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RECENT ADVANCES IN THE SYNTHESIS OF HETEROCYCLES FROM OXIMES

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Abstract – Modern methodologies of preparation of three-, five-, six- and seven-membered heterocyclic compounds from oximes and their derivatives have been reviewed. Syntheses of bicyclic and tricyclic ring systems from oximes are included.

4. SYNTHESIS OF SEVEN-MEMBERED RING SYSTEMS FROM OXIMES
5. SYNTHESIS OF BICYCLIC AND TRICYCLIC RING SYSTEMS FROM OXIMES

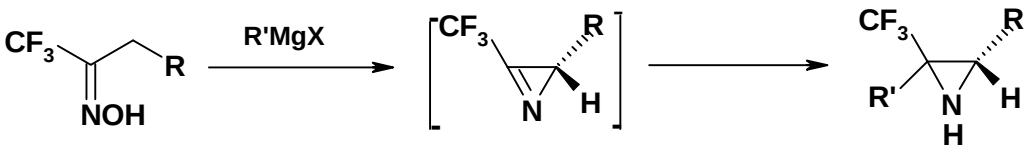
INTRODUCTION

Oximes and their derivatives are widely used in organic chemistry. A number of reviews are devoted to the chemistry and biological activity of oximes and their derivatives.[1-17] Although some of these reviews appeared regarding to the synthesis of heterocyclic compounds, no general reviews about the recent advances in the synthesis of heterocyclic compounds from oximes and their derivatives have been published. Synthesis of heterocycles from amino amide oximes is reviewed only.[18] Recently we have published a review dedicated to the synthesis of oximes, oxime *O*-ethers and esters.[19]

The aim of present review is to describe modern methodologies of synthesis of heterocyclic compounds from oximes and oxime derivatives. The literature data published between January 1990 and December 1999 are included in this review.

1. SYNTHESIS OF AZIRIDINES FROM OXIMES

Trifluoromethyl derivatives of aziridines are intensively studied as biologically active substances. Trifluoromethylaziridines (**2**) are prepared from trifluoromethyloximes (**1**) and Grignard reagents (Scheme 1).



1 **2**

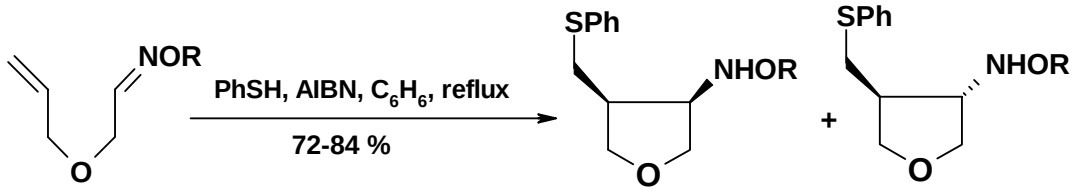
Scheme 1

However, this reaction is not general; when it works *Z* stereoisomer is formed. For example, reaction does not occur with phenyl and allyl Grignard reagent.[20, 21]

2. SYNTHESIS OF FIVE-MEMBERED RING SYSTEMS FROM OXIMES

2.1. Tetrahydrofuran

A thiophenol promoted radical cyclization of oxime ethers into tetrahydrofurans and pyrrolidines is recently described. For example, oxime derivative (**3**) in the presence of thiophenol and AIBN afforded substituted tetrahydrofurans (**4**) and (**5**) in a ratio 1.2-3 : 1 (Scheme 2).[22, 23]



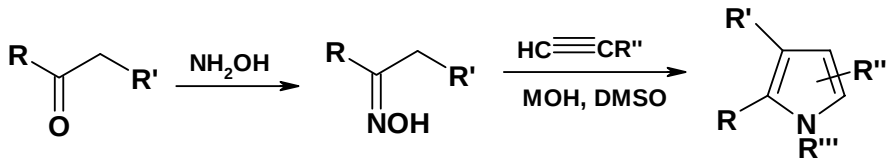
3 **4** **5**

R = alkyl, benzyl

Scheme 2

2.2. Pyrrole, pyrrolidine, and indole

General synthesis of pyrroles and 1-vinylpyrroles by reaction of ketoximes with acetylenes and their synthetic equivalents (vinyl halides and dihalomethanes) in the presence of the strongly basic KOH/DMSO system (Trofimov reaction) are well reviewed [24-27] in recent years and therefore in the present work it will be described very shortly. In principle pyrrole (**8**) synthesis can be carried out as a one-pot procedure by treating ketones (**6**) with hydroxylamine and then reacting the ketoximes (**7**) formed with acetylenes (Scheme 3).

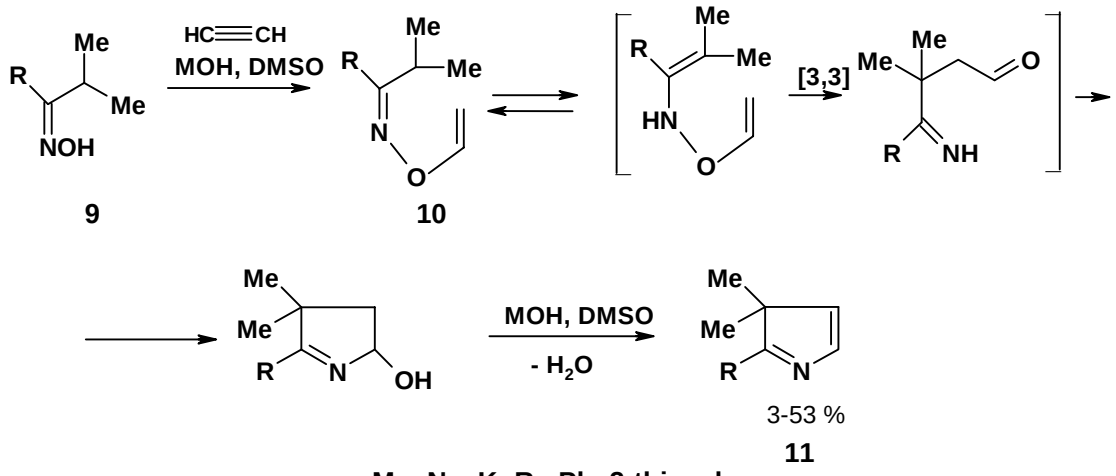


6 **7** **8**

R,R’ = alkyl, aryl, hetaryl; R’’ = H, Me, Ph; R’’’= H, CH_2=CH, PhCH=CH; M = Li, Na, K, Rb, Cs

Scheme 3

2-Phenyl- and 2-(2-thienyl)-3,3-dimethyl-3*H*-pyrroles (**11**) are obtained by reaction of corresponding ketoximes (**9**) with acetylene catalyzed by MOH (M = Na, K) in DMSO. As an intermediate of reaction there is observed the corresponding *O*-vinyl oxime (**10**) which undergo [3,3] sigmatropic rearrangement and cyclization to obtain products (**11**) (Scheme 4). The yield of obtained products strongly depends on the structure of the ketoxime and the reaction products.[28]

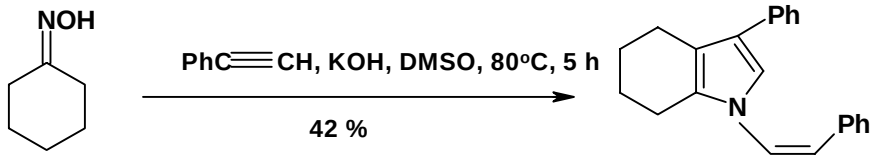


9 **10** **11**

M = Na, K; R= Ph, 2-thienyl

Scheme 4

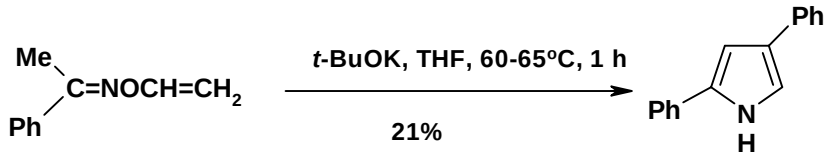
Reaction of cyclohexanone oxime (**12**) with phenylacetylene in the presence of KOH / DMSO afforded *Z*-[1-(2-phenylvinyl)]-3-phenyl-4,5,6,7-tetrahydroindole (**13**) as the main product (Scheme 5).[29]



12 **13**

Scheme 5

Transformation of *O*-vinylacetophenone oxime (**14**) in the system *t*-BuOK / THF has been studied. The reaction at 60-65°C afforded 2,4-diphenylpyrrole (**15**) and oligomeric products instead of desired 2-phenylpyrrole (Scheme 6).[30]

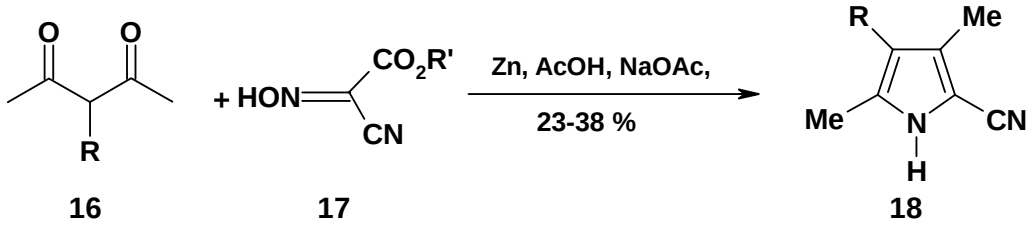


14 **15**

Scheme 6

Regioselective synthesis of 2-cyanopyrroles (**18**) using oximinocyanoacetate esters (**17**) in a Knorr-type reductive condensation with diketones (**16**) can be directed by the presence of water (Scheme 7). Thus, methyl oximinocyanoacetate was reacted with pentane-2,4-dione in hot acetic acid in the presence of zinc

dust to give exclusively 3,5-dimethylpyrrole-2-carbonitrile when the acetic acid was wet. However, in glacial acetic acid only 3,5-dimethylpyrrole-2-carboxylate was isolated (~40 % yield).[31]

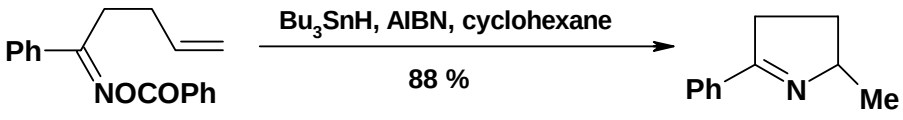


16 **17** **18**

R= H, $CH_2CH_2CO_2Me$

Scheme 7

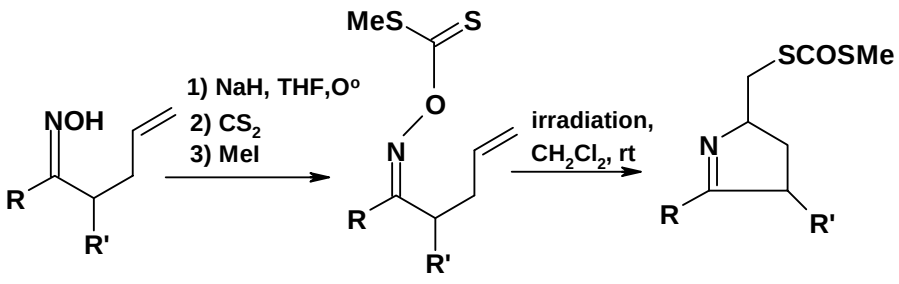
Oxime benzoates react with Bu_3SnH in the presence of AIBN to give iminyl radicals, which can be captured by an internal olefin. Thus, slow addition of Bu_3SnH and AIBN to refluxed solution of oxime (**19**) in cyclohexane afforded pyrrolenine (**20**) in good yield (Scheme 8).[32,33]



19 **20**

Scheme 8

Irradiation of ketoxime *O*-(*S*-methyl xanthates) (**22**)**,** prepared *in situ* from oximes (**21**) and NaH / CS_2 / MeI, leads to a dihydropyrroles (**23**) through cyclization of an intermediate iminyl radical in a radical chain reaction (Scheme 9). The last reaction step involves transfer of a dithiocarbonate group and various external radical traps can be incorporated into medium, allowing access to a variety of substituted dihydropyrroles.[34]



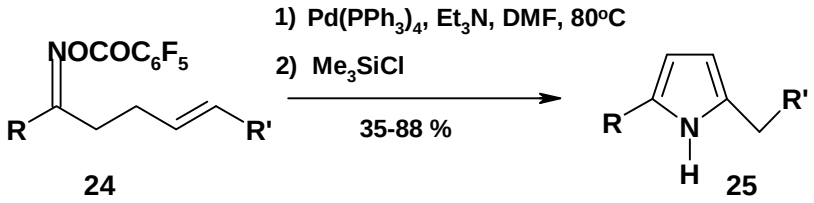
21 **22** **23**

R =alkyl, aryl; R' = H, alkyl; R,R' = cycloalkyl

Scheme 9

Substituted pyrroles (**25**) are synthesized from γ,δ-unsaturated ketone *O*-pentafluorobenzoyl oximes (**24**) by the intramolecular Heck-type amination of the olefinic moiety catalyzed by $Pd(PPh_3)_4$ (Scheme 10).

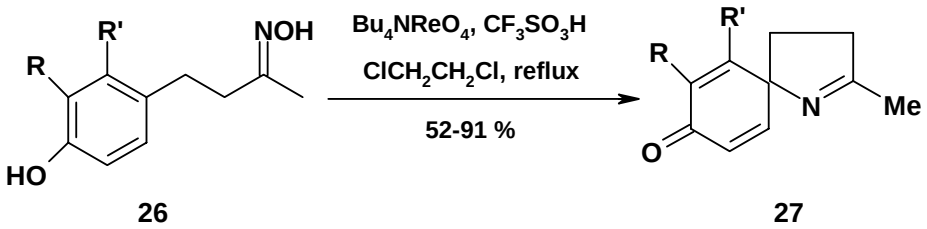
The formation of products (**25**) proceeds *via* 3,4-dihydro-2*H*-pyrroles, which undergo aromatization by treatment with Me_3SiCl.[35]



R = alkyl, aryl; R' = H, Me, CO_2Et

Scheme 10

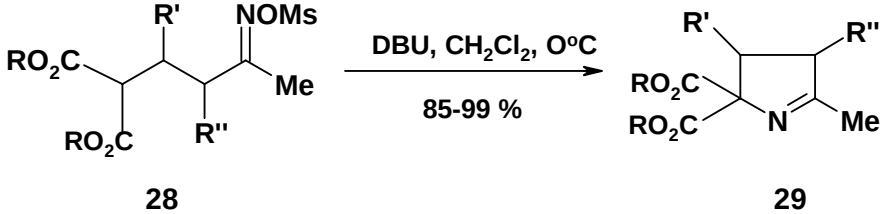
Cyclization of *p*-hydroxybenzylacetone derivatives (**26**) proceeds by treatment with tetrabutylammoniumperrhenate and trifluoromethanesulfonic acid in refluxing $ClCH_2CH_2Cl$ to afford azaspirodienones (**27**) in moderate to good yields (Scheme 11). The azaspirodienones are easily transformed into quinolines *via* dienone-phenol rearrangement. [36-38]



R, R' = H, alkyl

Scheme 11

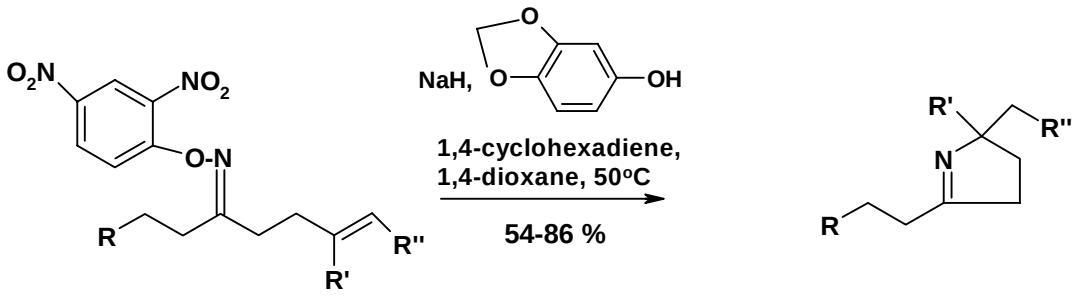
3,4-Dihydro-2*H*-pyrroles (**29**) are prepared from *(E)*-*O*-methylsulfonyl oximes (**28**) having an active methine group at γ–position by treatment with DBU (Scheme 12). The stereoselectivity of the cyclization is an evidence that S_N2 substitution occurs at the nitrogen of oximes (**28**).[39]



R = Me, Bn; R' = H, alkyl, Ph; R'' = H, Me

Scheme 12

Alkylidene radicals can be easily generated from *O*-2,4-dinitrophenyl oximes (**30**) of γ,δ-unsaturated ketones by treatment with NaH and 3,4-methylenedioxyphenol. The resulting radical species intramolecularly add to the olefinic moiety to afford 3,4-dihydro-2*H*-pyrroles (**31**) (Scheme 13) in moderate to good yields.[40, 41]

