CHAPTER I

Theoretical approach and Review work

General

The term "1,3-dipole", $\overset{+}{a}\text{——}b\text{——}\overset{-}{c}$ may be defined such that atom "a" possesses an electron sextet, that is an incomplete valence shell combined with a formal positive charge and the atom c, the negatively charged center, has an unshared pair of electrons and undergoes 1,3- dipolar cycloaddition to a multiple bond system called "dipolarophile".

Since compounds with 6 electrons in the outer shell of an atom are usually not stable, the a-b-c system is actually canonical form of a resonance hybrid for which at least one other structure may be drawn e.g.
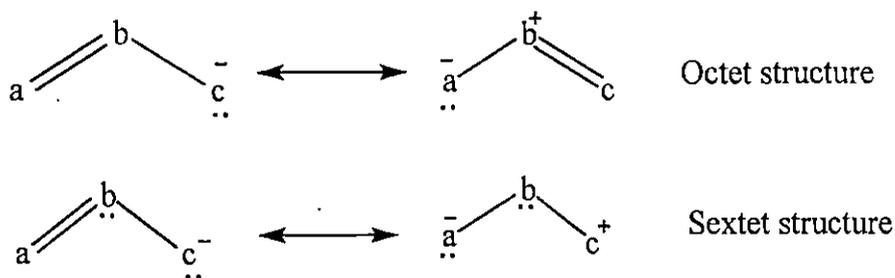

Octet structure

Sextet structure

Fig 1

1,3-dipoles can be further stabilized by internal octet stabilization. 1,3-dipolar compounds can be divided into two main types:

(1) Propagyl - Allenyl type

Those in which the dipolar canonical form has a double bond on the sextet atom and other canonical form a triple bond on that atom.

$$\overset{+}{a}\!\!=\!\!b\text{——}\overset{-}{c} \quad\longleftrightarrow\quad a\!\!\equiv\!\!\overset{+}{b}\text{——}\overset{-}{c}$$

Fig 2

(2) Allyl type

Those in which the dipolar canonical form has a single bond on the sextet atom other form a double bond.

$$\overset{+}{a}\text{---}b\text{---}\overset{-}{c} \longleftrightarrow a\text{==}\overset{+}{b}\text{---}\overset{-}{c}$$
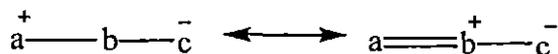
Fig 3

1,3-dipoles can be represented as depicted in Fig III. In this 1,3-dipoles, the central atom is never a carbon atom. If the central atom be a carbon function then internal octet stabilization is prevented by lack of an available free electron pair. Such systems are therefore extremely reactive and short lived. Examples of this type are unsaturated carbenes and azenes.

1, 3-dipole

1,3-dipole participates in the [3+2] cycloaddition reactions which form 5-membered ring systems, in an analogous way to the Diels-Alder process which forms 6 membered rings. The reactive partners in this reaction are 1,3-dipoles and dipolarophiles (c.f. diene and dienophile in the Diels-Alder reaction). It is a $4\pi+2\pi$ process as well.
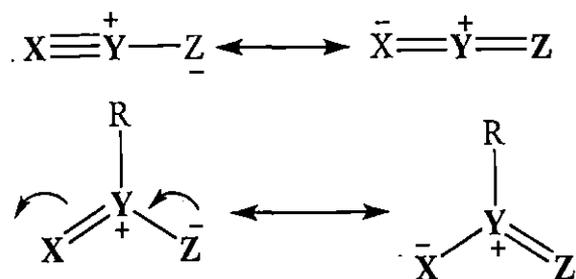
$$X\equiv\overset{+}{Y}\text{---}\overset{-}{Z} \longleftrightarrow \overset{-}{X}\text{==}\overset{+}{Y}\text{==}Z$$

X, Y, Z = C, N, O, S, P......

Fig 4

1,3-dipoles vary in stability greatly. Some can be isolated and stored, others are relatively stable, but are usually made the same day as their use.

In order to compare the stability of nitrones the secular determinant could be set up using the suggested parameter values[1] for hetero atoms for the use of simple LCAO (Linear combination of atomic orbitals) treatment viz.

$h_N^+ = 2$; $h_O^- = 2$; $K_{C-N} = 1.1$; $K_{N-O} = 0.7$ etc.

$$\begin{vmatrix} \alpha_0-\varepsilon & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_0-h_N+\beta_0-\varepsilon & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_0+h_0+\beta_0-\varepsilon \end{vmatrix} = 0$$

Putting the above values and $\alpha_0 - \varepsilon / \beta_0 = x$

$$\begin{vmatrix} x & 1.1 & 0 \\ 1.1 & x+2 & 0.7 \\ 0 & 0.7 & x+2 \end{vmatrix} = 0$$

The secular polynomial of the system was

$X^3 + 4X^2 + 2.3\,X - 2.4 = 0$

i.e. $X = 0.5175,\ -1.58775\ \&\ 2.9297$

Therefore the energy levels were

$\varepsilon_1 = \alpha_0 + 0.5175\,\beta_0$

$\varepsilon_2 = \alpha_0 - 1.58775\,\beta_0$

$\varepsilon_3 = \alpha_0 - 2.9297\,\beta_0$

and the total Π energy of system was

$E_\Pi = 4\alpha_0 + 5.03495\,\beta_0$

Approximate HMO calculation of nitrone 1

In order to verify the stability of N-phenyl-α-chloro nitrone (I), N-cyclohexyl-α-chloro nitrone[2] was taken as an example for the approximate HMO calculation.

The secular determinant for Nitrone 1 (N-phenyl-α-chloro nitrone) could be studied in two ways.

$$\begin{vmatrix} \alpha_0+2\beta_0-\varepsilon & \beta_{12} & \beta_{13} & \beta_{14} \\ \beta_{21} & \alpha_0-\varepsilon & \beta_{23} & \beta_{24} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\varepsilon & \beta_{34} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\varepsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0.4 & 0 & 0 \\ 0.4 & x & 1.1 & 0 \\ 0 & 1.1 & x+2 & 0.69 \\ 0 & 0 & 0.69 & x+2 \end{vmatrix} = 0$$

Thus solving x = 0.578; –1.5607; –2.9436; –2.0656.

The energy levels were

$\varepsilon_1 = \alpha_0 - 0.578\ \beta_0$

$\varepsilon_2 = \alpha_0 - 1.5607\ \beta_0$

$\varepsilon_3 = \alpha_0 - 2.9436\ \beta_0$

$\varepsilon_4 = \alpha_0 - 2.0656\ \beta_0$

the total Π energy of the system was

$E_\Pi = 4\alpha_0 + 7.1479\ \beta_0$

$$
\begin{vmatrix}
\alpha_0+2\beta_0-\varepsilon & \beta_{12} & \beta_{13} & \beta_{14} & \beta_{15} \\
\beta_{21} & \alpha_0-\varepsilon & \beta_{23} & \beta_{24} & \beta_{25} \\
\beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\varepsilon & \beta_{34} & \beta_{35} \\
\beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\varepsilon & \beta_{45} \\
\beta_{51} & \beta_{52} & \beta_{53} & \beta_{54} & \alpha_0+2\beta_0-\varepsilon
\end{vmatrix} = 0
$$

$$
\begin{vmatrix}
x+2 & 0.4 & 0 & 0 & 0 \\
0.4 & x & 0.9 & 0 & 0 \\
0 & 0.9 & x & 1.1 & 0 \\
0 & 0 & 1.1 & x+2 & 0.69 \\
0 & 0 & 0 & 0.69 & x+2
\end{vmatrix} = 0
$$

The energy levels were

$\varepsilon_1 = \alpha_0 - 1.129\ \beta_0$

$\varepsilon_2 = \alpha_0 - 1.20\ \beta_0$

$\varepsilon_3 = \alpha_0 - 0.555\ \beta_0$

$\varepsilon_4 = \alpha_0 - 2.954\ \beta_0$

$\varepsilon_5 = \alpha_0 - 2.4195\ \beta_0$

Total Π energy of the system was

$E_\Pi = 5\alpha_0 + 8.2575\ \beta_0$

Considering the calculated energy levels, associated with nitrone 1 it was expected to be moderately stable. The above assumption also could be rationalized on the basis of Fukui's Frontier Orbital Theory (FMO)[3]. Recently reported DFT study on the stability

of *C*-aryl-*N*-methyl nitrones basing upon Gaussian–2003 series computational programs[4,5,6] along with their graphical user interface Gauss view 2003 inspired us to use the program to study the stability of the reported nitrone **1**. Although we could not use series of computational program but elementary application of this methodology suggests that *N*-phenyl-α-chloro nitrone (**1**) is moderately stable & hence the nitrone is used in-situ for the 1,3-dipolar cycloaddition reactions.

The molecular orbital calculations performed by DFT study using B3LYP theory for *N*-phenyl-α-chloro nitrone shows -0.154 & -0.032 for HOMO & LUMO energies in Hartrees (1 Hartree = 27.21 eV). *N*-phenyl-α-chloro nitrone has a chlorine group at *β*-position of the nitrone which has a strong electron withdrawing nature & therefore the nitrone should be electrophilic in nature. The high reactivity of *N*-phenyl-α-chloro nitrone could also be explained on the basis of perturbation theory where the HOMO level of parent nitrone is raised in energy by the introduction of chlorine group on the *β*-carbon atom & the stabilization of the dipole LUMO level thereby providing the stabilization to the transition state for the cycloaddition & consequently increasing the rate of the reactions.

There are two general classes of dipole sometimes referred to as sp^2 and sp hybridized dipoles.

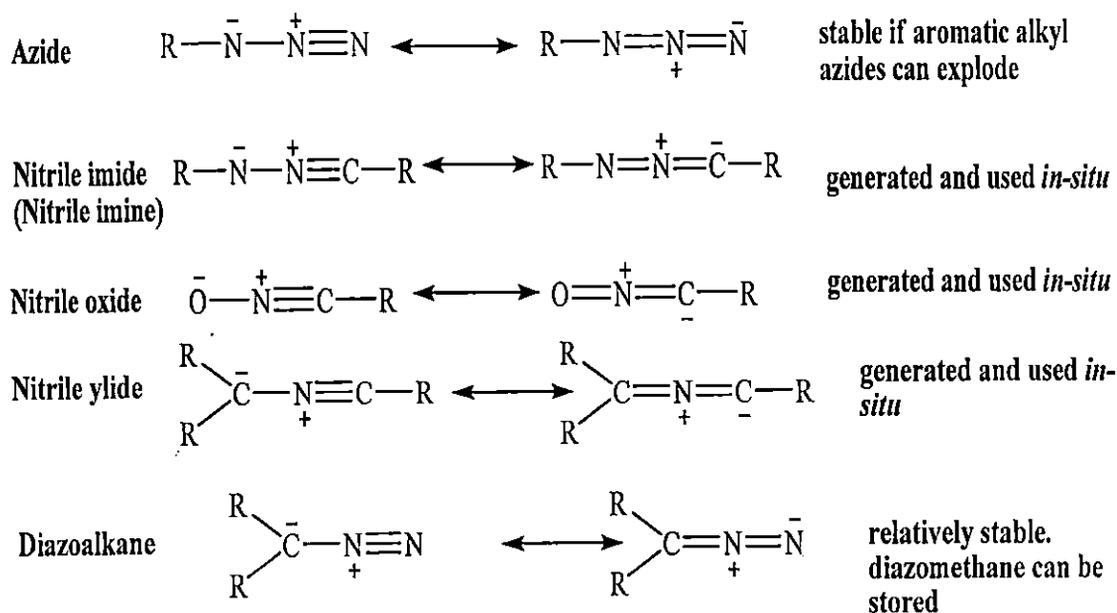*sp-dipolarophile* (linear dipoles like the propagyl anion)

Fig 5

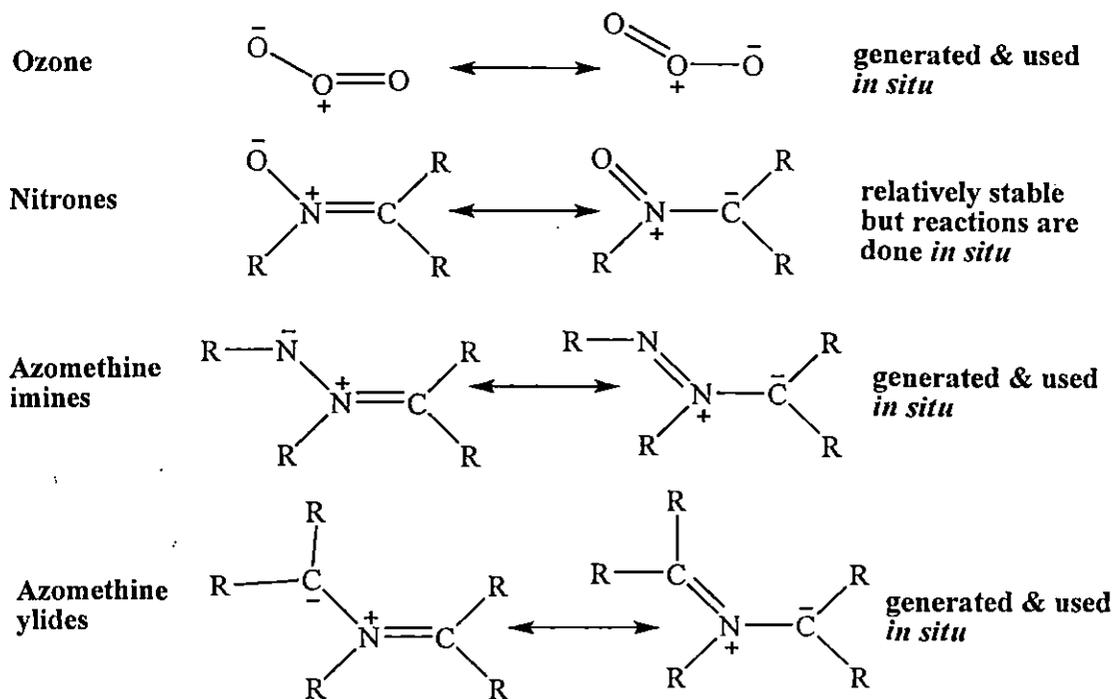*sp² hybridised* (bent dipoles like the allyl anion)

Fig 6

Reactivity profile of 1, 3-dipoles

The reaction between dipoles and dipolarophiles fit the following general profile:

(a) It is currently accepted that cycloadditions are concerted processes *i.e.* they have no distinct intermediates but the bond formation may be asynchronous.

