn* and *anti*) isomers of dioxime **206** and isoxazoline **207** (ring-chain isomer). The alternative cyclization of **203** involving the oxime hydroxyl and the carbonyl carbon connected to the R^3 group occurred only in the case of difluoromethylchromone **202** ($R^1 = R^2$ = H, $R^3 = HCF_2CF_2$) and resulted in formation of salicyloylisoxazole **205a** and its oxime **205b**.


p-BrC6H4
O
N
N
OMe
(186)
–78 °C to RT
KN(TMS)2
p-BrC6H4
O–
N
N
OMe
(187)
p-BrC6H4
O
–N
N
OMe
(188)
p-BrC6H4
O
HN
N
O
–CH2
(189)
–HC – NH
p-BrC6H4
O
N
O
(190)
C6H4Br-p
HN
HO
N
O
(191)
80%

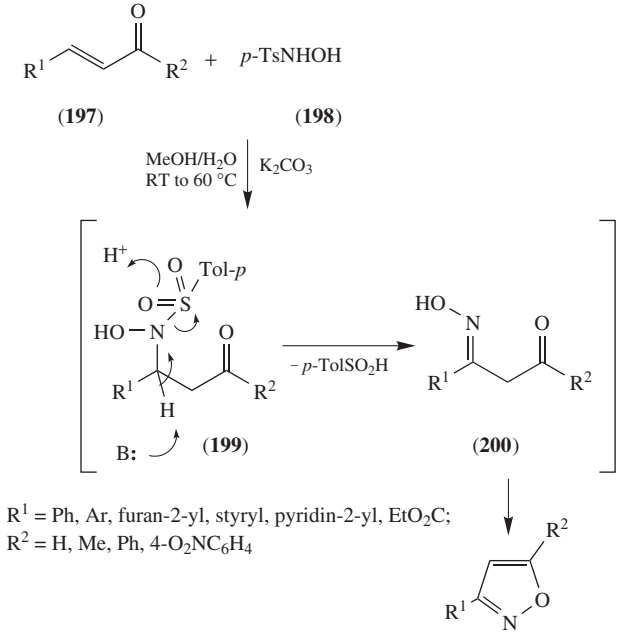
SCHEME 20



(**194**) (**195**) (**196**)

R = alkylamines and alkylhydroxylamines

SCHEME 21

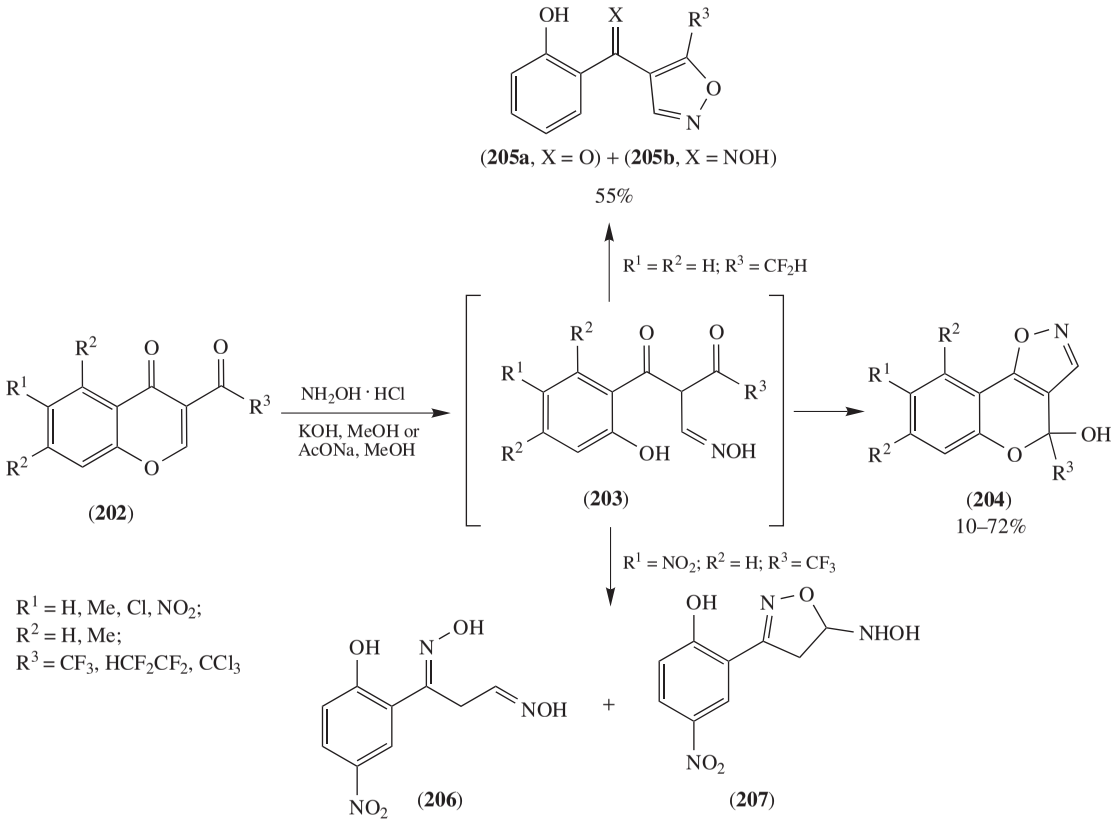


(**197**) (**198**) (**199**) (**200**) (**201**)

R^1 = Ph, Ar, furan-2-yl, styryl, pyridin-2-yl, EtO_2C;
R^2 = H, Me, Ph, 4-$O_2NC_6H_4$

41–92%

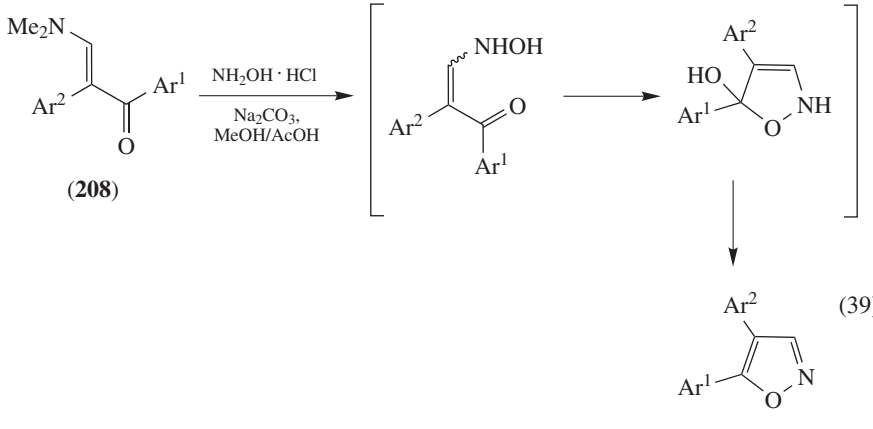
SCHEME 22


OH
X
R3
O
N
(205a, X = O) + (205b, X = NOH)
55%
R1 = R2 = H; R3 = CF2H
R2
O
O
R1
R3
R2
O
NH2OH · HCl
KOH, MeOH or
AcONa, MeOH
R2
O
O
R1
R3
R2
OH
NOH
(203)
R2
O–N
R1
OH
R2
O
R3
(204)
10–72%
(202)
R1 = H, Me, Cl, NO2;
R2 = H, Me;
R3 = CF3, HCF2CF2, CCl3
R1 = NO2; R2 = H; R3 = CF3
OH
N
OH
OH
NOH
NO2
(206)
+
OH
N–O
NHOH
NO2
(207)
40% (206 + 207)

SCHEME 23

A reaction of β-ketonitriles with hydroxylamine under basic conditions provided 5-aminoisoxazoles. This synthetic approach was applied to the preparation of the indol-3-yl[225] and indol-7-yl[226] derivatives of isoxazole.

An amine exchange reaction of enaminoketone was used for the regioselective synthesis of substituted isoxazoles[227, 228]. Thus, a series of 4,5-diarylisoxazoles (**209**) as potential antimitotic agents was prepared by the reaction of the enaminoketones **208** with hydroxylamine hydrochloride (equation 39)[227].

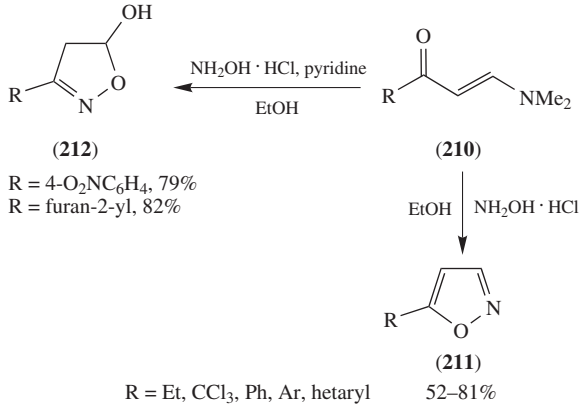


(**208**) (**209**) (39)

Ar^1 = 4-$MeOC_6H_4$, 3-BnO-4-$MeOC_6H_3$, 2,3,4-$(MeO)_3C_6H_2$;
Ar^2 = 4-$MeOC_6H_4$, 3-BnO-4-$MeOC_6H_3$, 3-O_2N-4-$MeOC_6H_3$, 3,4,5-$(MeO)_3C_6H_2$

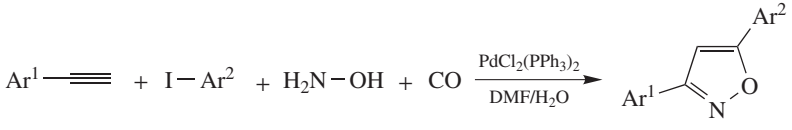
Treatment of the β-dimethylaminovinyl ketones (**210**) with an excess of hydroxylamine in refluxing ethanol also led to regioselective formation of 5-substituted isoxazoles **211** (Scheme 24)[228]. Addition of pyridine to the reaction mixture diminished the regioselectivity of the ring closure. For example, 3-nitrophenyl- and 3-furanyl-4,5-dihydroisoxazoles (**212**) were the main products in this case. The regioselectivity observed when the reaction was carried out without pyridine could be explained by the stronger reactivity of a β-carbon atom, which was increased as the concentration of HCl, coming from hydroxylamine hydrochloride, increased. Therefore, the addition of the NH_2 group on a β-position occurred first, followed by the addition of the OH group to the carbonyl carbon to give the 5-substituted-isoxazoles **211**. If pyridine was used in a stoichiometric amount with hydroxylamine hydrochloride, all HCl was trapped and free hydroxylamine could attack both electrophonic centers (β-carbon and carbonyl carbon) of enaminone **210**[228].

Isoxazole derivatives were obtained by palladium[229] or copper[230] catalyzed multicomponent reaction. One-pot four-component coupling of a terminal alkyne, hydroxylamine, carbon monoxide, and an aryl iodide at room temperature and a 1 atm pressure of carbon monoxide in the presence of $PdCl_2(PPh_3)_2$ gave isoxazole derivatives **213** (equation 40)[229]. The reaction is regioselective; an aryl group from the acetylene derivative incorporates in the 3rd position, and from iodide in the 5th position, of isoxazoles **213**. Presumably the reaction proceeded via carbonylative Sonogashira coupling followed by a ring closure of formed α,β-alkynyl ketone with hydroxylamine.



SCHEME 24

Recently, Fokin's group described a one-pot three-step process for the synthesis of 3,5-disubstituted isoxazoles from aldehydes and alkynes[230]. At first, the aldehyde **214** was converted to the corresponding aldoxime **215** by the reaction with hydroxylamine. Without isolation, the oxime **215** was transformed to the corresponding nitrile oxide **216** that underwent a stepwise addition to a copper(I) acetylide giving the 3,5-disubstituted isoxazole **217** (Scheme 25).



(40)

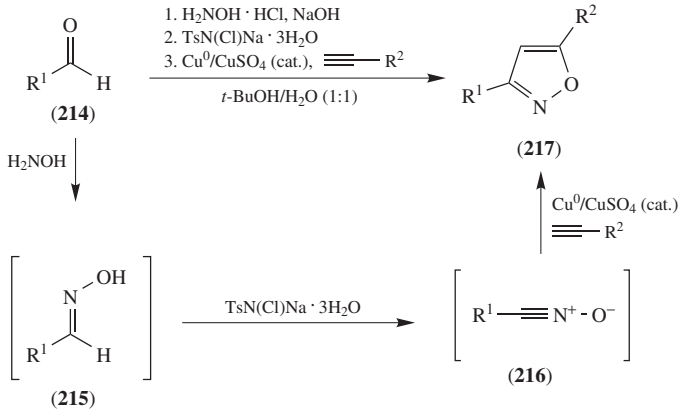
(**213**)

Ar^1 = Ph; Ar^2 = 4-$MeOC_6H_4$, 66%;
Ar^1 = 4-$MeOC_6H_4$; Ar^2 = Ph, 54%

A general method for preparation of 3-hydroxybenzoisoxazoles is the cyclodehydration of 2-hydroxybenzohydroxamic acids. For example, some 3-hydroxybenzoisoxazoles (**219**) were obtained by treatment of salicylohydroxamic acids (**218**) with 1,1-carbonyldiimidazole (CDI) (equation 41)[231, 232]. However, this procedure can also result in the formation of the oxazinediones **220** and the benzoxazolones **221** as side or even major products[232].

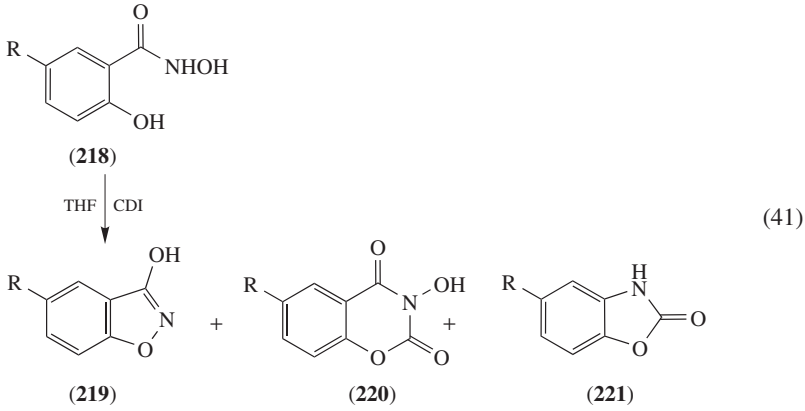
In order to overcome such side reactions, it was recommended to synthesize the 3-hydroxybenzoisoxazole derivatives **219** from *N*-trimethoxybenzyl-protected 2-fluoroarylhydroxamic acids (**222**) by intramolecular S_N-type arylation with subsequent cleavage of the protecting group (equation 42)[232].

N-Substituted benzoisoxazole derivatives **224** were prepared from the salicylohydroxamic acids **223** by intramolecular Mitsunobu reaction (equation 43)[233, 234]. If hydroxamate **223** had additional free hydroxyl group at the 4th position, only benzoxazolones were formed via Lossen rearangement[233].



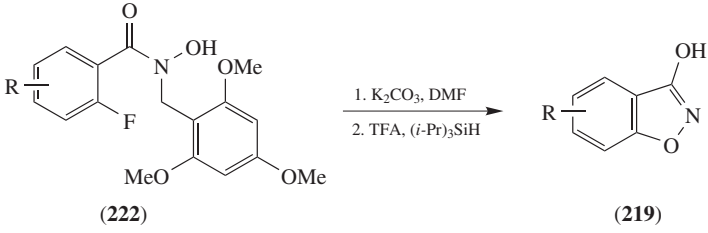
R^1 = styryl, Et, *n*-Bu, *c*-Hex, *t*-Bu, Ph_2Me, Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-BrC_6H_4, C_6F_5, furan-2-yl;
R^2 = *n*-Pen, *c*-Hex, CH_2OH, CO_2H, CH_2OR, Ph

SCHEME 25



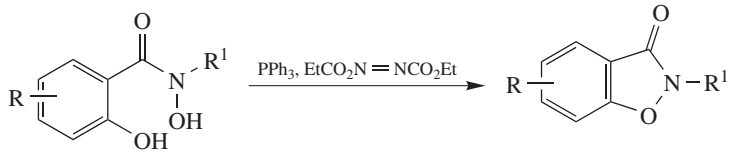
(41)

R = Cl, OMe, Ac 42–89%



(42)

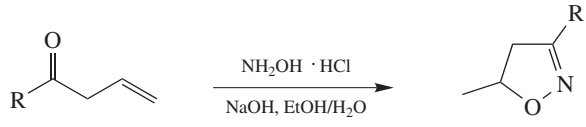
R = 4-CF_3, 6-CF_3, 6-F 47–99%



(43)

(**223**) (**224**)

R = H, 6-CHO, 5-OMe, 6-NO_2, 6-AcNH;
R^1 = Ph, *t*-Bu, Me, *c*-Hex, *i*-Pr, 4-BrC_6H_4, 4-NCC_6H_4



(44)

(**225**) (**226**)

37–63%

R = *n*-Pen, 2-phenylethyl, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-Naph, 2-Naph

Dihydroisoxazoles were prepared through either the 1,3-cycloaddition of nitrones or the condensation of hydroxylamines and unsaturated ketones[235]. For example, 3-substituted 5-methyl-4,5-dihydroisoxazoles (**226**) were obtained from β,γ-unsaturated ketones **225** and hydroxylamine hydrochloride (equation 44)[236].

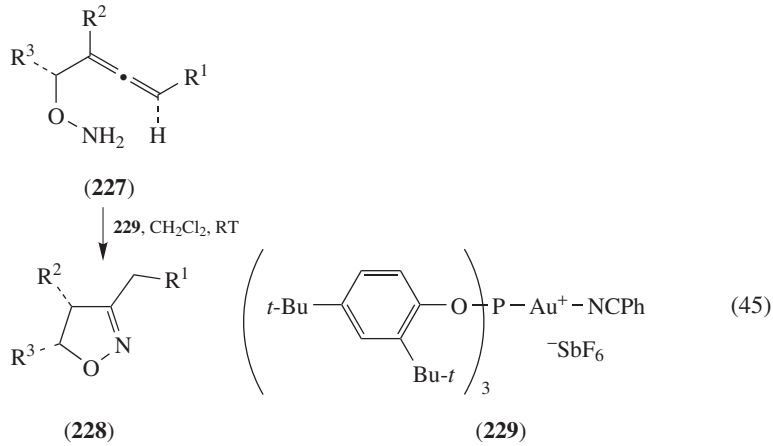
In recent years intramolecular cyclization procedures of hydroxylamine derivatives bearing an allene[120] or alkyne[237–240] group were developed for the regioselective synthesis of dihydroisoxazoles.

The 4,5-dihydroisoxazolines **228** were obtained from the allenic hydroxylamines **227** in high yields in the presence of the gold catalysts **229** (equation 45)[120]. The diastereoselectivity depends on substituents at the 1st position of hydroxylamine **227**. Thus, with a *tert*-butyldimethylsilyl (TBDMS) ether group ($R^3 = CH_2OTBDMS$) a 1:1 mixture of diastereomers **228** was obtained, but the benzyloxymethyl derivatives **228** ($R^3 = CH_2OBn$) were formed with high *cis* selectivity.

2,5-Dihydroisoxazoles were successfully synthesized from *O*-propargylic hydroxylamines (Scheme 26)[237, 238]. The alkynyl hydroxylamine derivatives **230** underwent 5-*endo*-*dig* cyclizations by interaction with 3 equivalents of molecular iodine to give respectable yields of the corresponding 4-iodo-functionalized isoxazolines **231**[237]. Gold(I)-catalyzed intramolecular hydroamination of compound **230** led to formation of 2,5-dihydroisoxazoles **232**[238].

2,3-Dihydroisoxazoles **234** were obtained from propargylic *N*-hydroxylamines **233**[239, 240] either in the presence of catalytic amounts of ZnI_2 and DMAP[239] (**234**, R = Bz) or by palladium acetate mediated cyclization (**234**, R = Boc)[240] (equation 46).

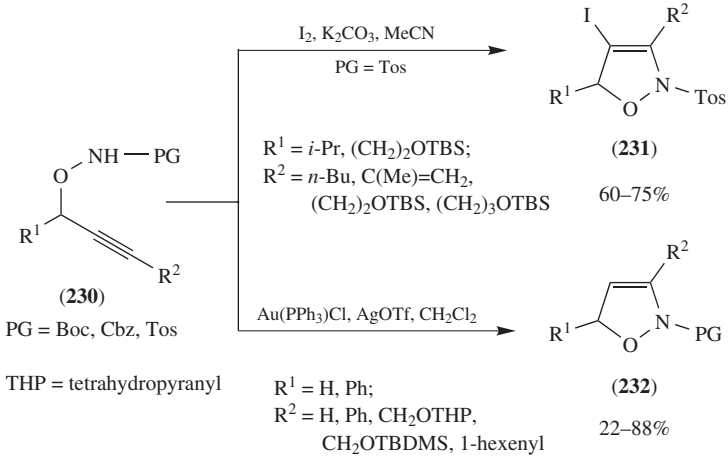
Isoxazolidin-3-ones generally were prepared by nucleophilic intramolecular cyclization of propionhydroxamate derivatives[241–243] and isoxazolidin-5-ones from 3-hydroxyaminopropionates[16, 244–247]. In recent years more attention was devoted to the stereoselective synthesis of isoxazolidin-5-ones, because they can be transformed to enantiopure β-amino acids[248] by a simple hydrogenation procedure with H_2 in the presence of Pd/C.



(45)

72–86%
dr from 51:49 to 94:6

R^1 = H, Me, *i*-Pr, *n*-Bu;
R^2 = H, Me;
R^3 = Me, CH_2OBn, $CH_2OTBDMS$, $(CH_2)_2Ph$, $(CH_2)_2CO_2Et$



SCHEME 26

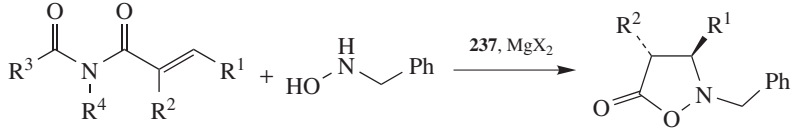
A conjugate addition of *N*-benzylhydroxylamine to α,β-unsaturated amide derivatives **235** in the presence of the chiral ligand **237** and magnesium salts as Lewis acids was studied (equation 47)[249–251]. The pyrrolidinone[249] or the 5,5-dimethyl-1-naphthalenemethylpyrazolidinone[250] moieties were found as the most suitable amide structural fragments for enantioselective synthesis of 4-unsubstituted isoxazolidin-5-ones (**236**, R^2 = H). Products **236** were obtained in good yields and enantioselectivities using

MgI_2 or $Mg(ClO_4)_2$ at −60 °C. For synthesis of disubstituted isoxazolidin-5-ones (**236**, $R^2 \neq H$), *N*-isopropylamides (**235**, $R^3 = i$-Pr, $R^4 = H$) were the optimal substrates with combination of magnesium triflimide[251].

(**233**) (**234**) (46)

R = Bz; R^1 = *i*-Pr, *t*-Bu, Ph; R^2 = Ph, $(CH_2)_2Ph$, $CH_2OTBDMS$; 82–97%

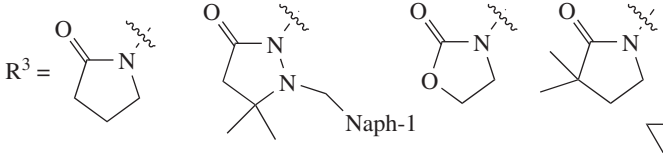
R = Boc; R^1 = *i*-Bu; R^2 = Ph 85%



(**235**) (**236**)

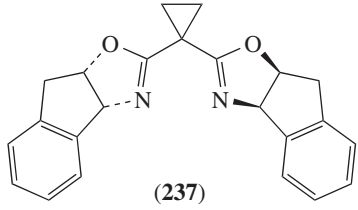
R^1 = Me, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-ClC_6H_4, furan-2-yl, furan-3-yl; R^2 = H 58–90%; *ee* 60–96%

R^1 = Alk, Ph; R^2 = Me, Et, Ph, Br 28–95%; *ee* 60–96%



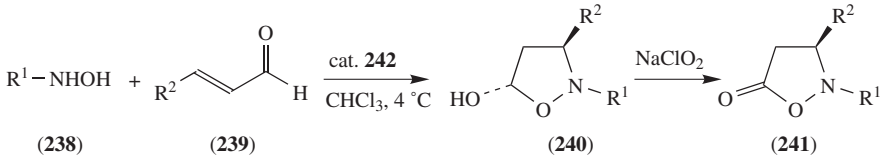
(47)

R^3 = *t*-Bu, *i*-Pr, *c*-Hex, Ar; R^4 = H, Me



(**237**)

The organocatalytic approach was also applied for asymmetric synthesis of isoxazolidin-5-ones and 5-hydroxyisoxazolidines (Scheme 27)[252]. The double addition of *N*-carbamate-protected hydroxylamines **238** to α,β-unsaturated aldehydes **239** occurred in high yields and enantioselectivity in the presence of the pyrrolidine catalyst **242**. The 5-hydroxyisoxazolidines **240** obtained can be isolated or transformed in a one-pot procedure into isoxazolidin-5-ones **241** by oxidation with $NaClO_2$.

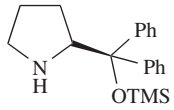


(**238**) (**239**) (**240**) (**241**)

75–94%
ee 90–99%

74–81%
ee 95–99%

R^1 = Boc, Cbz; R^2 = *n*-Bu, *n*-Pr, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-NCC_6H_4, 4-$O_2NC_6H_4$, 2-Naph, CO_2Et



(**242**)

SCHEME 27

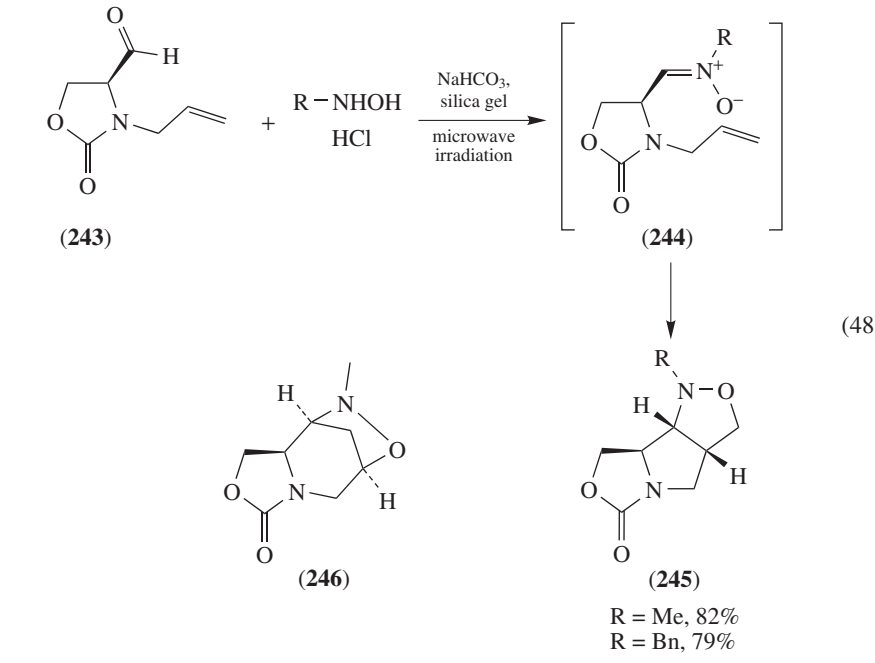
For the construction of an isoxazolidine ring directly from the hydroxylamine derivatives three main methodologies are generally used. One of them exploits [3 + 2] cycloaddition reaction of alkenes with nitrones generated *in situ* by oxidation of secondary hydroxylamines[253–256] or by condensation of carbonyl compounds and monosubstituted hydroxylamines[114, 257–265]. The other is based on Michael-type addition to the activated double bonds[266–269]. The third employs simultaneous cyclization and electrophilic addition of *O*- or *N*-allylic or homoallylic hydroxylamine derivatives[270–275] to the double bond. All three approaches are illustrated below with recent examples.

Tricyclic compounds **245** bearing the isoxazolidine moiety were obtained from the aldehyde **243** and methyl- or benzylhydroxylamine by solvent-free microwave-assisted procedure (equation 48)[263]. The reaction involves *in situ* formation of the nitrone **244** and stereoselective ring closure. If conventional heating was used, the yields of products were lower and bridged isoxazolidine **246** formation was observed.

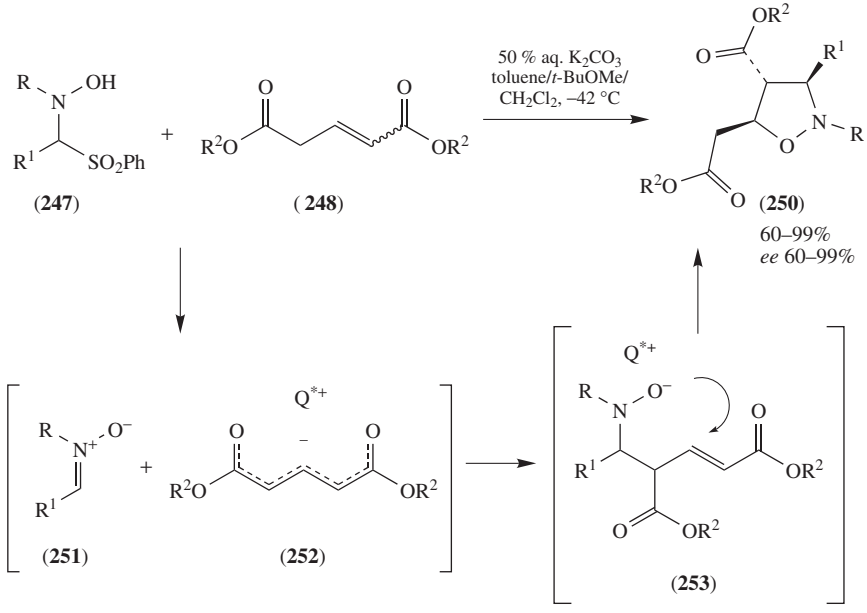
A reaction of *N*-hydroxy-α-amidosulfones **247** with glutaconates **248** in the presence of 10% of *Cinchona* alkaloid-derived ammonium salts **249** as catalyst produces isoxazolidines **250** in good to excellent yields and high enantioselectivity under phase-transfer conditions (Scheme 28)[256]. Initially, *N*-carbamoyl nitrones **251** that were generated by elimination of phenylsulfone group from compounds **247** were added in an enantioselective fashion to the chiral enolate **252**. The resulting anionic adducts **253** then cyclized diastereoselectively to the corresponding isoxazolidines **250**.

Intramolecular Michael addition to the activated double bond occurs very easily. For example, isoxazolidine **255** was formed from hydroxycarbamate **254** upon removal of the silyl group by fluoride ion (equation 49)[268].

Electrophilic cyclizations of various *O*-homoallylhydroxylamines **256** were studied (equation 50)[274]. *N*-Sulfonyl derivatives **256** (R = $PhSO_2$, R^1 = Ph) provided isoxazolidines **257** with moderate *cis* selectivity, from 3.8:1 to 7:1, but *N*-acylamines **256** (R = Ac) afforded iodoisoxazolidines **257** (X = I) with higher stereoselectivity (10.8–12.5:1) by reaction of *N*-iodosuccinimide. However, no substantial difference in stereoselectivity was observed when *N*-acyl or *N*-sulfonyl derivatives **256** were used in the reaction with PhSeBr or *N*-bromosuccinimide as electrophiles.

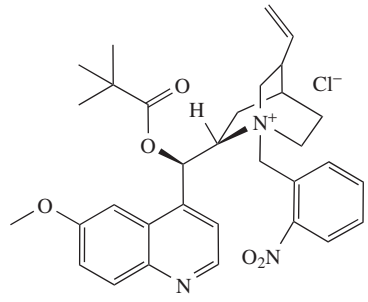


(48)



R = Boc, Cbz; R^1 = Alk, cycloalkyl, Bn, $Ph(CH_2)_2$, Ar; R^2 = Alk, All, Bn

SCHEME 28



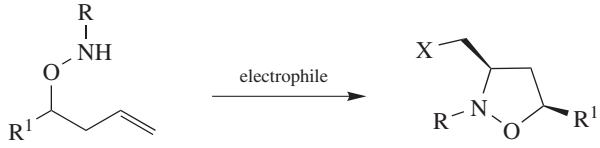
(**249**, Q*)

SCHEME 28. (*continued*)

N-Trimethylsilyloxy-*N*-benzylhomoallylhydroxylamine **258** underwent stereospecific 5-*exo*-*trig* iodocyclization reaction to afford 4,5-*cis*-isoxazolidines **259** (equation 51)[275]. A single isoxazolidine **259** was obtained from each adduct **258**; in particular, *syn*-**258** afforded 3,4-*cis*-4,5-*cis*-**259**, while 3,4-*trans*-4,5-*cis*-**259** was obtained from *anti*-**258**. The resulting 3,4-*cis*-4,5-*cis*- and 3,4-*trans*-4,5-*cis*-3-alkyl-4-acetoxy-5-iodomethyl isoxazolidines **259** can be versatile starting materials for the synthesis of pyrrolidine azasugars.

In recent years several procedures for synthesis of isoxazolidines by palladium catalyzed cyclofunctionalization were published. Both *N*- and *O*-homoallylhydroxylamine derivatives are suitable starting materials for the isoxazolidinine ring respective O—C[276–279] or N—C[279–283] bond formation.

(**254**) (**255**) 99% (49)

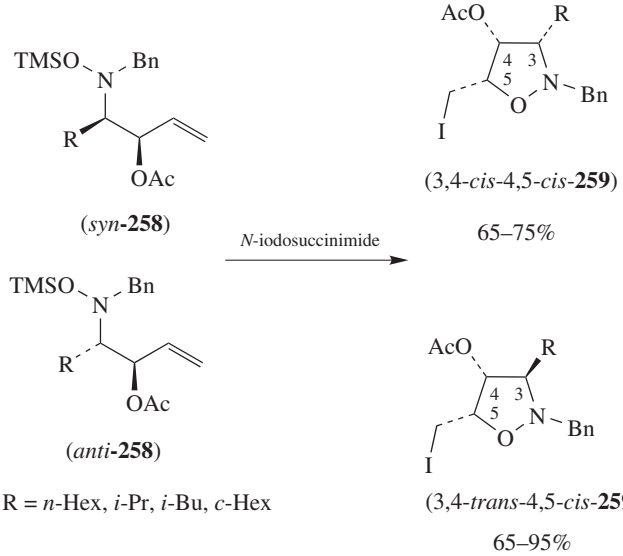


(**256**) (**257**) (50)

R = $PhSO_2$, Ac; R^1 = Me, C_6H_{11}, Ph; X = Cl, Br, I, PhSe

61–77 %
cis:*trans* from 3.8:1 to 12.5:1

electrophile = PhSeBr, NaOCl, I_2, *N*-bromo- or iodosuccinimide



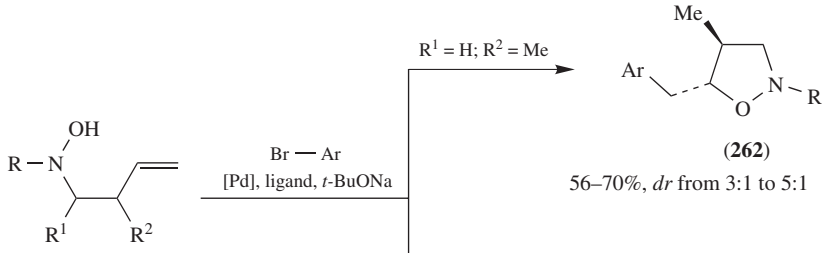
(51)

5-Arylmethyleneisoxazolidines **262**, **263** and **264** were obtained from hydroxylamine derivatives **260** and **261** and aryl or heteroaryl bromides in the presence of $Pd(OAc)_2$ and bis(2-diphenylphosphinophenyl)ether (DPEPhos)[276] or tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos)[277] (Scheme 29). The stereoselectivity of this transformation was moderate; only bicyclic isoxazolidines **264** were isolated as single diastereomers[277]. Also attempts to cyclize unprotected hydroxylamines (**260**, R = H) or Boc-protected derivatives of **260** (R = Boc) were unsuccessful[276].

Synthesis of isoxazolidines from *O*-homoallylhydroxylamine derivatives by Pd-catalyzed N−C(3) bond formation reaction proceeds with better stereoselectivity than the related O−C(5) ring closing presented above. Thus, *cis*-3,5-disubstituted *N*-carbamoylisoxazolidines **266** (R = Boc, MeOCO) were prepared from *O*-homoallylhydroxylamines **265** and aryl bromides in a good yield and high stereoselectivity (up to >20:1 *dr*) in the presence of $Pd_2(dba)_3$ and *t*-Bu_3P (equation 52)[279]. The reaction of *N*-unsubstituted *O*-homoallylhydroxylamines **265** (R = R^2 = R^3 = H) with aryl bromides afforded the corresponding *N*-arylisoxazoles **266** (R^4 = Ar) as a single diastereomer by $Pd_2(dba)_3$ and Xantphos catalyzed consecutive *N*-arylation, cyclization and *C*-arylation[281].

Palladium-catalyzed cyclofunctionalization is not limited to synthesis of only aryl-substituted isoxazoles. For example, isoxazolidine-2-carboxylic acid methyl esters (**268**) were prepared from *N*-protected *O*-homoallylhydroxylamines **267** in the presence of carbon monoxide, $Cu(OAc)_2 \cdot 2H_2O$, tetramethylguanidine (TMG) as a base and $PdCl_2$ as a catalyst (equation 53)[282].

5-Vinylisoxazolidines **270** were synthesized by the intramolecular Pd-mediated allylic alkylation of *N*-homoallylhydroxylamines **269** (equation 54)[278]. Depending on both the reaction conditions and the substrates, *cis* or *trans* isomers of compound **270** were preferentially obtained. The *syn* precursor **269** (R = 2,2-dimethyldioxolan-4-yl) gave exclusively a *trans*-substitution pattern of product **270** by using $Pd(OAc)_2$ with LiCl and *anti* precursor **269** afforded only the *cis* isomer of isoxazolidine **270**.



(**260**)

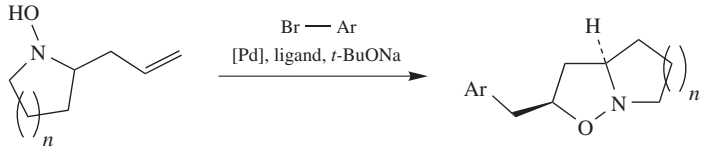
(**262**)

56–70%, *dr* from 3:1 to 5:1

(**263**)

61–93%, *dr* up to 3:1

R = Bn, *t*-Bu, *c*-Hex; R^1 = H, Ph; R^2 = H, Me;
Ar = aryl, biphenyl, hetaryl,



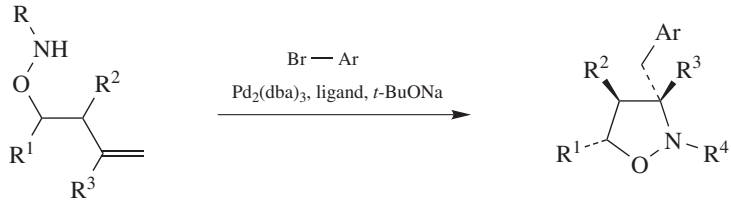
(**261**)

(**264**)

82–94%, *dr* from 9:1 to 100:0

n = 1, 2;
Ar = 2-MeC_6H_4, 3-$MeOC_6H_4$,
4-ClC_6H_4, 2-ClC_6H_4, 3-pyridyl

SCHEME 29



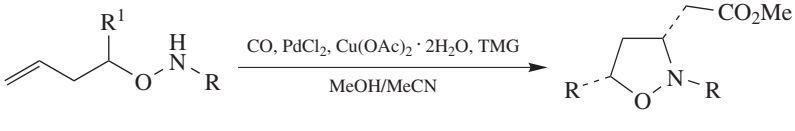
(52)

(**265**)

(**266**)

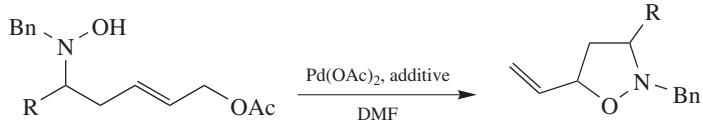
R = H, Boc, CO_2Me; R^1 = H, Me, *i*-Pr, $BnOCH_2$, Ar;
R^2 = H, Ph; R^3 = H, Me; Ar = aryl, hetaryl, alkenyl;
R^4 = R or Ar

42–90%
dr from 14:1 to 100:1

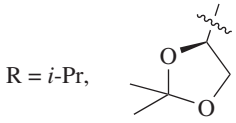


(**267**) (**268**) 30–79% (53)

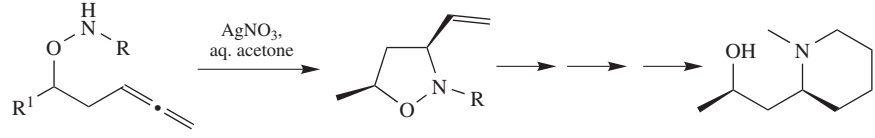
R = Boc, MeOCO, Cbz, 4-$O_2NC_6H_4SO_2$; R^1 = *i*-Pr, Ph, $TBSOCH_2$



(**269**) (**270**) 70–99% (54)



3-Vinylisoxazolidines **272** were obtained in a high yield by treatment of allenic hydroxylamines **271** with $AgNO_3$ (Scheme 30)[283]. However, the diastereoselectivity of this reaction was moderate and the *N*-unsubstituted (R = H) and the *N*-sulfonyl (R = 2-$O_2NC_6H_4SO_2$) derivatives of **271** failed to yield any cyclized product. Notwithstanding, this methodology had been used in a short synthesis of the alkaloid (+) sedamine (**273**).



(**271**) (**272**) (**273**)

R = Boc, Cbz; R^1 = Ph, Me

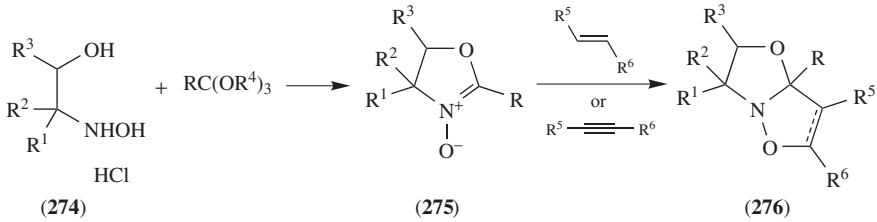
83–98%,
cis/*trans* from 4:1 to 7:1

SCHEME 30

F. Oxazolones, Dihydrooxazoles and Oxazolidines

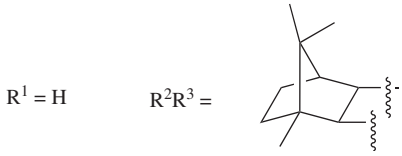
Two pathways were described for the synthesis of oxazole derivatives from hydroxylamines and hydroxamic acids. One involves formation of nitrone species by reaction of β-hydroxyhydroxylamines with orthoesters[284–286] followed by cycloaddition. The other exploits a cleavage of the N−O bond with subsequent addition and rearrangement processes.

Nitrones **275**, that can be considered as 4,5-dihydrooxazole-*N*-oxides, were obtained from hydrochlorides of β-hydroxy-α,α-dimethylhydroxylamines[284, 285] **274** ($R^1 = R^2 = Me$, $R^3 = H$) or 3-(hydroxylamino)borneol[286] (**274**, $R^1 = H$, $R^2R^3 = 1,7,7$-trimethylbicyclo[2.2.1]heptan-2,3-ylidene) and orthoesters (Scheme 31). Compounds **275** can be isolated or, in the borneol derivative case, directly subjected to reaction with various dipolarophiles, such as alkenes and alkynes with electron-withdrawing groups to produce bicycles **276**.



(**274**) (**275**) (**276**)

R = Me, Et, Pr, $(CH_2)_4OPh$, Ph; $R^1 = R^2 = Me$; R^4 = Me, Et;
R^5 = H, Alk, Ph, CO_2Alk, CN, SO_2Ph; R^6 = H, CO_2Alk, Ph;

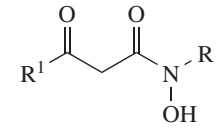


SCHEME 31

3-Aryloxazol-2-ones **280** (R = Ar, R^1 = Alk) were synthesized from β-carbonyl derivatives of hydroxamic acids **277** by treatment with 4-nitrophenylsulfonyl chlorides in the presence of NEt_3 (equation 55)[287]. The reaction mechanism was proposed to be as follows: the carbanionic carbon of intermediate **278** attacks the nitrogen atom of the hydroxamate with the expulsion of the sulfonate ion to give the α-lactam **279**, which isomerizes to oxazol-2-ones **280**. 5-Ethoxy-3-methyloxazol-2-one (**280**, R = Me, R^1 = OEt) was made in 60% yield by sonification of a mixture of the corresponding *N*-mesyloxymalonamide and NaH[189].

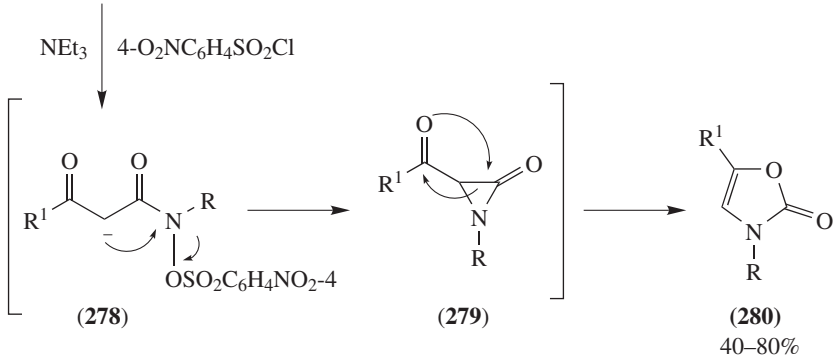
The addition of *N*-oxycarbonyl-*O*-4-nitrophenylsulfonylhydroxylamines (**282**) to α-acylacrylonitriles **281** resulted in formation of 2,5-disubstituted 4-cyano-2,3-dihydrooxazoles **284** (equation 56)[288]. Since 6-oxocyclohex-1-enecarbonitrile yielded stable bicyclic aziridines **285**, it was postulated that the formation of compounds **284** proceeds via rearrangement of the aziridine intermediate **283**. Similarly, 5-trifluoromethyl-2-ethoxy-2,3-dihydrooxazole (**286**) was obtained from 4-ethoxy-1,1,1-trifluorobut-3-en-2-one[289].

Acylnitrenium ions **288**, generated from salicylhydroxamates **287** by treatment with $SOCl_2$ [290] or with Ph_3P/diethyl azodicarboxylate[291], underwent a Lossen rearrangement affording 7-nitro-3-phenylbenzoxazol-2-one[290] (**289**, R = Ph, $R^1 = NO_2$, R^2 = H) or the 5-iodo derivative[291] **289** ($R = R^1 = Me$, R^2 = I) (equation 57).



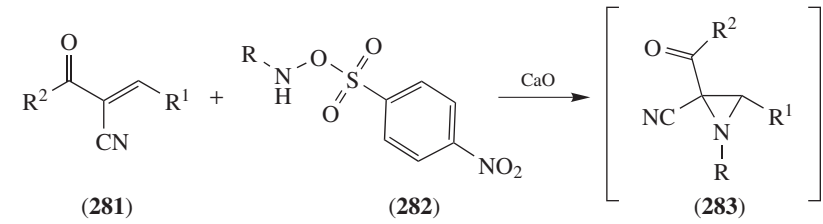
(**277**)

R = Me, Ar; R^1 = Alk, OEt



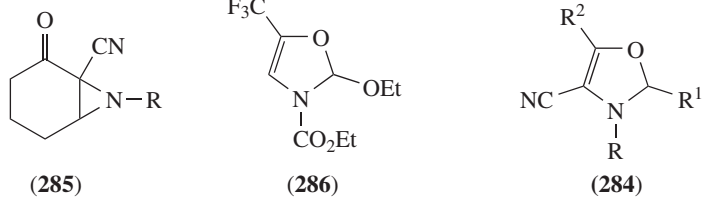
(**278**) (**279**) (**280**) 40–80%

(55)



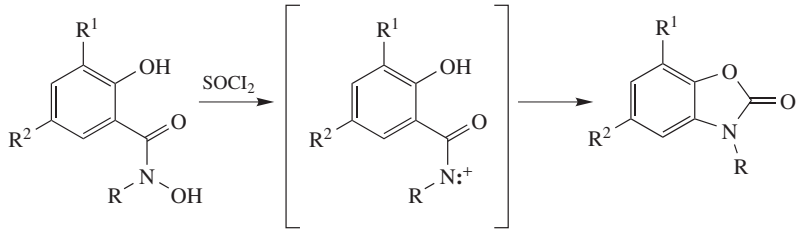
(**281**) (**282**) (**283**)

R = CO_2Et, CO_2Bu-*t*, CO_2Bn; R^1 = Alk, Ph; R^2 = *t*-Bu, Ph



(**285**) (**286**) (**284**) 55–95%

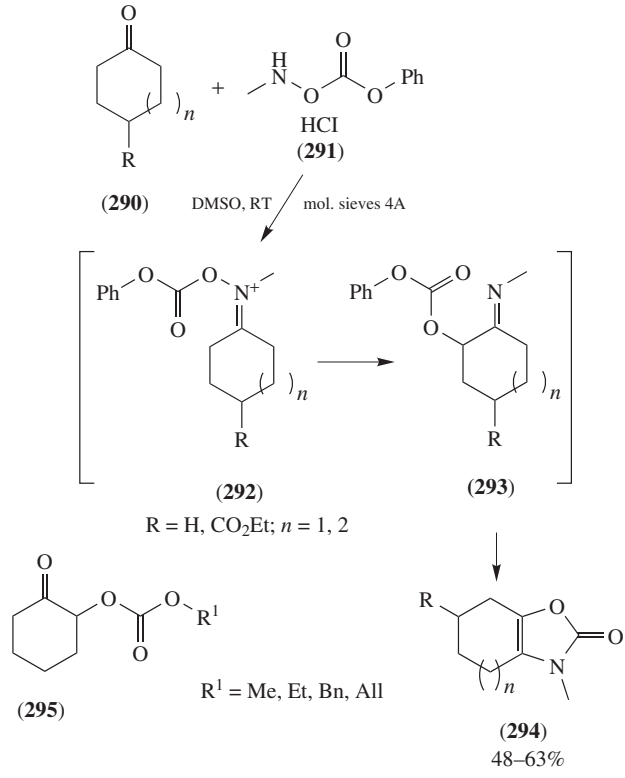
(56)



(57)

R = Ph; $R^1 = NO_2$; R^2 = H;
R = Me; R^1 = Me; R^2 = I

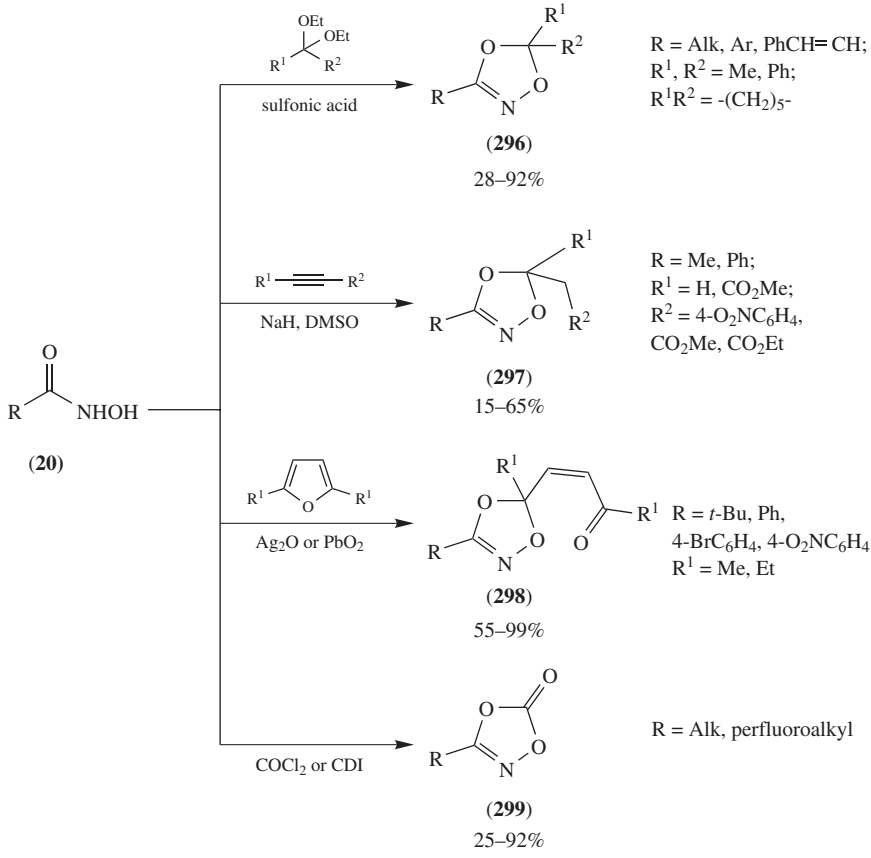
The reaction of *N*-methyl-*O*-phenylcarbonylhydroxylamine hydrochloride (**291**) with cyclic ketones **290** leads to formation of oxazole derivatives **294** (equation 58)[292]. The reaction pathway includes formation of enamine intermediate **292**, [3,3]-sigmatropic rearrangement affording imines **293** and intramolecular cyclization with elimination of phenol as a good leaving group. If other carbonates were used for this transformation or the reaction was performed in the presence of water, only cyclohexanone derivatives **295** were isolated.



(58)

G. Five-membered Cycles with Three and More Heteroatoms

Hydroxamic acids are universal starting materials for construction of heterocyclic structures containing nitrogen at the 2nd and oxygen at the 1st and the 4th positions of the cycle. The application for the synthesis of 1,4,2-dioxazoles are demonstrated in Scheme 32.

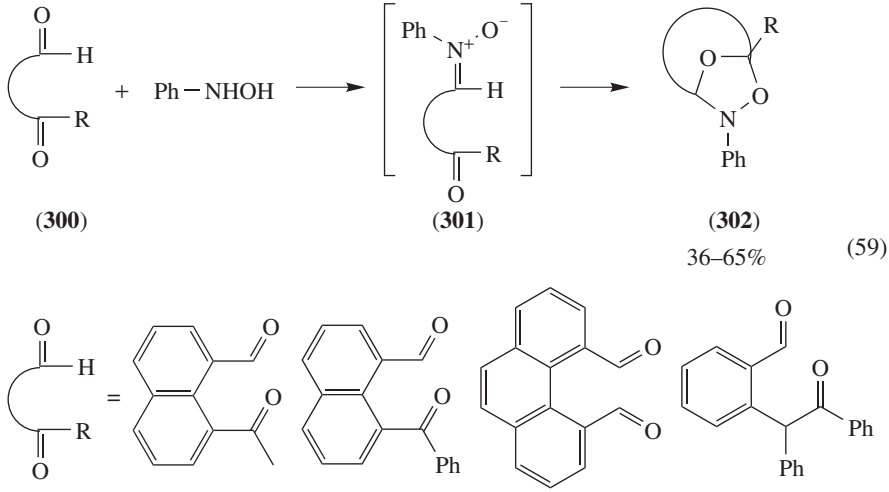


SCHEME 32

The treatment of hydroxamic acids **20** with ketals in the presence of *p*-toluenesulfonic acid[293] or camphorsulfonic acid[294] afforded 3,5,5-trisubstitued 1,4,2-dioxazoles **296**. 5,5-Dimethyldioxazoles **296** ($R^1 = R^2 =$ Me) were recommended as versatile aprotic hydroxamic acid protecting groups, because they are stable to a wide variety of reaction conditions and can be converted back to the parent structure by treatment of Nafion-H[294]. Dioxazoles **297** were also produced by reaction of compounds **20** with electron-deficient alkynes[295]. Hydroxamic acids **20** in the presence of 2,5-dimethyl- or 2,5-diethylfuran and Ag_2O[296] or PbO_2 [297, 298] yielded 5-(*cis*-3-oxobutenyl)-[1,4,2]dioxazoles **298**. The proposed reaction pathway[296] involved initial formation of a nitroso intermediate by oxidation, that underwent [2 + 4] cycloaddition reaction with furan, and isomerization of the

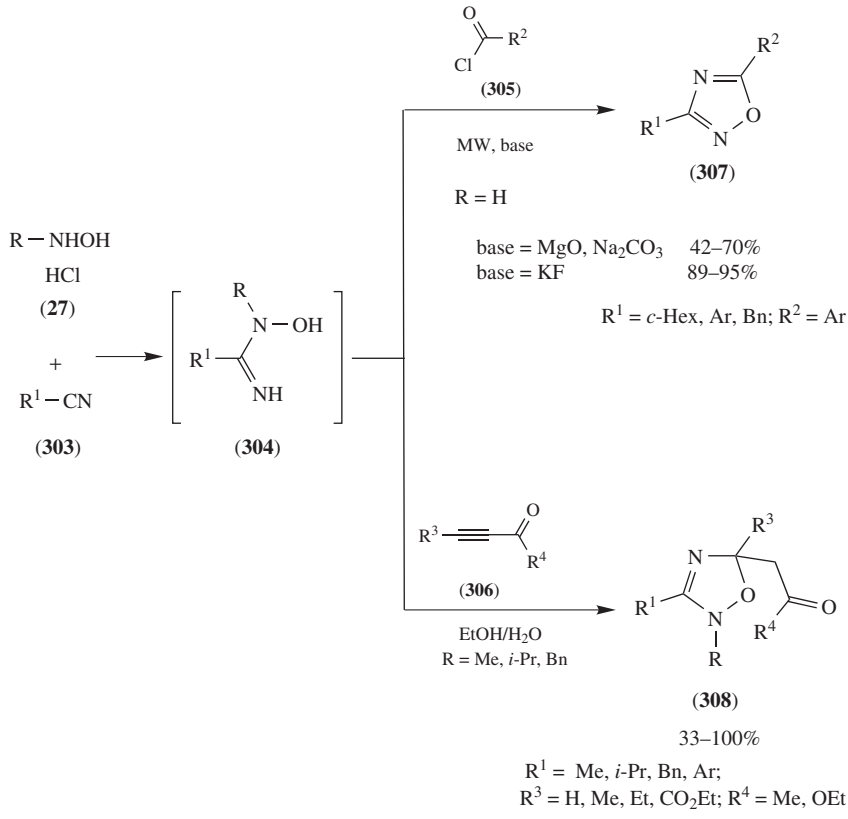
Diels–Alder adducts to dioxazoles **298**. Treatment of hydroxamic acids by phosgene[299, 300] or 1,1′-carbonyldiimidazole[301, 302] (CDI) provided 1,4,2-dioxazol-5-ones (**299**). The CDI method allowed one to make dioxazol-5-ones **299** even from hydroxamic acids **20** bearing hydroxyl group at the α- or β-position. Oxazetidin-3-ones **41** or 1,5,2-dioxazinane-3,6-diones **45** were prepared from *N*-substituted α-hydroxyhydroxamic acid **44** under similar conditions (Scheme 6).

Several derivatives of 1,4,2-dioxazolidine **302** were obtained in moderate yields in a reaction of aromatic dicarbonyl compounds **300** and *N*-phenylhydroxylamine (equation 59)[303]. The reaction proceeds through formation of the nitrone moiety **301** from the aldehyde group followed by intramolecular [3 + 2] cycloaddition between the nitrone and carbonyl functions.



Derivatives of hydroxylamine were used to introduce an N−O moiety into 1,2,4-oxadiazoles by reaction with nitriles[304–308]. For example, 3,5-disubstituted 1,2,4-oxadiazoles **307** were obtained from nitriles **303**, hydroxylamine hydrochloride (**27**, R = H) and aroyl chlorides **305** in a one-pot procedure under microwave irradiation[304, 305] (Scheme 33). If magnesia-supported sodium carbonate is used, the yields of oxadiazoles **307** were moderate (42–70%)[304], but in the presence of KF as solid support heterocycles **307** were isolated in 89–95% yields[305]. Amidoximes **304** (R ≠ H), which were also generated *in situ* from nitriles and the corresponding hydroxylamines, underwent consecutive Michael additions to electron-deficient alkynes **306** in aqueous solution providing 2,3,5,5-substituted 1,2,4-oxadiazolines **308**[306, 307].

A regioselective method for the synthesis of 5-imino-1,2,4-oxadiazolidin-3-ones (**310**) and 3-imino-1,2,4-oxadiazolidin-5-ones (**311**) from hydroxylamines and *N*-aryl-*N*-cyanoamides **309** was reported (Scheme 34)[308]. The reaction of *N*-cyanocarbamoyl chloride **309** (X = Cl) with hydroxylamines in the presence of $NaHCO_3$ in dry MeOH gave compounds **310** in almost quantitative yields, but under similar conditions 1,2,4-oxadiazolidin-5-ones **311** were obtained from *N*-methoxycarbonyl-*N*-cyanoamide **309** (X = OMe).

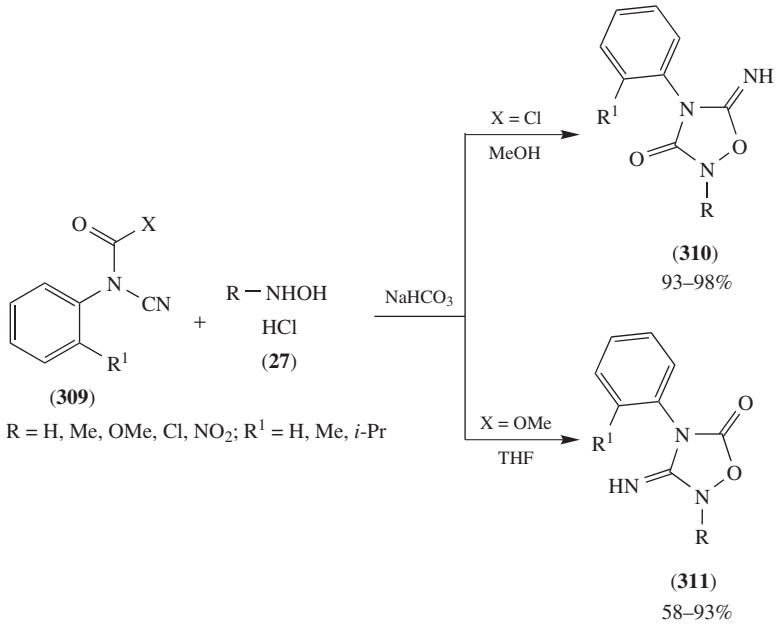


SCHEME 33

Numerous 1,2,4-oxadiazolidine-3,5-diones **312** were synthesized from different hydroxylamine group-containing compounds by treatment with chlorocarbonyl isocyanate (equation 60) and tested for various biological activities[309–312]. For example, substances with the general formula **312a** were claimed[310] as potential drug candidates for treatment of type 2 diabetes.

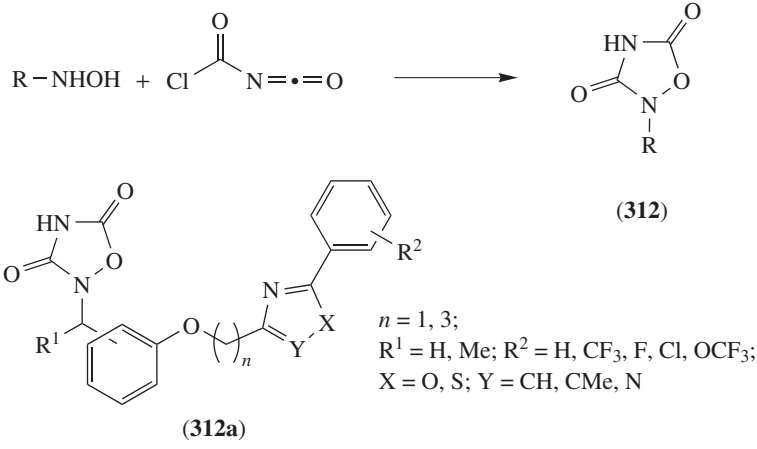
Reactions of hydroxylamines with isocyanates were exploited also for the synthesis of several heterocycles bearing the 1,2,4-oxadiazole structural element. For example, 5-*tert*-butyl-2-methyl-5-phenyl-1,2,4-oxadiazolidin-3-one[313] was obtained from corresponding α-bromo isocyanate and methylhydroxylamine and 2,5-diphenyl-1,2,4-oxadiazol-3-one[314] was made from thiobenzoyl isocyanate and phenylhydroxylamine.

An interesting transformation of 3-ethoxycarbonyl-5-perfluoroalkyl-1,2,4-oxadiazoles (**313**) by reaction with hydroxylamines was recently reported (Scheme 35)[315]. The reaction of compound **313** with methylhydroxylamine (**27**, R = Me) exclusively afforded 4-perfluoroacylamino-2-methyl-2*H*-1,2,5-oxadiazol-3-ones (**314**) that hydrolyzed to the

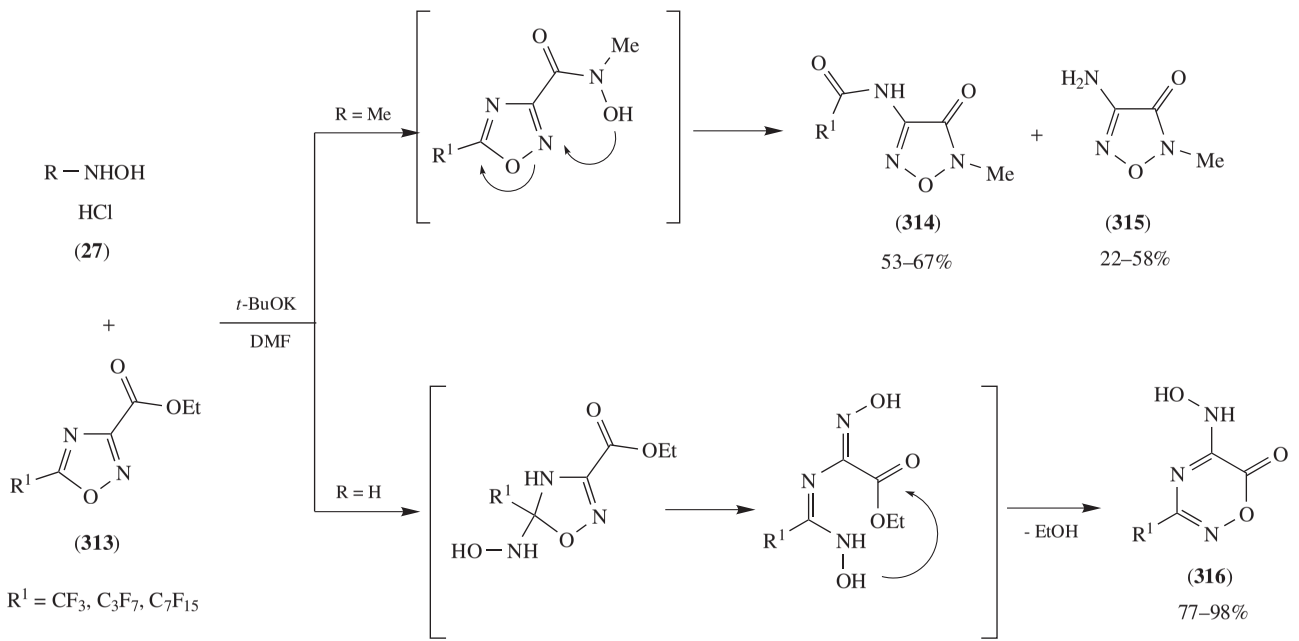


SCHEME 34

corresponding amino derivatives **315** upon chromatographic purification. However, the nucleophilic addition of hydroxylamine (**27**, R = H) occurred at the 5th position of the oxadiazoles **313**, that initiated consecutive ring-opening and ring-closure steps leading to the formation of 5-hydroxyamino-3-perfluoroalkyl-6*H*-1,2,4-oxadiazin-6-ones (**316**).

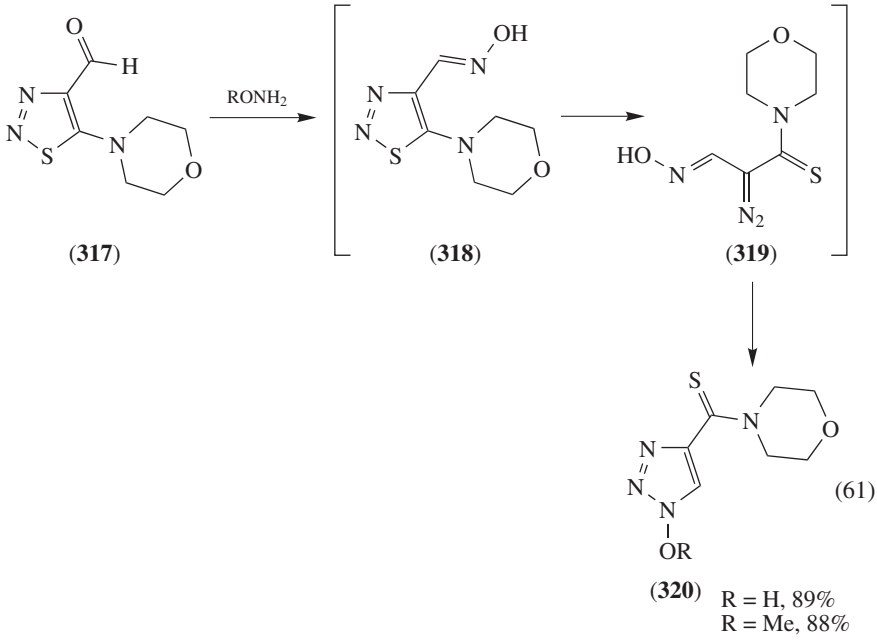


(60)


R — NHOH
HCl
(27)
+
(313)
R1 = CF3, C3F7, C7F15
t-BuOK
DMF
R = Me
R = H
(314)
53–67%
(315)
22–58%
- EtOH
(316)
77–98%

SCHEME 35

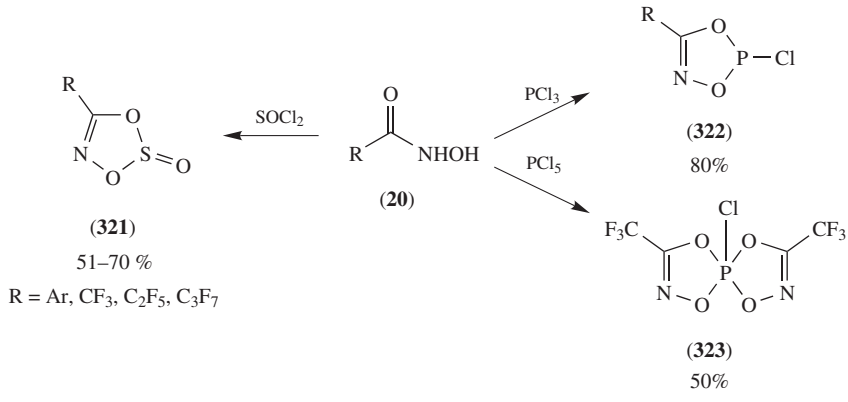
Several examples, where hydroxylamines were used for the introduction of nitrogen with exocyclic oxygen function in triazoles, have been reported[316–319]. Thus, 4-benzyloxy-1,2,4-triazole[316] was prepared from *N*,*N*-dimethylformamidazine dihydrochloride and *O*-benzylhydroxylamine hydrochloride in pyridine as a solvent, and 3-hydroxy-3*H*-1,2,3-triazolo[4,5-*b*]quinoline[317] was obtained from intramolecular cyclization reaction of *N*-(3-aminoquinolin-2-yl)hydroxylamine by a diazotation procedure. The yields of triazoles were moderate in both cases, 42% and 34% respectively. Derivatives of 1-hydroxy- or 1-methoxy-1,2,3-triazol-4-yl-thioamide **320** were synthesized by the reaction of 5-morpholino-1,2,3-thiadiazole-4-carboxaldehyde (**317**) with hydroxylamine or methylhydroxylamine at −20 °C in EtOH solution (equation 61)[319]. The initially formed oximes **318** had not been isolated, because under the reaction conditions they underwent a rearrangement through diazo compounds **319** providing 1,2,3-triazoles **320** in good yields.



(61)

Some five-membered cycles containing four heteroatoms were obtained from hydroxamic acids (Scheme 36). 1,3,2,4-Dioxathiazole-2-oxides **321** were isolated from reaction of aryl-[320] or perfluorohydroxamic[299] acids **20** with $SOCl_2$. 2-Chloro-5-methyl-1,3,4,2-dioxazaphosphole (**322**) was obtained from acetohydroxamic acid and PCl_3 [321] and spiro phosphorane[299] **323** was made from trifluoroacetohydroxamic acid and PCl_5.

A mixing of *N*-methylacetohydroxamic acid (**324**) and boron trifluoride–diethyl ether complex gave compound **325** (equation 62)[322]. Since both B–O bonds in the product **325** were essentially equal in length (1.496(3) and 1.497(3) Å) according to X-ray crystallographic analysis, compound **325** can be regarded as a dioxazaborole derivative **325a** rather as the difluoroboron hydroxamate with formal structure **325b**.



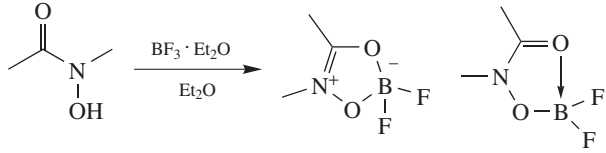
(**321**)
51–70 %
R = Ar, CF_3, C_2F_5, C_3F_7

(**20**)

(**322**)
80%

(**323**)
50%

SCHEME 36



(62)

(**324**) (**325a**) (**325b**)
77%

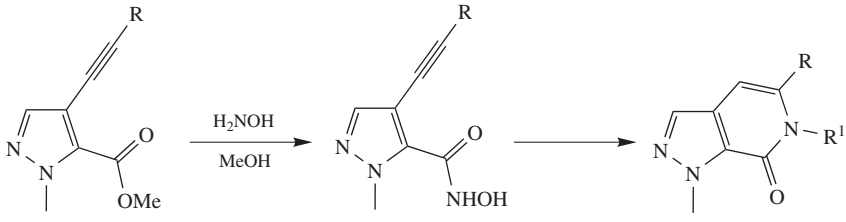
V. SIX-MEMBERED RINGS

Syntheses of several six-membered heterocycles from hydroxylamines and hydroxamic acids were exemplified in the previous subsections. Thus, *N*-oxypiperidine derivatives can be obtained in Cope–House cyclization (equation 13)[134–136], piperidinones were prepared by oxidation of hydroxamic acid derivatives bearing alkene moiety (equation 22)[160] or by intramolecular nucleophilic cyclization of oxyaminoesters (equation 24)[163]. Derivatives of 3,4-dihydroquinolin-2-one and piperidin-2-one are available from cyclization via *N*-alkoxy-*N*-acylnitrenium ions (Scheme 12[146] and equation 18[149]). Pyrazine bis-*N*-oxides, similar to structures **178**[201] and **183**[206], were obtained in the reaction of bis -1,2-hydroxylamines and 1,2-dicarbonyl compounds[323]. Therefore, only such heterocycles and procedures which were not mentioned before will be reviewed in the following subsections.

A. Pyridinones, Piperidinones and Tetrahydroquinolines

Several examples for the synthesis of *N*-oxypyridin-2-one derivatives from hydroxamic acids were reported[324, 325].

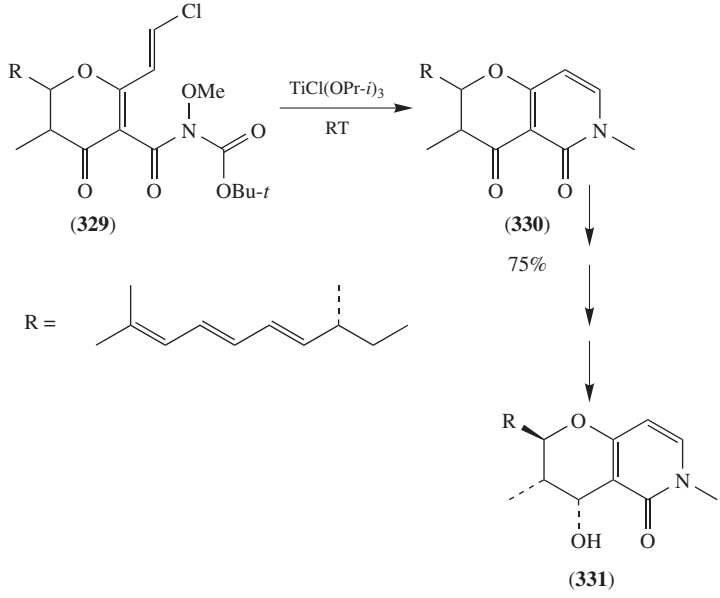
CuCl-catalyzed cyclization of pyrazole-3-hydroxamic acid (**327**) bearing a phenylacetylene moiety afforded pyrazolo[3,4-*c*]pyridin-7-one **328** (R = Ph, R^1 = H) in only 20%



SCHEME 37

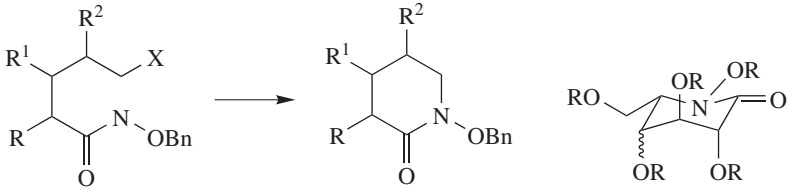
yield (Scheme 37)[324]. However, pyridinone **328** (R = Ph, R^1 = OH) was obtained in 50% yield in the presence of NEt_3 in refluxing butanol, and cyclization of phenyloxymethylene derivative **326** (R = $PhOCH_2$) occurred directly by treatment with excess hydroxylamine in the hydroxamic acid synthesis step, providing compound **328** (R = OH, R^1 = $PhOCH_2$) in 44% yield.

The cyclization of a hydroxamic acid was also applied in the total synthesis of a Ca^{2+} signaling inhibitor YCM1008A **331**. Thus, chlorovinylhydroxamic acid **329** in the presence of TiCl(OPr-*i*)$_3$ underwent successive reactions including removal of a Boc group and *N*-Michael addition–elimination reaction to give pyranopyridone **330** in a good yield (Scheme 38)[325].



SCHEME 38

N-Oxypiperidin-2-ones can be obtained from derivatives of *N*-hydroxypentanamide by the same methods that are applicable for synthesis of β- or γ-lactams. For example, aminopiperidones **333** were made by cyclization of δ-bromo- or δ-hydroxy-*O*-benzylhydroxamic acids **332** in the presence of K_2CO_3 [326] or PPh_3/ethyl azodicarboxylate, respectively[326–328] (equation 63). The Mitsunobu conditions were also applied for synthesis of iminosugars derivatives **334**[329] from the corresponding fully TBDMS-protected hydroxamates.



(63)

(**332**) (**333**) (**334**)

X = Br, OH; 60–98% R = TBDMS

R = H, CbzNH;

R^1 = H, OH, Bn(Bz)N;

R^2 = H, CbzNH, BocNH

A new synthesis of 2-substituted tetrahydroquinolines **338** from *N*-indanyl-*O*-methylhydroxylamines **335** was reported (equation 64)[330]. It was proposed that indanylhydroxylamine **335** was initially chelated with Grignard reagents to generate the intermediate **336**, which was interconverted into the imines **337** via elimination of an alkoxy group and rearrangement of an aryl group. Finally, the addition of organomagnesium to the imine double bond produced 2-substituted tetrahydroquinolines **338** in good (70–92%) yields, except for 4-phenyl derivatives **338** (R^4 = Ph) that were isolated only in 14–18% yields due to several side reactions.

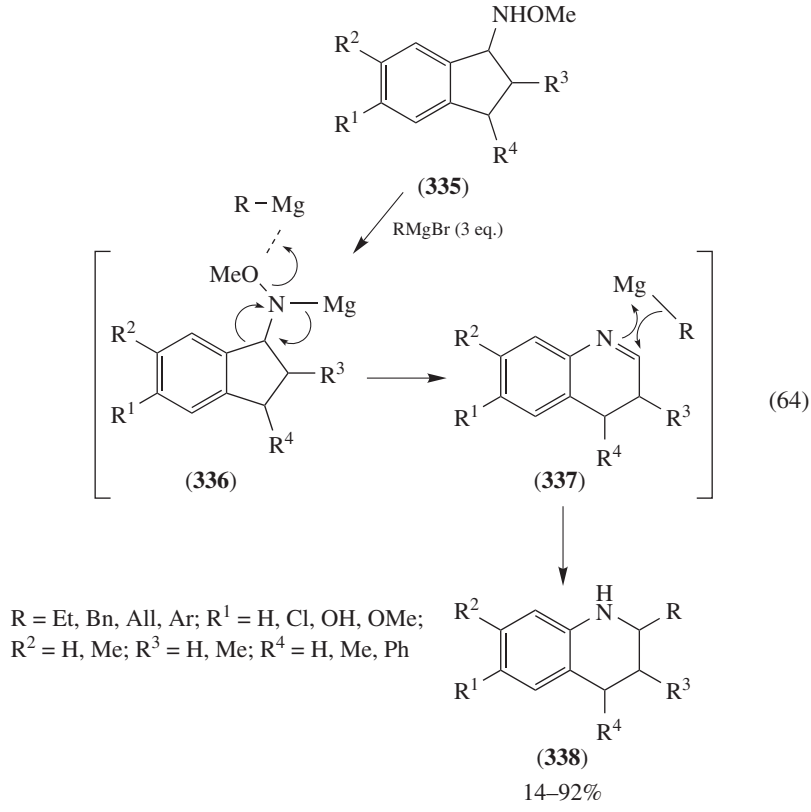
B. Pyrimidine and Pyrazine Derivatives

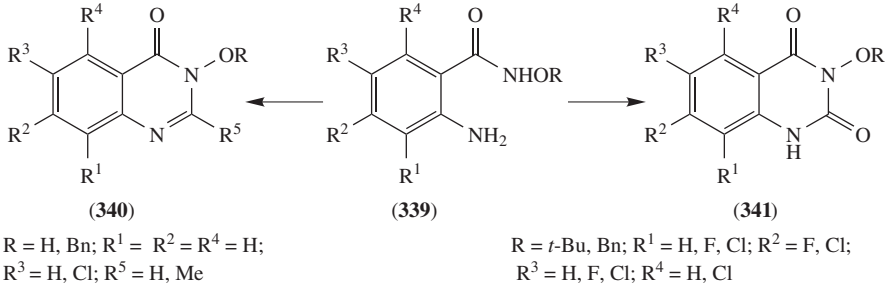
Hydroxamic acids were used for incorporation of *N*-oxycarbamoyl (CONO) fragment in derivatives of pyrimidine or pyrazine. For example, 2-amino-*N*-hydroxybenzamides **339** can serve as starting materials for synthesis of quinazolin-4-ones and quinazoline-2,4-diones (Scheme 39). 3-Hydroxyquinazolin-4-ones **340** were made from hydroxamates **339** by reaction with formic acid (R = R^5 = H) or acetyl chloride (R = Bz, R^5 = Me) followed by hydrogenolysis on palladium[331]. Compounds **340** were tested as additives in carbodiimide-based peptide coupling to replace the known *N*-hydroxybenzotriazole derivatives. A series of quinazoline-2,4-diones **341** was also obtained from hydroxamic acids **339** by treatment with phosgene[332] or triphosgene[333].

3,5-Substituted 1-hydroxy-2(1*H*)pyrazin-2-ones were readily available from the reaction of the corresponding α-aminohydroxamic acids and 1,2-dicarbonyl compounds[334].

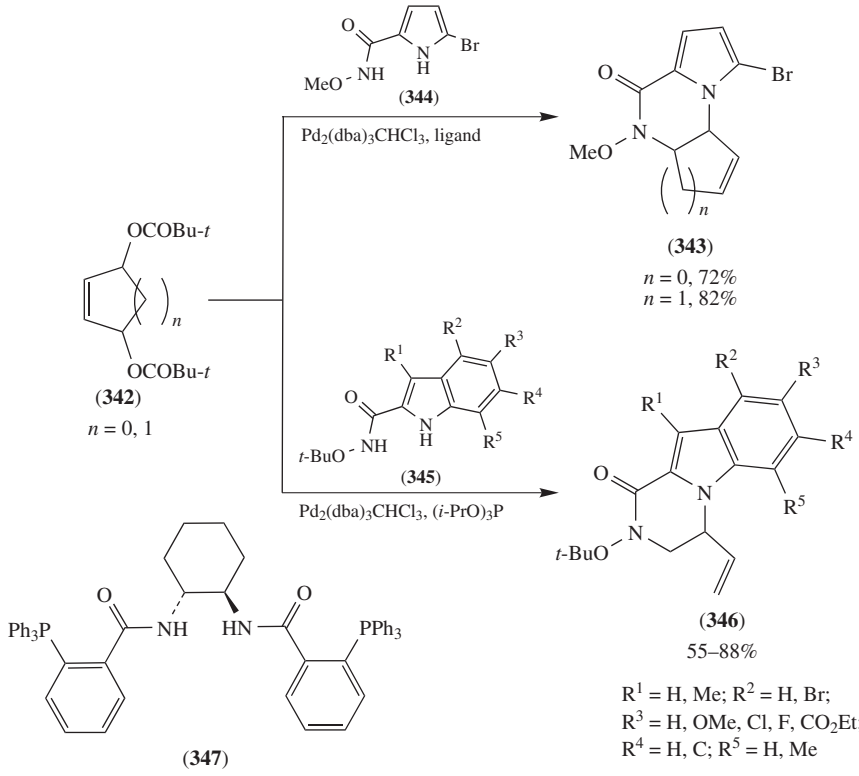
A palladium-catalyzed double allylic alkylation of pyrrole- or indole-2-hydroxamic acids with butene or cyclopentene derivatives was developed (Scheme 40)[335–337]. Tricyclic 4,8*a*-diaza-as-indacen-5-one **343** (n = 1) was obtained from *cis*-cyclopent-4-ene-1,3-di-*tert*-butyl dicarbonate (**342**, n = 1) and pyrrole-2-hydroxamic acid **344** in the presence of $Pd_2(dba)_3$ and Trost ligand **347** as a single diastereomer[335]. Triisopropyloxyphosphine (i-PrO)$_3$P appeared the best ligand for the synthesis of 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1-one **343** (n = 0) and 3,4-dihydro-2*H*-pyrazino[1,2-*a*]indol-1-one derivatives **346** from the

corresponding hydroxamic acids **344**, **345** and buten-2-ene-1,4-di-*tert*-butyl dicarbonate (**342**, $n = 0$)[336, 337]. These allylic alkylations were the key steps in total synthesis of agelastatin A[335] and longamide B[336].



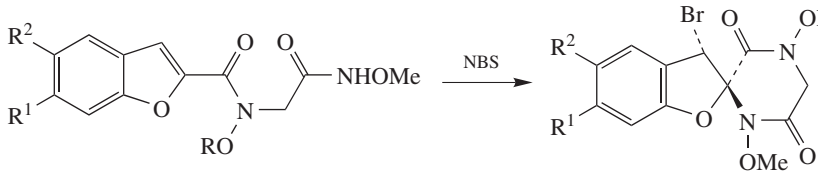


SCHEME 39



SCHEME 40

Spiro[benzofuran-2(3*H*), 2′-piperazine] ring system **349** was accessed from derivatives of benzofuranhydroxamic acid **348** by treatment with *N*-bromosuccinimide in ethanol-free chloroform (equation 65)[338]. The cyclization of compound **348** to tricyclic bromide **349** proceeded via *anti*-addition and resulted in single *trans*-diastereomer.



(65)

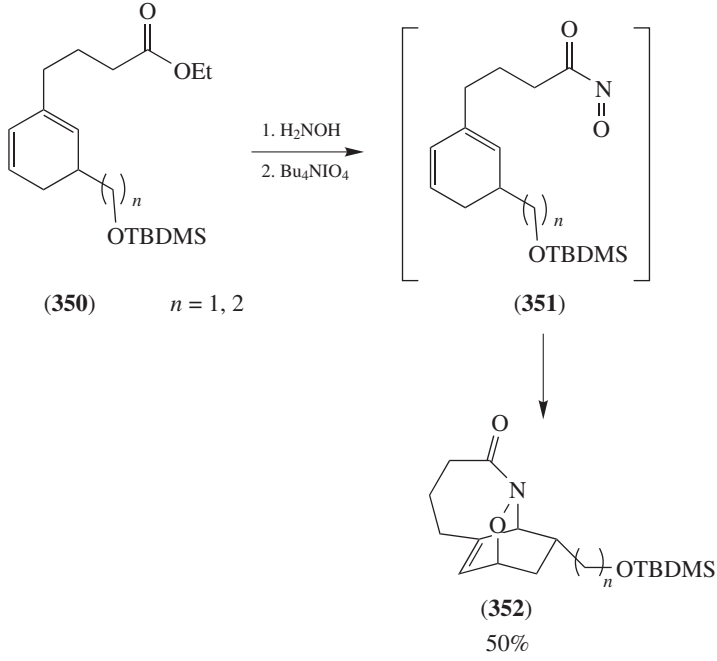
R = 4-MeOC$_6$H$_4$CH$_2$, 2-O$_2$NC$_6$H$_4$CH$_2$; 50–67%
R^1 = H, AcO; R^2 = H, Cl

C. Oxazines

The 1,2-oxazine ring can be constructed from hydroxylamines or hydroxamic acids by several methods. In the presence of 1,3-dienes, nitroso species **3** generated by oxidation provide 2,6-dihydro-1,2-oxazines by hetero Diels–Alder reaction[182, 339–351]. Intra- and intermolecular nucleophilic addition and substitution reactions also were utilized for the synthesis of 1,2-oxazine derivatives[352–364]. Reactions of *N*-substituted hydroxylamines with aldehydes produce nitrones **5** that can undergo cycloaddition with an appropriate three-carbon atom source[365–371].

An application of nitroso Diels–Alder reaction for a synthesis of 1,2-oxazines was reviewed[339–342], therefore only recent examples are presented to illustrate this approach.

1,2-Oxazine fragment-containing tricycles **352**, the key intermediates for alkaloid stetine synthesis, were synthesized from cyclohexane-1,3-diene derivatives **350** (equation 66)[343]. Hydroxamic acids, which were obtained from the reaction of ester **350** with hydroxylamine, were used in the next step without purification. An oxidation with Bu_4NIO_4 generated acylnitroso species **351** that underwent *in situ* intramolecular cycloaddition to compounds **352**.



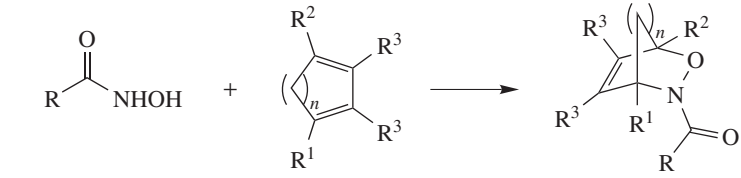
(**350**) $n = 1, 2$ (**351**) (66)

(**352**)
50%

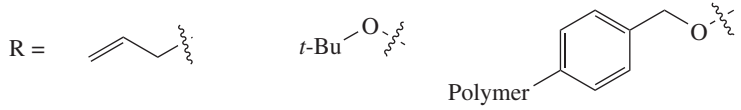
An intermolecular reaction of 3-butenoic hydroxamic acid (**20**, R = CH_2CHCH_2) with cyclopentadiene afforded bridged dihydrooxazine **354** ($n = 1$, R = $R^1 = R^2 = R^3 = H$) in 80% yield[344] (equation 67). In this case Swern oxidation ($(COCl)_2$, DMSO) was applied, because periodate oxidants can promote double bond isomerization of unsaturated hydroxamic acid **20** from the β,γ- to α,β-position.

The methodology for generation of nitroso dienophile by oxidation of *N*-Boc-hydroxylamine (**20**, R = *t*-BuO) with H_2O_2 in the presence of Cu^I, Cu^{II}, Fe^{III} salts and amine ligands was reported[345]. The produced nitroso species were trapped by several dienes **353**. 1,2-Oxazine derivatives **354** ($n = 0–2$, R = *t*-BuO, R^1, R^2, R^3 = H,

Me) were isolated in 54–95% yields. In addition, solid-phase synthesis of 1,2-oxazine derivatives **354** from polymer-supported hydroxylamine **20** (polymer = modified Wang or Rink resin) and various dienes **353** via nitroso Diels–Alder reaction was developed[346] (equation 67).

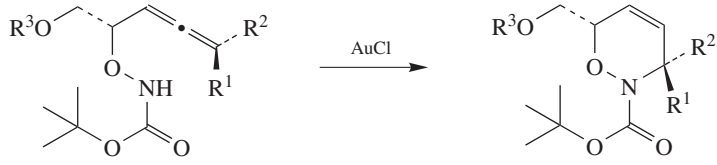


(**20**) (**353**) (**354**) (67)



n = 0, 1, 2; R^1 = H, Me, Ph; R^2 = H, Me, Ph, CH_2OH, CO_2H, CO_2Et, OCOMe; R^3 = H, Me

Dihydrooxazine **356** were also obtained from *N*-Boc-protected allenic hydroxylamines **355** by gold-catalyzed intramolecular addition reaction (equation 68)[120]. Application of unprotected hydroxylamine ethers resulted in considerable amounts of 4,5-dihydroisoxazolines **228** (see equation 45).



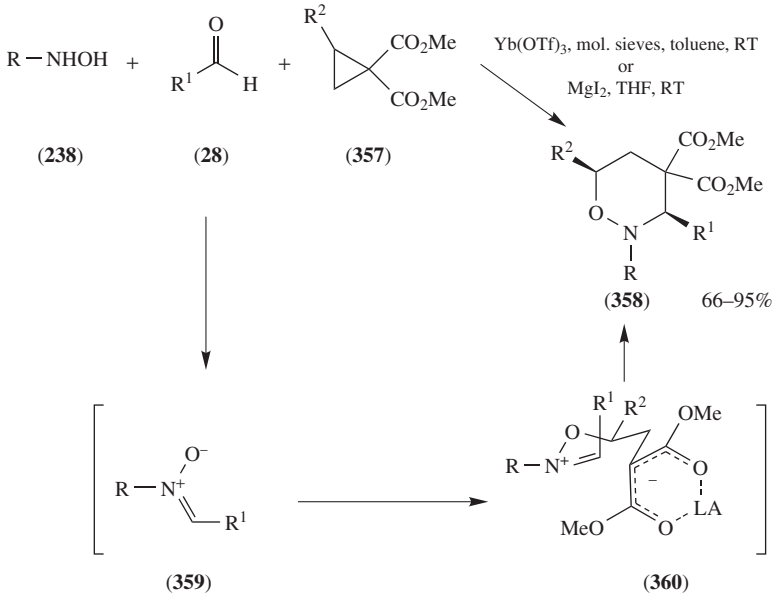
(**355**) (**356**) (68)

R^1 = Me, *i*-Pr, *n*-Bu, Ph; R^2 = H, Me; R^3 = Me, Bn 30–85%

Other methods for assembling 1,2-oxazine ring involve intramolecular addition of allenes to the hydroxylamine oxygen atom[352–355], simultaneous alkylation of both the NH and OH functions with dibromobutane derivatives[356–359], stepwise acylation of the NH and alkylation[360] or acylation[361] of the OH group and intramolecular nucleophilic cyclization[362].

An efficient method for synthesis of highly functionalized tetrahydro-1,2-oxazines **358** from *N*-substituted hydroxylamines **238**, aldehydes **28** and cyclopropane derivatives **357** in the presence of MgI_2 or $Yb(OTf)_3$ as catalysts has been developed (Scheme 41)[365–371]. The 1,2-oxazines **358** were isolated in good to excellent yields and with high 3,6-*cis* diastereoselectivity (>95%). It was postulated[365, 369] that the reaction proceeds through ring opening of the cyclopropane **357** by the nitrone **359** with formation of the malonate **360**, where substituent R^1 is in axial and R^2 is in equatorial positions. Closure of intermediate **360** would give *cis* product **358**. This three-component reaction was used in synthesis of several alkaloids[366–368, 370].

Hydroxamic acids containing a hydroxyl group in appropriate position are used for synthesis of 1,3-oxazinones. For example, salicylhydroxamates **361** (X = C) afforded



R = Bn, 4-MeOC$_6$H$_4$CH$_2$, Ar; R^1 = Alk, alkenyl, Ar, hetaryl;
R^2 = H, Me, alkenyl, Ph, hetaryl; LA = MgI$^+$, Yb(OTf)$_2^+$

SCHEME 41

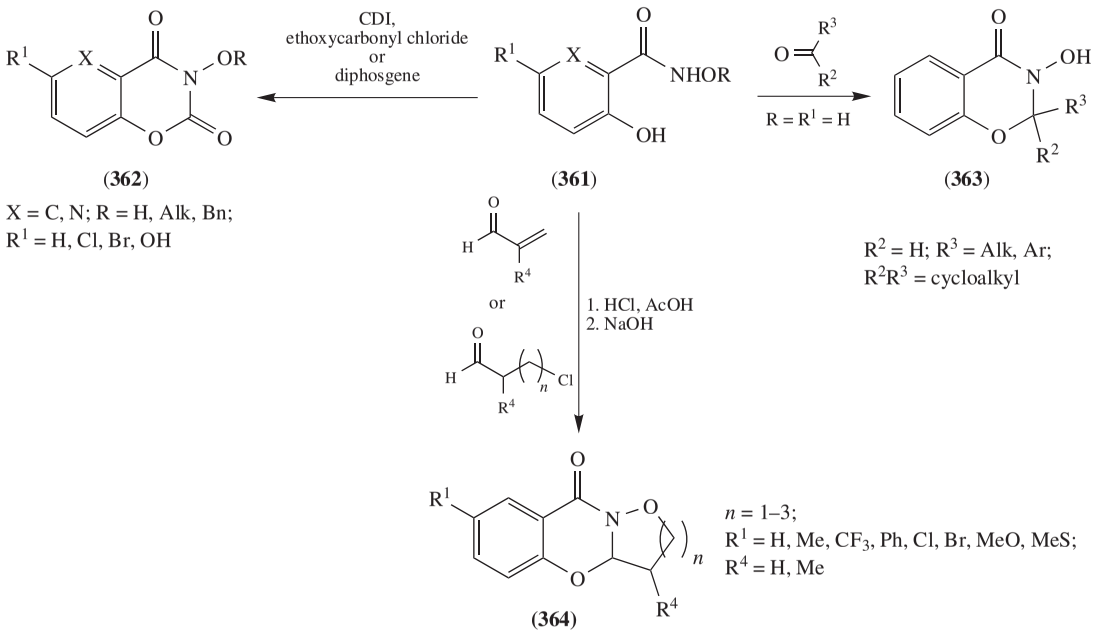
benzo-1,3-oxazine-2,4-diones **362** (X = C) by treatment with CDI[372] or ethoxycarbonyl chloride[373, 374] and pyridooxazines **362** (X = N) were obtained from the corresponding pyridine derivatives **361** (X = N, R^1 = H) and diphosgene[375] (Scheme 42). Reaction of compounds **361** with aldehydes or ketones provided 2,3-dihydrooxazin-4-ones **363**[374, 376, 377]. Tricyclic structures **364** were generated in a two-step procedure from hydroxamates **361** and α,β-unsaturated or γ- or δ-chloro aldehydes[377].

The reaction of *N*-benzyloxy-2-hydroxyhydroxamic acid **365** with oxalyl chloride afforded 1,4-morpholine-2,3,5-triones **366** (equation 69)[378]. Oxazolidine-2,4-diones **367** were also formed in considerable amounts if dimethyl- or diphenylhydroxamic acids **365** (R^1 = R^2 = Me, Ph) were subjected to this transformation.

D. Dioxazines and Oxadiazines

Generally, dioxazines and oxadiazines can be assembled from carbonyl compounds and hydroxylamine derivatives having hydroxy, amino or amide functions at a suitable location[379–387]. However, synthesis through formation of acylnitroso species was also reported[388–390].

Thus, 1,5,2-dioxazine-3,6-diones **369** (X = Y = O) were obtained by reaction of α-hydroxyhydroxamic acids **368** (X = O) with CDI[109, 379] and 6-thioxo-1,5,2-dioxazine-3-ones (X = O, Y = S) were obtained from the same starting material by treatment with 1,1′-thiocarbonyldiimidazole[380] (Scheme 43). Similarly, 1,2,5-oxadiazine-3,6-diones[381] **369** (X = NH, Y = O) and 6-thioxo-1,2,5-oxadiazine-3-ones[382] **369** (X = NH, Y = S) were



(**362**)

X = C, N; R = H, Alk, Bn;
R^1 = H, Cl, Br, OH

(**361**)

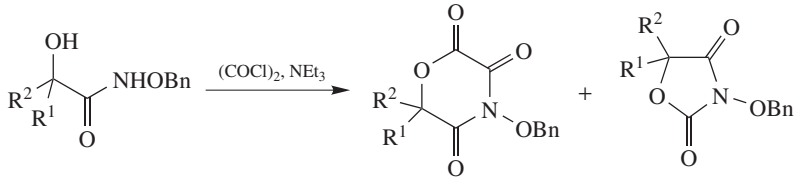
(**363**)

R^2 = H; R^3 = Alk, Ar;
R^2R^3 = cycloalkyl

(**364**)

SCHEME 42

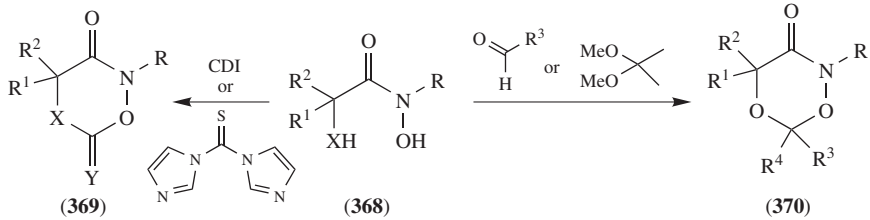
produced from α-aminohydroxamic acids **368**. 1,5,2-Dioxazine-3-ones **370** were made from *N*-substituted hydroxamic acids **368** (X = O) and dimethylacetal[383, 384] or aromatic aldehydes[383].



(**365**) (**366**) (**367**) (69)

$R^1 = R^2 = Me$, 51%
$R^1 = R^2 = Ph$, 28%
$R^1 = R^2 = H$, 52%
$R^1 = H$; $R^2 = Ph$, 54%

$R^1 = R^2 = Me$, 21%
$R^1 = R^2 = Ph$, 50%



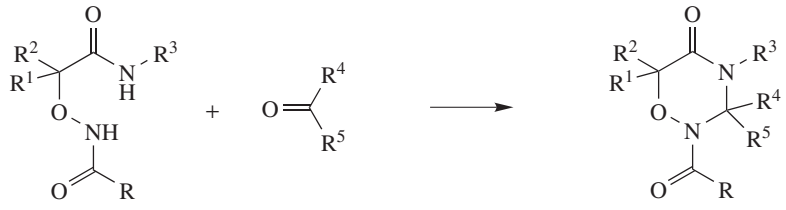
(**369**) (**368**) (**370**)

Y = O, S;
X = O, R = Alk, Ar;
R^1, R^2 = H, Alk, Ar, hetaryl;
X = BnN, 4-$ClC_6H_4CH_2N$, 4-$MeOC_6H_4CH_2N$, $Ph(CH_2)_2N$, PhN;
R^1 = H; R^2 = H, Ph

R = Alk, Ar; R^1, R^2 = H, Alk, Ar, hetaryl;
R^3 = vinyl, Ar; R^4 = H; $R^3 = R^4$ = Me

SCHEME 43

An acid-catalyzed reaction of aldehydes or ketones with α-(acylaminooxy)carboxylic acid amides **371** was used for synthesis of 1,2,4-oxadiazinan-5-ones **372** (equation 70)[385].

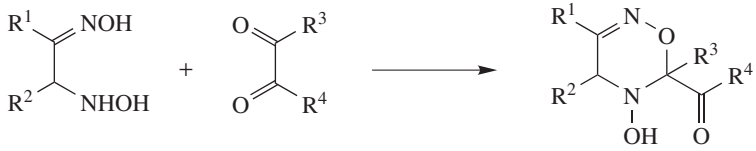


(**371**) (**372**) (70)

R = Ac, Bz, CBz; R^1 = H, Me, Ph; R^2 = H, Me, Et, Bn, Ph;
R^3 = H, Me; R^4 = H; R^5 = Me, Pr, Ar, hetaryl; R^4R^5 = cyclopentyl

16–88%

The 1,2,5-oxadiazine ring **375** can also be constructed from 1,2-hydroxylaminooximes **373** and 1,2-diketones **374** (R^3 = Me, R^4 = Me, Ar)[386] or α-oxoaldehydes **374** (R^3 = H, R^4 = Me, Ar)[387] (equation 71). In this case the oxime group from compound **373** wholly incorporates in the oxadiazine cycle, but the hydroxylamine moiety provides nitrogen with exocylic OH function at the 5th position.



(**373**) (**374**) (**375**) (71)

R^1 = Ar; R^2 = H, Alk; R^3 = H, Me; R^4 = Me, Ar 25–97%

Derivatives of 3,6-dihydro-2*H*-1,2,5-oxadiazines[388] **377** were obtained from acylnitroso species, generated *in situ* by oxidation of hydroxamic acids **20** (R = BnO, PhO), and 2-azadienes **376** by hetero Diels–Alder reaction (Scheme 44). When hydroxamic acids **20** (R = Bn, Ph) were applied for this transformation with *N*-acyl-1,2-dihydropyridines **378**, 2-oxa-3,5-diazabicyclo[2.2.2]octane derivatives **379** were obtained as major products. However, the reaction of hydroxamic acids **20** (R = MeO, BnO) with dihydropyridines **378** produced a mixture of **379** and its regioisomer 3-oxa-2,5-diazabicyclo[2.2.2] octane **380**[389, 390].

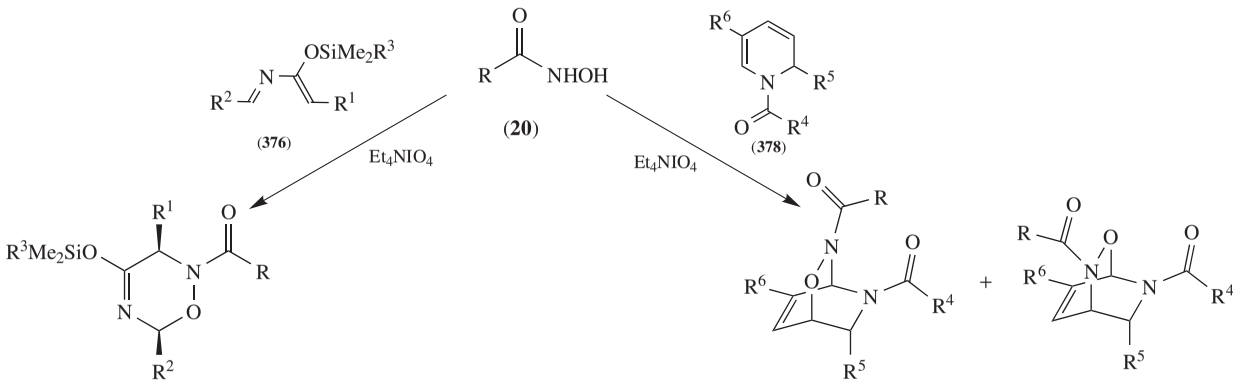
VI. SEVEN-MEMBERED RINGS

Several general methods, such as intramolecular electrophilic aromatic substitution via nitrenium ions[391–394], [3 + 2] cycloaddition reactions of nitrones[395–397] and nucleophilic alkylation[398–401], which in general were surveyed in the previous subsections, as well as cycle expansion reactions[402–404] were also adapted for the synthesis of seven member heterocycles.

N-Methoxy-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one[391] (**383**, X = CH_2) and derivatives of benzo[*e*][1,4]diazepin-2-one[392] **383** (X = NCO_2Et) were synthesized from methyl hydroxamates **381** by treatment with phenyliodine(III)-bis-(trifluoroacetate) (PIFA) via acylnitrenium ions **382** (equation 72). Benzo- or naphthopyrrolodiazepine-5,11-diones[393] **384** as well as thieno- and pyrrolodiazepine-2,5-diones[394] **385**, **386** were obtained under similar conditions.

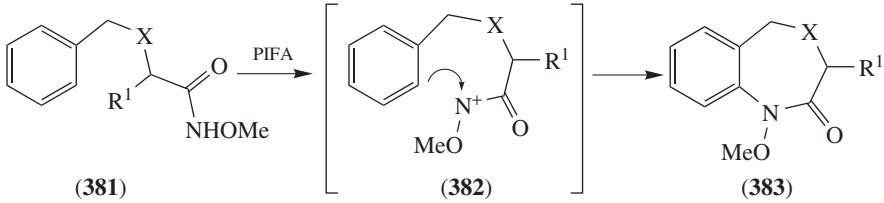
Medium-size cycles together with isoxazole rings can be constructed by intramolecular [3 + 2] cycloaddition reaction of nitrones that possess a double bond at an appropriate distance[395]. Such an approach was successfully applied for the synthesis of bridged tricyclic β-lactams **389** (equation 73)[396] and derivatives of 9-oxa-1-azabicyclo[4.2.1]nonane **392** (equation 74)[397]. In the first example generation of nitrones **388** by the reaction of hydroxylamines **238** and unsaturated aldehydes **387** was employed, but in the latter case reaction was accomplished from aldehydes **391** and hydroxylamine **390** having an alkene moiety. In both cases a high degree of regio- and stereoselectivity was achieved under optimized reaction conditions.

Bicycle **392a** ($R^1 = R^4 = H$, $R^2 = BnOCH_2$, $R^3 = OBz$) was the only isolable compound from the reaction of hydroxylamine **390** (R^3 = OBz, R^4 = H) and 2-(benzyloxy)acetaldehyde (**391**, R = $BnOCH_2$) in the presence of molecular sieves in refluxing toluene (equation 74)[397]. The formation of the other diastereomer **392b**


OSiMe2R3
R2
N
R1
(376)
Et4NIO4
O
R
NHOH
(20)
R6
N
R5
O
R4
(378)
Et4NIO4
R1
O
R3Me2SiO
N
R
N
O
R2
(377)
30–70%
R = BzO, PhO, Ph; R1 = Bz, Ph;
R2 = i-PrO, Ph; R3 = Me, t-Bu
O
R
N
O
R6
O
N
R4
R5
(379)
25–100%
+
O
R
O
R6
N
O
N
R4
R5
(380)
0–75%
R = Bn, Ph, MeO, BzO, Me2N;
R4 = Me, MeO; R5 = H, n-Bu, Ph;
R6 = H, CO2Me

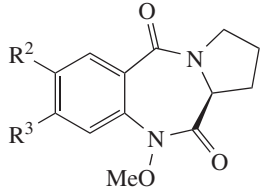
SCHEME 44

($R^1 = BnOCH_2$, $R^2 = R^4 = H$, $R^3 = OBz$) and the alternative regioisomer (an 8-oxa-1-azabicyclo[4.2.1]nonane with a bridgehead methylene group) was not observed. A mixture of diastereomers **392a** ($R^1 = CO_2Me$, $R^2 = R^3 = H$, $R^4 = OBz$) and **392b** ($R^1 = R^3 = H$, $R^2 = CO_2Me$, $R^4 = OBz$) in a ratio 3:1 was obtained under similar conditions from hydroxylamine **390** ($R^3 = H$, $R^4 = OBz$) and methyl glyoxylate (**391**, R = CO_2Me). However, if the reaction was carried out in the chiral ionic liquid ((*S*)-3-ethyl-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-3-ium hexafluorophosphate), the azabicyclononane **392a** ($R^1 = CO_2Me$, $R^2 = R^3 = H$, $R^4 = OBz$) was achieved as the sole product in 79% yield.



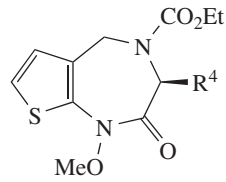
(**381**) (**382**) (**383**)

X = CH_2; R^1 = $NHCO_2Bn$, 85%
X = NCO_2Et; R^1 = H, 60%
R^1 = Me, 70%



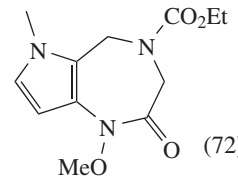
(**384**)

$R^2 = R^3 = MeO$, 70%
$R^2 = MeO$; $R^3 = H$, 57%
$R^2R^3 = C_4H_4$, 70%



(**385**)

R^4 = H, 55%
R^4 = Me, 76%

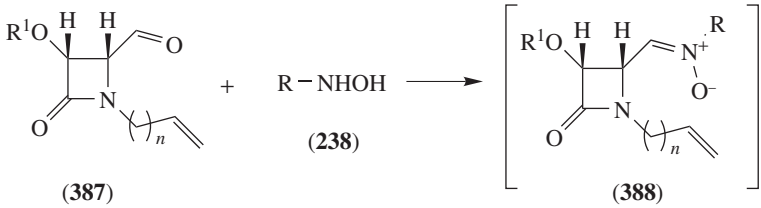


(72)

(**386**)

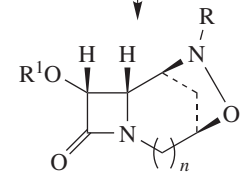
33%

The (*S*)-3-amino-1-hydroxyazepan-2-one cycle, a versatile structure that appears in several natural products[398, 399, 405–408], was obtained in 36–55% yields by intramolecular cyclization of 2-benzoyloxycarbonylamino-6-hydroxyaminohexanoic acid using traditional peptide coupling agents[63, 409–411] or by the 'hydroxamate approach' (see Section III. A, Scheme 3) from hydroxamate **393** (equation 75)[398, 399]. If Mitsunobu reaction conditions (PPh_3, diethyl azodicarboxylate) were applied for ring closure of compound **393** (X = OH), the product **394** was obtained in 43% yield, along with 35% *O*-cyclized oxepan-2-one oxime **395**. A better yield of azepan-2-one **394** was achieved by conversion of the hydroxyl group to mesylate, followed by cyclization in the presence of *t*-BuOK or K_2CO_3. In this case the yields of product **394** and its isomer were 63% and 21%, respectively.



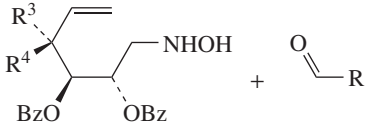
(**387**) (**238**) (**388**)

n = 1–3; R = Me, Bn; R^1 = Me, Bn, Ph



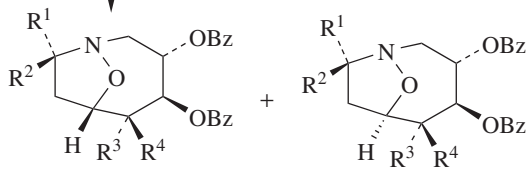
(**389**)
62–75%

(73)



(**390**) (**391**)

R = $BnOCH_2$, CO_2Me

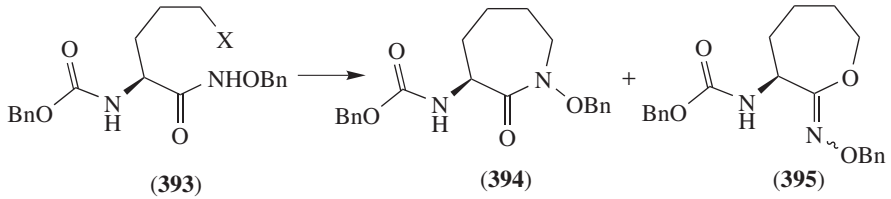


(**392a**) (**392b**)

R^1 = H; R^2 = $BnOCH_2$;
R^3 = OBz; R^4 = H 28%
R^1 = CO_2Me; R^2 = H;
R^3 = H; R^4 = OBz 48–79%

R^1 = H; R^2 = CO_2Me;
R^3 = H; R^4 = OBz 8–16%

(74)

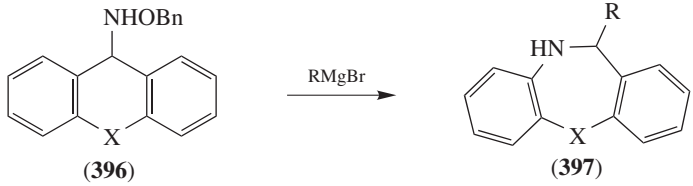


(**393**) (**394**) (**395**)

X = OH, $MeSO_2O$

(75)

Dibenzo-1,4-oxazepines **397** (X = O) and 1,4-thiazepines **397** (X = S) were obtained by treatment of hydroxylamine derivatives **396** with 4 equivalents of Grignard reagents (equation 76)[402]. The reaction mechanism is identical to the one described for the synthesis of tetrahydroquinolines (equation 64)[330]. Similarly, tetrahydrobenzoazepines **398** (X = CH_2) and 1,5-benzothiazepines **398** (X = S) were made from the corresponding tetrahydronaphthalene- or thiochroman-4-yl hydroxylamines[402].

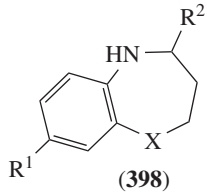


(**396**) (**397**)

82–94%

X = O, S; R = Et, All, vinyl, Ph

(76)



(**398**)

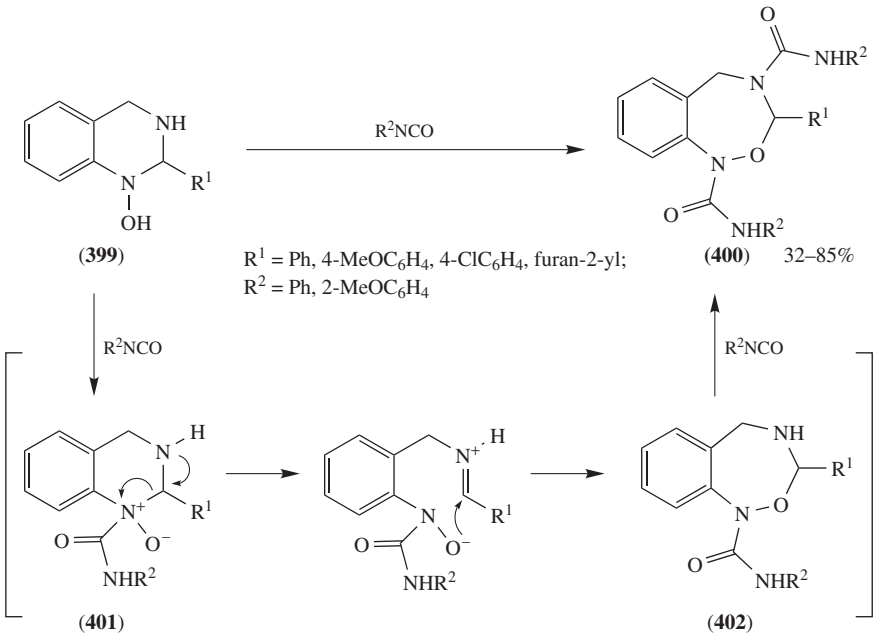
X = CH_2; R^1 = MeO; R^2 = Et, *n*-Bu, Ph, 61–66%

X = S; R^1 = H; R^2 = Et, *n*-Bu, All, vinyl, Ph, 75–90%

An interesting ring expansion, which resulted in the formation of 6-oxa-5,8-diazabenzocycloheptene **400**, was observed by treatment of 2-aryl-3,4-dihydro-2*H*-quinazolin-1-oles (**399**) with excess of aryl isocyanates (Scheme 45)[403]. A plausible reaction mechanism was based on the statement that the nitrogen not engaged in hydrogen bonding would be more appropriate to attack isocyanate to give the intermediates **401**. The following ring opening and closure steps afforded 6-oxa-5,8-diazabenzocycloheptenes **402**. Finally, reaction with the second isocyanate led to the end product **400**.

VII. SUMMARY

Hydroxylamines and hydroxamic acids have found extensive application in syntheses of many classes of heterocyclic compounds. Nucleophilic substitution or addition reactions at either N or O as well as at both N and O atoms allow closing rings from size of three



SCHEME 45

to seven and even more atoms. Hydroxamates can be selectively alkylated at the nitrogen atom in the presence of other amide or carbamate groups and its oxygen-containing part is easily removable from the amide function by reduction. These distinguished features of hydroxamic acids are widely used for synthesis of functionalized cyclic lactams.

Nitrogen-containing cycles of different size fused with aromatic rings are accessible from *N*-alkoxy-*N*-acylnitrenium ions by electrophilic intramolecular aromatic substitution reaction.

The oxygen-containing moiety of hydroxylamine derivatives can serve as a leaving group in certain cyclization and isomerization reactions that result in formation of aziridines, benzofurans, indoles, pyrroles, quinolines and related heterocycles.

Nitroso compounds are extensively applied for the synthesis of 1,2-oxazines by [2 + 4] cycloaddition reactions, and pyrroles, indoles, isoxazoles, oxazoles, 1,4,2-dioxazoles and 1,2-oxazines are assembled from nitrones and an appropriate dipolarophile. Although nitroso and nitrone derivatives can be isolated in several cases, generation of these species *in situ* from hydroxylamines or hydroxamic acids by oxidation or by reaction with carbonyl compounds, respectively, allows extending the scope of starting materials and significantly improving the total yields of products.

Much attention is devoted to stereoselective synthesis of saturated heterocycles especially isoxazolidines and 1,2-oxazinenanes, because mild cleavage of the N−O bond give access to enantiopure aminoalcohols. Chiral amino acids can be made from hydroxamic acid derivatives by consecutive cyclization, reduction and amide bond cleavage reactions.

In our opinion, notwithstanding the huge number of publications devoted to synthesis of heterocycles from derivatives of hydroxylamines and hydroxamic acids, their synthetic potential as starting materials for cyclic products has not been exhausted.

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Mass spectrometry of hydroxylamines, oximes and hydroxamic acids

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I. INTRODUCTION

A lot of mass spectrometry (MS) ionization techniques, such as electron ionization (EI), chemical ionization (CI), particle beam (PB), fast atom bombardment (FAB), electrospray (ESI), and different MS experiments, such as high resolution, study of metastable ions, collision-induced dissociations, together with chemical modifications, such as stable isotope labeling, have been used for characterizing the gas-phase behavior of hydroxylamines, oximes and hydroxamic acids.

All this has allowed one to investigate the gas-phase properties and reactivity of radical cations as well as positively and negatively charged species produced by these classes of molecules.

II. MASS SPECTROMETRY OF HYDROXYLAMINES

The electron ionization mass spectrum of hydroxylamine shows the molecular ion (m/z 33) that constitutes the base peak and low abundance fragment ions with relative intensities below 30%. Among them, the most abundant are at m/z 32, 31, 30, 17 and 16[1].

$[NH_2OH]^{+\bullet}$ possesses a planar structure. The unpaired electron is mainly located on the nitrogen atom, but there is also exchange with the adjacent oxygen lone pairs[2].

The isomerization of hydroxylamine radical cation $[NH_2OH]^{+\bullet}$ involves 1,2-hydrogen shifts: that from the nitrogen to the oxygen atom yields the ammonia oxide $[NH_3O]^{+\bullet}$, while that from the oxygen to the nitrogen atom produces the imine–water complex $[HNOH_2]^{+\bullet}$, whose calculated relative energies are 0, 21.4, 36.4 kcal mol^{-1}, respectively[2].

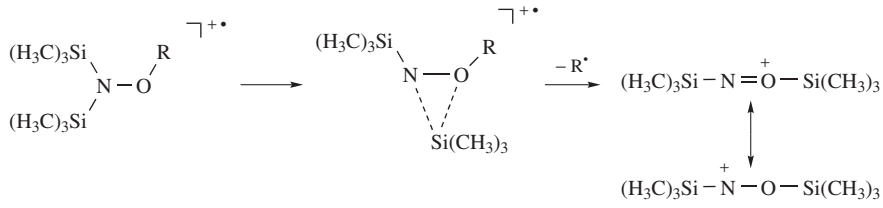
The study of metastable ions, collisional activation and neutralization/reionization experiments have suggested the gas-phase existence of the long-sought ammonia oxide[2].

The hydroxylamine photoionization mass spectrum shows prominent ions at m/z 32 and 31[3]. For the latter, two distinct thresholds were observed and attributed to onsets for formation of HNO^+ and NOH^+. The corresponding heats of formation $\Delta H^\circ_{f,0}(HNO^+)$ and $\Delta H^\circ_{f,0}(NOH^+)$ are 256.8 ± 1.4 and 274.8 ± 0.7 kcal mol^{-1}, respectively[3]. The heat of formation for the species at m/z 32, tentatively ascribed to H_2NO^+, corresponds to 224.6 ± 0.2 kcal mol^{-1}. To rationalize these data, a theory within the framework of quasi-equilibrium theory has been proposed[3].

The unimolecular chemistry of protonated hydroxylamine, produced by chemical ionization with hydrogen as reagent gas, has been investigated by MS and tandem mass spectrometry (MS/MS) experiments[4]. The main peaks in the mass analyzed ion kinetic energy (MIKE) spectrum of protonated hydroxylamine (m/z 34) are at m/z 19 and 33, corresponding to the losses of NH and $H^\bullet$, respectively. A weak peak at m/z 17, due to the loss of $^\bullet OH$, and a very feeble one at m/z 32, due to loss of H_2, are also present. The experimental value of proton affinity (PA) of hydroxylamine determined by the bracketing method is 194 kcal mol^{-1} [5]. Calculated values by the G2 method are 195 kcal mol^{-1} for protonation on nitrogen and 170 kcal mol^{-1} for protonation on oxygen[4], while calculations with the G1 methods produce values of 194 and 167 kcal mol^{-1}, respectively[5]. It follows that protonation of hydroxylamine occurs preferentially on the nitrogen atom. It is noteworthy that isomerization from NH_3OH^+ to $NH_2OH_2^+$ is calculated to require 50.4 kcal mol^{-1} and it is the lowest energy process. Therefore, reactions from both isomers are possible and total scrambling of the hydrogen atoms must be assumed. The ions at m/z 19 (H_3O^+) present in the MIKE spectrum of protonated hydroxylamine are due to the loss of NH from $NH_2OH_2^+$ via cross-over from the singlet to triplet potential energy surface to yield $^3NH + H_3O^+$[4].

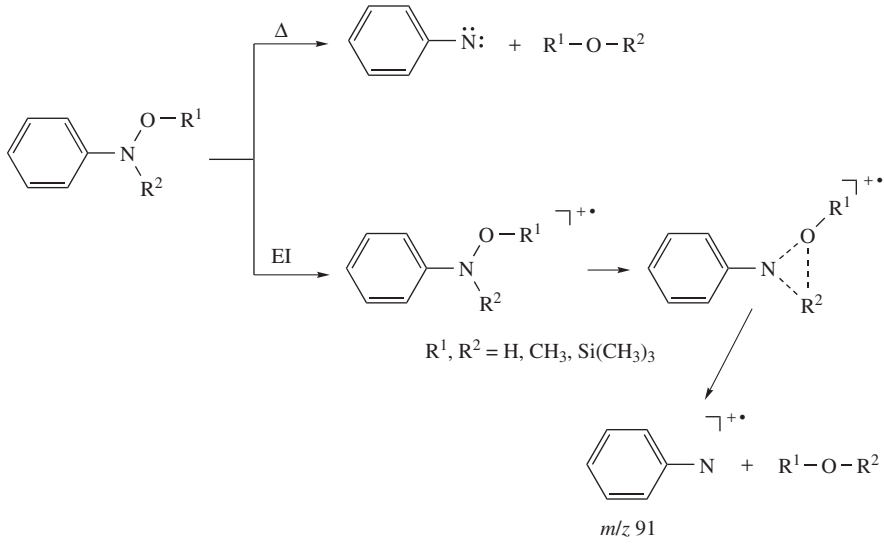
Aliphatic silylated hydroxylamines, such as *N*,*O*-bis(trimethylsilyl)hydroxylamine, when ionized by electron ionization, show elimination of neutral nitrenes that has been rationalized as a symmetry-allowed 1,1-elimination, while ionized nitrenes are

produced with only very low intensity[6]. In the case of *N*,*N*-bis-silylated hydroxylamine derivatives, electron ionization produces a cleavage of the O–C bond, anchimerically assisted by migration of the trimethylsilyl group to the ether oxygen (Scheme 1)[7].



SCHEME 1

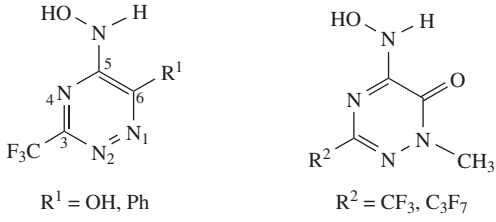
Differently, the molecular ions of hydroxylamine *N*-aryl derivatives produce intense aryl nitrene ions whose formation has been explained by a 1,1-elimination with the characteristics of a linear cheletropic reaction (Scheme 2)[8]. Their reactivity under electron ionization is comparable to that observed under thermolytic conditions.



SCHEME 2

Radical cations, protonated molecules and anions of hydroxylamino derivatives of perfluoroalkyl-1,2,4-triazines (Scheme 3) have been recently studied[9,10] together with their gas-phase reactivity[11].

Thermal degradation of 1,2,4-triazine derivatives (Scheme 3, left side) causes elimination of the hydroxylamino oxygen atom. It follows that the resulting electron ionization mass spectra are relevant to the species (M–O), in which the hydroxylamino function has been replaced by an amino group[10].



R^1 = OH, Ph R^2 = CF_3, C_3F_7

SCHEME 3

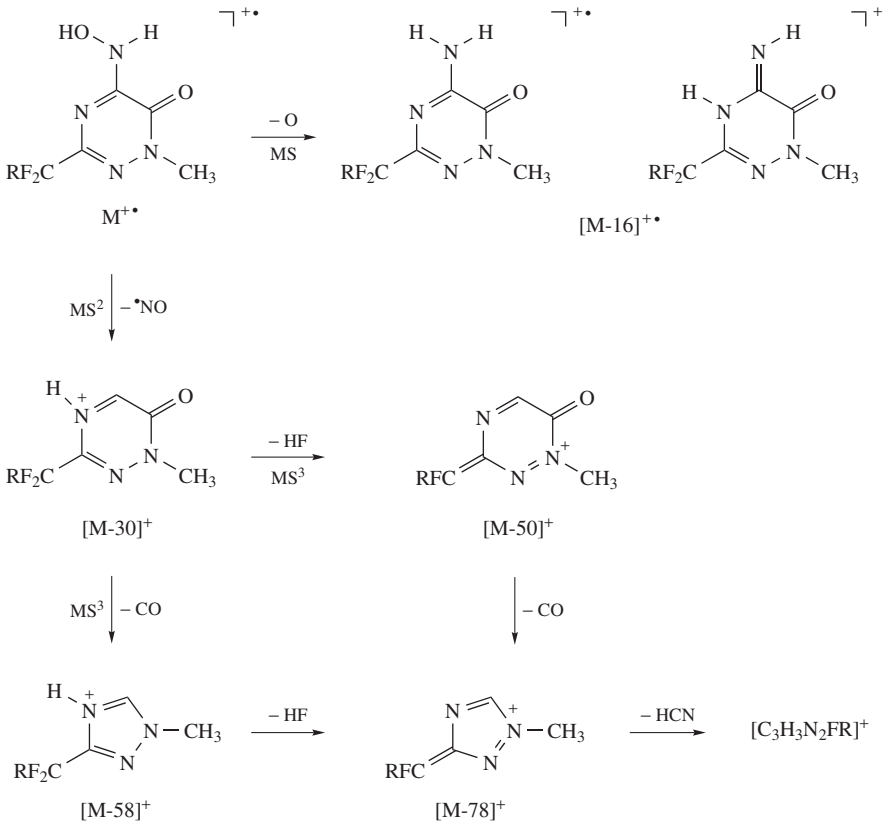
Differently, 6-oxo derivatives (Scheme 3, right side) maintain their own structure after heating. Density functional theory (DFT) calculations have shown that when $R^2 = CF_3$, the unpaired electron in the radical cation is mainly located on the exocyclic nitrogen while the positive atomic charge is at C(6), thus producing a distonic molecular ion[10]. The molecular ions of 6-oxo derivatives (Scheme 3, right side) constitute the base peak and a lot of intense fragment ions, like $[M-NO]^+$, $[(M-NO)-HF]^+$ and $[(M-NO)-CO]^+$, are present in their electron ionization mass spectra (Scheme 4). They are also formed owing to low-energy collision-induced dissociations, while elimination of an oxygen atom from the molecular ion occurs only in the ion source (Scheme 4)[10].

All these compounds (Scheme 3) can be also protonated by electrospray ionization. DFT calculations have shown that protonation on nitrogen atoms is highly favored, with N(2) being the preferred site, followed by N(4) and N(1). Product ion low energy collision-induced dissociation (CID) spectra obtained in an ion trap by selecting the species $[M + H]^+$ show the presence of puzzling ions that differ 2, 22, 24 u from their precursors, and of clusters of ions that differ by 2 u from each other[9, 11].

This behavior has been explained by the occurrence of hydration/elimination reactions, mainly consisting of successive eliminations of HF followed by nucleophilic addition of water in the ion trap[9, 11]. This latter reaction is not observed when a triple quadrupole is used. Gas-phase decompositions, strictly dependent on the chemical structure of the ions, have been also observed. An uncommon loss of a hydroxyl radical, against the even electron rule, occurs from protonated 5-(hydroxyamino)-1-methyl-3-(perfluoropropyl)-1,2,4-triazin-6(1*H*)-one. The resulting odd-electron cations follow two decomposition routes, both involving elimination of radicals, i.e. $^{\bullet}CF_3$ and $HCO^{\bullet}$, thus re-establishing even-electron cations[11].

When the same compounds (Scheme 3) are deprotonated, they have a different gas-phase behavior and three main features can be highlighted in their low energy CID spectra: (a) hydration reactions, observed for cations in IT-MS^2 experiments, do not occur for anions; (b) successive eliminations of HF, that are important gas-phase decompositions of cations, are not observed for anions; (c) their decompositions are initiated by loss of a hydroxyl radical and proceed through eliminations of neutral species, such as CO, so their MS/MS product ion spectra are dominated by radical anions[11].

Theoretical calculations have shown that proton abstraction in 5-(hydroxyamino)-3-(trifluoromethyl)-1,2,4-triazin-6-ol (Scheme 3, $R^1 = OH$) is more favored from the hydroxyl group in position 6 of the triazine ring, followed by the nitrogen and the oxygen of the hydroxylamino moiety. The MS^2 spectrum of the deprotonated species shows ions at *m/z* 178 due to the loss of a hydroxyl radical, produced with high abundance in the ion trap and in a triple quadrupole instrument. Further decompositions of ions at *m/z* 178 produce the species at *m/z* 151, 150, 122 that, supported by high resolution measurements, have been attributed to the losses of HCN, CO, $(CO + N_2)$[11].



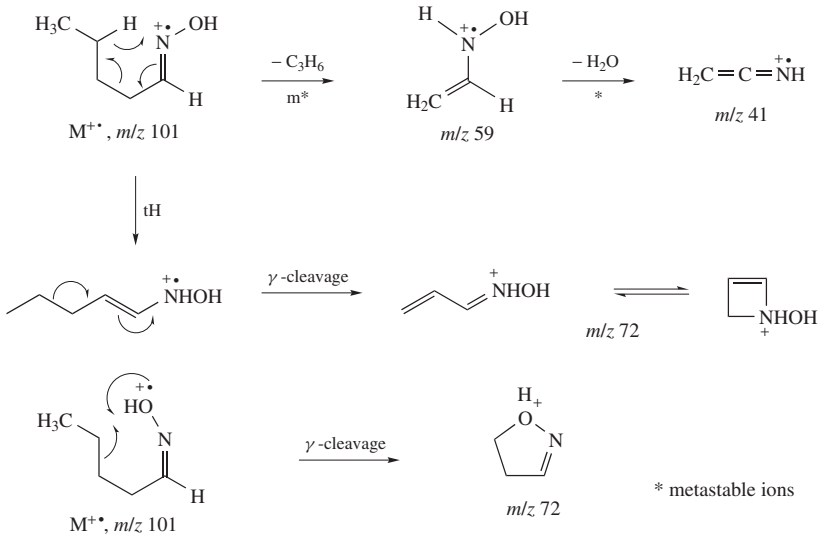
SCHEME 4

III. MASS SPECTROMETRY OF OXIMES

A. Aliphatic Oximes

1. Aldoximes

Electron ionization mass spectra of simple aliphatic aldoximes show molecular ions with low abundance and few, but highly diagnostic, fragment ions that retain the oxygen function[12]. Butanal and pentanal oxime radical cations yield McLafferty rearrangement (Scheme 5) producing the base peak in their electron ionization mass spectra. The main fragmentation pathways for pentanal oxime are reported in Scheme 5. One path is initiated by a McLafferty rearrangement, yielding loss of C_3H_6, followed by elimination of a water molecule[13]. Another fragmentation pathway consists in a γ-cleavage that might occur from the tautomeric form of the molecular ion yielding azacyclobutene ring formation (Scheme 5). If the charge were localized on the oxygen atom, then γ-cleavage yields an isoxazolene ring (Scheme 5)[12].



SCHEME 5

Aldoximes, such as acetaldehyde oxime and butyraldehyde oxime, have been studied by surface ionization mass spectrometry, but the resulting mass spectra are quite poor and characterized by $[M\text{-}H]^+$ and a few ions at very low intensity level[14].

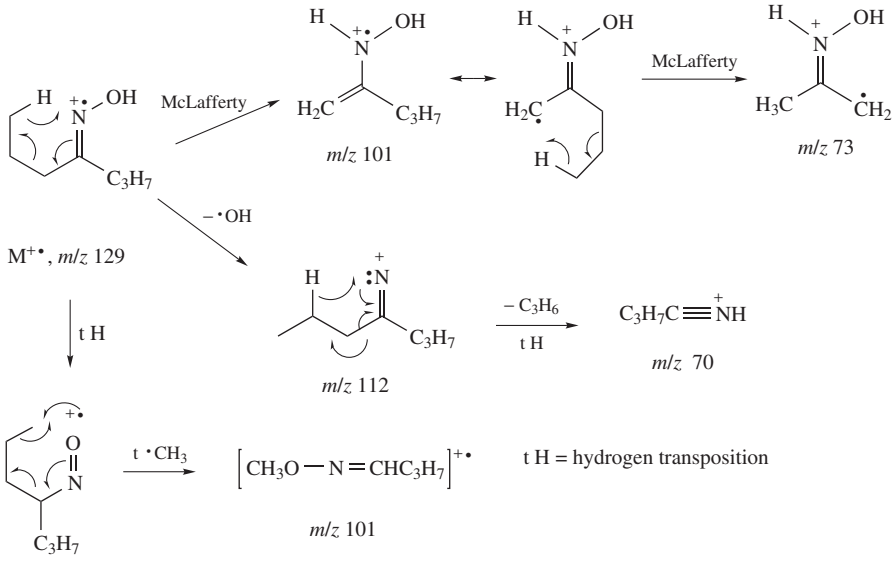
2. Acyclic ketoximes

Owing to electron ionization, aliphatic ketoximes behave in a similar way to aldoximes with the γ-cleavage again representing a preferred fragmentation process. Single and double McLafferty rearrangements also occur and they can be better rationalized by considering charge localization on the oxime nitrogen (Scheme 6)[12, 13]. It is worth noting for oximes the insensitivity of the McLafferty rearrangement with respect to the nature, primary or secondary, of the transferred hydrogen atom.

The molecular ion of aliphatic ketoximes can be also in its tautomeric nitroso form, with electron deficiency on the oxygen atom, that can decompose by methyl migration and loss of alkene (Scheme 6)[12].

As for aldoximes, most of the fragment ions present in the electron ionization mass spectra of ketoximes do not contain the oxygen atom. An example is represented by the initial loss of a hydroxyl radical from the molecular ion, as depicted in Scheme 6.

Low energy (electrons with nominal energy of 12 eV), low temperature (source temperature of 77 °C) mass spectra (LELTMS) of a series of alkyl ketoximes have been obtained[15]. Their molecular ions have appreciable intensities that generally decrease in importance as the size of one or both alkyl groups is increased in ascending a homologous series of compounds. Branching at either the α- or β-carbon atom enhances molecular ion abundance. The principal fragmentation pathway observed in LELTMS is the loss of an alkene from their molecular ion. Regarding oximes possessing a γ-hydrogen atom, the proposed pathway occurs via a process analogous to the McLafferty rearrangement (Scheme 7), even if the possibility of reciprocal hydrogen transfers owing to the formation of ion/neutral complexes cannot be rigorously excluded[15].



SCHEME 6

When both the alkyl chains contain a γ-hydrogen atom, consecutive losses of an alkene molecule from each group occur yielding abundant secondary fragment ions at *m/z* 73 (Scheme 7).

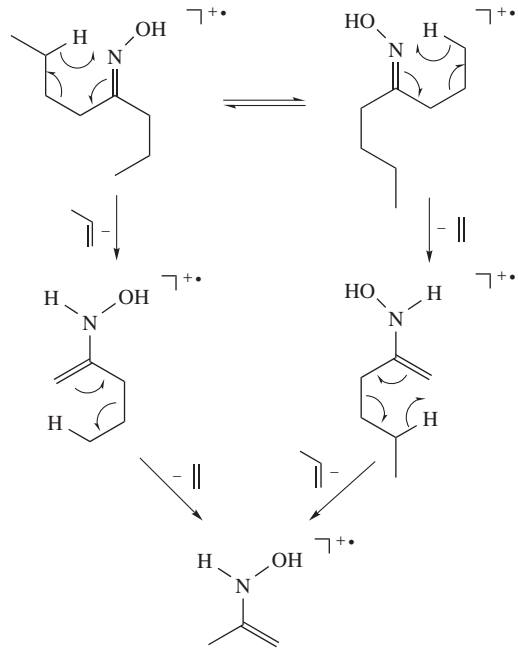
Oximes without a γ-hydrogen atom also form prominent peaks at *m/z* 73 in their LELTMS. A tentative rationalization of this pathway is initiated by a 1,2-CH_3 shift from the α-carbon atom to the sp^2 carbon of the oxime moiety and followed by 1,4-hydrogen shift that affords an ionized nitroso species. A γ-hydrogen transfer may occur from the latter with elimination of an alkene molecule (Scheme 8)[15].

Ketoxime carbamates can have different properties, and some of them are systemic and contact insecticides. Electron ionization[16], thermospray[17] and negative ion chemical ionization[18] have been used for their characterization in the gas phase. Owing to electron ionization, sulfur-containing ketoxime carbamates fragment mainly by two competing pathways, involving loss of CH_3NCO, yielding the corresponding oxime, or that of a sulfur-containing molecule. The favored process is dependent on the oxidation state of the sulfur: in sulfide, the loss of CH_2S, occurring via a McLafferty rearrangement, competes quite favorably. An example of this class of compounds is thiofanox whose fragmentation is reported in Scheme 9[16].

Differently, the fragmentation patterns of the sulfoxide and sulfone ketoxime carbamates are dominated by the loss of CH_3NCO followed by simple cleavage, and resemble the gas-phase behavior of their corresponding oximes[16].

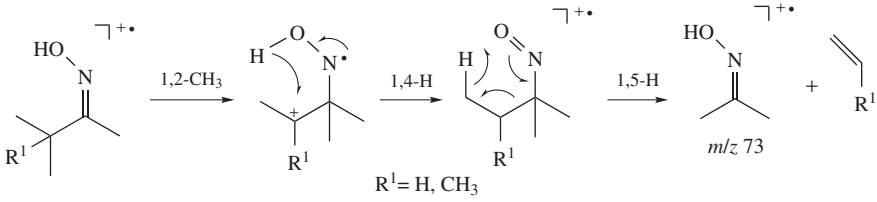
Negative ion chemical ionization mass spectra of aldicarb and its sulfoxide and sulfone derivatives (Scheme 10) show the presence of very intense ions $[M + 74]^-$ attributed to the gas-phase adduct with *N*-methylcarbamic acid formed in the ion source[18].

Differentiation of (*E*)- and (*Z*)-α-hydroxyoximes has been obtained by electron ionization. Both stereoisomers of 5,8-diethyl-7-hydroxydodecan-6-one oxime show scarce molecular ions and abundant fragment ions whose relative intensity differs markedly among the individual isomers[19]. The molecular ion decomposes by cleavage at the hydroxy



m/*z* 73

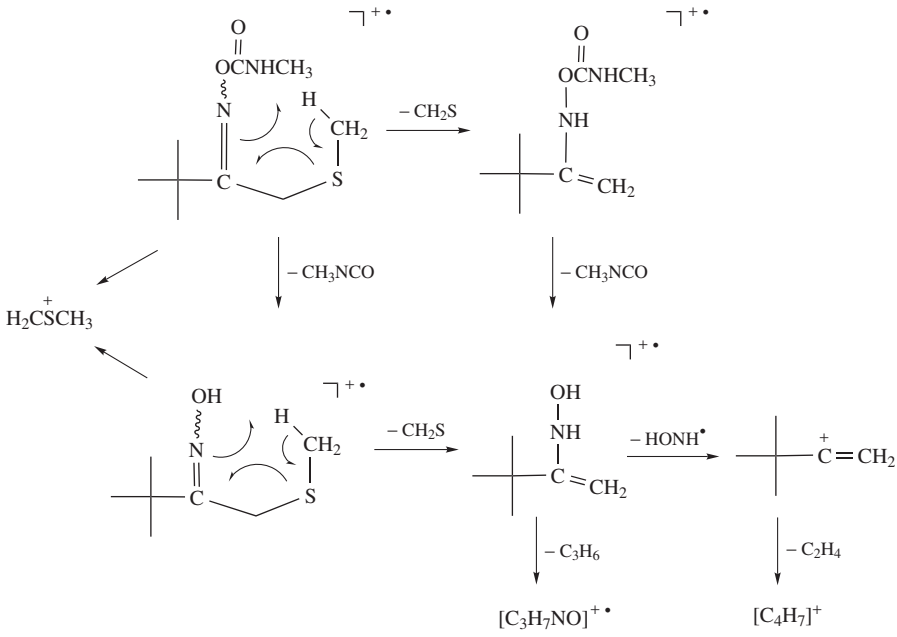
SCHEME 7



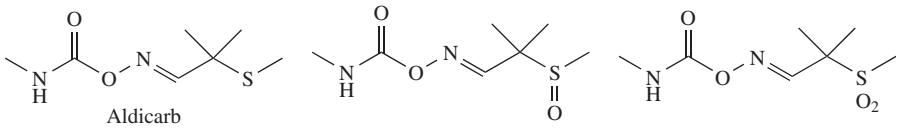
SCHEME 8

function with hydrogen transfer yielding ions at *m*/*z* 173, whose formation is highly favored for the *Z* isomer in comparison to the *E* analogue. Further consecutive losses of water and a CHO radical produce fragment ions at *m*/*z* 155 and 126, respectively, whose relative abundances are much higher in the mass spectrum of the *Z* isomer than in that of its *E* analogue (Scheme 11)[19].

Stereoisomeric differentiation of (*E*)- and (*Z*)-*tert*-butyl 2-hydroxyimino-3-oxo-butyrates and of their methyl and ethyl ethers has been carried out by using gas chromatography coupled with electron ionization and chemical ionization[20]. Under EI conditions, the isomeric oximes produce mainly common fragment ions, such as those at *m*/*z* 57 and 131, due to *tert*-$C_4H_9^+$ and to loss of isobutene respectively (Scheme 12),



SCHEME 9



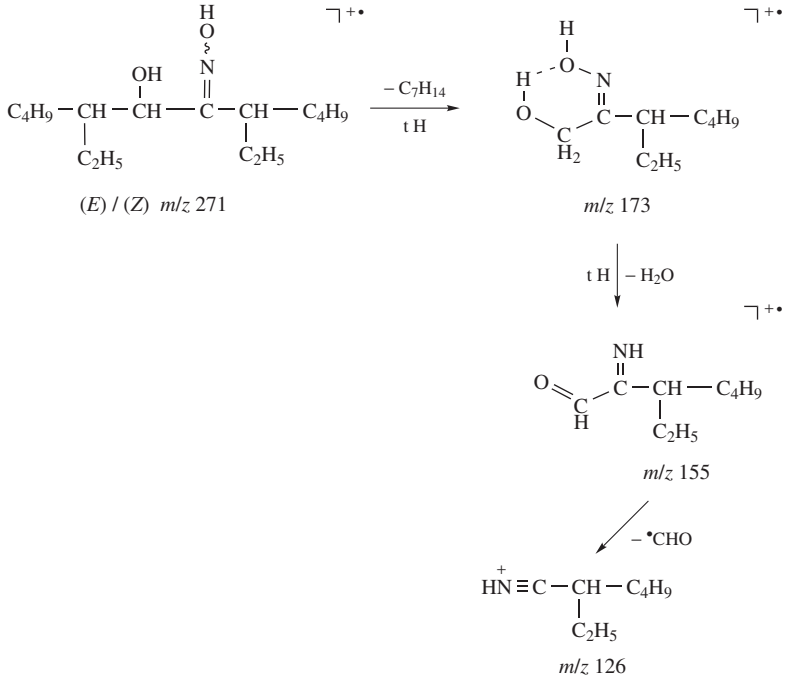
SCHEME 10

but marked differences in their relative intensities are present. These ions are also present in the mass spectra of their methyl and ethyl ethers.

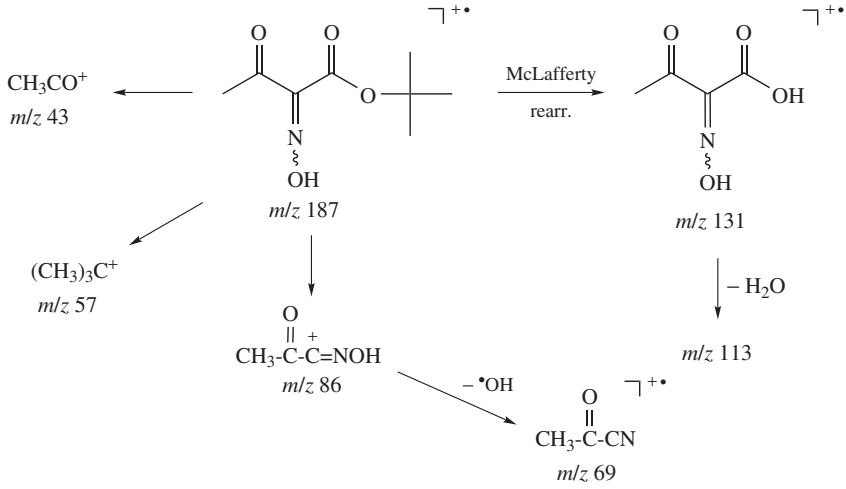
Owing to chemical ionization, the fragmentation of the $[M + H]^+$ ions seems to be controlled by protonation at several sites. Elimination of a *tert*-butyl radical from the protonated species yields ions at *m/z* 131 whose abundance is much higher for the *E* than the *Z* isomer, probably due to steric hindrance[20].

Some oximes can decompose under different conditions. As an example, α-chloro-α-oximino-4-hydroxyacetophenone (COHAP) can be ionized by electron ionization through a direct insertion probe, but it cannot be analyzed either by GC-MS, as it decomposes in the GC oven[21], or by liquid chromatography with a particle beam interface[22, 23]. In fact its dissolution in the aqueous phase produces the corresponding hydroxamic acid, which is dehydrated gradually to form the nitrile oxide derivative that, in turn, can dimerize and further decompose[21].

The gas phase ion chemistry of anions produced by ketoximes has been also studied[24–26]. Molecular anions of aldo- and keto-oximes of α-diketones, produced by electron ionization, show common fragmentation pathways consisting in the loss of

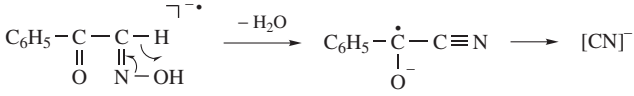


SCHEME 11



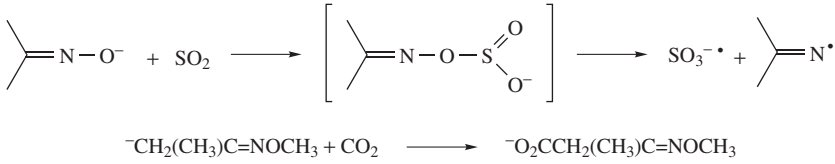
SCHEME 12

hydrogen and water[24]. For 2-oxo-2-phenylacetaldehyde oxime radical anion, loss of water can occur through a four-center transition state to form a α-keto nitrile which fragments further to yield the cyanide anion (Scheme 13)[24].



SCHEME 13

The acetone oximate anion is a moderate gas-phase oxidizing agent and its reactivity with CO_2, COS, CS_2, SO_2 and CH_3I has been studied[25]. Although the observed adduct-ion formation in the reactions with CO_2 and formation of I^- in the substitution with CH_3I don't exclude reaction via the carbon nucleophilic center, the fast reactions through efficient transfer of $O^{-\bullet}$ from $(CH_3)_2C{=}N{-}O^-$ to COS, CS_2 and SO_2, to form $CO_2S^{-\bullet}$, $CS_2O^{-\bullet}$ and $SO_3^{-\bullet}$, respectively, has been considered to proceed via initial addition of the oxygen nucleophilic center (Scheme 14)[25]. When the oxime hydrogen is replaced by a methyl group, as occurs in acetone oxime *O*-methyl ether, addition complexes are formed with CO_2, CS_2 and SO_2 (Scheme 14).

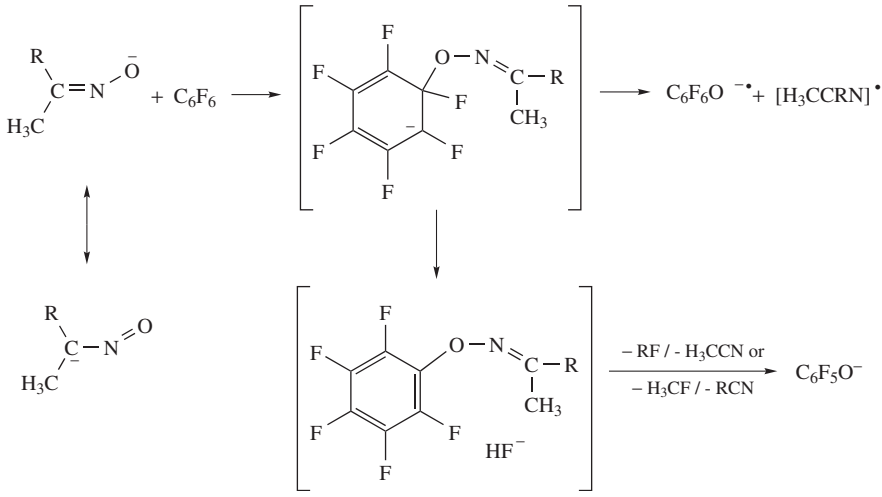


SCHEME 14

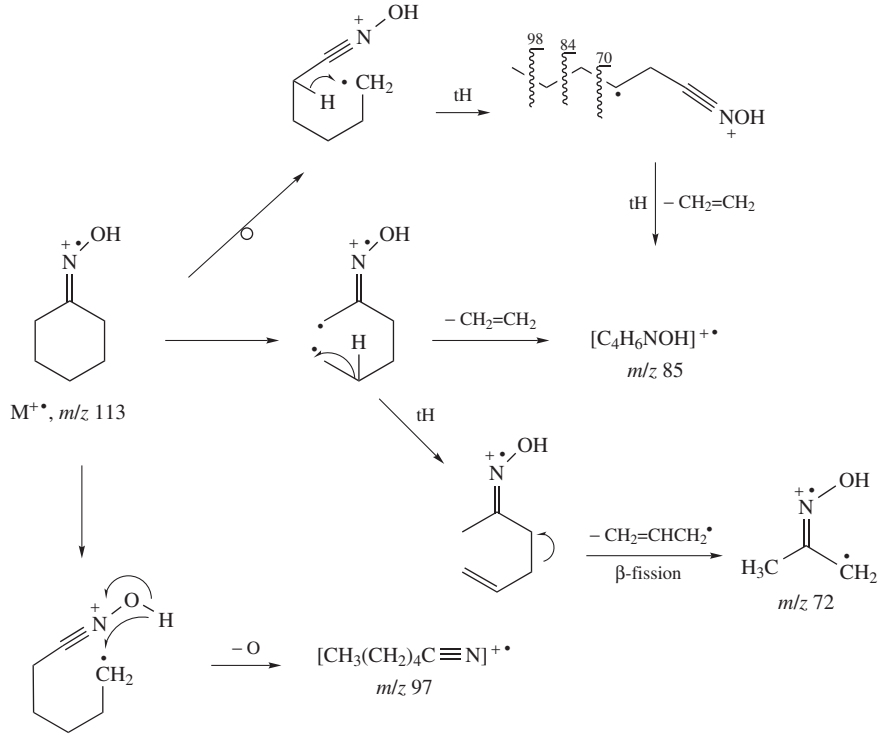
Acetaldoxime and acetone oximate anions exclusively react via the oxygen nucleophilic center with a series of unsaturated polyfluorocarbon compounds (C_xF_y). Two reaction pathways are followed: an oxidation, consisting in the transfer of $O^{-\bullet}$ to the polyfluorocarbon compound, thus forming $C_xF_yO^{-\bullet}$, and an addition–elimination reaction yielding the species $C_xF_{y-1}O^-$ (Scheme 15)[26]. This reactivity, promoted by electrostatic interactions in the reaction complex and by charge distribution, as also shown by theoretical calculations[27, 28], is significantly different from that followed by enolate anions in which competition occurs between addition via the carbon and oxygen nucleophilic centers [26].

3. Alicyclic ketoximes

Alicyclic ketoximes, such as cyclopentanone and cyclohexanone oximes, yield complex electron ionization mass spectra. The increasing propensity for these compounds to undergo α-cleavage yields a characteristic heteroatom fission with loss of the oxygen atom from the molecular ion (Scheme 16). This reaction also occurs in aromatic derivatives, such as benzophenone oxime, but it is not observed in the mass spectra of aliphatic acyclic oximes. The oxygen atom is eliminated as hydroxyl radical and water molecule. Fragmentations involving β-fission also occur (Scheme 16)[12].

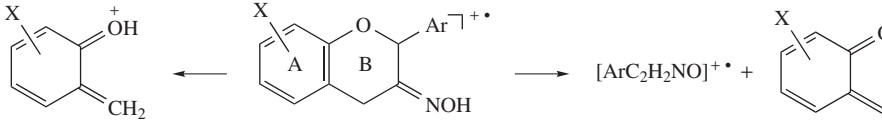


SCHEME 15



SCHEME 16

Owing to electron ionization, arylchroman-3-one oximes produce intense molecular ions that eliminate a hydroxyl radical. In this case, the presence of the corresponding metastable ions suggests that the latter process occurs, at least in part, owing to ionization and it is not merely a thermal degradation[29]. Dismantling of ring B yields structurally informative complementary ions (Scheme 17).



X = 8 –OCH_3; 6 –NO_2 Ar = phenyl; 1-naphthyl

SCHEME 17

Electron and chemical ionizations have been used for studying the gas-phase behavior of 2,2-diphenyl-3-arylcyclobutanone oximes[30]. The base peak of their EI spectra is due to the ions at *m/z* 167, attributed to the diphenylmethyl cation, reasonably formed by an α-cleavage followed by migration of hydrogen from the oxime group to C(2), ring opening and C(2)−C(3) bond fission. These ions contain the two phenyl groups at C(2), and can be stabilized by a rearrangement yielding a phenyltropylium structure (Scheme 18). Analogously to that observed for benzophenone oxime[13], ions at *m/z* 167 can eliminate a methyl radical yielding a biphenylene radical cation (*m/z* 152). Another α-cleavage followed by hydroxyl migration to C(2) and ring opening has been proposed for the formation of the abundant diphenylmethylene oxonium ions (*m/z* 183) that can further decompose through consecutive losses of benzene and CO (Scheme 18)[30].

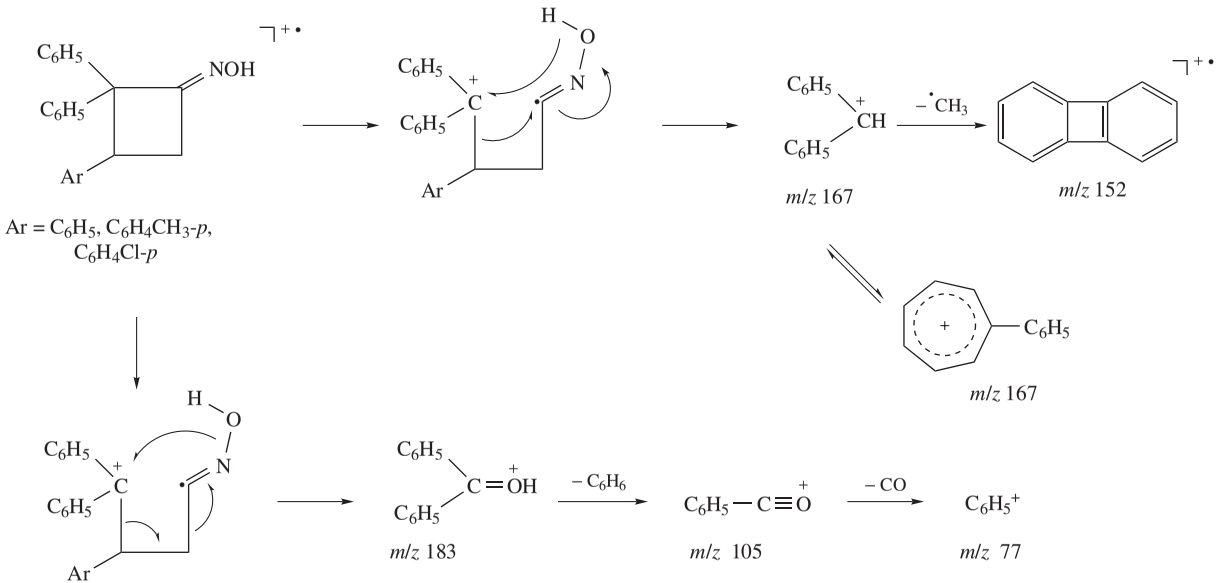
Also owing to chemical ionization, in source fragmentation of the species $[MH]^+$ is quite extensive. The site of the initial protonation may be the oxime group[31] or the phenyl/aryl groups[32], even if the former possibility seems to be excluded because loss of water, observed for acetophenone oxime and benzaldoxime[31], does not occur. Similarly to electron ionization, fragment ions at *m/z* 167 and 183 are still present in the CI mass spectra[30]. For the formation of this latter species a reverse secondary kinetic isotope effect[33] has been proposed[30]. Further, ions $[M + 3H]^+$ have been assigned to a chemical reduction of the double bond of the oxime moiety[30].

An important class of alicyclic ketoximes is represented by cyclohexanedione oxime herbicides, such as alloxydim, clethodim and sethoxydim (Scheme 19), used to control annual and perennial grasses in dicotyledonous crops such as soybean, sugarbeet and oilseed rape. They have been successfully characterized and quantified by HPLC-ESI mass spectrometry with no derivatization or special cleanup steps, other than solid-phase extraction as part of a concentration step[34].

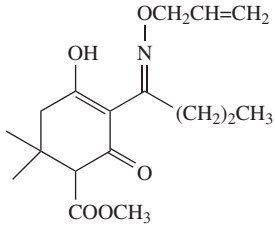
In-source fragmentation, initiated by fission of the N−O bond with loss of the neutral alkenol/alkanol, has been obtained by setting suitable capillary exit and entrance voltages.

Oxime moieties are also present in large molecules. Roxithromycin (Scheme 20) is a commercially available macrocyclic lactone antibiotic belonging to the family of Erythromycins. It contains a 14-membered polyketide lactone ring, a desosamine sugar moiety at the 5-position and an oxime substituent on the 9-position[35].

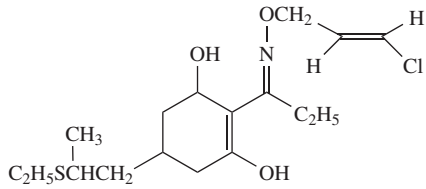
As results from its ESI-CID-MS/MS spectrum, the protonated molecule loses the cladinose sugar and the oxime substituent group on the 9-position. The latter process is analogous to the loss of water from the carbonyl group of Erythromycin A. After the losses of cladinose and the oxime group, the fragmentation pattern is completed by further losses of H_2O and ring-opening[35].


C6H5
C6H5
NOH
Ar
Ar = C6H5, C6H4CH3-p, C6H4Cl-p
H
O
N
C
C6H5
C6H5
Ar
CH
– CH3
m/z 167
m/z 152
C6H5
m/z 167
C=OH
– C6H6
C6H5 — C≡O
– CO
C6H5+
m/z 183
m/z 105
m/z 77

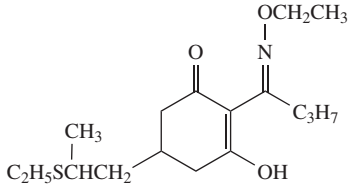
SCHEME 18



Alloxydim

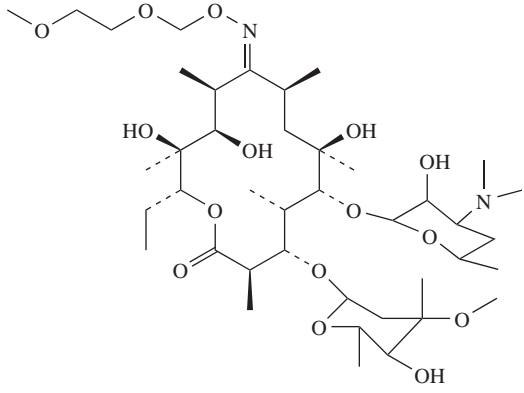


Clethodim



Sethoxydim

SCHEME 19



SCHEME 20

Conjugate transoximation peptides can be obtained as by-products of chemoselective ligation in the synthesis of proteins. MS and MS/MS methods have been used for their characterization[36].

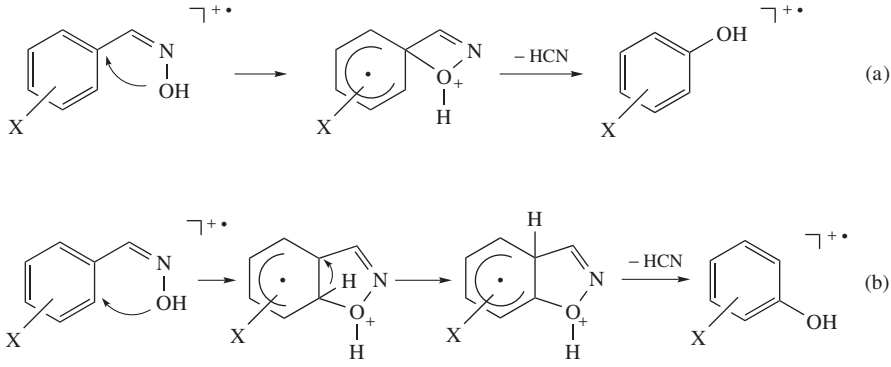
B. Aromatic Oximes

1. Aldoximes

Owing to electron ionization, primary fragmentations of benzaldoxime include loss of $^{\bullet}H$, $^{\bullet}OH$, HCN, CO and HCNO[37]. Loss of water and of an oxygen atom has been

proven to be due to thermal degradation. In the latter case, a decomposition into an imine prior to ionization has been proposed[37]. The elimination of a hydrogen atom from the molecular ion of benzaldoximes mainly involves an aromatic hydrogen, probably forming a stable cyclic structure that hardly shows any further fragmentation[37]. The loss of a hydroxyl radical is not simply a direct cleavage but it is a quite complex pathway, involving different hydrogen atoms depending on the internal energy of the ions[37]. It seems that for low-energy molecular ion, ring and hydroxyl hydrogen atoms become equivalent before fragmentation[37, 38], while for ions with higher internal energy the hydroxylic hydrogen atom is lost almost exclusively[39]. In this light, different mechanisms, most of them involving a cyclohexadiene-type intermediate, have been proposed for elimination of $^{\bullet}$OH from the molecular ions of aromatic aldoximes[37–39].

Loss of HCN from the molecular ion of benzaldoxime is a rearrangement process in which a hydroxyl group is transferred to the phenyl ring. This elimination produces a composite metastable peak: the broad component, associated with a kinetic energy release ($T_{0.5}$) of 670 meV, has been assigned to a mechanism involving a four-membered ring (Scheme 21(a)). The narrow component ($T_{0.5} = 50$ meV) has a 3–10% contribution and it has been assigned to a process in which both the methine and ring hydrogens participate in the loss of HCN through a five-membered intermediate (Scheme 21(b))[37, 39]. When all ring hydrogens are replaced by fluorine atoms only a narrow metastable peak is detected, while in 2-, 3- and 4-fluoro benzaldoximes the narrow peak is highly prevailing over the broad one[37].

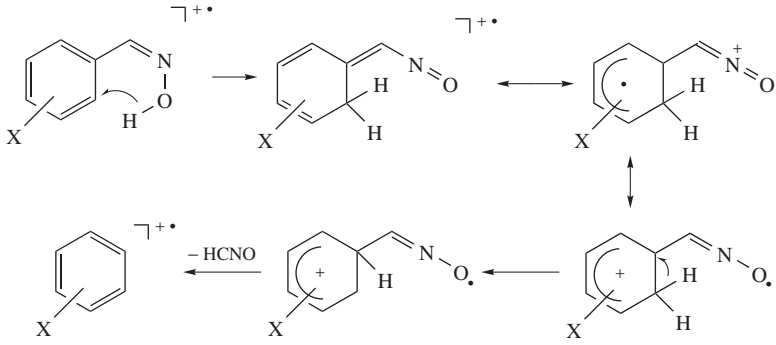


SCHEME 21

Similar mechanisms involving 4- and 5-ring intermediates have been proposed to occur in ion source reactions for the loss of HCN from a series of *para*-substituted aromatic oxime *O*-methyl ethers[40]. Substituent effects on the elimination of HCN are negligible and their nature is much more important than their position. The different behavior observed for *m*- and *p*-methoxybenzaldoximes is due mainly to the difference in internal energy content of the ions[39].

The loss of HCNO from the molecular ion of benzaldoximes is another important fragmentation pathway[41, 42]. A possible mechanism consisting of a transfer of the hydroxyl hydrogen to the 1-position of the phenyl ring via a five-membered ring transition state has been initially proposed[43]. A second mechanism involves a six-membered ring transition state, produced by rearrangement of the hydroxyl hydrogen to the *ortho* position of the

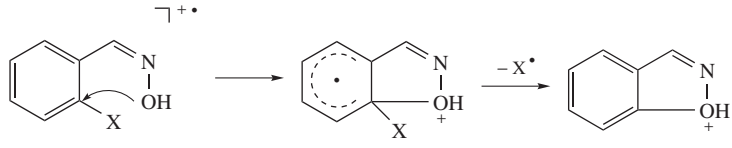
phenyl ring, with a cyclohexadiene-type structure (Scheme 22)[41]. Subsequent hydrogen shift from the 2-position of the cyclohexadiene intermediate to position 1 precedes the elimination of HCNO (Scheme 22)[41].



SCHEME 22

Concerning the loss of CO from the molecular ion of benzaldoximes, a mechanism involving cyclopentadienylimine-type product ions, generated via the nucleophilic attack of the oxygen lone pair at the *ortho* position of the phenyl ring, has been proposed[44]. A similar structure (a substituted cyclopentadiene ring) has been suggested also for benzophenone oxime[45].

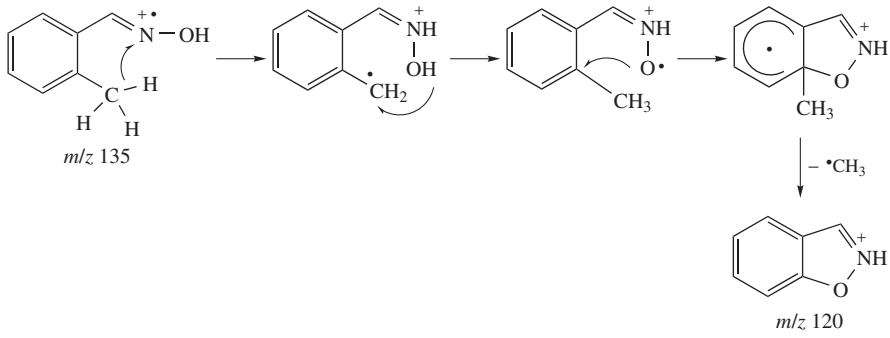
Loss of the substituent $X^{\bullet}$ from the molecular ion of aromatic aldoximes appears to be strongly dependent upon its position on the phenyl ring. This elimination is of lesser importance in the *para*-substituted compounds, whereas rather intense $[M - X]^+$ ions are formed when the substituent is in *ortho* or *meta* positions[41]. It has been proposed that the elimination of the substituent radical from the *ortho* position involves a nucleophilic attack of an oxygen lone pair at the aromatic ring with the formation of a protonated indoxazene and a successive elimination of $X^{\bullet}$ (Scheme 23)[41]. By comparison of differently substituted aromatic oximes, it is likely that more than one structure is generated, presumably indoxazene ions protonated at either the oxygen or the nitrogen atom. The resulting $[C_7H_6NO]^+$ ions undergo three further fragmentations with losses of CO, water and HCN[41]. Loss of the substituent from the *meta* position involves participation of the hydroxyl hydrogen atom through different decomposition pathways[41].



SCHEME 23

An interesting behavior is shown by *o*-methylbenzaldoxime: its molecular ion eliminates a methyl radical both in the ion source and especially in the metastable time frame,

thus suggesting a low energy and high entropy of activation for this reaction. It has been shown that one hydrogen atom of the eliminated methyl radical is a hydroxylic hydrogen, and a pathway involving an isomeric nitrone-like structure, due to an *ortho* effect, has been proposed (Scheme 24)[46].



SCHEME 24

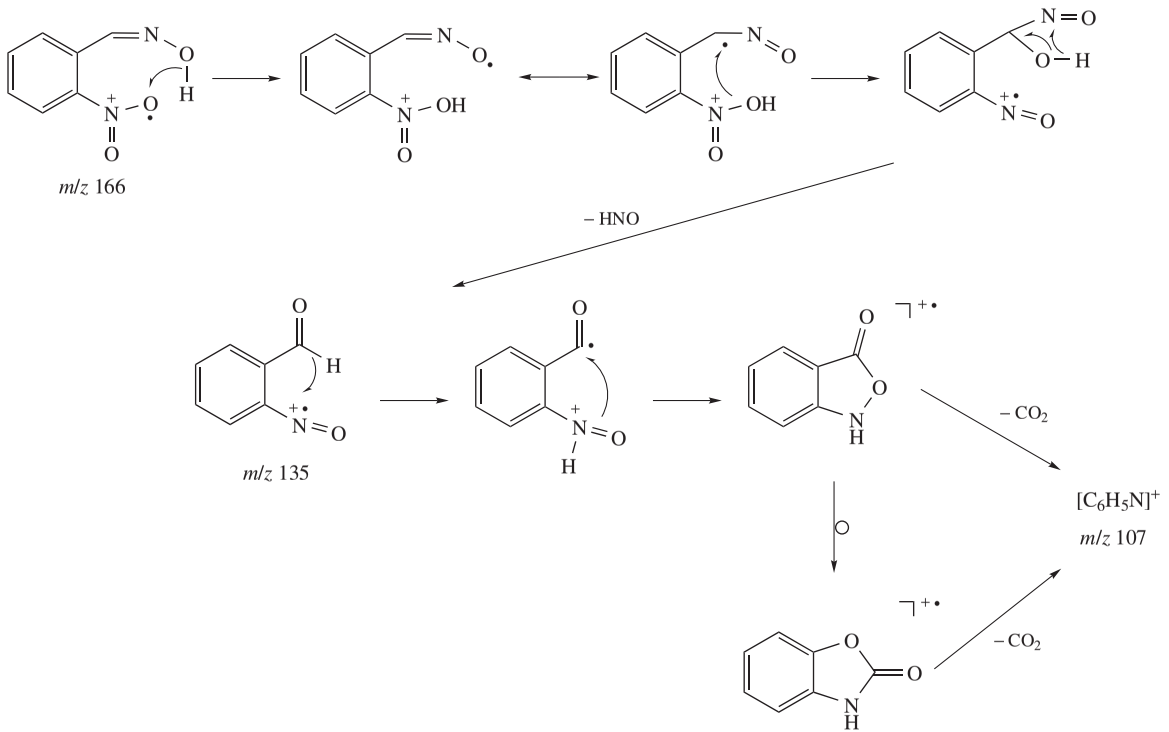
Other experiments suggest that isomerization of the molecular ions of aromatic aldoximes into nitrones requires an *ortho* substituent that can transfer a hydrogen atom to the nitrogen[46].

By examination of metastable peak shapes, an *ortho* effect has been also invoked for explaining the specific loss of a hydroxyl radical in 2-methyl-, 2-hydroxy-, 2-amino- and 2-methoxybenzaldoximes[47]. It has been proposed that loss of $^{\bullet}OH$ involves both participation of the *ortho* substituent in the formation of a five-membered heterocyclic ring and the formation of a protonated isocyanide-type ion via a three-membered ring transition state[47]. Loss of $^{\bullet}OCH_3$ from the corresponding *O*-methyl ethers probably occurs by similar mechanisms[47].

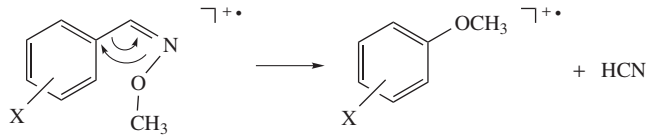
In the electron ionization mass spectrum of *o*-nitrobenzaldoxime the base peak is produced by the species $[M\text{-}HNO]^{+\bullet}$ [48]. An initial transfer of the hydroxyl hydrogen atom to an oxygen atom of the nitro group, followed by migration of a hydroxyl group to the benzylic radical center, has been proposed (Scheme 25)[48]. The resulting ions, after cyclization, can produce a benzisoxazolone radical cation. Both these species can lose CO_2, thus explaining the composite nature of the corresponding metastable ion (Scheme 25)[48].

The molecular ions of benzaldoxime *O*-methyl ethers show elimination of HCN through two different mechanisms: a five-membered cyclic rearrangement involving the *ortho* position occurs in the ion source for high internal energy ions, while, depending upon the substituent, either this process or the four-membered cyclic rearrangement (Scheme 26) is dominant in fragmenting ions of lower internal energy[49–51]. The energy partitioning quotient, $T/\in_{excess}$ (T being the translational energy of the reaction products, and $\in_{excess}$ the sum of the reverse activation energy and internal energy excess of the activated complex at threshold), is strongly substituent-dependent and it varies from 0.20 for the *p*-cyano substituent to 0.73 for the *p*-methoxy group[40, 50].

O-Benzaldoxime ethers and some aliphatic oximes with alkyl chains longer than ethyl[52] show an interesting rearrangement, originally proposed for *O*-*n*-propyl ether of benzaldoxime[42], involving functional group migration and consisting in consecutive losses of CH_2O and a hydrogen atom. This mechanism is initiated by a 1,5-H shift from the terminal $-CH_3$ group of the *n*-propyl chain to the oxime nitrogen atom and elimination

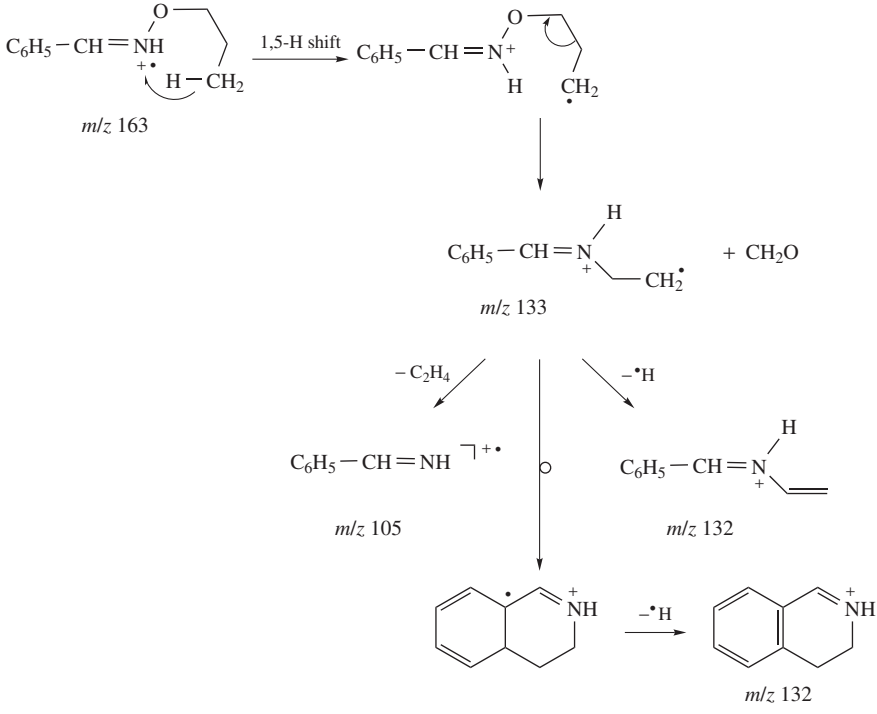


SCHEME 25



SCHEME 26

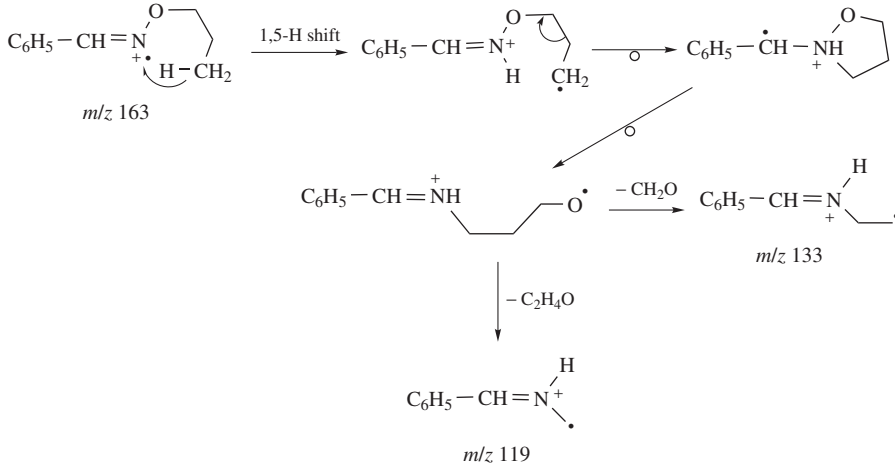
of CH_2O through a four-membered transition state, yielding ions at m/z 133. The α-CH_2- group of the *O*-alkyl chain is specifically lost without any preceding H/D exchange. H-elimination from the resulting β-distonic *N*-ethylene benzaldiminium ion can yield a *N*-vinyl benzaldiminium ion at m/z 132 (Scheme 27)[42]. A further investigation showed that this elimination involves a hydrogen atom almost exclusively from the aromatic ring[52]. In this light, another possible reaction pathway of the β-distonic ion is a ring closure by intramolecular aromatic substitution to yield a stable dihydroisoquinolinium ion (Scheme 27)[52].



SCHEME 27

More recently, the mechanism of the elimination of CH_2O and C_2H_4O from the molecular ion of benzaldoxime-*O*-*n*-propyl ether has been studied in more detail by using

deuterated derivatives, tandem mass spectrometry and density functional theory calculations[53]. It has been proposed that the elimination of CH_2O and of C_2H_4O occurs from a distonic intermediate in which the benzaldiminium group has migrated from the O-atom to the γ-carbon atom of the original propoxy chain. This process occurs through a α-distonic *N*-benzyl-1,2-oxazolidinium ion that, after ring opening, produces a δ-distonic ion that can eliminate CH_2O and C_2H_4O (Scheme 28). The overall transformation occurs with a large energy gain[53].



SCHEME 28

Owing to electron ionization, quinoline-2-carboxaldehyde oxime and its 8-hydroxy derivative show abundant molecular ions that fragment by losses of NO, water and HCN[54].

The different stereochemistry of *syn*- and *anti*-aromatic oximes does not yield specific ions but variations in ion intensities have been observed[55]. The CID-MS/MS decompositions of the $[MH\text{-}H_2O]^+$ species produced in the ion source by chemical ionization of aromatic and aliphatic aldo- and ketoximes have shown the occurrence of stereospecific gas-phase reactions[31].

Combinatorial libraries of aromatic aldoxime ethers have been obtained by the reaction of a mixture of substituted benzaldehydes containing boronic acid units with a scaffold having several chemically similar attachment points (aminooxy groups)[56]. The complete structure elucidation, including substituent position and regiochemistry, of library components has been determined by using electrospray ionization and a combination of single MS and tandem mass spectrometry. The study has been extended to branched oxime ether libraries[57].

2. Ketoximes

The gas-phase behavior of benzophenone oxime owing to electron ionization[12, 13, 45] can be considered typical for other aromatic ketoximes.

The electron ionization mass spectrum of benzophenone oxime shows an abundant peak at *m*/*z* 180, due to elimination of a hydroxyl radical, which decomposes further to the ions at *m*/*z* 103 and 77, as confirmed by metastable measurements[45]. The loss

of $^{\bullet}OH$ is not just a simple elimination, but it involves a marked hydrogen exchange between the OH hydrogen atom and those of the phenyl ring. This might occur through a four-membered transition state[45], analogously to that proposed for benzaldoxime ethers[42]. Similarly, hydrogen exchange and rearrangement reactions occur in the loss of the HNOH radical from the molecular ion, yielding ions at *m/z* 165.

Another fragmentation pathway consisting of skeletal rearrangements yields elimination of CO from the molecular ion of benzophenone oxime. The resulting ions (*m/z* 169) eliminate a C_5H_5 radical, yielding the species at *m/z* 104 that contains about 70% of the hydrogen of the original OH moiety[45].

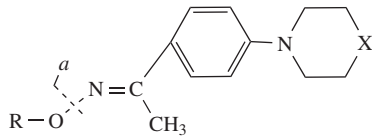
The occurrence of the electron ionization induced Beckmann rearrangement, with the consequent transformation of benzophenone oxime to benzanilide, was initially proposed[58], but later it was definitely disproved[13, 59, 60].

Benzophenone oxime, as a metabolite of the herbicide pyribenzoxim, has been also studied by electrospray. The protonated molecule decomposes under CID conditions yielding main product ions at *m/z* 180, 120 and 77, due to loss of water and benzene and to $[C_6H_5]^+$ [61].

Isomerization and degradation reactions have been found for benzophenone oxime. By using a direct insertion probe, benzophenone oxime isomerizes to benzanilide by a thermal mechanism prior to ionization[59], but this reaction was not observed when GC-MS was used[60]. Largely surface thermal reactions yield conversion of benzophenone oxime and its derivatives to the corresponding imines and another thermal process, mainly occurring at the front of the gas chromatographic column, decomposes benzophenone oxime to benzophenone[60].

Thermal reactions have been reported also for other aromatic oximes[62]. *O*-Acyl oximes of amino acids show thermal degradations at the *N*-terminal protecting groups of the amino acids, as deduced by comparing EI and FAB mass spectra[63].

Reductive degradation of aromatic *O*-acyl oximes occurring under FAB conditions, by using different matrices, has been investigated[64]. When thiol-containing matrices were used, characteristic fragment ions at *m/z* 203 or 205, due to reductive fission at the O–N bond of the oxime moiety, are produced and they have been attributed to iminium ions (Scheme 29).

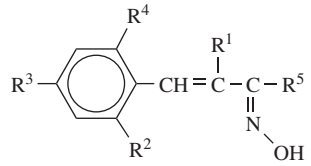


a: X = CH_2: *m/z* 201, +2H, *m/z* 203
X = O : *m/z* 203, +2H, *m/z* 205

SCHEME 29

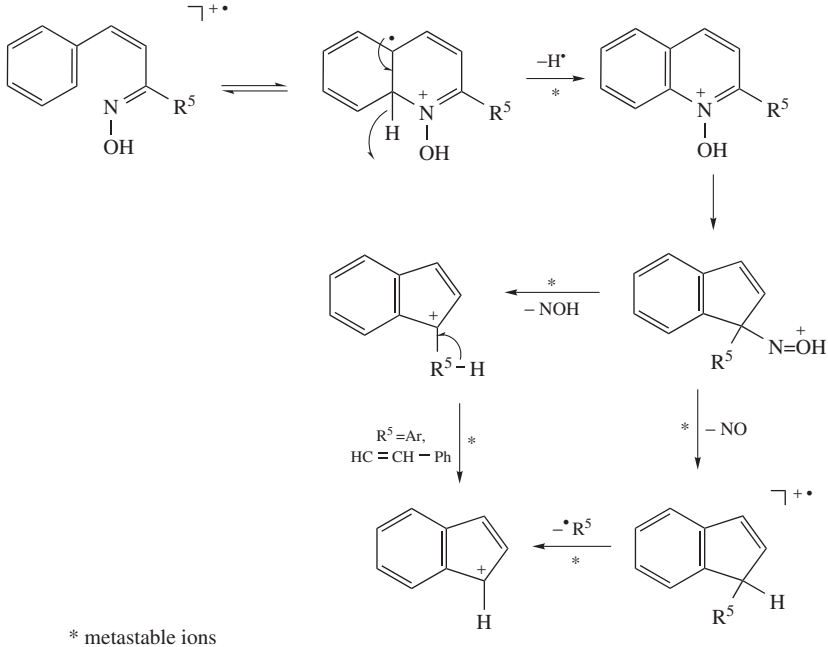
Aliphatic and aromatic α,β-unsaturated oximes (Scheme 30) produce quite complex electron ionization mass spectra[65]. The isomerization of their molecular ions to an ionized quinoline hydroxamic acid prior to fragmentation, and several hydrogen and skeletal migrations, yielding $[M - H]^+$, $[M - OH]^+$ ions and the formation of indenyl, fluorenyl and quinoline cations, have been proposed (Scheme 31).

Since for the loss of hydrogen from the molecular ion there is little exchange between the oxime hydrogen and the *ortho* position of the phenyl styryl hydrogen, it seems unlikely that exchange occurs between these two hydrogens in the loss of $^{\bullet}OH$[65].



R^1, R^4 = D, H; R^2 = D, H, Cl; R^3 = H, D, OCH_3;
R^5 = H, CH_3, CD_3, $CH{=}CHC_6H_5$, $CD{=}CHC_6H_5$, C_6H_5,
p-$CH_3OC_5H_4$, *p*-$CH_3C_5H_4$

SCHEME 30

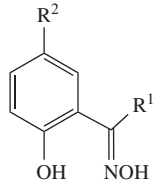


* metastable ions

SCHEME 31

Series of β-hydroxyaryl oximes (Scheme 32) have been studied by electron[66] and FAB[67, 68] ionizations. When $R^1 = CH_3$, the main fragmentation pathways of the molecular ions consist in hydroxyl elimination, simple β-cleavage of the alkyl substituent at R^2, and simultaneous loss of water and alkyl moieties. In the latter two cases, skeletal rearrangements that yield a cycloheptatrienyl ring, with a nitrone-like structure, or fused to a heterocyclic system, have been proposed[66].

When the alkyl substituent at R^1 becomes larger than a methyl group, fragments from alkene elimination, competing with alkyl radical losses, followed by a loss of water, occur together with McLafferty rearrangements[66].



R^1 = H, CH_3, C_2H_5, C_3H_7, C_5H_{11}, C_7H_{15}, C_9H_{19}, $C_{11}H_{23}$, C_6H_5

R^2 = H, CH_3, C_2H_5, C_4H_9, C_8H_{17}, C_9H_{19}, $C_{12}H_{25}$, C_6H_{17}

SCHEME 32

A nitrone → *O*-ether rearrangement at either neutral molecule or molecular ion level has been suggested for benzophenone oxime *O*-methyl and *O*-methylthiomethyl ethers[69].

Protonated aromatic β-hydroxyoximes (Scheme 32) are reduced to their corresponding imines (i.e. $[(M + H)\text{-}O]^+$ ions) by interaction of their solutions in glycerol solvent with a 7 keV argon atom beam as evidenced by FAB mass spectrometry[67, 68]. The first step of the reduction mechanism is the protonation of the analyte, followed by reduction and eventual desorption of the reduced species. The CID fragmentations of the imine derivatives so formed are almost entirely dominated by charge-remote processes with elimination of an alkane molecule[70].

Further to the reduction reaction, aromatic β-hydroxyoximes undergo unusual fragmentation reactions as protonated or cationized species, radical cations, or as deprotonated molecules[70]. The $[M + H]^+$ species expel $^{\bullet}OH$ from the oxime functionality, in violation of the even electron rule, thus forming an imine radical cation that, in turn, can eliminate alkyl groups, resulting in the overall loss of alkanols. These decomposition pathways are also observed for alkali-metal-ion cationized ($[M + Li]^+$ and $[M + Na]^+$) species together with additional charge-remote fragmentations and consequent elimination of alkanes. Deprotonated molecules behave in a similar way[70].

Deuterium labeling, metastable ion and accurate mass measurements have been used for studying gas-phase behavior of 2,4-dihydroxybenzophenone oxime[71]. Also in this case, loss of an oxygen atom is a result of a thermal process occurring prior to ionization. The *ortho* hydroxy substituent deeply alters fragmentation of its molecular ion that decomposes by losses of $^{\bullet}OH$, H_2O, $^{\bullet}NHOH$ and C_6H_5CNO, all substantiated by appropriate metastable peaks[71]. The elimination of water may occur by two different routes: a concerted loss of $H^{\bullet}$ and $^{\bullet}OH$ from the molecular ion, or loss of $H^{\bullet}$ from the $[M - OH]^+$ ion, both involving the hydrogen atom of the *ortho* hydroxyl and that of the oxime moiety. The resulting ion has been proposed as 6-hydroxy-3-phenylbenzisoxazole[71].

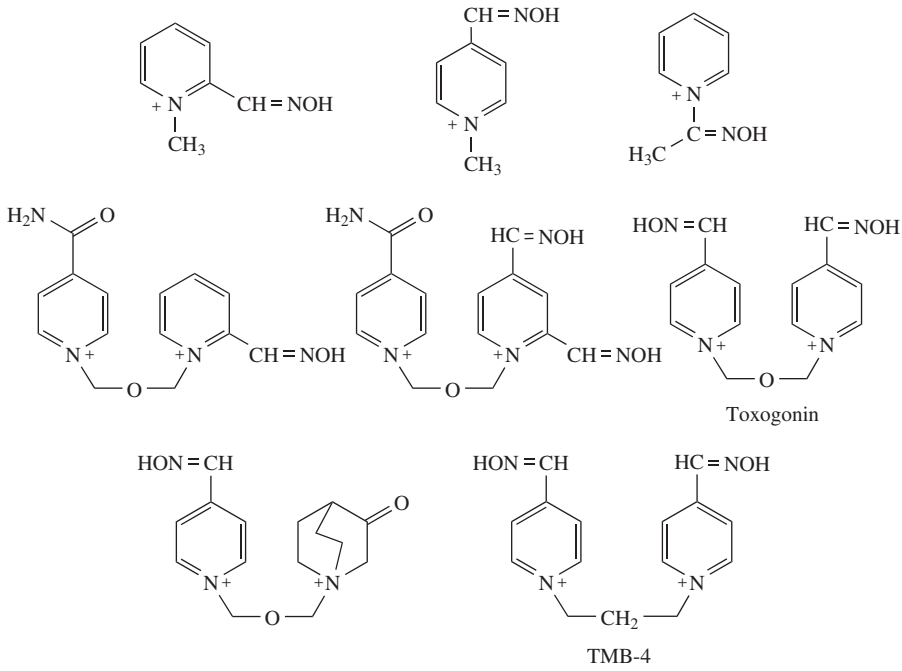
Different aryl heteryl (piperidino, pyrrolidino, morpholino, coumarinyl) ketoximes have been studied by electron ionization mass spectrometry[72]. Losses of oxygen, probably occurring prior to ionization, hydroxyl radical and aryl cyanate have been observed. In particular, the latter has been explained by considering a 1,4-shift of the oxime hydrogen to the hetero ring[72]. Electron ionization and chemical ionization have been used for studying the differentiation of stereoisomeric benzoin oximes[73]. Their electron ionization spectra are essentially identical, thus suggesting that the stereochemical information is not retained in the original molecular ion. It has been proposed that the participation of aromatic substituent(s) results in the formation of modified molecular ions that are common to both (*E*)- and (*Z*)-stereoisomers. This also occurs for other stereoisomeric oximes, like (*E*)- and (*Z*)-2-hydroxy-5-methylbenzophenone oximes[74].

On the other hand, the use of chemical ionization allows stereochemical differentiation of benzoin oximes and shows that the *E* isomer forms more stable $[MH]^+$ and $[MH\text{-}H_2O]^+$ ions than the *Z* isomer[73]. The likely explanation proposed is that protonation of the *E* isomer occurs at the benzylic hydroxyl group to form an ion stabilized by internal hydrogen bonding[73].

Recently, electrospray ionization coupled with MS/MS has been used to study *O*-alkyl aryl oximes[75]. As it occurs with conjugated oximes[76], their collision-induced dissociations show eliminations of radicals, such as $^{\bullet}CH_3$, $^{\bullet}OH$ and $^{\bullet}OCH_3$, yielding odd-electron species[75], that constitute exceptions to the even-electron rule[77].

C. Pyridinium Oxime Salts

Mono- and diquaternary pyridinium oxime salts can have different biological and therapeutical properties, being effective acetylcholinesterase reactivators and used in the treatment of organophosphate poisoning[78, 79]. Electron ionization and chemical ionization result in thermal decompositions of bis-pyridinium compounds, thus producing mass fragments indicative of each pyridinium ring but not representative of the intact compound[80]. For this reason, other ionization techniques, such as laser desorption[81], field desorption[82], secondary ion mass spectrometry (SIMS)[83], thermospray[80], fast atom bombardment[84, 85], liquid SIMS[84] and electrospray[85, 86] have been used for their characterization. The structures of some members of this class of compounds are reported in Scheme 33.



SCHEME 33

While doubly charged cations of diquaternary pyridinium oxime salts are the major species in most of the thermospray mass spectra[80], owing to field desorption, cationized monocharged species are produced[82]. Also by using laser desorption, only monocharged species, mainly produced by charge separation processes, are observed[81].

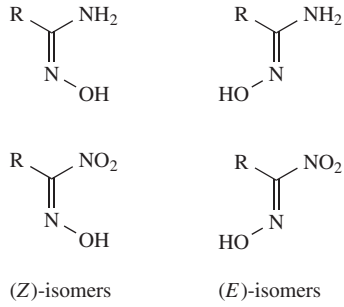
Secondary ion mass spectra of monoquaternary pyridine aldoximes yield prominent intact cations and fragmentation patterns, such as elimination of water, that are dominated by even-electron ions[83]. The presence of specific fragment ions allows isomer differentiation. The diquaternary pyridine aldoximes do not produce doubly charged ions under SIMS, but undergo charge separation reactions, sometimes accompanied by intramolecular aromatic substitution. Expulsion of a proton is also observed[83].

Different gas-phase reactions occur during the ionization of diquaternary pyridinium oxime salts by FAB or LSIMS[84]. They yield one-electron reduced doubly charge cations, deprotonated doubly charged cations (even if at a very low abundance (1–5%)) and anion-reduced doubly charged cations[84]. Eliminations of OH, NOH and CHNOH from the oxime moiety yield characteristic singly charged fragment ions. The effect of the matrix and the use of additive surfactant acids have been evaluated[84].

Electrospray ionization has been used also for characterizing pyridinium and bis-pyridinium oxime salts[85, 86]. With low sampling cone voltage intense dications and several less intense singly charged fragment ions are formed. Increasing the voltage led to a significant increase in the relative intensity of product ions and a decrease of the dication. In-source fragmentations consist in cleavage of the oxydimethylene bridge, eliminations of CO, HNCO and water molecules, as determined by accurate mass measurements[85]. The use of ESI coupled to tandem mass spectrometry allowed a clear differentiation of structural isomeric structures[85].

D. Amidoximes and Nitrolic Acids

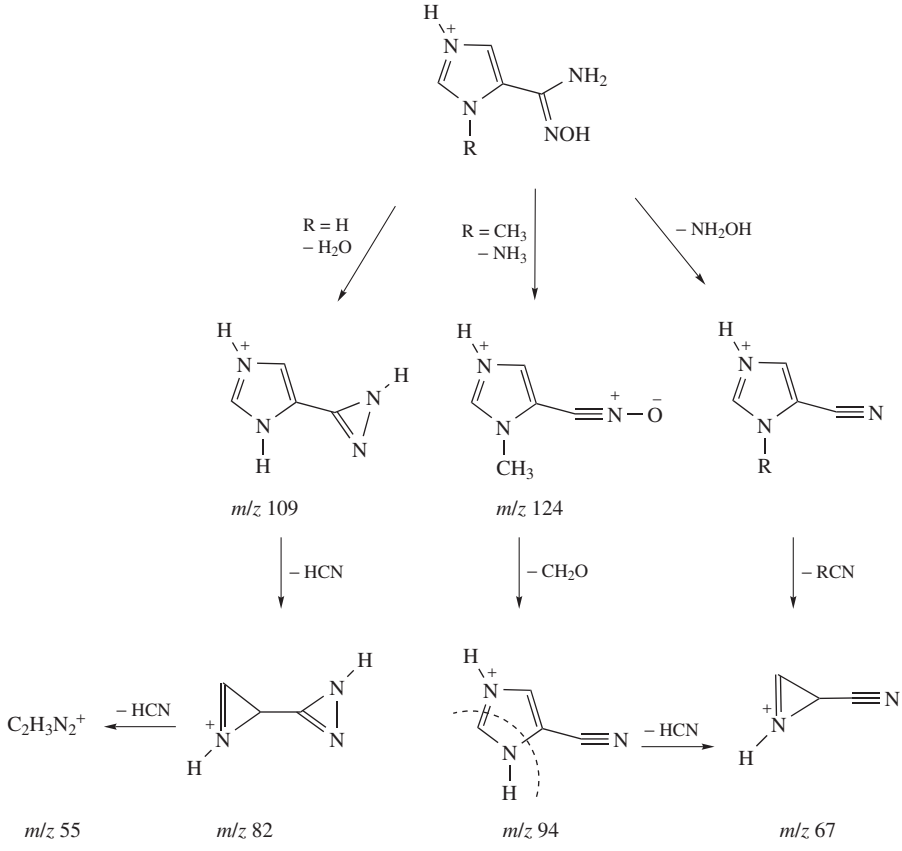
Amidoximes (Scheme 34, top row) and nitrolic acids (Scheme 34, bottom row) are structurally related compounds bearing an oxime group and differing only in the group attached to the double-bonded carbon. Both these classes of compounds are potential donors of nitric oxide (NO), the important mediator in various processes in living organisms[87].



SCHEME 34

Imidazole amidoximes are protonated by electrospray ionization. Theoretical calculations (HF/6-31G(d,p)) suggest that the most favorable protonation site is N(3) of the imidazole ring followed by the nitrogen of the oxime moiety[88]. Under CID conditions, the protonated molecules can follow common fragmentation pathways, such as elimination of hydroxylamine, or others, i.e. loss of water or ammonia, depending upon the substituent in the imidazole ring at position N(1) (Scheme 35)[88].

Similarly to their chemistry in solution, nitrolic acids behave in the same way in the gas phase and decompose via the formation of nitrile oxides. The fragmentation pathways



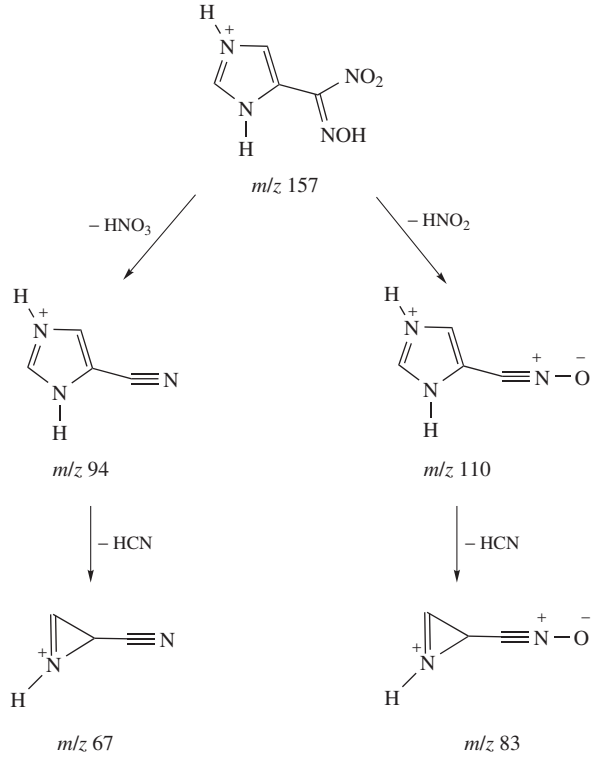
SCHEME 35

for imidazole nitrolic acids involve elimination of HNO_2 or HNO_3 from their protonated molecules. The resulting ions further decompose by loss of HCN (Scheme 36). Nitrolic acid esters decompose similarly to their parent compounds[88].

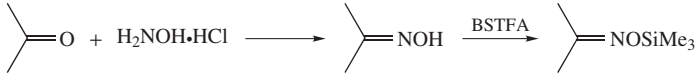
E. Oximes as Final Products of Derivatization Reactions

As shown above, mass spectrometry has been extensively used for the characterization of oxime derivatives. Beyond naturally occurring and specifically synthesized oximes, many derivatives are obtained by derivatization reactions of carbonyl groups (Scheme 37) to improve their gas-phase properties and characterization by mass spectrometry[89]. These reactions can be also done directly on a solid-phase micro-extraction fiber[90–92].

The oxime group, containing a weakly acidic OH group, may be then subjected to further derivatization to form silyl derivatives possessing high volatility and increased gas chromatographic properties. The use of a number of substituted hydroxylamines, such as *O*-methyl, *O*-benzyl[93], *O*-pentafluorobenzyl[94, 95] hydroxylamines, as derivatizing agents avoids additional silylation.



SCHEME 36



BSTFA = *N*,*O*-bis(trimethylsilyl)trifluoroacetamide

SCHEME 37

In this section, mass spectrometry data of oxime derivatives produced by derivatization reactions are presented. Most of the papers published in this field are mainly of analytical interest for identification and quantitation of a wide range of compounds and only few of them deal with details on gas-phase ion chemistry.

1. Saccharide oximes

For a long time, oxime derivatives of monosaccharides have been used for the determination of sugars in mixtures[96–101]. Typically, a mixture of sugars is treated with hydroxylamine hydrochloride and the resulting oximes are derivatized to form trimethylsilyl ethers before analysis by gas chromatography[102]. Stereoisomeric differentiation of

monosaccharide oximes has been done by using electron ionization[103] and fast atom bombardment coupled to tandem mass spectrometry[104]. In the latter case, decompositions of protonated molecules consist in: (a) a loss of water, either as a single molecule or as a concerted loss of two (xylose, arabinose, fructose, mannose, galactose, glucose) or three (mannose, galactose, glucose) molecules, and (b) a loss of the hydroxylamino moiety with or without a loss of water[104].

Muramic acid derivatized as pentafluorobenzyl oxime (PFBO) acetate has been characterized and quantified by GC-MS[105] and MS/MS[106]. Di- and trisaccharide trimethylsilyl oximes have been also prepared and studied by GC-MS for their qualitative and quantitative determination[107–110]. Oximate glycans have been characterized by electrospray ionization[111].

2. Steroid oximes

Different oxime derivatives of steroids have been obtained. *O*-Methyloxime derivatives have been studied by GC-MS methods based on electron ionization[112, 113]. Volatile PFBO derivatives of steroids are prepared by reaction with the reagent *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine (PFBHA). PFBO derivatives of neurosteroids have been quantified by gas chromatography-negative-ion chemical ionization mass spectrometry at low levels in discrete areas of the brain[114]. High-energy tandem mass spectrometric studies of PFBO derivatives of ketosteroids[115, 116] and of guneribone[117] have been carried out.

A lot of methods are based on electrospray ionization coupled to tandem mass spectrometry and high performance liquid chromatography (HPLC). Several model keto steroids, especially androgens and progestogens, have been studied by using nano-electrospray-MS/MS[118]. Upon CID, their protonated molecules produce fragmentation depending on the molecular structure. This method has been further refined to allow quantitation of steroids from brain tissue at low femtomole levels[119]. The oximation reaction has been also used to develop serum testosterone[120] and natural hormones in bovine serum[121] assay allowing one to reach very low levels of quantification.

Modification and optimization of the analytical method, regarding both HPLC separation and tandem mass spectrometry conditions, to promote the formation of analyte-solvent (acetonitrile) ion clusters, have made possible the detection of dihydrotestosterone to levels of about 700 attomoles on-column and still allow for the simultaneous analysis of testosterone[122]. HPLC-ESI-MS/MS has been also used in the characterization and quantitation of adrenal steroids from serum or plasma[123].

An alternative derivatization mode, consisting in the formation of testosterone ethyloxime acetate analyzed by liquid chromatography–atmosphere pressure chemical ionization tandem mass spectrometry, has been proposed[124].

Rapid screening of steroids in raw urine can be implemented without sample preparation using reactive desorption electrospray ionization[125]. Oxime formation occurs in the course of heterogeneous phase ion/molecule reaction between the solution-phase hydroxylamine and the solid-phase carbonyl compound, and it is demonstrated to be effective for selective ionization of anabolic steroids with low detection limits[126].

3. Derivatization of aldehydes to oximes

Different oxime derivatives have been obtained for increasing chromatographic and mass spectrometry properties of carbonyl compounds. Pentafluorobenzyl (PFB) oxime derivatization of aldehydes followed by GC-MS analysis has been a commonly employed technique for aldehyde analysis and quantification. Thus PFBO derivatives of short-chain

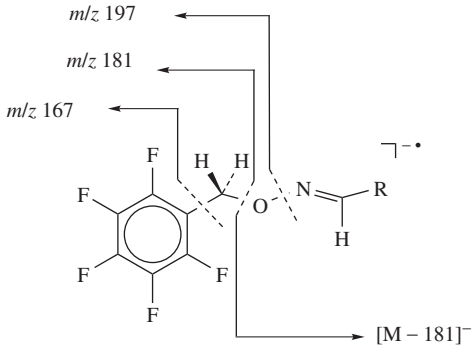
α-hydroxyaldehydes[127] and aldehydes produced from lipid peroxidation[128–130] have been analyzed and quantified by GC-MS.

The reaction between carbonyl groups and PFBHA can be carried out in a microwave oven to minimize reaction time compared to conventional methodology. This approach has been used for the determination of carbonyl compounds, either directly from gaseous phase or following a volatilization from liquid or solid samples, followed by GC-MS analysis[131].

The oxime-trimethylsilylation method was applied to the GC-MS analysis of hydroxycarbonyls, such as glycolaldehyde, which are important pyrolysis products of wood polysaccharides[132].

A rapid determination of acetone in human blood by derivatization with pentafluorobenzyl hydroxylamine followed by headspace liquid-phase microextraction and GC-MS (EI) analysis has been proposed[133].

Several mass spectrometric determinations of PFB oximes are based on the use of negative ion chemical ionization that can result in being more sensitive than positive ion methodologies[134]. A systematic mass spectrometric study of PFBO derivatives of reactive biological aldehydes, derived from lipid peroxidation and oxidation of α-amino acids, has employed GC-electron capture mass spectrometry, tandem mass spectrometry and exact-mass measurements[135]. Different fragmentation pathways have been observed: some involving simple bond cleavages along the exocyclic chain (Scheme 38) and others requiring rearrangement reactions (Scheme 39).

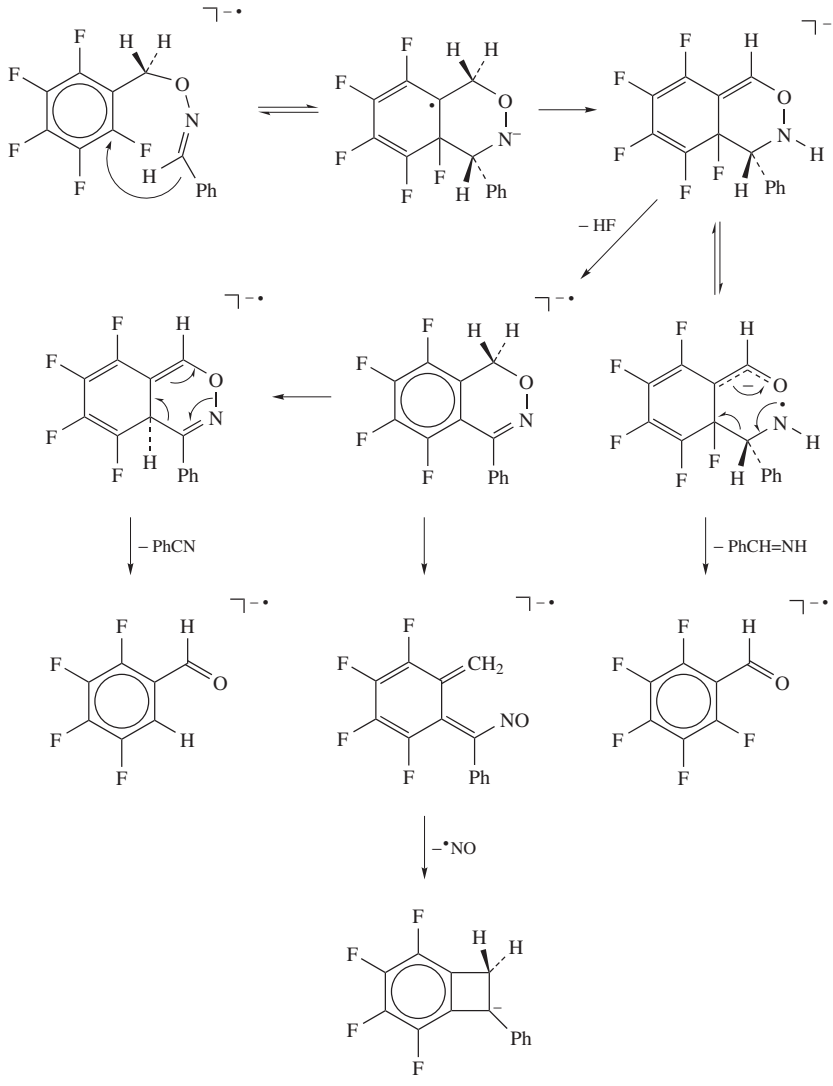


SCHEME 38

It has been proposed that all rearrangement-based fragmentations of $M^{-\bullet}$ proceed through a structure that features a six-membered ring and yet maintains isomeric identity. Major fragment ions are $[M - HF]^{-\bullet}$, that further decompose by loss of HF, HCN or NO. Most fragmentations allow one to differentiate (*E*) and (*Z*) geometrical isomers[135].

GC-MS with negative ion chemical ionization has been used for quantifying α-chlorinated fatty aldehydes and 2-hexadecenal as their PFB oximes[136, 137], and long-chain aldehydes[138] in lipidomic analysis. An analogous method has been developed and validated for the detection and quantification of low-molecular-weight aldehyde in excipients used in liquid/semi-solid based capsule dosage forms[139].

Methods based on the solid-phase micro-extraction and on-fiber derivatization of aldehydes, with PFBHA adsorbed onto a fiber and then exposed to the aldehydes, have been applied for analysis of carbonyl compounds in water, beer[140–142], human blood[143], and recently in maize and grass silages[144].



SCHEME 39

The carbonylic groups of isoprostans and prostaglandins can be derivatized to different oxime derivatives and analyzed by GC-MS, generally by using negative-ion chemical ionization. Methoxime[145–149] and PFB oxime derivatives[150] of different prostanoids have been obtained and characterized by GC-MS. Methoximes of prostenoid derivatives have been also studied by HPLC-ESI-MS/MS[151].

O-Methylhydroxylamine[152–156] and hydroxylamine hydrochloride[157–159] have been extensively used to form oxime products of keto-opiates analyzed by GC-MS.

4. Miscellanea

Different oxime derivatives have been also obtained in the derivatization of carbonyl groups of a wide range of pollutants, such as cholic acid derivatives[160] and in multiresidue analysis[161] by using GC-MS methods.

Anthocyanidins and flavanones can be derivatized in two consecutive steps, first with hydroxylamine•HCl in pyridine into oximes, thereafter in the second step with hexamethyldisilazane, in the presence of trifluoroacetic acid as catalyst, into trimethylsilyl oxime derivatives that can be characterized and quantified by gas chromatography–mass spectrometry[162].

Oxidized forms of carotenoids have been derivatized as ethyl oximes and analyzed by HPLC-ESI-MS/MS. All carotenoid ethyl oximes of zeaxanthin cleavage products were characterized by the losses of 60 and 61 Da in their MS/MS spectra[163].

N′-Aminooxymethylcarbonylhydrazino D-biotin, a biotinylated hydroxylamine derivative, reacts with aldehyde/keto groups in oxidatively modified proteins to form an oxime derivative that is amenable for detection, identification and characterization to tandem mass spectrometry[164]. Tandem mass spectrometry of the labeled oxylipid peptide conjugates indicates that the biotin moiety is at least partially retained on the fragment ion during the collisionally induced dissociation experiments, a prerequisite for the use of automated database searching of uninterpreted tandem mass spectra[164].

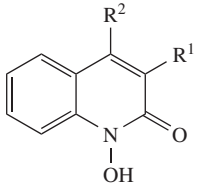
An electrospray ionization mass spectrometry method for detecting carbonyl groups in triterpenoids has been developed by using hydroxylamine hydrochloride (NH_2OH•HCl) as a derivatization reagent[165].

IV. MASS SPECTROMETRY OF HYDROXAMIC ACIDS

Different mass spectrometry ionization techniques have been used to study and characterize the gas-phase behavior of hydroxamic acids and their derivatives. Depending on the ionization technique used, radical cations, deprotonated or protonated molecules have been produced in the gas phase. This is also important for evaluating the role exerted by one-electron removal, or by elimination or addition of a proton on the gas-phase properties of the resulting odd- or even-electron ionic species.

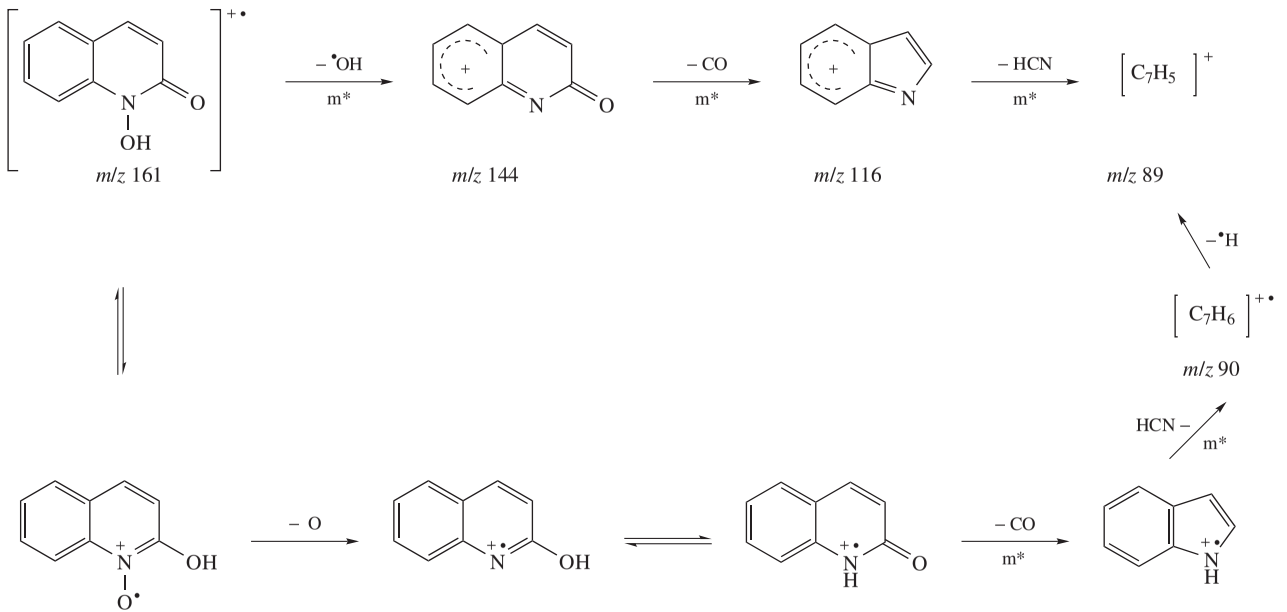
A. Radical Cations of Hydroxamic Acids

Different cyclic hydroxamic acids have been studied by electron ionization. Their decomposition pathways have been studied by deuterium labeling, high resolution mass spectrometry and metastable ions. Simple quinoline hydroxamic acids (Scheme 40) produce abundant molecular ions that fragment by elimination of an oxygen atom and eventually of a •OH radical[166].



R^1 = H, NH_2, CN, COOH R^2 = H, CH_3, OH

SCHEME 40



m* = metastable ions

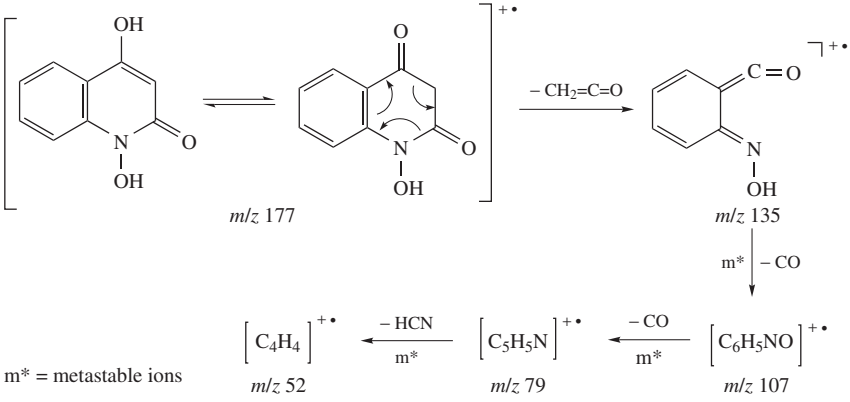
SCHEME 41

$[M-16]^{+\bullet}$ and $[M-17]^{+}$ ions decompose further by the expulsion of CO, thus producing ring contraction, followed by loss of HCN. The fragmentation pathway proposed for 1-hydroxyquinolin-2(1*H*)-one, that can exist in the tautomeric fully aromatic 2-hydroxyquinoline-*N*-oxide form, is reported in Scheme 41. Analogous derivatives, such as 1-hydroxy-4-methyl-2(1*H*)-quinolone, show similar decomposition pathways.

High resolution measurements have allowed one to determine that ions at *m/z* 132, present in the mass spectrum of 3-amino-1-hydroxyquinolin-2(1*H*)-one, are a mixture of $[C_8H_6NO]^{+}$, due to consecutive losses of $^{\bullet}OH$ and HCN from $M^{+\bullet}$, and $[C_8H_8N_2]^{+\bullet}$ in a ratio 94:6[166]. The latter minor component arises presumably by elimination of CO from the $[M-O]^{+}$ ions.

Owing to the *ortho* effect, the molecular ion of 1-hydroxy-2(1*H*)-quinolone-3-carboxylic acid shows elimination of water[166].

1,4-Dihydroxy-2(1*H*)-quinolone shows a distinctive loss of ketene from the molecular ion followed by elimination of two molecules of CO and HCN (Scheme 42)[166].

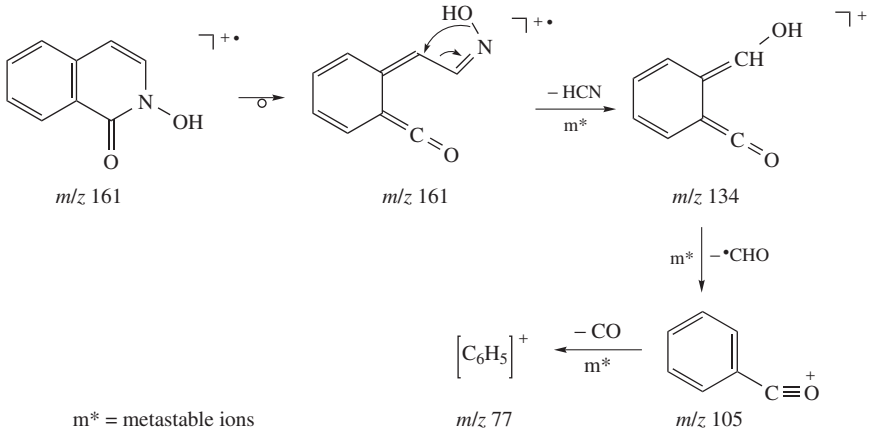


SCHEME 42

2-Hydroxyisoquinolin-1(2*H*)-one ($M^{+\bullet}$ *m/z* 161) shows a fragmentation similar to 1-hydroxyquinolin-2(1*H*)-one with specific decomposition pathways due to direct elimination of HCN from $M^{+\bullet}$. This has been explained by considering a pyridinone ring opening and 1,3 migration of the $^{\bullet}OH$ radical to the carbon atom (Scheme 43). Loss of HCN is followed by elimination of $^{\bullet}CHO$ and CO, yielding ions at *m/z* 134, 105 and 77, respectively (Scheme 43)[166].

The ethyl ester of 3,4-dihydro-1-hydroxy-2(1*H*)-quinolone-3-carboxylic acid shows elimination of the ethoxycarbonyl radical from the molecular ion yielding the base peak at *m/z* 162 in its electron ionization mass spectrum. Ions at *m/z* 162 can lose oxygen or, alternatively, show consecutive losses of $^{\bullet}OH$, CO and HCN (Scheme 44). Another fragmentation pathway is initiated by elimination of ethanol followed by the unusual loss of C_3O_2, confirmed by high resolution experiments. Further eliminations of CO and HCN yield ions at *m/z* 93 and 66, respectively (Scheme 44)[166].

The molecular ion of 3-cyano-3,4-dihydro-1-hydroxy-2(1*H*)-quinolone follows three parallel pathways initiated by loss of oxygen, $^{\bullet}OH$ or water, respectively, and followed



SCHEME 43

by consecutive eliminations of CO and two HCN molecules. The *ortho* effect causes the loss of HCNO from the species $[M\text{-}16]^{+\bullet}$ and $[M\text{-}17]^{+}$, as supported by the corresponding metastable ions[166].

The molecular ion of 3-hydroxy-2-methylquinazolin-4(3*H*)-one has a unique behavior. In fact, in addition to the expected eliminations of oxygen or $^{\bullet}$OH, it loses a nitric oxide radical yielding $[M\text{-}30]^{+}$ ions that are the most abundant fragment ions in its EI mass spectrum[166].

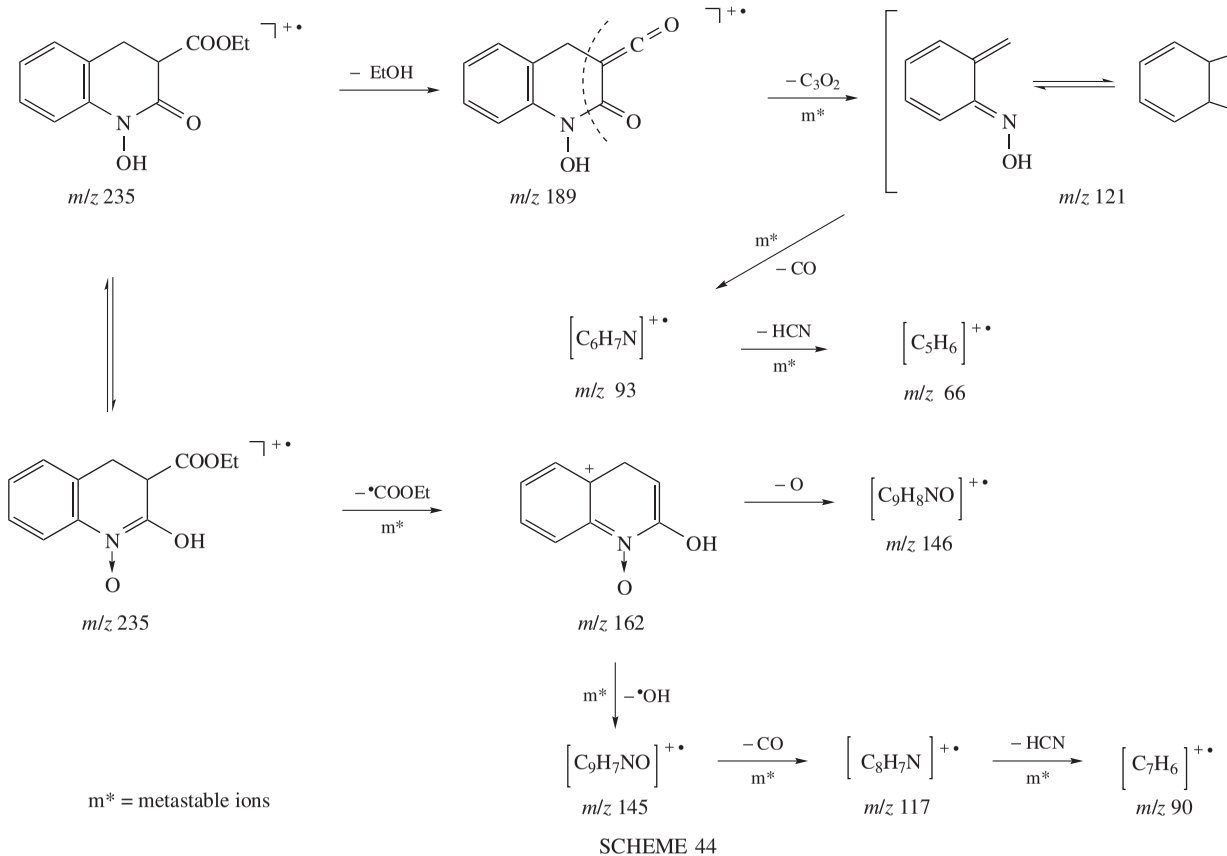
In contrast, the molecular ion of other cyclic hydroxamic acids (i.e. 4-hydroxy-2-methylquinazoline-3-oxide[166] and *N*-hydroxyphthalimide[167]) eliminate a nitric oxide radical yielding abundant $[M\text{-}30]^{+}$ ions. These compounds also show the formation of the $[M\text{-}16]^{+\bullet}$ and $[M\text{-}17]^{+}$ ions, although the abundance of the latter ion was very low.

A wide range of benzoxazine and benzothiazine hydroxamic acids (Scheme 45) has been characterized by electron ionization mass spectrometry, deuterium labeling and accurate mass measurements[168].

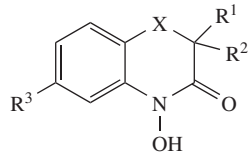
Abundant molecular ions were observed in all spectra. The benzoxazine hydroxamic acids fragment initially by expelling an O atom or a $^{\bullet}CO_2H$ radical from their molecular ions. The latter loss yields $[M\text{-}45]^{+}$ ions that generally are the base peak in the electron ionization mass spectra[168]. The fragmentation pathways followed by 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one, the parent compound in this series, is depicted in Scheme 46. The hydrogen atom of the methylene group is at least partially involved in the elimination of $^{\bullet}$CHO (Scheme 46)[168].

The molecular ion of 4-hydroxy-2,6-dimethyl-2*H*-1,4-benzoxazin-3(4*H*)-one behaves, as expected, by eliminating an oxygen atom and a $^{\bullet}$COOH radical (Scheme 47). The latter process yields a dimethyl benzoxazole cation (*m/z* 148) that loses acetonitrile and CO. The loss of oxygen from the molecular ion is followed by elimination of a methyl radical and CO (Scheme 47)[168].

Similarly to 2*H*-1,4-benzoxazino hydroxamic acids, their thiazino analogues (Scheme 45) decompose in the gas phase yielding fragment ions $[M\text{-}16]^{+\bullet}$ and $[M\text{-}45]^{+}$ [168]. Differently from benzoxazino derivatives, a metastable ion supporting the direct


COOEt
N
O
OH
m/z 235
– EtOH
C
O
m/z 189
– C3O2
m*
m/z 121
m*
– CO
[C6H7N]+•
m/z 93
– HCN
m*
[C5H6]+•
m/z 66
– •COOEt
m*
m/z 235
m/z 162
– O
[C9H8NO]+•
m/z 146
m* – •OH
[C9H7NO]+•
m/z 145
– CO
m*
[C8H7N]+•
m/z 117
– HCN
m*
[C7H6]+•
m/z 90
m* = metastable ions

SCHEME 44

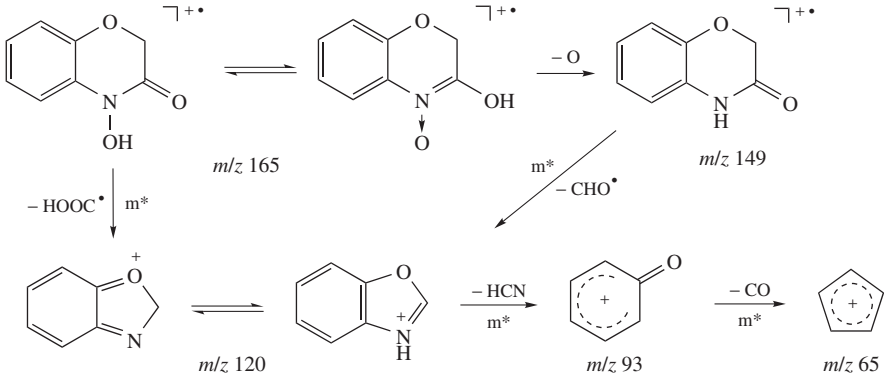


X = O, S, SO_2

R^1 = H, Me, Et, *n*-Bu; R^2 = H, Me

R^3 = H, Cl, Me, CF_3

SCHEME 45

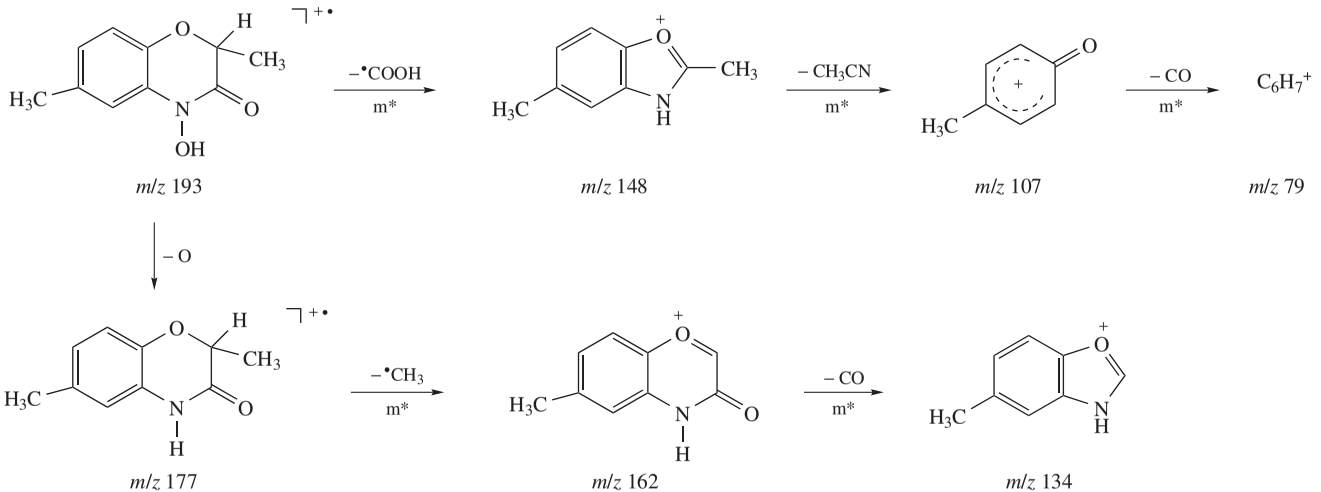


SCHEME 46

loss of the •COOH radical is missing for benzothiazino hydroxamic acids, so the loss of 45 u from their molecular ion has been attributed to consecutive elimination of •OH and CO (Scheme 48). In addition, the molecular ion of benzothiazino derivatives loses a hydroxyl radical, yielding abundant $[M\text{-}17]^+$ ions, not observed for their benzoxazole analogues (Scheme 48)[168].

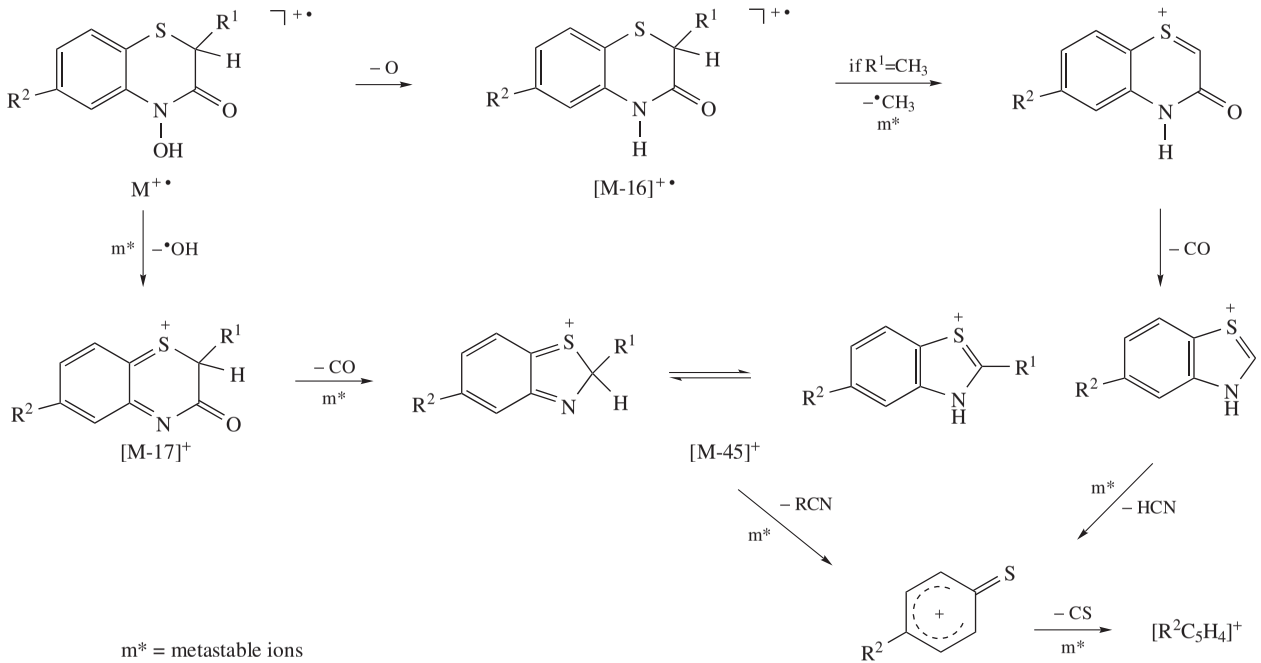
A different behavior is shown by 4-hydroxy-2,2-dimethyl-6-(trifluoromethyl)-2*H*-1,4-benzothiazin-3(4*H*)-one: the ions $[M\text{-}17]^+$ are undetectable while the base peak in its EI mass spectrum is due to $[M\text{-}43]^+$, attributable to consecutive losses of $^{\bullet}CH_3$ and CO from the molecular ion (Scheme 49). The easy loss of a methyl radical from position 2 is also shown by other 2-methyl derivatives. Among possible fragment ions that should potentially derive from decompositions of the trifluoromethyl moiety, only $[M\text{-}F]^+$ is observed[168].

The molecular ions of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one-1,1-dioxide derivatives (Scheme 45) do not show formation of the species $[M\text{-}17]^+$ and $[M\text{-}45]^+$, while losses of oxygen and substituted ketene yield abundant fragment ions[168]. The presence of abundant $[M\text{-}16]^{+\bullet}$ ions and the absence of $[M\text{-}45]^+$ ions constitute a similarity with the gas-phase behavior of benzoxazine hydroxamic acids, but distinct from the other benzothiazine derivatives. The main fragmentation pathways for 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one-1,1-dioxides are depicted in Scheme 50.

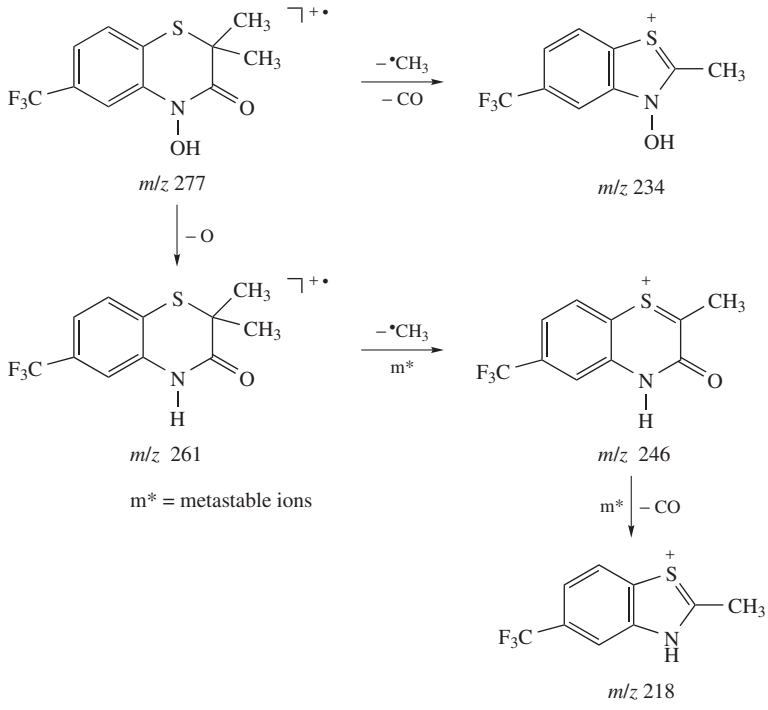


m* = metastable ions

SCHEME 47


M+•
[M-16]+•
if R1=CH3
−•CH3
m*
m*
−•OH
− O
− CO
[M-17]+
− CO
m*
[M-45]+
− CO
m*
− RCN
m*
m*
− HCN
− CS
m*
[R2C5H4]+
m* = metastable ions

SCHEME 48



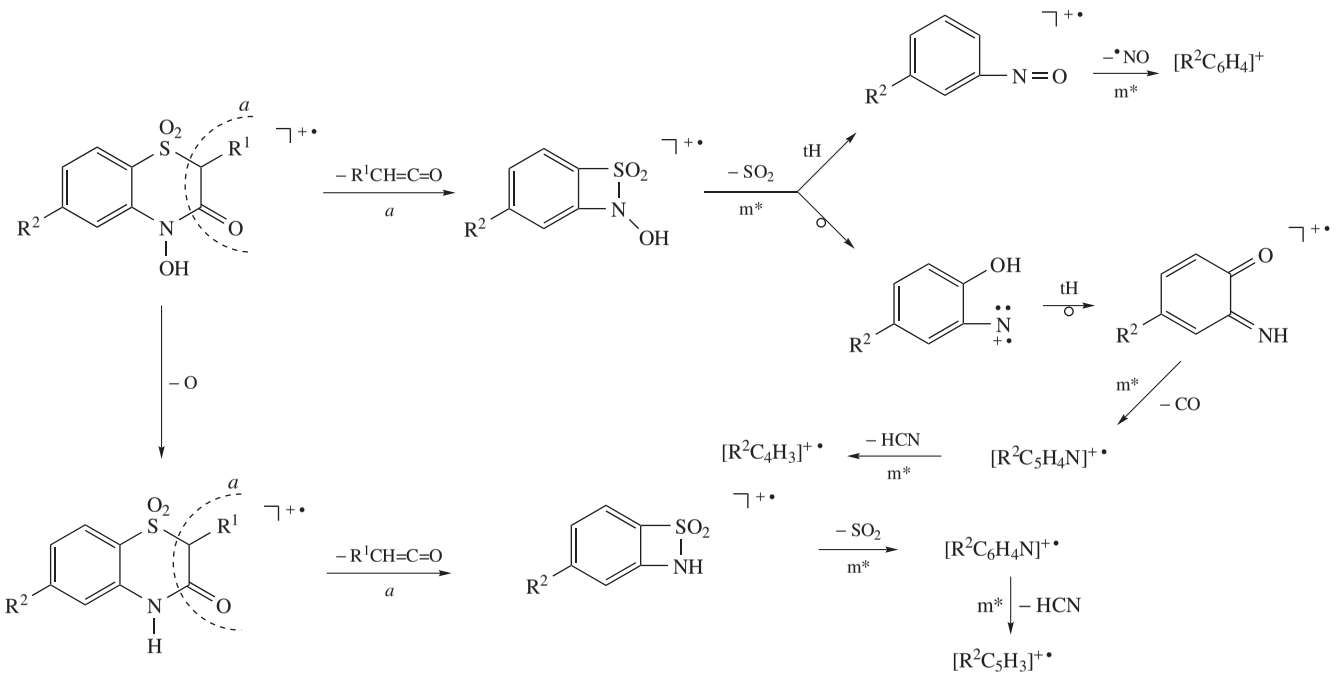
SCHEME 49

The presence of the corresponding metastable ions suggests that different decomposition pathways occur for the ionic species $[M - R^2CH{=}C{=}O - SO_2]^+$ that should involve different isomeric structures (Scheme 50)[168].

The nature of substituents on the molecule influences the decomposition pathways of its molecular ion. And indeed, the *O*-methyl ether of 4-hydroxy-1,4-benzothiazin-3(4*H*)-one-1,1-dioxide, in addition to the decompositions observed for its hydroxamic acid, shows distinctive fragmentations involving the methoxy group that is eliminated as formaldehyde from different ions (Scheme 51)[168].

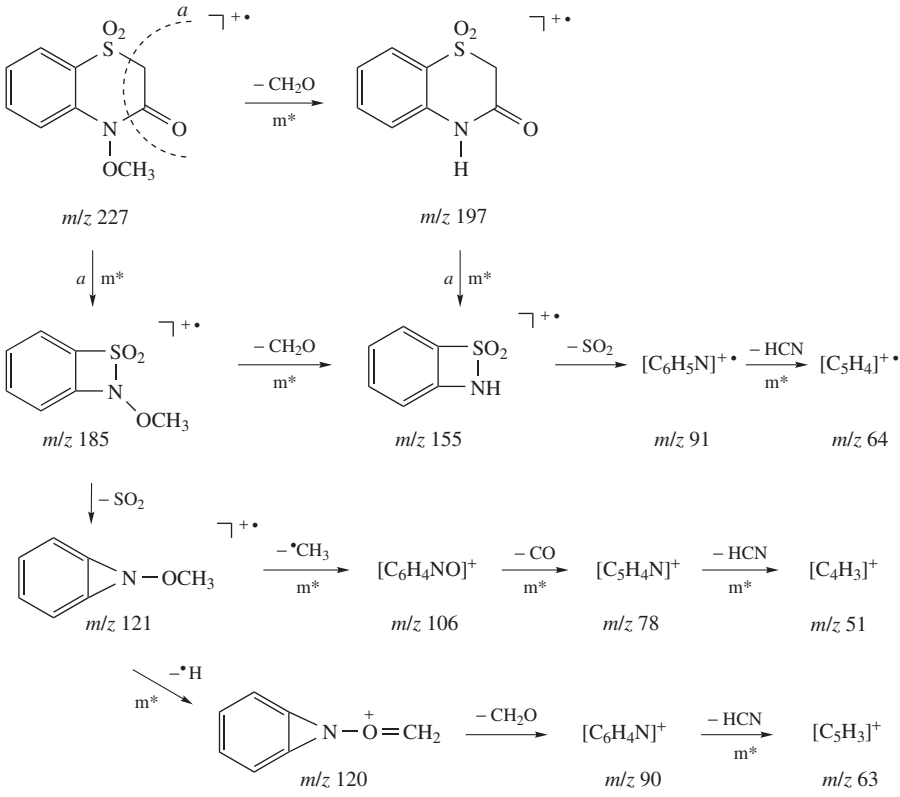
A series of *N*-arylacetylhydroxamic acids (Scheme 52), metabolites of *N*-arylacetamides, have been studied by electron ionization[169]. Characteristic of all hydroxamic acid derivatives ($R^1 = H$) is the loss of oxygen, possibly by transfer of hydrogen to the ring, to yield an ion isomeric with the parent arylacetamide, and ions $[M\text{-}58]^{+\bullet}$, obtained by successive elimination of ketene, as evidenced by metastable ion studies. The combination of $[M\text{-}16]^{+\bullet}$ and $[M\text{-}58]^{+\bullet}$ can be used to characterize *N*-hydroxylated-*N*-arylacetamides.

Methyl esters of hydroxamic acids ($R^1 = Me$, Scheme 52) generally lose CH_2O through three possible reaction pathways: hydrogen transfer from the methyl group to the ring; McLafferty rearrangement on the carbonyl group; or by transfer of hydrogen directly to the nitrogen. The species $[M\text{-}CH_2O]^{+\bullet}$ can further lose ketene yielding ions $[M\text{-}72]^{+\bullet}$[169].

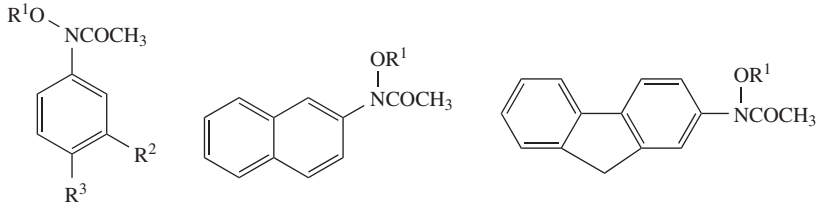


m* = metastable ions

SCHEME 50

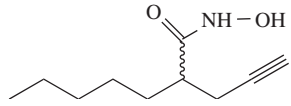


SCHEME 51



SCHEME 52

The electron ionization mass spectrum of the *N*-hydroxy-2-(prop-2-ynyl)heptanamide (Valproic hydroxamic acid, Scheme 53) shows ions due to $M^{+\bullet}$ (*m/z* 183 (23%)), $[M\text{-}O]^{+\bullet}$ (*m/z* 167 (14%)), to fragmentation at the hydroxylamino moiety, i.e. $[M\text{-}NHOH]^+$, $[M\text{-}CONHOH]^+$, together with ions due to fragmentation of the alkyl chain, such as $[M\text{-}C_3H_3]^+$, $[M\text{-}C_5H_{10}]^{+\bullet}$, $[M\text{-}C_5H_{11}]^+$ and ions at lower *m/z* values[170].

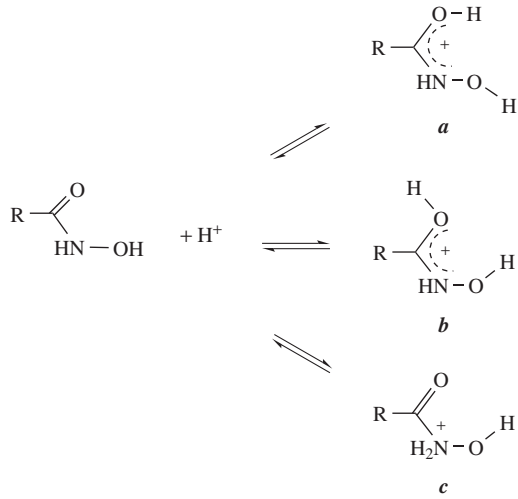


SCHEME 53

Hydroxamic acids are both strong acids[171] and bases in the gas phase[172] and therefore they can be easily deprotonated or protonated.

B. Protonated Hydroxamic Acid Derivatives

Hydroxamic acids can be protonated in the gas phase. As far as the site of protonation is concerned, in principle the most basic site should be the carbonyl oxygen atom or the nitrogen atom (Scheme 54). Several kinetic studies have assumed that it is the carbonyl oxygen (Scheme 54, structures ***a, b*** with possible hydrogen bonds) but without any proof, simply from an analogy with amides.



SCHEME 54

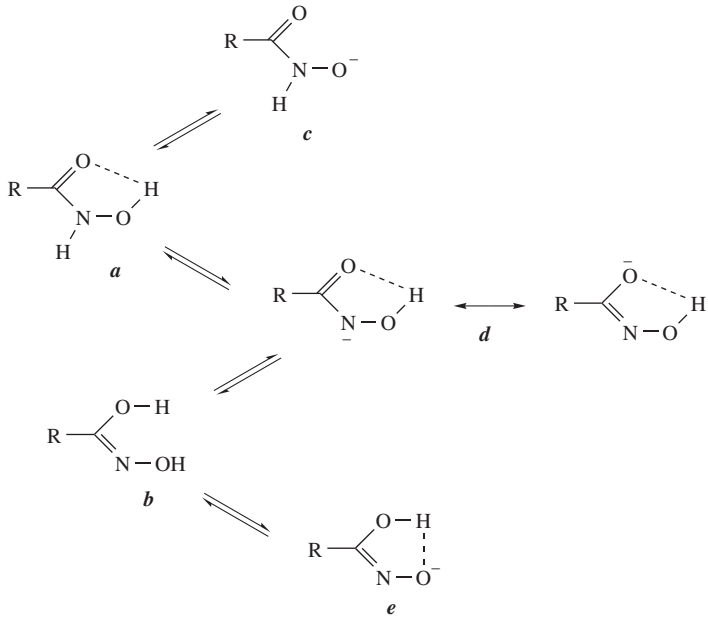
Acetohydroxamic acid, its *N*-methyl and the *O*-methyl derivatives show comparable basicity, thus suggesting that all the compounds are protonated at the same place, viz. on the carbonyl oxygen atom[172]. If a protonation on the nitrogen should also take place,

one could expect a strengthened basicity of *N*-methylacetohydroxamic acid which has the most basic nitrogen atom[172].

