CHAPTER – I

Introduction

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CHAPTER – I

PART I: CHEMISTRY OF 1,3-DIPOLAR CYCLOADDITION

1.1.0 Introduction:

Most of the organic reactions occur in several steps, the reaction mechanism involve, either intermediates or polar transition states or free radicals. But there are some reactions that give no evidence of involving intermediates when they are subjected to usual probes for studying the mechanisms. The lack of evidence for the existence of intermediates leads to the conclusion that, the reactions follow concerted mechanisms. An important class of concerted reactions is pericyclic reactions; the present understanding of the mechanism of pericyclic reactions is mainly due to the ingenious work of Woodward and Hoffman. Accordingly, the pathways of such reactions were determined by the symmetry properties of the orbitals, that are directly involved and that the symmetry of the each participating orbital must be conserved during the concerted process.¹

1.1.1 Cycloaddition reactions:

Cycloaddition reaction is proved to be a powerful tool in the construction of cyclic systems. Cycloaddition is a pericyclic reaction in which two or more unsaturated molecules or parts of the same molecule combine to form a cyclic adduct in which there is a net reduction of the bond multiplicity. The resulting reaction is a cyclization reaction. Many but not all cycloadditions are concerted. The most familiar of these cycloadditions are Diels-Alder reaction \([4\pi + 2\pi]\); extensively used in the stereospecific construction of 6-membered ring systems and 1,3-dipolar cycloaddition \([3 + 2]\); used in the construction of 5-membered ring systems.
1.1.2 Diel's-Alder reaction:

The Diel's-Alder reaction is the addition of a conjugated diene to an alkene, usually called as dienophile, to give a six membered ring system. This reaction is classified as \([4 + 2]\) cycloaddition reaction because diene component provides four atoms and dienophile provides two atoms to form a six membered adduct. In the terminology of orbital symmetry classification, the Diel's-Alder reaction is a \([\pi_4^s + \pi_2^s]\) cycloaddition, because this classification considers:

i) Number of electrons in each participating unit

ii) Nature of orbitals undergoing change, \(\pi\) or \(\sigma\)

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

1.1.3 1,3-Dipolar cycloaddition reactions:

1,3-Dipolar cycloadditions offer a very useful method for the preparation of five-membered ring heterocycles. The concept of 1,3-dipolar cycloadditions was initially suggested by Smith in 1938, but it was only after the generalization of the reaction by Huisgen in the 1960’s that the reaction became widely applicable. The concept of 1,3-dipolar cycloaddition reactions now known as Huisgen cycloaddition reactions was the monumental work by Huisgen and his Co-workers. Here, a five membered ring is formed by the cycloaddition of 1,3-dipole molecule (a three atom entity; \(a-b-c\)) and dipolarophile (a two atom entity; \(d-e\)) (Scheme-1).
In all 1,3-dipoles, there are four electrons in three parallel $\pi$-orbitals and are both nucleophilic and electrophilic in nature. This ambivalence of the 1,3-dipole is of key importance in understanding its reactivity. The nucleophilic character of the 1,3-dipole may be stronger than its electrophilic quality. Compounds such as nitrile ylides or diazomethane will cycloadd to electron deficient dipolarophiles much faster than with electron rich multiple bonds. The opposite is true for ozone, which combines preferably with electron rich dipolarophiles.

The 1,3-dipoles can be basically divided into two different types: the allyl anion type such as nitrones, azomethine ylides, nitro compounds, bearing a nitrogen atom in the middle of the dipole, carbonyl ylides or carbonyl imines, bearing an oxygen atom in the middle of the dipole and the linear propargyl/allenyl anion type such as nitrile oxides, nitrile imines, nitrile ylides, diazoalkanes or azides. Some typical 1,3-dipolar species are shown in Table-1.
The dipolarophile can be virtually any double or triple bonded species. The more common are alkenes, alkynes, carbonyls and nitriles. Other multiple bonded functional groups such as imines, azo and nitroso can also act as dipolarophiles.

1.1.4 Mechanistic considerations of 1,3-dipolar cycloaddition reactions:

2 \pi\text{-electrons of the dipolarophile and 4 electrons of the dipolar compound participate in a concerted, pericyclic shift. The addition is stereo conservative (suprafacial) and the reaction is therefore a } [2_1 + 4_s] \text{ cycloaddition (Scheme-2) and is similar to the Diels-Alder reaction.}

Based on kinetic measurements, stereochemical results, solvent effects and substituent effects; the mechanism for the 1,3-dipolar cycloaddition was elegantly demonstrated by Huisgen et al. In most of 1,3-dipolar cycloaddition, the reaction rate is not markedly influenced by the dielectric constant of the solvent. The independence
of the solvent polarity; the very negative entropy of activation; the stereo specificity and all regiospecificity point to a highly ordered transition state. However, this mechanism was passionately disputed for years between Huisgen and Firestone. Firestone favored the formation of a diradical intermediate in a two step mechanism.

The experimental efforts of several groups involved in this dispute lent support to the concerted mechanism based on the stereo specificity of the reaction. However, the general agreement that, the reaction is a [3 + 2] cycloaddition reaction and in terms of orbital symmetry classification, it is classified as a $\pi^4 + \pi^2$ cycloaddition reaction analogous to that of Diel's-Alder reaction (Scheme-3).

Criteria for the mechanism of 1,3-dipolar cycloaddition are provided by the stereoselectivity observed with cis-trans isomeric dipolarophiles; by the effect of solvent and substituents on the rate constants, activation parameters and orientation phenomena. A concerted addition, which can also be described in terms of molecular orbitals and in which the two new $\sigma$-bonds are formed simultaneously, although not necessarily at equal rates, offers the best explanation of the experimental facts. An appreciation of the stereo specificity of these cycloadditions can be illustrated through the use of FMO theory as well as experimental outcomes.

The most of 1,3-dipolar cycloaddition would proceed through a concerted reaction mechanism. Similar to the Diels-Alder reaction, this results in a stereospecific syn addition of the 1,3-dipole to the dipolarophile. By making the dipole electron deficient and the dipolarophile electron rich (or vice versa) the bond formation in the concerted reaction will become asynchronous. When this is taken to
the extreme, the bond formation becomes so asynchronous that a zwitter ionic intermediate is formed and non-stereospecific 1,3-dipolar cycloaddition occurs.