(b) The reaction rates are not influenced much by solvent polarity indicating little change in polarity between reactants and transition state.

The rate of reaction between dipoles and dipolarophiles vary considerably. This can be explained by Fukui's Frontier Molecular Orbital Theory (FMO approach) which considers the interaction between molecular orbitals of the dipole and dipolarophiles.
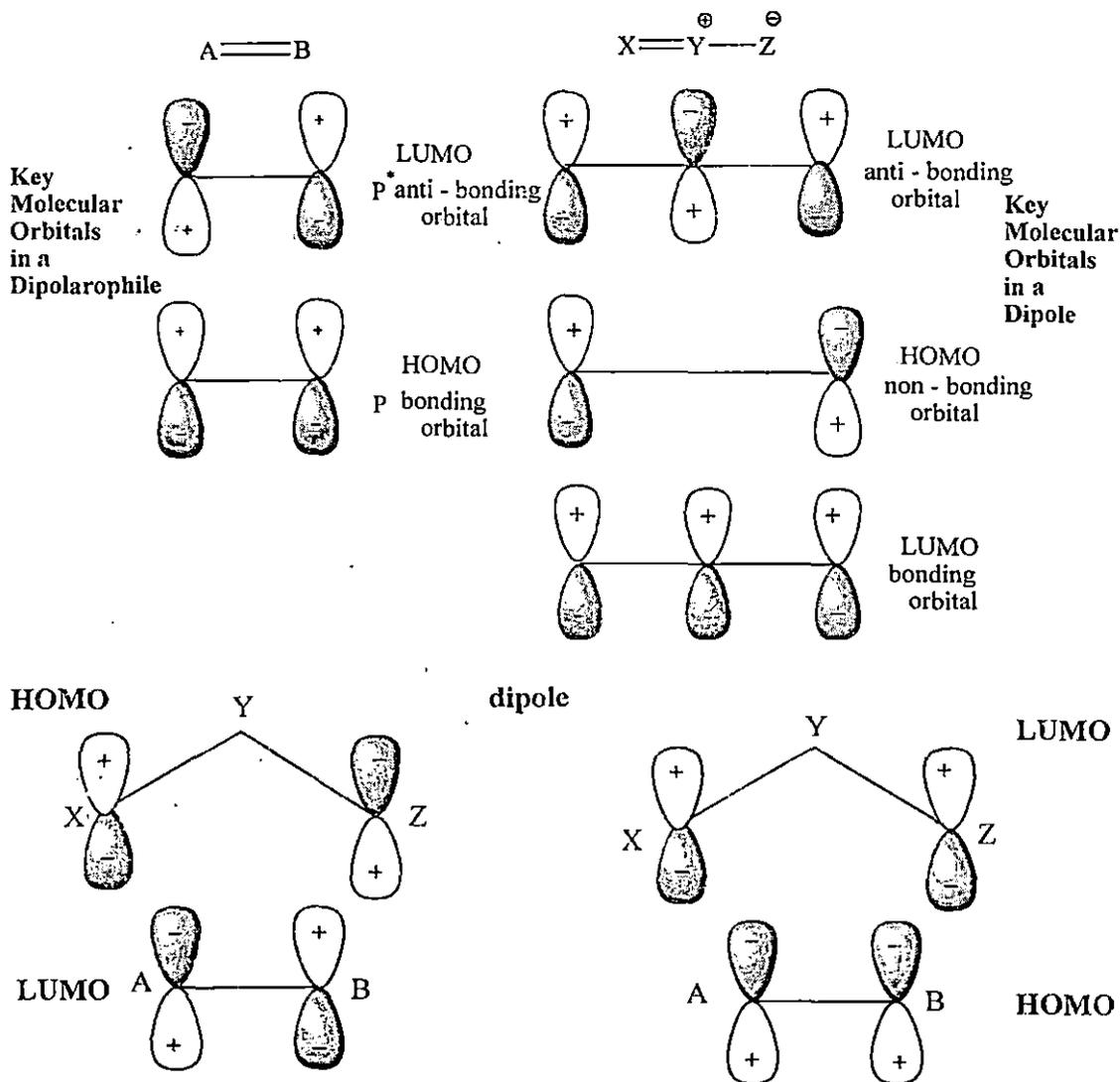
Fig 7

The term "nitrone" was coined from nitrogen ketone (azomethine oxide) in order to keep its resemblance to the carbonyl group in its several reactions[7].
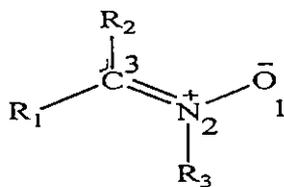

Fig 8

Nomenclature

The nitrones were known since 1887. The nomenclature employed by chemical abstract is as follows.

α-*N*-diphenyl nitrone

α-phenyl-α-(*p* –tolyl)-*N*-methyl nitrone.

The cyclic nitrones are named accordingly to the parent heterocyclic structures e.g. 2,4–dimethyl–Δ^1-pyrolidine-*N*-oxide, Δ^1–tetrahydropyridine-*N*-oxide etc. later, nitrones were named as *C*-cyclopropyl-*N*-methyl ketone, *C*-dicyclopropyl-*N*-methyl nitrone etc. The general term aldonitrones and ketonitrones have been employed occasionally. Aldonitrones contain a proton on the α-carbon atom.

$$RCH = N^+(O^-)\,R^1$$

While the ketonitrones contain the α-carbon fully substituted with alkyl or aryl group.

$$R, R^1\,C = N^+\,(O^-)\,R^2$$
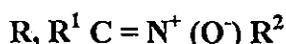
Geometrical isomerism

Nitrones may exhibit geometrical isomerism because of the double bond in nitrone molecule.

Fig 9

The existing geometrical isomerism was first demonstrated in 1918 for α-phenyl-α-(*p* -tolyl)-*N*-methyl nitrone[8] . The configuration of the isomers was established by dipole moment studies. The *cis* and *trans* forms were readily converted into the *trans* form by heating. Generally aldonitrones exist in stable *trans* form and this has been established by UV, IR, ^{1}H NMR studies[9]. The only example of geometrical isomerism is known for α-phenyl-*N*-tertiary butyl nitrone[10]. Therefore in such cases where geometrical isomerism is possible, *E* / *Z* notation may be employed for naming.

A nitrone is a 1, 3-dipole in 1, 3-dipolar cycloadditions. It reacts with alkenes to form *Isoxazolidines* and the scheme has been shown as follows.
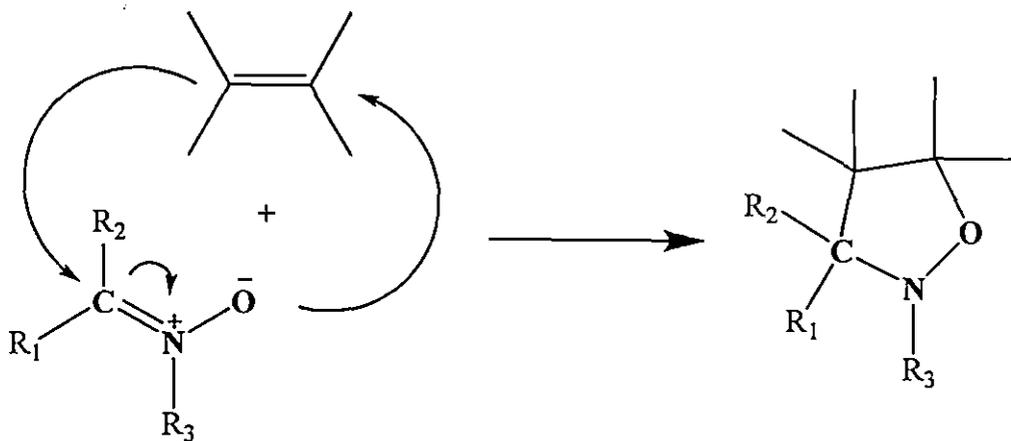
Fig 10

Similarly the nitrone can react as 1,3-dipole with alkynes in a in 1,3-dipolar cycloaddition reactions to form *Isoxazolines*.
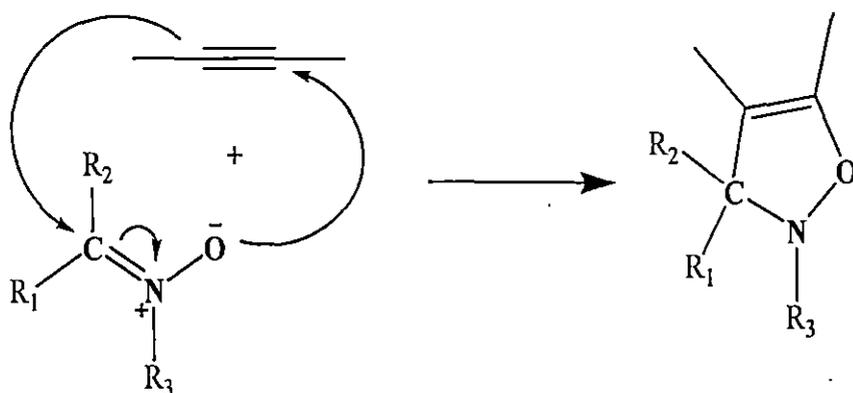

Fig 11

In allyl type of 1,3-dipole, if we restrict the atom a,b,c to carbon, nitrogen and oxygen, the nitrone results.
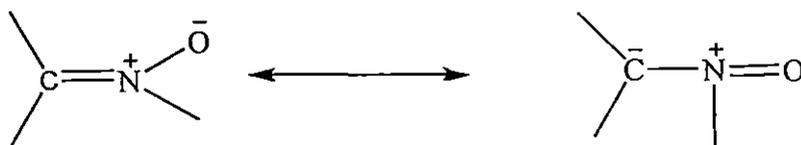

Fig 12

N-phenyl-α-chloro nitrone (**1**) has a chlorine group at β- position of the nitrone which has a strong electron withdrawing nature and therefore this nitrone is electrophilic in nature. In general, nitrones are HOMO-LUMO controlled 1,3-dipoles skewing towards LUMO controlled side.

Synthesis of nitrones

The chemistry and the synthesis of the nitrones have been reviewed several times. The general methods of synthesis of the nitrones are briefly discussed here.

a) By the oxidation of N, N-substituted hydroxylamines

$$R - N(OH) - CHR^1R^2 \longrightarrow R - N^+(O^-) = CR^1R^2$$
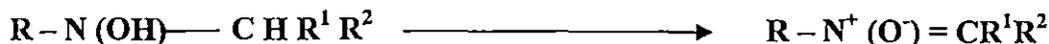
Both cyclic and acyclic nitrones were prepared by this method. Different oxidizing agents are used viz, yellow mercuric oxide[11], active lead oxide[12], potassium ferricyanide[13], hydrogen peroxide[14], potassium permanganate[15], diammine silver nitrate[16].

