Aromatic heterocycles 1: structures and reactions

43

Connections

Building on:

- Aromaticity ch7
- Electrophilic aromatic substitution ch22
- Nucleophilic attack on aromatic rings ch23
- Saturated heterocycles ch42

Arriving at:

- Aromatic systems conceptually derived from benzene: replacing CH with N to get pyridine
- Replacing CH=CH with N to get pyrrole
- How pyridine reacts
- How pyridine derivatives can be used to extend pyridine's reactivity
- How pyrrole reacts
- How furan and thiophene compare with pyrrole
- Putting more nitrogens in five- and six-membered rings
- Fused rings: indole, quinoline, isoquinoline, and indolizine
- Rings with nitrogen and another heteroatom: oxygen or sulfur
- More complex heterocycles: porphyrins and phthalocyanines

Looking forward to:

- Synthesis of aromatic heterocycles ch44
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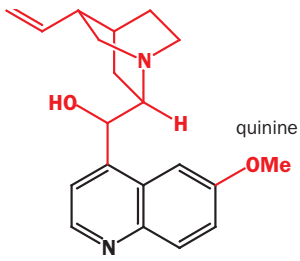
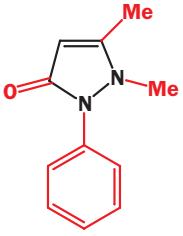
Introduction

Benzene is aromatic because it has six electrons in a cyclic conjugated system. We know it is aromatic because it is exceptionally stable and it has a ring current and hence large chemical shifts in the proton NMR spectrum as well as a special chemistry involving substitution rather than addition with electrophiles. This chapter and the next are about the very large number of other aromatic systems in which one or more atoms in the benzene ring are replaced by heteroatoms such as N, O, and S. There are thousands of these systems with five- and six-membered rings, and we will examine just a few.

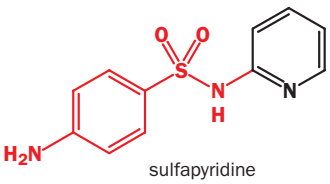
Our subject is **aromatic heterocycles** and it is important that we treat it seriously because most—probably about two-thirds of—organic compounds belong to this class, and they number among them some of the most significant compounds for human beings. If we think only of drugs we can define the history of medicine by heterocycles. Even in the sixteenth century quinine was used to prevent and treat malaria, though the structure of the drug was not known. The first synthetic drug was antipyrine (1887) for the reduction of fevers. The first effective antibiotic was sulfapyridine (1938). The first multi-million pound drug (1970s) was Tagamet, the anti-ulcer drug, and among the most topical of current drugs is Viagra (1997) for treatment of male impotence.



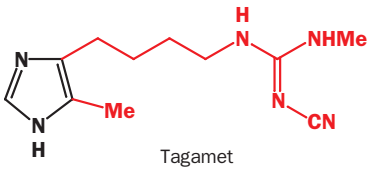
quinine



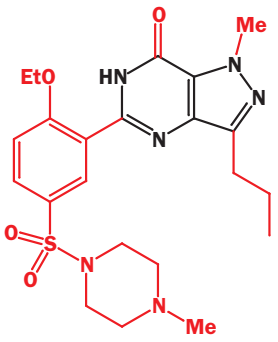
antipyrine



sulfapyridine



Tagamet



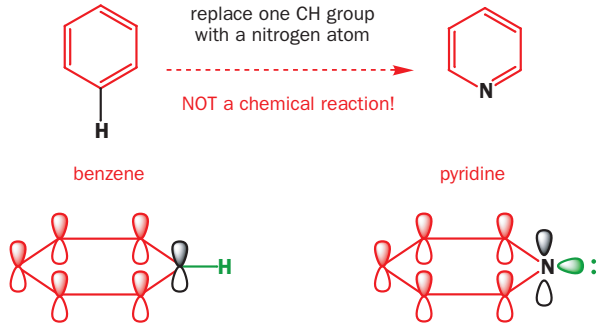
Viagra

■ Sir James Black, discoverer of Tagamet, worked on medicinal chemistry at Smith Kline French (later SmithKline Beecham) and was awarded the Nobel Prize for his analysis of drug receptors in 1988.

All these compounds have heterocyclic aromatic rings shown in black. Three have single rings, five- or six-membered, two have five- or six-membered rings fused together. The number of nitrogens in the rings varies from one to four. We will start by looking at the simple six-membered ring with one nitrogen atom. This is pyridine and the drug sulfapyridine is an example.

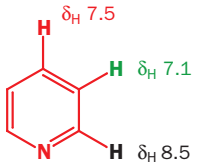
Aromaticity survives when parts of benzene's ring are replaced by nitrogen atoms

There is no doubt that benzene is aromatic. Now we must ask: how can we insert a heteroatom into the ring and retain aromaticity? What kind of atom is needed? If we want to replace one of the carbon atoms of benzene with a heteroatom, we need an atom that can be trigonal to keep the flat hexagonal ring and that has a p orbital to keep the six delocalized electrons. Nitrogen is ideal so we can imagine replacing a CH group in benzene with a nitrogen atom.



