Chapter 1

Introduction to 1,3-dipolar cycloaddition reaction
1.1 Brief Description of Cycloaddition Reaction

Cycloaddition reaction is a process in which two or more π electron system combines to form a stable cyclic molecule. During which, sigma bonds are formed between the terminal π systems and no fragments are lost. A concerted mechanism requires a single transition state and no intermediate, which lies on the reaction path between reactant and adducts. The two important cycloaddition reactions by concerted mechanism are

(a) Diels-Alder Reaction: This reaction is addition of conjugated diene to alkene, commonly called as dienophile, to give a six membered ring system. This reaction is classified as (4+2) cycloaddition reaction because diene component provides 4 π electrons and dienophile provides 2π electrons to form a six membered adduct.

\[ + \rightarrow \]

The reaction is easy and rapid. In the terminology of the symmetry classification, the Diels- Alder reaction is a (π⁴S+π²S) cycloaddition because, the classification consider

i) The number of electrons in each participating unit.

ii) The nature of orbital undergoing change either π or σ

iii) Stereochemical mode either Syn (supra) or anti (antra) addition with respect to both diene and dienophile.

Most dienophile are in the form,

\[
- \text{Z} \quad \text{or} \quad Z' \text{C} \text{C} Z
\]

Where Z, Z' are CHO, COR, COOH, COOR, COCl, COAr, CN, NO₂, Ar, CH₂OH, CH₂NH₂, CH₂COOH, Cl, Br, F

Beside carbon-carbon multiple bonds other double bond and triple bond compounds can be dienophile, giving rise to heterocyclic compounds. Among these are O=N, -C=O, and -C=N, -N=C-, -N=N- compounds. The term 1,3 dipole arose because such compounds can be
described in terms of dipolar resonance contributor in valence bond theory (VBT) as follows.

\[ \begin{array}{c}
\text{a} \quad \overset{\hat{b}}{\text{c}} \\
\end{array} \quad \leftrightarrow \quad \begin{array}{c}
\text{a} \quad \overset{b}{\text{c}} \\
\end{array} \]

(b) **1,3- dipolar cycloaddition (DC) reaction:** The (3+2) 1,3-dipolar cycloaddition is a reaction where two organic compounds, a dienophile, 1 and a 1,3 dipole (or ylide) 2, combine to form a five membered heterocycle 3 (Figure 1.1). The reaction is related to the Diels- Alder reaction where a diene and a dienophile, cycloaddition reaction can furnish very complex heterocycles, containing multiple stereogenic centres. Therefore this reaction is used for the preparation of molecules of fundamental importance for both academia and industry.

The history of 1,3-dipoles goes back to Crutius, who in 1883 discovered diazoacetic ester.\(^4\) Five years later his younger colleague Buchner studied the reaction of diazoacetic ester with α, β- unsaturated esters and described first 1,3 DC reaction.\(^5\) In 1893 he suggested that the product of the reaction of methyl diazoacetate and methyl acrylate was a 1-pyrazoline and the isolated 2-pyrazole was formed after rearrangement of the 1-pyrazole.\(^6\) Five years later nitrones and nitriloxide were discovered by the Beckmann, Warner and Buss respectively.\(^7,8\) The Diels-Alder were found in 1928,\(^9\) and synthetic values of this reaction soon became obvious. The chemistry of 1,3 dipolar cycloaddition reaction has thus evolved for more than 100 years, and a variety of different 1,3 dipoles have been discovered.\(^10\) However, only a few dipoles have found general application in synthesis during the first seventy years after discovery of diazoacetic ester. Two well known exception are ozone and diazo compounds.\(^11,12\) The general application of 1,3 dipole in organic chemistry was established by the systematic studies by Huisgen in the 1960s.\(^13\) At the same time the new concept of conservation orbital symmetry, developed by Woodward and Hoffman, appeared.\(^14,15\) There work was a milestone for the understanding the mechanism of concerted cycloaddition reactions. On the basis of the concept by Woodward and
Hoffmann, Houk et al., have further contributed to our present understanding and ability to predict relative reactivity and region selectivity of 1,3 DC reactions.\textsuperscript{16,17}

![Figure 1.1](image-url)

