



لجان التفتحات

PHARMACEUTICAL ORGANIC CHEMISTRY"2"

MORPHINE ACADEMY

MORPHINE
ACADEMY

SYNTHESIS OF HETEROCYCLIC SYSTEMS BY CYCLOADDITION REACTIONS

✳️ ال Target :-
تحفظ
← الهدف إنك تعلم كيف تكون حلقات دحتوي "heteroatoms" مثل N, O, S
· باستخدام تفاعلات اسمها Cycloaddition.
← دهج مركبين مع
بعض وتكون حلقة

5.1. THE DIELS–ALDER REACTION



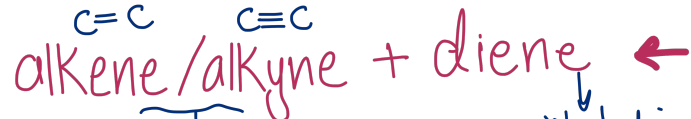
- In its simplest form, it consists of the reaction of a diene with an an alkene or an alkyne, generally those that are activated by the attachment of an electron withdrawing group.

غني بالالكترونات

diene

← مجموعة لساحبة للإلكترونات

تفاعل Diels-Alder ، هو تفاعل بين



لازم يكون هوي عشان يسحب الالكترونات
ويهيى reactive (EWG)

فيه رابطتين مزدوجتين

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

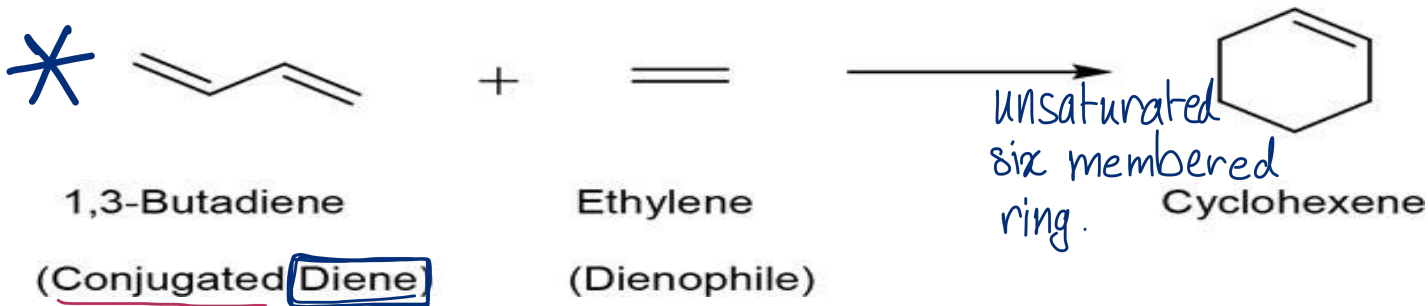
• the reaction involves the formation of a cyclic product via a cyclic transition state, it is also referred to as a "cycloaddition".

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

التفاعل يحدث على 8-

4 إلكترونات من الدياتين
2 = الدياتينوفيل

رابطين شائتين
مفصولتين
برابطة
احادية
واحدة



رهنج مشتقات الـ 3

Synthesis of Pyridine Derivatives.

CN

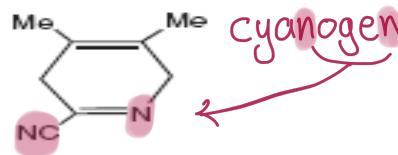
The use of a nitrile group as the dienophile is illustrated in Scheme 5.7, where cyanogen, CN-CN, cycloadds to a simple diene.

Normally, simple nitriles are unreactive to dienes.

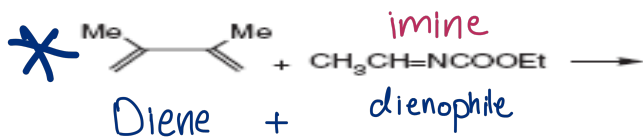
لأنه حرارة عالية ← CN غالباً ما يتفاعل بس الحالات معينة بعد يدخل التفاعل.



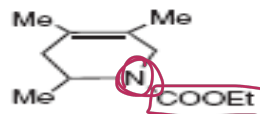
Scheme 5.7



An imine is used as the dienophile in Scheme 5.8.