**1.1.5 Stereochemistry of Huisgen cycloaddition reactions:**

Huisgen reported the first non-stereospecific two-step 1,3-dipolar cycloadditions, along with mechanistic and FMO rationalization. He found that by creating a large difference in electron demand between an electron-rich thiocarbonyl ylide dipole and electron-poor dicyano-substituted dipolarophile. He created a reaction that scrambled stereochemistry in the products; the $E$-alkene dipolarophile gave rise to both cis and trans products (Scheme-4).\(^{11}\)

![Scheme-4](image1)

The stereochemistry of 1,3-dipolar cycloaddition reaction is a stereospecific syn addition with respect to dienophile. For example, addition of cis and trans stilbenes to diphenyl nitrile imine gives tetraphenyl pyrazines (Scheme-5).\(^{12}\)

![Scheme-5](image2)

The regioselectivity can be interpreted in terms of interaction between the FMO of 1,3-dipole and dienophile. Usually, for dipolarophiles with electron-attracting groups; the dipole-HOMO and dipolarophile-LUMO interaction is dominant. The reverse is true for dipolarophiles with electron-donating groups. However, there are HOMO-LUMO interactions of comparable magnitude. According to the principle of maximum overlap, the preferred isomers of each interaction can be predicted by union of two sites of the reactants having the largest coefficient value.
The regioselectivity of the reaction depends on electronic and steric effects. For instance, the addition of alkynes to azides, which is an interesting reaction for the generation of 1,2,3-triazole libraries by the simple reaction of two molecules leads to regioisomers (Scheme-6).\(^ {13} \)

The lack of stereospecificity in some cases leads to the consideration of a non-concerted mechanism. In order to decide if the reaction is really non-concerted, other possible reasons for the apparent non-stereospecificity must first be ruled out. For instance, in the case of enamines, the reactions were carried out with the \((E)\)-isomer and under reaction conditions; no \((Z)\)-isomers were observed. Therefore, it is believed that the stereochemical integrity of the reactants was maintained under the reaction conditions. If cycloreversion was occurring then the more thermodynamically stable isomer would be allowed to form. Finally, a trapping experiment was performed using the highly reactive dipolarophile cyclooctyne, the results revealed that no cycloaddition products were found between the product and the newly introduced dipolarophile. These findings were consistent with the idea that no cycloreversion followed by recyclization was happening. Therefore it was concluded that stereochemical leakage was not occurring prior to or after the cyclization reaction.

Asymmetric cycloaddition reactions between nitrile oxides and 3-(2-alkenoyl)-2-oxazolidinones and 2-(2-alkenoyl)-3-pyrazolidonone derivatives carried out in the presence of binaphthylidiimine (BINIM)-Ni(II) complexes as catalysts. Using \((R)\)-BINIM-4-(3,5-xylyl)-2QN-Ni(II) complex (30mol%), good regioselectivity (4-Me/5-Me=85:15) along with high enatioselectivity (96% \(ee\)) of the 4-Me adduct
were obtained for the reaction between isolable 2,4,6-trimethylbenzonitrile oxide and 3-crotonoyl-5,5-dimethyl-2-oxazolidinone (Scheme-7).

1.1.6 FMO symmetry analysis of 1,3-dipolar cycloaddition reaction:

The synchronicity and regioselectivity of 1,3-dipolar cycloaddition reactions are rationalized through FMO theory. Generally, the orbital coefficients of HOMO-LUMO interaction will determine the regioselectivity. The atoms with the largest coefficients on the HOMO and on the LUMO will combine with each other preferentially and determine the regioselectivity. The concerted reaction results from the overlap of orbitals of one molecule (dipolar) with the orbitals of the other (dipolarophile). Similar to electrocyclic reactions, here also each HOMO has to overlap with an empty orbital. Therefore, a HOMO picks up the most stable of the empty orbitals LUMO. In the transition state; stabilization chiefly comes from the overlap between the HOMO of one reactant (dipole or dipolarophile) with the LUMO of the other (dipolarophile or dipole) in bonding fashion. FMO orbital diagram of dipole and dipolarophile is depicted in Figure-1.

![FMO diagram of dipole and dipolarophile](image-url)
The LUMO (dipole) - HOMO (dipolarophile) interaction is depicted in Figure-2.

![Fig-2: The LUMO (dipole)-HOMO (dipolarophile) interaction](image)

The HOMO (dipole) - LUMO (dipolarophile) interaction is depicted in Figure-3.

![Fig-3: The HOMO (dipole)-LUMO (dipolarophile) interaction](image)

Thus, 1,3-dipolar cycloaddition is a thermally allowed reaction.

In the cases, where the FMO energies of the dipole and the dipolarophile are very similar, a combination of both modes of interactions can occur and are referred to as either \textit{exo} or \textit{endo}, where the \textit{endo} transition state is stabilized by small secondary π-orbital interactions or via an \textit{exo}-transition state lacking such stabilization. However, steric effects can also be important factors for the \textit{endo}/\textit{exo} selectivity. Depending on the substitution pattern in the reacting partners, the process gives rise to either the \textit{endo}- or \textit{exo}-cycloadducts.

1,3-Dipolar cycloaddition reactions are photochemically forbidden. For photochemical process; HOMO in excited state of one reactant (dipole/dipolarophile) and LUMO in ground state of another (dipolarophile/dipole) has to be considered.

HOMO of excited state of 1,3-dipole is $\psi_3$ and LUMO of ground state of dipolarophile is $\pi^*$. 
HOMO of excited dipolarophile is $\pi^*$ and LUMO of ground state of 1,3-dipole is $\psi_3$.

Here, there is an antibonding situation on one side, hence no product is formed. Therefore, $[\pi^4_s + \pi^2_s]$ photochemical reaction is forbidden.

1.1.7 Applications of Huisgen cycloaddition reactions:

The simple, easy accessible and work up procedure involved in 1,3-dipolar cycloaddition reactions; makes it a useful tool for the synthesis of pharmacologically important five membered heterocycles, particularly with respect to the approach toward asymmetric synthesis is of major importance in both the pharmaceutical and agricultural industries. For instance; fused ring heterocycles were synthesized via the rhodium catalyzed isomerisation/regio and stereoselective 1,3-dipolar cycloaddition cascades in good yields (Scheme-8).\(^{16}\)

The thermal multicomponent 1,3-dipolar cycloaddition of diethyl amino malonate or $\alpha$-amino esters with ethyl glyoxylate and dipolarophile such as maleimides, methyl acrylate, methyl fumarate, $\mathit{(E)}$-1, 2-bis(phenylsulfonyl)ethylene, and electron deficient alkynes allows the diastereoselective synthesis of
polysubstituted pyrrolidine derivatives. Microwave-assisted processes give better results affording endo-cycloadducts as major stereo isomers (Scheme-9). In general, 2,5-cis-cycloadducts are preferentially formed, but in the 1,3-dipolar cycloaddition of the disulfone with phenylglycine and ethyl glyoxylate the corresponding exo-trans-cycloadduct was isolated.\(^\text{17}\)

![Scheme-9]

