chapter 4

lama nofal

Artery Academy

PI-DEFICIENT AROMATIC HETEROCYCLES

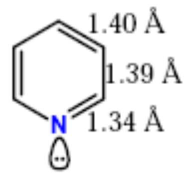
pyridine is the best example for pi-deficient

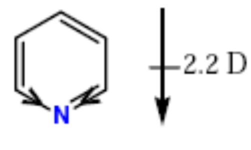
- **A Study of Pyridine as an Illustrative Model**
- **Properties of PyridineC_5H_5N**

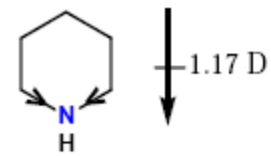
- Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating odours that are unpleasant. Pyridine is the hydrogen derivative of this ring, it is benzene in which one CH- or methine group is replaced by a nitrogen atom. The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N.
- **Pyridine**
- Molecular Weight/ Molar Mass 79.1 g/mol
- Density 982 kg/m^3
- Boiling Point 115 °C
- Melting Point −41.6 °C

Pyridines – Structure

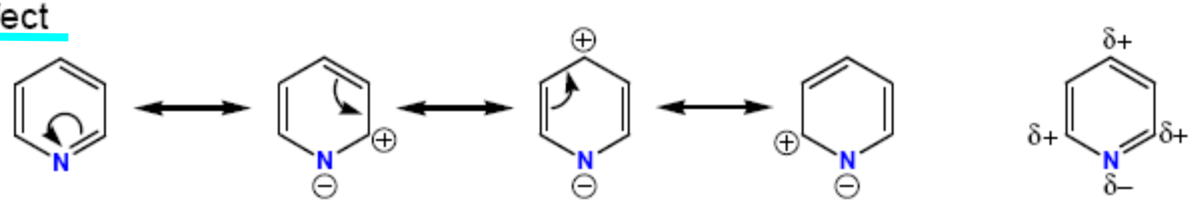
من بعض خصائصه



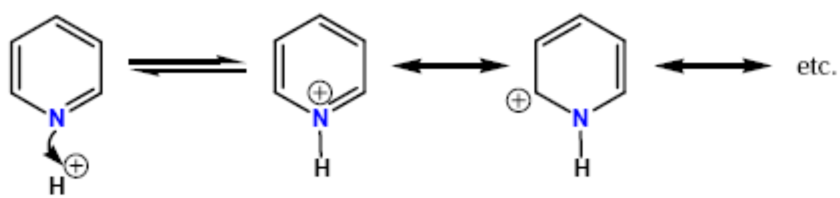




- Isoelectronic with and analogous to benzene
- Stable, not easily oxidised at *C*, undergoes substitution rather than addition
- –I Effect (inductive electron withdrawal)
- –M Effect



- Weakly basic – pK_a ~5.2 in H_2O (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more δ+ than in parent pyridine



polyatomic molecules فيه ذرات متعددة

- **Key Difference – Inductive Effect vs Mesomeric Effect**

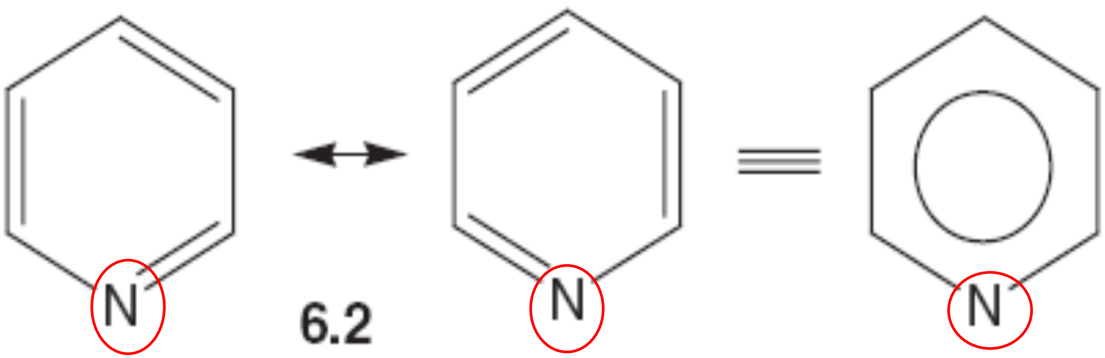
- Inductive effect and mesomeric effect are two types of electronic effects in polyatomic molecules. However, inductive effect and mesomeric effect arise due to two different factors. For example, **inductive effect is a result of the polarization of σ bonds and mesomeric effect is a result of the substituents or functional groups in a chemical compound**. Both mesomeric and inductive effect can exist in some complex molecules.

هدول الشغلتين باثرو على الحلقتين وعلى تفاعلاتهم

polarization : 2 atom different from each other and one of them is more electro negativity than the second

- It is weakly basic and is miscible with water.
- It is highly flammable and when inhaled or ingested it becomes toxic. احد سلبياته
- Some symptoms, when exposed to pyridine, are nausea, asthmatic breathing, vomiting, headache, laryngitis, and coughing.
- It is widely used in the precursor to agrochemicals and pharmaceuticals.
- Also, it is used as an important reagent and organic solvent.

- ***Electronic Structure of Pyridine. The presence of the*** electron-withdrawing nitrogen atom in pyridine has a profound effect on its properties.

