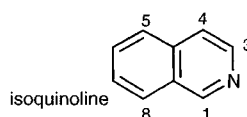
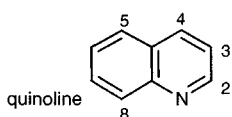
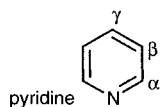
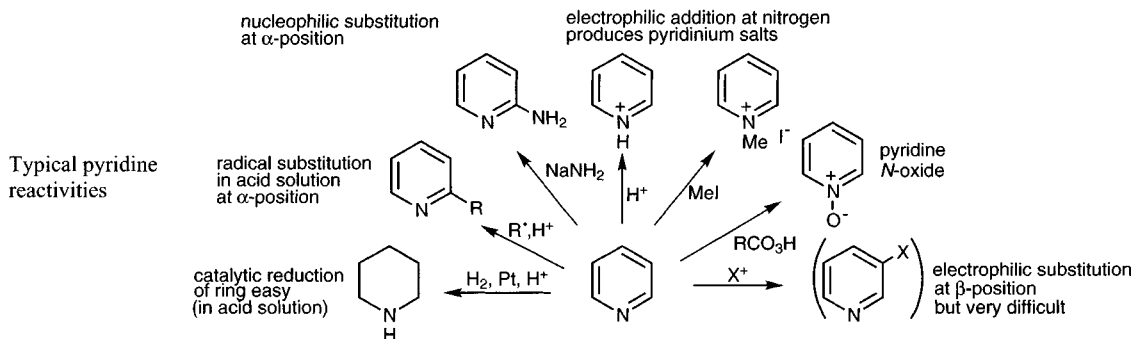


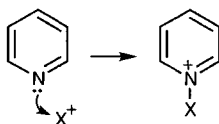
4 Typical reactivity of pyridines, quinolines and isoquinolines



Before detailed descriptions of the chemistry of the heterocyclic systems covered in this book, and at intervals during the book, we provide six highly condensed and simplified discussions of the types of reaction, ease of such reactions, and regiochemistry of such reactions for groups of related heterocycles. In this chapter the group comprises pyridine, as the prototype electron-poor six-membered heterocycle and its benzo-fused analogues, quinoline and isoquinoline. As in each of these summary chapters, reactions are shown in brief and either as the simplest possible example, or in general terms.

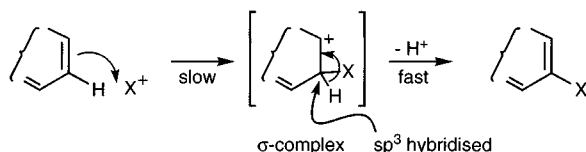


The formal replacement of a CH in benzene, by N, leads to far-reaching changes in typical reactivity: pyridines are much less susceptible to electrophilic substitution than benzene, and much more susceptible to nucleophilic attack. However, pyridine undergoes a range of simple electrophilic additions, some reversible, some forming isolable products, each involving donation of the nitrogen lone pair to an electrophile, and thence the formation of 'pyridinium' salts which, of course, do not have a counterpart in benzene chemistry at all. It is essential to understand that the ready donation of the pyridine lone pair in this way does not destroy the aromatic sextet (compare with pyrrole, chapter 12) – pyridinium salts are still aromatic, though of course much more polarised than neutral pyridines (see section 1.2.3).

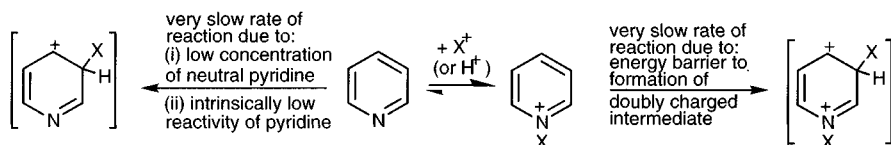


Electrophilic substitution of aromatic compounds proceeds *via* a two-step sequence – addition (of X^+) then elimination (of H^+), of which the former is usually the slower (rate-determining) step. Qualitative predictions of relative rates of substitution at different ring positions can be made by inspecting the structures of the σ -complexes

(Wheland intermediates) thus formed, on the assumption that their relative stabilities reflect the relative energies of the transition states which lead to them.