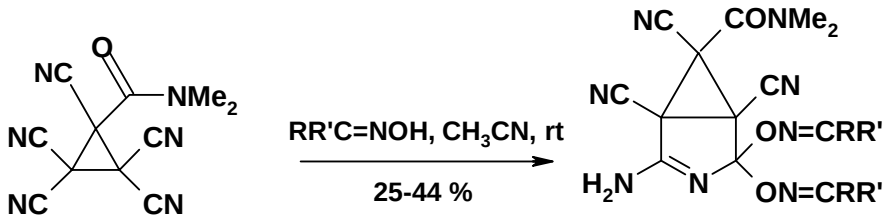


30 **31**

R = alkyl, Ph; R' = H, Me; R'' = H, Ph; R'R'' = cycloalkyl

Scheme 13

Recently it was described that interaction of 1,2,2,3,3-pentacyanocyclopropane-1-carboxamide (**32**), obtained by reaction of tetracyanoethylene and monobromocyanoacetamide, with oximes leads to 4,4-bis(alkylideneaminooxy)-2-amino-*N,N*-dimethyl-1,5,6-tricyano-3-azabicyclo[3.1.0]hex-2-en-6-carbox-amides (**33**) as main products (Scheme14).[42]

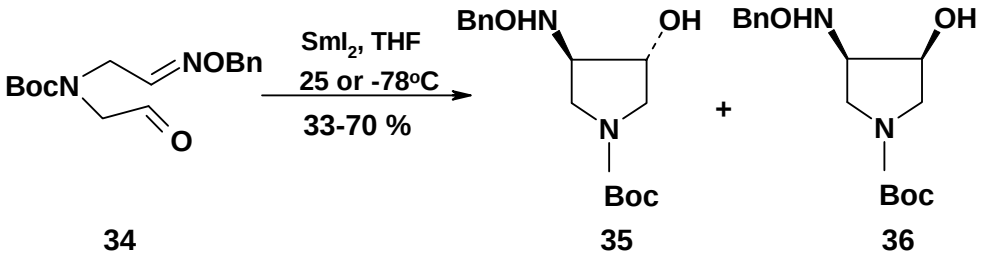


32 **33**

R = Me; R' = Me, Et; R,R' = cyclopentyl

Scheme 14

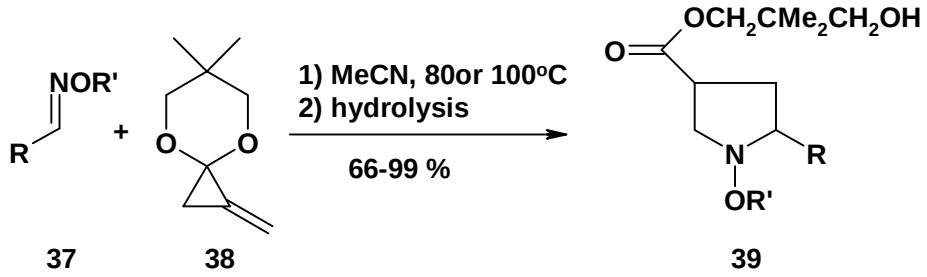
SmI_2 – induced 5-*exo*-*trig* radical cyclization of oxime ethers intramolecularly connected with the formyl group was found to be particularly effective for the preparation of cyclic *trans*-amino alcohols. For example, oxime (**34**) in the presence of SmI_2 in THF at 25°C or -78°C afforded pyrrolidin-3-ols (**35**) and (**36**) in a ratio 3:2 to 9:1 (Scheme 15).[43]



Scheme 15

Similar cyclizations can be carried out in the presence of stannyl radical generated in the system Bu_3SnH / AIBN / benzene.[44] The radical cyclization of oxime ethers anchored to a polymer support by triethylborane as a radical initiator was also reported.[45]

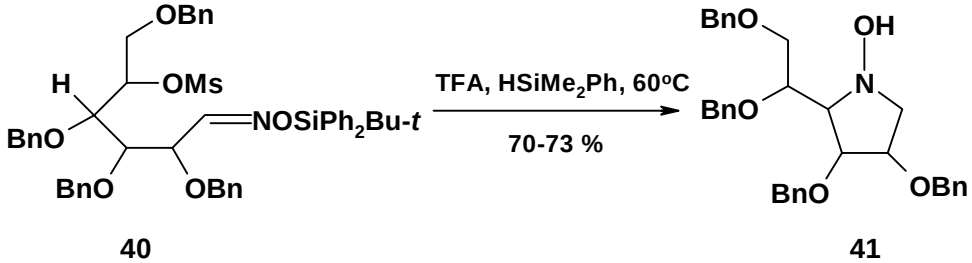
Thermal hetero [3+2] cycloaddition reaction of dipolar trimethylenemethane with *O*-alkyloximes produces substituted pyrrolidines. Thus, heating a mixture of alkylidenecyclopropane (**38**) with *anti*-*O*-alkyloximes (**37**) yields substituted pyrrolidines, which upon hydrolysis under mild conditions give 3-alkoxycarbonylpyrrolidines (**39**) in moderate to good yields (Scheme 16).[46]



R = aryl, hetaryl, CO_2Me; R' = Me, Bn

Scheme 16

The consecutive reduction and cyclization of *O*-benzoyl protected 5-*O*-methylhexose *O*-(*tert*-butyldiphenylsilyl)oximes (**40**) with dimethylphenylsilane in trifluoroacetic acid afforded *N*-hydroxypyrrolidine (**41**) ring system in good yield (Scheme 17). The mechanism involves a cascade of neighboring group participation steps involving the *O*-benzoyl protecting groups.[47]

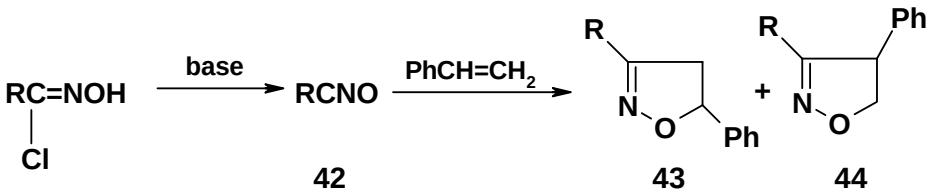


Scheme 17

2.3. Isoxazoles, isoxazolines, benzisoxazoles, oxazolinones, and benzoxazoles

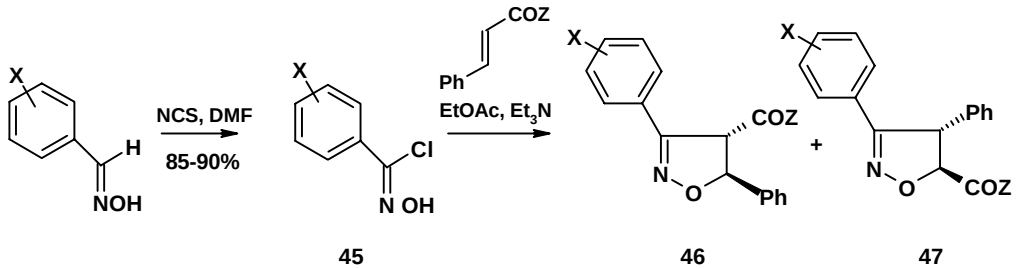
The [2+3] cycloaddition reaction of nitrile oxides, easily accessible from corresponding aldoximes and a weak base, with different alkenes is known as an excellent route to isoxazoline derivatives.[48,49] The reactions of asymmmetric addition [50] or addition of unsaturated germanes and stannanes to nitrile oxides[51] is reviewed in recent years. In this part of work main directions of synthesis of isoxazole derivatives were shortly reported.

Cycloadditions with monosubstituted olefins proceed rapidly and regioselectively to yield the 5-substituted dihydroisoxazoles. Thus, addition of styrene to nitrile oxide (**42**) results in the formation of the 5-phenyl- (**43**) and 4-phenyldihydroisoxazoles (**44**) in a 99: 1 ratio (Scheme 18).[49, 52]



Scheme 18

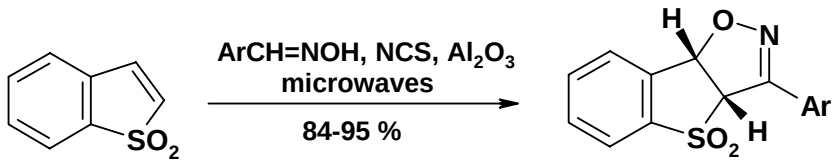
On the other hand, reactions of nitrile oxides with 1,2-disubstituted olefins are slower and regioselectivity usually was not so high. For example, benzonitrile oxide, obtained from corresponding chloro oximes (**45**)**,** undergo 1,3-dipolar cycloaddition reaction with methyl cinnamate to produce the 5-phenyl (**46)** and 4-phenyl (**47)** regioisomers in approximately an 80:20 ratio.[53] However, use of *N*,*N*-diethylcinnamide as the dipolarophile unexpectedly resulted in the formation of the 5-phenyl and 4-phenyl regioisomers in a 23:77 ratio (Scheme 19).



X = H, 2-, 3-, 4-Cl, 4-MeO, 3-NO_2; Z = OMe, NMe_2, NEt_2, NH_2, NHPh

Scheme 19

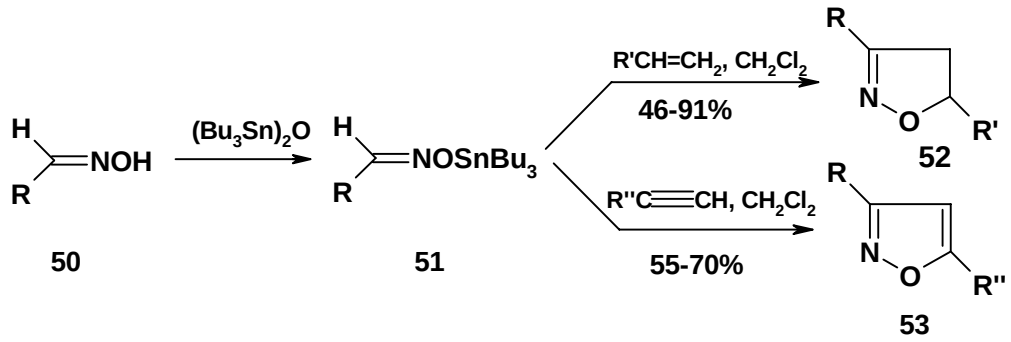
Usually nitrile oxide, necessary in the synthesis of isoxazoline derivatives, was generated from both hydroximoyl halides by interaction with Et_3N, [54] AgOAc in CH_2Cl_2 [55] and corresponding aldoximes in the presence of *N*-chloro- and *N*-bromosuccinimide / Et_3N, [56,57] NaOCl / Et_3N, [58] 1-chlorobenzotriazole / base, [59] $Pb(OAc)_4$, [60] hypervalent iodine compounds, [61] ceric ammonium nitrate, [62] dimethyldioxirane, [63] and MnO_2. [64] Isoxazolines are also prepared from aldoximes and olefins in the presence of $Ca(OCl)_2$ / CH_2Cl_2 [65] and 1-sodio 3,5-dichloro-s-triazine-2,4,6-trione / Al_2O_3 / CH_2Cl_2 systems [66] under ultrasonic or in the presence of Al_2O_3 and Al_2O_3 / NCS under microwave irradiation.[67-68] For example, benzothiophene derivative (**48**) can be easily transformed to corresponding fused isoxazoline (**49**) by treatment with aldoxime /NCS / Al_2O_3 under microwave irradiation (Scheme 20).



48 **49**

Scheme 20

Nitrile oxides were also readily generated by reaction of aldoximes (**50**) with *tert*-butyl hydroperoxide and bis(tributyltin) oxide. The reaction proceeded under mild conditions, in which *O*-stannylated aldoximes (**51**) are key intermediates. This reaction system was applicable to the one-pot synthesis of isoxazole derivatives (**52)** or (**53)** in the presence of alkenes or alkynes (Scheme 21).[69]

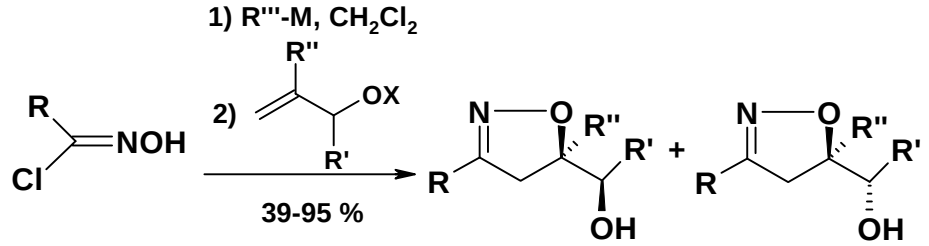


R = alkyl, Ph; R' = alkyl, alkyl, alkoxy, alkoxycarbonyl; R'' = alkyl, Ph, alkoxycarbonyl

Scheme 21

It has been shown that magnesium ions dramatically accelerate nitrile oxide cycloaddition reaction to allylic alcohols, improving both the regio- and stereoselectivity of the reaction. For example, cycloaddition of carbamoyl chloride (**54**) to terminal allylic alcohols bearing α-chirality produces *syn*-

stereoisomers of 2-oxazolines (**55**) selectively. Metal salts other than magnesium, such as lithium, zinc, and aluminium, are less effective (Scheme 22).[70]

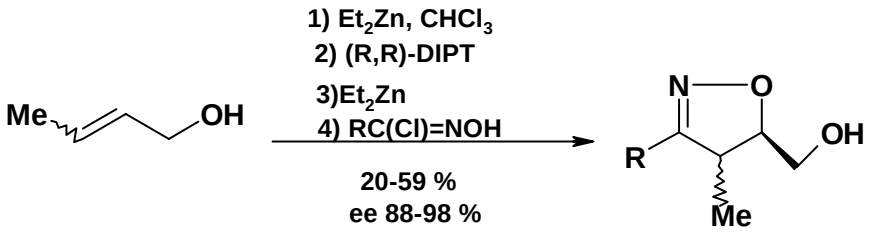


54 syn-**55** anti-**55**

R = aryl; R' = alkyl; R'' = H, alkyl; R'''-M = EtMgBr, Li, Et_2Zn, Et_3Al; X = H, MgBr

Scheme 22

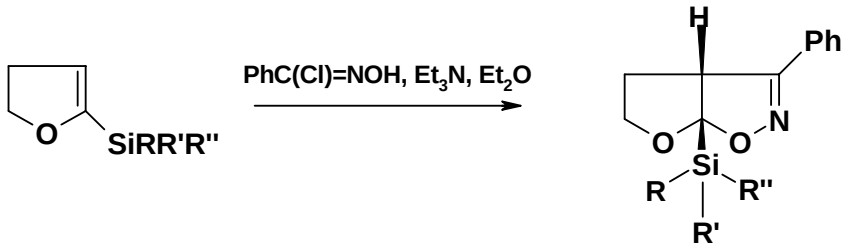
The excellent enantioselectivity is obtained in asymmetric 1,3-dipolar cycloaddition of nitrile oxide to (*E*)- and (*Z*)-2-buten-1-ols (**56**) (Scheme 23). The reactions were performed using diisopropyl (*R,R*)-tartrate ((*R,R*)-DIPT) as a chiral auxiliary to afford the corresponding 3,4,5-trisubstituted 2-isoxazolines (**57**) with high regioselectivity.[71]



56 **57**

Scheme 23

The synthesis of silylsubstituted tetrahydrofuro[2,3-*d*]isoxazoles (**59**) by [2+3] cycloaddition of benzonitrile oxide, prepared *in situ* from benzhydroxamic chloride and E_3N, to 5-(2,3-dihydrofuryl)silanes (**58**) was described (Scheme 24). Compounds with two condensed bicycles at the silicon atom are also prepared by the addition of acetonitrile oxide to the corresponding bis[5-(2,3-dihydrofuryl)]silanes.[72]

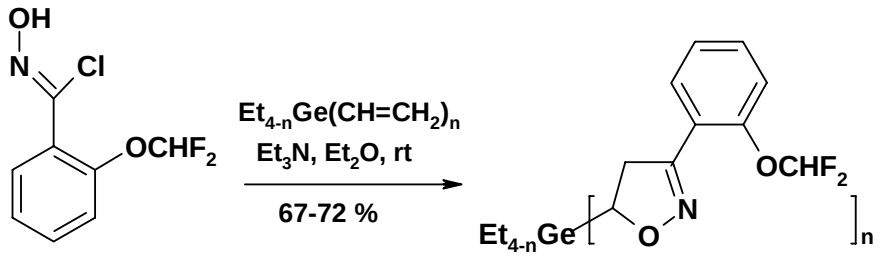


58 **59**

R,R', R'' = Me, phenyl, 2-thienyl

Scheme 24

Synthesis of silyl and germyl substituted 2-oxazolines from nitrile oxides and unsaturated silanes and germanes has been also reported.[73-74] Thus, the reaction of chloride of *o*-difluoromethoxybenzoxamic acid (**60**) with vinyl- and divinylgermanes in the presence Et_3N afforded 2-oxazolines (**61**) (Scheme 25).