**Figure 1.1**

**1.2. Nature of the dipole**

A 1,3-dipole is defined as an a-b-c structure that undergoes 1,3-DC reactions and is portrayed by a dipolar structure as outlined in Figure 1.1. Basically, 1,3-dipoles can be divided into two different types: the allyl anion type and the propargyl/allenyl anion type. The allyl anion type is characterized by four electrons in three parallel $P_z$ orbitals—perpendicular to the plane of the dipole and that the 1,3-dipole is bent. The resonance structures in which the three centers have an electron octet, and two structure in which a or c has an electron sextet, can be drawn. The central atom b can be nitrogen, oxygen, or sulfur (Figure 1.2(A)). The propargyl anion type has an extra $\pi$ orbital located in the plane orthogonal to the allenyl anion type molecular orbital (MO), and the former orbital is therefore not directly involved in the resonance structures and reactions of the dipole. The propargyl/allenyl anion type is linear and the central atom b is limited to nitrogen (Figure 1.2B). The three sextet resonance structures that also can be drawn are omitted in Figure 1.2. The 1,3-dipoles are occasionally presented as hypervalent structures (Figure 1.2C). The classification and presentation of the parent 1,3-dipole is depicted in Table 1.1.\textsuperscript{10}
(A) Allyl anion type

\[
\begin{array}{c}
a^+b\bar{c} \\
a^+b\bar{c}
\end{array}
\hspace{1cm}
\begin{array}{c}
a^{-}b\bar{c} \\
a^{-}b\bar{c}
\end{array}
\]

Octet-Structure

Sextet-Structure

(B) Propargyl/allenyl anion type

\[
\begin{array}{c}
a^+b\bar{c} \\
\bar{a}^+b\bar{c}
\end{array}
\hspace{1cm}
\begin{array}{c}
\bar{a}^+b\bar{c} \\
a^+b\bar{c}
\end{array}
\]

(C) Hypervalent representations

\[
\begin{array}{c}
a^+b\bar{c} \\
a^+b\bar{c}
\end{array}
\hspace{1cm}
\begin{array}{c}
\bar{a}^+b\bar{c} \\
\bar{a}^+b\bar{c}
\end{array}
\]

Figure 1.2
Table 1.1. Classification of the parent 1,3-dipoles

<table>
<thead>
<tr>
<th>Allyl anion type</th>
<th>Propagyl/allenyl anion type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen in the middle</td>
<td>Nitrogen in the middle</td>
</tr>
<tr>
<td>Nitrones</td>
<td>Oxygen in the middle</td>
</tr>
<tr>
<td>Azomethine Imines</td>
<td>Carbyl Lide</td>
</tr>
<tr>
<td>Azomethine Ylides</td>
<td>Carbyl Imines</td>
</tr>
<tr>
<td>Azimines</td>
<td>Carbyl Oxides</td>
</tr>
<tr>
<td>Azoxy Compounds</td>
<td>Nitrosoimines</td>
</tr>
<tr>
<td>Nitro compounds</td>
<td>Nitrosoxides</td>
</tr>
<tr>
<td>Ozone</td>
<td>Nitrilium Betaines</td>
</tr>
<tr>
<td>Nitrile Betaines</td>
<td>Nitrile Oxides</td>
</tr>
<tr>
<td>Nitrile Limes</td>
<td>Nitrile Imines</td>
</tr>
<tr>
<td>Nitrile Ylides</td>
<td>Nitrile Ylides</td>
</tr>
</tbody>
</table>

1.3. Nature of the Dipolarophile

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing $2\pi$ electrons. Thus, depending on which dipole that is present, $\alpha$ $\beta$-unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily. It must be noted that, other $2\pi$-moieties such as carbonyls and imines also can undergo cycloaddition with dipoles. The alkene moiety can be mono-, di-, tri- or even tetrasubstituted (only monosubstituted ones are shown here). However, mostly due to steric
factors, tri and tetra substituted ones often display very low reactivity in reactions with dipoles.

It must be pointed out that dipolarophiles (Figure 1.3) incorporating two conjugated double bonds such as dipolarophile 4 can exist in two different main confirmations, s-cis and s-trans respectively, where as the s-cis/s-trans descriptor refers to the single bond connecting the two double bonds. Such s-cis/s-trans isomerism can have a major impact on the outcome of an asymmetric 1,3-dipolar cycloaddition reaction.