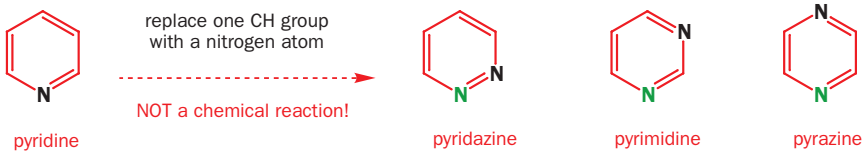
The orbitals in the ring have not changed in position or shape and we still have the six electrons from the three double bonds. One obvious difference is that nitrogen is trivalent and thus there is no NH bond. Instead, a lone pair of electrons occupies the space of the C–H bond in benzene.

In theory then, pyridine is aromatic. But is it in real life? The most important evidence comes from the proton NMR spectrum. The six protons of benzene resonate at δ_H 7.27 p.p.m., some 2 p.p.m. downfield from the alkene region, clear evidence for a ring current (Chapter 11). Pyridine is not as symmetrical as benzene but the three types of proton all resonate in the same region.

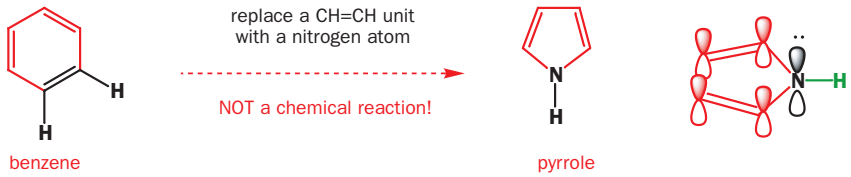


^{1}H NMR spectrum of pyridine

As we will see, pyridine is also very stable and, by any reasonable assessment, pyridine is aromatic. We could continue the process of replacing, on paper, more CH groups with nitrogen atoms, and would find three new aromatic heterocycles—pyridazine, pyrimidine, and pyrazine:



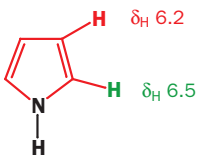
There is another way in which we might transform benzene into a heterocycle. Nitrogen has a lone pair of electrons so we could replace a CH=CH unit in benzene by a nitrogen atom providing that we can use the lone pair in the delocalized system. This means putting it into a p orbital.



We still have the four electrons from the remaining double bonds and, with the two electrons of the lone pair on nitrogen, that makes six in all. The nitrogen atom must still be trigonal with the lone pair in a p orbital so the N–H bond is in the plane of the five-membered ring.

The NMR of pyrrole is slightly less convincing as the two types of proton on the ring resonate at higher field (6.5 and 6.2 p.p.m.) than those of benzene or pyridine but they still fall in the aromatic rather than the alkene region. Pyrrole is also more reactive towards electrophiles than benzene or

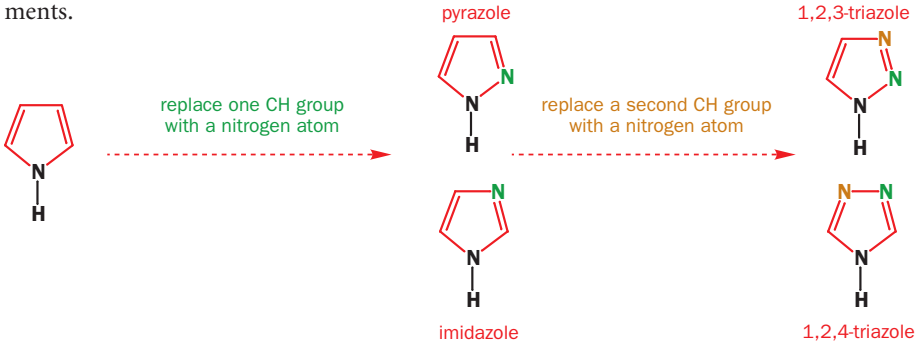
▶ One of the most annoying things about heterocyclic chemistry is the mass of what appear to be illogical names. You should not, of course, attempt to learn them all, but a basic idea of how they are designed will help you. We will give you a guide on which names to learn shortly. For the moment accept that 'amine' ends in '-ine' and any heterocyclic compound whose name ends in '-ine' is a nitrogen heterocycle. The syllable 'azo-' also implies nitrogen and 'pyr-' (usually) implies a six-membered ring. (except in pyrrole!)



δ_H~10

pyridine, but it does the usual aromatic substitution reactions (Friedel–Crafts, nitration, halogenation) rather than addition reactions: pyrrole is also aromatic.