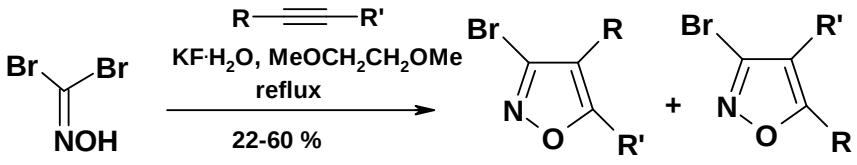


60 **61**

n = 1, 2

Scheme 25

Fluoride ion catalyzed 1,3-dipolar cycloaddition of bromo nitrile oxide, obtained *in situ* from dibromoformaldehyde oxime (**62**), to non-activated alkynes provides a new approach to the synthesis of neuroactive isoxazoles. However, the regioselectivity of cycloaddition in this case is not high - products (**63**) and (**64**) are obtained in a ratio 1: 1 to 1: 1.4 (Scheme 26).[75]

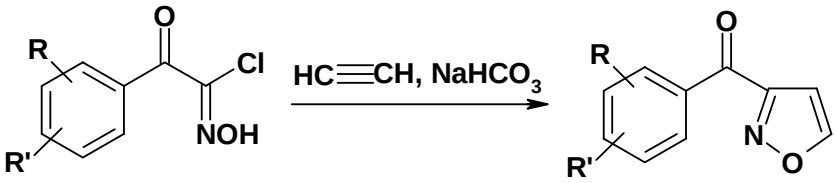


62 **63** **64**

R = Me, CH_2OH, CH_2Cl; R' = CH_2OH, CH_2CH_2OH, $(CH_2)_4Me$, CH_2OH, CH_2Cl

Scheme 26

Cycloaddition reaction of carbamoyl chlorides and acetylene is succesively carried out also in the presence of $NaHCO_3$ as a base.[76] For instance, α-keto oximes (**65**) was reacted with acetylene and $NaHCO_3$ to give isoxazoles (**66**) in good yields (Scheme 27).

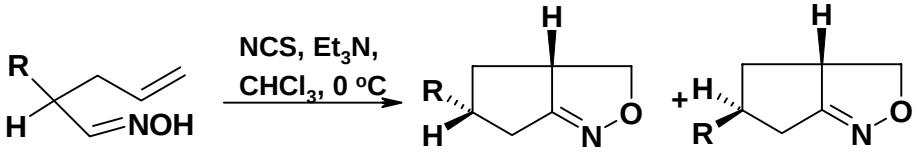


65 **66**

R, R' = H, alkyl, alkoxy, halo

Scheme 27

3-Substituted 5-hexenyl nitrile oxides, which are easily obtained *in situ* from corresponding unsaturated oximes (**67**), undergo intramolecular dipolar cycloaddition to afford bicyclic isoxazole derivatives (**68**) with good *cis*-diasteroselectivity (~9 : 1) (Scheme 28).[77]

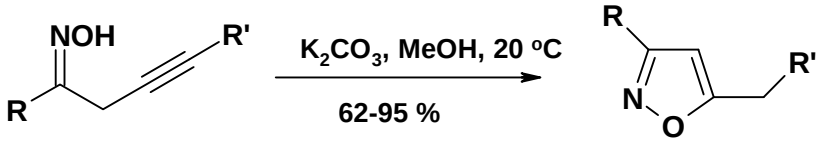


67 *cis*-**68** *trans*-**68**

Scheme 28

Intramolecular cycloaddition of nitrile oxide are used in the synthesis of A-ring fragments of 1α,25-dihydrovitamin D_3 and taxane diterpenoids,[78] sulfur containing isoxazoles,[79] fluoro substituted aminocyclopentanols [80] and aminocyclopentitols. [81] New *gem*- and *vic*-disubstituted effects in such cyclization reactions recently is reviewed by Jung.[82]

β,γ-Acetylenic oximes in the similar manner undergo convertion to 3,5-disubstituted isoxazoles. Thus, oximes (**69**) in the system K_2CO_3 / MeOH at room temperature afforded isoxazoles (**70**) in excellent yields (Scheme 29).[83]

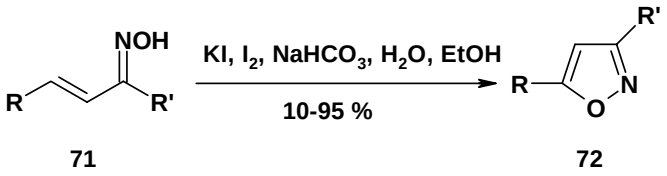


69 **70**

R = alkyl, aryl, hetaryl; R' = alkyl, aryl, $SiMe_3$

Scheme 29

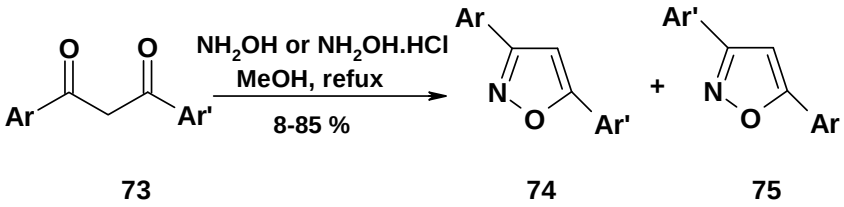
α,β-Unsaturated ketoximes (**71**) can be easily transformed to corresponding 5-arylisoxazoles (**72**) by treatment with iodine and potassium iodide. The presence of isoxazoline is detected in the reaction mixture. (Scheme 30).[84]



R = aryl, hetaryl; R' = alkyl, aryl

Scheme 30

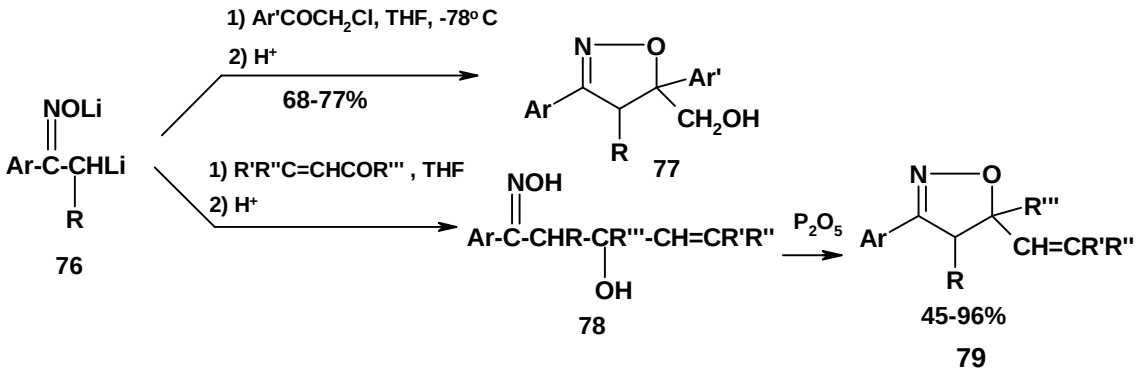
Synthesis of 3,5-diarylisoxazoles (**74**) and (**75**) by the reaction of asymmetrically substituted β-diketones (**73**) with hydroxylamine is investigated (Scheme 31). It has been found that the reaction occurs with a low degree of site-selectivity unless steric effects are operating. The isoxazole that has the more electron-deficient aryl group in position 3 is formed preferably when the reactions are run with hydroxylamine hydrochloride. When reactions are carried out in a neutral medium, a reversed site-stereoselectivity is observed.[85]



Ar , Ar' = aryl

Scheme 31

Reaction of *C,O*-dilithiooximes (**76**), obtained from corresponding oxime with BuLi, and α-chloro ketones afforded 5-hydroxymethylisoxazolines (**77**) (Scheme 32). α,β-Unsaturated aldehydes reacted

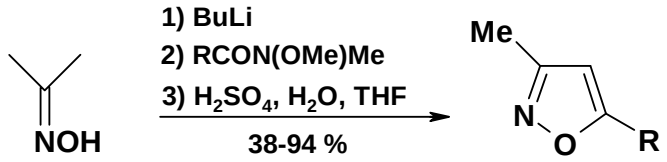


Ar, Ar' = aryl; R = H, alkyl; R', R'', R''' = H, alkyl, aryl

Scheme 32

with dilithio salts (**76**) to give the corresponding acyclic 1,2-addition products (**78**), which are easily cyclized to corresponding 5-vinylisoxazolines (**79**).[86]

3-Substituted 5-alkylisoxazoles (**81**) are successively obtained from oxime dianions, prepared from oximes (**80**) and BuLi, and *N*-methoxy-*N*-methylalkylamides (Scheme 33).[87]

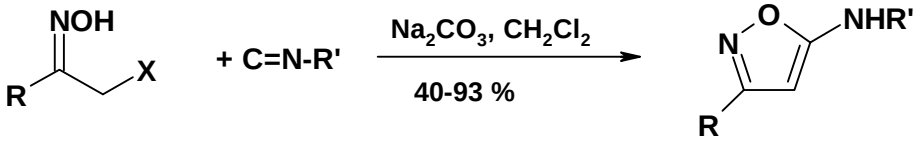


80 **81**

R = alkyl, cycloalkyl, aryl

Scheme 33

The reaction of α-bromo ketone oximes (**82**) with isocyanides leads to formation of 5-aminoisoxazole derivatives (**83**). The reaction involves formation of nitrosoalkenes as intermediates (Scheme 34).[88]

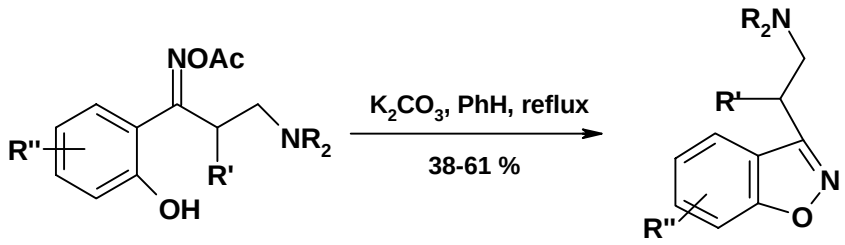


82 **83**

R, R' = alkyl, aryl; X = Cl, Br

Scheme 34

Surprisingly, that 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles (**85**) can be easily obtained by direct cyclization of the corresponding Mannich bases oxime acetates (**84**) in refluxing benzene in the presence of anhydrous K_2CO_3 (Scheme 35). The known methods for ring closure to 1,2-benzisoxazole were ineffective for this class of pharmacologically relevant compounds.[89]

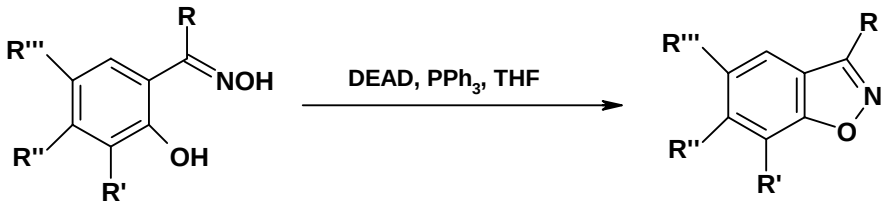


84 **85**

R' = H, Me; R'' = H, 5- and 6-Me; R''' = alkyl

Scheme 35

1,2-Benzisoxazoles (**87**) are also accessible in excellent yields by intramolecular Mitsunobu reaction of *o*-hydroxy oximes (**86**) in the presence DEAD and PPh_3 in THF (Scheme 36).[90]

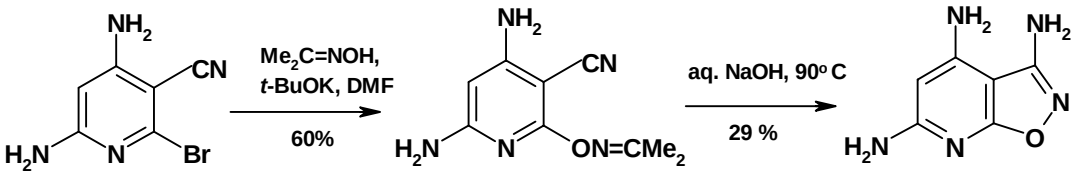


86 **87**

R = H, Me, Ph; R' = H, OMe; R'' = H, alkyl; R''' = H, Br

Scheme 36

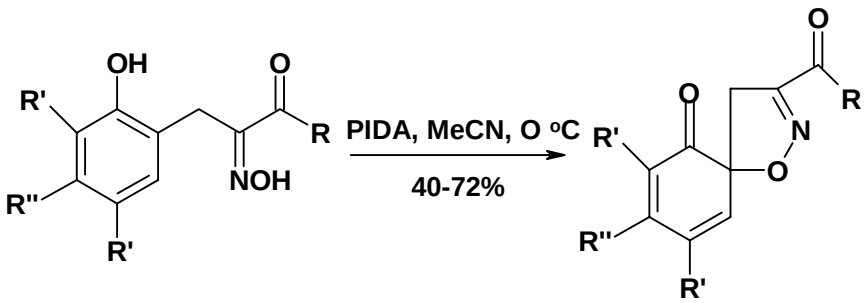
Interestingly, interaction of 2-bromo-3-cyano-4-6-diaminopyridine (**88**) with acetone oxime / *tert*-BuOK and subsequent treatment of intermediate (**89**) with aq. NaOH afforded 3,4,6-triaminoisoxazolo[5,4-*b*]pyridine (**90**) (Scheme 37).[91]



88 **89** **90**

Scheme 37

Effective synthesis of spiroisoxazoline derivatives was elaborated using hypervalent iodine reagents. Thus, treatment of *o*-phenolic oxime ethers (**91**) with phenyliodonium diacetate (PIDA) in MeCN at 0^oC afforded spirooxazolines (**92**) in moderate yields (Scheme 38).[92]



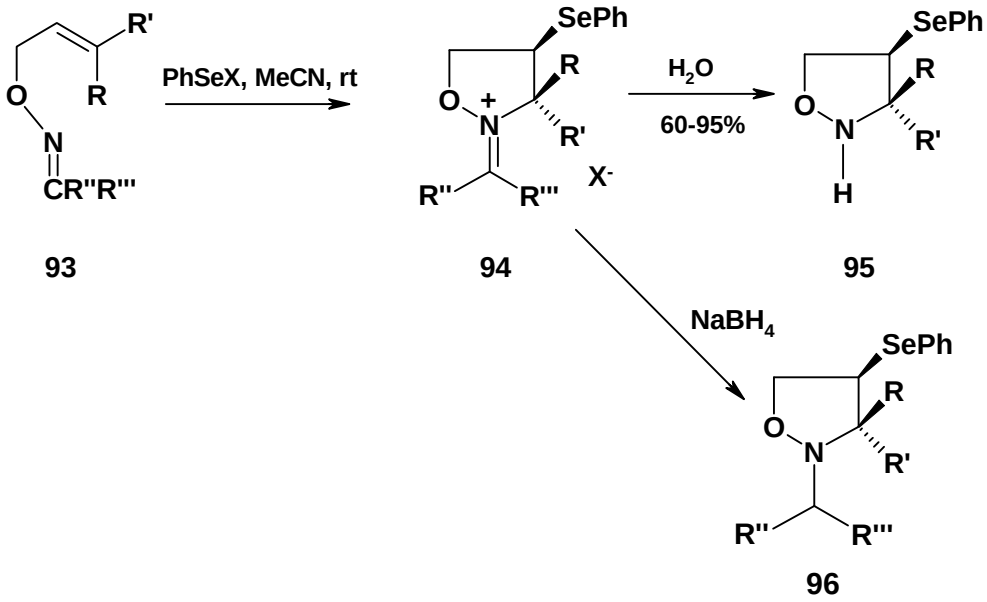
91 **92**

R = alkoxy, amino; R' = H, Br; R'' = H, OMe

Scheme 38

It has been shown that phenylselenyl halides easily reacted with *O*-allyl oximes (**93**) to give cyclic iminium salts (**94**) which by interaction with water afforded isoxazolidines (**95**) in moderate to good

yields (Scheme 39).[93] Compounds (**94**) can be reduced *in situ* by sodium borohydride to produce *N*-alkyl substituted isoxazolines (**96**) in 50-95 % yields.[94]

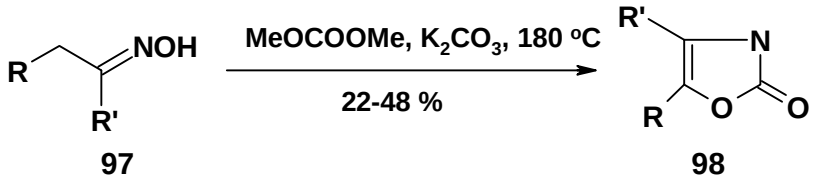


R = H, Me; R' = H, Me, Ph; R'',R''' = H, alkyl, Ph

Scheme 39

Dihydroisoxazole derivatives are successively obtained by single electron transfer (SET) cyclization of β,γ-unsaturated oximes [95,96] or addition of ketoximes to activated allenes or alkynes.[97] Isoxazole derivatives can be obtained also by thermal [4+2] cycloaddition of aldoximes or ketoximes to conventional dienophiles [98] or isomerization / cyclization of an *ortho* halogeno or nitro substituted amidoximes.[99] Preparation of 1,4-disubstituted 3-hydroximino-2-nitro-1-butenes and their oxidative cyclization to 4-nitroisoxazoles are reported.[100] Synthesis of fluorine containing substituted isoxazolidines,[101-102] as well as isoxazoles by solid phase [103] or ultrasonic methods [104] are also described.

