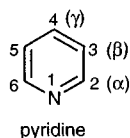
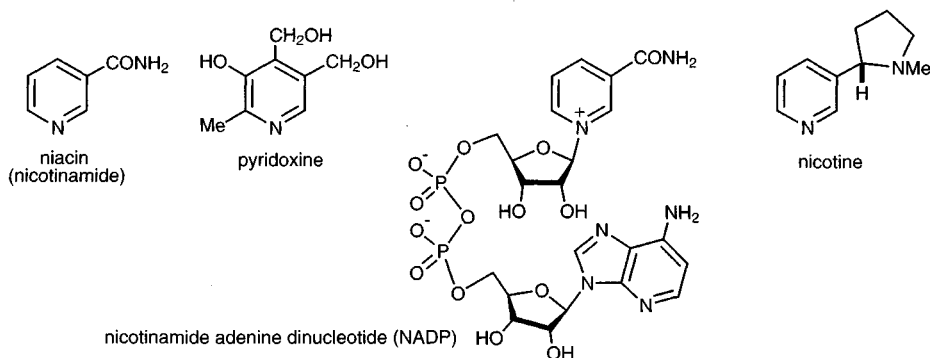


5 Pyridines: reactions and synthesis

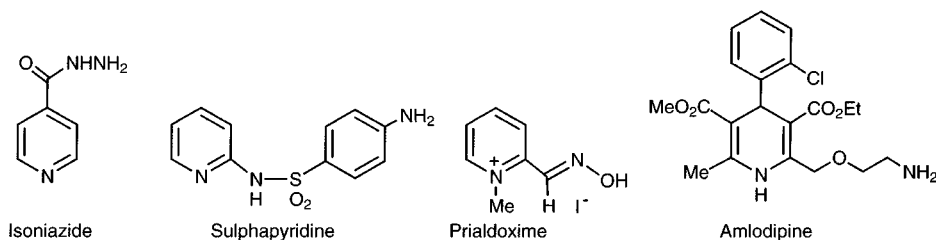


Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating odours that are unpleasant to some people. They are much used as solvents and bases, especially pyridine itself, in reactions such as *N*- and *O*-tosylation and -acylation. Pyridine and the monomethylpyridines (picolines) are completely miscible with water.

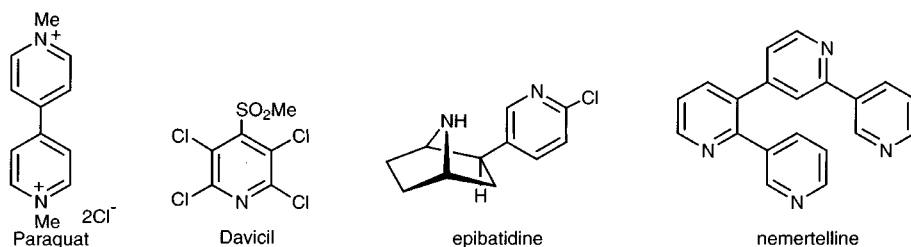
Pyridine was first isolated, like pyrrole, from bone pyrolysates: the name is constructed from the Greek for fire, '*pyr*', and the suffix '*idine*', which was at the time being used for all aromatic bases – phenetidine, toluidine, etc. Pyridine and its simple alkyl derivatives were for a long time produced by isolation from coal tar, in which they occur in quantity. In recent years this source has been displaced by synthetic processes: pyridine itself, for example, can be produced on a commercial scale in 60–70% yields by the gas-phase high-temperature interaction of crotonaldehyde, formaldehyde, steam, air and ammonia over a silica-alumina catalyst. Processes for the manufacture of alkylpyridines involve reaction of acetylenes and nitriles over a cobalt catalyst.



The pyridine ring plays a key role in several biological processes, most notably in the oxidation/reduction coenzyme nicotinamide adenine dinucleotide (NADP); the vitamin niacin (or the corresponding acid) is required for its biosynthesis. Pyridoxine (vitamin B₆) plays a key role as the coenzyme in transaminases. Nicotine, a highly toxic alkaloid, is the major active component in tobacco, and the most addictive drug known.¹



Many synthetic pyridine derivatives are important as therapeutic agents, for example Isoniazide is a major antituberculosis agent, Sulphapyridine is one of the sulfonamide antibacterials, Prialdoxime is an antidote for poisoning by organophosphates, and Amlodipine is one of several antihypertensive 1,4-dihydropyridines. Some herbicides (Paraquat)² and fungicides (Davicil) are also pyridine derivatives. Nemertelline (for a synthesis see section 5.15.2.4) is a neurotoxin from a marine worm; epibatidine, isolated from a South American frog, shows promise as an analgesic agent (for a synthesis see section 13.18.3.6).



5.1 Reactions with electrophilic reagents

5.1.1 Addition to 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.

5.1.1.1 Protonation of nitrogen

Pyridines form crystalline, frequently hygroscopic, salts with most protic acids. Pyridine itself, with $\text{p}K_{\text{a}}$ 5.2 in water, is a much weaker base than saturated aliphatic amines which have $\text{p}K_{\text{a}}$ values mostly between 9 and 11. Since the gas-phase proton affinity of pyridine is actually very similar to those of aliphatic amines, the observed solution values reflect relatively strong solvation of aliphatic ammonium cations;³ this difference may in turn be related to the mesomerically delocalised charge in pyridinium ions and the consequent reduced requirement for external stabilisation *via* solvation.

Electron-releasing substituents generally increase the basic strength; 2-methyl ($\text{p}K_{\text{a}}$ 5.97), 3-methyl (5.68) and 4-methylpyridine (6.02) illustrate this. The basicities of pyridines carrying groups which can interact mesomerically as well as inductively vary in more complex ways, for example 2-methoxypyridine (3.3) is a weaker, but 4-methoxypyridine (6.6) a stronger base than pyridine; the effect of inductive

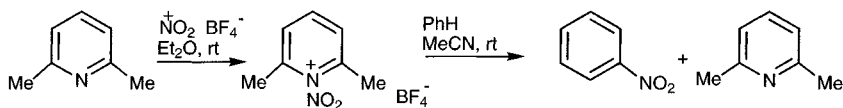
withdrawal of electrons by the electronegative oxygen is felt more strongly when it is closer to the nitrogen, i.e. at C-2.

Large 2- and 6-substituents impede solvation of the protonated form: 2,6-di-*t*-butylpyridine is less basic than pyridine by one pK_a unit and 2,6-di(tri-*i*-propylsilyl)pyridine will not dissolve even in 6N hydrochloric acid.⁴

5.1.1.2 Nitration at nitrogen (see also section 5.1.2.2)

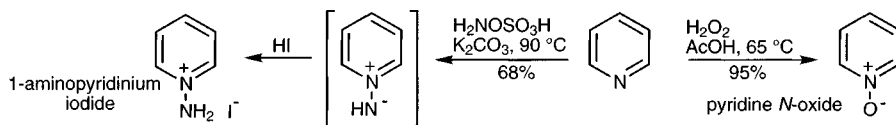
This occurs readily by reaction of pyridines with nitronium salts, such as nitronium tetrafluoroborate.⁵ Protic nitrating agents such as nitric acid of course lead exclusively to *N*-protonation.

1-Nitro-2,6-dimethylpyridinium tetrafluoroborate is one of several *N*-nitropyridinium salts which can be used as non-acidic nitrating agents with good substrate and positional selectivity. The 2,6-disubstitution serves to sterically inhibit resonance overlap between nitro group and ring and consequently increase reactivity as a nitronium ion donor, however the balance between this advantageous effect and hindering approach of the aromatic substrate is illustrated by the lack of transfer nitration reactivity in 2,6-dihalo-analogues.⁶



5.1.1.3 Amination of nitrogen

The introduction of nitrogen at a different oxidation level can be achieved with hydroxylamine *O*-sulfate.⁷

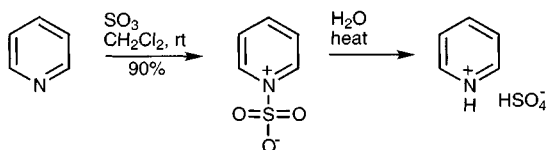


5.1.1.4 Oxidation of nitrogen

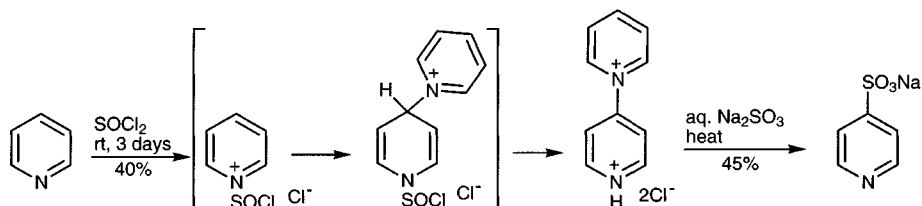
In common with other tertiary amines, pyridines react smoothly with percarboxylic acids to give *N*-oxides, which have their own rich chemistry (section 5.14).

