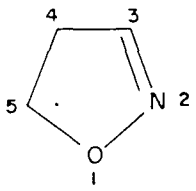
1. Introduction



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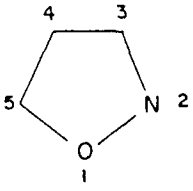

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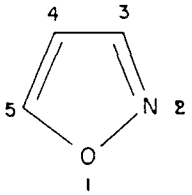

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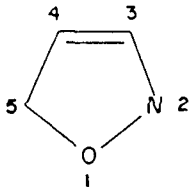

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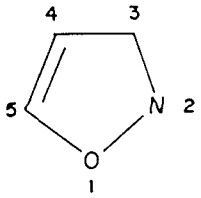

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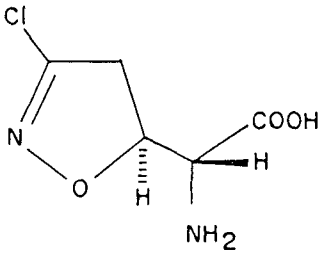

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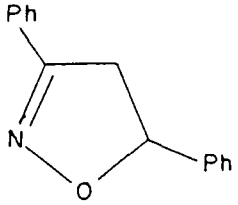

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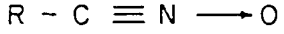

R = alkyl or aryl

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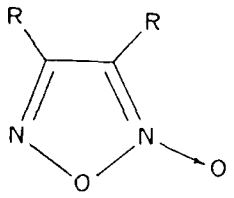
1. INTRODUCTION

The structures of isoxazoline (1), isoxazolidine (2) and isoxazole (3) are shown with numbering. Though all the three isoxazolines viz., 2-isoxazoline (1), 3-isoxazoline (4) and 4-isoxazoline (5) have been prepared, extensive studies on 2-isoxazolines (1) have only been documented.[1]

The antimetabolite AT-125, (αS,5S)α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (6), isolated from **Streptomyses sviceus**, is found to possess antitumour[2] and enzyme inhibitory[3] properties and a number of papers[4-8] has dealt with the total synthesis of 6. The first preparation of 3,5-diphenyl-2-isoxazoline (7), dates back to 1895 wherin it was obtained by the reaction of β-choloro-β-phenylpropiophenone with hydroxylamine[9]. Two major syntheses[10] of 2-isoxazolines are the cycloaddition of nitrile oxides (8) to alkenes and the reaction of α,β-unsaturated ketones with hydroxylamine.

1.1 GENERATION OF NITRILE OXIDES

Various methods are employed for the generation of nitrile oxides.[11] Mostly the nitrile oxides are generated insitu in the presence of an alkene with which it reacts to yield 2-isoxazolines. Hydroximic acid chlorides and primary nitroalkanes are the two important precursors used for the generation of



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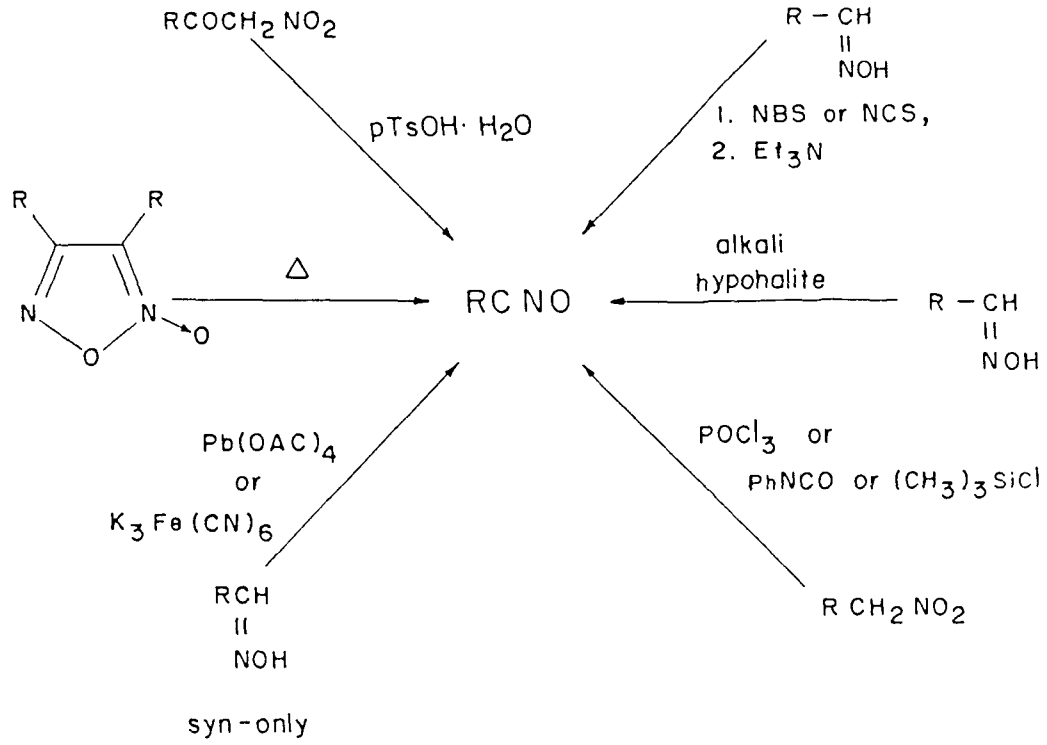
$PhCOCH_2NO_2$

10



Scheme 1

nitrile oxides. Hydroximic acid chlorides undergo dehydrohalogenation whereas primary nitroalkanes undergo dehydration to form the nitrile oxides. Less frequently employed methods involve aldoximes and furoxans (9) as precursors of nitrile oxides. ß-Nitroketones (10) have also been employed for the generation of nitrile oxides. Various methods of generating the nitrile oxides are shown in Scheme 1.

The earlier workers employed hydroximic acid chlorides for the preparation of nitrile oxides which yielded 2-isoxazolines on cycloaddition with alkenes. The main difficulty in this method is the chlorination of the aldoximes; chlorination of aromatic rings and side-chains being some of the undesired side reactions.[12] Dehydration of aldoximes has also been effected by lead tetraacetate,[12] potassium ferricyanide,[13] hypochlorites[14] and silver carbonate on celite.[12] Chloramine-T has also been employed for generating nitrile oxides from aldoximes.[15] Torssell's one pot synthesis of isoxazolines is advantageous in the sense that the hydroximic acid chloride is not isolated but used for the generation of nitrile oxide in the presence of an alkene.[16] Dehydration of primary nitroalkanes represents an elegant, mild and useful method for the preparation or generation of nitrile oxides. One of the most extensively used methods for the synthesis of isoxazolines is developed by Mukaiyama and Hoshino[17]

and it involves the use of phenyl isocynate with catalytic quantities of triethylamine. Phosphorous oxychloride has recently been shown to be an effective dehydrating agent for primary nitroalkanes.[18] The latter method has the alleged advantage over the former because of the easy removal of the transformation products by water. In the isocyanate method (Mukaiyama's method), the insolubility of the by-product, diphenylurea and low solubility of the product (isoxazoline) in the reaction medium lead to many disadvantages. Dehydration of primary nitroalkanes by acetyl chloride has also been reported.[19] Trimethylsilyl chloride and triethylamine have successfully been employed for the dehydration of primary nitroalkanes. Wade et al. developed two methods for the generation of nitrile oxides: one involving p-TsOH.H_2O as the dehydrating agent[20] (for ß-nitro-ketones) and another involving silver nitrate as the dehydrohalogenating agent[21] (for hydroximic acid chlorides). The former method is applicable to ß-nitroketones alone and provides an easy entry to 3-benzoyl-2-isoxazolines. Thermally induced cycloreversion of furazan-N-oxides[22-26] has been reported to be a promising way of generating nitrile oxides insitu, although the dimers themselves are obtained from nitrile oxides.

Various methods of generation of nitrile oxides are outlined in Table 1.