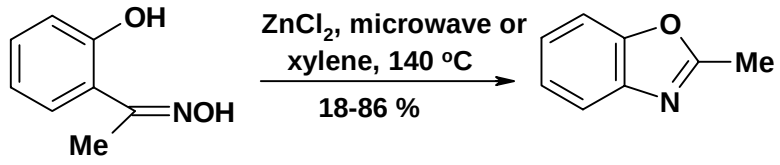
Oxazole derivatives are easily accesssible from oximes. Thus, the reaction of ketoximes (**97**) with dimethyl carbonate in the presence of K_2CO_3, carried out in an autoclave at 180-190°C, afforded 3-methyl-4,5-disubstituted 4-oxazolin-2-ones (**98**) as single products (Scheme 40).[105]



R = aryl; R' = alkyl; R,R' = cycloalkyl

Scheme 40

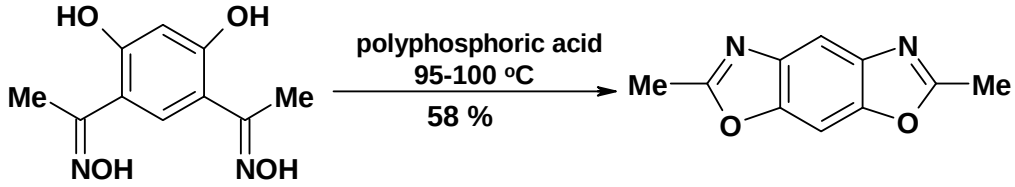
Benzoxazoles are widely applied in organic synthesis due to their importance as intermediates for the preparation of polyether antibiotics or fluorescent whitening agents. For example, 2-methylbenzoxazole (**100**) is succesively obtained from *o*-acetylphenol oxime (**99**) by Beckmann rearrangement, followed by intramolecular ring closure (Scheme 41). The best yield of the product (**100**) (86 %) is obtained in solvent-free conditions in the presence of equimolar amount of $ZnCl_2$ under microwave irradiation.[106]



99 **100**

Scheme 41

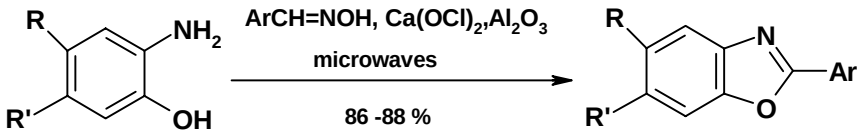
$POCl_3$ as Lewis acid is also used in the synthesis of benzoxazole derivatives.[107] Benzobisoxazole (**102**) were successsfully prepared by rearrangement-cyclization of dioxime (**101**) in the presence of polyphosphoric acid (Scheme 42).[108]



101 **102**

Scheme 42

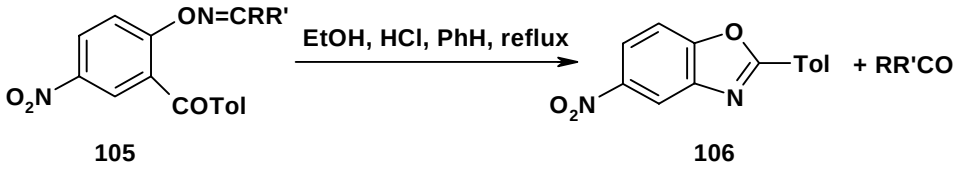
Three new ways of synthesis of 1,3-azoles (benzoxazoles, benzimidazoles and benzthiazoles) using mineral supports using $Ca(OCl)_2$ / Al_2O_3 or MnO_2 / SiO_2 or by fusion "in dry media" are described. For instance, benzoxazoles (**104**) can be obtained by reaction *o*-aminophenols (**103**) (R, R' = H, NO_2,Cl) with substituted benzaldehyde oximes in the presence of $Ca(OCl)_2$ / Al_2O_3 under microwave irradiation (Scheme 43).[109]



103 **104**

Scheme 43

O-Arylketoximes (**105**) in EtOH saturated with hydrochoric acid afforded 2-tolyl-5-nitrobenzoxazole (**106**), but not benzofurans expected (Scheme 44). The formation of (**106**) obviously involved acid



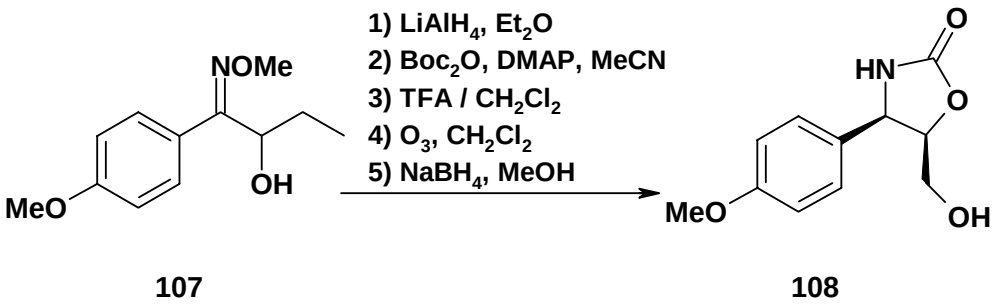
105 106

R, R' = alkyl, aryl

Scheme 44

catalyzed splitting of oximic C=N, followed by a cyclodehydration of intermediate.[110]

Thermal synthesis of 2-substituted phenanthroxazoles and related compounds by cyclization of *O*-methyl *o*-quinone oximes with compounds $ArCH_2Y$ (Ar = aryl, hetaryl; Y = H, OH, Cl, Br, OAc, SH, COR, NH_2) or with amines ($PhCH_2NMe_2$, PhNHMe, $PhNMe_2$) are described.[111] Cyclization of 2-hydroxy oxime ether is used in synthesis of alkaloid (-)-cytoxazone containing 4,5-disubstituted 2-oxazolidinone ring. [112] Thus, treatment of 2-hydroxy oxime ether (**107**) with $LiAlH_4$ / Et_2O and Boc_2O / DMAP / MeCN and then with TFA / CH_2Cl_2, O_3 / CH_2Cl_2 and $NaBH_4$ afforded racemic cytoxazone (**108**). Optical resolution of racemic (**108**) was readily accomplished *via* the conventional separation of the corresponding diasteroisomers obtained by acylation of racemic cytoxazone with (-)camphanic chloride (Scheme 45).

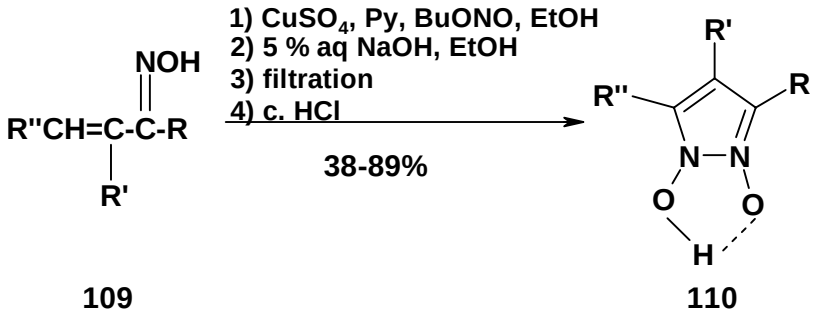


107 108

Scheme 45

2.4. Pyrazoles, imidazolines

Synthesis of some pyrazole derivatives from amidoximes was reviewed by Karbonits and Horwath.[18] It has been shown that acrylophenone or methacrylophenone oximes (**109**) on treatment with pyridine and copper(II) sulfate, with subsequent interaction with dilute NaOH and acidification gives 3(5)-phenyl-1-hydroxypyrazole 2-oxide or 4-methyl-3(5)-phenyl-1-hydroxypyrazole 2-oxide (**110**), correspondingly (Scheme 46).[113, 114]



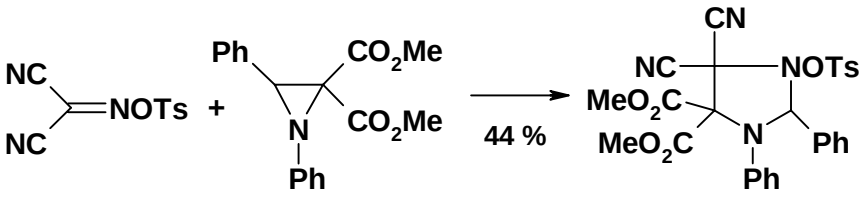
109 **110**

R, R', R'' = H, Me, Ph

Scheme 46

Conjugated oximes are converted to pyrazoles in a one-pot reaction by refluxing with hydrazine and iodine in ethanol.[115] The process proceeds *via* an inverse electron demand Diels-Alder reaction involving electron deficient heterodienes and diimide species as dipolarophiles.

O-Substituted oximes reacted with azomethide ylides only in some cases. Thus, reaction of *O*-substituted oxime $(NC)_2C$=NOTs (**111**) with azomethine ylide derived from aziridine (**112**) afforded imidazoline (**113**) (Scheme 47).[116]

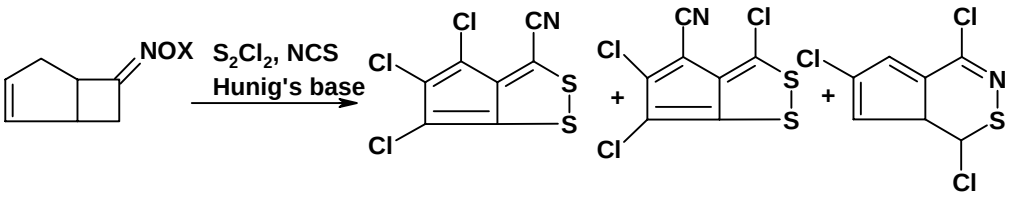


111 **112** **113**

Scheme 47

2.5. Dithioles

The cyclobutanone oxime derivatives (**114**) reacted with disulfur dichloride, *N*-chlorosuccinimide and Hunig's base to give three unexpected 10π pseudoazulenes in low yield: the dark blue cyclopenta-1,2-dithiole (**115**), its red isomer (**116**), as well as orange cyclopenta-1,2-thiazine (**117)** (Scheme 48). The formation of these compounds can be explained by a unified mechanism based on initial abnormal Beckmann rearrangement of the oximes to cyanides followed by cyclization and/or chlorination and dehydrochlorination. [117]



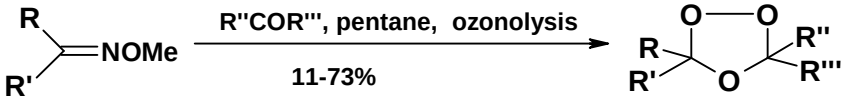
114 **115** **116** **117**

X = H, TMS

Scheme 48

2.6. Trioxolanes

Ozonolysis of acyclic ketoximes (**118**) in the presence of ketones results in the formation of tetrasubstituted cross-ozonolides (1,2,4-trioxolanes) (**119**) in yields up to 73 % (Scheme 49). Ozonolysis of *O*-methylated monooximes of 1,4-, 1,5- and 1,6-dicarbonyl compounds afforded bicyclic oxonides.[118]

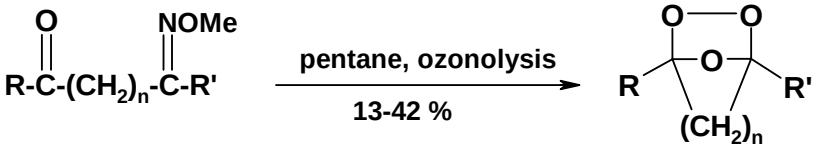


118 **119**

R, R’, R’’, R’’’ = alkyl, Ph; R’R’, R’’R’’’ = cycloalkyl

Scheme 49

Ozonolysis of the *O*-methylated monooximes (**120**) in pentane yielded bicyclic ozonides (**121**) (Scheme 50). The crude reaction product from the latter reaction exploded violently.[119]



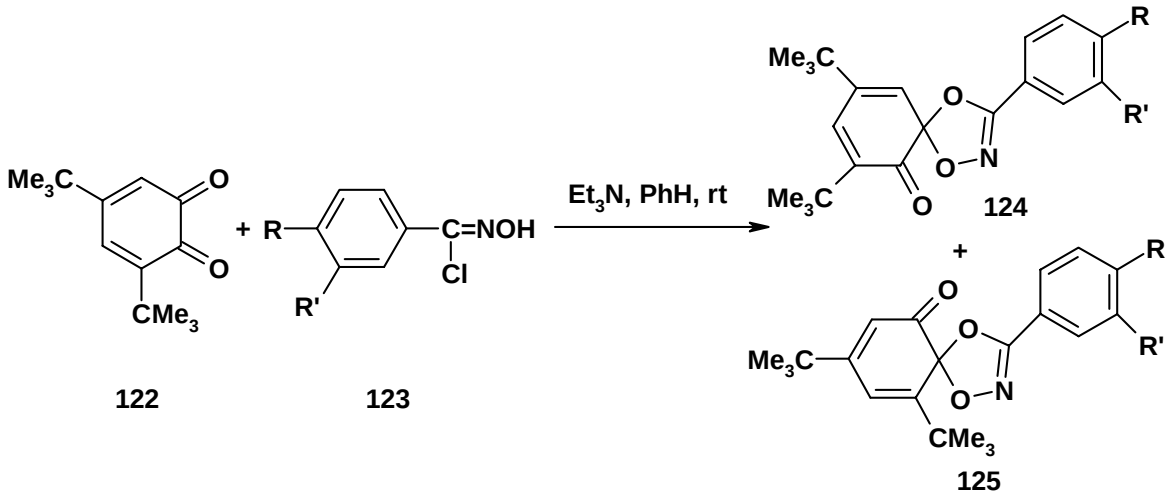
120 **121**

R, R’ = H, Me; n = 2-4

Scheme 50

2.7. Dioxazoles, oxadiazoles, oxadiazolines, thiadiazoles, and dithiazoles

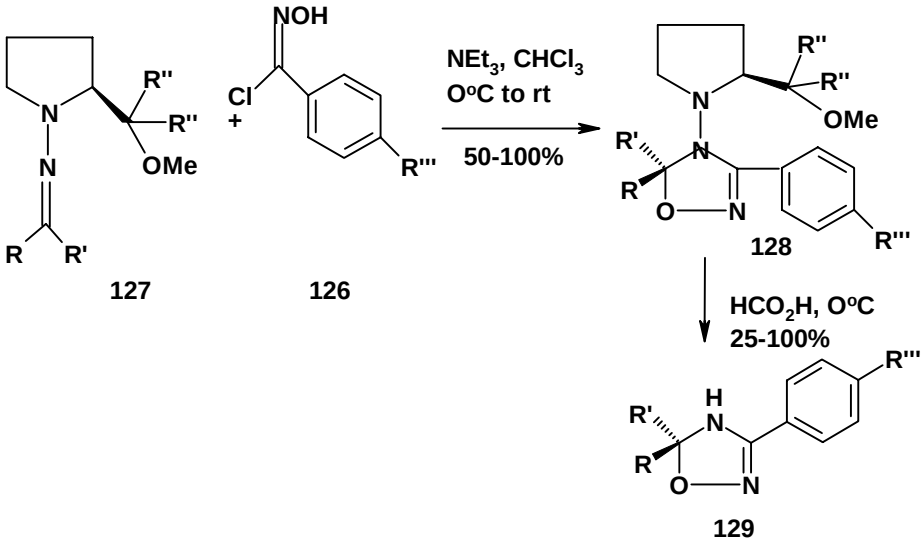
o-Benzoquinones are unique conjugated 1,2-diones which can easily react with various dipoles. Thus, di- (**122**) and tri-substituted *o*-benzoquinones on interaction with nitrile oxides, generated from corresponding benzohydroxymoyl chlorides (**123**) and Et_3N, afforded monospirodioxazole derivatives (**124**) and (**125**) in yields up to 100% in a ratio 1: 1 to 3 : 1 (Scheme 51). The reaction of monosubstituted *o*-benzoquinones with stable nitrile oxides (mesityl nitrile oxide and 2,6-dichlorobenzonitrile oxide) leads to formation of bis adducts.[120-121]