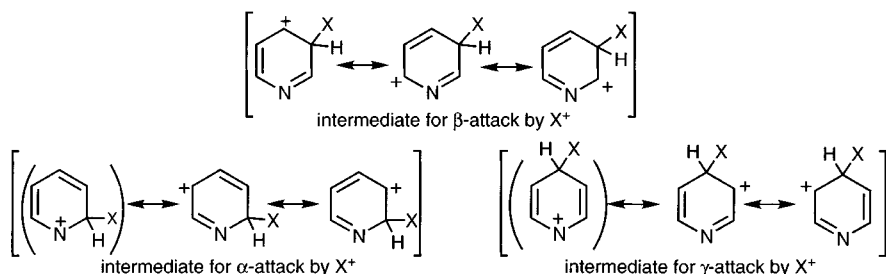


Electrophilic substitution at carbon, in simple pyridines at least, is very difficult in contrast to the reactions of benzene – Friedel-Crafts acylations, for example, do not occur at all with pyridines. This unreactivity can be traced to two factors:



(1) Exposure of a pyridine to a medium containing electrophilic species immediately converts the heterocycle into a pyridinium cation with the electrophile (or a proton from the medium, or a Lewis acid) attached to the nitrogen. The extent of conversion depends on the nature and concentration of the electrophile (or protons) and the basicity of the particular pyridine, and is usually nearly complete. Obviously, the positively charged pyridinium cation is many orders of magnitude less easily attacked at carbon by the would-be electrophile than the original neutral heterocycle. The electrophile, therefore, has Hobson's choice – it must either attack an already-positively charged species, or seek out a neutral pyridine from the very low concentration of uncharged heterocyclic molecules.

(2) The carbons of a pyridine are, in any case, electron-poor, particularly at the α - and γ -positions: formation of a σ -complex between a pyridine and an electrophile is intrinsically disfavoured. The least disfavoured, i.e. best option, is attack at a β -position – resonance contributors to the cation thus produced, do not include one with the particularly unfavourable sextet, positively-charged nitrogen situation (shown in parentheses for the α - and γ -intermediates). The situation has a direct counterpart in benzene chemistry where a consideration of possible intermediates for electrophilic substitution of nitrobenzene provides a rationalisation of the observed *meta* selectivity.

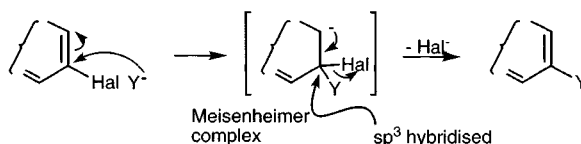


Substituents exert an influence on the ease of electrophilic attack, just as in benzene chemistry. Strongly electron-withdrawing substituents simply render the pyridine even more inert, however activating groups – amino and oxy, and even alkyl – allow substitution to take place, even though by way of the protonated heterocycle i.e. *via* a dicationic intermediate. The presence of halogen substituents, which have a

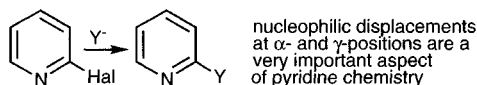
base-weakening effect and are only weakly deactivating, can allow substitution to take place in a different way – by allowing an appreciably larger concentration of the un-protonated pyridine to be present.

Pyridine rings are resistant to oxidative destruction, as are benzene rings. In terms of reduction, however, the heterocyclic system is much more easily catalytically reduced, especially in acidic solution. Similarly, *N*-alkyl- and *N*-arylpyridinium salts can be easily reduced both with hydrogen over a catalyst, and by nucleophilic chemical reducing agents.