Chemical ionization has been also used to ionize hydroxamic acid derivatives with biological activity, such as etzionin, an antifungal metabolite from a Red Sea tunicate[173].

C. Deprotonated Hydroxamic Acid Derivatives

In principle, hydroxamic acids can be represented by two possible tautomeric structures ***a*** and ***b*** that may produce three anions ***c*** –***e*** (Scheme 55). While ***a*** seems to be the only form detected under various conditions for the acid, the structure of the anion has been the subject of a lot of investigations. For a long time[174], the acidic properties of hydroxamic acids were attributed to the OH hydrogen leading to ***c***. The same structure was inferred from many experimental studies in the crystal state or in solution[175, 176]. Actually, it has been found that a lot of hydroxamic acid derivatives behave essentially as NH acid in the gas phase, yielding structure ***d*** (Scheme 55)[171, 177].

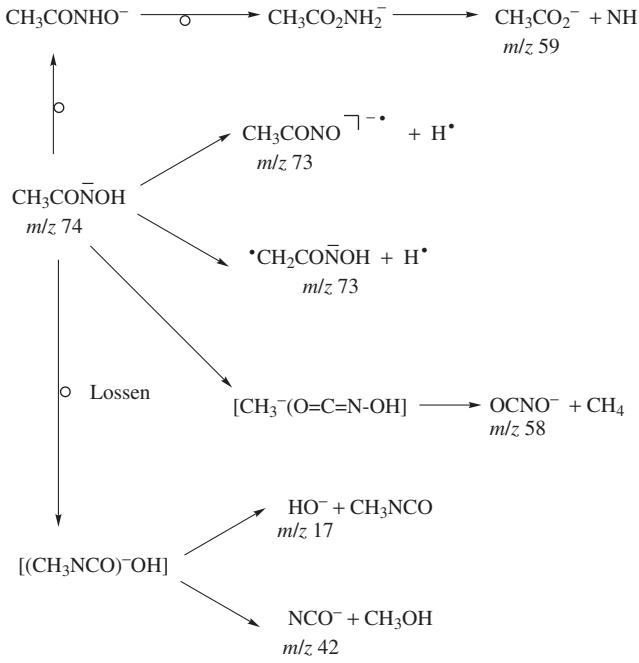


SCHEME 55

Deprotonation of hydroxamic acid can be obtained by negative-ion chemical ionization[177, 178] and electrospray ionization[179]. Low-energy CID experiments carried out in a FT-ICR mass spectrometer on deprotonated acetohydroxamic acid, its *O*-methyl analogue, acetamide and *N*-methylacetamide show that the most abundant product ions are due to CNO^-, suggesting that all these anions have similar structures, and confirming that parent hydroxamic acids behave as NH acids. *O*-Methylacetohydroxamic acid also yields product ions due to CH_3O^- (35%) and $C_2H_2N^-$ (10%). On the other hand, the same experiment carried out on *N*-methylacetohydroxamic acid produces the species

$C_2H_3O_2^-$ as the most abundant product ions and $C_2H_2O_2^-$ (42%), suggesting that rearrangement reactions have to occur.

Owing to collision-induced dissociations under a high-energy regime (7 keV), the fragmentations of deprotonated hydroxamic acids are complex, most of them involving rearrangement processes and being explicable in terms of reactions directed by the nitrogen anion site. In a series of deprotonated hydroxamic acids with formula $R^1CONHOR^2$ (R^1 = Me, Et, Pr, Ph; R^2 = H, Me)[178] the loss of a hydrogen atom, occurring by two possible pathways, is one of the most prominent processes yielding a stabilized radical anion (Scheme 56). All the compounds show the formation of the $OCNO^-$ anion that has been explained by the formation of a transient alkyl anion system that, in the case of the methyl derivative, loses methane (Scheme 56).

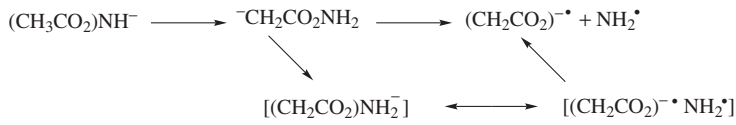


SCHEME 56

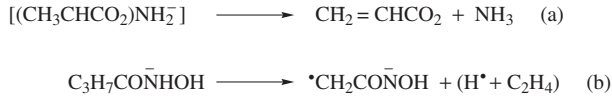
It is common that in the condensed-phase, hydroxamic acids can give a nitrogen anion rearrangement, known as the Lossen rearrangement[180], and it has been proposed that this reaction also occurs in the gas phase. In fact, in the MS/MS spectrum of acetohydroxamic acid, a number of decompositions, that require deep rearrangement reactions, yielding the species HO^- and NCO^-, have been rationalized in terms of fragmentations originating from the Lossen intermediate ($(CH_3NCO)^-OH$) (Scheme 56).

The elimination of $NH_2^•$ might proceed through a concerted mechanism or stepwise through anion/neutral complex or radical/radical anion complex (Scheme 57).

Other deprotonated hydroxamic acids fragment similarly, even if the alkyl chain can play a role in the fragmentation. In fact, if the substituent is larger than ethyl, elimination



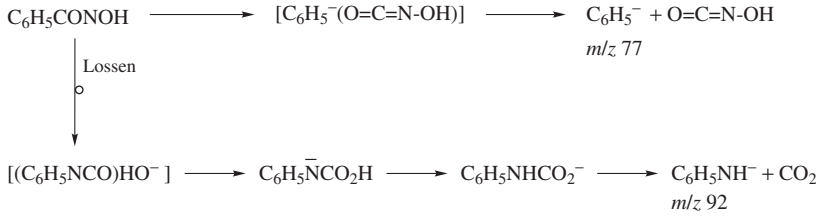
SCHEME 57



SCHEME 58

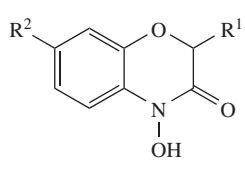
of ammonia can also occur (Scheme 58, *a*), while if the alkyl chain is a propyl group, consecutive eliminations of a terminal hydrogen atom followed by elimination of ethylene can also occur (Scheme 58, *b*)[181].

For the phenyl derivative, both $C_6H_5^-$, $OCNO^-$, $C_6H_5CO_2^-$ and $C_6H_5NH^-$ are formed. The latter species is produced through the Lossen intermediate (Scheme 59).



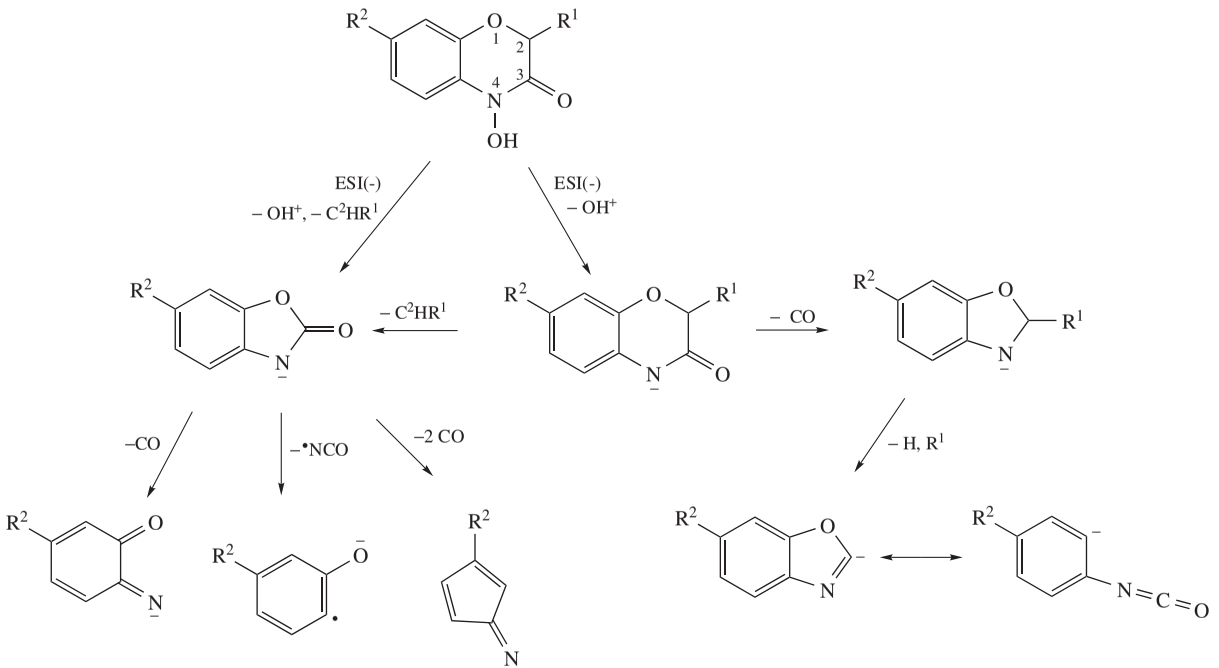
SCHEME 59

Hydroxamic acids have been studied as deprotonated molecules also by using electrospray ionization. A series of naturally occurring or synthesized 1,4-benzoxazin-3(4*H*)-one hydroxamic acid derivatives (Scheme 60) demonstrated extreme instability owing to electrospray ionization with a large number of fragment ions observed in their mass spectra[179].



$R^1 = OH$	$R^2 = H$	DIBOA
$R^1 = OH$	$R^2 = OCH_3$	DIMBOA
$R^1 = H$	$R^2 = H$	2′H-DIBOA
$R^1 = OCH_3$	$R^2 = H$	2′OMe-DIBOA

SCHEME 60

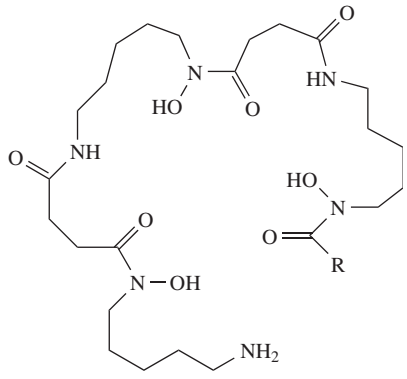


SCHEME 61

Two main fragment ions were produced in the ESI source: one at *m/z* 164, dominant at intermediate nozzle potential, arising from losses of the CR^1H and OH moieties, yielding a ring contraction of the oxazine ring; and other ions at *m/z* 149, formed at higher nozzle potentials, and attributed to a further loss of a methyl radical from ions at *m/z* 164. The use of a TOF analyzer has allowed elemental composition calculations. Among other fragment ions, there are $[M-H]^-$ ions, due to deprotonation of the N−OH moiety and $[M-OH]^-$ whose origin has been explained as not due to loss of oxygen from the $[M-H]^-$ ion but rather directly from the parent molecule. The fragmentation scheme is reported in Scheme 61[179].

D. Proferrioxamines

Proferrioxamines (pFOs) are naturally occurring siderophores produced by a variety of microbial species. They are mostly linear or cyclic trihydroxamates containing diaminobutane or diaminopentane residues with excellent metal complexation capability. For this reason they are useful as detoxification agents in iron and aluminum overload[182] and as bifunctional ligands in tumor imaging with radiolabeled antibodies[183]. Proferrioxamines may be viewed as peptides in which every second amide bond has been replaced by a hydroxamate (*N*-hydroxyamide) bond of opposite orientation (Scheme 62).

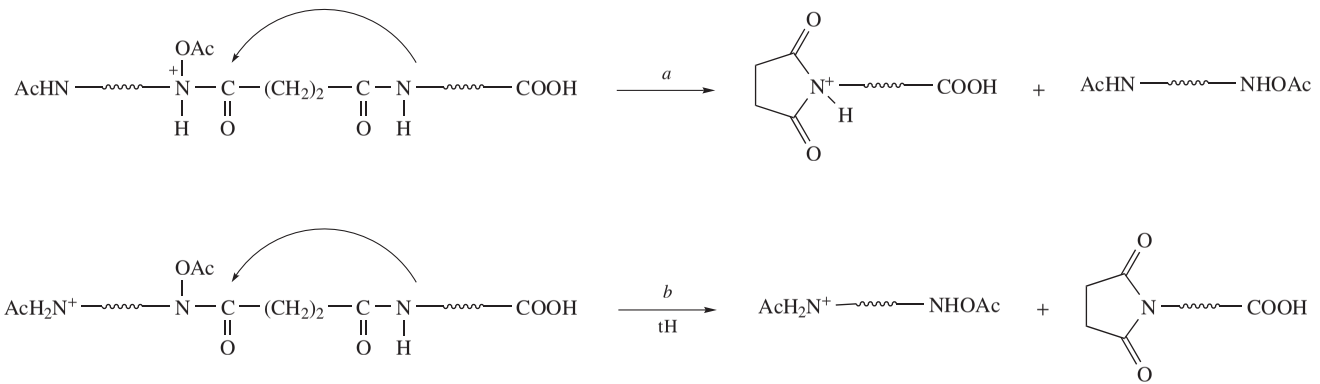


R = CH_3, CH_2CH_2COOH

SCHEME 62

The collision-activated fragmentation of protonated proferrioxamines was first investigated by de Hoffmann and Stroobant[184] by using fast-atom bombardment tandem mass spectrometry and later by Feistner and Hsieh[185]. Electrospray ionization and tandem mass spectrometry have been also used for their characterization[186]. The interpretation of the product ion spectra is not straightforward because several conceivable fragment ions are isobaric.

The initial proposal of a fragmentation mechanism resembling that observed in peptides[184] has been revised by Feistner and coworkers on the basis of a large amount of data[185, 186]. One of the main questions that had to be addressed was about the preferred cleavage between amide and hydroxamate bonds. It has been proposed that both cyclic and acyclic proferrioxamines preferentially fragment at hydroxamate bonds. This is


AcHN
OAc
N
C
(CH2)2
C
N
COOH
H
O
O
H
a
N+
COOH
H
O
O
+
AcHN
NHOAc
AcH2N+
OAc
N
C
(CH2)2
C
N
COOH
O
O
H
b
tH
AcH2N+
NHOAc
+
O
N
COOH
O

SCHEME 63

driven by energetically and sterically favorable succinimide formation and may be charge-driven (without proton transfer, Scheme 63(a)), to give the corresponding acylium ions, or charge-remote (with proton transfer), yielding the corresponding ammonium ions (Scheme 63(b)).

Once a hydroxamate bond is cleaved, the neighboring amide bond has become part of the newly formed succinimide ring and as such is protected from fragmentation. Cleavage of the inner hydroxamate bonds can proceed to give both the ammonium and acylium ions, while fragmentation of the *C*-terminal hydroxamate bond in most instances requires somewhat higher collision energy. Additional functional groups can produce specific fragmentations.

E. Metal Complexes of Hydroxamic Acid Derivatives

Different mass spectrometric studies of metal complexes of hydroxamate siderophores have been published[187–191]. Electrospray ionization has been also used to characterize binary and ternary 12-metallacrown-4 complexes of α-aminohydroxamic acids with Cu(II)[192].

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Hydroxylamine analogs and derivatives of amino acids. Aminooxy acids

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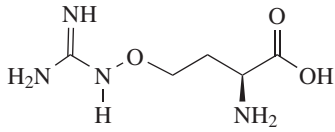
I. INTRODUCTION

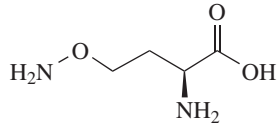
A. Preface

Hydroxylamine analogs of amino acids are widely described in the literature. Most of the natural aminooxy acids bear an additional basic group. There are two different domains of hydroxylamine analogs and derivatives of amino acids: one is the family of molecules where the hydroxylamine is attached to the carbon chain through the oxygen atom, designated as aminooxy acids; the second is the family of molecules where rather the nitrogen is involved in a covalent bond to the carbon, designated as N-hydroxyamino acids. The first amino acid with a substituted hydroxylamine moiety described in the

literature was L-canavanine (**1**), isolated from Jack bean (*Canvalia ensiformis*) by Kitagawa and Tomiyama[1] in 1929. The guanidinooxy group in canavanine was degraded[2] to yield L-canaline (**2**), which contains the free aminooxy group. Both Canavanine and canaline showed some antibacterial and cytotoxic properties. Another natural derivative of an aminooxy acid is D-cycloserine (**3**), a cyclic product of 2-amino-3-aminooxypropionic acid, which was isolated in 1955 and found to possess a broad spectrum of antibacterial activity[3]. The antibacterial and other biological activities as well as the syntheses are discussed in the following sections, which are devoted to the particular aminooxy acids. N^{δ}-L-hydroxyornithine (**4**) belongs to the family of N-hydroxyamino acids and was found as a major constituent of ferrichromes, which were first found in 1955 in several *Aspergillus* genus fungi[4]. The ferrichromes are iron-binding materials (siderophores). In recent years many similar siderophores containing N^{δ}-L-hydroxyornithine were found in different microorganisms. Synthetic siderophores containing both N^{δ}-L-hydroxyornithine and its analogs were studied as well. A comprehensive review of natural as well as synthetic siderophores was provided by Shanzer, Felder and Barda in *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Volume 1, Chapter 16 (2009).



(**1**)



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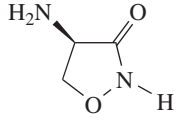

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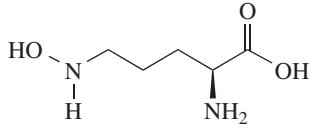


(**4**)

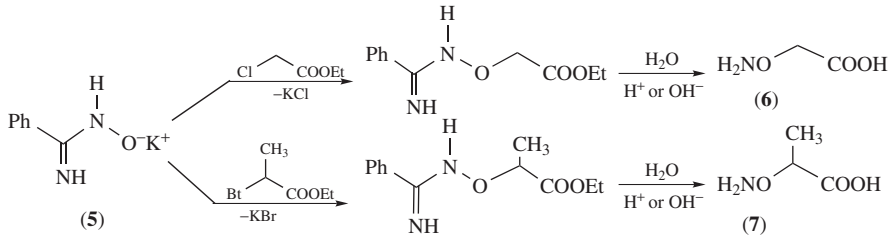
Since the discovery of canavanine (**1**) and canaline (**2**), numerous aminooxy acids and aminooxy derivatives of amino acids were studied and many of these hydroxylamine derivatives were found to have biological and therapeutic activities. This chapter provides information about the synthesis and properties of aminooxy acids. The closely related molecules that contain guanidinooxy or ureidooxy groups belonging to the canaline-urea cycle which exists in plants are discussed as well. A number of α-amino acids having the isoxazole ring that also contain the C−O−N bond are also discussed.

B. Major Methods for the Introduction of the Aminooxy Group into Carboxylic Acids

This section summarizes synthetic methods for the introduction of the aminooxy group into carboxylic acids. The difference between the various methods is both in the use of different N-protected hydroxylamine derivatives and different functional sites in the carboxylic acid chain. It starts with the old methods, some of which are still used, and proceeds to the recent modern methodologies. Syntheses of particular aminooxy acids and their derivatives are discussed in Sections II–VI.

1. Condensation of benzamidoxime with halogeno esters

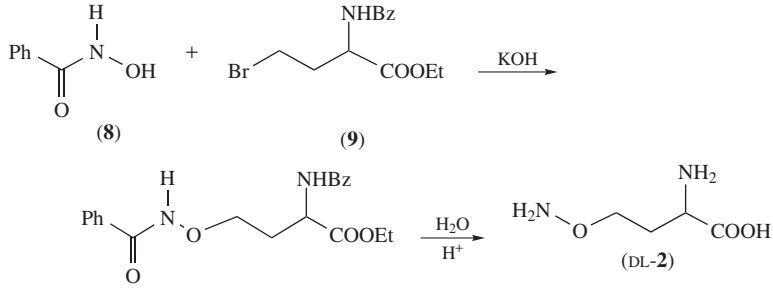
The first synthesis of aminooxyacetic acid (**6**) was described by Werner[5] in 1893 and was based on the condensation of the potassium salt of benzamidoxime (**5**) with ethyl chloroacetate. Subsequent hydrolysis led to the desired product (Scheme 1). DL-α-Aminooxypropionic acid (**7**) was synthesized in 1894 by the same group[6] from **5** and ethyl α-bromopropionate.



SCHEME 1

2. Condensation of benzohydroxamic acid salts with bromo esters

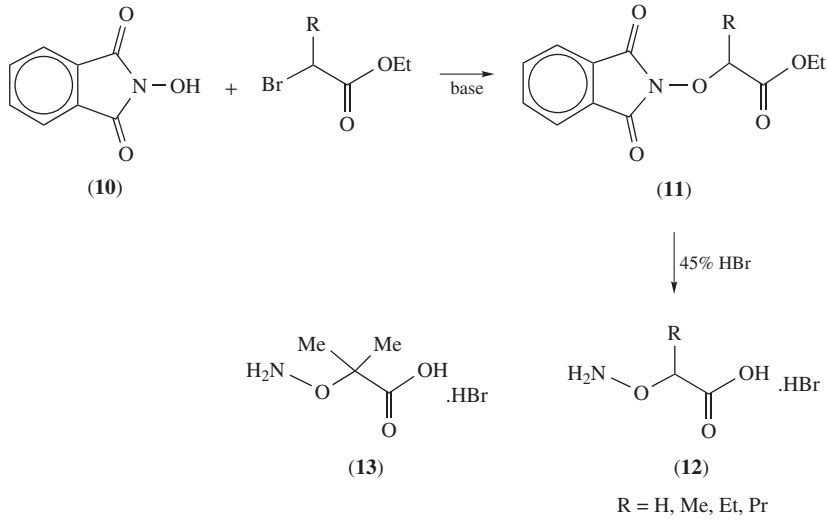
Some forty years later, after their discovery of canavanine (**1**) and canaline (**2**), Kitagawa and his coworkers improved the preparation of aminooxy acids by using an alkali salt of benzohydroxamic acid (**8**). They reported[7] the preparation of DL-canaline from N-protected ethyl ester of DL-homoserine. The latter was converted first to the γ-bromo ester (**9**) and then condensed with **8** (Scheme 2). In addition, they reported the syntheses of aminooxyacetic acid (**6**) and α-aminooxypropionic acid (**7**) by using benzohydroxamic acid (**8**) and the appropriate bromo esters[7]. A similar method was used by Frankel and Knobler[8a] in the synthesis of DL-canaline starting from γ-butyrolactone. The use of benzohydroxamic acid was reported by Schumann and coworkers[8b].



SCHEME 2

3. Condensation of N-hydroxyphthalimide salts with bromo esters

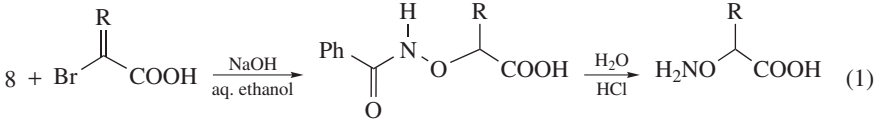
Suresh and Malkani[9] used *N*-hydroxyphthalimide (**10**) as a protected hydroxylamine in the condensation of α-bromo esters. The *N*-phthaloylaminooxy acid esters (**11**) were hydrolyzed with 45% HBr to the corresponding aninooxy acid hydrobromides (**12**) (Scheme 3). Branched acids like aminooxyisobutyric acid (**13**) were prepared as well. Aminooxyacetic acid tends to crystallize as a hemihydrobromide.



SCHEME 3

4. Condensation of benzohydroxamic acid salts with bromo acids

A series of aminooxy acids were synthesized by McHale, Green and Mamalis[10] by using the corresponding bromo acids, instead of their esters (equation 1). This report includes details on 15 α-aminooxy acids. Most of them gave crystalline hydrochlorides.



(1)

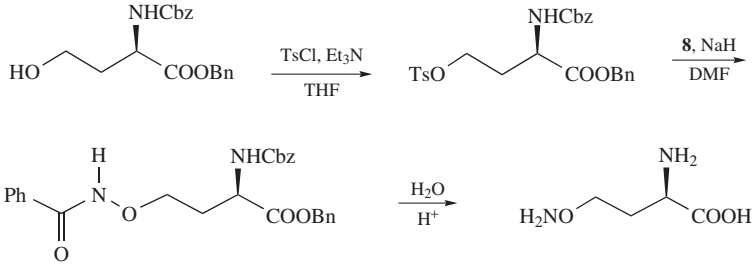
R = H, Me, Et, Pr, *i*-Pr, Bu, Pen, Hex, Hep, Oct, Non, Undec, Tridecyl, 5-(*c*-Hex)Pen

5. Condensation of benzohydroxamic acid salts with O-tosyl esters

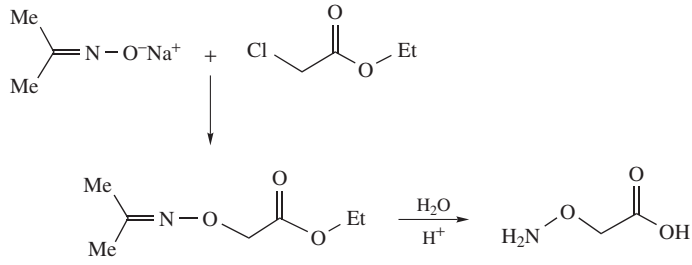
In 1986 Ozinskas and Rosenthal[11] applied the benzohydroxamic method in the conversion of hydroxy groups in available amino acid to an aminooxy group via tosylation and subsequent treatment with benzohydroxamic acid (**8**) in DMF in the presence of NaH (Scheme 4).

6. The use of oxime salts

Borek and Clarke[12a] were the first to use the condensation of α-bromo acids with the sodium salt of acetoxime in the synthesis of aminooxyacetic acid (Scheme 5) and in their unsuccessful attempt to synthesize DL-canaline[12b]. Schumann and coworkers used acetoxime in the synthesis of α-aminooxypropionic acid[8b].

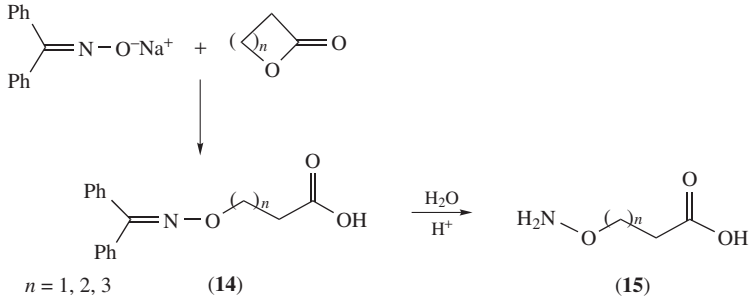


SCHEME 4



SCHEME 5

A different approach using oxime salts was reported by Gilon, Knobler and Sheradsky[13], which was based on the ring cleavage of lactones by oxime salts. β-Propiolactone, γ-butyrolactone, δ-valerolactone and ε-caprolactone were opened by salts of several oximes. Best results were obtained on using the sodium salt of benzophenone oxime. The intermediate ω-diphenylmethylideneaminooxy acids (**14**) were hydrolyzed in aqueous hydrochloric acid to yield ω-aminooxy acids (**15**) (Scheme 6).

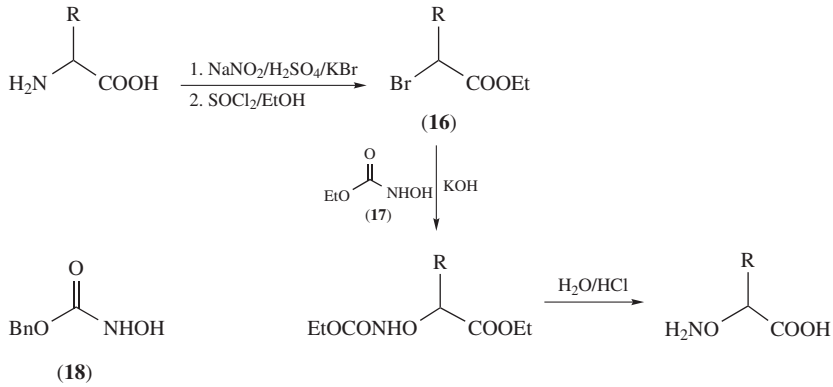


SCHEME 6

The nucleophilic addition of oximes to acrylic acid esters to produce β-aminooxypropionic acid derivatives is discussed below (Section II.C).

7. Transformation of natural amino acid esters to optically active aminooxy acids by converting the amino acids to bromo esters and condensing with N-hydroxyurethane or carbobenzoxyhydroxylamine

Testa and his coworkers[14a] reported in 1963 the conversion of natural α-amino acids, by one route, to optically active α-aminooxy acid. The α-amino ester was converted first to the α-bromo ester (**16**) in a one-pot reaction by treatment with $NaNO_2$ in the presence of KBr and 2.5N sulfuric acid, followed by esterification. The esterification was carried out with $SOCl_2$ and EtOH. The aminooxy group was introduced by the reaction of the bromo esters with *N*-hydroxyurethane (**17**), followed by acid hydrolysis (Scheme 7). *N*-Hydroxyurethane was extensively used by Undheim and coworkers[14b] in 1965 for the synthesis of racemic α-aminooxy acids.



SCHEME 7

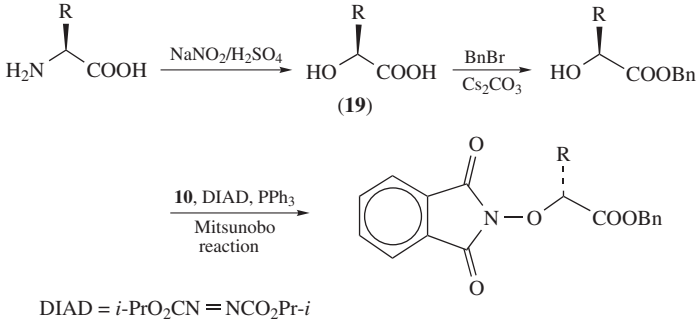
The authors claimed that the chiral products were obtained with an overall retention of configuration as a result of a double inversion. They suggested that the formation of the α-bromo acid is accompanied by inversion of configuration and then the nucleophilic displacement with the salt of *N*-hydroxyurethane occurs with a second inversion. They used the same method for the transformation of some unnatural α-amino acids to aminooxy acids as well.

Briggs and Morley[15a] in 1979 as well as more recently Yang and his coworkers[15b] in the preparation of α-aminooxy acids from available α-amino acids used *N*-carbobenzoxyhydroxylamine (**18**) instead of *N*-hydroxyurethane. A more thorough investigation showed that the conversion to α-bromo acids proceeded with a high retention of configuration and thus the overall result of the two-step reaction is rather inversion of configuration. Consequently, L-α-amino acids were transformed into derivatives of D-α-aminooxy acids and D-α-amino acids were transformed into derivatives of L-α-aminooxy acids. Other investigators noticed the same mistake reported by Testa and coworkers[14a], as discussed below in Section II.B dealing with particular chiral aminooxy acids.

8. Mitsunobu reaction of N-hydroxyphthalimide with optically active α-hydroxy acids generated from available optically active α-amino acids

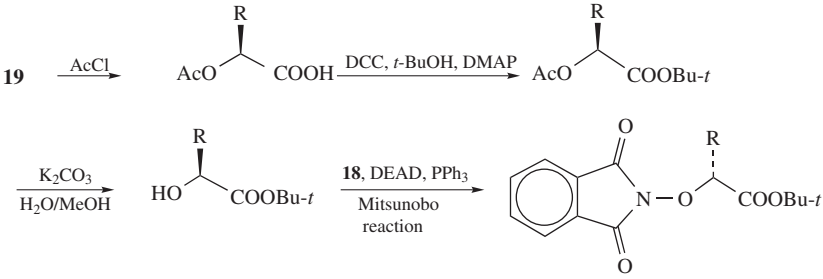
Shin and coworkers[16] suggested another route for the conversion of L-α-amino acids to D-α-aminooxy acids (Scheme 8). The key steps were the conversion of the amino

group to hydroxy group as above, by $NaNO_2$ and H_2SO_4 and the Mitsunobu reaction, a procedure which was described earlier by Iwagami and coworkers[17], using *N*-hydroxyphthalimide (**10**).



SCHEME 8

Yang and coworkers[15b], independently, described a similar route converting the resulting hydroxy acid (**19**) to the *t*-Bu ester and using diethyl azodicarboxylate (DEAD) instead of DIAD (Scheme 9).

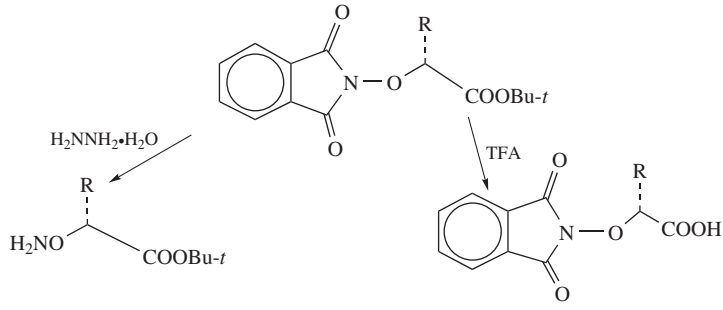


SCHEME 9

The overall yields were in the range of 36 to 56% and no purifications were needed in most of the steps. It was possible to remove the protecting groups selectively. The phthaloyl group could be removed with hydrazine hydrate and the *t*-Bu group with trifluoroacetic acid (TFA) (Scheme 10).

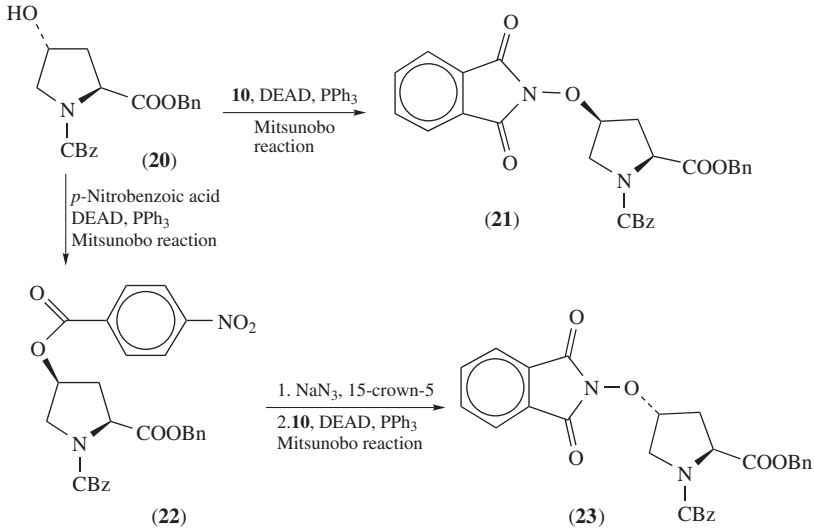
9. Mitsunobu reaction of N-hydroxyphthalimide with optically active α-amino acids carrying another hydroxy group

The combination of Mitsunobu reaction and *N*-hydroxyphthalimide (**10**) was also used by Liu and coworkers in the conversion of natural hydroxy amino acids, like L-hydroxyproline, to aminooxy derivatives of amino acids[18] (Scheme 11). The doubly protected (4*R*)-L-hydroxyproline (**20**) gave the (4*S*)-aminooxy derivative (**21**). The (4*R*)-aminooxy stereoisomer was achieved by initial transformation of the (4*R*)-L-hydroxyproline derivative (**20**) to the (4*S*)-isomer (**22**). Thus, applying the Mitsunobu



SCHEME 10

reaction with *N*-hydroxyphthalimide resulted in the (4*R*)-isomer (**23**). The same authors prepared by the same scheme the analogous (3*R*)- and (3*S*)-aminooxyproline derivatives from (3*S*)-3-hydroxyproline.



SCHEME 11

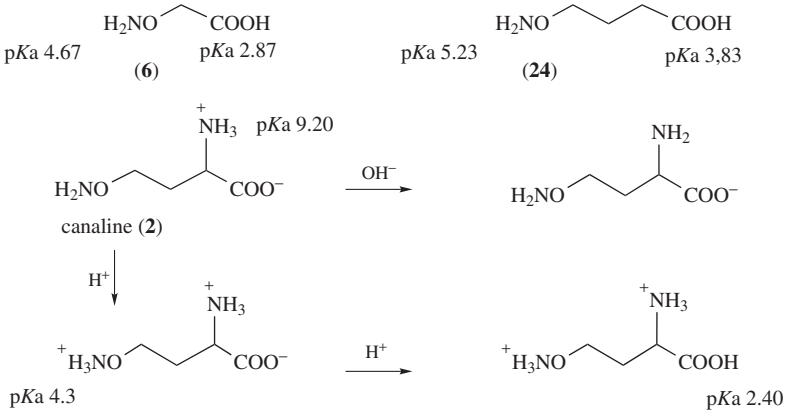
C. Properties of Aminooxy Acids

1. Dissociation constants

Borek and Clarke[12b] reported in 1938 the dissociation constants of several aminooxy acids. Because of the electronegativity of the adjacent oxygen the aminooxy group in aminooxyacetic acid (**6**) is almost 10^6 times a weaker base than that of the amino group in β-alanine. Its pKa is 4.67 as compared to 10.24 in β-alanine. The acidity of the carboxyl group is slightly higher (pKa 2.87) than in β-alanine (pKa 3.35). It was shown[19] that esterification of aminooxyacetic acid results in lowering the basicity of the aminooxy

group (p*K*a 3.3). Aminooxyacetic acid tends to crystallize in the presence of HCl as a hemihydrochloride.

As the distance between the aminooxy group and the carboxyl group grows, the basic group becomes a stronger base and the acid group a weaker acid, as shown in Scheme 12 for γ-aminooxybutyric acid (**24**), compared to aminooxyacetic acid (**6**). The course of the titration of canaline is a good example for showing the differences between the different functional groups (Scheme 12).



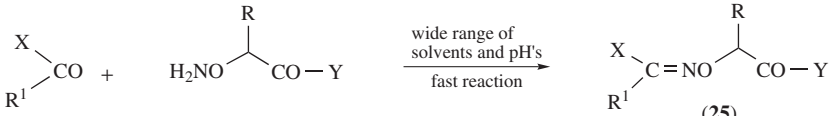
SCHEME 12

Warnke and coworkers[20] have reinvestigated the dissociation constants of several α-aminooxy acids and compared them to the corresponding α-amino acids. The α-aminooxy acids were prepared from the corresponding α-amino acids by the method of Testa and his coworkers[14a] described above. The acidities of the carboxyl group in six aliphatic derivatives (**12**, R = H, Me, Et, Pr, Bu, *i*-Bu) were in the range pKa$_1$ 2.80–2.66, which is a lower acidity as compared to α-amino acids (pKa$_1$ 2.33–2.39). The aromatic derivative (**12**, R = Bn) had a pKa$_1$ 2.49 as compared to pKa$_1$ 2.20 for L-phenylalanine. The pKa$_2$ values of the ONH_2 group in these aliphatic derivatives were in the range of pKa$_2$ 4.62–4.45 as compared to pKa$_2$ 9.71–9.61 for the corresponding α-amino acids. The aromatic derivative (**12**, R = Bn) had a pKa$_2$ 4.25 as compared to pKa$_2$ 9.11 for L-phenylalanine. Different results for the same compounds were reported at the same time by Malkani and coworkers[21].

2. Nucleophilic properties of the aminooxy group

The aminooxy group ($-ONH_2$) exhibits greater nucleophilicity than a primary amino group, in spite of the fact that it is a weaker base. The resulting oxime derivatives (**25**), which are formed by reaction of the aminooxy group with carbonyl compounds, are extremely stable. The enhanced nucleophilic character is the result of the effect of an adjacent atom with a lone pair of electrons and is known as the α-effect[22]. The reaction with aldehydes and ketones is fast at any pH (Scheme 13) and therefore aminooxy acids are used as building blocks for cross-linking reagent and facile access to bioconjugates[23, 24]. In the recent literature the aminooxy group of the incorporated aminooxy acids are called '*super nucleophiles*'. The use of aminooxy

acids in bioconjugation is discussed in the following sections and, in particular, in Sections II.A.7 and 8 and IV.D.



(**25**)

X and Y = peptide, protein, polynucleotide, polysaccharide, PEG or other functional biomolecules, etc.
R = H, Alkyl

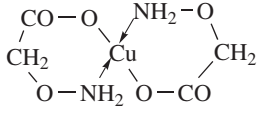
SCHEME 13

3. Colorimetric determination of aminooxy acids

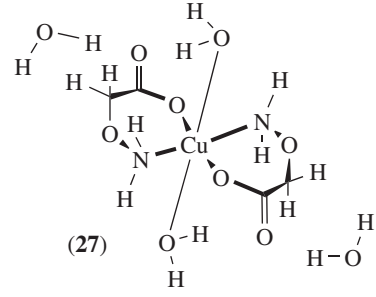
Kitagawa and Takani observed[25] that canaline gives an orange-red color with alkaline picrate. This color reaction (Jaffe's test) was attributed to the presence of the free aminooxy group. This qualitative reaction was applied by Knobler and Weiss to develop a colorimetric determination of aminooxy acids[26].

4. Complex formation with divalent metal ions

Contrary to an earlier report[14a], I reported in 1966 that aminooxyacetic acid forms a deep blue complex (**26**) upon reaction with cupric carbonate[27].



(**26**)



(**27**)

Sletten[28a], following this procedure, recrystallized this copper complex from water and proved its structure by X-ray diffraction. The slow crystallization in water without subsequent drying resulted in a bright blue prismatic crystal containing two molecules of water for each molecule of aminooxy acid and four molecules for each copper atom (**27**).

Warnke and coworkers[20], 'prompted' by Zvilivchovsky's report[27], determined the stability constants of several α-aminooxy acids complexes with some divalent metal ions [Cu(II), Ni(II), Co(II), Mn(II), Zn(II), Cd(II) and Pb(II)]. Altogether, seven α-aminooxy acids (**12**, R = H, Me, Et, Pr, Bu, *i*-Bu, Bn) were studied and the stabilities of the complexes follow the order Cu>Ni>Pb>Co>Cd>Zn>Mn. The stability was found to be proportional to the pK_{a_2} of the acids, similar to what is known for the analogous amino acids. However, the stability constants of aminooxy acid complexes are much lower than those of amino acids. For instance, the $\log K$ value for Cu(II) complexes is 4.88, whereas the value for the analogous alanine is 8.15. Some of the results are summarized in Table 1.

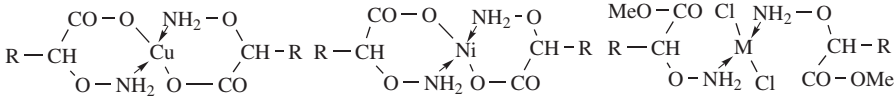
TABLE 1. Stability constants (log K) for 1:2 metal complexes of α-aminooxy acids $RCH(ONH_2)COOH$[a]

Metal \ R(pKa_2)	H(4.67)	Me(4.62)	Et(4.54)	Bu(4.48)	*i*-Bu(4.45)	Bn(4.25)
Cu	5.02	4.88	4.23	4.09	4.07	4.07
Ni	3.41	3.18	2.81	2.10	2.08	2.06
Pb	3.09	2.52		1.75		1.72
Co	3.04	2.43	2.36	1.73	1.71	1.71
Cd	2.98	2.42		1.52		1.51
Zn	2.90	2.34	1.95	1.48		1.47
Mn	1.94		1.53			

[a]Values taken from Reference 20.

Different results in another report are probably incorrect[21]. UO_2 complexes of a number of aminooxy acids were reported recently by Achpal and Verma[28b].

Warnke and Trojanowska[29, 30] have prepared additional blue solid complexes of aminooxy acids (**28** and **29**) and esters (**30**). They investigated the IR and ESR spectra as well as the magnetic susceptibility of these complexes. The results for both the Cu and Ni complexes (**28** and **29**) show similarity to complexes of α-amino acids. The Co and Pd complexes (**30**) consist of two molecules of ester and two chloride ions.



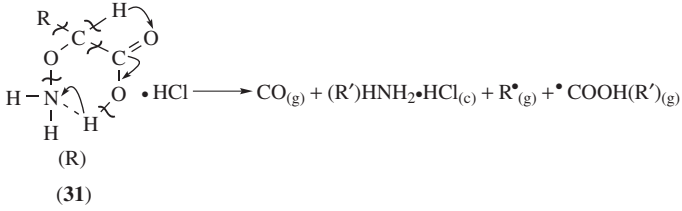
(**28**) R = Me, Pr, *i*-Bu, Bn

(**29**) R = H, Me, *i*-Bu, Bn

(**30**) M = Co, Pd; R = Me, Et, Bu, *i*-Bu

5. Thermal properties of aminooxy acids and their derivatives

Thermal properties of the hydrochlorides of some α-aminooxy acids and their esters of the general formula $RCH(ONH_2)COOR'\cdot HCl$, where R = H, Me, Et, *n*-Bu, *i*-Bu, Bz, and R′ = H, Me, Et, were reported[31, 32], using thermal analysis methods (DTA, TG, DTG). It was shown that heating of these compounds (**31**) at a constant rate leads to their total volatilization and thermal decomposition (Scheme 14). The latter is presumably initiated by the cleavage of the weakest bond in the molecule, i.e. the O−N bond.



(R)

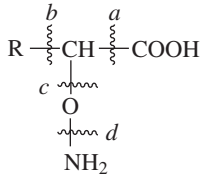
(**31**)

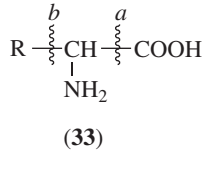
SCHEME 14

Recombination of the radicals $R^{\bullet}$ and $^{\bullet}COOH(R')$ occurs to form $RCOOH(R')$. Cross recombination of the radicals was not observed; however, rearrangements of the radicals were detected. All these facts imply that the radical process proceeds in a 'cage' created by the surrounding solid molecules and does not allow radical diffusion and cross recombination. Several thermochemical characteristics, such as the enthalpies of formation of gaseous α-aminooxy acids and their esters, were reported[32].

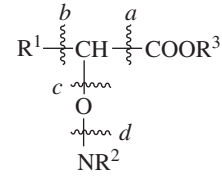
6. Mass spectra of aminooxy acids and their derivatives

Tamas and coworkers[33] had reported in 1974 the behavior of six α-aminooxy acids (**32**) under electron impact (70 eV), and compared it with results known for α-amino acids. The molecular peak was detected in each of the spectra of these derivatives as peaks of low intensity. Their mass spectra were more complex than those for the analogous amino acids $R(NH_2)CHCOOH$. There are three preferential sites of charge and radical localization, in aminooxy acids, i.e. the nitrogen atom and two oxygen atoms, one oxygen of the aminooxy group, while the two oxygens of the carboxyl group were probably considered as equivalent. Accordingly, the pattern of primary fragmentation should follow the cleavage shown in structure **32**, while in amino acids the predominant pattern of fragmentation is due to fissions *a* and *b*, as shown in amino acids **33**. In some of the aminooxy acids *c* and *d* are the primary cleavage routes, as shown in structures **32** and **34**.





(**33**)



(**32**) R = H, Me Et, Pr, $MeS(CH_2)_2$, Bn

(**34**) R^1 = Me, Et, *i*-Bu, Bn; R^2 = H, Ac; R^3 = Me, Et

In the α-aminooxy acids (**32**, R = H, Me, Et and Pr) the primary cleavages are *a* and *c* with considerable abundance of H_2O peaks. In acids that have either a sulfur group or an aromatic chain ($R = MeS(CH_2)_2$ and Bn), fragments which are the result of cleavage *d* are abundant and H_2O peaks are scarce. The methods for the synthesis of some of the aminooxy acids in this study are from various patents[34] and are cited in this report. Warnke and coworkers[35] studied in 1984 the electron impact fragmentations of aminooxy acid esters and their *N*-acetyl derivatives (**34**). The primary fragmentation pathway of these compounds were found to be similar to that of the free α-aminooxy acids (**32**). In both reports[33, 35], secondary fragmentations and mechanisms for the formation of the various fragments are discussed.

7. IR and NMR properties of aminooxy acids

IR and NMR spectral details are reported in recent literature together with the syntheses or isolation of particular aminooxy acids and derivatives. There are a number of publications where IR spectra were used for comparison and proof of a structure like in the case of cycloserine (**3**) (Section III.B.2) and its reactions (Section III.B.3.c), the structure of the amidooxy bond (Section IV.B.2) and the formation of foldamers (Section IV.C).

A systematic investigation of the IR and NMR spectral characteristics of α-aminooxy acids had been reported by Sohar and coworkers[36] in 1974. The spectra and the discussion mainly deal with spectra of α-aminooxypropionic acid and its hydrochloride. All spectra were in the solid state using KBr pellets. A comparison with alanine revealed that the bands characteristic for the aminooxy acid are in the ranges of 1290 and 990 cm^{-1}. The C−O vibration is around 1290 cm^{-1} and the O−N vibration is around 990 cm^{-1}. The latter vibration in the hydrocloride is around 1095 cm^{-1}. The IR spectra show that α-aminooxy acids exist as zwitterions. Minor differences were found between the racemic mixture of α-aminooxypropionic acid and the pure enantiomer in the range of 3300 cm^{-1}. The study of the proton NMR of α-aminooxy acids consists of comparison with the α-amino acids. The conclusion of this investigation was that there are no major differences between the α-aminooxy and α-amino acids. The only significant difference is in the chemical shift of the α-methine group which is up to 0.75 ppm downfield in the α-aminooxy acids, compared to that in α-amino acids. NMR data of metal complexes of aminooxy acids were reported by Warnke and Trojanowska[30] in 1993.

8. Folding properties of α-aminooxy acids incorporated in peptides (the N−O turn)

Besides the important biological properties of aminooxy acids and their derivatives, a very useful property is their ability to induce extended helical structure (1.8 helix, see Section IV.C) upon their incorporation in the backbone of peptides. A recent review[37] by Li and coworkers summarizes the efforts of his group to develop a novel class of peptidomimetic foldamers comprising α-aminooxy acids and to explore their applications in the simulation of ion recognition and transport processes in living systems. Additional investigations and applications of this phenomenon are discussed in Section IV.

D. Biological and Therapeutic Properties of Aminooxy Acids

The study of the bioactivity of aminooxy acids was initiated by the discovery of canavanine (**1**) and canaline (**2**), as mentioned in the introduction above. More attention has been devoted to these compounds since the confirmation of the structure of the antibiotic cycloserine (**3**) in 1955. The simple aminooxy acids like aminooxyacetic acid were found to possess bacteriostatic activity[10, 14, 38]. Their activity was associated with enzymes, which activate transamination[39]. These enzymes are associated with activities in the liver and in the brain, and a number of aminooxy acids showed therapeutic activity in the brain[40]. Furthermore, various aminooxy acids have antimalarial, antifungal and antitumor properties and additional neuroprotic features were found in other derivatives of aminooxy acids. Some aminooxy acids affect the production of hormones and some show anti-inflammatory activity. Information about these investigations and additional up-to-date results are given in the sections of this chapter dealing with the specific aminooxy acids.

II. AMINOOXY ACIDS

This Section summarizes information about aminooxy acids that contain only an aminooxy group.

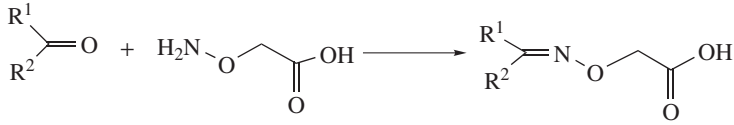
A. Aminooxyacetic Acid

The simplest aminooxy acid, aminooxyethanoic acid (**6**), is reported in most of the publications as aminooxyacetic acid (AOAA or AOA) and this name is the name of choice used in this chapter. In some early reports it was named carboxymethoxylamine.

1. Synthesis and chemical properties of aminooxyacetic acid

This acid was synthesized[5] by Werner as early as 1893. Improved syntheses were reported later by methods described above (Section I.B). Aminooxyacetic acid generally crystallizes from alcohol–water mixtures as a solid hemihydrochloride which melts[12] at 151 °C. Different melting points are reported for the monohydrochloride (mp[10] 115–6 °C and mp[6, 7] 156 °C). The monohydrochloride precipitates from saturated ethereal-HCl. Like most of the aminooxy acid hydrochlorides, the monohydrochloride of aminooxyacetic acid gradually loses hydrogen chloride to produce the hemihydrochloride.

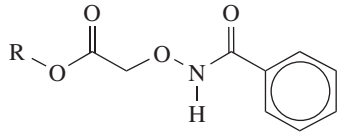
Aminooxyacetic acid reacts readily with aldehydes and ketones in different solvents and in water at any pH (equation 2), giving solid oxime products (**35**). Richardson[41] reported in 1964 the synthesis and properties of aldoximes derived from aromatic and heterocyclic aldehydes and of ketoximes from cyclic ketones, for investigation as potential therapeutic agents. His article includes melting points and IR spectra of 20 oxime derivatives of aminooxyacetic acid.



(2)

R^1 = alkyl or aryl R^2 = alkyl, aryl or H (**35**)

The ONH_2 group can be acylated by most known procedures. *N*-Bezoylaminooxyacetic acid (**36a**) is also an intermediate in the synthesis of the acid as described in Section I.B. Two modifications were described[10] differing in melting points and in solid-state infrared spectra. The same phenomenon was observed[42] in dipeptides of aminooxyacetic acid. An X-ray study of a single crystal of methyl *N*-benzoylaminooxyacetate (**36b**) combined with an intensive study of IR and Raman spectra was reported in 1996 by Lee and coworkers[43]. The results of this investigation suggested that there are two conformers differing in the orientation of the ester carbonyl group relative to the C–O (aminooxy) bond (Figure 1).



(**36**)

(**a**) R = H
(**b**) R = Me

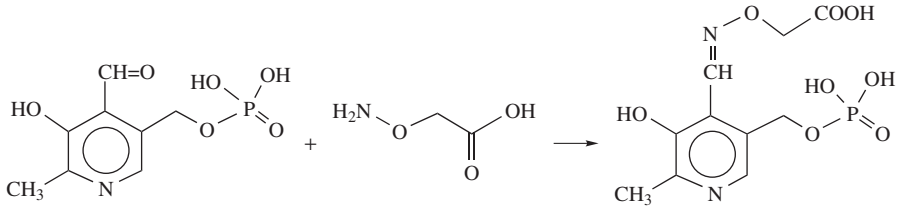
FIGURE 1. Two conformers of **36b**

2. Chemotherapeutic properties of aminooxyacetic acid

While aminooxyacetic acid has been known since 1893, attention has been devoted to it since the isolation of the bioactive acids canavanine (**1**) and canaline (**2**) and the antibiotic cycloserine (**3**).

a. Antibacterial properties of aminooxyacetic acid. Mild bacteriostatic activity was shown for this acid against *Staph. Aureus, E. coli and M. tuberculosis*[38]. Free and coworkers[44] found in 1967 that aminooxyacetic acid inhibits the enzyme alanine racemase which was obtained from *Pseudomonas* species and which, among other properties, controls the germination of spores of bacteria.

It is assumed that aminooxyacetic acid inhibits enzymes that involve pyridoxal phosphate (**37**) as a co-enzyme, presumably by reacting to produce an oxime derivative (**38**, Scheme 15).



(**37**) (**38**)

SCHEME 15

b. Anticonvulsant activity of aminooxyacetic acid. It was found that aminooxyacetic acid is a potent inhibitor of various aminotransferases. These enzymes are probably dependent on pyridoxal phosphate. It was found to inhibit γ-aminobutyric-α-ketoglutaric transaminase *in vitro* and cause accumulation of γ-aminobutyric acid (GABA) *in vivo*. Deficiency of GABA in brain tissues is associated with epilepsy and convulsions. This fact prompted investigators[45–47] to determine the anticonvulsant properties of aminooxyacetic acid, convulsions caused by thiosemicarbazide in rats, mice and cats and by methionine sulfoximine in cats.

Baxter and Roberts[48] in 1961 and Rubinstein and Roberts[40] in 1967 used the ability of aminooxyacetic acid to inhibit both glutamic acid decarboxylase (GAD) and γ-aminobutyric acid transaminase (GABA-T) to investigate the steady-state levels of γ-aminobutyric acid in the brain of mice. The effect of the level of γ-aminobutyric acid in rat and human brain were studied by Perry and Hansen[49] in 1978. Wood and coworkers[50, 51] investigated the aminooxyacetic acid induced GABA metabolism at the subcellular level. They found that the degree of inhibition is greater in the mitochondria than in the synaptosomal fraction. Administered aminooxyacetic acid caused at first convulsions, followed by immediate anticonvulsant activity. However, it is known that onset of seizures is associated with a decreased content of GABA and an increased content of glutamate in synaptosomes. Therefore, a hypothesis was formulated[51] that explained the convulsant versus anticonvulsant action of aminooxyacetic acid on the basis of compartmentation of GABA within the nerve endings.

An interesting investigation was carried out by Walters and his coworkers[52] who studied the effect of aminooxyacetic acid on GABA metabolism in specific brain regions in rats. It produced an increase in GABA levels in regions of cerebral cortex, subcortex

and cerebellum. Pretreatment with 25 mg kg^{-1} aminooxyacetic acid effectively inhibited GABA-2-oxoglutarate aminotransferase (GABA-T) and partially inhibited glutamic acid decarboxylase (GAD) activity.

c. Palliative activity of aminooxyacetic acid in patients with tinnitus. In the course of research designed to test whether GABA was involved in cochlear function[53, 54], Reed's group found that aminooxyacetic acid produced a completely reversible transient hearing loss in guinea pigs. Because of this presumed cochlear site activity they tested aminooxyacetic acid in patients with tinnitus of cochlear origin[55]. A total of 21% of all 66 patients reported a subjective decrease in tinnitus severity, usually within 3 to 4 days after the start of use of 75 mg a day. Patients with tinnitus caused by presbycusis or Meniere's disease were the most likely to respond to aminooxyacetic acid treatment, with a reduction in tinnitus severity, whereas those with drug-induced tinnitus were the least likely to respond. Nausea and disequilibria were the most common side effects.

d. Aminooxyacetic acid in renal therapy research. Horvath and Wanders[56] found in 1995 that aminooxyacetic acid is a selective inhibitor of alanine-glyoxalate aminotransferase. They reported the use of aminooxyacetic acid in the diagnosis of hyperoxalulria type I which is a recessively inherited, autosomal disease. This disease causes renal failure in humans and often results in an early death. Recent studies[57] in mice and rats have shown that nephrotoxicity of cisplatin can be blocked by aminooxyacetic acid. Cisplatin is a commonly used chemotherapeutic agent and is nephrotoxic. Aminooxyacetic acid was also used to study the mechanism by which cisplatin selectively kills the proximal tubule cells[57].

e. Stimulation of ethanol oxidation in liver cells by aminooxyacetic acid. Aminooxyacetic acid in high concentration stimulates ethanol oxidation in hepatocytes. However, at low concentrations it inhibits this oxidation. Harris and coworkers[39] have resolved this 'paradox'. They found that, on one hand, aminooxyacetic acid blocks the enzyme which is involved in ethanol oxidation and, on the other hand, it decomposes to glycolic acid which is known to stimulate ethanol oxidation in hepatocytes.

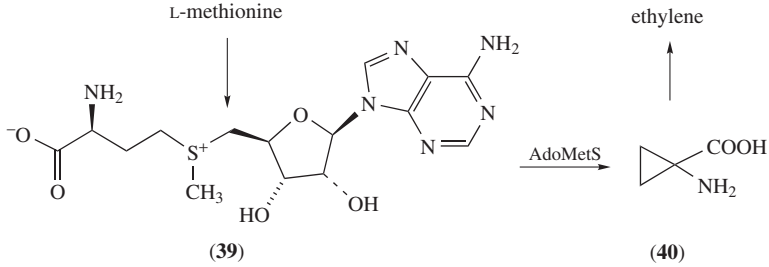
3. Growth hormone enhancement by aminooxyacetic acid

Another activity of aminooxyacetic acid that is related to its GABA-T inhibition was investigated by Takahara and coworkers[58]. They have shown that injection of aminooxyacetic acid in male rats increased the level of both serum-growth hormone and hypothalamic somatostatin. Injection of GABA resulted in a similar increase, suggesting that these phenomena are related to the GABA-T inhibition activity of aminooxyacetic acid. The influence of aminooxyacetic acid in plant metabolism is discussed in a subsequent section. The role of aminooxyacetic acid in the production of various bioconjugates is discussed below as well.

4. Ethylene biosynthesis inhibition in plants by aminooxyacetic acid

Aminooxyacetic acid was reported to affect many physiological functions in plants. The most investigated function has been the inhibition of ethylene production in higher plants. This phenomenon was first reported by Amrhein and Wenker[59]. They suggested that the mechanism of inhibition of ethylene production by aminooxyacetic acid is due to inhibition of a pyridoxal phosphate-dependent enzyme. This assumption was supported by Yu and coworkers[60] who found that the enzyme 1-aminocyclopropanecarboxylate synthase (AdoMetS) is involved in ethylene biosynthesis and was inhibited by

aminooxyacetic acid. It inhibits the decomposition of *S*-adenosylmethionine (**39**) to 1-aminocyclopropanecarboxylic acid (**40**, Scheme 16).



(**39**) (**40**)

SCHEME 16

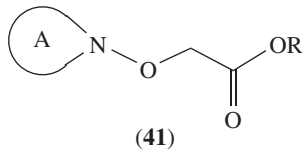
This bioactivity of aminooxyacetic acid was found to have many applications in agriculture, in the preservation of fruits and flowers. One of the recent examples is the investigation of prolonging storage time and increasing disease resistance in banana fruits[61]. A correlation between inhibition of flowering by aminooxyacetic acid derivatives and glutamic-oxaloacetic transaminase was shown in morning-glory plants (*Pharbitis nil*)[62]. Aminooxyacetic acid was found to be slightly more active than its esters. Several analogs and homologs of aminooxyacetic acid were tested as well[62].

Broun and Mayak[63] have evaluated the effect of aminooxyacetic acid on ethylene production in cut carnation flowers. The inclusion of aminooxyacetic acid into a solution in a vase of detached orchids (*Dendrobium*) resulted in low pH and contributed to a better water uptake and delayed turgor loss[64]. Flowers held in this treatment also showed a delay in discoloration and thinning of petals. These results may have significance in extending the longevity of cut flowers.

Another bioactivity of aminooxyacetic acid which is related to ethylene metabolism is its effect on sex expression in ferns. Aminooxyacetic acid had a pronounced sex expression effect on undifferentiated cells of fern gametophytes[65].

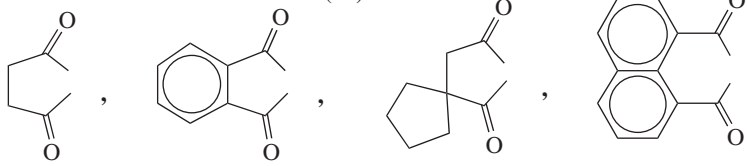
5. Bioactivity of imidooxy and oxime derivatives of aminooxyacetic acid

In the course of studying the anticonvulsant activity of aminooxyacetic acid, Edafiogho and coworkers[66] synthesized a number of imidooxy derivatives of aminooxyacetic acid (**41**). Medical as well as some chemical properties of these imidooxy derivatives are reported[66] in their interesting paper.

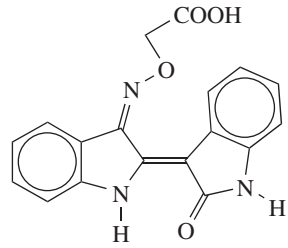


R = Me, Et

(**41**)

A = 

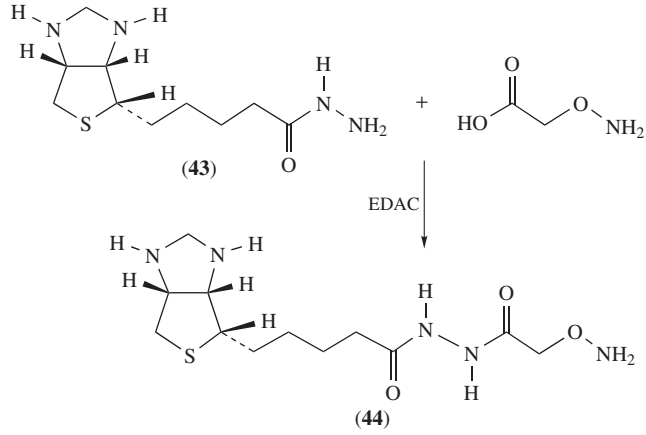
Indirubin derivative of aminooxyacetic acid (**42**) was shown[67] to be a competitive inhibitor of glycogen-phosphorylase, an enzyme that has been proposed as a therapeutic strategy for the treatment of Type 2 diabetes. A number of oxime derivatives with potential therapeutic properties were mentioned above (Section II.A.1)[41].



(**42**)

6. Aminooxyacetic acid derivatives as probes for the specific assay of abasic sites in DNA lesions and for labeling of proteins and cell surface

A specific reagent for detecting abasic sites in damaged DNA was prepared[68] by reacting aminooxyacetic acid with biotin hydrazide (**43**) in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDAC) (Scheme 17). This reagent (**44**), called Aldehyde Reactive Probe (ARP), specifically tagged abasic sites in DNA with biotin residues. The number of biotin-tagged sites was then determined colorimetrically by an ELISA-like assay using avidin/biotin complex conjugated to horseradish peroxidase as the indicator enzyme. Using this assay, femtomoles of abasic sites were detected in DNA, damaged in different ways. The aminooxy-biotin reagent gave oxime bonds with carbonyl sites which were found to be 100 times more stable than hydrazone bonds formed by the corresponding biotin hydrazide[69].



(**43**)

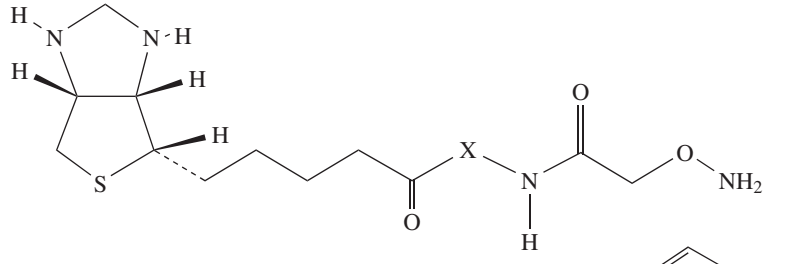
EDAC

(**44**)

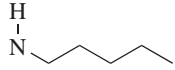
SCHEME 17

This aminooxy-biotin reagent was used to determine the abasic sites in damaged DNA in living cells by Atamna and coworkers[70] and in glucoseamine modified protein from brain cells[71]. Zeng and coworkers[72] developed a method by which the surface of living animal cells could be efficiently labeled using low concentrations of aminooxy-biotin reagent, at neutral pH. This was carried out on sialylated cell-surface glycoproteins while maintaining high cell viability. The aminooxy-biotin reagents were found useful in chemical modifications of recombinant proteins[73] and of various vaccines[74].

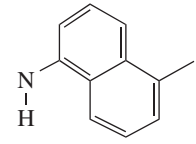
Recently, additional aminooxyacetyl derivatives of biotin which were applicable for the same analysis of damaged DNA were described by Komatsu and coworkers[75]. The new aminooxy-biotin derivatives (**45**–**48**) were more efficient than the earlier described derivative (**44**).



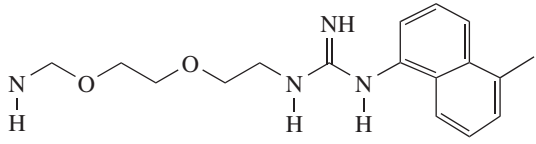
(**45**) X =



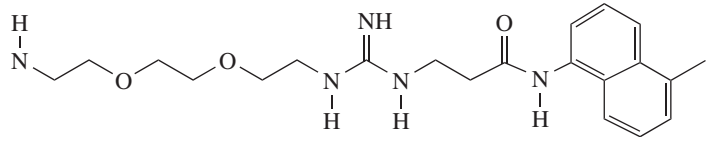
(**46**) X =



(**47**) X =

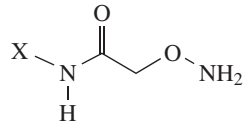


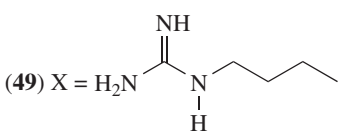
(**48**) X =



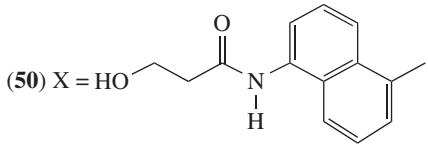
The same authors constructed some probes that do not contain the biotin group (**49**–**51**) which were useful for the detection of lesions in damaged DNA as well, however with less efficiency[75].

A fluorescent derivative of aminooxyacetic acid (**52**) for determination of abasic sites in damaged DNA was reported by Makrigiorgos and coworkers[76].

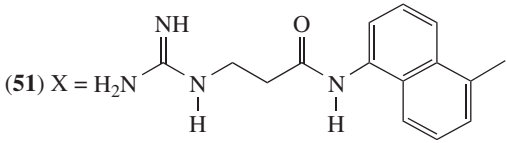




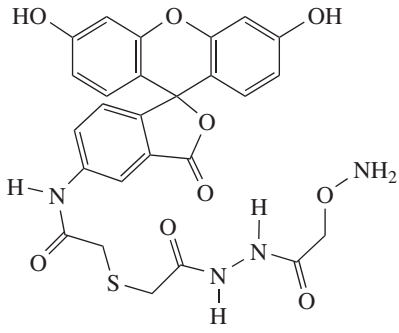
(**49**) X = H_2N



(**50**) X = HO



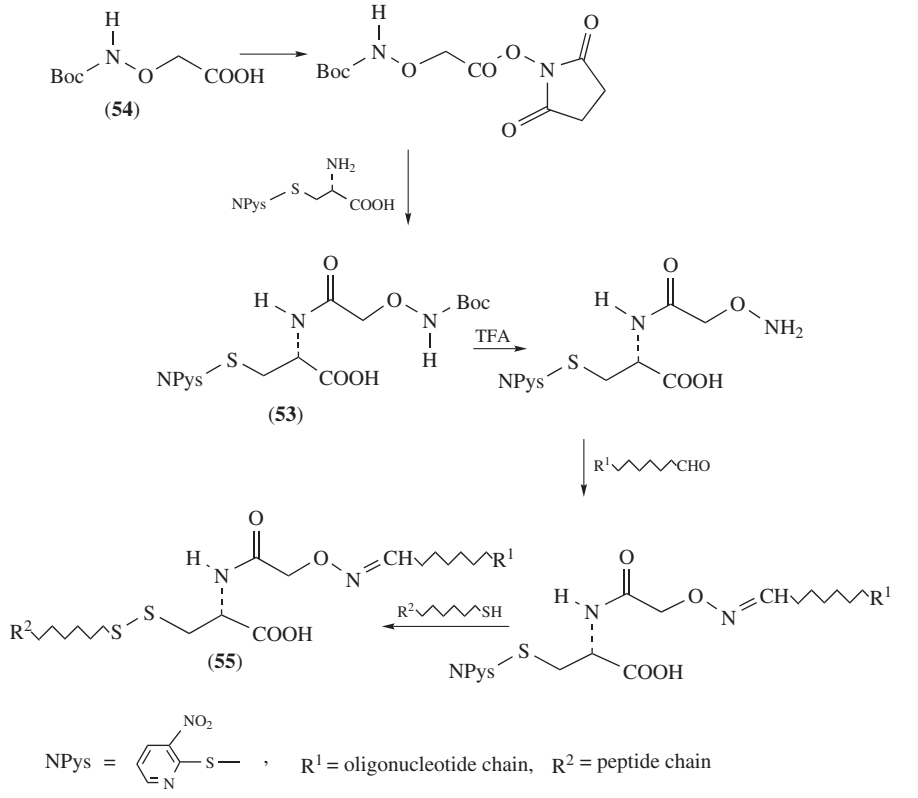
(**51**) X = H_2N



(**52**)

7. Aminooxyacetic acid derivatives synthesized as linkers for ligation in the preparation of bioconjugates and for incorporation in solid-phase peptide synthesis

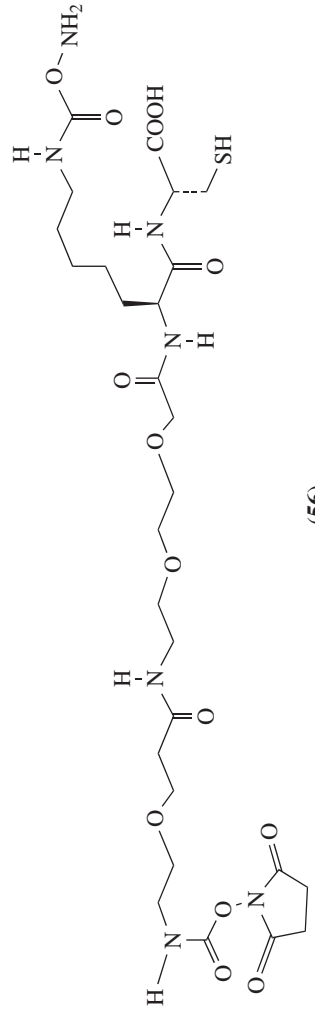
The facile condensation of the aminooxy group with aldehydes and ketones to produce the stable oxime bond has been extensively used to prepare bioconjugates such as peptide-oligonucleotide[77], carbohydrate-peptide[78] and carbohydrate-oligonucleotide conjugates[79]. It has also been used to anchor oligonucleotides and carbohydrates onto glass surfaces with potential applications in the area of microarray technology[80]. The oxime ligation is chemoselective, gives high coupling efficiency without additives and the oxime bond is stable over a pH range and yet can be hydrolyzed under harsh conditions. Thus, incorporation of aminooxyacetic acid into a variety of bioconjugation linkers was studied. Defrancq and coworkers[81] described a heterobifunctional linker **53** formed from **54**, suitable for cross coupling of two different biomolecules (Scheme 18). Thus they could employ this linker in the production of peptide–oligonucleotide conjugates **55**.



SCHEME 18

Clave and coworkers[82] reported the preparation of a heterotrifunctional linker (**56**) based on aminooxyacetic acid, for the purpose of linking a fluorescent group and for immobilization (linking to solid surface) as well.

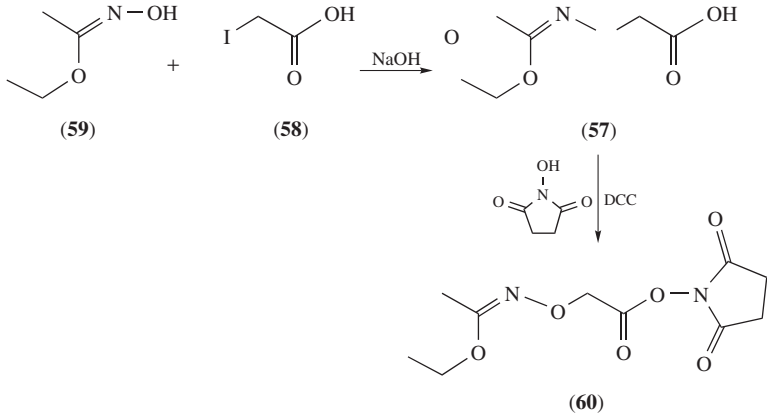
Protein-polysaccharide conjugate vaccines using *t*-butyloxycarbonyl aminooxyacetic acid (**53**) were reported. Lees and coworkers[74] used **53** for the preparation of aminooxy dextran derivatives and aminooxy peptide derivatives. These reagents were coupled either with aldehyde functionalized peptide or with aldehyde dextran derivative, respectively. The bioconjugates obtained by this approach were superior to those obtained by other methods. The approaches described are compatible and complementary to a number of chemistries currently used in conjugate vaccine synthesis. The formation of an oxime bond (oxime chemistry) was very efficient in the synthesis and increased yields of conjugate vaccines. Mice immunized with pneumococcal type 14 conjugates that were made by using oxime chemistry mounted significant anti-polysaccharide immune responses.



(**56**)

The protection of the H_2N-O group in aminooxyacetic acid with a non-hindered carbamate-based group is occasionally not perfect as overacylation is observed, e.g. two acyl groups replace the two hydrogens of the aminooxy group (see Section IV.D.2.a). Decostaire and coworkers investigated in 2006 the conditions for coupling of protected aminooxyacetic acid in order to avoid overacylation[83]. They found that overacylation is prevented when the COOH of the protected aminooxyacetic acid is engaged in an amide bond. In addition, coupling of aminooxyacetic acid protected with a non-hindered carbamate-group, like allyloxycarbonyl (Aloc), is effective in avoiding the overacylation side reaction when using dicyclohexylcarbodiimide (DCC) as the coupling reagent and 1-hydroxybenztriazole (HOBt) as an acidic additive. They also found that overacylation, favored by the use of uronium/aminium coupling reagents in the presence of *N*, *N*-diisopropylethylamine (DIEA), can be completely circumvented using a weaker base such as collidine. *N*, *N*-Doubly protected aminooxyacetic acid as in the case of phthaloyl protecting group is not suitable for solid-phase peptide synthesis. Therefore, these results made it possible to control the outcome of overacylation of N-protected aminooxyacetic acid, during the synthesis of an aminooxy-peptide for chemical ligation[83].

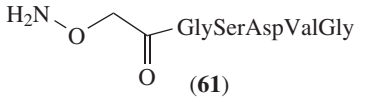
Shortly after this report Foillard and coworkers[84] reported the ultimate protecting group for the incorporation of aminooxyacetic acid using solid-phase peptide synthesis. The *N*-ethoxyethylideneaminooxyacetic acid (**57**) was prepared directly from iodoacetic acid (**58**) by reaction with ethoxyethylidene oxime (**59**). The activation was carried out by the reaction of **57** with *N*-hydroxysuccinimide and DCC (Scheme 19). The ethoxyethylidene protecting group was suitable for solid-phase peptide synthesis and was removed, after incorporation, by dilute trifluoroacetic acid, either in water (1%) or in acetonitrile (5%).



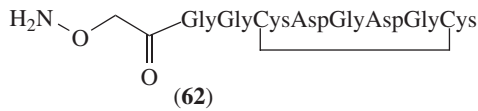
(**59**) (**58**) (**57**) (**60**)

SCHEME 19

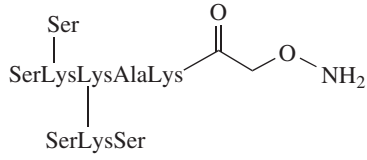
Several aminooxyacetic acid peptides targeted for ligation were prepared by applying the activated derivative **60** to solid-phase peptide synthesis[84]. The aminooxy peptide could be removed from the polymer and deprotected by using aqueous trifluoroacetic acid (TFA) and triisopropylsilane (TIS). Examples of peptides (**61**–**63**) were prepared by solid-phase peptide synthesis. A similar procedure using Boc protecting group resulted in impure peptides, contaminated with overacylation products[84].



(**61**)

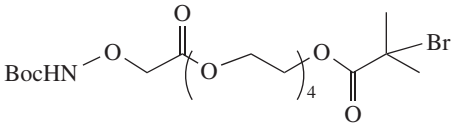


(**62**)

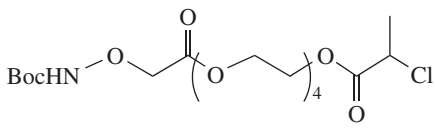


(**63**)

Heredia and coworkers[85] reported in 2007 a radical polymerization (ATRP) to produce reagents derived from aminooxyacetic acid. They have prepared two such active precursors, **64** and **65**.



(**64**)

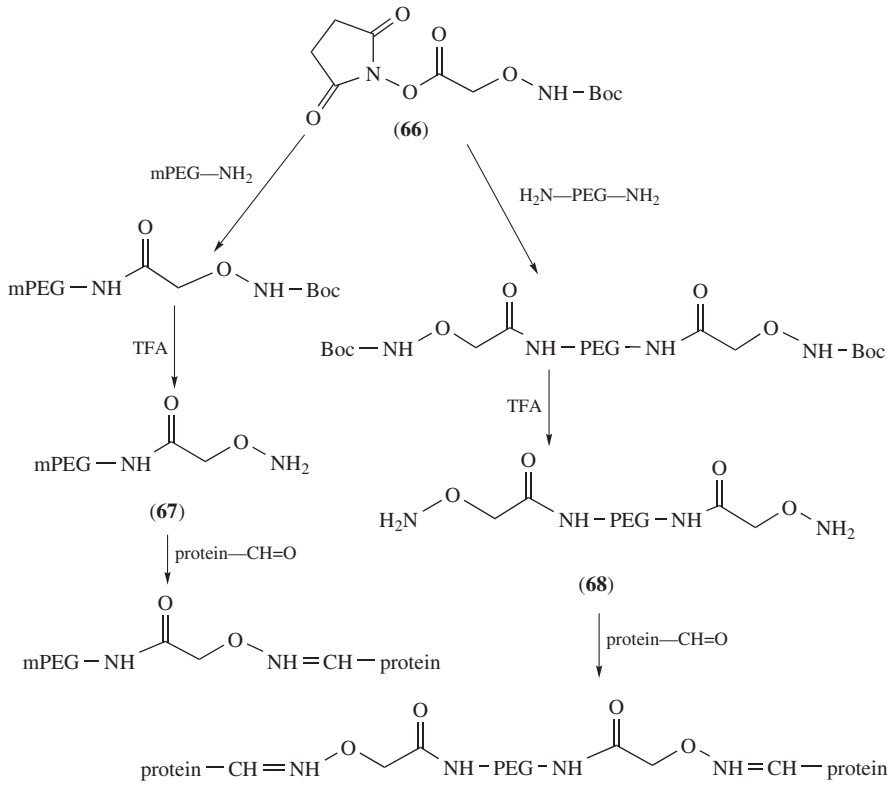


(**65**)

Aminooxy polymeric polyethylene glycol (PEG) linkers for the conjugation of proteins were prepared by Gaertner and Offord[86]. Aminopolyethylene glycol (H_2N-mPEG) of M_r 5000–20000 and diamino polyethylene glycol (H_2N-PEG_{20kD}-NH_2) were brought to reaction with carboxyl activated *N*-Boc-aminooxyacetic acid derivative **66**. Deprotection by TFA resulted in the mono- and difunctional reagents **67** and **68** respectively, for conjugation with proteins. The oxime bond was formed between the free aminooxy group and an aldehyde moiety, produced by oxidation of terminal serine residues in the proteins (Scheme 20). Branched coupling reagents were obtained by using lysine or tris(2-aminoethyl)amine[86].

Sethi and coworkers[87] have recently described a reagent (**69**) derived from aminooxyacetic acid for the synthesis of functionalized oligonucleotides, useful in microarrays and incorporation in bioconjugates. The preparation of **69** and its use in the stepwise solid-phase preparation of 3′/5′ aminooxy functionalized oligonucleotides is shown in Scheme 21. The Fmoc activated aminooxyacetic acid (**70**) was condensed with 3-amino-1,2-dihydroxypropane (**71**) to yield the dihydroxy derivative **72**. One of the hydroxy groups was protected by dimethoxytrityl group to give the reagent **69**, which could be attached to a polymer support, used in oligonucleotide solid-phase synthesis, through a succinic acid bridge (Scheme 21).

Another aminooxyacetic acid derivative suitable for solid-phase synthesis of aminooxy-functionalized peptides was described by Kessler and coworkers[88]. N^3-(*N*-Boc-aminooxyacetyl)-N^2-Fmoc-2,3-diaminopropionic acid (**73a**) was linked to the solid-phase resin trityl chloride polystyrene (TCP). Kessler and coworkers used the chemoselective oxime chemistry to prepare radioactive-labeled peptides, for tumor targeting, by condensing **73b** with a radioactive benzaldehyde derivative to produce the radioactive linker **74**. Removal of the Fmoc group from the solid-phase system is then followed by the solid-phase peptide synthesis (Scheme 22).

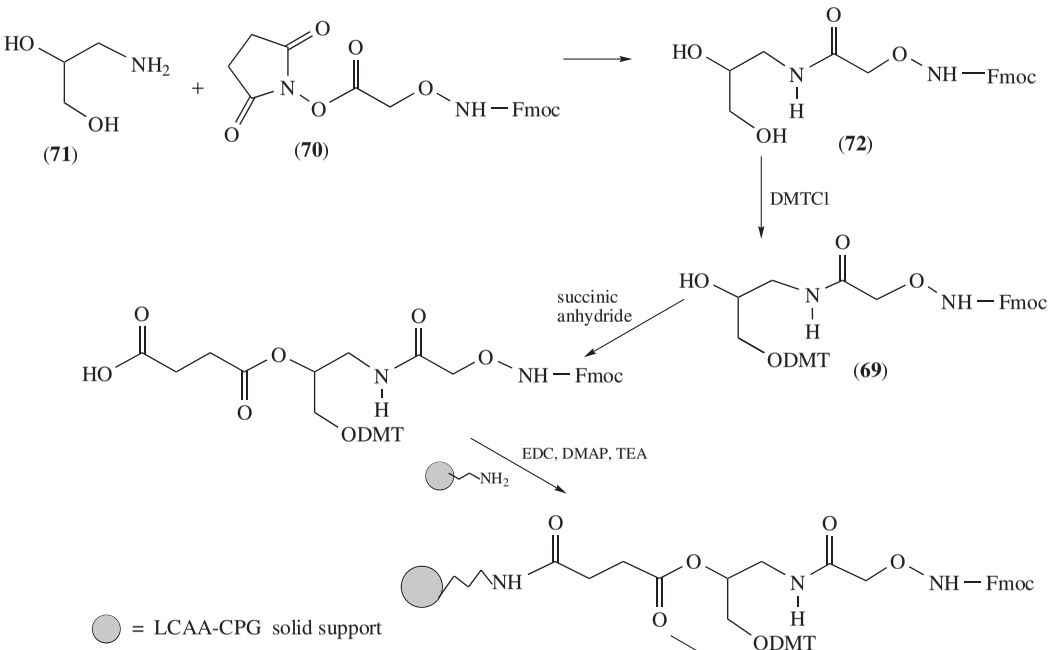


SCHEME 20

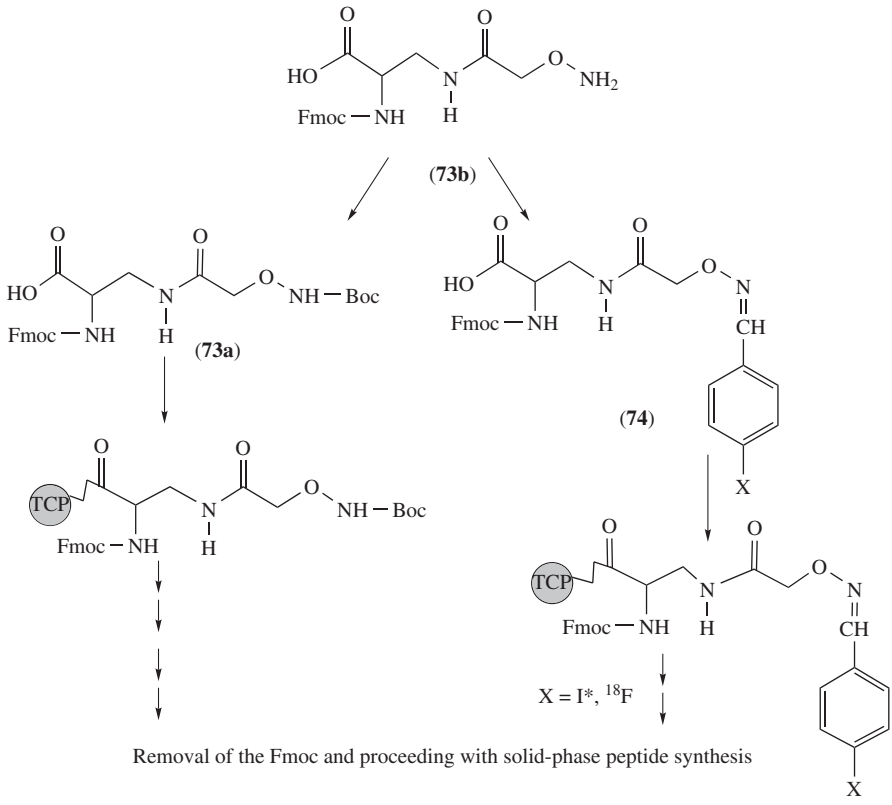
Chan and Yousaf[89] described ligation derivatives of aminooxyacetic acid as a part of surface chemistry methodology to immobilize ligands, proteins and cells linked to electroactive substrates based on the chemoselective oxime bond formation with quinone terminated monolayers (**75**). They showed that the oxime product is redox active at a different potential, thus allowing monitoring the immobilization reaction. Only the quinone form of the immobilized redox pair was reactive with soluble aminooxy groups, which allows the determination of the yield of reaction, the ability to immobilize multiple ligands at controlled densities and the *in situ* modulation of ligand activity. Among these were aminooxy terminated rhodamine (**76**) and FLAG peptide (**77**) derivatives. The aminooxy terminated FLAG peptide (**77**) was characterized by its binding to anti-FLAG antibodies, by voltametry[89].

8. Reagent for site-specific incorporation of aminooxyacetic acid into proteins

a. Reagents for biosynthesis. Eisenhauer and Hecht[90] described a site-specific incorporation of aminooxyacetic acid into enzymes. Aminooxyacetic acid was protected with 6-nitroveratryl chloroformate (**78**) and treated with chloroacetonitrile. The activated ester (**79**) was coupled to pdCpA (**80**), resulting in a $2', 3'$ isomeric mixture of *N*-(6-nitroveratryloxycarbonyl) aminooxyacetyl-pdCpAs (**81**) (Scheme 23). The


(71)
(70)
(72)
DMTCl
succinic anhydride
(69)
EDC, DMAP, TEA
= LCAA-CPG solid support
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
DMAP = 4-dimethylaminopyridine, TEA = triethylamine
Fmoc = N-(9-fluorenylmethyl)oxycarbonyl
DMT = 4,4′-dimethoxytrityl
Removal of the DMTr group and proceeding with solid-phase polynucleotide synthesis

SCHEME 21

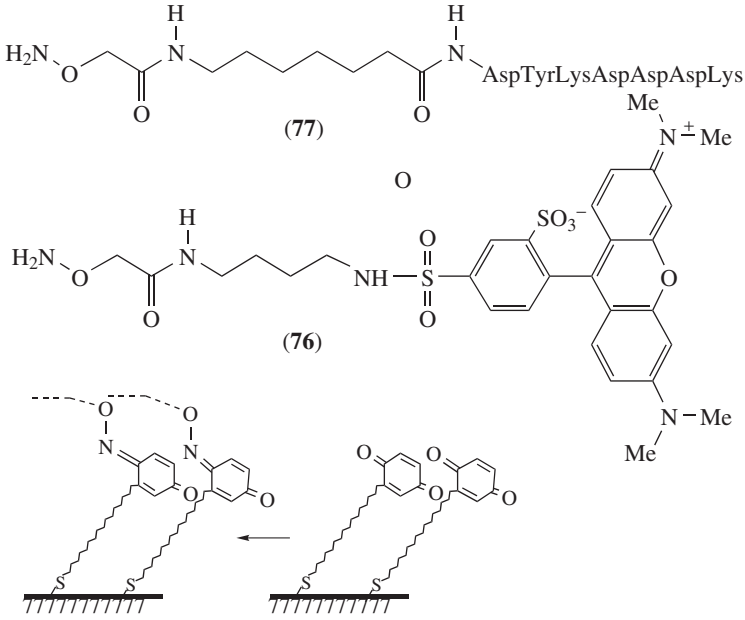


SCHEME 22

aminooxyacetyl dinucleotide (**81**) was then ligated to tRNA, mediated by T4 RNA ligase. This biochemical procedure resulted in the incorporation of aminooxyacetic acid into positions 10 and 27 of *Escherichia coli* dihydrofolate reductase. Incorporation of the amino acid proceeded with reasonable efficiency at codon position 10 but less well at position 27. Aminooxyacetic acid was also incorporated into position 72 of DNA polymerase. Peptides containing aminooxyacetic acid have been shown to adopt a preferred conformation involving an eight-membered ring that resembles a γ-turn. The latter conformational phenomenon is also discussed in Section IV.

b. Reagents for chemical incorporation. More derivatives of aminooxyacetic acid were prepared for the site-specific incorporation of radioactive agents. Kurth and coworkers[91] prepared the ^{125}I-phenylethylamine derivative of aminooxyacetic acid (**82**), with the free aminooxy group available for interaction with carbonyl sites.

Poethko and coworkers[92] had reported in 2004 and Dirksen and Dawson[93] in 2008 additional site-specific reagents involving aminooxyacetic acid. Recently, Hultsch and coworkers[94] reported the application of the solid-phase peptide synthesis for the preparation of an aminooxyacetic acid functionalized peptide for the production of ^{18}F-fluoroglucosylated cyclo(RGDfK) peptide (**83**).

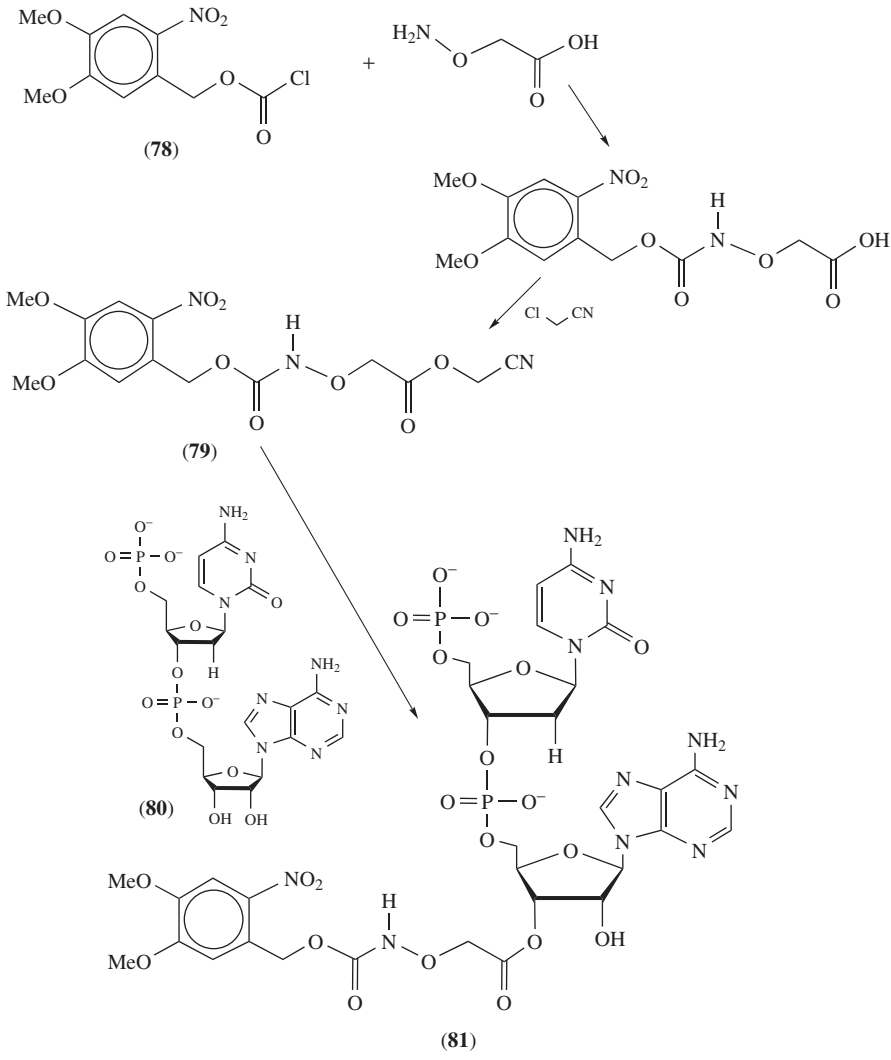


B. α-Aminooxy Acids Other than Aminooxyacetic Acid

The chirality of these acids is an important feature that does not exist in aminooxyacetic acid and other straight-chain ω-aminooxy acids. The racemic acids were prepared as early as the 19th century and at the first half of the 20th century by methods described above (Sections I.B.1–6). The methods that involve transformation of available optically active α-amino acids to optically active α-aminooxy acids were discussed above as well (Sections I.B.7–9). An interesting way for the resolution of racemic α-aminooxy acids was reported by Klumpp[95] in 1980, using *d*- and *l*-*cis*-diethylenediaminedinitrocobalt complex (**84**). The protected α-aminooxy acids, upon reaction of the bromide (**84**), replaced the bromide ion and formed a selective complex (**85**), which upon decomposition gave the optically active protected α-aminooxy acids (Scheme 24). A number of α-aminooxy acids are of interest and they are discussed in the following sections.

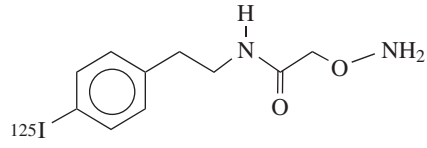
1. Aminooxypropionic acid and derivatives

a. Synthesis of α-aminooxypropionic acid. The racemic DL-aminooxypropionic acid was prepared by methods described above. The first[6] synthesis was in 1894 followed by other syntheses[7, 8a, 9, 10]. The hydrochloride of α-aminooxypropionic acid is a solid (dec. 163–168 °C). Optically active α-aminooxypropionic acid was obtained by using the methodology of the transformation of available optically active alanine by various procedures[14–16, 34], as described above. Both *N*-*t*-butyloxycarbonyl and *N*-benzyloxycarbonyl derivatives of DL-α-aminooxypropionic acid were resolved to the

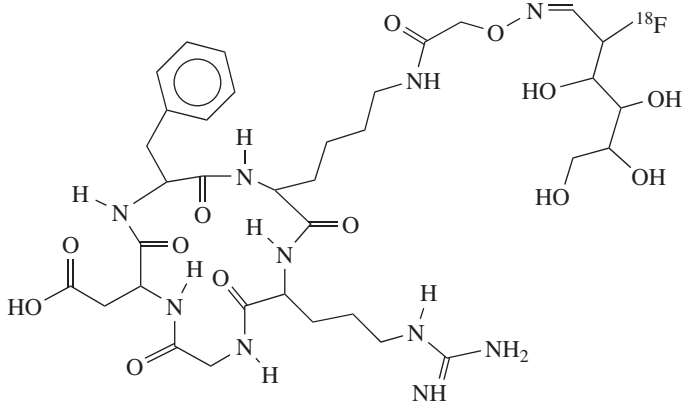


SCHEME 23

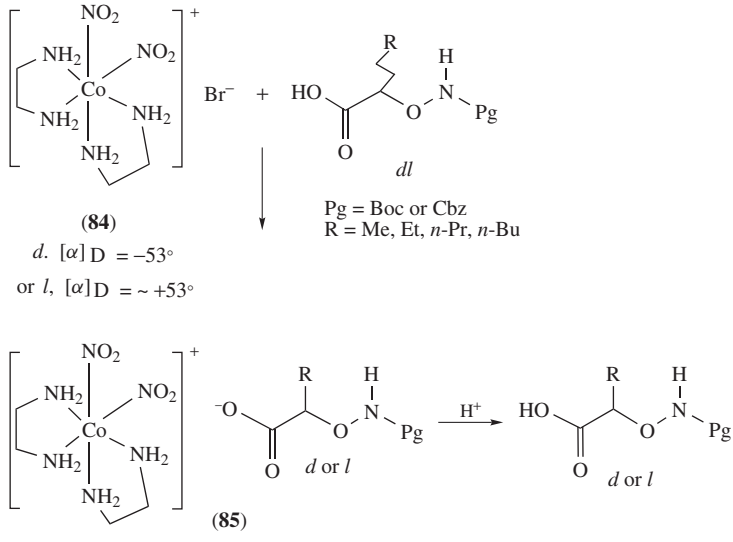
optical isomers by Klumpp using *d*- and *l*-*cis*-diethylenediaminedinitrocobalt complex (**84**)[95]. The isopropylidene derivative of DL-α-aminooxypropionic acid (**86**) was resolved by optically active ephedrines by Newman and Lutz[96]. The tetranitrofluorenylidene derivative of aminooxypropionic acid (**87**) was used by these investigators for the chiral resolution of aromatic hydrocarbons and ethers. Aromatic compounds like 1-naphthyl-2-butyl ether (**88**) and 2-(1-anthracenyl)propionate (**89**) could thus be resolved to their optical isomers (Scheme 25).



(**82**)



(**83**)



(**84**)

d. $[\alpha]_D = -53^\circ$

or *l*, $[\alpha]_D = \sim +53^\circ$

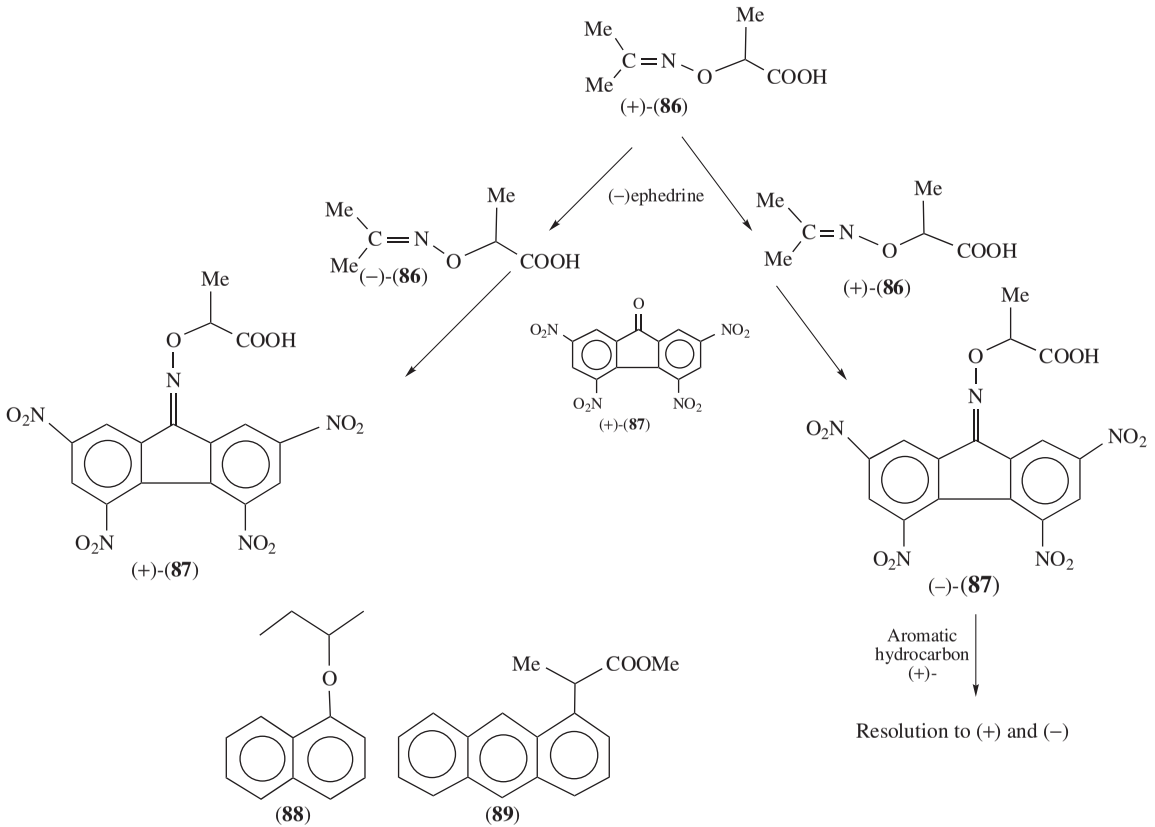
dl

Pg = Boc or Cbz

R = Me, Et, *n*-Pr, *n*-Bu

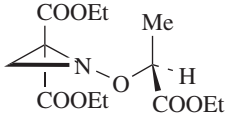
(**85**)

SCHEME 24

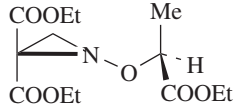

(+)-(86)
(–)ephedrine
(–)-(86)
(+)-(86)
(+)-(87)
(+)-(87)
(–)-(87)
Aromatic hydrocarbon (+)-
Resolution to (+) and (–)
(88)
(89)

SCHEME 25

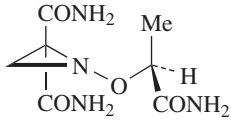
Diasterometrically pure aziridine derivatives of α-aminooxypropionic acids (**90**–**93**) were prepared[97] by Prosyanik and coworkers. The absolute configuration of these α-aminooxy acid derivatives were proved and determined by single-crystal X-ray diffraction analysis of the triamide (**93**).



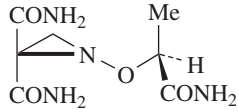
(*R*,*S*)-(**90**)



(*S*,*S*)-(**91**)



(*R*,*S*)-(−)-(**92**)



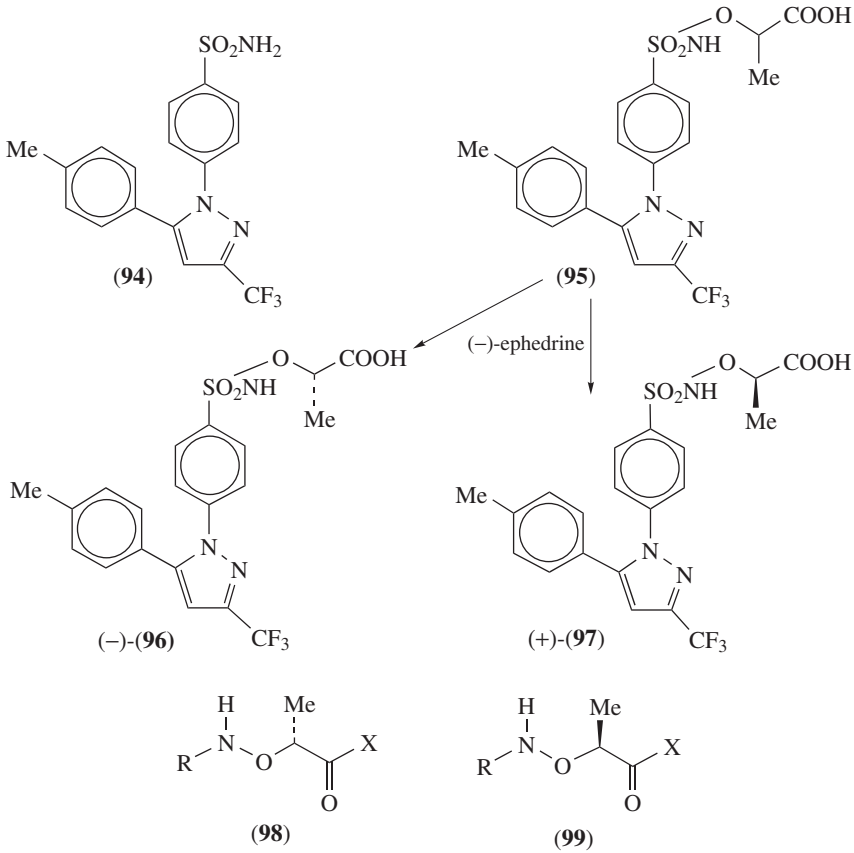
(*S*,*S*)-(+)-(**93**)

b. Properties of α-aminooxypropionic acid. The physical and spectroscopic properties of α-aminooxypropionic acid were investigated by various groups as models for this family of compounds. The IR, NMR, mass spectral and thermal properties data were discussed[31–33, 36] in Section I.B. Dissociation constants[12, 14, 20, 21] and metal complexses[20, 21, 29, 30] were reported as well (Section I.B). Calculation of the contribution of α-aminooxypropionic acid, incorporated in a peptide, to the tertiary structure of the chain was reported and discussed by Yang and coworkers[15b] and Li and coworkers[37]. The nature of the hydrogen bonds and the foldamers obtained were discussed both above and below (Section IV).

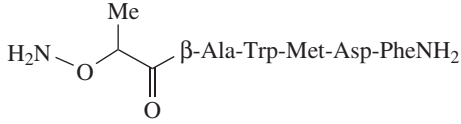
c. Bioactivity of α-aminooxypropionic acid and its derivatives. L-α-Aminooxypropionic acid inhibited ethylene production in plants about threefold less than aminooxyacetic acid. However, its benzyloxycarbonyl derivative had an inhibition effect at half the concentration than that of aminooxyacetic acid[59]. Bobarevic and coworkers[98] found that, contrary to other aminooxy acids, α-aminooxypropionic acid caused muscle relaxation in mice. Osuide and coworkers encountered[99] convulsing activity in young chicks but found[100] that benzylidene α-aminooxypropionic acid had anticonvulsant activity in young chicks. Lee and coworkers[101] discussed the observation that orally administered α-aminooxypropionic acid causes lesions in the retina, in eyes of male rats.

The modification of Celecoxib (**94**) by introducing DL-α-aminooxypropionic acid resulted in a potent anti-inflammatory agent (**95**)[102], more effective than Celecoxib itself. Aminooxyacetic acid and other α-aminooxy acids did not cause an enhancement of anti-inflammatory activity. The racemic (**95**) was resolved to its optically active components (**96** and **97**) by using (−)ephedrine. The (+) isomer (**97**) did not show any anti-inflammatory activity while the (−) isomer (**96**) showed moderate activity.

Short peptides containing α-aminooxypropionic acid were tested for antibacterial properties[103]. The uptake and transport of dipeptides and tripeptides containing L- and D-α-aminooxypropionic acid in *E. coli* and other bacteria were investigated by Payne and coworkers[104, 105]. These peptides **98** and **99** were found to be antibacterial. Peptides containing D-α-aminooxypropionic acid were found more toxic than their L-isomers.



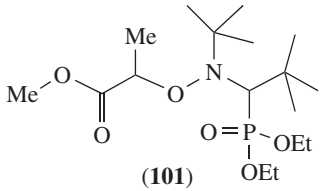
L-α-Aminooxypropionic acid was incorporated into pentagastrin and the aminooxy analog (**100**) was administered into rats in order to determine its effect on the stimulation of gastric flow. This modification of pentagastrin like other pentagastrin derivatives of α-aminooxy acids seemed to increase significantly the gastric secretory response[106].



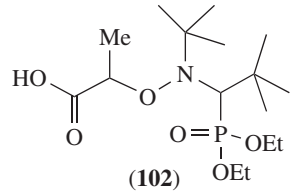
(**100**)

d. 2-[N-tert-butyl-2,2-(dimethylpropyl)aminooxy]propionic acid. Important derivatives of ethyl α-aminooxypropinate are compounds **101** and **102**. They produce the nitroxyl radical (**103**) and enable a controlled free-radical polymerization (CRP) in water-based

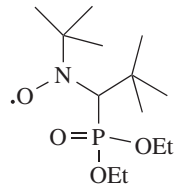
systems[107, 108]. The acid (**102**) is widely used and sold by the commercial name: '**NONAMS**'. It has been studied intensely during the last years[109, 110] as it combines the environmental and technical advantages of polymerization in aqueous dispersed media.



(**101**)



(**102**)



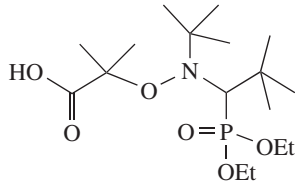
(**103**)

2. α-Aminooxybutyric acid and isomers

a. α-Aminooxybutyric acid. The racemic DL-α-aminooxybutyric acid was prepared by methods described above[9, 10]. Its hydrochloride is a solid (dec. 142 °C). The preparation of optically active α-aminooxybutyric acid was reported by Testa and coworkers[14a] and Kisfaludy and coworkers[111] and procedures are registered in a number of patents[34]. Its *N*-methyl derivative was reported by Testa and coworkers[14a]. The physical and spectroscopic properties were investigated by various groups. The IR, NMR, mass spectra and thermal properties were discussed[31–33, 36] in Section I.B. Dissociation constants[12, 14, 20, 21] and metal complexes[20, 21, 29, 30] were reported (Section I.B). α-Aminooxybutyric acid caused muscle relaxation when administered to mice[98]. This is unlike aminooxyacetic acid that caused convulsions in mice. α-Aminooxybutyric acid, like other aminooxy acids, inhibits the formation of ethylene in plants. The correlation between inhibition of flowering by L-α-aminooxybutyric acid derivatives and glutamic-oxaloacetic transaminase was investigated in morning-glory plants (*Pharbitis nil*)[62].

b. α-Aminooxyisobutyric acid. The racemic acid was synthesized by McHale and coworkers[10] in 1960 (Section I.A) and by Jiang and coworkers[112] in 1991 by the reaction of the salt of *N*-hydroxyphthalimide with ethyl α-bromoisobutyrate and subsequent hydrolysis. Dissociation constants and the UO_2 complex were reported by Achpal and Verma[28b] in 2006. The modification of Celecoxib (**94**) by introducing α-aminooxyisobutyric acid did not result in enhancement of anti-inflammatory activity[102]. The correlation between inhibition of flowering by α-aminooxyisobutyric acid derivatives and glutamic-oxaloacetic transaminase was investigated in plants[62]. A very important derivative of α-aminooxyisobutyric acid is compound **104** available commercially as 'BlocBuilder'. The latter gives the nitroxyl radical (**103**) and enables a controlled free-radical polymerization in water-based systems[113]. It was found[114] to be superior to the α-aminooxypropionic derivatives (**101** and **102**). It combines the environmental and technical advantages of polymerization in aqueous dispersed media with the ability to synthesize tailor-made macromolecular architectures. From the numerous articles[115–120]

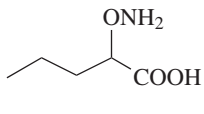
and patents published recently it appears to be of great interest in the future. One should be careful in understanding the systematic nomenclature used by polymer chemists as the 'BlocBuilder' is many times referred to as an α-aminooxypropionic acid derivative rather than an α-aminooxyisobutyric acid[120].



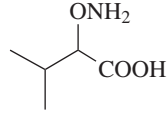
(**104**)

3. α-Aminooxyvaleric acid and isomers

Both α-aminooxyvaleric acid (**105**) and α-aminooxyisovaleric acid (**106**) were prepared first as racemic compounds and were resolved by reaction with optically active amines. The racemic acids were prepared by McHale and coworkers[10] in 1960 by the condensation of benzohydroxamic acid (**8**) with either α-bromovaleric acid or α-bromoisovaleric acid in the presence of NaOH in aqueous ethanol (Section I.A.3). In 1972, Suresh and Malkani[9] used the corresponding bromo esters and reacted them with *N*-hydroxyphthalimide (**10**) in the presence of KOH (Section I.A.3). Hydrolysis by HCl or HBr gave the corresponding hydrochlorides and hydrobromides, respectively. *N*-Hydroxyurethane (**18**) was used for the condensation with the esters of α-bromovaleric acid and α-bromoisovaleric acid as well[14]. Both optically active α-aminooxyvaleric acid (**105**) and α-aminooxyisovaleric acid (**106**) were synthesized by Testa and coworkers[14a] and by Kisfaludy and his coworkers and patents were claimed[34, 121]. Their route for synthesis was either by starting with either an optically active bromo acid (**107**), prepared from available α-amino acids, or by enantiomeric resolution of the protected intermediate (**108**) as shown[111] for α-aminooxyvaleric acid in Scheme 26. The condensation of *t*-Boc hydroxylamine occurs with inversion of configuration (Scheme 26).

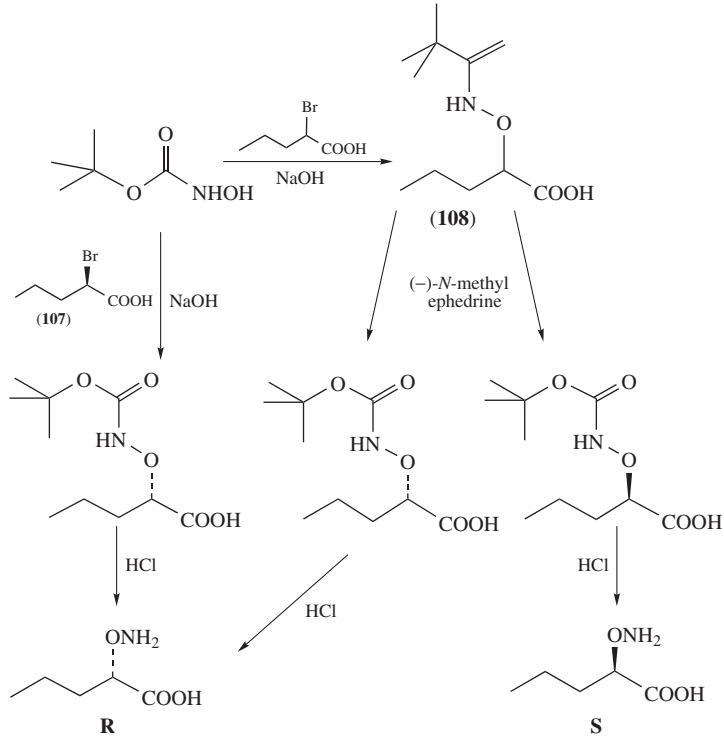


(**105**)



(**106**)

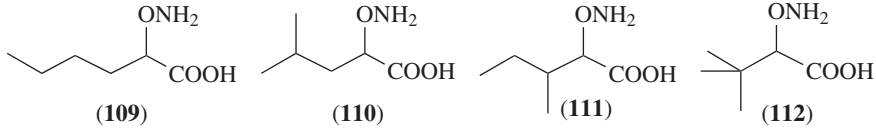
The IR and NMR spectra of **105** and **106** were investigated by Sohar and coworkers[36] (Section I.B.7) and dissociation constants and other physical properties by Testa and coworkers[14a] (Section I.B.1). Complexes with divalent metal ions like Cu, Ni and Co of α-aminooxyvaleric acid (**105**) were reported by Warnke and Trojanowska[29] (see Section I.B.4). The mass spectrum of **105** was investigated by Tamas and coworkers[33] in 1974. Both isomers **105** and **106** showed moderate inhibition activity of ethylene production in plants[59], weak *in vitro* antibacterial activity against *Staph. aureus* and *E. coli* and stronger activity against *M tuberculosis*[10]. *N*-Methyl derivatives of both isomers were prepared by Testa and his coworkers[14a].



SCHEME 26

4. α-Aminooxycaproic acid and isomers

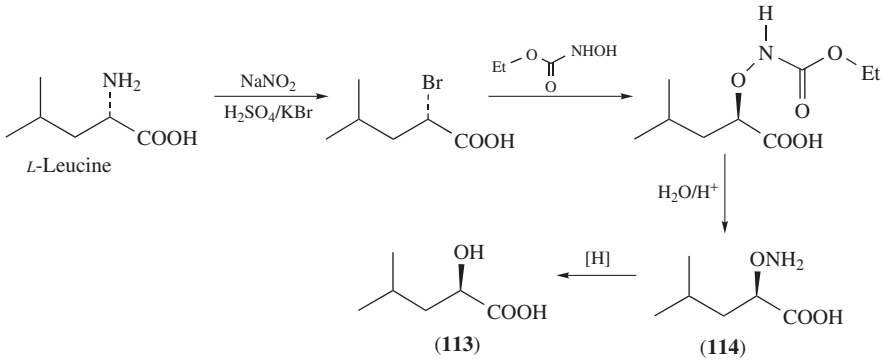
All four isomers of α-aminooxyhexanoic acids (**109**–**112**) are known and were reported by different groups.



a. α-Aminooxycaproic acid. McHale and coworkers synthesized the racemic compound **109** and tested it for antibacterial activity[10]. It was found to be weak in *in vivo* antibacterial activity against *Strept. pyogenes*[38]. Testa and coworkers[14a] as well as Kisfaludy and coworkers[34, 122] reported the synthesis of the optically active enantiomers of this acid by similar procedures as described above (Section I.B). The reagent that was used by Kisfaludy and coworkers for resolution to enantiomers was (+)-amphetamine. The purpose for preparing the various enantiomers of **109** was to investigate their antibacterial and

tuberculostatic activity. Dissociation constants were reported by Testa and coworkers[14a] and by Warnke and coworkers[20]; the latter group reported divalent metal complex formation and investigated their properties. The IR and NMR spectra of α-aminooxycaproic acid (**109**) were investigated by Sohar and coworkers[36]. Like in the case of some of the previously discussed aminooxy acids, α-aminooxycaproic acid (**109**) caused convulsions in mice[98] and demonstrated ethylene inhibition in plants[59, 62].

b. α-Aminooxy-4-methylvaleric acid. This acid is an analog of the natural amino acid L-leucine. Thus the preparation of the optically active D-α-aminooxy-4-methylvaleric acid (**110**) was achieved from L-leucine by methods described above (Sections I.B and II.B.2)[14a, 34, 111]. The L-configuration claimed by Testa and coworkers[14a] was shown later to be the D-configuration as a result of an inversion, occurring in the nucleophilic substitution by the hydroxylamine derivative. The absolute configuration of D-**110** (**114**) derived from L-leucine is *R* (D) since it has been hydrogenolyzed to D(+)-leucic acid (**113**) (Scheme 27) as shown by Liberek and Cupryszak[123].



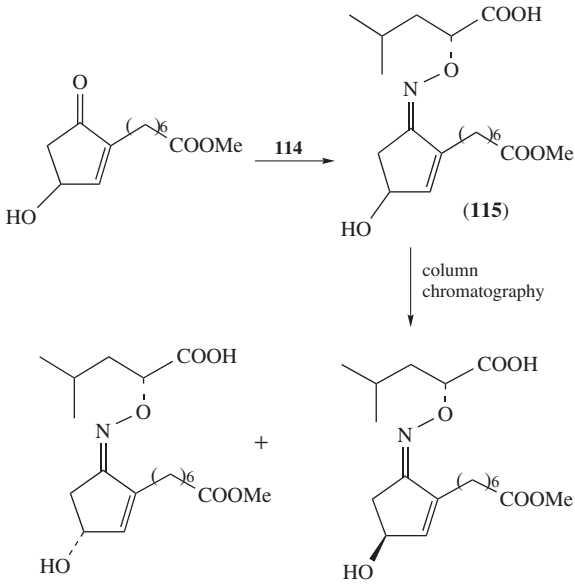
SCHEME 27

The formation of complexes with divalent metals was reported by Warnke and coworkers[20]. Dissociation constants were reported by the latter group and by Testa and coworkers[14a]. Thermal properties[31, 32] as well as spectroscopic properties[36] of α-aminooxy-4-methylvaleric acid (**110**) were reported as well. The convulsive activity in mice[98] and its ability to inhibit ethylene production in plants[59] were investigated as well.

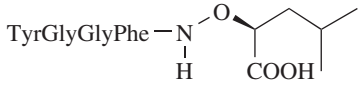
Pappo and coworkers developed a method for optical resolution of steroids and intermediates in the synthesis of prostaglandins using (*R*)-α-aminooxy-4-methylvaleric acid (**114**) as a resolving reagent[124]. Reaction of the racemic prostaglandin precursor gave with **114** an oxime (**115**) that could be separated by column chromatography to the two oxime enantiomers (Scheme 28).

The same group used both enantiomers of **110** in the optical separation of 19-norsteroids[125]. The *S*-enantiomer was prepared from D-leucine in a similar way as shown above (Scheme 27). Bruhn and coworkers[126a] and Baraldi and coworkers[126b] used the same procedure for obtaining an optically pure analog of prostaglandin PGE_2.

As α-aminooxy-4-methylvaleric acid (**110**) is an analog of the natural amino acid L-leucine, Salvadori and coworkers[127] synthesized an aminooxy analog of Leu-enkephalin (**116**) by introducing this aminooxy acid into the peptide chain. The latter analog did not show any biological activity *in vitro*.



SCHEME 28

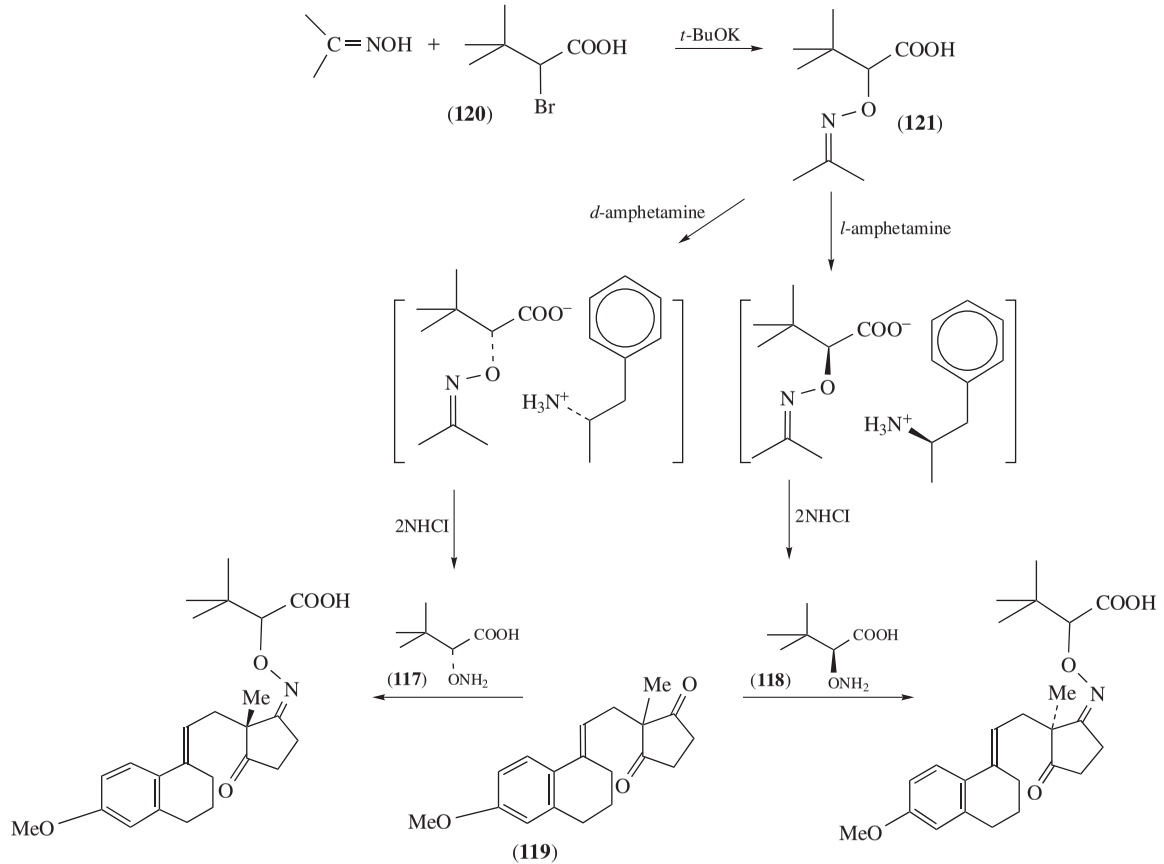


(**116**)

c. α-Aminooxy-3-methylvaleric acid and α-aminooxy-3,3-dimethylbutyric acid. α-Aminooxy-3-methylvaleric acid (**111**) was synthesized from α-bromo-3-methylvaleric acid by condensation of either *N*-hydroxyurethane[14a] or *t*-butyloxycarbonylhydroxylamine (*t*-BocNHOH)[34]. The available isoleucine was the source of L-α-bromo-3-methylvaleric acid[14a]. The assignment of the correct configuration was reported elsewhere[123]. Both enantiomers showed weak bacteriostatic activity[14a]. Both enantiomers of α-aminooxy-3,3-dimethylbutyric acid (**112**), isomers **117** and **118**, were also prepared by Pappo and coworkers[124, 125] and they were very useful in the optical resolution of a key intermediate in the synthesis of 19-norsteroids (**119**). The preparation was accomplished by the reaction of acetone oxime with 2-bromo-3,3-dimethylbutyric acid (**120**) in the presence of potassium *t*-butoxide. The racemic intermediate (**121**) was resolved through the (*l*)-amphetamine salt yielding predominantly the *S*-acid. The *R*-enantiomer was similarly obtained using (*d*)-amphetamine (Scheme 29).

5. Long-chain α-aminooxy acids

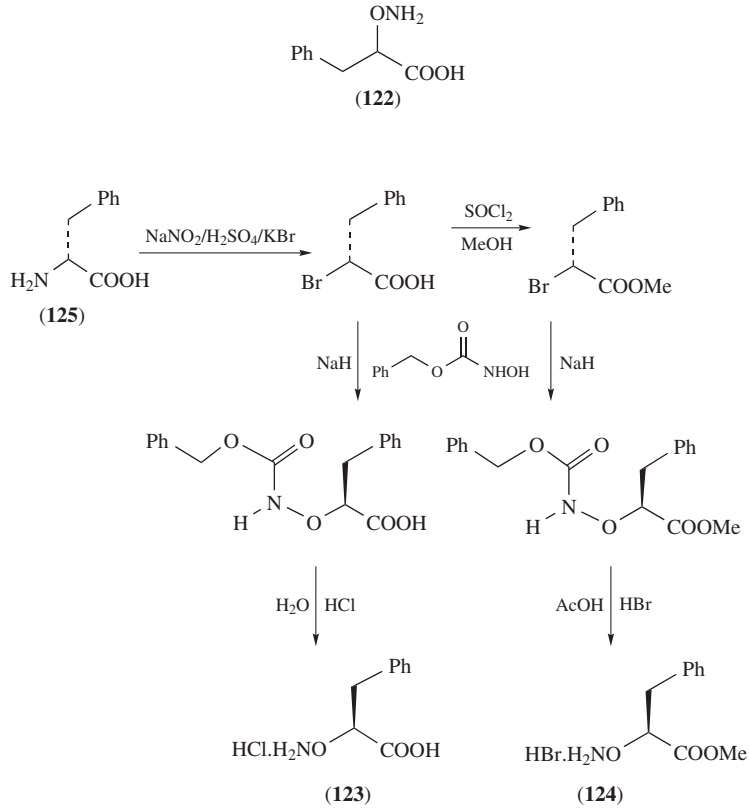
Long-chain α-aminooxy acids (C_7–C_{10}) were synthesized and tested for bacteriostatic activity by McHale and coworkers[10, 38]. α-Aminooxydecanoic acid was also tested for inhibition of ethylene production in plants[59].


C=NOH
COOH
Br
(120)
t-BuOK
COOH
N
O
(121)
d-amphetamine
l-amphetamine
COO⁻
H₃N⁺
2NHCl
2NHCl
COOH
ONH₂
(117)
(118)
Me
O
N
MeO
(119)

SCHEME 29

6. α-Aminooxy-β-phenylpropionic acid

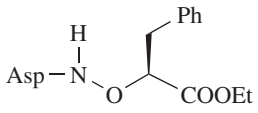
α-Aminooxy-β-phenylpropionic acid (**122**) is considered to be the analog of the amino acid phenylalanine. The natural L-phenylalanine served as the starting material for D-α-aminooxy-β-phenylpropionic acid[14a, 15a, 34, 111]. Briggs and Morley prepared[15a] the L-enantiomer **123** and its ester as the hydrochloride **124** from D-phenylalanine **125** as shown in Scheme 30.



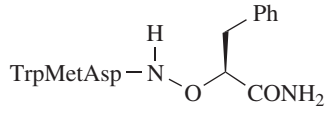
SCHEME 30

Dissociation constants and metal complexes of α-aminooxy-β-phenylpropionic acid were reported by Warnke and Trojanowska[20, 29]. Thermal properties were reported by Warnke and Blazejowski[31, 32]. NMR and IR spectra were investigated by Sohar and coworkers[36] and mass spectroscopy by Tamas and coworkers[33].

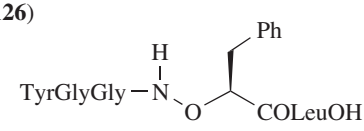
A non-sweet analog of aspartame (**126**), containing L-α-aminooxy-β-phenylpropionic acid, was prepared by Briggs and Morley[15a]. The analog of gastrin **127** was prepared; however, it did not stimulate gastric acid secretion[15a]. An analog of leu-enkephalin (**128**) was synthesized by Salvadori and coworkers[127], with no biological activity *in vitro*.



(**126**)



(**127**)



(**128**)

The L-enantiomer of α-aminooxy-β-phenylpropionic acid (**122**) was found as an inhibitor of the enzyme L-phenylalanine ammonia-lyase (PAL), which catalyzes the deamination of L-phenylalanine to *trans*-cinnamic acid. This process is a key step in the secondary metabolism of plants. It supplies C6–C3 precursors, especially phenolics that play regulatory and metabolic functions in plants and sometimes in microorganisms. The D-enantiomer was 10–20 fold less active than the L-enantiomer[127, 128]. It has been suggested that the L-enantiomer fits better into the active site of PAL[129]. The enzyme was inhibited irreversibly in cell culture of soybean[130] and L-**122** was applied in studies on regulation of the level of PAL in plant tissues[131, 132], on lignin formation[133] as well as in studies on the role of PAL in the regulation of cell elongation[134]. L-**122** was effective in accumulation of phytoalexin in pathogen resistance in soybean[135]. A short review by Janas up to 1993 with 34 references is available[136].

In 1994, Leubner-Metzger and Amrhein[137] investigated the ability of L-**122** to inhibit the enzyme phenylalanine synthetase. Chapple and coworkers found that L-α-aminooxy-β-phenylpropionic acid strongly inhibits tyrosine decarboxylase in plants[138]. Ni and coworkers investigated[139] the role of phenylpropanoid products as regulators in gene expression by treatment of plant cells with L-**122**. Brincat and coworkers[140] had reported the ability of L-1**22** to enhance Taxol production in plant cell culture. Various effects of L-**122** in different crops, such as in preserving lettuce[141a] or growing barley[141b], were reported as well.

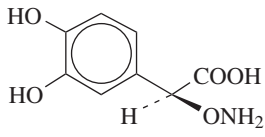
The antimalarial activity of α-aminooxy-β-phenylpropionic acid (no mention of enantiomer) was investigated by Berger[141c] and it was found tenfold more active than aminooxyacetic acid and about 18% of antimalarial activity than that of canaline (**2**).

7. (3,4-Dihydroxyphenyl)aminooxyacetic acid

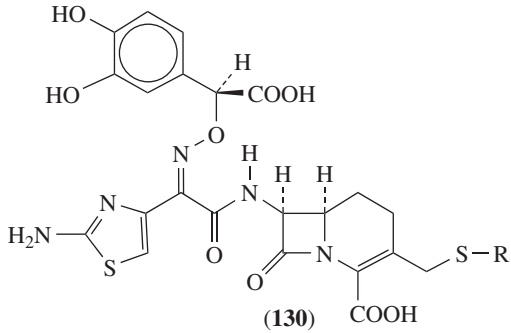
The *S*-enantiomer of (3,4-dihydroxyphenyl)aminooxyacetic acid (**129**) is an important constituent of cephalosporine antibiotics[142] like **130**. **129** was synthesized by Iwagami and coworkers[17a], from the corresponding protected bromo ester (**131**), by the *N*-hydroxyphthalimide method, followed by optical resolution. An improved route was reported later[17b] using as a starting martial the available hydroxy acid (**132**). A new method was reported in 1995 by Ace and coworkers[143] in which the reaction of *N*-hydroxyphthalimide, or other N-protected hydroxylamine agents, with the diazo ester (**133**) resulted in a good yield of the racemic product.

8. Other aromatic α-aminooxy acids

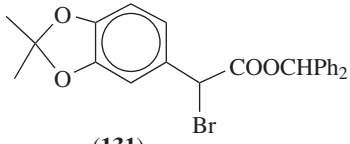
This section includes the aromatic α-aminooxyacetic acids (**134a–d**) and α-aminooxythiopheneacetic acid (**135**). α-Aminooxyphenylacetic acid (**134a**) was



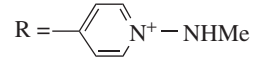
(**129**)

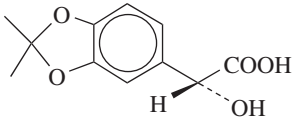


(**130**)

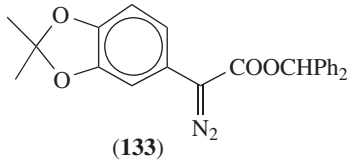


(**131**)

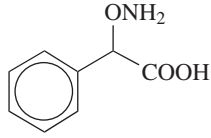




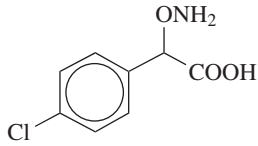
(**132**)



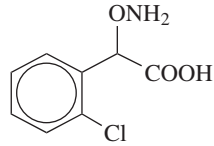
(**133**)



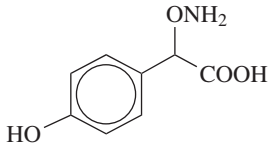
(**134a**)



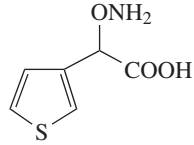
(**134b**)



(**134c**)



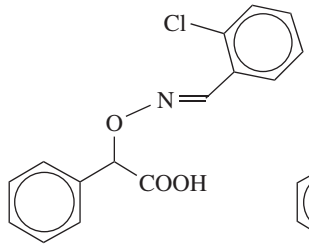
(**134d**)



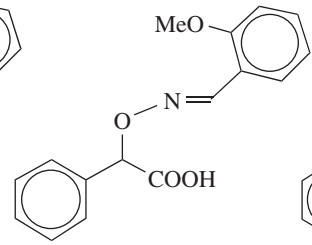
(**135**)

prepared in the sixties of last century from 2-bromophenylacetic acid by condensation with either *N*-hydroxyurethane[14] or benzohydroxamic acid[8b] and in the seventies by using *t*-butyloxycarbonylhydroxylamine[34]. There are more recent patents using *N*-hydroxyphthalimide[144] and acetoxime salt[145]. The antibacterial activity of α-aminooxyphenylacetic acid (**134a**) was investigated by Testa and coworkers[14a]. The inhibition of GABA transaminase *in vitro* and *in vivo* and its effect on convulsions

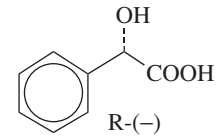
was investigated and compared to the activity of aminooxyacetic acid[8b, 98]. The effect of **134a** on the production of ethylene in plants and its inhibition of flowering in morning-glory plants (*Pharbitis nil*) were investigated[62] as well. Undheim and coworkers[14b] prepared numerous aldoximes from **134a**. Most of them were prepared from substituted benzaldehydes. Two of the aldoximes (**136a** and **136b**) were optically resolved and the relation to *R*(−)-mandelic acid (**136c**) was shown.



(**136a**)



(**136b**)

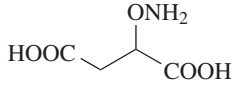


(**136c**)

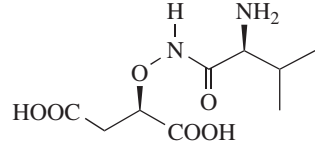
Undheim and coworkers also prepared the chloro derivatives of α-aminooxyphenylacetic acid (**134b** and **134c**) and α-aminooxy-2-thiopeneacetic acid (**135**) and a long list of their aldoximes[14b]. The preparation of both *R*- and *S*-enantiomers of α-aminooxy(4-hydroxyphenyl)acetic acid (**134d**) are included in a European patent[146] from 1980. The purpose of the synthesis of the aminooxy acids which are included in this patent is for agricultural uses in digestibility of fodder crops.

9. α-Aminooxysuccinic acid

In 1980, Takeuchi and his coworkers[147] discovered a new antibiotic that includes one of the enantiomers of **137**, produced by *Streptomyces lydicus*, which was named malioxamycin. Takahashi and coworkers[148] elucidated its structure as the dipeptide **138** of *R*-valine and *R*-α-aminooxysuccinic acid. They proved the structure by the synthesis of this new antibiotic from *R*-α-aminooxysuccinic acid and L-valine.

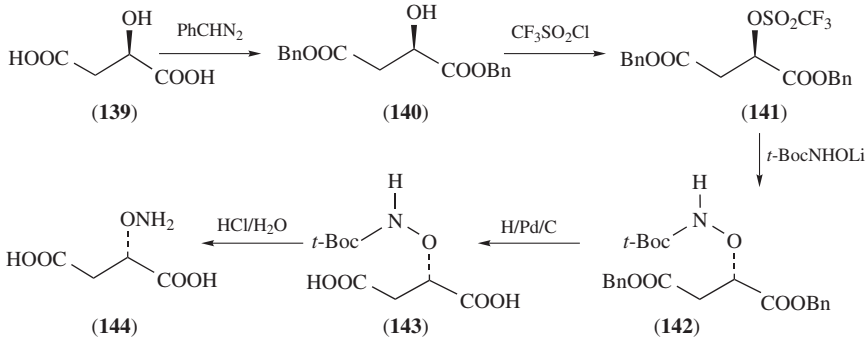


(**137**)



(**138**)

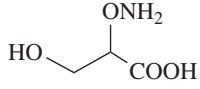
An elegant synthesis of the two enantiomers of **137** was reported by Scaman and coworkers[149] in 1991. They used the commercially available pure enantiomers of *R* and *S* malic acid. The synthesis of one of the enantiomers is shown in Scheme 31. The *R*-(+) malic acid (**139**) was converted to the dibenzyl ester (**140**) by phenyl diazomethane. Activation of the hydroxy group was performed with triflic chloride to produce intermediate **141** and followed by nucleophilic displacement with *t*-butyloxycarbonylhydroxylamine lithium salt, with inversion of configuration in **142**. Reduction and subsequent deprotection of the intermediates **142** and **143** led to the pure *S*-(−) enantiomer **144** (Scheme 31).



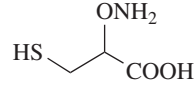
SCHEME 31

10. Additional α-aminooxy analogs of amino acids

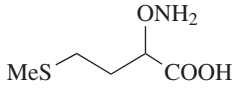
The analogs of serine, cysteine, methionine and lysine (**145, 146, 147** and **148**), respectively, were scarcely reported in the literature. One group in particular, that of Kisfaludy and coworkers[34, 111, 122], had reported their syntheses and some of their properties[33, 36]. Using the natural L-amino acids resulted in α-aminooxy acids with D-configuration. The analog of methionine (**147**) was also synthesized in the L-configuration. The purpose of the synthesis of these aminooxy acids was for testing their tubeculostatic activity. The patent[34, 122] includes the synthesis of numerous derivatives, including various amide derivatives. The *O*-benzyl and *S*-benzyl derivatives of **145** and **146**, respectively, were investigated as well.



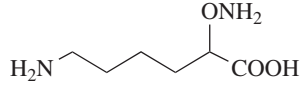
(**145**)



(**146**)



(**147**)

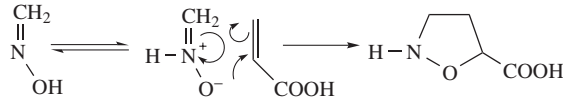


(**148**)

11. Cyclic derivatives of α-aminooxy acids

1,2-Isoxazolidine-5-carboxylic acid (**149**) is a cyclized α-aminooxy acid and could be regarded as an analog of proline. The synthesis of **149** was carried out by Hjeds and coworkers[150] by the 1,3-cycloaddition of formaldoxime to methyl acrylate (Scheme 32). This cyclic aminooxy acid was the subject of a number of investigations concerning the structure–activity relationships of selective GABA uptake inhibitors[151], in rat brain membrane[152] and brain cortex slices[153, 154].

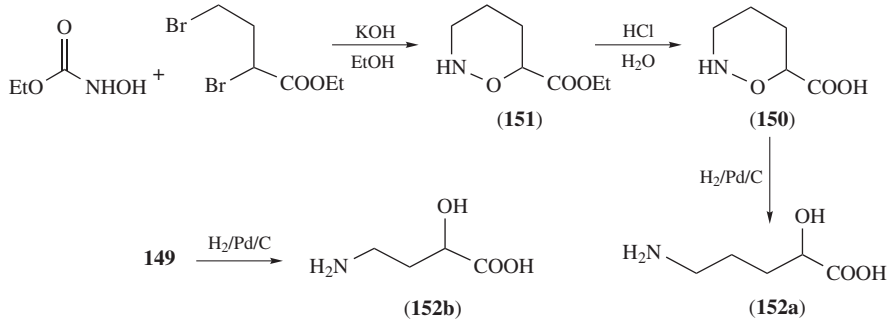
1,2-Oxazinan-6-carboxylic acid (**150**) was subject to the same bioactivity studies[151, 152, 155]. An elegant synthesis was described by Falch and coworkers[153] in 1986



(**149**)

SCHEME 32

(Scheme 33). The synthesis was carried out by the reaction of *N*-hydroxyurethane with ethyl 2,5-dibromobutyrate yielding the cyclized ester **151**, which upon hydrolysis yielded 1,2-oxazinane-6-carboxylic acid (**150**). Fission of the N−O bond was used to prepare α-hydroxy-δ-aminovaleric acid (**152a**) by hydrogenolysis. This hydrogenolysis can be considered as a proof for the regioselectivity in the production of **150**. The cleavage of the N−O bond in the five-membered ring in **149** to yield α-hydroxy-γ-aminobutyric acid (**152b**) was reported[154b] as well.



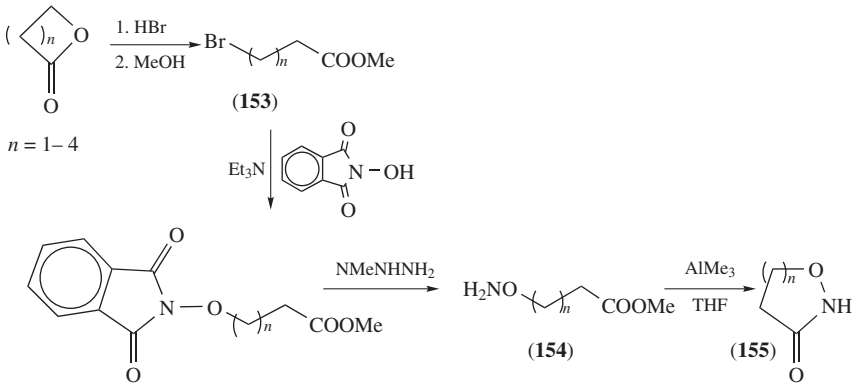
SCHEME 33

C. ω-Aminooxy Acids

Wolfe and coworkers[156] reported in 2003 the preparation of four ω-aminooxy acids C_3 to C_6, starting from the corresponding lactones (Scheme 34). Opening the lactones was carried by HBr and esterification by MeOH. The formed bromo esters (**153**) were reacted with *N*-hydroxyphthalimide followed by deprotection with methylhydrazine. The cyclization of these ω-aminooxy esters (**154**) to the cyclic aminooxy lactams (**155**) was performed by $AlMe_3$ in THF. Syntheses and properties of these ω-aminooxy acids are discussed in the following sections.

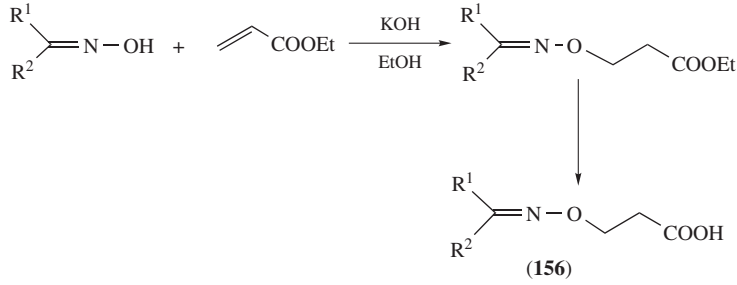
1. 3-Aminooxypropionic acid

This acid is often called in the literature 3- or β-aminooxypropoinic acid. While studying the structure of the antibiotic drug cycloserine (**3**), Hidy and his coworkers[3b] reported in 1955 the synthesis of 3-aminooxypropionoic acid and its cyclization product 5-isoxazolidinone. Gilon, Knobler and Sheradsky[13] reported in 1967 the production of 3-aminooxypropionic acid by ring cleavage of propiolactone with benzophenone oxime as shown above (Section I.A.6).



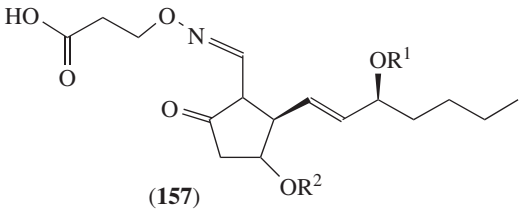
SCHEME 34

In 1981, Sugii and coworkers[157] reported the isolation of the cyclic product 5-isoxazolidinone (**155**, $n = 1$) from jack bean (*Canavalia ensiformis*) seedlings. This was the first time that this compound was found in nature. Its structure was proved by hydrolysis and comparison with the synthetic product. In 1990, Macchia and coworkers[158] synthesized numerous oxime derivatives (**156**) of 3-aminooxypropionic acid and tested their anti-inflammatory activity. The synthesis was performed by a nucleophilic addition of oximes to ethyl acrylate in the presence of KOH (Scheme 35). The pharmacological data showed that most of these oxime derivatives exhibit a significant anti-inflammatory activity. Structural and theoretical studies were carried out in order to compare their conformation and the molecular reactivity with arylacetic acid derivatives. Anti-inflammatory activity was recently also tested by Szabo and coworkers[102].

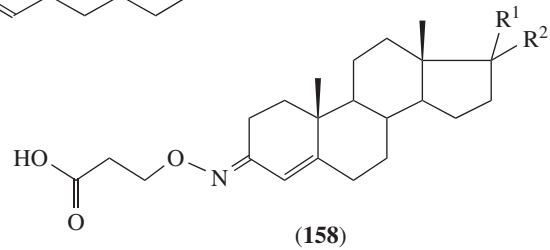


SCHEME 35

Buzzetti and coworkers[159] prepared 3-aminooxypropionic acid by a similar route, using ethyl acrylate as the starting material. They used it to produce prostaglandin analogs with the general formula **157**. Pouzar and Cerny[160] prepared a number of oxime derivatives of steroids of 3-aminooxypropionic acids with the general formulae **158**. More derivatives of 3-aminooxypropionic acid are included in a number of patents. An interesting list is claimed by Doll and Lalwani[161] in an international patent.



(**157**)

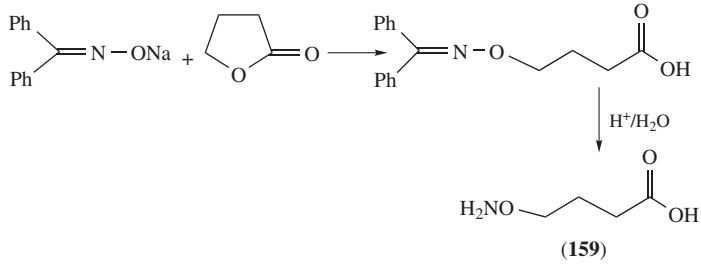


(**158**)

3-Aminooxypropionic acid, like most aminooxy acids, forms complexes with enzymes and co-enzymes and thus affects a number of bioactivities. Delbaere and coworkers[162] investigated the complex formed between this acid and the enzyme aspartate aminotranferase. The inhibition of ethylene production in plants was reported by Amrhein and Werker[59] in 1979. Na Phuket and coworkers[163] prepared this acid, among other products which are related to canaline, by the method described by Schumann and coworkers[8b], for their investigation as antitumor agents. Worthen and coworkers used 3-aminooxypropionic acid in the investigation of the structure–activity relations of L-canaline-mediated inhibition of porcine alanine aminotransferase[164].

2. 4-Aminooxybutyric acid

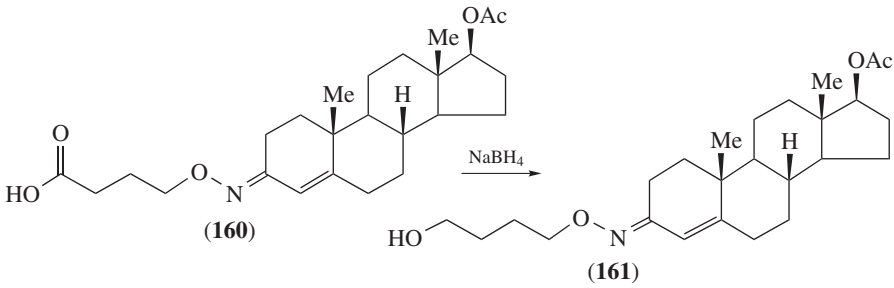
Gilon, Knobler and Sheradsky[13] reported in 1967 the production of 4-aminooxybutyric acid (**159**) by ring cleavage of γ-buryrolactone with benzophenone oxime sodium salt as shown in Scheme 36. Amagasa and coworkers[144] prepared this acid by the condensation of acetoxime with 4-bromobutyric acid in 1991.



(**159**)

SCHEME 36

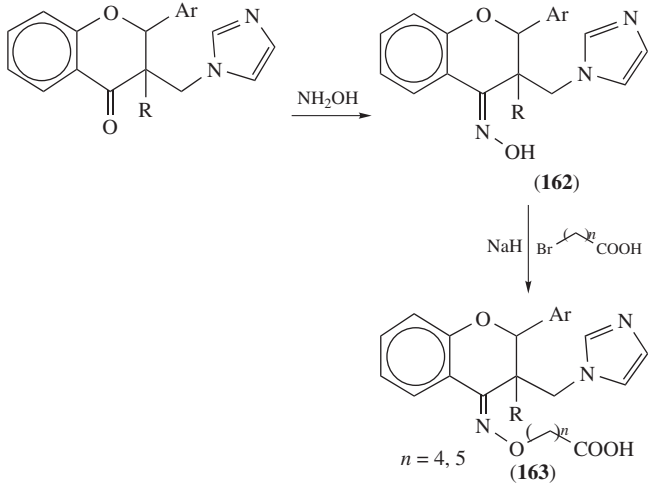
Slavikova and coworkers[165] and also Pouzar and coworkers[166] prepared 4-aminooxybutyric steroid derivatives. The derivative **160** could be reduced to the hydroxy derivative **161** by sodium borohydride.



4-Aminooxybutyric acid is considered as a de-amino canaline and was investigated as an inhibitor of enzymes that involve pyridoxal phosphate as a co-enzyme. Worthen and coworkers[164] used 4-aminooxybutyric acid in their investigation of the structure–activity relations of L-canaline-mediated inhibition of porcine alanine aminotransferase.

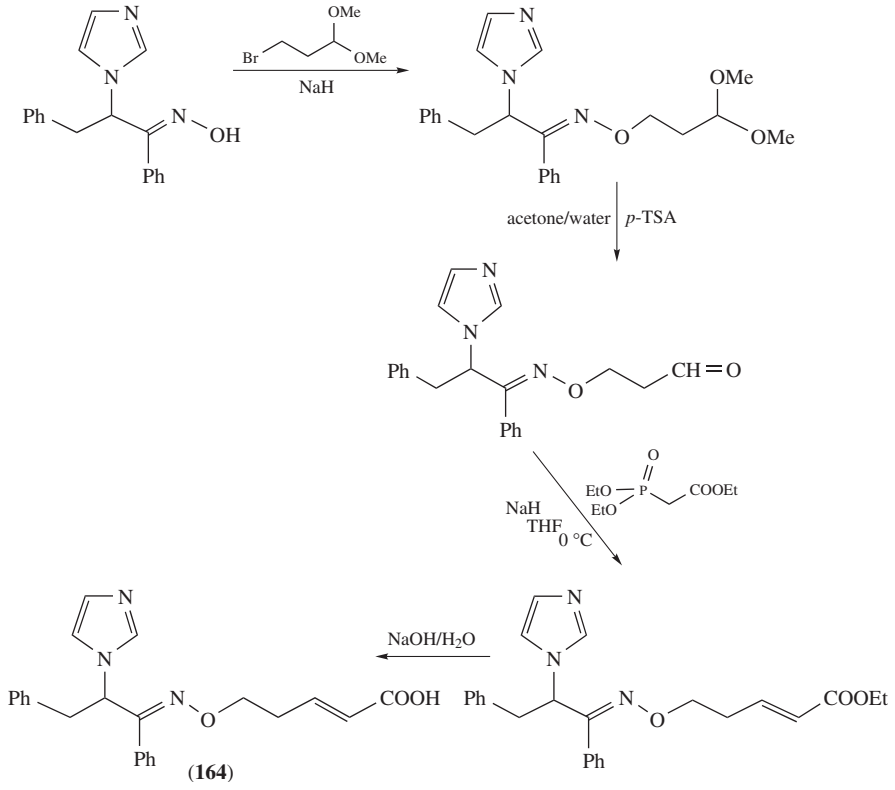
3. Long-chain ω-aminooxy acids (C_5–C_7)

The straightforward synthesis from the corresponding lactones (up to C_6), by ring cleavage with oximes, was described in 1967 by Gilon, Knobler and Sheradsky[13]; however, their use was reported only from the late 1980s. The neurotoxic activity related to GABA-T inhibition was studied by Gammon and coworkers[167] on insects. Cozzi and coworkers[168] prepared the 5-aminooxyvaleric acid and 6-aminooxycaproic acid oxime derivatives of chromans for testing as thromboxane A2 antagonists. They prepared the ω-aminooxy acids by using the *N*-hydroxyphthalimide method (Section I.A.3). An alternative way for the preparation of these derivatives was by preparing the oxime of the chromanone derivative (**162**) followed by substitution with a bromo ester as shown in Scheme 37. A series of analogs of **163** was tested as thromboxan A2 antagonists.



SCHEME 37

The same group[169] reported in 1994 an interesting modification for the preparation of imidazolyl derivatives of the unsaturated 5-aminooxy-2-pentenoic acid (**164**) (Scheme 38). A series of analogs of **164** was studied as thromboxane-synthase inhibitors.

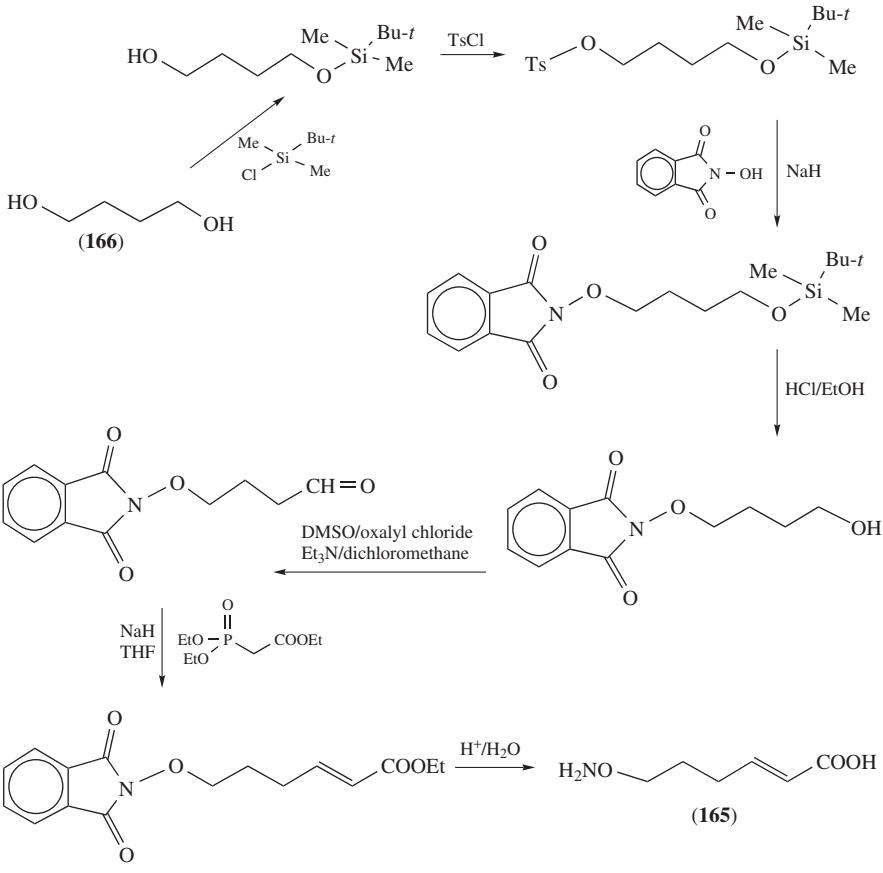


SCHEME 38

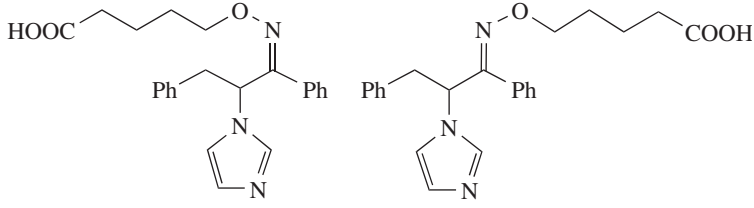
6-Aminooxy-2-hexenoic acid (**165**) was synthesized by Cozzi and coworkers[169] by a different and new approach (Scheme 39) from 1,4-butanediol (**166**).

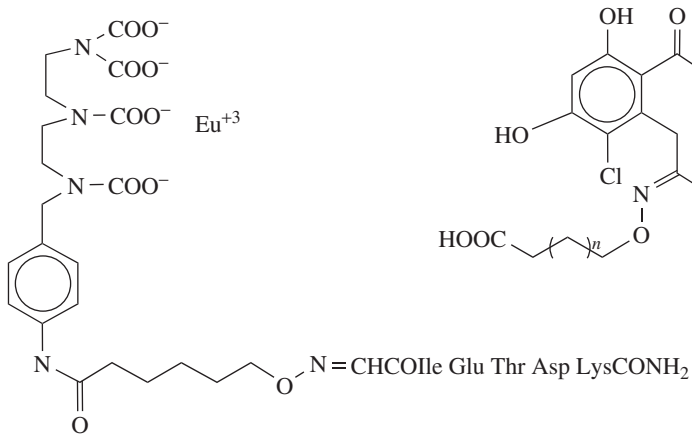
5-Aminooxyvaleric acid was also used in the enantiospecific synthesis of 2-imidazolyl-1,3-diphenylpropane derivatives[170] which are condensed with 5-aminooxyvaleric acids to produce *E* and *Z* isomeric derivatives (**167** and **168**).

Peuralahti and coworkers[171] synthesized in 2002 6-aminooxycaproic acid by the *N*-hydroxyphthalimide method and attached it to a lanthanide chelating agent for providing a linkage to biomolecules. Structure **169** is an example in which they demonstrated the chelation of europium ion with an oligopeptide.


HO
Me
Si
Bu-t
Me
O
TsCl
Ts
O
Me
Si
Bu-t
Me
O
Me
Si
Bu-t
Cl
Me
HO
OH
(166)
O
N – OH
O
NaH
O
N
O
O
Me
Si
Bu-t
Me
O
HCl/EtOH
O
N
O
CH = O
O
DMSO/oxalyl chloride
Et3N/dichloromethane
O
N
O
OH
O
NaH
THF
O
EtO – P
EtO
COOEt
O
N
O
COOEt
O
H+/H2O
H2NO
COOH
(165)

SCHEME 39


HOOC
O
N
Ph
Ph
N
N
(167)
N
O
COOH
Ph
Ph
N
N
(168)



(**169**)

(**170**), $n = 2$

(**171**), $n = 2$

Agatsuma and coworkers[172] synthesized in 2002 both 5-aminooxyvaleric acid and 7-aminooxyheptanoic acid, by the *N*-hydroxyphthalimide method. Their reaction products with radicicol (**170** and **171**) were tested as antitumor agents.

III. α-AMINO-ω-AMINOOXY ACIDS

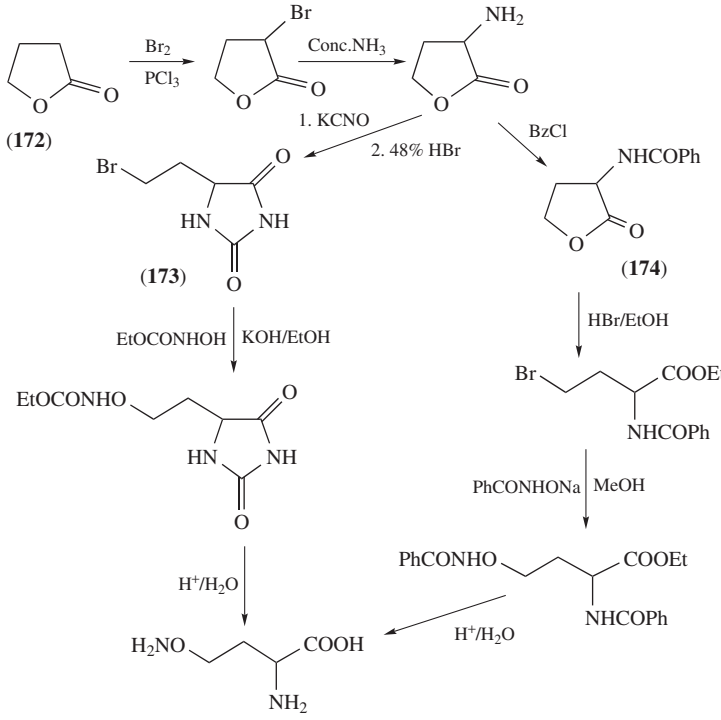
A. Canaline (α-Amino-γ-aminooxybutyric Acid)

There is a short review[173] by Rosenthal with 40 references that summarizes the biochemistry and toxicology of canaline. The present section includes some of the important information which is also included in that 'minireview', and additional information which is important to the chemist reader.

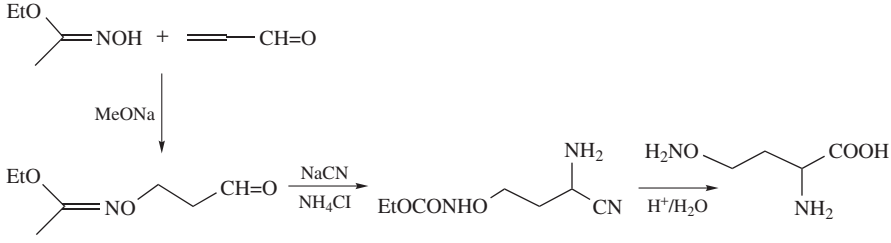
1. Isolation and preparation of canaline

L-Canaline (**2**) was first discovered[2] by Kitagawa and Yamada in 1933 by the degradation of L-canavanine (**1**) by the enzyme arginase isolated from liver. In 1936, Kitagawa[7b] reported the synthesis of canaline from α-*N*-benzoyl-γ-iodobutyric acid by condensation with the salt of benzohydroxamic acid as described in Section I.B.1. In 1967, Miersch[174a] reported the detection and isolation of L-canaline in seeds of *Canavalia ensiformis* (Jack beans), the same plant that was investigated earlier by Kitagawa and coworkers. In 1968, Inatomi and coworkers[174b] reported the isolation of L-canaline from unripe seeds of another plant, e.g. *Astragalus sinicus*. The extraction of L-canavanine from Jack beans and its enzymatic degradation was repeated in 1971 by Hunt and Thompson[175] and in 1973 by Rosenthal[176]. The latter report included a colorimetric quantitative determination of canaline, ignoring the earlier report of Knobler and Weiss[26]. The synthesis of DL-canaline, starting with γ-butyrolactone (**172**), was described by Nyberg and Christensen[177] in 1957, via the intermediate hydantoin (**173**), and by Knobler and Frankel[8a] in 1958, via the benzamido intermediate (**174**) (Scheme 40).

Karpeiskii and coworkers[178] described in 1962 the synthesis of DL-canaline, starting from acrolein, which was reacted with *N*-hydroxyurethane and followed by the Strecker procedure (Scheme 41). Ring opening of the benzamido lactone (**174**) with oximes by



SCHEME 40

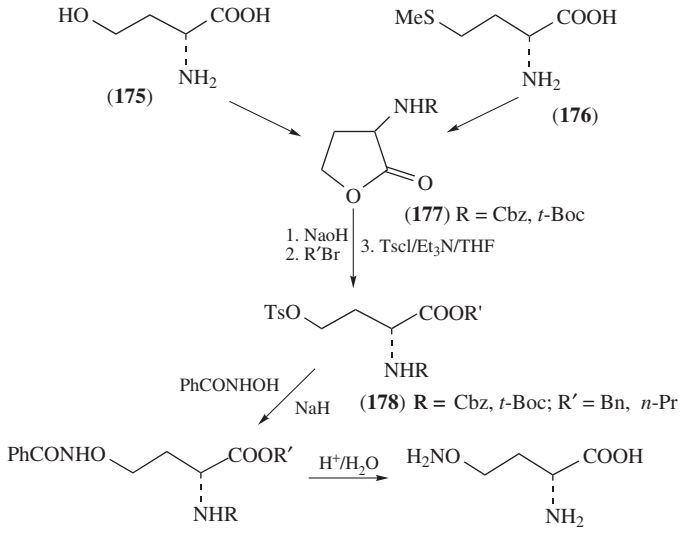


SCHEME 41

Gilon, Knobler and Sheradsky[13] provided a shorter route to DL-canaline. Korpela and coworkers[179] carried out a comparison of the last three methods for the preparation of DL-canaline and reported in 1977 that the best way to prepare it was by the method described by Frankel and Knobler. The other two methods gave either a poor yield or were completely unsuccessful.

L-Canaline was synthesized by Ozinskas and Rosenthal[11] by starting with the optically active acids, either L-homoserine (**175**) or L-methionine (**176**). Both **175** and **176** were converted to α-N-protected lactone (**177**), then converted to the γ-tosyl derivative esters

(**178**). Condensation with benzohydroxamic acid and subsequent hydrolysis led to the optically active L-canaline (Scheme 42).



SCHEME 42

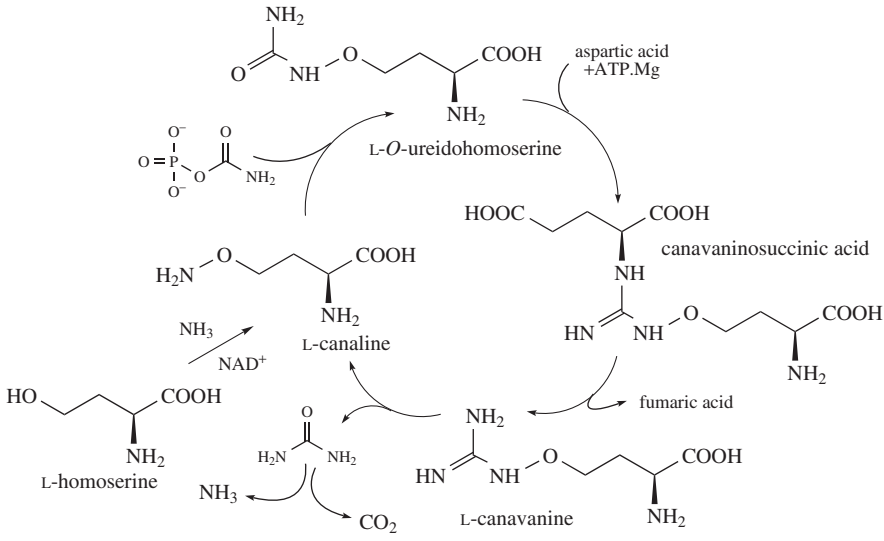
Labeled L-canaline was synthesized by Rosenthal and Berge[180] by a slight modification of the earlier procedure (Scheme 42) from ^{14}C-labeled L-homoserine. The labeled product was subjected to a metabolism investigation in *Canavalia ensiformis* plant.

Another important way of obtaining L-canaline is the *in vitro* production by the enzyme arginase from L-canavanine, which is available in large quantities from Jack beans and other leguminous plants. Such a procedure was described by Williamson and Archard[181] who reported the preparation and chromatographic purification of L-canaline. Purified L-canaline could be kept as the free acid, whereas it is otherwise kept as a picrate, flavianate or nitranilate[182].

The chemical degradation of canavanine to canaline needs harsh conditions. Rinderknecht prepared DL-canaline by 48 h reflux of DL-canavanine in 25% BaOH solution[183].

2. Canaline–urea cycle and specific enzymes

The best-known reaction of canaline metabolism is its arginase-catalyzed formation from canavanine. This reaction contributes significantly to the metabolism of canavanine-containing plants since the formation of canaline from canavanine is the principal pathway for mobilizing canavanine's nitrogen. There is a comprehensive minireview[184a] by Rosenthal that covers the biochemistry of L-canaline in higher plants up to the year 1978. As a result of a long and profound study, Rosenthal proposed[184b] in 1982 using labeled compounds, the scheme of the canaline–urea cycle (Scheme 43). The scheme is analogous to the known ornithine–urea cycle and the question is whether the various transformations are catalyzed by the same enzymes that lead to the synthesis of arginine, ornithine and argininosuccinic acid as was assumed earlier[185].

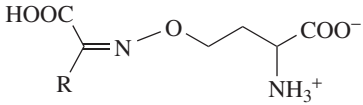


SCHEME 43. The canavanine-urea cycle

Natelson and coworkers[186] showed that the metabolic cycle of guanidino compounds in human liver involves the enzyme canaline-carbamoyl-aminotransferase, and proposed a similar cycle, e.g. the guanidino cycle. In their discussion there are arguments that suggest common enzymes for the formation of canaline and ornithine. Bolkenius and coworkers[187] showed in 1990 that DL-canaline deactivates ornithine-aminotransferase in mice brain. In 2001, Gafan and coworkers[188] showed the inhibition of the same enzyme by canaline in malarial bacteria. L-Canaline was found to interact with the enzyme ornithine-aminotransferase in tobacco hornworm, *Munduca sexta*[189]. In 2001, Lee and coworkers[190] described the characterization of a cDNA encoding OCT which prefers canaline to ornithine as a substrate.

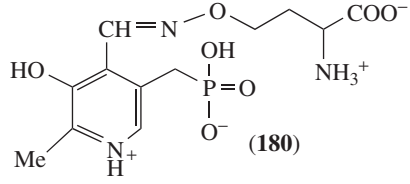
In 1992, Rosenthal discovered[191] a new NADH-dependent enzyme, canaline reductase, in *Canavalia ensiformis* that cleaves the N−O bond in L-canaline yielding L-homoserine.

Worthen and coworkers[164] reported an interesting study of the structure–activity relationship in L-canaline-mediated inhibition of porcine alanine-aminotransferase. Cooper[192] showed that L-canaline is oxidized by the enzyme amino acid oxidase. He also prepared a series of oximes (**179**) of L-canaline and α-keto acids.



(**179**)

R = H, Me, Et, *i*-Pr, *i*-Bu, CH_2Ph, CH_2CH_2COOH



(**180**)

3. The toxic activity of canaline

The role of canaline in the canaline–urea cycle was not found to be the sole reason for the toxicity of this acid. L-Canaline as well as DL-canaline inhibited a substantial number of enzymes that are not involved in the ornithine–urea cycle. Beeler and Churchich[193], who studied the reactivity of the pyridoxal phosphate group of the enzyme cystathionase, found that it is inactivated by the formation of a stable oxime derivative with canaline (**180**). The same derivative was observed by Rosenthal and Dahlman[189]. In a paper entitled *A mechanism of* L-*canaline toxicity*, Rosenthal[194] reported the preparation and characterization of this oxime derivative as well as its biochemistry in *Lemnu minor*, an aquatic eukaryotic organism, which provided a highly sensitive and effective means for evaluating the relative toxicity of various non-protein amino acids.

This theory gets further support by the study of the enzyme hydroxymethyltransferase by Baskaran and coworkers[195]. They found that canaline as well as other aminooxy acids react with pyridoxal phosphate in the same manner.

It was shown that many leguminous plants and seeds contain L-canaline in quantities that kill various insects[196a]. However, there are some species that survive by a process of detoxification. In 1978, Rosenthal and coworkers[196b] reported that these insects have a mechanism for the reduction of canaline to ammonia and L-homoserine. Such an enzyme was found later in the plant *Canavalia ensiformis*[191]. In 1989, Rosenthal and coworkers[197] published a paper entitled *A novel mechanism for detoxification of* L-*canaline* in which they showed that the toxicity of L-canaline occurs by the formation of the stable oxime derivative with glyoxalic acid (**179**, R = H).

4. Other biological activities of canaline

A comparison of the antitumor activity of L-canaline and some of its analogs was carried out by Na Phuket and coworkers[163] in 1999. An interesting finding was that the enantiomer D-canaline had the same effect as the natural L-canaline.

Canaline was assayed by Berger[198] in the year 2000 in combination with the ornithine decarboxylase inhibitor difluoromethylornithine, and the two drugs were found to be synergistic in anti-malarial activity. They assumed that synergism arises from the fact that they both inhibit the same enzymes that have to do with ornithine metabolism.

Williamson and Archard[199] reported the effect of canaline in *Vaccinia* virus replication. Their suggestion is that those effects are due to the fact that canaline is a pyridoxal phosphate agonist. Archard and Williamson[200] compared the mode of action of canaline to that of canavanine, and their conclusion was that canavanine interferes with the replication of these viruses as an analog of arginine and thus affects the arginine metabolism, whereas canaline inhibits the activity of pyridoxal phosphate. This fact was demonstrated by showing the reverse effect upon addition of pyridoxal phosphate.

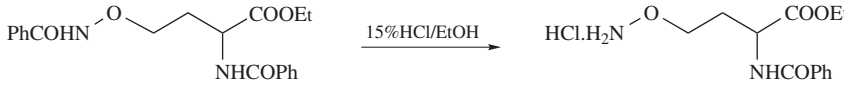
Bocheva and coworkers[201] reported in 2005 that L-canaline, unlike L-canavanine, increased the pain and seizures induced by pentylenetetrazole in rats.

L-Canaline was found to be an effective inhibitor of ethylene production in plants. The biochemical process and the uses of inhibiting ethylene production were discussed above (Section II.A.4).

5. Chemical properties of canaline and transformation to cyclocanaline (homocycloserine)

a. Chemical properties. The difference in basic properties between the α-amino group and the γ-aminooxy group in canaline by a factor of 10^4 was discussed above

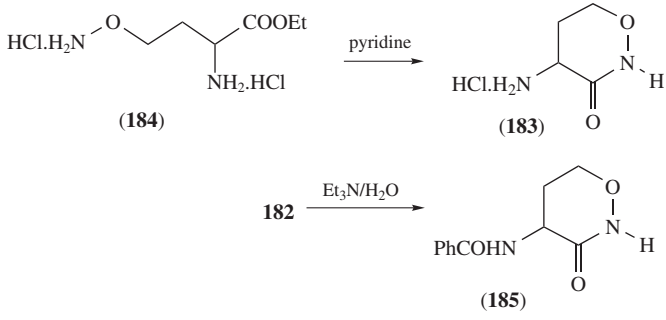
(Section I.B.1). The special chemical properties of canaline arise from this fact and the fact that the aminooxy group is a 'super nucleophile'. The weak basicity of the aminooxy group is expressed by its facile condensation with aldehydes and ketones which may take place in acidic conditions. There will be always some dissociation of the aminooxy salt that will permit the electrophilic carbonyl group to attack and, in addition, the liberated HCl catalyzes the condensation. The oximes that are formed can survive a prolonged reflux in ethanolic HCl. On the other hand, it was found[19] that an acyl group on the aminooxy group is easily removed with ethanolic HCl, thus a selective deprotection by an acyl group can spare the acyl group on the α-amino group. Therefore, ethyl dibenzoylcanalinate (**181**) could be selectively transformed to ethyl α-*N*-benzoylcanalinate hydrochloride (**182**) by reflux in 15% ethanolic HCl for 4 h without affecting the α-*N*-benzoyl group[202] (Scheme 44). Total deprotection needed a reflux of 4 h in aqueous 6N HCl. In the presence of a weak base, DL-canaline could be selectively alkylated at the γ-aminooxy group.



(**181**) (**182**)

SCHEME 44

b. Preparation and properties of cyclocanaline (homocycloserine). After the discovery of the broad-spectrum antibiotic compound cycloserine (**3**) in 1955, it was obvious that the next analog, which is the cyclized product of canaline (**2**), should raise the interest of chemists and especially medicinal chemists. In 1962, Khomutov and coworkers[203] reported the synthesis of the oxalate and picrate salts of cyclocanaline. They found that indeed cyclocanaline inhibits the enzyme glutamate-aspartate transaminase and has a definite activity against tuberculosis bacilli. An extensive study of the ways of cyclization of DL-canaline and its derivatives was published in 1969 by our group[204]. After exploring a number of procedures for the synthesis of DL-cyclocanaline (**183**), it was concluded that the best way was the facile synthesis starting with ethyl DL-canalinate dihydrochloride (**184**). Using a weak base like pyridine which only neutralizes the hydrochloride of the aminooxy group enabled the spontaneous cyclization at room temperature (Scheme 45). N^{α}-Benzoylcyclocanaline (**185**) could easily be prepared by treatment of the ester (**182**)

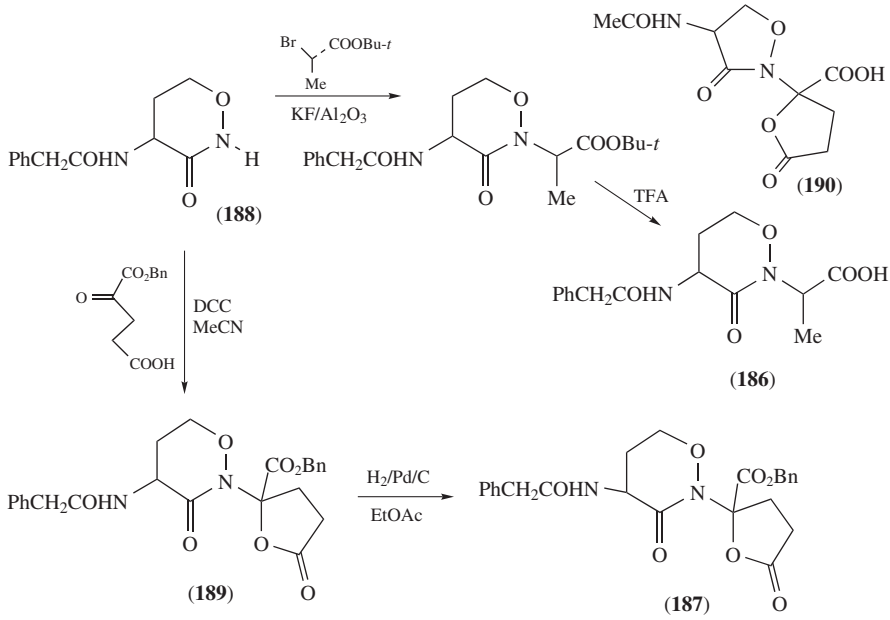


(**184**) (**183**) (**185**)

SCHEME 45

with aqueous Et_3N. This procedure was adopted in 1999 by Cordi and coworkers[205] and in 2003 by Wolfe and coworkers[156] in their pursuit of bioactive and antibiotic compounds.

Wolfe and coworkers synthesized some derivatives of cyclocanaline like **186** and **187** via intermediates **188** and **189**, respectively, as potential penicillin surrogates, since a similar compound lactivicin (**190**) is used as an antibiotic that replaces penicillin (Scheme 46). They also reported the single-crystal X-ray diffraction analysis of *N*-phenacetyl-DL-cyclocanaline (**188**).

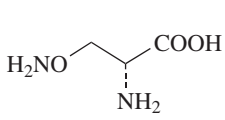


SCHEME 46

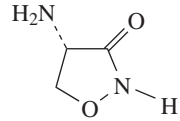
B. Cycloserine and 2-Amino-3-aminooxypropionic Acid

1. Biological properties of cycloserine

D-Cycloserine (**3**), which is the cyclic product of D-2-amino-3-aminooxypropionic acid, more often named β-aminooxy-D-alanine (**191**), was isolated in 1955 from several *Streptomyces* species, is a broad spectrum antibiotic agent and possesses versatile biological activities. The major importance of D-cycloserine is its remarkable tuberculostatic action. The antibacterial activity has been correlated with D-alanine metabolism in D-alanine ligase and alanine racemase[206, 207].



(**191**)



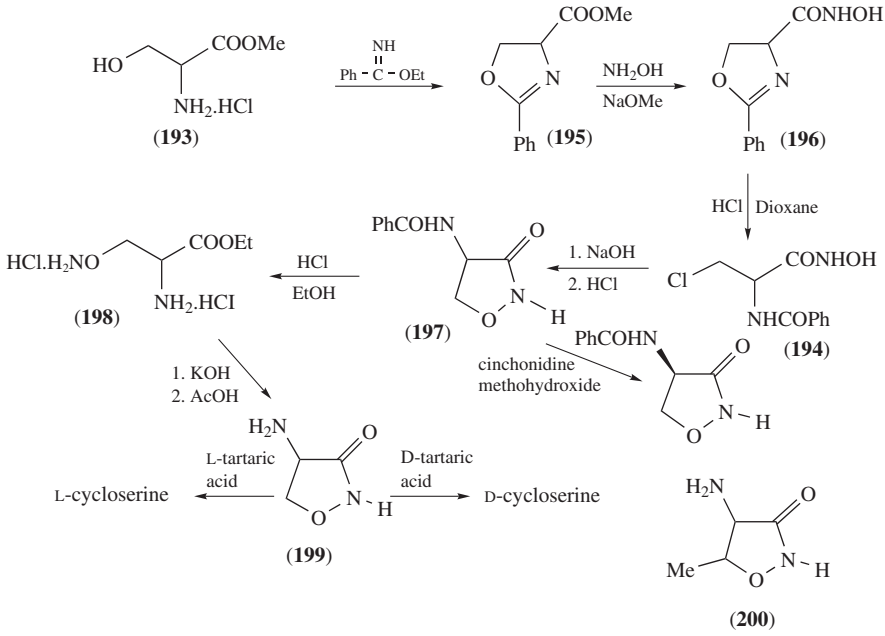
(**192**)

It was also found that D-cycloserine (**3**) is a *N*-methyl-D-aspartate receptor agonist and thus useful for anxiety disorders therapy. Grillon has recently[208] published a review about the use of D-cycloserine for anxiety therapy and fear extinction. Several studies showed a beneficial effect of D-cycloserine on negative symptoms in schizophrenia[209] and facilitates learning abilities[210, 211]. Numerous articles and reviews about the various activities were published since it was discovered in 1955, but they are beyond the scope of this chapter. In 1984, Shoji and coworkers[212] reported the isolation of the enantiomer L-cycloserine (**192**) from *Erwinia uredovora*, which showed antibiotic activity.

2. Synthesis of cycloserine

Hidy and coworkers[3b] proved the structure of D-cycloserine by the synthesis of DL-cycloserine from DL-serine and comparison of the IR spectra and other properties. Simultaneously and independently, Stammer and coworkers[213] reported the synthesis of DL-cycloserine by a similar procedure followed by enantiomeric resolution. DL-Serine methyl ester hydrochloride (**193**) was converted to 3-chloro-2-benzamidopropiohydroxamic acid (**194**) via the azalactones **195** and **196**, which upon cyclization gave the benzoyl derivative (**197**) of DL-cycloserine (Scheme 47). Acid alcoholysis to the dihydrochloride ester of 2-amino-3-aminooxypropionic acid (**198**) followed by recyclization afforded DL-cycloserine (**199**). Enantiomeric separation of the intermediate (**197**) was carried out by cinchonidine methohydroxide and separation of the final product (**199**) by both D and L-tartaric acid as well (Scheme 47).

The same report includes the synthesis of L-cycloserine from L-serine methyl ester hydrochloride and the methyl derivative (**200**), starting from DL-threonine, using the same

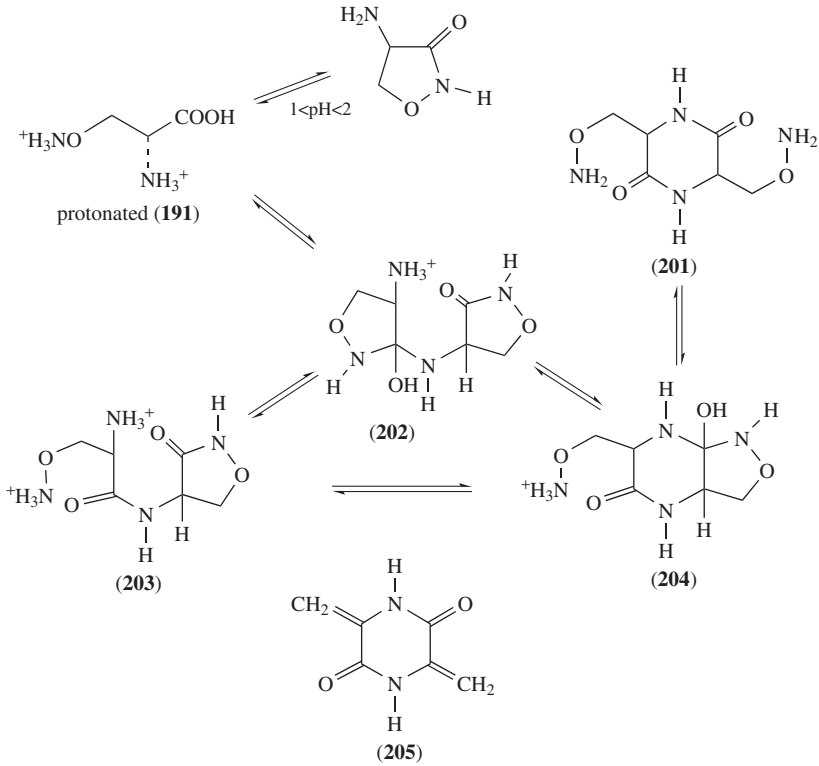


SCHEME 47

procedures that are shown in Scheme 47. Similar syntheses of the two enantiomers of cycloserine were published in the same year by Smrt and coworkers[214]. An improvement of optical resolution by tartaric acid was reported by Portelli and Soranzo[215] in 1962.

3. Reactions of cycloserine

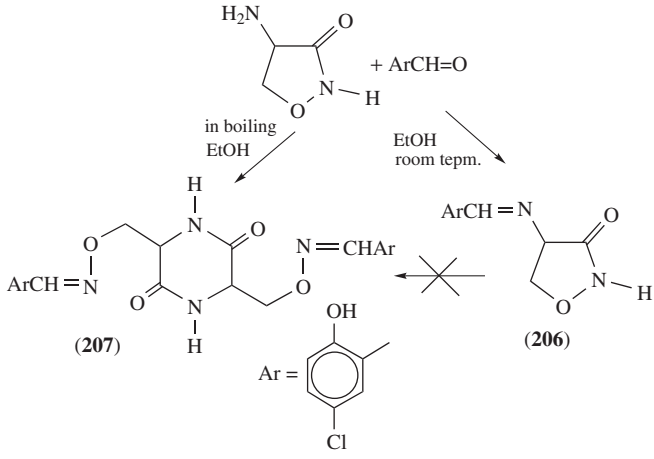
a. Spontaneous dimerization and hydrolysis of cycloserine. A pH-dependent dimerization of cycloserine was observed and studied by several groups[3b, 216, 217]. The equilibrium between cycloserine, the dimer diketopiperazine derivative (**201**) and the open-chain β-aminooxy-D-alanine (**191**) is shown in Scheme 48. Lassen and Stammer[216] carried out a kinetic investigation at several HCl concentrations and showed a rapid equilibrium in solutions of pH 1–2. Lassen and Stammer suggested the presence of intermediates (**202**–**204**). In basic media the diketopiperazine dimer (**201**) loses hydroxylamine molecules to produce the dimethylene derivative (**205**). Below pH 1, the reversible formation of β-aminooxy-D-alanine (**191**) was observed.



SCHEME 48

Lee and coworkers[217], who studied these equilibria by IR spectra in D_2O solutions, found substantial amounts of the diketopiperazine dimer (**201**) in neutral solutions. Therefore, they concluded that the non-ionized species of cycloserine are involved in these transformations.

b. The reaction of cycloserine with aldehydes. The antibiotic and other biological properties of cycloserine are attributed to its facile reaction with the co-enzyme pyridoxal phosphate. This prompted the study of its reaction with aldehydes. The question, which was asked, was whether the aldehyde forms a Schiff base with the amino group of cycloserine, or does it react with the aminooxy groups of the dimer (**201**). Stammer and coworkers[218–220] studied the reaction of aromatic aldehydes with D-cycloserine. Stammer[218] succeeded in showing that in certain conditions a Schiff base is formed by condensation with the amino group and avoiding the formation of the dimer. He showed that at room temperature the reaction between cycloserine and 5-chlorosalicylaldehyde yields the Schiff base **206**, which upon heating in ethanol was not converted to the dimer (**207**), while the latter dimer is obtained directly from cycloserine by heating in ethanol (Scheme 49).

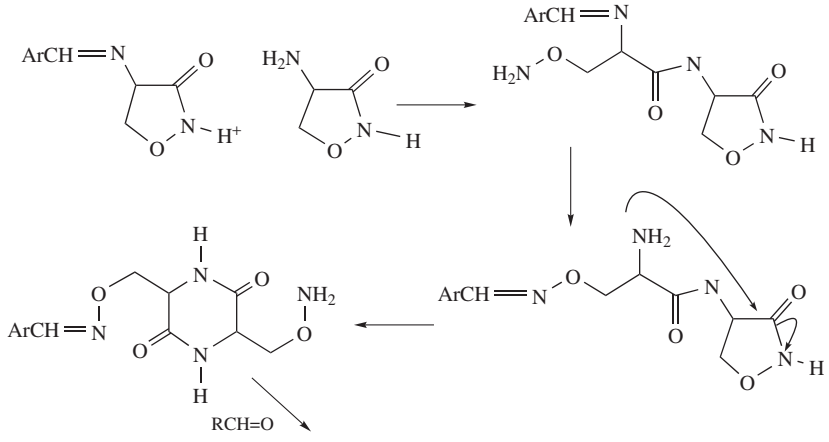


SCHEME 49

Stammer and McKinney[219] suggested a mechanism for the formation of the bis Schiff base dimer (**207**) which involves a ring opening of cycloserine by attack of the Schiff base (**206**), followed by rearrangement and ring transformation (Scheme 50). The stability of a Schiff base with 2-hydroxy-1-naphthaldehyde was discussed by Stammer and coworkers[220].

c. Alkylation of cycloserine. A study of amino group alkylation vs. N-ring alkylation was reported by Stammer and coworkers[220] and selective alkylation is described, using protecting groups.

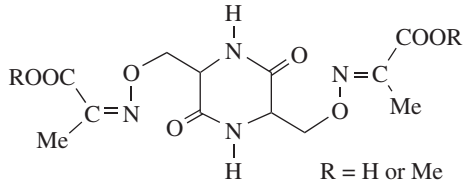
d. Reaction of cycloserine with α-ketoacids and esters. In order to explore the mechanism of inhibition of aminotransferase enzymes, Perez-Sala and coworkers studied the interaction of cycloserine with pyruvate and other biologically relevant α-ketoacids[221]. They have prepared the dimeric products (**208**) of pyruvic acid and methyl pyruvate. A study of the NMR and other spectral properties was reported as well. By following the depletion of pyruvic acid and other ketoacids, e.g. oxaloacetic acid and ketoglutaric acid,



(**207**)

SCHEME 50

by NMR in the presence of cycloserine, they have concluded that formation of a dimeric product like **208** is responsible for this depletion.

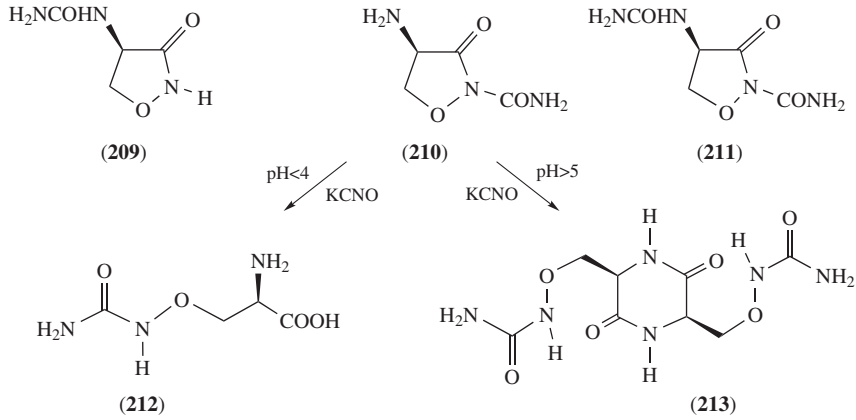


(**208**)

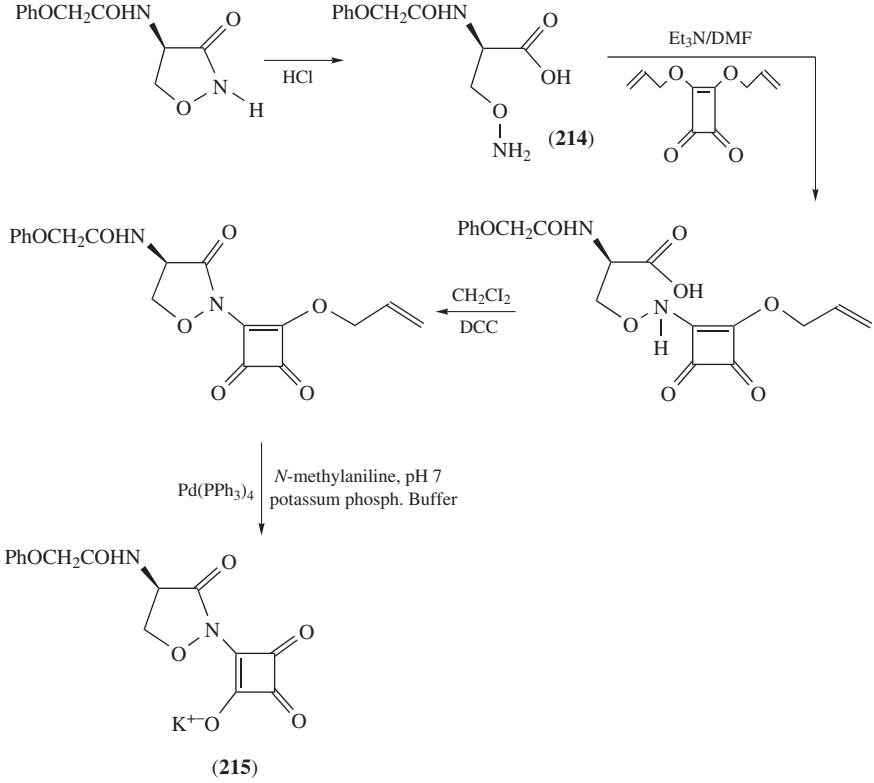
e. Cycloserine carbamates. The two mono carbamates **209** and **210** and the dicarbamate **211** were prepared by Weaver and coworkers[222] (Scheme 51). The mono derivatives were prepared by protection of one of the nitrogens by the carbobenzoxy group and reaction with KCNO. The *N*-carbamate **210** was unstable, at pH < 4 it was cleaved to D-β-ureidooxyalanine (**212**) and at pH > 5 it was converted to the dimer **213** (Scheme 51).

f. Synthesis of phenoxyacetyl(1-hydroxycyclobutene-2,3-dione-1-yl) derivative of cycloserine. The synthesis was carried out by Ueda and coworkers[223] in 1991, on the open-chain phenoxyacetyl derivative of β-aminooxyalanine (**214**) and re-closure by DCC in methylene chloride to the potential antibiotic material phenoxyacetyl (1-hydroxycyclobutene-2,3-dione-1-yl) derivative of cycloserine (**215**) (Scheme 52).

g. Cleavage of D-cycloserine to β-aminooxy-D-alanine. Stammer[224] reported in 1962 the hydrolysis of D-cycloserine (Scheme 53). Methanolysis in methanolic HCl gave methyl β-aminooxy-D-alaninate dihydrochloride (**216**). Hydrolysis in aqueous HCl gave the

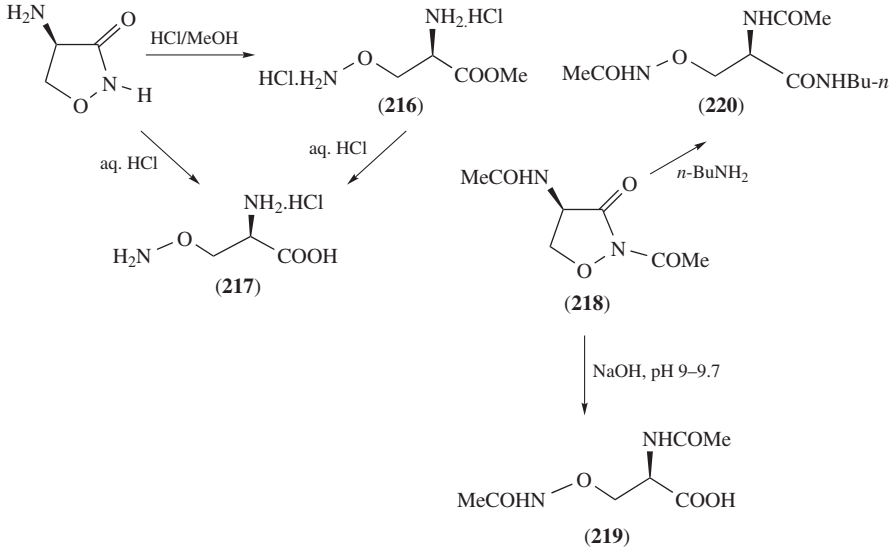


SCHEME 51



SCHEME 52

monohydrochloride of β-aminooxy-D-alanine (**217**) (Scheme 53). Korpela and Maekelae [225] in 1980 used both aqueous HCl and a strong cation exchange agent for the hydrolysis of D-cycloserine to β-aminooxy-D-alanine.



SCHEME 53

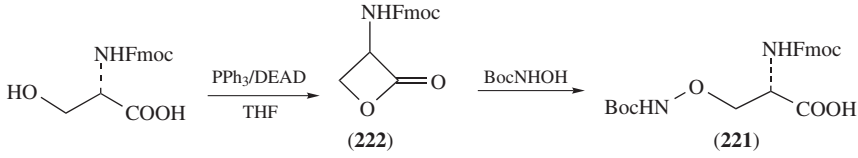
Howard and coworkers[226] reported the hydrolysis of diacetyl D-cycloserine (**218**) to the diacetyl derivative of β-aminooxy-D-alanine (**219**) upon addition of NaOH up to pH 9.7. The diacetyl derivative underwent a facile aminolysis upon adding cold *n*-butylamine to give the amide **220** (Scheme 53).

β-Aminooxy-D-alanine (2-amino-3-aminooxypropionic acid), which sometimes is referred to as '*O*-amino-D-serine', and its derivatives were tested for biological and biochemical activities. A condensation product with pyridoxal phosphate was isolated upon introduction of sheep liver serine-hydroxymethyltransferase[227]. Spetzler and Hoeg-Jensen prepared the N^{α}-Fmoc derivative of β-aminooxy-D-alanine by hydrolysis of Fmoc D-cycloserine[228].

C. Other α-Amino-ω-aminooxy Acids

1. β-Aminooxy-L-alanine

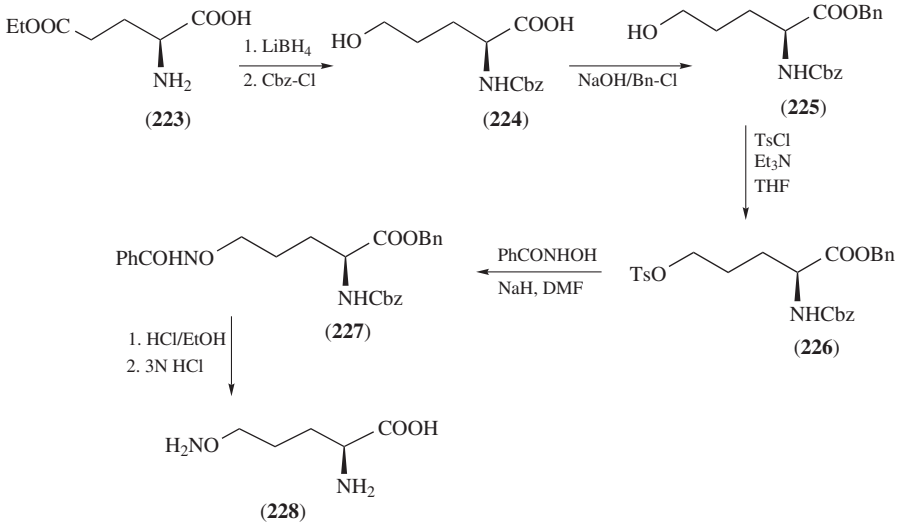
In 1999, Spetzler and Hoeg-Jensen[228] synthesized N^{α}-Fmoc N^{ω}-derivative of β-aminooxy-L-alanine (**221**) from available L-serine via the Fmoc serine β-lactone **222**, using *t*-butyloxycarbonylhydroxylamine (Scheme 54). The orthogonally protected β-aminooxy-L-alanine (**221**) that was formed in this reaction was utilized in solid-phase peptide synthesis.



SCHEME 54

2. L-2-Amino-5-aminooxyvaleric acid

In their study of the structure–activity of antitumor congeners of L-canaline, Rosenthal and coworkers[229] synthesized the canaline homolog L-2-amino-5-aminooxyvaleric acid starting from L-glutamic acid derivative (**223**) (Scheme 55). Reduction of the ester group was carried out by $LiBH_4$ and the amino group was protected by the carbobenzoxy group, giving **224**. After protection of the carboxyl group giving **225**, the hydroxyl group was converted to the tosyloxy group. The protected tosyl derivative (**226**) was condensed with benzohydroxamic acid after treatment with NaH. The resulting benzoylaminooxy derivative (**227**) was heated in 19% ethanolic solution and then hydrolyzed in aqueous HCl to produce L-2-amino-5-aminooxyvaleric acid (**228**).

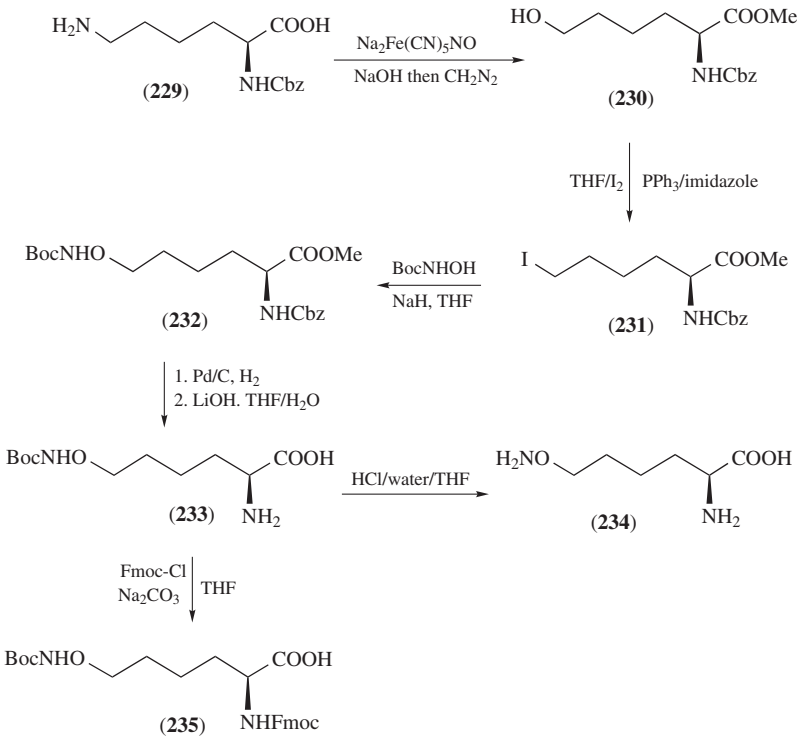


SCHEME 55

3. L-2-Amino-6-aminooxycaproic acid

In their pursuit of agents for site-specific immobilization of peptides, Adamczyk and Reddy[230] developed a synthesis for L-2-amino-6-aminooxycaproic acid (Scheme 56). The

starting material was the α-protected L-lysine derivative **229**, which upon heating with sodium nitroprusside followed by esterification with diazomethane resulted in fair yields of the 6-hydroxy methyl ester **230**. Substituting the hydroxyl group by iodine gave **231**, and reaction with *t*-butyloxycarbonylhydroxylamine afforded the doubly protected ester **232**. Deprotection to give **233** and hydrolysis led to the desired product L-2-amino-5-aminooxyvaleric acid (**234**). Changing the carbobenzoxy group to the Fmoc group afforded an orthogonally protected species (**235**) suitable for solid-phase peptide synthesis (Scheme 56).

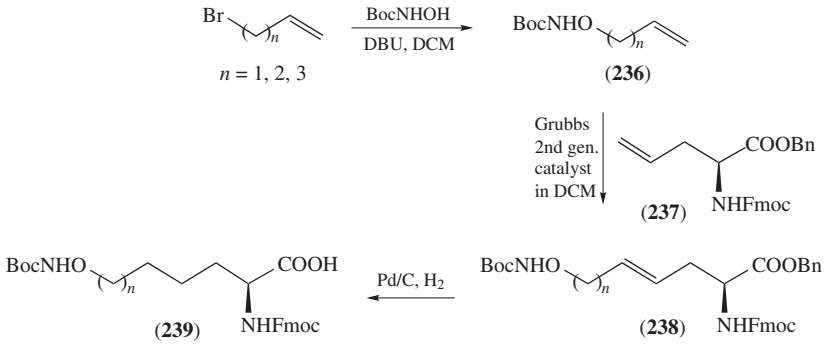


SCHEME 56

4. Long-chain α-amino-ω-aminooxy acids

Due to the increased need for peptide linkers and the extraordinary efficiency of the aminooxy group as a ligation function, Liu and coworkers[231] developed in 2008 an elegant and practical methodology for the synthesis of homologous series of side-chain-extended amino acids containing aminooxy functionality bearing orthogonal protection, suitable for Fmoc peptide synthesis. These reagents may be useful for the preparation of libraries containing fragments joined by peptide linkers. This procedure consists of using Grubbs 2nd generation catalyst ($(PCy_3)(Im(Mes)_2)Ru{=}CHPh$) that combines two unsaturated chains with the elimination of ethylene. The protected aminooxy ethylenic chain **236** is prepared by known methods and, brought to reaction with a protected optically active allyl glycine

237 (prepared by the procedure of Myers and coworkers[232]) in the presence of Grubbs 2nd generation catalyst, gave **238**. Hydrogenation in the presence of Pd/C brings about the saturation of the double bond and, removing the benzyl group to yield the orthogonally protected α-amino-ω-aminooxy acid (**239**), ready for solid-phase peptide synthesis. This way the C_6, C_7 and C_8 α-amino-ω-aminooxy acids derivatives were prepared (Scheme 57). In the same publication Liu and coworkers have reported improved procedures for derivatives of shorter α-amino-ω-aminooxy acids that were also discussed above, with carbon chains C_3-C_5.



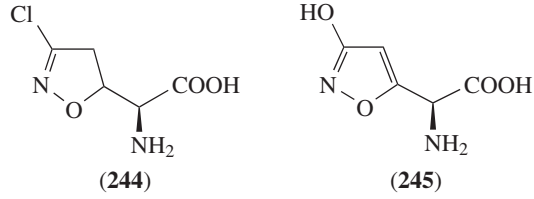
SCHEME 57

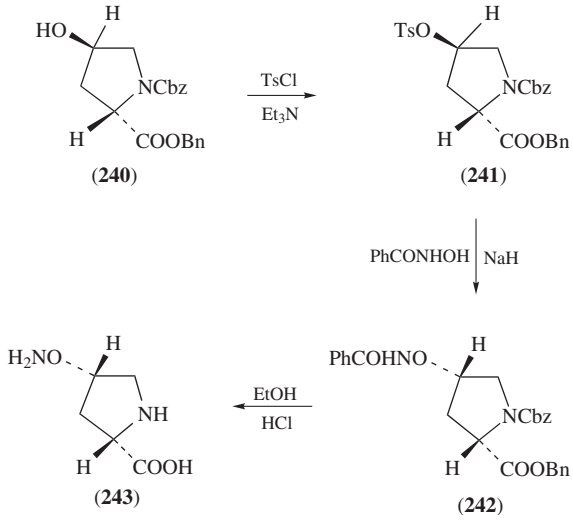
5. Cis-4-aminooxy-L-proline

Cis-4-aminooxy-L-proline was prepared by Na Phuket and coworkers[163] starting from the available natural L-proline. It was achieved by converting the 4-hydroxy group of the N-protected proline ester (**240**) to a tosyl derivative (**241**) and followed by condensation with benzohydroxamic acid, with conversion of configuration forming **242** as shown in Scheme 58. Deprotection and hydrolysis led to the desired *cis*-4-aminooxy-L-proline (**243**).

D. Isoxazolylamino Acids

This section reviews some of the non-proteinogenic α-amino acids that possess an isoxazole ring with C−ON bond like Acivicin (**244**), which is a potent antibiotic and antitumor agent, and Ibotenic acid (**245**), which is a non-selective NMDA agonist.





SCHEME 58

1. Acivicin

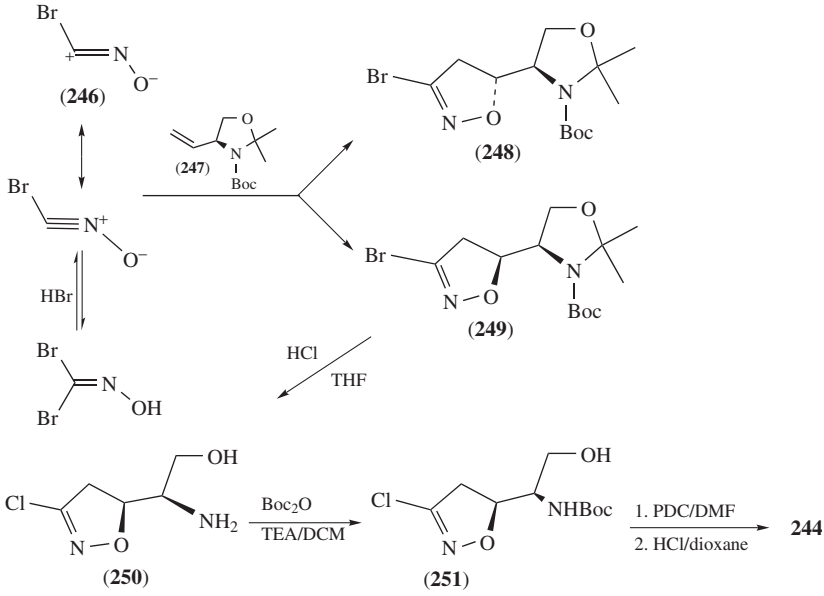
Acivicin was found by screening the fermentation broth of *Streptomyces sviceus* var. *sviceus* for antimetabolite activity. It was found to have *in vivo* antitumor activity. Its activity was antagonized by L-glutamine and by a combination of cytidine and guanosine. Acivicin was found to be an inhibitor of several glutamine-dependent amidotransferases, and of carbamoyl phosphate synthetase that has an important role in purine and pyrimidine metabolism. The biochemistry and chemotherapeutic activity were summarized in a number of reviews[233–235].

A number of methods were reported in the literature for the synthesis of **244**. In a very recent synthesis reported by Pinto and coworkers[236] in 2009, the 1,3-dipolar cycloaddition of the nitrile oxide **246** with *N*-protected (*S*-2,2-dimethyl-4-vinyloxazolidine (**247**) gave the two isomers, **248** and **249**. Replacement of the bromine by chlorine gave the intermediate **250**. Protection of the free amino group led to **251**. The oxidation of the hydroxymethyl group by pyridinium dichromate (PDC) followed by hydrolysis led to acivicin (**244**) in a good yield (Scheme 59).

This route is an improvement procedure of that described by Vyas and coworkers[237] in 1984. Baldwin and coworkers[238] reported in 1985, and Mzengeza and coworkers[239, 240] in 1987 and 1988, on similar procedures starting with N-protected vinylglycine rather than the N-and O-protected aminobutenol **247**.

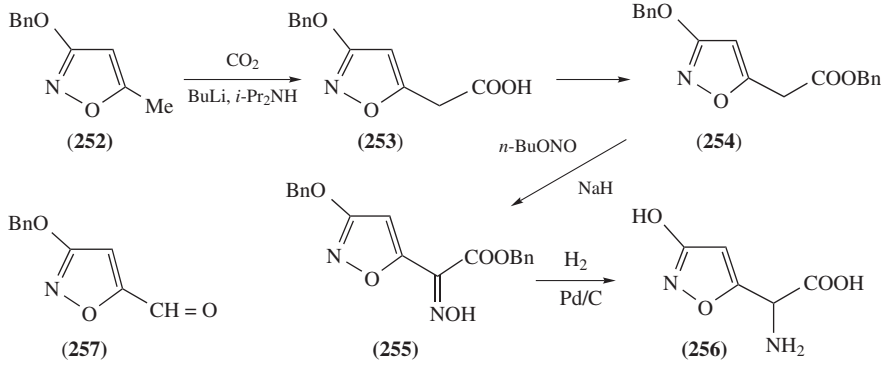
2. Ibotenic acid

Ibotenic acid is produced by the mushroom *Amanita muscaria* and it has a powerful neuroexcitatory effects which is mediated by *N*-methyl-D-aspartic acid (NMDA). Its neurologic activity was summarized in 1996 in the article by Krogsgaard-Larsen and coworkers[241] entitled *Design of excitatory amino acid receptor agonists, partial agonists and antagonists: Ibotenic acid as a key lead structure*. A synthesis of DL-ibotenic acid



SCHEME 59

was reported[242] by the same group in 1988, starting from 3-benzyloxy-5-methylisoxazole (**252**). The 3-benzyloxyisoxazolylacetic acid (**253**), which was obtained by the application of CO_2 and lithium diisopropylamide, was then converted to the benzyl ester **254** (Scheme 60). The oxime **255** which was obtained with *n*-BuONO, was hydrogenated on Pd/C affording DL-ibotenic acid (**256**). Another simple synthesis was described earlier by Gagneux and coworkers[243], via 3-benzyloxyisoxazolyl-5-carboxaldehyde (**257**), applying the Strecker synthesis procedure.

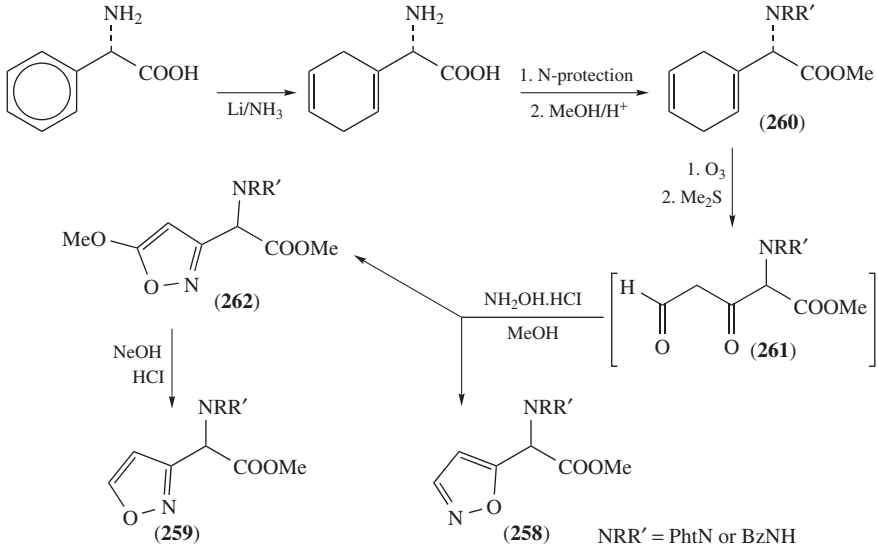


SCHEME 60

3. Transformation of aromatic amino acids to isoxazolylamino acids

A new methodology for the transformation of the benzene ring in aromatic amino acids and other benzene derivatives to a heterocyclic group was developed by Zvilichovsky and Gurvich[244, 245]. The basis of this procedure is the Birch reduction of the aromatic ring followed by ozonolysis of the cyclohexadiene system to produce 1,3-dicarbonyl compounds, which are excellent synthones for isoxazole and many other heterocyclic systems. This methodology provided a means for the synthesis of isoxazolylamino acids from available L-phenylalanine and L-phenylglycine derivatives.

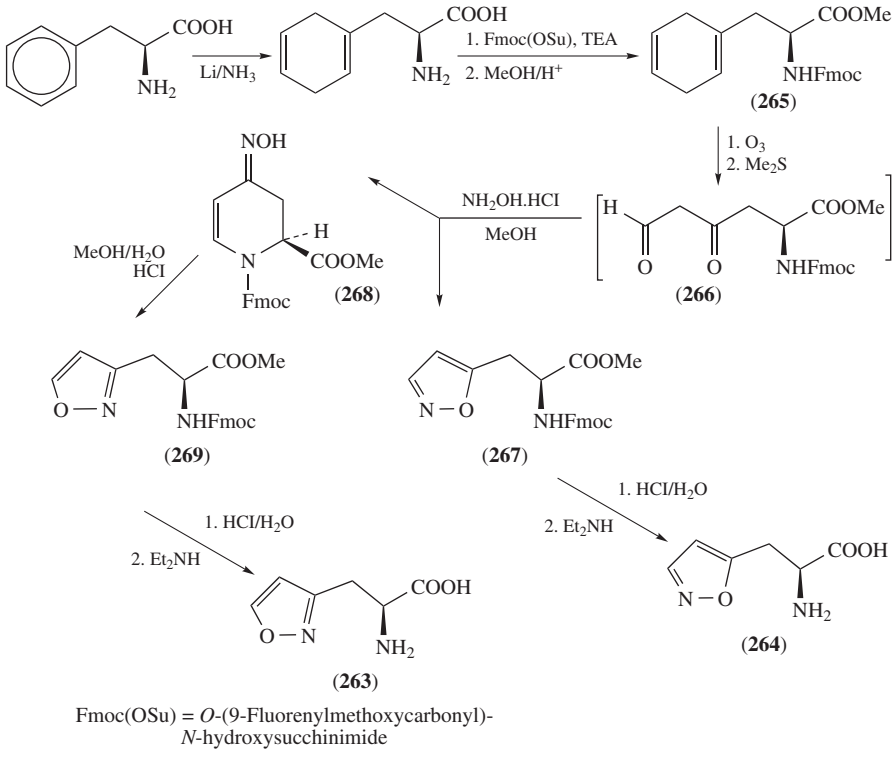
a. Synthesis of two isomers of isoxazolylglycine. The transformation of L-phenylglycine to derivatives of isoxazolylglycine is shown in Scheme 61. We reported[244] the synthesis of derivatives of both isomers of isoxazolylglycine (**258** and **259**), however, in the DL-configurations due to complete racemization during the work-up. Birch reduction of L-phenylglycine and protection of the amino group gave the product **260**. The reaction of the ozonolysis intermediate **261** with hydroxylamine hydrochloride in methanol resulted in two separable products. One was the 5-isoxazolylglycine derivative **258** and the other was the 5-methoxyisoxazolylglycine derivative **262**. Upon heating **262** in methanolic hydrochloric acid, it underwent elimination of methanol to produce 3-isoxazolylglycine derivative **259**.



SCHEME 61

b. Synthesis of two isomers of isoxazolylalanine. The transformation of L-phenylalanine to derivatives of isoxazolylalanine is shown in Scheme 62. Unlike in the case of the glycine derivatives where racemization occurred, we have obtained[245] the two optically active L-isoxazolylalanine isomers (**263** and **264**).

The Birch reduction of L-phenylalanine followed by protection of the amino group gave the cyclohexadiene derivative **265**, ozonolysis of which gave intermediate **266**. The



SCHEME 62

reaction of **266** with hydroxylamine hydrochloride in methanol resulted in two separable products, L-5-isoxazolylalanine derivative **267** and methyl pyridonecarboxylate oxime derivative **268**. Upon heating **268** in MeOH/water/HCl, it underwent ring opening and re-closure to produce the 3-isoxazolylalanine derivative **269**. Hydrolysis with 2N HCl followed by deprotection by diethylamine of both **269** and **267** gave the two optically active isomers L-3-isoxazolylalanine (**263**) and L-5-isoxazolylalanine (**264**), respectively.

IV. AMINOOXY PEPTIDES (AMIDOOXY PEPTIDES) AND BIOCONJUGATES

A. Preface

Concerning the nomenclature used in this chapter and throughout the literature, both the terms 'aminooxy peptides' and 'amidooxy peptides' are used. The first report in 1964[42] about the synthesis of aminooxy peptides was a part of the PhD thesis of the author of this chapter[42]. The methods of preparation of di- and tripeptides of aminooxyacetic acid and canaline were the DCC method and other classical procedures. This report included di- and tripeptides of aminooxyacetic acid and of canaline and a study of the stability of the aminooxy peptide bond (O=C−NH−O) in acidic and basic media, both in water and in ethanol, as well as its behavior in catalytic hydrogenation conditions. Of major importance was the study of the acidity of the amidooxy bond which explains the strong

hydrogen bonds and why this field became very important in the 21st century. The p*K*a values of the amidooxy bond in the studied peptides ranged from 6.1 to 7.1, which is many orders stronger than that of the amide bond, i.e. p*K*a around 20. The first report[27] about a homo oligomer of aminooxyacetic acid came from my laboratory in 1966, obtained by activation with phosgene. This report included a potentiometric titration of this oligomer and the formation of salts and complexes with metal ions.

A major breakthrough in the field of aminooxy peptides started at the end of the last century. Incorporation of aminooxy acids into peptides serves two major purposes. One purpose is due to the alteration of the secondary and the tertiary structure of the peptide or protein, producing chemically and biologically interesting foldamers. The amidooxy bond is also resistant to proteolytic enzymes, therefore such modified peptides are used in studying their biochemistry and their applications in therapy.

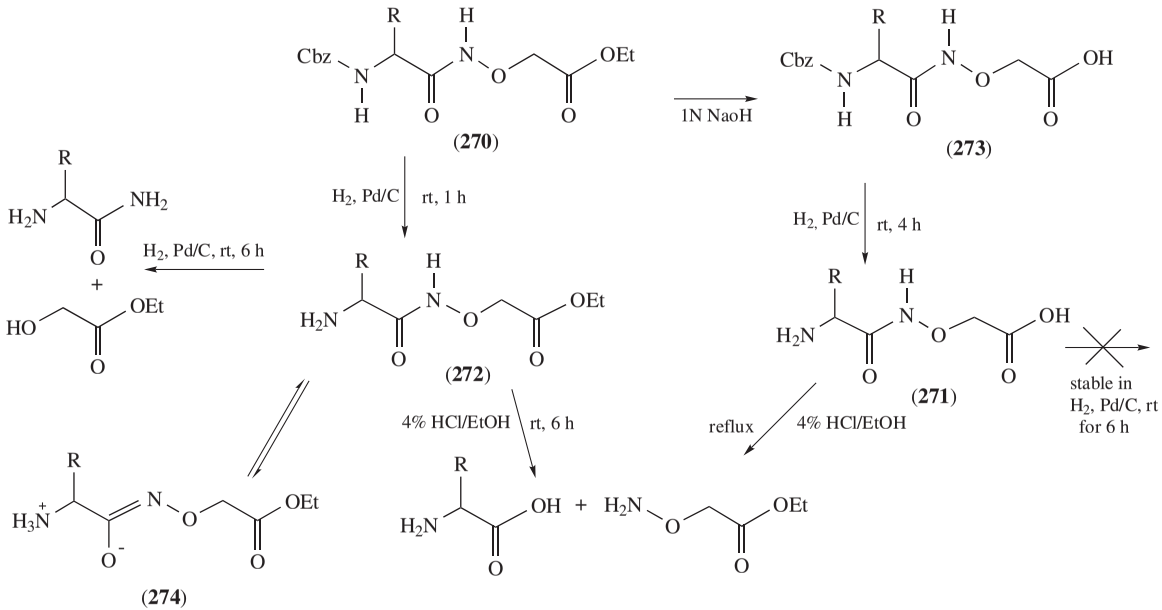
The second purpose for the introduction of aminooxy acids into peptides is due to the facile interaction of the aminooxy group with carbonyl functions. The aminooxy group serves as a linking function to other biologically active molecules. The conjugation with biologically active substances obtaining various biological probes was discussed above in Sections II and III, where the derivatives of aminooxyacetic acid and other aminooxy acids were summarized. Both peptides with a terminal aminooxy group and peptides that contain in their chain an α-amino-ω-aminooxy acid, possessing a free aminooxy group, were found to be excellent molecules for preparing peptidic bioconjugates. The latter are mainly peptides or glycopeptides, although there are examples of ligation to carbohydrates and glycosides. Synthetic and structural aspects of aminooxy peptides and their consequences will be discussed first and then particular examples of peptides and bioconjugates. Information and examples of peptides and bioconjugates are discussed in previous Sections II and III for the particular aminooxy acids.

B. Properties of the Amidooxy Bond in Aminooxy Peptides

1. Stability of the amidooxy bond in peptides

Scheme 63 summarizes the results of our study which was reported[42] in 1964. The amidooxy bond was stable in aqueous NaOH, a fact that enabled the hydrolysis of the ester group in the protected peptide esters (**270**). An amidooxy bond can undergo hydrogenolysis to glycolate and amide, however in the case of the free dipeptides (**271**) we have found that they survived hydrogenation in the presence of Pd/C at 3 atm for 6 h, whereas the dipeptide esters (**272**) underwent complete hydrogenolysis under these conditions. On the other hand, deprotection of the carbobenzoxy group in the protected dipeptide esters (**270**) was much faster than in the carbobenzoxy dipeptides (**273**), and thus by stepwise hydrogenation the peptide ester (**272**) could be isolated. The facile cleavage of the amidooxy bond in the esters was found to be due to zwitterion formation, in which the amidooxy bond is ionized (**274**) (Scheme 63). This was proved by studying a non-peptidic aminooxy compound, and observing that it was easily hydrogenolized in the presence of triethylamine (Scheme 63).

We have found that the amidooxy bond undergoes cleavage by ethanolic hydrogen chloride faster than regular amides. The esters (**272**) underwent complete ethanolysis in 4% ethanolic HCl in 6 h, even at room temperature. After 30 min at room temperature, 50–70% cleavage to the amino acid and the aminooxyacetic acid ester was observed. The ethanolysis of the free peptides (**271**) required reflux temperature for complete cleavage (Scheme 63).


Cbz
R
H
N
O
OEt
(270)
1N NaoH
OH
(273)
H2, Pd/C
rt, 1 h
H2, Pd/C
rt, 4 h
H2, Pd/C, rt, 6 h
H2N
NH2
HO
(272)
(271)
stable in
H2, Pd/C, rt
for 6 h
4% HCl/EtOH
rt, 6 h
reflux
4% HCl/EtOH
H3N+
O-
(274)

SCHEME 63

2. Dissociation and zwitterion formation in aminooxy dipeptides and dipeptide esters

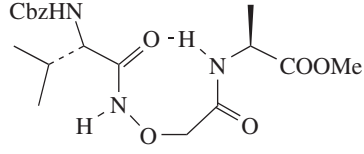
We have shown[42] by IR spectroscopy that the aminooxy dipeptide esters exist as zwitterions (**275**), which are possibly stabilized by charge delocalization as shown in structure **274**. The titration with NaOH proceeds by the elimination of the proton from the NH_3^+ group (Scheme 64). The difference in the dissociation constants between the aminooxy group and the NH_3^+ group is in agreement with the conclusion that the dipeptide esters exist predominantly as zwitterions (**275**). Titration of **275** with acid adds a proton to the ionized amidooxy bond. In the case of the free dipeptides, the zwitterions involve the carboxyl group as shown in **276** and the first equivalent of NaOH added to **276** ionizes the amidooxy bond while the second equivalent eliminates a proton from the NH_3^+ group and the dianion formed is stabilized by delocalization as shown in **277** (Scheme 64).

3. The reaction of the amidooxy bond with nitrous acid. The formation of depsipeptides

We have shown[246] in 1969 that treatment of aminooxy dipeptides with HNO_2 results in migration of the acyl group to the oxygen producing a depsipeptide with the elimination of N_2O (Scheme 65). Thus carbobenzoxy-DL-alanylaminooxyacetic acid (**273**, R = Me) gave *O*-(carbobenzoxy-DL-alanyl)glycolic acid (**278**) (Scheme 65).

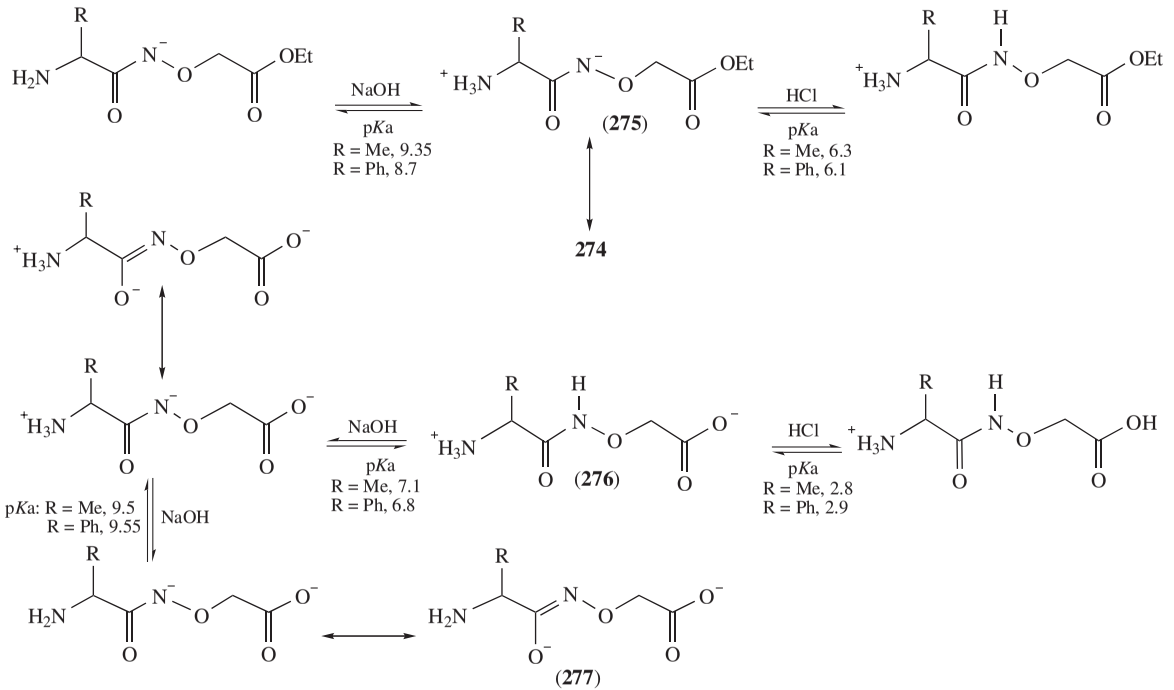
C. Structural Aspects of Aminooxy Peptides

The functions of proteins are associated with their compact three-dimensional structures, which in turn are derived from the secondary and tertiary structures. Yang and her coworkers together with Wu and coworkers[247] reported in 1996 the unusual structure of peptides containing D-α-aminooxy acids. They observed the formation of an eight-membered intramolecular hydrogen bond between adjacent residues, as shown in the ester of carbobenzoxyvalylaminooxyacetylalanine (**279**), which is different from seven-membered rings in regular peptides.

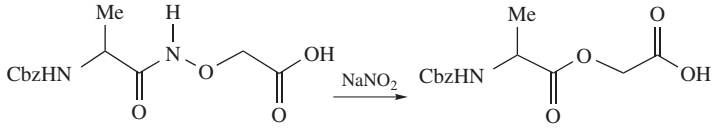


(**279**)

This interesting finding prompted them and other groups to investigate the nature of this phenomenon, both theoretically and for its potential applications. In an article[37] in 2008, Li, Yang and Wu summarized the results of intensive research since 1996. This publication includes new theoretical and experimental results as well. A good summary of the structural properties of peptides containing α-aminooxy acids is given as follows: 'Peptides constructed from α-aminooxy acids fold according to the following rules: (1) A strong intramolecular eight-membered-ring hydrogen bond forms between adjacent α-aminooxy acid residues (the α N−O turn). The chirality of the α-carbon, not the nature of the side chains, determines the conformation of this chiral N−O turn. (2) While homochiral oligomers of α-aminooxy acids form an extended helical structure (1.8_8 helix),


NaOH
pKa
R = Me, 9.35
R = Ph, 8.7
HCl
pKa
R = Me, 6.3
R = Ph, 6.1
(275)
274
NaOH
pKa
R = Me, 7.1
R = Ph, 6.8
HCl
pKa
R = Me, 2.8
R = Ph, 2.9
(276)
pKa: R = Me, 9.5
R = Ph, 9.55
NaOH
(277)

SCHEME 64



(**273**), R = Me (**278**)

SCHEME 65

heterochiral ones adopt a bent reverse turn structure. (3) In peptides of alternating α-amino acids and α-aminooxy acids, the peptide adopts a novel 7/8 helical structure.'

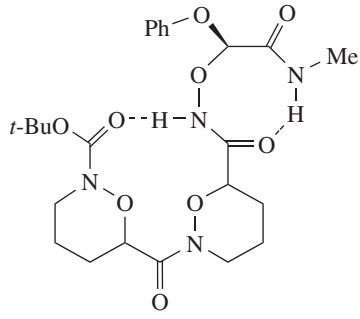
They also rediscovered the fact that was published 40 years earlier[42], that the amidooxy bond is more acidic than a regular amide bond, a fact that makes it a better hydrogen bond donor. This property makes aminooxy acids ideal building blocks for the construction of anion receptors and various other peptidomimetic foldamers.

In a Feature Article published in *Chemical Communications*, Li and Yang[248] had reported a summary in which they investigated, in addition to α-aminooxy acid, also β- and γ-aminooxy acids. They demonstrated that peptides consisting of aminooxy acids adopt several well-defined secondary structures, such as α N–O turns, which feature an eight-membered-ring hydrogen bond, β N–O turns with a nine-membered-ring hydrogen bond, γ N–O turns with a ten-membered-ring hydrogen bond, helices and β sheet-like structures.

Both publications[37, 248] include a comprehensive summary of this field. Preparation, calculations and potential uses of different kinds of peptides are described and discussed. Each publication has over sixty references and it is recommended that readers who are particularly interested in these works should refer to these publications. Derivatives of α-aminooxy acids were shown to be useful as building blocks in the construction of peptidomimetic foldamers. They established a set of rules for folding oligomers of aminooxy acids and peptides constructed of both amino acids and aminooxy acids. They have succeeded in the construction of ion receptors and channels to mimic anion recognition and transport processes in living systems. Their calculations showed the use and application of α-aminooxy acids in creating functional foldamers capable of binding specifically to various biological targets. The possibility of constructing foldamers as specific transmembrane carriers is studied as well.

Sharma and coworkers[249] have reported recently the preparation of peptides with alternating α-aminooxy acids and β-amino acids, achieving peptides with a mixed 12/10 helix. This result demonstrates that further expansion of the foldamer domain is possible by exploiting the oligomers derived from dipeptide repeats, containing the versatile building blocks, aminooxy acids and amino acids with different side chains. In view of the recent developments on tertiary and quaternary structures, these results create additional opportunities for the design and synthesis of several novel hybrid foldamers.

Baek and coworkers[250] reported the synthesis of tripeptides that have consecutive β- and γ-turn mimetics. They prepared and characterized α-aminooxy tripeptides (trimers) consisting of the cyclic aminooxy acid and one α-aminooxy acid. According to FT-IR and NMR data, as well as *ab initio* quantum mechanical calculations, the trimers adopted folded structures with consecutive β- and γ-turnlike conformations. Structure **280** shows such conformation produced by oxanopecotic acid dimer and L-α-aminooxy-β-phenylpropionic acid (so called aminooxyphenylalanine).

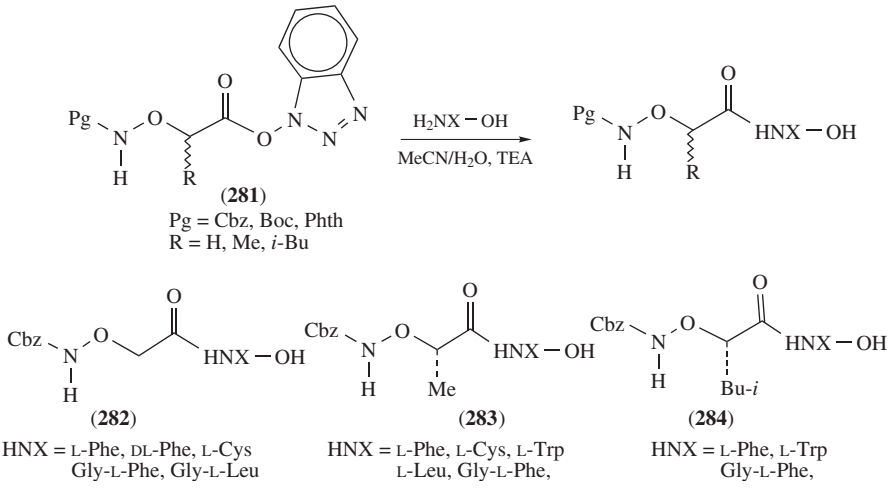


(**280**)

D. Synthetic Methods for Incorporation of Aminooxy Acids into Peptides

1. Synthesis of aminooxy peptides in solution

In light of the increasing interest in peptides containing aminooxy acids or both amino acids and aminooxy acids, Katritzky and coworkers[251] reported in 2009 a methodological study and proposed an efficient method for the preparation of aminooxyacyl amides, aminooxy hybrid peptides and α-aminooxy peptides. This new method is based on using N-protected aminooxy acid, activated by the formation of acylbenztriazoles (**281**). They tried some of the conventional protecting groups, and it seems that the most useful one was the carbobenzoxy group where all the resulting products were obtained without racemization (Scheme 66).



SCHEME 66

By using **281**, carbobenzoxy derivatives of peptides of aminooxyacetic acid (**282**), of L-aminooxypropionic acid (**283**) and of L-aminooxyisovaleric acids (**284**) were reported (Scheme 66). The nomenclature for these three aminooxy acids used is: AOglycine, L-AOalanine and L-AOvaline.

Sharma and coworkers[249] used elegantly the 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCl) method both for the acylation of the aminooxy group by N-protected β-alanine and for the formation of an amidooxy bond in their synthesis of an alternating oligomer (Scheme 67).

This oligomer, which was shown to have a robust 12/10 helix, is constructed from L-(*R*)-α-aminooxypropionic acid (**285**). The latter was prepared from available D-(*S*)-lactic acid. The ester group of the produced dipeptide derivative (**286**) was hydrolyzed and the product (**287**) condensed with the deprotected ester (**288**) to produce the alternating tetra peptide (**289**). The reader who is interested in the synthesis of more complex derivatives of aminooxy acids, e.g. α-amino-ω-aminooxy acids, should refer to Section II.C.4 and Reference 231 for the available syntheses of suitable protected aminooxy acids.

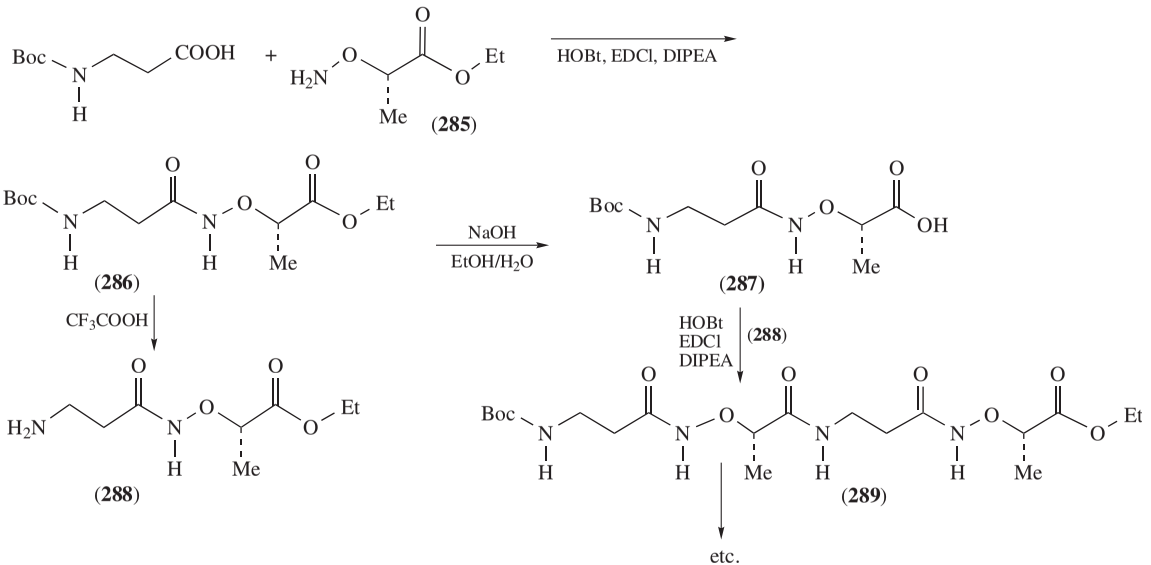
2. Solid-phase synthesis of aminooxy peptides (SPPS)

a. Conditions for preventing overacylation. Investigators noticed that in applying solid-phase synthesis of aminooxy peptides, they encountered the problem of overacylation, e.g. two acyl groups replace the two hydrogens of the aminooxy group. Several groups[24, 83, 84, 252] studied this problem and some of their observations were discussed above (Section II.A.7). The major conclusions (summarized also in the Section above) are to avoid strong bases in the acylation step. It was also suggested to use a new protecting group, e.g. ethoxyethylidene oxime (**59**), which could be removed from the polymer and deprotected by using trifluoroacetic acid (TFA) and triisopropylsilane (TIS) (Schemes 19 and 20). However, Boc and Fmoc groups are still widely used in this field.

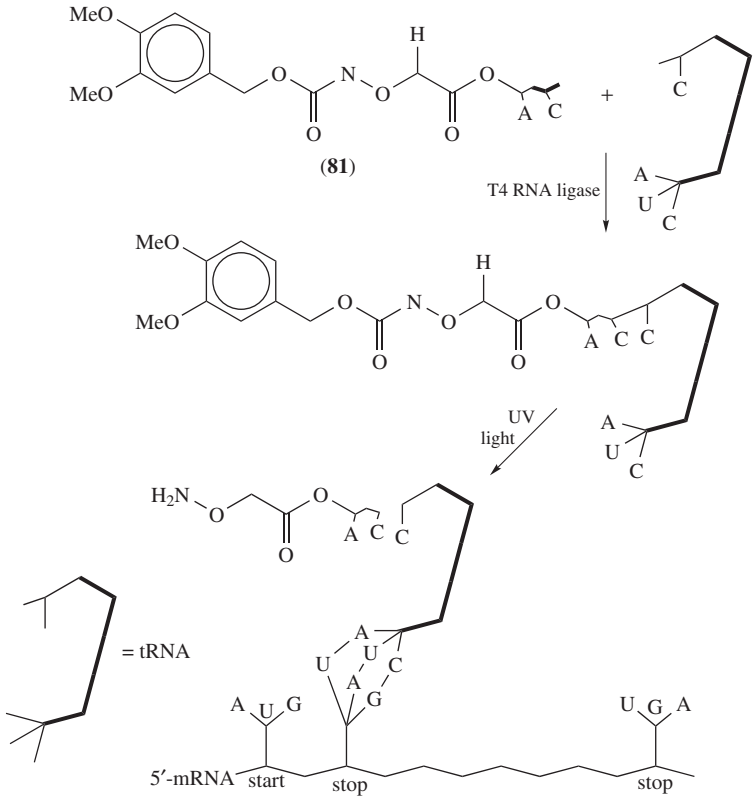
Many of the solid-phase syntheses of peptides containing aminooxy acids have to do with biconjugation. The easy and chemospecific formation of the oxime bond between chains that have an aminooxy end group and both aldehydes and ketones moieties is the reason for its extremely wide use in the preparation of biological probes and biosensors. Attaching an aminooxy acid to a solid support made it possible to prepare many types of molecules suitable for ligation. Such derivatives were also mentioned in Sections II and III, where references to and information on the solid-phase synthesis were reported. More information will be discussed in a subsequent Section that deals with bioconjugates as well.

3. Incorporation of aminooxy acids into peptides by ribosomally mediated protein biosynthesis

Eisenhauer and Hecht[90] reported site-specific incorporation of aminooxyacetic acid into proteins by employing a biosynthetic method for the preparation of proteins containing unnatural amino acid analogs. They incorporated aminooxyacetic acid into positions 10 and 27 of *Escherichia coli* dihydrofolate reductase. Introduction of the modified amino acid into the enzyme DHFR was accomplished in an *in vitro* protein biosynthesizing system by read through of a nonsense (UAG) codon with a suppressor tRNA that had been activated with aminooxyacetic acid (Scheme 68). The protected aminooxyacetic acid derivative which was used (**81**), described above (Section II.A.8), was subjected to a tRNA and translated to codon for methionine in the mRNA. Scheme 68 is a very schematic demonstration, but illustrates the general idea of ribosomal biosynthesis.


Boc
N
H
COOH
+
H2N
O
O
Et
Me
(285)
HOBt, EDCl, DIPEA
(286)
NaOH
EtOH/H2O
(287)
OH
CF3COOH
(288)
HOBt
EDCl
DIPEA
(288)
(289)
etc.

SCHEME 67



SCHEME 68

Incorporation of the amino acid proceeded with reasonable efficiency at codon position 10 but less well at position 27. Aminooxyacetic acid was also incorporated into position 72 of DNA polymerase. β-Peptides containing aminooxyacetic acid have been shown to adopt a preferred conformation involving an eight-membered ring that resembles a γ-turn.

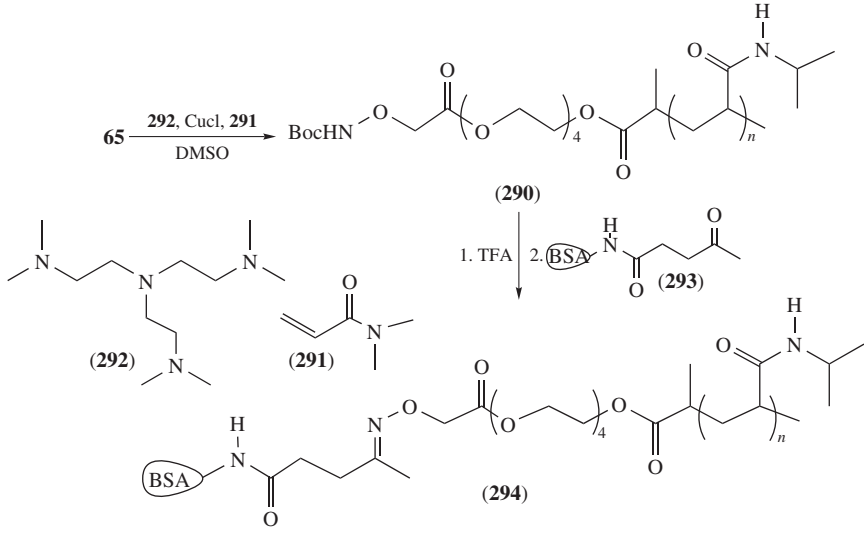
4. Oxidation of terminal hydroxy group in proteins: A general method for functionalizing proteins for oxime ligation

Proteins that contain a terminal serine or threonine are subjected to oxidation by a reagent like periodate, producing a terminal aldehydic function that reacts easily with a chain having an aminooxy moiety. A number of examples are discussed in Section II.A.7 and references are cited.

5. Aminooxy functionalized derivatives by radical polymerization

Heredia and coworkers[85] demonstrated the synthesis of Boc-protected aminooxy initiators like **290** from aminooxy end-functionalized polymers (**65**), for atom transfer radical

polymerization (ATRP) of acrylamide and methacrylate monomers. Copper-mediated atom transfer radical polymerization (ATRP) of *N*-isopropylacrylamide (**291**), in the presence of tris[2-(dimethylamino)ethyl]amine (**292**), resulted in a polymer, the end of which was deprotected with trifluoroacetic acid, exposing α-aminooxy moieties. Chemospecific reaction of the latter with *N*-levulinyl lysine modified bovine serum albumin (BSA) (**293**) to form 'smart' polymer conjugates (**294**) was demonstrated (Scheme 69).



BSA = bovine serum albumine

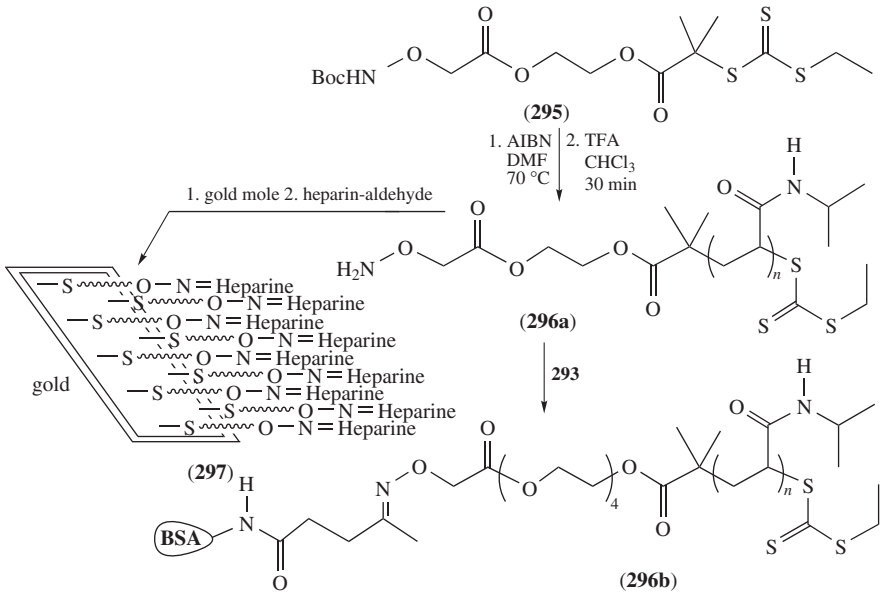
SCHEME 69

Vázquez-Dorbatt and coworkers[253a] from the same lab used a different kind of polymerization technique, e.g. a reversible addition–fragmentation transfer (RAFT) method. The polymerization took place in the presence of a similar N-protected aminooxy acid (**295**) derivative to produce an aminooxy active polymer (**296a**) that could be attached to biomolecules like **293** to produce **296b** (Scheme 70). The aminooxy end-activated polymer (**296a**) was also immobilized on a gold surface after reduction of the trithiocarbonate end group. The surface was then incubated with an aldehyde-modified heparin to yield the functionalized surface (**297**) (Scheme 70).

