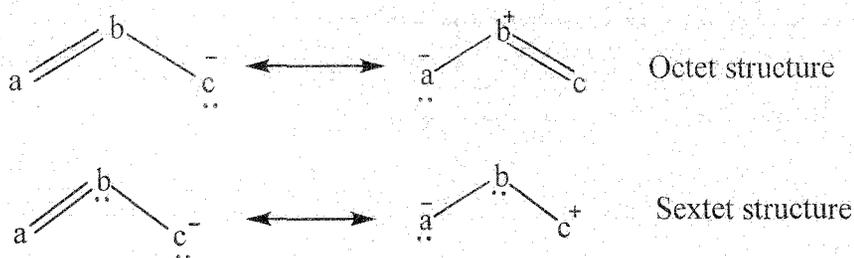


Theoretical approach and Review work**General**

The term "1,3-dipole", $a^+ \text{---} b \text{---} c^-$ 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 unstable, 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.

**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.

**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.

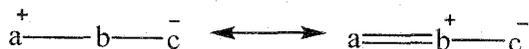


Fig 3

1,3-dipoles can be represented as depicted in Fig 3. 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.

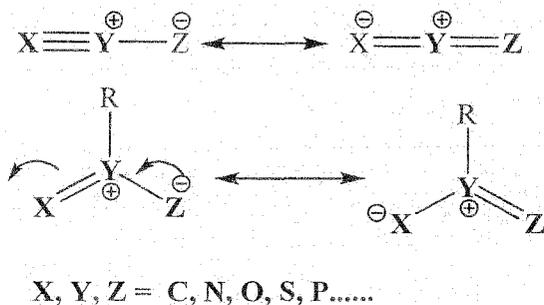


Fig 4

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 values¹ for hetero atoms for the use of simple LCAO (Linear combination of atomic orbitals) treatment viz.

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

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

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

$$x^3 + 4x^2 + 2.3x - 2.4 = 0$$

i.e. $x = 0.5175, -1.58775 \text{ \& } 2.9297$

Therefore the energy levels are

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

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

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

and the total Π energy of system was

$$\varepsilon_{\Pi} = 4\alpha_0 + 5.03495 \beta_0$$

Approximate HMO calculation of nitrene (1)

In order to verify the stability of *N*-phenyl- α -chloro nitrene (1), *N*-cyclohexyl- α -chloro nitrene² was taken as an example for the approximate HMO calculation.

The secular determinant for nitrene (1) (*N*-phenyl- α -chloro nitrene) 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

$$\varepsilon_{\Pi} = 4\alpha_0 + 7.1479 \beta_0$$

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

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

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

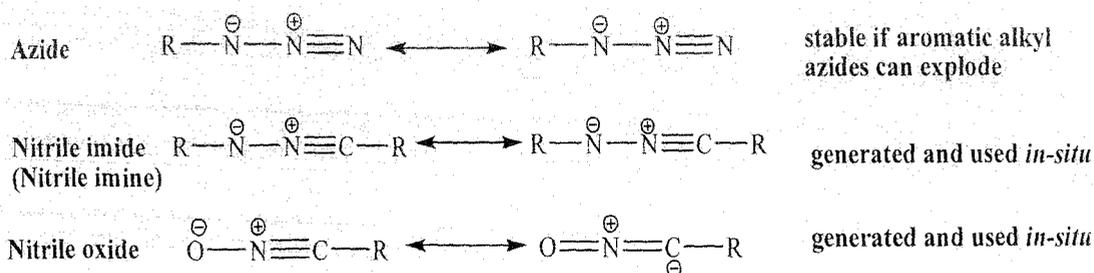
$$\epsilon_{\Pi} = 5\alpha_0 + 8.2575 \beta_0$$

Considering the calculated energy levels, associated with nitrene (**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 nitrenes 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 nitrene (**1**). Although we could not use series of computational program but elementary application of this methodology suggests that *N*-phenyl- α -chloro nitrene is moderately stable & hence the nitrene 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 nitrene shows -0.154 & -0.032 for HOMO & LUMO energies in Hartrees (1 Hartree = 27.21 eV). *N*-phenyl- α -chloro nitrene has a chlorine group at β - position of the nitrene which has a strong electron withdrawing nature & therefore the nitrene should be electrophilic in nature. The high reactivity of *N*-phenyl- α -chloro nitrene could also be explained on the basis of perturbation theory where the HOMO level of parent nitrene 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 propargyl anion)



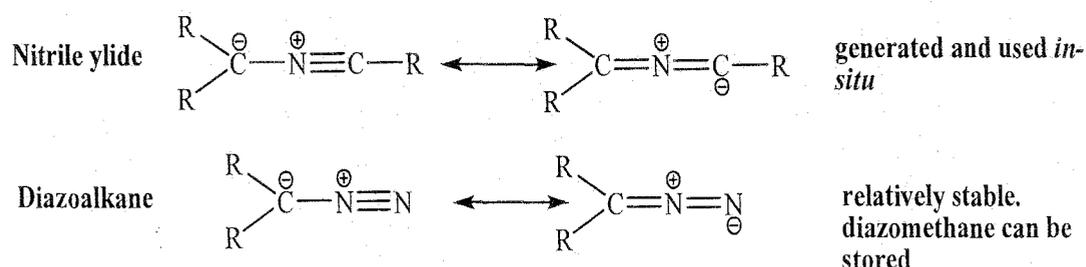


Fig 5

sp^2 hybridised (bent dipoles like the allyl anion)