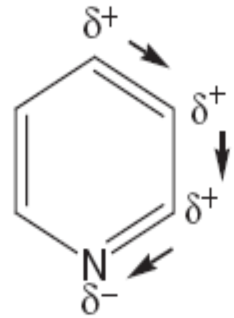


6.2

وجود النيتروجين بالحلقة رح يخليها تخسر electron ditinsy باتجاه النيتروجين

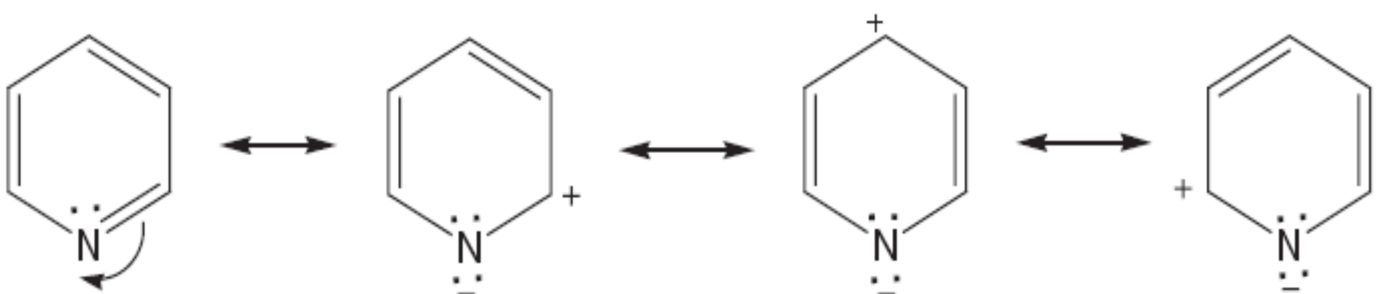
leading the ring to be partially positive and the N be partially negative atom

the electronegative nitrogen atom causes significant polarization of the molecule, as depicted in structure 6.3.



6.3

Also, additional resonance structures can be shown for pyridine, in which an electron pair from an attached double bond can be placed on nitrogen (Scheme 6.3).



Scheme 6.3

This form has divalent but negatively charged N, which is a stable condition for N.

The positive charge is dispersed to carbons around the ring, specifically to C-2 and C-4 (but not to C-3).

The net effect is to reduce the pi-electron density in the ring relative to benzene, and this is the source for the description of pyridine as being pi-deficient.

The combined action of electron induction and resonance delocalization makes pyridine a molecule of considerable polarity.

justify pyridine consider to be as a pi-deficient system NOT pi rich system ???

سؤال ممكن يجي بالامتحان

ansr:

1)N elecrto with drawing so it is pulled the e- towards it

2)leading the carbon system deficiency with e- in the ring

3) The combined action of electron induction and resonance

- ***Geometry of Pyridine. Because N is sp2 hybridized and***
- planar, the entire pyridine molecule is planar, and this is true for other aromatic heterocycles with more than one C=N unit.
- The C to N bonds are shorter than the C to C bonds of benzene; this causes the angles inside the ring (Figure 6.8) to be modified from the 120° observed for the perfect hexagon of benzene.
- The lone pair orbital on nitrogen falls in the plane of the ring, which makes it available for bonding to electrophiles or coordination to metal ions.

Pyridine as a Base. The lone electron pair on nitrogen of
C=N units is available for reaction with protic acids as well as Lewis acids, and this is certainly true for pyridine and other heterocycles.

Pyridine is a weak base and is widely used as a proton acceptor; it has a Kb of 1.*4 × 10−9 (pKb 8.8; pKa for the conjugate acid 5.2).*

*This*is much lower basicity than that of a saturated tertiary amine; triethylamine has Kb 5.*6 × 10−4 (pKb 3.2; pKa for the conjugate acid 10.8).*

This is primarily because of a hybridization effect; with sp2 hybridization (meaning 33% s-character in the orbitals) for C=N rather than sp3 (25% s-character) for tertiary amines, the lone pair orbital is contracted toward the nucleus and is less available for bonding.