E. Oligomeric Homo Peptides and Peptolides Derived from Aminooxyacetic Acid

The homo oligomer of aminooxyacetic acid (**298**) was reported[27] from this laboratory in 1966 (Scheme 71). It behaved like a weak acid and gave insoluble salts with $Ba(OH)_2$ and $Cu(OAc)_2$. In the case of the stronger base $Ba(OH)_2$, it was shown that all amidooxy bonds including the one in the terminal ring were deprotonated (**299**). In the salt obtained by the weaker copper base, it gave the hexa-valence salt **300** (Scheme 71).

N-Alkyl peptolide is a peptide in which each monomer unit has a different alkyl group, but these alkyl groups are linked to the amide nitrogen rather than to the α-carbon.

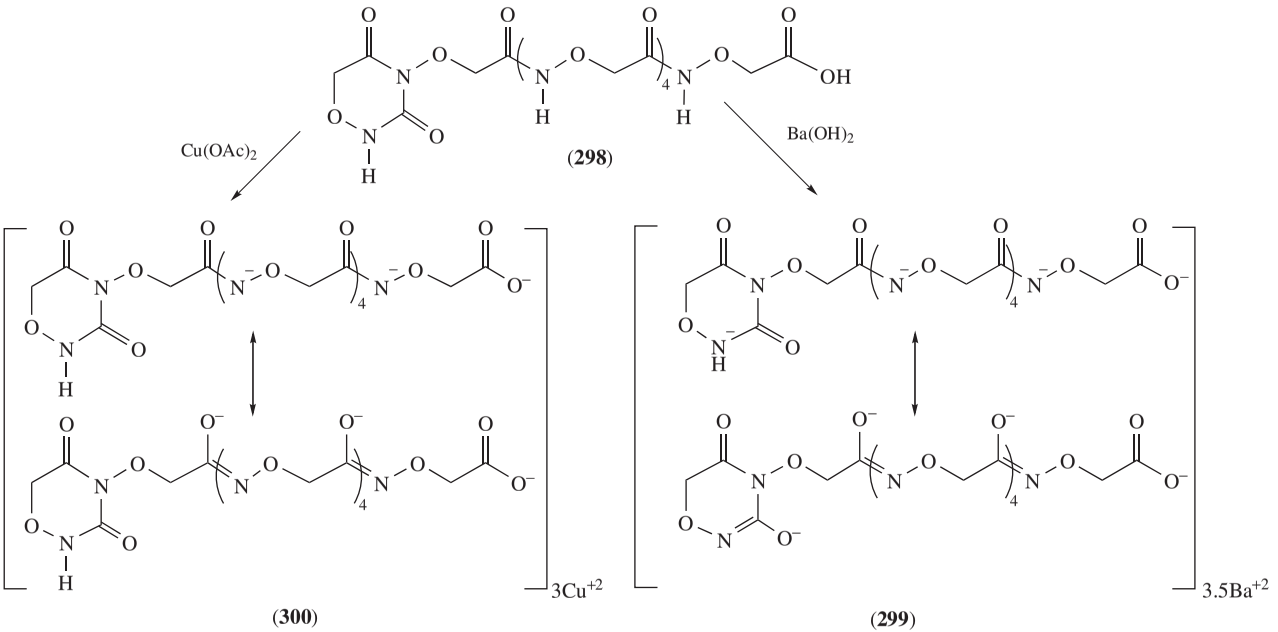


SCHEME 70

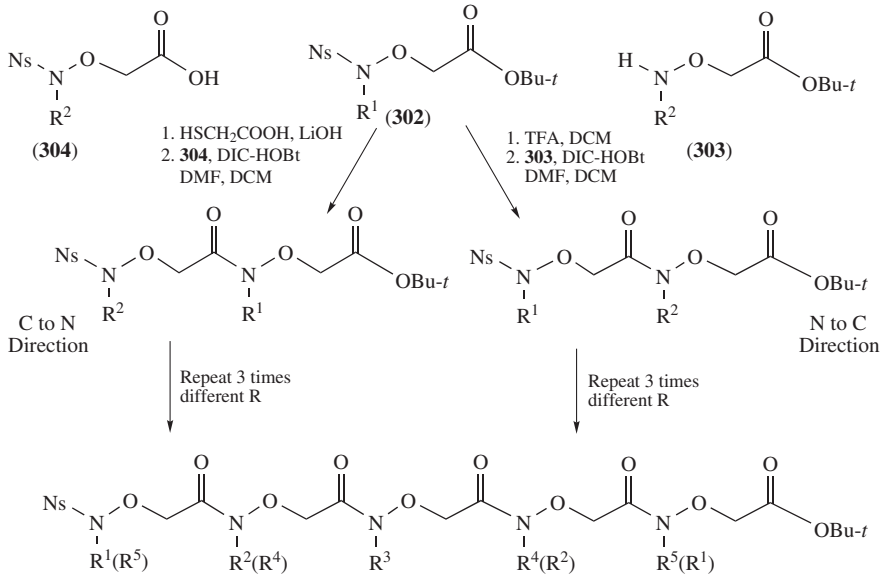
Shin and Park[253b] reported in 2002 a solution-phase stepwise synthesis of aminooxy pentapeptolids (**301**) in both C to N and N to C directions. The starting material doubly protected aminooxyacetic acid (**302**). The protection of the aminooxy group was done with the *o*-nitrobenzenesulfonyl (Ns) group and the carboxyl was protected by *t*-Bu ester (Scheme 72). The synthesis of the substituted monomers is described as well. In each step of the C to N direction the removal of the Ns group was carried out by thioglycolic acid-LiOH reagent to produce **303**, and in each step of the N to C direction the *t*-Bu was removed by TFA in dichloromethane to give **304**. The most efficient coupling reagent was diisopropylcarbodiimide (DIC) (Scheme 72).

F. Bioconjugates Derived from Aminooxyacetic Acid

Aminooxyacetic acid is the most common acid used in achieving bioconjugates, based on the facile and chemoselective oxime formation with molecules and chains functionalized with an aldehyde or ketone moiety. The main methods and publications were discussed extensively in Section II.A. The synthetic problems of overacylation were discussed above as well (Section IV.D.2.a). The application of aminooxyacetic acid as probes for the specific assay of abasic sites in DNA lesions and for labeling of proteins and cell surface were discussed in Section II.A.6. Their use as linkers for ligation in the preparation of bioconjugates and for incorporation in solid-phase peptide synthesis was discussed extensively in Section II.A.7. The chemistry of reagents for site-specific incorporation of aminooxyacetic acid into proteins, both for biosynthesis and for chemical synthesis, was discussed in Section II.A.8.



SCHEME 71



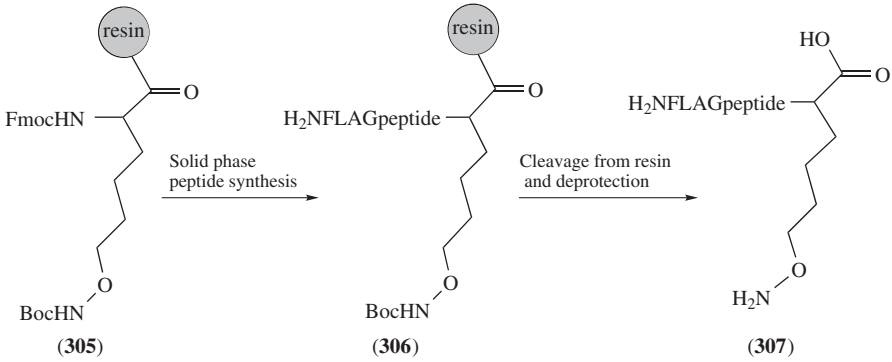
(**301**) R groups = Me, Bn, Bu, allyl, *p*-MeOBn, EtNHBoc, 1-NaphCH$_2$

SCHEME 72

G. Bioconjugates Derived from Other Aminooxy Acids

1. 2-Amino-6-aminooxycaproic acid

Adamczyk and coworkers[24] reported in 2001 the use of α-amino-6-aminooxycaproic acid on a solid support (**305**) for its incorporation in FLAG octapeptide (Scheme 73).

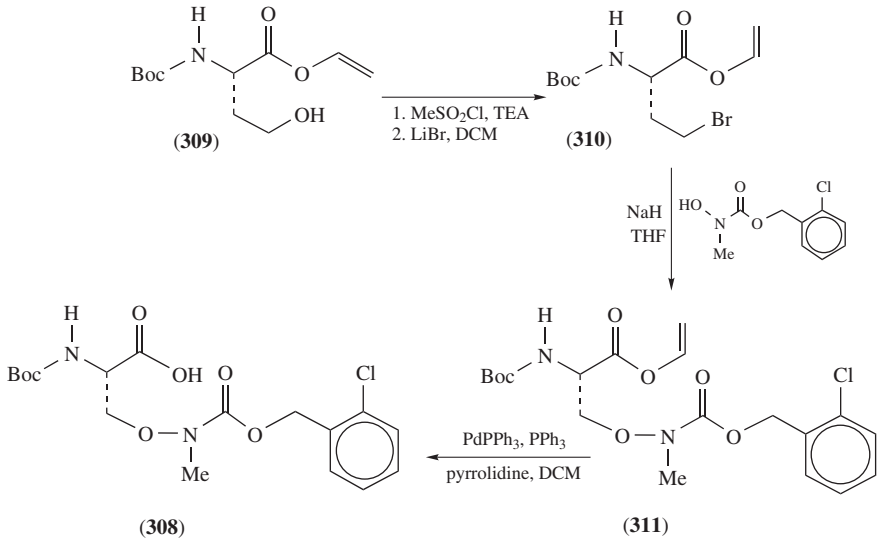


SCHEME 73

This way they were able to obtain biosensors and biotinylated probes. They found that this transformation of the FLAG octapeptide (**306**) preserved its epitopic properties. The functionalized peptide (**307**) obtained by deprotection could be added to recombinant DNA or immobilized by attachment to a solid support and used in isolation of protein complexes by affinity chromatography as well.

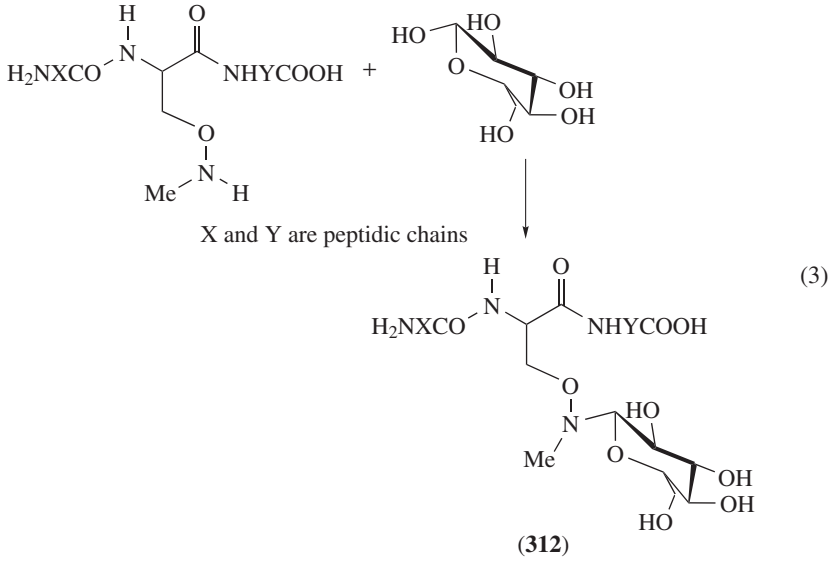
2. α-Amino-ω-N-methylaminooxy acids

Carrasco and coworkers[254] studied both α-amino-β-*N*-methylaminooxypropionic and α-amino-γ-*N*-methylaminooxybutyric acids for incorporation into the backbone of peptides, used for ligation with carbohydrates to produce neoglycopeptides[254]. They first synthesized α-amino-β-*N*-methylaminooxypropionic acid and found that during solid-phase peptide work-up elimination occurred, resulting in dehydroalanine formation. Therefore, they concentrated on the next homolog that was found adequate for their purpose. They prepared the *o*-ClCbz derivative (**308**) suitable for solid-phase peptide synthesis. Its preparation started with the O- and N-protected homoserine (**309**). The intermediate bromo derivative (**310**) was achieved by mesylation followed by treatment with LiBr. The ester (**311**) was then converted to the N-protected amino-aminooxy acid (**308**) (Scheme 74).



SCHEME 74

By applying the amimo-aminooxy derivative (**308**) in solid-phase peptide synthesis mixed peptides were obtained. Removal of the ClCbz group resuted in a peptide with *N*-methylaminooxy groups at specific intervals. These peptides reacted chemoselectively with carbohydrates to afford neoglycopeptides like **312** (equation 3). The methylaminooxy group was found to be advantageous over a non-alkylated aminooxy group, because the latter gave with reducing carbohydrates the open-chain sugar derivatives.



(3)

(**312**)

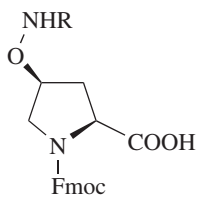
3. Aminooxypyrrolidine-2-carboxylic acid derivatives

The methods used by Liu and coworkers[18] for the preparation of these derivatives were discussed above in Section I.B.9. By a Mitsonubo reaction they have prepared a number of orthogonally protected derivatives of 3-and 4-aminooxypyrrolidine-2-carboxylic acid (**313**–**315**). Using solid-phase methodology similar to that reported for hydrazine-activated peptides[255], they have prepared the peptide (**316**) from which they obtained by oxime linkage libraries of Tsg101-directed-HIV-1 budding antagonists.

H. Antimicrobial and Therapeutic Studies of Aminooxy Peptides and Bioconjugates

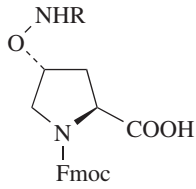
Short peptides containing α-aminooxypropionic acid were prepared by Morley and coworkers[103] using classical solution methods. These peptides were tested for antibacterial properties. The aminooxy peptides derived from aminooxyacetic acid and α-aminooxypropionic acid demonstrated some antibacterial activity. The uptake and transport of dipeptides and tripeptides containing both L- and D-α-aminooxypropionic acids in *E. coli* and other bacteria were investigated by Payne and coworkers[104, 105].

Wu and coworkers[73] used aminooxy FLAG, amimooxy biotin and aminooxy alexa fluor 488 for site-specific chemical modification of recombinant proteins produced in mammalian cells by using a genetically encoded aldehyde tag. Kurth and coworkers[91] prepared the ^{125}I-phenylethylamine derivative of aminooxyacetic acid (**82**), with the free aminooxy group available for interaction with carbonyl sites deriving a site-specific reagent to monoclonal antibodies, this way achieving increased radioactivity localization in tumors. Poethko and coworkers[92] in 2004, and Dirksen and Dawson[93] in 2008, reported additional site-specific reagents involving aminooxyacetic acid peptides. Recently, Hultsch and



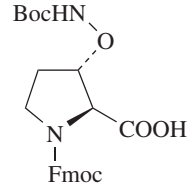
(**313**)

R = Boc, Mtt

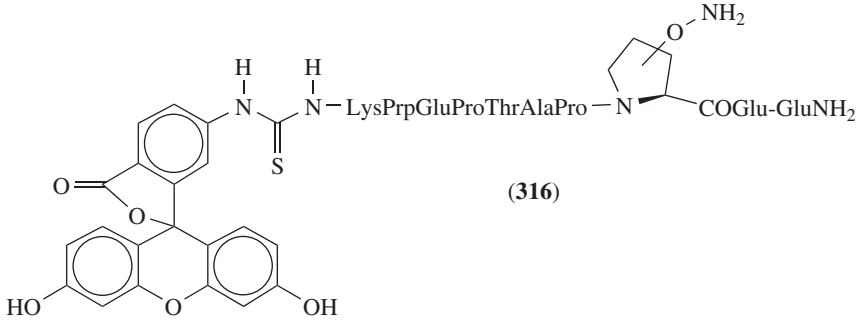


(**314**)

R = Boc, Mtt



(**315**)



(**316**)

coworkers[94] reported the application of the solid-phase peptide synthesis described above, for the preparation of an aminooxyacetic acid functionalized peptide for the production of a ^{18}F-fluoroglucosylated cyclo(RGDfK) peptide (**83**).

V. GUANIDINOOXY ACIDS

A. Canavanine (α-Amino-γ-guanidinooxybutyric Acid)

1. Isolation, biochemistry and bioactivity of canavanine

The history of L-canavanine starts with its discovery by Kitagawa and Yamada in 1929 as discussed in Section I.B.1. The part of L-canavanine in the canaline–urea cycle was discussed in Section II.B.2. In 1977, Rosenthal[256] published quite a comprehensive review entitled *Biological and mode of action of* L-*canavanine, a structural analog of* L-*arginine*. This review covers 120 references and is recommended if one is interested in the biological background of this interesting amino acid. In 1978, Bell and coworkers[257] reported a survey of leguminous plants in which canavanine is present in detectable quantities and pointed out the subfamilies that contain L-canavanine. In 1979, a review was published by Korhola[258] with 125 references discussing the bactericidal activity of canavanine.

a. Insecticidal properties of L-*canavanine.* As an analog of L-arginine, L-canavanine was found to be toxic to insects and plant predators. A review on the deleterious effect of L-canavanine on insects was published by Rosenthal[259] in 2001. The plants accumulate L-canavanine in their seeds for nitrogen storage and it acts as a chemical defense against

herbivores and diseases as well[260]. However, certain insects and their larvae can survive by developing the means for the detoxification The mechanism of the detoxification is the subject of several articles and reviews originating from Rosenthal and coworkers. The investigation concerning the biochemical adaptation of the *bruchid* beetle, *Caryedes brasiliensis*, to L-canavanine was summarized[261] in 1983. Insects could be divided[262, 263] into those which are canavanine-resistant, like *Heliothis virescens*, or those which are canavanine-sensitive, like *Manduca sexta*. The investigations about the biochemical basis for this phenomenon were summarized[264] in 1991. One of the reasons for the deleterious effect of L-canavanine that was discussed[260, 263, 264] is its incorporation in arginine proteins. The resulting pseudo arginine proteins lack a basic group that originates from arginine, and the tertiary structure of the protein is affected as well. The enantiomer D-canavanine affected minimal damage to *Manduca sexta* larvae as compared to the natural enantiomer L-canavanine[259].

b. L-canavanine as a potential anticancer agent. Bence and Crooks[265] published a review with 79 references discussing the research efforts in evaluating L-canavanine as an anti-cancer agents. The specific cancer that most of these investigators studied is a pancreatic cancer. The capacity of L-canavanine to act as a substrate for arginyl tRNA synthetase and be incorporated into proteins in place of L-arginine resulting in proteins with altered structure and function has clearly been demonstrated. However, it is still unclear whether L-canavanine incorporation disrupts the function of one particular protein crucial for cellular processes (e.g. cell surface adhesion proteins or arginine-rich histones) or non-specifically competes with L-arginine and alters the function of multiple critical proteins and/or enzymes. Identifying the pathway that ultimately leads to cellular death is an important step in the development of L-canavanine into an effective therapeutic agent. Despite the antitumor properties of L-canavanine and its selective localization in the pancreas, it was shown that high doses of L-canavanine may be required for therapeutic effect, since at low doses L-canavanine may not efficiently compete with dietary L-arginine for incorporation into protein.

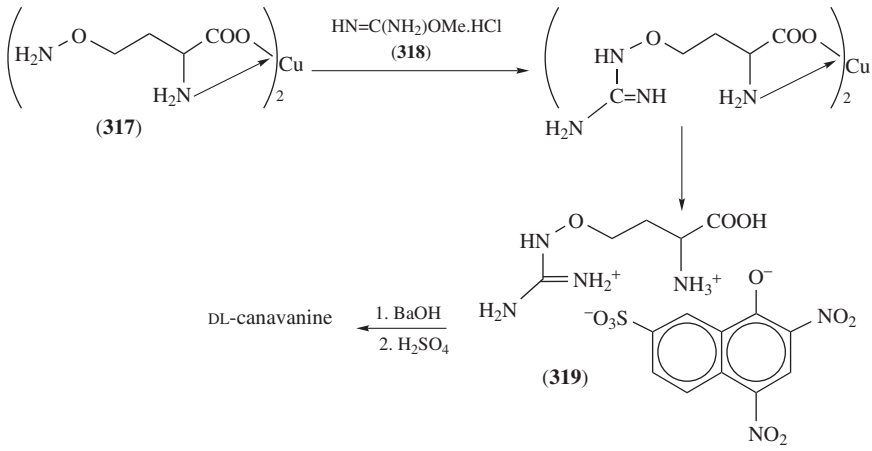
c. Development of systemic lupus erythematosus (SLE) by L-canavanine in humans and other mammals. Mammals, including humans and monkeys, who were fed with alfalfa seeds developed lupus-like autoimmunity. A review article about this unusual phenomenon was published[266] in 2006. The major conclusion of the investigations is that since L-canavanine is incorporated into virtually all proteins and affects their functions, it should be the cause for the development of autoimmunic symptoms like SLE.

2. The preparation of canavanine

After the discovery of L-canavanine and its structural relationship to L-canaline, attempts were made for the chemical synthesis of these products. Since the major syntheses of canaline were discussed earlier in Section II.A.1, the transformation to canavanine is one last step in converting the aminooxy group to the guanidinooxy group. This section will survey the efficient strategy for this purpose. On the other hand, during the last few years methods have been developed for large-scale preparation of L-canavanine from natural sources. Bass and coworkers[267] described in 1995 the extraction of over 20 g of L-canavanine from Jack beans.

The synthesis of DL-canaline by Nyberg and Christensen[177] was discussed above (Section II.A.1). The next step toward canavanine was performed by the reaction of the copper(II) complex of canaline (**317**) with *O*-methylisourea hydrochloride (**318**) (Scheme 75). After destroying the copper complex and removing the residual copper, the reaction

mixture was treated with flavianic acid to produce a precipitate of canavanine flavianate (**319**). The flavianate salt was decomposed by barium hydroxide and the residual barium ions removed by sulfuric acid. An impure solid was obtained on evaporation in a very low yield (Scheme 75).



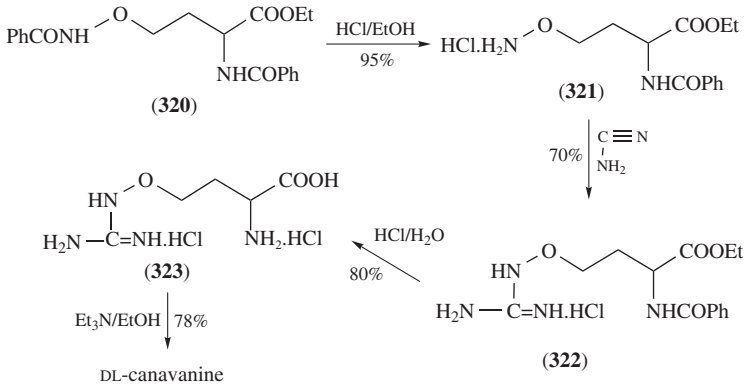
SCHEME 75

We[268] reported the most efficient and elegant synthesis of DL-canavanine in 1963 (Scheme 76). The available intermediate ethyl DL-N^{α}, N^{ω}-dibenzoylcanalinate (**320**) from the preparation of canaline[8b] was selectively debenzoylated by ethanolic HCl. The resulting ethyl DL-N^{α}-bezoylcanalinate (**321**) hydrochloride was treated with pure cyanamide to yield ethyl DL-N^{α}-benzoylcanavaninate hydrochloride (**322**). Hydrolysis in hydrochloric acid afforded a hygroscopic DL-canavanine dihydrochloride (**323**) (Scheme 76). By treatment with one equivalent of triethylamine in ethanol, the monohydrochloride of DL-canavanine was obtained. Using excess of triethylamine in ethanol resulted in a crystalline pure DL-canavanine. Each step in this synthesis resulted in about 80% yield (Scheme 76).

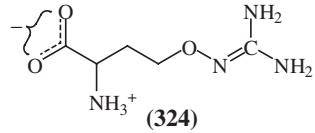
This excellent cyanamide method was used by Ozinskas and Rosenthal[269] to prepare ^{14}C-labeled L-canavanine from ^{14}C-labeled L-canaline in quantitative yield. The protection of the amino group was achieved by the copper(II) method and the cyanamide was activated by Zn.

3. The crystalline structure and dissociation constants of canavanine

Canavanine has two basic groups and one carboxyl group as in arginine; however, the guanidinooxy group is a weaker base than the gaunidino group in arginine. Furthermore, the guanidinooxy group is a weaker base than the α-amino group, thus the zwitterion should involve the α-amino group. This can be clearly observed in the single-crystal X-ray diffraction analysis reported by Boyar and Marsh[270] in 1982 (Figure 2). In addition, this study shows that the tautomeric structure of the guanidinooxy group consists of a O−N=C double bond rather than a C=NH double bond. The latter fact is derived from the bond distance and the observation of the location of four hydrogens on the NH_2 groups. Thus structure **324** presents the true structure of canavanine.



SCHEME 76



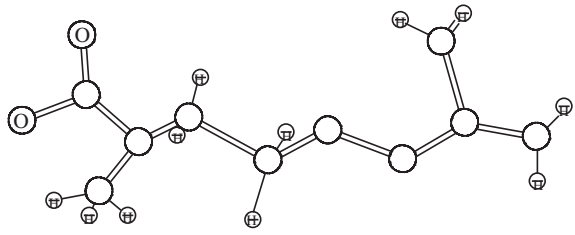


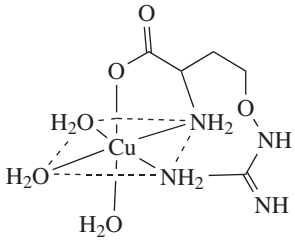
FIGURE 2. A drawing of the structure of L-canavanine from the report of single-crystal X-ray diffraction analysis by Boyar and Marsh

Boyar and Marsh[270] reinvestigated the dissociation constants of canavanine and reported the corrected values: p*K*a(COOH) 2.35, p*K*a(Guanidino) 7.01 and p*K*a(α-NH_2) 9.22. The previous values in the literature were 2.50, 6.60 and 9.25, respectively.

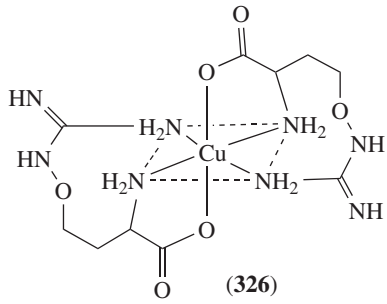
4. Metal complexes of canavanine

Albourine and coworkers[271] studied in 1989 the complex formed by L-canavanine with copper(II) and compared its stability to the copper complex of L-arginine. They studied canavanine-Cu (**325**) and (canavanine)$_2$Cu (**326**) and also the mixed arginine–Cu-canavanine complex. They concluded that the mixed complex is the most stable. It appears that the terminal guanidino group as well as the amino group and carboxyl group are involved in the complex formation.

Ratilla and coworkers[272] succeeded in crystallizing L-canavanine complex with platinum terpyridyl perchlorate. This complex [{Pt-(trpy)}$_2$canavanine]$(ClO_4)_3 \cdot 5.5H_2O$



(**325**)



(**326**)

consists of a bridging coordination between the donors and Pt(II). They found two types of complexes that coexist in the same crystal.

5. Quantitative determination of canavanine

The qualitative test that gave a red color with sodium nitroprusside, used by Kitagawa and coworkers[1, 2, 7] for the detection of canavanine, was developed by Archibald to a quantitative colorimetric determination of canavanine[273]. The nature of the colored product is unknown but the method is applicable in a dilute solution of canavanine. The color develops on exposure to sunlight for about 2 h. The reagent is prepared in phosphate buffer (pH 7.2).

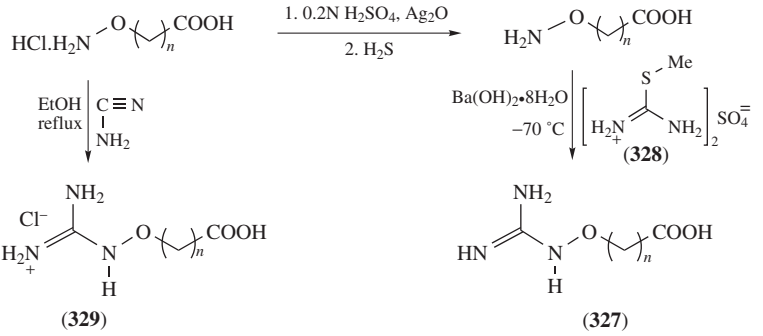
B. Other Guanidinooxy Acids and α-Amino-ω-guanidinooxy Acids

1. Guanidinooxy acids (not containing an amino group)

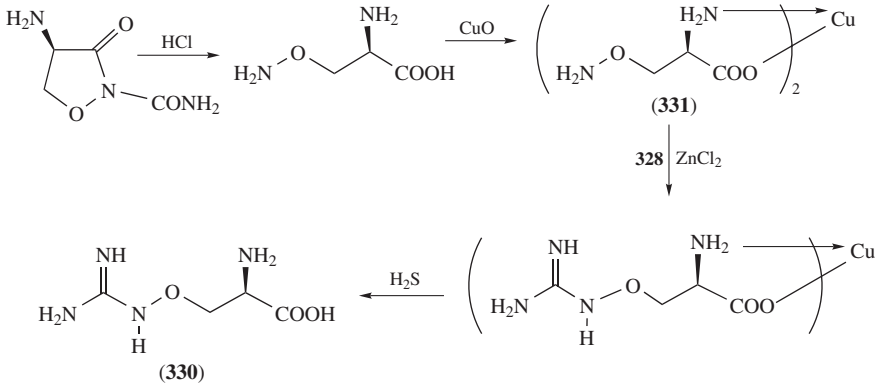
The interest in guanidinooxy acids (**327**, $n = 1$) was instigated by the discovery of canavanine by Kitagawa and coworkers, who tried to synthesize guanidinooxyacetic acid from aminooxyacetic acid[7]. The reagent for the transformation of the aminooxy group which they used was *O*-methylisourea hydrochloride. A major improvement was reported by Borek and Clarke[12b] using *S*-methylisothiourea sulfate (**328**). They reported the preparation of guanidinooxyacetic acid as well as γ-guanidinooxybutyric acid (**327**, $n = 3$) (Scheme 77). The use of *S*-methylisothiourea sulfate was published[274] as a general procedure for the preparation of **327** in the series 'Organic Syntheses'. Ludwig and coworkers[275] who studied the hypoglycemic activity of guanidines used the same methods for the preparation of a number of guanidinooxy acids (**327**, $n = 1$, 3 and 4) (Scheme 77). The reader should wonder why in 1970 they did not use the much less tedious procedure using the cyanamide method reported[268] in 1963 that leads directly from the hydrochloride of the aminooxy to the hydrochloride (**329**) (Scheme 77). In this method the isolation and purification is much easier, provided one uses pure cyanamide which is not contaminated by its dimer.

2. α-Amino-ω-guanidinooxy acids

Na Phuket and coworkers[276], in their study on the structure–activity relationship of antitumor congeners of L-canavanine, described the synthesis of D-2-amino-3-guanidinooxypropionic acid (**330**). The precursor 2-amino-3-aminooxypropionic acid



SCHEME 77



SCHEME 78

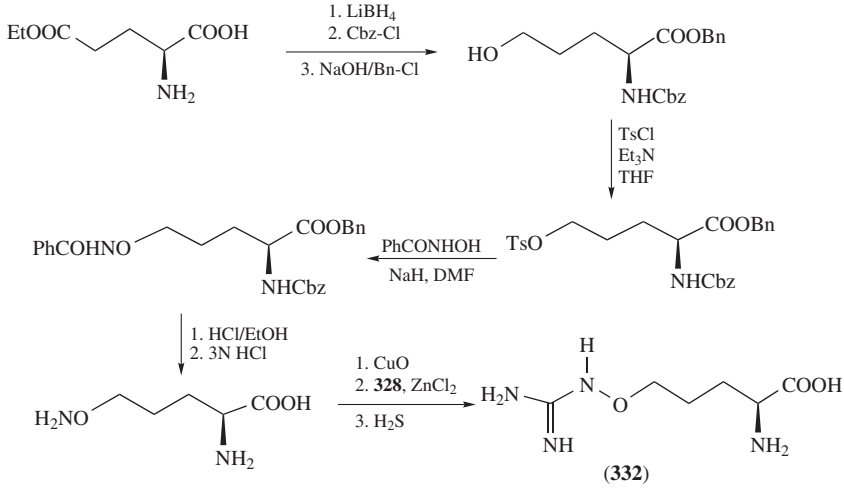
was obtained by the hydrolysis of D-cycloserine by aqueous HCl (Scheme 78). They used the cyanamide/$ZnCl_2$ method for the transformation of the aminooxy group to a guanidinooxy group. The protection of the 2-amino group was achieved by the formation of a copper complex (**331**).

The preparation of L-2-amino-5-guanidinooxyvaleric acid, also named L-homocanavanine (**332**), was reported[229] by the same group. Rosenthal and coworkers used the same procedure as in Scheme 78 for transforming the aminooxy group into the guanidinooxy group. They synthesized the L-2-amino-5-aminooxyvaleric acid from the monoester of L-glutamic acid (Scheme 79).

VI. UREIDOOXY ACIDS

A. 2-Amino-4-ureidooxybutyric Acid (*O*-Ureidohomoserine)

The interest in ureidooxy acids started after the discovery of canaline and canavanine as described in the previous sections. It was shown that L-2-amino-4-ureidooxybutyric acid (L-ureidohomoserine) (**333**) plays an important role in the canaline–urea cycle, which



SCHEME 79

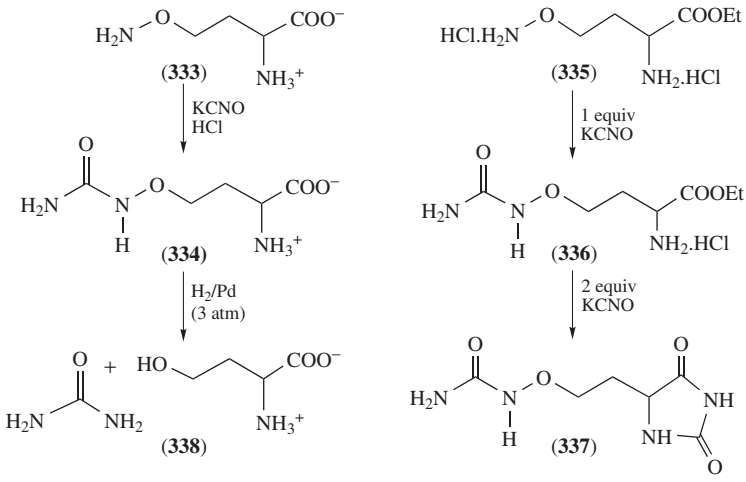
was described and discussed in Section III.A.2. Initially, this cycle was studied in plants but later it was found in animals as well. Koller and coworkers[277] studied the uptake of L-*O*-ureidohomoserine in human liver to produce canavaninosucinate. An important contribution was published[278] in 2008 by three American groups about the formation of *O*-ureidohomoserine in microbial deaminase activity.

1. Preparation and properties of O-ureidohomoserine

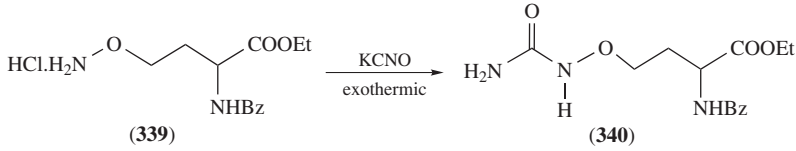
Kihara and Snell[279] tried in 1957 to prepare *O*-ureidohomoserine from canaline by protecting the 2-amino group by a copper complex. The structure of the product was proved merely by chromatographic comparison with the natural product. In 1966, I published[27] the most facile and easy transformation of canaline to DL-*O*-ureidohomoserine. Because of the great difference between the basicity of the amino group and the aminooxy group in canaline, there was no need for the protection of the 2-amino group. The latter group is involved in the zwitterion formation and the aminooxy group remains almost quantitatively un-ionized (**333**). Therefore, by introducing 1 equivalent KCNO and 1 equivalent HCl to the aqueous solution of DL-canaline and letting the solution sit for a while, crystals of pure DL-*O*-ureidohomoserine (**334**) settled (Scheme 80). Moreover, adding 1 equivalent of KCNO to the ester dihydrochloride (**335**), the ONH_2 group was freed from the HCl by the basic KCNO to react at room temperature to yield the hydrochloride ester of *O*-ureidohomoserine (**336**). By applying 2 equivalents of KCNO, at room temperature the hydantoin derivative (**337**) was obtained (Scheme 80).

Upon treatment of DL-*O*-ureidohomoserine with hydrogen on Pd (3 atm) for 4 h, it underwent hydrogenolysis to homoserine (**338**) and urea (Scheme 80). The reaction of the N^2-protected ester hydrochloride (**339**) with KCNO was exothermic and the *N*-benzoylated product (**340**) separated immediately (Scheme 81). However, the benzoyl group could not be hydrolyzed without decomposition of the ureidooxy group[27].

The ureidooxy moiety proved to be neutral, unlike the guanidino group that was protonized in aqueous acid. By potentiometric titration I was able[27] to determine the p*K*a of



SCHEME 80



SCHEME 81

the carboxyl group (p*K*a 2.5) and the 2-amino group (p*K*a 8.9). The p*K*a of the amino group in the ester (**336**) was 6.95. The hydantoin ring in **337** had an acidic p*K*a (8.6).

Rosenthal[280] used this procedure for the preparation of L-ureidohomoserine from the naturally available L-canaline. He also developed a colorimetric assay for *O*-ureidohomoserine based on the color formed upon its incubation with butanedione-monooxime and *N*-phenyl-*p*-phenylenediamine (measured at 532 nm).

An enzymatic synthesis of *O*-ureidohomoserine was reported by O'Neal[281], using a purified enzyme from Jack Bean (*Canavalia ensiformis*) leaves. The product was compared to a sample supplied from my laboratory.

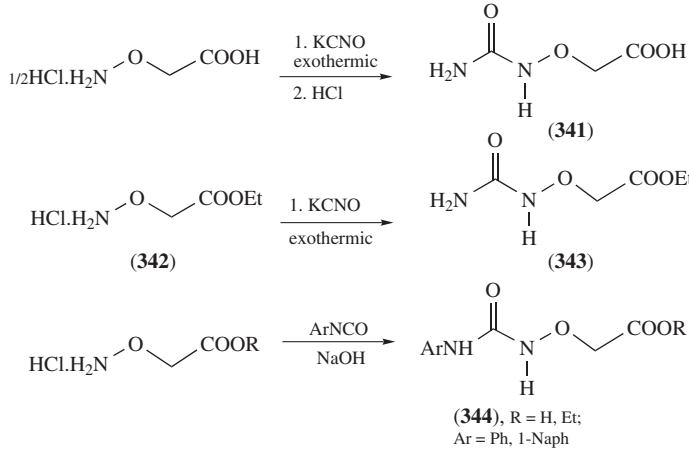
B. Other Ureidooxy Acids

1. Ureidooxyacetic acid

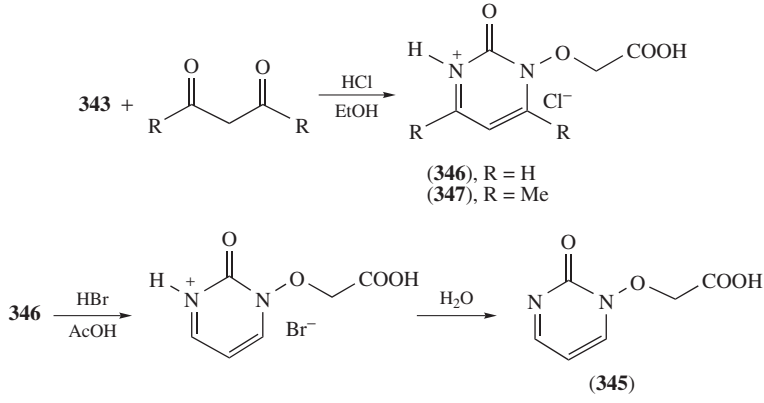
The reaction of aminooxyacetic acid hemihydrochloride with KCNO in a very small amount of water was exothermic and ureidooxyacetic acid (**341**) crystallized on acidification and cooling[27] (Scheme 82). A treatment of ethyl aminooxyacetate hydrochloride (**342**) in a small amount of water by dropwise addition of a concentrated solution of KCNO resulted in immediate precipitation, after the exothermic reaction ceased, of the ester (**343**). Derivatives of ureidooxyacetic acid (**344**) were obtained by reaction of both

aminooxyacetic acid and its esters with phenyl and 1-naphthylisocyanates[27] (Scheme 82). On heating all arylureidooxy derivatives (**344**) in xylene, symmetrical diarylureas were isolated. All aryl derivatives (**344**) gave, with 15% HNO_3, a specific yellow color reaction, sometimes accompanied by a yellow precipitate.

The reaction of ureidooxyacetic acid ester with 1,3-dicarbonyl compounds catalyzed by acid was studied in my laboratory[282, 283]. This reaction brought about the synthesis of cyclic derivatives of ureidooxyacetic acid (Scheme 83). The new products (at that time) demonstrated interesting properties. The IR spectra showed N−H stretching vibrations in the solid state, possibly due to association and hydrogen bond formation between the heterocyclic nitrogens and the carboxyl group. The carboxyl group of **345** had a pKa 2.4 and the pyrimidone ring pKa 0.6. Interestingly, one of the Me group in **347** had D_2O exchangeable protons as observed by NMR.



SCHEME 82

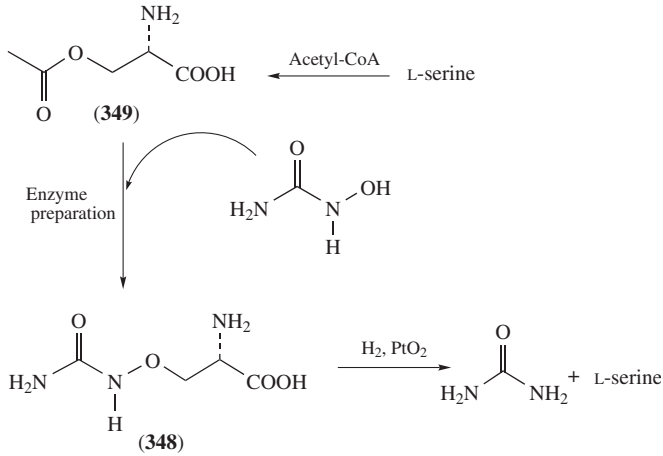


SCHEME 83

2. 2-Amino-3-ureidooxypropionic acid (O-ureidoserine)

D-2-Amino-3-ureidooxypropionic acid (D-*O*-ureidoserine), often named ureidooxyalanine, was obtained by the reaction of D-cylcoserine (**3**) with KCNO in acidic media[222] (pH < 4). The scheme of its formation was discussed in Section III.B.3.e.

L-*O*-Ureidoserine was reported by Murakoshi and coworkers[284] as a product of a specific enzyme extracted and purified from higher plants, especially from *Albizzia*. This enzyme catalyzes the formation of L-*O*-ureidoserine (**348**) from *O*-acetylserine (**349**) and *N*-hydroxyurea (Scheme 84). The enzyme was specific to these substrates, and the identity of the product was established by chromatography and its chemical hydrogenolysis to L-serine and urea (Scheme 84).



SCHEME 84

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Phosphorus derivatives of hydroxylamines, oximes and hydroxamic acids

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I. PHOSPHORUS SUBSTITUTED HYDROXYLAMINE DERIVATIVES

Hydroxylamines have been extensively reviewed[1] and compounds with N−O linkage in their substructure have been found to be an important class of chemical species due to their biological activity. Hydroxylamine derivatives have also become important as intermediates for synthesizing complex nitrogen-containing compounds, especially natural products and their analogues[2]. Such derivatives are found among iron sequestering siderophores[3], inhibitors of 5-lipoxygenase[4], inhibitors of DXP reductoisomerase[5] and inhibitors of metalloproteinase[6].

In this section we consider phosphorus functionalized hydroxylamines derived from phosphines, phosphine oxides, phosphonates etc. We first focus on the synthesis of phosphorus *O*-substituted hydroxylamines (**I**) and phosphorus *N*-substituted hydroxylamines (**II**) (Figure 1), after which their reactivity will be discussed.

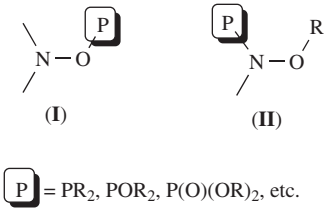
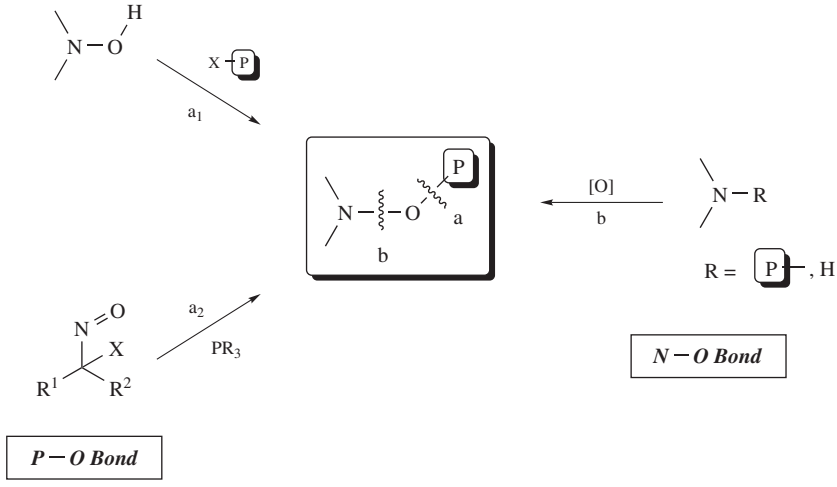


FIGURE 1

A. Synthesis of Phosphorus Substituted Hydroxylamine Derivatives

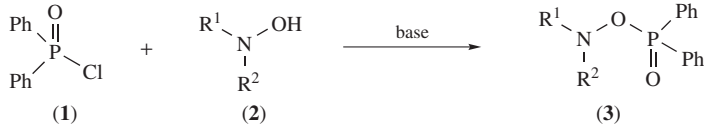
1. Phosphorus O-substituted hydroxylamines

Several strategies have been developed for the preparation of phosphorus *O*-substituted hydroxylamines, such as phosphorus–oxygen single bond formation either by reaction of hydroxylamines and phosphorated halides (Scheme 1, Route a_1) or by reaction of nitroso or nitroxyl derivatives and phosphorus reagents (Scheme 1, Route a_2), and by oxidation reactions where a nitrogen–oxygen single bond is formed (Scheme 1, Route b).



SCHEME 1

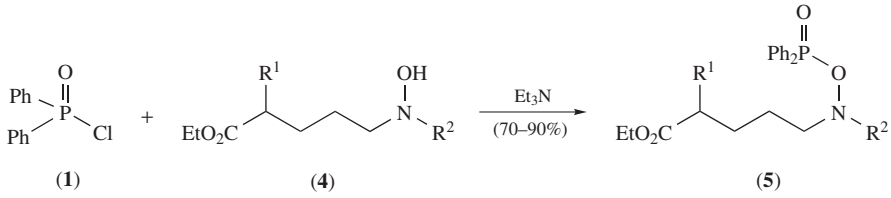
a. Phosphorus–oxygen single bond formation reactions (Scheme 1a). i. Reaction of hydroxylamine derivatives with phosphorated halides. *N*,*N*-Disubstituted and *N*-monosubstituted *O*-phosphinyl hydroxylamines **3** have been prepared by reaction of the corresponding hydroxylamines **2** and diphenylphosphinyl chloride (**1**) in the presence of a base (Scheme 2)[7, 8].



R^1, R^2 = alkyl, H

SCHEME 2

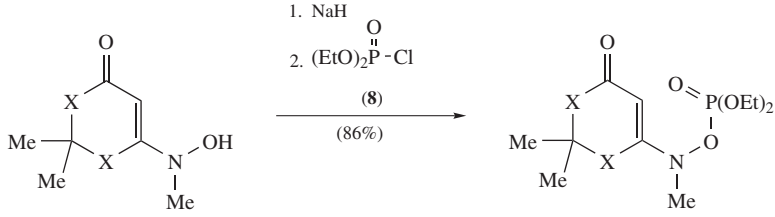
This process has been applied to the preparation of precursors of proline derivatives[9] involving the cyclization of 5-aminovaleric acid derivatives. The substrates **5** were prepared by the reaction of *N*-substituted hydroxylamines with 5-bromovalerate esters



SCHEME 3

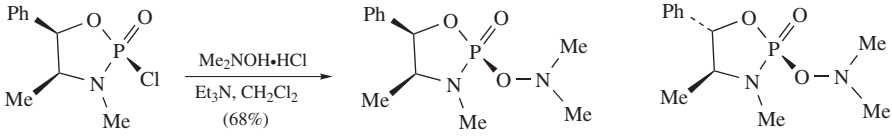
to give 5-(*N*-hydroxyamino) esters **4**, and subsequent reaction with diphenylphosphinyl chloride (**1**) (Scheme 3)[7e, 8b].

N-Vinylhydroxylamine **6** (X = CH_2) can be used as starting material for the preparation of phosphorus functionalized hydroxylamines and, when it reacts with diethyl chlorophosphate (**8**), *O*-phosphoryl hydroxylamine derivative **9** can be prepared (Scheme 4). Similarly, the process is also extended to the preparation of heterocyclic functionalized hydroxylamine compound **10** from pyrimidone derivative **7** (X = MeN)[10].



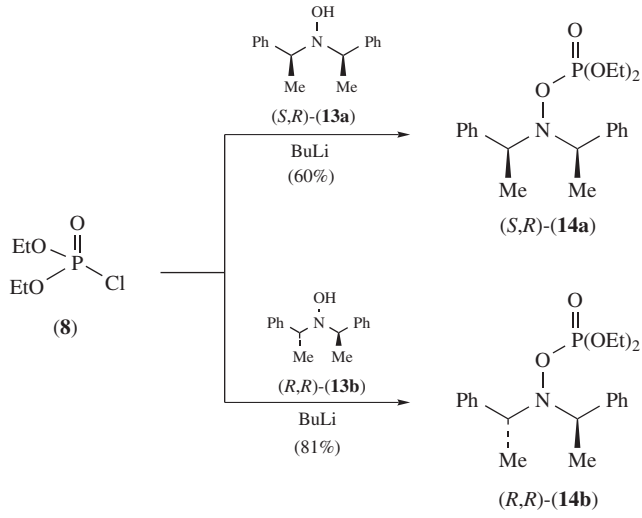
SCHEME 4

Chiral aminating reagents **12** are prepared in a 'one-pot' process from ephedrine, *N*,*N*-dimethylhydroxylamine and phosphorus oxychloride by means of nucleophilic substitution of **11** with *N*,*N*-dimethylhydroxylamine, with retention of configuration at the phosphorus atom (Scheme 5)[11]. These compounds are used (see Section I.B.1.d) for selective C–N bond construction.



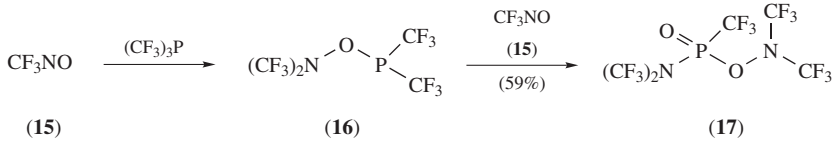
SCHEME 5

Similarly, diethyl hydroxylamino phosphate derivatives **14** have been prepared from reaction of optically active hydroxylamines **13** and diethyl chlorophosphate (**8**) in order to determine the stereochemistry of bis(*N*-phenylethyl)hydroxylamine derivatives **13**[12] (Scheme 6).



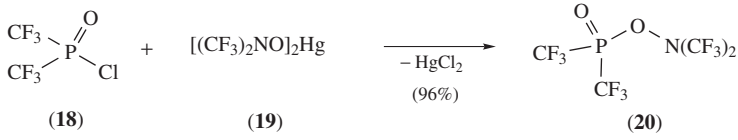
SCHEME 6

ii. Reaction of nitroso- and nitroxyl derivatives with phosphorus reagents. Reaction of trifluoronitrosomethane (**15**) with tris(trifluoromethyl)phosphine affords phosphine oxide derivative **17**[13], whose formation is explained by an initial generation of bis(trifluoromethyl)nitroxybis(trifluoromethyl)phosphine (**16**), followed by the addition of a second molecule of the nitroso compound **15** (Scheme 7).



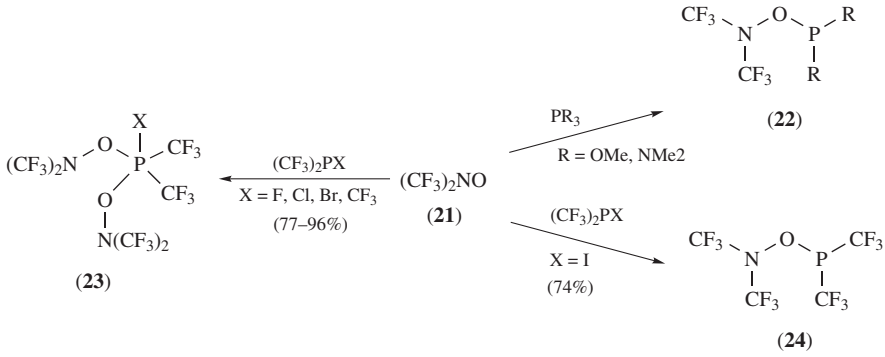
SCHEME 7

Phosphine oxide **20** can be prepared by reaction of bis(trifluoromethyl)phosphinic chloride (**18**) with mercury (II) bis(trifluoromethyl)nitroxide (**19**) in excellent yield (Scheme 8)[13]. Nitrosobis derivatives have also been employed in synthesis of *O*-phosphoryl hydroxylamines[14].



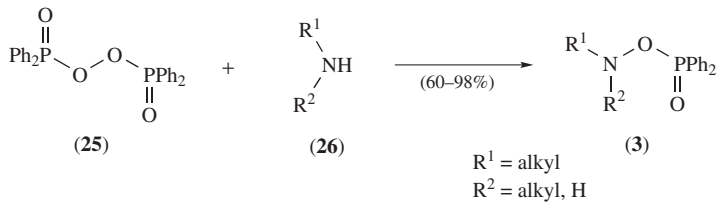
SCHEME 8

Radical reactions of several phosphines with nitroxyl compounds have been studied (Scheme 9). Several *O*-phosphorus compounds which contain the *N*,*N*-bis-(trifluoromethyl)hydroxylamine moiety are prepared from phosphorus halides as PF_3, PBr_3 and PF_2Cl[15]. Moreover, reactions of bis(trifluoromethyl)nitroxide (**21**) with other phosphorus compounds are varied, and it has been reported to undergo addition–elimination reaction with phosphite (R = OMe)[15] and phosphoramide ($R = NMe_2$)[15] derivatives affording phosphorus *O*-hydroxylamine derivatives **22**, and rather different kind of reactions with phosphine $P(CF_3)_3$ or halophosphines such as $P(CF_3)_2X$ to yield compounds **23**, **24** in good to excellent yields[16].



SCHEME 9

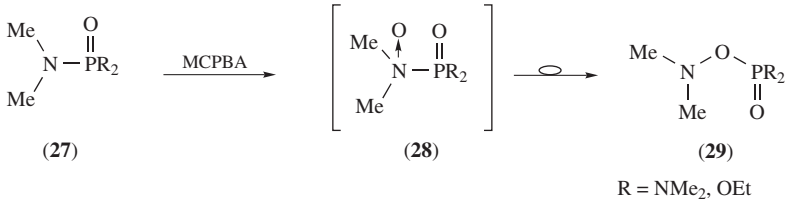
b. Nitrogen–oxygen bond formation reactions (Scheme 1b). Oxidation of primary and secondary amines **26** with bis(diphenylphosphinyl)peroxide (**25**) conveniently leads to the *O*-phosphinylated hydroxylamine derivatives **3** (Scheme 10)[17]. Since the peroxide **25** is easily accessible from the diphenylphosphinyl chloride and disodium peroxide, this is an appropriate method for the synthesis of *N*,*N*-disubstituted and *N*-monosubstituted *O*-phosphinyl hydroxylamines **3**.



SCHEME 10

Dimethyl phosphoramides **27** react with *m*-chloroperbenzoic acid (MCPBA) to yield novel phosphorus *O*-substituted hydroxylamine derivatives **29** via *N*-oxidation to **28** followed by a radical rearrangement with *O*-insertion into the P–N bond (Scheme 11)[18].

To test the sensitivity of the cyclic phosphinamide to MCPBA, as observed for acyclic phosphoramidates[18], the reaction of heterocyclic phosphine oxide **30** with MCPBA has

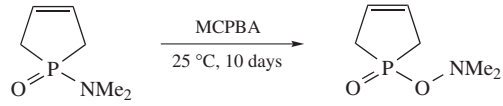


(**27**) (**28**) (**29**)

R = NMe_2, OEt

SCHEME 11

been performed. The formation of compound **31** can be explained by the replacement of the P-amino by a P−O-amino group through an insertion of an oxygen atom between the phosphorus and the nitrogen atoms of the precursor phosphinamide **30** (Scheme 12)[19].

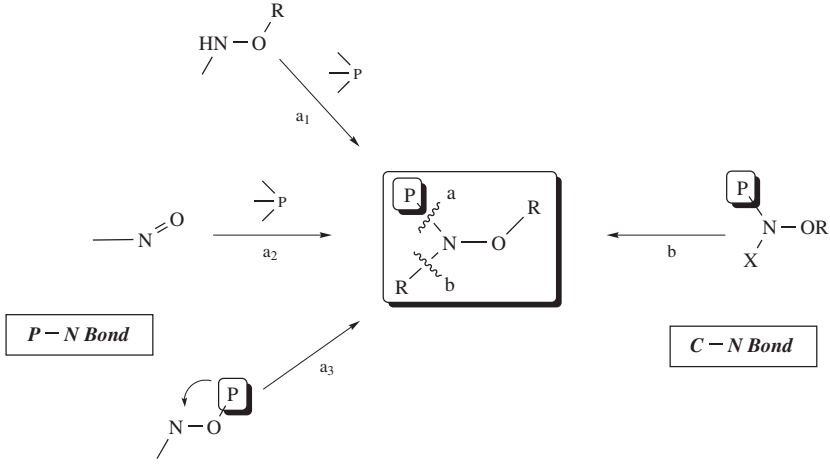


(**30**) (**31**)

SCHEME 12

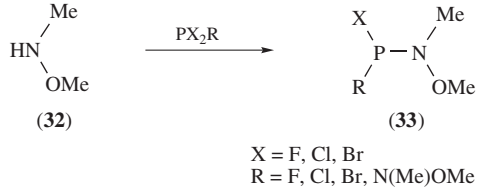
2. Phosphorus N-substituted hydroxylamines

The synthesis of *N*-phosphorus substituted hydroxylamines can mainly be approached by two strategies: first, by phosphorus–nitrogen single bond formation reaction between hydroxylamine derivatives or nitroso compounds and phosphorus reagents (Scheme 13, Routes a_1 and a_2) or by rearrangement reactions (Scheme 13, Route a_3), and second, by carbon–nitrogen single bond formation reaction (Scheme 13, Route b).



SCHEME 13

a. Phosphorus–nitrogen single bond formation reactions (Scheme 13a). i. Reaction of hydroxylamine derivatives with phosphorus reagents. *N*,*O*-Dimethylhydroxylamino halogenophosphines **33** have been prepared by hydroxylaminolysis reaction of halogenophosphines with **32** (Scheme 14)[20]. A restricted P–N rotation bond of bis(*O*,*N*-dimethylhydroxylamino)halogenophosphines has been detected[21].

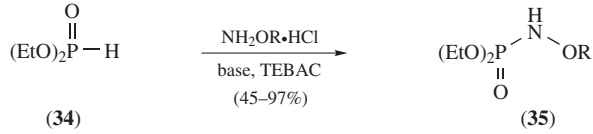


(**32**) (**33**)

X = F, Cl, Br
R = F, Cl, Br, N(Me)OMe

SCHEME 14

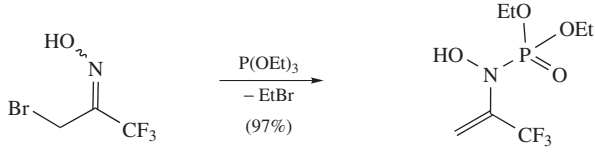
Dialkyl *N*-alkoxyphosphoramidates **35** can be prepared according to the Atherton–Todd method starting from the corresponding phosphite **34** and, for example, *O*-methylhydroxylamine, diethyl *N*-methoxyphosphoramidate[22] or diphenyl *N*-methoxyphosphoramidate[23]. However, due to the low yields obtained, a modified procedure, where the concentration of the base is increased and a catalytic amount of triethylbenzylammonium chloride (TEBAC) is used, was developed to afford the *N*-phosphorylated *O*-alkylhydroxylamines **35** (Scheme 15) in good yields[24].



(**34**) (**35**)

SCHEME 15

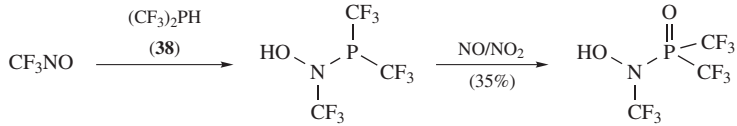
Trialkyl phosphites could react with α-bromo ketones to give either Arbuzov (phosphonate formation) or Perkow pathway products (enol phosphate formation). Triethyl phosphite and 3-bromo-1,1,1-trifluoropropane-2-oxime (**36**) reacted in a Perkow-type reaction with ene-oximophosphate formation to yield [*N*-hydroxy-*N*-(1-trifluoromethylethenyl)]amido diethylphosphate (**37**) (Scheme 16)[25].



(**36**) (**37**)

SCHEME 16

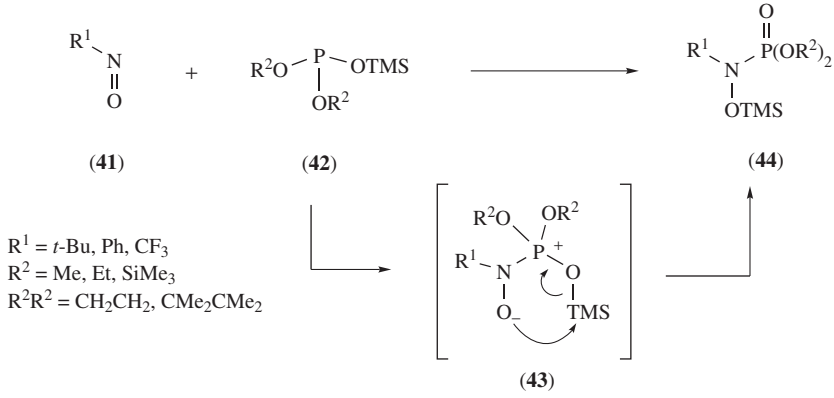
ii. Reaction of nitroso compounds with phosphorus reagents. Trifluoronitrosomethane (**15**) reacts with bis(trifluoromethyl)phosphine (**38**) to give the phosphoryl-substituted hydroxylamine **40**, via a *N*-phosphino hydroxylamine intermediate **39** (Scheme 17)[13].



(**15**) (**39**) (**40**)

SCHEME 17

Addition of *O*-silylated phosphites **42** to 2-methyl-2-nitrosopropane (**41**) ($R^1 = t$-Bu) or nitrosobenzene (**41**) (R^1 = Ph) furnished *N*-(trimethylsilyloxy)amidophosphates **44**, via 1,4-trimethylsilyl group shift in intermediate **43** (Scheme 18)[25b]. Trifluoronitrosomethane (**41**) ($R^1 = CF_3$) reacts with different phosphines, among them $(EtO)_2POSiMe_3$ or $(Me_3SiO)_3P$ to give the corresponding phosphinylhydroxylamine derivatives[13].



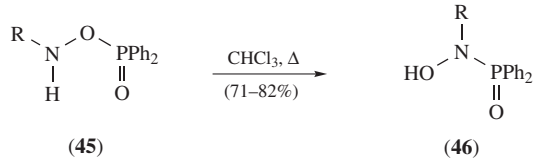
(**41**) (**42**) (**44**)

(**43**)

SCHEME 18

iii. Rearrangement reactions. *N*-Alkyl-*O*-(diphenylphosphinyl)hydroxylamines **45**, whose preparation has been outlined previously (see Section I.A.1.a.i), rearrange on heating to the thermodynamically more stable *N*-phosphinylated derivatives, the *N*-alkyl-*N*-(diphenylphosphinyl)hydroxylamines **46** (Scheme 19) (see Section I.B.1.a)[26].

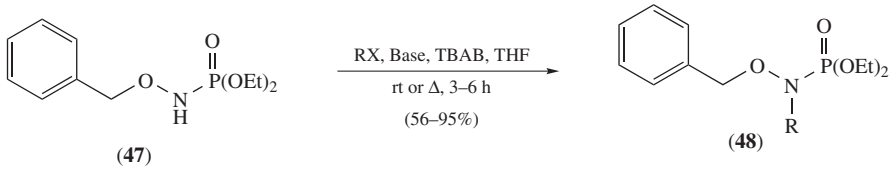
b. Carbon–nitrogen single bond formation reactions (Scheme 13b). Easily available *N*-(diethoxyphosphoryl)benzyloxylamine (**47**) was shown to be a convenient protected substrate for regioselective *N*-alkylation by means of diverse halides under basic conditions (sodium hydride/tetrabutylammonium bromide (TBAB))[27]. The phosphorylated compound **47** was prepared according to the literature procedure from *N*-benzyloxylamine hydrochloride and diethyl phosphonate[24]. *N*-Alkylation to **48** is performed using different



(**45**) (**46**)

R = Et, *n*-Pr, *n*-Bu, *t*-Bu, *n*-Pr_2CH

SCHEME 19



(**47**) (**48**)

R = Me, *i*-Pr, *i*-Bu, Allyl, $(CH_2)_3Br$, $(CH_2)_4Br$, Bn, Bu, $(CH_2)_3N(OBn)P(O)(OEt)_2$, $(CH_2)_3P(O)(OEt)_2$

SCHEME 20

bases for metallation, and the best yield is obtained at room temperature when sodium hydride and catalytic amounts of TBAB are used (Scheme 20).

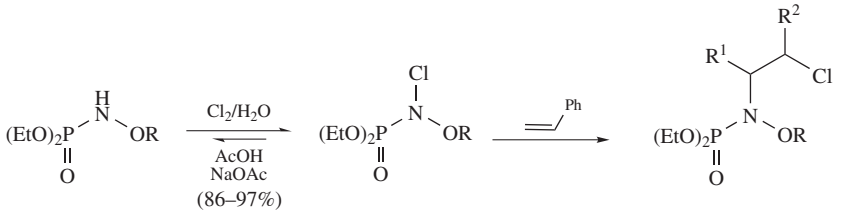
Dialkyl *N*-alkoxyphosphoramidates **35** are good starting materials for the synthesis of halophosphoramides **49**, which can serve as reagents for the regiospecific functionalization of terminal C−C double bonds[24]. The method of synthesis of halophosphoramides consists in the chlorination of diethyl *N*-alkoxyphosphoramidates **35** by means of gaseous chlorine at room temperature in an aqueous buffered solution containing acetic acid and sodium acetate (Scheme 21). The compounds **49** are much more reactive toward 1-alkenes than diethyl *N*,*N*-dichlorophosphoramidate, undergoing addition reaction to afford two regioisomers **50** and **51** in a 3:1 ratio, the *anti*-Markovnikoff adduct **50** being the main component of the mixture, apparently formed by a free-radical reaction.

B. Reactivity of Phosphorus Substituted Hydroxylamine Derivatives

1. Phosphorus O-substituted hydroxylamines

a. Rearrangement reactions. *N*-Alkyl-*O*-(diphenylphosphinyl)hydroxylamines rearrange on heating to the thermodynamically more stable *N*-phosphinylated derivatives and have been used for the preparation of *N*-alkyl-*N*-(diphenylphosphinyl)hydroxylamines (see Section I.A.2.a.iii)[26]. When bis(trifluoromethyl)nitroxybis(trifluoromethyl)phosphine (**24**) obtained by reaction of trifluoronitrosomethane (**15**) with tris(trifluoromethyl)-phosphine (see Section I.A.1.a.ii) is heated at 100 °C, it undergoes isomerization to give the corresponding phosphine oxide **52** (Scheme 22)[13].

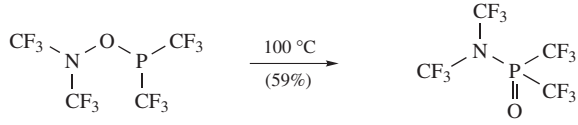
Cleavage of the N−O bond has been reported by thermal treatment of *O*-phosphoryl hydroxylamines **9** ($X = CH_2$) or **10** ($X = MeN$) obtained by reactions between enehydroxylamines and diethyl chlorophosphate (see Section I.A.1.a.i). Subsequent



(**35**) (**49**)

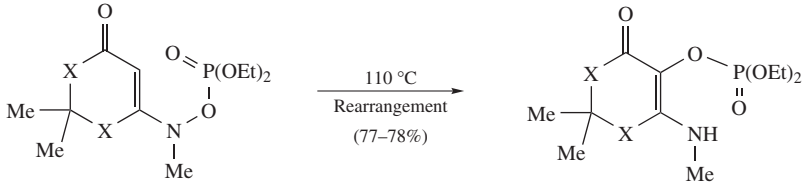
(**50**) R^1 = H, R^2 = Ph (20%)
(**51**) R^1 = Ph, R^2 = H (7%)

SCHEME 21



(**24**) (**52**)

SCHEME 22



(**9**) X = CH_2
(**10**) X = MeN

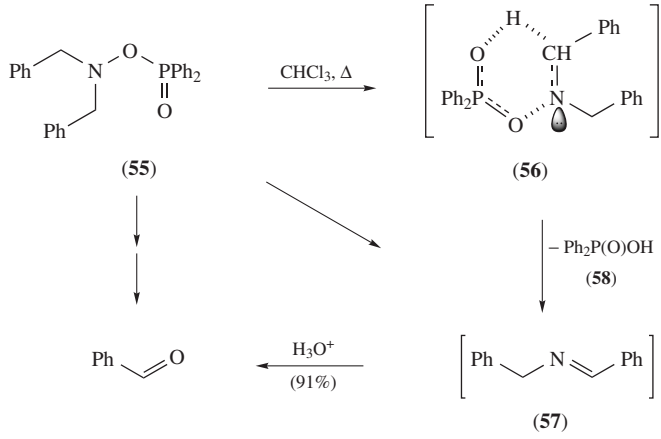
(**53**) X = CH_2
(**54**) X = MeN

SCHEME 23

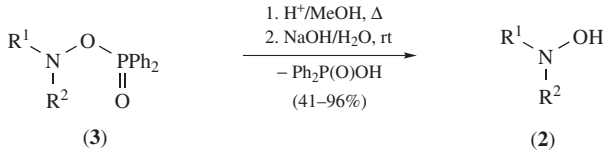
rearrangement affords functionalized enaminone **53** or 1,2-dihydropyrimidin-4-one **54**, respectively (Scheme 23)[10].

However, when *N*,*N*-dibenzyl-*O*-(diphenylphosphinyl)hydroxylamine (**55**) is heated, imine **57** and diphenylphosphinic acid **58** are obtained (Scheme 24)[17,28]. This mode of elimination may be rationalized by a cyclic transition state **56** involving the phosphinyl group. Thermal oxidative deamination of amines is achieved by reaction with bis(diphenylphosphinyl)peroxide (see Section I.A.1.b) without isolation of the intermediate *N*,*N*-disubstituted-*O*-(diphenylphosphinyl)hydroxylamines **55** which, upon heating, gives regioselectively the unstable imines **57**, isolated as benzaldehyde.

b. Hydrolysis reactions. Acidic hydrolysis of *N*-alkyl- ($R^2 = H$) or *N*,*N*-dialkyl *O*-(diphenylphosphinyl)hydroxylamines **3** can afford hydroxylamines **2** in good yields by means of P—O bond cleavage (Scheme 25)[7a,b,g]. Similarly, *N*,*N*-bis(trifluoro-



SCHEME 24



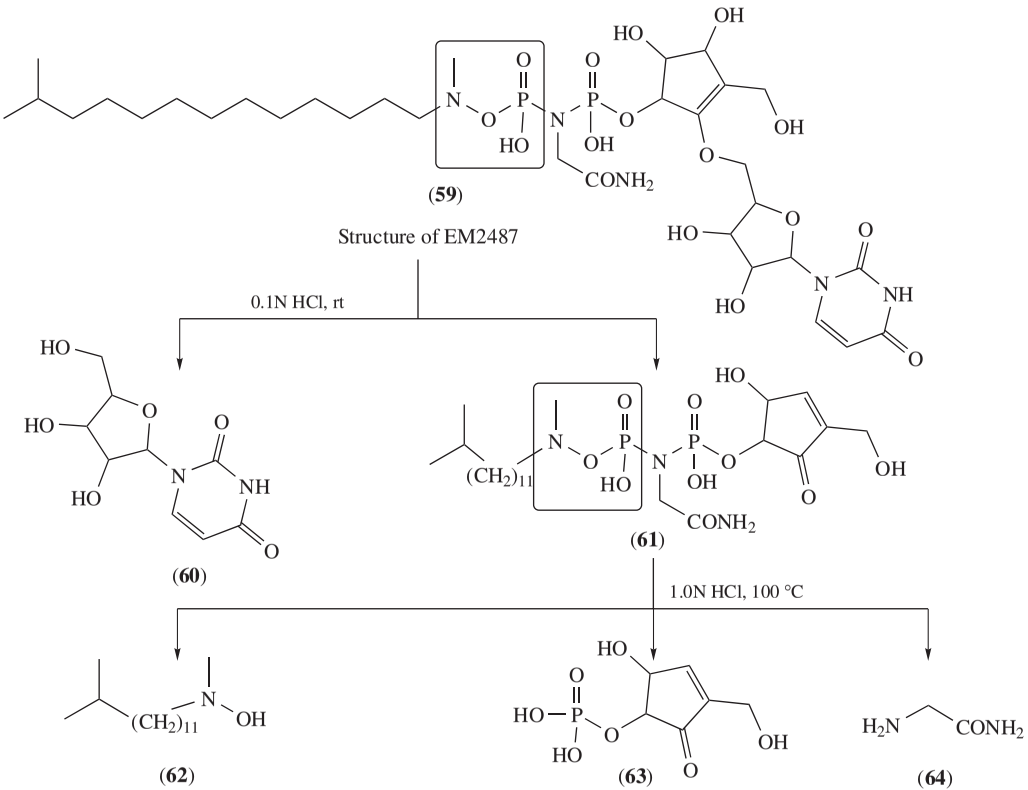
SCHEME 25

methyl)hydroxylamine **2** ($R^1 = R^2 = CF_3$) is obtained by the hydrolysis of *N*,*N*,*P*,*P*-tetratrifluoromethyl *O*-phosphinylhydroxylamine[13] in the presence of hydrochloric acid.

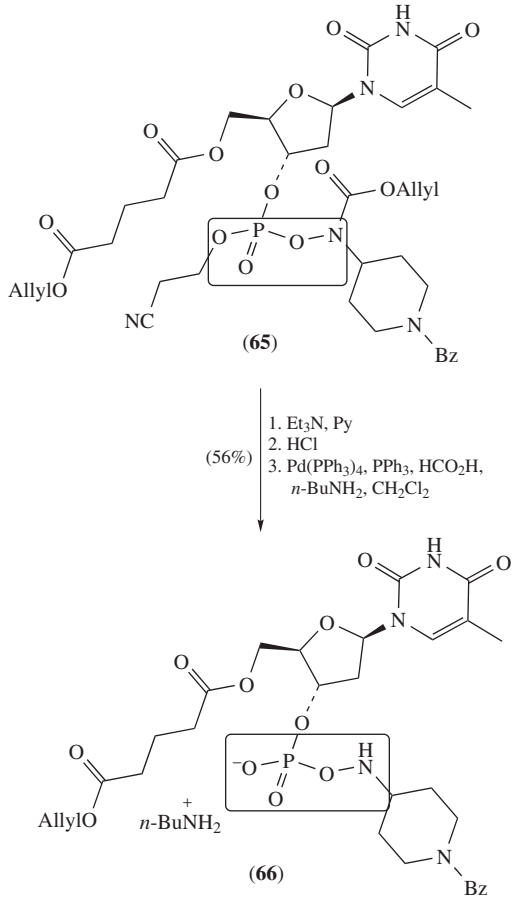
Compound EM2487 (**59**), a product isolated from *Streptomyces* sp. Mer-2487, has an inhibitory effect on HIV-1 replication in chronically infected cells as well as acutely infected cells[29]. EM2487 is a new class of secondary metabolites of microbial origin whose structure is completely different from that of known nucleoside antibiotics. In order to elucidate the unique structure of the title compound, hydrolysis reactions were performed. The fragments **60**–**64** support the presence of *O*-phosphorus substituted hydroxylamine moiety in the structure of compound EM2487 (Scheme 26).

On the other hand, the [P(O)−O−N] functionality has been rarely found in dinucleotides[30]. However, a protected-*O*-phosphorylhydroxylamine moiety occurs in the stable hapten **66**. Its preparation has been reported by deprotection of the cyanoethyl group of **65** (Et_3N in pyridine) followed by removal of the two allyl-based protecting groups ($Pd(PPh_3)_4$, PPh_3, *n*-$BuNH_2$ and HCO_2H in CH_2C1_2) to give the hapten **66** as the *n*-butylammonium salt (Scheme 27). The order of those deprotection steps is very important since an initial cleavage of the allyl groups from **65** could give an unidentified mixture.

c. Reduction reactions. Amino diethyl phosphate derivatives of hydroxylamine **14a**,**b** have been prepared in order to determine the stereochemistry of obtained *N*-phenylethylhydroxylamines (see Section I.A.1.a.i). The identity of hydroxylamines **14a**,**b** was established by lithium-ammonia reduction of their diethyl phosphate derivatives to the known *N*,*N*-bis(α-phenylethyl)amines **67a**,**b** (Scheme 28)[12].



SCHEME 26

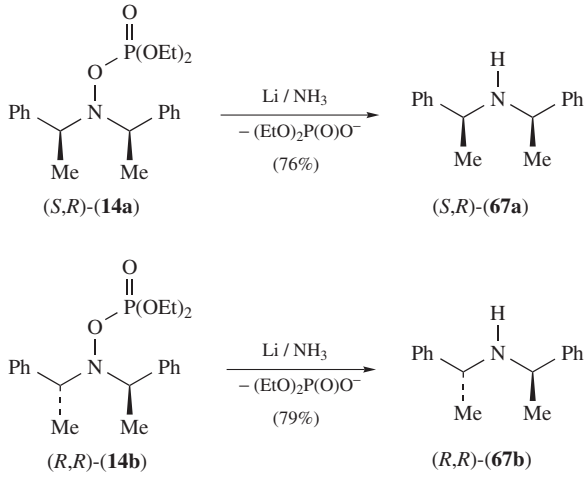


SCHEME 27

d. Electrophilic amination. *O*-Phosphorus substituted hydroxylamines **69** have been often used as aminating reagents[31] in an electrophilic amination. The process was applied for carbon–nitrogen or nitrogen–nitrogen bond formation, e.g. of amines or hydrazines **71** and salt **70** from **68** ($R^1 = R_3C$, R_2N) (Scheme 29).

When Grignard reagents derived from phenylacetylene are used with *O*-phosphinylated aminating reagents, the corresponding ethinylamino (ynamine) derivatives are obtained through carbon–nitrogen bond formation reaction[7c]. Likewise, the *O*-(trimethylsilyl)aldehyde cyanohydrin anions **74** react with *O*-phosphinylated aminating reagents **75** to give amines **76**. This electrophilic amination corresponds to a mild and specific oxidation of the aldehydes **72** to the amides **77** via **73–76** (Scheme 30), which proceeds in basic medium[7b].

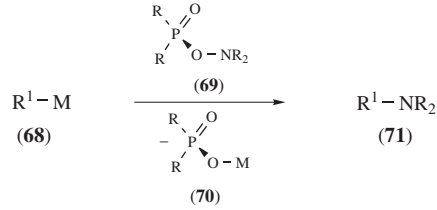
The preparation of proline derivatives has been attempted by intramolecular nucleophilic substitution on the nitrogen atom[9]. In this case, the cyclization of 5-aminovaleric acid derivatives with diphenylphosphinyloxy[7e, 8b] substituents as leaving group is involved



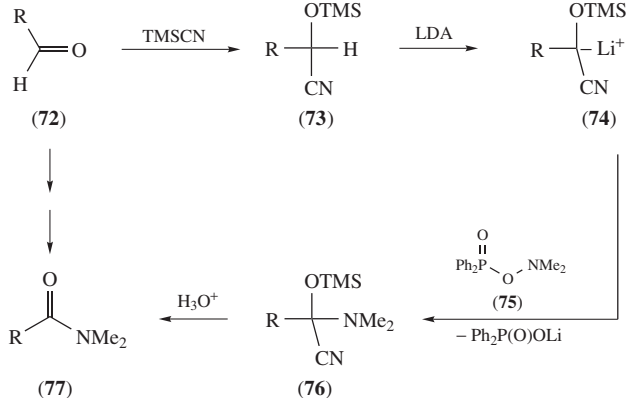
(*S*,*R*)-(**14a**) (*S*,*R*)-(**67a**)

(*R*,*R*)-(**14b**) (*R*,*R*)-(**67b**)

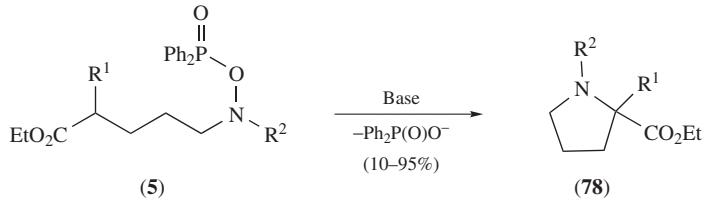
SCHEME 28



SCHEME 29



SCHEME 30

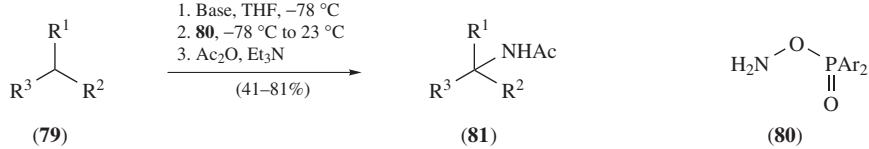


(**5**) (**78**)

SCHEME 31

(see Section I.A.1.a.i). Treatment of compounds **5** with a base affords the target pyrrolidines **78** through a cyclization process (Scheme 31).

O-Di(*p*-methoxyphenylphosphinyl)hydroxylamine (**80**) reacts efficiently with stabilized sodium or potassium enolates derived from malonates, phenylacetates and phenylacetonitriles **79** and it is sufficiently soluble for its use in solution at −78 °C (Scheme 32)[32]. As the pK_a of the substrate increases, amination yield to **81** decreases. Aminations using these reagents **80** are improved with respect to those using (diphenylphosphinyl)hydroxylamine (**80**) (Ar = Ph)[7e, 8b].



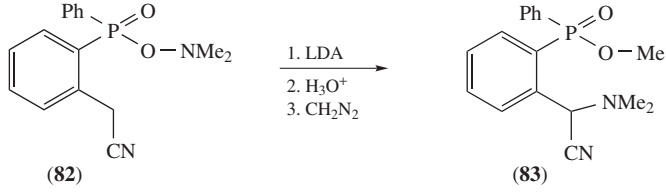
(**79**) (**81**) (**80**)

R^1 = H, Ph, CN
R^2 = CO_2Et, Ph, H
R^3 = CO_2Et, Ph

Ar = *p*-$MeOC_6H_4$

SCHEME 32

Boche and coworkers establish that nucleophilic substitution occurs at the nitrogen of *O*-(*N*,*N*-dimethylamino)diarylphosphinyl derivative **82**,[7b, 11, 17]. Compound **82** converts into **83** on treatment with LDA followed by reaction with water, acidification and treatment with diazomethane (Scheme 33).

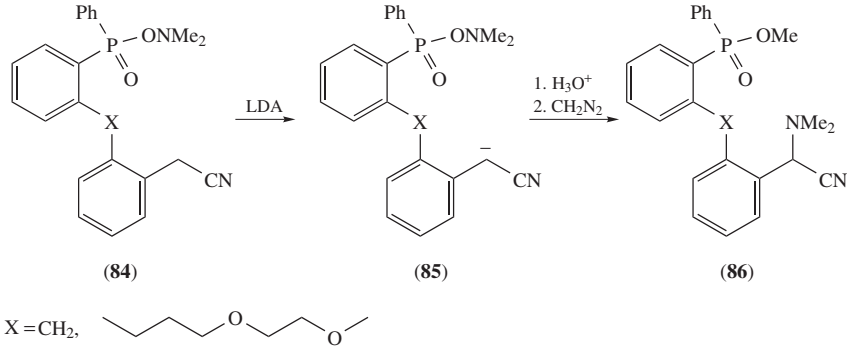


(**82**) (**83**)

SCHEME 33

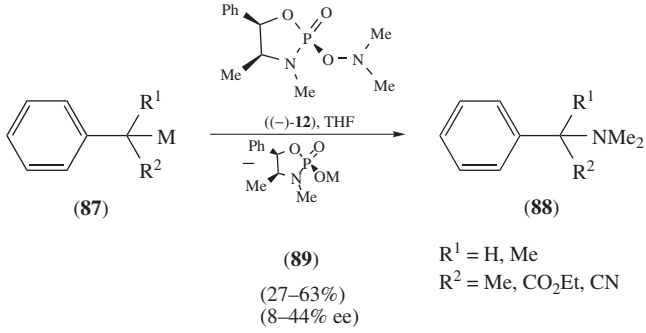
Transfer of nitrogen from oxygen to carbanions could take place within large endocyclic rings[33]. In order to distinguish between the intermolecular and intramolecular pathways,

the conversion of **84** to **86** via carbanion **85** is studied[8]. The results obtained show that the reaction proceeds via a trigonal bipyramidal transition structure and that a large bond angle is required for nucleophilic displacement at nitrogen. When a ring is of sufficient size to allow both the entering and leaving groups to be simultaneously apical in a trigonal bipyramidal transition structure, an intramolecular endocyclic reaction would be expected. This study has been carried out in a prospective 16-membered ring (Scheme 34).



SCHEME 34

The chiral aminating reagents (−)-**12** and (+)-**12** have been prepared in a 'one-pot' reaction from (−)-ephedrine and (+)-ephedrine[11] (see Section I.A.1.a.i). These compounds react with carbon nucleophiles **87** to yield **89** and the optically active amines **88** with moderate conversion and up to 44% ee (Scheme 35).



SCHEME 35

N−N bond formation can also be performed by the use of this kind of aminating agents. *N*,*N*-disubstituted *O*-(diphenylphosphinyl)hydroxylamines are useful reagents in electrophilic amination reactions[34]. The reactions of the *O*-(diphenylphosphinyl)hydroxylamines **90** with the amines **91**–**93** lead to the hydrazines **94**, formed via electrophilic amination, and the symmetrical azo compounds **96**[35]. The behavior of the acceptor substituted *O*-(diphenylphosphinyl)hydroxylamines **90** towards *N*-methylaniline

(**91**), morpholine (**92**) and di-*n*-propyl amine (**93**) has been studied, and it was shown that the acceptor qualities of substituents increase in the order COMe < CN < SO_2Me < NO_2 and the basicity of amines from **91** to **93** (Scheme 36). There is a competition between the nucleophilic attack of the amines **91**–**93** on the electrophilic nitrogen atoms of **90** to give hydrazines **94**, and a reaction starting with deprotonation which leads to symmetrical azo compounds **96** through the corresponding ammonium salts **95**.

The carcinogenic potential of aromatic amines has been related with the nucleophilic substitution reaction at an electrophilic nitrogen center. For example, in reaction between *N*-(4-cyanophenyl)-*O*-(diphenylphosphinyl)hydroxylamine (**97**) with *N*-methylaniline (**98**) the hydrazine **99** is obtained, according with a S_N2 reaction at the electrophilic nitrogen atom (Scheme 37)[8c].

e. Oxidation reactions. Derivatives **29** under oxidation conditions afford the corresponding phosphinic acid derivatives **102**, via *N*-oxide intermediate **101**, or the corresponding phosphinic anhydride **103** by reaction of the *N*-methylhydroxylamine derivative **100** with the aromatic carboxylic acid (Scheme 38)[18].

2. Phosphorus N-substituted hydroxylamines

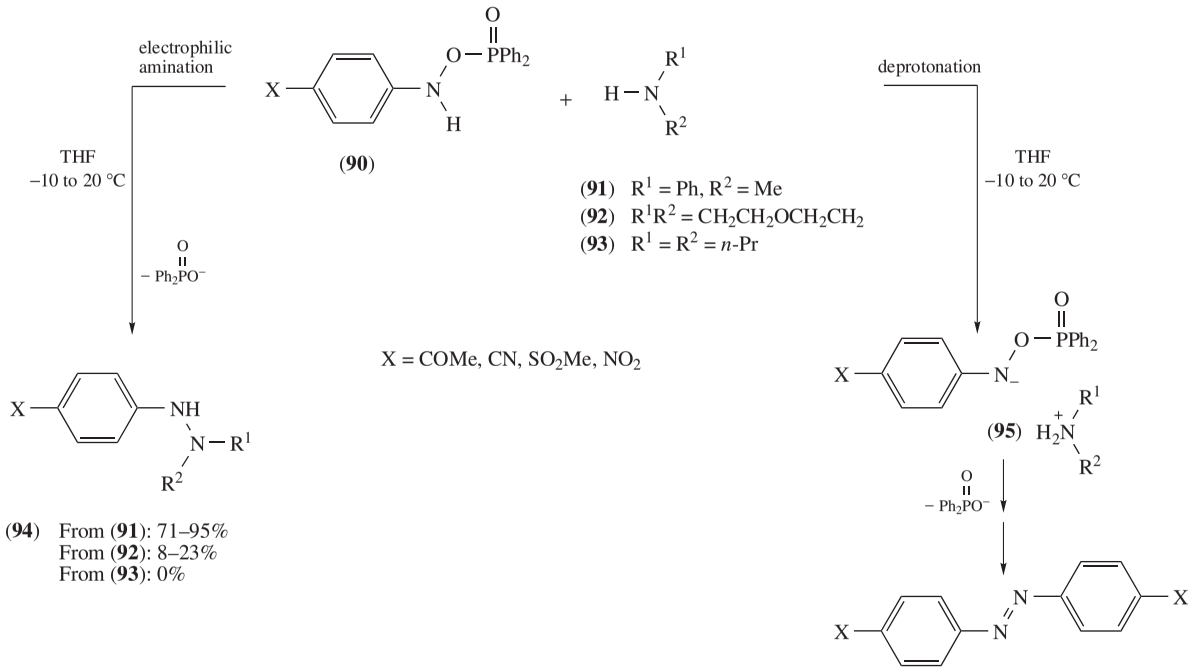
a. Rearrangement reactions. Among studies of amine oxidation with bis(diphenylphosphinyl)peroxide (**25**), a general method for the preparation and isolation of *N*-alkyl-*N*-(diphenylphosphinyl)hydroxylamines **46** (R = *n*-Bu) or *N*-alkyl-*O*-(diphenylphosphinyl) hydroxylamine (**106**) through intermediates **104** and **105** has been reported (see Section I.A.2.a.iii)[26]. In methanolic solution, **106** reacts with sodium methoxide at room temperature to give nearly equal amounts of diphenylphosphinic acid derivative **107** and methyl diphenylphosphinate (**109**) together with imine **108** and hydroxylamine **110**, by competing attack of methoxide at the O−NH moiety or at the phosphorus atom of **106**, respectively (Scheme 39). Similar rearrangements have been reported previously (R = H)[36].

b. Hydrolysis reactions. Taking into account the lability of the P−N bond, dephosphorylation of *N*-substituted-*O*-benzylhydroxylamines **48** (see Section I.A.2.b) has been carried out by treatment with 4M HCl in ethanol at reflux, and the corresponding dephosphorylated compounds **111** were obtained as crystalline hydrochlorides, as oxalate hemiacetals or as free amines (Scheme 40)[27]. Therefore, phosphoryl groups can be regarded as convenient protecting groups for hydroxylamines.

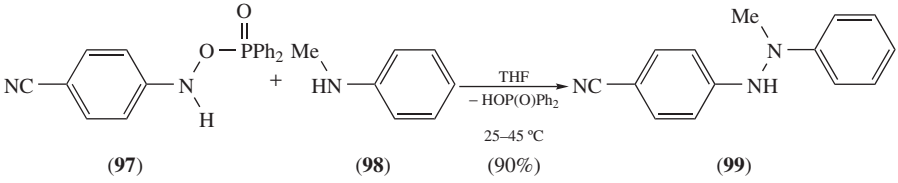
c. N-Alkylation reactions. N-Phosphorylated *O*-alkylhydroxylamines are good starting materials for the synthesis of halophosphoramides, which can serve as reagents for the regiospecific functionalization of terminal C−C double bonds[24], as has been reported by the reaction of diethyl *N*-alkoxyphosphoramidates with alkenes (see Section I.A.2.b).

d. Oxidation reactions. Trifluoronitrosomethane (**15**) reacts with bis(trifluoromethyl)-phosphine to give the phosphinyl substituted hydroxylamine **40**[37], probably via a *N*-phosphino-hydroxylamine followed by oxidation (see Section I.A.2.a.ii, Scheme 17)[13]. Similarly, previous reactions with diethyl phosphite affording hydroxamic acid derivatives have been reported[38].

e. Elimination reactions. [*N*-Hydroxy-*N*-(1-trifluoromethylethenyl)]amido diethylphosphate (**37**) is obtained by reaction of triethyl phosphite and 3-bromo-1,1,1-trifluoropropane-2-oxime (**36**) (see Section I.A.2.a.i). Compound **37** adds water in

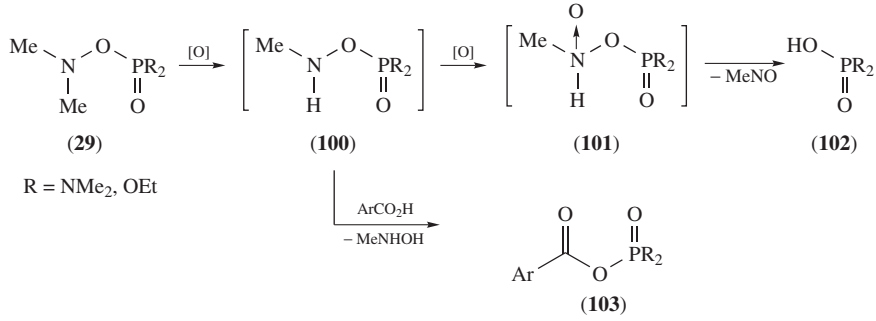

electrophilic amination
THF
−10 to 20 °C
− Ph2PO−
(90)
(91) R1 = Ph, R2 = Me
(92) R1R2 = CH2CH2OCH2CH2
(93) R1 = R2 = n-Pr
X = COMe, CN, SO2Me, NO2
deprotonation
THF
−10 to 20 °C
(95)
(94) From (91): 71–95%
From (92): 8–23%
From (93): 0%
(96) From (91): 0%
From (92): 70–80%
From (93): 90–93%

SCHEME 36



(**97**) (**98**) (90%) (**99**)

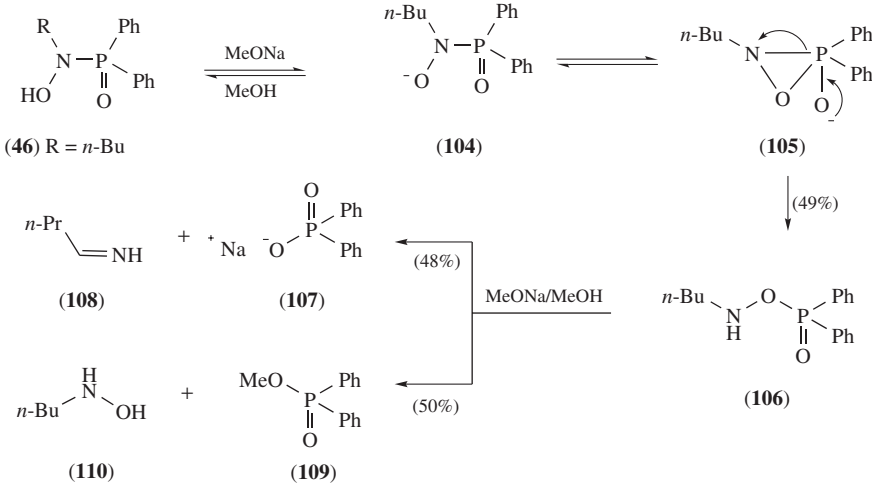
SCHEME 37



(**29**) (**100**) (**101**) (**102**)

(**103**)

SCHEME 38



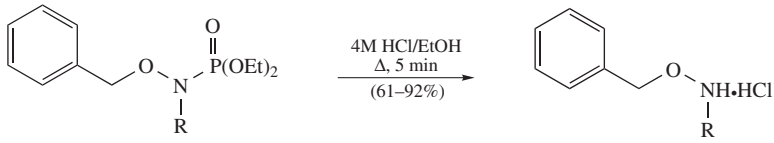
(**46**) R = *n*-Bu (**104**) (**105**)

(**106**)

(**108**) (**107**)

(**110**) (**109**)

SCHEME 39

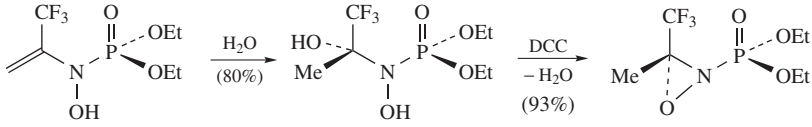


(**48**) (**111**)

R = Me, *i*-Pr, *i*-Bu, Allyl, $(CH_2)_3Br$, $(CH_2)_4Br$, Bn, Bu, $(CH_2)_3N(OBn)P(O)(OEt)_2$, $(CH_2)_3P(O)(OEt)_2$

SCHEME 40

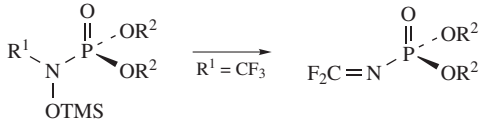
a Markovnikov manner across the C−C double bond to form [*N*-hydroxy-*N*-(1-trifluoromethyl-1-hydroxyethyl)]amido diethyl phosphate (**112**)[25]. Subsequently, water may be abstracted using dicyclohexylcarbodiimide (DCC) to give the corresponding *N*-phosphorylated 3-methyl-3-trifluomethyloxaziridine **113** (Scheme 41).



(**37**) (**112**) (**113**)

SCHEME 41

Addition of nitrosoalkanes to *O*-silylated phosphites furnished colorless *N*-trimethylsiloxyamidophosphates (see Section I.A.2.a.ii)[25b]. *N*-Phosphorylated-*O*-silylhydroxylamines **44** ($R^1 = CF_3$), prepared by addition of nitrosotrifluoromethane to *O*-silylated phosphites, such as $(EtO)_2POSiMe_3$, or to phosphines, as $(Me_3SiO)_3P$, lead to the formation of *N*-phosphorus substituted imines **114** by fluorine elimination (Scheme 42).



(**44**) (**114**)

SCHEME 42

II. PHOSPHORUS SUBSTITUTED OXIMES

Many reviews have appeared describing the occurrence and general studies of oximes[1]. The purpose of this section is to illustrate synthetic aspects of functionalized oximes containing phosphorus substituents. First the synthesis and then the reactivity of phosphorus *O*-substituted oximes (**III**), *C*-substituted oximes (**IV**) and oximes with α- and β-phosphorus substituents (**V** and **VI**, respectively) will be discussed. Oximes functionalized with phosphines (PR_2), phosphine oxides ($P(O)R_2$), phosphonates ($P(O)(OR)_2$) and phosphonium salts ($^+PR_3$), including some sulfur and nitrogen derivatives, are then considered (Figure 2).

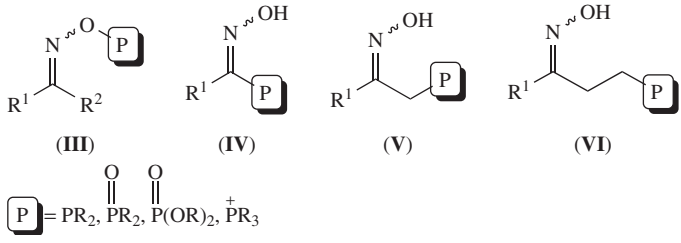
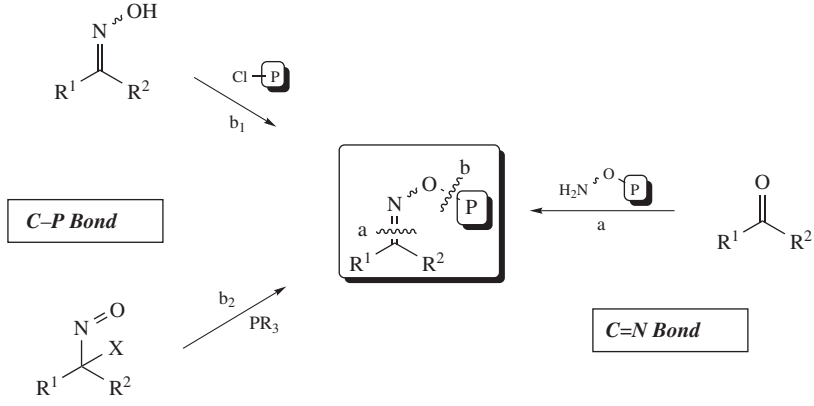


FIGURE 2

A. Synthesis of Phosphorus Substituted Oximes

1. Phosphorus O-substituted oximes

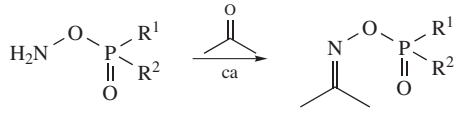
The most common approaches to synthesize phosphorus *O*-substituted oximes comprise the formation of a carbon–nitrogen double bond starting from carbonyl compounds and phosphorus *O*-functionalized hydroxylamines (Scheme 43, Route a). The formation of a phosphorus–oxygen single bond either from oximes and chlorophosphorus reagents (Scheme 43, Route b_1) or from halonitroso compounds and phosphines or phosphites (Scheme 43, Route b_2) are also described.



SCHEME 43

a. Carbon–nitrogen double bond formation. Reaction of ketones with hydroxylamine (Scheme 43a). *O*-Phosphinylated hydroxylamines **115** ($R^1 = R^2 =$ Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$; $R^1 =$ Ph, $R^2 =$ *p*-$MeOC_6H_4$) (see Section I.A.1.a.i) condense with acetone at room temperature to yield phosphinylacetone oximes **116** (Scheme 44)[7f].

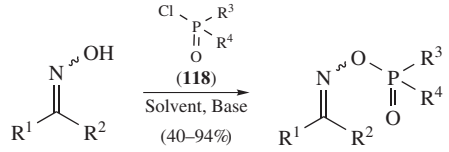
b. Phosphorus–oxygen single bond formation (Scheme 43b). i. Reaction of oximes with phosphorated halides. The preparation of *O*-phosphorated oximes **119** is usually carried out by direct *O*-phosphorylation of simple oximes **117** with phosphinoyl clorides **118** in



(**115**) (**116**)

SCHEME 44

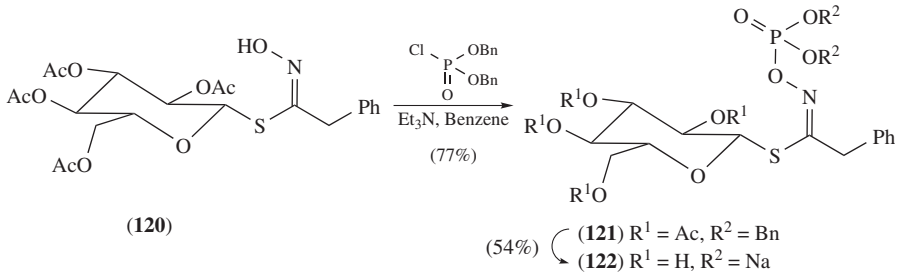
the presence of a base (Scheme 45). The process is quite general and can be applied to simple oximes derived from aldehydes ($R^1 = H$), ketones (R^1 and $R^2 \neq H$) and amidoximes ($R^1 = Me_2N$)[25a, 39].



(**117**) (**119**)

SCHEME 45

Following this strategy, the synthesis of a phosphate bio-isostere of glucosinolate glucotropaeolin **122** has been achieved by *O*-phosphorylation of glucose-derived oxime **120** with dibenzyl chlorophosphonate to give **121**, followed by catalytic hydrogenolysis of the benzyl groups and subsequent hydrolysis of the acetyl protecting groups (Scheme 46)[40].

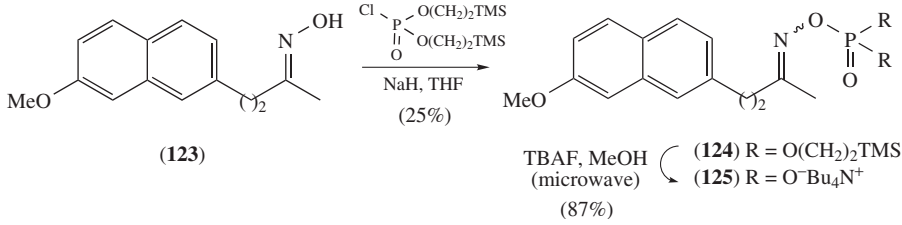


(**120**)

SCHEME 46

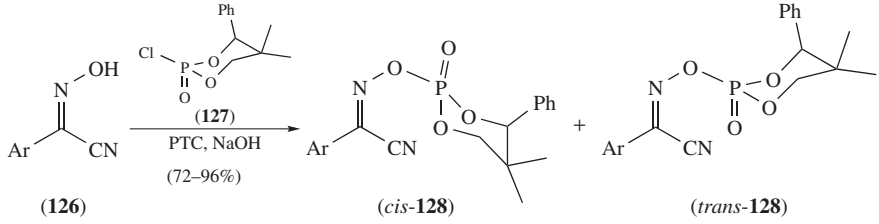
Water-soluble oxime **125** has been also prepared by phosphorylation of oxime **123** using a silylated phosphochloridate. The initially generated oxime **124** undergoes a dealkylation reaction of the phosphate using tetrabutylammonium fluoride (TBAF) under microwave irradiation. Phosphate promoieties attached to a hydroxyl group are hydrolyzed by alkaline phosphatase affording, in this case, a hydrogen free oxime **125** prodrug of ketone Nabumetone (Scheme 47)[41].

O-Functionalization reaction of oximes **126** (Ar = Ph, *o*-ClC_6H_4, *p*-ClC_6H_4, *p*-*t*-BuC_6H_4, *p*-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$) with a cyclic phosphorochloridate **127**,



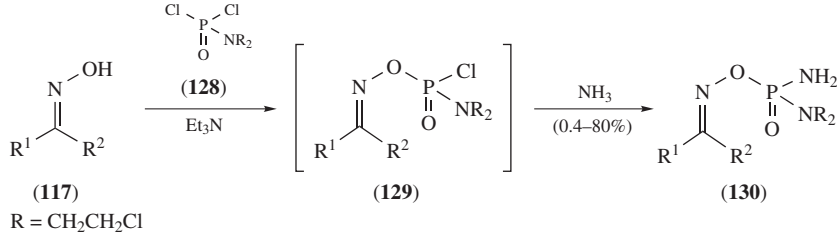
SCHEME 47

in its *trans* configuration, in the presence of a phase transfer catalyst and a base results in the randomization of configuration on the phosphorus center, to give both phosphorylated oxime isomers, *cis*-**128** and *trans*-**128**. The *trans* relative configuration between the phosphoryl oxygen and the Ar = Ph group in the 6-membered ring is preferred (*cis*/*trans* ratios from 1/9 to 1/99) (Scheme 48)[42]. The same effect has been observed in the phosphorylation of oximes **126** (Ar = Ph) with other 5- and 6-membered phosphorochloridates or phosphorochloridothioates[43].



SCHEME 48

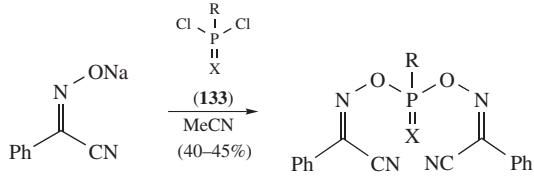
Dichlorophosphoramide **129** reacts with oximes **117** ($R^1 = R^2$ = Me, Et, *i*-Pr, *i*-Bu, Ph; R^1 = Me, R^2 = H, Et, Ph; R^1 = Ph, R^2 = H; $R^1R^2 = (CH_2)_4$, $(CH_2)_5$), affording *O*-phosphorated oxime **131** upon treatment of intermediate **130** with ammonia (Scheme 49)[44].



SCHEME 49

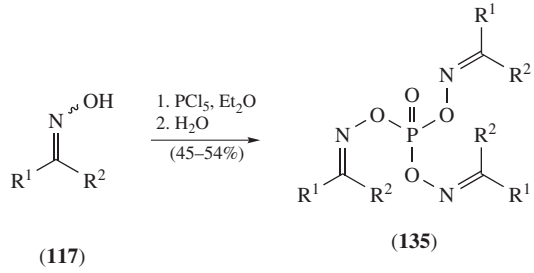
Oxime sodium salt **132** reacts with dichlorophosphate **133** (X = O, R = OEt), dichlorophosphinate **133** (X = O, R = *c*-C_6H_{11}), dichlorothiophosphate **133** (X = S,

R = OEt) or dichlorothiophosphinate **133** (X = S, R = *c*-C_6H_{11}) to yield the dimeric structure **134** (Scheme 50), where the phosphorus acts as bridging atom. As expected, lower reactivity is observed for thio derivatives, given the lower ability of the P=S group to activate the nucleophilic displacement of chlorine[43].



SCHEME 50

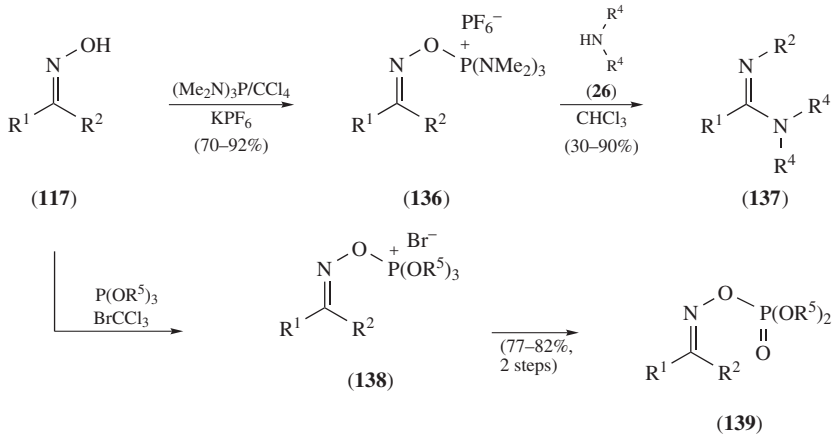
Reacting phosphorus pentachloride with oximes **117** derived from 3-(trifluoromethyl)-chromenone[45], 1,5,9-trioxacyclododecane-2,6,10-trione[46] or *iso*-propyl benzoate[47] derivatives followed by aqueous workup leads to the formation of phosphate trimers **135** (Scheme 51).



SCHEME 51

Phosphorylating agents for oximes can also be generated *in situ* when phosphorus reagents mixed with haloalkanes are used. Reaction of oximes **117** with hexamethylphosphorous triamide (HMPT) in the presence of carbon tetrachloride yields the corresponding phosphonium salts **136**, which are isolated in the form of hexafluorophosphates (Scheme 52)[48]. Their solutions in non-polar solvents like $CHCl_3$ give Beckmann rearrangement at room temperature. Trapping the cationic intermediates formed in the rearrangement with amine **26** leads to the formation of amidines **137**. Similarly, bromotrialkoxyphosphonium salts **138** can be used for indirect oxidative phosphorylation of oximes **117**. Stirring trialkyl phosphites (R^5 = Et, Me) in bromotrichloromethane salts, in the presence of oximes **117** (R^1 = H, R^2 = Ph, NO_2CH_2; R^1 = CN, R^2 = *m*-ClC_6H_4; $R^1 = R^2$ = Me), yields a phosphonium bromide intermediate **138** which undergoes spontaneous oxidation with elimination of alkyl bromide leading to the formation of phosphorylated oximes **139** (Scheme 52)[49].

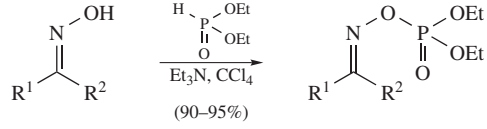
A different approach can also be applied for the phosphorylation of oximes **117** (R^1 = Me, R^2 = Et, *n*-Pr, *i*-Bu, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-ClC_6H_4; R^1 = Ph, R^2 = H; R^1R^2 =



(**117**) (**136**) (**137**) (**138**) (**139**)

SCHEME 52

$(CH_2)_5$, $(CH_2)_6$) by Atherton–Todd reaction with diethyl phosphite in the presence of triethylamine and haloalkanes. The phosphorochloridate generated from the phosphite and carbon tetrachloride is instantaneously consumed, leading to the formation of *O*-phosphorylated oximes **140** in a mild synthetic procedure (Scheme 53)[50].

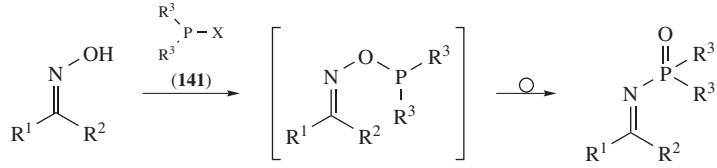


(**117**) (**140**)

SCHEME 53

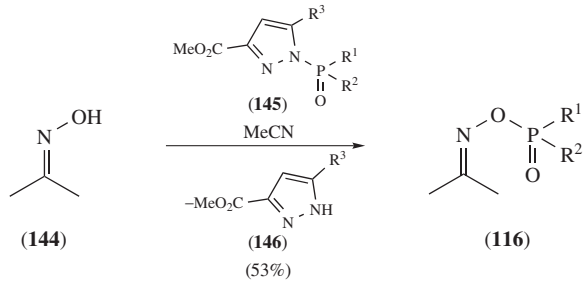
Many rearrangements of organophosphorus compounds involve a change in the oxidation state, P(III) → P(V), of which the best known is the Arbuzov reaction[51]. Most of these rearrangements generally involve the cleavage of a C–O bond. However, a wide class of intramolecular rearrangements of hydroxylamine derivatives proceeds at low temperatures through radical pairs. The existence of phosphorus(III) *O*-substituted oximes has been suspected by the fact that the reaction between oximes **117** and tervalent phosphorus compounds **141** gives phosphorus(V) *N*-substituted imines **143** (see Section II.B.1.a). The isomer **142** spontaneously rearranges by a radical-cage mechanism[52]. In general, the phosphorus(III) intermediate **142** (Scheme 54) cannot be isolated, but evidence of its formation has been observed by changes in the ^{31}P NMR spectra and the intermediate radicals are detectable by ESR spectroscopy.

ii. Reaction of oximes with other phosphorylating agents. N-Phosphinylpyrazoles **145** have also proved to be effective phosphorylating agents of hydroxy and amino derivatives. This includes *O*-phosphorylation of acetone oxime. Treatment of acetone oxime (**144**) with 1-phosphinylpyrazoles **145** (R^1 = Ph, R^2 = Et, R^3 = OMe) in boiling acetonitrile yields the corresponding *O*-phosphorylated oxime **116** (Scheme 55) together with pyrazole **146** that is easily removed by crystallization upon cooling. This method avoids the handling



(**117**) (**142**) (**143**)

SCHEME 54



(**144**) (**145**) (**146**) (53%) (**116**)

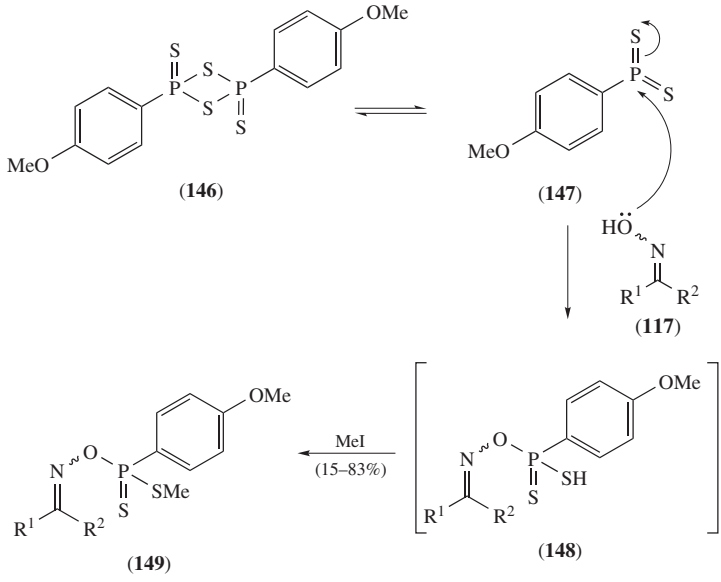
SCHEME 55

problems associated with the utilization of lacrimogen phosphoryl halides, as well as the utilization of bases or other problems connected with the formation of hydrogen halides such as cleavage of the N−O single bond or the C−N double bond[53].

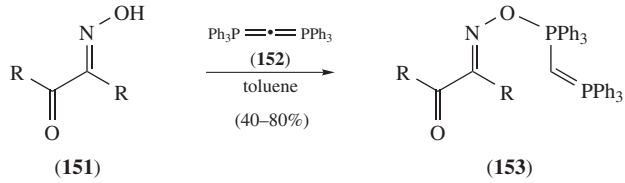
Lawesson's reagent **147** is also a suitable reagent for the phosphonylation of ketoximes **117** ($R^1 = Me$, $R^2 = Me$, Et; $R^1 = Ph$, $R^2 = Bn$; $R^1R^2 = (CH_2)_5$, $(CH_2)_6$) and the introduction of phosphine sulfur derivatives on the oxygen atom of oximes (Scheme 56). Lawesson's reagent is known to be in dynamic equilibrium with its monomeric form **148**. Nucleophilic attack of ketoximes **117** on the electrophilic monomer **148** affords intermediate **149** that is trapped with methyl iodide to yield phosphonodithioate oxime **150**[54]. The same kind of nucleophilic attack is suggested for the reaction of amidoximes **117** ($R^1 = Ph$, $R^2 = NH_2$) with Lawesson's reagent[55].

The high reactivity of diphosphaallenes can also be used for the introduction of phosphorus substituents at the oxygen atom of an oxime. When **151** reacted with phosphallene ylide, namely hexaphenylcarbodiphosphorane (**152**) in equimolar ratio, *O*-phosphorylated oximes **153**, which remained unchanged after 8 h on heating in toluene, were obtained (Scheme 57)[12, 56].

iii. Reaction of nitrosoalkanes with halophosphines and phosphites. α-Dichloronitrosoalkanes react with dichlorophosphines to give phosphorus *O*-substituted oximes. Accordingly, *O*-phosphoryl oximes **155** are easily obtained when α-dichloronitrosoalkane **154** ($R^1 = Me$, $R^2 = R^3 = Cl$) reacts with dichlorophosphines in the presence of an alcohol (Scheme 58)[57]. Also, reaction of nitrosoperfluoroalkanes with silylated phosphites has been reported by Hund and Röschenthaler[58]. Addition of silylated phosphites **156** to nitrosoperfluoroalkanes **154** ($R^1 = F$, CF_3; $R^2 = R^3 = F$) in a 2:1 molar ratio furnished the phosphate-phosphonates **160** (Scheme 58). The reaction seems to proceed via intermediate **157**, which could be detected by ^{19}F and ^{31}P NMR spectroscopy. Above 30 °C,



SCHEME 56

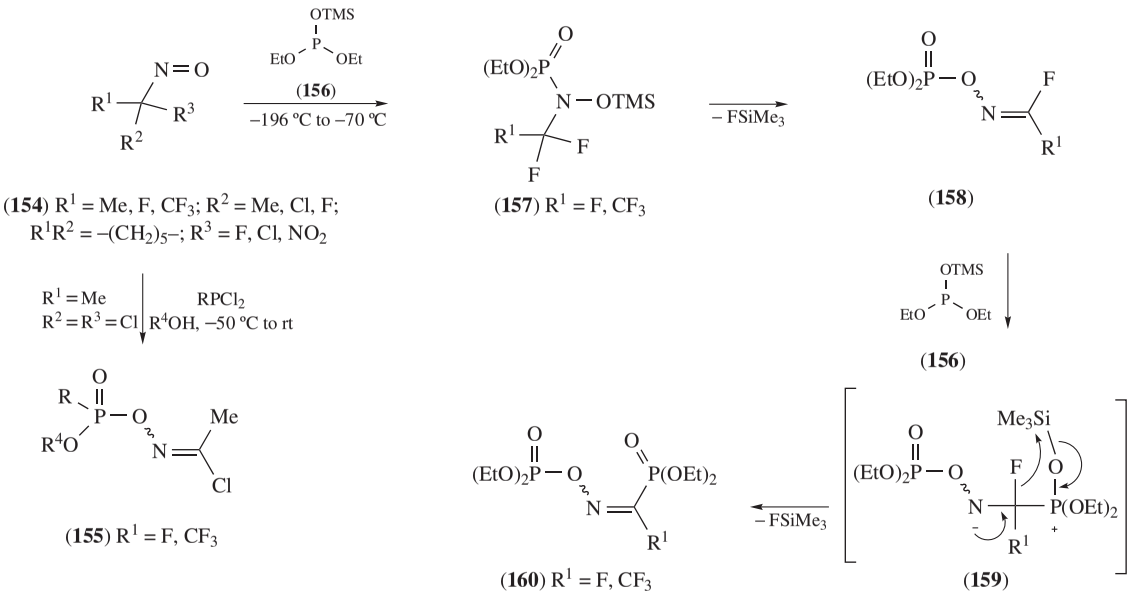


SCHEME 57

compounds **157** were thermally unstable and decomposed with loss of fluorotrimethylsilane. Intermediate **157** gave rise to the formation of the difluorocarbiminophosphate **158** following a Perkow reaction pathway. Finally, a second phosphite molecule **156** attacks the α-carbon forming intermediate **159**, which affords the phosphate-phosphonates **160** and fluorotrimethylsilane.

In a similar way, 2-nitro-2-nitroso compounds **154** ($R^1 = R^2 = Me$; $R^1R^2 = (CH_2)_5$; $R^3 = NO_2$) (Scheme 58) react with three equivalents of triethyl phosphite by deoxygenation of the nitroso group to give *N*-nitroketoimines and *O*-phosphorylated oximes. This reaction is almost certainly taking place at the nitroso group. In fact, nitroso compounds are known[59] to be much more reactive toward trivalent phosphorus compounds than nitro derivatives. Furthermore, some evidence for similar intermediates has been adduced[60] in the reaction of *gem*-chloro-nitroso compounds with triphenylphosphine.

iv. Reaction of nitro compounds with phosphorus reagents. In an attempt to confirm the reaction mechanism between α-halo-α-nitroesters and triphenylphosphine, early work by Leguern and coworkers[61] showed the preparation of *O*-phosphonylated oximes **163**,

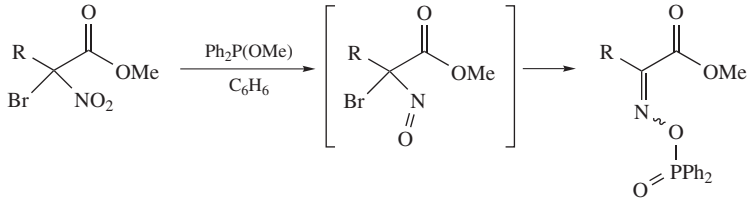


R = Me, EtS, BuS, PhO, $EtO(CH_2)_2O$, $CF_2HCF_2CH_2O$, $(C_2H_5)_2N$, $O(CH_2CH_2)_2N$

R^4 = Me, Et, Pr, *i*-Pr, Bu, *i*-Bu, *sec*-Bu, Pen, *i*-Pen

SCHEME 58

via nitroso intermediate **162**, through reaction of α-bromo-α-nitroesters **161** with methyl diphenylphosphinite (Scheme 59).



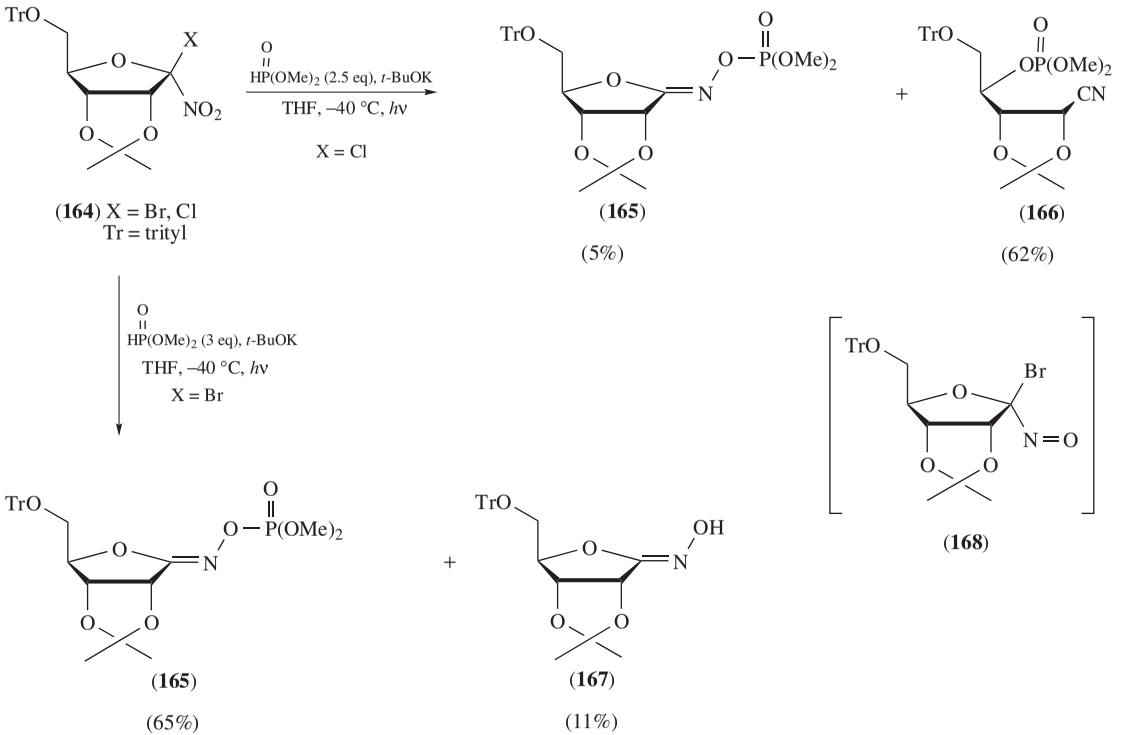
(**161**) R = Me, Bn (**162**) (**163**) R = Me, Bn

SCHEME 59

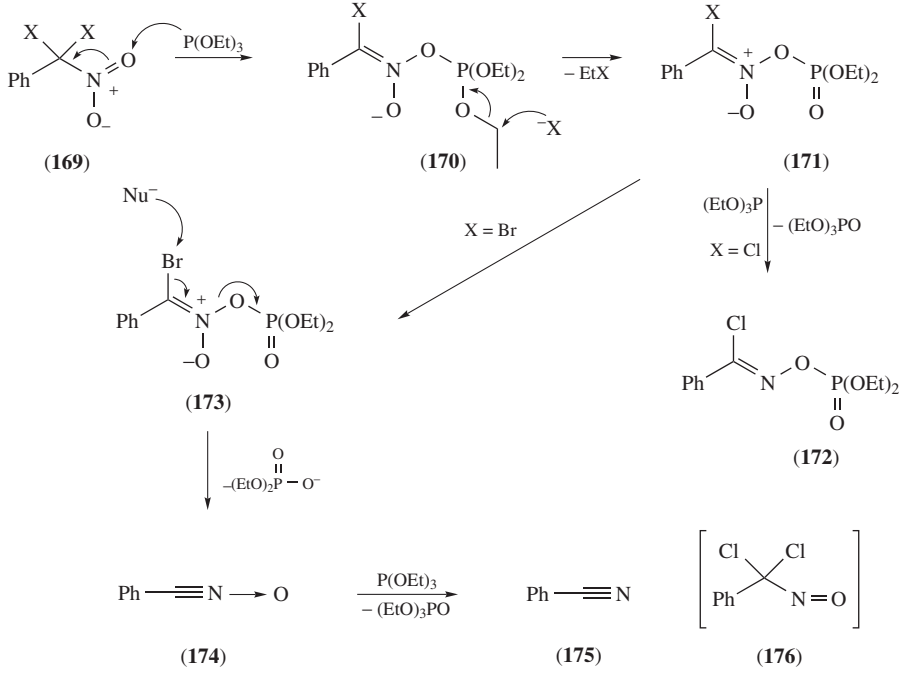
Similarly, *O*-phosphorylated oximes are prepared by reaction of dialkyl phosphate anions with geminal-halonitroalkanes. Chloronitroribofuranose (**164**) (X = Cl) with 2.5 equivalents of $KPO(OMe)_2$ in THF under irradiation gave the *O*-glycosylideneoximino phosphate **165** together with the nitrile **166** (Scheme 60)[62]. The more reactive bromonitro ether (**164**) (X = Br) also reacts with 3 equivalents of $KPO(OMe)_2$ under irradiation. In this case, a transient blue color is observed between -40 and $-30\,^{\circ}C$, indicating an intermediate bromonitroso compound **168**, and two main products, the oxime **167** and the *O*-glycosylideneoximino phosphate **165**, are isolated. Compound **165** is also obtained from **164** (X = Cl) by treatment with trimethyl phosphite[63]. Nitrosulfones are less reactive toward nucleophilic substitution than nitro halides; however, they are still good single-electron acceptors. Reaction of 1-*C*-nitroglycosyl sulfones with diethyl phosphate anions has also been reported by Meuwly and Vasella[62] to afford *O*-phosphorylated glycosyl oximes.

Dichloro(phenyl)nitromethane (**169**) (X = Cl) reacts exothermically with slightly more than two equivalents of triethyl phosphite with elimination of ethyl chloride. This gives phosphate **172** together with other secondary compounds (Scheme 61)[64]. It is presumed that ethyl chloride arises by the action of choride ion on the initially formed salt **170** in a reaction characteristic of the second stage of the Michaelis–Arbuzov reaction and that, when the halogen of the resulting phosphate **171** is chloride, the ester group is reduced by triethyl phosphite to phosphate **172**. However, when the halogen of the resulting ester **171** is bromine, an alternative reaction apparently takes place, presumably leading to the formation of benzonitrile oxide (**174**) by nucleophilic attack of the bromine of **173** (Scheme 61)[64]. A plausible mechanism for the formation of benzonitrile (**175**) involving the preparation of a *C*-phosphorylated oxime[65] followed by a fragmentation reaction (see Section II.B.2.c, Scheme 117) may not be ruled out. It is also conceivable that the phosphate **172** is formed by means of a nitroso intermediate **176** in a similar way to that reported in Scheme 60[63].

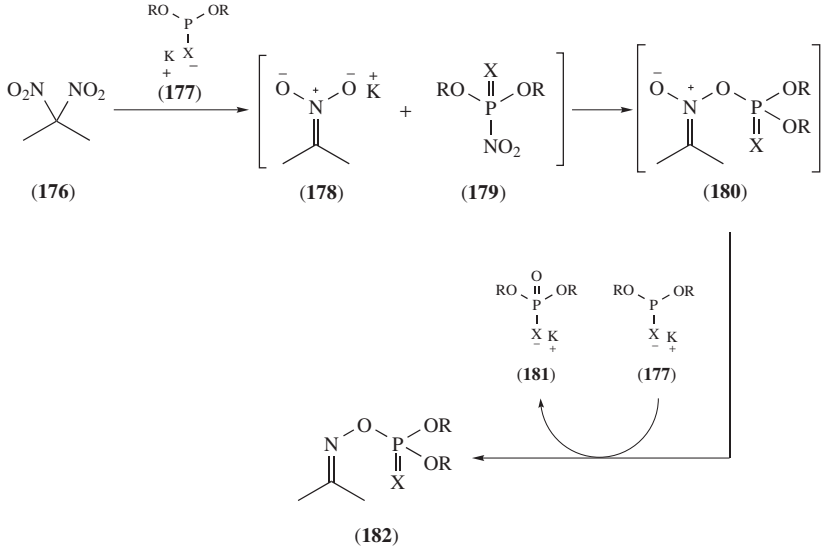
2,2-Dinitropropane (**177**) reacts with dialkyl phosphite or thiophosphite ions **178** to form dialkyl phosphate or thiophosphate esters of acetone oxime **183** (X = O, S; R = Me, Et). This process, competing with the normal *C*-phosphorylation through an $S_{RN}1$ mechanism, has been postulated to proceed by a nucleophilic attack of the phosphite or thiophosphite ion **178** on the nitro group to yield nitronate **179** and nitrophosphonate derivative **180** (Scheme 62). A second displacement by the nitronate would yield oxime *N*-oxide **181** which could transfer the nitrite oxygen to a second equivalent of phosphite or thiophosphite ion **178** releasing phosphorus species **182**[66].


TrO
X
O
NO2
O
O
HP(OMe)2 (2.5 eq), t-BuOK
THF, –40 °C, hν
X = Cl
(164) X = Br, Cl
Tr = trityl
(165)
(5%)
+
OP(OMe)2
CN
(166)
(62%)
HP(OMe)2 (3 eq), t-BuOK
THF, –40 °C, hν
X = Br
Br
N=O
(168)
P(OMe)2
(165)
(65%)
+
OH
(167)
(11%)

SCHEME 60



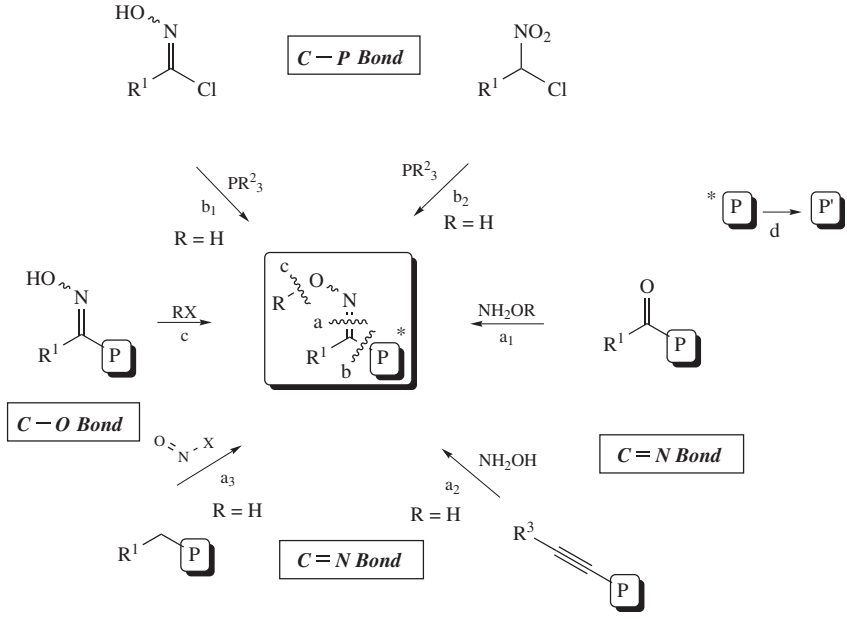
SCHEME 61



SCHEME 62

2. Phosphorus C-substituted oximes

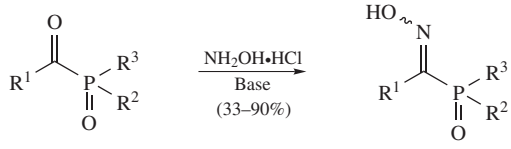
The most common approaches for the preparation of phosphorus substituted oximes involve the formation of C−N double bond by condensation reaction of hydroxylamine with acyl phosphorus derivatives or their precursors (Scheme 63, Route a_1), nucleophilic addition of hydroxylamine to alkynylphosphonates (Scheme 63, Route a_2) or nitrosation of the acidic methylene of alkylphosphonates or phosphinates (Scheme 63, Route a_3). Phosphorus *C*-substituted oximes can also be prepared from halooximes or halonitroalkenes and phosphites or phosphines where the key step is the formation of a P−C bond (Scheme 63, Routes b_1, b_2). The resulting oximes are susceptible to further derivatizations by functionalization of the free hydroxy group (Scheme 63, Route c) or by transformations in the phosphorus moiety (Scheme 63, Route d).



SCHEME 63

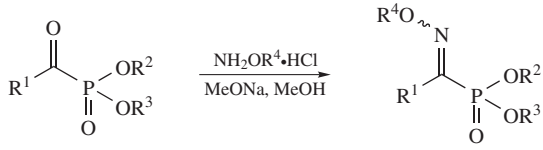
a. Carbon–nitrogen double bond formation (Scheme 63a). i. Condensation of acylphosphonates with hydroxylamine. Condensation reaction of hydroxylamine hydrochloride with acylphosphonates ($R^2 = R^3 = OR$), acylphosphinates ($R^2 = R$, $R^3 = OR$) or acylphosphonamidates **184** ($R^2 = OR$, $R^3 = NR_2$), generally in alcoholic media, represents the most frequently used route for the synthesis of phosphorus substituted oximes **185**. This reaction requires the presence of a base such as triethylamine or pyridine in order to capture hydrochloric acid (Scheme 64)[67].

Condensation of alkoxyamines with acylphosphonate derivatives **186** affords *O*-functionalized oximes. Methoxyamine free base, prepared by neutralization of the hydrochloride with pyridine, reacts with diethyl acylphosphonates **186** (R^1 = Me, Et, *n*-Pr, *n*-Bu, *n*-Pr, *i*-Bu, $R^2 = R^3$ = Et) to yield methoxyiminophosphonates **187** in 80–84% yield (Scheme 65)[68]. In the same way, the reaction of methoxyamine with



(**184**) (**185**)

SCHEME 64

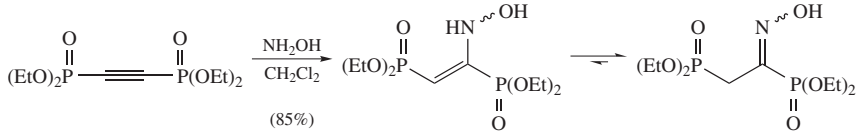


(**186**) (**187**)

SCHEME 65

benzoyl phosphonate sodium monosalts **186** (R^1 = Ph, R^2 = Na) yields the corresponding methoxyiminophosphonates **187** in 85–89% yield (Scheme 65)[67j]. Under the same conditions benzyloxyamine reacts with several acylphosphonates **186** (R^1 = Me, Et, *i*-Pr, Ph, Bn, $C_6H_5(CH_2)_2$), affording benzyloxyoximes **187** (R^4 = Bn) in 54–89% yield (Scheme 65)[69].

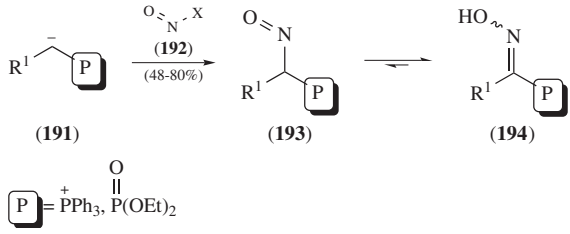
ii. Nucleophilic addition of hydroxylamine to alkynylphosphonates. A different strategy can also be applied to the preparation of *C*-phosphorylated oximes though C−N double bond formation. This strategy involves the nucleophilic addition of hydroxylamine free base in dichloromethane to the activated acetylenic bond of ethynyldiphosphonate **188** to afford the corresponding oxime bisphosphonate **190** via its isomer **189** (Scheme 66)[70].



(**188**) (**189**) (**190**)

SCHEME 66

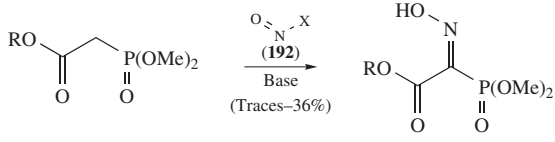
iii. Nitrosation reactions. Nitrosation is also a suitable method for the synthesis of phosphorated oximes **194**. Treatment of phosphorus ylides **191** (Ⓟ = $^+PPh_3X^-$; R^1 = PhCO, MeOCO) with nitrosyl chloride (**192**) (X = Cl) affords α-nitrosophosphonium salt **193**, which immediately tautomerizes to afford the oxime **194** (Ⓟ = $^+PPh_3X^-$) in good (72–80%) yields (Scheme 67)[71]. This process can be extended to the preparation of oximes **194** derived from diethyl phosphonate. The presence of a base is required in this case and an anion stabilizing substituent in the α-position is very convenient in order to favor the deprotonation of the α-methylene group. Generation of phosphonate anion **191** (Ⓟ = $PO(OEt)_2$; R^1 = 2-Py) with potassium *tert*-butoxide and subsequent treatment



SCHEME 67

with ethyl nitrite (**192**) (X = OEt) affords the corresponding phosphonate oxime **194** (Ⓟ = $PO(OEt)_2$) in 48% yield (Scheme 67)[72]. This methodology can also be applied to the synthesis of cyano oximes derived from phosphonate **194** (Ⓟ = $PO(OEt)_2$; R^1 = CN). The activated methylene in diethyl cyanomethylphosphonate is deprotonated with NaH for the generation of stabilized anion **191**. After nitrosation with *iso*-amyl nitrite (**192**) (X = *i*-PenO), the corresponding oxime **194** is obtained in good yield (80%) (Scheme 67)[73].

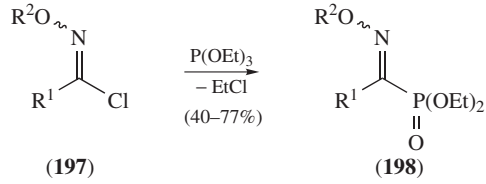
The same approach has been used for the synthesis of precursors of (hydroxyimino)phosphonoacetic acids or 'troika acids' **196** (R = H). Nitrosation of α-phosphorylated *tert*-butyl esters **195** (R = *t*-Bu) with *n*-pentyl or *tert*-butyl nitrite (**192**) (X = n-$C_5H_{11}O$ or *t*-BuO) in the presence of potassium *tert*-butoxide or sodium hydride only affords traces of oximes **196** (Scheme 68)[74]. However, moderate yields in the preparation of oximes **196** are obtained by using NaH and ethyl nitrite (**192**) (X = OEt) as nitrosating agent (Scheme 68)[74]. Nitrosation of benzyl ester derivatives **195** (R = o-$NO_2C_6H_4CH_2$) in the presence of tri(*iso*-propyl)aluminum as a base and nitrosyl chloride (**192**) (X = Cl) occurs at the central activated methylene to afford the functionalized oxime **196** (Scheme 68)[75].



SCHEME 68

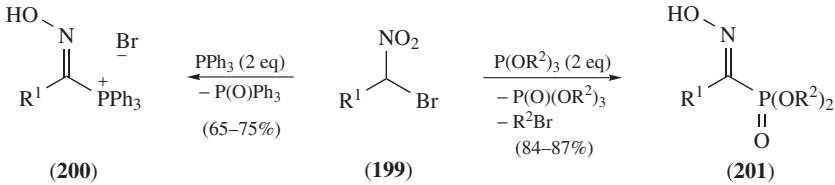
b. Carbon–phosphorus single bond formation (Scheme 63b). Following the pattern of the Arbuzov rearrangement, chlorooximes **197** react with phosphites to afford phosphorylated oximes **198**. In this sense, *N*-benzyloxyformhydroxamic chloride (**197**) (R^1 = H, R^2 = Bn) reacts with triethyl phosphite to afford the phosphorylated aldoxime **198** in moderate yield (Scheme 69)[69], while pyruvohydroxymoyl chloride (**197**) (R^1 = MeCO, R^2 = H) in the same reaction conditions[76] yields the acetyl oxime **198** in good yield (Scheme 69).

1-Bromonitroalkanes **199** (R^1 = Me, Et) react with two equivalents of triphenylphosphine to give triphenylphosphine oxide and hydroxyiminophosphonium salts **200** (Scheme 70)[77]. Analogously, treatment of 1-bromonitroalkanes **199** with an excess of trialkyl phosphite affords phosphonate oximes **201** (R^1 = Me, Et, *i*-Pr, *n*-Bu, R^2 = Me or R^1 = Me, Et, R^2 = Et) (Scheme 70)[65a].



(**197**) (**198**)

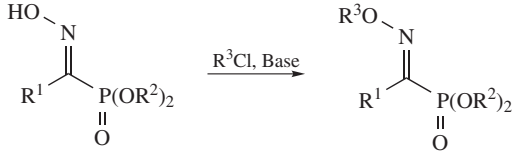
SCHEME 69



(**200**) (**199**) (**201**)

SCHEME 70

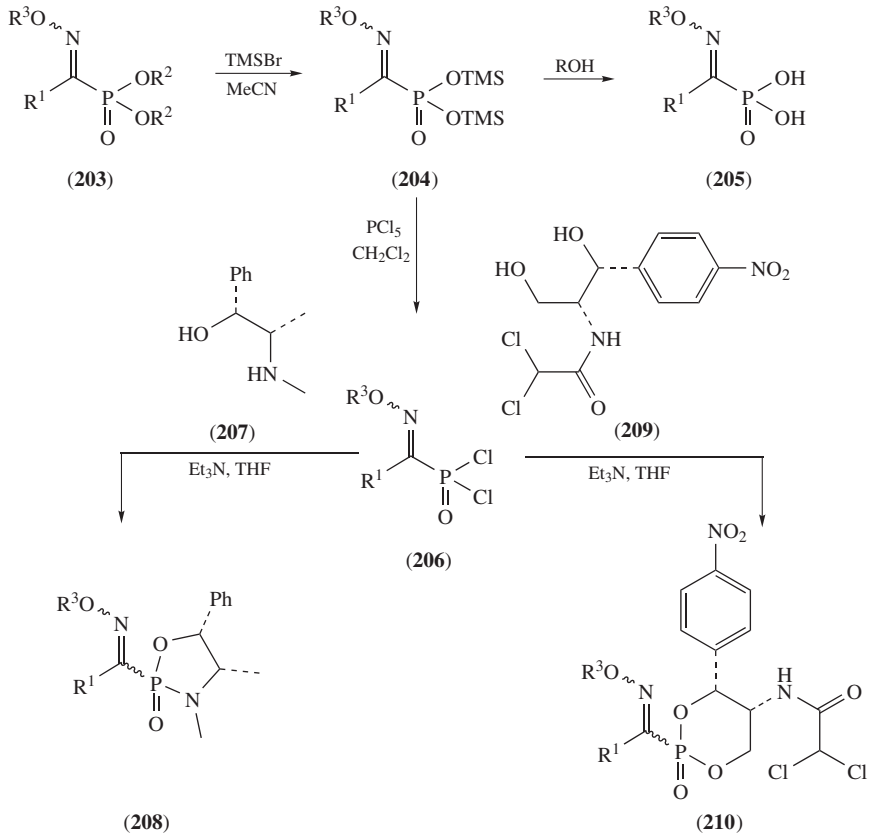
c. O-Functionalization of phosphorus C-substituted oximes (Scheme 63c). The free hydroxy group of the oximes can be functionalized with electrophiles. α-Allenyl oximes **201** ($R^1 = CH_2{=}C{=}CH{-}CMe_2$) are benzoylated by treatment with benzoyl chloride ($R^3 = PhCO$) in the presence of pyridine[78], while other alkyl oximes **201** ($R^1 =$ Me, Et, *i*-Pr, *i*-Bu) are *O*-benzylated using benzyl chloride ($R^3 =$ Bn) and sodium methoxide as base (Scheme 71)[69]. In a similar way, addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to oximes **201** ($R^1 =$ Me) followed by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl) affords new silylated oximes **202** in 86–92% yield (Scheme 71). Unlike oximes bearing a free hydroxy group **201** where the *Z*-isomer is usually predominant over the *E*-isomer, the new *O*-silylated oximes **202** show a preference for a *E*-configuration due to the impossibility to create hydrogen bonding, which may stabilize the *Z*-isomer, and to the steric crowding due to the presence of the large TBDMS group[65a].



(**201**) (**202**)

SCHEME 71

d. Dealkylation of phosphonates. Synthesis of phosphonic acid C-substituted oximes (Scheme 63d). Soft hydrolysis of dialkyl phosphonate moiety of oximes **203** ($R^2 =$ Me, Et, $R^3 =$ H) is performed by treatment with trimethylsilyl bromide (TMSBr) to afford an intermediate silylated phosphonate **204** which is easily hydrolyzed to the phosphonic



(**203**) (**204**) (**205**)

(**207**) (**209**)

(**206**)

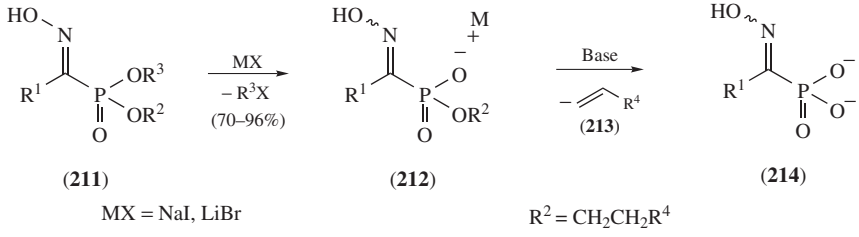
(**208**) (**210**)

SCHEME 72

acid **205** by simple treatment with water[75] or methanol in 62% yield (Scheme 72)[79]. This approach is often employed for the preparation of 'troika acids' **205** ($R^1 = CO_2H$)[75, 80]. Using this method, even the di-*i*-propyl phosphonate group in oximes **203** ($R^2 = i$-Pr) can be dealkylated. Despite the fact that only decomposition of the free oxime **203** ($R^2 = i$-Pr, $R^3 = H$) is observed after treatment with TMSBr, the phosphonic acid derivative **205** is obtained in 91% yield after hydrolysis of the silylphosphonate **204** with alcoholic NaOH if the benzyl protected oxime **203** ($R^2 = i$-Pr, $R^3 = Bn$) is used (Scheme 72)[81].

By means of this method, the synthesis of phosphonic dichloride derived benzyl oximes **206** ($R^1 =$ Me, Et, *i*-Pr, *i*-Bu, Ph, Bn, $R^3 = Bn$) is feasible. The direct substitution of alkoxy groups by chlorine requires, in general, harsh conditions which can alter the oxime functional group. However, in this case, the reaction of the silylated phosphonate intermediate **204** with PCl_5 affords the phosphonic dichloride **206** that can be used, preferably *in situ*, for the synthesis of diastereomeric mixtures of phosphorus containing heterocycles **208** and **210** by treatment with (−)-ephedrine (**207**) or chloramphenicol (**209**), respectively (Scheme 72)[69].

Controlled hydrolysis of phosphonates can be performed to afford monophosphonic acid derivatives. Monodealkylation of dialkylphosphonates **211** is performed by alkylation of NaI or LiBr in dry acetone or acetonitrile[67r, 82], sometimes with the assistance of a phase-transfer catalyst[83] (Scheme 73). Under these conditions 2-cyanoethoxy, *p*-nitrophenethoxy or 2,2,2-trihaloethoxy groups remain intact, which allows selective hydrolysis of 2-cyanoethyl[67j], *p*-nitrophenethyl[67j] or trihaloethyl[67l, 84] methyl phosphonates **211** ($R^2 = NCCH_2CH_2$, *p*-$NO_2C_6H_4CH_2CH_2$, CF_3CH_2, CCl_3CH_2, $R^3 = Me$) in 80–90% yield (Scheme 73). 2-Cyanoethyl and *p*-nitrophenethyl phosphonate oximes **212** ($R^2 = NCCH_2CH_2$, *p*-$NO_2C_6H_4CH_2CH_2$) undergo spontaneous dealkylation of the phosphonate group to **214** in alkaline media through β-elimination of oxyiminophosphonate anion with formation of alkene **213** (Scheme 73).

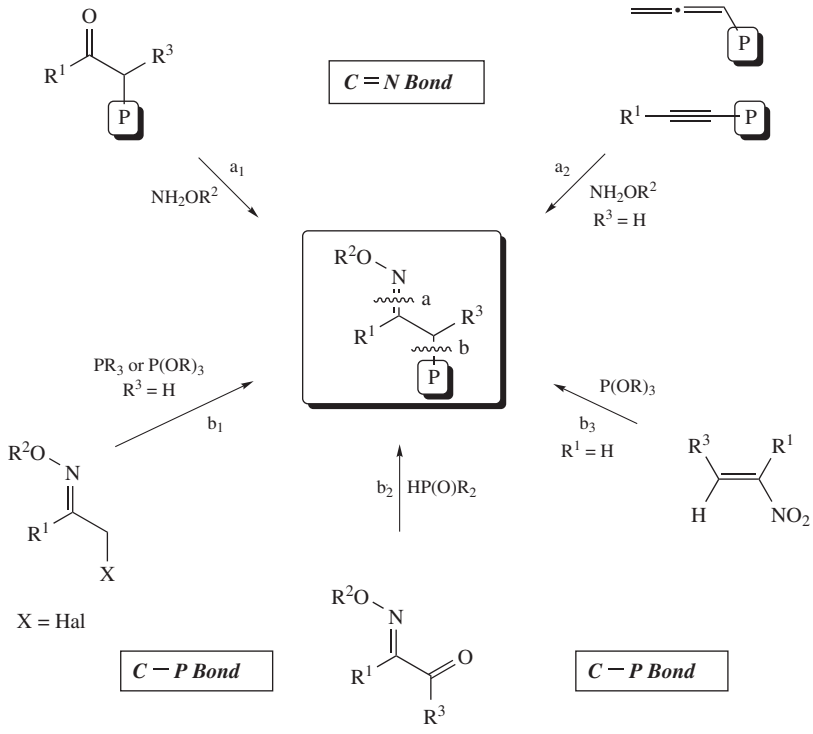


SCHEME 73

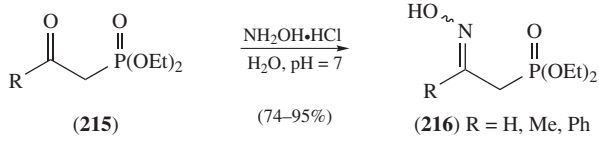
3. Phosphorus α-substituted oximes

Some general synthetic methods exist for the preparation of α-phosphorus substituted oximes. This section will be focused on the synthesis of substituted oximes containing a phosphine oxide, phosphonate or phosphonium salt moiety at the α-position. Depending on the type of bond formed in the reaction, some strategies for the preparation of these derivatives can be highlighted. Section II.A.3.a outlines their preparation through carbon–nitrogen double bond construction by condensation processes (Scheme 74, Route a_1) or addition of hydroxylamines to allenes or alkynes (Scheme 74, Route a_2). Section II.A.3.b will concentrate on the most practical routes for the synthesis of the target compounds, through carbon–phosphorus single bond formation, which are as follows: Arbuzov reaction (Scheme 74, Route b_1), nucleophilic addition of phosphorus reagents to carbonyl compounds (Scheme 74, Route b_2) and nucleophilic addition of phosphorus reagents to nitro olefins (Scheme 74, Route b_3).

a. Carbon–nitrogen double bond formation (Scheme 74a). i. Condensation reaction. One of the most common synthetic ways for the preparation of α-phosphorus substituted aldoximes or ketoximes via a carbonyl–nitrogen double bond forming process is the condensation reaction of carbonyl compounds with hydroxylamines. For example, nucleophilic addition of hydroxylamine to the keto carbonyl group of diethyl α-ketopropylphosphonate (**215**) (R = Me) in aqueous solution around pH = 7 leads to α-phosphorylated oxime **216** (R = Me) (Scheme 75)[85]. Following this strategy, α-phosphorylated oxime **216** (R = Ph) has been synthesized by our group[86] using triethylamine as the base and chloroform as solvent in 74% yield (Scheme 75). Also, aldoxime **216** (R = H) can be prepared through the same methodology in excellent yield[87].



SCHEME 74

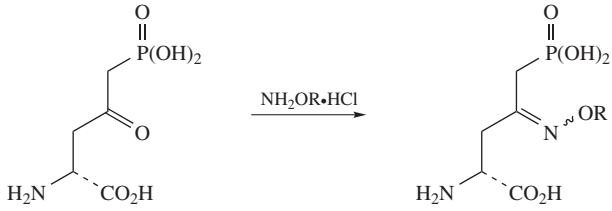


(**215**) (**216**) R = H, Me, Ph

SCHEME 75

Some α-phosphorylated oximes have been tested as *N*-methyl-D-aspartate (NMDA) receptor antagonists. Since it appears that the binding potency and relatively good bioavailability of **217** could be related to the α-ketophosphonic acid functionality, Whitten and coworkers[88] sought to modify the ketone with similar, less readily enolizable groups. Thus, a mixture of *syn*- and *anti*-oximes or their ethers **218** is synthesized through condensation reaction of readily available hydroxylamines with (*R*)-4-oxo-5-phosphononorvaline (**217**) by standard procedures (Scheme 76).

Condensation reaction of the anion derived from diethyl ethylphosphonate with dimethylformamide also affords a general method for the preparation of 1-formylalkanephosphonate **219**[89], which can be converted to the α-phosphorylated oxime **220** (R = OEt, R^1 = Me, R^2 = H) in 92% yield (Scheme 77)[90], or related α-phosphinyl aldoximes ($R^1 = R^2$ = H) in 86% yield, when starting from methyl diphenylphosphine

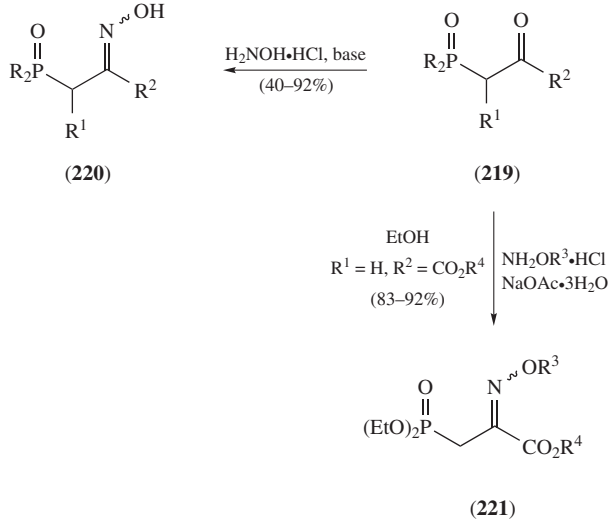


(**217**) (**218**) R = H, Me, Bn

SCHEME 76

oxide[91]. α-Substituted phosphorus oximes **220** containing a fluoroalkyl substituent can also be prepared by this approach[92]. Hence, condensation of alkyl diphenylphosphine oxides or alkylphosphonates with fluorinated esters affords fluorine substituted α-keto phosphorus compounds **219** (R = Ph, OEt; R^1 = H, Me; R^2 = CF_3, CHF_2, C_2F_5, C_7F_{15}). Subsequent treatment with hydroxylamine hydrochloride in the presence of pyridine in ethanol gives fluorinated oximes **220** (R = Ph, OEt; R^1 = H, Me; R^2 = CF_3, CHF_2, C_2F_5, C_7F_{15}) in 40–80% yield (Scheme 77). α-Phosphinyl oximes **220** (R = Ph, R^1 = H, R^2 = Me, *n*-Bu, Ph) can be similarly obtained in 42–70% yield[93]. Condensation of diethyl methylphosphonate anion with diesters can be used for the preparation of 3-phosphonopyruvate derivatives **219** (R^1 = H, R^2 = CO_2R^4). Oximation of these derivatives **219** affords functionalized oximes **221** (R^3 = H, Me, Bn, Pr; R^4 = Et, *i*-Pr) (Scheme 77)[94].

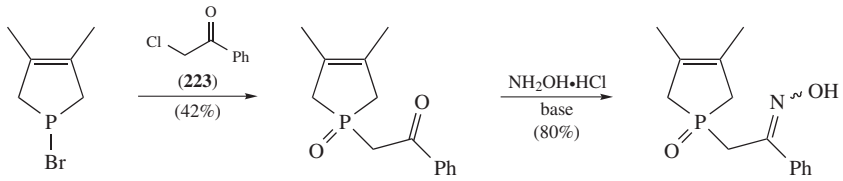
Oximes containing a phospholene ring at the α-position can be prepared by quaternization reaction of trivalent *P*-bromophospholene **222**. Its reaction with α-chloroketone **223**



(**220**) (**219**) (**221**)

SCHEME 77

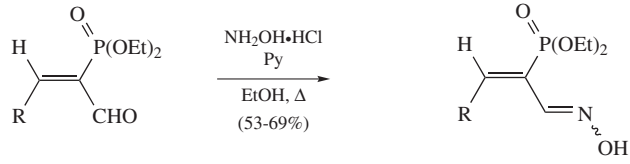
affords functionalized phospholene *P*-oxide **224** which, after condensation reaction with hydroxylamine hydrochloride, gives phosphorylated oxime **225** (Scheme 78)[95].



(**222**) (**224**) (**225**)

SCHEME 78

Minami and coworkers[96] have reported the use of α-formylvinylphosphonates **226** for the preparation of α,β-unsaturated oximes **227**. The C−N double bond formation in **227** takes place through treatment of **226** with hydroxylamine and pyridine in EtOH under reflux (Scheme 79).



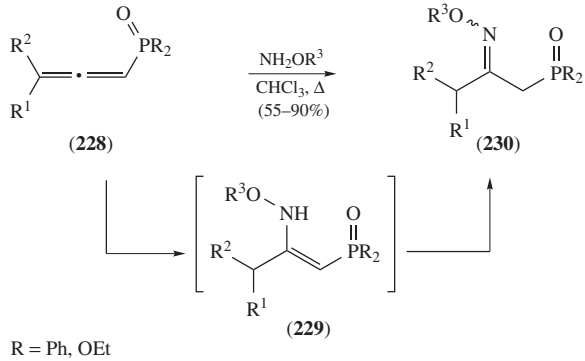
(**226**) (**227**) R = *t*-Bu, Ph, 2-thienyl, 2-furyl

SCHEME 79

ii. Nucleophilic addition of hydroxylamines to allenyl or alkynyl phosphorus derivatives. A different approach can also be applied for the preparation of these α-phosphorylated oximes though C−N double bond formation. This strategy involves addition of hydroxylamine hydrochloride to tetraethyl ethynyldiphosphonate **188**[70]. By means of this procedure, oxime bisphosphonate **190** can be synthesized in 85% yield (see Section II.A.2.a.ii, Scheme 66). In a similar way, nucleophilic addition of unsubstituted hydroxylamine ($R^3 = H$), *O*-methylhydroxylamine ($R^3 = Me$) or *O*-silyl substituted hydroxylamines ($R^3 = SiMe_3$, $SiMe_2Bu$-*t*) to allenes derived from phosphine oxides **228** (R = Ph) or phosphonates **228** (R = OEt) represents an easy procedure for the preparation of α-phosphorated oximes **230**, via **229**, in good yields (Scheme 80)[97].

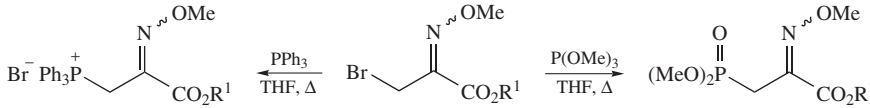
b. Carbon–phosphorus single bond formation (Scheme 74b). i. Reaction of α-halooximes with phosphines or phosphites. An important entry to α-phosphorated oximes is the C−P bond formation by alkylation of phosphorus reagents (Scheme 74, Route b_1). Reaction of α-bromooximes **231** with phosphines describes a general method for the preparation of oxime phosphonium salt **232** (Scheme 81). In a similar way, α-phosphorylated oximes **233** can be obtained through Arbuzov reaction of α-bromooximes **231** with phosphites, involving a C−P bond forming process (Scheme 81)[98]. Both strategies are also used for the preparation of other substituted oximes derived from phosphonium salts[99] or phosphonates[100].

Similarly, protection of α-halooxime **234** with dihydropyrane, before Arbuzov reaction, leads to the formation of *O*-THP oxime **235**, which can be converted into oxime



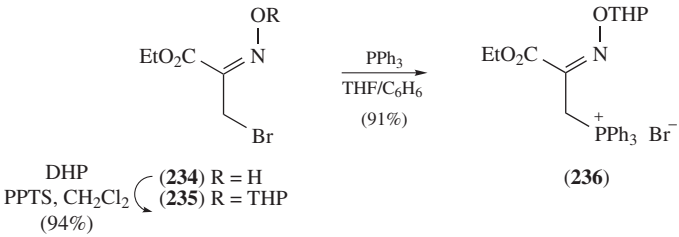
R = Ph, OEt
R^1 = H, Me, *p*-MeC_6H_4; R^2 = H
R^1R^2 = $-(CH_2)_5-$
R^3 = H, Me, $SiMe_3$, $SiMe_2Bu$-*t*

SCHEME 80



(**232**) R^1 = Et (**231**) (**233**) R^1 = Me, Et

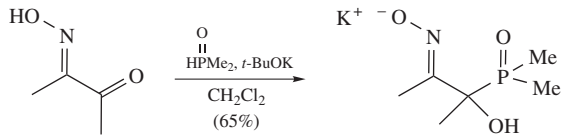
SCHEME 81



SCHEME 82

derived from phosphonium salt **236** in very good yield on reaction with triphenylphosphine (Scheme 82)[101].

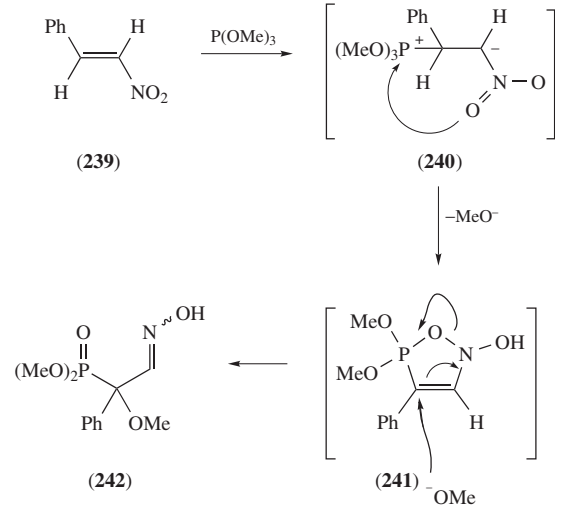
ii. Nucleophilic addition of phosphorus reagents to carbonyl compounds. Nucleophilic addition of phosphorus reagents to carbonyl compounds represents an easy strategy for the preparation of α-hydroxy-phosphorylated compounds (Scheme 74, Route b_2). This procedure has been applied to the ketoxime **237** for the preparation of α-hydroxy-α-phosphinylated oxime derivative **238**. In this way, addition of dimethyl phosphine oxide to ketooxime **237** in the presence of *t*-BuOK leads to the potassium salt of phosphinylated oxime **238** (Scheme 83)[102].



(**237**) (**238**)

SCHEME 83

iii. Nucleophilic addition of phosphorus reagents to nitro olefins. Nitro olefins have also proved to be useful intermediates in the synthesis of some biological active natural products. Due to the strong electron-withdrawing properties of the nitro group, conjugated nitroalkenes are excellent Michael acceptors with a variety of nucleophiles. Several papers describe the addition of phosphorus nucleophiles to nitro olefins as Michael acceptors. Krueger and coworkers[103] report that trimethyl phosphite reacts with β-nitrostyrene (**239**) in *tert*-butyl alcohol to produce α-phosphorylated acetaldehyde oxime **242** through C−P bond formation. A reaction pathway which is consistent with the experimental and spectroscopic results is proposed in Scheme 84. The mechanism involves initial attack of trimethyl phosphite at the α-carbon of β-nitrostyrene, to form a zwitterion **240**, which rearranges to the proposed cyclic intermediate **241**. Methoxide ion attack on **241** leads to the formation of oxime **242**. This compound has been characterized unambiguously by X-ray crystallography[103a]. The above-mentioned study has been followed by other authors[104], who report the addition reaction of anions derived from thiols and triethyl phosphite to β-nitrostyrene (**239**).

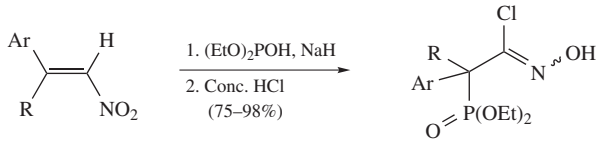


(**239**) (**240**) (**241**) (**242**)

SCHEME 84

α-Phosphorylated halooximes can be prepared from the reaction of conjugated nitroalkenes with diethyl phosphite. In such a way, treatment of conjugated nitroalkenes

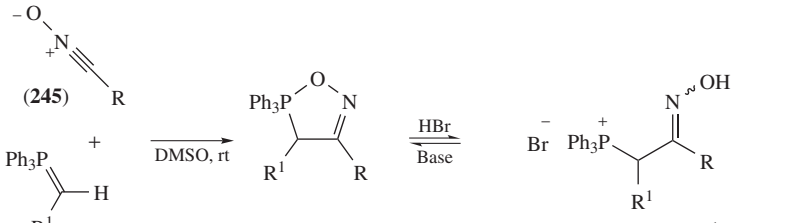
243 with diethyl phosphite in the presence of a base such as sodium hydride and subsequent addition of HCl gave halooximes **244** in very good yield (Scheme 85)[105].



(**243**) (**244**) R = H, Ph; Ar = Ph, *p*-MeC$_6$H$_4$

SCHEME 85

c. Ring opening of 1,2,5-oxazaphospholines. Umani-Ronchi and coworkers[99c] report the reaction between nitrile oxides **245** and phosphonium ylides **246** as a useful method for the preparation of 1,2,5-oxazaphosph(V)ol-2-ines **247**. The successful transformation of **247** into the corresponding 2-hydroxyimino phosphonium salts **248** involves the ring opening of **247** by P−O bond cleavage by the action of hydrobromic acid (Scheme 86).



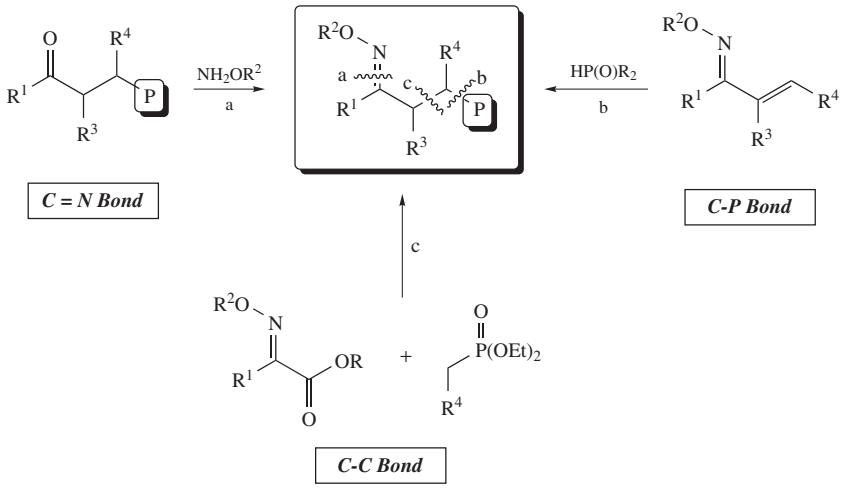
(**245**) (**246**) (**247**) (**248**) R = Ph, *p*-NO$_2$C$_6$H$_4$; R^1 = H, Me

SCHEME 86

4. Phosphorus β-substituted oximes

The most characteristic reaction for the preparation of phosphorus β-substituted oximes involves the C−N double bond formation by condensation reaction of carbonyl compounds with hydroxylamine derivatives (Scheme 87, Route a). Moreover, nucleophilic addition of phosphorylating reagents to olefins (Scheme 87, Route b) or addition of phosphorylated carbanions to esters derived from oximes (Scheme 87, Route c) can also be used for this goal via C−P or C−C single bond formation, respectively.

a. Carbon–nitrogen double bond formation. Condensation reaction (Scheme 87a). Several papers have been published on the formation of phosphorus β-substituted oximes through condensation reaction of a carbonyl compound with hydroxylamines. Along these lines, Van Calenbergh and coworkers[106] report the synthesis of 3-aryl-substituted 3-phosphorylpropanals as appropriate intermediates for the preparation of a small series of α-aryl-substituted analogues of antibiotic fosmidomycin **249**[107]. The carbon–nitrogen double bond formation to yield β-phosphorylated oximes **251** takes place by treatment of the corresponding aldehydes **250** (R^1 = H, Me, OMe, Cl; R^2 = H, Cl) with



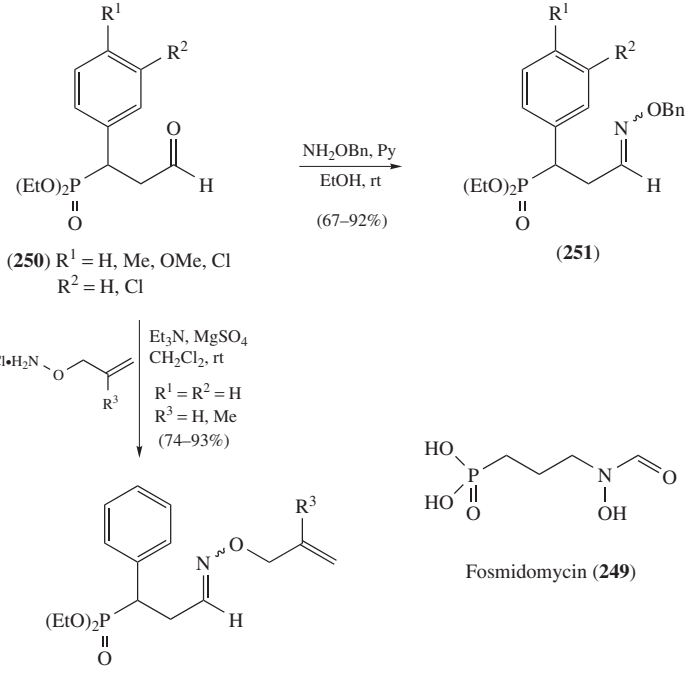
SCHEME 87

O-benzylhydroxylamine (Scheme 88). Similarly, an oxime precursor for the synthesis of oxazinyl analogues of fosmidomycin **249** using ring-closing metathesis (RCM) methodology has been described[108]. The preparation of the RCM precursors starts with the formation of oximes **252** through condensation reaction of aldehyde-phosphonate **250** ($R^1 = R^2 = H$) with two different *O*-substituted hydroxylamine hydrochlorides in the presence of triethylamine (Scheme 88).

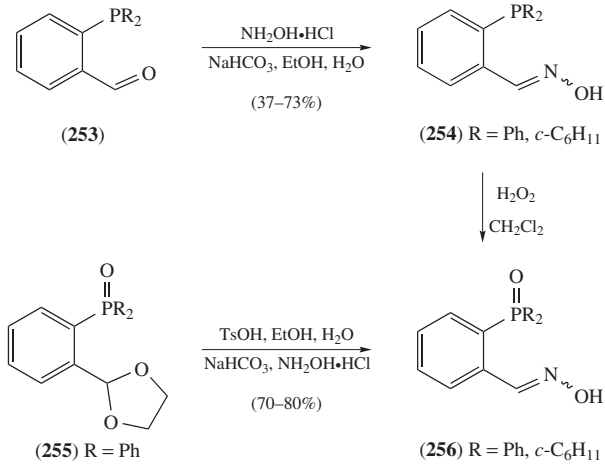
Wan and coworkers have developed the synthesis of some easily prepared ligands based on an oxime-phosphine or oxime-phosphine oxide combination (Scheme 89). Oxime-phosphine ligand **254** can be synthesized through condensation reaction of hydroxylamine hydrochloride with aldehyde **253**. The synthesis of oxime-phosphine oxide ligand **256** could be accomplished either by oxidation of the oxime-phosphine **254** or via intermediate **255**. Functionalized oxime-phosphine oxides **256** can be used efficiently as catalyst in C−N[109], C−C[110] and C−S[111] bond construction.

Carbohydrates derived from oximes are available chiral building blocks in transition-metal catalyzed reactions. However, a limiting factor for these products is their susceptibility to hydrolysis which often prevents chromatographic purification, further derivatization or the use of aqueous solvents. The tendency for hydrolysis is reduced for oximes, and especially for oxime ethers which are very stable toward hydrolytic conditions. An approach has been developed for the connection of carbohydrate derivatives and phosphorus-ligands via oxime ethers[112]. *O*-*β*-D-Glucopyranosylhydroxylamine (**257**) condenses with 2-diphenylphosphanylbenzaldehyde (**258**) under acidic conditions to afford the carbohydrate-derived oxime-phosphine ligand **259**. Oxime ether **259** is esterified with acetic anhydride in pyridine, resulting in the peracetylated oxime ether **260** (Scheme 90). An extension of the oxime ether concept to galactose[113], maltose[114] or lactose[114] leads to a broad variety of carbohydrate-containing ligands that are stable toward hydrolysis.

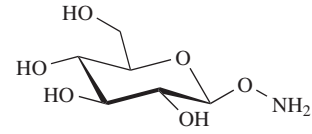
Addition of diphenylphosphine oxide to mesityl oxide (**261**), catalyzed by sodium hydride, occurs in the Michael sense to give the ketone **262**. Treatment of **262** with hydroxylamine hydrochloride and triethylamine in ethanol gives oxime **263** (Scheme 91)[115]. This reaction can be extended to the addition of primary phosphines to *α*,*β*-unsaturated ketones[116]. By simple addition of phenylphosphine to mesityl



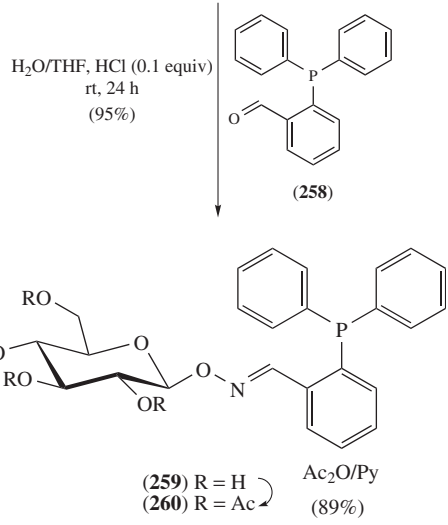
SCHEME 88



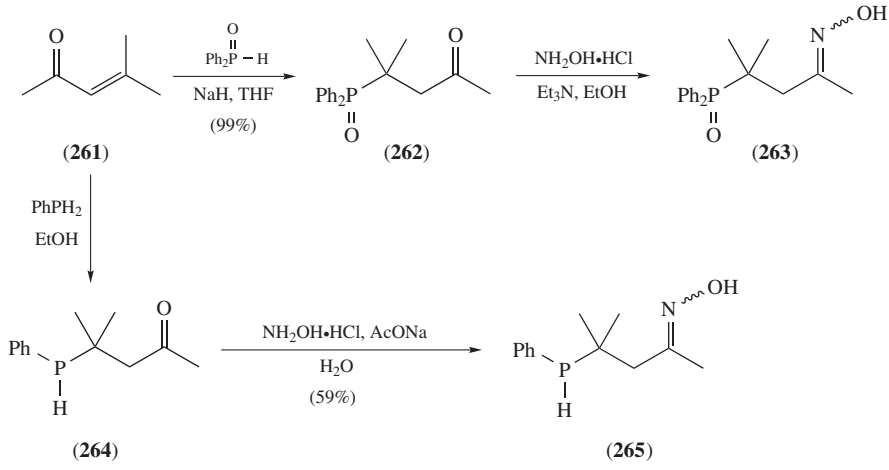
SCHEME 89



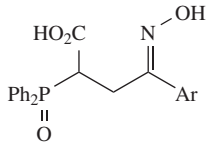
(**257**)



SCHEME 90

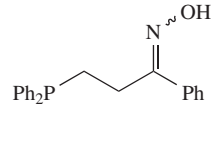


SCHEME 91



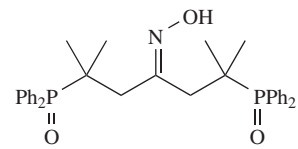
(**266**) Ar = Ph, *p*-MeC_6H_4, *p*-BrC_6H_4

(76–87%)



(**267**)

(62%)



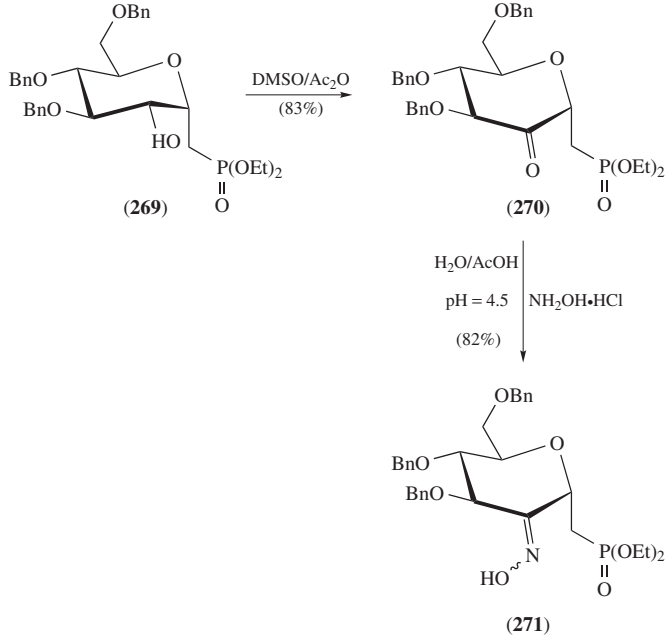
(**268**)

(77%)

FIGURE 3

oxide (**261**) adduct **264** is obtained. Phosphorylated ketone **264** can be converted to the corresponding oxime **265** by condensation with hydroxylamine hydrochloride (Scheme 91). The same approach has been used extensively for the synthesis of other β-phosphorus functionalized oximes such as those derived from β-aroyl-α-(diphenylphosphinyl)propionic acids **266**[117], phosphorated oxime derived from phosphines **267**[118] or symmetrical bis(diphenylphosphinyl)oxime **268**[119] (Figure 3).

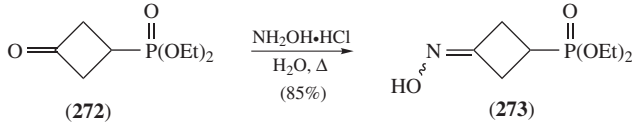
Glycosyl phosphates play a central role in the metabolism of carbohydrates. They act as glycosyl donors in the biosynthesis of oligo- and polysaccharides and glycoconjugates, and in some cases they also perform the role of metabolic regulators. Nicotra and coworkers[120] have reported the preparation of *N*-acetyl-α-D-glucosamine-1-phosphate and *N*-acetyl-α-D-mannosamine-1-phosphate in a stereoselective manner from β-phosphorus substituted oximes. As shown in Scheme 92, α-*C*-glucopyranosylmethanephosphonate **269**, with a



SCHEME 92

free hydroxyl group at $C-2$, was oxidized with DMSO/Ac_2O to afford the ketone **270**, which is converted into the oxime **271** by treatment with hydroxylamine at pH 4.5.

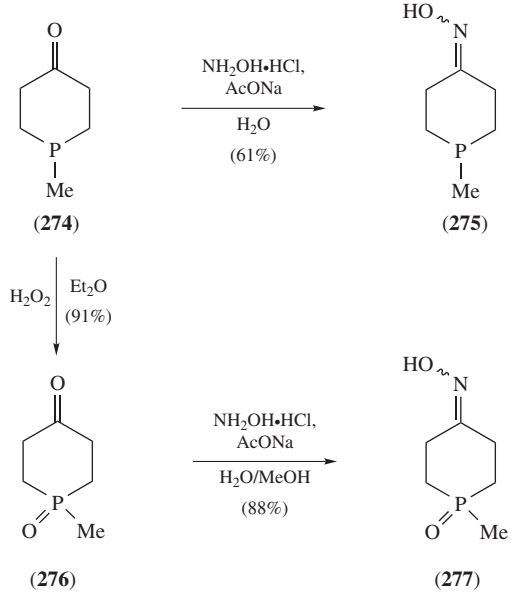
Hanrahan and coworkers[121] have reported the synthesis of 3-phosphonocyclobutyl oxime **273** analogue of glutamic acid, through C−N double bond formation, via condensation reaction of diethyl 3-oxocyclobutylphosphonate (**272**) with hydroxylamine hydrochloride in refluxing water (Scheme 93).



(**272**) (**273**)

SCHEME 93

Similarly, phosphorinanones **274** are precursors for the preparation of phosphorus β-substituted oximes **275** and **277** (Scheme 94)[122]. Phosphine oxide **276** can be prepared from **274** by oxidation with hydrogen peroxide. C−N double bond formation can be accomplished by oximation of **274** and **276** with hydroxylamine hydrochloride to give oximes **275** and **277**, respectively.

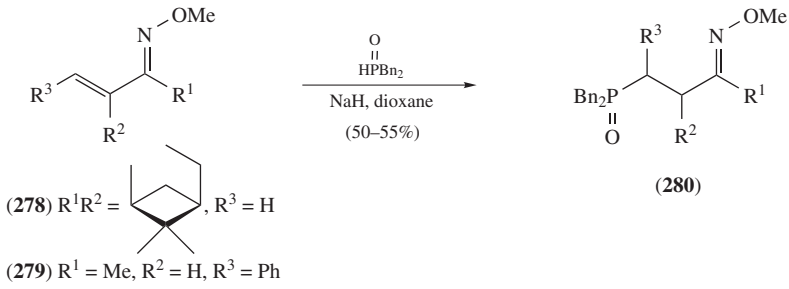


(**274**) (**275**) (**276**) (**277**)

SCHEME 94

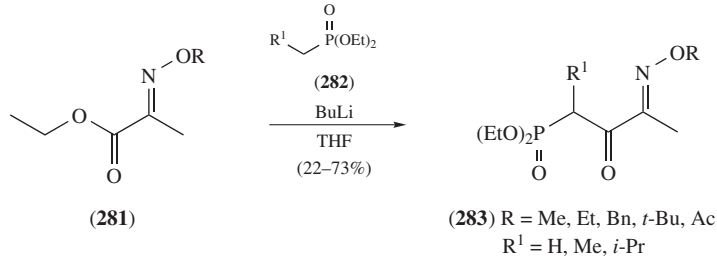
b. Carbon–phosphorus single bond formation. Michael addition of phosphorylating reagents to α,β-unsaturated oximes (Scheme 87b). Phosphorylation reactions of activated olefins could represent an important entry to β-phosphorated oxime derivatives. In this

way, reaction of unsaturated oximes **278** and **279** with dibenzylphosphine oxide as a phosphorylating agent results in the formation of the phosphorus β-substituted oximes **280**[123]. In this synthesis, phosphorylation of ketoximes is successful only with pinacarvone *O*-methyl oxime (**278**) and benzylideneacetone *O*-methyloxime (**279**) (Scheme 95). The double bond of **278** is very accessible and favorable for nucleophilic attack and, in the case of benzylideneacetone oxime **279**, the double bond is additionally activated by the phenyl group. However, attempts to involve oximes of other ketones in this reaction were unsuccessful.



SCHEME 95

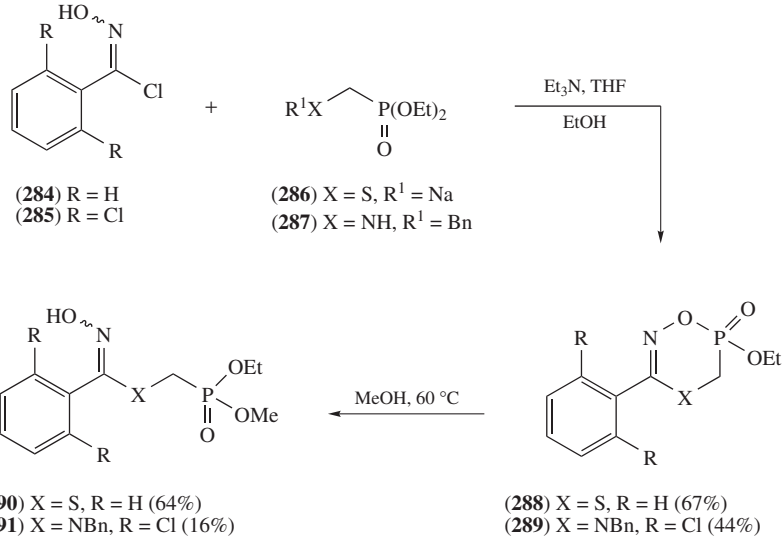
c. Carbon–carbon single bond formation. Addition of phosphonate carbanions to esters derived from oximes (Scheme 87c). Addition of carbanions derived from substituted phosphonates **282** to oximes derived from pyruvate constitutes an important entry to phosphorus β-substituted oximes **283** (R^1 = H, Me, *i*-Pr)[124]. More recently, and in the same way, Würthwein and coworkers[125] have reported the synthesis of phosphorus β-substituted oximes derived from pyruvate. Condensation reaction of **281** with diethyl alkylphosphonate **282** gives oximes **283** (R^1 = H) through carbon–phosphorus bond formation (Scheme 96).



SCHEME 96

d. Ring opening of oxathiazaphosphorines and oxadiazaphosphorines. Another method for the preparation of phosphorus β-substituted oximes involves the ring opening of oxathiazaphosphorine **288** (X = S) or oxadiazaphosphorine **289** (X = N). The sodium salt of diethyl mercaptomethylphosphonate **286** reacts with nitrile oxides, generated from

halooximes **284** in the presence of triethylamine, and, after treatment with anhydrous powdered sodium hydroxide in benzene, the oxathiazaphosphorine derivative **288** (X = S) is obtained in 67% yield (Scheme 97). Ring opening of **288** is successfully achieved through treatment with dry methanol at 60 °C to give oxime **290** as a mixture of *E*- and *Z*-isomers[126]. Similarly, halooxime **285** reacts with aminomethylphosphonate derivative **287** to give directly the 1,4,6,2-oxadiazaphosphorine ring system **289** (X = N) of which, after stirring in dry methanol, 84% remains unchanged while 16% forms the ring-opened compound **291** (Scheme 97)[127].



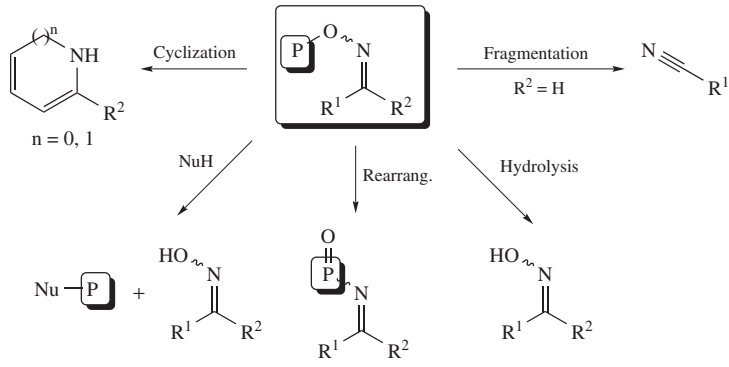
SCHEME 97

B. Reactivity of Phosphorus Substituted Oximes

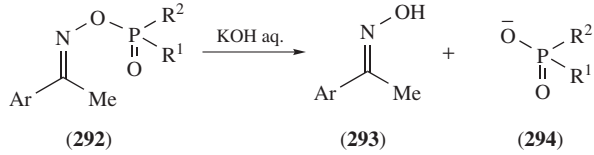
1. Phosphorus O-substituted oximes

The most general transformations involving phosphorus *O*-substituted oximes include elimination of the phosphorus moiety in aldoximes to yield nitriles and rearrangement of phosphorus(III) species to phosphorus *N*-substituted imines. Other reactions like nucleophilic substitution at the phosphorus atom and intramolecular cyclizations are also considered (Scheme 98).

a. Fragmentation and rearrangement reactions. *O*-Phosphorylated ketoximes **292** (Ar = Ph, 2-Py, 3-Py, 4-Py) decompose in alkaline solution to the parent oxime **293** and phosphate anion **294** (Scheme 99). The presence of alkyl groups at the phosphorus in oximes **292** increases the rate of oxime decomposition in the alkaline hydrolysis due to the greater susceptibility of the phosphorus atom in phosphinylated oximes to nucleophilic agents than in phosphorylated or phosphonylated oximes[128].

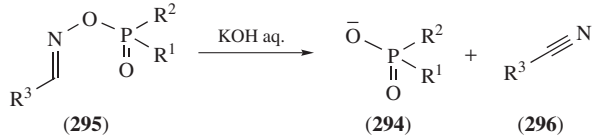


SCHEME 98



SCHEME 99

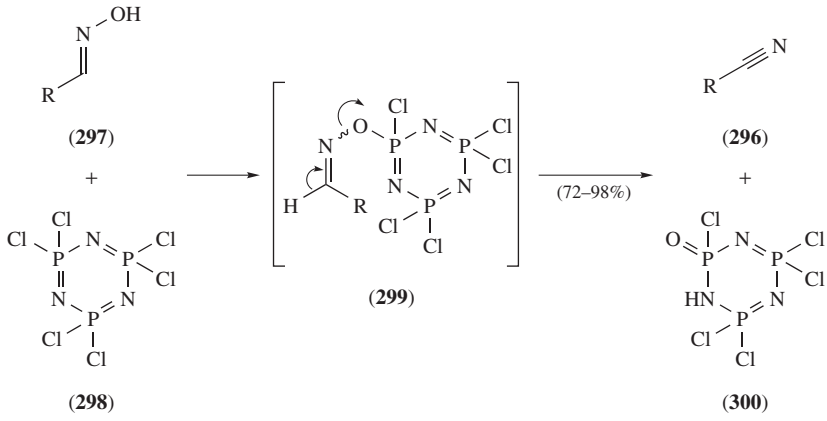
While ketoximes **292** only undergo P−O bond cleavage, aldoximes **295** (R^3 = Ph, 2-Py) mainly yield the fragmentation products phosphate **294** and nitrile **296** (Scheme 100)[128]. A similar behavior is observed with amidoximes **295** ($R^3 = NH_2$, NMe_2)[39a, 129].



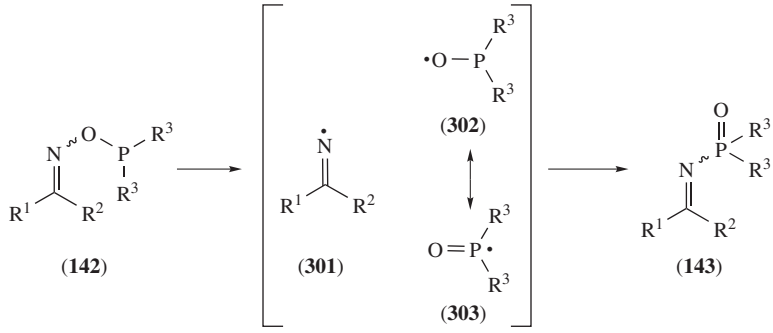
SCHEME 100

Phosphorylation of aldoximes **297** (R^3 = Ph, *p*-ClC_6H_4, Ph−CH=CH, $CH_3(CH_2)_9$, $CH_3(CH_2)_5$, 2-furyl, *p*-PhC_6H_4, 2-Py, $(CH_3)_2C$=CH−$(CH_2)_2$−(CH_3)C=CH, 3-indolyl) using cyclophosphazene **298** is a suitable method for the preparation of nitriles **296**. The process involved implies the formation of an *O*-phosphorylated oxime **299** that eliminates the phosphorus substituent to **300** leading to the formation of nitriles **296** (Scheme 101)[130].

Phosphorus(III) *O*-substituted oximes **142** are known to rearrange to *N*-phosphinylimines **143** through a radical mechanism. The spontaneous homolytic rupture of the N−O bond in oximes **142** gives the oxo radical species **302**. Its mesomeric form **303** can react with the iminyl radical **301** to afford phosphinylimines **143** (Scheme 102)[52]. Although the phosphorus(III) intermediates **142** normally cannot be isolated, their formation can be observed by changes in the ^{31}P NMR spectra while the intermediate radicals **301** and **302** are detectable by ESR spectroscopy. Using this strategy, 3,3-dialkyl-2-(diphenylphosphinyl)oxaziridines are prepared



SCHEME 101

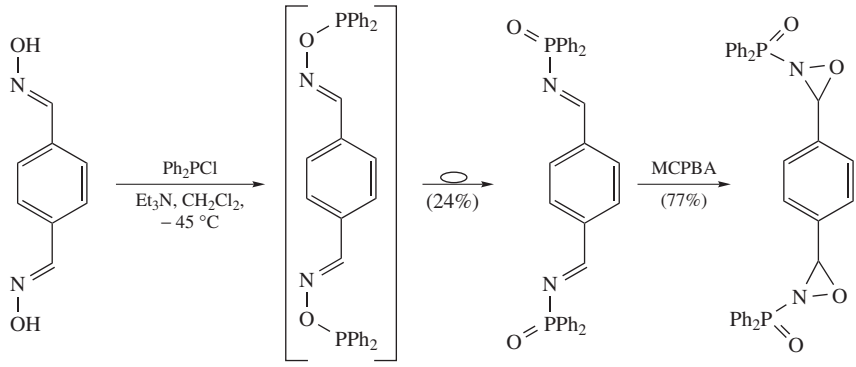


SCHEME 102

by the oxidation of *N*-(diphenylphosphinyl)imines **143** ($R^1 = R^2 = Me$, $R^3 = Ph$; $R^1R^2 = -(CH_2)_5-$, $R^3 = Ph$) with the MCPBA–KF complex[131]. The synthesis of *N*-phosphinyl **143** ($R^1 = CH{=}CH\text{-}R^4$, $R^2 = Me$, Et, $R^3 = Ph$) and *N*-phosphoryl azadienes **143** ($R^1 = CH{=}CHR^4$, $R^2 = Me$, Et, $R^3 = OEt$) is easily accomplished by means of the reaction of α,β-unsaturated oximes with chlorodiphenyl phosphine or diethyl chlorophosphite, respectively, followed by free-radical rearrangement[132].

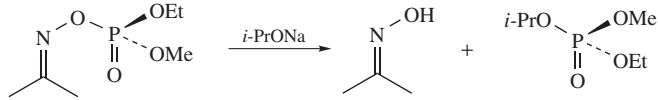
In syntheses of antifungals employed against *Pneumocystis carinii*, the novel bisoxaziridine **307** bearing two oxaziridinyl moieties was prepared from *O*-(diphenylphosphine)oxime **305** (Scheme 103)[133]. Compound **307** was prepared by Arbuzov-type P(III)–P(V) rearrangement of the *O*-(diphenylphosphine)oxime **305**, previously prepared from oxime **304**, to the bis(diphenylphosphinyl)imine **306**, and subsequent biphasic oxidation with MCPBA.

b. Nucleophilic substitution at the phosphorus atom. Enantiopure *O*-phosphorylated acetone oxime **308** undergoes nucleophilic substitution at the phosphorus atom to give



(**303**) (**304**) (**305**) (**306**)

SCHEME 103



(**308**) (**144**) (**309**)

SCHEME 104

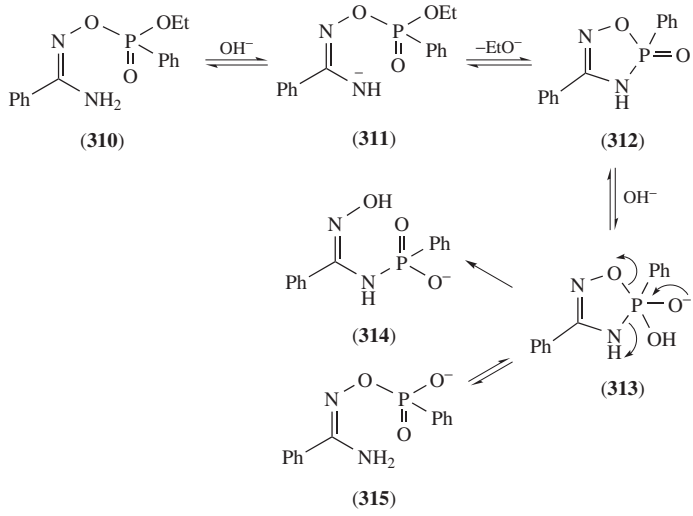
the parent free oxime **144** and chiral phosphate **309** with inversion of configuration (Scheme 104)[134].

O-Amidoxime **310** reacts intramolecularly in alkaline solution through a mechanism, implying ionization of the amino group to **311** followed by a rapid cyclization to form the cyclic intermediate **312**. Due to the considerable strain in the cyclic intermediate **312**, in alkaline solution it rapidly opens to the oxime derivative **314**. The product **313** initially formed in the alkaline reaction rearranges finally to give the *O*-phosphinylated oxime **315**, isolated as sodium salt (Scheme 105)[39a].

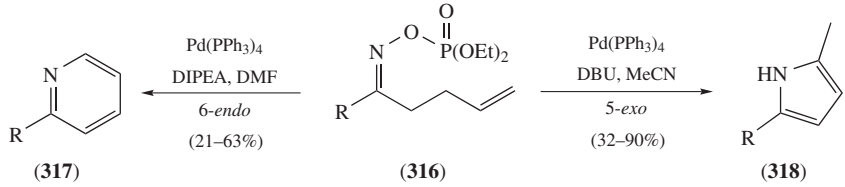
c. Intramolecular reactions. Synthesis of pyridines and pyrroles. Treating oxime **316** with diisopropylethylamine (DIPEA) in the presence of catalytic amounts of $Pd(PPh_3)_4$ using dimethylformamide as solvent afforded the 6-*endo* cyclization product pyridine **317** as major product (Scheme 106). On the other hand, using DBU as a base and acetonitrile as the solvent the 5-*exo* cyclization product pyrrole **318** is observed as the major product (Scheme 106)[39g,h].

2. Phosphorus C-substituted oximes

The most frequent transformations with phosphorus *C*-substituted oximes comprise reductive and oxidative transformations for the generation of α-aminophosphonates derivatives or nitro compounds. In addition, migration of a phosphorus substituent results in fragmentation or rearrangement reactions, yielding nitriles or phosphorus *N*-substituted aldimines, respectively, and radical reactions can be performed if iminyl



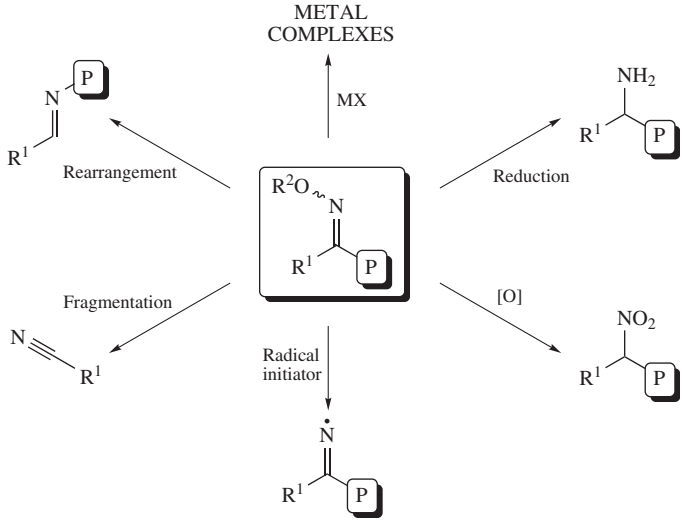
SCHEME 105



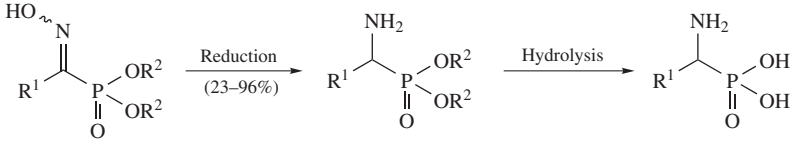
SCHEME 106

radicals are generated by the homolytic rupture of the N−O bond. Complexation of the different heteroatoms present in the structure with metallic salts is also feasible in order to construct diverse metal complexes. The various routes are presented in Scheme 107.

a. Reduction of carbon−nitrogen double bond. Synthesis of α-aminophosphonic acid derivatives. Several reports have demonstrated the usefulness of phosphorylated oximes **201** as starting materials for the preparation of α-aminophosphonic acid units. Normally, two reductive transformations are needed for the conversion of the oxime moiety into a free amino group: the reduction of the C−N double bond and the cleavage of the N−O bond. A final hydrolysis of the phosphonate group would afford α-aminophosphonic acids **320**. The direct transformation of *C*-phosphorylated oximes **201** into α-aminophosphonate derivatives **319** (Scheme 108) is achieved normally by reduction. Among the most used methods, such reductions are carried out over activated zinc dust in formic acid[67c, 135] or acetic acid (24−68%)[74]. On the other hand, there are a number of alternative methods such as catalytic hydrogenation over Raney−Nickel (23−90%)[67p, 136], reduction over aluminum amalgam in ether (38−85%)[67q,w, 73, 136], by sonication with Zn−Cu couple in ethanol (69%)[67m], with a mixture of lithium borohydride and trimethylsilyl chloride in THF



SCHEME 107

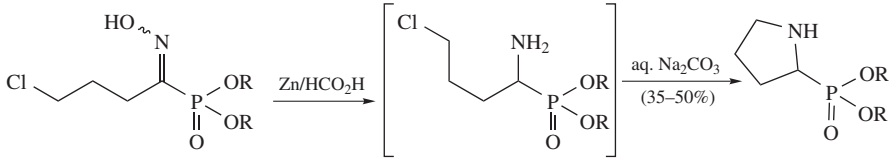


(**201**) (**319**) (**320**)

SCHEME 108

(43–90%)[137], with sodium borohydride in the presence of transition metals (85–96%)[138] or with diborane in THF (55–58%)[68].

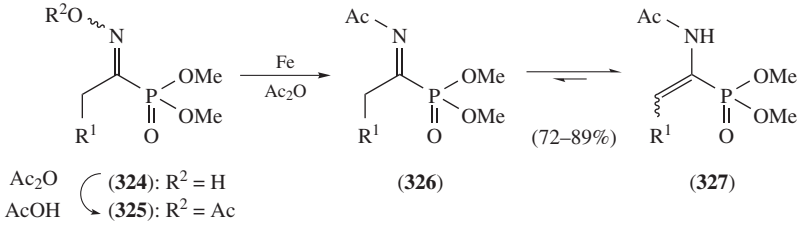
A special case is the reduction of phosphorylated 3-chloropropyl oximes **321** (R = Et, *n*-Bu) over activated zinc dust in formic acid. In this case, the 2-pyrrolidine phosphonate **323** is isolated after treatment of the expected intermediate α-aminophosphonate **322** with sodium carbonate and intramolecular alkylation of the resulting free amino group (Scheme 109)[139].



(**321**) (**322**) (**323**)

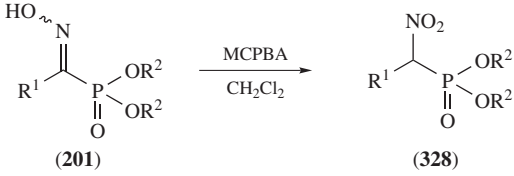
SCHEME 109

Reductive treatment of phosphorylated oximes **324** (R = Ph, Bn, *p*-FC_6H_4, *p*-BrC_6H_4, *m*-$MeOC_6H_4$, 1-naphthyl, *i*-Pr, *n*-Bu) in the presence of acetic anhydride results in the formation of enamines **327**. First the *O*-acetylation of oxime **324** to the phosphonate oxime **325** is expected, and then, reduction by electron transfer from metallic iron to the latter results in the rupture of the weak N−O bond. A second electron transfer leads to an anion that is captured by acetic anhydride to give imine **326** that isomerizes to the more stable enamine tautomer **327** (Scheme 110)[67e].



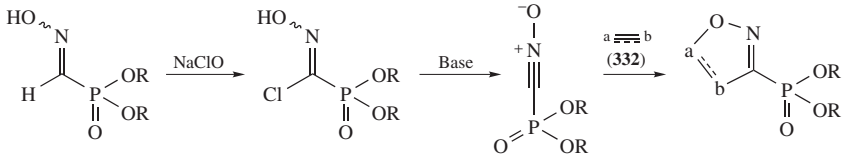
SCHEME 110

b. Oxidation reactions. Synthesis of nitroalkanes, nitrile oxides and nitrosoalkenes. Phosphorylated oximes **201** can be converted into α-nitro phosphonates **328** by oxidation with MCPBA in dichloromethane (Scheme 111)[67u, 140]. Through this transformation the electrophilic oxime carbon is transformed into a potential nucleophilic carbon if a subsequent deprotonation is performed. Although a very stabilized anion is expected due to the presence of two electron-withdrawing groups, the possible activating effect that the phosphorus substituent might provide is overcome by the steric demands by the phosphonate group and, as a consequence, lower conversions are obtained when larger phosphonate groups are present[140].



SCHEME 111

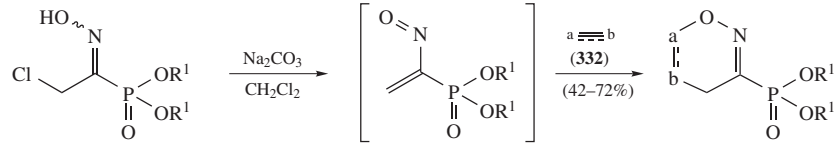
When treated with base, phosphorylated chlorooxime **330** (R = *i*-Pr) lead to highly reactive phosphorylated nitrile oxide **331** in 99% yield[141]. Nitrile oxides tend to polymerize at room temperature and, normally, they have to be generated in a temperature range of 0 °C and −60 °C. Chlorooximes **330** are known to be, in most cases, strong irritants and, as an alternative, phosphorylated nitrile oxides **331** can be generated from phosphorylated aldoxime **329** (R = Et) using bleach, which acts as a chlorinating agent and also provides the basic conditions to perform the dehydrochlorination step (Scheme 112)[67a]. The so-generated 1,3-dipoles **331** are trapped *in situ* with dipolarophiles **332** to give phosphorylated heterocycles **333**.



(**329**) (**330**) (**331**) (**333**)

SCHEME 112

Similarly, phosphorylated α-chlorooximes **334** (R^1 = Et, *i*-Pr) undergo dehydrochlorination in the presence of a base to afford phosphorylated conjugated nitrosoalkenes **335**. Those unstable conjugate double bond systems can be trapped *in situ* with dienophiles **332** to yield phosphorylated heterocycles **336** through a [4 + 2] cycloaddition reaction (Scheme 113)[142].



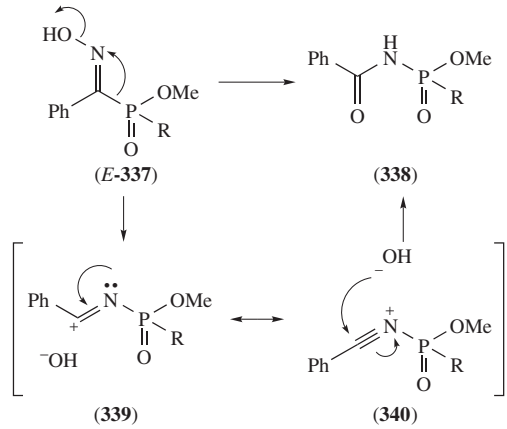
(**334**) (**335**) (**336**)

SCHEME 113

c. Rearrangement and fragmentation reactions. Aryl phosphonate (R = OMe) and phosphinate (R = Ph) (*E*)-oximes *E*-**337** heated in the presence of acids undergo Beckmann rearrangement to afford *N*-acyl phosphoramides **338** in 65–90% yield[67s]. According to the generally accepted view, the Beckmann rearrangement of phosphorylated oximes **337** would schematically involve the intermediacy of a nitrilium species **339/340** formed through a concerted *anti*-migration of the phosphonate group to the nitrogen with concomitant elimination of water. The nitrilium species **340** may then undergo nucleophilic addition of hydroxide anion to the carbon–nitrogen triple bond yielding phosphoramides **338** (Scheme 114).

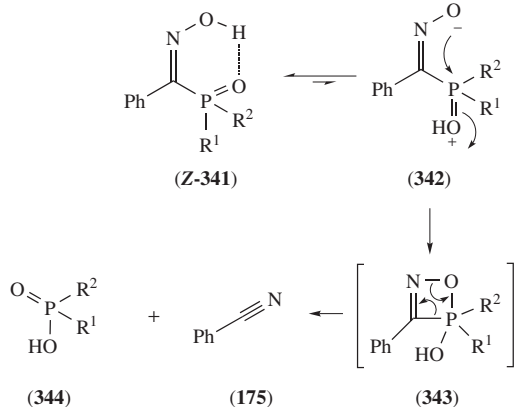
Phosphonamidate oximes **337** (R = Et_2N, pyrrolidinyl, piperidinyl, *i*-PrNH, *t*-BuNH) undergo Beckmann rearrangement more efficiently than the corresponding phosphonate or phosphinate derivatives (>90% in 1–7 h). This is due to the enhanced electron-releasing effect of the nitrogen compared to the oxygen which is reflected in an increased migratory aptitude of the phosphorated group[67g]. Beckmann rearrangement of phosphonamidate oximes **337**, bearing glycine ester (R = EtO_2C-CH_2-NH) or alanine ester (R = EtO_2C-(CH_3)CH-NH) substituents at the phosphorus, lead to the formation of peptide transition state analogs **338**. Those compounds can be viewed as dipeptide analogs with a missing α-carbon and the tetrahedral phosphoryl substituent replacing the carbonyl of one of the amino acid units (Scheme 114).[143]

Unlike phosphonate or phosphinate (*E*)-oximes *E*-**337**, heating the *Z*-isomers of dimethyl phosphonate oximes *Z*-**341** (R^1 = R^2 = OMe), dioxaphospholane oximes *Z*-**341** (R^1R^2 = $OCMe_2$-Me_2CO) or methyl phosphinate oximes *Z*-**341** (R^1 = OMe, R^2 = Ph) affords benzonitrile **175** in 70–90% yield together with phosphinic or phosphonic



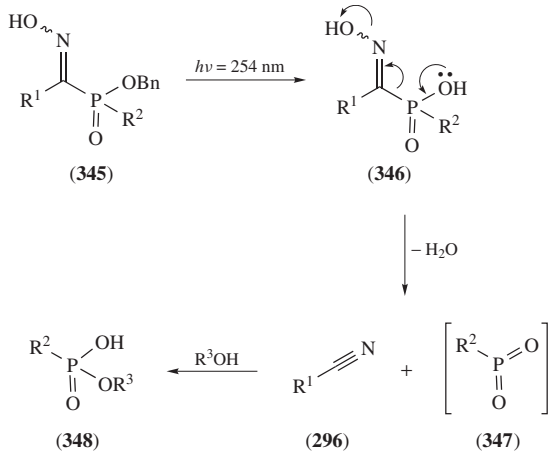
SCHEME 114

acid derivatives **344**[82c]. The formation of the nitrile can be rationalized by assuming a pre-equilibrium with a zwiterionic intermediate **342**, formed via an intramolecular hydrogen bond species *Z*-**341**. This would facilitate the intramolecular nucleophilic attack of the anionic oxygen on the phosphorus, leading to a 4-membered cyclic intermediate **343** which would decompose to the nitrile **175** and acid **344** (Scheme 115).



SCHEME 115

Hydroxyiminophosphonic acid **346** (R^1 = Ph, R^2 = OH)[67j, 79], their methyl monoesters **346** (R^1 = Ph, R^2 = OMe)[67t, 82a,c] and hydroxyiminophosphinic acids (R^1 = R^2 = Ph)[144] **346** undergo easy thermal, acid or base catalyzed fragmentation to afford benzonitrile (**296**) (R^1 = Ph) and metaphosphate **347**. Metaphosphate-like species **347** are known to have a high electrophilic character and undergo immediate addition of nucleophiles, normally the solvent of the reaction, water or alcohols to give **348** (Scheme 116). A comparable behavior has also been observed in hydroxyiminophosphonoacetic acids or 'troika acids' **346** (R^1 = CO_2H)[80]. Metaphosphate-like species **347** (R^2 = OMe, OEt)



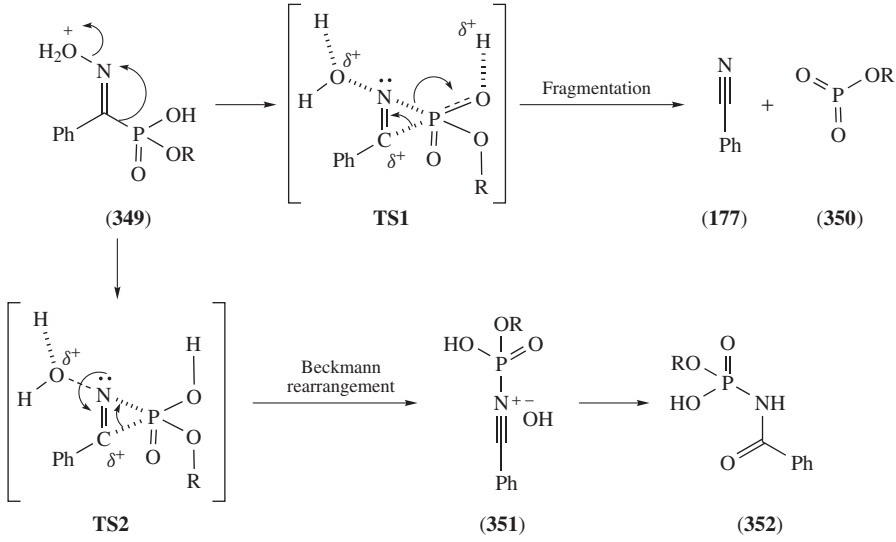
SCHEME 116

have been also trapped with silica gel[145]. Oximes **346** can therefore be considered as versatile phosphorylating agents. The use of phosphonates with photolabile ester groups is an elegant procedure for the generation of metaphosphate. Photoinduced phosphorylation can be performed by UV irradiation of hydroxyiminophosphonic acid benzyl ester **345** through photochemical debenzylation of the phosphonate group followed by immediate fragmentation to afford the electrophilic metaphosphate-like species **347** easily trapped with ethanol in 90% yield. This strategy can also be extended to dibenzylphosphonate oximes[67o]. A similar photoinduced phosphorylation can be performed using troika acids bearing photolabile phosphonate moieties[75].

Kinetic and theoretical studies on the fragmentation of phenyl (R = Ph)[67d] and methyl (R = Me)[146] monoesters of hydroxyiminophosphonic acids **349** led to the conclusion that the mechanism of the fragmentation of hydroxyiminophosphonates **349** can be viewed as taking place via a Beckmann-type transition state **TS1** which fragments to give benzonitrile (**175**) and metaphosphate species **350** (Scheme 117). The rearrangement products **352** would be obtained from nitrilium species **351** which result from the formation of a transition state **TS2** where the phosphorus moiety undergoes migration to the nitrogen atom. The fragmentation mechanism is blocked for phosphonate diesters which may explain why (*E*)-dialkylphosphonate oximes yield the Beckmann rearrangement products while (*Z*)-dialkylphosphonate oximes undergo fragmentation through a 4-membered ring transition state (see Scheme 115)[147].

d. Radical reactions. Generation of iminyl radicals **354** by homolytic rupture of the N−O bond is performed by treatment of benzoyl (R = PhCO) or pivaloyl (R = *t*-BuCO) oximes **353** with nickel and acetic acid in isopropanol or with tributylstannane in cyclohexane[67h,i, 148]. Subsequent capture of the intermediate radical **354** by the internal olefin affords exclusively the 5-membered cyclic iminophosphonate **355** (Scheme 118).

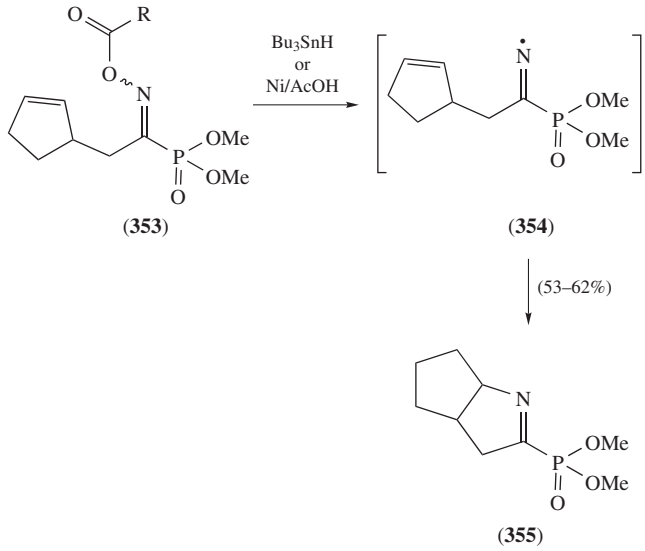
In the case of α-allenyl phosphorylated benzoyl oximes **356**, addition of the stannyl radical to the allene seems to be the preferential process. The obtained radical **357** undergoes a 6-*endo* cyclization, favored over 5-*exo* cyclization due to the steric and electronic effects of the phosphoryl group, leading to the formation of dihydropyridine **359** after radical debenzylation of the cyclic radical **358** (Scheme 119)[78].



(**349**) **TS1** (**177**) (**350**)

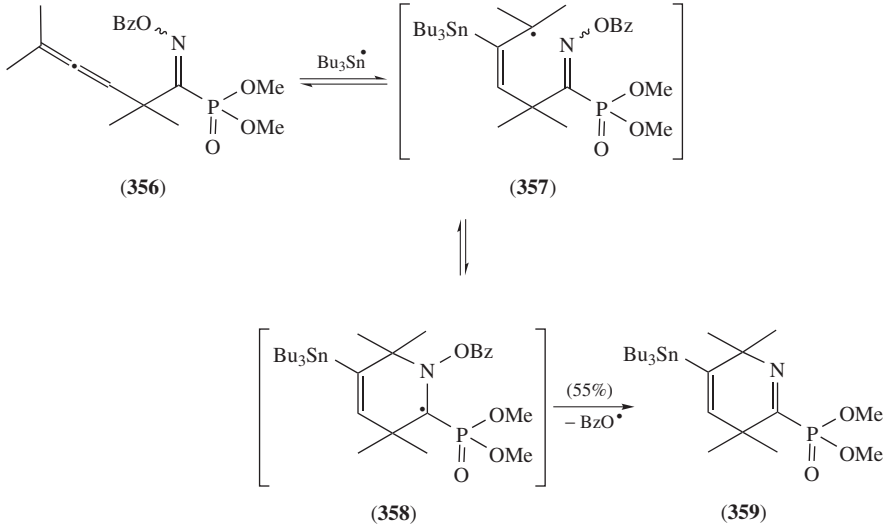
TS2 (**351**) (**352**)

SCHEME 117



(**353**) (**354**) (**355**)

SCHEME 118

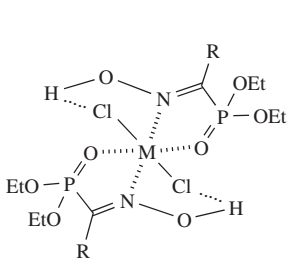


SCHEME 119

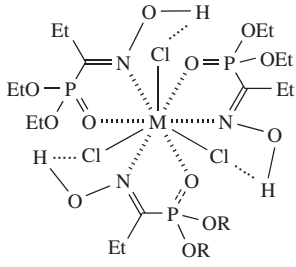
e. Metal complexes containing phosphorus C-substituted oximes. Phosphorylated oximes are interesting chelating agents, since they combine two coordinating functional groups, phosphonate and oxime, which show different affinity with hard or soft metal ions. The oxime moiety fragment can coordinate through the nitrogen or oxygen atoms that can be deprotonated or not, while phosphonate oxygen atoms can also chelate or bind to a neighboring metal center. Metal complexes are easily obtained by reaction of the oxime ligands and metallic salts in alcoholic or water solutions. Cobalt(II) and nickel(II) complexes **360** (M = Co, R = Et; M = Ni, R = Et, *c*-Pr) exhibit a symmetric bidentate octahedral mode of coordination via the imine nitrogen and the phosphoryl oxygen, where both oxime protons are coordinated to a chlorine atom via hydrogen bonding forming two 5-membered rings (Figure 4)[149, 150].

Similarly, praseodymium(III) and lanthanum(III) chloride complexes **361** (M = Pr, R = *i*-Pr; M = La, R = Et) show an asymmetric bidentate coordination mode with a nine-coordinate geometry, which may be envisaged as tricapped-trigonal prismatic[149, 151]. Chloride complexes **361** show an internal hydrogen bonding between the oxime hydrogen atom and the chloro ligand, effectively forming a 5-membered chelate ring. In contrast, the phosphorylated oxime ligand in neodymium(III) nitrate complex **362** adopts a monodentate bonding mode via only the phosphoryl oxygen, where the metal is also nine-coordinated but in an irregular polyhedron[151]. This preference of the neodymium ion for the oxygen ligand over the potential imine nitrogen donor is consistent with the hard nature of the *f*-elements. One of the imine nitrogens is involved in hydrogen bonding with the proton of the water molecule coordinated to the metal, forming a pseudo 7-membered ring. Both oxime hydrogens pointing to opposite directions establish hydrogen bonding with the nitrate oxygen atoms of adjacent molecules, resulting in polymeric chains (Figure 4)[149].

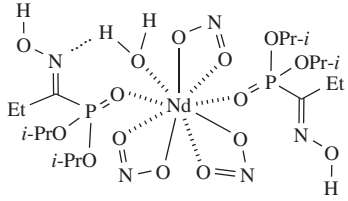
In general, cobalt salts show a preferential inclination to complex with *E*-isomers of *C*-phosphorylated oxime **363** in respect to *Z*-isomers (Scheme 120). This effect might be due to the presence of an intramolecular hydrogen bonding in solution between the oxime



(**360**)

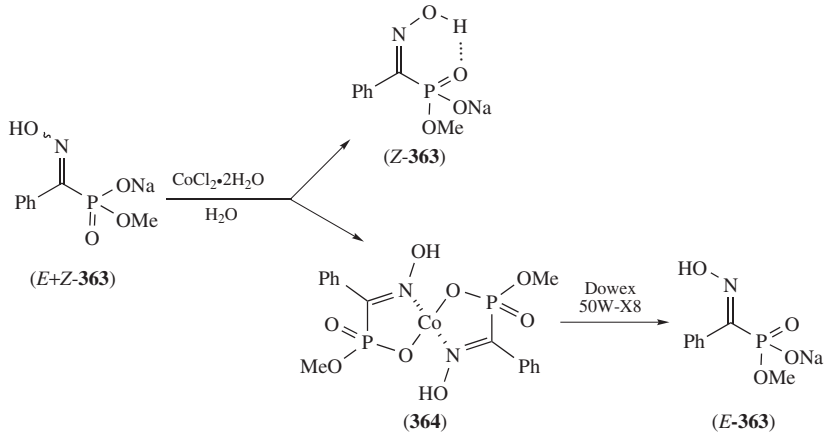


(**361**)



(**362**)

FIGURE 4

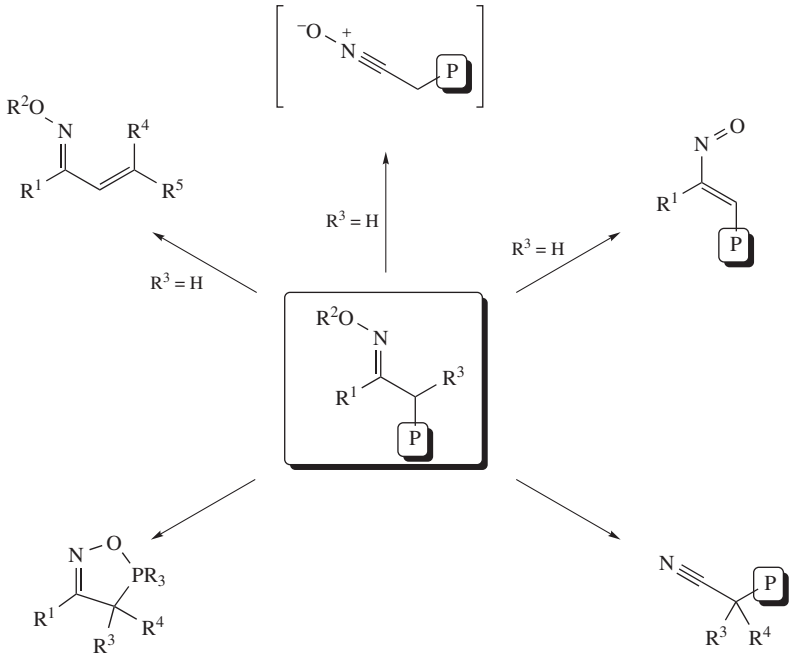


SCHEME 120

hydrogen and the phosphoryl oxygen in *C*-phosphorylated oxime *Z*-**363**, which prevents chelation with the metal. This preference for complexation can be taken as an advantage for the isolation of the pure isomers from *E*/*Z* mixtures of *C*-phosphorylated oximes *E* + *Z*-**363**. In this way, dinuclear cobalt complex of the *E*-isomer **364** precipitates from an aqueous solution, whose subsequent treatment in a cation interchange resin regenerates the sodium salt of oxime *E*-**363**. The pure *Z*-isomer of oxime **363** can be recovered from the mother liquor[152].

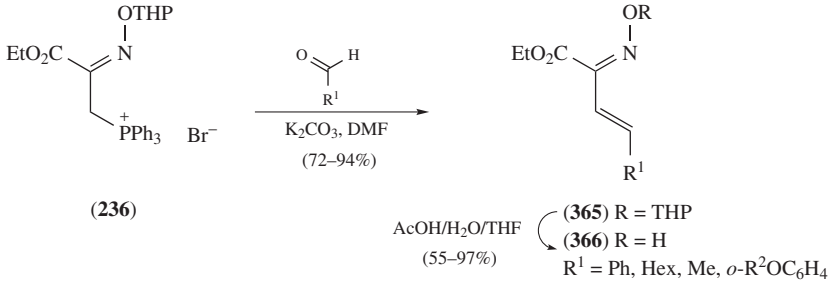
3. Phosphorus α-substituted oximes

The most characteristic reactions of oximes with a phosphorus-containing group substituent at alpha-position comprise reaction at the phosphorus atom through olefination reaction and oxidation of oximes to nitrile oxides by reaction at the C−N double bond of the oxime moiety. Moreover, some reports describe the oxidation of these substrates to nitrosoalkenes and nitrile oxides, and some reactions at the hydroxyl group of the hydroxyimino moiety (Scheme 121).



SCHEME 121

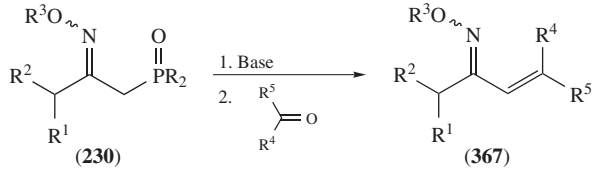
a. Olefination reactions. One of the most representative examples of the reactivity of phosphorus α-substituted oximes at the phosphorus atom entails the C−C double bond forming process, through Wittig reaction[153] or related processes of α-phosphorated oximes with carbonyl compounds. For carbon–carbon double bond construction, not only phosphonium salts (Wittig reaction) but also phosphine oxide derivatives (Horner reaction) or phosphonates (Horner–Wadsworth–Emmons reaction) are very useful reagents. Moreover, this is a very useful method for the preparation of 1-azabuta-1,3-dienes, important building blocks for the preparation of 6-membered nitrogen-containing heterocycles. For example, Boger and coworkers have described the preparation of 1-azabuta-1,3-dienes, based on the use of the stabilized Wittig reagent **236**, and their 4π participation in inter-[101, 154] and intramolecular[155] [4 + 2] cycloaddition reactions. 1-Azabuta-1,3-dienes **366** are prepared through Wittig reaction of the stabilized phosphorane generated *in situ* from the phosphonium salt **236** with aldehydes, followed by acid-catalyzed removal of the tetrahydropyranyl (THP) group in **365** (Scheme 122). α,β-Unsaturated oximes,



SCHEME 122

prepared through Wittig olefination reaction of α-hydroxyimino phosphonium salts, can be also used as building blocks for the preparation of indole-3-pyruvic acid oxime ethers by Heck cyclization[156].

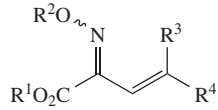
Our group[97] has reported an efficient method for the preparation of α,β-unsaturated oximes starting from α-phosphorus functionalized oximes through olefination reaction. Consequently, α-oximo phosphine oxides **230** (R = Ph) can be a suitable precursor for the homologation of oximes into their vinylogous compounds. Oximes **230** (R = Ph) are treated with a base such as methyl lithium, followed by addition of aromatic, heteroaromatic and aliphatic aldehydes and ketones, leading to *syn*- and *anti*-1-azadienes **367** with high *E*-stereoselectivity of the carbon–carbon double bond and in good yields (Scheme 123). This olefination reaction is not restricted to α-oximo phosphine oxides **230** (R = Ph) since *syn*- and *anti*-oximes **230** (R = OEt) derived from phosphonates can also be used in this approach. This strategy is also used for the preparation of functionalized α,β-unsaturated oximes **368** (Figure 5) derived from hydroxyimino ester derivatives[98, 100a, 157, 158].



R = Ph, OEt
R^1 = H, Me, *p*-MeC_6H_4; R^2 = H
R^1R^2 = $-(CH_2)_5-$
R^3 = H, Me, $SiMe_3$, $SiMe_2$Bu-*t*

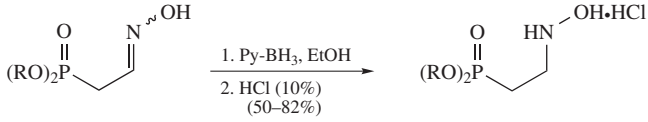
SCHEME 123

b. Oxime reductions. Through a simple oxime–hydroxylamine reduction, β-aminophosphonate derivatives may be prepared in satisfactory yields. This strategy is employed for the reduction of phosphorylacetaldehyde oximes **369** with pyridine–borane complex followed by treatment with 10% HCl, to afford phosphorylhydroxylamines **370** (Scheme 124)[159].



(**368**)

FIGURE 5

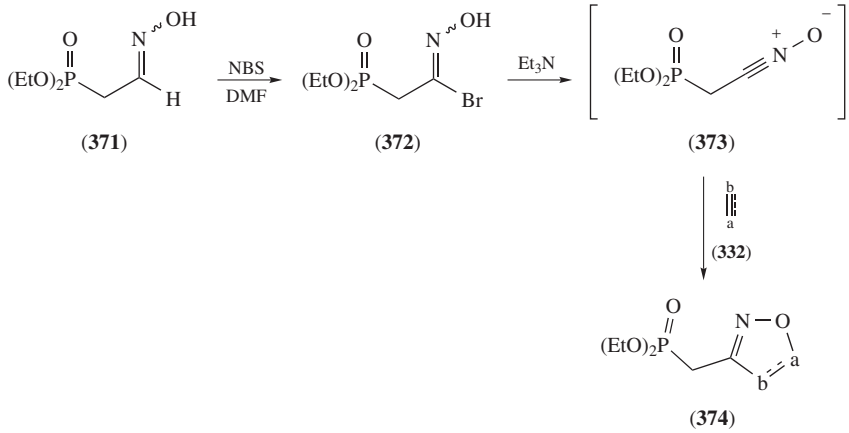


(**369**) (**370**) R = *n*-Pr, *i*-Pr, *i*-Bu

SCHEME 124

c. Oxidation reactions. Synthesis of nitrile oxides and nitrosoalkenes. Nitrile oxides are much more frequently used in organic synthesis, especially in the elaboration of complex molecules, than any other 1,3-dipoles[160]. Phosphorus functionalized nitrile oxides undergo regioselective 1,3-dipolar cycloadditions to olefins or acetylenes to furnish good yields of 2-isoxazolines or isoxazoles bearing a phosphorus substituent. For example, Tsuge and coworkers reported the first synthesis of phosphorus functionalized nitrile oxide and its cycloaddition with a variety of olefins. Nitrile oxide **373** is successfully accessible by the bromination of **371** with NBS (*N*-bromosuccinimide) followed by dehydrobromination of **372** with triethylamine. This nitrile oxide **373** can be trapped as cycloadduct with a variety of olefinic dipolarophiles giving the corresponding isoxazolines **374** as single regioisomers and in good yield (Scheme 125)[87, 161]. Cycloaddition of phosphorus functionalized nitrile oxide **373** to acetylenic alcohols is reported in the synthesis of *E*-isomers of furanone derivatives which are an essential part of the framework of furanone natural products such as geiparvarin[162]. Other dipolarophiles such as allyl[163] and homoallyl alcohols[164] or α,β-unsaturated esters[165] have been used for the cycloaddition reaction to **373** to give terpene, pyridine or furanone derivatives, respectively. Likewise, isoxazolinephosphonates and isoxazolephosphonates substituted at 4- and 5-positions have been obtained by cycloaddition of olefins and acetylenes to **373**[166]. The synthetic value of nitrile oxide cycloaddition is now growing as shown in its wide applications to natural product synthesis[90, 167, 168], and this approach has been recently used in the preparation of phosphorylated dihydroisoxazole nucleosides and in their study as antiviral agents[169].

Nitrosoalkenes are functionalized nitroso derivatives, and the presence of an adjacent double bond in conjugation with the nitroso moiety introduces new reactivity centers in these substrates, which increases the synthetic value of these compounds. Therefore, several papers report the usefulness of nitrosoalkenes[170] as conjugate addition acceptors[171], coupled with the easy conversion of the nitroso group into other functionalities, such as oximes and ketones[172], or their ability to act as dienes in hetero-Diels–Alder reactions for the preparation of 1,2-oxazine derivatives[173]. The synthesis of nitrosoalkenes containing a phosphorus substituent at C-4 has been scarcely explored. Only one example for the preparation of these systems has been recently reported[174]. As outlined in Scheme 126, the α-halooximes **376** required for the synthesis of phosphorylated nitrosoalkenes **377** are easily accessible from reaction of functionalized α-oximes **375** with an excess of



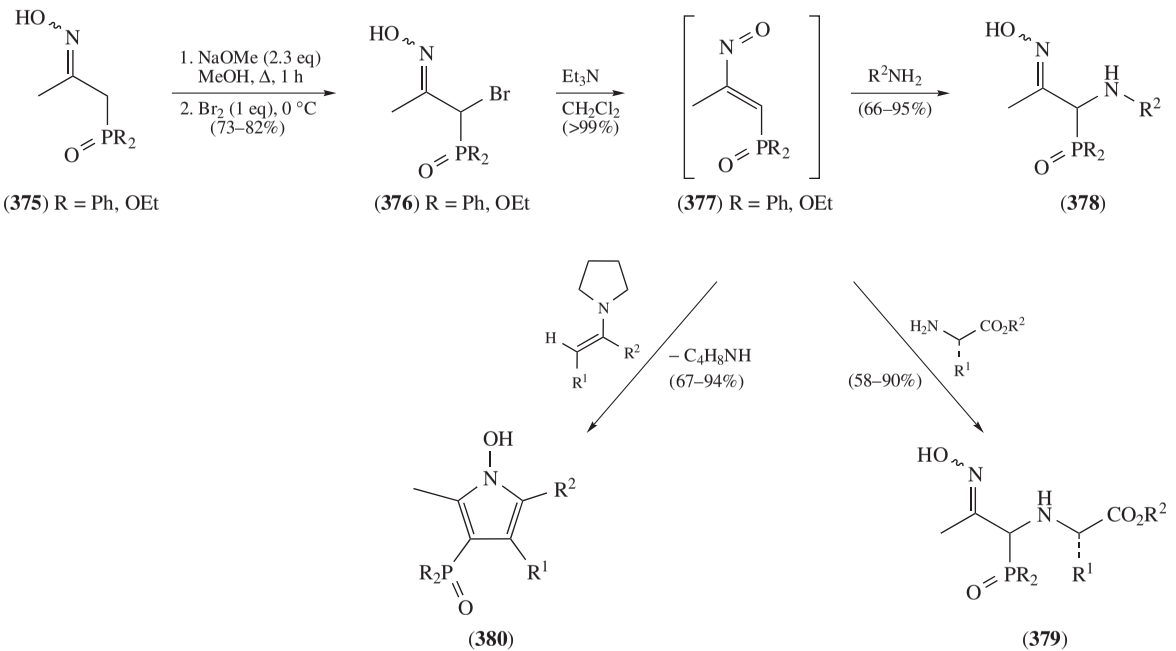
SCHEME 125

base and subsequent addition of bromine. Nitrosoalkenes **377** have been prepared in almost quantitative yield through base-mediated dehydrohalogenation of α-halooximes **376**. These functionalized nitrosoalkenes are useful Michael acceptors and thus conjugate addition of nucleophilic reagents such as ammonia, primary and secondary amines or optically active amino esters furnish α-aminophosphine oxides and phosphonates **378** and **379** (R = OEt) in a highly regioselective fashion (Scheme 126)[174]. More recently, the nitrosoalkenes **377** have been used for the preparation of 5-membered nitrogen-containing heterocycles such as *N*-hydroxypyrrole derivatives **380**, through conjugate addition of enamines at the terminal carbon atom of the heterodiene **377**, ring closure (formally a [3 + 2] dipolar cycloaddition) and elimination of the pyrrolidine residue (Scheme 126)[175]. The synthesis of *N*-hydroxypyrroles is also reported by other authors via conjugate addition of enolates derived from ketones to phosphorylated α-chlorooximes[176].

d. Reactions at the hydroxy group of the hydroxyimino moiety. i. Cyclization reactions. Some reports[99b,c, 177] describe the preparation of oxazaphospholine intermediates **382** by treatment of oxime phosphonium salts **381** with a base. These oxazaphospholines are readily converted, on pyrolysis at 100–150 °C, into 2*H*-azirines[178] **383** by an initial P–C bond cleavage, subsequent loss of triphenylphosphine oxide and ring contraction (Scheme 127).

A convenient synthesis of phosphono-substituted heterocyclic compounds has been reported through vinylphosphonates via a condensation–intramolecular 1,4-addition sequence[96]. α-Formylvinylphosphonates **384** were treated with hydroxylamine hydrochloride and pyridine in ethanol under reflux to afford 4-phosphonoisoxazoles **386**, via phosphorylated oxime **385** (Scheme 128). This result demonstrates that the oxime **385** clearly undergoes the 5-*endo*-trigonal cyclization to give the isoxazole **386**.

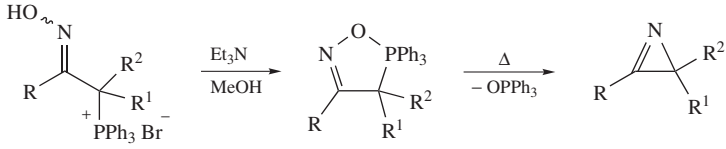
ii. Dehydration of oximes. Acetic anhydride-mediated dehydration of oximes can be applied to aldoxime **242** for the preparation of substituted phosphonate carbonitrile **388**. The synthesis of nitrile **388** was apparently preceded by acylation of the starting aldoxime **242** with formation of the intermediate acetate **387**, and subsequent elimination of acetic acid (Scheme 129)[103c]. A similar behavior has been observed by our group starting from *O*-tosyl aldoximes[179].



(**375**) R = Ph, OEt (**376**) R = Ph, OEt (**377**) R = Ph, OEt (**378**)

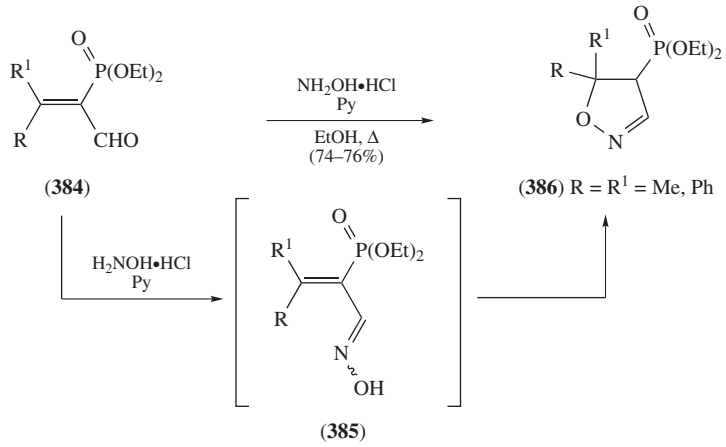
(**380**) (**379**)

SCHEME 126



(**381**) (**382**) (**383**)

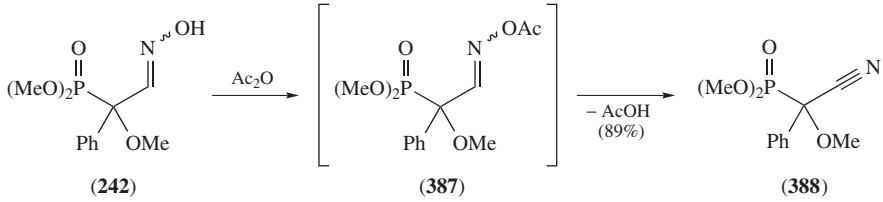
SCHEME 127



(**384**) (**386**) R = R^1 = Me, Ph

(**385**)

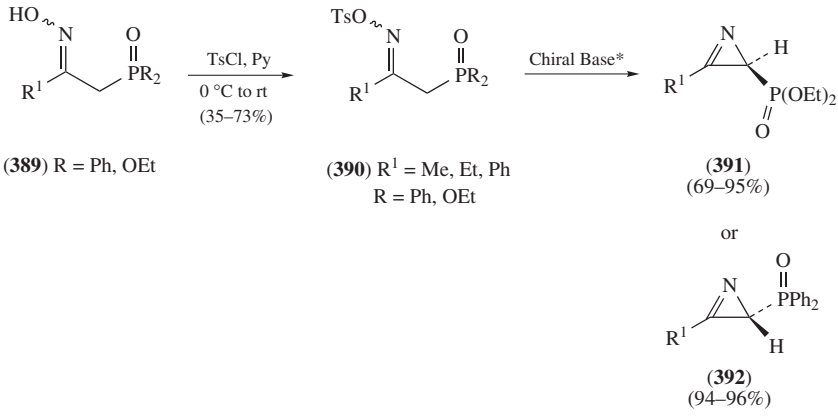
SCHEME 128



(**242**) (**387**) (**388**)

SCHEME 129

iii. O-Functionalization reactions. Functionalized *O*-tosyl oximes **390** can be easily formed by simple reaction of α-phosphorylated oximes derived from phosphonate **389** (R = OEt) or phosphine oxide **389** (R = Ph) with tosyl chloride in pyridine (Scheme 130). The synthesis of these phosphorylated tosyl ketoximes **390** has been applied to the asymmetric preparation of phosphorylated 2*H*-azirines **391** and **392** through the modified Neber reaction[180, 181]. The same approach has been applied to the synthesis of 2*H*-azirines **391** as building blocks for the preparation of oxazoles[182], and α- and β-aminophosphonates[86]. Similarly, these phosphorus substituted *p*-tosyl oximes **390** can be used as synthons for the preparation of phosphorus substituted pyrazines[183], and



(**389**) R = Ph, OEt

(**390**) R^1 = Me, Et, Ph
R = Ph, OEt

(**391**)
(69–95%)

(**392**)
(94–96%)

SCHEME 130

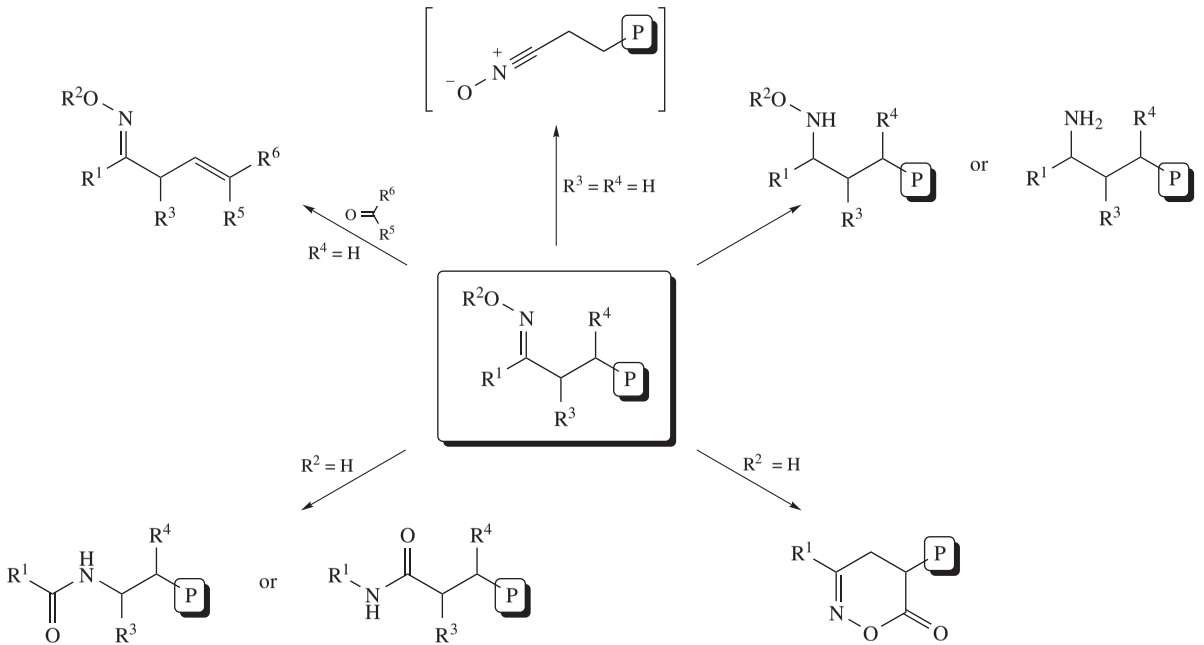
O-functionalization reaction of fluoroalkyl ketoximes for the preparation of α-phosphorylated fluoroalkyl *p*-toluenesulfonyl ketoximes has been recently reported[92].

4. Phosphorus β-substituted oximes

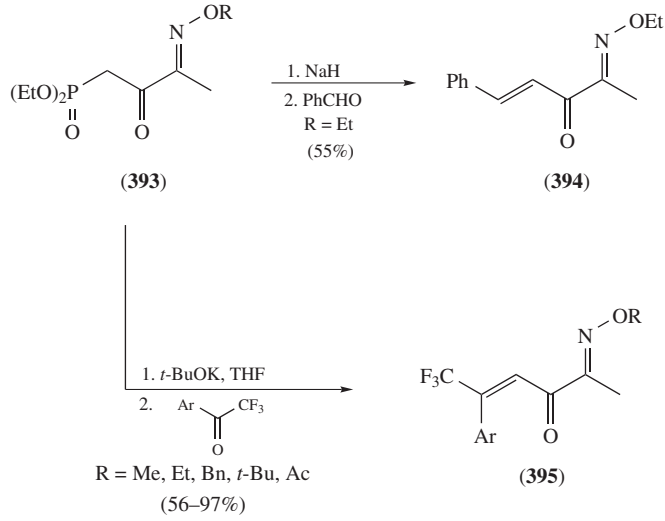
Several papers have been published on the reactivity of oximes with a phosphorus substituent at β-position. This section will concentrate on the most practical routes developed by using β-phosphorus substituted oxime as building blocks for the preparation of more elaborated molecules. These routes comprise: a) reactions at the phosphorus atom such as olefination reaction; b) reactions at the C−N double bond, including oxime reductions, oxidation to nitrile oxides or Beckmann rearrangement; and c) cyclization reactions involving reaction at the hydroxyl group of the hydroxyimine moiety (Scheme 131).

a. Olefination reactions. Some examples have been reported involving a C−C double bond formation by olefination reaction of carbonyl compounds to β-phosphorylated oximes. In this way, phosphorylated oximes **393** (R = Et) react by means of a Wadsworth–Emmons (W-E) reaction with benzaldehyde (PhCHO) to give 1-azapenta-1,4-dien-3-one (**394**) (Scheme 132)[124]. 1-Alkoxy-1-azapenta-1,4-dien-3-ones **395** were also accessible from oximes **393** (R = Me, Et, Bn, *t*-Bu, Ac) through olefination reaction using trifluoromethyl ketones (Scheme 132)[125]. These 1-aza-1,4-dien-3-ones systems undergo various types of cyclization reactions[184].

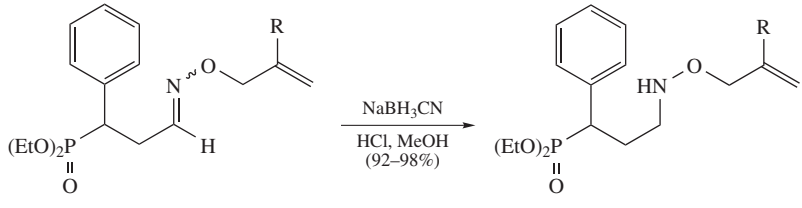
b. Oxime reductions. γ-Aminophosphonates may be prepared through a simple oxime-amine reduction. A strategy has been recently used for the preparation of oxazinyl analogues of fosmidomycin **249** (see Scheme 88), a promising antimalarial compound. These analogues, in which the hydroxamate moiety is incorporated into a ring structure, have been prepared through reduction of oximes **252** with sodium cyanoborohydride in methanol acidified with HCl to afford aminophosphonates **396** (Scheme 133)[108]. Use of other reducing agents usually results in the cleavage of the N−O bond as a side reaction. Since the hydroxylamine moiety is an important feature for antimalarial activity, this cleavage must be avoided. Other α-aryl-substituted fosmidomycin analogues have been prepared by other authors by using the same reduction conditions[106].