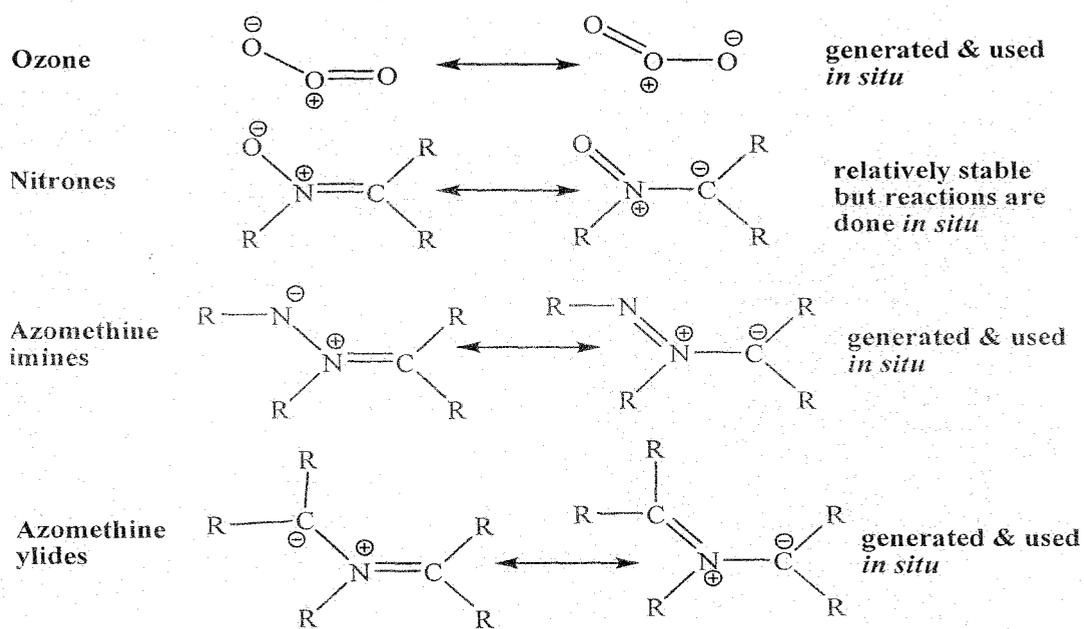


Fig 6

Reactivity profile of 1, 3-dipoles

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

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

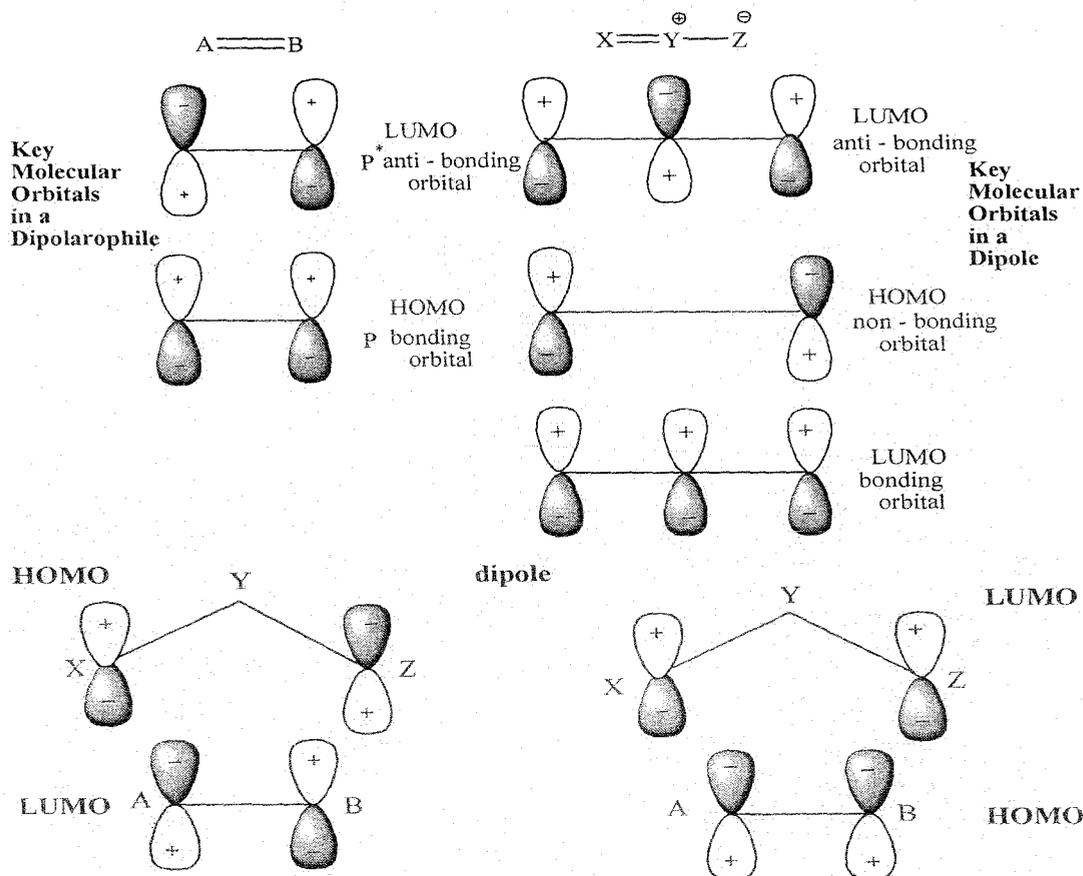


Fig 7

The term "nitrone" was coined from nitrogen ketone (azomethine oxide) in order to keep its resemblance to the carbonyl group in its several reactions⁷.

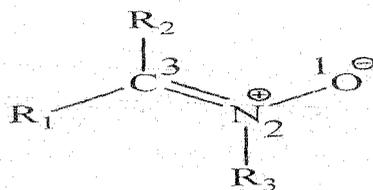


Fig 8

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 -pyrrolidine-*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.



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



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 nitrone⁸. 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, ¹H NMR studies⁹. The only example of geometrical isomerism is known for α -phenyl-*N*-tertiary butyl nitrone¹⁰. 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 in fig 10.

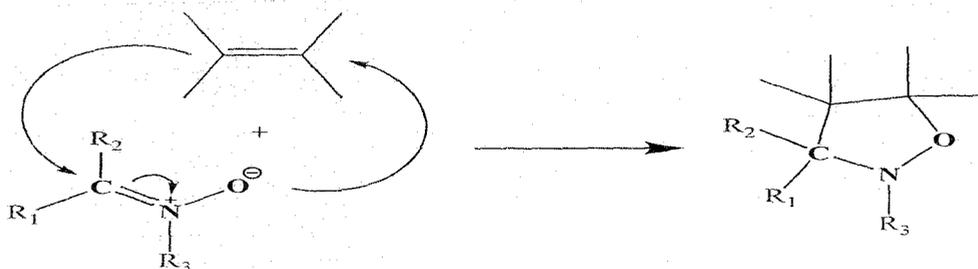


Fig 10

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

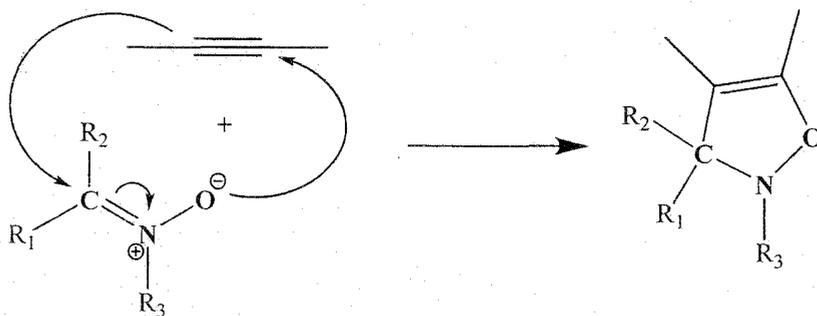


Fig 11

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



Fig 12

N-phenyl- α -chloro nitron (1) has a chlorine group at β -position of the nitron which has a strong electron withdrawing nature and therefore this nitron 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



Both cyclic and acyclic nitrones were prepared by this method. Different oxidizing agents are used viz, yellow mercuric oxide¹¹, active lead oxide¹², potassium ferricyanide¹³, hydrogen peroxide¹⁴, potassium permanganate¹⁵, diammine silver nitrate¹⁶.

The formation of the nitron salt was reported from the reaction between *p*-benzoquinone and 1-hydroxyl piperidine¹⁷.

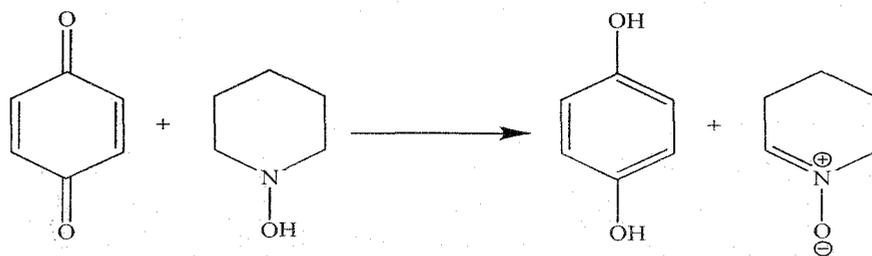


Fig 13

The formation of nitron from *N,N*-disubstituted and *N*-substituted hydroxylamines using palladium catalyst were also reported¹⁸. Recently a four membered cyclic nitron 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 nitron from corresponding hydroxylamine²⁰. Photolysis of *N*-hydroxylamines in presence of 1, 4 – dicyano naphthalene (DCN) as an electron acceptor gave high yields of nitron²¹.

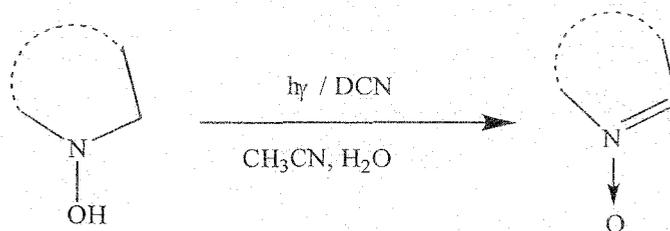
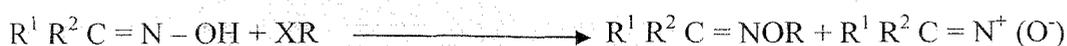


Fig 14

From oximes

The alkylation of the oximes was reviewed in 1938²². Disadvantage of this method was that nitrones were produced along with oxime ether.



Li, Na, K or tetramethyl ammonium oxime salts did not alter the product ratio of oxime ether to nitron significantly. Electron withdrawing group in the para, ortho- disubstituted benzophenone oxime salts markedly promoted the formation of nitrones while electron

donating group favours nitron 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 nitron²³. DMSO was employed in the various keto-oxime alkylations. *C,C*-dicyclopropyl-*N*-methyl nitron has been prepared by this method²⁴.

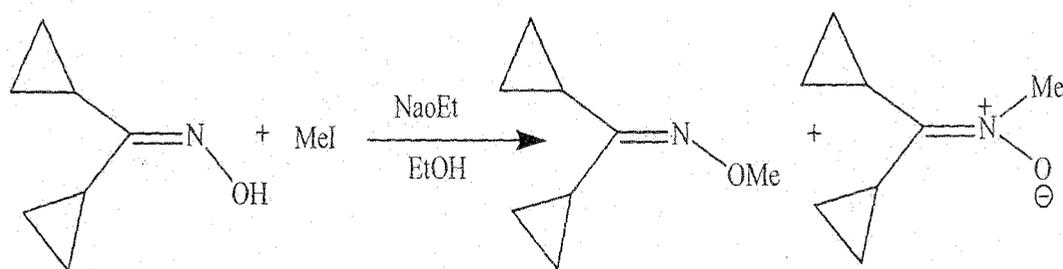


Fig 15

Formation of nitrons was also reported by the intramolecular Michael addition of aldoximes and ketoximes to electronegative olefins²⁵.

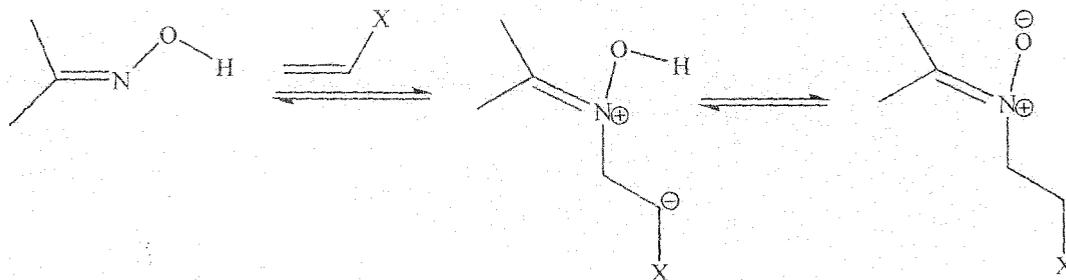


Figure 16

Recently oxime-*O*-allyl ether were converted to the corresponding *N*-allyl nitrons on treatment with 10 mole % of PdCl_2 (MeCN_2) by a formal [2+3] sigmatropic shift²⁶. Formation of cyclic *N*-vinyl nitrons were also reported from δ -alkenyl oximes by a concerted $2n + 2\pi + 2\delta$ 1, 3-azprotic cyclotransfer reaction²⁷. Both the reaction proceeds smoothly and high yields were reported. This is one of the best methods for the preparation of aldonitrons. *N*-phenylhydroxylamine has been treated with a variety of aldehydes and ketones. *N*-cyclohexyl methylene nitron²⁸ similar to *N*-phenyl methylene nitron²⁹ 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 examples of this type of reaction is shown in the following way.