Sydnones are masked 1,3-dipoles that by photolysis give nitrile imine intermediates and in thermal reactions react as cyclic azomethine imines. In the presence of acetylenic dipolarophiles, sydnones undergo 1,3-dipolar cycloaddition reactions, which can be induced thermally or photochemically giving different pyrazole derivatives (Scheme-10).\(^\text{18}\)

![Scheme-10]

Nitrile imines are a linear-type 1,3-dipoles and extensively used as versatile reactive intermediates in 1,3-dipolar cycloaddition reactions for constructing biologically potent five membered heterocycles such as pyrazolines and pyrazoles.\(^\text{19}\) For example, Broggini et al reported an effective synthesis of enantiopure pyrazolo [1,5-\(a\)]-pyrrolo [2,1-\(c\)][1,4]benzodiazepines, by a diastereoselective intramolecular 1,3-dipolar cycloaddition of nitrile imines. The exclusive formation of the trans diastereoisomers was due to the bulky and rather rigid pyrrolidine moiety worked against the intramolecular approach of the dipole to the \(re\) face of the ethylenic bond.\(^\text{20}\)
The one-step synthesis of bis[1,2,4-triazolo][4,3-a:3',4'-d][1,5]benzodiazepines by way of completely regio- and diastereoselective 1,3-dipolar cycloaddition of nitrilimines to 2,4-dimethyl-3H-1,5-benzodiazepines is reported to be a tentative rationalization for the observed diastereoselectivity.\textsuperscript{21}

A bisphosphoric acid-catalyzed 1,3-dipolar cycloaddition of buta-2,3-dienoates with azomethine ylides yields 3-methylenepyrrrolidine derivatives with excellent enatioselectivity up to 97% ee (Scheme-11).\textsuperscript{22}

![Scheme-11](image)

Solid-phase methods are of a great significance in organic synthesis. Recent developments of these methods are providing new ways to construct libraries of small organic molecules. Five-membered heterocyclic compounds are formed in the 1,3-dipolar cycloaddition reaction between dipolarophiles and dipoles on solid polymer support.\textsuperscript{23} The 1,3-dipolar cycloaddition reaction of nitrones with dipolarophiles has received considerable attention in asymmetric synthesis. Regio- and stereoselective nitrone cycloaddition followed by reduction of the N-O bond to produce both an amino and a hydroxyl function. One of the reasons for the success of the synthetic applications of nitrones is that, most nitrones are stable compounds that do not require an \textit{in situ} formation.\textsuperscript{24}

Varieties of Lewis acids have provided excellent results in the stereoselective metal-catalyzed 1,3-dipolar cycloaddition of azomethine ylides. However, among them, the Ag(I)-based processes stand out as the most used. For example, the 1,3-dipolar cycloaddition of 4-oxoazetidine-2-carbaldehyde-derived azomethine ylides with a variety of dipolarophiles in the presence of AgOAc/Et3N, affording the
corresponding chiral pyrrolidinyl-β-lactams with reasonable diastereoselectivities and moderate to good yields. The AgOAc-catalyzed 1,3-dipolar cycloaddition of azomethine ylides to vinyl sulfoxides evolved with complete regio- and endo-selectivities. The stereoselectivity could, however, be controlled by using THF or MeCN as solvents. The method was applied in the synthesis of highly substituted pyrrolidines.

(S)-QUINAP was successfully used as effective catalyst in the 1,3-dipolar cycloaddition of azomethine ylides derived from α-iminoesters with various α,β-unsaturated esters, giving excellent levels of diastereoselectivity (>90% de) and enatioselectivity (96% ee) (Scheme-12).

Nitrile oxides are reactive, relatively unstable, linear molecules, which may be generated from nitro compounds, hydroxymoyl halides and aldoximes by treatment with various reagents. It is important to note that nitrile oxides are prone to dimerization or polymerization, especially upon heating and hence are usually generated in situ. Nitrile oxides were considered as useful intermediates in 1,3-dipolar cycloaddition reactions leading to the formation of five membered heterocycles such as isoxazole and oxadiazole derivatives.

Intramolecular 1,3-dipolar cycloaddition of 2-phenoxy benzonitrile N-oxides to benzene rings, accompanied by de-aromatization, formed the corresponding isoxazolines in high yields (Scheme-13). The substituents on the benzene ring markedly affected the reaction rate, yield and structure of the final product.
In contrast to the cyclic dipoles, acyclic dipoles can undergo Z/E isomerisation around a double bond, this makes it difficult to realize a direct correlation between the product distribution and the E/Z isomer equilibrium distribution of the starting dipole, since one of the Z/E isomers can react faster under kinetic control. Various acyclic chiral nitrones have recently been involved in 1,3-dipolar cycloaddition reactions. For example, highly functionalized chiral β-lactams are obtained by regio- and stereoselective 1,3-dipolar cycloaddition reactions of optically active 2-azetidinone-tethered nitrones with electron-deficient alkenes such as dimethyl fumarate, dimethyl maleate (Scheme-14).33

Goti et al demonstrated the great potential of cycloaddition reactions applied to C-phenyl-N-glycosynitrone. Indeed, N-glycosynitrone underwent highly stereoselective 1,3-dipolar cycloaddition with dimethyl maleate, providing the corresponding 3,4,5-trisubstituted isoxazolidines (Scheme-15).34

When alpha-azido propargyl esters were subjected to [3 + 2] cycloaddition in MeCN/H₂O under microwave dielectric heating, the expected 4H-[1,2,3]triazolo[5,1-
c][1,4]oxazin-6-ones are not formed; rather, an oligomeric cyclic polyester is obtained via prevailing intermolecular cycloaddition. The reaction provides access to new condensed triazoles that can be considered as conformationally constrained peptidomimetics. Moreover, the following microwave-assisted lactam ring opening provides 1,4-disubstituted and 1,4,5-trisubstituted triazole amino acids (Scheme-16).\(^{35}\)

![Scheme-16](image)

1,3-dipolar cycloaddition afforded fast access to isoxazolidines bearing \(N\)-alkyl or \(N\)-benzyl substituents. The electronic effects of the substituents in the nitrones define the activity of the dipoles and modulate diastereoselectivity in the non-catalyzed reactions. Using a chiral one-point binding ruthenium Lewis acid catalyst, products were obtained in good yields and with excellent regio-, diastereo- and enatoselectivity (Scheme-17).\(^{36}\)

![Scheme-17](image)

Inter- or intra-molecular \(N\)-alkylation of oximes or their alkali metal salts furnishes nitrones; which can be trapped by activated and non-activated dipolarophiles in inter- and intra-molecular cycloaddition reactions in good yield.\(^{37}\)