5.1.1.5 Sulfonation at nitrogen

Pyridine reacts⁸ with sulfur trioxide to give the commercially available, crystalline, zwitterionic pyridinium-1-sulfonate, usually known as the pyridine sulfur trioxide complex. This compound is hydrolysed in hot water to sulfuric acid and pyridine (for its reaction with hydroxide see section 5.13.4), but more usefully it can serve as a mild sulfonating agent (for examples see sections 13.1.3 and 15.1.3) and as an activating agent for dimethylsulfoxide in Moffat oxidations.

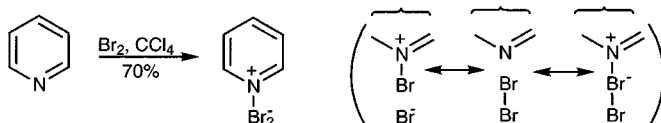


When pyridine is treated with thionyl chloride a synthetically useful dichloride salt is formed, which can, for example, be transformed into pyridine-4-sulfonic acid. The reaction is believed to involve initial attack by sulfur at nitrogen, followed by nucleophilic addition of a second pyridine at C-4 (cf. section 5.13.3).⁹

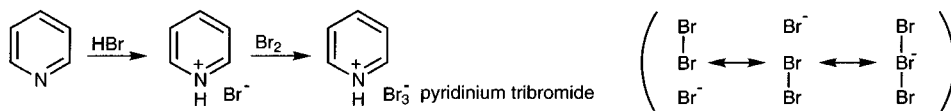


5.1.1.6 Halogenation at nitrogen

Pyridines react easily with halogens and interhalogens¹⁰ to give crystalline compounds, largely undissociated when dissolved in solvents such as carbon tetrachloride. Structurally they are best formulated as resonance hybrids related to trihalide anions. 1-Fluoropyridinium triflate is also crystalline and serves as an electrophilic fluorinating agent.¹¹

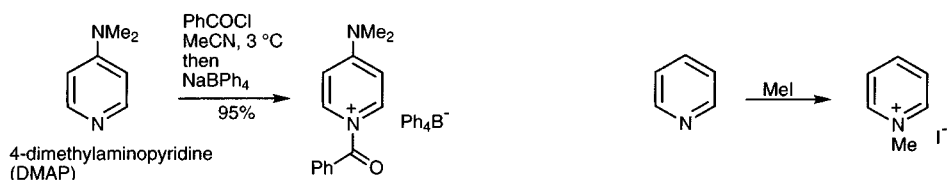


These salts must be distinguished from pyridinium tribromide, obtained by treating pyridine hydrobromide with bromine, which does not contain an *N*-halogen bond, but does include a trihalide anion. The stable, crystalline, commercially available salt can be used as a source of molecular bromine especially where small accurately known quantities are required.



5.1.1.7 Acylation at nitrogen

Carboxylic, and arylsulfonic acid halides react rapidly with pyridines generating 1-acyl- and 1-arylsulfonylpyridinium salts in solution, and in suitable cases some of these can even be isolated as crystalline solids.¹² The solutions, generally in excess pyridine, are commonly used for the preparation of esters and sulfonates from alcohols and of amides and sulfonamides from amines. 4-Dimethylaminopyridine¹³ (DMAP) is widely used (in catalytic quantities) to activate anhydrides in a similar manner. The salt derived from DMAP and *t*-butyl chloroformate is stable even in aqueous solution at room temperature.¹⁴

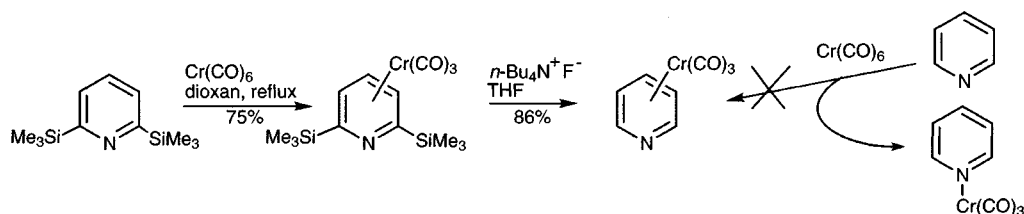


5.1.1.8 Alkylation at nitrogen

Alkyl halides and sulfates react readily with pyridines giving quaternary pyridinium salts. As with aliphatic tertiary amines, increasing substitution around the nitrogen, or around the halogen-bearing carbon, causes an increase in the alternative, competing, elimination process which gives alkene and *N*-proto-pyridinium salt, thus 2,4,6-trimethylpyridine (collidine) is useful as a base in dehydrohalogenation reactions.

5.1.1.9 Reaction with metal centres

The normal behaviour of pyridines in the presence of metal cations is complexation involving donation of the nitrogen lone pair to the metal centre. This means that for simple pyridines, formation of π -complexes like benzene-chromium carbonyl complexes, does not take place. However, if the nitrogen lone pair is hindered, then η^6 -complexes can be formed.¹⁵



5.1.2 Substitution at carbon

In most cases, electrophilic substitution of pyridines occurs very much less readily than for the correspondingly substituted benzene. The main reason is that the electrophilic reagent, or a proton in the reaction medium, adds preferentially to the pyridine nitrogen, generating a pyridinium cation, which is naturally very resistant to a further attack by an electrophile. When it does occur then, electrophilic substitution at carbon must involve either highly unfavoured attack on a pyridinium cation or relatively easier attack but on a very low equilibrium concentration of uncharged free pyridine base.

Some of the typical electrophilic substitution reactions do not occur at all – Friedel-Crafts alkylation and acylation are examples – but it is worth recalling that these also fail with nitrobenzene. Milder reagents, such as Mannich reactants, diazonium ions and nitrous acid, which in any case require activated benzenes for success, naturally fail with pyridines.

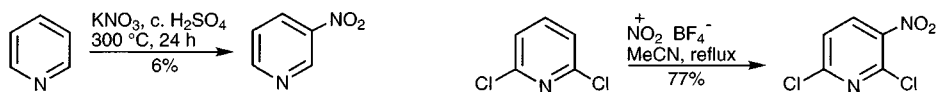
5.1.2.1 Proton exchange

H–D exchange *via* an electrophilic addition process, such as operates for benzene, does not take place with pyridine. A special mechanism allows selective exchange at the two α -positions in $\text{DCl-D}_2\text{O}$ or even in water at 200°C , the key species being an ylide formed by 2/6-deprotonation of the 1*H*-pyridinium cation (see also section 5.1.2).¹⁶

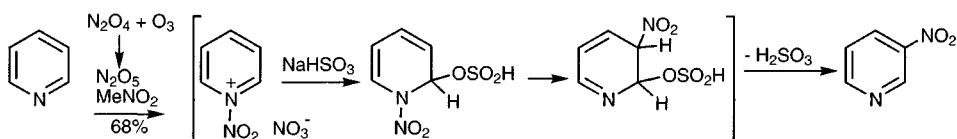
5.1.2.2 Nitration

Pyridine itself can be converted into 3-nitropyridine only inefficiently by direct nitration even with vigorous conditions,¹⁷ as shown below, however a couple of ring methyl groups facilitate electrophilic substitution sufficiently to allow nitration to

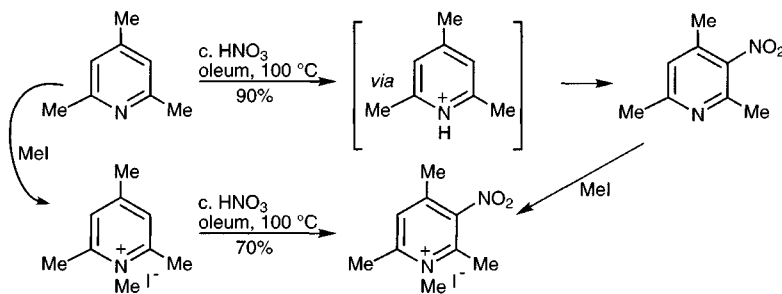
compete with side-chain oxidation.¹⁸ Steric or/and inductive inhibition of *N*-nitration allows *C*-substitution using nitronium tetrafluoroborate, an example is nitration of 2,6-dichloropyridine.⁶



3-Nitropyridine itself, and some of its substituted derivatives, can now be prepared efficiently by reaction with dinitrogen pentoxide as shown below. The initially formed *N*-nitropyridinium nitrate suffers addition of a nucleophile – sulfur dioxide when this is used as solvent or co-solvent, or sulfite, added subsequently – forming a 1,2-dihydropyridine. Transfer of the nitro group to a 3- or 5-position, via a [1,5]-sigmatropic migration, is then followed by elimination of the nucleophile regenerating the aromatic system.¹⁹

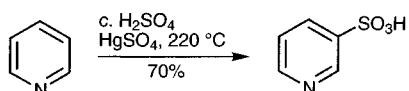


Both collidine and its quaternary salt are nitrated at similar rates under the same conditions, showing that the former reacts *via* its *N*-protonic salt.²⁰



