

chapter 3

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SYNTHESIS OF HETEROCYCLIC SYSTEMS BY **CYCLOADDITION** REACTIONS

الطريقة الثانية في تصنيع المركبات

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**.

تفاعل جدا بسيط مبني على اني افاعل مركب في تنتين من الرابطة الثنائية مع الكين او الكاين

diene = alkene + alkene (2 double bond)

conjugated : double , single , double

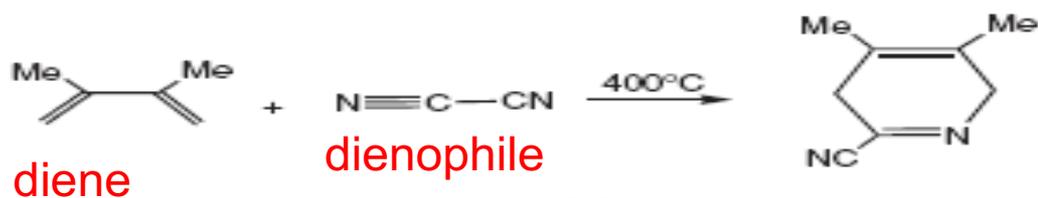
- The **Diels–Alder reaction** is the reaction between a conjugated diene and an alkene (dienophile) to form unsaturated six-membered rings.
- the reaction involves the formation of a cyclic product via a cyclic transition state, it is also referred to as a "cycloaddition".
- The Diels–Alder reaction 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.



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.

Normally, simple nitriles are unreactive to dienes.



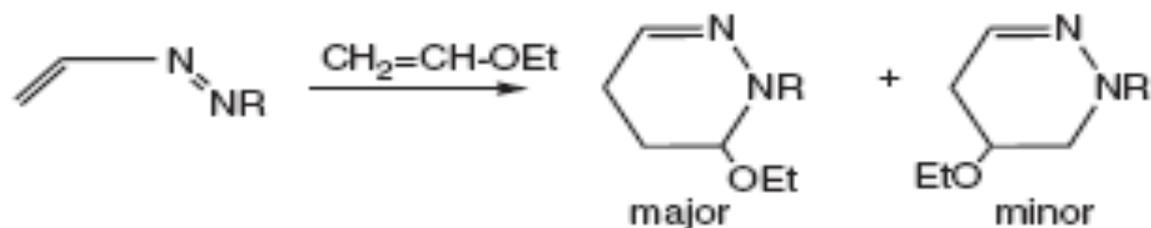
Scheme 5.7

An imine is used as the dienophile in Scheme 5.8.

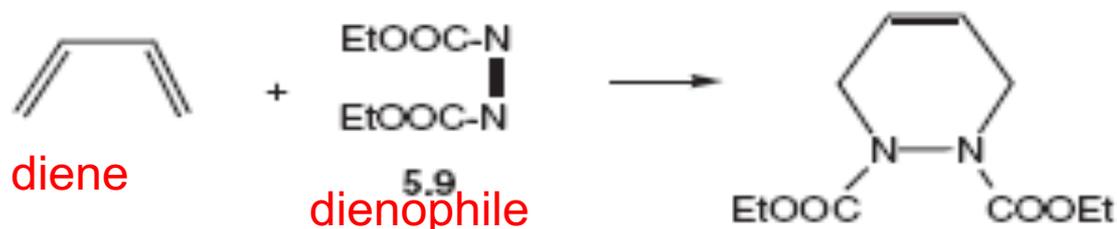


Scheme 5.8

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).