A first example of organo-\(N\)-heterocyclic carbene catalyzed click-type fast 1,3-dipolar cycloaddition of nitrile oxides with alkynes was developed for the regioselective synthesis of 3,5-di- and 3,4,5-trisubstituted isoxazoles.
Triethylamine was employed as an effective base to generate both nitrile oxide and the organo-N-heterocyclic carbene catalyst in situ. This catalytic approach was used to attach a variety of substituents onto the isoxazole ring to selectively design multi-nucleus structures. A catalytic cycle is proposed and the remarkable regiocontrol in the formation of isoxazoles was ascribed to a beneficial zwitter ion intermediate developed by the interaction of the strongly nucleophilic organo-N-heterocyclic carbene catalyst with alkyne followed by nitrile oxide (Scheme-18).\(^{38}\)

![Scheme-18]

Sharpless and co-workers introduced a new approach in organic synthesis click chemistry that involves a handful of almost perfect chemical reactions. Huisgen 1,3-dipolar cycloaddition was shown to be the most effective and versatile and thus became the prime example of click chemistry. Hence, these long-neglected reactions were suddenly re-established in organic synthesis.\(^ {39}\) For instance, A highly endo-selective asymmetric 1,3-dipolar cycloaddition reaction of methyl \(N\)-benzylidene glycinate as source of azomethine ylides with (\(E\))-acyclic \(\alpha\)-enones is catalyzed by a silver(I)/ThioClickFerrophos complex to give highly functionalized endo-4-acyl pyrrolidines in good yields with high enatioselectivity (Scheme-19).\(^ {40}\)

![Scheme-19]

A polymer supported catalyst for Huisgen’s [3 + 2] cycloaddition reaction between azides and alkynes was prepared from copper(I) iodide and Amberlyst A-21.
This catalyst was used in an automated synthesis of 1,4-disubstituted 1,2,3-triazoles giving access to these products in good yields. The intramolecular alkyne-azide Huisgen [3 + 2] cycloaddition reaction as a click-reaction without a metal catalyst has been studied under aerobic conditions. The synthesis of various pyrrolidine–triazole hybrid compounds has also been achieved in water with complete 1,5-regioselectivity. A copper(I)/ClickFerrophos complex catalyzed the asymmetric 1,3-dipolar cycloaddition of methyl N-benzylideneglycinates with electron deficient alkenes to give exo-2,4,5-trisubstituted and 2,3,4,5-substituted pyrrolidines with high diastereo- and enantioselectivities.
PART II: CHEMISTRY OF NITRILE OXIDES

1.2.0 Introduction:

Nitrile oxides, R-C≡N^+O^-, are organic compounds which contain a monovalent functional group -CNO, which bound directly to a carbon atom of the organic moiety of a molecule. Most nitrile oxides are highly reactive and in the absence of trapping agents they undergo rapid dipolar cycloaddition with themselves to give furoxans (2) (Scheme-20).

The dimerization is faster in the case of lower aliphatic nitrile oxides than in the case of aromatic nitrile oxides. Steric bulk increases the stability of nitrile oxide. For example, tertiary butyl nitrile oxide is readily generated and examined in solutions, whereas mesityl nitrile oxide is a stable crystalline solid. Similarly, the presence of both electron donor and accepter substituent in aromatic nitrile oxides in the para position stabilize the nitrile oxide, whereas the electron withdrawing group at the ortho position makes the nitrile oxide unstable. Huisgen categorized the nitrile oxide as being member of a broader class of 1,3-dipoles that were capable of undergoing (3 + 2) cycloaddition reactions.

1.2.1 Generation of nitrile oxides:

All known methods for the synthesis of nitrile oxides start with organic system already containing -C-N-O sequence of the nitrile oxide structure. Many methods are reported to generate nitrile oxide. The usual synthetic methods of nitrile oxides involve the oxidative dehydrogenation of aldoximes, dehydration of primary nitro compounds and the dehydrohalogenation of hydroxyiminoyl halides.
An oxidative dehydrogenation methods of aldoximes (3) to nitrile oxides (1) (Scheme-21) using oxidants such as lead tetraacetate, alkali hypohalite, N-bromosuccinimide in dimethylformamide followed by base treatment, 1-chlorobenzotriazole are reported. Literature reveals that t-butyl hypoiodite (t-BuOI) was found to be a powerful reagent for the in situ generation of nitrile oxides under mild conditions. Rai et al used chloramine-T as an oxidant for generating nitrile oxide in situ from aldoximes in presence of a dipolarophile and were successful in getting isoxazoline in good yield. Moreya et al reported the in situ generation of nitrile oxides by the reaction of aldoximes with tertiary butyl hypochlorite and bis(tributyl tin) oxide. The reaction proceeded efficiently under mild condition in which o-stannylated aldoximes are thought to be the intermediate.

\[
\text{R-CH}═\text{N-OH} \xrightarrow{} \text{R-C≡N-O}^\ominus \quad \text{Scheme-21}
\]

Rai and Co-workers have successfully reported the in situ generation of nitrile oxides by the reaction of aldoximes with mercuric acetate as mild oxidising agent, while Kiegiel et al reported the use of Mn(IV) oxide (MnO₂) for the same reaction. Iodobenzene diacetate in MeOH containing a catalytic amount of TFA efficiently oxidizes aldoximes to nitrile oxides at room temperature. Treatment of aldoximes with magtrieve (CrO₂) in acetonitrile at 80°C generates nitrile oxides which were trapped in situ by the dipolarophile to furnish a variety of isoxazolines and isoxazoles as 1,3-dipolar cycloaddition products.

Hydroxyiminoyl halides (4) are second most commonly used precursors for the preparation of nitrile oxides (1) (Scheme-22). For instance, Tokunaga et al utilized silver acetate for the generation of nitrile oxide starting from hydroxyiminoyl
halides. The dehydrohalogenation of hydroxyiminoyl halides leads to the formation of nitrile oxides.

\[
\begin{align*}
\text{R-} & \quad \text{C=N=O} \quad \xrightarrow{x\ 4\ \text{X}} \quad \text{R-} & \quad \text{C=\text{N}^\oplus\text{O}}
\end{align*}
\]

Scheme-22

The primary nitroalkanes (5) are found to be next common starting material for the preparation of nitrile oxides (1) (Scheme-23). For instance, the dehydration of primary nitro compounds with aryl isocyanate leads to the formation of nitrile oxides. Di-tert-butyl bicarbonate [(BOC)\(_2\)O] in presence of 4-dimethyl amino pyridine (DMAP) was also used for an in situ generation of nitrile oxide from nitro alkanes.

\[
\begin{align*}
\text{R-CH}_2\text{NO}_2 & \quad \xrightarrow{5\ \text{O}} \quad \text{R-} & \quad \text{C=\text{N}^\oplus\text{O}}
\end{align*}
\]

Scheme-23

It was reported that flash vacuum pyrolysis of furoxans generates nitrile oxides (Scheme-24), which were trapped in situ with alkenes to yield 2-isoxazolines.