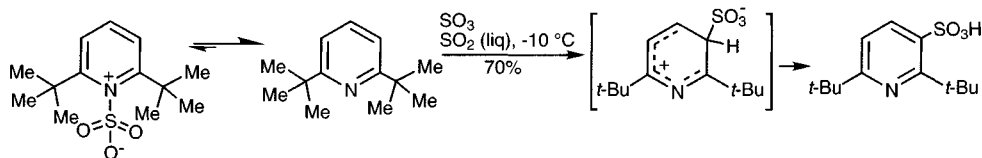
5.1.2.3 Sulfonation

Pyridine is very resistant to sulfonation using concentrated sulfuric acid or oleum, only very low yields of the 3-sulfonic acid being produced after prolonged reaction periods at 320 °C. However, addition of mercuric sulfate in catalytic quantities allows smooth sulfonation at a somewhat lower temperature. The role of the catalyst is not established; one possibility is that *C*-mercuration is the first step (cf. section 5.1.2.5).²¹



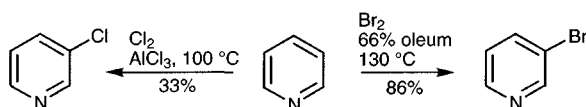
The *C*-sulfonation of 2,6-di-*t*-butylpyridine²² is a good guide to the intrinsic reactivity of a pyridine ring, for in this situation the bulky alkyl groups effectively prevent addition of sulfur trioxide to the ring nitrogen allowing progress to a 'normal' electrophilic *C*-substitution intermediate, at about the same rate as for sulfonation of nitrobenzene. A maximum conversion of 50% is all that is achieved

because for every C-substitution a proton is produced which 'consumes' a molecule of starting material by *N*-protonation.



5.1.2.4 Halogenation

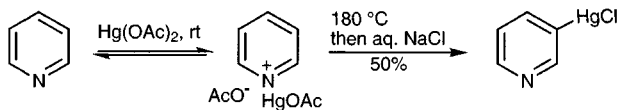
3-Bromopyridine is produced in good yield by the action of bromine in oleum.²³ The process is thought to involve pyridinium-1-sulfonate as the reactive species, since no bromination occurs in 95% sulfuric acid. 3-Chloropyridine can be produced by chlorination at 200 °C or at 100 °C in the presence of aluminium chloride.²⁴



2-Bromo- and 2-chloropyridines can be made extremely efficiently by reaction of pyridine with the halogen, at 0–5 °C in the presence of palladium(II) chloride.²⁵

5.1.2.5 Acetoxymercuration

The salt formed by the interaction of pyridine with mercuric acetate at room temperature can be rearranged to 3-acetoxymercuripyridine by heating to only 180 °C.²⁶ This process, where again there is *C*-attack by a relatively weakly electrophilic reagent, like that described for mercuric sulfate-catalysed sulfonation, may involve attack on an equilibrium concentration of free pyridine.

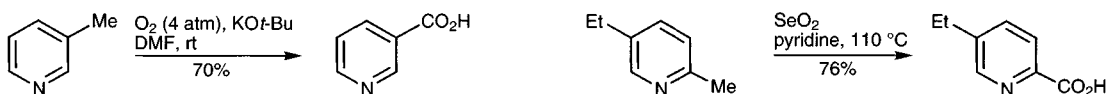


5.1.2.6 Substitution in pyridines carrying activating nitrogen and oxygen substituents

See sections 5.10.2.1 and 5.10.3.1

5.2 Reactions with oxidising agents

The pyridine ring is generally resistant to oxidising agents, vigorous conditions being required, thus pyridine itself is oxidised by neutral aqueous potassium permanganate at about the same rate as benzene (sealed tube, 100 °C), to give carbon dioxide. In acidic solution pyridine is more resistant, but in alkaline media more rapidly oxidised, than benzene.



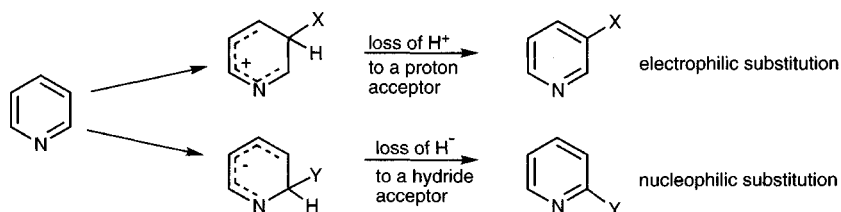
In most situations, carbon substituents can be oxidised with survival of the ring, thus alkylpyridines can be converted into pyridine carboxylic acids with a variety of

reagents.²⁷ Some selectivity can be achieved: only α - and γ -groups are attacked by selenium dioxide; the oxidation can be halted at the aldehyde oxidation level.²⁸

5.3 Reactions with nucleophilic reagents

Just as electrophilic substitution is the characteristic reaction of benzene and electron-rich heteroaromatic compounds (pyrrole, furan etc.), so substitution reactions with nucleophiles can be looked on as characteristic of pyridines.

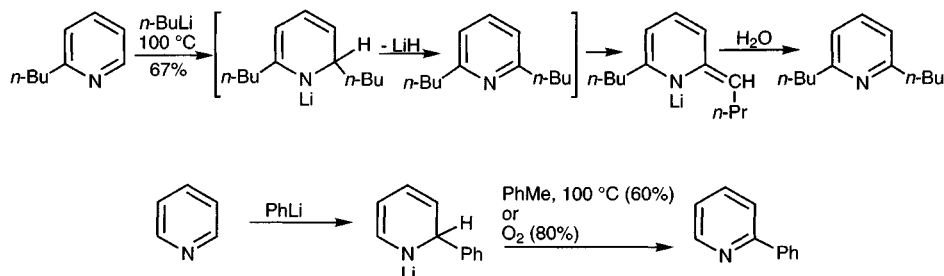
It is important to realise that nucleophilic substitution of hydrogen differs in an important way from electrophilic substitution: whereas the last step in electrophilic substitution is loss of proton, an easy process, the last step in nucleophilic substitution of hydrogen has to be a hydride transfer, which is less straightforward and generally needs the presence of an oxidising agent as hydride acceptor. Nucleophilic substitution of an atom or group which is a good anionic leaving group however is an easy and straightforward process.



5.3.1 Nucleophilic substitution with 'hydride' transfer²⁹

5.3.1.1 Alkylation and arylation

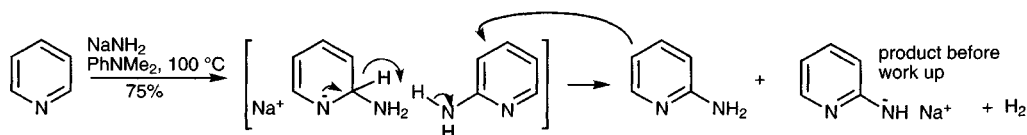
Reaction with alkyl- or aryllithiums proceeds in two discrete steps: addition to give a dihydropyridine *N*-lithio-salt which can then be converted into the substituted aromatic pyridine by oxidation (e.g. by air), disproportionation, or elimination of lithium hydride.³⁰ The *N*-lithio-salts can be observed spectroscopically and in some cases isolated as solids.³¹ Attack is nearly always at an α -position; reaction with 3-substituted-pyridines usually takes place at both available α -positions, but predominantly at C-2.³² This regioselectivity may be associated with relief of strain when the 2-position rehybridises to sp^3 during addition.



From the preparative viewpoint nucleophilic alkylations can be greatly facilitated by the device of prior quaternisation of the pyridine in such a way that the *N*-substituent can be subsequently removed – these processes are dealt with in section 5.13.2.

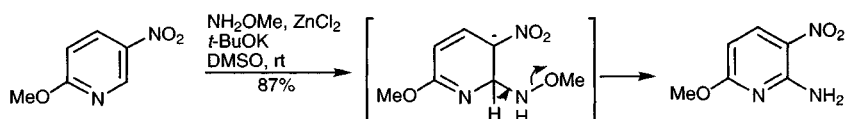
5.3.1.2 Amination

Amination of pyridines and related heterocycles, generally at a position α to the nitrogen, is called the Chichibabin reaction,³³ the pyridine reacting with sodamide with the evolution of hydrogen. The 'hydride' transfer and production of hydrogen probably involve interaction of aminopyridine product, acting as an acid, with the anionic intermediate. The preference for α -substitution may be associated with an intramolecular delivery of the nucleophile, perhaps guided by complexation of ring nitrogen with metal cation.