1.4. Synthesis and Reaction of Nitrones

The chemistry of nitrones and their cycloaddition reaction with unsaturated substrate has attracted considerable attention both from the point of synthetic and biological studies. The nitrone cycloadducts are attractive intermediates for the synthesis of several classes of biologically active compounds and natural products.\(^\text{18,19,20}\) Cycloaddition of nitrones to unsaturated substrate constitute the best procedure for the construction of 5-membered isoxazolidines ring system with regio and stereochemical control. The presence of nitrogen atom within isoxazolidines ring has made this heterocyclic moiety especially attractive for the synthesis of the β-lactum.\(^\text{21,22}\) The key step of this approach involves a reductive cleavage of the isoxazolidines ring to give a γ-amino alcohol, which undergoes subsequent cyclisation with neighbouring methoxy carbonyl group to form a lactum ring.

Nitrones represent a well known and thoroughly investigated class of 1,3-dipoles and used as an excellent spin trapping agent.\(^\text{23}\) Nitrogen are one of the members of the series of 1,3-dipoles. They can be considered of spiral interest, because they play role in the synthesis of
alkaloids and other natural compounds. Nitrones are compounds containing the group as follows:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\end{align*}
\]

The name nitrone is derived from nitrogen ketone in order to indicate a chemical relationship between nitrones and carbonyl compounds. The nitrogen group bears a marked resemblance to the carbonyl group in facilitating the removal of proton from an adjacent carbon under basic condition. The oxidation of methyl group, adjacent to the carbonyl group by means of selenium dioxide, the addition of organometallic reagents, the addition of hydrocyanic acid and reduction by complex metal hydrides.

The nomenclature employed by Chemical Abstract in recent years as follows:

\[
\begin{align*}
\text{H} & \quad \text{N} & \quad \text{O} \\
\end{align*}
\]

It is named as α, N-diphenylnitrone. In old literature it was called as N-phenyl “ether” of benzaldoxime.

Nitrones exhibit geometric isomerism because of the double bond in the nitrone group.

\[
\begin{align*}
& \text{R}_1 = \text{N} & \quad \text{R}_3 \\
& \text{R}_2 = \text{O} \\
\end{align*}
\]

The existence of geometric isomerism was first demonstrated in 1918 for α-Phenyl- α-(p-tolyl)-N-methylnitrone. The configurations of the isomers were established by dipole moment studies. For the cis form the dipole moments range between 5.6-6.3 D and the trans form between 0.9-1.7 D. The cis form convert easily into the trans form by heating. The resonance structure of nitrone may be written as follows,
Due to this resonance structure, it shows versatile reactivity with various reagents.

**Synthesis of Nitrones**

Nitrones are easily accessible and material can be synthesized by various methods. The most general preparation involves the condensation of N-monosubstituted hydroxylamines with carbonyl compounds and the oxidation of N,N-substituted amines.\(^{25,26,27}\)

**(a) Condensation of N-monosubstituted Hydroxylamine with carbonyl compounds**

\[
R\text{-NHOH} + R_1\text{O} \rightleftharpoons R\text{-N}+R_2\text{H}_2\text{O}
\]

The reaction proceeds smoothly and with high yield when R is an alkyl or aryl group and if R\(_1\) and R\(_2\) are of small size. Where R\(_1\) and R\(_2\) are bulky groups the reaction does not proceed.\(^{28}\) N-phenylhydroxylamines are treated with variety of aldehyde and ketones to from N-phenyl nitrone and N-phenylhydroxylamine and formaldehyde which in-situ undergoes an intermolecular 1,3-addition followed by the loss of hydrogen and the formation of dinitrone.\(^{29}\)

\[
\text{Ph-N=CH}_2 \rightarrow \text{Ph-N=C=C=Ph} \rightarrow \text{Ph-N=C=Ph}
\]

Ring substituted N-phenylhydroxylamines when treated with benzaldehyde nitrones were isolated in good yield. From N-methylhydroxylamine and cyclopentanone nitrone could be isolated. This nitrone is very hygroscopic, which instantly hydrolysed by water and decomposed by ethanol.
Nitrones have also been prepared by in-situ generation of the hydroxylamine in the presence of a carbonyl compound. The α, N-diphenylnitroline is obtained by the reaction of nitrobenzene, benzaldehyde and zinc dust in a mixture of water, ethanol and acetic acid.

