NEW CHEMISTRY OF OXAZOLES

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Abstract - Oxazoles are versatile compounds that can undergo reaction with electrophiles (e.g. bromine) leading either to aromatic substitution or to addition products. The latter reactions are shown to proceed via *N*-bromooxazolium salts and can also be used for introduction of 4-substituents. Intramolecular formation of oxazolium salts also can take place and subsequent reaction with nucleophiles leads via azomethine ylides to interesting products.

Diels-Alder reactions of oxazoles with olefins or acetylenes continue to be useful for synthesis of natural products containing pyridine or furan rings respectively.

Heterodienophiles (N=N, C=O, C=N, C=S, N=O) are shown to react with electron rich oxazoles either inter or intramolecularly and give rise to triazolines, oxazolines, imidazolines, thiazolines or oxadiazolines.

Lithiated oxazoles are useful intermediates either for isocyanides or for alkylated oxazoles.

1. Introduction

Oxazoles are generally considered heteroaromatic molecules. Indeed this definition is supported by nmr data (low field chemical shift value of the ring protons),[1] X-rays (bond lengths)[2] and MO calculations.[3] Predictions of the Dewar resonance energy for oxazole (3.24 kcal/mole),[4,5] indicate less delocalization than for pyrrole (5.3 kcal/mol)[1] and much less than for benzene (22.6 kcal/mol).[5] Geometric,[2] magnetic[1] and energetic[3a,4] characteristics of the oxazole ring as well as some theoretical indices for heterocycle aromaticity (such as bond order index,[6] I_5 index[7] or Katritzky's integrative index[4]) testify to a certain degree of aromaticity, likewise some experimental data indicate typical aromatic character of the ring, e.g. electrophilic substitution and stability to nucleophilic attack.

However, the oxazole ring consists of imino ether, enol ether and azadiene fragments. Indeed oxazoles undergo reactions typical of 1,3-dienes, e.g. they participate in Diels-Alder (DA) reactions[1] with various dienophiles and undergo 1,4-additions with singlet oxygen.[1,8]

This review is selective rather than comprehensive. It will concentrate on recent reactions of oxazoles, not covered by previous reviews[1,8-10] and will highlight the dual character of the oxazole ring (aromatic as well as azadiene character), including our own research in this area, as well as new synthetic methods for formation of oxazoles.

2. Reactions of Oxazoles with Electrophiles

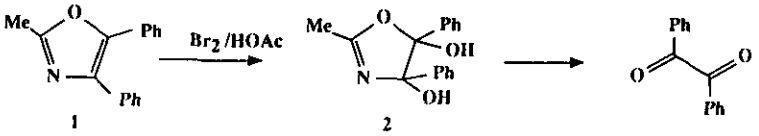
A. General

The oxazole core possesses two centers which are reactive towards electrophiles: the nitrogen atom and C-4 (or C-5). Of the ring carbons, C-4 is expected to be the most susceptible to electrophilic attack, since the electron donating resonance effect of the oxygen is most pronounced here. Position 2 is the least reactive due to the electron withdrawing effect of the nitrogen and oxygen atoms. These considerations are assessed by MO calculations which mostly place a higher electron density at C-4 than C-5 and the lowest at C-2. Activation of the electron deficient oxazole nucleus towards electrophiles is achieved by electron-donating groups such as amino or alkoxy groups.[5,11-12]

B. 2,5- and 4,5-Additions

Gompper and coworkers[13] had shown that oxazoles react with different halogenating agents (Br_2, Cl_2, NBS, *N*-bromophthalimide) to produce mainly aromatic substitution products (C-5>C-4>C-2). Mercuration with $Hg(OAc)_2$ gave similar results.[14] Vilsmeier-Haack formylation of 5-methyl-2-phenyloxazole with DMF-$POCl_3$ yielded the 4-aldehyde derivative.[15] Oxazoles did not undergo nitration reactions due to the highly electron deficient oxazolium cation which is formed under the reaction condition (HNO_3/H_2SO_4). Only in the case of the amino substituted oxazole (2-dimethylamino-4-phenyloxazole) was it possible to obtain nitration on the oxazole nucleus at C-5 (as well as on the phenyl ring).[12]

An exception to ring bromination is the cleavage of 4,5-diphenyloxazoles to benzil. This was interpreted[6] as resulting from reaction of the oxazole (see 1) with HOBr (presumably formed *in situ*) via intermediate (2).



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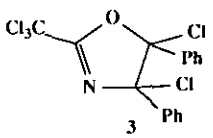

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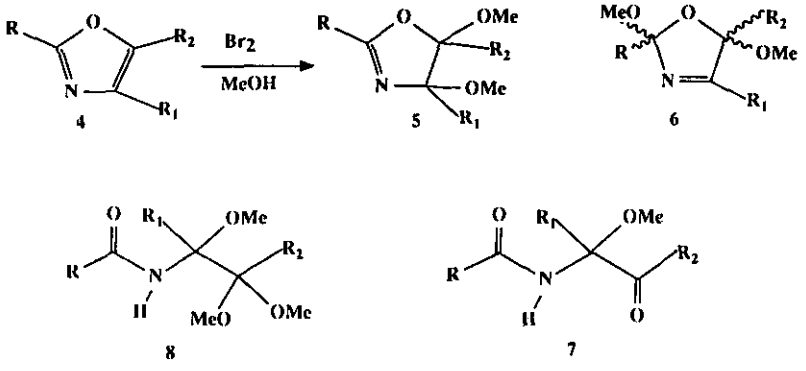
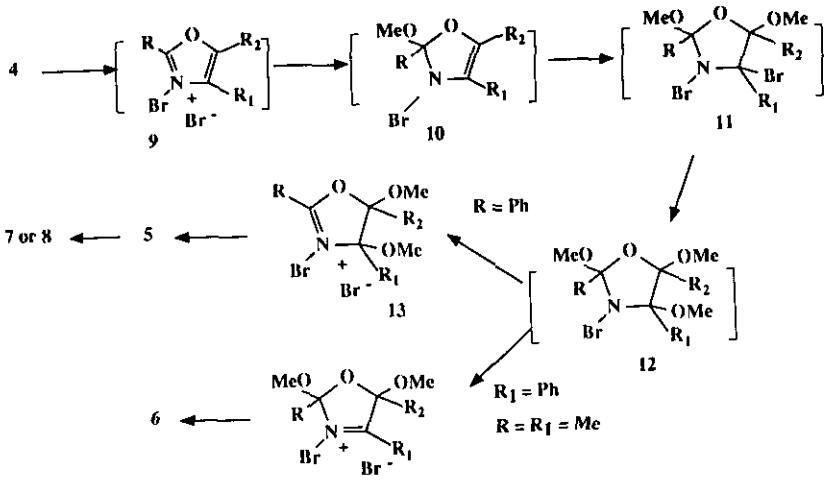
Electrophilic addition of chlorine as well as side chain substitution was noticed in a case where no free position was available on the oxazole ring; thus the product from **1** (47%) was assigned structure (**3**).[13]

We have recently shown,[17] that in contrast to bromination in HOAc, CCl_4 or DMF, bromination of oxazoles in the more nucleophilic solvent MeOH (in the presence of K_2CO_3 to trap HBr) leads to a variety of 4,5-addition (**5**), 2,5-addition (**6**) or ring opening (**7**,**8**) products depending on the substitution pattern on the starting oxazole and reaction time. When the 2-substituent R was aromatic and the 4-substituent was not, the products where either 2-oxazolines (**5**) and/or open chain keto amides (**7**) or (**8**). When the 4-substituent was aromatic only 3-oxazolines (**6**) were observed.[17]



4,5-Diphenyloxazoles gave in addition to 3-oxazolines (**6**) also some benzil.