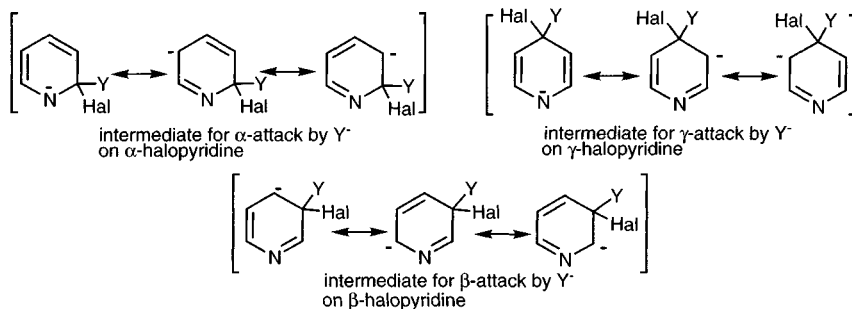
Nucleophilic substitution of aromatic compounds proceeds *via* an addition (of Y^-) then elimination (of a negatively charged entity, most often Hal^-) two-step sequence of which the former is usually rate-determining (the $S_N(AE)$ mechanism: Substitution Nucleophilic Addition Elimination). Rates of substitution at different ring positions can be assessed by inspecting the structures of the negatively charged intermediates (Meisenheimer complexes) thus formed, on the assumption that their relative stabilities (degree of delocalisation of negative charge) reflect the relative energies of the transition states which lead to them. For example 2- and 4-halonitrobenzenes react in this way because the anionic adduct derives stabilisation by delocalisation of the charge onto the nitro group(s).



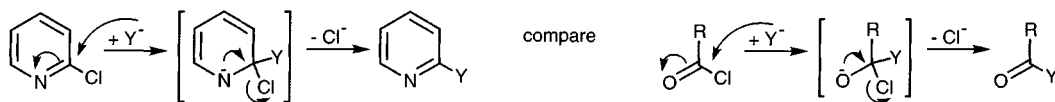
The electron-deficiency of the carbons in pyridines, particularly α - and γ -carbons, makes nucleophilic addition and, especially nucleophilic displacement of halide (and other good leaving groups), a very important feature of pyridine chemistry.



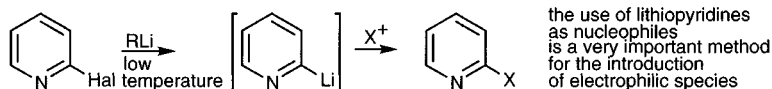
Such substitutions follow the same mechanistic route as the displacement of halide from 2- and 4-halo-nitro-benzenes, i.e. the nucleophile first adds and then the halide departs. By analogy with the benzenoid situation, the addition is facilitated by (i) the electron-deficiency at α - and γ -carbons, further increased by the halogen substituent, and (ii) the ability of the heteroatom to accommodate negative charge in the intermediate thus produced. Once again, a comparison of the three possible intermediates makes it immediately plain that this latter is not available for attack at a β -position, and thus β nucleophilic displacements are very much slower – for practical purposes they do not occur.



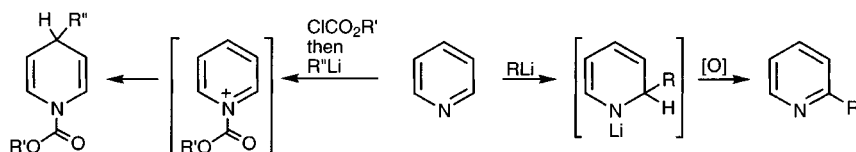
It is useful to compare the reactivity of α - and γ -halopyridines with the reaction of acid halides and β -halo- α,β -unsaturated ketones, respectively, both of which also interact easily with nucleophiles and also by an addition/elimination sequence resulting in overall displacement of the halide by the nucleophile.



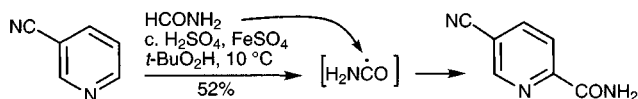
The generation of metallated aromatics has become extremely important for the introduction of substituents, especially carbon substituents, by subsequent reaction with an electrophile. It is very important, in the light of the discussion above on the ease of nucleophilic addition and substitution, to realise that iodine and bromine at all positions of a pyridine can be exchanged at low temperature *without* nucleophilic displacement or addition, with formation of the pyridyllithium.



