The Chemistry of Oxazoles

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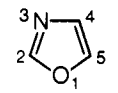
Contents

I. Introduction

The azoles are a class of five-membered ring, heteroaromatic compounds, isoconjugate with the cyclopentadienyl anion and derived from this species by replacing two of the carbons with a nitrogen atom and another heteroatom. Oxazole (**1**) has an oxygen atom and a pyridine-type nitrogen atom at the 1 and 3 positions of the ring, and, like pyridines, oxazoles are weakly basic substances.



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The literature concerning azole chemistry has been the subject of numerous, recent reviews.[1] Two comprehensive reviews on oxazole chemistry have appeared; the later of these covers the literature up to 1955.[2,3] The work of Cornforth and others carried out during World War II in connection with penicillin syntheses and related areas has greatly advanced our knowledge of the chemistry of oxazoles and oxazolones.[4]

This article covers the new methods and modifications of older methods for preparing oxazoles. These methods have been responsible for the ready availability of many substituted oxazoles and consequently have been instrumental in the advancement of oxazole chemistry. The coverage also includes reactions of oxazoles which have been developed in the past 20 years, some of which have been applied to the synthesis of biologically important compounds. The application of new theoretical methods and spectroscopic techniques such as nmr to oxazole chemistry is discussed.

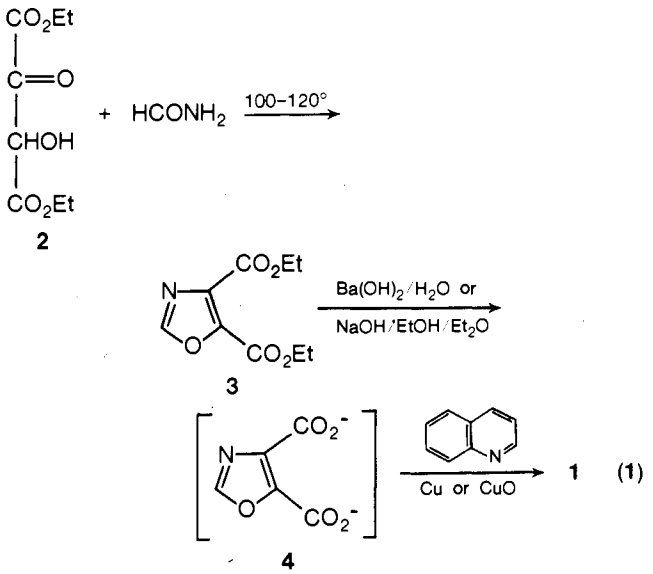
Although the main purpose of this review is to present a survey of the literature of oxazole chemistry, some of the commercial applications of oxazole derivatives are mentioned.

The present coverage of the literature from 1955 up to and including 1973 and part of 1974 does not incorporate work on benzoxazoles.[2] Oxazoles fused to other aromatic rings are considered only in instances where these are pertinent to the discussion at hand.

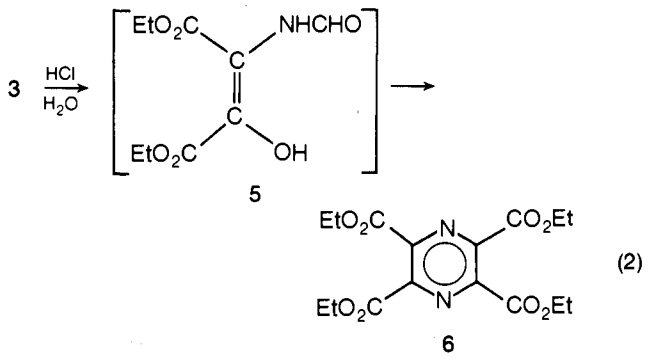
II. Synthesis

A. Synthesis of the Parent Oxazole

The parent oxazole (**1**) was first prepared by Cornforth and Cornforth utilizing a rather lengthy and complex reaction sequence.[5] More recently, however, a somewhat simpler approach to the synthesis was taken by Bredereck and Bangert.[6,7] Their method is an adaptation of an older synthesis of substituted oxazoles, i.e., the reaction of amides with α-hydroxy ketones.[2,3] Upon heating formamide with ethyl α-hydroxyketosuccinate (**2**), diethyl oxazole-4,5-dicarboxylate (**3**) is obtained. The diester was hydrolyzed with ether–ethanolic NaOH or aqueous $Ba(OH)_2$ and decarboxylation of the acid salt **4** is effected by heating **4** in quinoline in the presence of quinoline sulfate and copper or copper oxide to give oxazole (**1**) in 30–50% overall yield.



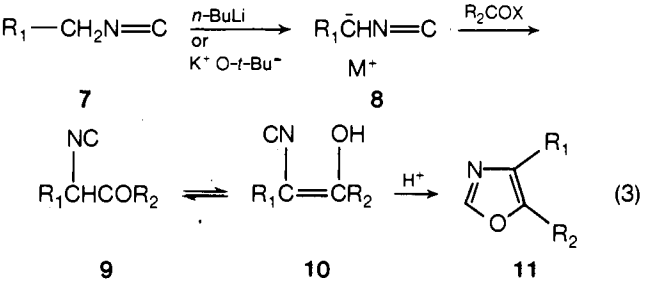
The oxazole diester **3** was hydrolyzed in aqueous HCl to give intermediate **5** which dimerized to a dihydropyrazine which was subsequently air-oxidized to afford ethyl pyrazinetetracarboxylate (**6**).



B. From Isocyanides

The synthesis of 2-unsubstituted oxazoles from formamide and α-halo or α-hydroxy ketones proceeds under vigorous conditions, affording low yields of oxazoles.[2,3] The synthesis also suffers from a lack of generality. Whereas 4- and 5-alkyl- or -aryloxazoles can be prepared using this reaction, oxazoles bearing other functional groups at these positions generally cannot be synthesized in this manner. Often the relative inaccessibility of the starting α-functionalized ketone may be a major drawback to the use of this method.

These disadvantages have, for the most part, been overcome by the use of the reaction of α-metalated isocyanides with carboxylic acid derivatives to give 2-unsubstituted oxazoles in moderate to high yields.[8-12] The synthesis, mechanism, and some representative yields are given in eq 3.

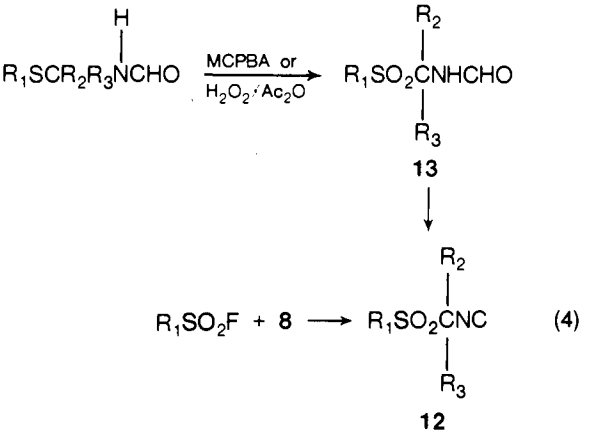


R_1 = CO_2Et	R_2 = Me	X = Cl	66%
R_1 = Ph	R_2 = H	X = OMe	76%
R_1 = H	R_2 = Et	X = $N(Me)_2$	48%
R_1 = SPh-*p*-Me;	R_2 = H	X = OMe	52%

When the α-metalated isocyanide is treated with an epoxide and the resulting intermediate is hydrolyzed with methanol or aqueous acid, 1,3-oxazines or 1,3-amino alcohols, respectively, are produced.[13]

A number of variations of this method have been developed. Yoshida et al. have prepared 5-alkoxy-4-alkyloxazoles by the pyrolysis of alkyl esters of α-isocyano carboxylic acids at 150–180° in yields of 5–28%.[14,15]

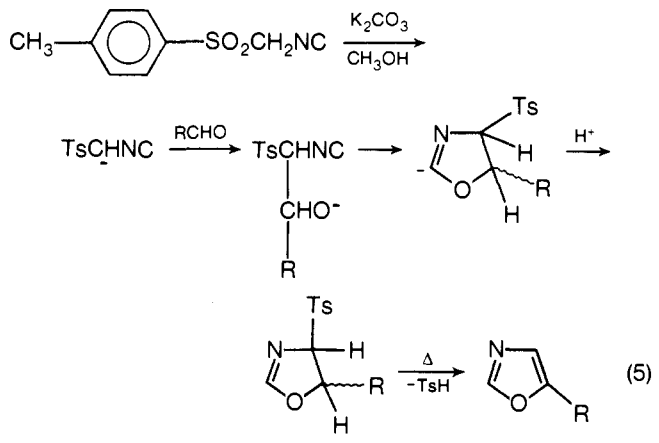
The synthesis of sulfonylmethyl isocyanides (**12**)[16] and their conversion to 2-unsubstituted oxazoles[17] has been investigated by van Leusen et al. The tosylmethyl isocyanide **12** can be prepared either by dehydration of the corresponding formamide **13** or by sulfonylation of α-lithio isocyanide (**8**) as shown (eq 4). When **12** is treated with K_2CO_3 and an aldehyde, acid chloride, or acid anhydride in methanol and the mixture heated, 5-substituted oxazoles are produced in good yields.[17]



Under similar conditions but at lower temperatures elimination of toluenesulfinic acid does not occur, and the corresponding 4-tosyl-Δ^2-oxazolines are formed. These results suggest the mechanistic pathway shown in eq 5.

Intermediates such as **10** (R_1 = H, R_2 = *p*-anisyl) can be prepared by dehydration of the corresponding formamide, and these yield the oxazoles **11** when heated.[18]

Deyrup and Killion describe the formation of the 5-aminooxazoles **15** from the BF_3-catalyzed reaction of *tert*-butyl isocyanide with *N*-acylimines **14**.[19] No yields were reported; however, this reaction deserves further study because of its potential utility as a general synthesis of 5-aminooxazoles.



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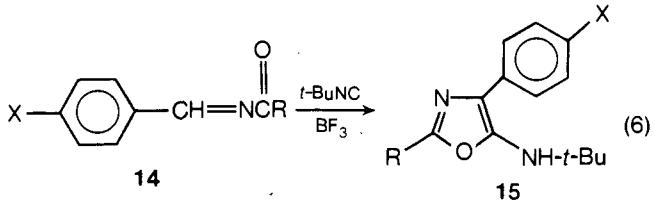
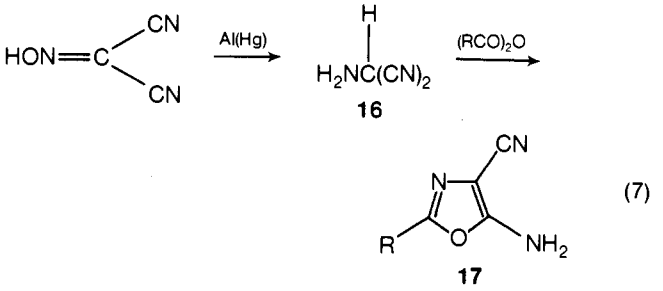


(6)

X = NO_2, H; R = Ph, Me

C. From Amino-, Imino-, and Amidonitriles and Nitrilium Salts

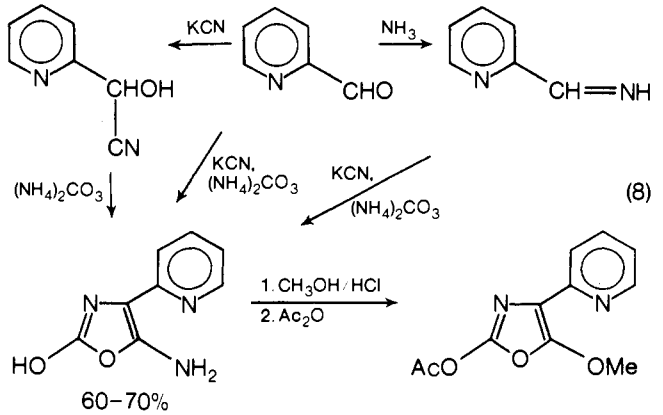
In their studies concerning prebiotic synthesis, Ferris and Orgel describe the synthesis of 4-cyano-5-aminooxazoles (**17**) from aminomalonitrile (**16**) and carboxylic acid anhydrides.[20,21] For example, **17** (R = H) was prepared in 43% yield from the reaction of the toluenesulfonic acid salt of **16** with acetic anhydride and formic acid.



(7)

R = H, Me, Et, Ph

A modification of the Fischer oxazole synthesis[22] has been utilized in the preparation of 2-hydroxy-4-pyridinyl-5-aminooxazole.[23] The ir spectra of these products are reported.



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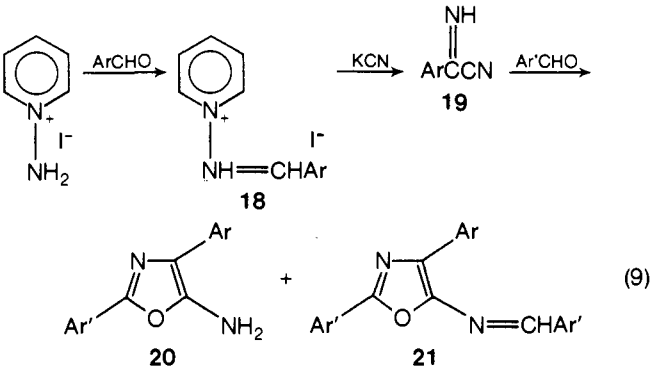
60–70%

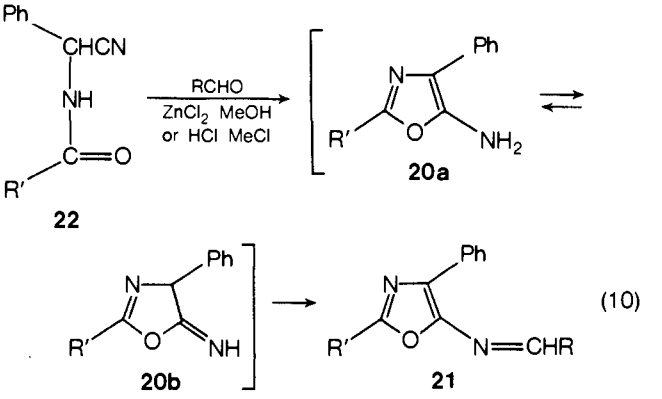
A modification similar to that described above was used in the synthesis of other 5-aminooxazoles (**20**) by the reaction



(9)

of the imino nitrile **19** with aromatic aldehydes (eq 9).[24] When aliphatic aldehydes are treated similarly, 2,4-disubstituted-3-oxazoline-5-ones can be obtained.

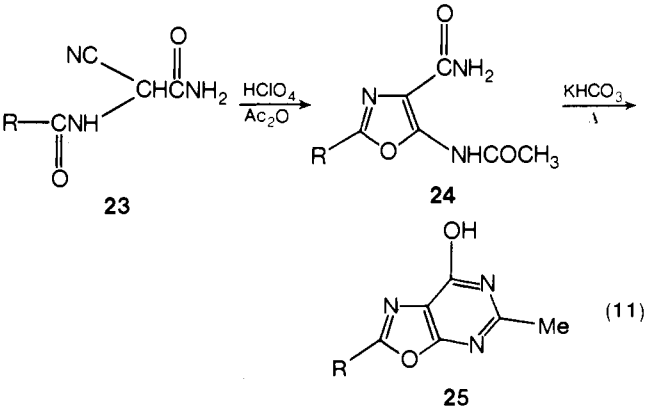
Fleury and coworkers have extensively studied the acid-induced cyclization of α-amidonitriles (**22**) to yield 5-aminooxazoles (**20**) and the subsequent reaction of **20** with aromatic aldehydes to form 5-arylideneaminooxazoles (**21**).[25,26] A number of substituted derivatives of **21** have been prepared in this manner, and their uv spectra and reactions are reported.



(10)

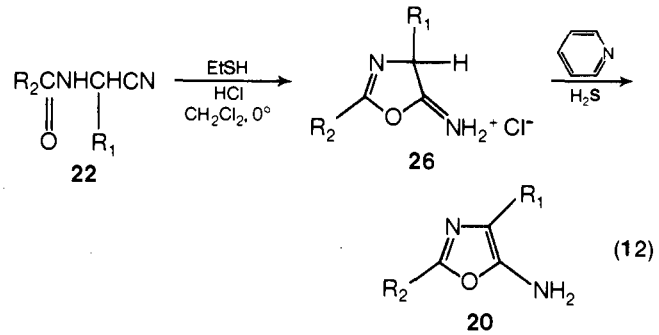
Fleury et al. also report the observation of two tautomeric forms of the 5-aminooxazoles **20a** and **20b** in their nmr spectra.[27]

The cyclization of 2-acylamino-2-cyanoacetamide (**23**) with $HClO_4$–acetic anhydride yields 5-acetamidooxazole-4-carboxamide (**24**).[28] The analogous formamidooxazoles are prepared by the reaction of **23** with HCO_2H–Ac_2O–HCl. In certain cases heating **24** with $KHCO_3$ affords oxazolo[5,4-*d*]pyrimidin-7-ols (**25**).



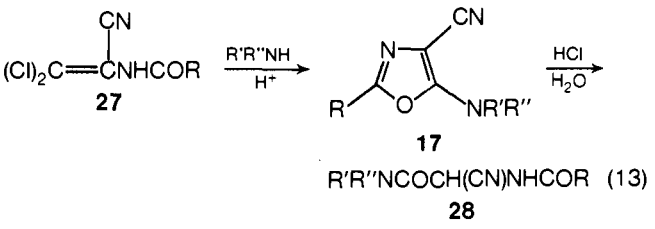
(11)

α-Amidonitriles (**22**) can be converted to 5-aminooxazoles (**20**) by treatment with ethanethiol and HCl in CH_2Cl_2 and subsequently treating the intermediate 5-imino-4,5-dihydrooxazole hydrochloride **26** with H_2S in pyridine.[29]



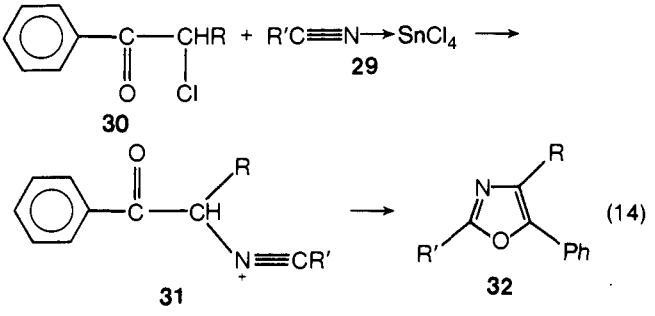
(12)

N-Acyl-1-cyano-2,2-dichlorovinylamines (**27**) react with secondary amines under acid catalysis to afford 4-cyano-5-(*N*,*N*-disubstituted)aminooxazoles (**17**) in 65–85% yields.[30] The ring opening of oxazole **17** with aqueous HCl gave **28.**



(13)

Nitrilium salts (**31**), generated by the reaction of the nitrile–$SnCl_4$ complex **29**, with substituted desyl chlorides (**30**) cyclize to give 2,4-disubstituted-5-phenyloxazoles (**32**).[31] No 3,4-dihydroisoquinolone products arising from the Friedel–Crafts alkylation of the phenyl ring of **31** were detected. The reaction is general for R = Ph, R' = alkyl, alkoxyalkyl, benzyl, and aryl with yields of 52–92%.



(14)

The copolymer of benzonitrile with 1-phenyl-3-chloro-2,3-epoxybutane is transformed into 2-phenylbenzylmethyloxazoles in the presence of Friedel–Crafts catalysts.[32]

D. The 1,3-Dipolar Addition of Carbonylcarbenes to Nitriles

The 1,3-dipolar cycloaddition of carbonylcarbenes to unsaturated compounds has been discussed in early reviews.[33] In these reviews the thermolysis of ethyl diazoacetate in the presence of benzonitrile is reported. At 145°, 2-phenyl-5-ethoxyoxazole is produced in 42% yield. The thermolysis of diazoacetophenone with benzonitrile at 150° gave a 0.40% yield of 2,5-diphenyloxazole. The reaction temperature could be lowered to 100° or less, and the yield of oxazoles increased to 17% upon catalysis of the reaction with copper or various copper salts. Decomposition of ethyl diazoacetate in the presence of benzonitrile and a copper catalyst at 80–85° gave 2-phenyl-5-ethoxyoxazole in 29% yield, and in the presence of acetonitrile 2-methyl-5-ethoxyoxazole was produced in 31% yield. Photolysis of the diazo ester in benzonitrile did not afford the expected oxazole.[34]

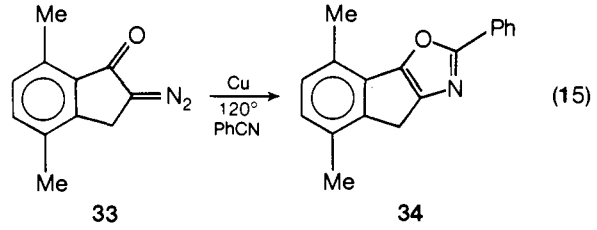
The effect of solvents on the decomposition of ethyl diazoacetate was investigated.[34] The rate of the decomposition in the polar solvent, nitrobenzene, is more than double the rate in the nonpolar hydrocarbon solvent, decalin, suggesting that the transition state for the formation of the carbene is somewhat more polar than the ground state.

The reaction of the carbenes derived from diazo ketones with nitriles was also investigated.[35a] Electron-withdrawing groups on the phenyl moiety of the diazoacetophenones substantially increased the yield of 2-phenyl-5-aryloxazoles in their uncatalyzed reaction with benzonitrile. The yield of oxazole increased from 0.4% for diazoacetophenone to 45% for *p*-nitrodiazoacetophenone. These substituents had little effect on the copper-catalyzed reactions. Photolysis of diazo ketones in benzonitrile gave negligible yields of oxazoles.

The effect of varying the nature of the copper catalysts on the decomposition of diazocarbonyl compounds and subsequent addition of the resulting species to nitriles was also noted. Copper(I) chloride gave the lowest yield of oxazoles (3.5%); copper acetylacetonate gave the highest yields (16%).[34,35a]

Tungsten hexachloride catalyzes the decomposition of diazocarbonyl compounds. When this decomposition occurs in the presence of a nitrile at room temperature, the corresponding oxazole is obtained in yields (20–65%) that are substantially greater than the Cu(II)-catalyzed reaction.[35b]

When the diazo ketone **33** was allowed to react with benzonitrile in the presence of a copper catalyst at 120°, the oxazole **34** was obtained in 34% yield.[35a]



(15)

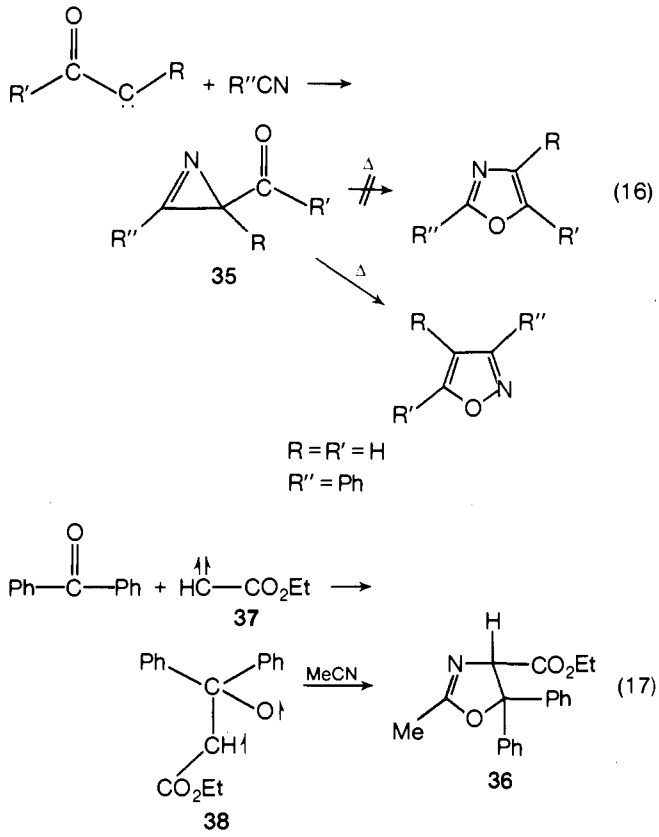
The copper-catalyzed reaction of ethyl α-diazopropionate with liquid HCN gave 4-methyl-5-ethoxyoxazole.[35c]

In most of the cases studied, copper catalysis of the decomposition of diazocarbonyl compounds suppresses the Wolff rearrangement (i.e., the rearrangement of carbonylcarbenes to ketenes). This is one possible rationale for the increase in yields of oxazoles when these reactions are so catalyzed.

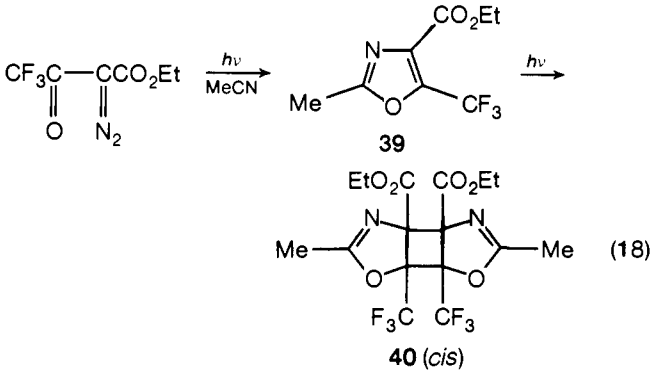
The most likely mechanism for this reaction is the 1,3-dipolar addition of a carbonylcarbene to a nitrile to yield an oxazole directly. Another mechanism which has been postulated involves the 1,2 addition of the carbene to the nitrile to afford the 3-carbonyl substituted azirine **35** and subsequent rearrangement of **35** to the oxazole (eq 16). Considerable doubt has been cast on the latter route for the thermal reaction because of the work of Padwa et al.[36] These investigators have shown that 3-phenylisoxazole arises from the thermolysis of 3-formyl-2-phenyl-1-azirine. Photolysis of this azirine gives 2-phenyloxazole (see section II.M).

A thorough study of the photodecomposition of diazo esters in acetonitrile was conducted by Buu and Edward.[37] Only singlet ethoxycarbonylcarbene reacts with nitriles to afford oxazoles. Upon benzophenone sensitization of the reaction, 2-methyl-4-carbethoxy-5,5-diphenyl-Δ^2-oxazoline (**36**) is formed. This product presumably arose from the addition of the triplet carbene **37** to benzophenone to give the diradical **38** which then adds to acetonitrile affording **36.**

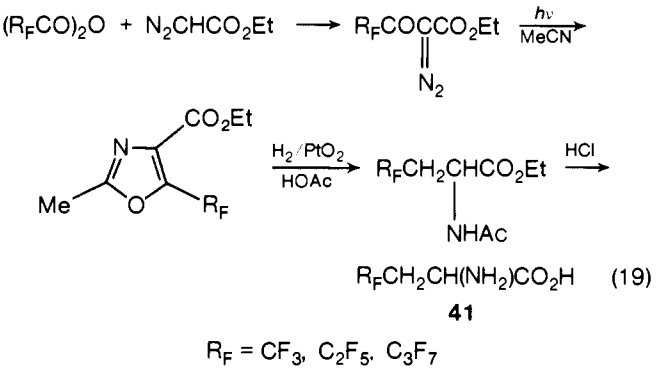
The reaction of nitriles with trifluoroacetylcarbethoxycar-



bene is a convenient and general method for the introduction of a trifluoromethyl group onto an oxazole ring. The reaction of acetonitrile with trifluoroacetyl diazoacetic ester (decomposed photochemically) gives ethyl 2-methyl-5-trifluoromethyloxazole-4-carboxylate (**39**) in 50% yield. Photolysis of the oxazole **39** afforded a 10% yield of a dimeric species **40** which is thought to arise from a formal [2 + 2] cycloaddition of two oxazole rings.[38,39]



Weygand et al. have developed a general procedure for preparing β-perfluoroalkylalanines (**41**) from perfluoroalkyloxazoles synthesized by the 1,3-dipolar addition of perfluoroalkyl diazoacetic esters to acetonitrile.[40] Overall yields of **41** are 35–50%.

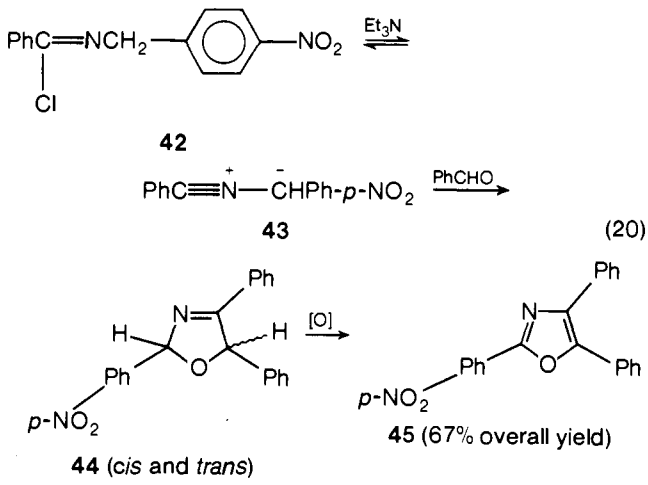


E. From Nitrogen Ylides

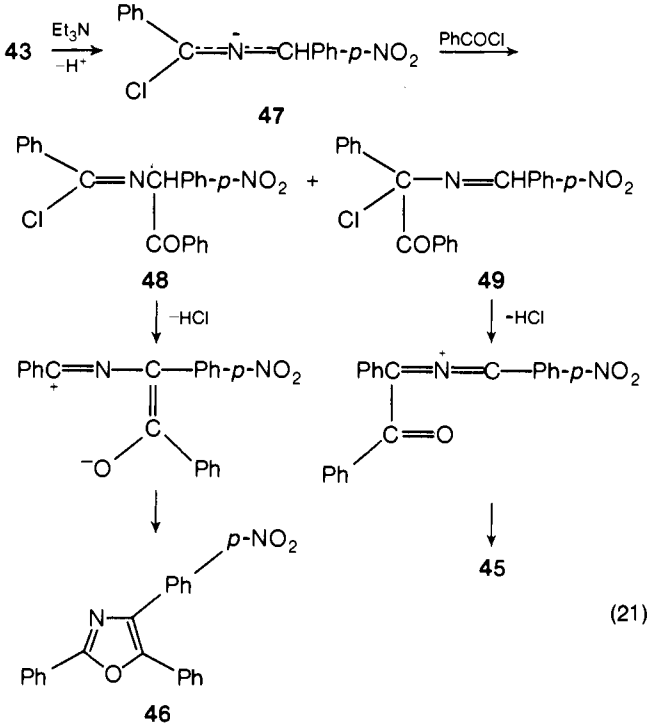
In the last section the 1,3-dipolar addition of carbonylcarbenes to nitriles was discussed as a synthesis of oxazoles.

The 1,3-dipolar addition of other dipolar species has been invaluable in the synthesis of five-membered ring heterocycles and has been the subject of extensive reviews.[33,41]

Nitrile ylides undergo 1,3-dipolar additions to aldehydes to give oxazolines which can be oxidized to the corresponding oxazoles.[42,43] The nitrile ylide **43** is generated from the imidoyl halide **42** by the 1,3-elimination of HCl with triethylamine as a base.



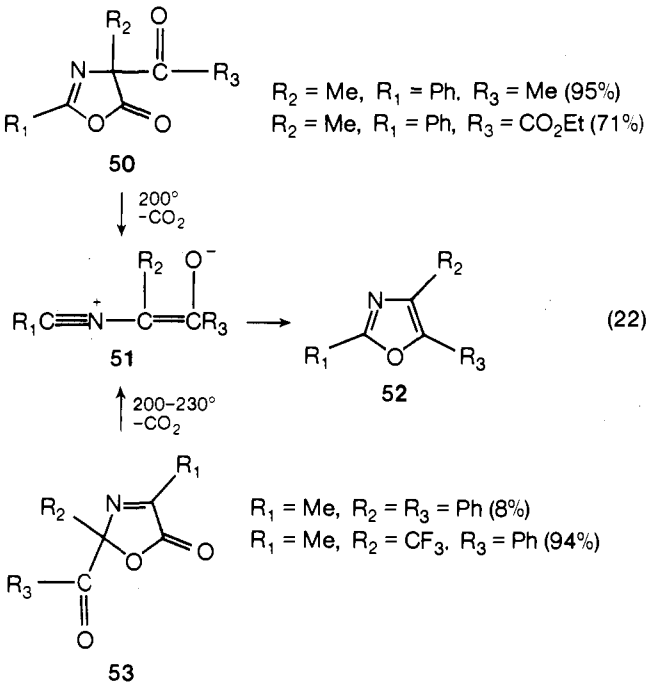
The mechanism of the reaction of **42** and triethylamine with acid chlorides is somewhat obscure. Three mechanisms for this reaction have been postulated.[42] The first of these involves the nonregiospecific 1,3-dipolar addition of **43** to benzoyl chloride and subsequent loss of HCl from the chlorooxazoline intermediate to yield **45** and the isomeric 2,5-diphenyl-4-(*p*-nitrophenyl)oxazole (**46**). The oxazoline intermediate could not be isolated. The second mechanism does not in-



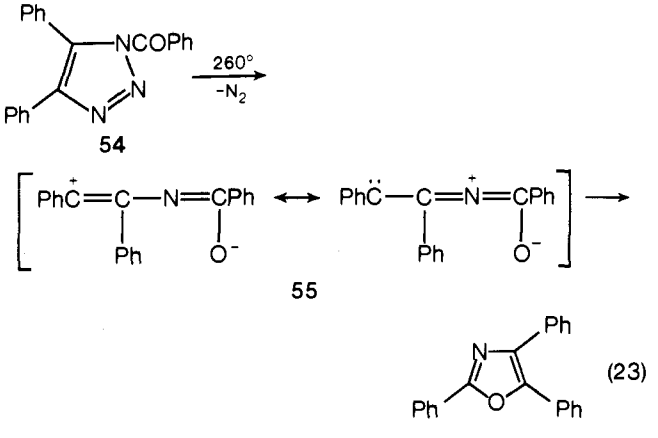
volve the nitrile ylide **43**, but an azaallyl anion **47** is postulated to attack benzoyl chloride to give intermediates **48** and **49** which lose HCl and cyclize to afford the isomeric oxazoles **45** and **46** (eq 21). A two-step addition of **43** to benzoyl chloride is also postulated.

Diethyl mesoxalate also undergoes a 1,3-dipolar addition to **43** to ultimately yield ethyl 2-(*p*-nitrophenyl)-4-phenyloxazole-5-carboxylate.[42]

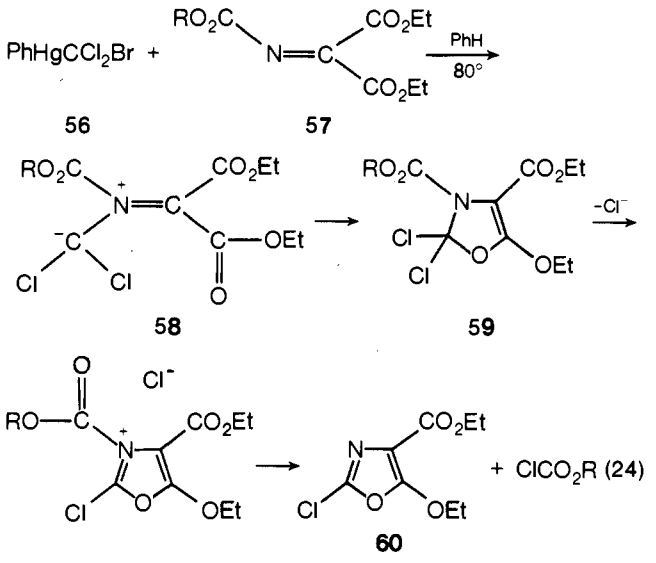
Nitrile ylides have been implicated as intermediates in the thermolysis of 2- and 4-acyloxazolones **50** and **53**.[44] These intermediates can undergo intramolecular cyclization to form oxazoles. The mechanism of this and analogous rearrangements will be discussed further in section IV.I.



The thermolysis of 1-benzoyl-4,5-diphenyl-1,2,3-triazoles (**54**) at 260° leads to the formation of the dipolar intermediate **55**. Cyclization of **55** affords 2,4,5-triphenyloxazole in 30% yield.[45]

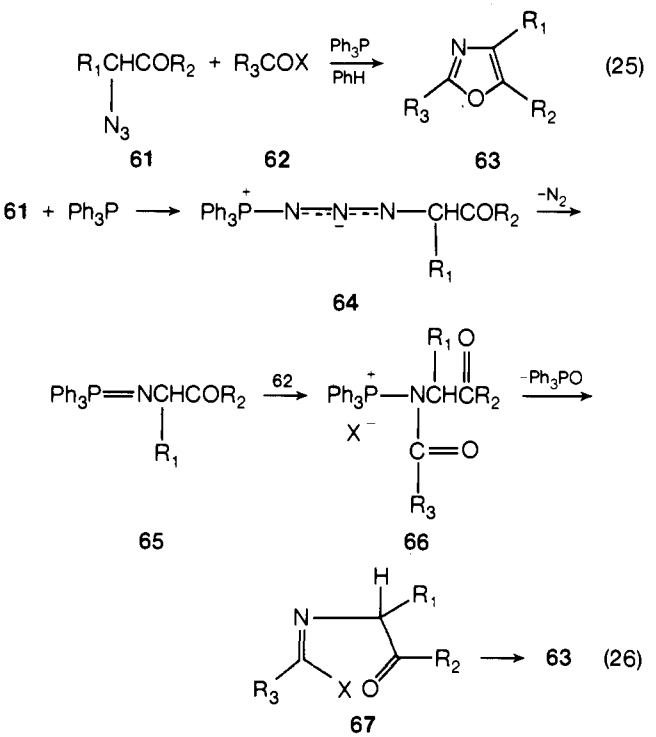


Dichlorocarbene, generated from the thermolysis of phenyl(bromodichloromethyl)mercury (**56**), reacts with the imine **53** to give ethyl 2-chloro-5-ethoxyoxazole-4-carboxylate (**60**) in 20–35% yield.[46] The oxazoline **59** arises from the formal 1,4-addition of dichlorocarbene to the N=C—C=O system in **57**. The C=C—C=O system does not undergo similar 1,4-addition with dichlorocarbene. This observation suggests that the terminal nitrogen atom of the heterodiene system of **57** facilitates addition by allowing the formation of the ylide **58**.



F. From Azidocarbonyl Compounds and Carbonylnitrenes

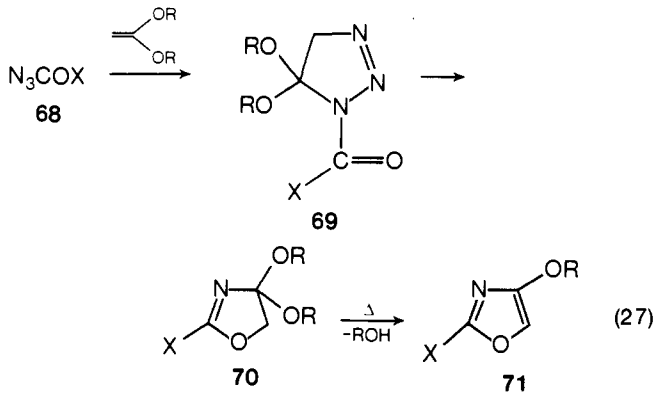
The reaction of α-azido ketones and azido esters (**61**) with aromatic or aliphatic acyl halides (**62**) in the presence of triphenylphosphine affords substituted oxazoles (**63**) in 22–68% yield (eq 25).[47,48] The proposed mechanism is given in eq 26.