The apparent incongruity of these results was resolved by monitoring the reaction at -78 to 25°C by ^1H nmr, ^{13}C nmr and by chemical studies[17] which established the following sequence of events and intermediates. The first step in the bromination of **4** is formation of an *N*-bromooxazolium salt (**9**), isolable from a benzene solution of **4** (R, R_2=Ph, R_1= Me or H) and bromine.[13a] On standing in MeOH for 24 h at room temperature, **9** was converted to **8**. The formation of **8** was preceded by fast conversion of **9** in MeOH to **12**, as detected by nmr. Most likely nucleophilic addition of MeOH to the oxazolium salt (**9**), activates the enol ether fragment of the molecule (see **10**) leading to Br-OMe addition (see **11**) and ultimately to **12**. It is at this point that the substitution pattern exerts an influence. When R is an aromatic group favoring conjugation with the C=N system, then **13** is formed and **5** is isolated on chromatography. When the 4-substituent R_1 is aromatic (or both R and R_1 are Me), then MeO-elimination from **12** or



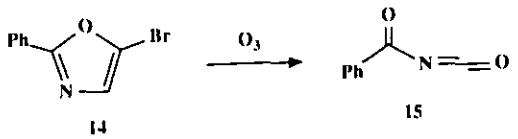
Br_2 elimination from **11**, leads to **6**. *It was further shown that* 2-oxazolines (**5**) are transformed on standing (or heating) under reaction conditions to **8** and/or **7**. 3-Oxazolines (**6**) were stable under reaction conditions.

Reaction of 2,5-diphenyloxazole with bromine in *t*-BuOH led to 4-bromo substitution as well as to the *t*-butoxy keto amide (**7**) (R_1,R_2=Ph, R_1=H, *t*-BuO instead of MeO), while reaction in ethylene glycol produced an analog of **8** among other products.[18] No reaction was observed with iodine in MeOH. Consistent with the proposed mechanism is the reaction of the above oxazole with PhSeBr in MeOH which led to **7** (R_1R_2=Ph). In this case PhSe, like Br, is able to play the dual role of an electrophile and of a leaving group to deliver **12** and from there **7**.[18]

Hence, the bromination of oxazoles in MeOH below O°C leads to 2,5- or 4,5-addition products (**6**) or (**5**) respectively; the latter are ultimately transformed at room temperature into keto amide derivatives (**7**) and/or (**8**). In other solvents such as HOAc, intermediates of type (**10**) (OAc instead of OMe) undergo bromination and elimination to bromosubstituted oxazoles.

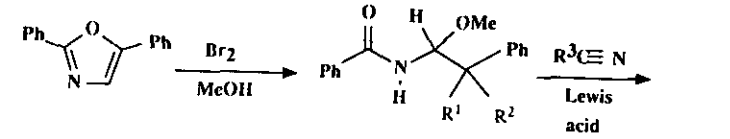
C. Ozonolysis

Ozonolysis of 2-phenyloxazoles (eq. 14) apparently proceeds by addition of ozone to the 4,5- and the 2,3-double bonds leading in many cases to *N*-benzoylisocyanate (**15**).[19]

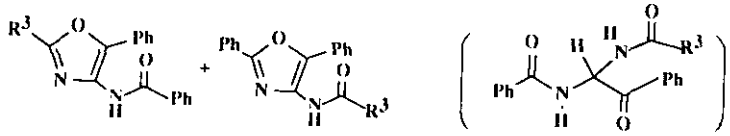


D. Addition leading to 4-substituted oxazoles

The ready availability of keto amide derivatives (**7**) and (**8**) from bromination of 2-phenyloxazoles in MeOH, suggested to us their use as amidoalkylating precursors, which in the presence of Lewis acids give rise to *N,C*-diacylimmonium ions.[22] The latter reacted with a variety of nitriles to form 4-amidooxazoles (**16a-b**), in almost the same ratio, in which the RCN moiety was incorporated either as the amide segment at C-4 or as part of the oxazole ring. Sometimes diamide products were isolated as well.



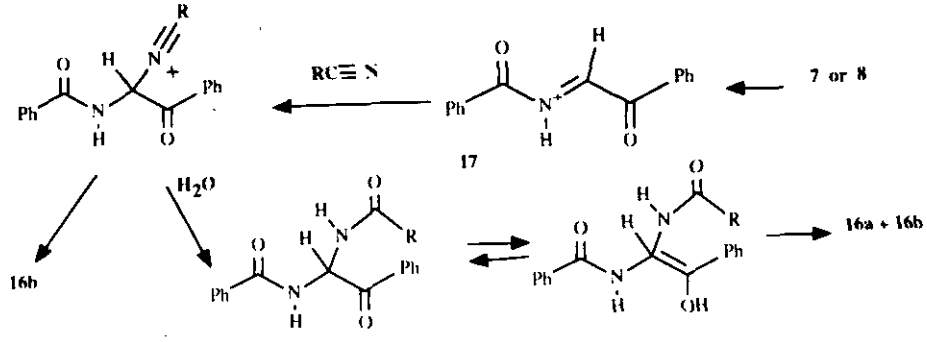
4 **8** $R^1 = R^2$: OMe; **7** R^1, R^2 : C=O



16a **16b**

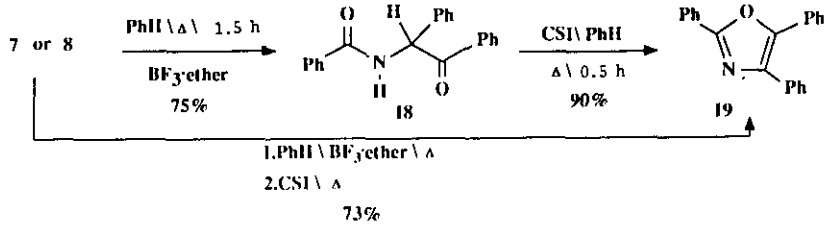
R^3 = Me , Et , pentyl , allyl , Ph

A mechanism explaining the formation of two isomeric 4-amido-oxazoles as well as for the products distribution was suggested, based on monitoring the reaction by nmr, chemical manipulations and comparison with literature precedents.