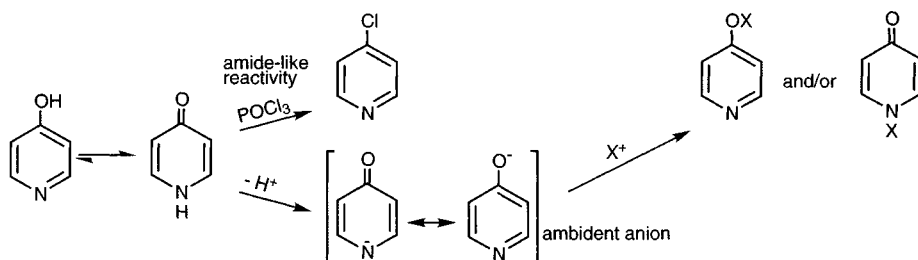
In the absence of an α - or γ -halogen, pyridines are less reactive and, of course, do not have a substituent suitable for leaving as an anion to complete a nucleophilic substitution. Nucleophilic additions do however take place, but the resultant dihydropyridine adduct requires an oxidant – to remove 'hydride' – to complete an overall substitution. Such reactions, for example with amide or with organometallic reagents, are selective for an α -position, possibly because the nucleophile is delivered *via* a complex involving interaction of the ring nitrogen with the metal cation associated with the reactant. The addition of organometallic or hydride reagents to N^+ -acylpyridinium salts is an extremely useful process: the product, dihydropyridines are stable because the nitrogen is an amide, most often a urethane.



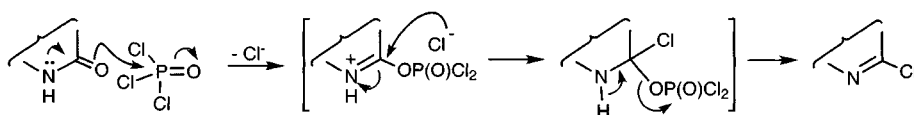
Radical substitution of pyridines, in acid solution, is now a preparatively useful process. For efficient reaction, the radicals must be 'nucleophilic', like $\cdot CH_2OH$, alkyl \cdot , and acyl \cdot – aminocarbonylation provides an example.



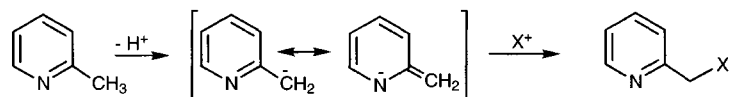
Pyridines carrying oxygen at an α - or γ -position exist as tautomers having carbonyl groups – pyridones. Nonetheless, there is considerable parallelism between their reactions and those of phenols: pyridones are activated towards electrophilic substitution, attack taking place *ortho* and *para* to the oxygen, and they readily form anions, by loss of the N -hydrogen, which are analogous in structure and reactivity to phenolates, though in the heterocyclic system the anion can react at either oxygen or nitrogen, depending on conditions.



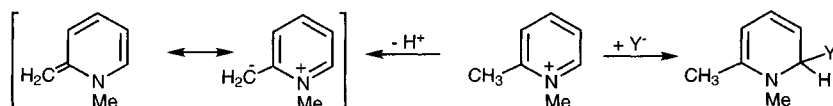
Where pyridones differ from phenols is in their interaction with phosphorus and sulfur halides, where transformation of the oxygen substituent into halide occurs. Here, the pyridones react in an amide-like fashion, the inorganic reagent reacting first at the amide-like oxygen.



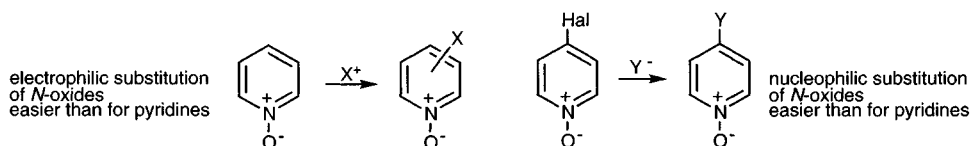
The special properties associated with pyridine α - and γ -positions show again in the reactions of alkylpyridines: the protons on alkyl groups at those positions are particularly acidified because the 'enamine' anions formed are delocalised. The ability to form side-chain anions provides an extremely useful means for the manipulation of α - and γ -side-chains.