The reaction of carbonylazides (**68**) with ketene dialkylacetals affords oxazolines (**70**) or 4-alkoxyoxazoles (**71**) via the intermediate triazoline **69** formed from a 1,3-dipolar addition of **68** to the ketene acetal.[49,50]

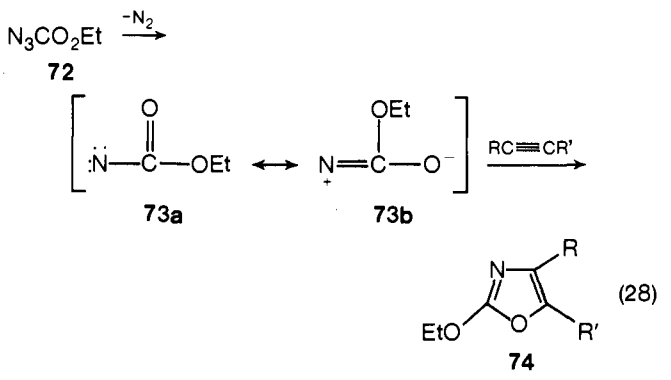
Carbonylnitrenes result when acyl azides are photolyzed or thermolyzed. The reaction of these nitrene species with alkynes produce 2-alkoxyoxazoles (**74**).

Huisgen and Blaschke studied the thermolysis of ethyl azidoformate (**72**) with alkynes to give 2-ethoxyoxazoles in 3–30% yield.[51–53] Meinwald and Aue investigated the formation of 2-ethoxy-4,5-diphenyloxazole from the reaction of ethoxycarbonylnitrene (**73**) with 2-butyne, the nitrene **73** being generated photochemically from the azide **72**.[54]



68 69 70 71

X = OEt, Ph (47%), *p*-NO_2Ph (62%) (27)

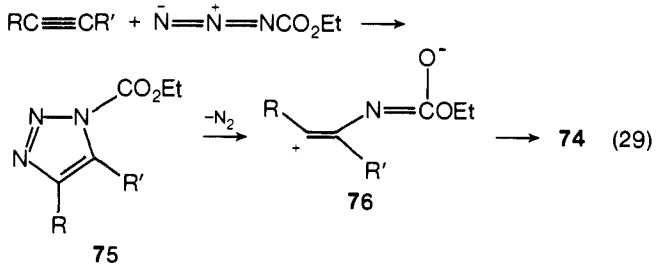


72 73a 73b 74

R = CO_2Et, R′ = Ph (30%)
R = Ph, R′ = H (16%)
R = R′ = CO_2Me (3%) (28)

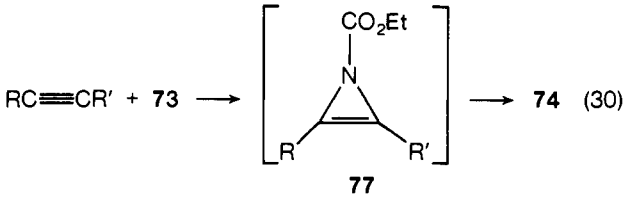
2-Alkoxyoxadiazoles are formed when carbonylnitrenes (**73**) are allowed to react with nitriles.[55]

Several mechanisms have been proposed for the formation of the oxazole products, the most attractive being the direct 1,3-dipolar addition of the carbonylnitrene (formally **73b**) to the alkyne. The 1,3-dipolar addition of the azide **72** to the alkyne followed by loss of nitrogen and subsequent cyclization of the zwitterionic intermediate **76** to yield the oxazole **74** has also been proposed.[52] The intermediate **76** may also arise from the direct attack of **73** on the alkyne.



75 76 74 (29)

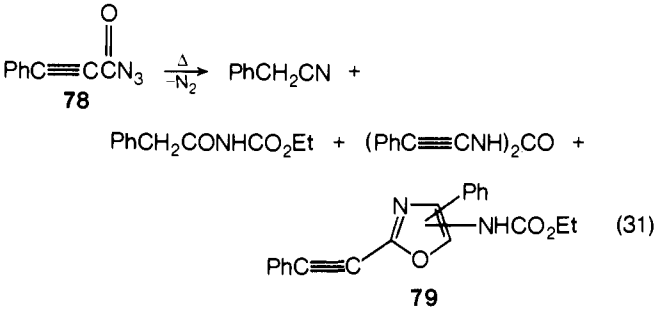
A third and somewhat less likely mechanism which has been proposed is the 1,2-addition of **73** to the alkyne yielding the 2-azirine **77.** Rearrangement of **77** would give the observed product **74.**[52,54]



77 74 (30)

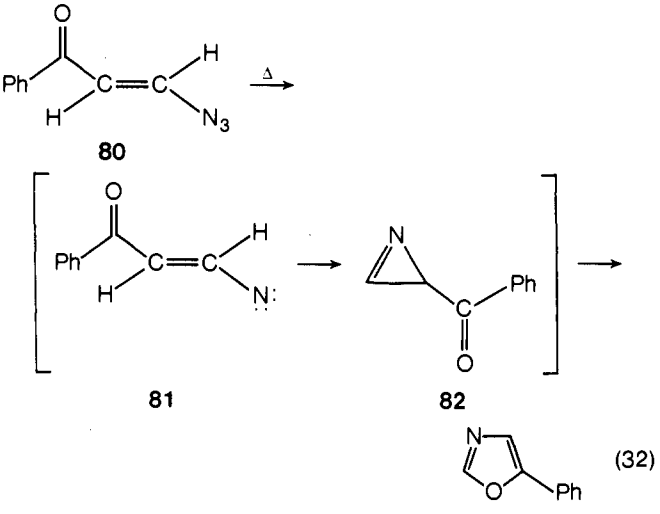
In an attempt to shed some light on the mechanism, Huisgen and Blaschke studied the kinetics of the reaction.[52] The 1,3-dipolar addition of the azide **73** to the alkyne could be discounted since the triazole **75** was stable at the temperature of the azide thermolysis (130°). From the results of the kinetic measurements obtained by these workers it is not possible to distinguish between the direct 1,3-dipolar addition mechanism and the 1,2-addition of nitrene **73** to the alkyne to form the 2-azirine intermediate **77.** One may argue against the intermediacy of the 2-azirine on the basis of its potential antiaromatic electronic nature; however, the results of molecular orbital calculations utilizing the MINDO/3[57] and NDDO[58] methods lend support to the possible intermediacy of structures such as **77.**[56]

Among the products formed when phenylpropiolyl azide (**78**) is thermolyzed in ethanol–water solution is the oxazole **79.**[59]



78 79 (31)

When *trans*-β-azidovinyl phenyl ketone (**80**) is thermolyzed, the main product is benzoylacetonitrile along with a low yield of 5-phenyloxazole. A trace amount of 5-phenylisoxazole was also isolated.[60] A mechanism for the formation of the oxazole involving 3-benzoyl-1-azirine (**82**) produced from the vinyl nitrene **81** was proposed.



80 81 82 (32)

G. From Alkynes

Propargyl alcohols and esters derived from these alcohols react with amides or nitriles in the presence of certain catalysts and cyclodehydrating agents to afford alkyl- or aryloxazoles.

The reaction of propargyl formate with formic acid and dry Dowex-50 resin (Hg type) gave formylacetone which was treated with formamide and concentrated H_2SO_4 to yield 4-methyloxazole.[61]

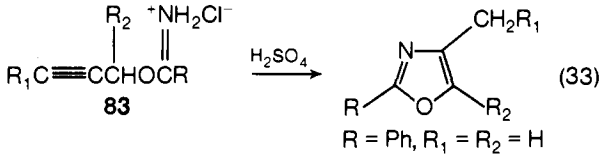
A 50% yield of 2-phenyl-4-methyloxazole was obtained when propargyl alcohol was caused to react with benzonitrile and H_2SO_4.[62]

Substituted propargyl alcohols combine with amides and acetic acid, the reaction being catalyzed by $HgSO_4$, to give alkyl- and aryloxazoles in high yields.[63] For example, acet-

amide, 1-butyn-3-ol, glacial acetic acid, and $HgSO_4$ afforded an 85% yield 2,4,5-trimethyloxazole. Similarly propargyl acetates react with acetamide, trichloroacetic acid, polyphosphoric acid, and a $HgSO_4$ catalyst to give various 2,5-disubstituted-4-methyloxazoles in 20–73% yield.[64] The effect of other catalysts on the reaction was studied (e.g., $NiCl_2$, $CdSO_4$, $ZnCl_2$, etc.). The mercury salts gave the highest yields of oxazoles in every case studied.

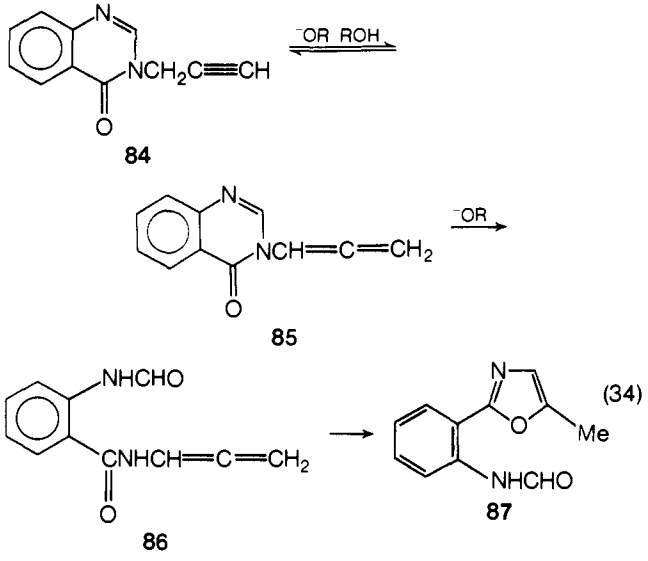
Alkyl- and aryloxazoles can also be prepared by the cyclization of propargyl amides. In the presence of concentrated H_2SO_4, 3-benzamido-1-propyne cyclized to 2-phenyl-5-methyloxazole.[65,66]

In a similar reaction, propargyl benzimidate hydrochloride (**83**) is converted to 2-phenyl-4-methyloxazole.[66]



(33)

An unusual rearrangement occurs when the acetylenic oxoquinazoline **84** is subjected to basic reagents.[67,68] The first step in the proposed mechanism is base-induced tautomerization of the acetylene to the allene **85.** The quinazoline ring is subsequently opened with base affording intermediate **86** which cyclizes as shown (eq 34) to yield 2-(o-formamidophenyl)-5-methyloxazole (**87**). The reaction was followed by a periodic tlc analysis. By this analysis it was observed that allene **85** was formed initially but was consumed in the course of the reaction and disappeared entirely after 2 hr.



(34)

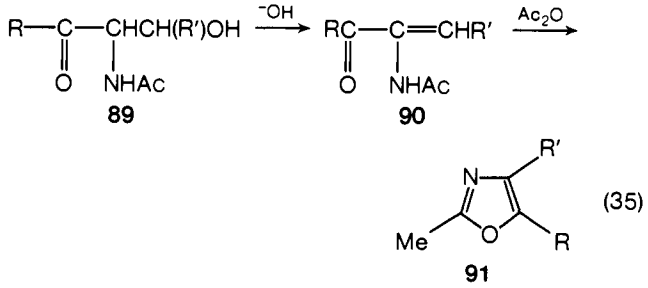
H. From Enamides, Enamines, and Imides

The title compounds having the structure **88** have been converted to oxazole derivatives by modifications of the existing cyclization reactions of 1-acylamino carbonyl compounds.[2,3] The nature of the substituents R, R', X, and Y will become apparent in the ensuing discussion.

RXC=C(R')NHY

88

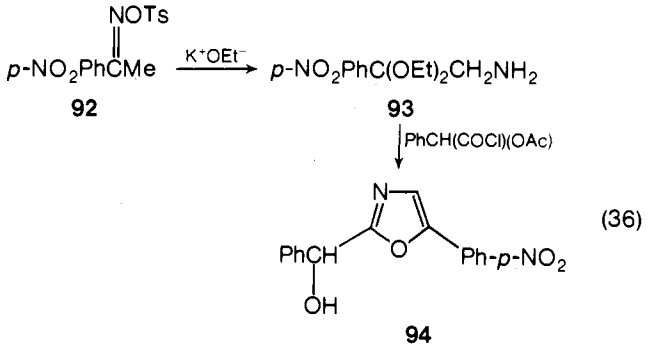
The reactions of 1-acetamido-2-hydroxypropyl ketone **89** with various reagents were studied.[69] Upon treatment of **89** with alkali, water was eliminated to form the enamide **90** which could be converted to the oxazole **91** with acetic anhydride in 40–50% yield. Other reagents which will effect the conversion of **90** to **91** are HCl–dioxane or $SOCl_2$.[70]



(35)

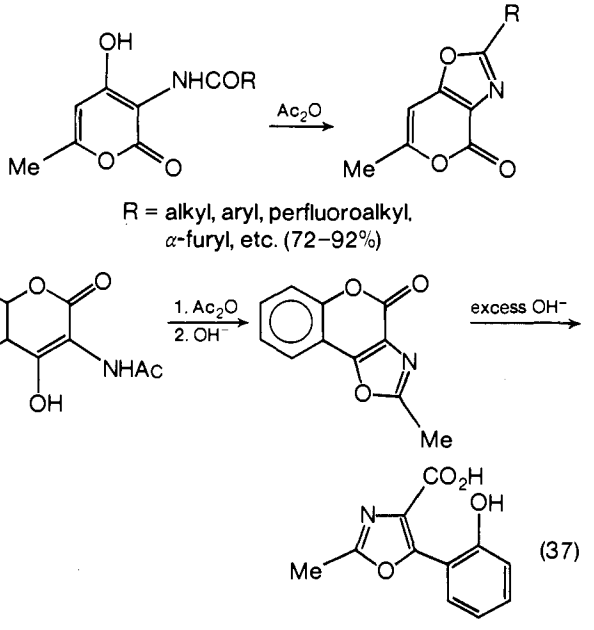
R' = CH_2OCO_2Et, CH_2OAc, CO_2H; R = p-NO_2Ph

When the oxime tosylate **92** is allowed to react with potassium ethoxide in ethanol, the diethyl acetal of α-amino-p-nitroacetophenone (**93**) is isolated. Acetal **93** cyclizes to the oxazole **94** in the presence of phenyl-1-acetoxyacetyl chloride.[71]



(36)

Cyclization reactions of α-hydroxy enamides have been utilized in the synthesis of oxazolopyranones and the novobiocin analogs, the oxazolocoumarins (eq 37).[72–74]

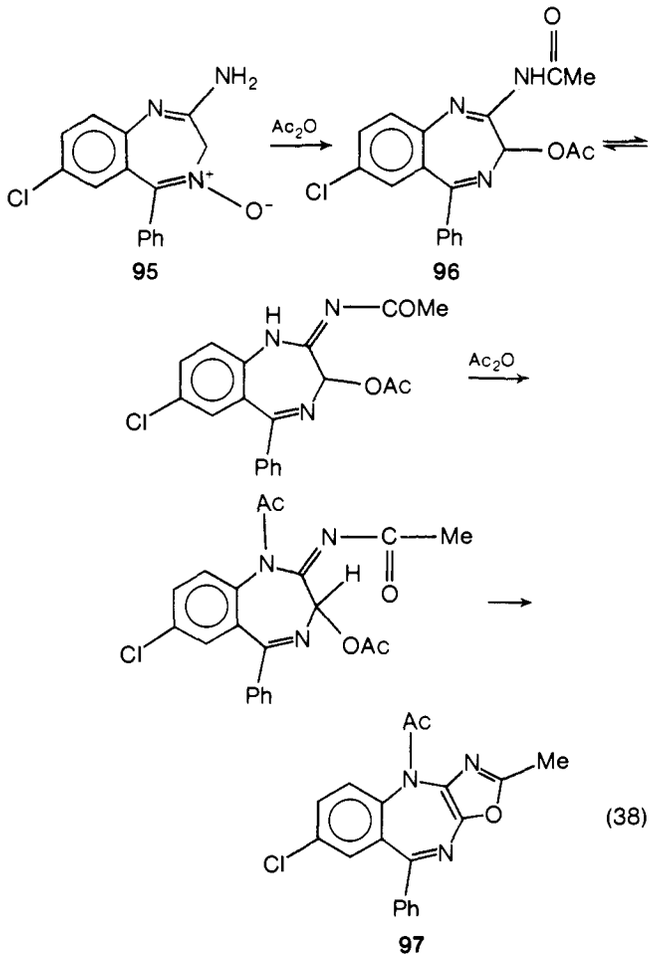


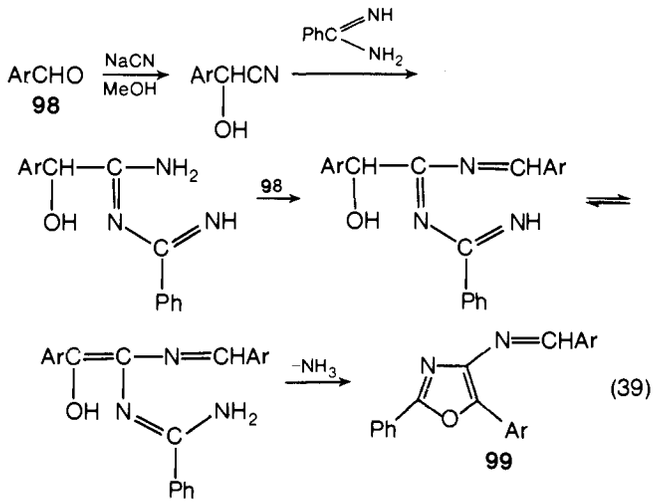
(37)

The reaction of 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**95**) with acetic anhydride presumably proceeds through the intermediate **96** which rearranges as shown (eq 38) to yield 10-acetyl-7-chloro-2-methyl-5-phenyl-10*H*-oxazolo[4,5-*b*][1,4]benzodiazepine (**97**).[75]

Aromatic aldehydes (**98**) react with benzamidine and NaCN in methanol to produce 4-arylidineamino-2-phenyl-5-aryloxazoles (**99**).[76]

The reduction of 1-(*p*-nitrophenyl)-2-acetamido-3-hydroxy-1-propanone with triisopropoxyaluminum affords the expected alcohol along with 2,4-dimethyl-5-*p*-nitrophenyloxazole as a byproduct.[77]



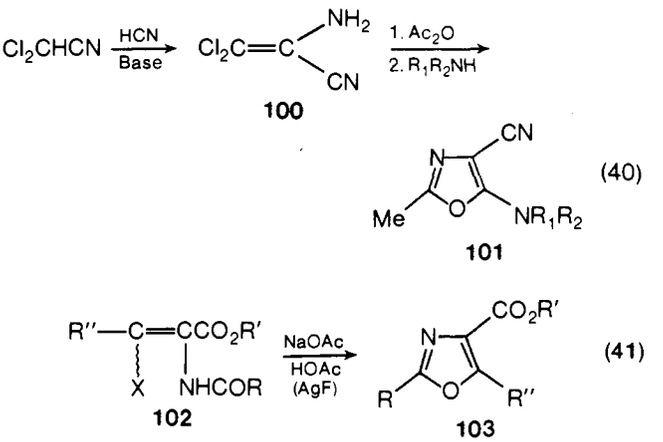


α-Acylamino acrylic acids can be decarboxylated in pyridine, and the intermediate derived from the decarboxylation will subsequently react with *p*-nitrobenzaldehyde to yield 4-methyl-5-*p*-nitrophenyloxazole.[78]

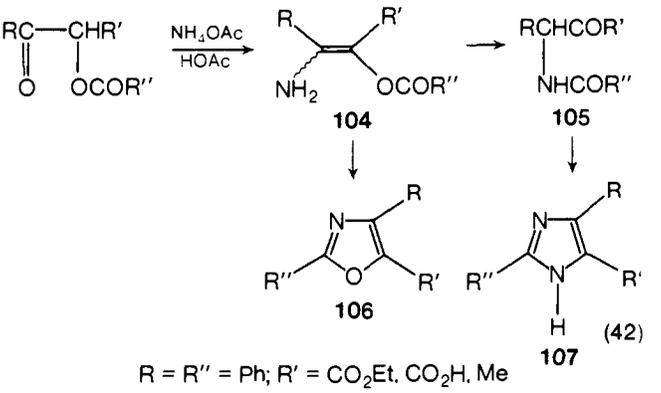
The synthesis of 4-cyano-5-(*N*-substituted amino)oxazoles (**101**) has been accomplished by the acetylation of β,β-dichloroaminoacrylonitrile (**100**) with primary and secondary amines and hydrazines.[79]

β-Halo-α-acylamino-α,β-unsaturated acids and esters (**102**) can be converted to oxazole-4-carboxylic acids and esters with NaOAc–HOAc when heated in a bomb or with a AgF catalyst.[80]

The intermediate in the reaction of α-acyloxy ketones with NH_4OAc–HOAc to form oxazoles is the acyloxy enamine **104**[81] rather than the isomeric α-acylamino ketone **105**.[82]



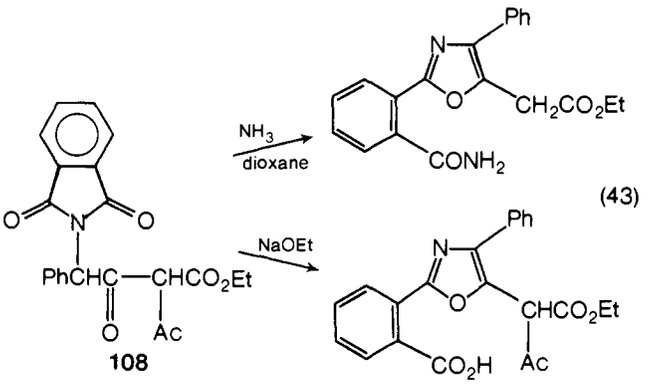
The enamine **104** reacts further to form the oxazole **106**, or rearrangement of **104** can occur under these reaction conditions to afford the imidazoles **107** (via **105**).



R = R'' = Ph; R' = CO_2Et, CO_2H, Me
R' = R'' = Ph; R = Me
R = Ph; R' = Me; R'' = 6-quinolyl

α-Amino-β,γ-unsaturated esters and ketones react with benzoyl peroxide to yield benzoyloxy enamines (**104:** R = CH_3; R' = CO_2Et, $COCH_3$; R'' = Ph). These compounds are easily transformed to the 2-phenyl-4-methyl-5-carboethoxy- or 5-acetyloxazoles with HOAc in 82 and 84% yields, respectively.[83]

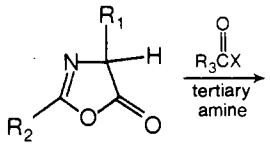
N-Substituted phthalimides (**108**) are of use in the synthesis of substituted isoxazoles, pyrazoles, oxazolones, and oxazoles among other heterocyclic systems (eq 43).[84,85]



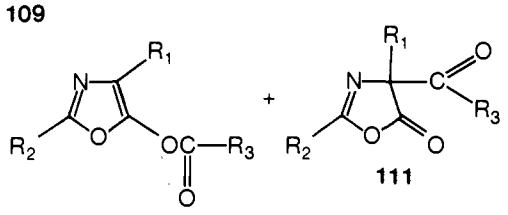
I. From Oxazolin-5-ones

Oxazolone chemistry has been the subject of several reviews.[3,4,86,87] 2-Oxazolin-5-ones are usually prepared by cyclodehydration of α-amino acids with acetic anhydride.[3,4,86,87] When the resulting oxazolones **109** are treated with acyl halides under kinetically controlled conditions, O-acylation occurs to give 5-acyloxyoxazoles (**110**).[88-91] The factors which favor O- over C-acylation are the use of acyl

bromides rather than acyl chlorides; increased solvent polarity (e.g., HMPA vs. THF); lower reaction temperatures; the use of more hindered tertiary amines (e.g., ethyldiisopropylamine vs. triethylamine); electron-releasing functionality on the acyl halides and on the 4 position of the oxazolone ring (R_1).[88]

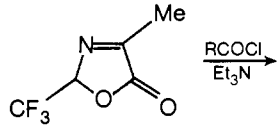


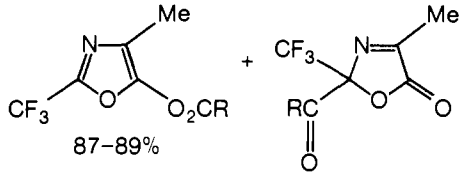
109



110 111 (44)

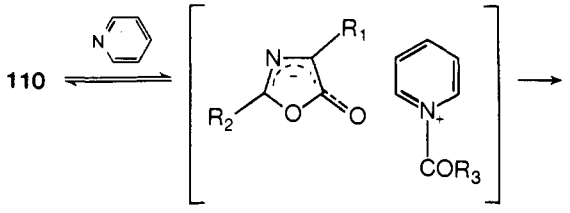
The 3-oxazolin-5-ones will also react under the same conditions to afford 5-acyloxyoxazoles (eq 45).[88,90-92]





87–89% (45)

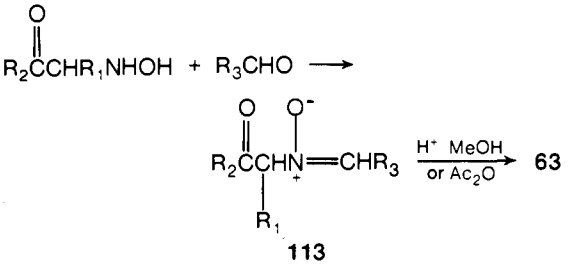
The acyloxyoxazoles **110** can be converted to the more thermodynamically stable 2- or 4-acyl-2-oxazolin-5-ones (**111**) by the thermolysis of **110** in pyridine or picolines, presumably via the ion-pair intermediate **112**.[92]



112 (46)

J. From 2-Oxo Nitrones

Substituted oxazoles can be prepared in high yields by cyclization of 2-oxo nitrones with acidic methanol or acetic anhydride.[93-95] The synthesis is outlined in eq 47.

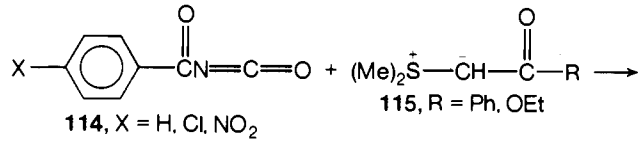


113 63 (47)

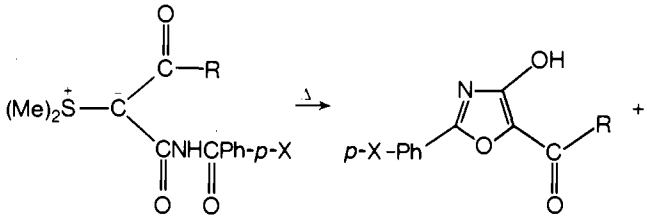
R_1 = H, Me; R_2 = Ph, *p*-Tol; R_3 = alkyl, aryl

K. From Aroyl Isocyanates

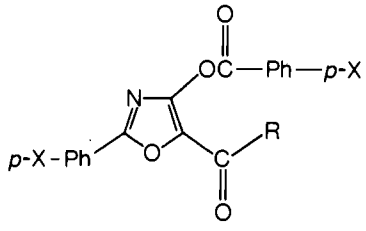
Aroyl isocyanates react with carbonyl stabilized sulfonium ylides (**115**) to give the 1:1 adducts **116** in good yields (75–90%).[96] Pyrolysis of the adduct **116** in refluxing decalin afforded oxazoles **117** and **118** in an approximate ratio of 6:1 with an overall yield of 60%.



114, X = H, Cl, NO_2 **115**, R = Ph, OEt

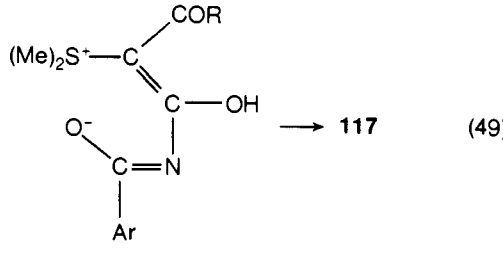


116 117



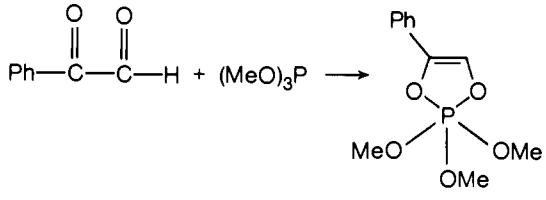
118 (48)

The proposed mechanism for the formation of **117** involves the cyclization of **116** through its enol form **116a.**

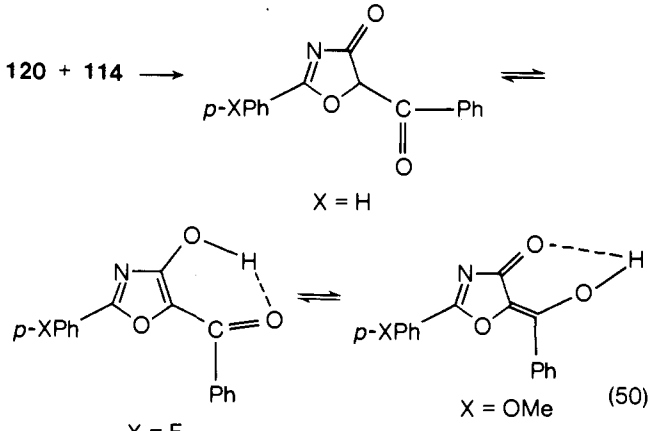


116a 117 (49)

A novel synthesis of 2-aryl-4-hydroxy-5-benzoyloxazoles (**119**) from the reaction of the phospholene **120** with aroyl



120

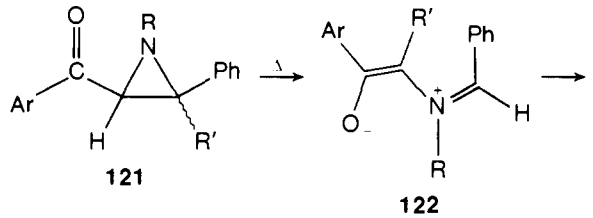


X = H X = F 119 X = OMe (50)

isocyanates (**114**) has been reported.[97] The phospholene **120** is formed by the reaction of phenyl glyoxal with trimethyl phosphite. The tautomer of **119** which predominates is dependent upon the substituent, X, on the 2-phenyl moiety. The 4-hydroxyoxazoles or their tautomeric oxazolones (**119**) could be methylated to give 4-methoxyoxazoles with ethereal diazomethane. Yields of **119** ranged from 65 to 71%.

L. Acylaziridine–Oxazole Rearrangements

Thermolysis of 1-substituted-2-aroyl-3-phenylaziridines (**121**) at 220° affords 2-phenyl-5-aryloxazoles.[98] The postulated intermediate is the azomethine ylide **122** formed via the heterolytic cleavage of the C–C of the aziridine **121.** The ylide **122** cyclizes to give the oxazoline **123** which is oxidized to the oxazole by a radical elimination mechanism. For example, when Ar = Ph and R = *tert*-butyl, a 96% yield of 2,5-diphenyloxazole (**123b**) was isolated.



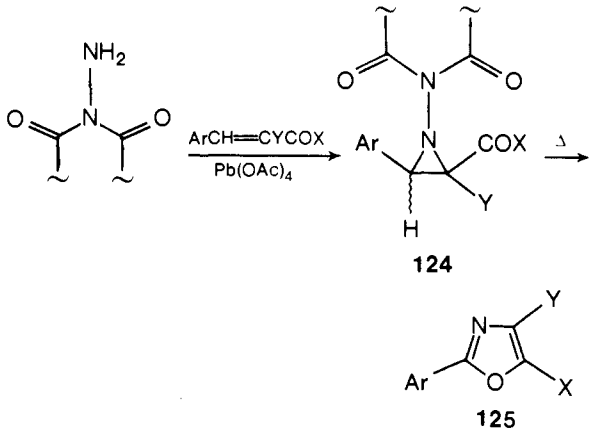
121 **122** **123**

132a, Ar = Ph; R′ = Cl
b, Ar = Ph; R′ = H

(51)

The photolysis of *cis*- or *trans*-*N*-*tert*-butyl-2-benzoyl-3-phenylaziridine gives 2,5-diphenyloxazole (**132b**) in 51 and 38% yields, respectively.[99,100] The trans aziridine also gives (β-*tert*-butylamino)-*trans*-benzalacetophenone (41%), whereas in the photochemical reaction of the cis aziridine this product is not observed. The reaction mechanism, which is thought to be analogous to the thermal rearrangement discussed above, was studied in detail.[100]

A similar mechanistic pathway is probably operative in the thermal rearrangement of 1-imido-2-aryl-3-carbonyl substituted aziridines (**124**) to 2-aryl-4,5-disubstituted oxazoles (**125**).[101] The aziridines **124** are prepared by the oxidation of *N*-amino imides with $Pb(OAc)_4$ in the presence of the corresponding olefin (ArCH=CYCOX).



124

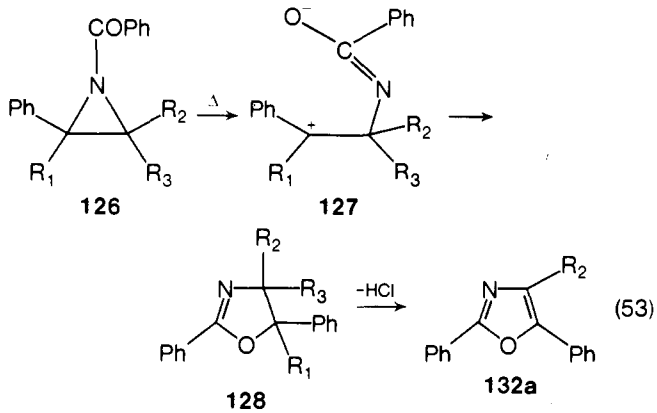
(52)

125

The *N*-phthalimidoaziridine **124** (i.e., Ar = Ph, X = NH_2, Y = CN) is converted to 2-phenyl-4-cyano-5-aminooxazole when heated in boiling ethanol. In the cases reported it was possible to trap the azomethine ylide intermediate analogous to **122** with dimethyl acetylenedicarboxylate to give a Δ^3-pyrroline.[101]

In contrast to the *C*-acylaziridine rearrangements, *N*-acylaziridines undergo a heterolytic C–N bond cleavage upon thermolysis. The dipolar intermediate **127** thus formed can cyclize to an oxazoline **128**[102] which if possible eliminates suitable fragments to produce oxazoles.

Zaugg and DeNet studied the thermal rearrangement of 1-benzoyl-2,2-dichloro-3-phenylaziridine (**126**) to the 4-chlorooxazole **132a** in refluxing xylene.[103]



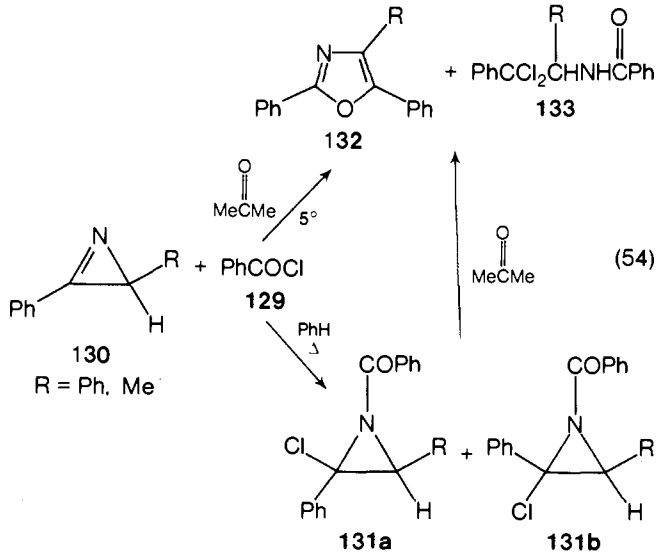
126 **127** **128** **132a**

R_1 = H; R_2 = R_3 = Cl

(53)

A variation of the *N*-acylaziridine–oxazole rearrangement is the reaction of 1-azirines with acylating agents to afford *N*-acylaziridines which undergo a rearrangement to yield oxazoles.

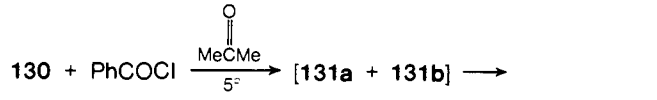
Fowler and Hassner studied the reaction of 2-phenyl-3-methyl-1-azirine and 2,3-diphenyl-1-azirine with benzoyl chloride in benzene and in acetone solutions.[104] In benzene, the *N*-aroyl-2-chloroaziridines **131** were formed (**131a**:**131b** = 6:4). In acetone at 5° the oxazole **132** and the amide **133** were produced. When **131a** and **131b** were treated with acetone at 5°, the same molar ratio of **132**:**133** as in the direct reaction of benzoyl chloride with the azirine **130** in acetone was obtained. This observation implies that **131** is an interme-



132 **133** **130** **129** **131a** **131b**

R = Ph, Me

(54)



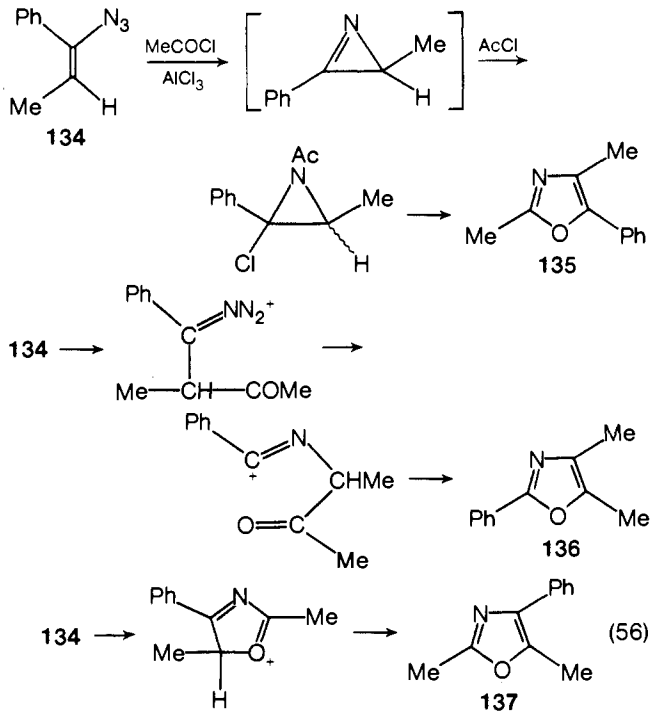
R_1 = Cl; R_2 = Me, Ph; R_3 = H

(55)

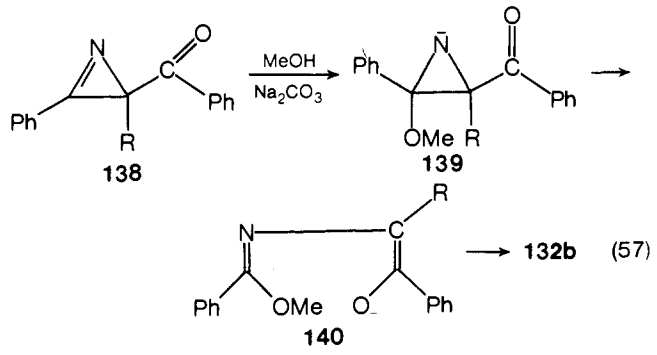
diate in the rearrangement. The amide **133** is probably formed by the attack of HCl on the aziridine **131.**

Sato and coworkers also studied the reaction of 2-phenyl-1-azirines with acylating agents.[105] 2-R-5-phenyloxazoles can be obtained from the reaction of RCOCl (R = CH_3, Ph, *p*-NO_2Ph, β-(5-nitro-2-furyl)acryloyl) with 2-phenyl-1-azirine and triethylamine in 28–43% yield.

