

**M.Sc. Semester-IV
Core Course-9 (CC-9)
Synthetic Organic Chemistry**



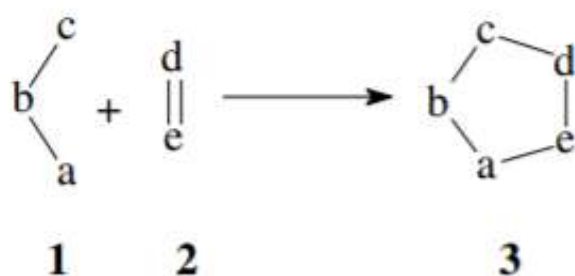
**II. Pericyclic Reactions
1. 1,3-Dipolar Cycloaddition Reaction**



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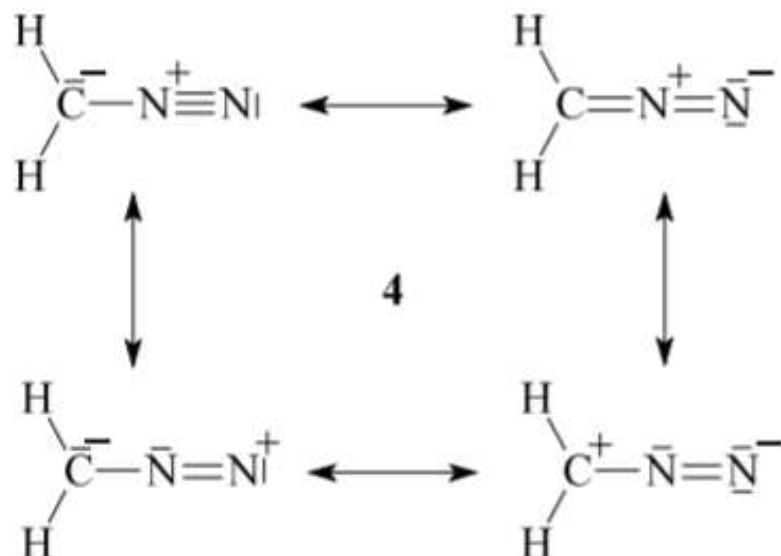
1,3-Dipolar Cycloaddition

Five-membered heterocycles through a cycloaddition reaction

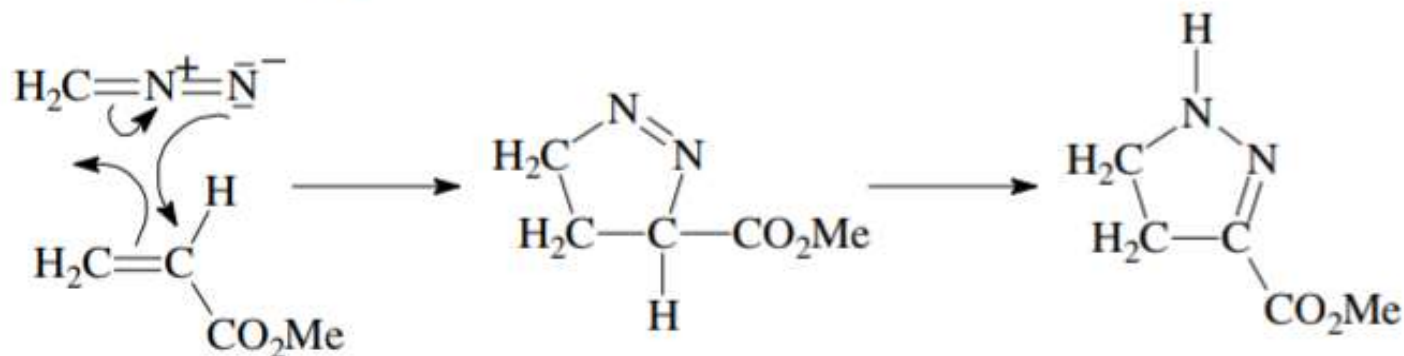


Huisgen^{1,2} has reported in 1963 about a systematic treatment of the *1,3-dipolar cycloaddition reaction*³⁻⁵ as a general principle for the construction of five-membered heterocycles. This reaction is the addition of a 1,3-dipolar species **1** to a multiple bond, e. g. a double bond **2**; the resulting product is a heterocyclic compound **3**. The 1,3-dipolar species can consist of carbon, nitrogen and oxygen atoms (seldom sulfur) in various combinations, and has four non-dienic π -electrons. The 1,3-dipolar cycloaddition is thus a $4\pi + 2\pi$ cycloaddition reaction, as is the *Diels–Alder reaction*.

