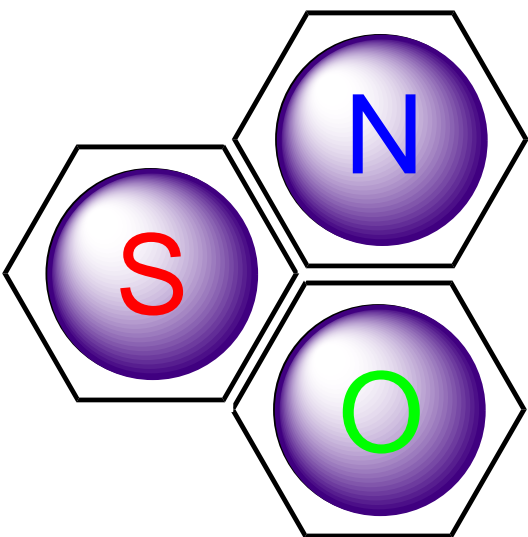
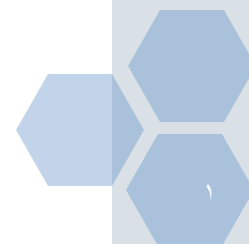




Heterocyclic Chemistry



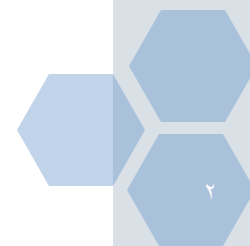
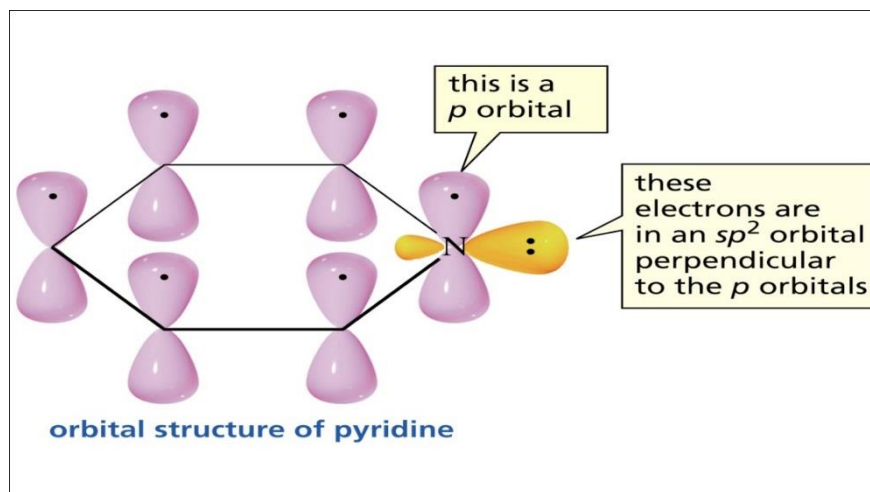
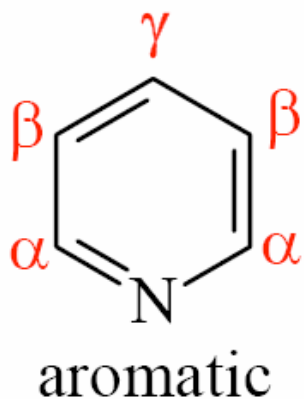
**Six-Membered
Aromatic Heterocycles:
Pyridine (Azine)**





PYRIDINE- Structure and Aromaticity

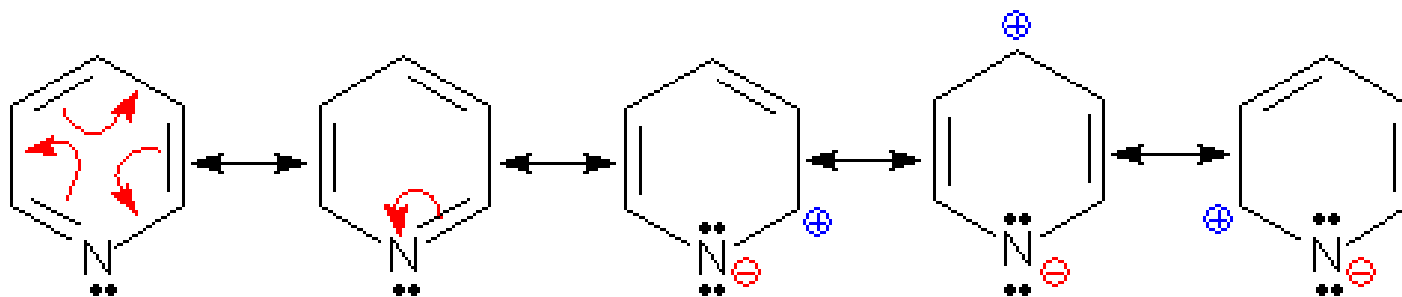
- Pyridine is a six membered heterocyclic compound with molecular formula of C_6H_5N and it is obtained from coal tar.
- It may be formally derived from the structure of benzene through the exchange of one ring carbon for a sp^2 hybridized nitrogen.
- Pyridine is **an aromatic compound**, however, the **nitrogen's lone pair** of electrons is in an **sp^2 orbital** orthogonal to the p orbitals of the ring, therefore it is not involved in maintaining aromaticity but it is available to react with protons thus **pyridine is basic**



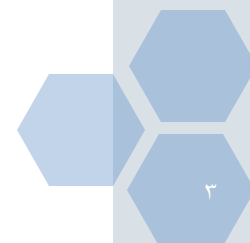


PYRIDINE- Structure and Aromaticity

- Pyridine can be represented as a resonance hybrid of the following structures.



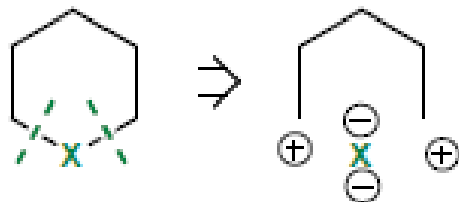
Due to the greater electronegativity of nitrogen (relative to carbons) it tends to withdraw the electron density from carbon atoms at positions 2, 4 and 6 which therefore acquire partial positive charges while the N atom acquires partial negative charge while the carbons at positions 3 and 5 remain neutral.