The formation of the nitrone salt was reported from the reaction between p-benzoquinone and 1-hydroxyl piperidine[17].
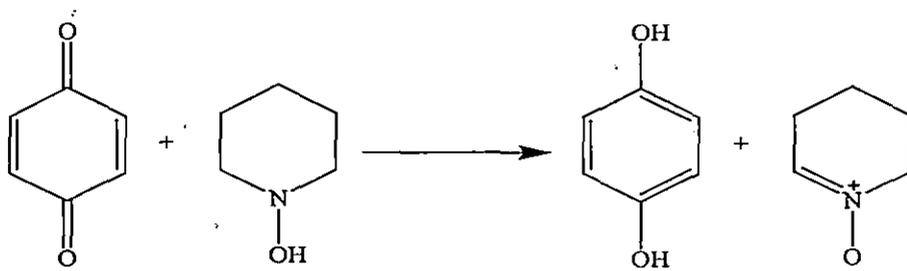

Fig 13

The formation of nitrone from N,N-disubstituted and N-substituted hydroxylamines using palladium catalyst were also reported[18]. Recently a four membered cyclic nitrone was also reported by the oxidation of 1-OH-azetidines with PbO_2[19].

Some other oxidative methods are also known e. g. diammino silver nitrate was used as the reagent for the preparation of α-styryl-α-benzyl-N-phenyl nitrone from corresponding hydroxylamine[20]. Photolysis of N-hydroxylamines in presence of 1, 4 – dicyano naphthalene (DCN) as an electron acceptor gave high yields of nitrone[21].
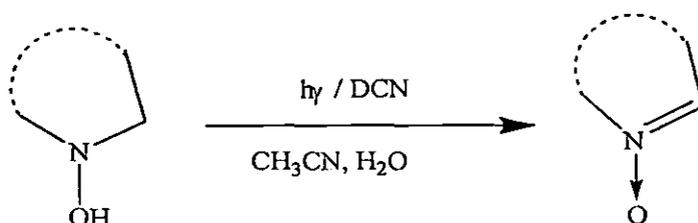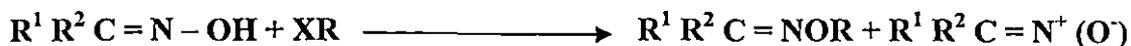

Fig 14

From oximes

The alkylation of the oximes was reviewed in 1938[22]. Disadvantage of this method was that nitrones were produced along with oxime ether.

$$R^1 R^2 C = N - OH + XR \longrightarrow R^1 R^2 C = NOR + R^1 R^2 C = N^+ (O^-)$$

Li, Na, K or tetramethyl ammonium oxime salts did not alter the product ratio of oxime ether to nitrone significantly. Electron withdrawing group in the *para, ortho-* disubstituted benzophenone oxime salts markedly promoted the formation of nitrones while electron donating group favours nitrone formation whereas longer side chain favours oxime – ether formation.

Heptanal oximes when treated with benzyl chloride in solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-*N*-benzyl nitrone[23]. DMSO was employed in the various keto-oxime alkylations. *C,C*-dicyclopropyl-*N*-methyl nitrone has been prepared by this method[24].
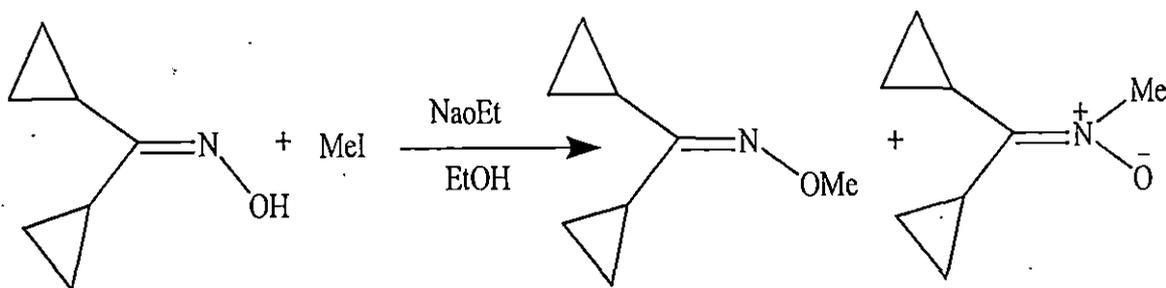

Fig 15

Formation of nitrones was also reported by the intramolecular Michael addition of aldoximes and ketoximes to electronegative olefins[25].
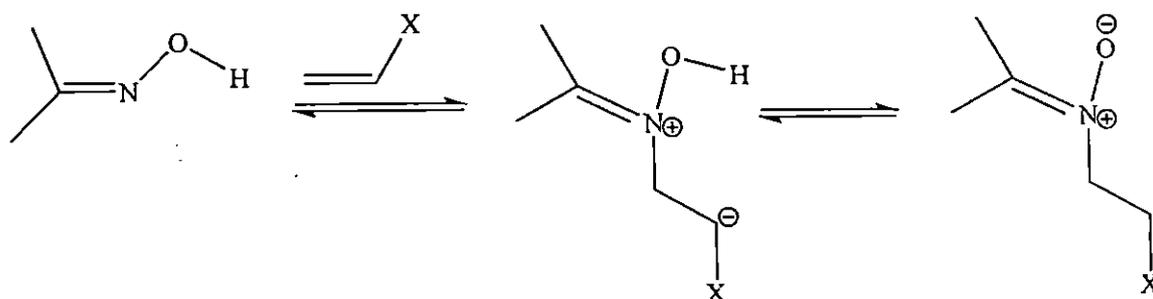

Figure 16

Recently oxime-*O*-allyl ether were converted to the corresponding *N*-allyl nitrones on treatment with 10 mole % of PdCl₂ (MeCN₂) by a formal [2+3] sigmatropic shift[26].

Formation of cyclic *N*–vinyl nitrones were also reported from δ-alkenyl oximes by a concerted 2n + 2π + 2δ 1, 3 − azprotio cyclotransfer reaction[27].Both the reaction proceeds smoothly and high yields were reported. This is one of the best methods for the preparation of aldonitrones. *N*-phenylhydroxylamine has been treated with a variety of aldehydes and ketones. *N*-cyclohexyl methylene nitrone[28] similar to *N*-phenyl methylene nitrone[29] can be prepared by passing formaldehyde gas through *N*-cyclohexylhydroxylamine in methylene chloride and anhydrous $MgSO_4$.

From aromatic nitroso compounds

Aromatic nitroso compounds react with a variety of compounds to form nitrones. 2, 4, 6-trinitro toluene, 9-methyl acrydine with sufficiently active methylene group react with aromatic nitroso compound to form nitrones[30,31]. The reaction is usually catalysed by trace amount of base (e.g. pyridine). One of the example of this type of reaction is shown in the following way.
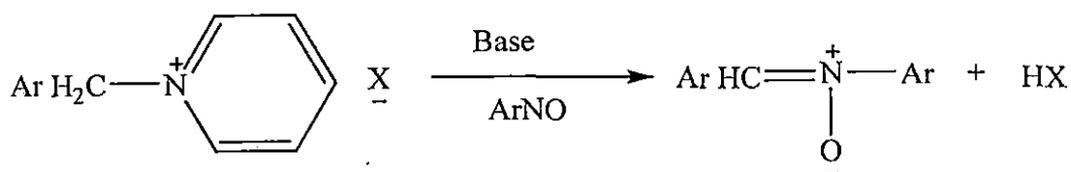

Fig 17

Aromatic nitroso compounds react with benzyl derivatives such as benzyl chloride in presence of some suitable base to yield nitrones[32,33].

Some other miscellaneous methods

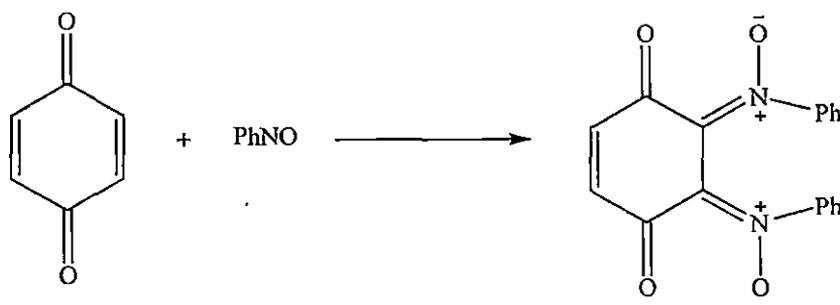Quinones yielded dinitrones upon treatment with nitrosobenzene[34].

Fig 18

12

N–methyl nitrones can be generated in good to excellent yields from aldehyde and ketone with stoichiometric amount of *N*-Me, *N-bis* (trimethyl silyl) hydroxylamine[35]. Nitrones can also be isolated in pure state from D – glucose oximes and benzaldehyde without employing any protection of hydroxyl group[36].
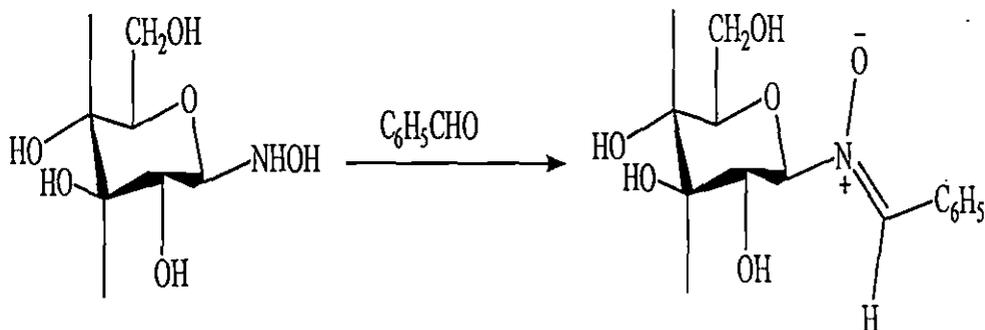

Fig 19

Nitrones can be obtained by the treatment of trimethyl silyl chloride and triethyl amine on nitroalkanes also[37].
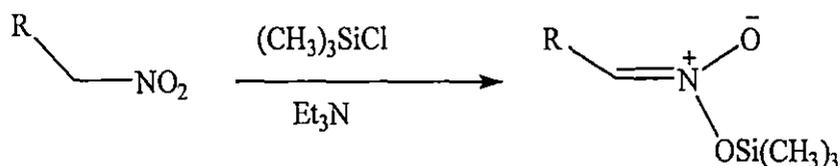

Fig 20

1,3 dipolar cycloaddition reaction

K. N. Houk et al[38] pointed out that mechanistic investigations have shown cycloadditions of 1,3-dipole to alkenes are stereospecifically suprafacial, solvent polarity have a little effect on reaction rates and small activation enthalpies. These facts along with reactivity and regioselectivity have been considered totally compatible with concerted five centered mechanism. Orbital symmetry consideration have provided permissive though not obligatory, theoretical evidence for the concerted mechanism and the observation of [4 π's and 6 π's] cycloaddition but not [4 π's + 4 π's] cycloaddition of 1,3-dipoles to diene has provided further evidence for the concerted mechanism. But the experimentally observed regioselectivity of most of the 1,3-dipolar cycloaddition has been the most difficult phenomenon to explain.

