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1,4-Dipolar cycloadditions and related reactions

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1. Introduction

Carbon–heteroatom bond-forming reactions are of pivotal importance in organic chemistry. Inter alia they offer viable routes for the construction of heterocyclic frameworks; the latter assume importance by virtue of their ubiquitous presence in a wide range of biologically active natural and unnatural molecules. Among the plethora of methods available for carbon–heteroatom bond formation, dipolar cycloaddition reactions are noteworthy for their ability to produce complex heterocycles endowed with significant biological activities. In this context, the Huisgen 1,3-dipolar cycloaddition reaction offers a unique protocol for the synthesis of five-membered heterocycles[1,2] comparable in its versatility to that of Diels–Alder cycloadditions in the synthesis of six-membered carbocycles. Surprisingly, however, very little is known about the cycloaddition behaviour of 1,4-dipoles whose transient existence was first postulated in 1969 by Huisgen.[3] As defined by Huisgen, the 1,4-dipole is a molecule *a–b–c–d*, in which the atom *a* bears a formal positive charge and atom *d* carries a formal negative charge.

Insight into the mechanistic underpinnings of 1,4-dipolar cycloaddition reactions was also provided by Huisgen.[4] In view of the pioneering efforts of Huisgen in laying the foundation of this promising area of research, the authors consider it appropriate to call this class of reactions as Huisgen 1,4-dipolar cycloaddition reactions. With the perception that the 1,4-dipolar cycloaddition will emerge as a synthetic protocol with wide range applications, herein we present the available literature relevant to the theme. For the most part, the review is concerned with the reactions of 1,4-dipoles generated by the addition of a nucleophile to an appropriate electrophilic receptor. However, selected examples of intramolecular 1,4-dipolar cycloadditions and reactions, which involve species that can be called ‘formal 1,4-dipoles’ are also included. We hope that this review will be of didactic value to the organic chemists in appreciating the reactivity of 1,4-dipolar species and will motivate them to investigate the reactivity profiles of these species in depth and breadth.

1.1. Diels–Alder cycloaddition versus 1,4-dipolar cycloaddition

1,4-Dipolar cycloaddition is comparable to the Diels–Alder cycloaddition in that both lead to a six-membered ring product, although there are noticeable differences between the two. The Diels–Alder reaction is a concerted reaction following the Woodward–Hoffmann rules[5] whereas the 1,4-dipolar cycloadditions occur step-wise. Another difference is that in Diels–Alder reaction a diene (4π component) reacts with a dienophile (2π component), the HOMO of either one reacting with the LUMO of the other, while in a 1,4-dipolar reaction the 1,4-dipole can add either to an electrophilic multiple-bond via path A or to a nucleophilic multiple-bond system via path B (Fig. 1). Thus when Diels–Alder reaction takes place in a single step, 1,4-dipolar cycloadditions occur in two steps in which two σ-bonds are formed in tandem to yield the six-membered ring. However, in the absence of any theoretical evidence, it is difficult to predict mechanistically the stabilization of the dipole by the addition of a dipolarophile either through a concerted or a step-wise reaction.

2. 1,4-Dipolar cycloaddition reactions

1,4-Dipolar cycloadditions can be classified into different categories on the basis of the 1,4-dipole species, which acts as the 4π component. This section describes the various 1,4-dipoles and their reactivity patterns towards electrophiles. The 1,4-dipoles are usually generated in situ during the course of the reaction by the combination of a nucleophilic and an electrophilic multiple-bond system. The most widely reported strategy for the generation of 1,4-dipole is by the attack of lone pair containing heteroatom on multiple bonds followed by an electron pair shift towards the heteroatom. Another method involves the addition of electron rich alkenes to electrophilic species like ketenes generating 1,4-dipolar intermediates in the process.

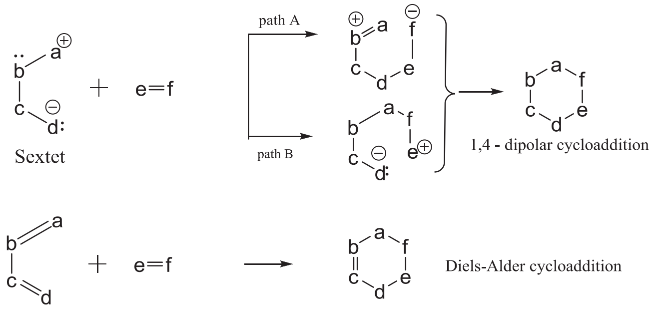
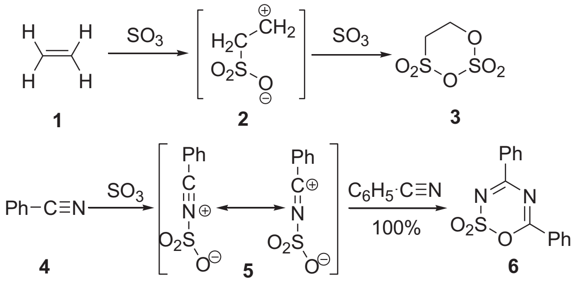


Fig. 1. Comparison of 1,4-dipolar cycloaddition with Diels–Alder cycloaddition.

2.1. 1,4-Dipole from sulfur trioxide

Around the dawn of organic chemistry, in 1838, Regnault reported that alkenes can add to sulfur trioxide leading to the formation of dioxothia heterocycles.[6] This reaction constitutes the first example of 1,4-dipolar cycloaddition reaction reported in the literature. Huisgen postulated that the mechanism of this reaction involved the formation of the 1,4-dipole **2** by the addition of the alkene to the sulfur–oxygen bond of the sulfur trioxide molecule, which then adds to a second molecule of sulfur trioxide to yield the final product. The nitrogen lone pair on benzonitrile was also reported to add to sulfur trioxide forming the 1,4-dipole **5**, which then adds to a second molecule of benzonitrile to yield the oxathiadiazine **6** in 100% yield.[7] Sulfur trioxide acts as an excellent dienophile in both these reactions (Scheme 1). Formation of a sulfur heterocycle was also reported in 1896 by Delépine who showed that carbon disulfide can be used as the electrophilic component of the 1,4-dipole, when he reacted the trimeric Schiff's base from formaldehyde and methylamine with carbon disulfide to obtain a 2:1 adduct **9** (Scheme 2).[8]



Scheme 1. Reactions of sulfur trioxide derived 1,4-dipoles.

2.2. 1,4-Dipoles from imines, enamines and ynamines

The formation of 1,4-dipoles by the engagement of nucleophilic N atom of imines, enamines and ynamines with electron