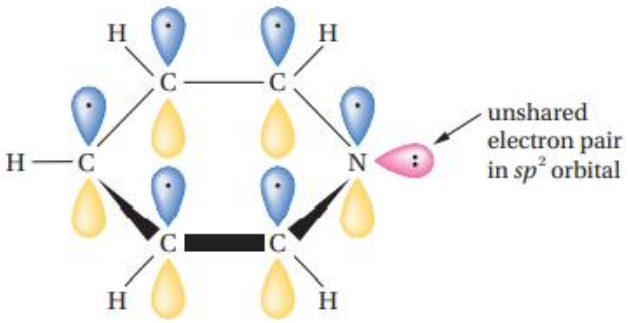
CH-3-I

Six-Membered Heterocyls

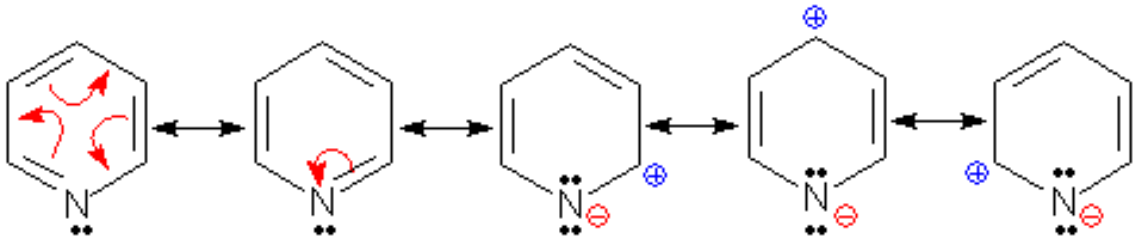
Pyridine (Azine)

Structure and Aromaticity

- Pyridine is a six membered heterocyclic compound with molecular formula of C_5H_5N and it is obtained from coal tar.
- Pyridine is an aromatic compound, however, the nitrogen's lone pair of electrons is in an *sp2* 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.

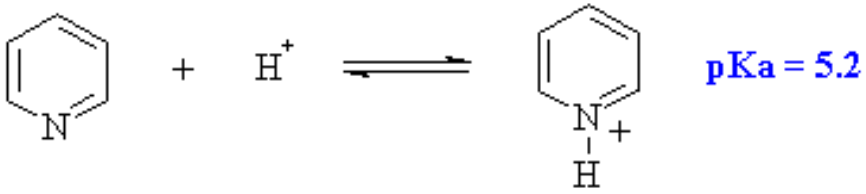


- Pyridine can be represented as a resonance hybrid of the following structures.