\[
\begin{align*}
\text{Flash vacuum pyrolysis} & \quad \xrightarrow{\text{N.O}} \quad \text{R-} & \quad \text{C=\text{N}^\oplus\text{O}}
\end{align*}
\]

Scheme-24

Nitrile oxides may be trapped in situ with olefins in a bimolecular or an intramolecular mode. Tandem oxidative dearomatization of phenols/intramolecular nitrile oxide cycloaddition sequences lead to useful synthetic intermediates. All the methods discussed above generate nitrile oxides in situ and in the presence of a dipolarophile. So far, only two isolable nitrile oxides are reported in the literature and the stability of these nitrile oxides is due to steric interaction. Rai et al methods not only allows in situ generation but also allows the isolation of nitrile oxides. By employing this method they have isolated and characterized the nitrile oxide, of which
some are liquids and some are solids. The unstable compound identified by NMR spectrometry slowly dimerizes on standing it alone or in presence of added vinyl sulfone, undergo cycloaddition to yield isoxazoline in good yield.\(^{62}\)

1.2.2 Reactions of nitrile oxides:

1,3-Dipolar cycloaddition of nitrile oxide to C=C bond of dipolarophile is of considerable importance in organic synthesis, since this reaction yields 2-isoxazolines. Isoxazole and isoxazolines act as versatile building blocks in the construction of new molecular systems for several reasons. First of all, they can be very efficiently prepared from readily available precursors; secondly, they can be conveniently modified, thus allowing transformation of molecule with simple structure to functionally complex derivatives; thirdly, a suitable pattern of substituents makes the isoxazoline ring survive under a variety of chemical reaction conditions, thus allowing manipulation in other parts of the molecule and finally the liability of the nitrogen-oxygen bond to catalytic or chemical reduction under mild conditions unravels a vast array of different functionalities.

Alkenes and alkynes serve as an excellent dipolarophiles. Cycloaddition of nitrile oxides to olefins yield isoxazolines while addition of nitrile oxides to alkyne yields isoxazole directly (Scheme-25).

If the dipolarophile posses more than one set of unsaturation as in an en-yne, addition to either (or both) site(s) may occur. Indeed with nitrile oxides as dipole and 1,3-en-yne as substrate, the chemoselectivity is very sensitive to the substitution pattern of the en-yne, either product (6) or (7) may predominate (Scheme-26).
Unlike the frequently unsel ective reaction of 1,3-en-yne with 1,3-dipole, nitrile oxides add chemo, regio and stereoselectively to the free double bond of (1,3-en-yne)Co(CO)$_6$ complexes to provide 5-alkenyl-2-oxazoline derivatives in moderate yield. The ability to add nitrile oxides is not restricted to C-C multiple bonds, they also add to C=O group to produce 1,3,4-dioxazoles. However C=O is less reactive as a dipolarophile and is clearly shown by the reaction of BNO with $p$-benzoquinone.

Though C=S group is not a good dipolarophile in Diel's-Alder reaction, but is a very reactive dipolarophile in 1,3-dipolar cycloadition of nitrile oxides. For instance; Cycloaddition of nitrile oxides to C=S group yields 1,2,4-oxathiazolines. Similarly, nitrile oxide addition to C=N is known to yield 1,2,4-oxadiazoline, however it is comparatively less reactive as a dipolarophile than C=S. The C-N group normally does not undergo 1,3-dipolar cycloaddition reaction because of its poorer dipolarophile nature compared to C=C group. Thus, in the case of acrylonitrile, nitrile oxide reacts with alkene to form cyano substituted 2-isoxazoline. However, if the C=C bond is deactivated by multiple substitution, the C-N group may become a better dipolarophile. Thus, tetracyano ethylene adds nitrile oxide yielding 1,2,4-oxadiazole derivative as one of the product. All these reactions were summarized (Scheme-27).
Nitrile oxides generated \textit{in situ} by the oxidative dehydrogenation of aldoximes with chloramine-T reacted with an $\alpha,\beta$-unsaturated compounds to afford ethyl 3,5-diarylisoazole-4-carboxylates (10) which exhibited remarkable antimicrobial activity. In a typical reaction an equimolar mixture of aldoxime, $\alpha,\beta$-unsaturated esters (8) and chloramine-T trihydrate in ethanol was refluxed on a water bath for 3h. After the completion of the reaction, the products (10) were obtained in good yield. Here, the usual expected cycloadducts (9) underwent elimination reaction to give of HCN under reaction conditions to give the more stable products (10) (\textbf{Scheme-28}).

Rai and co-worker\textsuperscript{66} reported the synthesis of series of trisubstituted 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition reactions. They carried out a cycloaddition reaction of imines and nitrile oxides generated \textit{in situ} by the catalytic dehydrogenation of aromatic aldoximes using chloramine-T reagent and obtained the cycloadducts in good yield. The cycloadducts have been tested for their antifungal and antibacterial activity, results of their study revealed that all the cycloadducts exhibited a promising activity (\textbf{Scheme-29}).
The unusual formal [3 + 3] cycloaddition of nitrile oxide with vinyl carbene (11) derived by the ring opening of the cyclopropane yield 1,2-oxazines (12) in moderate to good yield but it is not clear whether 1,2-oxazine is directly formed by concerted cycloaddition or by a stepwise process (Scheme-30).²⁷

1.2.3 Application of nitrile oxide cycloaddition reactions:

1,3-Dipolar cycloaddition of nitrile oxide to different dipolarophiles has been extensively used as a powerful tool in the synthesis of five membered heterocycles. For instance; Rai et al.⁶⁸ used intramolecular 1,3-dipolar cycloaddition reaction for synthesizing functionalized pyrrolidine, piperidine, hydroazepine, hydroazocine and tricyclic quinolinoisoxazoline starting from corresponding nitro alkenes. The starting nitro alkenes were prepared by the alkylation of N-tosyl allylamine with dibromoalkane followed by treating with silver nitrite. In situ transformation of (13) into a nitrile oxide was carried out by means of phenyl isocyanate and led to spontaneous cycloaddition with the formation of isoxazolines (14) fused to 5, 6 and 7 membered heterocycles. Under very high dilution, (13) formed an isoxazoline (14) fused to 8-membered azocaines in 10 % yield (Scheme-31).
Using the same procedure, tricyclic quinolinoisoaxazoline was formed on intramolecular cycloaddition of starting amino cyclohexene derivative (Scheme-32).\textsuperscript{68}

![Scheme-32](image)

Later they were succeeded in getting functionalized tetrahydrofuran and tetrahydropyran by the intramolecular nitrile oxide cycloaddition of 2-allyloxy aldoxime formed by the reduction of $\beta$-nitrostyrene with SnCl$_2$-2H$_2$O in the presence of an unsaturated alcohol (Scheme-33).\textsuperscript{69}

