chapter 2 part 2

lama nofal

PRINCIPLES OF SYNTHESIS OF AROMATIC HETEROCYCLES

Here, we will only describe some of the more versatile common methods that produce unsaturated rings of five and six members, for such rings constitute major backbones on which more complicated structures can be constructed.

the most common rings : six member

the most common ring hetero atom : nitrogen

معظم المركبات الطبيعية تحتوي على hetero cyclic system مكون من bond of N

اكثر الحلقات شيوعا هم : الخماسية والسداسية وتركيزنا رح يكون عليهم

اما الحلقات الثلاثية والرباعية والسباعية اقل شيوعيا والحلقات الثلاثية استخدامها في الادوية يكاد يكون معدوم

Most reactions that form heterocycles are of the following two general types:

(1) intramolecular reactions, discussed between two functional groups at the ends of a chain; and

(2)cycloaddition reactions, where two different molecules with the proper unsaturation interact with the formation of two new sigma bonds tying the two molecules together.

their are two way of reaction :

1)intra molecular interaction : التفاعل هون يحدث في نفس الذرة

2) cyclo addition : in which we make reaction

((هون بنعتمد على نظام الالكين double bond

جزئين مختلفين بفاعلهم مع بعض وبعطوني cyclic structure

رح يكون تركيزنا اليوم عن reaction intra molecular cyclization

I have to make reaction contain carbonyl group-

من خصائص مجموعة الكاربونيل :

1) a polarized atom : ذرة الكربون بتكون (+ partial) والاكسجين بتكون (- partial)

2) بقدر افاعلها مع الاكسجين والفسفور و النيتروجين

general mechanism of reaction :

1) لازم يكون عندي acidic condition

2) لما اضيف الحمض للوسط عندي الاكسجين رح ياخد الالكترونات لانه (partial -) بتصير شحنة الذرة موجبة

3) نتيجة لهاد الاشي بتنكسر الرابطة الثنائية مع مجموعة االكاربونيل بتصير الكربونة (electrophile) غير مستقرة وبتحمل شحنة موجبة

4) الي موجود بالوسط عندي وعلى سبيل المثال كان الامونيا رح neucleophile الـ ترتبط بالكاربونيل وبتكون عنا رابطة بينهم

The Use of Familiar Reactions of Aldehydes and Ketones

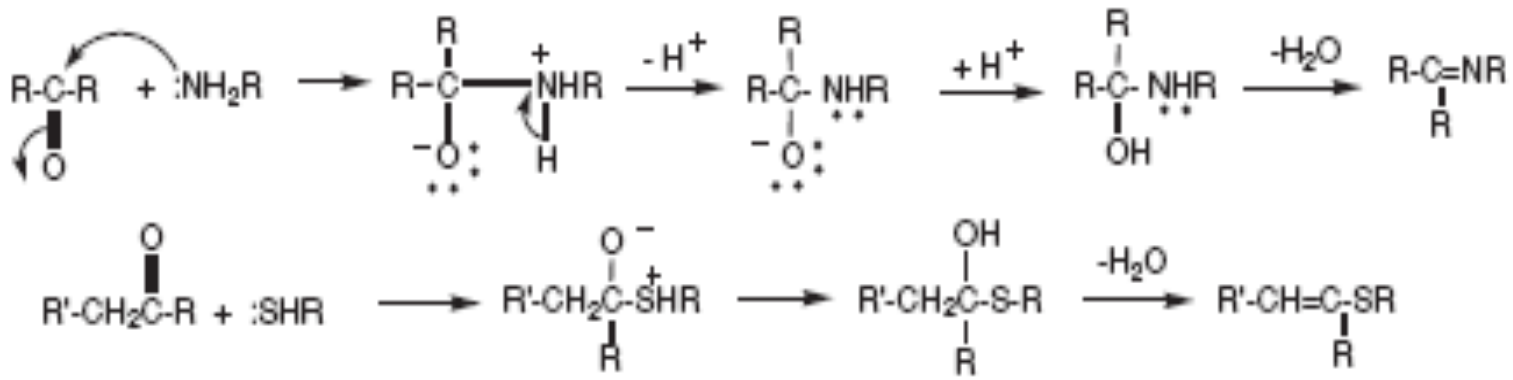
4.2.1.1. Review. The carbonyl group of aldehydes and ketones is

electrophilic and receptive to addition of common nucleophiles, generally those that have "active" (i.e., not bonded to carbon) hydrogen atoms.