Inventing heterocycles by further replacement of CH groups by nitrogen in pyrrole leads to two compounds, pyrazole and imidazole, after one replacement and to two triazoles after two replacements.

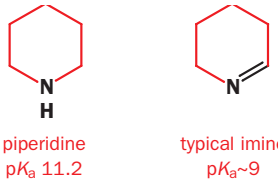


All of these compounds are generally accepted as aromatic too as they broadly have the NMR spectra and reactivities expected for aromatic compounds. As you may expect, introducing heteroatoms into the aromatic ring and, even more, changing the ring size actually affect the chemistry a great deal. We must now return to pyridine and work our way more slowly through the chemistry of these important heterocycles to establish the principles that govern their behaviour.

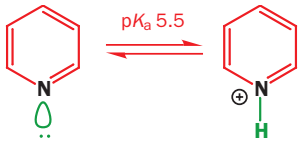
▶ The ending '-ole' is systematic and refers to a five-membered heterocyclic ring. All the five-membered aromatic heterocycles with nitrogen in the ring are sometimes called 'the azoles'. Strictly speaking, pyrrole is 'azole', pyrazole is '1,2-diazole', and imidazole is '1,3-diazole'. These names are not used but oxazole and thiazole are used for the oxygen and sulfur analogues of imidazole.

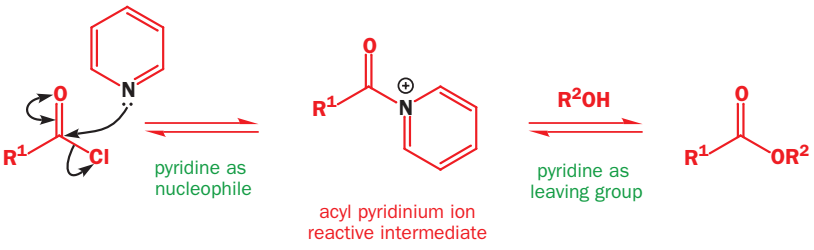
Pyridine is a very unreactive aromatic imine

The nitrogen atom in the pyridine ring is planar and trigonal with the lone pair in the plane of the ring. This makes it an imine. Most of the imines you have met before (in Chapter 14, for example), have been unstable intermediates in carbonyl group reactions, but in pyridine we have a stable imine—stable because of its aromaticity. All imines are more weakly basic than saturated amines and pyridine is a weak base with a pK_a of 5.5. This means that the pyridinium ion as about as strong an acid as a carboxylic acid.

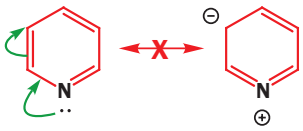


Pyridine is a reasonable nucleophile for carbonyl groups and is often used as a nucleophilic catalyst in acylation reactions. Esters are often made in pyridine solution from alcohols and acid chlorides (the full mechanism is on p. 000 of Chapter 12).

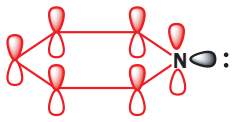




▶ Pyridine is also toxic and has a foul smell—so there are disadvantages in using pyridine as a solvent. But it is cheap and remains a popular solvent in spite of the problems.



Pyridine is nucleophilic at the nitrogen atom because *the lone pair of electrons on nitrogen cannot be delocalized around the ring*. They are in an sp^2 orbital orthogonal to the p orbitals in the ring and there is no interaction between orthogonal orbitals. Try it for yourself, drawing arrows. All attempts to delocalize the electrons lead to impossible results!

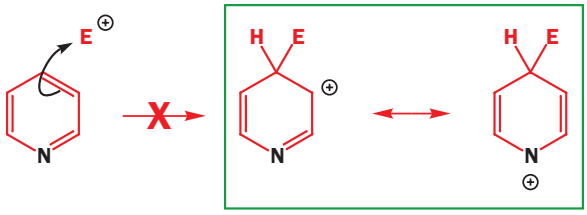


● **The lone pair of pyridine's nitrogen atom is not delocalized.**

Our main interest must be this: what does the nitrogen atom do to the rest of the ring? The important orbitals—the p orbitals of the aromatic system—are superficially the same as in benzene, but the more electronegative nitrogen atom will lower the energy of all the orbitals. Lower-energy filled orbitals mean a *less* reactive nucleophile but a lower-energy LUMO means a *more* reactive electrophile. This is a good guide to the chemistry of pyridine. It is less reactive than benzene in electrophilic aromatic substitution reactions but nucleophilic substitution, which is difficult for benzene, comes easily to pyridine.

