
CHAPTER I

Original theoretical approach and relevant review work s

General concept:

The term "*1,3-Dipole*" is usually represented by $\overset{+}{p}$——q——$\overset{-}{r}$, in which atom "p" occupies an electron sextet. Atom "p" has an incomplete valence shell which is combined with a formal positive charge. Atom "r", the negatively charged center has an unshared electron pair. 1,3-dipole reacts with alkene and alkynes commonly called "*dipolarophiles*" in 1,3-dipolar cycloaddition reaction leading to variety of 5-membered heterocycles with oxygen and nitrogen as hetero atoms.

Compounds having six electrons in the outer shell of an atom are usually unstable, so, it is expected that " p-q-r" system will exhibit canonical form of resonance structures (**Figure 1**).

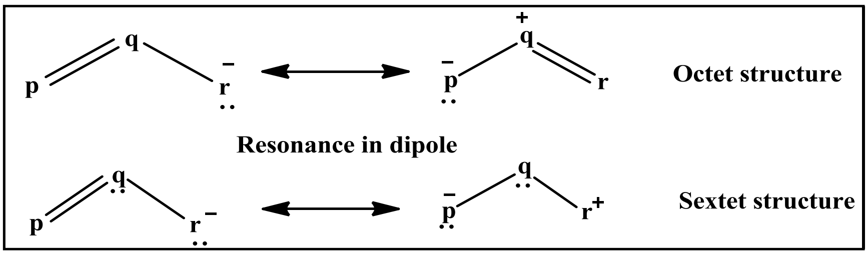
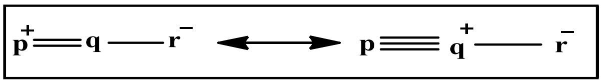


Figure 1

Stabilization of 1,3-dipoles may also occur by internal octet stabilization. 1,3-dipolar systems may be classified into two types viz,

a) Propargyl-Allenyl type

This type of dipolar canonical form contains double bond on the sextet atom while the other canonical form contains triple bond on that very atom (**Figure 2**).

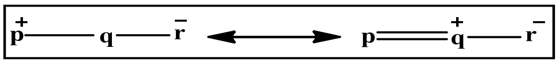


$$\overset{+}{p}{=}q{-}\overset{-}{r} \longleftrightarrow p{\equiv}\overset{+}{q}{-}\overset{-}{r}$$

Figure 2

b) Allyl type

This type of dipolar canonical form contains single bond on the sextet atom while the other cannonical form contains double bond on that very atom (**Figure 3**).



$$\overset{+}{p}{-}q{-}\overset{-}{r} \longleftrightarrow p{=}\overset{+}{q}{-}\overset{-}{r}$$

Figure 3

The central atom canot be a carbon atom in 1,3-dipole because if it is so then internal octet stabilization will be prevented by lack of available free electron pair. This type of species are very reactive as well as short lived. Examples of this class are Unsaturated carbenes and azenes are the examples of this class.

1, 3-dipole:

1, 3-dipoles are the most effective species responsible for [3+2] cycloaddition reactions leading to the generation of 5-membered heterocyclic ring systems. The nature of the reaction is similar to Diels-Alder reaction where 6 membered rings are developed. The reactive species in this kind of cycloaddition reactions are 1, 3-dipoles & dipolarophiles (known as diene & dienophile in Diels-Alder reaction). These reactions govern 4π+2π system (**Figure 4**).

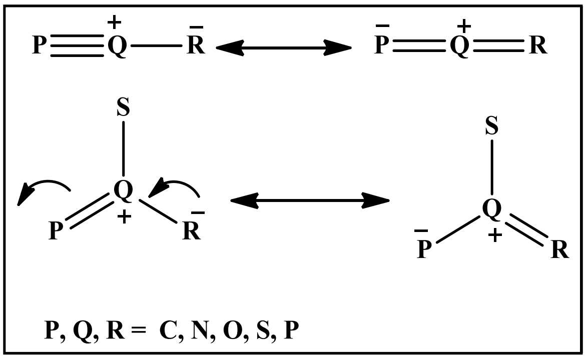


Figure 4

The stability of 1,3-dipoles vary greatly depending upon the nature of the species when generated. Some of the 1,3-dipoles may be isolated after their generation and may be preserved for sometime while majority of them are highly unstable. Usually, they are synthesized on the day of their use in cycloaddition reaction.

Dipoles are generally of two different classes viz, *sp*^{2} & *sp* hybridized dipoles.

sp hybridized dipole (they are linear dipoles similar to propargyl anion) [**Figure 5**]

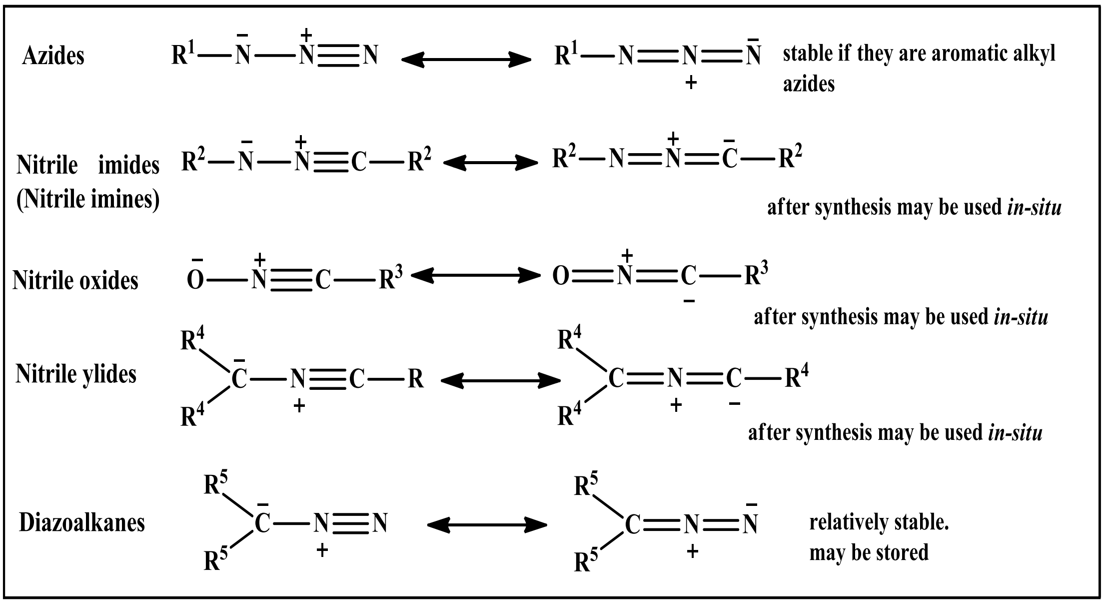


Figure 5

sp^2 hybridised dipole (they are bent dipoles similar to allyl anion) [**Figure 6**]

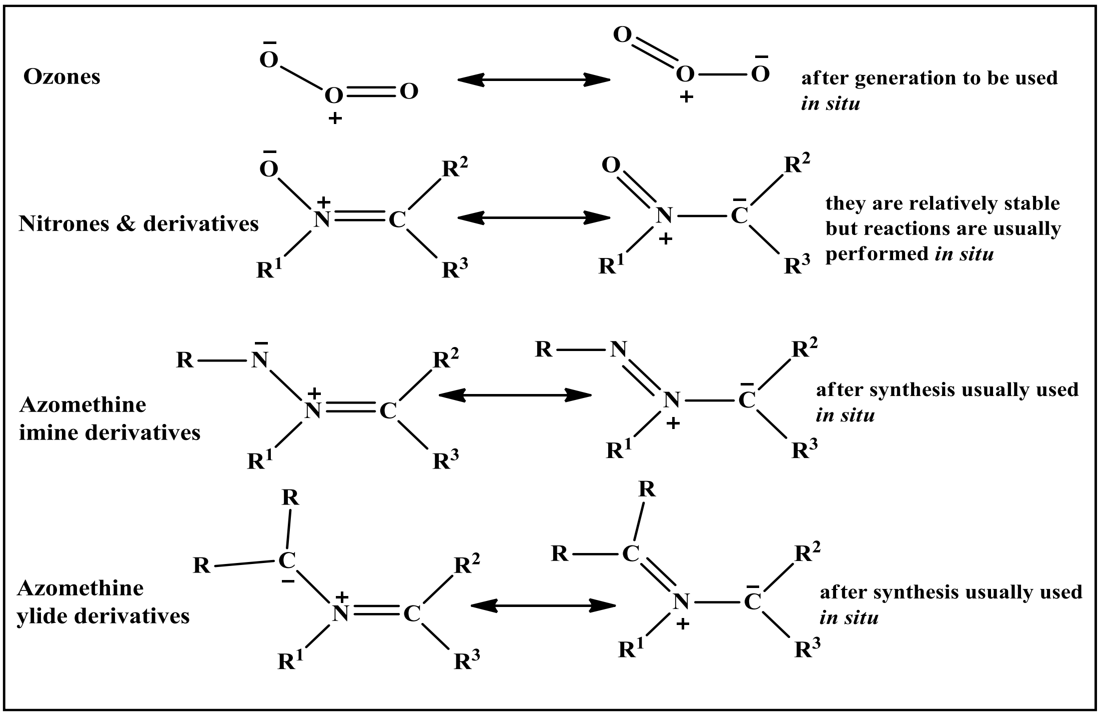


Figure 6

1, 3-dipole & its reactivity profiles

For a cycloaddition reaction, the general nature of reaction between the dipoles & dipolarophiles found to follow the following systematic procedure:

a) The concerted nature of cycloaddition reactions are widely accepted. Therefore, specific intermediates are expected in this process and the formation of new bond tmay not be synchronous.

b) Usually cycloaddition reactions are not greatly influenced by the polarity of solvents. So a small change in polarity of solvent cannot change the reactivity of 1,3-dipole and the transition state.

Usually, reaction rate between 1,3-dipoles & dipolarophiles varies considerably. K. Fukui with the help of his "*Frontier Molecular Orbital theory*" (FMO approach) explained the nature interactions between the dipole & dipolarophile (**Figure 7**)

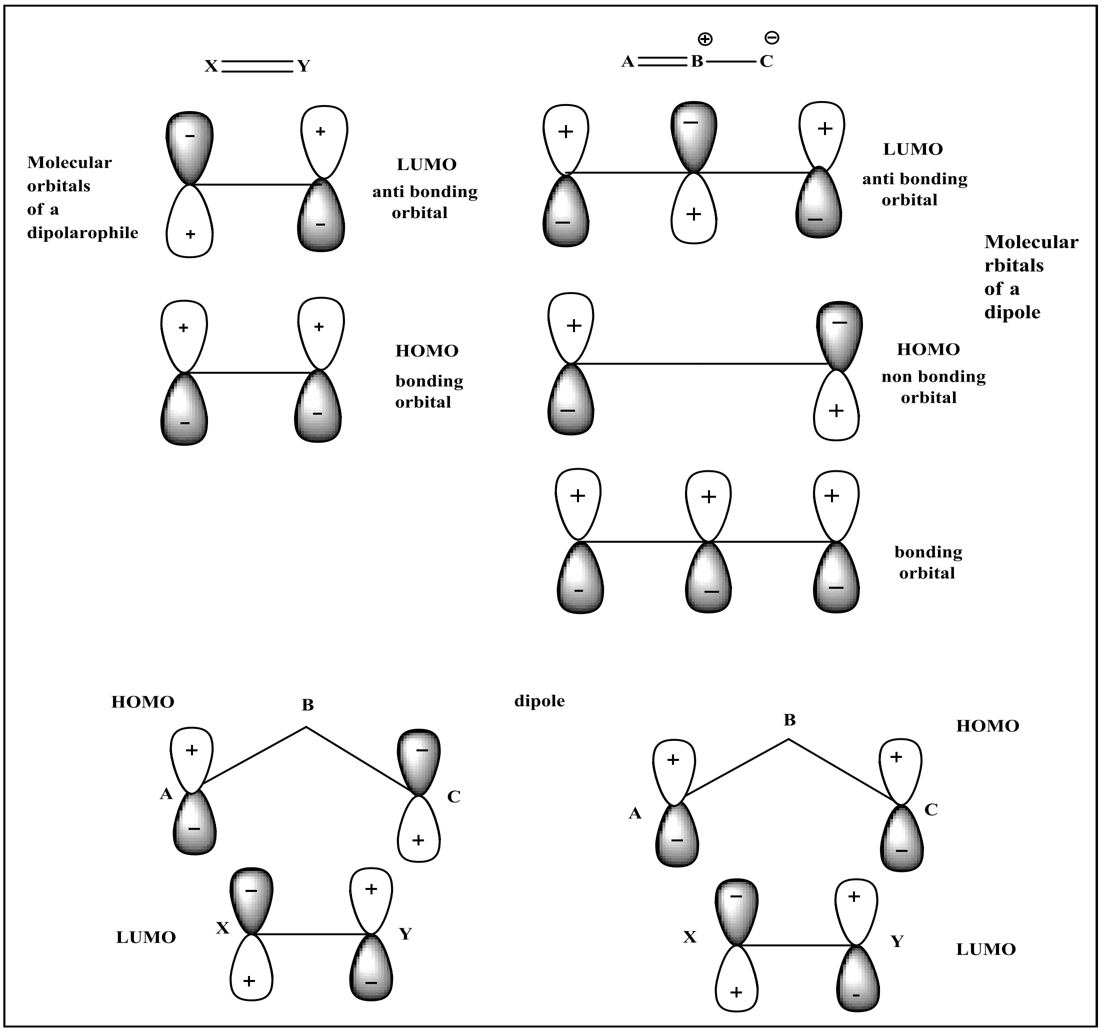


Figure 7

Pfeiffer[1] in 1916 first introduced the term “*nitrone*” from azomethine oxide-a nitrogen ketone molecule. He wanted to maintain its similiarity with carbonyl functionality as found in different reactions. The general representation of a “*nitrone*” may be depicted in **Figure 8**.

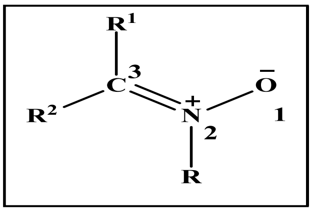
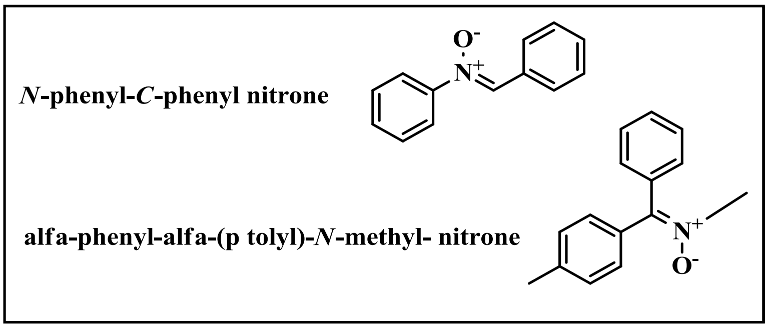


Figure 8

Nomenclature of nitrones

Since 1916, the nomenclature of ‘*nitrone*’ was adopted following chemical abstract guidelines and may be represented as under:



In case of cyclic nitrones, parent heterocyclic systems like 2,4–dimethyl–pyrolidine-*N*-oxide, tetrahydropyridine-*N*-oxide etc are taken into consideration. The nitrones are named as *C*-cyclohexyl-*N*-methyl nitrone, *C*-phenyl-*N*-methyl nitrone and *C*-methyl-*N*-phenyl nitrone etc. Two important terms ‘*aldonitrone’* & ‘*ketonitrone’* has been assigned as they are synthesized from aldehydes and ketones respectively. *Aldonitrones* possess a proton at the α-carbon atom while in *ketonitrones* α-carbon atom is substituted by alkyl/aryl groups.

$$\mathbf{R\text{-}CH = N^{+}\,(O^{-})\,R^{1}\ (Aldonitrone)}$$

$$\mathbf{R,\,R^{1}\text{-}\,C = N^{+}\,(O^{-})\,R^{2}\ (Ketonitrone)}$$

Geometrical isomerism in nitrones

The double bond between carbon & nitrogen atom helps the species nitrone to exhibit *geometrical isomerism* (**Figure 9**).

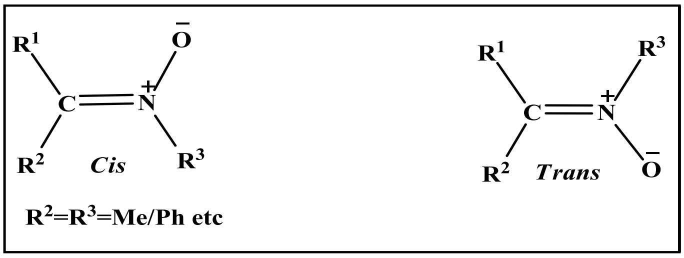


Figure 9

In 1918, α-phenyl-α-(*p* -tolyl)-*N*-methyl nitrone[2] was depicted as the first example of geometrical isomerism and dipole moment studies was employed to establish its configuration. Nitrones exist in both *cis* and *trans* forms and interestingly, *cis* form of nitrone may be converted into *trans* form when heated. From the spectroscopic studies (UV, IR, 1H NMR)[3], it has been observed that *aldonitrones* can exist in stable *trans* form. α-phenyl-*N*-tertiary butyl nitrone[4] molecule has been regarded as the most suitable example for geometrical isomerism. Hence, in such cases where geometrical isomerism is possible, In recent years, *E* / *Z* nomenclature is usually used if there is a possibility of geometrical isomerism in the synthesized nitrone specis.