This includes ammonia, primary and secondary amines, water,alcohols, and thiols (mercaptans). It is common after the addition for a water molecule to be eliminated, either forming a carbon-heteroatom double bond or a carbon-carbon double bond, as directed by the structures. Examples of each are shown in Scheme 4.1.

Note that the addition product always undergoes charge neutralization by proton loss from nitrogen and protonation of oxygen that creates the OH group.

This reaction is one of the easiest ways to form a carbon–heteroatom bond, and we will observe this sort of chemistry in many syntheses to follow. Note that the addition product always undergoes charge neutralization by proton loss from nitrogen and protonation of oxygen that creates the OH group.



Scheme 4.1

هاد التفاعل يعتمد على وجود the paal-knorr synthesis of pyrroles
dicarbonyl (aldedyde or ketone) and primary amines or ammonia
المركب رح يتفاعل مع نفسو ويعمل cyclization لانه هاد التفاعل intramolecular
المركبات عندي في حالة الـ intramolecular cyclization بتكون عبارة عن dicarbonyl compound
اذا بدي الامينو قروب تكون عبارة عن substitution رح اضيف بدل الامونيا primary amine

الأمين رح تهاجم اول مجموعة كاربونيل ورح تكون عندي imine
معظم التفاعلات في cyclization لازم يكون عندي dehydration يعني لازم اخسر مي عشان احصل على unsaturated form

**مركباتي ممكن تكون عبارة عن

1)keto aldehyde
2)diketone
3)dialdehyde

بمعنى اخر رح يكون عندي

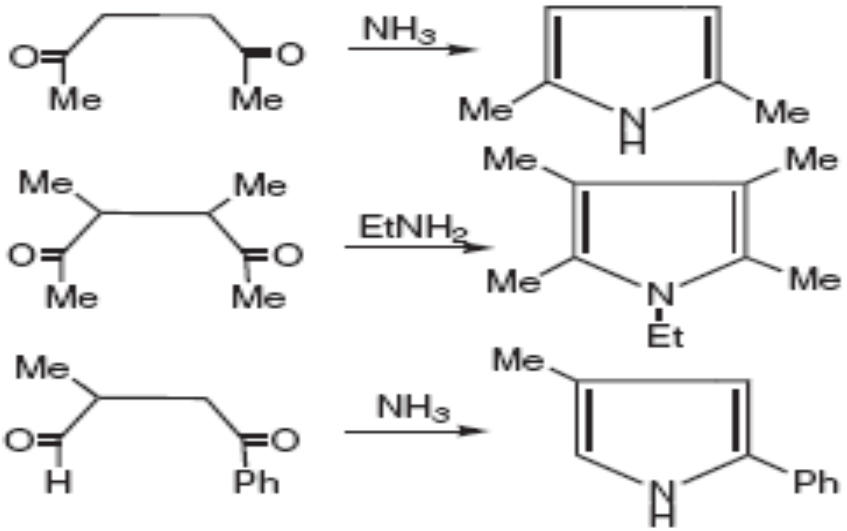
1) H H
2) CH3 H
3) CH3 CH3

ولازم ما ننسى انو تفاعلاتي هاي رح تصير بوسط حامضي acidic condition
ومارح تكون concentrationرح تكون (1.4) diluted acid with dicarponyl