1-Azido-1-phenylpropene (**134**) is converted to three isomeric oxazoles **135**, **136**, and **137** in 17, 7, and 1% yield, respectively, when treated with acetyl chloride and $AlCl_3$. The mechanism proposed for the formation of the major product **135** involves the rearrangement of an *N*-acyl chloroaziridine to the oxazole **135.**[106]



The action of refluxing methanol or methanolic Na_2CO_3 at room temperature on 2-phenyl-3-benzoyl-1-azirine (**138**) afforded 2,5-diphenyloxazole (**132b**).[107] Attack of methoxide at the imino carbon followed by opening of the aziridine ring to give the intermediate **140** and recyclization of **140** to give the oxazole is a likely mechanistic pathway for this conversion.



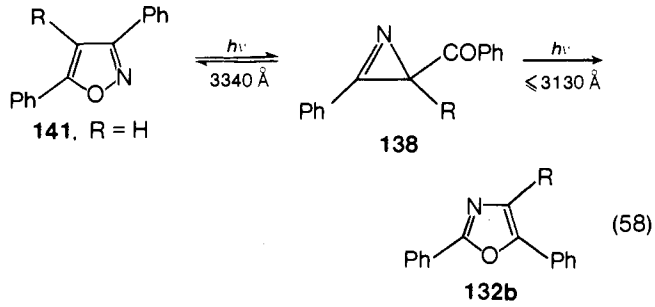
M. Photoinduced Isoxazole–Azirine–Oxazole (IAO) Rearrangement and Related Photochemical Reactions

The photochemically induced rearrangement of five-membered ring heteroaromatic compounds where two of the ring atoms are transposed has been an area of intensive investigation in organic photochemistry. Examples of these types of reactions are the photorearrangements of pyrazoles to imidazoles[108] and of 2-substituted thiophenes to 3-substituted thiophenes.[109]

An extremely intriguing example of this type is the photolysis of 3,5-diphenylisoxazole (**141**) to yield 2,5-diphenyloxazole (**132b**) at wavelengths of less than 3130 Å.[107,110,111]

Ullman and Singh[107,111] and Singh et al.[112a] have carried out a thorough study of the mechanism of the IAO rearrangement.

When 2-phenyl-3-benzoyl-1-azirine (**138**) is irradiated at less than 3130 Å, 2,5-diphenyloxazole (**132b**) was produced in 85% yield. Light of wavelength 3340 Å resulted in a nearly quantitative yield of 3,5-diphenylisoxazole (**141**). These results suggest the mechanistic scheme in eq 58.



An alternative to this proposed mechanism is that **138** rearranges to **141** at any wavelength of light and that **141** yields oxazole **132b** at less than 3130 Å. The azirine **138** would then be only a transitory side product rather than a true intermediate. This alternative was ruled out since it requires that **141** yields **132b** much more efficiently than would **138.** This was not the case since azirine **138** affords oxazole **132b** nearly eight times faster than the isoxazole **141** under identical conditions.[107]

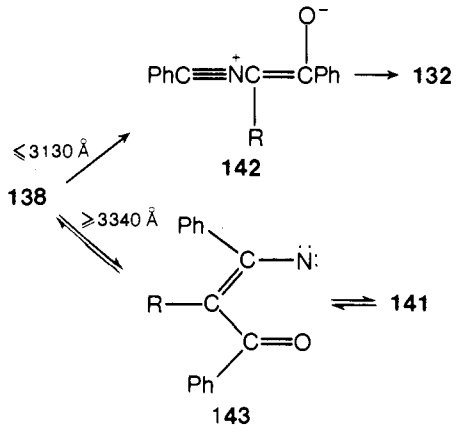
$$\mathbf{138} \rightleftharpoons \mathbf{141} \xrightarrow[3130\ \text{Å}]{h\nu} \mathbf{132b} \qquad (59)$$

The absorption and emission spectra of **132b**, **138**, and **141** were reported.

Sensitization experiments using the triplet sensitizers, acetone, Michler's ketone, and biacetyl were carried out.[107] Using the high-energy sensitizer, acetone (2530 Å), a photoequilibrium was established (95% isoxazole). With Michler's ketone (3130 Å) photolysis of the azirine **138** also led to the isoxazole **141** although the reverse reaction could not be established. Biacetyl as a triplet sensitizer (4350 Å) left the reactants unchanged. No oxazole **132b** was detected in any of these experiments. These observations suggest that triplet states of azirine **138** and isoxazole **141** are intermediates in their photosensitized interconversion and that the oxazole **132b** is derived from the singlet excited states of **138** and **141.**

The data obtained support the contention that the azirine **138** is excited to a high-lying vibrational level of S_1 or to S_2 at less than 3130 Å, and subsequently the C–C bond is cleaved to give the nitrile ylide **142** in its ground state. Ylide **142** cyclizes efficiently to 2,5-diphenyloxazole (**132b**). Intersystem crossing of the excited singlet azirine **138** to the triplet T_1 state followed by C–N bond cleavage produces the triplet nitrene intermediate **143** which cyclizes to afford 3,5-diphenylisoxazole (**141**).[113]

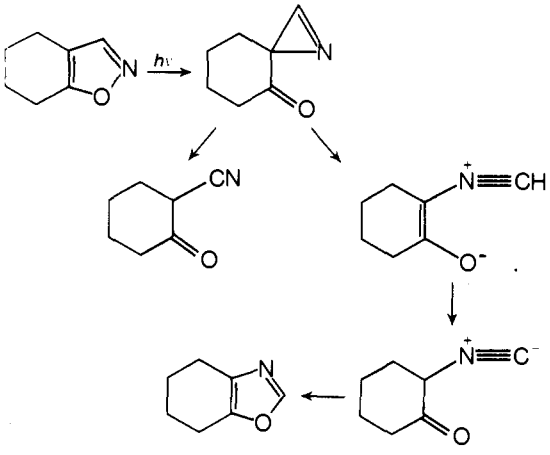
The wavelength dependence of the reaction was attributed to selective n → π* excitation of the carbonyl chromophore of **138** at the longer wavelengths. The electron deficiency thus produced at the carbonyl oxygen induces C–N single bond rupture to yield the isoxazole precursor, the nitrene **143.** Selective n → π* excitation of the ketimine chromophore of



(60a)

138 at the shorter wavelengths leads to electron deficiency at the nitrogen atom which induces the cleavage of the C–C bond in **138** giving the nitrile ylide **142.**[111] These hypotheses were supported by the results[112a] of extended Hückel MO calculations.[114]

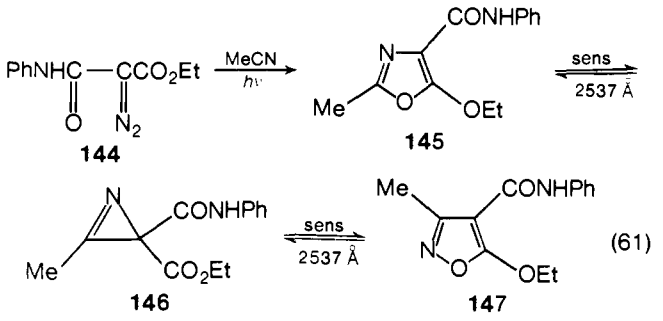
4,5,6,7-Tetrahydrobenzisoxazole affords 4,5,6,7-tetrahydrobenzoxazole upon photolysis along with a small amount of 2-cyanocyclohexanone.[112b] The oxazole arises via 2-isocyanocyclohexanone (section II.B). An azirine was not detected in this experiment; however, this does not rule out its intermediacy. The 2-unsubstituted azirine that may be formed in this conversion would be extremely unstable under the reaction conditions.[112c] An azirine of this type was found to rearrange to both nitrile and isonitrile.[112d] Equation 60b gives a possible mechanistic pathway for the reaction.



(60b)

Irradiation of ethyl diazomalonanilate (**144**) in acetonitrile gave results that were similar to Singh and Ullman's. The oxazole **145** is formed initially, and in the presence of benzophenone **145** rearranges to the isoxazole **147** (eq 61).[37] The azirine **146** has been implicated as the intermediate in the reaction although **146** could not be detected.

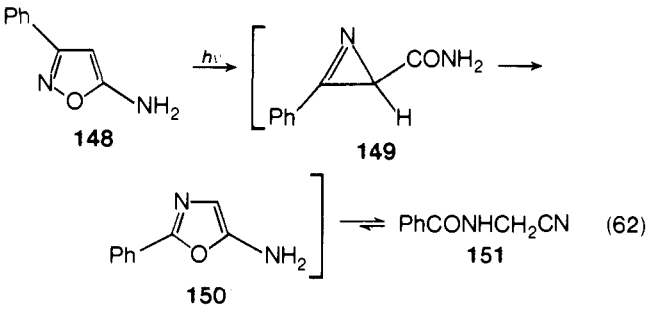
When molecular oxygen, a triplet quencher, is introduced into the reaction vessel the conversion of **145** to the isoxazole **147** is completely inhibited.



(61)

Good and Jones have utilized the IAO rearrangement in a synthesis of oxazole-2-carboxylic esters.[115] Photolysis of ethereal solutions of isoxazole-3-carboxylates gives oxazole-2-carboxylates in low (5–8%) yields.

Irradiation of 3-phenyl-5-aminoisoxazole (**148**) at 2537 Å afforded benzoylaminoacetonitrile (**151**).[116]

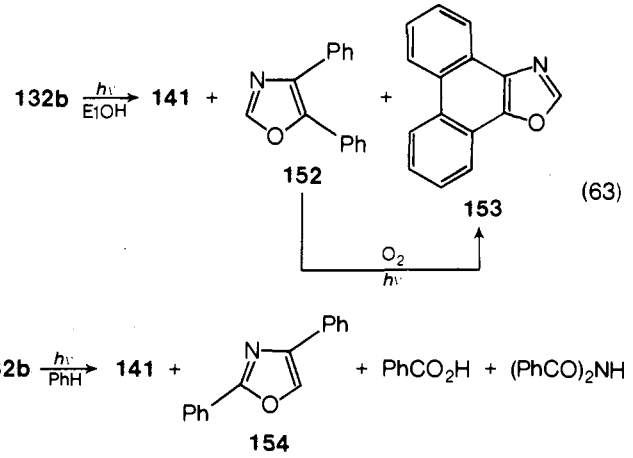


(62)

The observed product **151** is produced from the 5-aminooxazole **150** since, in certain cases, 5-aminooxazoles undergo a ring-chain tautomerization which highly favors the open-chain tautomer.[2] If the azirine **149** is irradiated at 2537 Å, **151** can be isolated, lending support to the intermediacy of **149** in this photochemical transformation. Similarly irradiation of 2-phenyl-3-carboethoxy-1-azirine yielded 2-phenyl-5-ethoxyoxazole (48%).[117]

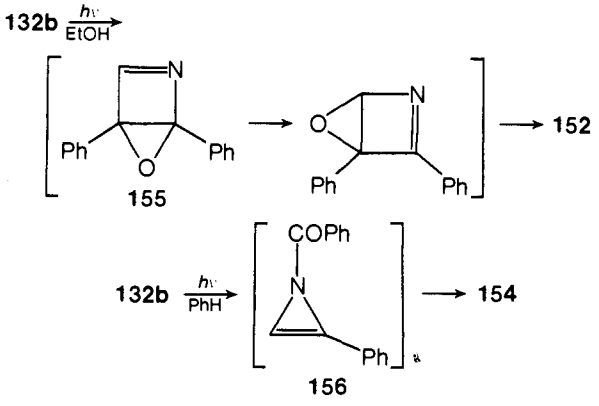
Wamhoff studied the photoinduced rearrangement of 4,5-dihydrofurans to cyclopropanes and ethyl 3-phenyl-5-aminoisoxazole-4-carboxylate to ethyl 2-phenyl-5-aminooxazole-4-carboxylate.[118] In contrast to the other photorearrangements discussed in this section, this rearrangement proceeded in the presence of triphenylene as a sensitizer. No explanation of this anomalous result was offered, but the production of the oxazole in the sensitized system could be due to the low rate of intersystem crossing of triphenylene. If the rate of singlet energy transfer from sensitizer to acceptor (azirine) ground state is on the order of the rate of sensitizer intersystem crossing, then (despite the high efficiency of the latter process) azirine singlet excited states will be produced which would lead to the observed oxazole product.

The photochemical rearrangement of oxazoles to isoxazoles was first observed by Kojima and Maeda in the photolysis of 2,5-diphenyloxazole (**132b**) in ethanol solution.[119] The products of the reaction are 3,5-diphenylisoxazole (**141**, 20%), 4,5-diphenyloxazole (**152**, 20%), phenanthr[9,10]oxazole (**153**, 1.5%), and a trace of benzoic acid. In benzene, however, the photolysis of **132b** gave **141** (7%), benzoic acid (2%), dibenzamide (0.4%), and 2,4-diphenyloxazole (**154**,



(63)

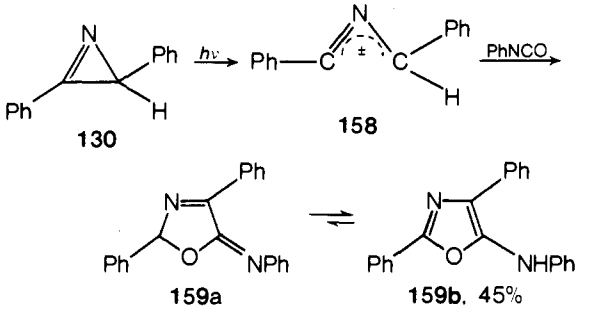
4.5%). Although the azirine **138** is a likely intermediate in the rearrangement of **132b** to **141**, it could not be isolated. 4,5-Diphenyloxazole (**152**) could have arisen from a valence tautomerism of the bicyclic intermediate **155**; 2,4-diphenyloxazole (**154**) is postulated to have arisen from the *N*-benzoyl-2-azirine **156**.



A similar series of products was obtained from photolysis of 2-phenyloxazole.[120] In this instance, however, it was possible to isolate the intermediate 2-phenyl-1-azirine-3-carboxaldehyde.

The irradiation of 2-methyl-4,5-diphenyloxazole in the presence of iodine and air at 3000 Å did not yield the 1-azirine nor any of photoproducts derived from it, but instead a 55% yield of 2-methylphenanthr[9,10]oxazole (**157**) was formed.[121]

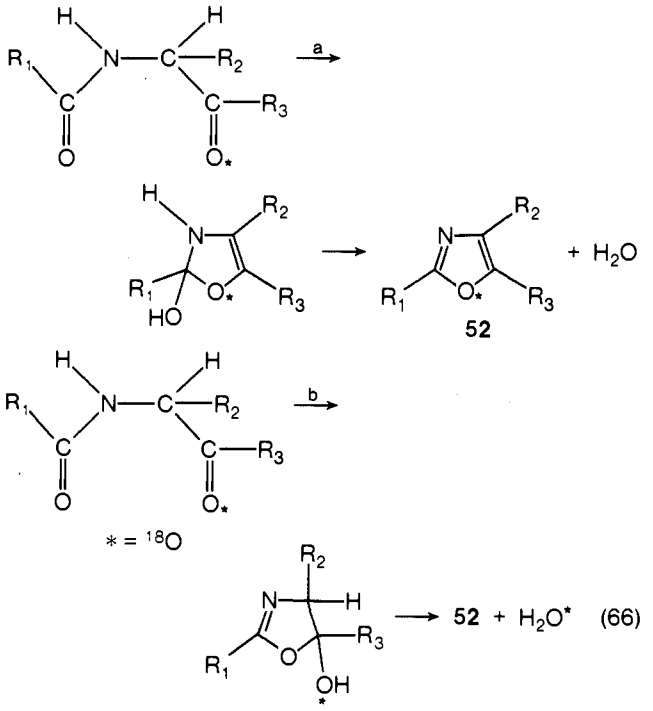
When 1-azirines which are not substituted in the 3 position by a carbonyl functionality are subjected to the conditions of these photolyses reactions, C–C bond cleavage occurs to give a nitrile ylide intermediate.[122] These nitrile ylides can undergo 1,3-dipolar additions to a variety of dipolarophiles.[41] Schmid et al. have studied the addition of the nitrile ylide **158** derived from the photolysis of 2,3-diphenyl-1-azirine (**130**) to cumulated double bonds and, in particular, to isocyanates.[123] The product of this reaction is 2,4-diphenyl-5-*N*-phenylaminooxazole (**159b**). The initial addition product, the 5-iminooxazoline **159a**, tautomerizes to **159b**.



N. Robinson–Gabriel Oxazole Synthesis. Mechanism and New Cyclodehydrating Reagents

One of the oldest and most useful syntheses of oxazoles is the reaction of α-acylamino carbonyl compounds with a cyclodehydrating agent (e.g., PCl_5, H_2SO_4, $POCl_3$, $SOCl_2$, etc.) or the Robinson–Gabriel synthesis.[124,125] Despite the utility of the synthesis, mechanistic details remained scarce until the recent work of Wasserman and Vinick.[126] These workers utilized ^{18}O-labeling techniques coupled with high resolution mass spectroscopy to differentiate between two possible mechanistic pathways for the reaction (eq 66).

When the ketone carbonyl oxygen is labeled with ^{18}O and this labeled ketone treated with concentrated H_2SO_4, essentially none of the ^{18}O is found in the oxazole ring. Conversely,

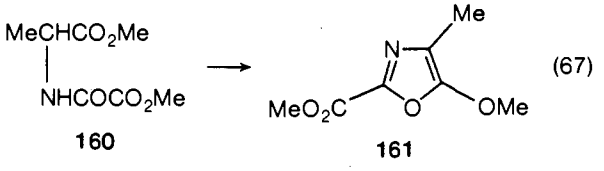


when the amide carbonyl oxygen is labeled, all of the label is found in the ring in accord with path b above.

The Robinson–Gabriel synthesis affords low yields of oxazoles in many cases when the cyclodehydrating agents are PCl_5, H_2SO_4, $POCl_3$, or $SOCl_2$. However, when polyphosphoric acid is used, the yields of oxazoles can be increased to 50–60%.[127–129]

Daub et al. found that *N*-aryl-α-amido ketones could be cyclized efficiently to oxazoles in yields of up to 96% using anhydrous HF as the cyclization agent.[130]

In another study it was necessary to prepare oxazole-2-carboxylates.[131] The reaction of a number of cyclodehydrating agents with methyl *N*-methoxalylalanate **160** to give methyl 4-methyl-5-methoxyoxazole-2-carboxylate (**161**) under a variety of conditions was investigated. The reagent of choice for this cyclization was phosgene in triethylamine, affording **161** in 80% yield at room temperature for 10 min. The only comparable result was obtained when the dehydrating agent was ethyl chloroformate, giving the oxazole **161** in 25% yield at 50° after 1 hr.



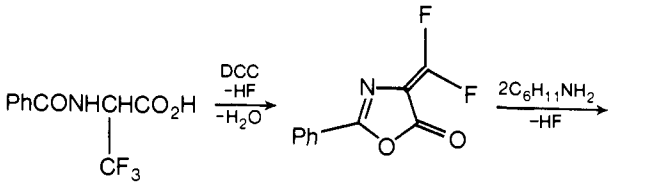
In their studies on fluorinated amino acids, Weygand et al. found that 3,3,3-trifluoro-*N*-benzoylalanine (**162**) can be converted to the 5-amino-4-oxazolecarboxamide **163** in 86% yield using dicyclohexylcarbodiimide and 2 equiv of cyclohexylamine (eq 68a).[132a]

Acetic and trifluoroacetic anhydrides have been utilized as cyclodehydrating agents for the conversion of secondary amides to oxazoles (eq 68b).[132b]

The ir and nmr spectra and reactions of the 5-aminooxazoles prepared in this manner were studied.

O. 2-Aminooxazoles

2-Aminooxazoles (**165**) can be readily prepared by the reaction of α-halo ketones with urea in DMF at 105°.[133] N-Monosubstituted and N,N-disubstituted ureas give N-substituted aminooxazoles.



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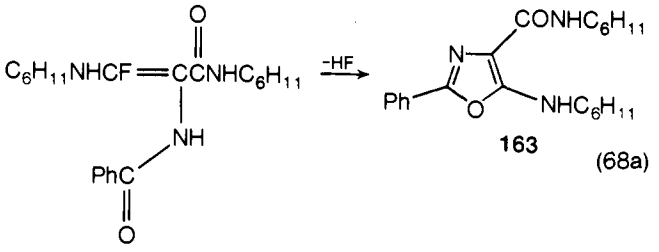
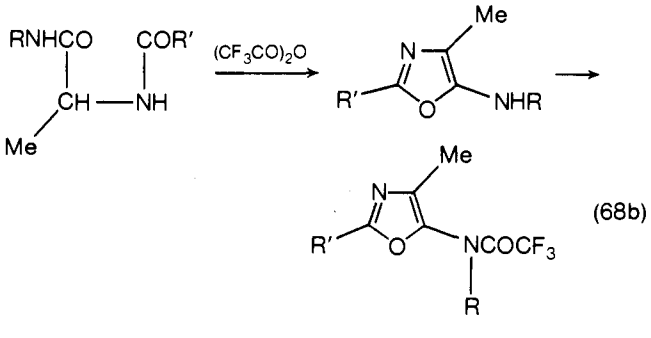
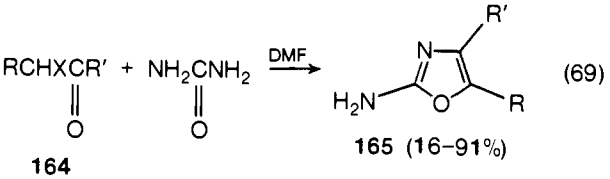


(68a)



(68b)

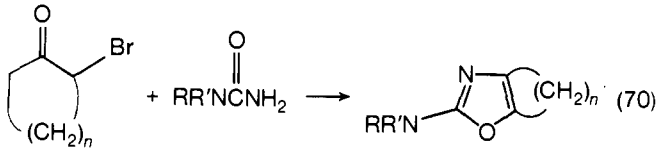


(69)

164

The reaction of substituted ureas with bromoacetaldehyde to afford 2-(*N*-substituted amino)oxazoles has been investigated. The ir and nmr spectra of several of these compounds prepared in this manner were reported.[134]

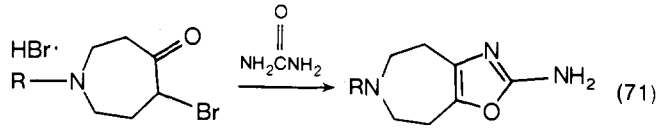
In a similar manner, 4,5-polymethylene-2-aminooxazoles (**167**) were prepared by the reaction of urea with α-bromocycloalkanones **166**.[135]



(70)

166 167, n = 4, 5.

The oxazolotetrahydroazepine system **169** has been synthesized from the α-bromoazepinone **168** and urea.[136] These compounds are useful as sedatives, antitussives, and hypoglycemic agents.

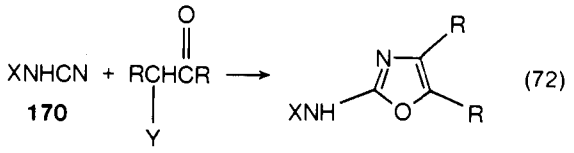


(71)

168 169 (14–26%)

R = $(Me)_2CHCH_2$, allyl, $PhCH_2$, *p*-$MePhCH_2$

A somewhat more general method for the preparation N-substituted 2-aminooxazoles is the reaction of substituted cyanamides or their salts (**170**) with α-hydroxy[137–140] or α-halo ketones (**164**).[141,142] The 4- and 5-substituents on the oxazole ring can be alkyl, aryl, or hydrogen; the N-substituents are CN, NH_2—C(=NH)—, RNH—C(=NH)—, R—C(=NH)—, and *p*-aminobenzenesulfonyl groups.

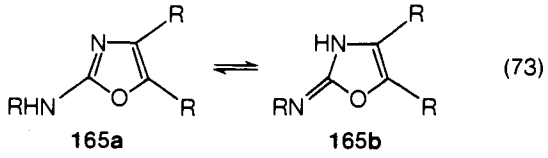


(72)

170 164

Y = halogen, OH

Ir, nmr, and uv data are reported for these oxazoles.[137,143] These data, as well as the spectral and pK_a data of other workers,[134,135] show the existence of two tautomeric forms of 2-aminooxazoles **165a** and **165b** although **165a** predominates and in many cases no **165b** can be detected spectroscopically.[143]



(73)

165a 165b

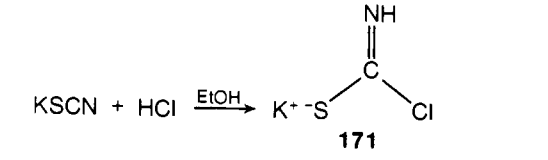
2-Aminooxazoles (**165**) can also be synthesized by the reaction of 2-chlorooxazoles with amines. This reaction will be discussed further in section IV.A.

P. Mercapto- and Alkylmercaptooxazoles

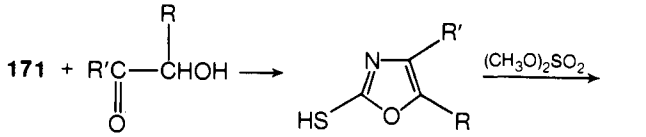
Only a few syntheses of oxazoles containing sulfur substituents are known. This fact is surprising in view of their potential utility in biological systems.

2-Mercapto-5-aryloxazoles can be prepared by the reaction of α-aminoacetophenones with carbon disulfide.[144] This method has not been extended to include 5-alkyl derivatives.

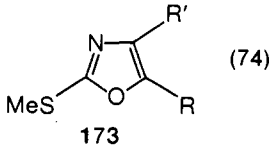
The reaction of the salt **171** with α-hydroxyalkyl aryl ketones gives 2-mercapto-4-aryloxazoles (**172**) in high yields.[145] The oxazoles **172** thus formed can be methylated with dimethyl sulfate in 10% aqueous NaOH to give 2-methylthiooxazoles (**173**).



171



R = H, aryl
R′ = Ph

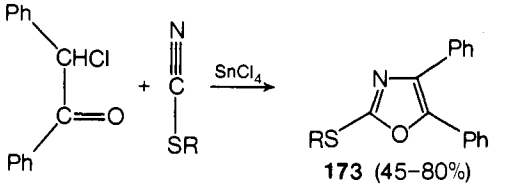


(74)

173

When thiocyanates are allowed to react with desyl chloride and $SnCl_4$, 2-alkylmercapto-4,5-diphenyloxazoles (**173**) are isolated (cf. section II.C).[146] Benzyl and *p*-nitrophenyl thiocyanates do not yield the expected oxazoles.

The intermediate nitrilium salts produced in this reaction will also react with 1-aryl-2-chloroethanes and α-chloro ketones

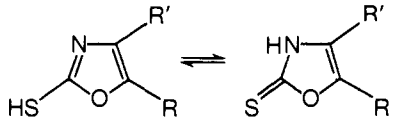


(75)

173 (45–80%)
R = Me, Et, Pr, Ph

to give 1,4-dihydroquinazolines and 4*H*-1,3-oxazines, respectively.[146]

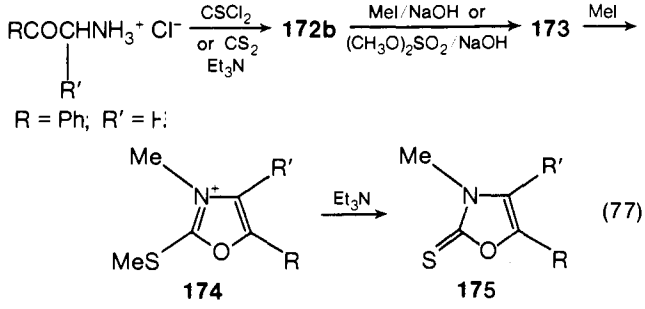
In order to study the equilibrium between 2-mercaptooxazoles (**172a**) and their thione tautomers **172b**, Kjellin and Sandstrom prepared a series of these compounds and their *N*- and *S*-methyl derivatives.[147] The synthesis of 5-phenyl-



(76)

172a **172b**

Δ^4-oxazoline-2-thione (**172b**, R = Ph; R' = H) by the reaction of α-aminoacetophenone with thiophosgene or carbon disulfide in the presence of triethylamine was effected. S-Methylation was accomplished by treating the anion of the free acid with methyl iodide or dimethyl sulfate. The *N*-methyl compound **175** was prepared by the reaction of the 2-methylthiooxazole **173** with methyl iodide to give the oxazolium salt **174** followed by heating **174** with triethylamine.



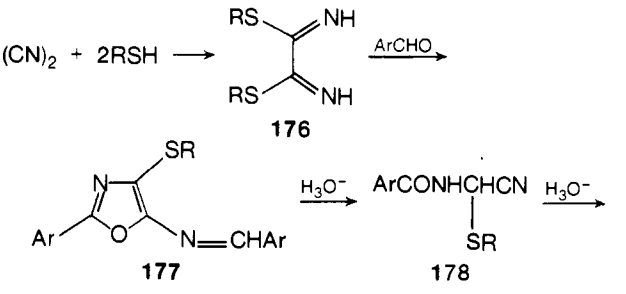
(77)

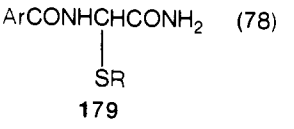
174 **175**

The *N*-methyloxazoline-2-thiones (**175**) and the *S*-methylthiooxazoles (**173**) were differentiated on the basis of the chemical shifts of the methyl groups in the nmr spectra of these compounds, the *S*-methyl of **173** being shielded 0.8–0.9 ppm relative to the *N*-methyl group of **175**.[148]

The position of the equilibrium, thione $\rightleftharpoons$ thiol, has been determined for a series of oxazoline-, thiazoline-, and imidazoline-2-thiones by measuring the acidity constants of the tautomers and their *N*- and *S*-methyl derivatives.[149] The ratio of thione:thiol is 10^5–10^7 for the oxazoline- and thiazolinethiones and somewhat higher for the imidazolinethiones. This high thione:thiol ratio has been rationalized in terms of the difference in π-electronic energy of the two forms as calculated by the Hückel MO method and also by the differences in solvation energy of the two tautomers.

In their studies of heterocyclic ring closure reactions, Ketcham et al. observed the formation of 2-aryl-5-benzylidineamino-4-aryl- or -alkylmercaptooxazoles (**177**) from the reaction of aromatic aldehydes and *S,S'*-diaryl- or dialkyl dithiooxaldiimidates (**176**).[150,151] Upon acidic hydrolysis the oxazole ring is cleaved yielding the α-mercaptonitrile **178** which hydrolyzes further to give the amide **179.** When *p*-nitrobenzaldehyde was allowed to react with **176** (R = CH_3, $-CH_2Ph$), the product formed was not the benzylideneaminooxazole but the 5-aminooxazole **180**. Compounds **177–179** were screened for antitumor activity.[150] A novel reaction of 4-benzamido-1,2-dithiol-3-thione (**181**) with KOH and methyl iodide affords methyl 2-phenyl-5-methylthiooxazole-4-carbodithioate (**182**).[152]





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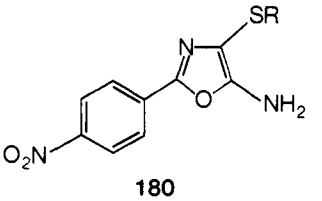
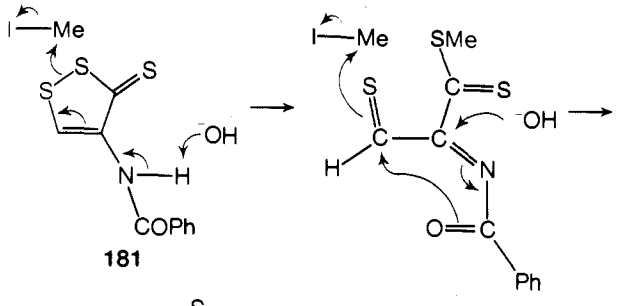
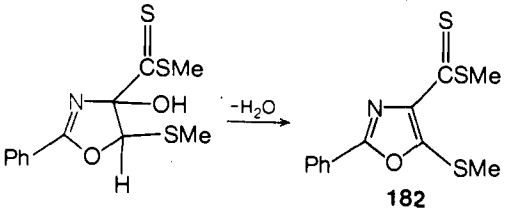


180
R = Me, $PhCH_2$

A synthesis of 2-alkoxy- and 2-alkylmercaptooxazole acetic esters from the reaction of 2-chlorooxazoles with hydroxy- and thiolacetic esters has recently been reported (eq 80).[153] These compounds are analgesics, antipyretics, and inflammation inhibitors.





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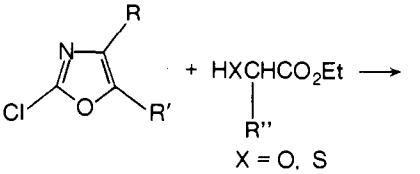
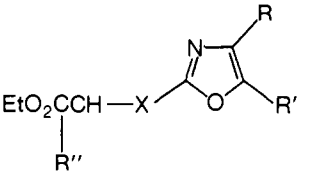


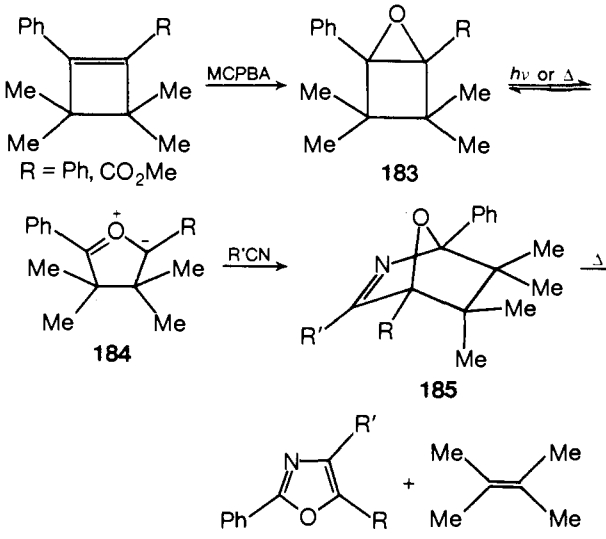


(80)

Q. Miscellaneous

An intriguing and synthetically useful reaction for the synthesis of certain substituted oxazoles is the 1,3-dipolar addition of the carbonyl ylide with the structure **184** generated by

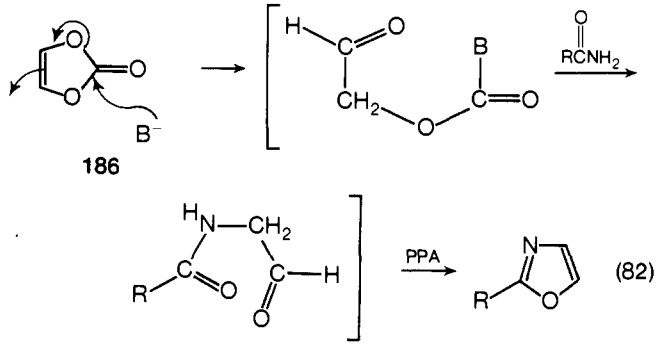
the photolysis of the oxirane **183** to a nitrile followed by a retro Diels–Alder reaction of the adduct **185** to give oxazoles in good yield.[154,155]



(81)

When the oxirane **183** possesses a carbomethoxy substituent (R = CO_2Me), the reaction is regioselective, only the methyl oxazole-5-carboxylate being formed. This observation is not surprising considering the known regioselectivity of 1,3-dipolar cycloadditions in general.[33,41]

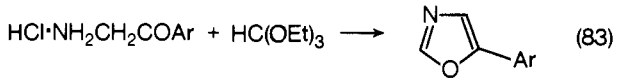
Oxazoles that are substituted at only the 2 position can be prepared in poor to moderate yields by the reaction of primary amides with vinylene carbonate **186** in polyphosphoric acid at 165°.[156] The mechanism shown in eq 82 was proposed for the reaction. Although this reaction does not seem to be a general method for the synthesis of 2-substituted oxazoles, it does offer the advantage of simplicity as compared with the more general synthesis reported by Cornforth and Cornforth which involves a five-step reaction sequence.[2,4]



(82)

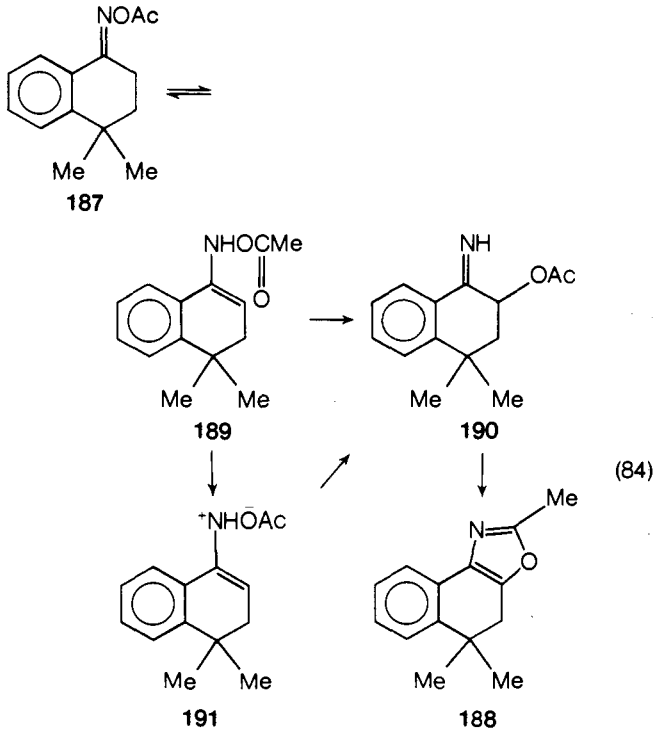
R = Ph, 34%
= *m*-NO_2Ph, 10%
= o-ClPh, 6%
= 2-pyridyl, 2%
= $PhOCH_2$, $PhCH_2$, *p*-Tol; 0%

A new method for the preparation of 5-aryloxazoles from the reaction of aminomethyl aryl ketones with triethyl orthoformate has been developed (eq 83).[157]



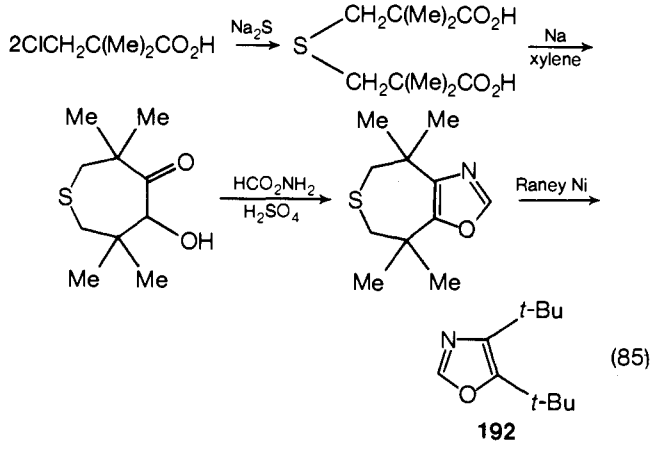
(83)

In their study of the Wolff–Semmler aromatization reaction of α-tetralone oximes **187** with Beckmann's mixture (HCl/HOAc/Ac_2O), Conley and Balling observed the formation of 3′,4′-dihydronaphth[1′,2′:4,5]oxazole **188** among other products.[158] The yields of **188** depend on the substituents present on the tetralone oxime. The proposed mechanism for the formation of the oxazole **188** involves the cyclization of the iminoacetate **190** which is derived from the *N*-acetoxy enamine **189.**



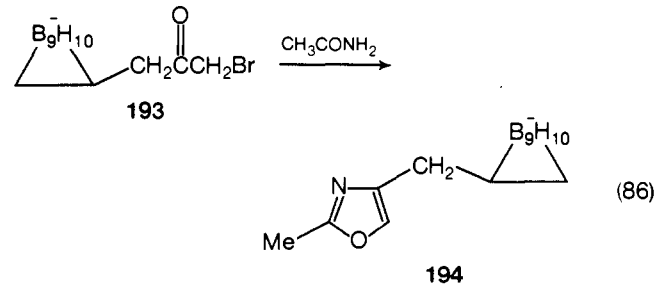
(84)

Recently a number of unusual oxazoles have been prepared by the reaction of amides with α-hydroxy and α-halo ketones. DeGroot and Wynberg have prepared various sterically crowded heteroaromatic compounds. Among these was 4,5-di-*tert*-butyloxazole (**192**) which was formed by the sequence in eq 85.[159]



(85)

The 4-carboranylmethyloxazole **194** was synthesized by the reaction of 1-carboranyl-3-bromo-2-propanone (**193**) with acetamide.[160]

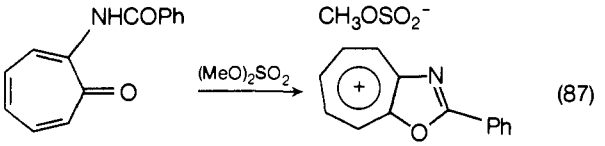


(86)

TABLE I. Charge Distributions in Oxazole (1)

	Ab initio			EHMO			MINDO/3
	q_σ	q_π	q_{net}	q_σ	q_π	q_{net}	q_{net}
O	−0.63	0.32	−0.31	−0.91	0.23	−0.68	−0.348
C_2	0.14	−0.06	0.08	0.57	0.33	0.90	0.352
N	−0.17	−0.08	−0.25	−0.49	−0.50	−0.99	−0.194
C_4	−0.09	−0.086	−0.176	0.14	−0.03	0.11	−0.053
C_5	0.04	−0.088	−0.048	0.33	−0.04	0.29	0.190

The synthesis of the novel oxazolotropylium salt **196** has been accomplished by treating 2-benzoylaminotropone (**195**) with dimethyl sulfate at 120°.[161]



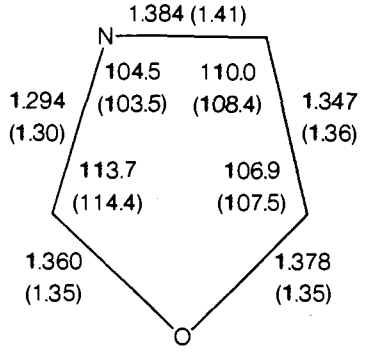
195 196 (87)

III. Physical Properties, Spectra, and Molecular Orbital Calculations

A. Geometry

The crystal structures of some 2-chloromethyl-5-(*p*-nitrophenyl)oxazoles have been obtained.[162-165]

The bond lengths and bond angles of 2,2'-*p*-phenylenebis(5-phenyloxazole) (**197**) were determined by an X-ray diffraction study.[166] These values for the oxazole portion of the molecule are given below along with the values (in parentheses) calculated by the MINDO/3[57] molecular orbital method.[167] As is evident from the data, the geometries calculated by MINDO/3 deviate by less than 0.03 Å and 2° from the experimental geometry. Reasonable agreement also exists between the experimental geometries and those calculated by ab initio[168] and other MO methods.[169]



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X-Ray techniques were also used to determine the structure of 10-bromo-2,3,5,6,7,11b-hexahydro-2-methyl-11b-phenylbenzo[6,7][1,4]diazepino[5,4-*b*]oxazol-6-one.[170]

B. Molecular Orbital Calculations of Charge Distribution, Ionization Potential, and Heat of Formation

The semiempirical SCF molecular orbital method has been utilized by several groups for the calculations of the π-electronic properties of oxazole and other five-membered ring heteroaromatic compounds and their benzo analogs. Orloff and Fitts first performed SCF-MO calculations on oxazole, and the results of these calculations agree qualitatively with experimentally observed properties.[171] The calculated negative π-electronic charge densities are in the order $q_5 > q_4 > q_2$ for the carbon atoms of oxazole. The same order was found in the SCF-MO calculations performed by other workers.[172,173] The results of the ab initio calculations of Berthier et al.[174] and of the improved LCAO method of Roche et al.[175] are in the order $q_4 > q_5 > q_2$ for the net negative charge densities. Table I lists the q_π, q_σ, and q_{net} for the positions in oxazole as calculated by the more sophisticated all-valence electron ab initio, extended Hückel,[176] and MINDO/3 MO methods.