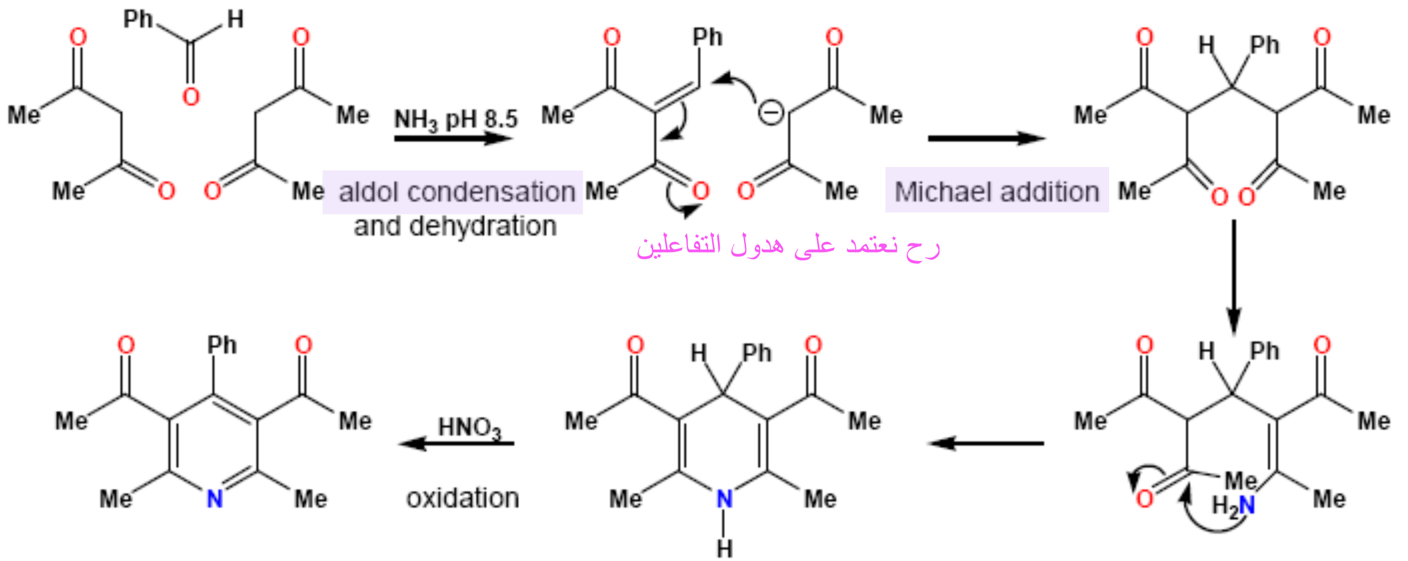
الجواب هاي الفقرة

justify pyridine is weaker base than the saturated tertiary amine ??

- Alkyl groups on the pyridine ring acting by induction and hyperconjugation increase electron density on N, and the three isomers of methyl pyridine (called alpha, beta, and gamma picolines) have greater basicity than does pyridine by 0.6–0.8 pKb units.
- Electron-withdrawing groups have a much more pronounced effect in the opposite direction; thus,
- a nitrogroup at the 2-position reduces the basicity of pyridine by 7.8 *pkb* units.
- This is partly inductive but primarily a pronounced resonance effect.

Pyridines – Synthesis

The Hantzsch synthesis ("5+1")

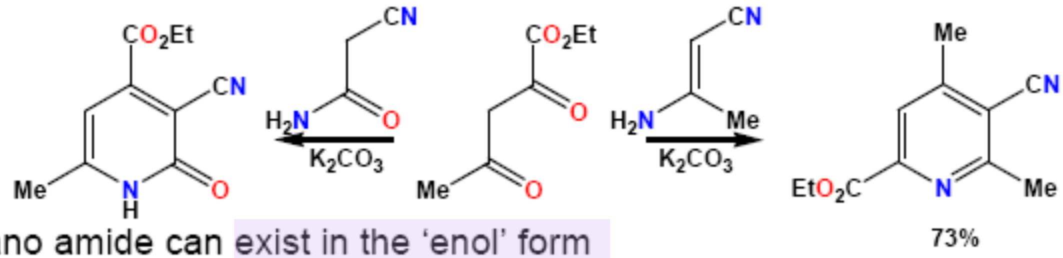


- The reaction is useful for the synthesis of symmetrical pyridines
- The 1,5-diketone intermediate can be isolated in certain circumstances
- A separate oxidation reaction is required to aromatise the dihydropyridine

justify we use HNO_3 ??
to get my reaction full oxidize or to make my ring aromatic

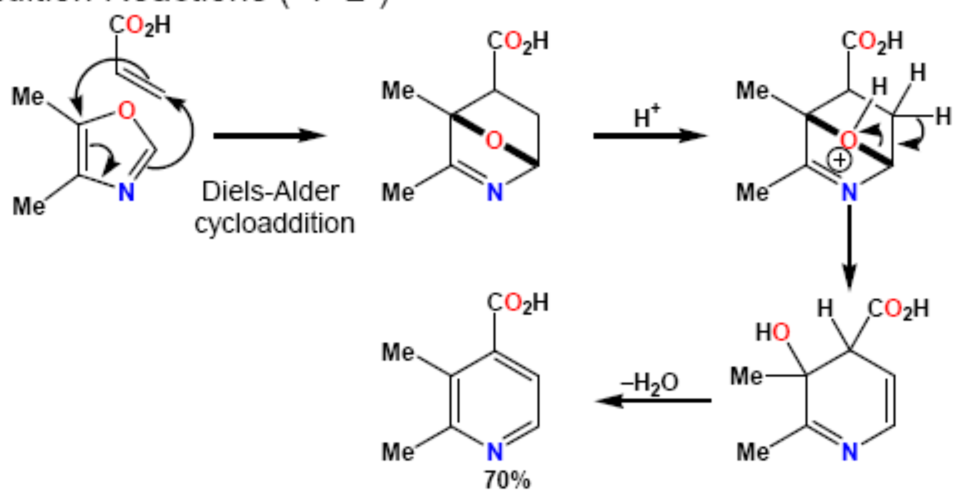
Pyridines – Synthesis

From Enamines or Enamine Equivalents – the Guareschi synthesis (“3+3”)



• The β-cyano amide can exist in the ‘enol’ form

Using Cycloaddition Reactions (“4+2”) diene



• Oxazoles are sufficiently low in aromatic character to react in the Diels-Alder reaction

Reactions Involving the Lone Electron Pair.