SCHEME 131



SCHEME 132

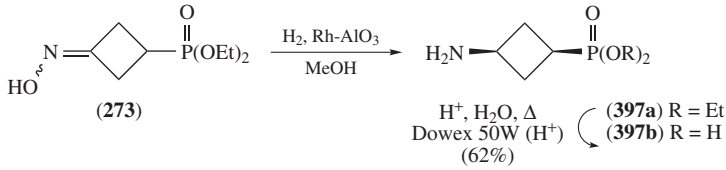


SCHEME 133

Hanrahan and coworkers[121] reported the diastereoselective hydrogenolysis of cyclobutyl oxime **273** by using hydrogen with rhodium on alumina as the catalyst (Scheme 134). The crude amine **397a** was hydrolyzed to the phosphono amino acid **397b** and purified by ion exchange chromatography. Since cyclobutanones are known to prefer to be distorted toward the inner *endo* face[185], it is plausible to assume that the oxime adopts a similar conformation. It is also likely that the bulky phosphonate group prefers to be in the pseudo-axial position to minimize steric interactions. In this conformation it is likely that hydrogenation occurs from the substantially less hindered top side of the cyclobutane ring rather than from the more hindered bottom side, leading to the *cis*-isomer.

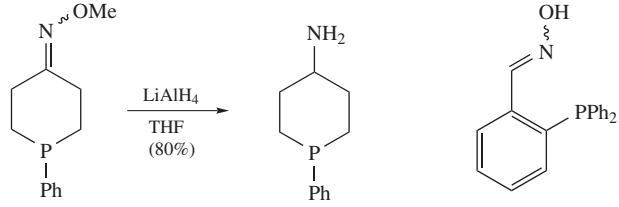
Treatment of phosphine-oxime **398** with $LiAlH_4$ gives 1-phenyl-4-aminophosphorinane (**399**) in good yield (Scheme 135)[186]. However, it has not been possible to achieve reduction of other phosphine-oximes such as **400** (Scheme 135)[187]. Reduction using Raney–Nickel or catalytic hydrogenations with Pd/C as catalysts results in complete recovery of the starting aldoxime.

The phosphono analogues of *N*-acetyl-α-D-glucosamine 1-phosphate and *N*-acetyl-α-D-mannosamine 1-phosphate, glycomimetics of great biological interest, can be obtained



(**273**)

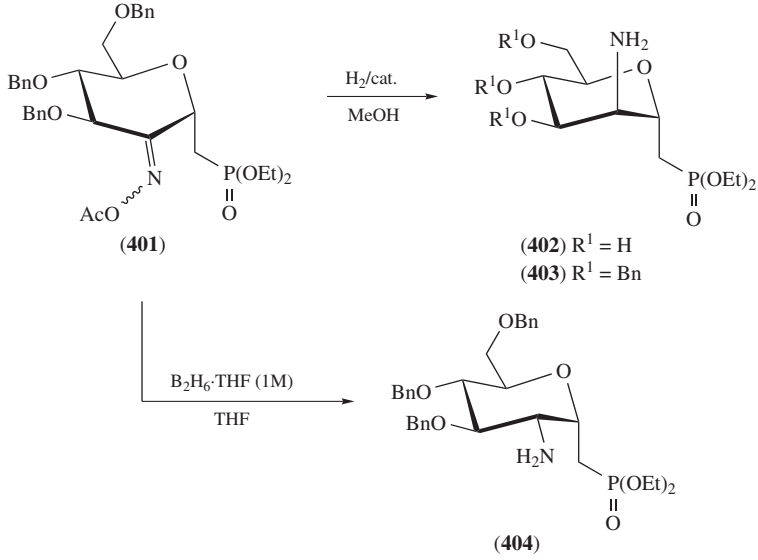
SCHEME 134



(**398**) (**399**) (**400**)

SCHEME 135

stereoselectively by reduction of the oxime moiety in compound **401** (Scheme 136)[120]. Reduction is affected by catalytic hydrogenation affording the product with the manno configuration. When $Pd(OH)_2$ is used as catalyst, in the presence of 2N HCl, the debenzylated manno derivative **402** is recovered quantitatively. However, when Ni–Raney was used the benzylated manno derivative **403** was obtained in 60% diastereomeric excess. Yields and



(**401**)

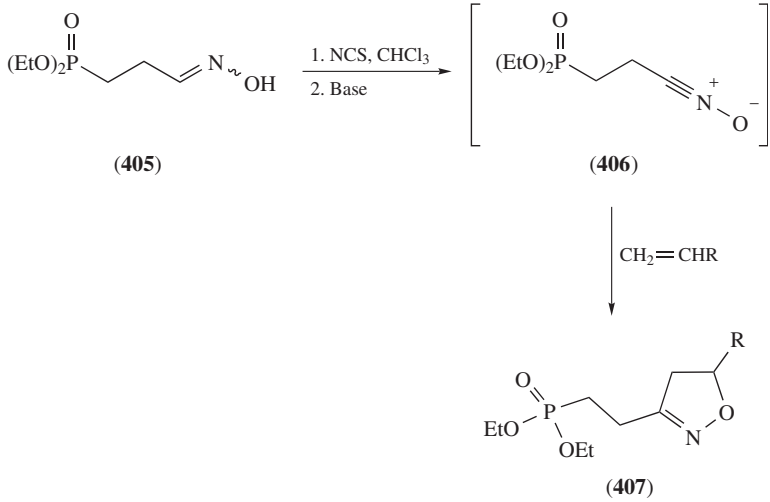
(**402**) R^1 = H
(**403**) R^1 = Bn

(**404**)

SCHEME 136

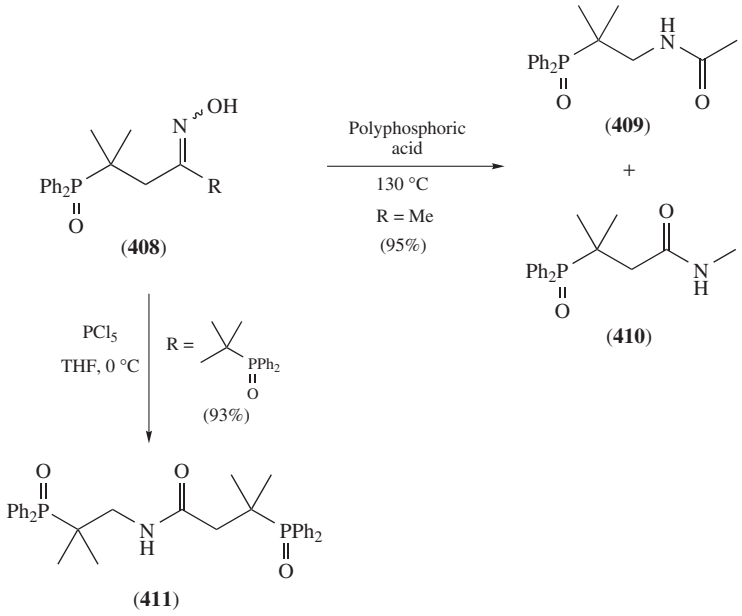
diastereoselection do not change when the corresponding methyloxime is reduced. These results suggest a coordination of the α-oriented phosphonic group with the metal catalyst, which favors the attack of the hydrogen from the α-face. Reduction of acetyloxime **401** with diborane in THF affords, on the contrary, 2-amino-2-deoxy-α-*C*-glucopyranoside **404** in 64% diastereomeric excess.

c. Nitrile oxide formation. The phosphorylated aldoxime **405**, prepared from condensation of β-phosphorylated aldehyde with hydroxylamine, is chlorinated with *N*-chlorosuccinimide (NCS) to provide a chloro oxime, precursor to the nitrile oxide **406** (Scheme 137)[188]. Addition of a chloroform solution of an excess of dipolarophile, before generation of the nitrile oxide by slow addition of triethylamine, affords the [3 + 2] cycloadducts **407** in 60–82% yield. The same approach has been used for the preparation of nucleoside phosphonates as isosteric alternatives for nucleoside phosphates as antiviral agents. In this case, nitrile oxide **406** can be prepared by the NCS oxidation of phosphorylated aldoxime **405** in the presence of pyridine (Scheme 137). This compound reacts smoothly with vinyl nucleoside bases (R = 6-chloropurinyl, adeninyl, thyminyl, uracilyl, cytosinyl) to produce analogues of nucleosides **407** in 34–84% yield[189].



SCHEME 137

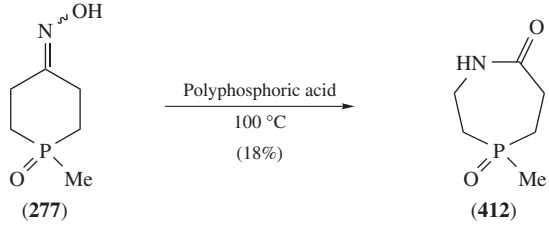
d. Beckmann rearrangement. The rearrangement of ketoximes to the corresponding amides, known as the Beckmann reaction, is a common method in organic chemistry[190] and is a topic of current interest. It accomplishes in one stroke both the cleavage of a carbon–carbon bond and the formation of a carbon–nitrogen bond. The reaction generally requires high reaction temperatures and strongly acidic and dehydrating media[190]. Thus, the reaction can lead to large amounts of byproducts and precludes its application to sensitive substrates. On these bases, oxime **408** (R = Me) rearranges in this manner with polyphosphoric acid at 130 °C to a mixture of amides **409** and **410** (Scheme 138)[115]. However, when symmetrical bisphosphine oxide oxime **408** ($R = CH_2CMe_2P(O)Ph_2$) were



SCHEME 138

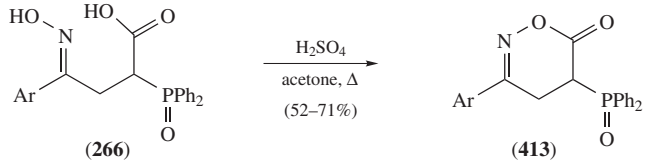
used in the Beckmann rearrangement using phosphorus pentachloride, only amide **411** was obtained (Scheme 138)[119].

However, in very low yield, methylphosphacaprolactam **412** can be prepared by means of an intramolecular Beckmann rearrangement starting from oxime **277** (Scheme 139)[122]. Polymerization of **412** affords a phosphorus-containing polyamide.



SCHEME 139

e. Cyclization reactions. Phosphono derivatives of 1,2-oxazin-6-ones **413** can be obtained by heterocyclization of oximes derived from β-aroyl-α-(diphenylphosphinyl)propionic acids **266**. Oximes **266** cyclize upon heating with a catalytic amount of sulfuric acid to give 6-membered heterocycles **413** (Scheme 140)[117].



SCHEME 140

III. PHOSPHORUS SUBSTITUTED HYDROXAMIC ACID DERIVATIVES

The chemistry of hydroxamic acids has already been reviewed[1]. In general, hydroxamic acid derivatives have attracted considerable interest because of their activity in inhibiting medically important enzymes such as metalloproteases[191] and lipoxygenases[192]. On the other hand, phosphorus compounds have also been shown to exhibit biological activity in various areas by virtue of their analogy to naturally occurring compounds. However, to date there are only a few reports in the literature on the combination of the phosphorated and hydroxamic functions in a molecule. We illustrate here several aspects of the synthesis and the reactivity of phosphorus *O*-substituted (**VII**) and *N*-substituted (**VIII**) hydroxamic acid derivatives. The phosphorus *C*-substituted derivatives (**IX**) are also included due to their structural similarity (Figure 6).

A. Synthesis and Reactivity

1. Phosphorus O-substituted hydroxamic acid derivatives

The most common approaches to synthesize phosphorus substituted hydroxamic acids comprise the phosphorus–oxygen single bond formation between the corresponding hydroxamic acid derivatives and phosphorated halides.

O-Phosphoryl hydroxamates can be prepared by P—O bond formation reaction between the corresponding hydroxamic acid derivatives and phosphorated halides. The synthesis of intermediate *O*-phosphodichloridate **415** is performed *in situ* from *N*-hydroxyurethane (**414**) and phosphorus oxychloride (Scheme 141)[193]. *O*-Phosphodichloridate **415** is an appropriate substrate for the synthesis of bis(aziridinyl)phosphinyl-*N*-hydroxyurethane derivatives **416**, useful as antineoplastic agents.

Phosphorus substituted compounds derived from hydroxylamine are prepared by dropwise addition of the diphenylphosphinyl chloride (**1**) to stoichiometric amounts of the hydroxamic acid **417** and triethylamine (Scheme 142)[194]. Some *O*-diphenylphosphinyl

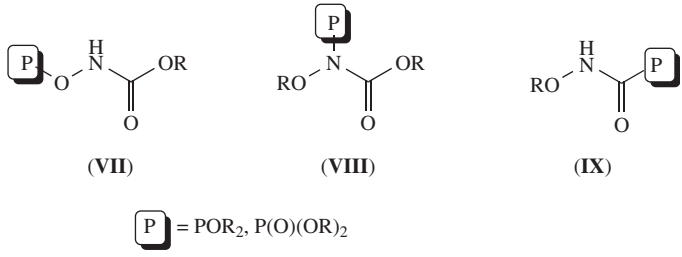
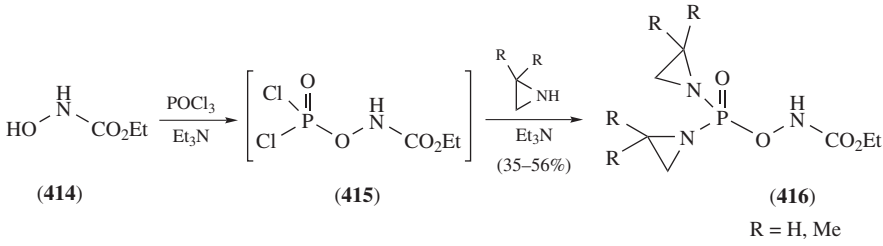


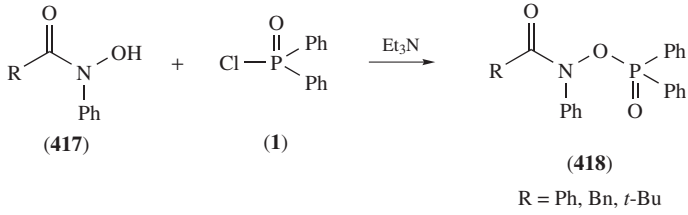
FIGURE 6



(**414**) (**415**) (**416**)

R = H, Me

SCHEME 141



(**417**) (**1**) (**418**)

R = Ph, Bn, *t*-Bu

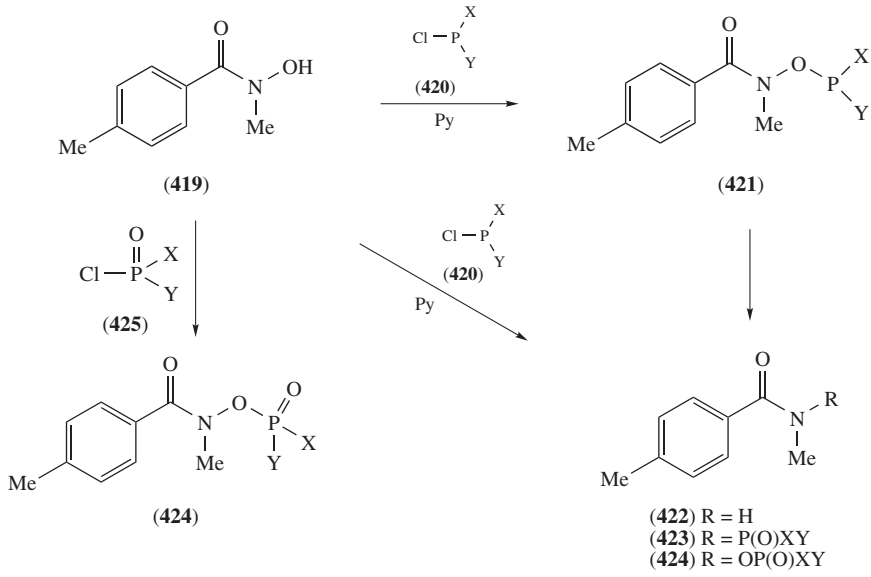
SCHEME 142

derivatives **418** (R = Ph, Bn) have been tested as potential inhibitors of neuropathy target esterase, although little activity of these compounds is observed against studied targets. *O*-(Diphenylphosphinyl)hydroxamate **418** (R = *t*-Bu), whose X-ray structure has been reported[195], has been used as electrophilic aminating agent[26, 39b, 196, 197] or in Schmidt reactions[35].

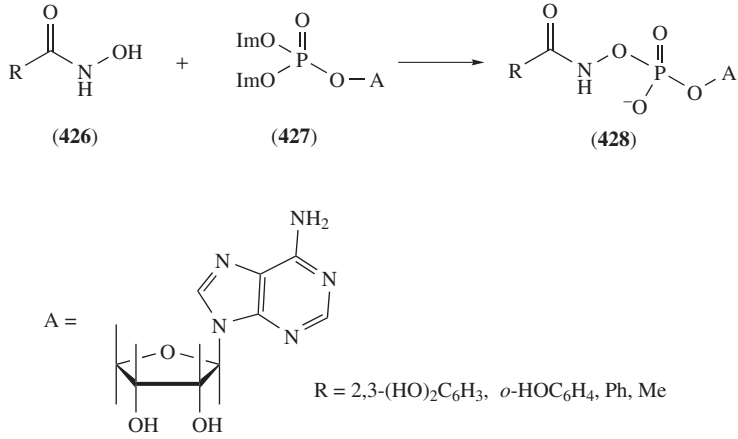
The reaction between *N*-methylbenzohydroxamic acid and various chlorides of tervalent phosphorous has been studied[198]. *N*-Methyl-*p*-(methylphenyl)hydroxamic acid (**419**) reacts rapidly with phosphorus compounds XYPCl **420** (X = Ph, Y = OEt and XY = OCH_2CH_2O) in the presence of pyridine to give P(III) intermediates **421** (Scheme 143). They decompose at room temperature with homolysis of the N−O bond to give isomeric *N*-phosphine oxides **423**, accompanied by varying amounts of *O*-hydroxamic acids **424**, *N*-methyl-4-methylbenzamide (**422**) and phosphoryl-radical related products. The origin of *O*-phosphinylhydroxamic acids **424** is not known, but presumably involves the combination of phosphinyl and acylnitroxyl radicals. Compounds **424** are also synthesized by treatment of hydroxamic acid **419** with the appropriate chlorophosphine oxide **425** in the presence of one equivalent of base (Scheme 143).

The synthesis of a new class of aryl adenylate analogs with potent inhibitory activity against enterobactin biosynthesis enzyme (EntE), an enzyme that catalyzes the synthesis of 2,3-dihydrobenzoyl adenylate (DHB-AMP) during the early stages of enterobactin biosynthesis, has been reported[199]. The authors design a stable mimic of DBH-AMP as a potential inhibitor, which contains an *N*-acyl hydroxamoylphosphate group in place of the labile carboxylic–phosphoric anhydride linkage. Compounds **428** are obtained by combining hydroxamic acids **426** with imidazole-activated adenosine 5′-phosphate (AMP-Im) **427** (Scheme 144).

O-Phosphorus substituted hydroxamates can also be prepared by P−O bond formation reaction between the corresponding hydroxamic acid derivatives and phosphorus derivatives as phosphonates or phosphinothioyloxy disulfanes. Direct thionation of hydroxamic

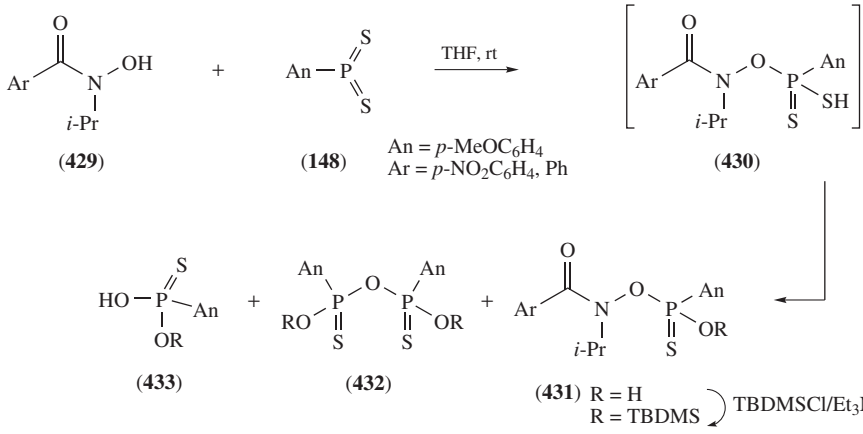


SCHEME 143



SCHEME 144

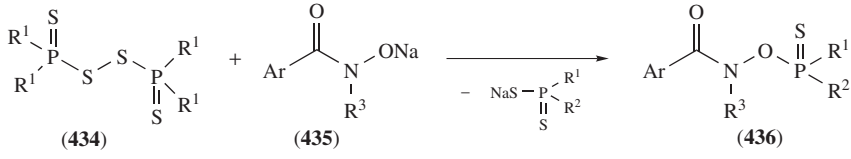
acids with Lawesson's reagent (LR) (**147/148**) can be very useful in the synthesis of thio analogues of natural hydroxamates and *N*-hydroxythiopeptides[200, 201]. Treatment of hydroxamic acids with LR gives a mixture of different phosphorus-containing products, such as *O*-thiophosphonylated **431** (R = H), pyrothiophosphonate **432** (R = H) and (4-methoxyphenyl)phosphothioic acid **433** (R = H, Scheme 145). The formation of these compounds **431**–**433** is explained by the electrophilic attack of metadithiophosphonate



SCHEME 145

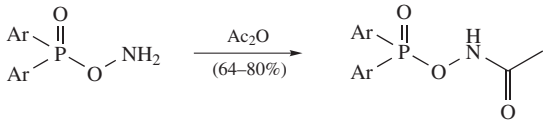
(AnPSS **148**, see Section II.A.1.b.ii) on the oxygen atom of the hydroxy group in the hydroxamic acid **429** to give the primary intermediate *O*-dithiophosphonylated hydroxamic thioacid **430** (detected by ^{31}P NMR). To confirm the formation of compound **431** the reaction mixture is treated with TBDMSCl in the presence of triethylamine, or with diazomethane or methyl iodide in the presence of triethylamine, and compound **431** is transformed *in situ* to a mixture of *O*- and *S*-methyl esters[200].

Reaction of various disulfanes **434** with *N*-alkylbenzohydroxamates **435** has been investigated (Scheme 146)[202]. Disulfanes **434** are treated with benzohydroxamate salts **435** to give *O*-phosphothioylated hydroxamic acids **436** (Scheme 146). The reaction has been also studied using optically pure disulfane. X-ray analysis shows that the product is formed with a complete inversion of configuration. Therefore, the reaction has an ionic character and proceeds via an S_N2P mechanism at the phosphorus atom.



SCHEME 146

N-Functionalization of phosphinylhydroxylamines can be achieved when *O*-(diarylphosphinyl)hydroxylamines **437** react with acetic anhydride to give the corresponding *N*-acetyl derivatives **438** (Scheme 147)[7f, 39b].

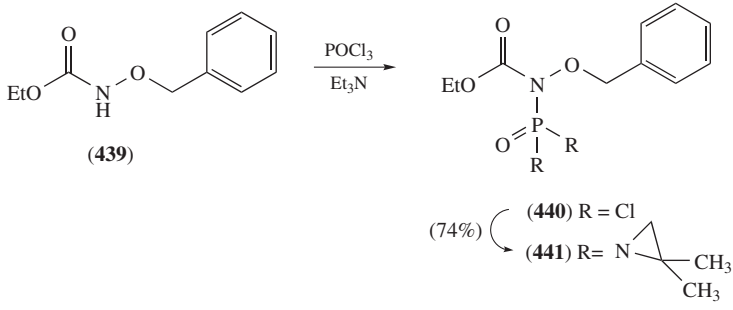


(**437**) (**438**)

SCHEME 147

2. Phosphorus N-substituted hydroxamic acid derivatives

Few examples of *N*-phosphoramidate hydroxamic acid derivatives have been reported, one of them being the synthesis of new 'dual antagonists' in which the 2,2-dimethylaziridine phosphinyl function is linked to the *N*-hydroxyurethane rather than to the urethane moiety[203]. *O*-Benzyl-*N*-hydrourethane **439** is used as the starting material and reacted with phosphinyl chloride to give the corresponding compound **440** by P—N bond formation. Subsequent reaction with 2,2-dimethylaziridine gives *O*-benzyl-*N*-phosphinyl derivative **441** (Scheme 148).

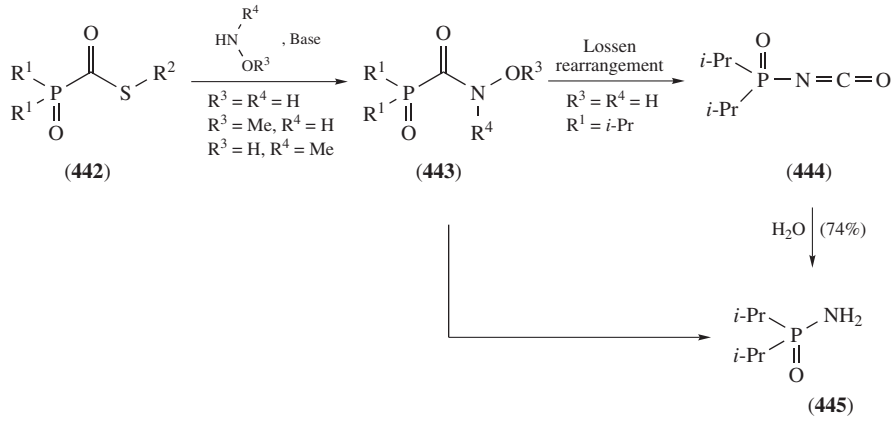


(**439**)

SCHEME 148

3. Phosphorus C-substituted hydroxamic acid derivatives

Phosphonates have also been shown to exhibit biological activity in various areas by virtue of their analogy to naturally occurring phosphates and carboxylic acids. *N*-Hydroxyphosphonoformamide **443** ($R^3 = R^4 = H$) can be prepared from bis(trimethylsilyl)[(methylthio)carbonyl]phosphonate (**442**) ($R^1 = OTMS$, $R^2 = Me$) (Scheme 149)[204, 205]. The hydroxamic acid derivative **443** ($R^1 = ONa$) is formed by adding a solution of *O*-(trimethylsilyl)hydroxylamine to a solution of phosphonate **442** in ethyl ether. The authors report this compound as an inhibitor of recombinant HIV-1 RT P-66 from the yeast, *Saccharomyces cerevisiae*[204], and as a powerful binding inhibitor of enolase[206a]. Analogously, several (phosphonoformyl)hydroxamates **443** (R = *i*-Pr) can be prepared. In these cases, thioester **442** is allowed to react with hydroxylamine and its *N*-methyl and *O*-methyl derivatives in the presence of pyridine and triethylamine[207]. The derivative obtained by reaction with hydroxylamine ($R^3 = R^4 = H$) suffers Lossen



SCHEME 149

rearrangement[208] which involves the cleavage of the carbon–phosphorus bond in order to make a new phosphorus–nitrogen single bond of derivative **444**, whose hydrolysis yields the corresponding compound **445** (Scheme 149).

IV. ACKNOWLEDGMENTS

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The Brønsted acid/base character of hydroxylamines, oximes and hydroxamic acids

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I. INTRODUCTION

A. Scope

The functional groups which are the subject of this volume all share the N−OH moiety, making them potentially capable of being Brønsted acids at the OH group, and being bases typically at the nitrogen site. As will be seen, there are exceptions to this pattern: hydroxamic acids are often but not always NH acids, if that structure is present, and are carbonyl oxygen bases. The acid/base character of these is pertinent to their ability to act as α-nucleophiles[1] and for the hydroxamic acids to function as metal chelators[2].

This chapter will examine experimental acidity and basicity values for these species in aqueous solution, acidity in DMSO solvent[3], and gas-phase acidities and basicities[4]. The latter will be supplemented by *ab initio* computational values, both from the literature and some conducted for the present article. It has been shown that at a reasonably high level of computation, such as the extrapolative Gn methods[5], gas-phase acidities and basicities can be reproduced to within 1–2 kcal mol^{-1} in an absolute sense, and far closer for relative values in a structurally related series.

The gas-phase values will be considered first for each functional group, being a measure of the intrinsic structural effect on proton transfer. The pK_as in DMSO and then aqueous solution will be commented on, to reflect how solvation alters the proton transfer ability. For space reasons, not all literature values will be included here, especially those in mixed solvents.

B. Thermochemical Values, Conventions and Terminology

In the gas phase[6], the enthalpy of basicity corresponding to the half-reaction 1 is usually termed the *proton affinity* (PA) of the base B, or $\Delta_{base}H(B)$. The equivalent free-energy quantity is its *gas-phase basicity* (GPB), or $\Delta_{base}G(B)$. These are usually reported in kcal mol^{-1} (as will be done here) or kJ mol^{-1}, and are typically in the range of 40–250 kcal mol^{-1} endothermic/endoergonic, as written. In this chapter, all reported free energies and enthalpies will be at a temperature of 298 K.

$$BH^+ \longrightarrow B + H^+ \tag{1}$$

The entropy of basicity for reaction 1, $\Delta_{base}S(B)$, is typically 26 ± 4 cal mol^{-1} K^{-1} for a wide range of bases. It is due mostly to the entropy of the free proton (26.03 eu) at 298 K, plus smaller terms for the change in symmetry of the base versus its conjugate acid, and for changes in rotational and vibrational frequencies on proton loss. Thus in general at 298 K the GPB is *ca* 8 ± 1 kcal mol^{-1} numerically less positive than the PA. This constancy of the entropy term also means that *relative* GPBs are comparable to *relative* PAs.

The *gas-phase acidity* of the neutral acid AH refers to the free energy for reaction 2, $\Delta_{acid}G(AH)$. Unlike for basicities, there is no commonly used separate term for the corresponding enthalpy quantity, $\Delta_{acid}H(AH)$, although *anion proton affinity*, APA, has sometimes been used. *Deprotonation enthalpy*, DPE, is also in use[7].

$$AH \longrightarrow A^- + H^+ \tag{2}$$

The reader must therefore be cautious as to which quantity is being referred to, if only a numeric quantity is given as an 'acidity'. Similarly to basicities, the entropy term $\Delta_{acid}S(AH)$ for reaction 2 is near-constant at 26 eu for most simple acids, making $\Delta_{acid}G(AH)$ *ca* 8 kcal mol^{-1} less positive than $\Delta_{acid}H(AH)$ at 298 K. The absolute values

of these acidities are larger than for basicities, typically in the 300–400 kcal mol^{-1} range. This increase is due to the Coulomb's Law energy price for separating oppositely charged species in reaction 2, in contrast to reaction 1 where the charges are balanced on each side of the reaction. Nevertheless, there is still just one acid/base scale in the gas phase, with basicities (that is, acidities of cationic species) in the 40–250 kcal mol^{-1} range, and acidities of neutral species even weaker, in the 300–420 kcal mol^{-1} range.

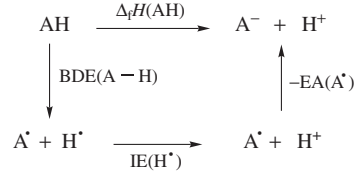
The careful reader will note the lack of the standard state symbol $^{\circ}$ after the thermochemical quantities stated above, such as $\Delta_{acid}H(AH)$. This is deliberate. Gas-phase ions are referenced to a different standard state than neutrals[6], and thus the symbol is omitted.

In discussing relative acidities and basicities, the terms 'weaker' and 'stronger' will be used here, in place of larger/smaller or higher/lower. The latter terms are ambiguous, in regard to place in a vertical graphic scale, versus numerical quantity, versus the favored side of an equilibrium.

Following the conventions in each area, gas-phase acid/base data will be expressed in units of kcal mol^{-1}, and solution-phase data in pK units. These are related as kcal mol^{-1} = RT• ln(10)•pK = 1.3640 pK at 298 K, and kJ mol^{-1} = 5.707 pK at 298 K.

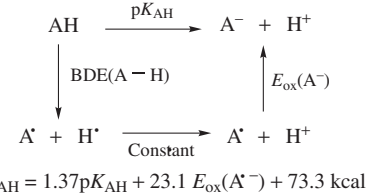
Although the focus of this chapter is Brønsted acid/base chemistry, there are certain other thermochemical quantities that can be derived from such values, which are important in the chemistry of NOH species. Schemes 1 and 2 present a thermochemical cycle that has been used in both gas-phase[8] and solution[9] chemistry, to derive homolytic bond dissociation energies (BDEs) from the acidity, plus the electron affinity (gas phase) or anion oxidation potential (solution).

For Scheme 1, electron affinities are readily available from photoelectron spectroscopy of gas-phase anions[10]. For Scheme 2, oxidation potentials of anions can be obtained via cyclic voltammetry. Bordwell and Bausch[9], following the lead of Nicholas and Arnold[11], found that irreversible oxidation potentials appeared to be adequate in obtaining BDEs consistent with literature values. Scheme 2 is actually a free-energy thermochemical cycle, but the entropy of homolytic bond cleavage appears fairly constant, so its $T\Delta S$ term,



$$\Delta_f H(AH) = BDE(A—H) - EA(A^{\bullet}) + IE(H^{\bullet})$$

SCHEME 1. The gas-phase 'D-EA' thermochemical cycle



$$BDE_{AH} = 1.37pK_{AH} + 23.1\ E_{ox}(A^{\bullet -}) + 73.3 \text{ kcal mol}^{-1}$$

SCHEME 2. The solution 'D-EA' thermochemical cycle

along with the oxidation potential of the hydrogen atom plus the conversions of $E_{ox}(A^-)$ to an absolute potential, are subsumed into the empirical constant of 73.3 kcal mol^{-1} in Scheme 2. This constant has changed in the series of papers regarding the Bordwell group's BDEs[12], due to referencing different standard electrodes (Ag/AgI versus ferrocene/ferrocenium). Thus, BDEs of many A−H bonds are obtainable for sites where the acidity can be measured. There have been problems with BDEs obtained from this method, notably for some OH acids, being appreciably stronger than those from more direct methods[13]. This likely arises from differential solvation of the acid versus anion in DMSO, and use of irreversible oxidation potentials rather than reversible ones. Caution is thus required in using these as 'thermodynamic' values.

C. Computational Basicity and Acidity Values

To supplement the sometimes sparse gas-phase acid/base data, quantum chemical calculations of these reaction quantities have been carried out by the author for the present article. These were obtained using the Gaussian 98[14] program, with the G3(MP2)B3 method[5, 15]. This method involves optimization of the geometry of species at the B3LYP/6-31G(d) DFT level, plus frequencies there likewise, then single-point energies by several higher non-DFT methods. These are used to extrapolate a total energy, followed by a small empirical atom-additivity addition. This method is claimed to yield single species' energies, such as heats of formation, good to 1–2 kcal mol^{-1}, or 'chemical accuracy'[5]. More pertinent to the present work, this method yields proton affinities and acidities to within 1–2 kcal mol^{-1} or better for the classes of compounds under consideration here, as will be shown below.

Because such computations refer to a standard state for ions completely different from those in experimental use, an integrated heat capacity of the proton of 1.481 kcal mol^{-1} at 298 K is used to derive the acid/base quantities here.

Throughout this article, any numeric acidity or basicity that is a computational value will be expressed in italic numerals.

D. Free Energies versus Enthalpies

The aqueous and DMSO solution pK_as are free-energy quantities, and thus are more temperature-sensitive than the corresponding enthalpies. As an example of where this becomes important, the pK_as of the aliphatic carboxylic acids, acetic through pivalic, are in the well-known increasing numeric order $MeCO_2H < EtCO_2H < i\text{-}PrCO_2H < t\text{-}BuCO_2H$ at room temperature, over a 0.27 pK unit/0.37 kcal mol^{-1} range[16]. This has long been taken as a premier example of the polar effect of varying the alkyl group: large alkyl groups are supposed to be more electron-donating[17]. At 0 °C, however, there is an inversion of pK_as: $i\text{-}PrCO_2H < EtCO_2H$[17]. Even more unsettling, the enthalpies of ionization are not just exothermic, but in almost the opposite order ($i\text{-}PrCO_2H < t\text{-}BuCO_2H < EtCO_2H < MeCO_2H$) over a −0.65 kcal mol^{-1} range[18]. For the N−OH structures that are the subject here, there appear to be very few enthalpies of ionization corresponding to pK_as and thus we must do our best in analyzing acid/base character with the more limited free-energy quantity, pK_a. There are a number of enthalpies of ionization known in DMSO[19], but none pertinent to the structures discussed here.

Because the entropy of acidity/basicity in the gas phase is mostly due to the entropy of the free proton, it varies little between different acids and bases. Thus, relative enthalpies of acidity/basicity are very close to relative free energies of acidity/basicity, even if the absolute value of the free-energy quantity is typically *ca* 7 kcal mol^{-1} less positive at 298 K

than the enthalpy. As the more fundamental quantity, as well as a better experimental/computational comparison, enthalpies of acidity/basicity will thus be used here to discuss structure–reactivity effects.

E. Sources of Data and Uncertainties

Gas-phase acidity and basicity values are drawn from the NIST WebBook[4]. The WebBook (http://webbook.nist.gov/chemistry) is an online database with the goals of collecting all numeric thermochemistry in one location, and having the values therein evaluated by experts in the respective areas. It is noted that the present author is the principal collector and evaluator of the acidity values for the WebBook. Values from the WebBook, rather than the primary literature, are cited because there have been adjustments in the anchoring of the relative acidity and basicity scales over time, and absolute values have thus changed. Cases in point are the 1998 adjustment of the basicity scale[20], and the 1988 adjustment of the acidity scale[21]. Gas-phase basicities and acidities are usually stated to have an uncertainty in the absolute sense of 2.0 kcal mol^{-1} or so, due to the problems in anchoring the relative values obtained from equilibrium methods[22]. The relative values are more accurate, being 0.1–0.2 kcal mol^{-1} uncertainty[22]. There are a few cases much more accurate, being obtained directly from Scheme 1, but those are not involved in the present work.

pK_a values in DMSO solvent are from the Bordwell group's efforts[3]. This is a spectrophotometric method, using colored Hammett-type indicator acids to construct a relative equilibrium pK scale[23]. It is anchored to direct electrochemical values in the single-digit pK region, but not at the very weakly acidic end, so the absolute values are less certain at the more weakly acidic end. The present chapter deals with acids over this whole range. Relative uncertainties are usually stated as 0.1 pK units, though for given close pairs of acids it may be less. For the BDEs, due to the assumption involving a constancy in entropy, plus the use of irreversible $E_{ox}(A^-)$ values, an uncertainty of at least 2 kcal mol^{-1} is likely[9,12].

Aqueous pK_as are taken from several standard compilations[18,24–29] with that of Palm[28] being the most extensive for the functional groups under consideration here. Because it appears that there are a few values in that last compilation with either incorrect references or wrongly transcribed values, only those pK_as that could be checked against their primary literature references are included here.

II. HYDROXYLAMINES

The hydroxylamines are structurally the simplest of the three functional groups under consideration here, and are thus discussed first. They are expected to be nitrogen bases and oxygen acids, with no π-resonance delocalization effects operating on either reactivity. The principal structural effect should be an inductive one of the adjacent electronegative atom affecting the reactivity of the amine base or oxyacid site.

A. Gas-phase Basicities/Proton Affinities of Hydroxylamines

Unfortunately, there are few experimental data in this class, including that of diethylhydroxylamine **1**[30], plus hydroxylamine **6** and *N*-methylhydroxylamine **4**[31]. These are presented in Table 1, along with computational values for them and for other small hydroxylamines, plus structurally similar amines. The latter are presented in part to establish the accuracy of the computational values for nitrogen bases, relative to experimental

TABLE 1. Gas-phase basicities of hydroxylamines, experimental[a] and *computed*[b], in kcal mol^{-1}

Base		$\Delta_{base}H$(exp)	$\Delta_{base}G$(exp)	$\Delta_{base}H$(calc)	$\Delta_{base}G$(calc)	$\delta\Delta_{base}H$[c]
Et_3N		234.7	227.3	*234.7*	*226.9*	*0.0*
Et_2NMe		232.3	224.9	*232.5*	*224.8*	*0.2*
Me_2NEt		229.7	222.3	*229.7*	*222.4*	*0.0*
Et_2NH		227.6	219.7	*227.6*	*220.2*	*0.0*
Me_3N		226.8	219.4	*227.2*	*219.7*	*0.4*
Me_2NH		222.2	214.3	*222.6*	*215.1*	*0.4*
Et_2NOH	**1**	219.0[d]	210.d[d]	*219.2*	*211.7*	*0.2*
$EtNH_2$		218.0	209.8	*218.5*	*211.0*	*0.5*
Me_2NOMe	**2**			*217.6*	*209.9*	
$MeNH_2$		214.9	206.6	*215.3*	*207.8*	*0.4*
Me_2NOH	**3**			*213.3*	*205.7*	
$PhNH_2$		210.9	203.3	*210.6*[e]	*204.1*	*−0.3*
MeNHOH	**4**	204.8[e]	197.2	*205.8*	*198.2*	*1.0*
PhNHOH	**5**			*205.8*[e]	*198.7*	
NH_3		204.1	195.8	*204.2*	*196.2*	*0.1*
$MeONH_2$		201.9	194.1	*202.2*	*194.4*	*0.3*
H_2NOH	**6**	193.7[f]	186.2	*195.0*	*187.5*	*1.3*
$H_2NOH_2^+$				*169.2*	*161.9*	

[a]Reference 4.
[b]Reference 5.
[c]$\Delta_{base}H$(exp) − $\Delta_{base}H$(calc).
[d]Reference 30.
[e]Reference 32.
[f]Reference 31.

ones. It is obvious that excellent accuracy is obtained from the computations: a worse case error for the PA of only 0.5 kcal mol^{-1} is seen for the alkylamines. This indicates that for these bases, computational and experimental values can be analyzed interchangeably.

Diethylhydroxylamine **1** is 13.3 kcal mol^{-1} weaker as a base than the isoelectronic diethylmethylamine, consistent with the electronegative hydroxyl group destabilizing the cation by a polar electron-withdrawing effect, relative to the methyl group. It is 8.6 kcal mol^{-1} weaker than Et_2NH, again consistent with the expected polar effect. Hydroxylamine itself, **6**, is a nitrogen base by almost *26* kcal mol^{-1} over the weaker OH site. Successive methylation on the nitrogen site of the parent hydroxylamine to yield **4** and **3** increases the PA by 10.8 and 7.5 kcal mol^{-1}, comparable to methylation of ammonia strengthening its PA by 10.8 and 7.3 kcal mol^{-1}. Methylation of dimethylhydroxylamine on oxygen to give **2** strengthens the PA by only 4.3 kcal mol^{-1}, consistent with its more distant placement from the charge site. Alkylhydroxylamines thus can be considered typical amine bases in the gas phase.

An exception to this is the aromatic hydroxylamine **5**. As with the amine analog aniline, there appears to be a close competition between N and *o*-, *p*-ring protonation, both experimentally and computationally[32]. G3(MP2)B3 calculations predict that N protonation in aniline is favored over *para* protonation only by 1.2 kcal mol^{-1}, and by only 0.3 kcal mol^{-1} in **5**. This is too close to make any call as to what the reality is.

B. Gas-phase Acidities of Hydroxylamines

Like the basicities, there is unfortunately only one experimental datum in this class, that of diethylhydroxylamine **1**[30], as shown in Table 2. The measured value is 1.1 kcal mol^{-1}

TABLE 2. Gas-phase acidities of hydroxylamines, experimental[a] and *computed*[b], in kcal mol^{-1}

Acid		$\Delta_{acid}H$	$\Delta_{acid}G$	$\Delta_{acid}S$	BDE	$\delta\Delta_{acid}H$[c]
H_2NOH	**6**	*387.0*	*379.7*	*24.5*	*78.3*	*−3.3*
CH_3OH		382.6	376.0	22.0	105.2[d]	
		383.7	*377.1*	*21.9*	*104.8*	
MeNHOH	**4**	*382.0*	*374.9*	*24.1*	*75.7*	*−2.1*
EtOH		379.1	372.5	22.0	105.0[d]	
		379.9	*372.7*	*24.1*	*104.8*	
Me_2NOH	**3**	*375.1*	*368.5*	*22.0*		
		376.8	*369.8*	*23.6*	*74.6*	*+0.6*
Et_2CHOH		372.8	366.2			
Et_2NOH	**1**	371.7[a]	364.0[a]			−1.1
		373.5	*366.5*	*23.9*	*75.5*	*+0.3*
(*t*-Bu)$_2$NOH	**7**	*372.0*	*364.9*	*23.9*		
$(CF_3)_2$NOH	**8**	*346.3*	*338.9*	*24.8*	*85.8*	*−1.1*
PhNHOH	**5**	*357.3*	*349.4*	*26.3*	*77.0*	
PhNHOH		*361.1*	*353.6*	*25.1*	*74.0*	*+7.8*

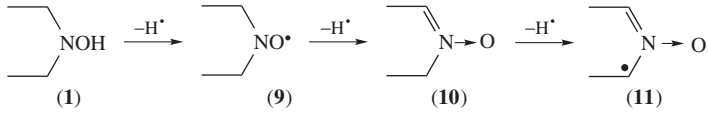
[a]Reference 21. Value revised from literature value based on re-evaluation of acidity ladder, Reference 5.
[b]Values in italics are computed by the present author with the G3(MP2)B3 method, Reference 5.
[c]$\Delta_{acid}H(R_2NOH) - \Delta_{acid}H(R_2CHOH)$.
[d]Reference 35.

more strongly acidic in terms of $\Delta_{acid}H$ than the isoelectronic alcohol 3-pentanol. This is consistent with the electron-withdrawing effect of a dialkylamino group, where $\sigma_I = +0.06$[33], relative to comparable alkyl groups with $\sigma_I = -0.06$. The use of the isoelectronic alcohol for comparison is to cancel the effect of polarizability on acidities; in the gas phase, this can be as important as polar and resonance effects[34].

Unlike the basicities in the last section, it is obvious that the computational values for gas-phase acidities do not line up as well with experimental values for OH acids, being consistently about 1–2 kcal mol^{-1} too weak. The relative values appear to be reasonable, however, and can be used in structural analysis. As with the alcohols, more and larger alkyl groups strengthen the acidity of hydroxylamines, and roughly as much as for the alcohols. Likewise, polar effects operate to strengthen acidity comparably in hydroxylamines and alcohols, as shown by $(CF_3)_2NOH$ **8** versus $(CF_3)_2CHOH$. Thus the alcohols' acidities can be used as reasonable guides to those of the hydroxylamines.

N-Phenylhydroxylamine **5** is a hydroxylamine with two reasonable sites for the preferred acidity. In the parent hydroxylamine H_2NOH, the N–H is weaker in acidity by 9.8 kcal mol^{-1} computationally, roughly the same as for water versus ammonia[4]. In PhNHOH, however, the intrinsically weaker NH site has the possibility of resonance stabilization and, as seen in Table 2, becomes a stronger acid than the OH site by 3.8 kcal mol^{-1}. It will be seen below that this persists in solution.

The loss of, not a proton, but a hydrogen atom from the OH site of hydroxylamines leads to the well-known stable nitroxide radicals **9**[36]. Such species are known to further react to give nitrones **10** by loss of an adjacent CH hydrogen if one is present, as per Scheme 3. G3(MP2)B3 computational values for the successive BDEs here are *75* kcal mol^{-1} for nitroxide **9** formation, *55* kcal mol^{-1} for nitrone **10** formation and *98* kcal mol^{-1} for loss of the third hydrogen to yield **11**. With the second hydrogen loss being from a BDE far weaker than even the first, it is thus thermochemically reasonable for nitroxide radicals with alpha hydrogens to be unstable with respect to disproportionation to a hydroxylamine and nitrone. The use of Scheme 1 with the known $\Delta_{acid}H(Et_2NOH)$ value plus the EA



(**1**) (**9**) (**10**) (**11**)

SCHEME 3. Successive H loss from hydroxylamines

of the radical should lead to a good BDE value; unfortunately, the EA measurement does not seem to have been done.

C. Hydroxylamine Acidities in DMSO Solvent

Bordwell and Liu have measured a number of hydroxylamine acidities in DMSO solvent as given in Table 3[12, 37]. The O−H BDEs obtained from Scheme 2 are shown there as well.

The data in Table 3 show an acid-weakening effect on enlarging the alkyl groups on a hydroxylamine, by 1.2 pK units on going from *N*-hydroxypiperidine **13** to its tetramethyl derivative **12**, and 1.5 pK units on going from Et_2NOH **1** to $(t\text{-Bu})_2NOH$ **7**. This is the opposite from the order in the gas phase, but in accord with a great many similar cases in solution[38]. Larger alkyl groups strengthen gas-phase acidities due to polarizability effects[34], but weaken solution-phase acidities due to a complex mixture of solvation effects[39].

In DMSO, replacing either the NH or the OH moiety in PhNHOH **5** with an *N*-alkyl or *O*-alkyl group makes little difference in the pK[12]. Both are slightly acid-strengthening. Bordwell and Liu[12] thus estimated that the NH site in PhNHOH is only 0.4 pK units (0.5 kcal mol^{-1}) stronger in acidity than the OH site, a 70%/30% equilibrium favoring $PhN(OH)^-$ over $PhNHO^-$. This is smaller than the 3.8 kcal mol^{-1} difference computed for the gas phase, but still favoring the NH site.

The substituted ArNHOH acids **5**, **14**, **15** give a 3-point Hammett plot with ρ of 5.6[12], equal to that of aniline pKs in DMSO[40]. This is also taken as evidence for the

TABLE 3. pKs and BDEs of hydroxylamines in DMSO solvent[a]

Hydroxylamine		pK	BDE
N-Hydroxy-8-azabicyclo[3.2.1]octane		32.4[b]	77.0[c]
$(t\text{-Bu})_2NOH$	**7**	31.1[b]	68.2
TEMPOH[d]	**12**	31.0[b]	69.7
Et_2NOH	**1**	29.6[b]	75.9
N-Hydroxypiperidine	**13**	29.80	77.0
PhNHOH[c]	**5**	24.20	77.5
$PhNHOCH_2Ph$		23.48	75.8
$p\text{-}BrC_6H_4NHOH$	**14**	22.90	78.2
$p\text{-}NCC_6H_4NHOH$	**15**	18.58	78.0
$PhN(CH_2Ph)OH$	**16**	23.87	74.8
$p\text{-}BrC_6H_4N(CH_2Ph)OH$	**17**	22.70	75.4
$p\text{-}NCC_6H_4N(CH_2Ph)OH$	**18**	19.40	77.4

[a] Reference 12, unless otherwise stated.
[b] Reference 37.
[c] 79.0, using the reversible $E_{ox}(A^-)$.
[d] *N*-Hydroxy-2,2,6,6-tetramethylpiperidine.

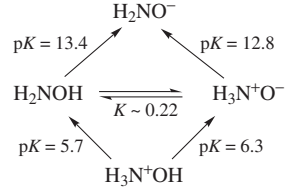
arylhydroxylamines being NH acids in DMSO. The $ArN(CH_2Ph)OH$ acids **16**–**18**, where the OH acidity is enforced, yield a ρ of 4.5, somewhat smaller, as expected for the more distant charge[12].

The BDEs obtained by Scheme 2 agree reasonably well with literature and computational values[13, 41] save for the value for Et_2NOH of 69.5 kcal mol^{-1} [42]. This agreement includes the trend of sterically bulky alkyl groups on nitrogen appreciably weakening the OH bond[13]. Caution must be used when dealing with OH BDEs from Scheme 2: it has been shown that this method can yield values too strong for such acids, due to hydrogen bonding by the acid to DMSO, plus possibly problems with the irreversible oxidation potentials used[13]. For hydroxylamines, the agreement appears good, however. The disagreement with the 1978 BDE value[39] for Et_2NOH may be due to the disproportionation shown in reaction 3, interfering with proper measurement of the activation energy in that case[42].

$$2\ Et_2NO^{\bullet} \longrightarrow Et_2NOH + MeCH{=}N(Et) \rightarrow O \qquad (3)$$

D. Hydroxylamine Acidities and Basicities in Aqueous Solution

Hydroxylamine in aqueous solution exists as a mixture of the neutral canonical form plus about 20% of the zwitterionic ammonia oxide structure, as shown in Scheme 4[43]. This corresponds to a log K of 0.65 units between the two isomers, in contrast to the difference of 26 kcal mol^{-1} in the gas phase, given by G3(MP2)B3 calculations. This solution-phase result is not from direct observation, but via a mixture of linear free-energy relationships and kinetic studies[40]. An amine should not normally be basic enough in aqueous solution to deprotonate an alcohol to form a zwitterion, but the ammonium group strengthens the acidity of the OH, while the O^- group strengthens the basicity of the NH_2, and the two effects are just sufficient to yield the close equilibrium shown. This is expected to occur only for the parent hydroxylamine in water: zwitterion stabilization by hydrogen bonding of all three ammonium hydrogens to water is needed, and for dialkylhydroxylamines, there is only one such site in the zwitterionic form.



SCHEME 4. The equilibria of H_2NOH in water

As evident in Table 4, the presence of a hydroxyl group on an amine nitrogen (row 1), replacing the isoelectronic methyl group (row 3), weakens the basicity by 4.6 to 4.9 pK units in *N*,*N*-dialkylhydroxylamines. This is consistent with an electron-withdrawing inductive effect of OH relative to Me, destabilizing the cationic conjugate acid and thus weakening the basicity. However, phenyl substitution on N (PhNHOH versus PhNHMe) only weakens the basicity by 1.6 pK units, a saturation effect[44]. In *O*-methylated hydroxylamines, the OMe group weakens the basicity another 1.2–1.4 pK units over OH, which agrees with the greater inductive withdrawing effect of OMe[33].

TABLE 4. Aqueous basicities[a] of hydroxylamines and related amines, as pK_{BH+} of R_2NR'

R′ :	**R:**	H,H		Me,H		Ph,H		Me,Me		Et,Et	
OH		5.7[b]	**6**	5.96	**4**	3.2	**5**	5.20	**3**	5.57	**1**
OMe		4.60		4.75				3.65			
Me		10.66		10.73		4.85		9.80		10.46	
H		9.25		10.66		4.60		10.73		10.91	

[a]Reference 26.
[b]Reference 43.

TABLE 5. Aqueous basicities as heats of ionization of hydroxylamines and amines[a]

Base	ΔH_i	pK_{BH+}	ΔS_i
NH_3	12.45	9.24	−0.5
H_2NOH	9.3[b]	5.7[c]	−3.8[b]
H_2NNH_2	9.97	7.96	−3.0
$MeNH_2$	13.29	10.84	−4.1
Me_2NH	12.04	10.73	−8.7

[a] ΔH_i in kcal mol^{-1}; ΔS_i in cal mol^{-1} K^{-1}. From Reference 18, unless otherwise stated.
[b]Reference 45.
[c]Reference 43.

For hydroxylamine itself, there is some limited enthalpy and entropy of ionization data available, shown in Table 5. Hydroxylamine appears to be a typical amine base, with the pK_a primarily controlled by the enthalpy.

In terms of solvation effects, although methylation on N is base-strengthening consistently in the gas phase, it is neutral or base-weakening in aqueous solution. As with the ammonia-to-trimethylamine series, this is likely due to a complex mixture of solvation effects on the base versus the cationic conjugate acids[46]. Increasing the size of the alkyl groups, as in **3** to **1** in Table 4, strengthens the basicity in both phases, but the effect in water is roughly 1/8 the size of that in the gas phase.

The parent hydroxylamine **6** has a pK_a in aqueous solution slightly more acidic than water itself, as seen in Table 6. Alkylated hydroxylamines would be expected to be even weaker acids, in parallel with the alcohols' behavior, and thus it is not surprising that pK_a values for these cannot be found in the literature. There are a few fluorinated alkylhydroxylamine **19**–**21** pK_as known[47], roughly equal in pK_a to the analogous alcohols CF_3CH_2OH, $pK_a = 12.37$[48]; $(CF_3)_2CHOH$, $pK_a = 9.42$[49]; $(CF_3)_3COH$, $pK_a = 5.30$[50].

The sulfonated hydroxylamines **22** and **23** in Table 6 show the electron-donating effect of the negatively charged substituent played against the electron-accepting effect of the sulfonyl group[33] resulting in a slight acid-strengthening effect for each successive group. It was unclear to the authors[53] whether these represent oxygen acids or nitrogen acids, because they cited the pK_a of $(^-O_3S)_2NH$ as 8.5.

The alkylated hydroxylamine Me_3N^+OH **24** is appreciably more acidic than any of these, at $pK_a = 4.60$. Examination of the pK_as of substituted XOH acids in Table 7 reveals a good correlation ($r = 0.991$) of the neutral acids pK_as with the inductive substituent constant σ_I, including the NH_2 group of hydroxylamine. Me_3N^+OH requires a σ_I of 0.68 to fit the correlation, somewhat smaller than the known one of 0.92 for NMe_3^+.

TABLE 6. Aqueous pK_as of hydroxylamines[a]

Acids		pK_a
H_2NOH[b]	**6**	13.4
CF_3CH_2NHOH	**19**	11.3
$(CF_3)_2CHNHOH$	**20**	8.5
$(CF_3)_3CNHOH$	**21**	5.9
$^-O_3SNHOH$[c]	**22**	12.5
$(^-O_3S)_2NOH$[c]	**23**	11.85
H_3N^+OH		6.3[d]
Me_3N^+OH	**24**	4.60[e]

[a]Reference 47, unless otherwise stated.
[b]Reference 51.
[c]Reference 53, $I = 1.6$. It is not clear whether these are NH or OH acids.
[d]Reference 43.
[e]Reference 52.

TABLE 7. pK_as of XOH acids versus σ_I(X)

XOH		pK_a[a]	σ_I[b]
H_2O		15.74	0.00
MeOH		15.6	−0.04
H_2NOH	**6**	13.4	0.12
CF_3CH_2OH		12.4	0.18[c]
HOOH		11.7	0.25
ClOH		7.42	0.46
H_3N^+OH		6.3[d]	0.60
Me_3N^+OH	**24**	4.6[e]	0.92

[a]Reference 27.
[b]Reference 33.
[c]Reference 54.
[d]Reference 43.
[e]Reference 52.

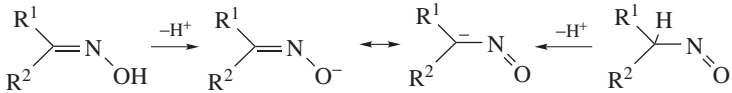
There is insufficient overlap between known gas-phase acidities and aqueous pK_as for any reasonable comparison at present.

III. OXIMES

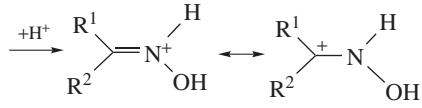
Oximes can be viewed as hydroxylamines with an sp^2 nitrogen and associated double bond. This allows resonance delocalization of the negative charge from the oxyanion to carbon in the conjugate base, and thus further stabilization, as per reaction 4. The sp^2 nitrogen should also be the basic site, albeit weaker than regular amines due to the greater electronegativity of the sp^2 nitrogen, plus the electron-accepting inductive effect of the hydroxyl group. This should be somewhat mitigated by the resonance stabilization of the positive charge on the carbon, as shown in reaction 5.

Oximes also have the possibility of *E*/*Z* isomerism, notably aldoximes and unsymmetric ketoximes. The older literature refers to α (higher melting) and β (lower melting) forms, with some debate over which structure corresponds to which[55], and no guarantee that

there is consistency from compound to compound. *Syn* and *anti* are used more recently for aldoximes, with those terms referring to the positions of the OH and the H on the C=N structure of aldoximes. The unambiguous (*E*) (∼ *syn*) and (*Z*) (∼ *anti*) will be used here, when the stereochemistry is clearly stated in the literature. A lack of such designation means that it is not clear which isomer was used originally. In general aromatic aldoximes exist in both forms, and thus may have acidities known for both. Aliphatic aldoximes tend to be either only *syn* or inseparable mixtures. Ketoximes exist in both forms, but which is which is not often known.



(4)



(5)

The less sterically hindered (*E*) isomer appears to be the more stable (the higher melting, or α form) in the solid state[55], and thus is likely the one that most solution- and gas-phase pK_as represent, unless there have been explicit efforts to measure both isomers. G3(MP2)B3 computations indicate that in the gas phase the (*E*) and (*Z*) forms of neutral acetaldoxime **26** are within 0.1 kcal mol^{-1} of each other, but that the (*Z*) form of pivaldoxime **28** is 2.3 kcal mol^{-1} higher in energy than the (*E*) form. Similarly the (*E*)-benzaldoxime **30** is 1.9 kcal mol^{-1} more stable than the (*Z*) form. This does not mean that experimental gas-phase acidities or basicities are of the more stable form, because these are unlikely to interconvert under mild conditions, and what is obtained in the gas phase by evaporation will be the form as it exists in the solid state. The thermochemistry of neutral oximes is currently not well understood[56].

There is a second isomerization pertinent to these data, the oxime/nitroso tautomerization shown in reaction 4. Unlike ketones and aldehydes where the keto form is favored over the enol, oximes appear to be consistently the more stable form here. G3(MP2)B3 calculations indicate that acetoxime is favored by 17.8 kcal mol^{-1} over *i*-PrNO in the gas phase. This also means that were *i*-PrNO to be investigated, it should be 17.8 kcal mol^{-1} stronger as an acid than acetoxime.

A. Gas-phase Basicities/Proton Affinities of Oximes

There are no experimental gas-phase basicities of oximes. The closest analog experimentally known is *N*-ethylacetoneimine, $Me_2C{=}NEt$, with a PA of 229.5 kcal mol^{-1} [20]. G3(MP2)B3 calculations yield a PA of 232.8 kcal mol^{-1} for this imine; this method frequently yields PAs too strong by 1–3 kcal mol^{-1} for resonance-delocalized cations. With that in mind, the G3(MP2)B3-level calculated PA of 209.5 kcal mol^{-1} for acetoxime **27** implies that 207 kcal mol^{-1} or so is an expected value here. That value is consistent with acetoxime being weaker than the *N*-ethyl imine, on both inductive and polarizability grounds, here by *ca* 22 kcal mol^{-1}. It is also between ammonia at 204.0 kcal mol^{-1} and $MeNH_2$ at 214.5 kcal mol^{-1} [20], weaker than expected for an amine of that size, due to the electronegativity of the sp^2 hybridization state of the nitrogen. The (*Z*) isomer of

acetaldoxime is computed to have a PA of 202.4 kcal mol^{-1}, and the protonated (Z) form is more stable than the protonated (E) form by 0.5 kcal mol^{-1}.

B. Gas-phase Acidities of Oximes

There are numerous experimental gas-phase acidities of oximes known, as presented in Table 8. Similar to the hydroxylamines, the G3(MP2)B3 calculated acidities are all slightly too weak, by 1–3 kcal mol^{-1}, but clearly are good at showing relative acidities. It is evident from the data, both experimental and computational, that successive methyl-for-hydrogen replacement in formaldoxime **25**, to give **26** and **27**, is acid-weakening. This agrees with the expected electron-donating inductive effect of sp^3 methyl on a more electronegative sp^2 carbon. Larger alkyl groups, such as *t*-Bu in **28** and **29**, are acid-strengthening for polarizability reasons[57]. Various groups with electron-accepting ability, such as phenyl and some acyl groups, are seen to strengthen the acidity even more, as in **30** and **31**. The trifluoromethyl-substituted oximes **32** and **33** are included with calculated acidities, even though there are no experimental data, for comparison to solution values, below. The two CF_3-for-hydrogen substitutions result in acid-strengthening effects of 19.6 and 14.5 kcal mol^{-1}, indicating a modest saturation effect for the second substitution. The inorganic oxime, nitrous acid **34**, is included for reasons of comparison; it is consistent in acidity with the other oximes shown. The range of gas-phase acidities shown stretch roughly from acetaldehyde and aniline ($\Delta_{acid}H = 367$ kcal mol^{-1}) to benzoic acid ($\Delta_{acid}H = 333$ kcal mol^{-1}).

An interesting comparison is that of formaldoxime **25** CH_2=NOH with the carbon analog ethenol CH_2=CHOH. The former has $\Delta_{acid}H = 363$ kcal mol^{-1}, based on the scaling of the calculated acidities versus experimental ones in Table 8, and the enol is stronger as an acid, at 356 kcal mol^{-1}. The latter is from the experimental acidity of acetaldehyde[4], minus the tautomerization enthalpy of 9.6 kcal mol^{-1} [62]. This is the opposite order from nitrous acid versus formic acid, 340 and 345 kcal mol^{-1} respectively for $\Delta_{acid}H$. The polarity of the C=N group, typified by the resonance form C^+-N^-, is such that it should be acid-weakening in oximes; the opposite polarity exists in nitrous and formic acids, and no equivalent one in the enol.

The O–H BDEs available for these oximes, from calorimetric studies[13], are in the 83 to 86 kcal mol^{-1} range, appreciably stronger than for the hydroxylamines. EPR methods indicate that the radical produced is a σ-radical[13]. This is consistent with their greater bond strength than for hydroxylamines, because there is both no π-delocalization, and the singly occupied orbital is an sp^2 hybridized one, not sp^3. An extensive computational study[63] indicates that most oxime BDEs are in the low to mid-80 kcal mol^{-1} range, that bulky alkyl groups weaken the OH BDE due to steric strain relief in the radical, that α-amino groups strengthen these bonds and appear to make the radical a π- rather than σ-radical, and that substituents in benzaldoximes have little effect on BDEs.

Badal and Mishima have recently reported the gas phase acidities of 12 substituted acetophenone oximes, with a sensitivity to structure 91% of that of benzoic acid gas phase acidities, and an enhanced acidity of up to 5 kcal mol^{-1} for the p-NO_2 and p-CN groups, over that seen for the same benzoic acids.[64]

C. Oxime Acidities in DMSO Solvent

Bordwell and coworkers[37, 65, 66] have measured both pKs and BDEs, the latter via Scheme 2, in DMSO solvent for many oximes and amidoximes, as given in Table 9. It is noted that the BDE values in Table 9 are appreciably stronger than those obtained from calorimetric methods as in Table 8[13], and are thus likely in error. It is unclear whether this is due to a solvation effect or due to use of irreversible oxidation potentials, or both[13].

TABLE 8. Gas-phase acidities of oximes, experimental[a] and *computed*, in kcal mol^{-1}

Oxime		$\Delta_{acid}H$	$\Delta_{acid}G$	BDE[b]	$\Delta_{acid}H$	$\Delta_{acid}G$	BDE
CH_2=NOH[c]	**25**	<372.2[d]	<364.8	83.4	*365.0*	*357.6*	*85.1*
MeCH=NOH(*Z*)[e]	**26**	365.5	358.6	82.6	*367.6*	*360.6*	*85.5*
MeCH=NOH(*E*)				84.7	*368.0*	*360.7*	*86.4*
Me_2C=NOH[e]	**27**	366.0	359.1	84.6	*368.7*	*362.0*	*86.3*
t-BuCH=NOH (*Z*)[e]	**28**	362.7	355.8	84.0	*361.6*	*354.5*	*85.9*
t-BuCH=NOH (*E*)					*365.5*	*357.6*	*87.3*
(*t*-Bu)$_2$C=NOH	**29**			77.6	*357.7*	*354.0*	
PhCH=NOH (*Z*)[e]	**30**	352.8	345.9	83.9	*353.7*	*346.5*	*80.7*
PhCH=NOH (*E*)					*354.5*	*347.4*	*84.4*
MeCOCH=NOH(*Z*)[f]	**31**	341.9	335.3		*343.5*	*336.6*	*86.8*
CF_3CH=NOH(*Z*)	**32**				*345.4*	*337.4*	*84.1*
CF_3CH=NOH(*E*)					*346.5*	*338.5*	*86.0*
MeSCH$_2$COCH=NOH(*Z*)[f]		336.7	330.1		*341.0*	*333.6*	*84.7*
MeSOCH$_2$COCH=NOH[f]		331.6	325.0				
MeSO$_2$CH$_2$COCH=NOH[f]		330.0	323.4				
(CF_3)$_2$C=NOH	**33**				*330.9*	*323.2*	*85.0*
O=NOH[g]	**34**	340.2	333.7	79.0[h]	*341.5*	*334.5*	*79.1*

[a] *Z* and *E* designations are for the computational forms; experimental values are likely for the *E* form; see text.
[b] Reference 13.
[c] Reference 59.
[d] Upper limit, derived from electron ionization appearance potential of CH_2=NO$^-$ from nitromethane.
[e] Reference 22.
[f] Reference 60.
[g] Reference 61.
[h] Reference 58.

3-Pentanone oxime is 4.4 pK units more acidic than the near-isostructural diethylhydroxylamine, showing the effect of the extra resonance stabilization in the oxime. In contrast to the gas-phase results above, the effect of methyl-for-hydrogen replacement on carbon is acid-strengthening, by 2.5 pK units on going from acetaldoxime to acetoxime, and 3.6 pK units from propionaldoxime to 3-pentanone oxime. Although there are numerous cases in the Bordwell DMSO pK data that show methyl-for-hydrogen replacement as acid-strengthening, those are all on carbon that rehybridizes from sp^3 in the acid to sp^2 in the conjugate base (e.g. nitromethane)[3]. All other cases where this structural change occurs on a carbon that is sp^2 in both the acid and conjugate base are acid-weakening, commonly as a substituent on a benzene ring. In light of the intrinsic acid-weakening effect of this replacement for oximes in the gas phase, in DMSO this must represent a desolvation of the acid form with increasing steric bulk, overcoming the inductive electron-donating effect.

Increasing alkyl group bulk also strengthens acidity. The sole exception is the smallest case, from acetaldoxime **26** to propionaldoxime **35** (weakening by 0.3 pK units). The largest groups (di-*t*-Bu, dibenzyl) strengthen acidity by up to 3.5 pK units in **29**, **37** and **38**, **27**. It is likely that part of this effect is steric, in widening the C−N−C angle; it is well-documented that that weakens the OH BDE in these oximes[13]. Cyclization, as in cyclohexanone oxime **39**, strengthens acidity by about 1 pK unit over the open-chain analog **36**.

As expected, electron-withdrawing groups appreciably strengthen acidity: phenyl (−8.3 pK units in **30**), acetyl (−13.4 pK units in **31**), benzoyl (−13.6 pK units in **43**), styryl

TABLE 9. Oxime pK_as and BDEs in DMSO solvent[a]

		pK	δpK[b]	BDE[c]
MeCH=NOH[d]	**26**	28.48	(0.0)	98.2
Me_2C=NOH	**27**	26.00	−2.5	95.8
EtCH=NOH[d]	**35**	28.80	+0.3	98.1
Et_2C=NOH	**36**	25.20	−3.3	92.3
t-BuC(*i*-Pr)=NOH[e]	**37**	25.50	−3.0	86.0
(*t*-Bu)$_2$C=NOH[e]	**29**	24.40	−4.1	82.9
$(PhCH_2)_2C$=NOH	**38**	22.50	−6.0	89.1
c-$(CH_2)_{11}C$=NOH		25.00	−3.5	90.3
c-$(CH_2)_5C$=NOH	**39**	24.27	−4.8	90.4
$Me_2NCH_2C(Me)$=NOH (*E*)	**40**	23.50	−5.0	92.0
$Et_2NCH_2C(Me)$=NOH (*E*)	**41**	23.82	−4.7	91.4
PhCH=CHCH=NOH (*Z*)	**42**	20.48	−8.0	88.6
MeCOCH=NOH	**31**	15.10	−13.4	89.6
PhCOCH=NOH	**43**	14.90	−13.6	88.9
Benzaldoximes				
PhCH=NOH (*E*)	**30**	20.20	(0.0)	90.2
PhCH=NOH (*Z*)		20.30	0.0	86.9
p-MeO (*E*)		20.80	+0.6	89.9
p-MeO (*Z*)		20.70	+0.6	87.5
p-Me (*E*)		20.55	+0.35	89.0
p-Me(*Z*)		20.64	+0.35	86.5
p-Cl[f]		19.30	−0.9	87.8
p-CF_3[f]		18.60	−1.6	87.9
p-NC[f]		18.00	−2.2	87.8
m-NO_2 (*E*)		17.70	−2.5	88.6
m-NO_2 (*Z*)		17.60	−2.5	86.9
p-NO_2 (*E*)		17.00	−2.9	88.4
Diaryloximes				
Ph_2C=NOH	**44**	20.10	(0.0)	88.7
9-Fluorenone=NOH	**45**	16.20	−3.9	87.5
2-SO_2Ph-9-fluorenone =NOH		14.20	−5.9	88.3
2,7-diBr-9-fluorenone =NOH		14.00	−6.1	89.6
Amidoximes				
H_2NCH=NOH	**46**	25.61		88.8
$MeC(NH_2)$=NOH	**47**	25.82		86.7
$PhC(NH_2)$=NOH	**48**	23.00		86.9
Acetophenoximes				
PhC(Me)=NOH (*Z*)	**49**	21.80		91.2
PhC(Me)=NOH (*E*)		21.17		91.1
p-$MeOC_6H_4C(Me)$=NOH[f]		22.80		90.0
p-$MeC_6H_4C(Me)$=NOH[f]		21.70		89.0
p-$ClC_6H_4C(Me)$=NOH[f]		20.50		89.0
p-$BrC_6H_4C(Me)$=NOH[f]		20.50		89.0
p-$CF_3C_6H_4C(Me)$=NOH[f]		19.50		88.9
p-$NCC_6H_4C(Me)$=NOH[f]		18.90		88.8
p-$NO_2C_6H_4C(Me)$=NOH[f]		18.20		88.8
p-$MeC_6H_4SCH_2C(Ph)$=NOH (*Z*)		18.89		89.4
N-Morpholino-$CH_2C(Ph)$=NOH (*Z*)		20.80		89.1
N-Morpholino-$CH_2C(Ph)$=NOH (*E*)		20.15		88.6

(*continued overleaf*)

TABLE 9. (*continued*)

		pK	δpK^b	BDE[c]
$Me_2NCH_2C(Ph)$=NOH (*E*)	**50**	20.52		88.5
$Me_2NCH_2C(Ph)$=NOH (*Z*)		21.00		87.6
$Me_2NCH_2CH_2C(Ph)$=NOH (*E*)		20.96		88.7

[a]Reference 65, unless otherwise stated.
[b]Relative to the last 0.0 value.
[c]kcal mol^{-1}. Likely to be in serious error, see text.
[d]*E*/*Z* mixture.
[e]Reference 37.
[f]Reference 66.

(−8.0 pK units in **42**) and amino (−2.9 pK units in **46**) replacing methyl in acetaldoxime **26**. A second phenyl, however, causes negligible additional strengthening in **44**, due to a resonance saturation effect. Enforcing planarity of the rings, as in fluorenone oxime **45**, results in an additional 4 pK units of acidity strengthening.

There is little difference in acidity between (*E*)- and (*Z*)-benzaldoximes **30**, over several cases with different substituents. For the substituted (*E*)-benzaldoximes, the Hammett ρ is +3.2, smaller than that for the substituted phenols in DMSO at +6.6, and larger than for benzoic acids at +2.6[3], indicating much less charge on the α-atom in the oxime anions than for the phenoxides. For the substituted acetophenone oximes **49**, $\rho = +3.5$. Although the data are sparse, in both cases the *p*-NO_2 and *p*-NC groups correlate better with σ_p than with σ_p^-, likewise consistent with little through resonance of the negative charge into the ring.

There is one other substituent effect: an amino or dimethylamino group is expected to be inductively electron-accepting but resonance-donating[33]. When substituted for a hydrogen on an sp^3 carbon, as in **40**, **41** and **50**, the resonance effect cannot operate, and this substituent is acid-strengthening by −2.5, −2.1 and −0.6 pK units, respectively. When it replaces a methyl group on the sp^2 carbon in the oxime group, the ambiguous nature is observed: it is acid-weakening in acetophenone oxime to **48** by 1.9 pK units, has little effect on acetoxime to **47** and is acid-strengthening by −2.9 pK units in acetaldoxime to **46**.

In comparison with the gas phase, these pKs in DMSO shown increased methylation at the oxime carbon to be acid-strengthening as in **26** to **27**, where it is weakening in the gas phase. Increasing alkyl bulk (**27** to **29**) is acid-strengthening in both phases, but only by 20% of the gas-phase amount in DMSO. Because DMSO is a good hydrogen bond acceptor solvent, this pattern may be due to 'ground state' effects: stabilization of the neutral acid by the solvent via hydrogen bond acceptance will strengthen relative acidity. Acetyl-for-methyl replacement in **26** to **31** is acid-strengthening in both phases, but by only 77% of the gas-phase effect in DMSO. Phenyl-for-methyl replacement in **26** to **30** likewise is moderated by DMSO to 81% of the gas-phase amount.

D. Oxime Acidities and Basicities in Aqueous Solution

There is only a single basicity—and that over 100 years old—found for an oxime in aqueous solution, as given at the start of Table 10. This lack of data may be due to oximes in general being too weakly basic in water to yield measurable pK_{BH^+} values. The pK_{BH^+} of 2.2 for protonated acetoxime[67] is, however, part of a series of weak basicities in that work, where the other compound's values have been reproduced more recently,

TABLE 10. pK_as of oximes in aqueous solution

Oxime		pK_a	References	Conditions[a]
$Me_2C{=}N(OH)H^+$		2.2	66	40 °C
$CH_3CH{=}NOH(Z)$	**26**	11.82	68	$I = 0.1$
n-HexCH=NOH(*E*)	**51**	11.60	54	
$CF_3CH{=}NOH$	**32**	8.9	46	
Benzaldoximes ArCH=NOH				
H-(*Z*)	**30**	10.68	54	
H-(*E*)		11.33	54	
p-Me_2N(*Z*)		11.25	54	
o-MeO (*Z*)		10.89	54	
m-MeO (*Z*)		10.59	54	
p-MeO (*Z*)		10.92	54	
3,4-diMeO(*Z*)		10.85	54	
3,4-OCH_2O-(*Z*)		10.85	54	
o-NO_2 (*Z*)		10.06	69	
o-NO_2 (*E*)		10.74	69	
m-NO_2 (*Z*)		10.15	69	
m-NO_2 (*E*)		10.74	69	
p-NO_2 (*Z*)		9.97	69	
o-aza-		10.10	68	$I = 0.1$
o-aza$^+$Me-	**52**	7.82	68	$I = 0.1$
m-aza$^+$Me	**53**	9.10	68	$I = 0.1$
p-aza$^+$Me	**54**	8.23	68	$I = 0.1$
o-O^-	**55**	11.78	70	$I = 1.6$
o-O^--3-MeO	**56**	11.56	70	$I = 0.1$
o-O^--4-MeO	**57**	11.81	70	$I = 0.1$
o-O^--5-MeO	**58**	11.92	70	$I = 0.1$
o-O^--5-NO_2	**59**	11.31	70	$I = 0.1$
o-O^--6-NO_2	**60**	11.79	70	$I = 0.1$
2-Furyl-CH=NOH(α)	**61**	10.82	69	
2-Furyl-CH=NOH(β)		10.85	69	
2-Furyl-CH=NOH(*E*)		11.16	71	
2-Thienyl-CH=NOH(*E*)		10.76	71	
PhCH=CHCH=NOH(α)	**62**	10.55	54	
PhCH=CHCH=NOH(β)	**63**	10.89	54	
o-$MeOC_6H_4CH{=}CH{-}CH{=}NOH(\alpha)$	**64**	10.80	69	
o-$MeOC_6H_4CH{=}CH{-}CH{=}NOH(\beta)$	**65**	11.35	69	
m-$NO_2C_6H_4CH{=}CHCH{=}NOH(\alpha)$	**66**	10.16	54	
MeCOCH=NOH	**31**	8.35	72	$I = 0.1$, 30 °C
MeCOCH=NOH(*E*)		8.30	68	$I = 0.1$
EtCOCH=NOH		8.37	68	
$Me_2C{=}CHCOCH{=}NOH$		8.90	72	$I = 0.1$, 30 °C
PhCOCH=NOH	**43**	8.40	72	$I = 0.1$, 30 °C
PhCOCH=NOH		8.25	68	$I = 0.1$
2-Thienyl-COCH=NOH		8.45	72	$I = 0.1$, 30 °C
MeCOC(Me)=NOH	**67**	9.30	68	$I = 0.1$
MeCOC(Et)=NOH	**68**	9.38	68	$I = 0.1$
MeCOC(*i*-Pr)=NOH	**69**	9.50	68	$I = 0.1$
$MeCOC(CH_2CH_2NMeEt_2{}^+){=}NOH$		8.60	72	$I = 0.1$, 30 °C
$MeCOC(CH_2NMeEt_2{}^+){=}NOH$		6.95	72	$I = 0.1$, 30 °C
$MeCOC(CO_2Et){=}NOH$		7.20	72	$I = 0.1$, 30 °C

(*continued overleaf*)

TABLE 10. (*continued*)

Oxime		pK_a	References	Conditions[a]
$(MeCO)_2C{=}NOH$	**70**	7.50	72	$I = 0.1$, 30 °C
		7.38	68	$I = 0.1$
MeCOC(Cl)=NOH(*Z*)		7.9	73	$I = 0.05$, 21 °C
PhCOC(Cl)=NOH(*Z*)		3.64	73	$I = 0.1$ (decomp)
Ketoximes				
$Me_2C{=}NOH$	**27**	12.42	74	
EtC(Me)=NOH	**71**	12.45	74	
$Et_2C{=}NOH$	**36**	12.60	74	
$(CF_3)_2C{=}NOH$	**33**	6.0	47	
PhC(Me)=NOH	**49**	11.48	69	
$Ph_2C{=}NOH$	**44**	11.30	69	
p-$NO_2C_6H_4C(Ph){=}NOH(\alpha)$	**72**	10.85	69	
p-$NO_2C_6H_4C(Ph){=}NOH(\beta)$		10.47	69	
Dioximes				
HON=CHCH=NOH(*E*)	**73**	9.02	75	$I = 0.05$
HON=C(Me)CH=NOH	**74**	9.69	75	$I = 0.05$
HON=C(Me)C(Me)=NOH	**75**	10.72	75	$I = 0.05$
HON=C(Me)C(Me)=NOH	**76**	10.48	76	[b]
HON=C(Et)C(Me)=NOH	**77**	10.41	76	[b]
HON=C(Et)C(Et)=NOH	**78**	10.67	76	[b]
HON=C(*n*-Pr)C(*n*-Pr)=NOH	**79**	10.81	76	[b]
Cyclohexane-1,2-dioxime		10.55	76	[b]
3-MeCyclohexane-1,2-dioxime		10.61	76	[b]
4-MeCyclohexane-1,2-dioxime		10.54	76	[b]
4-*i*-PrCyclohexane-1,2-dioxime		10.53	76	[b]
Cycloheptane-1,2-dioxime		10.71	76	[b]
$HON{=}C(NH_2)C(NH_2){=}NOH$	**80**	10.62	77	26.5 °C
HON=C(Cl)CH=NOH(*EE*)[c]	**81**	8.36	75	$I = 0.05$
HON=C(Cl)CH=NOH(*ZE*)	**82**	3.44	75	$I = 0.05$
HON=C(Cl)C(Cl)=NOH	**83**	2.94	75	$I = 0.05$
HON=C(Cl)C(Ph)=NOH(*Z*)		4.19	73	$I = 0.2$, 21 °C
HON=C(Cl)C(Ph)=NOH(*E*)		4.92	73	$I = 0.2$, 21 °C
HON=CHC(=O)CH=NOH		7.65	72	$I = 0.1$, 30 °C
O=NOH	**29**	3.17	27	

[a] $I = 0.0$, 25 °C, unless otherwise stated.
[b] Extrapolated to pure water from varying dioxane/water mixtures.
[c] Intramolecular hydrogen bonded isomer.

and thus it seems reasonable. That pK_a shows the oxime to be far more weakly basic than simple alkylamines is likely due to both the electron-withdrawing inductive effect of the hydroxyl group on the cation, and the more electronegative sp^2 orbital being the site of protonation.

The acidity pK_a collection in Table 10 is the most numerous for all the structures here. However, some of these pK_as are more than 80 years old, and even under nominally identical conditions, values differing by 0.1–0.2 pK units are found for the same acid in different references. Thus one must be cautious in interpreting structural effects on relative pK_as. There are few non-aromatic aldoxime pK_as available, due to facile base hydrolysis in aqueous solution.

Acetaldoxime **26** is stronger as an acid than acetoxime **27** by 0.6 pK units. Thus, methyl-for-hydrogen substitution on pK_as of the parent oxime is acidic weakening. Methyl-for-hydrogen substitution on the α carbon of MeCOCH=NOH **31** to give **67** weakens acidity by 1.0 pK unit, by 0.8 pK unit in PhCH=NOH **30** to give **49**, and by 0.7 and 1.1 pK units for the two substitutions in the dioxime HON=CHCH=NOH **73** to give **74** and **75**. Increasing the alkyl group size in the ketoximes (**27** to **71** to **36**) is slightly acid-weakening, in contrast to the acid-strengthening effect seen for the comparable species in DMSO. A similar effect is seen in the dioximes **75** to **77**, **78**, **79**. In the latter case, it may be due in part to steric hindrance to resonance: the coplanarity of the two oxime groups in these dioximes is part of the reason for their acidity, and large alkyl groups can twist them out of that planarity.

(*Z*)-Benzaldoxime **30Z** is 1.1 pK unit more acidic than the acetaldoxime **26**. Unlike in DMSO, where the stereoisomers have essentially equal acidity, in water (*Z*)-benzaldoxime **30Z** (the *anti* or higher melting α isomer) is 0.65 pK units stronger in acidity than the (*E*) form **30E**, and this persists through several substituted benzaldehydes as well. This also parallels the computational gas-phase results, where the (*Z*) form is more strongly acidic than the (*E*) by 0.8 kcal mol^{-1}. The six *meta*- or *para*-substituted (*Z*)-benzaldoximes give a Hammett $\rho = 0.78 \pm 0.05$ for their pK_as; a similar two-point (H and *m*-NO_2) ρ of 0.8 is found for the (*E*) isomers. This is a reasonable value, in that the ρ for phenol acidities in water is 2.1[68], and an intervening −CH=CH group attenuates the ρ for benzoic acid pK_as of 1.00 to 0.47 for cinnamic acids. Thus ρ should be *ca* $2.1 \times 0.47 = 0.98$ for ArCH=CHOH, close to what is observed here for ArCH=NOH. This also implies little negative charge on the α carbon in the benzaldoximes, consistent with *p*-NO_2 fitting the correlation with σ_p and not σ_p^-.

Replacement of a CH group in the benzaldoxime ring with a nitrogen atom, then alkylation of that to create a N^+Me ring structure, greatly strengthens the acidity. For the *para* case **54** a σ_p value of over +3 would be required to make it fit the Hammett plot cited above! Similarly, an O^- substituent on the ring in **55** through **60** weakens the acidity by over 1 pK unit, relative to the substituted benzaldoxime **30**. The pK_as of the salicylaldoximes **55**–**60** are actually the second pK_as of these; the first pK_a is for the phenol site. A three-point Hammett Plot (H, *p*-MeO, *p*-NO_2) of these shows $\rho = 0.7$ for the second pK_a (oxime acidity) and $\rho = 2.0$ for the first pK_a (phenol acidity). Replacing the phenyl group with a 2-furyl group, as in going from **30** to **61**, weakens the acidity by 0.2 pK units. For the cinnamaldoximes **62**–**66**, the pK_as are comparable to the benzaldoximes, and $\rho = 0.5$.

If a methyl group in acetoxime is replaced by an acetyl group, as in **67**, a 3.1 pK acid-strengthening effect is observed, consistent with the resonance and inductive effects expected for that group. A second such replacement, to **70**, is worth 1.9 pK units, a moderate saturation effect. In contrast, phenyl-for-methyl replacement in acetoxime **27**, to give **49** and then **44**, gives 0.9 and 0.2 pK units of acid-strengthening. The second phenyl group obviously interferes with the resonance effect of the first. For CF_3 groups, successive CF_3-for-alkyl replacements are acid-strengthening by 3.9 and 2.9 pK units in **32** and **33**, a modest saturation effect[44].

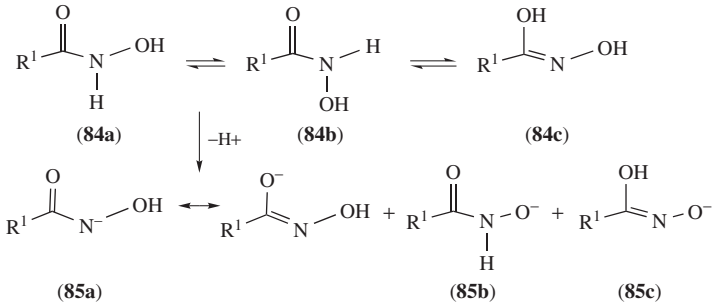
For *p*-$NO_2C_6H_4C$(Ph)=NOH **72**, the stronger acidity of the β form, compared to the α form, can be interpreted as the β form being the (*E*) isomer. In that case, the ring with the substituent can more easily become coplanar with the anionic system, being *trans* from the oxyanion.

Successive substitutions of chlorines for α-hydrogens in **73** to **82** and **83** strengthens the acidity by −5.6 and −0.5 pK units, while replacement by two amino groups, as in **80**, weakens the acidity by 1.6 pK units. The apparently anomalous acidity of the *EE* isomer **81**, relative to the much stronger *EZ* isomer **82**, is due to acid stabilization in the *EE* form by internal hydrogen bonding.

In contrast to the gas phase and to DMSO, water is a hydrogen bond donor and should thus stabilize the charge at the oxyanion in oximate anions. With less of the negative charge density on the carbon of the oximate group, smaller substituent effects are expected. This is seen: relative to the acidity of acetaldoxime **26**, benzaldoxime **30** is 12.7 kcal mol^{-1} stronger as an acid in the gas phase, 11.2 kcal mol^{-1} (8.2 pK units) more acidic in DMSO and only 1.5 kcal mol^{-1} stronger in water. Butanedione-monoxime **67** is similarly 25 kcal mol^{-1} stronger than acetoxime **27** in the gas phase, 15 kcal mol^{-1} stronger in DMSO and 5.6 kcal mol^{-1} stronger in water. Hexafluoroacetoxime **33** is 38 kcal mol^{-1} stronger than acetoxime in the gas phase, but only 8.8 kcal mol^{-1} stronger in water. The Hammett ρ for (Z)-benzaldoximes is +3.2 in DMSO, but +0.78 in water. All these are consistent with the expected solvent effect on charge stabilization.

IV. HYDROXAMIC ACIDS

These are of the general structure **84** and can be regarded as acylhydroxylamines or *N*-hydroxycarboxamides. They have the possibility of being either nitrogen or oxygen acids, giving anions **85a** and **85b**, plus possibly the tautomeric form **85c**. This competition is often a close one, as will be seen. The acids themselves can exist in several forms, as per Scheme 5. G3(MP2)B3 calculations indicate that in the gas phase, relative to the (Z) canonical form **84a** (R^1 = Me) with an internal hydrogen bond, the (E) conformer **84b** is 2.2 kcal mol^{-1} higher in enthalpy, and the (Z) tautomer **84c**, also hydrogen bonded, is only 0.6 kcal mol^{-1} higher in enthalpy than **84a**. This is in very good agreement with literature studies at a variety of computational levels[79–83].



SCHEME 5. Isomeric forms of hydroxamic acids and hydroxamate anion

In solution it appears that the mixture of forms is complex and dependent on the medium[82, 84, 85]. By NMR, in water acetohydroxamic acid is 3% *E*/97% *Z* form, and rapidly interconverting on the NMR time scale at room temperature[80]. For the anions, it likewise appears to be medium-dependent in terms of what forms are present, as will be seen below. The basic site is expected to be at the carbonyl oxygen, as is the case for carboxamides[84].

A. Gas-phase Basicities/Proton Affinities of Hydroxamic Acids

There are experimental gas-phase basicities known for acetohydroxamic acid **86** and its *O*- and *N*-methylated derivatives **87** and **88**, as shown in Table 11. These are reasonably

TABLE 11. Gas-phase basicities of hydroxamic acids, experimental[a] and *computed*[b], in kcal mol^{-1}

		PA(expt)	GB(expt)	PA(G3(MP2)B3)[b]	GB(G3(MP2)B3)[b]
MeCONHOH	**86**	204.1	196.7	*205.5*[c]	*197.7*
MeCONHOMe	**87**	209.9	202.5		
MeCON(Me)OH	**88**	209.4	202.0	*209.2*[d]	*202.6*
MeCONHMe	**89**	212.5	205.1	*214.4*[e]	*206.9*
$MeCONMe_2$		217.1	209.7	*216.5*	*208.6*
HCONHOH	**90**			*197.3*	*189.6*

[a]From Reference 20, unless otherwise indicated.
[b]From protonation on the carbonyl oxygen, *cis* to the NHOH group. Reference 5.
[c]N protonation is +18.9 kcal mol^{-1} higher in enthalpy. The (*E*) form of the base is 2.2 kcal mol^{-1} higher in enthalpy than the (*Z*) form.
[d]N protonation is +10.7 kcal mol^{-1} higher in enthalpy. The (*E*) form of the base is 1.5 kcal mol^{-1} higher in enthalpy than the (*Z*) form.
[e]N protonation is +16 kcal mol^{-1} higher in enthalpy.

closely modeled by the G3(MP2)B3 calculations, assuming protonation on the carbonyl oxygen *syn* to nitrogen. It is evident that methylation on either nitrogen or oxygen in acetohydroxamic acid **86** results in a strengthening of basicity by about 5 kcal mol^{-1}. The presence of the hydroxyl group, relative to a methyl in carboxamide **89**, weakens the basicity by about 8 kcal mol^{-1}. These effects are consistent with known polarizability and inductive effects on basicities. This hydroxyl-for-methyl substitution effect is smaller than the 13.3 kcal mol^{-1} seen for diethylhydroxylamine **1** or the 21 kcal mol^{-1} for acetoxime **27**, where protonation is on the nitrogen directly. The authors concluded that the basicities were consistent with protonation on the carbonyl oxygen but did not prove it[86]. The formohydroxamic acid **90** is over 8 kcal mol^{-1} weaker as a base than acetohydroxamic acid **86**, again consistent with expected polarizability effects.

B. Gas-phase Acidities of Hydroxamic Acids

There is one experimental study of the gas-phase acidities of these species[87], focused on whether hydroxamic acids are NH or OH acids. As shown in Table 12, the unsubstituted acetohydroxamic acid **86** is 4 to 8 kcal mol^{-1} stronger as an acid than either the *O*-methylated or *N*-methylated derivatives **87** or **88**, but the *O*-methylated case is stronger as an acid than the *N*-methylated. It would be expected that OMe is more electron-accepting than OH both inductively, based on σ_I constants[33], and due to polarizability[34]; it should thus be acid-strengthening, if the acidic site is the NH. The observed weakening of acidity of **87** was interpreted as due to a loss of the intramolecular hydrogen bond of the OH present in the anion **86** to the oxyanion in the conjugate base of **87**[87]. The stronger acidity, by 15.5 kcal mol^{-1}, of **87** compared to the isoelectronic *N*-methyl carboxamide **89** can be referred to the inductive effect of the electronegative OH substituent directly on the nitranion; however, an acid-destabilizing effect for this group has also been claimed[88]. A point not considered in the original work: deprotonation of acetohydroxamic acid **86** at the $-CH_3$ group is 3.9 kcal mol^{-1} weaker as an acid than for deprotonation at OH, by G3(MP2)B3 calculations. Over a wide range of computational methods[79, 80, 83, 89, 90], hydroxamic acids are more strongly acidic at the NH site than the OH site by 12 to 17 kcal mol^{-1}.

TABLE 12. Gas-phase acidities of hydroxamic acids, experimental[a] and *computed*[b], in kcal mol^{-1}

Hydroxamic acid		$\Delta_{acid}H$	$\Delta_{acid}G$	$\Delta_{acid}H$	$\Delta_{acid}G$	BDE
MeCONHOH	**86**	346.3	339.1	*344.3*	*337.4*	*84.1*
MeCONHOH				*361.0*	*353.9*	*83.2*
MeCONHOH				*364.9*	*357.8*	
MeCONHOMe(*Z*)	**87**	351.0	343.7	*350.2*	*342.8*	*85.7*
MeCON(Me)OH	**88**	354.4	346.9	*352.1*	*344.9*	*81.6*
PhCONHOH(*Z*)	**91**			*336.9*	*329.7*	
PhCONHOH(*Z*)				*354.8*	*347.3*	
MeCONHMe	**89**	361.8	354.5	*361.9*	*355.5*	*106.1*
MeCONH$_2$	**92**	362.0	355.0	*362.1*	*356.2*	*110.9*

[a]From Reference 87, unless otherwise indicated.
[b]Reference 5.

C. Hydroxamic Acid Acidities in DMSO Solvent

It is established that *E/Z* isomerization of these occurs readily in DMSO, and that a 90/10 *Z/E* ratio exists for acetohydroxamic acid **86** there[91]. Bordwell and coworkers[92, 93], in their studies of hydroxamic acid pKs in DMSO, first addressed the same point as in the gas-phase studies: the site of deprotonation of hydroxamic acids, as given in Table 13. Just as in the gas phase, in DMSO the *O*-methylated derivative **87** is weaker in acidity than the parent, but still stronger than the *N*-methylated form **88**. The differences are smaller in size in DMSO than in the gas phase, consistent with the solvent dispersing the charge, and opening-up of the internal hydrogen bond due to the solvent's basicity. Acetohydroxamic acid **86** is 9.5 pK units stronger as an acid than acetamide **92**, due primarily to the inductive effect of the OH group[93, 94].

Substituted benzohydroxamic acids **91**, **99**–**101** yield a 4-point Hammett ρ of 2.7 for their pKs in DMSO, while the analogous benzocarboxamides have $\rho = 2.8$, implying that the hydroxamic acids are NH acids like the carboxamides must be. The benzohydroxamic acids are *ca* 10 pK units more strongly acidic than the benzocarboxamides, again likely due to the inductive effect of the OH group[93].

The pKs of *N*-alkyl- and *N*-arylbenzohydroxamic acids have also been determined[12, 37], where the OH acidity is enforced. Increasing alkyl size in the *N*-alkyl cases **93**–**95** weakens the acidity, as is common for many such species in DMSO[3, 95]. A 3-point Hammett ρ of 6.7 is observed for the *N*-aryl substituted acids **96**–**98**, considerably larger than the ρ of 2.7 seen for aryl groups on the carbonyl (**91**, **99**–**101**), one atom farther away, and far larger than the 0.4 seen for $ArCH_2OH$ acidities[12]. This value of 6.7 must be treated cautiously, being based on only three points and two of those *para* substituents, but it may likely reflect the anion-stabilizing effect of structures such as **102**.

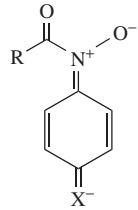
D. Hydroxamic Acid Acidities and Basicities in Aqueous Solution

There are few data on the basicity of hydroxamic acids in aqueous solution[84]. The OH group should weaken the basicity of a carboxamide due to its inductive effect, as seen above in regard to gas-phase basicities. The pK_a of a protonated carboxamide is -0.6[26], so the basicity of a hydroxamic acid is likely beyond the range accessible to measurement in water. There are pK_as available for sulfuric acid/water solutions, placing protonated arylhydroxamic acids such as **91** in the *ca* -1.0 to -1.6 pK_a region[97]. Via nitrogen NMR studies, acetohydroxamic acid **86** is reported to have $pK_{BH^+} = -1.15$ in aqueous sulfuric acid, and to be protonated on the carbonyl oxygen[79].

TABLE 13. pK_as and BDEs in DMSO solvent: hydroxamic acids and amides

Hydroxamic acid		pK	BDE[a]	Reference
MeCONHOH	**86**	16.00	89.6	91
MeCON(Me)OH	**88**	19.60	85.0	92
MeCONHOMe	**87**	17.00	91.2	91
PhCONHOH	**91**	13.70	88.0	91
PhCON(Me)OH	**93**	18.40	92.5	92
PhCON(*i*-Pr)OH	**94**	18.70	81.2	64
PhCON(*t*-Bu)OH	**95**	19.60	79.9	64
PhCON(Ph)OH	**96**	19.00	84.4	12
PhCON(C_6H_4Br-*p*)OH	**97**	17.85	83.9	12
PhCON(C_6H_4CN-*p*)OH	**98**	14.65	84.3	12
$PhCONHOCH_2Ph$		14.35	89.4	91
p-$ClC_6H_4CONHOH$	**99**	13.00		92
m-$ClC_6H_4CONHOH$	**100**	12.70		92
m-$CF_3C_6H_4CONHOH$	**101**	12.40		92
$MeCONH_2$	**92**	25.5	107.6	95
$PhCONH_2$		23.35	107.0	95

[a]Obtained from Scheme 2.



(**102**)

There is considerable debate over whether hydroxamic acids are NH or OH acids in aqueous solution[84, 93]. Although the NH site is considerably favored intrinsically, as shown above, it would be expected that solvation by protic solvents should favor the localized oxyanion as a hydrogen bond acceptor over the delocalized nitranion. From spectroscopic and acidity data, it appears that hydroxamic acids are NH acids in dioxane, methanol[85] and mixed aqueous solutions[93, 98]. An OH acidity site—or at least an equal competition with the NH site—has been claimed for substituted benzohydroxamic acids **91** in aqueous solution based on UV data[99] and acidities[100, 101]. In 2 M aqueous $NaNO_3$, OH acidity is claimed based on acidity data[102]. In water, by NMR, acetohydroxamic acid **86** is stated to be an OH acid, but benzohydroxamic acid **91** an NH acid[79]. In direct contrast to the last reference, another NMR study shows acetohydroxamic acid **86** to be an NH acid in water, with the anion undergoing *E/Z* isomerization more slowly than the NMR time scale[80]. Computations on the solvent effect on pK_as show the NH site still favored, but only by 2–9 kcal mol^{-1} (1.5–7 pK units) compared to 16 kcal mol^{-1} in the gas phase[80, 82, 83].

In light of these often contradictory studies, it appears that the NH and OH acidic sites can be comparable in acidity in protic solvents, are definitely solvent-dependent, and that any structure–pK_a relationship must be interpreted cautiously.

The data in Table 14 indicate that the simple hydroxamic acids are 4 to 6 pK units weaker as acids than the corresponding carboxylic acids, but this could still be due to either structure.

TABLE 14. pK_as in aqueous solution: hydroxamic acid RCONHOH acidities[a]

R		pK_a	pK_a(RCO$_2$H)[b]	ΔpK_a[c]	ΔH_i[d]
H	**90**	8.78[e]	3.75	5.03	4.62
Me	**86**	9.40[f]	4.76	4.64	
(*Z*)		9.35[g]			5.3
(*E*)		9.01[g]			
		8.86[h]			
Et		9.46[f]	4.87	4.59	
n-Pr		9.48[f]	4.82	4.66	
PhCH$_2$		9.19[f]	4.31	4.88	
Ph	**91**	8.89[f]	4.20	4.69	
		8.80[g]			
		8.89[e]			4.21
		8.31[h]			
p-ClC$_6$H$_4$		8.58[f,i]	3.99	4.59	
p-MeOC$_6$H$_4$		9.00[j]	4.47	4.53	
o-HOC$_6$H$_4$		7.38[j]	2.99	4.39	
		7.41[e]	3.00	4.41	3.37
p-HOC$_6$H$_4$		9.06[e]	4.57	4.49	4.62
o-H$_2$NC$_6$H$_4$		9.29[e]	4.80	4.49	5.05
5-NO$_2$-2-HOC$_6$H$_3$		6.89[e]			3.37
1-Naphthyl		7.70[j]	3.69	4.01	
ClCH$_2$		8.53[e]	2.87	5.66	4.62
H$_2$NCH$_2$		7.80[e]			3.79
p-HOC$_6$H$_4$CH$_2$CHNH$_2$		9.35[e]			5.89
H$_2$N(CH$_2$)$_4$CHNH$_2$		8.11[e]			5.47
MeCH(OH)		9.45[e]	3.86	5.59	3.37
H$_2$N		10.15[h]			
H$_2$NCON(Me)OH		9.79[h]			
PhCONHOMe		8.88[f]			
PhCON(Me)OH	**93**	8.59[j]			
p-MeOC$_6$H$_4$CON(Me)OH		8.80[f]			
MeCON(Me)OH	**88**	8.85[k]			
N-HO-phthalimide		6.10[l]			
PhCON(Ph)OH	**96**	8.41[e]			4.62
PhCH=CHCON(Ph)OH		9.11[e]			4.21
PhCON(2-furyl)OH		8.14[e]			5.05
MeCONH$_2$	**92**	15.1[b]	4.76	10.34	
PhCONH$_2$		13.14[b]	4.20	8.94	

[a] 25 °C, $I = 0.00$ unless otherwise stated.
[b] Reference 27.
[c] pK_a(RCONHOH)—pK_a(RCO$_2$H).
[d] Enthalpy of ionization, kcal mol^{-1}.
[e] Reference 103.
[f] Reference 104. All at 20 °C: pK_a at 25 °C is *ca* 0.05 pK units stronger than at 20 °C, Reference 103.
[g] Reference 80. $I = 0.2$M NMR indicates N deprotonation.
[h] Reference 106. $I = 2.0$ M.
[i] Reference 101. At 30 °C. pK_a at 25 °C *ca* 0.05 pK units weaker than at 30 °C, Reference 103.
[j] Data in Reference 104 do not support stated pK_a. Solubility problems were noted by the authors.
[k] Reference 100. $I = 1.0$ M.
[l] Reference 105. $I = 0.1$ M.

For substituted benzohydroxamic acids derived from **91**, Hammett ρ values of 1.02 (H_2O solvent)[107], 0.96 (12% EtOH, $I = 0.08$)[108], 0.96 (H_2O, 30.5 °C, $I = 0.1$)[109] have been obtained. At face value, these are consistent with these being NH acids, because the value is comparable to the defined $\rho = 1.00$ for benzoic acids, with the negative charge nominally two atoms away from the ring. However, $\rho = 1.05$ for *N*-*p*-tolylbenzohydroxamic acids[110] where the charge must reside on the oxygen site. These last data were obtained, however, in solvents of varying dioxane/water ratio down to 10% dioxane, and extrapolated to 0% dioxane for the reported ρ value. For 12% EtOH/H_2O solvent, with $I = 0.08$ M, ArCON(Me)OH gave a ρ of 0.6, and ArCONHOMe a ρ of 1.45[111]. The unsubstituted ArCONHOH acids[108] as noted above in the same solvent have a ρ of 0.96, halfway between the two substituted cases. It is thus possible that both sites have comparable acidities in these benzohydroxamic acids. Likewise, ArCON(*m*-tolyl)OH pK_as yield a Hammett ρ of 0.63 for the enforced OH site acidities[112]. Notably in this last study, the enthalpy and entropy of ionization were obtained as well. These indicate that the pK_as are entropy controlled: the enthalpies of ionization (+3 to +8 kcal mol^{-1}) become more positive by +5 kcal mol^{-1} as the pK_a decreases from H to *p*-NO_2 by 0.52 pK units. Similar enthalpies of ionization (+3 to +6 kcal mol^{-1}) are observed for a wide variety of RCONHOH species[103], but for the more general situation, there is no real correlation, positive or negative, between ΔH_i and pK_a: $r = 0.42$ for 14 hydroxamic acids.

V. FINAL COMPARISONS

Although there are no exact structural analogs across the three functional groups under consideration here, taking the arbitrary but roughly size-consistent series Et_2NOH **1**, $Me_2C{=}NOH$ **27** and MeCONHOH **86**, the data in the tables above indicate that in all 3 phases—gas phase, DMSO and water—the acidities are consistently in this order, and with the difference between the oxime and hydroxamic acid about twice that of the hydroxylamine–oxime difference in all three media. The total range, however, from hydroxylamine to hydroxamic acid in DMSO is about 75% of the gas-phase range (units corrected to pK), and in water about 20% of the gas-phase values. It is clear that solvent stabilization of charge moderates the intrinsic structural effects.

The major gap in the data of these functional groups is clearly the question of the structure of the hydroxamate anions in aqueous solution: are they nitranions or oxyanions? The spectroscopic evidence is limited in structural range, and contradictory.

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N-Arylhydroxylamines and chemical carcinogenicity

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I. INTRODUCTION

A. Abbreviations

AAs (arylamines): **2-AAF** (*N*-acetyl-2-aminofluorene), **2-AF** (2-aminofluorene), **4-ABP** (4-aminobiphenyl), **1-AP** (1-aminopyrene), **BZ** (benzidine), **2-NA** (2-aminonaphthalene), **1-NA** (1-aminonaphthalene). **HAA**s (heterocyclic arylamines): **AαC**

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(2-amino-α-carboline, 2-amino-9*H*-pyrido[2,3-*b*]indole), **MeAαC** (2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole), **IQ** (2-amino-3-methylimidazo[4,5-*f*]quinoline), **MeIQ** (2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline), **IQx** (2-amino-3-methylimidazo[4,5-*f*]quinoxaline), **MeIQx** (2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline), **Glu-P-1** (glutamic acid pyrolysis product 1, 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole), **Glu-P-2** (glutamic acid pyrolysis product 2, 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole), **Trp-P-1** (tryptophan pyrolysis product 1, 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]-indole), **Trp-P-2** (tryptophan pyrolysis product 2, 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole), **PhIP** (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine). Enzymes (corresponding genes italicized): CYP450 (cytochrome P450), NAT (*N*-acetyltransferase), SULT (sulfotransferase). Cofactors: AcCoA (acetyl coenzyme A), PAPS (3′-phosphoadenosine-5′-phosphosulfate). Purine and pyrimidine nucleosides: **G** (guanosine), **A** (adenosine), **X** (xanthosine), **I** (inosine), **8-MeG** (8-methylguanosine), **8-BrG** (8-bromoguanosine), **d-G** (2′-deoxyguanosine), **d-C** (2′-deoxycytidine). Other abbreviations: lfp (laser flash photolysis), QSAR (quantitative structure–activity relationship), log *m* (log [(histidine revertants)/(nanomoles of amine)]), log *P* (log of the octanol/water partition coefficient), Clog *P* (calculated log *P*), MAAs (monocyclic arylamines).

B. Introductory Comments

In the second half of the 20th century two important and related classes of carcinogens, arylamines (AAs) and heterocyclic arylamines (HAAs, also called HCAs), became the focus of considerable research[1–15]. Rehn had made the first epidemiological studies of excess bladder cancers in workers in the aniline dye industry in 1895[16], but studies of the molecular basis of AA carcinogenicity date from the late 1950s and early 1960s[17, 18]. AAs are important intermediates in the chemical industry, so a considerable amount of the evidence for the classification of AAs such as 2-naphthylamine (**2-NA**), 4-aminobiphenyl (**4-ABP**) and benzidine (**BZ**) (Chart 1) as substances 'known to be human carcinogens' in the 11th Edition of the U.S. Department of Health and Human Services' *Report on Carcinogens* was based on epidemiological studies of workers in the chemical industry[5, 19, 20]. Occupational exposure to AAs in the chemical industry has largely been controlled in Europe and North America, but is still a significant problem in developing economies in South America and Asia[5, 10, 21]. Significant non-occupational exposure to AAs, particularly **4-ABP**, occurs from inhalation of cigarette smoke[22]. AAs have been demonstrated to cause cancers in the liver, bladder and several other organs in laboratory animals, and, unfortunately, in humans[1–10, 19].

Widmark first demonstrated that extracts of fried horse meat caused cancers when applied to mouse skin in 1939[23], but the identification of the active carcinogenic components of fried and broiled meats as HAAs occurred in the 1970s and 1980s as a result of the investigations of Sugimura and coworkers[11–14, 24]. Feeding studies in rats and mice demonstrated that HAAs cause cancers in the liver, large and small intestine, mammary gland and other tissues of these animals[14]. Sufficient evidence from animal studies now exists to classify the HAAs shown in Chart 2 (and about 10 other HAAs) as likely human carcinogens[9, 11–15]. Four of the compounds listed in Chart 2 (**IQ, MeIQ, MeIQx** and **PhIP**) are specifically listed as 'reasonably anticipated to be human carcinogens' by the *Report on Carcinogens*[20]. Because of their ubiquitous formation during high temperature cooking of meats and fish from the proteins, amino acids, creatine and sugars present in animal flesh, HAAs are now considered to be a significant cancer risk for most human populations[25, 26]. The reactions giving rise to the HAAs during cooking have been investigated and reviewed elsewhere, and will not be considered here[27]. In addition to their

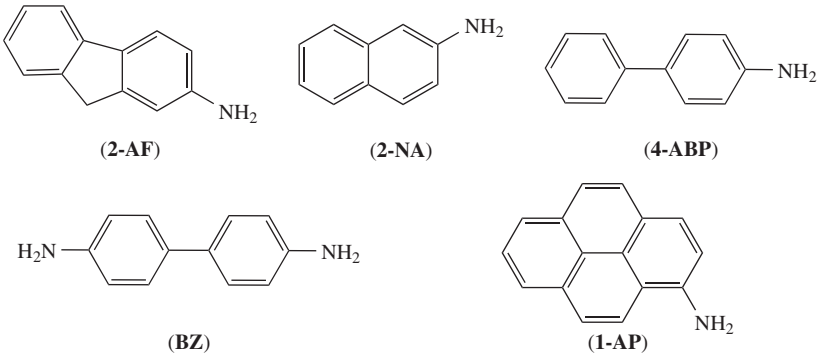


CHART 1. Selected carcinogenic arylamines (AAs)

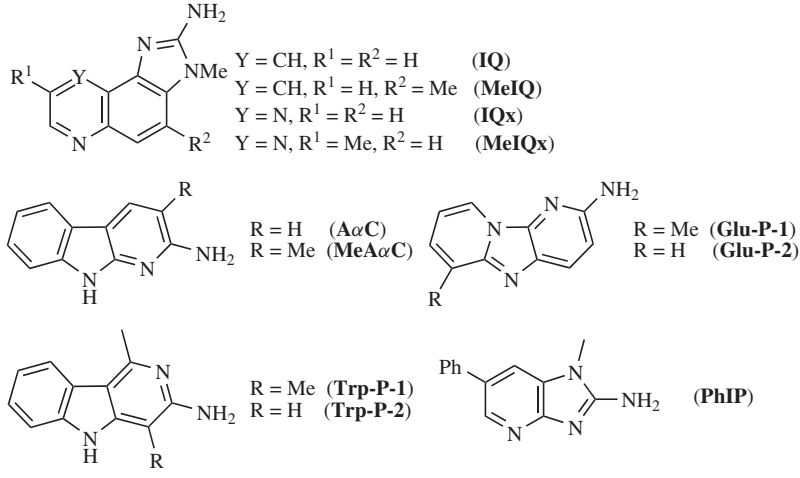


CHART 2. Selected carcinogenic heterocyclic arylamines (HAAs)

presence in cooked meats, HAAs have been detected in commercial food flavorings and sauces, beverages and tobacco smoke[27, 28].

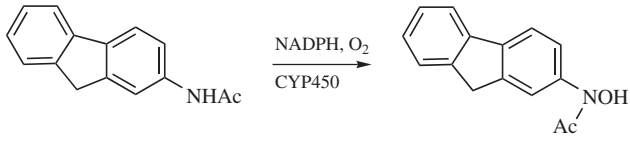
The AAs and HAAs shown in Charts 1 and 2 are properly classified as procarcinogens because they require metabolic activation[1–15]. The first step of the activation process is the oxidation of the exocyclic amino functionality into a hydroxylamine. Subsequent activation steps convert the hydroxyl group of the hydroxylamine into a good leaving group at physiological pH.

II. METABOLIC ACTIVATION OF AAs AND HAAs

A. Phase 1 Metabolism: *N*-Hydroxylation

Since AAs are not reactive with cellular constituents, it was assumed that metabolic activation was necessary to account for their carcinogenic properties[1]. Initial studies of the

metabolism of the hepatacarcinogen *N*-acetyl-2-aminofluorene (**2-AAF**) in rats detected ring hydroxylated products in the urine that are less carcinogenic than **2-AAF**[1, 17]. In 1960 a new metabolite, the hydroxamic acid **1** (equation 1), was detected in rat urine[18]. This metabolite was of particular interest since its excretion was reduced in the presence of 3-methylcholanthrene, an inhibitor of the carcinogenic activity of **2-AAF**[18]. This was the first observation of *N*-hydroxylation *in vivo*, and it proved to be an extremely important discovery. It was subsequently shown that the enzyme cytochrome P450 (CYP450) was responsible for the *N*-hydroxylation reaction[29], and the *N*-hydroxylation was shown to be a general reaction for a wider range of AA carcinogens including those shown in Chart 1[30]. The hydroxylamine derivatives are more carcinogenic at the site of application than are the corresponding amines, indicating that *N*-hydroxylation is responsible for the carcinogenic activation of AAs[1, 2]. Mutagenicity of AAs to *S. typhimurium* in the Ames test also requires the presence of mammalian liver preparations or purified CYP450 preparations[31]. The isomer of **2-NA**, 1-aminonaphthalene, **1-NA**, has not been shown to be carcinogenic in bioassays, and is not metabolized by mammalian CYP450, but its *N*-hydroxy derivative is carcinogenic at the point of application, demonstrating the importance of *N*-hydroxylation for carcinogenicity[3].



(**2-AAF**) (**1**) (1)

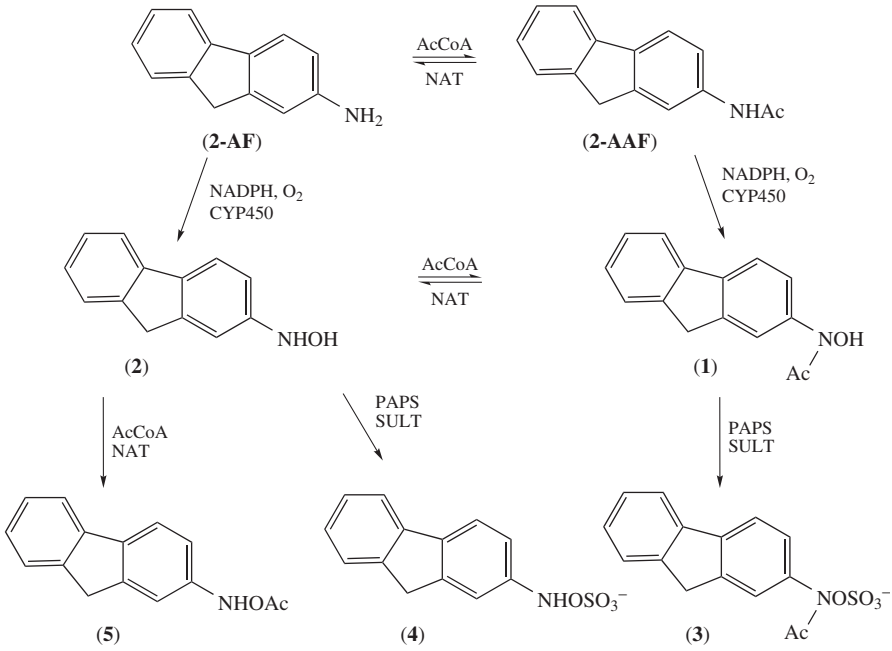
Initial mutagenesis studies of HAAs in *S. typhimurium* showed that these compounds were mutagenic only in the presence of mammalian liver homogenates or purified CYP450[25, 32]. Various purified CYP450 isozyme preparations showed markedly different levels of mutagenic activation of HAAs[32]. Levels of *N*-hydroxylation correlated with mutagenic activation under all experimental conditions[32]. It was apparent that *N*-hydroxylation was also a necessary step in the metabolic activation of HAAs[11–14, 25, 32].

Most AAs are preferentially *N*-hydroxylated by two isozymes of rat CYP450: 1A1 and 1A2[9, 33]. Since several isozymes of rat CYP450 (including 1A1 and 1A2) are also involved in detoxification of AAs through ring hydroxylation, and the activity of these isozymes for *N*-hydroxylation/ring hydroxylation is dependent on the individual AA, the balance between activation/detoxification varies considerably for each particular AA[9, 33, 34]. Studies with recombinant human CYP450 isozymes have generally concluded that human CYP4501A1 and 1A2 are the dominant activators of AAs and HAAs[9, 34–36].

Although *N*-hydroxylation is a necessary activation step for conversion of AAs and HAAs into carcinogens, the hydroxylamine metabolites are not the ultimate carcinogenic metabolites[1–3]. These materials are generally unreactive with DNA and other biological macromolecules under physiological conditions, although reaction with DNA does occur slowly for some of the hydroxylamines at pH $\leq$ 5[3, 37]. The hydroxylamine metabolites are proximate carcinogens that require further metabolic activation.

B. Phase 2 Metabolism: Esterification

The metabolic activation steps that have been established for **2-AF** and **2-AAF** are shown in Scheme 1[1–3, 38]. This scheme is oversimplified because detoxification pathways

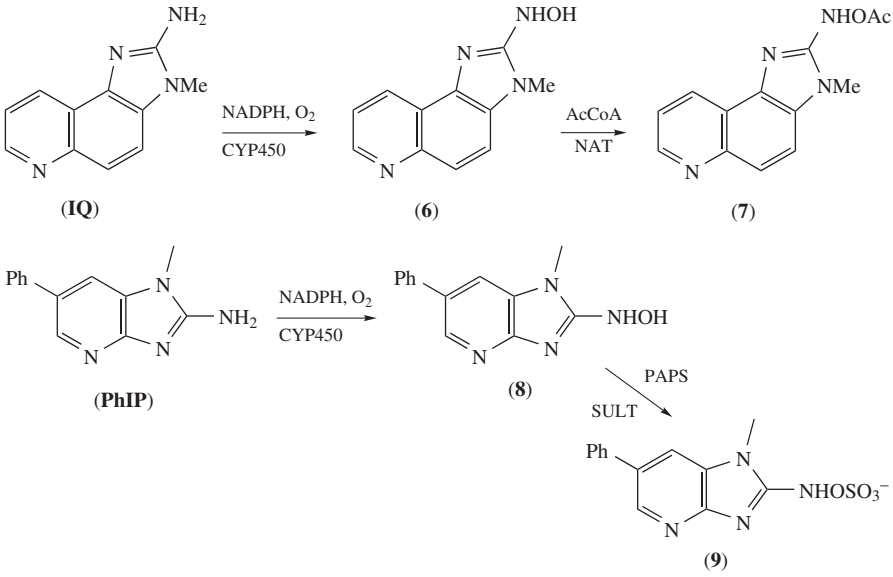


SCHEME 1. Simplified metabolic activation scheme for **2-AF** and **2-AAF**

and some minor activation pathways are not illustrated[9, 38]. The relative importance of these metabolic pathways is species specific[9, 38–43]. Evidence that in rats **3** is an ultimate carcinogen derived from sulfonation of **1** by 3′-phosphoadenosine-5′-phosphosulfate (PAPS) catalyzed by a sulfotransferase (SULT) was discovered first[39–41]. Since **3** is a highly reactive compound that cannot be isolated from biological samples, evidence for its formation was indirect, and was based on the effect of added sulfate ion on the formation of fluorenyl adducts with protein, RNA, and DNA in livers of rats dosed with **1**[39, 40], and on the effect of added sulfate on the carcinogenicity of **1** in rats treated with the hepatacarcinogen inhibitor acetanilide[41].

Subsequently, it was concluded that **4** is an important ultimate carcinogen in mice[42], and that **5** is generated from metabolism of both **2-AF** and **2-AAF** in rats and humans[43]. Since **4** and **5** are highly reactive materials that could not be isolated from *in vivo* experiments, the evidence for their formation was based on inhibition studies of the enzyme systems expected to generate them during metabolism, and on the structure of isolated products from their reactions with DNA[42, 43]. In addition to the AcCoA-dependent generation of **5** from **2**, catalyzed by a *N*-acetyltransferase (NAT), **1** can be isomerized into **5** in a reaction catalyzed by NAT that does not require AcCoA (not shown in Scheme 1)[43]. Other carcinogenic AAs appear to be metabolized via similar pathways[1–3, 9, 38, 42–44].

Metabolism of HAAs into their ultimate carcinogenic form follows similar pathways[45, 46]. Early studies indicated that SULT inhibitors do not decrease the mutagenicity of **IQ**, and that the synthetic acetic acid ester, **7** (Scheme 2), generated



SCHEME 2. Metabolic activation of **IQ** and **PhIP**

in situ reacts with DNA to form the same products as detected from *in vivo* studies[47, 48]. A subsequent study of the activation of *N*-hydroxy-**IQ**, **6**, and *N*-hydroxy-**PhIP**, **8**, in liver, kidney, colon and heart tissue of monkeys and rats showed that AcCoA enhances the binding of **IQ** derivatives to DNA in all tissues of both species, while PAPS is ineffective at enhancing the binding of **IQ** derivatives to DNA[49]. In contrast, PAPS significantly increases the binding of **PhIP** derivatives to DNA, particularly in monkey tissues[49]. This suggested that the major activation pathways for **6** and **8** diverge with an AcCoA-dependent NAT responsible for activation of **6** to **7** and a PAPS-dependent SULT responsible for activation of **8** to **9** (Scheme 2)[49]. Subsequent studies with recombinant human NAT and SULT enzymes in *S. typhimurium* confirmed that **6** is specifically activated by NAT and **8** by SULT[50].

There are two human *N*-acetyltransferase isozymes, NAT1 and NAT2, with overlapping, but distinct, substrate specificity[7, 45]. NAT1 is distributed ubiquitously throughout the body, while NAT2 is most highly expressed in the liver and intestine[45]. Both enzymes are highly polymorphic with at least 25 known alleles of the *NAT1* genome and over 50 alleles of the *NAT2* genome (following standard practice, the genome is italicized, the enzyme is in regular type face)[51, 52]. The allelozymes of each isozyme exhibit considerable differences in the rates at which they acetylate standard substrates[51, 52]. Both AAs and their hydroxylamine metabolites are substrates of NAT1 and NAT2 with the hydroxylamines undergoing *O*-acetylation[53–57]. The *N*-acetylation of an AA into the corresponding amide is generally considered to be a detoxification process since the amide is a poorer substrate for CYP450-catalyzed hydroxylation than the parent amine, but the *O*-acetylation of the hydroxylamine is an activation process for carcinogenicity[7, 51, 52]. The individual NAT2 allelozymes exhibit considerable differences in the efficiency at

which they *N*-acetylate **2-AF** (*ca* 200-fold difference) and *O*-acetylate *N*-hydroxy-**2-AF**, **2** (*ca* 30-fold difference)[52, 55, 56]. The *N*-acetyltranferase and *O*-acetyltransferase activities correlated strongly with each other ($r^2 = 0.88$)[56].

Attempts have been made to correlate cancer incidence in human populations with NAT2 phenotype characterized by the 'rapid' or 'slow' acetylator status of individuals[7, 52]. Except for smoking associated urinary bladder cancer, these epidemiological studies have not been able to find consistent correlations between cancer incidence and acetylator status[52]. One of the problems with these epidemiological studies has been that most of these studies used NAT2 phenotypes inferred from genotyping results, and the validity of the conclusions may be compromised by the uncertainty of NAT2 phenotype–genotype correlations[52]. The NAT2 phenotype is not simply a direct result of the activity of the allelozyme that is the product of gene transcription. It is also affected by protein stability, gene transcription rates and environmental factors[52]. In the case that does appear to have a well-established correlation, high risk of urinary bladder cancer is associated with a 'slow' NAT2 acetylator status[58]. This is presumably caused by inefficient detoxification of procarcinogenic AAs in the liver by NAT2 catalyzed *N*-acetylation in individuals with a 'slow' acetylator phenotype[58]. A recent study of **4-ABP** activation and resulting DNA adduct levels in Chinese hamster ovary cells transfected with a human *CYP4501A1* gene and one of three human *NAT2* alleles (one associated with a 'rapid' phenotype and the other two associated with 'slow' phenotypes of differing activity) suggested that more careful phenotyping/genotyping could lead to more precise correlations of disease with NAT2 phenotype[59].

HAAs (**IQ**, **MeIQx**, **Glu-P-1** and **PhIP**) are generally not as good substrates for *N*-acetylation by NAT1 or NAT2 as are AAs such as **2-AF** or **4-ABP**[53, 54]. It also appears that in most cases *N*-hydroxy-HAAs are poorly *O*-acetylated by NAT1[50, ,53–55]. However, NAT2 does effectively *O*-acetylate *N*-hydroxy-HAAs, although at lower rates than *N*-hydroxy-AAs[50, 53–55]. NAT2 catalyzed *O*-acetylation of **6** is *ca* 100-fold more effective than *O*-acetylation of **8**, while activation of **8** by SULT1A1 is *ca* 100-fold more effective than SULT1A1 activation of **6**[50]. As mentioned above, this is consistent with other evidence (see Scheme 2) that **6** is predominately activated into the acetic acid ester **7**, while **8** is predominately activated into the sulfuric acid ester **9**[49]. Preliminary studies showed that there are differences in the effectiveness of activation of *N*-hydroxy-HAAs such as **6** by the allelozymes of NAT2, but only over a range of about 3-fold compared to a 30-fold range for an *N*-hydroxy-AA such as **2**[55].

Epidemiological studies of NAT2 phenotype effects on colorectal cancer associated with red meat intake have been inconclusive to date[60]. Recent studies of **MeIQx**, **AαC** and **PhIP** activation and resulting DNA adduct levels in Chinese hamster ovary cells transfected with a human *CYP4501A1* gene and one of two human *NAT2* alleles (associated with a 'rapid' and a 'slow' acetylator phenotype) have shown a large increase in DNA adduct levels for the cells transfected with the 'rapid' acetylator *NAT2* compared to the 'slow' acetylator *NAT2* for both **MeIQx** and **AαC**[61]. For **PhIP**, the difference in DNA adduct levels was very small for the two *NAT2* alleles[62]. These results appear to be consistent with the finding that the major activation route for **PhIP** involves *O*-sulfonation, not *O*-acetylation[49, 50].

The involvement of sulfotransferases (SULTs) in the activation of AAs has been known for quite some time[39–41, 43, 44]. Early studies showed that cytosolic SULTs were involved in the activation, but initial characterization did not proceed much beyond that level[44]. Human cytosolic SULTs are a super family of enzymes that are grouped into four families: SULT1, SULT2, SULT4 and SULT6[63]. The SULT1 family has received the most attention

in studies of the metabolism of AAs and HAAs[64–66]. Nine genes have been discovered in the *SULT1* family. These have been categorized into four subfamilies: *1A1–1A4*, *1B1*, *1C1–1C3* and *1E1*[63]. Since *SULT1A3* and *1A4* code for the same protein, only eight human SULT1 enzymes have been characterized[63]. The SULT1A enzymes have received the most attention as activators of *N*-hydroxy-AAs and *N*-hydroxy-HAAs[64–66]. SULT1A1 is the major SULT present in human liver[63]. It is also found in the brain, gastrointestinal tract, platelets and placenta[63].

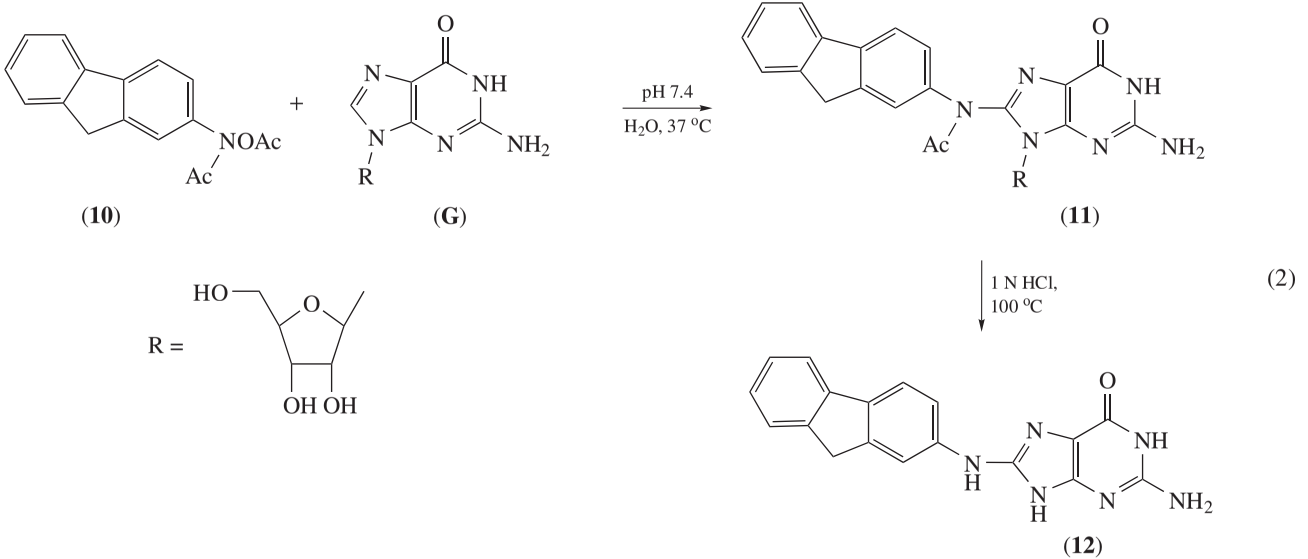
Initial studies of the activation of **1**, **2**, **8** and several other *N*-hydroxy-AAs and *N*-hydroxy-HAAs in human liver cytosol indicated that activation correlated with a thermostable phenol sulfotranferase activity (TS-PST) that is now associated with SULT1A1 and 1A2[44, 64]. Not all hydroxylamines studied were activated by SULTs; in particular, **6** and the closely related *N*-hydroxy-**MeIQx** were not activated in this study[44]. Subsequent studies with recombinant human SULTs showed that **8** was activated by SULT1A1 and 1A2[50, 67]. On the basis of inhibition studies SULT1A1 was identified as the isozyme responsible for activation of *N*-hydroxy-**Aαc** in human liver cytosol[68]. Studies with recombinant NAT1 and NAT2 showed that both of these enzymes also activated *N*-hydroxy-**Aαc**[68]. A study of the activation of **MeAαC** in Chinese hamster V-79 cells transfected with *CYP1A2* and *SULT1A1* or *NAT1* or *NAT2* showed that activation could only be detected in the cells transfected with the *SULT1A1* gene[69]. In *S. typhimurium* transfected with various human genes, *N*-hydroxy-**MeAαC** mutagenesis was markedly enhanced in cells transfected with *SULT1A1*, and moderately enhanced in cells transfected with *SULT1A2*, *SULT1B1*, *SULT1C2* or *NAT2*[69]. The SULTs also play a role in detoxification of some HAAs, particularly **IQ** and **MeIQx**, by *N*-sulfonation[70].

The *SULT1A1* genome is polymorphic, and there have been some studies of the effect of the polymorphism on carcinogen metabolism and cancer risk[65]. The two most common alleles, *SULT1A1*1* and *SULT1A1*2*, are widely distributed among all racial groups examined. Individuals homozygous for *SULT1A1*2* have only about 15% of the phenol sulfotransferase activity in platelets compared to individuals with other genotypes[65]. A substantial decrease in DNA binding of **8** and *N*-hydroxy-**ABP** has been observed in individuals homozygous for *SULT1A1*2*[71]. Epidemiological studies have suggested that both the activation and detoxification roles of SULT1A1 may play a role in mediating breast cancer and colorectal cancer risk[65].

III. THE STRUCTURES OF DNA ADDUCTS

A. Adducts from 2-AAF and 2-AF

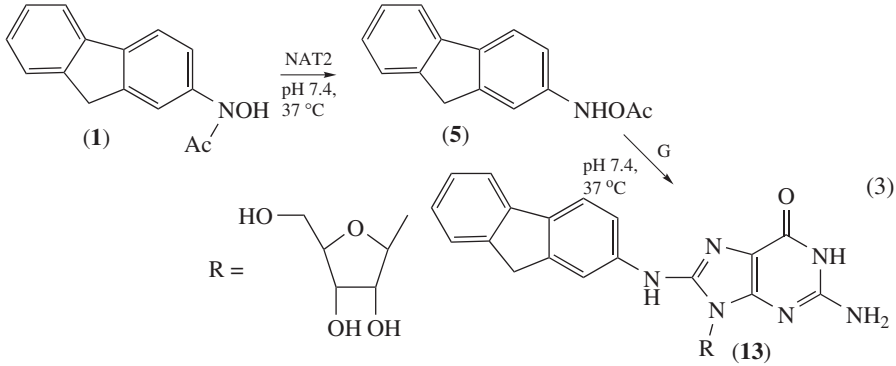
Metabolites of carcinogenic AAs and HAAs have been shown to react with DNA, RNA, proteins and smaller biologically relevant nucleophiles, but because of their status as carcinogens most attention has been paid to their reactions with DNA[1–4, 6–10]. The initial investigations of the reactions of AA carcinogens with DNA and monomeric DNA bases occurred with derivatives of hepatacarcinogenic **2-AF** and **2-AAF**. The reactions discovered were representative of those found later for derivatives of other AAs and HAAs[3]. The initial characterization of an adduct occurred in 1967, when it was shown that the synthetic ester **10** reacted with guanosine (**G**) in aqueous solution at pH 7.4 and 37 °C to generate the guanosine C-8 adduct **11**, which underwent hydrolysis in 1N HCl at 100 °C for 45 min to generate the deacetylated guanine adduct **12** (equation 2)[72]. Reaction of **10** with 2′-deoxyguanosine-5′-phosphate, RNA and DNA also produced adducts that underwent acid hydrolysis to generate **12**[72].



(**10**) (**G**) (**11**) (**12**)

(2)

Treatment of **1** with a soluble rat liver enzyme preparation in the presence of **G** and PAPS also generated **11**, presumably via formation of **3** (Scheme 1) and its subsequent reaction with **G**[73]. The same reaction mixture, in the absence of PAPS, led to the deacetylated guanosine adduct, **13** (equation 3)[73]. It was not known at the time that the rat liver preparation contained NAT2 which catalyzes the isomerization of **1** into **5**, and that **5** would then react with **G** to form **13** (equation 3)[43]. The presence of NAT2 in these preparations was subsequently verified[74].



(3)

It was later demonstrated that authentic **3** reacts with 2′-deoxyguanosine (**d-G**) to form the 2′-deoxy analogue of **11**, adduct **14** (shown in Chart 3)[75]. The formation of **15** (shown in Chart 3) in aqueous solution from authentic **5** and **d-G** was also verified[76]. Reaction of the derivatives of **2-AF** or **2-AAF** with bases other than **G, d-G** or the guanosine moiety in RNA or DNA could not be detected[72, 73, 75, 76]. Although the hydroxamic acid **1** is inert to DNA, RNA, **d-G** or **G**, the hydroxylamine **2** does exhibit a slow and inefficient reaction with these species at pH 7.4[73]. This reaction becomes more rapid under acidic conditions[3, 37].

Treatment of rats with **2-AAF** led to isolation of three major adducts, **14–16** (Chart 3), after hydrolysis of rat liver DNA[77–79]. The acetylated and deacetylated C-8 adducts **14** and **15** had been previously detected in other experiments, but the N^2 adduct **16**, in which a bond has been formed between C-3 of the carcinogen and the exocyclic amino group

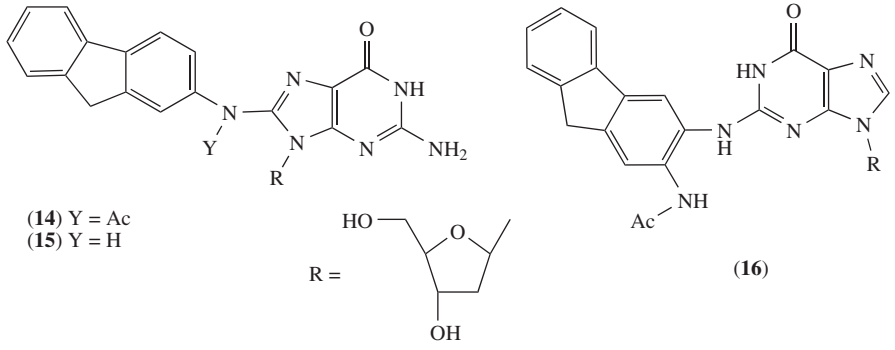


CHART 3. DNA adducts from reaction of **2-AF** or **2-AAF** derivatives *in vivo*

of **d-G**, was unique[79]. This product is not formed from reaction of **3** or **10** with **d-G** in predominately aqueous solution, but it can be formed from the reaction of **3** with **d-G** in DMSO-Et_3N[79]. The new adduct was detected as a minor product (*ca* 16%) of the reaction of **10** with native DNA, but denatured DNA yielded only **14**[80].

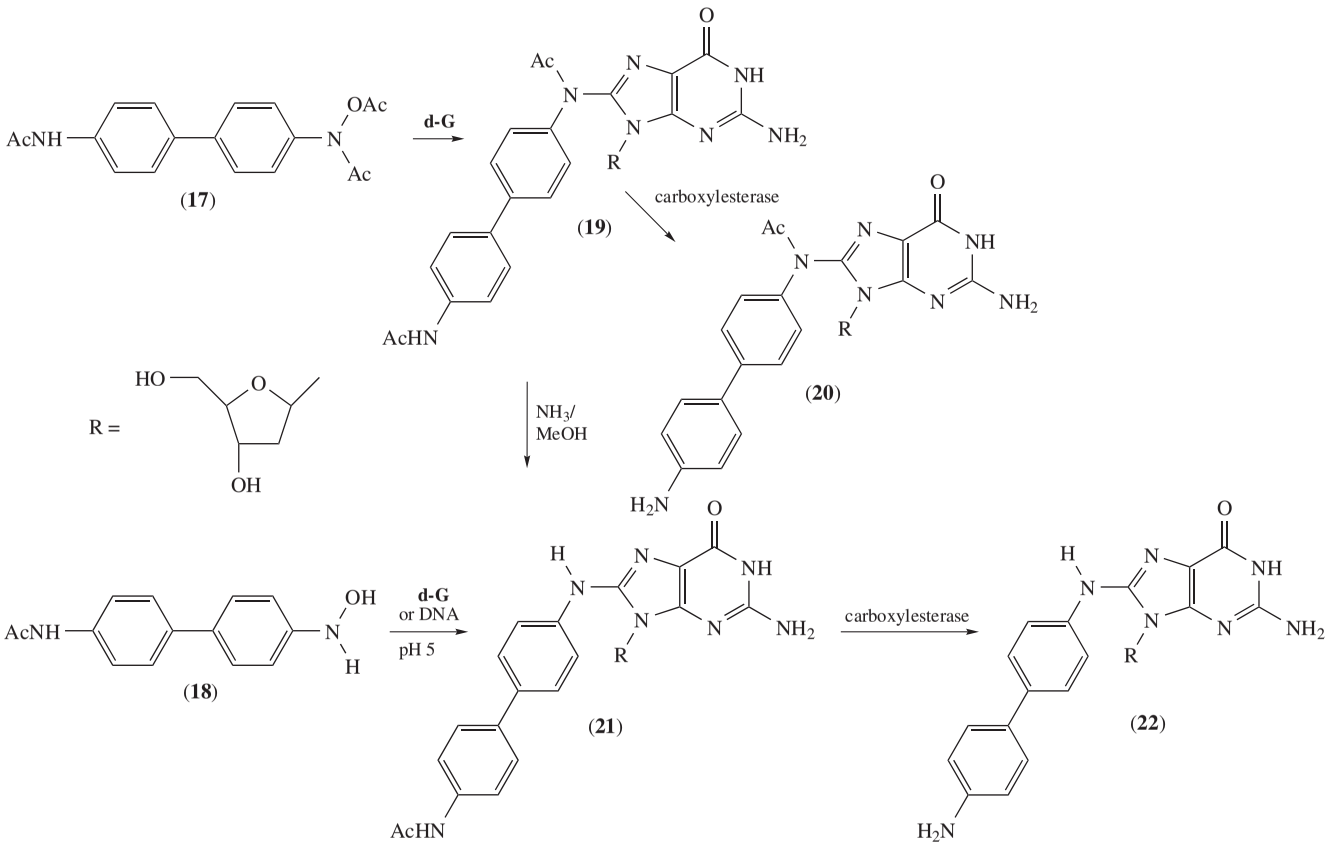
In an experiment meant to sort out the roles of the various metabolic paths, rats were pretreated with pentachlorophenol, a specific inhibitor of SULT, before administration of **1**[81]. Four hours after dosing, the animals were sacrificed and hepatic DNA was isolated. In control experiments **14** and **16** accounted for 40% of the total binding to DNA. The deacetylated adduct **15** accounted for the rest of the binding. In rats pretreated with pentachlorophenol, the same three adducts were found, but total DNA binding decreased by 26%. The adducts **14** and **16** accounted for only 13% of the total, while **15** accounted for 87% of total binding, and the amount of that adduct was not reduced compared to the control. This indicates that at least 70% of the acetylated adducts **14** and **16** in rat liver DNA, *in vivo*, is formed from **3** generated by the action of SULT on **1**[81]. The deacetylated adduct **15** is formed via a process that does not involve a SULT, presumably by a NAT2-dependent path that generates **5**.

In single-dose experiments involving **1** on male Sprague-Dawley rats, **14** accounts for about 15% of initial binding to DNA, while **15** accounts for about 80% and **16** for about 5%[77, 78]. The adduct **14** is excised with a half-life of about 7 days, while the other two adducts persist for extended periods[78, 82]. Similar results were found for these three adducts in rat liver cell cultures[83]. In a multiple-dose experiment, Sprague-Dawley rats were dosed at 14-day intervals for up to four times and DNA adducts formed in the liver and kidney were assayed either 1 or 14 days after the last dose[84]. In male rat liver, the C-8 acetylated adduct **14** was only detected on the first day after dosing, and it did not accumulate with time. Both **15** and **16** could be detected at day 1 and day 14 after the last dose, and their levels built up over time. In female rat liver, and in kidney from both sexes, only **16** was detected. It was found at both day 1 and day 14 after the last dose, and its level increased with time. These results show significant differences in metabolism of a single carcinogen related to sex and tissue type[84]. These differences are particularly intriguing because female Sprague-Dawley rats are resistant to **2-AAF** induced liver cancer, presumably because of their known lower sulfotransferase activity, and rat kidney is not a significant target for **2-AAF** induced cancers[84]. Generation and persistence of DNA adducts is not sufficient, by itself, to produce cancer. The type of adduct clearly plays a role, and genetic factors also appear to be important. Although the relationship between DNA adduct formation and cancer onset is complicated by a significant number of factors, the relationship between adduct formation and bacterial mutagenicity is much more straightforward. Treatment of *S. typhimurium* with **1** in the presence of rat liver homogenate supernatant S9 led to formation of the adduct **15**[85]. Smaller levels of the same adduct (*ca* 10% of that in the presence of S9) were formed in the absence of the rat liver homogenate. The log (revertants) correlated strongly with log (DNA adduct concentration) with $r^2 = 0.85$[85].

B. Adducts of Other AAs and HAAs

BZ is a urinary bladder carcinogen in humans and dogs, and a hepatacarcinogen in rats, mice and hamsters[3]. Four different **d-G** C-8 adducts were synthesized from potential metabolites of **BZ, 17** and **18**, for comparison to adducts generated *in vivo* (Scheme 3)[86]. These adducts are the *N*,*N*′-diacetyl C-8 adduct, **19**, the *N*-acetyl C-8 adduct, **20**, the *N*′-acetyl C-8 adduct, **21**, and the deacetylated adduct, **22**[86].

Administration of **BZ** to mice led to one detectable adduct in hepatic DNA, **21**, identified by comparison to authentic **21** after hydrolysis of the DNA[86]. Injection of



SCHEME 3. Synthesis of **BZ-d-G** adducts

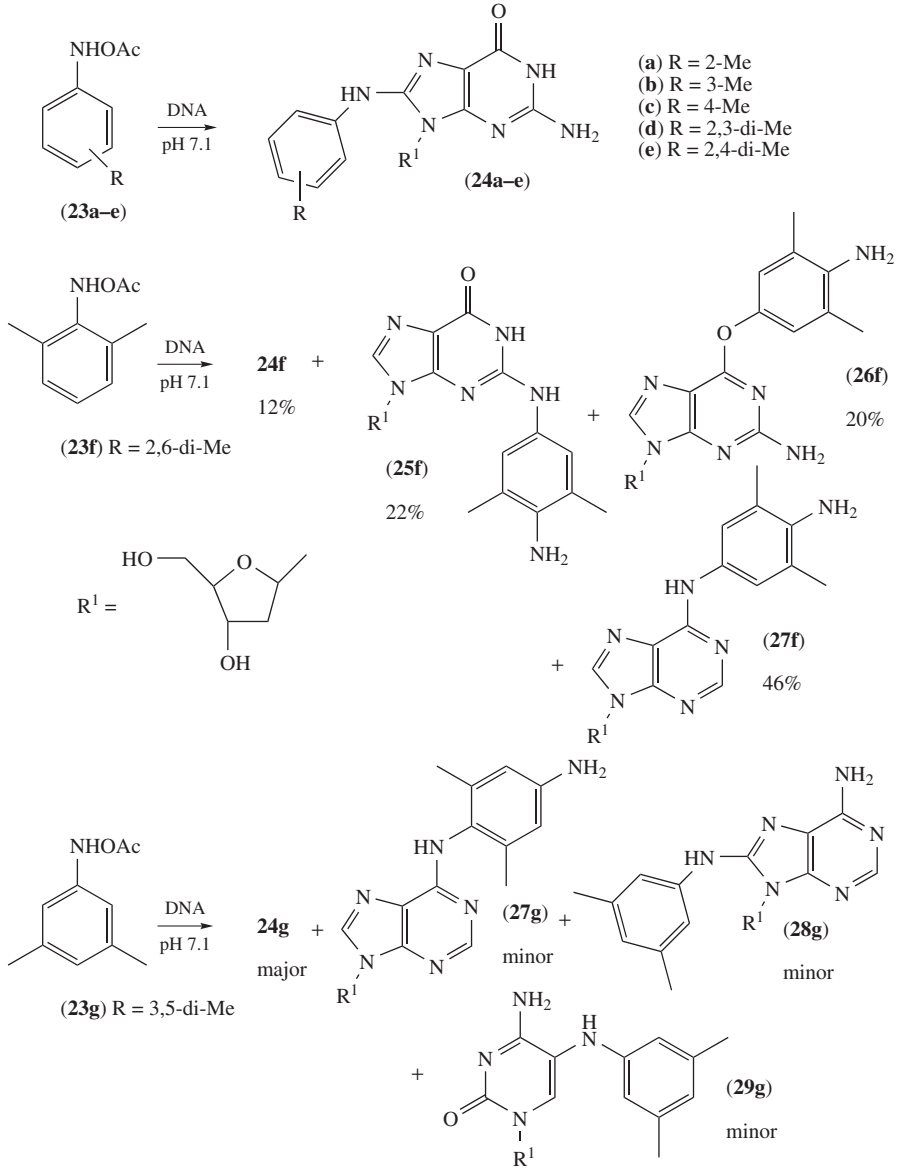
radio-labeled *N*-acetyl-**BZ**, **BZ** and *N*,*N*′-diacetyl-**BZ** into tails of rats led, after 24 h, to greatest incorporation of radioactivity in hepatic DNA for rats treated with *N*-acetyl-**BZ**, less incorporation for **BZ** treated rats and no detectable radioactivity in the hepatic DNA of rats treated with *N*,*N*′-diacetyl-**BZ**[86]. The major adduct detected in rats was also **21**. The presumed proximal metabolite of *N*-acetyl-**BZ**, **18**, was shown to react with DNA under mildly acidic conditions. Closer examination of DNA-binding in rat and hamster liver after treatment with *N*-acetyl-**BZ** and *N*,*N*′-diacetyl-**BZ** showed that **21** was the only adduct detected when *N*-acetyl-**BZ** was utilized[87]. Treatment of rats with *N*,*N*′-diacetyl-**BZ** led to very little DNA binding. The major adduct was still **21**, but a small amount of **19** was also detected[87]. Dogs are deficient in *N*-acetylase activity, and it appears that **22** may be the major adduct generated in the urinary bladder of dogs[3, 88]. **BZ** is not a substrate of CYP450, but it is oxidized by peroxidase to benzidine diimine that appears to react with DNA to generate **22**[88, 89]. The adduct **20** has not been reported in any *in vivo* experiments[87–90].

In humans the origin of **BZ**-induced bladder cancer is different[90]. The *N*′-acetylated adduct **21** is the major DNA adduct detected in peripheral white blood cells and exfoliated urothelial cells obtained from workers exposed to **BZ**[90]. This is the same major adduct found in mouse, hamster and rat liver[86, 87, 90]. Metabolism likely occurs via an initial acetylation to *N*-acetyl-**BZ**, a major human metabolite of **BZ**[91], followed by CYP450-mediated *N*-hydroxylation of *N*-acetyl-**BZ** to form **18**, and esterification of **18** to form the ultimate carcinogen that reacts with DNA[92], but the metabolism of **BZ** is very complicated and differs considerably from species to species and tissue to tissue, so alternative activation processes may occur[92–94].

The pattern of predominant reaction with **d-G** residues within DNA and predominant formation of C-8 adducts continues for the metabolites of other polycyclic carcinogenic AAs including **2-NA** and **4-ABP**[3, 95–97]. The reactions of monocyclic analogues of **5** with **d-G** are somewhat less predictable[98–100]. The *O*-acetoxyaniline derivatives **23a–e** (Scheme 4) react inefficiently with **d-G** to yield C-8 adducts **24a–e**, and **d-G** residues within DNA appear to be their main targets[98]. The *N*-acetoxy-2,6-dimethylaniline, **23f**, and *N*-acetoxy-3,5-dimethylaniline, **23g**, generate a much wider variety of products, including significant adducts with **d-G** (**24f**–**26f**, **24g**), 2′-deoxyadenosine, **d-A** (**27f**, **27g**, **28g**) and 2′-deoxycytidine, **d-C** (**29g**)[99, 100]. These studies are of interest because the monocyclic amines are found in tobacco smoke and as industrial pollutants, and recent evidence suggests that they may be involved in the development of some cancers[98–100].

Adducts of HAAs with DNA and DNA bases have been extensively investigated since 1979[101–124]. In general, formation of adducts requires activation of the HAAs to *N*-hydroxy-HAAs followed by esterification to produce materials that are reactive at neutral pH, although some *N*-hydroxy-HAAs are weakly reactive with DNA under mildly acidic conditions[102]. As was the case with AAs, the major target in experiments with monomeric nucleosides and DNA is **d-G**[101, 102]. This is also observed *in vivo*[101, 102]. The major adducts in all cases that have been examined are C-8 adducts, but other structures have been identified in a few cases[101, 102].

Some adducts that have been identified are gathered in Chart 4. Adducts of **Glu-P-1** (**30**) and **Trp-P-2** (**31**) were the first to be identified in 1979[103, 104]. These materials were isolated from DNA treated with **Glu-P-1** or **Trp-P-2** in the presence of rat liver microsomes[103, 104]. The acetic acid esters of both *N*-hydroxy-**Glu-P-1** and *N*-hydroxy-**Trp-P-2** were shown to react with DNA to generate the same two products[105, 106]. Both **30** and **31** were identified as the major DNA adducts obtained from the livers of rats fed the corresponding HAA[107]. The C-8 adducts **32a** and **32b** were obtained from rat liver in *in vitro* and *in vivo* experiments[108, 109]. Both adducts were also synthesized from the reactions of *N*-acetoxy-**Aαc** and *N*-acetoxy-**MeAαC** with DNA[110].



SCHEME 4. DNA adducts from monocyclic *N*-acetoxyarylamines

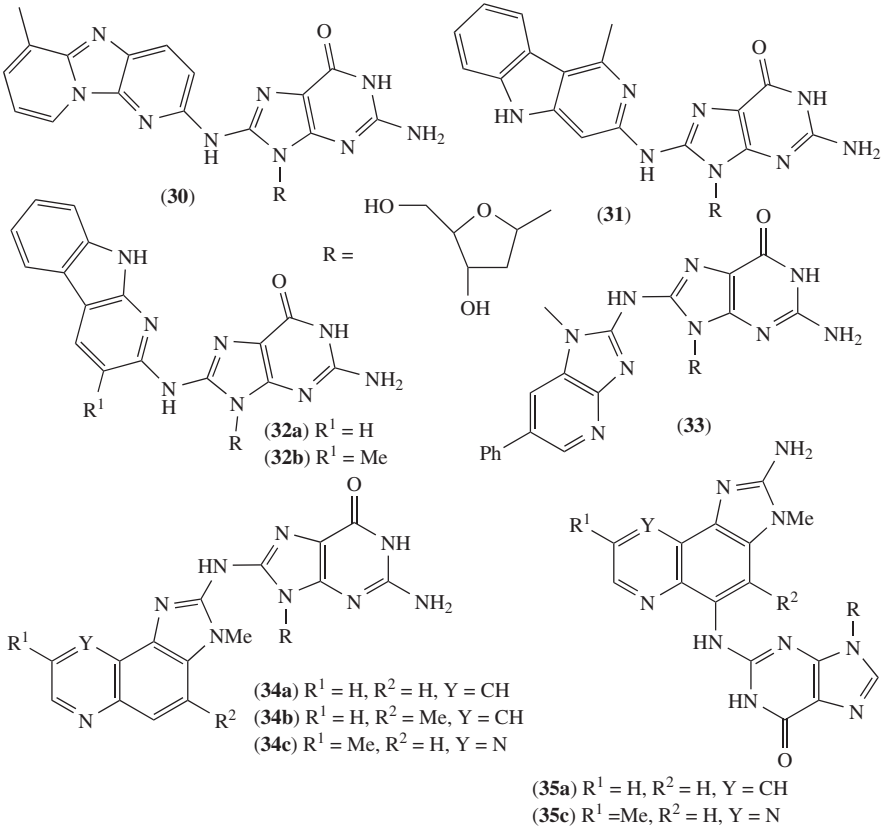


CHART 4. DNA adducts of HAAs

PhIP, **IQ**, **MeIQ**, **IQx**, **MeIQx** and related amines belong to a subclass of the HAAs identified as aminoimidazoazarenes (AIA), or IQ-type HAAs[12, 101]. They have obvious structural similarities and are thought to be produced in cooked meats in similar reactions that require creatine[12, 101]. Compared to other HAAs, they tend to have high mutagenicity to *S. typhimurium* in the Ames Test, and many of them have been shown to be significantly carcinogenic in laboratory animals[12–14, 101]. All four of the individual HAAs listed as 'reasonably anticipated to be human carcinogens' by the *Report on Carcinogens*[20] are in this subclass.

In 1992, *N*-acetoxy-**PhIP** was shown to react significantly only with **d-G** of the four nucleosides present in DNA, and the only adduct detected was the C-8 adduct **33**[111]. In short order, it was also shown that the ester reacted with DNA[112, 113], and that the same adduct could be detected in DNA isolated from colon, pancreas, lung, heart and liver of rats treated with **PhIP**[113]. This same adduct has been detected in exfoliated ductal epithelial cells in human breast milk[114].

The C-8 adducts of **IQ, MeIQ** and **MeIQx** (**34a–c**) were synthesized by reaction of the *in situ* generated acetic acid ester of the *N*-hydroxy-HAA with **d-G** or DNA[115–117], and all of the C-8 adducts were detected from *in vivo* experiments in rats (**IQ**[118], **MeIQx**[117]), mice

(**IQ**[119], **MeIQ**[116]) or monkeys (**IQ**[118–120], **MeIQx**[120]). Shortly after the C-8 adducts of **IQ** and **MeIQx** were discovered, the minor adducts **35a**,**c** were found from the reaction of the *N*-acetoxy derivatives of **IQ** and **MeIQx** with **d-G** and DNA[121]. These adducts accounted for 10–15% of the reaction with **d-G**, and with DNA. These adducts are reminiscent of the N^2 adduct **16** previously discovered for **2-AAF**[79]. The minor **IQ** adduct **35a** was discovered along with the major C-8 adduct **34a** in various tissues of rats and monkeys that were administered single or multiple doses of **IQ**[122–124]. In both species the level of DNA binding was greatest in the liver, but could be detected in all tissues examined[123, 124]. In all tissues, **35a** was initially the minor adduct (*ca* 15–20% of adducts), but in chronically treated monkeys, **35a** became the major adduct in slowly dividing tissues (heart, kidney, pancreas) in which the total DNA binding increased by 40–90-fold compared to animals given a single dose[124]. The proportion of **35a** also increased in liver where the total DNA binding only increased by 4–10-fold during the study[124]. There was no preferential accumulation of **35a** in the colon, a tissue with a high rate of cell division[124]. The results indicated that the C-8 adduct **34a** was preferentially excised, but both adducts accumulated in slowly dividing tissues of chronically treated animals[124].

C. Studies of Adduct Conformations in DNA

Extensive mutagenicity studies with **2-AF** and **2-AAF** have shown that the acetylated C-8 adduct **14** largely causes frameshift mutations, while the deacetylated C-8 adduct **15** leads predominately to point mutations, usually **G•C** → **T•A**[38, 125, 126]. However, both types of mutations are caused by each adduct in a sequence specific manner[125, 126]. The **2-AAF** adduct **14** acts as a strong block to DNA polymerases, while the **2-AF** adduct **15** usually does not prevent DNA synthesis, although this is also highly dependent on the sequence[126–128]. As discussed earlier, **14** is usually excised rapidly, while **15** is resistant to excision[78, 82–84]. The conformations of these two adducts and other AA adducts within DNA have been studied extensively in an effort to understand their differing effects on mutation, DNA synthesis and excision[8, 129]. NMR data and conformational analysis agree that the **2-AAF** adduct **14** in DNA takes on a major conformation (≥70% of conformer populations) in which the modified guanine adopts a *syn* conformation with respect to the sugar instead of the normal *anti* conformation[130, 131]. The fluorene moiety is intercolated into the helix, and the overall structure is highly perturbed in the neighborhood of the lesion. There is conformational mobility in the adduct, but it is mostly associated with *cis*/*trans* equilibration of the *N*-acetyl group[130, 131]. The **2-AF** adduct **15** exhibits considerably more conformational heterogeneity[132]. Two major conformations that are in slow equilibrium with each other have been detected by NMR studies: a structure in which the modified guanine adopts a normal *anti* conformation with all base pairs intact and the fluorene positioned in the major groove of a relatively unperturbed B-DNA helix, and a second structure in which the modified guanine is displaced from its normal conformation into a *syn* conformation and the fluorene is inserted into the helix[132]. The relative proportion of the two major conformers is dependent on the base sequence in the neighborhood of the lesion with the base displaced conformer accounting for 10% to 70% in various sequences[132]. A series of NMR and conformational analysis studies established that the surface area of the planar arylamine is also important in determining the position of equilibrium[133, 134]. The proportion of the base displaced structure in the adduct increased in the order: aniline (**36**) ∼ **4-ABP**(**37**) < **2-AF**(**15**) ≤ **PhIP**(**33**) < **1-AP**(**38**) (see Charts 3 and 5 for structures). The two examples of a **1-AP** adduct **38** incorporated into an oligomer that have been examined appear to be entirely in the base displaced conformation[134]. The

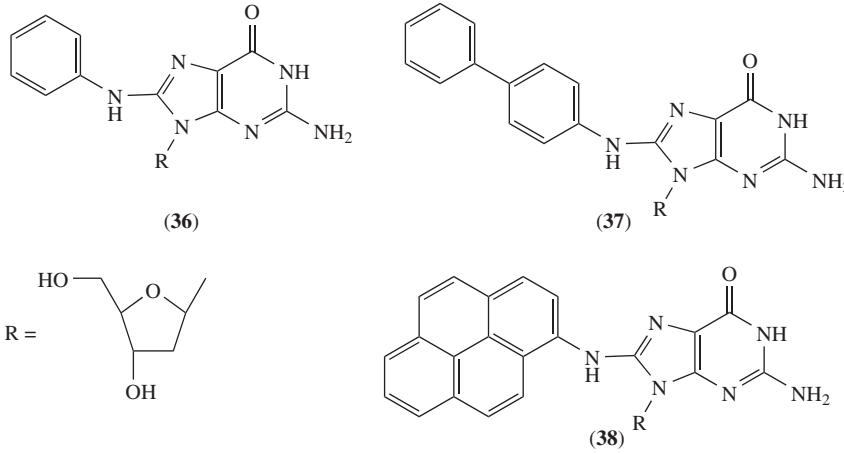


CHART 5. Some additional C-8 adducts of AAs

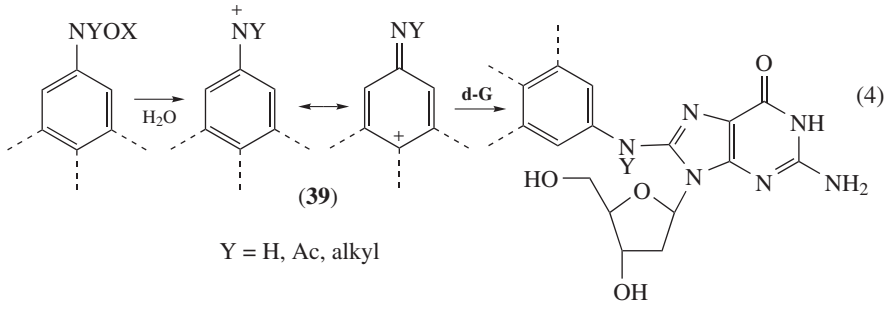
conformation of the **IQ** adduct **34a** has recently been investigated in three oligomers in which each of the guanine sites in the *Nar*I mutational hotspot (5′-CTCG1G2CG3CCATC-3′) were modified in turn by the C-8 **IQ** adduct[135]. The corresponding **2-AF**-modified oligomers had *ca* 30% (G1), 10% (G2) and 50% (G3) of the base displaced *syn* conformer, with the intact base pair *anti* conformation making up the rest of the conformation[132]. The **IQ**-modified oligomers are all apparently in the *syn* conformation, but the G1- and G2-modified oligomers have the **IQ** moiety in the minor groove of the helix, and the G3-modified oligomer has the **IQ** intercolated into the helix[135].

These structures have been used to rationalize the tendency of many **2-AF** adducts, and other adducts with similar base pair intact *anti* conformations, to generate point mutations and not to block DNA synthesis, while the **2-AAF** adducts, and related base displaced *syn* conformers with highly distorted structures, cause frameshift mutations, and tend to block DNA synthesis[8, 129]. Models for the frameshift mutations have been developed based on NMR derived solution structures of oligomers with the frameshift incorporated into the structure, and X-ray crystal structures of polymerases complexed with carcinogen-modified oligomers[8, 129, 136, 137].

There has been speculation about the role of minor N^2 adducts such as **16** and **35a**,**c** in the carcinogenicity of the AAs and HAAs that give rise to these adducts[77–84, 121–124]. Because these are minor adducts, that could not be generated in good yield by the reaction of ester derivatives of *N*-hydroxy-AAs or *N*-hydroxy-HAAs with DNA or **d-G**, detailed studies of the conformations of such adducts in DNA or their interactions with polymerases had not been performed. Recently, a palladium cross-coupling reaction has been utilized for efficient synthesis of monomeric C-8 adducts of **d-G**[138, 139]. These monomeric adducts can be incorporated as phosphoramidites into automated DNA synthesis to obtain specifically labeled oligonucleotides[135, 140]. This methodology has been utilized to make specifically labeled oligonucleotides containing the N^2 **d-G** adduct of IQ, **35a**[141]. This will make it possible to perform detailed studies of the conformations and interactions of these specifically labeled oligonucleotides.

IV. THE NITRENIUM ION HYPOTHESIS

From the time that the structures of the ultimate carcinogenic metabolites of AAs and their adducts with the DNA bases first became known during the 1960s, there has been considerable interest in the possible mechanisms of the formation of the DNA adducts and other adducts with biological macromolecules. An early proposal was due to James and Elizabeth Miller who surmised that the ester metabolites of AAs would decompose into reactive arylnitrenium ions (**39**), and that the nitrenium ions were responsible for the generation of the known DNA adducts (equation 4)[1,2]. The nitrenium ion hypothesis was rapidly accepted in the biochemical community by the early 1980s without definitive supportive evidence[3,4,7,9,11–14]. Support for the hypothesis came from the observation that some of the *N*-hydroxy-AAs reacted directly with DNA and the efficiency of that reaction increased with decreasing pH[3,37], a result reminiscent of the well-known pH dependence of the Bamberger rearrangement[142–144]. Although suggestive, this evidence cannot rule out other mechanisms including direct S_N2 displacement. The apparent acid-catalyzed reaction of the hydroxylamines with DNA was far less efficient than the reaction of the ester metabolites with DNA, so it was not clear that the hydroxylamines and their metabolites reacted with DNA through the same intermediate(s)[3,37]. Later, it was shown that 2-azidofluorene and azides derived from several other AAs and HAAs could be photolyzed in the presence of **d-G** and DNA to yield the same adducts previously characterized from the reactions of the ester metabolites[145]. The azide photolysis also led to reversion mutations in tester strains of *S. typhimurium*[145]. Again, this was suggestive, but without careful characterization of the photochemistry of the azide, this result could not provide support for a particular mechanism.



(4)

There were significant problems with the nitrenium ion hypothesis at the time it was originally proposed. Although there was indirect evidence for nitrenium ion intermediates during the Bamberger rearrangement of *N*-arylhydroxylamines, the available data suggested that these intermediates were highly reactive and unselective species[142–144,146]. In order to react with DNA to generate lesions, an arylnitrenium ion must have a significant lifetime in an aqueous environment ($\geq$ 10 ns) so that it could survive long enough to react with non-solvent nucleophiles, and it would have to react efficiently with the DNA bases on the DNA polymer. No nitrenium ion lifetimes in aqueous solution had been measured at that time, so it was not known if these species could be selective electrophiles in water. Very little data existed on the reactions of nitrenium ions with neutral non-solvent nucleophiles[146]. The data that were available suggested that these reactions were not efficient[146]. Furthermore, the structure of the major reaction products with DNA and monomeric DNA bases, the guanosine C-8 adducts such as **14** and **15**, were not those expected for the reaction of an electrophile with a DNA base. On guanine, N^2, O^6 and

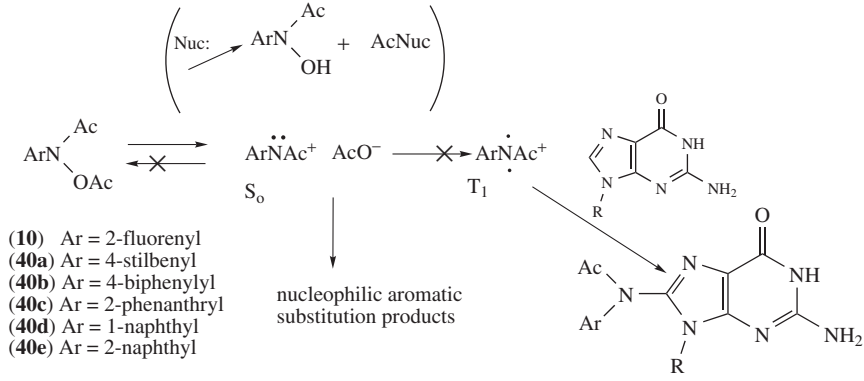
N-7 are the common nucleophilic sites for reactions with electrophilic species[147]. In fact, guanine C-8 was better known for reaction with radical intermediates[148]. The N^2 adduct **16** was easier to rationalize as a product of the reaction of a delocalized nitrenium ion with **d-G**, but this was a minor product that was only generated on the DNA polymer, or in a non-aqueous environment[77–80].

Although the nitrenium ion hypothesis was attractive because of the structures of the ultimate carcinogens that were emerging at the time, and because of its apparent simplicity, there was insufficient evidence available to provide strong support for the hypothesis.

V. THE HYPOTHESIS TESTED

A. Early Studies

Initial studies of the chemistry of **10** and the related *N*-acetoxy-*N*-arylacetamides, **40a–e**, were carried out in the laboratories of Scribner[149–151] and Underwood[152–154] in 40/60 acetone/H_2O (Scheme 5). Scribner used ^{14}C ester carbonyl labeled compounds and rates of reaction were measured by the generation of water-soluble ^{14}C[149]. Rates of formation of water-soluble ^{14}C depended on buffer concentration (citrate or methionine)[149]. Scribner noted that addition of ascorbic acid to solutions that contained **10** and **G** decreased the extent of C-8 adduct formation and led to the formation of the reduction product **2-AAF**[150]. The stable free radical 2,2-diphenylpicrylhydrazyl was decolorized by the addition of **10** in 20/80 EtOH/H_2O[150]. Scribner interpreted the data in terms of a reversibly formed nitrenium ion–acetate ion pair with intersystem crossing to a ground state triplet ion that reacted with **G** to form the C-8 adduct (Scheme 5)[149, 151].



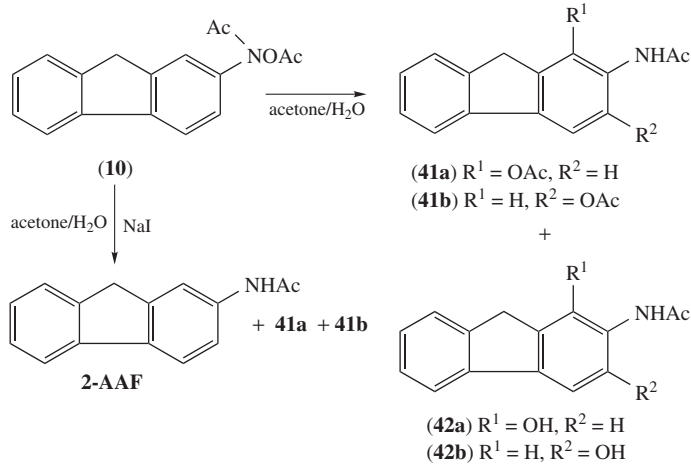
SCHEME 5. Scribner's original interpretation and Underwood's discoveries

Underwood and coworkers demonstrated that ^{18}O scrambling did not occur in carbonyl-^{18}O-labelled esters **10** and **40a**,**b**,**d**,**e** under the same reaction conditions, so reversible formation of an ion pair could not have occurred[152]. Overall kinetics of decomposition of the five esters was governed by equation 5, and careful product analysis showed that the hydroxide and buffer dependent terms generated the corresponding hydroxamic acids for all esters[152, 153].

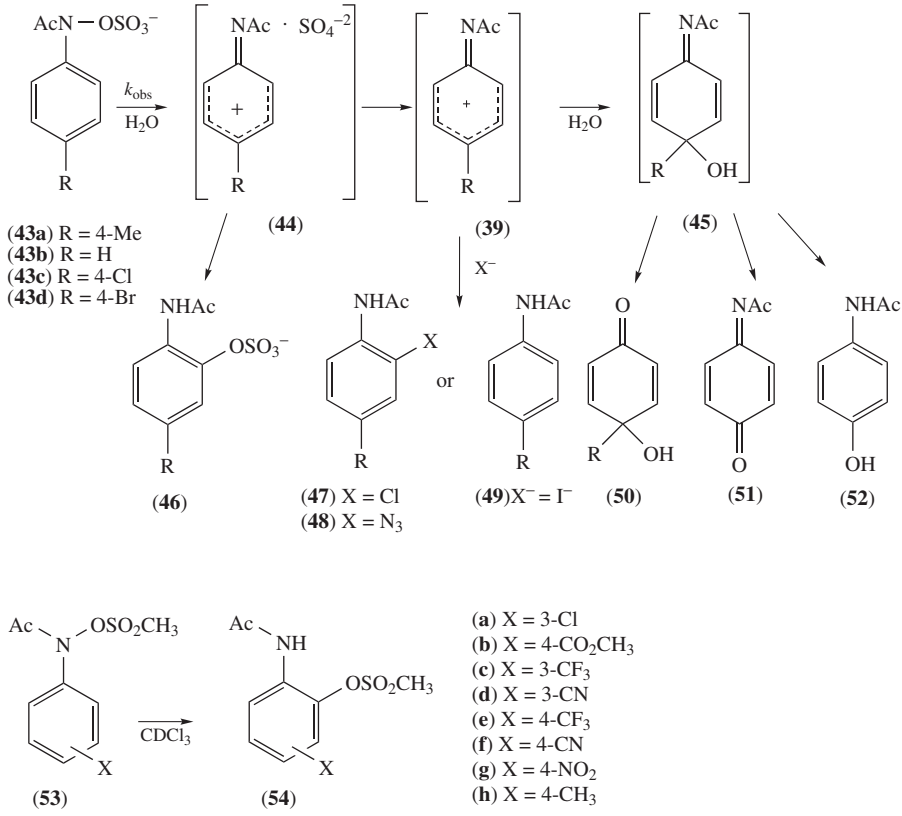
$$k_{obs} = k_o + k_{OH}[OH^-] + k_b[buffer] \quad (5)$$

The hydroxamic acids were also produced by the pH- and buffer-independent reaction for **40b** and **40e**[153]. Only **10** and **40d** yielded products that appeared to have been generated by N−O bond cleavage. Scribner had earlier shown that **40a** gave rise to products apparently derived from N−O bond cleavage[151]. A plot of log k_o vs. σ^+ for a series of *N*-acetoxy-*N*-arylacetamides that included **10**, **40b** and **40d** was non-linear with a slope of −6.2 for aryl substituents with $\sigma^+ < -0.3$ and a positive slope with a better correlation vs. σ ($\rho = +1.5$) for aryl substituents with $\sigma^+ > -0.3$[154]. The aryl substituents with $\sigma^+ < -0.3$ generated products consistent with N−O bond cleavage, while aryl substituents with $\sigma^+ > -0.3$ yielded hydroxamic acid products[154].

Hydrolysis of **10** under conditions in which k_o predominated led to a product mixture containing the rearranged products **41a**,**b** and the phenols **42a**,**b** (Scheme 6)[153]. In this system NaI, $Na_2S_2O_3$ and hydroquinone behaved as reducing agents leading to formation of **2-AAF** at the expense of all products except **41a**,**b**[153]. Novak and coworkers showed in a similar system, **43a–d** (Scheme 7), that I^-, Br^-, SCN^-, $S_2O_3^{2-}$ and $FeCl_2$ behaved as reducing agents intercepting all products except rearrangement products[155, 156]. These results are consistent with a mechanism in which the reducing agents trap a nitrenium ion, but the rearrangement products are produced by internal return from a tight ion pair[155, 156]. The yield of rearrangement products is negatively correlated with the lifetime of a nitrenium ion: short-lived ions are associated with significant yields of rearrangement products[157]. Singlet nitrenium ions are subject to reduction by both 2-electron and 1-electron reducing agents, so reduction of the ion by a particular reagent is not indicative of a triplet ground state[155–158]. These initial studies did not provide definitive supporting evidence for the hypothesis. Instead they showed that there was a balance between N−O and C−O bond cleavage in these esters, and that only some esters gave rise to N−O bond cleavage processes. No evidence requiring the existence of a nitrenium ion was presented for any of the esters **10** or **40a–e**. Since significant yields of rearrangement products were obtained from all compounds examined, the lifetimes of the cations in this solvent (40/60 acetone/H_2O), if they existed at all, were relatively short (< *ca* 20 ns)[156].



SCHEME 6. Hydrolysis products of **10** in 40/60 acetone/H_2O



SCHEME 7. Studies with monocyclic esters

The Novak[155–159] and Gassman[160] groups examined the chemistry of related monocyclic esters (Scheme 7). The hydrolysis of the *N*-sulfonatooxy-*N*-arylacetamides **43a–d** in 5/95 CH_3CN/H_2O provided evidence for three different reactive intermediates: the ion pair, **44**, the nitrenium ion, **39**, and the quinolimine, **45**[155–157, 159].

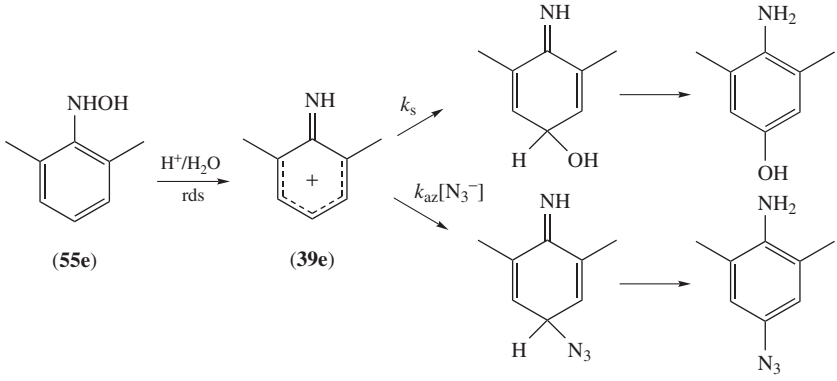
The existence of **44** was implied by the inability of nucleophilic traps such as N_3^- or Cl^- to reduce the yield of the rearrangement product, **46**[155–157]. The nitrenium ion **39** was indirectly detected by trapping experiments demonstrating that the cation could be trapped by non-solvent nucleophiles or reducing agents to yield products such as **47**, **48** and **49** without an accompanying increase in the rate of decomposition of the ester[155–157]. This observation requires a minimum of a two-step reaction mechanism with the first step (ionization) rate limiting[155]. The quinolimine **45a** was directly detected spectroscopically, and identified by its stable hydrolysis product, **50a**[156]. In other cases its existence could be inferred from its decomposition products, **51** or **52**[155].

Although the nitrenium ions could be indirectly detected by trapping experiments, they are very short-lived and non-selective cations. The 4-Me cation **39a** has an aqueous

solution lifetime of *ca* 0.1–0.2 ns based on azide trapping experiments if it is assumed that the rate constant for reaction with N_3^- is diffusion limited[157, 159].

The rate constants for rearrangement of **53a–h** into **54a–h** in $CDCl_3$ correlated with σ^+ with a slope, ρ^+, of −9.2[160]. The large dependence on substituent effects was taken as evidence for the rate limiting formation of an ion pair in the rearrangement mechanism. The hydrolysis of **43a–d** occurred with a substantial, but smaller, sensitivity to substituent effects. The measured ρ^+ of −4.5 suggests that solvent stabilization of the cation can significantly mitigate the sensitivity of ionization to substituent effects[155]. Solvents can also change the nature of the reaction. In EtOH, **43a–d** undergo S−O bond cleavage to generate the corresponding hydroxamic acids rather than generating the cation[155].

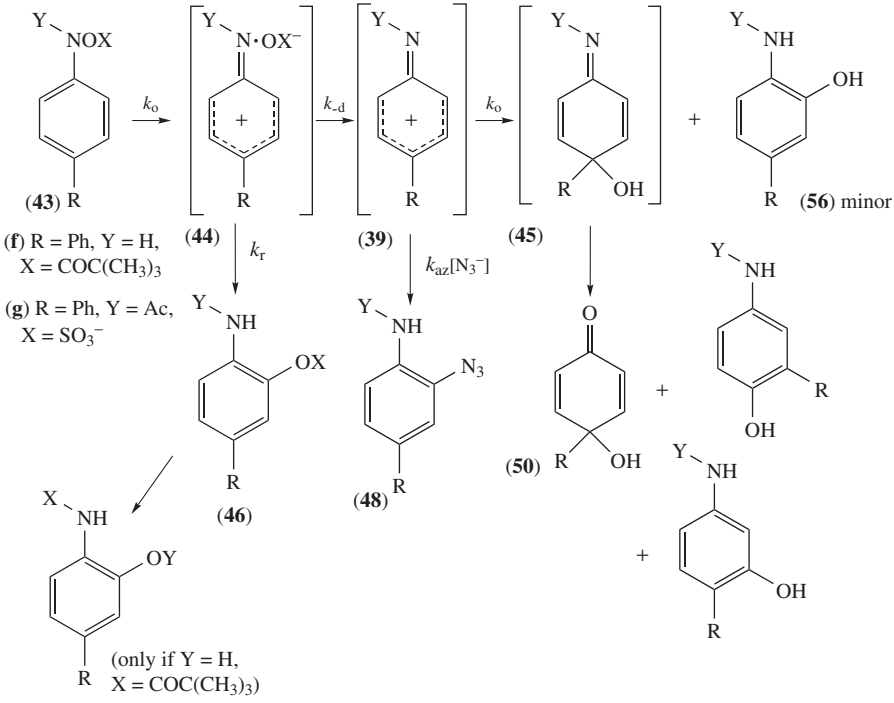
The first measurement of a nitrenium ion lifetime in aqueous solution was due to Fishbein and McClelland, who showed that N_3^- trapped an intermediate identified as **39e** during the Bamberger rearrangement of *N*-(2,6-dimethylphenyl)hydroxylamine, **55e** (Scheme 8)[161]. Based on the assumption that k_{az} is diffusion limited at $5 \times 10^9\ M^{-1}\ s^{-1}$ and the measured value of k_{az}/k_s of $7.5\ M^{-1}$, the rate constant for reaction with solvent, k_s, is $7 \times 10^8\ M^{-1}\ s^{-1}$. The lifetime of the ion, $1/k_s$, is *ca* 1.5 ns[161]. By the late 1980s it was clear that nitrenium ions could be generated from esters of *N*-arylhydroxamic acids[149–160] and *N*-arylhydroxylamines[162] in aqueous solution, but all ions that had been examined were short-lived, unselective species[155–162]. They did not appear to have the requisite properties to be potent carcinogens. Furthermore, it had not been demonstrated that any nitrenium ion could react with a monomeric DNA base or with DNA itself.



SCHEME 8. Azide trapping of nitrenium ion **39e**

B. Recent Results

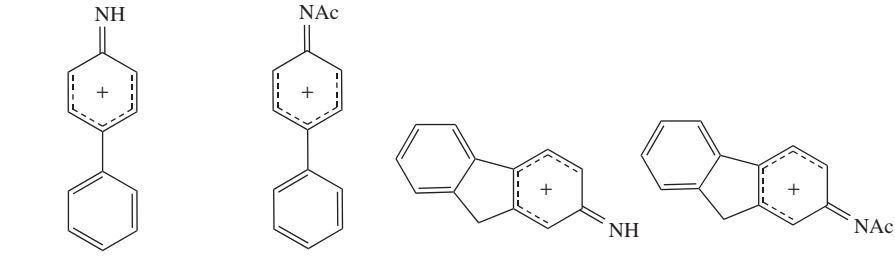
There were early hints that substituent effects on arylnitrenium ion lifetimes would not follow the same trend established for analogous carbocations[163]. For example, it appeared that the lifetime of the 4-Cl cation **39c** is longer than that of the 4-Me cation **39a** based on I^- and Cl^- trapping data[155, 156]. This was subsequently confirmed by trapping with N_3^-[157, 159]. Although a 4-Ph substituent does not stabilize a 1-arylethyl carbocation any more than a 4-Me substituent[163], that substituent has a remarkable effect on the lifetime of an arylnitrenium ion[164]. Novak and coworkers showed that the 4-biphenylylnitrenium ions **39f** and **39g** (Scheme 9) could be generated from appropriate ester precursors **43f** and **43g** in water, and trapped by N_3^- to yield **48f**,**g** at the expense of the solvent-derived



SCHEME 9. Generation and trapping of the 4-biphenylyl cations **39f** and **39g**

products **45f**,**g** and **56f**,**g**[164]. The overall reaction scheme discovered by the kinetics and trapping data was qualitatively very similar to that previously observed for the generation of **39a–d**[155–157], but there were important quantitative differences. The yield of rearrangement products **46f**,**g** was low (≤5%) in both cases, indicating that internal return via k_r was slow compared to diffusional separation of the ion pair via k_{-d}. For **43a–d** the yields of rearrangement products were in the range from *ca* 15% to 50%[155–157]. The more important difference was in the efficiency of N_3^- trapping; measured k_{az}/k_s based on product yields was $2.9 \times 10^3\ M^{-1}$ for **39f** and $1.0 \times 10^3\ M^{-1}$ for **39g**[164]. If k_{az} is diffusion limited, the lifetimes of **39f** and **39g** are 0.6 μs and 0.2 μs, respectively[164]. The lifetime of **39g** is *ca* 10^3-fold larger than that of **39a**. The 4-Ph substituent has a remarkably large effect on the kinetic lability of an arylnitrenium ion that is unprecedented in carbocation chemistry. These species have aqueous solution lifetimes that allow for selective reactions with DNA[164]. A subsequent measurement on the *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion, **39i** (Chart 6), provided k_{az}/k_s of $6.2 \times 10^4\ M^{-1}$ [165]. If N_3^- trapping of **39i** is diffusion limited, the aqueous solution lifetime of the cation is a remarkable 12 μs. These estimates relied on an assumed diffusion-controlled limit for k_{az}, but the lifetimes would be longer if k_{az} is smaller than the diffusion limit[164].

These estimated lifetimes depended on the measurement of product ratios and reaction kinetics as a function of $[N_3^-]$, and ultimately on an assumed value for k_{az}. Falvey and coworkers had directly detected several arylnitrenium ions via laser flash photolysis (lfp) of appropriate precursors followed by fast uv detection[166]. The structures of their cations were significantly different from those of interest to chemical carcinogenesis studies, and



(**39f**) $k_{az} = 5.0 \times 10^9\ M^{-1}s^{-1}$ $1/k_s = 0.56\ \mu s$

(**39g**) $k_{az} = 5.1 \times 10^9\ M^{-1}s^{-1}$ $1/k_s = 0.17\ \mu s$

(**39h**) $k_{az} = 4.0 \times 10^9\ M^{-1}s^{-1}$ $1/k_s = 29\ \mu s$

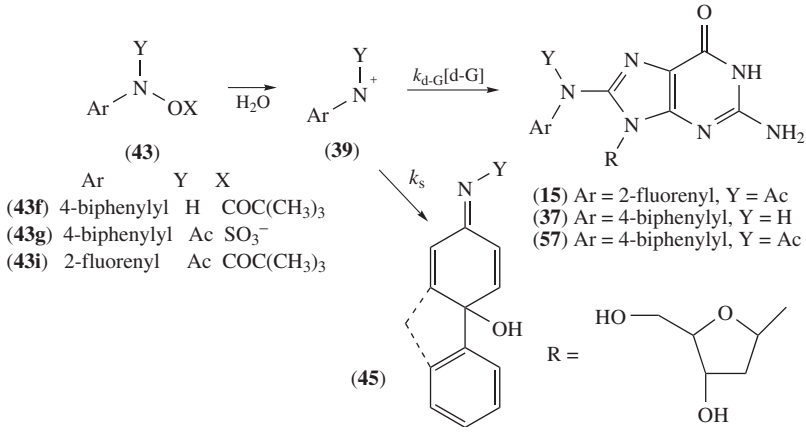
(**39i**) $k_{az} = 4.2 \times 10^9\ M^{-1}s^{-1}$ $1/k_s = 13\ \mu s$

CHART 6. Nitrenium ions directly detected by laser flash photolysis methods

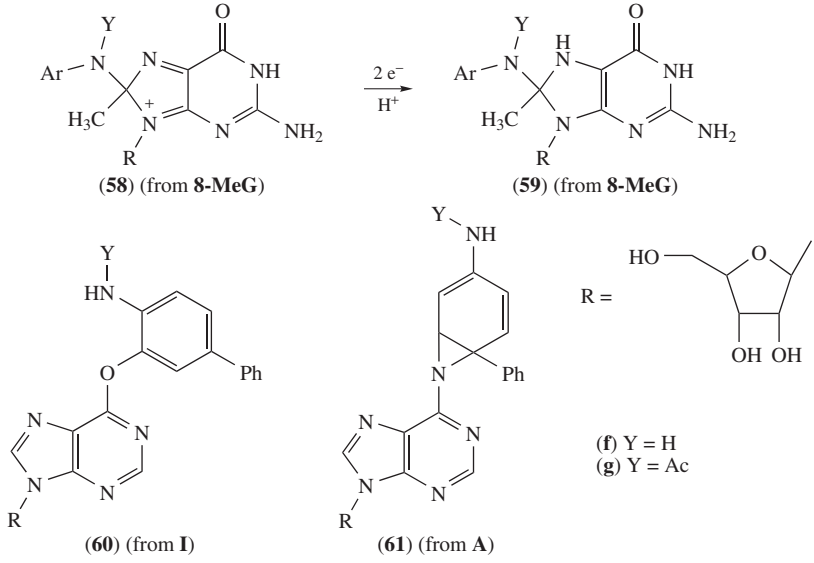
the measurements were made in CH_3CN, but they did demonstrate the feasibility of this approach for the study of nitrenium ions[166]. McClelland and coworkers demonstrated that the lfp method could be extended to the direct observation of arylnitrenium ions in aqueous solution[165, 167]. The ions **39f–i** (Chart 6) were directly detected by uv spectroscopy after lfp of their precursors; esters for **39g** and **39i**, and the corresponding azides for **39f** and **39g**[165, 167]. It was possible to directly measure k_{az} and k_s for these ions under conditions identical to those used in the trapping studies. Results are summarized in Chart 6. All four cations have k_{az} ranging from $4–5 \times 10^9\ M^{-1}\ s^{-1}$, indicating that the assumption of a diffusion-controlled reaction with N_3^- is valid. The lifetimes of these cations, $1/k_s$, are in excellent agreement with those estimated from the trapping studies. It was clear that these ions meet the requirement of a long aqueous solution lifetime that was necessary for a potentially selective reaction with DNA. These ions, and other arylnitrenium ions without highly electron-withdrawing aryl substituents, behave as ground state singlets[155–162, 164–167].

Hydrolysis of **43f**, **43g** and **43i** in the presence of **d-G** ($\leq$ 10 mM) proceeds without rate acceleration, but with 75% to 99% conversion of the ester into the corresponding C-8 adduct **15**, **37** or **57** (Scheme 10)[168, 169]. Kinetics of formation of **37** occurs with a rate that is independent of [**d-G**], with the same rate constant as the disappearance of **43f**. Adduct formation is not associated with the slower disappearance of **45f**, the initial product of attack of H_2O on the cation **39f**[169]. The adducts are generated by reaction of **d-G** with **39**, and not by reaction with **43** or **45**. The ratio $k_{d\text{-}G}/k_s$ for trapping the ions **39f**, **39g** and **39i** is pH independent from pH 3.5 to pH 7.5 and is only 2.5- to 7-fold smaller than k_{az}/k_s for the same ions[168, 169]. Based on the known values of k_s for these ions, $k_{d\text{-}G}$ is $1.9 \times 10^9\ M^{-1}\ s^{-1}$ for **39f** and **39g**, and $6.2 \times 10^8\ M^{-1}\ s^{-1}$ for **39i**[168, 169].

The purines guanosine (**G**), 8-methylguanosine (**8-MeG**), adenosine (**A**), inosine (**I**) and xanthosine (**X**) also trap **39f** and **39g**[169]. All show pH independent trapping from pH 3.5 to pH 7.5, except **X**. The pH dependence of k_X/k_s is consistent with trapping by **X** and its conjugate base $\mathbf{X}^-$[169]. The purines **d-G**, **G**, **8-MeG** and $\mathbf{X}^-$ generate a C-8 adduct exclusively with both cations with $k_{nuc} = ca\ 2 \times 10^9\ M^{-1}\ s^{-1}$. This appears to be the diffusion-controlled limit for reaction of these ions with purine nucleosides[169]. The **8-MeG** adduct **59** (Scheme 11) is the reduction product of the initial C-8 adduct **58** that was detected, but not isolated[169]. **I** generates both a C-8 adduct and an O-6 adduct **60**, while the exclusive product of the reaction with **A** is the benzene imine **61**[169]. These purines exhibit low selectivity (*ca* 1–10% of **d-G**) for trapping **39f** and **39g**. The pyrimidines thymidine, uridine and cytosine do not appear to react with either cation[169].



SCHEME 10. Reaction of arylnitrenium ions with **d-G**

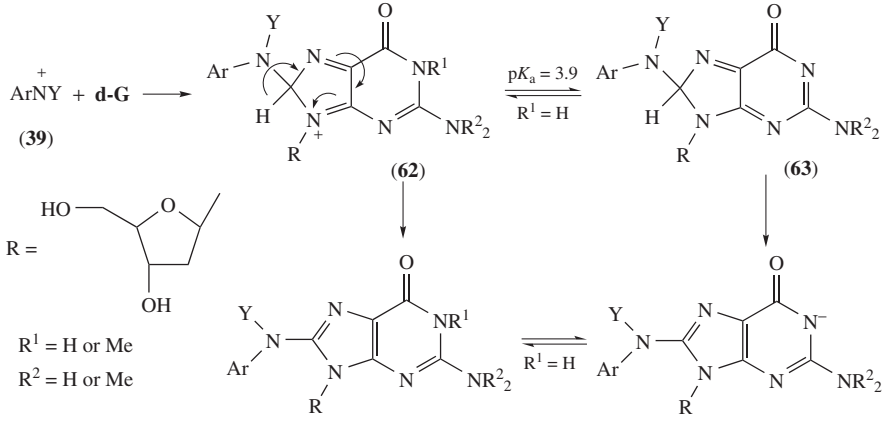


SCHEME 11. Other purine adducts formed from **39f** and **39g**

McClelland and coworkers verified the magnitude of $k_{d\text{-}G}$ for **39f**, **39g** and **39i** from lfp experiments[170–172]. They also provided data for other ions including **39h**. Their results confirm that $k_{d\text{-}G}$ reaches an apparent diffusion-controlled limit of *ca* $2.0 \times 10^9\ M^{-1}\ s^{-1}$ for many ions with $k_s \geq 10^6\ s^{-1}$ [171]. Even **39h** and **39i** that do not react with **d-G** at the diffusion-controlled limit have $k_{d\text{-}G} > 5 \times 10^8\ M^{-1}\ s^{-1}$ [171]. Carbocations with lifetimes similar to **39f–i** do not have detectable reactions with **d-G** in aqueous solution[171]. The high selectivity of these ions is not true for all nitrenium ions. The *para*-ethoxyphenylnitrenium

ion has $k_{d\text{-}G} \leq 2 \times 10^7\ M^{-1}\ s^{-1}$ and $k_{d\text{-}G}/k_s \leq 18\ M^{-1}$ [173]. This ion has a lifetime in H_2O that is similar to **39f**, and it generates C-8 adducts from its reaction with **d-G**[174], but it is at least 60-fold less selective toward **d-G** than **39f**. It appears that the positive charge in *para*-alkoxyphenylnitrenium ions is so localized at the *para*-O that there is insufficient cationic character at N for reaction with **d-G**[173]. This pattern appears to hold, with some exceptions, for the reaction of heteroarylnitrenium ions that have a dominant resonance structure with the charge on an endocyclic N[175]. High selectivity for reaction of nitrenium ions with **d-G** requires a combination of relatively long lifetime in water ($\geq$ 50 ns) and sufficient delocalization of the charge so that some cationic character remains on N.

There has been considerable interest in the detailed mechanism of C-8 adduct formation over the years[168, 169, 172, 176–182]. Initial proposals centered around nucleophilic attack by N-7 on the N of the nitrenium ion, followed by an intramolecular rearrangement to the observed adduct[169, 176]. Evidence for those proposals has been reviewed elsewhere[177, 178]. More recent discussions, based on direct observations of the reaction of **d-G** with the nitrenium ion **39h** generated by lfp of the corresponding azide, have favored direct attack of C-8 on the nitrenium N[172, 179–182]. McClelland's group identified an intermediate generated during the reaction as **62h** (Scheme 12, **62**, Ar = 2-fluorenyl, Y = H, R = 2′-deoxyribose)[172, 179]. Identification of the intermediate was based on its absorption spectrum that extends to 400 nm, suggesting a highly conjugated species, a pK_a of 3.9 that is consistent with deprotonation of **62h** to form **63h**, and a rate constant for decomposition of the intermediate that is independent of Ar for the intermediates derived from **39h**, **39f** and other 4′-substituted-4-biphenylylnitrenium ions. The pH dependence of the kinetics of decomposition of the intermediate into the C-8 adduct, buffer catalysis of decomposition of the intermediate, and a large H/D kinetic isotope effect of *ca* 6–7 for the decomposition of the intermediate derived from **8-D-d-G** are also consistent with the mechanism of Scheme 12[172]. Replacement of (N-1)H by Me removed the observed ionization of the intermediate and the pH dependence of its decomposition into the C-8 adduct[179].



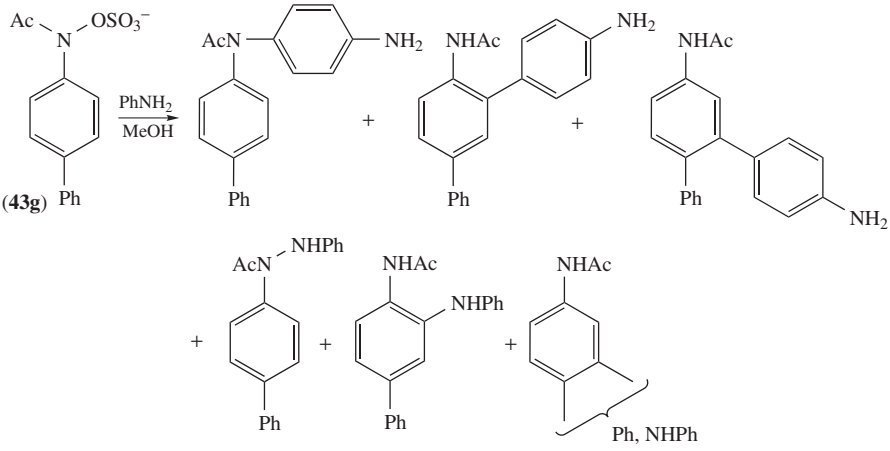
SCHEME 12. Currently favored mechanism for C-8 adduct formation

The rate of appearance of **62h** was identical to the rate of disappearance of **39h**. No other intermediate was detected[172]. The results cannot rule out initial attack by N-7, followed by rapid rearrangement to **62**, but the N-7 intermediate would have to be very

short-lived. The inverse H/D kinetic isotope effect of 0.88 observed for the activation limited reaction of 4′-methoxy-4-biphenylylnitrenium ion with **8-D-d-G** and the rate acceleration caused by substitution of $(N^2)H_2$ by $(N^2)Me_2$ is consistent with direct attack by C-8 in an electrophilic aromatic substitution[172, 179].

Phillips and coworkers characterized **39h** in CH_3CN/H_2O mixtures by time-resolved resonance Raman (TR^3) spectroscopy[180], and they used the same technique to monitor the reaction of **39h** with **G**[181, 182]. The TR^3 spectrum of the intermediate is consistent with the calculated (BPW91/cc-PVDZ) vibrational spectrum for **62h**[181, 182]. Spectra of intermediates generated from the reaction of **39h** with **8-MeG** and **8-BrG** are consistent with 8-Me and 8-Br substituted **62**[182]. Kinetics of formation of **62h** are consistent[182] with direct formation from **39h** and **G** as previously concluded by McClelland.

The high degree of regioselectivity exhibited by the reaction of **39f–i** with **d-G** is unusual. Nitrenium ions are known to react with arylamines such as *N*,*N*-dimethylaniline and aniline in reactions that mimic the formation of the **d-G** C-8 adduct, but multiple reaction products are isolated with no single product accounting for more than *ca* 35% of the overall yield[183]. A typical example for the reaction of aniline with **43g** is shown in Scheme 13[183]. The reaction was shown to involve **39g** because of the lack of dependence of the reaction rate on $[PhNH_2]$, but rather low regioselectivity of this reaction is in sharp contrast to that of the reaction of **39g** with **d-G**[168, 169].



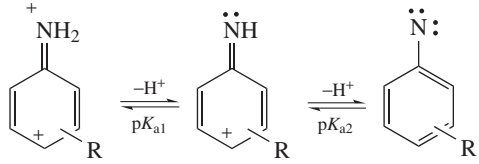
SCHEME 13. A typical example of a reaction of a nitrenium ion with an arylamine

The reasons for the high regioselectivity of the **d-G** reaction are not currently understood, but the high chemoselectivity of **39f–i** and related ions for reaction with **d-G** is a direct consequence of their long lifetimes. These ions are relatively unreactive species that react preferentially with the most nucleophilic component in solution even in an aqueous environment[169, 175, 178]. The considerably lower chemoselectivity of the ester metabolites of monocyclic arylamines **23a–g**[98–100] is a consequence of the much shorter lifetimes (< 2 ns) of the monocyclic nitrenium ions[157]. These are highly reactive and much less selective cations. It is likely that in most cases these ions react relatively indiscriminately through pre-association mechanisms with any nucleophile present in their solvation shell when they are generated[157]. It is of interest that these ions also tend to exhibit less regioselectivity for formation of the C-8 adduct when they do react with **d-G**. Significant reaction with N^2 and O^6 of **d-G** is often detected[98–100].

The Novak group compared the relative reactivities of **d-G**, single-stranded (**SS**) and double-stranded (**DS**) self-complementary d-ATGCAT and the super coiled plasmid pUC19 with **39i**[184]. The relative reactivity order **d-G** (1.00) > **SS**(0.27) ≫ **DS** (0.02) was established[184]. It was suggested that the strong inhibition of trapping caused by the tertiary structure of the DNA double helix may be responsible for the change in product distribution of **39i** adducts with **d-G**, and denatured DNA (exclusive C-8 adduct, **14**) and native DNA (5–20% N^2 adduct, **16**)[79, 80].

C. Acid–Base Chemistry

Acid–base chemistry plays a role in the reactivity of nitrenium ions, and may be of importance to the *in vivo* activity of some carcinogens[185–187]. 1° arylnitrenium ions can undergo both protonation and deprotonation (equation 6)[185].

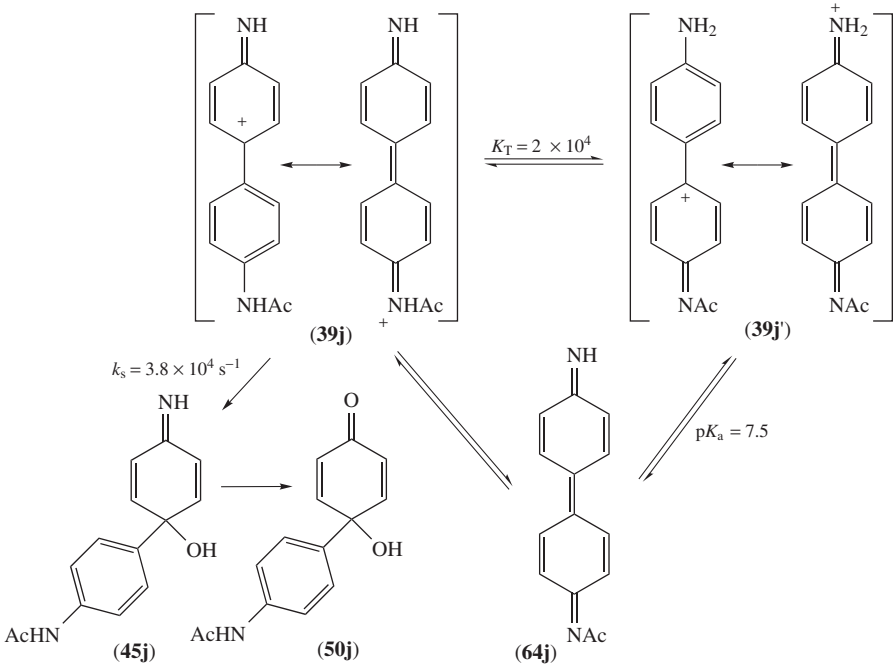


(6)

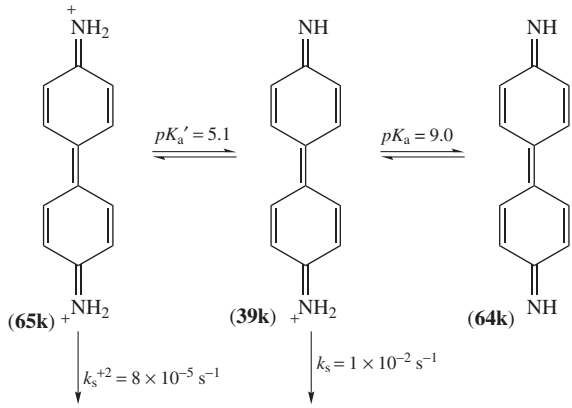
For ions such as **39f** and **39h** $pK_{a1} < 1.0$, so protonation of simple arylnitrenium ions is not physiologically relevant[185]. The potential deprotonation of nitrenium ions to form nitrenes is of considerable importance to the chemistry and biochemistry of nitrenium ions. McClelland and coworkers measured pK_{a2} of **39f** as 16.0[185]. They also concluded that $pK_{a2} > 12$ for most 1° arylnitrenium ions. Therefore, these species are present at physiological pH as nitrenium ions, not nitrenes, and the reactions that are observed under physiological conditions are due to nitrenium ions, not their conjugate bases. Recent measurements of the rate of protonation of singlet 2-fluorenylnitrene and 4-methoxyphenylnitrene in water have shown that protonation occurs with time constants in the range of *ca* 10–200 ps[188]. Therefore, photolysis of azides can provide an effective method to generate arylnitrenium ions with lifetimes > *ca* 10 ns if ring expansion of the nitrene, or decay to the triplet ground state of the nitrene, is slower than protonation[187]. Aryl azides have served as useful sources of nitrenium ions in a variety of cases, but the method is not appropriate for all arylnitrenium ions[145, 165, 167, 170–173, 179–182, 185–188].

Acid–base and tautomeric equilibria play a large role in the chemistry of nitrenium ions derived from benzidine[186, 187]. The equilibria for the *N*′-acetylated benzidinenitrenium ion are illustrated in Scheme 14[186]. There is a tautomeric equilibrium between the 4′-(acetylamino)-4-biphenylylnitrenium ion, **39j**, and 4′-amino-4-biphenylyl-*N*-acetylnitrenium ion, **39j**′. The equilibrium greatly favors **39j**′, which is in acid–base equilibrium with the neutral bis-imine, **64j**. At physiological pH the system consists primarily of **39j**′ and **64j**[186]; however, the major hydrolysis product, **50j**, is derived from the much more reactive **39j**[186]. The DNA adduct **21** observed in humans is also clearly derived from **39j**. In this system the long lifetime is imparted by the relatively stable cation **39j**′ and the bis-imine **64j**, but the reactivity is due to **39j**[186].

The acid–base equilibria for the benzidinenitrenium ion are illustrated in Scheme 15[187]. At physiological pH the dominant species is **39k**, but it is in equilibrium with the bis-imine **64k** and the dication **65k**. The system is quite long-lived, with **39k** reacting most rapidly with water[186]. Reactions that have previously been attributed to the bis-imine **64k**[88, 89] are most likely due to its conjugate acid, **39k**. The DNA adduct **22** is probably derived from **39k**.



SCHEME 14. Equilibria involving the 4′-(acetylamino)-4-biphenylylnitrenium ion, **39j**



SCHEME 15. Acid–base equilibria of the benzidinenitrenium ion

D. *N*-Hydroxy-HAA Esters

The chemistry of model esters of *N*-hydroxy-HAAs and the nitrenium ions derived from them were reviewed recently[175]. This section will concentrate on the properties of these materials that are most relevant to carcinogenicity.

Novak and coworkers examined the hydrolysis reactions of a series of esters, **66a–l**, of hydroxylamines or hydroxamic acids that are derived from carcinogenic and mutagenic HAAs (Chart 7)[189–194]. McClelland and Licence used the azides **67m**,**n** as photoprecursors of heteroarylnitrenium ions[195]. Hydrolysis rate constants for **66a–l** were fit to equation 7[189–194].

$$k_{obs} = (k_H[H^+]^2 + k_A[H^+] + k_B K_a)/(K_a + [H^+]) \quad (7)$$

Not all terms of the rate law applied to all esters[189, 190]. The ionization constant, K_a, is due to deprotonation of a pyridyl or imidazolyl N of the protonated ester under mildly acidic conditions. The kinetic pK_as are in good agreement with the spectrophotometric pK_as and range from *ca* 0.0 to 4.2 for the esters in Chart 7. The k_H and k_A terms involve ester hydrolysis to form the corresponding hydroxamic acids or hydroxylamines[191–194].

The k_B term predominates at pH $\geq$ pK_a and is the dominant term at physiological pH for all esters[175]. This term is consistent with uncatalyzed heterolysis of the N−O bond of the neutral ester to generate a heteroarylnitrenium ion. Products consistent with generation of a nitrenium ion are detected under these conditions, although ester hydrolysis to form the hydroxamic acid is also part of the k_B rate term for less reactive substrates[192, 193]. For all cases examined only the neutral form of the heterocyclic substrate undergoes N−O bond heterolysis[175].

The heterocyclic ions **68a–l** (Chart 7) were indirectly detected by azide trapping experiments, and were characterized by their reactions with N_3^-, **d-G** and water[189–194]. Scheme 16 shows the products derived from **68f** and **68g**, the *N*-acetyl-**IQx** and *N*-acetyl-**MeIQx** cations[191]. The solvent and azide products, **69f**,**g** and **70f**,**g**, are reminiscent of those obtained from AA-derived nitrenium ions[159, 161, 164]. The C-8 (**71f**,**g**) and N^2 (**72f**,**g**) **d-G** adducts are analogs of the **MeIQx** DNA adducts **34c** and **35c** and the **IQ** adducts **34a** and **35a** (Chart 8)[115–124]. For **68g** the N^2 adduct **72g** accounts for *ca* 20% of the **d-G** adduct yield[191].

The log (k_{az}/k_s) ratios derived from azide trapping studies or by direct measurement are provided in Table 1 with some comparisons to **39f–i** (Chart 6). Based on analogies to AA-derived ions, k_{az} should be at or near the diffusion limit for all ions with $k_{az}/k_s < 5 \times 10^5\ M^{-1}$ ($\log(k_{az}/k_s) < 5.7$)[178], so k_{az}/k_s can be used to evaluate the kinetic stability of these ions within those limits. A heterocyclic N can significantly stabilize a cation in which the lone pair on the N can participate in resonance stabilization. The comparison of **68m** and **68n** with **39i** demonstrates that stabilization effect. For **68d** and **68e**, k_{az}/k_s is beyond the range that k_{az} can be confidently predicted to be near the diffusion limit. These ions have k_{az}/k_s similar to that of 4′-methoxy-4-biphenylylnitrenium ion which has k_{az} within a factor of 2 of the apparent diffusion limit[196]. The measured k_{az} for the highly selective ions **68m** and **68n** are also close to the diffusion limit at *ca* $3 \times 10^9\ M^{-1}\ s^{-1}$ [195]. Therefore, k_{az} for all the ions **68a–n** will be in the range $2–5 \times 10^9\ M^{-1}\ s^{-1}$.

For most of the ions shown in Table 1, the relative selectivity for N_3^-/**d-G**, $k_{az}/k_{d\text{-}G}$, is *ca* 2.5–7.5, reflecting the fact that both k_{az} and $k_{d\text{-}G}$ are at or near their diffusion-controlled limits of *ca* $5 \times 10^9\ M^{-1}\ s^{-1}$ and $2 \times 10^9\ M^{-1}\ s^{-1}$, respectively. This has been noted before for a wider range of nitrenium ions[178]. However, N_3^- is *ca* 10^2-fold more reactive toward **68d–g** than is **d-G**. This is similar to what was previously observed for the *para*-methoxyphenylnitrenium ion and the 4′-methoxy-4-biphenylylnitrenium ion[173, 196]. The phenomenon appears to be related to the charge distribution in these ions[175, 178].

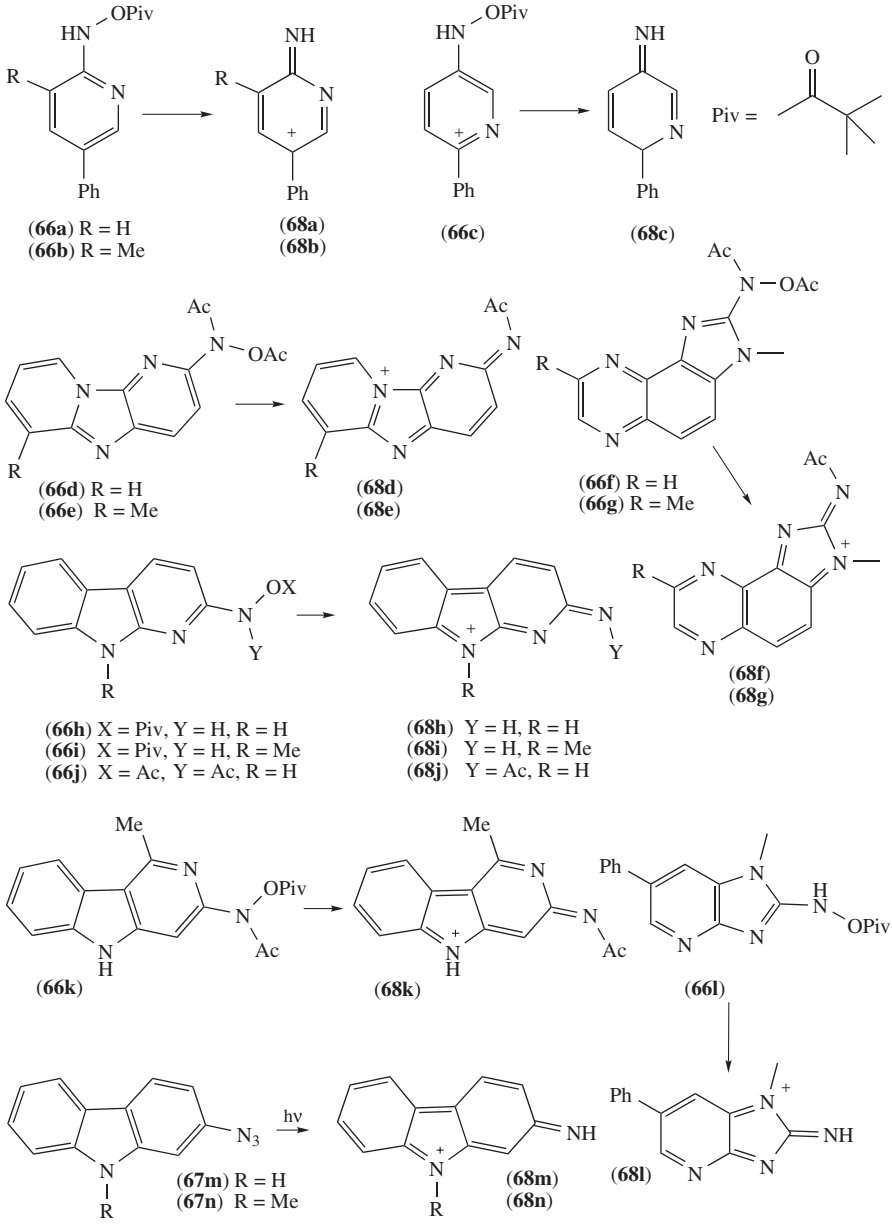
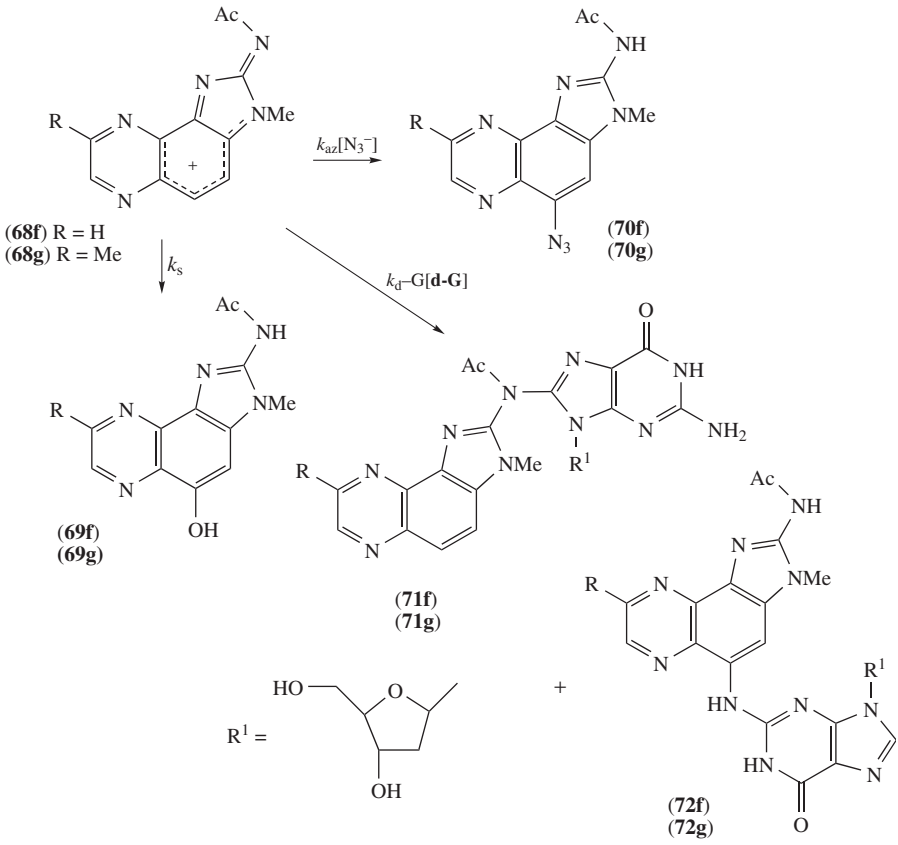


CHART 7. Esters, azides and corresponding nitrenium ions of HAAs



SCHEME 16. Reaction products from **68f** and **68g**

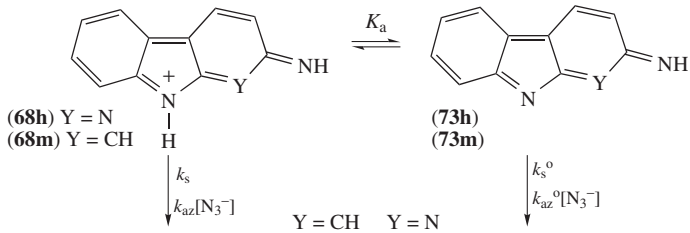
If the charge is significantly localized on a heteroatom other than the nitrenium N, the reactivity at the nitrenium N appears to be somewhat reduced. Even though this does occur for **68d–g**, these ions are still highly selective for reaction with **d-G**[191].

Some heterocyclic ions are subject to acid–base reactions that are important at physiological pH[190, 195]. For **68h**, the nitrenium ion derived from **AαC**, k_{nuc}/k_s for trapping by N_3^-, Br^- and **d-G** conforms to a titration curve, decreasing from pH 3 to 8[190]. These results are consistent with deprotonation of 9-NH to yield a neutral quinonoid **73h** that is trapped with less efficiency by non-solvent nucleophiles than **68h** (Scheme 17)[190]. It was found that the 9-NMe cation **68i** that cannot be deprotonated at 9-N exhibits a pH invariant k_{nuc}/k_s that is similar in magnitude to k_{nuc}/k_s for **68h** at low pH[190]. McClelland and Licence discovered similar pH-dependent trapping of the cation **68m** obtained from lfp of the corresponding azide, but no evidence for deprotonation of **68n**[195]. Measured or estimated values for the pK_a and the kinetic parameters are shown in Scheme 17. The neutral quinonoid compounds **73h** and **73m** show nitrenium-like reactivity with substantial azide/solvent selectivity that is *ca* 30-fold less than the corresponding nitrenium ions (Table 1), and **73h** is also trapped by **d-G**[190, 195]. At physiological pH the dominant

TABLE 1. Selectivity data for heterocyclic nitrenium ions and their conjugate bases[a]

Ion or conjugate base	$\log(k_{az}/k_s)$	$\log(k_{az}/k_{d\text{-}G})$
68a	1.00[b]	
68b	2.48[b]	0.56
68c	1.90[b]	
68d	6.36[c]	1.87
68e	6.71[c]	2.01
68f	4.72[c]	1.76
68g	5.08[c]	2.16
68h	4.54[d]	0.63
73h	3.08[d]	0.70
68i	4.65[d]	0.71
68l	4.36[e]	
68m	5.83[f]	
73m	4.33[f]	
68n	5.74[f]	
39f	2.97[g]	0.46
39g	3.45[h]	0.41
39h	4.76[i]	0.88
39i	5.07[j]	0.61

[a]Conditions: 5/95 CH_3CN/H_2O, $\mu = 0.5$ ($NaClO_4$), $T = 20°C$, unless otherwise indicated.
[b]Reference 189.
[c]Reference 191.
[d]Reference 190.
[e]Reference 194.
[f]Reference 195: 20 vol% CH_3CN, $\mu = 0.1$.
[g]References 164, 165, 168, 170, 171.
[h]References 164, 167, 169–171.
[i]References 165, 168, 170–172.
[j]References 167, 170, 171.



	Y = CH	Y = N
pK_a	5.8	3.0
k_s, s^{-1}	4.0×10^3	1.4×10^5
k_s^o, s^{-1}	4.7×10^1	1.7×10^3
k_{az}, $M^{-1}s^{-1}$	2.7×10^9	5.0×10^9 (est)
k_{az}^o, $M^{-1}s^{-1}$	1.0×10^6	2.0×10^6

SCHEME 17. Acid–base chemistry of the **AαC** nitrenium ions **68h**, and **68m**

AαC-derived electrophile is **73h**. This species is sufficiently reactive that all the reactions observed at physiological pH will be due to **73h** rather than the cation **68h**. Although it has not been examined, the same should be true for the nitrenium ion derived from **MeAαC**.

E. Correlation of Mutagenicity with Nitrenium Ion Selectivities

Considerable effort has been expended over the years to develop quantitative structure–activity relationships (QSARs) that correlate quantitative bacterial mutagenicity data or quantitative carcinogenicity data for AAs and HAAs with calculated or observed properties of the amines or the nitrenium ions derived from them. This work has been extensively reviewed[197–199]. The mutagenicity correlations most often employ as the dependent variable log [(histidine revertants)/(nanomoles of amine)], log m, for two *S. typhimurium* strains, TA 98 and TA 100, that are commonly used in Ames tests[200]. A number of multiple variable linear regression models encompassing between three and six independent descriptor variables have been reported to correlate data sets (*ca* 50–150 amines) containing both AAs and HAAs[201–208]. These models achieve good correlation ($r^2 \approx 0.8$), but physical interpretations are not always straightforward. Descriptor variables have included the log of the octanol/water partition coefficient (log P), the number of rings, molecular volume, the Huckel π-orbital energy of the molecule, E_π, the number of π-electrons, HOMO and LUMO energies of the amines, or LUMO energies of the nitrenium ions. Attempts have also been made to correlate mutagenicity data with the calculated ΔE for equation 8, where X is H or a leaving group such as OAc[209–211].

$$\mathrm{ArNHX} \longrightarrow \mathrm{ArNH^+} + \mathrm{X^-} \tag{8}$$

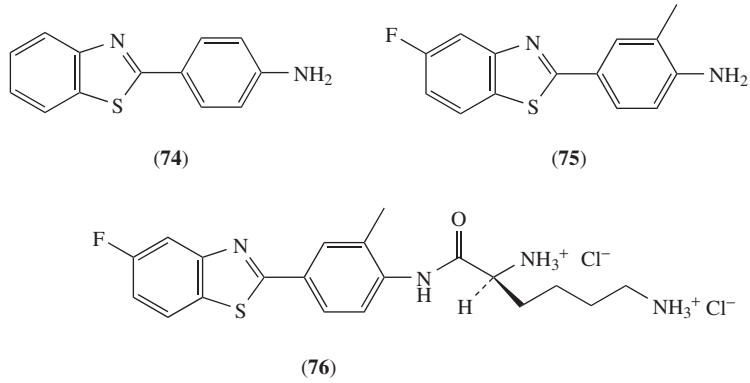
These correlations involving ΔE of equation 8 suggest that, to the extent that ΔE can be related to the rates of ionization of the hydroxylamine esters, mutagenicity correlates positively with the rate of nitrenium ion formation from their ester precursors[209, 210]. An alternative explanation of the correlation is that ΔE indirectly measures the lifetimes and, therefore, the selectivities of the nitrenium ions[212]. The Novak group used a direct measure of nitrenium ion lifetimes, log(S), where $S = k_{az}/k_s$, to develop a QSAR for bacterial mutagenicity[212]. Since k_{az} is at or near the diffusion limit for all the nitrenium ions used in the analysis, log(S) is a measure of the relative cation lifetimes. The study used 18 amines, 12 AAs and 6 HAAs, for which both mutagenicity data and experimental log(S) data are available. It was found that there was a strong positive correlation of log m with log(S) for both TA 98 and TA 100 strains[212]. Longer-lived nitrenium ions were associated with greater bacterial mutagenicity. It was also noted that monocyclic AAs (MAAs) had significantly smaller log m than polycyclic AAs or HAAs with similar log(S). Multiple variable linear regression analysis led to a two-parameter regression model, significant at the 95% confidence level for both variables, that includes log(S) and a ring index variable, I_{rings}, that is 0 for MAAs and 1 for all other amines. These models have $r_{adj}{}^2 = 0.8448$ for TA 98 and 0.8927 for TA 100. Inclusion of a third variable, Clog P[212], increases $r_{adj}{}^2$ to 0.8913 for TA 98 and 0.9011 for TA 100. Quantitative carcinogenicity data in mice and rats are more weakly correlated with log(S). In general, carcinogenicity correlations are less successful than mutagenicity correlations, probably reflecting the considerably greater complexity of carcinogensis[197].

The demonstrated correlation of log m for both *Salmonella* strains with log(S) in single variable and multiple variable regression analyses is necessary, but insufficient, to show that nitrenium ion selectivity plays an important role in determining the mutagenicity

potential of these amines, although the lack of a correlation could have been used to prove the negative. Correlations by themselves cannot prove cause and effect. Nonetheless, these correlations, and other data which show that the more long-lived and selective nitrenium ions are more effectively trapped by **d-G** in aqueous solution (Table 1), do strongly suggest a role for nitrenium ion selectivity in determining the effectiveness of these amines in bacterial mutagenicity assays.

F. Nitrenium Ions from Anti-Cancer Drugs

A number of arylamine-based compounds are being investigated as anti-cancer drugs. Several 3-arylamino and 3-alkoxy-nor-β-lapachone derivatives have been found to be highly potent against cancer cells SF295 (central nervous system), HCT8 (colon), MDA-MB435 (melanoma) and HL60 (leukemia), with IC_{50} below 2 μM[213]. Among the HAAs, Batracylin (8-aminoisoindolo[1,2-*b*]quinazolin-12(10 *H*)-one)[214] and 4-anilinoquinazoline derivatives[215] are effective against several cancer cell lines. The 2-(4-aminophenyl)benzothiazoles related to **74** (Chart 8) are a potentially important class of pharmaceuticals[216–225].



(**74**) (**75**)

(**76**)

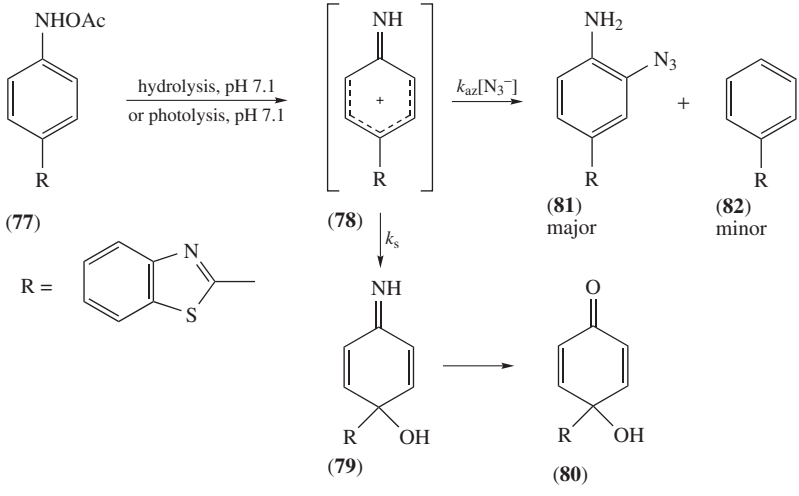
CHART 8. Anti-tumor 2-(4-aminophenyl)benzothiazoles

The original discovery of the anti-tumor activity of **74** was serendipitous[216]. It was originally generated as a synthetic intermediate, but was found to have remarkable activity against two human breast cancer cell lines (MCF-7 and MDA 468)[216]. Substitution at the 3′-position by methyl or halogens led to enhanced activity against the original cell lines and a broader spectrum of activity against certain colon, ovarian and renal cancer cell lines, although other cell lines were insensitive to the drugs[216, 217]. The 3′-methyl derivative outperformed all other derivatives in initial *in vivo* tests, so further developments concentrated on this derivative[216, 218]. Metabolism of these compounds into the active metabolite in sensitive cell lines requires the constitutive presence of CYP4501A1, that is also induced by the drug[219]. Insensitive cell lines contain neither constitutive nor inducible CYP4501A1[219]. Metabolism of these compounds is associated with translocation of the aryl hydrocarbon receptor (AhR) to the nucleus, and metabolism is significantly attenuated in AhR-deficient MCF-7 cells[220, 221]. The involvement of AhR binding in CYP4501A1 induction by other xenobiotics is well known[222]. Fluorination at C-5 preserves induction of CYP4501A1 and activity against sensitive cell lines, but suppresses C-hydroxylation

that leads to detoxification[222]. Finally, the low water solubility of the 3′-methyl-5-fluoro derivative, **75**, could be circumvented by conjugation to lysine to form **76**, the pro-drug that was approved for Phase 1 clinical trials in 2004. This compound, dubbed Phortress, is readily metabolized into the active drug, **75**[223, 224].

Based on the available data, the mechanism of action of **74** and its simple ring-substituted derivatives is thought to involve selective uptake into sensitive cells followed by AhR binding and translocation into the nucleus, induction of CYP1A1, oxidation and conversion of the drug into an electrophilic reactive intermediate, and formation of extensive DNA adducts resulting in cell death[225]. It is suspected that the active metabolite of **74** and its derivatives is a hydroxylamine or, more likely, an ester derivative, such as **77**, but neither of these compounds had been reported in the literature[225].

Novak and coworkers succeeded in synthesizing **77** and studied its decomposition under hydrolysis and photolysis conditions (Scheme 18)[226, 227]. They found that **77** generates a nitrenium ion **78** upon hydrolysis in pH 7.1 phosphate buffer or during photolysis at pH 7.1[226]. Addition of N_3^- to the hydrolysis solution does not affect the rate of decomposition of **77** but the yield of the major hydrolysis product **80**, produced by hydrolysis of the quinolimine **79**, is significantly reduced at $[N_3^-] < 1$ mM, demonstrating that N_3^- traps a long-lived nitrenium ion produced in the rate-limiting step of the hydrolysis. As the yield of **80** decreases, the yields of two new products, **81** and **82**, not generated in the absence of N_3^-, increase[226, 227]. The selectivity ratio, k_{az}/k_s, determined from trapping experiments is $2.6 \times 10^3\ M^{-1}$. This selectivity is in the range previously discovered for nitrenium ions such as **39f–i** derived from carcinogenic arylamines. Direct measurement of k_{az} and k_s for **78** detected by fast UV spectroscopy after lfp of **77** confirmed the magnitude of k_{az}/k_s obtained by trapping experiments, verified that the reaction with N_3^- is at the diffusion-controlled limit ($k_{az} = 4.9 \times 10^9\ M^{-1}\ s^{-1}$) and provided a lifetime ($1/k_s$) for **78** of 0.53 μs, about the same as **39f** (Chart 6)[223]. The hydrolysis of **77** in the presence of **d-G** has also been studied[227]. Like N_3^-, **d-G** does not affect the rate of decomposition of **77**, but it does reduce the yield of **80** at low [**d-G**]. The selectivity ratio $k_{d\text{-}G}/k_s$ is $1.6 \times 10^3\ M^{-1}$ indicating that $k_{d\text{-}G}$ is *ca* $3.0 \times 10^9\ M^{-1}\ s^{-1}$, in the range expected for a diffusion-controlled reaction of **78** with **d-G**[224]. The **d-G** adduct has the



SCHEME 18. Generation and reactions of the 4-(2-benzothiazolyl)phenylnitrenium ion, **78**

typical C-8 structure. It is clear that the nitrenium ion **78** has properties very similar to those of the nitrenium ions derived from well-known carcinogenic AAs and HAAs. It is intriguing that these characteristics may be put to use in an anti-cancer drug.

VI. CONCLUDING REMARKS

Some 50 years after the original discovery of the *N*-hydroxylation of **2-AAF** and the initial formulation of the nitrenium ion hypothesis, a great deal is known about the mechanisms by which AAs and HAAs induce cancer. The metabolism of these materials into *N*-arylhydroxylamines and subsequently into the ultimate carcinogens, the esters of the *N*-arylhydroxylamines, has been delineated for a significant number of these carcinogens. The major adducts of many of these carcinogens with DNA have been identified, and the conformations of these adducts in DNA oligomers has been examined in a number of cases. Structural information has led to some understanding of how particular mutations may be induced by these DNA lesions.

The nitrenium ion hypothesis spurred considerable research into the mechanism of formation of DNA adducts, and also led to considerable basic research into the properties of *N*-arylnitrenium ions derived from esters of *N*-arylhydroxylamines and related precursors. It was determined that aryl substituents and other substituents that extend the π-delocalization of the cationic charge increase the lifetime, and therefore the chemical selectivity, of nitrenium ions by a factor of 10^3 or more compared to non-conjugating substituents. Nitrenium ions derived from most carcinogenic AAs and HAAs have lifetimes that range from 0.1 μs to 10 ms. It is now clear that the adduct-forming reactions with DNA bases do involve a nitrenium ion if the nitrenium ion lifetime is sufficiently long ($> 10-50$ ns) to allow for diffusional processes to occur before the cation is quenched by solvent. Reactions with non-solvent nucleophiles, including DNA bases, must occur by pre-association processes for short-lived cations.

Although much has been learned over the last half century, there are a number of difficult questions that remain unanswered:

- What is the origin of the high regioselectivity exhibited by the reaction between nitrenium ions and **d-G**?
- What role does the DNA structure play in determining the regioselectivity of the adduct-forming reactions?
- What role does the minor N^2 adduct with **d-G** found for several carcinogenic AAs and HAAs play in carcinogenesis?
- What role do the excision and repair enzymes and DNA polymerases play in the mutational process?

Although there are multiple nucleophilic sites on **d-G**, the reaction of most long-lived nitrenium ions with **d-G** is remarkably regioselective when compared to their electrophilic substitution reactions with model electron-rich aromatics[168–172, 183]. The McClelland and Phillips groups have suggested that hydrogen bonding by H_2O plays a role in governing the regioselectivity[228, 229], but definitive experimental evidence is lacking.

It has been known since the **d-G** N^2 adduct of **2-AAF** was first detected that the yield of that adduct increases significantly on intact native DNA[80]. Although there has been speculation about this, there has never been any evidence to indicate why the tertiary structure of DNA alters the regioselectivity of the reaction[77–80,168–172]. One interesting clue comes from the study by the Novak group that showed that the selectivity for the reaction of **39i** with **d-G** residues on intact double stranded DNA is about 2% that of the same reaction with monomeric **d-G**[184]. The change in regioselectivity of the reaction that

favors a greater relative yield of the N^2 adduct on double-stranded DNA may be related to this observation.

The role that the N^2 adduct may play in mutagenesis and carcinogenesis has been difficult to determine because it is a minor adduct that has never been subjected to structural investigation. The recent preparation of a specifically labeled oligonucleotide containing the N^2 **d-G** adduct of **IQ**, **35a**, has made it possible to perform structural studies on these lesions that may lead to a greater understanding of their possible biological roles[141].

Although the structural features of AA and HAA lesions in DNA in a variety of contexts (double stranded with the original base pair intact, double stranded with a mismatched base pair, double stranded–single stranded junction) have been examined, how these lesions interact with DNA repair enzymes and DNA polymerases is not well understood[8, 129, 137]. A combination of NMR structural studies, X-ray crystallographic investigations and modeling studies are beginning to shed light on these interactions[137].

Investigation of the chemistry and biology of carcinogenic *N*-arylhydroxylamine derivatives has been a very productive area of research for the last fifty years. It promises to remain a productive field for the foreseeable future.

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Synthesis, structure and reactions of organometallic derivatives of oximes

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I. INTRODUCTION

Oximes and their derivatives are widely used in organic synthesis. Beside this, oximes are good ligands for the complexation with different metals. This possibility of forming coordinative compounds with different metals was widely used in analytical inorganic chemistry. Recently a review devoted to the use of oximes and hydroxamic acids as reagents in inorganic analytical chemistry was published[1]. Moreover, some excellent reviews on coordination chemistry of oximes were published[2]. Therefore, synthesis of transition metal complexes will be discussed briefly; only some novel aspects of the synthesis and biological activity of these compounds will be described.

Although the above-mentioned reviews discuss some organometallic derivatives of oximes, there are no general reviews on the synthesis, reactions and biological activity of alkali metal derivatives of oximes, as well as on silicon, germanium, tin and phosphorous derivatives of oximes.

The aim of the present review is to describe the synthetic reactions and biological activity of organometallic compounds of oximes. These derivatives were selected and presented according to the place of the metal in the periodic table.

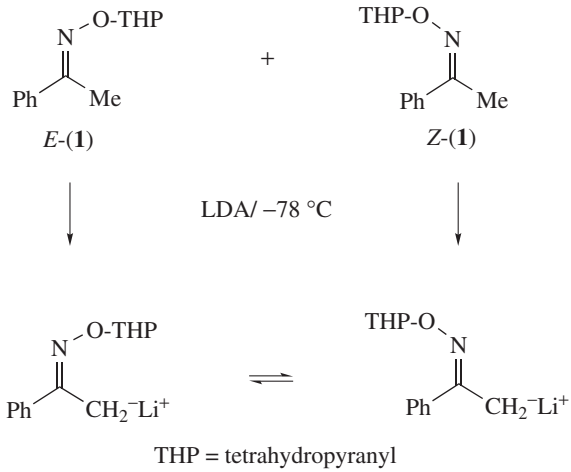
II. SYNTHESIS, STRUCTURE AND REACTIONS OF ORGANOMETALLIC DERIVATIVES OF OXIMES

A. Group 1

Many reactions of oximes proceeded via formation of the alkali metal salts of the oxime group (=NOM, where M = alkali metal). Such a type of metal compounds of oximes is not included in the present work. Generally, the interaction of strong bases (BuLi, LDA, KNH_2 etc.) with oximes $RC(CH_2R')$=NOH (R, R′ = H, alkyl, aryl) leads to formation of the disalts RC(CHMR′)=NOM. Oxime *O*-ethers ($RC(CH_2R')$=NOR″, R″ = alkyl, aryl) in the presence of strong bases afford monosalts RC(CHMR′)=NOR″. In the present chapter the possibilities of obtaining these types of alkali metal derivatives of oximes with respect to stereoselectivity and regioselectivity will be discussed. The main reactions of these oxime salts will also be presented.

1. Synthesis and structure of oxime anions and dianions

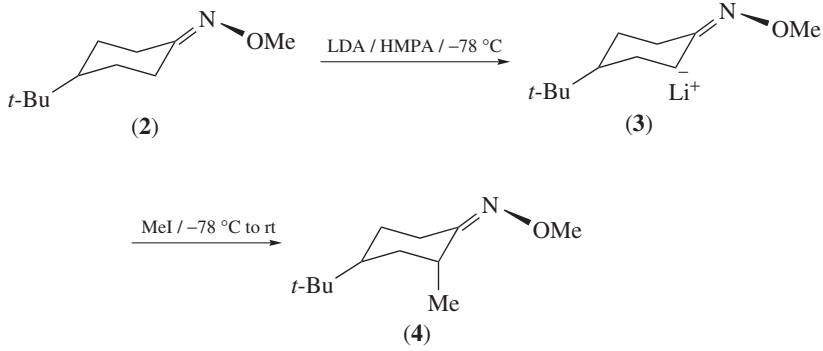
Kinetic and thermodynamic *syn*-deprotonation of *O*-tetrahydropyranyl oximes was described in an article in 1978[3]. For example, acetophenone *O*-tetrahydropyranyl oxime **1** was obtained as a 68:32 mixture of *E*- and *Z*-isomers. On treatment of this mixture with LDA at −78 °C followed by quenching with methanol, 94% of **1** was recovered. The recovery mixture consists of 80% of the *E*-isomer *E*-**1** and 20% of ***Z***-1. When the solution was allowed to warm to −50 °C, 95% yield of the *E*-isomer was obtained and the *Z*-isomer was not detected. These results are consistent with deprotonation of both the *E*- and *Z*-isomers to give the equilibrium of the anions (equation 1). These results indicate that formation of *syn*-anion is both kinetically and thermodynamically favored.



(1)

THP = tetrahydropyranyl

Lithiation and subsequent methylation of several conformationally fixed oxime *O*-methyl ethers has been shown to give only one product resulting from axial attack at the α-carbon *syn* to the oxygen atom. Thus, treatment of 4-*tert*-butylcyclohexanone *O*-methyl oxime (**2**) with LDA in THF at −78 °C in the presence of HMPA, followed by the reaction with MeI, gave the 2-methyl derivative **4** in 94% yield. The stereoselectivity of products **3** and **4** according to ^{13}C NMR was established as *syn* and *axial* (equation 2)[4].

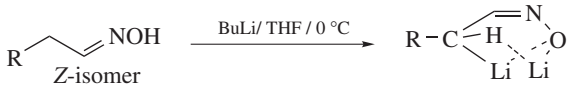


(2)

A series of cesium and lithium salts of benzylic oxime *O*-ethers MeON=C(CH_2Ar)$_2$ (Ar = Ph, 4-biphenyl, 1-naphthyl) was prepared in septum-capped NMR tubes and the equilibrium ion pair acidities in THF were determined. The lithium ion pair acidity of 1,3-diphenylacetone *O*-methyl oxime was found to be approximately 5 *pK* units lower than the corresponding cesium ion pair acidity. The oxime ethers are approximately 10 orders of magnitude less acidic than their corresponding ketones for cesium ion pairs[5].

Several papers were dedicated to the preparation and structure investigation of alkali metal dianions of oximes. Classically, 1,2-diphenylethanone oxime was converted to the dipotassium salt by interaction with potassium amide in liquid ammonia[6]. It was then shown that only the *Z*-isomers of aldoximes (**5**) (for example, the oxime of

phenylacetaldehyde) in the presence of LDA in THF at 0 °C afforded the corresponding dianions. It can be explained by stabilization of the structure by intramolecular chelation in **6** (equation 3)[7]. Similar results were obtained in the D-labelling of propanal oxime. Thus, when a 56:44 *E*/*Z* mixture of this oxime was treated with up to 5 equivalents of BuLi in hexane at 0 °C followed by quenching with D_2O, it led to quantitative deuteriation of *Z*-isomer, while no D was detectable by NMR in the *E*-isomer[8].

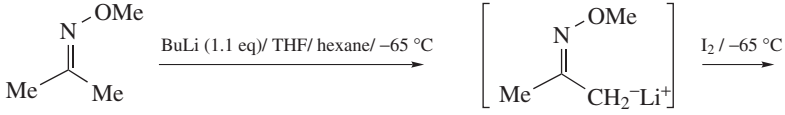


(**5**) (**6**) (3)

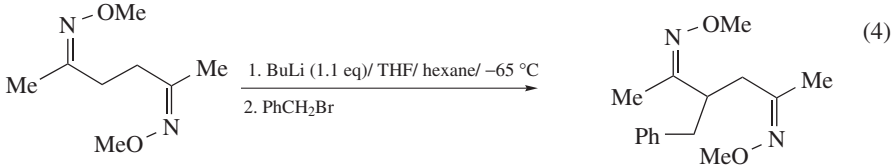
The reactions of dianions of cyclic oximes (for example, 4-*tert*-butylcyclohexanone oxime) have been shown to be highly regiospecific giving electrophilic substitution (for instance, with D_2O) only at the α-carbon[9]. The electrophile approaches the α-carbon from a direction perpendicular to the plane of the oximino group. Such an approach to 4-*tert*-butylcyclohexanone oxime would give two possible transition states—a chair-like and a boat-like transition state. Obviously, the chair-like transition state is more stable and should determine the configuration of the product. The ^1H NMR spectrum of the deuteriated 4-*tert*-butylcyclohexanone oxime, prepared from the corresponding dianion, showed that the α-hydrogen is *Z*-equatorial.

2. Reactions of oxime anions

(*Z*,*Z*)-Dioxime ether **8**, prepared from acetone *O*-methyl oxime **7** and BuLi/THF/hexane and I_2, afforded the benzylated oxime ether **9** in the presence of 1.1 equivalents of BuLi in THF/hexane and benzyl bromide at −65 °C (equation 4)[10]. Similar reaction of the (*E*,*E*)-dioxime ether **8** leads to **10**, the benzylation product of the oxime methyl group (equation 5)[10].

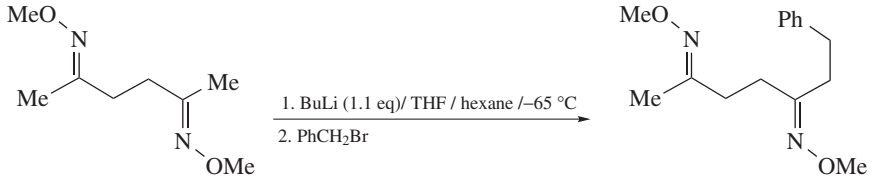


(**7**)



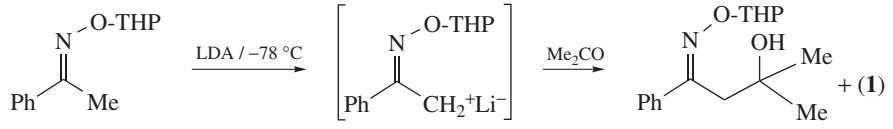
Z, *Z*-(**8**) (**9**) (4)

74%

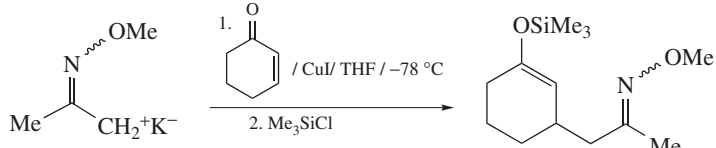


E, *E*-(**8**) (**10**) 60% (5)

Addition of acetone to the anion of acetophenone *O*-tetrahydropyranyl oxime (**11**), generated from the 68:32 mixture of *E*- and *Z*-isomers of oxime **1** and 1.1 equivalents of LDA at −78 °C, afforded a mixture of 25% *Z*-**1**, 10% of *E*-**1** and 65% of the *E*-isomer of oxime derivative **12** (equation 6)[3]. Conjugate addition of oxime anion **13** to cyclohexenone and further trapping with chlorotrimethylsilane leads to product **14** in 47% yield (equation 7)[11].

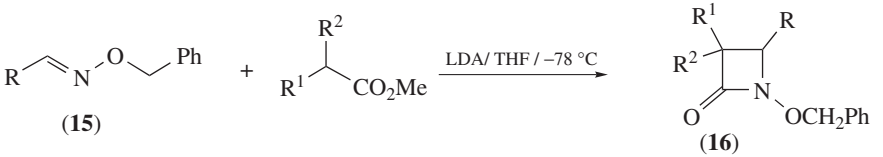


(**1**) (**11**) *E*-(**12**) 65% (6)



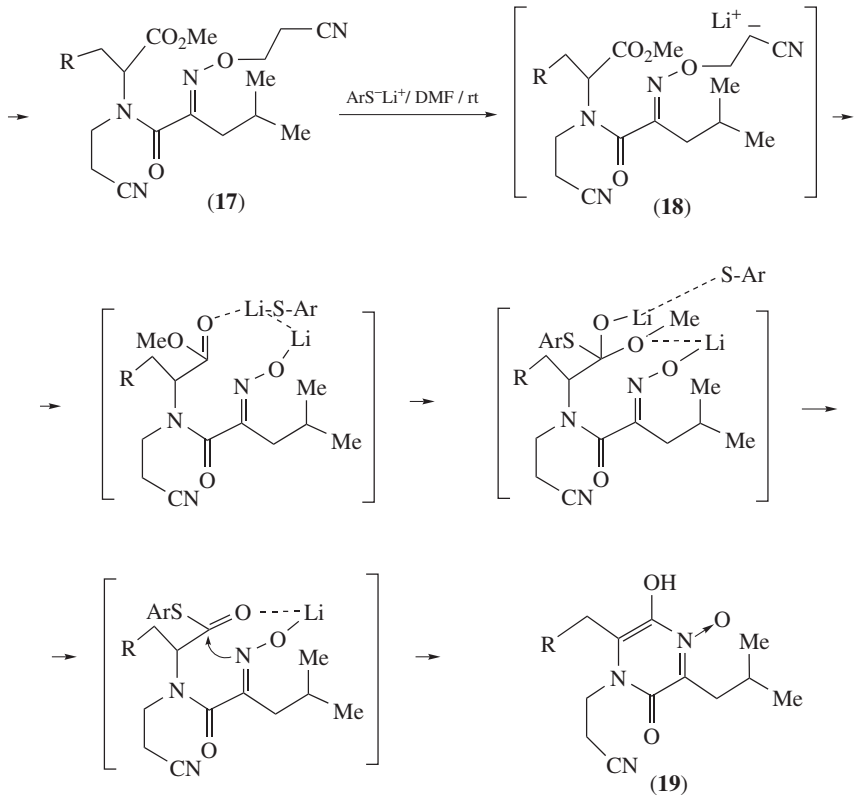
(**13**) (**14**) (7)

Oxime mono-carbanions were used in the preparation of heterocyclic compounds. Thus, reaction of aldoxime *O*-benzyl ethers **15** with methyl isobutyrate and related esters in the presence of LDA at −78 °C leads to *N*-benzyloxy-β-lactams **16** (equation 8)[12]. Cyclization of the anion of oxime *O*-ethers **18**, generated from oxime ether **17** and the lithium salt of 2-mercaptobenzimidazole (ArS^-Li^+), afforded pyrazine derivative **19** in 62% yield (equation 9)[13, 14].



