Introduction to 1,3-dipolar cycloaddition reaction

The chemistry of heterocyclic compounds is one of the most important branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures and for the biological and industrial applications. Over the decades, the cycloaddition chemistry has continued to maintain a significant place in synthetic organic chemistry, for the construction of mono- and polycyclic systems, as a consequence of being able to deliver high selectivity and molecular complexity from relatively simple and accessible compounds.

1,3-Dipolar cycloaddition reaction (herein after referred to as 1,3-DC reaction) has taken a prominent place for the preparation of biologically active nitrogen containing five-membered heterocycles.\(^1\) The 1,3-DC reactions has offered numerous diversity for the organic chemists to accomplish the synthesis of complex heterocyclic systems with high selectivity.\(^2\)\(^3\)

**Origin of 1,3-DC reactions:**

The 1,3-dipolar cycloadditions are pericyclic reactions like Diels-Alder reaction and proceed through a 6π-electron ‘aromatic’ transition state. The phenomenal difference is, in a Diels-Alder reaction, the \(\pi_4^4\) component having four atoms undergo cycloaddition with a \(\pi_2^2\) component resulting in a six-membered cyclic framework, whereas in 1,3-dipolar cycloaddition reaction the zwitterionic \(\pi_4^4\) component having triad of atoms undergo cycloaddition with a \(\pi_2^2\) component resulting in five-membered heterocycles (Fig. 1).

Although Huisgen\(^4\) classified the 1,3-dipoles and introduced the concept of 1,3-dipolar cycloaddition in 1963, it was not popular until the first intramolecular 1,3-DC reaction of azomethine ylide was reported by Padwa\(^5\) in 1976. Since then remarkable
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developments have taken place in 1,3-DC reaction, with the establishment of various useful methods for the formation of a variety of heterocycles.

![Figure 1. Schematic representation of 1,3-DC reaction](image)

**The dipole/ylide:**

The “1,3-dipole” can be represented as a zwitterionic resonance structures of a a-b-c unit having four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole, which undergoes 1,3-cycloaddition to a multiple bond system, the “dipolarophile” to give a five-membered ring system.

In general, 1,3-dipoles can be classified into two different types:

(i) The allyl anion type, and

(ii) 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 in which the dipole has bent structure. Two resonance structures in which the three centers have an electron octet and two structures in which ‘a’ or ‘c’ has an electron sextet, can be drawn. The central ‘b’ can be nitrogen, oxygen, or sulfur. The propargyl/allenyl anion type has an extra π electron 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. The 1,3-dipoles are occasionally represented as hypervalent structures ([Fig. 2]).
The 1,3-dipoles containing various combinations of carbon and hetero atoms are theoretically possible and Huisgen classified eighteen possibilities of 1,3-dipoles into allyl and propargyl type as shown below (Fig. 3).
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**Figure 3.** Classification of 1,3-dipoles

Of all the 1,3-dipoles, cycloaddition reaction of azomethine ylides has been more intensely studied than most of other dipoles due to their remarkable synthetic possibilities. According to Huisgen, “azomethine ylides are planar molecules composed of one nitrogen atom and two terminal sp² carbons and belong to a class of azomethine betaines that do not possess a double bond in the sextet structure but have internal octet stabilization”.

Generally cycloaddition of azomethine ylides to olefinic and acetylinic dipolarophiles leads to the formation of pyrrolidines and Δ³-pyrrolines, respectively.

Dipolarophile like a dienophile in Diels Alder reaction is a reactive alkene or alkyne containing 2π electrons. Therefore, α,β-unsaturated aldehydes, ketones, esters, allylic alcohols, allylic halides, vinylic ethers, and alkyynes readily act as good dipolarophiles. The alkene moiety may contain mono-, di-, tri- or even tetra-substituents (only monosubstituted ones are shown here), but due to steric factors, tri- and tetra-substituted alkenes often display very low reactivity in reactions with dipoles.
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Azomethine ylide-dipolarophile interaction:

1,3-dipolar cycloaddition of azomethine ylide with a 2π system involves a total of 6π electrons \([\pi^4 + \pi^2]\) and takes place by a thermally allowed suprafacial process according to Woodward–Hoffmann rule. The concerted nature of cycloaddition reaction leads to the formation of products with stereospecificity.

In terms of Frontier Molecular Orbital (FMO) theory, cycloaddition reaction takes place by the HOMO–LUMO interaction. Azomethine ylides can be considered to be electron-rich and the dominant interaction involves the HOMO of the azomethine ylide with the LUMO of the 2π-system (Fig. 5). This is borne out by the general preference for reactions of azomethine ylides with electron-poor alkenes. However, in intramolecular cycloadditions, the reaction can take place readily with an unactivated alkene and the frontier molecular orbital interaction is not necessarily obvious.