Two reactions at nitrogen are of great importance in the chemistry of pi-deficient systems based on this element: **quaternization and oxidation.**

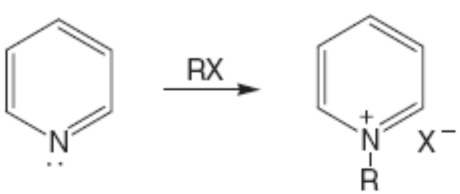
Both, of course, are well known among nonaromatic amines.

Pi-excessive nitrogen heterocycles generally do not participate in these reactions,

Quaternization involves the reaction of a tertiary amine with an alkylating agent.

Typically, primary and some secondary alkyl halides are used for this purpose, although alkyl sulfates have also been used.

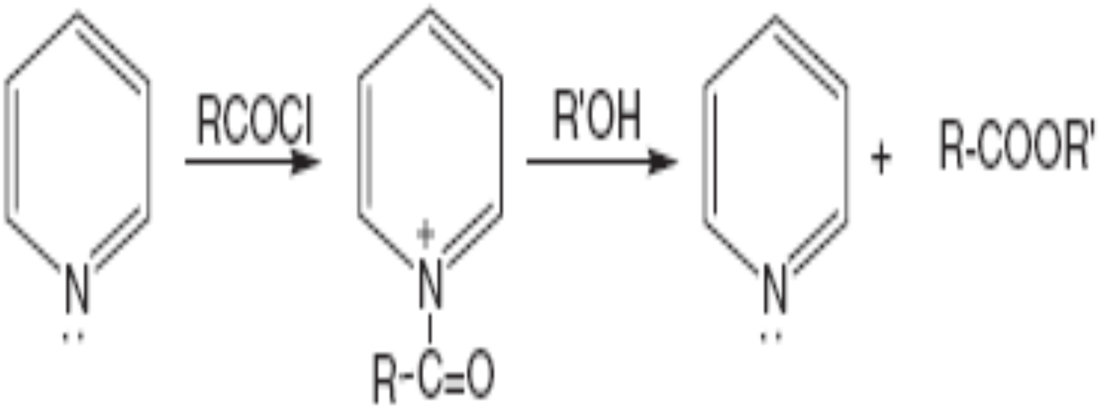
Tertiary halides are not useful because they undergo elimination rather than substitution. The reaction, which is an example of an SN2 process, proceeds readily to give crystalline, stable, and still-aromatic quaternary salts (Scheme 6.6).



Scheme 6.6

Pyridine is useful in promoting the formation of esters from acyl chlorides and alcohols; it may function by reacting first with the acyl chloride to form a salt, which then acts as the acylating agent to the alcohol (Scheme 6.7).

in this situation pyridine will become quaternary after become quaternary we will add alcohol and in this situation the O of alcohol will attack the carbonyl carbon of acyl halide so the linke will be breaking and the pyridine will be free



Scheme 6.7

electrophile : atom which is an electron deficient

في عنا 3 مواقع بقدر اضيف عليها هاد الجزيء

Pyridines – Electrophilic Reactions

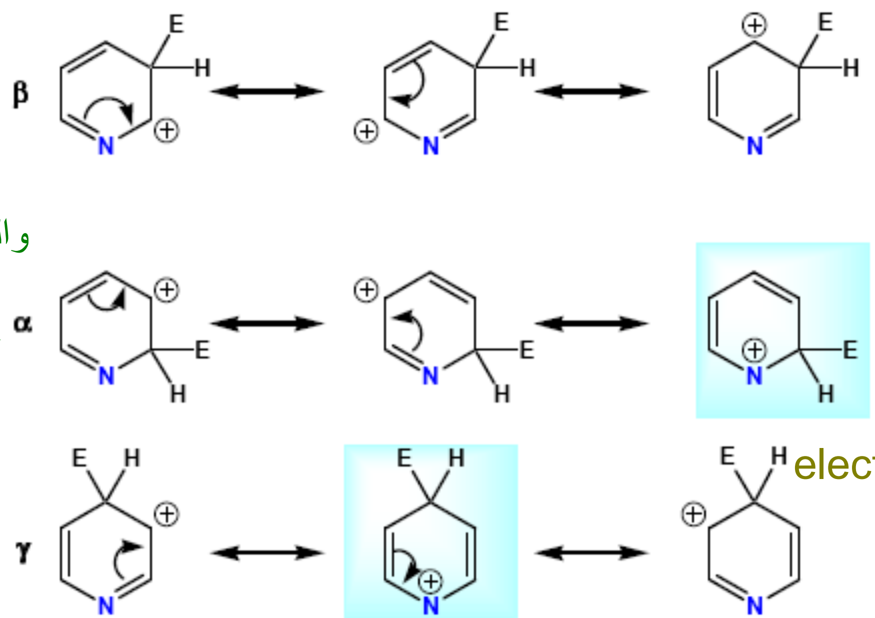
Regiochemical Outcome of Electrophilic Substitution of Pyridines

resonation effect لما بصير عندي

لتوزيع الشحنة الموجبة

electrophilic substitution is preferred in B position rather than a+y

والسبب بهاد انو لما نعمل عملية الإضافة في البيتا الشحنة الموجبة مارح تكون على جزيء النيتروجين ولكن لما نعمل الإضافة عند الالفا و الجاما الشحنة الموجبة رح تكون عند جزيء النيتروجين