(b) N-Alkylation of oximes: Alkylation of oximes were reviewed in 1938. The disadvantage of this method is that reaction products are mixture of oxime ethers and nitrones. Since alkylation may occur on either oxygen or nitrogen. Electron withdrawing groups in p-substituted benzophenone oxime salts markedly promoted the formation of nitrones.

\[
\begin{align*}
\text{R} \quad \text{NOH} + R_2-X & \rightarrow \text{R} \quad \text{NOR}_2 + \text{R} \quad \text{N} \quad R_3 + \text{HX}
\end{align*}
\]

While, electron–donating substituent favoured oxime ether formation. A pronounced steric effect was observed by comparing the reaction between benzophenone oxime sodium salt with methyl bromide or benzyl bromide, the small size of the alkylation agent favouring nitroline formation, the large size favoring oxime ether formation.

(c) Reaction of Aromatic nitroso compounds with active methylene compounds:

Aromatic nitroso compounds react readily with compounds such as 2,4,6-trinitrotoluene or 9-methylacridine, containing a sufficiently activated methyl group. The reaction products often are mixture of anils and nitrones. The reaction is normally catalyzed by small amounts of base such as pyridine, piperidine and sodium carbonate. The following sequences of steps have been proposed for the reaction (Scheme 1.1).
The methyl group in mononitrotoluene apparently were not sufficiently acidic, since a reaction was not observed with either nitrosobenzene or p-nitroso-N,N-dimethylaniline. On the other hand, 2,4-dinitrotoluene when refluxed with piperidine as catalyst, yield anil as sole product, but the use of potassium hydroxide as the catalyst produces the nitrone exclusively.\textsuperscript{34}

(d) \textbf{N-oxidation of imines (Schiff’s bases):} Imines or Schiff’s bases give initially oxazaridines, which under controlled condition thermally rearrange to nitrones.\textsuperscript{35}

(e) \textbf{From Diazo compounds:} This reaction was described previously, which involves the introduction of diazo compounds into a solution of an aromatic nitroso compounds leading to the formation of nitrone.

\textbf{Reaction of nitrones}

(a) \textbf{With alkenes:} The 1,3-cycloaddition of a nitrone with alkene leads to the formation of a five membered heterocyclic ring.
Unconjugated alkenes appear to react considerably slower than conjugated unsaturated systems. Intra molecular addition of the in-situ generated nitrone group was also reported in case of N-methyl-N-(5-hexynyl)hydroxylamine which upon treatment with mercuric oxide yields an isoxazolidines derivative, presumably through a nitrone intermediate.

Intramolecular 1,3-cycloaddition was also observed for cycloalkenes. 4-cyclopentene carboxaldehyde when treated with N-methylhydroxylamine, isoxazolidines derivative was obtained, but intramolecular addition was not observed with 3-cyclohexenecarboxaldehyde. Styrene and α, N-diphenylnitrotrone yields two isomeric adducts, presumably diastereoisomers.  

(b) With Benzyne: Benzyne forms stable adducts with simple nitrones, but those derived from heteroaromatic N-oxide can not be detected and are postulated to undergo rearrangement to phenolic derivatives.

(c) With Phosphoranes: Methylene, benzidine and isopropylidinetriphenylphosphoranes give oxazophospholidines on reaction with nitrones. So intersection of heteroatom helps a lot synthetic chemistry.
(d) **With Isocyanate:** The cycloaddition of isocyanate to nitrone is apex identification.

(e) **Addition of organometallic reagents:** Grignard reagents are added to aldonitrone in a 1,3-fashion, but the reaction with ketonitrone leads to imines.\(^{39}\)

(f) **Addition of HCN:** Generally nitrone form a 1,3-adduct with hydrogen cyanide. In the presence of base adduct readily lose to yield cyano imine.

1.5 **Rearrangements of nitrones**

(a) **The nitrone-amide rearrangements:** This common reaction observed in nitrones.\(^{40}\) Aldonitrone rearranged to the isomeric amides by treatment with a variety of reagents e.g. Phosphoruspentachloride, phosphorustrichloride, phosphorusoxychloride, sulfurdioxide, aceticanhydride, acetylchloride and solution of base in ethanol.

(b) **The nitrone-Oxime O-Ether rearrangement:** The isomerisation may occur either under the influence of heat or acid. Thus, by heating \(\alpha, \alpha\)-diphenyl-N-diphenylmethylnitrone to 160-200 °C, a quantitative yield of the O-ether was obtained.\(^{41}\)
(c) Behrend Rearrangement: Ketonitrones may undergo rearrangements by catalytic influence of base. This rearrangement has also been observed in the synthesis of nitrone.