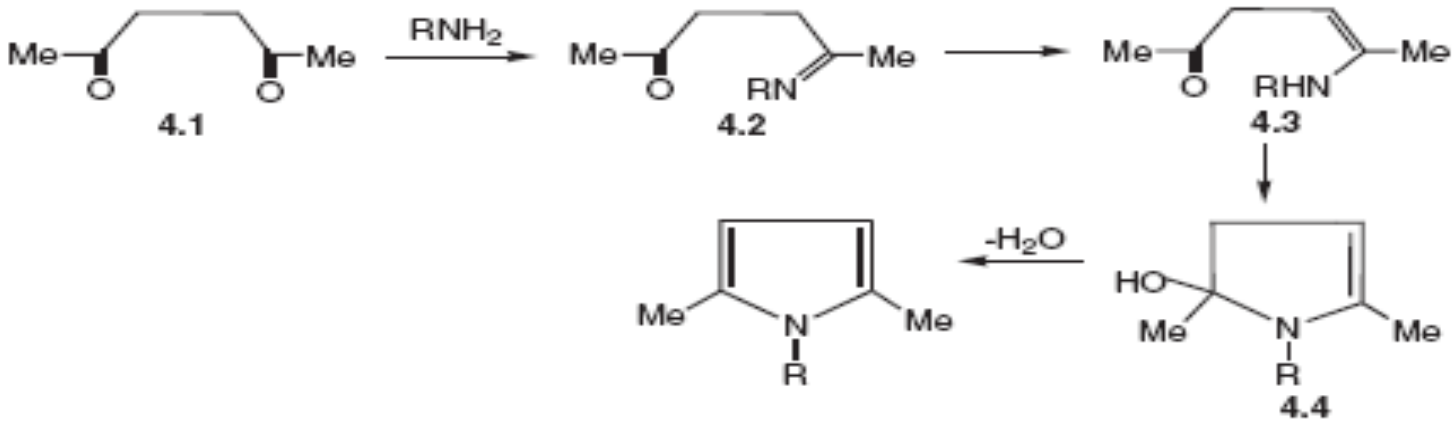
عبارة عن حلقة خماسية غير مشبعة unsaturated

هاد التفاعل عبارة عن intramolecular cyclization

4.2.1.2. The Paal-Knorr Synthesis of Pyrroles. The Paal–Knorr method makes use of a 1,4-di-carbonyl compound (aldehyde or ketone) in reaction with primary amines or ammonia. Many pyrroles have been made by this general process. Alkyl and some other substituents are allowed on the dicarbonyl chain. Diketones, dialdehydes, and ketoaldehydes all serve as reactants. Primary amines give rise to 1-alkylpyrroles. Examples of the overall process are shown in Scheme 4.2.



Scheme 4.2



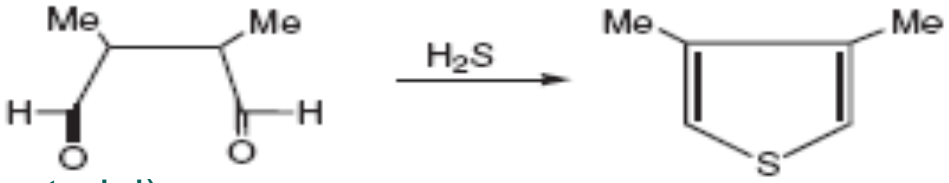
Scheme 4.3

The process is illustrated in Scheme 4.3. An important feature to note is that imine **4.2 rearranges to the enamine 4.3, which is the species supplying an N-H group for attack on the** second carbonyl group.