this will leave my ring deficient with e- in certain region …

if the ring deficient in e- in certain region

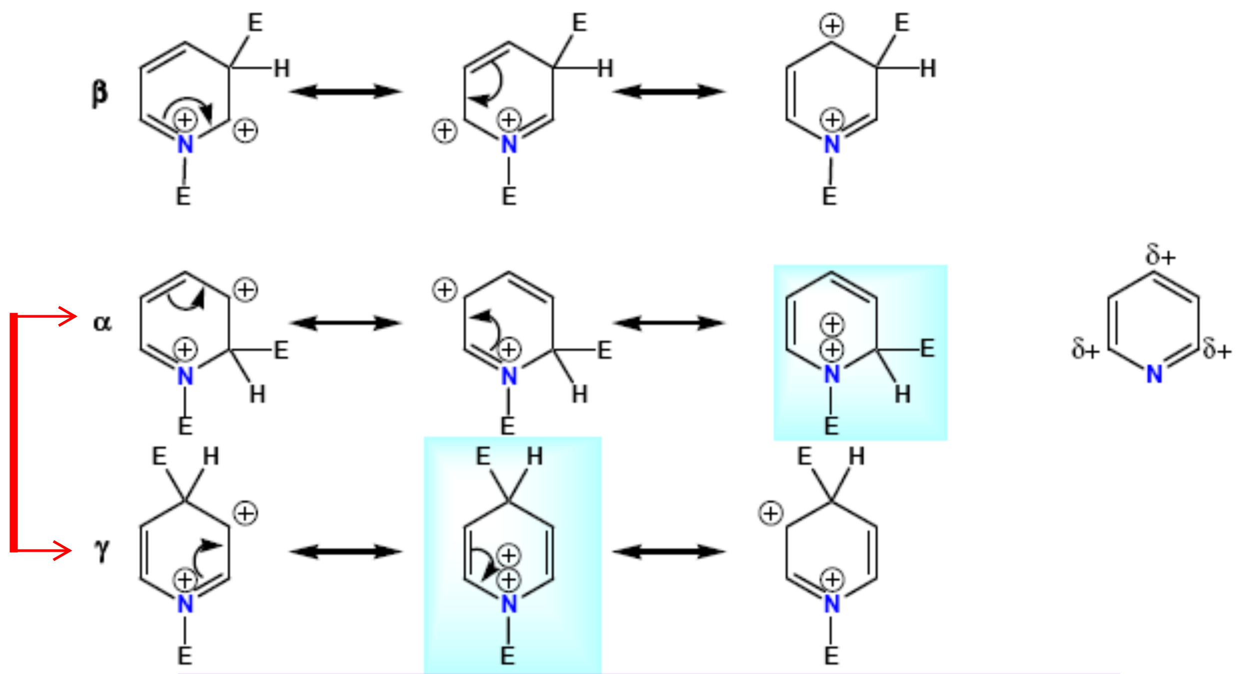
electrophile رح تكون عملية إضافة صعبة

- Resonance forms with a positive charge on *N* (i.e. 6 electrons) are very unfavourable
- The β-substituted intermediate, and the transition state leading to this product, have more stable resonance forms than the intermediates/transition states leading to the α /γ products

Pyridines – Electrophilic Reactions

Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions

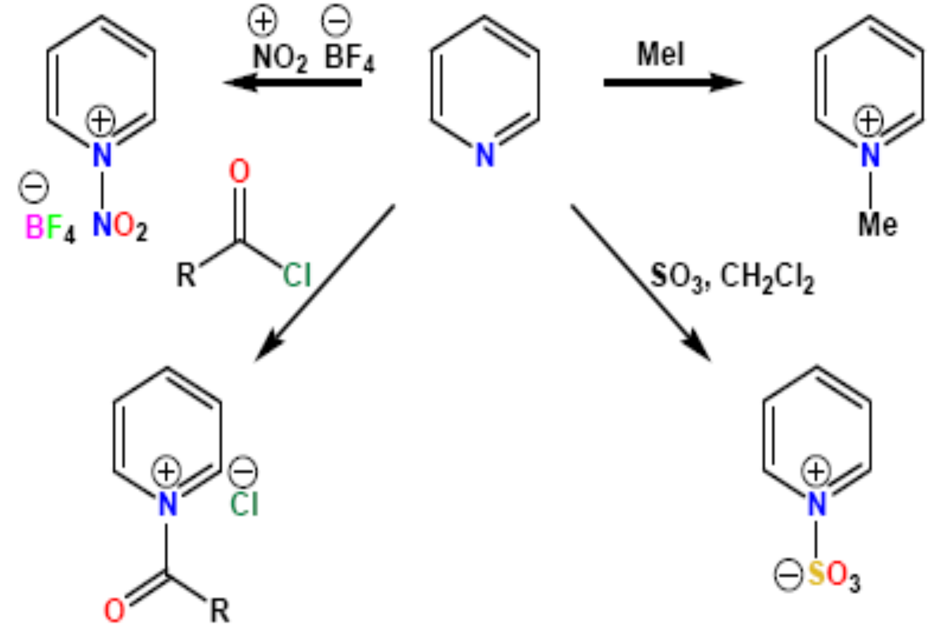
the positive charge will concentrate in N