The fundamental activities of nitrone in the form of 1,3-dipole in 1,3-dipolar cycloaddition reactions have been studied and well known. The species "*nitrone*" reacts with various alkenes/olefines to develop "***Isoxazolidines".*** The scheme may be depicted as under:

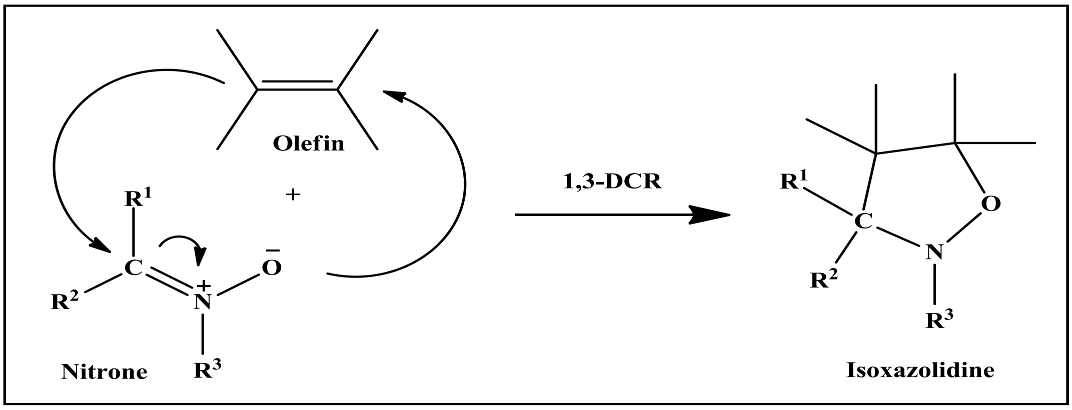


Figure 10

Similarly, nitrone behaving as 1,3-dipole, reacts with a variety of alkynes in 1,3-dipolar cycloaddition reaction resulting ***“Isoxazolines”*** (**Figure 11**)

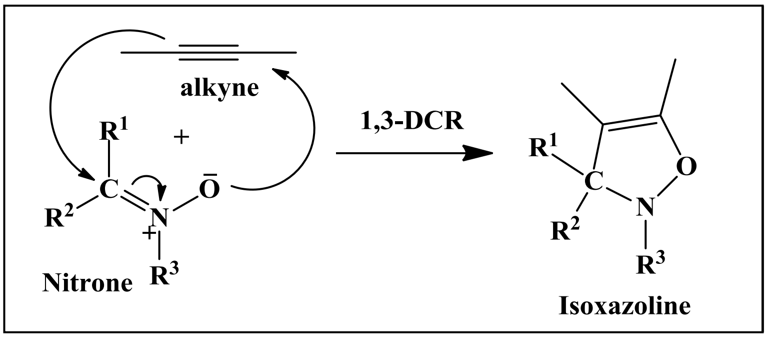


Figure 11

The most commonly represented resonating form of a nitrone may be represented as in **Figure 12.**

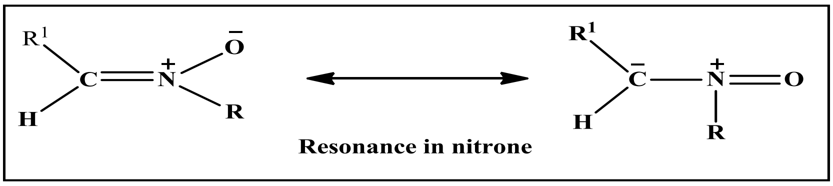
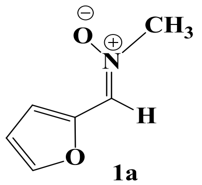


Figure 12

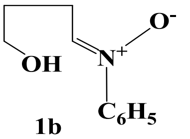
According to Huisgen and his group, 1,3-dipolar cycloadditions may also undergo through concerted nature with the involvement of diradical intermediates[5] though this concept was not widely accepted.

In this dissertation we have reported synthesis & cycloaddition of the nitrones viz, *N-methyl-C-furfuryl nitrone* (**1a**), *dihydrofuran derived nitrone* also known as *N-phenyl-4-hydroxy nitrone* (**1b**) and 2,6-difluoro benzaldehyde derived *N-benzyl-fluoro nitrone* (**1c**) respectively. In general, nitrones are HOMO-LUMO controlled in nature favouring towards a direction controlled by LUMO.



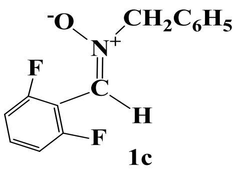
1a

N-methyl-C-furfuryl nitrone



1b

N-phenyl-4-hydroxy nitrone

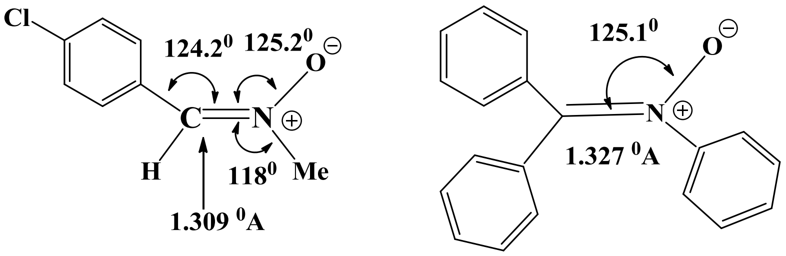


1c

N-benzyl-fluoro nitrone

Structural investigation study of nitrones using X-ray crystallography

Determination & identification of the structure of a nitrone is always a point of interest. Structures of few substituted nitrones have been determined by Folting, Lipscomb and Jerslev with the aid of X-ray crystallography. The *trans* disposition of the aryl and methyl groups and the *Z* configuration of the *C*-(4-chlorophenyl)-*N*-methyl nitrone[6] has been confirmed by X-ray crystallography. The N-O bond length in the nitrone has been found to be 1.284 Å. This is is considerably shorter than the N-O distance in isomeric *syn* oxime (1.480 Å) which indicates partial double bond character of this bond in the nitrone. Moreover, the C=N distance in nitrone is 1.309 Å which is larger than the corresponding bond in the O-methyloxime 1.260 Å. This is an indication for the reduction in double bond character (**Figure 13**).



N-methyl-C(4-Chloro)-phenyl nitrone *N-phenyl-C-diphenyl nitrone*

Figure 13 - Structural data of two different nitrones

Synthesis of different classes of nitrones

Oxidation reactions & condensation reactions of *N*-substituted hydroxylamine's is one of easiest procedures for the preparation of nitrones along with reactions of oximes with various electrophilic reagents. The chemistry of nitrone and its various synthetic procedures have been reported from early 1930's to recent years. In this dissertation, we have incorporated few of them which are very much relevant and also has got importance in cycloaddition reactions.

Few important general methods of synthesis of the nitrones are mentioned here.

a) Oxidation of *N, N*-substituted hydroxylamine molecules

$$R^1 - N\,(OH) - C\,H\,R^2\,R^3 \longrightarrow R^1 - N^+\,(O^-) = CR^2R^3$$

This procedure is application for the preparation of both cyclic and acyclic nitrones. Yellow HgO[5], active PbO[6], $[K_3Fe(CN)_6]$[7], H_2O_2[8], $KMnO_4$[9] & various diammine silver nitrates[10] are used as oxidizing reagents.

Nitrone salt (also known as *N*-oxide) was a new concept and was obtained when 4-benzoquinone reacts with *N*-hydroxy piperidine[11] (**Figure 14**)

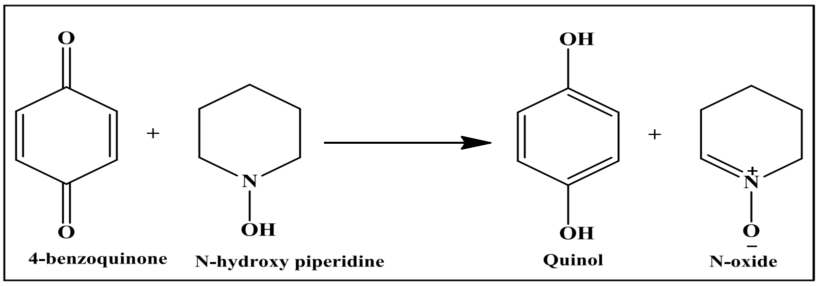


Figure 14

Reinhaudt D.N[12] and his group reported an important procedure for the synthesis of nitrones when *N*,*N*-disubstituted and *N*-substituted hydroxylamines are reduced with palladium. A four membered cyclic nitrone obtained from the oxidation of 1-OH-azetidines using PbO_2[13] has been recently reported.

Among different oxidative methods known an important methodology known from the literature is the synthesis of α-styryl-α-benzyl-*N*-phenyl nitrone diammino when $AgNO_3$ has been used in this process for the reaction with hydroxylamine[14]. High yield of nitrones[15] has been reported in the literature when 1,4–dicyano naphthalene (DCN) is used in the photolysis of *N*-substituted hydroxylamines. (**Figure 15**).

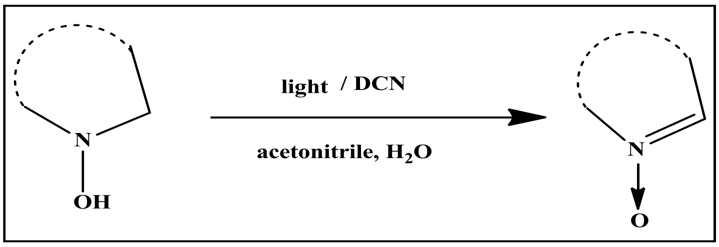


Figure 15

From oxime molecules

Alkylation reaction of the oxime molecule was reported as an important procedure for the synthesis of nitrone in 1938[16] but in this procedure oxime ether has been found to develop as a side-product with nitrones which was noted as a disadvantage in this process.

$$R^1 R^2 C = N - OH + XR^3 \longrightarrow R^1 R^2 C = NOR^3 + R^1 R^2 C = N^+ (O^-)$$

The noticeable fact in this reaction is the oxime ether to nitrone formation ratio which did not change to a great extent with the addition of Lithium, Sodium and Potassium salts. In case of *o,p*-disubstituted benzophenone oxime salts, electron withdrawing groups helps to increase the development of nitrones.

High yield of α-hexyl-*N*-benzyl nitrone[17] has been reported from Heptanal oxime during its reaction with benzyl chloride using NaOEt & EtOH. DMSO has been also used in the various keto-oxime alkylations. Two very important nitrones viz, *C,C*-dicyclopropyl-*N*-methyl nitrone & *N*-vinyl nitrone of this class have been synthesized using this procedure[18] (**Figure 16**).

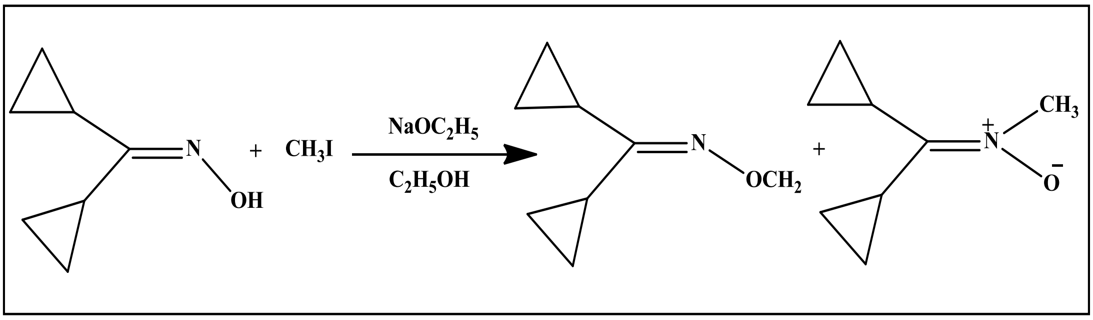


Figure 16

New classes of nitrones from aldoximes & ketoximes have been reported from electronegative olefins[19] using intramolecular Michael addition reaction (**Figure 17**).

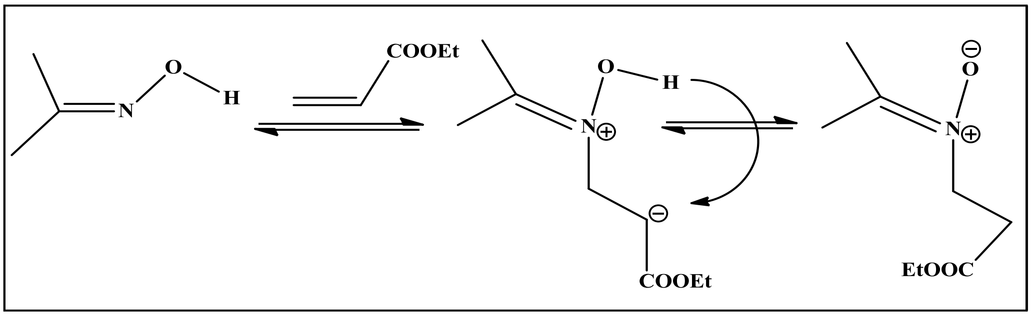
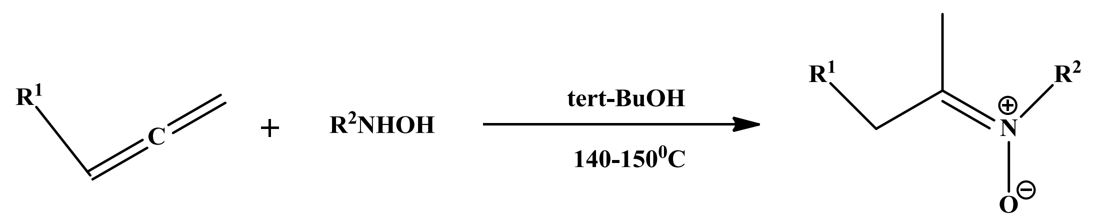


Figure 17

Beauchemin & his group[20] have shown that Cope-type hydroamination reaction may be employed for the the synthesis of ketonitrones from monosubstituted allenes using *N*-substituted hydroxylamines (**Figure 18**).



R^1 = O-C_6H_{11} ; R^2 = Bn ; 81% ; R^2 = CH_3 ; 69%
R^1 = n-C_6H_{13} ; R^2= O-C_6H_{11} ; 81%

Figure 18: Synthesis of ketonitrone from allenes

Terada & his group[21] recommended a new synthetic pathway for the synthesis of *N*-alkyl substituted- α,β-unsaturated keto-nitrones. Propargyloxyamines have been used as the starting molecule and the procedure happens via intramolecular hydroamination catalysed by copper iodide which is followed by electrocyclic ring opening of 3-isoxazoline (**Figure 19**).

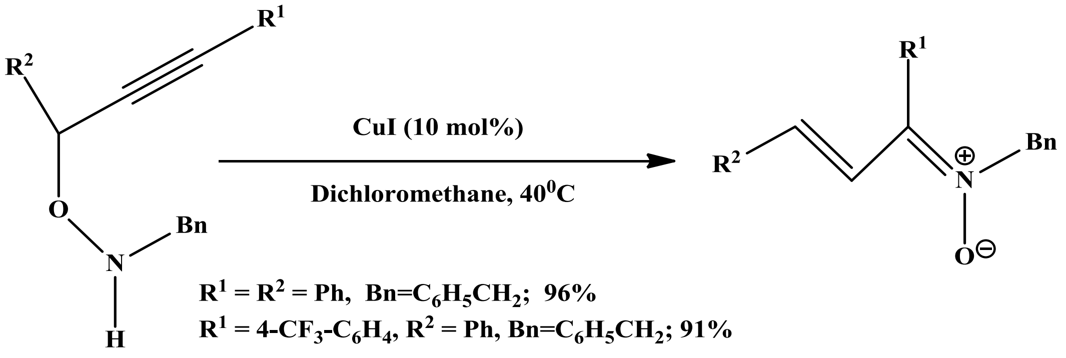


Figure 19: Synthesis of unsaturated nitrones from alkyne derivatives

Molins & co-workers[22] synthesized new cyclic nitrones of high synthetic potential using the oxidation reaction of bicyclic isoxazolidines. Meta-chloro per benzoic acid (m-CPBA) has been used as effective reagent to cleave the N-O bond of the fused isoxazolidine ring (**Figure 20**).

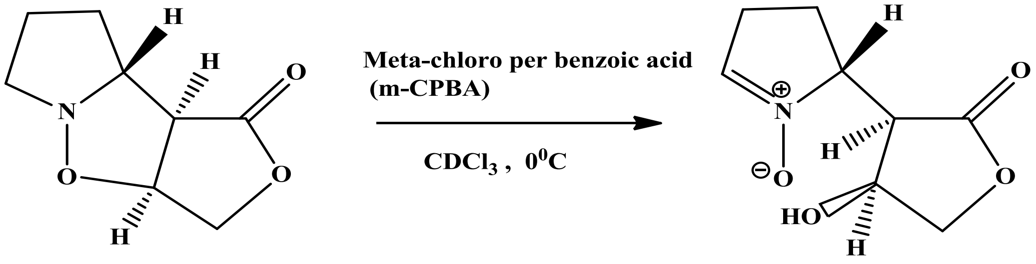


Figure 20: Synthesis of cyclic nitrones by the oxidation of bycyclic isoxazolidine

Synthesis of nitrones from aromatic nitroso compounds

A variety of new classes of nitrones may be synthesized from aromatic nitroso compounds when they are reacted with molecules having active methylene groups in presence of 2, 4, 6-trinitro toluene & 9-methyl acridine. Small amounts of base (pyridine) are used as catalyst in this synthesis (**Figure 21**).

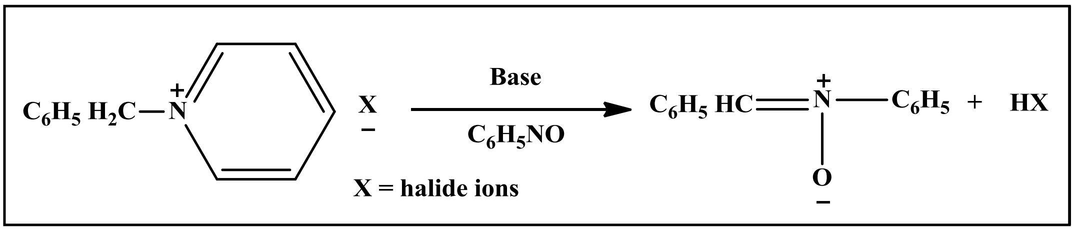


Figure 21

Morover, these aromatic nitroso compounds may also react with benzyl chlorides with the involvement of small amounts of base (pyridine) for the development of nitrones[24,25].

Miscellaneous methods for the synthesis of nitrones

The dinitrones are always a point of interest to a synthetic organic chemist for its high synthetic potential. Dinitrones are synthesized from p-benzoquinone when reacted with nitrosobenzene[26] (**Figure 22**).