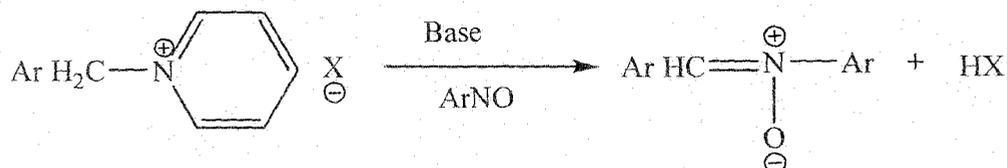


Fig 17

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 nitrosobenzene³⁴.

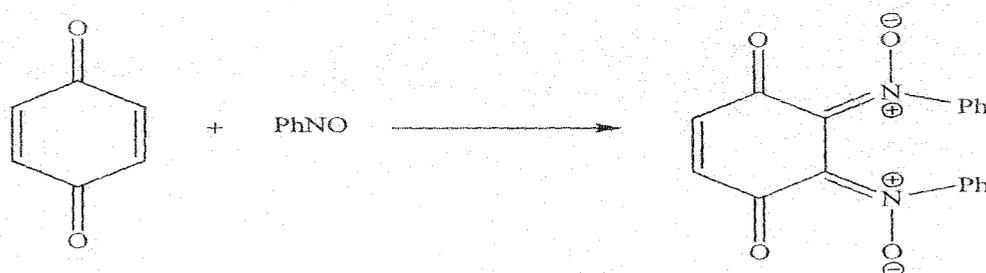


Fig 18

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) hydroxylamine³⁵. Nitrones can also be isolated in pure state from *D*-glucose oximes and benzaldehyde without employing any protection of hydroxyl group³⁶.

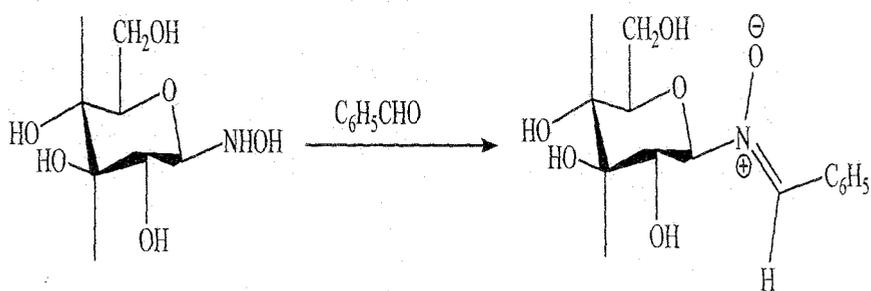


Fig 19

Nitrones can be obtained by the treatment of trimethyl silyl chloride and triethyl amine on nitroalkanes also³⁷.

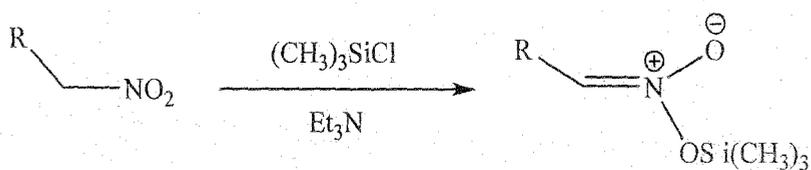
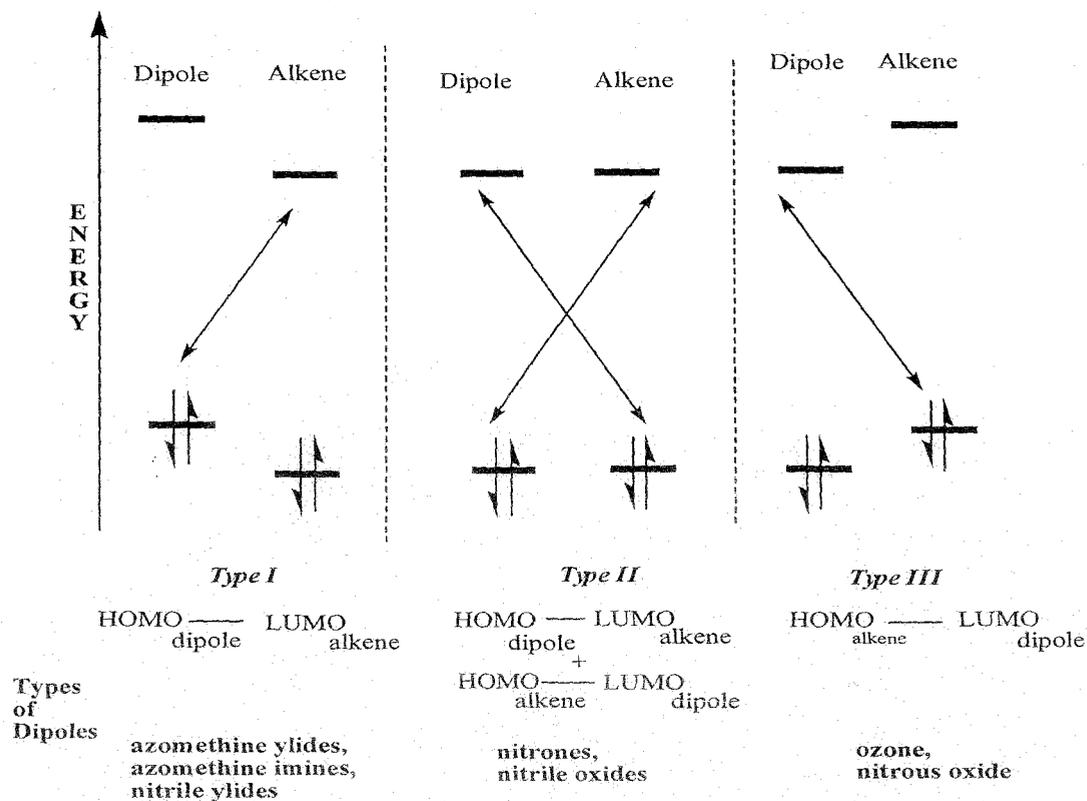


Fig 20

1,3-dipolar cycloaddition reaction

Mechanistic investigations by K.N.Houk et al³⁸ have shown that the cycloadditions of 1,3 dipole to alkenes are stereospecifically suprafacial and 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 $[4 \pi's$ and $6 \pi's]$ cycloaddition, but not $[4 \pi's + 4 \pi's]$ cycloaddition of 1,3-dipoles to diene. This 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 cyclo-addition reactions are 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 Sustman³⁹.



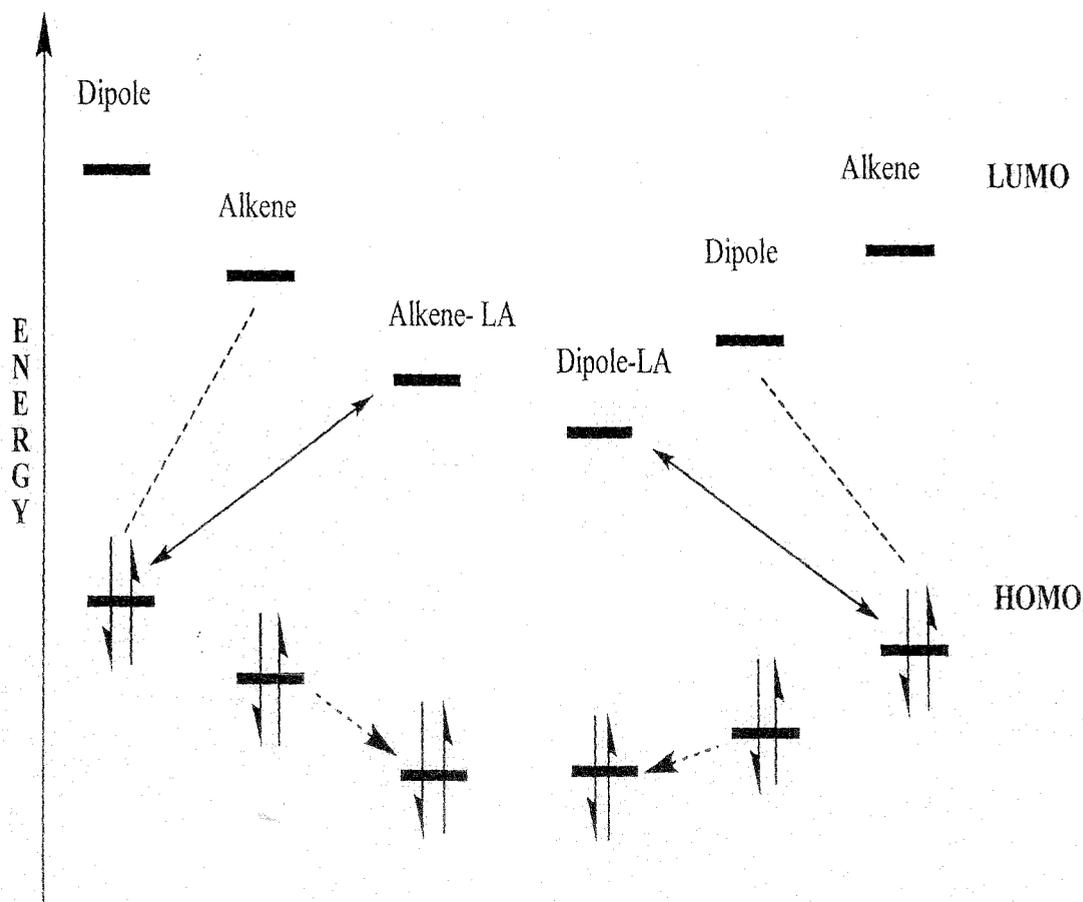
Type I: It involves dominant interaction between LUMO (dipole)-HOMO (dipolarophiles).