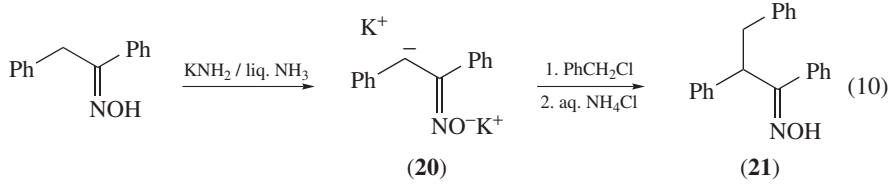
40–82% (8)

R = H, Me, Et; R^1, R^2 = Me, Et, Ph; R^1R^2 = $(CH_2)_5$, $(CH_2)_6$



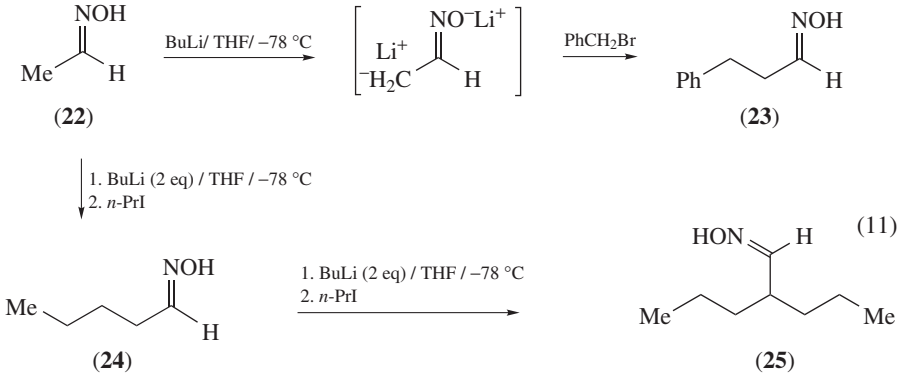
3. Reactions of oxime dianions

Historically, the first example of alkylation of oxime dianions was described in 1969[6]. Thus, 1,2-diphenylethanone oxime dipotassium salt (**20**) easily reacted with benzyl chloride in liquid ammonia to give the *C*-alkylation product **21** in 46% yield (equation 10). Alkylation of the oxime group did not occur. Benzylation of acetaldehyde oxime (**22**) gives the *C*-benzylated product **23** in quantitative yield. The interaction of oxime **22** with 2 equivalents of BuLi followed by *n*-propyl iodide afforded the *C*-alkylated product **24** in 96% yield. This product could be further alkylated affording product **25** (equation 11)[15].

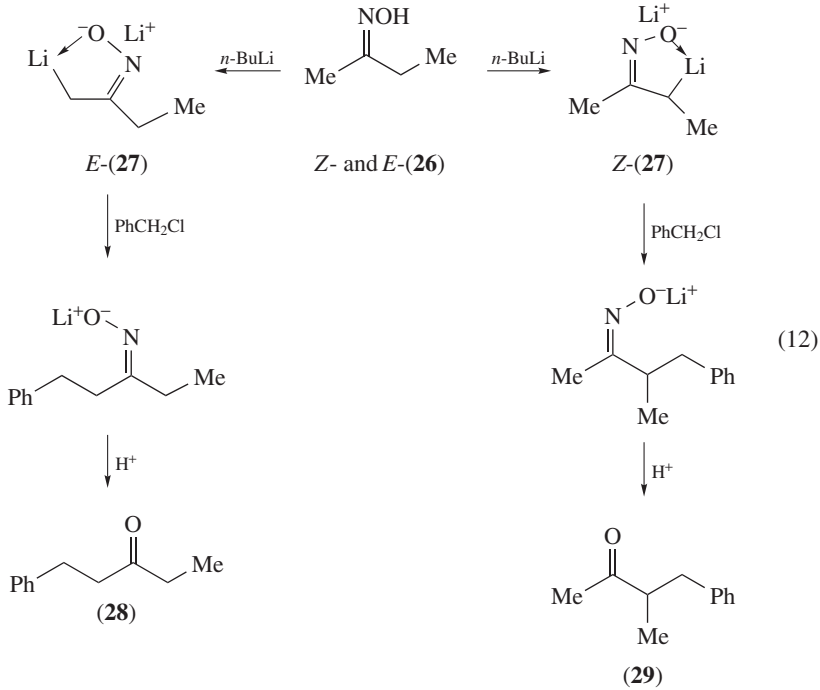


(9)

(10)

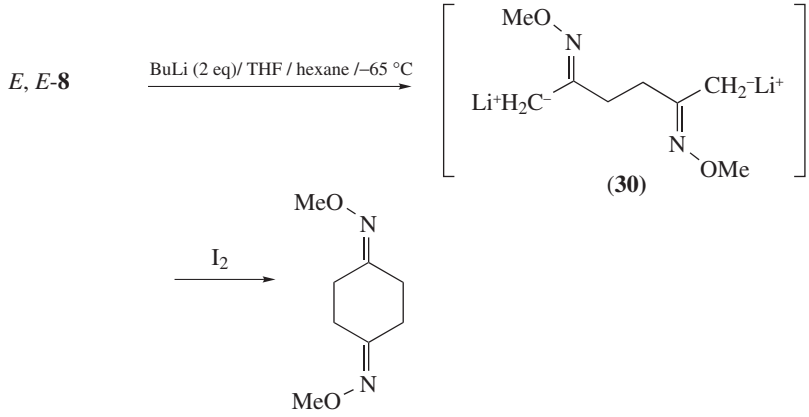


Interestingly, the benzylation of the dilithium salts 2-butanone oxime **27** (72:28 mixture of *E*/*Z*-isomers), generated from oxime **26** and BuLi in THF at −78 °C, proceeds in two ways. The *E*-isomer of dilithium salt *E*-**27** afforded after hydrolysis 1-phenylpentan-3-one (**28**). Reaction of (*Z*)-**27** with benzyl chloride and futher hydrolysis leads to 3-methyl-4-phenylbutane-2-one (**29**) (equation 12)[16].



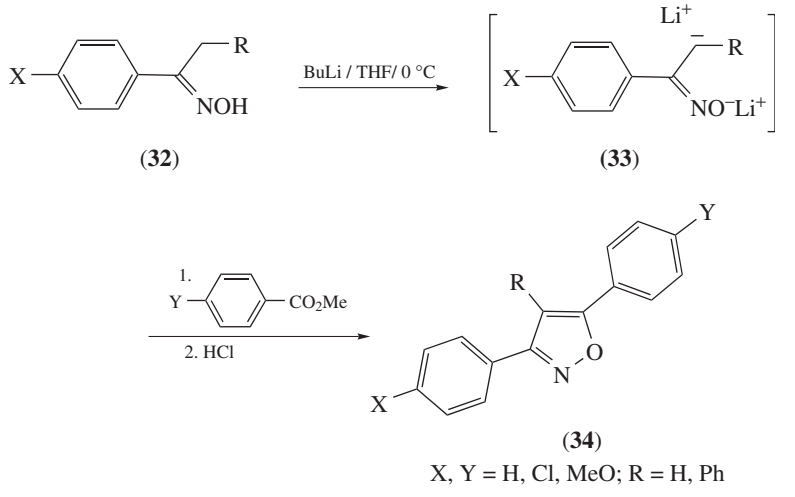
Methylation of cyclohexanone oxime dilithium salts in the presence of MeI afforded 2-methylcyclohexanone oxime[17].

(*E*,*E*)-Dioxime ether **8** and twofold excess of BuLi in THF/hexane at −65 °C afforded dianion **30** which, on treatment with an excess of iodine, afforded (*Z*,*Z*)-cyclohexane-1,4-dione bis(*O*-methyloxime **31** (equation 13)[10].

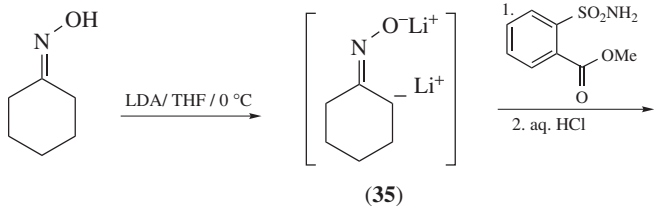


(13)

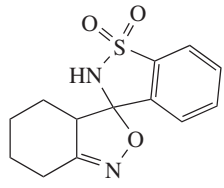
Synthesis of isoxazole derivatives from oxime dianions and various types of esters was described[18–27]. For example, the dilithium salts of substituted acetophenone oximes **33**, generated from oximes **32** and BuLi in THF at 0 °C, and aromatic esters afforded 3,4,5-trisubstituted isoxazoles **34** in yields up to 80% (equation 14)[18]. Treatment of cyclohexanone oxime dilithium salt (**35**) with methyl 2-sulfamoylbenzoate afforded spiroisoxazoline **36** (equation 15)[28].



(14)



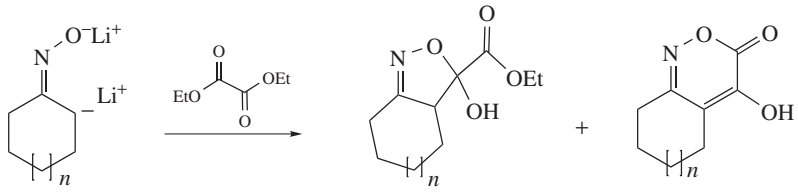
(**35**)



(**36**)
24%

(15)

The cyclization of dianions of cycloalkanone oximes **37** with diethyl oxalate afforded a mixture of 4,5-dihydro-5-hydroxyisoxazoles **38** and 1,2-oxazinones **39** (equation 16)[26].



(**37**)

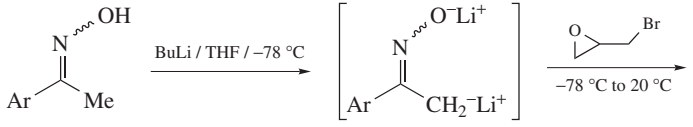
(**38**)
0–55%

(**39**)
0–47%

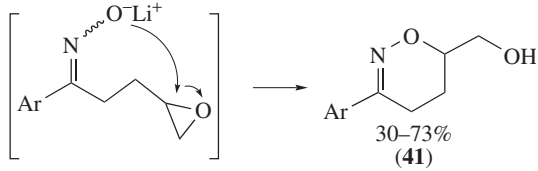
n = 1–3, 7

(16)

The one-pot cyclization of dilithiated oximes **40**, generated from the corresponding oximes and 2.5 equivalents of BuLi in THF at −78 °C, with epibromohydrin provided a convenient and regioselective approach to 6-hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazines **41** (equation 17)[29, 30].



(**40**)

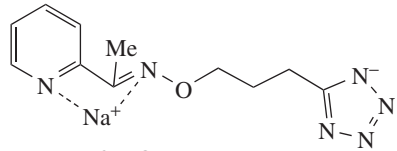


30–73%
(**41**)

(17)

4. Cytotoxicity of a sodium salt of an oxime

The sodium salt of *E*-isomer of *O*-[3-(5-tetrazolyl)propyl]oxime of 2-acetylpyridine (**42**) whose structure was confirmed by X-ray crystallography exhibits high cytotoxicity on a human fibrosarcoma (HT-1080, IC_{50} 1.4 μg kg^{-1}) cancer cell line[31].

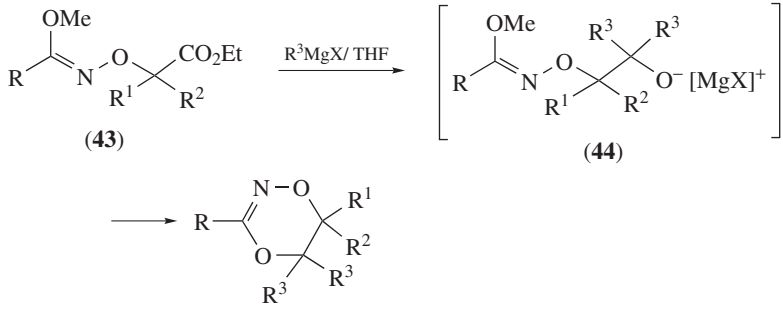


(**42**)

B. Group 2

1. Synthesis, structure and reactions

Some articles have been dedicated to the synthesis of metal derivatives of Group 2. It was known that Grignard reagents react with the oxime C=N double bond forming the corresponding addition products. However, sometimes the formation of such products does not occur. Thus, the oxime magnesium compounds **44** can be generated from the hydroximate esters **43** in the presence of two equivalents of Grignard reagent in dry THF at 0 °C. On prolonged stirring at 0 °C or at reflux, compounds **44** afforded 1,4,2-dioxazines **45** (equation 18)[32].

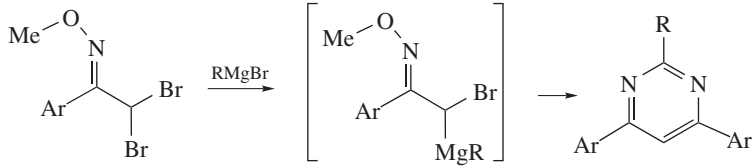


(**43**) (**44**) (**45**) (18)

R, R^2 = H, Me, Ph; R^3 = Me, Et, $CH_2CH{=}CH_2$

A magnesium intermediate was obtained from α,α-dibromooxime ethers **46** and Grignard reagent. This intermediate readily undergoes dimerization with loss of oxime ether groups and leads to 2,4,6-trisubstituted pyrimidines **47** (equation 19)[33].

The formation constants of metal complexes (for example, Ca(II)) with the oxime of 3-acetyl-4-hydroxycoumarin has been determined pH-metrically at 35 °C in 50% aqueous dioxane mixture. It was observed that, except in the cases of Co^{2+}, Ni^{2+} and Cu^{2+}, for which chelation through a nitrogen donor is more favored, all other ions prefer coordination through the oxygen donor forming both 1:1 and 1:2 complexes[34].



(**46**) (**47**) (19)

2. Catalysts for ethylene polymerization

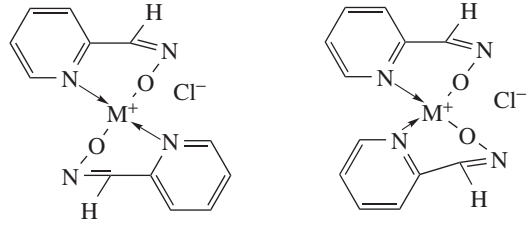
Oxime derivatives containing at least one element of Group 2 (for example, beryllium) were used as catalysts of ethylene polymerization[35].

C. Group 3 and Actinide and Lanthanide Series

1. Synthesis and structure

Syntheses of Group 3 metal complexes with oximes are well described in some reviews[2a–d]. Pyrazole-4,5-dione-4-oximes (LH) with metal ions (for example, Sc(III)) afforded complexes of type ML_2, $ML_2(H_2O)_2$ and $ML_2(py)_2$ (py = pyridyl)[36]. Sc^{3+}, Y^{3+} and La^{3+} violurate (isonitrosobarbiturate, VA) complexes were prepared. The IR spectra of these complexes showed that bonding takes place through coordination between the central metal ion and the oxygen atom of the oximino group. All the complexes detected by the X-ray powder patterns [the (2:3) Sc^{3+}–VA and (2:3) Y^{3+}–VA complexes, (1:2) Sc^{3+}–VA, (1:2) Y^{3+}–VA and (1:2) La^{3+}–VA complexes, and the (1:3) Y^{3+}–VA and (1:3) La^{3+}–VA complexes] have similar X-ray diffractions, electronic and IR spectra and chemical formula[37].

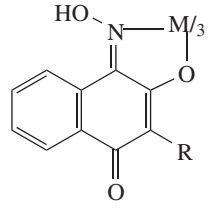
Some works were dedicated to structural investigation of lanthanoids complexes of oximes. Thus, work on bidentate 2-pyridine aldoxime complexes with lanthanoids such as samarium, europium, gadolinium, dysprosium and ytterbium showed that these complexes were published. These complexes **48a** and **48b** can be prepared from the corresponding metal chlorides and 2-pyridinealdoxime using a 1:3 MCl_3:ligand molar ratio in EtOH[38]. Reactions of pyridine oxime ligands with various lanthanoid salts were reviewed[2a]. The reactions between equimolar quantities of $[M\{(2\text{-Pyr})_2C{=}NOH\}_2(H_2O)_2](NO_3)_2$ (where M = Mn, Ni, Cu, Zn) and $Ln(NO_3)_3{\bullet}xH_2O$ (Ln = lanthanoid) in various solvents lead to hexanuclear clusters of the general formula $[M_3Ln_3\{(2\text{-Pyr})_2CNO\}_6(NO_3)_9$[1a]. Beside this Y^{3+}[39], La^{3+}[40], Nd^{3+}[41], Gd^{3+}[42], Er^{3+}[43] and U^{6+}[44–48] complexes with different oxime ligands were described.



(**48a**) (**48b**)

2. Antibacterial and antifungal activity

A series of Ho(III)[49] and Er(III)[50] complexes of 2-hydroxy-1,4-naphthalenedione-1-oxime **49** was tested against *S. aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Providencia stuartii, E. coli, Proteus morganii, Salmonella typhimurium, Xanthomonas campestris, Candida Albians* and *Acinetobacter baumannii*. The chelates of holmium with lawsonemonoxime (R = H) and 3-bromolawsonemonoxime showed high antibacterial activity against all microorganisms except *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *S. aureus*. Erbium(III) complexes of 2-hydroxy-1,4-naphthalenedione-1-oxime exhibit higher antifungal activity in comparison with antibacterial activity.



(**49**)

M = Er, Ho; R = H, Me, Cl, Br, I

D. Group 4

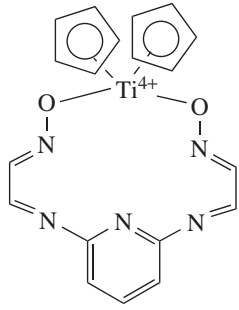
1. Synthesis and structure

Synthesis of metal alkoxide complexes of type $M(OR)_{n-x}(ON{=}CR^1R^2)_x$ (where M = Ti, Zr; R = alkyl, R^1, R^2 = H, alkyl, aryl; $n = 4$) was successfully realized in inert solvents (for example, benzene) by treatment of the corresponding metal alkoxides with oxime ligands[51–53]. More recently, it was shown that titanium and zirconium tetra-*n*-butoxide react with dimethylglyoxime and salicylaldoxime forming 1:2 complexes. On the other hand, both 1:1 and 1:2 complexation ratios of the same metal alkoxides were observed with the ligand acetone oxime[54]. Oximes of *o*-hydroxybenzaldehydes (H_2L) react with $Ti(OPr\text{-}i)_4$, forming complexes with general formula $Ti_3(L_2)(OPr\text{-}i)_8$ where each oxime bridges between the three titanium centers[55].

Oximate (Ox) complexes of bis(cyclopentadienyl)zirconium(IV) chloride (Cp_2ZrCl_2) having general formulae $Cp_2Zr(Ox)$, $Cp_2Zr(OxH)Cl$ and $Cp_2Zr(OxH)_2$ (where $OxH_2 = RC_6H_4C(OH)R^1{=}NOH$ and $PhC(=NOH)CH(OH)Ph$) have been synthesized from Cp_2ZrCl_2 and an oxime ligand in THF in the presence of triethylamine at room temperature[56]. Synthesis of zirconium poly-*O*-amidoximes from the corresponding amidoximes and Cp_2ZrCl_2 was also described[57]. Finally, the zirconium oxime complex $[(acac)Zr\{ONC(Me)(2\text{-}Pyr)\}_2]$, which exhibits the presence of a central zirconium atom in coordination number eight, can be obtained from the oxime of 2-acetylpyridine[58].

2. Antibacterial activity

The reaction of bis(cyclopentadienyl)titanium(IV) (or zirconium(IV)) dichloride with imineoxime ligands (LH_2) afforded metallocycles of type $[Cp_2M(L)]$. The antibacterial activity of complexes and ligands has been screened against Gram positive *Bacillus subtilis* and Gram negative *Escherichia coli*. The best activity was recorded with bis(cyclopentadienyl)titanium(IV) derivatives with a ligand derived from



(**50**)

2,6-diaminopyridine **50**. All zirconium complexes were less active than the titanium complexes[59].

E. Group 5

1. Synthesis and structure

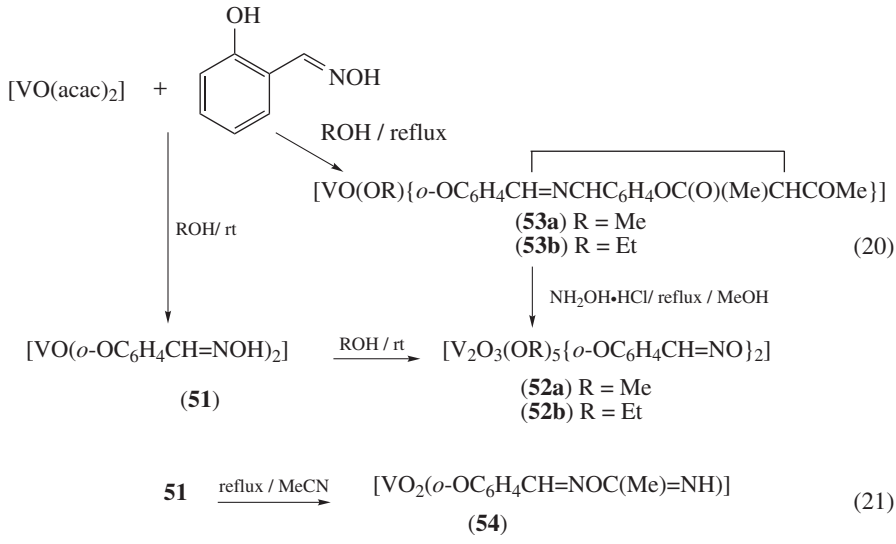
Synthesis, structure and reactions of metal complexes of Group 5 (mainly vanadium) with oximes were reviewed[2a–c]. Generally, reaction of vanadyl sulfate with phenolic oximes (H_2SalR) leads to the formation of neutral vanadium(IV) complexes [$VO(HSalR)_2$]. The complex [$VO(HSalMe)_2$] has pseudomacrocyclic structure with a hydrogen bond stabilized *trans* arrangement of ligands. New heteroleptic oxovanadium(V) chloro oximato complexes of the type [$VO\{Cl)_{3-n}\{ON{=}C(Me)(Ar)\}_n$ (where Ar = 2-furyl, 2-thienyl, 2-pyridyl; $n = 1, 2$) have been synthesized in excellent yields by the reaction of $VOCl_3$ with sodium salts of oximes in refluxing benzene. X-ray diffraction study of the product [$VOCl\{ON{=}C(Me)(2\text{-thienyl})\}_2$]•MeOH, obtained from recrystallization of [$VOCl_2\{ON{=}C(Me)(2\text{-thienyl})\}_2$] from a methanol–hexane mixture, shows that the vanadium(V) atom is heptacoordinated with distorted pentagonal bipyramidal geometry. The oxo-atom occupies the axial position while the weakly coordinated MeOH group is *trans* to the V=O atom. The two oximato ligands in the approximate plane are bonded to the central vanadium atom in a dihapto (η^2-N, O) manner with the formation of three-membered rings[60].

At room temperature the reaction of salicylaldoxime with [$VO(acac)_2$] in MeOH yields complex **51** isolated in 25% yield as a green powder. From the remaining solution brown crystals of complex **52a** were then isolated. Similarly, in the presence of EtOH complex **52b** was obtained. Heating salicylaldoxime with [$VO(acac)_2$] in methanol or ethanol afforded complexes **53** (equation 20)[61]. Electrochemical investigation of the redox properties of oxovanadium(IV) complexes with oxime ligands was recently published[62].

The μ-oxo-bis{diethoxy[salicylaldoximato]niobium(V) complex [$Nb_2O(C_7H_5NO_2)_2$-$(C_2H_5O)_4$] exhibits doubly deprotonated salicylaldoxime ($C_7H_5NO_2$) groups. The two niobium atoms are six-coordinate in an octahedral geometry[63].

2. Reactions

Recrystallization of complex **51** from acetonitrile afforded compound **54** (equation 21). The molecular structure of complex **54** displays a square pyramidal geometry with one oxo ligand in the apical position[61].



(20)

(21)

F. Group 6

1. Synthesis and structure

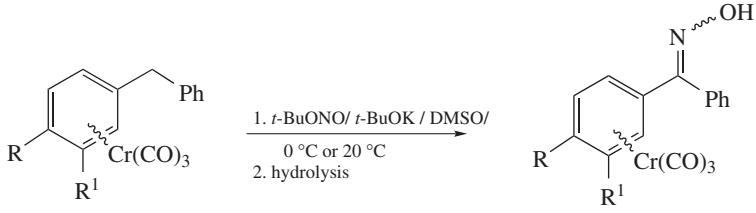
Syntheses of metal complexes of Group 6 with oximes were reviewed[2a–d] and a short review on the synthesis and reactions of complexes of di-2-pyridyl ketoxime with chromium carboxylate was recently published[64]. Thus, investigation of the ratio of the chromium derivative $[Cr_3O(O_2CCMe_3)_6(H_2O)_3](O_2CCMe_3)$ and di-2-pyridyl ketoxime, the reaction temperature and the nature of the counterion on the oxime complex formation was carried out. Depending on the reaction conditions, complexes of type $[Cr_2\{(Py)_2CNO\}_4]\bullet 2H_2O$, $[Cr_3OCl(O_2CCMe_3)_4\{(Py)_2CNO\}_2]\bullet 2Me_2CO$ and $[Cr_3O(O_2CCMe_3)_4\{(Py)_2CNO\}_2(H_2O)](NO_3)\bullet H_2O\bullet 0.5Me_2CO$ have been isolated and structurally characterized by X-ray studies[64]. Hexacoordinated cyanonitrosyl complexes of the type $[Cr(NO)(CN)_2(L)_2(H_2O)]$ have been prepared by the reaction of $K_3[Cr(NO)(CN)_5]\bullet H_2O$ with aromatic aldoximes (L) in aqueous AcOH[65].

Synthesis of arene chromium carbonyl complexes[66] with aromatic oximes was described in 1987[67]. Thus, in the basic media arene chromium complexes **55** were oximated in the benzylic position to afford a mixture of *Z*- and *E*-isomers of the oxime chromium complexes **56** (equation 22)[67]. Further studies of the enzymatic resolution of aromatic tricarbonyl benzaldehyde chromium complexes **57** using *Humicola lanuginosa* and *Pseudomonas cepacia* lipase allowed obtaining these compounds in an optically active form[68].

An asymmetrical dinuclear molybdenum complex $[Mo_2O_5(Hbao)_2]$ with benzamide oxime ($PhC(NH_2)NOH$, H_2bao) and rare linear tetranuclear molybdenum complex $[Mo_4O_{11}(H_2mbao)_2(Hmbao)(mbao)]$ with *p*-methylbenzamide oxime (H_2mbao) have been prepared and characterized by X-ray diffraction. In a typical experiment a solution of $(Bu_4N)_4[\alpha\text{-}Mo_8O_{26}]$ and $PhC(NH_2)NOH$ in acetonitrile was refluxed for 6 h and complex $[Mo_2O_5(HBao)_2]$ deposited as yellow-orange crystals[69].

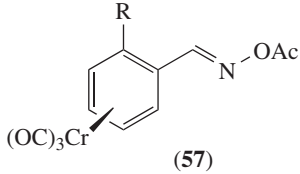
The reactivity of α-benzoin oxime (Ph(CHOH)−(C=NOH)Ph) (H_2L) with Mo(VI) ions depends on the pH of the aqueous metal ion solution and the ligand/metal ratio. Thus, a mixture of two complexes $[MoO_2(HL)_2]\bullet H_2O$ and $[Mo_2O_5(HL^1)_2(L^1)_2]\bullet H_2O$

(L^1 is the deprotonated oxidized form of α-benzoin oxime, Ph(C=O)(C=NO)Ph) was obtained[70]. High yield synthesis of oxodiperoxo-molybdate $PPh_4[MoO(O_2)_2(HPEOH)]$ and -tungstate $PPh_4[WO(O_2)_2(HPEOH)]$ complexes with 1-(2-hydroxyphenyl)ethanone oxime ($HPEOH_2$) ligand has been achieved by adding methanol solution of the ligand to a solution obtained by dissolving molybdic (or tungstic) acid in H_2O_2 and precipitating the complexes using tetraphenylphosphonium chloride[71]. Thermal reactions of $Mo(CO)_6$ with dimethylglyoxime (H_2DMG) in THF solution afforded a mixture of products $Mo(H_2DMG)_3$, $Mo_2O_6(H_2DMG)_2$ and $Mo_2O_4(CO)_2(H_2DMG)_2$[72].



(**55**) (**56**) 37–80% (22)

R, R^1 = H, OMe, alkyl



(**57**)
R = F, Me, OMe

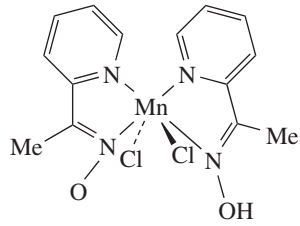
2. Molybdenum(VI) and tungsten(VI) complexes as catalysts

Complexes $PPh_4[MoO(O_2)_2(HPEOH)]$ and $PPh_4[WO(O_2)_2(HPEOH)]$ were successfully used as catalysts in olefin epoxidation with H_2O_2. These catalysts were used in the oxidation of alcohols, amines and sulfides. The catalysts exhibit high activity in olefin epoxidation, giving high yield of products, high turnover number and turnover frequency. The method is environmentally benign and cost effective[71].

G. Group 7

1. Synthesis and structure

Syntheses of metal complexes of Group 7 with oximes are extensively described in reviews[2a–d]. Manganese(II)[73–82] and manganese(III)[80–84] complexes with oxime ligands are presented. Thus, the dichloro[1-(2-pyridyl)ethanone oximato][1-(2-pyridyl)ethanone oxime]manganese(III) (**58**) or $[MnCl_2\{(2\text{-Pyr})C(Me)NOH\}\{(2\text{-Pyr})C(Me)NO\}]$ has been prepared by the reaction of the oxime of 2-acetylpyridine with $MnCl_2$. The metal ion is coordinated by a chloride ligand, an *N*,*N*′-chelating 2-acetylpyridine oxime and deprotonated oxime ((2-pyridyl)C(Me)NO) molecule. This six-coordinate molecule is the *cis-cis-trans* isomer considering the positions of the coordinated chlorine atoms, pyridyl



(**58**)

and oxime nitrogen atoms, respectively. There is an intramolecular OH···Cl coordinated hydrogen bond. The molecules are linked by intermolecular C−H···O and C−H···Cl hydrogen bonds[85].

The chemistry of technetium, including reactions with oxime ligands, is well described in a monograph[86] and articles[87, 88]. Typically, oxime complex $TcCl(DMG)_3$ and $TcCl(CDO)_3$ (DMG = dimethylglyoxime, CDO = cyclohexanedionedioxime) can be preapared from TcO_4^- and oxime ligand using triphenylphosphine or $SnCl_2$ as the reductant[89]. When the reaction of TcO_4-anion was carried out with threefold excess of dioxime ligands in the presence of boronic acids ($RB(OH)_2$), $SnCl_2$ and HX (X = halogen) complexes of the general structure of [TcX(dioxime)$_3$BR] were obtained[86].

The synthesis of rhenium complexes of oximes was described in several works[90–93]. Interestingly, the rhenium–dimethylglyoxime complex formed in hydrochloric acid solution has a metal-to-oxime ratio of 1:2, whereas in acetic acid solution it has a 1:3 ratio[90]. The oximes of 2-acetylpyridine (LOH) and $[Re(V)(NC_6H_4Y)Cl_3(PPh_3)_2]$ (where Y = H, Me, Cl) afford the complex $[Re(V)(NC_6H_4Y)Cl(PPh_3)(LO)]$[93].

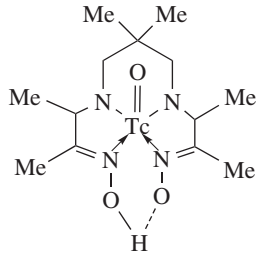
2. Manganese complexes as catalysts

Manganese complexes of benzoin oximes were investigated as catalysts for the oxidative coupling of phenolic monomers[94, 95]. For example, in the presence of α-benzoin oxime manganese complex 2,5-dialkylphenols undergo oxidative coupling to afford poly(2,5-dialkyl-1,4-phenylene oxides)[95].

3. Biological activity

Metal-to-ligand 1:2 complexes with molecular formula $[Mn^{2+}(HL)_2]$ (HL = 2-formyl thymol oxime) have been prepared and tested for antimicrobial activities against *Escherichia coli, Pseudomonas putida, P. fluorescence* and *Bradyrhizobium japonicum* and fungal cultures *Aspergillus niger, A. flavus, Fusarium oxysporum* and *Alternaria alternata*. It was found that complexation with manganese considerably increases antibacterial activity in all cases. Complexation was found to be effective in increasing antifungal activity of most of the complexes for all species except *Fusarium oxysporum*[96]. This fungicidal activity of oxime derivatives with manganese salts was also described in some patents[97, 98].

Biological activity of technetium complexes of oximes is described in a monograph[86]. Some recent studies of the application of technetium-99m oxime complex (**59**) (Ceretec™) and related oxime complexes for the diagnosis were described in several works[99–108].



(**59**)

H. Group 8

1. Synthesis and structure

Syntheses of metal complexes of Group 8 with oximes are widely described in reviews[2a–d]. One of the first works dedicated to synthesis of red color complexes of Fe(III) with different amidoximes was published in 1959[109]. Di-2-pyridyl ketoxime tetranuclear complex $[Fe_4O_2Cl_2(O_2CMe)_2\{(2\text{-}Pyr)_2CNO\}_4]$ can be synthesized by the 1:3 molar ratio reaction between $[Fe_3O(O_2CMe)_6(H_2O)_3]Cl$ and oxime. This complex was obtained also by 1:2:1 molar ratio reaction between Fe^{3+} ions, $MeCO_2^-$ and di-2-pyridyl ketoxime[110]. Synthesis of oligomeric iron–tetraoxime complexes was also described[111].

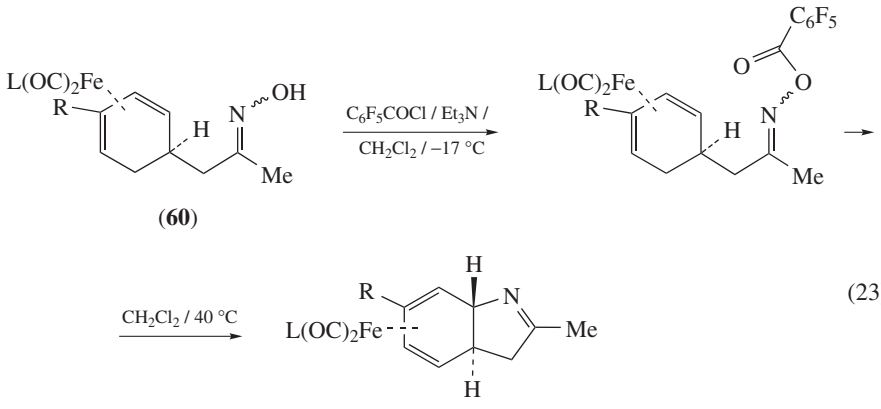
The formation and some reactions of ruthenium and osmium complexes with oximes were described in a review[112]. Synthesis of ruthenium(II)[112–116] and ruthenium(III)[117, 118] oxime complexes were described. Thus, ruthenium(III) choride with chalcone oxime (COH) afforded complex $[Ru(COH)_3Cl_3]$. However, 2-hydroxychalcone oxime (L) and $RuCl_3$ afforded complex $[Ru(L)_3]$ under similar conditions.

Synthesis of osmium oxime complexes were described in several works[119–121]. Reaction of $[Os_3(CO)_{11}(NCMe)]$ with phenyl 2-pyridyl ketoxime afforded clusters $[Os_3(CO)_8\{\mu\text{-}\eta^3\text{-}ON{=}CPh(2\text{-}Pyr)\}_2]$ and $[Os_3H(CO)_{11}\{\eta^2\text{-}ON{=}CPh(2\text{-}Pyr)\}]$ in 4 and 17% yields, respectively[122].

2. Reactions

Reaction of oximes **60** having (diene)$Fe(CO)_2L$ (L = CO, PPh_3) moiety with C_6F_5COCl/Et_3N in methylene chloride afforded unstable oxime esters, which easily undergo cyclization to dihydroindoles **61** in 61–100% yields (equation 23)[123].

Several works related to synthesis, structure and reactions of ferrocenyl oximes were published[124]. Ferrocenyl aldoxime **62** undergoes cycloaddition to excess of methyl acrylate to afford a mixture of four isoxazolines **63–66** in overall yields of 84% (equation 24)[125]. Ferrecenyl aldoxime also easily undergoes dehydration to the corresponding nitriles[126] and ferrocenyl ketoximes in the system acetylene/KOH/DMSO afforded ferrocenyl pyrroles[127]. Cycloplatination of ferrocenyl oximes by *cis*-$[PtCl_2(OSMe_2)_2]$ afforded Pt(II) and Pt(IV) complexes[128].



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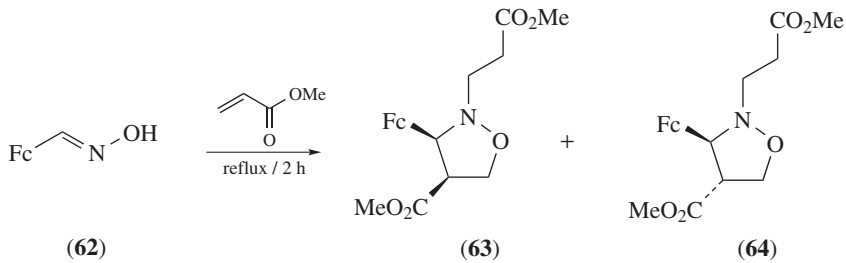


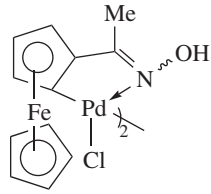
(24)

ratio **63**:**64**:**65**:**66** = 1:1.1:1.2:3.8

Fc = ferrocenyl

3. Ligands in catalysis

Cyclopalladated complexes of ferrocenyl oximes **67** exhibit high catalytic activity in the Mizoroki–Heck reaction[129].



(**67**)

4. Biological activity

Vicinal Ru(III) complexes with carbonyl oxime and oxime imine ligands exhibit superoxide dismutase mimetic activity (SOD). These complexes are able to inhibit the reduction of nitroblue tetrazolium. The results demonstrate that most of the complexes have promising SOD-mimetic activity[130].

I. Group 9

1. Synthesis and structure

Syntheses of metal complexes of Group 9 with oximes have been reviewed[2a–e]. Co(II)[73, 74, 131–134] and Co(III)[135–140] metal complexes with oxime ligands were extensively described in the literature. Typically, cobalt(II) halide and 2-furancarboxaldehyde oxime in ethanol at 50 °C afforded complexes $[CoX_2(oxime)_4]$ (X = Cl, Br)[73]. When (η^5-cyclopentadienyl)bis(ethylene)cobalt (Jones reagent), (η^5-cyclopentadienyl)di(carbonyl)cobalt and bis(η^5-cyclopentadienyl)cobalt (cobaltocene) were reacted with oximes, they gave the corresponding cobalt oxime sandwich complexes[141].

The stereochemistry of a new class of models of the vitamin B_{12} system, containing pyridylimino oxime $[C_5H_4N(CH_2)_nNC(Me)NO^-$; $n = 1$, L^1; $n = 2$, $L^2]$ and pyridylamino oxime $[C_5H_4N(CH_2)_nNHCH(Me)C(Me)NO^-$; $n = 1$, L^3; $n = 2$, $L^4]$ ligands have been investigated by molecular mechanics calculations. It was shown that among all possible diastereomers of the imino complexes $[Co(L^{1,2})_2]$, the minimum strain energy is exhibited in a *mer* configuration. For the amino complexes $[Co(L^{3,4})(HL^{3,4}]$, the minimum is exhibited in a *fac* configuration[142].

Rh(III) ions easily form various types of complexes with different oxime ligands[143–152]. Treatment of the acetonitrile complex *mer*-$[RhCl_3(MeCN)_3]$ with cyclopentanone oxime leads to two complexes that contain chelated iminoacetyl ligands $[RhCl_3\{NH{=}C(Me)ON{=}C(C_4H_8)\}\{HON{=}C(C_4H_8)\}]$ and $[RhCl_2\{NH{=}C(Me)ON{=}C(C_4H_8)\}_2]Cl{\bullet}1.5H_2O$[149]. Reaction of the oximes of salicylaldehyde, 2-hydroxyacetophenone and 2-hydroxy-1-naphthaldehyde (HL) with $[Rh(PPh_3)_3Cl]$ afforded rhodium(III) complexes of structure $[Rh(PPh_3)_2(HL)(L)]$[151]. Electrochemical investigation of Co- and Rh-oxime complexes was also described[153].

X-ray crystal structures of Ir(III) complexes with various oxime ligands were reported[154, 155].

2. Oxime complexes as polymerization inhibitors and catalysts

In order to shed light on the role of oxime additives as blocking agents of the cobalt-catalyzed autooxidative drying in the alkyd paints, various technologies have been applied. From $CoCl_2$ and methyl ethyl ketoxime (meko) the highly unstable complex $[Co(meko)Cl_2]_n$ has been isolated. It has been established that the free radicals formed in the coating composition may readily add to the C=N double bound of the oxime, producing stable radical addition products that could inhibit further free radical chain reactions[156]. Besides, this Co(II) and Cu(II) dinuclear complexes with oxime ligands were used as catalysts for hydrolysis of phosphate diester[157].

3. Biological activity

Reaction of the cyanide complexes of type $[Co(CN)(DH)_2L]$ (where L = thiourea, acetamide, formamide, semicarbazide, pyrazole and aniline, DH = dimethylglyoxime) with benzyl(aqua)cobaloxime $[PhCH_2Co(DH)_2OH_2]$ gives a series of cyano-bridged compounds of type $[PhCH_2Co(DH)_2(CN)Co(DH)_2L]$. The studied compounds exhibit high antibacterial activity against *Escherichia coli*[158]. Cobaloximes of type *trans*-$[Co(DH)_2(B)]X$ X = Cl, Br, I; B = pyrazine, pyrazinecarboxylic acid or pyrazine carboxamide) were also used as antibacterial agents[159].

The cobalt complexes of furan oximes exhibit high cytotoxicity to suspended tumor cell lines, e.g. leukemias, lymphomas, acute monocytic leukemia and uterine carcinoma. The cobalt complexes did not demonstrate dramatic cytotoxicity against the growth of tumors derived from solid tumor lines. The cobalt complexes preferentially inhibited L1210 DNA synthesis, followed by inhibition of RNA and protein synthesis from 25 to 100 μM over 60 minutes. These agents were inhibitors of DNA polymerase α activity[160]. Cobalt(III) salicylaldoxime complex was found to possess antiproliferative properties[161].

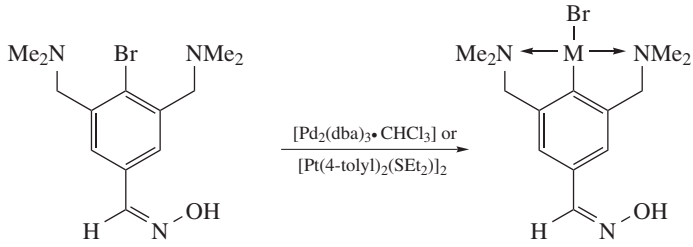
^{105}Rh complexes of 3-[*N*-(4-aminobenzyl)]amino-3-methyl-2-butanone oxime were used in internal radiotherapy[162].

J. Group 10

1. Synthesis and structure

Syntheses and reactions of Group 10 metal complexes with oximes were recently reviewed[2a–e]. Ni(II) metal complexes with oxime ligands are extensively represented in the literature[163–184]. Typically, the reaction of $Ni(NO_3)_3 \cdot H_2O$ with 2-[(2-pyridylethyl)imino]-3-butanone oxime (HDPE) in a 1:2 ratio afforded red crystals of $[Ni(HDPE)_2](NO_3)_2 \cdot 2H_2O$[168]. Several works were dedicated to the synthesis and investigation of the structure of nickel complexes of porphyrin oximes[185].

Different types of palladium(II) oxime complexes were also obtained[186–194]. Synthesis of oxime substituted palladium NCN-pincer complexes was recently described. Thus, irreversible chemoselective oxidative addition of $[Pd_2(dba)_3 \cdot CHCl_3]$ or $[Pt(4\text{-tolyl})_2(SEt_2)]$ to oxime ligand **68** afforded complexes **69** in almost quantitative yield (equation 25)[195].



(25)

(**68**) (**69**)

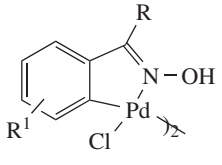
M = Pd, Pt

The structures of platinium(II) oxime complexes were studied in several works[187, 196–204].

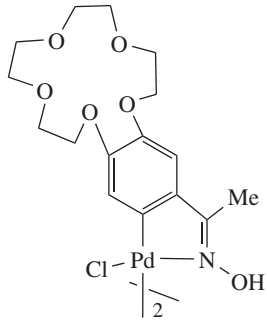
2. Oxime complexes as catalysts

Nickel(II) oxime derivatives were used as catalysts of vinyl polymerization[205], ethylene oligomerization[206] and cleavage of carboxylic esters in weakly acidic conditions[207].

Palladium(II) complexes with oximes are widely used in organic synthesis because of the high catalytic activity in the classical transition metal catalyzed reactions. The high potential of oxime palladacycles in catalysis is well reviewed[208–210]. Thus, oxime palladacycles **70**, obtained from an oxime and Li_2PdCl_4, exhibit high activity in carbon–carbon coupling reactions[211]. In addition, this type of oxime palladacycles shows high activity in Heck[212, 213] and Suzuki[214] reactions, as well as in the arylation of allyl alcohols[215] and siloxanes[216]. The catalytic activity of supported oxime–palladacycle catalysts was also investigated[217]. Pd(II) β-oximato phosphine complexes were used as catalysts in the Sonogashira coupling reactions[218]. Water-soluble oxime palladacycles **71** were used as potential 'green catalysts'[219].



(**70**)



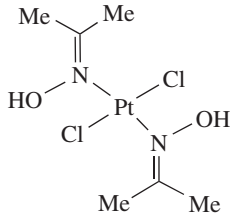
(**71**)

R = Me, aryl; R^1 = H, Cl, OMe

3. Biological activity

Mixed ligand complexes of type $[Ni(L)_2(L')_2]$ (LH = salicylaldoxime or 2-hydroxyacetophenone oxime; L′ = pyridine or imidazole) exhibit high nuclease

activity. Binding of metal complexes with calf thymus DNA is revealed by absorption spectrophotometry. The cleavage activity of complexes has been carried out on a double stranded pBR 322 circular plasmoid DNA by using gel electrophoresis in the presence and in the absence of oxidant (H_2O_2)[220]. The platinum complex with acetone oxime ligands *trans*-[Pt{$(Me)_2C{=}NOH$)}{$(Me)_2CHNH_2$}Cl_2] and its *cis*-isomer were investigated as cytotoxic agents. The ability of these complexes to cause either apoptotic or necrotic cell death was determined. Thus, these complexes were tested on NRK-52E (non-tumor, rat renal tubular) and HepG2 (human hepatoma) cells. The complex *cis*-[Pt{$(Me)_2C{=}NOH$)}{$(Me)_2CHNH_2$}Cl_2] was found to be the most active in NRK-52E cells, with an IC_{50} value of 5 μM at 48 h of treatment. The action of both platinum complexes was slower in HepG2 cells, but after 48 h the *cis*-isomer has an IC_{50} value of 89 μM[221]. The complex *trans*-[$PtCl_2$(acetoxime)$_2$] (**72**) exhibits high cytotoxicity on ovarian carcinoma cells[222].



(**72**)

K. Group 11

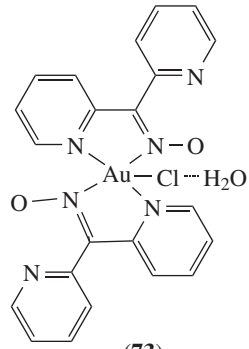
1. Synthesis and structure

Syntheses of metal complexes of Group 11 with oximes are described in reviews[2a–e]. Among metals of Group 11, the complexes of Cu(II) with oxime ligands are extensively represented in the literature[223–239]. Beside this, investigation of the synthesis and spectroscopic properties of the copper complex of porphyrin oxime was also described[240]. Ag(I)[241–243] and Ag(III)[244] complexes with oxime ligand are also documentated.

The crystal structure of chlorobis(*N*,*N*′-di-2-pyridyl ketone oximato)gold(III) hydrate (**73**) was also investigated. The structural analysis of this complex revealed the Au atom to be in a square-pyramidal coordination environment with the Au($C_{11}H_8N_3O)_2$Cl moieties linked by hydrogen bonds to water molecules to form centrosymmetric dimers. The gold atom achieves a coordination number of five with four N atoms nearly coplanar and the fifth position occupied by a Cl atom[245].

2. Corrosion inhibitors

The Cu surface was protected against corrosion with self-assembly formed oxime monolayers. Long alkyl chain oximes, such as dodecyl, hexadecyl and octadecyl, were synthesized and chemosorption conditions were established. The area occupied by octadecyl oxime and determined by a Lauda film balance was 0.27 nm^2. The best corrosion protection was found by Cu conductors modified with an octadecyl oxime monolayer, while the slowest dendritic growth was observed for conductor lines modified with a dodecyl oxime monolayer[246].



(**73**)

3. Biological activity

The copper complexes of furan oxime derivatives were found to be potent cytotoxic agents in both murine and human tissue cultured cell lines which were either suspended or solid tumors. These copper complexes of 2-furanaldoxime were effective inhibitors of L1210 (lymphoid leukemia) DNA synthesis followed by RNA synthesis. Purine synthesis regulatory enzyme activities were markedly reduced by the compounds with marginal inhibition of t-RNA polymerase, and nucleoside kinase activities[247]. Beside this antioxidant activity a curcuminooxime copper complex was described[248].

L. Group 12

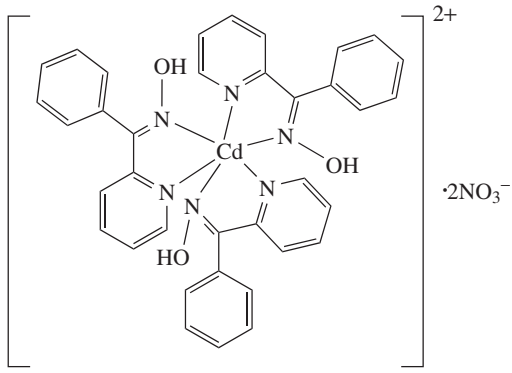
1. Synthesis and structure

Syntheses of metal complexes of Group 12 with oximes were recently reviewed[2a–f]. For example, zinc(II) ions readily afforded complexes with different oximes[249–252]. The reactions of an excess of 2-acetylpyridine oxime with $ZnCl_2$ in a mixture of ethanol and acetonitrile afforded the mononuclear complex $[ZnCl_2\{(2\text{-Pyr})C(Me)NOH\}_2]$ in moderate yield. The metal ion is coordinated by two chloro ligands and two *N*,*N*′-chelating 2-acetylpyridine oxime molecules. The reaction between equimolar quantities of $ZnCl_2$, 2-acetylpyridine oxime and $LiOH{\bullet}H_2O$ in EtOH/MeCN leads to the tetranuclear cluster $[Zn_4(OH)_2Cl_2\{(2\text{-Pyr})C(Me)NO\}_4]$ in high yield[252].

Cd(II)[253–258] and Hg(II)[256] complexes with oxime ligands were also described. Thus, addition of a solution of phenyl 2-pyridyl ketoxime in MeOH to a solution of $Cd(NO_3)_2{\bullet}4H_2O$ afforded complex **74** in 70% yield. The cadmium atom in **74** adopts a distorted octahedral geometry, being ligated by six *N*-atoms from three ketoxime ligands[258].

2. Corrosion inhibitors

Zinc pigments react with aqueous alkaline media (e.g. water-borne paints) by evolution of hydrogen. With the addition of aromatic 2-hydroxy oximes, aluminum and zinc pigments reacted completely differently. The overall corrosion inhibiting effect was significantly better for the aluminum than for the zinc pigment[259].



(**74**)

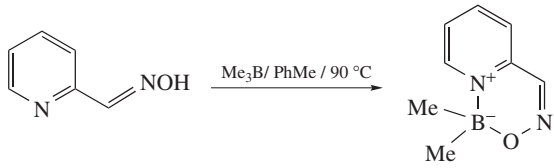
3. Biological activity

Fungicidal activity of oxime derivatives with ammoniacal zinc ethylene bisdithiocarbamate and zinc ethylene bisdithiocarbamate was described[97].

M. Group 13

1. Synthesis and structure

Syntheses of metal complexes of Group 13 with oximes were reviewed[2f]. Boron complexes with oxime ligands are described in the literature[260–262]. Thus, 2-pyridinecarboxaldehyde oxime **75** reacts with trimethylborane in toluene at 90 °C to form methane and complex **76** (equation 26)[262]. Beside this Al(III)[263, 264], Ga(III)[265–267] and Tl(I)[268] oxime complexes were also described.



(**75**) (**76**) (26)

2. Corrosion inhibitors

The overall corrosion inhibiting effect in the presence of 2-hydroxy oximes was significantly better for the aluminum than for the zinc pigment[259].

3. Biological activity

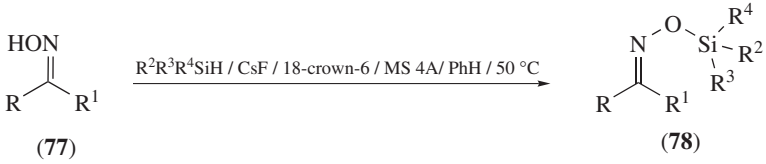
Radionucleotide procedures are useful in establishing or ruling out inflammatory bowel diseases in patients with intestinal complaints, in assessing disease severity in the

evaluation of extraintestinal septic complications. Widely available radionuclide procedures for ^{111}In oxime labeled white blood cells are described[269].

N. Group 14 (Silicon and Germanium)

1. Synthesis and structure of oxime O-silyl ethers

O-Silyl ethers of oximes are of interest as potential intermediates in organic synthesis[270, 271]. *O*-Trialkylsilyloximes were obtained in the reaction of the corresponding oxime with trialkylchlorosilane/Et_3N[272], hydrosilane/$ZnCl_2$[273], hydrosilane/H_2PtCl_6[272], hydrosilane/piperidine[274], Et_3SiNH_2[273], $(Me_3Si)_2NH$[275], $(Me_3Si)_2S$[276] and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide[277] or *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide[278]. Silyl ethers of oximes were also formed in the reaction of the corresponding carbonyl compounds with H_2NOSiR_3[279] or of imines with mono-, di- or trisilylated hydroxylamines[280]. Several works dealt with fluoride ion mediated silylation of oximes by azidotrimethylsilane[281], trimethylsilylacetylene[282] and hydrosilanes[283]. Thus, silylation of aromatic and heteroaromatic oximes **77** in the system hydrosilane/CsF/18-crown-6/PhH afforded silyl ethers **78** in yields up to 78% (equation 27). The mechanism includes formation of oxime anion and complex HF···Cs^+···18-crown-6. The positively charged complex [HF···Cs···18-crown-6]$^+$ serves as the source of proton. The next step of the reaction is the interaction of the oxime–hydrosilane complex with [HF···Cs···18-crown-6]$^+$. After formation of hydrogen molecule the oxime anion and silicon cation approach one another. The reaction is completed by formation of the desired products **78** (equation 28)[283].



(**77**) (**78**) (27)

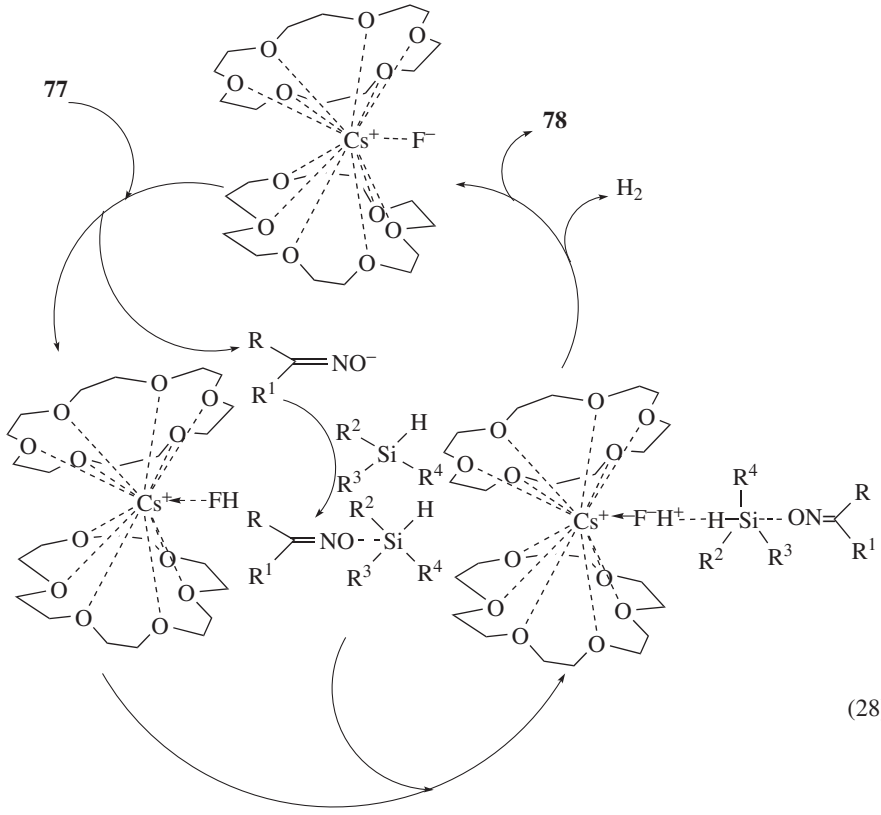
R = alkyl, Ph; R^1 = Et, Ph, 2-furyl, 2-pyridyl; R^2-R^4 = alkyl, aryl

Oxime silatranyl derivative **80** was successfully obtained by treatment of oxime **79** with 1-hydrosilatrane in refluxing xylene (equation 29)[284].

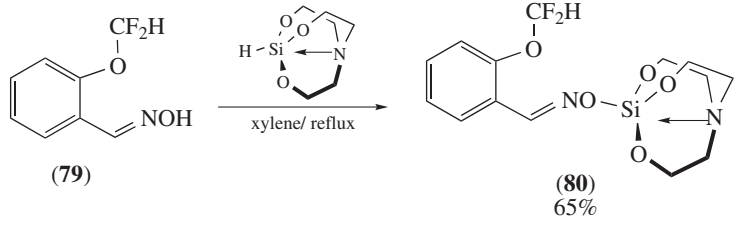
Synthesis of oxime *O*-silyl ethers by functionalization of *N*,*N*-bis(trialkylsiloxy)-enamines was widely presented in the literature[285–294]. Typically, reaction of enamines **81**, obtained by double silylation of the corresponding nitro compounds, with various nucleophiles (for example, Me_3SiCN) in the presence of base (for example, Et_3N) affords a mixture of modified *E*- and *Z*-isomers of oxime silyl ethers **82** (equation 30)[288].

Novel trimethylsilyl group mediated fragmentation in the cyclic nitronate leading to oxime silyl ether was described[295]. Thus, nitronate **83** in the presence of Me_3SiBr afforded cationic adduct **84**, which underwent [4 + 2] cyclofragmentation leading to silyl ether **85** in 75% yield (equation 31).

Ring opening of sugar derivatives by PPTS (pyridinium *p*-toluenesulfonate) and $MgSO_4$ followed by oximation ($H_2NOSiPh_2Bu$-*t*) afforded *O*-*tert*-butyldiphenylsilyl-oximes[296]. For example, sugar derivative **86** afforded silyl ether **87** in almost quantitative yield (equation 32).



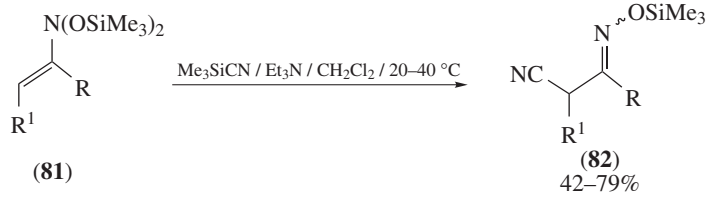
(28)



(**79**)

(**80**)
65%

(29)

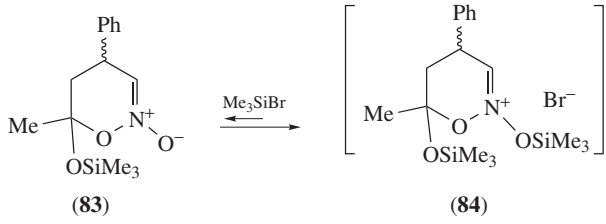


(**81**)

(**82**)
42–79%

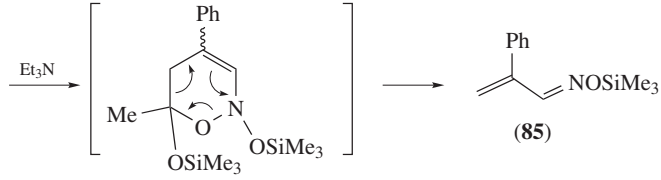
(30)

R = H, Me, Ph, CO_2Me, CO_2Et, $CH_2CH_2CO_2Me$; R^1 = H, Me

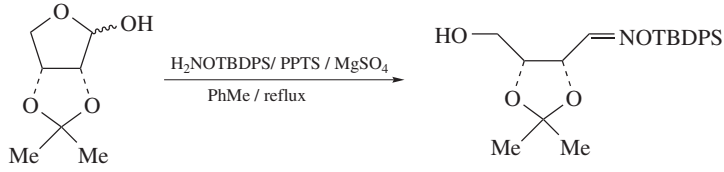


(**83**) (**84**)

(31)

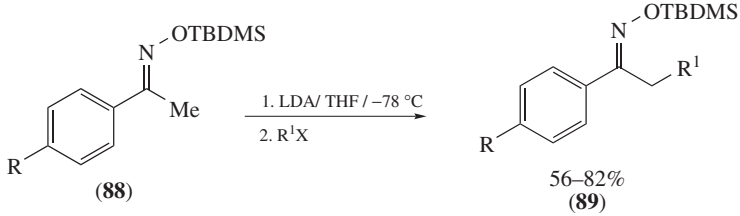


(**85**)



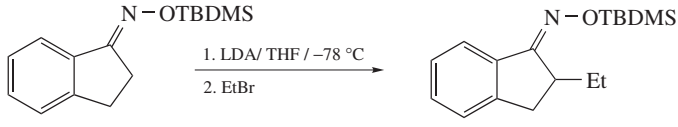
(**86**) TBDPS = $SiPh_2Bu$-*t* (**87**) (32)

Finally, *O-tert*-butyldimethylsilyl ketoximes **88** were selectively α-alkylated in the presence of LDA at −78 °C leading to oxime derivatives **89**. 1-Indanone oxime silyl ether **90** afforded ring-alkylated product **91** under similar conditions (equation 33)[297].



(**88**) 56–82% (**89**)

R^1X = MeI, EtBr, $PhCH_2Br$, Me_3SiCl (33)



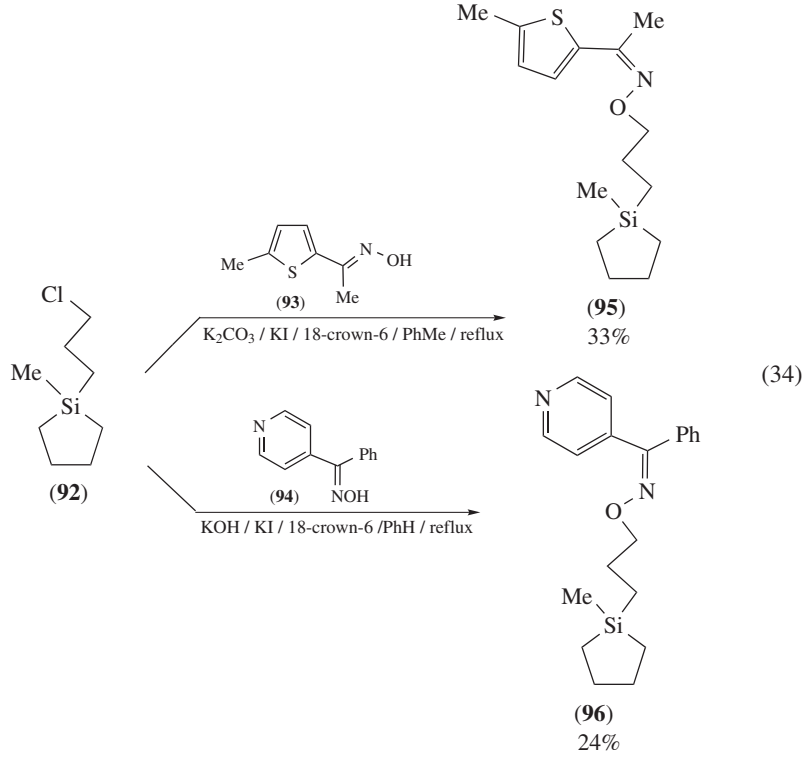
(**90**) 60% (**91**)

Silyl ethers of type $RSi(ON{=}CMe_2)_nCl_{3-n}$ easily react with Me_3SiNCO affording silanes $RSi(ON{=}CMe_2)_n(NCO)_{3-n}$ in 52−76% yields[298].

Structures of *O*-trialkylsilyloximes were investigated by using IR[299], mass spectroscopy[300] and NMR[301] methods. The structure of the monoclinic crystal phenyltris(acetoximoxy)silane ($Si(Ph)[ONC(Me)_2]_3$) was determined by using an X-ray crystallographic method. A feature of the investigated structure is the approach of the nitrogen atoms of the acetoxime groups to the central silicon atom by 2.50–2.55 Å, which leads to a decrease of the Si—O—N bond angles to 108.3–112.2° [302].

2. Synthesis of O-(trialkylsilylalkyl)oximes

O-(Trialkylsilylalkyl)oximes can be easily prepared using phase transfer catalytic alkylation of the corresponding oximes in the presence of solid KOH or K_2CO_3 [303, 304]. Thus, the best catalytic system for the alkylation of aromatic and thiophene oximes (e.g. **93**) with 1-(3-chloropropyl)-1-methylsilolane (**92**) was found to be solid K_2CO_3/solid KI/18-crown-6 at 100 °C. Oxime ether **95** was isolated in 33% yield. However, formation of **96** from solid KOH was preferable in the case of pyridine oxime **94** (equation 34)[304]. ^{13}C NMR chemical shifts of (*Z*)-3-(trimethylsilyl)propionaldehyde oxime were also recorded[305].



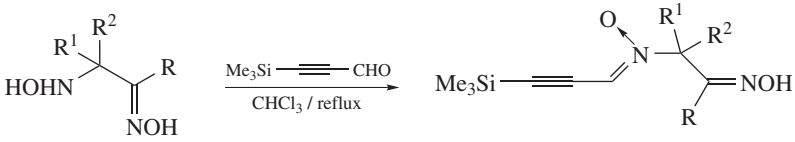
(34)

3. Synthesis of other silicon-containing oximes

Silicon-containing oximes were successfully obtained by treating the corresponding silicon-containing carbonyl compounds with $NH_2OH{\bullet}HCl$ in the presence of

pyridine/EtOH[306] or AcONa/EtOH[307]. Synthesis of silicon-containing *O*-methyl oximes was carried out starting from carbonyl compounds and *O*-methoxyamine hydrochloride in pyridine[308].

Trimethylsilylprop-2-ynal reacted with α-hydroxylamine oximes **97** in refluxing chloroform to give silylated oximes **98** (equation 35)[309].



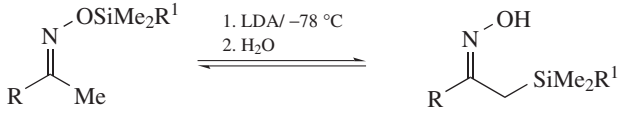
(35)

(**97**) (**98**)

R, R^1 = alkyl; R^2 = H, Me

52–80%

Anions generated from silyl ethers of methyl ketoximes **99** undergo rearrangement with 1,4-migration of the silyl group. Protonation of the oxime anion by water afforded α-trialkylsilyl ketoximes **100** in almost quantitative yield (equation 36). However, compounds **100** readily undergo thermal migration of the silyl group from carbon to oxygen leading to compounds **99**[310].



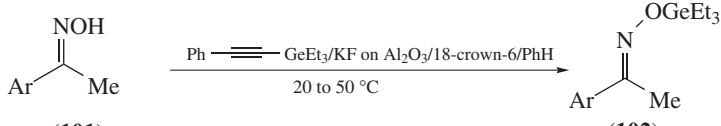
(36)

(**99**) (**100**)

R, R^1 = alkyl, aryl

4. Synthesis of germanium-containing oximes

The main group of methods for the synthesis of *O*-trialkylgermyloximes was based on the reactions of the corresponding oximes with trialkylchlorogermane in the presence of base, *O*-trialkyltin oximes with trialkylchlorogermane, oximes with Bu_3GeOEt[311] or oxime salts with triethylchlorogermane[312]. The reaction of oximes **101** with phenylethynyltriethylgermane in the PTC system KF on Al_2O_3 (1 equivalent)/18-crown-6/PhH at 20 to 50 °C led to *O*-triethylgermyloximes **102** in 71–100% yields (equation 37)[281].



(37)

(**101**) (**102**)

Ar = Ph, 2-furyl, 2-pyridyl

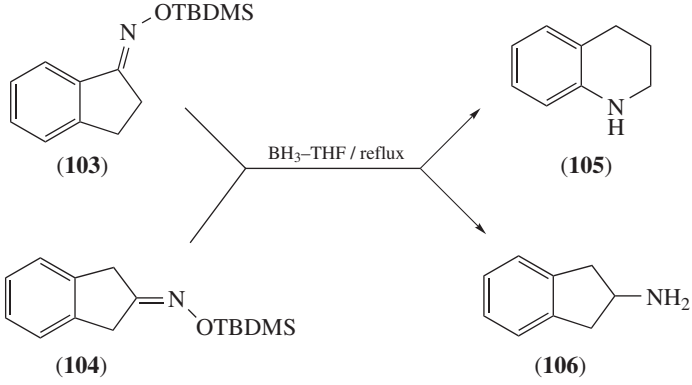
Germanium-containing oximes were successfully obtained by treatment of germanium-containing carbonyl compounds with $NH_2OH{\bullet}HCl$ in the presence of sodium carbonate[313]. Synthesis of germanium-containing *O*-benzyl oximes was carried out from carbonyl compounds and *O*-benzyloxylamine in methylene chloride[314].

The synthesis and characterization of complexes modified by germanium(IV) isopropoxide with oximes and their transformation to pure nano-sized germanium has been described[315]. Reaction of [Ge(OPr-*i*)$_4$] with oximes of 2-acetylfuran or 2-furancarboxaldehyde in 1:1 or 1:2 ratio afforded complexes of

the type $[Ge(OPr\text{-}i)_{4-n}\{ONC(R)(2\text{-furyl})\}_n]$ (where R = H or Me, $n = 1$ or 2). Tris(trifluoromethyl)germanium iodide is a new cross-linking agent in the synthesis of different types of mono- and binuclear iron(II) complexes with oxime ligands[316].

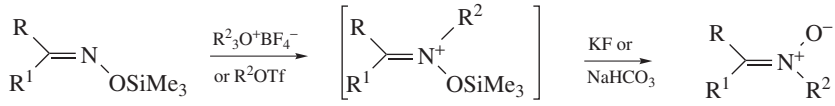
5. Reactions of silicon- and germanium-containing oximes

O-Silylated 4-substituted acetophenone oximes are readily reduced with borane in THF to *N*-ethylanilines[317]. Interestingly, 1-indanone *O*-*tert*-butyldimethylsilyloxime (**103**) in the presence of borane—THF complex afforded 1,2,3,4-tetrahydroquinoline (**105**) in 88% yield. 2-Indanone oxime *O*-*tert*-butyldimethylsilyl ether (**104**) gives only 2-aminoindane (**106**) under similar conditions (equation 38). Asymmetric reduction of ketoxime *O*-trimethylsilyl ethers by borane in the presence of chiral 1,3,2-oxazaborolidine derived from (−)-ephedrine afforded primary amines in excellent yields with *ee* up to 90%[318].



(**103**) (**105**) (**104**) (**106**) (38)

Aldoxime and ketoxime *O*-trimethylsilyl ethers **107** can be alkylated with trialkyloxonium tetrafluoroborates or alkyl triflates in CH_2Cl_2 to afford nitrones **108** in yields up to 93% (equation 39)[319].

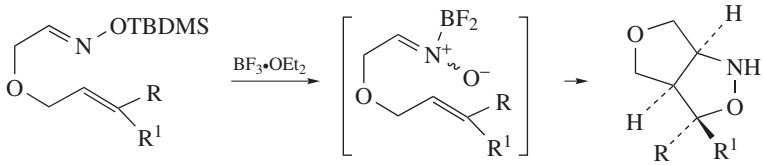


(**107**) BF_4^- or $(OTf)^-$ (**108**) (39)

R = alkyl, aryl; R^1 = H, Me; R^2 = Me, Et, $CH_2CH{=}CH_2$

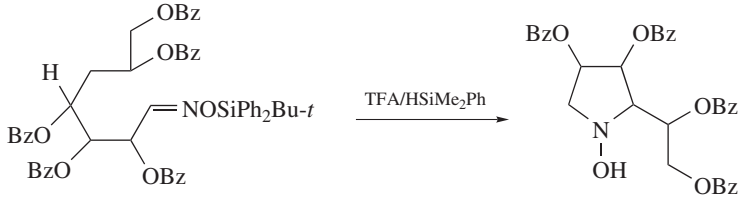
Synthesis of heterocyclic compounds from *O*-trialkylsilyloximes was widely presented in the literature. Intramolecular cycloaddition reaction of *O*-*tert*-butyldimethylsilyloximes having allyloxy moieties (**109**) was efficiently catalyzed by $BF_3{\bullet}OEt_2$. Bicyclic products **110** were isolated in yields up to 87% (equation 40)[320, 321].

The consecutive reduction and cyclization of *O*-benzoyl protected 5-*O*-methylhexose *O*-(*tert*-butyldiphenylsilyl)oxime (**111**) with dimethylphenylsilane in trifluoroacetic acid afforded the *N*-hydroxypyrrolidine (**112**) ring system in good yield (equation 41). The mechanism involves a cascade of neighboring group participation steps involving the *O*-benzoyl protecting groups[322].



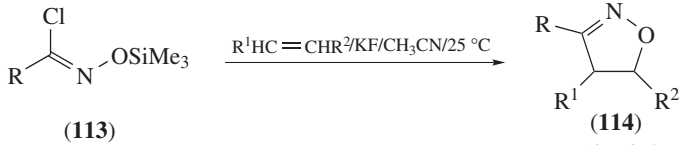
(**109**) (**110**) (40)

TBDMS = *t*-$BuMe_2Si$; R, R^1 = H, Me, Ph



(**111**) (**112**) 70–73% (41)

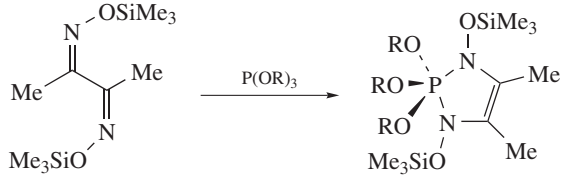
Some articles were dedicated to the synthesis of different isoxazole ring-containing compounds from silylated oximes[323–329]. Typically, silylated hydroxamoyl chlorides **113** easily react with various olefins in the presence of base (for example, KF) leading to isoxazolines **114** (equation 42)[323].



(**113**) (**114**) 10–79% (42)

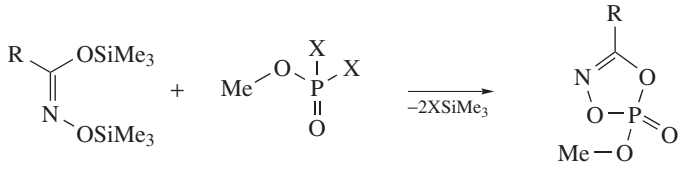
R = Me, Ph; R^1, R^2 = H, alkyl, CN, CO_2Me, $SiMe_3$

The silyl ether of dioxime **115** and phosphites afforded [1,3,2]diazaphosphole **116** (equation 43)[330]. Silyl ethers **117** and $(MeO)P(=O)X_2$ (X = Cl, F) (**118**) afforded 5-substituted 2-methoxy-[1,3,4,2]dioxazaphosphole 2-oxides **119** (equation 44)[331].



(**115**) (**116**) (43)

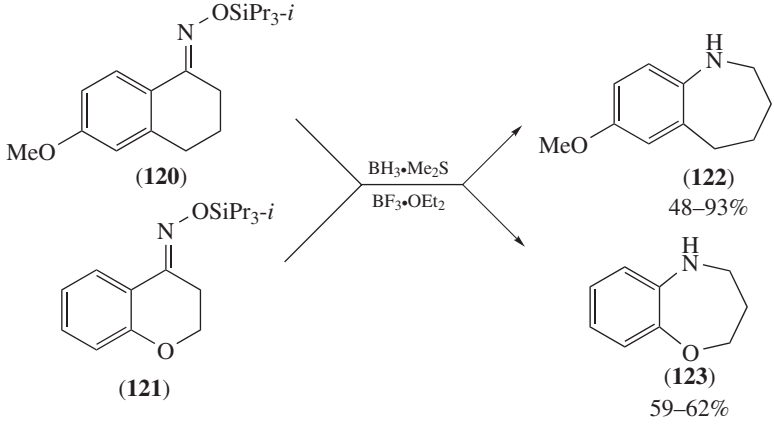
R = Me, Et, Ph



(**117**) (**118**) (**119**) 64–68% (44)

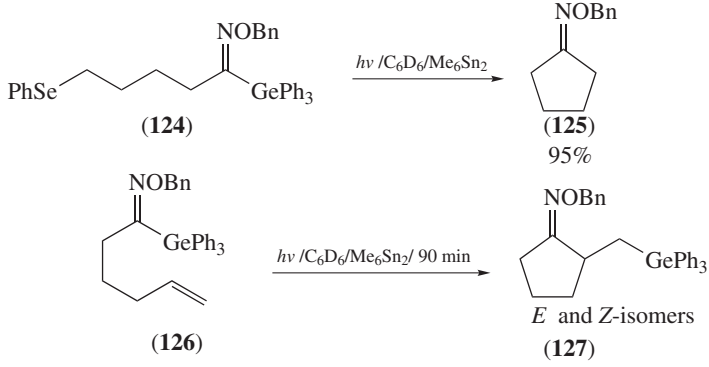
X = F, Cl; R = CF_3, *p*-$NO_2C_6H_4$

Large-membered rings **122** and **123** were successfully obtained by reduction of oxime silyl ethers **120** and **121**, respectively, in the system BH_3•Me_2S/BF_3•OEt_2 at reflux (equation 45)[332].



(45)

Irradiation of 5-phenylselanyl-1-triphenylgermylpentan-1-one *O*-benzyloxime (**124**) in the presence of Me_6Sn_2 afforded cyclopentanone *O*-benzyloxime (**125**) in 95% yield. Cyclization of unsaturated oxime ether **126** led to a 6.7:1 ratio of a mixture of the *E*- and *Z*-isomers of 2-[(triphenylgermyl)methyl]cyclopentanone *O*-benzyloxime (**127**) (equation 46)[314].



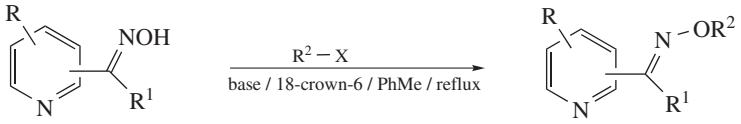
(46)

6. Silicon- and germanium-containing oximes as coupling agents and their use in low infrared emissivity paints

Silicon derivatives of oximes were used in crosslinking of polymers in the presence of moisture[333]. Oximes containing silane groups were used in the coupling of polymers[334]. In addition, manufacture of low emissivity paints comprising an oxime cured silicon binder was described[335].

7. Biological activity of silicon- and germanium-containing oximes

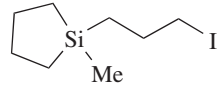
Acute and repeated oral and dermal rat toxicology studies of methyl ethyl ketoxime and methyl isobutyl ketoxime silyl derivatives were studied. With the exception of the methyl and vinyl difunctional silanes, the silane portion of silane oximes does not appear to contribute any significant toxicity to the compounds studied[336]. Cytotoxicity of silicon- and germanium-containing silanes were investigated more widely[303, 337–340]. Thus, silicon- and germanium-containing oxime ethers **129** were prepared using the PTC system oxime **128**/alkyl halide/solid KOH, K_2CO_3 or Cs_2CO_3/18-crown-6/PhMe (equation 47). *O*-[3-Trialkylsilylpropyl]- and *O*-[3-(1-methylsilacyclopentyl)]oximes of pyridine aldoximes and ketoximes exhibit high cytotoxicity. The leading compound **129** (2-pyridyl; R, $R^1 = H$, $R^2 = (1\text{-methylsilacyclopentyl})CH_2CH_2CH_2$) exhibited high cytotoxicity on HT-1080 (IC_{50} 1.85 μg ml^{-1}) and M-22A (mouse hepatoma, IC_{50} 6 μg ml^{-1}) cell lines. The presence of a methyl group in the pyridine ring considerably decreased the acivity of amidoxime *O*-ethers **129**. Oxime ethers containing two elements (both silicon and germanium) were essentially inactive. For 2-acetylpyridine oxime *O*-ethers the activity increases in the order: $Et_3GeCH_2CH_2SiMe_2CH_2 < Et_3SiCH_2CH_2CH_2 < c\text{-}[(CH_2)_4Si](Me)CH_2CH_2CH_2$[303].



2-, 3- and 4-pyridyl (**128**) → *E*-(**129**) 31–65% (47)

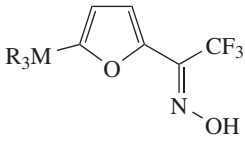
R = H, Me; R^1 = H, NH_2, Me; $R^2X = Et_3Si(CH_2)_3Br$, $Me_2EtSiCH_2CH_2Si(Me)_2CH_2I$,

$Et_3GeCH_2CH_2Si(Me)_2CH_2I$,



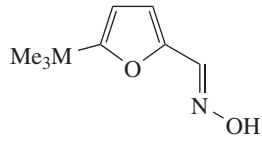
Cytotoxicity of silyl and germyl substituted oximes of trifluoroacetylfurans **130**[337] and 2-furancarboxaldehyde **131**[338], as well as of oximes of 2-acetyl-5-trimethylsilylfuran and -thiophene **132** was also described. Among all studied compounds the germanium derivatives **130** (R = Et) and **131** exhibit the highest activity on MG-22A cell line (IC_{50} 6 and 4 μg ml^{-1}, respectively). The silicon derivatives of oximes **130–132** were considerably less active.

Silicon derivatives of oxime ethers were investigated as ion channel modulators and were used in the treatment of sickle cell diseases[340].



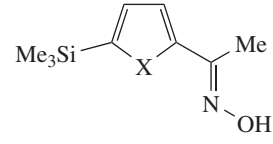
(**130**)

R_3M = Me_3Si, Me_2PhSi, Me_3Ge, Et_3Si, Et_3Ge



(**131**)

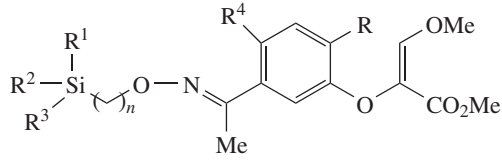
M = Si, Ge



(**132**)

X = O, S

Silicon-containing oxime ethers were used as fungicides[341], insecticides, acaridides, microbicides[342] and pesticides[343] in agrochemistry. Thus, the silicon ethers **133** (R-R^2 = Me, R^3 = Ph, R^4 = H, n = 1) showed >80% control of Adoxophyes orana fasciata larvae at 500 ppm[342].



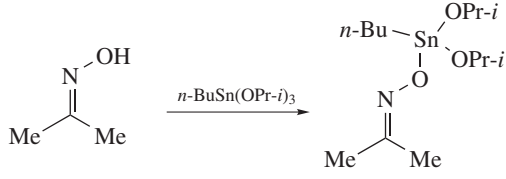
(**133**)

R, R^4 = H, halo; R^1-R^3 = alkyl, Ph, PhO, naphthyl, naphthoxy, heteroaryl, heteroaryloxy, n = 1, 3

O. Group 14 (Tin)

1. Synthesis and structure of oxime O-stannyl ethers

O-Trialkylstannyloximes were obtained by the reaction of the corresponding oxime with Bu_3SnH/Et_3N[344], R_3SnNPh_2[345], R_3SnOH[345], R_3SnOEt[345], R_3SnOPr-*i*[346] or $Bu_3SnOSnBu_3$[346, 347] or of the oxime salts with Me_3SnX (X = halogen)[346, 348]. Reaction of acetone oxime (**134**) with butyltin triisopropoxide afforded stannylated oxime derivative **135** as the single product (equation 48)[349].



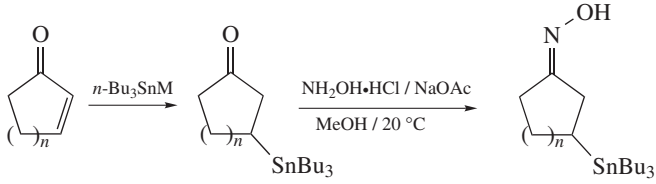
(**134**) (**135**)

(48)

2. Synthesis of other Sn−C ordinary bond containing oximes

There are two general methods for the preparation of tin-containing oximes from the corresponding carbonyl compounds or oxime derivatives. Thus, β-tributylstannyl oximes **138** were prepared by conjugate addition of Bu_3SnM (M = Li, Cu) to α,β-unsaturated

ketones **136**, followed by interaction of intermediates **137** with $NH_2OH{\bullet}HCl$ in the system NaOAc/MeOH (equation 49)[350–352].



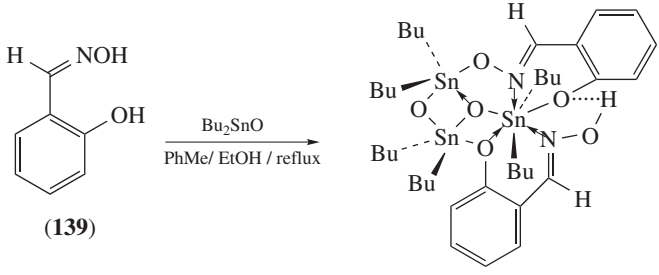
(**136**) (**137**) (**138**) (49)

n = 1, 2; M = Li, Cu

The second method of preparation of β-tributylstannyl oximes is based on the alkylation of oxime salts with $ICH_2Sn(Bu\text{-}n)_3$[351, 352].

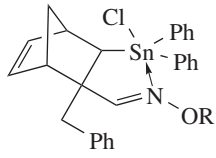
3. Synthesis of tin oxime complexes

Syntheses of tin complexes with oxime ligands are widely described in reviews[2a–e]. Examples involve synthesis of Sn(II)[353] and Sn(IV)[354–362] complexes. Salicylaldoxime complex **140** was obtained from salicylaldoxime (**139**) and dibutyltin(IV) oxide (equation 50). The structure of this monoclinic complex was determined by single crystal X-ray diffraction. The compound contains two five-coordinate trigonal-bipyramidal tin atoms with the two butyl groups in equatorial positions; the third tin atom has seven-coordinate pentagonal-bipyramidal geometry with the two butyl groups in apical positions[358].



(**139**) (**140**) 91% (50)

Oximation of the corresponding aldehyde with hydroxylamine or *O*-methylhydroxylamine leads to formation of oximes **141**. Their structures were confirmed by X-ray crystallography which provided evidence for coordination of the tin by the nitrogen[363].

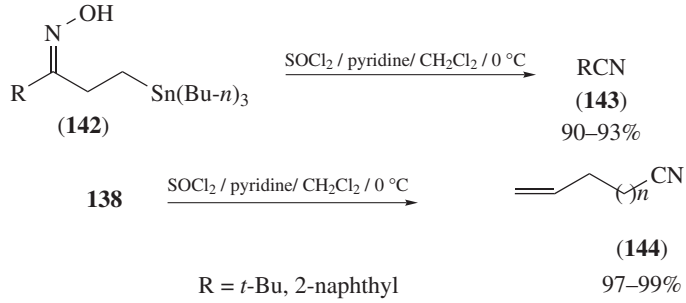


(**141**)

R = H, Me

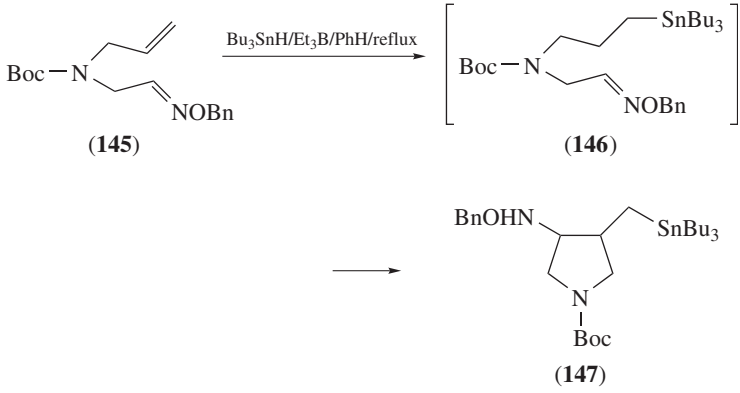
4. Reactions of tin-containing oximes

β-Tributylstannyl oximes **142** upon treatment with thionyl chloride give nitriles **143** in 93–96% yields. Similar reaction of cyclic oxime derivatives **138** leads to cyanoalkenes **144** (equation 51)[352].



(51)

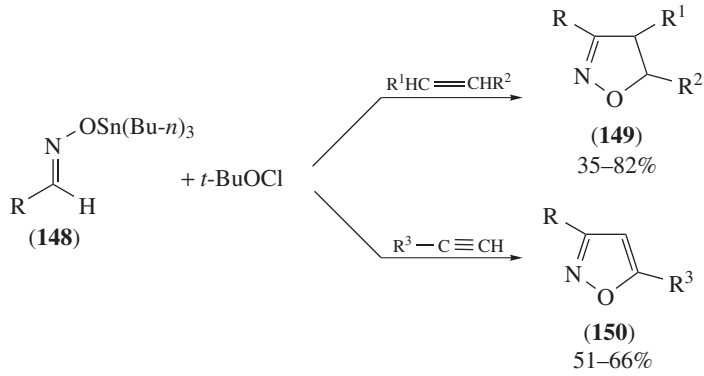
Free radical cyclization of unsaturated oxime *O*-ethers occurred readily in the presence of Bu_3SnH or Ph_3SnH and AIBN or Et_3B[364–368]. In all the cases these reactions proceed via stannylated oxime intermediates (for example, intermediate **146**). Thus, oxime ether **145** in the system Bu_3SnH/Et_3B/benzene at reflux afforded pyrrolidine **147** in a yield up to 81% (equation 52)[364].



(52)

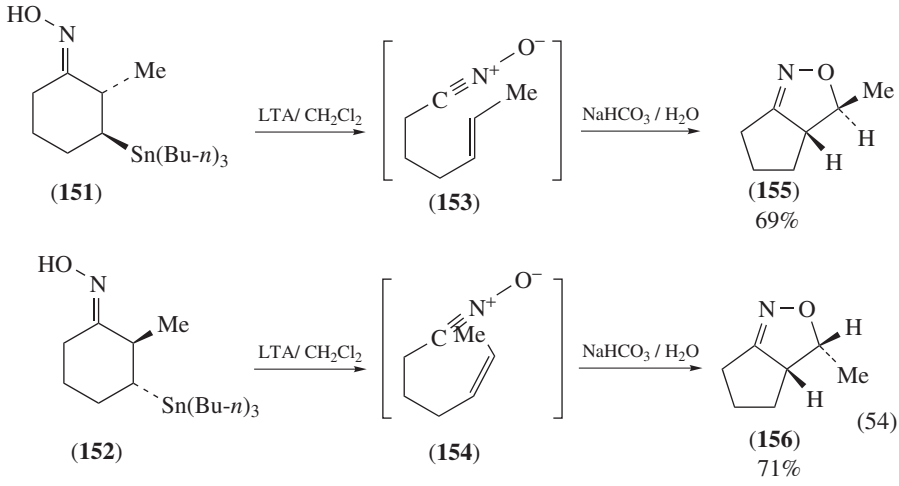
Stannylated oxime derivatives were used in the preparation of isoxazolines and isoxazoles. Thus, nitrile oxides, generated from *O*-tributylstannyl aldoximes **148** and *tert*-butyl hypochlorite in dichloromethane at −20 °C, undergo [3 + 2] cycloaddition in the presence of alkenes and alkynes leading to products **149** and **150** (equation 53)[344, 369].

Oxidation of β-tributylstannyl oximes with lead tetraacetate (LTA) provides an excellent route for the stereoselective generation of nitrile oxides. Thus, addition of LTA (1.3 equivalents) to dichloromethane solution of oximes **151** and **152** at −60 °C to −20 °C afforded isomeric nitrile oxides **153** and **154**. Addition of aqueous $NaHCO_3$ solution and dilution of the reaction mixtures with Et_2O leads stereoselectively to isoxazolines **155** and **156** (equation 54)[351].



(53)

R = Me, Ph; R^1 = H, alkyl; R^2 = alkyl, aryl; R^3 = CH_2Br, Ph, CO_2Me



(54)

5. Biological activity of tin-containing oximes

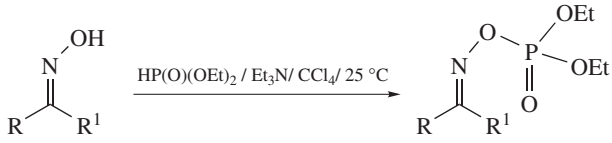
Organotin(IV) complexes with cyanoxime ligands (L = $NH_2COC(CN)$=NOH and (4-pyridyl)C(CN)=NOH) of type $R_{4-x}SnL_x$ (R = Me, Et, *n*-Bu, Ph; $x = 1, 2$) and $R_8Sn_4(OH)_2O_2L_2$ (R = *n*-Bu, Ph) were studied *in vitro* for antiproliferating activity, using human cervical cancer HeLa and WiDR colon cancer cell lines. The two dibutyltin(IV) cyanoximates showed cytotoxicity similar and greater than that of cisplatin[370]. Antitumor activity of tin(IV) complexes of benzohydroxamic acids was described[371, 372]. The ^{99}Tc–Sn–dimethylglyoxime complex as radiopharmaceutical in diagnostic nuclear medicine was also described[373].

Tin-containing oxime ethers were widely used as fungicides[374, 375], acaridides[376], bactericides[374] and pesticides[375] in agrochemistry. These *O*-trialkylstannyloximes also exhibit plant protective activity[377, 378].

P. Group 15

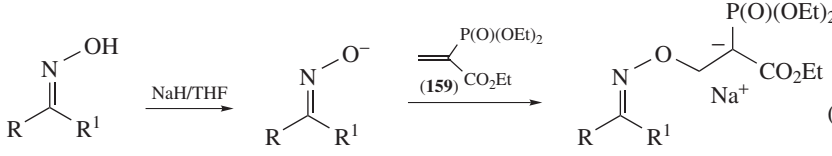
1. Synthesis and structure of phosphorus-containing oximes

Oxime *O*-phosphoryl ethers **158** were synthesized easily from the corresponding oximes **157** and phosphoryl chlorides (e.g. diethylphosphoryl chloride)[379] or diethyl phosphonate/Et_3N (Atherton–Todd reaction) (equation 55)[380]. Phosphoryl-stabilized carbanions **160** were generated from oxime anions and α-ethoxycarbonyl vinylphosphonate **159** in THF (equation 56)[381].



(**157**) (**158**) 90–95% (55)

R = alkyl, aryl; R^1 = H, alkyl

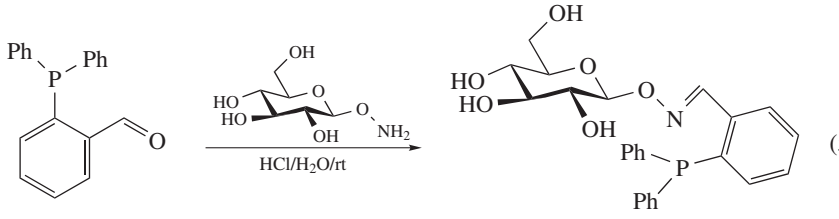


(56)

R, R^1 = alkyl (**160**)

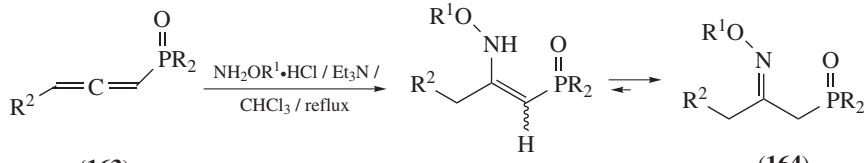
Interestingly, the zinc(II)-catalyzed hydrolysis of 2-acetylpyridine oxime phosphonate (2-pyridyl)C(Me)=NOPO$(OPh)_2$ occurred through a hydrated intermediate (2-pyridyl)C(Me)=NOP$(OH)_2(OPh)_2$[382].

Phosphorus-containing oximes were obtained by treating the corresponding phosphorus-containing carbonyl compounds with NH_2OH•HCl in the presence of pyridine[383], pyridine/MeOH[384], pyridine/EtOH[385] or AcONa/EtOH/H_2O[386]. *O*-(β-D-Glucopyranosyl)-2-diphenylphosphanylbenzaldoxime (**162**) was synthesized from aldehyde **161** in the system *O*-β-D-glucopyranosylhydroxylamine/HCl (0.1 equivalent)/H_2O at room temperature (equation 57)[387].



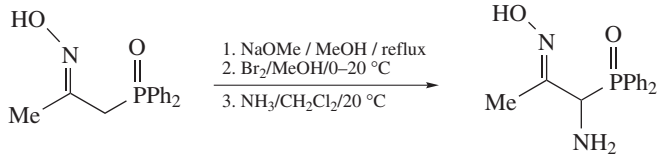
(**161**) (**162**) 95% (57)

Functionalized phosphine oxide containing oximes **164** (yields 67–90%) were prepared by addition of hydroxylamine to allenyl phosphine oxides **163** (equation 58)[388–390]. *E*-β-(*N*-Hydroxyimino)propyldiphenylphosphine oxide (**165**) was easily transformed to amino derivative **166** by reaction, first with sodium methoxide and then with bromine and ammonia (equation 59)[391].



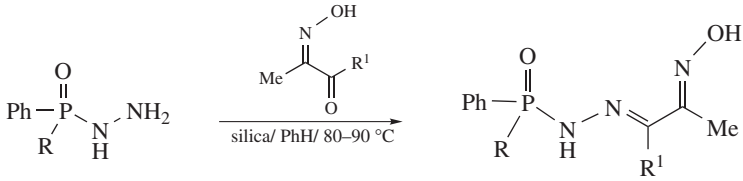
(**163**) (**164**)

R = OEt, Ph; R^1 = H, alkyl, $SiMe_3$, $SiMe_2Bu$-*t*; R^2 = H, alkyl, aryl (58)



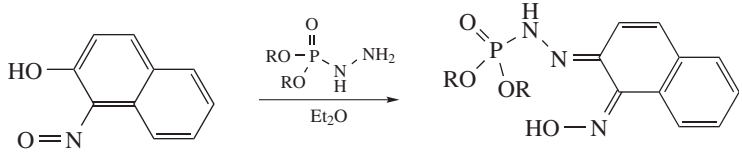
(**165**) (**166**) (59)

Reaction of phosphonohydrazides **167** with α-ketoximes in the presence of activated silica in benzene afforded oximes **168** in 73–94% yield (equation 60)[392]. Treating of 1-nitroso-2-naphthol (**169**) with phosphonohydrazides in Et_2O leads to phosphorylated hydrazones of 1,2-naphthoquinone oxime **170** in 75–86% yields (equation 61)[393].



(**167**) (**168**) (60)

R = $NAlkyl_2$, OAlkyl; R^1 = Me, Ph



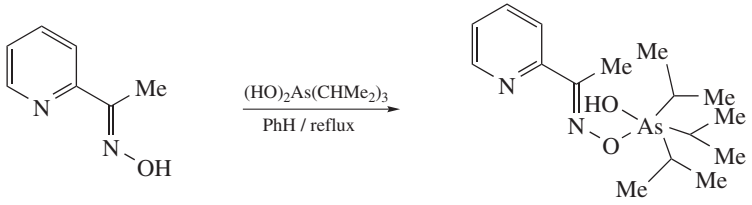
(**169**) (**170**) (61)

R = Et, Pr, Me_2CH

Oximes of phosphorylated aldehydes and ketones represent mixtures of *Z*- (dimers) and *E*-isomers (trimers, chains) that are associated via hydrogen bonds at the oxime function. Together with the *Z*- and *E*-isomers, the formations of hydrogen bonds involve phosphoryl oxygen in the acid chloride of α-diphenylphosphinylpropiohydroxamic acid[394].

2. Synthesis and structure of arsenium- and antimony-containing oximes

O-(Dimethylarsino)oximes were obtained in the reaction of $Me_2N{-}AsMe_2$ with oximes[395]. Five-coordinated oxime *O*-arsonyl ethers were synthesized easily from the corresponding oximes and $AsMe_5$[396] or from oxime salts with halogenated arsoranes[397, 398]. Oxime arsonium ether **172** was obtained by thermal reaction between 2-acetylpyridine oxime (**171**) and dihydroxytriisopropylarsorane (equation 62)[398].



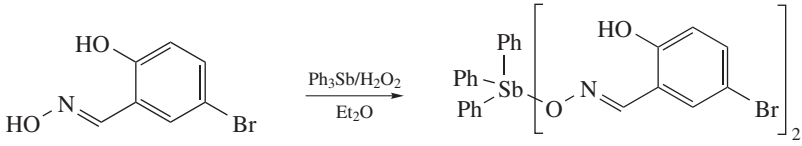
(**171**) (**172**)
93%

(62)

Arsenic-containing oximes were obtained by treatment of the corresponding arsenic containing carbonyl compounds with $NH_2OH{\bullet}HCl$ in the presence of pyridine[399].

General methods for the synthesis of antimony(V) oxime derivatives are similar to those for arsenium oximes[400–402]. Thus, triorganoantimony(V) complexes $[R_3Sb\{ON{=}C(Me)Ar\}_2]$ have been prepared by the reaction of R_3SbBr_2 with oximes in 1:2 molar ratio in anhydrous benzene. Treatment of these complexes with R_3SbX_2 (X = Br, OH) afforded redistribution products $[R_3Sb(X)\{ON{=}C(Me)Ar\}]$. The crystal structures of complexes $[Me_3Sb\{ON{=}C(Me)(2\text{-furyl})\}_2]$ and $[Me_3Sb\{ON{=}C(Me)(2\text{-thienyl})\}_2]$ were reported. The geometry of the antimony atom in the complexes is distorted trigonal bipyramidal with the carbon atoms of the $SbMe_3$ unit in equatorial positions and the two oxygen atoms of the oxime group occupying axial positions[403].

The reaction of triphenylantimony with 5-bromo-2-hydroxybenzaldoxime (**173**) in the presence of oxidant (H_2O_2) in ether leads to the oxime derivative **174** (equation 63)[404]. Beside this, synthesis and characterization of antimony(V) polyoximes was described[405].

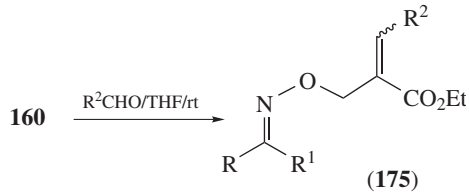


(**173**) (**174**)

(63)

3. Reactions of phosphorus-containing oximes

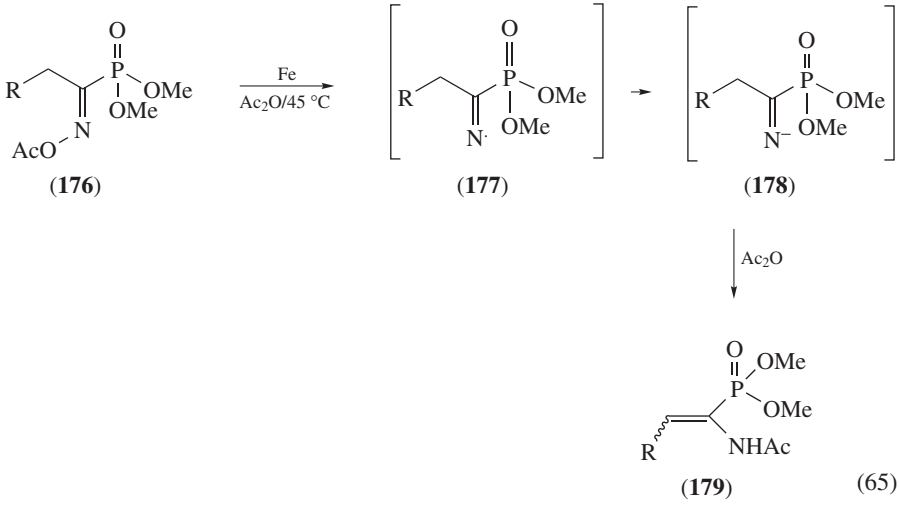
Phosphorus-containing oximes readily undergo Wittig-type reaction with aldehydes in the presence of base[381, 388]. For example, the interaction of phosphoryl-stabilized carbanions **160** with aldehydes afforded allyl substituted oxime ethers **175** (equation 64)[381].



(64)

R, R^1 = alkyl; R^2 = aryl, hetaryl

Iron-mediated electron transfer reduction of α-oximinophosphonates **176** in acetic anhydride leads to an intermediate iminyl radical **177**. A second electron transfer reduction of this intermediate leads to the iminyl anion **178**, which then reacts with acetic anhydride to give α-phosponoenamides **179** in 71–89% yields (equation 65)[384].

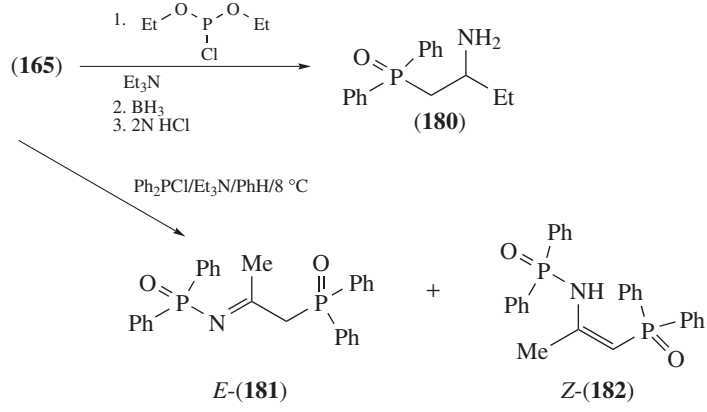


(65)

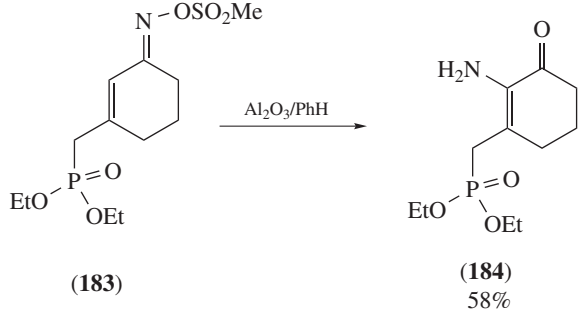
R = alkyl, aryl

Multistep reaction of (*E*)-2-hydroxyiminopropyldiphenylphosphine oxide (**165**) with phosphorochloridous diethyl ester in the presence of Et_3N and then with borane leads to phosphine **180**. Reaction of oxime **165** with diphenylphosphoryl chloride leads to a mixture of the tautomeric *E*-imine **181** and *Z*-alkene **182** (equation 66)[406].

Neber rearrangement of oxime mesylate **183** in the presence of basic Al_2O_3 in benzene afforded diethyl (2-amino-3-oxocyclohexen-1-enyl)methylphosphonate (**184**) (equation 67)[407].

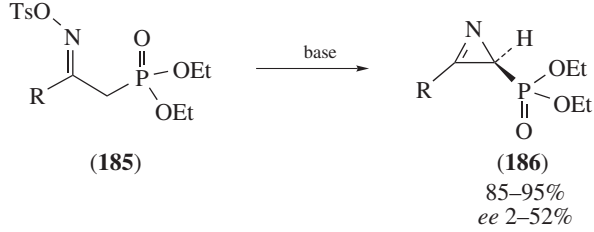


(66)



(67)

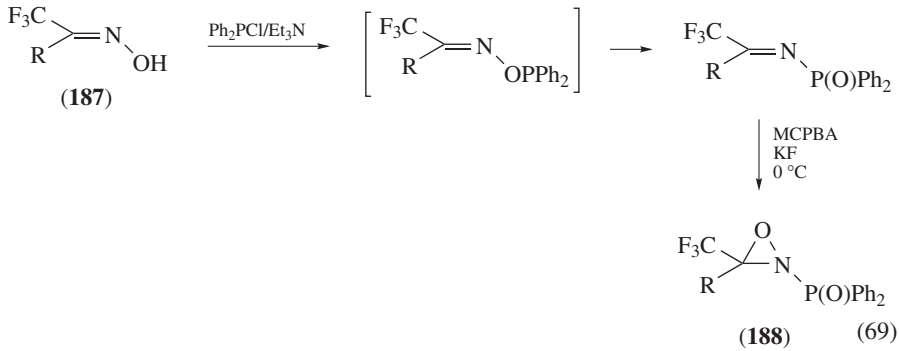
Synthesis of heterocyclic compounds from phosphorus-containing oximes was widely described in the literature. An efficient synthesis of 2*H*-azirines **186** substituted with a phosphate group is described. Its key step is an alkaloid[408] or Et_3N[386] catalyzed Neber reaction of β-ketoxime tosylates **185** (equation 68).



(68)

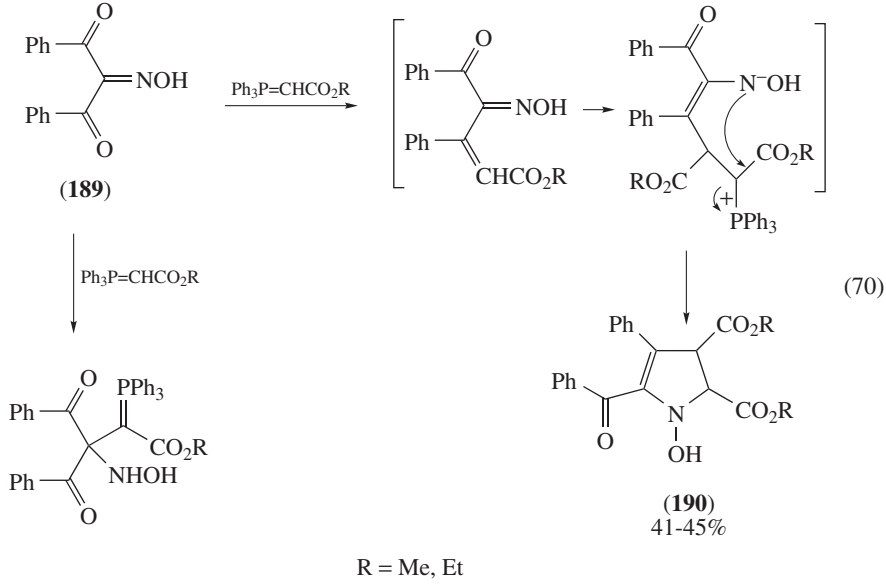
base = quinidine, (−)-sparteine, hydroxyquinidine, quinine; R = alkyl

An oxaziridine ring system has been formed by the oxidation of a C=N double bond in phosphorus-containing oximes. The two-step synthesis of *N*-phosphinoyloxaziridines **188** from oximes **187** was described (equation 69)[409].



(69)

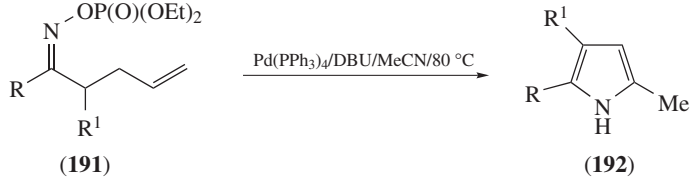
1,3-Diphenyl-2-hydroxyimino-1,3-propanedione (**189**) reacted with phosphonium ylides to give 1-hydroxy-2,3-dihydropyrroles **190** as the main products. Formation of the products proceeded through phosphorylated oxime intermediates (equation 70)[410]. Pyrrole derivatives **192** were also prepared from γ,δ-unsaturated ketone *O*-diethylphosphinyloximes **191** in the system $Pd(PPh_3)_4$/DBU/MeCN at 80 °C (equation 71)[411].



(70)

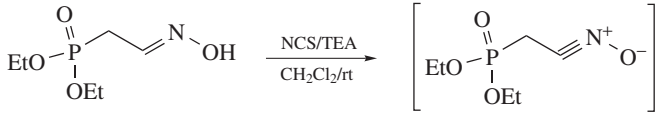
R = Me, Et

Synthesis of isoxazole[385, 390, 412] and oxazole[413] rings from phosphonated oxime derivatives was also documented. Typically, treatment of aldoxime **193** with NCS and Et_3N afforded unstable nitrile oxides **194**, which easily undergo cycloaddition in the presence of alkenes leading to isoxazolines **195** (equation 72)[413].

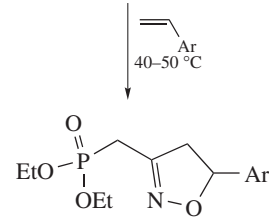


(**191**) (**192**) (71)

R = alkyl, aryl; R^1 = H, alkyl



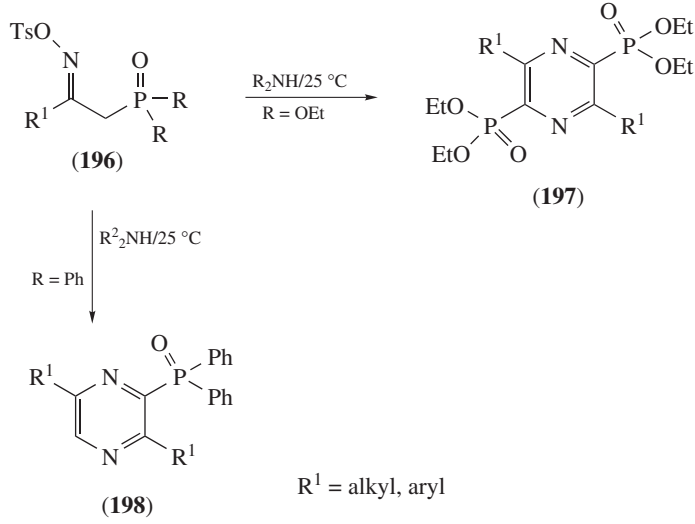
(**193**) (**194**)



(**195**)
60–70% (72)

Ar = hetaryl

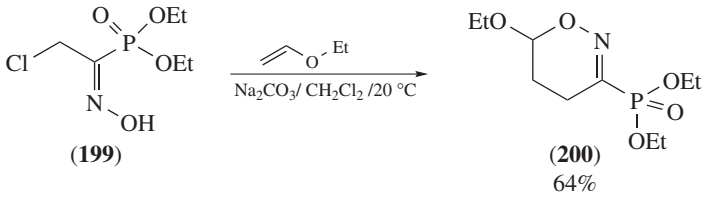
Treatment of oxime tosylates **196** (R = OEt) with primary or secondary amines at room temperature gave pyrazines **197**. Similarly, pyrazine phosphine oxide **198** can be obtained from tosylate **196** (R = Ph) in the presence of piperidine (equation 73)[414].



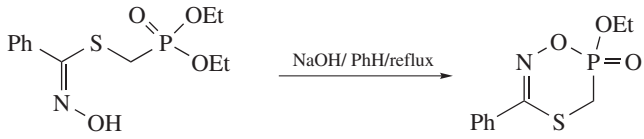
(**196**) (**197**) (**198**) (73)

R^1 = alkyl, aryl

Reaction of chlorooxime **199** with vinyl ethyl ether in the presence of Na_2CO_3/CH_2Cl_2 at 20 °C afforded 5,6-dihydro-1,2-oxazine **200** (equation 74)[415]. Construction of 1,2,3,4-tetrahydro-1,4,6,2-oxathiaazaphosphorine ring **202** was realized from oximes **201** in the presence of NaOH in benzene (equation 75)[416].



(**199**) (**200**) 64% (74)



(**201**) (**202**) 67% (75)

4. Biological activity

The reactivators of acetylcholinesterase are very important components in the treatment of intoxications caused by organophosphate inhibitors (‘nerve gases’, for example, tabun, sarin, soman etc.). These inhibitors bind covalently to an active site above the enzyme and irreversibly inhibit its activity. The oxime derivative reactivator breaks the inhibitor–enzyme covalent bond and restores its activity. Simultaneously, formation of oxime *O*-phosphoryl ethers occurred[417]. Beside this, novel chemoluminiscent detection of ‘nerve gases’ using oxime derivatives was recently presented[418].

A new method of preparation of peptide–oligonucleotide conjugates through chemoselective glyoxylic oxime linkage was reported. A novel phosphoramidite reagent, readily accessible from serine, was prepared and used in an automated DNA synthesis to prepare oligonucleotides carrying a glyoxylic aldehyde at the 5′ terminus. This was efficiently coupled to a peptide functionalized with aminooxy group. This method is general for the preparation of a broad range of oligonucleotide conjugates[419].

Phosphonohydrazido oximes **168** are potential marine fish toxin analogues[392]. Phosphorus-containing oxime derivatives exhibit herbicidal[420] and insecticidal activity[421].

III. CONCLUSIONS

Oxime derivatives are readily transformed to the corresponding salts in the presence of strong bases (BuLi, LDA, KNH_2 etc.). This opens new directions for the modification of this type of compounds due to the possibility of oximes $RC(CH_2R')=NOH$ (R, R′ = H, alkyl, aryl) forming disalts $RC(CHMR')=NOM$. Oxime *O*-ethers ($RC(CH_2R')=NOR''$, R″ = alkyl, aryl) in the presence of strong bases afford monosalts $RC(CHMR')=NOR''$. Reactions of these salts with different electrophiles allow one to obtain new types of oxime derivatives and heterocycles.

Oxime metal derivatives (for example, oxime palladacycles) are valuable catalysts in organic synthesis. In addition, oxime metal complexes exhibit a wide spectrum of biological activity. For example, technetium-99m hexamethylpropyleneamine oxime (**59**) (Ceretec™) and related oxime complexes are used in diagnosis. Silicon and tin oxime complexes are excellent agrochemical agents. Some cobalt-, platinium- and silicon-containing oxime ethers exhibit high antitumor and cytotoxic activity and will be prospective targets for further investigations.

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N-Hydroxylamines for peptide synthesis

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I. ABBREVIATIONS

AOMP	5-(7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl-*2H*-pyrrolium hexachloroantimonate
AOP	(7-azabenzotriazol-1-yl)oxy-tris(dimethylamino)phosphonium hexafluorophosphate
BDDC	bis[4-(2,2-dimethyl-1,3-dioxolyl)methyl]carbodiimide
BDMP	5-(*1H*-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-*2H*-pyrrolium hexachloroantimonate
BDP	benzotriazol-1-yl diethylphosphate
BEC	*N*-*tert*-butyl-*N′*-ethylcarbodiimide
BOMP	2-(benzotriazol-1-yloxy)-1,3-dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	*N*,*N′*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BPMP	1-(*1H*-benzotriazol-1-yloxy)phenylmethylene pyrrolidinium hexachloroantimonate
BroP	bromo-tris(dimethylamino)phosphonium hexafluorophosphate

BTCFH	bis(tetramethylene)chlororformamidinium hexafluorophosphate
CF_3-BOP	[6-(trifluoromethyl)benzotriazol-1-yl]-*N*-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate
CF_3-HBTU	2-[6-(trifluoromethyl)benzotriazol-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate
N-CF_3-HBTU	*N*-[6-trifluoromethyl(*1H*-benzotriazol-1-yl)(dimethylamino)-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
6-CF_3-HOBt	6-trifluoromethyl-1-hydroxybenzotriazole
CF_3-NO_2-PyBOP	[4-nitro-6-(trifluoromethyl)benzotriazol-1-yl)oxy]tris(pyrrolidino) phosphonium hexafluorophosphate
CF_3-PyBOP	[6-(trifluoromethyl)-benzotriazol-1-yl]-*N*-oxy-tris(pyrrolidino)-phosphonium hexafluorophosphate
N-CF_3-TBTU	*N*-[6-trifluoromethyl(*1H*-benzotriazol-1-yl)(dimethylamino)-methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
CIC	*N*-cyclohexyl, *N′*-isopropyl carbodiimide
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
6-Cl-HOBI	6-chloro-*N*-hydroxy-2-phenylbenzimidazole phosphonium hexafluorophosphate
6-Cl-HOBt	6-chloro-1-hydroxybenzotriazole
CloP	chloro-tris(dimethylamino)phosphonium hexafluorophosphate
CMBI	2-chloro-1,3-dimethyl-*1H*-benzimidazolium hexafluorophosphate
COMU	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino morpholinomethylene)] methanaminium hexafluorophosphate
CPC	*N*,*N′*-dicyclopentylcarbodiimide
DCC	*N*,*N′*-dicyclohexylcarbodiimide
DEBP	diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate
DEPAT	3-(diethoxyphosphoryloxy)-1,2,3-pyridino[*b*]triazin-4-(*3H*)-one
DEPB	diethyl phosphorobromidate
DEPBO	*N*-diethoxyphosphoryl benzoxazolone
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(*3H*)-one
DEPC	diphenyl phosphorochloridate
DIC	*N*,*N′*-diisopropylcarbodiimide
DIEA (DIPEA)	diisopropylethylamine
DKP	diketopiperazine
DNAs	*3H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl-2,4-dinitrobenzenesulfonate
DNBs	*1H*-benzo[*d*][1,2,3]triazol-1-yl-2,4-dinitrobenzenesulfonate
DOEPBI	phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester
DOMP	5-(3′,4′-dihydro-4′-oxo-1′,2′,3′-benzotriazin-3′-yloxy)-3,4-dihydro-1-methyl-*2H*-pyrrolium hexachloroantimonate
DOPBO	*N*-(2-oxo-1,3,2-dioxaphosphorinanyl)benzoxazolone
DOPBT	3-[*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)oxy]-1,2,3-benzotriazin-4(*3H*)-one
DOPPBI	phosphoric acid diphenyl ester and 2-phenylbenzimidazol-1-yl ester
DPPA	diphenylphosphoryl azide
DPPAT	3-(diphenoxyphosphoryloxy)-1,2,3-pyridino[*b*]triazin-4-(*3H*)-one
DPPBI	diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester
DPP-Cl	diphenylphosphinic chloride
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Fmoc	9-fluorenylmethyloxycarbonyl

FOMP	5-(pentafluorophenyloxy)-3,4-dihydro-1-methyl-*2H*-pyrrolium hexachloroantimonate
HAE_2PipU	*O*-(*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate
HAE_2PyU	*O*-(*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate
HAMDU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HAM_2PipU	*O*-(*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate
HAM_2PyU	*O*-(*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate
HAMTU	*O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate
HAPipU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HAPTU	(7-azabenzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate
HAPyTU	1-(1-pyrrolidinyl-*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinium hexafluorophosphate *N*-sulfide
HAPyU	1-(1-pyrrolidinyl-*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinium hexafluorophosphate *N*-oxide
HATeU	*O*-(*1H*-1,2,3-triazolo[4,5-b]pyridin-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
N-HATU	*N*-[(dimethylamino)-*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HATTU	*S*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
N-HATTU	*N*-[(dimethylamino)-*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-sulfide
N-HBPyU	(*1H*-benzotriazol-1-yl)(1-pyrrolidinylmethylene)pyrrolidinium hexafluorophosphate *N*-oxide
N-HBTU	*N*-[(*1H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methyl methanaminium hexafluorophosphate *N*-oxide
HBE_2PipU	*O*-(*1H*-benzotriazol-1-yl)-1,1-diethyl-3,3-pentamethyleneuronium hexafluorophosphate
HBE_2PyU	*O*-(*1H*-benzotriazol-1-yl)-1,1-diethyl-3,3-tetramethyleneuronium hexafluorophosphate
HBM_2PipU	*O*-(1*H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-pentamethyleneuronium hexafluorophosphate
HBM_2PyU	*O*-(*1H*-benzotriazol-1-yl)-1,1-dimethyl-3,3-tetramethyleneuronium hexafluorophosphate
HBMDU	*O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HBMTU	*O*-(benzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate

HBPipU	*O*-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate
HBPTU	(7-benzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate
HBPyU	*O*-(benzotriazol-1-yl)oxy-bis(pyrrolidino)uronium hexafluorophosphate
HBTeU	*O*-(*1H*-benzotriazol-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDAPyU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-bis(tetramethylene) uronium hexafluorophosphate
HDATU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDMA	1-((dimethylamino)(morpholino)methylene)-*1H*[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate-3-oxide
4-HDMA	3-((dimethylamino)(morpholino)methylene)-*1H*[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate-1-oxide
HDMB	1-((dimethylamino)(morpholino)methylene)-*1H*-benzotriazolium hexafluorophosphate-3 oxide
HDMC	6-chloro-1((dimethylamino)(morpholino)methylene)-*1H*-benzotriazolium hexafluorophosphate-3 oxide
6-HDMFB	6-trifluoromethyl-1-((dimethylamino)(morpholino)methylene)-*1H*-benzotriazolium hexafluorophosphate-3-oxide
HDMODC	1-[(1-(dicyanomethyleneaminooxy)dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate
HDMODeC	1-[(1,3-diethoxy-1,3-dioxopropan-2-ylideneaminooxy)-dimethylaminomorpholinomethylene)] methanaminium hexafluorophosphate
HDMOPC	*N*-[(cyano(pyridine-2-yl)methyleneaminooxy)-(dimethylamino)methylene)]-*N*-morpholinomethanaminium hexafluorophosphate
HDMP	1-((dimethyamino)(morpholino))oxypyrrolidine-2,5-dione methanaminium hexafluorophosphate
HDMPfp	1-((dimethylamino)(morpholino))oxypentafluorophenyl-metheniminium hexafluorophosphate
HDmPyOC	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethyl-amino pyrrolidinomethylene)] methanaminium hexafluorophosphate
HDmPyODC	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino pyrrolodinomethylene)] methanaminium hexafluorophosphate
HDmPyODeC	1-[(1,3-diethoxy-1,3-dioxopropan-2-ylideneaminooxy)-dimethylamino pyrrolodinomethylene)] methanaminium hexafluorophosphate
HDPyU	*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate
HDTMA	1-((dimethylamino)(thiomorpholino)methylene)-*1H*[1,2,3]triazolo[4,5-*b*] pyridinium hexafluorophosphate-3-oxide

HDTMB	1-((dimethylamino)(thiomorpholino)methylene)-*1H*-benzotriazolium hexafluorophosphate-3-oxide
HDTU	*O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HMPyOC	1-((1-cyano-2-ethoxy-2-oxoethylideneaminooxy)-(morpholino)methylene) pyrrolidinium hexafluorophosphate
HMPyODC	1-((dicyanomethyleneaminooxy)morpholinomethylene)-pyrrolidinium hexafluorophosphoate
HOAt	1-hydroxy-7-azabenzotriazole
4-HOAt	4-aza-1-hydroxybenzotriazole
5-HOAt	5-aza-1-hydroxybenzotriazole
6-HOAt	6-aza-1-hydroxybenzotriazole
HOBI	*N*-hydroxy-2-phenylbenzimidazole
HOBt	1-hydroxybenzotriazole
HOCt	ethyl-1-hydroxy-*1H*-1,2,3-triazole-4-carboxylate
HODhad	3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene
HODhat	3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene
HODhbt	3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium hexafluorophosphate
HOI	*N*-hydroxyindolin-2-one
HONB	*N*-hydroxy-5-norbornene-*endo*-2,3-dicarboxyimide
HONP	*p*-nitrophenyl active ester
HOPy	1-hydroxy-2-pyridinone
HOSu	*N*-hydroxysuccinimide
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HPFTU	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPTU	2-(2-oxo-1(*2H*)-pyridyl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPyONP	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-2-nitrophenyluronium hexafluorophosphate
HPyOPfp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPyOTCp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium hexafluorophosphate
HPySPfp	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*S*-pentafluorothiophenyluronium hexafluorophosphate
HSTU	2-succinimido-1,1,3,3-tetramethyluronium hexafluorophosphate
HTODC	*O*-[(dicyanomethylidene)amino]-1,1,3,3-tetramethyluronium hexafluorophosphate
HTODeC	*O*-[(diethoxycarbonylmethylidene)amino]-1,1,3,3-tetramethyluronium hexafluorophosphate
HTOPC	*N*-[(cyano(pyridine-2-yl)methyleneaminooxy)-(dimethylamino)methylene)-*N*-methyl methanaminium hexafluorophosphate

MPTA	dimethylphosphinothioyl azide
MPTO	3-dimethylphosphinothioyl-2(*3H*)-oxazolone
NAs	3-((naphthalen-2-ylsulfonyl)methyl)-*3H*-[1,2,3]triazolo[4,5-*b*]pyridine
2-Nas	*3H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl 2-nitrobenzenesulfonate
4-Nas	*3H*-[1,2,3]triazolo[4,5-b]pyridin-3-yl 4-nitrobenzenesulfonate
NBs	1-((naphthalen-2-ylsulfonyl)methyl)-*1H*-benzo[*d*][1,2,3]triazole
2-NBs	*1H*-benzo[*d*][1,2,3]triazol-1-yl 2-nitrobenzenesulfonate
4-NBs	*1H*-benzo[*d*][1,2,3]triazol-1-yl 4-nitrobenzenesulfonate
NDPP	norborn-5-ene-2,3-dicarboximidodiphenylphosphate
NMM	*N*-methylmorpholine
6-NO_2-HOBt	1-hydroxy-6-nitrobenzotriazole
NO_2-PyBOP	(6-nitrobenzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate
NpsOPy	2-oxopyridin-1(*2H*)-yl naphthalene-2-sulfonate
NpsOXY	ethyl 2-cyano-2-(naphthalen-2-ylsulfonyloxyimino)acetate
Oxyma	ethyl 2-cyano-2-(hydroxyimino)acetate
P-DCT	polymer supported 2,4-dichloro-1,3,5-triazine
P-EDC	polymer supported 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide
P-HOBt	polymer supported 1-hydroxybenzotriazole
P-HOSu	polymer supported *N*-hydroxysuccinimide
P-SO_2-HOBt	polymer supported 1-hydroxy-6-disulfoxide benzotriazole
P-TBTU	*N*-[(*1H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methyl methanaminium tetrafluoroborate *N*-oxide
PTF	benzyltriphenylphosphonium dihydrogen trifluoride
PyAOP	[(7-azabenzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyBOP	benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	bromotri(pyrrolidino)phosphonium hexafluorophosphate
PyCloK	(6-chlorobenzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate
PyCloP	chloro-tri(pyrrolidino)phosphonium hexafluorophosphate
PyDAOP	[(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl]tris(pyrrolidino) phosphonium hexafluorophosphate
PyDOP	[(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate
PyFNBOP	[4-nitro-6-(trifluoromethyl)benzotriazol-1-yl)oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyFOP	[[6-(trifluoromethyl)benzotriazol-1-yl]oxy]tris-(pyrrolidino)phosphonium hexafluorophosphate
PyNOP	[(6-nitrobenzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyOxB	*O*-[(1-cyano-2-ethoxy-2-oxoethyliden)amino]oxytri(pyrrolidin-1-yl)phosphonium tetrafluoroborate
PyOxP	*O*-[(1-cyano-2-ethoxy-2-oxoethyliden)amino]oxytri(pyrrolidin-1-yl)phosphonium hexafluorophosphate
PyPOP	(pentafluorophenyloxy)tris(pyrrolidino)phosphonium hexafluorophosphate

PyTOP	(pyridyl-2-thio)tris(pyrrolidino)phosphonium hexafluorophosphate
SOMP	5-(succinimidyloxy)-3,4-dihydro-1-methyl-*2H*-pyrrolium hexachloroantimonate
TAs	*3H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 4-methylbenzenesulfonate
TATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
N-TATU	*N*-[(dimethylamino)-*1H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
TBs	*1H*-benzo[*d*][1,2,3]triazol-1-yl 4-methylbenzenesulfonate
TBTU	*O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
N-TBTU	*N*-[(*1H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
TCFH	tetramethylchloroformamidinium hexafluorophosphate
TCP	2,4,5-trichlorophenyl active ester
TDATU	*O*-(3,4-dihydro-4-oxo-5-azabenzo-1,2,3-triazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TDTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEMP	2,3,5,6-tetramethylpyridine
TMP	collidine
TMU	tetramethylurea
TNTU	2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TODT	*S*-(1-oxido-2-pyridinyl)-1,3-dimethyl-1,3-trimethylenethiouronium tetrafluoroborate
TOPPipU	2-[2-oxo-1(*2H*)-pyridyl]-1,1,3,3-bis(pentamethylene)uronium tetrafluoroborate
TOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate
TOTU	*O*-[cyano(ethoxycarbonyl)methyleneamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TPFTU	*N*,*N*,*N*′,*N*′-bis(tetramethylene)-*O*-pentafluorophenyluronium tetrafluoroborate
TPhTU	2-phthalimido-1,1,3,3-tetramethyluronium tetrafluoroborate
TPTU	2-(2-oxo-1(*2H*)- pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TsOPy	2-oxopyridin-1(*2H*)-yl 4-methylbenzenesulfonate
TSTU	2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate

II. INTRODUCTION

Modern peptide chemistry, which has fuelled the renaissance of peptides as active pharmaceutical ingredients, shows three key cornerstones: (i) the solid-phase methodology developed by R. Bruce Merrifield; (ii) the fluorenylmethoxycarbonyl (Fmoc) group as temporary protecting group for the α-amino function developed by Louis A. Carpino; and (iii) 1-hydroxybenzotriazole (HOBt) for the coupling reaction by König and Geiger. Nowadays, solid-phase, Fmoc and HOBt (or an alternative *N*-hydroxylamine) are present

in any scientific paper or industrial process related to peptides. The first use of 1-hydroxybenzotriazole (HOBt) was just to reduce the reactivity of the active specie, *O*-acylisourea, formed by the reaction of the protected amino acid and the carbodiimide. The OBt active ester prepared *in situ* is more stable than the *O*-acylisourea and therefore the completion of the coupling step is more easily reached and reduces the loss of chirality of the protected amino acid due to the reduced activity. Although, the OBt active esters and related triazole analogues do not show enough stability for being prepared, isolated and stored; other *N*-hydroxylamine derivatives, mainly succinimide ones, can be used for this purpose. Later, *N*-hydroxylamine derivatives were the base for the development of stand-alone coupling reagents (phosphonium, aminium/uronium salts), which are being used as substitutes of the carbodiimides. Finally, as *N*-hydroxylamine derivatives show mild acid properties they are used during solid-phase peptide synthesis for minimizing side reactions, such as aspartiimide formation, or masking of the guanidine group of the arginine for masking its reactivity.

In this chapter, we will discuss the most frequent use for *N*-hydroxylamines in peptide chemistry. *N*-Hydroxylamine derivatives are summarized, first describing their preparation and physical properties, and then their application in peptide chemistry.

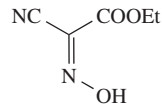
III. PREPARATION AND PROPERTIES

A. Oxyma (Ethyl 2-cyano-2-(hydroximino)acetate)

Ethyl 2-cyano-2-(hydroximino)acetate (Oxyma, **1**, Figure 1) is a water-soluble, white crystalline solid, obtained as needles, which allows easy handling and presents a melting point described in the range 128–133 °C, with little variation depending on the author[1–11]. Alternatively, **1** has been named as ethyl cyanoglyoxylate-2-oxime, and also abbreviated as HECO[6]. As a ketoxime, **1** shows high stability, in contrast to several oximes presenting α-carbon hydrogens, which prompted its commercial availability[2, 3, 12]. **1** is used as starting material in the preparation of 5-halo-1,2,3-triazoles, cyanopyrroles, 5-aminoimidazole nucleosides, phosphoesterase inhibitors or mGluR5a receptor antagonists[8, 13–15].

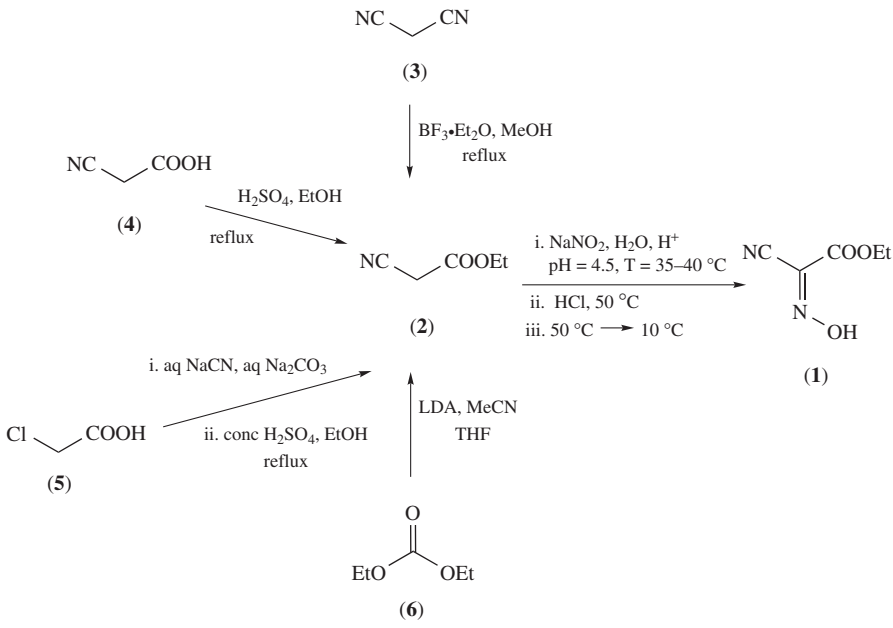
Most of the synthetic approaches used for **1** are based on the nitrosation of ethyl 2-cyanoacetate (**2**) in the presence of acetic acid and sodium nitrite, as an *in situ* source of nitrous acid (Scheme 1)[1, 6, 16]. Conrad and Schulze[16] were one of the first authors to propose this transformation for **2** and, since then, this method has been extensively used by other authors[1, 3, 5, 6, 14]. Slight changes have been introduced, such as the addition of sodium hydroxide or the use of ethyl nitrite[8, 13]. Phosphoric or sulfuric acid are also used to induce acidic pH, resulting in the yield being raised[17]. So far, the best optimization of the method was described by Parker, using phosphoric acid to set pH = 4.5; **1** was obtained almost quantitatively[10]. Other non-nitrosating strategies have been reported, by oxidizing **2** with nitrogen dioxide or forming an adduct with nitroprusside, which decomposes to **1**[7, 9]. These approaches, however, are associated with poor yields.

Ethyl 2-cyanoacetate (**2**) is readily and efficiently prepared from simple starting materials (Scheme 1). Malononitrile (**3**) can be converted to **2**, after reflux with boron trifluoride



(**1**)

FIGURE 1. Structure of ethyl 2-cyano-2-(hydroximino)acetate



SCHEME 1. Synthetic approaches for the preparation of Oxyma

etherate in methanol (MeOH)[18]. The reflux time is the key to the efficiency of this reaction, since one day-reflux renders 90% of the target activated-methylene compound, whereas 36 hours afford **1** quantitatively[18]. Alternatively, it can be obtained from 2-cyanoacetic acid (**4**), by esterification in refluxing ethanol and H_2SO_4 in 95–97% yield (Scheme 1)[19, 20]. Remarkably, 2-chloroacetic acid (**5**) can be also transformed into **1** in a one-pot process with simultaneous introduction of the cyano group and esterification (80% yield) (Scheme 1)[21]. Finally, another interesting approach is the addition of diethyl carbonate (**6**) into a mixture of acetonitrile and lithium diisopropylamide (LDA) in THF, rendering **2** in 76% yield (Scheme 1)[22].

Unlike previously reported *N*-hydroxylamines, oximes such as **1** contain a nitrogen double-bonded to one single carbon, which accounts for some of its properties[1]. As a result, both types of compounds are known to possess similar acidity[23]. Consequently, **1** shows a high dissociation constant ($pKa = 4.60$), obtained by an automatic titration of an aqueous solution in 0.02M potassium hydroxide, which is almost identical to the value reported for 1-hydroxybenzotriazole (HOBt, **95**, see Section III.H.1)[1, 3, 4, 24]. Achmatowicz and Szymoniak reported the IR of **1** in KBr analysis of **1**, showing a band for the hydroxyl group of the *N*-hydroxylamine, at high frequency of $\nu(O{-}H) = 3200{-}3100\,cm^{-1}$, and other bands at $\nu(C{=}N) = 2200\,cm^{-1}$, $\nu(C{=}O) = 1720\,cm^{-1}$, $\nu(C{-}O) = 1030\,cm^{-1}$ [7]. Additional bands were described by Cheng and Lightner at $\nu = 3600$, 3008, 2851 (C–H), 1636, 1594, 1452, 1319, 820, 763, 513 cm^{-1}.[8] **1** shows a characteristic absorption in the UV-visible region at $\lambda_{max} = 235{-}240\,nm$[2]. The conjugated anion, however, presents a yellow color, meaning a weak absorption in the visible area of the spectrum ($\log \varepsilon = 1.30{-}2.30$), due to a known transition corresponding to the nitroso group of deprotonated ethyl 2-cyano-3-isonitrosoacetate (**1′**, Figure 2), instead of the hydroximino species **1**[6, 8, 10, 25–27]. This conclusion is supported by the IR spectra of the potassium salt

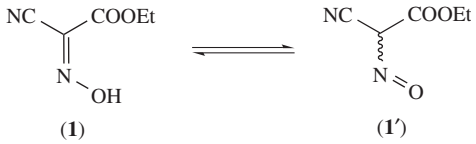


FIGURE 2. Tautomeric species of ethyl 2-cyano-2-(hydroximino)acetate

of **1**, reported by Eddings and coworkers[6], showing many similarities to the protonated **1**, except for the absence of *N*-hydroxylamine hydrogen and the presence of the characteristic nitroso band of the predominant anionic tautomer at ν(C=N) = 2209 cm^{-1}, ν(C=O) = 1674 cm^{-1}, ν(N=O) = 1280 cm^{-1} and ν(CNO) = 1140 cm^{-1} [6]. Additional bands were detected at ν(N=O) = 1265 cm^{-1} and ν(CNO) = 1115 cm^{-1}, corresponding to ^{15}N isotopomers[6]. GC-MS characterization, also described by Cheng and Lightner, show most fragmentations related to the ethoxy carboxylate and hydroxyl groups at (t_R = 7.2 min): (m/z) = 142 ($M^{+\bullet}$), 125 (M − OH), 114 (M − CH_2CH_3), 97 (M − OEt), 69 (M − CO_2Et)[8].

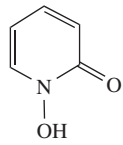
The ^{1}H-NMR spectra of **1** in DMSO-d_6 showed the *N*-hydroxylamine hydrogen at a considerably high frequency at δ 15.05[6]. In deuterated chloroform, this acidic proton was observed close to the methylene hydrogens at δ 4.833[8]. Regarding the ^{13}C-NMR (DMSO-d_6) spectra at room temperature, 5 carbon signals were detected[6]. A ^{13}C-NMR experiment, carried out in a range of temperatures from 20 to 110 °C, showed one set of 5 lines, which provides the information that the isomer composition of **1** is not a mixture of *syn* and *anti* isomers[6]. This result is in agreement with the findings of Conrad and Schulze[16] that **1** is present as the *Z* isomer[18]. The presence of intramolecular hydrogen bonding between the hydroxyl and the carbonyl groups might stabilize this isomer.

Recently, the stability of **1** has been evaluated and compared to that of the potentially explosive HOBt (**95**, Section III.H.1) and HOAt (**116**, Section III.I.1) by means of calorimetry assays (dynamic DSC and ARC)[2]. The outcome of both experiments showed that **1** decomposes in a slow and constant manner, releasing low pressure (61 bars), in contrast to **95** (Section III.H.1) and **116** (Section III.I.1), that showed a totally distinct behavior, decomposing very fast with 3-fold higher associated pressure, showing a typical explosive profile[33]. The onset of decomposition could be accurately set at 124 °C, after performing the ARC assay. Interestingly, **1** decomposed just after melting, unlike **95** (Section III.H.1) and **116** (Section III.I.1). As a result, it is recommended to keep the temperature <74 °C, in order to work safely[28, 29]. Nevertheless, microwave experiments using **1** at 80 °C proceeded without incidents[30].

B. Hydroxypyridines

1. HOPy, N-hydroxy-2-pyridinone

N-Hydroxy-2-pyridinone (HOPy, **8**, Figure 3) is a colorless crystalline solid, present in the form of needles or blades, soluble in hot water and ethanol, which melts at 148–151 °C, after recrystallization from ethyl acetate or methanol[31–38]. **8** (alternatively abbreviated as HOPO or Hhpno) contains a rather chemically stable hydroxamic acid moiety, being resistant to boiling aqueous acid or catalytic reduction[35, 39]. The presence of the cyclic hydroxamic acid is often confirmed after observing a characteristic deep red color in contact with a solution of ferric chloride[33, 34]. This acid moiety has also great impact on the significant antibactericidal properties exhibited by **8**, since the 3-hydroxy and 4-hydroxy isomeric pyridones do not have this activity[33, 34, 40]. Novel applications of **8** are



(**8**)

FIGURE 3. Structure of *N*-hydroxy-2-pyridinone

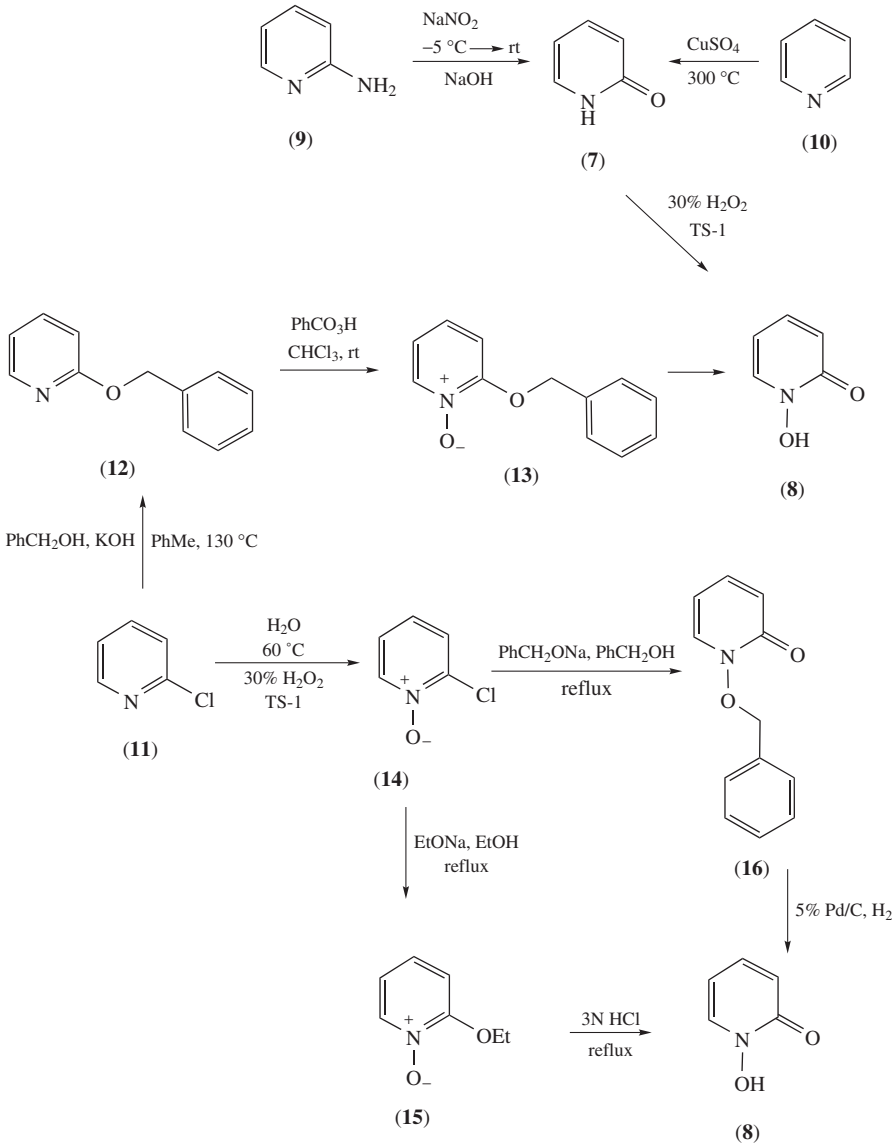
still discovered, such as the reduction of the percentage of ruthenium in the media, after performing Ring Closing Metathesis[39]. Recently, nanostructure silica materials functionalized with **8** (1,2-HOPO-SAMMS) have been shown to be effective sorbents for the abstraction of both free and chelated gadolinium-based contrast agents, in order to prevent nephrogenic systemic fibrosis[38]. Some derivatives of **8** have also been employed in obtaining hair preparations or the generation of guanine radicals[41].

Probably, the best method for preparation of **8** consists in the oxidation of 2-pyridinone (**7**), which is optimally conducted using green chemistry in the presence of hydrogen peroxide and zeolite catalysts to afford **8** in 92% yield (Scheme 2)[42]. Other selective oxidation methods include the action of *tert*-butyl hydroperoxide or molecular oxygen, using Mo or Ru catalysis (52–70% yield)[43, 44]. Perbenzoic acid did not give satisfactory results[35]. **7** can be successfully obtained from 2-aminopyridine (**9**) by diazotization in sodium hydroxide at low temperature or by intramolecular nucleophilic hydroxylation of pyridine (**10**), although the latter strategy requires 300 °C to afford **8** in 95% yield[45–47]. Similar procedures were reported by hydrolysis of 2-fluoro, or demethylation of 2-methoxy to afford **8** in 47–81% yield[48–51].

Alternatively, one of the other indirect routes to **8** from 2-chloropyridine (**11**) starts with the preparation of the 2-benzyl ether (**12**) from **11**, by treatment with benzyl alcohol and potassium hydroxide (96–97% yield)[52, 53]. 2-Pyridinone, 2-fluoro or 2-bromopyridine, also lead to **12**, by means of microwave irradiation, silver catalysis or in solvent-free conditions[54–57]. **12** is then slowly oxidized to 2-benzyloxypyridine-1-oxide (**13**) in the presence of perbenzoic acid in moderate yield (45%), although other authors claim that this method yields mainly 1-benzyloxy-2-pyridinone[34, 36]. Subsequent debenzylation by hydrochloric acid-mediated hydrolysis or catalytic reduction of **13** affords **8** in 68–69% yield[34]. A more efficient route results from the selective monooxidation of **11** using green chemistry and titanosilicate zeolites or *m*-chloroperbenzoic acid, to give 2-chloropyridine-1-oxide (**14**) in almost quantitative yield[37, 58]. **14** could be converted to 2-ethoxy analogue (**15**) by refluxing in EtOH and EtONa (80% yield) or selectively *N*-benzylated with sodium benzyloxide, to give 1-benzyloxy-2-pyridinone (**16**) in 56% yield[36]. Pd-catalyzed reduction of **16** affords **8** in 83% yield, whereas hydrolysis of **15** by refluxing in hydrochloric acid is slightly less efficient and affords **8** in 73% yield[33, 36, 59].

8 is a highly acidic heterocycle ($pKa = 5.9$), as determined by potentiometric titration[34, 36]. Infrared spectra of **8** in Nujol mulls showed a broad band at 3200–2200 cm^{-1} and additional signals at 3070, 2940 and 2400 cm^{-1} [36]. The same strong signal at 3200–2200 cm^{-1} was observed in chloroform[36]. A more detailed spectrum has been reported using KBr pellets[42]. **8** presents a strong UV absortion in ethanol at 228 nm and 305 nm (log $\varepsilon = 3.85$, 3.66 or 3.81, 3.60)[34, 40]. Aromatic hydrogens can be detected by means of ^{1}H-NMR spectra[42].

The hydroxamic acid (**8**, *N*-hydroxy-2-pyridone) and *N*-oxide (**8′**, 2-hydroxypyridine-*N*-oxide) species is well reported from the time of the earliest synthesis (Figure 4)[33, 34, 39, 40, 42, 60]. Some authors claim to obtain the *N*-oxide form **8′**, which is extraordinarily acidic ($pKa = -0.8$), whereas others find the *N*-hydroxy form



SCHEME 2. Synthetic strategies for preparation of *N*-hydroxy-2-pyridinone

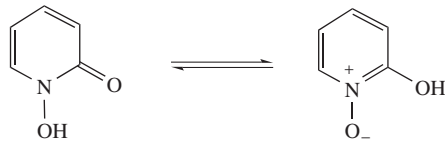


FIGURE 4. Tautomeric forms of *N*-hydroxy-2-pyridinone

(**8**) to be more consistent with the spectroscopic data received[33, 36, 42, 43]. Although Jaffe[61] found by calculations that the *N*-oxide (**8′**) is more stable than the *N*-hydroxy (**8**) by 20 kcal mol^{-1}, evaluation of **8** suggested the contrary[36]. Shaw[34] reported that 1- and 2-benzyloxy derivatives of **8** led, after hydrolysis in HCl, to the *N*-hydroxy (**8**) and that during this reaction, 2-benzyloxypyridine-1-oxide rearranges to 1-benzyloxypyrid-2-one, suggesting that both *N*-benzyloxy and *N*-hydroxy species are the most stable species[34]. Comparison with UV spectra in ethanolic mixtures containing sulfuric acid and sodium ethoxide[34, 36] showed the *N*-hydroxy tautomer (**8**) to be the preferred one. Moreever, ultraviolet spectra were similar to **7** and the 1-benzyloxypyridinone derivative[34, 40]. UV and IR spectroscopy showed the presence of a strong intramolecular hydrogen bonding, regardless of the predominant tautomeric form[32, 36].

2. HOTPy, N-hydroxy-2-pyridinethione

N-Hydroxy-2-pyridinethione (HOTPy, **19**, Figure 5) is a white monoclinic crystalline solid, with melting point 68–70 °C after recrystallization from aqueous ethanol. Some authors reported a lower melting point (63 °C)[62–67]. **19**, also referred to as pyrithione, is an allergenic compound, causing sneezing or sternutatory response[65, 66]. The esters formed with **19** are highly sensitive to decomposition under visible light irradiation, from a Tungsten lamp[63]. Some derivatives of **19**, such as Zn chelates, possess a marked antibacterial and antifungal activity[64–66].

One of the first designed routes to **19** consists in the regioselective direct lithiation of pyridine-*N*-oxide (**18**), followed by sulfurization with molecular sulfur, in a one-pot fashion (Scheme 3)[65, 68]. This method optimally renders **19**, when LiH is used instead of butyllithium or lithium amide, at room temperature, although the yields do not rise above 21%[64, 68]. One of the available methods enabling quantitative conversion to **19**, oxidative decarboxylation of 2-pyridinecarboxylic acid (**17**), using hydrogen peroxide as oxidant and Pressler's anion as green catalyst, affords **19** in 54–93% yield[69]. In addition, pyridine (**20**) transformed into **18** to treatment with methyltrioxorhenium-hydrogen peroxide, Keggin-type heteropolyoxo tungstates, perfluorinated ketones or magnesium monoperoxyphthalate as catalysts (Scheme 3)[70–73].

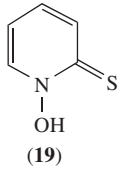
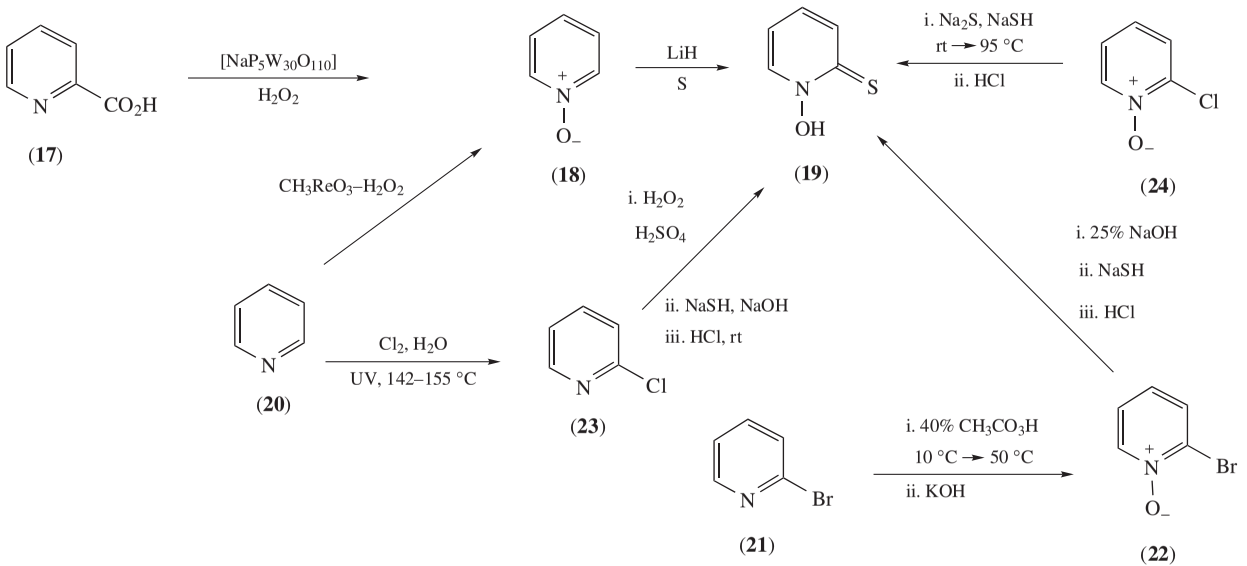


FIGURE 5. Structure of *N*-hydroxy-2-pyridinethione



SCHEME 3. Synthetic strategies for preparation of *N*-hydroxy-2-pyridinethione

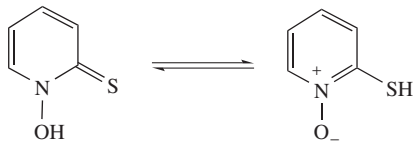
Alternatively, moderate yields (60–61%) are obtained by nucleophilic substitution of 2-bromopyridine-*N*-oxide (**22**) with sodium sulfide or sodium hydrosulfide, under mild conditions (Scheme 3)[65, 74]. The percentage of **19** strongly depends on the purity of the sodium hydrosulfide employed, and the use of fresh reagent is recommended[65]. 2-Bromopyridine-*N*-oxide (**22**) is obtained by oxidation of 2-bromopyridine (**21**) with peracetic or perbenzoic acid in one day (60–70% yield) (Scheme 3)[65].

Excellent yields (71–81%) are obtained from 2-chloropyridine (**23**) by oxidation with H_2O_2 and H_2SO_4 or maleic anhydride, followed by nucleophilic substitution with sodium hydrosulfide (Scheme 3)[75]. Chlorination of pyridine (**20**) to 2-chloropyridine (**23**) is accomplished with high *o*/*p* regioselectivity under UV irradiation or high temperature (88–90% yield)[76]. However, the most efficient approach consists in the reaction of conversion of 2-chloropyridine-*N*-oxide (**24**) with sodium sulfide or hydorsulfide, followed by acidification to afford **19** in 94% yield (Scheme 3)[77].

The *N*-hydroxy (*N*-hydroxy-2-pyridinethione, **19**) and *N*-oxide (2-mercaptopyridine-*N*-oxide, **19′**) species (Figure 6) are well documented, similarly to **8** (Section III.B.1)[65, 66, 74, 78]. **19** crystallizes as the *N*-hydroxythione tautomeric form **19**, the predominant species as established by UV and IR spectroscopy[66, 67]. The presence of the cyclic thiohydroxamic acid moiety of the *N*-hydroxy form (**19**) is confirmed by the appearance of a deep blue color with ferric chloride[63–65]. The intramolecular hydrogen bonding between the *N*-hydroxyl and 2-thione groups also stabilizes this structure[66].

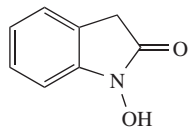
C. HOI, *N*-Hydroxyindolin-2-one

N-Hydroxyindolin-2-one (HOI, **26**, Figure 7) is a pale yellow solid whose melting point has been described as 198–199 °C or 199–201 °C[79–81]. **26**, also named *N*-hydroxy-2-oxindole, is reported to melt at 200.5–202 °C when recrystallized from DCM–MeOH[80, 82, 83]. Remarkably **26**, having only one nitrogen atom, is not explosive and is regarded as a safer heterocyclic compound[79]. From a biomedical point of view, **26** is a weak inhibitor of mandelate racemase and is also used as template in the synthesis of agents to treat multiple sclerosis[82].



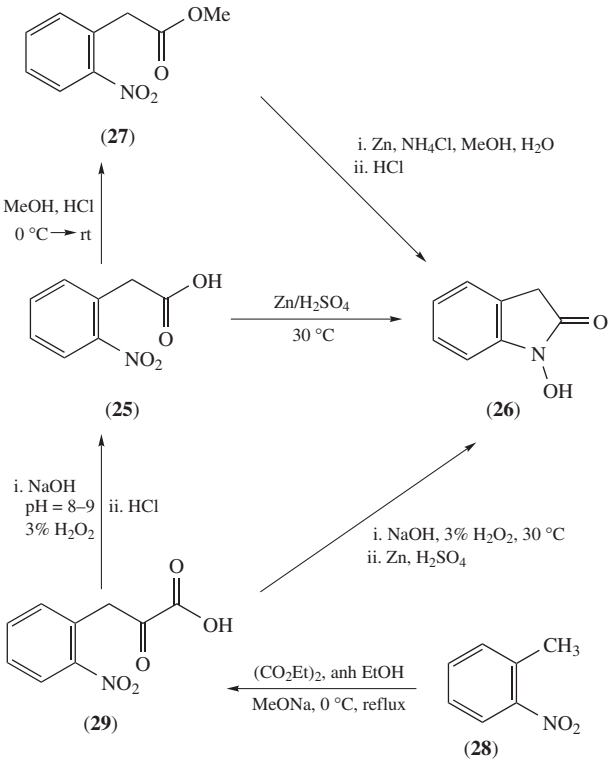
(**19**) (**19′**)

FIGURE 6. Tautomeric forms of *N*-hydroxy-2-pyridinethione



(**26**)

FIGURE 7. Structure of *N*-hydroxyindolin-2-one



SCHEME 4. Synthetic strategies for preparation of *N*-hydroxyindolin-2-one

26 is obtained by various routes, as shown in Scheme 4. It is obtained by reductive cyclization of *o*-nitrophenylacetic acid (**25**) in the presence of Zn and H_2SO_4, as described by Reissert many decades ago, along with some oxindole as byproduct (Scheme 4)[84]. Later, Wright and El-Faham and their coworkers adapted this methodology, affording **26** in 20–22% yield[79, 80]. Other Zn-based reducing agents were scrutinized by Wright and coworkers, such as Zn/Ca chloride and Zn/Ca sulfhydrate, with few or no percentage of **26** obtained[80]. Another strategy consists in the esterification of **25** with MeOH in the presence of HCl to afford **27**, and then subsequent reduction of **27** by treatment with Zn and ammonium chloride afforded **26** in 48% yield[83, 85, 86]. One of the other routes is treatment of *o*-nitrophenylpyruvic acid (**29**) with 3% hydrogen peroxide at a controlled basic pH, followed by acidification, to render **25** in 93% yield[80, 87]. An alternative is the direct conversion of **29** to **26** in 47% yield[80, 88]. Formation of **29** can be accomplished starting from *o*-nitrotoluene (**28**) in good yield, after reflux in the presence of diethyl oxalate and sodium methoxide, with subsequent acidification (51% yield)[80, 81, 87]. The direct transformation of **29** into *o*-nitrophenylacetic acid **25** is less efficient than the above-mentioned route[80].

The ^{1}H-NMR spectroscopic analysis of **26** showed the *N*-hydroxyl hydrogen resonating at high frequencies and the aromatic and aliphatic methylene protons[79]. In MeOD, the aromatic and, especially, the *N*-OH hydrogens are down-shifted[83]. The IR spectra of **26** in KBr displayed the hydroxamic acid carbonyl bands at 1675 and 1617 cm^{-1} [83].

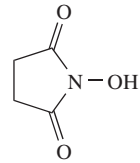
D. *N*-Hydroxysuccinimides

1. HOSu, N-hydroxysuccinimide

N-Hydroxysuccinimide (HOSu, **31**, Figure 8) is a colorless solid, obtained as crystalline plates with a melting point in the range 94–100 °C[31, 89–91]. **31** is highly soluble in H_2O, but decomposes on heating[31, 89, 92, 93]. Some derivatives or salts of **31** have found wide application in many fields, such as its esters, regarded as acylating reagents, especially for amino acids, certain silver complexes that are used to form silver film, or ethylenediamine-based analogues, which serve as crosslinking agents for the preparation of gels with wound-healing and nerve-regenerating properties[89, 91–95].

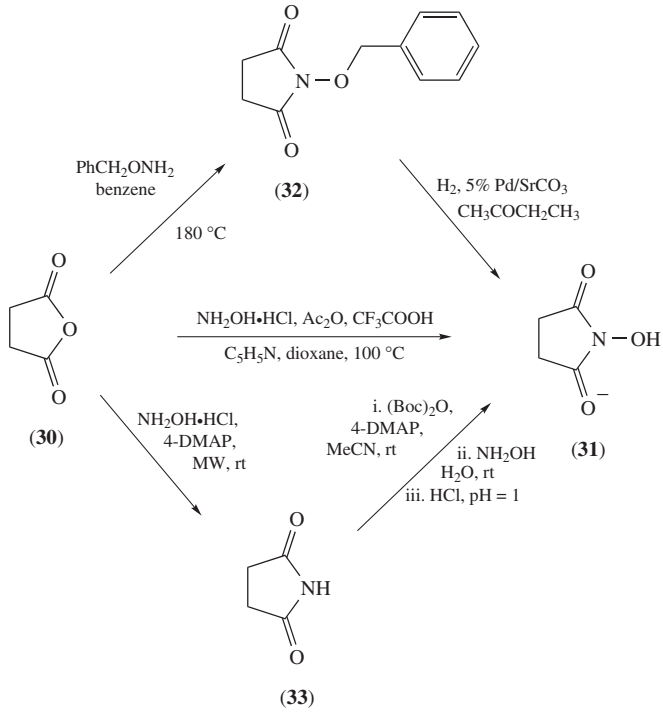
Various synthetic approaches to **31** have been proposed, many of which are based on succinic anhydride (**30**, Scheme 5). One of the earliest syntheses was described by Ames and Grey in 1955, which afforded **31** through catalytic hydrogenation of *N*-benzyloxysuccinimide (**32**) with palladium absorbed on strontium carbonate[31]. This intermediate is readily obtained from **30** by reaction with benzyloxyamine at high temperature (76% yield)[31]. An almost identical strategy was chosen by Chenavas, although few experimental details were given[96]. However, a more convenient direct conversion of **30** to **31** has been widely reported. Some approaches describe the use of free hydroxylamine to carry out such transformation, although usually higher yields are obtained with its hydrochloride salt[97]. The presence of an aqueous base, such as sodium hydroxide, is required in the first step to generate the free hydroxylamine *in situ*, followed by reflux in ethyl acetate[89, 91]. Alternatively, succinimide (**32**) can also lead to **33** (Scheme 5), adapting an analogous one-pot procedure for the synthesis of *N*-hydroxyphthalimide (HONP, **42**, see Section III.D.4) through formation of an intermediate *N*-carbamate, since direct oxidation of the imide is a difficult methodology[87, 98, 99]. In the first step, the intermediate *N*-(*tert*-butoxycarbonyl)succinimide is first formed in the presence of catalytic 4-*N*,*N*-dimethylaminopyridine (DMAP), which is rapidly transformed into the hydroxylammonium salt by addition of aqueous sodium hydroxide[87]. Final acidification to pH = 1 and recrystallization from EtOAc affords **31** in 83% yield (Scheme 5)[87].

The acidity of **31** in H_2O reported by Ames and Grey ($pK_a = 6.0$) is considerably high as an organic compound, and thus it can be considered as a suitable additive for peptide synthesis[31]. The work of Pop and coworkers, titrating a 9% MeOH in H_2O solution, led to the same dissociation constant[100]. A similar acidity at room temperature was also obtained by Koppel and coworkers ($pK_a = 6.09 \pm 0.03$) by using the standard Albert potentiometric technique[24]. However, at 54 °C, the acidity of **31** described by König and Geiger, in a 50:40 mixture of diethylene glycol dimethyl ether/H_2O, was higher ($pK_a = 5.1$) than that from the previous methods[101] with properties closely resembling the routinely used solvents in peptide synthesis. The dissociation constant determined by Koppel and coworkers, by potentiometric titration with Bu_4NOH in a solvent mixture benzene/isopropanol, was lower than in H_2O ($pK_a = 14.0 \pm 0.1$)[24]. Regarding ultraviolet spectra of a 95% ethanolic



(**31**)

FIGURE 8. Structure of *N*-hydroxysuccinimide



SCHEME 5. Synthetic pathways for preparation of *N*-hydroxysuccinimide

solution of **31**, strong absorption was detected around 200–210 nm ($\lambda_{max} = 265.5$ nm, log $\varepsilon = 2.79$; $\lambda_{max} < 205.0$ nm, log $\varepsilon > 3.89$), possibly due to the presence of a tautomeric *N*-oxide species (**31′**), which could be also involved in the high acidity of HOSu (Figure 9)[31].

Consistent with the reports on the acidity of **31**, ^{1}H NMR in C_6D_6 revealed that the *N*-OH proton resonates at high frequencies (11.0 ppm), a lower value than HOBt, **96** (Section III.H.1) (13.6 ppm)[100]. Methylene protons of **31** are clearly distinguishable from those of the sodium salt of **31** in D_2O (2.77 vs 2.63 ppm)[102]. The IR spectra of **31** resembles those of **32** and some *N*-alkyl derivatives, showing intense imide bands at 1789 and 1709 cm^{-1}, especially the latter[31]. Other bands are observed at lower frequencies (1692 cm^{-1} and 1511 cm^{-1})[31].

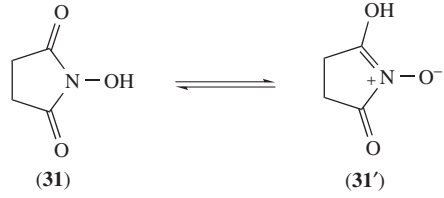
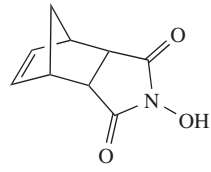


FIGURE 9. Tautomeric forms of *N*-hydroxysuccinimide

2. HONB, N-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide

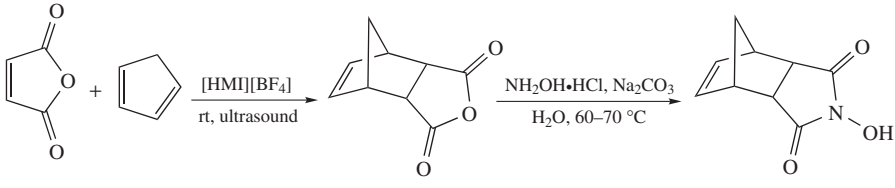
N-Hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide (HONB, **36**, Figure 10) is a white crystalline solid, obtained as colorless plates, melting at 165–166 °C from EtOAc[103–105]. Other authors describe a sligthly lower melting point (162–163 °C)[106]. **36** is also named *cis*-*N*-hydroxy-5-norbornene-*endo*-2,3-dicarboximide or *N*-hydroxybicyclo[2.2.1]hept-5-ene-2,3-dicarboximide[104, 106–109]. **36** is used for the preparation of primary *O*-alkoxyamines, a similar application to the one exhibited by HONOD (**39**, Section III.D.3)[106]. Its *O*-substituted derivatives possess herbicidal properties and show high phytotoxic activity even in small amounts[108].

The synthetic strategies for **36** are based on the reaction of *endo*-*cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride (**35**, or 5-norbornene-*endo*,*cis*-2,3-dicarboxylic anhydride) with hydroxylamine (Scheme 6)[103]. This transformation was first accomplished by Stolberg and coworkers[103], who described the synthesis of **6**, after 24 hours, in the presence of MeONa at room temperature (80%). However, they claimed that they synthesized, in fact, the 'phthaloxime', in reference to the analogous structural debate that arose with *N*-hydroxyphthalimide (HONP, **42**, Section III.D.4)[103]. The titration of **36** with base suggested the absence of cyclic amide, although it gave a red color with ferric chloride[103]. Shortly thereafter, Bauer and Miarka improved the yield, by adapting the Orndorff methodology described for the synthesis of HONP (**42**, Section III.D.4), heating **35** with aqueous hydroxylamine hydrochloride and sodium carbonate (91% yield)[104]. Since then, similar procedures have been reported, altering the base (sodium hydroxide) or experimental details, but without further enhancement of the efficiency[105, 106]. **35** is obtained by stereoselective *endo* Diels–Alder cyclization of cyclopentadiene (**33**) and maleic anhydride (**34**) as dienophile (Scheme 6). This conversion can be quantitative and highly *endo* selective in the presence of imidazolium-based ionic liquids as solvent and under ultrasound[110]. Other highly efficient strategies which use SnW2-800 catalysts or Montmorillonite have been recently described[111, 112].



(**36**)

FIGURE 10. Structure of *N*-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide



(**33**) (**34**) (**35**) (**36**)

SCHEME 6. Synthetic strategies for preparation of *N*-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide

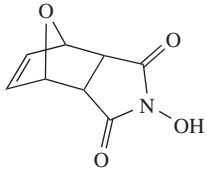
The p*K*a of 5.9 of **36** is one of the highest in the *N*-hydroxyl cyclic imide series, showing a higher dissociation constant than **42** (Section III.D.4)[103]. In the latter case, the lower acidity is due to the presence of the aromatic ring, which decreases the CO polarization and hence the *N*-OH dissociation constant[106]. IR analysis of **36** showed carbonyl bands with strong absorption at 1695, 1710 and 1770 cm^{-1} and the *N*-hydroxyl signal at high frequency (3100 cm^{-1})[103, 104]. Other bands were detected at 2850, 1610 and 720 cm^{-1} [106]. The expected ^{1}H-NMR spectra for the proposed structure was provided by Rougny and Daudon in DMSO-d_6[106]. **36** affords colorless anions when deprotonated, in contrast to the colorful anions of aromatic *N*-hydroxy imides[104].

3. HONOD, N-hydroxy-3,6-epoxy-1,2,3,6-tetrahydrophthalimide

N-Hydroxy-3,6-epoxy-1,2,3,6-tetrahydrophthalimide (HONOD, **39**, Figure 11) is a white crystalline solid, structurally derived from HOND (**42**) (Section III.D.4) or *N*-hydroxysuccinimide (**31**, Section III.D.1)[113, 114]. Alternatively, it has been abbreviated as HOEC (*N*-hydroxy-1,4-epoxy-5-cyclohexene-2,3-dicarboximide) and HONCE (*N*-hydroxy-1,4-epoxylcyclohex-5-ene-2,3-dicarboximide), or named as *exo*-*N*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide or 4-hydroxy-10-oxa-4-azatricyclo[5.2.1.0]dec-8-ene-3,5-dione[115–120]. Some of its applications consist of the preparation of *N*-substituted maleimides by retro Diels–Alder reaction, which cannot be synthesized from maleamic acids due to detrimental isomaleimide formation, and molecularly imprinted polymers[113, 116, 121]. **39** also serves as a building block to form ring-opening metathesis polymers (ROMP), which are used as acyl transfer reagents in the synthesis of amides, carbamates, ureas or Mosher amides[117]. Arylantimony analogues of **39** show promising anticancer properties, whereas phosphates and *N*-aryloxyacetyl derivatives are useful herbicides, parasiticides and rodenticides[122, 123]. Conjugation of kidney imaging agents with antibodies has also been accomplished with the help of **39**[120].

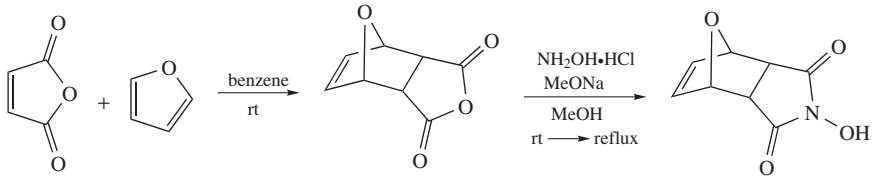
Narita and coworkers reported the one-pot synthesis of **39** from furan (**37**) and maleic anhydride (**33**) in 64% yield (Scheme 7)[113]. In the first step, the Diels–Alder cycloaddition of **33** and **37** yields the maleic anhydride-adduct of furan: 3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (**38**), which is present exclusively in the *exo* form[113, 124]. This intermediate is then converted to **39** by refluxing with hydroxylamine hydrochloride in the presence of NaOMe[113]. In the following decades, analogous strategies to that of Narita have been described, without significant variation or improvement[114, 125].

The melting point of **39** has given rise to some controversy, since some authors claim it melts at 187–188 °C, with decomposition at 150 °C, whereas others reported a considerably lower melting value (167–170 °C)[113]. **39** shows thermal instability, decomposing at 190 °C. However, in contrast with *O*-alkoxy derivatives, no reverse Diels–Alder cycloaddition products are observed[113]. **39** displays medium-to-strong infrared absorption at 1785



(**39**)

FIGURE 11. Structure of *N*-hydroxy-3,6-epoxy-1,2,3,6-tetrahydrophthalimide



SCHEME 7. Synthesis strategy for the synthesis of **39**

and 1725 cm^{-1}, corresponding to the cyclic imide moiety, and medium-absorbance *N*-hydroxyl bands at 3470 and 3300 cm^{-1} [113].

4. HONP, N-hydroxyphthalimide

N-Hydroxyphthalimide (HONP, **42**, Figure 12) is a colorless monoclinic crystalline solid, forming needles or rods, melting with decomposition at 232–233 °C[187, 99, 126–128]. Other authors reported a slightly lower melting point (230 °C)[99, 127]. The cyclic imide **42** is stable to air, causing allergenic response and dermatitis in contact with skin or eyes[129, 130]. **42**, which is also named phthalylhydroxylamine or abbreviated as NHPH, is poorly soluble in water, in contrast to the less hydrophobic *N*-hydroxysuccinimide (**31**, Section III.D.1) except in basic conditions, resulting in tedious work-ups[89, 99, 127, 131]. **42** is also rather insoluble in many organic solvents, such as benzene, chloroform, diethyl ether, toluene or petroleum ether[127]. Only in EtOH, acetone, EtOAc, HOAc and acetonitrile does **42** display a high solubility[127]. In spite of this general limitation **42** is widely used in the preparation of *O*-substituted hydroxylamines[132, 133]. Its radical also participates in hydrogen-abstraction mediated reactions, being considered as a suitable catalyst in the oxidation of hydrocarbons in mild conditions[134–137]. Even in biochemical oxidating processes, **42** is used as an initiator[138, 139]. Some of its derivatives have also been useful in electrocatalytic oxidations or as asymmetric catalysts[140–143].

During many years in the first part of the last century, it was considered that the reaction of phthalic anhydride with hydroxylamine yielded a compound regarded as a 'phthaloxime', the phthalic anhydride mono-oxime[144–146]. Brady and coworkers reported two isomeric versions for this phthaloxime, obtained as yellow and white solids, respectively[146]. Later, some authors, like Putokhin[127] or Ames and Grey[126], claimed that the above-mentioned white isomer was, in fact, **42**, the *N*-hydroxy cyclic imide of phthalic acid. Ames and Grey, who were unable to obtain the yellow isomer described by Brady, argued that the UV profile of the white isomer was very similar to phthalimide and also

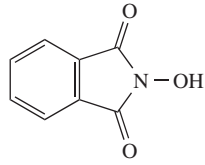
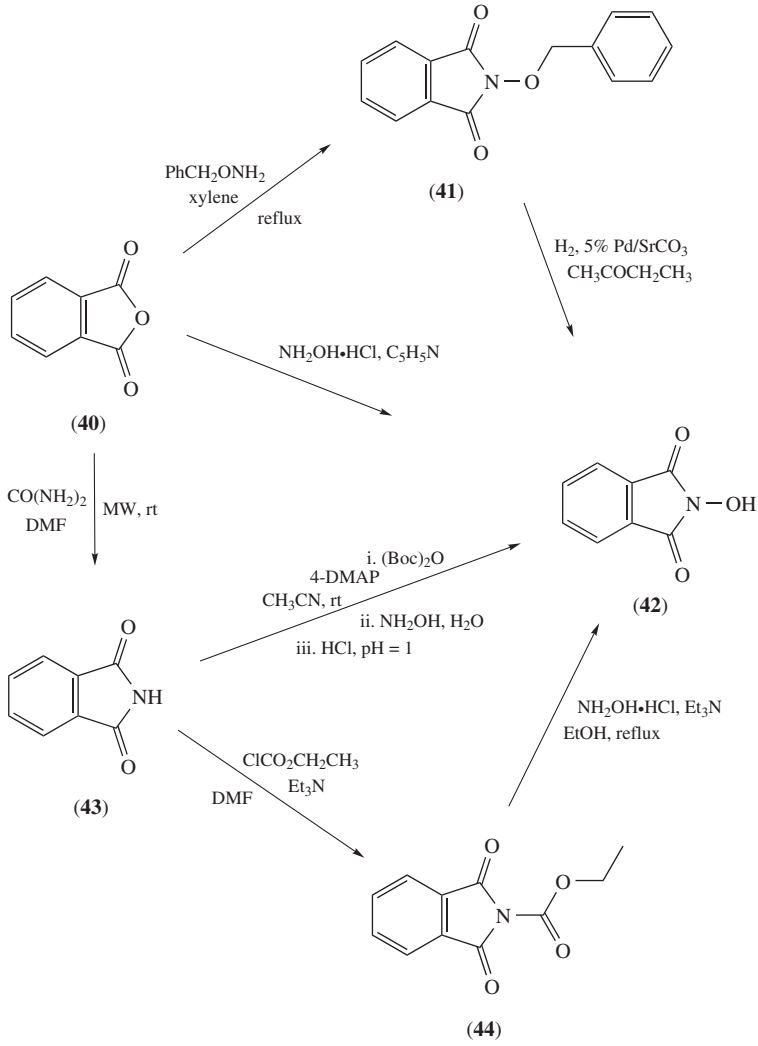


FIGURE 12. Structure of *N*-hydroxyphthalimide

that the pKa was off the range considered for oximes[126, 147]. A simultaneous report by Roderick and Brown concluded that both 'phthaloxime' isomers, including the yellow one, whose color is probably due to the presence of certain impurities, corresponded to the **42** structure[148].

Various methods to prepare **42** are given in Scheme 8. Ames and Grey adapted the method for preparing aliphatic cyclic imides to the synthesis of **42** (Scheme 8)[31]. First, phthalic anhydride (**40**) is converted to *N*-benzyloxyphthalimide (**41**) after reflux with *O*-benzyloxyamine in xylene[126]. Then, **41** is catalytically hydrogenated in the presence



SCHEME 8. Synthetic approaches for the synthesis of *N*-hydroxyphthalimide

of strontium carbonate over Pd, to afford **42** in 74% overall yield (Scheme 8)[126]. Later approaches have been designed to carry out the transformation of **40** to **42** by treatment with hydroxylamine hydrochloride[133, 149]. Sugamoto and coworkers recently reported a fast conversion using microwave irradiation[150]. Alternatively, **42** can also be efficiently synthesized from phthalimide (**43**). One of the first strategies consisted in the conversion of phthalimide or its potassium salt to *N*-(ethoxycarbonyl)phthalimide (**44**, the Nefkens reagent) by the action of ethyl chloroformate, followed by reflux with hydroxylamine hydrochloride (70% overall yield)[99, 127]. However, direct synthesis has also been reported by Einhorn and coworkers, through intermediate formation of *N*-(*tert*-butoxycarbonyl)phthalimide and subsequent reaction with aqueous hydroxylamine and acidification, in one-pot (92% yield)[90]. Alternatively, **43** can be slowly transformed into **42** with 350-nm UV irradiation in the presence of titanium dioxide[151]. Both pathways, starting from **41** or **43**, which is quantitatively obtained from the former after MW-assisted treatment with urea, lead to **42** in high yields[152].

The acidity of **42** reported by Ames and Grey in 50% aqueous methanol ($pK_a = 7.0$) was high enough to reconsider the initial assumption of the phthaloxime structure, since usually oximes show p*K*a in the range 10–12 (except for those bearing electron-withdrawing substituents)[3, 126, 147]. Later, Koppel and coworkers also investigated the acidity of **43** in H_2O, showing that it was slightly less acidic ($pK_a = 6.32 \pm 0.03$) than the parent HOSu (**31**, Section III.D.1)[24]. In DMSO, a more similar solvent to those routinely used in peptide synthesis, the difference between the dissociation constants was higher ($pK_a = 14.0 \pm 0.1$), as determined by potentiometric titration with Bu_4NOH in the solvent mixture benzene/isopropanol[24]. Compared to **42**, **43** was 2 p*K*a units more acidic in H_2O, confirming the impact of the *N*-hydroxylamine group in the acidity[24]. The ^1H- and ^{13}C-NMR analysis revealed that the *N*-hydroxyl hydrogen resonates at high frequencies close to those of the analogous group of HOSu (**31**, Section III.D.1)[100].

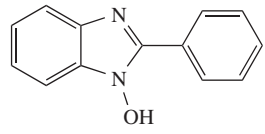
Ames and Grey also characterized **42** by means of IR spectroscopy, showing imide bands at 1745 and 1795 cm^{-1}, along with other signals (1721 and 1866 cm^{-1})[126]. Later, Wei and coworkers considered that bands appearing at 1780, 1720, 1375 and 1120 cm^{-1} were all related to the cyclic imide moiety[131]. The same authors also observed carbonyl and *N*-hydroxy signals at 1700 and 3120 cm^{-1} [131]. However, Krishnakumar and colleagues detected the *N*-hydroxy band at higher frequencies (3592 cm^{-1}), along with an additional intermolecular O–H bond (3442 cm^{-1})[128]. The ultraviolet spectrum of **42** resembles phthalimide (**43**), showing strong absorption at 220.5 nm ($\log \varepsilon = 4.48$) and at 298.0 nm ($\log \varepsilon = 3.20$)[126].

E. *N*-Hydroxy-2-phenylbenzimidazoles

1. HOBI, N-hydroxy-2-phenylbenzimidazole

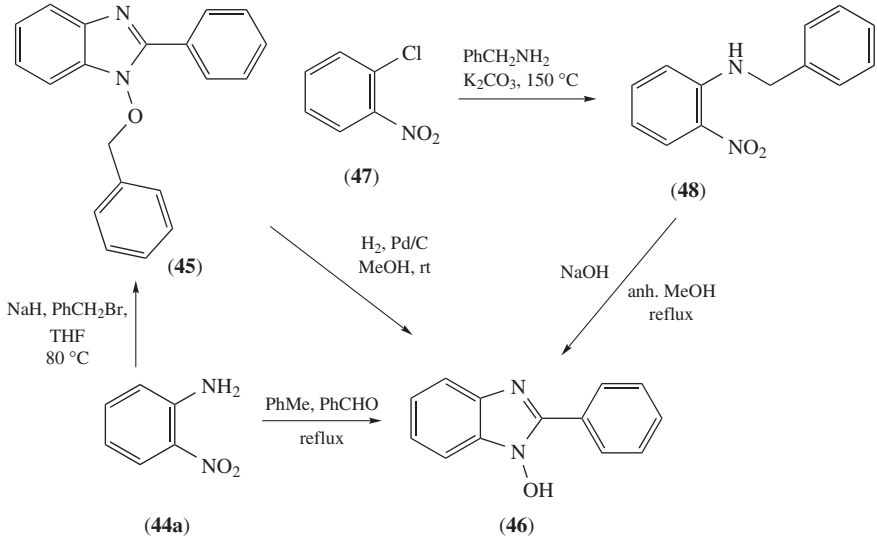
N-Hydroxy-2-phenylbenzimidazole (HOBI, **46**, Figure 13) is obtained as a white crystalline solid, with melting point 220 °C from ethanol[79, 153–155]. In contrast to benzotriazoles, which contain three consecutive nitrogen atoms in their heterocyclic core, **46** (alternatively abbreviated as HOPBI) displays carbon atoms between the two nitrogens, and therefore a safer decomposition profile is expected[79]. Benzimidazoles are included, on many occasions, in biologically active biomolecules[60, 156]. In particular, **46**, a photosensitive heterocyclic compound, serves as template for designing inhibitors of bacterial transcription factors[155, 157]. Its *N*-alkoxy derivatives show activity as central nervous system depressants in certain animals and also analgetics effects[158, 159].

The simplest way to **46** would consist in the oxidation of 2-phenylbenzimidazole. However, direct *N*-oxidations have not been reported for these aromatic systems and, consequently, the strategies designed to date have focused on indirect methods (Scheme 9).



(**46**)

FIGURE 13. Structure of *N*-hydroxy-2-phenylbenzimidazole



(**45**) (**47**) (**48**) (**44a**) (**46**)

SCHEME 9. Synthetic strategies for the synthesis of *N*-hydroxy-2-phenylbenzimidazole

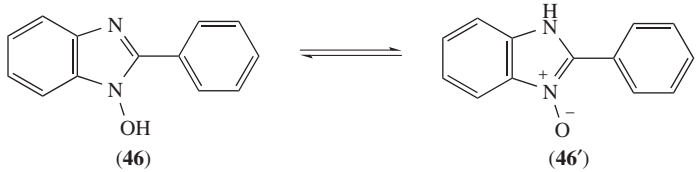
One method starts from *o*-nitroaniline (**44a**), which is converted into *N*-benzyloxy-2-phenylbenzimidazole (**45**) through a tandem cascade process, in which *N*-alkylation is followed by imidazole *N*-oxide formation and *in situ O*-alkylation, in the presence of a refluxing mixture of NaH and benzyl bromide (Scheme 9)[60]. A proposed mechanism is the generation of an α-amino carbanion, after the initial *N*-alkylation, with subsequent dehydration, prior to *N*-benzyloxy formation[61]. Surprisingly, benzimidazole *N*-oxide has never been found in the crude mixture, although the *N*-alkylated linear compound, coming from the first step of the reaction, is sometimes obtained as a byproduct[60]. Two distinct procedures have been developed for carrying out this one-pot preparation of **45**, as described by Gardiner and coworkers: in the first, the full amount of reagents are added almost simultaneously followed by reflux, whereas in the second, 1 equivalent is employed at the beginning, and the rest is poured over 12 hours[60, 158]. Gardiner and coworkers reported that the latter system was more efficient (79% yield), although some years later Kokare and colleagues reported a 97% yield of **45** with the former method[153, 154]. A careful evaluation of both procedures was recently performed by Albericio and coworkers, concluding that the former method leads to unreacted starting material, whereas slow addition of sodium hydride and benzyl bromide afforded 88% of **45**[79]. Subsequent Pd-catalyzed hydrogenation of **45** afforded **46** in an almost quantitatively manner[79, 153, 154].

An alternative strategy was designed by Stacy and coworkers from **44a**, which directly affords **46**, by treatment with benzaldehyde in anhydrous toluene, through intermediate formation of the *N*,*N*-benzylidene-*o*-nitroaniline Schiff base, in 86% yield, although prolonged reaction times (3 days) are necessary[155]. The *N*-alkylated byproduct from Gardiner's approach, *N*-benzyl-*o*-nitroaniline (**48**), might also be useful for the preparation of **46**, as outlined by Stacy and coworkers, by means of a base-catalyzed cyclization in the presence of sodium hydroxide in refluxing anhydrous methanol (71% yield) (Scheme 9)[155]. Nucleophilic attack of benzylamine onto *o*-chloronitrobenzene (**47**), in potassium carbonate-induced basic media and high temperature, renders **48**, in 80% yield, as reported by Stacy and coworkers, following the Gibson methodology[155, 160]. Bowser and coworkers recently envisioned an analogous synthesis of **46** based on *o*-fluoronitrobenzene, by treatment with benzylamine and sodium carbonate, followed by addition of sodium hydride, although no yields were reported[157].

IR and UV spectra of **46** revealed its similarity to 2-phenylbenzimidazole and 1-hydroxybenzimidazole[155]. The infrared spectra displayed *N*-hydroxyl and aromatic C=C bands at 3120 cm^{-1}, whereas ultraviolet spectra in EtOH showed a maximum at 298 nm ($\log \varepsilon = 4.33$)[155]. Regarding the ^{1}H-NMR spectra in DMSO-d_6 of **46**, they display the *N*-hydroxyl proton at high frequency at δ 12.22, indicating its high acidity[79, 153]. Finally, **46** can exist in two tautomeric forms, the *N*-hydroxy (**46**) and *N*-oxide (**46′**) species (Figure 14)[60, 155]. Initial studies on the parent *N*-hydroxybenzimidazole suggested the predominance of the *N*-oxide tautomer, due to the consistency of this structure with experimental results on the reactivity with various compounds[161]. A similar ratio of the *N*-hydroxy (**46**) and *N*-oxide (**46′**) forms could be envisaged in the case of **46**. Nonetheless, NMR spectra of **46** in TFA were consistent with the *N*-hydroxy species (**46**), as the more stable, preferred tautomer[155]. The tautomeric equilibrium of **46** has also been shown to be solvent-dependent[60].

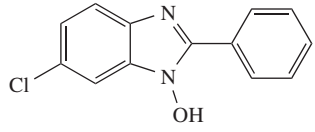
2. 6-Cl-HOBI, 6-chloro-N-hydroxy-2-phenylbenzimidazole

6-Chloro-*N*-hydroxy-2-phenylbenzimidazole (**53**, Figure 15) is an off-white solid, melting at 262–264 °C[79]. Surprisingly, a considerably lower melting point is reported by other



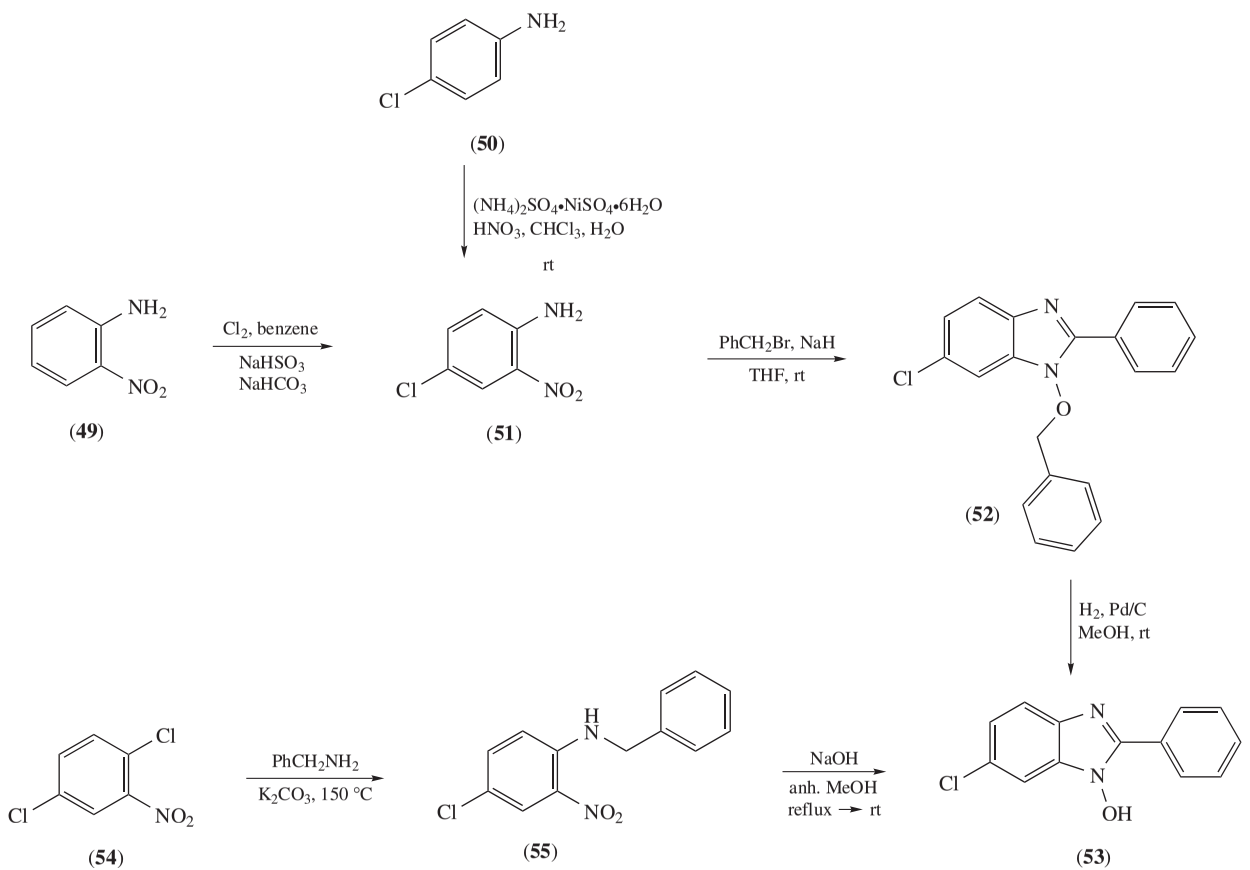
(**46**) (**46′**)

FIGURE 14. Tautomeric forms of *N*-hydroxy-2-phenylbenzimidazole



(**53**)

FIGURE 15. Structure of 6-chloro-*N*-hydroxy-2-phenylbenzimidazole



SCHEME 10. Synthetic approaches for the synthesis of 6-chloro-*N*-hydroxy-2-phenylbenzimidazole

authors (241 °C)[158]. The imidazole ring of **53** does not contain consecutive nitrogens, contrary to the triazole ring of benzotriazoles, and thus safer decomposition behavior is predicted. In general, benzimidazoles units are present in a wide range of pharmacologically active compounds[156]. *N*-Alkoxy derivatives of **53**, alternatively abbreviated as 6-Cl-HOPBI, induce a depressant effect on the central nervous system[129].

Direct oxidation of benzimidazoles to *N*-hydroxybenzimidazoles has never been achieved. As a result, synthetic approaches to **53** have been directed toward cyclization methods generating the *N*-hydroxy moiety (Scheme 10). **53** can be obtained from 4-chloro-2-nitroaniline (**51**), as described by Gardiner and coworkers, through a one-pot tandem process involving *N*-alkylation, ring formation and subsequent *O*-alkylation, in analogy to the synthesis of HOBI (**47**), followed by hydrogenation (Scheme 10)[60]. From the two described procedures for conducting this transformation, Gardiner recommended the one in which the reagents, sodium hydride and benzyl bromide, are added in small portions over many hours[60]. However, although high conversion to **52** was achieved in 81% yield with almost 50% impurities[60], El-Faham and Albericio used the same method successfully, obtaining **53** in 66% yield[79, 162]. The same authors reported the hydrogenation of this intermediate, catalyzed by Pd/C in methanol at room temperature, to give **53** in 73% yield (Scheme 10)[79]. The starting material, 4-chloro-2-nitroaniline (**51**), can be obtained either from **49** or **50**. The chlorination of **49** might be performed in the presence of chlorine and sodium bicarbonate (Scheme 10), although no yields were detailed by Chapman and coworkers[163]. The approach based on **50** was reported by Tasneem and coworkers, and efficiently yields **51** by nitration with ammonium nickel sulfate and nitric acid (92% yield)[164].

Similarly to the synthesis of **47** (Section III.E.1), an alternative strategy has been designed, consisting in the base-catalyzed cyclization of **55** by treatment with NaOH in anhydrous MeOH (Scheme 10)[158]. The conversion of **54** to **55** can be performed using the Gibson methodology, in the presence of benzylamine and potassium carbonate, above 100 °C (yields not described)[160].

^{1}H NMR in DMSO-d_6 data for **53** showed the presence of the highly acidic proton at δ 12.19 and aromatic protons[79]. Like **46** (Section III.E.1), two tautomeric species are found for **53**: the *N*-hydroxy (**53**) and *N*-oxide (**53′**) forms (Figure 16)[155]. Kew and Nelson[161] studied the composition of the parent *N*-hydroxybenzimidazole, concluding that the *N*-oxide tautomer might be favored, due to higher consistency with experimental results on its reactivity with various compounds. Thus, similar relative percentages of *N*-hydroxy (**53**) and *N*-oxide (**53′**) species could be envisioned for 6-Cl-HOBI (**53**). The tautomeric equilibrium of 6-Cl-HOBI is known to be solvent-dependent[60].

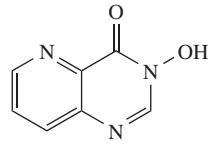
(**53′**) (**53**)

FIGURE 16. Tautomeric forms of 6-chloro-*N*-hydroxy-2-phenylbenzimidazole

F. HODhad, 3-Hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene

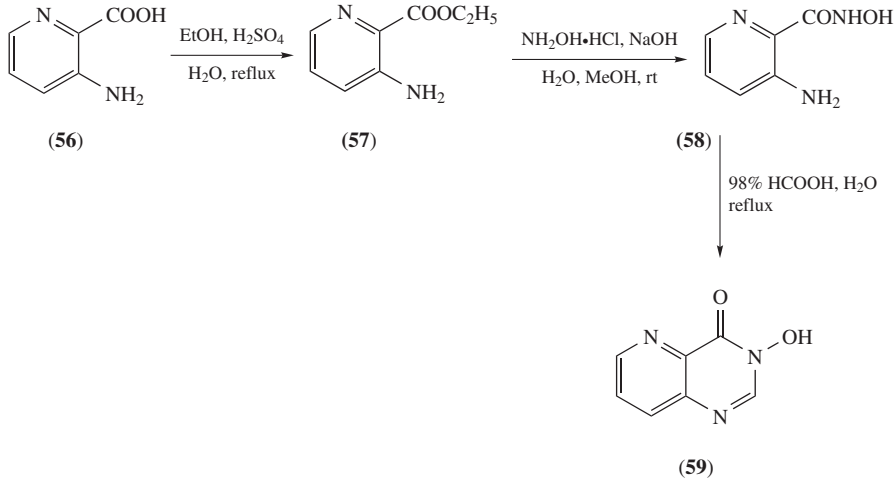
3-Hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene (HODhad, **59**, Figure 17) is a yellow solid with melting point 318.5–320 °C from EtOH[165]. Its synthesis is essentially identical to that of the parent triazene HODhat (**158**, Section III.K) described by Carpino and coworkers, except for the last cyclization step, which was performed by refluxing 3-amino-2-picolinehydroxamic acid (**58**) with 98% formic acid, in 55% yield (Scheme 11)[165]. The hydroxamic acid (**58**) can be obtained quantitatively from ethyl 3-aminopicolinate (**57**), after treatment with hydroxylamine hydrochloride and NaOH in a H_2O–EtOH mixture (Scheme 11), during 2 days, improving the method designed by Harrison and coworkers[165, 166]. Carpino and coworkers also improved the esterification of **56** to **57**, by using an extensive reflux of the acid in absolute EtOH and concentrated H_2SO_4 (68% yield, Scheme 11)[165, 167, 168]. **56** was obtained from available precursors as described for HODhat (**158**, Section III.K)[165, 23, 169–174].

^{1}H-NMR data for **59** showed the hydrogens of the pyridine and diazine rings in the aromatic region[165]. The infrared spectra of **60** in KBr displayed a broad *N*-hydroxyl band at higher frequency than the corresponding signal of **158** (Section III.K): 2625 cm^{-1}, and another band corresponding to the hydroxamic acid amide moiety at 1683 cm^{-1} [165]. Other bands were observed at 1600, 1446, 1410, 1359, 1223, 990, 902 and 791 cm^{-1} [165].



(**59**)

FIGURE 17. Structure of 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene



(**56**) (**57**) (**58**) (**59**)

SCHEME 11. Synthetic approaches for the synthesis of 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,3-diazene

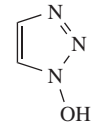
G. Triazoles

1. 1-Hydroxy-1,2,3-triazole

1-Hydroxy-1,2,3-triazole (**64**, Figure 18), initially known also as azimidole, is a solid melting at 92–93 °C, which represents the template of a family of additives in peptide synthesis, including many 5-substituted analogues[175–177]. The synthesis of **64** raised the interest of organic chemists more than a century ago, when Wolff reported its isolation from hydroxylamine and diazoketone, followed by partial reduction[177]. Since then, improved routes have been designed, which can be classified as these that obtain the triazole core by 1,3-cycloaddition of modified acetylenes and azides, followed by oxidation (Scheme 12), and those that directly obtain the hydroxytriazole core by a single oxidative cyclization step (Scheme 12).

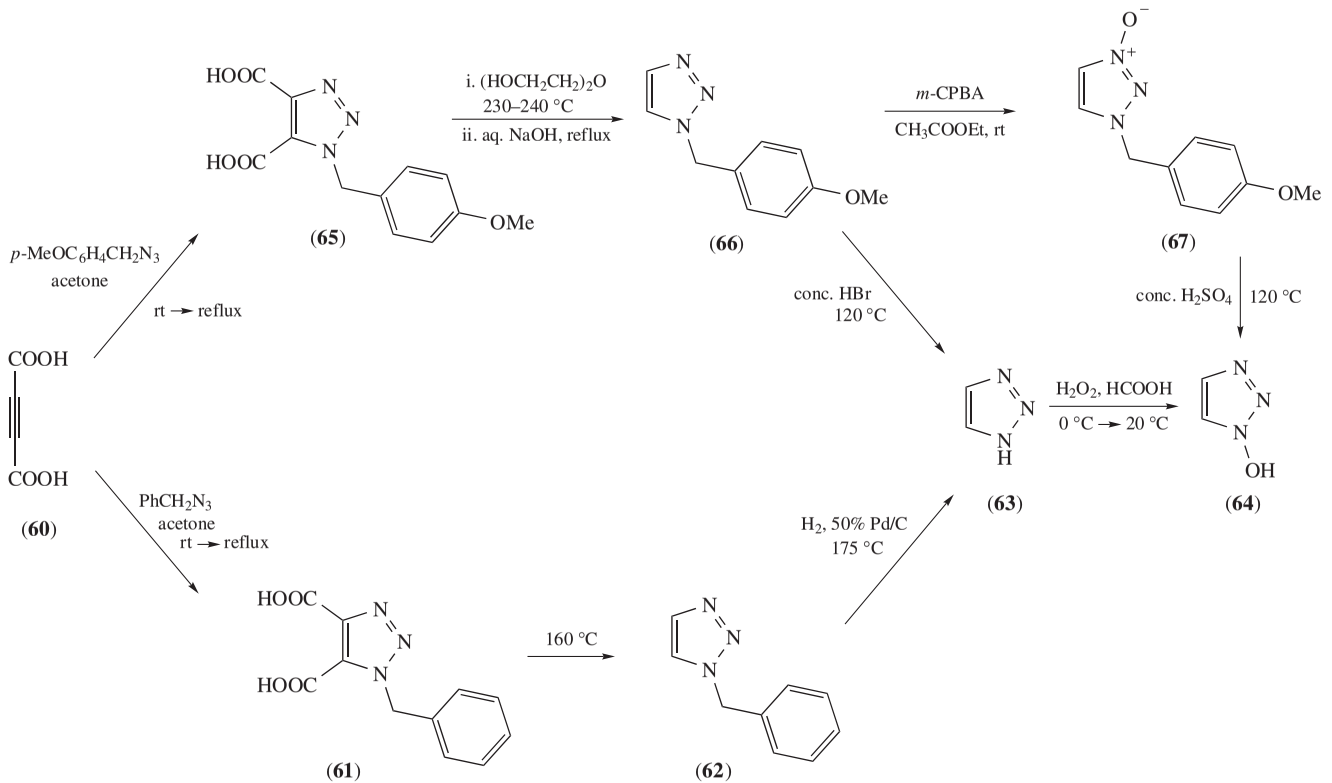
One of the approaches corresponding to the former class was developed by Wiley and coworkers, and affords the intermediate 1,2,3-triazole (**63**) via 1-benzyl-protection (Scheme 12)[178]. In the first step, acetylene dicarboxylic acid (**60**) is refluxed with benzyl azide to form a substituted triazole **61**, conversion that implies a lower risk than cyclization of unmodified acetylene and azide[178–180]. The route from **61** to **62** takes place preferably by decarboxylation at high temperature, followed by Pd-mediated debenzylation of **62** in 3–4 days (Scheme 12)[178]. The key step is the oxidation of **63**, which is most efficiently performed with stepwise addition of oxidant, although this optimization of yield (65%) is accompanied by a significant increase in the reaction time (up to 30 days)[181]. Many oxidants have been tested, such as 3-chloroperbenzoic acid or sodium perborate, but the reaction is best conducted in the presence of H_2O_2[175]. This approach has been improved by using 4-methoxybenzyl azide in the cycloaddition step, forming **65**, which leads to its decarboxylated derivative **66** (Scheme 12)[176, 182]. Subsequent debenzylation of **66** takes place with concentrated hydrobromic acid, in considerably shorter time than the above-mentioned synthesis. It also results in enhanced overall yield of **65** from **61** (30% vs. 28%)[176]. Alternatively, **66** can be transformed into its 1-oxide derivative (**67**) which, after treatment with concentrated sulfuric acid, also affords **64** in 23% overall yield (Scheme 12), although the long-time oxidation of **63** is avoided[176].

The above-mentioned strategies are based on the cycloaddition of acetylenes with azides; both, although substituted, present a high explosive potential[178]. Furthermore, the oxidation steps, even in the 4-methoxybenzyl modification, are only completed after a few days, which delays affording of the desired **64**. All these inconveniences can be avoided with the safer and quicker route starting from glyoxal (**65a**, Scheme 13)[176, 181, 183]. The success of this method partially lies on the optimally close to natural pH of the reaction medium. In the first step, **65a** is transformed into glyoxal *O*-benzyloxime (**66a**) by addition of benzyloxyamine hydrochloride[181, 184]. This intermediate then reacts with hydrazine hydrate to form *in situ* the derived hydrazone, which undergoes oxidative cyclization (presumably by a one-electron mechanism) with copper sulfate to yield **67a**[185, 186]. Final hydrogenolysis catalyzed by Pd in cold methanol affords the target **64** in a higher efficiency than the above-mentioned approaches (50% overall yield) (Scheme 13)[181]. Similar

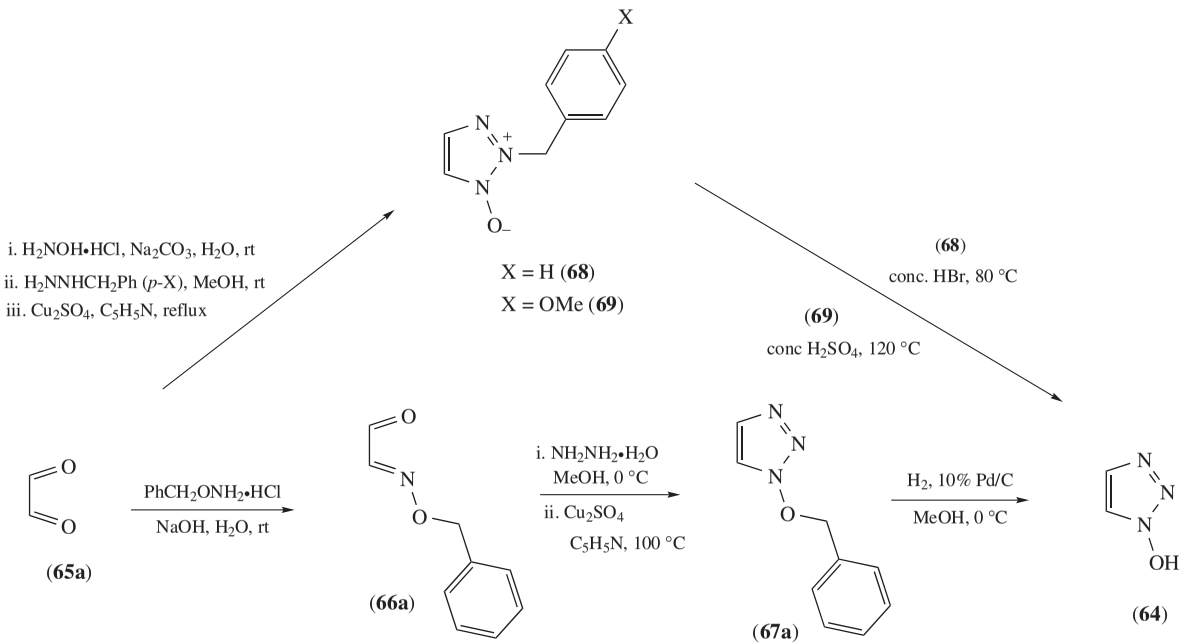


(**64**)

FIGURE 18. Structure of 1-hydroxy-1,2,3-triazole



SCHEME 12. Synthetic approaches for the synthesis of 1-hydroxy-1,2,3-triazole, based on 1,3-cycloadditions followed by oxidation



SCHEME 13. Synthetic strategies for the synthesis of 1-hydroxy-1,2,3-triazole, based on oxidative cyclizations

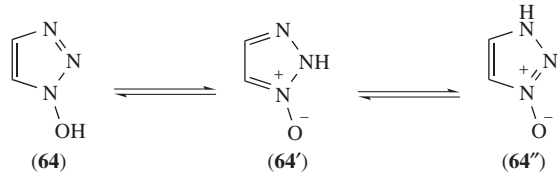
strategies using benzylhydrazine or 4-methoxybenzylhydrazine lead to 2-benzyl-1,2,3-triazole-1-oxide (**68**) or 2-(4-methoxybenzyl)-1,2,3-triazole-1-oxide (**69**) as intermediates, followed by debenzylation with concentrated hydrobromic or sulfuric acid (iodotrimethylsilane might form iodine-based byproducts)[176, 181, 183, 187]. However, yields are lower than the 1-benzyloxy approach (26% and 27% vs. 50%).

The C4 and C5 hydrogens of the triazole ring of **64** are observed at similar frequencies, according to ^{1}H-NMR data of **64** in CD_3COCD_3[175]. The dissociation constant of **64** has not been reported, although **64** is known to show a strong acidic character, similar to the parent HOBt (**96**, Section III.H.1)[177]. In comparison with the latter, **64** permits easier tuning of acidity on introduction of substituents in the ring, due to its proximity to the *N*-OH group[178, 179]. The known explosive behavior of *N*-hydroxybenzotriazoles, *N*-hydroxytetrazoles and *N*-alkylimidazoles and pyrazoles could lead to the assumption that 1-hydroxy-1,2,3-triazoles share a similar decompostion behavior[2, 181, 188–191]. Nonetheless, **64** is regarded as non-sensitive to drop-weight impact of a hammer-head from 50 cm distance and therefore no safety precautions need to be taken in handling it[188].

Three main tautomers are considered for 1-hydroxy-1,2,3-triazole (**64**, **64′**, **64″**), excluding the possible non-aromatic species, which are not observed by ^{1}H-NMR spectra (Figure 19)[192]. The composition of the tautomeric equilibrium was studied by Guimon and coworkers using UV (HeI) photoelectron spectroscopy and semiempiral quantum methods[192]. The composition of **64** in the gas phase was based on the similarity of spectra and ionization potentials with the *O*-methyl ester. This result was supported by the MNDO (modified neglect of diatomic overlap) semiempirical calculations, which found that **64** is the most stable tautomer in a broad range of temperatures. This method, using the Koopmans approximation, was generally in agreement with experimental values, except for the potential of the non-bonding nitrogen orbitals[193, 194]. Anders and coworkers extended the semiempirical study of this triazole system to the AM1 (Austin model 1) and PM3 (parametric method 3) calculations[195]. Whereas the former method agrees with the higher stability of **64** predicted by MNDO, the latter obtains similar energies of tautomers **64** and **64″**. However, the reliability of the PM3 method for these *N*-hydroxy/*N*-oxide tautomeric equilibria has been questioned[196]. The *N*-oxide form **64′**, which is slightly non-planar as calculated by *ab initio* methods (whereas **64** and **64″** are planar), is always calculated to be the least stable form. From *ab initio* calculations the bond lengths of 1-hydroxy-1,2,3-triazole are almost identical to those of 1,2,3-triazole and slightly longer than certain N−N bonds of HOBt (**96**, Section III.H.1)[195].

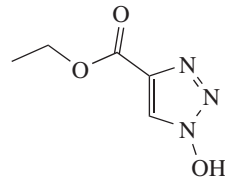
2. HOCt, ethyl 1-hydroxy-1,2,3-triazole-4-carboxylate

Ethyl 1-hydroxy-1,2,3-triazole-4-carboxylate (**75**, Figure 20) is one of the few 4-substituted derivatives of **64**, proposed as additive for peptide synthesis and also serves as starting material for building β-lactamase or tuberculosis inhibitors[197–199]. **75**, obtained as a colorless crystalline solid melting at 110–112 °C, is stable in air at room temperature



(**64**) (**64′**) (**64″**)

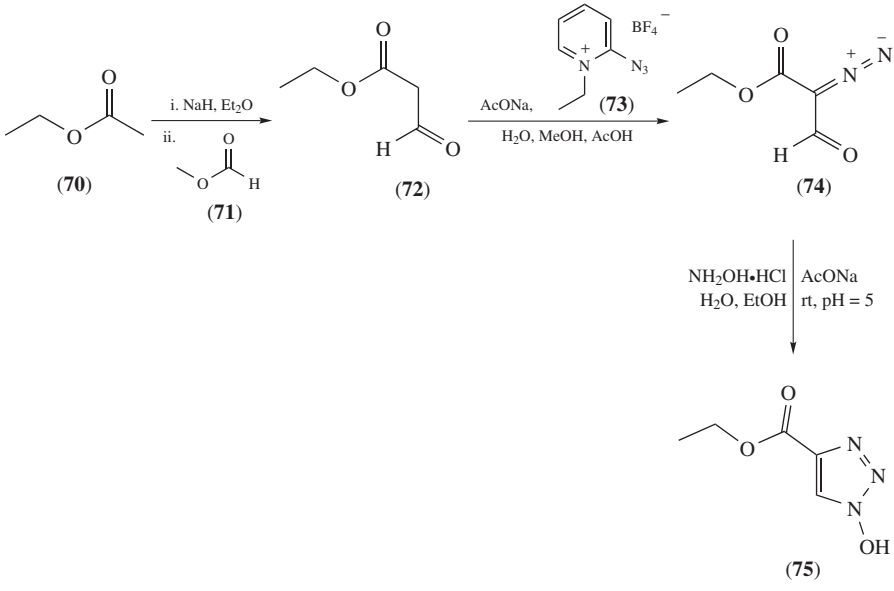
FIGURE 19. Tautomeric forms of 1-hydroxy-1,2,3-triazole



(**75**)

FIGURE 20. Structure of ethyl 1-hydroxy-1,2,3-triazole-4-carboxylate

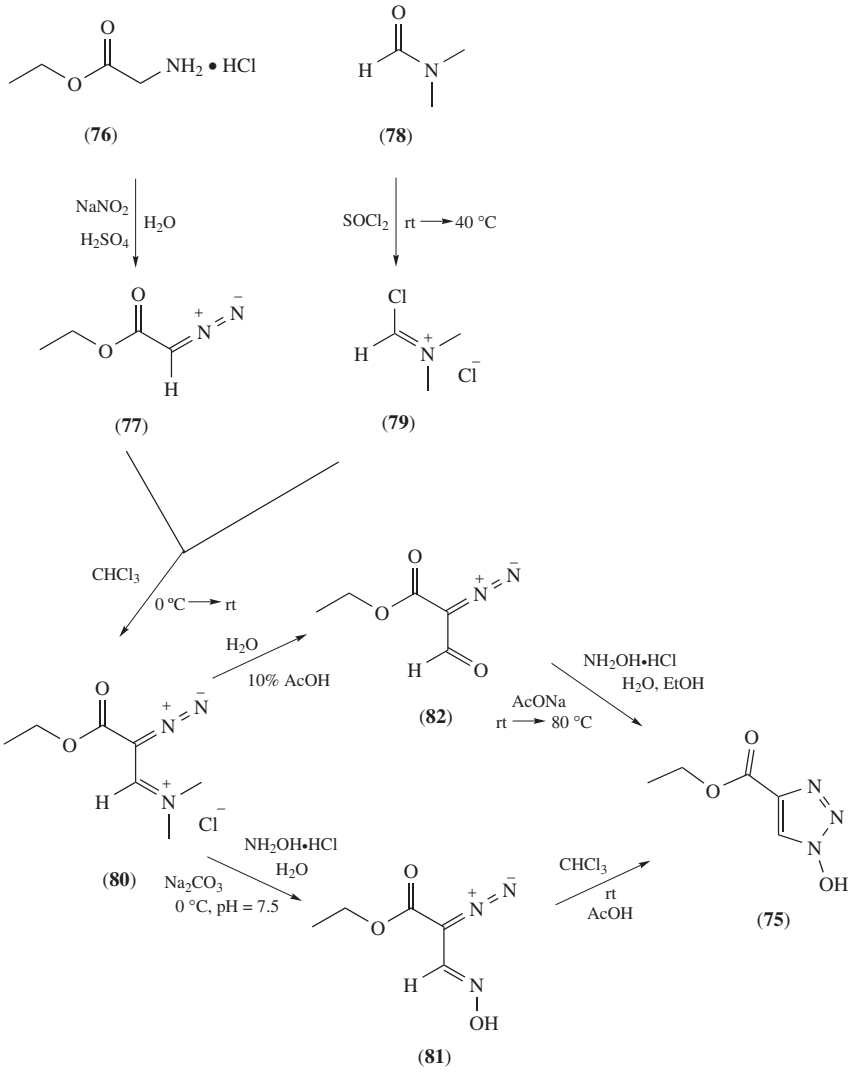
for years and is highly soluble in H_2O and many organic solvents, such as DMF, DCM or EtOH[198]. Unlike most 1,2,3-triazole derivatives, its synthesis does not involve heterocyclic ring formation by means of 1,3-cycloaddition of azides with acetylenes, but through condensation of 2-diazo-1,3-dicarbonyl compounds with hydroxylamine. An example of the latter approach is the route designed by Sezer and coworkers, affording **75** in 3 steps (Scheme 14)[200, 201]. Claisen condensation of ethyl acetate (**70**) with methyl formate (**71**) yielded ethyl 3-oxopropanoate (**72**), which was diazotized in the presence of 2-azido-1-ethylpyridinium tetrafluoroborate (**73**)[200, 201]. Apart from ethyl 2-diazo-3-oxopropanoate (**74**), the deformylated byproduct was also generated in considerable amounts, although it didn't interfere in the last cyclization step with hydroxylamine hydrochloride, performed at moderate acidic pH during 2 days[200, 201]. This methodology, however, rendered the target **75** in a poor 6% overall yield (Scheme 14) and a melting point (161–162 °C) differs significantly from the one reported by other authors[198, 201].



(**70**) (**71**) (**72**) (**73**) (**74**) (**75**)

SCHEME 14. Synthetic approach for the synthesis of ethyl 1-hydroxy-1,2,3-triazole-4-carboxylate

Jiang and coworkers attempted an alternative strategy from ethyl 2-oxo-3-oximinopropanoate, but initial transformation of ethyl 2-oxopropanoate to render this intermediate failed[198]. Re-evaluation of the synthetic design led to ethyl 2-diazo-3-dimethyliminium propanoate chloride (**80**) as key precursor of **75**, which was obtained by formylation of ethyl 2-diazoacetate (**77**) with dimethyl formamidinium chloride (**79**), using the Stojanovic and Arnold method (Scheme 15)[202]. Slow addition of the former reagent is advised, in order to modulate heat and gas release from the reaction vessel[198]. The route to **79** starts from ethyl glycinate hydrochloride (**76**),



SCHEME 15. Improved synthesis of ethyl 1-hydroxy-1,2,3-triazole-4-carboxylate

which is quantitatively diazotized in the presence of sodium nitrite[198, 203]. Replacement of H_2SO_4 with HCl did not improve the yield[198, 204]. The Vilsmeier reagent **79** is also used for the synthesis of nitriles, acyl and sulfonyl chlorides and is obtained by chlorination of *N*,*N*-dimethylformamide (**78**) with thionyl or oxalyl chloride[198, 205–208]. This transformation can be driven to completion and, in the absence of byproducts, by heating the mixture at 40 °C[198]. The product **80** obtained after formylation is highly unstable, and hydrolysis with 10% HOAc leads to ethyl 2-diazo-3-oxopropanoate (**82**), as reported by Stojanovic and Arnold[202]. Conversion of the latter to **75** takes place with hydroxylamine at 80 °C. Bennett and coworkers also reported the extension of the Stojanovic synthesis of **82** to **75**, although no reaction conditions were detailed[197]. The overall yield of **75** with this approach, however, was not enhanced (5%) with respect to the previous Sezer strategy. Alternatively, **80** could be transformed, dissolved in the minimum amount of H_2O, to **81** by treatment with hydroxylamine and sodium carbonate at a controlled pH = 7.5 (Scheme 15)[198]. This intermediate was quickly used, without drying, in the final cyclization step in chloroform, with a drop of acetic acid as catalyst[198]. After 2 days at room temperature and recrystallization from ethyl acetate, **75** was obtained in 37% overall yield[198]. Use of anhydrous ethanol in the synthesis of **81**, followed by reflux in benzene, resulted in enhanced yield (44%), although this approach also increases the risk of explosion of the diazo compound, due to evaporation of ethanol to almost dryness conditions and final treatment at high temperature[198].

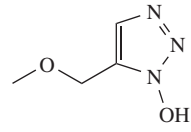
The *N*-hydroxylamine moiety of **75** shows a strong dissociation constant ($pKa = 2.16$), higher than the most acidic 1-hydroxybenzotriazole derivatives[198, 209, 210]. In agreement with these acidity measurements, the *N*-hydroxylamine proton resonates at high frequencies (12.5 ppm), according to ^{1}H-NMR spectroscopy[198]. IR spectra of **75** indicated the presence of a strong broad band at 3200–2000 cm^{-1}, corresponding to the *N*-hydroxyl group, and a characteristic ester band at 1730 cm^{-1}, apart from additional signals at 1447 and 1406[198, 201].

One of the main advantages of **75** for its use in peptide synthesis is that is doesn't present absorption at 302 nm ($\lambda_{max} = 260$ nm, log $\varepsilon = 3.63$), which enables monitoring of the coupling process, prior to Fmoc removal[198]. EI-MS analysis has also been described[201]. **75** contains the N-N-N moiety, but although its decomposition profile has not been reported when drop-hammer assays were performed on the 1-hydroxy-1,2,3-triazole (**64**, Section III.G.1) and some 5-substituted derivatives (Section III.G)[188]. Therefore, a similar safety assessment of its parent triazole analogues is envisaged for **75**.

3. 1-Hydroxy-5-(methoxymethyl)-1,2,3-triazole

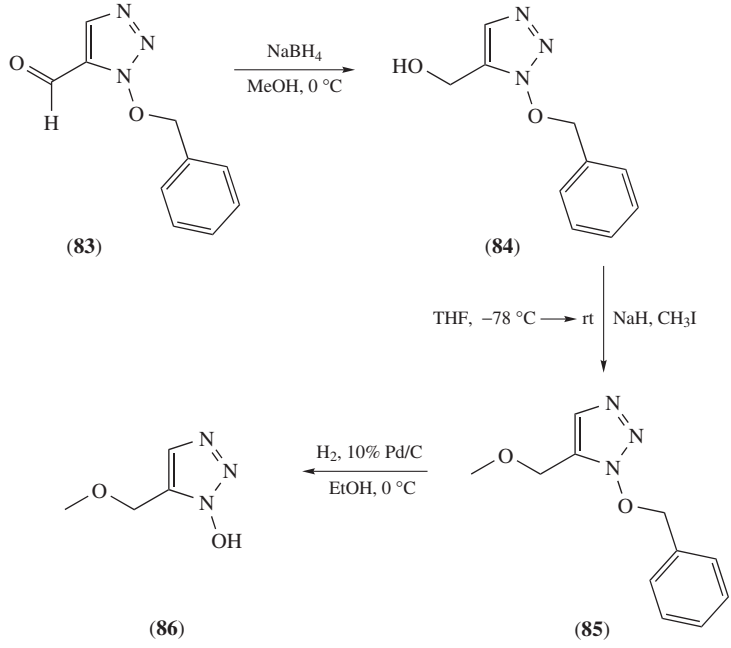
1-Hydroxy-5-(methoxymethyl)-1,2,3-triazole (**86**, Figure 21) was described, along with its 5-acetyl analogue, by Spetzler and coworkers as a solid, melting at 108–110 °C[188]. The synthetic strategy developed by these authors started from 1-benzyloxy-5-formyl-1,2,3-triazole (**83**), which was efficiently converted into the target **86** in 3 steps with high yield (82%, Scheme 16)[188]. In the first stage, 1-benzyloxy-5-(hydroxymethyl)-1,2,3-triazole (**84**) is obtained by reduction of the formyl moiety at C-5 of **83** with $NaBH_4$, and is then methylated to afford the 5-methoxymethyl derivative (**85**). Subsequent selective removal of the benzyl protecting group by Pd-mediated hydrogenolysis at low temperature yields the desired **86** (Scheme 16)[181, 188].

The starting material (**83**) for the above-mentioned strategy can be readily obtained from simpler compounds, as reported by Uhlmann and coworkers (Scheme 17)[181]. The C-5 formyl side chain is introduced into the triazole ring of 1-benzyloxy-1,2,3-triazole (**88**) by means of selective lithiation upon treatment with *n*-butyllithium at −78 °C, followed by rapid quenching with an excess of DMF as electrophile (87% yield)[181, 211].



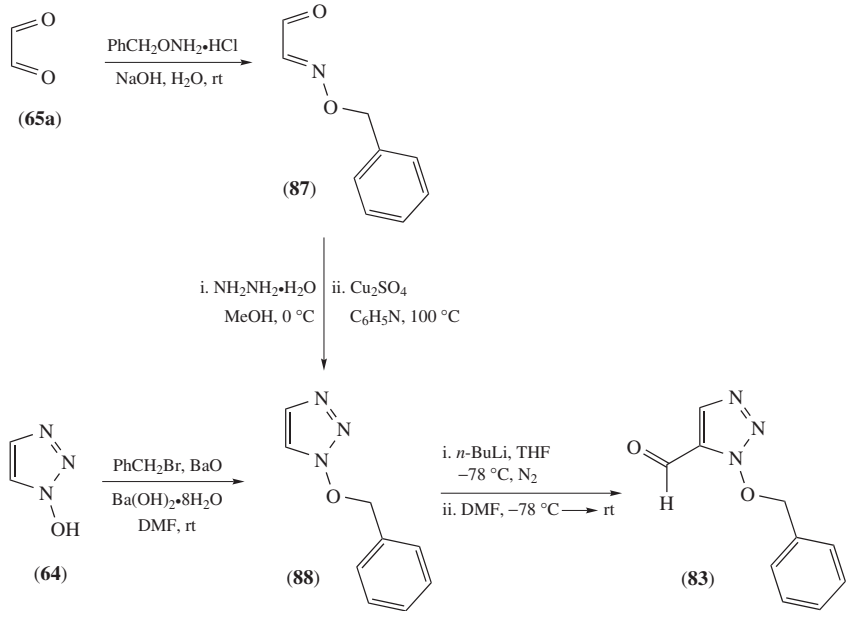
(**86**)

FIGURE 21. Structure of 1-hydroxy-5-(methoxymethyl)-1,2,3-triazole



SCHEME 16. Synthetic strategy for the synthesis of 1-hydroxy-5-(methoxymethyl)-1,2,3-triazole

The *N*-benzyloxy group plays a key role in this directed *o*-metalation (DoM), since it is known to be strongly *o*-promoting, as previously observed in pyrazoles[211]. **88** can be obtained by two distinct methods. The first method, with 1-hydroxy-1,2,3-triazole (**64**, Section III.G.1), is *O*-protected under mild conditions with benzyl bromide in the presence of barium oxide and barium hydroxide octahydrate, conditions that minimize (<5%) unwanted side alkylation at *N*-3 (87% yield, Scheme 17)[176, 212]. The second method, and a more direct route, designed by Uhlmann and coworkers, successfully accomplishes the synthesis of 1-benzyloxy-1,2,3-triazole (**88**) from glyoxal (**65a**), after reaction with benzyloxyamine hydrochloride and subsequent oxidative cyclization of 2-hydrazonoglyoxal *O*-benzyloxime, formed *in situ* by the addition of hydrazine hydrate to glyoxal *O*-benzyloxime (**87**) (52–63% overall yield from **65a**, Scheme 17)[181, 184–186]. The latter method is preferred over the 1-hydroxy-1,2,3-triazole (**64**, Section III.G.1) protection approach, which is considerably more time-consuming, and moreover, its more convenient synthesis partially contains the described glyoxal **65** route (see Section III.G.1)[181].



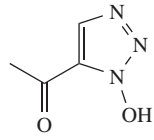
SCHEME 17. Synthetic approaches for preparation of **83**

86 presents good solubility in H_2O, in contrast to many benzotriazoles[188]. The ^{1}H-NMR spectra in D_2O clearly showed the presence of the methoxymethyl substituent at C-5 position and of H-4[188]. Bearing in mind the widely reported explosive character of *N*-hydroxybenzotriazoles, *N*-hydroxytetrazoles and *N*-alkylimidazoles and pyrazoles, a similar behavior would be expected for *N*-hydroxytriazoles due to its nitrogen-rich core[2, 181, 188, 190, 191]. Surprisingly, when subjected to drop-hammer tests, no incidents were observed for 1-hydroxy-1,2,3-triazole and some 5-substituted derivatives[188]. Therefore, a similar behavior would be envisaged in the case of **86**, based on structural similarity, although no experimental confirmation is reported.

4. 5-Acetyl-1-hydroxy-1,2,3-triazole

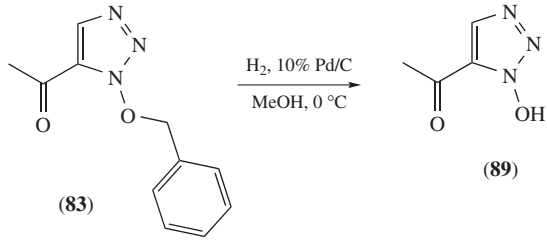
5-Acetyl-1-hydroxy-1,2,3-triazole (**89**, Figure 22) has been reported, along with other 5-substituted analogues, as a peptide additive by Spetzler and coworkers[188]. Decomposition occurs when heating **89** close to its melting point (143–145 °C), one of the highest for the triazole derivatives discussed in this section[188]. **89** can be obtained from structurally simple compounds by two distinct routes to afford **83**, as described in Scheme 18. Final hydrogenolytic debenzylation of **83** at low temperature affords the desired **89** in 93% yield[181].

After analysis by ^{1}H-NMR spectra in CD_3OD showed the presence of the acetyl moiety, the presence of H-4 was unequivocally confirmed[188]. The presence of three vicinal nitrogens in the heteroaromatic core of *N*-hydroxy-1,2,3-triazoles certainly could lead to the assumption of a similar explosive behavior to that observed for the parent *N*-hydroxybenzotriazoles, *N*-hydroxytetrazoles and *N*-alkylimidazoles and pyrazoles[2, 181, 188, 190, 191].



(**89**)

FIGURE 22. Structure of 5-acetyl-1-hydroxy-1,2,3-triazole



(**83**) (**89**)

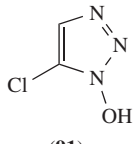
SCHEME 18. Synthetic strategy for the synthesis of 5-acetyl-1-hydroxy-1,2,3-triazole

5. 5-Chloro-1-hydroxy-1,2,3-triazole

5-Chloro-1-hydroxy-1,2,3-triazole (**91**, Figure 23) was described separately by Uhlmann and Begtrup, together with many 5-substituted triazole derivatives, as a solid presenting decomposition, after melting at 128 °C[176, 181]. Two alternative routes have been designed for the synthesis of **91** based on the use of **88** (Uhlmann and coworkers)[181] or **92** (Begtrup and coworkers)[176] (Scheme 19). Regardless of the pathway chosen, **91** is obtained in fewer steps than its analogues (**86** and **89**, see Sections III.G.3 and III.G.4)[188].

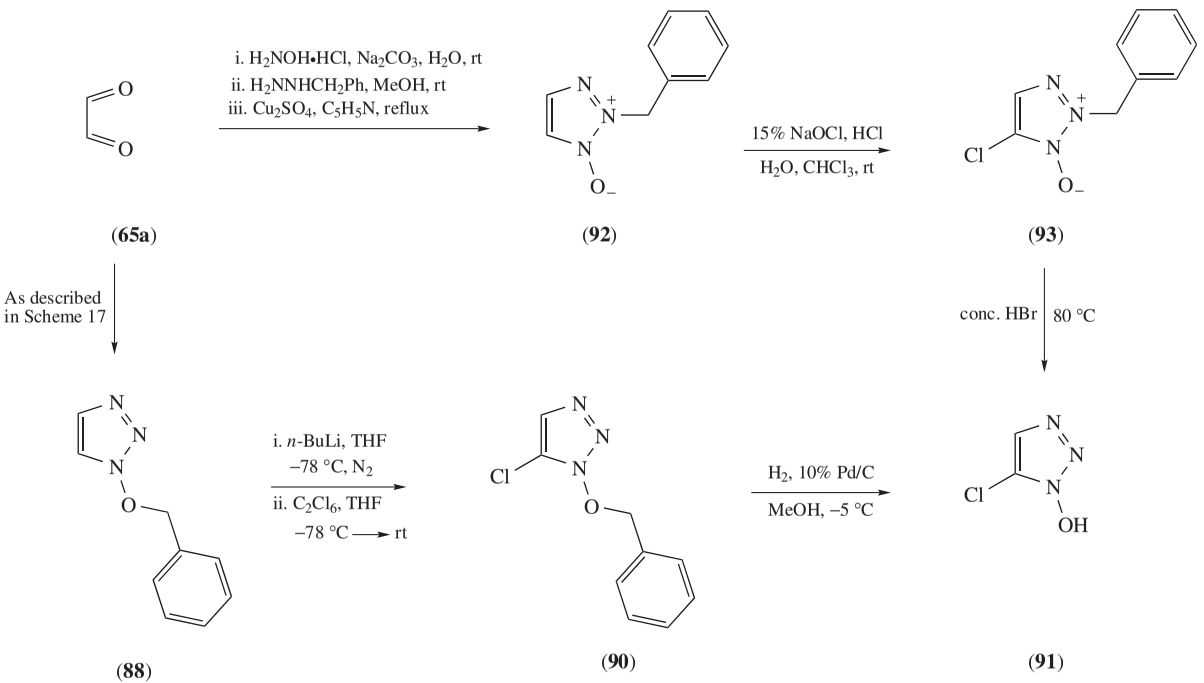
With regard to the synthesis of **88**, as mentioned for the synthesis of **83** (Section III.G.3, Scheme 17), the synthesis represents a more efficient and convenient approach, being achieved in fewer steps than the one starting from unsubstituted **64**[181]. Regioselective directed *o*-metalation (DoM) of **88** is accomplished with *n*-butyllithium at −78 °C, and upon quenching with hexachloroethane as electrophile **90** is isolated in 88% yield[181]. Subsequent benzyl removal with Pd catalysis, carried out at −5 °C in order to avoid detrimental dechlorination, affords the desired **91** in a quantitative manner (Scheme 19).

Alternative synthesis of **65a** also starts with **87**, which is converted in a one-pot fashion to 2-benzyl-1,2,3-triazole-1-oxide (**92**) via oxidative cyclization of the *in situ* generated α-oximinobenzylhydrazone, in a similar manner to the above-mentioned opposite strategy, but in lower yield (27%)[183]. Neutral conditions were found to be critical



(**91**)

FIGURE 23. Structure of 5-chloro-1-hydroxy-1,2,3-triazole



SCHEME 19. Synthetic strategies for the synthesis of 5-chloro-1-hydroxy-1,2,3-triazole

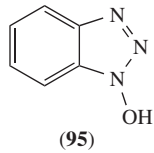
for the success of this method, since acidic or basic conditions led to side reactions. **92** was then selectively chlorinated at C-5 (even at 60 °C) by means of aqueous hypochlorite and hydrochloric acid at room temperature to render the 5-chloro derivative (**93**)[183]. Finally, debenzylation takes place with concentrated hydrobromic acid in 78% yield, affording **91** (Scheme 19)[176]. In comparison to the previously mentioned route, the target compound is obtained in considerably lower overall yield (15% vs. 46%). Moreover, the 1-(benzyloxy) methodology enables parallel synthesis of a wide variety of 5-substituted derivatives.

^{1}H-NMR spectra of **91** in $CDCl_3$ showed the proton of the hydroxyl group at δ 11 ppm, which indicates a strong acidic character[176]. Considering the presence of up to 3 vicinal nitrogens in the triazole ring, a similar decomposition behavior to *N*-hydroxybenzotriazoles, *N*-hydroxytetrazoles and *N*-alkylimidazoles and pyrazoles, which are known for its explosive nature, could be estimated[2, 181, 188, 190, 191]. However, when **91** was subjected to the drop-weight impact of a hammer-head from 50 cm distance, an explosive event did not occur, thereby indicating that this compound can be handled safely.

H. Benzotriazoles

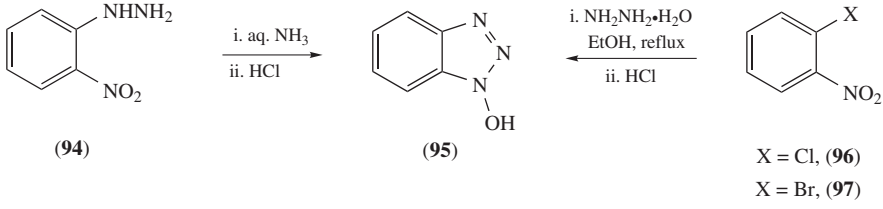
1. HOBt, 1-hydroxybenzotriazole

1-Hydroxybenzotriazole (**95**, Figure 24) is the template in which many analogues have been inspired, seeking to enhance its original properties and applications in many fields. **95** is a white crystalline powder, forming needles, whose melting point is described in the range 156–158 °C[190, 213–218]. **95** forms stable, semiconductor complexes with Cu, Co and Ni, which has been found to be linked to its anticorrosive properties when applied to metals[218]. Its synthesis was first accomplished separately by Nietzki and Zincke and their coworkers from *o*-nitrophenylhydrazine (**94**) by reaction with warm alkalis, such as aqueous ammonia (Scheme 20)[213, 214]. In those studies, **95** was named azimidolbenzene. A few years later, Brady and Reynolds obtained **95** in almost quantitative yield using the Zincke method (with 25% potassium hydroxide) from the monosulfonate sodium salt of **94**[219]. Alternatively, other routes starting from



(**95**)

FIGURE 24. Structure of 1-hydroxybenzotriazole



(**94**) (**95**)

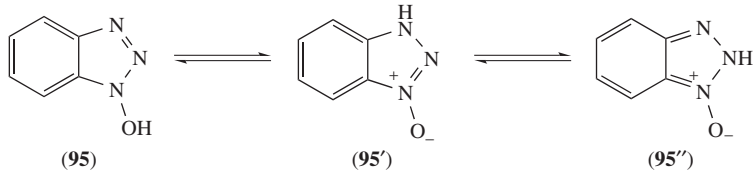
X = Cl, (**96**)
X = Br, (**97**)

SCHEME 20. Synthetic strategies for preparation of 1-hydroxybenzottriazole

o-chloronitrobenzene (**96**) or *o*-bromonitrobenzene (**97**) were developed by Müller and Brady, which under reflux with hydrazine hydrate afforded **95** in 88% and 60% yield, respectively (Scheme 20)[215, 216, 219, 220]. Interestingly, Brady and Reynolds found that when **97** was reacted with 50% hydrazine hydrate at 160 °C, **95** was not obtained but rather its reduction product (benzotriazole)[219]. In all these approaches **95** was usually obtained as the monohydrate, which is considerably unstable, losing water standing in air[219, 220].

95 is a strong acid ($pKa = 4.60$), compared with the average acidity of the majority of organic compounds[221]. The work of Pop and coworkers supported this value ($pKa = 4.64$)[100]. Koppel and coworkers also investigated the acidity of **95** at room temperature, obtaining the same value ($pKa = 4.60 \pm 0.03$), with a standard potentiometric technique[24, 200]. A slightly higher dissociation constant was reported by König and Geiger[101] ($pKa = 4.3$), in a 50:40 mixture of diethylene glycol dimethyl ether/H_2O at 54 °C, and also by Martinez and Bodanszky[221]. The acidity in DMSO, which closely resembles solvents used in standard peptide synthesis, was also determined by Koppel and coworkers ($pKa = 9.3 \pm 0.1$), by potentiometric titration of **95** with Bu_4NOH in a solvent mixture benzene/isopropanol[24]. In both solvents, **95** is more acidic than benzotriazole (by 2.6 and 3.8 p*K*a units in DMSO and H_2O, respectively), due to the replacement of *N*-H by *N*-OH[24]. Recently, the acidity of **95** was also determined in EtOH–H_2O and dioxane–H_2O mixtures at various temperatures (20–40 °C), observing an increase of p*K*a with decreasing temperature or increasing percentage of organic solvent[218]. In 100% H_2O, a similar p*K*a to these reported previously was obtained ($pKa = 4.53 \pm 0.01$ at 20 °C)[218]. In agreement with these dissociation constants, ^1H NMR in C_6D_6 showed a chemical shift of 13.6 ppm for the *N*-OH of **95**. The R_f in CH_2Cl_2 has been described (0.77)[218]. **95** shows an IR band at 3273 cm^{-1}, corresponding to OH stretching and also ν(C=C) = 1616.2 cm^{-1}, ν(O–N) = 1394.4–1357.8 cm^{-1} and ν(N=N) = 1222.8–1110.9 cm^{-1} [218]. This high acidity confers on **97** ideal properties for its use as additive to carbodiimides in peptide synthesis[189].

Tautomerism between *N*-OH **95** and *N*-oxide form **95′** (Figure 25) was first described by Brady and Day in 1923 after discovering that, during methylation of the benzotriazole, two isomers with distinct UV profile were formed[23]. Shortly after, Brady and Reynolds reported that experiments with methyl iodide or methyl sulfate in basic water yielded mainly the *N*-oxide **95′** derived product[219]. The same conclusion was extracted by Macbeth and Price, although in alcoholic solutions the *N*-hydroxy form **95** appeared to be the most favored one[222]. A deeper investigation on this tautomeric equilibrium was conducted by Boyle and Jones by means of basicity measurements, acidic function correlations and UV spectroscopy[215]. Mason equations suggested a mixture of the tautomers in water, although H_a correlations and UV spectra comparisons of **95** ($\lambda_{max} = 265$ nm, log $\varepsilon = 3.5$; $\lambda_{max} = 280$ nm, log $\varepsilon = 3.6$; $\lambda_{max} = 310$ nm, log $\varepsilon = 3.8$) and the methylation products clearly indicated the predominance of the *N*-oxide form **95′** (84%). In ethanolic solution, UV spectra of **95** ($\lambda_{max} = 265$ nm, log $\varepsilon = 3.6$; $\lambda_{max} = 285$ nm, log



(**95**) (**95′**) (**95″**)

FIGURE 25. Tautomeric forms of 1-hydroxybenzotriazole

$\varepsilon = 3.5$; $\lambda_{max} = 315$ nm, log $\varepsilon = 3.1$) confirmed the main presence of the *N*-hydroxy form (**95**)[215]. The same tautomer was found to be predominant in DMSO, suggested by ^{13}C-NMR spectra[223]. In DMF, **95** also showed λ_{max} at 265 and 280 nm[218]. In 1997, Horiki investigated the effect of solvent polarity on a mixture of acylated *N*-hydroxy and *N*-oxide tautomers once equilibrium was reached, observing that increasing percentages of acetone in H_2O gave rise to higher amounts of the less polar *N*-hydroxy acylated derivative[224]. In the solid state, forms **95** or **95′** were obtained as monoclinic crystals, depending on the polarity of the recrystallization solvent[192, 225]. The distinct ratio of forms **95** to **95′** based on solvent polarity has been previously observed in the parent benzimidazoles and imidazoles[226–228]. In the acyl-transfer process between both tautomers, intramolecular or intermolecular mechanisms have been proposed[195, 224, 229, 230]. Semiempirical methods have also been employed to analyze the composition of the tautomeric equilibrium[195]. The AM1 approach clearly indicates the higher stability of *N*-hydroxy form **95** over **95′**; but the controversial PMS method as well as *ab initio* calculations suggest a similar stability of both forms[195, 196]. All the methods agree that the *N*-oxide form **95″**, which has not been experimentally detected, is the least stable among the tautomers, probably due to its high energy owing to loss of the benzene ring aromaticity[195]. Carpino and coworkers achieved an easier analysis of the tautomeric equilibrium by means of ^{1}H NMR, using the integration of the methyl group of both methylation products (4.39 ppm vs. 4.11)[231].

The acidity of **95**, considering the percentages of the tautomers in water, was determined potentiometrically using the Albert method (pKa = 7.88)[232]. Later, a separate dissociation constant for each tautomer was calculated (pKa of *N*-oxide = 8.05; pKa of *N*-hydroxy = 7.39)[220]. These are considerably higher values than those obtained by titration methods[100].

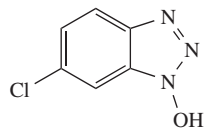
In 2005, Dunn and coworkers[191] predicted the explosive behavior of monohydrate **95**[227] by using a Yoshida plot[233], which is based on results of thermal instability. **95** was expected to be shock-sensitive, although the authors did not find experimental proof after drop-hammer tests[191]. Nevertheless, other studies found evidence of its explosivity when **95** was heated close to its melting point, which had caused some relevant incidents when handled on a large scale[191]. Actually, more than a century ago, the lead salt of **95** was already reported to explode at 270 °C, and so did other substituted derivatives[203, 234–236]. Shortly after, Dunn and coworkers investigated extensively the explosive properties of **95** and some derivatives[190]. These benzotriazoles were not only sensitive to heating in a closed confinement or under mechanical stimulus, but also were able to propagate a detonation or deflagration, regardless of the percentage of water in the sample, which acts as a desensitizer[190]. Special attention should be taken when handling **95**, dry or hydrated with <10% of water, which are considered Class 1 explosives, thereby compromising its transport[237]. Even samples containing >10% of water, placed in soft packages, are regarded as sensitized explosives, according to Division 4.1 of UN Recommendations[238]. The presence of the *N*-hydroxyl/*N*-oxide mixture might play a key role in the hazardous nature of **95**, since its parent 1*H*-benzotriazole does not display explosive properties, although it must be handled with precaution due to the high exothermic decomposition energy that is released above 100 °C[239]. Lately, an assessment of the thermal safety of **95** monohydrate (12.8% of water) has been conducted calorimetrically by dynamic DSC and ARC assays[2]. The combination of both techniques shows a decomposition behavior that matches the profile of an explosive compound: fast degradation with high released pressure (178 bars)[27]. The onset of decomposition, accurately set at 145 °C after the ARC assay, took place before melting (mp = 157 °C). As a result, it is recommended to keep the temperature at values $T < 95$ °C, in order to work safely[28, 29].

2. 6-Cl-HOBt, 6-chloro-1-hydroxybenzotriazole

6-Chloro-1-hydroxybenzotriazole (**99**, Figure 26) is obtained as a colorless crystalline powder, which decomposes after melting at a higher temperature than the unsubstituted 1HOBt (mp = 189–192 °C, 195 °C or 198 °C have been reported)[190, 240, 241]. Methods for obtaining **99** were developed by Booy and Dienske in 1926[240] and by Joshi and Derhoa in 1952[241] (Scheme 21). These reactions started by refluxing 2,5-dichloronitrobenzene (**98**) in the presence of hydrazine hydrate to afford the desired benzotriazole in rather low yields. An optimization of the process (90.1% yield) was accomplished by Hagedorn and coworkers in 1997, obtaining the sodium salt of **99** from **98** after cyclization of the hydrazino derivative in the presence of sodium hydroxide, as an intermediate for the synthesis of HOBt after dechlorination[242].

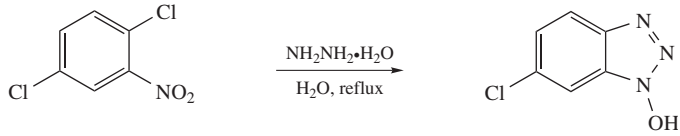
98 can be prepared from *p*-dichlorobenzene (**101**) by nitration with HNO_3 and H_2SO_4 in near-quantitative yields, although this transformation can take place in milder conditions in the presence of sieve catalysts mixed with MgO in good yields and 99–100% regioselectivity (Scheme 22)[243, 244]. The use of Sb-based catalysts in aprotic non-polar solvents also represents an efficient strategy for the nitration of **101**[245]. Several catalysts have been proposed for the *p*-chlorination of chlorobenzene (**100**), such as ferric chloride, kaolinitic clay or the mixture hydrogen peroxide-2,2,2-trifluoroethanol[246, 247]. Another approach to the synthesis of **98** consists in the chlorination of *o*-chloronitrobenzene (**102**), an intermediate for obtaining **95** (Section III.H.1), with chlorine and ferric chloride (Scheme 22)[248].