The extended Hückel method, like the simple HMO treatment, tends to exaggerate the charge densities of nonalternate systems and systems containing heteroatoms. This is apparent in the higher magnitudes of the q_{net} calculated by the EHMO as opposed to those calculated by the other methods.[177]

In all of these calculations, C_2 is predicted to possess the highest positive charge density of the carbons in oxazole. This result is consistent with the fact that the 2 position of oxazoles is usually the most susceptible to attack by nucleophiles. This is true for both the neutral and protonated molecules (see section IV.B).

The rather limited data concerning the reaction of oxazoles with electrophiles suggest that the relative order of reactivity is $C_5 \geq C_4 \gg C_2$ (section IV.D). It is difficult to predict the order of reactivity of C_5 vs. C_4 toward electrophilic reagents on the basis of charge density considerations; nevertheless, most of the MO methods predict q_π to be slightly more negative at the 5 than at the 4 position, and consequently the 5 position should be slightly more reactive than the 4 position for the neutral oxazole molecule.

The calculated free valence indexes predict that the 5 position is more reactive toward radicals (and other neutral nonpolar reagents) than either the 2 or the 4 positions; however, there are no experimental data available concerning reactions of this type.[171]

A notable result of the all-valence electron calculations[167,168,176] is that the σ-bond framework of oxazole and the other azoles is polarized to a great extent. The formal σ-charges on the atoms of these heterocycles follow the electronegativity order O > N > C. On the other hand, the π charges do not reflect this electronegativity order (q_π on oxygen is less than q_π on nitrogen). The π-polarization may in fact be opposed to the σ-polarization in these systems. It is evident from the results given in Table I that the total charge distributions are dominated by the contribution of the σ charges.[168,176]

The order of increasing net negative charge density as calculated by the all-valence electron calculations is $q_4 > q_5 > q_2$. This order is reflected in the chemical shifts of the protons at these positions, the proton at C_4 being at higher fields (τ 2.91) than the proton at C_5 (τ 2.31) which is at higher fields than the proton at C_2 (τ 2.05).[177] This observation lends credence to the accuracy of the relative order of the calculated net charge densities.

MINDO/3 calculations give a value of 8.03 eV for the first ionization potential of oxazole, whereas the π SCF-MO method gives a much higher estimate.[172] The experimental ionization potentials are not available at this time.

Heats of formation of many systems have been estimated quite reliably by the MINDO/3 MO method.[178] The heat of formation of oxazole as calculated by MINDO/3 is −7.63 kcal/mol.[167] Although no thermochemical data concerning oxazole and its derivatives are available at the present time, this calculated value seems to be a reasonable estimate in light of the experimental ΔH_f of furan (−14.9 kcal/mol).[179]

The EHMO method was used in calculating the energies of the conformations of certain oxazole dimers.[180] A perpendicular disposition of the two oxazole moieties is predicted to be the most stable conformation.

C. Nuclear Magnetic Resonance Spectra

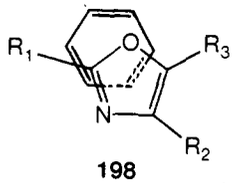
Brown and Ghosh have published proton chemical shift data and proton–proton coupling constants for a variety of substituted oxazoles and for the parent oxazole (**1**).[177] For oxazole (**1**) the proton chemical shift values (τ) are ν_2 = 2.05, ν_4 = 2.91, ν_5 = 2.31 (CCl_4 solution). Methyl substituents shield the remaining ring protons by 0.2–0.8 ppm relative to **1**. The chemical shifts of the methyl protons are (τ): 2-methyl, 7.7–7.8; 4-methyl, 7.8–8.1; 5-methyl, 7.75–7.85. A proton at C_2 is slightly deshielded by phenyl substitution at C_4 or C_5, whereas a C_4 phenyl deshields a C_5 proton and a C_5 phenyl deshields a C_4 proton. Electron-withdrawing groups such as CO_2R, CN, $COCH_3$, $CONH_2$, CO_2H, etc., deshield the ring protons and to a lesser degree the protons on methyl substituents. Deuteration of the oxazole nitrogen atom with DCl/D_2O produced large downfield shifts of the ring protons. This effect will be discussed further in section V.A.

The H–H coupling constants, J, for the oxazoles were: $J_{4,5}$ = 0.8–0.9 Hz, $J_{2,5}$ = 0.8–1.0 Hz, $J_{5,Me-4} = J_{4,Me-5}$ = 1.0–1.4 Hz. The value of $J_{4,5}$ increased from 0.8 to 1.2 Hz upon deuteration of 2-methyloxazole; however, $J_{2,5}$ remained unchanged upon deuteration of 4-methyloxazole.

The chemical shifts of the oxazole ring protons and the ability of its π system to transmit long-range coupling have been taken as evidence which suggests that oxazole is aromatic.[181]

Changing the solvent from CCl_4 to D_2O produced a downfield shift of H_2 and H_4 (0.3 ppm) and H_5 (0.2 ppm).[177]

The effect of changing the solvent from CCl_4 to benzene on the proton nmr of various alkyl- and aryloxazoles has been investigated.[182] The Δ values [$\delta(CCl_4) - \delta(C_6H_6)$] for methyl groups at the 2 and the 5 positions of the ring range from +0.22 to 0.37 ppm with the 5-methyl substituent exhibiting the larger upfield shift. A methyl group at the 4 position is nearly unaffected by the change in solvents. The formation of a 1:1 solute–solvent complex having the structure **198** was postulated. The Δ values for oxazoles bearing a bulky substit-



198

uent at the 2 or 5 position suggest that the benzene ring in the complex **198** is moved further across R_1 when R_3 is bulky and across R_3 when R_1 is bulky. The Δ values for the methyl group of 2-n-alkyl-4,5-diphenyloxazoles decreases from 0.44 for 2-methyl to 0.16 for 2-n-pentyloxazole, illustrating the effect of distance on the benzene-induced shift.

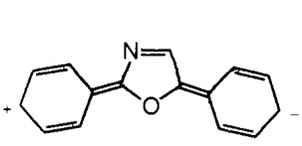
One of the first compilations of ^{14}N chemical shifts included that of 2,5-diphenyloxazole (**132b**) at 125 ppm relative to nitromethane.[183] This compilation included the ^{14}N shifts of a wide variety of compounds. Unfortunately, the data did not include most of the azoles and benzazoles which could be compared to the oxazole. About 10 years later, Witanowski et al. obtained the ^{14}N chemical shifts of a number of pyrroles, azoles, di-, tri-, and tetrazoles and their benzo analogs.[184] The value found for oxazole (**1**) was 125 ppm relative to nitromethane, indicating that phenyl substituents at the 2 or 5 position have little effect on the ^{14}N chemical shift. Isoxazole is deshielded relative to oxazole by 119 ppm owing to the proximity of the electronegative oxygen atom to the nitrogen in the former. Benzoxazole is shielded by 15 ppm relative to oxazole. This upfield shift is presumably due to the shielding of the nitrogen atom by the ring-current of the fused benzene ring. A fairly linear correlation of ^{14}N chemical shifts with π charge densities as calculated by an SCF–MO procedure was noted.

D. Ultraviolet Spectra

Uv spectra of a series of oxazole derivatives are given in Table II. The spectra of the oxazoles are quite similar to the corresponding thiazoles. This resemblance is not surprising in view of the similarity of the π systems of these compounds.

In general, the uv spectra of monophenyloxazoles exhibit one major band of strong intensity at 245–270 nm. Alkyl substitution on the oxazole ring has little effect on the position or intensity of this band.[185] The spectra of 2,5-diaryloxazoles consists of two or three bands depending upon the nature of the aryl substituents; the low-energy wavelength maximum is at 315–350 nm ($\epsilon_{max} > 10^3$), and that of the higher energy bands is at 260–299 nm ($\epsilon_{max} < 10^3$) and 220–240 nm ($\epsilon_{max} > 10^3$).[186] Alkyl substitution on the phenyl moieties of 2,5-diphenyloxazoles causes only small changes in the spectra.[186,192]

The uv spectrum of 2,5-diphenyloxazole (**132b**) shows a high intensity absorption at >300 nm, whereas the spectrum of 2,4-diphenyloxazole (**154**) exhibits no such absorption above 276 nm. The low-energy peak in the spectrum of the 2,5-diphenyl isomer (**132b**) is attributed to extended conjugation via the resonance structure **199.** The spectrum of 2,4-diphenyloxazole is nearly a superimposition of the spectra of the 2- and 4-phenyloxazoles. This suggests that the resonance structure **200** contributes little to the total structure of the oxazole and that oxazoles show a great deal of diene character.[177]



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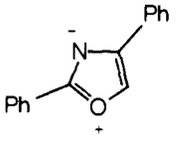


200

Several π SCF–MO treatments were utilized in the calculation of spectral transitions for oxazole and its excited states,[171,172,175,193] one of which included configuration interaction.[173] The experimental value for the first observed $\pi \rightarrow \pi^*$ transition for oxazole in methanolic solution is 6.0 eV.[185] The calculated transition energies are in excellent agreement with this experimental value.

E. Dipole Moments and Nuclear Quadrupole Coupling Constants[194]

Mackrodt et al. have determined the dipole moment and NQR coupling constants due to ^{14}N for oxazole and isoxazole from their microwave spectra.[195] These quantities have also been calculated by SCF–PPP,[196] CNDO/2,[197] VESCF[198,199] (dipole moments only), and ab initio[168,200,201] molecular orbital methods. The all-valence electron calculations (CNDO/2 and ab initio) give better results in most cases than the π-electron (SCF–PPP and VESCF) calculations. The experimentally determined and theoretical values of the dipole moment (μ) and NQR coupling constants for oxazole are listed in Table III.

The dipole moments of substituted oxazoles have also been measured.[202] For example, $\mu_{gs} \doteq 3.6$ D and $\mu_{es} = 8.0$ D for 2,5-di(4-biphenylyl)oxazole.

F. Infrared Spectra

The ir spectrum of the parent oxazole (**1**) was first recorded by Bredereck and Bangert.[7] Since then, several groups have recorded the ir and Raman spectra of oxazole and alk-

TABLE II. Uv Spectra of Oxazoles

Compound	Solvent	λ_{max} (log ϵ)	Ref
Parent	MeOH	205 (3.59)	185
4-Me-5-Ph	MeOH	265 (4.23)	185
2,4-$(Me)_2$-5-Ph	MeOH	264 (4.29)	185
4-Ph	MeOH	245 (4.25)	185
5-Me-4-Ph	MeOH	247 (4.18)	185
5-Et-4-Ph	MeOH	247 (4.14)	185
2,5-$(Me)_2$-4-Ph	MeOH	247 (4.06)	185
2-Me-5-Et-4-Ph	MeOH	248 (4.08)	185
4-Me-5-benzyl	MeOH	250–270 (2.6)	185
2,4-$(Me)_2$-5-benzyl	MeOH	250–270 (2.1–2.5)	185
2,5-$(Ph)_2$	C_6H_{12}	224 (2.05), 302 (2.81)	186
2-(1-Np[a])-5-Ph	C_6H_{12}	235 (3.01), 281 (1.20), 330 (2.31)	186
2-Ph-5-(1-Np)	C_6H_{12}	229 (4.12), 279 (1.44), 323 (2.33)	186
2-Ph-5-(4-An[b])	C_6H_{12}	237 (4.36), 286 (1.44), 337 (2.83)	186
2-Ph-5-(3-Phen[c])	C_6H_{12}	252 (4.08), 280 (2.53), 339 (4.05)	186
2-Ph-5-(4-Biph[d])	C_6H_{12}	220 (3.21), 259 (1.36), 322 (4.15)	186
2-Ph-5-(2-Fl[e])	C_6H_{12}	221 (2.86), 273 (0.94), 341 (5.32)	186
2,5-$(1\text{-Np})_2$	C_6H_{12}	234 (5.31), 339 (2.30)	186
2-(1-Np)-5-(4-An)	C_6H_{12}	240 (5.64), 350 (2.88)	186
2-(1-Np)-5-(4-Biph)	C_6H_{12}	239 (3.60), 293 (1.90), 339 (3.42)	186
2-(1-Np)-5-(2-Fl)	C_6H_{12}	237 (3.46), 299 (1.87), 346 (3.96)	186
5-Ph-2-(4-Biph)	C_6H_{12}	220 (2.00), 260 (1.05), 320 (3.84)	186
2-(4-Biph)-5-(1-Np)	C_6H_{12}	254 (1.53), 290 (2.44), 337 (3.44)	186
2-(4-Biph)-5-(4-An)	C_6H_{12}	240 (3.20), 296 (1.89), 342 (3.22)	186
2-(4-Biph)-5-(3-Phen)	C_6H_{12}	252 (2.86), 293 (2.37), 338 (3.68)	186
2,5-$(4\text{-Biph})_2$	C_6H_{12}	236 (1.60), 273 (1.34), 334 (4.20)	186
2-(4-Biph)-5-(2-Fl)	C_6H_{12}	230 (1.30), 282 (1.35), 350 (4.33)	186
2-(*N*,*N*-$(Ph)_2NH_2$-4,5-$(Ph)_2$	MeOH	225 (4.35), 270 (4.16), 318 (4.18)	187
2-(*N*-$PhNH_2$)-4,5-$(Ph)_2$	MeOH	225 (4.23), 268 (4.35), 320 (4.24)	187
2-Methylthio-4,5-$(Me)_2$	H_2O	251 (3.83)	149
2-Methylthio-5-Ph	H_2O	248 (3.85), 289 (4.33)	149
2-Benzyl-5-Me-4-COOH	MeOH	216 (4.33)	188
2-Ph-5-Me-4-COOH	MeOH	270 (4.34)	188
2,5-$(Ph)_2$-4-COOH	MeOH	303 (4.66)	188
2-Styryl-5-Me-4-COOH	MeOH	226 (4.21), 309 (4.65)	188
2,5-$(Ph)_2$-*N*-Me	H_2O	241 (4.11), 298 (4.30)	189
2-(1-Np)-5-Ph-*N*-Me	H_2O	270 (4.07), 321 (4.11)	189
2-(2-Np)-5-Ph-*N*-Me	H_2O	252 (3.87), 312 (4.27)	189
2-(2-Furyl)-5-Ph-*N*-Me	H_2O	253 (4.30), 326 (4.07)	189
2-(2-Thienyl)-5-Ph-*N*-Me	H_2O	250 (4.27), 331 (3.95)	189
2-Ph-4,5-$(Me)_2$ *N*-oxide	Dioxane–EtOH	260 (4.06), 303 (4.47), 316 (4.36)	190
2-Ph-4-Ac-5-Me *N*-oxide·HCl		230 (4.37), 300 (4.32)	191
2-Styryl-4-Ac-5-Me *N*-oxide·HCl		275 (4.41)	191

[a] Np = naphthyl. [b] An = acenaphthyl. [c] Phen = phenanthryl. [d] Biph = biphenylyl. [e] Fl = fluorenyl.

yloxazoles both in the liquid and vapor phases, and detailed assignments of the observed absorption frequencies have been put forth.[204-208] The strong band at 1555–1585 cm^{-1} was assigned to the –N=C—O– ring stretching frequency.[206,208] In the parent oxazole this band occurs at 1558 cm^{-1}, and substituents usually cause it to shift to higher frequencies.[204] Ir spectra of various aryloxazoles have been tabulated and discussed.[209]

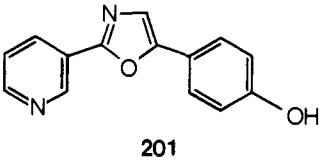
TABLE III. Dipole Moments (μ) and NQR Coupling Constants for Oxazole (1)

	μ, D	NQR coupling constants aa	bb	cc	Ref
Exptl	1.50	−3.99	1.58	2.41	195
SCF–PPP	1.80	−3.79	0.88	2.91	196
CNDO/2	1.38	−4.29	1.95	2.34	197
VESCF	2.01				198, 199
Ab initio	1.47		1.82		168
Ab initio		−4.98	1.57	3.41	200, 201

The thermodynamic functions—free energy, entropy, and heat content—were calculated for oxazole and other five-membered heterocyclic compounds from their fundamental vibrational frequencies.[210,211]

G. Mass Spectra[212]

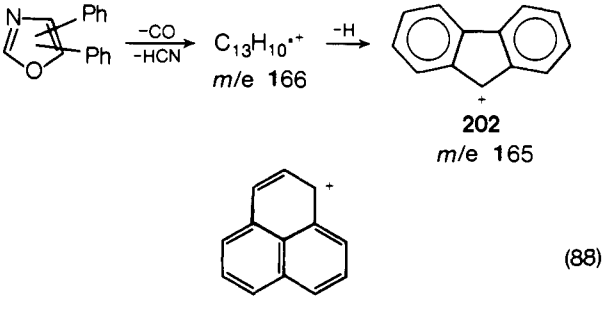
The first published account of the mass spectrometry of oxazoles was concerned with the structure proof of the oxazole alkaloid halfordinol (**201**) and its derivatives.[213] Previous chemical investigations[214,215] afforded evidence that the oxazole ring possesses a pyridyl and a hydroxyphenyl substituent. A comparison of the mass spectrum of **201** with the model 2,5-, 2,4-, and 4,5-diphenyloxazoles strongly suggested that halfordinol (**201**) is 2-(3-pyridyl)-5-(*p*-hydroxyphenyl)oxazole.



201

Mechanisms for the formation of the major fragments (*m/e* 166 and 165) from aryloxazoles have been postulated. The origin of the *m/e* 165 ion noted in the mass spectra of diaryloxazoles, diarylimidazoles, and diarylthiazoles has been studied by deuterium-labeling techniques.[216] The *m/e* 165 ion is thought to be the fluorenyl cation (**202**) or the phenalenium cation (**203**).

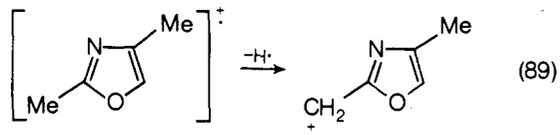
A detailed and thorough investigation of the mass spectra of oxazole and a variety of alkyl-, aryl-, and aralkyloxazoles was made with the aid of deuterium labeling techniques and high resolution mass spectrometry.[217] Several useful and interesting characteristics of the fragmentation patterns of these oxazole derivatives were pointed out. The spectra of 2,4- and 4,5-dimethyloxazoles exhibited several differences in their fragmentation patterns. The M − 1 peak in the spectrum of 2,4-dimethyloxazole was far less abundant than that of the 4,5-dimethyl isomer. This behavior was attributed to the insta-



202
m/e 165

203
m/e 165

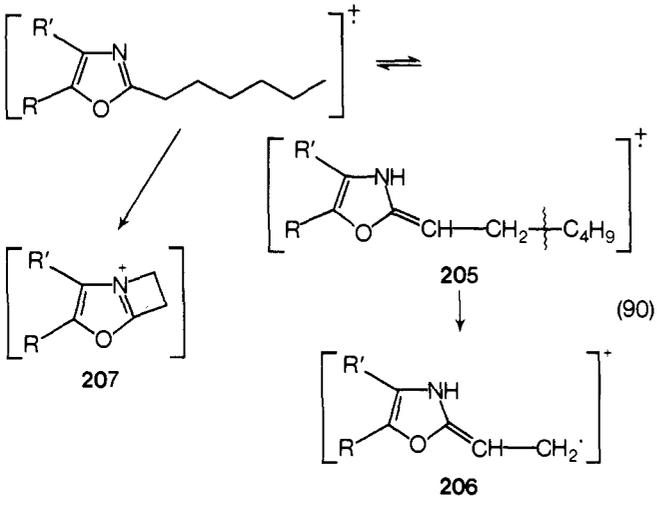
(88)



(89)

204

bility of the ion **204** which would be formed from the molecular ion of 2,4-dimethyloxazole by loss of a hydrogen atom. A similar situation exists in the spectra of the isomeric methyl-n-hexyloxazoles. The rate of β-scission of the *n*-hexyl group is lower when this group is in the 2 position on the oxazole ring; however, the rate of γ-scission is enhanced relative to the 4- and 5-n-hexyloxazoles. The slower rate of β-scission for the 2-*n*-hexyl derivative is attributed to the production of unstable ions corresponding to **204**, whereas the enhanced rate of γ-scission can be rationalized by invoking allylic cleavage of the tautomeric form **205** of the molecular ion to give **206** or by the formation of a stabilized cyclic ion **207.** This behavior is similar to that shown in the mass spectra of 2- and 3-ethylpyridines.



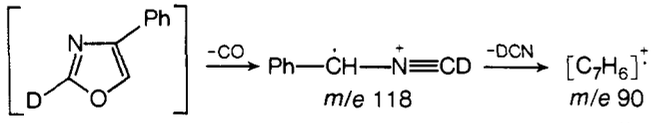
(90)

207

205

206

The isomeric 2- and 4-phenyloxazoles exhibit many similarities in their fragmentation reactions. Both molecular ions sequentially eliminate CO and HCN to give the peak at *m/e* 90; the species thus formed loses a hydrogen atom. The hydrogens on the ring are not scrambled to a great extent in the M − CO ion from 4-phenyloxazole since the M − CO fragment from 4-phenyloxazole-2-*d* decomposes mostly by loss of DCN (94%) rather than HCN (4%).



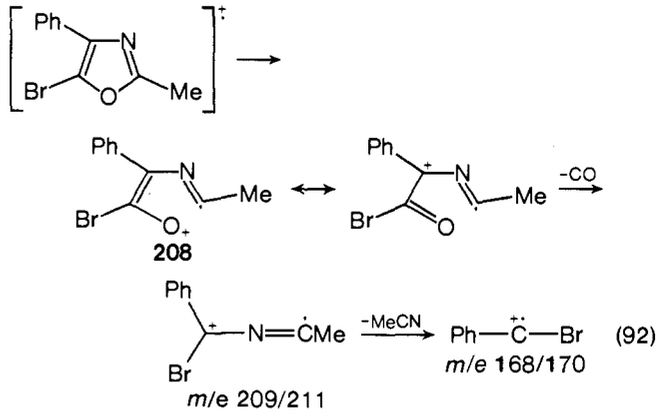
m/e 118 *m/e* 90

(91)

A mechanism for the formation of the more abundant fragments in the mass spectrum of 2-methyl-4-phenyl-5-bromooxazole has been postulated (eq 92).[217] The loss of CO from other 2,5-disubstituted oxazoles was also explained on the basis of the ring opening to give an ion analogous to **208** followed by or concomitant with migration of the original C_5 substituent to C_4 affording the M − 28 ion.

A *p*-fluorophenyl labeling study of partial scrambling before fragmentation in 2-(*p*-fluorophenyl)-4,5-diphenyloxazole and -imidazole, 2,5-bis(*p*-fluorophenyl)-4-phenylthiazole, and 3,5-diphenyl-4-(*p*-fluorophenyl)isoxazole was undertaken by Bursey and Nunnally.[218]

A noteworthy correlation between the photochemical behavior of 3,5-diphenylisoxazole (**141**), 2-phenyl-3-benzoyl-1-



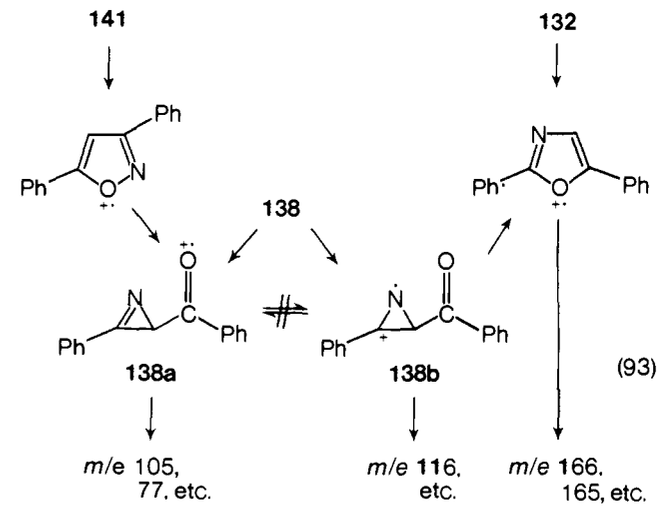
208

m/e 209/211

(92)

m/e 168/170

azirine (**138**), and 2,5-diphenyloxazole (**132b**) (cf. section II.M) and the behavior of these substances upon electron impact has been observed by Nakata et al.[219] The mass spectra of these compounds show striking similarities; however, the peaks at *m/e* 166 and 165 for the azirine **138** and the oxazole **132** are absent from the spectra of the isoxazole **141.** The tentative conclusion that the fragmentation of **141** takes place only via **138** which upon electron impact is converted in part to **132b** was made on the basis of the near correspondence of the spectra of these compounds. The absence of the *m/e* 165 and 166 ions in the spectrum of **141** suggests that the ion **138a** is formed from **141** and that both ions **138a** and **138b** are formed from the azirine **138.** Ions **138a** and **138b** are not interconvertible and react in different ways to form the fragment ions (eq 93).



141 132

138

138a 138b

m/e 105, 77, etc. *m/e* 116, etc. *m/e* 166, 165, etc.

(93)

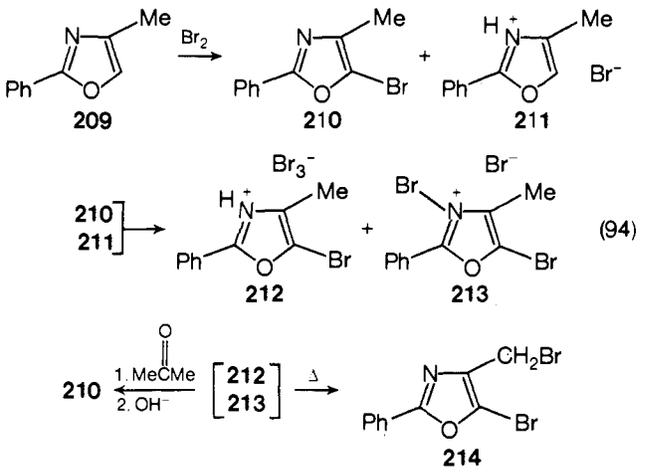
These workers proposed that the selective ionization of the carbonyl and imine functionalities of the azirine **138** leads to formation of the molecular ions of the isoxazole **141** and the oxazole **132**, respectively (analogous to the process which is presumed to occur in the photochemical reactions of **138**[111,112]).

IV. Reactions

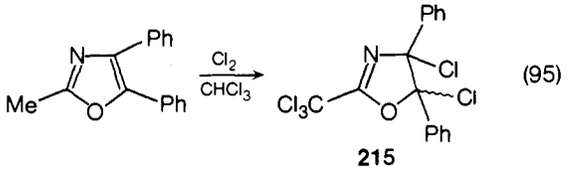
A. Syntheses and Reactions of Halooxazoles

The first detailed study of the bromination of 2-substituted oxazoles was made by Gompper and Ruhle.[220,221] Bromination of 2,4-disubstituted-5-unsubstituted oxazoles readily produced 5-bromooxazoles in good yields when either *N*-bromosuccinimide (NBS) or NBS/Br_2 was used as the brominating agent. 2-Methyl-5-phenyloxazole gave 2-methyl-5-phenyl-4-bromooxazole in up to 63% yield under these conditions. Methyl substituents on the 4 or 5 position of 2-aryloxazoles are monobrominated with a 4-methyl reacting in preference to a 5-methyl group.

The mechanism of the bromination of 2-phenyl-4-methyloxazole (**209**) is thought to proceed via direct ring bromination and by bromination of the oxazole hydrobromide **211.** The reaction of **211** with bromine presumably gives the perbromide species **212** and **213.** In the presence of acetone, only the product of ring bromination **210** is obtained. Elevated temperatures allow isolation of 2-phenyl-4-bromomethyl-5-bromooxazole (**214**). This study also included the effect of solvents on the reaction of oxazoles with brominating agents.



In the presence of molecular chlorine, 2-methyl-4,5-diphenyloxazole yields 2-trichloromethyl-4,5-dichloro-4,5-diphenyl-Δ^2-oxazoline (**215**) after 14 days at room temperature.[220]



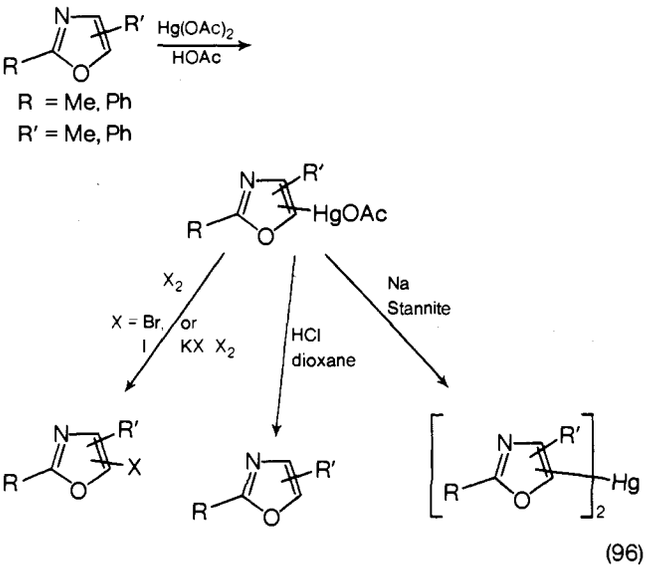
The data of Gompper and Ruhle suggest that the relative ease of the attack of bromine on the oxazole ring is $C_5 \geq C_4 > C_2$.[221] Although C_5 and C_4 are known with some certainty to be a great deal more reactive toward electrophiles than is C_2, a more thorough investigation of the relative reactivities of the 4 and 5 positions of the oxazole ring is warranted. A consideration of the charge densities at these positions (section III.B) indicates that the relative reactivity is very similar and highly dependent upon reaction conditions and substituents.

Bromination of 2-phenyloxazoles occurs exclusively at the 5 position of the oxazole ring, whereas the reaction of these substrates with nitrating agents usually gives (*p*-nitrophenyl)oxazoles.[3,222]

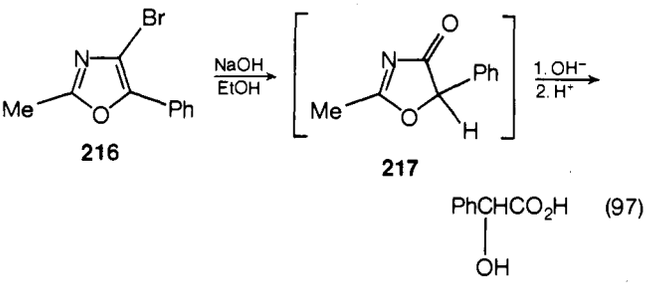
The rates of the bromination of 2-(*p*-X-phenyl)-4-chloromethyl- or -hydroxymethyloxazoles were determined.[223] A plot of log k/k_0 vs. σ was linear for variation of the substituent X, with $\pi = -0.69$ for the 4-chloromethyloxazole and -0.75 for the hydroxymethyloxazole. These negative values of ρ suggest that the attack of bromine on the oxazole nucleus is electrophilic in nature.

The synthesis of 4- or 5-bromo- or -iodooxazoles was effected via the reaction of bromine or iodine with 4- or 5-oxazolylmercuric acetates (eq 96).[224-226] The observed order of reactivity was the same as in the direct electrophilic bromination, i.e., $C_5 > C_4$. The mercuration of phenyl substituents was not observed.

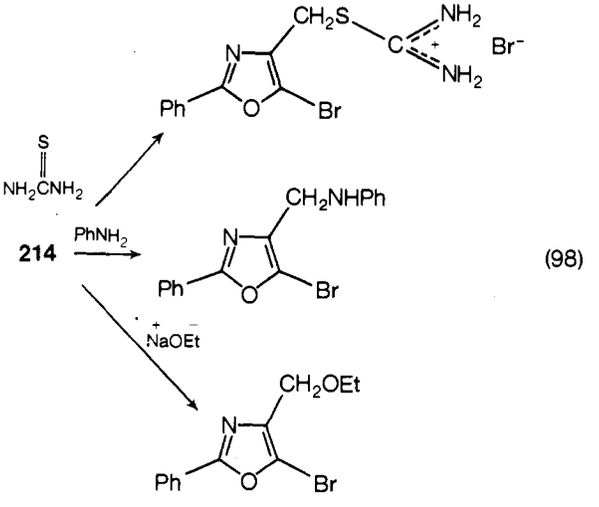
A halogen–lithium exchange reaction has been utilized in the position-specific deuteration of oxazole derivatives for mass spectral studies.[216,217] When 4- or 5-bromooxazoles are treated with *n*-butyllithium at −65° and the resulting oxazolyllithium is quenched with D_2O, the 4- or 5-deuteriooxazole is obtained. Deuteration of nonhalogenated oxazoles such as 4-phenyloxazole occurs only at the 2 position. Furthermore, 2-methyl-4-phenyl-5-bromooxazole gives the 5-deuteriooxazole under these conditions, whereas 2-methyl-4-phenyloxazole afforded only the 2-(methyl-d_1)-4-phenyl derivative.



