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Progress in 1,3-dipolar cycloadditions in the recent decade: an update to strategic development towards the arsenal of organic synthesis

Maya Shankar Singh *, Sushobhan Chowdhury, Suvajit Koley

Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India

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1. Introduction

The synthetic strategies involving the construction and cleavage of a bond represent the central theme in organic synthesis. The cleavage of a bond is achieved either by weakening or by polarizing

* Corresponding author. Tel.: +91 542 6702502; fax: + 91 542 2368127; e-mail address: mayashankarbhu@gmail.com (M.S. Singh).

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or by cleaving with suitable reagent. The driving force behind the formation of a bond is possession of opposite dipoles in nucleophilic and electrophilic substrates. Substrates bearing opposite dipoles react to the counter dipoles of other component forming desired bonds. The 1,3-dipolar cycloaddition utilizes this concept where each indivisual substrate holds opposite dipoles to form the desired molecular framework. Thus, 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring.

In the present era, the prime challenge to synthetic organic chemist is to develop efficient, atom-/pot-/cost-economic (APCE) and eco-compatible strategies to construct useful molecules. One approach to address this challenge is the development of 1,3-dipolar cycloaddition reactions. The idea of 1,3-dipolar cycloaddition reaction was initially proposed by L. I. Smith.[1] The synthetic scope of this revolutionary reaction has been recognized and explored by German chemist Rolf Huisgen.[2] Henceforth, the reaction is sometimes referred to as the Huisgen cycloaddition (this term is often used to specifically describe the 1,3-dipolar cycloaddition between an organic azide and an alkyne to generate 1,2,3-triazole). The subsequent systematic progress and modifications over the years made it as one of the most powerful tool of organic synthesis. The notable modification was made by Sharpless and Meldal in terms of 'click chemistry' making the [3+2] cycloaddition more popular among the synthetic chemists.[3] Now a days, 1,3-dipolar cycloaddition reactions are being frequently exploited towards the synthesis of complex cyclic scaffolds for medicinal, biological, and mechanistic studies.[4]

Herein, we present an overview of the open literature on the development of 1,3-dipolar cycloadditions over the recent years. Cycloaddition (3+2) has engulfed almost every section of organic chemistry, and a number of methodologies for the synthesis of triazoles and allied five membered heterocyclic cores have been reported, and are emerging regularly. Therefore, no page number is sufficient for all of them to discuss at one place. Furthermore, several reviews regarding the application of 1,3-dipolar cycloaddition reactions and click chemistry in various fields like polymer, drug discovery, and materials have been specifically reported.[4] However, a concise and well directed database on the recent methodological advances in 1,3-dipolar addition chemistry including their merits-demerits has not yet been reported. Hence, such a procedural database is highly desirable for the successful application of this magical reaction in pure and applied sciences. Here, we made an attempt to quench the thirst of such kind of review by limiting our discussion towards the progress of the 1,3-dipolar cycloaddition reactions. A detailed account of the methodologies developed over the recent years (from 2006 onwards) is presented in a concise systematic manner. Starting with a brief mechanistic overview, we expanded our discussion to the methodologies categorized on the basis of several kind of diploes employed in the reactions. The discussion on the asymmetric version of the 1,3-dipolar addition is kept apart since a number of reviews has already been published where this perspective is well discussed.[5–7]

2. Mechanistic overview

There were originally two proposals that describe the mechanism of the 1,3-dipolar cycloaddition. Depending on several features of 1,3-dipolar cycloaddition such as solvent effects, stereochemistry and thermodynamic parameters, Huisgen proposed a one-step concerted process with a single transition state most likely as a pericyclic reaction.[8a] Whereas, Firestone proposed a stepwise mechanism with rate-determining first step involving a spin-pared discrete diradical intermediate.[8b] Although, there exists few examples of stepwise mechanism, but the former one is the generally accepted mechanism for the 1,3-dipolar cycloaddition reaction.[8c] Huisgen investigated a series of cycloadditions between the 1,3-dipolar diazo compounds and various dipolarophilic alkenes. 1,3-dipolar cycloadditions usually result in retention of configuration with respect to both the 1,3-dipole and the dipolarophile. Such high degree of stereospecificity is a strong support for the concerted over the stepwise reaction mechanisms.

In the mechanistic course, the 1,3-dipole reacts with the dipolarophile in a symmetry-allowed $\pi^4s+\pi^2s$ fashion and creats a six-electron Huckel aromatic transition state (HATS) leading to the bond formation between dipole and dipolarophile. There are two pathways I and II to enroute to the transition state. The dominant pathway possesses the smallest HOMO-LUMO energy gap (Fig. 1).[5d,9] *cis*-Substituents on the dipolarophilic alkene end up *cis*, and *trans*-substituents end up *trans* in the resulting five-membered cyclic adduct. The stereochemistry of the dipole is not of major concern because only few dipoles could form stereogenic centres, and resonance structures allow bond rotation which scrambles the stereochemistry. However, the study of azomethine ylides has verified that cycloaddition is also stereospecific with respect to the dipole component.

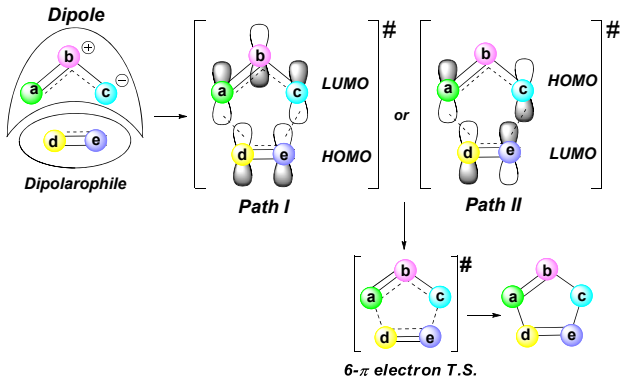

Fig. 1. Orbital interaction diagram of 1,3-dipolar cycloaddition reaction.

3. Dipole and dipolarophile

A 1,3-dipole is an organic molecule that can be represented as either an allyl-type or a propargyl/allenyl-type zwitterionic octet/sextet structures. Both types of 1,3-dipoles share four electrons in the π-system over three atoms. The allyl-type is bent whereas the propargyl/allenyl-type is linear in geometry. Formally the charges on different centres are assigned on the basis of the most contributing resonating structures. There are a total of 18 s-row 1,3-dipoles known to be usually used in 1,3-dipolar cycloaddition (Fig. 2).[2] 1,3-Dipolar cycloaddition occurs between a dipole and dipolarophile. During the course of the reaction, they get fused in head–head/tail–tail or head–tail/tail–head fashion to generate the corresponding cycloadducts. Often due to the selectivity in the manner of fusion, regio- and stereo-selectivity arises in the cycloadducts. In 1,3-dipolar cycloadditions, identity of the dipole-dipolarophile pair determines whether the HOMO or the LUMO character of the 1,3-dipole will dominate. Examples of [3+2]-cycloadditions with phosphorus and sulfur containing dipoles also exists but they are used less frequently.

Consequently, the termini of a 1,3-dipole can be treated as both nucleophilic and electrophilic at the same time. The extent of nucleophilicity and electrophilicity at each terminus can be evaluated using the frontier molecular orbitals (FMO), which can be obtained computationally. In general, the atom that carries the largest orbital coefficient in the HOMO acts as the nucleophile, whereas that in the