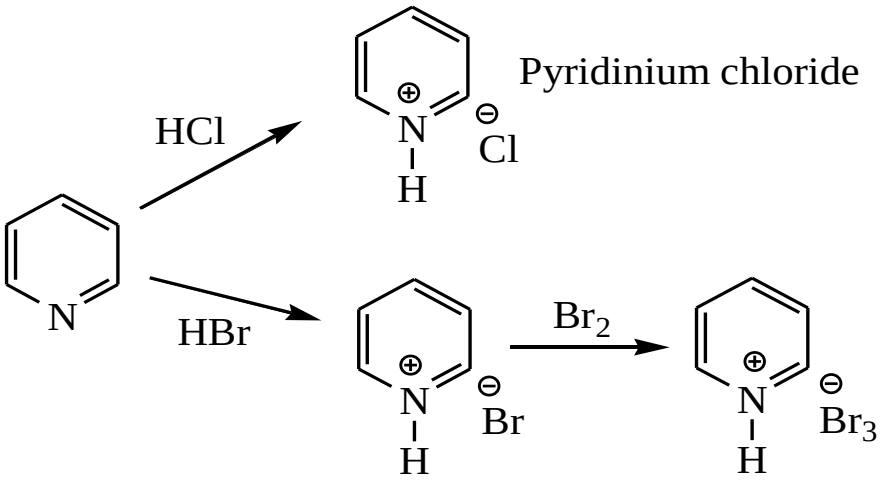
Basicity of pyridine

- Pyridine is a weak base



Pyridinium salt

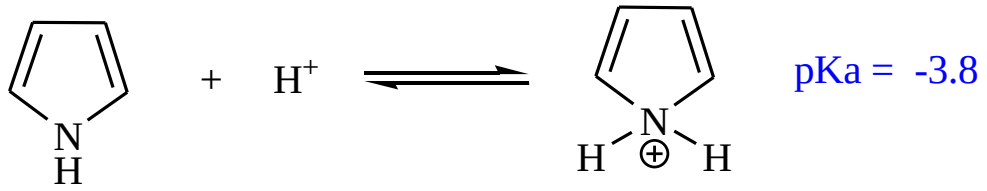
- It undergoes many reactions typical of amines such as reaction with Bronsted acids such as chromic acid and hydrobromic acid.



Pyridinium chloride

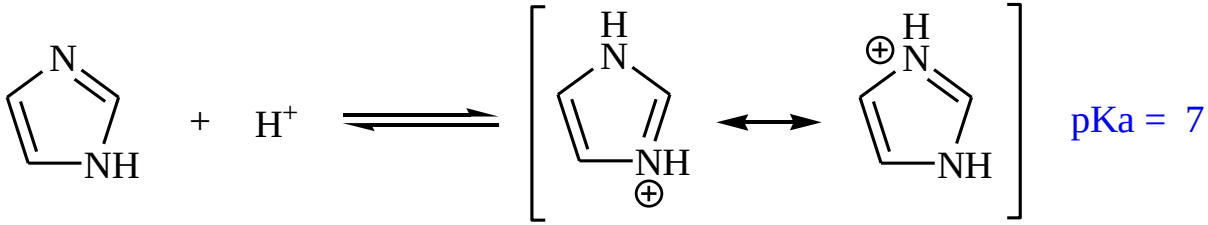
Basicity of pyridine

- 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 π electrons. Protonation of pyrrole on N atom results in loss of aromaticity.



pKa = -3.8

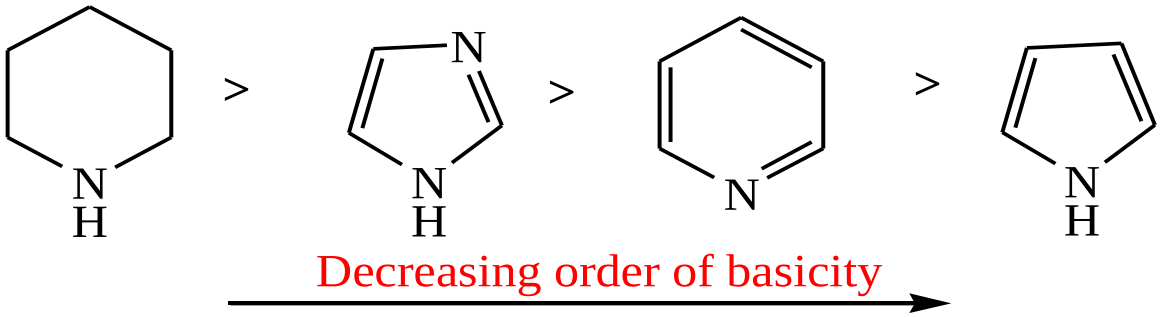
- Compared to imidazole, pyridine is less basic this is because protonated imidazole has two resonance forms such that both nitrogens participate equally in carrying the positive charge.