Table 1

General Methods of

Generation of Commonly Employed Nitrile Oxides

R - C ≡ N -> O

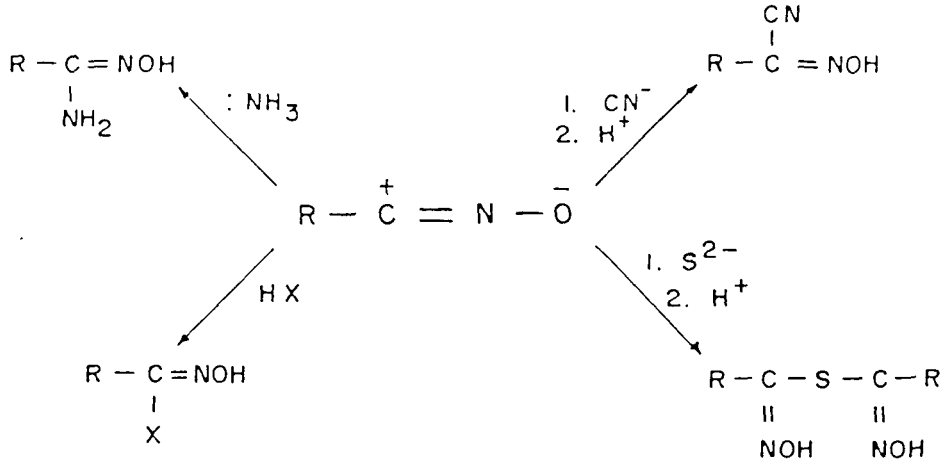
R	Method of generation of nitrile oxides
Me, Et, Pr	Mukaiyama's method / Torssell's method
Ph, substituted phenyl, COOEt	Hydroximic acid chloride/Torssell's procedure
Furyl, substituted furyl, Thiophenyl, substituted thiophenyl	,,
PhCO	p-TsOH.H_2O (Wade's procedure)[20]
PhNHCO	From furoxans[24]
PhS	Mukaiyama's method[17]
$PhSO_2$	Wade's procedure/oxidation of 3-Marcaptophenylisoxazolines

1.2 PROPERTIES OF NITRILE OXIDES

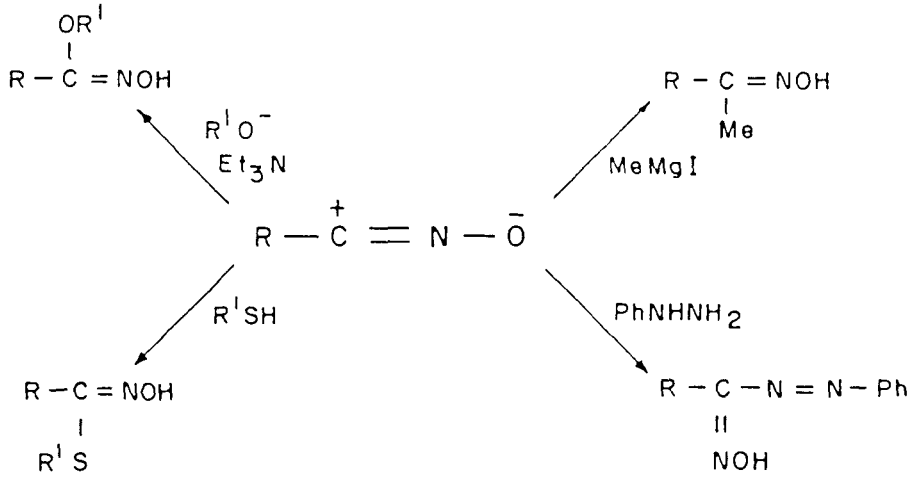
Nitrile oxides (8) are isomeric with cyanates (11) and isocyanates (12). In nitrile oxides the organic moiety is connected to a carbon atom whereas in cyanates it is connected to the oxygen and in isocynates to the nitrogen atom.

$R-C\equiv N\longrightarrow O$ $R-O-C\equiv N$ $R-N=C=O$

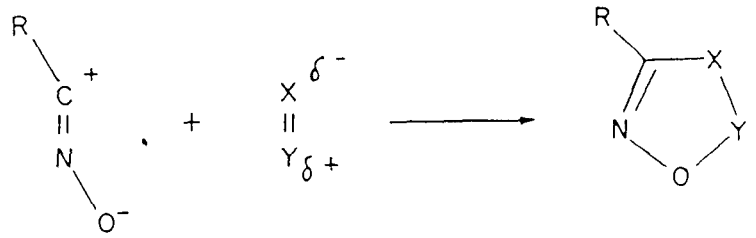
8 11 12



Scheme 2



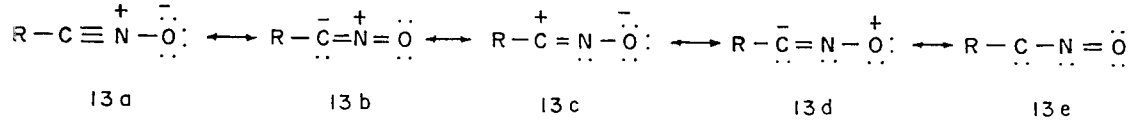
Scheme 3



· · · (Eq. I)

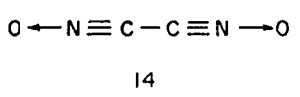
1.2.1 EXPLOSIVE NATURE OF NITRILE OXIDES

The structure of nitrile oxide[27] is represented as the resonance hybrid of the structures 13a-13e. Since nitrile oxides



13a 13b 13c 13d 13e

are energy-rich compounds, all low molecular weight nitrile oxides and polynitrile oxides are considered as potential explosives.[27] Fulminic acid undergoes polymerization below -20°C while its heavy metal salts and even the alkali metal salts are highly explosive in nature. Oxalo-bis-nitrile oxide (14) decomposes around -45°C and detonates a few minutes later at that temperature while terephthalonitrile oxide (15) explodes at 160°C.



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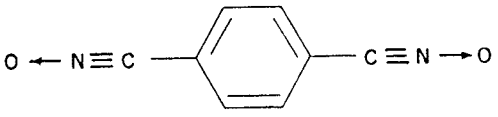

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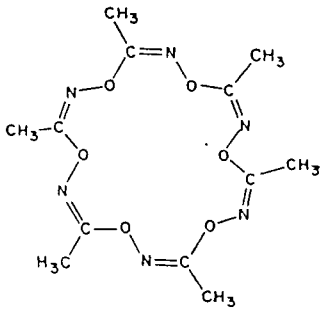

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1.2.2 POLYMERIZATION OF NITRILE OXIDES

Spontaneous polymerization rather than the explosivity is the main difficulty in working with the nitrile oxides. Most frequently the nitrile oxides undergo dimerization to furoxans (9). Other oligomers such as 16 have also been isolated as polymerization products.[28]

1.2.3 STABILITY AND DEOXYGENATION OF NITRILE OXIDES

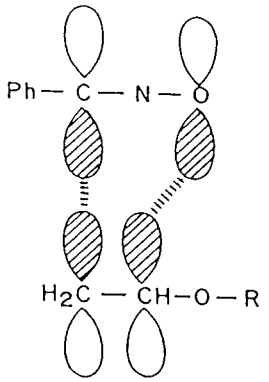
Nitrile oxides (8) when heated above their limits of stability, undergo two different competing reactions viz., dimerization to furoxans (9) and rearrangement to isocyanates (10). Deoxygenation of nitrile oxides to nitriles has been effected by zinc-dust and acetic acid or tin and hydrochloric acid.[29-34] Isocyanides,[35] dicobalt-octa-carbonyl,[36] trialkyl- and triarylphosphines or trialkylphosphites[37] are employed for the deoxygenation of nitrile oxides, the most effective of all the methods being the reaction with phosphorous compounds.

1.3 ADDITION REACTIONS OF NITRILE OXIDES WITH NUCLEOPHILES

Owing to their dipolar structure, the nitrile oxides manifest very high reactivity and undergo 1,3-addition reaction with organic as well as inorganic (Scheme 2 and Scheme 3) nucleophiles or cycloaddition with alkenes to form heterocyclic compounds.[26,27]

1.4 1,3-DIPOLAR CYCLOADDITION REACTIONS OF NITRILE OXIDES

The reaction between a nitrile oxide and an unsaturated compound (dipolarophile) follows Eq.1, where the more negatively



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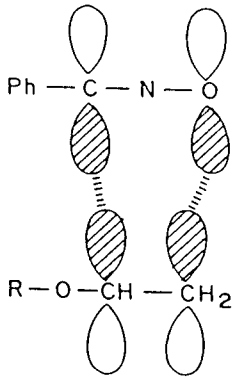