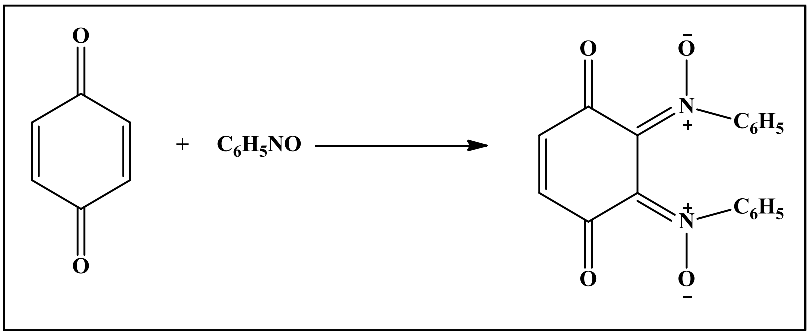


Figure 22

Different *N*–alkyl nitrones (*N*-methyl nitrone, *N*-ethyl nitrone, *N*-butyl nitrone etc) are usually synthesized from aldehyde and ketones using corresponding *N-methyl/ethyl/butyl* hydroxylamines with good yields[27,28,29]. A new concept of synthesis of nitrone from D-glucose hydroxylamine has been reported without protecting the hydroxyl groups of glucose when treated with benzaldyde[30,31,32,33,34] (**Figure 23**).

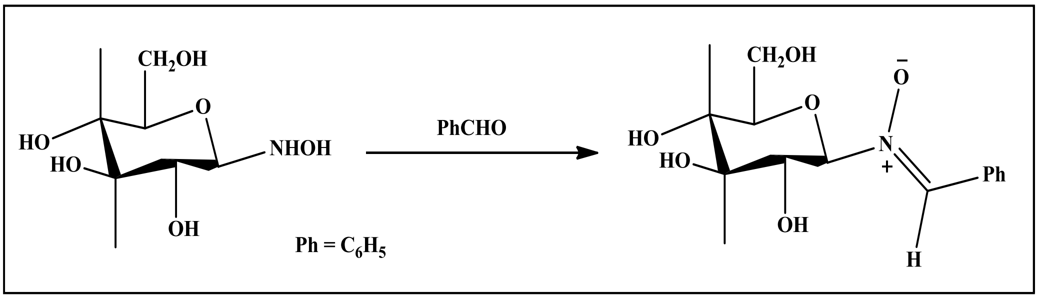


Figure 23

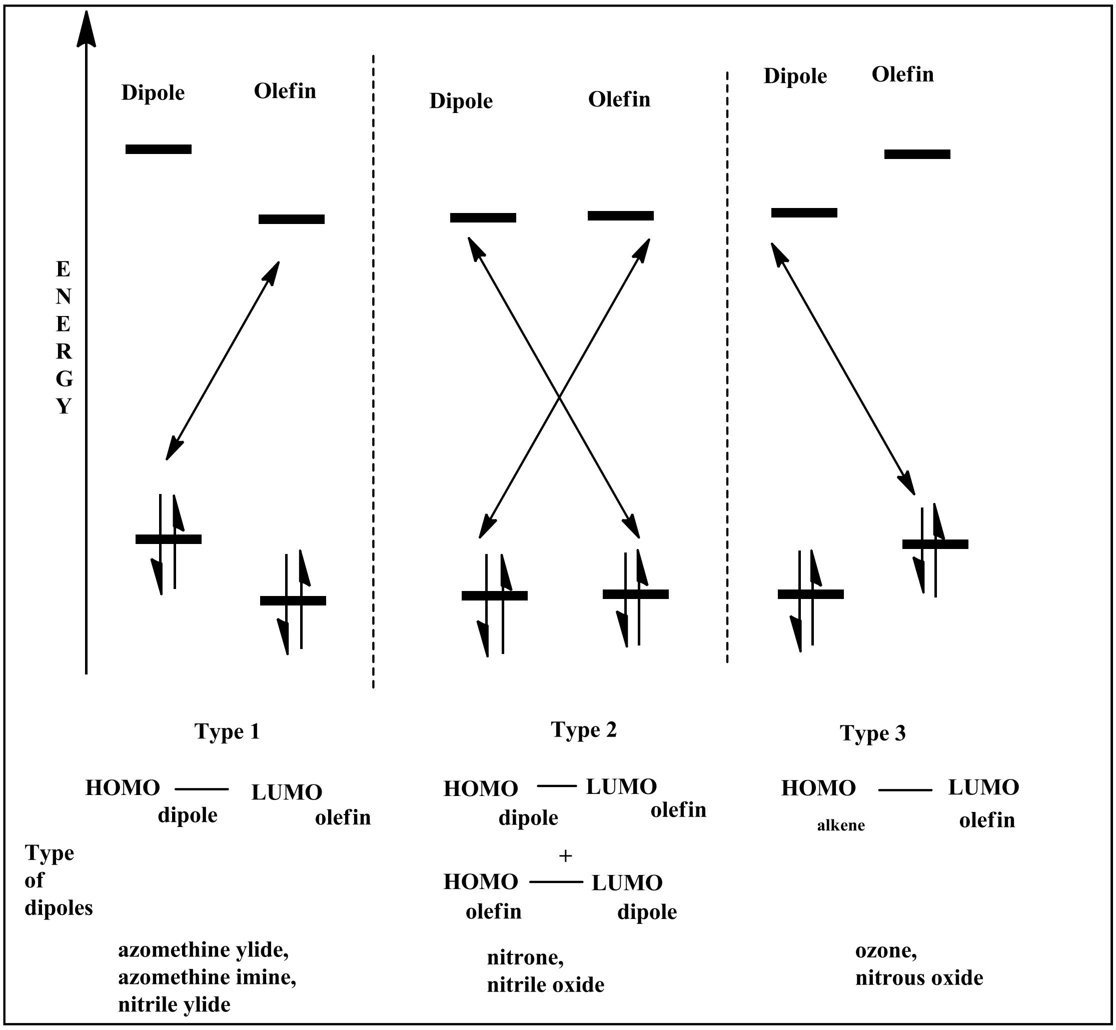
The concept of 1,3-Dipolar cycloaddition reaction

For a synthetic organic chemist working with heterocycles, 1,3-dipolar cycloaddition reaction is the fundamental reaction for the synthesis of heterocyclic ring systems especially five membered oxygen-nitrogen heterocycles. In fact, 1,3-dipolar cycloaddition reactions are found to be the best method for the synthesis of a variety of oxygen-nitrogen hetero atom containing five-membered heterocyclic molecules, widely known as '*Isoxazolidine*' & '*Isoxazoline derivatives'*. The structural units of most of the natural products mainly constituted with either *isoxazolidine* or *isoxazoline moieties.* It is generally accepted that the cycloaddition reaction happens in a concerted nature. Therefore all the bonds (C-C, C-N, C-O & O-N) are developed simultaneously.

1,3-dipolar cycloaddition reaction takes place only when a 1,3-dipole (nitrone) reacts with alkene/olefin and alkynes in a suitable reaction reaction to furnish isoxazolidine and isoxazoline derivatives. These derivatives are also the precursors for the synthesis of various *1,3-amio alcohols* & *1,3-amino ketones* and also for alkaloids. From the beginning till date along with synthesis of these derivatives major focus has also been given in the excellent medicinal properties of these cycloadducts which include *anticancer, antibacterial, antifungal, anticonvulsant, antibiotic and antitubercular activity.*

K. N. Houk and his group[35] worked on the detailed mechanistic aspects of 1,3-dipolar cycloaddition reactions of alkenes with 1,3-dipoles and found that these reactions are stereospecifically *suprafacial* in nature. They also observed that polarity of solvent had minimal effect on cycloaddition reaction rates as well as activation enthalpies. These theorical concepts along with orbital symmetry considerations and also considering regioselectivity in the cycloaddition reaction, the 1,3-dipolar cycloaddition reaction was considered as *concerted five centered mechanism*. A detailed theoretical study on $[4\pi + 6\pi]$ and $[4\pi + 4\pi]$ cycloaddition reactions of 1,3-dipoles with alkene favours strong evidence for concerted mechanism although determination of regioselectivity in the majority of cycloaddition reaction remains very difficult work.

With the aid of generalized frontier molecular orbitals of 1,3-dipoles and dipolarophiles and also considering K. Fukui's concept on frontier molecular orbital theory Houk & his group workers[35] solved this problem. According to Sustman & his group workers[33] the symmetry properties of the HOMO and LUMO orbitals of dienes and dipolarophiles can predict if 1,3-dipolar cycloaddition reaction is allowed or forbidden.



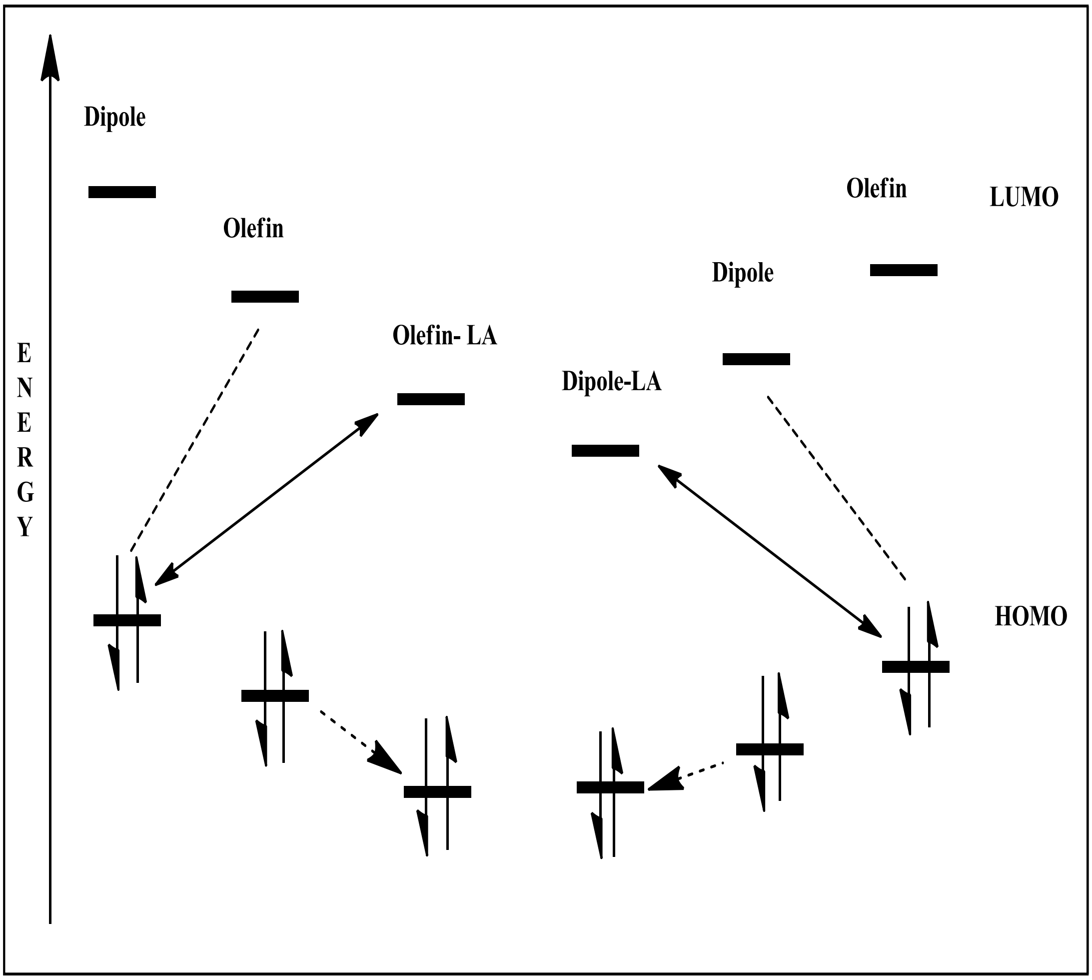
Type 1: Involves strong interactions between HOMO (dipole) & LUMO (dipolarophiles).

Type 2: Involves interactions between LUMO (dipole) &HOMO (dipolarophiles). But determination of reactivity and regioselectivity depends upon the interactions of both LUMO (dipole) & HOMO (dipolarophile) and HOMO (dipole) & LUMO (dipolarophile). Type 2 dipoles are referred as HOMO controlled 1,3-dipoles with high lying HOMO's & LUMO's.

Type 3: They are LUMO controlled dipoles with low lying frontier molecular orbital's (FMO's).

M.O (molecular orbital) theory on 1,3-dipolar cycloaddition reactions

Application of lewis acid activation



Bonding of lewis acid to dipole and alkene developing LUMO lowering as well as faster reaction rate in the process

With the aid of M.O theory, Houk & his coworkers[35] analysed the nature of all common 1,3-dipoles and found that the experimental results were in good agreement with the predicted values. The dipoles viz, nitrile ylides, diazoalkanes & azomethine ylides are HOMO controlled and they react rapidly with olefins which contain at least one or more electron withdrawing substituents. On the other, HOMO-LUMO controlled dipoles viz, nitrile imines, azides & azomethyne imines react very fast with electron rich and electron deficient dipolarophiles. Nitrones are known as HOMO-LUMO controlled dipoles but they are inclined towards LUMO controlled side while 1,3-dipoles e.g, nitrous oxide and ozone are also LUMO controlled in nature.

1,3-dipolar cycloaddition reaction is always controlled by LUMO (dipolarophile) – HOMO (dipole) or LUMO (dipole) – HOMO (dipolarophile) interaction and is dependent upon the nature of the dipole and the dipolarophiles though in some cases a combination of both the interactions are found to be involved. The formation of cycloadduct is materialized only when the interaction between the HOMO (dipolarophile) and LUMO (dipole) is favourable with the substituent (S) on the carbon atom adjacent to Z. On the other, regioisomers are developed when the opposite interaction i.e LUMO (dipolarophile) and HOMO (dipole) favours. The of the In 1,3 dipole system, HOMO's used to possess larger terminal co-efficient on the group Z but the LUMO's used to have greater co-efficient on the opposite terminus. The HOMO's & LUMO's of allyl anion are very much similar to those of 1,3 dipoles. When the two terminals differ greatly in electronegativity, The difference in terminal co-efficient occurs when the electronegativity difference between the two terminals are very high (**Figure 24**).

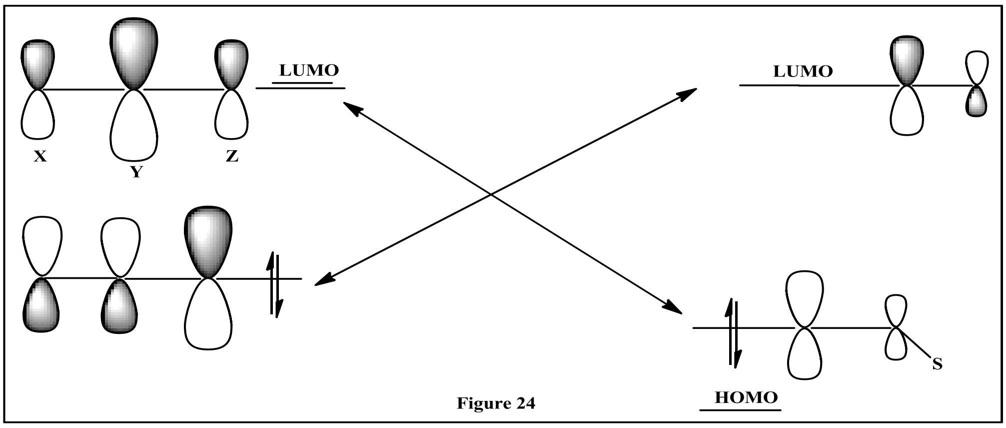


Figure 24

When nitrones and nitrile oxides react with electron deficient olefins e.g, acrylonitrile or ethyl acrylate *5- substituted* cycloadduct is obtained. It has been observed that in nitrone-olefin cycloaddition, good interactions between the HOMO's & LUMO's of the electron deficient olefines are noticed. For regioselective cycloadduct formation, the influence of LUMO (dipole) & HOMO (dipolarophile) has more impact and this is in good agreement with experimental results. R.Huisgen & his coworkers[36] worked in detail with triple bonded dipolarophiles (acetylene derivatives) and suggested that these dipolarophiles have large gap between the HOMO & LUMO. They also noticed that during cycloaddition reaction LUMO plays important role hence acetylenic dipolarophiles are less reactive than alkenes. Huisgen also suggested that *4-substituted* cycloadducts are favourable when the interactions between the dipole (HOMO) & dipolarophile (LUMO) appears prominent in cycloaddition reactions.

formation of 4-substituted adducts. Regioisomeric adducts may be formed when both the dipole and the dipolarophile are nonsymmetric in nature.

Concept of stereoselectivity in cycloaddition reactions

The *C*-4 & *C*-5 protons of an isoxazolidine ring always play an importent role for determining the stereochemistry along with *C*-3 proton. In most often cases the addition of nitrone species to the alkene (dipolarophiles) are *syn* in nature and also depends upon the substituents of the alkene. During the course of cycloaddition reaction, development of *syn & anti* isoxazolidine derivatives depends upon two important factors viz, approach of dipole & dipolarophile (considering steric factors) and also probability of hydrogen bonding. These factors are responsible for the generation of *diastereomeric cycloadducts.* In cycloaddition reactions, the approach of dipolarophiles (*exo or endo*) towards dipole (nitrone) is relevant while it has been observed that steric interactions between the diene & dienophile become important in Diels-Alder reaction and not the secondary orbital interactions. Therefore, it is expected *syn* addition of dipolarophiles to dipole develops *syn* isoxazolidines via *exo* transition state.