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 HOMO-LUMO controlled dipoles.

Type III: It has low lying FMO's and referred to as LUMO controlled or electrophilic 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, 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 α 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.

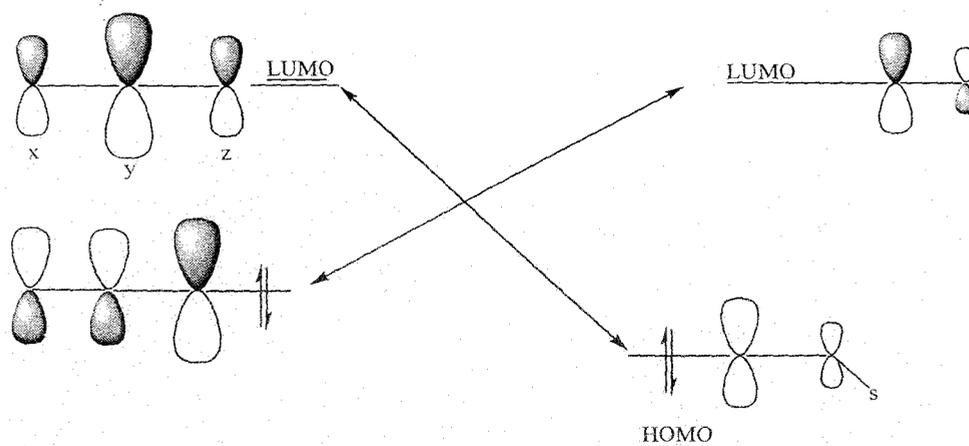


Fig 21

Nitrile-oxides and nitrones react to give mainly the five substituted adduct with weakly electron deficient alkenes like acrylo nitrile 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. Huisgen⁴⁰ observed that acetylinic dipolarophiles are less reactive than expected on basis of their ionization potentials. Since alkynes have large HOMO-LUMO gap than alkenes, it is expected that during interactions with the alkyne, LUMO plays the most significant part and hence alkynes are less reactive than 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 C₄ and C₅ 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 π -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.

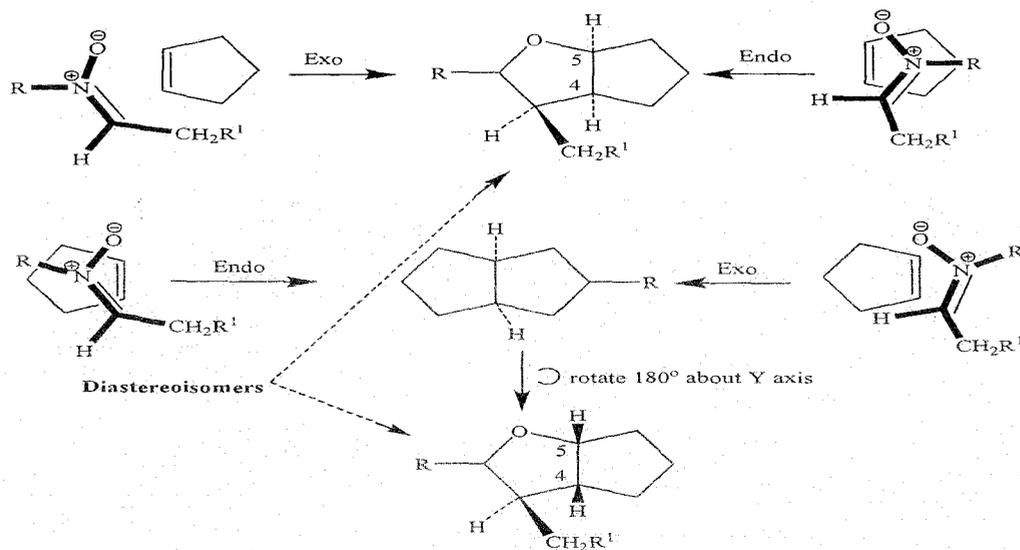


Fig 22

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

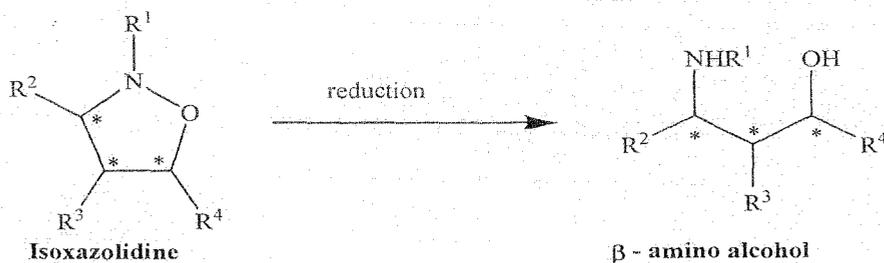


Fig 23

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 unstability, 1, 3-dipolar cycloaddition reactions are carried out by trapping the nitrones at the time of their formation. This process avoids dimerization of the nitronium 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 green 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 nitron and their cycloaddition reactions now-a-days are mainly performed in 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 above cases, the reaction conditions are mild, can be easily carried out and the isolation of the compounds are not very difficult. Interestingly, in all these cases, yields are much better in very short time period as compared to the conventional methods of cycloaddition reaction. Now-a-days aqueous phase cycloaddition reaction is mostly carried out to avoid hazardous solvents and also to get higher yields in a short reaction time and is completely a greener approach towards the cycloaddition reaction of nitrones. Three research articles in this regard have been 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 nature⁴⁴. 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 pyrrolidine or piperidine ring in extremely good yield. From 2000 onwards it has been found that High Resolution Mass Spectra (HRMS), ¹³C NMR and X-ray crystallography of single crystal studies are commonly used for the characterization of nitron and cycloadducts. In the present study, we have used HRMS, ¹³C NMR techniques along with ¹H 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 even 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 group⁴⁴, they have found from the spectral analysis that the spectra of one of the oxime that gets converted to nitron by microwave irradiation, gives authentic HRMS value in support of the structure of the nitron.

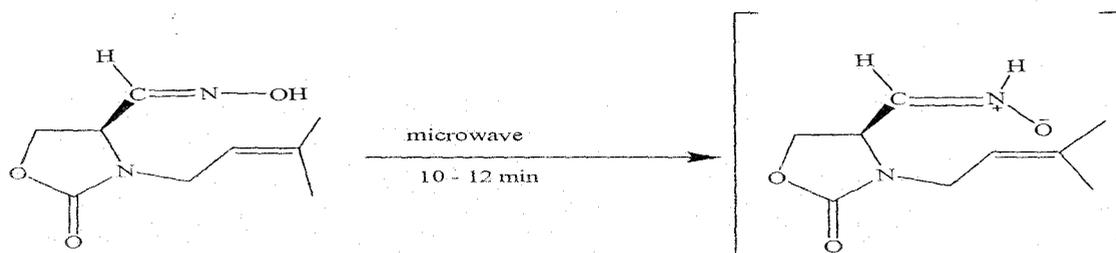
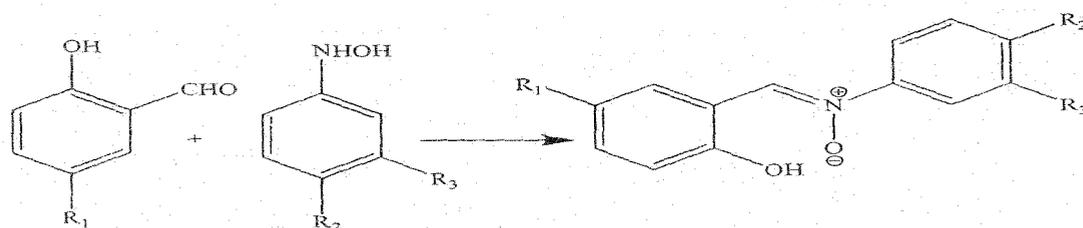


Figure 24

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 review⁴⁵ 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. Muthusubramanian and his co-workers. They synthesized α -(5-substituted-2-hydroxyaryl)-*N*-arylnitrones. They have shown that in microwave, the required time for the cycloaddition reaction is comparatively less and at the same time, the yield is much higher than the conventional methods.