Houk et al solved this problem with the use of generalized frontier orbitals of 1,3-dipoles and dipolarophiles within the frame work of frontier molecular orbital theory. Whether 1,3-dipolar cycloaddition reaction to be allowed or forbidden may be judged according to the symmetry properties of the HOMO and LUMO orbitals of the dienes and the dipolarophiles as proposed by Sustman[39].
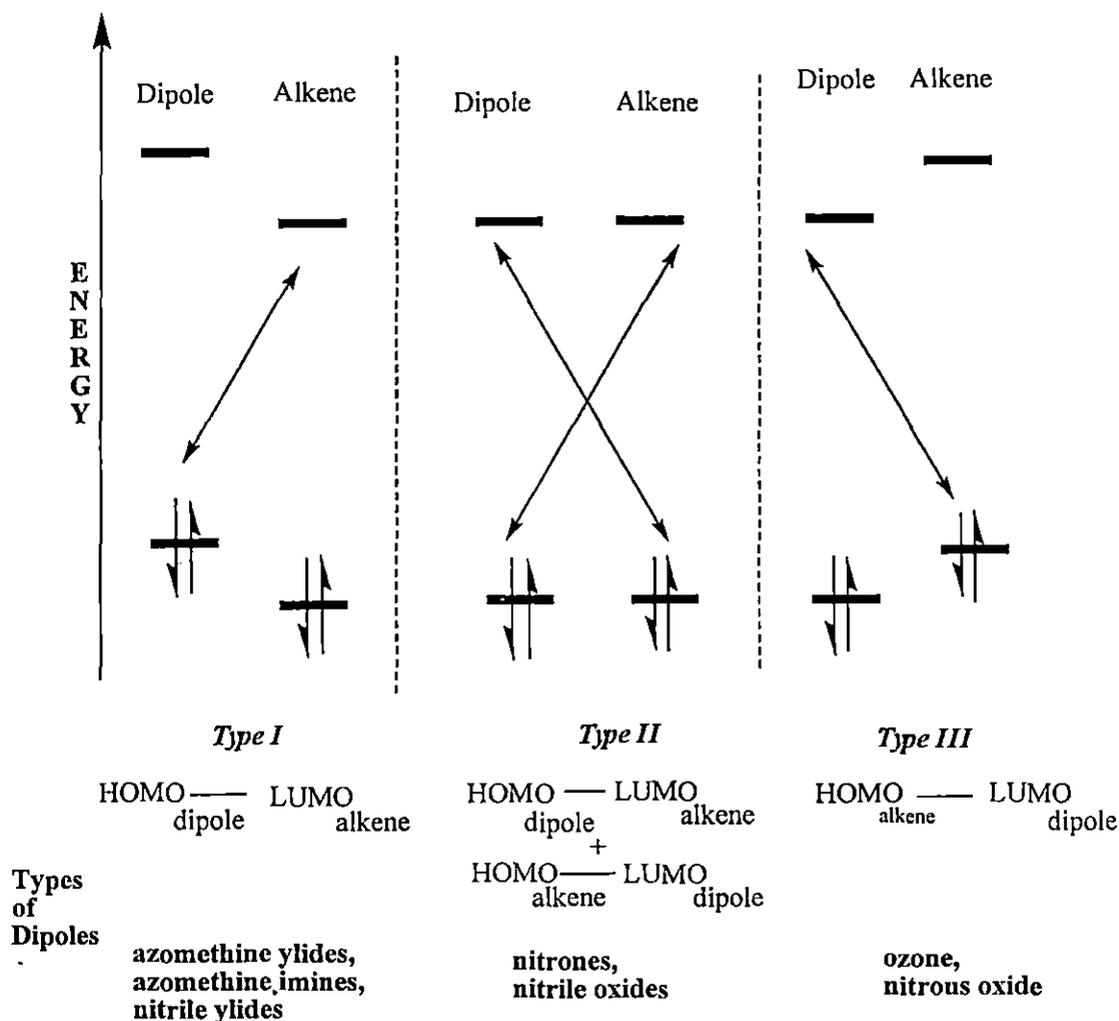

Type I: It involves dominant interaction between LUMO (dipole)–HOMO (dipolarophiles).

Type II: It involves LUMO (dipole)-HOMO (dipolarophiles). But in type II, both the LUMO (dipole)-HOMO (dipolarophiles) and HOMO (dipole)-LUMO (dipolarophiles) are important in determining reactivity and regioselectivity. Type I dipoles are those having high lying HOMO's and LUMO's and referred to as HOMO controlled or nucleophilic 1,3-dipoles. It is referred to as HUMO-LUMO controlled dipoles.

Type III: It has low lying FMO's and referred to as LUMO controlled or electophilic dipoles.

Molecular orbital theory behind 1,3-dipolar cycloadditions
Lewis acid activation
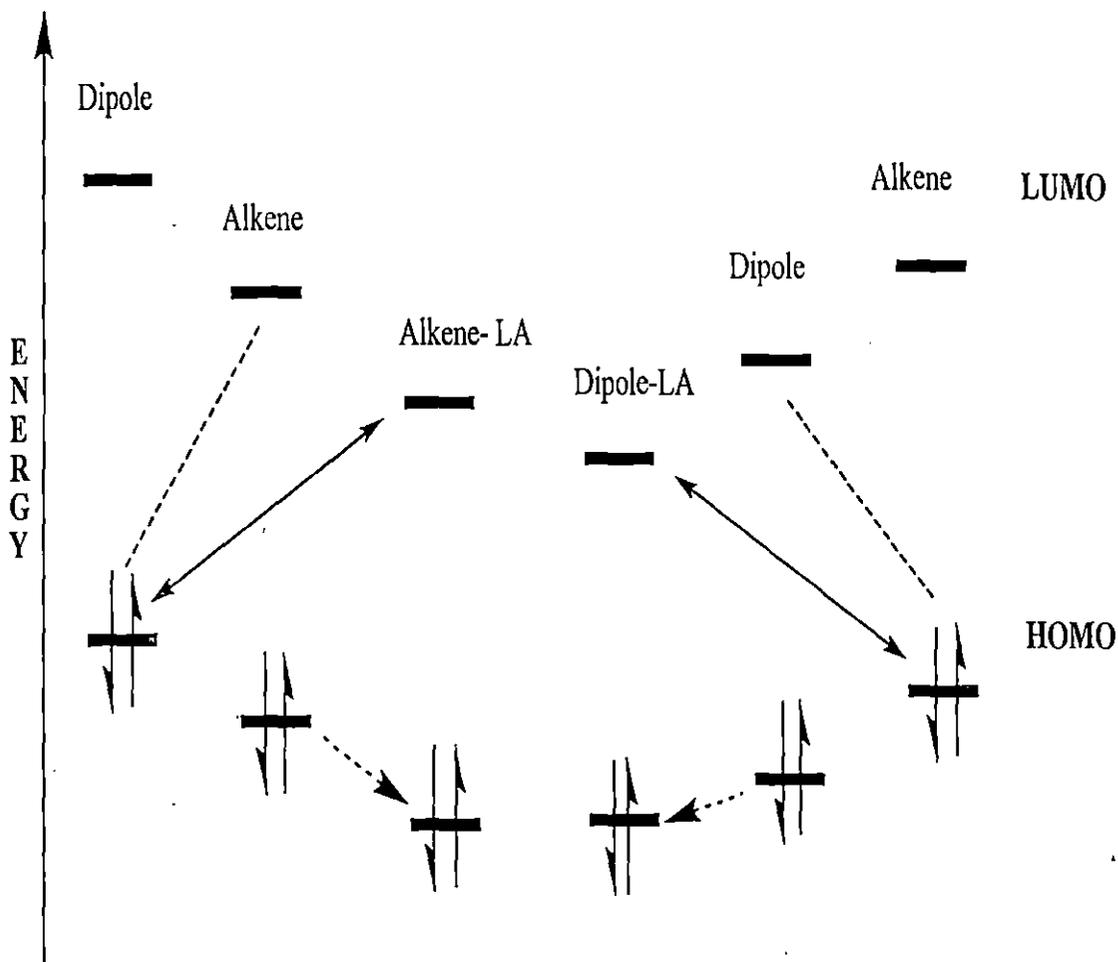
Coordination of LA to either the dipole or the alkene results in LUMO lowering and a faster reaction rate

Hauk et al have treated all common 1,3-dipoles according to this simple model and have shown that the prediction satisfactorily explains all the experimental results. The nitrile ylides, diazoalkanes and azomethine ylides are HOMO controlled 1,3 dipoles, reacting readily with alkenes having one or more electron withdrawing substituents. The nitrile imines, azides and azomethyne imines are HOMO-LUMO controlled dipoles which react rapidly with both electron rich as well as electron deficient dipolarophiles. The nitrile oxides and nitrones are also HOMO-LUMO controlled dipoles, but these species are skewed towards the LUMO controlled side. Finally,

15

species with several electro negative atoms are LUMO controlled 1,3 dipoles. *e.g.* – nitrous oxide and ozone.

The interaction of the dipole LUMO with dipolarophiles HOMO favours the formation of the product with the substituent on carbon adjacent to z while the opposite frontier orbital interaction favours opposite regioisomers. The HOMO's of the 1,3 dipolar system generally have larger terminal co-efficient on the group z while the LUMO's have larger co-efficient at the opposite terminus. The HOMO's and LUMO's of 1,3 dipoles are quantitatively similar to those of allyl anion. The greater differences in terminal co-efficient occur when the two terminal differ greatly in electronegativity.
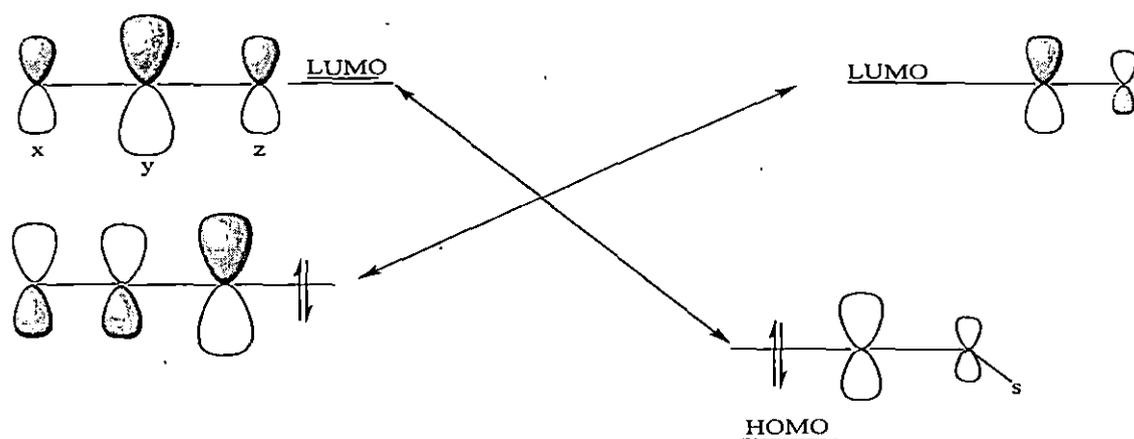

Fig 21

Nitrile oxides and nitrones react to give mainly the five substituted adduct with weakly electron deficient alkenes like acrylonitrile and ethyl acrylate. The HOMO's and LUMO's of these electron deficient alkenes both interact fairly with the LUMO's and HOMO's of the nitrile oxides and nitrones so that the orientation is influenced by both the interactions. The experimental results shows that the dipole LUMO – dipolarophile HOMO has more influence on regioselectivity. Huisgen[40] observed that acetylinic dipolarophiles are less reactive then expected on basis of their ionization potentials. Since alkynes have large HOMO – LUMO gap then alkenes, it is expected that during interactions with the alkyne, LUMO plays the most significant part and hence alkynes are less reactive then as expected. However, the reactivity of nitrones with both electron deficient alkynes and alkenes are actually determined by dipole (HOMO)-dipolarophiles (LUMO) interactions and the regiochemistry in former case is still controlled by dipole (LUMO)-dipolarophiles (HOMO) interaction therefore in

case of alkyne, the dipole (HOMO)-dipolarophiles (LUMO) interactions become very important and dominates the reaction for the formation of 4- substituted adducts.

Stereoselectivity in nitrone cycloaddition

Nitrone addition is always *cis* to dipolarophiles, so the relative stereochemistry at C_4 and C_5 is always determined by the geometric relationship of the substituents on the alkene. *Syn* and *anti* isomers of dipole (stability and therefore proportion of each depends on steric considerations and hydrogen bonding etc.) can lead to diastereoisomeric products depending on approach of dipole and □dipolarophiles. *Exo / endo* approach of dipolarophiles needs to be considered. Secondary orbital interactions are not relevant, as in Diels-alder reactions, steric interactions are important. So the *exo* product is the more stable product.
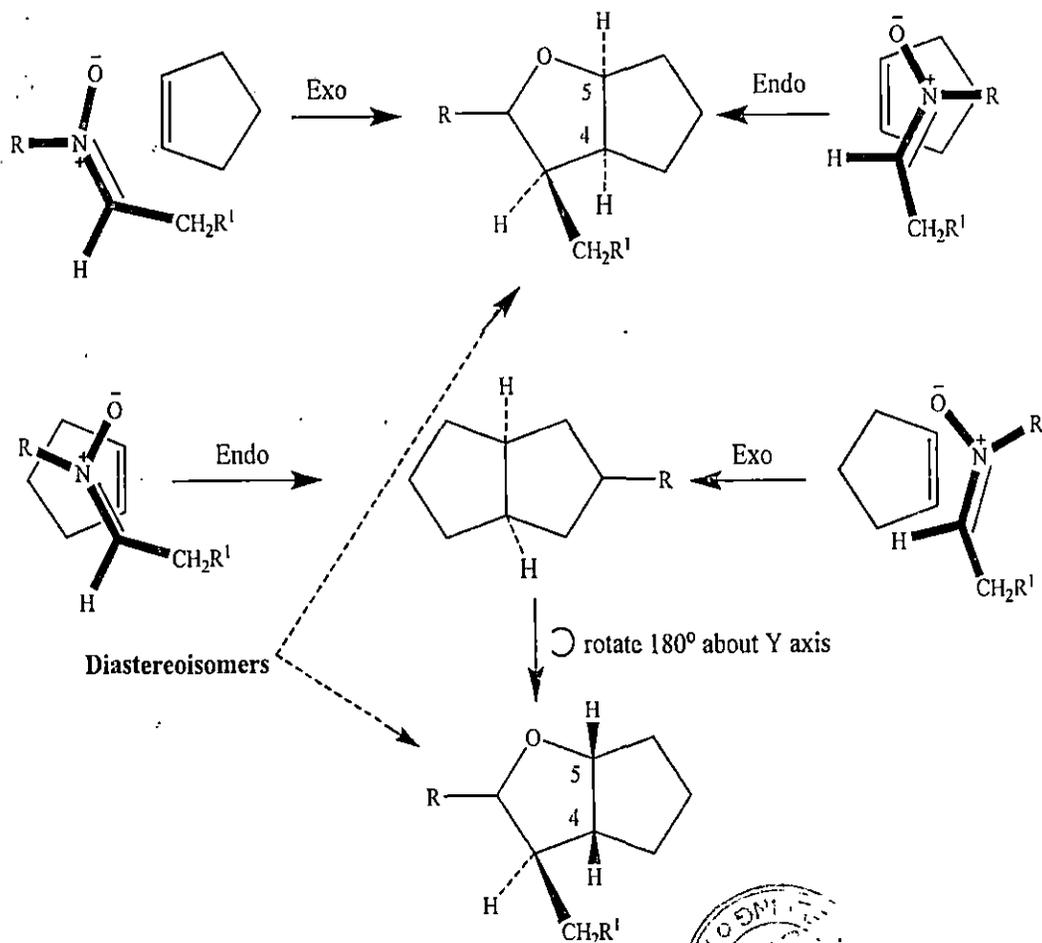