pKa = 7

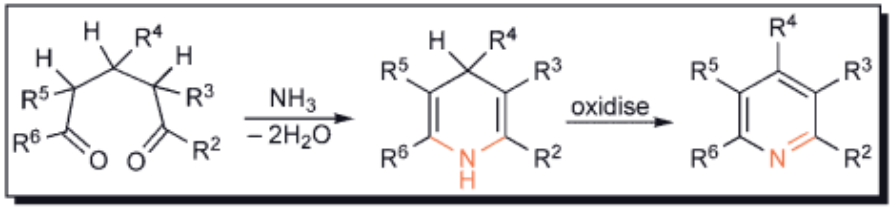
Basicity of pyridine

- Compared to analogous aliphatic amines, pyridine is less basic this is due to the nitrogen atom in pyridine is *sp2* hybridized (more electronegative) and the lone pair of electrons occupies an *sp2* orbital thus it is held more tightly by the nucleus than the lone pair of electron in aliphatic amines with *sp3* hybridized N atom and the lone pair of electrons occupies an *sp3* orbital (less electronegative).



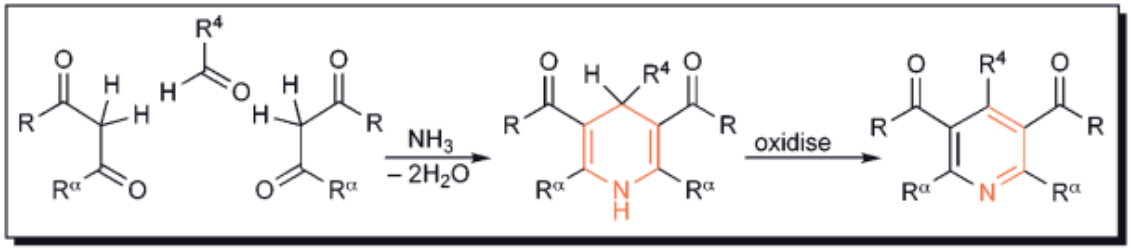
Synthesis of Pyridine

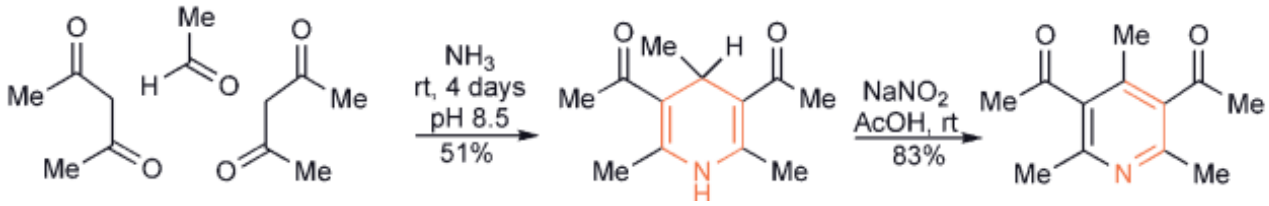
1) From 1,5 - Dicarbonyl Compounds and Ammonia