$R_1 = t\text{-Bu, } i\text{-Pr, Ph}$

$R_2 = \text{H, Me, Cl}$

$R_3 = \text{H, Me}$

Fig 25

Another important work by A. Goti and his co-workers⁴⁶ of Italy, working with *C, N*-diphenyl nitron and butyrolactones (dipolarophiles) have shown that the reactions are highly

stereoselective in nature giving both the enantiomers a high yield and it has been found in the following figure 26.

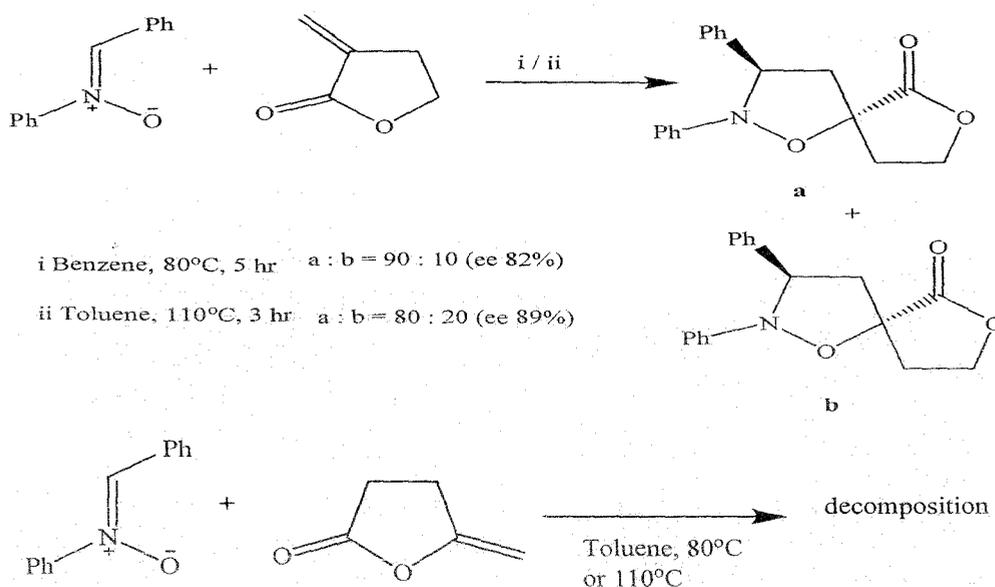


Fig 26

Another brilliant work was by R. Shintani and Gregory C. Fu⁴⁷ suggests a copper catalysed [3+2] cycloaddition reaction, which is an enantioselective coupling of terminal alkenes with azomethine imines to generate five membered heterocycles.

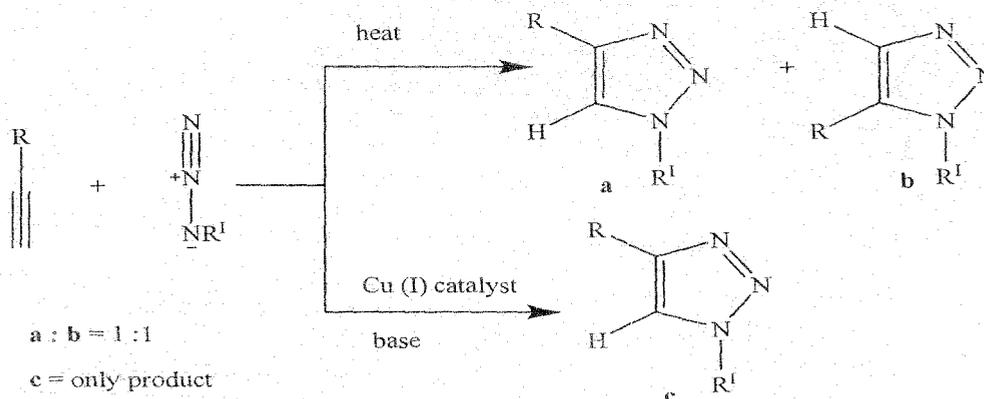


Fig 27

Some new works on nitronene cycloaddition reaction has been suggested by K. V. Kudryavtsev and V. Irkha⁴⁸ which suggest 1,3-dipolar cycloaddition reaction of homo protein, involving protein chemistry using *N*-methyl maleimide. The most important feature of this reaction is the multi component reaction.

Anup Bhattacharya et. Al.⁴⁹ suggests some remarkable work on glucose derivatives. In the year 2005 they have suggested intramolecular 1,3-dipolar nitron and nitrile oxide cycloaddition of 2 and 4 allyl and properglyl glucose derivatives. This is the versatile approach to chiral cyclic ether fused isoxazolidines, isoxazolines and isoxazoles.

With the help of 1,3-dipolar cycloaddition reaction, natural products also can be synthesized and was shown by G. W. Gribble and his coworkers⁵⁰ 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).

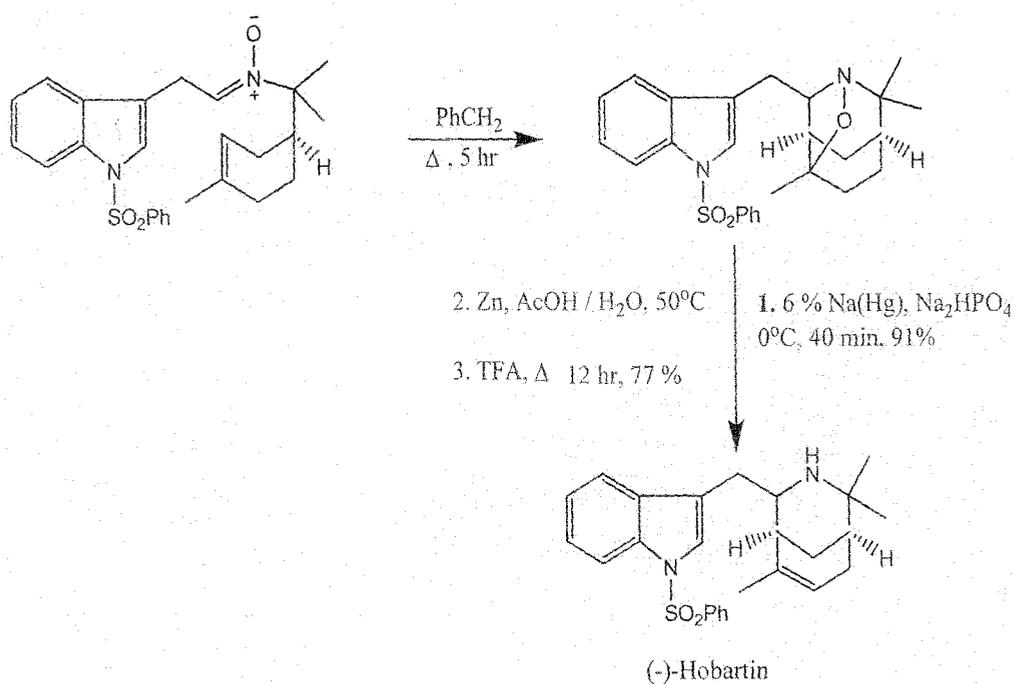


Fig 28

It has been found from 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-workers⁵¹ from the intramolecular low temperature 1,3-dipolar cycloaddition reaction of nitrones where chromano heterocycles are synthesized.

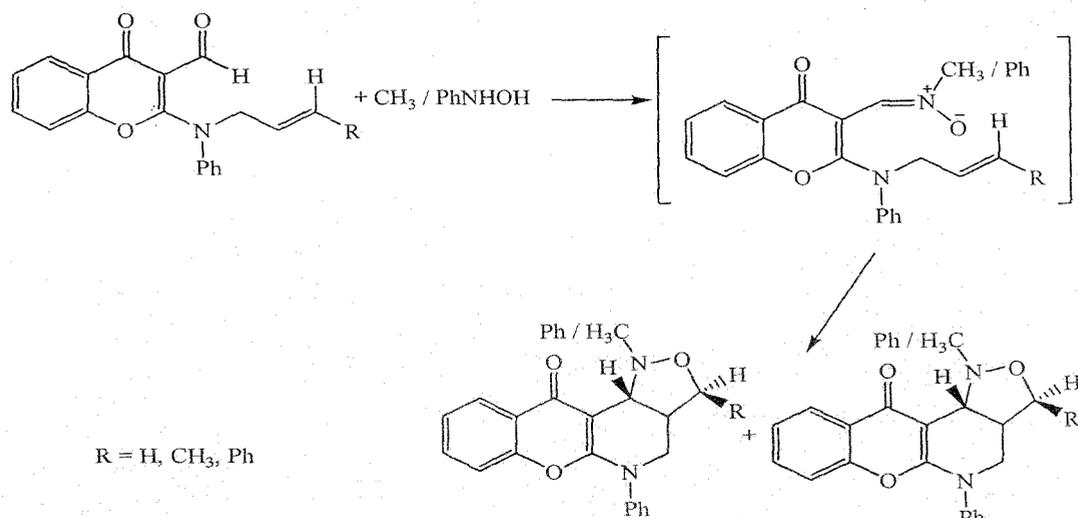
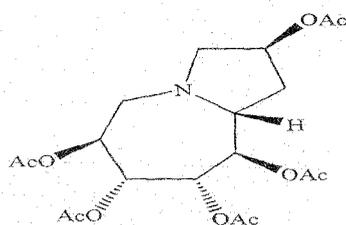


Fig 29

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 pyrrolidinyl glycines from nitrones also report moderate antifungal activities as reported by P. Merino and his co-workers⁵².

