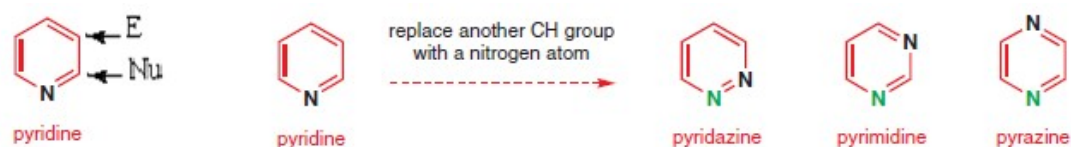


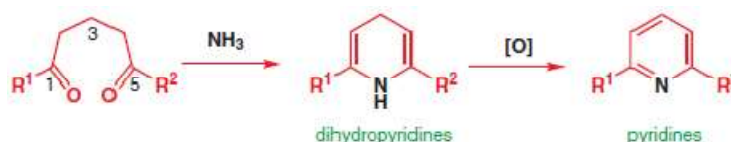
Heterocyclic chemistry [six – membered ring with two heteroatoms pyridine, pyridazine, pyrimidine, and pyrazine]:

Pyridine is aromatic, is also very stable and is a weak base. Pyrimidine is more important than either of the others because of its involvement in DNA and RNA.



Synthesis of six – membered heterocyclic compounds:

1- Pyridines made by this strategy from 1,5-dicarbonyl compounds with oxidation.

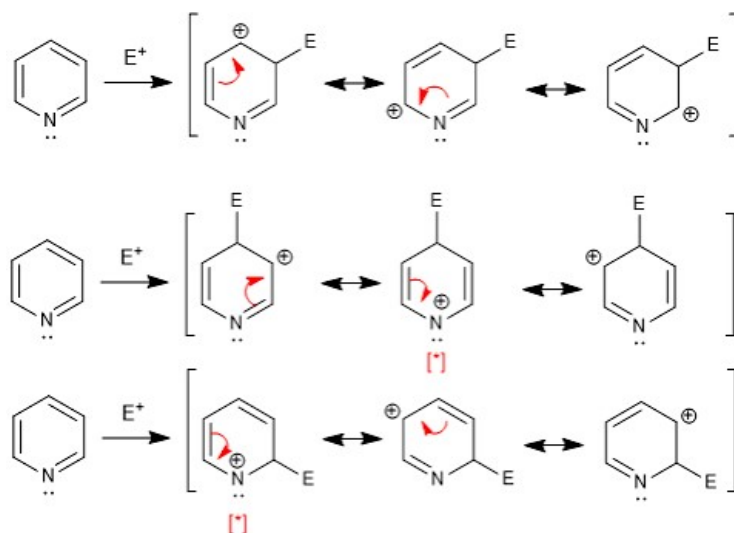


2- Pyridazines ideally made by this strategy from 1,4-dicarbonyl compounds with oxidation.



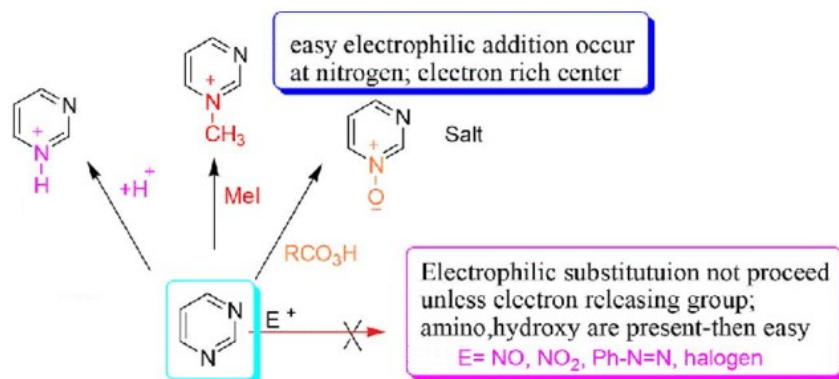
a- **six member heterocyclic** inter electrophilic substitution in **(3 pyridine) and (5 pyrimidine) postion:**

Pyridine is less reactive than benzene in electrophilic aromatic substitution reactions.

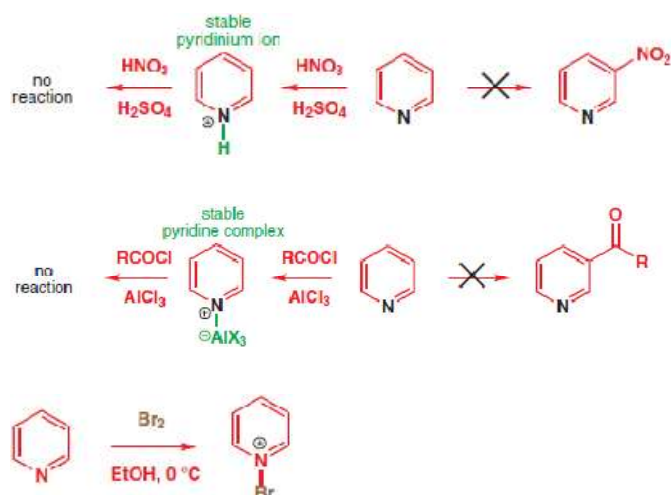


■ Contrast the unstable electron-deficient cationic intermediate with the stable pyridinium ion. The nitrogen lone pair is used to make the pyridinium ion but is not involved in the unstable intermediate. Note that reaction at the 3-position is the best option but still doesn't occur. Reaction at the 2- and 4-positions is worse.