Fig. 22

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Formation of biologically active amino alcohol from isoxazolidine formed by 1, 3 – dipolar cycloaddition reaction
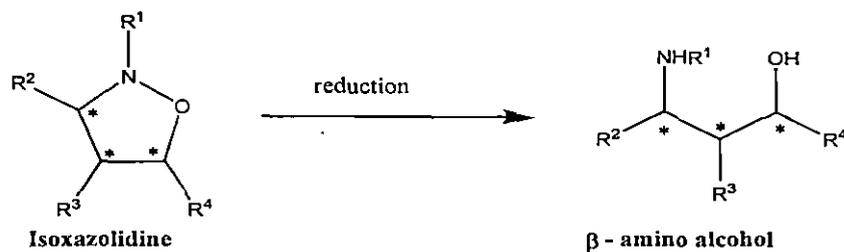

Fig. 23

1,3 – dipolar cycloaddition reaction can create up to three asymmetric centers (* = stereocenter).

A comprehensive review on the generation of different type of nitrones and their 1,3-dipolar cycloaddition reaction has been studied along with their biological properties *viz*; antimicrobial, antitumor, antifungal, antibacterial, activities. From the literature consultation it has been found that majority of the nitrones are generated in situ. Because of their instability, 1,3-dipolar cycloaddition reactions are carried out by trapping the nitrones at the time of their formation. This process avoids dimerization of the nitrone and the yield of the cycloadducts is also extremely high.

Current literature survey:

The recent reviews (from 2001 onwards) suggest that the greater emphasis has been given to the greener chemistry. Environment friendliness and sustainable development being the need of the hour, instead of using conventional solvents like benzene, dichloromethane, tetrahydrofuran etc, synthesis of the nitrone and their cycloaddition reactions nowadays are mainly performed in the following ways:

> Microwave assisted synthesis of nitrones and their cycloaddition reactions
> Solid phase synthesis of nitrones and their cycloaddition reaction
> Aqueous phase synthesis

In all the cases the reactions are mild, easy work up and the isolation of the compounds are not so difficult. Interestingly in these cases better yields, lesser required time are reported compared to conventional methods. Nowadays aqueous phase cycloaddition reaction is mostly applied to avoid hazardous solvents and also to get higher yields in a short reaction time and is completely a green approach of cycloaddition reaction of nitrones. Some research articles in this regard have been

18

already published in *Indian Journal of Heterocyclic Chemistry and Indian Journal of Chemistry, Section B* from our laboratory[41,42,43].

Microwave induced intramolecular 1,3-dipolar cycloaddition reactions of *N*-substituted oximes, nitrones etc. are highly stereoselective in nature[44]. These reactions are generally carried out on the surface of silica gel without adding a solvent and have been conducted under microwave irradiation to form functionalized tricyclic isoxazolidines fused with pyrolidine or piperidine ring in extremely good yield. From 2000 onwards it has been found that High Resolution Mass Spectra (HRMS),^{13}C NMR and X-ray crystallography of single crystal studies are commonly used for the characterization of nitrone and cycloadducts.In the present study, we have used HRMS, ^{13}C NMR techniques along with ^{1}H NMR and IR studies. The most important advantage of the microwave studies regarding the formation of cycloadducts is that within a very short period of time (3 to 8 min) generally 70 − 90 % and sometimes 100 % yield are found to be reported. It has been also suggested from the new works found in the literature that microwave irradiation is also potentially useful for the chiral synthesis of functionalized nitrogen heterocycles using suitable starting materials.

From the research article published by Q. Chang and his group[44], it has been found from the spectral analysis that the spectra of one of the oxime that gets converted to nitrone by microwave irradiation, gives HRMS authentic value in support of the structure of the nitrone.
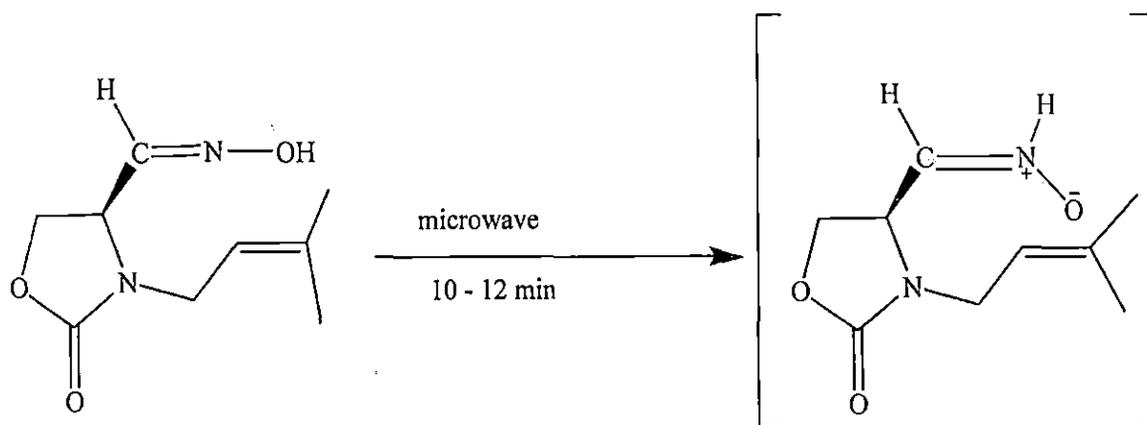

Figure 24

From the structure, calculated value for $C_9H_{14}N_2O_3$ (M) has been found to be 198.1003 while the experimental value is found to be 198.1006.

A good review[45] on microwave assisted 1,3-dipolar cycloaddition reaction was published on 2003 in *Indian Journal of chemistry Sec B* from Madurai Kamraj University ·by S. Muthusubramaniun and his co – workers. They synthesized α-(5-substituted-2-hydroxyaryl)-N-arylnitrones. They have shown that in microwave reaction the required time for the cycloaddition is much less and the yield is much higher than the conventional methods.


R_1 = t-Bu, i-Pr, Ph

R_2 = H, Me, Cl

R_3 = H, Me
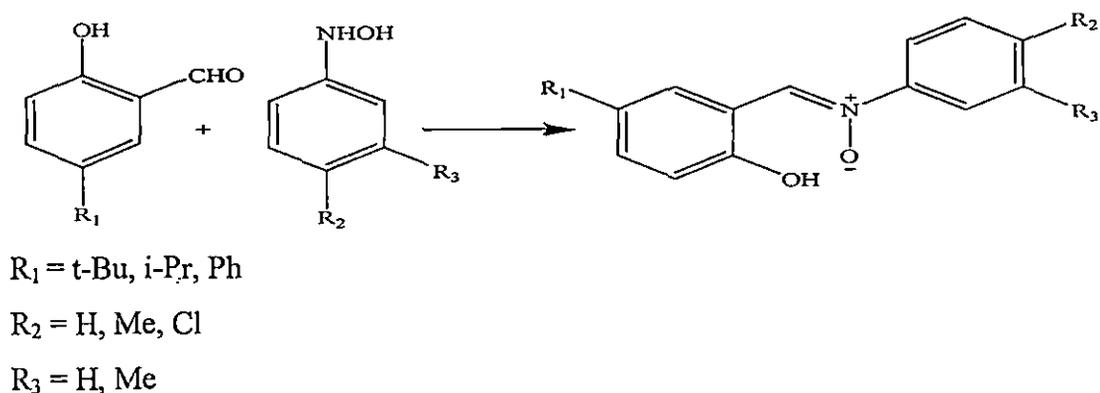
Figure 25

Another important work suggested by A. Goti and his co-workers[46] in Italy, working with *C, N*-diphenyl nitrone and the dipolarophiles were used are butyrolactones. The reactions are highly stereoselective in nature giving both the enantiomers having high yield. It has been found in the following scheme:
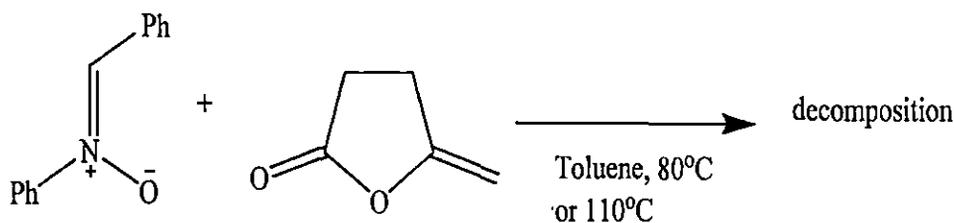

i Benzene, 80°C, 5 hr   a : b = 90 : 10 (ee 82%)

ii Toluene, 110°C, 3 hr   a : b = 80 : 20 (ee 89%)
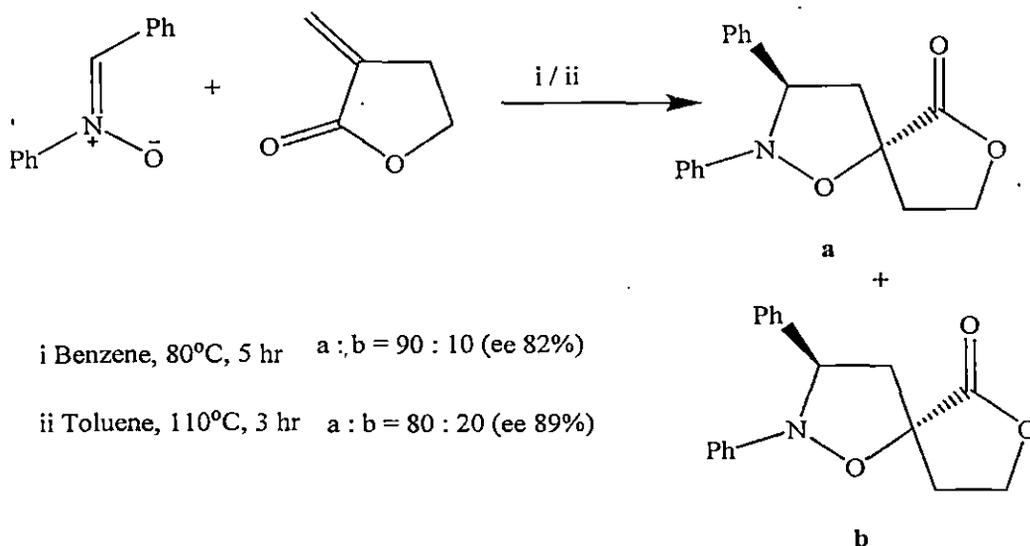
Figure 26

Another brilliant work was suggested by R. Shintani and Gregory C. Fu[47] suggest a copper catalysed [3+2] cycloaddition reaction which is a enantioselective coupling of terminal alkenes with azomethyne imines to generate five membered heterocycles.
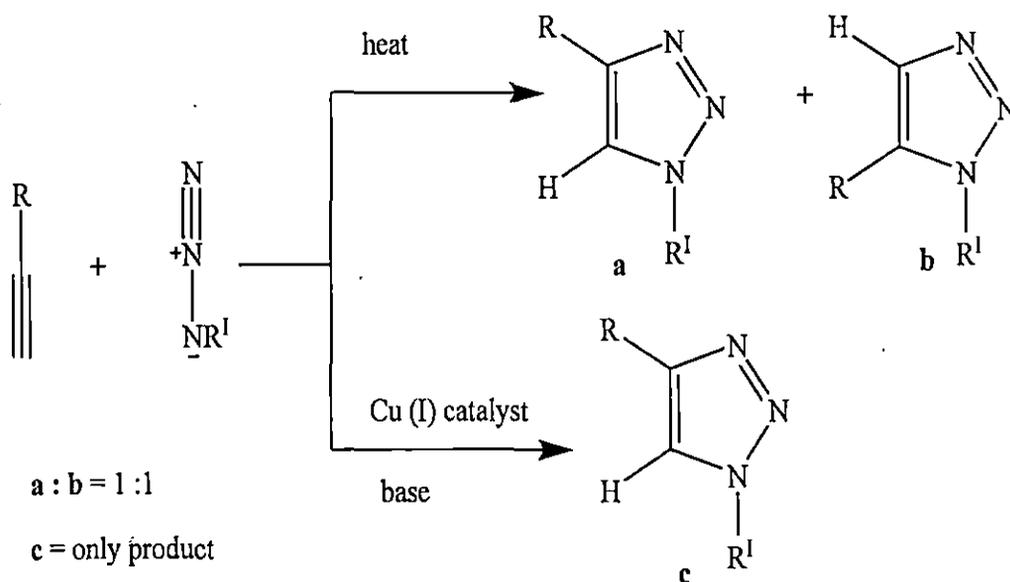

a : b = 1 :1

c = only product

Figure 27

Some new works on nitrone cycloaddition reaction has been suggested by K. V. Kudryavtsev and V. Irkha[48] which suggest 1,3-dipolar cycloaddition reaction of homoprolein, involving protein chemistry using N-methyl maleimide. The most important feature of this reaction is the multicomponent raction.