R , R' = H, Me, OMe, Cl

Scheme 51

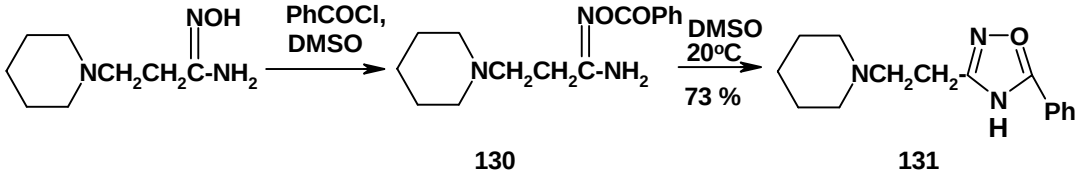
1,2,4-Oxadiazoles are widely used as pharmacologically active compounds.[122] One of methods of synthesis of these compounds is based on addition of nitrile oxides to imines [123] or hydrazones. It has been reported that interaction of hydroximoyl chlorides (**126**) with chiral hydrazones (**127**) in the presence of Et_3N leads to intermediates (**128**) with diastereoselectivity up to 97 % . A subsequent N-N bond cleavage to remove chiral auxiliary by formic acid leads to 1,2,4-oxadiazolines (**129**) with *ee* up to 91 % (Scheme 52).[124]



R = alkyl, aryl; R' = alkyl; R, R' = cyclopentyl; R'' = H, alkyl, Ph; R''' = H, F, OMe

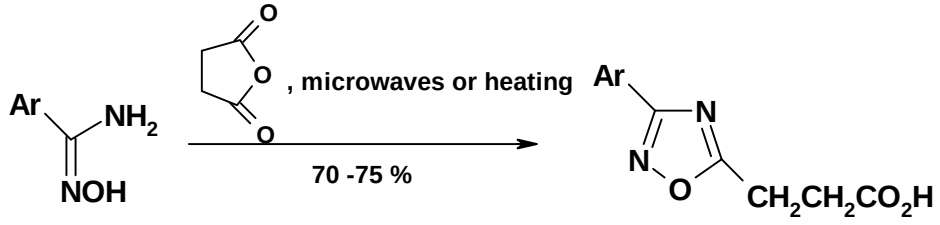
Scheme 52

The second group of methods for the preparation of 1,2,4-oxadiazole ring is based on cyclization of amidoxime derivatives in the presence of acylating agents.[122, 125- 127] A surprisingly easy cyclization of *O*-benzoyl-β-piperidinopropioamidoxime (**130**) to oxadiazole (**131**) in DMSO at room temperature was described (Scheme 53).[128]



Scheme 53

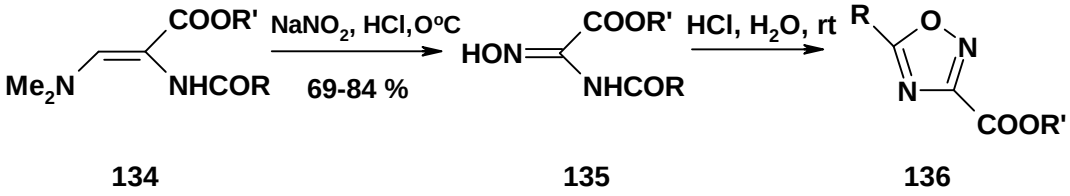
3-[3-Aryl-1,2,4-oxadiazol-5-yl]propionic acids (**133**) are obtained by reaction of amidoximes (**132**) with succinic anhydride under microwave irradiation or conventional heating (Scheme 54).[122, 129]



Ar = aryl

Scheme 54

Alkyl 2-(substituted cinnamoylamino)-3-dimethylaminopropenoates (**134**) are transformed to *N*-cinnamoyloxalic acid hydroxyimidic amides (**135**) by treatment with sodium nitrite in aqueous HCl at 0^{o} C. The latter can be further transformed into substituted 5-styryl-1,2,4-oxadiazole-3-carboxylates (**136**) by standing in aqueous HCl at room temperature (Scheme 55).[130]

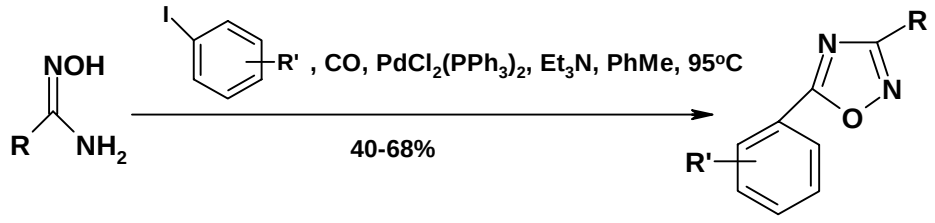


134 **135** **136**

R = $CH{=}CH_2Ar$; Ar = aryl; R' = Me, Et

Scheme 55

It has been found that 1,2,4-oxadiazoles (**138**) can be obtained from amidoximes (**137**) and aryl iodides by the palladium-mediated reaction in the presence of carbon monooxide. This reaction was applicable to both electron-rich and deficient aryl iodides (Scheme 56).[131]

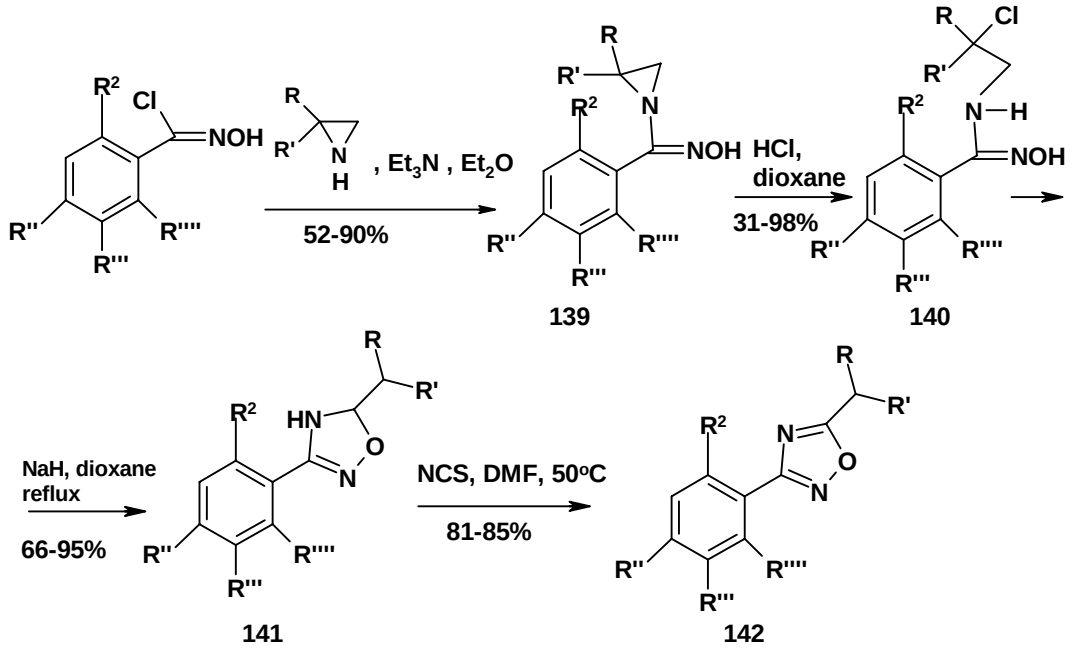


137 **138**

R = Me, CO_2Et; R' = 4-CO_2Me, 2-, 4-OMe, 4-NO_2, 4-Br

Scheme 56

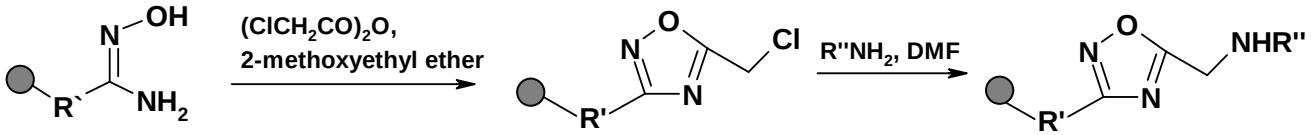
A two step synthesis of 1,2,4-oxadiazoles from aziridinylbenzaldoximes is described. Thus, aziridinyloximes (**139**), obtained by reaction of hydroxymoyl chlorides with 2,2-dialkylaziridines in the presence of Et_3N, undergo ring opening in hydrogen chloride – dioxane solution to give *(Z)-N*-hydroxy-*N'*-(2-chloro-2-methylpropyl)benzenecarboximidates (**140**). Reaction of oximes (**140**) with NaH in dioxane afforded 4,5-dihydro-1,2,4-oxadiazoles (**141**) which on treatment with *N*-chlorosuccinimide gave heteroaromatic 1,2,4-oxadiazoles (**142**) (Scheme 57).[132]



R,R' = alkyl; R'', R''', R'''' = H, Me, Cl, NO_2; R^2 = H, Cl

Scheme 57

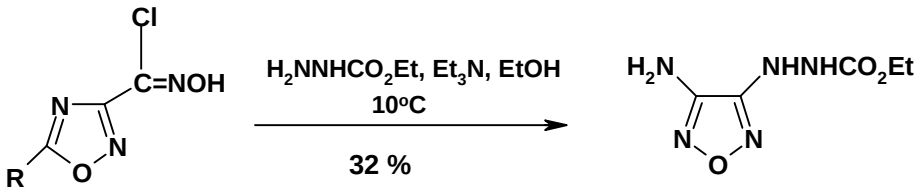
Aliphatic and aromatic nitriles linked to solid support were converted to amide oximes, and cyclized to 1,2,4-oxadiazoles using *N*-protected amino acid anhydrides. 1,2,4-Oxadiazoles (**144**) can be also successfully obtained from oximes (**143**) linked to solid resin and $(ClCH_2CO)_2O$ in 2-methoxyethyl ether. Compounds (**144**) are easily transformed to 5-amino oxadiazoles (**145**) by interaction with primary amines in DMF (Scheme 58).[133]



143 **144** **145**

Scheme 58

Reactions of oximes of 3-acyl-2-oxa-2-azoles (1,2,4-oxadiazoles, 1,2,5-oxadiazoles etc.) in the synthesis of furazans (1,2,5-oxadiazoles) are reviewed.[134] Interestingly, that 1,2,4-oxadiazole-3-carbohydroxymoyl chlorides (**146**) by treatment with ethyl hydrazinecarboxylate rearranged to 4-amino-3-(2-ethoxycarbonylhydrazino)-1,2,5-oxadiazole (**147**) (Scheme 59). The formation of product (**147**) proceeded through unstable hydrazidoximes.[135]

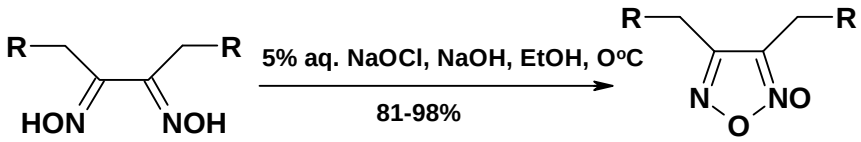


146 **147**

R = H, Me, CF_3

Scheme 59

The main group of methods of 1,4,5-oxadiazoles synthesis is based on cyclization of 1,2-dioxime derivatives. The chemistry of dioximes is reviewed by Kotali and Papageorgiou.[8] Thus, interaction of dioximes (**148**) with 5% aq. NaOCl in the presence of NaOH in EtOH afforded 1,2,5-oxadiazole-2-oxides (**149**) in good yields (Scheme 60).[136]

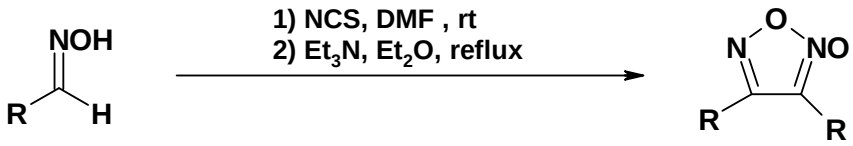


148 **149**

R = aryl, cyclohexyl

Scheme 60

Bromocyan,[137] N_2O_4 / CH_2Cl_2,[138] bis(trifluoroacetoxy)iodobenzene [139] and SiO_2 [140] were also used as oxidants in the cyclization of 1,2-dioximes to 1,2,5-oxadiazoles. 1,2,5-Oxadiazole-2-oxides (**151**) can be obtained by treatment of aldoximes (**150**) with *N*-chlorosuccinimide / THF with subsequent interaction with Et_3N in Et_2O (Scheme 61).[141]

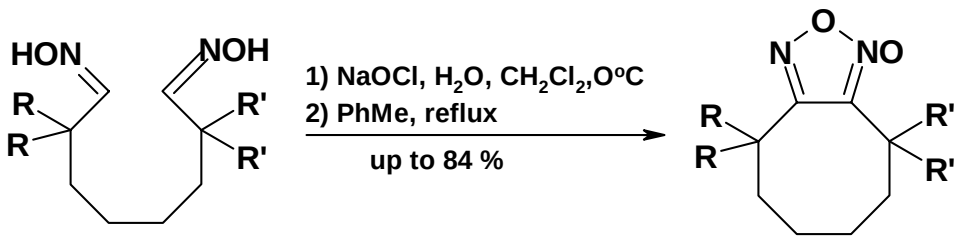


150 **151**

Scheme 61

Bicyclic derivatives of furazan 1-oxide are prepared by nitrile oxide dimerization reaction. For example, oxime (**152**) (R, R' = Me) undergo cyclization to corresponding 4,4-tetramethylperhydrocyclo-

octa[*c*]furazan 1-oxide (**153**) (yield 84 %) by treatment with NaOCl / H_2O / CH_2Cl_2 and then with toluene at reflux. However, in the cases of sterically less hindered oximes (**152**) (R = H, Me; R' = H) only complex mixtures of oligomerization and cyclization products could be obtained (Scheme 62).[142]

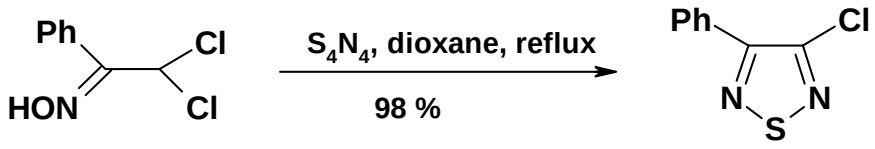


152 **153**

R, R' = H, Me

Scheme 62

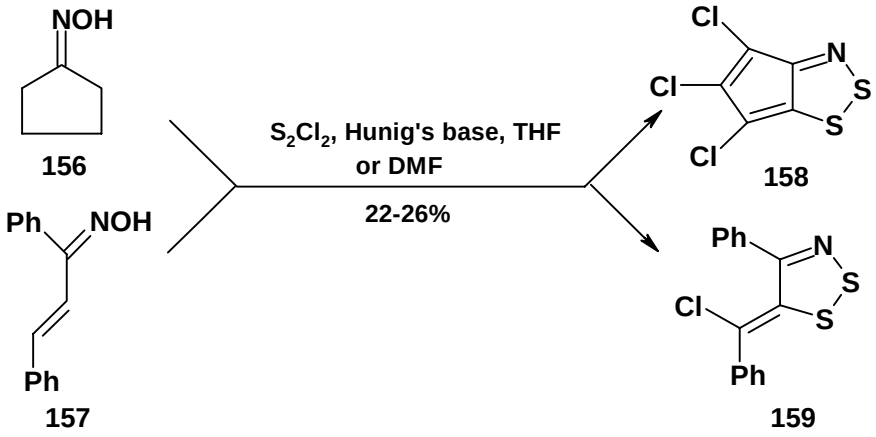
3-Aryl-1,2,5-thiadiazoles or 3-aryl-4-halogeno-1,2,5-thiadiazoles can be readily prepared from 1-aryl-2-haloethanone or 1-aryl-2,2-dihalogenoethanone oximes and tetrasulfur tetranitride.[143-145] For instance, interaction of dichloroacetophenone oxime (**154**) with S_4N_4 / dioxane at reflux afforded 3-phenyl-4-chloro-1,2,5-thiadiazole (**155**) in 98 % yield (Scheme 63).