Pyridine is bad at electrophilic aromatic substitution

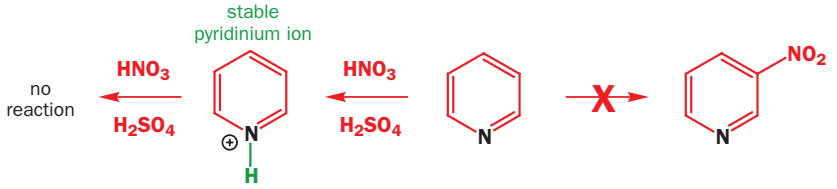
The lower energy of the orbitals of pyridine's π system means that electrophilic attack on the ring is difficult. Another way to look at this is to see that the nitrogen atom destabilizes the cationic would-be intermediate, especially at the 2- and 4-positions.



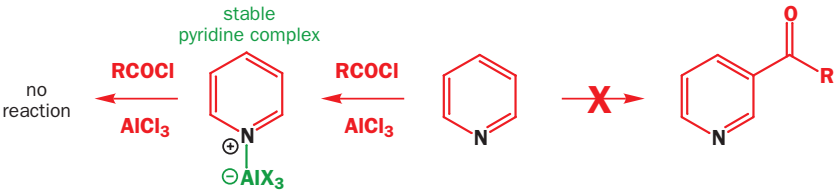
unstable electron-deficient cation

▶ 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.

An equally serious problem is that the nitrogen lone pair is basic and a reasonably good nucleophile—this is the basis for its role as a nucleophilic catalyst in acylations. The normal reagents for electrophilic substitution reactions, such as nitration, are acidic. Treatment of pyridine with the usual mixture of HNO_3 and H_2SO_4 merely protonates the nitrogen atom. Pyridine itself is not very reactive towards electrophiles: the pyridinium ion is totally unreactive.



Other reactions, such as Friedel–Crafts acylations, require Lewis acids and these too react at nitrogen. Pyridine is a good ligand for metals such as Al(III) or Sn(IV) and, once again, the complex with its cationic nitrogen is completely unreactive towards electrophiles.

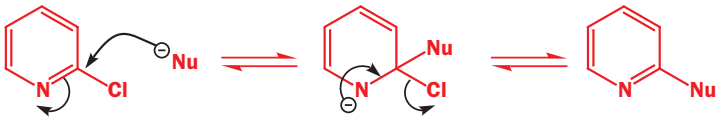


● Pyridine does not undergo electrolytic substitution

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. Avoid nitration, sulfonation, halogenation, and Friedel–Crafts reactions on simple pyridines.

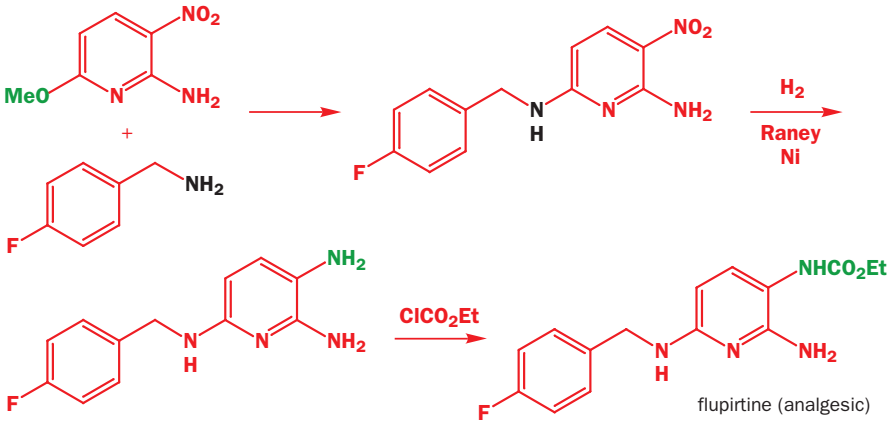
Nucleophilic substitution is easy with pyridines

By contrast, the nitrogen atom makes pyridines *more* reactive towards nucleophilic substitution, particularly at the 2- and 4-positions, by lowering the LUMO energy of the π system of pyridine. You can see this effect in action in the ease of replacement of halogens in these positions by nucleophiles.



The intermediate anion is stabilized by electronegative nitrogen and by delocalization round the ring. These reactions have some similarity to nucleophilic aromatic substitution (Chapter 23) but are more similar to carbonyl reactions. The intermediate anion is a tetrahedral intermediate that loses the best leaving group to regenerate the stable aromatic system. Nucleophiles such as amines or thiolate anions work well in these reactions.

The leaving group does not have to be as good as chloride in these reactions. Continuing the analogy with carbonyl reactions, 2- and 4-chloropyridines are rather like acid chlorides but we need only use less reactive pyridyl ethers, which react like esters, to make amides. The 2- and 4-methoxypyridines allow the completion of the synthesis of flupirtine.