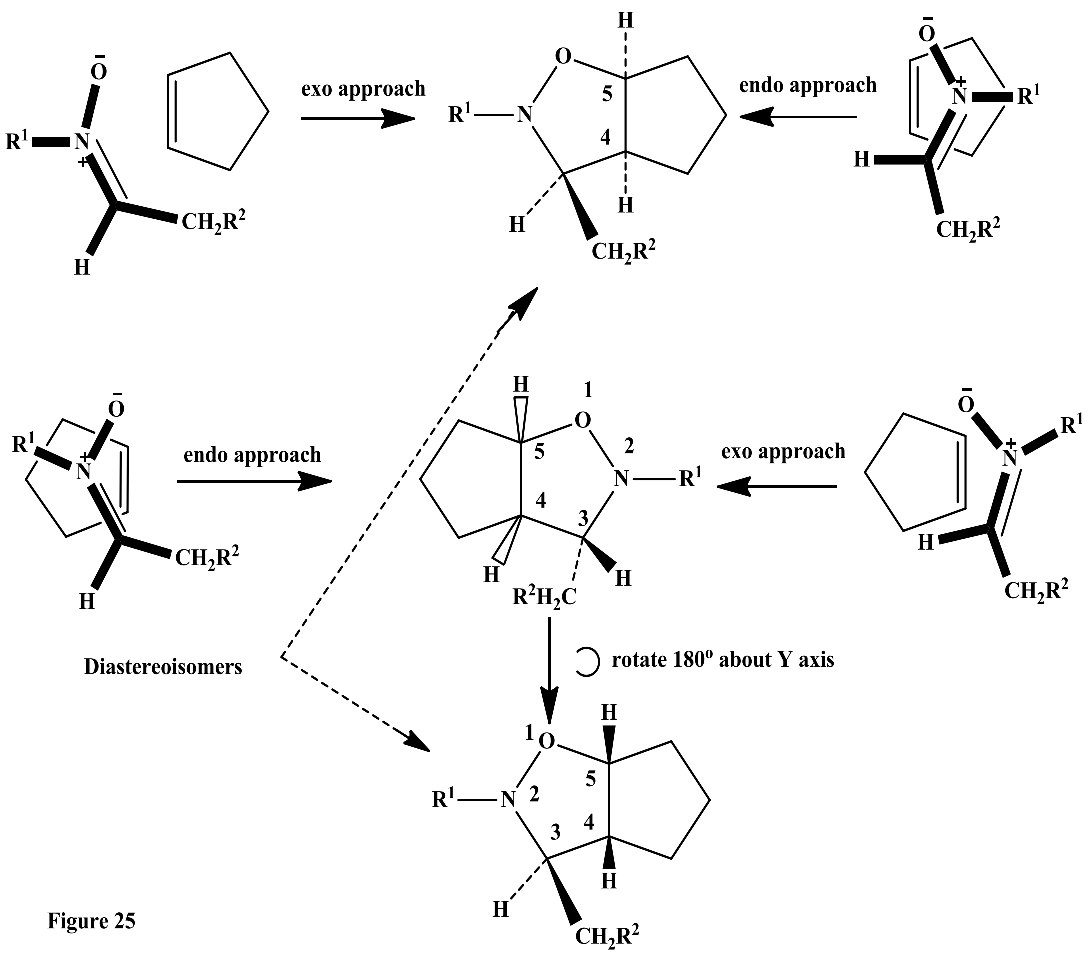


Figure 25

In nitrone-olefin cycloaddition reaction, usually pair of diastereomeric isoxazolidines is obtained while either a single regioselective isoxazolidine (5 or 4-substituted) derivative or rarely a pair of regioisomeric isoxazolidines is developed. It solely depends upon the *exo & endo* approach of the dipolarophiles (alkenes) towards dipole (nitrone)[35] [**Figure 26**].

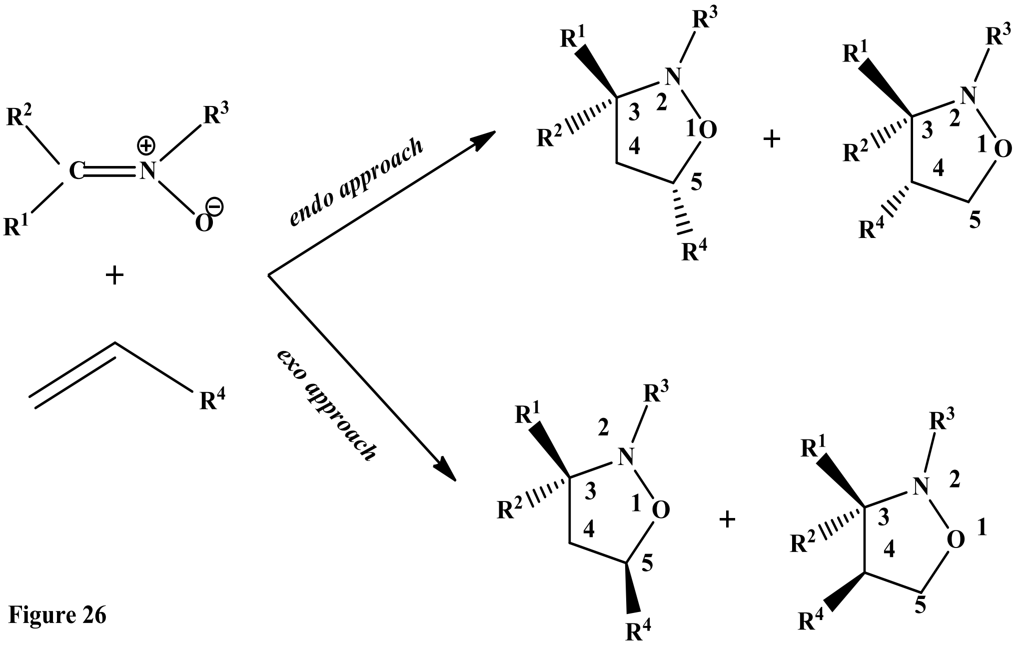


Figure 26

Due to this vast scope of selectivity (diastereoselectivity & regioselectivity) in 1,3-dipolar cycloaddition reaction, scientists working in this area of research started focusing in the detailed study of intermolecular & intramolecular 1,3-dipolar cycloaddition reactions especially partaining to regio & diastereoselectivity. *Endo* & *exo* representation in cycloaddition reactions has been implemented from the Diels-Alder reaction[36]. The *endo* isomer in cycloaddition reaction develops if the *N*-atom of 1,3-dipole is pointed to the same direction of the substituent of olefin. Sometimes, the secondary π-orbital interactions between the nitrogen p_z orbital and p_z orbital of the olefin involves in stabilization of the *endo* isomer[37]. It has been observed that the nature of the substituents of the olefin (dipolarophile) and the presence of catalyst in cycloaddition reaction plays significant role in *endo* or *exo* selectivity.

Concept of regioselectivity in cycloaddition reactions

Regioselectivity in 1,3-dipolar cycloaddition is basically controlled by electronic and steric effects[38]. Although, in few cycloaddition reactions, electronic effects[39] are found to be stronger while steric effects are weaker. The *5-substituted* isoxazolidines are readily developed when the cycloaddition reaction takes place between an electron-rich olefin and a nitrone and it is understood that this type of cycloaddition reactions are based upon the favourable interactions between (LUMO) dipole & (HOMO) dipolarophile. From the theoretical concept, it was concluded that LUMO (dipole i.e, nitrone) has the highest coefficient at the carbon atom while HOMO olefin (dipolarophile) has the highest coefficient at the terminal carbon atom. Therefore, during cycloaddition reaction between nitrone and olefins, regioselective 5-substituted adducts are formed. When the cycloaddition reaction takes place between a nitrone and an olefin having electron withdrawing group, HOMO (dipole) is found to have the highest coefficient at the oxygen atom while LUMO (dipolarophile) is found to have the highest coefficient at the terminal carbon atom. Under this circumstances a mixture of *4-substituted* regioselective isoxazolidines are usually developed[40]. A typical regioselective mixture (**p & q;** 4 & 5-substituted isoxazolidines) development from the reaction between a nitrone and an alkene having electron withdrawing group (e.g, -COOEt; COOMe) may be represented following K.Fukui's FMO approach (**Figure 27**).

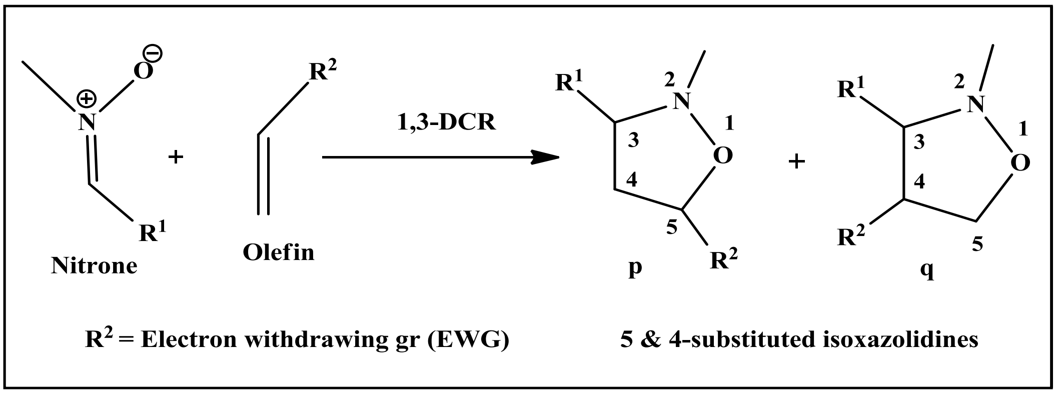


Figure 27

Literature survey on some pioneering contributions in nitrone-cycloaddition reactions

After a detailed literature survey, we had selected few relevent areas of synthesis of nitrones and cycloaddition reactions and decided to undertake the problems as well as tried to solve these problems in this dissertation. The literature survey also helped us to assess the importance of nitrone cycloaddition reactions and their further applications in organic synthesis. This dissertation will certainly help to the researcher's working in this field to understand how to solve the problem undertaken and also to reach the final target.

We understood from the literature that since majority of the nitrones are unstable so nitrones are usually generated *in situ* and suiatable dipolarophiles are added into the reaction system (trapping the generated nitrones) for performing 1,3-dipolar cycloaddition reaction. One of the advantages of this *in situ* reaction is that we may control dimerization of nitrone in this procedure.

Recent updated literature survey

"*Green Chemistry*" methodologies[41] are finding top most priority in recent years (**January 2000 – January 2021**) in nitrone-cycloaddition reactions because of its environment friendly procedures. The procedures adopted nowadays for the synthesis of various nitrones and inter or intramolecular 1,3-dipolar cycloaddition reactions may be summarized as follows.

- ✓ *Synthesis &1,3-dipolar cycloaddition reactions of nitrones in water or on water*
- ✓ *Solid phase (microwave induced) synthesis of nitrones and cycloaddition reactions*
- ✓ *Mechanochemical procedure (solvent less ball-milling methodology) for the synthesis & cycloaddition reactions*
- ✓ *Synthesis & 1,3-dipolar cycloaddition reactions in room temperature ionic liquids*
- ✓ *Atom efficient reactions in cycloaddition chemistry (use of side products)*

All the procedures mentioned are very attractive as we are finding mild reaction conditions, very short reaction time and selectivity (diastero & regioselectivity).

1,3-dipolar cycloaddition reactions "in water" & "on water"

Increased attention has been received in recent years by the organic reactions "in water" & "*on water*", primarily due to the environmental acceptability, high abundance, high selectivity & low cost of water[42,43,44]. However, conventional organic solvents does not possess such properties and cannot attain the unique reactivity and selectivity which water exhibits[45,46,47].

An excellent example of "*on water reaction*" leading to the generation of regioselective isoxazoline derivative via organocatalyzed 1,3-dipolar cycloaddition reaction was reported by Pedro de Armas and his group[48a] & Sharpless and his co-workers[48b] (**Figure 28**).

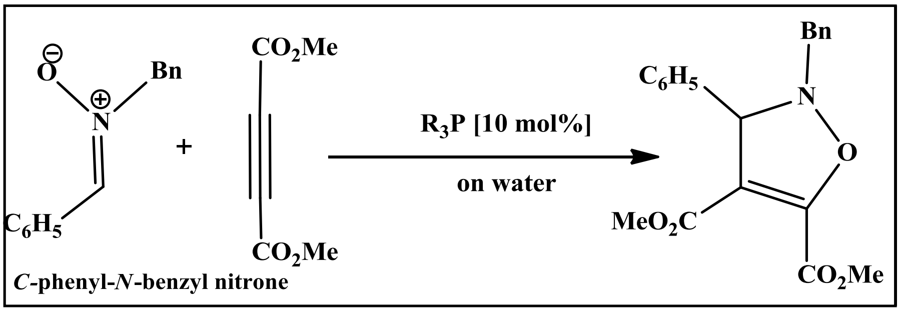


Figure 28

Excellent stereoselectivity using water as solvent in nitrone-cycloaddition reactions has been reported by Butler & his co-workers[49]. They studied the influence of water in the reaction rates of 1,3-dipolar cycloadditions using water super and water normal dipolarophiles.

P.K Bhattacharya and his group[50] reported a very nice example of water exclusion reaction of synthesis of nitrone using surfactant. This was followed by 1,3-dipolar cycloaddition reaction of the nitrone with active dipolarophiles (ethyl acrylate) in the same reaction vessel. This was really one of the new concepts of synthesis & cycloaddition reaction of nitrone following *green chemistry methodology.* A mixture of 5 & 4-substituted regioselective isoxazolidine derives were developed in which 5-substituted isoxazolidine was favoured using NMR spectroscopy (**Figure 29**).

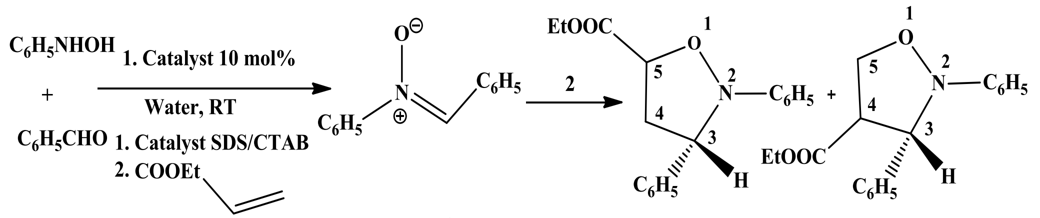
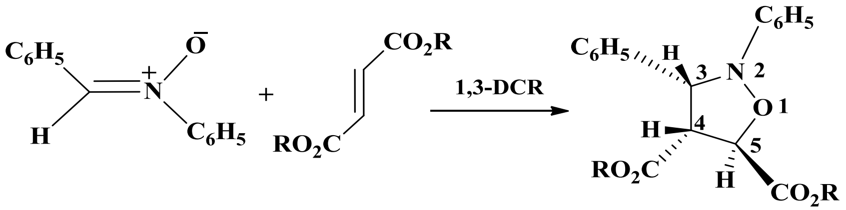


Figure 29

A beautiful example of 1,3-dipolar cycloaddition reactions of *N*-phenyl-*C*-phenyl nitrone with di-*n*-butyl fumarate and dimethyl fumarate in water involving with steric factors was reported by Gholami et al[51] (**Figure 30**). They reported faster reaction rate & high yield in case of dimethyl fumarate compared with di-n-butyl fumarate due to steric factors of the bulky n-butyl group.

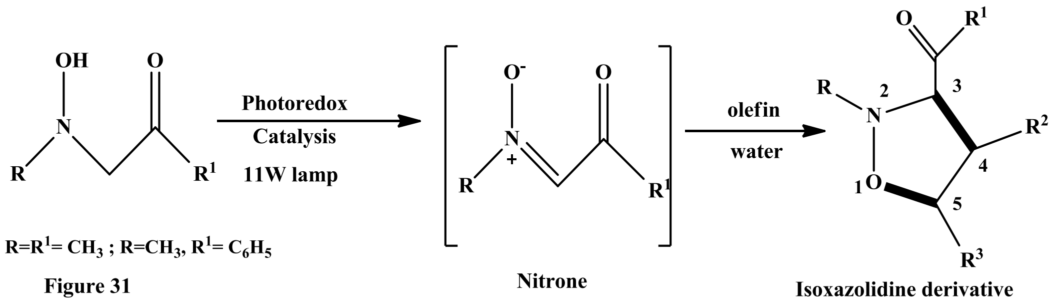
The cycloaddition reaction was also studied using organic solvents viz, n-hexane and ethanol. They found that when the cycloaddition reaction was performed in water the reaction rate was found to be 125 times higher. Hence high polarity of water also considered as an important factor in the rate of this cycloaddition reactions.



R = methyl, n-butyl

Figure 30

A new concept of oxidative cycloaddition reaction of *N*-di-substituted hydroxylamines with olefines using visible light photoredox catalytic procedure was reported by Shaoqun Zhu & his co-workers[52]. Once the nitrone generated, it was trapped *in situ* with various olefins in water to develop isoxazolidine derivatives (**Figure 31**). This was indeed a new protocol in green chemistry for the synthesis & cycloaddition reaction of nitrone which is fast and very mild in all aspects.



$R=R^1=CH_3$; $R=CH_3$, $R^1=C_6H_5$

Figure 31

Solid phase (microwave induced) synthesis of nitrones & cycloaddition reactions

One of the most important techniques in modern organic synthesis is microwave induced solid phase reactions and this methodology is widely accepted due to high purity & excellent yield of the products[53]. This technique is applied especially in those reactions where final work-up and separation of isolated products in column chromatography is difficult[53]. As solvents and column chromatography is not mendatory in this technique therefore, microwave induced reactions are considered as eco-friendly in nature and is known as an important application of *green chemistry* methodology[54]. Like many other organic synthesis, plenty of applications of nitrone-cycloaddition reactions using microwave technology are nowadays reported with excellent yield in a short reaction time and good selectivity[54].

Application of microwave technology and its eco-friendly nature in the synthesis of 5-membered oxygen-nitrogen heterocycles (isoxazolidine & isoxazoline derivatives) was reviewed by Pineiro Melo and her group[55]. In this excellent review work synthesis of nitrones and different isoxazolidine, isoxazoline derivatives are reported with excellent yield in a short reaction time and with good stereoselectivity. This review also nicely compared conventional organic synthetic procedures with microwave induced reactions.

The first microwave induced nitrone-cycloaddition reaction was reported by Loupy and his co-workers[56]. They have shown successfully how microwaves can be utilized as a source of energy for the cycloaddition reaction between *N*-methyl-α-phenyl nitrone and fluorinated substituted olefin as dipolarophile in solvent-free condition with excellent yield in a very short reaction time. When the same reaction was conducted following conventional methodolgy it required refluxing the mixture of nitrone and dipolarophile in toluene at a high temperature (110 to 120^{0}C) and the yield of the reaction was also found nearly 45-50% (**Figure 32**). Loupy and his co-workers also reported an interesting example of microwave induced solvent free reaction for the synthesis of fluoro isoxazoline derivative with excellent yield and regioselectivity[57](**Figure 33**).