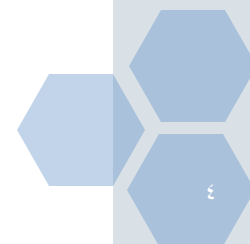
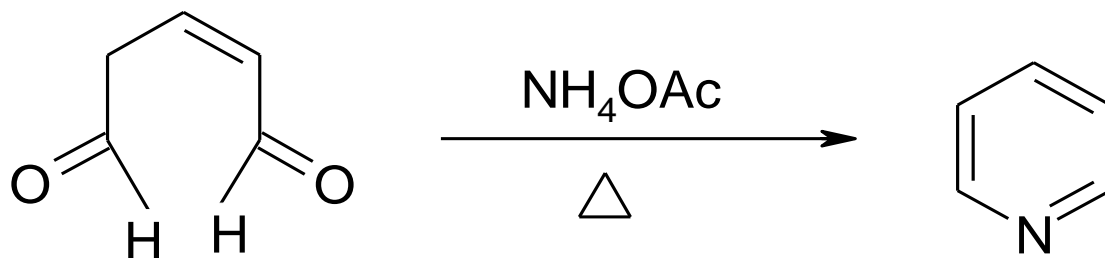
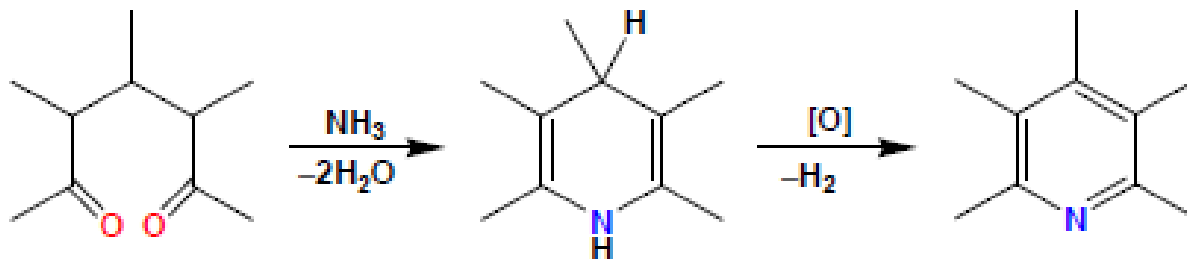


Synthesis of Pyridine

1- Common Strategy "5 + 1"



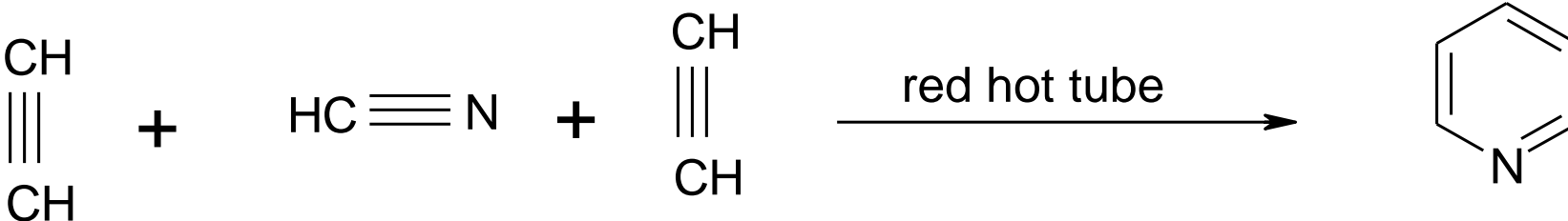
From 1,5-dicarbonyl compounds:



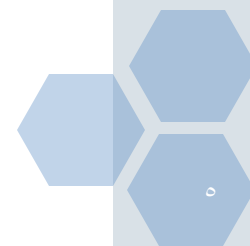
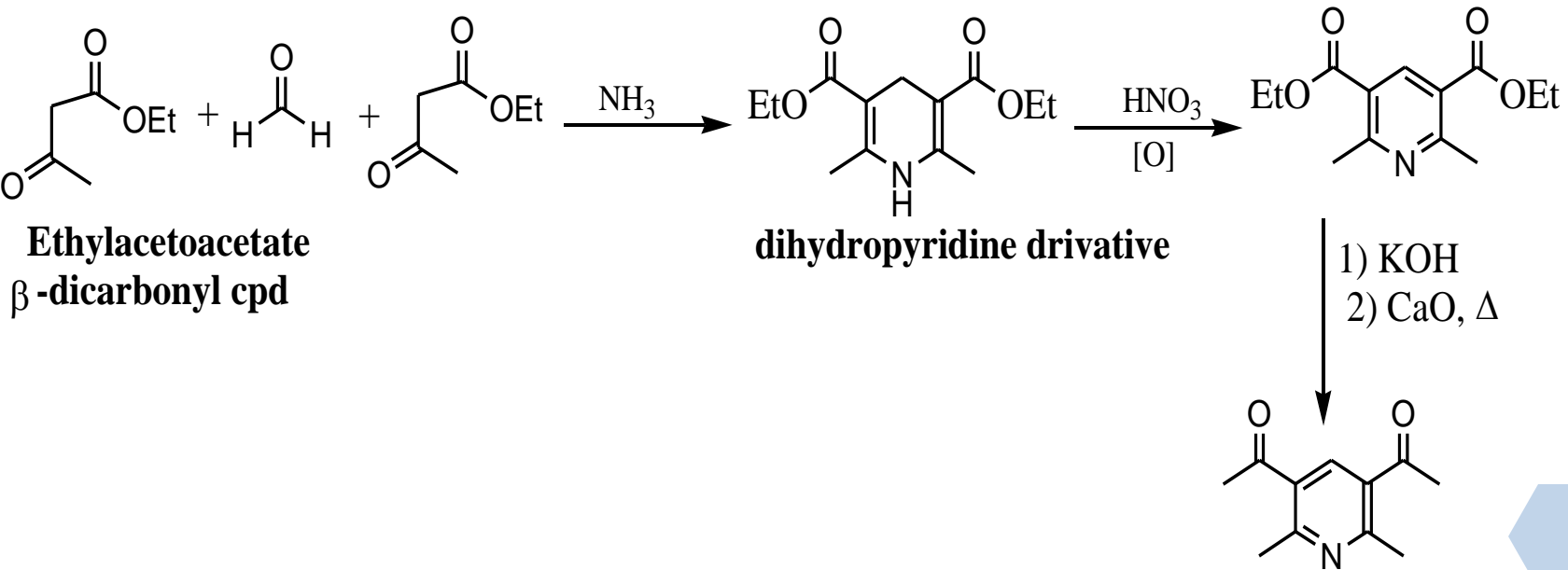