More vigorous conditions are required for the amination of 2- or 4-alkylpyridines since proton abstraction from the side-chain by the amide occurs first and ring attack must therefore involve a dianionic intermediate.³⁴ Amination of 3-alkylpyridines is regioselective for the 2-position.³⁵

Vicarious nucleophilic substitution (section 2.3.3) permits the introduction of amino groups *ortho* to nitro groups by reaction with methoxyamine as illustrated below.³⁶

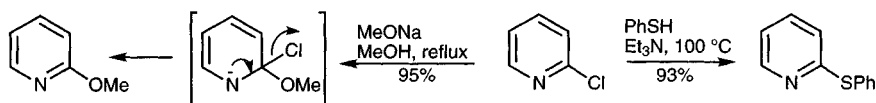


5.3.1.3 Hydroxylation

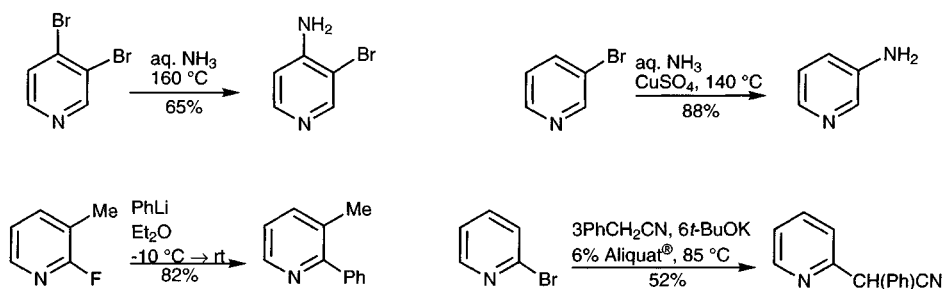
Hydroxide ion, being a much weaker nucleophile than amide, attacks pyridine only at very high temperatures to produce a low yield of 2-pyridone,³⁷ which can be usefully contrasted with the much more efficient reaction of hydroxide with quinoline and isoquinoline (section 6.3.1.3) and with pyridinium salts (section 5.13.4).

5.3.2 Nucleophilic substitution with displacement of good leaving groups

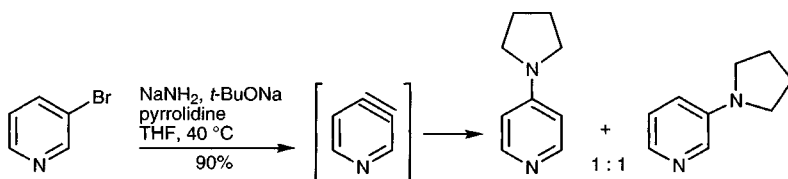
Halogen, and also, though with fewer examples, nitro,³⁸ alkoxy sulfonyl,³⁹ and methoxy⁴⁰ substituents at α - or γ -positions, but not at β -positions, are relatively easily displaced by a wide range of nucleophiles *via* an addition-elimination mechanism facilitated by (a) electron withdrawal by the substituent and (b) the good leaving ability of the substituent. γ -Halopyridines are more reactive than the α -isomers; β -halopyridines are very much less reactive, being much closer to, but still somewhat more reactive than halobenzenes. Fluorides are more reactive than the other halides.⁴¹



Replacement of halide by reaction with ammonia can be achieved at considerably lower temperatures under 6–8 kbar pressure.⁴² The inclusion of Aliquat is an alternative means for improving the efficiency of such nucleophilic displacements.⁴³



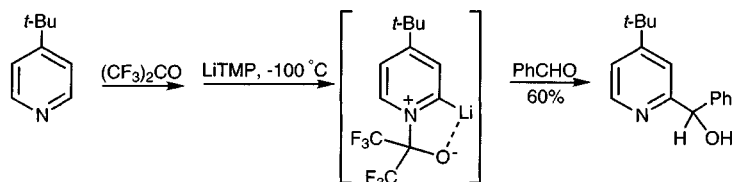
In some, apparently straightforward, displacements, more detailed mechanistic study reveals the operation of alternative mechanisms. For example the reaction of either 3- or 4-bromopyridine with secondary amines in the presence of sodamide/sodium *t*-butoxide, produces the same mixture of 3- and 4-dialkylaminopyridines; this proceeds *via* an elimination process ($S_N(EA)$ – Substitution Nucleophilic Elimination Addition) and the intermediacy of 3,4-didehydropyridine (3,4-pyridyne).⁴⁴ That no 2-aminated pyridine is produced shows a greater difficulty in generating 2,3-pyridyne, it can however be formed by reaction of 3-bromo-2-chloropyridines with butyllithium⁴⁵ or via the reaction of 3-trimethylsilyl-2-trifluoromethanesulfonyloxypyridine with fluoride.⁴⁶



5.4 Reactions with bases

5.4.1 Deprotonation of C-hydrogen

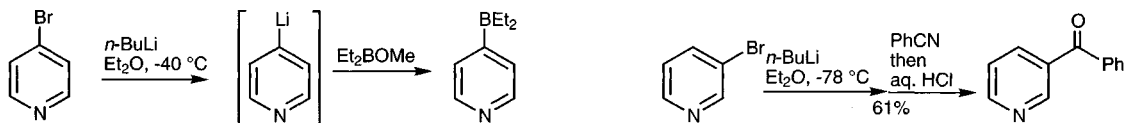
When pyridine is heated to 165 °C in MeONa–MeOD, H–D exchange occurs at all positions *via* small concentrations of deprotonated species, at the relative rates $\alpha : \beta : \gamma$, 1 : 9.3 : 12.⁴⁷ However, using the combination *n*-butyllithium/potassium *t*-butoxide, efficient formation of 2-pyridylpotassium or 4-pyridylpotassium has been achieved.⁴⁸ Some pyridines have been selectively lithiated at C-2 *via* complexes with hexafluoroacetone;⁴⁹ complexation removes the lone pair (cf. section 5.5.1) and additionally provides inductive and chelation effects to assist the regioselective metallation. In practice, simple lithiopyridines are generally prepared by metal–halogen exchange, however the presence of chlorine or fluorine, or other substituents which direct *ortho* metallation, allows direct lithiation (section 5.5.1).



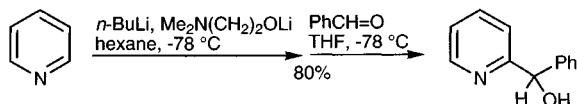
5.5 Reactions of C-metallated pyridines

5.5.1 Lithium and magnesium derivatives

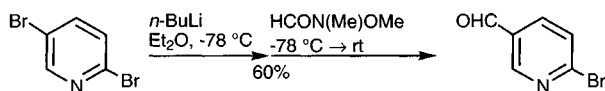
Lithium derivatives are easily prepared and behave as typical organometallic nucleophiles,^{50–52} thus for example, 3-bromopyridine undergoes efficient exchange with *n*-butyllithium in ether at -78°C . In the more basic tetrahydrofuran as solvent, and at this temperature, the alkyllithium becomes more nucleophilic and only addition occurs, although the exchange can be carried out in tetrahydrofuran at lower temperatures.⁵³ Lithiopyridines can also be prepared from halopyridines, including chloropyridines, via exchange with lithium naphthalenide.⁵⁴ 2-Bromo-6-methylpyridine can be converted into its lithio derivative without deprotonation of the methyl.⁵⁵



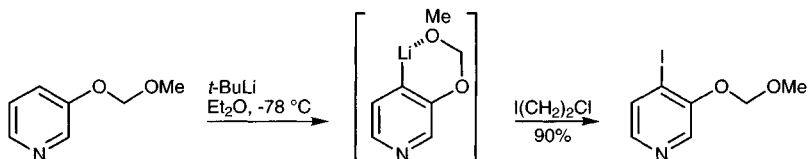
Direct regioselective α lithiation of pyridine, 2-methoxypyridine, or 2-methylthiopyridine, can be carried out using a complex base consisting of a mixture of butyllithium and the lithium salt of 2-dimethylaminoethanol. The process may be more complex than simple deprotonation, possibly involving a radical anion intermediate.⁵⁶



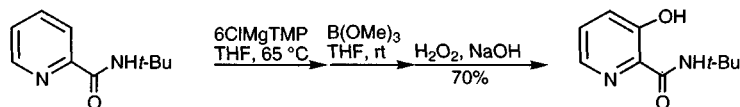
Metal/halogen exchange with 2,5-dibromopyridine leads exclusively and efficiently to 2-bromo-5-lithiopyridine in a thermodynamically controlled process;⁵⁷ it has been suggested that the 2-pyridyl anion is destabilised by electrostatic repulsion between nitrogen lone pair and the adjacent anion;⁴⁶ this same factor is probably important in the greater difficulty found in generating 2,3-pyridyne (see section 5.3.2). The example below illustrates the use of the 'Weinreb amide' of formic acid as a formyl-transfer reagent.⁵⁸



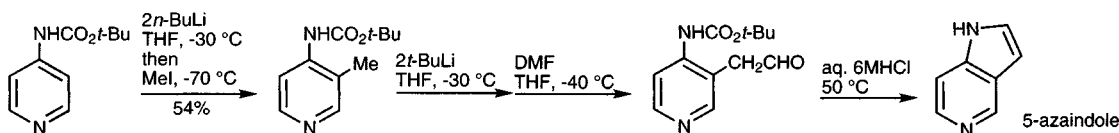
Monolithiation of 2,6-dibromopyridine is best achieved by 'inverse addition' – dibromide to *n*-butyllithium, or by using dichloromethane as solvent – probably a unique application of this solvent to lithiation.⁵⁹ A normal lithiation of 2,5-dibromopyridine, but at -90°C , produces clean 2-substituted product with a hindered silicon electrophile.⁶⁰