The ease of nucleophilic displacement of halogens on the oxazole ring is Hal-2 ≫ Hal-4 > Hal-5. The reaction of 2-methyl-4-bromo-5-phenyloxazole (**216**) with ethanolic NaOH afforded a low yield of 2-hydroxyphenylacetic acid via the intermediate 4-oxazolone **217.**[221]

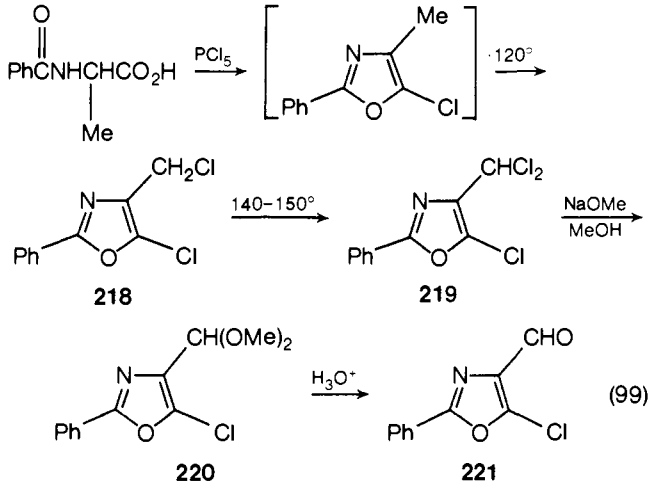


When 2-phenyl-4-bromomethyl-5-bromooxazole (**214**) reacts with nucleophilic reagents, bromine is displaced only from the side chain.[221]



The cyclization of benzoylalanine with PCl_5 at 120° results in the formation of 2-phenyl-5-chloro-4-chloromethyloxazole

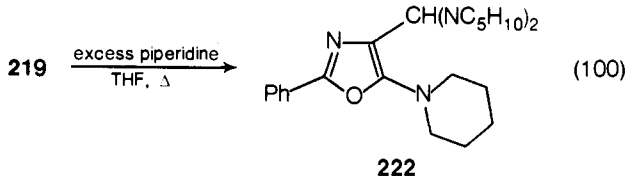
(218).[227] At elevated temperatures (140–150°) the 4-dichloromethyl derivative (219) is isolated.



(99)

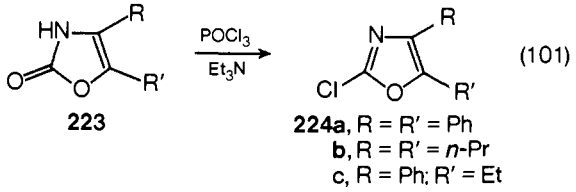
Hydrogenolysis of 218 or 219 affords 2-phenyl-4-methyloxazole. Nucleophiles such as methoxide or piperidine displace only the side-chain chlorine of 218. When 219 is treated with 2 equiv of NaOMe, the acetal 220 is formed which is hydrolyzed on work-up to afford 2-phenyl-5-chlorooxazole-4-carboxaldehyde (221).

The action of piperidine on 218 in refluxing THF gives only 2-phenyl-4-piperidinomethyl-5-chlorooxazole. With 219, however, an excess of the amine yields 2-phenyl-4-dipiperidinomethyl-5-piperidinooxazole (222).



(100)

The direct chlorination of oxazoles is not an effective method for the preparation of 2-chlorooxazoles because of the low reactivity of the 2 position toward electrophiles. These compounds can be synthesized by treating Δ^4-oxazolin-2-ones (223) with phosphoryl chloride in the presence of a tertiary amine.[187]

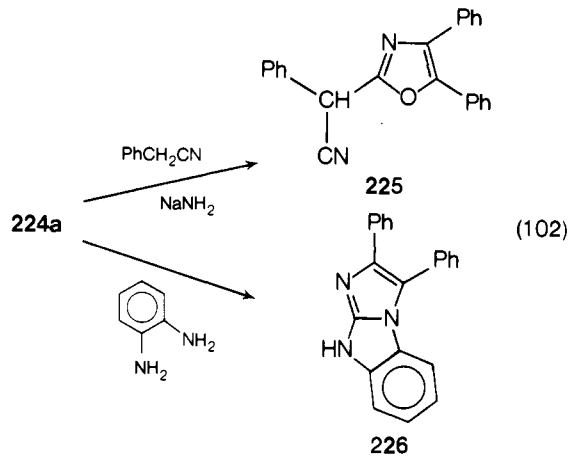


(101)

Nucleophilic displacement of the 2-chloro group is an extremely facile process which has found utility in the preparation of 2-amino-[187], 2-alkoxy-[187], and 2-hydrazinooxazoles.[228,229] Phenylacetonitrile reacts with 2-chloro-4,5-diphenyloxazole (224a) in the presence of $NaNH_2$ to give [4,5-diphenyloxazolyl-(2)]benzyl cyanide (225). The reaction of 224 with o-phenylenediamine gives the imidazoloindole derivative 226.[187]

The attempted N-alkylation of 224a with dimethyl sulfate or benzyl bromide was unsuccessful; however, this substrate can be N-alkylated with triethyloxonium tetrafluoroborate in methylene chloride. The resulting *N*-ethyloxazolium salt 227 reacts with primary amines to yield the 2-amino-*N*-ethyloxazolium salt 228 which when treated with triethylamine gives 2-imino-4,5-diphenyl-Δ^4-oxazoline (229).[187]

The thermal rearrangement of 5-alkoxy-4-oxazolecarboxy-



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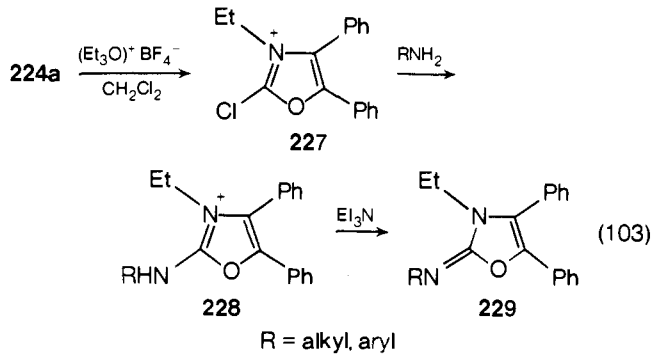


(103)

R = alkyl, aryl

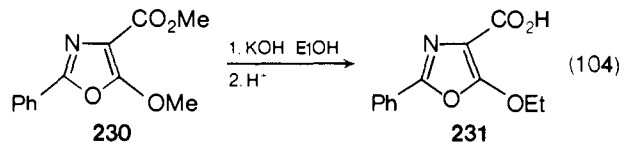
lic acid chlorides results in the formation of alkyl 5-chloro-4-oxazole-carboxylates in high yields. This reaction will be discussed in detail in section IV.I.

B. With Nucleophiles

1. Nucleophilic Substitution

Nucleophilic substitution reactions on the oxazole ring are rare and will only occur if certain functional groups are present. The substitution of halogens with various nucleophiles has been discussed in the previous section (IV.A).

When the 4 position of the oxazole ring is substituted by an ester functionality, the normally unreactive 5 position becomes activated toward nucleophilic attack. The action of NaOEt on 2-n-amyl-5-chlorooxazole-4-carboxylic acid in refluxing ethanol affords 2-*n*-amyl-5-ethoxyoxazole-4-carboxylic acid.[4] Under somewhat less vigorous conditions the 5-methoxy substituent of methyl 2-phenyl-5-methoxyoxazole-4-carboxylate (230) is replaced by an ethoxy group in the presence of ethanolic/KOH at room temperature to give 2-phenyl-5-ethoxyoxazole-4-carboxylic acid (231).[167]



(104)

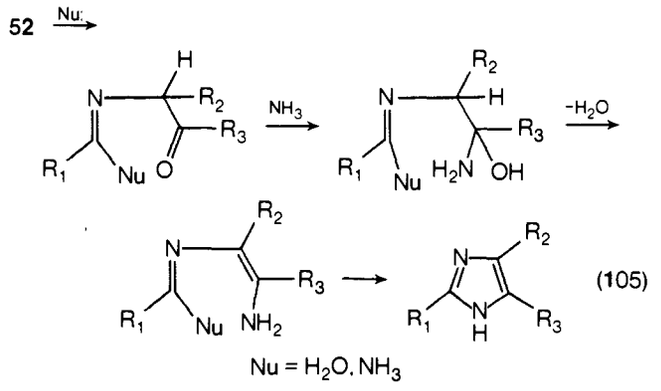
2. Ring Cleavage by Nucleophiles

The cleavage of the oxazole ring by nucleophiles is a much more common reaction than nucleophilic substitution reactions. The initially formed acyclic intermediates derived from this type of ring cleavage reaction may be stable toward further reactions and isolable as such. Processes such as this are extensively discussed in the Cornforth[2] and Wiley[3] reviews. In several instances, however, the acyclic intermediates undergo a subsequent cyclization reaction whereby a new ring system is formed. The structure of this new system is largely dependent upon the structure of the attacking nu-

cleophile and on the functional groups on the oxazole substrate. Reactions of this type are also known for the analogous furans. Examples of these are the conversion of furan derivatives to pyrroles by the action of ammonia or amines[230] and to thiophenes with H_2S.[231]

The reaction of ammonia or amines with alkyl- or aryloxazoles at temperatures in excess of 220° gives imidazoles.[2] 2-Methyl-4-phenyloxazole reacts with alcoholic ammonia at 220–230° to afford 2-methyl-4-phenylimidazole. Oxazole-4-carboxylic acids give imidazoles and CO_2 with ammonia at somewhat lower temperatures.

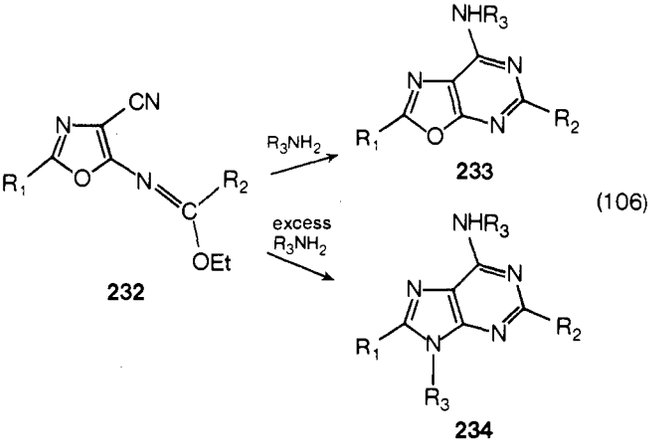
Heating oxazoles with formamide at 180° also produces imidazoles.[2] It is believed that the oxazole ring is cleaved by water or ammonia which is present in the reaction mixture. The resulting intermediate reacts further with NH_3 and subsequently cyclizes to the imidazole. The origin of the NH_3 is due to the equilibrium between formamide and ammonium formate in the presence of water.



(105)

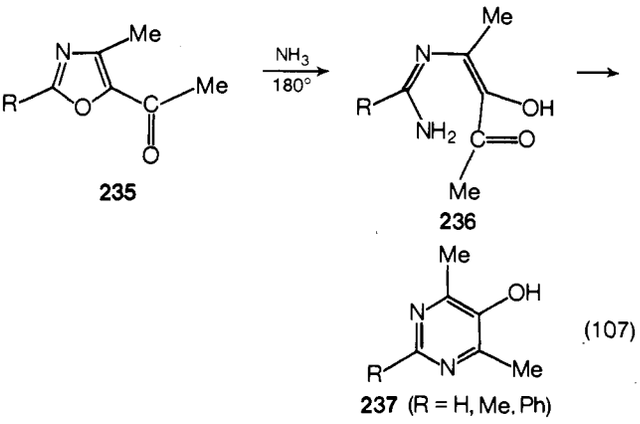
Theilig et al.[232,233] and Bredereck et al.[234–236] have conducted extensive investigations into the scope and mechanism of this reaction. The presence of bulky aliphatic substituents at the 2 or 5 position on the oxazole ring tend to inhibit imidazole formation; a phenyl substituent at the 4 position promotes the reaction.[233] The reaction of α-halo ketones with formamide at 130° yields 4,5-disubstituted oxazoles. When the reaction is carried out at 180° with an excess of formamide, 4,5-disubstituted imidazoles are obtained directly without the isolation of the intermediate oxazole.[232–236]

The oxazole–imidazole rearrangement has been utilized in the synthesis of 7-amino-9-substituted hypoxanthines (**234**).[237] The reaction of 5-ethoxymethyleneamino-4-cyanooxazoles (**232**) with primary amines affords the oxazolo[4,5-*d*]pyrimidines **233.** The transformation of **232** to **234** occurs directly when an excess of the amine is used.



(106)

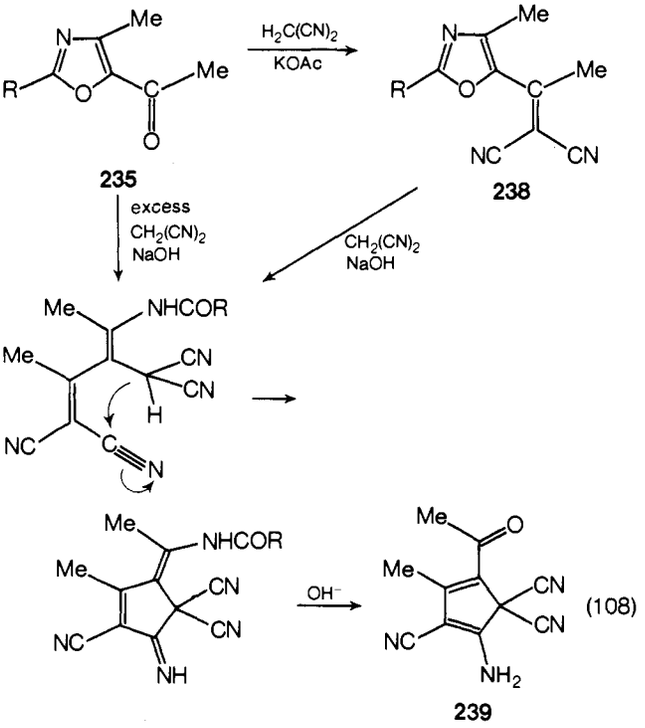
The reaction of 4-methyl-5-acetyloxazoles (**235**) with aqueous NH_3 does not yield the expected 4-methyl-5-acetylimidazole; the presence of the 5-acetyl group causes the reaction to follow a new pathway.[238] The first step in the proposed mechanism is nucleophilic attack of ammonia on **235** to give the acyclic intermediate **236.** The intermediate **236** recyclizes as shown to afford 4,6-dimethyl-5-hydroxypyrimidines (**237**) in high yields.



(107)

When the anion of malononitrile is allowed to react with 4- or 5-acetyloxazoles, substituted pyridines (**242**) or cyclopentadienes (**239**), respectively, are formed.[239] The formation of these products can be rationalized on the basis of the nucleophilic ring-opening–ring-closure mechanism described above. The initial intermediates formed in both cases are the dicyanovinyl condensation products **238** and **241.** These intermediates can be isolated when equimolar amounts of malononitrile and oxazole react in the presence of KOAc. Further reaction of **238** and **241** with malononitrile and NaOH leads to the observed products (eq 108 and 109).

Another rather intriguing example of the nucleophilic ring-opening–ring-closure reactions of oxazoles is the thermal rearrangement of 1-(4,5-diphenyloxazol-2-yl)-4-phenylthiosemicarbazone (**243**) to 3-desylamino-4-phenyl-1,2,4-triazole-5-thione (**245**).[228] The intramolecular attack of the 4-thiosemicarbazone nitrogen on the 2 position of the oxazole ring followed by the tautomerization of the intermediate **244** is a likely rationale for the formation of the observed product.



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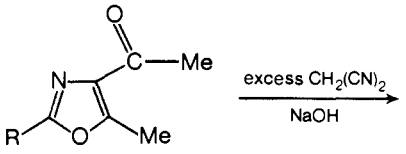

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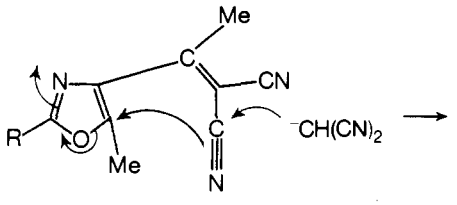

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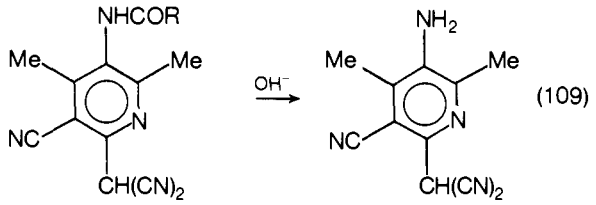

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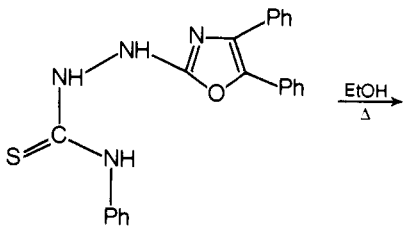

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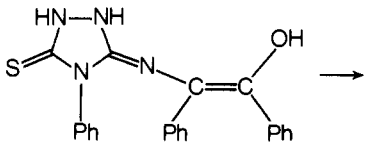

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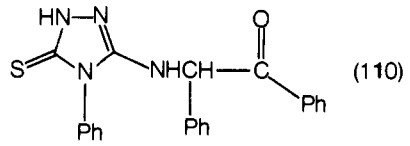
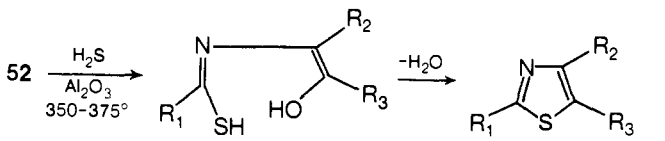


245 (110)

The mechanism for the conversion of alkyloxazoles to alkylthiazoles by the passage of the oxazole over hot alumina (350°) in a stream of H_2S is not known with certainty; however, an attractive possibility is the nucleophilic attack of H_2S at C_2 of the oxazoles followed by ring closure of the resulting intermediate **246** with subsequent dehydration to afford the thiazoles **247** in 13–15% yield.[240] It was concluded that the



246 247 (111)

$R_1 = R_3 = Me; R_2 = H$
$R_2 = R_3 = Me; R_1 = H$
$R_1 = R_2 = Me; R_3 = H$
$R_1 = R_2 = R_3 = Me$

replacement of the oxazole oxygen atom by other heteroatoms proceeds to a greater extent the lower the acidity of the nucleophilic reagent employed. For example, imidazoles are formed in high yields from oxazoles and ammonia or amines, whereas thiazoles are formed in much lower yields from the reaction of the more acidic reagent, H_2S, with oxazole substrates.

The replacement of the oxazole oxygen atom with a new oxygen atom can occur in the reaction of suitably substituted oxazoles with hydroxide ion (section IV.I).

C. With Electrophiles

1. Electrophilic Substitution at Aryl Side Chains

Furan and its derivatives are quite reactive toward electrophilic reagents. However, owing to their instability in acidic media, furans will only undergo normal electrophilic substitution reactions under weakly acidic conditions. Often the products of these apparent direct electrophilic substitutions arise from 2,5-dihydrofuran intermediates.[1] Oxazoles, on the other hand, do not readily undergo electrophilic substitution reactions although many oxazoles are stable to acidic conditions. The presence of the pyridine-type nitrogen of the oxazole ring deactivates this system to a great extent. Early attempts to nitrate phenyloxazoles produced only *p*-nitrophenyloxazoles.[3] More recently it was observed that the nitration or chlorosulfonation of 2-methyl-4,5-diphenyloxazole afforded the di-*p*-nitrophenyl or di-*p*-chlorosulfonylphenyl derivatives. Sulfonation of this substrate led to substitution only at the para position of the 5-phenyl substituent.[241] The *p*-nitrophenyl groups could be reduced chemically to the anilines which were subsequently diazotized. The diazonium salts readily underwent the normal reactions of these salts. This and other work[3] suggested that the relative reactivities toward electrophilic substitution reactions of phenyl groups on the oxazole ring is in the order 5-Ph > 4-Ph > 2-Ph and that substitution almost exclusively occurs at the para position.

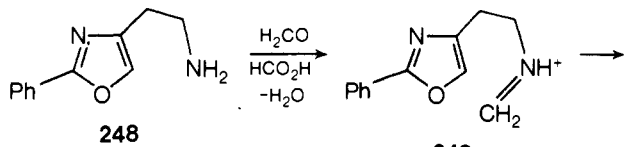
The nitration of 4-phenyloxazole with fuming nitric–sulfuric acid mixture gives 4-*p*-nitrophenyloxazole.[242]

2. At Carbons 4 and 5

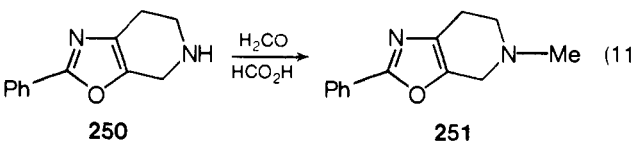
Electrophilic attack at the 4 or 5 position of the oxazole ring occurs easily if the ring is activated by electron-donating substituents such as amino or hydroxyl groups.

Thus far the only successful attempt to nitrate the oxazole nucleus afforded 2-dimethylamino-4-(*p*-nitrophenyl)-5-nitrooxazole in 97% yield with KNO_3/H_2SO_4.[133] Undoubtedly the presence of the 2-dimethylamino substituent is responsible for the facile nitration of this oxazole.

The reductive formylation of 2-phenyl-4-(β-aminoethyl)oxazole (**248**) by the Eschweiler–Clarke procedure[243] resulted in the cyclization of **248** to afford 2-phenyl-5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (**251**).[244] The mechanism for this cyclization may be viewed as an electrophilic attack of the aminomethylene group of the intermediate **249** on the 5



248 249

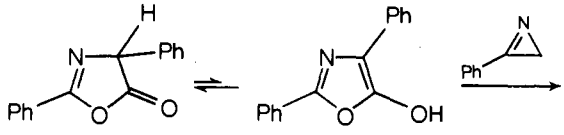


250 251 (112)

position of the oxazole ring. From the data presented it is impossible to determine whether the cyclization proceeds prior or subsequent to the N-methylation.

The reaction of 2,4-diphenyl-5-hydroxyoxazole (**252**) with

2-phenyl-1-azirine probably proceeds via the electrophilic attack of the azirine on the 4 position of the oxazole to yield 2,4-diphenyl-4-(2'-phenylaziridinyl)-Δ^2-oxazolin-5-one (**253**).[245] The electron-donating ability of the 5-hydroxy substituent on the oxazole along with the relief of ring strain in the azirine are factors which contribute a great deal to the success of this reaction.



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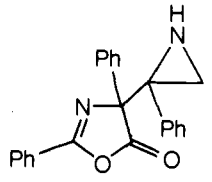
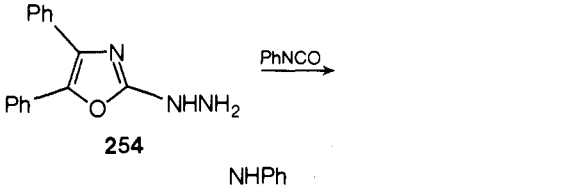


(113)

253

3. At Nitrogen

Intramolecular cyclization reactions of 2-(*N*-substituted amino)oxazoles where the N-substituent bears a carbonyl carbon atom as the third or fourth atom from the oxazole ring appear to result from the electrophilic attack of this carbonyl carbon on the oxazole nitrogen. When 2-hydrazino-4,5-diphenyloxazole (**254**) is treated with phenyl isocyanate and the resulting semicarbazone **255** is allowed to react with H_2O_2/NaOH, 3-anilino-5,6-diphenyloxazolo[2,3-*c*]-1,2,4-triazole (**256**) is formed (eq **114**).[228]



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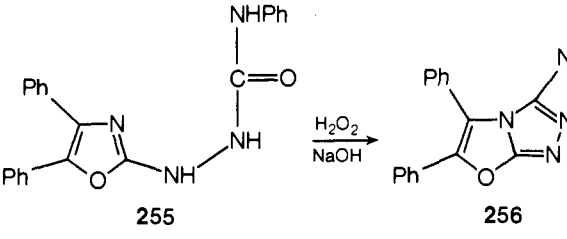

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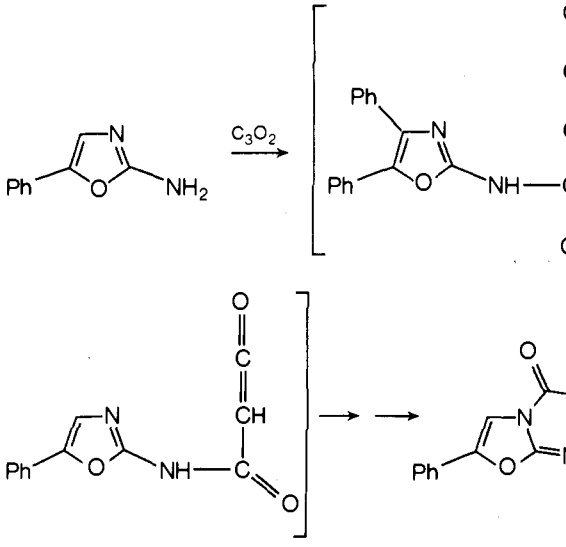
255 **256**



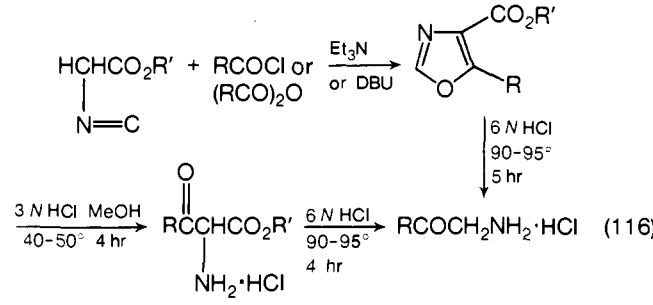
(115)

A similar cyclization occurs in the reaction of 2-amino-5-phenyloxazole with carbon suboxide (eq **115**).[246]

D. Acid-Induced Ring Cleavage

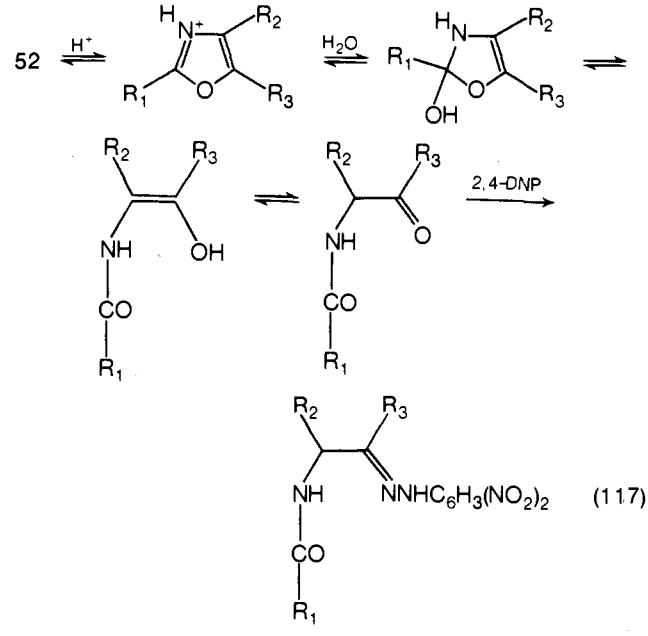
In contrast to furans, alkyl- and aryloxazoles show remarkable stability toward ring cleavage by acids. The 5-alkoxyoxazoles are, however, readily cleaved by dilute mineral acids as are 5-aminooxazoles. 2-Aminooxazoles show much greater stability to acidic conditions than their 5-amino isomers. Most of the available data concerning the reactions of oxazoles with acids have been discussed in the earlier reviews.[2-4]

A recent example of the acidic cleavage of oxazole derivatives in a preparative role is in the synthesis of α-*C*-amino esters and α-amino ketones from oxazole-4-carboxylates.[247,248] The oxazoles were prepared by an adaptation of the method of Schöllkopf and Schröder.[8,9] The utility of this synthesis is demonstrated by the high yields of amino esters and amino ketones obtained and by the variety of 5-alkyl and -aryl substituents (R) which may be present on the ring.



(116)

The formation of the 2,4-dinitrophenylhydrazone of ethyl α-acetamidomalonaldehyde from the reaction of ethyl 2-methyloxazole-4-carboxylate with 2,4-dinitrophenylhydrazine in HCl was first noted by Cornforth.[2,4] Gompper et al. performed a thorough study of this reaction and proposed a mechanism which involved the acid-induced ring opening of the oxazole to give an α-amido ketone which reacts with 2,4-DNP to afford the hydrazone.[249]



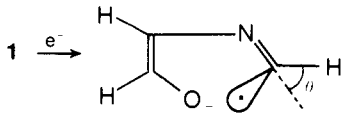
(117)

E. Reductive Ring Cleavage

Oxazoles are, for the most part, remarkably stable toward a variety of reducing agents. Sodium in refluxing ethanol will reduce oxazoles to oxazolidines which may be reduced fur-

ther to acyclic products.[2,3] Gaylord and Kay observed the reduction of 2,5-diphenyloxazole (**132b**) to 2-benzylamino-1-phenylethanol with lithium aluminum hydride in THF solution.[250] In ether solution no reduction occurred. The same product is obtained when **132b** is reduced with Na in ethanol.[2]

The anion radicals produced by the one-electron reduction of oxazole and other oxygen-containing heteroaromatic compounds were observed by ESR spectroscopy in an argon matrix at 4°K.[251] The ESR of the oxazole-derived anion radical exhibited a simple doublet with a hyperfine coupling constant of 35 G. On the basis of its ESR spectrum, the open-chain structure **257** was assigned to this anion radical.

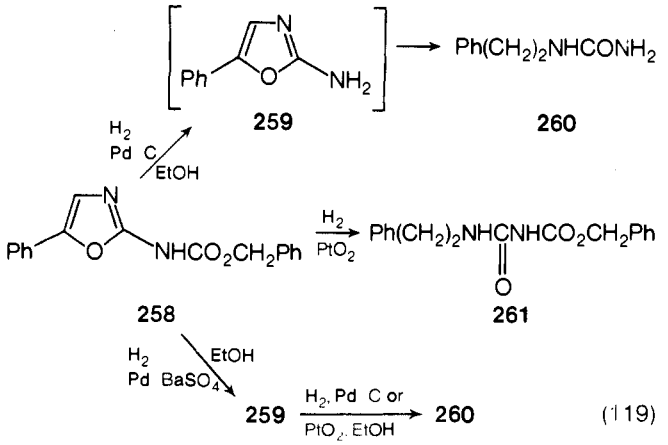


(118)

257

Similar acyclic structures were assigned to the anion radicals derived from the reduction of furan, isoxazole, and benzoxazole. Further substantiation for these assignments was obtained by consideration of the results of INDO[252] and extended Hückel[114] molecular orbital calculations. The angle θ in **257** is predicted to be approximately 50° which agrees with the observed ESR coupling constant. Overlap populations for the heterocycles under study were calculated by the EHMO method. For the neutral oxazole molecule the calculations predict that the C_5–O bond is weaker than the C_2–O bond. The transfer of an electron to the neutral oxazole weakens the C–O bonds since this electron is now in an orbital which possesses strong antibonding character across these bonds. For this case the C_2–O bond is calculated to be the weaker of the C–O bonds and consequently it is this bond which is cleaved in the reduction.

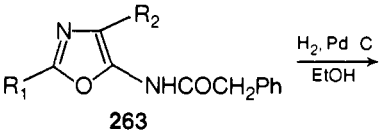
The catalytic reduction of benzyl 5-phenyl-2-oxazolecarbamate (**258**) and 2-amino-5-phenyloxazole (**259**) was studied by Tanaka.[253] When **258** was subjected to catalytic reduction in the presence of Pd/C in ethanol, phenethylurea (**260**) was isolated. 2-Amino-5-phenyloxazole (**259**) was implicated as the intermediate in this transformation. Hydrogenation of **258** using a PtO_2 catalyst gives 1-carbobenzyloxy-3-phenethylurea (**261**). Reduction of **258** in the presence of Pd–$BaSO_4$ catalyst affords **259** selectively. 2-Amino-5-phenyloxazole (**259**) is reduced with Pd/C or PtO_2 to phenethylurea (**260**), lending some support to the proposal that it is an intermediate in the transformation of **258** to **260**. Ethyl 5-phenyloxazole-2-carboxylate and 5-phenyloxazole are stable to these reaction conditions.



(119)

Reductive ring cleavage reactions of oxazoles are markedly inhibited by bases; however, in the presence of HCl the reaction is enhanced. The above transformations are not observed with a Raney Ni catalyst. Para substituents on the 5-phenyl ring of **258** are found to have little effect on the reductions.

Tanaka and Asai investigated the hydrogenolysis and reductive ring cleavage reactions of benzyl 4- and -5-oxazolecarbamates, **262** and **263**, respectively.[254] The catalytic reduction of **262** with Pd/C in ethanol yielded an unidentifiable resin. Under the same conditions **263** was hydrogenolyzed to the 5-aminooxazole **264** which was isolated as the chain tautomer, the acylaminonitrile **265.**



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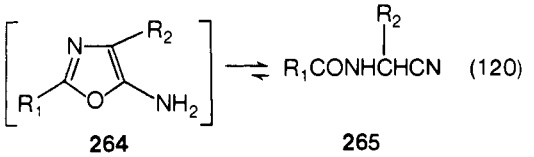
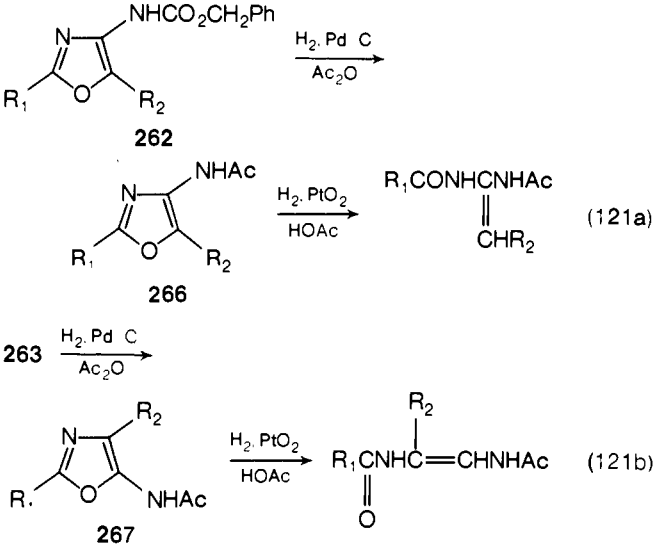


(120)

264 **265**

If the catalytic reduction of **262** or **263** is allowed to proceed in the presence of acetic anhydride, 4- or 5-acetamidooxazoles **266** and **267**, respectively, are formed. Reduction of **266** and **267** proceeds smoothly with a PtO_2 catalyst in HOAc to afford the corresponding enamides (eq 121).



(121a)

262

266

(121b)

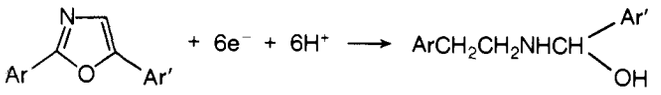
267

F. Electrochemical Reduction

The polarographic reduction of oxazole derivatives in the protic solvent methanol was studied extensively by the Russian chemist Bezuglyi and his coworkers.[255-257,263]

These investigators found that most of the 2,5-diaryloxazoles exhibit two polarographic waves and that substituents at the 2 position of the oxazole had a much greater effect on the ease of the first reduction than a substituent at the 5 position.[255] Oxazoles with an alkyl group at the 2 position are not reduced at a dropping mercury electrode. The results indicate that the C=N of the oxazole ring is the most easily reduced bond. Subsequent to the reduction of the C=N bond, an aromatic moiety at the 2 position has no conjugative influence on the C=C of the ring and consequently has little influence on the half-wave potential of the second wave which corresponds to the reduction of the C=C. A correlation between the λ_{max} of the uv absorption spectra of these compounds, their half-wave potentials, and their scintillation effectiveness was noted.

The mechanism of the reduction of 2,5-diaryloxazoles and oxadiazoles was studied at various pH's.[256] For each compound studied, lowering the pH caused a shift toward more positive potentials. For the 2,5-diaryloxazoles, six electrons are required for the reduction with the exception of 2-(1- and 2-naphthyl)-5-phenyloxazole which required only two electrons for this process. The reduction of the former substances is suggested to proceed as in eq 122. For the naphthyl derivatives only the C=N of the ring is reduced. The ir spectra of the starting materials and the reduced products support these conclusions.



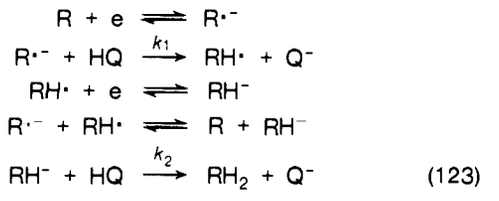
268 (122)

A polarographic study of the reduction of 2-(*p*-vinylphenyl)-5-aryloxazoles and -oxadiazoles showed that the first wave at −1.77 to −1.84 V was due to the reduction of the vinyl substituent.[257] This first product is further reduced at more negative potentials with the consumption of six electrons to give an open-chain compound analogous to **268.**

The effect of nitroaryl substituents on the polarographic reduction of oxazoles was investigated.[258] The temperature dependence of the polarographic behavior of these substrates was also determined.[259]

Greig and Rogers have obtained electrochemical data concerning the reduction of 2,5-diphenyl- and -2-(1-naphthyl)-5-phenyloxazoles in the aprotic solvent DMF.[260] These oxazoles are reduced in two polarographic steps: the first produces a stable anion radical from a reversible one-electron transfer followed by a second one-electron transfer to give the dianion which is rapidly protonated. Potentials which are more anodic than that corresponding to the formation of the anion radical will oxidize the protonated dianion back to the starting material.

Data derived from cyclic voltammetry implies that 2-(1-naphthyl)-5-phenyloxazole (as well as some oxadiazoles) is reduced to a dihydro species at the first polarographic wave by a two-electron transfer in the presence of hydroquinone.[261] The steps shown in eq 123 have been proposed as the mechanism of this process.



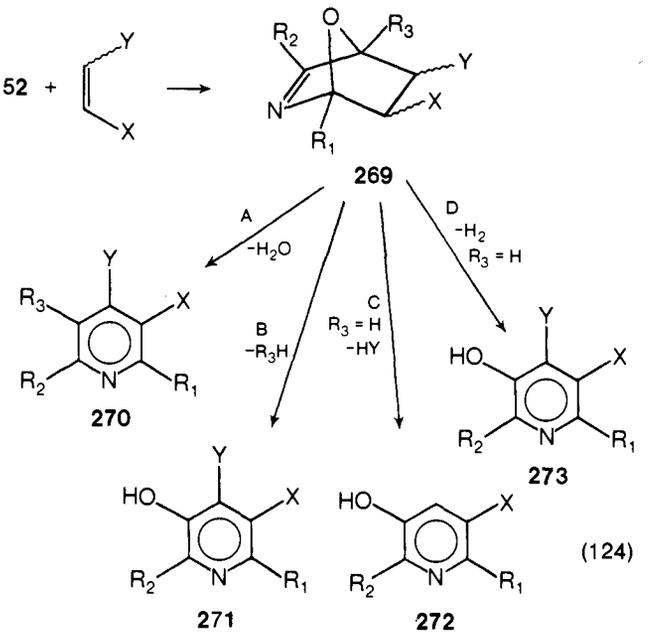
(123)

Bis(2,5-diphenyl-4-oxazolyl)mercury is reduced electrochemically in DMF solution to 2,5-diphenyloxazole (**132b**) and elemental mercury.[262] The second and third waves of the voltammogram of the oxazolylmercury derivative are exactly analogous to **132b**, implying that the latter is the species which undergoes further reduction. Similar results were obtained by Bezuglyi et al. for the polarographic reduction of bisoxazolylmercury compounds in protic solvents.[263] These authors also report the reduction of the C-halogen bond of halooxazoles by a two-electron process.