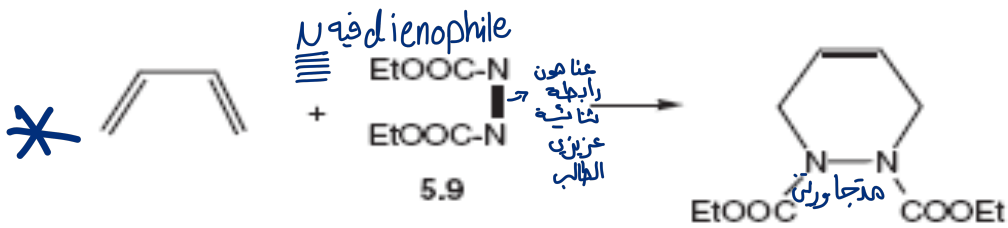
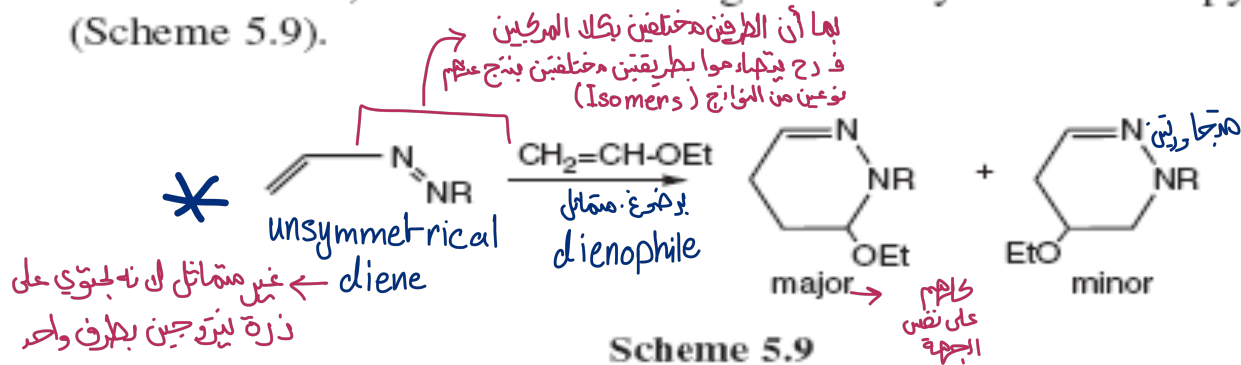


Scheme 5.8

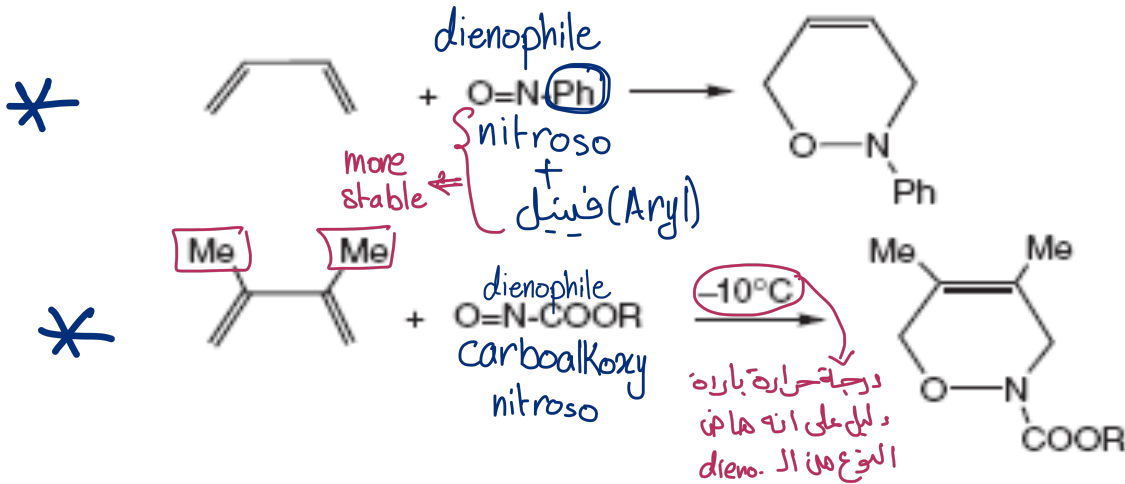


← حلقة لساد لسيه دحتوي على نرتي نيتروجين متجاورتين

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).



5.1.3.4. Synthesis of 1,2-Oxazine Derivatives. The N=O group in certain nitroso compounds (R-N=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 N=O group is also more stable with a carboalkoxy substituent on nitrogen, and it too is useful as a dienophile (Scheme 5.11).

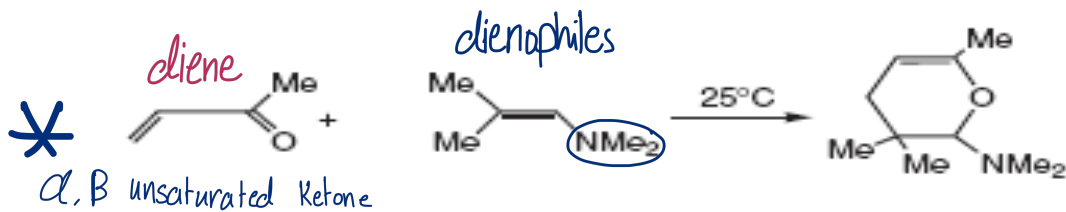


Scheme 5.11

نشط جدا

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.