Synthesis of Pyridine

2- Bönemann cyclization:



3- Hantzsch Synthesis:





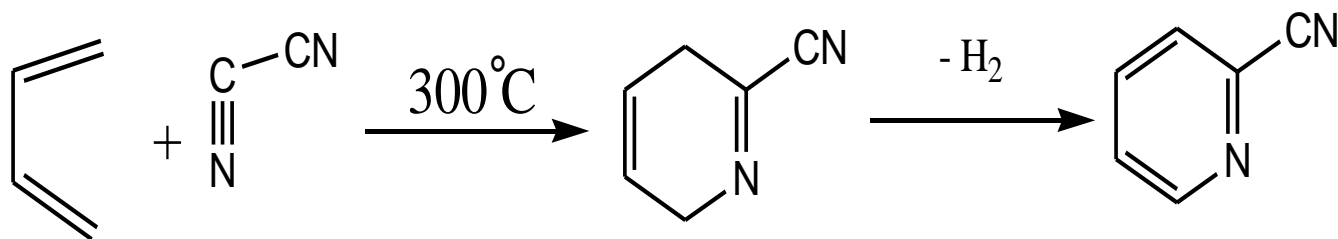
Synthesis of Pyridine

4- From pyrrole:

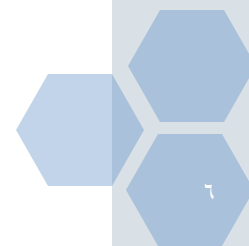


Pyrrole

5- By Diels Alder reaction



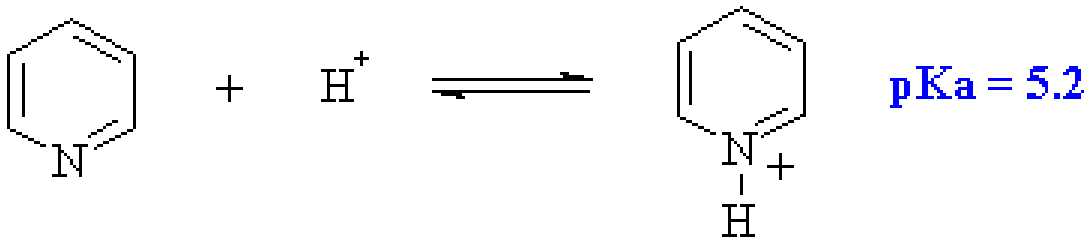
1,3-butadiene





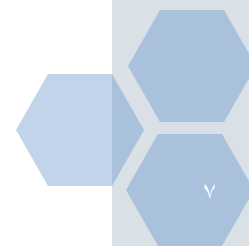
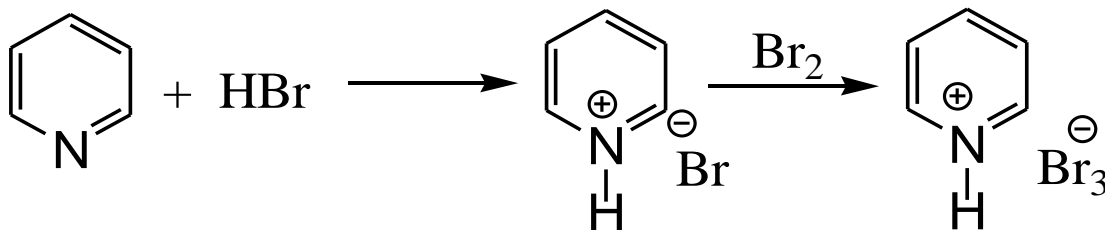
Basicity of pyridine

- Pyridine is a **weak base**; since lone pair is in an sp^2 hybrid orbital. Is the conjugate acid aromatic?



Pyridinium salt

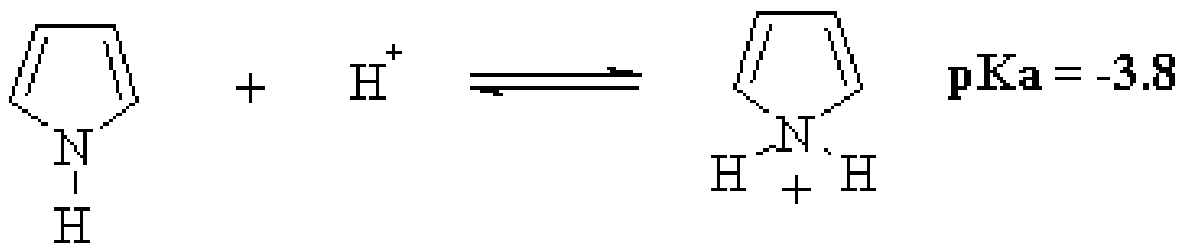
- It undergoes many reactions typical of amines such as reaction with Bronsted acids such as chromic acid and hydrobromic acid.





Basicity of pyridine

Compared to pyrrole, pyridine is much stronger base this is due to the nitrogen lone pair is not involved in maintaining the aromaticity thus it free for protonation, however, in pyrrole the lone pair on the N atom is already involved in the aromatic array of p electrons. Protonation of pyrrole on N atom results in loss of aromaticity and is therefore unfavorable.