- Regiochemical control is even more pronounced in the case of pyridinium ions
- In both pyridine and pyridinium systems, β substitution is favoured but the reaction is slower than that of benzene
- Reaction will usually proceed through the small amount of the free pyridine available

Pyridines – Electrophilic Reactions

N Substitution



C Substitution

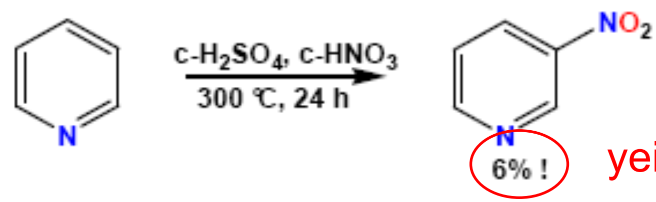
تحتاج ظروف قوية جدا لتتفاعل فيها

- Reaction at *C* is usually difficult and slow, requiring forcing conditions
- Friedel-Crafts reactions are not usually possible on free pyridines

ما يكون عليها أي نوع من أنواع substitution

Pyridines – Electrophilic Reactions

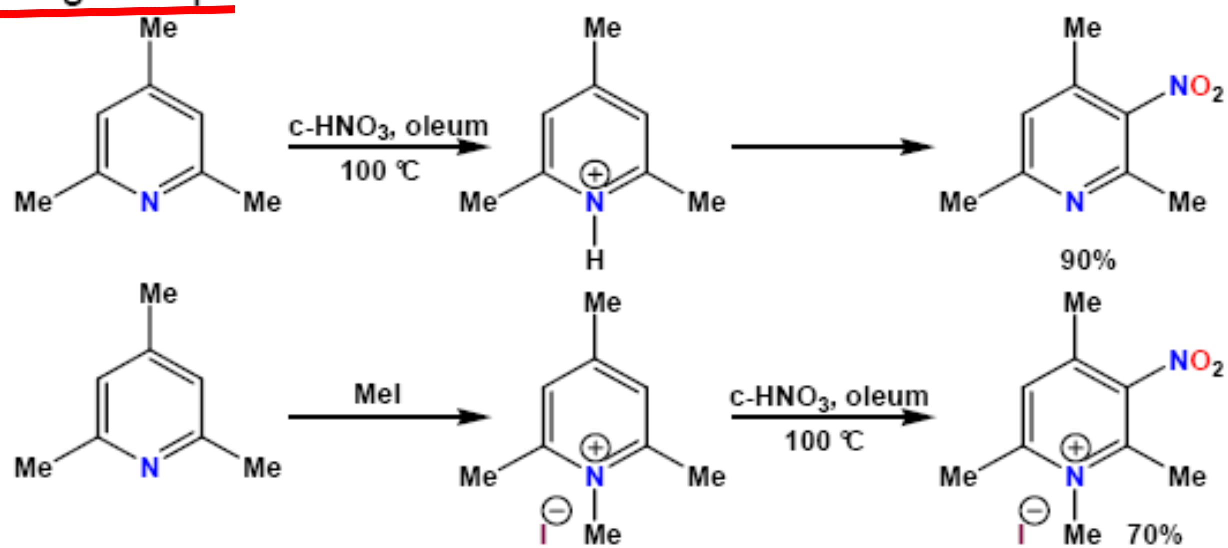
Nitration of Pyridine



yeild قليلة

Use of Activating Groups yeild عشان نزيد

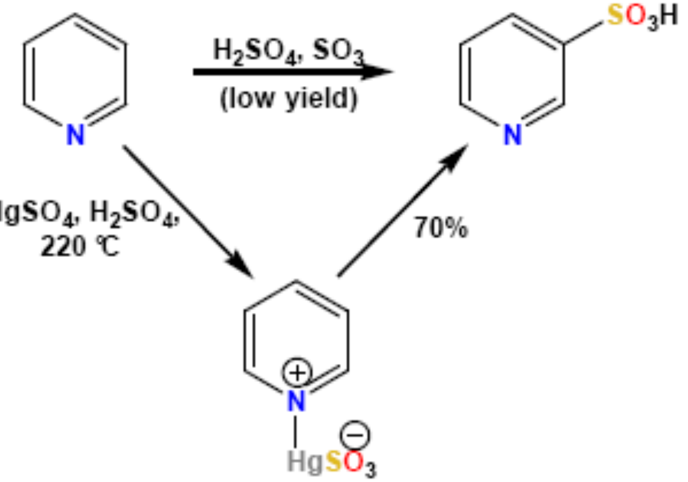
عبارة عن
alkyle group



- Multiple electron-donating groups accelerate the reaction
- Both reactions proceed at similar rates which indicates that the protonation at *N* occurs prior to nitration in the first case