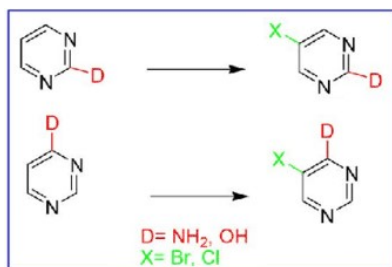
Note: Aromatic electrophilic substitution on pyridine is not a useful reaction. The ring is unreactive and the electrophilic reagents attack nitrogen, making the ring even less reactive.



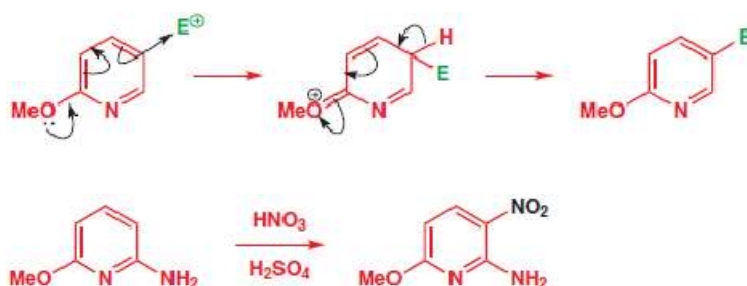
Examples:



Note: Pyridines and pyrimidine can undergo electrophilic substitution only if they are activated by electron-donating substituents such as NH_2 , OCH_3 ,...

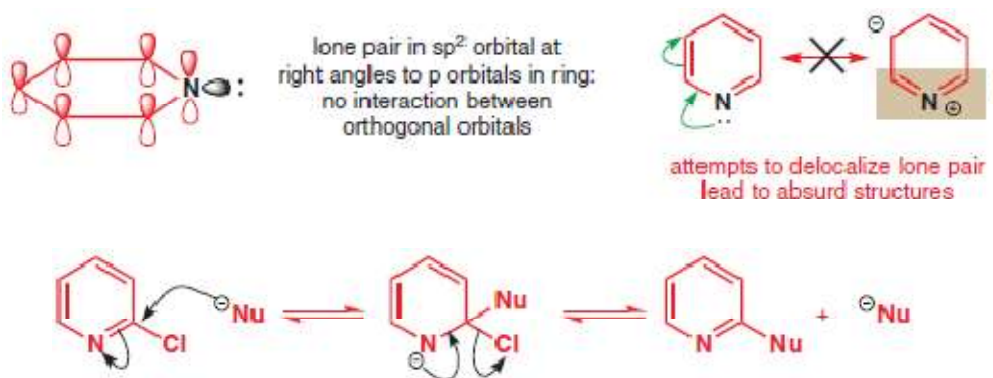


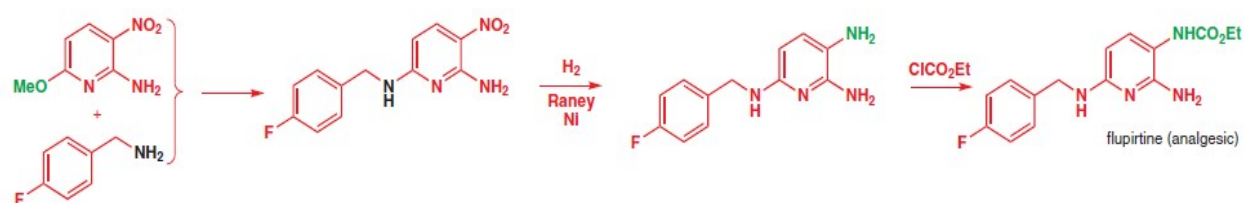
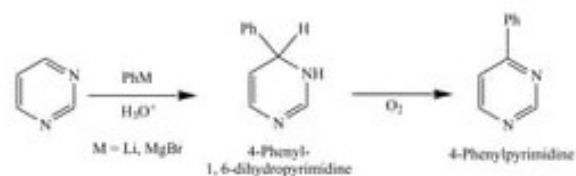
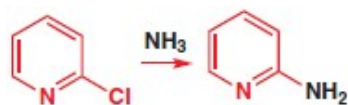
Examples:



b- six member heterocyclic inter nucleophilic substitution in (2 Pyridine) and (2,4,6 pyrimidine) postions:

Pyridine is more reactive than benzene in nucleophilic aromatic substitution reaction; it is nucleophilic at the nitrogen atom because the lone pair of electrons on nitrogen cannot be delocalized around the ring. They are in a sp^2 orbital orthogonal to the p orbitals in the ring and there is no interaction between orthogonal orbitals.



Examples:

Note: Pyridazine is slightly **more basic** than the other two because the two adjacent lone pairs repel each other and make the molecule more nucleophilic.