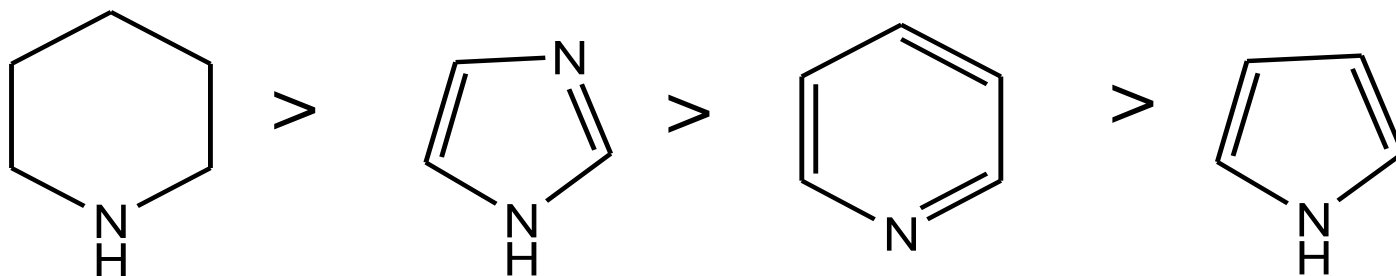
Compared to imidazole, pyridine is less basic this is due to the on protonation the + ve charge can be delocalized over two nitrogen atoms while in case of pyridine it is delocalized over the ring which interrupt aromaticity.





Basicity of pyridine

Compared to analogous aliphatic amines, pyridine is less basic this is due to the nitrogen atom in pyridine is sp^2 hybridized (more electronegative) and the lone pair of electrons occupies an sp^2 orbital thus it is held more tightly by the nucleus than the lone pair of electron in aliphatic amines with sp^3 hybridized N atom and the lone pair of electrons occupies an sp^3 orbital (less electronegative).



Decreasing order of basicity

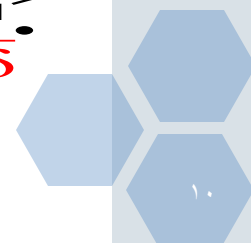
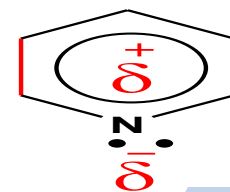
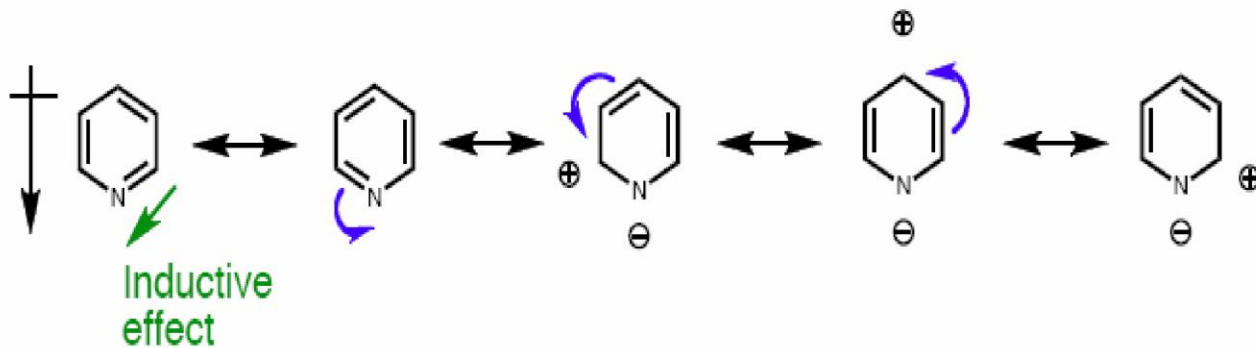




Chemical properties:

1-Electrophilic substitution

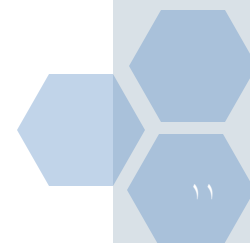
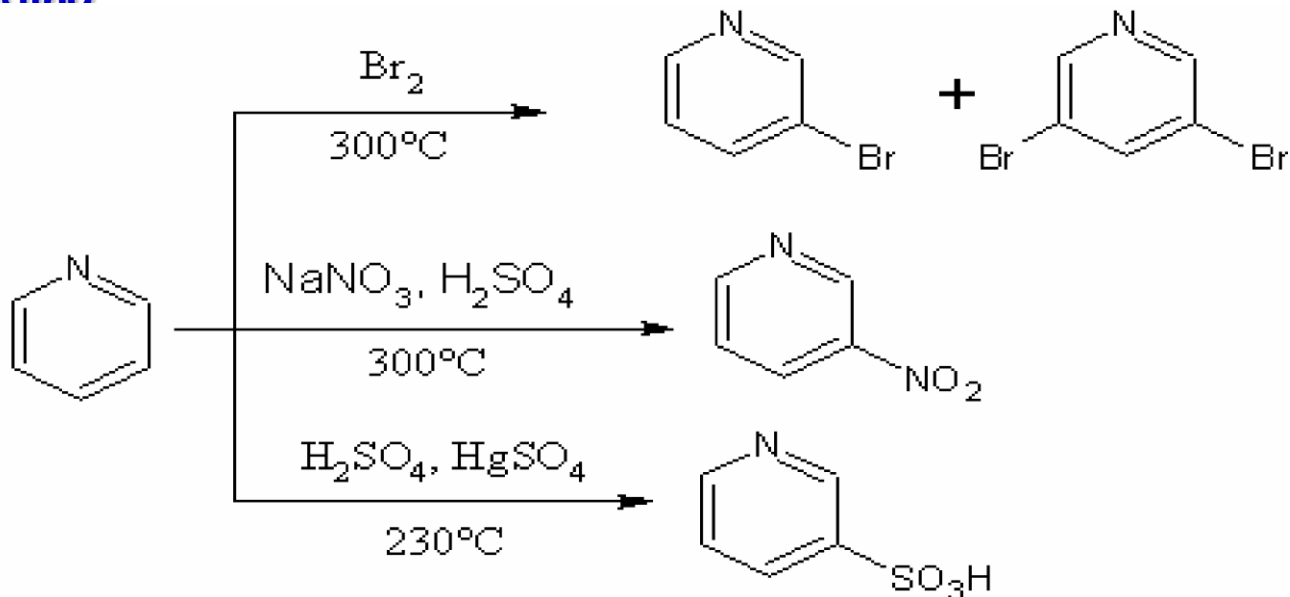
- the negative pole in pyridine ring is at N while the positive pole is at carbon skeleton which is opposite to what happens in pyrrole.
- This is due to the greater electronegativity of nitrogen (relative to carbons) it tends to withdraw the electron density from carbon atoms at positions 2, 4 and 6 which therefore acquire partial positive charges while the N atom acquires partial negative charge and the carbons at positions 3 and 5 (β -position) remain neutral therefore these positions are the most preferred for electrophilic attack.