![Scheme-33](image)

An aryl substrate with dual functionality consisting of a nitrile oxide and a pinacolyl boronate ester was prepared by mild hypervalent iodine oxidation (diacetoxy iodosobenzene) of the corresponding aldoxime, without decomposition of the boronate functionality. The nitrile oxide was trapped \textit{in situ} with a variety of dipolarophiles to yield aryl isoxazolines with the boronate ester function intact and available for subsequent reaction.\textsuperscript{70}

Ajay kumar \textit{et al}\textsuperscript{71} reported the synthesis of a series of thirteen cycloadducts 3-aryl-5N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7,8-dihydroisooxazolines(15) by the reaction of \textit{in situ} generated nitrile oxides obtained from the catalytic dehydrogenation of aldoximes with chloramine-T on N-aryl maleimides (Scheme-34). Later they demonstrated the use of nitrile oxide as a dipolarophile in 1,3-dipolar cycloaddition with acetyl acetone and obtained the substituted isoxazolines (16) in good yield. Here the nitrile oxide gets added to enolic double bond of acetyl acetone (Scheme-34).\textsuperscript{72}
Alkylidene pyrrolidines undergo reactions with nitrile oxides generated in situ from hydroxymoyl chlorides and nitrile imines to give a range of novel heterocyclic compounds. With hydroxymoyl chlorides give isoxazoles, presumably by cycloaddition/elimination. A series of 3-aryl-5-(4-methoxyphenyl)-isoxazole-4-carbonitriles have been synthesized by the in situ generated nitrile oxides obtained by the catalytic oxidation of aldoximes with chloramine-T in alcohol and 3-(4-methoxyphenyl)propiononitrite in moderate yield. The products tested for their antibacterial and antifungal activity against different organism.

1.2.4 Synthesis of natural products via cycloaddition of nitrile oxides:

The application of intramolecular nitrile oxide cycloaddition reaction to the synthesis of complex natural products has recognized as powerful synthetic tool, one equally akin to the intramolecular Diel's-Alder reaction in its potential scope of application. This is particularly the case with nitrile oxide and the intramolecular nitrile oxide cycloaddition reaction has been extensively utilized in total synthesis. The intramolecular nitrile oxide cycloaddition reaction generally displays exceptional regio- and stereochemical control, which undoubtedly accounts for the popularity of this reaction. Internal cycloaddition of nitrile oxides has been found to offer a powerful solution to many problems in complex natural product synthesis.
Confalone and coworkers have utilized the intramolecular nitrile oxide cycloaddition reaction for the stereospecific synthesis of the key amino alcohol, which was converted to (±) biotin through several steps (Scheme-35). $^{75}$

![Scheme-35](image)

Mukayama *et al.*$^{58}$ synthesized chanoclavine (17), a member of ergot alkaloids via intramolecular nitrile oxide-olefin cycloaddition. The key step for the synthesis of hexahydropyridazine portion of the hypocholesterolemic agent, compactin (18)$^{76}$ antibiotic vermiculene (19),$^{77}$ the spirocyclic alkaloid sibirine (20),$^{78}$ lignans such as Burseren, Brassilignan, Dehydroxycubebin$^{79}$ and the prostaglandin$^{80}$ involves the intramolecular nitrile oxide cycloaddition reaction of the corresponding cycloalkenyl oximes.

![Molecules](image)

Stereoselective 1,3-dipolar addition of bromonitrile oxide S (+)-isopropylidene-3-butene-1,2-diol represent the key step in the preparation of potent muscarinic receptor.$^{81}$ A new approach to the synthesis of the aglycon portion (21) of calicheamicin, an anticancer antibiotic possessing phenomenal anticancer properties is based upon an intramolecular alkenyl nitrile oxide dipolar cycloaddition reaction which leads directly to the incorporation of the full functionality of the aglycon.$^{82}$ The same strategy was utilized for the stereoselective synthesis of the ptilocaulein (22), an
anti-leukemic and antimicrobial agent isolated from marine sponges involving formation of the β-ring by intramolecular nitrile oxide cycloaddition.\(^8^3\)

An effective and chiral specific synthesis of DMP 754 (23), a novel peptide, orally active and extremely potent platelet GP 11b 1111a antagonist involves 1,3-dipolar cycloaddition of nitrile oxide to isobutyl vinyl acetate as key step.\(^8^4\) 5-Aroylpyrimidine nucleoside oximes (24) were prepared by the reaction of corresponding pyrimidine nucleosides with stable nitrile oxides. The nitrile oxides are generated \textit{in situ} from the corresponding hydroxymoyl chlorides.\(^8^5\)

In summary, it seems that nitrile oxide cycloaddition chemistry can be seen as a powerful strategic tool for crafting the diverse molecules of nature. Not only can one build a variety of carbocyclic and heterocyclic ring system through its agency, but additionally, one can to exploit diastereofacial selective cycloaddition reaction in a rational way so as to achieve a satisfactory solution to the problem of acyclic stereo control. The nitrile oxide thus seems a reasonably mild reagent in affording C-C double bond forming reactions with the simultaneous incorporation of manipulable heteroatom functionality.
PART III: CHEMISTRY OF NITRILE IMINES

1.3.0 Introduction:

The concept of 1,3-dipolar cycloaddition was developed in the early 1950s by Huisgen and co-workers; which has led to one of the most versatile methods for the construction of five-membered ring heterocycles. Most nitrile imines are highly reactive and in the absence of trapping agents they undergo rapid dipolar cycloaddition with themselves. Although first known only as transient intermediates, nitrile imines have been at the heart of mechanistic studies of 1,3-dipolar cycloaddition reactions.

Although hundreds of mechanistic papers on nitrile imines were appeared in 1970s; reliable spectroscopic observations were achieved in the early 1980s both at low temperatures and in the gas phase; the first crystalline nitrile imine was reported in 1988. The unusual structures found by X-ray analysis as well as the facile rearrangements observed experimentally have fostered a new interplay between experiment and theory.

The story of nitrile imines, from matrix characterization to stable compounds, nicely illustrates the role that main group elements can play in organic chemistry. Hans Bock et al\textsuperscript{86} reported the photoelectron spectra of nitrile imines obtained by flash vacuum pyrolysis of tetrazoles; their study accounts the geometry and electronic structure of nitrile imines. An isomer of diazomethane, the nitrile imine, HC≡N=NH is reported to be a stable molecule in the gas phase. Upon neutralizing the $\alpha$-distonic HCNNH$^+$ cation in a beam experiment, this long-time predicted ylide can be generated.
Four alternative structures have been postulated for the non-stabilized nitrile imines: propargylic (25a), allenic (25b), 1,3-dipolar (25c), and carbonic (25d) structure.