Anup Bhattacharya et. al[49] suggests some remarkable work on glucose derivatives in the year 2005 which suggests intramolecular 1,3-dipolar nitrone and nitrile oxide cycloaddition of 2 and 4 allyl and propergyl glucose derivatives. This is the versatile approach to chiral cyclic ether fused isoxazolidines, isoxazolines, isoxazoles.

With the help of 1,3-dipolar cycloaddition reaction natural products also can be prepared and was shown by G. W. Gribble and his coworkers[50] in the year 1985 and has been published in *Journal of Organic Chemistry*. Later on A. Padwa in his latest

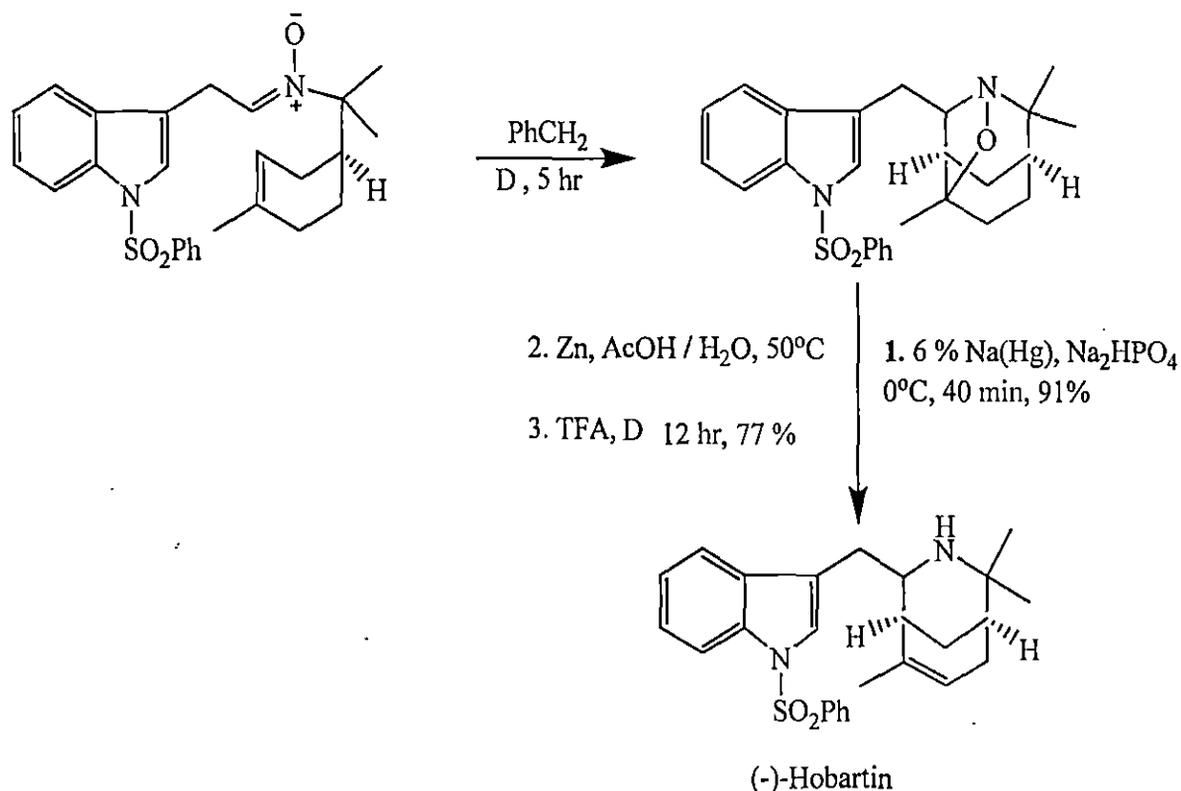review has given emphasis on the synthetic application of nitrones towards natural products (Ref 54).

Figure 28

It has been found from various literature survey that newly formed cycloadducts as reported by different workers contain antifungal , antitumor activities but antitumor activities of the said cycloadducts are however not so common. The different workers suggest in various publications that the antitumor activities are characteristic properties of those five membered heterocycles containing oxygen and nitrogen forming the isoxazolidine and Isoxazoline or their derivatives.

Another new development in the field of antibacterial activity of isoxazolidines has been shown by Gurpinder Singh and his co – workers[51] from the intramolecular low temperature 1,3-dipolar cycloaddition reaction of nitrones where chromano heterocycles are synthesized.
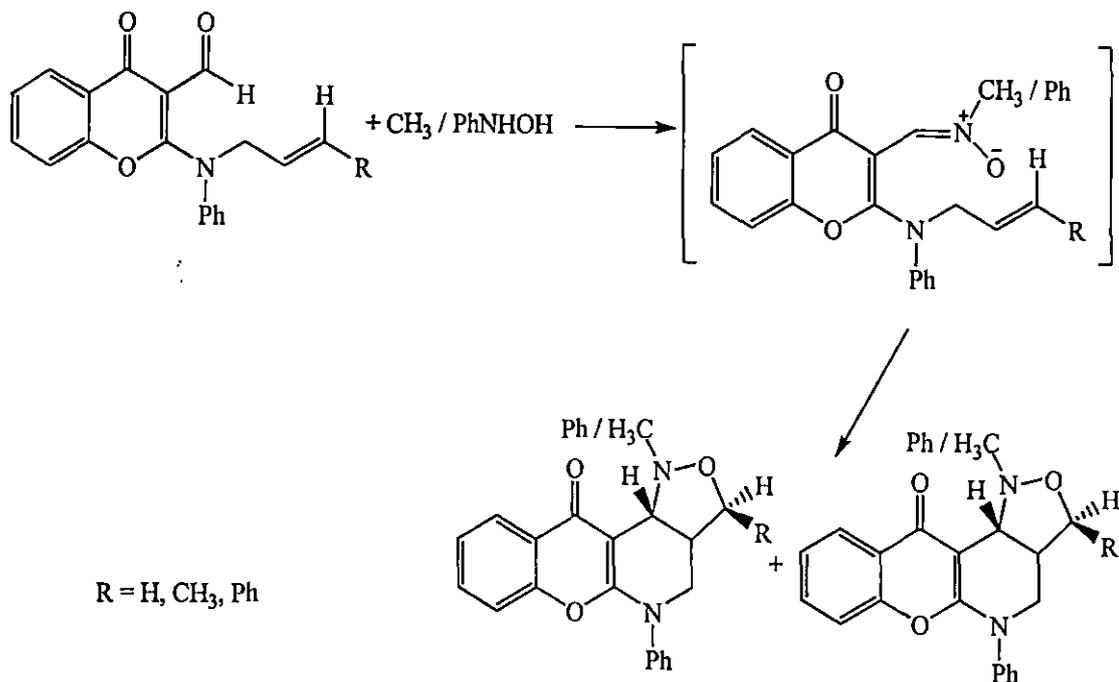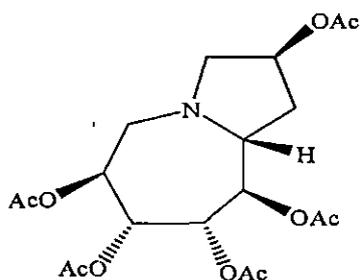
Figure 29

R = H, CH₃, Ph

From the D – galactose derived nitrone 1, 3-dipolar cycloaddition reaction some per hydro aza azulene alkaloids has been synthesized. This compound has been found to have very good antimicrobial activities as reported.

During the synthesis of new amino cyclo-hexitols by the intramolecular nitrone, antifungal activities of the compounds are also reported. One of the synthesized compounds can be shown in the following way

Acetoxy-perhydroazazulene

Figure 30

Some stereoselective synthesis of pyrolidinyl glycines from nitrones also report moderate antifungal activities as reported by P. Merino and his co-workers[52].
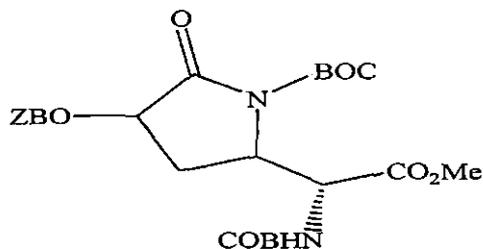
23

Figure 31

Penta substituted cyclopentanes have been prepared from monosaccharide. The reductive fragmentation of 5-bromo-5-deoxy hex-5-enones (a) which upon treatment with N-methylhydroxylamine followed by intramolecular cyclization afford chiral isoxazolidine (b) in very good yield [53].
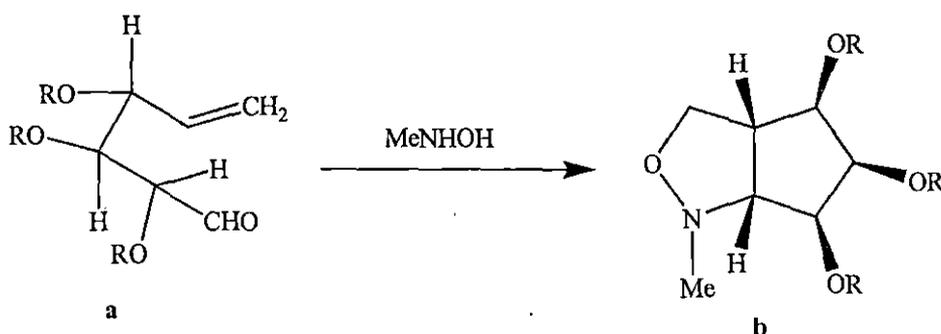

Figure 32

This compound is good antifungal agent as reported. Some of the antitumor activities shown by the cycloadducts formed between α-phenyl-N-methyl nitrone with p-methoxy styrene and p-methyl styrene. It has been found from the detailed survey work that isoxazolidines are more powerful antifungal, antibacterial agents compared to isoxazolines.

In addition to all literature survey shown above, we have also reported antitumor, antibacterial, antifungal activities of isoxazolidine derivatives (Ref 43) which are synthesized in our laboratory following the method which are represented earlier.