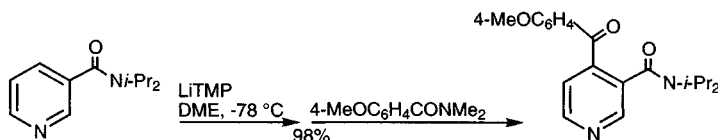
Halo-, particularly chloro-, or better, fluoropyridines, but even bromopyridines⁶¹ undergo lithiation by deprotonation *ortho* to the halogen best using lithium di-*i*-propylamide, 3-halopyridines reacting mainly at C-4 and 2- and 4-halopyridines necessarily lithiating at a β -position.⁶² In the lithiation of methoxypyridines using mesityllithium, the 3-isomer metallated at C-2.⁶³ 3-Methoxymethoxypyridine,⁶⁴ 3-di-*i*-propylaminocarbonyl-⁶⁵ and 3-*t*-butylcarbonylamino-⁶⁶ -pyridines all lithiate at C-4. Lithiation assisted by the dimethyloxazoline group requires lithium 2,2,6,6-tetramethylpiperidide, otherwise C-4-addition of alkyl lithium or Grignard occurs; subsequent aerial oxidation produces 4-alkylated derivatives efficiently.⁶⁷ A directed magnesiation required a much higher temperature, as shown below.⁶⁸



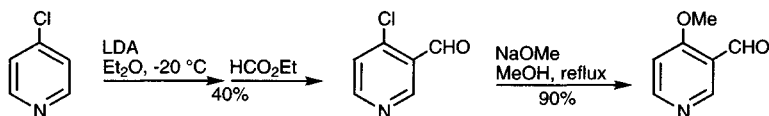
Lithiation of 2- and 4-*t*-butoxycarbonylaminopyridines can only take place at C-3; a neat sequence involving first, ring lithiation to allow introduction a methyl group and secondly side-chain lithiation (section 5.11) at the introduced methyl group provided a route to azaindoles (section 17.17.7), as illustrated below for the synthesis of 5-azaindole (pyrrolo[3,2-*c*]pyridine).⁶⁹



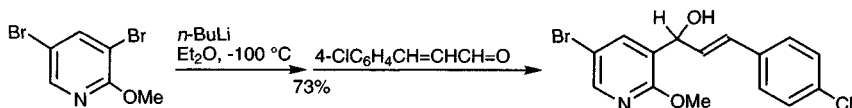
Lithiated pyridines react with the normal range of electrophilic species, for example they are acylated by tertiary amides.⁷⁰

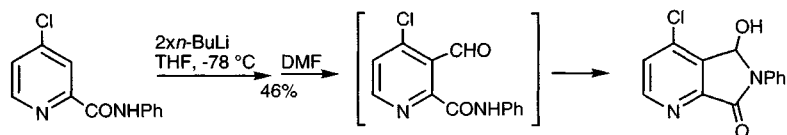


The use of halogen to direct lithiation can be combined with the ability to subsequently displace the halogen with a nucleophile.⁷¹

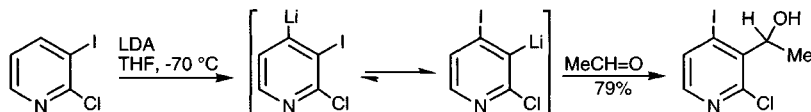


The combination of metal-halogen exchange with the presence of a directing substituent can permit regioselective exchange;⁷² two 1,3-related directing groups causes lithiation between the two groups.⁷³



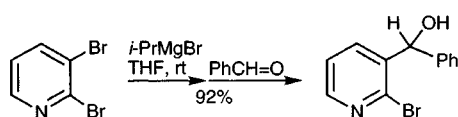
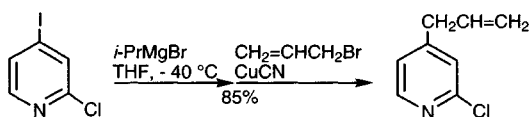
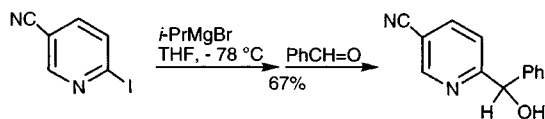


Bromine and iodine also direct lithiations, but isomerisation ('halogen dance', see section 14.5.1) can be a problem. The sequence below shows how advantage was taken of the isomerisation to the more stable lithio derivative i.e. that in which the formally negatively charged ring carbon is located between two halogen-bearing carbon atoms.⁷⁴



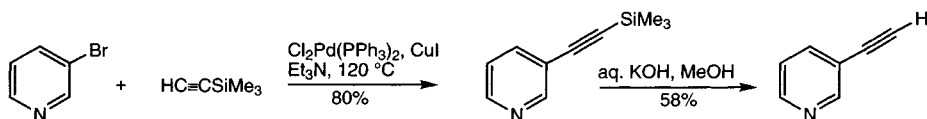
The selective 2-lithiation of pyridine *N*-oxides can be achieved in favourable circumstances: one instructive example is the regioselective 6-lithiation of 2-pivaloylaminopyridine *N*-oxide, i.e. adjacent to the *N*-oxide group, and not adjacent to the *ortho*-directing 2-substituent. The regioselective C-2-lithiation of 3,4-dimethoxypyridine *N*-oxide also shows the influence of the *N*-oxide functionality.⁷⁵

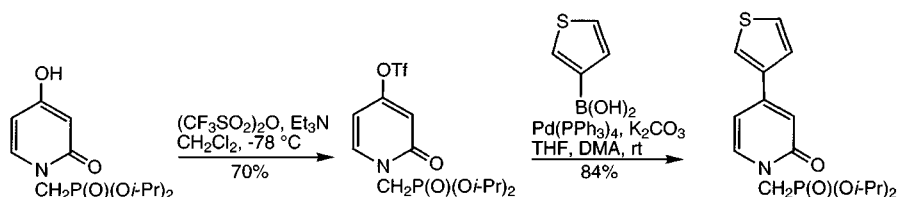
Pyridyl Grignard reagents are readily prepared by exchange of bromine or iodine using *i*-propyl Grignard reagents.⁷⁶ It is notable that in 2,5-dibromopyridine, the exchange follows the same pattern as in lithium exchange that is, selective reaction at C-5; other dibromopyridines also give clean mono-exchange. Formation of pyridyl Grignard species in this way will even tolerate functional groups such as esters and nitriles, provided the temperature is kept low. While they are probably not quite as versatile as lithium compounds, the pyridinyl Grignards have obvious advantages in some circumstances.



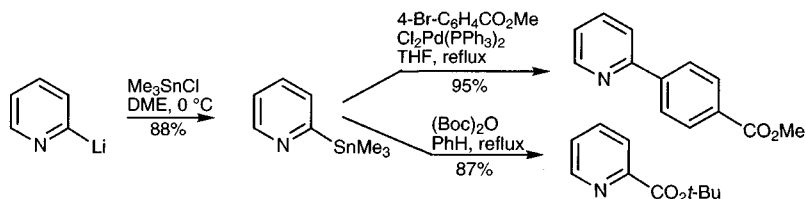
5.5.2 Palladium-catalysed reactions

Halopyridines or pyridinyl triflates^{77,78} take part in palladium-catalysed reactions – Heck,⁷⁹ carbonylation,⁸⁰ and coupling reactions, for example with alkynes,⁸¹ or in Suzuki reactions with arylboronic acids,^{78,82} and cyclopropylboronic acids.⁸³



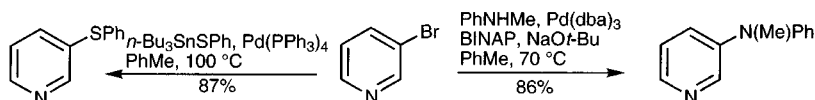


Couplings requiring pyridyl organometallic species are best achieved with boron, zinc, or tin compounds; the last are available either by reaction of pyridyl halides with sodium trialkylstannate or, in the opposite sense, by the reaction of a pyridyllithium with chlorotrimethylstannane.⁸⁴ Pyridyltin compounds have been coupled for example with haloarenes⁸⁵ and with halopyridine *N*-oxides.⁸⁶



Pyridinyltin reagents also provide a means for the effective acylation of a pyridine, unachievable by conventional Friedel-Crafts processes, as discussed earlier, and illustrated above by 2-*t*-butoxycarbonylation.⁸⁷

Palladium(0) catalysis also provides an excellent means for the overall displacement of halide with nitrogen⁸⁸ or sulfur,⁸⁹ taking place equally well at all three pyridine ring positions, *i.e.* not relying on the increased susceptibility to nucleophilic displacement at α - and γ -positions (section 5.3.2).