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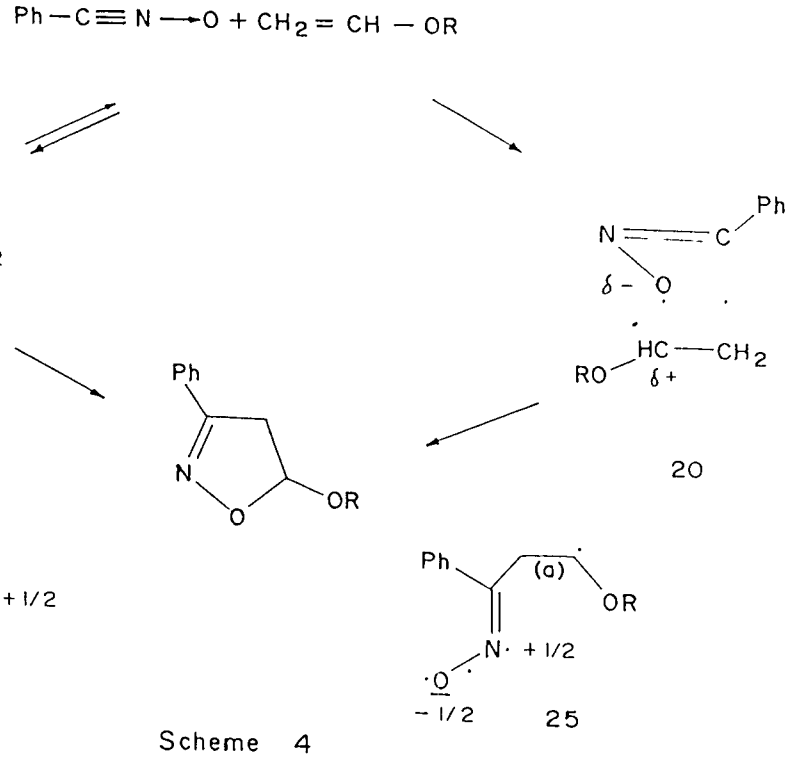
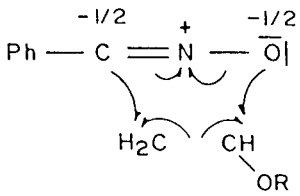
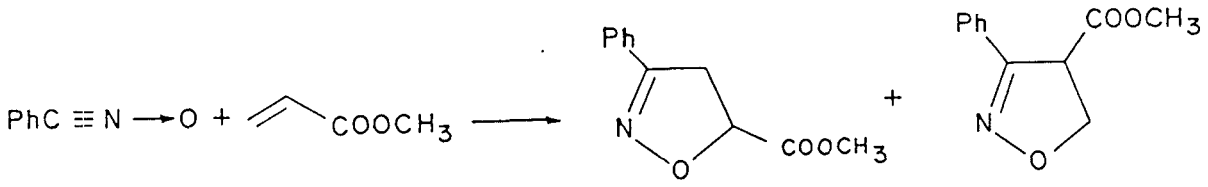


Scheme 4



26

charged end of the dipolarophile attacks the carbon atom of the nitrile oxide. However, the above equation does not represent the reaction completely; but only to a minor extent (usually <1 to 10%), the inverse addition is observed.[38] Since the nitrile oxides react in their 1,3-dipolar mesomeric structure and since the products are cyclic compounds, these reactions are termed 1,3-dipolar cycloaddition reactions.[38] When benzonitrile oxide (17) cycloadds to methyl acrylate, besides the normal product 18, a minor amount of the 'wrong' adduct 19 is also formed(Eq.2). With



17 18 (96%) 19 (~4%)

· · · (Eq. 2)

methyl β,β-dimethylacrylate, aliphatic and aromatic nitrile oxides yielded exclusively the 'wrong' adduct of type 19. This serves to emphasise that no single charge distribution formula should be considered to be solely responsible for the 1,3-dipolar cycloadditions of nitrile oxides and that steric factors are far more important in determining the reactivity of the dipolarophile than electronic influences.

1.4.1 MECHANISM OF 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES

The question of concertedness (that is, the timing of the formation of the new bonds) in 1,3-dipolar cycloadditions of nitrile oxides has been under debate for the whole of the last decade.[39] The more widely accepted Huisgen mechanism, a concerted but not synchronous reaction entails a two-plane approach of the reactants to give a transition state (TS) 21 which bears partial charges and occurs early along the reaction coordinate (Scheme 4).[40,41]

Reactivity and selectivity in nitrile oxide cycloadditions have been accounted by Huisgen mostly on the basis of effects such as conjugation, stabilization of partial charges in the TS, maximum gain in σ-bond energy and steric effects.[40] Application of molecular orbital (MO) perturbation theory with special emphasis on HOMO-LUMO interaction has been used to explain the selectivity and reactivity problems of nitrile oxide cycloadditions. For example in the reaction of benzonitrile oxide with vinyl ether, the dominant interaction is $LUMO_{1,3\text{-dipole}}$-$HOMO_{dipolarophile}$ and the orientation complex 25 is more favoured than 26 as proved by the regiospecificity of the reaction.[12] On the other hand the higher stability of spin-paired cyclodiradical 23, in comparison with 24, explains the regiospecificity of the reaction in terms of Firestone's mechanism.[42] However, in the

latter mechanism one has to accept that diradicals of the type 23 isomerise considerably more slowly by rotation around bond (a) than they revert to the starting addends or collapse to products. This assumption is essential to account for the experimentally observed strict stereospecificity of nitrile oxide cycloadditions. Moreover, Harcourt, on the the basis of quantum-mechanical calculations has shown that a concerted diradical (26) mechanism seems more reasonable than a stepwise one.[43] Poppinger[44,45] and Schaefer and associates[46], on the basis of ab initio MO studies on the reaction of fulminic acid plus acetylene, have shown that the predicted transition state resembles more closely the reactants than products, the most relevant change being marked trans bending of the HCNO skeleton. In contrast with Huisgen's two-plane approach, all the atoms in the transition state lie in one plane. Even if this atomic array were to be correct, Poppinger[45,46] suggested that conjugative stabilization should be very small in such an early transition state (TS) and consequently does not entail an appreciable increase in reactivity of alkyne dipolarophiles compared with alkenes.

Although the TS looks relatively symmetric on geometrical grounds, this does not necessarily mean that the process is a synchronous one. In fact the force constants calculated by Schaefer[46] for the C...C and C...O bonds in the TS are 3.07 and

0.31 mdyn/A°, respectively, implying that the C...C bond is about ten times stronger than the C...O bond. The similarity in the bond lengths is simply due to the fact that C-O is shorter than C-C, so when both bonds are stretched to ca.2.20 A° C...C is still strong while C...O has almost vanished. MNDO calculations magnify this asynchronism indicating the possibility of zwitterionic intermediates in the reaction.[47] However MNDO tends to exaggerate interatomic repulsions around van der Waal's distances and consequently fails to reproduce very weak bonds (such as C...O in the TS). A study by Houk and associates has evidenced that calculations which include overlap (EH, ab initio) favour a two-bond symmetrical TS for fulminic acid plus acetylene, whereas semiempirical calculations which neglect overlap (MINDO/2, MINDO/3 and CNDO/2) favour one-bond unsymmetrical geometry for the TS.[48] This discrepancy has been attributed to an inherent defect (neglect of overlap) of the latter methods which leads to an underestimation of closed-shell repulsion in a highly asynchronous transition state.

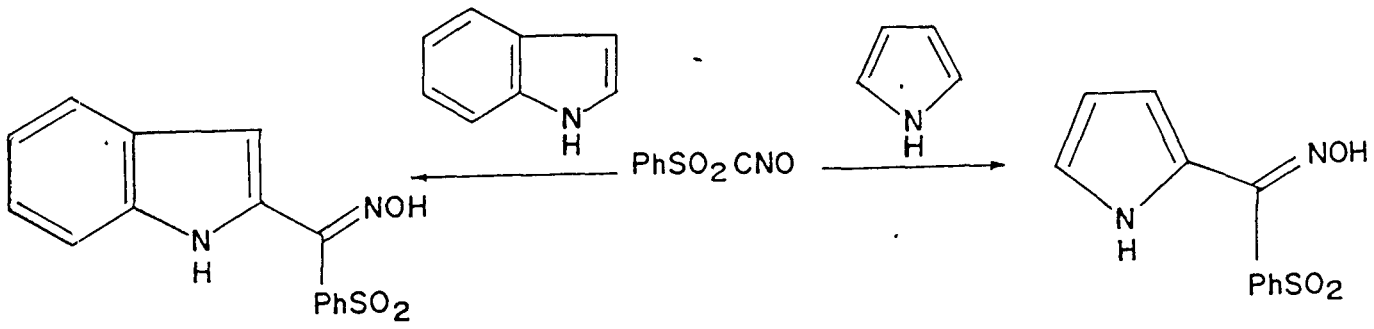
The conclusions are (i) a diradical intermediate may not be excluded a priori in the reaction of nitrile oxides with dipolarophiles of very similar FO energies (that is in the case of large HOMO-LUMO separations) when dipolarophiles bear a good radical stabilizer, (ii) the possibility of a dipolar intermediate must be

considered when an electron-poor nitrile oxide reacts with an electron-rich dipolarophile bearing also a good cation stabilizer and (iii) all experimental and theoretical data make, at present, the 1,3-dipolar cycloadditions of nitrile oxides one of the best examples of concerted but not synchronous cycloadditions.[49]