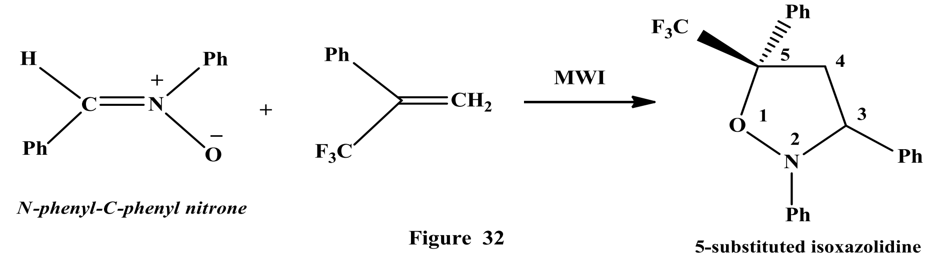


Figure 32

MWI	**no Solvent**	**3min**	**170°C**	**98%**
Conventional heating	**No solvent**	**3 min**	**170°C**	**55%**
Conventional heating	**Solvent**	**48hrs**	**110°C**	**65%**

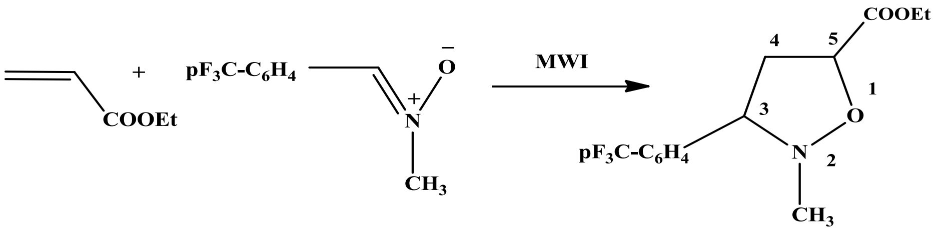
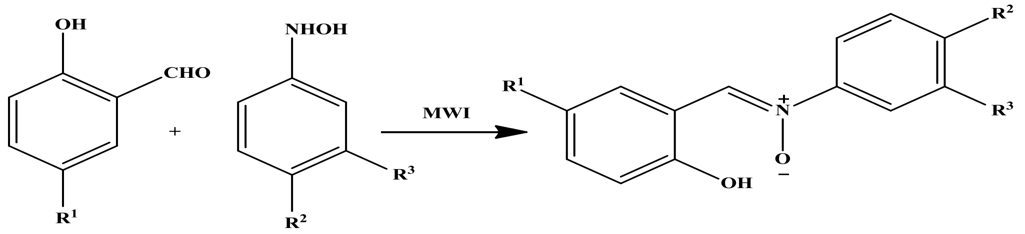


Figure 33

MW	**50%**
Conventional heating	**17%**

An excellent work on the synthesis of stable α-(5-substituted-2-hydroxyaryl)-*N*-aryl nitrones using microwave induced reaction was reported by Muthusubramaniun & his group[58]. Further they have successfully utilized the nitrone in 1,3-dipolar cycloaddition reaction following microwave technology. In both the reactions (synthesis of nitrone & cycloaddition reactions) they observed higher yield of products in a very less time compared with conventional procedures for the synthesis & cycloaddition reactions of nitrones (**Figure 34**).

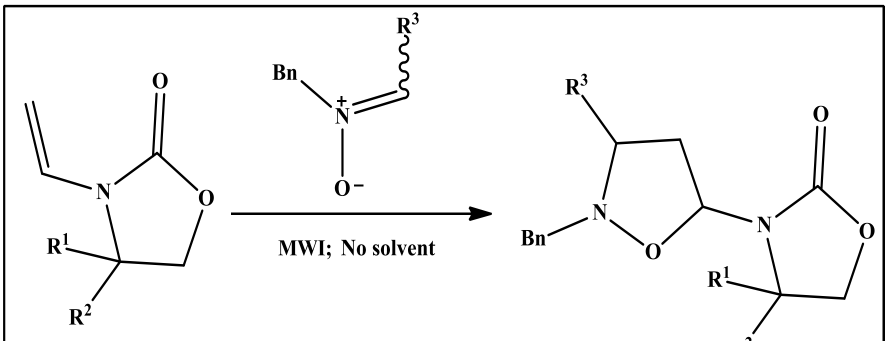


R^1 = t-Bu, i-Pr, Ph
R^2 = H, Me, Cl, Br
R^3 = H, Me, Ph

Figure 34

A new dimention in the review work on *microwave induced cycloaddition* was reported by Antonio de la Hoz & his group[59]. They have studied plenty of cycloaddition reactions using microwave technology and observed that this methodology is capable of introducing high selectivity (regio & diastereoselectivity) in the synthesized isoxazolidine & isoxazoline derivatives. This technology is also capable of changing the transition state for the development of cycloadducts during cycloaddition reactions. Even few heterocyclic molecules which are having difficulties to undergo cycloaddition reactions (pyrazoles) takes part easily in cycloaddition reactions under microwave technology. With some exceptions, in case of some newly developed molecules like *[60] fullerene* derivatives employed for cycloaddition reaction this methodology was not found suitable related to poly-cycloaddition reactions. In general in most often cases, we found excellent yields, short reaction times and high selectivities in cycloaddition reactions performed with microwave technology.

A very efficient solvent free 1,3-dipolar cycloaddition reaction of *N*-substituted dipolarophiles (*N*-vinyl amide dipolarophiles) with *N*-benzyl nitrones using microwave technology has been reported Dujardin & his group[60]. Excellent yield of novel isoxazolidine derivatives were reported in a very short reaction time also they have observed very less probabilty of degradation of the cycloadducts (**Figure 35**).



R^1=R^2=H; CH$_3$; R^3= alkyl or aryl substiteuent

Figure 35

Use of room temperature Ionic liquids (RTIL's) in 1,3-dipolar cycloaddition reactions

Although not universally accepted by the scientific community but still room temperature ionic liquids are regarded as one of the good green solvents for not only cycloaddition reactions but also in various organic synthesis[61]. This is attributed to the excellent greener properties of room temperature ionic liquids viz, good thermal stability & solvating ability, capable of change in polarity, a wide range of its applicability, capable of introducing selectivity and ofcourse its capability of recycling for at least 3 to 4 runs[61]. Based on these properties room temperature ionic liquids are frequently used as "*Designer solvent*"[62] in plenty of nitrone-cycloaddition reactions (avoiding conventional procedures of synthesis) taking the advantage of its hydrophilicity, hydrophobicity, its properties of behaving like Lewis acids and greater selectivity. The structure of the room temperature ionic liquids can be changed using suitable organic cation, inorganic anion and we may also change the length of the alkyl group linked with the organic cation (**Figure 36**).

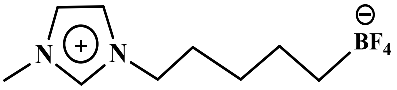


Figure 36: Structure of room temperature ionic liquid

Since there is a scope of changing the structural pattern of room teperature ionic liquids, therefore we have the opportunity to use different suitable derivatives of room temperature ionic liquids in nitrone-cycloaddition reactions. Having good charge stabilization capacity, the room temperature ionic liquids are usually found to increase the reaction rate unexpected selectivity (regio & diastereoselectivity) [63]. With all these green chemistry credentials, room temperature ionic liquids are also used for conducting difficult 1,3-dipolar cycloaddition reactions[64]. Few important nitrone-cycloaddition reactions using room temperature ionic liquids are reported here.

A brilliant example of room temperature ionic liquid mediated 1,3-dipolar cycloaddition reaction catalyst by “Triflate” [Erbium (III) trifluoromethanesulfonate] between *N*-benzyl/methyl-*C*-phenyl nitrone and olefins substituted with ether linkage has been reported by Bortolini & his group[65] (**Figure 37**).

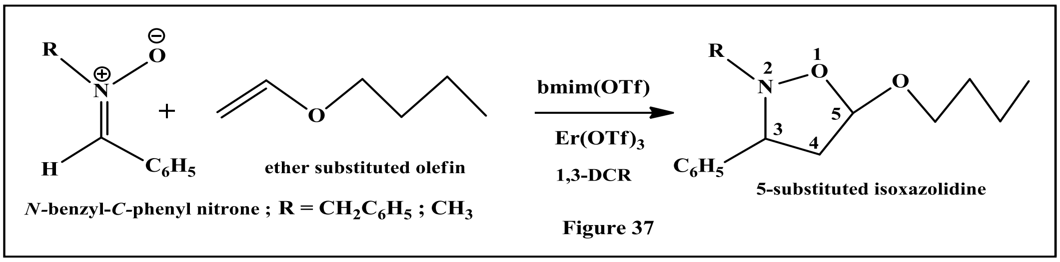


Figure 37

An excellent example of both regio & diastereoselectivity in the 1,3-dipolar cycloaddition reaction between *N*-phenyl-*C*-phenyl nitrone and olefins containg electron withdrawing groups in *imidazolium based ionic liquids* has been reported by Yadav & his co-workers[66]. In addition to excellent stereoselectivity they also reported very faster reaction rate and high yield of cycloadducts (**Figure 38**).

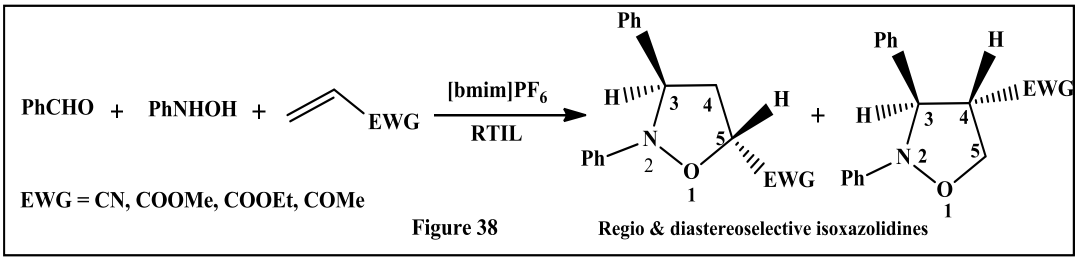


Figure 38 Regio & diastereoselective isoxazolidines

A notable 1,3-dipolar cycloaddition between between 2-ethoxy benzaldehyde derived nitrone & dipolarophiles having electron withdrawing groups in 1-ethyl-3-methylimidazolium chloride based room temperature ionic liquid has been reported by Bazureau & his co-workers[67] with faster reaction rate & high yield of the cycloadducts.

Another very nice example of room temperature ionic liquid based isoxazoline synthesis via 1,3-dipolar cycloaddition reaction between *N*-Phenyl-*C*-phenyl nitrone & dimethyl acetylene dicarboxylate has been reported by Dinparast & his coworkers[68] (**Figure 39**).

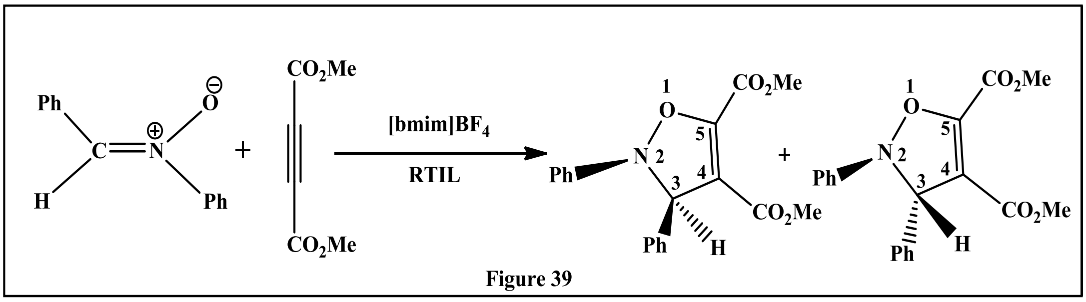
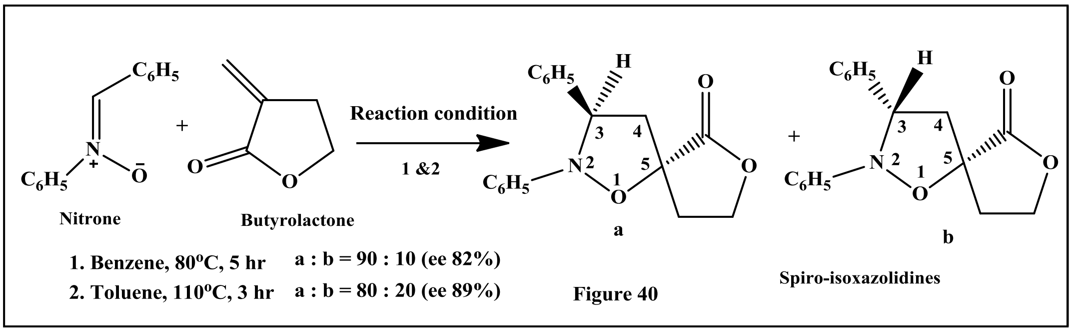


Figure 39

Few very important contributions in nitrone-cycloaddition reactions but not with green chemistry protocols

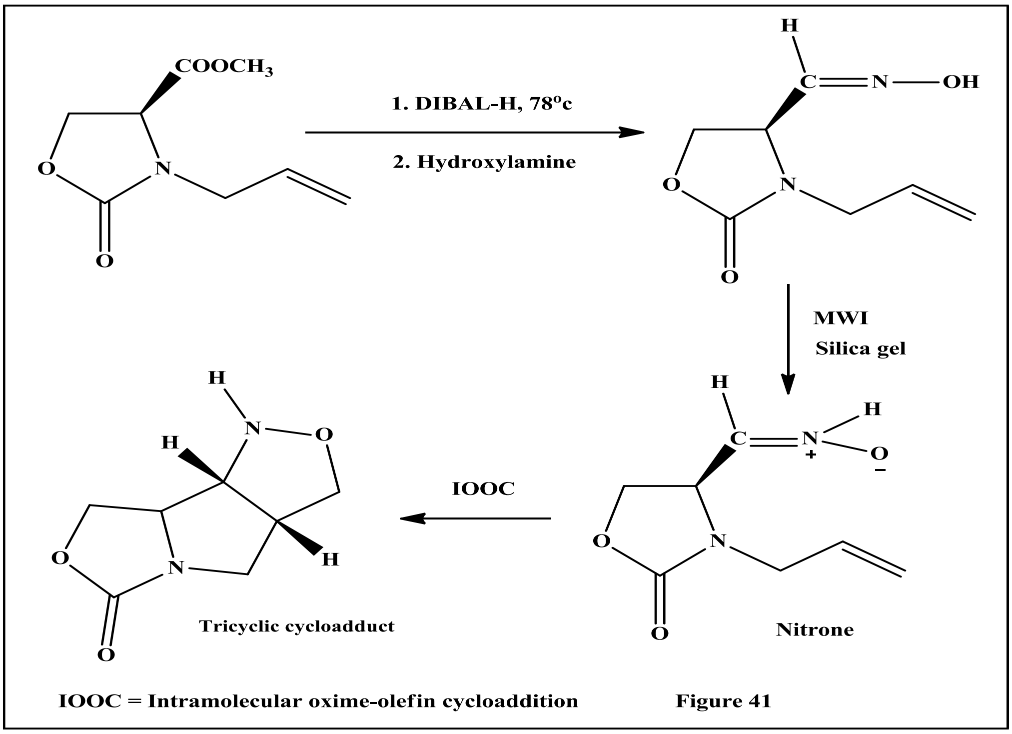
Highly stereoselective 1,3-dipolar cycloaddition reaction between *N*-phenyl-*C*-phenyl nitrone & γ-butyrolactone leading to the generation of spiro-isoxazolidine derivatives has been reported by Goti & his co-workers[69]. High enantioselectivity & yield is the notable feature in this synthesis (**Figure 40**).



1. Benzene, 80°C, 5 hr a : b = 90 : 10 (ee 82%)
2. Toluene, 110°C, 3 hr a : b = 80 : 20 (ee 89%)

Figure 40

Intramolecular highly stereoselective 1,3-dipolar cycloaddition reactions of unsaturated *N*-substituted oximes with nitrones along with azomethyne ylides leading to the generation of tricyclic isoxazolidines combined with pyrroline or piperidine ring has been reported by Cheng and co-workers[70]. The synthesis was carried out using microwave irradiation and on the surface of silica gel. No solvent was used (**Figure 41**).



IOOC = Intramolecular oxime-olefin cycloaddition

Figure 41

A significant 1,3-dipolar cycloaddition reaction has been reported by Abhijit Banerjee and coworkers[71] where unexpected cycloadducts are also obtained along with expected cycloadducts when 3,4-dihydro morpholine *N*-oxide is subjected to undergo cycloaddition reaction with piperidine amides of cinnamic acid and *4*-substituted cinnamic acids. This is an extremely rare instance where unexpected cycloadducts are having equal importance with expected cycloadducts and certainly opens a new route for the future researchers (**Figure 42**).

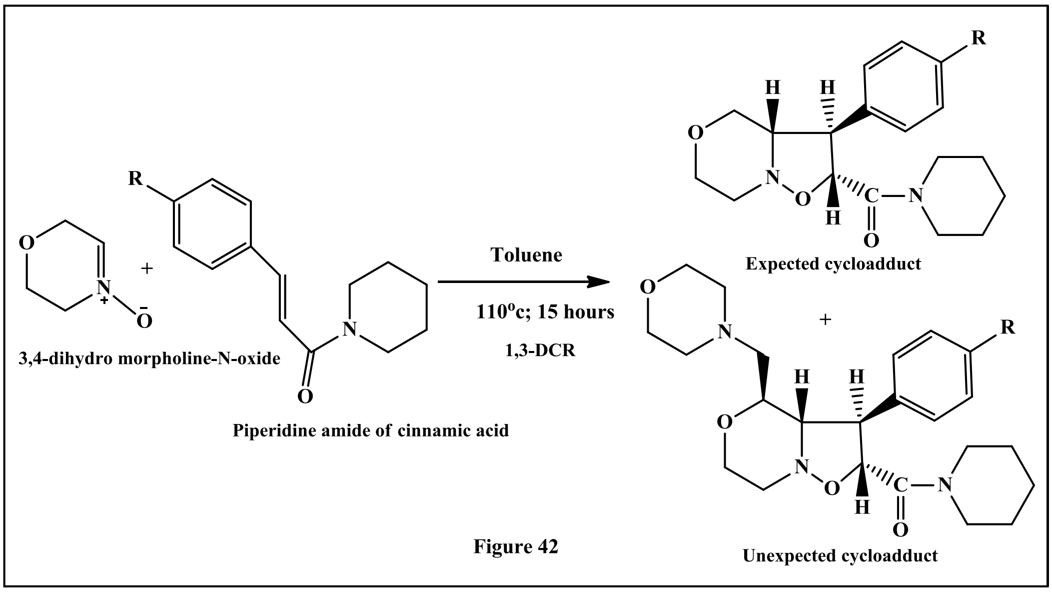


Figure 42

A remarkable synthesis of bisnitrone (from terepthalaldehyde) for the first time and subsequently 1,3-dipolar cycloaddition of bisnitrone with dipolarophiles (*N*-substituted maleimides) leading to the synthesis of bis-isoxazolidines has been reported by Francis Heaney & his group[72]. This diastereoselective reaction also opens a new pavement for the researchers in this chemistry (**Figure 43**).