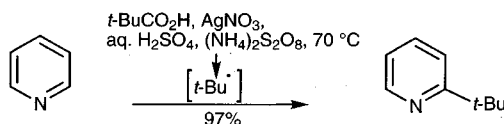
5.6 Reactions with radical reagents; reactions of pyridyl radicals

5.6.1 Halogenation

At temperatures where bromine (500 °C) and chlorine (270 °C) are appreciably dissociated into atoms, 2- and 2,6-dihalopyridines are obtained *via* radical substitution.⁹⁰

5.6.2 Carbon radicals

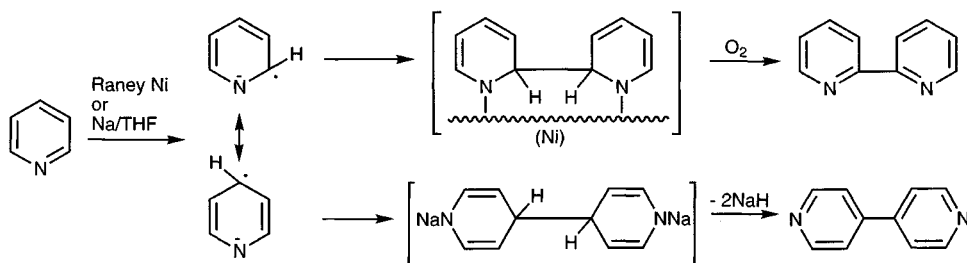
This same preference for α -attack is demonstrated by phenyl radical attack, but the exact proportions of products depend on the method of generation of the radicals.⁹¹ Greater selectivity for phenylation at the 2- and 4-positions is found in pyridinium salts.⁹²



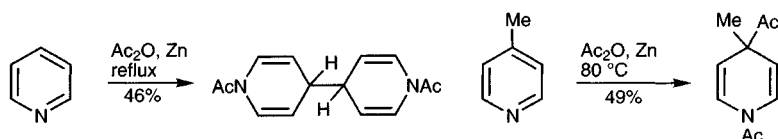
Of more preparative value are the reactions of nucleophilic radicals, such as $\text{HOCH}_2\cdot$ and $\text{R}_2\text{NCO}\cdot$ which can be easily generated under mild conditions. These substitutions are carried out on the pyridine protonic salt, which provides both increased reactivity and selectivity for an α -position; the process is known as the Minisci reaction (cf. section 2.4.1).⁹³ It is accelerated by electron-withdrawing substituents on the ring.

5.6.3 Dimerisation

Both sodium and nickel bring about 'oxidative' dimerisations,⁹⁴ despite the apparently reducing conditions, the former giving 4,4'-bipyridine and the latter 2,2'-bipyridine.⁹⁵ Each reaction is considered to involve the same anion-radical resulting from transfer of an electron from metal to heterocycle, and the species has been observed by ESR spectroscopy when generated by single electron transfer (SET) from lithium diisopropylamide.⁹⁶ In the case of nickel, the 2,2'-mode of dimerisation may be favoured by chelation to the metal surface. Bipyridyls are important for the preparation of Paraquat-type weedkillers.

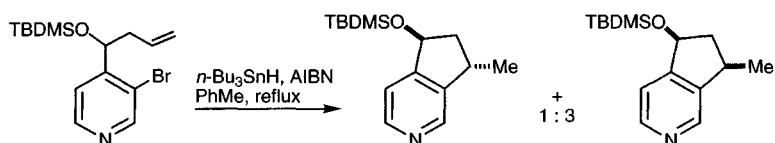


Intermediate, reduced dimers can be trapped under milder conditions,⁹⁷ and reduced monomers when the pyridine carries a 4-substituent.⁹⁸



5.6.4 Pyridyl radicals

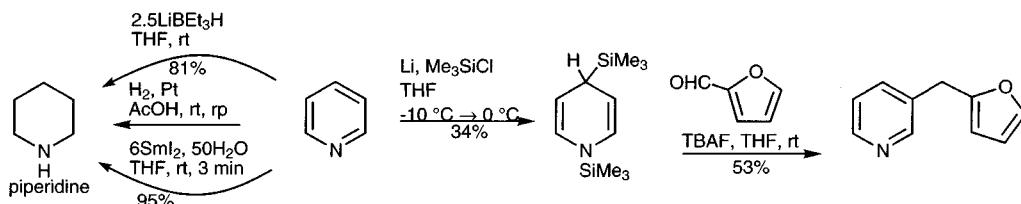
Irradiation of iodopyridines generates pyridinyl radicals which will effect radical substitution of aromatic compounds.⁹⁹ Pyridinyl radicals, like aryl radicals, can also be generated from halopyridines using tin hydrides and participate in typical radical reactions, as in the cyclisation shown below.¹⁰⁰



5.7 Reactions with reducing agents

Pyridines are much more easily reduced than benzenes, for example catalytic reduction proceeds easily at atmospheric temperature and pressure, usually in weakly acidic solution but also in dilute alkali over nickel.¹⁰¹

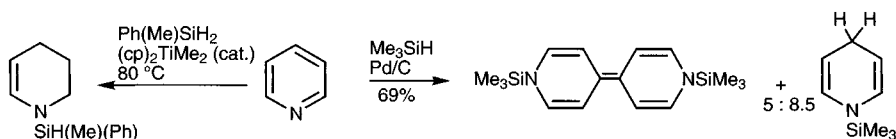
Of the hydride reagents, sodium borohydride is without effect on pyridines, though it does reduce pyridinium salts (section 5.13.1), lithium aluminium hydride effects the addition of one hydride equivalent to pyridine,¹⁰² but lithium triethylborohydride reduces to piperidine efficiently.¹⁰³



The combination lithium/chlorotrimethylsilane produces a 1,4-dihydro doubly-silylated product, the enamine character in which can be utilised for the introduction of 3-alkyl groups *via* reaction with aldehydes.¹⁰⁴

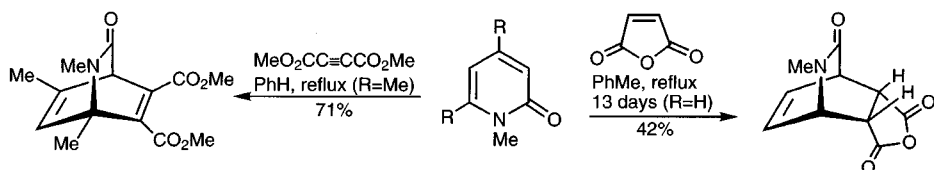
Sodium in liquid ammonia, in the presence of ethanol, affords the 1,4-dihydropyridine¹⁰⁵ and 4-pyridones are reduced to 2,3-dihydro-derivatives.¹⁰⁶ Metal/acid combinations, which in other contexts do bring about reduction of iminium groups, are without effect on pyridines. Samarium(II) iodide in the presence of water smoothly reduces pyridine to piperidine.¹⁰⁷

Trimethylsilane in the presence of palladium gives 1,4-dihydro-1-trimethylsilylpyridine, together with silylated dimer,¹⁰⁸ titanium-catalysed hydrosilylation produces a tetrahydro-derivative cleanly.¹⁰⁹

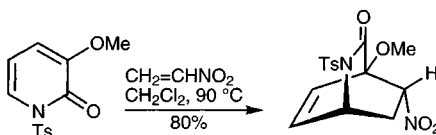


5.8 Electrocyclic reactions (ground state)

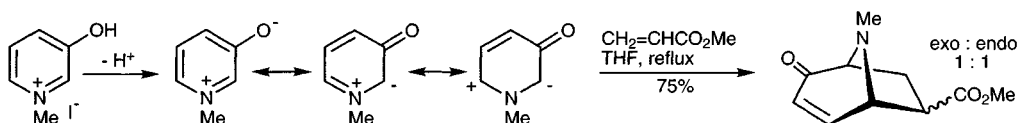
There are no reports of thermal electrocyclic reactions involving simple pyridines; 2-pyridones however participate as 4π components in Diels-Alder additions, especially under high pressure.¹¹⁰



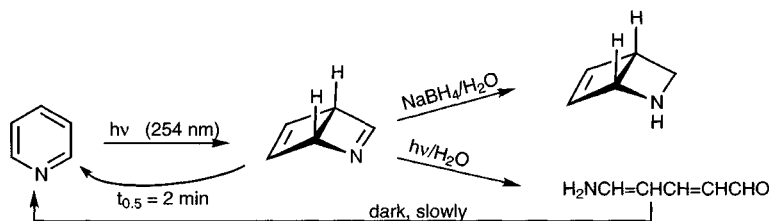
N-Tosyl-2-pyridones with a 3-alkoxy or 3-arylthio substituent, undergo cycloaddition with electron-deficient alkenes under milder conditions, as illustrated below.¹¹¹