nucleophile عبارة عن

4.2.1.3. The Paal–Knorr Synthesis of Thiophenes and Furans.

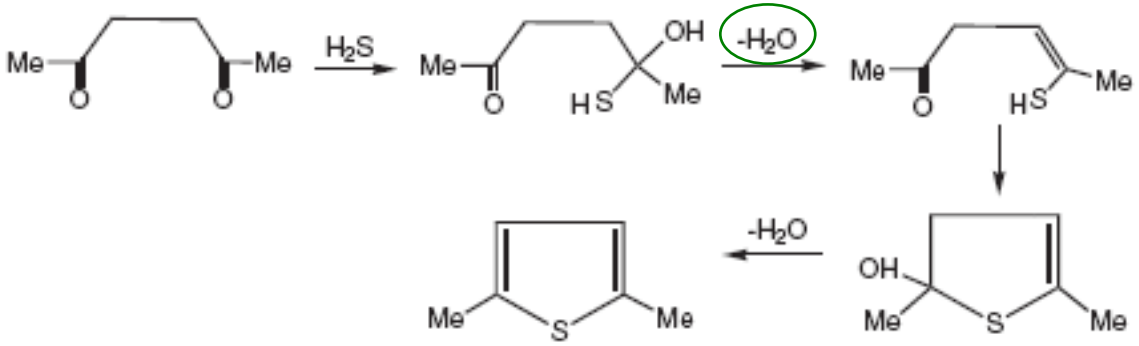
Hydrogen sulfide can replace ammonia in the Paal–Knorr process and provide a synthesis of the thiophene ring. As in the synthesis of pyrroles, many 1,4-dicarbonyl compounds can be used in this process, which is exemplified by the synthesis of 3,4-dimethylthiophene (Scheme 4.4).



dicarbonyl (starting material)
thiophene وبنتج عندي H2S بفاعلهم مع

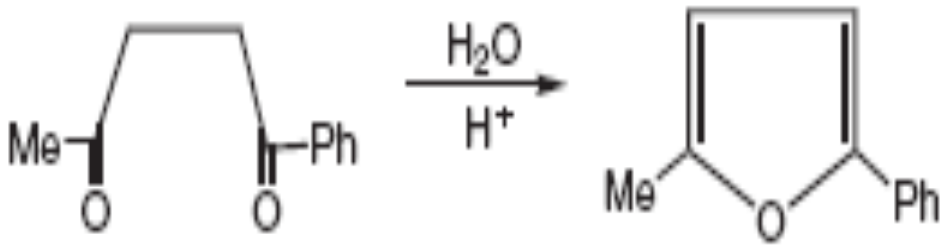
Scheme 4.4

dehydration



Scheme 4.5

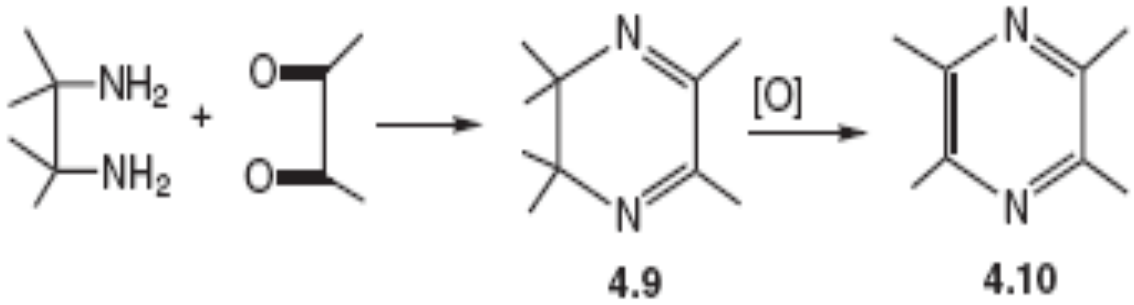
When dilute aqueous acid is reacted with a dicarbonyl compound, the reaction presumably follows the same course through water addition to a carbonyl and provides furans (Scheme 4.6).



Scheme 4.6

حلقة سداسية النيتروجين موجود عالموقع الأول والرابع

4.2.1.5. Synthesis of Pyrazines from 1,2-Diamines. The condensation reaction of amines and carbonyl compounds can be applied to the synthesis of pyrazines (1,4-diazines). Here, a 1,2-diamine is reacted with an alpha-dicarbonyl compound. The usual reaction takes place to form two C=N bonds thus tying the two reactants together as viewed in Scheme 4.8. The product is a dihydropyrazine (**4.9**).
Mild oxidation converts the dihydropyrazine to the aromatic pyrazine (**4.10**).