Thus, isolation of the rare 4-amidooxazoles (**16**) was achieved in a two step process from the corresponding 2-phenyl-4-unsubstituted oxazoles (e.g. **4** → **7** → **16**). Hydrolysis of amides (**16**) led to decomposition. 4-Aminooxazoles are apparently unstable[20] and remain so far elusive compounds; a report[21] of their synthesis could not be repeated.[22]

When benzene or anisole was used in place of RC≡N the mentioned keto amides (**7**) and (**8**) were converted (presumably via intermediates (**17**) and (**18**)) to 4-aryl substituted oxazoles (**19**).[18] Formally this constitutes a two-step arylation of oxazole (**4**).

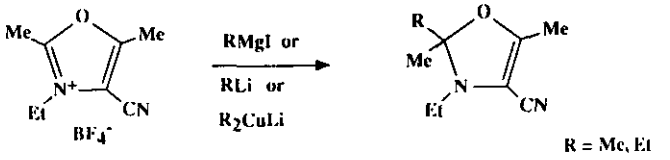


3. Reactions Of Oxazolium Salts

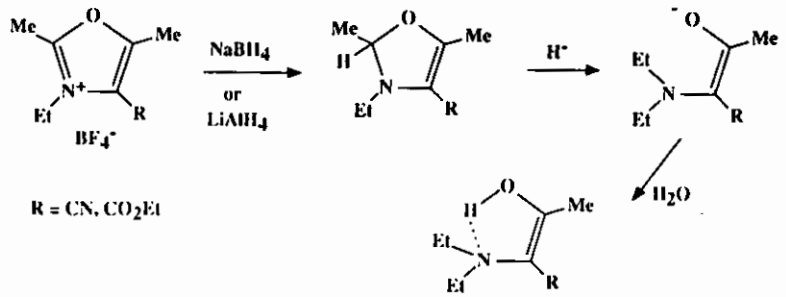
In spite of the lower basicity of oxazole (pK_{BH^+} ~1)[23] compared to imidazoles or even thiazoles, oxazoles do react with alkyl halides,[24] methyl tosylate[25] or triethyloxonium tetrafluoroborate[26] to form oxazolium salts.

Nucleophile attack on the neutral oxazole ring takes place only with difficulty, either at elevated temperatures (over 180°C) or in the presence of electron withdrawing substituents.[28] On the other hand, protonated oxazoles or oxazolium salts do react with nucleophiles, leading to ring cleavage.[29]

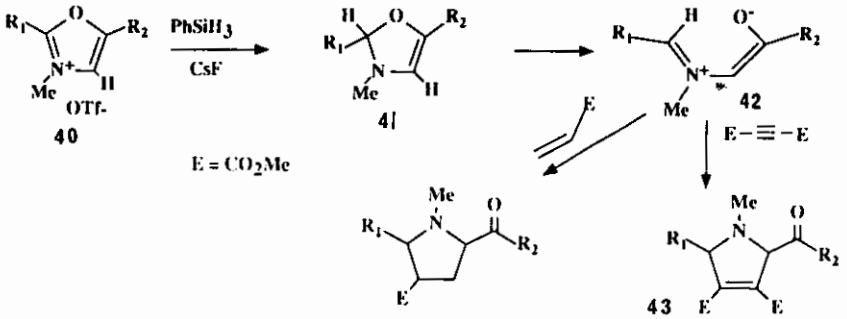
Alberola[30] reported the reaction of 4-cyanooxazolium salts with Grignard, alkyllithium or alkylcopper lithium reagents to yield 4-cyano-4-oxazolines in reasonable yield; variable amounts of hydrolytic ring



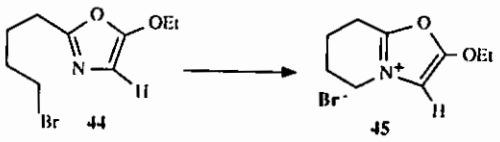
opening products were obtained as well. Reaction of the same starting materials with metallic hydrides, $LiAlH_4$, $NaBH_4$ or $LiAlH(OtBu)_3$, led to β-amino enols. The authors suggested the pathway described in the Scheme below. Vedejs *et al.*[31] demonstrated that treatment of oxazolium salts (**40**) with hydride,



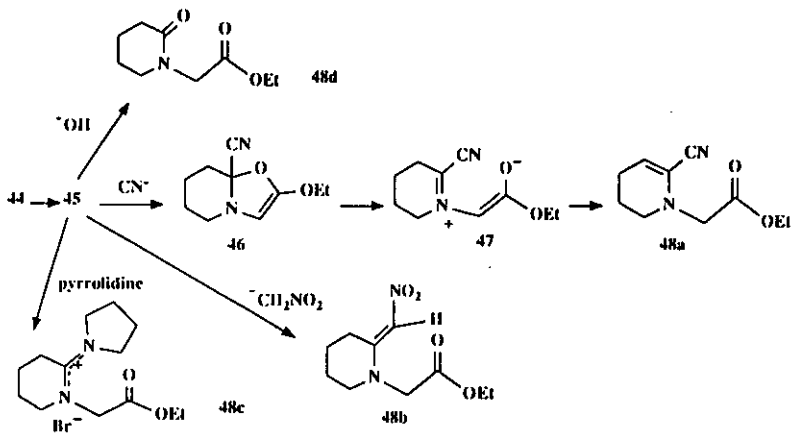
cyanide or thiolate ions leads via unstable 4-oxazolines (**41**), to azomethine ylide intermediates (**42**), which are trappable by electron poor dipolarophiles. This provides an entry into substituted pyrrolines and pyrroles (see **43**).



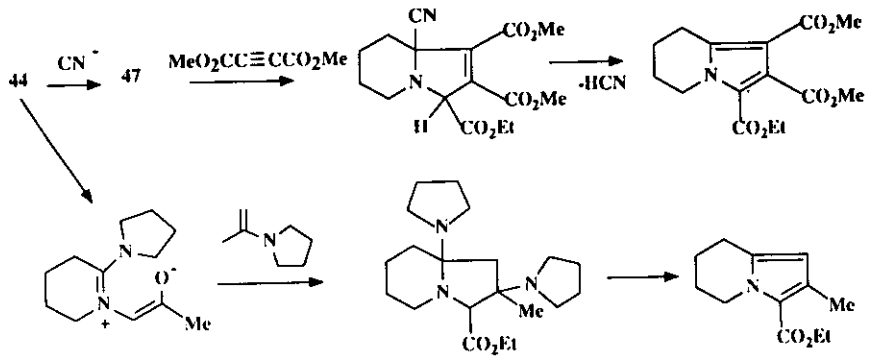
Intramolecular formation of oxazolium salts is rarer[5,13] but has recently been demonstrated by us[27] to occur when **44** was warmed with a catalytic amount of NaI in MeCN. The presence of oxazolium salt (**45**) was evidenced by nmr spectra as well as reaction with certain nucleophiles (see below).



Rate constants and activation parameters of the intramolecular alkylation were established. In the presence of various nucleophiles such as CN^-, $^-CH_2NO_2$, ^-OH or pyrrolidine, oxazolium salt (**45**) gave rise to a new heterocycle, viz., piperidine derivatives (**48**).