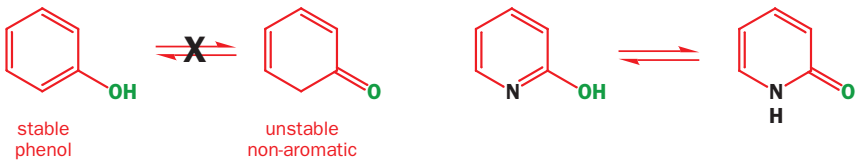
■ Two of the problems at the end of the chapter concern this synthesis: you might like to turn to them now.

The first step is a nucleophilic aromatic substitution. In the second step the nitro group is reduced to an amino group without any effect on the pyridine ring—another piece of evidence for its aromaticity. Finally, one amino group is acylated in the presence of three others.

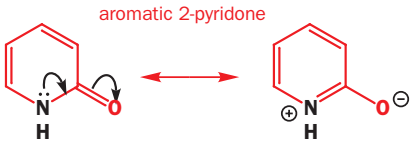
Pyridones are good substrates for nucleophilic substitution

The starting materials for these nucleophilic substitutions (2- and 4- chloro or methoxypyridines) are themselves made by nucleophilic substitution on pyrid*ones* and we need now to discuss these interesting molecules. If you were asked to propose how 2-methoxypyridine might be made, you would probably suggest, by analogy with the corresponding benzene compound, alkylation of a phenol. Let us look at this in detail.

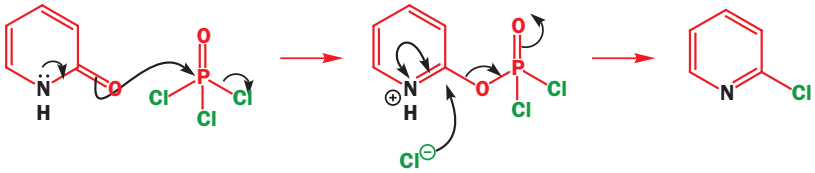
The starting material for this reaction is a 2-hydroxypyridine that can tautomerize to an amide-like structure by the shift of the acidic proton from oxygen to nitrogen. In the phenol series there is no doubt about which structure will be stable as the ketone is not aromatic; for the pyridine both structures are aromatic.



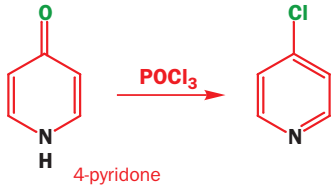
In fact, 2-hydroxypyridine prefers to exist as the 'amide' because that has the advantage of a strong C=O bond and is still aromatic. There are two electrons in each of the C=C double bonds and two also in the lone pair of electrons on the trigonal nitrogen atom of the amide. Delocalization of the lone pair in typical amide style makes the point clearer.

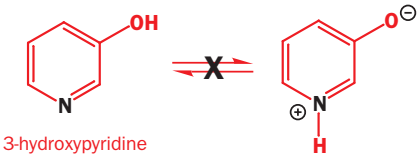


Pyridones are easy to prepare (see Chapter 44) and can be alkylated on oxygen as predicted by their structure. A more important reaction is the direct conversion to chloropyridines with $POCl_3$. The reaction starts by attack of the oxygen atom at phosphorus to create a leaving group, followed by aromatic nucleophilic substitution. The overall effect is very similar to acyl chloride formation from a carboxylic acid.



The same reaction occurs with 4-pyridone, which is also delocalized in the same way and exists in the 'amide' form; but not with 3-hydroxypyridine, which exists in the 'phenol' form.



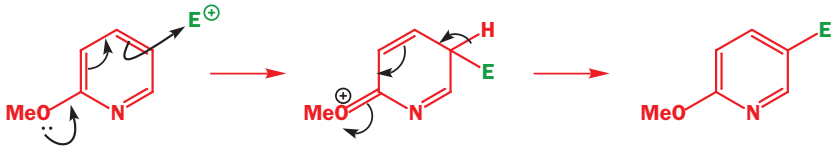


● Pyridines undergo nucleophilic substitution

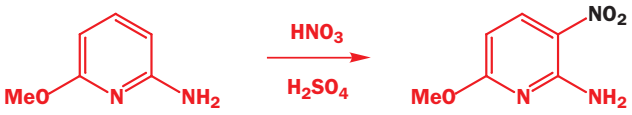
Pyridines can undergo *electrophilic* substitution only if they are activated by electron-donating substituents (see next section) but they readily undergo *nucleophilic* substitution without any activation other than the ring nitrogen atom.

Activated pyridines will do electrophilic aromatic substitution

Useful electrophilic substitutions occur only on pyridines having electron-donating substituents such as NH_2 or OMe. These activate benzene rings too (Chapter 22) but here their help is vital. They supply a nonbonding pair of electrons that becomes the HOMO and carries out the reaction. Simple amino- or methoxypyridines react reasonably well *ortho* and *para* to the activating group. These reactions happen in spite of the molecule being a pyridine, not because of it.