The acidity of **99** is one of the highest found among substituted 1-hydroxybenzotriazoles ($pK_a = 3.35$), along with that of the 6-nitro derivative (6-NO_2-HOBt, **112**, Section III.H.4)[24, 249]. Koppel and coworkers reported a slightly higher value ($pK_a = 4.15 \pm 0.03$) using the Albert potentiometrical technique[24, 232]. The same authors also determined, by means of potentiometric titration with Bu_4NOH in a mixture benzene/isopropanol, the acidity of **99** in DMSO ($pK_a = 8.6 \pm 0.1$), a solvent that closely resembles the conditions in which peptide synthesis is conducted[24]. Verma and Parmar characterized **99** by infrared spectroscopy in KBr; it is observed as a band for the acidic *N*-OH vibration at 1210 cm^{-1} and, as expected, with no sign of typical C=N absorption at 1650–1700 cm^{-1} [ν(N=N) = 1625 cm^{-1}, ν(O–N) = 1210 cm^{-1}, ν(C–Cl) = 670 cm^{-1}][210]. Vibrational frequencies of the ring system are observed in the range 910–1510 cm^{-1}. Surprisingly, the *N*-OH



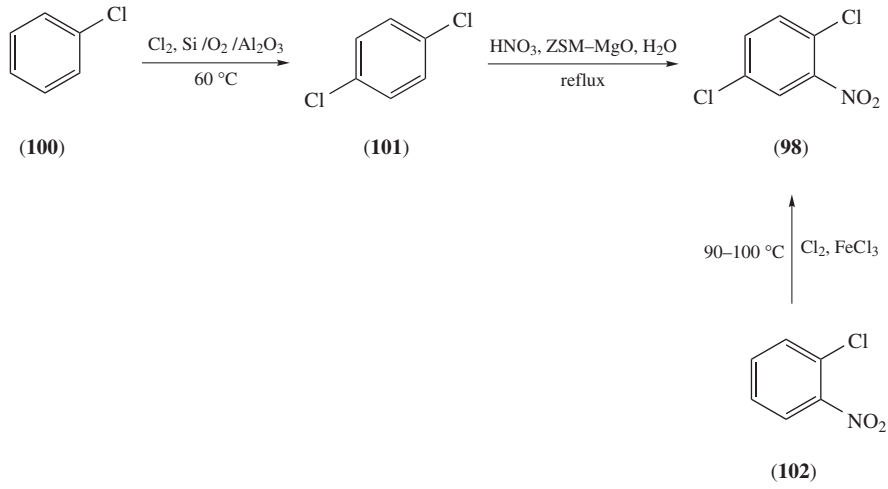
(**99**)

FIGURE 26. Structure of 6-chloro-1-hydroxybenzotriazole



(**98**) (**99**)

SCHEME 21. Synthetic strategy for preparation of 6-chloro-1-hydroxybenzotriazole



SCHEME 22. Synthesis of the intermediate **98**

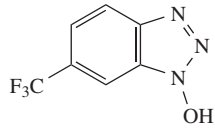
stretching band and C=C bands are not detailed, contrary to the IR spectra of **95** (Section III.G.1)[210, 218]. With regard to N=N absorption, it is observed around 1600 cm^{-1}, a considerably higher frequency than the one reported for **95**[210, 218].

99 has been reported to be safer than **95**[210, 218, 233, 250]. Dry **101** is regarded as a Class 1 explosive, compromising its transport in a similar way to **95**[237].

3. 6-CF_3-HOBt, 1-hydroxy-6-trifluoromethylbenzotriazole

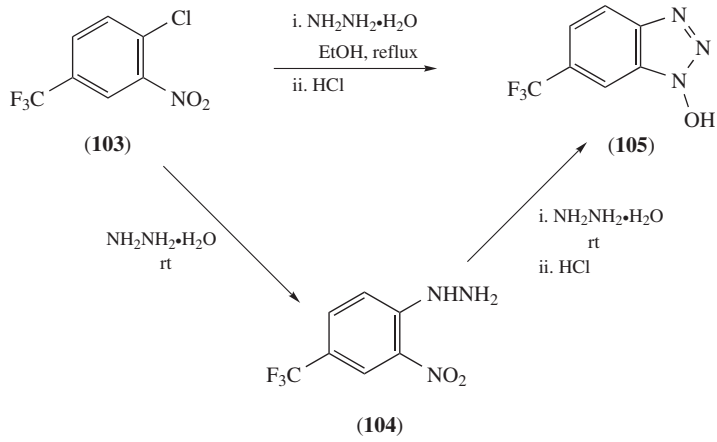
1-Hydroxy-6-trifluoromethylbenzotriazole (6-CF_3-HOBt, **105**, Figure 27) is a crystalline solid, with a lower melting point than its parent unsubstituted HOBt (**95**) (described in the range 143–149 °C)[189, 250–252]. Inspired by the method developed by Müller and Zimmermann in 1925,[216] König and Geiger[189] described the formation of **105** from 3-nitro-4-chlorotrifluoromethylbenzene (**103**) by the action of hydrazine hydrate in refluxing ethanol (Scheme 23)[250]. Later, Takeda and coworkers revised the former method and enhanced the yield (96%) by refluxing with 99% ethanol during 24 hours[251]. Alternatively, **105** can be obtained from **104** by treatment with hydrazine hydrate under mild conditions (Scheme 23)[149].

The starting material for the above-mentioned synthetic strategy, i.e. **103**, is obtained after nitration of *p*-chlorotrifluoromethylbenzene (**108**) (Scheme 24). This nitration can be achieved regioselectively in the absence of solvent with concentrated nitric acid (95%



(**105**)

FIGURE 27. Structure of 1-hydroxy-6-trifluoromethylbenzotriazole



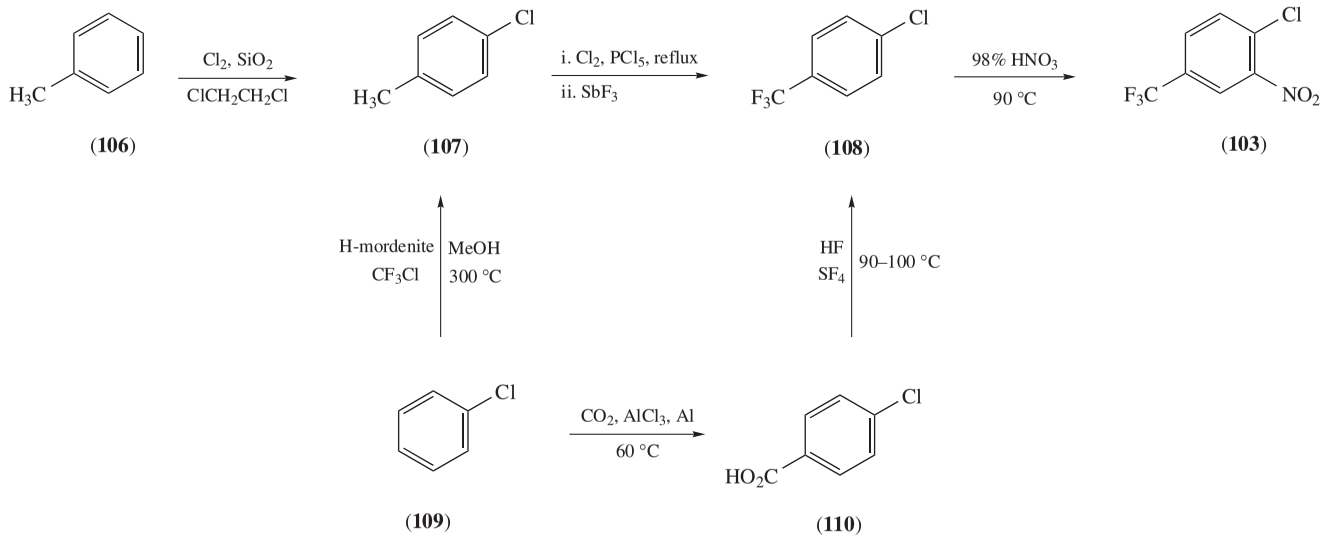
SCHEME 23. Synthetic approaches for the synthesis of 1-hydroxy-6-trifluoromethylbenzotriazole

yield), although classical nitration in the presence of H_2SO_4 was also described[149, 253]. **108** can be efficiently synthesized from *p*-chlorotoluene (**107**) or *p*-chlorobenzoic acid (**110**). The latter **110**, obtained in high regioselectivity by carboxylation of chlorobenzene (**109**) with aluminum trichloride in reasonable yields, affords **108** by fluorination in the presence of sulfur tetrafluoride at high temperature (70% yield) (Scheme 24)[253–255]. The former is transformed into **109** in two steps, after chlorination with phosphorus pentachloride catalysis and subsequent fluorination with tetrafluoroantimonate or hydrogen fluoride (88% yield) (Scheme 24)[256]. **107** is synthesized either from chlorobenzene (**109**), by treatment at high temperature with methanol and H-mordenite as catalyst (in low regioselectivity), or from toluene (**106**) in regioselectivity close to 90% using zeolites as catalysts (best yields using K-L type ones) (Scheme 24)[257, 258]. Interestingly, some methodologies have been developed to obtain **108** directly from **109** by trifluoromethylation, using distinct catalysts, such as trifluoromethyl iodide, bis (trifluoromethyl) telluride or bis (trifluoroacetyl) peroxide[259–261].

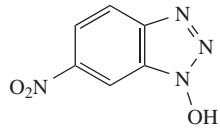
The inclusion of the trifluoromethyl group confers on **105** a higher acidity ($pKa = 3.80 \pm 0.03$) than that of the parent **95**, as determined by Koppel and coworkers by means of a standard potentiometric technique at room temperature[24, 232]. The acidity was also measured in DMSO ($pKa = 7.4 \pm 0.1$) by potentiometric titration of **105** following the tendency observed in H_2O relative to **95**[24]. Regarding IR spectra of **105** in KBr, a strong band is observed at 1630 cm^{-1}, corresponding to the aromatic benzotriazole core[251]. ^{1}H-NMR spectra in acetone-d_6 showed the aromatic hydrogens and the highly acidic *N*-hydroxylamino hydrogen at δ 7.50 and 10.94[251].

4. 6-NO_2-HOBt, 1-hydroxy-6-nitrobenzotriazole

1-Hydroxy-6-nitrobenzotriazole (6-NO_2-HOBt, **112**, Figure 28) is a dark yellow solid, arranged in large prisms or leaflets, and presents solubility in hot H_2O and EtOH[215, 262]. **112** has been described to melt at 190–192 °C, with decomposition, or at 200–204 °C[261, 262]. Other authors claim that no melting point is observed, the heating causing a violent detonation or deflagration at 206 °C[23, 242, 263]. A synthetic route to **112** was achieved separately by Brady, Curtius and their coworkers almost a century ago (Scheme 25)[23, 262]. Brady and Day

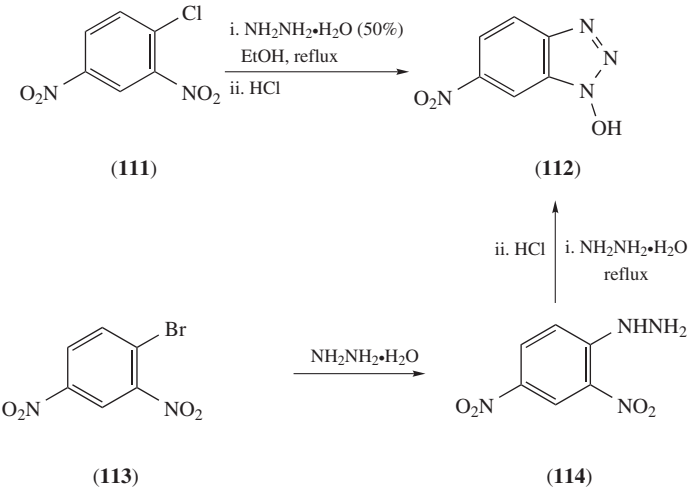


SCHEME 24. Synthetic approaches for the synthesis of **103**



(**112**)

FIGURE 28. Structure of 1-hydroxy-6-nitrobenzotriazole

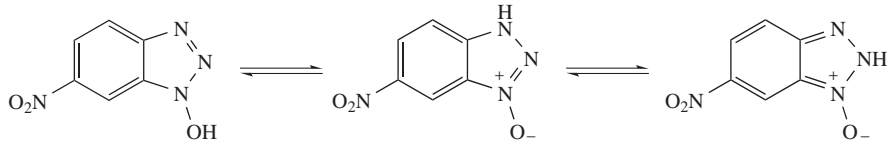


SCHEME 25. Synthetic approaches for the synthesis of 1-hydroxy-6-nitrobenzotriazole

successfully obtained **112** in a few hours, after refluxing 2,4-dinitrochlorobenzene (**111**) with 50% hydrazine hydrate in alcohol with subsequent acidification, in 50–60% yield (Scheme 25)[23]. Earlier, Curtius and coworkers similarly used pure or aqueous hydrazine to afford **112** in 80% yield from 2,4-dinitrophenylhydrazine (**114**), which can be obtained from 2,4-dinitrobromobenzene (**113**) with hydrazine hydrate (Scheme 25)[262, 264]. Several bases have been tried as alkali catalysis for the transformation of **114** into **112**, such as potassium, barium and sodium hydroxide or aqueous ammonia, the yield strongly depending on the concentration of base[214, 215, 265, 266]. The preparation of **114** from **113** has also been reported.

The presence of the nitro group has a great impact on the acidity of **112** ($pKa = 2.75$), a similar effect to that introduced by Cl (see **98**, Section III.G.2)[24, 215]. The IR spectra of **112** in KBr has been reported by Verma and Parmar [ν(N=N) = 1610 cm^{-1}, ν(O−N) = 1210 cm^{-1}, ν(C−NO$_2$) = 1510 cm^{-1}][210]. Similarly to **98** (Section III.G.2), a band corresponding to the acidic N−OH vibration was observed at 1210 cm^{-1} and, as could be expected, no sign of typical C=N absorption at 1650–1700 cm^{-1} was detected[210]. Typical vibrational frequencies of the aromatic ring system are observed in the range 850–1490 cm^{-1} and a strong *C*-NO$_2$ band is located in the range 1510–1525 cm^{-1} [210], unlike the reported IR spectra of **95**[218].

Tautomerism between *N*-hydroxy and *N*-oxide species (**112**, **112′**, **112″**) and other substituted benzotriazoles (Figure 29) was first envisaged by Brady and Day in 1923, after



(**112**) (**112′**) (**112″**)

FIGURE 29. Tautomeric forms of 1-hydroxy-6-nitrobenzotriazole

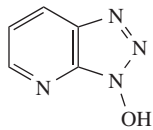
observing two isomeric methylation products[23]. However, this study was not conclusive concerning the predominant form **112**, due to the unavailability of a suitable method to separate the different tautomers[23].

In 1936, Macbeth and Price reported the tautomeric equilibrium by means of UV spectroscopy[222], revealing that 6-NO_2-HOBt was mainly in the *N*-hydroxy form **112** in EtOH and H_2O, although in H_2O solvent it was presented as the anion due to its high dissociation constant. Many decades later, Boyle and Jones[215] re-evaluated this equilibrium, based not only on UV specroscopy, but also on basicity parameters and acidic function correlations. Although tautomeric predictions using Mason equations suggested that *N*-hydroxy species **112** were the most stable in H_2O, the correlation of H_o and H_a values indicated the contrary. The UV spectra supported the hypothesis of predominance of the *N*-oxide form **112′** (75%) in H_2O ($\lambda_{max} = 260$ nm, log $\varepsilon = 4.2$; $\lambda_{max} = 335$ nm, log $\varepsilon = 3.7$) at strongly acidic pH and confirmed the predominance of the *N*-hydroxy form **112** (85%) in EtOH ($\lambda_{max} = 250$ nm, log $\varepsilon = 4.0$; $\lambda_{max} = 280$ nm, log $\varepsilon = 3.9$; $\lambda_{max} = 320$ nm, log $\varepsilon = 3.4$). The dependence of the *N*-hydroxy/*N*-oxide ratio on the solvent polarity is consistent with the analogous reports in benzimidazoles and imidazoles[226–228]. The least stable 2*H*-tautomer (**112′**) has not been observed.

I. Azabenzotriazoles

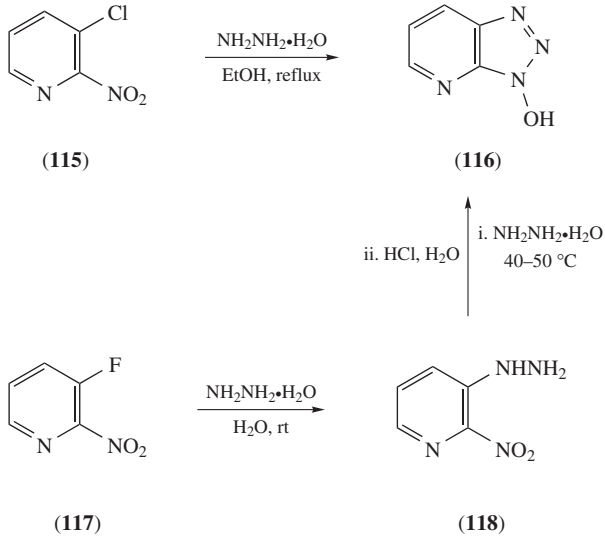
1. 7-HOAt, 7-aza-1-hydroxybenzotriazole

7-Aza-1-hydroxybenzotriazole (7-HOAt, **116**, Figure 30), also named 3-hydroxytriazolo[4,5-*b*]pyridine, is a pale yellow (nearly colorless) crystalline solid, which melts at 215–217 °C with decomposition[252, 257, 258]. Its synthesis was first described in 1973 by Sacher and coworkers from 3-chloro-2-nitropyridine (**115**) adapting the Müller methodology[216] for benzotriazoles (Scheme 26)[252]. Shortly after this study, Mokrushina and coworkers reported an alternative route to **116** from 3-fluoro-2-nitropyridine (**117**, Scheme 26)[267, 268]. Its enhanced reactivity toward aromatic nucleophilic substitution with respect to **117** precludes the need for strong reaction conditions, which in the case of **115** are known to cause unwanted substitution in the 2-nitro position[229]. The



(**116**)

FIGURE 30. Structure of 7-aza-1-hydroxybenzotriazole



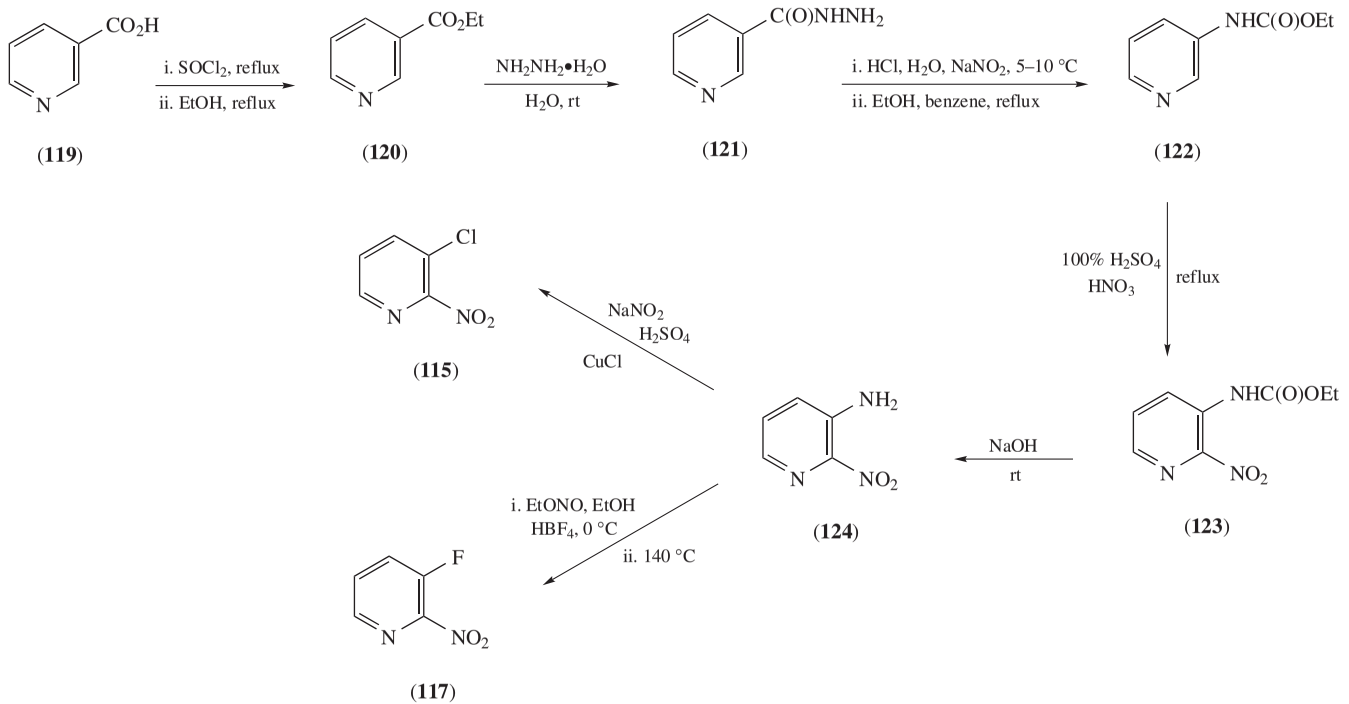
SCHEME 26. Synthetic approaches for the synthesis of 7-aza-1-hydroxybenzotriazole

authors found that in the presence of hydrazine hydrate, **117** is transformed into 3-hydrazino-2-nitropyridine (**118**) or the hydrazinium salt of **116**, depending on the conditions. Thus, at 20 °C mainly **118** is obtained, although the cyclized product is also detected. Reaction of **118** with a large excess of hydrazine hydrate (or other bases like morpholine or sodium carbonate) or at 40–50 °C affords, after acidification of the hydrazinium salt, **116** in 70% yield.

Both 3-halo-2-nitropyridines are easily obtained from the 3-amino derivative **124** (Scheme 27). The 3-chloro analogue (**115**) is formed via the Sandmeyer reaction in sulfuric acid (65% yield), whereas the Schieman method adapted to heterocycles, forming the diazonium tetrafluoroborate in the presence of fluoroboric acid with subsequent decomposition, afforded **117** in 25% yield[269, 270]. Starting from nicotinic acid (**119**), Clark-Lewis reported facile and high yield synthesis of **122** (Scheme 27)[271]. The first step consists of formation of ethyl nicotinate (**120**), after refluxing the *in situ*-formed acyl chloride in ethanol, which is then converted into nicotinhydrazide (**121**) with hydrazine hydrate[272, 273]. Then, **121** is transformed into 3-ethoxycarbonylaminopyridine (**122**) through intermediate formation of the acyl azide in an acidic aqueous solution of sodium nitrate[274]. Optimization of the Curry and Mason nitration method by refluxing **122** in 100% H_2SO_4 and HNO_3 gave **123**, and subsequent removal of the carbamate after a 2-day treatment with sodium hydroxide afforded **124** in 35% yield[275].

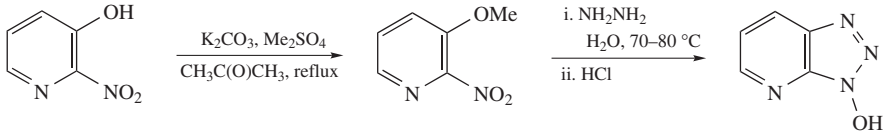
The above-mentioned routes were shortened by Carpino few decades later, accomplishing an efficient synthesis of **116** in 2 steps from the commercially available 3-hydroxy-2-nitropyridine (**125**, Scheme 28)[276]. In the first step, **125** is methylated with dimethyl sulfate in the presence of base, generating 3-methoxy-2-nitropyridine (**126**) in 95% yield. This electron-deficient pyridine (**126**) is heated with an excess of hydrazine hydrate for 24 h affording the desired **116** in 47% yields.

The vicinity of the nitrogen at position 7 to the *N*-hydroxylamino moiety confers on **116** one of the highest acidities found in benzotriazoles and their derivatives ($pKa = 3.28$), one p*K*a unit more acidic than HOBt (**95**, Section III.G.1), yielding a yellow



(**119**) (**120**) (**121**) (**122**) (**123**) (**124**) (**115**) (**117**)

SCHEME 27. Synthetic strategies for the synthesis of **115** and **117**



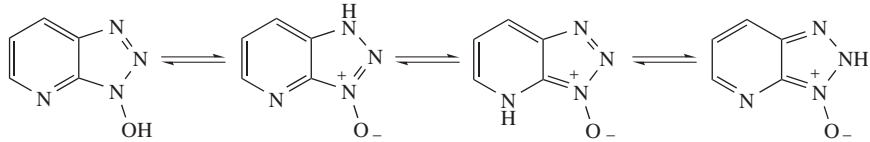
(**125**) (**126**) (**116**)

SCHEME 28. Carpino's approach for the synthesis of 7-aza-1-hydroxybenzotriazole

colored anion[267, 276]. A similar dissociation constant in H_2O was reported by Koppel and coworkers[24] using the Albert potentiometric method[232]. The acidity in DMSO was also determined ($pKa = 3.47 \pm 0.03$), which is more relevant than H_2O to the solvents regularly used in peptide synthesis, by potentiometric titration[267]. Aromatic protons at δ 7.35–8.66 in $CDCl_3$–DMSO-d_6 are identified by ^{1}H-NMR spectroscopy[276].

As found for other benzotriazoles, tautomerism between *N*-hydroxy and *N*-oxide forms of 7-HOAt (**116**, **116′**, **116″**, **116‴**) is envisaged, only that in this particular compound the 7-nitrogen permits the presence of two additional *N*-oxide species (Figure 31). The equilibrium in alcohol solution was studied by comparing the UV spectra of **116** ($\lambda_{max} =$ 260 nm, log $\varepsilon = 2.82$; $\lambda_{max} = 295$ nm, log $\varepsilon = 2.89$) with its methylated product and that of HOBt, which was previously reported, suggesting that in this media the *N*-hydroxy form was predominant[262, 267]. Mass spectrometric analysis[267] of the fragmentations of **116** led to the same conclusion. Carpino and coworkers investigated this equilibrium based on the ^{1}H-NMR chemical shift of the methyl group after methylation ($\delta = 4.49$), also indicating the predominance of the *N*-hydroxy specie (**118**)[231]. The intensity of the electronic absorption spectra in water ($\lambda_{max} = 220$ nm, log $\varepsilon = 4.10$; $\lambda_{max} = 280$ nm, log $\varepsilon = 3.78$; $\lambda_{max} = 325$ nm, log $\varepsilon = 3.40$) depends on the pH, showing an isosbestic point at 300 nm[268]. The presence of a maximum near 330 nm indicates a strong contribution of the anion, further supporting the high acidity attributed to **116**.

The triazole ring of the aromatic core is responsible for the explosive character of *N*-hydroxybenzotriazoles, and **116** is not an exception[190]. Some reports state that the high shock sensitivity of **116** is even stronger than that of the parent HOBt (**95**)[191]. Dunn and coworkers[191] found that this behavior resembles the one predicted with the Yoshida plot[233], based on thermal instability experiments. Its sensitivity to high temperatures when placed in a closed confinement, as extracted from the parameters of the Koenen test, is high enough to be labeled as Class 1 explosive substance, according to U.S. Department of Transportation and U.N. regulations[190, 237]. Recently, a thermal evaluation of **116** using two different calorimetry techniques (dynamic DSC and ARC) provided more details on its handling safety[2]. After careful analysis of the results obtained in both assays, it can be concluded that **116** behaves as an explosive compound, due to the extremely quick degradation associated with high pressure (167 bars)[27]. ARC assay also enabled a



(**116**) (**116′**) (**116″**) (**116‴**)

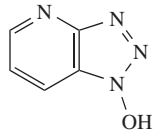
FIGURE 31. Tautomeric forms of 7-aza-1-hydroxybenzotriazole

precise determination of the onset of decomposition (178 °C), which is connected with the maximum temperature ($T = 128$ °C) at which working conditions can be certainly considered safe[28, 29].

2. 4-HOAt, 4-aza-1-hydroxybenzotriazole

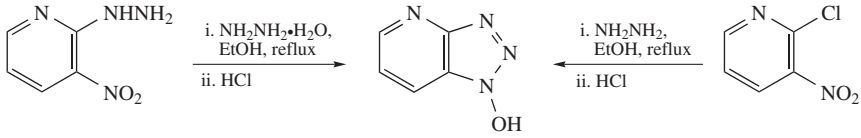
4-Aza-1-hydroxybenzotriazole (4-HOAt, **129**, Figure 32) is a yellow crystalline solid, which melts at 203–211 °C (after recrystallization) according to Carpino, although it has also been reported to melt at 220–222 °C and 209–210 °C[267, 168]. **129** can be obtained from 2-hydrazino-3-nitropyridine (**128**) or 2-chloro-3-nitropyridine (**127**) (Scheme 29) by refluxing with an alcoholic solution of hydrazine or its hydrate, followed by acidification (90% from **128**, Scheme 29), as described by Azev and coworkers[267, 268]. However, synthetic procedure from **127** requires a large excess of hydrazine in order to afford **129**.

Two decades later, Carpino accomplished the synthesis of **129** from **127** in two steps, using anhydrous ethanol as solvent (Scheme 30)[276]. Addition of hydrazine to **127** at room temperature caused in a short time the precipitation of the 2-hydrazino analogue (**128**) as a straw-yellow solid, a reaction already reported in 81% yield by Lewis and Robert in 1971[277]. Once **128** is isolated, this intermediate is readily transformed into the desired **129** upon reflux with 95% hydrazine and subsequent acidification, in 31% overall yield after recrystallization.



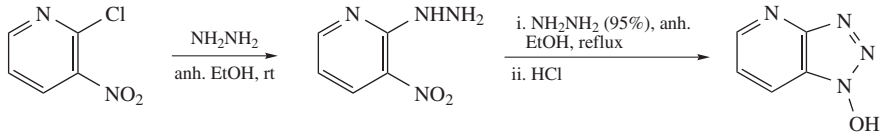
(**129**)

FIGURE 32. Structure of 4-aza-1-hydroxybenzotriazole



(**128**) (**129**) (**127**)

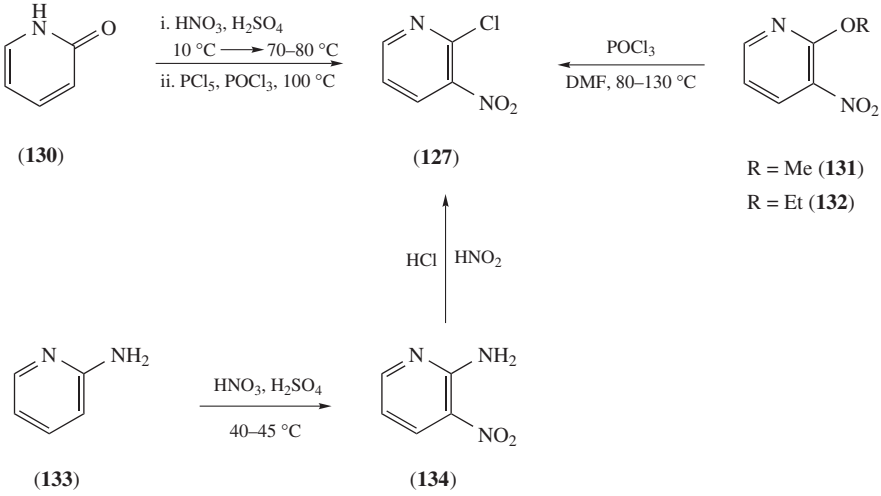
SCHEME 29. Synthetic approaches to 4-aza-1-hydroxybenzotriazole



(**127**) (**128**) (**129**)

SCHEME 30. Carpino's strategy for preparation of 4-aza-1-hydroxybenzotriazole

Few synthetic routes have been reported toward **127** (Scheme 31), the critical intermediate for obtaining **129**. The strategy proposed by Zakhs and coworkers[278] starts from pyridin-2(*1H*)-one (**130**), which is selectively nitrated by means of concentrated nitric and sulfuric acid in an ice–salt mixture, followed by 1-hour heating (14% yield) (Scheme 31)[278–280]. An alternative route has been described by Lai and coworkers from some 2-alkoxy-3-nitropyridine derivatives (**131**, **132**), after treatment under Vilsmeyer–Haack conditions (Scheme 31)[281]. High yields are obtained with this procedure from either the 2-methoxy (**131**, 90%) or 2-ethoxy (**132**, 87%) analogues. Finally, diazotization of 2-amino-3-nitropyridine (**134**) also leads to **127** (Scheme 31), as reported by Chichibabin and Builinkin[59]. Nonetheless, nitration of 2-aminopyridine (**133**) to yield **134** is not completely selective, as various percentages of the 5-nitro analogue are described[59, 282]. Selectivity issues also occur during introduction of chlorine to 3-nitropyridine *N*-oxide, a less efficient approach to afford **127**.



SCHEME 31. Synthetic pathways for the synthesis of **127**

The ionization constant of **129** is slightly higher than that of the 7-isomer ($pKa = 3.02$) and is one of the highest found in *N*-hydroxybenzotriazoles[267]. Koppel and coworkers[24] also found a high acidity ($pKa = 3.14 \pm 0.03$) when using a standard potentiometric methodology at room temperature[232]. The same authors described the dissociation constant in DMSO ($pKa = 8.1 \pm 0.1$), a solvent that resembles more closely than H_2O the solvents used in standard peptide synthesis[24]. As observed with **116** (Section III.I.1), in a crystalline sample the intensity of the IR band from 2200 to 2700 cm^{-1} decreases when the *N*-hydroxy hydrogen is replaced by deuterium, which indicates a strong contribution of the polar form of **129**[267].

Tautomeric equilibrium between the *N*-hydroxy form **129** and the three *N*-oxide species (**129′**, **129″**, and **129‴**) may take place with 4-HOAt (Figure 33). Azev and coworkers studied the tautomery in alcohol solutions by analyzing the UV spectra of **129** ($\lambda_{max} = 280$ nm, $\log \varepsilon = 2.94$) and that of the methylation product[267]. Neither of these resembled the UV spectra of *O*- and *N*-methylated HOBt (**95**, Section III.H.1), suggesting that 4-HOAt exists predominantly in alcoholic solution as one of the *N*-oxide species involving

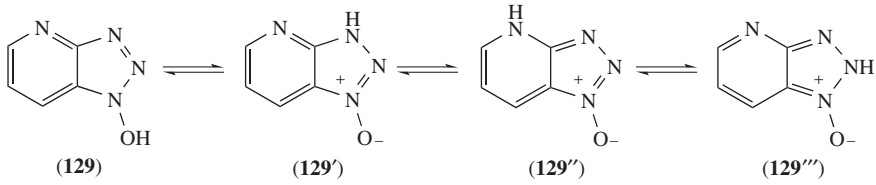


FIGURE 33. Tautomeric forms of 4-aza-1-hydroxybenzotriazole

participation of the pyridine ring due to its basic character as shown in forms **129′** and **129″**[222]. This was identified as **129′**, after analysis of the degradation fragments from mass spectroscopy. Consequently, 4-HOAt is also named triazolo[4,5-*b*]pyridine 1-oxide. In H_2O ($\lambda_{max} = 220$ nm, log $\varepsilon = 4.22$; $\lambda_{max} = 280$ nm, log $\varepsilon = 3.87$; $\lambda_{max} = 324$ nm, log $\varepsilon = 3.50$), different electronic curves are obtained depending on the pH, with an isosbestic point at 300 nm[268]. The spectra also show a maximum at 330 nm, indicating the high ionization constant of 4-HOAt.

Nevertheless, some controversy exists about the predominance of the *N*-oxide form in solution[231]. Carpino and coworkers claimed that the melting point of the methylation product of 4-HOAt does not coincide with the one reported by Azev and coworkers. Moreover, ^{1}H-NMR and X-rays analysis are consistent with the *N*-hydroxy species (**129**).

3. 5-HOAt, 5-aza-1-hydroxybenzotriazole

The synthesis of 5-aza-1-hydroxybenzotriazole (5-HOAt, **140**, Figure 34) has been reported by Carpino and coworkers, along with that of the 6-isomer[231]. The synthetic route starts from 3-fluoro-4-nitropyridine *N*-oxide (**135**), a highly electron-deficient heterocycle which can react with a wide variety of sulfur-, oxygen- or nitrogen-based nucleophiles, by displacing the 3-fluorine (Scheme 32)[283]. When mixing **135** with hydrazine hydrate, the 3-hydrazino-4-nitropyridine intermediate (**136**) is quickly formed, a reaction that was already described by Talik and Talik in 1966[283]. Cyclization to afford the benzotriazole core was accomplished upon refluxing **136** with excess hydrazine hydrate, followed by acidification. The *N*-oxide benzotriazolic intermediate **137** was transformed into **140** via **138** and **139**, after methylation of the 1-hydroxy group, 5-deoxygenation and demethylation (Scheme 32) for obtaining **140**.

The starting material of Carpino's strategy toward 5-HOAt, **135** can be obtained from 3-aminopyridine (**141**) in 35% yield, as described by Talik and Talik (Scheme 33)[284]. The fluorine at 3-position is introduced into the aromatic ring within a few hours upon reaction with the intermediate diazonium salt. The *N*-oxide is formed from 3-fluoropyridine (**142**) after extensive treatment with AcOH and H_2O_2 and this is then selectively converted into the desired 4-nitro analogue (**135**) (Scheme 33).

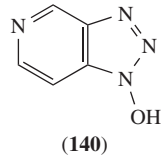
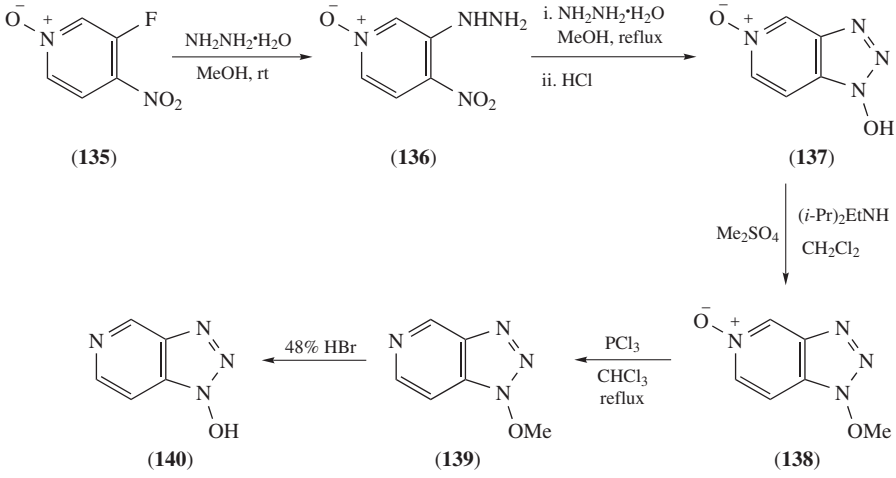
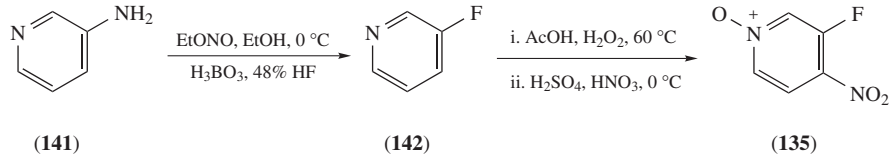


FIGURE 34. Structure of 5-aza-1-hydroxybenzotriazole



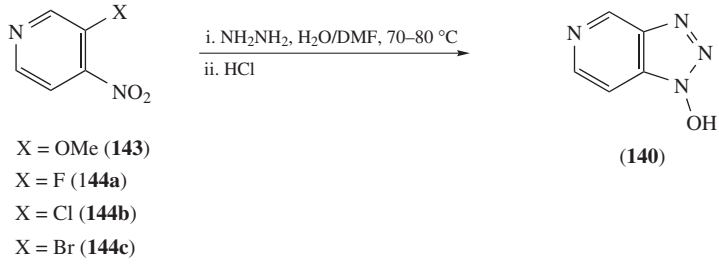
SCHEME 32. Synthetic strategies for 5-aza-1-hydroxybenzotriazole



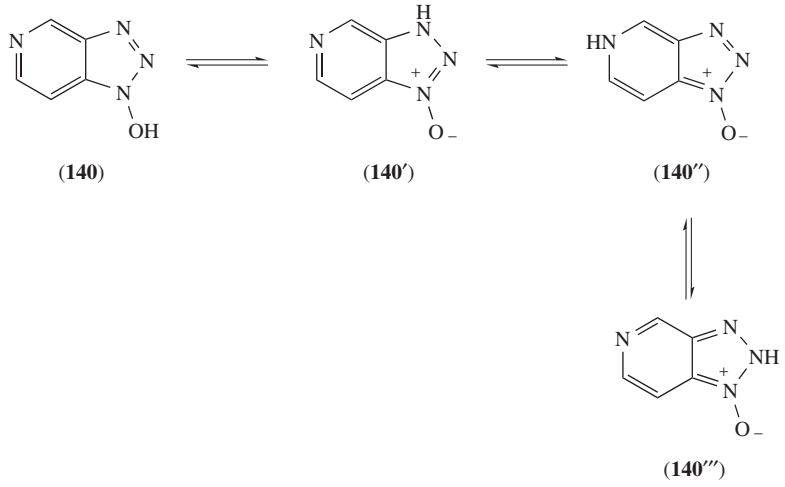
SCHEME 33. Synthetic strategies for the synthesis of **135**

Carpino proposed an alternative strategy for obtaining **140** with no need for the *N*-oxide pyridine, by extensively treating 3-methoxy-4-nitropyridine (**143**) or a range of 3-halo-4-nitropyridines (**144a–c**) with an excess of hydrazine hydrate, followed by acidification (Scheme 34)[231].

Unfortunately, an ionization constant for **140** has not yet been established, due to its instability under the conditions in which the Isaacs method is applied[285]. Nonetheless,



SCHEME 34. Carpino's alternative strategy for 5-aza-1-hydroxybenzotriazole



(**140**) (**140′**) (**140″**)

(**140‴**)

FIGURE 35. Tautomeric forms of 5-aza-1-hydroxybenzotriazole

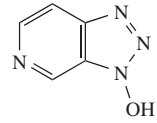
bearing in mind the relative reactivity as peptide additives for the 4-, 5-, 6- and 7-isomers (which is linked to their quality as leaving groups and so, to a great extent, with their acidity), an intermediate pKa between the 4- and 7-analogues can be estimated[231].

As for other benzotriazoles, tautomeric equilibrium between N-hydroxy (**140**) and N-species (**140′**, **140″**, **140‴**) has been studied (Figure 35)[231]. ^{1}H-NMR analysis of the methylation product in alcoholic solution showed a chemical shift for the methyl group ($\delta = 4.43$ ppm) that corresponds to its N-hydroxy form (**140**), indicating its predominance in this solvent[231].

4. 6-HOAt, 6-aza-1-hydroxybenzotriazole

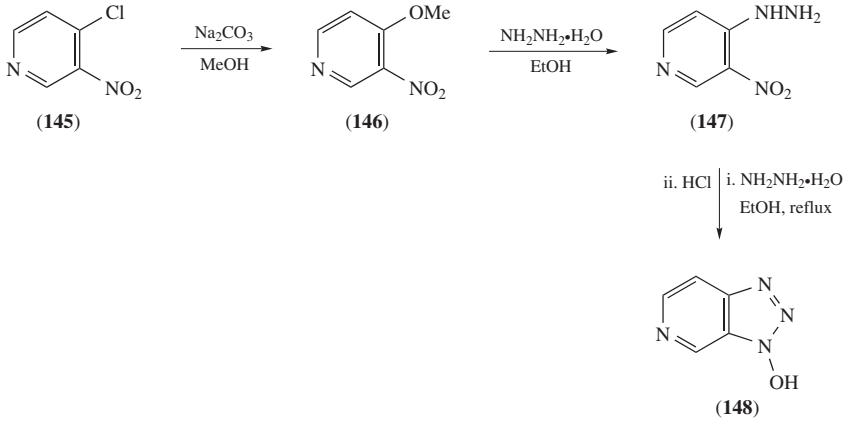
6-Aza-1-hydroxybenzotriazole (6-HOAt, **148**, Figure 36) is one of the four isomers of HOAt which find application as additives to carbodiimides in peptide synthesis. It was obtained in a few steps from 4-chloro-3-nitropyridine (**145**) by Carpino and coworkers (Scheme 35)[231]. **145** presents a marked activation toward nucleophilic aromatic substitution, which turns into high instability (self-reaction)[286]. Its lacrimatory and skin-irritant properties have also been described[287]. Reaction of **145** with MeOH yields the 4-methoxy derivative **146**, which is then converted into 4-hydrazino-3-nitropyridine (**147**) by adding hydrazine hydrate in EtOH, an improved preparation of the old method which was developed by Königs and Freter[288] and Hünig and Köbrich[289]. A refluxing mixture of **147** with hydrazine hydrate followed by acidification affords **148**. Carpino also described direct synthesis of **148** from **145** or its 4-fluoro/bromo analogues[231].

The hydrazino derivative **147** can be alternatively prepared from 4-hydroxy-3-nitropyridine (**150**), through intermediate formation of the 4-chloro (**145**) or 4-methoxy (**146**) activated species (paths **A** and **B**, Scheme 36). Path **A**, reported by Reich and coworkers, involves formation of the highly reactive **145** by heating **150** in the presence of phosphorus pentachloride and oxychloride[290]. **147** is then obtained after long treatment with hydrazine hydrate in ethanol, without isolating the 4-ethoxy intermediate, in 67% yield (Scheme 36). A few decades earlier, Fleet and Fleming described the synthesis

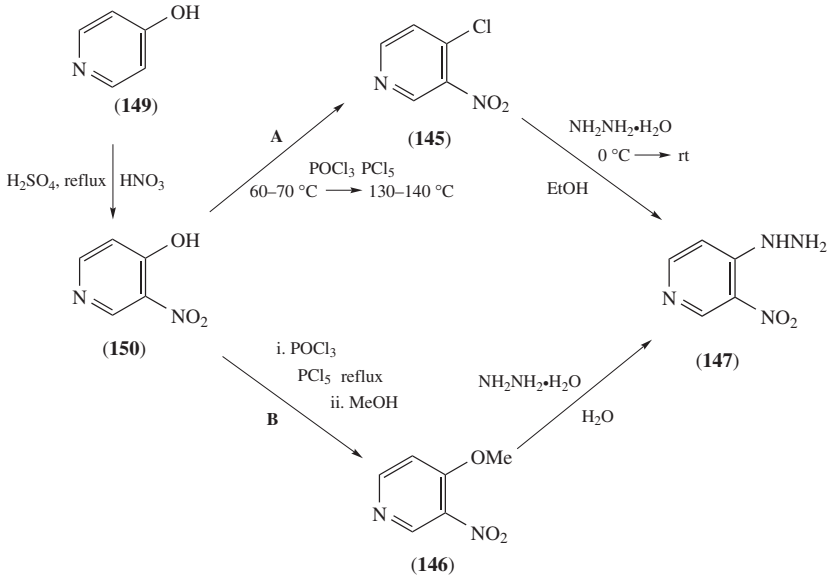


(**148**)

FIGURE 36. Structure of 6-aza-1-hydroxybenzotriazole



SCHEME 35. Synthetic strategy for 6-aza-1-hydroxybenzotriazole



SCHEME 36. Synthetic approaches for the synthesis of **147**

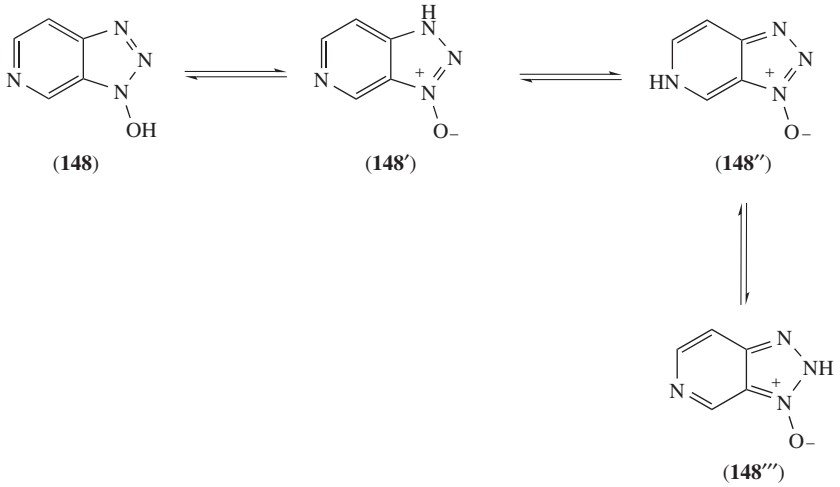


FIGURE 37. Tautomeric forms of 6-aza-1-hydroxybenzotriazole

of **147** from **146**, which is directly obtained in a short time from **150** by halogenation in methanol (75% overall yield, path **B**)[291]. Nitration of **149** in red fuming HNO_3 and fuming H_2SO_4 (18–24% SO_3) affords in a few hours the starting material for both routes (**150**) in 70–90% yield (Scheme 36)[288, 292].

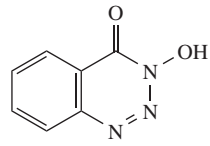
Similarly to the case of the 5-isomer, degradation of **148** under the conditions of the Isaacs method[285] for determining the pKa has lead to uncertainty about its ionization constant. Nevertheless, a pKa between those of the 4- and 7-analogues can be predicted considering the relative performance of 4-, 5-, 6- and 7-isomers as peptide additives (which is connected to their quality as leaving groups, and therefore with their acidity).

The tautomerism between *N*-hydroxy (**148**) and *N*-oxide (**148′**, **148″**, **148‴**) forms of 6-HOAt has been investigated, in a similar manner to those of most of *N*-hydroxybenzotriazoles (Figure 37)[271]. ^{1}H-NMR spectra of the methylation product indicated the predominance of the *N*-hydroxy form (**148**) in alcoholic solution, since the methyl group appeared in the typical area for this tautomer ($\delta = 4.49$ ppm)[231].

J. Hydroxybenzotriazine

1. HODhbt, 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine

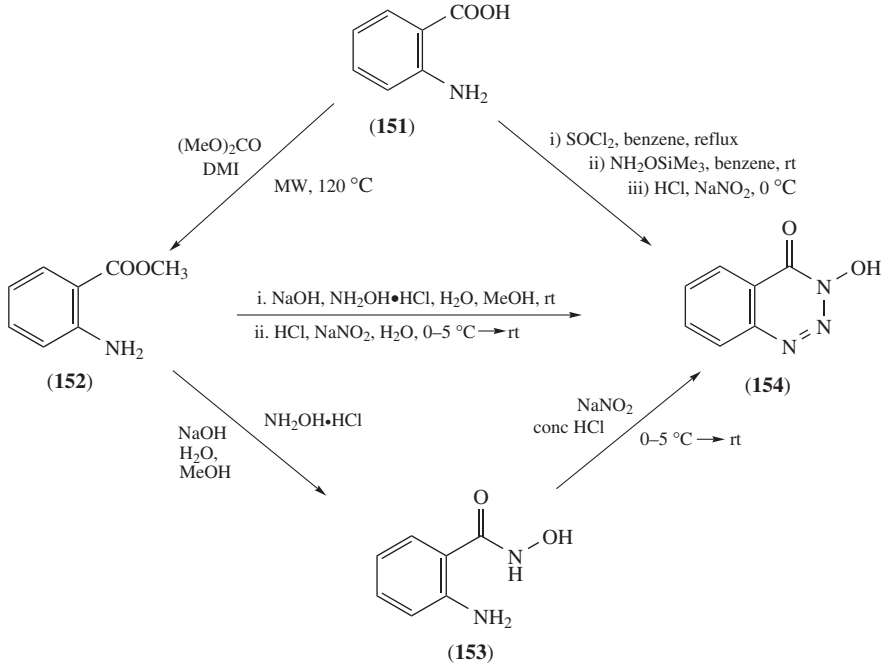
3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HODhbt, HOOBt, **154**, Figure 38) is a commercially available colorless solid (pale yellow before recystallization), which decomposes after melting at 180–181 °C, according to Harrison and Smith[293]. Some authors claimed a higher melting point for **156**: 182–185 °C or 186–187 °C[32, 294]. Alternatively, **154** has also been abbreviated as HOOBt[24, 101, 295]. It is a cyclic hydroxamic acid-containing compound, which gives a red color after reaction with ferric chloride. It is unstable in strong alkaline medium, leading to *o*-azidobenzoic acid (in 20% sodium hydroxide, complete degradation is observed after 1 h reflux), although it is stable in dilute conditions[32, 293]. The thermal breakdown byproducts have been widely studied. Unfortunately, such high reactivity might also lead to side reactions at room temperature, as a result of nucleophilic attack at the 4-carbonyl[32, 187, 276, 295–298].



(**154**)

FIGURE 38. Structure of 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine

Formation of the triazine ring of **154** from *o*-aminobenzhydroxamic acid (**153**) was already reported in 1960 by Harrison and Smith, adapting an old method (Scheme 37)[293]. Diazotization of the amino group of **153** in the presence of $NaNO_2$ and concentrated HCl, with subsequent heterocyclization, afforded **154** in 86% yield (Scheme 37)[293]. A similar process was reported by Ahern and coworkers in lower yield[32]. The synthesis of **153** can be achieved from methyl anthranilate (**152**) by reaction with hydroxylamine hydrochloride in a basic mixture of NaOH in H_2O/MeOH (70% yield) (Scheme 37)[299]. Previously, Vaughan and coworkers[300] separately proposed a similar, but less effective methodology. **152** can be obtained almost quantitatively from anthranilic acid (**151**), by selective methylation with dimethyl carbonate and 1,2-dimethylindole (DMI), forming an intermediate imidazolidium ion (98% yield) (Scheme 37)[301]. A similarly efficient approach



SCHEME 37. Synthetic strategies for the synthesis of 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine

consists in the reaction of **151** with diazomethane, rendering the target methyl ester **152** in mild conditions and high yield[302]. Possibly, the best strategy to afford **154**, although giving rise to lower yields than the above-mentioned method, was proposed by Jakobsen and coworkers in 1990[294]. They designed a one-pot method from **151** to the desired **154**, in which, in the first step, a ketenimine intermediate is formed after reflux with thionyl chloride[303]. This species has been found to be also present in the thermal breakdown of **154**[32, 294]. Next, the trimethylsilylated hydroxamic acid is generated *in situ* which, upon treatment with sodium nitrite in diluted hydrochloric acid, is hydrolyzed, diazotized and cyclized (68% overall yield) to afford pure **154** (Scheme 37) after recrystallization from H_2O/MeOH[294].

The presence of a cyclic hydroxamic acid contained within a triazine ring conferred on **154** a remarkable acidity. By means of a standard potentiometric technique, Koppel and coworkers measured the dissociation constant of **154** at room temperature ($pKa = 3.97 \pm 0.03$)[24, 232]. The acidity in DMSO was also investigated ($pKa = 8.9 \pm 0.1$), by potentiometric titration of **154** with Bu_4NOH in a solvent mixture benzene/isopropanol[24]. In both solvents, **154** was slightly more acidic than the parent benzotriazole HOBt (**95**, Section III.H.1). In a related study, the same dissociation constant was reported by König and Geiger[101] for both *N*-hydroxylamines ($pKa = 4.3$), in a 50:40 mixture of diethylene glycol dimethyl ether/H_2O at 54 °C, and also by Martinez and Bodanszky[221]. In spite of the almost identical acidities, **154** is regarded as a stronger nucleophile than **95**[101]. Infrared spectra of **154** in KBr showed a strong hydroxyl band at 2700 cm^{-1}, and a broad carbonyl signal at 1660 cm^{-1} [32]. The broadness of the two bands indicates the presence of an intramolecular hydrogen bond between those moieties[32]. Another signal at 1700 cm^{-1} was detected. Jakobsen and coworkers reported a slightly different IR spectra regarding the carbonyl region, and also identified a band corresponding to the triazine double-bond diaza group: ν(O−H) = 3200–2500 cm^{-1}, ν(C=O) = 1670 cm^{-1}, ν(N=N) = 1635 cm^{-1} [294]. The UV spectra of **154** has been studied in EtOH: λ_{max} (nm) = 221, 260, 303, 384. Most of the UV maxima, except the last one, were also observed in acylated derivatives[32]. In DMF, a band at 302 nm (log $\varepsilon = 3.76$) was also detected[294]. In the presence of a tertiary base (10 microliters of Et_2-NH), mimicking coupling conditions, strong absorptions had been observed near 400 nm: λ_{max} = 358 nm (log $\varepsilon = 3.87$), 430 nm (log $\varepsilon = 3.61$)[294]. Due to this UV absorbance, **154** shows a bright yellow color when ionized[276]. This enables practical detection of the final point in acylation reactions, such as peptide bond formation, since the absence of free amine results in negligible ionizaion[187, 276, 294, 296].

Jakobsen and coworkers reported the ^{1}H-NMR and ^{13}C-NMR spectra of **154** in DMSO-d_6, showing the proton of the N−OH at δ 2.51[294]. Vaughan and coworkers reported the fully decoupled, and without NOE, ^{15}N-NMR spectra of **156**: ^{15}N-NMR (DMSO-d_6) = δ 24.7 (*N*-2), −23.8 (*N*-1), −113.4 (*N*-3)[300]. The chemical shift for the three nitrogens lie in the typical area for the triazine ring[300]. Interestingly, the hydroxylamine-type *N*-3 is 40 ppm downshifted in comparison with the 3-methyl analogue of **154**. ^{15}N NMR also

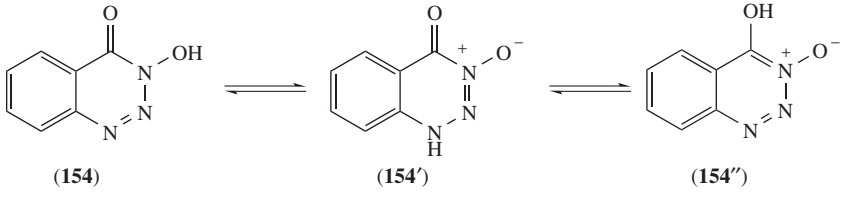


FIGURE 39. Tautomeric forms of 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine

gave information about the tautomeric equilibrium of **154**[300] (Figure 39). The presence of the tautomeric form with a hydrogen bonded to *N*-1 (**154′**) or the *N*-3 oxide, hydroximic acid species (**154″**) is still unkown in solid-state or solution NMR[32, 293, 299]. However, a NOE study on the parent 4-oxobenzotriazine suggested the predominance of the hydroxylamide form **154** over the hydroxylimide one (**154″**), similarly to other *N*-hydroxy-α-oxo compounds[32, 61, 300]. Thus, a similar percentage of tautomers might be expected from **154**.

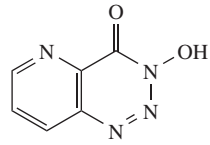
K. Hydroxyazabenzotriazine

1. HODhat, 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene

3-Hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene (HODhat, **158**, Figure 40) is a yellow solid, which may cause an explosion after melting at 195 °C[165, 166, 293]. When **158**, also named 3-hydroxy-4-oxo-1,2,3,5-tetraazanaphthalene, is recrystallized from EtOH/H_2O (9:1), light orange-yellow needles are obtained, showing a higher melting point (203 °C)[165, 293], as a triazine-based cyclic hydroxamic acid **158** forms red-colored solutions upon reaction with ferric chloride[293]. The structural relationship to the parent **154** (Section III.J.1) translates into similar properties, like the possibility of clearer monitoring of the extension of acylation reactions (bright yellow to orange-red color)[165]. Unfortunately, **158** might also undergo ring-opening by a second molecule, when activated in acylations, leading to 3-(3′-azidopicolinoyloxy)-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazine[165].

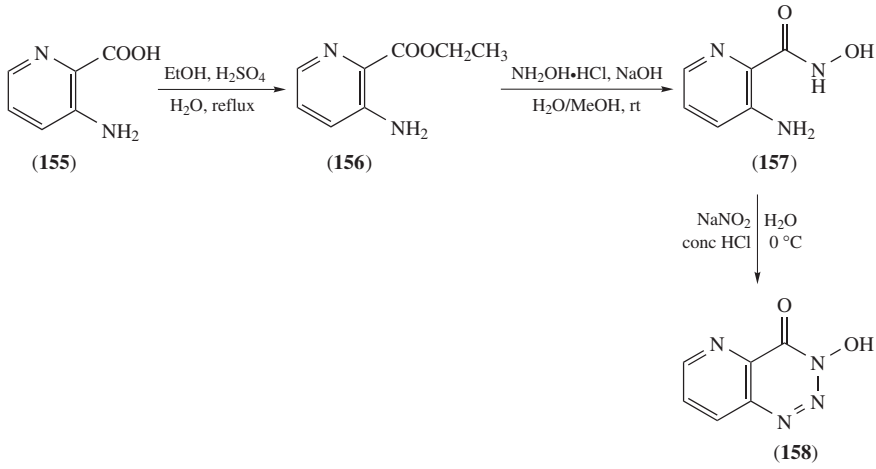
3-Hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene (**158**) was first synthesized by Harrison and Smith[293] from 3-amino-2-picolinehydroxamic acid (**157**), by diazotization with $NaNO_2$ and HCl, followed by intramolecular cyclization, in 32% yield (Scheme 38)[293]. Interestingly, a trial reaction on the 2-aminonicotin analogue was unsuccessful, due to the low reactivity of the 2-aminopyridine group[293]. However, few experimental details were given, such as the formation of the linear hydroxamic acid (**157**)[293]. Later, Carpino and coworkers detailed a synthetic approach to **157**[165]. The conversion of ethyl 3-aminopicolinate (**156**) into **157** can be quantitative in the presence of hydroxylamine hydrochloride and sodium hydroxide, during 2 days, improving the yield obtained by previous work from Harrison and Smith[166]. Carpino and coworkers also optimized the esterification of 3-aminopicolinic acid (**155**), leading to **156** (Scheme 38), by extensively refluxing the acid in absolute ethanol and concentrated sulfuric acid (68% yield)[165].

Carpino and coworkers also reported an efficient strategy for obtaining **155** from pyridine-2,3-dicarboxylic acid (**160**, Scheme 39)[165]. The transformation of **160** to the cyclic 2,3-pyridine dicarboximide (**161**), by refluxing in acetic anhydride, followed by the addition of acetamide was already reported by Sucharda many decades before (75% yield) (Scheme 39)[170]. Recently, microwave-induced condensation of **160** with ammonia has been reported with identical efficiency, but in a shorter time[171]. Subsequent Hoffmann rearrangement of the cyclic imide **161** to **155**, in the presence of sodium hypobromite



(**158**)

FIGURE 40. Structure of 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene



SCHEME 38. Synthetic strategies for the synthesis of 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene

or sodium hydroxide and bromide, has been described by some authors, sometimes with side formation of 2-aminonicotinic acid (Scheme 39)[167, 169, 170]. The detailed procedure provided by Carpino afforded the highest yield, using sodium hypobromite (60% yield)[165]. Regarding the formation of **160**, various strategies have been reported from quinoline (**162**), 2-pyridinecarboxylic acid (**159**) or 8-hydroxyquinoline (**163**) (Scheme 39). Ozonolysis and ring cleavage of quinoline (**162**) with ozone and sulfuric acid has been studied, with the highest yield being 84%[304]. Similar efficiency, although avoiding sulfuric acid, can be achieved from **159** by regioselective lithiation, with subsequent carbonylation in lithium tetramethylpiperidide (LTMP)[174]. Higher yields are obtained from **163**, which can be quantitatively and chemoselectively oxidized to **160** by treatment with dilute nitric acid[170, 172, 173].

The expected structure of **158** was confirmed after ^{1}H-NMR analysis, showing the upshifted hydrogens of the pyridine ring as double doublets[210]. Infrared spectra of **158** in KBr displayed a broad *N*-hydroxyl band at 2600 cm^{-1} and a signal, corresponding to the amide moiety of the hydroxamic acid, at 1713 cm^{-1} [165]. Additional bands were detected at 1574, 1420, 1230, 1185, 1066, 974 and 794 cm^{-1} [165]. Similarly to **154** (Section III.J.1), the tautomeric equilibrium of the hydroxylamide form of **158** with the species presenting a hydrogen bonded to *N*-1 (**158′**) or the *N*-3 oxide (**158″**) has not been studied in solid state or solution (Figure 41)[32, 293, 299].

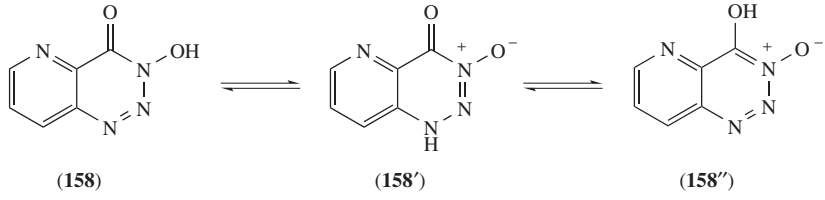
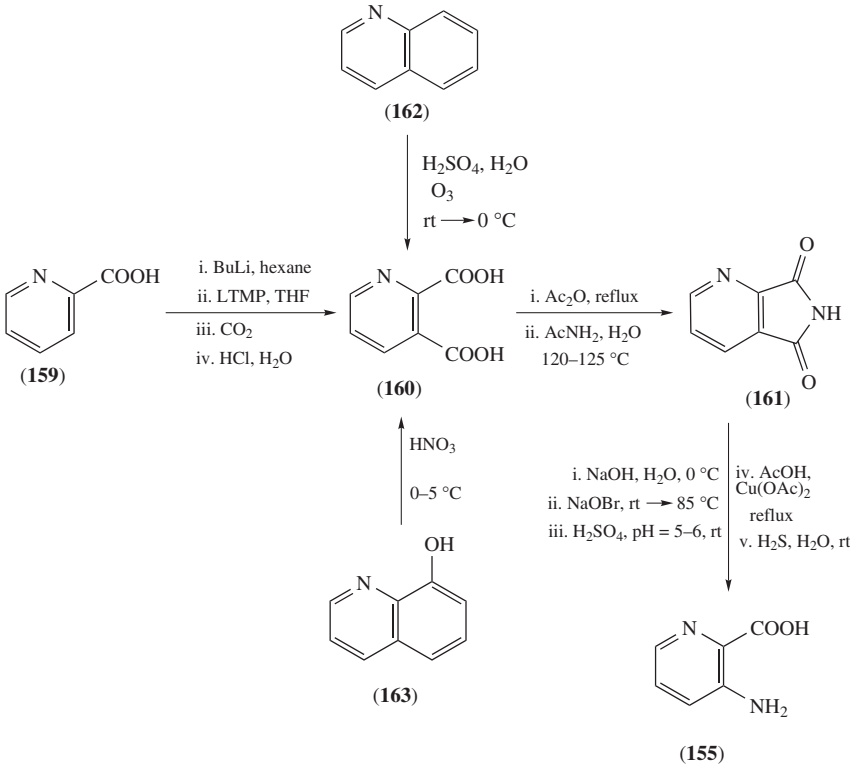


FIGURE 41. Tautomeric forms of 3-hydroxy-4-oxo-3,4-dihydro-5-azabenzo-1,2,3-triazene

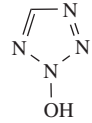


SCHEME 39. Synthetic approaches for the synthesis of **155**

Considering the NOE experiments performed on the parent 4-oxobenzotriazine, suggesting that the hydroxylamide form **158** predominates over the hydroxylimide one (**158′**), in agreement with other *N*-hydroxy-α-oxo compounds, a similar tendency is expected for **158**[32, 61, 300].

L. 2-Hydroxytetrazole

2-Hydroxytetrazole (**167**, Figure 42) is a non-natural heterocyclic compound, melting at 143–146 °C, after recrystallization from ethyl acetate[175, 176, 305]. **167** finds application as a

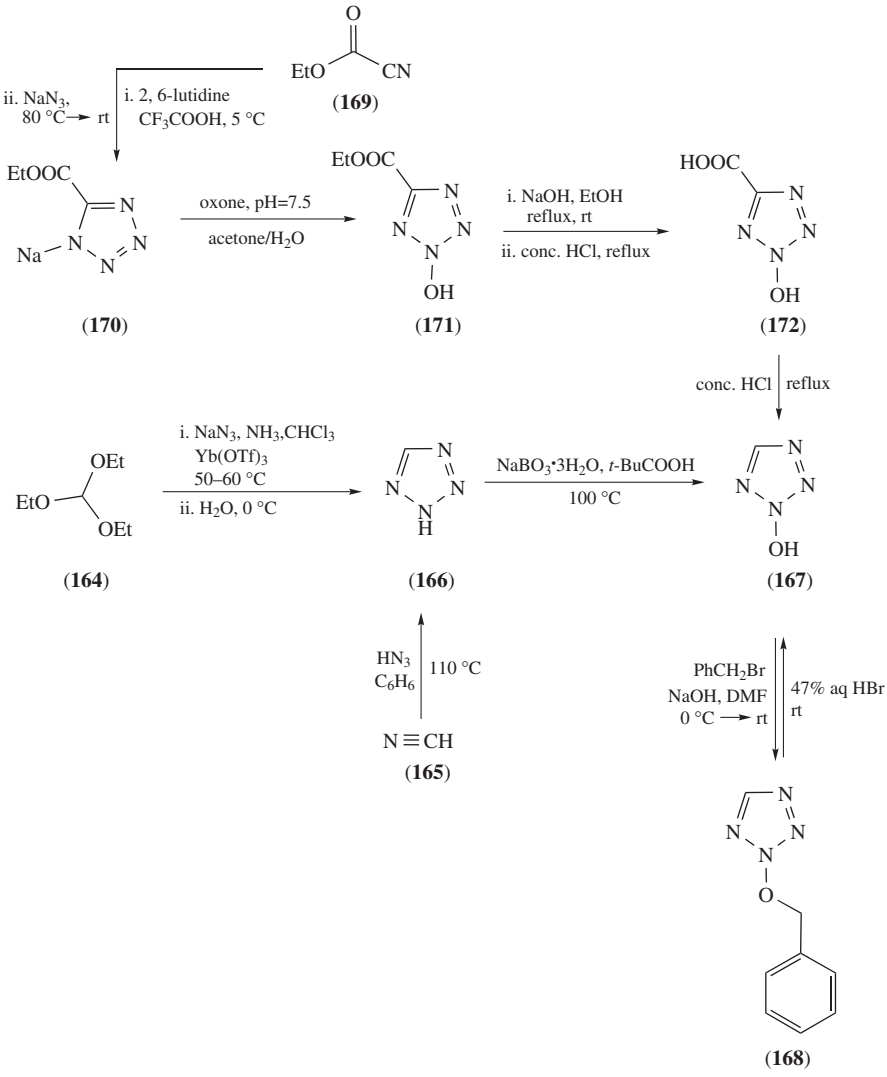


(**167**)

FIGURE 42. Structure of 2-hydroxytetrazole

propellant, apart from the high acylating character of its esters. Moreover, the remarkable stability of **167** to metabolic conditions combined with certain pharmacological activity results in an attractive drug-like profile[305–309].

Few synthetic strategies toward **167** have been reported, in contrast to its 1-hydroxy isomer, which was obtained in the 1950s[175, 310]. Its first synthesis was accomplished by Begtrup and Vedsoe fifteen years ago, by oxidation of tetrazole (**166**, Scheme 40)[175]. The analogous transformation in substituted tetrazoles is demanding, since the low HOMO of



SCHEME 40. Synthetic approaches for the synthesis of 2-hydroxytetrazole

these heterocycles poses difficulties in the oxidative process, even when strong oxidizing agents are used[305]. Nevertheless, *N*-3 oxides of 1,5- or 2,5-disubstituted tetrazoles have been recently reported, by action of hypofluorous acid[305]. The oxidation of **167** with 60% hydrogen peroxide and 3-chloroperbenzoic acid completely failed (0–3% conversion)[175]. However, **167** was observed with sodium perborate trihydrate in pivalic acid as solvent. Unfortunately, 1-hydroxytetrazole was also generated by this method (*N*-2/*N*-1 ratio = 2:1), due to its poor chemoselectivity[175]. The difficult separation of the two isomers forced the authors to carry out an extra *O*-benzylation step with sodium hydroxide and benzyl bromide, in order to facilitate the isolation of 2-benzyloxytetrazole (^{13}C NMR shows distinct C-5 signals for the *O*-benzylated derivatives)[175]. Subsequent debenzylation of 2-benzyloxy tetrazole (**168**) in the presence of aqueous hydrobromic acid afforded in 16 hours the desired **169** in a low 17% overall yield (Scheme 40)[230]. The starting **168** can be obtained from triethoxymethane (**164**), sodium azide and ammonium chloride as nitrogen source, in moderate yield and in a cost-friendly manner, or by cyclization of hydrogen cyanide (**165**) with hydrogen azide (Scheme 40)[311].

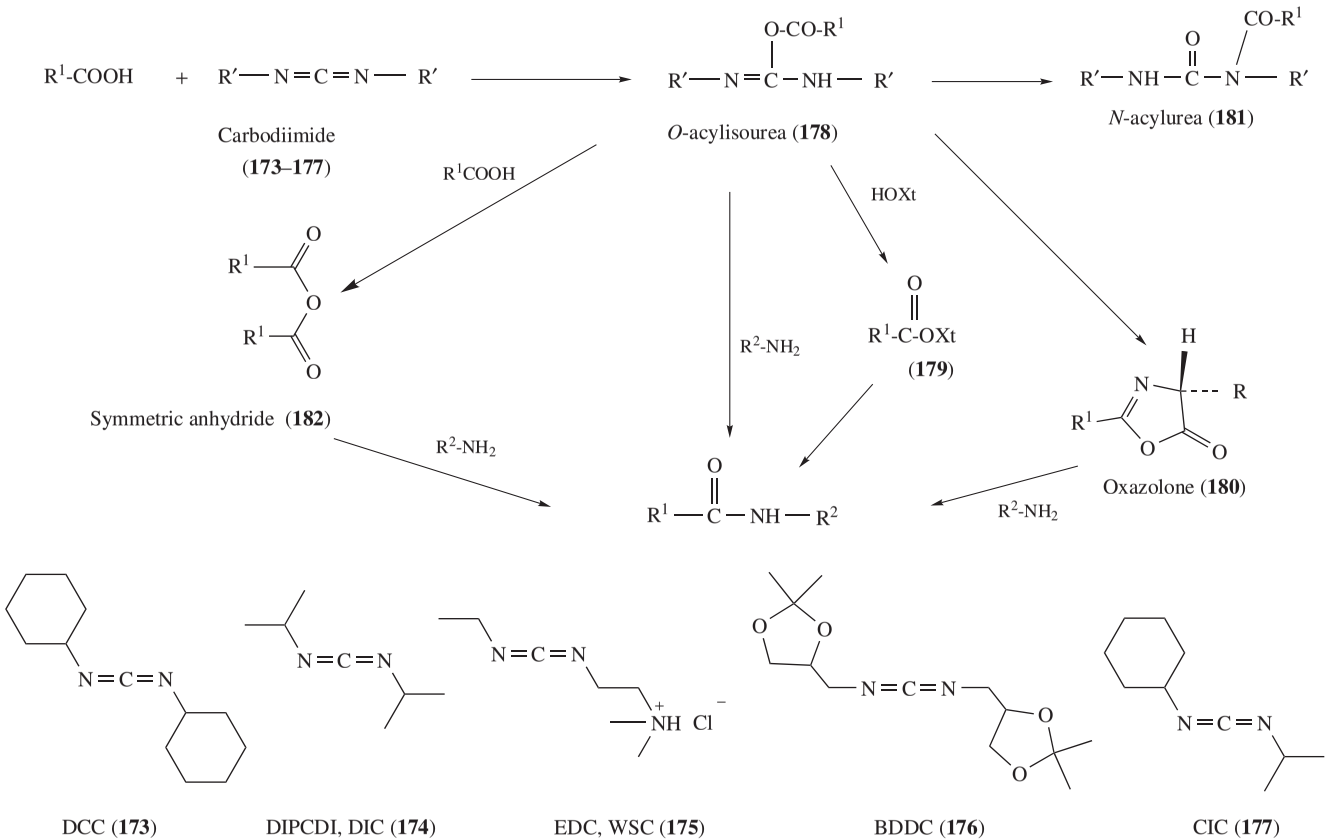
The low efficiency of Begrup's strategy prompted the search for alternative approaches. Giles and coworkers designed a facile, more efficient strategy, starting from the sodium salt of ethyl tetrazole-5-carboxylate (**170**), which can be obtained in 84% yield from ethyl cyanoformate (**169**) in the presence of 2,6-lutidine and TFA, followed by treatment with NaN_3 (Scheme 40)[312]. Oxidation of **170** takes place selectively, rendering almost exclusively ethyl *N*-2-hydroxytetrazole-5-carboxylate (**171**) by means of oxone (potassium peroxymonosulfate, $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) in 80% yield (*N*-2/*N*-1 ratio = 70:1) (Scheme 40)[312]. Subsequent hydrolysis of **171** with NaOH in refluxing EtOH affords 2-hydroxytetrazole-5-carboxylic acid (**172**) in 65% yield (Scheme 40). **167** is obtained after decarboxylation of this intermediate **172** in refluxing, concentrated hydrochloric acid for 4 days in 40% yield[312].

^{1}H-NMR spectra of **167** in D_2O display the H-5 aromatic hydrogen at δ 8.67[174]. In general, *N*-hydroxytetrazoles are more stable than C-hydroxy analogues, in light of the shorter single bonds of the former, observed by DSC. Charge distribution of the molecule also supports this hypothesis[313]. In particular, the almost planar and aromatic **167** shows enhanced stability in comparison with the 1-hydroxy isomer, according to the corresponding heats of formation (HOF), 71.9 and. 75.4 kcal mol^{-1}, respectively, calculated by the density functional method (DFT-B3LYP)[309, 313]. In spite of this relative stability, the explosive character of **167** is well known, especially when carrying out melting-point determinations[174, 312]. As a result of this observed behavior, **167** is widely used as an explosive detonator[313].

IV. *N*-HYDROXYLAMINES FOR CARBODIIMIDE-MEDIATED REACTIONS

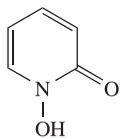
Nowadays, carbodiimides (**173**–**177**) are used with a HOXt additive as a trapping agent of the *O*-acylisourea (**178**) intermediate to form the corresponding active esters **179** (Scheme 41), which decrease the degree of racemization in numerous cases[314–321]. The highly reactive *O*-acylisourea can lead to oxazolone (**180**) formation, which facilitates the loss of chiral integrity (Scheme 41), or to an unreactive *N*-acylurea (**181**)[189, 276]. HOBt (**95**) or HOAt (**116**) and other HOXt (**8**, **31**, **46**, **53**, **64**, **75**, **86**, **89**, **91**, **99**, **105**, **112**, **129**, **140**, **148**, **154**) additives give the corresponding active esters after reaction with the *O*-acylisourea[189, 276]. The presence of a tertiary amine favors formation of the active ester[320]. Alternatively, the symmetric anhydride **182**, which is formed when 2 equivalents of *N*-protected amino acid are used with 1 equivalent of carbodiimide, can be employed as the active species (Scheme 41).

Compared with other additives, **116** forms superior active esters in terms of yield and degree of racemization in both solution and solid-phase synthesis, even when the coupling

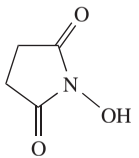


SCHEME 41. Mechanism of peptide bond formation using carbodiimide and the most common additives

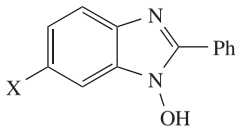
HOXt =



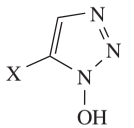
HOPy (**8**)



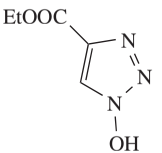
HOSu (**31**)



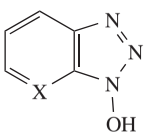
X = H, HOBI (**46**)
X = Cl, 6-Cl-HOBI (**53**)



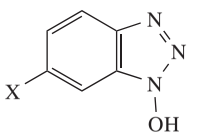
X = H (**64**)
X = CH_2OCH_3 (**86**)
X = $COCH_3$ (**89**)
X = Cl (**91**)



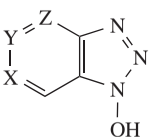
HOCt (**75**)



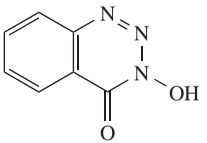
X = CH, HOBt (**95**)
X = N, HOAt (**116**)



X = Cl, 6-Cl-HOBt (**99**)
X = CF_3, 6-CF_3-HOBt (**105**)
X = NO_2, 6-NO_2-HOBt (**112**)



Y = X = CH, Z = N, 4-HOAt (**129**)
X = Z = CH, Y = N, 5-HOAt (**140**)
Y = Z = CH, X = N, 6-HOAt (**148**)



HODhbt (**154**)

SCHEME 41. (*continued*)

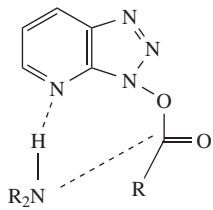
takes place with the hindered α-aminoisobutyric acid (Aib)[322–324]. The key behind the outstanding behavior of **116** is the nitrogen atom located at position 7 of the benzotriazole, which provides a double effect[276]. First, the electron-withdrawing influence of a nitrogen atom (regardless of its position) led to a better leaving group, thereby leading to greater reactivity. Second, placement of this nitrogen atom specifically at position 7 enables one to achieve a classic neighboring group effect (**183**, Figure 43), which can both increase reactivity and reduce the loss of configuration[322]. Compared to HOBt (**95**), the corresponding 6-HOAt (**148**), 5-HOAt (**140**) and 4-HOAt (**129**) all lack ability due to such a neighboring group participation, and have little influence on the extent of stereomutation during the segment coupling reaction[231, 325].

3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HODhbt, **154**) forms highly reactive esters, but their formation is accompanied by the byproduct 3-(2-azidobenzyloxy)-4-oxo-3,4-dihydro-1,2,3-benzotriazine (**184**), which can then react with the amino group to terminate chain growth (Figure 44)[189, 324].

Several coupling additives (**64**, **75**, **86**, **89**, **91**, **154**) have been evaluated in solid-phase Fmoc-based peptide synthesis in the presence of DIC (**174**)[188]. These reagents are advantageous because they don't have a UV absorption at 302 nm, thus allowing one to monitor the coupling process, a feature incompatible with Fmoc-methodology in the case of HOBt (**95**) or HOAt (**116**).

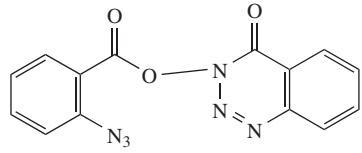
Recently, 6-Cl-HOBt (**99**) has been used in solid-phase synthesis. It is a good compromise between **95** and **116** in terms of reactivity and price[326]. Later, Carpino and coworkers described the aza derivative of **154** (HODhat, **158** and HODhad **59**, Section III.K.1)[165]. Active esters of **158** are slightly more reactive than OAt ones, which are considered the most reactive derivatives among these esters; however, the additive **158** gives the side product **185** (Figure 45), as occurs with HODhbt (**154**)[165, 324].

Because most of the benzotriazole derivatives, such as **95** and **116**, exhibit explosive properties, El-Faham and Albericio reported several *N*-hydroxylamine derivatives



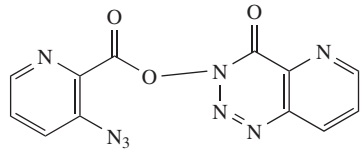
(**183**)

FIGURE 43. Neighboring group effect for HOAt



(**184**)

FIGURE 44. 3-(2-Azidobenzyloxy)-4-oxo-3,4-dihydro-1,2,3-benzotriazine as byproduct from HODhbt



(**185**)

FIGURE 45. Structure of the side product from HODhat

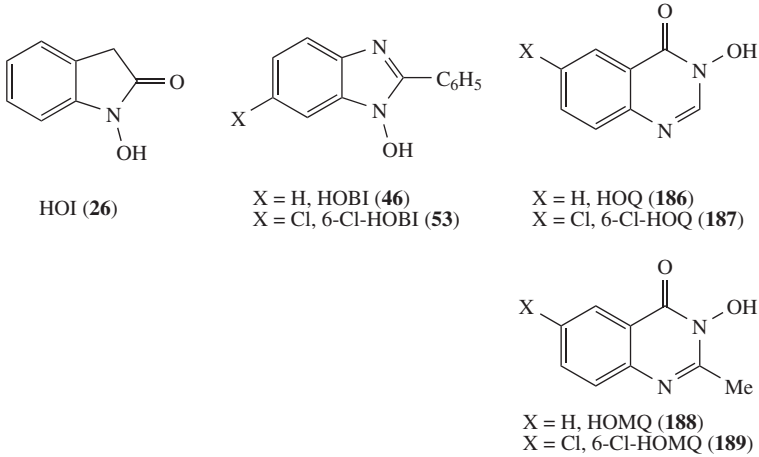


FIGURE 46. Structure of *N*-hydroxylamine derivatives reported by El-Faham and Albericio

26, **53** and **186**–**189** (Figure 46) to be used as substitutes for the **95** and **116**[79]. These *N*-hydroxylamines (**26**, **47**, **53**, **186**, **187**, **188** and **189**) performed well with DIC activation, but they did not show the same efficiency as **95** and **116** for racemization depression[79].

Later, Subirós-Funosas and colleagues reported a safe and highly efficient additive, ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma, **1**, Section III.A), to be used mainly in the carbodiimide approach for forming the peptide bond[2]. **1** displays a remarkable capacity to suppress racemization and an impressive coupling efficiency in both automated and manual synthesis. These effects are superior to those shown by **95** and comparable to **116**. Stability assays show that there is no risk of capping the resin in standard coupling conditions. Finally, calorimetry assays (DSC and ARC) confirm the explosive potential of the benzotriazole-based additives and demonstrate the lower risk of explosion induced by **1**[2].

V. *N*-HYDROXYLAMINES FOR THE PREPARATION OF ACTIVE ESTERS

The substituted hydroxylamines are designed to render the carbonyl of the acyl moiety susceptible to nucleophilic attack by an amine at room temperature to afford the active esters. Activated esters undergo aminolysis due to the electron-withdrawing ability of the

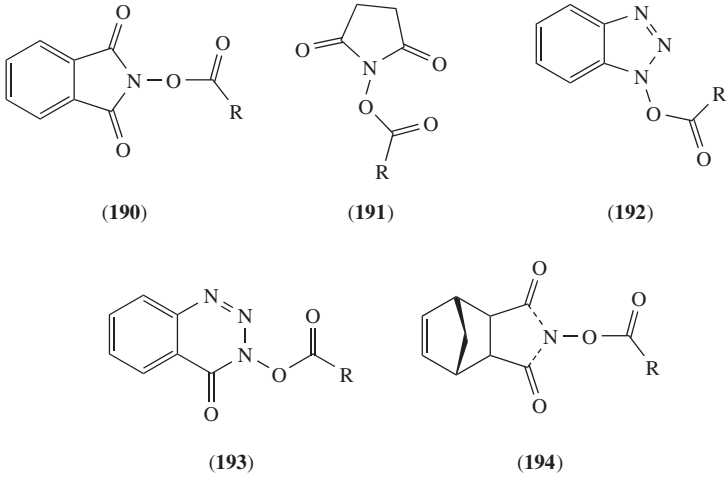


FIGURE 47. Structure of hydroxamic active esters

ester moiety. However, the esters formed from substituted hydroxamic acids are so highly activated that their reactivity cannot be explained on the basis of this property alone. An additional phenomenon is operative, i.e. neighboring atoms assist in the union of the two reactants. This neighboring group participation in the formation of a new chemical bond is referred to as *anchimeric assistance*. The reaction is, in fact, an intramolecular general base-catalyzed reaction[189, 327, 328].

The first activated esters derived from hydroxamic acids were the *o*-phthalimido (**190**) esters that liberate a water-insoluble side product, but these were soon replaced by the more versatile succinimido esters (**191**). The latter generate water-soluble *N*-hydroxysuccinimide that is easy to remove from target peptides. Additional examples of esters derived from hydroxamic acids are benzotriazolyl (**192**), 4-oxo-3,4-dihydrobenzotriazinyl esters (**193**) and *N*-hydroxy-5-norbornene-*endo*-2,3-dicarboxyimide (HONB, **194**) esters (Figure 47)[329, 330]. These are activated not so much because of the electron-withdrawing effect of the ring moieties, but because of the nature of the heterocyclic rings. All the esters mentioned above can be used as shelf-stable reagents, except benzotriazolyl esters, which decompose too readily. In addition to their use as activated forms of the *N*-alkoxycarbonylamino acids, the esters derived from hydroxamic acids are implicated as intermediates in coupling reactions in which the *N*-hydroxy compounds have been added to promote efficient coupling between an acid and a primary or secondary amine. The aminolysis of activated esters generally occurs more readily in polar solvents and is catalyzed by mild acid or 1-hydroxybenzotriazole (**95**). Transesterification and using mixed anhydrides are other methods by which activated esters can be obtained[104, 123, 327, 331–335].

VI. *N*-HYDROXYLAMINES FOR THE PREPARATION OF PHOSPHONIUM SALTS

A. HOBt Phosphonium Salts

HOBt (**95**) is currently the most frequently used activating agent for the carboxyl group of amino acids[336]. The procedure is fast and suppresses racemization, but the

intermediate esters are moisture sensitive[336]. HOBt–DCC or DIC methodology can be used in all peptide couplings. DIC is often preferred because its urea byproduct is more soluble in organic solvents than that formed from DCC. Solid-phase peptide synthesis with HOBt–DCC is widely used in combinatorial peptide synthesis taking advantage of fast reactions.

95 has been found to be a useful tool, providing simplified workup and purification procedures[337–340]. Moreover, HOBt-based phosphonium, uronium or onium salts are more reactive and their preparation will now be discussed.

1. BOP, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate

Kenner and coworkers were the first to describe the use of acylphosphonium salts as coupling reagents[341]. These species were widely adopted only after the extensive studies of Castro, Coste and coworkers, who introduced CloP (**195**) and BroP (**196**) as peptide-coupling reagents with noticeable racemization (Figure 48)[342–348]. After HOBt was discovered as a racemization suppressant, a new coupling reagent, known as BOP (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate) (**197**), was introduced in 1975 (Figure 48). **197** is a non-hygroscopic crystalline material that can be prepared effortlessly in large amounts, is easy to use and promotes rapid coupling[347, 349–351].

With regard to the mechanism, several authors have proposed that in the absence of the nucleophile that is incorporated in the reagent, for example HOBt in **197**, the active species is the acyloxyphosphonium salt[352–355]. Castro, Dormoy and coworkers have suggested that this salt is very reactive and even at low temperatures will react immediately with carboxylate ions present in the medium to give the symmetrical anhydride[342–344]. This pathway is supported by kinetic studies carried out by Hudson (Scheme 42)[356]. Several years later, Kim and Patel reported that this intermediate (**198**) could exist at −20 °C when **197** was used as a coupling reagent[357]. However, Coste and Campagne suggested that this species is very unstable and even at low temperatures undergoes conversion to an active ester[358]. In spite of this controversy, it is widely accepted that the active species is an active ester when phosphonium salts containing nucleophilic derivatives are used.

The formation of OBt ester is achieved in the presence of 1 equivalent of a tertiary base such as DIEA, NMM or TMP[343, 359, 360]. The presence of an extra equivalent of HOBt accelerates the coupling and also reduces the loss of configuration[344].

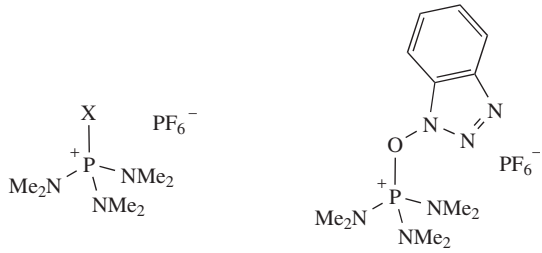
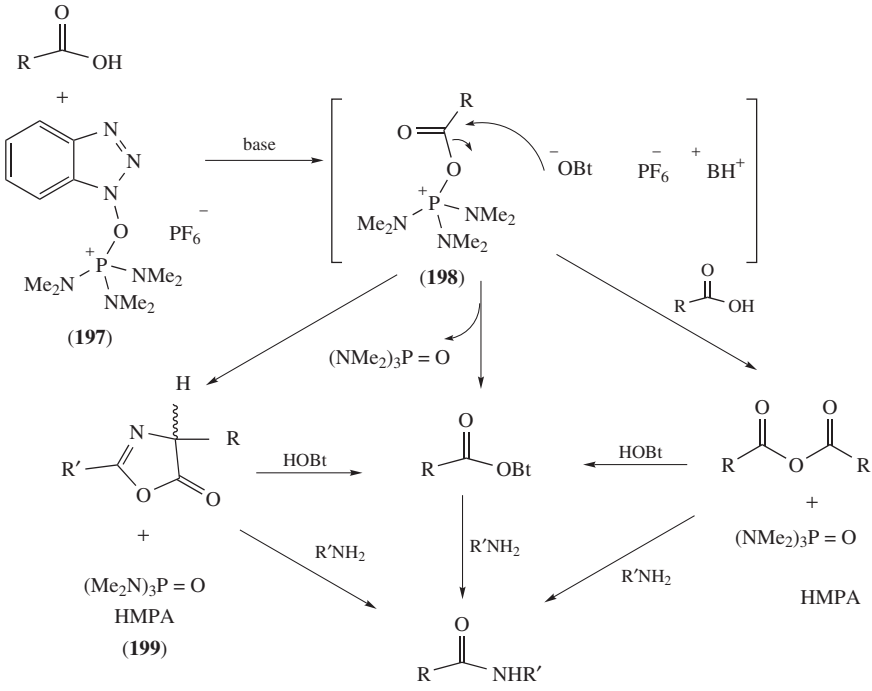


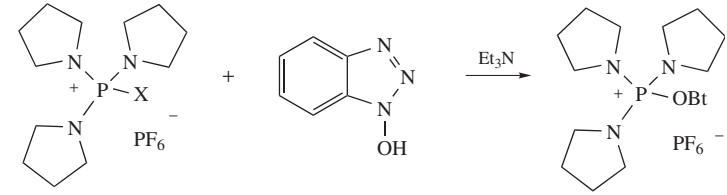
FIGURE 48. Structure of tris(dimethylamino)phosphonium salts



SCHEME 42. Mechanism of BOP-mediated reaction

2. PyBOP, benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate

PyBOP (**202**) was prepared by reaction of PyCloP (**200**) or PyBroP (**201**) with HOBt (**95**) in the presence of triethyl amine (Scheme 43). In these compounds the dimethylamino moiety is replaced by pyrrolidine[342, 361, 362]. These reagents prevent the generation of poisonous hexamethylphosphoramide (HMPA, **199**, Scheme 42) byproduct[356]. In a subsequent study Castro, Dormory and coworkers reported that halogenophosphonium reagents



SCHEME 43. Synthesis of PyBOP

often give better results than other phosphonium–HOBt reagents for the coupling of *N*-methylated amino acid[344].

3. Other HOBt phosphonium salts

Since the discovery of HOBt-mediated coupling reagents, many racemization suppressants have been exploited as a part of the composition of new peptide-coupling reagents. For example, 2-(benzotriazol-1-yloxy)-1,3-dimethyl-2-pyrrolidin-1-yl-1,3,2-diazaphospholidinium hexafluorophosphate (BOMP, **203**) was introduced as a useful reagent for peptide assembly[363]. PyNOP (**204**), PyFOP (**205**) and PyFNBOP (**206**), PyCloK (**207**) were prepared in this regard and serve as efficient peptide-coupling reagents for the synthesis of dipeptides bearing *N*-methyl amino acids (Figure 49)[165, 360–365].

B. HOAt Phosphonium Salts

Phosphonium salts derived from HOAt, such as (7-azabenzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate (AOP, **208**) and (7-azabenzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP, **209**) (Figure 50), have also been prepared and are generally more efficient than BOP and PyBOP as coupling reagents (Figure 48)[323, 366–370]. The pyrrolidino derivative **209** is slightly more reactive than the dimethylamino derivative **208**, and does not release HMPA (**199**) in the activation step.

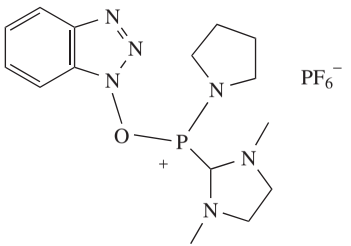
C. HODhbt Phosphonium Salts

HODhbt (**154**) has been reported as a coupling additive that can indicate the completion of acylation by color change[101, 189]. Unfortunately, **154** has been reported to give a relatively higher degree of racemization than other azole derivatives in the presence of DIC when poly(ethylene glycol)-cross-linked polyamide (PEGA)-bound dipeptide was used for peptide synthesis[188]. Fully protected amino acid esters of HODhbt are stable crystalline solids, which can be stored for long periods at low temperature. However, a ring-opening side-reaction leading to 2-azidobenzoic acid Dhbt ester **184** was observed in DCC-mediated HODhbt conditions[296]. Fmoc-amino acid esters with HODhbt have been prepared in high yield[371, 372].

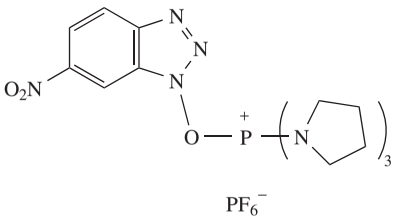
Recently, Carpino and coworkers described the phosphonium salts of HODhbt (PyDOP, **210**) and the aza derivative (PyDAOP, **211**) (Figure 51)[165]. The active esters of **211** additive are slightly more reactive than OAt ones, which are considered the most reactive derivatives among these esters; however, **211** gives the side product **185**, as occurs with **154** (Figure 45)[165].

D. Oxyma Phosphonium Salts (PyOxP, PyOxB)

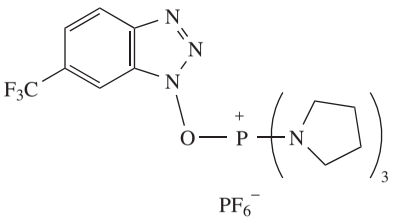
Very recently, Subirós-Funosas, El-Faham and Albericio reported the phosphonium salts of Oxyma (**1**), *O*-[(1-cyano-2-ethoxy-2-oxoethyliden)amino]oxytri(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyOxP, **212**) and its tetrafluoroborate (PyOxB, **213**) (Figure 52) version, as an efficient, racemization-suppressing coupling reagent for the assembly of hindered peptides, performing better than classical benzotriazole aminium salts and similarly to the recently introduced uronium salt COMU (that will be discussed later)[373]. Cyclization models revealed the advantages of the use of **213**, which rendered a higher percentage of cyclic peptide than other known phosphonium salts[373].



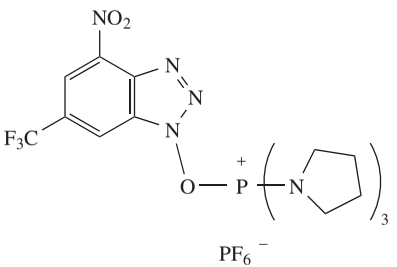
BOMP (**203**)



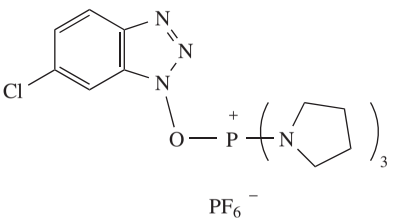
PyNOP (**204**)



PyFOP (**205**)

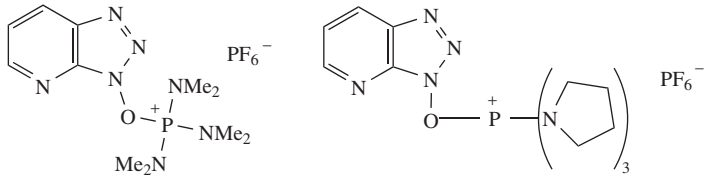


PyFNBOP (**206**)



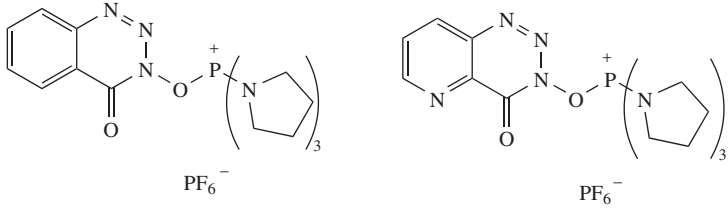
PyCloK (**207**)

FIGURE 49. Structures of other HOBt-derived phosphonium salts



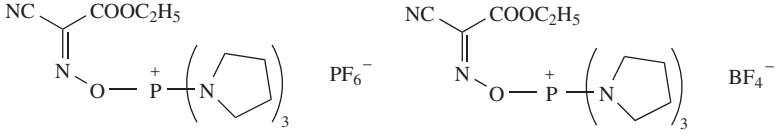
AOP (**208**) PyAOP (**209**)

FIGURE 50. Structure of HOAt-based phosphonium salts



PyDOP (**210**) PyDAOP (**211**)

FIGURE 51. Structure of HODhbt- and HODhat-based phosphonium salts



PyOxP (**212**) PyOxB (**213**)

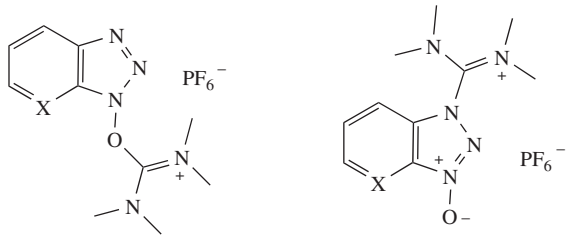
FIGURE 52. Structure of Oxyma-based phosphonium salts

VII. *N*-HYDROXYLAMINES FOR THE PREPARATION OF URONIUM/IMINIUM SALTS

Iminium salts were initially assigned to be as uronium-type structure **214**, presumably by analogy with the corresponding phosphonium salts, which bear a positive carbon instead of the phosphonium residue[366]. Nevertheless, it has been shown by X-ray analysis that the salts crystallize as aminium salts (guanidinium *N*-oxides) (**215**) rather than the corresponding uronium salts (Figure 53)[374–384].

A. *N*-Hydroxylamines for the Preparation of Tetramethyl Uronium/Iminium Salts

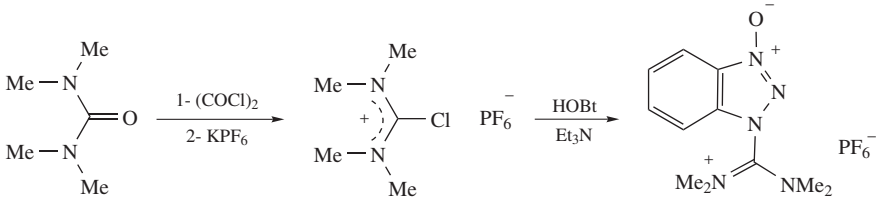
The preparation of these commercially available reagents is achieved by treatment of tetramethylurea (TMU, **216**) with $(COCl)_2$ in toluene followed by transformation of the dichloro salts into the corresponding chlorouronium hexafluorophosphate salt (TMU-Cl, **217**, Scheme 44), by exchange with NH_4PF_6 or KPF_6 and then reaction of **217** with



X = CH; *O*-HBTU (**214a**)
X = N; *O*-HATU (**214b**)

X = CH; *N*-HBTU (**215a**)
X = N; *N*-HATU (**215b**)

FIGURE 53. Structure of HOBt and HOAt-derived uronium/iminium salts



TMU (**216**) TMU-Cl (**217**) *N*-HBTU (**218**)

SCHEME 44. Synthesis of *N*-HBTU

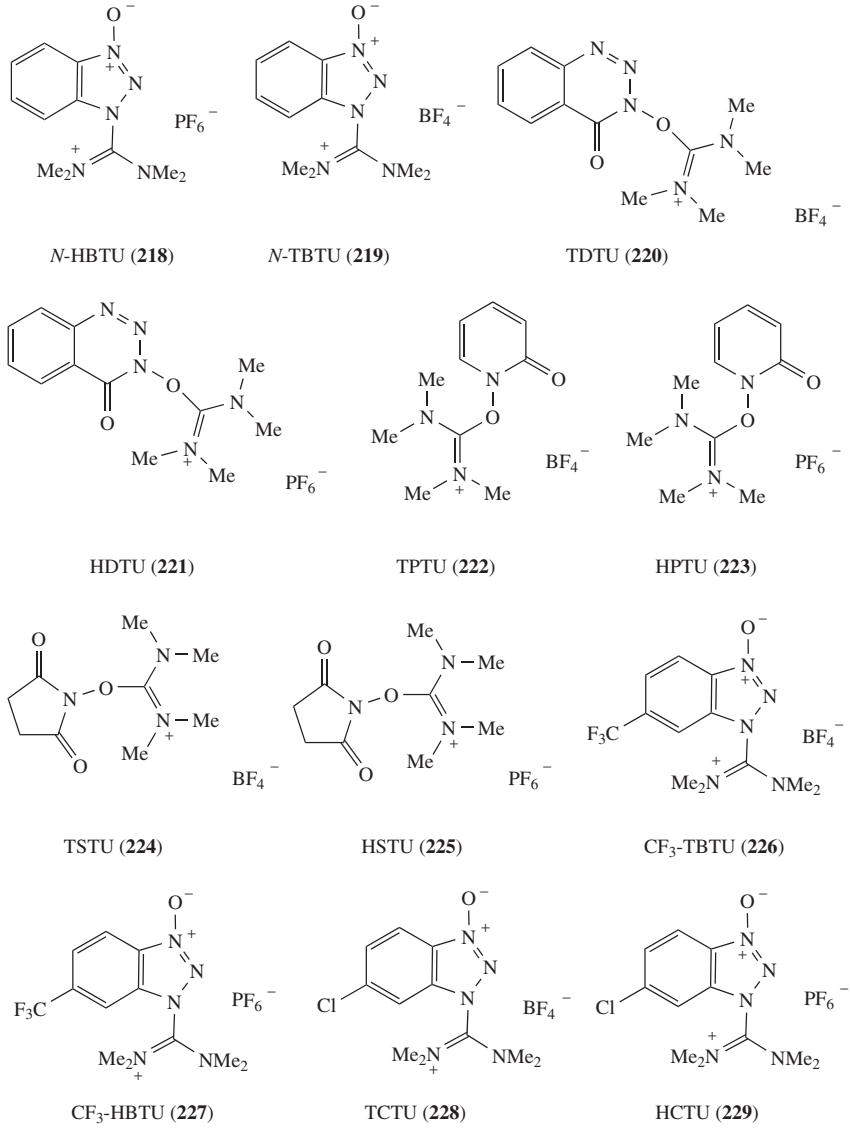
HOXt to afford the corresponding iminium/uronium salts **218**–**223** (Figure 54)[380, 381]. Chlorouronium salt **217** has also been prepared by replacement of the extremely toxic $COCl_2$ by oxalyl chloride or $POCl_3$[382–384]. *N*-HBTU (**218**) has been obtained using a one-pot procedure in organic solvents, and the analogous tetrafluoroborate reagent (*N*-TBTU, **219**) procedure was prepared similary (Scheme 44).

This one-pot method has also been applied to the preparation of the HODhbt derivatives 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDTU, **220**) and HDTU (**221**), the pyridinone derivatives 2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU,**222** and HPTU, **223**) and the hydroxysuccinimide derivatives 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU, **224**), which are also commercially available (Figure 54)[380]. The hexafluorophosphate analogue (HSTU, **225**) has also been prepared following the same strategy (Figure 54)[382, 383].

Other 1-hydroxybenzotriazole derivatives containing electron-withdrawing groups, such as the 6-trifluoromethyl derivative (CF_3-TBTU, **226** and CF_3-HBTU **227**) and 6-chloro derivative (TCTU, **228** and HCTU, **229**), have been prepared from tetrafluoromethyl chloroformamidinium hexafluorophosphate (Figure 54)[364].

The analogue uronium salts containing the HOAt structure (**116**) instead of HOBt (**95**) have been prepared from the TMU-Cl (**217**) salts to give the corresponding reagents *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate (*N*-HATU, **230**) and tetrafluoroborate (*N*-TATU, **231**)[379], which have been shown to be *N*-oxides with aminium structures (Figure 54)[101, 188, 369, 370]. The two tetramethylurea-derived thiouronium reagents, the HOAt derivative **232** (HATTU) and the *N*-hydroxy-2-pyridinethione derivatives **233** (HOTT), have been prepared,

both following Knorr's strategy (Figure 54)[382, 383, 385–387]. The *O*-[(ethoxycarbonyl) cyanomethylene amino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TOTU **234** and HOTU **235**) has been reported and developed with other derivatives (**236**–**238**) by El-Faham, Albericio and coworkers (Figure 55)[162]. TNTU (**239**) and TPhTU (**240**) were prepared using the same strategy (Scheme 44)[388].



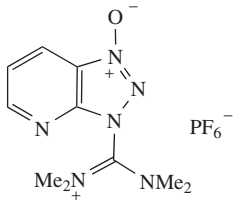
N-HBTU (**218**) *N*-TBTU (**219**) TDTU (**220**)

HDTU (**221**) TPTU (**222**) HPTU (**223**)

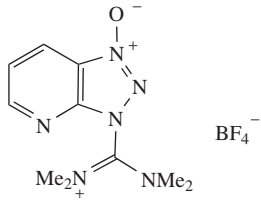
TSTU (**224**) HSTU (**225**) CF_3-TBTU (**226**)

CF_3-HBTU (**227**) TCTU (**228**) HCTU (**229**)

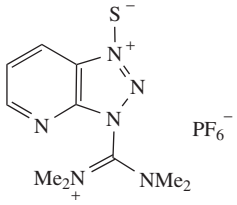
FIGURE 54. Structure of various uronium/iminium salts



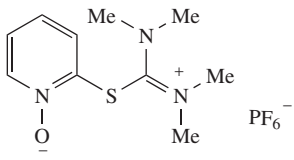
N-HATU (**230**)



N-TATU (**231**)



N-HATTU (**232**)



N-HOTT (**233**)

FIGURE 54. (*continued*)

B. *N*-Hydroxylamines for the Preparation of bis-Pyrrolidino Iminium Salts

The chlorouronium salts (BTCFH, **242**) derived from dipyrrolidin-1-methanone (dipyrrolidinocarbonyl) **241** have been prepared by chlorination with phosgene, oxalyl chloride or $POCl_3$ followed by treatment with aqueous KPF_6[380–384]. HOBt (**95**) has been reacted with these chlorouronium reagents to give the corresponding iminium salt HBPyU **243** (Scheme 45).

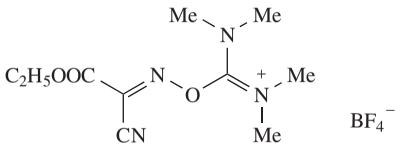
The related HXPyU derived from HOAt (**116**), HODhbt (**154**) and HODhat (**158**) have been prepared by a similar method to that described above and afford HAPyU (**244**), HATPyU (**245**), HDPyU (**246**) and HDAPyU (**247**) (Figure 56). NMR spectral analysis showed that both **244** and **245** exist in the *N*-form (Figure 56)[375, 376].

C. *N*-Hydroxylamines for the Preparation of bis-Piperidino Iminium Salts

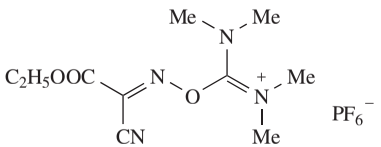
The chlorouronium salts derived from dipiperidinocarbonyl have been prepared by using the above method and then treated with HOXt to give the corresponding iminium salts HBPipU (**248**), HAPipU (**249**) and TOPPipU (**250**) (Figure 57)[323, 389, 390].

D. *N*-Hydroxylamines for the Preparation of Imidazolium Uronium Salts

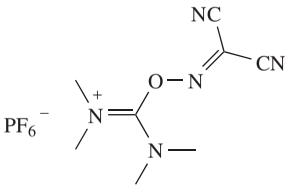
The chloroimidazolium salt **252** (CIP) has been obtained by chlorination of the commercial 1,3-dimethylimidazolidin-2-one (**251**) with phosgene or oxalyl chloride followed by anion interchange with NH_4PF_6, followed by reaction with HOXt to afford the corresponding uronium salts HBMDU (**253**) and HAMDU (**254**) (Scheme 46)[390].



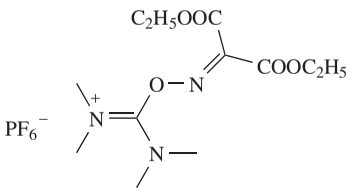
TOTU (**234**)



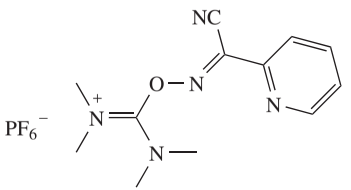
HOTU (**235**)



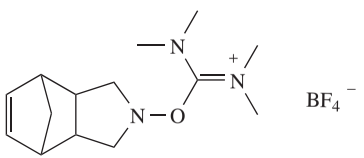
(**236**)



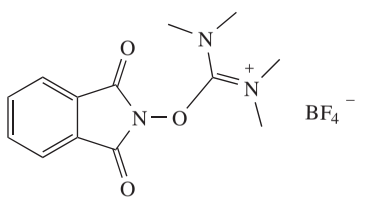
(**237**)



(**238**)

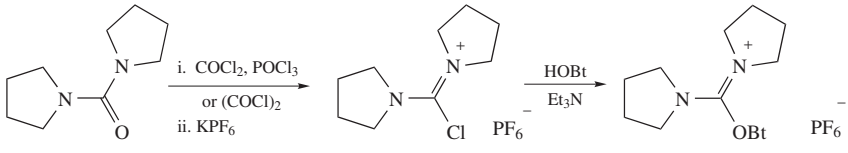


TNTU (**239**)



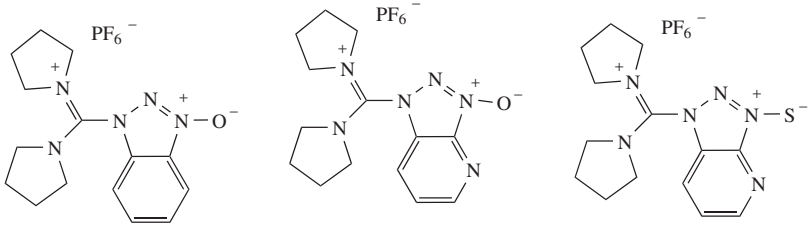
TPhTU (**240**)

FIGURE 55. Structure of various uronium/iminium salts

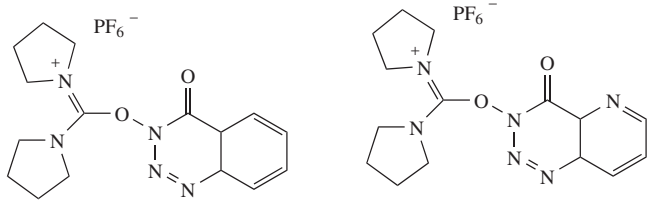


(**241**) BTCFH (**242**) HBPyU (**243**)

SCHEME 45. Synthesis of HBPyU

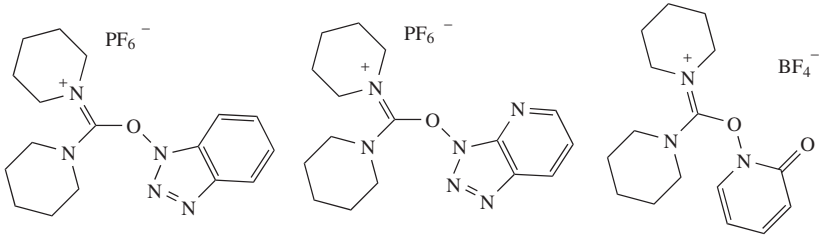


HBPyU (**243**) HAPyU (**244**) HATPyU (**245**)



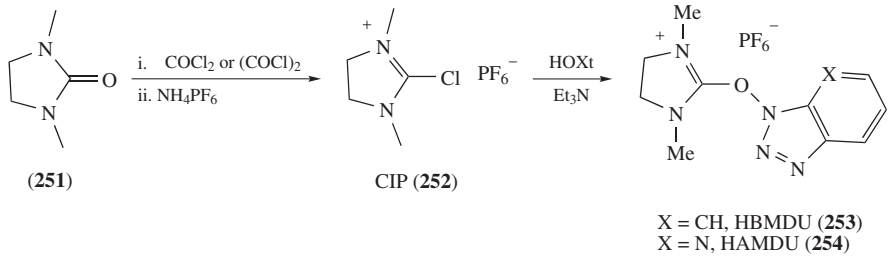
HDPyU (**246**) HDAPyU (**247**)

FIGURE 56. Structure of various bis-pyrrolidino iminium salts



HBPipU (**248**) HAPipU (**249**) TOPPipU (**250**)

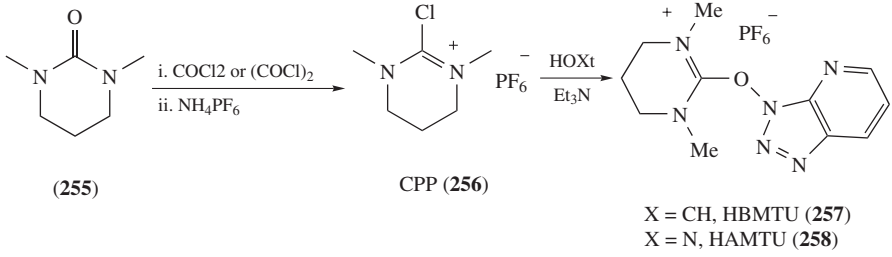
FIGURE 57. Structure of various bis-piperidino iminium salts



SCHEME 46. Synthesis of imidazolium uronium salts

E. *N*-Hydroxylamines for the Preparation of Pyrimidinium Uronium Salts

The chloro pyrimidinium salt (CPP, **256**) has been obtained by chlorination of the commercial 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (**255**) with phosgene or oxalyl chloride followed by anion interchange with KPF_6, followed by reaction with HOXt to afford the corresponding uronium salts HBMTU (**257**) and HAMTU (**258**) (Scheme 47)[390].

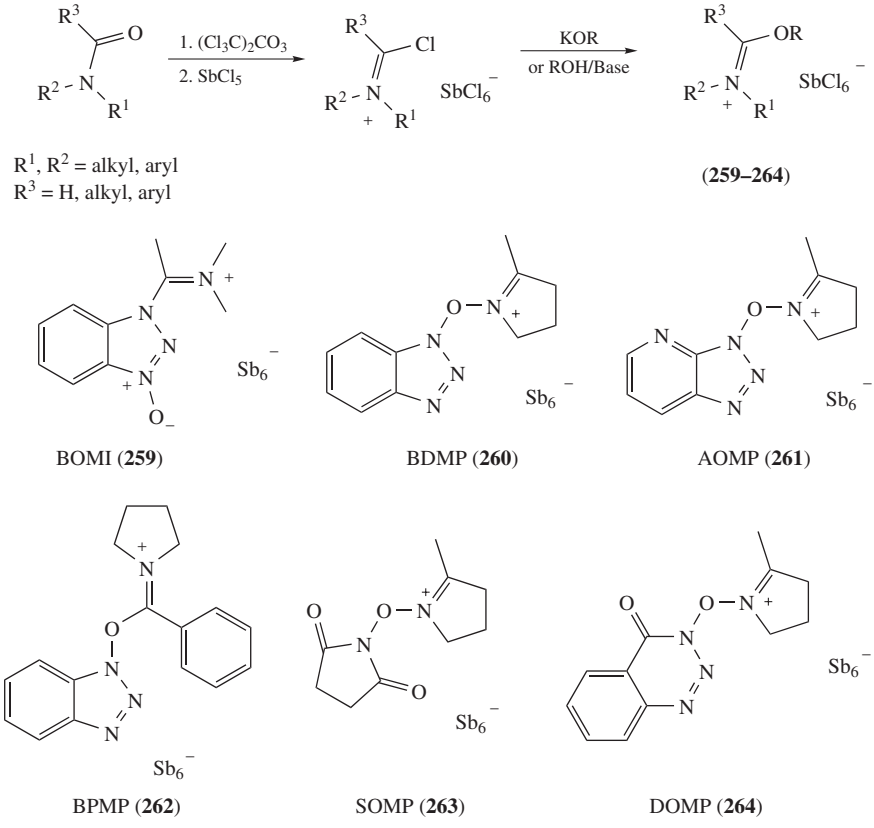


SCHEME 47. Synthesis of pyrimidinium uronium salts

F. *N*-Hydroxylamines for the Preparation of Unsymmetric Uronium/Iminium Salts

Several iminium salts derived from carboxamides have been prepared[391]. Thus, DMF has been transformed into an iminium chloride by reaction with triphosgene followed by stabilization with $SbCl_5$. Subsequent reaction with HOBt (**95**) gives benzotriazol-1-yloxy-*N*,*N*-dimethylmethaniminium hexachloroantimonate **259** (BOMI) (Scheme 48). Its structure was determined by X-ray analysis. The same methodology has been employed for the preparation of the immonium reagent **260** (BDMP) from *N*-methylpyrrolidine (NMP) and HOBt (**95**), in 80% overall yield (Scheme 48)[392]. When **95** is replaced by HOAt (**116**), the related reagent **261** (AOMP) is obtained[393]. The HOBt derived reagent **262** (BPMP), succinimide derived reagent **263** (SOMP) and the HODhbt derived reagent **264** (DOMP) have also been prepared from the more highly substituted *N*,*N*-tetramethylenebenzamide (Scheme 48)[393].

A few years ago, El-Faham and Albericio described a new family of iminium-type coupling reagents based on the differences in the carbocation skeletons of the coupling reagents, which correlated with differences in stability and reactivity[394, 395]. The unsymmetric tetra-substituted urea have been prepared from commercially available *N*,*N*-dialkylcarbamoyl chloride to afford the corresponding urea. The urea derivatives have been

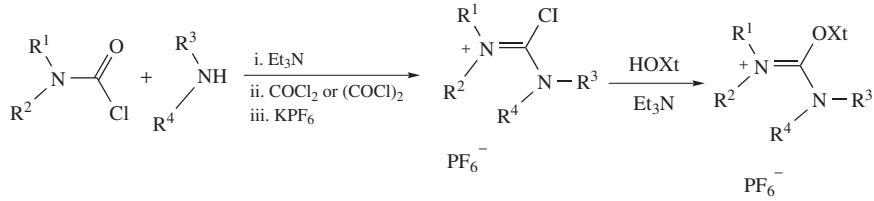


SCHEME 48. Synthesis of antimonate uronium salts

transformed into the corresponding chlorouronium salt by treatment with phosgene or oxalyl chloride followed by anionic interchange with KPF_6. Finally, reaction with HOBt (**95**) or HOAt (**116**) in the presence of triethylamine gave the corresponding aminium salts **265**–**276** (Scheme 49).

G. *N*-Hydroxylamines for the Preparation of Morpholino-based Uronium/Iminium Salts

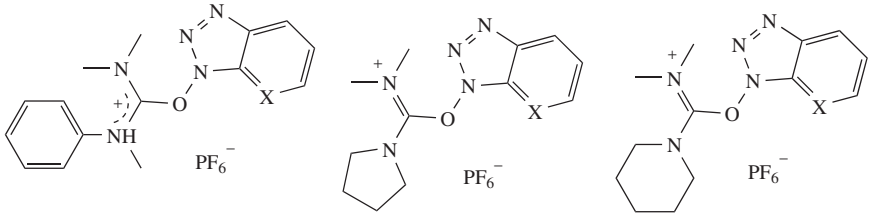
Very recently, El-Faham and Albericio described a new family of immonium-type coupling reagents derived from dimethylmorpholino urea[396, 397]. The morpholine moiety has a remarkable effect on the stability and reactivity as well as decreasing the racemization extent. The recent uronium-type reagents can be readily prepared by treating *N*,*N*-methylcarbamoyl chloride (**277**) with morpholine (**278**) to give the corresponding urea derivatives (Scheme 50). The urea derivatives then react with oxalyl chloride to yield the corresponding chloro salts **279**, which are stabilized by the formation of a PF_6 salt (Scheme 50). Subsequent reaction with HOXt (HOBt, HOAt or 6-Cl-HOBt) in the



$R^1 = R^2 = CH_3$ or $R^1 = R^2 = C_2H_5$

$R^3 = CH_3$, $R^4 = C_6H_5$
$R^3R^4 = -(CH_2)_4-$,
$R^3R^4 = -(CH_2)_5-$,
or $R^3 = R^4 = C_2H_5$

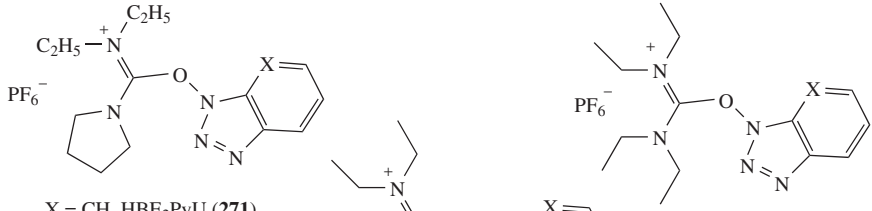
(**265–276**)



X = CH, HBPTU (**265**)
X = N, HAPTU (**266**)

X = CH, HBM_2PyU (**267**)
X = N, HAM_2PyU (**268**)

X = CH, HBM_2PipU (**269**)
X = N, HAM_2PipU (**270**)



X = CH, HBE_2PyU (**271**)
X = N, HAE_2PyU (**272**)

X = CH, HBE_2PipU (**273**)
X = N, HAE_2PipU (**274**)

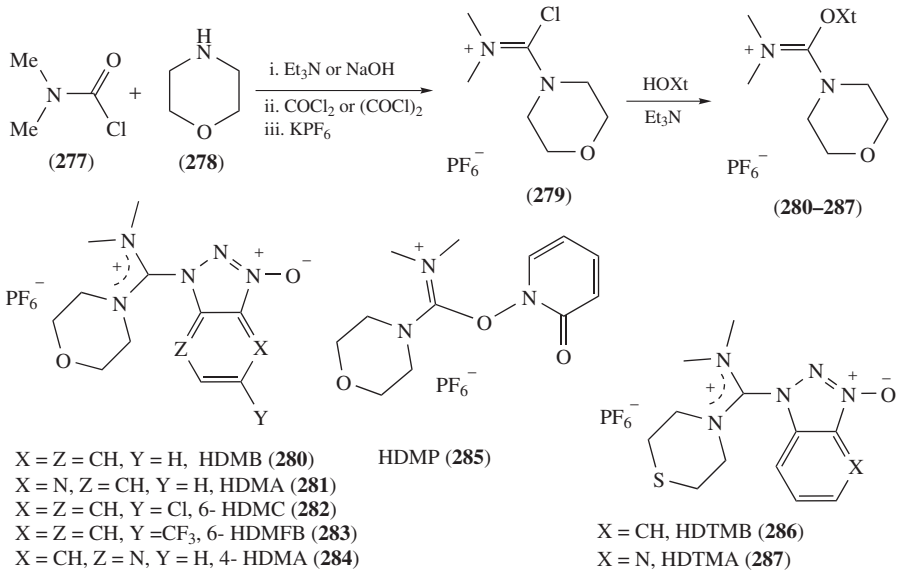
X = CH, HBTeU (**275**)
X = N, HATeU (**276**)

SCHEME 49. Synthesis of unsymmetrical uronium/iminium salts

presence of a tertiary amine such as Et_3N affords the desired compounds **280**–**287** as crystalline and shelf-stable solids (Scheme 50).

H. Oxyma for the Preparation of Uronium Salts

In a recent study, Subirós-Funosas, El-Faham and Albericio and coworkers showed that Oxyma (**1**) is an excellent replacement for HOBt (**95**) and its analogues[2]. Also, a third generation of uronium salt, COMU (**289**), which involves the combination of a



SCHEME 50. Synthesis of morpholino uronium/iminium salts

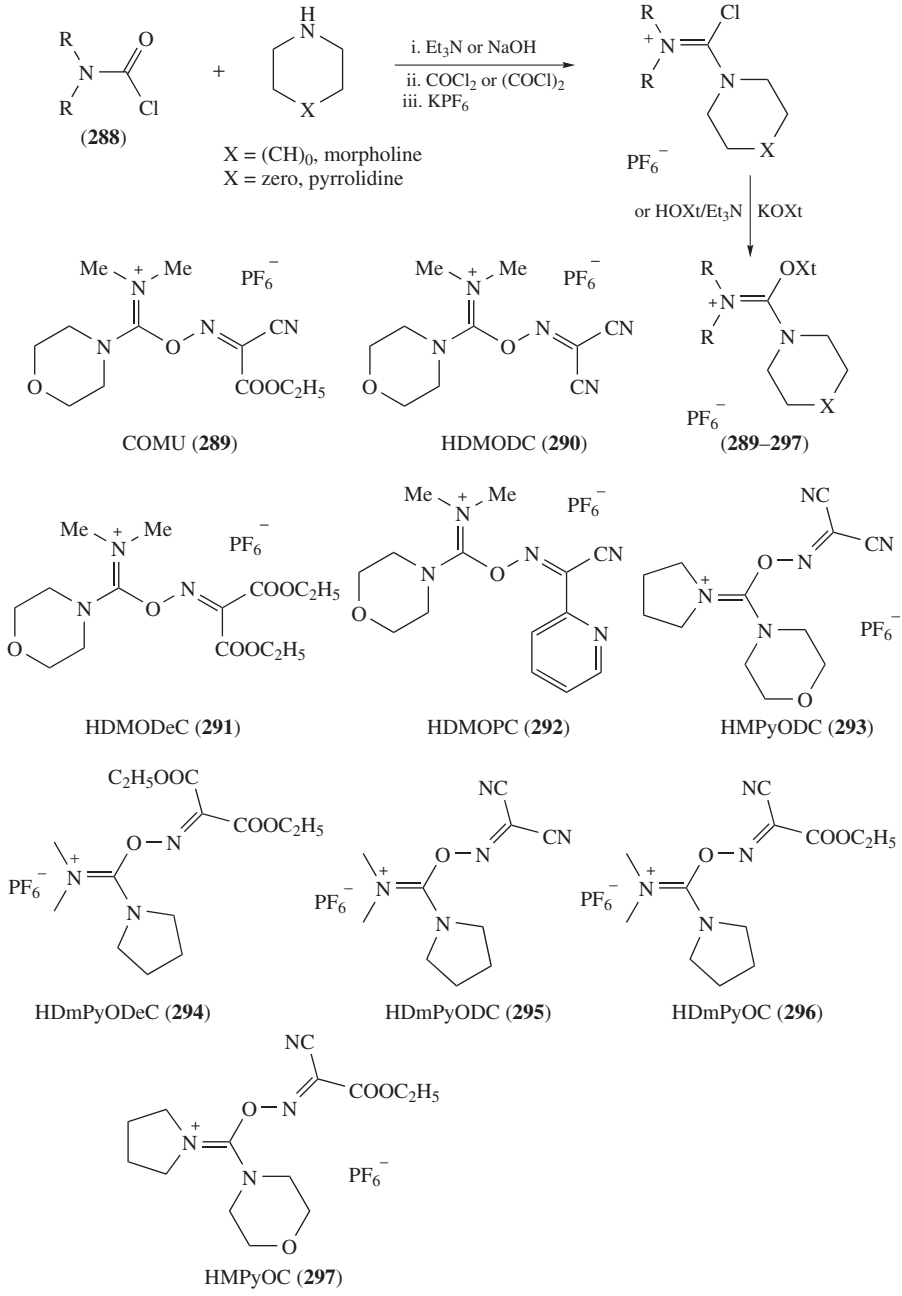
morpholinium-based immonium moiety as proton acceptor and **1** as leaving group, was devised by the same authors to provide a superior and safe coupling reagent for amide bond formation starting from **288** (Scheme 51)[162, 396, 397].

The oxygen in the iminium structure increased the stability of the coupling reagent compared with the tetramethyl derivatives. Furthermore, Oxyma (**1**) derivatives have higher stability than the benzotriazole derivatives, **230** and **218**. These observations are of practical relevance for both solid-phase and solution strategies. Although a typical protocol for the use of these reagents involves 2 equivalents of base, usually DIEA, the presence of the morpholinium moiety also allows good results with **289** when just 1 equivalent of DIEA is used. Alternatively, the less basic TMP (2 or even 1 equivalent) can be used instead of DIEA and provides good yields and reduces racemization[162].

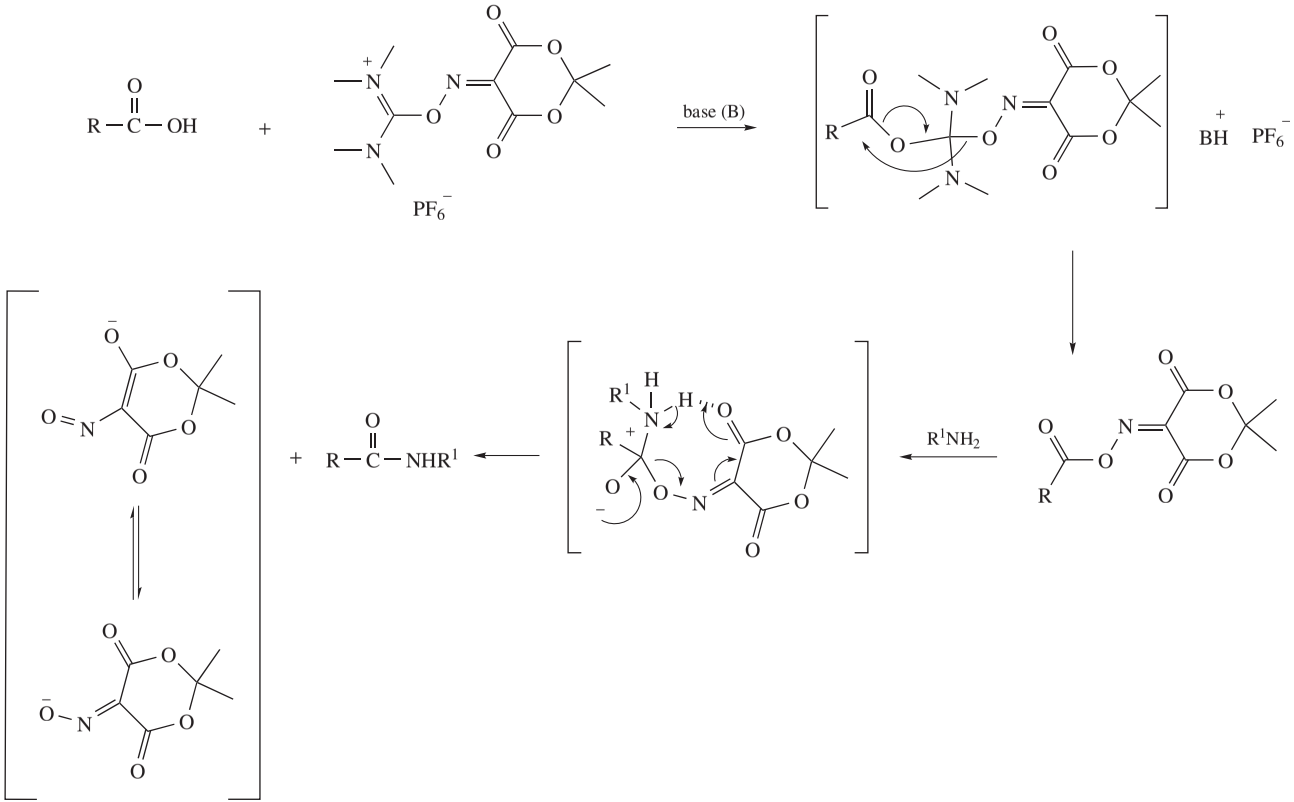
Furthermore, **289** is compatible with microwave-assisted peptide synthesizers[30]. Consistent with previous reports, **290** displayed higher efficiency than **230** and **218** in the demanding synthesis of the Aib derivative of the Leu–Enkephalin pentapeptide and produced no Oxyma-based byproducts. Thus, the combination of microwave irradiation and **289** resulted in a similar performance to that observed by manual synthesis in a considerably shorter time. Also, the Oxyma-based salts showed much better results than other oxime derivatives (**290**–**297**, Scheme 51)[215].

I. Isonitroso Meldrum's Acid Reagents for the Preparation of Uronium Salts

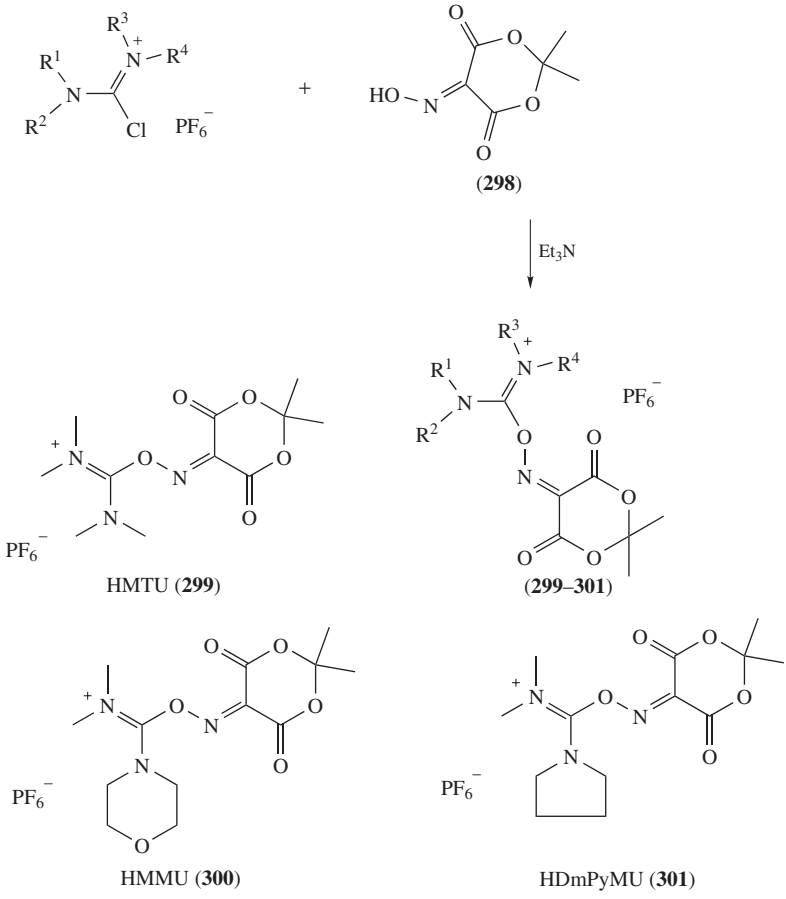
Very recently, El-Faham, Subirós-Funosas and Albericio reported a new family of morpholino coupling reagents based on isonitroso Meldrum's acid (**298**), because of its structural similarity to Oxyma (**2**) with consideration that the introduction of two carbonyl groups in the six-member cyclic structure should enhance its reactivity due to the electron-withdrawing effect of the carbonyl group (Scheme 52)[398]. Although related to



SCHEME 51. Synthesis of Oxyma-based coupling reagents



SCHEME 52. Proposed reaction mechanism with uronium salt of isonitroso Meldrum's acid



SCHEME 53. Synthesis of uronium salt of isonitroso Meldrum's acid

Oxyma in the same way, esters of Oxyma are not able to participate in the neighboring group effects commonly thought to enhance the effectiveness of cyclic Oxyma derivatives relative to those of Oxyma. Any neighboring group effect occurring in either case would involve the carbonyl function, as shown in the proposed mechanism in Scheme 52.

The novel uronium coupling reagents were prepared by reaction of the isonitroso Meldrum's acid (**298**) with the chloro salts in the presence of a tertiary amine such as Et_3N which afford the desired compound **299**–**301** as crystalline solids (Scheme 53).

The novel uronium coupling reagents were tested and compared to classical immonium salts HDMB (**280**) and HDMA (**281**) by using these models, which involve stepwise and also [2+1] segment coupling as well as solid-phase peptide synthesis[398].

VIII. *N*-HYDROXYLAMINES FOR THE PREPARATION OF PHOSPHORIC ACID DERIVATIVES

Since Takeuchi and Yamada[399] introduced the mixed carboxylic-phosphoric anhydride method using DPPA (**302**) from diphenylphosphorochloridate and sodium azide to peptide chemistry in 1972, various organophosphorus compounds have been developed as peptide-coupling reagents (Figure 58)[399–403].

On the basis of the earlier development of organophosphorus reagents, a great amount of effort has been focused on developing various coupling reagents of a similar kind, such as NDPP (**303**) and BDP (**304**) (Figure 58)[404–408].

A wider variety of phosphorous reagents, DEPAT (**305**), DPPAT (**306**), DEBPO (**307**), DOPBO (**308**), DOPBT (**309**) and DEPBT (**310**), have been prepared following a similar protocol (Scheme 54)[407–409]. **310** has been evaluated against other peptide-coupling reagents and gave good results in segment coupling reactions. Although the racemization-suppressing capacity of HODhbt (**154**) is greater than that of HOBt (**95**), its utility was limited due to side reactions.

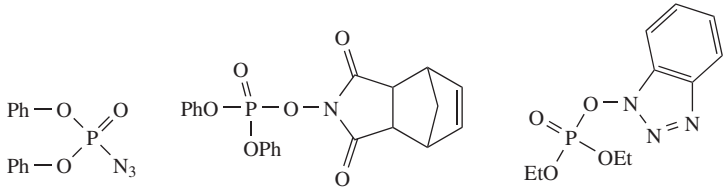
Carpino and coworkers introduced the organophosphorus reagents DEPAT (**305**) and DPPAT (**306**) (Scheme 54)[165]. In this case the neighboring group effects believed to be relevant to the properties of HOAt (**116**) are superimposed on the effects that enhance the efficiency of the phosphorus moiety. On the basis of the results described, these effects are related to the larger rate with which protected amino acids are converted to their active esters by the phosphorus derivatives.

Recently, phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester, diphenylphosphinic acid 2-phenylbenzimidazol-1-yl ester (Scheme 55) and phosphoric acid diphenyl ester and 2-phenylbenzimidazol-1-yl ester (**311**–**313**) have been reported as highly efficient coupling reagents[153, 156]. Their efficiency was evaluated through the synthesis of a range of amides and peptides, and the extent of racemization was found to be negligible[153].

IX. *N*-HYDROXYLAMINES FOR THE PREPARATION OF SULFONIC ACID DERIVATIVES

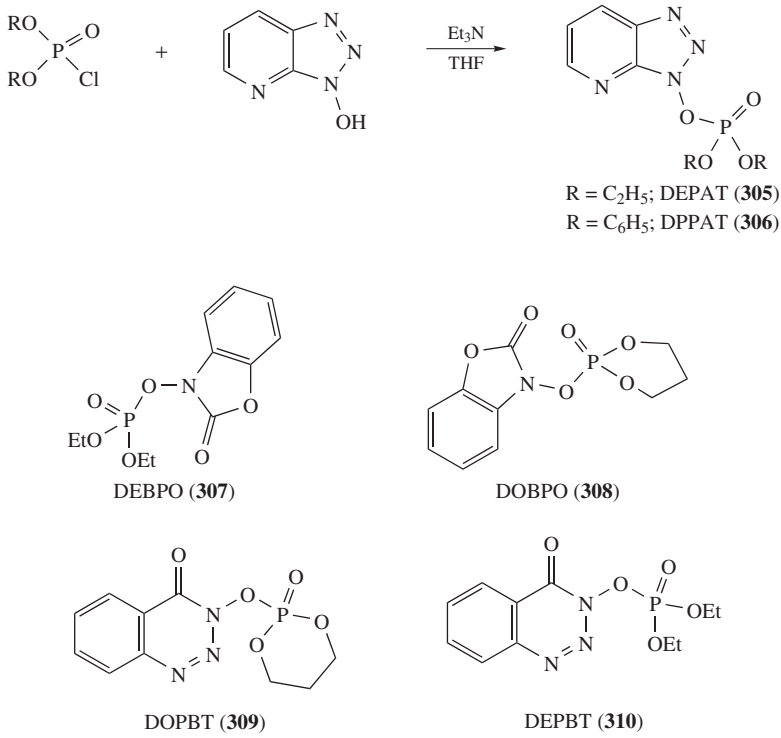
Esters of sulfonic acids and HOBt (**95**) related to those described for the phosphorus series have also been used for peptide coupling[4, 410–413]. The reactivity of such sulfonate esters was shown to be directly related to the presence of electron-withdrawing substituent in both **95** and the sulfonic acid moieties[414–417].

This methodology has seen little practical application however, since, depending on the basicity or reactivity of the amino component of the coupling process, the use of such sulfonate esters (**314**–**327**) for *in situ* coupling via the formation of an active ester is often compromised by formation of a sulfonamide byproduct (Scheme 56)[407, 408]. Such



DPPA (**302**) NDPP (**303**) BDP (**304**)

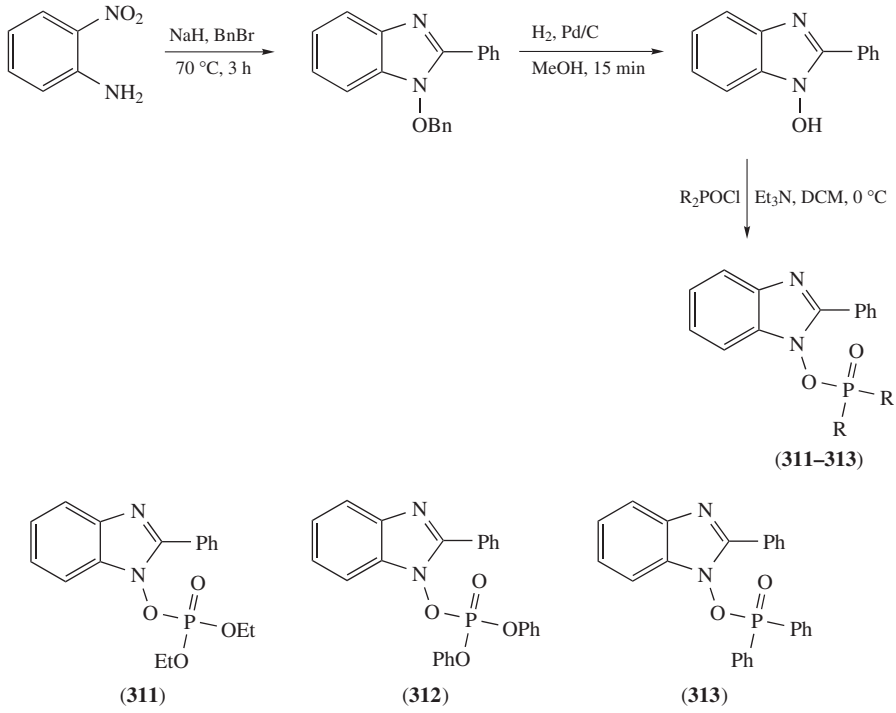
FIGURE 58. Stucture of DPPA, NDPP and BDP



SCHEME 54. Synthesis and structure of various organophosphorus coupling reagents

byproduct formation which, among amino acid derivatives, is particularly prominent with proline derivatives, can be avoided by preactivation of the reactive carboxylic acid component[418]. On the other hand, in the use of these reagents for segment coupling, especially if such conversions are slow, use of a preactivation step is counterproductive since loss of configuration at the C-terminal carboxylic acid residue directly increases with preactivation time[419]. As demonstrated in other systems, the substitution of HOAt (**116**) for **95** is expected to reduce the extent of configurational loss, although the advantages of **116** are lost at long preactivation times. The sulfonate esters were prepared by reaction of HOXt with the sulfonyl chloride in the presence of triethylamine (Scheme 56).

Khattab described a new family of sulfonate ester-type coupling reagents which differs in its leaving group[420]. The sulfonate ester coupling reagents ethyl 2-cyano-2-(naphthalen-2-ylsulfonyloxyimino)acetate (NpsOXY, **324**) and ethyl 2-cyano-2-(*p*-tosyloxyimino)acetate (TsOXY, **325**) are more efficient alternatives to the benzotriazole sulfonate esters in terms of racemization suppression and coupling effectiveness (Scheme 56). Both Oxyma (**1**) and its related sulfonate esters can be handled with a considerably lower risk than the explosive benzotriazole and its derivatives. 2-Oxopyridin-1(*2H*)-yl naphthalene-2-sulfonate (NpsOPy, **326**) and 2-oxopyridin-1(*2H*)-yl 4-methylbenzenesulfonate (TsOPy, **327**) sulfonate esters derived from 1-hydroxypyridin-2(*1H*)-one were also successfully used as new coupling reagents, requiring a longer preactivation time during the coupling process (Scheme 56). An improvement in yield



SCHEME 55. Synthesis of phosphorus reagents derived from 1-hydroxy-2-phenylbenzimidazole

and almost comparable optical purity to that of the 1-hydroxybenzotriazole (**95**) and 1-hydroxy-7-azabenzotriazole (**116**) analogues was observed[420].

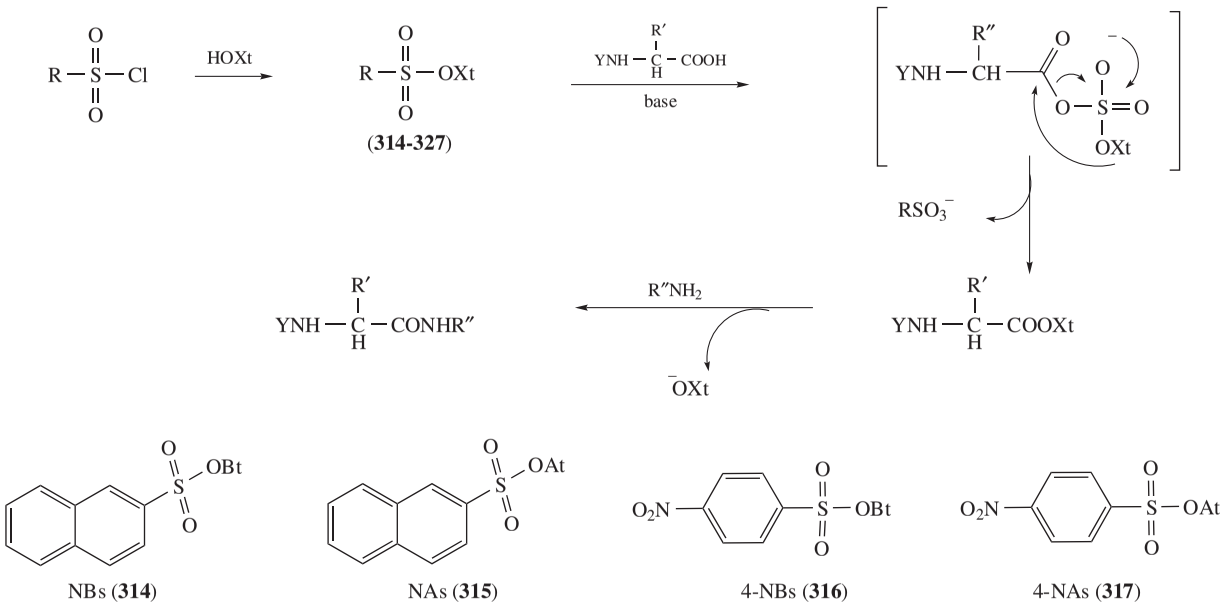
X. *N*-HYDROXYLAMINES FOR THE PREPARATION OF POLYMER-SUPPORTED REAGENTS

For the synthesis of peptides in solution phase, only a few solid-phase-supported reagents have been described.

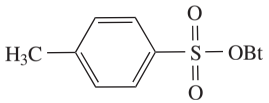
A. Polymer-bound HOBt Reagents

Polymer-bound HOBt (**328**) has been used for the formation of medium ring lactams with DCC in the presence of resin-bound esters and also for amides from primary and secondary amines (Figure 59). Polymer-bound TBTU (**329**) has also been used for the same purpose (Figure 59)[421–423].

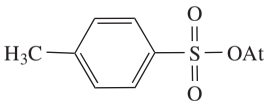
The polymer-supported HOBt derivative **330**, bonded by a sulfonamide group to polystyrene, reacted with carboxylic acids in the presence of PyBroP (**201**) to give the corresponding active ester (Figure 60). Subsequent addition of amines afforded the corresponding amides in an automated procedure[100].



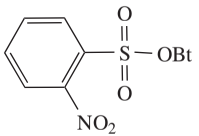
SCHEME 56. Synthesis and mechanism of peptide bond formation of organosulfur reagents



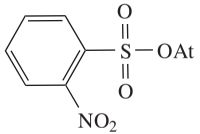
TBs (**318**)



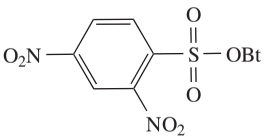
TAs (**319**)



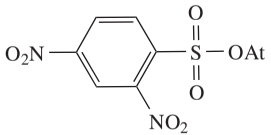
2-NBs (**320**)



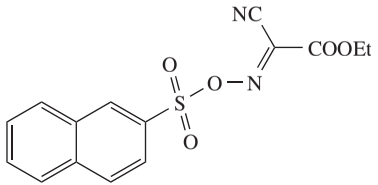
2-NAs (**321**)



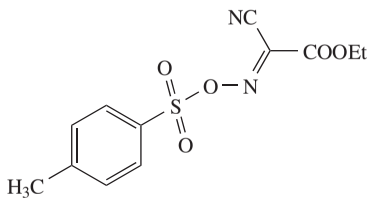
DNBs (**322**)



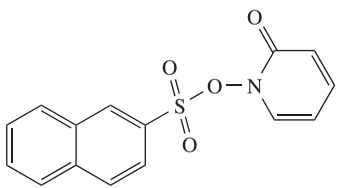
DNAs (**323**)



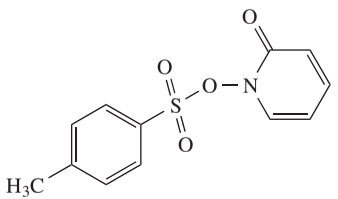
NpsOXY (**324**)



TsOXY (**325**)

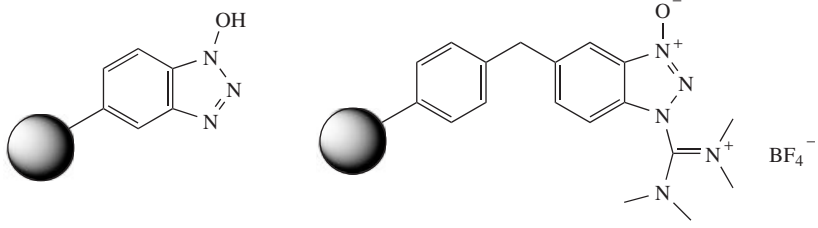


NpsOPy (**326**)



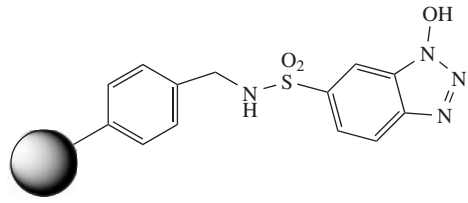
TsOPy (**327**)

SCHEME 56. (*continued*)



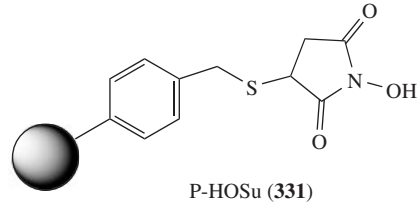
P-HOBt (**328**) P-TBTU (**329**)

FIGURE 59. Stucture of P-HOBt and P-TBTU



P- SO_2-HOBt (**330**)

FIGURE 60. Stucture of P-SO_2-HOBt



P-HOSu (**331**)

FIGURE 61. Stucture of P-HOSu

B. Polymer-bound HOSu Reagents

N-Hydroxysuccinimide bound to Merrifield and Argopore™ resins (**331**) also give resin-bound active esters, which are transformed into amides when reacted with primary, branched primary and secondary amines (Figure 61)[424].

XI. OTHER APPLICATIONS IN PEPTIDE SYNTHESIS

Peptide chemistry is often accompanied by the appearance of side reactions, occurring during activation of the *C*-terminal acid and coupling with the *N*-terminus. Acid or basic treatments include premature removal of the *N*-protecting group of a proresidue, and the deguanylidation of an Arg containing peptide leading to the corresponding Orn analogue when the side-chain of the Arg is unprotected[101, 425–431]. One of the most relevant undesired reactions is the intramolecular cyclization of aspartic acid (Asp) residue to give

amino-succinyl units, commonly called aspartimides (abbreviated as Asi, Asu or Asc), as a result of the nucleophilic attack of the amide nitrogen of the preceding residue to the β-carboxyl moiety of Asp[432, 433]. This amino-succinyl moiety can subsequently undergo opening by many nucleophiles, like water, obtaining a mixture of the isoaspartyl-β-peptide, the unmodified α-peptide and even the racemized versions[221, 434, 435].

Aspartimide formation is reported to arise under mild basic coupling conditions and after treatment of the peptide with strong acids, such as TFA or HF[432, 435–439]. In addition, the required piperidine treatment for removal of the Fmoc group also generates α- and β-piperidides[432, 437, 440, 441]. The extent of aspartimide formation and the ratio of byproducts is influenced by the type of base/acid used, β-carboxyl group, resin, temperature, solvent, sequence and conformation[434, 435, 437, 442–447]. Like most peptide-associated byproducts arising in peptide synthesis, formation of aspartimides and derivatives results in permanent modification of the peptide chain, posing significant difficulties in their purification. This event is especially troublesome in the case of APIs, even when such impurities are found in minimal amounts.

Besides its application in peptide bond formation and in the minimization of related side reactions, *N*-hydroxylamine-based additives are also beneficial in reducing the impact of other non-coupling derived byproducts. Thus, after the removal of the Fmoc group from the *N*-terminal of the peptide resin and the corresponding washings with the solvent, 3–4 washings with 0.1 M HOBt (**95**, Section III.H.1)/Oxyma (**1**, Section III.A) solution in DMF/NMP minimizes the removal of the Fmoc group of the next amino acid. Similarly, in a peptide resin containing an Arg residue with unprotected side-chain, before the incorporation of the incoming amino acids, washing with 0.1 M HOBt (**95**, Section III.H.1)/Oxyma (**1**, Section III.A) solution in DMF/NMP reduces Orn formation. The positive effect induced by *N*-hydroxyamines has also been observed in the base-catalyzed unwanted cyclization of Asp to generate aspartimide units[2, 162, 249, 276, 337, 382]. This strategy might not completely suppress aspartimide formation, but in syntheses of low- to mid-prone sequences it is usually sufficient. Alternative approaches have been developed, such as the use of sterically-hindered bases and protecting groups, mild-cleavable *N*-α-protecting groups, or the pseudo-proline approach, but they are rather expensive, difficult to synthesize/introduce, require additional steps and depend on the protection scheme[436, 440–452]. In contrast, *N*-hydroxylamines commonly used as additives in peptide synthesis are easily available, are of low cost and their reaction is faster.

The unique acidic properties of *N*-hydroxylamines ($pKa = 2–10$) are assumed to be responsible for this behavior, since they create a competition with the Asp-X amide backbone for the base, considered as the key step of aspartimide formation[221]. The positive effect induced by the presence of acidic *N*-hydroxylamines was first and unexpectedly observed during coupling in a Asp(OBzl)-Gly dipeptide model[280]. Addition of *N*-hydroxysuccinimide (HOSu, **31**, Section III.D.1) ($pKa = 5.1$) resulted in a 3-fold decrease in the cyclization rate of Asp to amino-succinyl residue, whereas 1-hydroxybenzotriazole (**95**, Section III.H.1) ($pKa = 4.3$) induced 20 times more inhibition than the experiment without additive[221]. It was also found that concentration of the additives is a key factor in the suppression of aspartimides, and that use of an equimolar amount of base and additive is the most efficient combination[221]. Interestingly, it was also noted that the DIC/HOBt approach gives rise to a lower percentage of byproducts than using HOBt-based TBTU and DIEA, presumably due to the absence of base in the coupling mixture[453]. In addition, an excess of coupling reagents leads to an increase in the extent of this side reaction[450].

Later, with the rise of the Fmoc/*t*-Bu scheme as the predominant protecting strategy, the impact of the inclusion of *N*-hydroxylamines in piperidine solutions was evaluated[442, 446, 447]. Similarly to what was observed during coupling in solution, equimolar amounts of weakly acidic additives, in respect to the base, substantially reduce aspartimide formation[442]. Thus, 2% of **95** (Section III.H.1) in 20% piperidine in DMF

resulted in an increase of the target peptide from 40% to 67%[447]. The presence of **95** was also beneficial in reducing to traces the amount of amino-succinyl peptide formed in peptides adopting conformations favorable toward this intramolecular cyclization[446, 447]. Increasing amounts of additive have been shown to induce higher suppression[447, 454].

Outstanding aspartimide-suppressant procedures have been described using *N*-hydroxylamines, like the combination of **95**, piperazine and microwave irradiation or the use of the cocktail hexamethyleneimine/*N*-methylpyrrolidine/HOBt/NMP/DMSO 4:50:4:71:71 (v/v/w/v/v), which minimizes to 1–5% the impact of aspartimide formation[453, 455–457]. Recently, HOAt (**116**, Section III.I.1), the 7-aza-analogue of HOBt (**95**, Section III.H), proved to be at least equally efficient as the parent benzotriazole[454]. The best results, however, are achieved by the presence of Oxyma (**1**, Section III.A)[454].

XII. ACKNOWLEDGMENT

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Diazohydroxides, diazoethers and related species

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I. INTRODUCTION

Diazohydroxides, Ar−N=N−OH, diazoethers, Ar−N=N−OR, and related species can be considered to be derived from oximes, R^1R^2C=N−OH, by substitution of the trigonal carbon by nitrogen. As expected from such atom substitution, oximes will have a different reactivity compared to that of diazohydroxides or diazoethers in spite of sharing some common features such as the *Z*−*E* (*cis*−*trans*, *syn*−*anti*) isomerism. Oximes are usually obtained by nucleophilic addition of hydroxylamine to aldehydes or ketones, and probably their most important reaction is the Beckmann rearrangement to yield amides, while diazohydroxides and diazoethers are obtained by nucleophilic addition to diazonium ions, and the formed diazohydroxides and, especially, the diazoethers are rather labile species that may split homolytically to yield reduction products.

It may be convenient, therefore, to highlight such reactivity features by providing a brief introduction to the chemistry of diazohydroxides and diazoethers. Since different aspects of the chemistry of oximes are covered by different authors in the present volume, the reader is referred to the corresponding chapter for further information on their properties and reactivity.

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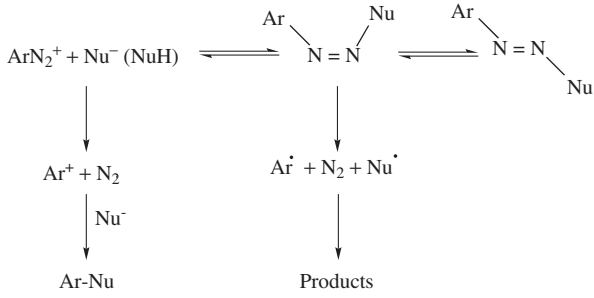
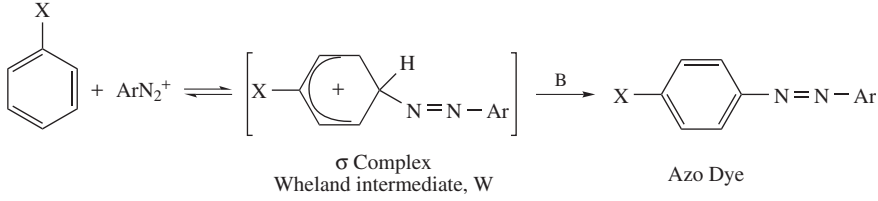
Arenediazonium (ArN_2^+) ions may function as Lewis acids reacting with nucleophiles (Lewis bases, Nu^- or NuH followed by loss of a proton) to give covalently bonded adducts, $ArN_2{-}Nu$, at the β-nitrogen of the arenediazonium ion, which is the electrophilic reactive center (Scheme 1)[1–3].



SCHEME 1. Basic representation of the nucleophilic addition mechanism leading to the formation of Ar−N=N−Nu adducts in the (*Z*)- and (*E*)-configurations. The competitive spontaneous decomposition of ArN_2^+, which takes place through the formation of a highly reactive aryl cation, is also shown

Examples of covalently bonded adducts are the azo dyes (C-coupling). Their formation has been extensively studied[4] and takes place when ArN_2^+ ions react with aromatic substrates containing strong electron donors such as hydroxy or amino groups; the reactivity order was found to be $-O^- > NR_2 > NHR > OR, OH \gg Me$[4]. C-coupling reactions are believed to proceed through the general electrophilic aromatic substitution (EAS) mechanism (Scheme 2), involving the formation of a covalent complex (or σ complex, the Wheland intermediate, W)[2,4,5], followed by proton loss in a step which is usually considered, for the azo-coupling reaction, to be irreversible[6]. The C-coupling reactions are probably the EAS reactions characterized to the highest degree by their sensitivity to orientation and, in practically all cases investigated, the reaction takes place exclusively at the *o*- and *p*-positions and, in fact, *m*-substitutions have never been observed[2,4,5].

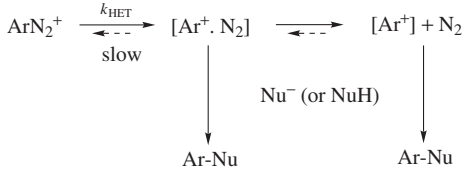


SCHEME 2. Basic representation of an electrophilic aromatic substitution mechanism (C-coupling) leading to the formation of an azo dye

Atoms other than C may be involved[1,2] and the present chapter will mainly focus on the chemistry of O-coupling adducts of the type ArN=N−Nu, e.g. where $Nu = OH^-$ (formation and decomposition of diazohydroxides and diazoates), $Nu = RO^-$, ArO^-, ROH and cyclodextrins (formation and decomposition of diazoethers). It is not intended to be

exhaustive in covering all the literature, but is rather aimed to provide the reader a broad view of the state of the art of the topic, with special emphasis on the kinetics and mechanism of the reactions involved. We will also cover to a lesser extent those reactions with other nucleophiles leading to S-, N- and P-adducts. Alkanediazonium (RN_2^+) ions are much less stable than the aromatic ones and they will not be covered here[7, 8].

Isolation and identification of the transient O-adducts formed may be difficult because their stability depends strongly on the leaving ability of the nucleophile involved in the reaction (Scheme 1), so that if Nu^- is a good leaving group such as halide or acetate ions, the equilibrium lies largely on the side of the reactants and ArN_2^+ ions undergo spontaneous decomposition reactions which are believed to take place through a $D_N + A_N$ mechanism (Scheme 3)[2, 9, 10]. On the other hand, if Nu^- is a good nucleophile but a relatively poor leaving group, such as the ascorbate or gallate (3,4,5-trihydroxybenzoate) ions, some stabilization may occur by conversion to a thermodynamically stable isomer (e.g. $Z-E$ isomerization)[11, 12]. In some circumstances, isomerization is not possible and the adduct splits homolytically to finally give reduction products[13–15].



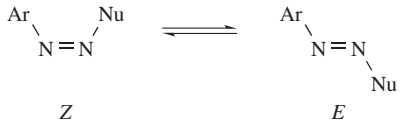
SCHEME 3. Currently accepted reaction mechanism for the spontaneous decomposition of ArN_2^+ ions showing the rate-determining formation of an extremely reactive aryl cation (as an ion–molecule complex or a solvated cation) which further reacts with available nucleophiles in its solvation shell

All O-coupling reactions are thus complicated by two major features. First, the formed adducts may display geometrical isomerism, leading to the *E*- (*syn*) and *Z*- (*anti*) forms, which show different stability and can be interconverted to each other by acid-catalyzed processes. Second, some of the O-adducts formed may be, in turn, components of a Lewis acid–base equilibrium, for example between ArN_2^+ and OH^- ions, and hence may undergo further reactions.

In spite of extensive work and effort that have been devoted to studying their chemistry, some, but not all, mechanistic problems have been solved nowadays. A literature survey reveals that some aspects of those reactions have not been further investigated in the last years and only a brief summary of the current knowledge will be given. Areas where significant research activity has been carried out include, among others, the formation and decomposition of diazoethers with neutral and ionic nucleophiles under acidic conditions, where both heterolytic and homolytic processes are competitive and can be easily modulated[16].

II. *Z*–*E* ISOMERIZATION OF Ar–N=N–Nu ADDUCTS

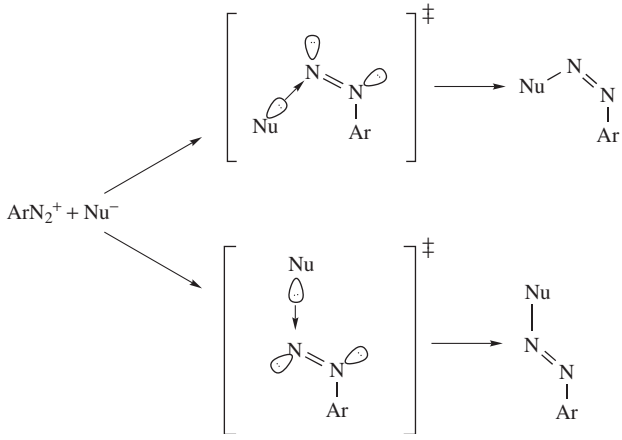
$Z-E$ isomerism (Scheme 4), denoted in the past as *syn*–*anti* isomerism, is possible in reactions of nucleophiles with diazonium ions where double-bonded nitrogen compounds of the type R–N=N–R′ are formed, where R and R′ stand for either alkyl or aryl residues. Their formation was recognized experimentally as early as 1938 by Hartley[17] after Hantzsch and Werner[18] put forward the hypothesis of their existence[2].



SCHEME 4. $Z-E$ isomerism. The particular isomerization process depends on the nature of the nucleophile as we show in the subsequent sections. With N nucleophiles (formation of triazenes), only the *E*-isomer is obtained

The suspected configurational isomerism was first confirmed by dipole measurements by Le Fèvre and coworkers[19–21], but other physical methods such as diamagnetic susceptibility and spectroscopic techniques (UV.VIS, IR, NMR and X-ray) were also employed[1–3]. Early work on the topic was focused on diazo compounds of the type Ar−N=N−Nu, obtained by reacting ArN_2^+ ions with nucleophiles such as $Nu = O^-$ (diazoates), $Nu = RO^-$ (diazoethers), $Nu = SO_3^-$(sulfonates), $Nu = -SO_2-Ar$ (sulfones), $Nu = CONH_2$ (carboxamides) and $Nu = S-R$, $S-Ar$ (diazothioethers), $Nu = CN^-$ (cyanides) and $Nu = R^1-NH-R^2$ (triazenes). Analyses of the reaction mixtures showed that the ratio of the *Z*- to *E*-isomers may be very different ranging from almost 100:1 to 1:100, depending on the type of nucleophile involved and on the reaction conditions. In many cases, the *Z*-isomer is the kinetically controlled product, in spite of the fact that the *E*-isomers are thermodynamically more stable. *Z*-isomers are formed in reactions with OH^-, CN^-, RO^-, CN^- and SO_3^{2-}, whereas *E*-compounds are formed in most reactions with amines (leading to the formation of triazenes) and with diazo coupling components such as phenols and tertiary amines.

Zollinger[2] interpreted the very different $Z-E$ ratios in terms of 'early' and 'late' transition states (Scheme 5) based on the comparison of two repulsive interactions, steric and electronic. If the transition state is 'reactant-like' (i.e. 'early' transition state on the reaction coordinate), the repulsive steric interaction between the nucleophile and the aryl nucleus is small because the N_β–Nu distance is relatively large. Therefore, the repulsion



SCHEME 5. Proposed early and late transition states for the reaction of nucleophilic attack on ArN_2^+ ions

between the lone pair on the β-nitrogen and the aryl nucleus becomes a decisive factor. It favors an *E*-configuration on the N_β lone pair with respect to the aryl nucleus and therefore the Nu attacks N_β in the *Z*-configuration. Alternatively, if the transition state is product-like ('late'), the N_β–Nu distance is relatively short, and steric repulsion between Nu and the arene nucleus is stronger than that between the N_β lone pair and the arene nucleus, and therefore the formation of the E-isomer is favored.

Support for this interpretation comes from a comparison of Hammet ρ values for rates of addition of nucleophiles with ρ values for the corresponding equilibria. Ritchie and coworkers[22–25] found ρ values in the range 2.3–2.8 for the rates of coordination of arenediazonium ions with a number of nucleophiles (e.g. OH^-, CN^-, N_3^-) whereas ρ values are in the range 3.5–5.2 for the corresponding equilibria. However, the ρ values for the rate constants of 3.5–4.3 for the diazo coupling reactions with amines, phenols or either 1- or 2-naphthols are significantly larger than those for reactions with other nucleophiles, but are comparable to the ρ values for the equilibria mentioned.

This can be interpreted by assuming that the transition states of diazo coupling reactions, which, as mentioned above, lead to the *E*-isomers, are more product-like than for ArN_2^+ ions reacting with anions such as OH^-, CN^- or N_3^-. Moreover, the attraction of strong nucleophiles such as OH^- or RO^- to the π-system of the aryl nucleus may favor the *Z*-attack. Recently, Hanson and coworkers[12] investigated the Sandmeyer hydroxylation and chlorination reactions in aqueous solution, and concluded that Cu^I reductants react via a nucleophilic bridging ligand at the N_β to give unstable, short-lived *Z*-adducts which are transformed to the *E*-isomers by an N–N bond rotation mechanism.

Z-Benzenediazoates rearrange to the *E*-isomer with a half-life of about 100 h at room temperature, but the rate is strongly dependent on the nature of the substituents in the aromatic ring[26]. Arenediazonium ions bearing electron-withdrawing substituents (e.g. 2- or 4-NO_2, 4-Cl) are rearranged by more than 4 orders of magnitude faster than the unsubstituted benzenediazoate. However, diazohydroxides isomerize faster than the corresponding diazoates; e.g. *Z*-4-Cl-ArN_2OH is isomerized by almost 4 orders of magnitude faster than the corresponding *Z*-diazoate. Hanson and coworkers[12] pointed out that aryl substituents with −M effects which conjugate with the N=N double bond reduce its bond order and so facilitate the rotation around the N–N axis leading to isomerization; in contrast, aryl substituents with +M effects do not reduce the barrier to rotation. Some representative values for the isomerization rate constants, which correspond to the kinetic processes indicated in equations 1 and 2, are given in Table 1.

$$Z\text{-}ArN_2OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E\text{-}ArN_2OH \tag{1}$$

$$Z\text{-}ArN_2O^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E\text{-}ArN_2O^- \tag{2}$$

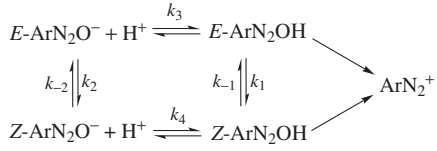
Interesting results were obtained from investigations of the reverse transformation of *E*-diazoates to diazonium ions, i.e. from the reaction rates of the diazoates with acid (Scheme 6). However, the investigation of the acidification of *E*-4-nitrobenzenediazoates is difficult due to irreversible decomposition, as first shown by Lewis and Suhr[28].

E-Diazoates derived from reactive diazonium ions can be prepared by pouring the solution of diazonium salt into a dilute sodium hydroxide solution. With less reactive ArN_2^+ ions, the rearrangement was carried out in more concentrated solutions (the higher the pH_m (see equation 8 below for definition), the more concentrated the solution is needed in order to reduce the decomposition of diazonium salt) and at higher temperatures. The transformation of *E*-diazoate into the ArN_2^+ ions was monitored by injecting into the

TABLE 1. Values of the rate constants and equilibrium constants of isomerization of substituted arene diazohydroxides and diazoates. Data from Reference 27. The pK_a values are for the dissociation constant of the diazohydroxide

$$E\text{-ArN}_2\text{OH} + \text{OH}^- \rightleftharpoons E\text{-ArN}_2\text{O}^- + \text{H}_2\text{O}$$

Substituent in Ar	$10^3 k_2(\text{s}^{-1})$	$10^5 k_{-2}(\text{s}^{-1})$	$10^3 k_{-1}(\text{s}^{-1})$	$K_2 = k_2/k_{-2}$	pK_a
H	2×10^{-3}	$\sim 2 \times 10^{-4}$	~0.5	1 000	7.3
4-NO_2	54	9.0	4.8	600	6.1
2-Cl- 4-NO_2	32	9.2		350	
2-NO_2	1.5	8.3	19	18	6.2
4-Cl-2-NO_2	4.3	37	27	11.5	5.8
5-Cl-2-NO_2	10	83	40	12	5.6
2,4-$(NO_2)_2$	20 900		240		5.0
2,6-Cl_2-4-NO_2	5.5	1.8	64	3.0	4.7



SCHEME 6. Transformation of diazoates into diazonium ions by acids[26]

buffer (or acid) solution containing a sufficient amount of a highly reactive coupling component (such as 2-naphthol-3,6-disulfonic acid), which is able to react immediately with the diazonium ion, leading to the formation of a stable azo dye whose concentration can be determined spectrophotometrically, preventing the reverse reaction.

Evaluation of the kinetics of the formation of ArN_2^+ ions has been proven to be complex, however, because of the very different dependence of the various steps in Scheme 6 on the nature of the substituents. Kinetic curves[26] show two-to-three pH regions in which the slope d(log(k_{obs}))/d(pH) is approximately -1, with intermediate regions where the slope is negligible or zero. At the high pH values, k_{obs} increases with increasing proton concentration, because the diazohydroxide concentration increases. At intermediate pH < pK values, k_{obs} becomes independent of [H^+] because practically all the starting compound is present as the *anti*-diazohydroxide. At the highest pH values, E-ArN_2O^- exists in equilibrium with a slight amount of Z-ArN_2OH, and the rate is limited by the splitting of Z-ArN_2OH. Increasing proton concentration makes the transformation of Z-ArN_2OH to ArN_2^+ faster than its dissociation to diazoate, and the rate-limiting step is the isomerization of E-diazoate to Z-diazoate. Further experimental details and interpretation of the complex kinetic curves obtained can be found elsewhere[2, 26].

III. KINETICS AND MECHANISM OF FORMATION OF O-ADDUCTS

A. Diazohydroxides and Diazoates

Aromatic diazonium ions behave as Lewis acids, because they can react with OH^- ions to form diazohydroxides, ArN_2OH. The diazohydroxides then became Brönsted acids, and may lose a proton to yield diazoates. As shown before, both diazohydroxides, diazoates

and diazoethers show $Z-E$ isomerism, and, in the present section, the formulas ArN_2OH and ArN_2O^- will refer only to the Z-isomers, which are the first ones formed as kinetically controlled products.

The equilibria sequence is given by reactions 3–5, and at first glance one may think that the behavior of the system will be formally analogous to those of classical dibasic systems such as sulfuric or oxalic acids, but, as we will see, this is not the case.

$$ArN_2^+ + OH^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} ArN_2OH \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} ArN_2O^- + H^+ \tag{3}$$

$$ArN_2^+ + H_2O \underset{}{\overset{K_1}{\rightleftharpoons}} ArN_2OH + H^+ \tag{4}$$

$$ArN_2OH \underset{}{\overset{K_2}{\rightleftharpoons}} ArN_2O^- + H^+ \tag{5}$$

Investigations by Wittwer and Zollinger[29] showed that the acidity dependence on the degree of neutralization is different from that expected for dibasic acid: They found that the neutralization curves showed only one single step although each ArN_2^+ ion consumed two OH^- ions. This unusual behavior was interpreted in terms of the relative size of the equilibrium constants by assuming that $K_2 > K_1$, in contrast with typical dibasic acids where $K_1 > K_2$.

The condition $K_2 > K_1$ means that the diazohydroxide formed is rapidly transformed into the diazoate, hence its concentration is very low throughout the measurement. This result was confirmed later also by spectral determination of the diazonium–diazoate equilibrium[30]. The spectrum only contained the absorption bands corresponding to the starting diazonium ion and diazoate. The slope of the pH dependence of $[ArN_2^+]/[ArN_2O^-]$ had the value of -2, in accordance with the fact that the diazonium ion reacts with two equivalents of OH^- ion practically in a single step, and therefore one cannot observe, as in common dibasic acids, an intermediate region of a few pH units where the monobasic acid is stable.

Wittwer and Zollinger[29] estimated, from neutralization curves, that $K_2 > 10^3 K_1$, and for this reason it was not possible to separate, at that time, the individual values of K_2 and K_1 but only their product K_2K_1 could be determined. Individual values were first determined by Lewis and Suhr[28] by taking advantage of the fact that the rate constant for the addition of OH^- ions to ArN_2^+ ions (k_3 in equation 3) is slower than the rate of deprotonation of the diazohydroxide (k_4).

From the preceding discussion it follows, therefore, that the diazohydroxides cannot be isolated from aqueous solution and that the slope of the pH dependence of $[ArN_2^+]/[ArN_2O^-]$ should have a value of -2 in accordance with the fact that ArN_2^+ ions react with two equivalents of OH^- ions practically in a single step.

Bearing in mind equations 4 and 5, equations 6–8 can be derived.

$$K = K_1K_2 = \frac{[ArN_2O^-][H^+]^2}{[ArN_2^+]} \tag{6}$$

$$pH = \frac{pK_1 + pK_2}{2} + \log \frac{[ArN_2O^-]}{[ArN_2^+]} \tag{7}$$

$$pH_m = \frac{pK_1 + pK_2}{2} \tag{8}$$

From equations 7 and 8, it follows that the ratio $[ArN_2^+]/[ArN_2O^-]$ is changed by a factor of 100 when the pH is changed by one unit, and therefore at $pH = pH_m+1$, most (>99%) of the ArN_2^+ ions are converted into the diazoate and only less than 1% of the initial $[ArN_2^+]$ remains in solution. Note that the concentration of the diazohydroxide is always negligible except for extremely reactive diazonium ions at $pH = pH_m$. Table 2 shows a number of K and pH_m values measured at room temperature at the ionic strength $I = 1$ mol l^{-1} for a number of substituted ArN_2^+ ions.

The value of the equilibrium constant K (and hence also pH_m) depends on the ionic strength of the medium[2, 26, 30]. If I is increased from 0.1 to 1 mol l^{-1}, the K value decreases by about one order of magnitude[23]. The dependence of $\log K$ upon the Hammett σ constants is linear with the slope $\rho = 6.6$[31]. This very large value arises from the fact that K is a product of two equilibrium constants, hence ρ is a sum of ρ_1 and ρ_2 corresponding to the equilibrium constants K_1 and K_2, respectively. It is also possible to correlate the dependence of pH_m with the σ constants; in this case the ρ value is negative and one half of that for $\log K$, which follows from equation 7[26]. The substituents o- and p-NR_2 and $-O^-$ exhibit such high negative σ values that the pH_m values of the respective diazonium ion cannot be measured.

As indicated before, the pH dependence of ArN_2^+ ions on the degree of neutralization is different from that expected for dibasic acids because $K_2 > K_1$, and therefore the individual equilibrium constants K_1 and K_2 cannot be determined from measurements of the pH dependence of the concentrations of the reacting components. But since determining the individual K_1 and K_2 equilibrium constants was the main problem and of general interest, several elegant approaches were developed.

Lewis and Suhr[28] took advantage of the fact that the rate constants involved in equation 3 are quite different from each other and can be estimated independently by choosing appropriate experimental conditions and by employing UV-VIS spectrometry. For instance, k_3 is slower than the deprotonation of the diazohydroxide (k_4) and the relationship $k_{-4} > k_{-3}$ also holds. If the values of k_3 and k_4 can be determined, then one can calculate the equilibrium constant K_1 and, if the product K_1K_2 is known, K_2 can be calculated. Ritchie and Wright[22, 23] and Sterba and coworkers[27, 32] employed stopped-flow measurements to evaluate the rate constants, and Ritchie and Wright[22, 23] were able to show that the forward reaction occurred not only with OH^- ions (equation 3) but also with H_2O molecules (equation 4), followed by fast deprotonation by hydroxide ions.

Table 3 displays some pK_1 and pK_2 values for a series of arenediazonium ions. The general conclusion that can be drawn from the data in Table 3 is that K_2 is greater than K_1 by 3–5 orders of magnitude, depending on the nature of the substituent in the aromatic ring. Since all substituents employed are acidifying substituents, one can reach

TABLE 2. pH_m (equation 8) and equilibrium constant K (mol^{-2} l^{-2}) for the reaction $X\text{-}ArN_2^+ + 2OH^- \rightleftharpoons X\text{-}ArN_2O^- + H_2O$

X	pH_m	10^4K	X	pH_m	10^4K
H	11.90	1.6	4-CF_3	10.55	790
3-CF_3	10.34	2100	4-SO_3^-	10.48	1 100
3-Cl	10.70	400	4-I	11.21	38
3-$COCH_3$	10.71	380	4-Br	11.09	66
3-CO_2^-	11.54	8.3	4-Cl	11.21	38
3-CH_3	12.22	0.36	4-CO_2^-	11.24	33
4-NO_2	9.44	130 000	4-F	11.53	8.7
4-CN	9.77	29 000	4-CH_3	12.59	0.07

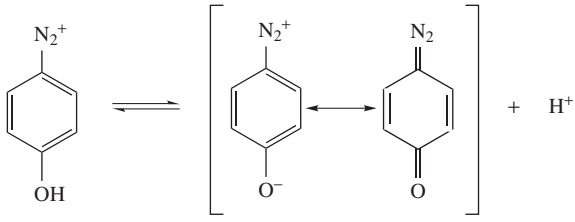
TABLE 3. Values of k_3, k_{-3}, K_1 and K_2 (defined in equations 3–5) for a series of arenediazonium ions

X in X-ArN_2^+	$10^{-5}k_3$ (l mol^{-1} s^{-1})	$10^{-2}k_{-3}$ (s^{-1})	pK_1	pK_2
4-Cl-3-NO_2[a]	7.4	1.95	2.42	6.90
3,5-Br_2[a]	3.6	4.96	2.14	7.00
3,5-Cl_2[a]	3.8	6.03	2.20	7.05
3-NO_2[a]	4.5	5.34	2.08	7.15
3,4-Cl_2[a]	1.3	3.00	2.35	7.30
4-N_2^+[a]			4.83	5.83
4-NO_2[b]			6.3	
$CH_3(CH_2)_{15}$[c]			7.5	

[a]See Reference 31.
[b]See Reference 13.
[c]See Reference 33.

the conclusion that for the ArN_2^+ ions with basifying ones and for the parent ion, K_2 should be more than $10^5 K_1$.

For ArN_2^+ ions with substituents that are subject to their own acid–base equilibria, the situation is more complex. For example, the −OH group of the 4-OH−ArN_2^+ ions has a pK_a of 3.40, and the O^- group of the conjugate base greatly reduces the acidity of the diazonium group, as indicated in the mesomeric structures in Scheme 7. In an analogous way, heteroaromatic diazonium ions that contain an acidic NH group in the heteroaromatic ring lose that proton even in weakly to strongly acidic solutions, and it is therefore likely that addition of OH^- ions to the diazonium group takes place only in strongly alkaline solutions.



SCHEME 7. Mesomeric structures of the phenolate of 4-hydroxybenzenediazonium ions

A different approach was recently developed by Bravo-Díaz and coworkers[13, 34, 35], who took advantage of the electrochemical properties of ArN_2^+ ions and were able to estimate the equilibrium constant K_1 by employing electrochemical methods. ArN_2^+ ions are easily reducible compounds[13, 35–39], and the electrochemical reduction of a number of substituted ArN_2^+ ions has been investigated in aqueous and some non-aqueous solvents as well as in the presence of macromolecular and colloidal systems such as micelles and emulsions[35, 40, 41]. Their reductive properties to functionalize carbon surfaces are also being explored[42, 43]. Voltammograms of ArN_2^+ ions show two electrochemical reduction peaks, the first one at peak potentials of E_p *ca* − 0.1 V (vs Ag/AgCl), which corresponds to the uptake of an electron to yield an arenediazenyl radical (Figure 1), and a second one (not shown) at peak potentials of E_p *ca* − 0.7 to −1.0 V, which finally yields the corresponding

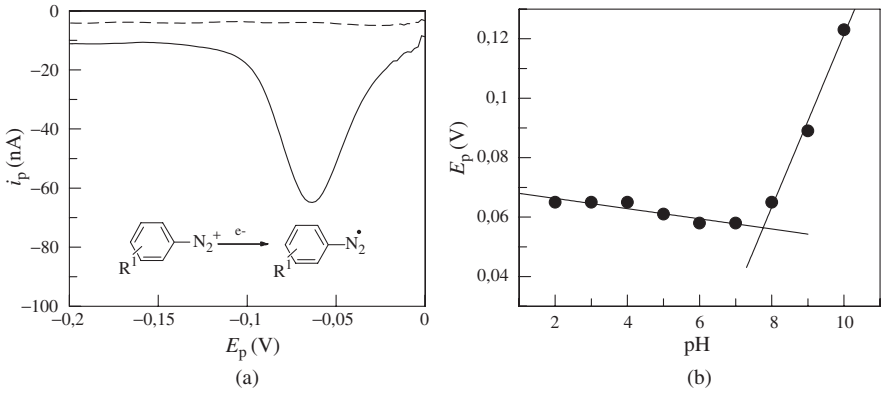


FIGURE 1. (a) Typical voltammogram (LSV) of ArN_2^+ ions showing the first reduction peak and the associated electrochemical process. The dashed line is the background signal. (b) Variation of the peak potential of the first reduction peak with the acidity of the medium showing the break point associated to the formation of the corresponding diazohydroxide

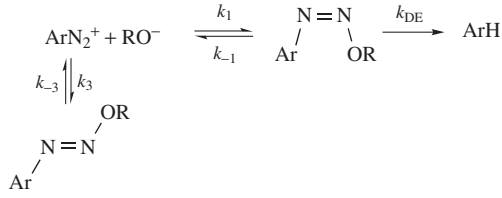
hydrazine (the overall electrochemical reaction is $ArN_2^+ + 4e^- + 3H^+ \rightarrow ArNHNH_2$). Owing to the formation of the diazohydroxides, both the peak potential and peak current of the first reduction peak is sensitive to the acidity of the medium as shown in Figure 1, and from the intercept of the two lines a pK_1 value can be determined.

B. Diazoethers

The reactions of diazonium ions with alkoxide ions, RO^-, lead to the formation of diazoethers of the type Ar−N=N−O−R. These are compounds structurally similar to those obtained from the reaction with OH^- ions, but the kinetics and mechanism of these O-coupling reactions are quite different because the primary product, a *Z*-diazoether, cannot further react with a second RO^- molecule to form a stable anion, i.e. deprotonation is not possible as in the case of diazohydroxides.

The addition of methoxide ion has been investigated by several groups on the basis of kinetic and product distribution measurements. In combination with earlier investigations[44], it can be concluded that the primary product is the *Z*-diazomethyl ether, and that a second, much more stable, product (the *E*-isomer) is formed with half-lives of 0.1 to several seconds. However, because the alkoxide ions are much less solvated in alcohols than OH^- ions are in water, and because the relative permittivity of the alcohols is substantially lower than that of water, the reaction of ArN_2^+ with RO^- is much faster than that with OH^-, and the reverse reaction is much slower; the equilibrium is strongly on the side of the O-adduct ($K = 5.6 \times 10^7 M^{-1}$).

The mechanism of the *Z*−*E* isomerization differs also from that with OH^- ions. Broxton and Roper concluded that, for diazoethers of the type Ar−N=N−OR, there is no direct *Z* to *E* conversion, with the *Z*-isomer being the kinetically controlled product while the *E*-isomer is the thermodynamic product, as shown in Scheme 8. Broxton and Roper[45] concluded that the *Z*−*E* isomerization proceeds through an ionization–recombination pathway. Basically, the reaction takes place through two different kinetic steps. In the first one, which is very rapid, the *Z*-isomer is formed. This is followed by a second, much slower step. A small amount of the ArN_2^+ ions which are in equilibrium with the



SCHEME 8. Proposed mechanism for the $Z-E$ isomerization of Ar−N=N−OR adducts[2, 45]

Z-isomer react with MeO^- to yield the E-diazoether, and the rest decomposes to form reduction products, mainly the corresponding benzene derivative.

The reactions of 4-NO_2 and 4-CN-ArN_2^+ in buffered solutions of metoxide ion in methanol reach an equilibrium with a stoichiometry involving the addition of 1 mol of MeO^- to 1 mol of ArN_2^+ with a rate that is close to the diffusion-controlled rate. For the reaction of 4-NO_2-ArN_2^+ ions with MeO^- (Scheme 8), $k_1 = 3.0 \times 10^8 mol^{-1} l^{-1}$ s^{-1} at $T = 23\,^\circ C$, while that for the reverse reaction is[24] $k_{-1} = 5.4$ s^{-1}, i.e. more than 4 orders of magnitude higher than K_1 for the reaction of 4-NO_2-ArN_2^+ with OH^- ions. The rate constant for the formation of the E-isomer is $k_3 = 2.5 \times 10^6$ mol^{-1} l^{-1} s^{-1}, i.e. about 120 times smaller than that for the formation of the Z-isomer, while $k_{-3} = 2.9 \times 10^{-4}$ s^{-1}, which means that the equilibrium constant of isomerization is about 500, i.e. approximately the same as for 4-nitrobenzenediazoate in water[26].

Other arenediazoalkyl ethers have been investigated but less thoroughly. Broxton investigated the reaction of 4-NO_2-ArN_2^+ with RO^- ions in a number of alcohols and found for R the reactivity order Me > Et > 2-Pr, probably reflecting that an increase in the basicity of the leaving group increases the N−O bond strength. For the reaction with EtO^- in EtOH, $k_{-3} = 1.9 \times 10^{-5}$ s^{-1}, i.e. more than one order of magnitude lower than that in MeOH[46].

The decomposition of the E-diazomethylethers is general acid-catalyzed, as shown by Broxton and Stray[47] using acetic acid and a number of other aliphatic and aromatic carboxylic acids. The observation of general acid catalysis suggests that the proton transfer takes place in the rate-determining step of the reaction. The Brönsted value[2] of $\alpha = 0.32$ indicates that in the transition state the proton is closer to the carboxylic acid moiety than to the oxygen atom of the methanol to be formed. If the benzene ring of the diazoether contains a carboxy group in the 2-position, intramolecular acid catalysis may be observed[48–50].

The addition of acetate ions to an arenediazonium ion solution may also lead to the formation of O-coupling adducts. However, the equilibrium of this reaction lies very much to the side of the starting ions (K *ca* 1×10^{-5}), and the formation of the O-adduct is not usually considered important[1].

Of much more interest are the reactions of arenediazonium ions with antioxidants bearing OH groups in their molecular structure, such as ascorbic acid (vitamin C, VC) and its hydrophobic derivatives. Doyle and coworkers[51] first investigated the reaction of a number of arenediazonium ions with ascorbic acid and Bravo-Díaz and coworkers extended the investigations to their hydrophobic derivatives both in aqueous, micellar and in emulsified systems[11, 41, 52–54]. All results are consistent with the formation of an O-adduct, which was detected experimentally[11, 41, 54] (Figure 2), and unambiguously identified by ^1H and ^{13}C NMR spectroscopy as 3-*O*-arenediazo ascorbic acids[51].

VC and their hydrophobic derivatives behave as weak acids with pK_a *ca* 4.2 for the C_2 hydroxyl group. Analyses of the acid dependence of the observed rate constant k_{obs} show that the reactive molecular form of Vitamin C is the monoanionic one[11], and this

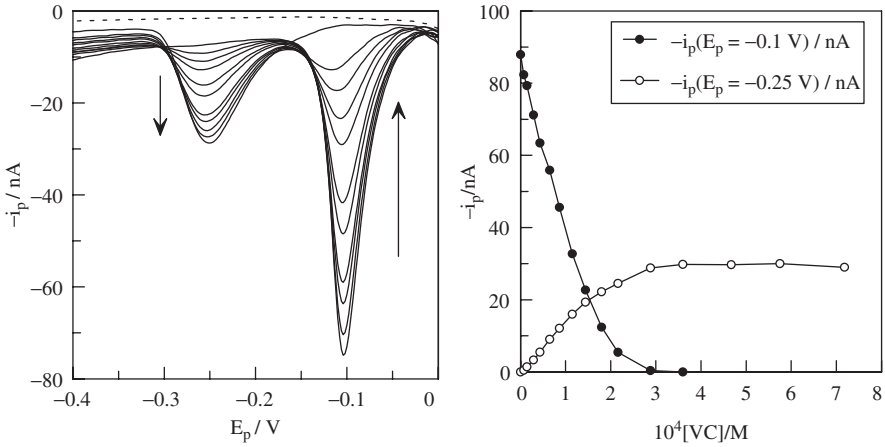
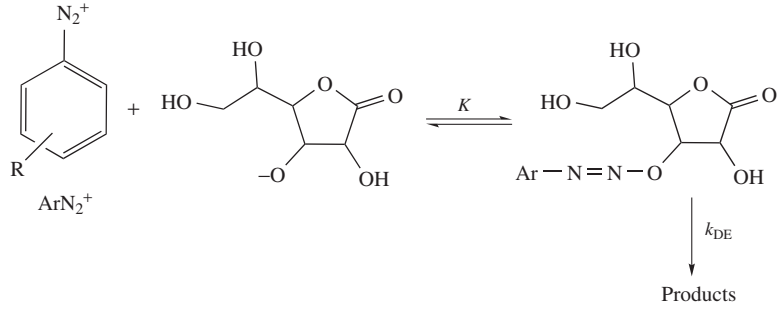


FIGURE 2. Left: Typical voltammograms of ArN_2^+ ions showing the effects of addition of increasing amounts of Vitamin C on the first reduction peak of ArN_2^+ ions and the formation of a new one, not previously detected, at E_p *ca*−0.25 V, associated to the formation of the corresponding diazoether. Right: Variation in the peak currents of the voltammograms obtained at constant [ArN_2^+] upon increasing [Vitamin C] showing the formation of a 1:1 adduct. Voltammograms were registered immediately after addition of the aliquots of VC. $T = 25°C$, [ArN_2^+] *ca* 3.2×10^{-4} M, [VC] = $0 - 2.2 \times 10^{-4}$ M

observation together with the finding of saturation kinetic curves prompted the proposal of a reaction mechanism comprising a rate-limiting formation of the O-adduct (Scheme 9), which was confirmed in subsequent studies[41, 52–54].

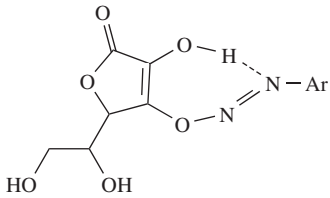


SCHEME 9. Proposed reaction mechanism for the formation of 3-*O*-arenediazo ascorbic acids. The spontaneous decomposition of ArN_2^+ is not indicated for the sake of simplicity

HPLC analyses of the reaction products show that, in the absence of VC, quantitative conversion to the phenol derivative ArOH is obtained. On increasing [VC], yields of ArOH decrease and a concomitant increase in the yield of the reduction product ArH is obtained, so that total yields are close to 50%. At pH 4 and 5, ArOH yields decrease very rapidly to only 20% when [VC] is *ca* 2.5×10^{-2} M and then more slowly, in contrast

with the smooth ArH formation. Total yields ($Y_{ArOH} + Y_{ArH}$) are close to 50% at high [VC], independently of the pH of the reaction mixture. These results show that some stabilization of the O-adduct takes place[11, 52–54].

It is surprising, however, that treatment of arenediazonium ions with VC does not result in an electron transfer reaction, since oxidation–reduction reactions of hydroquinone and VC are formally equivalent and it is known that arenediazonium ions are reduced by hydroquinone[55], but no transient intermediates are formed. The formation of relatively stable O-adducts can be interpreted in terms of the bond-rotation mechanism proposed by Hanson and coworkers[12] to explain the *Z*-to-*E* isomerization mechanism. In the case of VC, there exists the possibility of hydrogen bonding between the N_α of the diazonium group and the ascorbate 2-OH group (Scheme 10), and hence the formation of the *Z*-isomer should be attenuated and the *E*-adduct could be formed directly. According to Scheme 10, the N–N bond rotation necessary for radical formation is inhibited by the fact that the π-bond is stronger than in the *Z*-adduct due to the lack of steric effects, and also because the *E*-configuration is stabilized against isomerization by the H-bond. The formation of increasing proportions of the stable *E*-adduct explains the low homolytic yields found in such reactions[11, 52–54, 56].



SCHEME 10. Stabilization of the *E*-isomer by hydrogen bonding between N_α of the diazonium group and the ascorbate 2-OH group

The reactions of ArN_2^+ ions with phenoxide (ArO^-), ions or with aromatic amines (anilines or 1-, 2-naphthylamines) proceed mainly through C-coupling pathways (EAS mechanism, Scheme 2) rather than through the O-coupling pathway. C-coupling reactions take place with substances containing hydroxy or amino groups, which increase the C-nucleophilicity of the coupling component. The reactions are strongly affected by the pH; aromatic amines react through the free base while the reactive species in the reaction with phenols or naphthols are the phenoxide or naphthoxide ions, which react as much as 10^{10} times faster than the non-ionized forms[1, 4, 5].

Phenoxide ions in water are very weak nucleophiles, hence the equilibrium constants of formation of Ar–N=N–O–Ar′ are very small and no reliable values have been determined for the equilibrium constants of these reactions. The presence of two ionizable groups (e.g. two hydroxy groups) at the nucleophilic arene nucleus increases the reactivity of the substrate, but their effect is not additive and depends strongly on their relative positions in the benzene ring[1–3]. For instance, resorcinol (1,3-$C_6H_4(OH)_2$) has two nucleophilic centers able to couple, with the dianion coupling more than 10^4 times faster than that of the monoanion[2, 32]. In contrast, catechol (1,2-$C_6H_4(OH)_2$) and hydroquinone (1,4-$C_6H_4(OH)_2$) are oxidized by ArN_2^+ ions.

Reactions with trihydric phenols such as gallic acid (3,4,5-trihydroxybenzoic acid, GA) and methyl gallate (methyl 3,4,5-trihydroxybenzoate, MG) have been recently investigated[57–59]. Analyses of the acid dependence of k_{obs} suggest that the reactive species is the dianion (GA^{2-}) or the monoanion (MG^-). To discern which of the three

OH groups of both GA or MG is the first one undergoing deprotonation, the geometries of the resulting anions were optimized by using B3LYP hybrid density functional theory (DFT) and a 6-31G(d, p) basis set.

The deprotonation energies suggest that the OH group at the 4-position is the first one which is deprotonated. The computational studies also indicate that the highest electron density is located at the O-atom of the C(4)-position, and very little electron densitiy is located at the C(2) and C(6) atoms, suggesting that an electrophilic attack is likely to take place on the O-atom at the C(4)-position.

This prediction was confirmed by the experimental results, which allowed us to detect experimentally the formation and decomposition of a transient intermediate in the course of the reaction (Figure 3)[57–59].

The kinetic behavior found is, however, quite complex for both antioxidants even though their reaction mechanisms share some common kinetic features. The analyses of the dependence of the observed rate constant on [GA] show kinetic saturation profiles with non-zero, pH-dependent intercepts.

The results appear to be consistent with consecutive reversible steps involving a fast, bimolecular step, in which ArN_2^+ ions associate with GA^{2-} to form a *Z*-diazoether complex which is subsequently isomerized to the ionized form of the much more stable *E*-diazoether in a slow unimolecular step. Some relevant rate and equilibrium constants for the reaction are displayed in Table 4. However, in the case of MG, the k_4 step in the second equilibrium (Scheme 11) can be considered negligible and saturation kinetics leading to the formation of the *Z*-adduct which subsequently decomposes has been proposed[58, 59].

Diazoethers can also be formed with neutral nucleophiles such as alkanols ROH, as shown by Bunnett and coworkers[60, 61] as early as in 1977. They published two papers focused on the thermolysis of arenediazonium ions, ArN_2^+, in acidic methanol. On the basis of kinetic and product distribution measurements, Bunnett and coworkers[60, 61] concluded that, in acidic methanol, dediazoniations take place through competing ionic and radical mechanisms, a conclusion substantiated in subsequent investigations by other

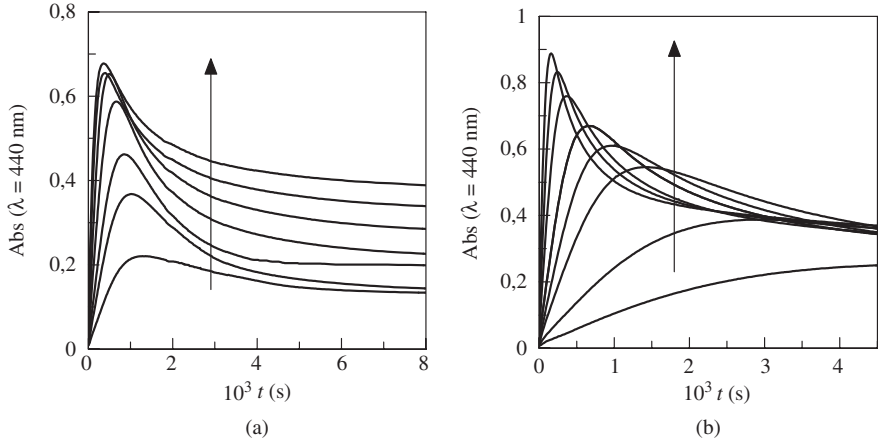
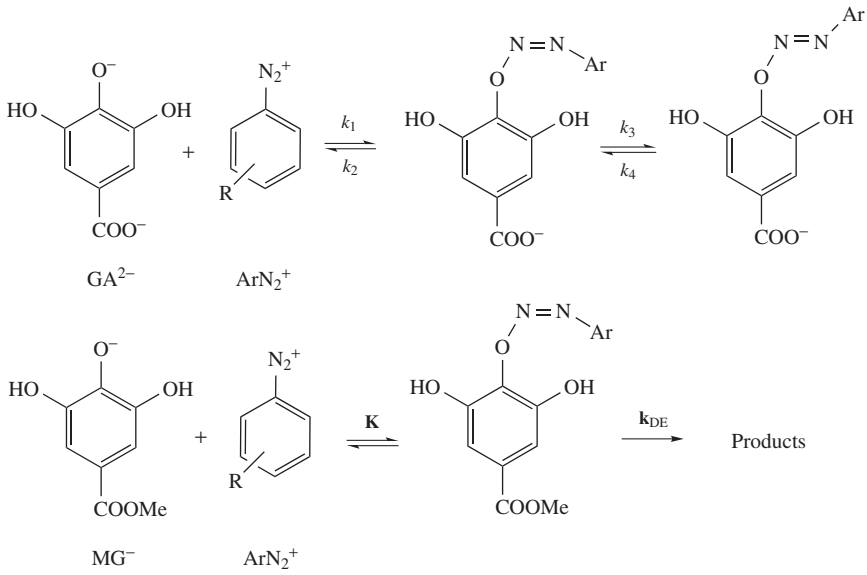


FIGURE 3. Variation in the absorbance at 440 nm with time due to product formation in the course of the reaction between 3-methylbenzenediazonium (3MBD) ions and methyl gallate (MG). (a) Fixed pH = 5.0 and different [MG] ranging 0.001–0.08 M. (b) Fixed [MG] = 0.04 M and different acidities ranging pH = 3.7–5.3. The arrows indicate the direction of increasing [MG] (a) and pH (b). [3MBD] *ca* 3×10^{-4} M, $T = 30°C$

TABLE 4. Values for k_4, k_3 and for the ratio k_1/k_2 (first equilibrium step in Scheme 10) for the reaction of gallic acid with 3-methylbenzenediazonium ions. Data from Reference 59

pH	$10^4 k_4$ (s^{-1})	$10^3 k_3$ (s^{-1})	$10^{-5} k_1/k_2$
4.1	4.96 ± 0.01	4.93 ± 0.20	2.98 ± 0.14
4.3	10.58 ± 0.02	5.46 ± 3.76	2.89 ± 0.13
4.5	17.22 ± 0.05	9.92 ± 1.71	1.99 ± 0.40
4.7	32.37 ± 0.14	14.10 ± 2.09	2.07 ± 0.37
5	65.96 ± 0.66	21.97 ± 2.41	1.77 ± 0.27



SCHEME 11. Proposed reaction mechanisms for the reaction between ArN_2^+ ions and gallic acid derivatives. In all cases, the ionic form of the nucleophile is the reactive species[58, 59]

researchers[9, 10, 62, 63]. The finding of substantial amounts of reduction products made them postulate that hydrodediazoniations take place by direct electron transfer from the solvent to the arenediazonium ion and Bunnett and coworkers[60, 64] proposed the reaction mechanism indicated in Scheme 12. However, no convincing evidence for this or other mechanistic alternatives was provided, and the initiation process of solvent-induced hydrodediazoniations has remained a matter of debate for a long time because no obvious reductants were employed in those experiments[2, 65].

Recently, Bravo-Díaz's group[14, 15, 66–68] proposed that the initiation pathway of the solvent-induced homolytic dediazoniations is not an electron transfer from the solvent but proceeds through the formation of *Z*-diazoether adducts, Ar−N=N−O−R. These kinetically controlled products undergo isomerization to the stable *E*-isomer or homolytic bond rupture initiating a radical process (Scheme 13), leading to the formation of reduction products.

$$ArN_2^+ + CH_3\ddot{O}H \xrightarrow{k_1} Ar^{\bullet} + N_2 + H^+ + {}^{\bullet}CH_2OH$$

$$Ar^{\bullet} + CH_3OH \xrightarrow{\text{fast}} ArH + {}^{\bullet}CH_2OH$$

$$ArN_2^+ + {}^{\bullet}CH_2OH \xrightarrow{\text{fast}} ArN_2^{\bullet} + CH_2O^+H$$

$$CH_2O^+H \rightleftharpoons CH_2O + H^+$$

SCHEME 12. Solvolytic dediazoniation mechanism proposed by Bunnett's group[60, 61] showing the initiation, rate-determining step k_1, which was assumed to be an electron transfer from the solvent to the arenediazonium ion, and the subsequent propagation steps

$$ArN_2^+ + MeOH \overset{K}{\rightleftharpoons} Ar\text{-}N{=}N\text{-}O\text{-}Me + H^+$$

$$Ar\text{-}N{=}N\text{-}O\text{-}Me \xrightarrow{k_{HOM}} Ar^{\bullet} + N_2 + {}^{\bullet}OMe$$

$$Ar^{\bullet} + MeOH \xrightarrow{\text{fast}} ArH + {}^{\bullet}CH_2OH$$

$$Ar^{\bullet} + {}^{\bullet}OMe \xrightarrow{\text{fast}} ArOMe$$

$$2Ar^{\bullet} \xrightarrow{\text{fast}} Ar\text{-}Ar$$

$$2\,{}^{\bullet}CH_2OH \xrightarrow{\text{fast}} CH_3OH + CH_2O$$

SCHEME 13. Newly proposed solvolytic dediazoniation mechanism showing an initation step comprising the formation of a highly unstable diazoether in a rapid pre-equilibrium step that subsequently decomposes homolytically initiating a radical process. The spontaneous decomposition of ArN_2^+, which takes place through the rate-determining formation of an aryl cation (k_{HET}) that further reacts with available nucleophiles ($D_N + A_N$ mechanism), is not shown for the sake of clarity

Experimental evidence supporting this mechanism is based on the sigmoidal variations in both k_{obs} and product yields with acidity for a number of arenediazonium ions[14, 15, 67, 68] (Figure 4). Product distribution analyses of the reaction mixtures indicate that at relatively high acidities ($-\log([HCl] = 2)$ only heterolytic products (phenols, ArOH, ethers, ArOEt, halo derivatives, ArCl) are formed, but upon decreasing the acidity the reduction products become predominant at the expense of the heterolytic ones, suggesting a change in the reaction mechanism. In addition, sigmoidal variations of k_{obs} with acidity are usually observed in reactions of acid–base pairs where both forms are attainable and show different reactivities[69]. However, under our experimental conditions, the solvent ionization is negligible and a potential reaction between ArN_2^+ and OH^- ions is unlikely[14, 15, 67], and therefore the formation of an O-adduct (the diazoether) that initiates a radical process is proposed.

The results of our solvolytic studies[14, 15, 67] permit the identification of the dual role of ROH molecules as nucleophiles. They can either (i) solvate the diazonium ions (allowing them to undergo thermal heterolytic decomposition, i.e., decomposing through an ionic mechanism), or (ii) react directly with arenediazonium ions to yield O-coupling adducts in a highly unstable *Z* configuration, i.e., *Z*-diazoethers. The *Z*-diazoethers then undergo homolytic fragmentation initiating radical processes, leading to the formation of quantitative amounts of the reduction product. These results suggest a simple, effective and quick practical method for replacing an aromatic primary amino group by hydrogen. It represents an improved alternative to the method using hypophosphorous acid as reducing agent

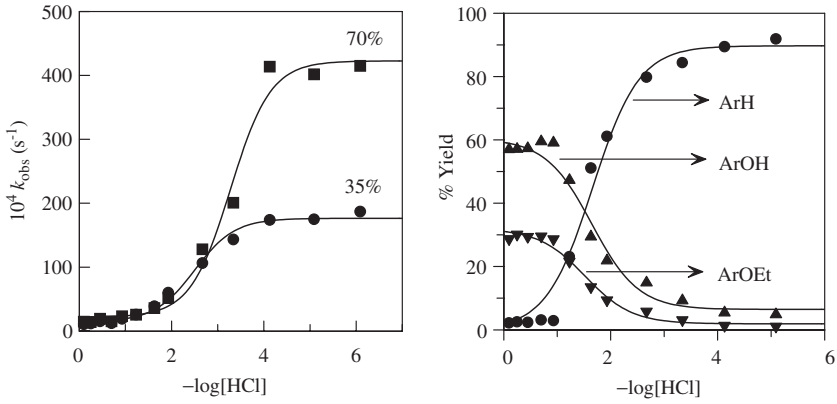


FIGURE 4. Left: Effects of acidity on k_{obs} for the solvolytic decomposition of 4-methylbenzenediazonium (4MBD) ions in 35% and 70% EtOH–H_2O mixtures. Right: Effects of acidity on the dediazoniation product distribution obtained in a 70% EtOH–H_2O mixture. The main solvolytic products were cresol (ArOH), methylphenetole (ArOEt) and toluene (ArH). Note the quantitative formation of the reduction product ArH under acidic conditions (pH = 3–5). [4MBD] *ca* 1×10^{-4} M, $T = 60°C$

proposed by Kornblum and coworkers[70] or that proposed by Bravo-Díaz and coworkers[13] using cyclodextrins as shown below. Because arenediazonium salts can be prepared easily from readily available aromatic primary amines, these deamination processes involving reductive removal of the primary amine groups are particularly useful in synthetic aromatic chemistry owing to the strong directing effects associated with amine substituents[71, 72].

The kinetics of methanolysis of 4-NO_2- and 4-Br-benzenediazonium ions under acidic conditions provides an excellent example of the influence of solvent composition and temperature on the change from a heterolytic mechanism to a homolytic one[15, 67]. For these compounds, the formation of the diazoethers is favored on increasing [ROH] due to the mass action effect, but is inhibited by the medium effect on the equilibrium constant for the formation of the diazoether, which decreases upon increasing [ROH][15, 67].

We also investigated the solvolysis of arenediazonium ions bearing electron-releasing substituents such as the methylbenzenediazonium ions and found similar S-shaped variations of k_{obs} with acidity, and, from the temperature dependence of such variations, relevant thermodynamic parameters for the heterolytic and homolytic pathways as well as for the formation of the diazoether were obtained.

Substituents on the aromatic ring have a marked effect on the stability of arenediazonium ions[9, 62], and their effects are not understandable in terms of the Hammet equation but can be interpreted in terms of a dual substituent parameter equation separating the resonance (associated with the ability to transfer charge) and inductive (associated with the polarity) effects[1, 2, 73]. Electron-withdrawing substituents such as 4-NO_2 or 4-Br destabilize the aryl cation by induction, more than they destabilize the parent arenediazonium ions, and therefore its spontaneous decomposition is much lower than that of the parent ion, or of ArN_2^+ ions bearing electron-releasing groups such as 4-Me. For instance, the half-life value for decomposition of 4-methylbenzenediazonium ions[74] in H_2O at $T = 60\,°C$ is $t_{1/2} = 3450$ s, compared with $t_{1/2}$ *ca* 83 000 s for the decomposition of 4-nitrobenzenediazonium ions[75] at the same temperature (Table 5). However, since arenediazonium ions decompose spontaneously through the formation of an extremely reactive aryl cation ($D_N + A_N$ mechanism, Scheme 2), the k_{HET} values are not quite sensitive

TABLE 5. Values of the half-lives and activation energies for the heterolytic (HET) and homolytic (HOM) dediazoniation processes for some arenediazonium ions in different solvents

Substituent	Solvent	$t_{1/2}$ (HET)[a] (s)	$t_{1/2}$ (HOM)[a] (s)	E_a (HET) (kJ mol^{-1})	E_a (HOM) (kJ mol^{-1})
4-Me	H_2O[b]	3 450	—	110	—
	70–30 EtOH-H_2O[c]	359	35	116	77
	90–10 BuOH-H_2O[d]	1 000	144	103	74
	72.5 BuOH[d]	1 200	4	—	76
4-NO_2	H_2O[e]	*ca* 83 000	—	119	—
	80–20 MeOH-H_2O[f]	*ca* 16 000	1 375	—	—
	95–5 MeOH-H_2O[f]	3 648	1824	—	—
4-Br	H_2O[f,g]	*ca* 180 000	—	*ca* 100	—
	25–75 MeOH-H_2O[g]	—	2390	*ca* 100	71
	75–25 MeOH-H_2O[g]	—	2 980	*ca* 100	74

[a] $T = 50^{\circ}$C.
[b] From Reference 10.
[c] From Reference 68.
[d] Results submitted for publication.
[e] From Reference 75.
[f] From Reference 15.
[g] From Reference 67.

to changes in the solvent composition as shown in this and in previous dediazoniation reports[1–3].

The formation of the diazoethers derived from reaction of 4-NO_2 and 4-Br arenediazonium ions with MeOH depends on both pH and MeOH concentration[15,67]: at low percentages of ROH, the corresponding diazoethers are formed because the equilibrium constant for their formation is high, and consequently the reaction proceeds through the radical mechanism (Scheme 13). However, its formation is not so favored at high %ROH in spite of the much higher [ROH] because of the medium effect on K, and in these situations the ionic and radical mechanisms become competitive (Table 5).

Once the diazoether is formed, it decomposes initiating a radical process whose activation energy seems to be independent of the nature of the substituent in the aromatic ring (Table 5).

Finally, we will briefly consider the reactions of arenediazonium ions with neutral polyalcohols such as cyclodextrins, which provide an example on how the geometry of the nucleophile and the nature of the substituents in the aromatic ring can affect the reaction mechanism. Cyclodextrins, CDs, are well-known cyclic oligomers of n-α-D-glucose units connected through glycosidic $\alpha - 1,4$ bonds[76–78]. This bonding leads to a doughnut-shaped three-dimensional structure. An oversimplified picture of CDs (Figure 5) show them as a shallow truncated cone[77,78] with the primary hydroxyl rim of the cavity opening having a smaller diameter than that of the secondary hydroxyl rim.

This cavity makes CDs very attractive for studies of their influence on chemical reactivity because they can act as hosts of molecules capable of entering in whole, or in part in their relatively non-polar cavities, about half of that of water[77,79–81], forming non-covalent host–guest inclusion complexes[76,77,82]. The dimensions of their cavities are known[76,77,83] (Figure 5) and, as a rule of thumb, α-CD hosts substituted benzene molecules, β-CD, naphthalene molecules and γ-CD, antracene ones.

The unique physical and chemical properties of cyclodextrins are a result of their structures[76–78]. In aqueous solutions their cavity is occupied by water molecules, which less polar guest molecules can readily replace. The formation of the inclusion complexes

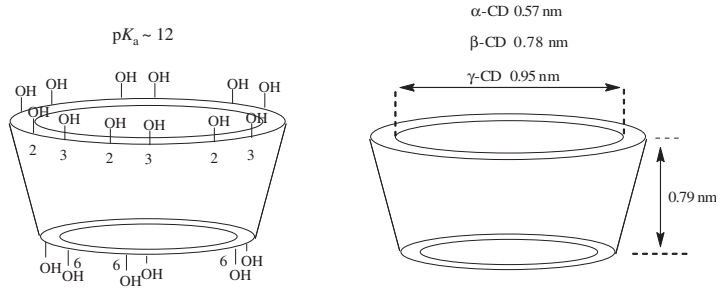
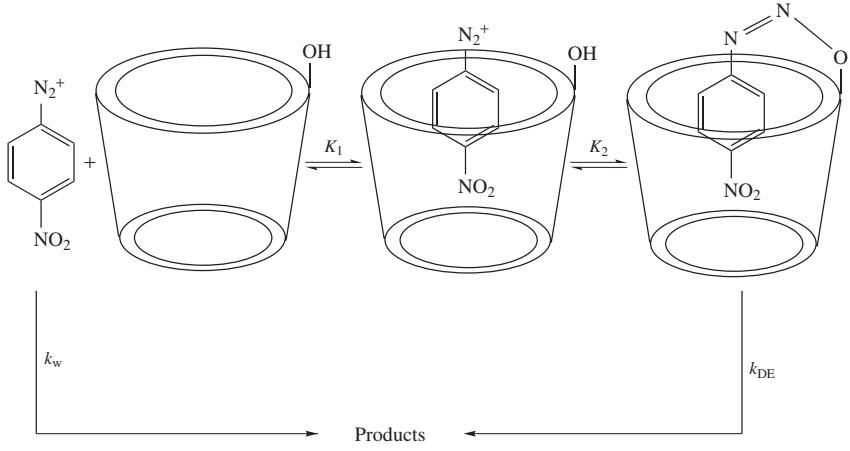


FIGURE 5. Typical structures for the native α-, β- and γ-cyclodextrins and their dimensions

is based on interactions of a non-covalent nature (electrostatic interactions, van der Waals forces, $\pi-\pi$ interactions) and on steric effects.

Bravo-Díaz and coworkers[84] studied, at different HCl concentrations, the dediazoniation of methylbenzenediazonium ions in the presence of α-, β- or γ-CD, showing that only heterolytic dediazoniation products were formed in significant amounts and that the total yield found, higher than 90% in all runs, suggests that reaction of arenediazonium ions with CDs is negligible. In addition, spectrophotometric, HPLC and electrochemical kinetic data studies show that both acidity and cyclodextrin concentration have no effect on the observed rate constant.

However, when using arenediazonium ions with electron-withdrawing substituents such as the 4-$NO_2-ArN_2^+$ ions[40], addition of β-CD results in the formation of a 1:1 inclusion complex with the NO_2 group inserted into the CD cavity. The adopted geometry of the complex allows solvation of the positive charge of the N_2^+ group mainly by the secondary hydroxyl groups of β-CD (Scheme 14), favoring further reaction to yield a



SCHEME 14. Proposed mechanism for the reaction between 4-nitrobenzenediazonium ions and cyclodextrins, showing the formation of an inclusion complex leading to the formation of a highly unstable diazoether which splits homolytically, giving rise to quantitative formation of the reduction product nitrobenzene

highly unstable transient intermediate, a *Z*-diazoether, which was detected experimentally. Due to its configuration, the formed diazoether is so unstable that it splits immediately, leading to the formation of quantitative amounts of the reduction product nitrobenzene when [CD] > 40 [4-NO_2−ArN_2^+].

IV. REACTIONS OF ARENEDIAZONIUM (ArN_2^+) IONS WITH −S$^-$, −CN$^-$, −P and − N NUCLEOPHILES

ArN_2^+ ions react readily with thiophenols, thiols and thiocarboxylic acids to yield diazothioethers. As expected, these S-coupling reactions do not involve the thioalcohol molecule but rather their anions. The higher nucleophilic character of thiol anions compared with that of alkoxide ions makes diazothioethers more stable than the corresponding diazoethers, and because the nucleophilicity of an S^- substituent is much higher than that of the C atoms in the 2- or 4-positions of the aromatic ring, C-coupling reactions are not competitive. The formation of diaryl sulfides may be competitive with the formation of the diazothioether as shown in Scheme 15.

$$Ar-N_2^+ + Ar'S^- \longrightarrow Ar-N_2-S-Ar' + Ar-S-Ar'$$

SCHEME 15. Representation of the reaction between ArN_2^+ ions and thiophenoxide ions yielding diazothioethers

Cuccovia and coworkers[85] exploited the reaction of ArN_2^+ ions with sodium methyl sulfate, $NaMeSO_4$, and sodium methanesulfonate, $NaMeSO_3$, which yield the corresponding O-adducts, $ArOSO_3Me$ and ArO_3SMe, respectively, to determine the local head group concentration in sodium dodecyl sulfate and sodium dodecanesulfonate micelles by employing the chemical trapping method developed by Romsted[86].

As expected, the primary product of the reaction is the *Z*-isomer, which slowly rearranges to the *E*-isomer[2, 24]. Ritchie and Virtanen[24] determined the rate constant for the formation of the *Z*-isomer for the reaction of 4-nitrobenzenediazonium ions in methanolic buffers at $T = 23\,^{\circ}C$, finding a value of $k_1 = 8.7 \times 10^9\ l\ mol^{-1}s^{-1}$, i.e. almost 1.5 orders of magnitude higher than that of the reaction with MeO^- ions, whereas the equilibrium constant is $K_1 = 1.9 \times 10^{10}$, i.e. higher by 2 orders of magnitude. The k_1 value is very close to the diffusion-controlled value and the effect of substituents on k_1 is much smaller than in the reactions with other nucleophiles.

Ritchie and coworkers[44] measured the rates of forward and reverse reactions of substituted ArN_2^+ ions with substituted benzenesulfinic acids and found no evidence of *Z*−*E* isomerism in the diazosulfones formed. It is likely, therefore, that the final product is the *E*-isomer.

ArN_2^+ ions can also react easily with the thiol groups of S-aminoacids such as *N*-acetylcysteine, yielding compounds of the type Ar−N_2−S−$CH_2CH(NHAc)COOH$, and the formation of diazosulfones and diazosulfonates can also be described as S-coupling reactions. In the latter cases, the S-atom of the sulfinic acid or sulfite ions appear to be the basic center of the nucleophilic component, whereas the oxygen atoms are not.

Substituted ArN_2^+ ions react rapidly and reversibly with CN^- ions in aqueous media to give the corresponding *Z*-diazocyanides, which are slowly isomerized to the much more stable *E*-isomers[23]. The substituent effects on the rate of formation of the *Z*-isomer (k_1) and on the equilibrium constant of its formation (K_1) are expressed quantitatively in the

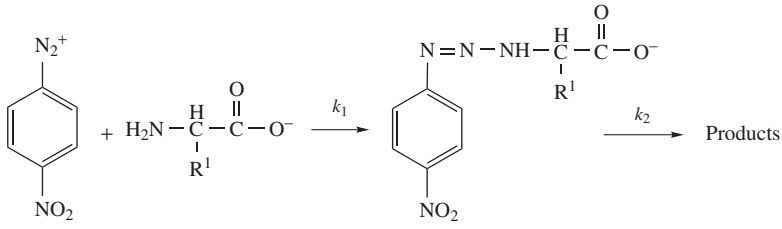
following Hammett relationships[23] (equations 9 and 10):

$$\log k_1 = 2.31\sigma + 2.32 \tag{9}$$

$$\log K_1 = 3.53\sigma + 1.82 \tag{10}$$

The relatively low value of $\rho = 3.53$ (as compared, e.g., with the value of 5.4 for the reaction of diazonium ions with OH^- ions, equation 3) is ascribed to the strong $-M$ effect of the CN group. This effect also has the consequence that, in contrast to diazoates and diazohydroxides, the isomerization is retarded by electron-withdrawing substituents[26].

ArN_2^+ ions may also react with nucleophiles containing an NH reactive center such as amino acids. The most important and thoroughly studied among them are the triazene formation by reaction of diazonium ions with primary and secondary aliphatic and aromatic (or heteroaromatic) amines (Scheme 16). So far, it has not been proved that these products undergo $Z-E$ isomerization since the measured dipole-moment values indicate that the isolated products are the E-isomers.



SCHEME 16. The proposed reaction mechanism for the reaction of 4-nitrobenzenediazonium ions and amino acids

These N-coupling reactions have attracted considerable attention from the biochemical point of view because arenediazonium ions are employed as specific reagents and probes of protein conformation[87] and because the coupling of diazonium ions with free histidine and tyrosine has been studied as a basis for quantitative investigation of the behavior of proteins[88]. For instance, Tracey and Shuker[89] characterized azo coupling adducts of benzenediazonium ions with aromatic peptides and proteins, and Patt and Patt[90] prepared radiolabeled peptides by reacting [^{18}F] 4-fluorobenzenediazonium ions with cysteine.

The estimated values for the second-order rate constant k_1' for the reaction between 4NBD and glycine and serine are $k_1' = 2390 \pm 16 M^{-1}s^{-1}$ and $376 \pm 7 M^{-1}s^{-1}$, respectively[91]. The intrinsic reactivity of glycine is thus about 5 times higher than that of serine, which is related to the presence of the hydroxy group. Remes and coworkers[92] studied the reaction between 4-chlorobenzenediazonium ions and a number of amino acids, finding no significant correlation between the second-order rate constants and the pK_a values of the latter, and assumed that the differences were related to the presence of heteroatoms in the molecule. This important point was not further investigated and probably needs extra attention.

As noted in previous sections, 4NBD reacts readily with MeOH and other alcohols under acidic conditions through the oxygen atom, leading to the formation of transient diazoethers of the type Ar–N=N–O–R′ [14, 15]. Serine has a hydroxyl group in its structure, and so one may hypothesize that a similar reaction may take place. However, in spite of

employing serine concentrations close to its solubility limit[93], a hypothetical reaction between 4NBD and serine through the OH group under the experimental conditions employed was deemed unlikely, i.e. no competing O-coupling reaction was detected.

The reaction of ArN_2^+ ions with an aromatic amine can result either in a reversible attack of the amine nitrogen atom to give a triazene, or in an attack of the aromatic carbon atom to give a very stable azo compound. The azo coupling reaction is negligible when aniline reacts in mildly acid medium. It takes place to a small extent with alkylanilines, but it becomes the main reaction in the cases of more reactive aromatic amines such as naphthylamines. An increase in the acidity of a medium speeds up the reverse reaction of triazene, and the percentage of azo compound in the reaction mixture increases.

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Properties, structure and reactivity of cobaloximes

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I. INTRODUCTION

A. Abbreviations

α	interplanar angle between dmgH moieties
AdoCbl	5′-deoxy-5′-adenosylcobalamin
BDE	bond dissociation energy
Bu	butyl
c-	cyclo
CCTP	controlled chain transfer polymerization
CH_2Ph	benzyl
CRP	controlled radical polymerization
CV	cyclic voltammetry
d	displacement of Co out of the equatorial plane in cobaloximes
DCE	dichloroethylene
Et	ethyl
EXAFS	extended X-ray absorption fine structure
i-	iso
Im	imidazole
Me	methyl
MeCbl	methylcobalamin
1-Me-Im	1-methylimidazole
1,2-Me_2-Im	1,2-dimethylimidazole
Me_3-Bzm	1,5,6-trimethylbenzimidazole
n-	normal
NH_2Ph	aniline
NMR	nuclear magnetic resonance
PCE	perchloroethylene
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine
t-	tertiary
TAP	trigonal antiprismatic
TCE	trichloroethylene
TP	trigonal prismatic
tu	thiourea

B. General Introduction

Cobaloximes are cobalt complexes containing the $Co(dmgH)_2$ moiety, where dmgH is the monoanion of dimethylglyoxime. Generally, the two dmgH units are H-bonded to each other, with the result that the four N donor atoms are coplanar. These intramolecular H-bonds assemble the $(dmgH)_2$ 'macrocyclic' equatorial ligand. The two remaining axial positions can be occupied by two neutral (L), two anionic (X) or one L and X ligand. The last case is the most common, giving neutral $LCo(dmgH)_2X$ species (Figure 1a). In organocobaloximes, X is a C-donor ligand and it is denoted by R. The non-organometallic cobaloximes are generally called 'inorganic' cobaloximes. In contrast to organocobaloximes, which are always octahedral Co^{III} complexes, the inorganic cobaloximes exhibit the less common five-coordinated geometry with the Co oxidation state from +3 to +1, in addition to the octahedral Co^{II} and Co^{III} species. No X-ray structural information on the Co^{IV} coordination is available.

Cobaloximes have been widely studied, on the one hand because of their extensive coordination chemistry and on the other because of the parallels between their chemistry and that of cobalamins, including the cofactors of B_{12} enzymes, methylcobalamin (MeCbl) and 5-adenosylcobalamin (AdoCbl) (Figure 1b). In fact, the alkylcobaloximes are the most extensively studied B_{12} models, with particular attention paid to the properties of the axial L-Co-R moiety, which can be transferred to some extent to the same fragment in cobalamins (Figure 1b)[1, 2]. Furthermore, it has been proven

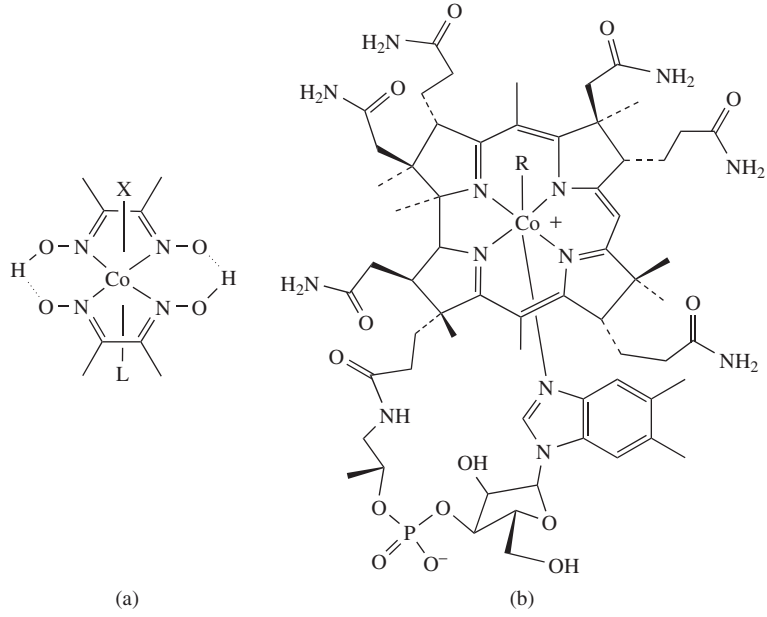


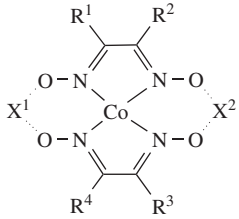
FIGURE 1. Scheme of (a) $LCo(dmgH)_2X$ and (b) cobalamins (Cbl). R = CN in vitamin B_{12}, and Me and 5′-deoxy-5′-adenosyl, respectively, in the two cofactors MeCbl and AdoCbl

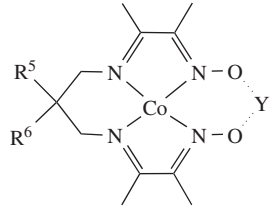
that cobaloximes behave as functional models of cobalamins toward the reductive dechlorination of chloroethylenes[3]. Alkylcobaloximes have also been shown to have catalytic applications in organic chemistry[4,5] and in polymerization reactions[6]. Recently, inorganic cobaloximes have been shown to catalyze hydrogen evolution in the presence of a proton source[7].

In the past, the systematic study of $LCo(dmgH)_2X$ has provided a considerable amount of structural, spectroscopic, thermodynamic, kinetic and reactivity data for a wide variety of X/R (from the weak electron donor, NO_3^-, to the bulky and strong electron donor, 1-adamantyl) and L ligands containing O-, N- or P-donor. The trends in these properties have been interpreted in terms of steric (bulk) and electronic (electron-donating ability) properties of the axial ligands X(R) and L (*cis* and *trans* influences and effects)[8–11]. Let us clarify what we mean by these effects in octahedral metal complexes with a 'macrocyclic' equatorial ligand such as $(dmgH)_2$. These effects have been clearly highlighted by Pratt[12] for L-Co(chel)-X complexes. They can be studied by examining: (a) the ground state effects, i.e. the effects of varying X (or L) on physical properties, such as bond lengths, NMR chemical shifts and stretching constants, of the *trans* L (or X) (*trans* influence) and *cis* chel ligands (*cis* influence); (b) thermodynamic effects on the equilibrium constants, e.g. for the L ligand substitution in complexes with the same chel and different X ligands (*trans* influence), or varying the chel ligand for the same X (*cis* influence); these influences involve the difference in free energy between two ground states of potentially known structure; (c) kinetic effects, which involve the difference in free energy between the ground state and the transition state, are usually called *cis* and *trans* effects. Often, the electronic and steric effects/influences superimpose and sometimes neither is clearly dominant. Attempts to quantify and to separate them have been carried out successfully[13]. This was accomplished by Principal Component Analysis applied to structural, kinetic and spectroscopic data of alkylcobaloxime[13]. The obtained t_i parameters, reflecting the electron-donating ability (t_1), the bulk (t_2) and angular deformation (t_3) of the alkyl group, respectively, are the predominant descriptors of alkylcobaloxime properties. These t_i parameters were also used to rationalize the chemical properties of the rhodoximes[10], the cob(III)aloxime valence isolectronic complexes of general formula $LRh^{III}(dmgH)_2X$. Up to 1999, unlike the very well established *trans* influence/effect, relatively few data were available[10] to clearly establish the influence of changes in the equatorial ligand on the axial fragment (*cis* influence of the equatorial ligand) in *modified* cobaloximes. We call *modified* cobaloximes the complexes with an equatorial ligand formally derived from the $(dmgH)_2$ moiety, with modifications of either glyoxime methyl side substituents or OH···O oxime bridges (Scheme 1). Herein, we refer to all of these as cobaloximes, when further specification is not necessary. The cationic imino-oximates, $[LCo\{(DO)(DOH)pn\}X]^+$ (Scheme 1), less studied B_{12} models, are also included in this definition.

In addition to new results on $(dmgH)_2$ complexes, both organometallic[14–19] and inorganic[20–24], many synthetic, X-ray structural and NMR studies have appeared in the last decade which describe the influence of the change of the dioxime side substituents[25–29] and of the OH···O bridge modifications[30–33]. In the latter case, the modification has also allowed the synthesis of new supramolecular Co complexes[34–37]. Products of an internal cyclization involving the oxime moiety have been reported[38]. Particularly interesting are the reports of dioximate clathrochelates, with Co in the lower +1 and +2 oxidation states[39–41], as well as in the +3 oxidation state[42]. Finally, in contrast to the huge amount of data on cob(III)aloximes, only a few Co^I penta-coordinated[43] and hexa- and penta-coordinated Co^{II} dioximate structures have been thus far reported[20,27,43,44].

In the present chapter, reference to studies published during the last decade is generally performed by reporting the most recent paper of a series of articles on the same subject,





R^1	R^2	R^3	R^4	X^1	X^2	
H	H	H	H	H	H	$(gh)_2$
Me	Me	Me	Me	H	H	$(dmgH)_2$
Me	Me	Me	Me	BF_2	BF_2	$(dmgBF_2)_2$
Me	Me	Me	Me	BPh_2	H	$(dmgH)(dmgBPh_2)$
Me	Me	Me	Me	BPh_2	BPh_2	$(dmgBPh_2)_2$
Ph	Ph	Ph	Ph	H	H	$(dpgH)_2$
Ph	Ph	Ph	Ph	BF_2	BF_2	$(dpgBF_2)_2$
Me	Ph	Ph	Me	H	H	*cis* $(mpgH)_2$
Me	Ph	Me	Ph	H	H	*trans* $(mpgH)_2$
H	H	Ph	Ph	H	H	(gH)(dpgH)
Me	Me	Ph	Ph	H	H	(dmgH)(dpgH)
2,4,6-$Me_3C_6H_2$	2,4,6-$Me_3C_6H_2$	2,4,6-$Me_3C_6H_2$	2,4,6-$Me_3C_6H_2$	H	H	$(dmsgH)_2$
	$-(CH_2)_4-$		$-(CH_2)_4-$	H	H	$(chgH)_2$
	$-(CH_2)_4-$	Ph	Ph	H	H	(chgH)(dpgH)
Cl	Cl	Cl	Cl	H	H	$(Cl_2gH)_2$

R^5	R^6	Y	
H	H	H	(DO)(DOH)pn
H	H	BF_2	$(DO)(DOBF_2)pn$
Me	Me	H	$(DO)(DOH)Me_2pn$

SCHEME 1

where the previous publications are cited. The X-ray structures reported in the present chapter are taken from the Cambridge Crystallographic Data Centre (CCDC).

II. COB(III)ALOXIMES

A. Synthesis

Inorganic cob(III)aloximes are readily obtained by reaction of a stable cobalt(II) salt, such as cobalt acetate or cobalt chloride, with dioxime in stoichiometric amounts and subsequent oxidation by exposure to air[45]. The organometallic derivatives can be prepared starting from Co^{III}, Co^{II} or Co^{I} reagents. The most common route to organocobalt species involves the reduction of an inorganic Co^{III} complex to Co^{I} with $NaBH_4$ in alkaline medium, followed by the oxidative addition of the appropriate alkyl halide[45]. The alkylation of a Co^{II} species is less convenient, because it leads to equimolar amounts of organo-

and halo-complexes, whose separation is often difficult. The reaction of an inorganic Co^{III} complex with a Grignard reagent has been used to obtain aryl derivatives[45].

B. Structural Aspects in Solution and in the Solid State

The structural studies on cobaloximes, in solution and in the solid state, concern for the most part Co^{III} derivatives. These studies were mainly aimed to obtain further insight into the mutual interactions among the Co ligands and their influence on the cobalt center. In the following sections, results up to 1999 and their rationalization will be summarized and then the more recent results will be discussed.

1. Equatorial moiety

In previous reviews[8–10], a statistical analysis of the geometry of the $Co(dmgH)_2$ and $Co(gH)_2$ (Scheme 1) units gave the mean bond length values of the equatorial moiety, reported in Table 1, together with the bond lengths in dimethylglyoxime and glyoxime ligands. Comparison of the distances of the ligands in the complex with those in the free ligands shows, for both dioximates, that deprotonation and coordination cause a significant decrease in the N–O distance and only small variations in the other distances. The H-bond of the bridge is likely asymmetric. In fact, the O···O distance of about 2.5 Å is intermediate between the symmetric H-bond of 2.38 Å in the hydrated proton, $H_2O\cdots H^+\cdots OH_2$, and the asymmetric one of 2.70 Å between two water molecules. The overall pattern of the bond lengths indicates that the electron delocalization in the CoN_2C_2 cycles is small[8–10]. Finally, the data in Table 1 show that the change of the glyoximate side substituents does not affect significantly the geometry of the equatorial moiety. It is worthwhile to recall that no appreciable variation in the distances of the $(dmgH)_2$ moiety is observed irrespective of the axial fragment in all the cobaloximes so far characterized by X-ray crystallography[8–10].

2. Trans influence and trans effect

In cobaloximes, the lengthening of the Co–L bond when the *trans* ligand X is varied has been mainly attributed to the electron-donating ability of X (electronic *trans* influence of X). The *trans* effect, measured by the change of several orders of magnitude in the pseudo-first-order rate constant k for the displacement of L, follows the same trend of the *trans* influence as measured by the increase in the Co–N axial distance of up to 0.2 Å

TABLE 1. Mean bond lengths (Å), with their estimated standard deviations in parentheses, in the $Co(dmgH)_2$ and $Co(gH)_2$ units and the corresponding distances in the $dmgH_2$ and gH_2 ligands

	$Co(dmgH)_2$[a]	$dmgH_2$	$Co(gH)_2$[b]	gH_2
Co–N	1.8901(9)	—	1.884(9)	—
C–C	1.462(3)	1.474(3)	1.44(1)	1.453(1)
C–N	1.301(1)	1.288(3)	1.30(1)	1.2849(8)
N–O	1.3492(9)	1.410(3)	1.34(1)	1.3854(8)
C–Me	1.501(1)	1.487(2)	—	—
O···O	2.487(2)	—	2.49(1)	—

[a]Reference 8. Average values over 75 compounds.
[b]Reference 9. Average values over 10 compounds.

TABLE 2. Axial Co–N distances (Å) and log k for $LCo(dmgH)_2X/R$ complexes. The cone angles (°), CA, for L ligands are also reported. The pseudo-first-order rate constant k (s^{-1}) refers to the L substitution reaction. Data are from References 8–10 and 56

X(R)/L		Cl^-	CH_2NO_2	$CHCl_2$	Me	*i*-Pr	1-Adamantyl
1-Me-Im	Co–N	1.936(3)	—	—	2.032(3)	—	2.069(4)
CA = 95.5	Log k	—	—	—	*−3.60*	*−0.80*	—
Me_3-Bzm	Co–N	1.959(2)	2.013(3)	2.047(2)	2.060(2)	2.097(2)	2.137(4)
CA = 101.2	Log k	—	—	*−4.50*	*−2.38*	*0.58*	*1.61*
py	Co–N	1.959(2)	2.028(3)	2.045(2)	2.068(2)	2.099(2)	—
CA = 101.1	Log k	—	—	*−4.32*	*−2.10*	*0.47*	*2.26*
1,2-Me_2-Im	Co–N	—	2.049(3)	—	2.086(1)	2.121(2)	—
CA = 108.6	Log k	—	—	—	*−1.96*	*1.04*	—
2-NH_2-py	Co–N	—	—	—	2.121(3)	2.194(4)	—
CA = 110.7	Log k	—	*−3.42*	*−0.62*	*0.54*	—	—

(Table 2)[8–10]. An analogous trend has been observed for the γ-^{13}C(py) NMR chemical shift, which varies from 138.89 ppm ($X = N_3^-$) to 137.00 ppm (R = 1-adamantyl) in the series $pyCo(dmgH)_2X/R$. In the series 4-*t*-Bu-$pyCo(dmgH)_2X$, with numerous X ligands, the α-^{1}H resonance of the axial 4-*t*-Bu-py shifts to lower field as the *trans* X ligand is changed from a very weakly electron-donating ligand such as NO_3^- (7.87 ppm) to a very strong electron-donating R group such as *i*-Pr (8.41 ppm). On the contrary, for the same series the γ-^{13}C resonance of the 4-*t*-Bu-py shifts to higher field from 164.33 ($X = NO_3^-$) to 161.37 (R = *i*-Pr) ppm[8]. Finally, the ^{31}P resonance in $P(OMe)_3Co(dmgH)_2X$ shifts to lower field from 89.0 ($X = NO_3^-$) to 131.9 (R = *i*-Pr) ppm. These and similar trends in NMR chemical shifts found in other series[8,9] principally reflect the electronic *trans* influence of X and very often are linearly correlated with the axial Co–L distances in each L series.

The Co–C distances do not appear to undergo electronic *trans* influence by the L ligand, whereas the Co–C bond dissociation energies are significantly influenced by the basicity of L. In the series 4-Y-$pyCo(dmgH)_2CH(Me)Ph$, the Co–C BDE was found to increase linearly with the pK_a of the sterically invariant 4-substituted pyridines. The BDE values range from 74.8 kJ mol^{-1} for Y = CN to 88.6 kJ mol^{-1} for $Y = NH_2$ (Table 3). This trend can be understood as arising from the stabilization of the Co^{III} oxidation state by more basic *trans* ligands (electronic *trans* influence)[46]. The BDE of 69.3 kJ mol^{-1} in the *endo* coordinated 2-NH_2-py analogue is significantly smaller than that expected on the basis of the pK_a[47]. This result was interpreted as due to the steric interaction of the 2-NH_2-py ligand with the equatorial moiety, which lengthens the Co–N bond (steric *cis* influence exerted by the $(dmgH)_2$ equatorial moiety on L, see below), so that the ligand becomes a poorer electron donor and, hence, weakens the *trans* Co–C bond[47]. In fact, an abnormally elongated Co–N(*endo*) bond (2.194(4) Å) in 2-NH_2-$pyCo(dmgH)_2Pr$-*i*, as compared with that of 2.099(2) Å in $pyCo(dmgH)_2Pr$-*i*, was found (Table 2)[11].

Previous results[8–11] have shown that in alkylcobaloximes, the Co–R bond, especially with bulky R ligands, can be lengthened by an increase in bulk of L (steric *trans* influence of L), which provokes the bending of the $(dmgH)_2$ moiety toward R (Table 4), thereby pushing away the R ligand. Significant changes in the α bending between the two dmgH moieties toward the less bulky axial ligand and in the Co displacement, d, out of the four equatorial N donors plane toward the more bulky axial ligand are found (Table 4). The

TABLE 3. Co−C BDE (kJ mol^{-1}) in LCo(dmgH)$_2$R. Data are from Reference 9 unless otherwise specified

L/R	BDE	L/R	BDE
4-NH_2-py/CH(Me)Ph	88.6	PMe_2Ph/CH_2Ph	127
4-Me-py/CH(Me)Ph	84.0	P(Bu-*n*)$_3$/CH_2Ph	120
py/CH(Me)Ph	81.5	$PEtPh_2/CH_2Ph$	112
4-CN-py/CH(Me)Ph	74.8	PPh_3/CH_2Ph	107
Im/CH(Me)Ph	86.9	P(Hex-*c*)$_3$/CH_2Ph	95
2-NH_2-py/CH(Me)Ph	69.4	PMe_2Ph/CH(Me)Ph	100
Acetone/CH(Me)Ph	70.6	P(Bu-*n*)$_3$/CH(Me)Ph	87
py/Me[a]	138.4	$PEtPh_2$/CH(Me)Ph	83
py/CH_2Ph[a]	130.4	P(CH_2CH_2CN)$_3$/CH(Me)Ph	79
py/*i*-Pr[a]	89.0	PPh_3/CH(Me)Ph	71

[a]Reference 57.

TABLE 4. Co−C (Å) distances, α (°) bending, the interplanar angle between the two dmgH moieties, and d(Å) displacements of Co out of the four equatorial N-donors plane, in 1-adamantyl- and methyl-cobaloximes with L ligands having different bulk. The positive sign of α and d indicates bending toward R and displacement toward L, respectively, and vice versa. Data are from Reference 9

	R = 1-adamantyl			R = Me		
L	Co−C	α	d	Co−C	α	d
H_2O	2.129(3)	−15.8	−0.093	1.990(5)	−4.6	−0.002
1-Me-Im	2.154(5)	−9.7	−0.057	1.980(4)	+4.1	+0.050
NH_2-Ph	2.159(4)	−10.0	−0.065	1.992(2)	+3.8	+0.035
Me_3-Bzm	2.179(6)	−7.5	−0.027	1.989(2)	+3.0	+0.056
$P(OMe)_3$	2.214(3)	−7.2	−0.015	2.01(1)	+10.2	+0.093
PPh_3[a]	2.217(7)	−3.2	−0.011	2.026(6)	+11.2	+0.111

[a]For the methyl derivative, L = PPh_2Et.

α and d parameters essentially respond to the difference in bulk between the two axial ligands. Accordingly, in the series LCo(dmgH)$_2$CH(Me)Ph, with L varying from PMe_2Ph to PPh_3, the Co−C BDE decreases from 100 to 71 kJ mol^{-1} (Table 3), respectively, and is linearly related to the bulk, as measured by the cone angle, and not to the pK_a of the phosphine (steric *trans* influence)[9, 10]. A similar trend was found with the less bulky CH_2Ph ligand in the analogous series phosphineCo(dmgH)$_2$$CH_2Ph$, where the Co−C BDE decreases with the increase in bulk of the phosphine by about 30 kJ mol^{-1} (Table 3). Correspondingly, the Co−CH_2CMe_3 distances range from 2.084(3) Å when L = PMe_3 to 2.116(10) Å when L = PPh_3[9].

Very recently, a study of chlorovinylcobaloximes has been undertaken to investigate the mechanism of reductive dechlorination of perchloroethylene by vitamin B_{12}[14, 15] (see Section VII.B). Comparison of the axial fragment in a series of mono- and di-chlorovinyl cobaloximes with L = py[14] and in the corresponding vinyl derivative showed that the Co−py distance appears to slightly increase by 0.02 Å in the order *cis*-1,2-dichlorovinyl < 1-chlorovinyl < *trans*-2-chlorovinyl ≈ *cis*-2-chlorovinyl < vinyl, reflecting the decreased electron-withdrawing ability of R in this series (electronic *trans* influence of R on L). On the other hand, the Co−C distance does not vary significantly in all these compounds, being significantly shorter by about 0.08 Å than that found[8−10] in

4-CN-pyCo(dmgH)$_2$Et. This is expected on the basis of the different hybridization of the C atom bonded to Co. It is worth noting the Co−C−C angle of about 140° in *cis*-2-chlorovinyl as compared to those found in the other vinyl derivatives, which vary from 121 to 128°. Also, the Co−N distances do not vary significantly in all these vinyl derivatives, being significantly shorter by about 0.04 Å than that found[8−10] in the analogous ethyl derivative. Short Co−N and Co−C bond lengths attributable to electronic influences have been already observed in cobaloximes with fluorinated alkyl-groups[10]. Recently, a slight shortening of the axial Co−N bonds in 4-*t*-Bu-pyCo(dmgH)$_2$2-F-Hex-*c* as compared to that in Me$_3$-BzmCo(dmgH)$_2$Hex-*c* was found[16], but no significant change in the corresponding Co−C bond was observed.