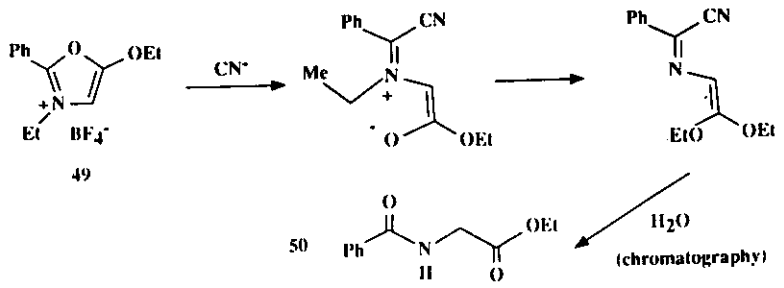


Nucleophilic attack on **45** yielded 4-oxazolines (**46**) which is a valence tautomer of **47**. The intermediacy of **47** was proved by trapping experiments with either electron poor or electron rich dipolarophiles (see Scheme 1).[27]

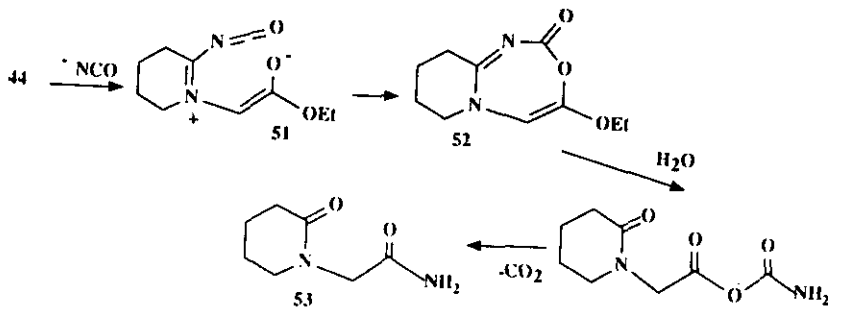


Scheme 1

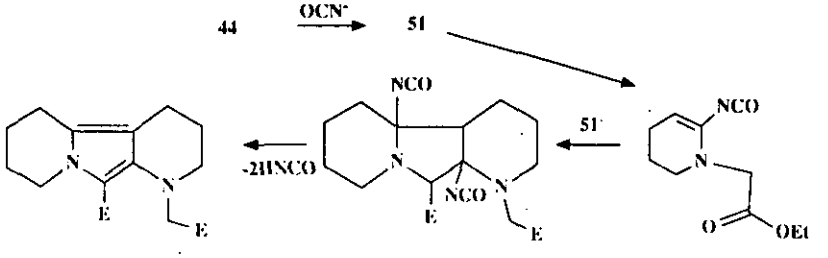
Formation of the piperidine derivative from azomethine ylide (**47**) is a result of neutralizaton process which is a proton transfer in cases **48a - 48d**. However, if proton transfer is impossible, alkyl transfer can occur, as in transformation **49 → 50**.



A third mode of internal neutralization of azomethine ylide (**47**) was observed with isocyanate and ethyl carbamate anions,[32] where an intramolecular nucleophilic transfer, via a cyclic intermediate, gave rise to the product (e.g. **53**).



This mechanism is supported by an STO-3G calculation for dipole (**51**), which indicates the enolate oxygen to be within bond forming distance of 1.44Å to the isocyanate carbon (effectively structure (**52**)).[32] A unique mode of neutralization of azomethine ylide was observed with isocyanate ion, where ylide (**51**) served both as a dipole, and as the dipolarophile precursor, leading upon 1,3-dipolar cycloaddition to the tricyclic dimer.



4. Oxazoles Participate in Diels-Alder (DA) Reactions

A. General

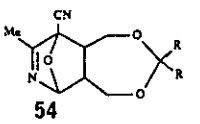
The oxazole ring possesses an electron deficient azadiene which is suited for participation in inverse electron demand Diels-Alder (DA) reactions. Indeed, additional substitution of the oxazole with electron withdrawing groups accentuates its electron deficient nature and permits the use of electron rich or even simple olefins as dienophiles. However, substitution of the oxazole with strong electron donating substituents (e.g. OR, $OSiR_3$, NR_2) is sufficient to overcome the electron deficient nature of the azadiene and permits the use of electron poor dienophiles (normal DA reaction). This is a thermal reaction which

usually takes place at elevated temperatures (80-180°C), but when the reactants are activated by suitable groups it can take place even at 0°C.[33]

Numerous papers on the Diels-Alder reaction of oxazoles with various dienophiles have been published since Kondrat'eva's report in 1957[34] and several reviews have appeared.[8-10] The methodology was applied to the synthesis of natural products, the most famous being the synthesis of vitamin B_6.[9] In addition to olefins or acetylenes, heteroatom double bonds have been utilized recently as dienophiles, either intermolecularly or intramolecularly.

B. Isolation of DA adducts

Oxazoles react with alkenes and alkynes to form DA adducts which are usually too unstable to be isolated (for exceptions see below). The adducts undergo spontaneous decomposition, whose outcome depends on the nature of the substituents on the oxazole and the dienophile, on whether alkenes or alkynes have been employed and on the reaction conditions. The existence of DA adducts has been proven by isolation of a few stable primary adducts, for instance the adducts of maleimide with a 5-cyanooxazole (**54**),[35] 5-unsubstituted oxazole (**55**),[36] a 5-aminooxazole (**56**),[37] and a 5-methoxyoxazole (**57**).[38] To date only two examples are know for isolation of a DA adduct of an oxazole with an alkyne, namely with DMAD (dimethyl acetylenedicarboxylate) (**58**)[39] or with benzyne (**59**).[40]



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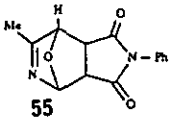

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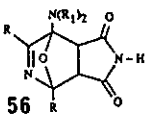

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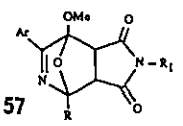

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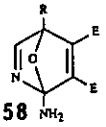

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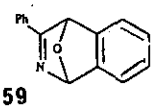

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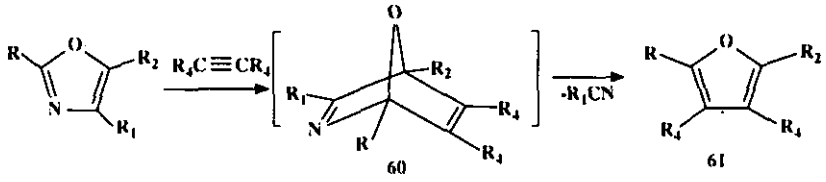
C. Reactions of oxazoles with acetylene.

