

SYNTHESIS OF HETEROCYCLIC SYSTEMS BY CYCLOADDITION REACTIONS

5.1. THE DIELS–ALDER REACTION

- In its simplest form, it consists of the reaction of a diene with an an alkene or an alkyne, generally those that are activated by the attachment of an electron withdrawing group.
→ alkyne or alkene

← ساجبة إلى الكيتونات

→ this reaction mean

• The **Diels–Alder reaction** is the reaction between a conjugated diene and an alkene (**dienophile**) to form **unsaturated** six-membered rings. (dien) لحدب

• the reaction involves the formation of a cyclic product via a cyclic transition state, it is also referred to as a "cycloaddition".

→ مرحلة حركية تمر بها الجزيئات المتفاعلة

• The Diels–Alder reaction is an electrocyclic reaction, which involves [4+2]-cycloaddition of 4 π -electrons of the conjugated diene and 2 π -electrons of the dienophile (an alkene or alkyne).

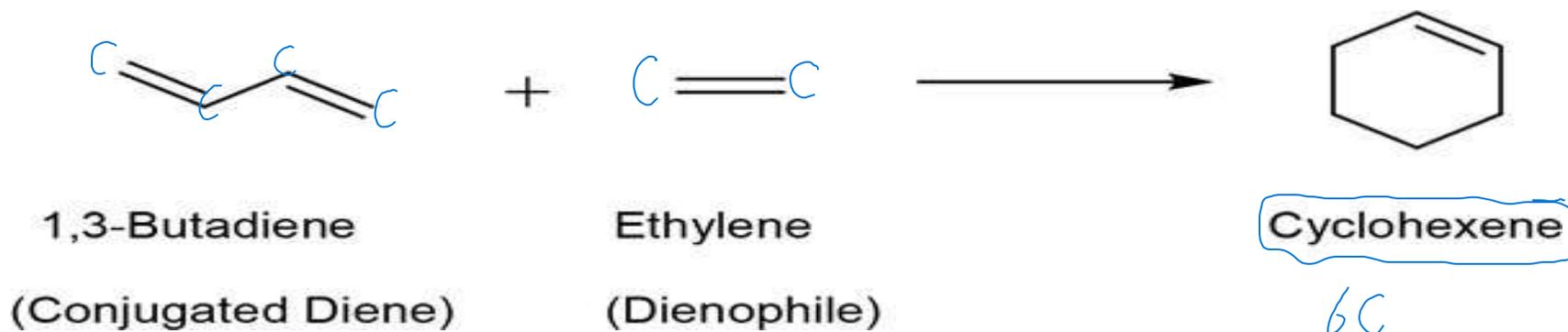
→ from two double bond

→ from one double bond

The reaction involves the formation of new σ -bonds, which are energetically more stable than the π -bonds.

→ electrons from double and triple bond

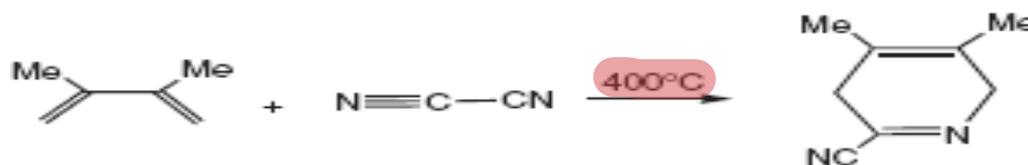
→ ينتج ناتج حلقي (مغلي) نواتج جانبية مثل ماء وغازات



Synthesis of Pyridine Derivatives.

The use of a nitrile group as the dienophile is illustrated in Scheme 5.7, where cyanogen, CN-CN , cycloadds to a simple diene. → in Cyanogen

Normally, simple nitriles are unreactive to dienes.