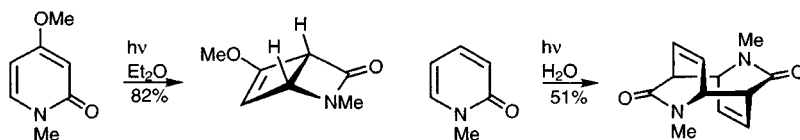
The quaternary salts of 3-hydroxypyridines are converted by mild base into zwitterionic, organic-solvent-soluble species for which no neutral canonical form can be drawn. These 3-oxidopyridiniums undergo a number of dipolar cycloaddition reactions, especially across the 2,6-positions.¹¹²



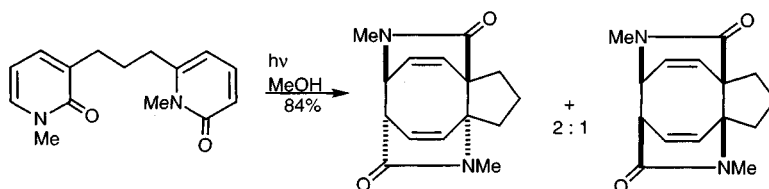
5.9 Photochemical reactions



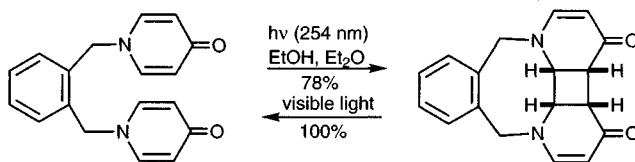
Ultraviolet irradiation of pyridines can produce highly strained species which may lead to isomerised pyridines or can be trapped. From pyridines¹¹³ and from 2-pyridones¹¹⁴ 2-azabicyclo[2.2.0]hexadienes and -hexenones are obtained; in the case of pyridines these are usually unstable and revert thermally to the aromatic heterocycle, but 2-alkylpyridines with an electron-withdrawing group on the alkyl substituent give stable products by base-catalysed proton shift.¹¹⁵ Pyridone-derived bicycles are relatively stable, 4-alkoxy- and -acyloxy-pyridones are converted in particularly good yields.



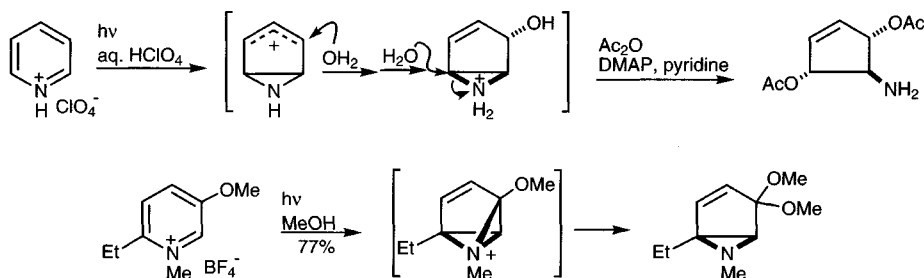
Irradiation of *N*-methyl-2-pyridone in aqueous solution produces a mixture of regio- and stereoisomeric dimers such as the one shown above;¹¹⁶ such 4π plus 4π photo-cycloadditions of 2-pyridones¹¹⁷ have also been conducted between two tethered pyridones as illustrated below¹¹⁸ and between a side-chain 1,3-diene and a 2-pyridone.¹¹⁹



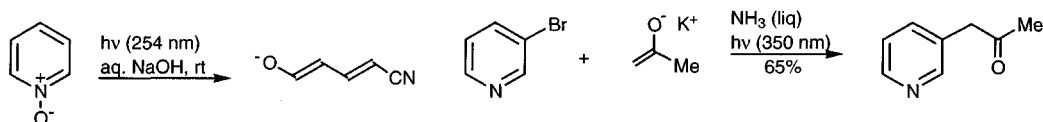
Photocatalysed 2π plus 2π cycloadditions between a pair of tethered 4-pyridones¹²⁰ as shown below, can also generate complex rings systems spectacularly easily. Photocatalysed 2π plus 2π cycloaddition between the 5,6-bond of 2-pyridones and an alkene tethered to nitrogen are also known.¹²¹



The photoreactions of pyridinium salts in water give 6-azabicyclo[3.1.0]hex-3-en-2-ols or the corresponding ethers, which can undergo regio- and stereoselective ring openings of the aziridine by attack of nucleophiles under acidic conditions. These products are useful starting materials for the synthesis of aminopentanol-derived natural products.¹²² At a higher oxidation level, comparable irradiation of 3-methypyridinium salts in neutral solution produces bicyclic aziridines as final products; the sequence shown below shows the first photo-intermediate as an azabenzvalene – an alternative interpretation of its structure.¹²³



On photolysis of pyridine *N*-oxides in alkaline solution, ring opening produces cyano-dienolates.¹²⁴



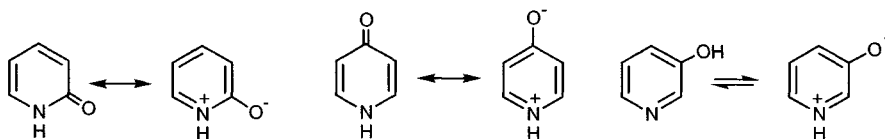
The displacement of bromine, in the relative order $2 > 3 > 4$, by an enolate or related anion under irradiation, known as an $S_{RN}1$ process (Substitution Radical Nucleophilic, unimolecular), involves photostimulated transfer of an electron from the enolate to the heterocycle, loss of bromide to generate a pyridyl radical which then combines with a second mol of enolate, generating the radical anion of product, transfer of an electron from which sustains the chain process.¹²⁵ The equivalent photo-catalysed displacement of bromide by hydroxide gives 3-hydroxypyridine.¹²⁶

5.10 Oxy- and aminopyridines

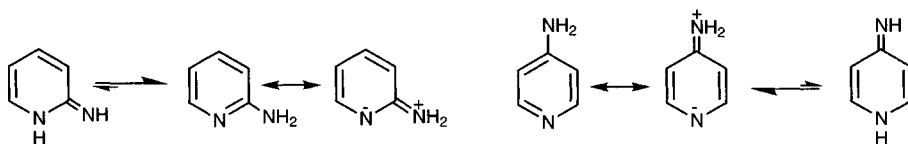
5.10.1 Structure

The three oxy-pyridines are subject to tautomerism involving hydrogen interchange between oxygen and nitrogen, but again with a significant difference between α - and γ - on the one hand and β -isomers on the other.

Under all normal conditions, α - and γ -isomers exist almost entirely in the carbonyl tautomeric form, and are accordingly known as pyridones; the hydroxy tautomers are detected in significant amounts only in very dilute solutions in non-polar solvents like petrol, or in the gas phase where, for the α -isomer, 2-hydroxypyridine is actually the dominant tautomer by 2.5:1.¹²⁷ The polarised pyridone form is favoured by solvation.¹²⁸ 3-Hydroxypyridine exists in equilibrium with a corresponding zwitterionic tautomer, the exact ratio depending on solvent.



All three aminopyridines exist in the amino form; the α - and γ -isomers are polarised in a sense opposite to that in the pyridones.

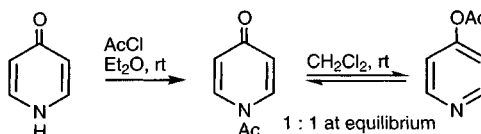


5.10.2 Reactions of pyridones

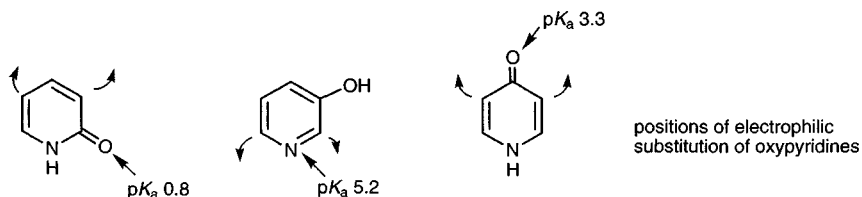
5.10.2.1 Electrophilic addition and substitution

3-Hydroxypyridine protonates on nitrogen, with a typical pyridine pK_a of 5.2; the pyridones however are much less basic, and both, like amides, protonate on oxygen.¹²⁹ 2,6-Dimethyl-4-pyridones produce isolable 4-hydroxypyridinium bromides on reaction with *t*-butyl bromide.¹³⁰

An apparent exception to this pattern is the reaction of 4-pyridone with acid chlorides producing *N*-acyl derivatives. 1-Acetyl-4-pyridone subsequently equilibrates in solution affording a mixture with 4-acetoxypyridine.¹³¹



Electrophilic substitution at carbon can be effected much more readily with the three oxy-pyridines than with pyridine itself, and it occurs *ortho* and *para* to the oxygen function, as indicated below. Acid catalysed exchange of 4-pyridone in deuterium oxide, for example, gives 3,5-dideuterio-4-pyridone, *via* C-protonation of the neutral pyridone.¹³²