Chemical properties: 1-Electrophilic substitution

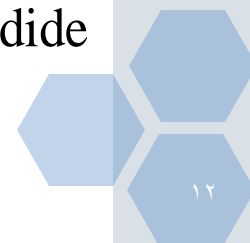
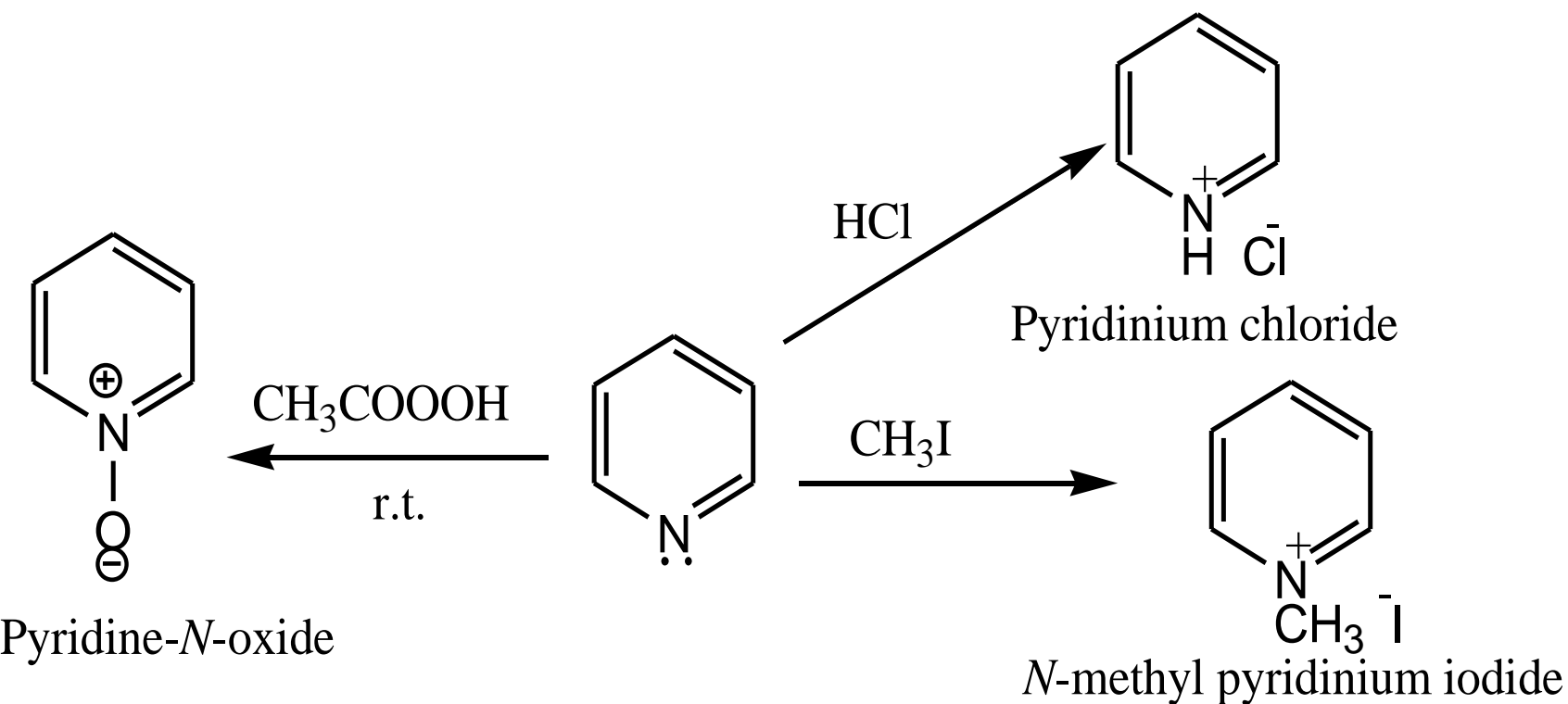
- Also as a consequence of electron deficiency on pyridine ring, **pyridine is less reactive towards electrophiles than pyrrole and benzene** (it resembles highly deactivated benzene derivatives), where it does not undergo Friedel-Craft's alkylation or acylation or coupling with diazonium salts.
- Moreover, electrophilic substitution reactions of pyridine require very harsh conditions (e.g. v. high temp.) to take place and are **low yielding**





2-Pyridine as a nucleophile (reactions on N atom)

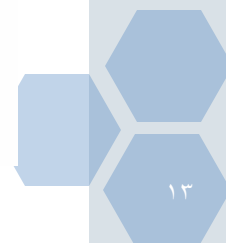
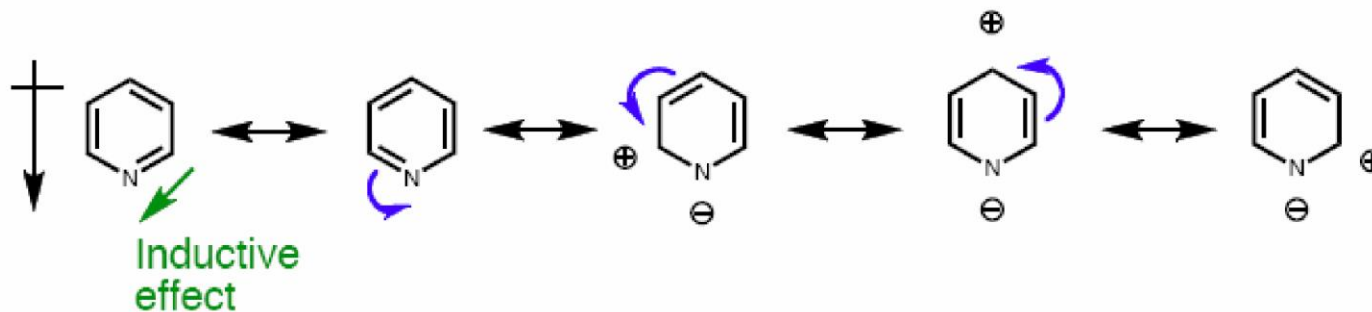
- As a tertiary amine pyridine has nucleophilic properties thus it reacts with electrophiles:





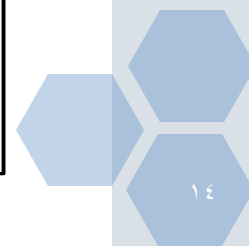
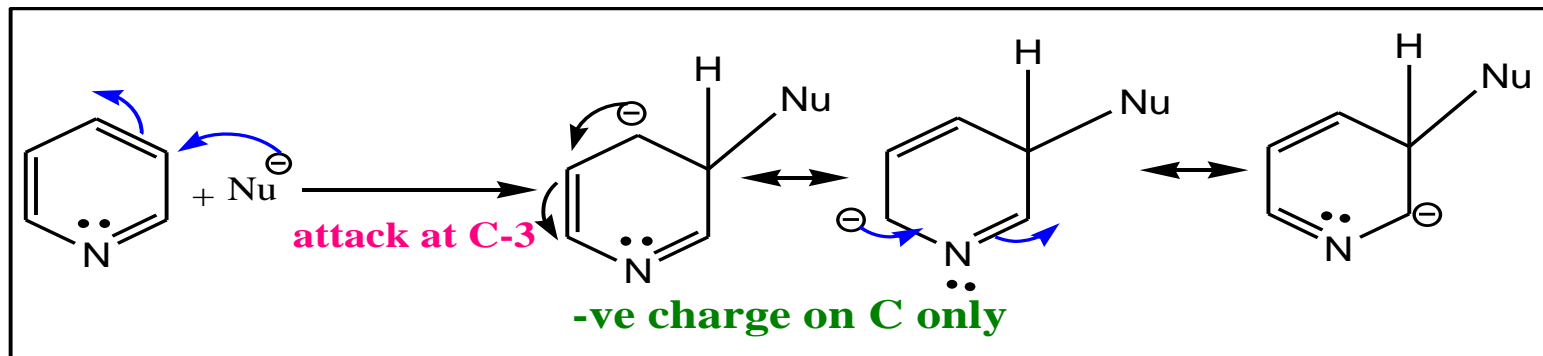
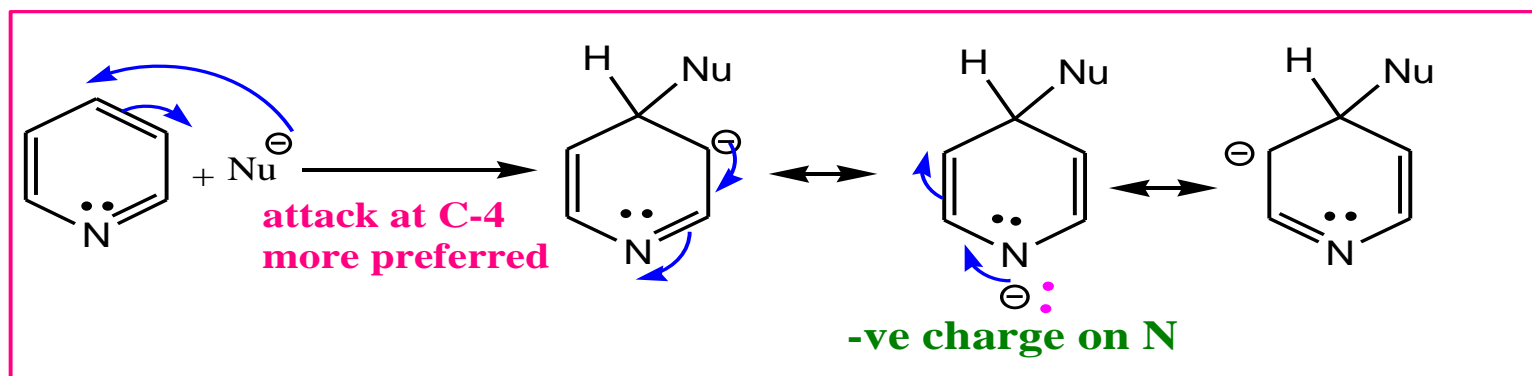
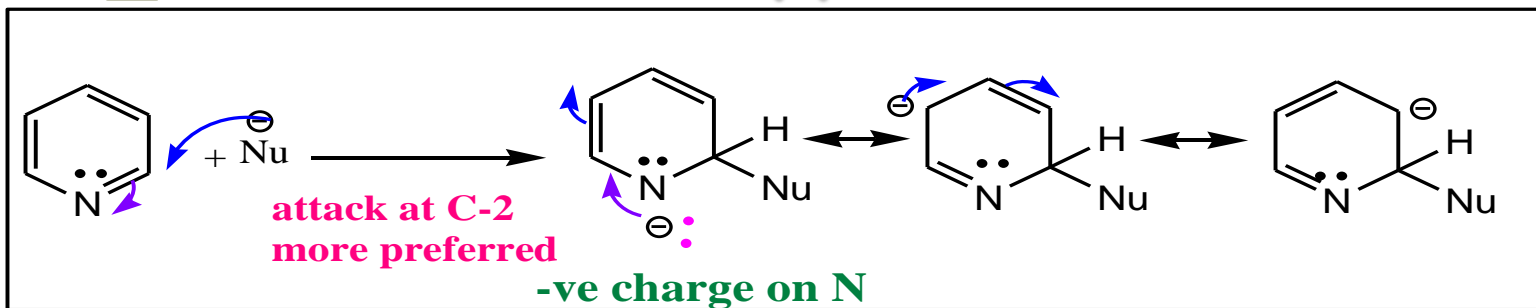
3-Nucleophilic substitution on carbon

- **Pyridine is very reactive towards nucleophiles** than benzene it resembles benzene having strong E.W.G due to the withdrawing effect of the electronegative N atom .
- **AS** appeared from the canonical structures of pyridine positions 2, 4 and 6 carry partial positive charges thus nucleophilic substitution proceeds readily at the 2-position followed by 4-position but **not at** the 3-position.
- Additionally, attack at positions 2, 4 or 6 results in resonance structure in which the negative charge is delocalized at N thus it is more preferred while attack at position 3 or 5 results in resonance structures in which the negative charge is delocalized over carbons only.