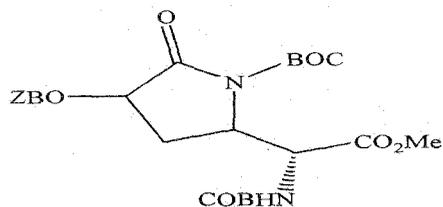


Figure 31

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 yield⁵³.

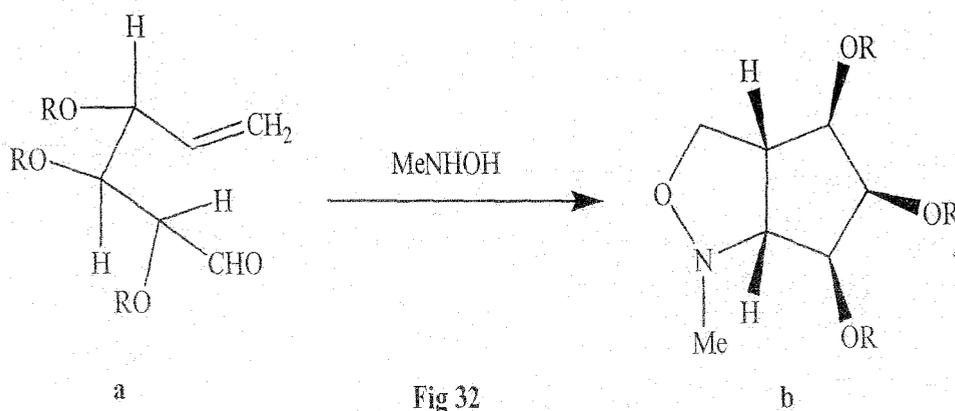


Fig 32

This compound is good antifungal agent as reported. Some of the antitumor activities shown by the cycloadducts formed between α -phenyl-*N*-methyl nitrene 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 the literature survey shown above, we have also reported antitumor, antibacterial, antifungal activities of isoxazolidine derivatives (Ref 43) which were synthesized in our laboratory following the methodology represented earlier. The recent reviews of A. Padwa⁵⁴ 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.

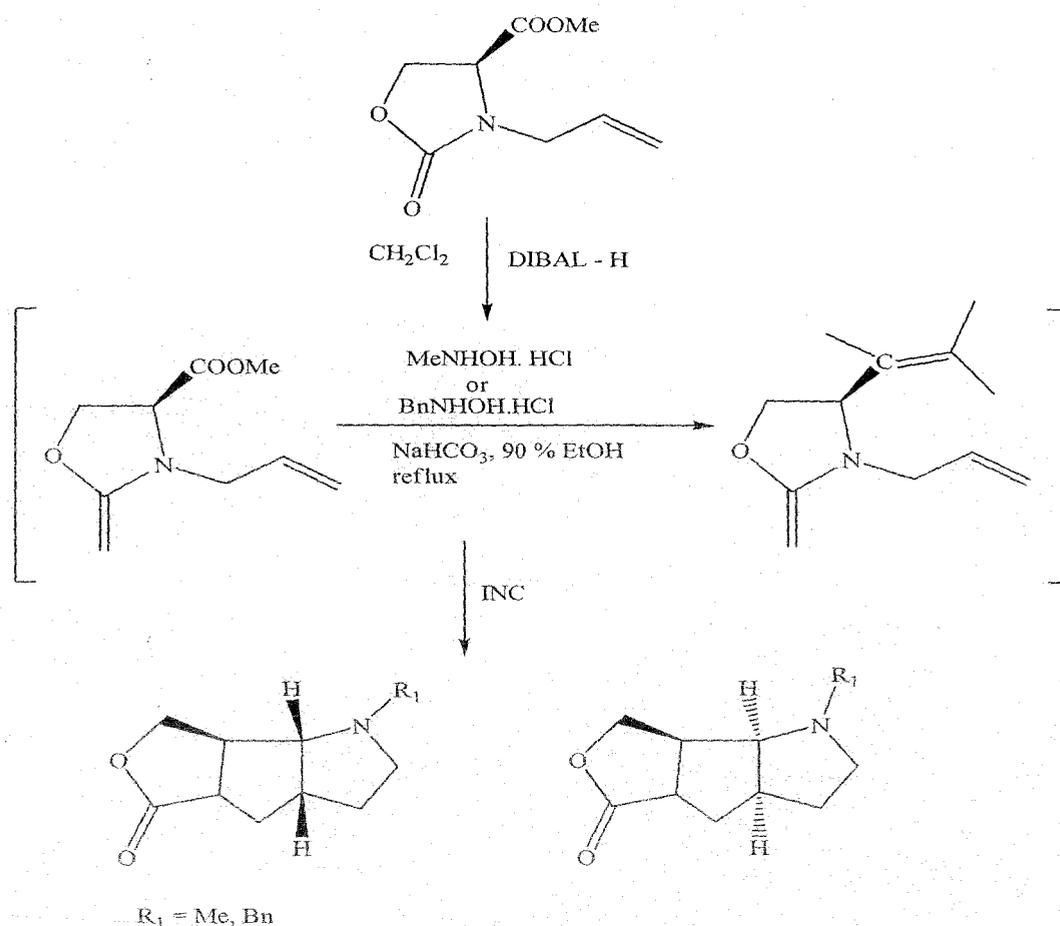
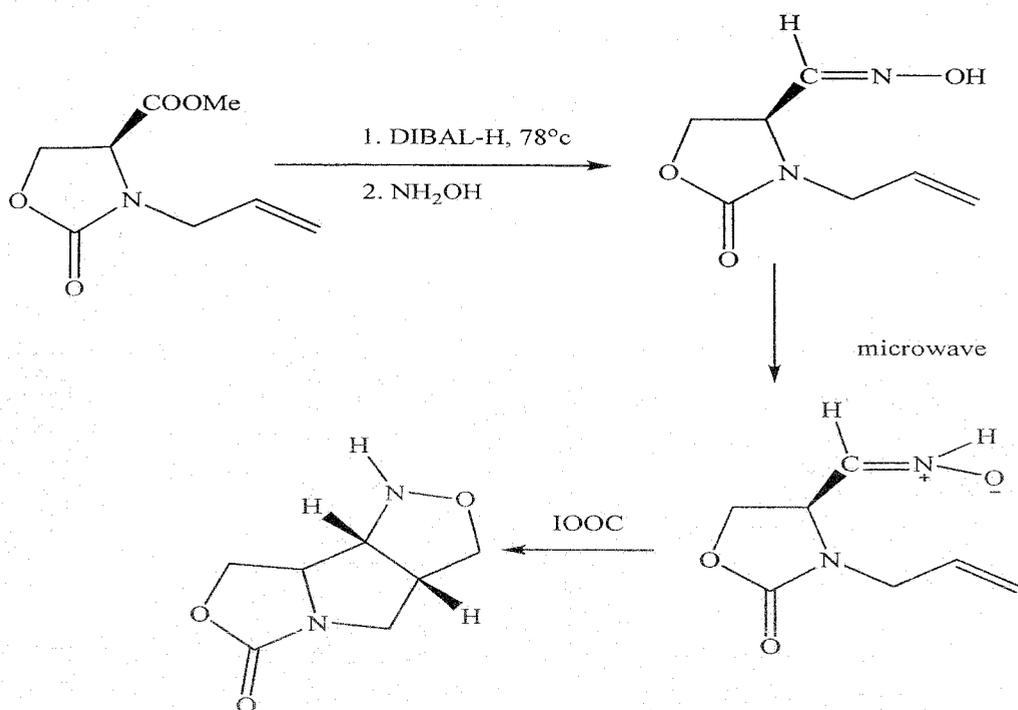


Fig 33

From the review work, it has been found 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 method⁵⁵. *Tetracycline* 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.

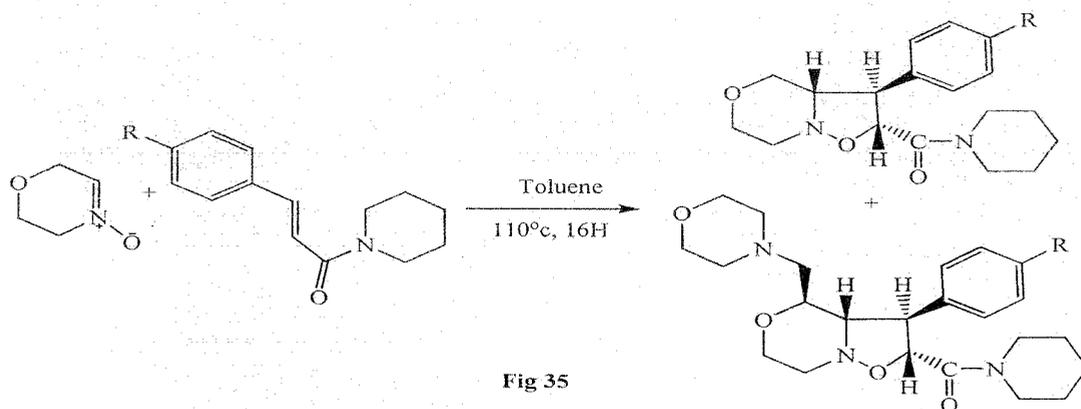
Highly stereoselective intramolecular cycloaddition reactions of unsaturated *N*-substituted oximes, nitrones and azomethyne ylides on the surface of the silica gel without a solvent have been conducted under microwave irradiation to produce tricyclic isoxazolidines fused with pyrroline or pipyridine ring in good yields as reported by Q. Chang, W. Zhang, Y. Tagan and their group in the year 2001⁵⁶.