G. Diels–Alder Reaction

1. *With Olefinic Dienophiles*

The Diels–Alder reaction of oxazoles as dienes with olefinic dienophiles to yield pyridine derivatives has by far been the most thoroughly explored reaction in oxazole chemistry. Since its discovery in the late 1950's,[264] over 70 papers and patents have been published which deal with the scope, mechanism, and synthetic utility of this process and especially in the synthesis of vitamin B_6 and various pyridoxine analogs. Karpeiskii and Florent'ev discuss the mechanistic and synthetic aspects in their excellent review which covers the literature up to mid-1968.[265] The various processes which can occur are outlined in eq 124.

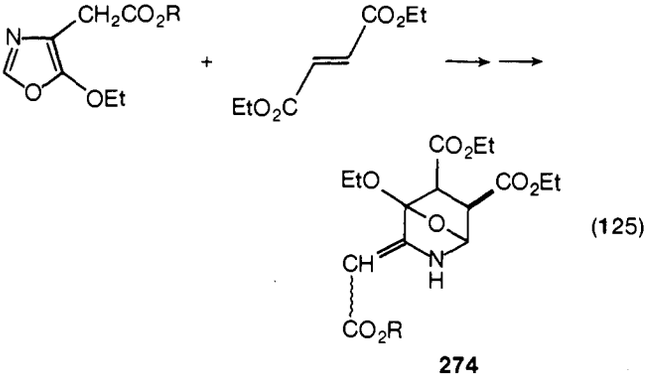


(124)

The transition state leading to the adduct **269** is thought to be highly polar in nature and the observed regioselectivity of the addition should be governed by the π-electron densities of the atoms which participate in bonding in the transition state. This hypothesis is not completely satisfactory, and consideration of the calculated π-charge densities does not always lead to the correct prediction of the regiochemistry of the adduct **269** (X ≠ Y).[265,267,268] The orientation of oxazole–dienophile systems is correctly predicted through the use of localization energy calculations.[266] A general rule for predicting the orientation of the addition is that the more electronegative substituent on the dienophile (Y) occupies the 4 position of the adduct.[269]

As is the case with other Diels–Alder reactions, electron-releasing substituents on the diene and electron-withdrawing substituents on the dienophile facilitate the reaction (e.g., 5-alkoxyoxazoles are similar in reactivity to all-carbon dienes).

The adducts **269** are normally unstable and are not isolated; however, the isomerized adduct **274** from the reaction of 5-ethoxyoxazole-4-acetic acid and its esters with diethyl fumarate is more stable than **269** and can be isolated. This is thought to be due to the conjugation of the exocyclic double bond with the carbonyl group of the ester.[265,270]



(125)

TABLE IV. Products of the Diels-Alder Reaction of 5-Alkoxyoxazoles with Olefinic Dienophiles

Oxazole			Olefin		271				
R_1	R_2	R_3	X	Y	R_1	R_2	X	Y	Ref
H	CH_2CO_2Et	OEt	CO_2Et	CO_2Et	H	CH_2CO_2Et	CO_2Et	CO_2Et	274, 275
H	CH_2CO_2Et	OEt	CN	CN	H	CH_2CO_2Et	CN	CN	276
H	CH_2CO_2Et	OEt	X, Y = $RCH(OCH_2-)_2$		H	CH_2CO_2Et	$RCH(OCH_2-)_2$		277
H	CH_2CO_2Et	OEt	CN	CN	H	CH_3	CN	CN	278
H	CH_2CO_2Et	OEt	CH_2OH	CH_2OH	H	CH_3	CH_2OH	CH_2OH	278
H	CH_2CO_2H	OEt	CH_2OH	CN	H	CH_3	CN	CH_2OH	284
H	CH_3	OCO_2Et	CN	CN	H	CH_3	CN	CN	279
H	CH_3	OCO_2Et	CO_2Et	CO_2Et	H	CH_3	CO_2Et	CO_2Et	279
H	CH_3	OEt	CO_2Et	CO_2Et	H	CH_3	CO_2Et	CO_2Et	280, 281, 285
H	CH_3	OEt	CH_2OR	CH_2OR	H	CH_3	CH_2OR	CH_2OR	282–286
H	CH_3	OPr^n	H	$COCH_3$	H	CH_3	H	$COCH_3$	287
H	CH_3	OPr^n	CH_3	$COCH_3$	H	CH_3	CH_3	$COCH_3$	287
H	CH_3	$O(CH_2)_2OR$	X, Y = $RCH(OCH_2-)_2$		H	CH_3	$RCH(OCH_2-)_2$		288 289
CO_2R	CH_3	OEt	X, Y = $RCH(OCH_2-)_2$		CO_2R	CH_3	$RCH(OCH_2-)_2$		290, 291
CO_2R	CH_3	OEt	X, Y = $-CH_2OCH_2-$		CO_2R	CH_3	$-CH_2OCH_2-$		290, 291

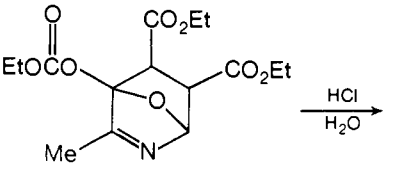
Activation parameters and solvent effects on the rate of the reaction of alkyl 5-ethoxyoxazoles with diethyl azodicarboxylate have been determined.[266]

Studies on the relative rates of various diastereomeric dienophiles with 5-ethoxyoxazoles show that the trans dienophiles add to the oxazole faster than their cis isomers.[271] This is similar to the behavior of other dienes. The only exception to this trend is that maleonitrile (cis) adds somewhat faster than fumaronitrile (trans). Steric effects which are relatively important in the transition states for the addition of dienophiles bearing large substituents (e.g., CO_2R, COPh) apparently have little effect on the rate of the addition of maleo- and fumaronitrile to oxazoles and other dienes. The interaction of the π-electron systems of the dienophile and the diene in the latter addition is the dominant factor which accelerates the rate of addition of the cis over the trans nitrile. This rationalization would only be applicable if the adduct possessed the endo stereochemistry. Although the stereochemistry was not determined in this case, it is known that cis dienophiles normally give endo adducts.

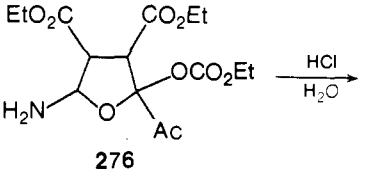
The aromatization of the adduct **269** depends on the nature of the groups at the 4 and 5 positions (R_3 and Y). In general, if R_3 is not a good anionic leaving group (e.g., alkyl) pathway A will be followed, whereas if R_3 is a good leaving group (e.g., OR) pathway B will occur. If R_3 = H and Y is a good leaving group, then pathway C leading to **272** arises. Finally if R_3 = H and Y is not a good leaving group, oxidation of the adduct can take place (pathway D). This is not a favorable process; however, if a hydride acceptor such as nitrobenzene or H_2O_2 is present in the reaction mixture the yields of the corresponding pyridines are increased to 50–60%. The reaction conditions are also largely responsible for the mode of decomposition of **269**. A complete discussion of these mechanisms and reaction conditions is available in the review of Karpeiskii and Florent'ev.[265]

The adduct **269a** (R^1 = H, R^2 = CH_3-, R^3 = OCO_2Et, Y = X = CO_2Et) obtained from 4-methyl-5-ethoxycarbonyloxyoxazole and diethyl fumarate gave, upon treatment with HCl, diethyl 2-methyl-3-hydroxypyridine-4,5-dicarboxylate and diethyl 2-acetylpyrrole-3,4-dicarboxylate (**275**).[265,272,273]

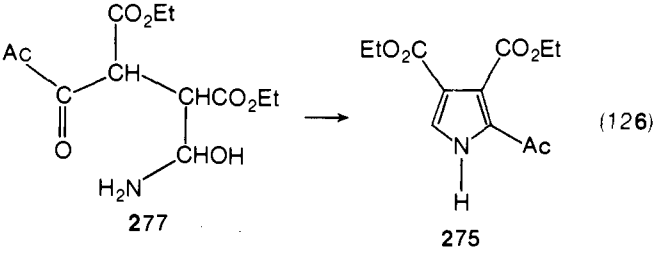
The ratio of the yield of **275** to that of the pyridine is dependent on the conditions used for the aromatization of the adduct. The mechanism for the formation of **275** is believed to proceed by the cleavage of the C=N bond of **269** to give a



269a



276



277 **275**

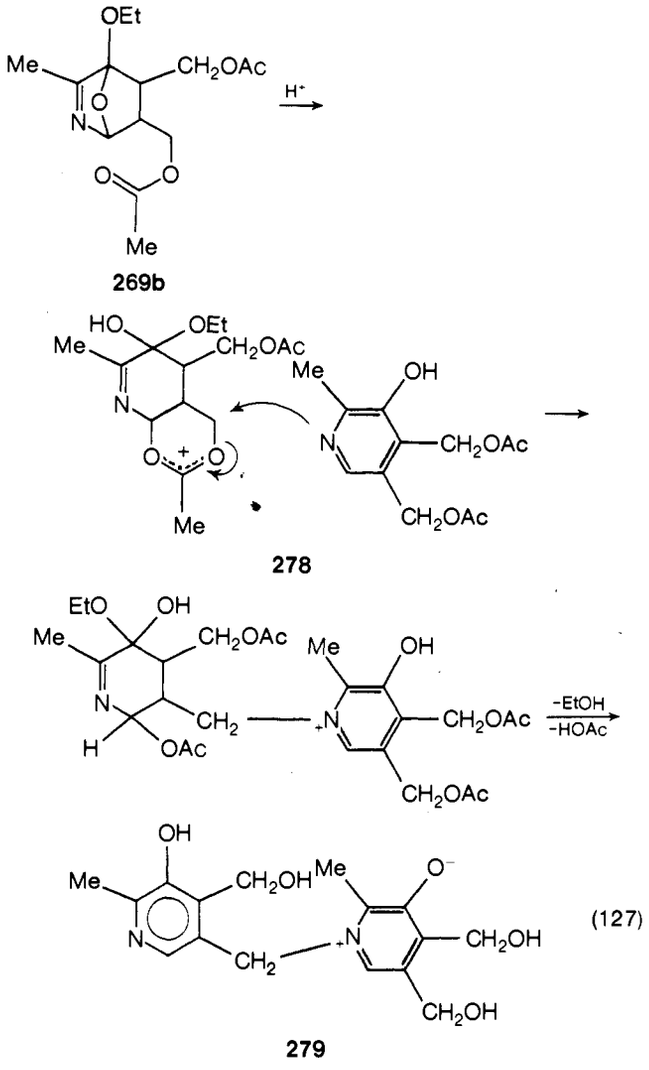
(126)

tetrahydrofuran derivative **276** which undergoes ring opening followed by recyclization and loss of water to afford **275**.

The synthetic utility of the Diels–Alder condensation of oxazoles with dienophiles to form pyridines and especially of 5-alkoxyoxazoles which react by pathway B to yield pyridoxine and pyridoxine precursors is well documented.[265] The new and convenient methods for the preparation of the 5-alkoxyoxazoles have increased the potential of this synthetic approach to B_6 and its analogs many-fold (e.g., section II.B).

Table IV lists various combinations of 5-alkoxyoxazoles and dienophiles which undergo the Diels–Alder reaction along with the corresponding 3-hydroxypyridines **271** derived from these combinations which have been reported since 1968.

4-Methyl-5-ethoxyoxazole is known to give pyridoxol (**271**; R^1 = H, R^2 = Me, X = Y = CH_2OH) upon Diels–Alder condensation with *cis*-1,4-diacetoxy-2-butene in moist HOAc and other solvents.[265,283–287] At high concentrations of the adduct **269b** (R^1 = H, R^2 = Me, R^3 = OEt, X = Y = CH_2OAc), however, the yield of pyridoxol decreases and a new product was isolated which was identified as *N*-(5-desoxypyridoxo-



269b

278

279

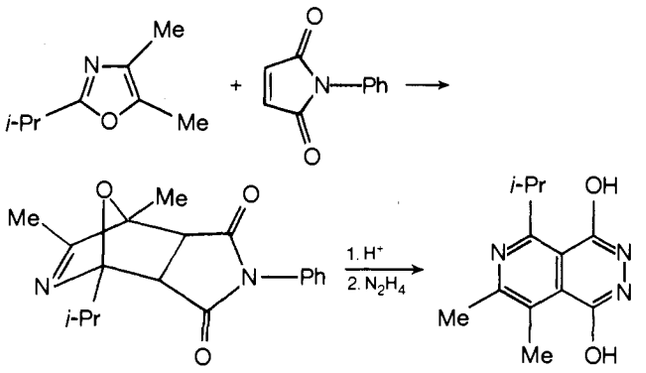
(127)

lyl)pyridoxol (**279**).[292] The proposed mechanism for the formation of **279** is given in eq 127. Although the stereochemistry of the acetoxymethyl groups of the adduct is not certain, an endo disposition of these substituents would lead to backside displacement of the oxido bridge by the carbonyl oxygen of the acetoxy group to give the oxonium ion (**278**). This seems to be the most likely stereochemistry in view of the tendency of cis dienophiles to form endo adducts. The addition of an external nucleophile, 3-hydroxypyridine, gives a high yield of products corresponding to **279** by the attack of 3-hydroxypyridine on **278.**

The potential of pathways A, C, or D as synthetic routes to substituted pyridines has not been thoroughly investigated because of the low reactivity of oxazoles not bearing a 5-alkoxy substituent. Nevertheless, several examples of these reaction pathways have been reported to give moderate yields of pyridines.[265]

The parent oxazole (**1**) reacts with acrylonitrile or acrylic esters in the presence of a trace of triethylamine to afford isonicotinonitrile and esters of isonicotinic acid by pathway A.[293] Similarly the reaction of 4,5-dimethyl- and 2,4,5-trimethyloxazoles with fumaronitrile results in the formation 2,3-dimethyl-4,5-dicyanopyridine (58%) and 2,3,6-trimethyl-4,5-dicyanopyridine (50%), respectively.[294]

3,4 - Dimethyl-5,8-dihydroxy-1-isopropyl-2,6,7-triazanaphthalene (**281**) was synthesized by the reaction of 2-isopropyl-4,5-dimethyloxazole with *N*-phenylmaleimide. Hydrolysis of the adduct **280** followed by treatment of the residue from this reaction with hydrazine afforded **281** in 47% overall yield.[295]

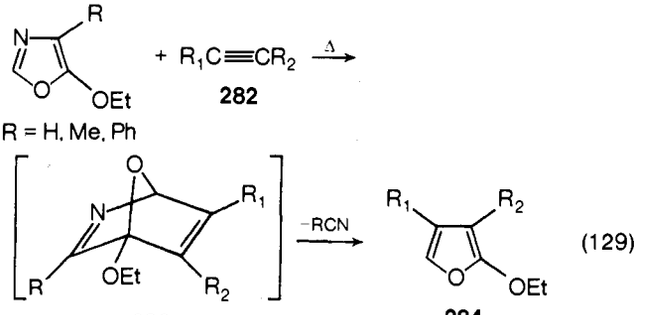


280 281

(128)

2. With Acetylenic Dienophiles

In contrast to the vast quantity of data which has been reported on the Diels–Alder reaction of oxazoles with olefinic dienophiles, only a few reports concerning this reaction with acetylenic dienophiles have appeared in the literature. Grigg et al.[296,297] and Huisgen et al.[298] reported the first examples of the thermal elimination of HCN or nitriles from the adduct **283** formed in the reaction of 5-ethoxyoxazoles with acetylenic dienophiles (**282**) to give the 2-ethoxyfurans **284** (eq 129). The adducts **283** could not be isolated although attempts were made to achieve this end.



282

R = H, Me, Ph

283 284

(129)

a, $R_1 = R_2 = CO_2Me$
b, $R_1 = Ph$; $R_2 = CO_2Me$
c, $R_1 = CO_2Me$; $R_2 = Ph$

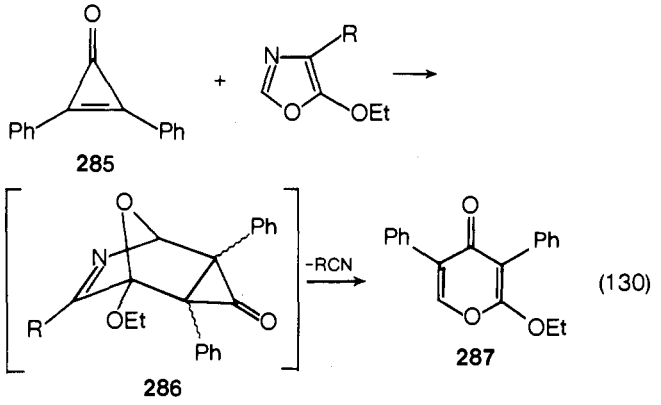
As in the case of unsymmetrical olefinic dienophiles unsymmetrical acetylenic dienophiles will add to oxazoles regioselectively to give adducts **283** with the carbon bearing the more electronegative group of the dienophile adding preferentially to the 5 position of the oxazole.[297,299]

For example, when the 5-ethoxyoxazoles are allowed to react with **282b** the isomeric 2-ethoxyfurans **284b** and **284c** are obtained in a ratio of 3:2. The rate of this reaction was enhanced by the addition of a BF_3 catalyst; however, the isomer distribution is unchanged.

The stabilization energies of the assumed transition states leading to the adducts **283** were calculated by the HMO method.[300] The predicted orientation of the addition generally agreed with the experimental results when these quantities were used as an index of reactivity.

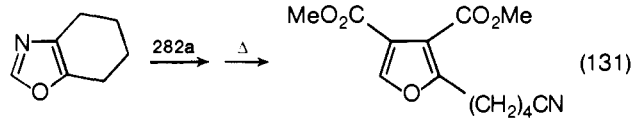
The reaction of diphenylcyclopropenone (**285**) with the 5-ethoxyoxazoles affords γ-pyrones (**287**).[296,297] The adduct **286** could not be isolated and consequently its stereochemistry could not be ascertained.

Stable adducts were obtained when 5-ethoxyoxazoles were allowed to react with diethyl azodicarboxylate or triphenylcyclopropene.[296] Although the yields of these products were given, no physical properties were reported nor was the stereochemistry of the latter adduct determined.



(130)

The reaction of 4,5-tetramethyleneoxazole with dimethyl acetylenedicarboxylate (**282a**) in refluxing ether gives methyl 2-(4-cyanobutyl)furan-3,4-dicarboxylate.[301] The bicyclic structure of the oxazole prevented the complete separation of a nitrile molecule in the retro Diels–Alder reaction. The addition of hydroquinone to the reaction mixture was generally found to increase the yield of furans.



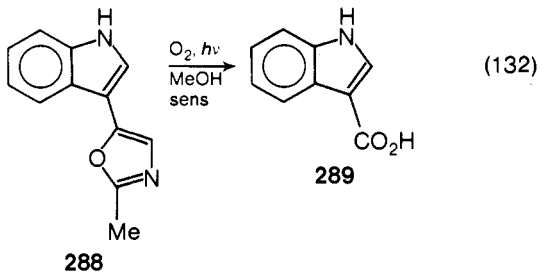
(131)

The use of dienophiles that are less reactive than **282a** such as AcC≡CH, AcC≡CAc, and butynediol diethyl acetal prohibit the Diels–Alder reaction with any but the most reactive oxazole dienes, the 5-alkoxyoxazoles. With each of these three dienophiles the corresponding 2-alkoxyfurans were obtained.[302]

H. With Singlet Oxygen

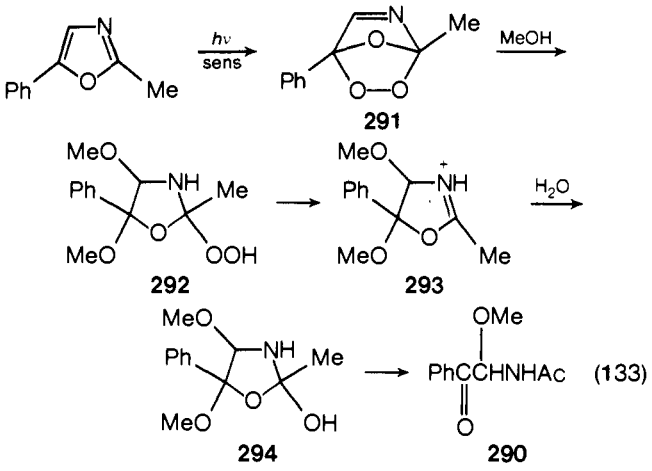
The reaction of oxazole derivatives with singlet oxygen was extensively studied by Wasserman and coworkers.

Wasserman and Floyd found that when the natural product pimprinine (**288**) was irradiated in methanol as the solvent, air as the oxidizing agent, and Methylene Blue as the sensitizer, a nearly quantitative conversion to indole-3-carboxylic acid (**289**) was effected.[303]



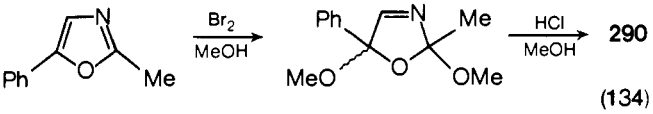
(132)

Similarly, 2-methyl-5-phenyloxazole was converted to benzoic acid (83%) and α-acetamido-α-methoxyacetophenone (**290**; 10%). The 1,4-addition of singlet oxygen to the oxazole to give the bicyclic ozonide **291** followed by attack of methanol leads to the methoxy hydroperoxide **292.** Intermediate **292** eliminates the hydroperoxide anion to afford the oxazolinium ion **293** which is attacked by water to form the oxazolidine **294.** The conversion of **294** to the product **290** is effected by the cleavage of the oxazolidine ring with elimination of methanol.[304] This pathway is analogous to that proposed for the photoxidation of furan derivatives.[305] The rupture of the C–O bond of the peroxide linkage of **291** with methanol is a known reaction of ozonides.[306] The amido ketone **290** was



(133)

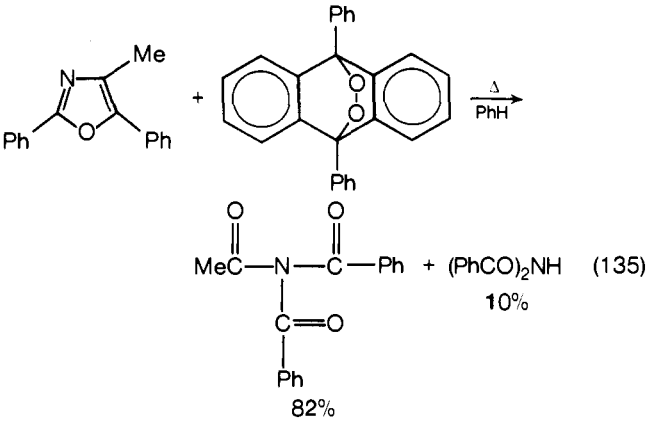
independently synthesized by the reaction of 2-methyl-5-phenyloxazole with Br_2/MeOH followed by treatment of the resulting Δ^3-oxazoline with methanolic HCl.



(134)

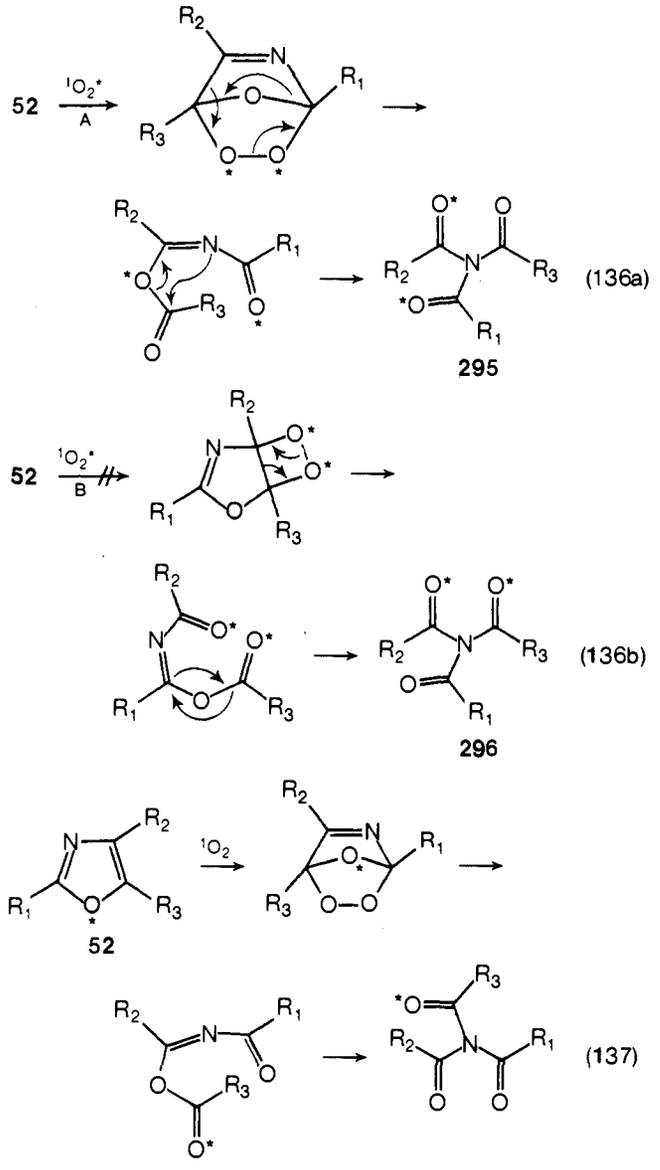
The participation of singlet oxygen in these photoxidation reactions was not confirmed until subsequent studies by Wasserman and coworkers were performed in which they investigated the thermal decomposition of 9,10-diphenylanthracene peroxide in the presence of known singlet oxygen acceptors.[307,308] This work established the fact that the thermal decomposition of the anthracene peroxide yielded singlet oxygen, and when oxazole derivatives were the acceptors the same products arose as those which resulted in the oxazole photoxidation.

Triamides are formed upon reaction of singlet oxygen with trisubstituted oxazoles in methanol.[303,308,309] When 2,4,5-triphenyloxazole is allowed to react with singlet oxygen, tribenzamide is obtained in 55% yield with small amounts of benzamide and benzoic acid being produced. Kurtz and Schechter[110] found that irradiation of 2,4,5-triphenyloxazole in ether or benzene in the presence of O_2 at >3000 Å yields tribenzamide, benzonitrile, and benzoic anhydride. The reaction of 2,5-diphenyl-4-methyloxazole with 9,10-diphenylanthracene peroxide gave *N*-acetyldibenzamide in 82% yield.[308]



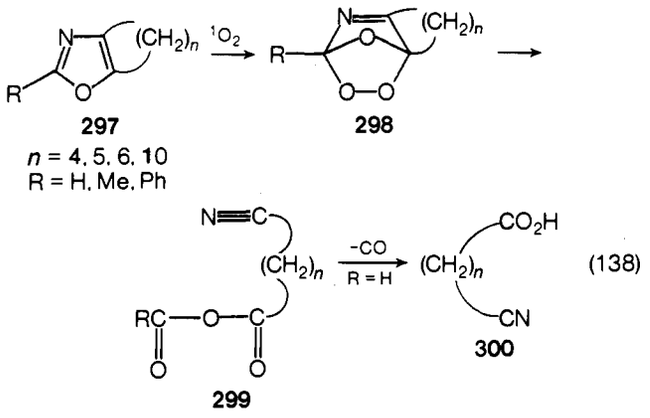
(135)

Two modes of addition of singlet oxygen to the oxazole nucleus are possible, i.e., 1,2- and 1,4-addition. To distinguish between these two pathways, labeled singlet oxygen (generated chemically from ^{18}O-labeled 9,10-diphenylanthracene peroxide) was added to an unsymmetrical trisubstituted oxazole (eq 136; * = ^{18}O).[310] A detailed mass spectral analysis of the reaction product demonstrated that **295** was formed

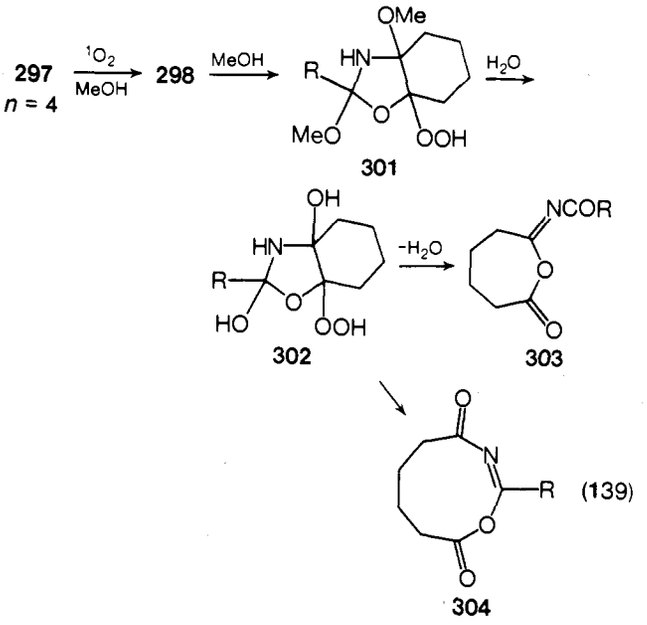


and consequently pathway A, the 1,4-mode of addition, is operative. Complementary results were obtained when the oxazole was labeled with ^{18}O (eq 137).

Oxazolocycloalkanes (**297**, R = H) combine with singlet oxygen in an inert solvent such as methylene chloride to afford cyano acids (**300**) in 80–90% yields.[311] The mixed anhydride **299** can be isolated when R = Me or Ph.

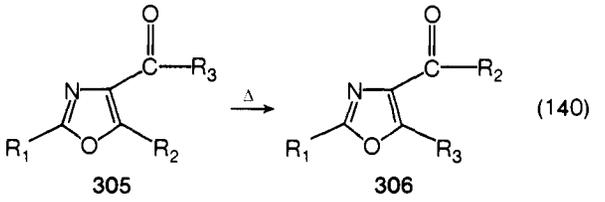


The reaction of **297** with singlet oxygen proceeds by a different course in a reactive solvent such as methanol, the *N*-acylimino anhydrides **303** and **304** being formed.[311] The mechanism of this transformation is analogous to those discussed above.[304] The hydroxy hydroperoxide **302** can decompose in two ways to give the observed products **303** and **304** (eq 139).



I. The Cornforth Rearrangement

The thermal rearrangement of 4-carbonyl substituted oxazoles was first observed by Cornforth.[2,4] When **305** is thermalized, the isomeric product **306** is obtained.



A special case of this rearrangement is the pyrolytic or base-induced isomerization of 4-hydroxymethylene-5-oxazolones or their potassium salts (**305a**) to oxazole-4-carboxylic acids (**306a**).[2,188] Stuckwisch and Powers have investigated the mechanism of this base-induced rearrangement by isotopic labeling experiments.[312] When the carbonyl carbon of the oxazolone ring was labeled with ^{14}C and the compound subjected to treatment with base, the rearranged oxazole-4-carboxylic acid was labeled only at the carboxyl carbon atom. The authors propose the initial attack of hydroxide ion at the 2 position of the oxazolone ring with subsequent ring opening to **307** and ring closure to yield the ^{14}C-labeled acid **306a**.

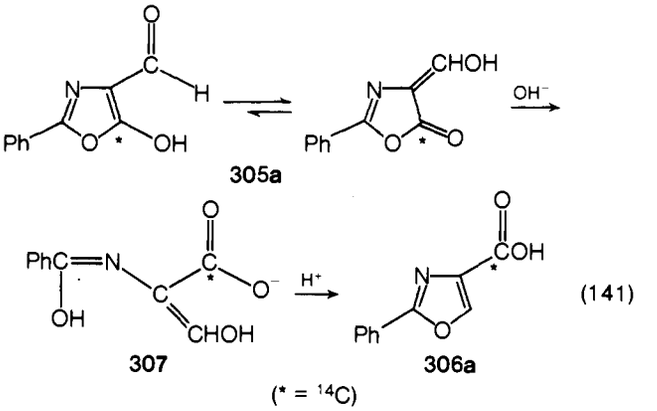


TABLE V. Derivatives of 305 Which Undergo the Cornforth Rearrangement

305	R_1	R_2	R_3	Ref
a	Ph	OH	H	4
b	n-C_5H_{11}	O^-	H	4
c	$C_3H_7CH{=}CH$	O^-	H	4
d	n-C_5H_{11}	OEt	Cl	4
e	Ph	OEt	Cl	4
f	$PhCH_2$	OEt	Cl	4
g	n-C_5H_{11}	Cl	H	4
h	Ph	Cl	H	4
i	Ph	OR[a]	NH_2	4, 313, 315
j	$PhCH_2$	OR[a]	NH_2	
k	X-Ph[b]	OR[a]	NR'R''[c]	313, 315
l	Ph	OR[a]	1-Imidazolyl	167

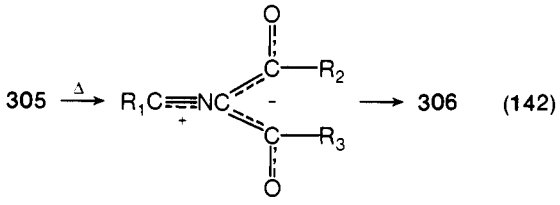
[a] R = Me, Et. [b] X = *p*-OMe, *p*-Me, *p*-*t*-Bu, *p*-F, *p*-Br, *p*-CF_3. [c] R', R'' = Y-Ph, H; Me, Me; Me, H; *t*-Bu, H; Ph, Me.

Table V summarizes the 4-carbonyl oxazoles (**305**) which will undergo thermal rearrangement to **306.**

The extent of the rearrangement **305** to **306** is dependent on the thermodynamic stability of **305** *vs.* **306.** All of the examples given in Table V are irreversible, affording **306** in yields of greater than 90% at temperatures of 90–120°.

The thermal isomerization of **305** (R_1 = Ph, R_2 = OEt, R_3 = OMe) to **306** (R_1 = Ph, R_3 = OMe, R_2 = OEt) produced an equilibrium mixture of **305:306** in a ratio of 65:35 at 95°. The rearrangement did occur for **305** (R_1 = Ph, R_2 = OMe, R_3 = SPh).[167]

The mechanism proposed for the thermal isomerization of **305** to **306** involves ring opening of the oxazole to the nitrile ylide intermediate (**308**) with subsequent ring closure to give the rearranged product **306.**[4,314] In aprotic solvents the rate of isomerization increased slightly with an increase in solvent polarity,[313] whereas a substantial increase in rate was observed in going from an aprotic ($PhNO_2$) to a protic solvent ($PhCH_2OH$).[315] The small rate increase upon increasing the solvent polarity in aprotic solvents suggests that little positive charge is built up in the transition state; however, the rate increase in the protic solvent suggests that a developing negative charge in the transition state is stabilized considerably by hydrogen bonding to the solvent.



(142)

308

The effect of varying the substituent X on the rate of the rearrangement of **305k** (R' = Me, R'' = Ph) was investigated.[313] A plot of log k vs. σ^+ was linear with $\rho^+ = -1.16$. The negative value of ρ^+ implies that a small positive charge develops at the 2 position of the oxazole ring in passing from **305** to the transition state leading to the intermediate **308.** The effect on the rate of isomerization upon varying the Y substituent of the *N*-aryl moiety of **305** (R_1 = Ph, R_2 = OMe, R_3 = NHPh–Y) was also noted. A plot of log k vs. σ was again linear with ρ = 0.34. The small positive value of ρ suggests that some negative charge develops in the amide moiety in going from **305** to the transition state. Increasing alkyl substitution on the amide nitrogen in **305k** decreased the rate of rearrangement.[315] The activation energy for the isomerization of **305l** to **306** is 26.8 kcal/mol.

The implications of the kinetic study of the Cornforth rearrangement were substantiated by the results of MINDO/3 calculations carried out in our laboratories.[167] Full details of these calculations will be published in due course.

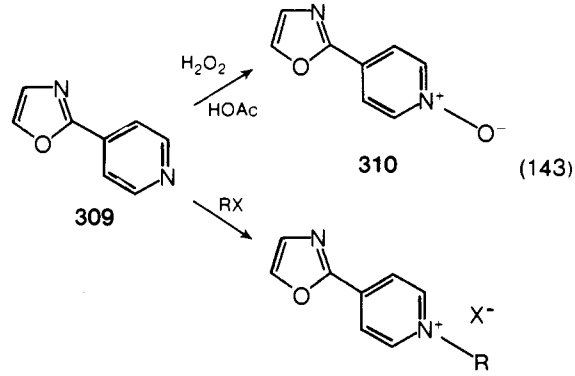
The thermal rearrangements of 4-acryl-Δ^2-oxazolin-5-ones (**50**) and 2-acyl-Δ^3-oxazolin-5-ones (**53**) to oxazoles appear to be mechanistically analogous to the Cornforth rearrangement.[44] The mechanism proposed is the thermal extrusion of CO_2 leading to the nitrile ylide intermediate **51** (analogous to **308**) which upon cyclization affords the oxazoles **52** in high yields (eq 22).

This rearrangement has been utilized in the synthesis of 3,3,3-trifluoro-*N*-acylalanines, derivatives of 3,3,3-trifluoro-2-aminopropiophenone,[44] and other alanine derivatives.[316]

J. Miscellaneous Functional Group Transformations

Because of the stability of the oxazole ring toward a variety of reagents and conditions, it is possible to effect many functional group modifications. The oxazole ring is normally not stable to oxidative conditions. Cold permanganate, chromic acid, sodium hypobromite, fuming nitric acid, and ozone cleave most oxazole derivatives.[2] Osmium tetroxide–H_2O_2, however, will oxidize 2-(1-pentenyl)-4-styryl-5-ethoxyoxazole to the corresponding 2-carboxaldehyde. This is the only reported example of the synthesis of an oxazole-2-carboxaldehyde. Systems of this type are also stable toward $Pb(OAc)_4$ oxidation.[2]

Studies on the hypoglycemic activity of 4-(2-oxazolyl)pyridinium *N*-oxides[317] and 4-(2-oxazolyl)-*N*-alkylpyridinium salts[318] have shown the greater reactivity of the pyridine nitrogen relative to the oxazole nitrogen atom under conditions of oxidation and alkylation, respectively. When 4-(2-oxazolyl)pyridine (**309**) was treated with H_2O_2/HOAc (peracetic acid), only the pyridine *N*-oxide **310** was isolated. This result is not surprising considering the fact that 2,5-diphenyloxazole (**132b**) is not oxidized under these conditions (section VI). A similar observation was made when **309** was allowed to react with alkyl halides affording only the *N*-alkylpyridinium salts (**311**).

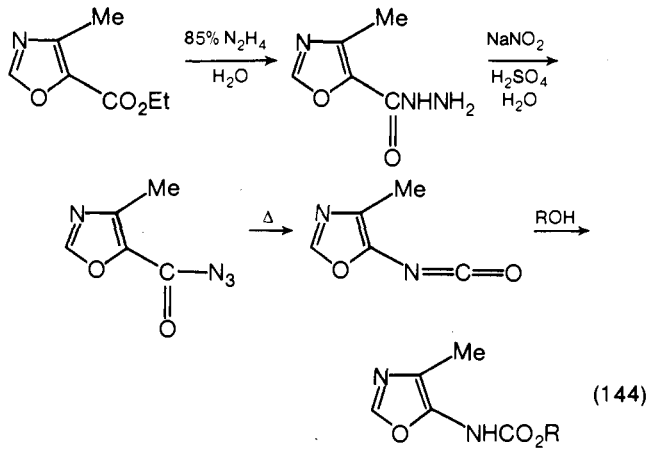


(143)

Numerous examples of functional group conversions of substituted oxazoles have been reported by Cornforth.[4] These reactions demonstrate the wide variety of conditions to which oxazoles may be subjected without ring cleavage. Unfortunately, very little data exist concerning the reactions of oxazole derivatives with the myriad of new reagents developed in the last 15 or 20 years by synthetic chemists.