2) The Hantzsch Synthesis

From an Aldehyde, Two Equivalents of a 1,3 - Dicarbonyl Compound and Ammonia

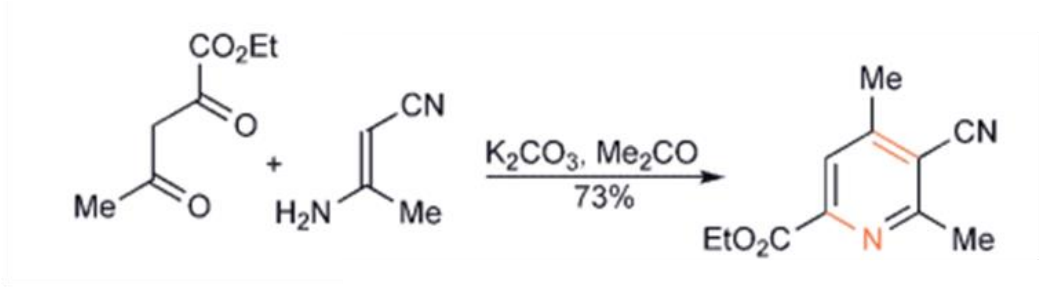




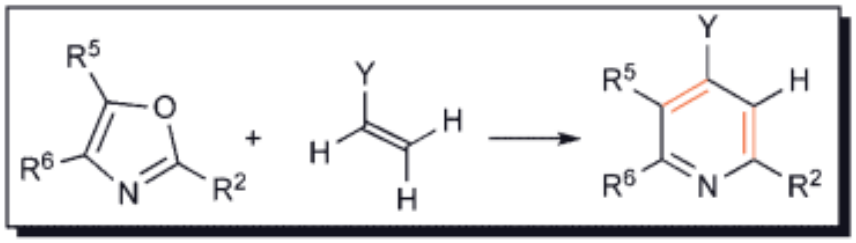
Synthesis of Pyridine

3) The Guareschi Synthesis

From 1,3 - Dicarbonyl Compound and Enamine



4) From Oxazole



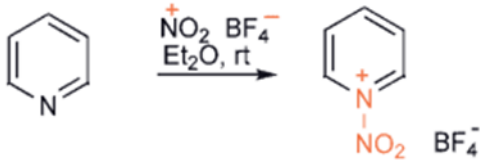
Electrophilic substitution

- 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.
- Also as a consequence of electron deficiency on pyridine ring , pyridine is less reactive towards electrophiles than pyrrole and benzene, where it does not undergo Friedel-Craft's alkylation or acylation or coupling with diazonium salts.