Mechanistically the 1,3-dipolar cycloaddition reaction very likely is a concerted one-step process *via* a cyclic transition state. The transition state is less symmetric and more polar as for a Diels–Alder reaction; however the symmetry of the frontier orbitals is similar. In order to describe the bonding of the 1,3-dipolar compound, e.g. diazomethane **4**, several Lewis structures can be drawn that are resonance structures:



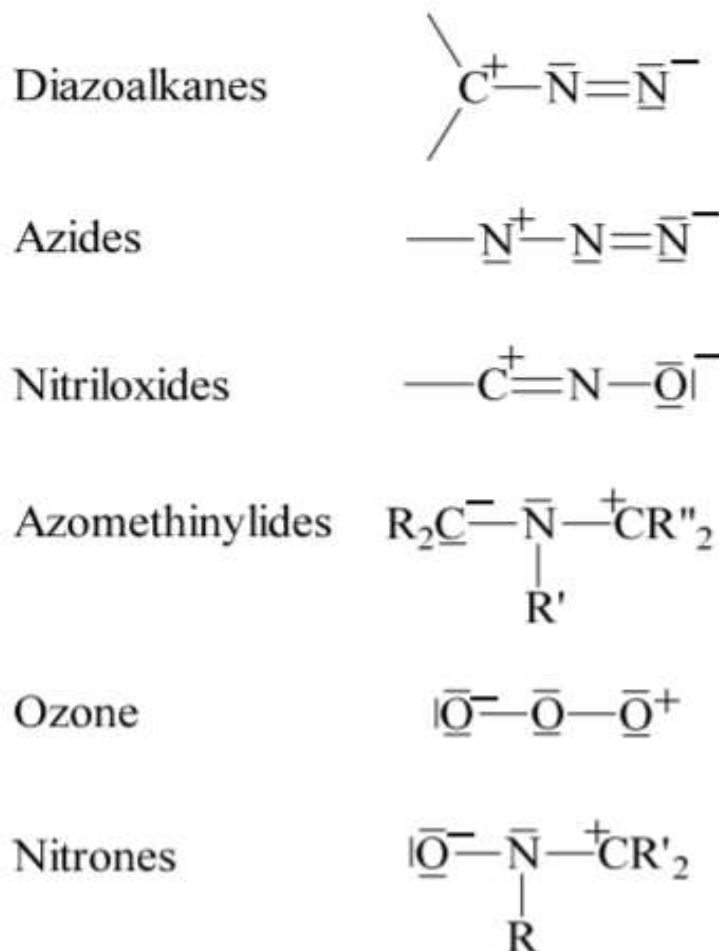
The cycloaddition reaction of diazomethane **4** and an olefin, e.g. methyl acrylate **5**, leads to a dihydropyrazole derivative **6**:



The shifting of electrons as shown in the scheme should be taken as a simplified depiction only. A more thorough understanding follows from consideration of the frontier orbitals and their coefficients;⁶ this may then permit a prediction of the regiochemical course of the cycloaddition.

A well-known example for a 1,3-dipolar compound is ozone. The reaction of ozone with an olefin is a 1,3-dipolar cycloaddition (see *ozonolysis*).

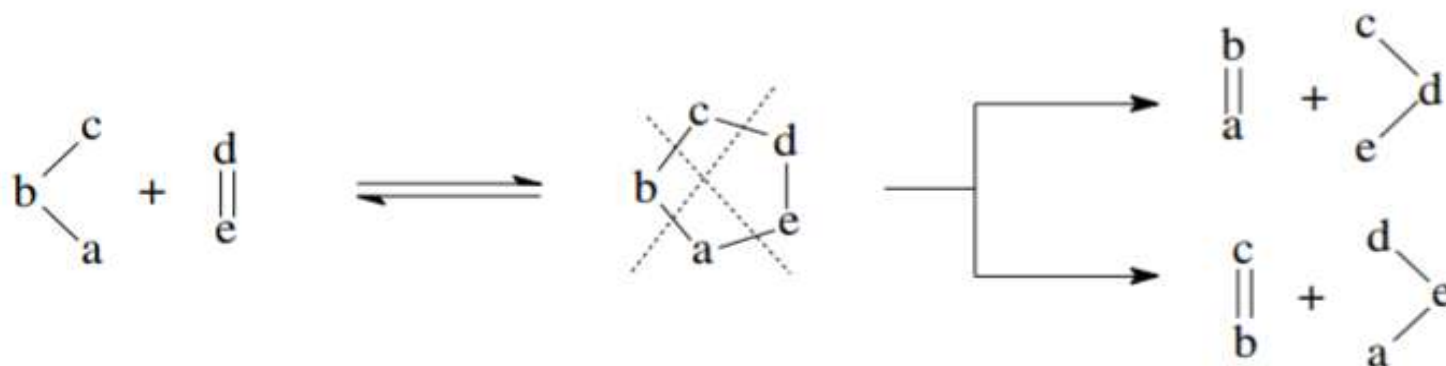
Further examples of 1,3-dipolar compounds:⁴



Dipolar compounds often are highly reactive, and therefore have to be generated *in situ*.