The recent reviews of A. Padwa[54] suggest some brilliant work regarding antimicrobial and antitumor activities of cycloadducts formed. The results are at par with the works we have completed in our laboratory to study antimicrobial, antifungal activities along with normal cycloaddition reactions.
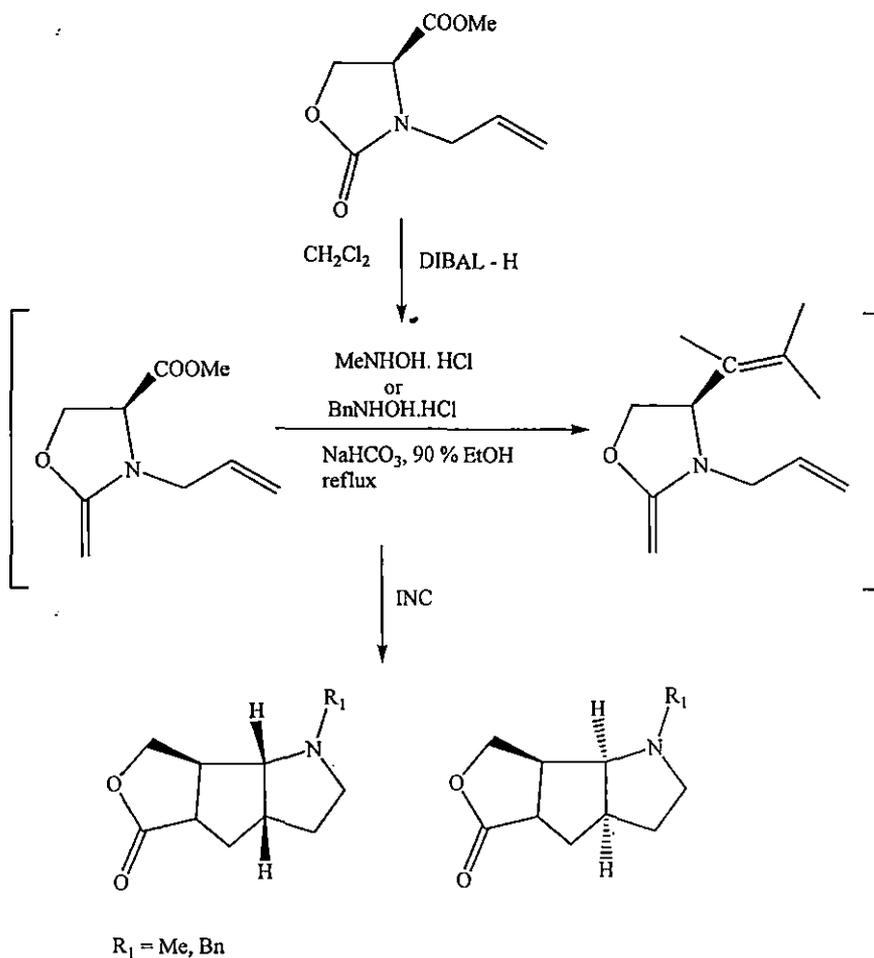
Figure 33

It has been found from the review work that the newly synthesized compounds were screened for antimicrobial activities in vitro using gram positive bacteria *E. Coli* and gram negative bacteria *Serrative Marcesens* by disc diffusion method[55]. T*etracycline* was employed as reference standard (10 microgram) to evaluate the potential of tested compounds. Among the selected compounds screened for antimicrobial activities, very few showed potential antibacterial activity.

Highly stereoselective intramolecular cycloaddition reactions of unsaturated *N*-substituted oximes, nitrones and azomethyne ylides on the surface of the silica gel without a solvent have been conducted under microwave irradiation to produce tricyclic isoxazolidines fused with pyroline or pipyridine ring in good yields were reported by Q. Chang, W. Zhang, Y. Tagan and their group in the year 2001[56].
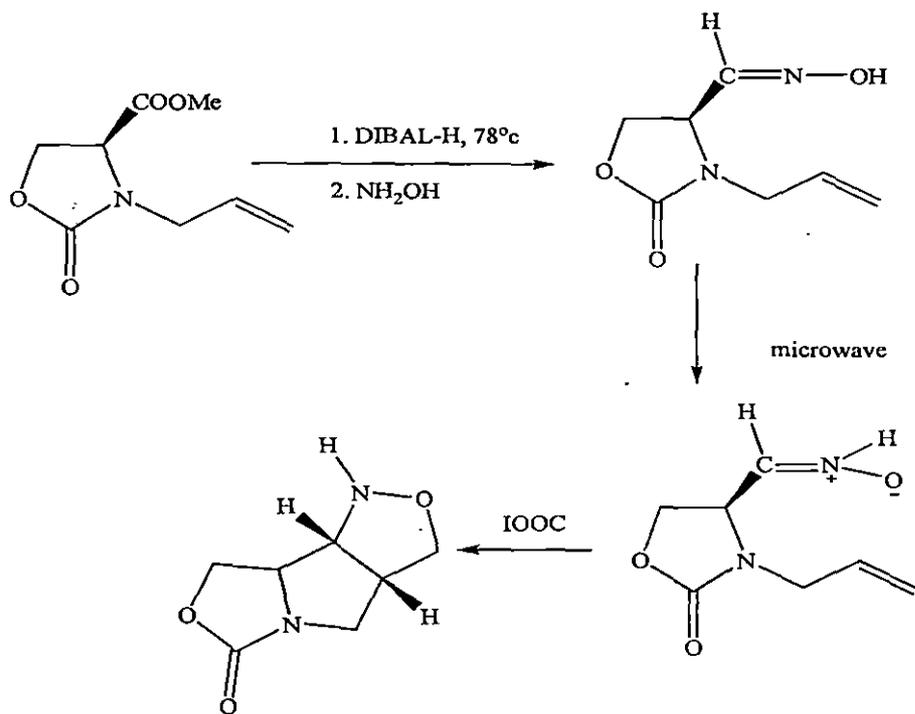
IOOC = Intramolecular oxime-olefin cycloaddition

Fig 34

A series of unexpected cycloadducts along with normal cycloadducts have been reported by Abhijit Banerjee and his group[57] using 1,3-dipolar cycloaddition reaction of 3,4-dehydro morpholine *N*-oxide with pipyridine of cinnamic acid and *p*-substituted cinnamic acids. Since unexpected cycloadducts are quite rare therefore this work has immense interest for the workers of nitrone cycloaddition reactions.
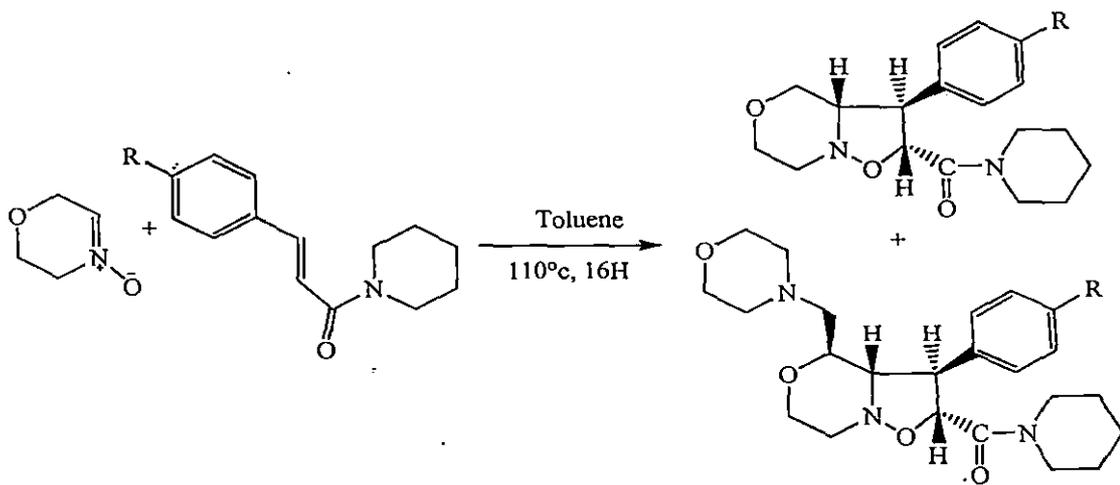

Fig 35

A brilliant work reported by Francis Heaney, Oliver Rooney in 2001[58] which reports the formation of *bis* isoxazolidines involving *bis* nitrones using *N*-methyl maleimide

26

as □dipolarophiles. The reaction as reported is highly diastereospecific in nature. This has the first reported case of bis isoxazolidines.
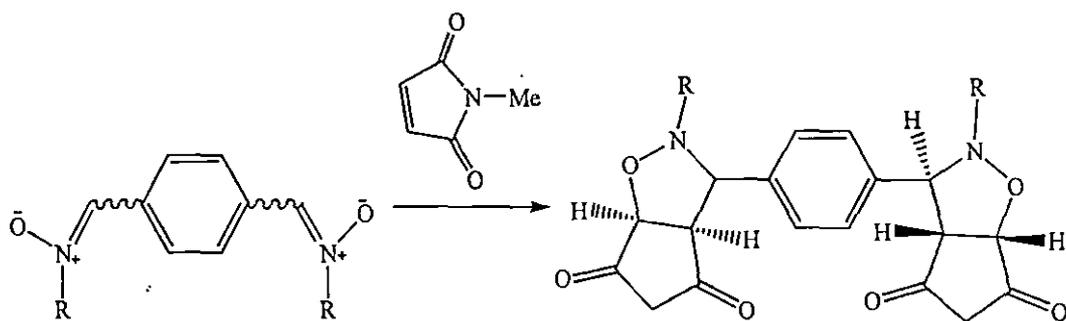

Fig 36

Reports of 1,3-dipolar cycloaddition reaction of nitrones in aqueous solution was first ever reported by O. Mersbergen and his group[59] in 1988 where the reaction rate and yield of the reactions were reported as much higher compared to usual or conventional cycloaddition reactions. The common dipolarophiles used were cyclohexene, methyl vinyl ketone, styrene and N-methyl maleimides respectively.
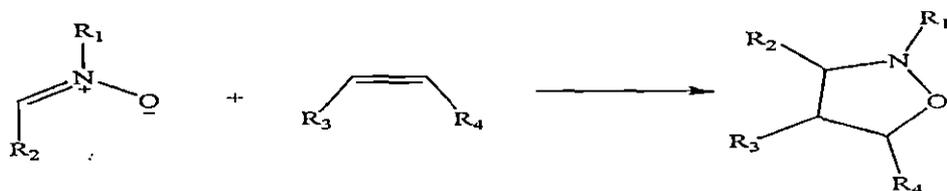

$$R_1 = R_2 = Ph \text{ or } R_1 = Me; R_2 = Ph$$

Fig 37

Development of nitrones and their cycloaddition reactions from oxaziridines involving N-sulphonyl nitrones were reported recently in 2008 by K. M. Patridge and their group[60]. This work is novel, as far the formation of nitrone is concerned.
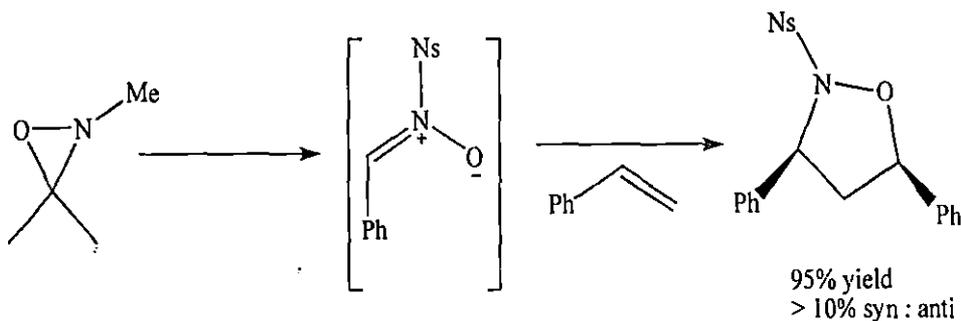

95% yield
> 10% syn : anti

Fig 38

In the year 2007, Sheikh Ali and his group[61] reported a new stereochemical approach of 1,3-dipolar cycloaddition reaction of internally H-bonded chiral methylene nitrones.
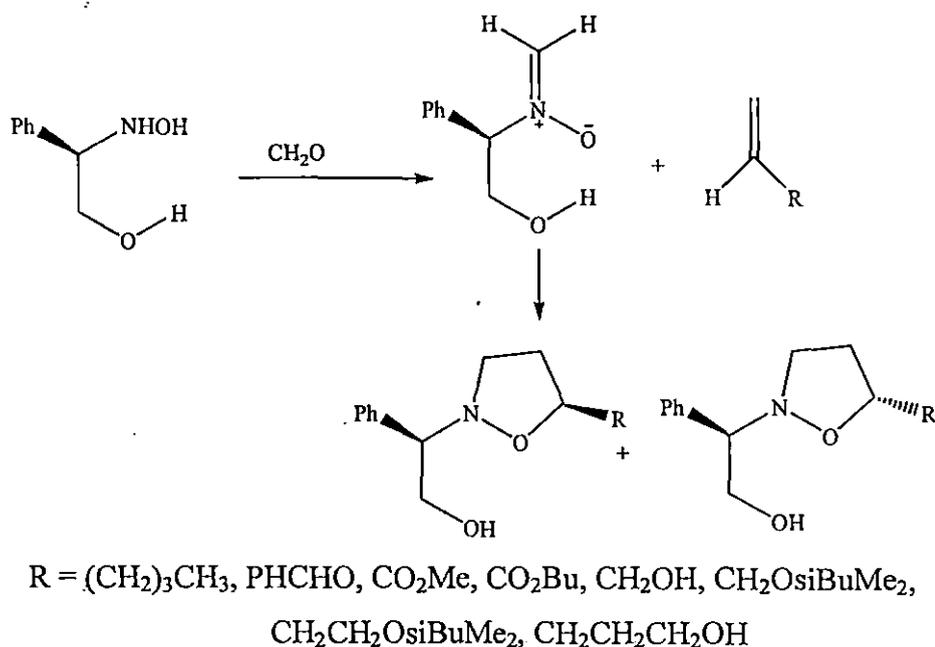
27

$R = (CH_2)_3CH_3$, PHCHO, CO_2Me, CO_2Bu, CH_2OH, $CH_2OSiBuMe_2$,

$CH_2CH_2OSiBuMe_2$, $CH_2CH_2CH_2OH$

Fig 39

Lubor Fisera and his group[62] reported some novel cycloaddition reactions in early 2009 where the nitrones are derived from sugars. The work is actually diastereoselective synthesis of isoxazolidinyle nucleosides by means of 1,3-dipolar cycloaddition reaction of chiral sugar derived nitrone as the key step.