The Curtius rearrangement of acyl azides to isocyanates has been applied to the synthesis of 2-[253] and 5-oxazole[319] carbamate esters. Equation 144 exemplifies the utility of this conversion.

Several methods for the synthesis of oxazolylethylenes have been reported. The condensation of nitroethane with 2-benzyloxazole-4-carboxaldehyde (**312**) in the presence of *n*-butylamine affords 1-(2-benzyloxazol-4-yl)-2-nitropropene (**313**).[320]



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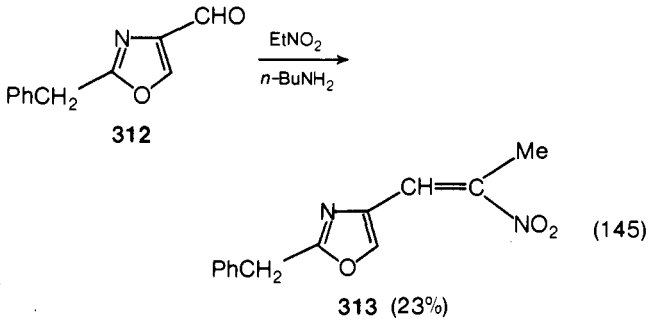
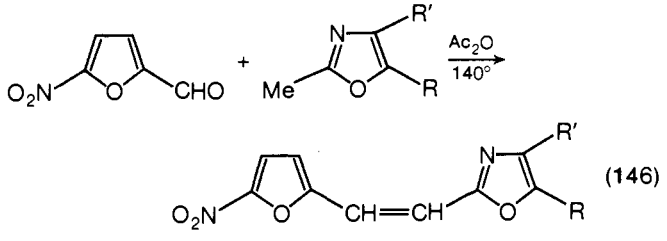


312

(145)

313 (23%)

2-(5-Nitro-2-furylvinyl)oxazoles were prepared by the reaction of 2-methyloxazoles with 5-nitro-2-furfural and Ac_2O.[321] These compounds are active against a variety of bacteria, trichomonads, and fungi. The reaction of 2-methyloxazoles with other aldehydes was not reported; however, this condensation is a potentially general synthesis of 2-azolylethylenes.



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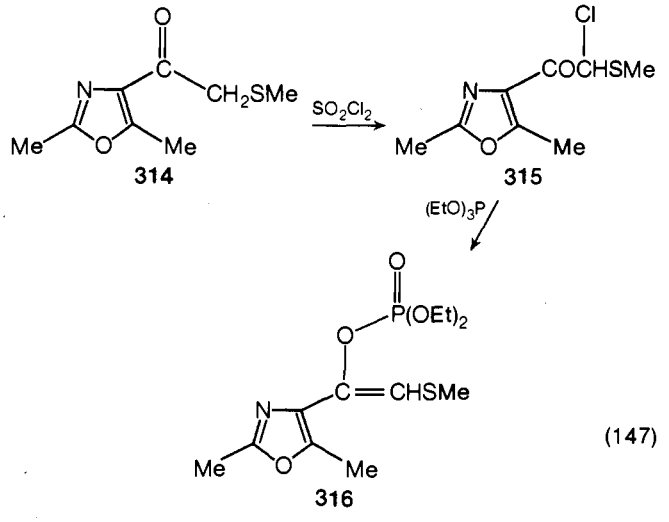
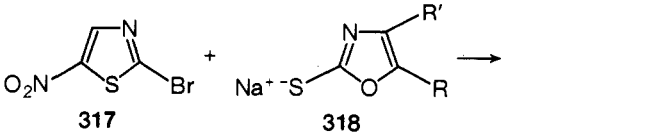
Methyl thiomethyl-4-(2,5-dimethyloxazolyl) ketone (**314**) undergoes chlorination with SO_2Cl_2 to give the chloro ketone **315.** When **315** is treated with triethyl phosphite in refluxing toluene, the oxazolylethylene **316** is formed in 47% yield.[322] Compound **316** and other (alkylthio) vinyl phosphate esters are useful as insecticides and acaricides.



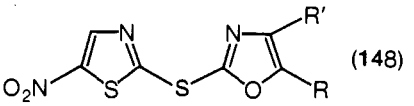
(147)

316

The synthesis of 2-(5-nitro-2-thiazolyl)thiooxazoles (**319**) by the nucleophilic displacement of bromine from 5-nitro-2-bromothiazole (**317**) with the Na salt of 2-mercaptooxazoles (**318**) has been reported.[323]



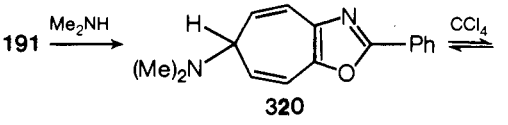
317 318



(148)

319

The preparation of oxazolotropylium salts (**191**) has been discussed in section II.Q. When these salts are treated with dimethylamine, 6-dimethylamino-2-phenyl-6*H*-cycloheptoxazole (**320**) is produced.[324] The nmr spectra of **320** in CCl_4 solution changed after several days at room temperature. The new nmr spectrum was due to the products formed upon the rearrangement of the dimethylamino group from the 6 to the 4 position and subsequently to the 8 position of the cycloheptatriene ring (**321** and **322**, respectively).



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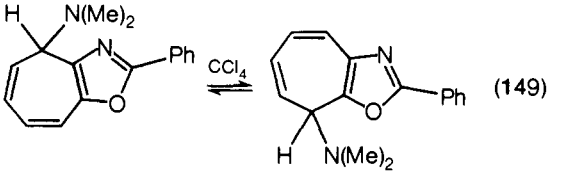


(149)

321 322

The structures of **321** and **322** were deduced by observing the NMR spectra of their deuterated analogs. The equilibrium ratio of **320:321:322** was found to be 3:5:2 after 3 days in CCl_4 solution. The rate of the rearrangement of **320** to **321** and **322** was much greater in methanol than in CCl_4, suggesting that the isomerization is ionic in nature. A *p*-nitro group on the 2-phenyl substituent of the oxazole ring diminishes the rate whereas a *p*-methyl group accelerates the rate of this rearrangement, again suggesting an ionic process. Crossover experiments suggest that the rearrangement is intermolecular. The compound analogous to **320** bearing 6-*p*-toluidino substituent did not isomerize under these conditions.

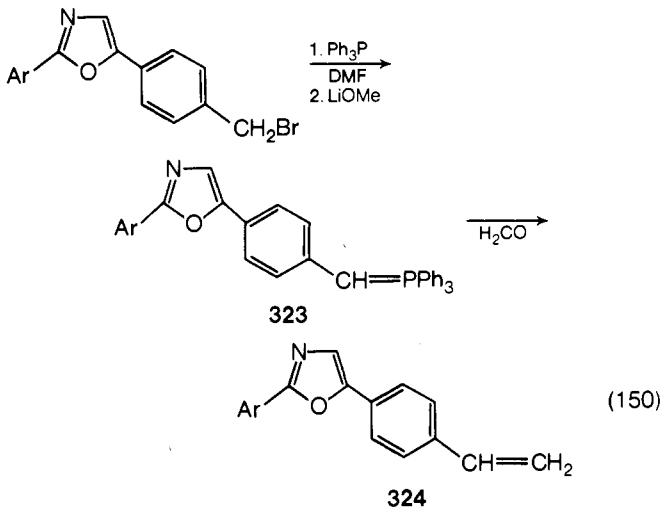
K. Polymerization Studies

The Robinson–Gabriel oxazole synthesis has been used in the preparation of 2-vinyl- and 2-isopropenyloxazoles. Radical homo- and copolymerization of the monomeric vinyloxazoles with styrene was initiated with azobisisobutryonitrile.[325-328] The anionic polymerization of these monomers was studied with sodium naphthalenide or α-methylstyrene tetramer as an initiator. Equilibrium concentrations of monomers and polymers were determined at various temperatures, and the thermodynamic quantities, ΔH and $\Delta S°$ were calculated.[329]

The Wittig condensation of the phosphorus ylides **323** with formaldehyde gave 2-[330] or 5-(*p*-vinylphenyl)oxazole[331] monomers (**324**) in moderate yields.

Copolymerization of 2-(*p*-vinylphenyl)-5-phenyloxazole with styrene (AIBN initiator) was studied.[332] A 9:1 molar ratio of the oxazole monomer to styrene gave a copolymer containing 98% oxazole and 2% styrene.

Polyamides containing the structural unit **326** were prepared by the reaction of bis(4-ω-aminoacetylphenyl) ether

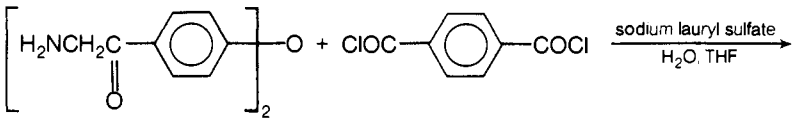


323

324

(150)

(325) with terephthaloyl chloride. Cyclodehydration occurred upon heating **326** to 300° (2 mm) to give the polymeric oxazole **327**.[333]



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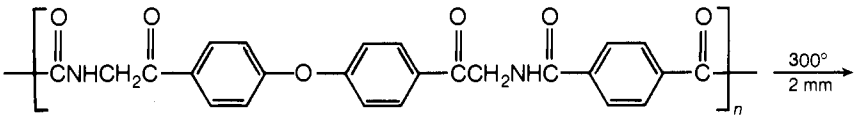

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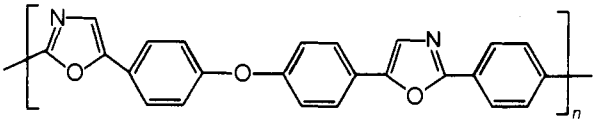

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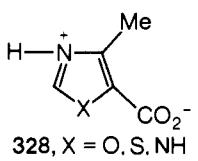
327

V. Oxazolium Salts

A. Basicity of Oxazoles

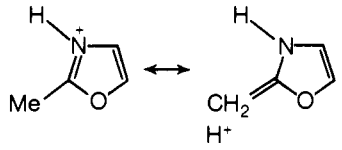
Oxazoles are extremely weak bases as is evidenced by the instability of their N-protonated salts.[2] If a 2-pyridyl substituent is present on the oxazole ring, the former is alkylated preferentially.[189,318,334] A 4- or 5-pyridyl substituent gives diquaternary salts with excess of the alkylating agent, the pyridine nitrogen presumably being alkylated first.

A comparison of the basicities of oxazoles, thiazoles, and imidazoles resulted in the first reported pK values for oxazoles.[335] The basicity of 4-methyloxazole (pK_{BH^+} = −1.07) was *ca.* 10^2 times less than 4-methylimidazole. The pK_{HA} values for the azolecarboxylic acids were also reported. The values obtained for 4-methyloxazole-5-carboxylic acid (2.88) and 4-methylthiazole-5-carboxylic acid (3.51) were consistent with the ionization of the CO_2H functionality rather than the ionization of the zwitterionic form of these compounds **328**. This behavior is in contrast to that of the corresponding imidazole which does undergo ionization of the N^+–H moiety of **328**.



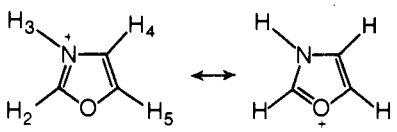
328, X = O, S, NH

Brown and Ghosh reported a thorough and quantitative study of the basicities of oxazole and several of its derivatives.[177] The pK_a values of these compounds were estimated from a plot of the chemical shift of the 2-proton vs. the pH or H_0 values of the acidic solutions used to measure the nmr spectra. The pK_a for the parent oxazole (**1**) was found by this method to be 0.8 which indicates that pyridine is some 10^4 times stronger as a base than oxazole (**1**). A plot of pK_a vs. the Hammett σ_m for 4-methyl- and 2,4-dimethyl-5-substituted oxazoles gave two nearly parallel lines both having negative slopes indicating that electron-withdrawing 5-substituents decrease the basicity of oxazoles. Introduction of a 2-methyl substituent increases the pK_a by 1.6 units whereas a 4- or 5-methyl substituent increases this value by only 0.6 unit. The difference between the 2- and 4-methyl compounds seems too large to be rationalized by a simple inductive effect. A possible rationale for the abnormally large increase in the base strength of the 2-methyl- vs. the 4-methyloxazole would be a consideration of the hyperconjugative stabilization of the oxazolium cation by the 2-methyl group (i.e., **329**). Similar hyperconjugative interaction between a 4- or 5-methyl substituent and the ring nitrogen atom leading to resonance structures analogous to **329** is clearly impossible for the 4- and 5-methyloxazolium cations.



329

A considerable downfield shift of the oxazole ring protons occurs upon deuteration with DCl/D_2O.[177] The downfield shift ranged from 1.09 to 1.64 ppm for the 2-proton, 0.62–0.67 for the 4-proton, and 0.42–0.63 for the 5-proton. The larger downfield shift of the 2- relative to the 4- and 5-protons is attributed to the partial positive charge of the oxygen atom in the oxazolium cation.



B. Acidity of Oxazoles and Oxazolium Salts

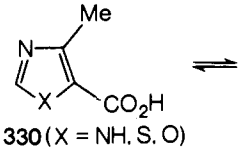
Breslow has established that ionization of the 2-proton in the thiazolium cation is crucial to the mechanism of thiamine

action.[336] Subsequent to Breslow's work, several groups have undertaken studies of acidities and exchange rates of the labile 2- and 4-protons in thiazolium, oxazolium, and imidazolium cations and their free bases and ^{13}C–H coupling constants in these heterocyclic compounds. The ^{13}C–H coupling constants for 4-methyloxazole are 231 and 209 Hz for the 2 and 5 positions, respectively and for the 4-methyloxazolium ion 247 and 224 Hz for these positions. The unusually high ^{13}C–H coupling constants reflect the high acidity of the 2 and the 5 positions in these systems.[337,338]

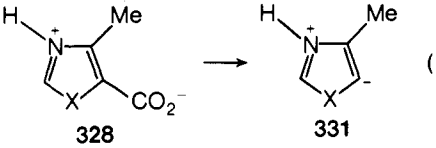
Deuterium exchange rates for the proton at C_2 in the 3,4-dimethyloxazolium cation is 10^2 times faster than that of the corresponding thiazolium ion and approximately $10^{5.5}$ times faster than the imidazolium cation.[339,340] The relatively rapid exchange rate for the 2-proton of the oxazolium ion is probably due to the high electronegativity of the adjacent oxygen atom relative to nitrogen or sulfur. Arguments concerning d–σ overlap stabilization of thiazolium ylides have been put forth in order to explain the much greater exchange rate for thiazolium vs. the imidazolium cations.[340]

Instantaneous deuteration occurred at the 2 position of oxazole and a slower 5-deuteration occurred in a DMSO-d_6 solution in the presence of NaOMe.[177] This result implies that the electron density at the oxazole carbon atoms is in the order 4 > 5 > 2, which agrees qualitatively with the results of all-valence electron MO calculations.[167,168,176] Electron-releasing substituents decreased the rate of 2-deuteration of oxazole, whereas electron-withdrawing groups increased this rate.[177,341,342]

Data which suggest that the decarboxylation of the azole-5-carboxylic acids (**330**) proceeds via the zwitterionic tautomers **328** has been obtained.[343] Decarboxylation of 3,4-di-

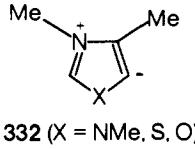


330 (X = NH, S, O)



328 331 (152)

methyloxazolium and thiazolium cations proceeds much faster than the same reaction of **330** (X = O, S) owing to a low equilibrium concentration of the zwitterion **328** which leads to decarboxylation in the neutral species. The relative rates for the decarboxylation of 3,4-dimethyloxazolium and thiazolium-5-carboxylic acids and 1,3,4-trimethylimidazolium-5-carboxylic acid are $10^{5.4}$, 10^3, and 1, respectively. This reactivity order is rationalized on the basis of the stability of the ylide **332.** It is assumed that the transition state for decarboxylation is similar in structure to this intermediate.



332 (X = NMe, S, O)

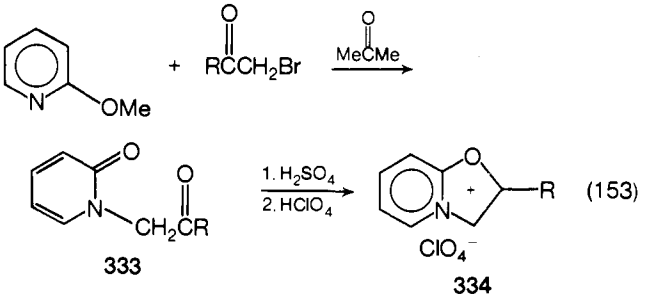
Thiamine is known to catalyze the conversion of pyruvate to acetoin in aqueous base solutions.[344] Complete loss of this catalytic activity was noted when the thiazolium ring of thiamine was replaced with an oxazolium ring.[345] Similarly, 3,4-dimethyloxazolium iodide had no catalytic activity in the benzoin condensation.[339] The factors which cause the loss of thiamine type activity in the oxazolium analogs of thiamine are not known; however, it is thought that the oxazolium ylide is so stable that it will not condense with the carbonyl compounds or that at pH's of 8 or higher the oxazolium ring is cleaved forming a catalytically inactive "pseudo-base."[345]

Hückel MO calculations predict that the 2 position of the azolium cations bears a large net positive charge. It has been proposed that it is this electron deficiency which is responsible for the lability of the proton at the 2 position of these systems.[346]

C. Syntheses and Reactions

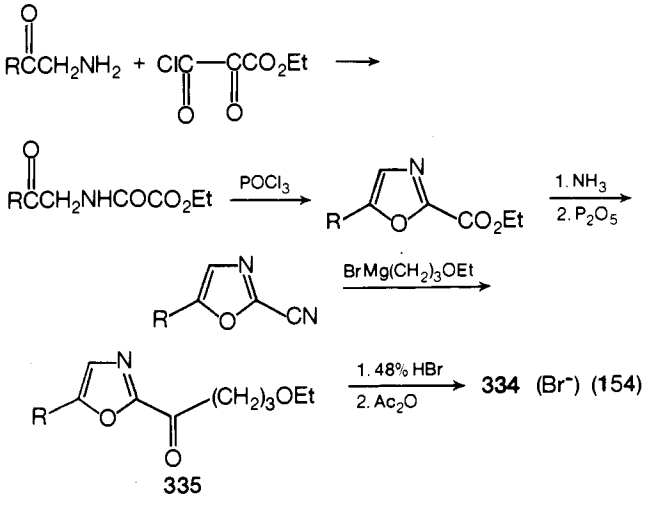
N-Methyloxazolium tosylates are readily obtainable by the reaction of methyl *p*-toluenesulfonate with oxazole derivatives. Anion exchange yields the chlorides, iodides, and perchlorates.[189,334]

Two synthetic approaches have been utilized in the preparation of the pyrido[2,1-*b*]oxazolium cation (**334**). The first involves the cyclization of the *N*-acyl-2-pyridone (**333**) with H_2SO_4.[347,348]



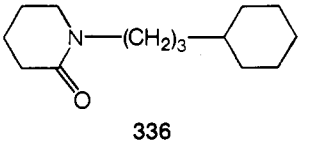
333 334 (153)

In the second route the 2-ethoxybutyryloxazole (**335**) is treated with 48% HBr, and the bromide obtained in this step is converted to **334** with acetic anhydride.[349] The nitration of



335 334 (Br⁻) (154)

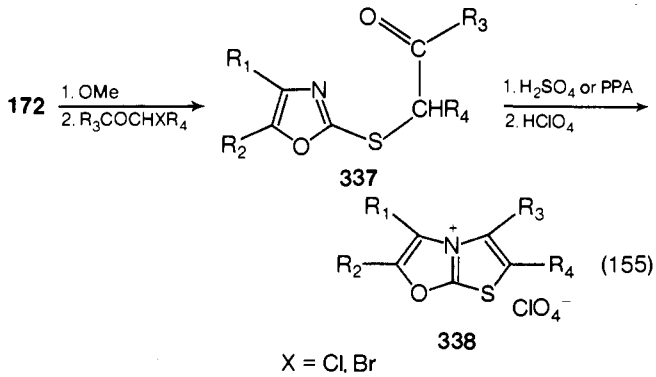
334 could not be effected: hydrogenation of **334** (R = $PhCH_2$) in the presence of Adam's catalyst led to the piperidone **336.**



336

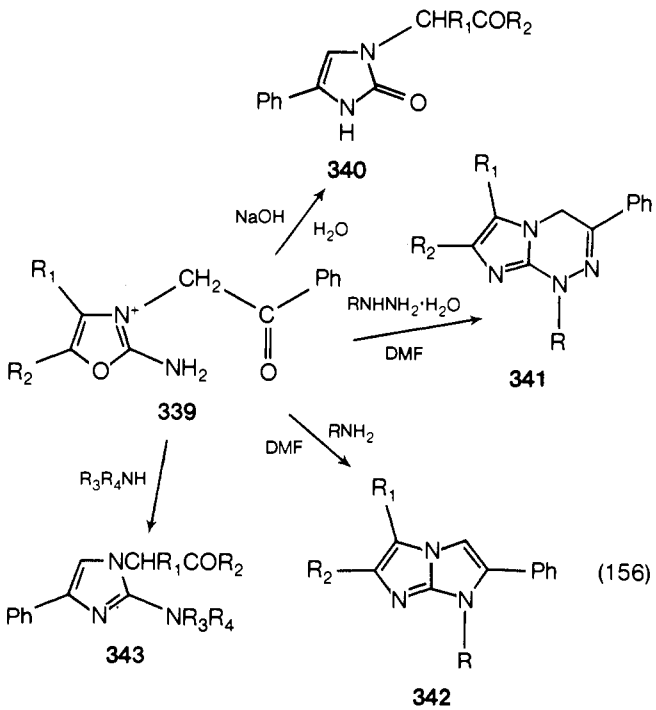
The ir, uv, and NMR spectra of **334** were recorded.[347-349] A notable point concerning the NMR spectrum of **334** (R = Me) was the presence of allylic coupling (1 Hz) between the 2-methyl substituent and the 3-proton.

The acid-catalyzed cyclodehydration of α-(2-oxazolylthio) ketones (**337**) resulted in the formation of novel thiazolo[2,3-*b*]oxazolium salts (**338**).[350] The salts **338** are less resistant toward alkaline hydrolysis than the corresponding thiazolo[2,3-*b*]thiazolium salts.



(155)

Hetzheim and coworkers have investigated the reaction of 2-amino-*N*-phenacyloxazolium salts (**339**) with nucleophilic reagents to form new heterocyclic systems. With aqueous NaOH, **339** yields the 2-imidazolone (**340**);[351] hydrazine hydrate reacts with **339** to afford 1,4-dihydroimidazo[2,1-*c*]-*as*-triazines (**341**);[352] primary and secondary amines give the imidazole derivatives **342** and **343**, respectively.[353] The imidazole derivatives **340–343** are postulated to have arisen via the nucleophilic attack of hydroxide ion or amines at the 2 position of **339** followed by opening of the oxazole ring and subsequent recyclization to form the products.

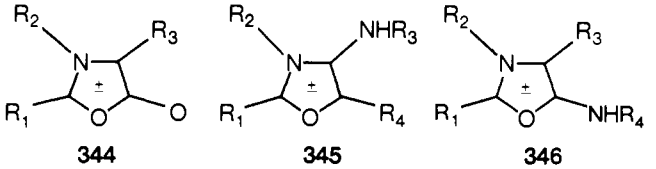


(156)

An analogous series of reactions has been observed for *N*-phenacyl-1,3,4-oxadiazolium cations.[354]

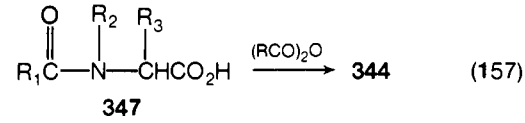
D. Mesoionic Oxazoles

The synthesis of 5-oxo-3,5-dihydrooxazoles (**344**), 4-imino-3,4-dihydrooxazoles (**345**), and 5-imino-3,5-dihydrooxazoles (**346**) and the reactions of **344** have been the subject of a review covering the literature up to 1967.[355]



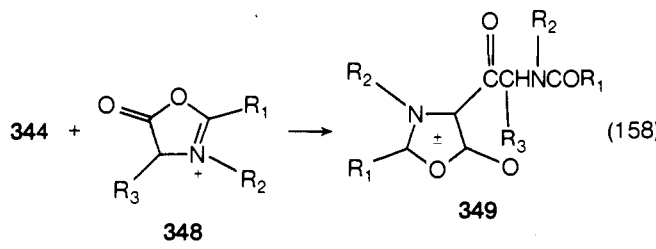
a, $R_1 = R_3 = Ph$; $R_2 = Me$

Compounds possessing the structure **344** are prepared by the cyclodehydration of N-substituted-α-acylamino acids (**347**) with acid anhydrides.[355]



(157)

The mesoionic oxazoles **344** with R_3 = H have not been isolated, these being immediately acylated by the anhydride. If dicyclohexylcarbodiimide is used as the dehydrating agent, a dimeric material with the structure **349** is obtained.[356] Com-



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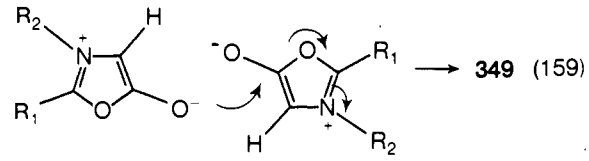
pound **349** presumably arises via the nucleophilic attack of **344** (R_3 = H) on the oxazolone **348** with subsequent proton removal. The mechanism of this reaction was investigated by



(159)

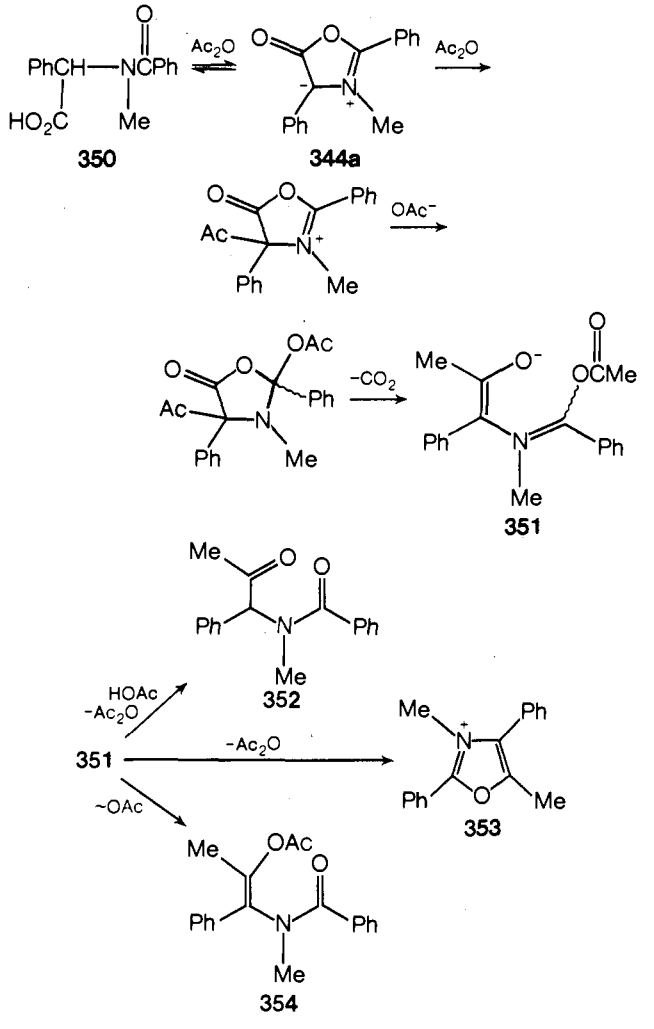
Boyd and Wright.[357,358] When triethylamine was added to 3-methyl-5-oxo-2-phenyl-Δ^2-oxazolonium perchlorate (**348**, R_1 = Ph; R_2 = Me)[359,360] in CH_2Cl_2 the mesoionic oxazole **349** is immediately formed. On the other hand, the formation of **349** was much slower when **348** was added to a methylene chloride solution of triethylamine. These results suggest that, in the first experiment, as soon as **344** is formed it is rapidly acylated in the normal manner by **348** which is present in excess. In the inverse addition, however, **348** is converted to **344** which then undergoes the dimerization reaction involving the nucleophilic attack on the free mesoionic oxazole which is less reactive in this respect than the oxazolonium salt (**348**).

The ir spectrum of the unstable mesoionic oxazole (**344**, R_3 = H) exhibited strong absorptions at 1730–1740 cm^{-1}. These bands are assigned to **344** owing to their gradual decrease in intensity.[358]

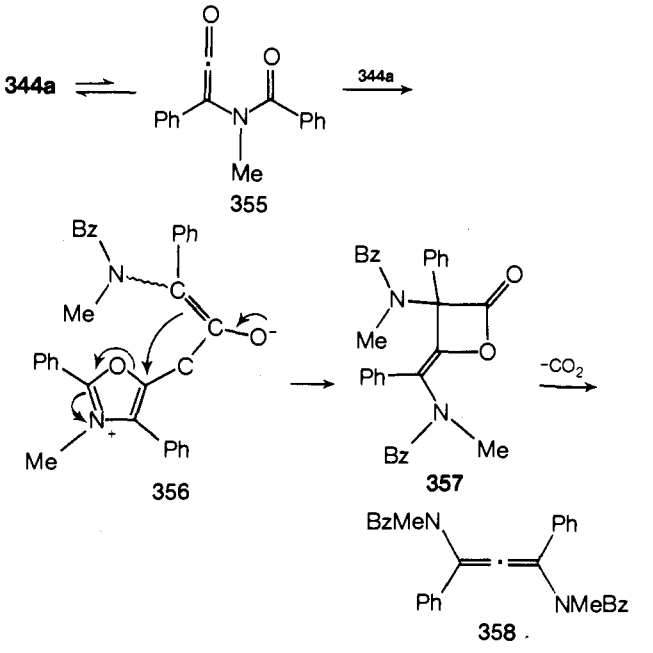
Kinetic experiments on this dimerization show that the *N*-methyl compounds (**344**, R_2 = Me) react more slowly than *N*-phenyl mesoionic oxazoles (**344**, R_2 = Ph). Phenyl substitution at the 2 position of **344** slows the dimerization; **344** possessing a 2-methyl substituent reacts immeasurably fast.[358]

The reaction of *N*-alkyl-α-acylamino acids (**350**) with Ac_2O/pyridine to afford *N*-alkyl-α-acylamino ketones (**352**) (*i.e.*, the Dakin–West reaction[361]) is thought to proceed via an intermediate mesoionic oxazole. Knorr and Huisgen investigated the reaction of 3-methyl-2,4-diphenyloxazolium 5-oxide (**344a**) with Ac_2O at 90°.[362] The results of their study led to the proposal of the mechanism in Scheme I for the Dakin–West reaction. The zwitterionic intermediate **351** may react further to give the normal Dakin–West product **352**, or cyclization may occur which leads to the oxazolium ion (**353**). The intramolecular nucleophilic attack by the enolate oxygen of **351** on the acetate carbonyl carbon leads to the rearranged product **354**. The product distribution depends upon the con-

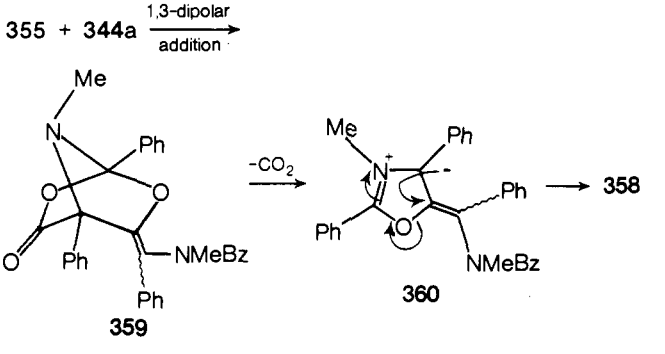
SCHEME I



MECHANISM I



MECHANISM II



centration of HOAc in the acetic anhydride used. High HOAc concentrations lead to the Dakin–West product **352.** Low HOAc content gives more of the side products **353** and **354** along with 1,3-dimethyl-2,5-diphenylpyrrole-4-carboxylic acid and 1-methyl-2,5-diphenyl-3-acetoxypyrrole. The formation of the latter two products, which is more difficult to explain by this mechanism, was rationalized on the basis of the zwitterionic intermediate **351.**

Huisgen and coworkers reported the ir and uv spectra of several derivatives of **344** (R_1 = Ar, R_2 = Me, R_3 = Ar').[363]

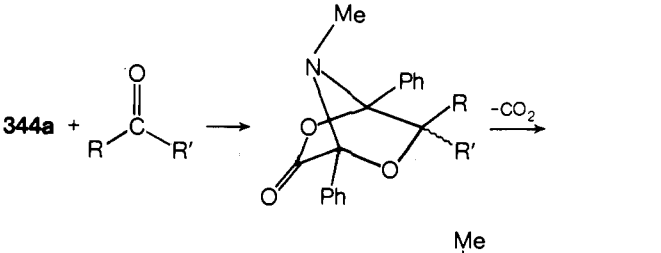
The rate of the thermolysis of **344** at 115–140° to give the 1,3-allene diamide **358** was also studied.[363] Two mechanisms (I and II) both involving a ketene valence tautomer (**355**) of **344a** have been postulated for this reaction.

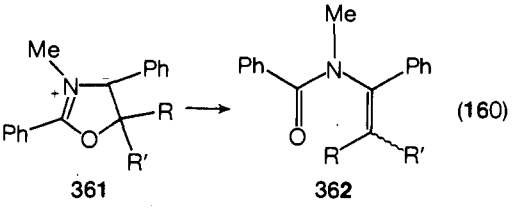
Mechanism I was discounted owing to the fact that ketene dimers analogous to **357** are known to eliminate CO_2 to give allenes at much higher temperatures (450–600°) than the temperature of the thermolysis of **344.** The more likely pathway, Mechanism II, is analogous to the 1,3-dipolar addition of carbonyl compounds to **344** yielding a cyclic ylide intermediate **361** followed by rearrangement of **361** to an *N*-vinylamide derivative (**362**).[364]

The activation parameters for the thermolysis of **344** were $\Delta H^{\ddagger}$ = 19.1 kcal/mol and $\Delta S^{\ddagger}$ = −17.5 eu as determined from the kinetic data. The ketene valence tautomer **355** has not, however, been observed spectroscopically presumably owing to its low equilibrium concentration.

The ring opening of **344** with various nucleophiles HX (X = OH, OMe, OEt, NHPh-*p*-Me) to give the N,N-disubstituted benzamides **363** was also investigated by these workers.

The valence tautomer **355** of **344a** adds to imines or carbodiimides in a 1,2 manner to give azetidinones or azetidinone imines, respectively.[355,365] Similarly, a 1,2-addition of **355** to the C=C of 1-morpholino-1-cyclopentene followed by rupture of the four-membered ring of the adduct **364** affords the β-morpholino-α,β-unsaturated-α-acylamino ketone (**365**).[365,366]





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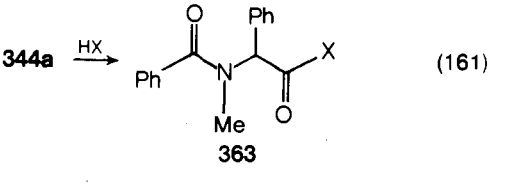

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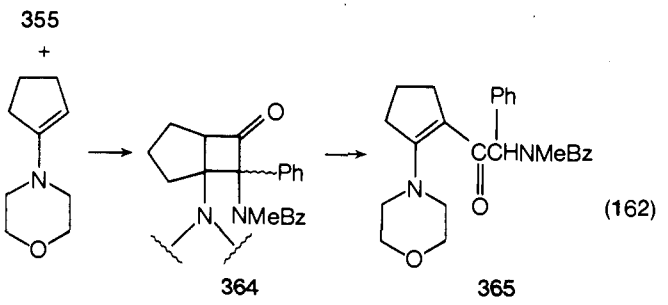
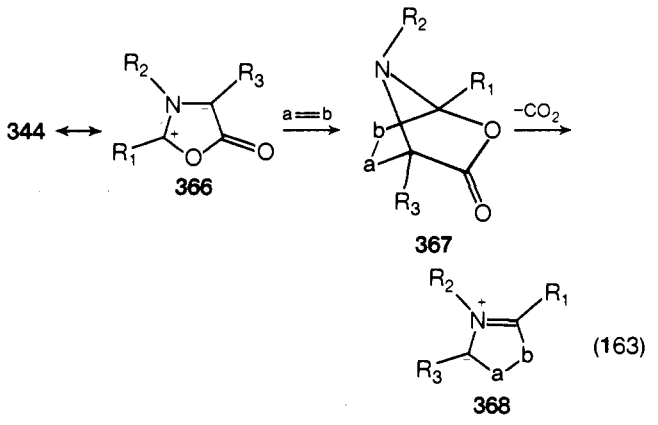


(162)

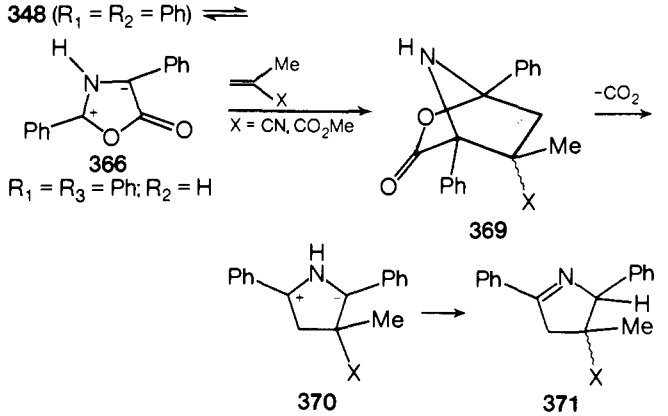
1,3-Dipolar additions of a variety of dipolarophiles to **344** have been studied.[355] The dipolarophile adds to C_2 and C_4 of **344** via the resonance structure **366** to give an adduct **367** which is not isolable. The adduct **367** will, in every case, eliminate CO_2 to give a new five-membered ring **368**. Intermediate **368**, a cyclic azomethine ylide, will undergo further transformations, the nature of which are determined by the structure of the dipolarophile, a=b.