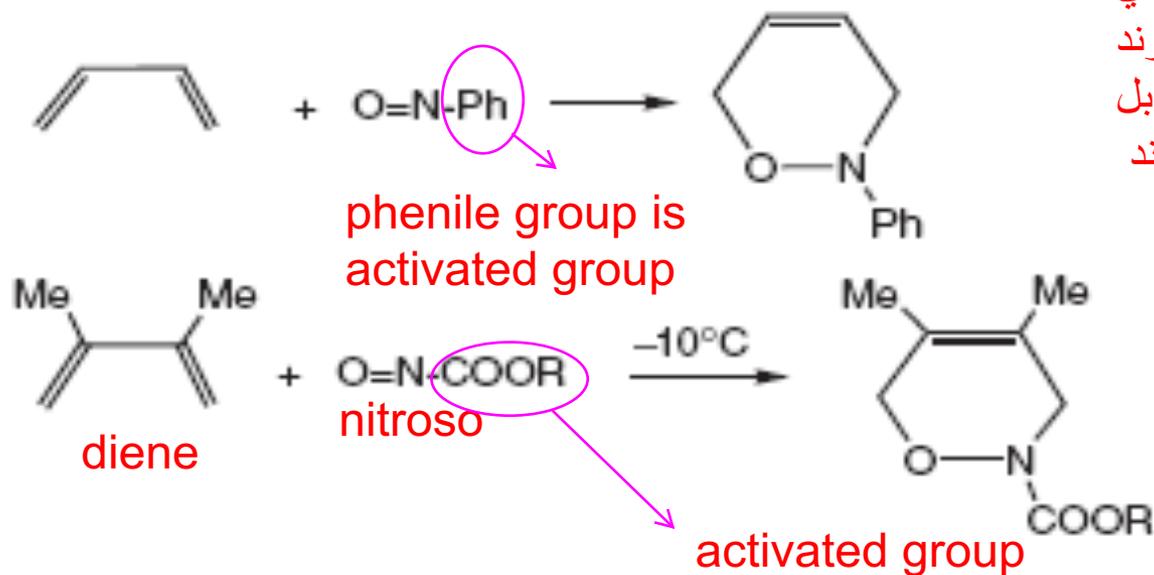
Scheme 5.9



Scheme 5.10

not fully unsaturated compound \longrightarrow oxidation \longrightarrow fully unsaturated compound

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).

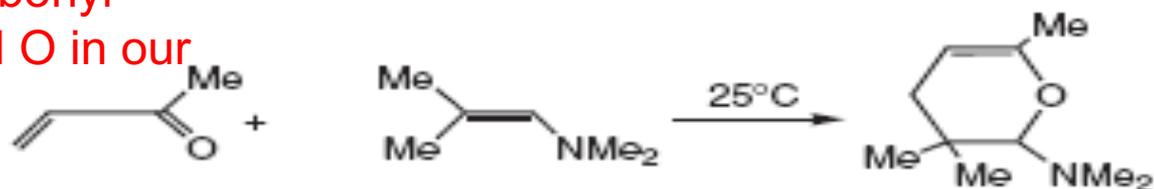


Scheme 5.11 is ester

باختصار لازم يكون عندي طرف فيه تنتين دبل بوند والطرف الثاني فيه دبل بوند وحدة او تربل بوند

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.