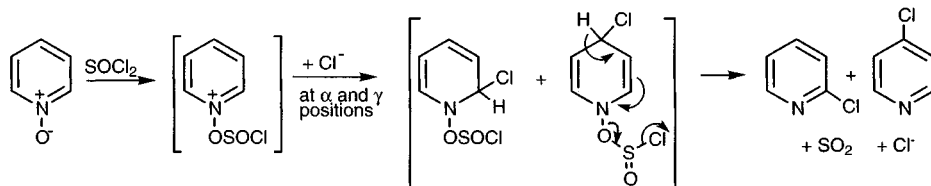
Pyridinium salts show the properties which have been discussed above, but in extreme: they are highly resistant to electrophilic substitution but, conversely, nucleophiles add very easily. The hydrogens of α - and γ -alkyl side-chains on pyridinium salts are further acidified compared with the uncharged alkylpyridine.



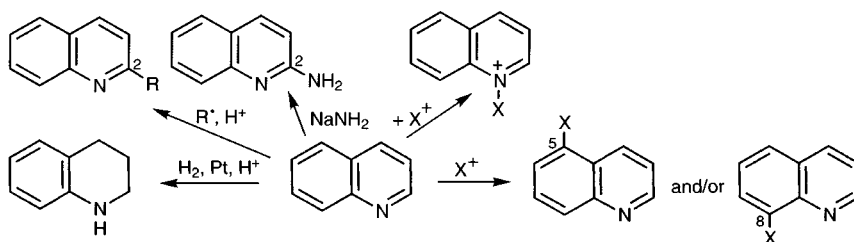
Pyridine *N*-oxide chemistry, which clearly has no parallel in benzenoid chemistry, is an extremely important and useful aspect of the chemistry of heterocycles of the pyridine series. The structure of these derivatives means that they are both more susceptible to electrophilic substitution *and* react more easily with nucleophiles – an extraordinary concept when first encountered. On the one hand, the formally negatively charged oxygen can release electrons to stabilise an intermediate from electrophilic attack and, on the other, the positively charged ring nitrogen can act as an electron sink to encourage nucleophilic addition.



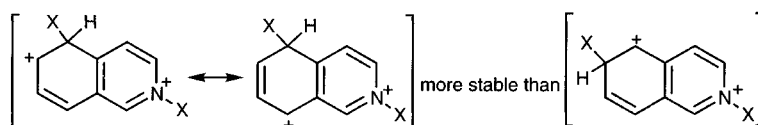
There are a number of very useful processes in which the *N*-oxide function allows the introduction of substituents usually mainly at an α position and in the process, the oxide function is removed; reaction with thionyl chloride is an example.



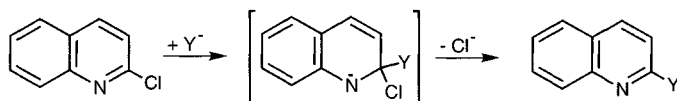
Quinoline and isoquinoline, the two possible structures in which a benzene ring is annelated to a pyridine ring, represent an opportunity to examine the effect of fusing one aromatic ring to another. Clearly, both the effect the benzene ring has on the reactivity of the pyridine ring, and *vice versa*, as well as comparisons with the chemistry of naphthalene must be considered. Thus the regioselectivity of electrophilic substitution, which in naphthalene favours an α -position, is mirrored in quinoline/isoquinoline chemistry by substitution at 5- and 8-positions. It should be noted that such substitutions usually involve attack on the species formed by electrophilic addition (often protonation) at the nitrogen, which has the effect of discouraging (preventing) attack on the heterocyclic ring.



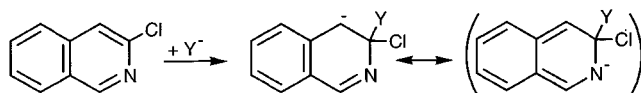
Just as for naphthalene, the regiochemistry of attack is readily interpreted by looking at possible intermediates: those for attack at C-5/8 allow delocalisation of charge without disruption of the pyridinium ring aromatic resonance, while those for attack at C-6/7 would necessitate disrupting that resonance in order to allow delocalisation of charge.