1.4.2 REACTIVITY OF NITRILE OXIDES WITH ALKENES

Nitrile oxides readily undergo cycloaddition with alkenes. Cycloaddition is faster with less substituted alkenes and conjugation enhances reactivity.[12] Terminal alkenes react easily while the reactivity of disubstituted ethylenes is more sluggish. For example, tetramethylethylene does not react with benzonitrile oxide at all[12] while benzenesulphonylcarbonitrile oxide undergoes cycloaddition with tetramethylethylene proving the high reactivity of the above oxide over the other nitrile oxides.[50] Cyclohexene does not react with equimolar quantities of benzonitrile oxide, nevertheless isoxazolines can be prepared from cyclohexene when the nitrle oxides are generated insitu.[51] More strained double bonds such as those in bicyclo[2.2.1]hept-2-ene, cyclopentene, cyclobutene, cyclopropene, benzvalene, hexamethyldecabenzene, benzocyclopropene, acenaphthylene, methylenecyclobutane etc. show higher dipolarophilic activity.[52] Exocyclic double bonds are found to react far more easily than endocyclic double bonds.[53]

Cycloaddition with heteroaromatic systems such as furan, thiophene, benzofuran, benzothiophene have been observed when these are reacted with nitrile oxides generated insitu.[54,55] Pyrrole and indole derivatives have been found to react with benzenesulphonylcarbonitrile oxide and the sulphonyl oximes (**27a and 27b**) are obtained as the products instead of the isoxazolines (Eq.4).[56] Thiophene-1,1-dioxide, benzothiophene-s-oxide,



27 a

27 b

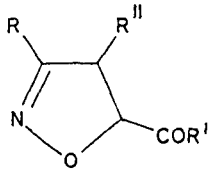
...(Eq. 4)

benzothiophene-s,s-dioxide have also been reacted with nitrile oxides and the selectivity of cycloaddition to these systems is on record.[57]

α,ß-Unsaturated carbonyl compounds[58] undergo cycloaddition with nitrile oxides in a very facile manner to yield varying amounts of the two regioisomers 28 and 29 (Table 2).

Table 2

Ratio of Regioisomers Formed from the Reaction of Substituted Benzonitrile Oxides to α,β-Unsaturated Ketones[58]



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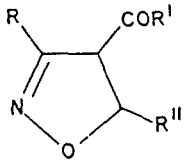

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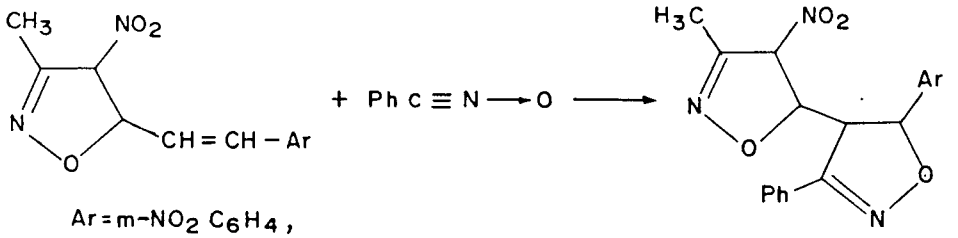
S.No	R	R'	R"	Ratio of 28 : 29
1	Ph	Me	Ph	58 : 42
2	Ph	Et	Ph	48 : 52
3	p-$CH_3C_6H_4$	Me	Ph	54 : 46
4	2,4,6-$(CH_3)_3C_6H_2$	Me	Ph	28 : 72
5	p-BrC_6H_4	Me	Ph	66 : 34
6	p-$CH_3OC_6H_4$	Me	Ph	56 : 44
7	p-$NO_2C_6H_4$	Me	Ph	67 : 33

Mixtures of regioisomers have been isolated in the reactions of β-substituted-α,β-unsaturated esters, sulphides, sulphones etc. Olefines such as indene, benzofuran, benzothiophene also yield mixtures of regiomers with nitrile oxides.[59] The ratio of regioisomers formed by the cycloaddition of benzonitrile oxide with benzofuran and benzothiophene are shown in Table 3.



Ar = m-NO_2 C_6H_4 ,

o -Cl C_6H_4 etc

32

Ar = m – NO_2 C_6H_4 ,

o -Cl C_6H_4 etc

33

··· (Eq. 5)

34

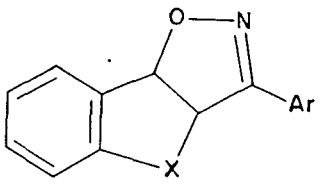
R = Me, Ph

35

··· (Eq. 6)

Table 3

Ratio of Regioisomers Formed by the Benzonitrile Oxide Cycloaddition to Benzofuran, Indene and Benzothiophene[59]



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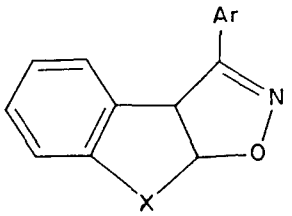

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S.No	X	Ratio of 30 : 31
1	O	70 : 30
2	S	78 : 22
3	CH_2	98 : 2

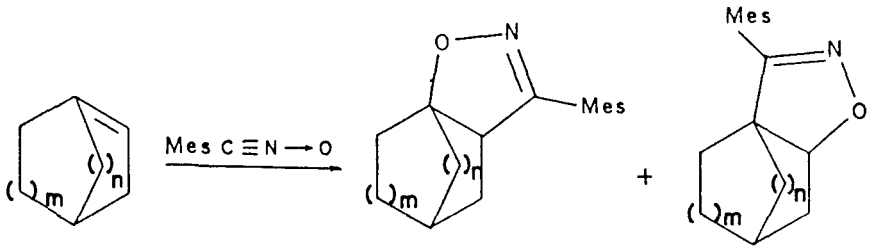
Benzonitrile oxide cycloaddition[60] to 3-methyl-4-nitro-5-styrylisoxazole (32) has been studied by Krishna Murthy et al. (Eq.5). Formation of adduct 33 in 15-25% yield has been ascribed to the polarization of the ethylenic double bond in 32 towards isoxazole nucleus due to the strong mesomeric effect of the nitro group which makes the ß-carbon positively charged. When 4-amino-3-methyl-5-styrylisoxazole (34) has been subjected to cycloaddition with acetonitrile oxide and benzonitrile oxide(Eq.6), addition of the nitrile oxide to the nucleophile viz., the amino group has taken place instead of the desired

cycloaddition.[61] This is in accordance with the earlier observations that the ethylenic linkage is less reactive than the primary amino group towards nitrile oxides.[12]

Regioisomers are isolated in the cycloaddition of nitrile oxides with Bredt alkenes (36) also.[62] Mesitonitrile oxide cycloaddition with these alkenes yielded the regioisomers 37 and 38 in the ratios shown in Table 4.

Table 4

Ratio of Regioisomers Formed by the Cycloaddition of Mesitonitrile Oxide to the Bredt Alkenes (36)[62]

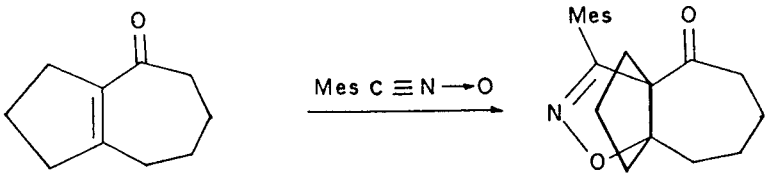


36 37 38

···(Eq. 7)

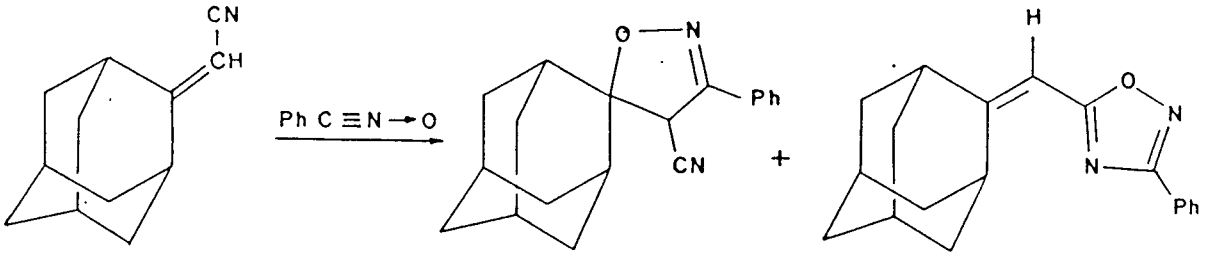
S.No	m	n	Ratio of 37 : 38
1	2	2	90 : 10
2	3	1	77 : 23
3	1	3	64 : 36

