

Pyridine is the simplest heterocycle of the azine type. It is derived from benzene by replacement of a CH group by a N-atom.

- The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N.
- The key differences are:
- I. The departure from perfectly regular hexagonal geometry caused by the presence of the hetero atom, in particular the shorter carbon-nitrogen bonds,
- II. The replacement of a hydrogen in the plane of the ring with an unshaired electron pair, likewise in the plane of the ring, located in an sp² hybrid orbital, and not at all involved in the aromatic π -electron sextet; it is this nitrogen lone pair which is responsible for the basic properties of pyridines, and

III.A strong permanent dipole, traceable to the greater electronegativity of the nitrogen compared with carbon.



The following reactions can be predicted for pyridines on the basis of their electronic structure:

- I. The heteroatom make pyridines very unreactive to normal electrophilic aromatic substitution reactions. Conversely pyridines are susceptible to nucleophilic attack. Pyridines undergo electrophilic substitution reactions (S_EAr) more reluctantly but nucleophilic substitution (S_NAr) more readily than benzene.
- II. Electrophilic reagents attack preferably at the Natom and at the β -C-atoms, while nucleophilic reagents prefer the α - and χ -C-atoms.

Reactions of Pyridine

Electrophilic Addition at Nitrogen

In reactions which involve bond formation using the lone pair of electrons on the ring nitrogen, such as protonation and quaternisation, pyridines behave just like tertiary aliphatic or aromatic amines.



When a pyridine reacts as a base or a nucleophile it forms a pyridinium cation in which the aromatic sextet is retained and the nitrogen acquires a formal positive charge.

Protonation at Nitrogen



Pyridines form crystalline,frequentlyhygroscopic,salts with most protic acids.



This occurs readily by reaction of pyridines with nitronium salts, such as nitronium tetrafluoroborate.

Protic nitrating agents such as nitric acid of course lead exclusively to N-protonation.

Acylation at nitrogen

Acid chlorides and arylsulfonic acids react rapidly with pyridines generating 1-acyl- and 1arylsulfonylpyridinium salts in solution.



Alkylation at nitrogen

Alkyl halides and sulfates react readily with pyridines giving quaternary pyridinium salts.



substitution

Electrophilic substitution at Carbon atoms of the pyridine ring

- Electrophilic substitution of pyridines at a carbon is very difficult. Two factors seem to be responsible for this unreactivity:
- I. Pyridine ring is less nucleophilic than the benzene ring; nitrogen ring atom is more electronegative than carbon atoms and therefore it pulls electrons away from the carbon atoms inductively leaving a partial plus on the carbon atoms.

II. When pyridine compound is exposed to an acidic medium, it forms pyridinium salt. This increases resistance to electrophilic attack since the reaction will lead to doubly positive charged species.



Less reactive than pyridine

When an electrophile attacks the pyridine ring, only position 3 is attacked.



Hint: draw resonance structures that result from electrophilic attack at various positions. The positive charge residing on an electronegative element with sextet configuration is unfavoured. For example, 3-bromopyridine is formed when pyridine is reacted with bromine in the presence of oleum (sulfur trioxide in conc. sulfuric acid) at 130°C.





Pyridine can be activated to electrophilic substitution by conversion to pyridine-N-oxides.



A series of preparatively interesting reactions on pyridine can be carried out by means of pyridine *Noxides* such as the introduction of certain functions into the ring and side-chain which cannot be achieved in the parent system by direct methods.



The activating oxygen atom can be removed by the pyridine N-oxide reacting with phosphorous trichloride.



In such reactions there is a balance between electron withdrawal, caused by the inductive effect of the oxygen atom, and electron release through resonance from the same atom in the opposite direction. Here, the resonance effect is more important, and electrophiles react at C-2(6) and C-4.



Thionyl chloride, for example, gives a mixture of 2and 4-chloropyridine N-oxides in which the 4-isomer is predominant.



However, pyridine N-oxide reacts with acetic anhydride first to give 1-acetoxypyridinium acetate and then, on heating, to yield 2-acetoxypyridine through an addition-elimination process.