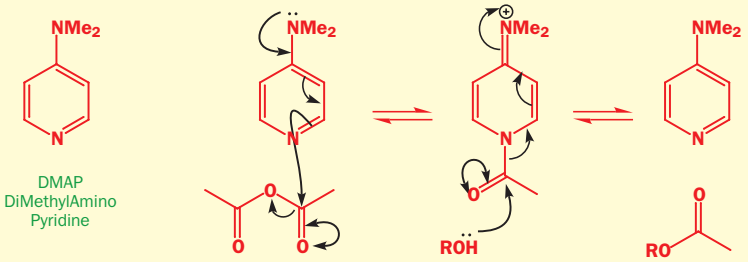


A practical example occurs in the manufacture of the analgesic flupirtine where a doubly activated pyridine having both MeO and NH_2 groups is nitrated just as if it were a benzene ring. The nitro group goes in *ortho* to the amino group and *para* to the methoxy group. This sequence is completed in the next section. The activation is evidently enough to compensate for the molecule being almost entirely protonated under the conditions of the reaction.



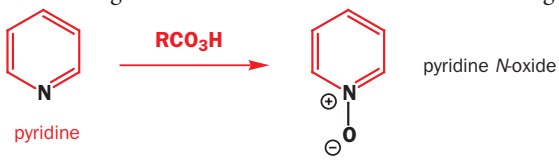
DMAP

One particular amino-pyridine has a special role as a more effective acylation catalyst than pyridine itself. This is DMAP (DiMethylAminoPyridine) in which the amino group is placed to reinforce the nucleophilic nature of the nitrogen atom. Whereas acylations 'catalysed' by pyridine are normally carried out in solution in pyridine, only small amounts of DMAP in other solvents are needed to do the same job.

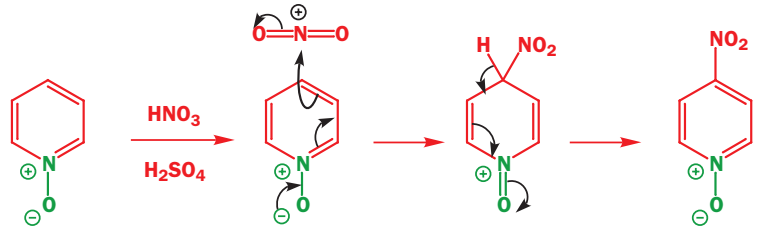


Pyridine *N*-oxides are reactive towards both electrophilic and nucleophilic substitution

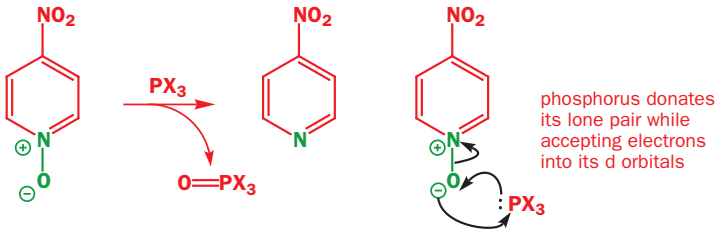
This is all very well if the molecule has such activating groups, but supposing it doesn't? How are we to nitrate pyridine itself? The answer involves an ingenious trick. We need to activate the ring with an electron-rich substituent that can later be removed and we also need to stop the nitrogen atom reacting with the electrophile. All of this can be done with a single atom!



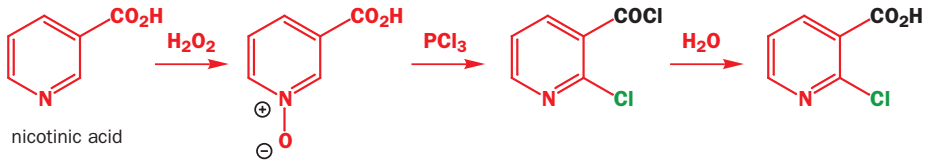
Because the nitrogen atom is nucleophilic, pyridine can be oxidized to pyridine *N*-oxide with reagents such as *m*-CPBA or just H_2O_2 in acetic acid. These *N*-oxides are stable dipolar species with the electrons on oxygen delocalized round the pyridine ring, raising the HOMO of the molecule. Reaction with electrophiles occurs at the 2- ('*ortho*') and 4- ('*para*') positions, chiefly at the 4-position to keep away from positively charged nitrogen.