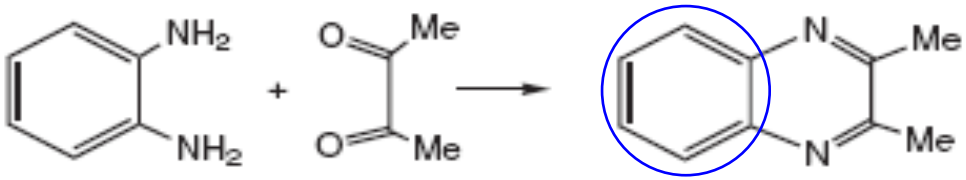


4.9 **4.10**

Scheme 4.8

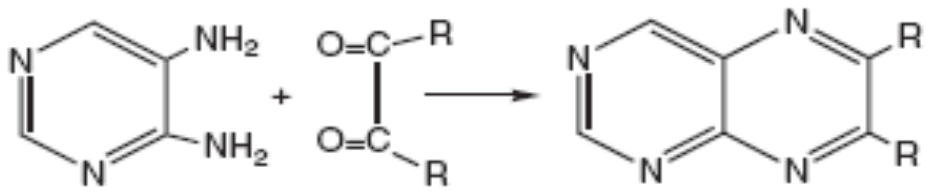
In practice, aliphatic diamines are less useful than ortho-diaminobenzenes (also called ortho-phenylenediamines), and the reaction is best known as a synthesis of benzopyrazines (quinoxalines, Scheme 4.9).

رح استغل وجود البنزين عشان اعمل مركب حلقي
بالتالي رح يهاجم البنزين مجموعة الكاربونيل ويكون بينهم رابطة
إضافة الكاربونيل تحتم علي اخسر هيدروجين لانه تفاعل استبدال



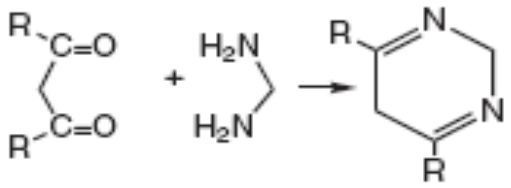
Scheme 4.9 حلقة بنزين

A valuable extension of this process is to react a heterocyclic diamine with a diketone. In Scheme 4.10, a diaminopyrimidine is employed.



Scheme 4.10

4.2.1.6. Formation of Pyrimidines from beta–Dicarbonyl and 1,1-Diamino Compounds. Yet another application of the amine–carbonyl reaction is viewed in the construction of the pyrimidine ring. Here a 1,1-diamino compound reacts with a beta-dicarbonyl compound, as is outlined in Scheme 4.12.