dienophile >> carbonyl
because we need O in our
structure

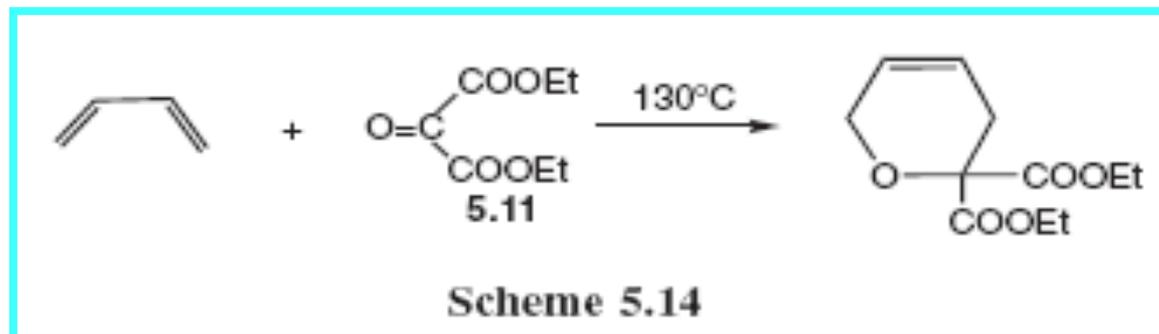


Scheme 5.13

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

طريقة ثانية للتصنيع
ولكن تحتاج طاقة
اكبر والي هي عبارة
عن

alpha beta
unsaturated
system



Scheme 5.14

انتبهو هون كل المركبات الي صنعناهم عبارة عن حلقات سداسية

1,3 dipoles

هاد التفاعل بعني اني استخدم مركب مكون من 3 أجزاء

لازم يكون عندي central atom

تحتوي على e- pair

الفكرة من وجودها انها بتعمل

stabilization to positive charge in the compound

بالتالي هاي الذرة ممنوع تكون كربون

الجزء الأول شحنته سالبة

الجزء الثاني يحتوي على

زوج من الالكترونات ولازم

يكون عبارة عن اكسجين او

نيتروجين او سلفر

الثالث شحنته موجبة

بعدين بفاعلهم مع الكين او الكاين
وهاي الطريقة هي اكثر طريقة شائعة

لتصنيع مركب خماسي

5.2. DIPOLAR CYCLOADDITIONS

5.2.1. Definitions and Examples of 1,3-Dipoles

هون رح نصنع حلقات خماسية

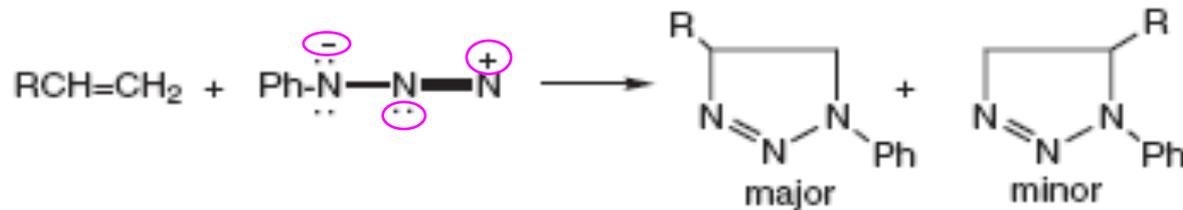
- Many compounds, while neutral overall, have a positive and a negative atom and for which no resonance structure can be written that has no charges.*
- In cycloaddition chemistry, we are dealing with the case where the charged atoms are separated by a single atom and are called 1,3-dipoles.
- These compounds are reactive to alkenes and alkynes, as well as to heteroatom derivatives of these, in a cycloaddition process that forms 5-membered heterocycles.
- These unsaturated participants are called dipolarophiles.
- Dipolar cycloadditions are perhaps the most versatile of all syntheses of 5-membered heterocycles.

- 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.

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

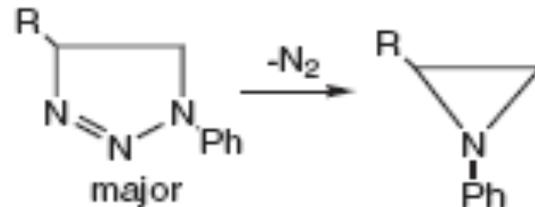
3 ذرات N

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



Scheme 5.26

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

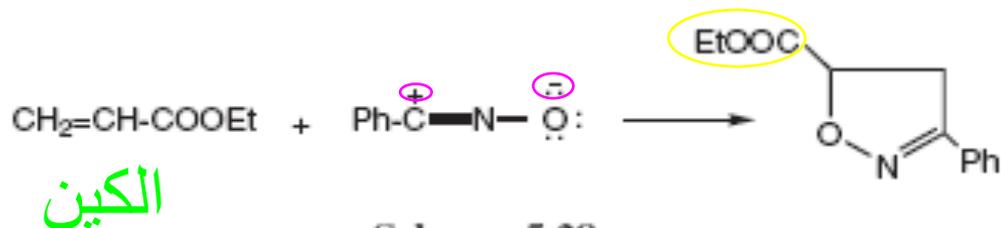


Scheme 5.27

highly active

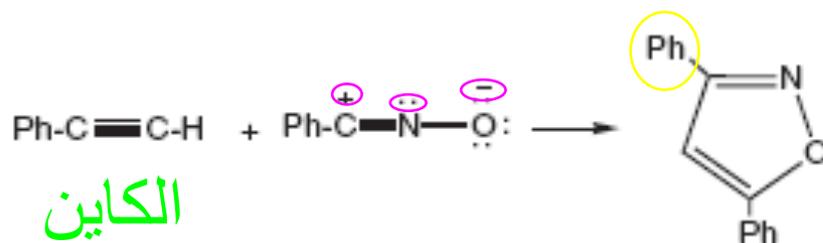
يستخدم في تصنيع
مركبات السرطان

5.2.2.2. Isoxazole Derivatives from Nitrile Oxides.



Scheme 5.28

5.2.2.3. Isoxazoles from Nitrile Oxides.



Scheme 5.29

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.