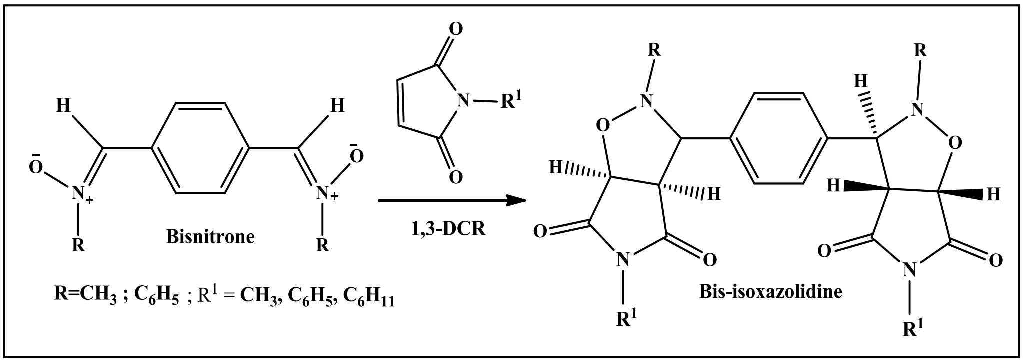


Figure 43

A completely new approach for the synthesis of nitrone from oxaziridines and subsquently its regioselective 1,3-dipolar cycloaddition reaction has been reported by Patridge & coworkers[73]. The novel *N*-sulphonyl nitrone was trapped *in situ* by substituted olefins to produce isoxazolidines (**Figure 44**).

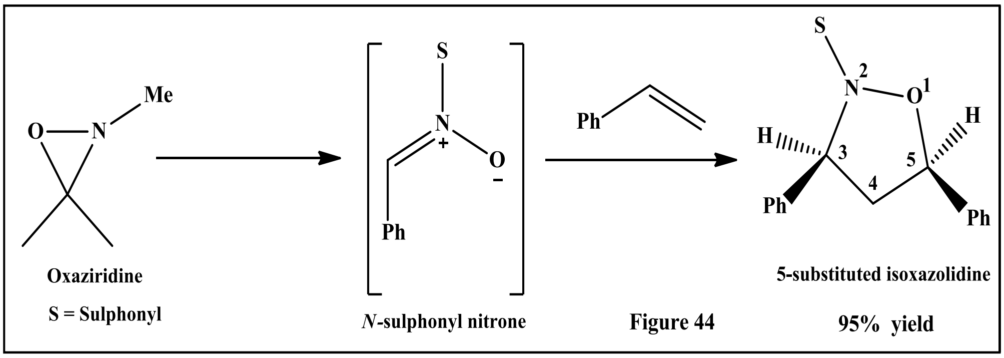
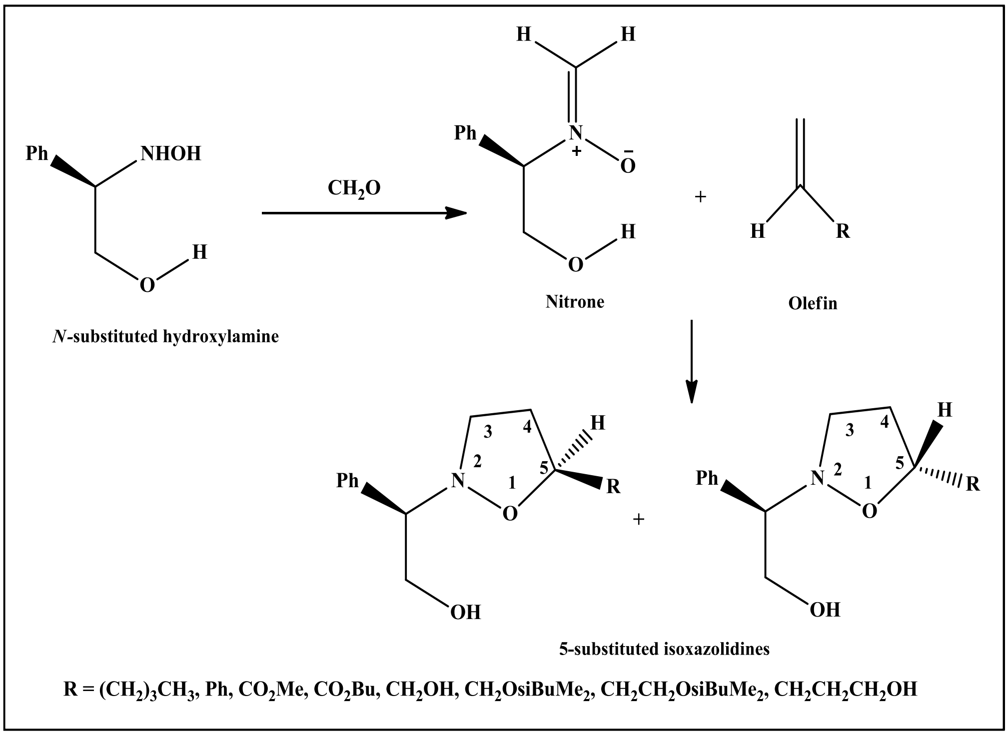


Figure 44

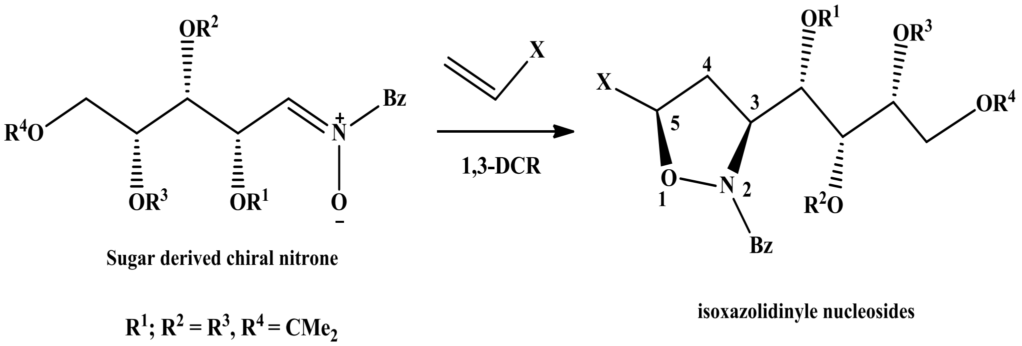
A new significant approach in the 1,3-dipolar cycloaddition reaction involving internally H-bonded chiral methylene nitrones with activated olefins has been represented by Sheikh Ali & co-workers[74]. Their work has been considered as one of the pioneering contributions in nitrone-cycloaddition chemistry (**Figure 45**).



R = $(CH_2)_3CH_3$, Ph, CO_2Me, CO_2Bu, CH_2OH, $CH_2OsiBuMe_2$, $CH_2CH_2OsiBuMe_2$, $CH_2CH_2CH_2OH$

Figure 45

A novel procedure for the synthesis of chiral nitrones from sugars and 1,3-dipolar cycloaddition reactions of the nitrone with activated olefins has been reported by Lubor Fisera &co-workers[75]. This diastereoselective synthesis of isoxazolidinyle nucleosides has a great contribution in nitrone-cycloaddition chemistry undoubtedly (**Figure 46**).



$R^1; R^2 = R^3, R^4 = CMe_2$

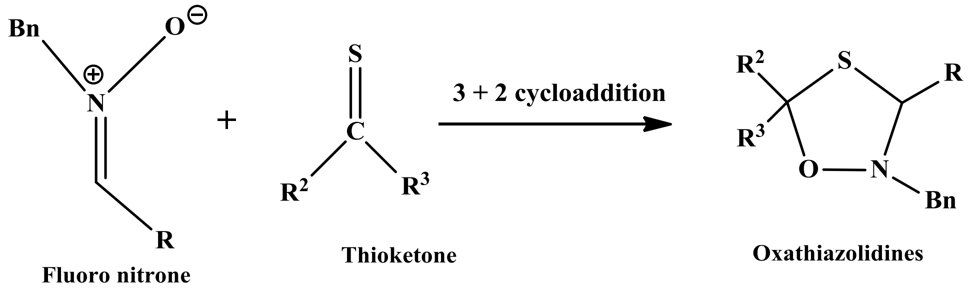
$R^1; R^2 = CMe_2, R^3 = Bz$ (Benzyl), $R^4 = TBDPS$

$R^1; R^2 = CMe_2, R^3 = Bz$ (Benzyl), $R^4 = TBDPS$

$X = C_6H_5, CN, COOMe, COMe, COOCH_2CH_3$

Figure 46

A new concept of [3 + 2] cycloaddition reaction involving fluoral derived fluoro nitrone with thioketones producing oxathiazolidines has been reported by Obijalska & co-workers[76]. The reaction is very high yielding and regioselective in nature. One of the most important part in this cycloaddition reaction is that the synthesized cycloadduct is very stable and do not decompose in crystalline form or in solution at RT (**Figure 47**).



$R = CF_3 ; CHF_2 ;$ Bn = Benzyl

Figure 47

Yield 71-89 %

A new procedure of cycloaddition reaction involving *N*-phenyl-*C*-phenyl nitrone with acetonitrile derivatives using solar heating for the first time leading to the synthesis of isoxazolidine derivatives has been reported by Mekheimer & coworkers[77]. The synthesized isoxazolidines undergoes further rearrangement to develop unexpected 3-aryl-2-cyanothioacrylamide and 3-aryl-2-(hetaryl)acrylonitrile derivatives respectively via 1,3 H- shift. The salient features in this synthesis include easy work up, high yielding and the whole procedure follows *green chemistry methodology* (**Figure 48**).

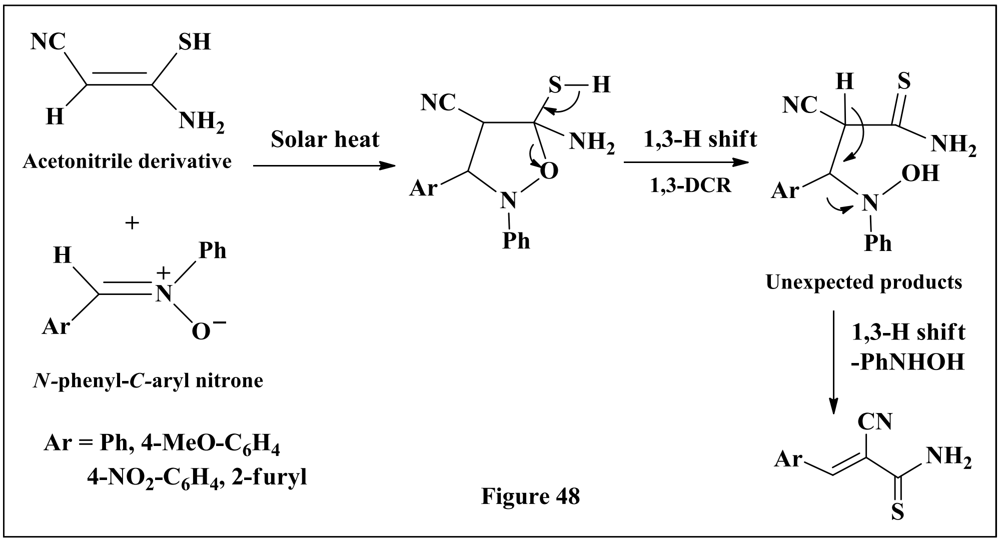


Figure 48

Solvent less, high yielding and simply using grinding technique at room temperature synthesis of alkyl & aryl *N*-methyl nitrones has been reported by Serkan Y & Yilmaz Y[78]. The methodology was found to be very efficient & environment-friendly and the nitrones were found to be moderately stable. *N*-methylhydroxylaminehydrochloride along with Sodium carbonate & Sodium sulphate was used as reagents in this synthesis (**Figure 49**).

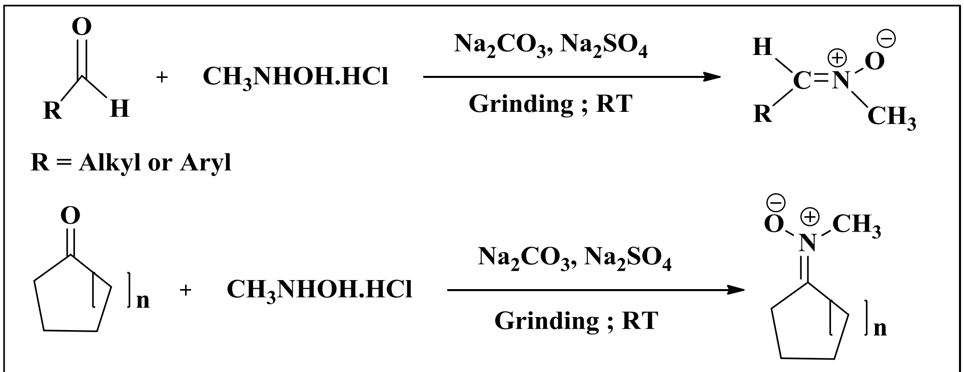


Figure 49

Mechanochemical (Ball-milling) technique in nitrone-cycloaddition reactions

Mechanochemistry using ball-milling technique, has become very popular among all greener credentials in organic synthesis in recent years and this technique has attracted the attention of synthetic organic chemists[79]. Mechanochemistry is usually performed using ball-milling or by simply hand grinding. For hand grinding process, a mixer, or shaker mill or a planetary mill is used maintaining a frequency of 5–60 Hz. Ball-milling technology is more sophisticated and reliable methodology compared with hand grinding technique because the later provides much more higher energy. Due to the development of variable energy and speed hand-grinding technique may lead to expose different experimental results. Hence this procedure may create confusion and should be avoided. Only Retsch RM100 mortar grinder involving a mortar and pestle may sometimes recommended for its uniformity in the reaction process.

Mechanochemistry using ball-milling technique is always preferred because of uniform speed of the balls used and development of energy at a required level throughout the reaction. Ball-milling technique can be set-up in the laboratory using high speed vibration mill (HSVM), commercially available Retsch mixer mill, Spex CertiPrep mixer mill, AGO-2 planetary centrifugal mill etc. In ball-milling technique, milling frequency and milling time is considered the most important foctors among all technical variables which include milling frequency, milling time, size & number of milling balls, and the material of which the milling balls prepared, as well as beakers. The efficiency of a chemical reaction is altered when the reaction is conducted in two different working mechanisms viz, a mixer mill and a planetary mill. For a mechanochemical reaction carried out with mixture mill is termed as MM whereas if the reaction is performed in a planetary mill it is denoted by PM.

Mechanochemistry using ball-milling technique has many green chemistry credential which include solvent free reaction, mild reaction conditions, purification of the synthesized products without column chromatography and high yield of products. Keeping our environment & mankind safe and performing tougher organic synthesis is always a challenge and in this contest mechanochemistry may be uesd as an important green chemistry protocol to fullfil the target. Therefore mechanochemistry may be an alternative (compared with other green chemistry procedures like microwave induced reactions, sonication etc) to the organic chemists as an effective & greener protocol for different organic transformations[80].

The wide range of mechanochemistry in synthetic organic reactions involve plenty of interesting synthesis viz, synthesis of carbon–carbon & carbon–hetero atom covalent bonds, metal–ligand coordination bonds, non covalent interactions such as hydrogen bonds, halogen bonds and π- π arene interactions. Plenty of review works on mechanochemistry and its procedures reports metal organic frameworks (MOFs), cocrystallization, pharmaceutical aspects, supramolecular synthesis and industrial aspects[79]. The reviews on mechanochemistry also depicts fullerene and it's derivatives, a unique family of cage shaped all carbon molecules[81]. Sometimes we need to use some toxic chemicals in critical organic transformations and performing these reactions following traditional methodology is not only a high risk issue for the working researchers but to the surrounding environment as well. Mechanochemistry can show a new pathway to overcome these difficulties. With the advantage of its techniques, we may perform the critical transformations in a very short reaction time,without using a solvent, using minimum energy and high yield of products[79].

Ball-milling technique involves frictional force which initiates and advances the reactions in a typical mechanochemical procedure. Mechanochemical synthesis using ball milling has been found to be one of the best procedures for performing various standard reactions in organic chemistry viz, Aldol condensation,[82] Michael addition,[83] Knoevenagel condensation,[84] Morita–Baylis–Hillman reaction,[85] Cross-coupling reaction,[86] Click reaction,[87] Heck-type cross-coupling reaction[88] and many more. Manual grinding[89] procedure using a mortar and pestle has certain limitations though the procedure has been applied to condensation reactions[90] including Schiff's base formation,[91] oxime formation[92] with some exceptions.[93] Therefore, this is an extremely helpful methodology for the laboratory due to uncomplicated & hazardless experimental conditions. Mechanochemistry is equally applicable nowadays in the synthesis of oxygen-nitrogen heterocyclic compounds especially isoxazolidine & isoxazoline derivatives[94].

A catalyst free high yielding nitrone-cycloaddition reaction leading to the synthesis of chromano isoxazoles using mechanochemical technique have been reported by A. Chatterjee & her group[95]. The nitrone was synthesized *in situ* which subsquently underwent intramolecular cycloaddition reaction when the reaction mixture was ground for 10 to 100 minutes (**Figure 50**).