IOOC = Intramolecular oxime-olefin cycloaddition

Fig 34

A series of unexpected cycloadducts along with normal cycloadducts have been reported by Abhijit Banerjee and his group⁵⁷ using 1,3-dipolar cycloaddition reaction of 3,4-dihydro morpholine *N*-oxide with piperidine of cinnamic acid and *p*-substituted cinnamic acids. Since unexpected cycloadducts being quite rare, this work has given immense interest to the workers of nitrene cycloaddition reactions.



A brilliant work of Francis Heaney, Oliver Rooney in 2001⁵⁸ reports the formation of bis isoxazolidines involving *bis* nitrones using *N*-methyl maleimide as dipolarophiles. The

reaction as reported is highly diastereospecific in nature. This has been the first reported case of *bis* isoxazolidines.

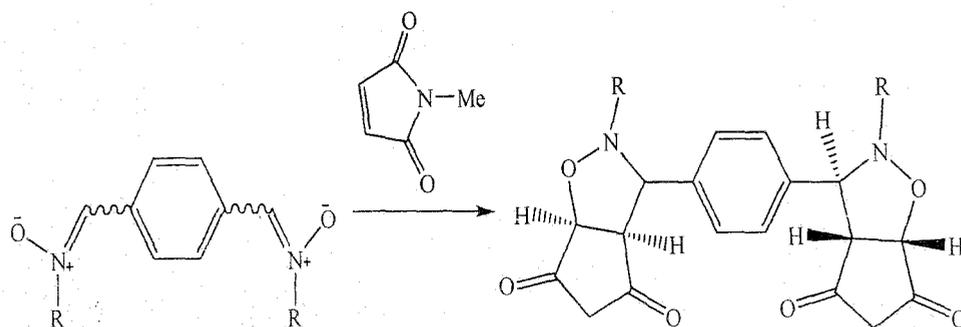
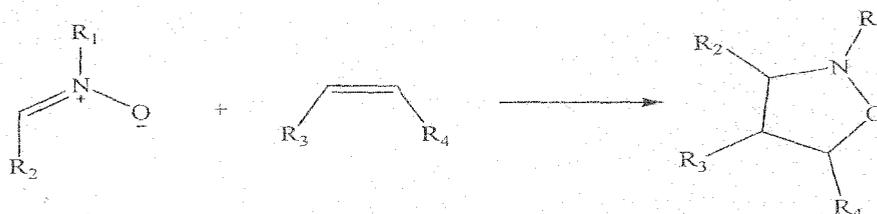


Fig 36

Reports of 1,3-dipolar cycloaddition reaction of nitrones in aqueous solution was first ever reported by O. Mersbergen and his group⁵⁹ 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.



$R_1 = R_2 = \text{Ph}$ or $R_1 = \text{Me}; R_2 = \text{Ph}$ **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 group⁶⁰. This work is novel, as far the formation of nitronium is concerned.

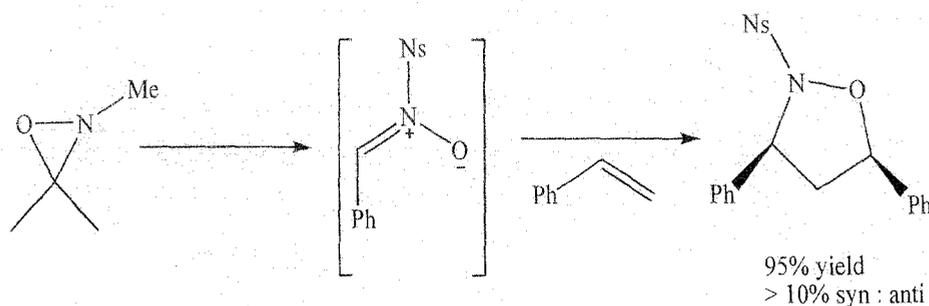


Fig 38

In the year 2007, Sheikh Ali and his group⁶¹ reported a new stereochemical approach of 1,3-dipolar cycloaddition reaction of internally *H*-bonded chiral methylene nitrones.

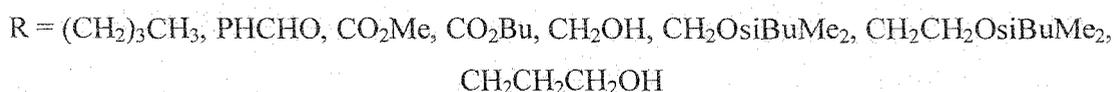
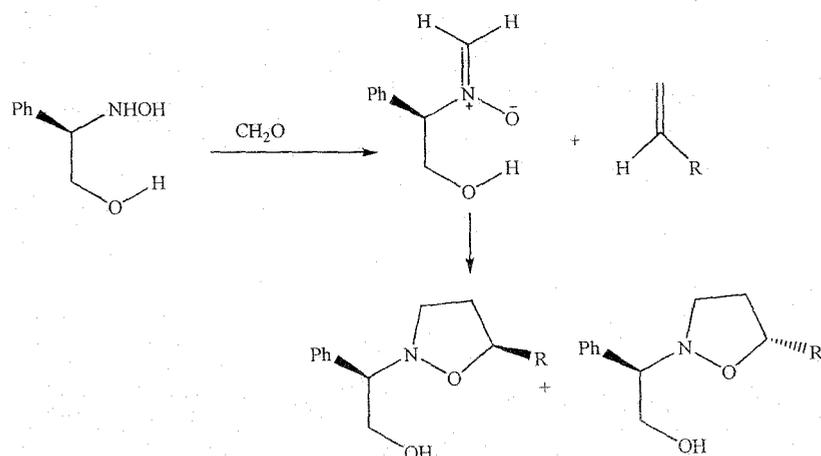


Fig 39

Lubor Fiserá and his group⁶² reported some novel cycloaddition reactions in early 2009 where the nitrones were derived from sugars. The work is actually diastereoselective synthesis of isoxazolidinone nucleosides by means of 1,3-dipolar cycloaddition reaction of chiral sugar derived nitron as the key step.

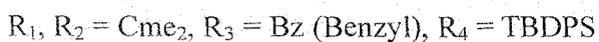
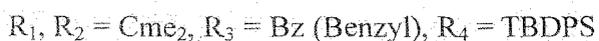
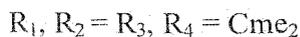
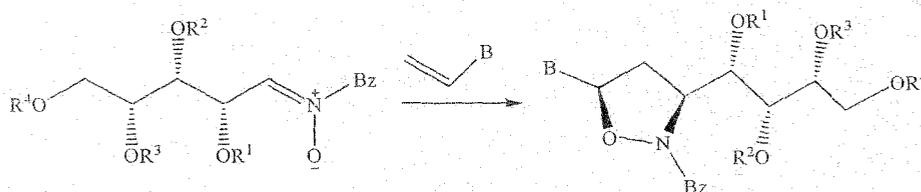


Fig 40

An interesting example of the formation of nitron in water exclusion reaction in aqueous media using surfactant and subsequent cycloaddition reactions in the same pot has been reported by P. K. Bhattacharya⁶³. 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 aqueous medium.

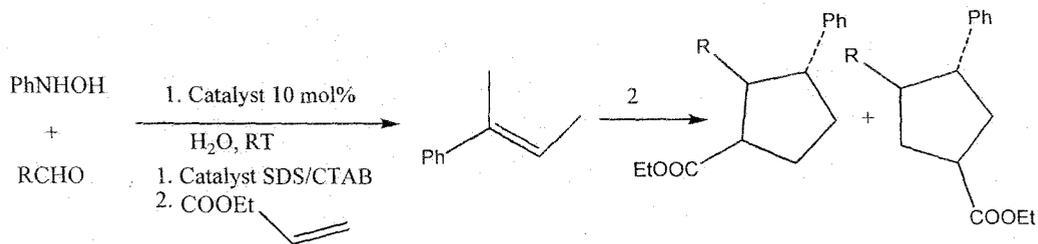


Fig 41

An example of highly efficient solvent free 1,3-dipolar cycloaddition reaction of *N*-substituted dipolarophiles and nitron was reported by T. B. Nguyen and his group⁶⁴. 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.