154 **155**

Scheme 63

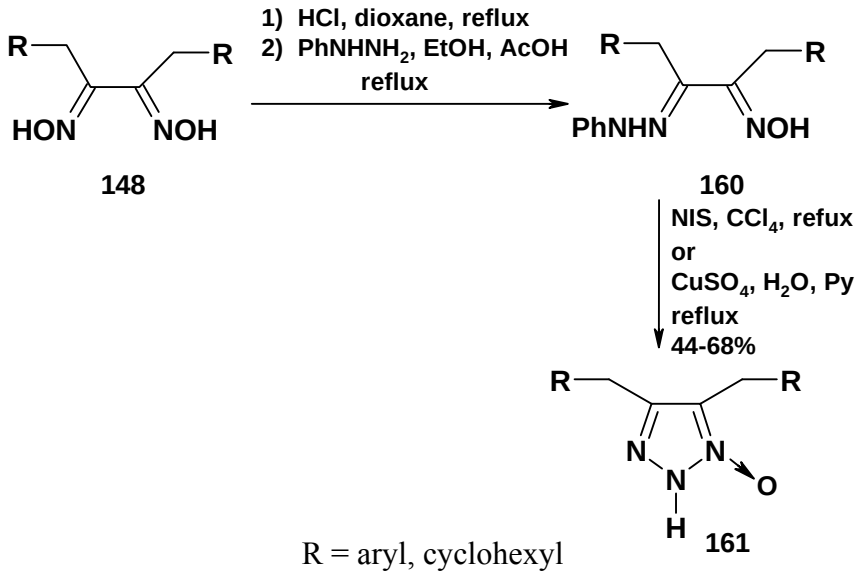
Cyclopentanone oxime (**156**) reacts with S_2Cl_2 at 4°C in tetrahydrofuran containing Hunig's base, or in dimethylformamide without base, to give trichlorocyclopenta-1,2,3-dithiazole (**158**) without isolable intemediates. Similarly, benzylidene acetophenone oxime (**157)** afforded monocyclic dithiazole (**159**) (Scheme 64).[146]



Scheme 64

2.8. Triazoles, triazolines, and benzotriazoles

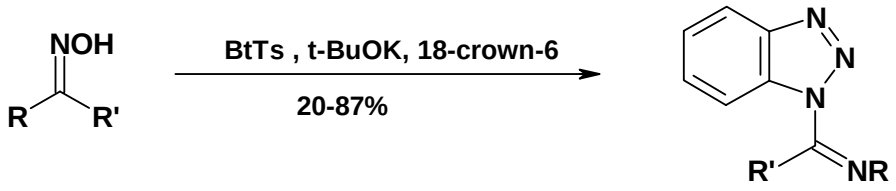
4,5-Disubstituted 2-phenyl-*2H*-1,2,3-triazole-1-oxides (**161**) can be easily obtained from corresponding bis(hydroxyimino)butanes (**148**) in three steps. Thus, treatment of dioximes (**148**) with diluted HCl in dioxane with subsequent interaction with $PhNHNH_2$ / EtOH / AcOH afforded α-hydrazinooximes (**160**) in good yields. Reaction of (**160**) with *N*-iodosuccinimide (NIS) in CCl_4 or $CuSO_4$ in aq. pyridine afforded triazoles (**161**) (Scheme 65).[136]



R = aryl, cyclohexyl

Scheme 65

Oximino cyanoacetate or malonate esters ($MeO_2CC(CN)=NOTs$ or $(MeO_2C)_2C=NOCOPh$) reacted with dizoalkanes ($RCHN_2$) to give unstable 1,2,3-triazolines.[147] *N*-imidoylbenzotriazoles (**163**) are obtained under mild condition by reaction of oximes (**162**) *via* benzotriazole tosylate mediated Beckmann rearrangement (Scheme 66).[148]



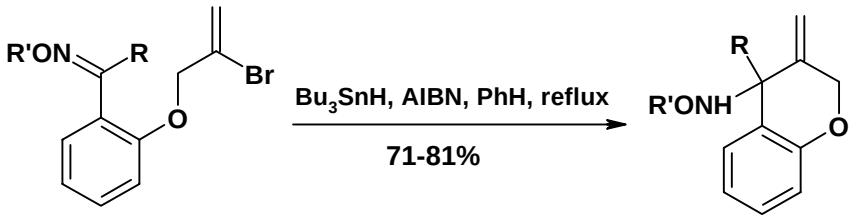
162 **163**

Scheme 66

3. SYNTHESIS OF SIX-MEMBERED RING SYSTEMS FROM OXIMES

3.1. Chromanes, pyrones, and pyrylium salts

2-(2-Bromoallyloxy)phenyl oxime *O*-ethers (**164**) have been cyclized with AIBN and Bu_3SnH to alkoxyamino-3-methylidenechromanes (**165**) (Scheme 67). The cyclization of **164** proceeds through formation of vinyl radicals.[149]

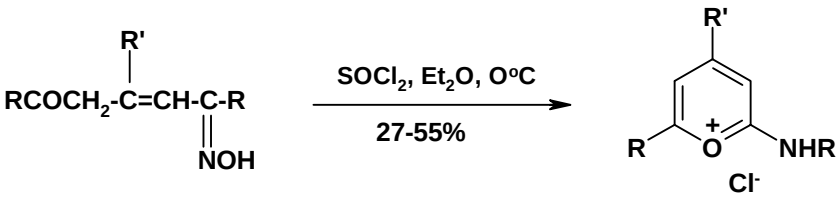


164 **165**

R = H, Me; R' Me, Bn

Scheme 67

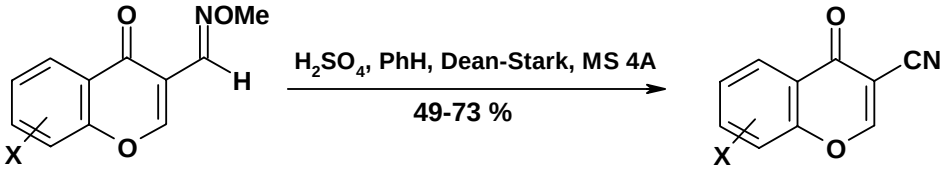
Beckmann rearrangement of ketoximes (**166**) (R,R' = alkyl, aryl) with thionyl chloride unexpectedly afforded 2-aryl(or alkyl)amino-4,6-disubstituted pyrylium salts (**167**) (Scheme 68). This reaction is the first example of rearrangement / cyclization involving carbonylic oxygen as terminator.[150]



166 167

Scheme 68

A rare acid-promoted elimination of *O*-methyloximes as a route to 3-cyano-4-benzopyrones is also described.[151] Thus, 4-oxo-4*H*-1-benzopyran-3-carbonitriles (**169**) are prepared from corresponding *O*-methyloximes (**168**) in the presence of H_2SO_4 and molecular sieves (Scheme 69).



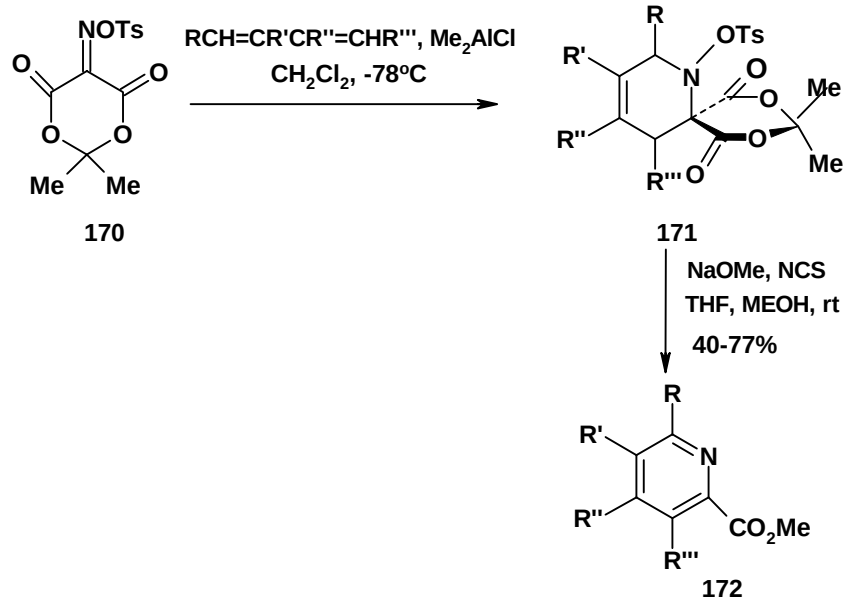
168 169

X = alkyl, halo

Scheme 69

3.2. Pyridines and quinolines

Oximes of type XON=CW_2 (X = Ts, Tf, Ac; W = CN, CO_2Et) are of interest as cycloaddition partners in



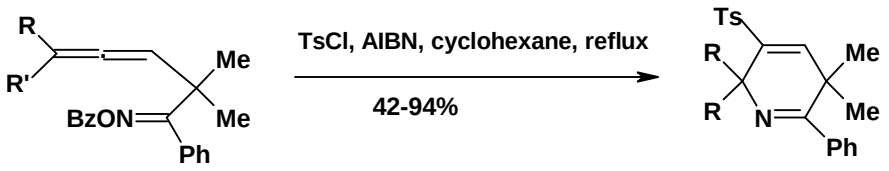
170 171 172

R, R', R'', R''' = H, alkyl; R'', R''' = cyclohexyl

Scheme 70

[4+2] cycloaddition reactions of dienes.[152,153] For example, addition of acetoxyimino Meldrum's acid to dienes at high pressure afforded tetrahydropyridine derivatives.[154] Such reactions were studied in details by Renslo and Danheiser.[155] Thus, Diels-Alder cycloaddition of oximinosulfonate (**170**) with a variety of 1,3-dienes afforded tetrahydropyridines (**171**), which can be easily transformed to corresponding pyridines (**172**) by treatment with NaOMe / NCS in MeOH / THF (1:1) (Scheme 70).

3,6-Dihydropyridines (**174**) can be successfully prepared by 6-*endo* radical cyclization of β-allenyl ketoximebenzoates (**173**) in the presence of tosyl bromide and AIBN in cyclohexane (Scheme 71).[156]

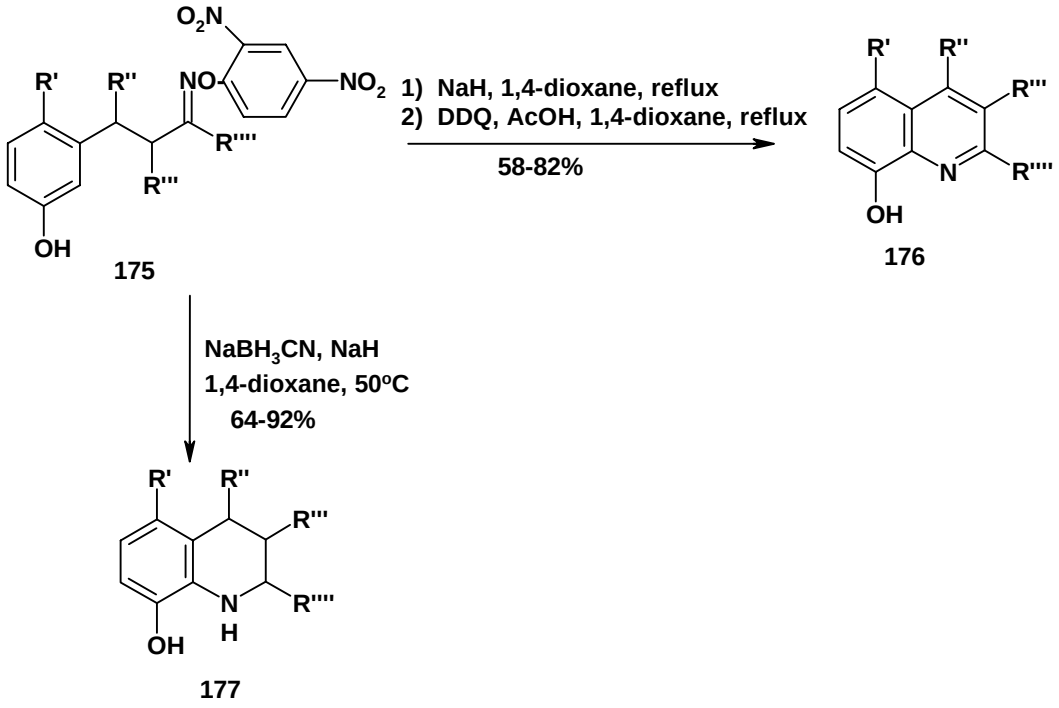


173 **174**

R = Me; R' = H, Me; RR' = cyclopentyl

Scheme 71

8-Hydroxyquinolines (**176**) are synthesized from *O*-2,4-dinitrophenyloximes of *m*-hydroxyphenethyl ketones (**175**) by the treatment with NaH and then with 2,3-dichloro-4,5-dicyano-*p*-benzoquinone DDQ).[157] However, 8-hydroxy-1,2,3,4-tetrahydroquinolines (**177**) are obtained by cyclization of oxime ethers (**175**) in the presence of system $NaBH_3CN$ / NaH / 1,4-dioxane (Scheme 72).[158]

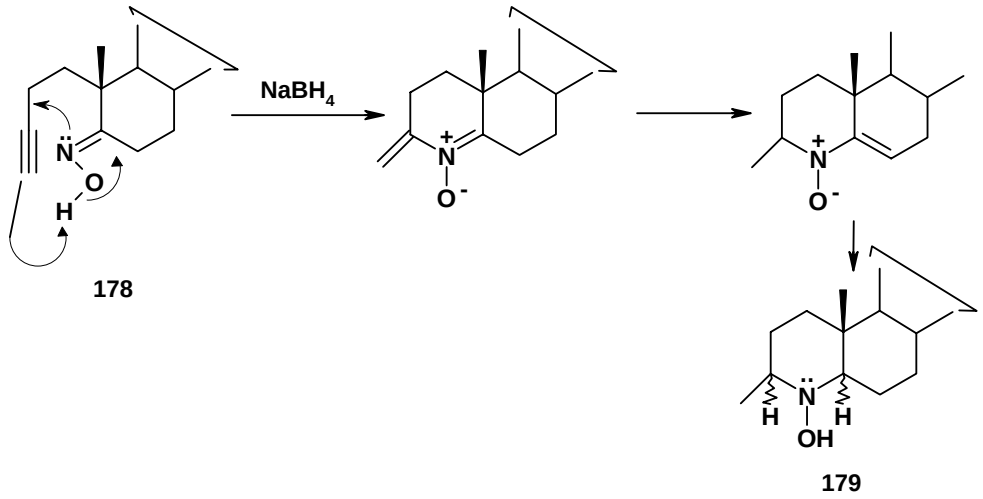


175 **176** **177**

R, R', R'', R''', R'''' = H, alkyl

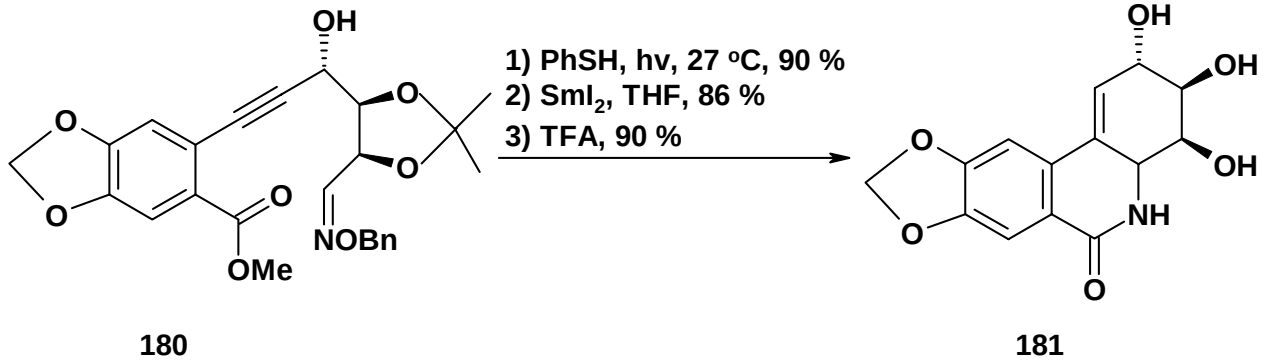
Scheme 72

Interestingly, that *N*-alkyl- and *N*-arylisoquinolinium salts reacted with free NH_2OH in pyridine to give isoquinoline 2-oxide as final product. The intermediate of this reaction is dioxime 2-$HON{=}CHC_6H_4CH_2CH{=}NOH$, which can be cyclized to 3-aminoisoquinoline 2-oxide by interaction with $(CF_3CO)_2O$ / Et_3N.[159] Fused heterocyclic compounds containing partially hydrogenated pyridine and quinoline rings are prepared by intermolecular 1,3-dipolar cycloaddition reaction to unsaturated oxime derivatives.[160,161] For example, δ-alkynyl oximes (secosteroid oximes) (**178**) undergo a concerted [2n + 2π + 2δ]azaprotio cyclotransfer to give cyclic hydroxylamines (**179**) (Scheme 73).



Scheme 73

Total synthesis of (-)-lycoricidine, (+)-lycoricidine and (+)-narciclasine *via* 6-*exo* cyclization of substituted vinyl radicals with oxime ethers are also reported.[162] Thus, cyclization of *O*-benzyloxime (**180**) by interaction with PhSH under irradiation and then SmI_2 / THF and trifluoroacetic acid afford (+)-lucoricidine (**181**) (Scheme 74).