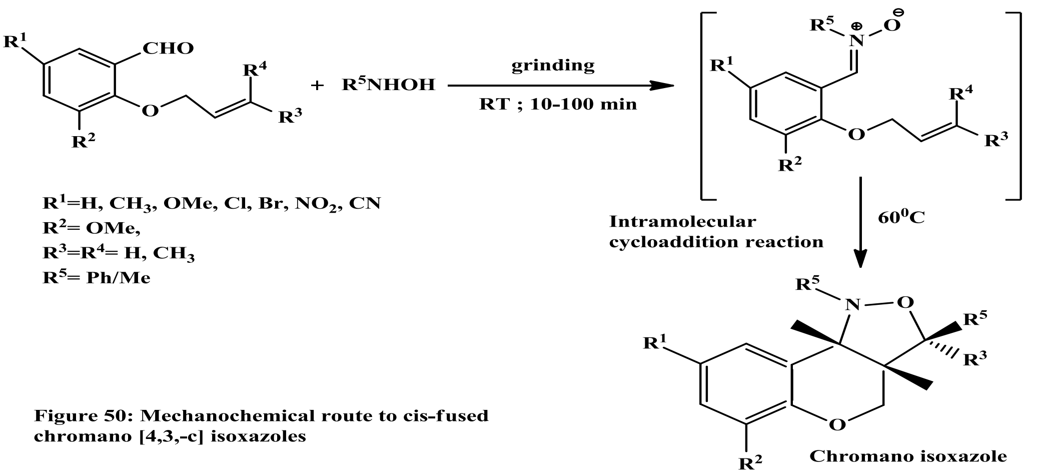


Figure 50: Mechanochemical route to cis-fused chromano [4,3,-c] isoxazoles

An excellent example of solvent free ball-milling technique for the synthesis of *N*-methyl-*C*-phenyl nitrone has been reported by F Lamaty & his coworkers[96]. This is an ideal example of mechanochemical procedure for the researchers in synthetic organic chemistry because the procedure provides one of the best techniques of green chemistry pertaining to high yield, selectivity & minimum reaction time (**Figure 51**).

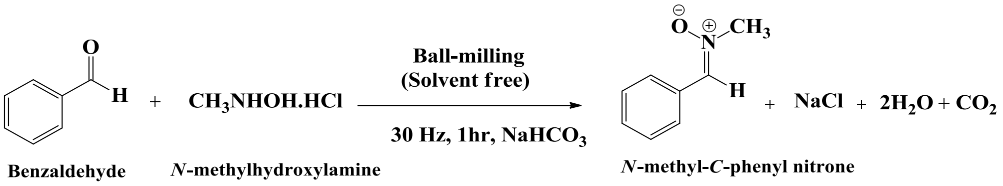


Figure 51: Synthesis of N-methyl-C-phenyl nitrone

A very fast method for the synthesis of alkyl & aryl-*N*-methylnitrones using ball-milling technique has been reported by Y Yildirir & coworkers[97] (**Figure 52 & 53**). Because of hazardous free procedure the technique has been widely accepted for further applications.

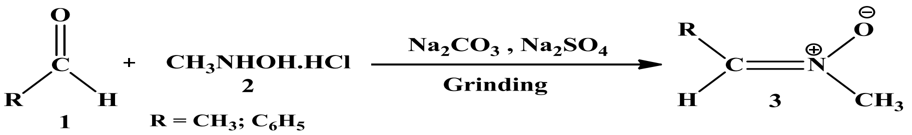


Figure 52: Ball-milling technique for the synthesis of alkyl/aryl nitrones

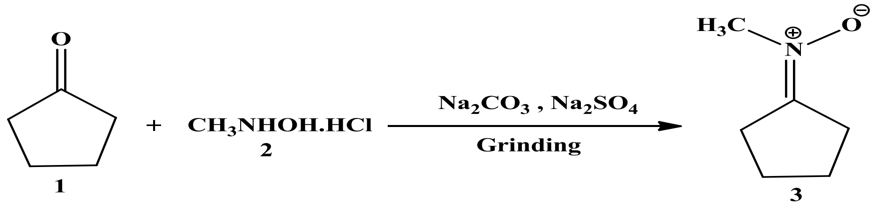


Figure 53: Ball-milling technique for the synthesis of alkyl/aryl nitrones

Synthesis of a series of new cyclo-metalated iridium hydrides derived via C−H bond activation of various aromatic nitrones & also the biological activity of the newly developed iridium hydrides as antitumor agents has been reported by Y Qian & coworkers[98]. *C*-phenyl-*N*-tert-butylnitrone (PBN) acts as an active ligand and also as an antioxidant. From the detailed biological screening the authors also suggested that the newly developed iridium hydride complex exhibit better “antitumour activity” than “cisplatin” and hence novel metal hydrides may be regarded as good “antitumour agents” (**Figure 54**).

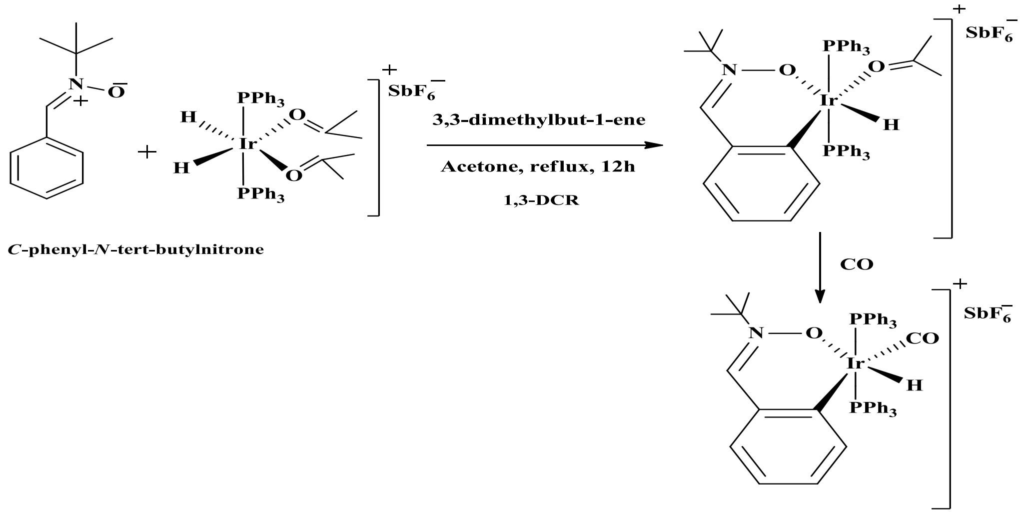
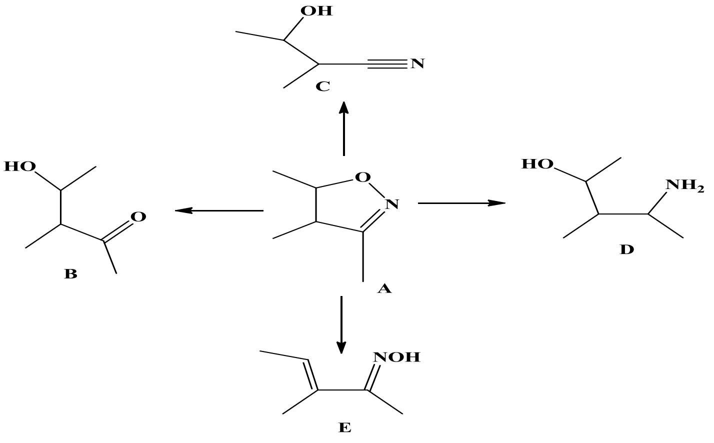


Figure 54 : Synthesis of Iridium hydride as antitumour agent

Padwa A[94d] & Jorgensen K[99] highlighted the importance of isoxazoline derivatives in their respective review works. Based on a detailed study of a variety of isoxazoline derivatives it may be reckoned that these derivatives may act as excellent precursors for a variety of new molecules for further applications (**Figure 55**).

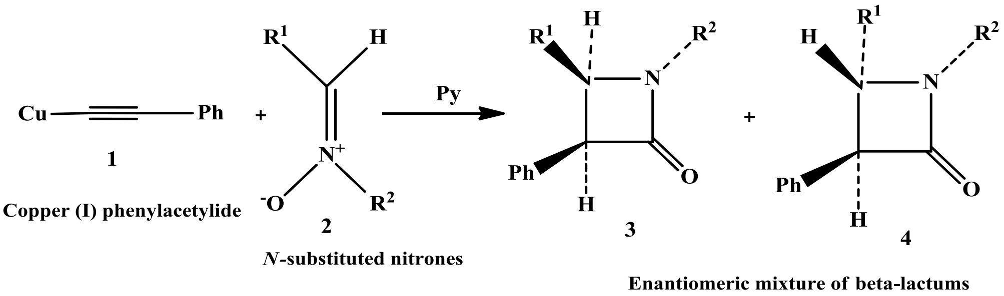


B,C,D,E = newly developed molecules from isoxazolines as precursor

Figure 55

The synthesis of *β*-lactam derivatives & their further applications is a highly demanding area of research in synthetic organic chemistry and these kind of reaction have been reviewed in recent years[100,101]. Few important examples of synthesis of *β*-lactam derivatives have been represented here.

The most popular method for the synthesis of *β*-lactam derivatives is nitrone-cycloaddition reaction. As this kind of cycloaddition reaction leading to the synthesis of *β*-lactam derivatives was discovered by Kinugasa hence the reaction is popularly called Kinugasa reaction. The simplest example of Kinugasa reaction is when *N*-substituted nitrones react with copper (I) phenylacetylide in presence of a strong base (pyridine) leading to the generation of enantiomeric *β*-lactams (**Figure 56**)[102].



4a :R^1**= Ph,** $OMeC_6H_4$, $O\text{-}ClC_6H_4$

4b : R^2**= Ph,** $O\text{-}ClC_6H_4$

Figure 56 **Synthesis of beta lactam by Kinugasa reaction**

An excellent contribution in this chemistry has been provided by A.Basak & coworkers[103]. They introduced asymmetric version of Kinugasa reaction and for this purpose they have used Evans's oxazolidinone as an asymmetric auxiliary in the synthesis (**Figure 57**).

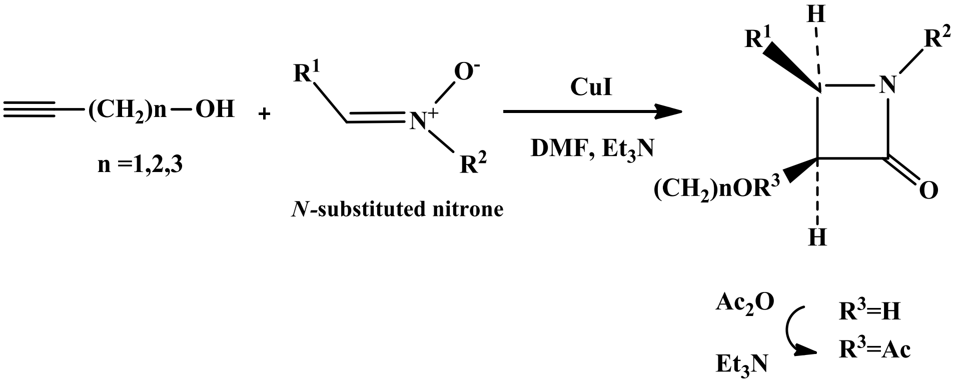


Figure 57 **Asymmetric Kinugasa reaction**

Motivated with the excellent principles of green chemistry methodology (**Figure 58**) recommended by Anastas P & Warner J[41] in 1998 in their famous book "Green Chemistry: Theory & Practice", our research group started working on these principles and communicating research publications from 2008. Few important recently published research contributions have been enlisted here as an integral part of this dissertation (**I-VI ; Figure 59-64**).

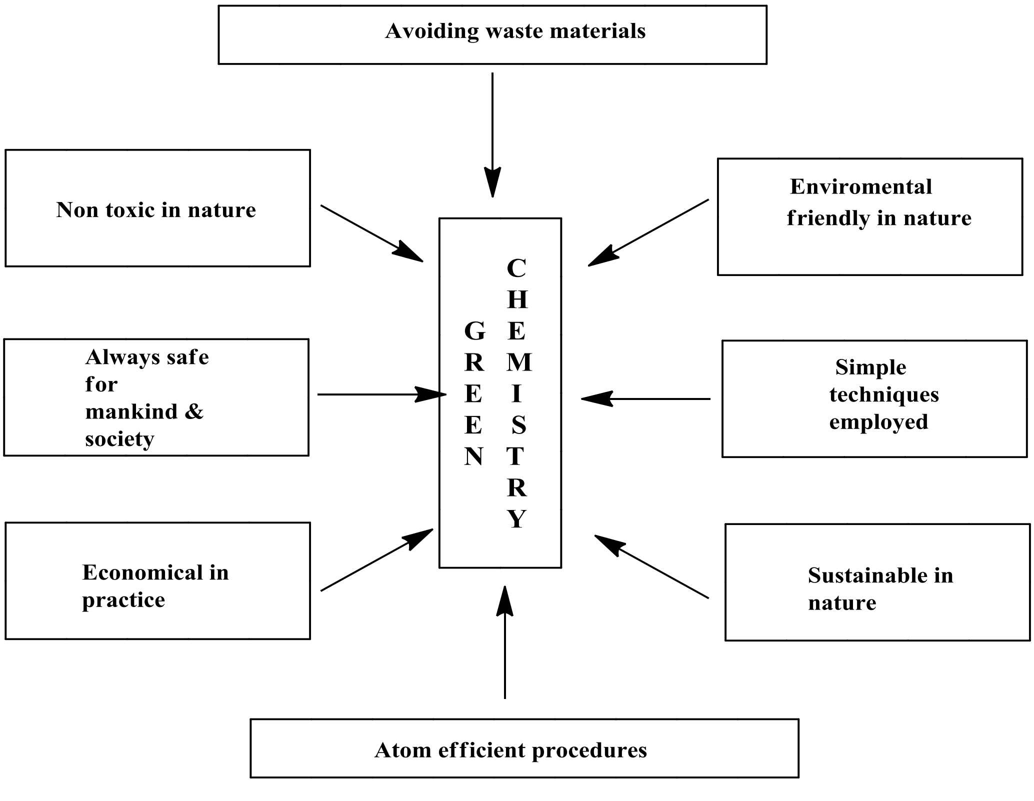
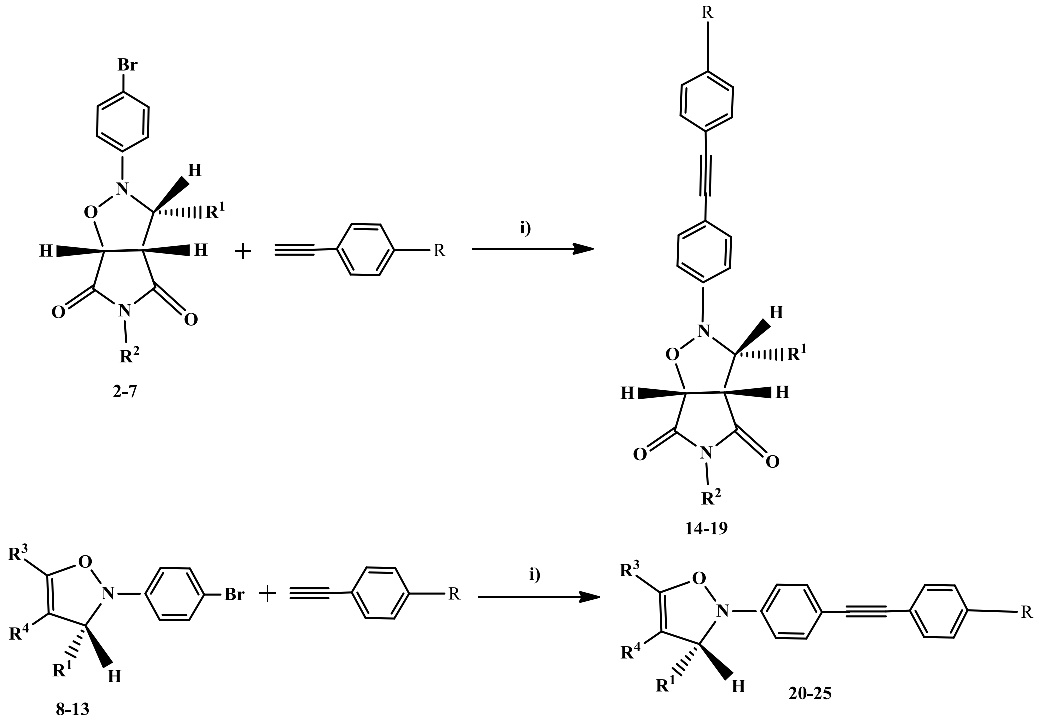


Figure 58: Basic principles of green chemistry recommeded by Anastas P & Warner W

Recently contributed research works based on green chemistry methodologies from our laboratory (I-VI)

I. Mechanochemical synthesis of some heterocyclic molecules using Sonogashira cross-coupling reaction and their anticancer activities[104] (**Figure 59**).



i) Reaction condition: Ball-milling, 20 Hz, 20 min, DABCO, Pd (OAc)$_2$

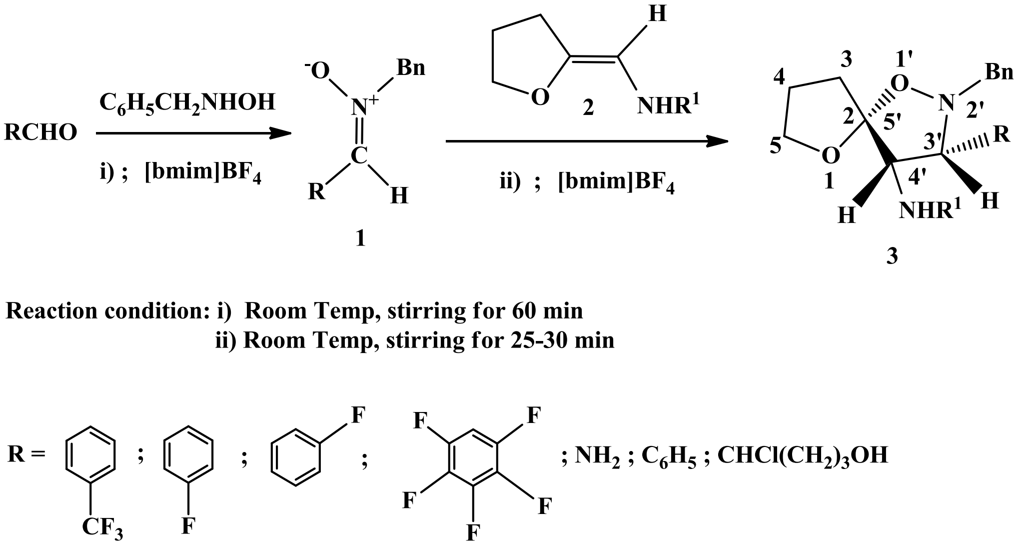
R = H ; Br; R^1 = Furyl; Phenyl; 2,6-difluoro-phenyl; 4-fluoro phenyl; 4-hydroxy phenyl; 3-NO$_2$ Phenyl; 4-methyl phenyl; -NH$_2$; -NMe$_2$

R^2 = Ph ; Me ; cyclo-C$_6$H$_{11}$

R^3 = R^4 = COOCH$_3$; R^3= R^4 = COOH ; R^3 = COOCH$_3$, R^4 = C$_6$H$_5$

Sonogashira cross-coupling reaction of isoxazolidine & isoxazoline derivatives to new heterocycles

II. Synthesis of Some Novel class of Regioselective Spiro isoxazolidine derivatives via 1,3-Dipolar Cycloaddition reaction of *N*-Benzyl-*C*-fluoro substituted-phenyl nitrones in ionic liquid[105] **(Figure 60).**



Reaction condition: i) Room Temp, stirring for 60 min
ii) Room Temp, stirring for 25-30 min

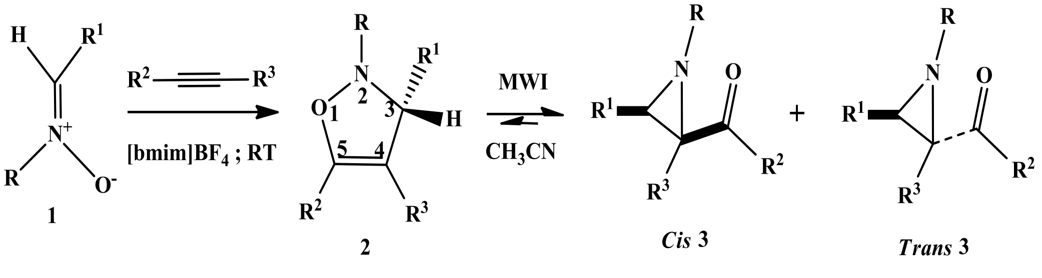
R = ; ; ; ; NH_2 ; C_6H_5 ; $CHCl(CH_2)_3OH$

R^1= CH_3; C_6H_5; $C_6H_5CH_2$; p-OHC_6H_4; p-$NO_2C_6H_4$; p-BrC_6H_4; o-$NO_2C_6H_4$; o-OHC_6H_4
Bn = $C_6H_5CH_2$

Synthesis of new regioselective spiro isoxazolidine derivatives **Figure 60**

III. Highly stereoselective synthesis of new aziridines via Baldwin rearrangement and their potential biological activities[106] (**Figure 61**).