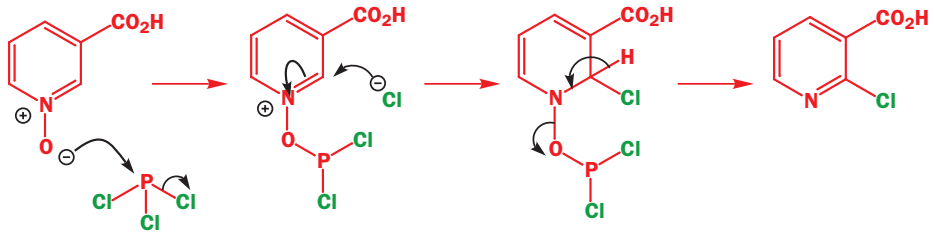
Now the oxide must be removed and this is best done with trivalent phosphorus compounds such as $(MeO)_3P$ or PCl_3. The phosphorus atom detaches the oxygen atom in a single step to form the very stable P=O double bond. In this reaction the phosphorus atom is acting as both a nucleophile and an electrophile, but mainly as an electrophile since PCl_3 is more reactive here than $(MeO)_3P$.



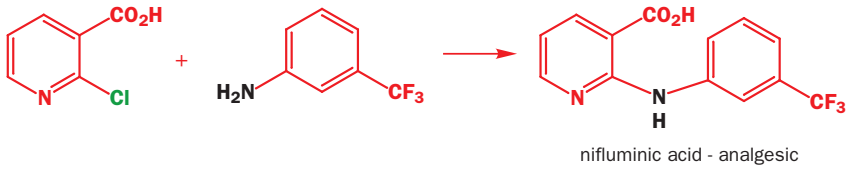
The same activation that allowed simple electrophilic substitution—oxidation to the *N*-oxide—can also allow a useful nucleophilic substitution. The positive nitrogen atom encourages nucleophilic attack and the oxygen atom can be turned into a leaving group with PCl_3. Our example is nicotinic acid whose biological importance we will discuss in Chapter 50.



The *N*-oxide reacts with PCl_3 through oxygen and the chloride ion released in this reaction adds to the most electrophilic position between the two electron-withdrawing groups. Now a simple elimination restores aromaticity and gives a product looking as though it results from chlorination rather than nucleophilic attack.



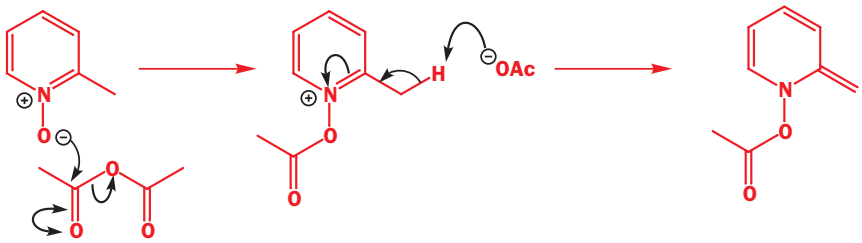
The reagent PCl_3 also converts the carboxylic acid to the acyl chloride, which is hydrolysed back again in the last step. This is a useful sequence because the chlorine atom has been introduced into the 2-position from which it may in turn be displaced by, for example, amines.



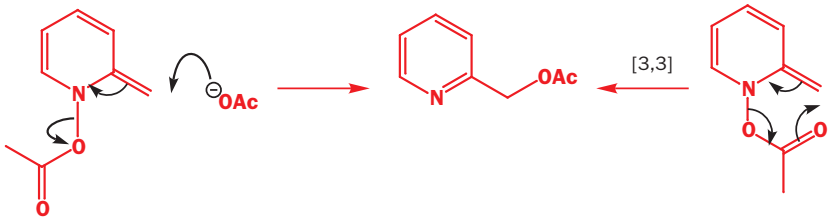
● Pyridine-*N*-oxides

Pyridine *N*-oxides are useful for both electrophilic and nucleophilic substitutions on the same carbon atoms (2-, 4-, and 6-) in the ring.

Nucleophilic addition at an even more distant site is possible on reaction with acid anhydrides if there is an alkyl group in the 2-position. Acylation occurs on oxygen as in the last reaction but then a proton is lost from the side chain to give an uncharged intermediate.



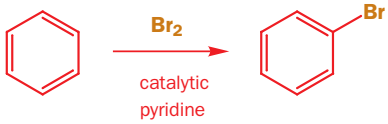
This compound rearranges with migration of the acetate group to the side chain and the restoration of aromaticity. This may be an ionic reaction or a [3,3]-sigmatropic rearrangement.



Since pyridine is abundant and cheap and has an extremely rich chemistry, it is not surprising that it has many applications.