1.6 Reduction of Nitrones

Nitrones upon treatment with either lithium aluminium hydride or sodium borohydride yields the corresponding hydroxylamines, generally in high yields, presumably by a 1,3-addition mechanism.

Deoxygenating of nitrones has been accomplished by zinc, tin, or iron dust, phosphines, sulfurdioxide, sulfur and catalytic hydrogenation, N-diphenylnitroge and zinc in aceticacid forms the corresponding anils.

1.7 Oxidation of Nitrones

Leadtetraacetate (LTA) oxidizes aldonitrones to (N) O-acetylhydroximic acids which are used in the synthesis of nucleoside adduct.
1.8. Mechanistic considerations: 1,3–dipolar cycloaddition reaction

Huisgen and coworkers have systematically studied the mechanism of 1,3 dipolar cycloadditions. The most of 1,3-cycloadditions, the reaction rate is not markedly influenced by the dielectric constant of the solvent medium in which the reaction is conducted. The independence of solvent polarity, the very negative entropies of activation and stereo specificity and regio specificity point of a highly ordered transition state. In most of 1,3-DP reactions, when two isomers are possible as a result of the use of unsymmetrical reagents, one isomer usually predominates, often to the exclusion of the other. The principal question that arises when considering the regio specificity of the 1,3-dipolar additions is whether the two new σ-bonds formed on addition of the 1,3 dipole to the dipolarophile are formed simultaneously or one after the other. The mechanism that has emerged from Huisgen’s group is that of a single step, four center, ‘no mechanism’ cycloaddition, in which the two new bonds are both partially formed in the transition state, although not necessarily to the same extent. A symmetry energy correlation diagram reveals that such a thermal cycloaddition reaction is an allowed process. A proposed alternative mechanism is a two step process involving a spin-paired diradical intermediate.
On the basis of an extraordinary series of investigation, which led to a monumental collection of data Huisgen et al., developed a detailed rationale for a concerted mechanism for the 1,3-dipolar cycloaddition reaction (Scheme 1.2, eq 1). Firestone considered the 1,3-DC reaction to proceed via singlet diradical intermediate (Scheme 1.2, eq 2). Both sides in the debate based their arguments on a series of experimental facts. On the basis of the stereo specificity of the 1,3-DC reaction, the dispute was settled in favour of the concerted mechanism. The 1,3 DC reaction of benzonitrile oxide with trans-diduterated ethylene gave exclusively the trans-isoxazoline (Scheme 1.2, eq 3). A diradical intermediate would allow for a 180° rotation of the terminal bond and would thus be expected to yield a mixture of the cis and trans isomers. Huisgen et al. have later shown that the 1,3-Dc reaction can take place by a stepwise reaction involving an intermediate and in these cases the stereo specificity of the reaction may be destroyed.

**Stepwise Mechanism**

The stereo specificity observed in many 1,3-dipolar cycloaddition is often considered to be compelling, if not conclusive, evidence for the concert in these reactions. However, if the rate constant for rotation (k_r) about bond ‘a’ in a diradical intermediate, was much smaller than the rate constant for cyclisation (k_c), high stereo specificity would still be
observed **Scheme 1.3**. The reported examples of stereo specific 1,3-dipolar cycloaddition involved di-, tri-, or tetra- substituted alkenes. Barriers to rotation of simple primary, secondary and tertiary alkyl radicals are only 0-1.2 Kcal mol\(^{-1}\) (1 Kcal = 4.18 kJ)\(^{51}\) but more highly substituted radicals have barriers to rotation estimated to be as high as 4 kcal mol\(^{-1}\)\(^{52}\). The rate ratio of rotation to ring closure is highly dependant on the degrees of the substitution at the terminal-labelled methylene rotor offers the highest chance to bring about an intermediate in the cycloaddition reaction. This was the reason why Houk and Firestone studied the 1,3-dipolar cycloadditions of 4-nitrobenzonitrile oxide to cis- and trans-dideuterioethylene (**Scheme 1.3**: R=D)\(^{53}\). These experiments establish that the reaction is >98% stereo specific. If a diradical intermediate were formed, the barrier to rotation barrier about bond ‘a’ would have to be at least, 2.3 kcal mol\(^{-1}\) higher than the barrier to cyclisation. Since the rotational barrier of bond ‘a’ is that expected for a normal primary radical (i.e <0.4 kcal mol\(^{-1}\)), there can be no barrier to cyclization. Thus, the most reasonable mechanism for 1,3-dipolar cycloadditions appears to be a concerted one.