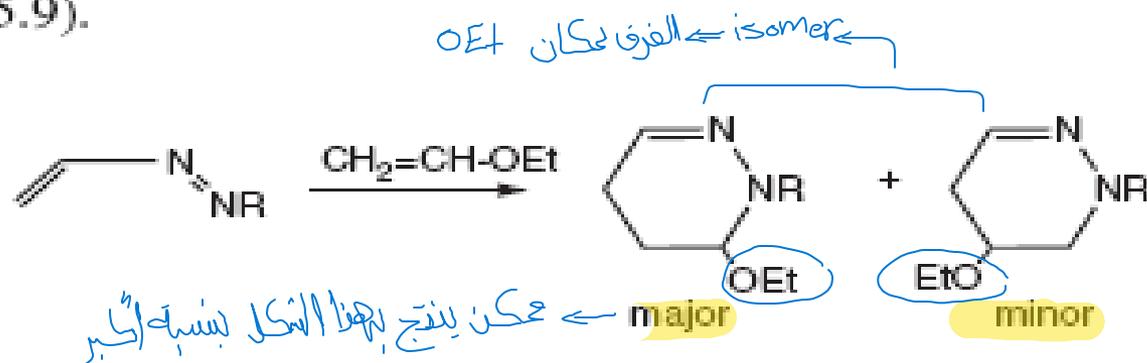
Scheme 5.7

An imine is used as the dienophile in Scheme 5.8.

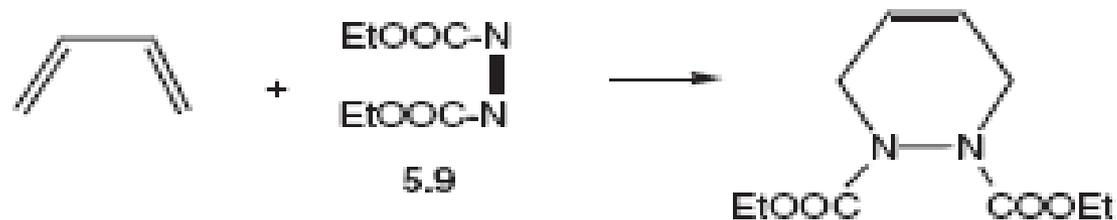


Scheme 5.8

5.1.3.3. Synthesis of Pyridazines. In some hetero Diels–Alder reactions, two isomers can be formed from the use of an unsymmetrical dienophile with an unsymmetrical diene. That was the case in Scheme 5.6, and it is shown again in a synthesis of a pyridazine (Scheme 5.9).