Atom-economical synthesis of *N*-substituted aziridines from *N*-substituted isoxazoline derivatives through Baldwin rearrangement have been reported using microwave technology.

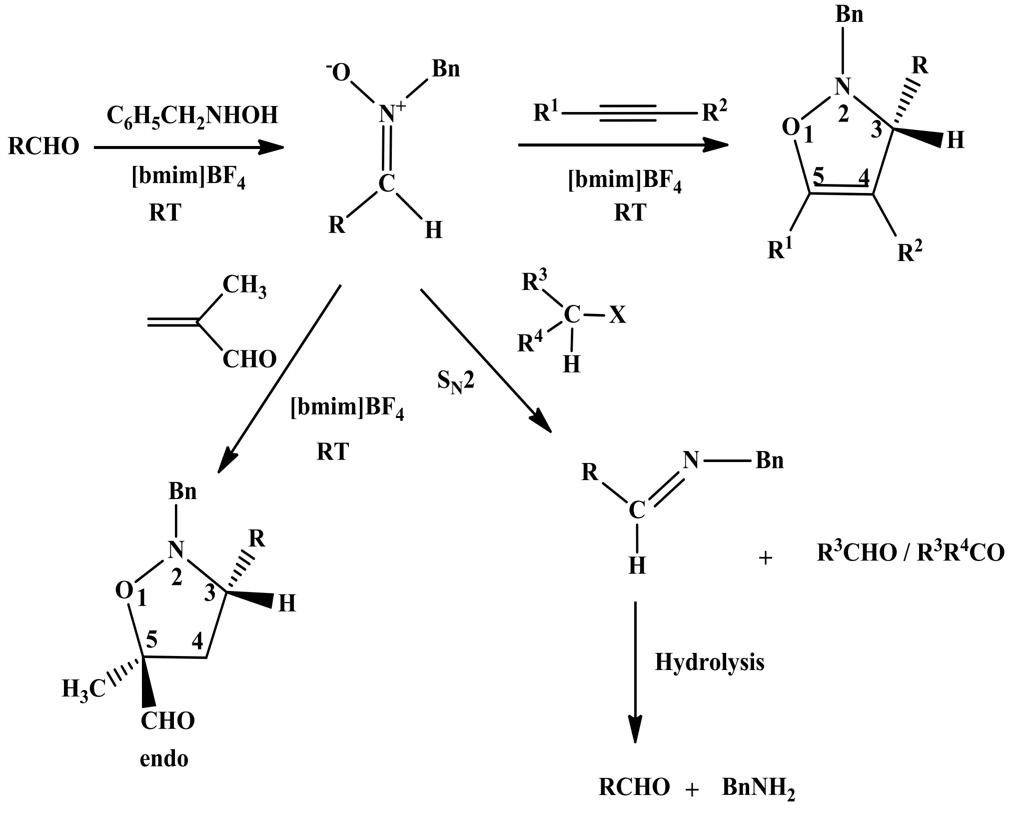


R = CH_3/C_6H_5/C_6H_{11}/ $C_6H_5CH_2$/4-OHC_6H_4/2-OHC_6H_4
R^1 = C_6H_5; 2,6-difluoro phenyl; 2-furyl; -$(CH_2)_4OH$
R^2 = $COOCH_3$; R^3 = H
R^2 = $COOCH_2CH_3$; R^3 = H
R^2 = COOH; R^3 = H
R^2 = $SiMe_3$; R^3 = H
R^2 = CMe_3; R^3 = H

Rearrangement of 2 into *cis*-3 and *trans*-3 (aziridine derivatives) **Figure 61**

IV. *Synthesis of some novel isoxazoline and isoxazolidine derivatives using N-benzyl fluoro nitrone via cycloaddition reactions in ionic liquid*[107](**Figure 62**).

1-Butyl-3-methylimidazolium based ionic liquids have been found to increase significant reaction rate in the 1,3-dipolar cycloaddition reactions of *N*-benzyl-fluoro nitrones with electron deficient alkynes and methacrolein respectively.



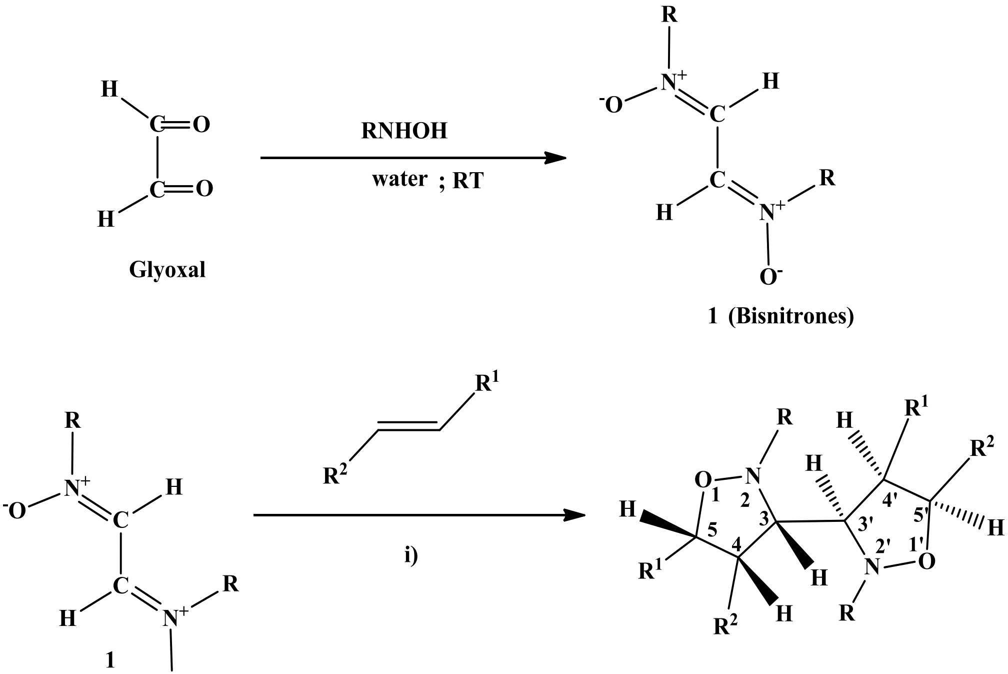
R = 2,6 difluro/ 2 fluoro/ 3,4 difluoro/ 4 fluoro/ 4 hydroxy benzene/ Ph ; Bn = $C_6H_5CH_2$
R^1 = Ph ; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = Et ; Ph ; R^4 = H etc
R^3 = R^4 = Ph ; R^3 = Me ; R^4 = Ph etc
X = Cl/Br/I

Synthesis of isoxazoline, isoxazolidines and aldehyde/ketones using *N*-benzyl fluoro nitrone in ionic liquid

Figure 62

V. Synthesis of Some novel class of bisisoxazolidine derivatives have been synthesized from glyoxal derived bisnitrones utilizing simultaneous double cycloaddition reactions using water as solvent[108] (**Figure 63**).

We have described simultenous double 1,3-dipolar cycloaddition reactions of bis-nitrone in water with significant reaction rate accleration and selectivity.



Glyoxal

1 (Bisnitrones)

1

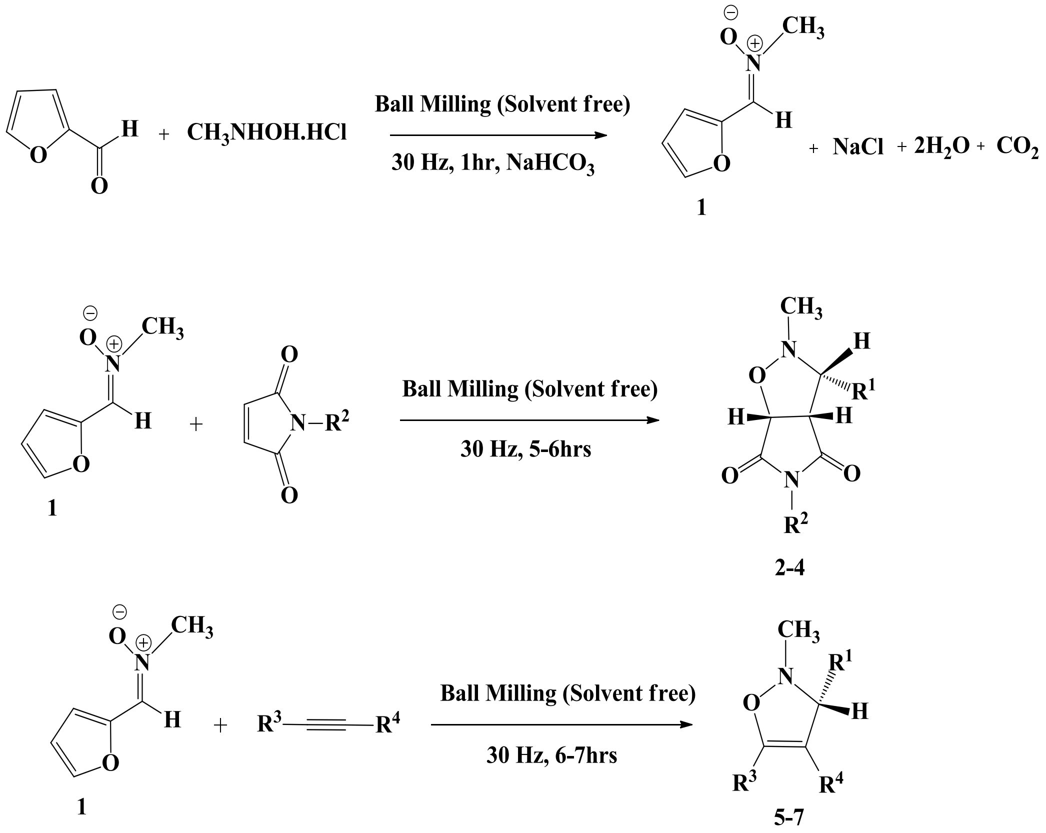
2 to 7 (Bis-isoxazolidines)

i) water, RT, 3-5 hr, N_2 atmosphere

$R = CH_3$; C_6H_5 ; $CH_2C_6H_5$
2 : R^1, R^2 = -CONMeCO- ; 3: -CONPhCO- ; 4: -CONCyCO- 5: -CONEtCO-
6: R^1 = H ; R^2 = $-CO_2CH_3$; 7: R^1= H ; R^2 = $-C_6H_5$

Synthesis of bisnitrone and bisisoxazolidine derivatives from glyoxal Figure 63

VI. Mechanochemical synthesis & 1,3-dipolar cycloaddition reactions of *N*-methyl-C-(2-furyl) nitrone in a ball-mill & anticancer activities of the new cycloadducts[109] **(Figure 64).** 1,3-dipolar cycloaddition reactions with activated alkenes & electron deficient alkynes have been studied using ball-milling technique. Significant increase in reaction rate, yield and environment friendly procedure are the salient features in this synthesis.



R^1 = Furan molecule
R^2 = Ph; Me ; cyclo-C_6H_{11}
R^3 = Ph ; R^4 = $COOCH_3$
R^3 = R^4= $COOCH_3$
R^3 = R^4 = COOH

Synthesis of new isoxazolidine & isoxazoline derivatives using ball-milling technique Figure 64

Host-Guest inclusion complexation using cyclodextrin & phenyl maleimide cycloadduct

Cyclodextrin molecules have a unique structure. It has a hydrophobic cavity & a hydrophilic surface where a guest molecule can be entrapped. Cyclodextrin molecule can develop inclusion complex with a large variety of solid, liquid & gaseous compounds. The complex formed is a dimensional and geometrically fitted between the cyclodextrin cavity & the guest molecule[110].

Cyclodextrins (CD) molecules are composed of cyclic oligosaccharides having glucopyrasyl units linked with α-(1,4) bonds. The most commonly used cyclodextrins are γ, β & γ cyclodextrins containing 6.7 & 8 glucopyranose units respectively. The cyclodextrin molecules have unique property for encapsulation of bioactive compounds and it can protect the compounds from different environmental conditions & can also improve the aqueous stability and therby increasing their capacity to functionalize the products. There are some cases where the water solubility of β-cyclodextrin has to be increased by the addition of hydroxyalkyl groups on the β-cyclodextrin surface. In inclusion complex formation when a small molecule enters into the cavity of a large sized molecule to form a stable complex, then the complex is known as "*Host-Guest inclusion complex*"(**Figure 65**). An example of this kind using cyclodextrin & *N*-phenyl maleimide cycloadduct may be represented as follows.

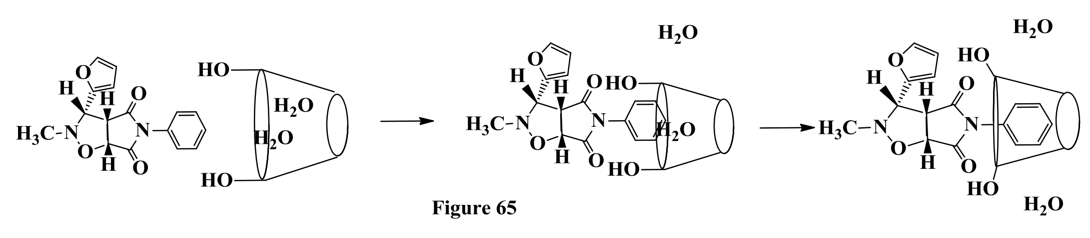


Figure 65

Cyclodextrin molecule possess an internal non polar whole and the hydroxy groups are placed on the surface. Inclusion of hydrophobic molecules takes place basically when the hydrophobic interactions between the guest molecule and the cavities of the walls of cyclodextrin molecule occurs[111]. Some other forces viz, Van der Walls & dipole-dipole interactions can be involved for binding the guest molecule. Inspite of different factors and forces involving during the complex formation with cyclodextrin, the procedure still remains very simple. Many methods are available to obtain Host-Guest complexations.

1. Kneading methodology

The methodology is suitable for weekly soluble guests as the guest is dissolved slowly during complex formation[112]. Yields are good in this process but not recommended for large scale preparations[113].

2. Co-precipitation methodology

This technique is applicable for the compounds which are not soluble in water. The yield in this process is very low. This is due to the competitive inhibition from the organic solvents which are used as precipitant[114].

3. Heating in a sealed container methodology

The method involves adsorbtion of a definite amount of water vapour, a physical mixture of active compound & the host molecule in a sealed container. The container is heated to temperature ranging from 42^0C to 142^0C resulting a crystalline inclusion complex. The technique may also be performed using nitrogen gas pressure.

4. Spray drying methodology

In this method cyclodextrin & the guest molecule is dissolved in deionized water and the solution is dried using spray dryer. The spray dryer has to be operated in most appropiate conditions which include inlet temperature & sample feeding speed[115]. The methodology is applicable for only thermostable compounds since 50^0-70^0C temperature is used.

Confirmation of inclusion complexes

The development of inclusion complex may be confirmed considering the interaction between a guest molecule & cyclodextrin. The instrumental techniques used for this purpose are UV-VIS spectroscopy & Differential scanning calorimetry (DSC).

Application of UV-VIS spectrocopy

The development of inclusion complex between cyclodextrin & guest molecule (β-caryophyllene) changes the original visible or ultraviolet absorption of the guest molecule and also for cyclodextrin which indicates or characterize the inclusion complex formation. Both the samples are diluted in ethanol and the UV-VIS spectra of the physical mixture of β-caryophyllene & β-cyclodextrin are identified at 205 nm. Single β-cyclodextrin molecule in ethanol has no UV absorption peak.

Application of Differential scanning calorimetry (DSC)

This methodology is a thermoanalytical technique where the difference between the amount of heat required of the sample under study & the reference molecule is measured as a function of temperaturer. DSC study is a relative measure of heat flow which is related to molecular motion. Two different types of DSC techniques are known i) Heat-flux DSC ii) Power differential DSC. In the heat-flux DSC technique, heat-flux remains constant while in power differential DSC technique, power supply remains constant. The development of inclusion complex formation can be confirmed using DSC technique comparing the thermal stability of the free molecule with the encapsulated form[116].

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