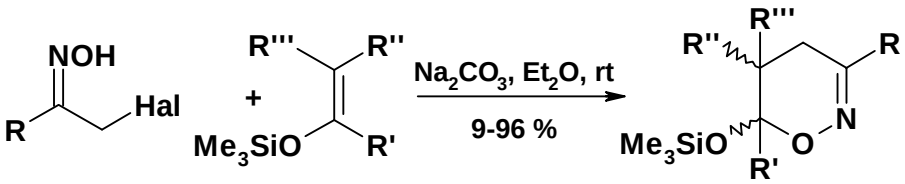


180 **181**

Scheme 74

3.3. Oxazines

Nitroso alkenes, generated from α-halogeno oximes and base, undergo addition with olefinic compounds affording 5,6-dihydro-*4H*-1,2-oxazines as main products.[163] Silyl enol ethers also can be used as dienophiles in this hetero Diels-Alder reaction. Thus, interaction of α-halogeno oximes with silyl enol ethers (**182**) in the presence of Na_2CO_3 in ether afforded oxazine derivatives (**183**) in yields up to 96 % as mixture *cis*- and *trans* isomers (Scheme 75).[164]

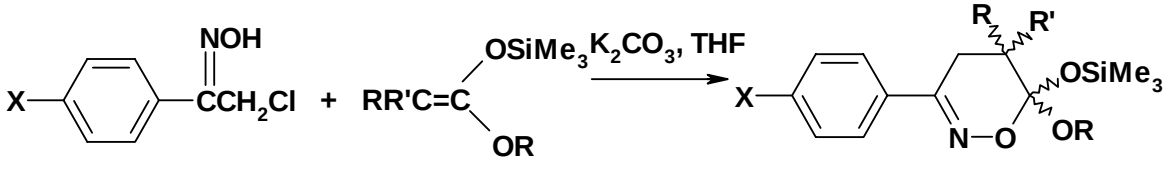


182 *cis* and *trans* **183**

R = Ph, CO_2Et; R', R'', R''' = H, alkyl, $OSiMe_3$

Scheme 75

Similarly, ketene silyl acetals (**185**) and substituted α-chloroacetophenone oximes (**184**) in the presence of K_2CO_3 in tetrahydrofuran afforded 6-alkoxy-3-aryl-6-trimethylsiloxy-5,6-dihydro-4*H*-1,2-oxazines (**186**) in moderate yields (Scheme 76). These products gave 3-aryl-5,6-dihydro-4*H*-1,2-oxazin-6-one and 4-aryl-4-(hydroxyimino)butyric acid esters in acid catalyzed hydrolysis.[165]

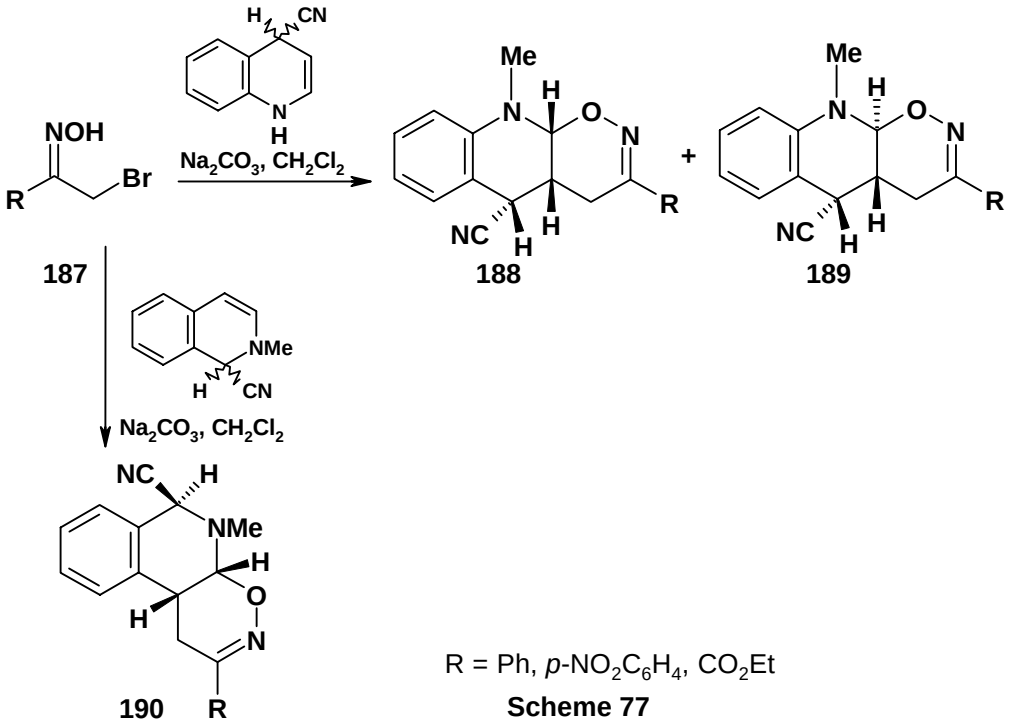


184 **185** **186**

Scheme 76

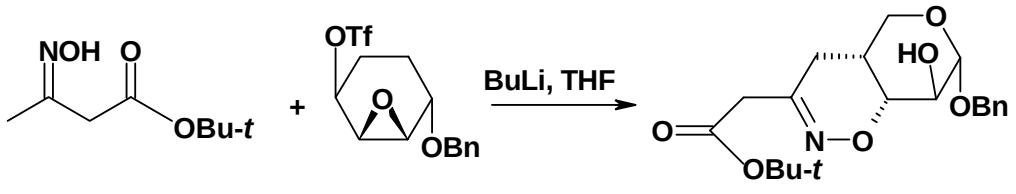
Substituted nitrosoalkenes, prepared *in situ* from corresponding α-bromo oximes, can be added to different heterocycles (furan, thiophene) to afford fused oxazine derivatives.[166] Recently, there was reported a preparation of novel heterocyclic oxazinotetrahydroquinoline (**188**) and (**189**) or

oxazinotetrahydroisoquinoline (**190**) derivatives by reaction of corresponding heterocycles with α-bromo oximes (**187**) in the presence of Na_2CO_3 in CH_2Cl_2 (Scheme 77).[166]



Scheme 77

Enantiomerically pure oxazine derivatives can be obtained from epoxy pyranosides and β-ketoester oximes in the presence of base.[167] For instance, oxime (**191**) and epoxy pyranoside (**192**) in the presence BuLi / THF gives oxazinoid (**193**) in 70 % yield (Scheme 78).

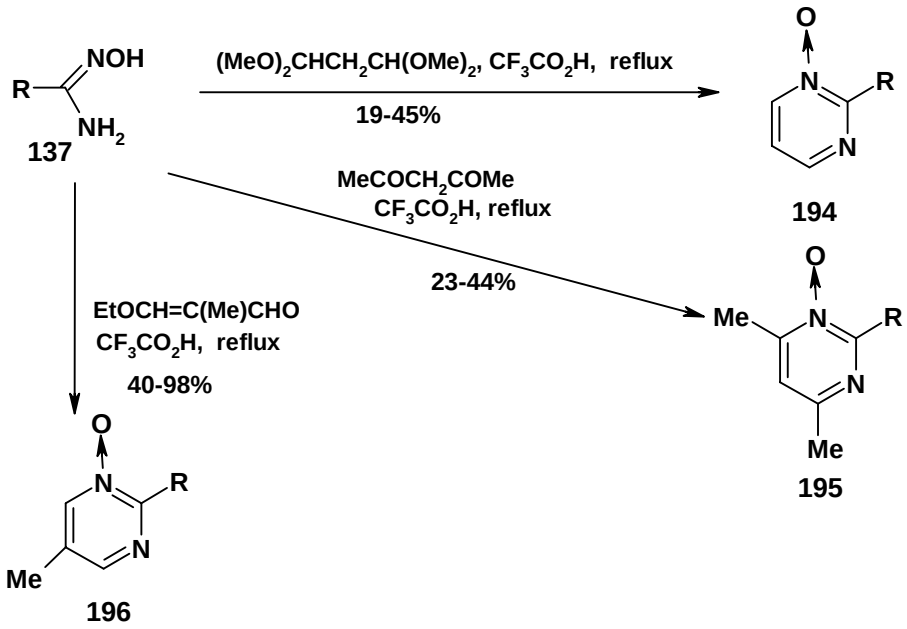


191 **192** **193**

Scheme 78

3.4. Pyrimidine, pyrazine, and quinazoline

A general method for the synthesis of pyrimidine *N*-oxides from carboxamides is described. The conversion involves treatment of various carboxamide oximes (**137**) with 1,1,3,3-tetramethoxypropane, 2,4-pentanedione or 3-ethoxy-2-methylpropenal in the presence of CF_3COOH to afford pyrimidine 1-oxides (**194**), (**195**) or (**196**), correspondingly (Scheme 79).[168, 169]

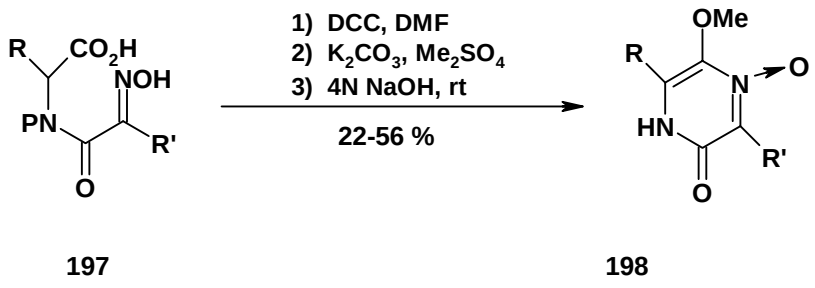


R = alkyl, aryl

Scheme 79

4,4-Dimethoxy-2-butanone and 4-methoxy-3-butene-2-one also can be used as substrates in the synthesis of pyrimidine *N*-oxides.[169]

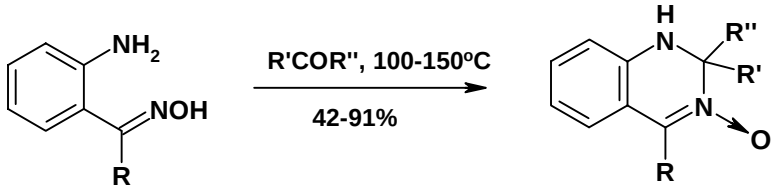
General route to 5-methoxypyrazine-2-one *N*-oxides (**198**) from oxime derivatives (**197**) by one-pot cyclization in the presence of DCC / DMF with subsequent interaction with Me_2SO_4 / K_2CO_3 and NaOH is described (Scheme 80).[170]



R, R' = alkyl, aryl; P = protecting group

Scheme 80

Heating of *o*-substituted ketoximes or amidoximes (**199**) with aldehydes or ketones afforded quinazoline-*N*-oxides (**200**) as main products (Scheme 81).[171] The formation of products (**200**) proceeds via *o*-imino oximes as intermediates.[172]



199 **200**

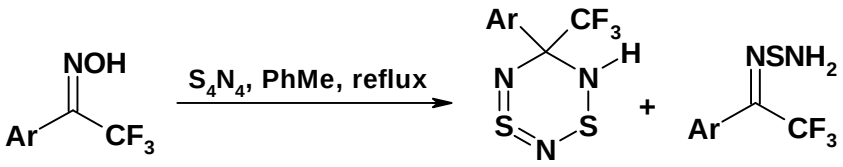
R = CH_3, Ph, NH_2; R', R'' = H, alkyl, aryl

Scheme 81

Quinazoline amidines reacted with hydroxylamine too. Thus, 2,4-oxadiazolylnaphthylamino-formaldehyde oximes are prepared by the reaction of benzo[h]quinazolinyl amidine derivatives with an excess of hydroxylamine.[173]

3.5. Dithiatriazines

The reactions of 1-aryl-2,2,2-trifluoroethanone (**201**) oximes with tetrasulfur tetranitride (S_4N_4) in toluene at reflux gave 5-aryl-5-trifluoromethyl-4*H*-1,3,2,4,6-dithitriazines (**202**), 1-aryl-2,2,2-trifluoroethanonylideneaminosulfenamides (**203**) and sulfur (Scheme 82). Treatment of (**202**) with Bu_3SnH and AIBN in benzene at 80°C afforded imine (**169**) in 64-99 % yield.[174]



17- 37 % **7-53 %**

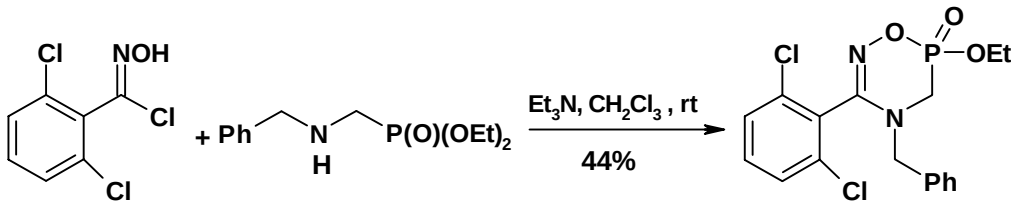
201 **202** **203**

Ar = aryl

Scheme 82

3.6. Oxadiazaphosphorines

A derivative of the new heterocyclic ring system – 1,2,3,4-tetrahydro-1,4,6,2-oxadiazaphosphorine (**206**) is prepared by the reaction of sterically hindered hydroximoyl chloride (**204**) with aminomethylphosphonate (**205**) (Scheme 83).[175]

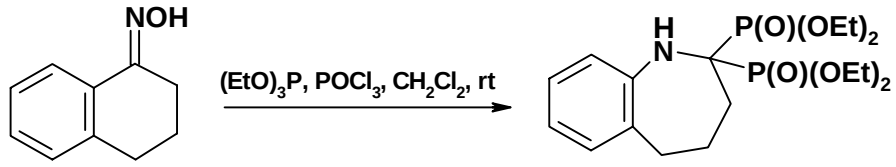


204 **205** **206**

Scheme 83

4. SYNTHESIS OF SEVEN-MEMBERED RING SYSTEMS FROM OXIMES

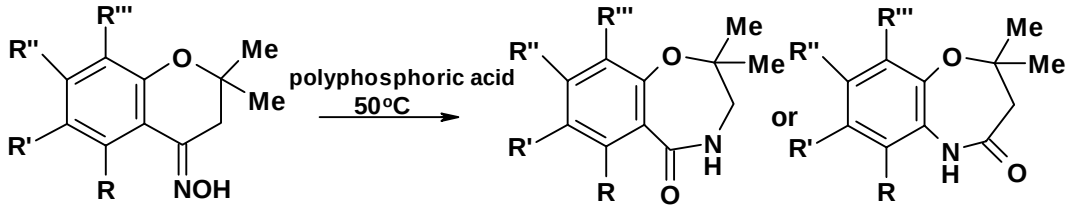
Beckmann rearrangement is extensively used in organic chemistry for construction of heterocyclic seven-membered ring system. Beckmann rearrangement of cyclohexanone oxime derivatives to corresponding ε–caprolactams [176] by sulfuric acid, [177] tetrabutylammonium perrhenate / trifluorometanesulfonic acid,[178] *N*-bromosuccinimide,[179] borate-pillared layered double peroxides, [180] montmorilonite KSF, [181] K-10 montmorilonite / microwave irradiation [182] or other similar methods are reported. Beckmann rearrangement of oximes in the presence *P*-nucleophiles ($(EtO)_3P$ and $HP(O)(OEt)_2$) afforded corresponding aminomethylene *gem*-diphosphonates. For example, interaction of tetralone oxime (**207**) with $(EtO)_3P$ and $POCl_3$ in CH_2Cl_2 afforded 2,2-bis(diethylphosphono)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**208**) in 30 % yield (Scheme 84).[183]



207 **208**

Scheme 84

Beckmann rearrangement of 2,2-dimethyl-4-chromanone oximes (**209**) in the presence of polyphosphoric acid at 50°C afforded substituted 2,2-dimethylbenzoxazepinones (**210**) and (**211**) (Scheme 85).[184]



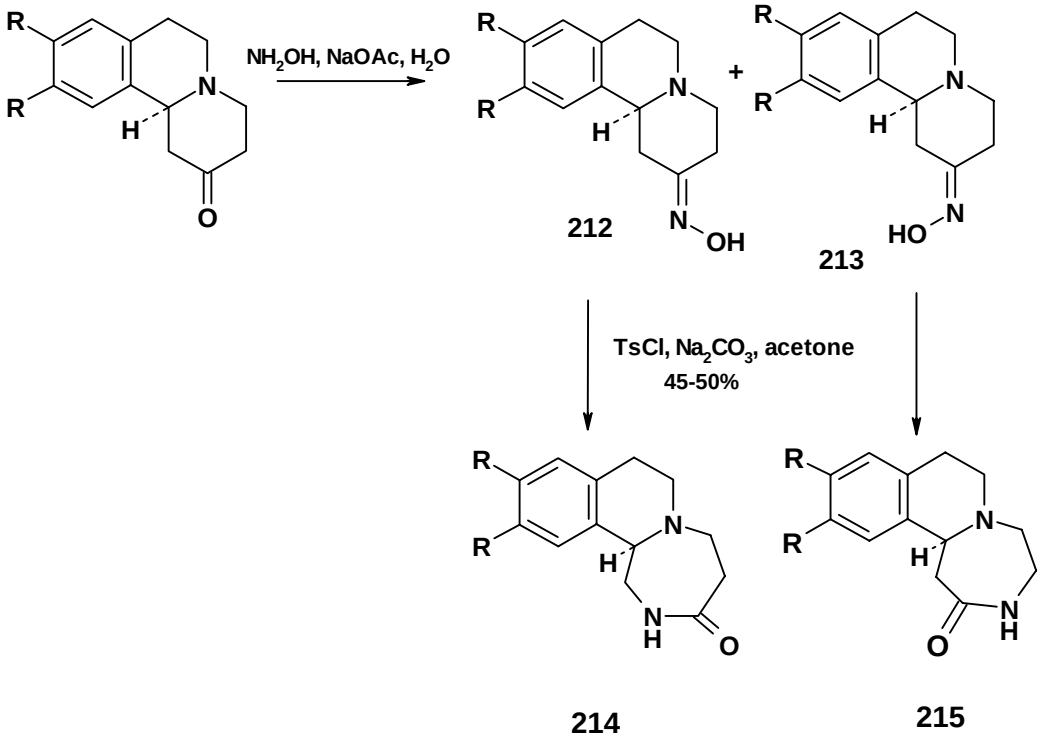
36-55 % **29-30%**

209 **210** **211**

R, R', R'', R''' = H, alkyl, alkoxy

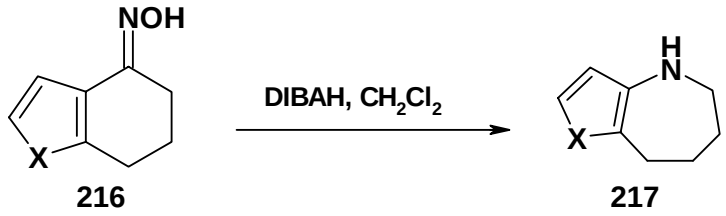
Scheme 85

Z- and *E*-oximes of benzoquinolizidones (**212**) and (**213**) were converted into isomeric diazepinoisoquinolines (**214**) and (**215**), correspondingly, by treatment with TsCl and Na_2CO_3 in acetone (Scheme 86).[185]