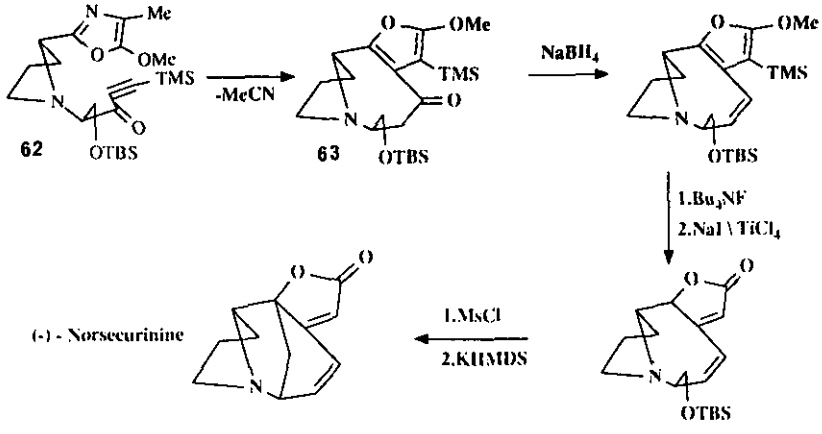
Furans are the consequence of oxazole DA reactions with acetylenes. The primary adduct (**60**) undergoes spontaneous retro DA reaction to liberate a nitrile and another diene, namely the furan ring system (**61**).



Studies on the reaction of alkyl- or aryl-substituted oxazoles with various monosubstituted alkynes demonstrated the lack of regioselectivity in this process;[41] 2,3- and 2,4-disubstituted furans were formed in nearly equal amounts in most cases. However, polarized, electron rich oxazoles do participate in regioselective intermolecular alkyne oxazole DA reactions.

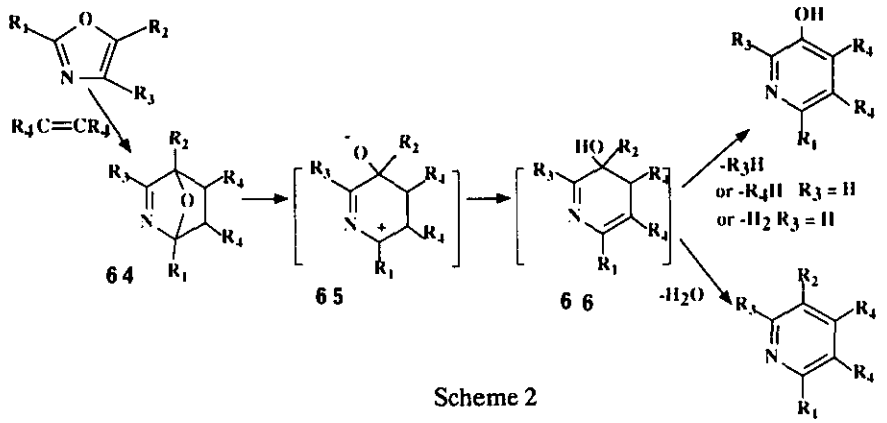
Jacobi[42] performed pioneering work in the application of the DA reaction of oxazoles to intramolecular systems for the syntheses of several furanosequiterpenes. He coined the term 'bis heteroannulation'[42a] which implies that two rings, one heterocyclic and one carbocyclic, are being formed simultaneously. This methodology was applied to a (±)- paniculide A synthesis.[42c]

Another recent example of *bis* heteroannulation is the synthesis of (-)-norsecurinine from proline, in which the relevant step is the conversion of **62** to **63**.[43]



D. Reaction of oxazoles with olefins

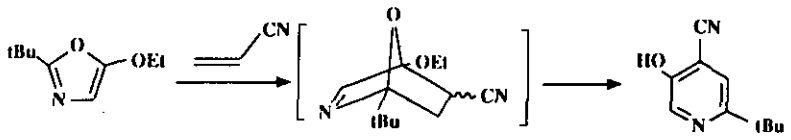
Olefins react entirely differently than acetylenes with oxazoles and lead to substituted pyridines. The latter are apparently the consequence of cleavage of the initial adduct (**64**) to zwitterion (**65**) followed by aromatization of **66**. The latter step takes place via four possible pathways: **a)** loss of water; **b)** loss of EtOH, HCN; **c)** loss of HCN or HCO_2Et; **d)** dehydrogenation (Scheme 2).



Scheme 2

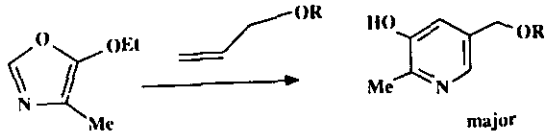
The course of aromatization depends on R^2 and R^4 in **66** and on the reaction conditions (e.g. the use of benzene or alternatively acetic acid as the solvent; addition of DBN, etc.). Usually mixtures of products are formed. Pathway **b** is dominant when R^2, the substituent on C-5 of the oxazole, is a reasonably good leaving group such as OEt or CN. In such a case EtOH or HCN are eliminated in preference to water.[44] On the other hand, when R^2 is an aryl or alkyl group, elimination of water via path **a** takes place.[45] The presence of hydrogen on C-5 (R^2=H) enables two additional pathways to occur: elimination of HR^4 when R^4 is CN or CO_2Et[46] (pathway **c**) or oxidation[46] (-H_2, pathway **d**). The latter pathway is rare but occurs efficiently if a hydride acceptor (e.g. H_2O_2, nitrobenzene) is present.

With alkenes, unlike with most alkynes, regioselectivity is observed. The general rule for the reactions of alkyl and alkoxy substituted oxazoles is that the more electronegative substituent of the dienophile occupies position 4 in the pyridine ring (or adduct)[47] (e.g. Scheme 3).



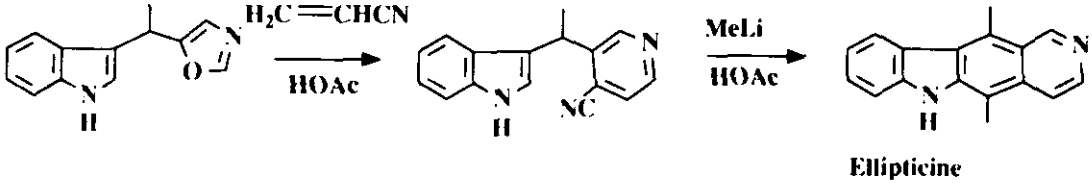
Scheme 3

Terminal olefins possessing electron releasing substituents react in the opposite regiochemical sense[48] (Scheme 4). Reaction with 1-hexene or 3-methyl-1-butene showed no regioselectivity.[48]



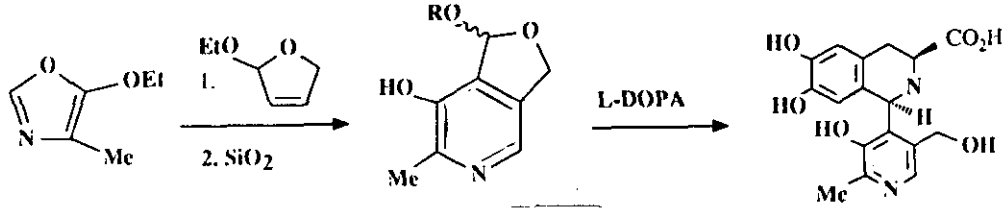
Scheme 4

An example for the utilization of olefins for the construction of a pyridine ring in natural product synthesis is Kozikowski's[49] synthesis of ellipticine (Scheme 5) (pyridine aromatization by water elimination).