The literature reveals that the theoretical calculations of the nitrile imine structures have generated the conflicting results. For instance, a high-level calculation study with the configuration interaction (QCISD) and a large basis-set concluded that the stable nitrile imine structure has a non-planar, allenic geometry and that the propargylic structure does not correspond to a local minimum on the potential energy surface. DFT calculations in combination with the natural resonance theory indicated that all four resonance structures are necessary for a full description and that the carbenic form dominates for F-CNN-F and H2N-CNN-NH2.

In contrast, a spin-coupled valence bond calculation using the geometry from a CASSCF calculation suggested that the stable electronic structure of H-CNN-H is predominantly propargylic. To overcome this; Zheng et al88 conducted photo-crystallography experiments and reported the direct observation of a bent geometry for a non-stabilized nitrile imine in a metal-coordination crystal. The photo induced tetrazole ring rupture to release N2 appears to depend on the size of voids around the N(3)-N(4) bond in the crystal lattice. According to their studies, the bent nitrile imine geometry agrees with the 1,3-dipolar structure, a transient reactive species that mediates the photo-induced 1,3-dipolar cycloaddition in the aqueous medium.

1.3.1 Generation of nitrile imines:

The usual synthesis of nitrile imines (27) involves the thermolysis or photolysis of tetrazole (26),89 flash vacuum pyrolysis of tetrazoles (Scheme-36).87
Catalytic oxidation of aldehyde hydrazones (28) with lead tetraacetate, Chloramine-T, mercuric acetate leads to the formation of nitrile imines (29) (Scheme-37); which can be trapped in situ by various dipolarophiles to produce five membered heterocycles such as pyrazolines, pyrazoles, triazoles, tetrazoles etc.

Dehydrohalogenation of hydrazonoyl chlorides (30) by treating with a base triethylamine or with silver carbonate in dioxane also leads to the generation of nitrile imines (29) (Scheme-38). There were reports that nitrile imines are also generated by the photolysis of sydnones.

The spectral and kinetic behavior of nitrile imines photo-generated from sydnones and tetrazoles in fluid solutions has been studied by laser and lamp flash photolysis. The nitrile imines are characterized by lifetimes of milliseconds and are quenchable by the dipolarophile dimethyl acetylenedicarboxylate and by carboxylic acids. The phototransformation of 3,4-diaryl-sydnones to the corresponding N,C-diaryl nitrile imines occurs rapidly; this suggests that bicyclic diaziridine, diazirine or 1,2,3-oxadiazolin-5-one intermediates, postulated in the literature as precursors for nitrile imines, are either very short lived or not involved at all. The laser flash photolysis of the sydnones unsubstituted at the 4-position or bearing a methyl group at this position gives rise to additional, fast-decaying, transient species which become
progressively longer lived upon interaction with hydroxylic reagents. Possible assignments of these transient species in terms of ylide structures are discussed in the light of the results of steady state photolysis at low temperatures.  

1.3.2 Application of nitrile imine cycloaddition reactions:

Rai and co-workers reported a new approach for the synthesis of pyrazoles via 1,3-dipolar cycloaddition of acetyl acetone and \textit{in situ} generated nitrile imines by the catalytic dehydrogenation of phenylhydrazones using chloramine-T as oxidant. The reaction afforded the regioselective cycloadducts in good yield. They developed and first reported the \textit{in situ} generation of nitrile imines by the reaction of aldehyde hydrazones with mercuric acetate. They carried out the reaction of aldehyde hydrazones with mercuric acetate in the presence of olefins and obtained the 1,3,5-trisubstituted 2-pyrazolines in good yield.

The reaction of homochiral hydrazonoyl chlorides (31) with silver carbonate in dioxane produced corresponding nitrile imine; which undergo intramolecular cycloaddition in the absence of trapping agents to give diastereoisomeric mixture of 3,3a-dihydro-pyrazolo[1,5-\textit{a}][1,4]benzodiazepine-6(4\textit{H})-ones (32) and (33) in enantiopure form (Scheme-39).

![Scheme-39](image)

The nitrile imines (34) undergo rearrangement reaction between -78 and +55°C, the rearrangement temperature depending on the substituents to produce rearranged products (35). The nitrile imines can be characterized in solution by NMR
and IR spectroscopy. Compounds (34), $E = \text{SiMe}_3$ and $\text{SiPh}_3$, have also been trapped with methanol and with methyl acrylate (Scheme-40).$^{95}$

\[
\begin{align*}
&\begin{array}{c}
\text{S} \\
\text{(PrN)}_2\text{P} - \text{C\text{=N}_2}
\end{array} \\
&\xrightarrow{\text{Li}} \xrightarrow{\text{EX}} \begin{array}{c}
\text{S} \\
\text{(PrN)}_2\text{P} - \text{C\text{=N}_2}
\end{array} \\
&\xrightarrow{\text{LDX}} \begin{array}{c}
\text{S} \\
\text{(PrN)}_2\text{P} - \text{C\text{=N}_2}
\end{array}
\end{align*}
\]

Scheme-40

Compound (36) which first melts above 300°C without decomposition, is formed via nitrile imine–imidoylnitrene rearrangement upon reaction of the nitrile imine (37) with tetrachloro-\(\sigma\)-benzoquinone. The surprising thermal stability of (36) could be due to the coordination of an oxygen atom to the nitrene nitrogen atom ($R = \text{NiPr}_2$).$^{96}$

\[
\begin{align*}
&\begin{array}{c}
\text{S} \\
\text{(PrN)}_2\text{P} - \text{C\text{=N}_2}
\end{array} \\
&\xrightarrow{\text{S} \xrightarrow{\text{PR}_2}} \begin{array}{c}
\text{S} \\
\text{(PrN)}_2\text{P} - \text{C\text{=N}_2}
\end{array}
\end{align*}
\]

$N$-Aryl-\(C\)-ethoxycarbonylnitrile imines react with \textit{meso}-tetrakis(pentafluorophenyl) porphyrin in 1,3-dipolar cycloadditions to yield novel pyrazolochlorins in moderate yields. The nitrile imines were generated \textit{in situ} by base-induced dehydrobromination of ethyl hydrazono-\(\alpha\)-bromoglyoxylates. A number of different experimental conditions were considered for these cycloadditions namely different bases, solvents and temperature; the best results were obtained using potassium carbonate in refluxing toluene. The photo physical properties of the new chlorins were investigated and the results suggest that two of them have potential for use in photodynamic therapy.$^{97}$

Nitrile imines are found to be useful reactive intermediates in azaheterocyclic synthesis; they undergo two main cyclization reactions: 1,3-dipolar cycloaddition reactions with multiple bonds and cyclo condensation reactions with nucleophilic
substrates containing suitably located electrophilic centers leading to various heterocyclic compounds. For instance; C-Aroyl-N-arylnitrilimines generated by the reaction of hydrazonoyl halides with triethylamine in tetrahydrofuran was trapped in situ by alkanal methylhydrazones to afford 1,3,4,6-tetrasubstituted 1,2,4,5-tetrazines in good yield (Scheme-41).