~~Isoxazolines of type 40 are formed by the nitrile oxide~~



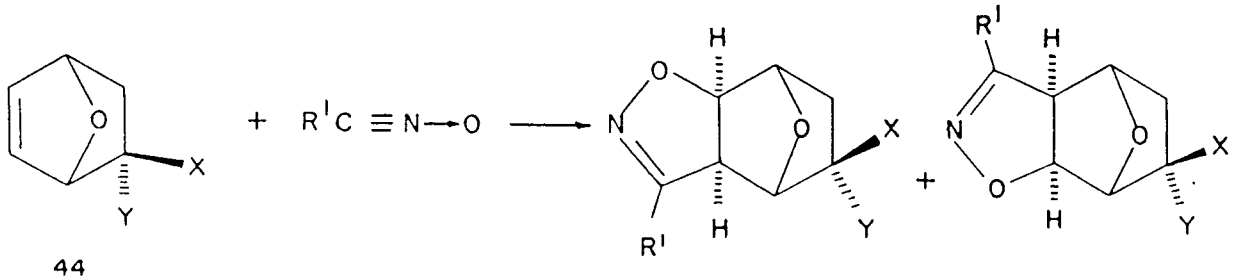
39 40

· · · (Eq. 8)



41 42 43

· · · (Eq. 9)



44 45 46

· · · (Eq. 10)

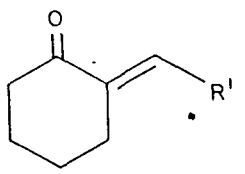
Isoxazolines of type 40 are formed by the nitrile oxide cycloaddition with propellanes (39) (Eq.8).[63] Higher reactivity of heteromultiple bonds with nitrile oxides than C-C-double bonds is exemplified by Eq.9. In this case C-N triple bond undergoes cycloaddition with benzonitrile oxide to form the adduct 43 in 50% yield whereas the isoxazoline 42 is formed in 2.75% only.[64]

Arjona et al.[65] have studied the cycloaddition of nitrile oxides with a series of 7-oxabicyclo[2.2.1]hept-2-enes (44) and concluded that only those 7-oxanorbornene derivatives bearing substituents at the double bond exhibit regioselectivity (Eq.10). The ratio of regioisomers formed in the above series are listed in Table 5.

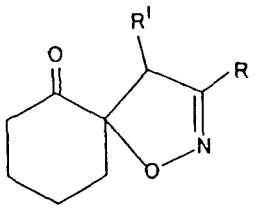
Table 5

Ratio of Regioisomers Formed by the Nitrile Oxide Cycloaddition with 7-Oxanorbornene Derivatives (44)[65]

S.No	X	Y	R	Ratio of 45 : 46
1	CN	OAC	Ph	60 : 40
2	CN	OAC	Mesityl	50 : 50
3	----- O -----		Ph	65 : 35
4	----- O -----		Mesityl	55 : 45
5	--OCH_2CH_2--		Ph	53 : 47
6	--OCH_2CH_2--		Mesityl	55 : 45

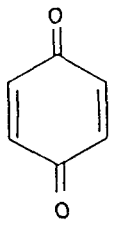


47

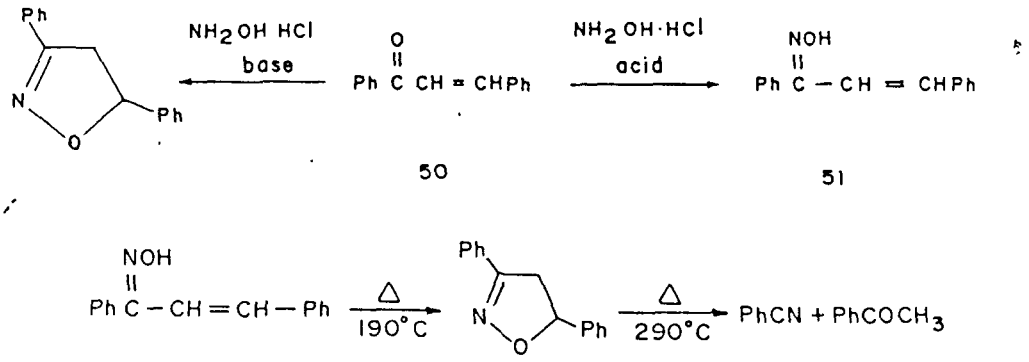


R^1, R = alkyl or aryl

48



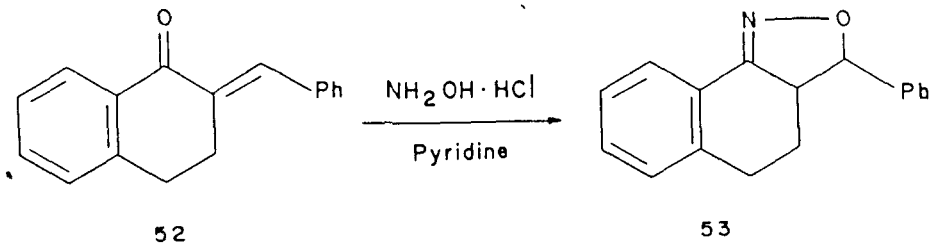
49



50

51

Scheme 5



52

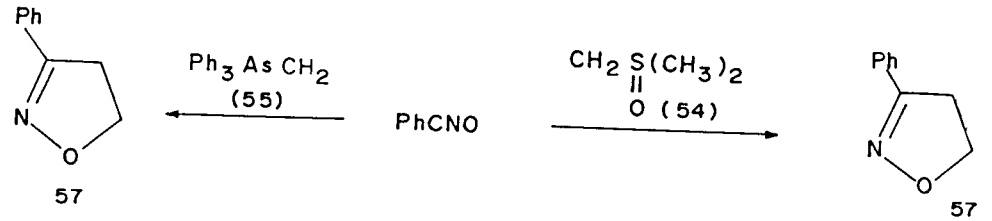
53

... (Eq II)

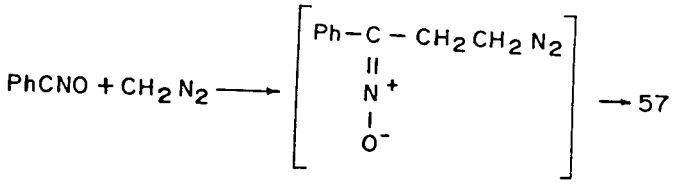
Alkylidene or arylidene cycloalkanones (47) yield spiro-isoxazolines of type 48 when treated with nitrile oxides.[12] Double bonds of p-quinones (49) also take part in cycloaddition with nitrile oxides to yield isoxazolines.[12]

1.5 REACTION OF α,β-UNSATURATED KETONES WITH HYDROXYLAMINE

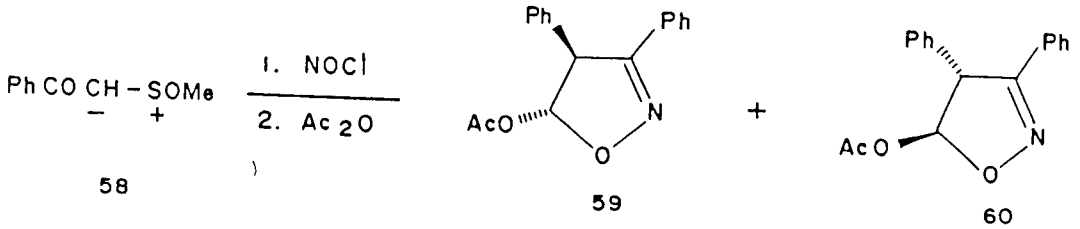
The reaction of hydroxylamine with α,β-unsaturated ketones or its precursors is one of the oldest methods used for the synthesis of 2-isoxazolines.[1] Other products such as simple oximes, oxime-hydroxylamine and Michael type products have been isolated in these reactions. The reaction of chalcone (50) with hydroxylamine yields 3,5-diphenyl-2-isoxazoline under basic conditions[66] whereas the simple oxime (51) is formed under acidic conditions.[67] However, the chalcone oxime (51) when heated to 190°C, is converted to 2-isoxazoline and further heating to 290°C leads to ring rupture (Scheme 5).[68] Isoxazoline 53 is formed when 2-benzal-1-tetralone (52) is treated with hydroxylamine hydrochloride (Eq.11).[69] α,β-Unsaturated ketone oximes yield 2-isoxazolines and isoxazoles when treated with reagents such as N-bromosuccinimide, I_2 or acid or when heated.[70,71]



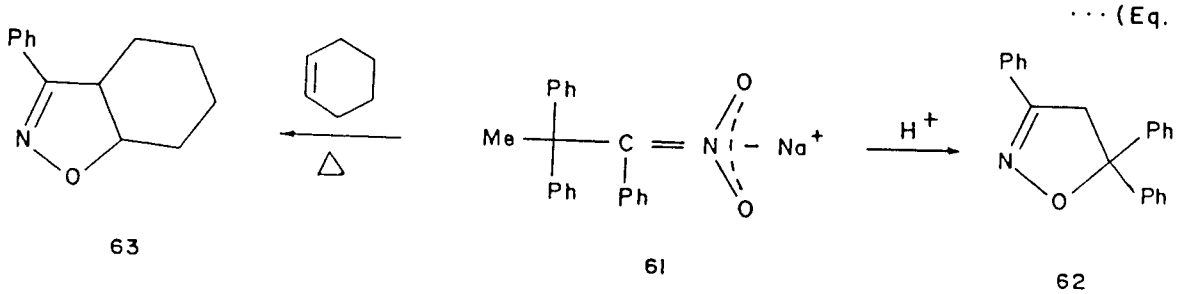
· · · · (Eq. 12)