Scheme 5

The syntheses of pyridoxal and pyridoxyl alkaloids[50] demonstrate the construction of 3-hydroxypyridines via DA reaction (aromatization by elimination of EtOH) (Scheme 6).



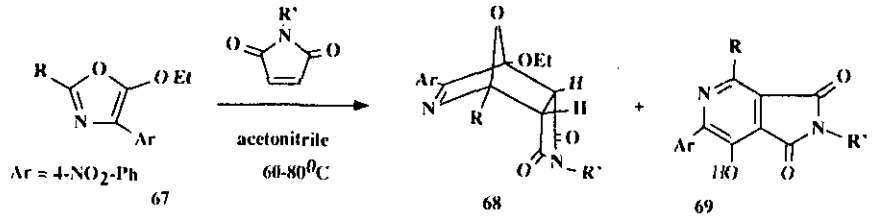
Scheme 6

Several examples of the utilization of olefinic dienophiles in the intramolecular DA reaction towards the synthesis of natural products were published by Weinreb,[51] as well as by Shimada,[52] for instance, the key step for the construction of the ABC rings (Scheme 7) in the total synthesis of the marine alkaloid Amphimedine.[51a]

E. 5-Ethoxy (amino) oxazoles as the diene partner

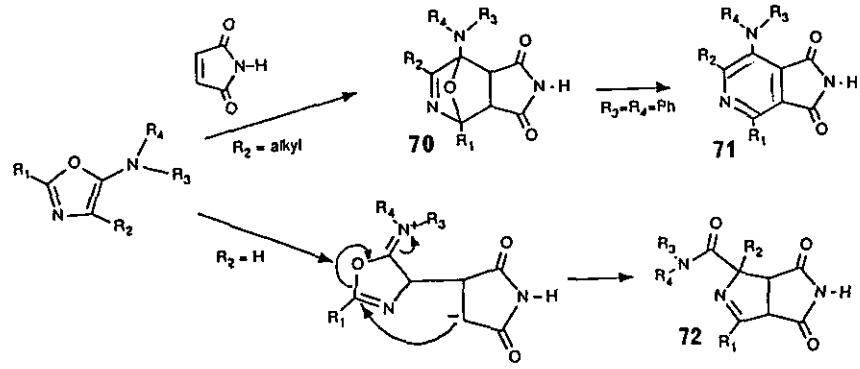
Electron donating groups such as alkoxy and amino compensate for the electron poor nature of the oxazole ring and facilitate the DA reaction. Thus, 5-ethoxyoxazoles are the most reactive oxazoles and are similar in reactivity to all carbon dienes.[9]

Ibata[38] studied the reaction of 5-ethoxy-2-alkyl-4-aryloxazole (**67**) with *N*-ethylmaleimide in refluxing toluene and obtained the primary endo adduct (**68**) (as well as the exo isomer) as proved by X-ray. Under different reaction conditions, (in acetonitrile at 60-80°C) variable amounts of hydroxypyridine (**69**) (due to EtOH elimination) were formed as well.



Reaction of oxazole (**67**) with dimethyl maleate or fumarate was achieved only under high pressure (60°C/10 K bar). Both the original adducts and hydroxy pyridines were obtained.[38]

Unusual products via pathways that are not fully elucidated have sometimes been observed. Thus, the reaction of 5-(*N,N*-disubstituted) aminooxazoles with maleimide produced 3-aminopyridines (**71**), DA adducts (**70**) or 1-pyrrolines (**72**) depending on the nature of R^2, R^3 and R^4.[37] In HOAc, protonation of the 5-amino substituent occurred, resulting in the formation of DA products (**70,71**) exclusively.

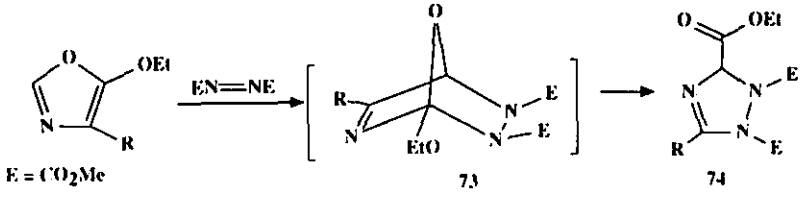


Dondoni[53] found that reaction of 2-(*N,N*-disubstituted) aminooxazoles withn electron poor diene (3,4,5,6-tetrachloro-*o*-quinone) led to a DA adduct, in which the C4-C5 double bond of the oxazole took the role of the dienophile, due to its high electron density in comparison to alkyloxazoles (Scheme 8).

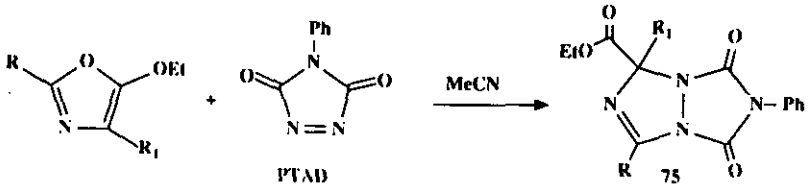
5. Heterodienophiles in Intermolecular Oxazole DA Reactions

A. N=N dienophiles.

The first to use a heterodienophile were Grigg and coworkers[41b] who employed DEAD (diethyl azodicarboxylate) with 4-alkyl-5-ethoxyoxazole and claimed to have obtained the primary DA adduct (**73**). Based on subsequent studies with 5-ethoxyoxazoles (see below) the correct structure is **74**.[11]



Ibata[38] examined the reaction of 4-aryl-5-ethoxyoxazoles with DEAD and PTAD (*N*-phenyl-1,2,4-triazoline-3,5-dione). The products, obtained in high yield, were first described as the primary DA adducts, then correctly as 1,2,4-triazolines (**75**).[38c,54] 2,5-Diaryloxazoles were inactive.

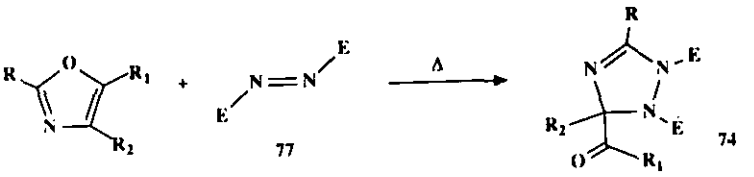


The authors suggested the intermediacy of zwitterions (formed upon nucleophilic attack of the oxazole unto PTAD).

An extensive investigation of the reaction of 5-ethoxy- and of 2-ethoxyoxazoles with a variety of heterodienophiles (N=N, C=N and C=O) was carried out by Hassner and Fischer.[54] No Diels-Alder adducts were isolated but rather different azolines, triazolines (**74**) and (**75**), oxazolines (**79**) and (**80**) or imidazoline (**83**).