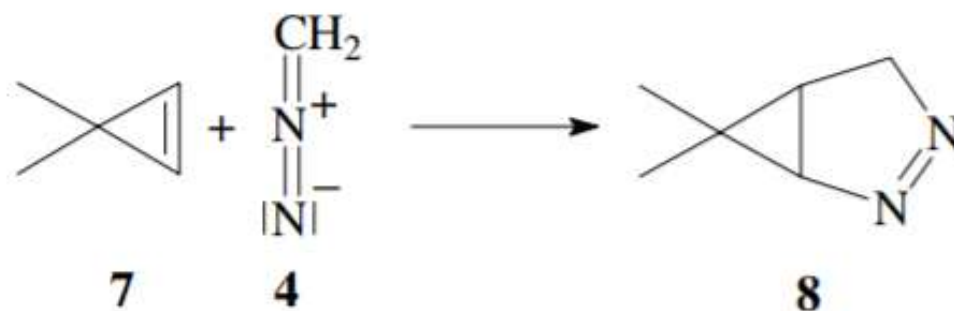
The 2π component **2**, the so-called *dipolarophile* (analogously to the dienophile of the Diels–Alder reaction) can be an alkene or alkyne or a heteroatom derivative thereof. Generally those substrates will be reactive as dipolarophiles, that also are good dienophiles.

An interesting perspective for synthesis is offered by the reaction sequence cycloaddition/cycloreversion.^{7,8} It often does not lead to the initial reactants, but to a different pair of dipole and dipolarophile instead:

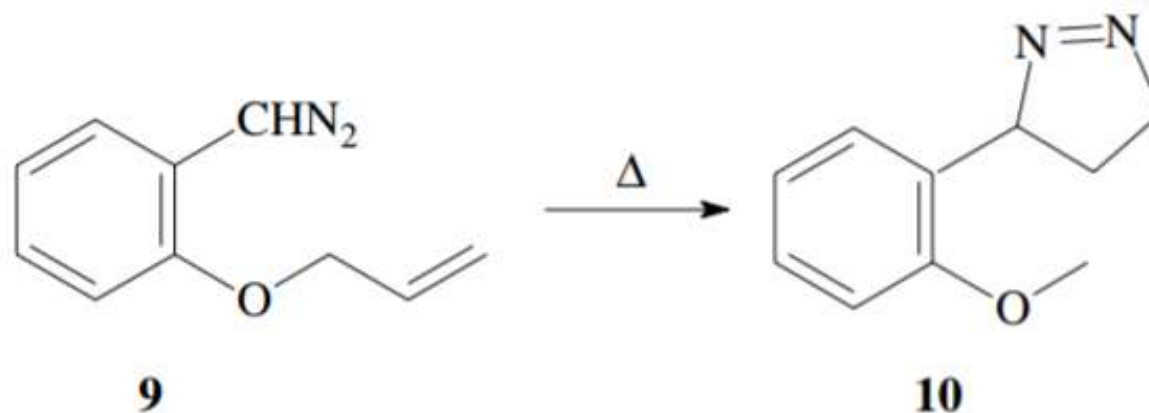


By analogy to the *alkene metathesis*, this reaction sequence is called *1,3-dipole metathesis*.

Strained bicyclic compounds can be obtained e.g. when cyclopropenes are used as dipolarophiles. Reaction of 3,3-dimethylcyclopropene **7** with diazomethane **4** gives the heterobicyclic cycloaddition product **8** in 85% yield:⁹



The importance of the 1,3-dipolar cycloaddition reaction for the synthesis of five-membered heterocycles arises from the many possible dipole/dipolarophile combinations. Five-membered heterocycles are often found as structural subunits of natural products. Furthermore an intramolecular variant¹⁰ makes possible the formation of more complex structures from relatively simple starting materials. For example the tricyclic compound **10** is formed from **9** by an intramolecular cycloaddition in 80% yield:¹¹



In many cases a change of the solvent has little effect on the 1,3-dipolar cycloaddition; but similar to the Diels–Alder reaction, the intermolecular 1,3-dipolar cycloaddition exhibits a large negative volume of activation, and therefore a rate enhancement is often observed on application of high pressure.¹² Inert solvents such as benzene, toluene or xylene are often used, or even no solvent at all. Depending on the reactivity of the starting materials the further reaction conditions can range from a few minutes at room temperature to several days at 100 °C or higher.

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