$R_1, R_2 = R_3, R_4 = CMe_2$

$R_1, R_2 = CMe_2, R_3 = Bz$ (Benzyl), $R_4 = TBDPS$

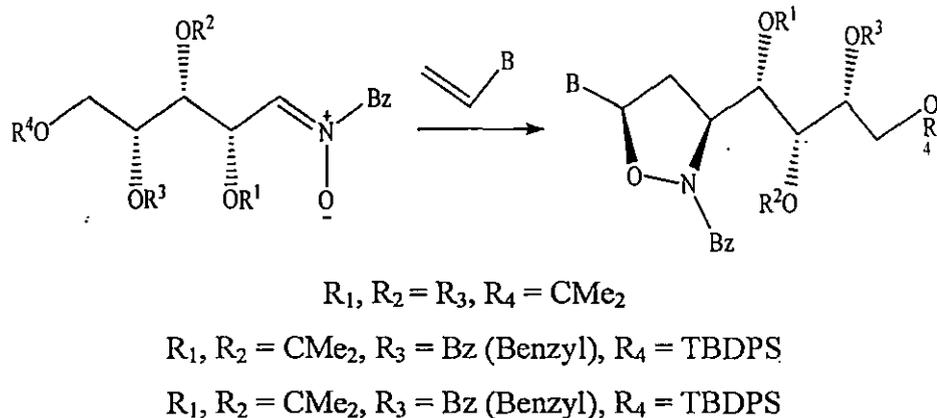$R_1, R_2 = CMe_2, R_3 = Bz$ (Benzyl), $R_4 = TBDPS$

Fig 40

An interesting example of the formation of nitrone in water exclusion reaction in aqueous media using surfactant and subsequent cycloaddition reactions in the same pot has been reported by P. K. Bhattacharya[63] as reported. This is a new example of green chemistry and it will not only lead to environmentally benign system but also provides a new aspect of reactions in water.
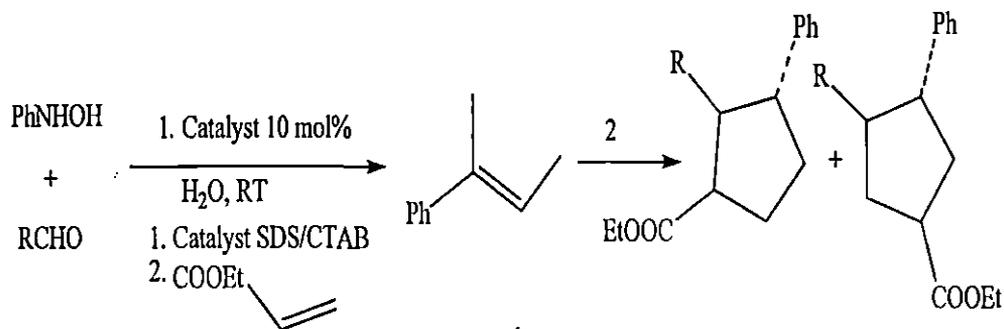
Fig. 41

An example of highly efficient solvent free 1,3-dipolar cycloaddition reaction of *N*-substituted dipolarophiles and nitrone was reported by T. B. Nguyen and his group[64]. New isoxazolidines were synthesized in good to excellent yields by 1,3-dipolar cycloaddition reactions of *N*-vinyl amide dipolarophiles and nitrones. Strikingly solvent free condition gave high conversion and yields, shortened reaction time and minimized degradation products.
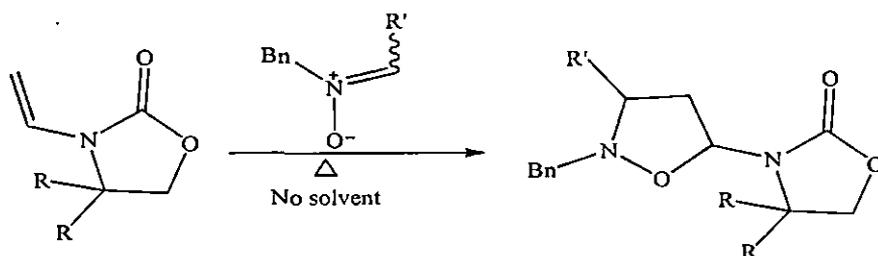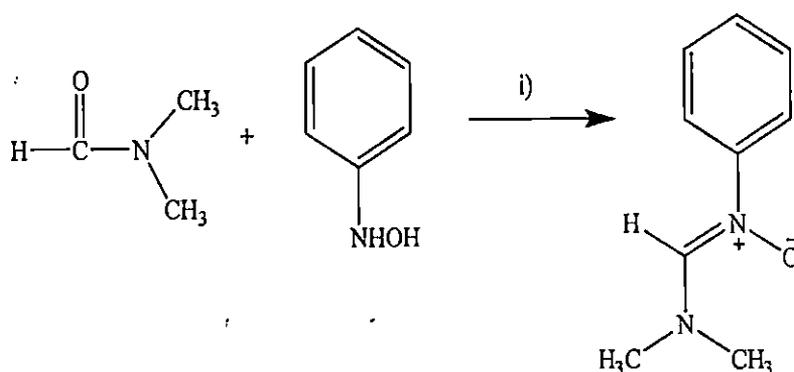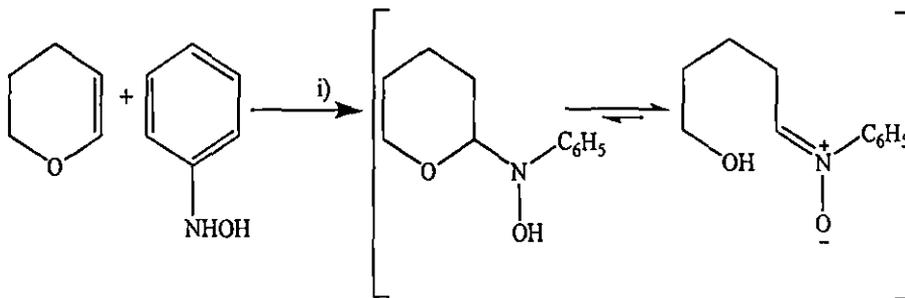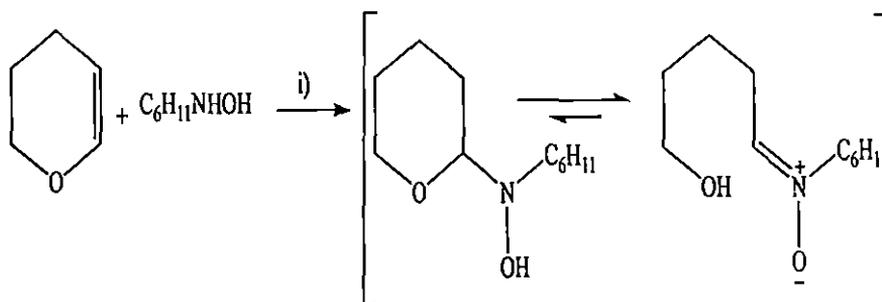

Fig 42

Synthesis of different *N*-cyclohexyl, *N*-phenyl-α-chloro nitrone along with other nitrones have also been reported from our laboratory[41- 43,65-78]. Few of the nitrones thus reported are prepared by the following way.

i) Anhydrous MgSO₄, N₂ atmosphere, RT, 12 hours
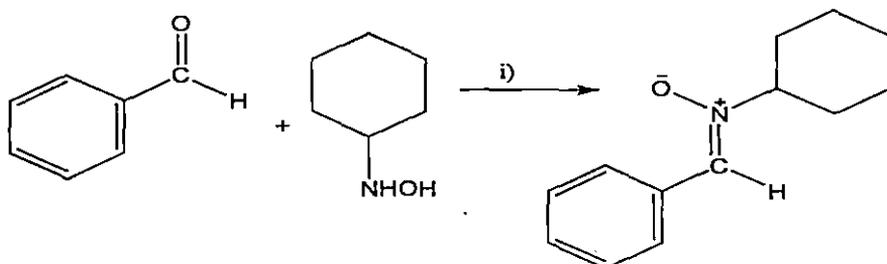
29

i) Anhydrous MgSO$_4$, N$_2$ atmosphere, Reflux, 24 hours
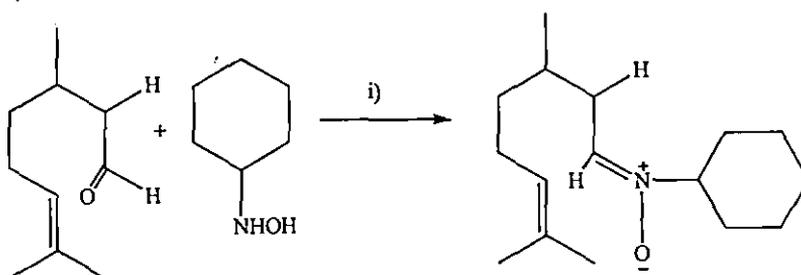

i) Anhydrous MgSO$_4$, N$_2$ atmosphere, Reflux, 20 hours
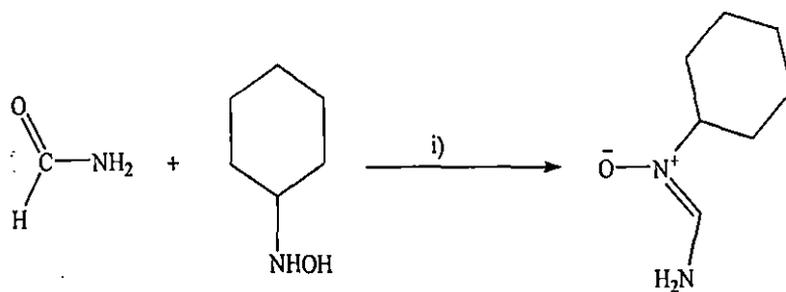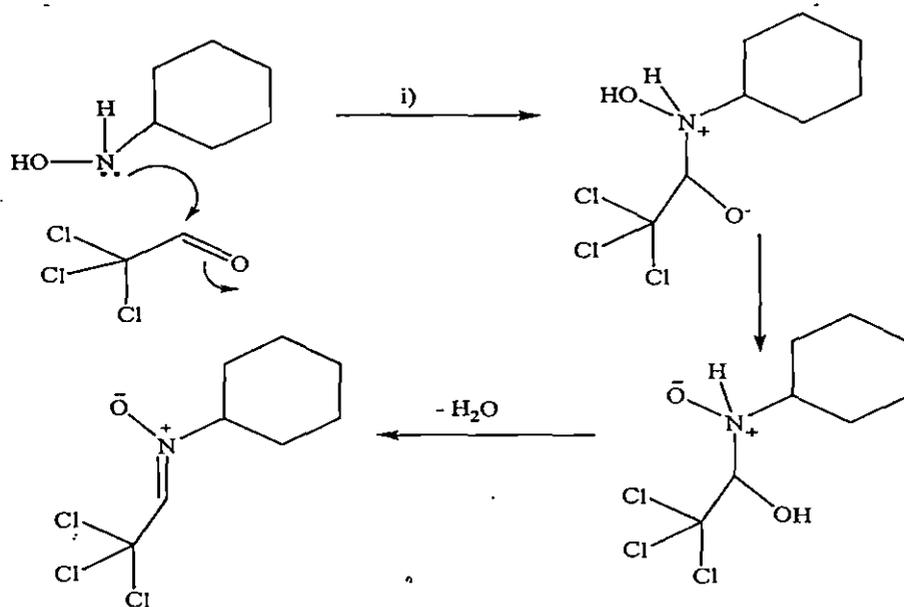

i) Dry benzene, N$_2$ atmosphere, RT, 18 hours

i) Dry benzene, N$_2$ atmosphere, Reflux, 8-9 hours

i) Dry benzene, anhydrous MgSO$_4$, N$_2$ atmosphere, RT, 8 hr

i) Methylene chloride, N$_2$ atmosphere, 0-5^{0}C, anhydrous MgSO$_4$

Fig 43

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