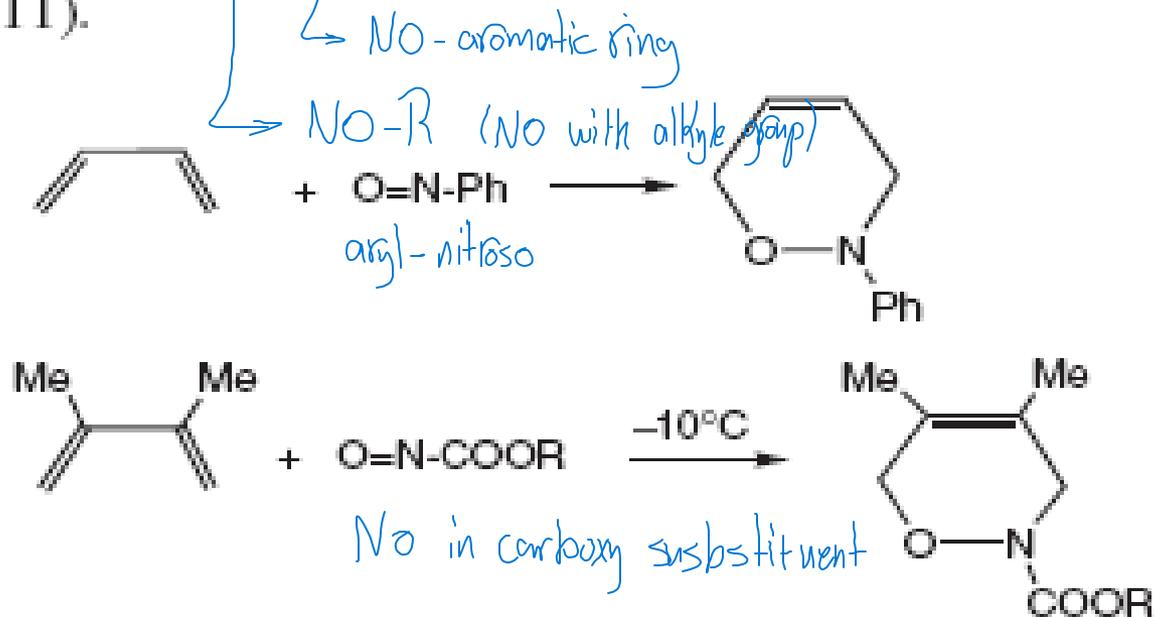


Scheme 5.9



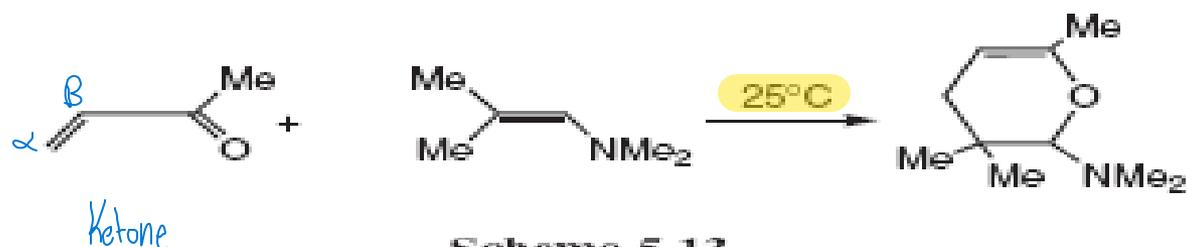
Scheme 5.10

5.1.3.4. Synthesis of 1,2-Oxazine Derivatives. The $\text{N}=\text{O}$ group in certain nitroso compounds ($\text{R}-\text{N}=\text{O}$) is well known to function as a dienophile, and it provides easy access to the 1,2-oxazine family. However, simple alkyl nitroso compounds are generally not stable and tend to dimerize. Aryl nitroso compounds are more stable and are useful in this process. The $\text{N}=\text{O}$ group is also more stable with a carboalkoxy substituent on nitrogen, and it too is useful as a dienophile (Scheme 5.11).



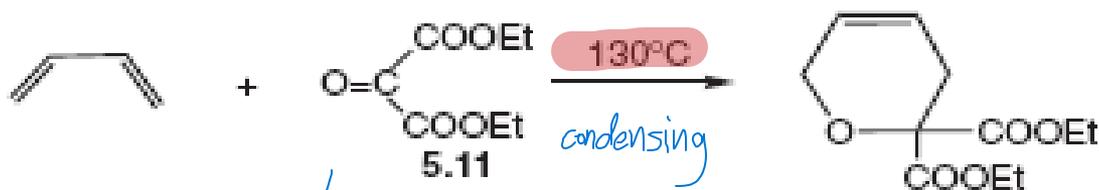
Scheme 5.11

5.1.3.5. Synthesis of Oxygen Heterocycles. Alpha, beta-unsaturated ketones can cycloadd dienophiles of sufficient reactivity (thus with inverse electron demand). This is the case in the reaction in Scheme 5.13 where a pyran derivative is formed.



Scheme 5.13

Pyran derivatives can also be prepared by condensing an activated carbonyl group, as in 5.11, with dienes (Scheme 5.14).



Scheme 5.14

activated carbonyl group

5.2. DIPOLAR CYCLOADDITIONS

5.2.1. Definitions and Examples of 1,3-Dipoles

يعني فيه جز جواعلى الذرات
شحنات بس المجموع إلهم يساوي صفر

← الشحنة الكلية تساوي صفر

- Many compounds, while neutral overall, have a positive and a negative atom and for which no resonance structure can be written that has no charges. ← كما بقدر نرسم المركب بدون حاليه فتح الشحنات صفر لوجاهه*

- In cycloaddition chemistry, we are dealing with the case where the charged atoms are separated by a single atom and are called 1,3-dipoles.

تتفاعل

- These compounds are reactive to alkenes and alkynes, as well as to heteroatom derivatives of these, in a cycloaddition process that forms 5-membered heterocycles. (حلقة خماسية)

→ are alkene, alkyne

- These unsaturated participants are called dipolarophiles. and heteroatoms
- Dipolar cycloadditions are perhaps the most versatile of all derivative. syntheses of 5-membered heterocycles.