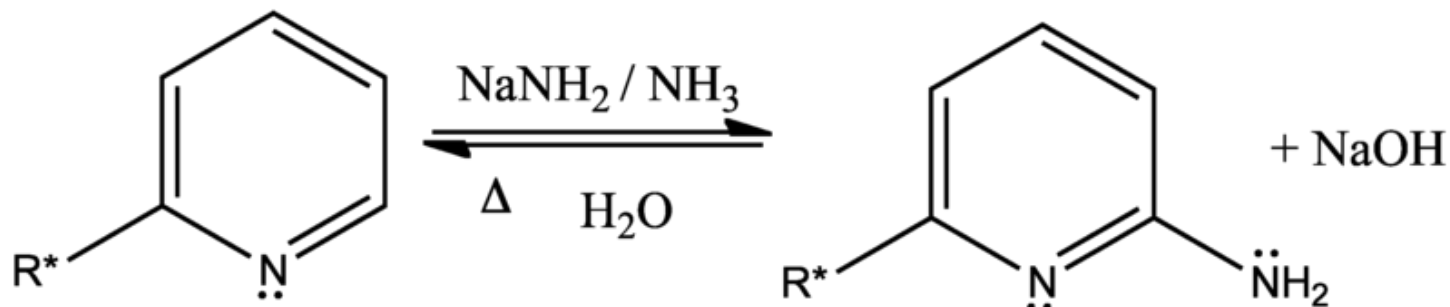
Orientation of nucleophilic substitution in pyridine





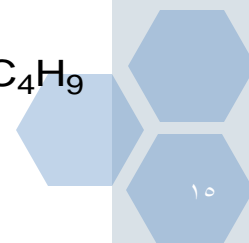
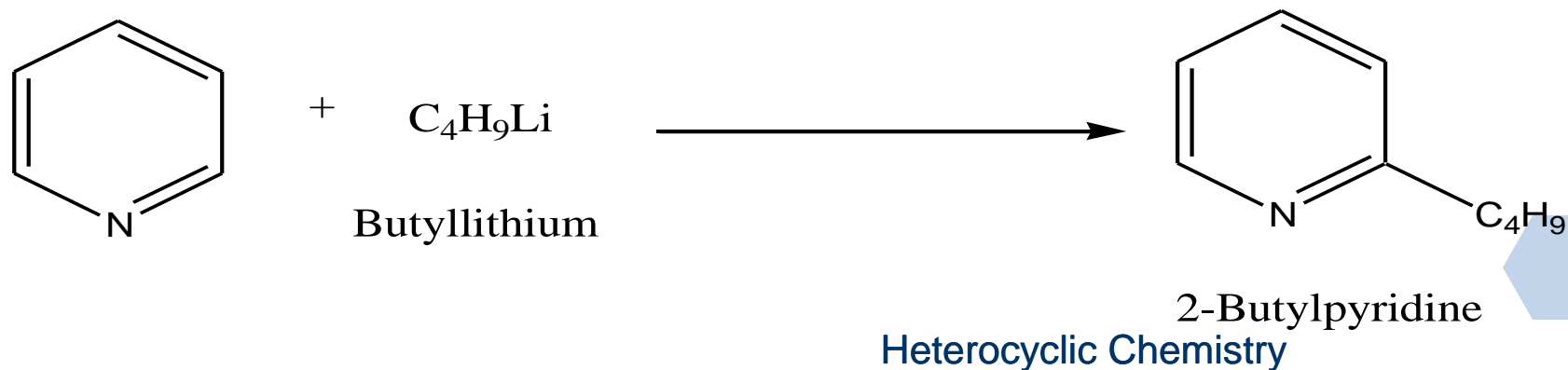
3- Nucleophilic Substitution reactions

i) The Chichibabin reaction



R can be *o*-, *m*-, or *p*- substituent

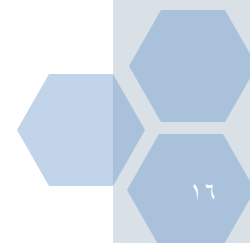
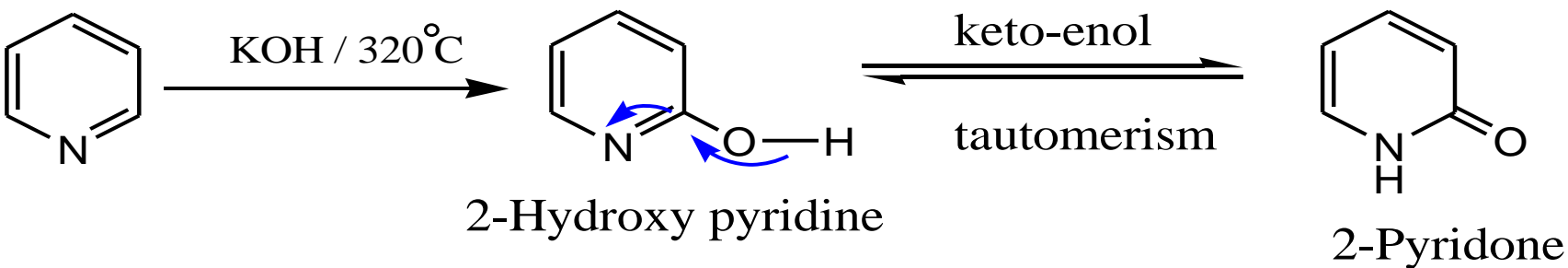
ii) Reaction with organometallic compounds lithium reagents