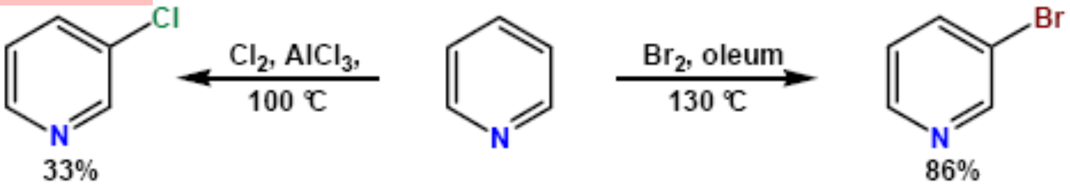
Pyridines – Electrophilic Reactions

Sulfonation of Pyridine



- Low yield from direct nitration but good yield via a mercury intermediate

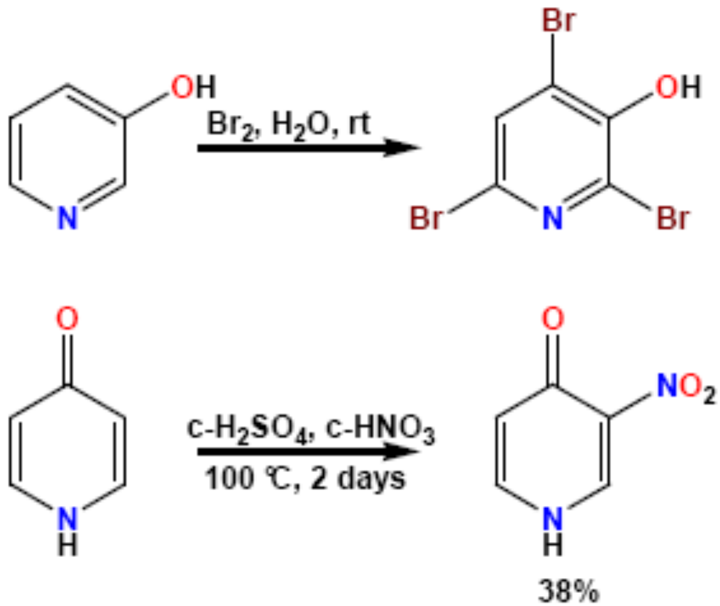
Halogenation of Pyridine



- Forcing reaction conditions are required for direct halogenation

Oxy-Pyridines – Reactions

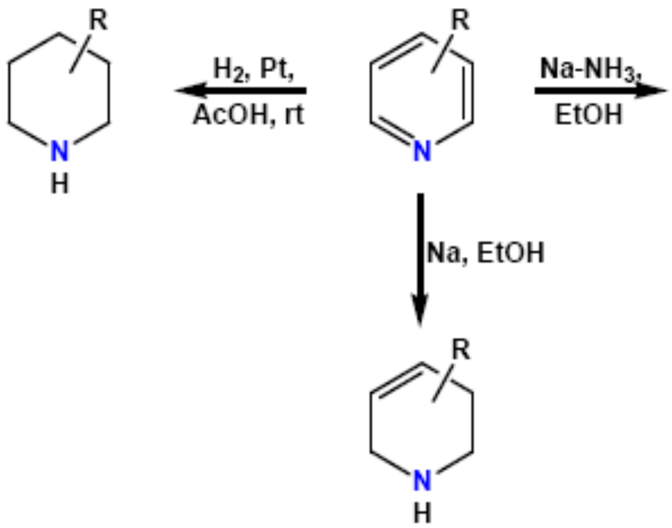
Electrophilic Substitution



- Reactions such as halogenation, nitration, sulfonation etc. are possible
- *N* is much less basic than that in a simple pyridine
- Substitution occurs ortho or para to the oxygen substituent (cf. phenols)

Pyridines – Reduction

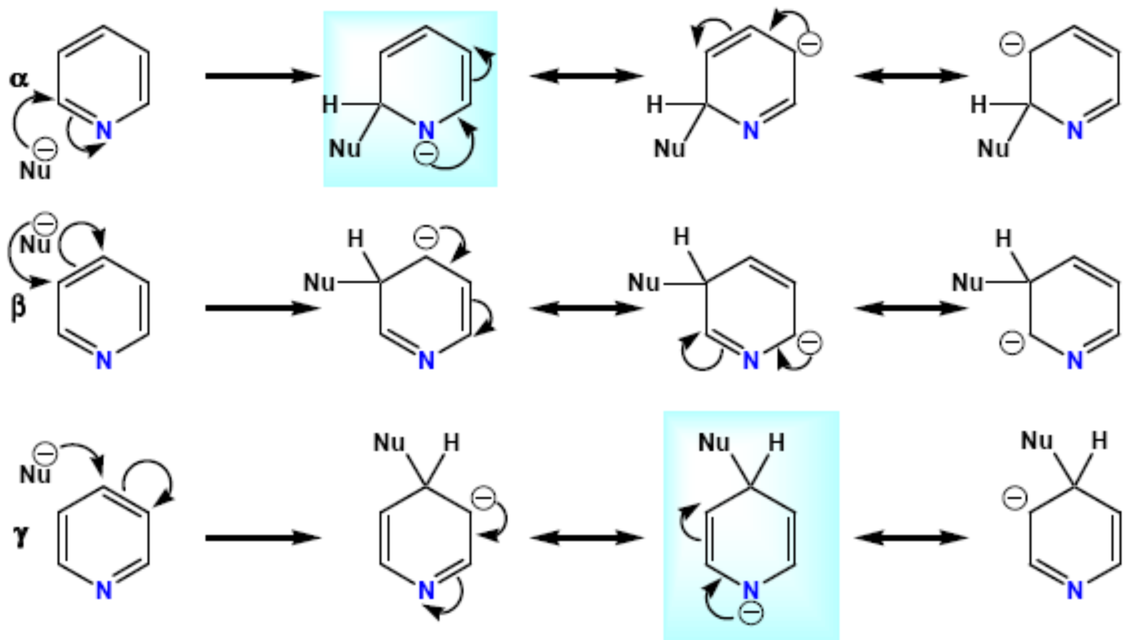
Full or Partial Reduction of Pyridines



- Pyridines generally resist oxidation at ring carbon atoms and will often undergo side-chain oxidation in preference to oxidation of the ring
- Full or partial reduction of the ring is usually easier than in the case of benzene