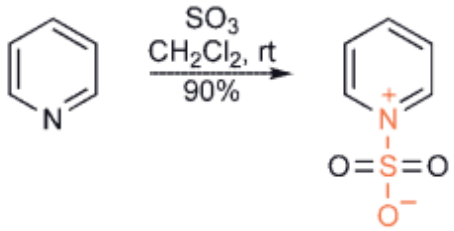
Reactions with Electrophilic Reagents

1) Addition to Nitrogen

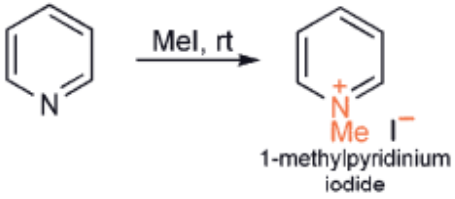
Nitration at Nitrogen



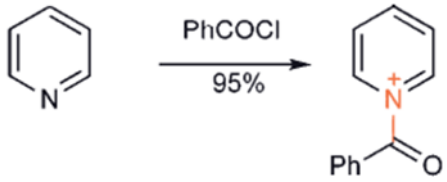
Sulfonation at Nitrogen



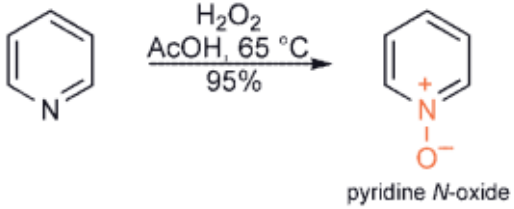
Alkylation at Nitrogen



Acylation at Nitrogen



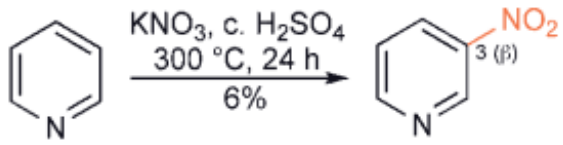
Oxidation of Nitrogen



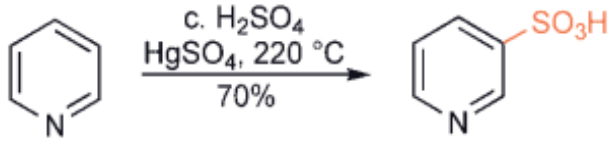
Reactions with Electrophilic Reagents

2) Substitution at Carbon

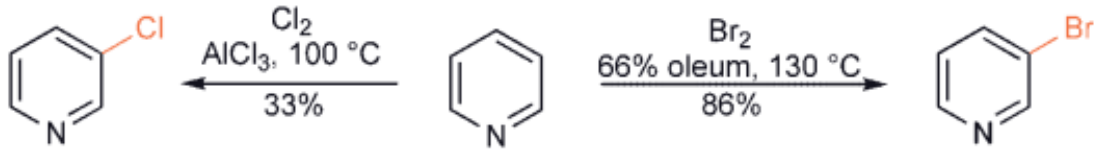
Nitration



Sulfonation



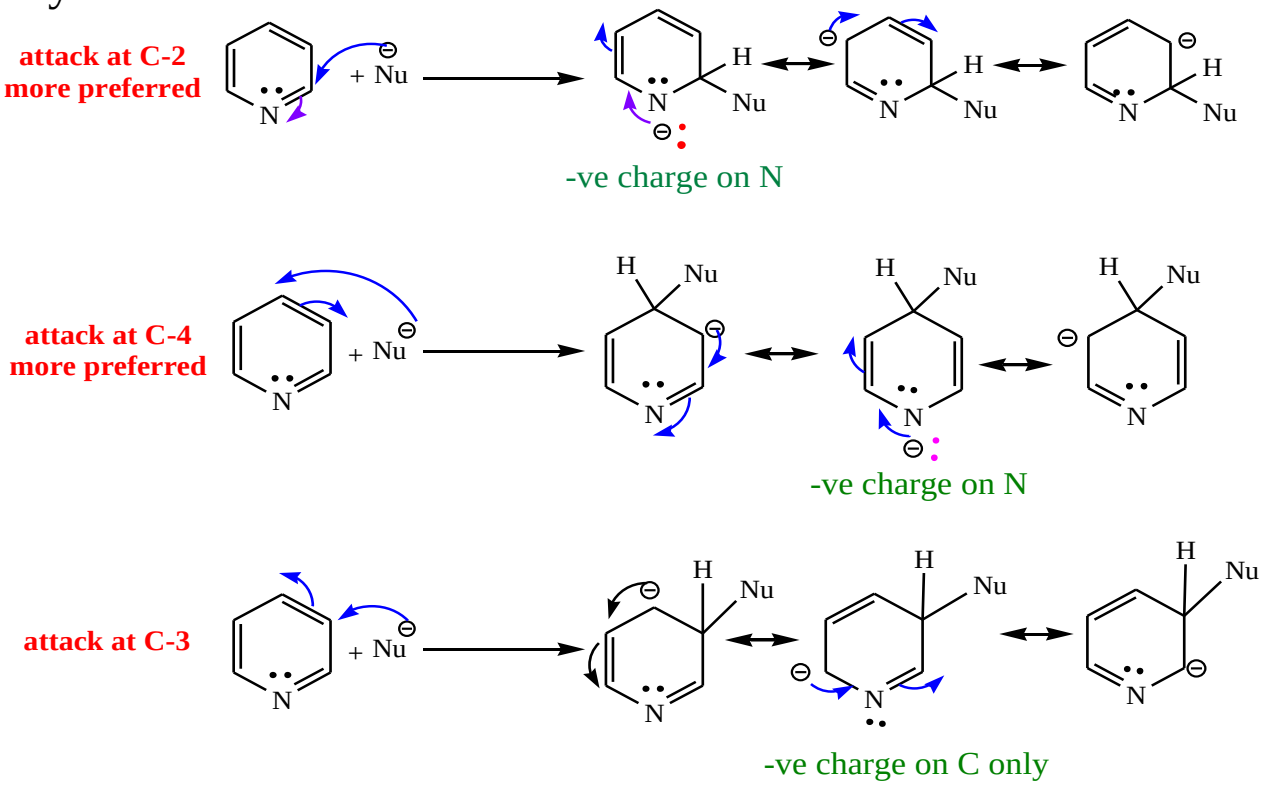
Halogenation



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 .