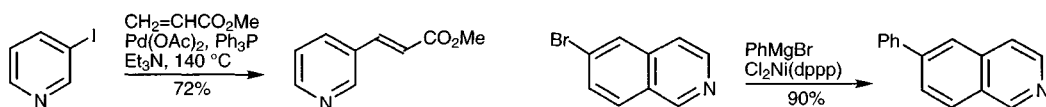
So, just as quinoline and isoquinoline are reactive towards electrophiles in their benzene ring, so they are reactive to nucleophiles in the pyridine ring, especially (see above) at the positions α and γ to the nitrogen and, further, are more reactive in this sense than pyridines. This is consistent with the structures of the intermediates for, in these, a full and complete, aromatic benzene ring is retained. Since the resonance stabilisation of the bicyclic aromatic is considerably less than twice that of either benzene or pyridine, the loss in resonance stabilisation in proceeding from the bicyclic system to the intermediate is considerably less than in going from pyridine to an intermediate adduct. There is an obvious analogy: the rate of electrophilic substitution of naphthalene is greater than that of benzene for, in forming a σ -complex from the former, less resonance energy is sacrificed.



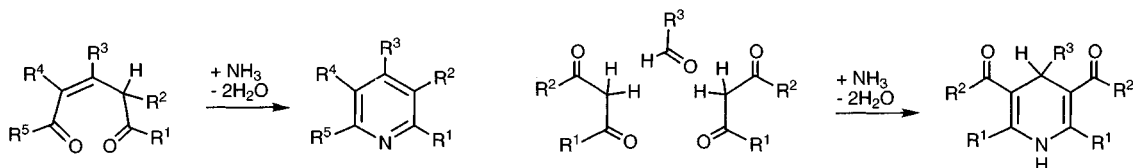
A significant difference in this typical behaviour applies to the isoquinoline 3-position – the special reactivity which the discussion above has developed for positions α to pyridine nitrogen, and which also applies to the isoquinoline 1-position, does not apply at C-3. In the context of nucleophilic displacements, for example, an intermediate for reaction of a 3-halo-isoquinoline cannot achieve delocalisation of negative charge onto the nitrogen unless the aromaticity of the benzene ring is disrupted. Therefore, such intermediates are considerably less stabilised and reactivity considerably tempered.



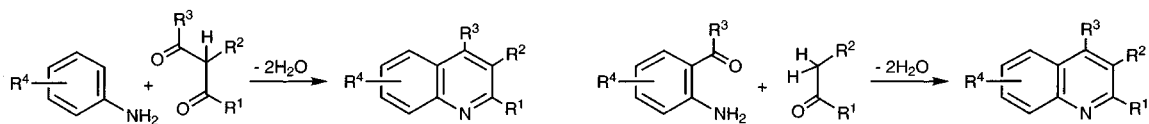
The displacement of halogen at all positions of the pyridine and isoquinoline nucleus is achievable using metal, usually palladium(0), catalysis (see section 2.7 for a detailed discussion). Couplings with alkenes (Heck reactions), with alkynes, with alkenyl- or aryltin or -boron species are complemented by couplings in the opposite sense using pyridinyl/quinolinyl/isoquinolinyl metal (often tin) reagents, with alkenyl- or arylhalides or triflates. This extremely useful methodology allows transformations in one step which would formerly have required such an extensive sequence of steps that they might not even have been attempted: two examples are shown below.



A great variety of methods is available for the ring synthesis of pyridines: the most obvious approach is to construct a 1,5-dicarbonyl compound, preferably also having further unsaturation and allow it to react with ammonia, addition of which at each carbonyl group, with losses of water, producing the pyridine. 1,4-Dihydropyridines, which can easily be dehydrogenated to the fully aromatic system, result from the interaction of aldehydes with two mol equivalents of 1,3-diketones (or 1,3-ketoesters, *etc.*) and ammonia; aldol and Michael reactions and addition of ammonia at the termini, produces the heterocycle.



Nearly all quinoline syntheses begin from an arylamine: that shown generally below – the acid-catalysed interaction with a 1,3-diketone – involves addition of the amine nitrogen to one of the carbonyl groups and a ring closure onto the aromatic ring having the character of an electrophilic substitution. Another much-used route utilises the aldol-type interaction of an *ortho*-aminoaldehyde (or -ketone) with a ketone having an α methylene.



The amides of 2-(aryl)ethanamines can be made to ring close producing 3,4-dihydroisoquinolines (which can be easily dehydrogenated to the aromatic systems) using reagents such as phosphoryl chloride; again, the ring-closure step is an intramolecular electrophilic substitution of the aromatic ring.