In the last decade, fewer inorganic cobaloximes have been characterized structurally in comparison to the organometallic complexes. The insertion of sulfur dioxide into the Co−C bond of several pyCo(dioxime)$_2$CH$_2$(4-XC$_6$H$_4$) leads to a mixture of pyCo(dioxime)$_2$SO$_2$CH$_2$(4-XC$_6$H$_4$), pyCo(dioxime)$_2$Cl and, in the case of dpgH (Scheme 1), to a neutral trinuclear species [pyCo(dpgH)$_2$Co^{III}-μ-SO$_3$-Co^{II}(MeOH)$_4$-μ-SO$_3$Co^{III}(dpgH)$_2$py][48]. This represents the first structurally characterized dioximate with an O$_3$S-Co-py axial fragment thus far reported. Comparison of the Co−py distance *trans* to sulfite of 2.044(4) Å with those found in pyCo(dpgH)$_2$X with X/R = Me[49], SO$_2$CH$_2$C$_6$H$_5^-$[48] and Cl$^-$[49] suggests the following order of structural *trans* influence: Me (2.085(2)Å) > SO$_3^{2-}$(2.044(4)Å) > SO$_2$CH$_2$C$_6$H$_5^-$(2.011(3)Å) > Cl$^-$(1.978(3)Å). A similar trend was previously found in cobalamins[2] and in (PhNH$_2$)Co(dmgH)$_2$X cobaloximes[8, 9]. The EPR spectra of the trinuclear species in solution and in the solid state give only a broad signal and no hyperfine structure, in accord with previous findings in similar trinuclear complexes[49].

The synthesis and the structural characterization of 4-*t*-Bu-pyCo(dmgH)$_2$EPh$_3$ (E = Sn, Pb) have been reported[44]. Both the SnPh$_3^-$ and PbPh$_3^-$ are strong *trans* influencing ligands, as shown by their similar ^{1}H and ^{13}C NMR spectra closer to those of the 4-*t*-Bu-pyCo(dmgH)$_2$Me than to those of 4-*t*-Bu-pyCo(dmgH)$_2$Cl[8, 9]. Correspondingly, the axial Co−N distances of 2.056(2) and 2.049(2) Å for the Sn and Pb derivatives, respectively, are much closer to that found in pyCo(dmgH)$_2$Me (2.068(3) Å) than to that found in pyCo(dmgH)$_2$Cl (1.959(2) Å)[8−10].

The X-ray structures of some azido derivatives, LCo(dmgH)$_2$N$_3$ (L = H$_2$O, py, N$_3^-$, PPh$_3$) complexes, have been reported[50−52]. The Co−N$_3$ distances exhibit the following order: 1.919 (3) Å (L = H$_2$O) < 1.952(2)Å(L = py) < 1.968(2)Å(L = N$_3^-$) < 2.014(4)Å(L = PPh$_3$), indicative of the increase of the *trans* influencing ability from the H$_2$O to PPh$_3$ *trans* ligand. This also shows that H$_2$O is the weakest, thus far known, *trans* influencing ligand in cobaloximes.

A series of XCo(dmgH)$_2$L, with X = Cl$^-$, NO$_2^-$ and L = variously substituted pyridines, has been synthesized and characterized crystallographically[22]. Interestingly, when X is Cl$^-$, a very weak electron-donating species, it was found that the Co−Cl distance undergoes a significant *trans* influence of the neutral base in the order py (2.229(1) Å)[53] < 4-Br-py (2.252(2) Å) < 4-Cl-py (2.314(1) Å), whereas the Co−L distance does not vary appreciably, from 1.950(3) to 1.959(2) Å. With the same L bases and X = NO$_2^-$ (a better electron donor than Cl$^-$ but dramatically worse than an alkyl group) a similar but less enhanced trend was found for the axial Co−NO$_2$ distances, which varied from 1.943(3) Å (L = py) to 2.003 (2) Å (L = 4-Cl-py)[22]. This is the first example of *trans* influence due to different substituted pyridines. This lengthening cannot be detected in alkylcobaloximes, owing to the strong *trans* influencing ability of the alkyl group.

Recent kinetic studies of the substitution reaction of water with several L ligands in H$_2$OCo(chel)R (chel = (dmgH)$_2$ and (DO)(DOH)pn) with various R groups have been carried out[54]. The *trans* effect of R was confirmed. Rate and activation parameters indicate

that the reaction mechanism is influenced by both the R group and the entering L ligand. These data suggest that, along the cobaloxime series with R groups from *c*-Hex to CH_2CF_3, the mechanism gradually changes from dissociative (D) to interchange (I) with a partial association and dissociation of the entering and leaving ligands[55].

3. Cis influence and cis effect

In the series $LCo(dmgH)_2R$, with several R groups, the increase in bulk of L (L = 1-Me-Im < Me_3-Bzm ≈ py < 1, 2-Me_2-Im < 2-NH_2-py) causes a significant lengthening of the Co−L bond by steric interaction of L with the equatorial moiety (steric *cis* influence of L)[10, 11] (Table 2). In the methyl derivatives a lengthening by about 0.1 Å is observed. Correspondingly, an increase of several orders of magnitude is found in the rate constant *k*, which changes by four orders of magnitude from 1-methylimidazole to 2-aminopyridine when R = Me[8–11] (Table 2) (steric *cis* effect). More in general, the trends of log *k* and the axial Co−N distances, for the same R and different planar L ligands, reflect the bulk of the latter following the order 1-Me-Im < Me_3-Bzm ≈ py < 1, 2-Me_2-Im < 2-NH_2-py. Similarly, the Co−P distance in the $PR_3Co(dmgH)_2Me$ series ranges from 2.256(4) Å for $P(OMe)_3$ to 2.463 (5) for P(Hex-*c*)$_3$ according to the following sequence: $P(OMe)_3$ < $P(OMe)_2Ph$ ≈ PMe_3 < $P(OMe)Ph_2$ < PPh_3 < P(Hex-*c*)$_3$[8]. The Co−Me distance did not show any appreciable change along the series. Very recently, the analysis was extended, for R = Me, *i*-Pr, to more sterically hindered L ligands, such as 4-methylquinoline and the results confirmed these findings (Table 5)[56]. Furthermore, the study has shown that, for both the R series, the relationships between the Co−N distances and the L cone angle are fairly linear (Table 5). These relationships only slightly improve when the contribution of the basicity of L, measured by its pK_a, is also included, confirming that the steric *cis* influence is the dominant factor. As expected, the Co−C distances are scarcely influenced by the change of the L planar ligand (Table 5). The ratio of the integration of ^{1}H NMR signals between the *ortho* proton of the coordinated and free L ligand provides a qualitative assessment of the association constants related to the binding ability of L to $MeCo^{III}(dmgH)_2$ moiety[56]. This ratio at −20 °C ranges from 9.9 for L = 2, 4-lutidine to 0.4 for L = 2-vinylpyridine and follows the order of the sterically hindered L ligand 2,4-lutidine > 4- methylquinoline ≈ quinoline ≈ 2-picoline ≈ 2-methoxypyridine > 2-ethylpyridine > 2-vinylpyridine.

The *cis* influence is also apparent from the trend of the ^{13}C resonances of the glyoxime C=N and CH_3 carbon atoms. In the series $LCo(dmgH)_2X$, with L = py, 4-*t*-Bu-py and $P(OMe)_3$ and numerous X ligands with different electron-donating ability, these

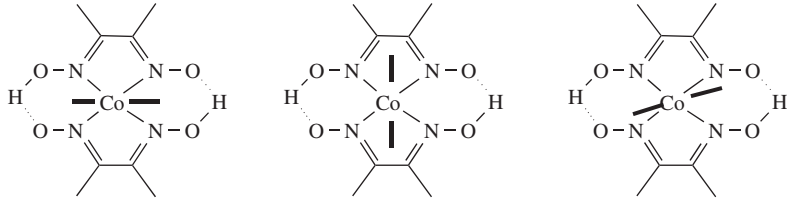
TABLE 5. Co−C and Co−N distances (Å) for $LCo(DH)_2R$ (R = Me, *i*-Pr) and L cone angles (°). Data are from Reference 56

L	R = Me		R = *i*-Pr		Cone angle
	Co−C	Co−N	Co−C	Co−N	
Im	1.985(3)	2.019(3)	—	—	95.5
Me_3-Bzm	1.989(2)	2.060(2)	2.076(2)	2.097(2)	101.2
py	1.98(5)	2.068(2)	2.085(3)	2.099(2)	101.1
1,2-Me_2-Im	2.001(2)	2.086(1)	2.096(3)	2.121(2)	108.6
2-NH_2-py	1.986(4)	2.121(3)	2.097(4)	2.194(4)	110.7
2-Picoline	1.988(3)	2.142(4)	—	—	112.8
2-Vinylpyridine	1.953(5)	2.143(4)	—	—	113.8
4-Methylquinoline	1.995(3)	2.193(3)	—	—	113.9

resonances shift upfield by about 3 and 1 ppm, respectively, from the very weakly electron-donating N_3^- group to the very strong electron-donating *i*-Pr group[8, 9].

For several L ligands, the weakening of the Co−C bond is measured by a lengthening of up to 0.2 Å on going from Me to 1-adamantyl (Table 4) and by a decrease in BDE up to about 50 kJ mol^{-1} in py derivatives, on going from Me (138.4 kJ mol^{-1}) to *i*-Pr (89.0 kJ mol^{-1}) (Table 3)[9, 57]. This is related to the increase in bulk of R, which interacts sterically with the dmgH ligands (steric *cis*-influence of X). A similar trend is observed in inorganic cobaloximes. In fact, in $LCo(dmgH)_2Cl$, where L = NH_3, $NHMe_2$ and NH_2Ph, the axial Co−N distances are 1.965(4), 1.994(5) and 2.019(2) Å, respectively, and follow the increase in bulk of the L ligands, regardless of their basicity[8].

Up to 1999, unlike the very well studied interactions between the equatorial $(dmgH)_2$ and the axial ligands, relatively few data were available to clearly establish the influences of changes in the equatorial ligand on the axial fragment (*cis* influence). Systematic kinetic and structural studies[8–10] for several L and X axial ligands were essentially limited to the imino-oxime complexes, $[LCo\{(DO)(DOH)pn\}X]^+$ (Scheme 1). In the latter complexes, it was found that the axial distances follow the same trends found in cobaloximes of Figure 1a, reflecting the bulk and the electron-donating ability of the axial ligands. For several L groups, such as py and Me_3-Bzm, the planar ligand was found in the orientation B, in contrast to the orientation A generally observed in cobaloximes (Scheme 2). Correspondingly, for the same *trans* X group, the axial Co−N distance increases by about 0.03 Å and the α bending angle increases by about 10° in the imino−oxime complexes with respect to cobaloximes. Such a difference was attributed to the steric *cis* influence between the equatorial moiety and the L ligand. In the series $[Me_3\text{-}BzmCo\{(DO)(DOH)pn\}X]^+$ the rate constants for the displacement of Me_3-Bzm are ten times greater than those of the analogous cobaloximes (Table 6)[58]. The log *k* for the (DO)(DOH)pn series is linearly related to the log *k* of the corresponding $(dmgH)_2$ series (Table 6) with an excellent regression ($R^2 = 0.997$) of the equation, $\log k_{(DO)(DOH)pn} = 0.945 \log k_{(dmgH)_2} + 0.994$. This relationship is unequivocal evidence of a *cis* effect. The trend of log *k* is consistent with longer Co−N axial distances and larger α bending angles in the imino−oxime (DO)(DOH)pn complexes than those in cobaloximes[9], showing that the *cis* effect parallels the *cis* influence.



SCHEME 2

Since then, Gupta and coworkers have published numerous papers, aimed at studying the *cis* influence/effect[28, 49, 59–61] on the axial fragment[25] and on the O_2 insertion reaction into the Co−CH_2Ph bond[26, 59]. The synthesis and characterization by X-ray crystallography and ^{1}H and ^{13}C NMR of a huge number of modified cobaloximes, with variously substituted glyoxime side groups and L = py (Scheme 1), showed that for cobaloximes having the same axial R group the changes in the equatorial moiety do not significantly affect the geometry of the axial fragment. An analogous finding

TABLE 6. Logarithm of the first-order rate constant k (s^{-1}) for Me_3-Bzm exchange of [Me_3-BzmCo{(DO)(DOH)pn}R]-(ClO_4) and Me_3-BzmCo$(dmgH)_2$R in CH_2Cl_2 (25 °C). Data are from Reference 58

R	Log k	
	(DO)(DOH)pn	$(dmgH)_2$
CH_2CF_3	−3.63	−4.89
CH_2Br	−2.58	−3.91
Me	−1.36[a]	−2,38
Et	−0.086	−0.95
CH_2CMe_3	1.00	−0.090
i-Pr	1.64[b]	0.58
c-Hex	1.72	0.79

[a]Log $k = -1.40$ for the PF_6^- salt.
[b]Log k given is for the PF_6^- salt.

was found for $H_2OCo(chgH)_2R$ complexes[62, 63]. A scale for the steric *cis* influence of the modified 'macrocyclic' equatorial ligand was suggested to be based on small differences observed on the α-bending angles in different dioximates with the same axial fragment[49]. A scale based on α values is, however, questionable because of the small change in α and, more importantly, since they are strongly influenced by the crystal packing. The ^{1}H resonances of the pyridine *ortho* proton and of the OH···O oxime bridge and the ^{13}C resonances of C=N were the only NMR signals sensitive to the change of the equatorial dioxime and of the axial fragment[49, 63]. The differences in the ^{13}C signal of C=N between cobaloximes having the same axial fragment and different equatorial ligands were assumed to parallel the *cis* influence scale based on the α bending[49]. The two scales, based on the chemical shifts values and on the X-ray structural data, were not completely consistent[49]. This is unsurprising because this ^{13}C NMR signal is mainly influenced by the change of the electronic properties of the glyoxime side substituents. However, this disputable assumption of a *cis* influence scale was extended with some incongruity also to mixed dioxime ligands. For example, in one paper the decreasing order of the overall *cis* influence was reported to be $(dmsgH)_2 > (dpgH)_2 > (gH)(dpgH) > (dmgH)(dpgH) > (chgH)(dpgH) > (chgH)_2 > (dmgH)_2 > (gH)_2$ (Scheme 1)[26], whereas a different order was reported for the last three members—$(dmgH)_2 > (gH)_2) > (chgH)_2)$—in another paper[25]. This research group has also studied[26–28, 59] the insertion of O_2 into the Co−C bond in a series of pyCo(dioxime)$_2$$CH_2Ph$ complexes with different equatorial ligands. These complexes reacted with oxygen during photolysis to give the corresponding peroxo complexes pyCo(dioxime)$_2$O−OCH_2Ph, some of which were crystallographically characterized. It was found that the rate of insertion reflects the *cis*-effect of the equatorial ligand on the axial Co−C bond reactivity. This reaction was found to be two orders of magnitude slower in pyCo$(dmsgH)_2$R (R = Me, *n*-Bu) than in the corresponding CH_2Ph analogues[28]. This difference was ascribed to the '*stabilization* of the axial R group due to the interaction between axial and equatorial ligands', i.e. a $\pi-\pi$ interaction between the benzyl group and the glyoxime moiety[27]. In several dioximes, pyCo$(dmgH)_2CH_2Ar$ (Ar = 2-XC_6H_4, 2-naphthyl), the non-equivalence of the ^{1}H signals of the Co−CH_2 and dmgH methyl group protons at subzero temperatures has been attributed to such an interaction, which is claimed to cause hindered rotation around the Co−C and/or C−Ar bonds[29].

Analogous complexes of $pyCo(dpgH)_2X$ ($X = Cl^-$ and several R alkyl groups with different bulk and electron-donating ability) were synthesized and characterized[64]. Comparison of ^1H and ^{13}C NMR spectra with those of the corresponding cobaloximes suggests that the dpgH ligands are poorer electron donors than dmgH. The X-ray structure of the derivatives with $R = CF_3$, CH_2CMe_3 and CH_2SiMe_3 have been obtained. Comparison with the analogous dmgH derivatives showed that the axial fragment is very similar for $R = CF_3$ and CH_2CMe_3, whereas when $R = CH_2SiMe_3$ the dpgH derivative exhibits a significantly shorter Co–N axial distance than that of the dmgH analogue[8,9]. This difference of 0.03 Å is about six times higher than the estimated standard deviation of the less accurate of the two compared distances. Correspondingly, an α bending angle toward py of 7.3° in the dpgH and of 1.2° in the dmgH derivatives, respectively, was observed.

Whereas modifications in the glyoxime side substituents do not substantially affect the axial distances, there was evidence that modifications in the OH···O bridges slightly, but significantly, affect the geometry of the axial fragment and the equatorial Co–N distances. The results of a comparison of structural and conformational properties of $LCo(dmgH)_2Me$ and LCo(chel)Me (chel = $(dmgBPh_2)_2$, $(dmgBF_2)_2$, (dmgH)(dmgBPh$_2$), (DO)(DOH)pn and (DO)(DOBF$_2$)pn (Scheme 1)) have been reviewed[10]. It was found that the equatorial Co–N distances for oxime versus imine nitrogen donors are shorter by *ca* 0.03 Å, whereas in complexes with $X^1 \neq X^2$ (Scheme 1) the chemically equivalent equatorial distances are very close to those found in complexes with $X^1 = X^2$ and increase in the order $(dmgBF_2)_2 < (dmgBPh_2)_2 < (dmgH)_2 \approx$ (DO)(DOH)pn. The reduction potential, $E_{1/2}$, for Co^{III}/Co^{II} and Co^{II}/Co^{I} in $MeCo(dioxime)_2$ was found to become less negative in the order $(dmgH)_2 <$ (DO)(DOH)pn $< (dmgBF_2)_2 <$ (DO)(DOBF$_2$)pn, varying from −1.361 to −0.631 V and from −1.60 to −0.85 V, respectively. The Co—Me distance is not significantly affected by the change of the equatorial moiety, whereas the length of the Co–N axial bond appeared to be related to the orientation of the L ligand (L = py, Me_3-Bzm, Im, 1-Me-Im) (Scheme 2). In fact, for all chel ligands the orientation A corresponds to shorter distances than those corresponding to orientation B, whereas the orientation C corresponds to the longest Co–N axial distances[10]. Very recently[32], new data for the LCo(chel)Me series, with L = py, Me_3-Bzm, Im, 1-Me-Im, have confirmed that the Co–Me distance does not substantially change in all the chel derivatives, being about 2.00 Å. The trend of the equatorial Co–N distances was also confirmed. However, the interaction between L and chel was found to be related not only to the L orientation. In fact, the axial $Co–N_{axial}$ distance in the series with L = imidazole varies from 2.014(9) to 2.067(7) and increases in the order $(dmgH)_2 \approx$ (dmgH)(dmgBPh$_2$) < (DO)(DOH)pn ≈ (DO)(DOBF$_2$)pn < $(dmgBF_2)_2 < (dmgBPh_2)_2$ (steric *cis* influence). Correspondingly, the orientation of the L ligand is close to A (Scheme 2) for the first two complexes and the Co is nearly in the plane of the four equatorial donors[32]. In the other methyl complexes the orientation is close to B or C and *d* is about 0.05 Å. When L = py, the $Co–N_{axial}$ distance varies from 2.064(4) to 2.119(4) Å in the order $(dmgH)_2 \approx$ (DO)(DOBF$_2$)pn < (dmgH)(dmgBPh$_2$) ≈ $(dmgBPh_2)_2 <$ (DO)(DOH)pn < $(dmgBF_2)_2$. The orientation of py is close to B in all the complexes, except those of $(dmgH)_2$ and (dmgH)(dmgBPh$_2$), where it is close to A. Correspondingly, in the latter, *d* is close to zero Å, whereas in the others it is close to 0.1 Å. On the basis of these observations, it was concluded that the steric interactions between L and the equatorial ligands (steric *cis* influence) are alleviated by a combination of $Co–N_{axial}$ bond elongation and opening of the $N_{axial}–Co–N_{equatorial}$ angles, i.e. of an increase in *d*[32]. Quite dramatic changes occur in the ^1H NMR shifts of the CH groups of the axial py and Me_3-Bzm ligands as the equatorial ligand is changed. The ^1H NMR shift data for Me_3-Bzm compounds clearly support chel ligand anisotropy as a major factor influencing the shift of L proton signals[32].

In several papers[20, 21], Simonov, Malinovskii and coworkers have studied the structure of several $[trans\text{-}(tu)_2Co(dioxime)_2]_xX \bullet nH_2O$ (dioxime = dmgH, chgH and $x = 1, 2, 3$) complexes, with *trans* axial S-bound thiourea ligands. The counter-anion X was either a metal-fluorine anion MF_n (M = Zr, Al, Si, B, Be) or NO_3^-, SO_4^{2-} and F^-. Examination of the structure of these complexes revealed that the tu mean plane may assume two orientations, one approximately parallel (PA), the other approximately perpendicular (PE) to the dioxime equatorial plane. The latter orientation (with interplanar angles varying from 62 to 88°) is characterized by a H-bond from the thiourea NH_2 group to one O atom of the oxime bridge. The approximately parallel arrangement PA (with interplanar angles varying from 19 to 25°) is due to the $\pi-\pi$ interaction between tu and the equatorial metallocycle. In fact, in orientation PA the Co-S-C$(NH_2)_2$ fragment is characterized by Co–S–C angles and Co–S distances varying from 104.2(2) to 109.0(2)° and from 2.293(3) to 2.3294(6) Å, respectively. The ranges of the corresponding angles and distances in orientation PE vary from 113.1(2) to 117.9(2)° and from 2.278(3) to 2.2994(2) Å, respectively. The increase of the Co–S bond length and the corresponding decrease of the Co–S–C angle in orientation PA with respect to orientation PE could be due to a $\pi-\pi$ interaction. However, the orientation of thiourea is dictated by a complicate network of H-bonds formed by the complex molecules and the crystallization water molecules[21].

The structure of complexes containing Co^{III} cationic species $[trans\text{-}L_2Co(dioxime)_2]^+$ (dioxime = dmgH, chgH, L = PPh_3, aniline, *p*-toluidine) have been reported[65]. No evidence of structural *cis* influence on the axial fragment, attributable to the change of the equatorial ligand, is apparent.

4. Implications of interligand interactions in cobalamins

Some decades ago, alkylcobaloximes (Figure 1a) were proposed as alkylcobalamin model systems because they exhibit similarity in the Co center reactivity with reference to the Co−C bond cleavage[66]. In principle, in both alkylcobalamin and alkylcobaloximes (RCo(chel)), the Co-C fission can take place by homolysis (equation 1) or by one of the two heterolytic mechanisms (equations 2 and 3):

$$RCo^{III}(chel) \longrightarrow Co^{II}(chel) + R^{\bullet} \quad (1)$$

$$RCo^{III}(chel) \longrightarrow Co^{III}(chel)^+ + R^- \quad (2)$$

$$RCo^{III}(chel) \longrightarrow Co^{I}(chel)^- + R^+ \quad (3)$$

All the above reactions have been widely studied in alkylcobalamins and alkylcobaloximes[46, 67]. Reaction 3 is accepted to formally occur in methyltransferase enzymes having methylcobalamin as cofactor, such as methionine synthase[1, 2, 68]. AdoCbl (Figure 1b) thermolysis and photolysis occur through reaction 1, with a rate constant $k = 1.16 \cdot 10^{-8}\ s^{-1}$ down to 30 °C, and homolysis is favored over heterolysis at higher temperature[1, 11, 46, 69]. It is generally accepted that the homolysis of the Co−C bond in AdoCbl is the initial step in the AdoCbl enzymatic mechanism (reaction 1). It has been documented[1, 66] that the rate constant of AdoCbl homolysis in the holoenzyme increases enormously (more than twelve orders of magnitude) with respect to that found in the isolated coenzyme. The precise manner in which the binding of AdoCbl to the apoenzyme accomplishes this rate enhancement remains unknown, in spite of a large number of studies, and it is still their subject of research. However, some suggestions have been furnished by the alkylcobaloxime studies[11, 46].

Before analyzing the relationship between cobalamins and cobaloximes, let us first summarize the results obtained for cobalt dioximates. The Co−C BDE values respond to

the electronic *trans* influence of L, for L with similar moderate bulk. Vice versa, they respond to the steric *trans* influence when L is bulky. Furthermore, the Co–C distance is influenced by the increase in bulk of R, which interacts with the equatorial moiety (steric *cis* influence). The Co–L distances and log *k* for the L displacement reactions respond to the electron-donating ability of R (electronic *trans* influence/effect) and to the change in bulk of L (steric *cis* influence/effect), and they follow the same trend. On the other hand, the influence of the bulk of R on the equatorial moiety (steric *cis* influence) is evidenced by the bending of the equatorial moiety.

The above conclusions clearly rationalize the interactions between ligands in alkylcobaloximes in terms of their electronic and steric properties. A qualitatively similar behavior is found in cobalamins, as far as the structural *trans* influence is concerned. However, a quantitative comparison between the geometry of the axial fragments of Cbl's and cobaloximes has shown that the change of the equatorial ligand results in a significant structural *cis* influence on the axial Co–N bond, but not on the Co–C bond in alkyl derivatives[2]. The axial Co–N bond is more sensitive to the *trans* influencing ligand R in cobalamins than in cobaloximes. These structural quantitative differences, which are consistent with the comparison of the corresponding IR and electrochemical data, have been attributed to the higher electronic charge on Co due to corrin than that due to dimethylglyoximates[2].

The Co–C bond in alkylcobaloximes can be weakened by steric *cis* and *trans* influence on one side and by the electronic *trans* influence on the other. These findings support one of the mechanisms, the 'trigger mechanism', proposed for the activation of the Co–C bond toward homolysis in the AdoCbl-based enzymes[2, 10]. That mechanism suggested that the binding of AdoCbl to the protein provokes an upward distortion of the equatorial corrin ligand (Figure 1b) toward the Ado ligand, which stretches the Co–C bond (steric *cis* influence). The binding of AdoCbl to the protein also provokes a lengthening of the Co–N bond, which contributes to weaken the *trans* Co–C bond (electronic *trans* influence)[10, 11] in a way similar to that observed in alkylcobaloximes (see Section II.B.2). The rate enhancement of the homolytic cleavage has been attributed to these two effects[2, 46]. However, further studies are needed to support this suggestion, which at the present time is not conclusive.

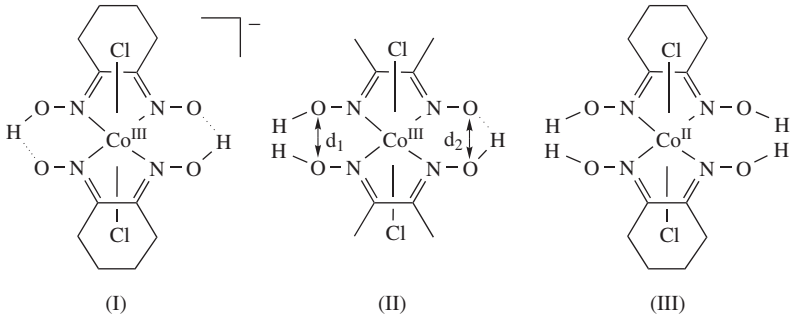
5. Other structural studies on hexacoordinated Co^{III} dioximates

Continuing their previous work on crystalline and solid state photo-isomerization reactions[9], Ohashi and coworkers have produced a series of papers[18, 19] which analyze these reactions in $LCo(dmgH)_2R$ compounds. These reactions, which generally do not occur in solution, are solid state specific and the reactivity is related to the 'reaction cavity'[18, 19] of the alkyl group in the crystal. The crystal structure analysis was carried out before and after irradiation of the single crystal. Two types of reactions have been studied by X-ray and neutron diffraction from powders and from single crystals. Alkyl groups with an asymmetric C_α atom bonded to Co, $C_\alpha HR^1R^2$, undergo complete or partial racemization after irradiation. The other type of reaction is the partial isomerization of alkyl groups $C_\alpha H_2(CH_2)_nCN$ ($n = 1$, 2 and 3) to $C_\alpha H(CH_3)(CH_2)_{n-1}CN$ and to $C_\alpha H(CN)(CH_2)_{n-1}CH_3$ for $n = 2$, 3. The proposed mechanism occurs in three steps: (i) homolysis of the Co–C bond by photo-irradiation; (ii) rearrangement of the produced alkyl radical; (iii) reformation of the Co–C bond. Neutron diffraction on suitable deuterated complexes was shown to be a powerful tool to assess a mechanism based on 1,2-deuterium–hydrogen exchange[19].

Several inorganic $H_2OCo(dioxime)_2NO_2$ complexes have been structurally characterized in order to study the reciprocal influence between the crystal packing

and the formation of the dioxime intramolecular and intermolecular H-bonds with the axial ligand[22]. Similar studies were carried out on several $H_2OCo(dioxime)_2R$ complexes[62]. Comparison of the crystal packing of some $LCo(dmgH)_2X$ (L = *R*-, *S*-, *rac*-1-phenylethylamine and $X = CN^-$, NO_2^- and NCO^-) cobaloximes indicated a higher packing efficiency for the racemate and the quasi-racemate than for the enantiopure compound[23].

The compound [*trans*-$Cl_2Co(chgH)_2](H_3O)$ was obtained by reaction of $CoCl_2$ with $chgH_2$ in strongly acidic medium (pH = −0.06/−0.1) and in the presence of oxygen[20]. The same reaction under Ar gave the Co^{II} species *cis*-$Cl_2Co(chgH_2)_2$ (see Section IV.B). On the basis of the X-ray structure, the complex anion, arranged on a crystallographic symmetry center, was formulated as the octahedral Co^{III} compound, [*trans*-$Cl_2Co(chgH)_2](H_3O)$, sketched as **I** in Scheme 3. However, the Co–Cl distance of 2.4710(4) Å is dramatically longer by about 0.25 Å than those found in the [*trans*-$Cl_2Co^{III}(dmgH)_2]^-$ anion (range from 2.231(5) to 2.259(5) Å)[70, 71], and close to those found in *cis*-$Cl_2Co^{II}(chgH_2)_2$ (2.430(7) and 2.4223 (8) Å)[20] (see Section IV.B). Furthermore, the O···O oximic bridge distance of 2.726(6) Å in [*trans*-$Cl_2Co(chgH)_2]^-$ is longer by 0.3 Å than those found in octahedral Co^{III} cobaloximes (Table 1), whereas it is not far from the analogous distances of 2.587(2) and 2.660(2) Å (d_1 and d_2, respectively in **II** of Scheme 3) reported in the neutral Co^{III} species [*trans*-$Cl_2Co(dmgH)(dmgH_2)$][72], with a diprotonated oximic bridge. Therefore, the O···O distance in [*trans*-$Cl_2Co(chgH)_2]^-$ may be indicative of a diprotonated bridge, in agreement with the synthesis in strongly acidic medium. All the above considerations point toward the formulation as the neutral Co^{II} species **III** in Scheme 3.



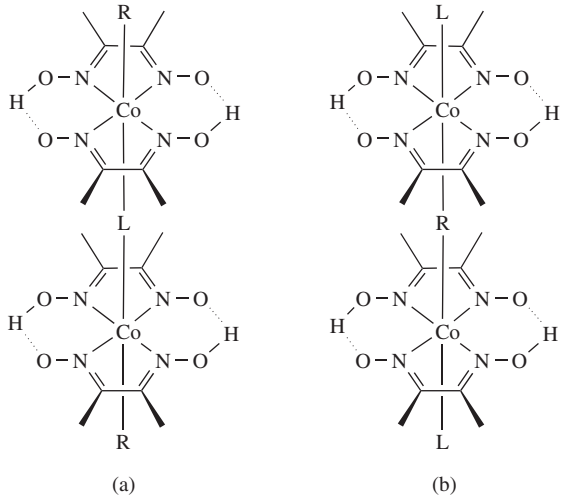
SCHEME 3

6. Pentacoordinated Co^{III} dioximates

To our knowledge, the crystallographically characterized Co^{III} dioximates are all, but two, hexacoordinated. The only two Co^{III} pentacoordinated species, reported over 20 years ago[73], are the inorganic $NOCo(dioximate)_2$ (dioximate = dmgH, dpgH) complexes with a bent NO bonded in the apical position. In the past, there was discussion[8, 9] about the existence of a pentacordinated $MeCo(dmgH)_2$ species in solution of non-coordinating solvents. However, it was concluded that the $MeCo(dmgH)_2$ species exists as dimeric species $[MeCo^{III}(dmgH)_2]_2$ with a six-coordinated cobalt atom[74]. The sixth axial position of each Co of methylcobaloxime unit is occupied by an oxime O atom of the other unit. In this respect, the cobaloxime behavior parallels that of cobalamins. In fact, no X-ray structure of any pentacoordinated cob(III)alamin has been thus far reported[2].

III. POLYCOB(III)ALOXIMES

The possibility of using cobaloximes or modified cobaloximes to obtain dinuclear species has been recently investigated in order to understand how the formation of a dicobaloxime affects the properties of the mononuclear complex, and particularly of the Co−C bond. Two paths have been followed: either to connect directly the Co centers, obtaining ditopic ligand- or organo-bridged dicobaloximes (Scheme 4), or to connect two cobaloxime units through modifications of the equatorial ligand (Scheme 5).



SCHEME 4

A. Co-bridged Dicobaloximes

1. Synthesis

Dinuclear Co^{III} dioximates bridged by a ditopic nitrogen donor ligand L (Scheme 4a) are generally obtained by mixing $H_2OCo(dmgH)_2R$ with the stoichiometric amount of L[73]. $[MeCo(dmgBF_2)_2(\mu\text{-imidazolate})Co(dmgBF_2)_2Me]AsPh_4$ was obtained from $ImCo(dmgBF_2)_2Me$ by deprotonation of the imidazole with NaOMe[75]. Organobridged cobaloximes (Scheme 4b) were prepared by oxidative addition of an alkyl or aryl dihalide to a Co^{I} complex[76].

2. Structural properties

To our knowledge, the first example of ditopic ligand bridged dicobaloximes whose X-ray structure has been determined is $[(O_2NCo(dmgH)_2\text{-}\mu\text{-}4,4'\text{-bipyridine-}Co(dmgH)_2\text{-}NO_2]$[73]. The structure of $[MeCo(dmgBF_2)_2\text{-}\mu\text{-imidazolateCo}(dmgBF_2)_2Me]AsPh_4$ in the solid state and in solution was then reported and compared to the analogous monocobaloxime[75]. The main structural difference with respect to $ImCo(dmgBF_2)_2Me$ concerns the imidazolate coordination to Co. The two $Co-N_{axial}-C$ angles in the dinuclear species are significantly different, being 125 and 131°, respectively. In $ImCo(dmgBF_2)_2Me$ those

angles are essentially equal, being 128°. The axial Co–N distance of 2.053(2) Å in the mononuclear species is significantly longer than the analogous distances of 2.017(3) and 2.018(3) Å in the dicobaloxime anion. However, the Co–Me distances are very similar in mono- and di-cobaloximes. The shortening of the axial Co–N distance was attributed to the better electron-donating ability of imidazolate with respect to imidazole, as suggested by the different $^1J_{CH}$ of the Co–Me group in the two compounds[75]. More recently, some pyrazine-bridged modified cobaloximes were also synthesized and characterized by NMR spectroscopy, cyclic voltammetry and X-ray analysis[77]. The X-ray structures of $PhCH_2Co(dioxime)_2$-μ-pyrazine$Co(dioxime)_2CH_2Ph$ (dioxime = $(dpgH)_2$, (dmgH)(dpgH)) were reported, which show that the geometry of the two halves of the dicobaloxime closely resembles that of the corresponding monocobaloxime. Very recently, dicobaloximes with two [$MeCo(dmgH)_2$] moieties bridged by other ditopic ligands (4,4′-bipyridine, α,α'-diamino-*p*-xylene and 1,6-diaminohexane) have been reported and characterized in solution and in the solid state[37].

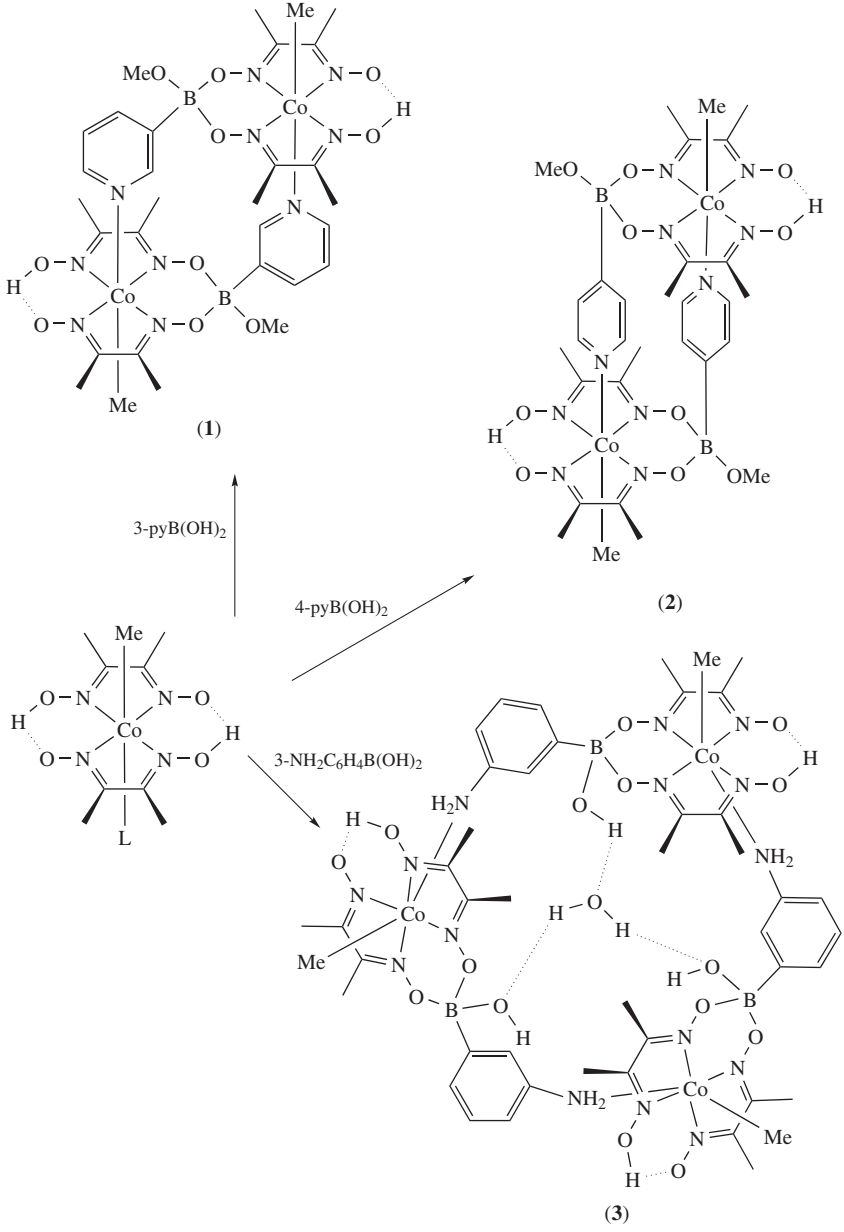
Organobridged dicobaloximes (Scheme 4b) are formed by bridging two $pyCo(dioxime)_2$ units through polymethylene or aromatic bridges[78, 79]. A series of $pyCo(dmgH)_2Co(\mu$-$CH_2)_nCo(dmgH)_2py$, where $n = 4$, 5, 6, 12, has been reported and characterized[78]. These complexes are reminiscent of the analogous B_{12} dimer $Cbl(CH_2)_4Cbl$[80], whose crystal structure revealed that the two cobalamin moieties are bridged by a tetramethylene chain bridging the two cobalt centers on the opposite side of the benzimidazole residue. Dicobaloximes with aromatic bridges, $pyCo(dioxime)_2Co(\mu$-CH_2-Y-$CH_2)Co(dioxime)_2py$, where dioxime is dmgH, dpgH and Y is a substituted phenyl or diphenyl group, have been characterized by NMR, CV and X-ray diffraction[79]. The X-ray structural parameters show that each cobaloxime unit behaves as an independent benzylcobaloxime.

B. Polycob(III)aloximes Bridged through Modification of the Oxime Moiety

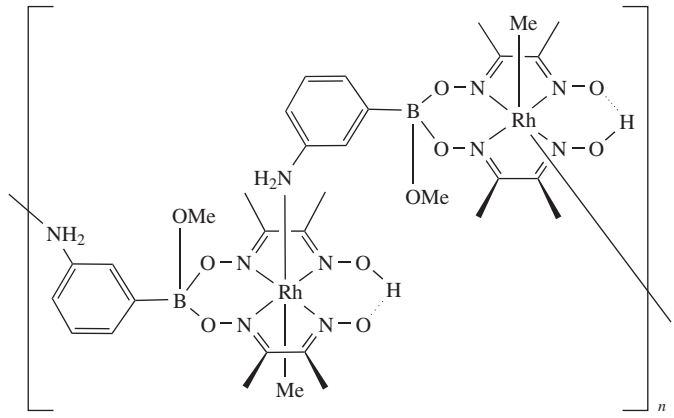
1. Synthesis

Organocobaloximes, with one or both H atoms of the oxime bridges replaced by BR_2 organoboryl groups, have been reviewed[30]. They are easily obtained by reacting the corresponding cobaloxime with the appropriate boron reagent.

The supramolecular species **1**–**3** (Scheme 5) have been assembled from $LCo(dmgH)_2Me$ and the functionalized boronic acids 3-pyridinylboronic (3-$pyB(OH)_2$), 4-pyridinylboronic (4-$pyB(OH)_2$) and 3-aminophenylboronic acid (3-$NH_2C_6H_4B(OH)_2$) through the reaction of the $B(OH)_2$ group with the oxime bridge of one bis(dioximate) moiety, with simultaneous coordination of the nitrogen atom to the metal center of another unit[34]. The reactions are strongly pH dependent because these boronic acids are zwitterionic species. In order to obtain the supramolecular species, the reactions must be carried out at neutral pH. A striking demonstration of the crucial role of pH arises from the reaction of $H_2OCo(dmgH)_2Me$ with 3-$NH_2C_6H_4B(OH)_2$[81]. When the pH of an aqueous solution of organoaquacobaloxime and 3-aminophenylboronic acid in approximately equimolar amounts is adjusted to about 7, the trimeric supramolecular species **3** precipitates immediately. Further acidification of the solution to below pH 4 results in the dissolution of the aggregate, which is re-formed by restoring the pH of the solution back to neutrality and is re-dissolved at alkaline pH values (above pH 9). Furthermore, it has been shown that modifications of the side groups of the equatorial ligand strongly affect the geometry of the assembled supramolecular species[35, 82] **2′**, **3′**


Me
MeO
B
O–N
N–O
Co
H
N
OMe
(1)
3-pyB(OH)2
4-pyB(OH)2
(2)
3-NH2C6H4B(OH)2
L
H2N
NH2
(3)

SCHEME 5



(**4**)

SCHEME 5. (*continued*)

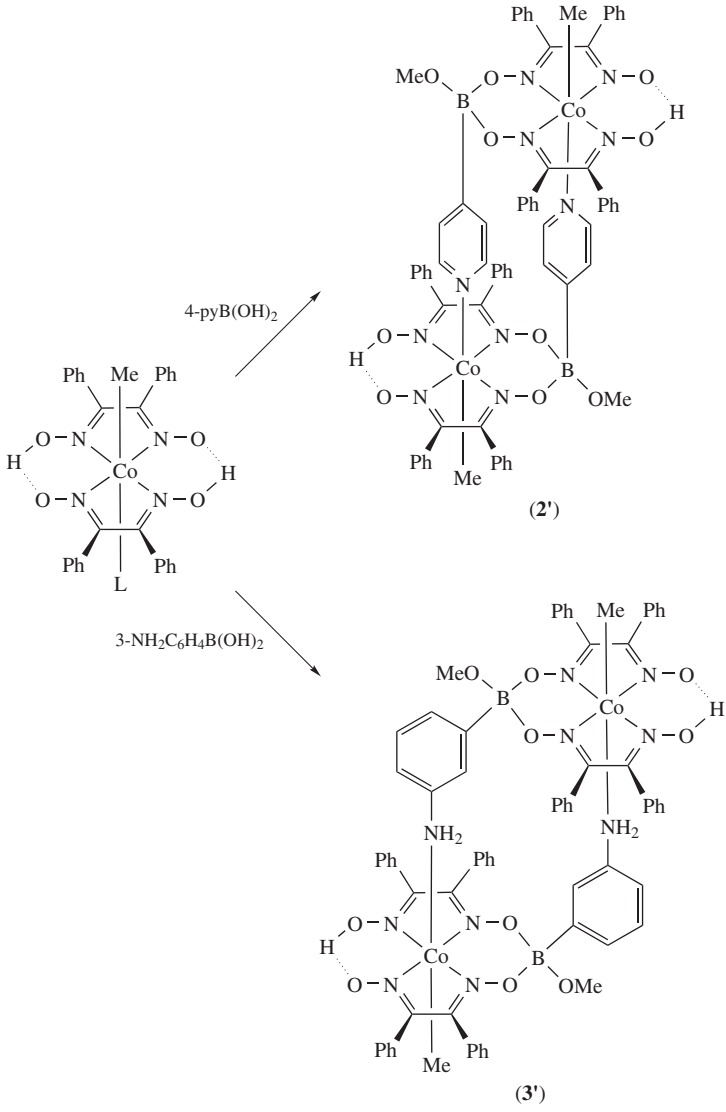
(Scheme 6) and **1**″, **2**″, **1**‴ and **2**‴ (Scheme 7). It is worthwhile recalling that the reaction of the rhodoxime $H_2ORh(dmgH)_2Me$ with 3-aminophenylboronic acid gives instead the polymeric arrangement of [MeRh(dmgH)(dmgB(OMe)(3-$NH_2C_6H_4$)] units, **4** (Scheme 5)[35, 82].

In another approach, 1,4-phenyldiboronic[36] and 4,4′-biphenyldiboronic acids[37] were used as connecting elements between two cobaloxime units to generate a supramolecular structure, by exploiting the reaction of the $B(OH)_2$ groups with the oxime bridges. It is noteworthy that the assembly of 'filled boxes' occurred only for the systems pyrazine/1,4-phenyldiboronic acid, **5**, and 4,4′-bipyridine/4,4′-biphenyldiboronic acids,**6** (Scheme 8), the other tested systems leading only to a partial assembly (Scheme 9).

The self-assembly of **5** and **6** was monitored by ^{1}H NMR spectroscopy. In both cases, the spectra exhibited the preliminary formation of a partially assembled species, containing the ditopic ligand and only one boronic acid residue. This intermediate (**7**) was isolated, by using a boronic acid/cobaloxime ratio of 1:2, and structurally characterized for the system 4,4′-bipyridine/4,4′-biphenyldiboronic acid (Scheme 9). The self-assembly process was completely convergent in solution for **5**, but not for **6**. In fact, for the latter compound, the intermediate did not transform completely in the 'filled box' with time, but the lower solubility of **6** caused its selective precipitation. These studies show that the ditopic ligand is not included in a preformed box assembled by methylcobaloxime and diboronic acid, but rather its coordination thermodynamically drives the assembly process toward the formation of the 'filled box' itself[36].

2. Structural properties

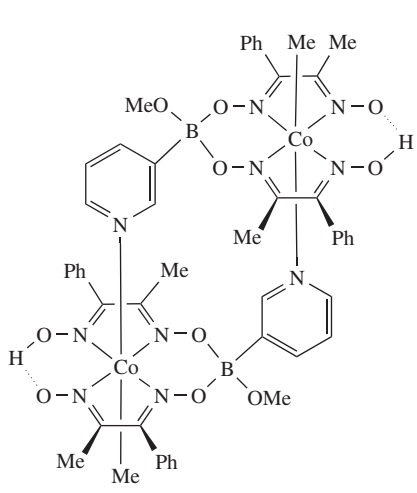
The first supramolecular species was obtained from the reaction of methylcobaloxime with 3-py$B(OH)_2$, **1** (Scheme 5) in methanol[34]. The X-ray analysis showed that **1** has a structure which can be considered a 'molecular parallelogram'. The B(3-py)(OMe) group (the methoxy substituent is formed by esterification of the boron OH group by the methanol solvent), which has substituted the H atom of one oxime bridge, coordinates the cobalt of the other unit by the 3-py residue, and vice versa. The two pyridinyl residues,



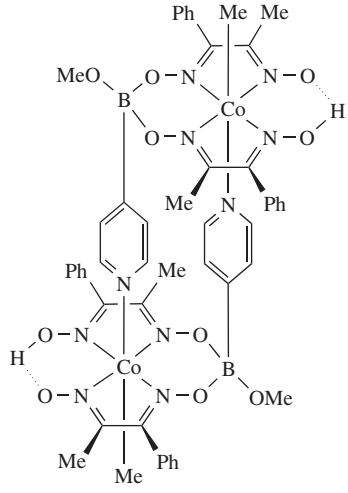
SCHEME 6

nearly coplanar with the Co_2B_2 plane, are on two opposite edges and the two cobaloxime units on the other two edges, nearly perpendicular to the Co_2B_2 plane.

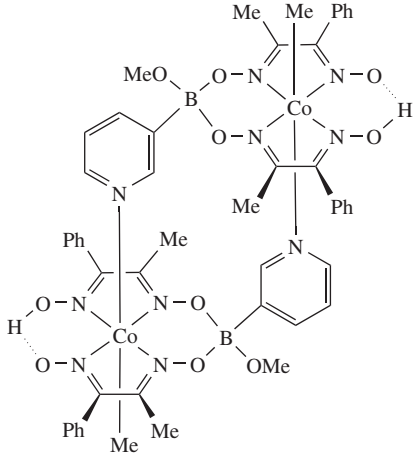
Several new supramolecular complexes have been reported in recent years and have been reviewed[34]. The reaction of $H_2OCo(dmgH)_2Me$ with 4-pyB(OH)$_2$ afforded the 'molecular box'[83] **2** in Scheme 5. The X-ray structure showed that the two pyridinyl groups face each other and are, differently from **1**, nearly perpendicular to the Co_2B_2



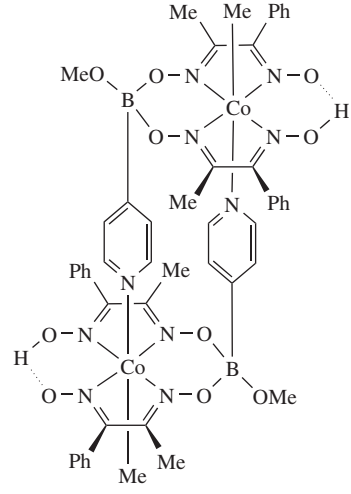
(**1''**)



(**2''**)



(**1'''**)

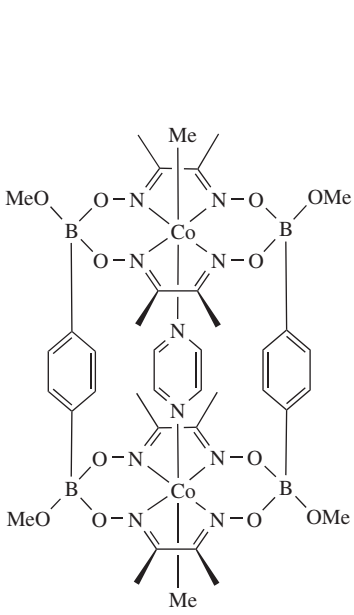


(**2'''**)

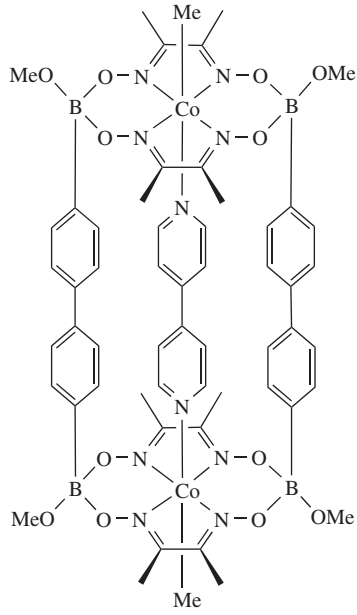
SCHEME 7

plane, where the Co atoms are separated by 7.6 Å, similar to the value of 7.4 Å found in **1**. The pyridinyl groups constitute two opposite faces of the box, the other two faces being the cobaloxime moieties, approximately perpendicular to the pyridinyl planes. ^{1}H NMR spectra of **1** and **2** in $CDCl_3$ are completely consistent with the structures found in the solid state, suggesting that they are stable in solution of non-coordinating solvent.

The reaction of $H_2OCo(dmgH)_2R$ (R = Me, Et) with 3-$NH_2C_6H_4B(OH)_2$ acid in water[81] gave the tricobaloxime **3** (Scheme 5). The X-ray structure of the derivative with



(**5**)

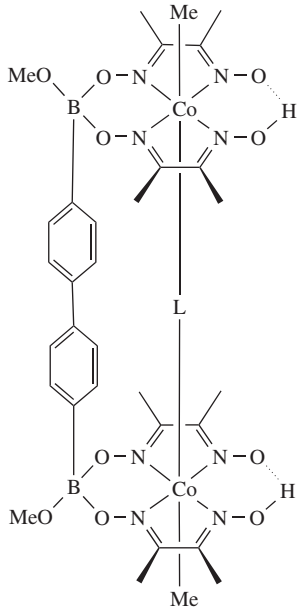


(**6**)

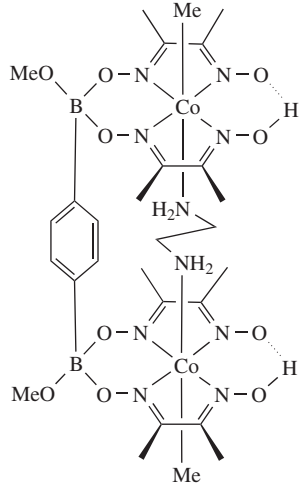
SCHEME 8

R = Me revealed that the cobalt atoms are arranged at the vertices of a nearly equilateral triangle, whose side is about 9.5 Å. The connection along each side of the triangle is made, on one side, by the reaction of the $B(OH)_2$ group with the oxime bridge of one cobaloxime and, on the other side, by coordination of the amino group to the cobalt of the other cobaloxime, resulting in the chiral supramolecule **3** with approximate C_3 symmetry (Scheme 5). A water molecule is H-bonded to the three boron OH groups at O···O distances about 2.8 Å and lies approximately at the middle point of the three hydroxyl groups. ^{1}H NMR spectra for both derivatives, with R = Me and Et, agree well with the trimeric structure found in the crystal[34]. The X-ray structure of the polymeric species obtained by reaction of $H_2ORh(dmgH)_2Me$ with 3-aminophenylboronic acid showed that the connection between each unit is similar to that found in **3**. However, conformational changes due to the significant variations in the B–C and C–NH_2 torsion angles with respect to **3** lead to the chain arrangement of **4** instead of the triangular arrangement.

In order to study the influence of the steric hindrance of the dioxime side substituents on the structure of the assembled polynuclear systems, the reaction products of $LCo(dpgH)_2Me$ (L = H_2O, py) with 3-py$B(OH)_2$, 4-py$B(OH)_2$ and 3-$NH_2C_6H_4B(OH)_2$, respectively, were studied[34, 82]. Well-defined products were obtained only with the last two boronic acids (**2′** and **3′**, respectively), and were characterized both in solution by NMR spectroscopy and in the solid state by X-ray diffraction (Scheme 6). The reaction with 3-py$B(OH)_2$ gave a complex mixture of products which cannot be identified, in spite of several attempts at different pH values and different solvents. The geometry of compound **2′** of Scheme 6 is very similar to that of **2** of Scheme 5, with the same



(**7**) L = 4,4′-bipyridine
(**8**) L = α,α′-diamino-*p*-xylene
(**9**) L = 1,6-diaminohexane



(**10**)

SCHEME 9

Co···Co separation of 7.6 Å. Compound **3′** can be considered a molecular box similar to that of **2**, but more distorted and with a Co···Co separation of 8.4 Å. Comparison of the above results clearly indicates that the most important consequence of the increase in bulk of the cobaloxime, from dmgH to dpgH, is the change in the nuclearity of the supramolecular species assembled by the 3-$NH_2C_6H_4B(OH)_2$ acid. The formation of a trimeric arrangement is prevented in the reaction with the dpgH derivative because of the steric hindrance of the side phenyl groups. The dinuclear molecular box **3′** is formed instead.

Finally, the reactions of 4-py$B(OH)_2$, 3-py$B(OH)_2$, 3-NH_2-py$B(OH)_2$ with the asymmetric H_2OCo$(mpgH)_2$Me complexes, either *cis* or racemic mixture of the chiral *trans*-derivative (Scheme 1), were investigated[35]. X-ray quality crystals were obtained only from the solutions containing the racemic mixture of the *trans*-derivative with either 3-py$B(OH)_2$ or 4-py$B(OH)_2$, obtaining the species **1″** and **2″**, respectively. The crystals of **1″** and **2″** are built up by dimeric *meso* units arranged on a crystallographic symmetry center, sketched in Scheme 7. The geometry of **2″** is very similar to the molecular boxes found in **2** and **2′**, whereas the geometry of **1″** is a distorted molecular box, recalling that of **2** and differing from the molecular parallelogram **1**. The reaction of the racemic *trans* isomer with boronic acids can produce three dimeric species, two chiral homodimers and one *meso* heterodimer, but only the last-mentioned species was isolated. ^{1}H NMR analysis of the reaction mixture showed that the *meso* form is isolated out from the solution by virtue of preferential crystallization[35]. Crystals suitable for X-ray analysis were not obtained for the products of the reaction of the *cis* py$Co(mdgH)_2$Me isomer

with 3-pyB(OH)$_2$, **1**‴, or 4-pyB(OH)$_2$, **2**‴. The structures of **1**‴ and **2**‴ were inferred from NMR spectra, which clearly resemble those of **1**″ and **2**″, respectively, as shown in Scheme 7.

Alternatively, supramolecular species were obtained using diboronic acid residues as linkers between two cobaloxime units in the presence of a ditopic ligand. The reaction of $H_2OCo(dmgH)_2Me$ with 1,4-phenylenediboronic acid, in the presence of pyrazine, gave the dicobaloxime **5**[83] (Scheme 8)[83]. The X-ray structure showed that **5** may be described as a molecular box whose opposite faces are two diborylated cobaloximes and two phenylene groups. The box is filled by the pyrazine ligand which bridges the two Co atoms in the axial position *trans* to the Me ligand. The plane of pyrazine is almost parallel to the phenyl planes at a mean distance of 3.27 Å. A similar 'filled box' **6** was formed by the assembly of two methylcobaloxime units with 4,4′-biphenyldiboronic acid in the presence of 4,4′-bipyridine (Scheme 8), and characterized by X-ray analysis[37]. The diphenyl planes are almost parallel to the plane of the nearly planar 4,4′-bipyridyl ligand, in a face-to-face $\pi-\pi$ manner at a mean distance of 3.49 Å. Other ligand/diboronic acid couples, such as α,α'-diamino-*p*-xylene/4,4′-biphenyldiboronic acid, 1,6-diaminohexane/4,4′-biphenyldiboronic acid and ethylenediamine/1,4-phenylenediboronic acid, allowed only a partial assembly, giving both in solution and the solid state the open boxes **7**–**10** (Scheme 9), which were characterized by ^{1}H NMR and X-ray crystallography[37].

IV. COB(IV)ALOXIMES, COB(II)ALOXIMES AND COB(I)ALOXIMES

A. Synthesis

Many years ago, it was shown that $LCo^{III}(dmgH)_2R$ can be oxidized electrochemically[84] and chemically[85]. More recently, the chemical oxidation of a series of alkylcobaloximes by $[M(2,2'\text{-bipyridine})_3]^{3+}$ (M = Fe^{3+}, Ru^{3+}) and the subsequent cleavage of the unstable $Co^{IV}-C$ bond were investigated in the presence of variously substituted pyridines[86]. It was found that the alkyl group is transferred to the pyridine N atom as carbocation. A similar behavior was observed for the electrochemical oxidation of trifluoromethylcobaloxime[87].

Both cob(II)aloximes and cob(I)aloximes are air-sensitive species and must be synthesized under strictly anaerobic conditions. Cob(II)aloximes are formed by mixing Co^{II} acetate with dimethylglyoxime in dry methanol[45]. Cob(I)aloximes are generally prepared by reduction of a Co^{III} or Co^{II} species by $NaBH_4$ in alkaline solution.

Cob(II)aloximes are odd-electron species and, as such, are active catalysts in radical polymerization. The Co^{I} complexes are extremely powerful nucleophiles and their use as catalysts for electrochemically or photochemically driven hydrogen evolution and for dehalogenation of chloroalkenes relies on this property (see Section VII).

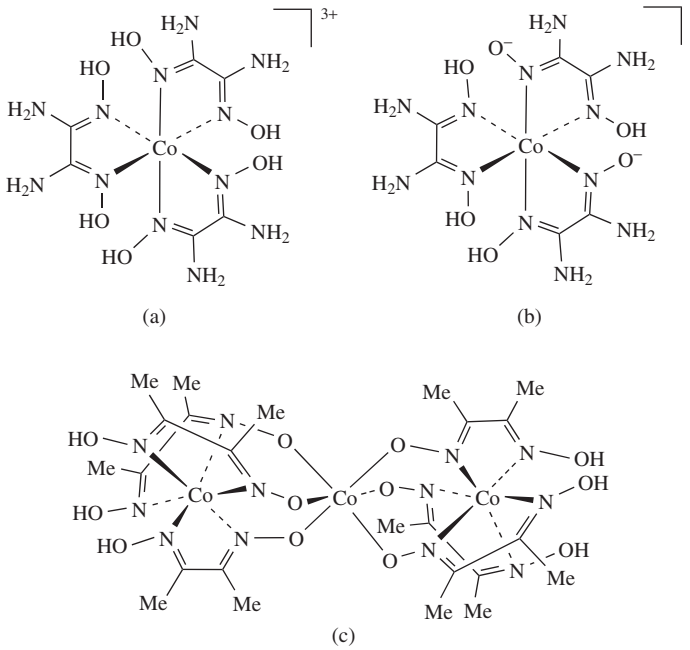
B. Structural Properties of Cob(II)aloximes

The X-ray structures of cob(II)aloximes are very few as compared with those of the Co^{III} analogues. Only a few octahedral Co^{II} complexes, of formula *trans*-$L_2Co^{II}(dmgH)_2$, have been characterized structurally. Comparison with the analogous Co^{III} complex, [*trans*-$L_2Co^{II}(dmgH)_2]^+$ (L = neutral ligand), shows a dramatic elongation of the axial distances, but no appreciable variation in the Co–N equatorial distances, which are about 1.90 Å. The latter value in Co^{II} species compares well with the average value of 1.8901(9) Å in Co^{III} analogues[8,9] (Table 1). When L = H_2O, a dramatic increase (of about 0.40 Å) in the axial Co–O distances was observed in the centrosymmetric Co^{II} derivative (Co–O distance 2.296(1) Å)[88] with respect to that found in the Co^{III} analogue (1.900(3) Å)[89]. When L = py, a similar elongation (about 0.30 Å) of the axial Co–N

bond was observed in the low-spin Co^{II} species[90], with respect to the centrosymmetric cationic Co^{III} complexes, [*trans*-$py_2Co(dmgH)_2]^+$, where the Co–py distance was found, in two separate structural determinations, to be 1.965(3) Å[40] and 1.966(3) Å[91]. The axial elongation can be due to the Jahn–Teller effect in the low-spin d^7 Co ions. The X-ray structure of *trans*-$(MeCN)_2Co^{II}(dpgBF_2)_2$ complex has been determined. The complex is arranged on a crystallographic symmetry center and exhibits long axial Co–NCMe distances of 2.241(3) Å and a mean Co–N equatorial distance of 1.886(3) Å, very close to that found in the corresponding Co^{III} complexes[8,9] (Table 1). The Co–NCMe distance of 2.241(3) Å is dramatically longer than that of 1.973(2) Å found in the pentacoordinate $[(MeCN)Co^{I}(dpgBF_2)]^-$ anion (see Section IV.C). The coordination geometry is similar to that found in the low-spin *trans*-$(MeOH)_2Co^{II}(dmgBF_2)_2$ complex, with a long axial Co–O bond of 2.264(4) Å and a mean equatorial Co–N bond of 1.878(4) Å[92].

Mononuclear Co^{II} complexes with neutral dioxime have also been found to have a *cis* arrangement of the two dioximes, as, for example, in the high-spin complex *cis*-$(CF_3COO)_2Co^{II}(dmgH_2)_2$[93]. The complex *cis*-$Cl_2Co^{II}(dpgH_2)_2$ was obtained under argon in strongly acidic medium and characterized structurally[20]. The $Co–N_{oxime}$ distances are significantly longer than those found in the *trans* species. The two Co–N distances *trans* to Cl^- average 2.161 (2) Å, the other two 2.076(2) Å, possibly indicating *trans* influence of Cl^-. These values are similar to the Co–N distances in *cis*-$(CF_3COO)_2Co^{II}(dmgH_2)_2$, which range from 2.126 to 2.149 (3) Å[93]. It should be pointed out that in the recent X-ray structure of the $[Co^{III}(oxadoH_2)_3]^{3+}$ ($oxadoH_2$ = oxamide dioxime) (Scheme 10a)[94] and $[Co^{III}(oxadoH_2)(oxadoH)_2]^+$ (Scheme 10b)[95] cations, the Co–N distances are in the range 1.900–1.935(1) Å, significantly shorter than those observed in the Co^{II} *cis* complexes. An interesting trinuclear Co^{II} complex of formula $[Co_3(dmgH)_6]$ was obtained by simply heating an ethanol/water solution of dimethylglyoxime and $Co(CF_3SO_3)_2$[40]. The X-ray structure showed the structure sketched in Scheme 10c. The three octahedral cobalt atoms are aligned, each of the two terminal ones being *cis* coordinated by three dmgH ligands, whereas the central Co is coordinated by the six deprotonated O atoms of the dioximates, which act as μ-ONN tridentate ligands. The structure is similar to that found in the trinuclear cation $[Co^{III}(dmgH)_3Co^{II}(dmgH)_3Co^{III}]^{2+}$ with a central Co^{II} center and two terminal Co^{III} atoms[96]. The geometry of the glyoximate ligand binding to Co recalls that found in clathrochelates (see Section V).

In the period analyzed in the present chapter, only one Co^{II} pentacoordinate complex was reported in the CCDC. The X-ray structure of the 4-*t*-Bu-py$Co^{II}(dmgH)_2$ complex showed[44] that the Co center has a distorted square-pyramidal geometry, with the apical 4-*t*-Bu-py ligand at a distance from Co of 2.096(2) Å, shorter by 0.15 Å than that found in the octahedral *trans*-$py_2Co^{II}(dmgH)_2$ species (2.25 Å)[40,91]. The Co atom is displaced by 0.077 Å from the plane of the four basal N atoms toward the apical ligand. The Co–N basal distances are in the range 1.877–1.891(2) Å, not significantly distinguishable from those found in both Co^{II} and Co^{III} *trans* octahedral species. In the crystal, the square-pyramidal molecule is closely associated with a second molecule. The two pyramids face their basal planes, which are nearly parallel. The two approximately planar $(dmgH)_2$ units are rotated by about 90° with respect to each other and the two Co atoms are one above the other at a distance of 3.209 Å. This arrangement has been suggested to explain why the magnetic moment, μ_{eff}, of 1.40 μ_B, measured on the crystal, is somewhat smaller than the spin-only moment of 1.73 μ_B expected for a low-spin d^7 complex. The coordination geometry about Co is very similar to that found in the low-spin py$Co^{II}(dpgBPh_2)_2$ analogue, where the apical Co–py distance is 2.092(8) Å, the Co–N basal distance varies from 1.870 to 1.877(6) Å and the Co displacement out of the basal plane toward py is 0.13 Å[97].



SCHEME 10

C. Structural Properties of Cob(I)aloximes

To our knowledge, the X-ray structure of only two anionic cob(I)aloximes, with formula $[LCo^{I}(dioxime)_2]^-$, have been thus far reported. That with dioxime = $dmgBF_2$ and L = py[98] has been already reviewed[10]. The other, with dioxime = $dmgBF_2$ and L = MeCN, has been recently reported[43]. In the latter complex, Co^{I} has a distorted square-pyramidal coordination, with the apical ligand MeCN at a Co–N distance of 1.973(2) Å, 0.268 Å shorter than that in *trans*-$(MeCN)_2Co^{II}(dpgBF_2)_2$ (see Section IV.B). The average Co–N basal distance is 1.851(6) Å (range 1.846–1.859(2) Å). The apical Co–py and the average Co–N basal distance in the analogous pentacoordinate $[pyCo^{I}(dmgBF_2)_2]^-$ anion are 2.019(3) and 1.839(4) Å, respectively. In both complexes, the displacement of Co out of the 4-N basal plane toward the apical ligand is very similar, being 0.268 Å for L = MeCN and 0.257 Å for L = py. Comparison with the above-described 4-*t*-Bu-$pyCo^{II}(dmgH)_2$ complex, which has, however, a different equatorial ligand, suggests that in the pentacoordinate Co^{I} complexes there is a significant shortening of the apical and basal distances and a significant increase in the displacement of Co out of the plane of the four basal N atoms toward the apical ligand. The shortening of the Co–N basal distances of about 0.05 Å in Co^{I} derivatives with respect to Co^{II} and Co^{III} ones has been attributed to the higher degree of metal-to-ligand π-back-bonding in the electron-richer Co^{I} complexes[43, 98].

We would like to stress a point, which concerns the utilization of the knowledge obtained from the simple models to the chemistry of cobalamins in B_{12} enzymes. In the catalytic cycle of methionine synthase enzyme[68], the cobalamin cycles between methyl-cob(III)alamin and cob(I)alamin, a four-coordinate square-planar species, as determined

by EXAFS measurements[99]. However, we observe that the thus far known X-ray structures of Co^{I} complexes, which are presumed to be models of vitamin B_{12}, are square pyramidal with short apical bond. This suggests a strong tendency of Co^{I} to assume such a coordination, at least in the models.

V. DIOXIMATE CLATHROCHELATES

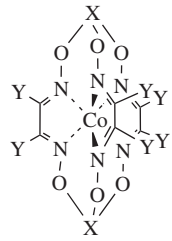
Clathrochelates[39–41] are complexes, containing encapsulated metal ions, which afford extremely high thermodynamic stability and kinetic inertness to usually labile and reactive metal ions. The thus far known cobalt clathrochelates, containing a bis X-capped tris(dioximate) ligand, have general formula $[Co(dioximate)_3X_2]$. The charge of the anionic encapsulating $[(dioximate)_3X_2]^{-n}$ ($n = 2, 4$) ligand depends upon the nature of capping group X (Table 7).

Generally, these complexes are prepared by template synthesis from a mixture of three equivalents of dioxime, anhydrous cobalt chloride and an excess of the boron reagent[39–41]. A sketch of the clathrochelate structure is shown in Table 7, where the values of the φ angle indicate the Co coordination polyhedron in the regular trigonal prismatic (TP, $\varphi = 0^{\circ}$) and trigonal antiprismatic (TAP, $\varphi = 60^{\circ}$) arrangements. The angle φ represents the rotation angle between the two triangular bases of the polyhedron defined by three N atoms. To our knowledge, the synthesis and the proposed structure of the first clathrochelate, containing Co^{III} and dmg ligands, of formula $[Co^{III}(dmg)_3(BF)_2]^{+}$ (**11** in Table 7), was reported[100] in 1968. The X-ray structure of $[Co^{III}(dmg)_3(BF)_2]^{+}$ and of the neutral analogue $[Co^{II}(dmg)_3(BF)_2]$ was published three years later[101]. Only recently, several X-ray structures of other dioximate clathrochelates, with different X grouping and containing cobalt in the oxidation states +1, +2 and +3, have been reported and their electrochemical behavior studied[39–42].

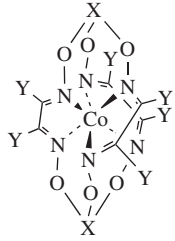
The Co^{III} clathrochelates **11**–**16** are listed in Table 7, together with the corresponding Co–N mean distance and the angle φ. These complexes have similar geometry with only small differences, depending upon the X grouping[41, 42, 101]. The Co coordination geometry is intermediate between TP and TAP with φ *ca* 30° for X = BF and closer to TP for the others (**12**–**15**), which have angles φ in the range 41–45°. However, the Co–N distances are very similar in each compound and the average value in all the compounds is about 1.90 Å. This average value does not differ significantly from that in octahedral $LCo(dmgH)_2X$ complexes[8, 9]. Electrochemistry studies have found reduction waves assignable to Co^{III}/Co^{II} and Co^{II}/Co^{I} processes. The $E_{1/2}$ values for the cationic clathrochelates **11** and **16** (Table 7) and for $[Co^{III}(dmg)_3(B2,4,6\text{-}F_3C_6H_2)_2])$ (**21**) vary from 0.46 to 0.28 V for the Co^{III}/Co^{II} step and from −0.38 to −0.73 V for the Co^{II}/Co^{I} step, in the order **16** > **11** > **21** for both steps. Changes in the boron and glyoxime substituents can act as a synthetic tool for tuning the redox potential[41]. It is worth noting that coordinatively saturated boron capped glyoximates have shown catalytic activity for hydrogen production at potentials as positive as −0.55 V.

The neutral Co^{II} clathrochelates thus far characterized structurally are the boron capped complexes **17**–**19** listed in Table 7. In all the three complexes, the Co coordination geometry is close to TP with angles φ in the range 3–16°. In **19**, the Co–N distances are all equal to 1.973(2) Å, as imposed by the D_3 crystallographic symmetry of the whole molecule[101]. In contrast, the Co–N distances exhibit a large variability, from 1.897(1) to 2.055(1) Å in **17**[39] and from 1.878(1) to 2.111(1) Å in **18**[41]. The Co^{II}–N distances are on average longer than those found in the Co^{III} clathrochelates. Correspondingly, the angles φ are largely smaller than those in Co^{III} analogues. To our knowledge, the dark blue compound **20**, $[Co^{I}(Cl_2g)_3(Bn\text{-}Bu)_2]$ (Scheme 1), is the only Co^{I} clathrochelate so

TABLE 7. Relevant geometrical parameters of some clathrochelates. The fully deprotonated dioximate symbol is indicated by the corresponding notation of Scheme 1 removing H



TP ($\varphi = 0°$)



TAP ($\varphi = 60°$)

Compound	Co–N (Å)[a] Δ (Å)[b]	φ (°)	X	Y	Reference
11 $[Co^{III}(dmg)_3(BF)_2]^+$	1.893(4) 0.01	31.2	BF	Me	101
12 $[Co^{III}(dmg)_3(SbEt_3)_2]^+$	1.900(5) 0.011	42.3	$SbEt_3$	Me	42
13 $[Co^{III}(chg)_3(SnCl_3)_2]^-$	1.91(1) 0.03	41.0	$SnCl_3$	[c]	42
14 $[Co^{III}(dmg)_3(SnBr_3)_2]^-$	1.89(2) 0.08	45.1	$SnBr_3$	Me	42
15 $[Co^{III}(dmg)_3(SnCl_3)_2]^-$	1.90(1) 0.03	42.8	$SnCl_3$	Me	42
16 $[Co^{III}(dpg)_3(BF)_2]^+$	1.881(7) 0.009	31	BF	Ph	41
17 $[Co^{II}(Cl_2g)_3(BBu\text{-}n)_2]$	1.897–2.055(1)	7.8	BBu-*n*	Cl	39
18 $[Co^{II}(dpg)_3(BPh)_2]$	1.878–2.111(1)	16	BPh	Ph	41
19 $[Co^{II}(dmg)_3(BF)_2]$	1.973(2)	3	BF	Me	101
20 $[Co^{I}(Cl_2g)_3(BBu\text{-}n)_2]^-$	2.003(3) 0.030	1.3	BBu-*n*	Cl	39

[a]Mean value, when the Co–N distances are very similar. The e.s.d.'s of the distances are given in parentheses.
[b]Δ is the difference between the lowest and the highest values of Co–N distances. For **17** and **18** the values of the shortest and longest distances are given.
[c]The glyoximato side substituents are 1,2-cyclohexanedione residues (see Scheme 1).

far characterized structurally and studied[39]. The Co coordination geometry is essentially TP with an angle φ of 1.3°. The Co–N distances are similar and range from 1.988 to 2.018(3) Å. The electrochemical behavior of **20** is characterized by two successive oxidation waves. The first, at $E_{1/2} = -0.44$ V, is reversible and was attributed to the Co^I/Co^{II} process; the other at $E_{1/2} = 0.63$ V was irreversible and was attributed to the Co^{II}/Co^{III} process[39]. Possibly, the stabilization of the Co^I oxidation state can be attributed to the electron-withdrawing Cl substituents of the oxime fragment. Compound **17** can be both irreversibly oxidized and reversibly reduced electrochemically. The location and shape of the reduction wave of **17** coincides with the first oxidation wave of **20**, whereas the irreversible oxidation wave of **17** coincides with the second oxidation wave of **20**[39].

VI. INTRAMOLECULAR CYCLIZED COMPLEXES

The intramolecular cyclization in haloalkyl cobaloximes has been recently reviewed[38]. In summary, the internal cyclization has been observed to occur by a nucleophilic attack of a negatively charged N or O atom of the equatorial moiety on the axial haloalkyl ligand. The reaction of $[LCo\{(DO)(DOH)pn\}CH_2X]^+$ and $[LCo\{(DO)(DOH)Me_2pn\}CH_2X]^+$ (X = halogen) with base affords as major product the cyclized species **22a–c** and **23**, respectively (Scheme 11), which contain a three-membered metallocycle. The X-ray structures of **22a** (L = py), **22b** (L = 1-Me-Im) and **22c** (L = Me_3-Bzm) have shown that cyclization leads to the formation of a methylene bridge from Co to an equatorial nitrogen, with a C–Co–N angle of about 44°. The ring closure causes the simultaneous conversion of the imine N=C–Me grouping to the enamine moiety, N–C=CH_2. The Co–CH_2 distance, about 1.92 Å, and the axial Co–L distances are significantly shorter than those found in almost all organocobalt(III) compounds. The cyclized compound **23**, obtained from $[LCo\{(DO)(DOH)Me_2pn\}CH_2Br]^+$, was shown to have a similar structure by NMR spectroscopy[38].

By simple heating of an aqueous solution of $LCo(dmgH)_2(CH_2)_3Br$ (L = py, Me_3-Bzm, Im) the nucleophilic attack of one of the oxime oxygen atoms at the bromopropyl axial ligand occurred with formation of the six-membered cycle in the cationic species **24a–c** (Scheme 11). When L = H_2O, the neutral cyclized species was obtained, in which Br has displaced water from the axial position (**24d**). Compound **25** (Scheme 11), containing a seven-membered cycle, was obtained by evaporation of an aqueous solution of $H_2OCo(dmgH)_2(CH_2)_4Br$ in the presence of β-cyclodextrin. The crystal structure showed that **25** co-crystallizes with cyclodextrin and that the four CH_2 groups of the seven-membered metallocycle fit snugly inside the cyclodextrin cavity[102]. The cyclized compound was not obtained[102] in the absence of cyclodextrin.

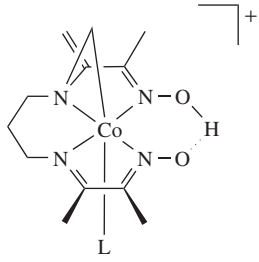
Reaction of dichloroacetylene with cob(I)aloxime, in the presence of pyridine, gave compound **26** as the main product (Scheme 11). This time, cyclization occurs at one carbon atom, C_a, of the dioximate five-membered ring, which forms a C–C bond with the 2-acetylenic carbon to give the [2.2.1]-tricyclic structure with Co and the quaternary C_a at the bridgehead positions. Protonation of the equatorial N atom adjacent to the attacked C_a atom also occurs[103]. We can conclude this section with the observation that cyclization may occur at one of the three atoms of the O–N=C fragment of the dioximate ligand, through a suitable reaction involving the axial halo ligand.

VII. RECENT APPLICATIONS OF COBALOXIMES

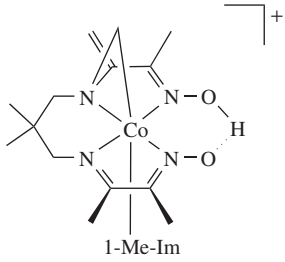
A. Radical Polymerizations

Cob(II)aloximes are active catalysts either in controlled radical polymerization (CRP) or in controlled chain transfer polymerization (CCTP), depending on the propensity of the polymer to undergo hydrogen elimination and the ability of the cobalt complex to promote H-abstraction[6]. Acrylic and vinyl monomers, deprived of α-methyl groups and therefore less prone to H-abstraction by cobalt complexes, are the most widely used monomers in CRP.

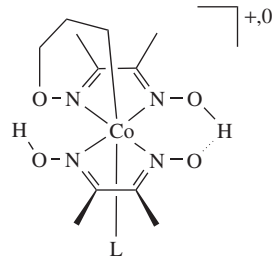
The first controlled radical polymerization using alkylcobaloximes as the controlling species was reported by Harwood and coworkers[104]. Exposition of the alkylcobalt complex to light or heat triggers the reversible homolytic Co–C bond cleavage, because of the low Co–C bond strength, and generates a transient carbon-centered radical and a persistent radical, the Co^{II} complex (Scheme 12). The transient $R^\bullet$ radical adds a first monomer unit and initiates the polymerization. The Co^{II} radical species reacts with the polymeric



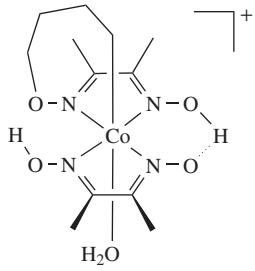
(**22a**) L = py
(**22b**) L = 1-Me-Im
(**22c**) L = Me_3-Bzm



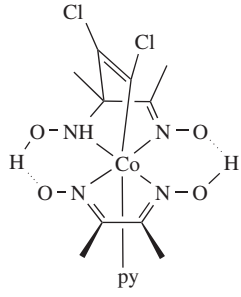
(**23**)



(**24a**) L = py
(**24b**) L = Me_3-Bzm
(**24c**) L = Im
(**24d**) L = Br^-



(**25**)

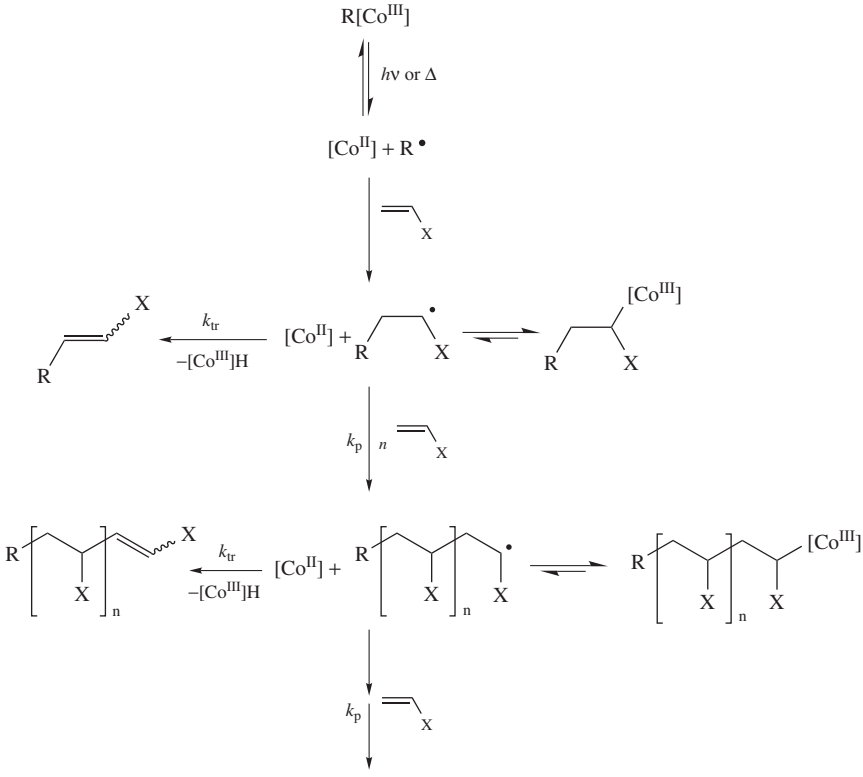


(**26**)

SCHEME 11

radical giving an alkyl–Co^{III} complex, so that the polymer chains can further propagate (k_p).The instantaneous radical concentration must always be sufficiently low to avoid cross-coupling reactions between the chains but sufficiently high to sustain polymerization. In the absence of hydrogen atoms prone to abstraction on the growing polymer chains, the dehydrocobaltation pathway (k_{tr}) is negligible and the polymerization is controlled by the reversible Co−C bond formation. Thus, the Co−C bond strength, which depends on the cobalt complex structure, is a key parameter in the choice of the catalyst.

Monomers having a methyl group with hydrogen atoms prone to abstraction, such as methacrylates, methylstyrene and methacrylonitrile, are CCTP-active monomers[105]. In this mechanism, the growing chain undergoes hydrogen atom abstraction by the Co^{II} species with release of a polymer with an unsaturated end-group and formation of a cobalt hydride. The Co^{III}−H intermediate can subsequently react with a monomer molecule, resulting in the regeneration of the active Co^{II} species and the formation of a monomeric radical, which can further propagate. The hydrogen abstraction is assumed to be the rate-determining step in the Co^{II}-mediated chain transfer process. The catalytic chain transfer is responsible for reducing the molar mass of polymers prepared by radical polymerization. Moreover, all the polymer chains formed by CCTP bear an unsaturation at the chain end, which makes them potential macromonomers and thus precursors of graft copolymers[105].

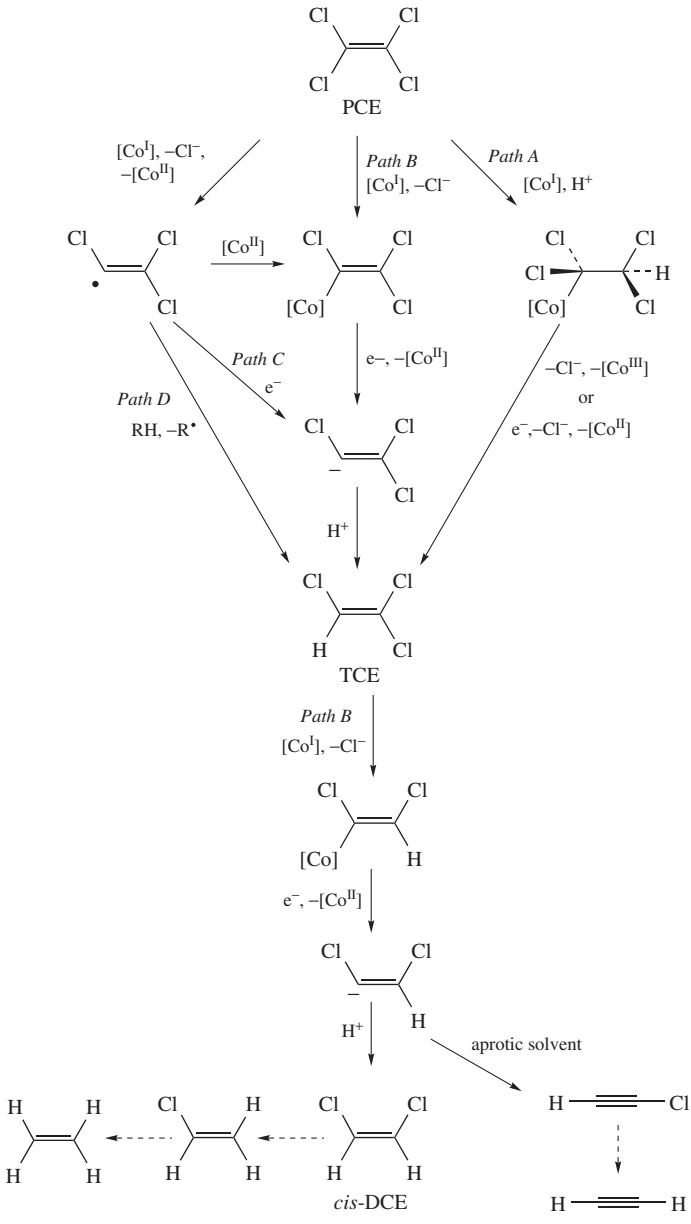


SCHEME 12. [Co] = Co(chel)

B. Dechlorination of Chloroethylenes

Cobalt-mediated dehalogenation reactions, specifically those that employ cob(I)alamin, have attracted particular attention because these complexes rapidly degrade tetrachloroethylene (PCE) and trichloroethylene (TCE), which are common groundwater contaminants. Cobaloximes have been used as functional models of cobalamin to study the mechanisms of the dechlorination reaction. Although these studies have been carried out under a range of experimental conditions, a relatively consistent mechanistic picture emerges from the product distribution and rate data[3].

Several mechanisms have been proposed for the reductive dehalogenation of PCE. The initial step can involve either an outer-sphere or an inner-sphere process (Scheme 13). In an inner-sphere process, the cobalt(I) nucleophile can attack PCE and form either a 1,1,2,2-tetrachloroethyl complex (path A, nucleophilic addition) or eliminate chloride to form a trichlorovinyl complex (path B, nucleophilic substitution). In an outer-sphere process, cobalt(I) transfers an electron to PCE forming a trichlorovinyl radical and a Co^{II} radical. The trichlorovinyl radical can be reduced to form a trichlorovinyl anion (path C), quenched by a hydrogen atom donor to form TCE (path D), or trapped by the Co^{II} species to form a trichlorovinyl Co^{III} complex, the same product as in path B. Experimental evidence supports the participation of radicals in the dechlorination of PCE, but cannot



SCHEME 13. [Co] = Co(chel)

rule out an inner-sphere process with formation of Co−C bonded intermediates[106, 107]. Recent computational studies indicate that trichlorovinyl or tetrachloroethyl intermediates may be formed[108, 109] but, in spite of several synthetic efforts, trichlorovinylcobaloxime, the hypothetical intermediate along path B, could not be isolated[103].

The mechanisms proposed for TCE dehalogenation are essentially the same as those postulated for PCE. In this case, the hypothesis of the nucleophilic substitution (path B) was supported by successful independent synthesis of *cis*-dichlorovinylcobaloxime by treatment of cob(I)aloxime with TCE[14]. Chlorinated vinylcobaloximes are stable compounds that are unlikely to undergo homolytic Co−C bond cleavage at a sufficient rate to support dechlorination of chlorinated alkenes[17]. However, they are unstable to reduction, yielding a dichlorovinyl anion[110] which may evolve either to *cis*-dichloroethylene (*cis*-DCE) (in protic solvent) or chloroacetylene (in aprotic solvents), which are the same products observed in the cobalamin-mediated dechlorination of TCE. On the basis of this experimental evidence, organometallic intermediates, specifically dichlorovinyl complexes, are believed to play an important role in the TCE dechlorination.

In all cases, transformation from PCE to TCE is the fastest, transformation from TCE to dichlorinated hydrocarbons is slower, and transformation from *cis*-DCE to vinyl chloride is the slowest. Although subsequent conversions from vinyl chloride to ethylene are relatively fast, the slow rate of conversion from *cis*-DCE to vinyl chloride results in a build-up of *cis*-DCE.

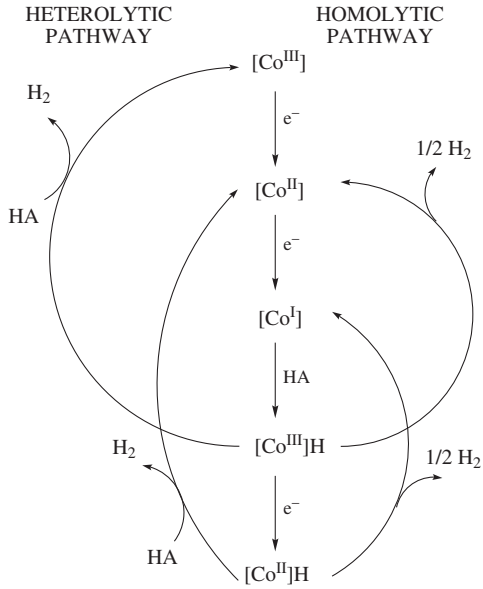
C. Hydrogen Evolution

Cobaloximes have been shown to catalyze the hydrogen evolution by proton reduction[7]. The first steps of the catalytic cycle involve the reduction of a Co^{III} or Co^{II} complex to a Co^{I} species by chemical, electrochemical or photochemical methods. The reduced deprotonated Co^{I} complex may pick up a proton from a proton source to give $Co^{III}-H$ species. Subsequently, two $Co^{III}-H$ species may react in a bimolecular step to eliminate H_2 in a homolytic pathway. Alternatively, if the acid used is strong enough to protonate the $Co^{III}-H$ species, the protonated hydride can produce H_2 and a Co^{III} species, in a heterolytic pathway. With acid of lower strength, $Co^{III}-H$ can be reduced further to give $Co^{II}-H$, which can in turn react via a homolytic or heterolytic pathway (Scheme 14).

Connolly and Espenson first reported that *trans*-$L_2Co^{II}(dmgBF_2)_2$ (see Section IV.B) catalyzes the reduction of protons to hydrogen in aqueous acidic solution in the presence of Cr^{II} ions[111]. That species was later shown to catalyze H_2 evolution after an electrochemical reduction in CH_3CN. In this solvent, the complex undergoes a reversible, one-electron reduction at −0.55 V vs SCE. In the presence of a sufficiently strong acid, catalytic currents were observed near the Co^{II}/Co^{I} couple. Increasing the acid concentration produced an increase in peak current, a slight positive shift in peak position and loss of the return oxidation wave, since Co^{II} is regenerated during H_2 production[112].

Photocatalytic hydrogen-evolving systems are more complex than the electrocatalytic systems and generally involve a light-harvesting photosensitizer, a sacrificial electron donor and a proton-reduction catalyst. Homogeneous photochemical hydrogen production catalyzed by the cobaloxime was initially studied by Lehn and coworkers[113].

Eisenberg and coworkers have shown that $pyCo^{III}(dgH)_2Cl$ catalyzes H_2 evolution in CH_3CN/H_2O solutions, with triethanolamine as sacrificial reductant, using a platinum(II) terpyridyl phenylacetylide complex[114] or the less expensive Eosine Y and Rose Bengal[115] as photosensitizer. Recently, supramolecular devices, with a ruthenium or an iridium chromophore directly linked with a bridge to the cobaloxime catalyst, were employed for photochemical hydrogen generation[116–118]. In the field of hydrogen evolution, the use of cobaloximes and related complexes is still a subject of intensive research[119, 120].



SCHEME 14. [Co] = Co(chel)

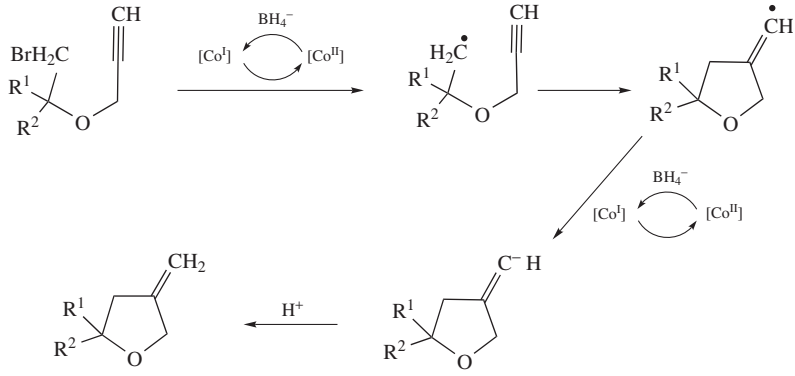
D. Organocobaloximes in Organic Synthesis

1. 1,5-exo-Cyclizations

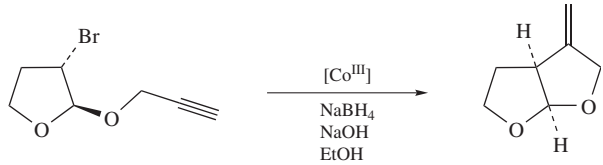
For many years, free radical species have been used to produce polymers of industrial importance, but their use for the synthesis of homogenous, low molecular weight molecules has been developed only recently. Among the organic syntheses, the 1,5-*exo*-cyclization has been studied extensively starting from the early 1980s. The source of radicals was initially tributyltin hydride, but in 1982 Tada and coworkers[121] developed a two-step procedure for the synthesis of α-methylene-γ-butyrolactones using a catalytic amount of the cob(I)aloxime under reductive conditions (Scheme 15) to generate the organic radical. The synthetic procedure mediated by the cobalt complex has several advantages over that mediated by tributyltin hydride: lower toxicity, lower cost, no need of high dilution to avoid direct reduction of organic halide and the retention of the olefin as a functional group. The main limitation is the fact that the β-position of alkylcobaloxime must be occupied by a group (R^1, R^2) different from H, to avoid the formation of a terminal double bond (Scheme 15). The cobalt-mediated radical cyclization was reviewed by Tada[5] in 1999. Recent examples of cobaloxime-mediated syntheses of α-methylene-γ-butyrolactones are reported by Tabatabaeian and coworkers[122]. Very recently[123], Quayle and coworkers used the cobaloxime-catalyzed 1,5-cyclization in one step for the formal synthesis of aflatoxin B2 (Scheme 16).

2. Cycloaddition reactions

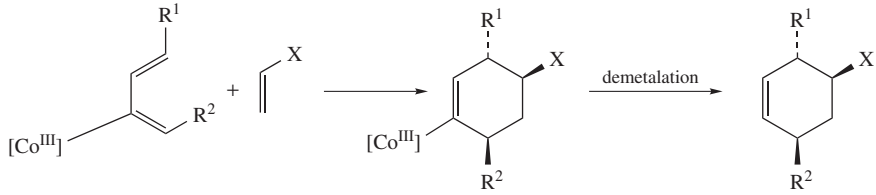
The groups of Welker[4] and Tada[5], independently, reported the synthesis of 1,3-dien-2-yl cobaloximes with various L ligands (Scheme 17). The cobalt dienyl complexes reacted with a variety of dienophiles both regioselectively and stereoselectively (with high



SCHEME 15. [Co] = Co(chel)



SCHEME 16. [Co] = Co(chel)



SCHEME 17. [Co] = Co(chel), X = electron withdrawing group

exo diastereoselectivity and enantioselectivity) to produce air-stable cobalt-substituted cyclohexenes in high yield. The subsequent cleavage of the cobalt–carbon bond in the cycloadducts, accomplished by different substances such as $AlMe_3$ or variously substituted silanes, yielded organic products as well as a cobalt complex, which could be recycled into the synthesis. The *exo* diastereoselectivity of these [4+2] cycloaddition reactions provides access to cyclohexene stereochemistries which are complementary to those obtained from traditional *endo* selective Diels-Alder reactions. The topic was reviewed by Welker[4] in 2001. A [6+4] cycloaddition of 1,3-dien-2-yl cobaloximes with tropones which do not contain electron-withdrawing substituents has recently been reported[124]. Subsequent efforts were devoted to develop a cobalt-catalyzed Diels–Alder sequence, i.e. a series of reactions which were catalytic rather than stoichiometric in metal complex[125].

3. Cobaloxime π-cation for C–C and C–heteroatom bond formation

(β-Hydroxyalkyl)- and (β-acetoxyalkyl)-cobaloximes can undergo facile acid-catalyzed β-heteroatom exchange with oxygen and nitrogen nucleophiles through a cationic metal–alkene π-complex. The term 'cobalt π-cation' has been used to describe the metal–alkene π-complex intermediates involved in nucleophilic substitution reactions at β-centers in organocobalt compounds[126]. Nishikubo and Branchaud[127] and Kettschau and Pattenden[128] have used these cobaloxime π-cations for heterocyclic and carbocyclic ring construction since 1996. In fact, cobaloxime π-cations are reasonably good electrophiles, sufficiently reactive to add to the electron-rich sp^2 centers. They can be trapped by nucleophiles, but unfortunately the loss of the alkene can be a major side-reaction.

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The chemistry of NO- and HNO-producing diazeniumdiolates

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I. INTRODUCTION

A. Nomenclature

Inorganic salts containing the diazeniumdiolate functional group ($-N(O)=NO^-$) have been known for over 200 years[1], but only relatively recently has a consensus been reached

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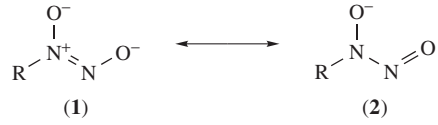


FIGURE 1. Diazeniumdiolate resonance structures and nomenclature

concerning the structural characteristics and the nomenclature of this functional group[2–4]. The structure of these compounds is best represented by the resonance forms **1** and **2** (Figure 1), with form **1** being dominant as indicated by crystallographic studies[5]. In agreement with these crystallographic studies, calculations show the *Z* isomer to be lower in energy. While the *E* isomer can be synthesized, the barrier for isomerization is approximately 40 kcal mol^{-1} for most derivatives[6]. Although these compounds have been called nitrosohydroxylamines, methoxazonyl compounds, isonitramines, and named as azoxy compounds, it is this resonance structure from which the IUPAC name, *diazeniumdiolate*, is derived (Figure 1)[2]. The substituent R is attached at position 1, so formally these anions are named diazen-1-ium-1,2-diolates. In most cases, R is a carbon-, nitrogen- or oxygen-based substituent.

Although most diazeniumdiolates are stable as solid salts, current interest in their chemistry stems from their ability to produce nitric oxide (NO), nitroxyl (HNO) and/or a mixture of NO and HNO upon decomposition in aqueous solution. An excellent, comprehensive review on the chemistry of diazeniumdiolates has previously appeared[2]. Following a discussion concerning the synthesis of diazeniumdiolates, this chapter will focus on how the substituent (R) and experimental conditions influence decomposition chemistry and NO/HNO production. Representative applications of NO- and HNO-producing diazeniumdiolates will also be provided.

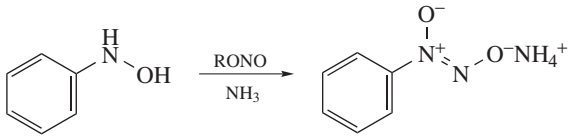
B. Synthesis

Synthetic strategies for diazeniumdiolate production typically fall into two categories: (a) nitrosation of hydroxylamines or oximes and (b) reaction of NO with nucleophiles under basic conditions. Nitrosation is typically carried out with standard nitrosating reagents such as HONO for acidic nitrosations or alkyl nitrites for basic nitrosations[2,7]. Due to the acid-sensitive nature of many diazeniumdiolates (*vide infra*), nitrosation under basic conditions is often favorable.

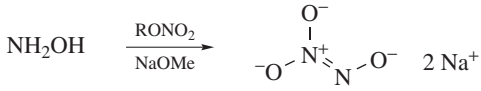
The nitrosation strategy is most commonly employed for the synthesis of carbon-bound diazeniumdiolates from the corresponding hydroxylamines[7]. For example, equation 1 shows the synthesis of ammonium-*N*-nitroso-*N*-phenylhydroxylamine (Cupferron) (**3**)[7]. Cupferron derives its name from the compound's ability to precipitate copper and iron from solution, though it forms complexes with many metals[8].

The synthesis of the classic oxygen-bound diazeniumdiolate, disodium diazen-1-ium-1,2,2-triolate (**4**) (commonly known as Angeli's salt, though sodium hyponitrate and trioxodinitrate^{2-} have been used as well), is accomplished via nitration of hydroxylamine under basic conditions as shown in equation 2[9–11]. This reaction is similar to

the nitrosation reactions used to make carbon-bound diazeniumdiolates except an alkyl nitrate is used instead of an alkyl nitrite.



(**3**) (1)



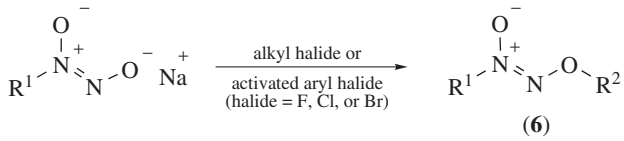
(**4**) (2)

Reaction of NO with nucleophiles, most commonly amines, is a useful synthetic tool for the production of diazeniumdiolates as well[7, 12–18]. The synthesis of diazeniumdiolates from nucleophiles and NO, however, can be challenging since special care and equipment must be employed to handle NO gas. (NO is a reactive species, especially with oxygen[19].) Also of concern in some cases is the choice of base. Although methoxide is commonly used, Keefer and coworkers have recently shown that NO will react with methoxide[16]. As a result, they suggest the use of sodium trimethylsilanoate as an alternative base in these reactions. Despite these concerns, the reaction of amines with NO remains the primary synthetic route to nitrogen-bound diazeniumdiolates such as the diethylamine/nitric oxide adduct, sodium 1-(*N*,*N*-diethylamino)diazen-1-ium-1,2-diolate (DEA/NO) (**5**)[7, 15, 18], as shown in equation 3. Note that a commonly encountered naming convention for amine-based diazeniumdiolates does not follow IUPAC standards. Rather, they are often named by an abbreviation for the parent amine (e.g. diethylamine = DEA) followed by/NO to denote the NO complex (e.g. DEA/NO)[2, 20].

(**5**) (3)

Due to the nucleophilic nature of the terminal oxygen (O^2 position), derivatives of diazeniumdiolates can be prepared as well. Of particular utility has been alkylation and arylation at the terminal oxygen to produce a variety of O^2-substituted derivatives generically represented in equation 4 by compound **6**[3, 21, 22].

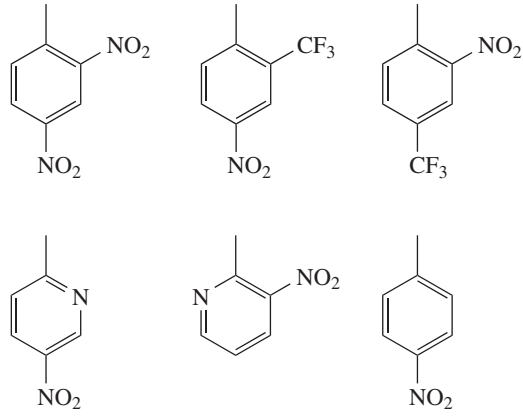
Although the diazeniumdiolate functionality is not robust to all synthetic conditions, its reactivity has been explored and, depending upon the characteristics of R^2, further derivatization is possible. Possible transformations include dehydrohalogenation to give **7** (equation 5)[21, 23] and nucleophilic displacement of halogens on R^2 to give **8** and **9** (equations 6 and 7)[21]. In addition, other reactions including the modification of sugars such as deacylation of acetylated O^2-glycosylated derivatives to give **10** (equation 8)[24] and the conversion of thioethers to alkyl chlorides using sulfuryl chloride to give **11** (equation 9)[24] have also been reported.

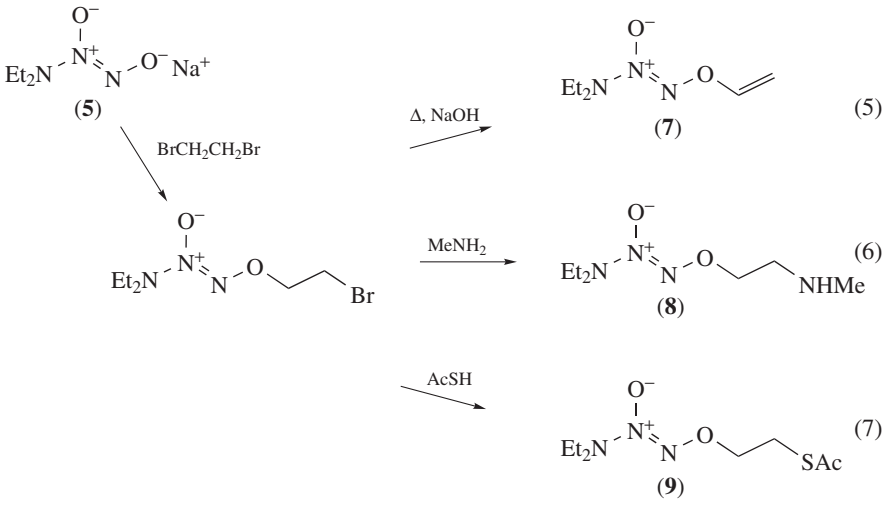


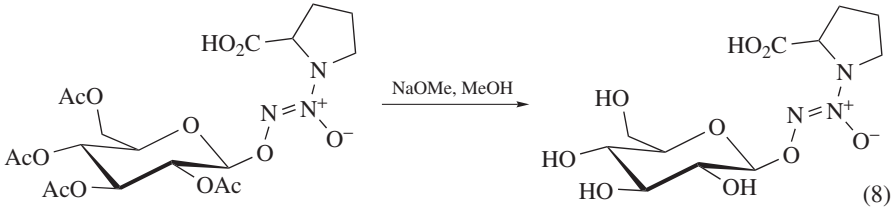
(**6**) (4)

$R^1 = CR_3$ or NR_2

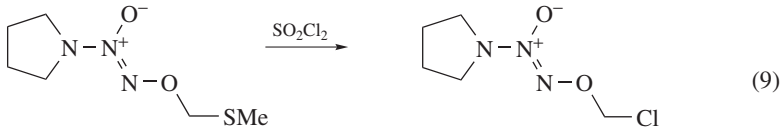
R^2 = alkyl or







(**10**)

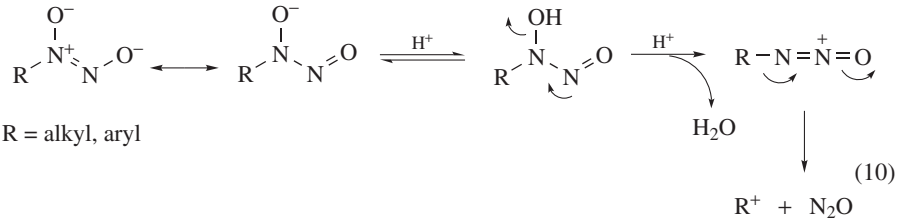


(**11**)

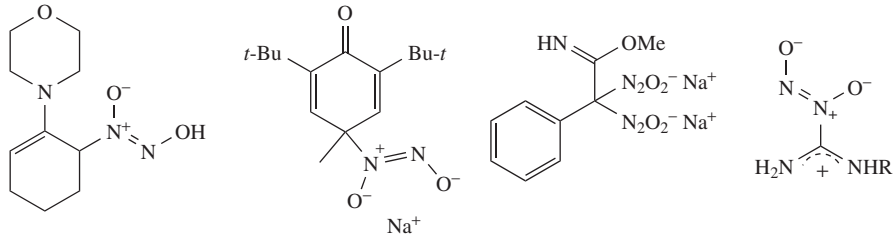
II. NO-PRODUCING DIAZENIUMDIOLATES

A. Carbon-bound Derivatives

The decomposition mechanism of diazeniumdiolates has been extensively studied by both experimental and computational methods[2, 6, 25–28]. The two main classes of NO-producing diazeniumdiolates are carbon-bound and nitrogen-bound derivatives. Most carbon-bound diazeniumdiolates do not release NO but, as shown in equation 10, release nitrous oxide (N_2O) upon decomposition[2, 28].



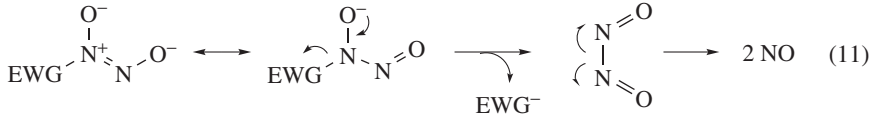
However, NO formation from carbon-bound diazeniumdiolates has been reported in some cases. For example, Cupferron (**3**) and its derivatives have been suggested to decompose to yield NO via enzymatic oxidation, thermal and photochemical means[29–34]. Other carbon-based diazeniumdiolates that have been reported to release NO include compounds derived from enamines (**12**)[35], phenolates (**13**)[36], nitriles (**14**)[37] and *N*-hydroxyguanidines (**15**)[37] (Figure 2). While NO production from these carbon-based diazeniumdiolates is



(**12**) (**13**) (**14**) (**15**)

FIGURE 2. Some carbon-bound diazeniumdiolate derivatives that have been reported to release NO

nonquantitative, it has been suggested that electron flow leading to an anion fragment and the NO dimer may be applicable (equation 11)[35].

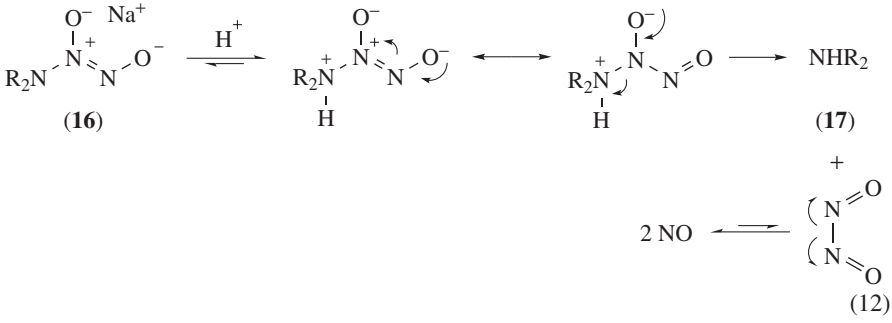


(11)

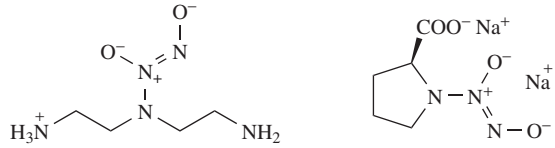
B. Nitrogen-bound Derivatives

Unlike carbon-bound derivatives, many nitrogen-bound diazeniumdiolates readily decompose to yield NO under acidic and, more importantly, physiological conditions[2, 30, 38]. Generally, diazeniumdiolates based on secondary amines are considered NO donors while those based on primary amines have additional decomposition pathways available (*vide infra*).

Decomposition of diazeniumdiolates into two equivalents of NO and the corresponding amine occurs by initial protonation of the amine nitrogen followed by subsequent release of the NO dimer. Further dissociation of the dimer yields NO. This process has been examined by computational methods and is represented in equation 12, where the decomposition of a generic dialkylamino-substituted diazeniumdiolate **16** to amine **17** is shown[27, 39].



(**16**) (**17**) (12)



DETA/NO (**18**) PROLI/NO (**19**)

half-life (pH 7.4, 37°C): 20 h 2 s

FIGURE 3. Examples of secondary amine-based diazeniumdiolates with long (**18**) and short (**19**) half-lives (DETA = diethylenetriamine; PROLI = proline)

Since many nitrogen-bound diazeniumdiolates readily produce NO under physiological conditions, particular interest has been focused on derivatization and decomposition of these compounds. The parent amine plays an important role in the stability of nitrogen-bound diazeniumdiolates and compounds with half-lives in pH 7.4 buffer covering a range from 2 seconds to 20 hours (e.g. **18** and **19**, Figure 3) have been reported[3, 39, 40].

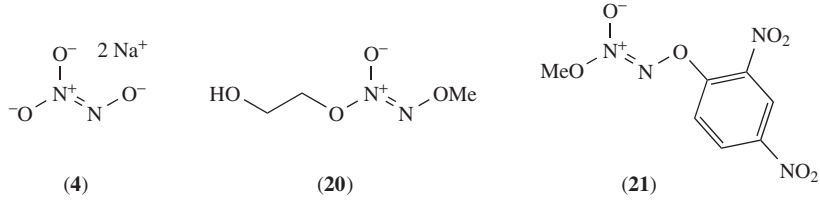
As shown in equation 12, protonation at the secondary amine nitrogen initiates diazeniumdiolate decomposition to NO and the parent amine. Thus, the structure of the secondary amine has a significant influence on the steric and electronic properties of the diazeniumdiolate and subsequently its decomposition rate[39]. Generally, more readily protonated amines result in faster decomposition rates[3, 20, 39, 41]. As a result, secondary amine-based diazeniumdiolates represent a convenient and very versatile source of NO.

III. HNO-PRODUCING DIAZENIUMDIOLATES

A. Oxygen-bound Derivatives

Aside from producing NO, certain diazeniumdiolates have the ability to produce HNO. Currently, the most commonly used compound for production of HNO under physiological conditions is the oxygen-based diazeniumdiolate, Angeli's salt (**4**)[9, 10, 42]. Compounds **20** and **21** are the only other oxygen-bound diazeniumdiolates that have been reported (Figure 4). They are not known precursors to either HNO or NO and can be considered O^2-substituted diazeniumdiolated alcohols[2, 43, 44].

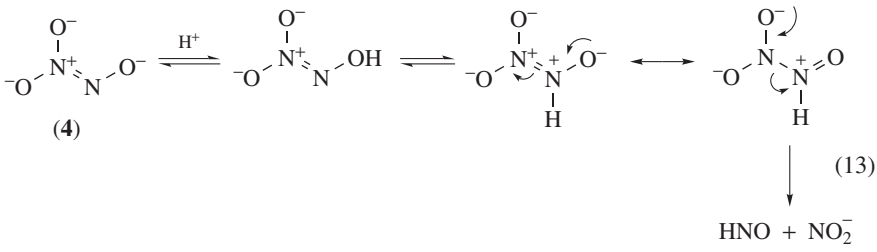
The decomposition mechanism of Angeli's salt has been well studied[9, 27, 42, 45]. The accepted mechanism for Angeli's salt decomposition at physiological pH involves production of HNO and nitrite (NO_2^-) following protonation at the nitrogen and subsequent



(**4**) (**20**) (**21**)

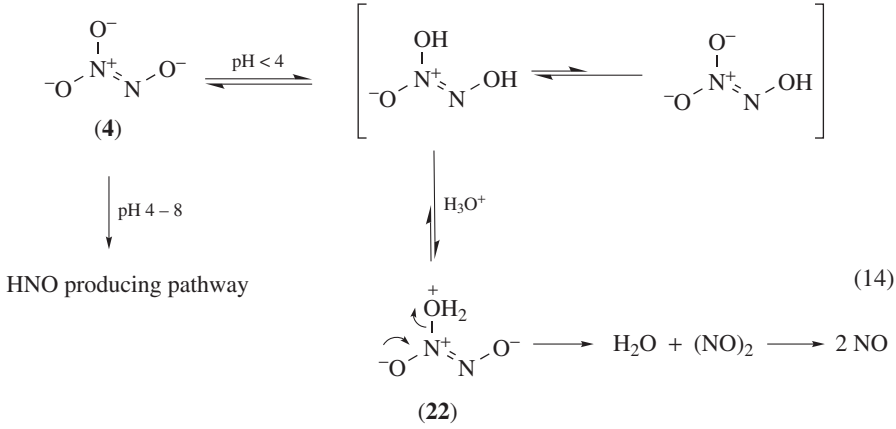
FIGURE 4. Oxygen-bound diazeniumdiolates

cleavage of the N−N bond as shown in equation 13[9, 27, 42, 45].



(13)

Under more acidic conditions (pH < 4) Angeli's salt is no longer an exclusive HNO-donor and starts to exhibit NO production as well[27, 42]. Computational studies suggest that this is the consequence of the multiple potential sites of protonation of Angeli's salt[27]. As the pH of the solution is lowered diprotonation begins to become important. As shown in equation 14, computations suggest that the doubly protonated salt will, through a series of equilibria, form species (**22**) which can irreversibly dehydrate to give the NO dimer and water[26].

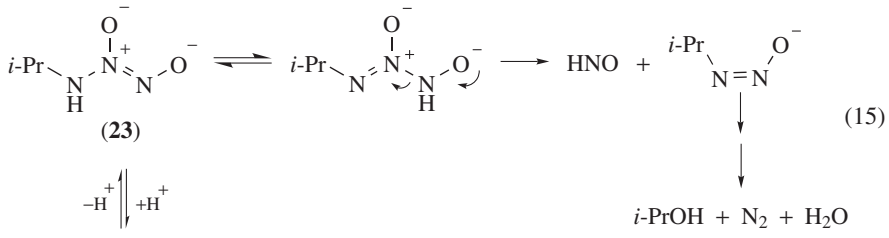


(14)

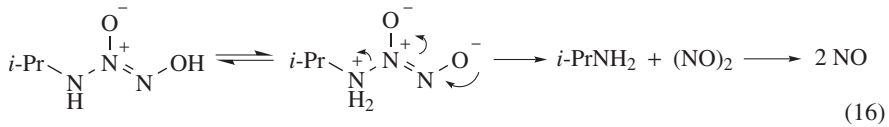
B. Primary Amine-based Derivatives

Though Drago and Karstetter observed that primary amine-based diazeniumdiolates are less stable than their secondary amine-based cousins, they have received some attention because of their ability to generate both HNO and NO[15, 46, 47]. Most of the research on primary amine-based diazeniumdiolates to date has focused on the *i*-propyl amine-based diazeniumdiolate (IPA/NO) (**23**) due to its stability compared to other primary amine-based derivatives[15]. Computations show that like secondary amine-based diazeniumdiolates, primary amine-based compounds also prefer the Z conformation[48]. Similar to Angeli's salt, IPA/NO exhibits a pH dependence to its decomposition, with higher pH favoring HNO production and lower pH favoring NO production (equations 15 and

16)[27, 46]. An approximate 50:50 mixture of HNO and NO is produced at neutral pH.



(15)



(16)

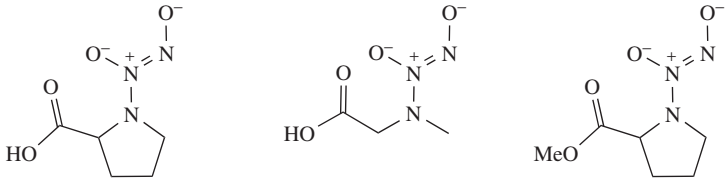
IV. APPLICATIONS

A. O^2-substituted Diazeniumdiolates as Prodrugs

NO participates in a wide array of physiological processes including immune response, platelet aggregation, neurotransimission and blood pressure regulation and as such has been the focus of much research culminating with Murad, Furchgott, Ignarro's receipt of the Nobel prize in physiology or medicine in 1998[49–51]. More recent research has shown that HNO also has important and unique biological activity, especially as a potential alternative to current treatments of cardiac failure[52–54], generating increased interest in its chemistry[46, 55–57]. Since both NO and HNO are reactive species, utilization and study of NO/HNO must be done through release from precursors such as diazeniumdiolates. Due to the array of pharmacological effects that both NO and HNO exhibit, precursors to these molecules have become attractive targets for drug design.

Since secondary amine-based diazeniumdiolates are considered prodrugs of NO, derivitization of these diazeniumdiolates can be thought of as pro-prodrugs, i.e. molecules that upon decomposition release prodrugs, which further decompose to deliver the drug payload. In the case of secondary amine-based diazeniumdiolates, most pro-prodrug strategies focus on O^2-substitution, since this is the most easily substituted site[2, 3, 58, 59]. Since the free amine is the primary byproduct of secondary amine-based diazeniumdiolate decomposition (equation 12), biocompatible secondary amines are commonly chosen as the substrate for diazeniumdiolation when prodrug strategies are employed[59, 60]. Two common choices are the proline derivative, PROLI/NO (**24**), and the sarcosine derivative, SARCO/NO (**25**)[60]. Also of note, the methyl ester of PROLI/NO (**26**) has been shown to have increased cell permeability compared to PROLI/NO[61]. Structures of these derivatives are shown in Figure 5.

Many examples of O^2-protecting groups have been reported, with enzymatic deprotection a commonly employed strategy. Some examples of O^2-protecting groups that have been utilized include those cleaved by cytochrome P450[62–67], glutathione *S*-transferase[68, 69], glucosidase[60, 70, 71], neuraminidase[72], esterase[73], prostate-specific antigen[24], α-chymotrypsin[24] and *N*-acetylglucosaminidase[60]. Other strategies that have been employed for O^2-deprotection include hydrolysis[74] and photolysis[75].

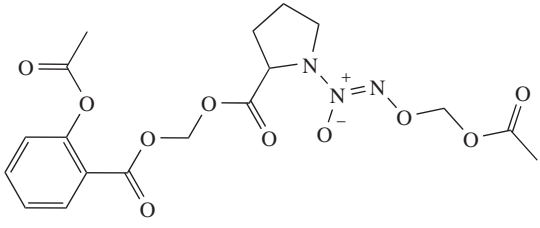


(**24**) (**25**) (**26**)

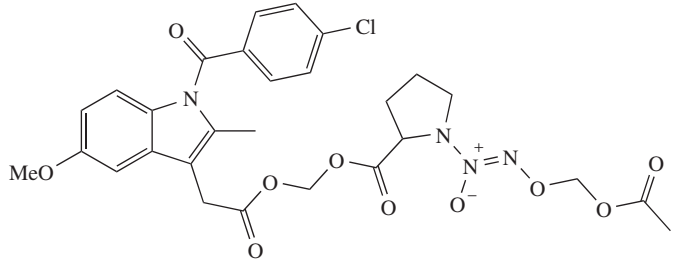
FIGURE 5. Diazeniumdiolates that release biocompatible secondary amines along with NO

B. Diazeniumdiolate Amine Functionalization

To extend the utility of secondary amine-based diazeniumdiolate NO prodrugs, efforts have been made to functionalize the amine to provide further pharmacological benefit after the diazeniumdiolate moiety has decomposed. One strategy is use of diazeniumdiolates in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDS)[76–78]. NSAIDS are one of the most commonly used medications to treat pain, inflammation and fever. However, due to their mode of action, they can be responsible for undesirable gastrointestinal (GI), renal, hepatic and cardiovascular side effects[77]. The use of NO-producing prodrugs of NSAIDS has been shown to be effective in alleviating adverse GI side effects while maintaining efficacy as NSAIDS[77, 79–82]. Examples of such diazeniumdiolate-substituted



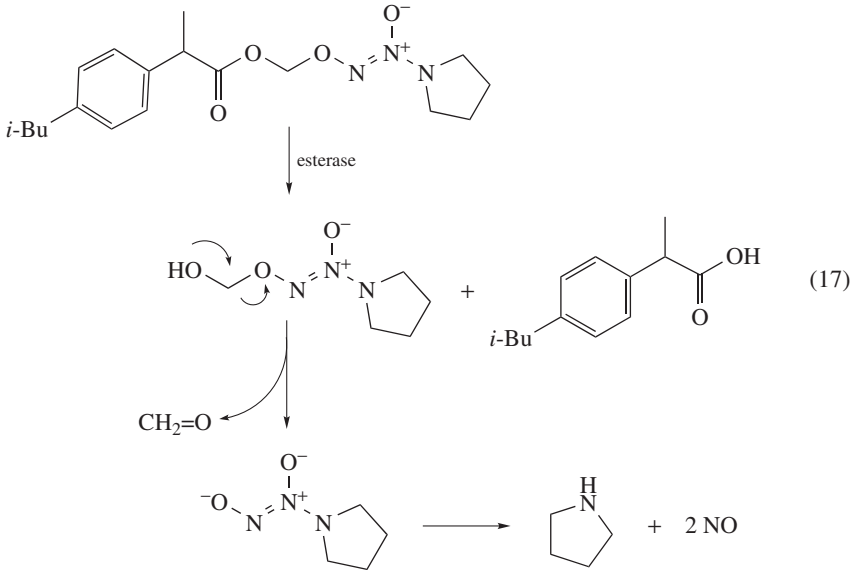
(**27**)



(**28**)

FIGURE 6. Diazeniumdiolate-substituted nonsteroidal anti-inflammatory drugs

NSAIDS are illustrated in Figure 6 by the aspirin derivative (**27**) and indomethacin derivative (**28**). The metabolic decomposition of an ibuprofen/diazeniumdiolate derivative is shown in equation 17[76].



(17)

C. NO-releasing Polymers

The most significant problem concerning the use of synthetic biomaterials in blood-contacting applications is the rapid onset of thrombosis (i.e. the formation of a blood clot). Recent research in the field has focused on the development of more thromboresistive surfaces[83, 84]. A completely thromboresistive surface must exhibit a range of biological activity including inhibition of both fibrinogen adsorption and its subsequent conversion to fibrin and a reduction of adherence, aggregation and release reactions of platelets at the surface. The most thromboresistive material known is the natural endothelium, which regulates the above responses by a variety of mechanisms, including prostacyclin release and NO generation. Many new biomaterials are designed to mimic the properties of natural endothelium.

NO is continually released by the endothelium at a flux of approximately 1×10^{-10} mol cm^{-2} min^{-1} [85]. This naturally controlled release has been shown to regulate vascular tone and also to inhibit platelet adhesion and aggregation strongly[86–89]. Much recent research has focused on the development of biomaterials that mimic the NO-releasing properties of the endothelium. Smith, Keefer and coworkers first reported the preparation and study of NO-releasing polymers containing diazeniumdiolates in 1996[90]. They examined the three generalized polymer types shown in Figure 7. In the first type (Figure 7a), diazeniumdiolates were noncovalently dispersed through water-soluble polyethylene glycol (PEG) or biodegradable polycaprolactone (PCL) matrices by simple mechanical mixing of the melted polymer and a variety of different diazeniumdiolates. A recently reported modification to this strategy to prolong NO release and increase thermal stability of the diazeniumdiolate was to O^2-substitute the

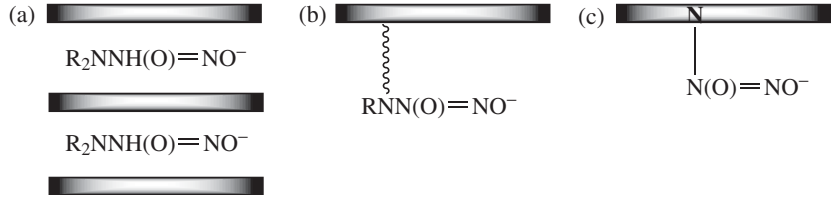


FIGURE 7. Different approaches to the incorporation of diazeniumdiolates into polymers

diazeniumdiolate with a substrate sensitive to hydrolytic cleavage prior to incorporation in the polymer substrate[91].

The release of NO from these polymer blends is significantly slowed when compared to free diazeniumdiolates in solution. This is expected since the aqueous phase must diffuse into the polymer in order to initiate diazeniumdiolate decomposition. Release rates from the polymers were shown to be dependent, at least in part, on the hydrogen ion activity of the solid. Rates of diffusion of small molecules (specifically NO) are also dependent on the physical properties of the polymers, including the amount and type of plasticizers[92]. Also of note for polymeric diazeniumdiolate systems is the necessity of added lipophilic salt. Meyerhoff and coworkers found that the inclusion of these lipophilic salts such as potassium tetrakis-4-chlorophenyl borate (KTpClB) were essential to provide an acid-buffering environment to the decomposing diazeniumdiolates so that the resultant amine byproduct did not prevent further dissociation of the diazeniumdiolate in the polymer matrix[93].

Polymeric materials with covalently bound diazeniumdiolates have been obtained by grafting them onto a polysaccharide (dextran) using cyanogen bromide as the coupling agent (Figure 7b), or by reacting a polyethyleneimine (PEI)-based polymer with NO to form a diazeniumdiolate functionality bonded directly to the polymer backbone (Figure 7c)[90]. Studies incorporating diazeniumdiolates covalently into polyurethane (PU) backbones have also been reported recently[94].

Meyerhoff and coworkers have made significant advances in the development of new NO-releasing polymers for use in blood-contacting medical devices (e.g. thromboresistant chemical sensors capable of monitoring physiologically important ions and gases[95–97]). A range of different diazeniumdiolate-containing polymeric materials (e.g. PVC[98–100], PU[98], silicone rubber (SR)[101], polymethacrylate (PMA)[102] and fumed silica particles blended into PU[103]), employing one or more of the incorporation approaches shown in Figure 7, have been examined during the course of these investigations. Despite their diversity of structure, the PVC-, PU-, SR- and PMA-based polymers all reduce platelet activation and thrombosis when used as coatings on either extracorporeal circuits in a rabbit model of venovenous extracorporeal circulation or functional oxygen sensors in a porcine model[99, 102, 103].

In addition to polymeric materials, work has also been done to incorporate the diazeniumdiolate functional group into nanoparticles. One approach has been to make dendrimer-based nanoparticles[104, 105]. These polypropylenimine-based nanoparticles are able to release large quantities of NO from dendritic scaffolds upon decomposition under physiological conditions[104]. Functionalization of gold nanoparticles has been reported as well[106]. By tethering a secondary amine to alkanethiols bound to a gold surface, 2-nm nanoparticles were synthesized and were shown to release significant amounts of NO upon decomposition at physiological conditions[106]. Other nanoparticles that have been synthesized containing diazeniumdiolate moieties designed to release NO include silica based particles[107, 108] and nanofiber gels[109].

V. SUMMARY

The diazeniumdiolate functional group has come to the forefront as a convenient source of NO and/or HNO. In the 200-plus years since the first description of this novel functional group, a rich and broad body of work has focused on the chemistry of these compounds. The two most frequently used diazeniumdiolates to date are DEA/NO (**5**) and Angeli's salt (**4**). DEA/NO has become one of the standard diazeniumdiolates used for NO production, while Angeli's salt continues to be the most studied source of HNO. Recent research has shown the potential pharmacological utility of NO- and HNO-producing diazeniumdiolates, and their incorporation into prodrug and biocompatible polymer design will ensure continued interest in this versatile functional group.

VI. ACKNOWLEDGMENT

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Hydroxylamine, oxime and hydroxamic acid derivatives of nucleic acids

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I. INTRODUCTION

A. Background

Hydroxylamines and their related derivatives, oximes and hydroxamic acids are frequently used as functional groups with attractive chemical properties. Hydroxylamine-containing molecules are readily subjected to reduction and oxidation, producing amines and nitrons, respectively[1]. In addition, the hydroxylamino group functions as a potent nucleophile because of the N−O structure which can serve as an α-nucleophile[2], and has a tendency to generate nitroxide radicals[3,4]. Hydroxamic acids and oxime derivatives can form strong complexes with a variety of metal ions[5]. These groups play roles not only as reactants but also as hydrogen-bonding donors or acceptors.

These reactive hydroxylamino derivatives attack the base moieties of ribonucleosides or 2′-deoxynucleosides causing genetic mutations[6–8]. Over the last three decades, a number of nucleoside and nucleotide analogues consisting of these functional groups have been synthesized to develop novel therapeutic agents. Therefore, it is very important to understand the chemical properties and functions of hydroxylamine, oxime and hydroxamic acid groups for molecular biology studies and creation of therapeutic agents.

B. Scope

We describe in this chapter classifications of the functions and the applications of hydroxylamine, oxime and hydroxamic acid groups on nucleic acids based on their chemical properties. In Section II, we start with the description of the mutagenicities of hydroxylamine and *O*-methylhydroxylamine, which react directly with nucleobases. The mechanisms of reactions and mutations are also discussed in this section. In Section III, we present a series of nucleoside and nucleotide analogues consisting of hydroxylamine, oxime or hydroxamic acid. There are some nucleoside analogues that have biological activities. Section IV describes a series of oligonucleotides that have a backbone and sugar moieties modified with these functional groups. Displacement of phosphodiester linkages with neutral and hydrophilic hydroxylamino linkages can improve the thermal stability as well as nuclease resistance of oligonucleotides. Finally, in Section V, we describe applications for the detection and quantification of DNA lesions by taking advantage of the chemical properties of hydroxylamine derivatives. We show the close relationships of these functional groups with nucleic acid chemistry in this chapter.

II. REACTIONS OF HYDROXYLAMINE AND *O*-METHYLHYDROXYLAMINE WITH NATURAL NUCLEOBASES

Both hydroxylamine and *O*-methylhydroxylamine react with bases of nucleosides[8]. As the damaged nucleobases alter the genome sequences through non-canonical hydrogen bondings during replication[7–9], their mutagenic actions on nucleic acids have been studied extensively from the early 1960s[6,10–13]. On the other hand, there are only a few studies regarding the effect of *N*-methylhydroxylamine. It was shown that *N*-methylhydroxylamine has less or even no mutagenicity than either hydroxylamine or *O*-methylhydroxylamine[10,11,14].

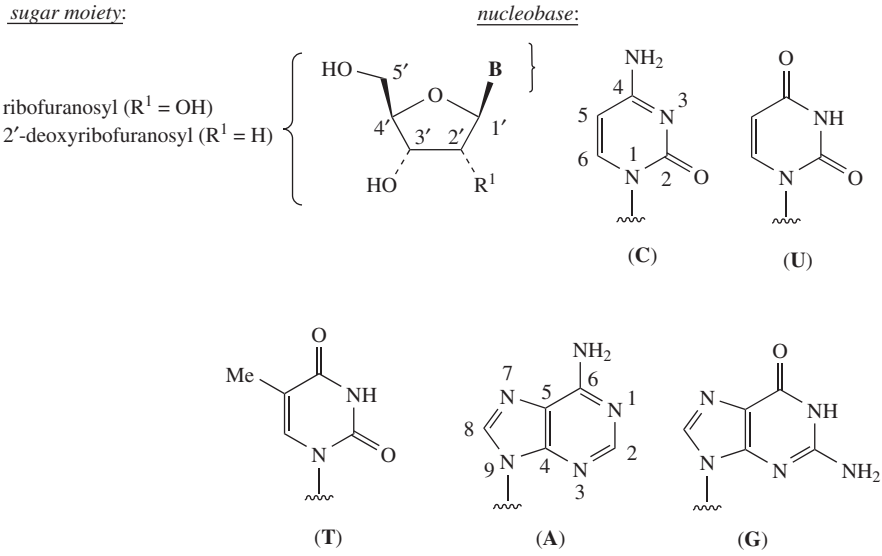


FIGURE 1

Figure 1 shows the chemical structures of the natural nucleosides of DNA and RNA. Pyrimidine bases involve cytosine (**C**), uracil (**U**) and thymine (**T**), and purine bases adenine (**A**) and guanine (**G**). The sugar moiety consists of either a ribofuranosyl group or a 2′-deoxyribofuranosyl group.

Cytidine is most susceptible to hydroxylamine and *O*-methylhydroxylamine reactions, forming mutagenic nucleosides[15, 16]. These mutagenic nucleosides account for the greatest number of mutations derived from hydroxylamine and *O*-methylhydroxylamine. Uridine also reacts with hydroxylamine, but not with *O*-methylhydroxylamine[17]. Adenosine is less reactive to these reagents than the pyrimidine nucleosides[18]. Guanosine and thymidine are practically inert to these reagents[17, 19]. When nucleic acids are exposed to hydroxylamine or *O*-methylhydroxylamine, these reagents are much more reactive on single-stranded DNA than on double-stranded DNA because of the steric factors of the bihelical structure[17, 20].

This section describes the chemical reactions of hydroxylamine and *O*-methylhydroxylamine on pyrimidine and purine nucleosides. The mechanisms to induce genetic alterations by damaged nucleobases are also described.

A. Reactions with Pyrimidine Bases

Both N^4-hydroxycytidine (cytidine with hydroxylated amino group at 4-position) (**4**, $R^2 = H$) and N^4-hydroxy-6-hydroxyamino-5,6-dihydrocytidine (**3**, $R^2 = H$) are major products formed after treatment of cytidine (**1**) with hydroxylamine (Figure 2)[15, 16]. Similarly, N^4-methoxycytidine (**4**, $R^2 = Me$) and N^4-methoxy-6-methoxyamino-5,6-dihydrocytidine (**3**, $R^2 = Me$) are produced upon treatment with *O*-methylhydroxylamine (see Figure 1 for numbering of the nucleobase).

The mechanisms and kinetics of the reactions have been extensively studied by several groups. The addition of hydroxylamine and *O*-methylhydroxylamine occurs through

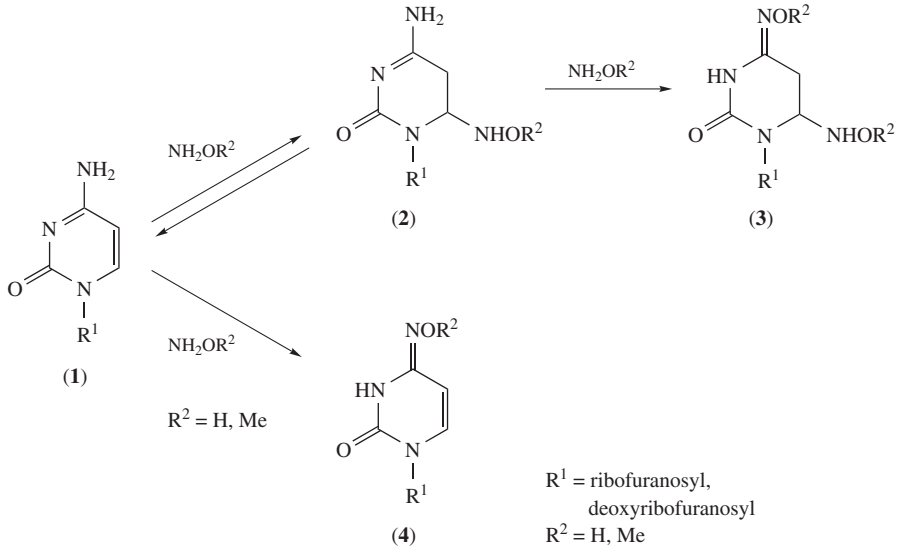


FIGURE 2

two individual pathways, as shown in Figure 2[16]. The first pathway involves reversible addition of reagents to the $C_{(5)}-C_{(6)}$ double bond of the cytosine base (**1**) to form intermediates (**2**), which is subsequently followed by irreversible substitution on the 4-amino group to form **3**. In the second pathway, hydroxylamine and *O*-methylhydroxylamine react with **1** by direct substitution on the 4-amino group to give **4**. It is suggested that unprotonated hydroxylamine ($pK_a = 6.0$) or *O*-methylhydroxylamine ($pK_a = 4.6$) react with the protonated cytosine base ($pK_a = 4.2$). The optimum pH for these two pathways is 6.0 for hydroxylamine and 5.0 for *O*-methylhydroxylamine. At neutral pH, **3** is predominantly formed in preference to **4**. On the other hand, under more acidic conditions, the formation of **4** becomes predominant. These changes in ratio are caused because of the reversible reaction between **1** and **2**. Development of **4** in DNA induces genetic mutations, while **3** has no mutagenicity[16]. Thus, it is particularly important to understand the reaction conditions that favor the second pathway.

The mechanism of the mutagenic action by **4** is mediated by the formation of base pairs with adenine base (**A**) in addition to the canonical guanine base (**G**), as shown in Figure 3[19]. The tautomeric equilibrium between the amino- and imino-forms of N^4-hydroxyamino group allows these two base pairs. Accordingly, **4** in genomic DNA can induce the C → T transitional alterations by the incorporation of deoxyadenosine opposite **4** residues upon replication[19]. In contrast, A → G transitions are induced when the nucleotide monomers are damaged by hydroxylamine. This results from the incorporation of **4** opposite adenosine (**A**) residues in the template strand[21, 22]. The A → G transitions are preferentially induced in P22 and T4 phages, and in *E. coli* when they are treated with hydroxylamine[22].

Methylation of a $C_{(5)}-C_{(6)}$ double bond increases the electron density in the aromatic ring system by the inductive effect of the methyl group, and disfavors nucleophilic attack to the cytosine base[23]. Consequently, 5-methylcytidine is much less reactive to hydroxylamine and *O*-methylhydroxylamine than cytidine[6].

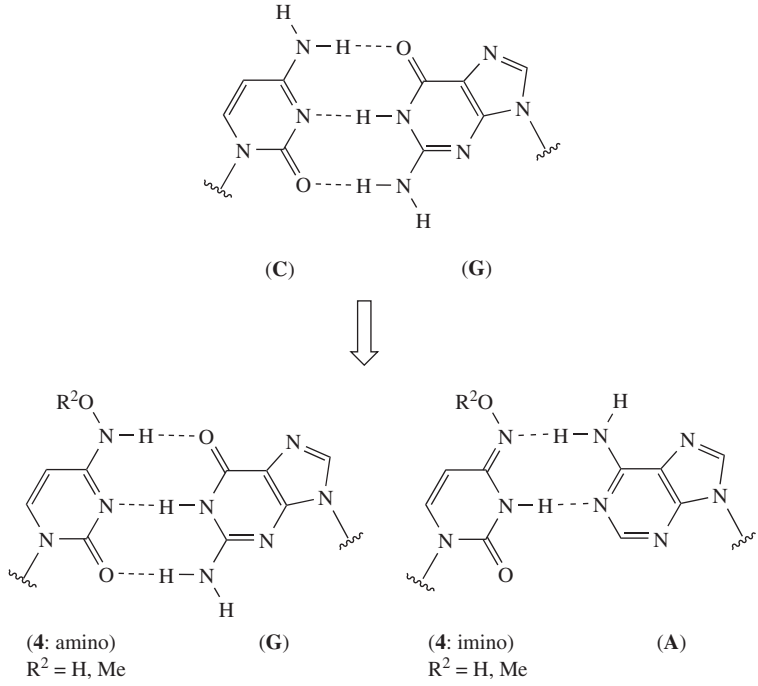


FIGURE 3

Uridine (**5**) reacts with only hydroxylamine at the $C_{(5)}-C_{(6)}$ double bond to form 6-hydroxyamino-5,6-dihydrouridine (**6**), which is further decomposed into ribosylurea (**7**) and isoxazolone (**8**) with optimum pH 8 (Figure 4)[17]. Formation of **7** and **8** proceeds via the intermediate **9**, which is formed by the intramolecular attack of the hydroxyl group on the $C_{(4)}$ carbonyl. *O*-Methylhydroxylamine is unreactive to uridine and this is due not only to the lower nucleophilicity of the reagent, but also to the absence of a free hydroxyl group to form intermediate **9**[17]. The products **6** and **7** have no functional activity, thus they are non-mutagenic[15, 16].

B. Reactions with Purine Bases

Both hydroxylamine and *O*-methylhydroxylamine react with adenosine (**10**) in an acidic medium[18], resulting in N^6-hydroxyadenosine and N^6-methoxyadenosine (**11**), respectively (Figure 5). The optimum pH of the reaction with hydroxylamine is between 4 and 5. It is proposed that the unprotonated hydroxylamine attacks the $C_{(6)}$ carbon of $N_{(1)}$-protonated adenosine ($pK_a = 3.6$). The rate of the reaction, however, is two orders of magnitude smaller than the reaction with cytosine base under similar conditions[24, 25].

Generation of **11** in genome DNA mediates the A → G transition[26–28]. **11** exists as a tautomeric mixture of the amino- and imino-forms, and base-pairing properties also depend on the orientation of $N-OR^2$ groups, which may be *syn* or *anti* to the purine nitrogen $N_{(1)}$ (Figure 6)[29, 30]. The amino-*anti* conformer (**11**: amino-*anti*) can form a base pair with the canonical thymine base (**T**). On the other hand, both the imino-*anti*

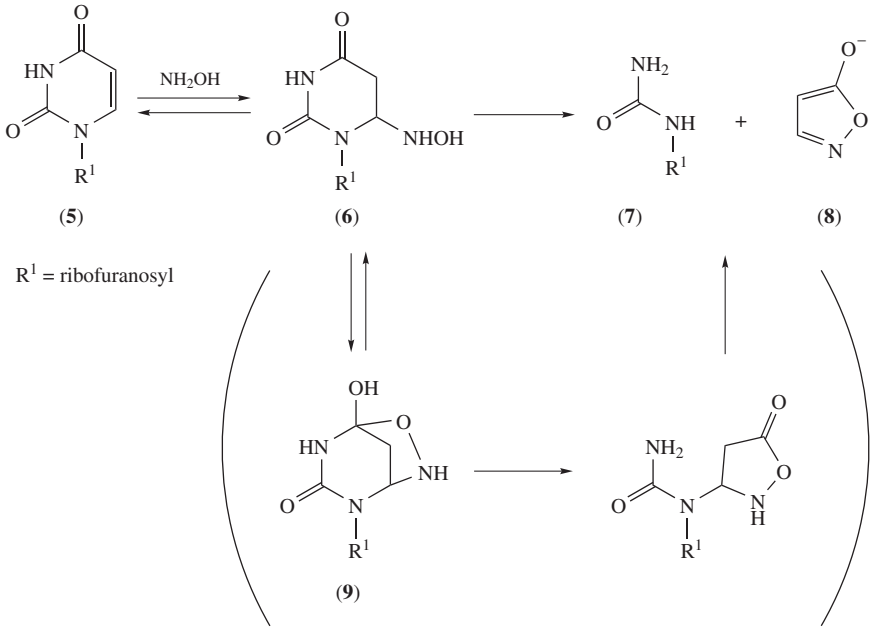


FIGURE 4

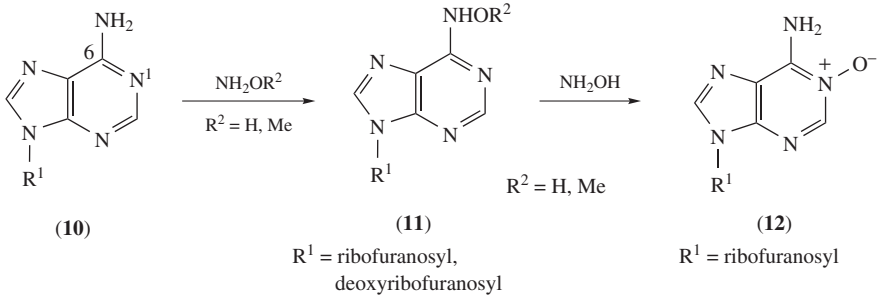


FIGURE 5

(**11**: imino-*anti*) and imino-*syn* (**11**: imino-*syn*) forms are able to pair with the cytosine base (**C**), the base pair that leads to the A → G transition. It is this equivocal feature of the modified base (**11**) that causes genetic mutations.

Treatment of N^6-hydroxyadenosine (**11**, $R^2 = H$) with hydroxylamine in a heated solution (65 °C or 100 °C) results in the formation of adenosine-I-oxide (**12**) (Figure 5)[25]. Although this reaction has been demonstrated only under relatively vigorous conditions, this reaction could occur *in vivo* also. **11** is mutagenic in both *in vitro* and *in vivo* experiments, as mentioned above, but not carcinogenic when it was tested *in vivo*[25–27]. On the other hand, **12** is shown to be carcinogenic *in vivo*[25, 31].

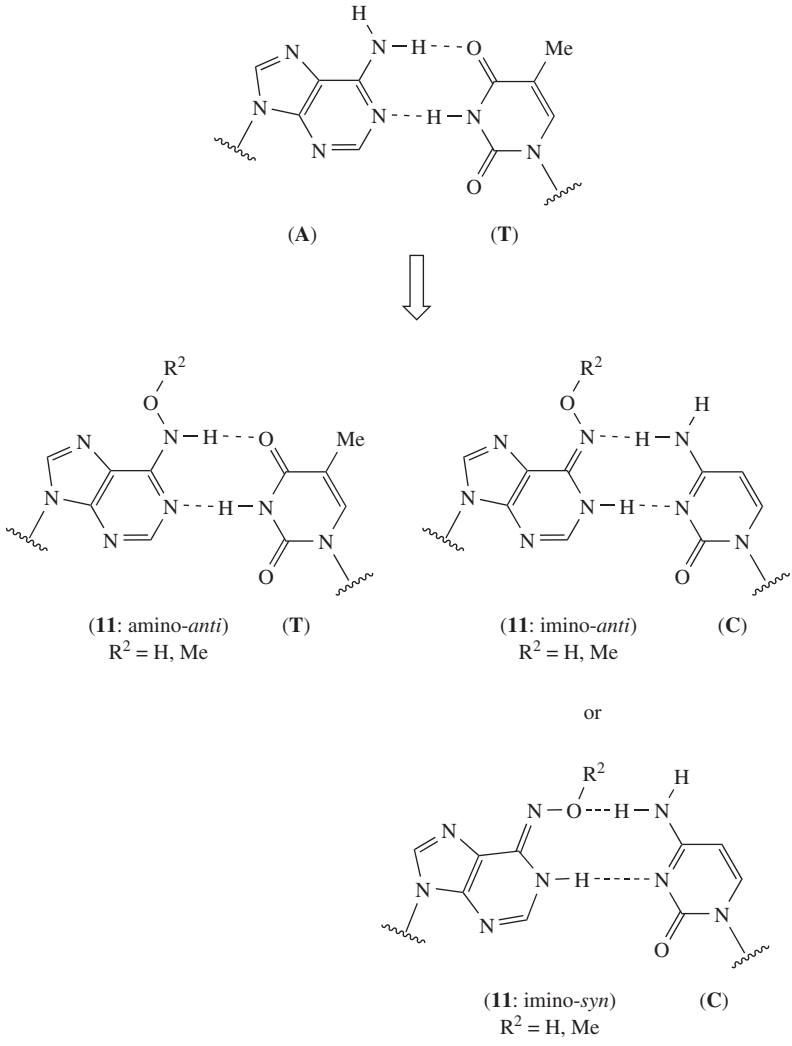
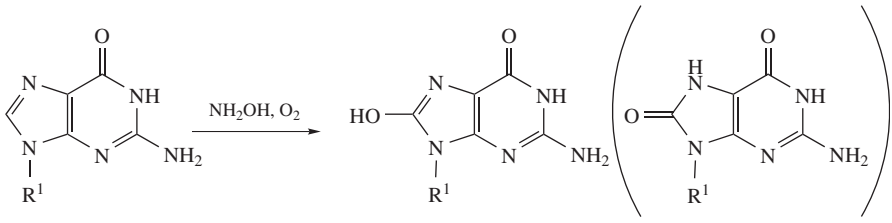


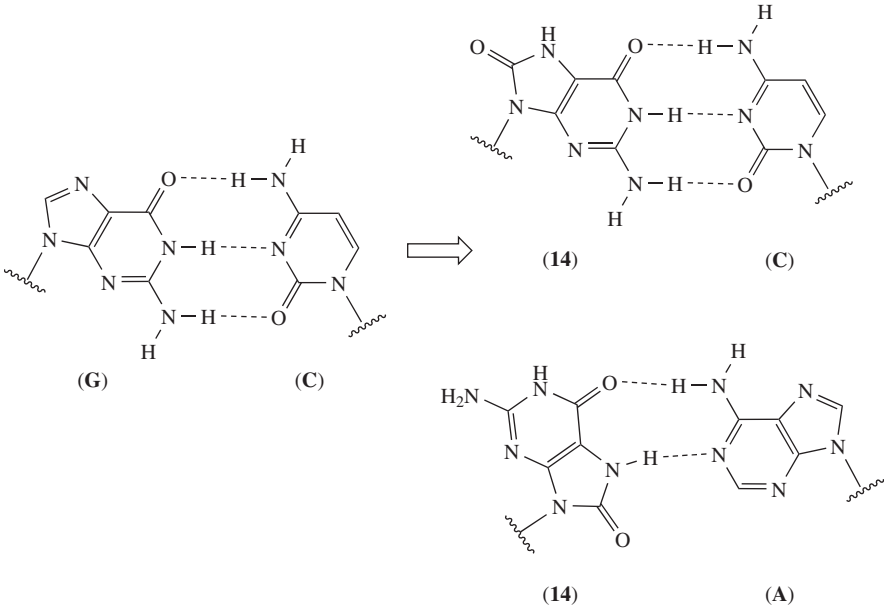
FIGURE 6

Guanosine did not react with either hydroxylamine or *O*-methylhydroxylamine in any pH range. However, hydroxylamine has been shown to mediate the formation of 8-hydroxydeoxyguanosine (8-oxodeoxyguanosine, **14**), as shown in Figure 7[32]. Generation of **14** is observed when 2′-deoxyguanosine (**13**) is incubated with hydroxylamine in the presence of oxygen (O_2). This reaction is originally found in the reaction of **13** with ascorbic acid and O_2, and is also effective with other reducing agents, such as hydrazine or sodium bisulfite. The OH radical produced from the reducing agents and O_2 is indicated as an active species for the reaction.



(**13**) (**14**)

FIGURE 7



(**G**) (**C**) (**14**) (**C**) (**14**) (**A**)

FIGURE 8

The generation of **14** in genomic sequence is mutagenic and leads to a G → T transversion alteration[33]. This is based on the equivocal feature of **14** to form a base pair not only with a cytosine base (**C**) but also with an adenine base (**A**), as shown in Figure 8.

III. NUCLEOSIDE ANALOGUES CONTAINING HYDROXYLAMINE, OXIME AND HYDROXAMIC ACID GROUPS

This section describes a series of nucleoside analogues consisting of hydroxylamine, oxime and hydroxamic acid groups. We present the modifications of sugars (Section III.A) and bases (Section III.B) in this section.

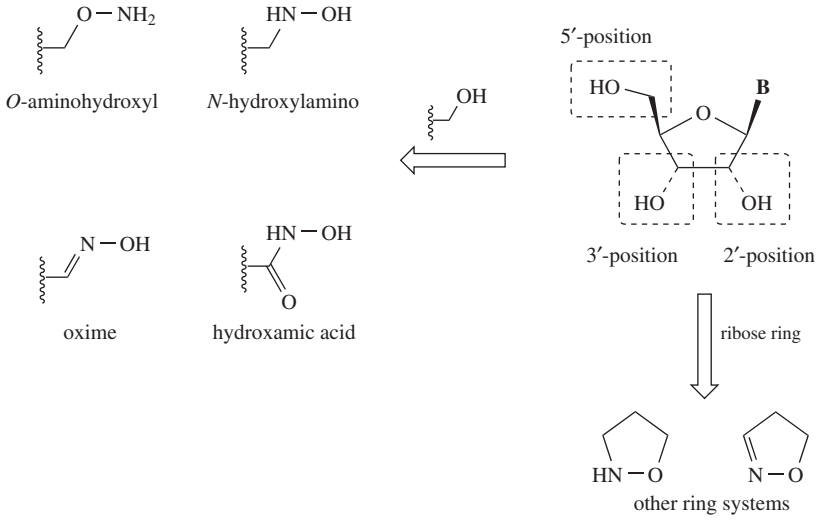


FIGURE 9

A. Sugar-modified Nucleosides

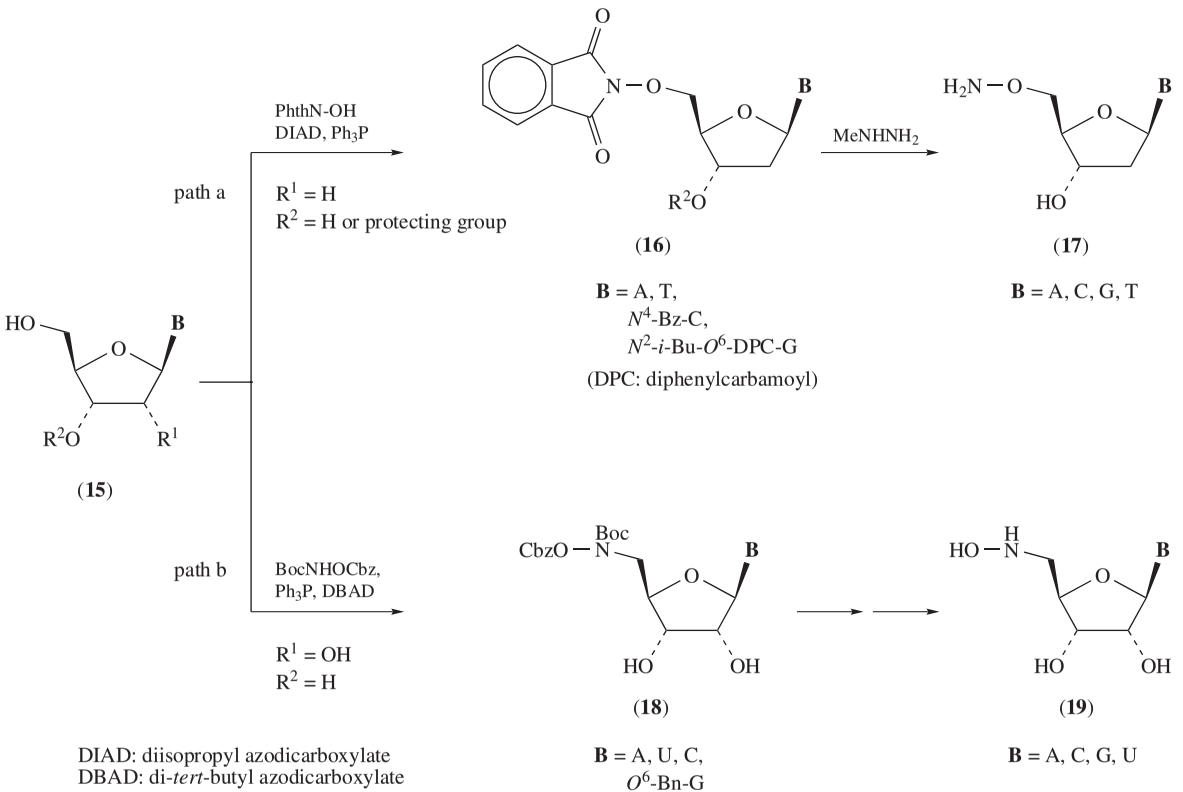
Hydroxylamine, oxime and hydroxamic acid groups are introduced into ribose moiety by replacing each hydroxyl group, as shown in Figure 9. We first present modifications of the hydroxyl groups, followed by modifications of the ribose ring structure.

1. Modification at C-5′ position

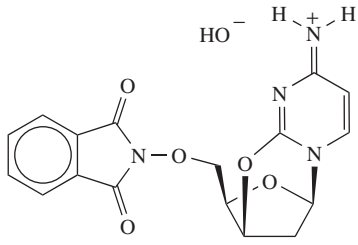
Replacement of the 5′-hydroxyl group of 2′-deoxynucleoside with an *O*-aminohydroxyl group has been reported by Sanghvi and coworkers. They used these nucleosides for the synthesis of backbone-modified oligonucleotides (see Section IV.A.1)[34]. They used *N*-hydroxyphthalimide and the Mitsunobu reaction to introduce *O*-aminohydroxyl group into the 5′-hydroxyl group of 2′-deoxynucleosides (**15**, $R^1 = H$), and obtained 5′-*O*-aminonucleosides (**17**) (Scheme 1, path a). Thymidine and 2′-deoxyadenosine analogues (**17**, B = T, A) can be synthesized without the protection of nucleobase moieties. On the other hand, synthesis of 2′-deoxycytidine and 2′-deoxyguanosine analogues (**17**, B = C, G) require protecting groups on the nucleobases.

The syntheses of 5′-deoxy-5′-*N*-hydroxylamino nucleosides have been achieved by using *O*-protected hydroxylamine, instead of *N*-protected hydroxylamine, in the Mitsunobu reactions (Scheme 1, path b). Li and Miller used *N*-(*tert*-butoxycarbonyl)-*O*-(benzyloxycarbonyl)hydroxylamine (BocNHOCbz), and synthesized adenosine, cytidine and uridine analogues (**19**, B = A, C, U) without any base protection[35]. Guanosine analogue (**19**, B = G) is synthesized from O^6-protected **15**. These 5′-deoxy-5′-*N*-hydroxylamino nucleosides (**19**) are used for the synthesis of another type of backbone-modified oligonucleotide (see Section IV.A.2)[35].

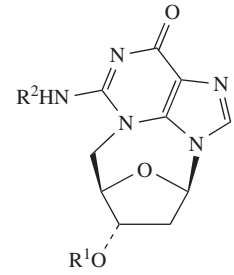
When the Mitsunobu reaction of 2′-deoxycytidine (**15**, R^1,$R^2 = H$) is carried out without the base protecting group, 2,3′-anhydro nucleoside (**20**, Figure 10) is formed by an intramolecular displacement reaction along with **16**. However, this side reaction


PhthN-OH
DIAD, Ph3P
path a
R1 = H
R2 = H or protecting group
MeNHNH2
(16)
B = A, T,
N4-Bz-C,
N2-i-Bu-O6-DPC-G
(DPC: diphenylcarbamoyl)
(17)
B = A, C, G, T
(15)
path b
BocNHOCbz,
Ph3P, DBAD
R1 = OH
R2 = H
(18)
B = A, U, C,
O6-Bn-G
(19)
B = A, C, G, U
DIAD: diisopropyl azodicarboxylate
DBAD: di-tert-butyl azodicarboxylate

SCHEME 1



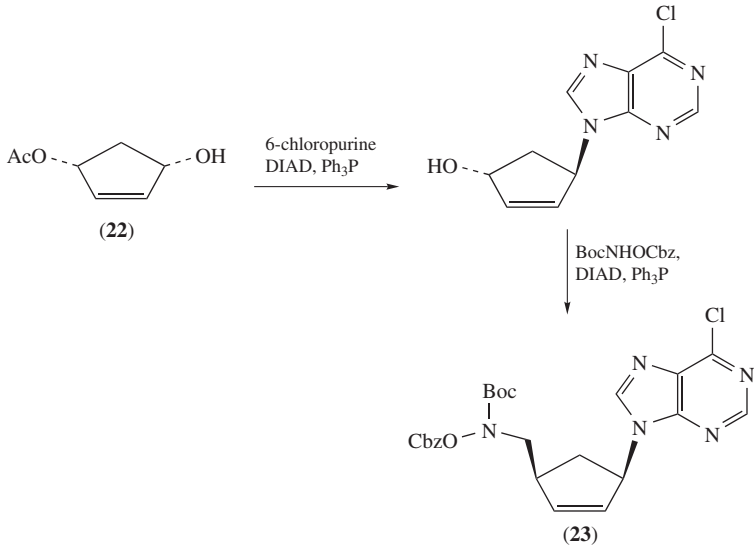
(**20**)



R^1 and R^2 = H or protecting group

(**21**)

FIGURE 10



(**22**)

(**23**)

SCHEME 2

is not reported in the synthesis of **18**. On the other hand, protection of the acidic 6-hydroxyl group of guanine base is required for the synthesis of guanosine analogues (**17** and **19**, B = G) to prevent the formation of N^3,5′-cyclonucleoside (**21**, Figure 10).

Mulvihill and Miller have also reported the syntheses of 5′-hydroxylamino carbocyclic nucleoside analogues (Scheme 2)[36]. The syntheses include consecutive Mitsunobu reactions of enantiomerically pure **22** with 6-chloropurine and then with BocNHOCbz to give **23**. Adenine carbocyclic analogues of diol (**24**), dideoxy (**25**) and dideoxy-didehydro (**26**) derivatives (Figure 11) are prepared from **23**.

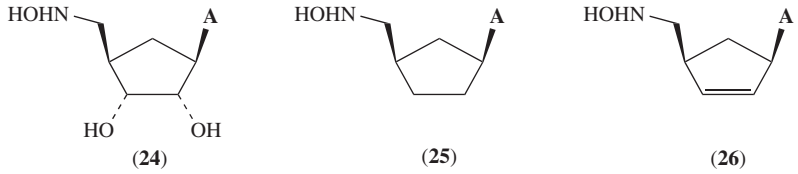


FIGURE 11

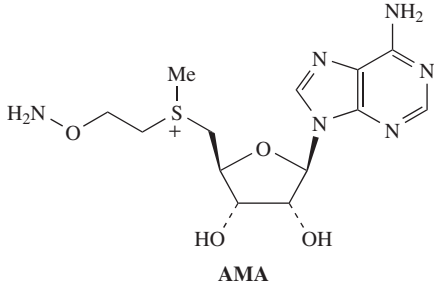
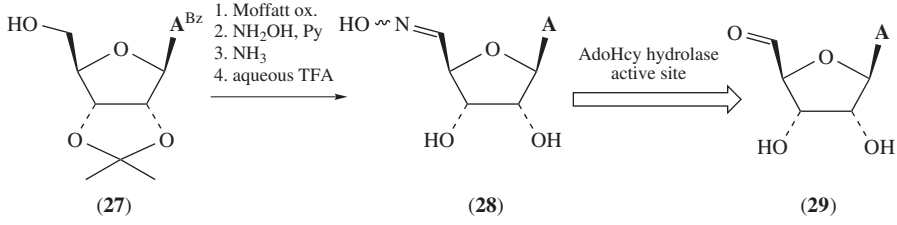


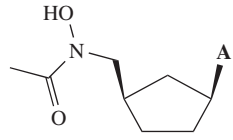
FIGURE 12

O-{*S*-(5′-Deoxy-5′-adenosyl)methylthioethyl}hydroxylamine (AMA, Figure 12), having a hydroxylamine at 5′-position, is known to be a non-toxic inhibitor of *S*-adenosylmethionine decarboxylase (SAMDC)[37], which is one of the two rate-limiting enzymes regulating polyamine synthesis in a cell. Since polyamine synthesis is activated in colon cancer cells rather than in normal cells, AMA acts as a potent inhibitor of colon cancer cell proliferation and is, therefore, a therapeutically promising anti-colorectal cancer agent.

Introduction of an oxime group at the 5′-position has been reported by Robins and coworkers (Scheme 3)[38]. Nucleoside **28** is synthesized from N^6-benzoylated adenosine analogue **27** by Moffatt oxidation (dimethyl sulfoxide/dicyclohexylcarbodiimide/dichloroacetic acid) of the 5′-hydroxyl, followed by a reaction with hydroxylamine. Oxime **28** exists as a mixture of *E*- and *Z*- isomers. **28** is found to inhibit *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, and is also cytotoxic against several tumor cell lines[38]. The authors suggested that upon binding to the active site of AdoHcy hydrolase, **28** releases 5′-carboxaldehyde adenosine (**29**), an inhibitor of AdoHcy hydrolase.



SCHEME 3



(**30**)

FIGURE 13

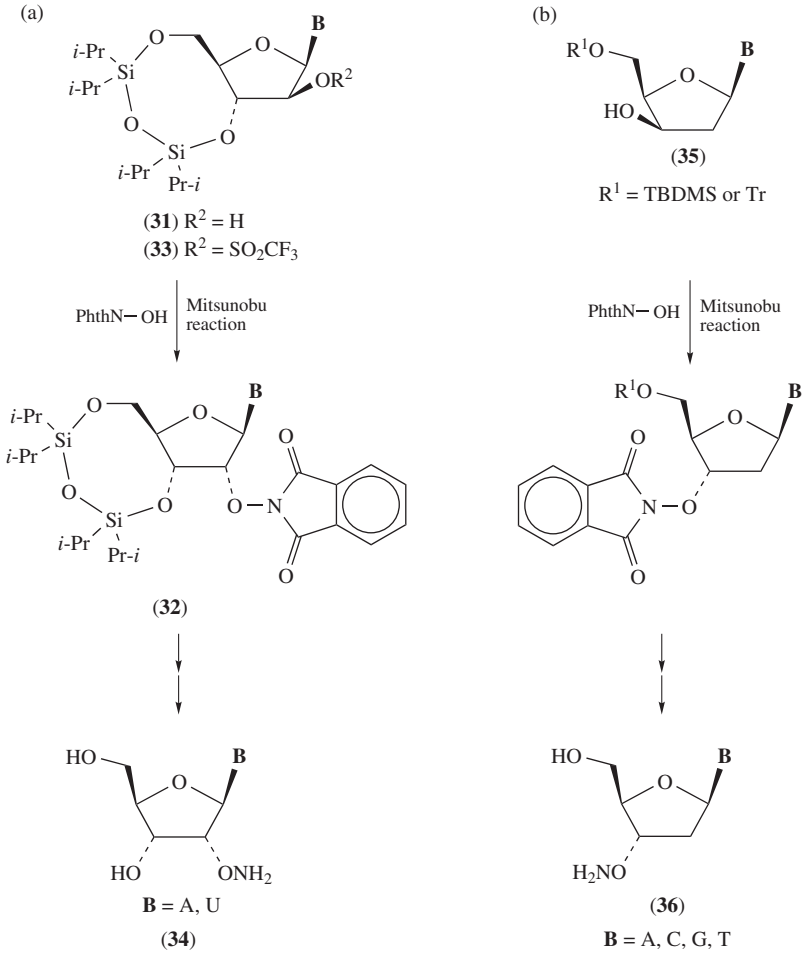
5′-Hydroxamic acid derivatives can be synthesized by the acylation of the corresponding 5′-deoxy-5′-hydroxylamino derivatives. One example of such an analogue (**30**) is shown in Figure 13, which has been prepared from 5′-hydroxylamino carbocyclic nucleoside (**25**)[36].

2. Modification at C-2′ and C-3′ positions

Mitsunobu reactions of the 2′-hydroxyl and 3′-hydroxyl groups of the nucleosides result in inversion of the configuration[39]. Thus, it is necessary to use 2′-β-hydroxyl and 3′-β-hydroxyl nucleoside precursors as starting materials for the preparation of 2′- and 3′-substituted analogues (Scheme 4). The Mitsunobu reactions of *arabino*-analogue (**31**, $R^2 = H$) with *N*-hydroxyphthalimide provide phthalimidyl compounds (**32**) but only in a low yield (Scheme 4a)[40]. This is because the Mitsunobu reaction to 2′-β-hydroxyl group is prohibited by steric repulsions between the phosphonium intermediate and the vicinal nucleobases. On the other hand, displacement reactions of 2′-arabinofuranosyl-*O*-triflates (**33**) with *N*-hydroxyphthalimide proceed nearly quantitatively to give 2′-*O*-phthalimido nucleosides **32**. Thus, 2′-*O*-amino uridine and adenosine derivatives (**34**) are prepared from **32**[40]. In contrast, 3′-*O*-amino nucleosides (**36**) can be prepared by the Mitsunobu reactions of the corresponding *xylo*-analogues (**35**) with *N*-hydroxyphthalimide, as shown in Scheme 4b[41]. Among the 2′-*O*-amino (**34**) and the 3′-*O*-amino (**36**) nucleoside analogues, 3′-*O*-amino derivatives (**36**) have been shown to have activities against human retrovirus, particularly against human immunodeficiency virus (HIV)[41].

2′-Deoxy-2′-*N*-hydroxylamino and 3′-deoxy-3′-*N*-hydroxylamino nucleoside analogues have been synthesized by intramolecular nucleophilic additions (Scheme 5) and stereoselective reductions (Scheme 6), respectively. Since nitrogen nucleophiles attack the $C_{(2)}$ position of the base moiety of 2,2′-*O*-anhydrouridine (**37**), giving isocytidine analogues[42], an alternative method was first reported by Sebesta and coworkers[42], and lately modified by Matsuda and coworkers, as shown in the synthesis of 2′-deoxy-2′-*N*-hydroxylamino pyrimidines (Scheme 5)[43, 44]. In this method, 2,2′-*O*-anhydrouridine (**37**) reacted with *N*, *N*′-carbonyldiimidazole (Im_2CO) and (2-tetrahydrofuranyl)oxyamine ($THFONH_2$), followed by an intramolecular nucleophilic addition of the 3′-carbamate. After hydrolysis of the cyclic product **38**, 2′-deoxy-2′-(*N*-hydroxylamino)uridine (**39**) or cytidine (**40**) analogues were prepared. On the other hand, 2′-deoxy-2′-*N*-hydroxylamino adenosine analogue (**41**) was synthesized from an arabinofuranosyl precursor (**42**) using the same intramolecular nucleophilic cyclization as in the syntheses of 2′-deoxy-2′-(*N*-hydroxylamino)pyrimidine derivatives.

Matsuda and coworkers have utilized the stereoselective reduction of 3′-oximes for the synthesis of 3′-deoxy-3′-*N*-hydroxylamino nucleosides (**45** and **46**, Scheme 6)[44]. The 3′-oxime nucleoside (**43**) was reduced with sodium triacetoxyborohydride, and this reaction proceeded extensively from the β-face producing 3′-deoxy-3′-α-(*N*-hydroxylamino) nucleoside (**44**). In this reduction, a 5′-hydroxyl group was required for the stereoselective reduction because a complex formation between 5′-hydroxyl group and the reductive

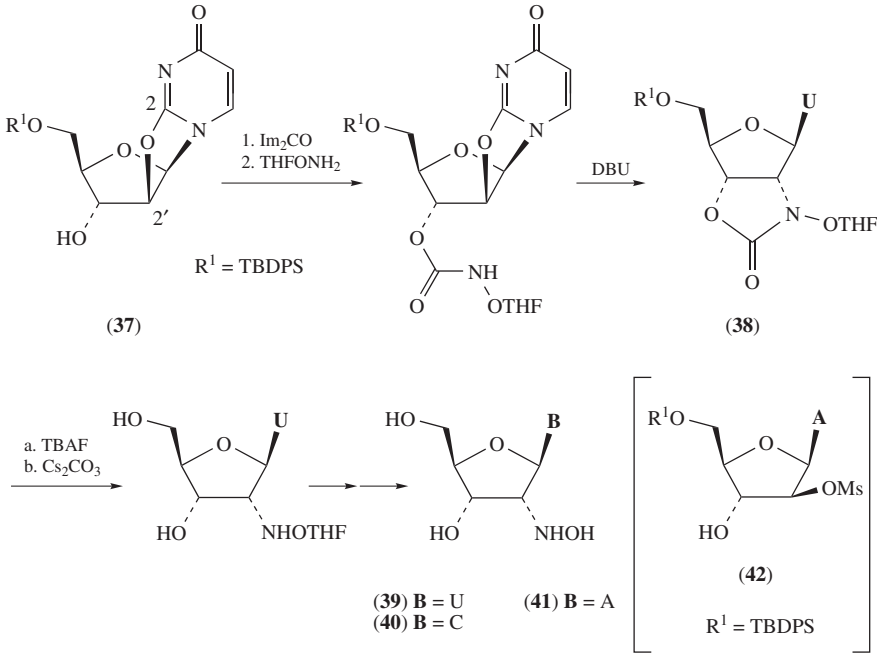


SCHEME 4

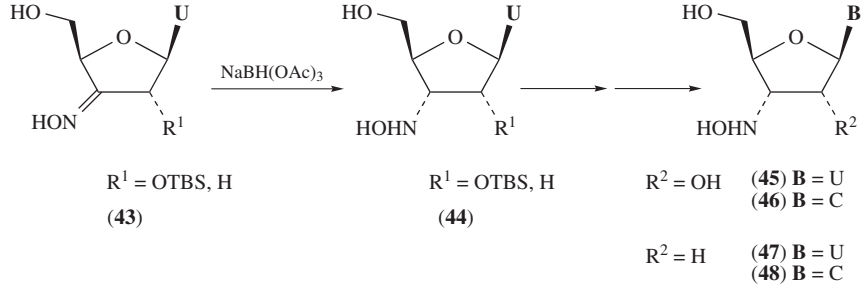
agent would be involved[45,46]. 2′,3′-Dideoxy-3′-*N*-hydroxylamino analogues (**47** and **48**) are also prepared by a similar method.

The pK_a values of the hydroxylamino moieties of **40** and **46** are determined by ^{13}C NMR to be 2.9 and 3.4, respectively[44]. These values are considerably lower than that of *N*-methylhydroxylamine (pK_a = 5.96)[47]. The authors have suggested that the low pK_a values of these hydroxylamino groups are due to the intramolecular hydrogen bonding with a vicinal hydroxyl group. Both **40** and **46** are easily decomposed in a phosphate buffer (pH 7.0), and these decompositions seem closely related to the generation of aminooxy radicals because the generation of a 2′-NHO$^{\bullet}$ radical is detected in the electron spin resonance (ESR) spectrum[43].

2′-Deoxy-2′-*N*-hydroxylaminocytidine (**40**) inhibited the growth of murine leukemia L1210 and human epidermoid KB cells with IC_{50} values of 1.58 and 1.99 μM,



SCHEME 5



SCHEME 6

respectively[44]. It was also effective against human tumor cells with IC_{50} values in the micromolar range. It is suggested that the effect of **40** is derived from the inhibition of DNA synthesis, although it has a ribonucleoside structure.

3′-Deoxy-3′-oxime (**49**) and 2′-deoxy-2′-oxime (**50**) derivatives (Figure 14a) have been prepared from the corresponding keto nucleosides[48]. The same authors also reported the synthesis of **51** (Figure 14b) to trap and inactivate the tyrosyl radical of ribonucleotide reductases that catalyze the transformation of ribonucleotides to deoxyribonucleotides[48], which showed no biological activities. Other types of 3′-oxime analogues (**52, 53**) and hydroxamic acid analogue (**54**) (Figure 14c) were prepared from 3′-*O*-amino nucleoside

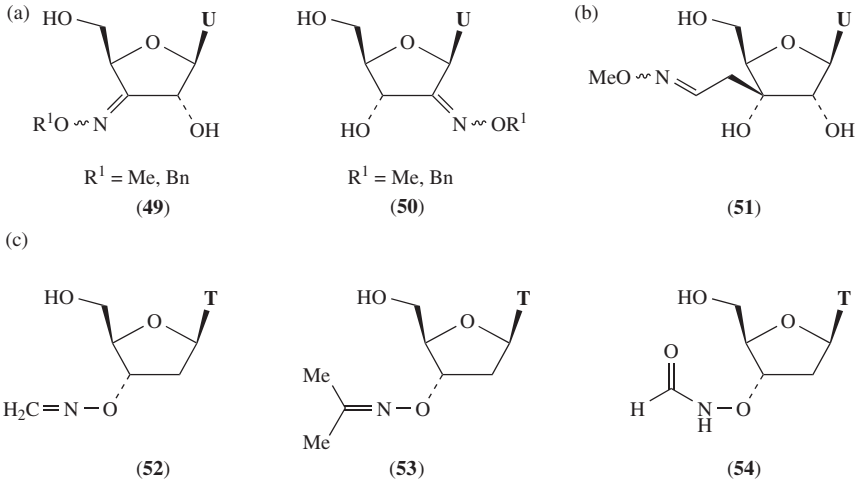


FIGURE 14

analogue (**36** in Scheme 4)[41]. These *N*-substituted 3′-*O*-amino nucleoside analogues have been shown to have anti-HIV activities, similarly to those of 3′-*O*-amino nucleoside **36**[41].

Oximes can be readily prepared by the reaction of hydroxylamines and carbonyl compounds. In addition, oximes can be easily hydrogenated to *N*-substituted hydroxylamines or to amines. As a result of these characteristics, 3′-deoxy-3′-oxime and 2′-deoxy-2′-oxime derivatives are often used as intermediates for the synthesis of modified nucleoside and nucleotide analogues. These examples can be found in Scheme 6 (in Section III) and in Scheme 18 (in Section IV).

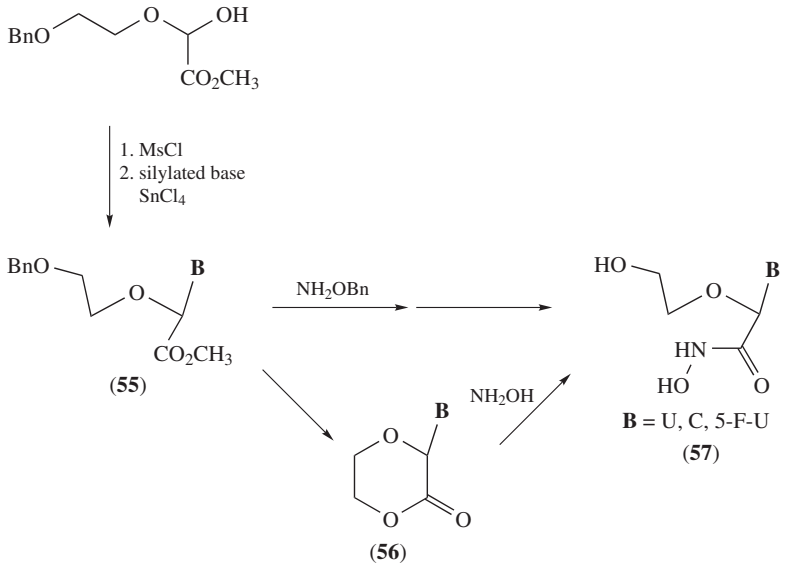
Hydroxyurea[49], a hydroxamic acid derivative[50], is an anticancer drug that is shown to inhibit ribonucleoside diphosphate reductase (RDPR), an enzyme which catalyzes the reduction of ribonucleotides to 2′-deoxyribonucleotides, by trapping the free tyrosyl radical present in the active site of the enzyme[51]. To search for more effective RDPR inhibitors as anticancer agents, 2′-hydroxamic acid nucleoside analogues have been synthesized as shown in Schemes 7 and 8, since nucleoside analogues have the structures closely resembling RDPR substrates.

Farr and coworkers reported the first nucleoside hydroxamic acid analogues (Scheme 7)[52]. The syntheses of hydroxamic acid acyclonucleosides **57**, consisting of open-chain sugar structures, include direct substitution of ester **55** with hydroxylamino derivative, or a nucleophilic ring-opening of the lactone **56**, prepared from **55**, with hydroxylamine. All compounds (**57**) were 3- to 10-fold less potent than hydroxyurea against calf thymus diphosphate reductase *in vitro*, although 5-fluorouracil derivative (**57**, B = 5-F-U) was nearly equipotent with hydroxyurea in inhibiting the growth of HeLa cells[52].

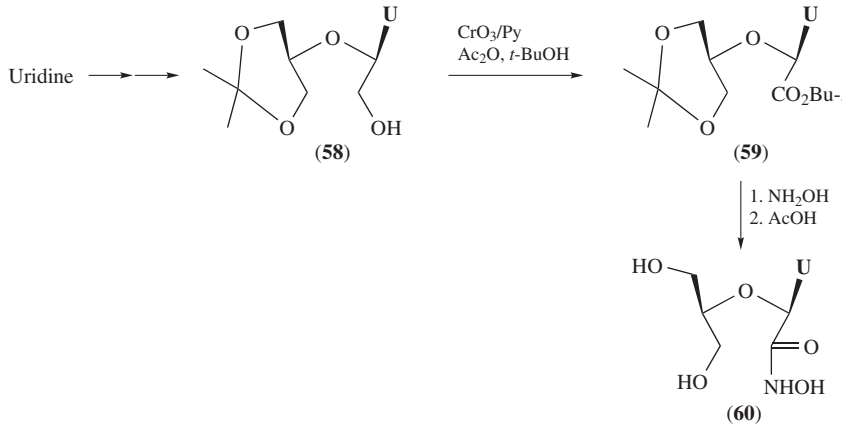
The structurally related analogue **60** (Scheme 8) was synthesized from a secouridine derivative **58**, by one-step oxidation to the corresponding ester (**59**), followed by hydroxylamine treatment[53]. Biological activity of **60** has not been reported in the literature yet.

3. Modification of ribose ring structures

Many 2′,3′-dideoxynucleosides and their analogues have been found to possess effective antiviral activities, including anti-HIV activity (Figure 15a)[54]. These nucleoside analogues



SCHEME 7



SCHEME 8

inhibit viral DNA or RNA syntheses by terminating the elongation reactions when they are phosphorylated to 5′-triphosphate derivatives by cellular kinases[55]. Isoxazolidinyl and isoxazolinyl nucleosides are analogues of 2′,3′-dideoxynucleoside, and these modifications contain hydroxylamino or oxime structures in five-membered ring systems (Figure 15b)[56]. The nitrogen atom in the ring structure can act as both a hydrogen-bonding donor and an acceptor site that mimics the 3′-hydroxyl group. We describe here these isoxazolidinyl and isoxazolinyl nucleoside analogues.

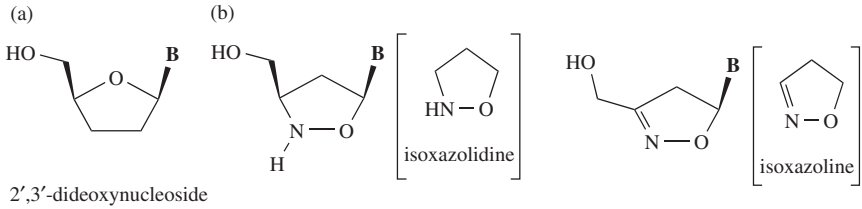
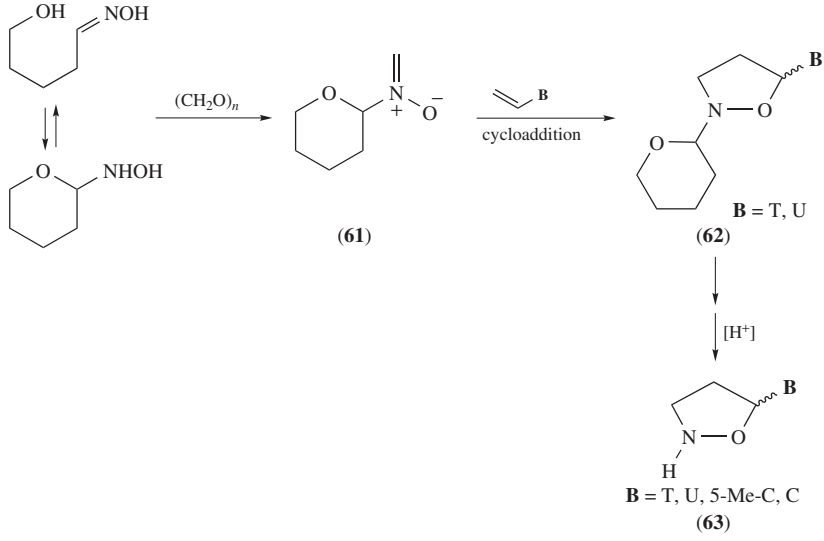


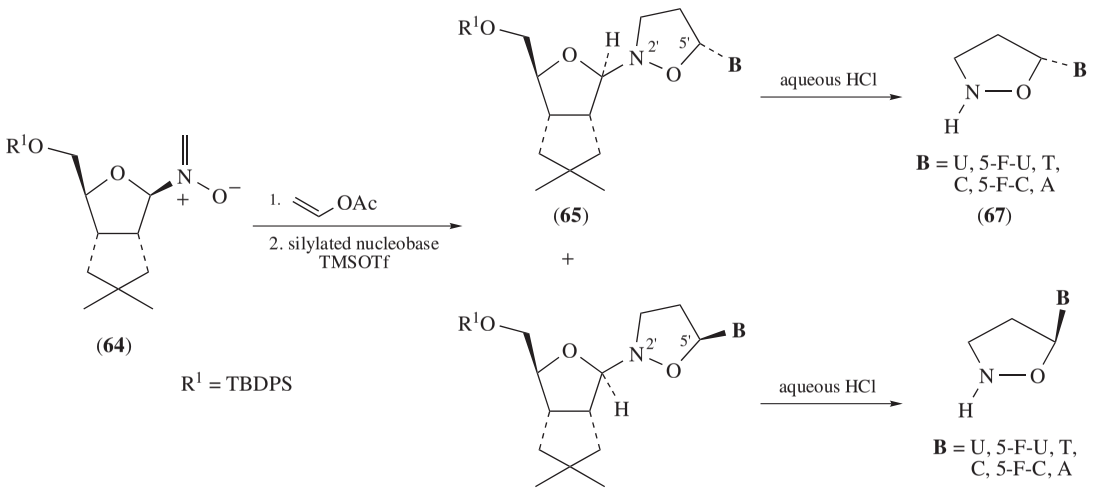
FIGURE 15

a. Isoxazolidinyl analogues. The first isoxazolidinyl nucleoside analogue, reported by Tronchet and coworkers in 1992, was synthesized using 1,3-dipolar cycloaddition reaction of nitrone[57]. After this report, many isoxazolidinyl analogues were prepared by the cycloaddition methodology[56]. Sindona and coworkers used 1,3-dipolar cycloaddition of nitrone (**61**) and vinyl nucleobases and obtained isoxazolidine **62**, as shown in Scheme 9[58,59]. The cycloaddition proceeded with good regioselectivity, such that the oxygen atom of the nitrone group is connected to the more hindered side of the substituted olefin[60]. This regioselectivity is commonly observed in other 1,3-dipolar cycloadditions[56]. Removal of the tetrahydropyranyl group provided isoxazolidinyl analogues (**63**). Although **63** were prepared as a racemic mixture, thymine analogue (B = T) showed good anti-HIV 1 activity *in vitro*, comparable to that of 3′-deoxy-3′-azido thymidine (AZT), a clinically used anti-HIV agent.

As a racemic mixture of **63** was shown to have antiviral activity, the syntheses of isoxazolidinyl nucleoside analogues were then focused on the enantioselective preparation. This was achieved by Chiacchio and coworkers by the use of chiral *N*-glycosyl nitrone (**64**) as a building block, as shown in Scheme 10[61]. Cycloaddition of **64** to vinyl



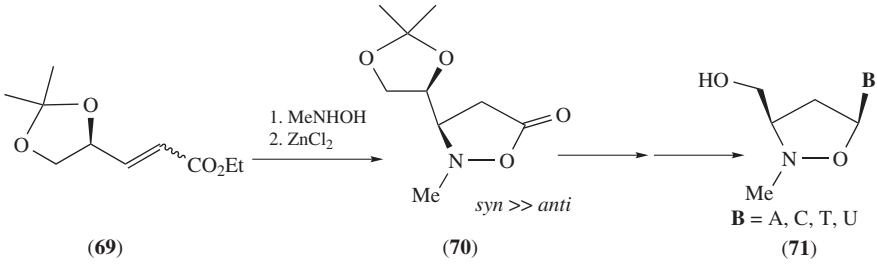
SCHEME 9


R1O
O
N
+
O−
(64)
R1 = TBDPS
1.
OAc
2. silylated nucleobase
TMSOTf
R1O
H
O
N
2'
5'
O
B
(65)
+
R1O
O
N
2'
5'
O
B
H
(66)
aqueous HCl
N
O
H
B
B = U, 5-F-U, T,
C, 5-F-C, A
(67)
aqueous HCl
B
N
O
H
B = U, 5-F-U, T,
C, 5-F-C, A
(68)

SCHEME 10

acetate followed by glycosidation affords a pair of homochiral isoxazolidines **65** and **66**, which is epimeric at $C_{(5')}$ of the isoxazolidine. Both anomers possess the same *trans* disposition of their $N_{(2')}$ and $C_{(5')}$ substituents, and diastereomeric *cis* isomers inverted at the $N_{(2')}$ position are not observed. Most importantly, these homochiral isomers could be separated by column chromatography, and cleavage of the ribose moieties provides the enantiomerically pure isoxazolidinyl nucleosides (**67** and **68**). Among the chiral isoxazolidinyl derivatives, the 5-fluorouracil analogue (**68**, B = 5-F-U) was shown to be a good inductor of apoptosis on lymphoid and monocytoid cells, while showing a low level of cytotoxicity[62].

Another enantioselective approach for the isoxazolidinyl nucleoside analogues has been reported by Zhao and coworkers using the Michael addition reactions[63]. They prepared chiral isoxazolidinyl analogues (**71**) from *N*-methylhydroxylamine and chiral α,β-unsaturated ester **69** (Scheme 11)[64, 65]. Cyclization of the adduct predominantly gives the *syn* product (**70**). This stereoselective Michael addition is induced by the intermolecular hydrogen-bond formation between the *N*-methylhydroxylamine and the dioxolane moiety. The lactone **70** is converted into chiral isoxazolidinyl pyrimidine and purine analogues (**71**).

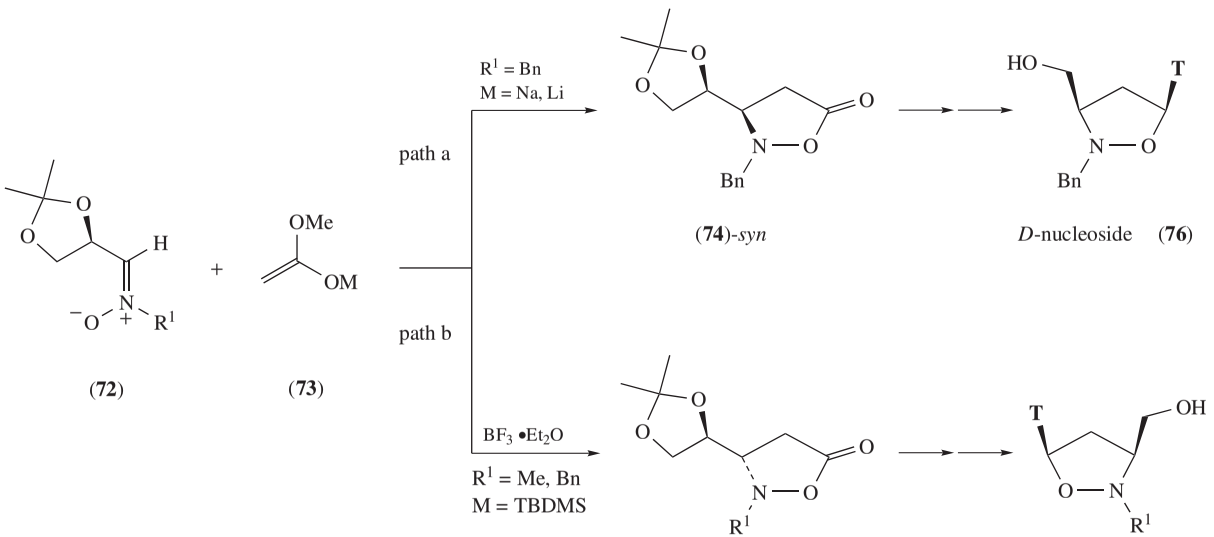


(**69**) (**70**) (**71**)

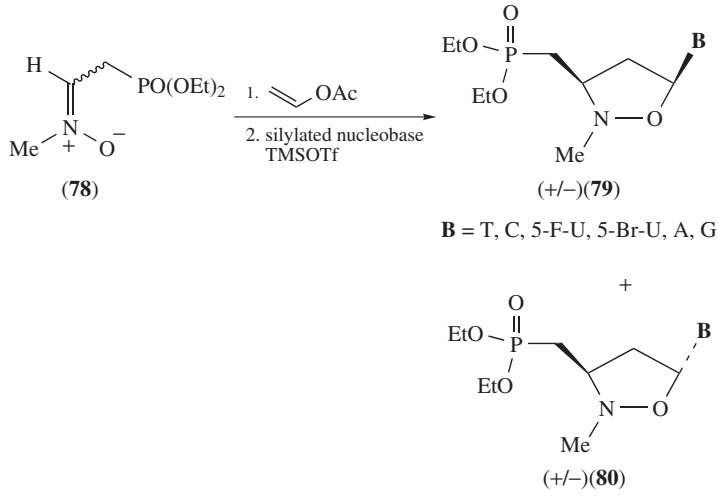
SCHEME 11

Subsequently, Merino and coworkers reported another stereoselective approach (Scheme 12)[66], which showed that the addition of sodium or lithium enolate **73** (M = Na, Li) to *N*-alkyl nitrones **72** afforded isoxazolidin-5-one (**74**) with a high degree of *syn*-selectivity. This stereoselective addition is induced by the stereodirecting effect of the dioxolane group (path a). On the other hand, addition of 2 equivalents of Lewis Acid (BF_3•Et_2O) to the reaction of *O*-methyl-*O*-silyl ketene acetal **73** (M = TBDMS) with **72** proceeded exclusively with *anti*-selectivity to afford another cyclized product (**75**) in high yields (path b)[67]. As a result, the stereocontrolled syntheses of both *D*- and *L*-isomer of isoxazolidinyl nucleosides **76** and **77**, respectively, have been achieved from the same nitrone (**72**).

Recently, these synthetic approaches for isoxazolidinyl analogues were applied for the preparation of phosphonated nucleoside analogues, as phosphonated nucleosides could potentially be effective antiviral agents. The phosphonated analogues mimic nucleoside monophosphates but the phosphate moiety has been changed to isosteric and isoelectronic phosphonate group, which are also enzymatically and chemically stable. At the same time, phosphonated nucleosides are expected to bypass the initial enzymatic phosphorylation step, which is necessary for expressing biological activities in cells. Chiacchio and coworkers have reported a series of phosphonated isoxazolidinyl nucleosides, and investigated their antiviral activities (Scheme 13)[68, 69]. The synthesis of these analogues relies on the 1,3-dipolar cycloaddition methodology. The reaction of the nitrone **78** with vinyl acetate followed by glycosidation provides α- and β-anomers of isoxazolidine (**79** and **80**).


R1 = Bn
M = Na, Li
path a
path b
BF3 •Et2O
R1 = Me, Bn
M = TBDMS
(72)
(73)
(74)-syn
(75)-anti
D-nucleoside (76)
L-nucleoside (77)
R1 = Me, Bn

SCHEME 12



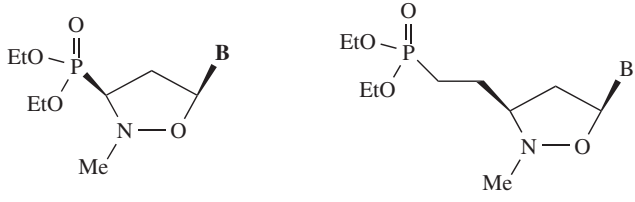
(**78**)

(+/–)(**79**)

B = T, C, 5-F-U, 5-Br-U, A, G

(+/–)(**80**)

SCHEME 13



(+/–)(**81**)

B = T, 5-F-U

(+/–)(**82**)

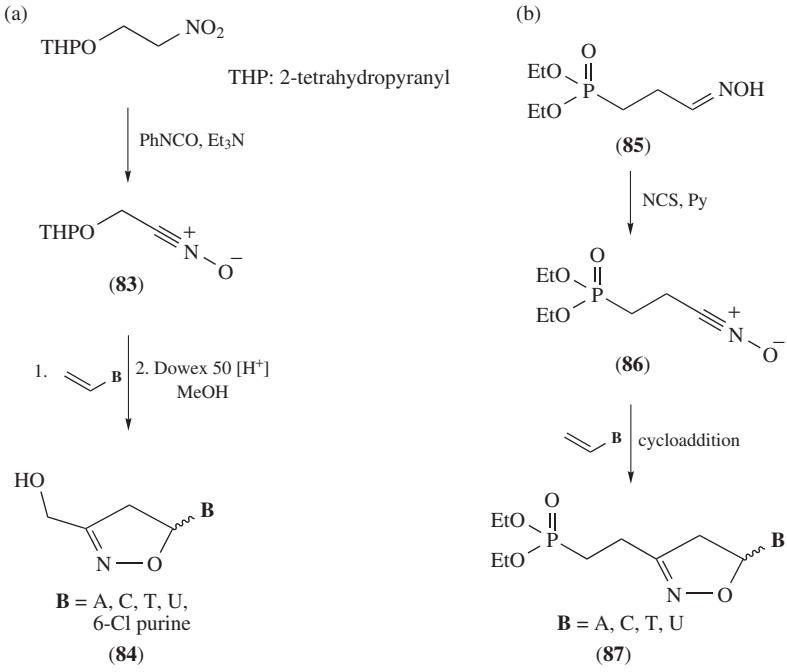
B = T, C, 5-F-U

FIGURE 16

Truncated isoxazolidinyl nucleosides (**81**)[70] and the extended analogues (**82**)[71] have been similarly synthesized from their corresponding phosphonated nitrones (Figure 16).

Pyrimidine derivatives of **79** inhibited reverse transcriptases of different retroviruses, including human retrovirus T-cell leukemia/lymphotropic virus type-1, with an activity comparable to or higher than that of AZT[68, 69]. Truncated **81** also inhibited the reverse transcriptase activities of Avian Moloney Virus (AMV) and HIV[70]. It is proposed that **79** and **81** are converted to phosphonic acid diphosphates, a triphosphate analogue, by cellular kinases and acted as chain terminators. Properly orientated nucleobases and phosphonate groups accommodated **79** and **81** to these enzymatic activations. In contrast, α-anomers (**80**) and extended derivatives (**82**) were completely inactive[71].

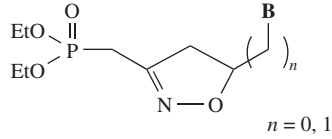
1,3-Dipolar cycloaddition of nitrone was also applied to the synthesis of isoxazolidinyl analogue of Tiazofurin[72], a potent anticancer nucleoside agent, and bicyclic isoxazolidinyl nucleoside analogues[73]. In addition, isoxazolidinyl intermediate prepared by 1,3-dipolar cycloaddition of nitrone was used for the preparation of 2′,3′-dideoxynucleoside analogues[74].



SCHEME 14

b. Isoxazolinyl analogues. Zhao and coworkers have applied 1,3-dipolar cycloaddition for the syntheses of isoxazolinyl nucleosides (Scheme 14a)[75]. Regioselective cycloaddition of nitrile oxide **83** with vinyl nucleobases, after removal of the 2-tetrahydropyranyl (THP) group, provides isoxazolinyl analogues (**84**). A similar method has also been applied to the synthesis of phosphonated analogues **87** (Scheme 14b)[76]. Here, nitrile oxide **86** is prepared by the oxidation of oxime **85**, and is coupled with vinyl nucleobases. Purine analogues of **84** exhibited moderate anti-HIV activity *in vitro*, thus representing the first example of potential antiviral nucleoside analogues derived from isoxazolinyl structure[75].

Romeo and coworkers have reported the synthesis of another type of phosphonated analogue **88** (Figure 17)[77]. They used a similar 1,3-dipolar cycloaddition approach to that reported by Zhao and coworkers shown in Scheme 14[76]. In contrast to the phosphonated



B = T, C, 5-fluorouracil
(**88**)

FIGURE 17

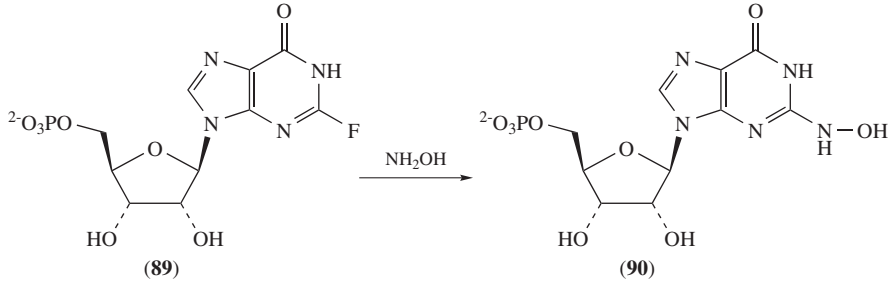
isoxazolidinyl nucleosides **79** in Scheme 13, the isoxazolinyl analogues (**88**) with the rigid *N*,*O*-heterocycle moiety were found to be weak inhibitor of viral reverse transcriptases.

B. Base-modified Nucleosides

Compared to sugar modifications, there are only a limited number of examples of a nucleoside in which the base moieties have been modified with hydroxylamine, oxime and hydroxamic acid groups.

As described in Section II, the potential mutagenic pyrimidine analogues N^4-hydroxycytidine and N^4-methoxycytidine (**4**, $R^2 = H$, Me), and purine analogues N^6-hydroxyadenosine and N^6-methoxyadenosine (**11**, $R^2 = H$, Me) are formed by the reaction of hydroxylamine or *O*-methylhydroxylamine with cytidine and adenosine, respectively. In the search for their mutagenic actions, such as hybridization selectivity or recognition by DNA/RNA polymerases, chemical syntheses of the corresponding nucleosides, nucleotides and their behaviors when incorporated into oligonucleotides have been extensively studied[27, 78–81].

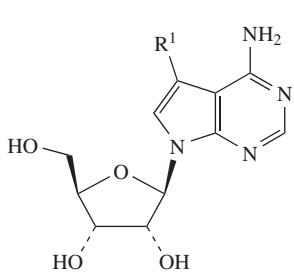
Another example of a nucleoside modified at the base moiety with hydroxylamino group is shown in Scheme 15. As hydroxylamine is known to inhibit guanosine monophosphate synthetase (GMPS; an enzyme that converts xanthosine 5′-monophosphate to guanosine 5′-monophosphate) activity, N^2-hydroxyguanosine 5′-monophosphate (**90**) was designed on the hypothesis that hydroxylamine would react with guanosine 5′-monophosphate at the active site of the enzyme and inhibit the activity[82]. Synthesis of **90** is achieved by direct hydroxylamine displacement of fluorine in 2-fluoroinosine 5′-monophosphate (**89**). Time-dependent inhibition of the *E. coli* GMPS was found for **90**.



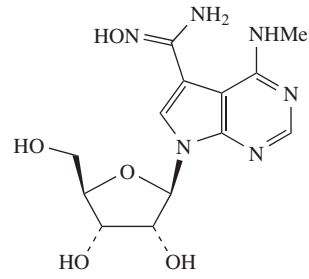
(**89**) (**90**)

SCHEME 15

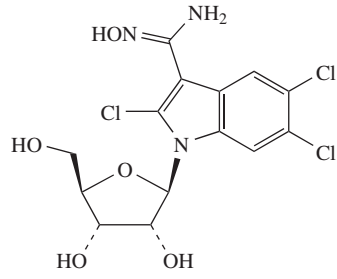
Both Toyocamycin and Sangivamycin (Figure 18) are naturally occurring nucleoside analogues and they are known to possess antiviral and antitumor activities[83]. Accordingly, a series of Toyocamycin and Sangivamycin analogues have been synthesized and their antiviral activity was investigated. The purine nucleoside possessing carboxamide oxime functionality (**91**, Figure 18) was reported to have good antiviral activity and selectivity against Hepatitis C virus (HCV) with an EC_{50} value of 0.6 μM and CC_{50} of 200 μM[83]. The carboxamide oxime functionality was synthesized from the corresponding cyano precursor and hydroxylamine. Also, the nucleoside mimic possessing the same functionality (**92**, Figure 18) was reported by Townsend and coworkers[84]. Carboxamide oxime **92**



Toyocamycin: $R^1 = CN$
Sangivamycin: $R^1 = CONH_2$



(**91**)



(**92**)

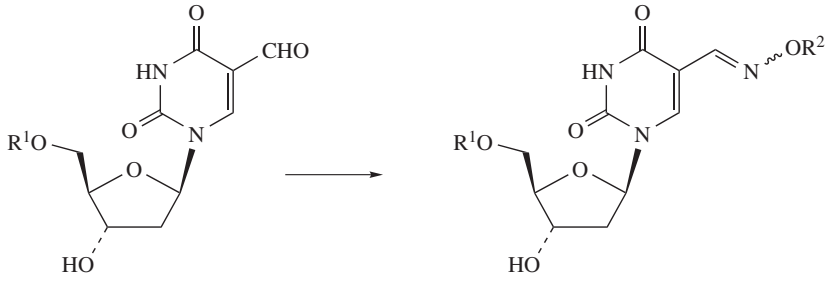
FIGURE 18

showed antiviral activity against human cytomegalovirus (HCMV) with feeble cytotoxicity ($IC_{50} = 0.30\,\mu M$, $CC_{50} > 100\,\mu M$). These analogues are supposed to inhibit viral RNA-dependent RNA polymerase (RdRp), a centerpiece enzyme for viral replication.

Pyrimidine derivatives described in the following sections are modified at the 5-position of nucleobases. This is because pyrimidine analogues substituted at this position can be phosphorylated by cellular enzymes to the corresponding 5′-mono-, di- and triphosphates. The triphosphate analogues can then be incorporated into DNA by viral reverse transcriptase[85]. These are the key steps for analogues in expressing biological activity.

The oxime derivatives **95** to **97** have been prepared as an analogue to antiviral agent 5-formyl-2′-deoxyuridine **93** (Figure 19)[86]. Oxime **95** was shown to have anti-HSV-1 activity equal to that of **93**, but was less active against HSV-2 or vaccinia virus. The study using monophosphates **94** and **96** has revealed that these analogues inhibit thymidylate synthetase, the enzyme that catalyzes the reductive methylation of 2′-deoxyuridine 5′-phosphate (dUMP) to 2′-deoxythymidine 5′-phosphate (dTMP)[87]. The other oxime analogue (**97**) was less active than **93** and **95** as an antiviral agent[88].

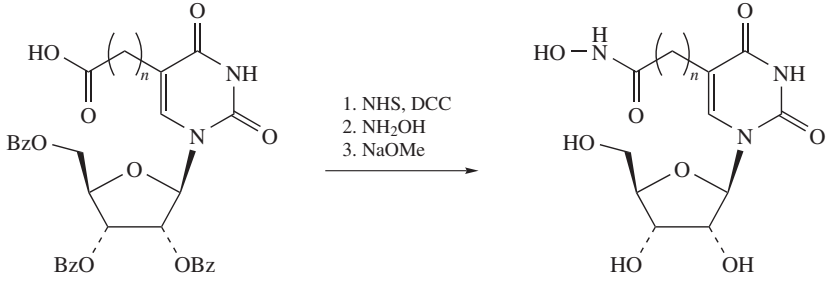
The following three nucleoside analogues have been designed as ribonucleoside diphosphate reductase (RDPR) inhibitors. As hydroxamic acid and its derivatives are known to trap free radical species, it is anticipated that hydroxamic acid group placed at the β-face of a ribose unit could trap nearby tyrosyl radical, which is essential for RDPR activity[51]. The first examples shown in Scheme 16 have hydroxamic acid connected to the 5-position of



(**93**) R^1 = H
(**94**) R^1 = PO_3H_2

(**95**) R^1 = H, R^2 = H
(**96**) R^1 = PO_3H_2, R^2 = H
(**97**) R^1 = H, R^2 = Me, Bn, allyl

FIGURE 19



n = 0, 1 (**98**)

n = 0, 1 (**99**)

SCHEME 16

pyrimidine (**99**)[89]. The hydroxamic acid groups were synthesized from the corresponding carboxylic acid nucleosides (**98**) by a condensation reaction with hydroxylamine.

The preparation of nucleoside hydroxamic acid (**102**) utilized a solid-phase method (Figure 20)[90]. Alkyne hydroxamic acid attached to polystyrene resin (**100**) was cross-coupled with 5-iodopyrimidine (**101**), and subsequent cleavage from the resin provided a hydroxamic acid analogue (**102**). This solid-phase method, developed by Khan and Grinstaff, is also applicable in developing other types of nucleoside hydroxamic acids[90].

Kim and Ryu have reported a series of 5-aroylpyrimidine nucleoside oximes (**105**) (Scheme 17)[91]. These uridine analogues are prepared by the reaction of the corresponding nucleosides (**103**) with stable nitrile oxides generated from hydroximoyl chlorides and triethylamine. Investigation of the reaction mechanism has revealed that 1,3-addition products (**105**) are formed from the ring-opening reactions of initially formed 1,3-dipolar cycloaddition products (**104**). There have been no studies of biological activities reported yet for the nucleosides **99, 102** and **105**.

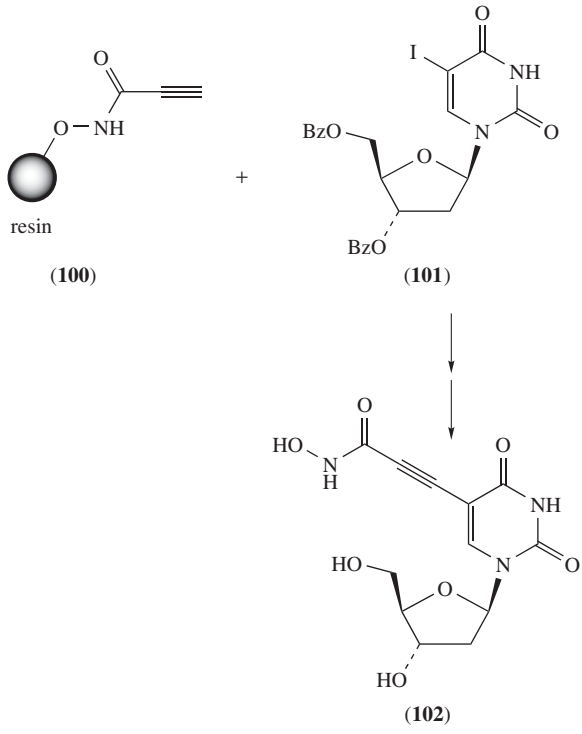


FIGURE 20

IV. MODIFICATIONS OF OLIGONUCLEOTIDES

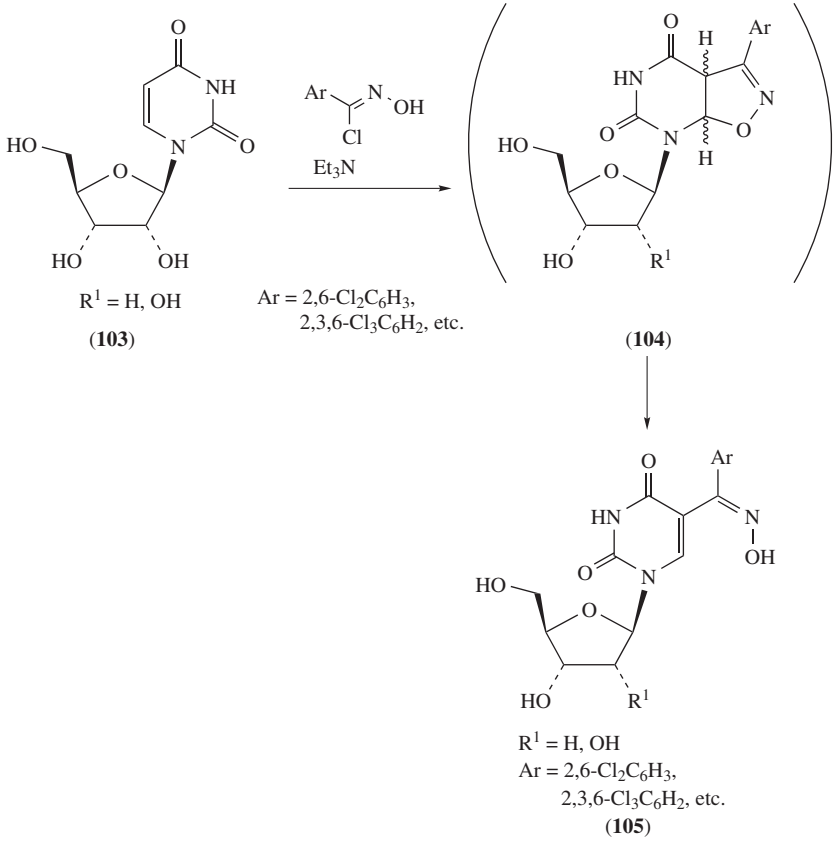
A. Backbones

Hydroxylamine, oxime and hydroxamic acid groups have been applied to the backbone linkages of oligonucleotides (Figure 21)[92]. Since these hydroxylamino derivatives offer neutral and achiral linkages, electrostatic repulsion observed in phosphodiester linkages is eliminated resulting in the formation of stable duplexes[93]. Oligonucleotides with these neutral linkages have advantages in membrane permeability[94], chemical stability and nuclease resistance[93]. As a result, oligonucleotides constructed with hydroxylamino derivatives are thought to be an attractive modification for antisense[95–97] and antigene molecules[98].

In this section, we describe the syntheses and properties of oligonucleotides having backbones modified with methylene(methylimino), *N*-hydroxycarbamate and other related structures.

1. Methylene(methylimino) linkage

Oligonucleotides linked with methylene(methylimino) (MMI) group have been developed by Sanghvi and coworkers as non-ionic, neutral linkages (Figure 21)[99, 100].

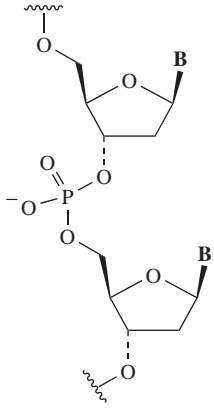


SCHEME 17

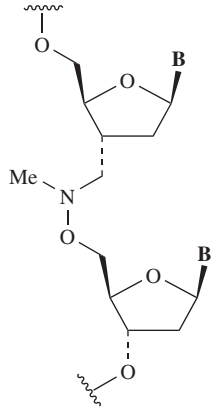
A methylene group of MMI replaces the 3′-oxygen atom and an *N*-methylhydroxylamine replaces the phosphodiester group.

A dimer of the MMI linkage is synthesized from the coupling of 3′-deoxy-3′-*C*-formyl nucleoside (**106**) with a 5′-*O*-amino nucleoside (**107**)[34], as shown in Scheme 18[99–101]. The oxime-linked dinucleoside **108** is subjected to reduction and alkylation, providing the dimer nucleoside **109** with the MMI linkage. This strategy is also used for the synthesis of MMI-linked oligonucleotides on solid-support[102].

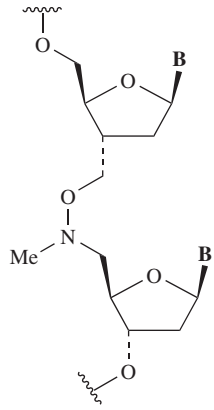
Another synthetic approach involves free radical coupling of 3′-iodo nucleoside (**111**) and 5′-formaldoxime nucleoside (**112**), mediated by bis(trimethylstannyl)benzopinacolate (**113**) (Scheme 19)[103]. In this reaction, thermal decomposition of **113** provides a trimethylstannyl radical, which reacts with a nucleoside 3′-iodide to give a $C_{(3')}$ radical. The $C_{(3')}$ radical is then trapped by a 5′-oxime nucleoside from the α-face to provide a methylene imino-linked dimer (**114**). The reaction proceeds in a chemo-, regio- and stereoselective manner, and the resultant methylene imino linkage can be readily converted into an MMI linkage (**109**) by reductive methylation.



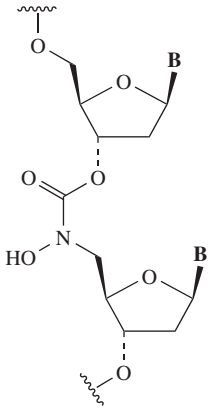
phosphodiester linkage



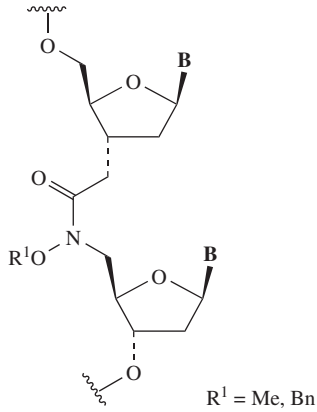
methylene(methylimino)
(MMI) linkage



methyleneoxy(methylimino)
(MOMI) linkage



N-hydroxycarbamate linkage

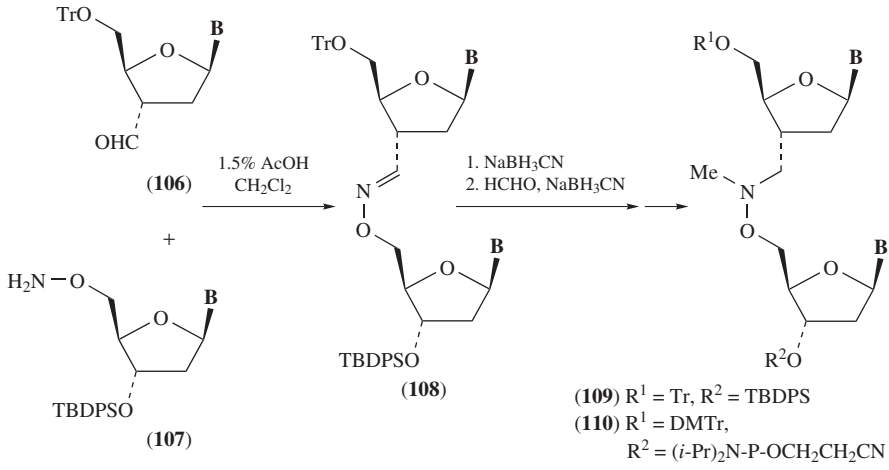


hydroxamate linkage

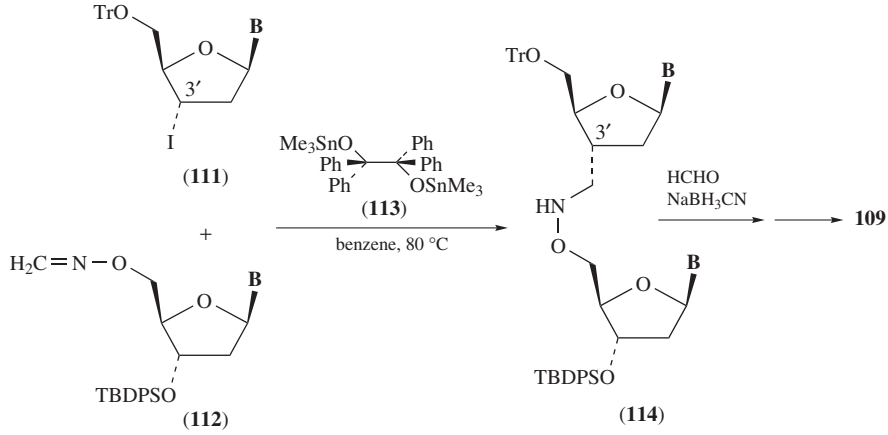
FIGURE 21

The radical coupling method is also applied for the synthesis of MMI dimer having a 2′-*O*-methyl group[104]. In this case, a pinacolate coupling reaction of the corresponding 2′-*O*-methyl nucleosides proceeds with good efficiency but with lower stereoselectivity than that of 2′-deoxy nucleosides, and gives 5%–25% contamination of *xylo* configuration at the $C_{(3')}$ position of the dimer.

The dimeric MMI unit **109** is then converted into a phosphoramidite unit **110** and the chimeric oligonucleotides containing both MMI and phosphodiester linkages are chemically synthesized on a DNA/RNA synthesizer[99, 100]. The chimeric oligonucleotides were found to hybridize to complementary RNA with better affinity and specificity compared to unmodified oligonucleotides. Furthermore, MMI linkages were not cleaved by *exo*- or *endo*-nucleases[102].



SCHEME 18

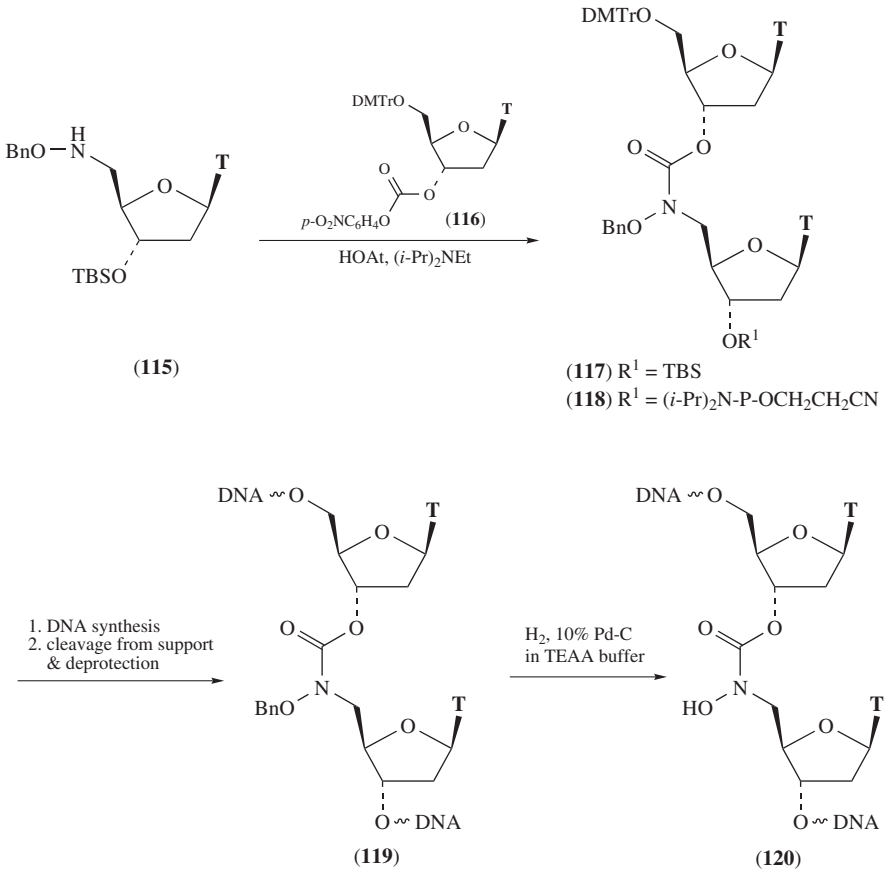


SCHEME 19

Sanghvi and coworkers also reported the synthesis of methyleneoxy(methylimino) (MOMI) linkage as a positional isomer of the MMI linkage (Figure 21)[105]. However, oligonucleotides containing MOMI linkages showed lower affinity for duplex formation with complementary RNA compared to unmodified or MMI-modified oligonucleotides.

2. N-Hydroxycarbamate linkage

Miller and coworkers have developed *N*-hydroxycarbamate (3′-O-CO-NOH-5′) linkage as a backbone modification (Figure 21)[106, 107]. Their synthesis of the nucleoside dimer



SCHEME 20

is shown in Scheme 20. The *N*-hydroxylamino derivative **115**[35] is coupled with nucleoside 3′-*O*-(*p*-nitrophenyl)carbonate (**116**) in the presence of 1-hydroxy-7-azabenzotriazole (HOAt) to afford an *O*-benzylated nucleoside dimer **117**. The dimer (**117**) is then converted into a phosphoramidite unit **118** and chimeric oligonucleotides, containing both *O*-benzyl-*N*-hydroxycarbamate and phosphodiester linkages, are synthesized on a synthesizer. After deprotection and removal of the oligonucleotides from the solid-support by ammonia treatment, the remaining benzyl groups on the oligonucleotides (**119**) are removed by hydrogenolysis in TEAA (triethylammonium acetate) buffer to afford chimeric oligonucleotides containing *N*-hydroxycarbamate linkages (**120**)[106].

Chimeric oligonucleotide **120** showed a slightly lower thermal stability in hybridization with complementary DNA compared with the unmodified oligonucleotide, while the nuclease resistances of **120** increased with increase in the number of *N*-hydroxycarbamate linkages[107].

Interestingly, *N*-hydroxycarbamate modification is shown to selectively cleave complementary DNA strand sequences under Fenton chemistry conditions[106]. Since hydroxamic

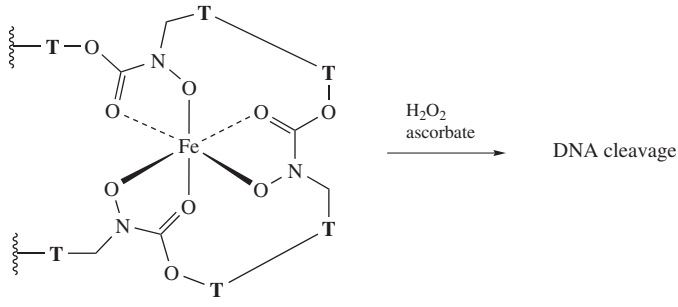
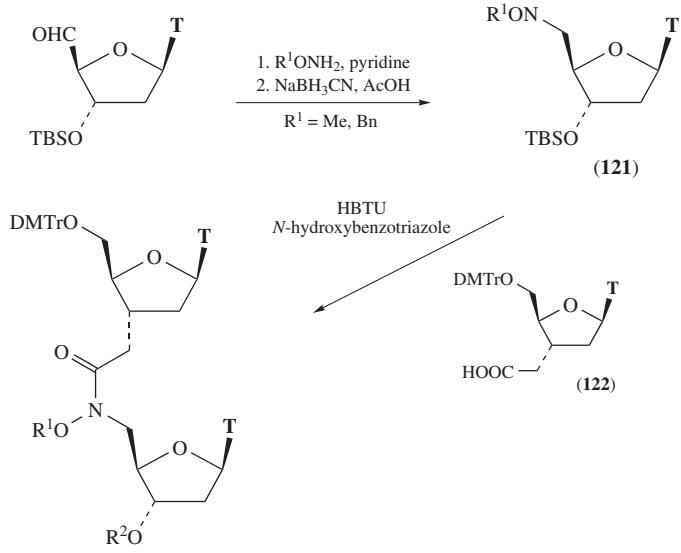


FIGURE 22

acids are known to chelate ferric ions[5], the authors suggested that this site-selective cleavage occurred through the generation of hydroxyl radicals by a hexadentate octahedral iron complex formed with three *N*-hydroxycarbamate linkages in the sequence (Figure 22).

Hydroxamate linkage (Figure 21), a similar linkage to the *N*-hydroxycarbamate, has been reported by Ramasamy and coworkers[108]. This hydroxamate linkage has a methylene group replacing the 3′-oxygen atom. The researchers have prepared dimer nucleoside units (**123**) by coupling of a carboxylic acid derivative (**122**) and 5′-deoxy-5′-*N*-hydroxylamino nucleosides (**121**), as shown in Scheme 21. Phosphoramidite units (**124**), converted from



R^1 = Me, Bn

(**123**) R^2 = TBS
(**124**) R^2 = $(i\text{-Pr})_2$N-P-OCH_2CH_2CN

SCHEME 21

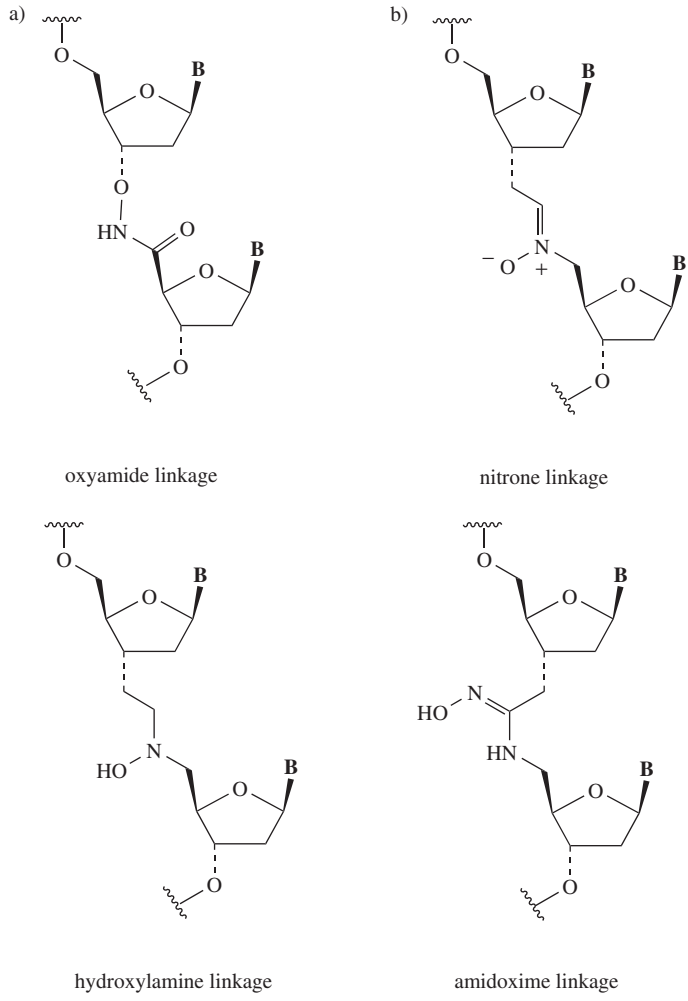
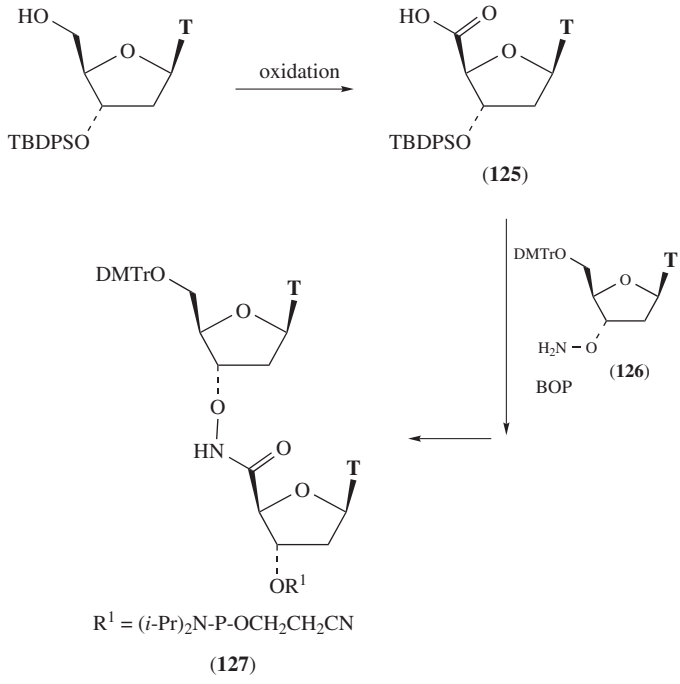


FIGURE 23

123, are then incorporated into oligonucleotides, which showed similar hybridization properties and enhanced resistance to *exo*-nucleases compared to unmodified oligonucleotides.

3. Other modifications

Oligonucleotides modified with a 3′,5′-oxyamide linkage have been reported by Burgess and coworkers (Figure 23a)[109]. The 3′,5′-oxyamide-linked dimer unit (**127**) is prepared from a 5′-carboxy acid monomer (**125**), which is condensed with a 3′-*O*-amino nucleoside (**126**)[41] in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent (Scheme 22). The oligonucleotide containing a single



SCHEME 22

oxyamide linkage is shown to hybridize to complementary DNA with nearly the same affinity as the natural oligonucleotide, although the 3′,5′-oxyamide linkage in the backbone has one atom less than the natural phosphodiester linkage.

Gallos and Dellios have reported the syntheses of oxime-based backbone modifications (Figure 23b)[110]. These nitrone, hydroxylamine and amidoxime linkages are synthesized by oxime bond formation, reductive alkylation, and by the reaction of chloroxime and amino derivative, respectively. In all these modifications, existing 3′-methylene substituents favor the $C_{(3')}$-*endo* conformation, which is beneficial for an RNA binding. However, the properties of oligonucleotides have not yet been reported.

B. Sugar Moiety

Other promising modifications in antisense technology are the introduction of bridge structures to lock the sugar conformation of nucleotides, and the representative is $O_{(2')}$,$C_{(4')}$-methylene-bridged nucleic acid (2′,4′-BNA, Figure 24), reported by Imanishi and coworkers[111, 112]. The same compound was also reported by Wengel and coworkers as locked nucleic acid (LNA)[113]. 2′,4′-BNA is particularly useful because of its unprecedented hybridizing affinity and sequence-selectivity for the target RNA. In 2′,4′-BNA, sugar puckering of the nucleotide is locked in *N*-conformation, which is beneficial for RNA binding. The 2′,4′-BNA also has higher nuclease resistances compared with natural oligonucleotides; however, this is not sufficient[112]. To improve the nuclease resistance of the 2′,4′-BNA, Imanishi and coworkers have developed another type of bridged nucleic

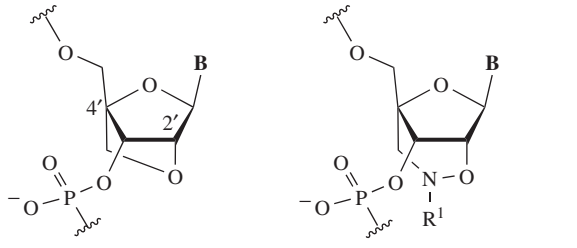
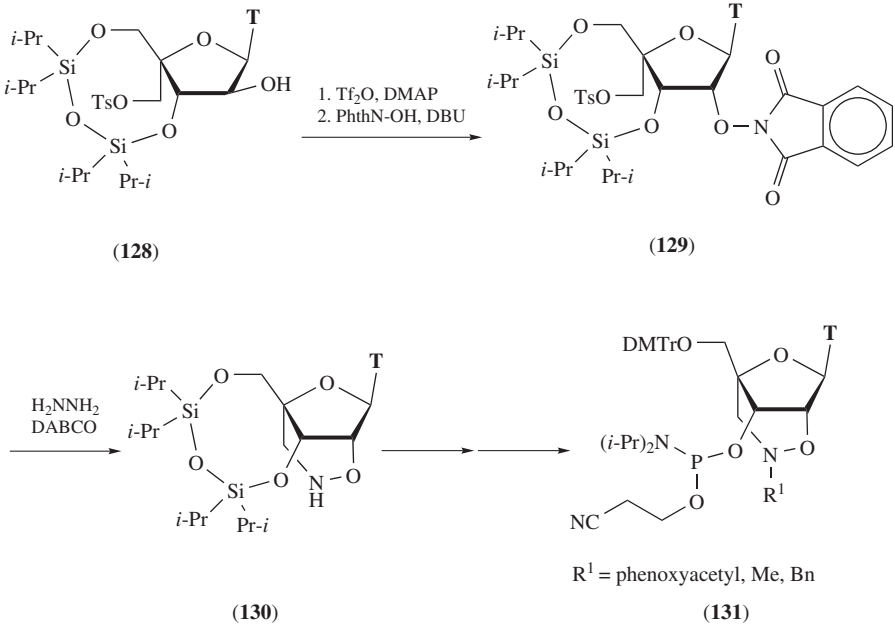


FIGURE 24

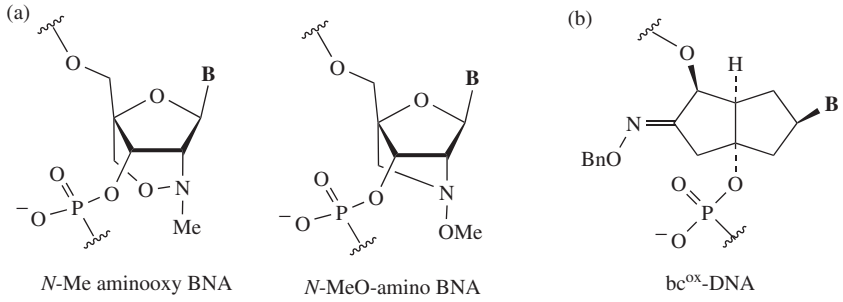
acid called 2′,4′-BNA^{NC} [114–116]. In this modification, $C_{(2')}$-hydroxyl and the $C_{(4')}$-position of the furanose ring are bridged with an aminomethylene group, forming a six-membered bridged structure with an N−O linkage (Figure 24).

Monomer phosphoramidite units (**131**) for oligonucleotide synthesis are prepared, as shown in Scheme 23[116]. The key step is the construction of a bridged structure containing a hydroxylamino group. This is accomplished by hydrazine treatment of the intermediate **129**, prepared by S_N2 reaction of **128**[40], in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). This reaction proceeds with simultaneous deprotection and intramolecular cyclization to afford a bridged compound **130**, which is subsequently converted into **131**.



(**128**) (**129**) (**130**) (**131**)

SCHEME 23



N-Me aminooxy BNA *N*-MeO-amino BNA bc^{ox}-DNA

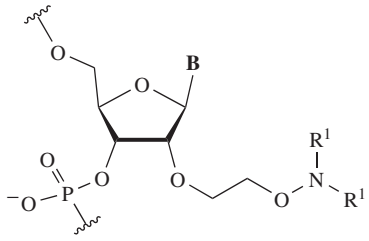
FIGURE 25

Compared to 2′,4′-BNA, oligonucleotides containing 2′,4′-BNA^{NC} showed equal or higher binding affinity against RNA complements with excellent single-mismatch discriminating ability[116]. Also, stabilization is more selective to RNA complements than to DNA. In addition, insertion of 2′,4′-BNA^{NC} remarkably increased nuclease resistances of oligonucleotides, compared to 2′,4′-BNA[114]. The authors have suggested and shown by the structural analyses that these superior profiles of 2′,4′-BNA^{NC} are because of the six-membered bridged structure instead of the five-membered bridged unit of 2′,4′-BNA. Moreover, the nitrogen atom on the bridge can be alkylated without hampering hybridization affinity, allowing the introduction of a wide range of functional molecules[116].

Most recently, *N*-Me aminooxy BNA and *N*-MeO-amino BNA have been reported by Prakash and coworkers as analogous modifications to 2′,4′-BNA^{NC}, which are shown in Figure 25a[117]. Oligonucleotides containing these bridged nucleotides have high hybridization affinities for target RNA and increased nuclease resistances, which are equal to that of 2′,4′-BNA^{NC}. These two modifications, as well as 2′,4′-BNA^{NC}, are applied to *in vivo* assays and are proven to be effective antisense molecules[117].

Luisier and Leumann have reported another type of bridged nucleic acid that contains an oxime group (bc^{OX}-DNA, Figure 25b)[118]. In their bicyclonucleotide monomer, lipophilic benzyl group is connected via an oxime linkage to the second ring of the sugar moiety. When incorporated into an oligonucleotide, the analogue destabilizes the duplex with DNA complement, while it is shown to stabilize the duplex with RNA complement. In addition, because of the presence of lipophilic benzyl group, the rate of transfection into Hela cell is significantly increased relative to natural DNA when a modified oligonucleotide forms a complex with a transfecting reagent, lipofectamine[118].

Oligonucleotides modified at the 2′-*O* position with *N*-substituted hydroxylamino groups are also other promising candidates for antisense technology. Both 2′-*O*-{2-(*N*, *N*-dimethylaminooxy)ethyl} (2′-*O*-DMAOE)- and 2′-*O*-{2-(*N*, *N*-diethylaminooxy)ethyl} (2′-*O*-DEAOE)-modified oligonucleotides, reported by Manoharan and coworkers, are representatives of this series (Figure 26)[119]. Oligonucleotides partially modified with these monomers showed duplex stabilization of 1.0 to 1.5°C per modification toward RNA complements compared with the natural oligonucleotide. In contrast, hybridization with complementary DNA led to a duplex that is less stable than those formed with an unmodified oligonucleotide; hence, the stabilization effects of these modifications are RNA-selective. Both modifications also possess higher nuclease resistances and favorable lipophilicity, which can affect cellular permeation capabilities of oligonucleotides.



2′-*O*-DMAOE (R^1 = Me)
2′-*O*-DEAOE (R^1 = Et)

FIGURE 26

V. APPLICATION OF HYDROXYLAMINO COMPOUNDS

DNA is frequently damaged by exogenous and endogenous factors, and quantification of DNA lesions is absolutely required for studying causal relationships between genetic mutations and environmental factors. There are some DNA lesions containing an aldehyde group, and they can be quantified by reaction with aminooxy compounds when the aminooxy groups are conjugated with reporter groups such as a biotin or fluorophores[120]. In this section, we describe these aminooxy probes applied for the detection and quantification of DNA lesions.

A. Detection of Abasic Sites with Aminooxy Probes

Abasic sites (AP site) are most common DNA lesions that contain aldehyde group (Figure 27)[121]. It arises from spontaneous hydrolysis of the *N*-glycosidic bond, or generated by exposure to various chemical carcinogens, radiation and oxidative stresses. AP sites are also produced as an intermediate stage of enzymatic base excision repair of damaged DNA bases[120]. As shown in Figure 27, AP sites in DNA strands exist in two different forms in equilibrium, the cyclic hemiacetal form and the open-chain aldehyde form, and the percentages of the aldehyde form is 1% in double stranded DNA[120].

Another type of AP site, $C_{(4')}$-oxidized abasic site (C4-AP), is produced by the actions of antitumor agent bleomycin or enediyne natural products. C4-AP also contains aldehyde group in the open-chain form (Figure 27)[122]. Although these AP sites generated in DNA are normally repaired by cellular enzymes, they sometimes lead to genetic mutations through bypass replication of DNA[123, 124].

In 1969, Coombs and Livingston reported that both aminooxy and hydrazine compounds efficiently and selectively react with AP sites[125]. Although hydrazine compounds also led to degradation of the DNA strand, aminooxy compounds react with AP sites without degrading the DNA strand. Based on these findings, ^{14}C-labeled methoxyamine[126] or *O*-(nitrobenzyl)hydroxylamine[127] has been applied to detect and quantitate the AP sites. These aminooxy reagents react efficiently with aldehyde groups in AP sites by forming a stable oxime linkage (Figure 28).

To achieve more sensitive detection of these aldehydic AP sites, Kubo and coworkers have developed a smart chemical probe, Aldehyde Reactive Probe (ARP) (Figure 29)[128, 129]. ARP reacts with AP sites through an oxime bond formation, and

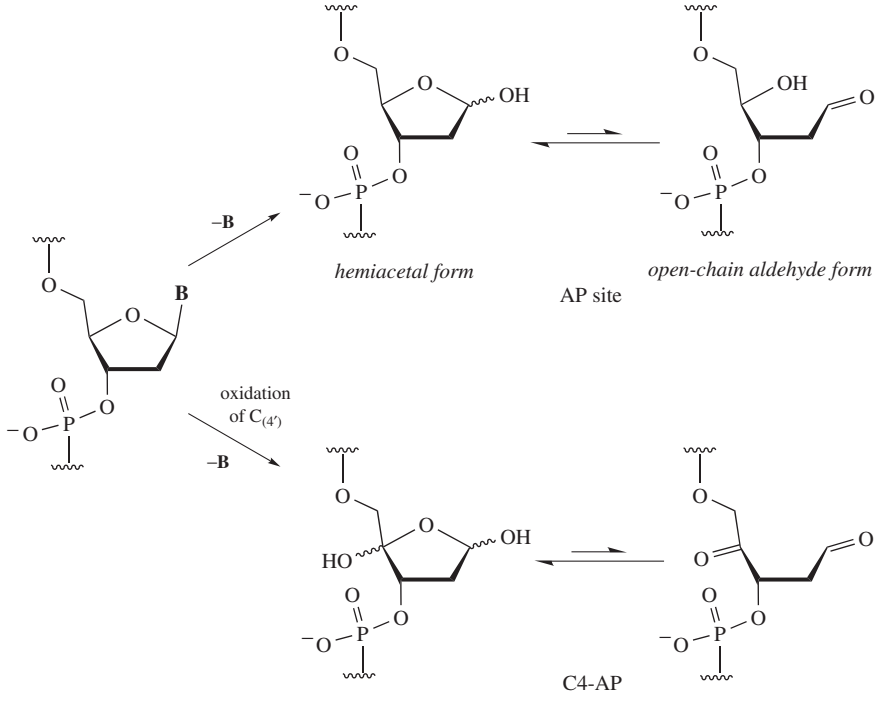


FIGURE 27

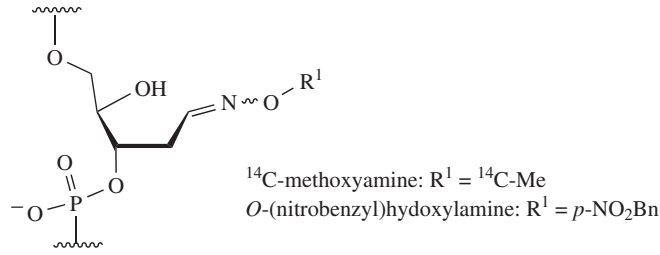
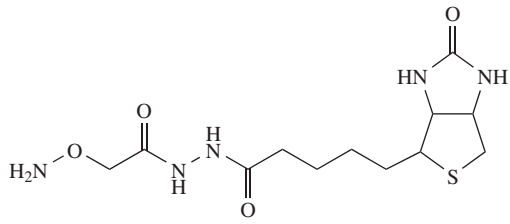


FIGURE 28

since ARP tethers a biotin residue, the resultant biotin-tagged AP sites can be quantified colorimetrically by various biological assays[130, 131].

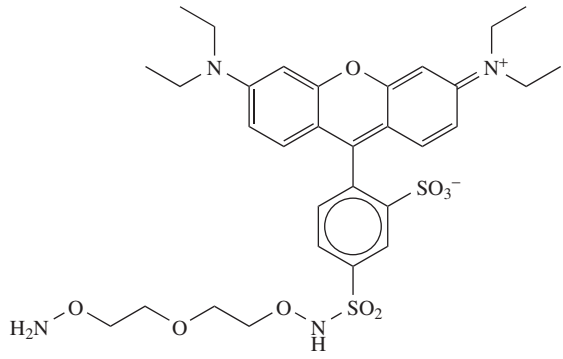
Likewise, fluorescent (**132**)[132–134] and chemiluminescent (**133**)[135] compounds conjugated with an aminooxy group have been developed by other researchers to detect and quantitate AP sites more sensitively (Figure 30). Specific detection of the oxidized AP sites, such as C4-AP, has been reported by Greenberg and coworkers using ARP and other chemical probes[136, 137].

Recently, we have developed novel aminooxy probes (aoN-g-bio, aoN-dg-bio) that were designed on the basis of the ARP structure (Figure 31)[138]. In these probes, both a positively

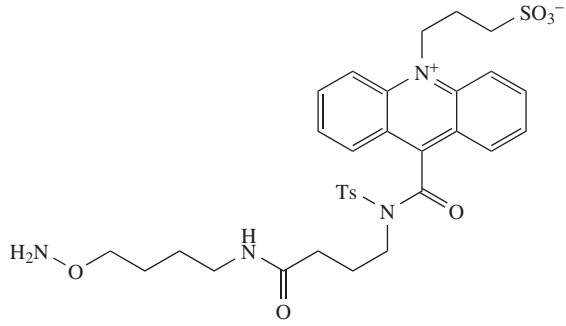


ARP

FIGURE 29

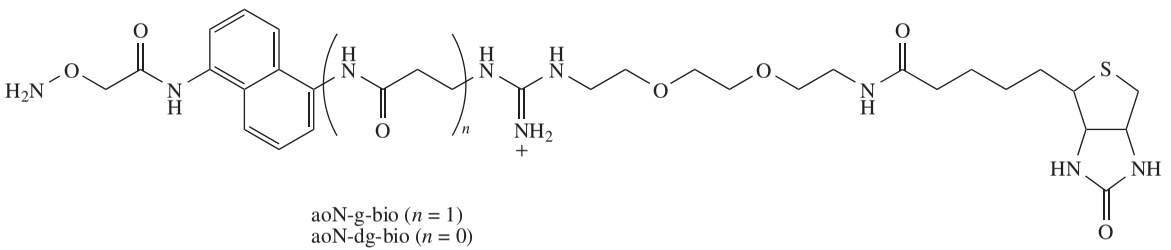


fluorescent probe
(**132**)



chemiluminescent probe
(**133**)

FIGURE 30



aoN-g-bio (n = 1)
aoN-dg-bio (n = 0)

FIGURE 31

charged guanidino group and an aromatic naphthalene residue are connected with an aminooxy group to promote association of the probes with DNA. These hydrophilic and hydrophobic interacting parts work synergistically in the conjugation reactions, and these probes enable more sensitive detection of AP sites in DNA than ARP. We think that these probes can also be applicable in various genetic assays utilizing AP sites.