(163)

The reaction of olefinic or acetylenic dipolarophiles with **344** (R_2 = Me,Ph) affords Δ^2-pyrrolines or pyrroles, respectively.[355] Olefinic dipolarophiles add to **344** (R_2 = H) to give Δ^1-pyrrolines (**371**) after loss of CO_2 from the adduct **369** and tautomerization of the azomethine ylide **370** (Scheme II).[122,367] The Δ^1-pyrroline **371** is the only regioisomer formed, and the major stereoisomer produced has the 4-R substituent situated trans to the 5-phenyl group.[122]

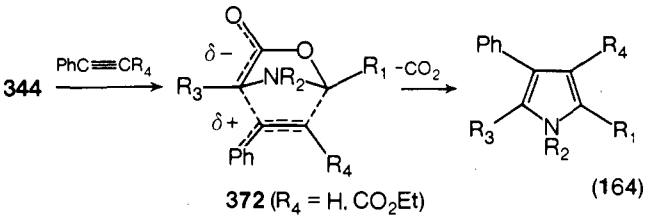
SCHEME II



The results of earlier work suggested that only olefins or acetylenes which are activated by electron-withdrawing groups will undergo the addition to **344.** Later research has expanded the scope of the addition to include alkyl and aryl olefins[368] and acetylenes.[369,370]

Unstable mesoionic oxazoles (e.g., **344**, R_3 = H) may be generated in situ and trapped with alkynes to give the corresponding pyrrole derivatives.[358,369,371]

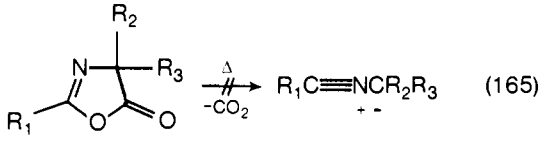
The observed orientation of the 1,3-dipolar addition of phenylacetylenes to **344** has been rationalized in terms of the possible transition state **372** leading to the adduct.[369] Electronic considerations such as the stabilization of the developing positive charge on **372** by the phenyl substituent are primary factors in determining the orientation of these additions, whereas steric interactions seem to play a secondary role.



(164)

Huisgen et al. have demonstrated that **344** will undergo 1,3-dipolar cycloadditions to a variety of heterodipolarophiles such as nitriles, nitro, nitroso, and azo compounds,[372] carbonyl,[364,373] and thiocarbonyl[374] compounds. A thorough discussion of the types of products formed in these additions is presented in the review of Ohta and Kato.[355]

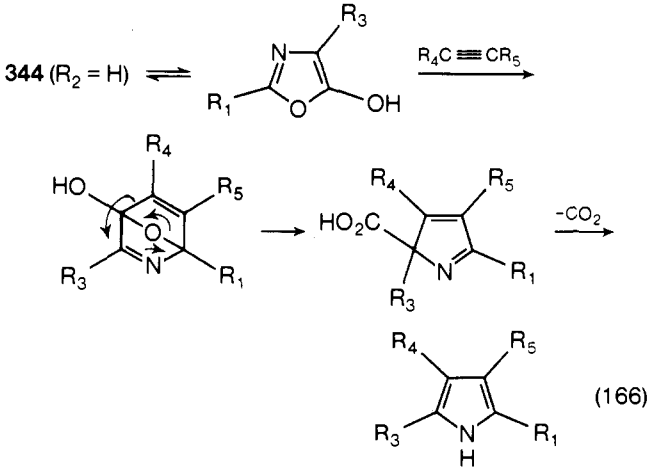
Further mechanistic studies concerning the Δ^2-oxazolin-5-ones **373** (R_2 = H) and their mesoionic oxazole tautomers **344** (R_2 = H) have established with some certainty that these compounds behave as 1,3-dipoles in their reactions with dipolarophiles.[298] The thermal extrusion of CO_2 from **373** (R_2 = H) initially leads to an acyclic ylide. Addition of a dipolarophile to this ylide also rationalizes the observed products. This alternative is unlikely, however, in view of the stability of 4,4-disubstituted Δ^2-oxazolin-5-ones (**373**, $R_2 = R_3$ = Me) toward thermal extrusion of CO_2.



(165)

373 ($R_2 = R_3$ = Me)

A second alternative to the direct 1,3-dipolar addition to **344** is the Diels–Alder addition of the dipolarophile (dienophile) to a 5-hydroxyoxazole tautomer of **344** (R_2 = H) and subsequent rearrangement of the adduct to give the observed products.



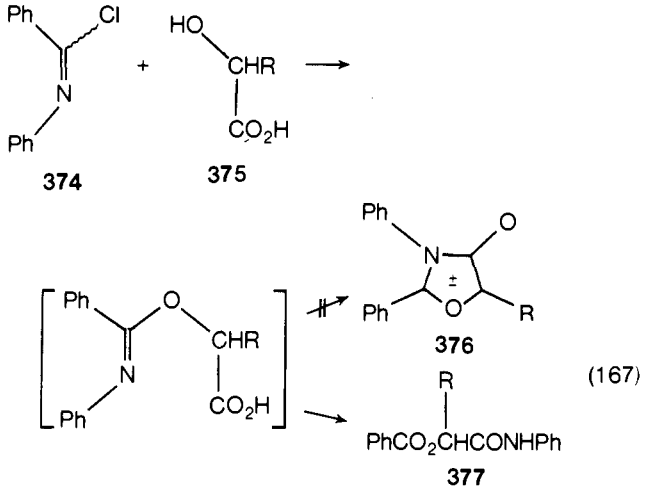
(166)

This mechanism is also unlikely because the Diels–Alder adducts of 5-alkoxyoxazoles with acetylenic dienophiles give furans with the elimination of a nitrile fragment, and, with olefinic dienophiles, pyridines are formed (section III.G).

Dissolution of the colorless Δ^2-oxazolin-5-one **373** (R_1 = R_3 = Ph, R_2 = H) in polar solvents imparts a yellow color to the solution. The position and intensity of the absorption band corresponding to the color (403–450 nm) is dependent upon the polarity of the solvent. Solvents of high polarity shift the band to lower wavelengths and markedly increase the extinction coefficient. This behavior is attributed to the equilibrium **373** ⇌ **344** (R_2 = H). Ir spectroscopy confirms the existence of this equilibrium.[298,375]

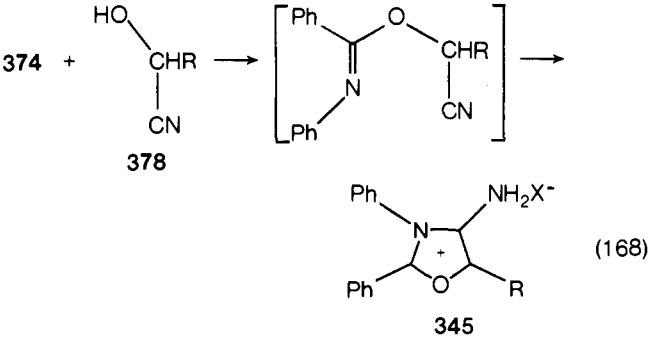
The relative rates and activation parameters for the cycloaddition of various dipolarophiles to **344a** have been determined.[376] The reactivity sequence for the dipolarophiles under study parallels the relative reactivity of these substances with other 1,3-dipoles. The large negative entropies of activation observed (−17 to −43 eu) are characteristic of 1,3-dipolar cycloadditions.[33,377]

Attempts at the synthesis of 4-oxo-3,4-dihydrooxazoles (**376**) by the cyclization of *N*-phenylbenzimidoyl chloride (**374**) with α-hydroxyacetic acid derivatives gave instead a rearranged product, the benzoyloxyacetanilide **377**.[378]



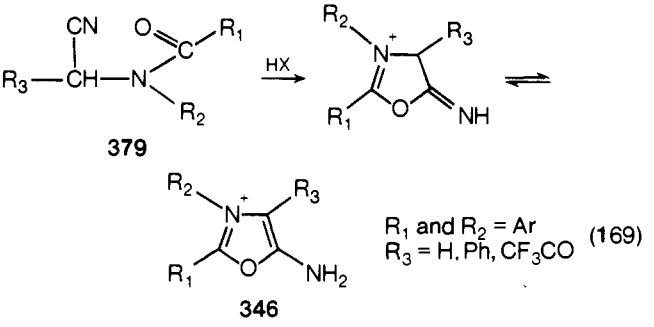
374 **375** **376** **377** (167)

These investigators did succeed, however, in preparing 4-imino-3,4-dihydrooxazoles (**345**) via the condensation of **374** with α-hydroxyacetonitrile derivatives (**378**). The ir exhibited strong bands at 3150–3350 cm^{-1} which are attributed to N–H stretching and at 1630–1680 cm^{-1} resulting from ring vibrations. The absorption maxima in the uv was around 300 nm.



378 **345** (168)

The synthesis of 5-imino-3,5-dihydrooxazole derivatives (**346**) was reported by Fleury et al.[379,380] and independently by Ohta et al.[381] by the cyclization of α-acylaminonitriles (**379**) with trifluoroacetic acid or HCl. The ir and NMR spectra of **346** are reported.[380] The uv spectrum of **346** (R_3 = CF_3CO) exhibits two maxima at 346–384 and 245–253 nm in ethanolic solution.[382] This is in contrast to 4-imino-3,4-dihydrooxazoles (**345**) whose long-wavelength maximum is at 300 nm.

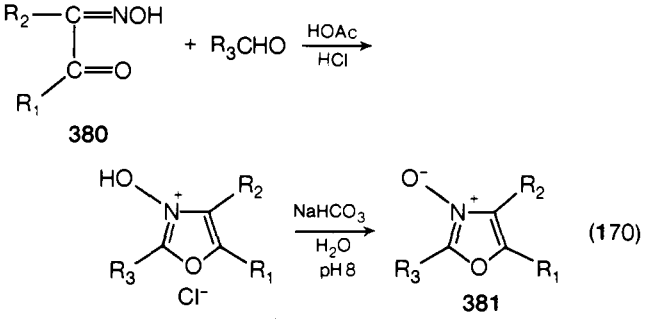


379 **346** R_1 and R_2 = Ar, R_3 = H, Ph, CF_3CO (169)

VI. Synthesis and Reactions of Oxazole N-Oxides

Although the first derivatives of oxazole *N*-oxides were prepared near the turn of the century,[383] very little is known concerning their syntheses, structure, and reactivity.[2,3,384] Oxazole *N*-oxides are unstable to light and decompose upon storage. Neither the parent nor any monosubstituted derivatives have been prepared thus far. The direct oxidation of 2,5-diphenyloxazole (**132b**) with peracetic acid failed to give the *N*-oxide; only starting material, benzamide, and benzoic acid were recovered. On the other hand, 2,5-dimethylthiazole formed its *N*-oxide in good yield under the same conditions.[334]

The only method which has been devised for the synthesis oxazole *N*-oxides (**381**) is that of Diels and Riley[383] which has been modified by Dilthey and Friedrichson[385] and by Selwitz and Kosack.[386] The method consists of the condensation of an aromatic aldehyde and an α-diketone monoxime (**380**) in glacial acetic acid saturated with HCl. Recently Weintraub has extended the scope of this synthesis to include aliphatic and heteroaromatic aldehydes.[387] With aliphatic aldehydes such as phenylacetaldehyde a phenyl moiety at C_4 and C_5 is necessary for the success of the reaction. (See Table VI.)



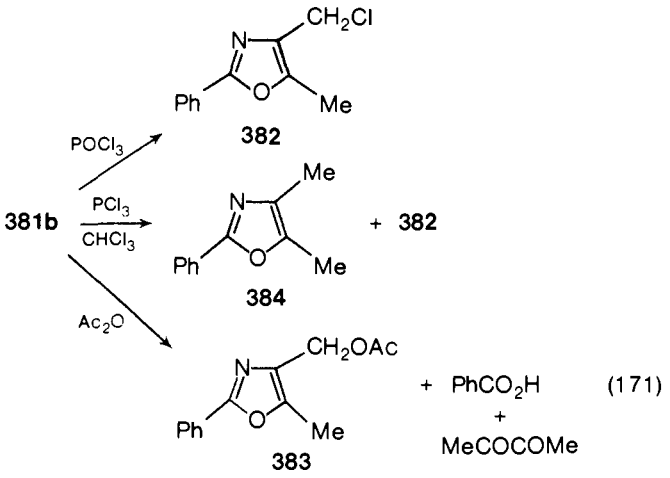
380 **381** (170)

Oxazole *N*-oxides (**381**) can be reduced to the corresponding oxazoles with Zn/HOAc[2,3] or triphenyl phosphite.[388] This conversion finds utility in the synthesis of substituted 4-acetyloxazoles.[191,388]

Deoxygenation of **381** also occurs with reagents such as PCl_3, $POCl_3$, and Ac_2O; however, when **381** bears a 4-methyl substituent, the 4-chloromethyl- and 4-acetoxymethyloxazole derivatives **382** and **383** are obtained using the phosphorus reagents and with Ac_2O, respectively, along with the 4-methyloxazole **384**. A 5-methyl substituent is inert to attack by these reagents.[190]

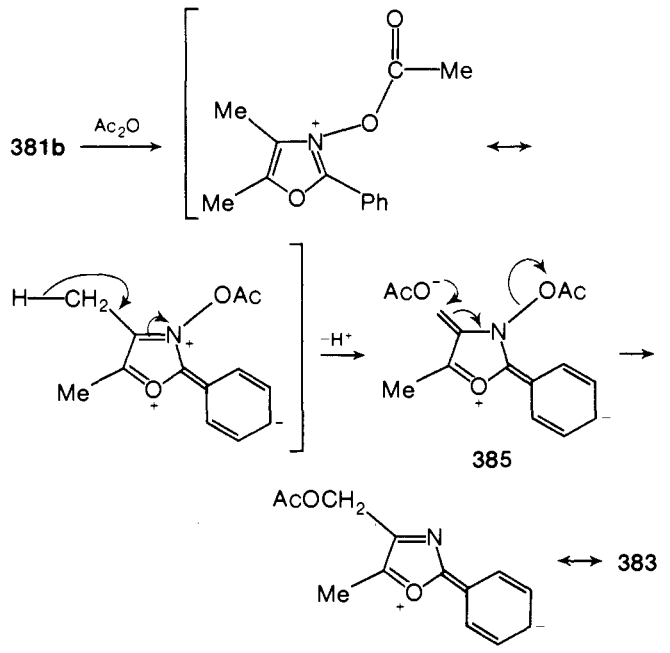
Mechanisms for the chloro- and acetoxymethylations as well as for the formation of ring-opened products were proposed. Both mechanisms involved O-phosphorylation or acetylation of **381** followed by loss of a proton from the 4-methyl group to give the intermediate **385** which is subsequently attacked by chloride or acetate anions to afford **382** or **383**, respectively (Scheme III shows the formation of **383**).

The Reissert reaction, i.e., the reaction of azaaromatics or their *N*-oxides with KCN and benzoyl chloride,[389] has been

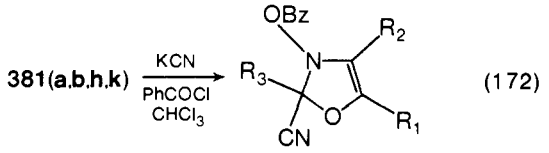


(171)

SCHEME III



applied to the synthesis of 2-cyano-*N*-benzoyloxy-2,3-dihydrooxazoles (**386**) from **381**.[390]

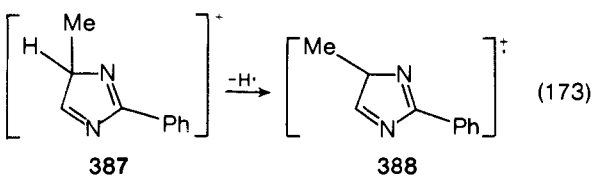


(172)

386

	R_1	R_2	R_3
a	Me	Me	*p*-anisyl
b	Me	Me	Ph
c	Ph	Me	*p*-anisyl
d	Ph	Me	Ph

The ir, uv, and mass spectral analyses of **389** were reported. The mass spectra of **386b** and **386d** showed peaks at *m/e* 157 and 156 which correspond to the 2*H*-imidazolium cation **387** and imidazole cation radical **388**. A mechanism for this fragmentation was proposed.



(173)

387 388

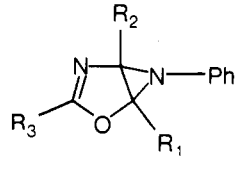
TABLE VI. Oxazole *N*-Oxides (381) Formed in the Reaction of 380 with Aldehydes[a]

381	R_1	R_2	R_3	Ref
a	Me	Me	*p*-Anisyl	384, 385
b	Me	Me	Ph-	384, 385
c	Me	Me	*p*-NO_2Ph	385
d	Ph	Me	*p*-NO_2Ph	385
e	Ph	Me	*m*-NO_2Ph	385
f	Ph	Ph	*m*-NO_2Ph	385
g	Ph	Me	*o*-NO_2Ph	385
h	Ph	Me	*p*-Anisyl	385
i	Ph	Ph	*p*-Anisyl	385
j	Ph	Ph	Ph	385
k	Ph	Me	Ph	385
l	Me	Me	PhCH=CH	385
m	Ph	Me	3,4-Dioxymethylenephenyl	385
n	Me	Me	3,4-Dioxymethylenephenyl	385
p	Ph	Me	*o*-HOPh	385
q	Me	Me	*o*-HOPh	385
r	Me	Me	2,4-$(HO)_2$Ph	385
s	Et	Me	Ph	190
t	Me	Ph	Ph	190
u	Me	Ph	*p*-Anisyl	190
v	Me	Ac	Ph	388
w	Me	Ac	*p*-ClPh	388
x	Me	Ac	*p*-Anisyl	388
y	Me	Ac	PhCH=CH	388
z	Me	Ac	*p*-NO_2Ph	388
aa	Me	CO_2Et	Ph	387
bb	Ph	H	Ph	387
cc	Me	Me	*p*-$(Me)_2$NPh	387
dd	Ph	H	*p*-NO_2Ph	387
ee	Ph	H	*m*-NO_2Ph	387
ff	Ph	Me	4-Biphenylyl	387
gg	Me	Me	*m*-(4,5-Dimethyloxazolyl-3-oxide)-phenyl	387
hh	Me	Me	4-Pyridyl *N*-oxide	387
ii	Me	Me	5-Nitrofuryl	387
jj	Me	Me	2-Thienyl	387
kk	Me	Me	5-Nitrofurylvinyl	387
ll	Ph	Ph	$PhCH_2$	387
mm	Ph	$PhCH_2$	Et	387
nn	Ph	Ph	H	387

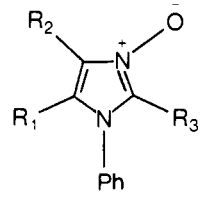
[a] Yields usually >50%.

The hydrochloride salt formation of various derivatives of **381** was studied.[391]

The reaction of **381a** and **381b** with phenyl isocyanate was reported to give a bicyclic compound with the structure **389**.[383] Later Cornforth and Cornforth considered structure **389** unlikely as the product of this reaction and alternatively proposed the imidazole *N*-oxide **390** to be the product.[5,384]



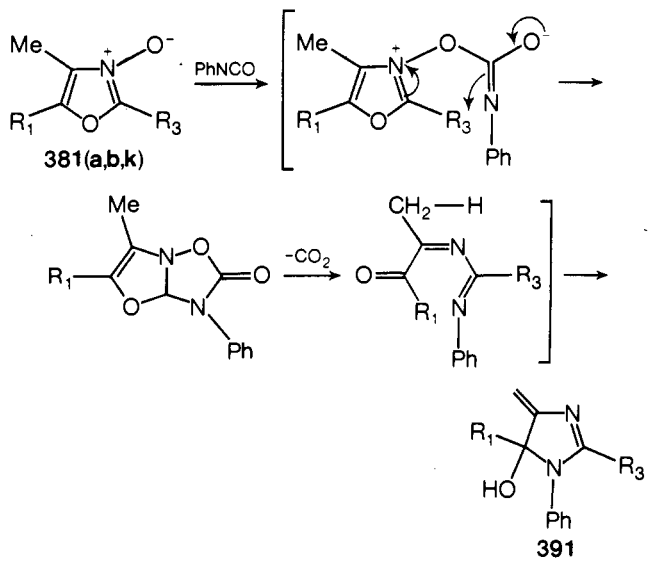
389



390

More recently Goto et al. have shown by spectral and chemical means that the correct structure is 1-phenyl-2-aryl-5-hydroxy-4-methylene-4,5-dihydroimidazole (**391**).[392] The mechanism proposed for the formation of **391** is the nucleophilic attack by the *N*-oxide oxygen on the carbonyl carbon of the isocyanate. Subsequent nucleophilic attack by the isocyanate nitrogen on the 2 position of the oxazole ring followed

SCHEME IV

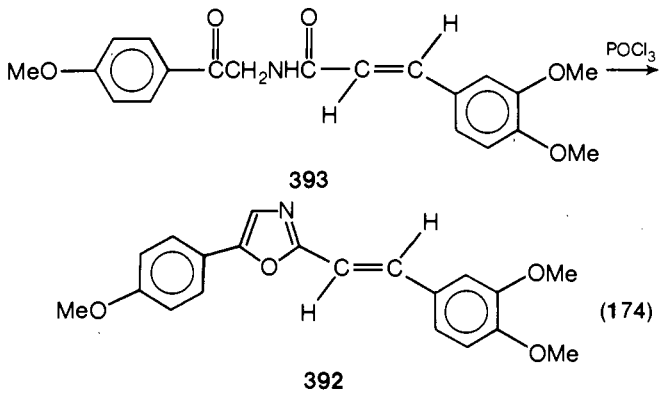


by ring opening with loss of CO_2 and ring closure affords **391** (Scheme IV).

VII. Naturally Occurring Oxazoles and Oxazole Analogs of Natural Products

The oxazole ring system seems to be extremely rare in nature, and all but one of the naturally occurring oxazoles are structurally simple substances bearing substituents at the 2 and 5 positions of the ring.

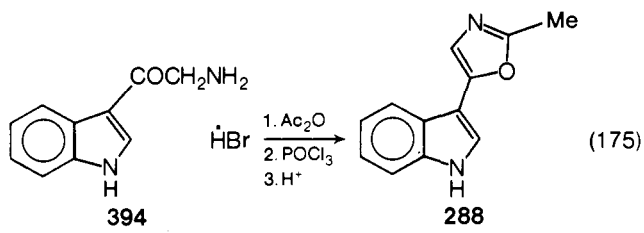
The first of the oxazole natural products to be isolated, characterized, and synthesized was annuloline (**392**), an alkaloid derived from *Lolium multiflorum*.[393,394] The structure of **392** was confirmed by spectral data and by its reaction with $KMnO_4$ to give anisic and varatric acids and by catalytic hydrogenation. Dehydration of the α-amido ketone **393** with $POCl_3$ afforded the natural product **392.**



(174)

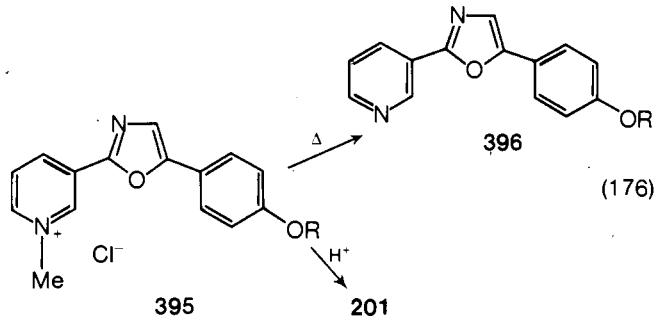
Studies concerning the biosynthesis of **392** were carried out using ^{14}C-labeling techniques.[395,396] Cinnamic, caffeic, and *p*-coumaric acids and tyramine were shown to be intermediates in the biosynthesis.

Pimprinine (**288**), obtained from *Streptomyces pimprina*, was shown to be 5,3'-indolyl-2-methyloxazole.[397] The key step in the synthesis of **288** was the dehydration of the corresponding α-amido ketone **394.**



(175)

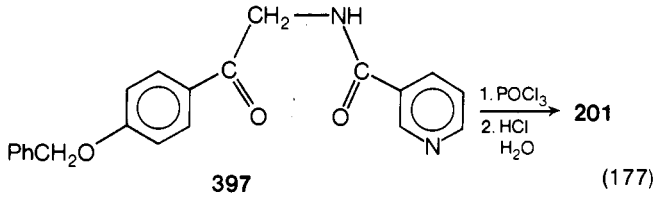
N-Methylhalfordinium chloride (**395**) was among the numerous alkaloids isolated from *Halfordia scleroxyla*.[214,215] Pyrolysis of **395** gave halfordine (**396**); strong acid hydrolysis of **395** produced halfordinol (**201**). On the basis of these and other chemical properties such as known oxazole degradation reactions as well as spectral analyses (see section III.G for a discussion of the mass spectral analysis), the structure **395** was assigned to *N*-methylhalfordinium chloride.



(176)

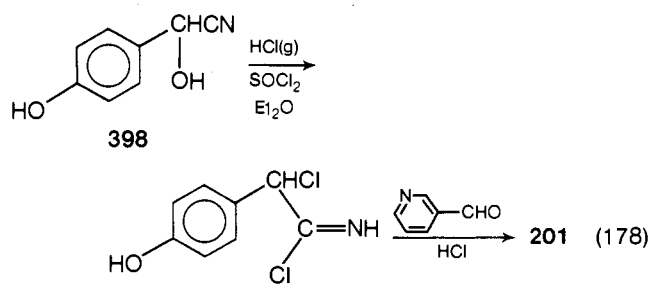
Dryer has demonstrated that the isomeric halfordinol isopentenyl ethers **396** (R = $CH_2CH{=}C(Me)_2$, $Me(CH_2)_2C(Me)H{=}CH_2$) occur in *A. chevalieri*.[398] These alkaloids are believed to be intermediates in the biosynthesis of halfordine (**396**).

Halfordinol (**201**) was first prepared by Brossi and Wenis via the usual cyclodehydration reaction of the α-amido ketone **397** and subsequent acid hydrolysis of the resulting *O*-benzylhalfordinol.[399]



(177)

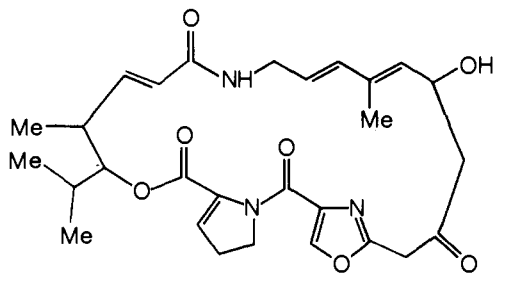
A modification of the Fischer oxazole synthesis was utilized in a convenient, one-step synthesis of **201.**[400] When *p*-hydroxymandelonitrile (**398**) was treated with nicotinaldehyde and dry HCl gas in the presence of $SOCl_2$, a 16% yield of **201** was obtained. Thionyl chloride apparently acts to prevent the dissociation of **398** to HCN and the aldehyde and thereby inhibits the formation of nicotinaldehyde cyanohydrin.



(178)

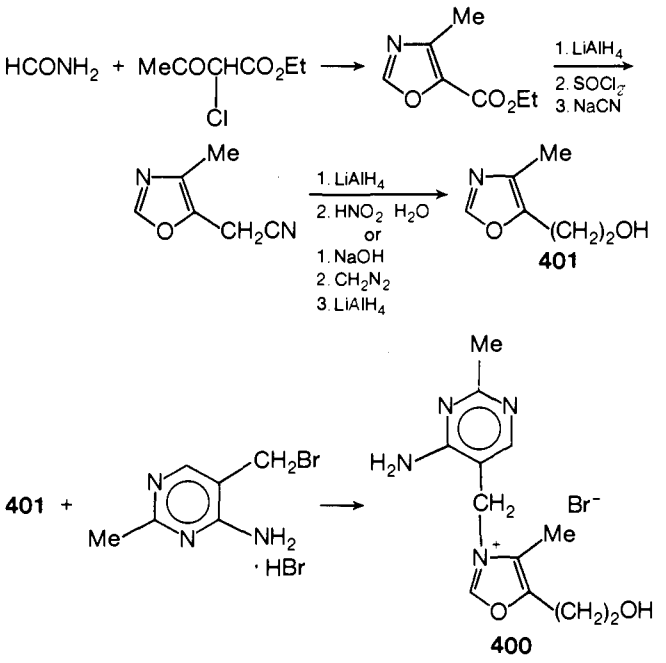
By far the most complex of the naturally occurring substances containing an oxazole ring is ostreogrycin A, one of a group of antibiotics isolated from the soil organism *Streptomyces ostreogriseus*.[401] The structure of ostreogrycin A (**399**) was elucidated by Todd et al. using a lengthy degradation scheme[402] and spectral analysis which included high resolution mass spectrometry and nuclear magnetic double resonance techniques.[403]

As a part of their studies on the structural specificity of vitamin B_1,[404] Dornow and Hell synthesized the oxazole analog **400** of thiamine (Scheme V).[405]



399

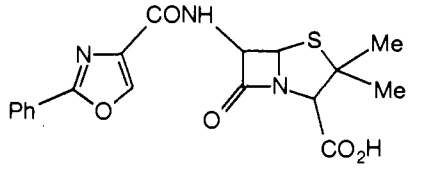
SCHEME V



401

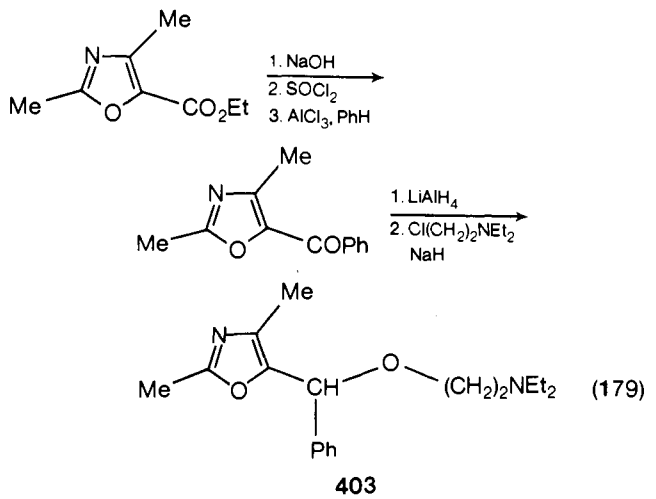
400

When 6-aminopenicillanic acid is allowed to condense with 2-phenyl-4-oxazolecarboxylic acid chloride, the oxazole analog of benzylpenicillin **402** is produced.[406]



402

A series of simple functional group transformations were utilized in the synthesis of heterocyclic analogs of the antihistaminic drug, diphenhydramine. Replacement of one of the phenyl groups of diphenhydramine by a 2,4-dimethyloxazolyl group gave the oxazole analog **403** of this drug. The antihistaminic activity of diphenhydramine is unequalled by any of its heterocyclic analogs.



403 (179)

The synthesis and anticonvulsant and hypnotic activity of oxazole isosteres of clomethiazole [5-(2-chloroethyl)-4-methylthiazole] were investigated by Lindberg et al.[408,409]

The cyclization of α-hydroxy enamides to oxazole novobiocin analogs has been discussed in section II.H. These compounds have also been prepared by the reaction of aromatic aldehydes with 3-amino-4-hydroxycoumarins in refluxing nitrobenzene.[410] Several of the oxazole novobiocin analogs were found to possess bacteriostatic and fungistatic activity.

VIII. Applications

A. Scintillator Properties[411]

The fluorescence properties of certain aryloxazoles were first investigated near the turn of the century.[412] Some 50 years later their effectiveness as solutes in liquid scintillators was discovered by Hayes et al.[413-415] The Robinson–Gabriel synthesis has been most effective in preparing 2,5-diaryloxazoles which can function as scintillator solutes.[416,417]

An *N,N*-dialkylaminophenyl group enhances the fluorescence of 2,5-diaryloxazoles. This phenomenon has been studied chiefly by Hayes and coworkers.[418]

The fluorescence and absorption spectra of 2,5-diaryloxazoles have yielded valuable information concerning the effects of molecular structure on scintillation ability.[419-427]

Investigations into the mechanism of energy transfer from solvents to organic scintillators have been undertaken in order to improve the efficiencies of liquid scintillators.[428-433] The effects of viscosity,[434] oxygen quenching,[435-439] and dimer and eximer formation[440-443] on the energy transfer process have also been investigated.

The luminescence decay times of oxazole scintillator solutes excited by uv and X-ray irradiation have been determined by Burton et al.[444,445] Yguerabide and Burton also investigated the effect of solute concentration on luminescence decay times.[446]

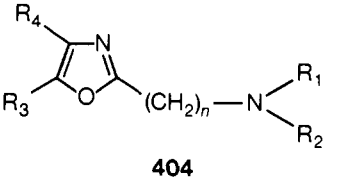
The properties of 2,5-diaryloxazoles and -oxadiazoles as solutes in plastic scintillator solutions have been studied. These compounds are more effective in this respect than are terphenyls.[447-449]

An improved liquid scintillant using 2,5-diphenyloxazole (**132b**) and naphthalene as solutes and Dow Corning Silicone-555 fluid as a solvent has been developed.[450] A resin which possesses both scintillator and ion-exchange properties utilizing the scintillator solutes *p*-terphenyl and 1,4-bis(5-phenyl-2-oxazolyl)benzene has been reported.[451]

Molten scintillator compounds, including 2,5-diphenyloxazole, were examined as solvents for electrochemical and electrogenerated chemiluminescence studies.[452]

B. Pharmaceuticals

Oxazoles having the structure **404** (*n* = O,[453-455] n = 1,2[456]) and **405** (X = CH_2,[457,458] CH_2CH_2,[459-461] OCH_2, and SCH_2[153]) are known to possess antiinflammatory and analgetic properties.



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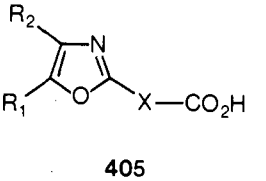
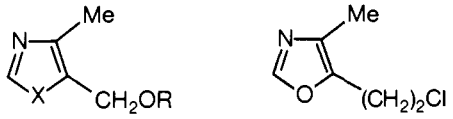


405

Certain 2-aminooxazoles,[462,463] oxazol-4-yl-2-nitropropene,[228,464] compounds containing an oxazole moiety and another heterocyclic ring such as a thiazole[221] or a furan,[227,465-467] and other miscellaneous oxazole derivatives[468-471] are useful as antibacterial, antimicrobial, antiviral, and analgesic drugs.

Oxazole-4-acid hydrazides[472] and 4-thioamides[473] are believed to be potentially antitubercular substances.

A study of the hypnotic activity and anticonvulsant effects of oxazoles related to clomethiazole demonstrated that these compounds (**406**[474] and **407**[475]) are hypnotics.



406 **407**

X = O, S

2-Aminooxazoles are useful as hypertensive agents for increasing arterial pressure and diuresis.[476,477]

Blood glucose was decreased 21–90% in mice by the hypoglycemic drugs, the 4-(2-oxazolyl)-*N*-alkylpyridinium salts.[318]

C. Fluorescent Whitening Agents

The fluorescent properties of 2,5-diaryl-[478-480] or arylstyryloxazoles[481-484] have made these compounds ideally suited for use as whitening agents for cotton and polyester fibers.

D. Photography

The synthesis of oxazole cyanine and merocyanine dyes by standard methods[485] and studies of their optical properties[486-489] have been reported. These compounds are useful as optical sensitizing dyes in silver halide emulsions. Similar utility has been found for 2-mercaptooxazoles[144] and their silver salts.[490] Aminophenyloxazoles have been used in the photoconductive layer of electrophotographic materials.[491-493]

E. Miscellaneous

2,5-Diphenyloxazole (**132b**) is an efficient high-temperature antioxidant for silicone hydraulic fluids and lubricants[494,495] and also reduces damage by ionizing radiation to vulcanizates of natural or synthetic rubber.[496]

2-Mercaptooxazoles, -oxazolines, -thiazoles, and -thiazolines are useful as additives to polyphosphate detergents to reduce the tarnishing of metals by the detergent.[497]

IX. Addendum

A review dealing with oxazole chemistry has been published.[498]

When 2-thienylcarboxamide is condensed with diethyl chloromalonate, diethyl 2-thienyloxazole-4,5-dicarboxylate is obtained.[499] When this oxazole diester is allowed to react with hydrazine, 4,7-dioxo-4,5,6,7-tetrahydrooxazolo[4,5-*d*]pyridazine is produced.[500]

The cyclization of propargylamides with mercury(II) acetate, concentrated H_2SO_4, or NaH in refluxing dioxane gives 2-aryl-5-methyloxazoles in 28–74% yield, while *N,N*-disubstituted-*N'*-propargylureas give *N,N*-disubstituted-2-amino-5-methyloxazoles in 30–84% yield.[501]

The carbene produced by the thermolysis (220°) of 1-phenyl-2,2-dimethoxy-2-(*N*-alkoxycarbonylamino)diazoethane undergoes an intramolecular cyclization yielding 2-ethoxy-4-methoxy-5-phenyloxazole as the main product.[502]

The reaction of ethyl diazoacetate with acrylonitrile in the presence of $Pd(OAc)_2$ (25°) affords 2-vinyl-5-ethoxyoxazole in 30% yield by the 1,3-dipolar addition of the ketocarbene (carbenoid) to the nitrile function, whereas without catalyst, 1,3-dipolar addition of the diazo compound occurs to give ethyl 5-cyano-1-pyrazoline-3-carboxylate which tautomerizes to the corresponding 2-pyrazoline.[503] The 1-pyrazoline loses N_2 at 100° to yield the expected cyclopropane.

The thermolysis of 3-phenyl-4-benzoyl-5-methylisoxazole at 220° gives 3,5-diphenyl-4-acetylisoxazole (8%), 2,5-diphenyl-4-acetyloxazole (29%), 2-phenyl-4-benzoyl-5-methyloxazole (39%), and unreacted starting material (24%).[504] A mechanism involving the intermediacy of a 1-azirine was postulated to rationalize the formation of the oxazoles.

The mechanism of the acid-catalyzed ring opening of 5-(*N*-morpholino)oxazoles was studied by isotopic tracer techniques.[505] When the reaction was carried out in the presence of $H_2{}^{18}O$, the label was found at the *N*-morpholino carbonyl oxygen atom of the resulting α-acylamino morpholino amide, suggesting that 5-aminooxazoles are opened *via* nucleophilic attack of H_2O at the 5 position of the ring. The mechanism of the cyclization of α-phenacylaminoamides with trifluoroacetic anhydride was also studied using ^{18}O-enriched starting material.

Benzaldehyde, benzaldehyde cyanohydrin, and cyanamide combine to form 2-amino-4,5-diphenyl-Δ^2-oxazoline which undergoes elimination of HCN in the presence of KOH to yield 2-amino-4,5-diphenyloxazole (59% overall yield).[506]

In a study of the interaction of 2,5-diphenyloxazole with nitrogen heterocyles, it was observed spectroscopically that the oxazole formed 1:1 complexes with quinoline and pyridine.[507]

The molecular Zeeman effect and magnetic susceptibility anisotropies of oxazole and isoxazole have been observed and measured from their microwave spectra.[508] These data suggest that no large difference in the electron delocalization in oxazole and isoxazole exists.

The Cornforth rearrangement (section IV.I) of 2-(2-phenyl-5-ethoxyoxazolyl)-Δ^2-oxazoline (110°) affords 5-phenyl-7-carboethoxyimidazo[5,1-*b*]-2,3-dihydrooxazole in 97% yield.[509]

The reaction of 4,5-diphenyl-3-alkyloxazolium salts with dialkyl acyl phosphonates gives $PhCOCH_2NRCOCHPhO\text{-}P(O)(OMe)_2$. When the reaction is run in the presence of triethylamine, 1,4-oxazin-3-one derivatives and β-lactams are obtained.[510] The intermediate phosphonate also affords the latter heterocycles when treated with triethylamine or Amberlite-IRA-400.

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