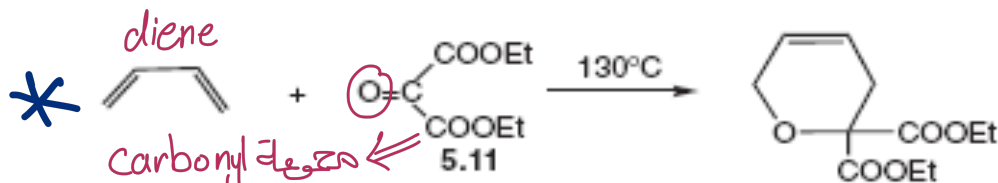
نوع التفاعل
Inverse
electron
demand
cycloaddition



احفظ لثوبه ان
لتوي

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

5.2. DIPOLAR CYCLOADDITIONS

5.2.1. Definitions and Examples of 1,3-Dipoles

- 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.*
- 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.
← الشحنة الموجبة على الذرة رقم واحد + الشحنة (-) على 3 + الذرة رقم 2 هي التي تفصل بينهم
- 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.
حلقات خماسية غير متجانسة
- These unsaturated participants are called dipolarophiles.
محببة
- Dipolar cycloadditions are perhaps the most versatile of all syntheses of 5-membered heterocycles.
هي الطريقة الأكثر تنوعاً وهرونية لتخليق الحلقات الخماسية غير المتجانسة

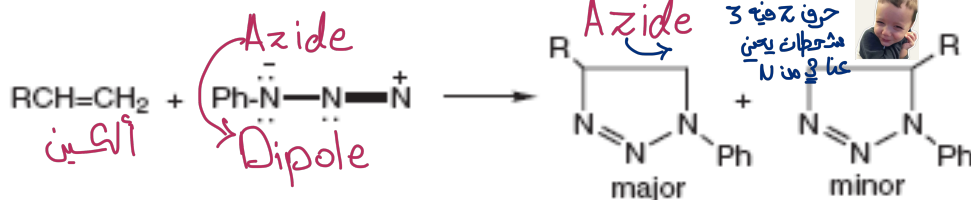
- 1,3-Dipoles have another characteristic feature:
- The central atom must have an electron pair to stabilize the species by dispersal of the positive charge.
- The central atom therefore cannot be carbon; it is in fact usually nitrogen, although oxygen and sulfur are other possibilities.

لأنهما لا يمتلكان زوج الإلكترونات الحر لتكامله وتوزيع الشحنة
Why?
يمكن تكون

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

نتيجه من الازايد

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

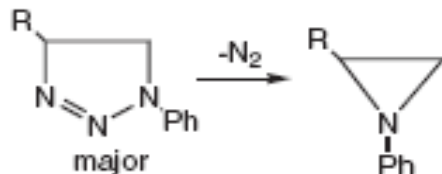


Scheme 5.26

Ph/R يحاد عن بعض
 يتفقد الاله بسهولة

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

تكوين
 aziridine

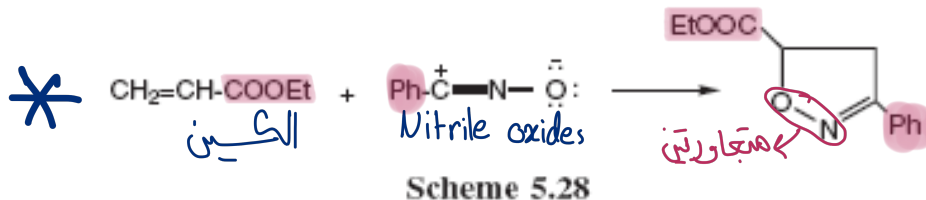


Scheme 5.27

بعد ما يطالع التروجين
 بتكتمش الحلقة من عكاسية
 ال حلقة تك بيتة متغيرة
 اسمها Aziridine

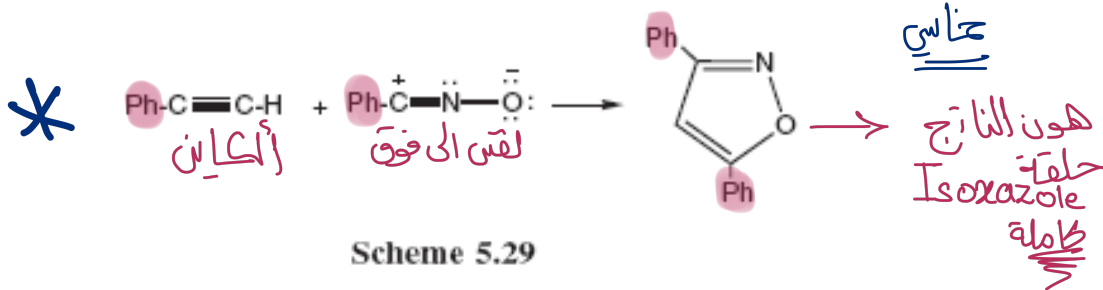
Dipole

5.2.2.2. Isoxazole Derivatives from Nitrile Oxides.



خماسي

5.2.2.3. Isoxazoles from Nitrile Oxides.



خماسي

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.

* Diels - Alder :-

→ Diene + Dienophile

→ يَكُونُ حَلَقَةً سداسية

* Dipolar cycloaddition :-

→ 1,3-dipole + Alkene

→ يَكُونُ حَلَقَةً خماسية