Among the oxazoles examined, 5-ethoxy-2-phenyloxazole and 5-siloxy-2-phenyloxazole (**76a**, **76b**) proved to possess the same reactivity, while changing the C-2 substituent from a phenyl to a methyl (**76c**) reduced the activity. The most dramatic reduction of reactivity was observed when the ethoxy group was substituted on C-2 (**76d**) rather than on C-5. A non activated oxazole (**76e**) was inert even with the most reactive dienophile PTAD). The latter reacted with the alkoxyoxazoles at room temperature to give **75**,

while DEAD **77** required 80-110°C. The structure of products (**74**) was elucidated by spectral means as well as by chemical manipulations and independent synthesis in one case.



77 **74**

76a, R=Ph; R_1=OEt; R_2=H

b, R=Ph; R_1=$OSiMe_3$; R_2=H

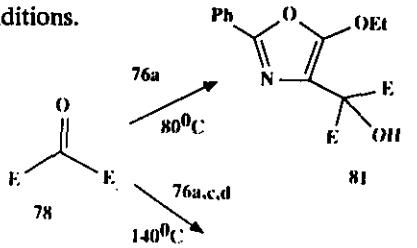
c, R=Me; R_1=OEt; R_2=H

d, R=OEt; R_1=Ph; R_2=H

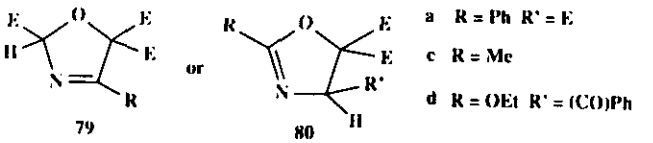
e, R=Ph; R_1=Me; R_2=Ph

B. C=O Dienophiles

Simple carbonyl compounds were unreactive but diethyl ketomalonate (**78**) reacted with 5-ethoxyoxazole (**76a**) at 140°C to produce two regioisomeric oxazolines (**79**) and (**80**), as well as a 4-hydroxyalkylation product (**81**).[54a] The presence of the Lewis acid BF_3-etherate not only improved the reactivity (80°C instead of 140°C) but also produced solely the 2-oxazoline (**80**). 3-Oxazoline (**79**) was stable under reaction conditions.



78 **81**



79 **80**

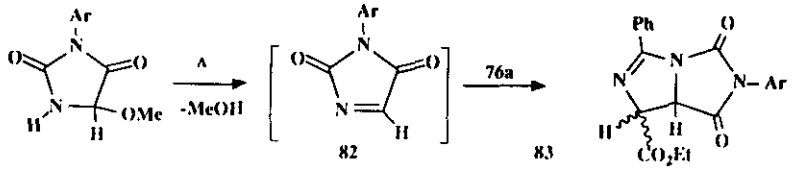
a R = Ph R' = E

c R = Me

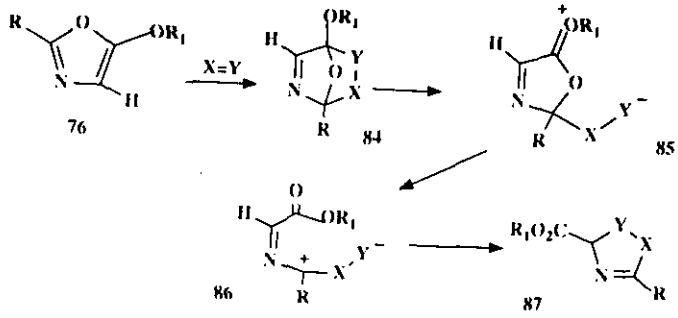
d R = OEt R' = (CO)Ph

C. C=N Dienophiles

Among several C=N dienophiles tested only dehydrohydantoin (**82**) reacted with **76a** at 140°C or by BF_3 catalysis at 110°C to produce a single regioisomer (**83**) as a *cis-trans* stereoisomer mixture.



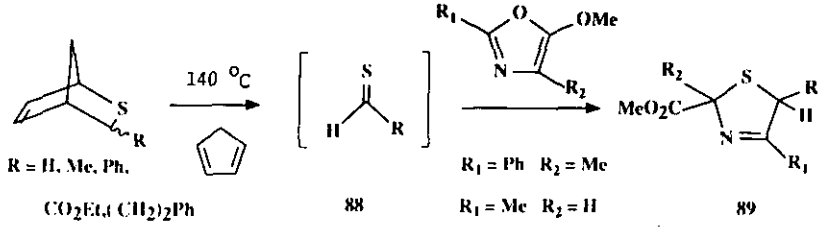
The results are consistent with a Diels-Alder addition of the heterodienophiles to the activated oxazoles (except in the formation of **81** which involves a nucleophilic addition of **76** onto the heterodiophile (**78**),



followed by ring opening of **84** (or **84a**) to **85**, then to **86** and final ring closure to **87**.[54a] A nucleophilic addition of oxazoles (**76**) unto the heterodienophile leading to **85** or its isomer cannot be ruled out, especially since frontier molecular orbital analysis predicts preferential formation of **79** over **80**.

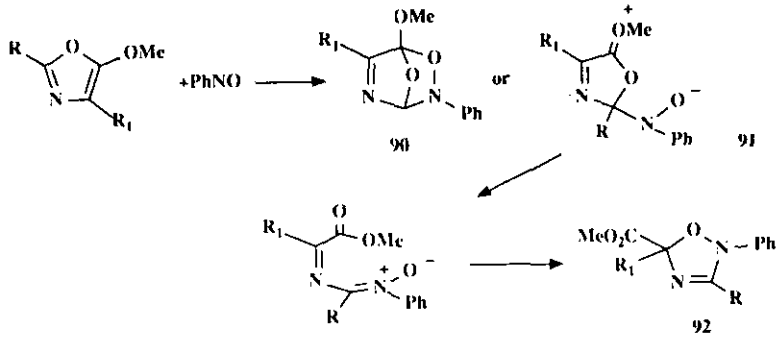
D. C=S Dienophiles

Thioaldehydes (**88**) also undergo cycloaddition to 5-alkoxyoxazole to afford 3-thiazolines (**89**) as a single regioisomer.[55] Alkyl or aryloxazoles were inactive.