Scheme 4.12

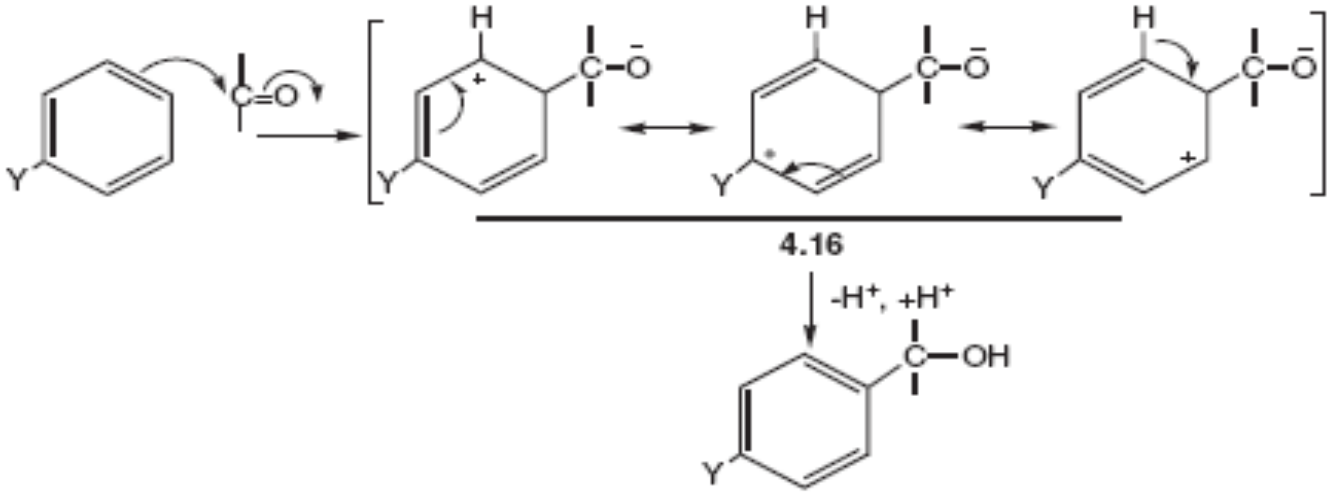
nucleophile : O/N/S

ممكن اعتبر الرابطة الثنائية كمان لانها نظام غني بالاكترونات

لازم ما ننسى انو هاد الحكي كلو بوسط حامضي

acidic condition

4.2.1.7. Electrophilic Attack of Carbonyl Groups on the Benzene Ring. The benzene ring, if properly activated, can react with aldehydes and ketones according to Scheme 4.15, wherein an electron pair from the ring is donated to the electrophilic C=O group to form a C–C bond. The intermediate carbocation (**4.16) is stabilized by resonance** and then loses a proton. The formation of an aromatic ring drives the reaction forward.



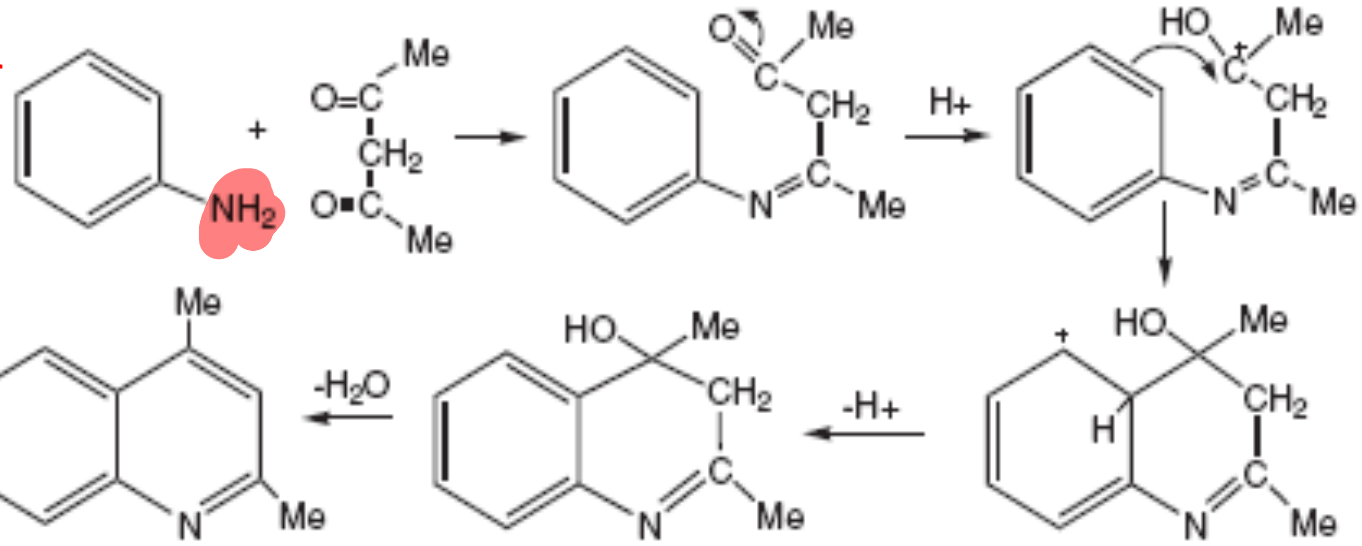
Scheme 4.15

benzene + pyridine

This reaction is employed in **the Combes synthesis of quinolines**(Scheme 4.16). A side-chain with a terminal carbonyl group is first attached to the benzene ring. Acid catalysis then promotes the attack of C=O on the ring by the adding of a proton to the carbonyl oxygen to increase its electrophilicity; acid also catalyzes the elimination of water from the intermediate to generate the aromatic pyridine component of quinoline.