← أفضل الطرق لتكوين

مركب يحتوي على خمس ذرات

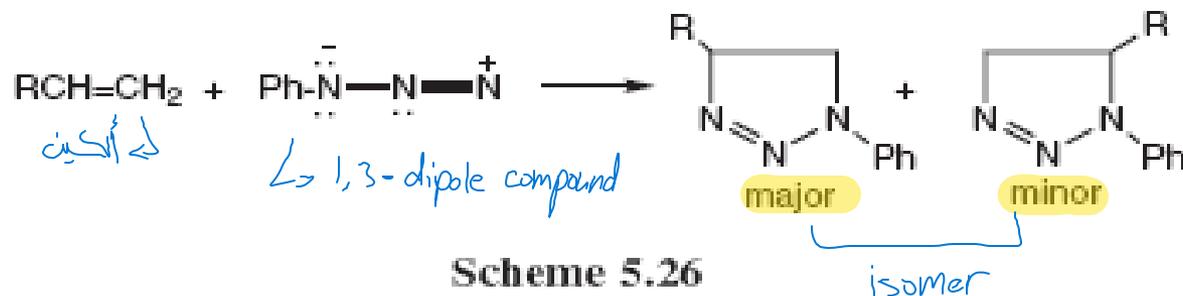
(حلقة خماسية) تحتوي على

ذرات غير متجانسة

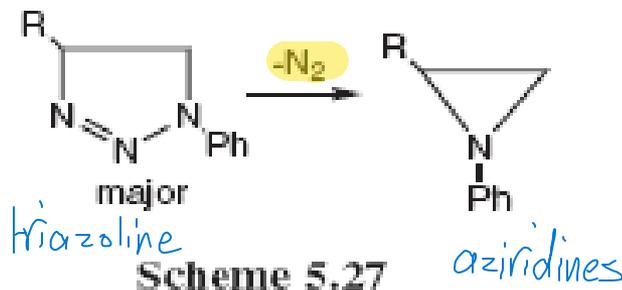
- 1,3-Dipoles have another characteristic feature:
- The central atom must have an electron pair to stabilize the species by dispersal of the positive charge. why?!
للتثبيت الجزئي عن طريق توزيع الشحنة الموجبة
- The central atom therefore cannot be carbon; it is in fact usually nitrogen, although oxygen and sulfur are other possibilities.

5.2.2. Cycloadditions of Alkenes and Alkynes with 1,3-Dipoles

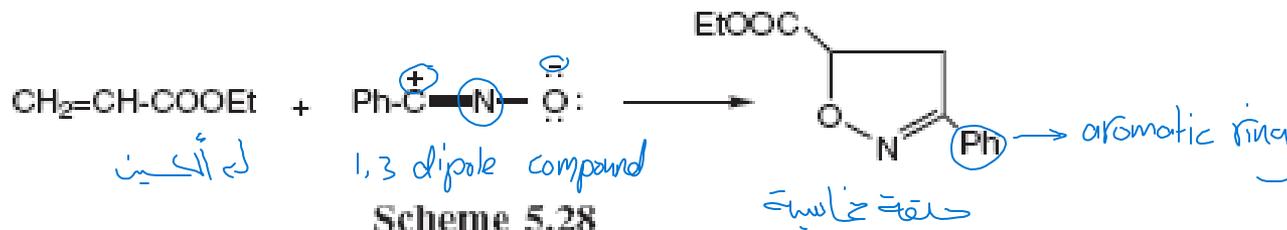
- 5.2.2.1. 1,2,3-Triazole Derivatives from Azides.



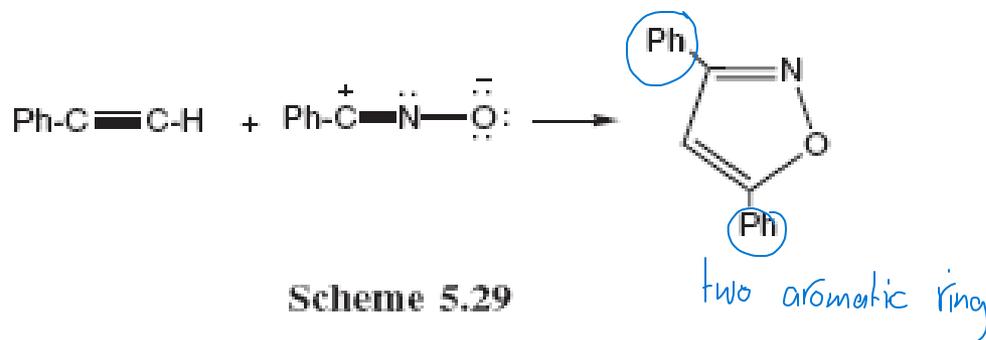
Such triazolines are unstable and smoothly eliminate N_2 , leaving an aziridine as a product. This is a useful synthetic method for making aziridines.



5.2.2.2. Isoxazole Derivatives from Nitrile Oxides.



5.2.2.3. Isoxazoles from Nitrile Oxides.



Note the useful feature that using an alkyne as the dipolarophile with an unsaturated dipole leads to the valuable fully unsaturated, aromatic ring system. See also Scheme 5.30 for another example of heteroaromatic synthesis.