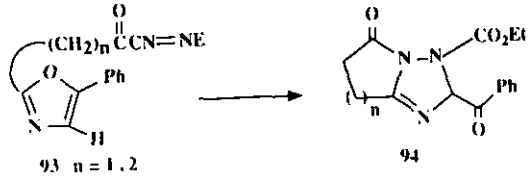
E. N=O Dienophiles

The nitroso group of nitrosobenzene was shown to react with various 5-methoxyoxazoles and even with 2,4,5-trimethyloxazoles to produce 1,2,4-oxadiazolines (**92**), presumably via **90** or Diels-Alder adduct (**91**).[56]

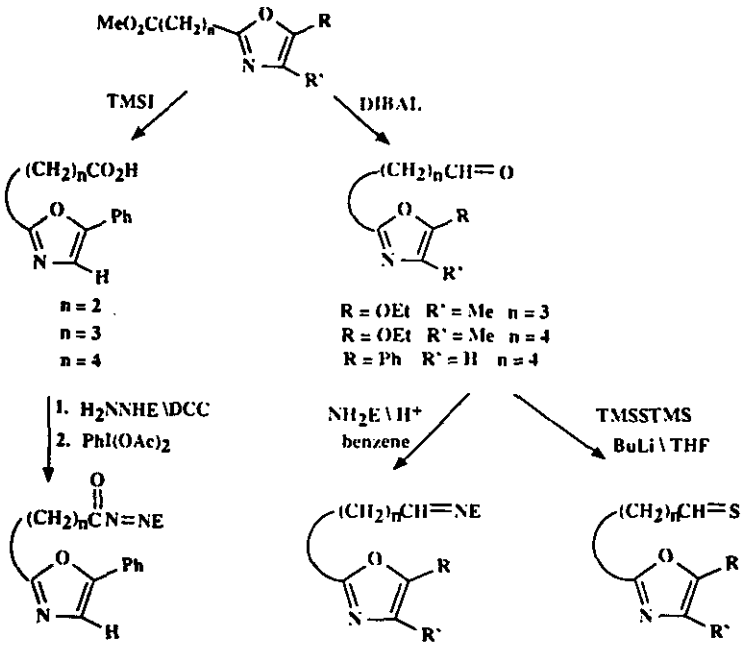


6. Heterodienophiles in Intramolecular Oxazole DA Reactions

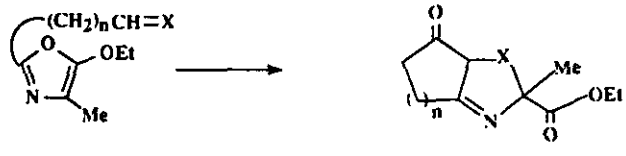
The *bis*-heteroannulation concept was applied by Hassner and Fischer to the intramolecula cycloaddition of oxazoles to heterodienophiles containing N=N, C=O, C=N and C=S bonds. [54b] In all cases the reaction was consistent with the pathway outlined for intermolecular additions, **76** → **84** → **85** → **86** → **87**. Thus, intramolecular cycloaddition of the N=N system (**93**) led to bicyclic triazolines (**94**).



The starting oxazoles (**93**) were prepared as shown.



Intramolecular addition of the C=N bond of **97** led to 3-imidazolines (**100**) and unlike in the intermolecular case, even aldehyde (**95**) cycloadded to produce 3-oxazoline (**98**). Thioaldehyde (**96**) reacted already at room temperature to produce 3-thiazoline (**99**).[54b]



95, X=O

96, X=S

97, X=N-CO_2Et

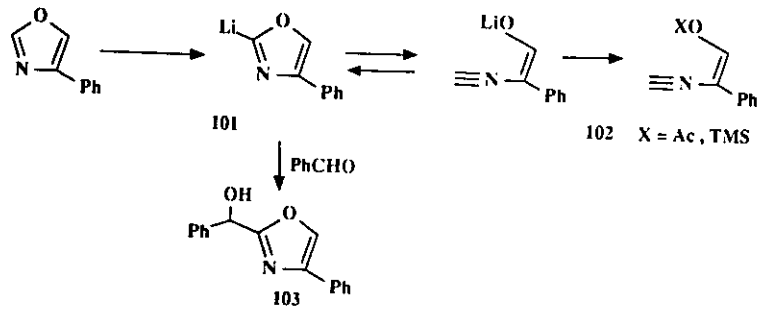
98, X=O

99, X=S

100, X=N-CO_2Et

7. Lithiation of Oxazoles

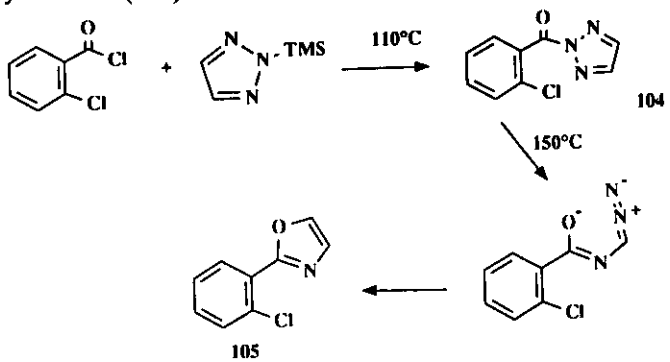
4-Phenyloxazole was deprotonated by butyllithium preferentially at C-2. The lithiated product (**101**) gave ring opened products (**102**) with AcCl or Me_3SiCl, but was alkylated with benzaldehyde to afford **103** if sufficient time was allowed.[57] In 2,5-diphenyloxazole lithiation at C-4 is accompanied by lithiation of the



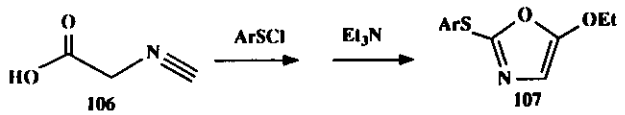
phenyl ring but this can be avoided by using sec-butyllithium and lithium tetramethylpiperidide.

8. Some New Oxazole Syntheses

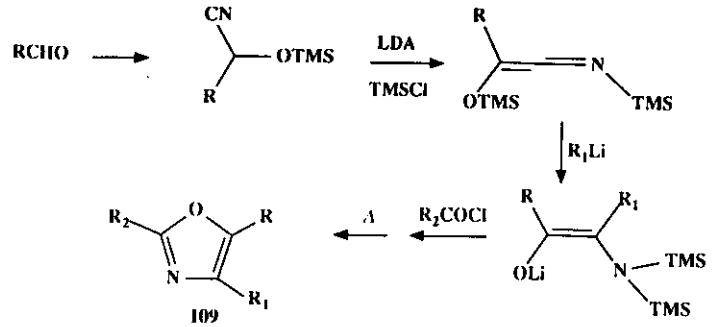
In addition to the well tried methods for synthesis of oxazoles,[1,8-10] some modifications were reported recently. For instance, 2-substituted oxazoles (e.g. **105**) were readily prepared from acid chlorides via pyrolysis of 1-acyltriazoles (**104**) at 150°C as shown.[58]



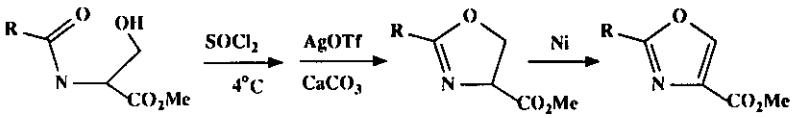
5-Ethoxy-2-arylthiooxazoles (**107**) were obtained by reaction of ArSCl with α-isocyanido esters (**106**).[59]



Aldehydes can be converted via silylated cyanohydrins (**108**) in a multistep reaction with alkyllithium and acid chlorides to trisubstituted oxazoles (**109**).[60]



The oxazole part of calyculins was prepared from amides of serine (e.g. **110**) via 2-oxazolines as shown below.[61]



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