Many quinolines have been prepared by this and related methods in the search for new antimalarial drugs.

حلقة بنزين + امينو

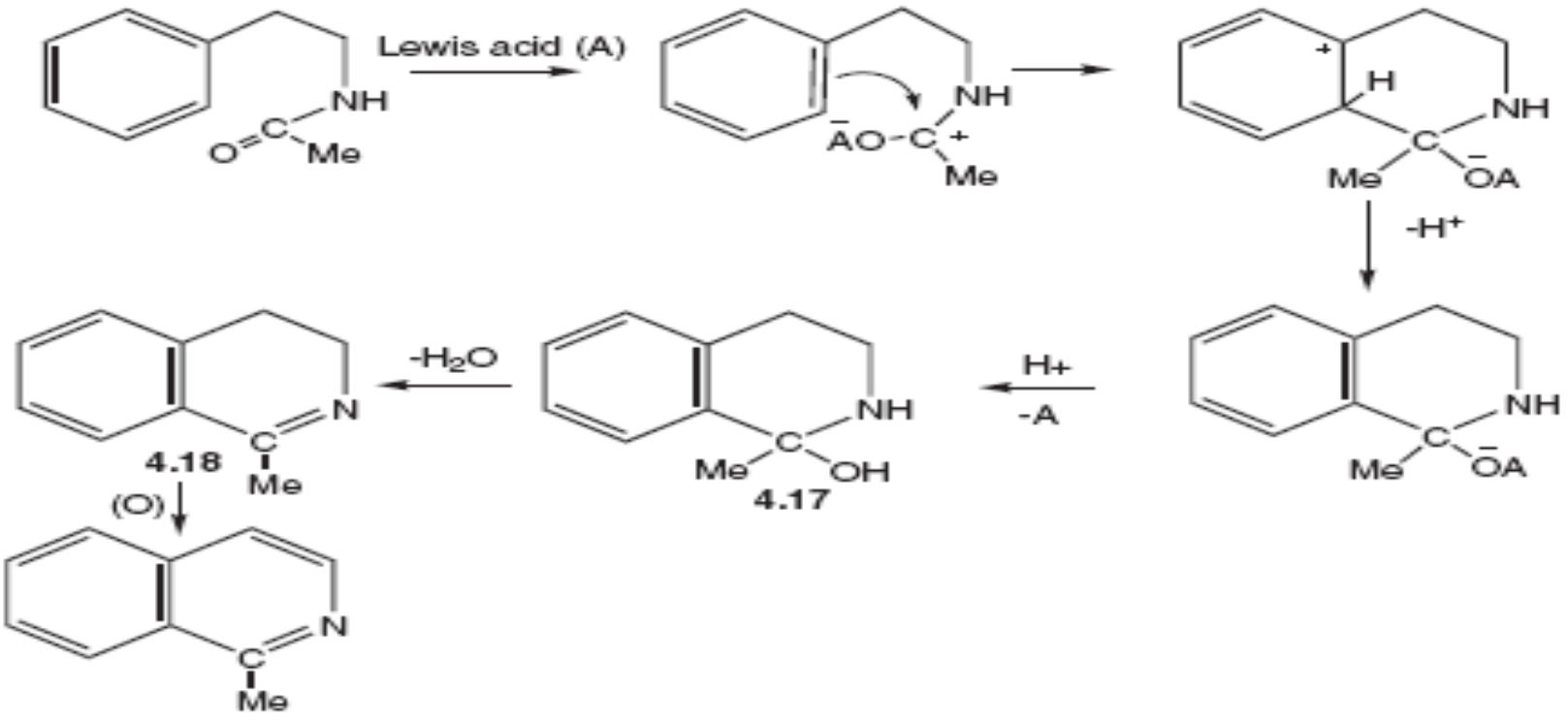


Scheme 4.16

in the first step the ameno work as nucleophile

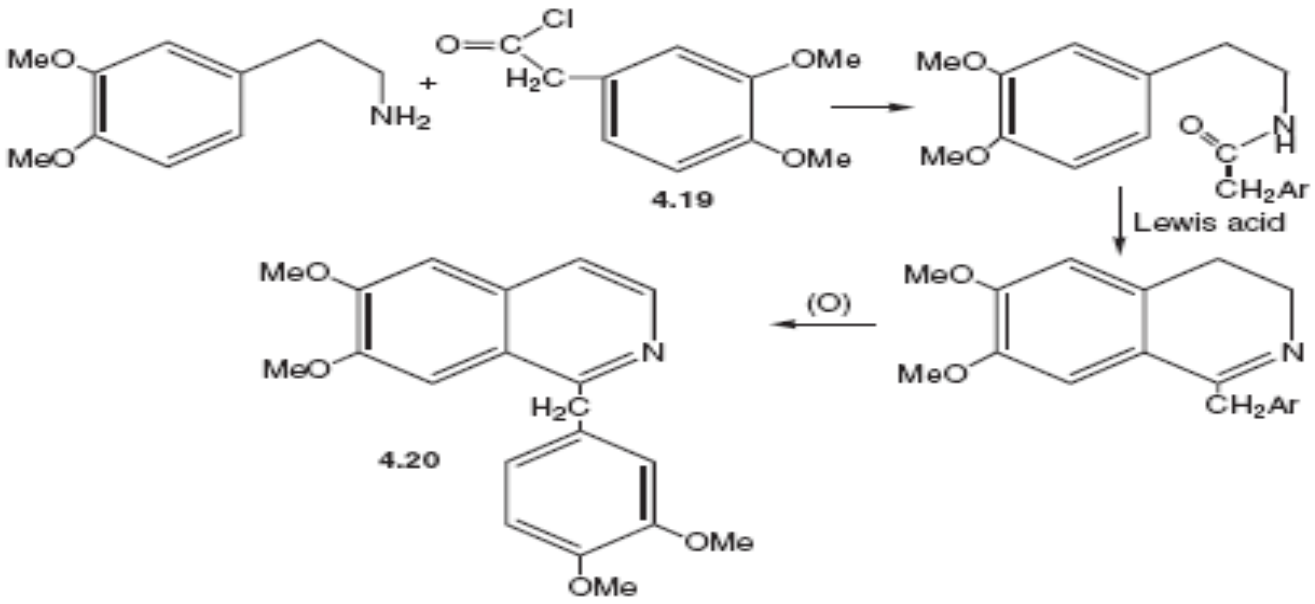
the second step the benzene work as nucleophile

Similar chemistry is employed in the important Bischler–Napieralski synthesis of isoquinolines. Here the carbonyl is in the form of an amide group, at the end of a chain on the benzene ring. The carbonyl attack on the ring is promoted with such reagents as Lewis acids, $POCl_3$, and P_2O_5. The reaction with a Lewis acid may be visualized as in Scheme 4.17, where the hydroxy intermediate **4.17** is formed and eliminates water to give a C=N bond. The product is a dihydroisoquinoline (**4.18**), which is easily oxidized (aromatized) to the isoquinoline. The reaction with the phosphorus reagents probably involves phosphorus-containing intermediates.[2]



Scheme 4.17

Many structures are found in the isoquinoline family of alkaloids (see section 3.2), and the **Bischler–Napieralsk**i method has been of considerable value in synthesizing some of them. An example is the synthesis of papaverine, **4.20 (Scheme 4.18, where Ar refers to the** dimethoxyphenyl substituent).



Scheme 4.18