An Orbital Symmetry Analysis

**Frontier molecular orbital (FMO) Method:** The transition state of concerted 1,3-DC reaction is thus controlled by the frontier molecular orbitals (FMO) of the substrates. The LUMO\(_{dipole}\) can interact with the HOMO\(_{alkene}\) and HOMO\(_{dipole}\) can interact with the LUMO\(_{alkene}\). Sustman has classified 1,3-DC reactions into three types, on the basis of the
relative FMO energies between the dipole and the alkene (Figure 1.4)\textsuperscript{46,54,57}

In \textbf{Type I}, 1,3-DC reactions the dominant FMO interaction is that of the HOMO\textsubscript{dipole} with the LUMO\textsubscript{alkene} as outlined in \textbf{Figure 1.4}. For \textbf{Type II} 1,3-DC reactions the similarity of the dipole and alkene FMO energies implies that both HOMO-LUMO interactions are important. 1,3-DC reactions of \textbf{Type III} are the dominated by the interaction between the LUMO\textsubscript{dipole} and the HOMO\textsubscript{alkene}.

1,3-DC reactions of \textbf{Type I} are typical for substrates such as azomethine ylides and azomethine imines, while reactions of nitrones are normally classified as \textbf{Type II}. 1,3-DC reactions of nitrile oxides are also classified as \textbf{Type II}, but they are better classified as borderline to \textbf{Type III}, since nitrile oxides have relatively low lying HOMO energies. Examples of \textbf{Type III} interactions are 1,3-DC reactions of ozone and nitrous oxides. However, introduction of the electron donating or electron withdrawing substituent on the dipole or the alkene can alter the relative FMO energies, and therefore the reaction type dramatically.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1_4}
\caption{The Classification of 1,3-DC reactions on the basis of the FMOs:
\textbf{Type I}: a HOMO\textsubscript{dipole}-LUMO\textsubscript{alkene} interaction
\textbf{Type II}: interaction of both HOMO\textsubscript{dipole} and LUMO\textsubscript{alkene}
\textbf{Type III}: a LUMO\textsubscript{dipole}-HOMO\textsubscript{alkene} interaction}
\end{figure}

\textbf{Endo and Exo-approach}: Depending on the nature of the dipole and dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a LUMO (dipolarophile)-HOMO (dipole)- or a LUMO (dipole)-HOMO (dipolarophile) interaction but in some cases a combination of both interactions is involved. An example of a LUMO (dipolarophile)-HOMO
(dipole) controlled reaction is depicted in **Scheme 1.4**. The approach of the dipole (eg. 1, **Scheme 1.4**) to the dipolarophile (eg. 2, **Scheme 1.4**) can occur in an *endo* or *exo* mode resulting in two diastereomeric *endo/exo* cycloadducts, *endo*-3 and *exo*-3 respectively. An overview over both these approach is stabilized by small secondary π-orbital interactions, contributing to the *endo/exo* selectivity of the reaction. However, other factors such as steric ones can have a major influence on this *endo/exo* selectivity and can often override this stabilizing effect.

**Scheme 1.4**. Example of an *endo* and an *exo* approach of a LUMO(dipolarophile)-HOMO (dipole) controlled reaction. Primary orbital interactions are indicated with double headed arrows and secondary orbitals interactions with dotted lines.
1.9. Scope of the present work

The 1,3-dipolar cycloaddition reactions of nitrones, nitrile oxide with olefins is highly useful reaction for the construction of five membered heterocyclic ring. It is attractive to apply this reaction for the synthesis of biologically interesting isoxazoli(di)nes since these compounds have drawn attention for their potential synthetic applications. Currently, there is an immediate need to address the following problems for the successful treatment of inflammation and fungal infection disease.

1. Development of effective and less toxic new molecules for the treatment of fungal infection as well as inflammation.
2. Understanding the mechanism of action on various enzymes as well as in microbes.

In the direction of finding suitable solution to the above problems, the candidate has synthesized biologically significant isoxazolidine, isoxazoline derivatives of imdazolyl, trimethoxyphenyl, and tricyclic azepines and studied the regio and stereochemistry using $^1$H, $^{13}$C, 2D NMR experiment. The synthesized isoxazoline derivatives were subjected to antifungal evaluation, phospholypase inhibition study. It is found that some novel isoxazolidines shown to be more effective antifungal and PLA$_2$ inhibition agents than standard drugs used in the experiment.
1.10 References

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