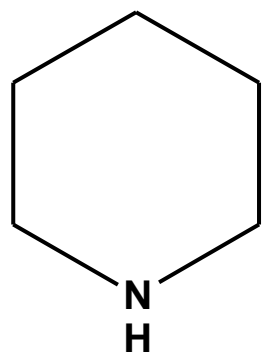
3-Nucleophilic substitution Reactions

iii) Reaction with potassium hydroxide

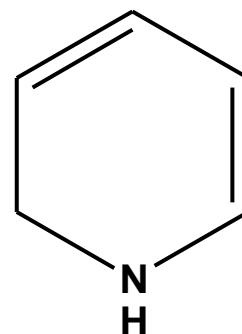
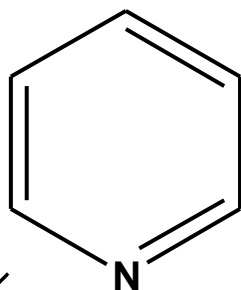
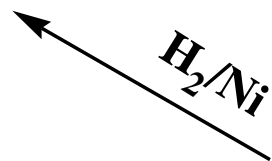




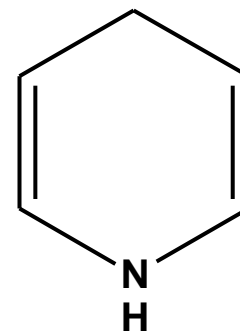
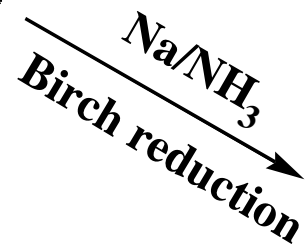
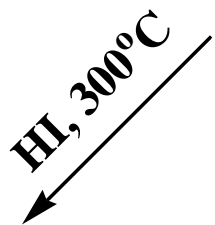
4-Reduction Reactions



piperidine



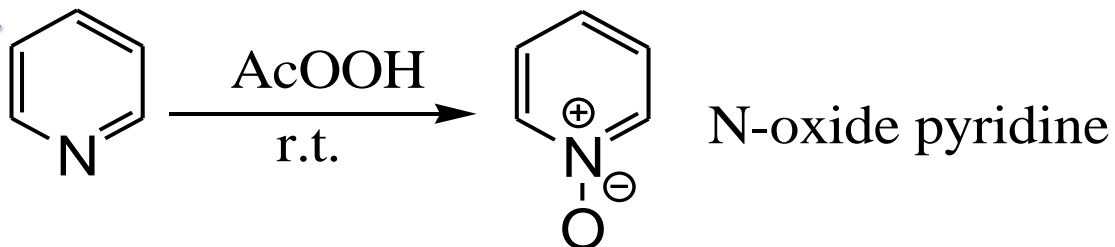
1,2-Dihydropyridine



1,4-Dihydropyridine

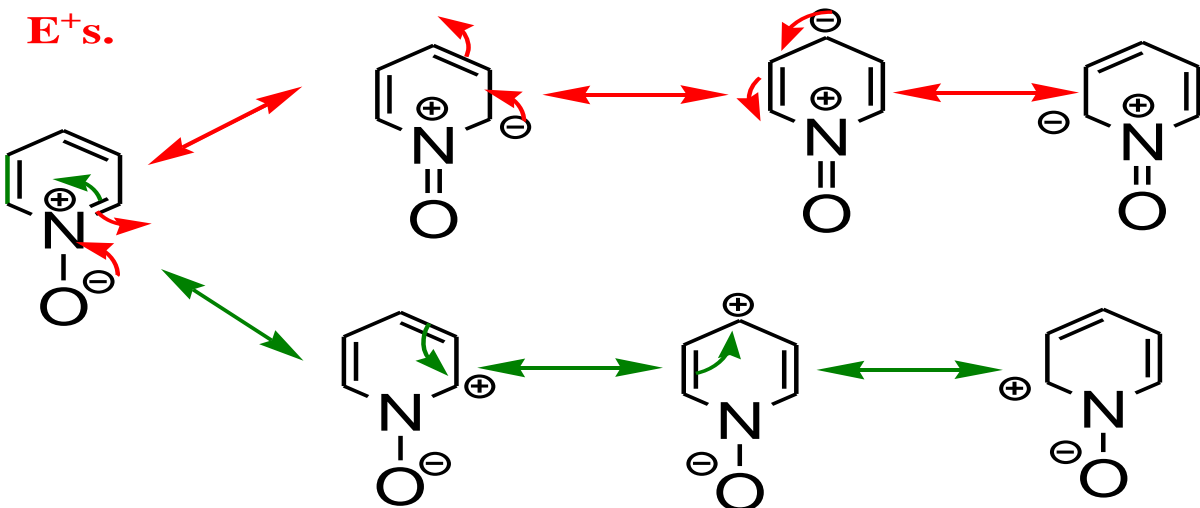
Derivative of pyridine: N-oxide pyridine

- Pyridine can be oxidized easily to N-oxide pyridine by peracids.

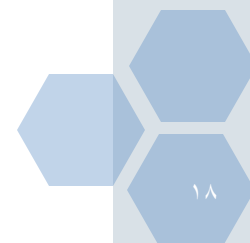


- On the basis of dipole moment studies, N-oxide pyridine is considered as a resonance hybrid of the following structures

The -ve. charges appear at positions 2, 4 thus active towards E^+ s.



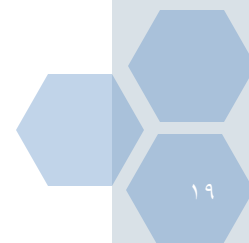
The +ve. charges appear at positions 2, 4 thus active towards nucleophiles





N-oxide pyridine

- As appears from the previous canonical forms, there are positive and negative charges at positions 2 and 4 thus **N-oxide pyridine is more activated for electrophilic and nucleophilic attack at these positions than pyridine itself.**
- N-oxide pyridines are very important intermediates for preparing pyridine derivatives that are difficult to prepare due to the easiness of removal of oxygen atom by reduction.
- For instance, nitration of pyridine is very difficult and low yielding reaction and it occurs at position 3, however using N-oxide pyridine will direct the nitration to position 4 and then the oxygen can be easily removed by reduction as shown in the following scheme.





Reactions of N-oxide pyridine