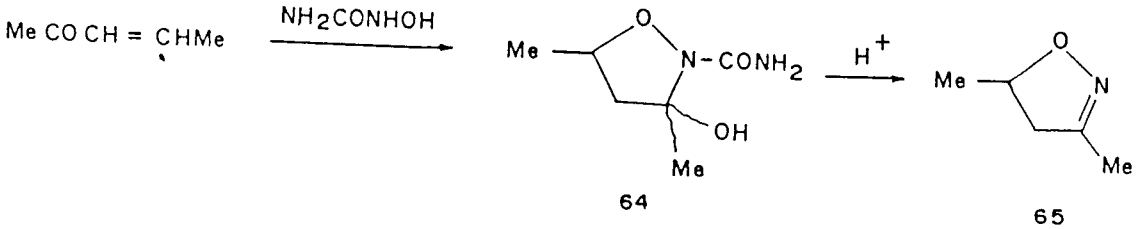
· · · (Eq. 13)



· · · (Eq. 14)



· · · (Eq. 15)



· · · (Eq. 16)

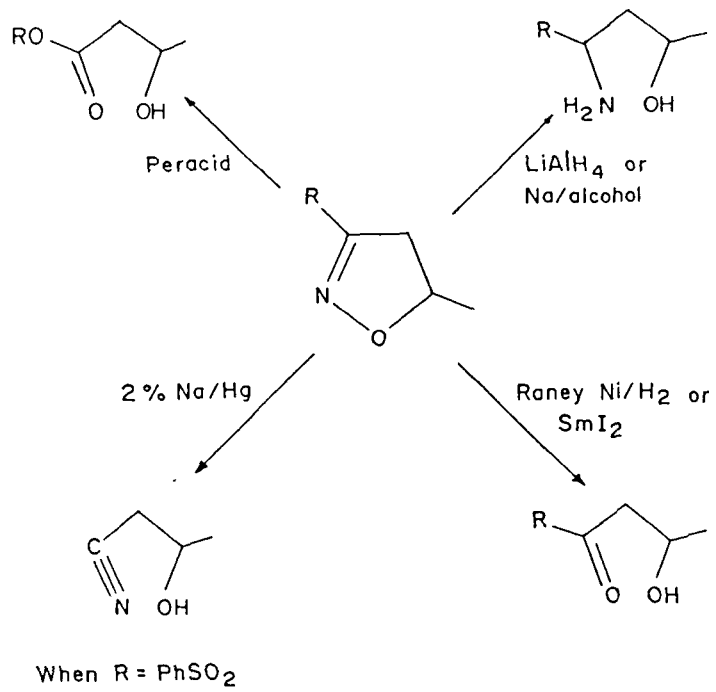
1.6 OTHER METHODS OF SYNTHESES OF 2-ISOXAZOLINES

The reaction of benzonitrile oxide with dimethylsulfonium methylylide (54) or triphenylarsonium methylylide (55) yields 3-phenyl-2-isoxazoline[72] (57) as shown in Eq.12. Isoxazoline 57 is formed when bezonitrile oxide reacts with diazomethane via the intermediate 56, as shown (Eq.13). Reaction of nitrosyl chloride with benzoyl methylylide 58 results in the formation isoxazolines[73] with trans configuration (Eq.14). Treatment of the sodium salt 61 with hydrochloric acid gave the isoxazoline 62 whereas the decomposition of 61, in the presence of cyclohexene, yielded the adduct 63 as shown (Eq.15).[74] Ketones when reacted with urea and N-hydroxyurea yield 2-isoxazolines and 3-hydroxy-2-carbamoylisoxazolidines, respectively (Eq.16) and the latter is converted to 2-isoxazolines by treatment with acid.[75]

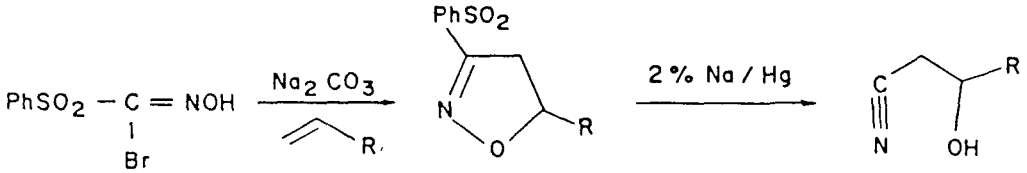
Other less frequently employed methods include reaction of phenyldiazonium salts with malanaldioxime, reaction of diphenylcyclopropane with nitrosyl chloride, thermolysis of aziridinyl phenyl ketone oxime and photolysis of diazoketone.[76]

1.7 `REDUCTIVE AND OXIDATIVE OPENING OF 2-ISOXAZOLINES

The products of 1,3-dipolar cycloaddition of nitrile oxides with alkenes, 2-isoxazolines, serve immensely as useful building blocks for several complex molecules.[77,78] The presence of

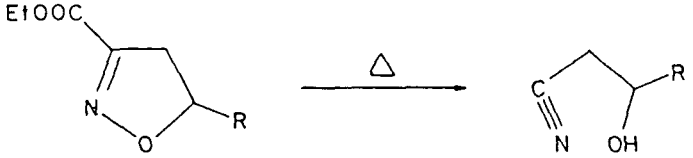


Scheme 6



66 67 68

···(Eq. 17)

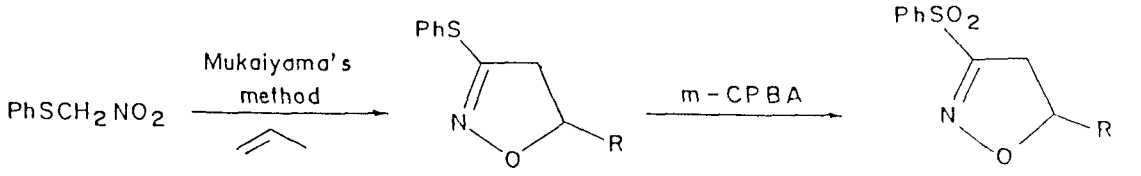


69 68 ···(Eq. 18)

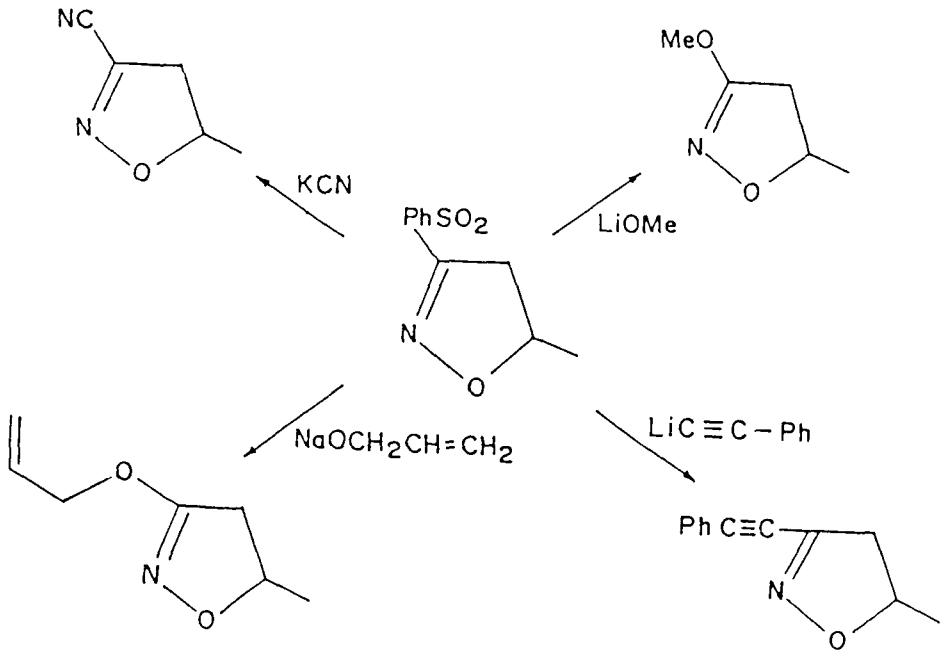
relatively stable -C=N-O- moiety allows manipulation at other parts of the isoxazoline molecule and after the desired functional groups have been introduced (by way of modification), the isoxazoline ring is cleaved to give the required acyclic products. The isoxazoline ring is cleaved by various reagents (Scheme 6) such as $LiAlH_4$, Ni/H_2, Na/Hg, peracetic acid, Ti^{3+} etc. Reductive opening of isoxazolines are widely explored.[79-83]