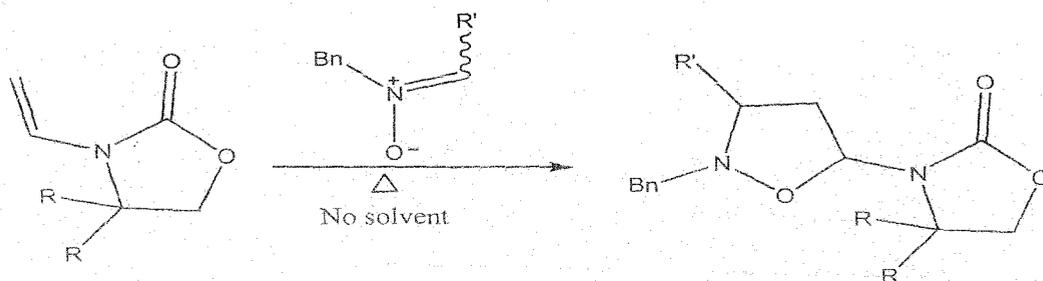
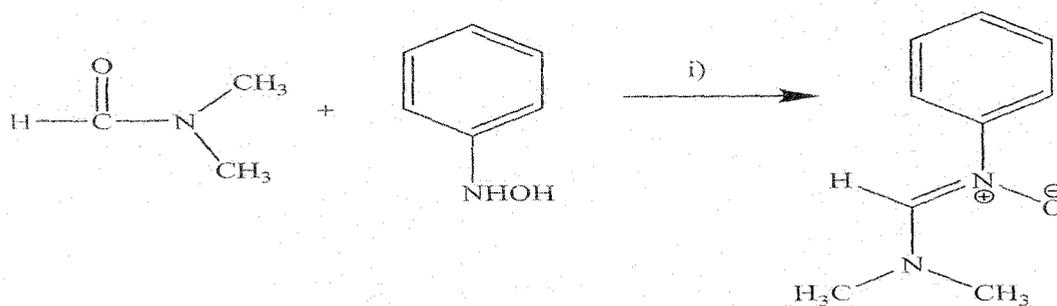
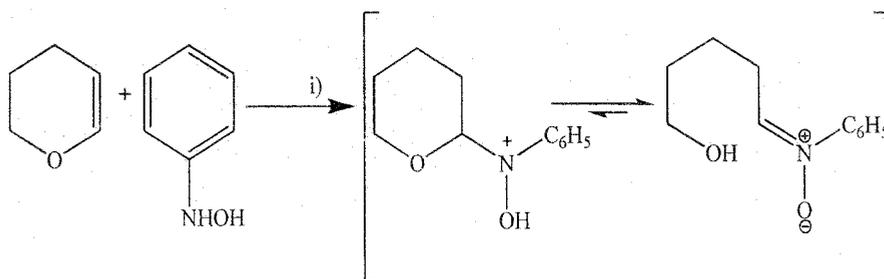


Fig 42

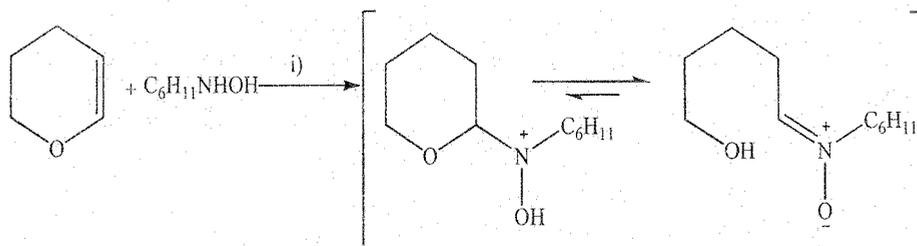
Synthesis of different *N*-cyclohexyl, *N*-phenyl- α -chloro nitron along with other nitrones have also been reported from our laboratory^{41-43 65-78}. Few of the nitrones thus reported are prepared by the following way.



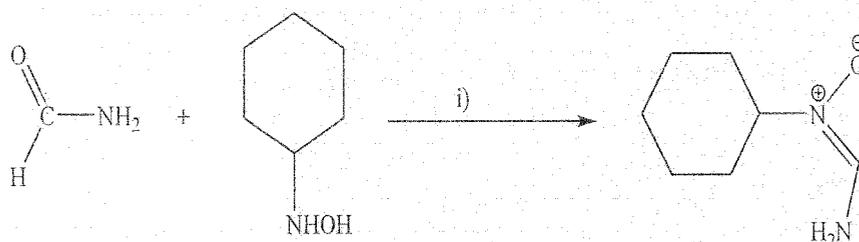
i) Anhydrous MgSO_4 , N_2 atmosphere, RT, 12 hours



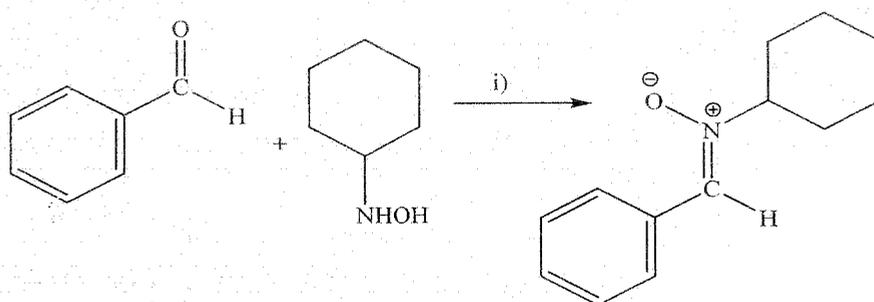
i) Anhydrous MgSO_4 , N_2 atmosphere, Reflux, 24 hours



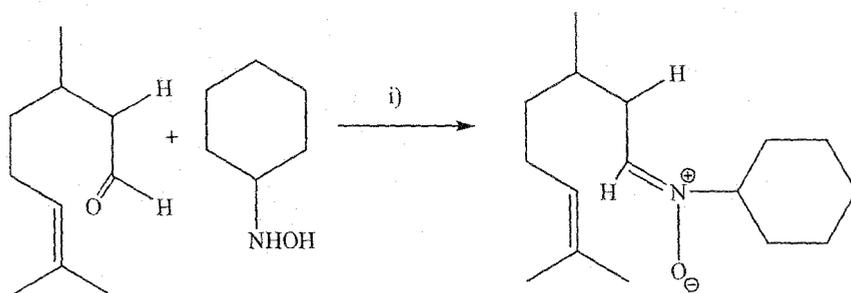
i) Anhydrous MgSO_4 , N_2 atmosphere, Reflux, 20 hours



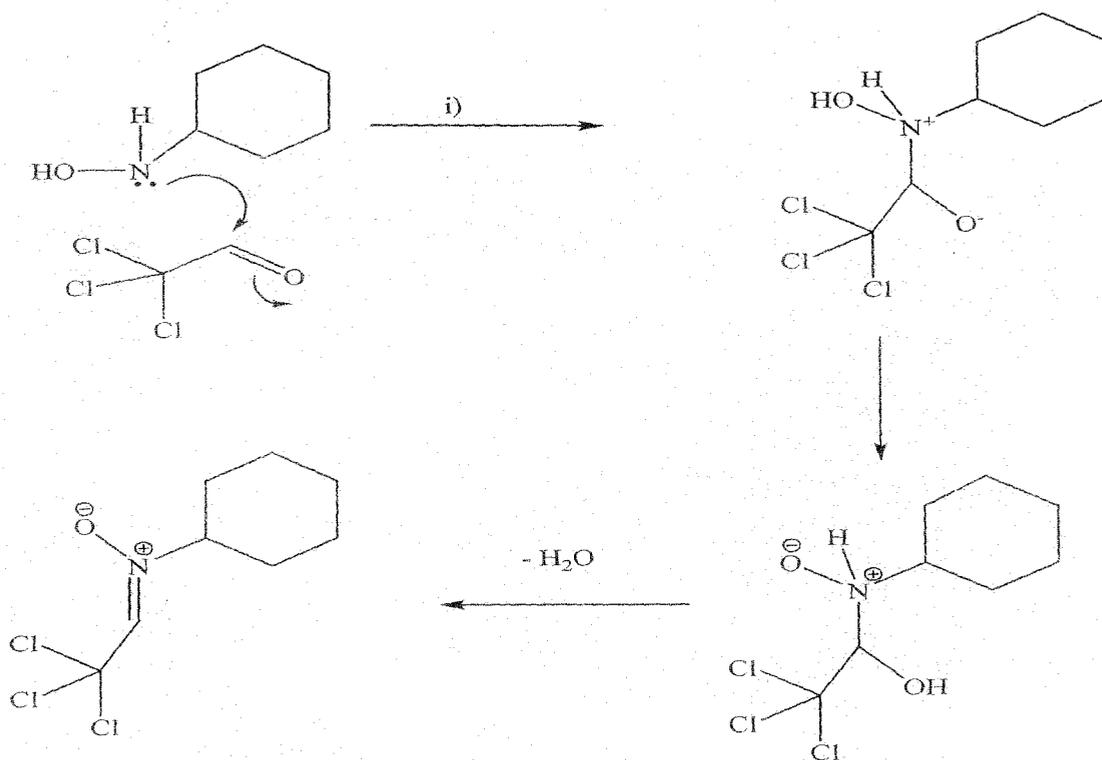
i) Dry benzene, N_2 atmosphere, RT, 18 hours



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, $0-5^\circ\text{C}$, anhydrous MgSO_4

Fig 43

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