![FMO diagram of 1,3-DC reaction](image)

Figure 5. FMO diagram of 1,3-DC reaction

The approach of the 1,3-dipole to the dipolarophile can take place in an endo or exo fashion resulting in two diastereomeric endo/exo cycloadducts, respectively. The transition state (TS) structures of endo and exo approaches are depicted below (Fig. 6), where the endo approach is stabilized by small secondary orbital interactions (SOI), contributing to the endo/exo selectivity of the reaction. However, steric factors can have a major influence on this endo/exo selectivity and can often override this stabilizing effect.
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![Diagram of 1,3-dipolar cycloaddition reaction]

**Figure 6.** TS structures of *endo* and *exo* approaches

**Regio- and stereoselectivity:**

The regioselectivity in the cycloaddition of azomethine ylide can be predicted on the basis of frontier molecular orbital (FMO) theory. If the relative sizes of the atomic orbitals are known for the frontier orbitals of both the azomethine ylide and the dipolarophile, then a prediction of the regioselectivity in the cycloaddition reaction of an unsymmetrical dipole and dipolarophile can be made.

In addition to regioselectivity, the dipolar cycloaddition reaction can lead to mixtures of stereoisomers, with the generation of maximum of four new chiral centers. The chiral centers at C-2 and C-5 of the five-membered ring products are derived from the azomethine ylide. As the cycloaddition reactions are concerted processes and stereospecific, the relative orientation of substituent’s of the dipolarophile are maintained in the product. Azomethine ylide can adopt different geometries, during cycloaddition reaction, which influence the stereochemistry of the substituents in the resulting cycloadduct (Fig.7).

![Geometry of azomethine ylide]

**Figure 7.** Geometry of azomethine ylide
**1,3-dipolar cycloaddition reaction**

For intramolecular cycloaddition reactions, the dipolarophile is tethered to azomethine ylide in that the dipolarophile may be linked to one of the carbon atoms (**Type I**) or to the nitrogen atom (**Type II**) of the azomethine ylide. These two types are analogous to two variants of intramolecular Diels-Alder reaction. In the former case, with relatively shorter linkage, a bicyclic fused product is preferred over the bridged products. As far as the stereochemical outcome across the two new rings is concerned, both *cis-* and *trans-* fused products can be formed, although the *cis-* fused product often predominates (**Fig. 8**).

![Diagram of intramolecular 1,3-DC reaction](image)

**Figure 8.** Intramolecular 1,3-DC reaction

With type II arrangement in which the dipolarophile tethered to the nitrogen atom, cycloaddition necessarily creates a bridged bicyclic product. While there is no regioselectivity issue with a symmetrical dipole, an unsymmetrical dipole may favor one regioisomeric product over the other.

**Generation of Azomethine ylides:**

Azomethine ylides are mostly generated *in situ* and a number of methods have been developed for their generation. Some important methods are given below.

**(i) Aziridine route:**

The well-known and extensively studied carbon-carbon bond cleavage of aziridines generates an azomethine ylide through conrotatorial (thermolysis) or disrotatorial (photolysis) process.
(ii) Desilylation route:

In this protocol, silyl amines are desilylated$^{12}$ to yield an azomethine ylide.

(iii) Tautomerisation route:$^{13}$

The hydrogen adjacent to the imine nitrogen of $\alpha$-amino ester imines or $N$-benzyl imines is highly acidic because the conjugated bases, generated after decomposition, can be stabilized by both imine and ester/aromatic groups.

(iv) $N$-Metallation route:

Metallo imines are precursors of metallo dipoles, which can be generated in situ from the corresponding imines of $\alpha$-amino acid esters and organic or inorganic bases. Only a mild reaction conditions required for the cycloaddition process and due to the highly coordinated transition state make this methodology a very useful tool in organic synthesis for the stereoselective synthesis.$^{14}$
(v) Decarboxylation route:  

This is the most widely used route for the *in situ* generation of an azomethine ylide. The general protocol is based on the thermal decarboxylation of an iminium salt or an imine obtained by the condensation reaction of the *N*-substituted or an unsubstituted α-amino acid.\(^{15}\)

![Scheme 5](image)

It has been established that azomethine ylides can be generated in a range of solvents (chloroform, methanol, acetonitrile, toluene, *N*, *N*-dimethyl formamide, etc.) at temperatures ranging from room temperature to 140 °C.
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References