1.7.1 syn-CYANOHYDROXYLATION OF ALKENES VIA 3-PHENYLSUPHONYL-2-ISOXAZOLINES

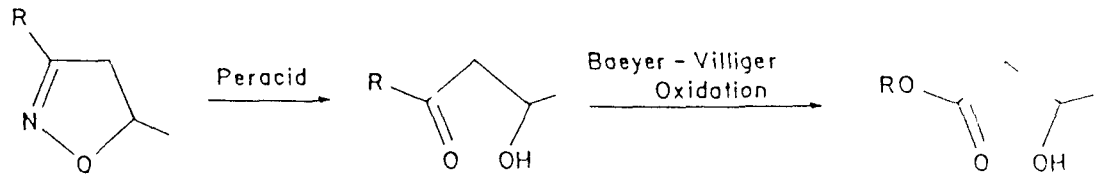
syn-Cyanohydroxylation of alkenes has been achieved through a 2 step process involving 3-phenylsulphonyl-2-isoxazolines (67) by Wade et al. (Eq.17). The required 3-phenylsulphonyl-2-isoxazolines have been obtained by the cycloaddition of benzenesulphonylcarbonitrile oxide to various alkenes. Treatment of these 3-phenylsulphonyl-2-isoxazolines (67) with 2% Na/Hg afforded the ß-cyanohydrins (68) in good yields.[84] The method of Kozikowski's group employed 3-carbethoxy-2-isoxazolines (69) which under pyrolytic conditions to yield ß-cyanohydrins (Eq.18).[85] Recently Curran and Chao[86] reported the preparation of 3-phenylsulphonyl-2-isoxazolines (67) from phenylthionitro-methane (70) as shown (Eq.19). This method overcomes the difficulty in preparing the phenylsulphonylbromooxime (66) which is used as the precursor in Wade's method.



69 70 ···(Eq 19)



Scheme ' 7



71 72

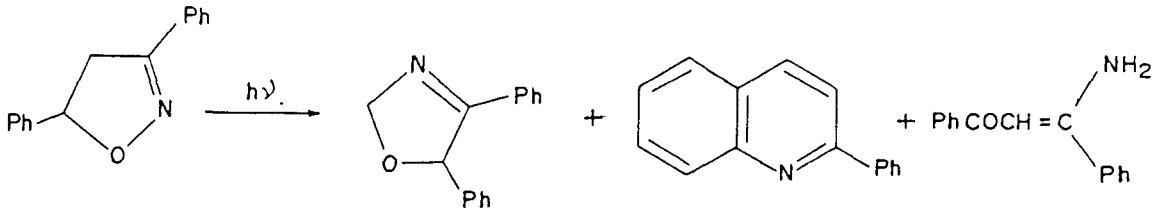
(Eq 20)

1.7.2 NUCLEOPHILIC SUBSTITUTION REACTIONS OF 3-PHENYLSULPHONYL-2-ISOXAZOLINES

Wade et al. have developed a novel method of synthesis of a wide variety of 3-substituted isoxazolines via 3-phenylsulphonyl-2-isoxazolines. The phenylsulphonyl group has been substituted by nucleophiles such as -CN,-OMe etc. which provides an easy entry to these 3-substituted isoxazolines (Scheme 7).[87] For example introduction of an -OMe or -CN group at 3-position of the isoxazolines is very difficult under normal conditions and the method involving 3-phenylsulphonylisoxazolines does this in a facile manner.

1.7.3 SYNTHESIS OF DIOL MONOACETATES BY PERACID OXIDATION OF 2-ISOXAZOLINES

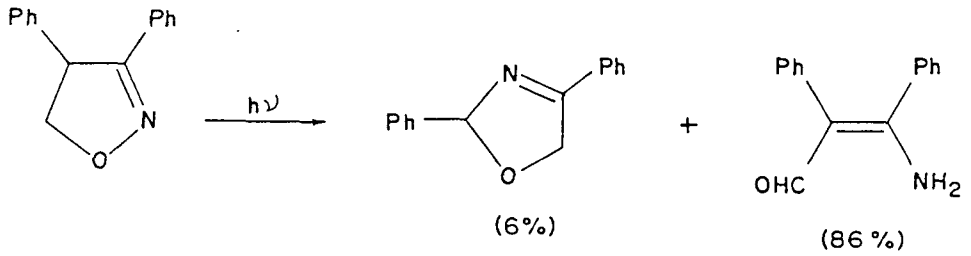
Kozikowski and Park have discovered the conversion of 2-isoxazolines to diol monoacetates (72) during the total synthesis of streptazolin (Eq.20).[88] Several authors have previously employed peracids for the oxidation of side-chains of 2-isoxazolines and they failed to observe the opening of 2-isoxazoline ring.[89] In the reaction reported by Kozikowski and Park, the isoxazoline ring is cleaved to ß-hydroxy ketone followed by Baeyer-villiger oxidation to form the diol monoacetates.



(19%) (15%) (3%)

73 74 75

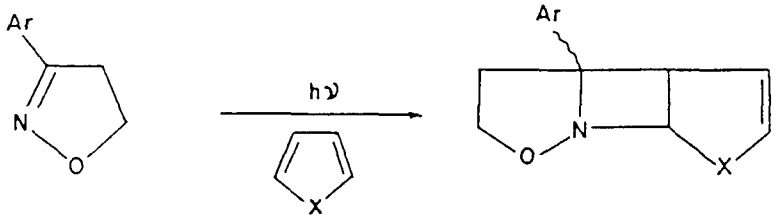
···(Eq. 21)



(6%) (86%)

76 77 78

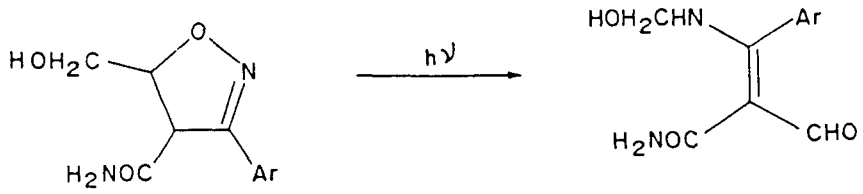
···(Eq. 22)



79 X = S, O

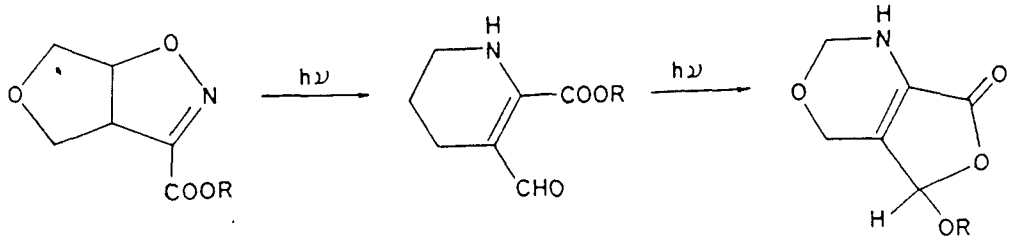
80

·(Eq. 23)



81 82

···(Eq. 24)



83 84 85

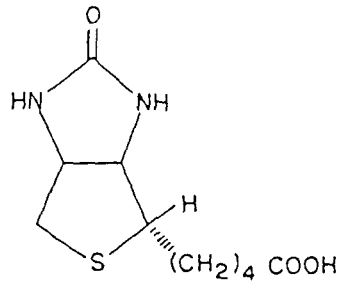
···(Eq. 25)

1.8 PHOTOCHEMICAL TRANSFORMATIONS OF ISOXAZOLINES

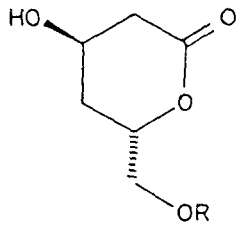
Isoxazolines upon irradiation undergo nitrogen-oxygen bond fission as the primary process (Eq.21) to produce a variety of products.[90-92] In these reactions rotation about C(4)-C(5) bonds brings about the conversion of isoxazolines to oxazolines[93] (Eq.22). When furan or thiophene is used as solvent, irradiation of isoxazolines leads to [2+2] addition products[94] (Eq.23). Fisera et al. have reported the conversion of 2-isoxazolines to ß-enaminoaldehydes by photochemical means.[95-97] Irradiation of 5-hydroxymethyl-2-isoxazolines yields the ß-enaminoaldehyde (82) (Eq.24) while 3-alkoxycarbonyl-2-isoxazolines yield the alkoxy furanone (85) via the enaminoaldehyde[98] (Eq.25).