![Scheme-41](image)

1,3-Dipolar cycloaddition between aromatic selenoaldehydes and aromatic N-phenyl nitrile imines generated in situ by the dehydrochlorination of hydrazonoyl chlorides with triethylamine proceeded efficiently to give the corresponding [3 + 2] cycloadducts as a single isomer 1,3,4-selenadiazoles (38) in good yields (Scheme-42). The study reports that these selenium containing five-membered heterocycles were stable at room temperature in the atmosphere.

![Scheme-42](image)

The reaction of nitrile imines generated in situ by the dehydrochlorination of C-(2-furoyl)-, C-(2-thenoyl)- and C-(phenylaminocarbonyl)hydrazonoyl chlorides with triethylamine with cycloalkanone oximes (39) give unexpected 3-substituted 1-aryl-1,2,4-triazaspiroalk-2-enes (40) (Scheme-43). Although initially, the reaction was expected to produce cycloaddition products 1,2,4-triazoles or cyclocondensation products 1,2,4,5-oxatriazines, it produced (40); the formation of compounds (40) is assumed to involve cycloaddition adducts 1,2,4-triazoles which tautomerize to amine oxide-type intermediates that are deoxygenated by triethylamine.
Huisgen reaction of nitrile imines generated in situ in the presence of N-benzylmaleimide afforded regiospecifically the corresponding cycloadducts (41)\textsuperscript{101} in good yield.

Reaction of 5-substituted-2-methyl-3(2H)-pyridazinones with diarylnitrile imines generated in situ with chloramine-T has been shown to afford diarylpyrazolo[3,4-d]pyridazin-4(5H)-ones (Scheme-44).\textsuperscript{102} Reactivity and regiochemistry were analyzed by FMO theory.

3-Mercaptopropionic acid-nitrile imine acyclic adducts undergo cyclocondensation with 1,1'-carbonyldiimidazole to afford the respective 1,3,4-thiadiazol-2-(3\textit{H})-ones or 1,3,4-thiadiazol-2(3\textit{H})-thiones with consequent elimination of the propionate moiety (Scheme-45).\textsuperscript{103} The constitution of these heterocyclic products follows from analytical and spectral data and is confirmed by single crystal X-ray structure determination.
Extremely fast fluorescence labeling (<1 min) of a recombinant alkene-encoded protein in living *Escherichia coli* cells was observed with tetrazole. The electron-donating methoxy substituent raises the energy of the highest occupied molecular orbital of the nitrile-imine intermediate derived from tetrazole. This strategy greatly accelerates the functionalization of alkenes by 1,3-dipolar cycloaddition in living systems.\(^{104}\)

Huisgen reaction of nitrile imines generated *in situ* in the presence of N-benzylmaleimide afforded regio-specifically the cis-3-aryl-5-benzyl-1-(2',4'-dibromophenyl)-3a,4,6,6a-tetrahydro-1\(H\),5\(H\)-pyrrolo[3,4-\(c\)]pyrazole-4,6-diones in good yield.\(^{101}\) Nitrile imines react with 1-phenylsulphonyl-2-benzoyl (or methoxycarbonyl)alkenes to give 4-phenylsulphonyl-5-benzoyl (or methoxycarbonyl) substituted pyrazolines.\(^{105}\) The cycloaddition regioselectivity is discussed in terms of Frontier Orbital energies and coefficients.

Recently Ajay Kumar and co-workers\(^{106}\) reported the use of *in situ* generated nitrile imines in the synthesis of 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-\(d\)]-7,8-dihydropyrazoles. They carried out a reaction of a mixture of \(N\)-aryl maleimide, aldehyde hydrazone and chloramine-T in ethyl alcohol and obtained the cycloadducts in moderate to good yield (Scheme-46). The synthesized 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-\(d\)]-7,8-dihydropyrazoles have been evaluated *in vitro* for their antibacterial, antifungal and antioxidant activities. The results of the study indicated that some of the compounds posses promising activity.\(^{107}\)
Aldehyde phenyl hydrazones undergo oxidative dehydrogenation with chloramine-T to give nitrile imines, which are trapped \textit{in situ} by ethyl oleate to afford 8-(5-aryl-4-octyl-2-phenyl-3,4-dihydro-2\(H\)-pyrazol-3-yl)-octanoic acid ethyl esters in good yield (Scheme-47). The pyrazole derivatives have shown moderate antimicrobial and antioxidant activities.

The intramolecular cycloaddition of nitrile imines generated \textit{in situ} from the aryl hydrazones in the presence of chloramine-T with \(\alpha,\beta\)-unsaturated ketones results in the formation of tetrasubstituted pyrazolines in moderate yield. 1,3-Dipolar cycloadditions of \(\text{C-carboxymethyl-N-aryl} \) nitrile imines with cyclic \(\alpha,\beta\)-unsaturated ketones; after cycloaddition, oxidative aromatization gives the ring-fused pyrazoles. Computational studies and the use of topological analysis of the Fukui functions allow a theoretical description of the local reactivity was in agreement with the experimentally observed regiochemistry.

Dihydropyrazoles bearing a chiral quaternary center at the 5-position have been prepared by enantioselective 1,3-dipolar cycloaddition of nitrile imines to \(\alpha\)-substituted- and \(\alpha,\beta\)-disubstituted-\(\alpha,\beta\)-unsaturated carbonyl substrates. Use of \(\alpha,\beta\)-unsaturated carbonyl substrates with a 1-benzyl-5,5-dimethylpyrazolidin-3-one auxiliary in conjunction with \(\text{MgI}_2\) and a bisoxazoline ligand derived from \((1R, 2S)\)-\((+)-\text{cis-1-amino-2-indanol} \) was proved optimal to obtain chiral dihydropyrazoles with high enantioslectivity.
The [3 + 2] dipolar cycloaddition reaction of nitrile imines with 3-alkylidene oxindoles produces the pyrazoline spiroadducts in high yields and with excellent regio- and diastereoselectivities. These spirocyclic intermediates have been elaborated to synthetically versatile 3-amino oxindole building blocks such as β-amino nitrile, 1,3-diamine, and pyrrolo[2, 3-b]indoline derivatives. A synthesis of 1-substituted-1H-indazoles via 1,3-dipolar cycloaddition of nitrile imines to benzyne was reported to be completed within 5 min, affording the corresponding N(1)-C(3) disubstituted indazoles in moderate to excellent yields.