When a similar reaction is carried out upon the 2,3dimethyl analogue, the acetoxy group rearranges from N-1 to the C-2 methyl group, at 180°C, to form 2-acetoxymethyl-3-methylpyridine.





Anion Chemistry of Pyridine



Works for 2(6)- and 4-alkylpyridines not for 3(5)-alkyl pyridines, why?





Another approach to electrophilic substitution involves the chemistry of 2-pyridone and 4-Pyridones which are obtained from the diazotization of the corresponding 2-aminopyridine and 4aminopyridines, respectively.



Both pyridones can react with electrophiles at positions *ortho* and *para* to the activating oxygen atom. Reaction with phosphorous oxychloride gives chloropyridines.



Nucleophilic substituition of pyridine



a) X=H b) X=Good leaving group

X=H, Substitution with "hydride" transfer

Nu: NaNH₂ - amination Nu: BuLi, PhLi etc - alkylation / arylation Nu: NaOH - "hydroxylation"



At high temperature the intermediate anion can aromatize by loss of a hydride ion, eventhough, it is a poor leaving group.

b) X=LG, The nucleophilic substitution is much more facile when good leaving group such as X: Halogen (F>>Cl,>Br,>l), -OSO₂R, -NO₂, -OR, are employed.







-H: is a bad leaving group



Halogenopyridines can undergo metal-halogen exchange when treated with butyllithium. The lithium derivatives then behave in a similar manner to arylithiums and Grignard reagents and react with electrophiles such as aldehydes, ketones and nitriles.











Furans, pyrroles and thiophenes from 1,4-dicarbonyl compounds: Paal Knorr synthesis







Furans, pyrroles and thiophenes from 1,3-dicarbonyl (β-ketocarbonyl) compounds



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The Feist-Benary synthesis is an organic reaction between α -haloketones and β -dicarbonyl compounds to give substituted furans in the presence of base.





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Knorr-pyrrole synthesis

This involves the condensation of α -amino ketones with a β -diketone or a β -ketoester to give a substituted pyrrole in the presence of a base like pyridine.



 α -amino ketones



1,3-Dicarbonyl compounds or β -chlorovinyl aldehydes react with thioglycolates or other thiols possessing a reactive methylene group to give thiophenes in the presence of pyridine.





Synthesis of Pyridine



1,5-Dicarbonyl compound :Nu = RNH₂

I. Reaction between a 1,5-diketone and ammonia

Ammonia reacts with 1,5-diketones to give unstable 1,4-dihydropyridine, which can be easily dehydrogenated (using nitrobenzene or nitric acid) to give pyridine.



II. The Guareschi synthesis

Unsymmetrical pyridines can be synthesised from a reaction between a β -dicarbonyl compound and a β -enaminocarbonyl compound or nitrile.







III. The Hantzsch synthesis

Symmetrical 1,4-dihydropyridines, which can be easily dehydrogenated (to form pyridines), are produced from the condensation of an aldehyde, ammonia, and two equivalents of a 1,3-dicarbonyl compounds (commonly a β -ketoester) which must have a central methylene.

The product from the classical Hantzsch synthesis is necessarily a symmetrically substituted 1,4dihydropyridine. Subsequent oxidation (or dehydrogenation) gives a symmetrical pyridine compound.

STEP I

The reaction is believed to proceed via Knoevenagel Condensation.



A second key intermediate is an ester enamine, which is produced by condensation of the second equivalent of the β -ketoester with ammonia:

$$R' O O O + NH_3 - H_2O R' + NH_3 - H_2O CR''$$

STEP III

Further condensation between these two fragments gives the dihydropyridine derivative:









Nifedipine

is in a group of drugs called calcium channel blockers. It works by relaxing the muscles of heart and blood your vessels. Nifedipine is used to treat hypertension (high blood pressure) and angina (chest pain).









Diazepam (Valium) used for the treatment of anxiety disorders. Diazepam also is used for the treatment Of agitation, tremors, delirium, seizures, and hallucinations resulting from alcohol withdrawal. It is used for the treatment of seizures and relief of muscle spasms in some neurological diseases



Diazepam



Antifungal drug



Pyridotriazine





Clopirac Nonsteroidal Antiinflammatory Drug)