Pyridines – Nucleophilic Reactions

Regiochemical Outcome of Nucleophilic Addition to Pyridines



- Nitrogen acts as an electron sink
- β Substitution is less favoured because there are no stable resonance forms with the negative charge on *N*
- Aromaticity will is regained by loss of hydride or a leaving group, or by oxidation

Pyridines – Nucleophilic Reactions

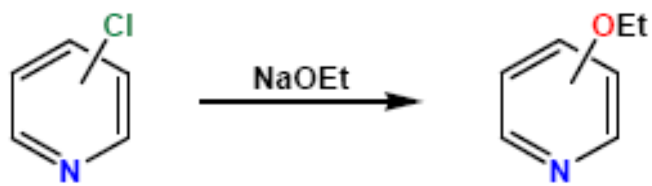
Nucleophilic Substitution

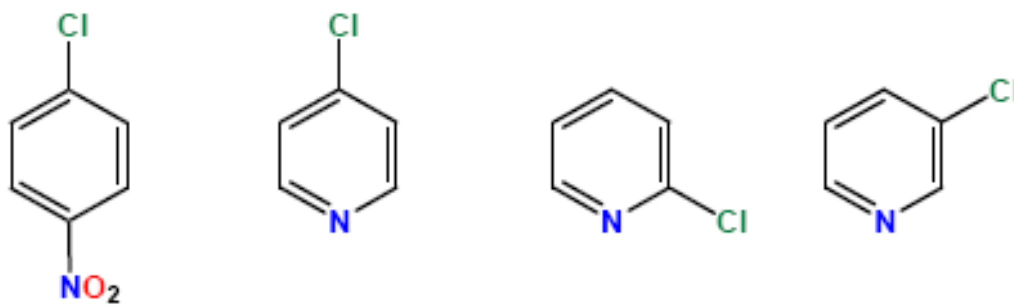
good leaving group

X = Cl, Br, I, (NO_2)

Nu = $MeO^{\ominus}$, NH_3, PhSH etc.

- Favoured by electron-withdrawing substituents that are also good leaving groups
- The position of the leaving group influences reaction rate ($\gamma > \alpha >> \beta$)

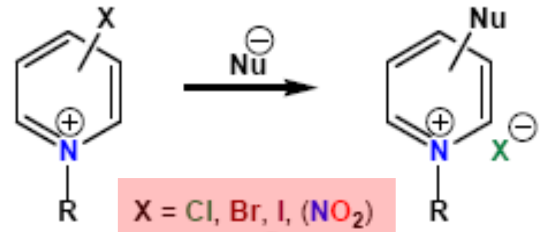




Relative rate	80	40	1	3×10^{-4}
	gamma		alpha	beta

Pyridinium Ions – Nucleophilic Reactions

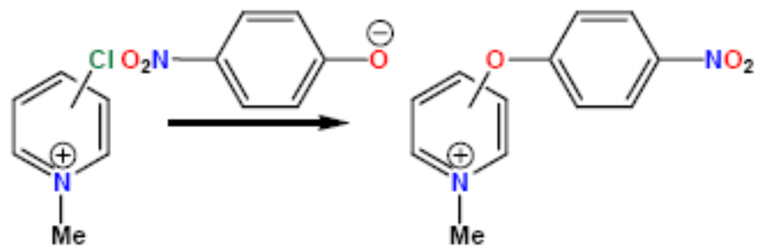
Nucleophilic Substitution

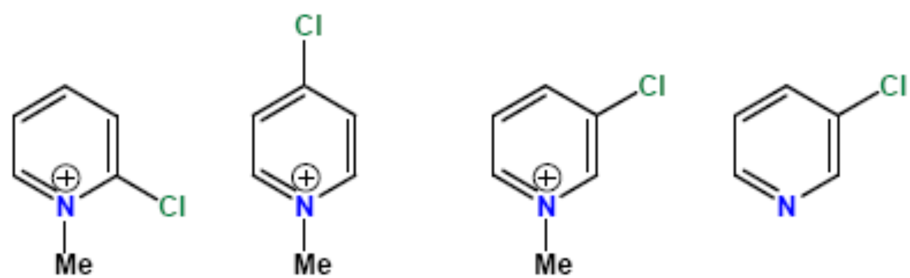


X = Cl, Br, I, (NO_2)

Nu = MeO^{-}, NH_3, PhSH etc.

- Conversion of a pyridine into the pyridinium salt greatly accelerates substitution
- Substituent effects remain the same (α, γ >> β) but now α > γ





Relative rate	5×10^{7}	1.5×10^{4}	1	10^{-4}
	alpha	gamma	beta اقل اشي	