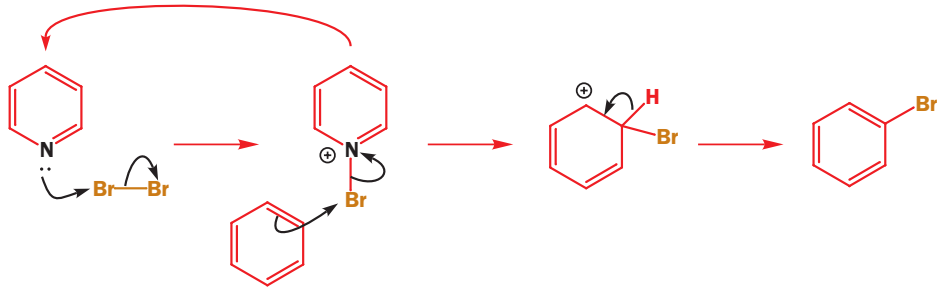
Some applications of pyridine chemistry

One of the simplest ways to brominate benzenes is not to bother with the Lewis acid catalysts recommended in Chapter 22 but just to add liquid bromine to the aromatic compound in the presence of a small amount of pyridine. Only about one mole per cent is needed and even then the reaction has to be cooled to stop it getting out of hand.

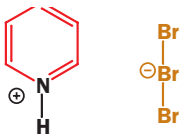


As we have seen, pyridine attacks electrophiles through its nitrogen atom. This produces the reactive species, the *N*-bromo-pyridinium ion, which is attacked by the benzene. Pyridine is a better nucleophile than benzene and a better leaving group than bromide. This is another example of **nucleophilic catalysis**.

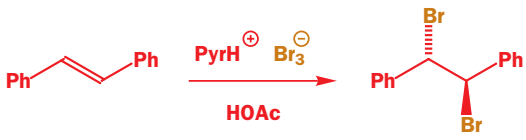
Nucleophilic catalysis is discussed on p. 000.



Another way to use pyridine in brominations is to make a stable crystalline compound to replace the dangerous liquid bromine. This compound, known by names such as pyridinium tribromide, is simply a salt of pyridine with the anion Br_3^-. It can be used to brominate reactive compounds such as alkenes (Chapter 20).

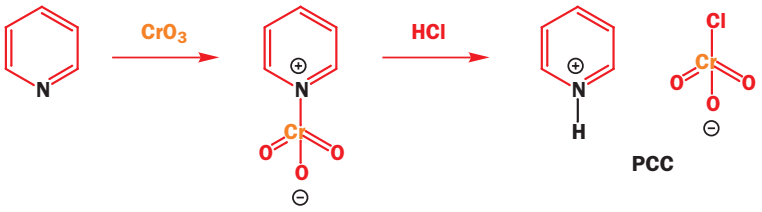


Both of these methods depend on the lack of reactivity of pyridine's π system towards electrophiles such as bromine. Notice that, in the first case, both benzene and pyridine are



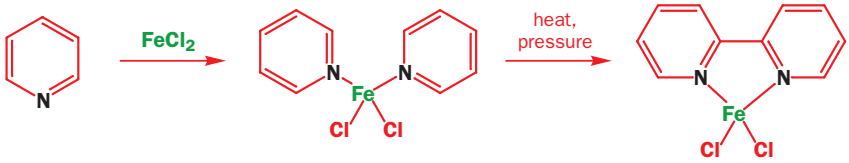
present together. The pyridine attacks bromine only through nitrogen (and reversibly at that) and never through carbon.

Oxidation of alcohols is normally carried out with Cr(VI) reagents (Chapter 24) but these, like the Jones' reagent ($Na_2Cr_2O_7$ in sulfuric acid), are usually acidic. Some pyridine complexes of Cr(VI) compounds solve this problem by having the pyridinium ion (pK_a 5) as the only acid. The two most famous are 'PDC' (Pyridinium DiChromate) and 'PCC' (Pyridinium Chloro-Chromate). Pyridine forms a complex with CrO_3 but this is liable to burst into flames. Treatment with HCl gives PCC, which is much less dangerous. PCC is particularly useful in the oxidation of primary alcohols to aldehydes as overoxidation is avoided in the only slightly acidic conditions (Chapter 24).



The ability of pyridine to form metal complexes is greatly enhanced in a dimer—the famous ligand 'bipy' or 2,2′-bipyridyl. It is bidentate and because of its 'bite' it is a good ligand for many transition metals but shows a partiality for Fe(II).

It looks like a rather difficult job to persuade two pyridine rings to join together in this way to form bipy. It is indeed very difficult unless you make things easier by using a reagent that favours the product. And what better than Fe(II) to do the job? ICI manufacture bipy by treating pyridine with $FeCl_2{\cdot}4H_2O$ at high temperatures and high pressures. Only a small proportion of the pyridine is converted to the Fe(II) complex of bipy (about 5%) but the remaining pyridine goes back in the next reaction. This is probably a radical process (Chapter 39) in the coordination sphere of Fe(II).



Six-membered aromatic heterocycles can have oxygen in the ring

Though pyridine is overwhelmingly the most important of the six-membered aromatic heterocycles, there are oxygen heterocycles, **pyrones**, that resemble the pyridones. The pyrones are aromatic, though α-pyrone is rather unstable.