1.9 ELECTROCHEMICAL REACTIONS OF ISOXAZOLINES

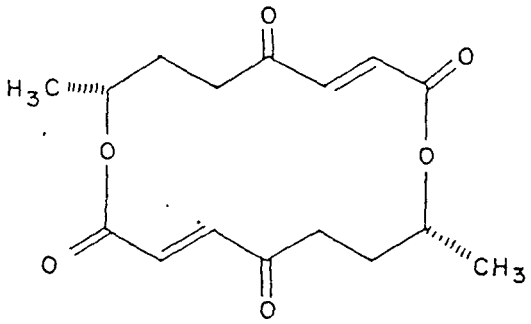
Electrochemical studies on 2-isoxazolines have not been exploited much though chemical reduction and oxidation of isoxazolines have been investigated in detail. Electrochemical reduction of benzoxazinone,[99] ketimines, oximes, azines, phenylhydrazones, semicarbazones etc.,[100] have been investigated. Electrochemical oxidative hydrolysis[101] of ketonoximes has been studied. Anthranils,[102-104] oxazoles and thiazolidine[105] have also been reduced electrochemically. Lund and Surov studied the reduction of 2-isoxazolines and their quarternized derivatives by



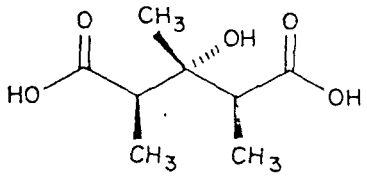
86 Biotin



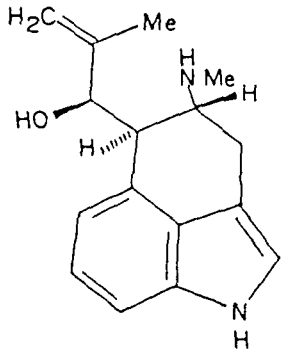
87 Compactin Lactone



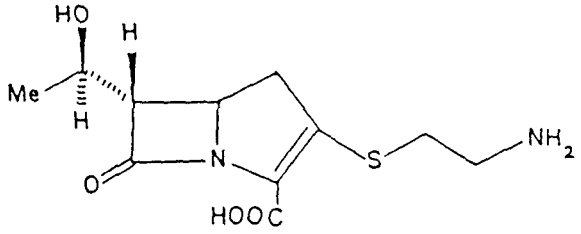
88 (+) Pyrenophorin



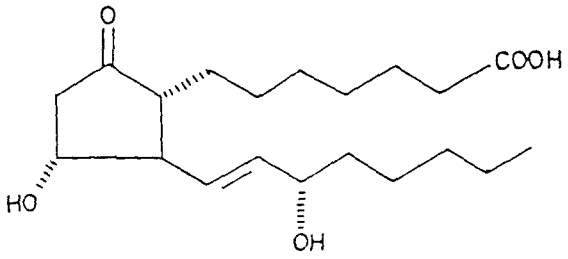
89 Crispatic acid



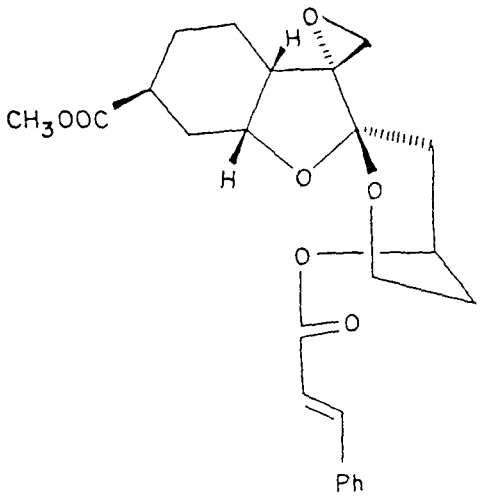
90 (+) Polyclavine



91 Thienamycin



92 Prostaglandin



93 (+) Phyllanthocin

polarography.[106] Reductive cleavage of the C-N double bond occured for the quarternized compounds in protic media whereas this occured for isoxazolines in aprotic media. Thus hydroxy ketones are formed by the reduction of the quanternized compounds. 3,5-Diphenyl-2-isoxazoline showed a four-electron wave at the dropping mercury electrode (DME) in acidic solution. They found that quarternization activates the cleavage of the nitrogen-oxygen bond which makes them reducible at a less negative potential, thus paving a way to ß-hydroxyketones via 2-isoxazolines.

1.10 SYNTHESIS OF BIOLOGICALLY IMPORTANT COMPOUNDS VIA 2-ISOXAZOLINES

Application of nitrile oxide cycloaddition to the synthesis of natural products has gained importance and several papers have appeared in the literature concerning the total synthesis of antitumor active compounds,[4-8] polyether antibiotics[107] etc. Chalcones, flavones, isoflavones[108], furans are some of the other classes of compounds synthesised through nitrile oxide cycloaddition. Biotin[109] (86), compactin lactone[110] (87), (±)pyrenophorin[111] (88), crispatic acid[112] (89), (+)polyclavine[113] (90), thienamycin[114] (91), prostanoids[115] (92), steroids[116] (93), (+)phyllanthocin[117] (94) have been synthesised through the intermediacy of 2-isoxazolines.

1.11 CONVERSION OF 2-ISOXAZOLINES TO ISOXAZOLES

Oxidation of the isoxazolines have been carried out with NBS, SeO_2, $KMnO_4$ and γ-MnO_2.[118] Of all the reagents, γ-MnO_2 effects the conversion to nearly quantitative yields of isoxazoles. Other products such as 4-bromoisoxazolines are formed when NBS is used. Ring rupture leading to acyclic products have been observed with $KMnO_4$ oxidation of isoxazolines. Khisamutidinov's group has converted 4-nitroisoxazolines to isoxazole derivatives[119] by treatment with $KMnO_4$, while oxidation with hydrogen peroxide yielded 4-isoxazolones.[120] DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) has also been employed for the dehydrogenation of 2-isoxazolines.[121]

1.12 SCOPE OF THE PRESENT WORK

In view of the pseudorotating nature of five-membered rings with heteroatoms, it is proposed to study the effect of introduction of heteromultiple bonds on the conformational mobility of five-membered rings by choosing isoxazolines. It is quite evident that tetrahydrofuran, tetrahydrothiophene, etc. exist in nearly planar conformations due to pseudorotation. However, incorporation of multiple bonds in the ring prevents such conformational mobility as observed in the case of pyrazolines.

Since isoxazolines are similar to pyrazolines in the arrangement of heteroatoms and multiple bond, we wished to know whether there exists any similarity in the conformations of these two dihydroaromatic systems. For this purpose the proton nmr spectra for the isoxazolines 1-11 have been recorded. The effect of changing the bulkiness of the substituent at C-5 position of the isoxazoline, on the conformational mobility of the heterocyclic ring could be derived from the proton nmr spectra of these compounds. Isoxazolines with cyclohexyl group as C-5 substituent have been chosen with a view to know whether there arises any conformational equilibrium because of the ring flipping of the cyclohexane ring.

Evaluation of methyl substituent parameters for heterocyclic compounds has been studied extensively. In order to know the effect of methyl substitution in isoxazoline system, the ^{13}C nmr spectra for isoxazolines 1a - 1e, 2a - 2e, 4a - 4e and 5a - 5e have been recorded. The methyl substitutent parameters (α, β, γ and δ effects) could be derived from the spectral data of these isoxazolines. Also aimed in the present investigation is to know the effect of changing the substituent at C-3 from alkyl to aryl group, on the chemical shift values of the isoxazoline and ring carbons.

The effect of substitution of isoxazoline ring for one of the hydrogens in 1-butane and dimethyl sulphide, could be evaluated from the ^{13}C nmr spectral data of the isoxazolines 6a-6e, 7a-7e. The parameters derived out of this set of compounds represent α, β, γ and δ effects.

Mass spectral fragmentation patterns of different isoxazolines have been obtained by analysing the mass spectra of the isoxazolines 1-11. The effect of changing the substituent at C-5, on the mass spectral fragmentation pattern of the isoxazolines has been studied. When there are two substituents at C-5 position of the isoxazolines either one of them may be lost preferentially over the other. In order to know the preferential loss of the substituents at C-5, 5,5-disubstituted isoxazolines 2a-2e, 5a-5e have been chosen. The mass spectra of these compounds will show which group will be lost preferentially when there are (i) alkyl and aryl groups and (ii) alkyl and $COOCH_3$ at the C-5 position. The mass spectra for isoxazolines with 2-methylphenyl group at C-5 position have been recorded with an idea of knowing whether the CH_3 group is lost preferentially from the molecular ion over the 2-methylphenyl group or vice versa.

The results of the above studies are discussed below.