VI. CONCLUSIONS

Hydroxylamine and its related derivatives react directly with nucleobases in genomic DNA because of their potent reactivity, and the DNA lesions induce genetic mutations by forming non-canonical base pairs with natural bases. On the other hand, some nucleoside analogues containing hydroxylamine derivatives have antiviral and anticancer activities because these analogues can mimic natural nucleosides and thus are recognized by various enzymes or proteins. In addition, oligonucleotides of neutral charge and nuclease resistance can be obtained when hydroxylamino derivatives are introduced into the backbone structure.

Although the hydroxylamine, oxime and hydroxamic acid groups are very small molecules, they are useful in creating various biologically active molecules. In the future, novel and valuable nucleoside analogues will be constructed using these functional groups.

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Hydroxamic acids: Biological properties and potential uses as therapeutic agents

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I. INTRODUCTION

Hydroxamic acids are normally positive ion-complexing agents, thus they take their biological properties from the ability to chelate metal ions which are important for a variety of biological processes, as well as for the catalytic activity of a number of metalloenzymes. In particular, the preference for chelation of iron and zinc ions by hydroxamates led to derivatives endowed with high potential as therapeutic agents.

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II. HYDROXAMATES AS 5-LIPOXYGENASE INHIBITORS

Inflammation is mediated by several families of mediators. Among these, the eicosanoids, a family of lipid mediators produced through the arachidonic acid (AA) metabolism, represent one of the most investigated family[1]. Usually in response to extracellular stimuli, phospholipase A2 (PLA2) liberates AA from membrane phospholipids and starts the biotransformation into prostanoids (prostaglandins, prostacyclin and tromboxanes) (Figure 1, pathway A) and leukotrienes (LTs, Figure 1, pathway B) via the cyclooxygenase (COX) or via the lipoxygenase (LO) pathways, respectively. These lipid hormones have inflammatory and anti-inflammatory properties and affect a number of biological systems. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX pathway (pathway A), and the non-selective inhibition of the two COX isoforms was assumed to be responsible for the gastric side-effects associated with their use, thus pushing the research towards the development of COX-2 selective inhibitors[2–4]. Nevertheless, gastric side-effects are also produced by LTs, that significantly contribute to gastric injury, and whose formation from AA in the gastric mucosa is increased under COX inhibition[5]. Moreover, recent studies suggest that highly selective COX-2 inhibitors display adverse cardiovascular events[6]. Thus, the search of inhibitors of LT biosynthesis (pathway B) seems to warrant potent anti-inflammatory therapeutic agents with less side-effects. In pathway B, 5-lipoxygenase (5-LO) catalyzes the incorporation of molecular oxygen into the AA structure giving rise to 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which is then dehydrated to the metastable epoxide LTA_4[7]. Further metabolism of the reactive epoxide LTA_4 involves stereospecific hydration by LTA_4 hydrolase (neutrophils and monocytes) to provide LBT_4 or conjugation with glutathione via a specific glutathione-*S*-transferase (LTC_4 synthetase) to produce LTC_4 (mast cells and eosinophils)[8]. Successive proteolytic cleavage steps convert LTC_4 into LTD_4 and LTE_4. LTB_4 promotes neutrophil chemotaxis and adhesion to vascular endothelium through specific integrin, and can cause inflammatory reactions and acute airway obstruction[9].

LTC_4 and LTD_4 are potent bronchoconstrictors, produce airway mucus secretion, contract the rat stomach and colon, and at high concentration provoke acid secretion[10]. Moreover, overproduction of LTs has been shown in cancer diseases such as human prostate or colon cancer[11]. Since its discovery in 1983, 5-LO was subjected to extensive studies, and numerous inhibitors have been reported. However, few of them have progressed to clinical trials, maybe because the block of 5-LO interferes with an entire metabolic process and could produce some undesired effects. In the design of inhibitors, many researchers targeted the active site, non-heme iron atom, and built in a weak chelator such as the hydroxamic acid group. The hydroxamic acid analogue of AA (**1**) was the first, potent *in vitro* inhibitor of 5-LO. After this, analogues of the related eicosanoids 15-hydroxyeicosa-5,8,11,13-tetraenoic acid (15-HETE)[12] and 5-hydroxyeicosa-6,8,11,14-tetraenoic acid 5-HETE[13], bearing at different positions the hydroxamate moiety (see compounds **2** and **3**, Figure 2), confirmed the potent inhibitory effect of this function. To transfer this strategy to simpler, smaller compounds, many arylhydroxamates were prepared and, when tested, were found to be potent *in vitro* inhibitors of 5-LO activity. A-61442 (**4**) (Figure 2) was one of the most potent hydroxamates ($IC_{50} = 22$ nM), nevertheless it did not provide satisfactory inhibition *in vivo* in rats by oral administration[14, 15]. Pharmacokinetic analysis revealed that hydroxamates such as **4** were readily absorbed but rapidly metabolized to the corresponding carboxylic acid that were inactive against 5-LO. To overcome this problem, the hydroxamate function was replaced by the retro-hydroxamate one, which is more stable to hydrolysis. Retro-hydroxamates displayed similar activity as the corresponding hydroxamates, while the *in vivo* activity was enhanced corresponding to improved plasma levels (compare, for example, A-63788 (**5**) and its retro-analogue A-63162 (**6**), Figure 2)[16, 17].

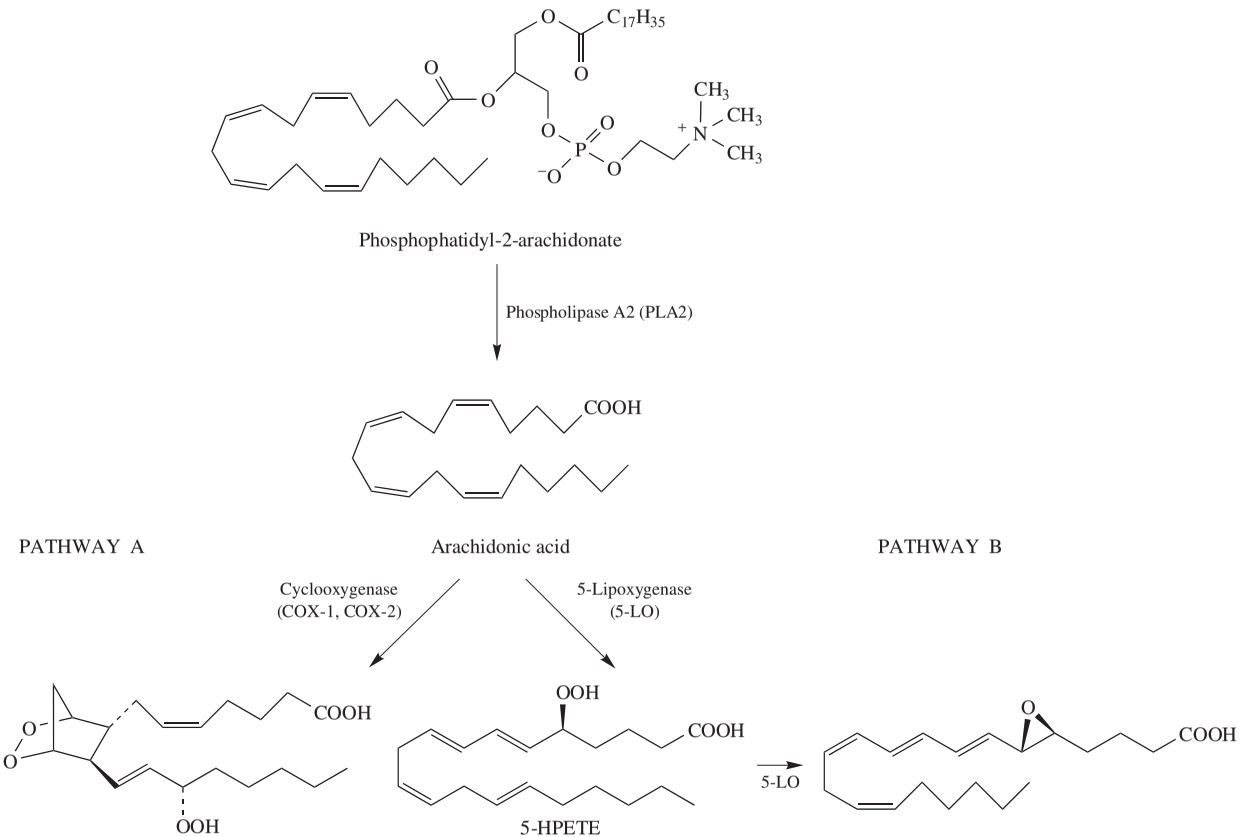


FIGURE 1. The arachidonic acid cascade

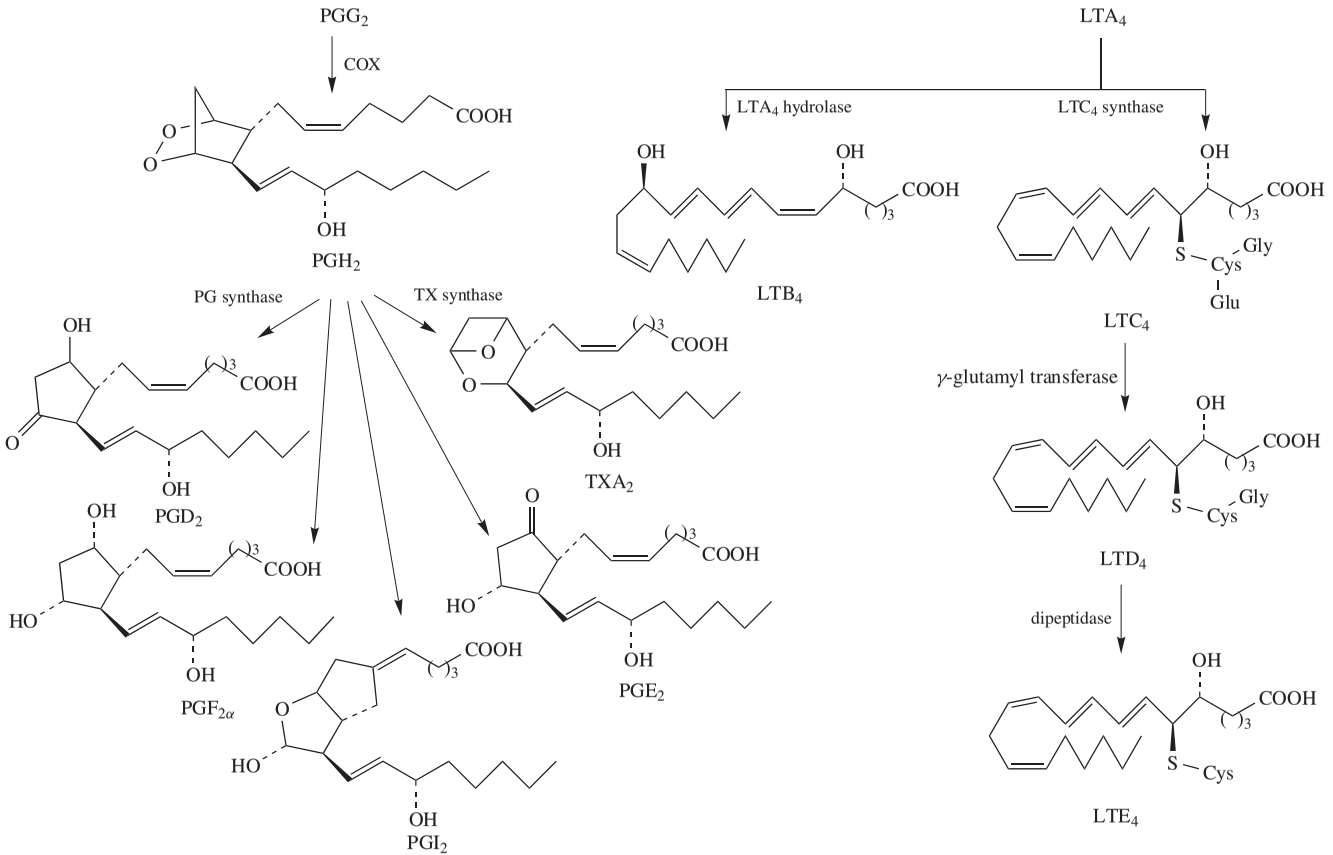
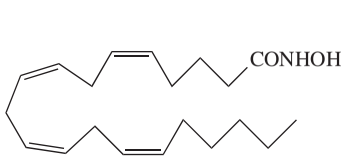


FIGURE 1. (*continued*)

SAR studies performed on hydroxamate and retro-hydroxamate 5-LO inhibitors highlighted the importance of an aryl moiety linked to a pharmacophore function. Aryl templates were often superior than saturated ring systems, and furan and thiophene as well as fused bicyclic rings such as benzofuran and benzothiophene furnished more potent scaffolds than nitrogen-containing heterocycles. Searching bioisosteres of the retro-hydroxamate, a new series of *N*-hydroxyurea derivatives has been prepared, to further stabilize the pharmacophore group against hydrolytic cleavage or other metabolic routes. *N*-Hydroxyurea compounds showed potent *in vitro* inhibition of 5-LO, and provided greater plasma levels and longer plasma half-lives after oral administration in several animal species. Among them, zileuton (**7**)[18] was the first clinical candidate 5-LO inhibitor for the prophylaxis and chronic treatment of asthma, and was approved by FDA for clinical use in 1996. Zileuton (**7**) is a potent and selective *in vitro* inhibitor of 5-LO ($IC_{50} = 0.5\,\mu M$), and was a very effective inhibitor *in vivo* in the rat anaphylaxis model ($ED_{50} = 5\,mg\,kg^{-1}$), a classical model for studying inhibition of LT formation. Clinical studies performed with **7** showed its efficacy in ulcerative colitis (reduction in LTB_4 levels)[19], allergic rhinitis (reduction in nasal congestion)[20], rheumatoid arthritis (RA) (relief of symptoms) and asthma (reduction in LTB_4 and LTE_4 levels)[21].

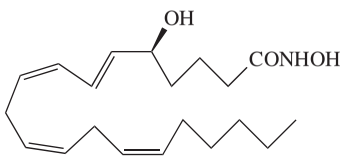
The aryl template of **7**, i.e. the benzothiophene moiety, can be replaced by a thiophene, furan or phenyl ring properly substituted with a phenyl, benzyl or phenoxy group without losing the 5-LO inhibitory action, and the branched ethyl linker connecting the benzothiophene to the pharmacophore hydroxyurea group can be changed with a propenyl/propynyl or butenyl/butynyl spacer, obtaining higher metabolic stability. The phenylfuran derivative A-70493 (**8**) (Figure 2), for example, shows a propenyl group as a spacer and exhibited improved *in vitro* potency to **7** but lower plasma concentrations in the rat. The furan A-69412 (**9**) (Figure 2) was instead less potent *in vitro* than **7** but showed similar *in vivo* potency, with excellent pharmacokinetic properties (plasma half-life in animal models is 2- to 10-fold greater than zileuton). From a process of lead optimization, two zileuton analogues (second generation 5-LO inhibitors) designed as conformationally constrained *aci*-reductone mimics of AA were obtained, with enhanced potency against 5-LO and improved metabolic stability: A-78773 (**10**)[22, 23] and VIA-2291 (atreleuton, **11**)[24, 25] (Figure 2). The increased hydrophobicity assured by the 4-fluorophenoxyfuran (**10**) or the 4-fluorobenzylthiophene (**11**) moiety provided an increase in potency together with excellent bioavailability, while the 1-methylpropynyl linker was a key factor in reducing the rate of glucuronidation and subsequent elimination. Zileuton (**7**) and atreleuton (**11**) are actually in clinical trials for the treatment of asthma, fibrosis and pulmonary disease, coronary disease and cancer (Table 1).

In a different approach, dual inhibitors of 5-LO and other inflammatory targets were built inserting the anti-5-LO pharmacophore (hydroxamate, hydroxyurea) into chemical structures of antihistaminic or anti-COX agents. Thus, a series of *N*-hydroxyureas containing a histamine H1 antagonist pharmacophore was constructed and exhibited the desired dual activity profile[26]. Preclinical work in the guinea pig ovalbumin model showed **12** (Figure 3) to have a better overall profile than a traditional 5-LO analogue such as zileuton. The carboxylic acid function of indomethacine (**13**), a well-known COX inhibitor, was easily replaced with a hydroxamate (**14**)[27], internal hydroxyurea (**15**) or terminal hydroxyurea (**16**) group[28] (Figure 3). Whereas **14** can be classified as a prodrug of indomethacine due to the rapid *in vivo* hydrolysis of the hydroxamate to regenerate indomethacine, the hydroxyurea derivatives **15** and **16** possess chemical stability and do not undergo hydrolysis and showed comparable inhibitory potency against 5-LO and COXs. By combining the diarylpyrazole moiety of the COX-2 selective inhibitor celecoxib (**17**) with a hydroxamate group, the dual COX-2/5-LO inhibitor tepoxalin (**18**) was obtained[29] (Figure 3). Tepoxalin (**18**) inhibited the production of 5-HETE (as a marker of 5-LO activity) and



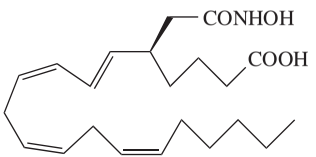
(**1**)

5-LO IC_{50}: 2.2 μM



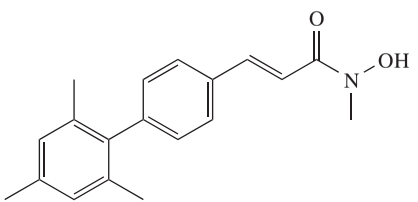
(**2**)

2.1 μM



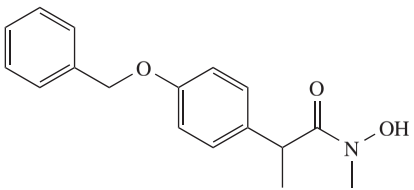
(**3**)

0.19 μM



A-61442 (**4**)

5-LO IC_{50}: 0.022 μM

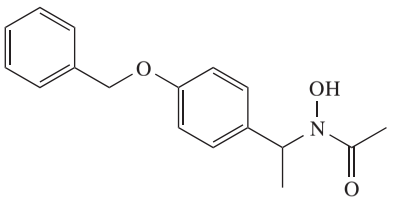


A-63788 (**5**)

0.28 μM

rat Cmax @ 1h: 8 μM

rat anaphylaxis ED_{50}: 40 mg kg^{-1}



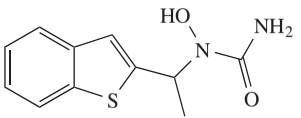
A-63162 (**6**)

0.27 μM

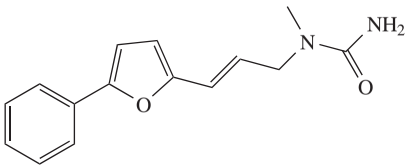
110 μM

8 mg kg^{-1}

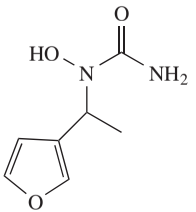
FIGURE 2. The process of discovery of 5-LO inhibitors



zileuton (**7**)

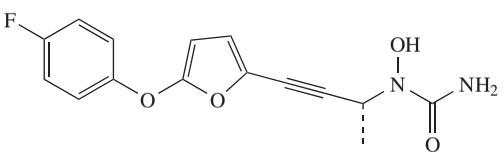


A-70493 (**8**)



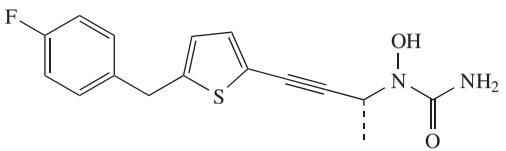
A-69412 (**9**)

	zileuton (**7**)	A-70493 (**8**)	A-69412 (**9**)
5-LO IC_{50}:	0.5 μM	0.19 μM	15 μM
plasma concentration:	rat: 137 μM	14 μM	161 μM
	monkey: 22 μM	<1 μM	57 μM
	dog: 86 μM	4 μM	166 μM
plasma half life:	rat: 2.3 h		6.7 h
	monkey: 0.3 h		3.1 h
	dog: 7.5 h		5.6 h



A-78773 (**10**)

5-LO IC_{50}: 0.085 μM



VIA-2291 (atreleuton) (**11**)

0.023 μM

FIGURE 2. (*continued*)

TABLE 1. 5-LO inhibitors in clinical trials

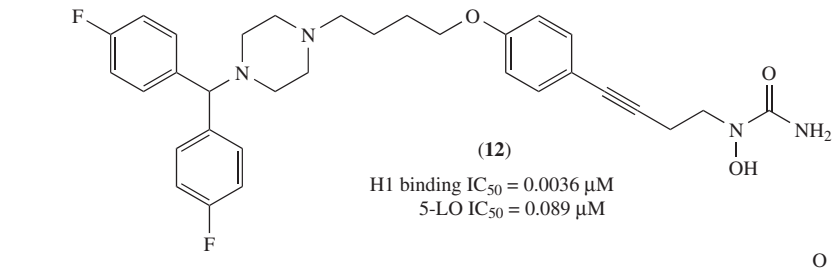
Drug	Study	Phase	Disease	NCT	Status[a]
Atreleuton (**11**)	Phase 2 Study in Vascular Inflammation on Patients After an Acute Coronary Syndrome Event	II	Acute Coronary Syndrome	NCT00552188	C
Zileuton (**7**)	Safety Study of Zileuton Injection in Patients With Asthma	I/II	Asthma	NCT00299065	C
Zileuton (**7**)	Study of Oral Zileuton in the Treatment of Moderate to Severe Facial Acne Vulgaris	II	Acne Vulgaris	NCT00098358	A, NR
Zileuton (**7**)	Zileuton and Exhaled Nitric Oxide in Asthmatics	IV	Asthma	NCT00575861	C
Zileuton (**7**), Celecoxib (**17**)	Modulation of Arachidonic Acid Metabolism by Chemopreventive Agents in Smokers	I/II	Cancer	NCT01021215	R
Zileuton (**7**), Celecoxib (**17**), Carbo-platin,Gemcitabine	Carboplatin and Gemcitabine Combined With Celecoxib and/or Zileuton in Treating Patients With Advanced Non-small Cell Lung Cancer	II	Lung Cancer	NCT00070486	C
Zileuton (**7**), Losartan, *N*-Acetylcysteine; Prevastatin, Erythromycin	Pilot Study of a Multi-drug Regimen for Severe Pulmonary Fibrosis in Hermansky–Pudlak Syndrome	I/II	Hermansky–Pudlak Syndrome (HPS); Pulmonary Fibrosis; Oculocutaneous Albinism; Platelet Storage Pool Deficiency; Metabolic Disease	NCT00467831	R
Zileuton (**7**)	Zileuton in Preventing Lung Cancer in Patients With Bronchial Dysplasia	II	Head and Neck Cancer, Lung Cancer	NCT00056004	C
Zileuton (**7**), Azathio-prine/Prednisone	Zileuton for the Treatment of Idiopathic Pulmonary Fibrosis	II	Idiopathic Pulmonary Fibrosis	NCT00262405	A, NR

(*continued overleaf*)

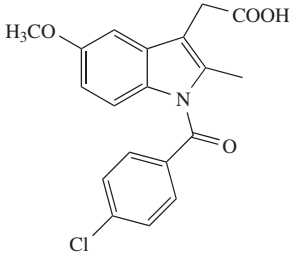
TABLE 1. (*continued*)

PF-04191834, Zileuton (**7**)	PF-04191834 Single Dose Bronchodilatory Study in Asthma.	II	Asthma	NCT00723021	C
Zileuton (**7**)	Assessment of PFT, Safety, and PK of Zileuton Injection in Asthma Patients	II	Asthma	NCT00534625	C
Zileuton (**7**) controlled-released (CR)	Zileuton CR vs Placebo in Poorly Controlled Asthma Patients on Moderate Dose Inhaled Corticosteroids (ICS)	IV	Asthma	NCT00486343	T
Zileuton (**7**)	Zileuton to Treat Adults With Chronic Obstructive Pulmonary Disease (The LEUKO Study)	III	Pulmonary Disease, Chronic Obstructive	NCT00493974	T
Zileuton (**7**)	Study to Evaluate the Safety of Zileuton (Zyflo) . . .	I	Chronic Myelogenous Leukemia	NCT01130688	R

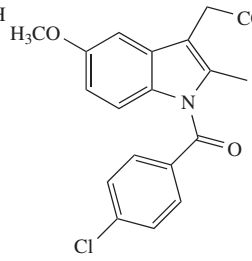
[a]C: completed; A, NR: active, not recruiting; R: recruiting; T: terminated.



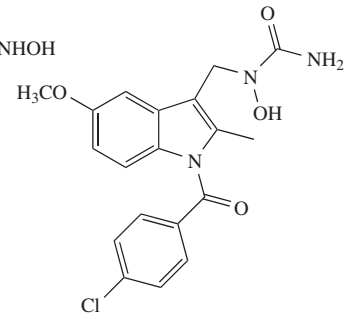
(**12**)
H1 binding IC_{50} = 0.0036 μM
5-LO IC_{50} = 0.089 μM



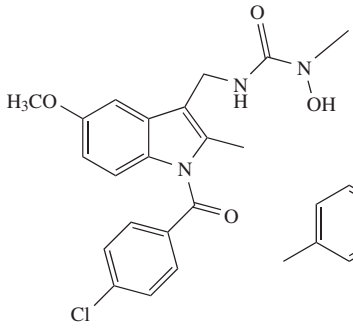
indomethacine (**13**)



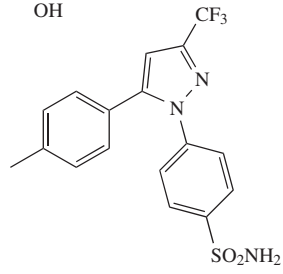
(**14**)
COX IC_{50} = 1.1 μM
5-LO IC_{50} = 7.5 μM



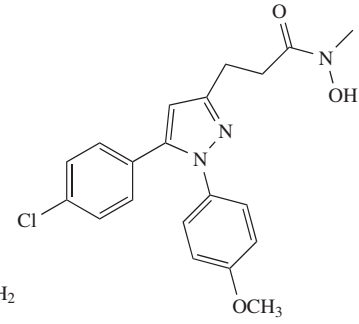
(**15**)
COX-1 inhbtn = 9% @ 10 μM
COX-2 inhbtn = 48% @ 10 μM
5-LO IC_{50} = 0.34 μM



(**16**)
COX-1 inhbtn = 64% @ 30 μM
COX-2 inhbtn = 88% @ 30 μM
5-LO IC_{50} = 0.2 μM



celecoxib (**17**)

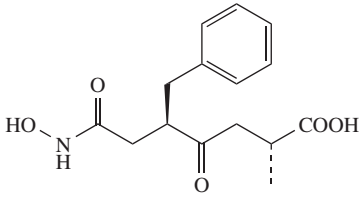


tepoxalin (**18**)
COX IC_{50} = 2.85 μM
5-LO IC_{50} = 0.15 μM

FIGURE 3. Dual H1/5-LO and COX/5-LO inhibitors

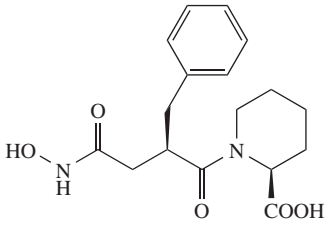
COX activity in intact rat basophilic leukemia cell line with IC_{50} of 0.15 μM and 2.85 μM, respectively.

To obtain an interference in the LT biosynthetic pathway, also the enzyme LTA_4 hydrolase can represent a valuable target to inhibit. LTA_4 hydrolase is a zinc-containing metalloenzyme involved in the rate-limiting step for the production of LTB_4 through the hydrolysis of the epoxide moiety. Early inhibitors were designed on the structure of the



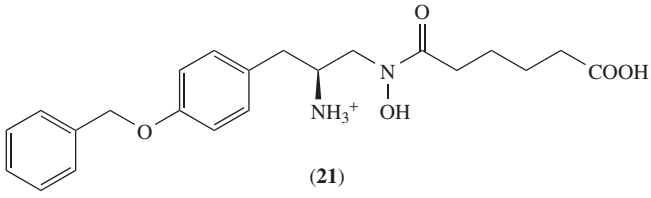
kelatorphan (**19**)

LTA_4 hydrolase IC_{50} = 0.005 μM
Aminopeptidase IC_{50} = 0.007 μM
NEP IC_{50} = 0.046 μM
ACE IC_{50} = > 10 μM



(**20**)

LTA_4 hydrolase IC_{50} = 0.008 μM
Aminopeptidase IC_{50} = 0.01 μM
NEP IC_{50} = 17 μM
ACE IC_{50} = 40 μM



(**21**)

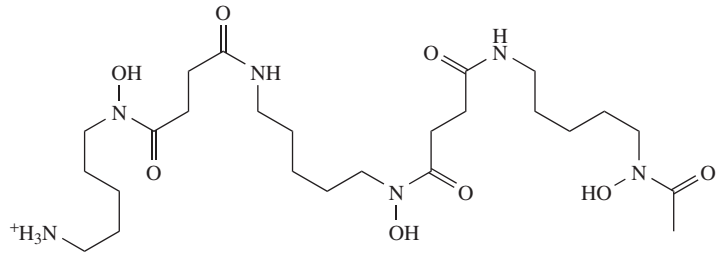
LTA_4 hydrolase IC_{50} = 0.0016 μM

FIGURE 4. LTA_4 hydrolase inhibitors

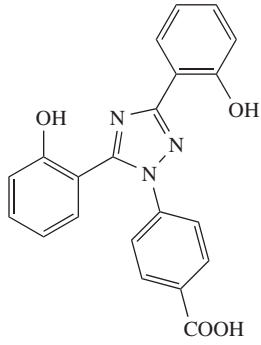
natural substrate, LTA_4. Later approaches led to a number of peptide and non-peptide analogs which contained potential zinc-chelating moieties, including thiols, hydroxamates and norstatines, such as kelatorphan (**19**) (Figure 4), a highly active but not selective LTA_4 hydrolase inhibitor[30]. A systematic study of the peptide and substituent SAR demonstrated that potent compounds could be derived (see, for example, **20**, Figure 4) with selectivity against neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). Overall, the analogs retained their aminopeptidase activity. Potent LTA_4 hydrolase inhibitors such as **21** (Figure 4) were also obtained using an amino-hydroxamate scaffold[31].

III. HYDROXAMATES AS IRON CHELATORS

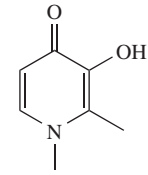
Recent developments in the understanding of the molecular control of iron homeostasis provided novel insights into the mechanisms responsible for normal iron balance. In chronic anemias associated with iron overload, such mechanisms are no longer sufficient to offer protection from iron toxicity. In absence of regular use of chelators, iron stores steadily increase and patients die from iron-induced cardiac disease[32]. Thus, iron chelating therapy is the only method available for preventing early death caused mainly by myocardial and hepatic damage. Deferoxamine (DFO) (**22**) (Figure 5), a linear tridentate molecule comprising three sequential hydroxamate iron binding groups, was available for treating transfusional iron overload from the early 1960s, but started to be used for iron chelating therapy only 20 years later with the introduction of subcutaneous DFO infusions by portable pumps. DFO (**22**) is able to reduce cardiac iron and to improve cardiac function in patients with severe iron overload. Today, long-term DFO therapy is useful



deferoxamine (DFO, **22**)



deferasirox (**23**)



deferiprone (**24**)

FIGURE 5. Iron chelators in clinical trials

for the management of thalassemia, sickle cell disease and other transfusion-dependent anemias, with a major impact on well-being and survival[32–35]. DFO (**22**) is also used for the treatment of myelodysplastic syndrome (MDS), a hematopoietic stem cell disease characterized by ineffective blood cell production, with the risk of transformation to acute myeloid leukemia (AML)[36, 37]. MDS patients require red blood cell (RBC) transfusion for the management of the refractory anemia, and they can suffer from iron overload when the iron acquired by transfusion exceeds body storage capacity[38]. Parenteral administration of **22** is currently used in MDS when the oral iron chelation therapy (deferasirox (**23**), deferiprone (**24**)) is not tolerated by patients or is ineffective[39].

Iron has also great importance in cancer cell growth. Due to their rapid proliferation, neoplastic cells have a high iron requirement, and, to attain more iron, they express higher levels of the transferring receptor (TfR1) and take up iron at a greater rate than the normal cells. Thus, iron chelation may be a suitable therapeutic strategy for cancer treatment. DFO (**22**) was shown to reduce bone marrow infiltration of tumor cells in 7 of 9 neuroblastoma patients[40]. Unfortunately, in some clinical trials the effect of **22** alone or in association with other anticancer drugs was discontinuous, it being beneficial in inoperable hepatocellular carcinoma and limited (if any) in advanced hormone-refractory prostate cancer and refractory non-Hodgkin's lymphoma[41–43].

Iron plays also an important role in intracerebral hemorrhage (ICH) and in ICH-induced brain injury[44, 45]. In this context, iron overload causes formation of highly reactive oxygen species (ROS) that induce oxidative stress and cell death, lipid peroxidation

and excitotoxicity. The result is brain edema and neuronal death. In embryonic cortical neuronal cultures, **22** decreased free iron's availability for the production of ROS and prevented apoptosis induced by glutathione depletion and oxidative stress, by activation of the activation of transcription factor 1/cAMP response element-binding protein (ATF-1/CBP) pathway[46, 47]. In mixed neuronal and astrocyte cell cultures, **22** markedly attenuated neuronal death blocking the neurotoxic effects of hemoglobin, which increases the glutamate neurotoxicity[48]. In rat models of ICH, **22** reduced ICH-induced brain edema, neuronal death, brain atrophy and neurological deficits, thus representing a new hope for the treatment of iron-based neurotoxicity[49]. DFO (**22**) is actually in clinical trials both as single agent and in combination for the treatment of iron overload-based diseases, β-thalassemia, MDS and other hematologic diseases (Table 2).

Iron is essential for the life of bacteria also, and constitutes a critical virulence factor during the course of a pathogenic infection[50]. Bacteria have developed their own systems of siderophores, low molecular weight iron chelators that are able (i) to chelate iron in extracellular distrects, and (ii) to actively transport it into the cell[51]. Such siderophores, linked to antibacterial agents, can be used as drug delivery agents ('Trojan Horse') because they can bypass membrane associated resistance mechanisms and improve the potency of the antibacterial agents up to 100-fold with respect to passive diffusion[52–54]. In addition, this new siderophore-based drug delivery system limits the selection of bacterial resistance to non-pathogen strains deficient in siderophore-receptor proteins. Desferridanoxamine (Dan) (**25**)[55] (Figure 6) is an analogue of DFO (**22**) which has been used as a Trojan Horse for treating bacterial infections. Dan (**25**) has been conjugated with lorabid (**26**), a β-lactam antibiotic, ciprofloxacin (**27**), a well-known quinolone, and triclosan (**28**), a polychlorophenoxy phenol endowed with antibacterial and antifungal activities (Figure 6)[54]. The succinic terminal portion of the fully *O*-benzyl protected Dan precursor **29** has been efficiently coupled with either the primary amine function of lorabid, or the piperazine moiety of ciprofloxacine, or the phenol function of triclosan to give, after hydrogenolysis of the benzyl-protected intermediates **33–35**, the final Dan-antibiotic conjugates **30–32** (Figure 6 and Scheme 1). When tested against a panel of both Gram-positive and-negative bacteria strains (*Bacillus subtilis, Staphylococcus aureus*, methicillin-resistant *S. aureus, Mycobacterium luteus, Mycobacterium vaccae, Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Pseudomonas aeruginosa*), Dan-lorabid (**30**) and Dan-ciprofloxacin (**31**) conjugates showed lower antibacterial activity with respect to the corresponding free drugs, maybe because there was no efficient (if any) release of drug from the siderophore. In contrast, Dan-triclosan (**32**) displayed similar or higher activity than the free drug alone for almost all the strains screened (Table 3). Further studies in this direction are due to establish the real efficacy of the approach and to determine the best combination between siderophore and drug, also in view of overcoming at least in part the problem of bacterial resistance.

IV. HYDROXAMATES AS INHIBITORS OF TWO TARGETS FOR BACTERIAL GROWTH AND VIABILITY: PEPTIDE DEFORMYLASE (PDF) AND UDP-3-*O*-(*R*-3-HYDROXYMYRISTOYL)-*N*-ACETYLGLUCOSAMINE DEACETYLASE (LPXC)

A. Targeting Bacterial Peptide Deformylase (PDF)

The protein synthesis processes for bacterial and mammalian cells are very similar. Nevertheless, a major difference between the two processes is the use of formylmethionine as the initiator[56, 57]. Unlike cytosol protein synthesis in mammalian cells, which is initiated with methionine, protein synthesis in bacteria is initiated with *N*-formylmethionine[58, 59],

TABLE 2. Clinical trials involving DFO (**22**)

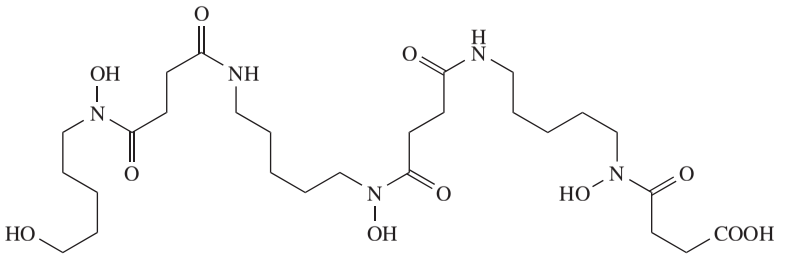
Drug	Study	Phase	Disease	NCT	Status[a]
DFO (**22**), Deferasirox (**23**)	Evaluating Use of Deferasirox as Compared to Deferoxamine in Treating Cardiac Iron Overload	II	Transfusional Iron Overload, Transfusional Hemosiderosis	NCT00600938	R
DFO (**22**)	Thrombolysis and Deferoxamine in Middle Cerebral Artery Occlusion	II	Acute Ischemic Stroke	NCT00777140	R
DFO (**22**), Deferasirox (**23**)	Iron Balance Study of Deferasirox, Deferoxamine and the Combination of Both	I/II	Thalassemia	NCT00738413	R
DFO (**22**) mesylate	Deferoxamine in Myeloablative Allogeneic Stem Cell Transplantation for Patients With Myelodysplastic Syndromes or Acute Leukemia and Iron Overload		Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Myelodysplastic Syndrome	NCT00658411	R
ICL670, DFO (**22**)	Safety & Efficacy of ICL670 vs. Deferoxamine in β-Thalassemia Patients With Iron Overload Due to Blood Transfusions	III	β-Thalassemia	NCT00061750	C
ICL670, DFO (**22**)	Safety of ICL670 vs. Deferoxamine in Sickle Cell Disease Patients With Iron Overload Due to Blood Transfusions	II	Anemia, Sickle Cell	NCT00067080	C
DFO (**22**) mesylate	Dose Finding and Safety Study of Deferoxamine in Patients With Brain Hemorrhage	I	Intracerebral Hemorrhage	NCT00598572	R
N-Acetylcysteine, DFO (**22**)	*N*-Acetylcysteine Plus Deferoxamine for Patients With Hypotension	II	Hypotension, Acute Renal Failure	NCT00870883	R
DFO (**22**), Deferiprone (**24**)	Efficacy Study in Removing Excess Iron From the Heart	IV	Thalassemia Major, Hemosiderosis	NCT00105495	C
DFO (**22**), Deferasirox (**23**)	Combo Chelation Trial	IV	Thalassemia, Iron Overload	NCT00901199	R
DFO (**22**), Deferiprone (**24**)	Study Using Deferiprone Alone or in Combination With Desferrioxamine in Iron Overloaded Transfusion-dependent Patients	II	Hemochromatosis	NCT00349453	A, NR

(*continued overleaf*)

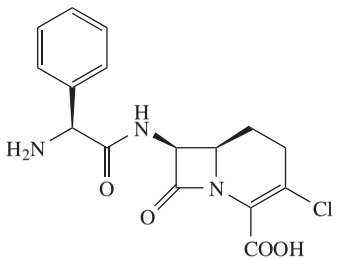
TABLE 2. (*continued*)

DFO (**22**), Deferiprone (**24**)	Intensive Combined Chelation Therapy for Iron-induced Cardiac Disease in Patients With Thalassemia Major	IV	Iron Overload, Cardiomyopathy	NCT00800761	C
DFO (**22**)	Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis	II	Anemia (Iron-loading), β-Thalassemia, Hemoglobinopathies, Iron Overload, Hemochromatosis	NCT00000595	C
DFO (**22**), Deferasirox (**23**)	Pilot Study for Patients With Poor Response to Deferasirox	IV	Transfusion-dependent Hemachromatosis, Thalassemia Major, Sickle Cell Disease	NCT00749515	A, NR
DFO (**22**), Deferiprone (**24**)	Combination Therapy Compared With Single-drug Therapy in Patients With Cardiac Diseases	II	Cardiovascular Diseases, Heart Diseases, β-Thalassemia	NCT00115349	T
DFO (**22**), Deferiprone (**24**)	Efficacy Study of the Use of Sequential DFP-DFO Versus DFP	IV	β-Thalassemia, Thalassemia Major	NCT00733811	C
DFO (**22**), Deferiprone (**24**), Arginine, Sildenafil, Decitabine	Thalassemia (Cooley's Anemia) Clinical Research Network (TCRN)		Cooley's Anemia, β-Thalassemia, Hematologic Diseases; Osteoporosis, Pulmonary Hypertension,	NCT00000623	C

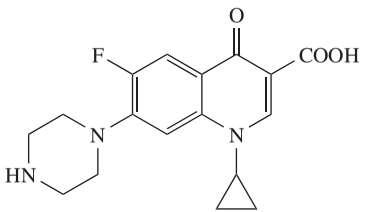
[a]C: completed; A, NR: active, not recruiting; R: recruiting; T: terminated.



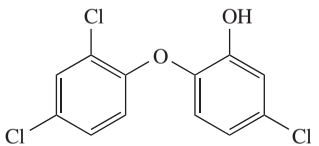
desferridanoxamine (Dan, **25**)



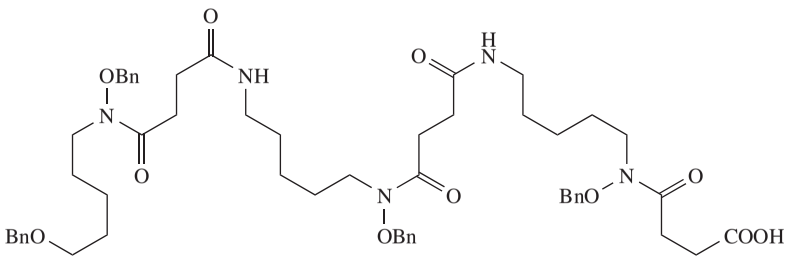
lorabid (**26**)



ciprofloxacin (**27**)



triclosan (**28**)



(**29**)

FIGURE 6. Desferridanoxamine (Dan, **25**) and Dan-antibiotic conjugates

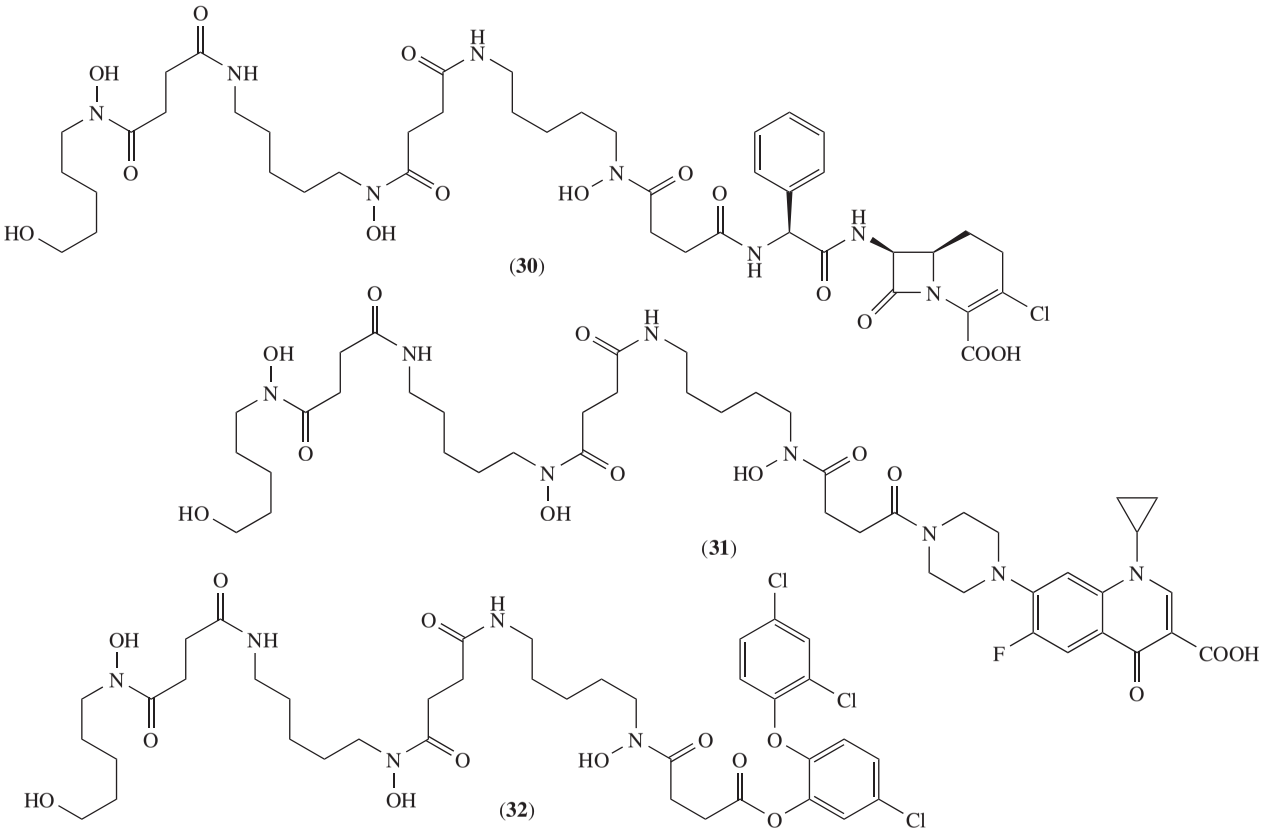
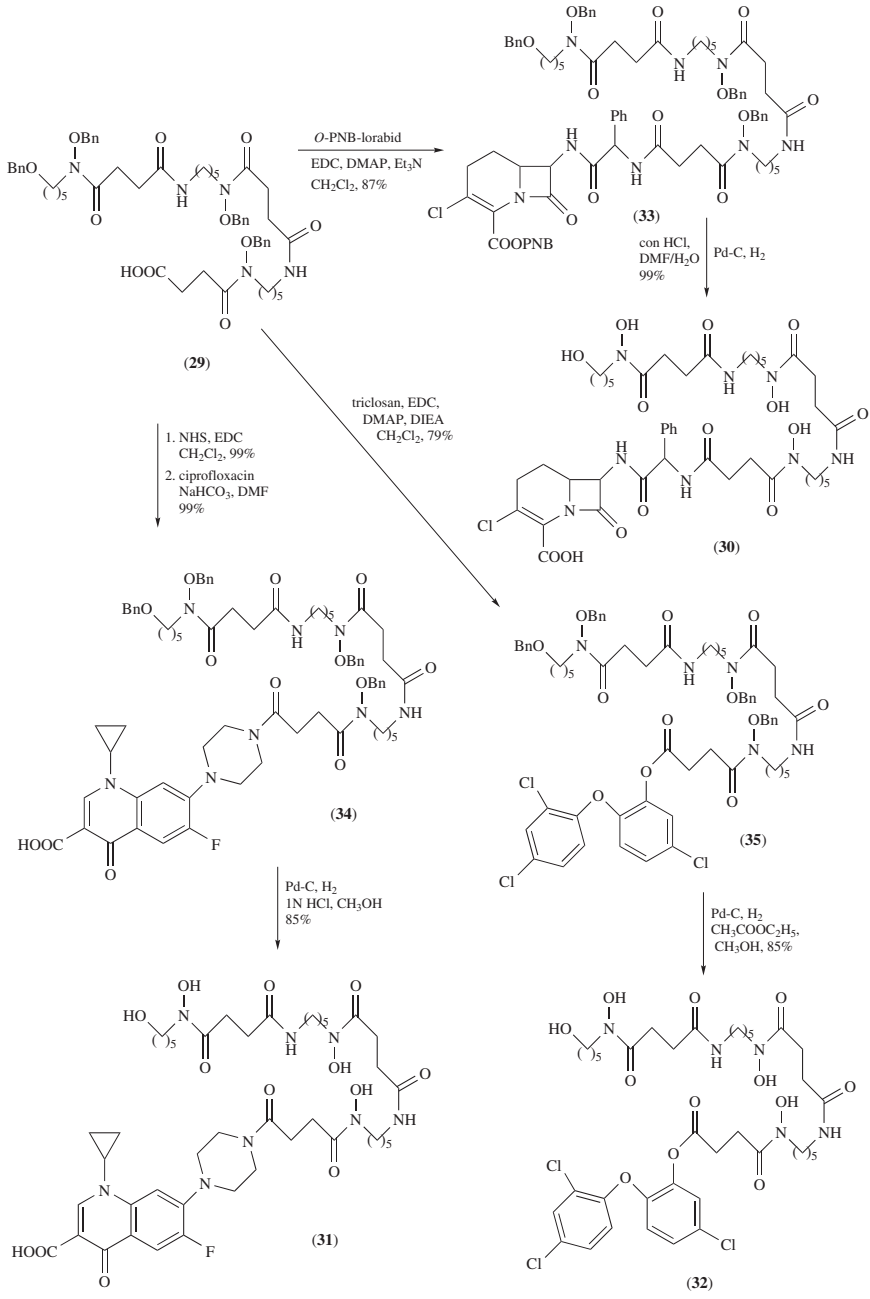


FIGURE 6. (*continued*)



SCHEME 1. Synthesis of Dan-antibiotic conjugates **30–32**

TABLE 3. Antibacterial activity of Dan-antibiotic conjugates **30–32**

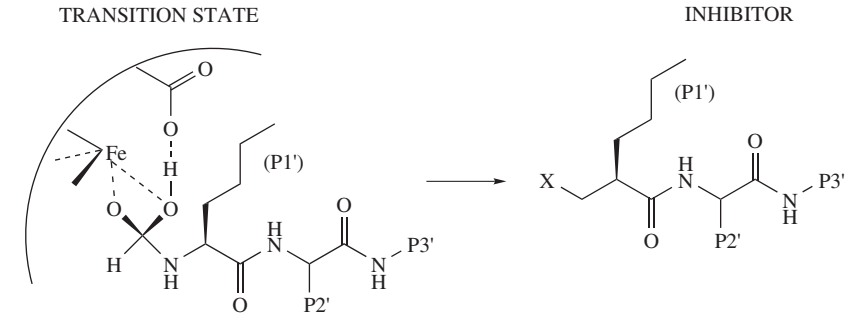
Bacterial strain	Zone of growth inhibition (mm) after 24 h at 37 °C						
	Dan 2 mM	**30** 2 mM	Lorabid (**26**) 2 mM	**31** 0.2 mM	Ciprofloxacin (**27**) 0.2 mM	**32** 0.2 mM	Triclosan (**28**) 0.2 mM
B. subtilis	0	14	34[a]	26	36	21	18
S. aureus	0	18	28	25	52	41	29
MRSA	0	0	0	0	13	25	26
M. luteus	0	11	38	0	19	16	20
M. vaccae	23	20.5	0[a]	20	44	28	32
E. faecalis	0	0	0[a]	16	24.5	15	16
E. cloacae	12[b]	NT[c]	0	18	29	22.5	29
E. coli	17	17	25	20	33.5	25	31
P. aeruginosa	0	0	0	0	25	0	0

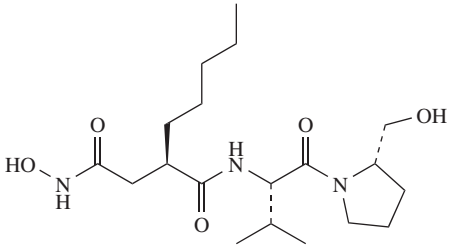
[a]Concentration = 0.2 mM. [b]Concentration = 0.5 mM. [c]NT = not tested.

which is generated through enzymatic transformylation of methionyl-tRNA by formylmethionine tRNA transferase. The *N*-formyl methionine of the nascent protein in bacteria is removed by the sequential action of peptide deformylase (PDF) and a methionine amino peptidase in order to afford the mature protein[58, 60]. This formylation–deformylation cycle is essential for bacterial growth and is conserved among all studied bacterial species, while it is not required for mammalian cells because nuclear encoded proteins are not *N*-formylated[61]. Thus, the specific bacterial requirement for PDF in protein synthesis could provide a rational basis for selectivity, making it an attractive drug discovery target. However, a human peptide deformylase (HsPDF) was recently shown to be present in mitochondria, involved in deformylation of mitochondrial proteins[62–64], making more complicated this drug discovery process.

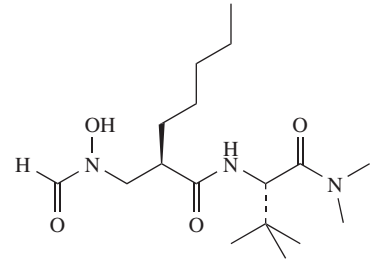
In 2009 the structure of such HsPDF was disclosed[65], and the elucidation of structural differences between bacterial and human PDFs will be the key for designing new selective antimicrobials that are not toxic to mammalian cells. Bacterial PDF utilizes a Fe^{+2} ion as the catalytic metal ion[66–68], but the ferrous ion in PDF is very unstable and can be quickly and irreversibly oxidized to the ferric species, resulting in an inactive enzyme[69]. Since PDF is a metalloprotease, one possible approach to design inhibitors is to couple a non-specific chelating group, able to bind to the catalytic metal ion, with a second moiety that binds to the active site, thus correctly positioning the chelator and providing the necessary selectivity and physicochemical properties. Based on mechanistic and structural information, a generic PDF inhibitor structure (Figure 7) was proposed[70]. In this structure, X represents a chelating pharmacophore that will be the major component to provide binding energy. As chelating groups, hydroxamates and *N*-formylhydroxylamines (retrohydroxamates) were the most effective. Linked to the pharmacophore, the *n*-butyl group (P1′ position) mimics the methionine side chain of the PDF substrate, and P2′ and P3′ are regions of the inhibitor that can provide additional binding energy, selectivity and favorable pharmacokinetic properties.

Actinonin (**36**) (Figure 7), a naturally occurring antibiotic with a hydroxamate moiety and a tripeptide binding domain isolated in 1962 from an actinomycete[71], was shown to be a PDF inhibitor[72]. In recent years, several classes of PDF inhibitors have been reported[73–75]. While all of these compounds inhibit PDF activity, most of them do not have antibacterial activity, presumably due to weak potency against PDF and/or an inability to penetrate the bacterial cell. In particular, those compounds showing IC_{50} values greater than 1 μM had no antibacterial activity. A *N*-formylhydroxylamine derivative strictly

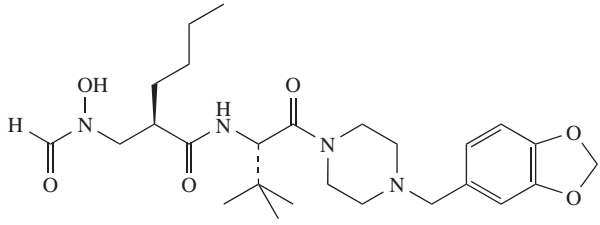




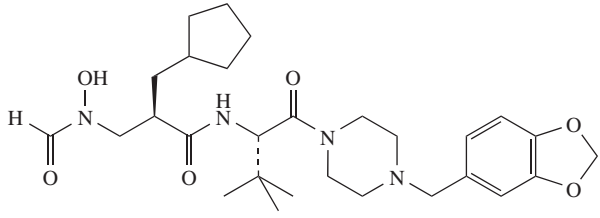
actinonin (**36**)



BB-3497 (**37**)

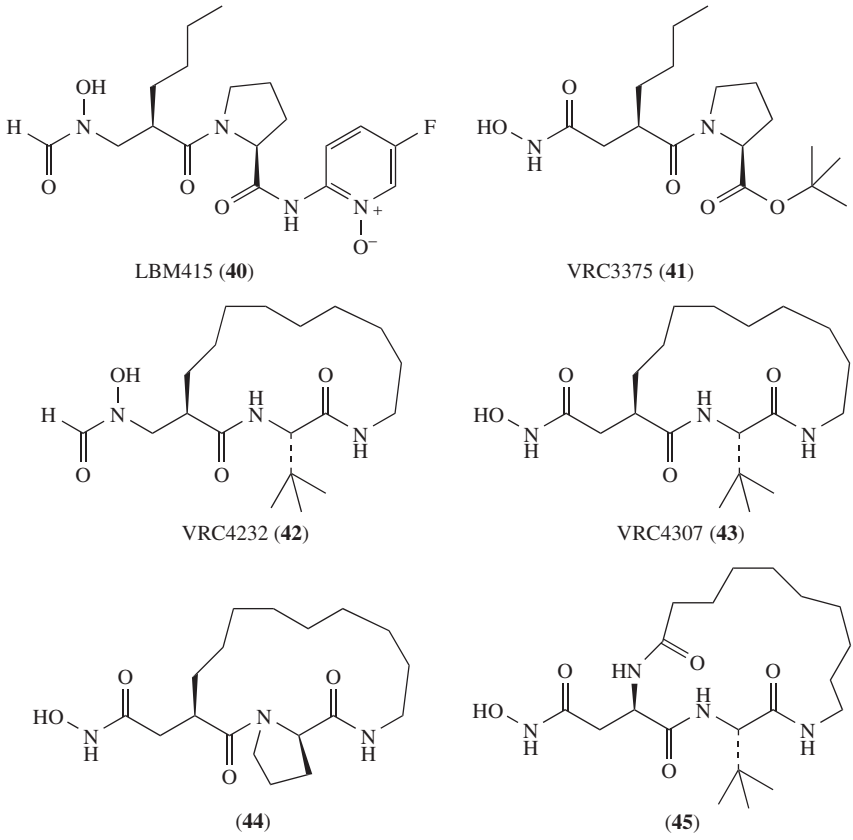


BB-81384 (**38**)



BB-83698 (**39**)

FIGURE 7. Peptide deformylase (PDF) inhibitors



LBM415 (**40**)

VRC3375 (**41**)

VRC4232 (**42**)

VRC4307 (**43**)

(**44**)

(**45**)

FIGURE 7. (*continued*)

related to actinonin (**36**), BB-3497 (**37**) (Figure 7), having a strong structural resemblance to the known PDF substrate fMet-Ala-Ser, showed PDF inhibitory activity at nanomolar level and high selectivity over other mammalian metalloenzymes (Table 4)[76]. With respect to actinonin, BB-3497 (**37**) displayed higher, wide-spectrum antibacterial activity extended to Gram-negative pathogens (Table 5), and it was well absorbed following oral administration and was effective in animal models of infection, whereas actinonin (**36**) was totally inactive in *in vivo* assays[76].

Optimization of BB-3497 (**37**) led to the discovery of BB-81384 (**38**)[77] and then of BB-83968 (**39**)[78], the first-in-class PDF inhibitor to enter clinical trials. In BB-83968 (**39**), the *n*-butyl chain of **37** at P1′ was replaced with a cyclopentylmethyl chain, and the *N*,*N*-dimethylamide moiety at P3′ was changed into a *N*-[(3,4-methylenedioxy)benzyl]piperazinamide moiety, thus improving Gram-positive activity over BB-3497 (**37**). BB-83968 (**39**) showed excellent antibacterial activity against the most important community respiratory tract pathogens, including drug-resistant isolates. *In vitro* BB-83698 was tested against 281 streptococcal strains, 154 strains of *S. aureus*, 110 strains of *Haemophilus influenzae* and 50 *Moraxella catarrhalis* strains, all selected for their resistance phenotypes, and showed MIC_{90} values between 0.25 and

TABLE 4. Spectrum of metalloenzyme inhibition by actinonin (**36**) and BB-3497 (**37**)

Enzyme	IC_{50}, μM	
	Actinonin (**36**)	BB-3497 (**37**)
PDF	0.010	0.007
MMP-1[a]	1	2
MMP-2	3	15
MMP-3	6	>100
MMP-7	60% @ 100 μM	>100
Enkephalinase	7	50
ACE[b]	>100	>100

[a]MMP = matrix metalloproteinase. [b]ACE = angiotensin-converting enzyme.

TABLE 5. Antibacterial *in vitro* activity of actinonin (**36**) and BB-3497 (**37**)

Bacterial strain	MIC ($\mu g\,ml^{-1}$)	
	Actinonin (**36**)	BB-3497 (**37**)
S. aureus	32	4
MRSA	32	16
S. epidermidis	2	4
E. faecalis	64	32
E. faecalis (Van^r)[a]	128	8
S. pneumonia	32	8
H. influenza	2	0.25
E. coli	64	8
K. pneumonia	128	8
E. cloacae	>128	8
P. aeruginosa	128	128

[a]Van^r = vancomycin-resistant.

0.5 $\mu g\,ml^{-1}$ (depending on drug resistance phenotype) for *Streptococcus pneumoniae* strains, including penicillin-, erythromycin-, levofloxacin- and multidrug-resistant strains (Table 6)[78]. However, it showed weaker activity against *S. aureus* (MIC_{90} : 8 $\mu g\,ml^{-1}$) and *H. influenza* (MIC_{90}: 32–64 $\mu g\,ml^{-1}$). *In vivo*, BB-83698 (**39**) displayed oral, subcutaneous and intravenous (i.v.) efficacy against *S. pneumoniae* and *S. aureus* in peritoneal, lung and thigh infections in murine models[79].

LBM415 (**40**) (Figure 7) was the second formylhydroxylamine-based PDF inhibitor that entered clinical trials as antibacterial agent, the first for oral administration. LBM415 (**40**) carried, in addition to the *n*-butyl chain at P1′, a proline moiety at P2′ and a 2-amino-5-fluoropyridine *N*-oxide substituent at P3′. In *in vitro* assays, LBM415 (**40**) showed potent activity against a collection of Gram-positive species, clinical strains of staphylococci, streptococci, enterococci, *M. catarrhalis, Legionella pneumophila* and *H. influenzae*, without difference in activity against strains susceptible or resistant to other classes of antibiotics (Table 7)[80]. The *in vivo* efficacy of LBM415 (**40**) was evaluated in mice against systemic infections caused by *S. aureus* (wild-type and methicillin-resistant) and *S. pneumoniae* (wild-type and penicillin-resistant), as well as in a mouse thigh infection and a mouse pneumonia lung infection model[81].

TABLE 6. *In vitro* antibacterial activity of BB-83698 (**39**)

Bacterial strains (nr.)	MIC ($\mu g\,ml^{-1}$)		
	range	50%	90%
S. pneumoniae, penicillin-susceptible (91)	0.06-1	0.25	0.5
S. pneumoniae, penicillin-intermediate (47)	0.015-0.5	0.25	0.5
S. pneumoniae, penicillin-resistant (75)	0.12-0.5	0.25	0.25
S. pyogenes (21)	0.015-0.25	0.06	0.12
S. agalactiae (21)	0.03-0.12	0.06	0.12
Viridans streptococci (26)	0.03-1	0.12	0.5
S. aureus, oxacillin-susceptible (74)	1-32	4	8
S. aureus, oxacillin-resistant (80)	1-256	4	8
H. influenza, β-lactamase-negative (60)	0.25–128	8	32
H. influenza, β-lactamase-positive (50)	0.06–128	16	64
M. catarrhalis, β-lactamase-negative (25)	0.004-0.12	0.06	0.12
M. catarrhalis, β-lactamase-positive (25)	0.004-0.25	0.12	0.12

TABLE 7. *In vitro* antibacteral activity of LBM415 (**40**)

Bacterial strains (nr.)	MIC ($\mu g\,ml^{-1}$)		
	range	50%	90%
S. aureus, oxacillin-susceptible (53)	0.12-2	1	2
S. aureus, oxacillin-resistant (51)	0.25-2	0.5	2
CoNS, oxacillin-susceptible (10)	0.25-2	1	2
CoNS, oxacillin-resistant (39)	0.25-4	1	2
S. pneumoniae, penicillin-susceptible (65)	0.03-2	0.5	1
S. pneumoniae, penicillin-intermediate (52)	$\leq 0.016 - 1$	0.5	1
S. pneumoniae, penicillin-resistant (53)	0.06-1	0.25	0.5
β-Haemolytic streptococci (69)	0.06-4	0.5	1
Viridans group streptococci (81)	0.03–4	0.25	0.5
Enterococci, vancomycin-susceptible (74)	0.06–8	2	4
Enterococci, vancomycin-resistant (30)	0.25-8	2	4
H. influenzae, ampicillin-susceptible (170)	0.03–16	1	4
H. influenzae, ampicillin-resistant (130)	0.5–32	2	8
M. catarrhalis (103)	0.03-0.5	0.25	0.5
L. pneumophila (50)	$\leq 0.015 - 0.12$	0.12	0.12

The insertion of a proline moiety at P2′ was demonstrated to produce PDF inhibitors that, although not the most potent in terms of MIC, still provided sufficient antibacterial activity accompanied by a low cytotoxicity liability, and appreciable solubility, which may also result in good pharmacokinetic properties. Thus, several proline-containing compounds showing the hydroxamate moiety as a pharmacophore (such as VRC3375 (**41**), VRC4232 (**42**) and VRC4307 (**43**), Figure 7) were synthesized and tested. VRC3375 (**41**) was equally potent in inhibiting the growth of drug-susceptible and -resistant bacteria such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci, and showed modest *in vivo* efficacy in a mouse *S. aureus* septicemia infection model without any toxicity[82]. VRC4232 (**42**) and VRC4307 (**43**) carried an aminocarbonylproline scaffold joined to a *N*-alkylurea lipophilic substituent at P1′ and to the hydroxamate function. VRC4232 (**42**) and VRC4307 (**43**) exerted bactericidal activity against *S. pneumoniae* and

TABLE 8. *In vitro* antibacterial activity of VRC4232 (**42**) and VRC4307 (**43**)

Bacterial strains (nr.)	MIC ($\mu g\,ml^{-1}$)	
	VRC4232 (**42**)	VRC4307 (**43**)
S. aureus (3)	0.25-1	0.5-1
S. pneumoniae (3)	1-4	1
E. faecium (2)	8	2-4
H. influenzae (3)	2-4	2-4
M. catarrhalis (1)	0.06	0.06
E. coli (1)	>64	64
E. coli acr[a] (1)	0.125	0.25
C. albicans (2)	>256	>256

[a]*E. coli acr* mutant that lacks the Acr efflux pump.

H. influenza and bacteriostatic effect against *S. aureus* (Table 8)[83]. Against *H. influenza*, neither compound displayed a significant degree of inhibition over the initial hours of the experiments, but showed significant death of this species by 24 h of drug exposure. In a *S. aureus* septicemia model, both compounds showed moderate protective activity after s.c. but not p.o. administration[83]. Another chemical modification fully compatible with the anti-PDF and antibacterial activity of PDF inhibitors is to link the lipophilic P1′ substituent to the P3′ one: thus various series of macrocyclic peptidyl formylhydroxylamines (such as **42**[84]) and hydroxamates (such as **43**–**45**[85]) were prepared, incorporating or not a proline moiety at P2′. Some of these compounds showed potent inhibition of *E. coli* PDF and bactericidal activity against Gram-positive bacteria.

B. Targeting UDP-3-*O*-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine Deacetylase (LpxC)

The outer membrane of Gram-negative bacteria is formed by charged lipopolysaccharide (LPS) molecules[86] that serve a barrier to prevent entry of hydrophobic agents into the cell and to protect the bacterium from many antibiotics, such as erythromycin, vancomycin and linezolid[87,88]. Lipid A, the hydrophobic anchor of LPS, is essential for bacterial growth and viability[89,90], and is synthesized in a 10-step pathway (Figure 8). The first committed step (second overall step) is the deacetylation of UDP-3-*O*-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine by LpxC, a zinc-dependent UDP-3-*O*-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine deacetylase[91–94] that has been proposed to act through either single acid–base metalloprotease-like (Scheme 2A) or dual acid–base mechanistic models (Scheme 2B)[95–97]. Inhibition of LpxC *in vivo* leads to diminished production of lipid A and, in many cases, to decreased viability of Gram-negative bacteria. Thus, the development of LpxC inhibitors opened a new avenue for the discovery of novel antibacterial agents.

The first synthetic small-molecule inhibitors of LpxC were reported in 1996 by Onishi and coworkers[98]. The prototype L-573,655 (**46**) (Figure 9) was characterized by a 2-phenyloxazoline ring substituted at the C4 position with a hydroxamate function. The oxazoline at C4 shows a chiral center, and its *R* configuration is preferred for LpxC inhibiting activity. Structure–activity relationship performed on the 2-phenyloxazolinyl-4-hydroxamate scaffold showed that the system can be decorated by methoxy or other electron-donating groups to enhance potency. Optimization of the series resulted in L-161,240 (**47**) (Figure 9), a potent inhibitor of *E. coli* LpxC ($K_i = 53$ nM) that also inhibited

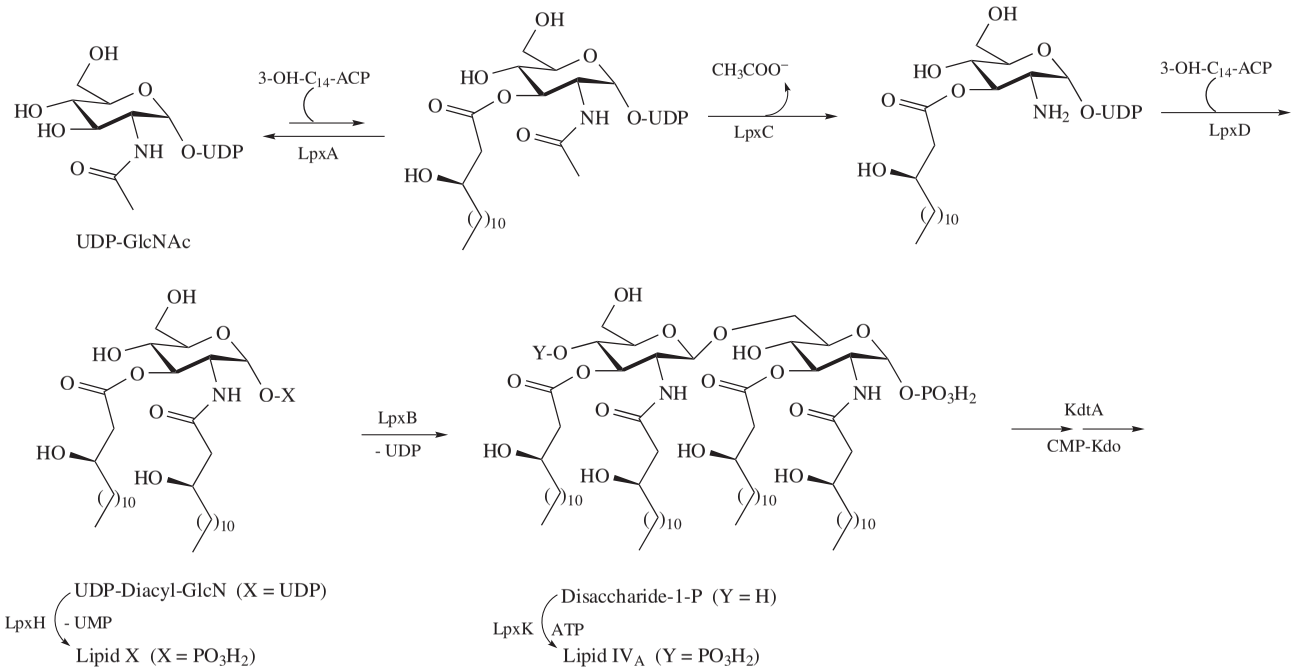


FIGURE 8. The pathway for biosynthesis of lipid A in *E. coli* and integration into outer membrane

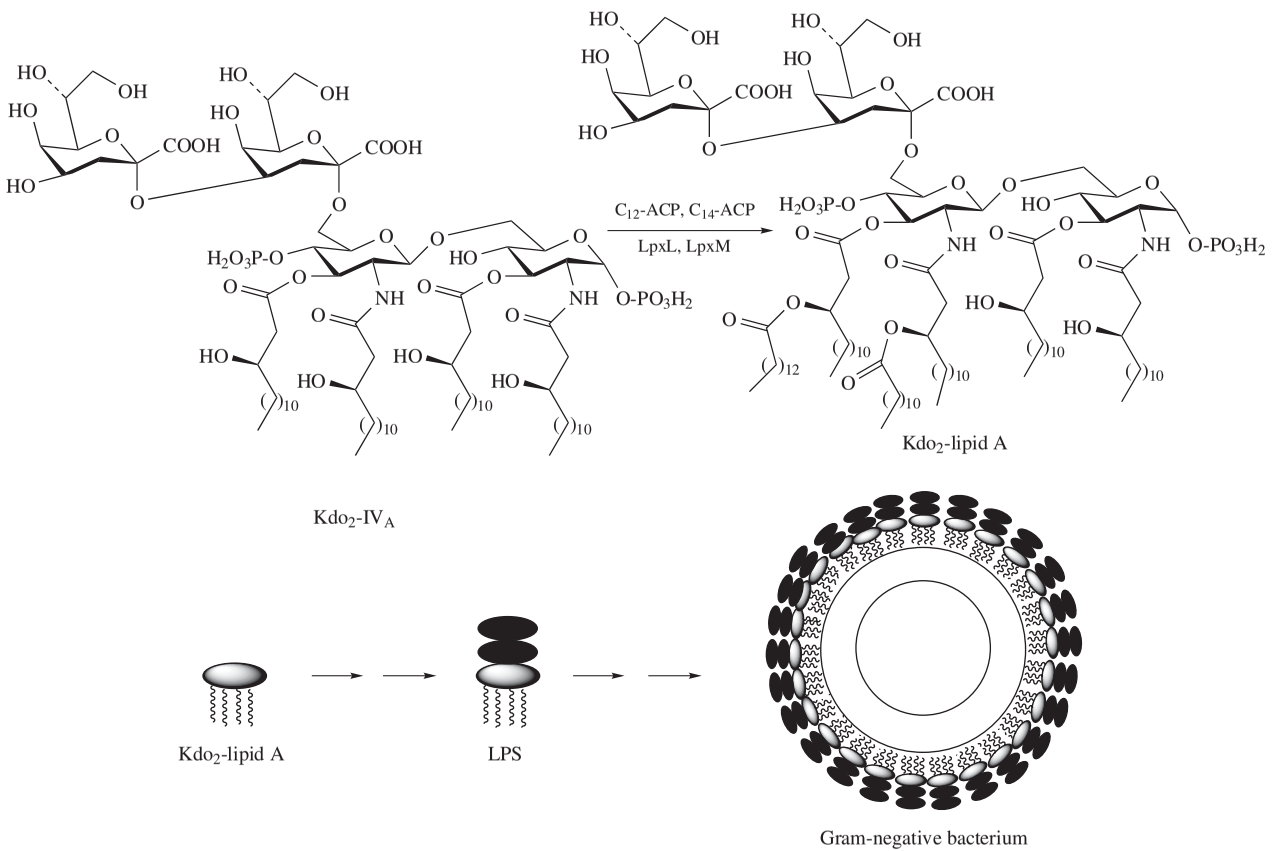
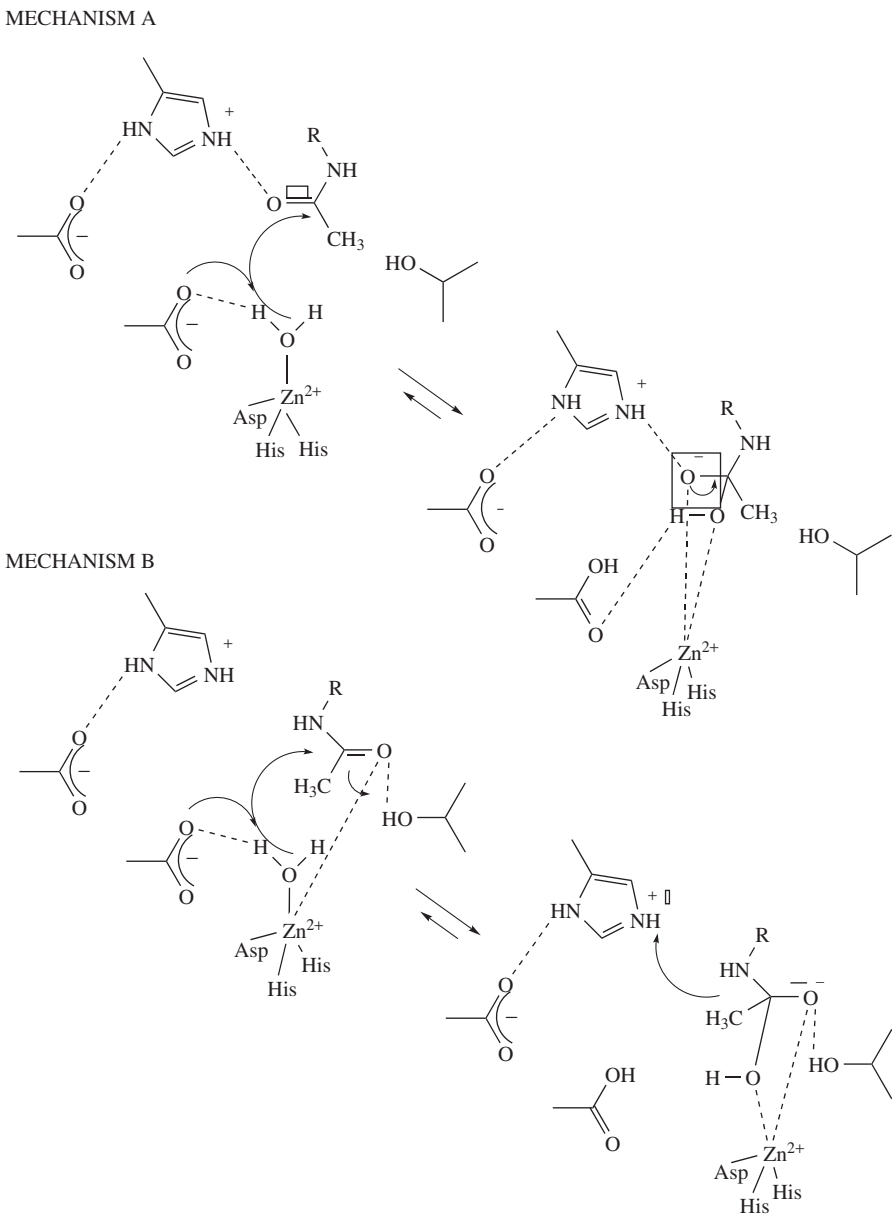


FIGURE 8. (*continued*)



SCHEME 2. Proposed catalytic mechanisms for LpxC

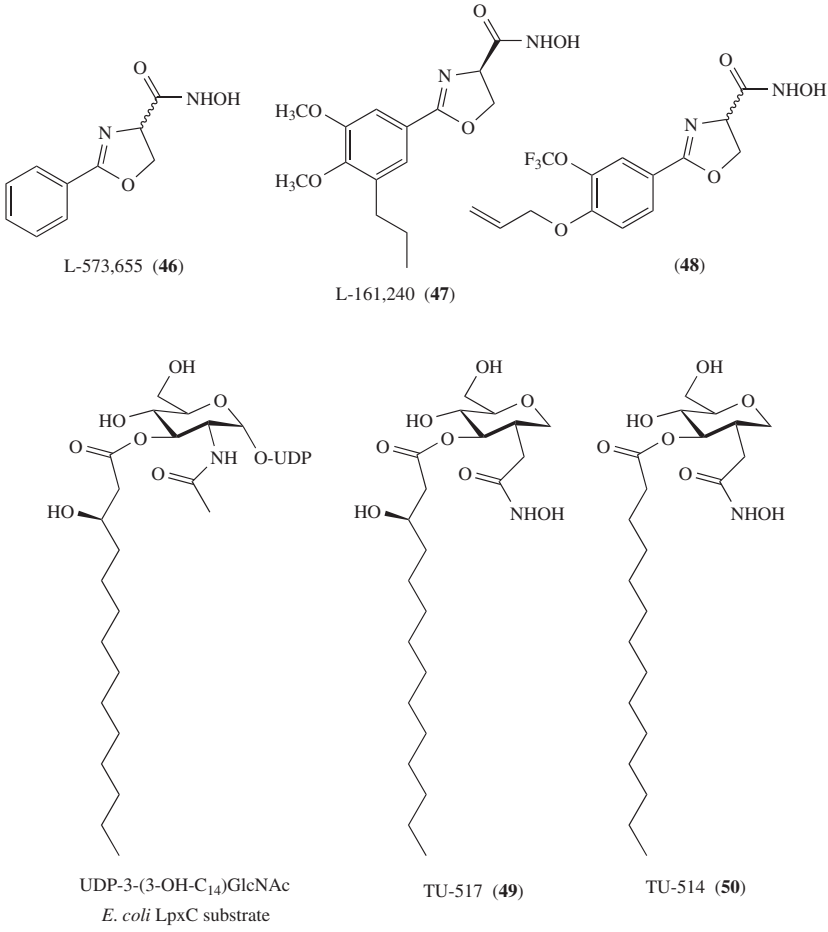
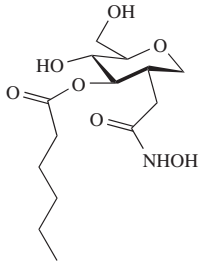


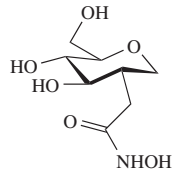
FIGURE 9. LpxC inhibitors

the growth of the bacterium (MIC = 1 μg ml^{-1}). However, this compound had no effect on the growth of *P. aeruginosa* or *Serratia* (MIC >50 μg ml^{-1}), and showed 50- to 100-fold weaker *in vitro* activity toward the *P. aeruginosa* LpxC[98], thus it was not developed further as antibacterial drug.

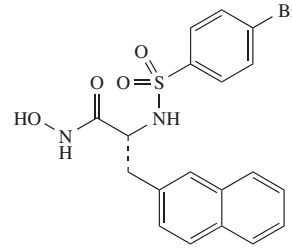
Further studies on analogues of **47** led to the discovery of some polyfluoroalkyl-substituted hydroxamates (such as **48**, Figure 9) highly active (IC_{50} <1 μM) against *P. aeruginosa in vitro*[99]. A number of analogues of this prototype have been synthesized and tested, by changing the oxazoline moiety with an isooxazoline, thiazoline, oxazine or serine group, or by replacing the hydroxamate function with other zinc ion chelating groups (thiols, β-hydroxythiols, sulfones, sulfonamides, hydrazine, formylhydrazine, phosphinic acids, heterocyclic amines)[99, 100]. Nevertheless, all these compounds showed less potency against the enzyme or lower efficacy against bacterial strains with respect to the oxazolinyl hydroxamates.



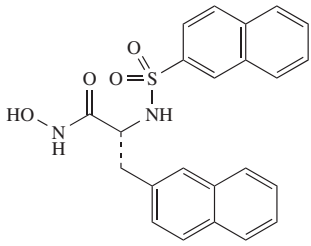
TU-521 (**51**)



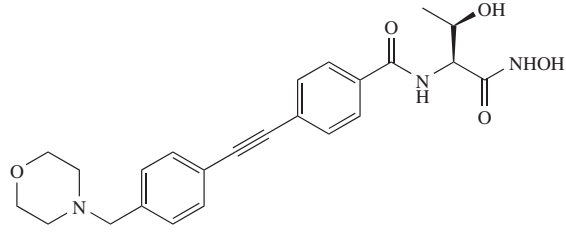
TU-519 (**52**)



BB-78484 (**53**)



BB-78485 (**54**)



CHIR-090 (**55**)

FIGURE 9. (*continued*)

A series of substrate-based hydroxamates has been disclosed (TU-517 (**49**), TU-514 (**50**), TU-521 (**51**), TU-519 (**52**), Figure 9), designed on the UDP-3-(3-OH-C_{14})GlcNAc structure (see Figure 9) and having different range of activity against *E. coli* and *Aquifex aeolicus* LpxC (Table 9)[101]. In particular, TU-517 (**49**) and TU-514 (**50**), bearing the 3-hydroxymyristoyl (3-OH-C_{14}) chain linked to the glucose scaffold, displayed high inhibitory activity against the two LpxC enzymes with IC_{50} values in the low micromolar range (Table 9). The analogue TU-521 (**51**), with a shorter (6-carbon units) acyl chain, was active only against *E. coli* LpxC similarly to the oxazolinyl hydroxamate L-161,240 (**47**), and TU-519 (**52**) lacking the acyl chain was totally inactive against both enzymes. Nevertheless, despite their high LpxC inhibiting activity TU-517 (**49**) and TU-514 (**50**)

TABLE 9. Inhibition of *E. coli* and *A. aeolicus* LpxC by substrate analogues

Compound	IC_{50}, (μM)	
	E. coli LpxC	*A. aeolicus* LpxC
TU-514 (**49**)	7.2	7.0
TU-517 (**50**)	2.0	18.1
TU-521 (**51**)	41	>3100
TU-519 (**52**)	>4500	>4500
L-161,240 (**47**)	50	>5000

TABLE 10. *In vitro* antibacterial activity of BB-78484 (**53**) and BB-78485 (**54**)

Bacterial strain	MIC ($\mu g\,ml^{-1}$)	
	BB-78484 (**53**)	BB-78485 (**54**)
E. coli	2	1
K. pneumoniae	4	2
E. cloacae	32	4
P. aeruginosa	>32	>32
P. aeruginosa C53[a]	>32	4
M. morganii	8	4
H. influenzae	>32	4
M. catarrhalis	>32	4
B. cepacia	16	1
S. marcescens	2	1
S. aureus	>32	32
S. epidermidis	>32	>32
M. luteus	>32	>32

[a] *P. aeruginosa* semipermeable strain.

failed in inhibiting *E. coli* growth, maybe because they are prevented from entering cells, or metabolized, or extruded.

Using the screening of a proprietary metalloenzyme inhibitor library, a series of sulfonamide derivatives of the α-(*R*)-amino hydroxamic acid, exemplified by BB-78484 (**53**) and BB-78485 (**54**), has been reported having potent inhibitory activity against *E. coli* LpxC in an *in vitro* assay (IC_{50} values: 400 (**53**) and 160 (**54**) nM), and antibacterial activity against a wider panel of Gram-negative pathogens including *Enterobacteriaceae, H. influenzae, Serratia marcescens, Morganella morganii, M. catarrhalis* and *Burkholderia cepacia* (Table 10)[102]. Although no antibacterial activity was seen against wild-type *P. aeruginosa*, some activity of BB-78485 (**54**) was reported for a semipermeable *P. aeruginosa* bacterial strain (C53), suggesting that the limiting factor for the potency of these inhibitors could be the ability to reach the target, rather than the lack of LpxC inhibitory activity.

Novel small molecules targeting *P. aeruginosa* were discovered by using a threonine hydroxamate scaffold, in which the amino group was acylated with aroyl moiety (lead compound: CHIR-090 (**55**), Figure 9)[103–105]. CHIR-090 (**55**) potently (75% or more by 4 nM CHIR-090) inhibited a diverse range of LpxC orthologs from diverse

TABLE 11. *In vitro* antibacterial activity of CHIR-090 (**55**)

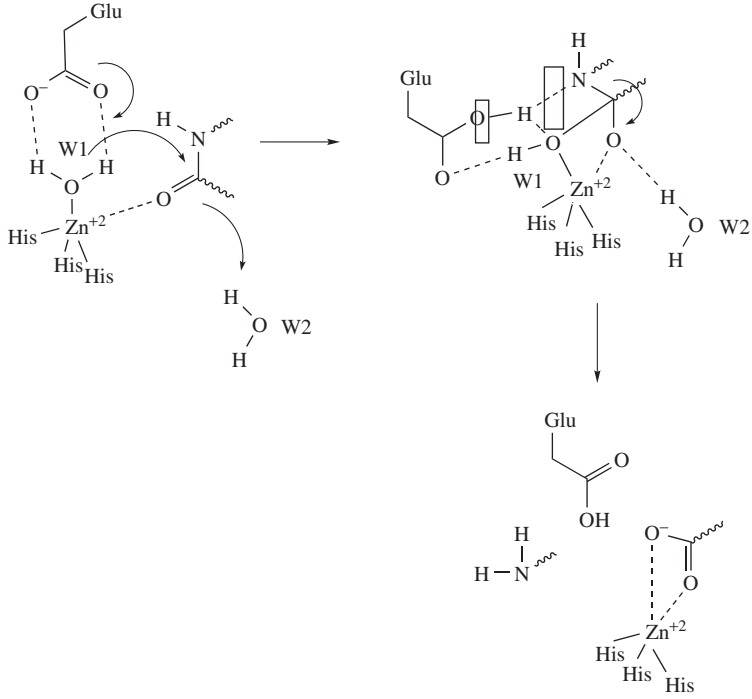
Compound	mm killing[a]		
	E. coli	*E. coli* G17S[b]	*P. aeruginosa*
CHIR-090 (**55**)	36	38	34
TU-514 (**50**)	<6	<6	<6
L-161,240 (**47**)	19	30	<6
Ciprofloxacin	35	37	40
Tobramycin	26	28	24

[a]Halo of killing after overnight incubation at 37 °C. [b]Partially-inactivated LpxC mutant G17S *E. coli* strain, hypersusceptible to LpxC inhibitors.

Gram-negative pathogens, including *E. coli, P. aeruginosa, Neisseria meningitidis* and *Helicobacter pylori*, generally by a two-step, slow, tight-binding mechanism. In antibacterial assays, CHIR-090 (**55**) showed remarkable growth-inhibiting activity against *E. coli* and *P. aeruginosa*, comparable to ciprofloxacin or tobramycin (Table 11). Structural studies have been performed on the complexes between LpxC and the substrate analogue TU-514 (**50**)[106] as well as the small molecule inhibitors BB-78485 (**54**)[107] and CHIR-090 (**55**)[105], thus obtaining a number of interaction information that can be useful for the design of new more potent, broad-spectrum inhibitors.

V. HYDROXAMATES AS INHIBITORS OF MATRIX METALLOPROTEINASES AND TNF-α CONVERTING ENZYME (TACE)

Protease enzymes play key roles in many physiological as well as pathological processes, such as protein degradation/digestion, blood coagulation, protein (i.e. antigens, peptide hormones, cytokines, chemokines, growth factors, transcription factors) processing, cell surface molecule shedding, and apoptosis. Among protease enzymes, matrix metalloproteinases (MMPs) form a large family of calcium- and zinc-containing endopeptidases that have a role in extracellular matrix (ECM) degradation, regulation of cell environment and cell behavior[108, 109]. Their mechanism of catalysis, originating from crystallographic studies for the hydrolysis by thermolysine, can be generalized to the whole MMP class[110].



SCHEME 3. Catalytic mechanism of MMPs

It starts from a reactant complex, in which the zinc ion is chelated by three His (His201, His205 and His211) residues, and is coordinated with a conserved Glu residue (Glu202) through a water molecule (W1) (Scheme 3). When the substrate makes contacts with the reactant complex (that is, the zinc ion) through an auxiliary water molecule (W2), the oxygen of the W1 performs a nucleophilic attack on the peptide carbon, generating a *gem*-diolate intermediate bidentately coordinated to the zinc ion. Concertedly, Glu202 abstracts the proton from the W1 oxygen and shuttles it toward the nitrogen of the scissile amide. After a second extraction of a proton from the W1 oxygen, mediated by the same Glu202, the final breakdown of the amide bond occurs (Scheme 3).

The activity of MMPs is regulated by α_2-macroglobulin and endogenous tissue inhibitors of metalloproteinases (TIMPs)[111–114]. When the balance between MMPs and their endogenous inhibitors is altered, such as after specific stimuli like cytokines and growth factors, an overregulation of MMPs occurs leading to chronic activation of MMPs and excessive degradation of ECM components, which are believed to contribute to numerous pathological conditions. To date 26 MMPs have been described (Table 12). They are grouped into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs) and others, according to their domain organization and substrate preference[115]. As many other proteases, MMPs are produced as inactive forms (zymogens), and are activated after their release from cells. The basic structure of MMPs consists of a zinc-containing catalytic domain of about 170 amino acids linked, in the zymogen form, to a pro-peptide of about 80 amino acids which prevents the binding of the substrate. After activation and cleavage of pro-peptide, the substrate is

TABLE 12. Overview of MMPs

Class	MMP no.	Alternative name
Collagenases	MMP-1	Collagenase-1
	MMP-8	Neutrophil collagenase
	MMP-13	Collagenase-3
	MMP-18	Collagenase-4
Gelatinases	MMP-2	Gelatinase-A
	MMP-9	Gelatinase-B
Stromelysins	MMP-3	Stromelysin-1
	MMP-10	Stromelysin-2
	MMP-11	Stromelysin-3
	MMP-27	51.6% homolog to stromelysin-2
Matrilysins	MMP-7	Matrilysin PU MP
	MMP-26	Matrilysin-2
Membrane type (MT-MMPs)	MMP-14	MT1-MMP
	MMP-15	MT2-MMP
	MMP-16	MT3-MMP
	MMP-17	MT4-MMP
	MMP-24	MT5-MMP
	MMP-25	MT6-MMP
Others	MMP-12	Macrophage metalloelastase
	MMP-19	RASI 1
	MMP-20	Enamelysin
	MMP-21	Identified on chromosome 1
	MMP-22	Identified on chromosome 1
	MMP-23	From human ovary cDNA
	MMP-28	Epilysin
	MMP-29	unnamed

free to interact with the catalytic site. Next to the catalytic site, most MMPs contain a linker peptide of variable length and a hemopexin domain of about 200 amino acids. MMP-7, MMP-26 and MMP-23 are exceptions because they lack the linker peptide and the hemopexin domain. Such a modular structure allows MMPs to specifically interact with their endogenous inhibitors (α_2-macroglobulin and TIMPs)[116].

Physiologically, MMPs are involved in many stages of mammalian development, from embryonic implantation to morphogenesis of new tissues, as well as in cell growth, wound healing, angiogenesis, ovulation and nerve growth processes[117–119]. Pathologically, MMPs are implicated in many diseases such as cancer, angiogenesis, skin ulceration, pulmonary emphysema, periodontal disease, atherosclerosis, osteoarthritis, rheumatoid arthritis, multiple sclerosis and central nervous system diseases[120–124]. In particular, in cancer MMPs drive the process of tumor invasion through degradation of ECM, basement membranes, basal laminae and interstitial stroma, thus allowing invasive cells to migrate into adjacent tissues[125, 126].

Typically, MMPs are absent in normal adult cells, but a variety of stimuli, such as cytokines, growth factors and alterations in cell–cell and cell–ECM interactions can induce their expression, that is normally localized to stromal cells surrounding malignant cancer cells. MMPs can contribute to tumor progression not only through degradation of ECM but also through release of sequestered growth factors or production of bioactive fragments, such as the vascular endothelium growth factor (VEGF), released by MMP-9 from ECM[127]. MMP-1 and MMP-2 have been shown to mediate breast cancer metastasis to lungs in human patients[128], and MMP-12, MMP-13 and cathepsin K were upregulated in human lung tumors[129]. The sixth member of MT-MMP, MMP-25, is expressed at high levels in brain tumors and colon carcinoma cells but not in normal brain or colon[130, 131]. In contrast, MMP-26 is widely expressed in cancer cells of epithelial origin[132].

One of the most recently discovered members of MMPs is MMP-28. Structurally, it is relatively similar to MMP-19 and is overexpressed in testis and keratinocytes as well as in carcinomas[133]. Despite these findings, sometimes MMPs seemed to play a protective role in cancer development. Indeed, after chemical carcinogenic treatment *Mmp8*-null and *Mmp9*-null mice developed a greater number of skin papillomas and more aggressive skin tumors, respectively[134, 135]. Accordingly, a distinction has been made between target MMPs (MMP-1, MMP-2, MMP-7, MMP-11 should be further validated), that unambiguously contribute to cancer initiation or progression, and anti-target MMPs (MMP-3, MMP-8, MMP-9, with MMP-12 and MMP-14 that should be further validated), that play essential roles in normal cells, and when downregulated give clinically unacceptable side effects, initiation of disease, or severe alterations in disease progression. Also in vascular diseases the concept of bad and good MMPs can be invoked, but in this case the existing data from animal model studies are not clear[115].

In arthritis patients the balance between joint destruction and homeostasis is altered. Current pharmacotherapy, including the administration of non-steroidal anti-inflammatory drugs or steroids, alleviates the mild-to-moderate pain and inflammation that are associated with osteoarthritis (OA). However, such agents do not protect the articular cartilage and have not demonstrated utility in modifying disease progression, allowing the disease to progress into irreversible ECM loss and chronic disability. Therefore, there is great interest in identifying and characterizing the proteases responsible for cartilage degradation as potential targets in the development of therapeutics that prevent joint destruction in arthritis.

A typical feature of both rheumatoid arthritis (RA), an autoimmune disease accompanied by inflammation, and OA, an age-related disorder characterized by degradation of the cartilaginous matrix, is an overexpression of MMPs. Some of them are involved in many tissues while others are specific joint components like cartilage or bone. For arthritis

therapy, after many years of researches most MMPs have been excluded as valuable therapeutic targets, with the exception of MMP-13 and aggrecanase, an enzyme structurally related to MMPs that catalyze the aggrecan degradation[136, 137]. MMP-13 has been found to play a key role in the connective tissue destruction in OA[138]. MMP-13 catalyzes the degradation the type II collagen, the fundamental constituent of articular cartilage, as its primary substrate, and is the most efficient among MMPs in this degradation activity. To further validate MMP-13 as a valuable target for OA, MMP-13 has been found overexpressed in the synovial fluid of OA patients. Inhibition of MMP-13 therefore seems to be a critical goal for the treatment of OA, and although modulation is possible at several biochemical sites, direct inhibition of enzyme action by small molecules that selectively bind to the active site of the enzyme is an attractive goal for therapeutic intervention.

Aggrecan, one of the major ECM components of cartilage, is a large proteoglycan that provides cartilage with the ability to resist compressive forces[139, 140]. Aggrecan fills the interstices of the collagen meshwork by forming large aggregated complexes interacting with hyaluronan and link proteins. The high negative-charge density of the glycosaminoglycan (GAG) chains on aggrecan monomers, with the associated water molecules, is essential so that articular cartilage withstands compressive deformation during joint articulation. Degradation of aggrecan is an important manifestation of OA, and its depletion in osteoarthritic cartilage can be ascribed to increased proteolytic cleavage of the core protein and is mediated by aggrecanases[141, 142]. Two recently identified aggrecanase isoforms (ADAMTS-4 and ADAMTS-5) are members of the 'A Disintegrin And Metalloproteinase with ThromboSpondin motifs' (ADAMTS) gene family[143, 144], and there has been much interest in the possible role of these isoforms as therapeutic targets in OA[145, 146].

Also, tumor necrosis factor-α (TNF-α) converting enzyme (TACE), a non-MMP zinc-containing enzyme which cleaves a membrane-bound protein (pro-TNF-α) releasing to the circulation TNF-α, a 17-kDa pro-inflammatory and immunomodulatory cytokine, is an attractive target for arthritis therapy[147, 148]. TNF-α and its receptors are overexpressed in the synovium and cartilage-pannus junction of RA joints, and it plays a key signaling role not only in arthritis and RA but also in other inflammatory diseases such as multiple sclerosis and Crohn's disease, it being also involved in regulation of inflammatory mediators such as prostaglandins and leukotrienes.

The earliest MMP inhibitors (MMPi) were built according to the amino acid sequence (Gly:Ile and Gly:Leu) of human triple helical collagen at the site of cleavage by MMP-1 (Figure 10), and subsequently using information derived from substrate specificity studies. The most important feature of these substrate-based inhibitors is the zinc binding group (ZBG): the hydroxamate moiety proved to be the most effective ligand to enhance the potency of MMPi, the ranking being hydroxamate $\gg$ formylhydroxylamine > sulfhydryl > phosphinate > aminocarboxylate > carboxylate[149]. The hydroxamate acts as a bidentate ligand with each oxygen at an optimal distance (1.9–2.3 Å) from the active-site zinc ion, the hydroxamate nitrogen being protonated and forming a hydrogen bond with a carbonyl oxygen of the enzyme backbone.

Three classes of substrate-based MMPi have been developed: those in which the ZBG is flanked on both sides by amino acid residues (P1, P2 and P3 on the left and P1′, P2′ and P3′ on the right, corresponding to the enzyme subsites S1–S3 and S1′–S3′, respectively), and those in which the amino acid residues are present on only the left-site (L-S) or the right-site (R-S) of the ZBG. In general, compounds built on the R-S (P1′–P3′) of the active site linked to a hydroxamate moiety as ZBG exhibited particularly potent MMP inhibition, whereas the corresponding L-S (P1-P3) compounds were only weakly potent MMPi.

An example of this last series of inhibitors is **56** (Figure 11), endowed with only micromolar activity against MMP1-3[150, 151]. R-S inhibitors normally show MMP inhibiting activity in the nanomolar range, and received much more attention. Early studies performed on R-S inhibitors showed that succinyl hydroxamates are more potent against

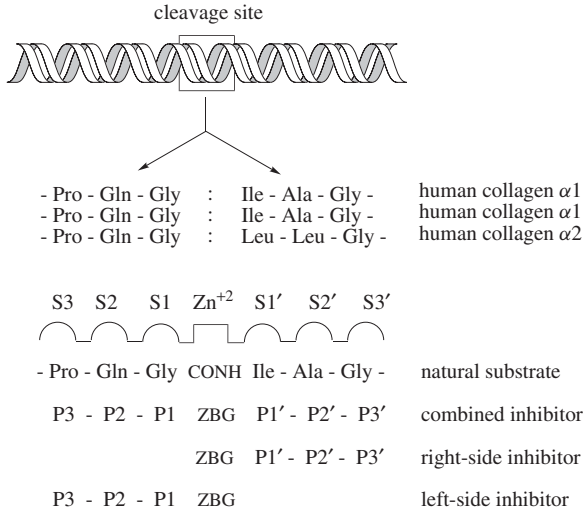
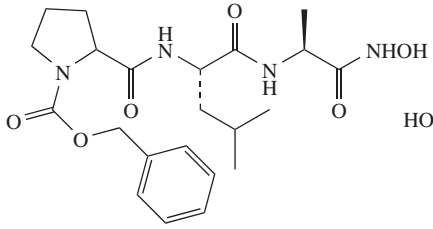


FIGURE 10. Design of MMPi based on the sequence of human collagen at the site of cleavage by MMP-1

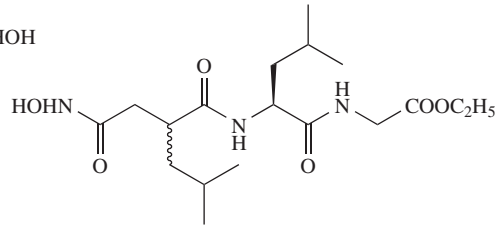
MMP-1 than the corresponding malonyl and glutaryl analogues (compare, for example, **57** with **58** and **59**, Figure 11)[152]. Given the general structure for succinyl hydroxamates HOHNCOCH(Rα)CH(R^1)CONHCH(R^2)CONHR^3, in which the substituent Rα (P1 substituent) is immediately near to the hydroxamate function and interacts with the S1 subsite of the enzymes, and R^1, R^2 and R^3 correspond to the P1′, P2′ and P3′ substituents of the inhibitors interacting with the S1′, S2′ and S3′ subsites, respectively, a lot of work was conducted to elucidate the structure–activity relationship (SAR) required for the highest inhibiting activity. The insertion of a Rα substituent at the succinyl hydroxamate scaffold generally improves the MMP inhibiting activity of the derivatives. A beneficial effect is conferred by both lipophilic and polar substituents, the last being able to make hydrogen bonds. Typical examples are batimastat (**60**)[153–155], in which Rα is a 2-thienylthiomethyl substituent, Ro 32–0554 (**61**) with a phthalimidomethyl group at Rα, and marimastat (**62**)[156], substituted with an hydroxyl group at Rα (Figure 11). All these are highly potent, broad-spectrum inhibitors of MMPs, active at nanomolar range. Marimastat (**62**) is the only orally available, in part because of the increase in aqueous solubility due to the α-hydroxy group. Certain substituents at Rα such as allyl (see BB-1101 (**63**)) and 2-thienylsulfonylmethyl (see **64**) improve the activity of the derivatives against TACE (Figure 11). This dual activity is beneficial in diseases involving both inflammation and ECM remodeling, and indeed BB-1101 (**63**) has been tested in animal models of arthritis and multiple sclerosis[157–159].

Also, the introduction of a cyclopentyl substituent at Rα led to compounds (e.g. **65**) highly active against MMPs and TACE and endowed with oral availability (Figure 11)[160]. X-ray crystal structure of batimastat (**60**) complexed with MMP-8 showed that the α-2-thienylthiomethyl as well as the Phe side chain at P2′ of the inhibitor point away from the enzyme[161]. Thus, it seemed reasonable to join the P1 (α position) and P2′ substituents together to obtain a cyclic inhibitor. Indeed, compound **66** possesses similar potency and improved water solubility to uncyclized analogues (Figure 11)[161]. The S1′ subsite is a deep pocket for the majority of MMPs (such as MMP-2, MMP-3, MMP-8), but is occluded



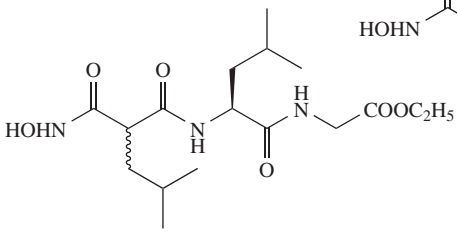
(**56**)

IC_{50} MMP-1 = 8 μM
MMP-2 = 8 μM
MMP-3 = 3.5 μM



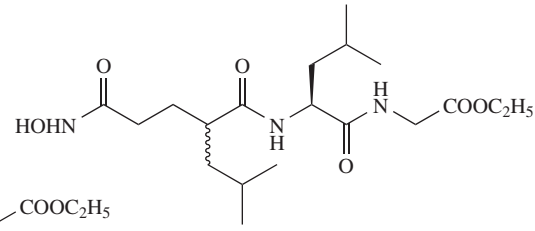
(**57**)

IC_{50} MMP-1 = 0.04 μM



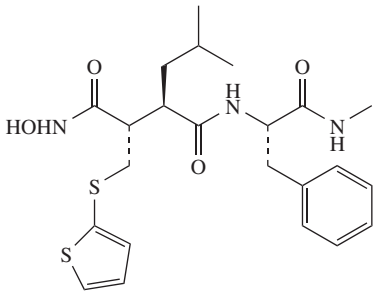
(**58**)

IC_{50} MMP-1 = 29 μM



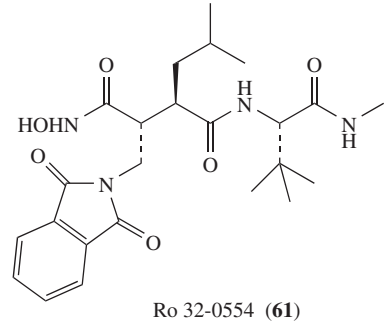
(**59**)

IC_{50} MMP-1 = >10 μM



batimastat (**60**)

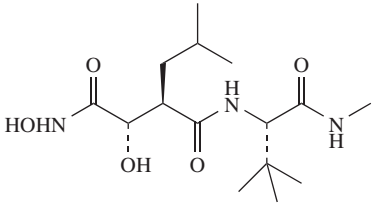
IC_{50} MMP-1 = 10 nM
MMP-2 = 4 nM
MMP-3 = 20 nM
MMP-8 = 10 nM
MMP-9 = 1 nM
MMP-14 = 3 nM



Ro 32-0554 (**61**)

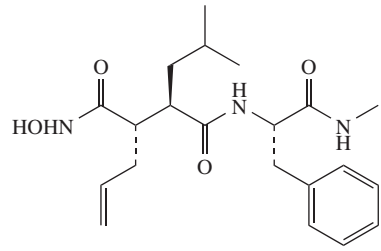
IC_{50} MMP-1 = 0.5 nM
MMP-3 = 9.1 nM
MMP-9 = 4.3 nM

FIGURE 11. MMP inhibitors



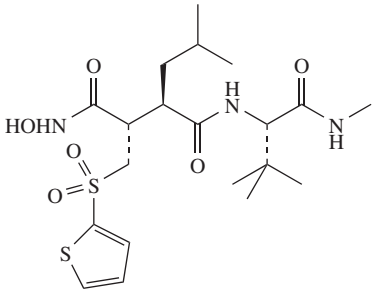
marimastat (**62**)

IC_{50} MMP-1 = 5 nM
MMP-2 = 6 nM
MMP-3 = 200 nM
MMP-7 = 20 nM
MMP-8 = 2 nM
MMP-9 = 3 nM
MMP-14 = 1.8 nM
TACE = 3800 nM



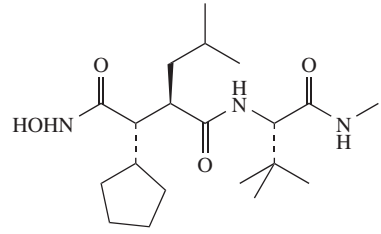
BB-1101 (**63**)

IC_{50} MMP-1 = 10 nM
MMP-2 = 5 nM
MMP-3 = 30 nM
MMP-8 = 3 nM
MMP-9 = 3 nM
TACE = 550 nM



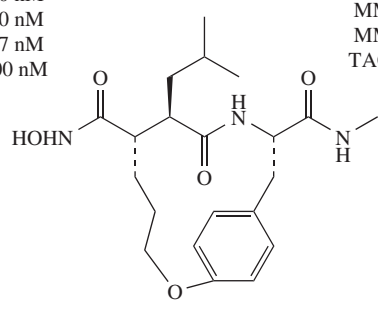
(**64**)

IC_{50} MMP-1 = 2 nM
MMP-2 = 20 nM
MMP-3 = 30 nM
MMP-7 = 20 nM
MMP-9 = 7 nM
TACE = 800 nM



(**65**)

IC_{50} MMP-1 = 4 nM
MMP-2 = 3 nM
MMP-3 = 30 nM
MMP-7 = 20 nM
MMP-8 = 20 nM
MMP-9 = 9 nM
TACE = 900 nM



(**66**)

K_i MMP-1 = 1.2 nM
MMP-3 = 32.7 nM
MMP-9 = 1.8 nM
TACE = 1200 nM

FIGURE 11. (*continued*)

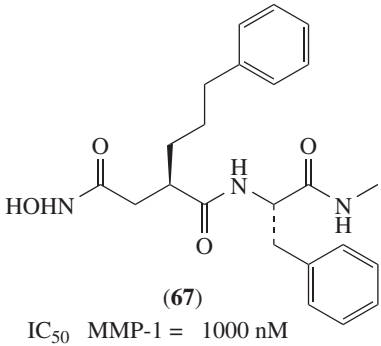
for a few MMPs (such as MMP-1 and MMP-7)[162]. Thus, the introduction of opportune, large substituents at the P1′ position (interacting with the S1′ pocket) seems to be crucial for the development of isoform-selective MMPi.

One of the first deep pocket selective MMPi is **67**, bearing a 3-phenylpropyl substituent at P1′, and showing high potency against MMP-2, -8, -9 and (to a lesser extent) MMP-3 over MMP-1 and -7[162]. An extended alkyl or arylalkyl group at P1′ provided deep pocket selectivity (high activity against MMP-2, -3, -8 and -9, and scarce inhibitory activity against MMP-1 and MMP-7): see, for example, the activity profiles of **68–71**, carrying a C_9 alkyl, C_{16} alkyl, benzyloxybutyl and 4-chloro-4-biphenylpropynyl chain at P1′ (Figure 12)[163–166]. Nevertheless, in some cases (see, for example, **72** and **73**, in which the P1′ substituent is a C_{10} alkyl or a phenoxybutyl chain) the S1′ subsite can undergo conformational changes to accommodate a few extended P1′ substituents, thus leading to compounds with high activity against MMP-1 (Figure 12)[164–166]. With respect to the S2′ subsite, X-ray crystallographic studies on MMP-inhibitor complexes showed that the P2′ substituent of succinyl hydroxamates points out of the enzyme, making only few contacts with S2′[167]. Thus, modification at the P2′ position has little influence on the potency of the compounds, but it could be very important for their pharmacokinetic properties. In particular, the insertion at the P2′ level of a sterically bulky group such as a *tert*-butyl or a phenyl group (see, for example, marimastat (**62**), Ro 31-9790 (**74**), CT1746 (**75**) and KB-R7785 (**76**)[168, 169]) can shield the adjacent amide bond leading to reduced hydration and more facile desolvation of the peptide backbone, and resulting in a conformational effect that preorganizes the compound to binding into the active site of the enzyme (Figure 12)[170].

As a beneficial outcome, all the cited compounds are orally available. Truncated P2′–P3′ analogues, in which the succinyl hydroxamate moiety directly ends with a tertiary amide (morpholide or piperidide), joined to the presence of a cyclic imide-containing group at Rα (P1 position), displayed high selective inhibitory activity against collagenases (MMP-1, -8 and -13) (see compounds **77** and Ro 32–3555 (**78**), Figure 13[171–173]), and when a sulfonamide moiety is inserted at Rα (compound **79**), a strict selectivity toward MMP-1 over other MMPs was obtained. Replacement of P2′–P3′ moiety with a sulfonylhydrazino group led to a potent and selective TACE inhibitor (compound Ro 32–7315 (**80**)) selected for clinical development[174]. *N*-Sulfonylaminoacyl hydroxamates such as CGS 27023A (**81**) and CGS 25966 (**82**) (Figure 13) behave as broad-spectrum MMPi, **81** being also orally available[175–177].

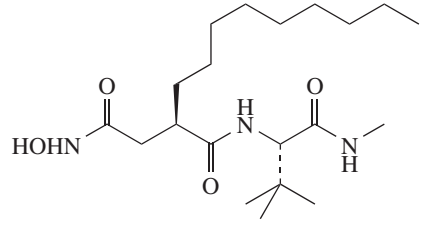
X-ray crystallographic studies performed on **82** and MMP-1 showed that the 4-methoxyphenyl group of **82** resides in the S1′ pocket of the enzyme, the *N*-benzyl substituent lies in the S2′ pocket and the isopropyl group is located in the S1 subsite of MMP-1[167]. In addition, the isopropyl group is relatively close to the *N*-benzyl substituent, this suggesting to prepare compounds like prinomastat (**83**) (Figure 13), in which the isopropyl substituent at P1 is partially cycled, together with the nitrogen of the sulfonamide group, through the introduction of a substituted thiomorpholine moiety[178]. Compound **83** was widely studied in animal models of cancer growth and metastasis and it revealed high activity and a good oral bioavailability in rats[179–182]. In addition to sulfonamido hydroxamates, also sulfone hydroxamates were developed as MMPi, such as, for example, **84** (Figure 13) which displayed both MMP and phosphodiesterase type 4 (PDE4) inhibitory activity[183].

Such combined type of action can be useful in the treatment of inflammatory diseases, since inhibition of PDE4 results in increased intracellular concentration of cyclic AMP that in turn gives an anti-inflammatory effect. Two sulfone hydroxamates, RS-113,456 (**85**) and RS-130,830 (**86**) (Figure 13), were described bearing a cyclic pyrano moiety at the β,β- or α,α-position to the hydroxamate function, respectively[184, 185]. Among the two compounds, **85** showed the highest MMP inhibitory activity, while **86** was less potent



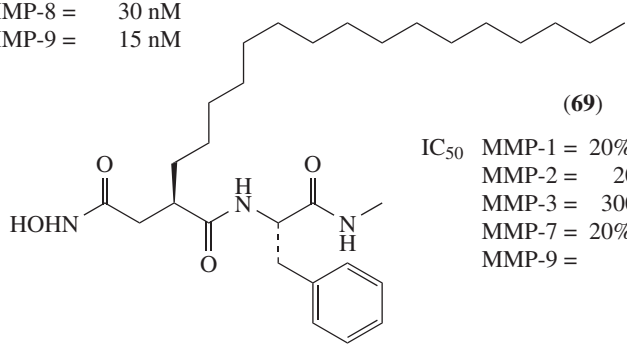
(**67**)

IC_{50} MMP-1 = 1000 nM
MMP-2 = 15 nM
MMP-3 = 500 nM
MMP-7 = 10000 nM
MMP-8 = 30 nM
MMP-9 = 15 nM



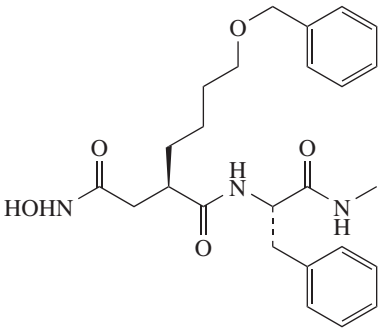
(**68**)

IC_{50} MMP-1 = 375 nM
MMP-2 = <0.15 nM
MMP-3 = 18 nM
MMP-9 = 1.5 nM



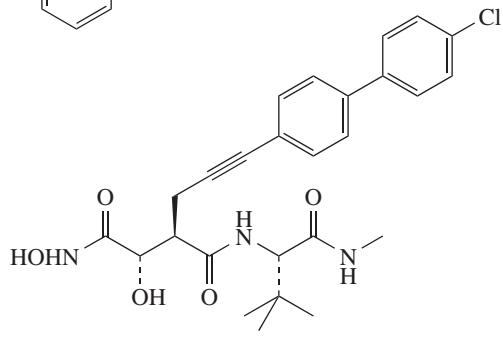
(**69**)

IC_{50} MMP-1 = 20% at 100 μM
MMP-2 = 20 nM
MMP-3 = 300 nM
MMP-7 = 20% at 100 μM
MMP-9 = 1 nM



(**70**)

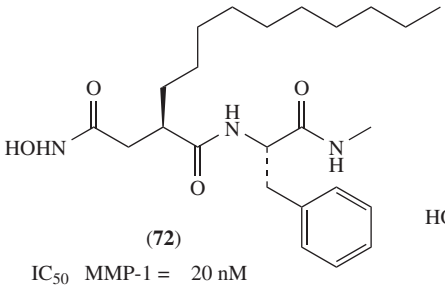
K_i MMP-1 = 1450 nM
MMP-3 = 15 nM
MMP-8 = 2 nM
MMP-9 = 3 nM



(**71**)

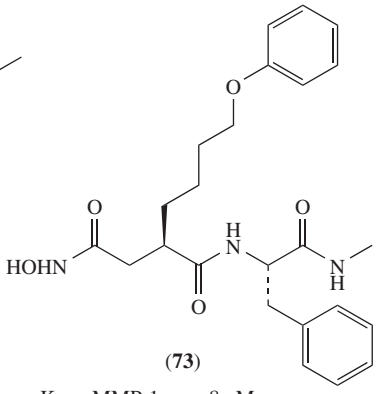
IC_{50} MMP-1 = 100 nM
MMP-2 = 0.07 nM
MMP-3 = 3 nM
MMP-7 = 700 nM
MMP-8 = 4 nM
MMP-9 = 1 nM

FIGURE 12. Isoform-selective MMPi



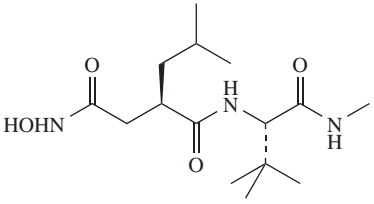
(**72**)

IC_{50} MMP-1 = 20 nM
MMP-2 = 2 nM
MMP-3 = 100 nM
MMP-9 = 2000 nM



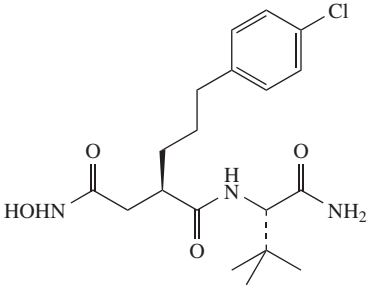
(**73**)

K_i MMP-1 = 8 nM
MMP-3 = 28 nM
MMP-8 = < 2 nM
MMP-9 = 1 nM



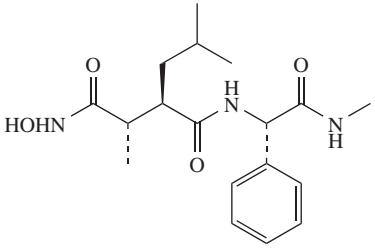
Ro 31-9790 (**74**)

IC_{50} MMP-1 = 10 nM
MMP-2 = 8 nM
MMP-3 = 700 nM
MMP-14 = 1.9 nM



CT1746 (**75**)

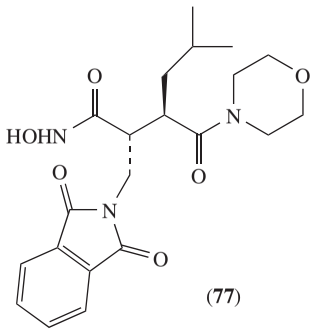
K_i MMP-1 = 122 nM
MMP-2 = 0.04 nM
MMP-3 = 10.9 nM
MMP-7 = 136 nM
MMP-9 = 0.17 nM



KB-R7785 (**76**)

IC_{50} MMP-1 = 3 nM
MMP-2 = 7.5 nM
MMP-3 = 1.9 nM
MMP-9 = 3.9 nM
MMP-14 = 56 nM

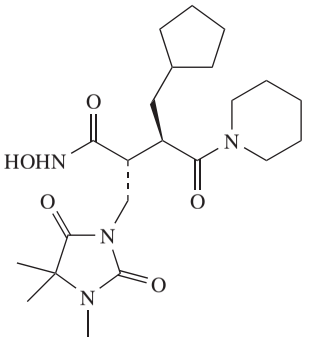
FIGURE 12. (*continued*)



(**77**)

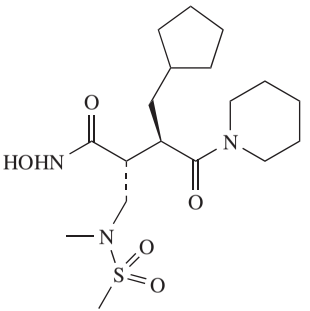
IC_{50} MMP-1 = 10 nM
MMP-2 = 400 nM
MMP-3 = 4500 nM

• HCl



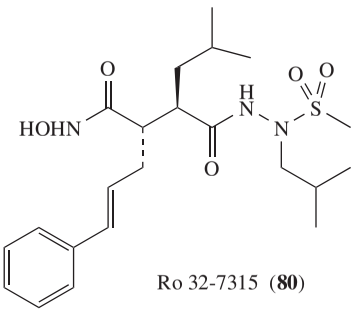
Ro 32-3555 (**78**)

K_i MMP-1 = 10 nM
MMP-2 = 400 nM
MMP-3 = 4500 nM



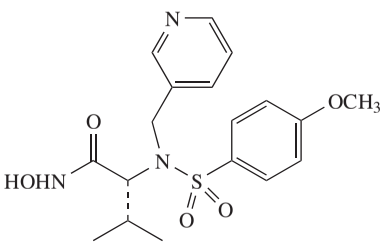
(**79**)

IC_{50} MMP-1 = 6 nM
MMP-2 = 900 nM
MMP-3 = 200 nM
MMP-7 = 200 nM
MMP-8 = 200 nM
MMP-9 = 2000 nM
MMP-13 = 400 nM



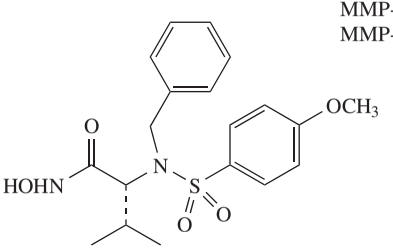
Ro 32-7315 (**80**)

IC_{50} MMP-1 = 500 nM
MMP-2 = 250 nM
MMP-3 = 210 nM
MMP-7 = 310 nM
MMP-9 = 100 nM
MMP-12 = 11 nM
MMP-13 = 110 nM
TACE = 5 nM



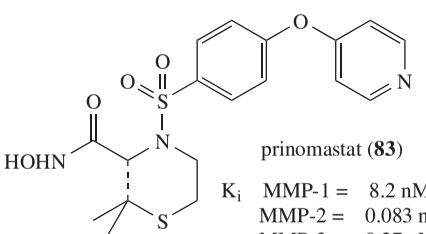
CGS 27023A (**81**)

K_i MMP-1 = 33 nM
MMP-2 = 20 nM
MMP-3 = 43 nM
MMP-9 = 8 nM



CGS 25966 (**82**)

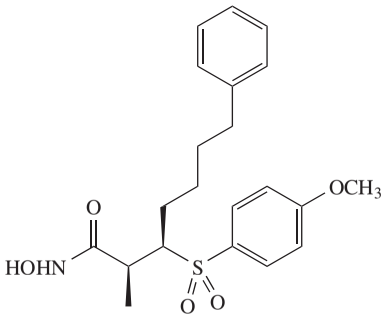
K_i MMP-3 = 92 nM



prinomastat (**83**)

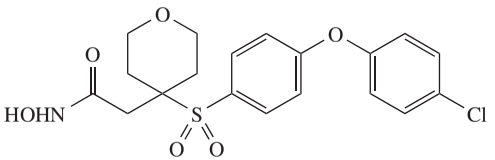
K_i MMP-1 = 8.2 nM
MMP-2 = 0.083 nM
MMP-3 = 0.27 nM
MMP-7 = 54 nM
MMP-13 = 0.038 nM

FIGURE 13. Truncated and sulfur-containing MMPi



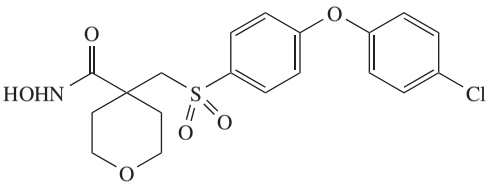
(**84**)

K_i MMP-1 = 2000 nM
MMP-2 = 10 nM
MMP-3 = 500 nM
IC_{50} PDE4 = 30 nM



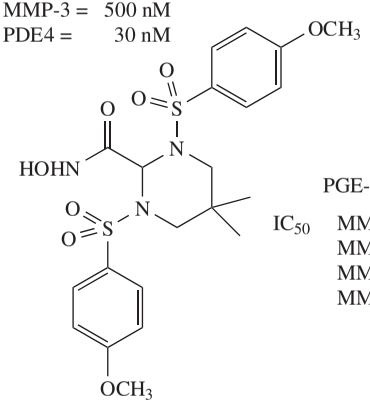
RS-113, 456 (**85**)

K_i MMP-1 = 70000 pM
MMP-2 = 54 pM
MMP-3 = 5200 pM
MMP-7 = 240000 pM
MMP-8 = 130 pM
MMP-9 = 65 pM
MMP-12 = 150 pM
MMP-13 = 170 pM



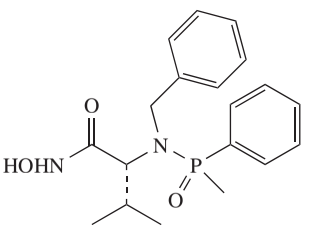
RS-130, 830 (**86**)

K_i MMP-1 = 590 nM
MMP-2 = 0.22 nM
MMP-3 = 9.3 nM
MMP-7 = 1200 nM
MMP-9 = 0.58 nM
MMP-13 = 0.52 nM



PGE-4410186 (**87**)

IC_{50} MMP-1 = 24 nM
MMP-3 = 18.4 nM
MMP-7 = 30 nM
MMP-9 = 2.7 nM



(**88**)

IC_{50} MMP-1 = 20.5 nM
MMP-2 = 13.3 nM
MMP-3 = 24.4 nM
MMP-7 = 886 nM
MMP-8 = 5.3 nM
MMP-9 = 20.6 nM
MMP-13 = 7.4 nM

FIGURE 13. (*continued*)

but displayed the best bioavailability. For this reason, **86** was tested in clinic for the treatment of osteoarthritis. Differently from the majority of MMPi, **85** and **86** lack any chiral center, yet retain the biological activity. This prompted one to develop some non-chiral MMPi such as PGE-4410186 (**87**), that was endowed with broad-spectrum MMP inhibitory activity and was evaluated in an *in vitro* cartilage permeation model[186]. In some cases, the sulfone/sulfonamide group has been replaced by a phosphinamide group, like in the **82-**analogue **88** (Figure 13), a potent inhibitor of a great number of MMPs but less potent against MMP-7[187]. Moreover, the easy hydrolysis of the phosphinamide bond at low pH halted the development of such a drug as an orally available agent.

MMPi may be beneficial for the treatment of disorders such as cancer, vascular diseases and arthritis[188–190]. Compounds tested in clinical trials as hydroxamate MMP inhibitors include batimastat (**60**), marimastat (**62**) and prinomastat (**83**). All these compounds have been applied to treat different types of cancer, such as ovarian cancer, breast cancer, malignant glioma, pancreatic cancer, non small cell lung cancer (NSCLC) and advanced bladder carcinoma[191, 192]. Although these compounds possess different inhibitory potencies toward the various MMPs, none of them was found to be selective for a particular enzyme. Unfortunately, most of these clinical trials of MMPi's have yielded disappointing results so far.

Batimastat (**60**) was the first broad-spectrum MMPi of the hydroxamate series which was tested for treatment of cancer. In rat mammary carcinoma, treatment with batimastat (**60**) decreased the number of lung metastases and halted the developed lymph node metastases at a silent, micrometastase stage[193]. In MBA-MD-435 breast cancer, batimastat (**60**) prevented the local regrowth of the carcinoma after resection in nude mice[155], and showed cytostatic effect in a variety of tumor models such as pancreatic cancer, colorectal carcinoma and hepatocellular carcinoma[194–196]. In a human ovarian cancer model, batimastat (**60**) in combination with cisplatin displayed additive cytotoxic effects without additional marked toxicity[154]. Batimastat (**60**) was assayed as chemopreventive agent, and in a *Min* model of intestinal tumorigenesis it suppressed by 50% the development of tumors[197]. Batimastat (**60**) was also widely studied in non-cancer diseases. In an arthritis model, it was able to significantly reduce paw edema bone degradation and cartilage breakdown, and gave significant good results against restenosis post angioplasty and a model of aortic aneurysm[198]. Moreover, batimastat (**60**) was active in a model of meningococcal meningitis, by reduction of intracranial pressure and blood–brain barrier breakdown[199]. Nevertheless, development of batimastat (**60**) in clinical trials for all indications, including cardiac failure and cerebral infarction, was discontinued.

Differently from batimastat (**60**), marimastat (**62**) is orally available. Marimastat (**62**) worked preclinically, improving median survival time and suppressing tumorigenesis in a variety of mouse cancer models[200, 201]. In clinical trials, four out of nine phase II studies showed a beneficial effect based on tumor biomarkers for the treatment of pancreatic and colorectal cancer[202–205]. In phase III clinical trials, marimastat (**62**) did not show any beneficial effect over placebo in patients with metastatic breast cancer, advanced ovarian cancer, inoperable colorectal cancer liver metastases, pancreatic, colorectal and small cell lung cancer[206–209]. Glioblastoma multiforme is the most commonly diagnosed malignant primary brain tumor in adults. Oral treatment with temozolomide was found to be beneficial for patients with recurrent glioblastoma multiforme and therefore a combination of temozolomide and marimastat (**62**) was evaluated[210]. Despite promising results in a phase II study, a phase III clinical trial involving 162 patients with glioblastoma multiforme or gliosarcoma following surgery and radiotherapy showed no significant difference between the marimastat- and placebo-treated groups in terms of survival[211]. Another phase III clinical study was conducted in patients with advanced gastric cancer. Overall survival in this group of patients was 18% compared with 5% in the placebo group[208]. These data support the utility of marimastat (**62**) as a maintenance treatment in gastric cancer patients following chemotherapy. Severe musculoskeletal syndrome was evident in all phase II

and III efficacy studies, and all these studies required some patients to decrease the dose, or to suspend the treatment[212].

Prinomastat (**83**) inhibited tumor growth in animal models of human glioma, human colon carcinoma, Lewis lung carcinoma and human NSCLC[178, 179, 213]. In some cases, the formation of secondary tumors was reduced by 90%. In combination with carboplatin, prinomastat (**83**) showed additive cytostatic effect in a human lung cancer model. A number of phase II clinical trials was performed with prinomastat (**83**) to evaluate its effects in esophageal adenocarcinoma, glioblastoma multiforme, metastatic melanoma and progressive breast cancer. The study in esophageal adenocarcinoma was prematurely terminated due to a high number of patients suffering unexpected life-threatening thromboembolic events[214]. The glioblastoma multiforme and metastatic melanoma clinical trials failed to show clinical efficacy. However, promising results were obtained in the metastatic breast cancer study. Phase III clinical studies involving patients with metastatic, hormone-refractory prostate cancer and in patients with NSCLC did not show significant differences in progression-free survival or overall survival[215]. Actually, prinomastat (**83**) is the only one hydroxamate MMPi in clinical trials in combination with other drugs for the treatment of NSCLC, glioblastoma multiforme and metastatic prostate cancer (Table 13).

Another sulfonamide hydroxamate, CGS 27023A (**81**), failed in producing tumor regression in a phase I clinical study in advanced solid cancer[216], but inhibited cartilage proteoglycan loss in arthritis and OA models[217].

Dual MMP/TACE inhibitors were tested in inflammation diseases. BB-1101 (**63**), for example, was shown to reduce paw edema and bone degradation when administered orally in adjuvant arthritis in rodents[157], and decreased the inflammation and kidney damage in a glomerulonephritis model in rats when administered prior to disease induction[218]. Additionally, BB-1101 (**63**) prevented the development of symptoms and reduced disease

TABLE 13. Clinical trials involving prinomastat (**83**)

Drug	Study	Phase	Disease	NCT	Status[a]
Prinomastat (**83**), temozolomide	Prinomastat plus Temozolomide following Radiation Therapy in Treating Patients with Newly Diagnosed Glioblastoma Multiforme	II	Glioblastoma multiforme	NCT00004200	C
Prinomastat (**83**), cisplatin, gemcitabine hydrochloride	Prinomastat and Combination Chemotherapy in Treating Patients with Metastatic or Recurrent Non-small Cell Lung Cancer	III	Lung cancer	NCT00004199	C
Prinomastat (**83**), mitoxantrone hydrochloride, prednisone, endocrine-modulating drug therapy	Chemotherapy in Treating Patients who have Metastatic Prostate Cancer	III	Prostate cancer	NCT00003343	C

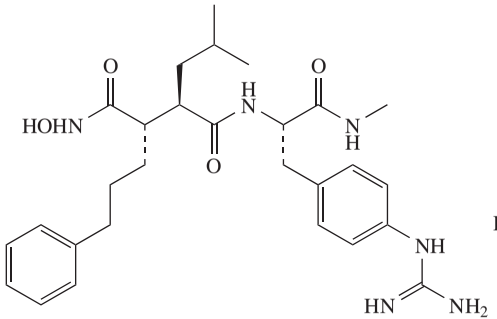
[a]C, completed.

severity in experimental autoimmune encephalomyelitis (EAE)[158] and delayed-type hypersensitivity response (DTH)[219], two multiple sclerosis (MS) models in rodents, as well as in experimental autoimmune neuritis (EAN)[220], a rodent model of Guillan Barré syndrome (GBS), and in a stroke model in rats[221, 222]. Despite structural similarities between the active site of MMPs and TACE, the angular and deep S1′–S3′ pocket of TACE is a distinguishing characteristic. Differential affinity for this unique S1′–S3′ pocket of TACE and the S1′ pocket of the MMPs offered design opportunities to enhance potency against TACE and optimize selectivity versus MMPs, thus furnishing compounds, such as the cited **80** (Figure 13) and **89–92** (Figure 14), more potent against TACE than against MMPs[223–225].

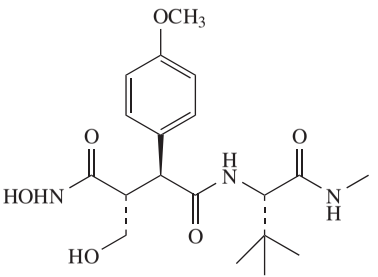
GW-3333 (**92**), for example, is an orally active retro-hydroxamate which is highly potent against TACE and efficient in inhibiting joint swelling and limp response in an arthritis model in rats[226]. Taking into account all the strategies and structure–activity relationship (SAR) information from decennial studies on MMPi, and combining the principles of medicinal chemistry, X-ray crystallography and molecular modeling, unique classes of potent TACE inhibitors have been obtained. Representative examples of TACE inhibitors are compounds **93–100** (Figure 14). Some of them (**93–97**)[227–232] are analogues or modified analogues of prinomastat (**83**), others (**98**)[233, 234] are related with **66**, a MMPi with cyclized P1–P2′ substituents, carrying opportune substituents leading to selective TACE inhibition. Systematic identification of new scaffolds and their modification afforded improved *in vivo* profiles, physical characteristics and pharmacokinetic/pharmacodynamic properties. Introduction of novel P1′ groups and further functionalization have yielded enhanced potency and selectivity. Significant advances in inhibitor design and lead optimization have been realized. Nonetheless, direct translation of potent enzyme inhibition to cellular activity remains elusive. Musculoskeletal side effects are still an issue and the definition of the requisite enzyme inhibitory profile or combination still awaits solution.

Particularly in inflammation diseases such as arthritis, RA and OA, MMP-13 and aggrecanase, an enzyme structurally related to MMPs, are actually the only MMP/MMP-like enzymes retained as a valuable target to inhibit. Thus specific MMP-13 inhibitors as well as aggrecanase inhibitors have been developed. Some MMP-13-selective inhibitors carry a bulky P1 substituent, either linked at the Cα position of the hydroxamate group through a spiro-linkage (see compounds **86** (Figure 13), **101** and **102**, Figure 15)[235, 236], or included in a cycle (**103**, a prinomastat (**83**) analogue, and **104**, Figure 15)[237, 238], or bearing at Cα a dioxolane substituent such as in the retro-hydroxamate **105** (Figure 15)[239]. Aggrecanase is very specific for proteoglycans leaving fragments found in high concentration in the joints of OA patients. While structurally related to MMPs, these ADAM-TS family members contain a specific proteoglycan recognition motif that aligns the MMP machinery to recognize and digest a specific epitope found in proteoglycans. Thus, aggrecanase inhibitors preserve proteoglycans in cartilage explants after IL1β treatment, show chondroprotective effects and represent, for arthritis patients, new disease-modifying and joint-preserving agents. Some specific aggrecanase inhibitors are shown (**106–108**, Figure 15)[240–242], again following the lesson for MMPi design.

In conclusion, a worldwide effort on MMP research generated a remarkable number of lower molecular-weight (both hydroxamate and non-hydroxamate) MMPi, that after preclinical evaluation entered clinical trials. Unfortunately, the results of these trials have been extremely disappointing and have led many investigators to conclude that MMPi have no therapeutic benefit in human cancer as well as inflammatory or cardiovascular diseases. The first-generation MMPi exhibited poor bioavailability, while second-generation compounds revealed that prolonged treatment caused severe musculoskeletal syndrome and inflammation or had a lack of efficacy. Overall, the development of MMPi as therapeutic tools has been more challenging than originally expected, also because there are still not available (or there is a paucity of) adequate animal models for testing the *in vivo* activity



(**89**)



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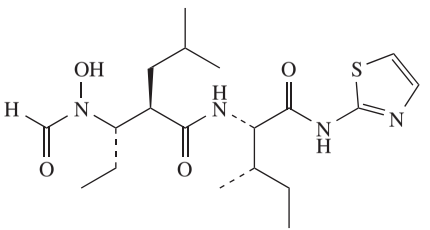

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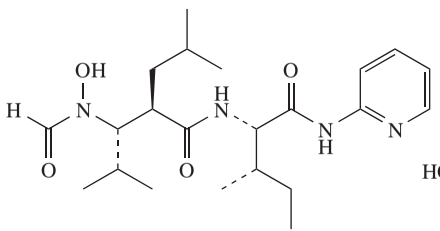
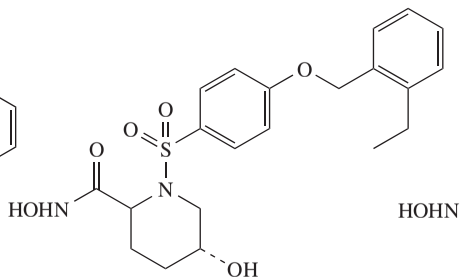
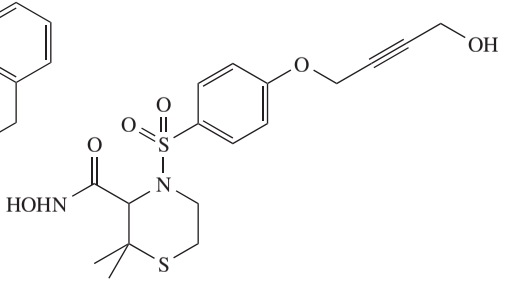


GW3333 (**92**)

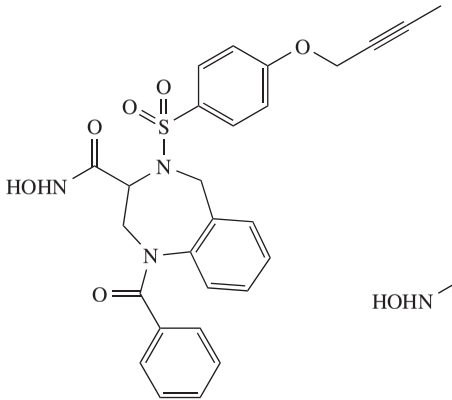


(**93**)



TMI-005 (**94**)

FIGURE 14. TACE inhibitors



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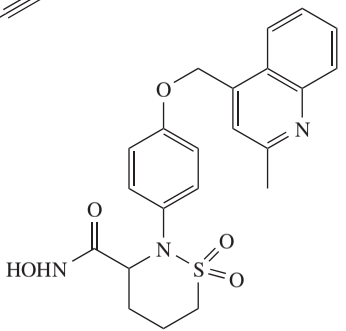
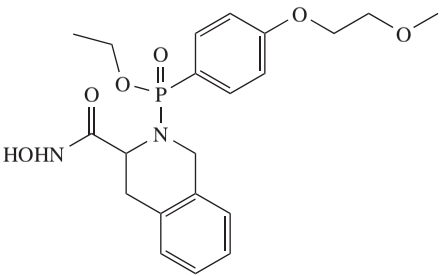
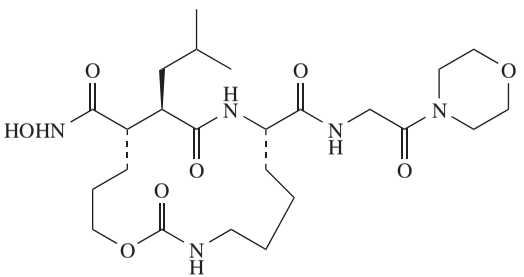


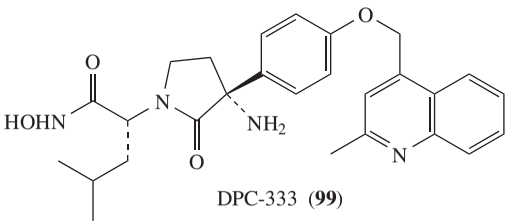
(**96**)



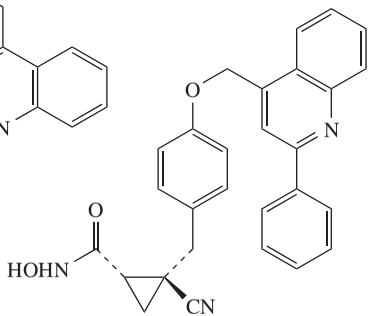
(**97**)



(**98**)



DPC-333 (**99**)



(**100**)

FIGURE 14. (*continued*)

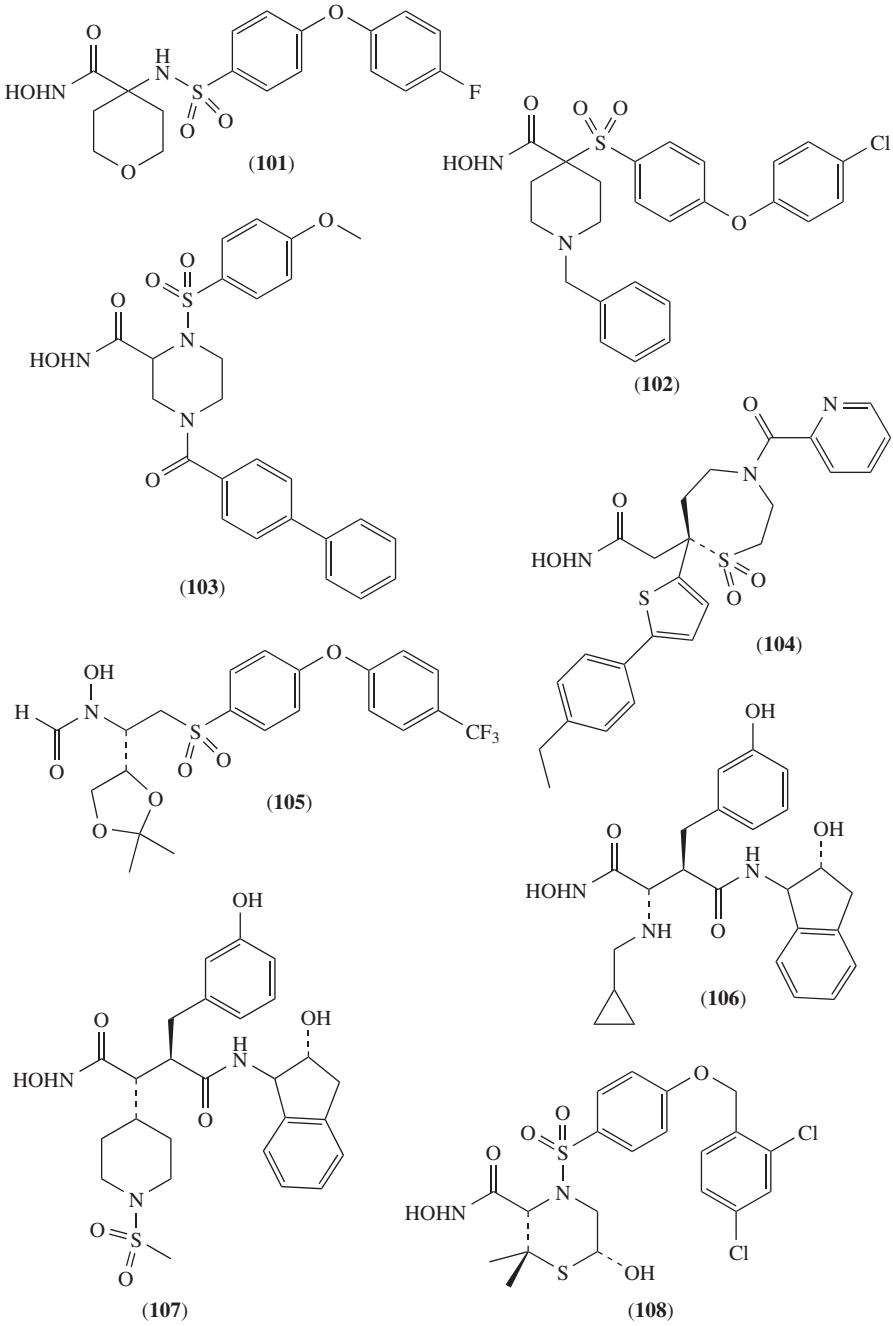


FIGURE 15. MMP-13-selective and aggrecanase inhibitors

of MMPi, or there is a great discrepancy between the often optimal results observed in preclinical experiments and the low efficacy in clinical studies. Maybe it seems feasible that rather than treating the primary cause of the disease, MMPi would serve as disease modifying agents which would stabilize the patient condition.

VI. HYDROXAMATES AS INHIBITORS OF HISTONE DEACETYLASES (HDACs)

Within the past decade our understanding of malignant cell growth and the underlying molecular alterations has offered new opportunities for molecular targeted cancer therapy. Carcinogenesis and tumor progression are controlled by both genetic and epigenetic events. Unlike genetic events, epigenetic aberrations evident in cancer cells, such as DNA hypermethylation at the promoter of selected genes, can be reversed, thus reactivating epigenetically silenced genes[243]. The deposition of epigenetic marks on chromatin, post-translational modifications of nucleosomal proteins and methylation of DNA is accomplished by enzymes often embedded in multi-subunit complexes. The control of the enzymatic machinery implicated in the (un)packing of chromatin, such as the reversible acetylation (histone acetyltransferases, HATs)/deacetylation (histone deacetylases, HDACs) of lysine residues, the methylation (histone methyltransferases, HMTs)/demethylation (LSD1 or JMJ-containing enzymes) of histone lysine and arginine residues, and the DNA methylation (DNA methyltransferases, DNMTs)/demethylation, is an important step in the regulation of transcriptional events[244–249]. As a consequence, DNMTs as well as chromatin-remodelling enzymes, particularly HDACs, have recently emerged as new promising targets for the treatment of cancer[250–252]. Histones H2A, H2B, H3 and H4 exhibit acetyl groups at the ε-amino-terminal lysine residues within the tails extending from the histone octamer of the nucleosome core. Among them, histones H3 and H4 constitute the main targets of HDAC enzymatic activity. After recruitment to transcription factors and co-regulators, such as Sin3, NuRD, CoREST, PRC2, heterochromatin protein 1 (HP1) and C-terminal-binding protein (CTBP), HDACs led to transcriptional repression by removing the acetyl groups and restoring the positive charge on lysine side-chains of histones: in this way, a tightness of nucleosomal integrity and gene silencing is obtained[253–255].

Mammalian HDACs are zinc- (class I/II/IV) or NAD^+- (class III) dependent deacetylases grouped into four classes according to their structural and functional homology with yeast equivalent enzymes[252]. The class I comprises HDAC1, HDAC2, HDAC3 and HDAC8, homologues of the *Saccharomyces cerevisiae* transcriptional regulator RPD3. Such enzymes are predominantly nuclear and are ubiquitously expressed. HDAC11 is most closely related to the class I HDACs, but its overall sequence similarity is too low for classifying it into class I, and a class IV of human HDACs has been proposed. Complexes containing class I HDACs bind to numerous transcription factors, either directly or indirectly through nuclear-hormone corepressor NCoR and SMRT. After recruitment to chromatin, class I HDACs deacetylate histone tails and induce transcriptional repression. Class II HDACs comprise HDAC4–7, 9 and 10, showing homology to *S. cerevisiae* HDA1.

Class II HDACs are divided into two subclasses, IIa (HDAC4-7, and 9) and IIb (HDAC6 and 10, containing as unique feature two deacetylase domains), according to the sequence homology and domain organization of their enzymes[256]. Class IIa HDACs shuttle between the nucleus and the cytoplasm, depending on their CaMK-mediated phosphorylation extent and subsequent binding of 14-3-3 proteins. Class IIb HDACs are mainly cytoplasmic, but show significant nuclear amounts in several cell lines. Differently from class I HDACs that are ubiquitarian, class II HDACs are expressed in a restricted number of cell types. Most class IIa HDACs (HDAC4, 5 and 9) are abundant in heart,

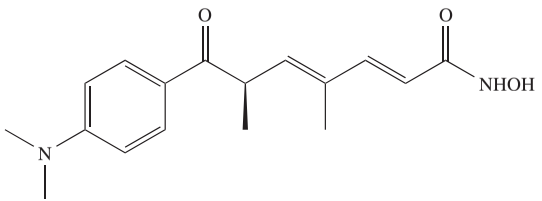
skeletal muscle and brain, and HDAC7 is highly expressed in CD4/CD8 double-positive thymocytes, heart, placenta, platelet, pancreas and skeletal muscle. Class IIb HDAC6 is predominantly expressed in heart, liver, kidney and pancreas, and HDAC10 is expressed in liver, spleen and kidney[252]. Class I HDACs are well-known transcriptional co-repressors, acting through the block of the expression of some tumor suppressor genes. Class IIa HDACs have been reported to interact with one or more DNA-binding transcription factors, as well as with transcriptional co-repressors. Among these interactions, the class IIa HDACs-MEF2 interaction is the most studied[257]. MEF2 plays a critical role in cardiac and skeletal myogenesis, in negative selection of developing thymocytes, and in the transcriptional regulation of Epstein–Barr virus (EBV). Moreover, MEF2 has a role in neuronal resistance to excitotoxicity. By binding to MEF2 several promoters, class IIa HDACs can act as transcriptional repressors in a variety of biological functions, from myogenesis to EBV latency. Differently, class IIb HDAC6 takes part, together with the class III HDAC SIRT2, in the microtubule network, and acts as specific α-tubulin deacetylase *in vitro* and *in vivo*[258]. Although all class I and II HDACs can deacetylate histone tails, it is now clear that other non-histone cellular proteins can be specifically targeted by different HDACs. The third class of mammalian HDACs comprises the sirtuins (SIRT1-7) which are homologous to the yeast Sir2 family and are NAD^+-dependent deacetylases without any homology to class I/II/IV enzymes[259].

First in 1999, the X-ray crystal structure of a deacetylase protein from the hyperthermophilic bacterium *Aquifex aeolicus* with sequence homology to the class I and II HDACs (termed histone deacetylase-like protein, HDLP) was determined[260], alone and in complex with two hydroxamate inhibitors, trichostatin A (TSA, **109**)[261] and suberoylanilide hydroxamic acid (SAHA, vorinostat, **110**)[262, 263] (Figure 16). These crystal structures have suggested a mechanism for the deacetylation reaction (Scheme 4), in which the zinc ion, close to a bound water molecule, coordinates the carbonyl oxygen of the *N*-acetylamide bond and activates it for a nucleophilic attack by the water. The nucleophilicity of the water molecule, in turn, can be enhanced by an interaction with the negative charge of the buried Asp166-His131 charge-relay system to which the water is hydrogen bonded. The attack of the water molecule on the carbonyl carbon produces an oxy-anion intermediate, stabilized by the zinc ion and by hydrogen bond to Tyr297. The collapse of this intermediate results in cleavage of the carbon–nitrogen bond, with the nitrogen accepting a proton from His132, and thereby produces the observed acetate and lysine products[260].

With respect to the mechanism of HDAC activity inhibition (Scheme 5), hydroxamates such as TSA (**109**) and vorinostat (**110**) are substrate mimics: they insert their aliphatic chain into the catalytic tube of HDAC and make multiple contacts at the rim, walls and bottom of the pocket. Particularly, their hydroxamate group reaches the polar bottom of the pocket and coordinates the zinc ion in a bidentate fashion (through CO and OH groups), and also contacts active-site residues (forming two hydrogen bonds between its NH and OH groups and the two charge-relay systems, and another one between its CO and the Tyr297 hydroxyl group). Moreover, the hydroxamic acid function replaces the zinc-bound water molecule of the active structure, crucial for the deacetylase activity, with its OH group[260].

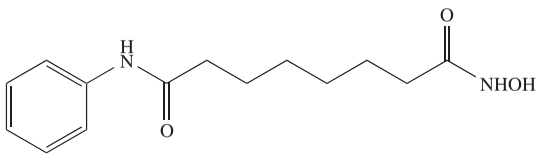
In recent years, a number of HDAC inhibitors (HDACi) have been reported as useful tools to study the function of chromatin acetylation/deacetylation and gene expression. According to their chemical structure, HDACi can be mainly classified into short chain fatty acids (SCFAs), such as sodium butyrate[264] and valproate[265], hydroxamates (the most numerous class), cyclic peptides, such as trapoxin[266], apicidin[267, 268] and romidepsin[269], and benzamides, with entinostat (MS-275)[270, 271] and mocetinostat (MCGD0103)[272, 273] being the most interesting derivatives.

The chemical features of TSA (**109**), vorinostat (**110**) and related HDACi are (i) a hydrophobic CAP group, able to interact with the rim of the catalytic tunnel of the enzyme, (ii) a polar connection unit (CU), present not in all but in most HDACi, which



trichostatin A (TSA, **109**)

IC_{50}	HDAC1 =	2 nM
	HDAC2 =	3 nM
	HDAC3 =	4 nM
	HDAC4 =	6 nM
	HDAC6 =	3 nM
	HDAC7 =	5 nM
	HDAC8 =	456 nM
	HDAC9 =	6 nM



vorinostat (SAHA, **110**)

IC_{50}	HDAC1 =	68 nM
	HDAC2 =	164 nM
	HDAC3 =	48 nM
	HDAC4 =	101 nM
	HDAC6 =	90 nM
	HDAC7 =	104 nM
	HDAC8 =	1524 nM
	HDAC9 =	107 nM

FIGURE 16. TSA (**109**), vorinostat (**110**) and pharmacophore model for HDACi design

Pharmacophore model for HDAC inhibitor design

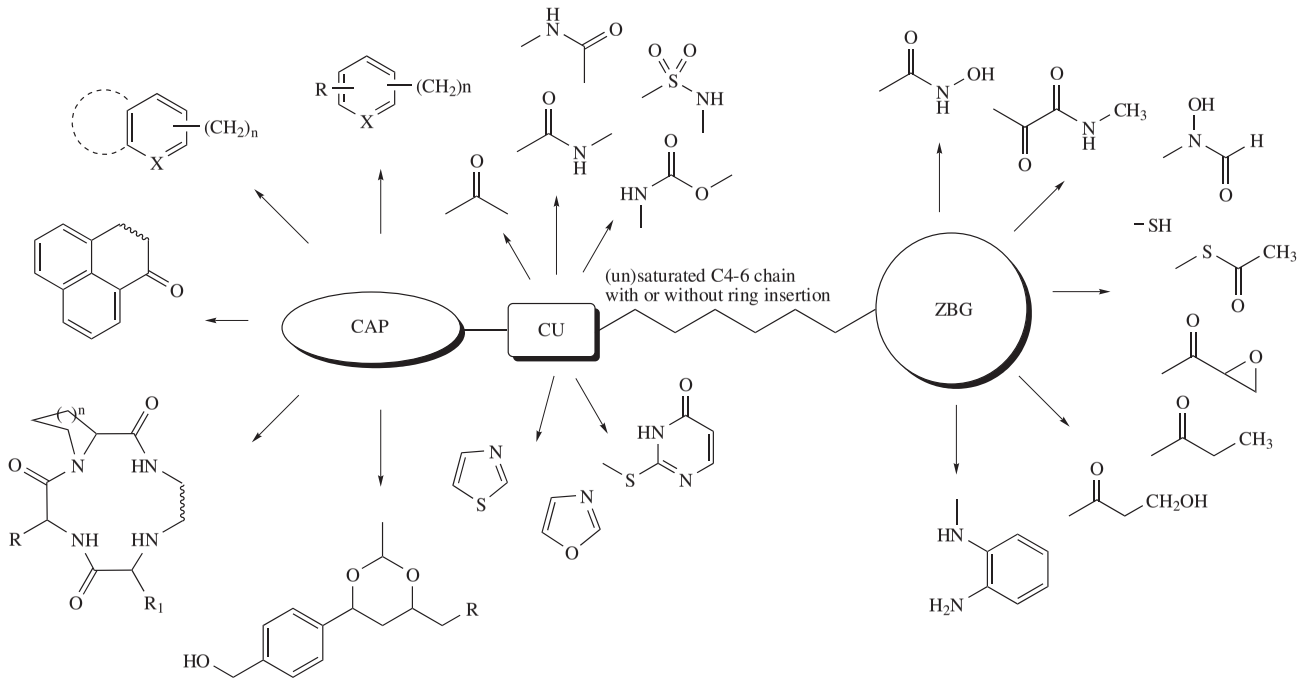
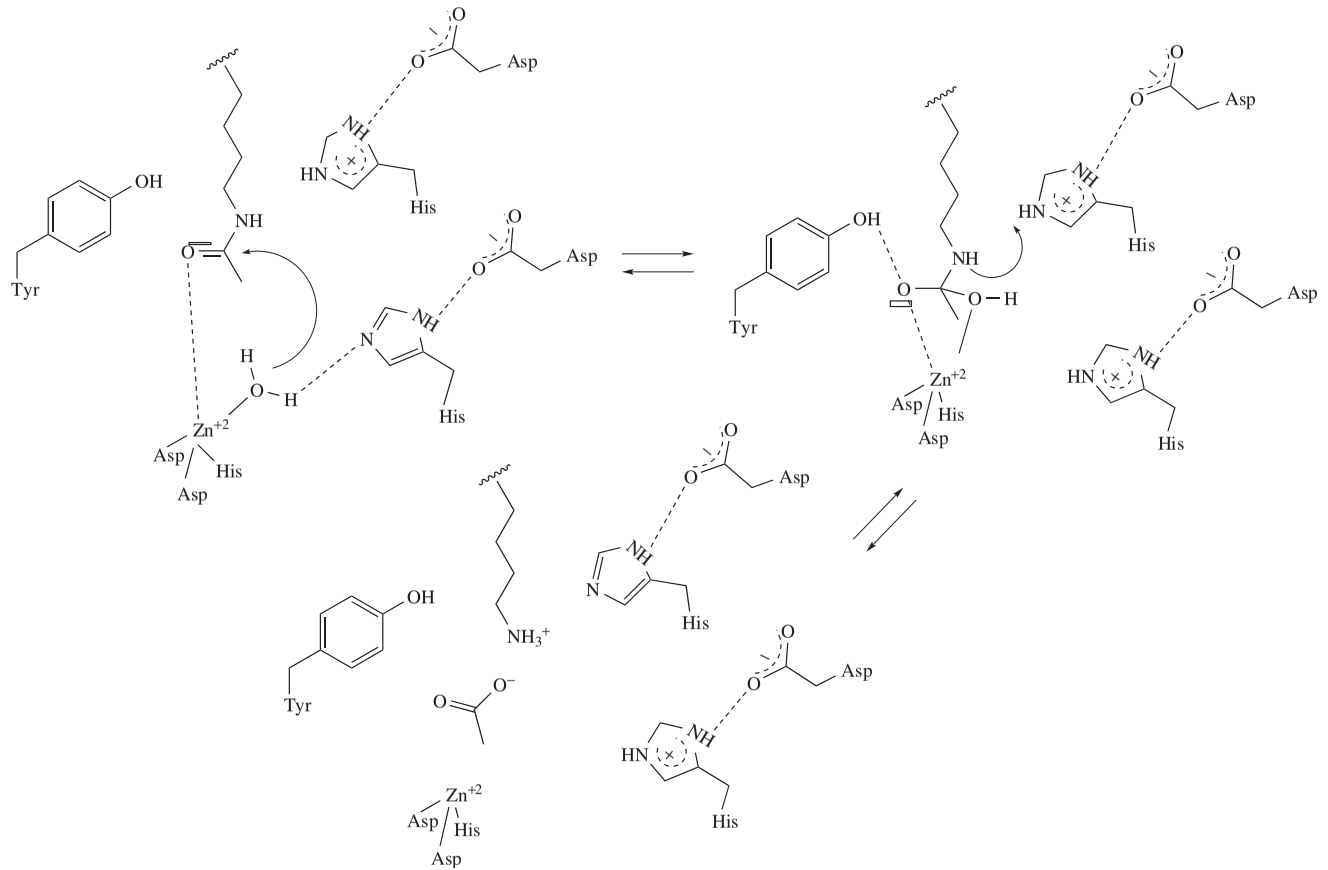
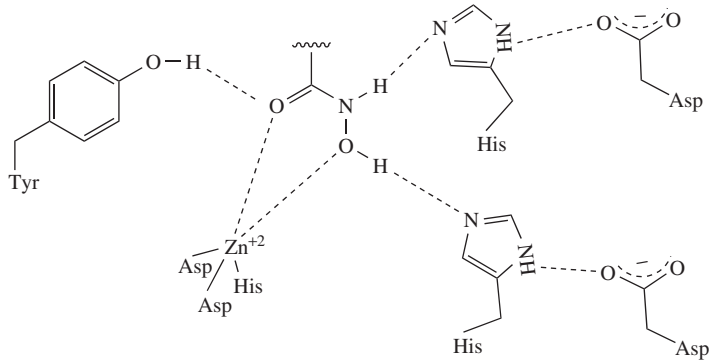


FIGURE 16. (*continued*)



SCHEME 4. Proposed mechanism for HDAC-mediated deacetylation



SCHEME 5. Schematic representation of hydroxamate/HDAC catalytic core interactions

can make hydrogen bonds with some amino acid residues in the tunnel, (iii) a 4- to 6-carbon unit hydrophobic spacer (linker), which allows the following (iv) zinc binding group (ZBG) (such as the hydroxamate group) to reach and to complex the zinc ion, and thus to inhibit the enzyme[274–276] (Figure 16). As a CAP, there is a wide tolerability for the groups to use for designing new inhibitors, because CAP interacts with the rim and/or the external part of the catalytic tunnel, in which the amino acid residues are less or not conserved among the various HDAC enzymes (also structural information in this region is lacking). CAP can range from a simple phenyl ring (see vorinostat) to a tetracyclic peptide (see trapoxin and cyclic hydroxamic acid peptides (CHAPs)[277], a sort of chimera between trapoxin and TSA), passing through imide-containing macrocyclic structures[278], bi- and tricyclic heteroaromatic moieties[279, 280], linked to CU directly or through alkyl (i.e. ethyl) groups. A branch can be inserted near the CAP and/or the CU group: the corresponding derivatives are usually most potent as HDACi than their unbranched counterparts. CU is preferentially a sp^2-hybridized, polar group able to make a hydrogen bond, such as ketone, amide, retro-amide, sulfonylamide, retro-sulfanylamide, oxime, ether, thioether, sulfoxide, sulfone, urea, carbamate or nitrogen atom[280–283]. Also, some properly substituted heterocyclic rings can be used as CU, such as oxazole, thiazole and uracil[284–286]. The hydrophobic space (HS) can be represented by a C_4–C_6 carbon linear alkyl chain, with or without insaturation, with or without little branched substituents, with or without (hetero)aromatic or aliphatic ring insertion. The main classification of hydroxamate HDACi according to their HS has been made into: (i) hydroxamates with an linear HS[287–291]; (ii) hydroxamates with a cinnamoyl HS[280, 282, 292–296]; (iii) hydroxamates with an aryl or heteroaryl HS[297, 298].

In vitro and *in vivo* results of the use of HDACi in tumor models, and reports of aberrant HDAC activity in a number of tumor types, indicate that inhibition of HDACs represents a viable anticancer strategy. Recently, two HDACi, vorinostat (**110**) (Figure 16) and romidepsin (depsipeptide, FK-228), have been approved by FDA for the treatment of refractory cutaneous T-cell lymphoma (CTCL), and a number of HDACi are currently undergoing clinical trials, alone or in combination with other chemotherapeutics, as anticancer drugs. Among hydroxamates, TSA (**109**) and vorinostat (**110**) represent the natural and synthetic prototype, respectively. TSA (**109**) and its glucopyranosyl derivative trichostatin C were first isolated from cultures of *Streptomyces hygroscopicus* as antifungal antibiotics active against *Trichophyton* species[299, 300]. Ten years later, the trichostatins were found to have potent antiproliferative and differentiating activity at nanomolar concentrations against Friend murine erythroleukemia cells in culture[301]. While dimethyl

sulfoxide and sodium butyrate were previously known to induce differentiation in this cell line, TSA (**109**) was orders of magnitude more potent[302]. The TSA (**109**) chemical structure is characterized by a 4-(*N*,*N*-dimethylamino)phenyl moiety linked through a carbonyl group to an aliphatic unsaturated chain (4,6-dimethyl-2,4-hexanedienoic acid) bearing at the end an hydroxamate portion. Moreover, it possesses a chiral center at the C6 position. Stereoselective synthesis of its enantiomers and subsequent analysis showed that the natural configuration is (*R*)-TSA, and (*S*)-TSA is 70-fold less potent as inducer of Friend erythroleukemia cell differentiation[303]. The extremely potent biological activity and the chiral specificity of (*R*)-TSA suggested the binding of the molecule to a specific molecular target. In later studies, TSA (**109**) was found active in a number of normal and tumor cell lines[304]. Nuclear histones from cells treated with TSA (**109**) were highly acetylated and on pulse-chase analysis this was not due to increased acetylation but rather, to decreased deacetylation[261]. In *in vitro* experiments using partially purified HDAC from mouse mammary tumor cells (FM3A), TSA (**109**) was a potent non-competitive inhibitor with the K_i value of 3.4 nM, strictly close to the effective antiproliferative concentration seen in the cell lines. Furthermore, in a mutant cell line named TR303 derived from FM3A and resistant to TSA (**109**), HDACs were inhibited by TSA (**109**) with highly increased K_i value ($K_i = 31$ nM), suggesting that HDAC was the primary target of TSA[261].

TSA (**109**) inhibits HDAC1, −2 and −3 (class I) and HDAC4, −6, −7 and −9 (class II) HDACs at single-digit nanomolar level (IC_{50}s = 6 to 2 nM), being less efficient against HDAC8 ($IC_{50} = 0.4\,\mu M$)[305]. The NAD^+-dependent class III HDACs (sirtuins) are not affected by TSA treatment. In Non-Small Cell Lung Cancer cells (NSCLC) or in melanoma, TSA (**109**) induces histone acetylation and the expression of p21 mostly independently of p53. Treatment with it results in a transient G2/M phase delay and in accumulation of retinoblastoma (Rb) protein. Moreover, it inhibits Cyclin D1 expression in an NF-κB-dependent manner in JB6 mouse epidermal cells[306]. The latest studies reveal that TSA (**109**) also inhibits telomerase activity. TSA (**109**) has a wide range of anti-cancer effects, but it has not so far been used in clinical trials, due to its side effects. Being active at nanomolar concentration, it was widely used as a tool for studying the involvement of HDACs in different contexts, not only in cancer (infectious diseases[307], neurodegenerative disorders[308] etc.).

Vorinostat (**110**) was discovered during a search for potent inducers of cancer cell differentiation. It falls in the series of compounds called hybrid polar compounds (HPCs), characterized by two polar groups separated by an apolar 5- to 6-carbon methylene chain. The first HPC prototype was hexamethylenebisacetamide (HMBA), which was found to be a potent inducer of differentiation of murine erythroleukemia (MEL) cells and of a wide variety of other cancer cells[309, 310]. Although treatment with HMBA induced remissions in patients with myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML), it could not be used as clinical agent because of the high dosage required (millimolar blood levels) and following toxic side effects (thrombocytopenia). From structural modification performed on the HMBA template, vorinostat (**110**) and some of its analogues were described by Marks and coworkers in 1996[262,263] as potent inducers of differentiation and/or apoptosis in a variety of cancer cells at low micromolar concentrations (second generation HPCs). The structure of vorinostat (**110**) is closely related to TSA (**109**), suggesting to test vorinostat (**110**) and other HPCs against HDAC enzymes[263]. Indeed, differently from HMBA that induces differentiation by different pathways, it strongly inhibited HDAC activity *in vitro* and caused accumulation of hyperacetylated histone H4 in cultured cells. Analogously to TSA (**109**), vorinostat (**110**) efficiently inhibits HDAC1, −2, −3, −4, −6, −7 and −9 (IC_{50}s = 164 to 48 nM), and displays lower potency against HDAC8 ($IC_{50} = 1.5\,\mu M$)[305].

Approved by FDA in October 2006 for the therapy of CTLC, vorinostat (**110**) is actually in clinical trials as single agent or in combination for the treatment of hematologic

TABLE 14. Clinical trials involving vorinostat (**110**) as anticancer agent, either as single agent or in combination

Drug	Study	Phase	Disease	NCT	Status[a]
Vorinostat (**110**)	Vorinostat After Stem Cell Transplant in Treating Patients With High-Risk Lymphoma	I	Lymphoma, Small Intestine Cancer	NCT00561418	R
Vorinostat (**110**), Capecitabine and Cisplatin	Study of Vorinostat Plus XP for 1st Line Treatment of Metastatic or Recurrent Gastric Cancer	I, II	Metastatic or Recurrent Gastric Cancer	NCT01045538	NYR
Vorinostat (**110**) and Capecitabine	HDAC Inhibitor Vorinostat (SAHA) With Capecitabine (Xeloda) Using a New Weekly Dose Regimen for Advanced Breast Cancer	I, II	Advanced Breast Cancer	NCT00719875	R
Vorinostat (**110**) and NPI-0052	Proteasome Inhibitor NPI-0052 and Vorinostat in Patients With Non-Small Cell Lung Cancer, Pancreatic Cancer, Melanoma or Lymphoma	I	Non-Small Cell Lung Cancer, Pancreatic Cancer, Melanoma Lymphoma	NCT00667082	R
Vorinostat (**110**), Bortezomib	Study of Vorinostat (MK0683) an HDAC Inhibitor, or Placebo in Combination With Bortezomib in Patients With Multiple Myeloma	III	Multiple Myeloma	NCT00773747	R
Vorinostat (**110**), bortezomib; dexamethasone	Study of Vorinostat (MK0683), an HDAC Inhibitor, in Combination With Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma	II	Relapsed or Refractory Multiple Myeloma	NCT00773838	R
Vorinostat (**110**), Carboplatin, Gemcitabine	Vorinostat, Carboplatin and Gemcitabine Plus Vorinostat Maintenance in Women With Recurrent, Platinum-Sensitive Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer	I, II	Ovarian Cancer, Fallopian Tube Cancer, Peritoneal Cancer	NCT00910000	R
Vorinostat (**110**)	Suberoylanilide Hydroxamic Acid in Treating Patients With Metastatic and/or Locally Advanced or Locally Recurrent Thyroid Cancer	II	Head and Neck Cancer	NCT00134043	C

(*continued overleaf*)

TABLE 14. (*continued*)

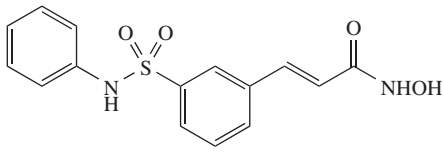
Vorinostat (**110**), Paclitaxel, Trastuzumab, Doxorubicin, Cyclophosphamide	Trial for Locally Advanced Her2 Positive Breast Cancer Using Paclitaxel, Trastuzumab, Doxorubicin and Cyclophasmide on a Weekly Basis	I, II	Breast Cancer	NCT00574587	R
Vorinostat (**110**)	Vorinostat and Palliative Radiotherapy (PRAVO)	I	Pelvic cancer	NCT00455351	C
Hydroxychloroquine, Vorinostat (**110**)	Hydroxychloroquine + Vorinostat in Advanced Solid Tumors	I	Advanced Solid Tumors	NCT01023737	A, NR
Paclitaxel, Carboplatin and Vorinostat (**110**)	A Phase I/II Study of Paclitaxel Plus Carboplatin Plus Vorinostat in Recurrent Ovarian Cancer	II	Ovarian Cancer	NCT00772798	R
SAHA (**110**) and Tamoxifen	Phase II Trial of SAHA & Tamoxifen for Patients With Breast Cancer	II	Breast Cancer	NCT00365599	R
Vorinostat (**110**) and Radiotherapy	Vorinostat in Combination With Palliative Radiotherapy for Patients With Non-Small Cell Lung Cancer	I	Non-Small Cell Lung Cancer (NSCLC)	NCT00821951	R
Rituximab, Cyclophosphamide, Etoposide, Prednisone, and Vorinostat (**110**)	Trial of Vorinostat in Combination With Cyclophosphamide, Etoposide, Prednisone and Rituximab for Elderly Patients With Relapsed Diffuse Large B-Cell Lymphoma (DLBCL)	I, II	Hodgkin's Disease, Lymphoma	NCT00667615	R
Gemtuzumab ozogamicin, Idarubicin, Cytarabine, and Vorinostat (**110**)	Vorinostat Combined With Gemtuzumab Ozogamicin, Idarubicin and Cytarabine in Acute Myeloid Leukemia	II	Acute Myeloid Leukemia	NCT01039363	NYR
Vorinostat (**110**) and Bexarotene	An Investigational Study of a Histone Deacetylase (HDAC) Inhibitor Plus Targretin in Cutaneous T-Cell Lymphoma Patients	I	Lymphoma	NCT00127101	T

(*continued overleaf*)

TABLE 14. (*continued*)

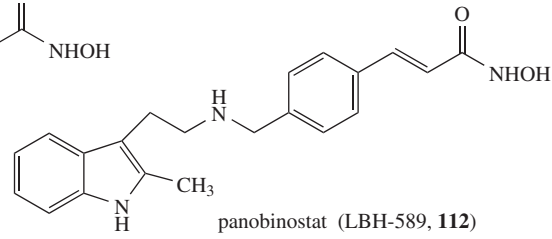
Drug	Study	Phase	Disease	NCT	Status[a]
Radiation Therapy, 5-Fluorouracil, Vorinostat (**110**)	Vorinostat in Combination With Radiation Therapy and Infusional Fluorouracil (5-FU) in Patients With Locally Advanced Adenocarcinoma of the Pancreas	I, II	Pancreatic Cancer, Adenocarcinoma of the Pancreas	NCT00948688	R
Vorinostat (**110**) and Gefitinib	Study of Vorinostat and Gefitinib in Relapsed/or Refractory Patients With Advanced Non-small Cell Carcinoma (NSCLC)	I, II	Non-small Cell Carcinoma (NSCLC)	NCT01027676	NYR
AMG 655, Vorinostat (**110**), Bortezomib	Phase 1b Lymphoma Study of AMG 655 in Combination With Bortezomib or Vorinostat	I	Hodgkin's Lymphoma, Low Grade Lymphoma, Mantle Cell Lymphoma, Non-Hodgkin's Lymphoma, Diffuse Large Cell Lymphoma	NCT00791011	R
MK-0683 (**110**)	A Study of the Efficacy of MK-0683 in Patients With Polycythaemia Vera and Essential Thrombocythaemia	II	Polycythaemia Vera, Essential Thrombocythaemia	NCT00866762	R

[a]R: recruiting; NYR: not yet recruiting; C: completed; A, NR: active, not recruiting; T: terminated.



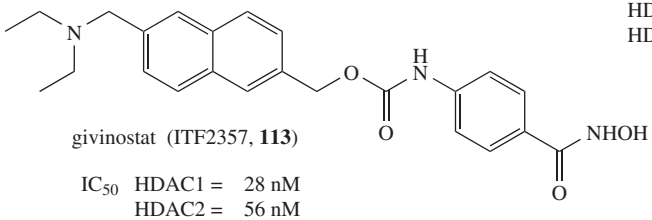
belinostat (PXD-101, **111**)

IC_{50} HDAC1 = 41 nM
HDAC2 = 125 nM
HDAC3 = 30 nM
HDAC4 = 115 nM
HDAC6 = 82 nM
HDAC7 = 67 nM
HDAC8 = 216 nM
HDAC9 = 128 nM



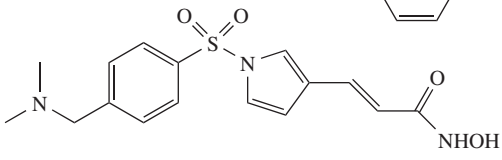
panobinostat (LBH-589, **112**)

IC_{50} HDAC1 = 3 nM
HDAC2 = 3 nM
HDAC3 = 4 nM
HDAC4 = 12 nM
HDAC6 = 61 nM
HDAC7 = 14 nM
HDAC8 = 248 nM
HDAC9 = 3 nM

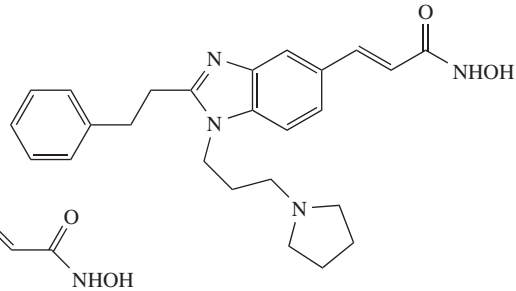


givinostat (ITF2357, **113**)

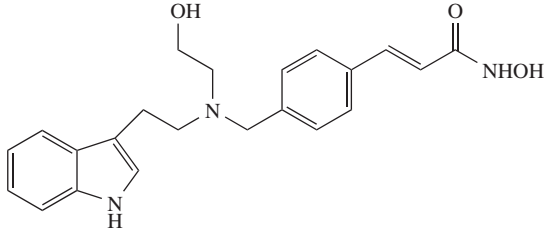
IC_{50} HDAC1 = 28 nM
HDAC2 = 56 nM
HDAC3 = 21 nM
HDAC4 = 52 nM
HDAC6 = 27 nM
HDAC7 = 163 nM



resminostat (**115**)



SB939 (**114**)



LAQ-824 (**116**)

IC_{50} HDAC1 = 5 nM
HDAC2 = 5 nM
HDAC3 = 12 nM
HDAC4 = 23 nM
HDAC6 = 7 nM
HDAC7 = 18 nM
HDAC8 = 162 nM
HDAC9 = 6 nM

FIGURE 17. Hydroxamate HDACi in clinical trials as anticancer agents

TABLE 15. Clinical trials involving panobinostat (**112**) as anticancer agent

Drug	Study	Phase	Disease	NCT	Status[a]
Panobinostat (**112**) (LBH589)	ERB-B4 After Treatment With HDAC Inhibitor in ER + Tamoxifen Refractory Breast Cancer	0	Breast Cancer	NCT00993642	R
Panobinostat (**112**), bicalutamide	Safety and Efficacy Studies of Panobinostat and Bicalutamide in Patients With Recurrent Prostate Cancer After Castration	I, II	Prostate Cancer, Prostatic Neoplasms	NCT00878436	R
Panobinostat (**112**), Everolimus	Panobinostat and Everolimus in Treating Patients With Recurrent Multiple Myeloma, Non-Hodgkin Lymphoma, or Hodgkin Lymphoma	I, II	Hematopoietic/Lymphoid Cancer, Recurrent Multiple Myeloma, Non-Hodgkin Lymphoma, Hodgkin Lymphoma	NCT00918333	R
LBH589 (Panobinostat) (**112**) and RAD001 (Everolimus)	A Safety Study of LBH589 (Panobinostat) and RAD001 (Everolimus) to Stabilize Kidney Cancer	I, II	Renal Cell Carcinoma, Metastatic Renal Cell Carcinoma	NCT01037257	NYR
LBH589 (**112**), erlotinib	Phase I/II Study of LBH589 & Erlotinib for Advanced Aerodigestive Tract Cancers	I, II	Lung Cancer, Head and Neck Cancer	NCT00738751	R
Panobinostat (**112**)	Panobinostat in Treating Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia	II	Leukemia	NCT00723203	R
Panobinostat (**112**)	Study of LBH589 (Panobinostat) to Treat Malignant Brain Tumors	II	Recurrent Malignant Gliomas	NCT00848523	R
LBH589 (Panobinostat) (**112**)	Dose-escalating Study of LBH589 in Adult Patients With Advanced Solid Tumors	I	Cancer, Advanced Solid Tumor	NCT00739414	R
Panobinostat (**112**) and Trastuzumab	A Trial of Panobinostat and Trastuzumab for Adult Female Patients With HER2 Positive Metastatic Breast Cancer Whose Disease Has Progressed on or After Trastuzumab	I, II	Breast Cancer	NCT00567879	R

(*continued overleaf*)

TABLE 15. (*continued*)

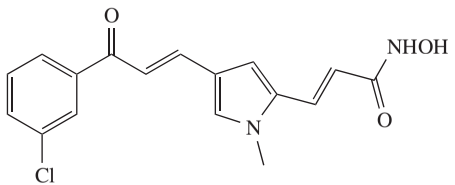
Panobinostat (**112**), Trastuzumab and Paclitaxel	A Trial 1 of Panobinostat Given in Combination With Trastuzumab and Paclitaxel in Adult Female Patients With HER2 Positive Metastatic Breast Cancer	I, II	HER2 Positive Metastatic Breast Cancer	NCT00788931	R
LBH589 (**112**)	A Study to Investigate the Effect of Food on Oral LBH589 Absorption in Patients With Advanced Solid Tumors	I	Cancer	NCT00570284	A, NR
LBH589 (**112**)	LBH589 in Adult Patients With Advanced Solid Tumors or Cutaneous T-cell Lymphoma	I	Tumors, Cutaneous T-Cell Lymphoma	NCT00412997	A, NR
LBH589 (**112**)	A Study of Oral LBH589 in Adult Patients With Advanced Hematological Malignancies	I, II	Lymphoma, Leukemia, Multiple Myeloma	NCT00621244	A, NR
LBH589 (**112**)	Study of Oral LBH589 in Adult Patients With Refractory/Resistant Cutaneous T-Cell Lymphoma	II, III	Cutaneous T-Cell Lymphoma	NCT00490776	R
Panobinostat (**112**) and Imatinib Mesylate	LBH589 and Imatinib in Treating Patients With Previously Treated Chronic Phase Chronic Myelogenous Leukemia	I	Leukemia	NCT00686218	R
Sorafenib and LBH589 (**112**)	Sorafenib and LBH589 in Hepatocellular Carcinoma (HCC)	I	Hepatocellular Carcinoma	NCT00823290	R
LBH589 (**112**)	LBH589 Treatment for Refractory Clear Cell Renal Carcinoma	II	Renal Cell Carcinoma	NCT00550277	S
Panobinostat (**112**) and Bortezomib	Study of Bortezomib and Panobinostat in Treating Patients With Relapsed/Refractory Peripheral T-cell Lymphoma or NK/T-cell Lymphoma	II	Peripheral T-cell Lymphoma, Angioimmunoblastic T-cell Lymphoma, Extranodal NK/T-cell Lymphoma Nasal Type, Enteropathy- Type T-cell Lymphoma, Hepatosplenic T-cell Lymphoma, Anaplastic Large Cell Lymphoma (ALCL) (ALK-1 Negative), Relapsed ALCL (ALK-1 Positive) Post Autologous Transplant	NCT00901147	R

(*continued overleaf*)

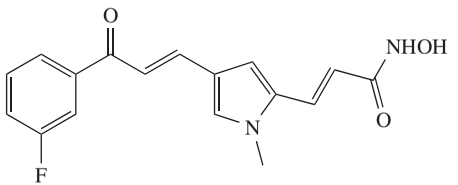
TABLE 15. (*continued*)

Drug	Study	Phase	Disease	NCT	Status[a]
Panobinostat (**112**) and Methylprednisolone	A Study of Panobinostat (LBH589) as Second-Line Therapy in Patients With Chronic Graft-Versus-Host Disease	II	Graft-Versus-Host Disease	NCT01028313	NYR
Panobinostat (**112**)	Study of Oral LBH589 in Patients With Cutaneous T-cell Lymphoma and Adult T-cell Leukemia/Lymphoma	II	Cutaneous T-cell Lymphoma and Adult T-cell Leukemia/Lymphoma	NCT00699296	T
LBH589/panobinostat (**112**), Epoitin Alfa HEXAL®	LBH589 Alone or in Combination With Erythropoietin Stimulating Agents (ESA) in Patients With Low or Int-1 Risk MDS (GEPARD)	II	Myelodysplastic Syndrome (MDS)	NCT01034657	R
LBH589 (**112**), Decitabine	LBH589 Plus Decitabine for Myelodysplastic Syndromes or Acute Myeloid Leukemia	I, II	Myelodysplastic Syndromes, Acute Myeloid Leukemia	NCT00691938	R

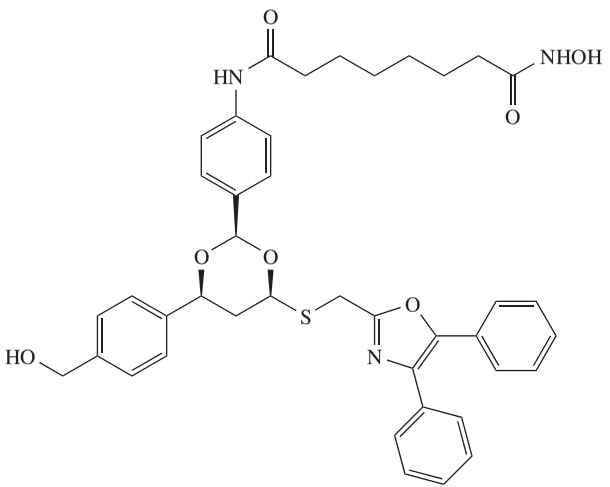
[a]R: recruiting; NYR: not yet recruiting; A, NR: active, not recruiting; S, suspended; T: terminated.



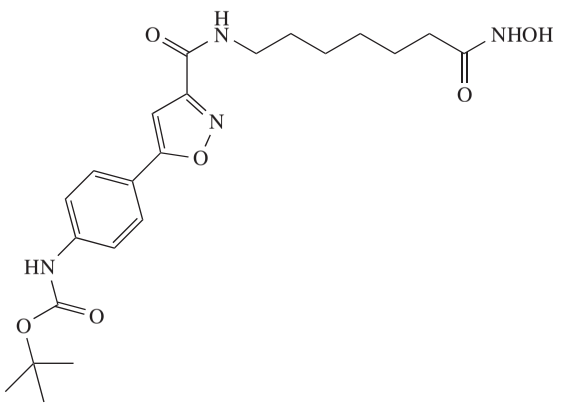
MC1575 (**117**)



MC1568 (**118**)



tubacin (**119**)



(**120**)

FIGURE 18. Class II- or HDAC6-selective hydroxamate HDACi

malignancies as well as solid tumors (Table 14). Similarly to TSA (**109**), vorinostat (**110**) also has been widely used for non-cancer uses[307, 308]. In addition to it, a number of hydroxamates such as belinostat (**111**), panobinostat (**112**), givinostat (**113**), SB939 (**114**) and resminostat (**115**) (Figure 17) are in Phase I–III clinical trials as anticancer agents[311–314]. Belinostat (**111**) (Figure 17) (formerly PXD-101) is a cinnamyl hydroxamate showing a sulfanilide function as CAP + CU moiety. It inhibited both class I and class II HDACs in the submicromolar range (IC_{50}s = 30 to 216 nM), and is in Phase II clinical trials alone for CTCL, peripheral T-Cell lymphoma, non-Hodgkin lymphoma and myelodysplastic syndromes, and in Phase I/II in combination with cisplatin and etoposide for SCLC and other advanced cancers, and with dexamethasone for multiple myeloma[315].

Panobinostat (LBH589) (**112**) belongs to the series of indolylethylaminomethylcinnamyl hydroxyamides[280], and shows a 3-ethylindole ring as a CAP, a nitrogen atom as CU, and a cinnamyl hydroxamate moiety as linker + ZBG. It is highly active (IC_{50}s = 14 to 3 nM) against HDAC1, −2, −3 (class I), −4, −7, −9 (class IIa), less potent against HDAC6 (IC_{50} = 61 nM, class IIb) and one or two orders of magnitudes less active against HDAC8 (IC_{50} = 0.25 μM). The first clinical candidate of this series, LAQ-824 (**116**) (Figure 17)[280], was abandoned possibly for toxicity problems, whereas panobinostat (**112**) is currently in Phase II/III clinical trial for a number of cancer diseases as single agent or in combination (Table 15). Givinostat (ITF2357) (**113**) is a 2-naphthylmethyl 4-(*N*-hydroxycarboxyamide)phenylcarbamate derivative actually in Phase II clinical trials for the treatment of chronic lymphocytic leukemia and Hodgkin's lymphoma[316]. SB939 (**114**) inhibited both class I and class II HDACs in the submicromolar range, shows a 2-butyl-1*H*-benzo[*d*]imidazol-5-yl-*N*-hydroxyacrylamide moiety and is in clinical trials for both hematological malignancies and solid tumors[317]. Resminostat (**115**) is a *N*-benzenesulfonylpyrrole-3-*N*-hydroxyacrylamide currently in Phase II clinical trials for the Hodgkin's lymphoma[318].

As shown in Figures 16 and 17, hydroxamate HDACi typically behave as pan-HDACi, not being selective for a particular class/isoform of the enzymes. Most of them are less potent against HDAC8. Among hydroxamate HDACi, only few molecules inhibit a restricted number of HDACs: some (aryloxopropenyl)pyrrolyl hydroxamates (such as MC1575 (**117**) and MC1568 (**118**), Figure 18)[319–322], class II-selective inhibitors prepared as analogues of aroyl-pyrrolyl-hydroxyamides (APHAs), a class of pyrrole-containing HDACi[275, 296], tubacin (**119**) (Figure 18), a HDAC6-selective inhibitor identified through a screening of 7200 molecules[323, 324], and **120**, having picomolar activity against HDAC6[325]. Since the implications of chromatin remodeling enzymes in biology and in the development of a variety of diseases, including cancer, have been only partially understood, additional modulators are required for further investigation, and the development of new compounds with a higher grade of selectivity or specificity is still in the front line.

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Peroxynitrogen: A study of nitrogen/oxygen heterocycles with N—O and O—O or N—O—O bonding

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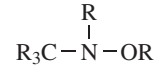
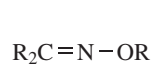
I. INTRODUCTION: DEFINITION AND SCOPE

In this volume, as in the earlier two-part monograph[1], hydroxylamines, oximes and hydroxamic acids are species with the generic structures **1**, **2** and **3**, respectively, where no assumption is made as to the identity of the affixed R groups nor are the R groups necessarily identical. Their *N*-peroxy derivatives include species with the **4**, **5** and **6** substructures, respectively. However, the peroxy group can be anywhere within the molecule and so there are variously substituted peroxyhydroxylamines, peroxyoximes and peroxyhydroxamic acids wherein the peroxy group is attached as a substituent to carbon. We choose to be both brief and selective by limiting our attention only to heterocycles that contain both the nitrogen and peroxy substructure. In many cases, different mechanistic pathways and/or synthetic alternatives to these substructures have been suggested by us or others and so these species represent plausible, but still inadequately characterized classes of compounds awaiting more investigation. As such, much of this chapter remains recognized as much a challenge as a chronicle[2].



(**1**)



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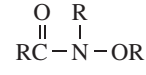

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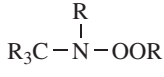

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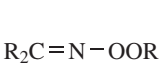

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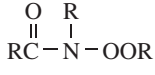


(**6**)

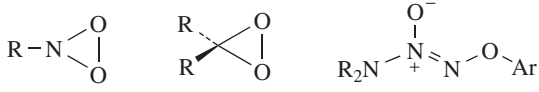
II. COMPOUNDS WITH 3-MEMBERED RINGS

The simplest cyclic peroxy derivative of hydroxylamines has a 3-membered ring composed of one nitrogen and two oxygens. These species, properly called dioxaziridines (**7**), are

isomeric with nitro compounds (RN(O)O)) and nitroso-*O*-oxides (RNOO). Isomerization amongst these three classes of compounds is well-established[3–5]. Unlike for the structurally similar dioxiranes (**8**)[6], the usefulness of dioxaziridines in synthetic organic chemistry has not been demonstrated. The recent review[7] presents a thorough discussion.

Both aryl azide (ArN_3) and *O*-substituted diazeniumdiolate (**9**) form triplet nitrenes[8], and then nitroso-*O*-oxides, from photooxidation with $^3O_2$. Cyclization of the nitroso-*O*-oxide generates the dioxaziridine[9, 10]. Also formed in the reaction are other reactive species such as azide excited states and tetraoxadiazinines and more conventional species such as azo compounds/diazenes. To take one example, the UV photooxidation of an *O*-substituted diazeniumdiolate led to an *O*-substituted nitrene and $Et_2NN{=}O$[11]. A first-order pathway for the nitroso-*O*-oxide led to dioxaziridine. Low laser power resulted in low steady-state concentrations of nitroso-*O*-oxide, which favored its unimolecular conversion to dioxaziridine[11].

Aqueous nitrate solution irradiated by 200-nm light produces[12] the *cis* rotamer of peroxynitrite, $ONOO^-$, in 48% yield. The authors suggest the intermediacy of an electronically excited, pyramidally shaped form of NO_3^- as a transient species. We wonder about the intermediacy of a dioxaziridine (**7**, R = O^-). An even simpler species would be the triangular dioxaziridinide with a negatively charged nitrogen atom. Both the well-known acyclic ONO^- ion and its isomer, NOO^-, are found in the gas phase[13]. That the isomerization of the latter into the former is slow has been interpreted to mean that the remaining isomer, the aforementioned triangular ion, is very high in energy, whether it be an actual intermediate or merely a transition state. No experimental evidence is known for the corresponding dioxaziridinyl radical or the parent dioxaziridine itself.

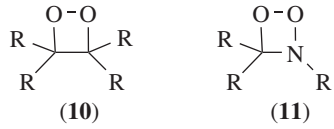


(**7**) (**8**) (**9**)

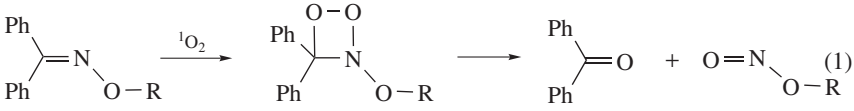
III. COMPOUNDS WITH 4-MEMBERED RINGS

A. Dioxazetidines and Dioxazetes

1,2-Dioxetanes (**10**) comprise a class of readily accessible heterocycles synthesized from singlet oxygen ($^1\Delta_g$)—alkene reactions[14, 15]. Adamantyl- or alkoxy-substituted 1,2-dioxetanes are often isolable, while other 1,2-dioxetanes rapidly cleave to two carbonyl compounds[16]. Analogously, 1,2,3-dioxazetidines (**11**) should form by reaction of singlet oxygen with imines, and then cleave as do 1,2-dioxetanes[17, 18]. Indeed, this reaction sequence was first observed with benzophenone oxime, the corresponding oximate anion, and *O*-methyl ether (**12**, R = H, CH_3, or non-bonded electron pair, equation 1)[19]. Other studies[20] show photooxygenations of a number of C=N-containing compounds, but document the conclusion that, in general, oximes and their silyl ethers are unreactive to singlet oxygen while oximate anions cleaved cleanly via the 1,2,3-dioxazetidines. However, the extent of reaction is dependent on conditions and structure. The 1,2,3-dioxazetidine formation and cleavage reaction was later shown[21] for a variety of types of oximes (alicyclic ketoximes, aromatic aldoximes and ketoximes, and ketoximes/α-oximino ketones[22]) under conditions that avoided secondary photochemical reactions of the products. The observed formation of benzaldehyde, instead of cinnamaldehyde, from singlet oxygen reaction with cinnamaldoxime (PhCH=CHCH=NOH) was explained by competition from C=C bond oxidation. Similarly, amidoximes—but only in their anionic form—react with singlet oxygen to result in nitriles and amides via acyclic peroxy intermediates, not 1,2,3-dioxazetidines[23].



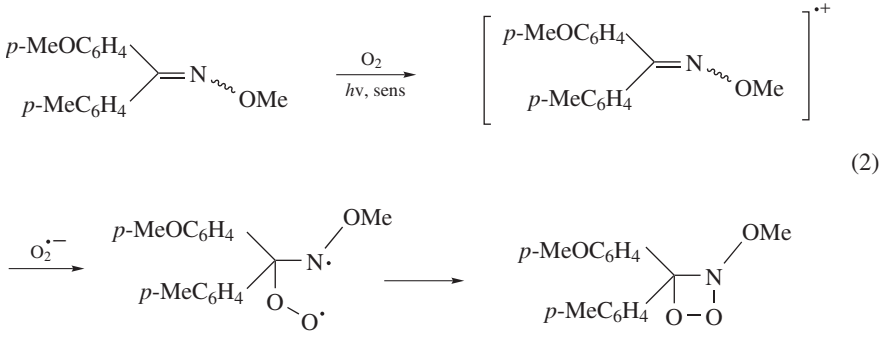
(**10**) (**11**)



(**12**)

(R = H, CH_3, or non-bonded electron pair)

A 1,2,3-dioxazetidine intermediate was proposed to form via a non-singlet oxygen pathway, as shown in equation 2, upon UV photooxidation of *N*-methoxy-4-methoxyphenyl-4′-methylphenylmethanimine with the photosensitizer 9,10-dicyanoanthracene[24, 25]. The 1,2,3-dioxazetidine is cleaved to the diaryl ketone and methyl nitrite, but loss of oxygen was also observed with photoisomerization of the C=N double bond[24]. Oxime carbamates, RCH=NO(C=O)NR_2, solvolytically cleave by singlet oxygen but seemingly not via a pathway involving the 1,2,3-dioxazetidine species[26].

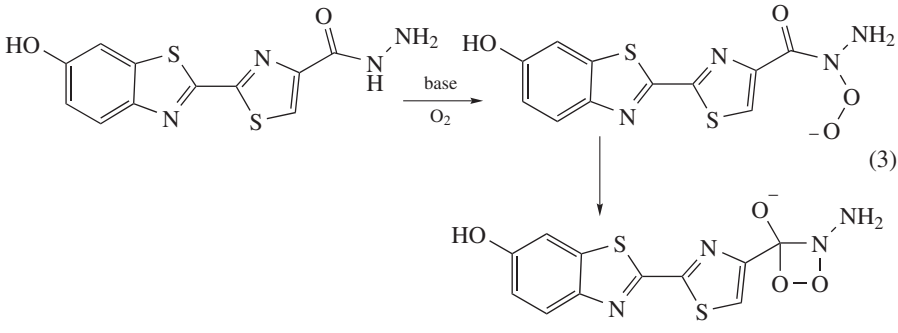


(2)

Ene hydroperoxide products, rather than 1,2,3-dioxazetidines, arise from triplet oxygen reactions with N−H hydrazone[27]. A computational study showed that both the azo and hydrazone tautomers of aminopyrazolinyl azo dyes react with singlet oxygen to produce the same hydroperoxide end product by both cycloaddition and ene reactions[28]. The facile cleavage of substituted benzalphenylhydrazones, $XC_6H_4CH{=}NN(Me)C_6H_4Y$, by singlet oxygen has been observed where substituted benzaldehydes and substituted *N*-aryl-*N*-methylnitrosamines are products[29]. Substituent effects on the rate are consistent with an electron transfer from the hydrazone to singlet oxygen leading to an anion-radical caged pair prior to forming the 1,2,3-dioxazetidine intermediate[29]. The reactivity of *N*,*N*-dimethylhydrazones was found to be inversely temperature-dependent (lower reactivity at higher temperatures) and an ene reaction was implicated.

A 1,2,3-dioxazetidine (**13**) was proposed to be an intermediate in the luminescence reaction mechanism of an acyl hydrazide derivative of 5-methyldehydroluciferin that has been treated with a strong base in the presence of oxygen[30] (equation 3).

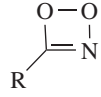
Silylnitronates[20] and nitronate anions[20, 31] were cleaved by singlet oxygen, perhaps via a 1,2,3-dioxazetidine, although the cycloaddition is not required to account for the products.



(**13**)

The oxidation of hydroxamic acids to acylnitroxyl radicals, (RC=O)N(O•)R, is well-chronicled[32, 33]. Isomerism to the cyclic 1,2,3-dioxazetidinyl radical, or further oxidation to the corresponding 6π, and so plausibly aromatic, cation is unreported.

1,2,3-Dioxazetes are valence isomers of acylnitroso species but isomerization remains unobserved. There is no evidence *per se* for the unsaturated 1,2,3-dioxazete parent compound (**14**, R = H) or any of its substituted derivatives. By the criteria for inclusion in the current chapter, we may consider 1,2,3-dioxazete-4-yl radical, cyclo-$CNO_2^{\bullet}$, where the substituent group is replaced by a single electron. In principle, this species may be formed by the reaction of CN and O_2. Indeed, the diatomic radical and diradical react[34] in the gas phase but the 4-membered ring species, even as a transition state, seemingly contributes little to the observed chemistry since it is a low probability reaction channel. The same conclusion for an unstable dioxazete was derived from a study[35] of the photochemical reaction of CO and NO in a cryogenic matrix. 4-Methylene-1,2,3-dioxazetidines, isomers of alkylated 1,2,3-dioxazetes, are not formed by the reaction of ketenimines $R_2C{=}C{=}NR$ with singlet oxygen. Rather, iminodioxetanes are formed by cycloaddition of singlet oxygen to the C=C double bond and not to the C=N double bond[36]. That the last compounds have become quite accessible suggests the study of isomerization with acylnitroso compounds is a reasonable aspiration.



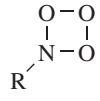
(**14**)

In principle, superoxide anion can react with nitriles to form the radical anion of 1,2,3-dioxazetes and/or the ring-opened acylnitroso species. No such reaction product has been reported, nor even suggested, even though there are reported studies of superoxide ion in acetonitrile solvent[37, 38] and of hydrated superoxide ion clusters with acetonitrile in the gas phase[39]. In solution, haloacetonitriles react[40] with superoxide ion by displacement of the halide ion. Aromatic nitriles smoothly react with superoxide[41] in the presence of catalytic nitrobenzene, to result in the corresponding amide. In none of these reactions

have 1,2,3-dioxazete intermediates been postulated. The gas-phase reaction of dioxygenyl cation and acetonitrile is dominated[42, 43] by cluster and charge transfer reactions.

B. Trioxazetidines

It is well-established that nitroso compounds, such as *N*,*N*-dimethyl-4-nitrosoaniline, are bleached in reactions of singlet oxygen with imidazole or histidine[44] through the intermediacy of endoperoxides[45, 46]. We know of no documentation for initial [2 + 2]-cycloaddition between the nitroso moiety and O_2 to form a trioxazetidine (**15**), however transient. Then again, isotope exchange reactions such as equation 4 seemingly have not been investigated, nor have the related reactions involving any ions of either the nitroso compound or molecular oxygen. In principle, nitrenes can react with ozone to form trioxazetidines as well, but this has not been demonstrated.



(**15**)

$$RN^{18}O + {}^{16}O_2 \rightarrow RN^{18}O^{16}O_2 \rightarrow RN^{16}O + {}^{16}O^{18}O \quad (4)$$

The reaction between aqueous azide ion and ozone has been reported to form peroxynitrite ion[47], $ONOO^-$. A simple mechanism could involve the coupling of the terminal atoms of both species to form the acyclic $[OOONNN]^-$ ion. Loss of N_2 and cyclization would produce an intermediate trioxazetidinide anion which then opens to form the peroxynitrite ion. However, no nitrogen is formed during the reaction to support this pathway.

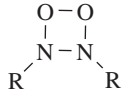
In the earlier-mentioned irradiation of aqueous nitrate solutions to form *cis*-peroxynitrite[12], no evidence was shown for the trioxazetidinide anion, i.e. **15** with no R group, nor were spectroscpic peaks ascribed to this species in the matrix reaction of NO, O_2 and diverse metals[48].

C. Dioxadiazetidines

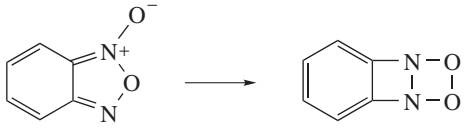
1,2,3,4-Dioxadiazetidines (**16**) are formally dimers of nitroso compounds. They are also the formal [2 + 2]-cycloaddition products of azo compounds and oxygen. However, they remain uncharacterized. The reaction of singlet oxygen with azo dyes[49, 50] was dominated by other phenomena such as redox reactions, singlet oxygen physical quenching and reactions with the isomeric hydrazones. For example, the total rate constant (k_T) values of dialkylamino azo compounds—singlet oxygen reactions ranged from 10^6–10^8 $M^{-1}\,s^{-1}$, showing that physical quenching predominates over the chemical reaction. The chemical reaction rate constant (k_r) 10^3–10^4 $M^{-1}\,s^{-1}$ measured by competition with 9,10-dimethylanthracene was ascribed to a charge-transfer interaction (azo compound + $^1O_2$ → azo compound$^{\bullet+}$/$O_2^{\bullet-}$), which then led to oxidized products. Interestingly, 1,2,3,4-dioxadiazetidines were not discussed as possible products or intermediates. However, 1,2,3,4-dioxadiazete and its radical cation have been postulated in gas-phase ion–molecule reactions[51]. A three-ring 1,2,3,4-dioxadiazetidine (**18**) was

also investigated by *ab initio* methods as a high-energy species in the isomerization of benzofurazan 1-oxide (benzofuroxan) (**17**)[52] as shown in equation 5.

Finally, *N*-nitrosohydroxylamines and the related anionic diazeniumdiolates are simultaneously an old and new class of molecules with current intense interest. That being said, their electrochemical oxidation to the cyclic, and plausibly 6π aromatic, 1,2,3,4-dioxazetinium ions remains unreported. By contrast, the study of their electrochemical reduction is over 50 years old[53].



(**16**)

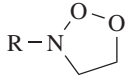


(**17**) (**18**) (5)

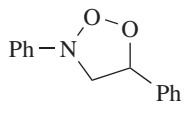
IV. COMPOUNDS WITH 5-MEMBERED RINGS

A. Dioxazoles

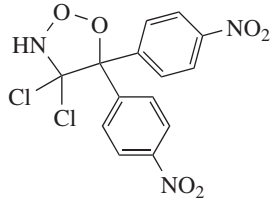
1,2,3-Dioxazolidines (**19**) are postulated as intermediates in nitroso-*O*-oxide/olefin reactions[8, 11]. Nitroso-*O*-oxides are not thought to add directly to olefins via [3 + 2]-cycloaddition, although this concerted process has been calculated with density functional theory methods, specifically the formation of **20**[54]. The structure and reactivity of nitroso-*O*-oxides has been studied[55], and the formation of 1,2,3-dioxazolidine is thought to take place via stepwise addition of nitroso-*O*-oxide to an olefin by first forming a diradical intermediate which then cyclizes, as shown for styrene and phenylnitroso-*O*-oxide in equation 6. In another example, the reaction of 1,1-dichloro-2,2-bis(4-nitrophenyl)ethylene with sodium nitrite afforded 4,4′-dinitrobenzophenone through a suggested 1,2,3-dioxazolidine intermediate **21**[56]. Formation of a 4-membered *N*-hydroxyoxazetidine is also consistent with the observed products.



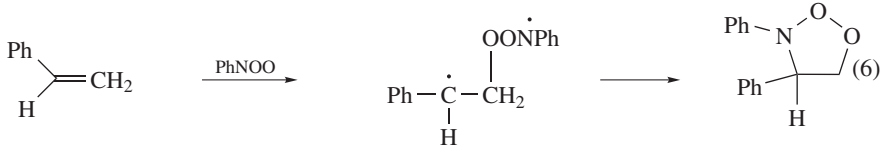
(**19**)



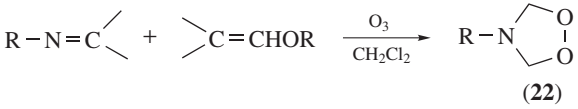
(**20**)



(**21**)

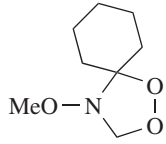


Ozonolysis of vinyl ethers, $R_2C{=}CHOR$, produces the corresponding carbonyl-*O*-oxides, R_2COO and RO(H)COO. In the presence of imines, the carbonyl oxides react in a [3 + 2]-cycloaddition to form 1,2,4-dioxazolidines, **22** (equation 7), with a variety of substituent groups on the ether and the imine, in isolated yields of 14–97%[57]. Because of the high degree of stereoselectivity in the product in some instances, the authors suggest the reaction is a concerted cycloaddition.

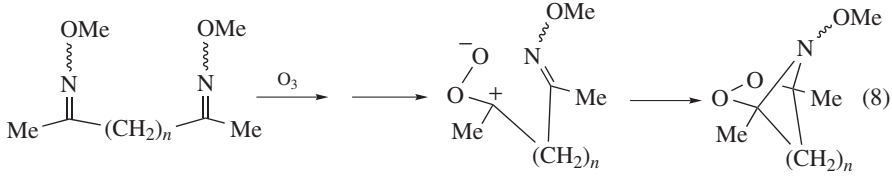


(**22**) (7)

Likewise, *O*-methyl cyclohexanone oxime reacts with the carbonyl-*O*-oxide derived from ethyl vinyl ether to form 4-methoxy-1,2-dioxa-4-azaspiro[4.5]decane (**23**) in 13% yield[58]. Reaction with substituted carbonyl-*O*-oxides did not produce a product. Ozonolysis of oxime ethers also produces carbonyl-*O*-oxides, although these species do not then react with the remaining oxime ether[59]; however, ketones[58] and Schiff bases[60] are reactive. Surprisingly, because the monoozonolysis of the *O*-methyl dioxime produces a disubstituted carbonyl-*O*-oxide, the related reaction (equation 8) yields bicyclic derivatives such as the *N*-methoxy-1,2-dioxa-7-azabicyclo[2.2.1]heptane and -6,7-dioxa-8-azabicyclo[3.2.1]octane; cf. species **24** with $n = 2$ and 3 (equation 8)[58].

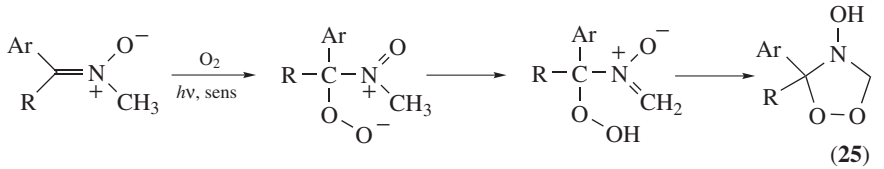


(**23**)



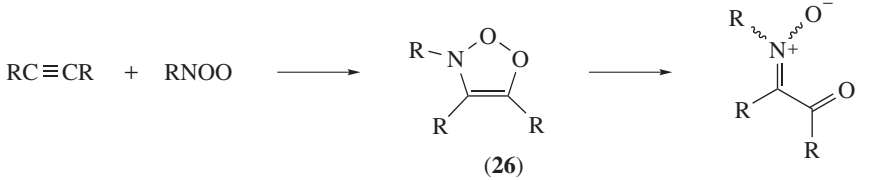
(**24**) (8)

A 4-hydroxy-1,2,4-dioxazolidine (**25**) was proposed as an intermediate in the photooxygenation of *N*-methylnitrones[30], as shown in equation 9. Nitrones that lack a CH group bonded to nitrogen do not react.



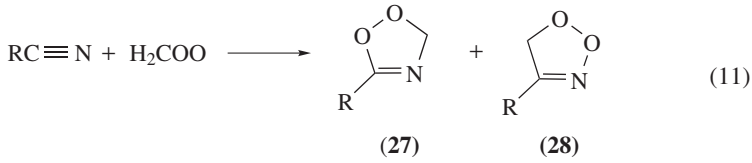
R = H, CH_3; Ar = *p*-MeC_6H_4, *p*-$NO_2C_6H_4$ (9)

Surprisingly, the reaction of nitroso-*O*-oxides with acetylenes remains unstudied. The so-derived ring-closed product would be a 1,2,3-dioxazole (**26**). Ring opening would then form an α-oxonitrone, a relatively unstudied class of compounds (equation 10). These species, in turn, exist as *E*- and *Z*-isomers for which photochemically induced isomerism of the former to the latter has been observed without any dioxazoline found as an associated byproduct[61].



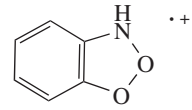
(10)

The cycloaddition reaction of carbonyl-*O*-oxide with acetonitrile (equation 11, R = Me) has been studied theoretically[62]. In principle, the reaction can proceed to give either the 1,2,4-dioxazole **27** (‘*ortho*’) or 1,2,3-dioxazole **28** (‘*meta*’). The *ortho* reaction has a rather small activation barrier, while that for the *meta* reaction is quite large. In addition, the Gibbs free-energy value for the *ortho* reaction is strongly negative. However, the authors point out that because of the high reactivity of the carbonyl-*O*-oxides and associated side reactions, this cannot serve as a synthetic route to 1,2,4-diazoles[63].



(11)

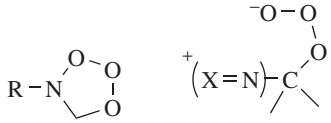
The computed energy of benzo[*d*]-1,2-dioxa-3-azolidine radical cation (**29**) showed it to be slightly stabilized compared to the isomeric nitrobenzene radical cation[64].



(**29**)

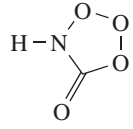
B. Trioxazoles

1,2,3,4-Trioxazolidines (**30**) may be invoked as intermediates in the reaction between C=N-containing compounds and ozone. In the most comprehensive study and discussion[60], only for the case of a Schiff base, where there is no atom attached to the nitrogen that can donate a lone pair of electrons, is it conceded that a 5-membered ring might be the initial adduct. For species such as oximes[60, 65], hydrazones[60] and nitrones[66], the intermediate is shown as an acyclic zwitterion, **31**.



(**30**) (**31**) X = OH, NR_2, R(O)

The parent 1,2,3,4-trioxazolidinone (**32**) is not formed by a gas phase cycloaddition reaction between HNCO and O_3 molecules[67]. Rather, the photochemistry of the ozone and HNCO mixture is dominated by reactions of atomic $O(^1D)$. That alkyl isocyanates are formed in good yield by the reaction of the corresponding isocyanide with ozone documents that the corresponding cycloaddition for substituted species does not proceed either[68].

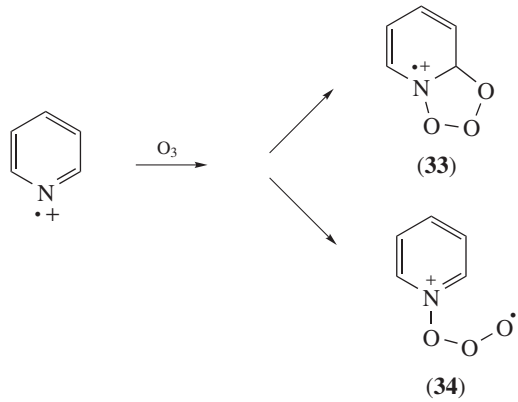


(**32**)

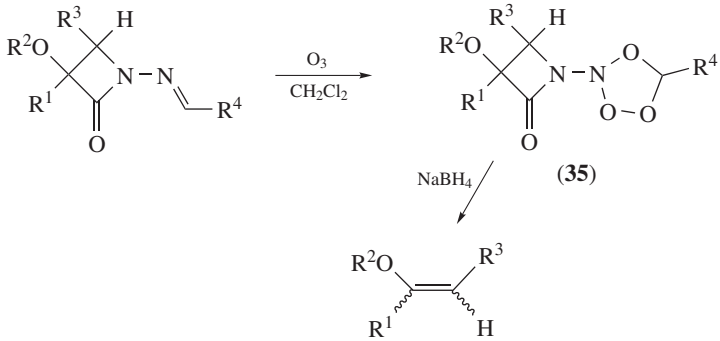
Ozone reaction with pyridine radical cation in the gas phase (equation 12) could lead to the 1,2,3,4-trioxazoline radical cation **33**, although the acyclic trioxy species **34** was computed to be more stable by 24 kcal mol^{-1} [69].

Ozonolysis of *N*-imino-β-lactams, followed by reduction with $NaBH_4$, yields vinyl ethers with moderate to excellent E/Z stereoselectivities (equation 13)[70]. The authors postulated a '1,2,4-trioxolane' ozonide intermediate (1,2,4,3-trioxazolidine derivative, **35**) without mentioning the possibility of prior formation of the '1,2,3-trioxolane' in accordance with the classic alkene ozonolysis pathway. Subsequent *ab initio* studies of the Gibbs energies in solution[71] considered alternate pathways (equation 14, $R^1 = H$, R^2, R^3, $R^4 = Me$). It was found that the primary ozonide (a 1,2,3,4-trioxazolidine, **36**) is formed first in a nearly barrierless process and is 11.8 kcal mol^{-1} more stable than the separated reactants. As in the classic mechanism, the ozonide fragments to give the Criegee intermediates, an *N*-nitroso-β-lactam and the carbonyl-*O*-oxide. The recombination of the carbonyl-*O*-oxide with the nitroso lactam can occur at two sites: the N=O and the C=O to form the ozonides **35** and **37**, respectively. The latter intermediate is formed in a nearly barrierless process, while the energy barrier for formation of the former is 24 kcal mol^{-1}. The 1,2,4-trioxolane derivative **37** is *ca* 21 kcal mol^{-1} more stable than the

1,2,4,3-trioxazolidine, **35**, which in turn is *ca* 23 kcal mol^{-1} more stable than the 1,2,3,4-trioxazolidine, **36**.

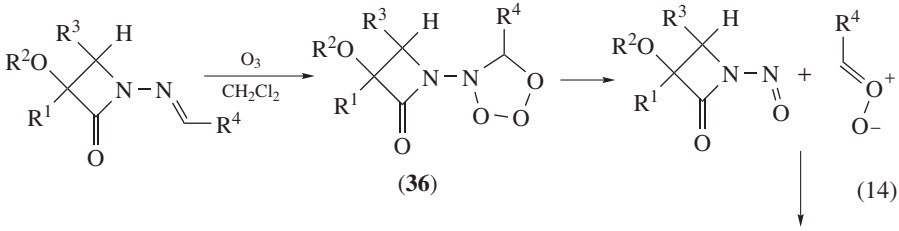


(12)

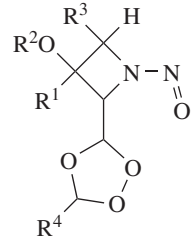


(13)

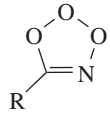
In principle, nitriles can react with ozone to form 1,2,3,4-trioxazoles (**38**). The simplest nitrile is cyanide ion. Fragmentation of the addition product to form oxygen and either a nitrile oxide, acylnitrene or isocyanate could suggest formation of such a heterocycle, at least as an intermediate. However, there is no evidence for this. Cyanide ion reacts[72] with ozone to form cyanate but kinetics show there is little reason, and less evidence, to suggest ring formation as opposed to oxygen atom transfer via radical reactions. Hydrogen cyanide reacts with ozone in a cryogenic matrix to form a O_3−HCN complex where the hydrogen atom interacts with both terminal atoms of O_3. Upon photolysis, HNCO is formed[73]. No evidence for the trioxazole was found. On the other hand, a hydrogen bond complex of monoatomic O with HCN was observed for which intramolecular addition and rearrangement to hydrogen isocyanate and/or cyanic acid is plausible. The theoretical study of the ozone–acetonitrile reaction to give **38**, R = Me, indicates that for the N−O−O fragment, the N−O has some double-bond character, while the O−O bond is considerably weakened, which leads to easy decomposition[62].



(**36**) (14)

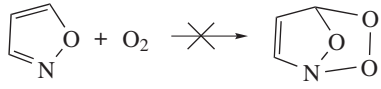


(**37**)



(**38**)

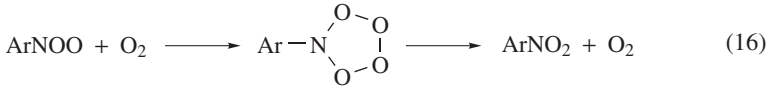
Isoxazoles seemingly do not react with singlet oxyen to form the bicyclic **39** trioxazole (equation 15)[74]. No related singlet oxygen reaction has been reported for any benzo-annelated isoxazole, either anthranil or its isomer benzo[*d*]isoxazole.



(**39**) (15)

C. Tetroxazolidines

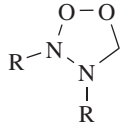
We know of no reports for a [3 + 2]-cycloaddition reaction to form a tetroxazolidine, a cycloNO$_4$ species. Consider equation 16. It is not known whether arylnitroso-*O*-oxides react in the presence of excess oxygen to form nitro compounds with a tetroxazolidine intermediate. This could be tested by using a mixture of $^{16}O^{16}O$ and $^{18}O^{18}O$, since then the nitro compound would contain some $ArN^{16}O^{18}O$ isotopomer.



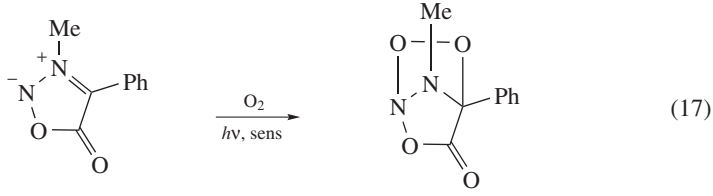
(16)

D. Dioxadiazoles

1,2,3,4-Dioxadiazolidines (**40**) are thought to arise in photooxidation reactions of azomethine imines[75]. For example, the photooxygenation of 3-methyl-4-phenylsydnone (**41**) likely led to the formation of a bicyclic 1,2,3,4-dioxadiazolidine (**42**), as in equation 17, and then to *N*-nitroso compounds upon loss of carbon dioxide, which were further oxidized to benzoic acid[75].

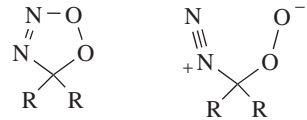


(**40**)



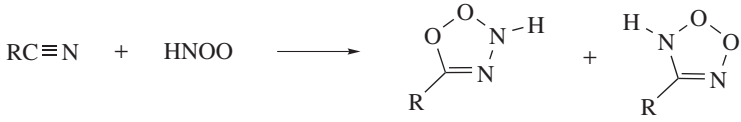
(**41**) (**42**) (17)

Commonly, reactions of diazo compounds, R_2CN_2, with singlet oxygen are used to generate carbonyl-*O*-oxides *in situ*[76–82]. The unstable 1,2,3,4-dioxadiazole intermediate **43** could be formed either directly in a concerted [3 + 2]-cycloaddition or via an acyclic zwitterionic species (**44**)[76]. The dioxadiazole quickly and simultaneously undergoes cycloreversion reactions to the carbonyl-*O*-oxide and N_2 and to the ketone and N_2O. The mechanism of the reaction has been investigated by nanosecond time-resolved UV-vis and IR spectroscopy for R = Ph[77]. The product ratios of N_2/N_2O have been used to indicate the selectivity in the carbonyl-*O*-oxide/ketone formation based on GC/MS[78, 82].



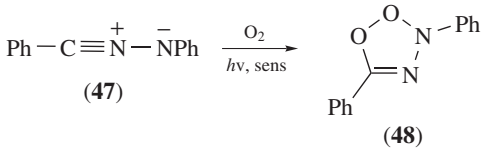
(**43**) (**44**)

The cycloaddition reaction between nitroso-*O*-oxide and acetonitrile was studied by *ab initio* methods[62]. Although the reaction is expected to give the two product dioxadiazoles, **45** and **46** (equation 18, R = Me), no minima corresponding to them were found. In concert with the expected low stability of the heterocycles as well as the nitroso-*O*-oxide, O−O bond cleavage occurred to give the more stable acyclic products.



(**45**) (**46**) (18)

1,2,3,4-Dioxadiazole (**48**) was considered, but not found to be an intermediate in the photooxygenation of nitrilimine **47** (equation 19), which itself arose from the photooxygenation of 3,4-diphenylsydnone[75].



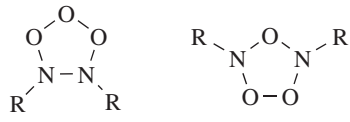
(**47**) (**48**) (19)

For the 1,2,3,5-dioxadiazoles (**46**), a synthesis and the chemistry of the parent dinitrosomethanide ion, $HC(NO)_2^-$ and the corresponding acid was reported[83–87]. Derivatives were reviewed in 2009[88]. The 2005 study[87] complements a set of studies 100 years previously[83] on some C-substituted derivatives of the dinitrosomethanide. This invites the question of whether these anions can be transformed into the corresponding cations and salts derivable from both charge states. If so, the $RC(NO)_2$ framework may possibly be 'ambisaline'[89] with R = alkyl or aryl providing stabilization of the positive central carbon. While the anions have been demonstrated to have a 'w' geometry, the cations are plausibly 'u'-shaped or closed to form the isomeric O–O bridged 1,2,3,5-dioxadiazolium derivatives. Such species have not been observed experimentally, but computational studies are in progress[90]. We acknowledge the possibility of the 's' isomer or even of rapid, irreversible decomposition of the latter cations to the nitrile oxide ($RCNO + NO^+$) or even the nitrile ($RCN + NO_2^+$). The nitronium ion reactions are often conducted in acetonitrile[91], and indeed, NO_2^+ forms gas-phase complexes/cluster ions with acetonitrile[92]. 1,2,3,5-Dioxadiazolium derivatives remain unknown, and indeed, undiscussed.

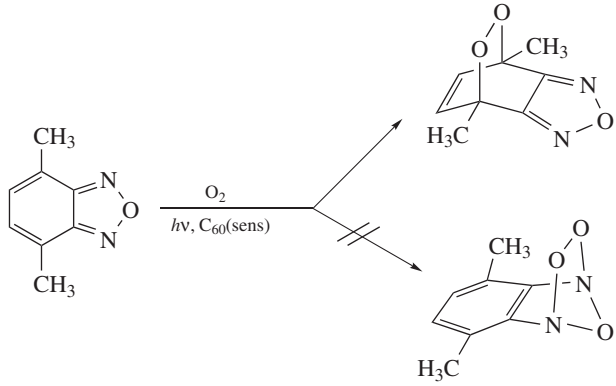
E. Trioxadiazoles

The destruction of azo dyes by ozone has long been observed[93, 94]. The intermediacy of 1,2,3,4,5-trioxadiazolidines (**49**) by concerted [3 + 2]-cycloaddition may be postulated. As part of a combined experimental/theoretical study[95], it was mentioned that such a reaction intermediate was not found on the potential energy surface for the reaction of dimethyldiazene (R = Me) with ozone. The ozonide instability was attributed to lone pair–lone pair repulsion that is not relieved by puckering. It was noted that a planar ozonide would be a 10π electron system. Interestingly, the dimethyldiazene instead reacts with ozone to yield the diazene-*N*-oxide and singlet oxygen. In this same study, a 1,2,4,3,5-trioxadiazolidine (**50**, R = Me) was a postulated intermediate in the ozonolysis of dimethylhydrazine to dimethyldiazene. For the same reasons cited for the diazene–ozone reaction, this species was also not found.

It is well-established that phenylnitroso-*O*-oxides transfer oxygen atoms to nitrosoarenes[55]. As the corresponding nitroarene is formed, but not also nitrobenzene, this provides evidence against the formation of a 1,2,4,3,5-trioxadiazolidine derivative as an intermediate in this reaction. Singlet oxygen reacts reversibly and nearly quantitatively with 4,7-dimethylbenzofurazan (but not benzofurazan or the 5,6-derivative) to form the corresponding 4,7-endoperoxide[96]. This last species is thus not a derivative of 1,2,4,3,5-trioxadiazolidine, as would be produced by 1,3-cycloaddition to the furazan ring (equation 20).



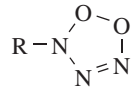
(**49**) (**50**)



(20)

F. Dioxatriazoles

Studies show the production of N_2O, nitro and nitroso products via nitrene–O_2 formed from photooxidations of aryl azides and *O*-substituted diazeniumdiolates[97]. 1,2,3,4,5-Dioxatriazoles (**51**) as intermediates have been postulated[98, 99], but there is no evidence for their existence. The direct addition of singlet oxygen to organic azides also does not appear to form 1,2,3,4,5-dioxatriazoles[100]. For example, photolysis of nitro-substituted aromatic azides produced a complex series of reactions derived from primary (singlet nitrene, triplet nitrene, triplet azide) and secondary intermediate species (nitroso-*O*-oxide, dioxaziridine, 1,2,4,5,3,6-tetroxa-3,6-diazine and ring-expanded dehydroazepine). Tars also form in photooxidations of aryl azides, although one study showed formation of a trace amount of an azide hydroperoxide[101]. The ability of the inorganic sodium azide to convert $^1O_2$ to $^3O_2$ (physical quenching) is well documented[102, 103]. The reaction does not appear to proceed by 1,1- or 1,3-addition to form either an intermediate dioxaziridinide or a 1,2,3,4,5-trioxadiazolide ion that results in $NO_2^- + N_2$ or $NO^- + N_2O$ as final products.

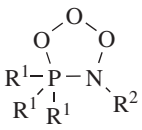


(**51**)

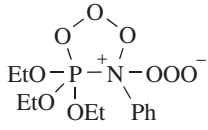
G. Trioxazaphospholes

Phosphine and phosphite imines (iminophosphoranes) react with ozone to form the corresponding phosphine oxide (phosphate) and nitro compounds in a synthetically

useful reaction[104]. ^{31}P NMR evidence has been offered for the intermediacy of 1,2,3,4,5-trioxaphospholidines (**52**), such as the 4-phenyl-5,5,5-triethoxy species ($R^1 = OEt$, $R^2 = Ph$), as well as an "overoxidized" N-trioxy derivative (**53**)[105].



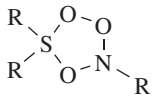
(**52**)



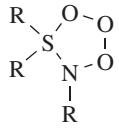
(**53**)

H. Trioxathiazoles and Related Rings

In Reference 10 are found the expected oxygenation reactions of nitroso-*O*-oxides with sulfides to form sulfoxides and with sulfoxides to form sulfones, as well as the deoxygenation reaction of sulfoxides to form sulfides. A possible intermediate, but disqualified by isotope labeling, was the heterocycle λ^4-1,2,4,3,5-trioxathiazolidine **54**. The isomeric heterocycle, λ^4-1,2,3,4,5-trioxathiazolidine **55**, plausibly formed by ozonolysis of sulfide imines remains unstudied. The ring contracted λ^4-1,2,3,4-dioxathiazetidines, **56**, likewise are unreported, whether arising from alternative reactions of nitroso-*O*-oxides with either sulfides and sulfoxide, or sulfide imines with singlet oxygen, or even sulfoxides with nitroso compounds. Indeed, the closest we get to the last ring system, but in its non-hypervalent form (i.e. there are no affixed groups on the sulfur), arises from the reaction of a transiently formed thionitrosoarene with oxygen wherein its acyclic counterpart, a *N*-sulfinylaniline *O*-oxide, was suggested as an intermediate[106]. While synthesis of 1,2,4,3,5-dioxathiadiazolidines (**57**) from 1,2,5-thiadiazoles and singlet oxygen appears plausible, no such reaction occurs. The latter ring system (in admittedly highly annelated form) is useful in the production of singlet oxygen[107] but there is no evidence for the intermediacy of its endoperoxide, i.e. a transient 1,2,4,3,5-dioxathiadiazolidine derivative.



(**54**)



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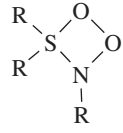
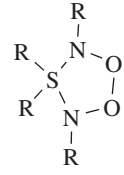


(**56**)



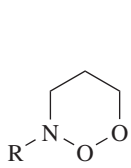
(**57**)

V. COMPOUNDS WITH 6-MEMBERED RINGS

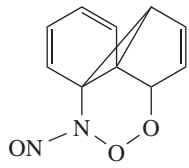
A. Dioxazines

Nearly all of the dioxazines found in the literature are bis-1,4-oxazine derivatives (dibenzo-annelated 1,5-dioxa-4,8-diazaanthracenes), much as phenoxazine itself is 9-oxa-10-azaanthracene. There are some derivatives of 1,4,2-dioxazine in the literature as well. Monocyclic 1,2,3-dioxazines (**58**) appear to be unknown, although a related polycyclic compound (**59**) was suggested in a singlet oxygen reaction with 1,6-imino[10]annulene[108]. The 9,10-endoperoxide of acridine (**60**) has been suggested, but was poorly characterized[109]. Acridines such as trypaflavine are $^1O_2$-generating

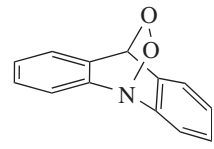
photosensitizers and chemically unreactive toward singlet oxygen[110]. Interestingly, acridine endoperoxides are similar structurally to anthracene endoperoxide systems, which are very well-established compounds[111, 112].



(**58**)



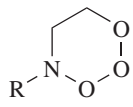
(**59**)



(**60**)

B. Trioxazines

1,2,3,4-Trioxazines (**61**) appear to be unknown. (Trioxazine is also a trivial name for *N*-(3,4,5-trimethoxybenzoyl)morpholine, a tranquilizer, and so is an interesting verbal contradiction to the high-energy species we expect 1,2,3,4-trioxazines to be.) 1,2,4,3-Trioxazines (**62**) are also unknown.



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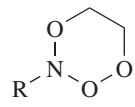
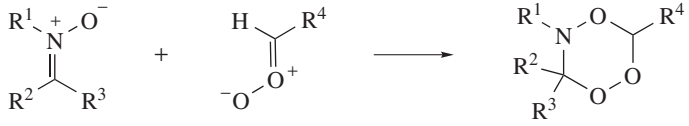


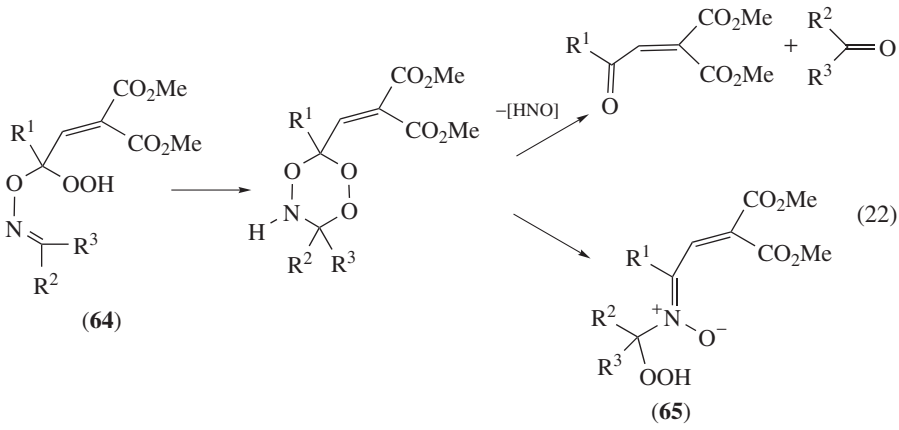
(**62**)

Nitrones are isoelectronic analogs of carbonyl-*O*-oxides. While nitrones are quite common and remain monomeric[113], carbonyl-*O*-oxides are generally transient and can dimerize to form 1,2,4,5-tetroxanes[114, 115]. The [3 + 3]-dimerization of a carbonyl-*O*-oxide is thermally forbidden, and thus probably occurs in a stepwise process[116, 117]. Consider the mixed dimers of nitrones and carbonyl-*O*-oxides, the dihydro-1,2,4,5-trioxazines (**63**). Examples are known of these species formed from [3 + 3]-cycloaddition reactions of the two fragments (equation 21), where the carbonyl-*O*-oxide was prepared *in situ* by ozonolysis of vinyl ethers[118, 119]. Examples include the crystallographically characterized dihydro-3,5,6-triphenyl-l,2,4,5-trioxazine (**63a**) and dihydro-3-cyclohexyl-5-methyl-6,6-dipheny1-1,2,4,5-trioxazine (**63b**). A different entry to the 1,2,4,5-trioxazines is through an intramolecular cyclization of α-oxime ether hydroperoxides[120], **64**. For the cases where $R^2 = H$ and R^3 is aliphatic, the trioxazine rearranges to form a hydroxyperoxyketonitrone, **65**. With R^3 aromatic or when neither substituent is hydrogen, decomposition occurs (equation 22). *Ab initio* and semiempirical calculations have been performed on 1,2,4,5-trioxazine and some alkyl and phenyl derivatives[121]. The chair conformation is generally the most stable one.



(21)

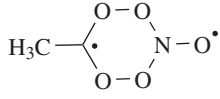
(**63**) (**a**) $R_1 = R_2 = R_4 = Ph$, $R_3 = H$
(**b**) $R_1 = Me$, $R_2 = R_3 = Ph$, $R_4 = c$-Hex



(22)

C. Tetroxazines

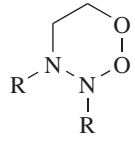
Isomerizations of peroxyacetyl nitrate, $CH_3C(O)OONO_2$, have been examined by *ab initio* calculations[122]. Peroxyacetyl nitrate is found in the atmosphere and possesses a weak OO−N bond making it prone to fragment to $CH_3C(O)OO$ and NO_2 radicals. Although 6-methyl-1,2,4,5,3-tetroxazin-6-oxyl diradical (**66**) was considered as an isomer, there is no experimental evidence for its existence. Neither is there evidence for either of its ring-closed counterparts, a 2,3,6,7-tetraoxa-1-aza-norbornane or a 2,3,5,6-tetraoxa-1-azabicyclo[2.2.0]hexane.



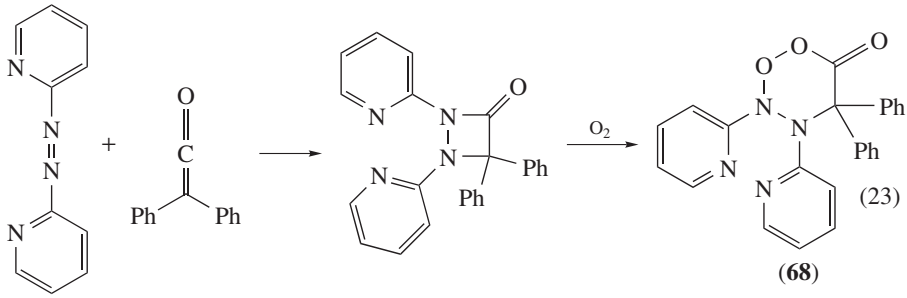
(**66**)

D. Dioxadiazines

1,2,3,4-Dioxadiazines, **67**, have scarcely been studied. Cycloaddion of 2,2′-azodipyridine and *in situ* formed diphenylketene (generated from 'azibenzil' i.e. 2-diazo-2-phenylacetophenone, PhC(O)C(NN)Ph) followed by autooxidation of the initially formed 1,2-diazetidinone results in dihydro-5,5-diphenyl-3,4-di-2-pyridyl-1,2,3,4-dioxadiazin-6-one (**68**) (equation 23)[123]. The corresponding 2-quinolinyl derivative was also observed.

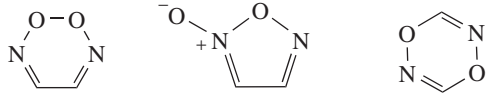


(**67**)



(**68**) (23)

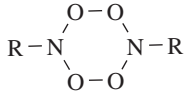
From the late 19th century until the middle of the 20th century, a class of compounds known as 'glyoxime peroxides' was extensively chronicled. The class name reflected their provenance and purported peroxide functionality—the oxidative dehydrogenation of α-dioximes (glyoximes) was initially thought to produce 1,2,3,6-dioxadiazines (**69**)[124]. Subsequently, these compounds were instead proposed to be the isomeric furoxanes (**70**) based primarily on chemical and IR spectroscopic evidence[125–128]. An alternative route to 1,2,3,6-dioxadiazines could involve the addition of oxygen to 1,4-diazabutadienes (α-diimines). While numerous products have been observed, these peroxynitrogen heterocycles are not among them[74, 129, 130]. There has been a renaissance of the chemistry of derivatives of 1,4,2,5-dioxadiazine (**71**) by the molecular metallosupramolecular[131] and high-energy density materials[132] communities. Accordingly, we encourage reinvestigation of the isomeric peroxide-containing 1,2,3,6-dioxadiazine ring system as its derivatives look plausible, if yet unrealized.



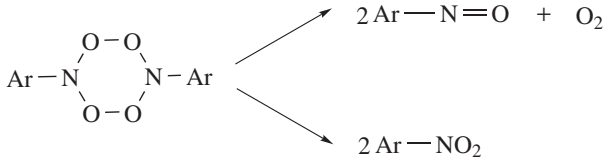
(**69**) (**70**) (**71**)

E. Tetroxadiazines

Occasionally accompanying the nitroso-*O*-oxides are their dimers (1,2,4,5-tetroxa-3,6-diazine, **72**). For example, the photooxidation of *p*-nitrophenyl azide involved the reaction of *p*-nitrophenyl nitrene with O_2 yielding the corresponding nitroso-*O*-oxide. Dimerization of the arylnitroso-*O*-oxide was suggested to give the tetroxadiazine, which rapidly cleaved to yield the aryl nitroso, ArN=O, and O_2 or fragmented to give two equivalents of $ArNO_2$ as shown in equation 24[133–135].



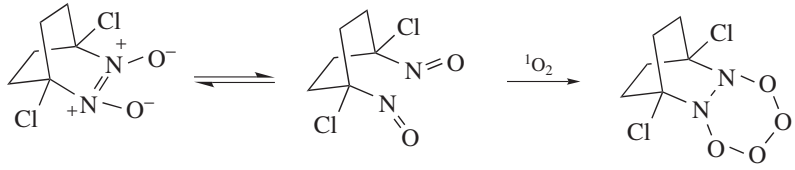
(**72**)



(24)

An observation that variation of the laser irradiation power leads to different product distributions of tetroxadiazine vs dioxaziridine constitutes an important discovery[11]. High concentrations of nitroso-*O*-oxide can favor its dimerization to the tetroxadiazine, rather than intramolecular cyclization to the dioxaziridine. For further discussion of the tetroxadiazine and decomposition pathway (equation 24), see a recent review[7].

It has been found that *cis*-nitroso dimers, such as azodioxide **73**, quench singlet oxygen[136]. At least part of the singlet oxygen quenching by **73** was due to **74** (equation 25). If a cyclic product were involved, it would be a 1,2,3,4,5,6-tetraoxadiazine (**75**) derivative.

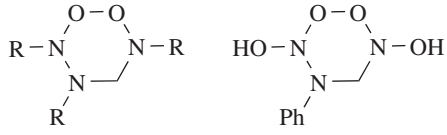


(**73**) (**74**) (**75**)

(25)

F. Dioxatriazines

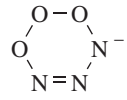
Over 100 years ago, compounds containing the 1,2,3,4,6-dioxatriazine ring system (**76**) were studied. For example, the 4-(2-methylphenyl) and 3,6-dihydroxy-4-phenyl (**77**) derivatives were claimed to have been produced[137] from the reaction of a related ethyl carboxylate[138] with alkali. However, there is no structural corroboration for these findings, nor seemingly even a reinvestigation of the early experiments.



(**76**) (**77**)

G. Trioxatriazines

Aqueous azide ion is known to react with ozone to form nitrogen, nitrous oxide and singlet oxygen[139]. The mechanism, and even the mass balance, remains unknown. We wonder about the possible intermediacy of 1,2,3,4,5,6-trioxatriazine anion (**78**). The reaction of organic azides with ozone to form covalent derivatives of **78** remains unreported.

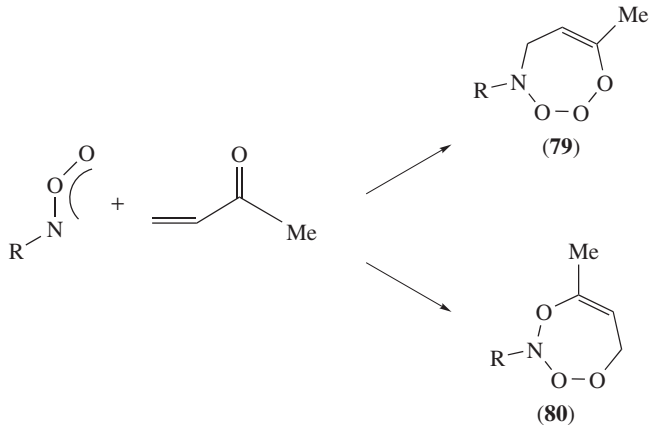


(**78**)

VI. COMPOUNDS WITH 7-MEMBERED OR LARGER RINGS

A. Oxazepines

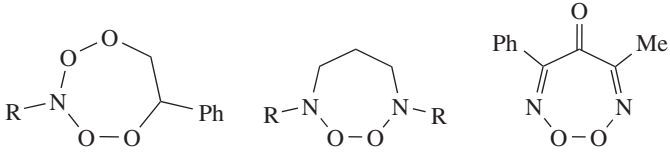
The reaction of nitroso-*O*-oxides with methyl vinyl ketone was shown to be anomalously rapid compared to that with a variety of other olefins[140]. The possibility of formation of the 4,5-dihydro-1,2,3,4-trioxazepine (**79**) and/or 4,5-dihydro-1,2,4,3-trioxazepine (**80**) by [4 + 3]-cycloaddition or a stepwise radical reaction is intriguing (equation 26). Studies of simple conjugated and unconjugated dienes are welcomed.



(**79**) (**80**) (26)

Sequential reactions of a substituted styrene, phenylnitroso-*O*-oxide and dioxygen form the nitrosobenzene and the styrene-related ketone[55]. While 'the carbonyl oxide H_2COO was not ascertained', the intermediacy of the ring-closed 1,2,4,5,3-tetraoxazepine (**81**) seems plausible.

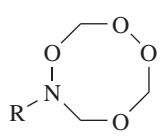
We know of no dioxadiazepines such as 1,2-dioxa-3,7-diazepine (**82**). Associated with studies of the aforementioned glyoxime peroxides was a claim for 4-methyl-6-phenyl-1,2,3,7-dioxadiazepin-5-one (**83**) and its oxime[141–143], formed in the reactions of HNO_3 and HNO_2 with PhCH=CHC(=NOH)Me and its related aryl derivatives. However, no corroboration was offered for this structure in later studies. As the glyoxime peroxide structures were incorrectly identified, we are accordingly doubtful as to this species being a dioxadiazepine.



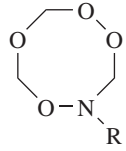
(**81**) (**82**) (**83**)

B. Oxazocines

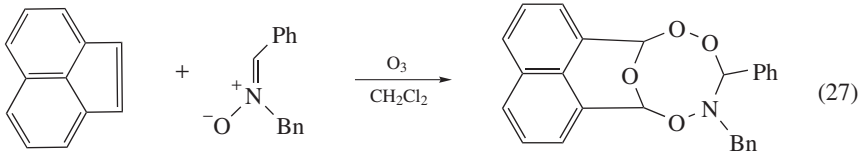
We know of no examples of monocyclic oxazocines, **84** and **85**. Dihydrotetroxazocines may be formed by formal [3 + 3 + 2]-cycloaddition reactions of carbonyl compounds, carbonyl-*O*-oxides and nitrones. Such species in ring-annelated form, more precisely 1,7-epoxy-1*H*,7*H*-naphtho[1,8-*gh*][1,2,5,4] trioxazecines, have been synthesized (equation 27)[144] and the structure of the 4-phenyl-5-benzyl derivative, **86**, was determined crystallographically.



(**84**)

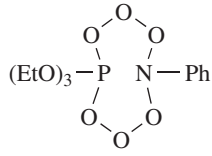


(**85**)



(**86**) (27)

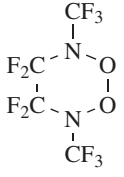
From the reaction of triethylphosphite *N*-phenylimine with ozone, an 8-membered ring species, 1,2,3,5,6,7,4,8-hexoxazaphosphocine (**87**)[105], was suggested.



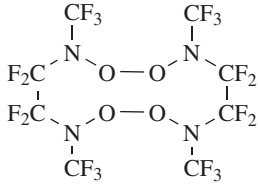
(**87**)

C. Larger Rings

The perfluorinated bis-nitroxide radical, $CF_3N(O)CF_2CF_2N(O)CF_3$, is rather readily synthesized[145, 146] and shows no sign of ring closure to form the saturated 1,2,3,6-dioxadiazine (**88**). However, an all-electron-paired dimer has been suggested[147], which could be a saturated 1,2,7,8,3,6,9,12-tetroxatetrazadodecin derivative (**89**).



(**88**)

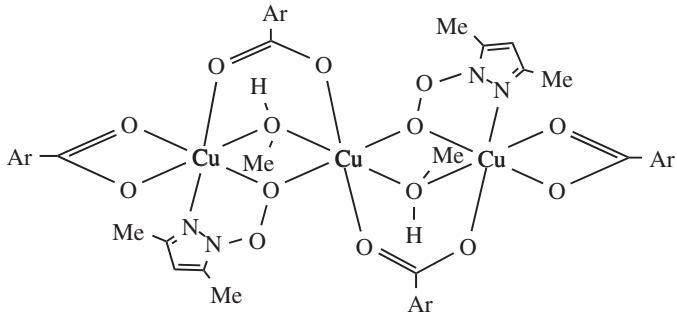


(**89**)

VII. METALLOCYCLES

There are four recently reported examples of metallocycles where a metal ion is incorporated in the ring that also contains the peroxynitrogen groups.

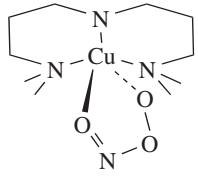
An aminoperoxide radical complex is formed in a one-pot reaction between copper(II)acetate, 3,5-dimethylpyrazole, *p*-chlorobenzoic acid and hydrogen peroxide[148]. The N−O−O$^{\bullet}$ radical is formed from the oxidation of the pyrazole by a loss of hydrogen. The crystal structure shows the complex is trimetallic and includes two bridging methanol groups (cf. **90**). Using benzoic acid instead of *p*-chlorobenzoic acid results in a polymeric chain-like structure.



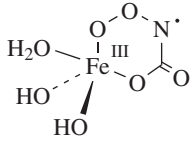
(**90**) Ar = *p*-ClC$_6$H$_4$

Bubbling O_2 through a solution of a copper nitrosyl complex produced a peroxynitrite complex $[Cu^{II}(AN)(ONOO^-)]^+$ (AN = 3, 3′-iminobis(*N*,*N*′-dimethylpropylamine)) (**91**)[149]. Although an X-ray structure was not determined, DFT calculations found the lowest energy structure to contain a cyclic bidentate peroxynitrite ligand bound to copper with two different Cu−O distances. Thermal isomerization to a nitrate complex, as in iron complexes, is not observed, but rather 0.5 mol equivalents of O_2 is evolved to form the nitrite complex, similar to what is found for manganese[150]. In an earlier study, the same research group verified by X-ray the structure of the nitrite complex after oxygen evolution, but with the TMG_3tren ligand ($TMG_3tren = (Me_2N)_2C{=}N{-}(CH_2)_3{-}NH{-}(CH_2)_3{-}N{=}C(NMe_2)_2$) instead of AN[151].

The mechanism of cyanide oxidation by ferrate in aqueous solution was studied by DFT calculations[152]. One of the intermediates in the pathway is a 6-membered ring containing iron and is the only example we know of a perhydroxamic acid (**92**).



(**91**)



(**92**)

VIII. ACKNOWLEDGMENTS

A.G. thanks the National Institutes of Health (SC1 GM093830) for support.

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