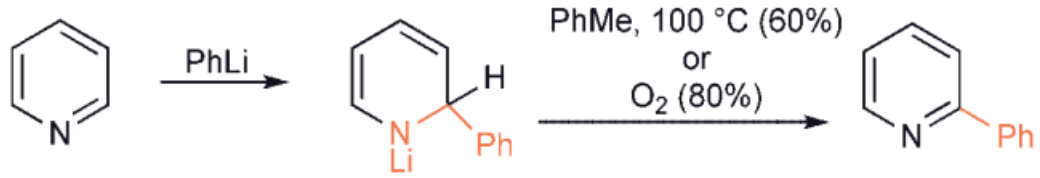
- Additionally, attack at positions 2, 4 or 6 results in resonance structure in which the negative charge is delocalized at N thus it is more preferred while attack at position 3 or 5 results in resonance structures in which the negative charge is delocalized over carbons only.



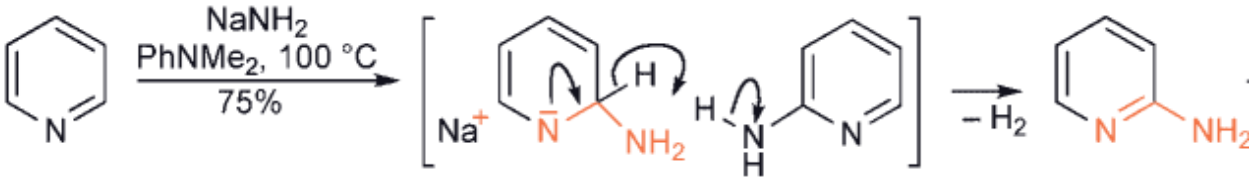
Nucleophilic substitution on carbon

Nucleophilic Substitution with ‘ Hydride ’ Transfer.

Alkylation and Arylation

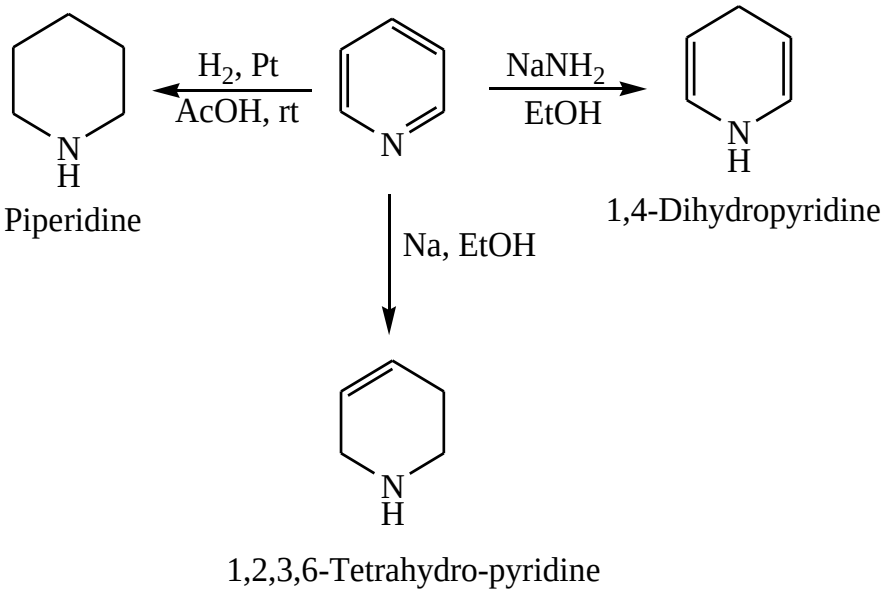


Amination



Reduction Reactions

Full and Partial Reduction



N-oxide pyridine

- 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.