Scheme 86

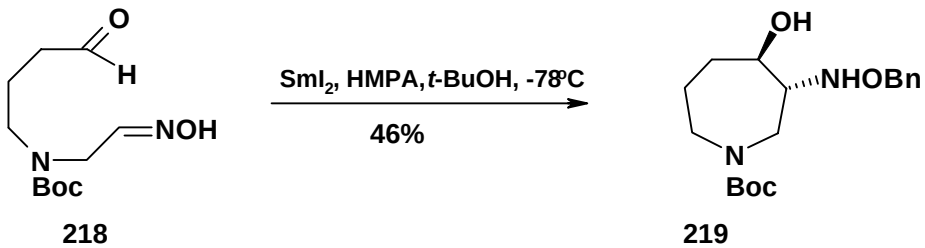
5,6,7,8-Tetrahydrothieno[3,2-*b*]azepine, 5,6,7,8-tetrahydro-1*H*-furo[3,2-*b*]azepine and 1,4,5,6,7,8-hexahydropyrrolo[3,2-*b*]azepine derivatives (**217**) can be easily obtained by ring expansion of heterocyclic fused cyclohexanone oximes (**216**) with diisobutylaluminium hydride (Scheme 87).[186]



X = O, S, NH, NMe

Scheme 87

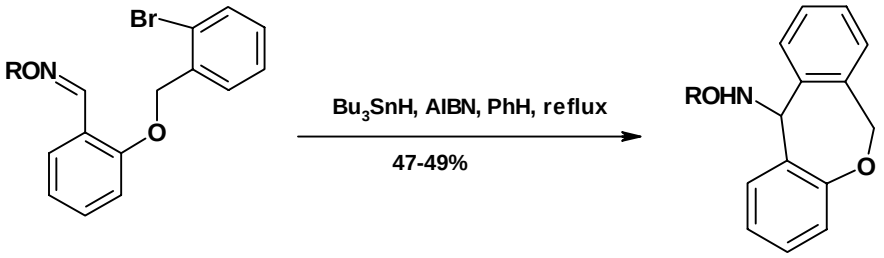
A free radical cyclization of oxime ethers tethered to an aldehyde has been used in the synthesis of azepine derivatives. [187] For example, oxime ether (**218**) is cyclized to azepine (**219**) by interaction with SmI_2 in HMPA and *t*-BuOH at –78°C (Scheme 88).[188]



Scheme 88

Similar free radical cyclization of oxime ethers can be carried out also in the presence of Bu_3SnH / AIBN in benzene.[189,190]

2-(2-Bromobenzyloxy)benzaldehyde *O*-alkyloximes (**220**) are converted with Bu_3SnH and AIBN to the corresponding dibenzo[*b*,*e*]oxepines (**221**) by radical addition reaction (Scheme 89).[149]



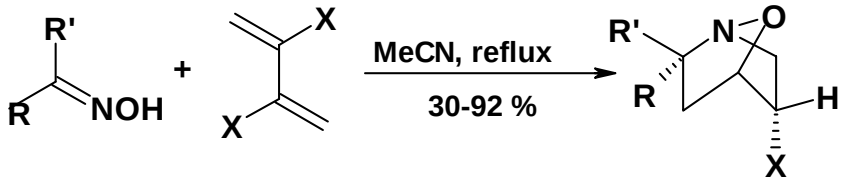
220 **221**

R = Me, *t*-Bu

Scheme 89

5. SYNTHESIS OF BICYCLIC AND TRICYCLIC RING SYSTEMS FROM OXIMES

Oximes reacted with bifunctional Michael acceptor-dipolarophile substrates comprising functionalized 1,3-, 1,4- and 1,5-dienes via tandem process involving *N*-alkenylnitrone intermediate. Thus, reaction of oximes (**222**) and 1,3-dienes (**223**) afforded 1-aza-7-oxabicyclo[2.2.1]heptanes (**224**) in good yields (Scheme 90).



222 **223** **224**

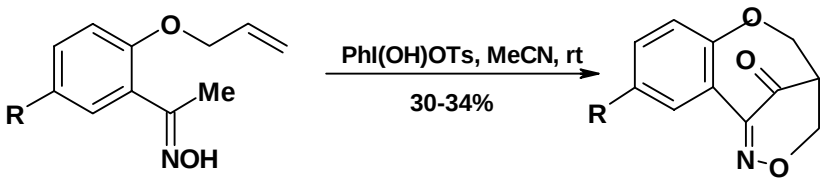
R, R' = alkyl, aryl, cycloalkyl; X = CO_2Me, $P(O)Ph_2$, SO_2Ph

Scheme 90

Sterically unencumbered aryl aldoximes and 1,4-dienes gave 1-aza-2-oxabicyclo[3.2.1]octane derivatives. Ketoximes and 1,4-dienes afforded mixture of 1-aza-2-oxa- and 1-aza-8-oxa-bicyclo[3.2.1]octanes. 1,5-Dienes and ketoximes react regio- and stereospecifically to give 1-aza-8-bicyclo[3.2.1]octane derivatives, whilst benzaldehyde oxime gives a 1 : 1 mixture of epimeric 1-aza-8-oxabicyclo[3.2.1]octanes with a traces of two epimeric 1-aza-2-oxabicyclo[3.2.1]octanes.[191]

The tandem 1,3-azaprotio cyclotransfer-cycloaddition reaction between ketoxime and divinyl ketone or its equivalents (2-chloroethyl vinyl ketone and bis(2-chloroethyl)ketone) affords high yields of substituted 1-aza-7-oxabicyclo[3.2.1]octan-4-ones and 1-aza-8-oxabicyclo[3.2.1]octan-ones.[192]

Recently an easy construction of 8,12-dioxa-13-azatricyclo[8.3.1.$0^{2,7}$]tetradeca-2(7),3,5,13-tetraen-14-ones (**226**) by treatment of *o*-allyloxyacetophenones (**225**) with [hydroxy(tosyloxy)iodo]benzene was reported (Scheme 91).[193]

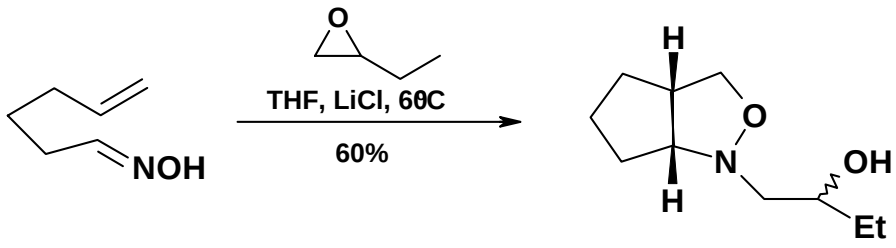


225 **226**

R = H, Me, Cl

Scheme 91

Regioselective nucleophilic substitution reactions involving attack of the nitrogen atom of oximes on epoxides are used to generate nitrones, which are trapped in 1,3-dipolar cycloaddition reactions. For example, 5-hexenaldoxime (**227**) in the presence of 1,2-epoxybutane and LiCl in THF afforded 2-(2'-hydroxybutyl)-2-aza-3-oxabicyclo[3.3.0]octane (**228**) as a 1 :1 mixture of diastereoisomers (Scheme 92).[194]

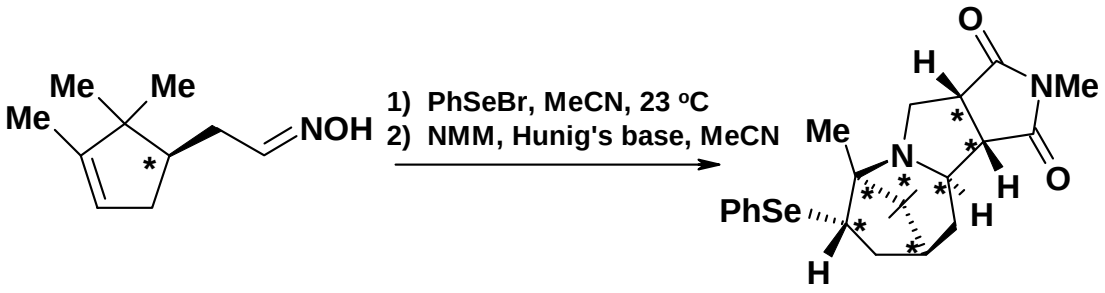


227 **228**

Scheme 92

One-pot synthesis of the hydroximoyl chlorides and [3.3.0] bicyclic systems from the reaction of β–nitrostyrenes with stabilized nucleophiles are reported too.[195] Electrophile induced 6-*exo*-*trig* spirocyclization of oximes onto 5-, 6- and 7-membered cycloalkanes occurs stero- and regiospecifically in good yield. Subsequent bridged – ring forming reactions creating bicyclo-[3.3.1]- and bicyclo-[3.2.1]-ring systems also occur in good yield. Chiral bridged-ring systems are synthesized, *via* the latter processes, that involve multiplication of chiral centers from one to six or seven in *one pot* reaction.[196] Thus, (-)-pinene oxime (**229**) (*E*/*Z* isomers – 1:1) undergoes cycloaddition in the presence of PhSeBr / MeCN and

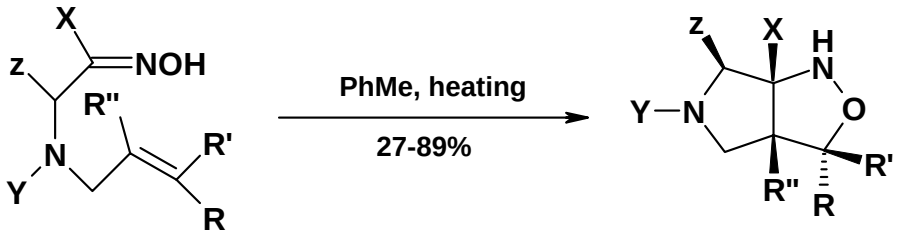
N-methylmaleimide (NMM) / Hunig's base to give single tricyclic product (**230**) in 72% yield (Scheme 93).



229 **230**

Scheme 93

Thermal intramolecular oxime olefin cycloaddition of α-allylamino aldoximes and ketoximes (**231**) led stereospecifically to formation of oxadiazabicyclo[3.3.0]octanes (**232**) in excellent yields (Scheme 94).[197]

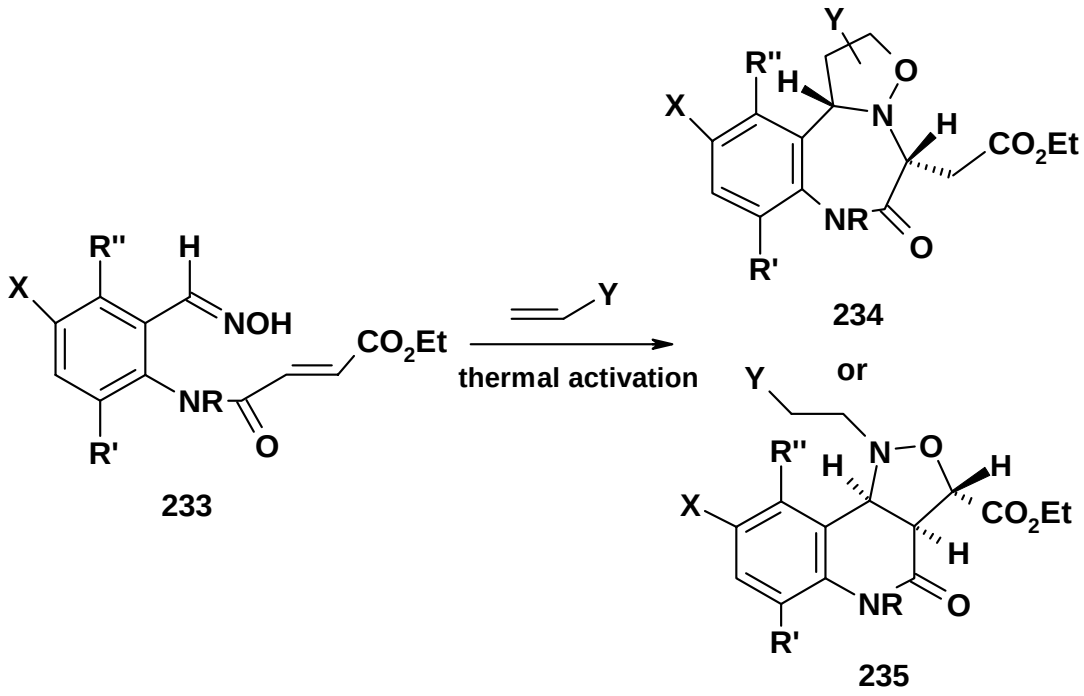


231 **232**

X, Z, Y, R, R', R'' = H, alkyl, aryl

Scheme 94

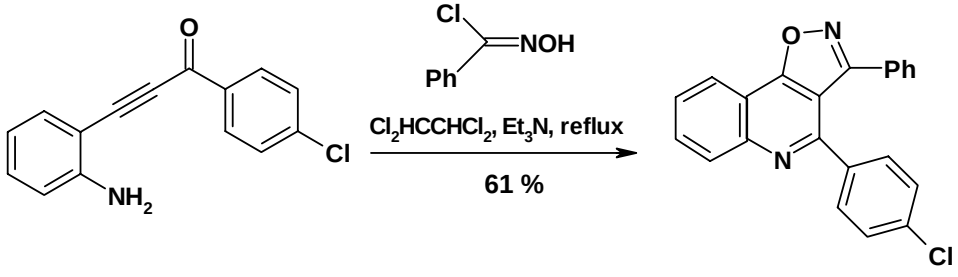
Similar intramolecular cycloadditions can be used in the synthesis of isoxazolo[3,4-*d*][1]benzopyrano[4,3-*b*]pyridine [198], benzopyrano[4,3-*c*]isoxazole [199], and isoxazolo[4,3-*c*]pyridine. [200] 5,6,7-Tricyclic isoxazolobenzodiazepinone (**234**) or 5,6,6-tricyclic isoxazoloquinolinone (**235**) are prepared from aldoximes (**233**) and electron poor olefin [201]. In each case the ring system formed depends on the relative electrophilicity of the added and internal olefin (Scheme 95).



R, R', R'', X = H, Me, Cl

Scheme 95

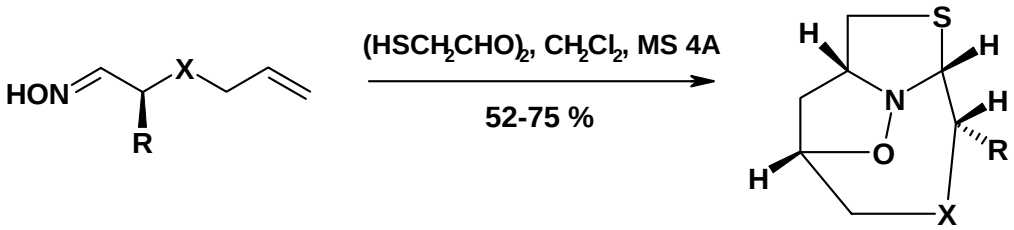
Interestingly, functionalized quinoline derivatives can be obtained through tandem addition – annulation reaction of β–(2-aminophenyl)-α,β-ynones. For example, addition of ynone (**236**) to benzaldehyde chlorooxime in presence of Et_3N afforded 3-phenylisoxazole[4,5-*c*]-2-(4'-chlorophenyl)quinoline (**237**) (Scheme 96).



236 **237**

Scheme 96

Finally, 5-alkenal oximes (**238**) undergo a domino reaction with mercaptoaldehyde affording tricyclic compounds (**239**) (Scheme 97). The formation of compounds (**239**) proceeds through intermediate nitrones.[203]



238 **239**

X = O, NR'; R = H, Me

Scheme 97

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