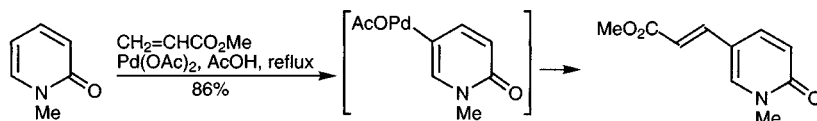


Substitutions in acidic solutions usually proceed *via* attack on the free pyridone,¹³³ but in very strong acid, where there is almost complete protonation, 4-pyridone

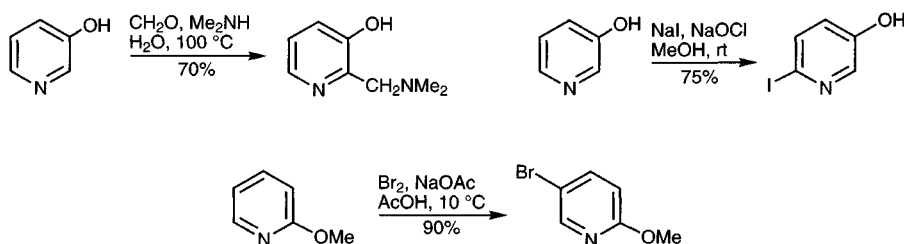
undergoes a slower nitration, *via* the *O*-protonated salt, but with the same regioselectivity.¹³⁴



N-Methyl-2-pyridone undergoes electrophilic palladation at C-5, allowing a subsequent direct coupling *via* a modified Heck reaction (cf. section 2.7.2.1).¹³⁵

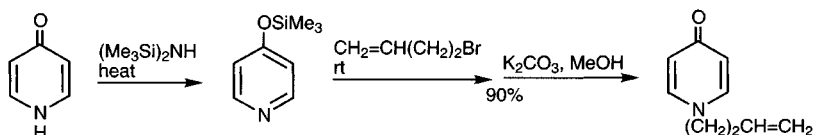


Some electrophilic substitutions of 3-hydroxypyridine take place at C-2 and some at C-6 thus nitration gives 3-hydroxy-2-nitropyridine¹³⁶ and Mannich condensation also takes place at C-2,¹³⁷ but iodination goes at C-6¹³⁸ (complimentarily, 2-methoxypyridine brominates at C-5).¹³⁹

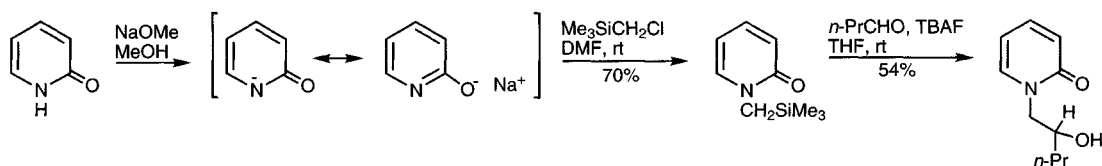


5.10.2.2 Deprotonation and reaction of salts

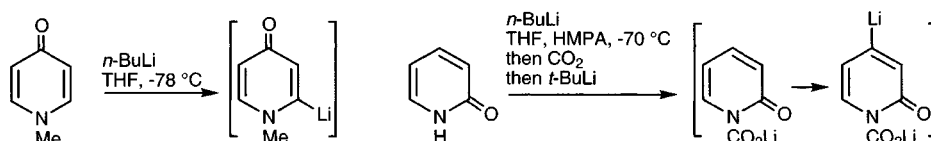
N-Unsubstituted pyridones are acidic, with pK_a values of about 11 for deprotonation giving mesomeric anions. These ambident anions can be alkylated on either oxygen or nitrogen, producing alkoxy-pyridines or *N*-alkylpyridones, respectively, the relative proportions depending on the reaction conditions;¹⁴⁰ *N*-alkylation is usually predominant for primary halides; *O*-alkylation for secondary halides.¹⁴¹ A clean method for the synthesis of *N*-alkylated 4-pyridones is to convert the pyridone first into the *O*-trimethylsilyl ether¹⁴² which can then be reacted selectively at nitrogen, subsequent removal of the silicon giving the *N*-alkylpyridone.¹⁰² 2-Pyridone is sufficiently acidic to take part in Mitsunobu reactions with alcohols though again, mixtures of *O*- and *N*-alkylation products result.¹⁴³



Alkylation of the sodium salt of 2-pyridone with chloromethyltrimethylsilane allows subsequent introduction of further groups on to the nitrogen substituent.¹⁴⁴

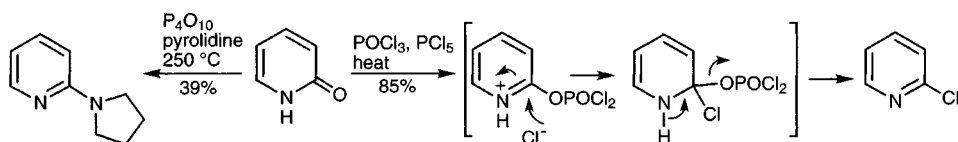


Aqueous sodium hydroxide at 100 °C causes exchange of the α -protons in 1-methyl-4-pyridone¹⁴⁵ and synthetically useful metallation at an α -position can be effected with *n*-butyllithium;¹⁴⁶ 1-methyl-2-pyridone, in contrast, metallates on the methyl,¹⁴⁷ but 2-pyridones, protected by carboxylation at nitrogen, lithiate at C-4.¹⁴⁸ The metallated *N*-methylpyridones tend to dimerise in the sense that they add to free pyridone in a Michael fashion. Metallation then condensation at side-chain methyl in a pyridone is also known.¹⁴⁹



5.10.2.3 Replacement of oxygen

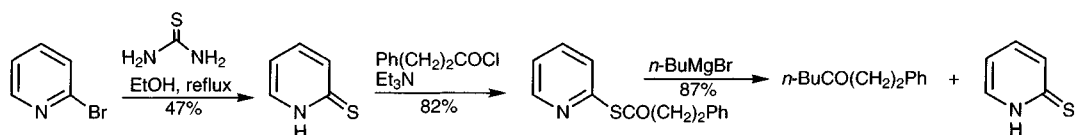
The conversion of the carbonyl group in pyridones into a leaving group has a very important place in the chemistry of these compounds, the most frequently encountered examples involving reaction with phosphoryl chloride and/or phosphorus pentachloride leading to the chloropyridine, *via* an assumed dichlorophosphate intermediate as indicated below. Conversion into halo derivative can also be conveniently achieved with *N*-bromosuccinimide and triphenylphosphine in refluxing dioxane.¹⁵⁰ Similarly, treatment with a secondary amine and phosphorus pentaoxide, or of 2- or 4-trimethylsilyloxypyridines with secondary amines produces aminopyridines.¹⁴²



The usual way to remove oxygen completely from a pyridone is by conversion, as described, into halogen followed by catalytic hydrogenolysis.¹⁵¹ Alternatively, reaction of the pyridone salt with 5-chloro-1-phenyltetrazole then hydrogenolysis of the resulting ether can be used.¹⁵²

5.10.2.4 Thio-2-pyridone

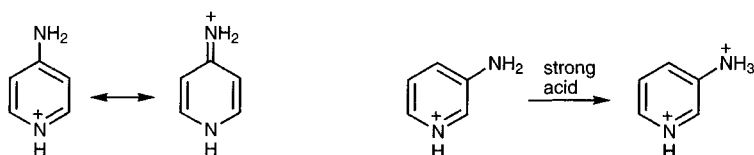
Thio-2-pyridone¹⁵³ can be converted efficiently into 2-acylthiopyridines by reaction with an acid chloride in the presence of triethylamine; the combination of an acid, triphenylphosphine, and 2,2'-pyridyldisulfide also produces such thioesters.¹⁵⁴ These 2-acylthiopyridines react smoothly with Grignard reagents giving ketones, the thiopyridone anion being the leaving group. 2-Acylthiopyridines have also been used as acyl-transfer reagents to nitrogen, in peptide synthesis,¹⁵⁵ and to oxygen in medium-sized lactone construction.¹⁵⁶



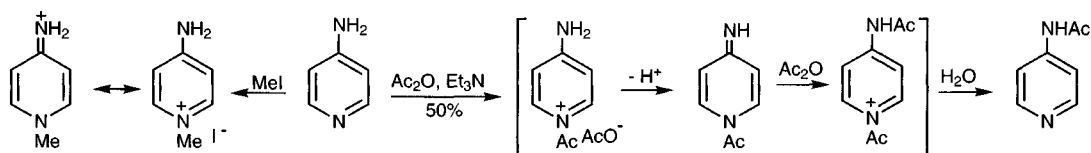
5.10.3 Reactions of aminopyridines

5.10.3.1 Electrophilic addition and substitution

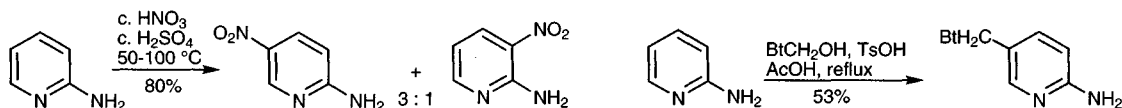
The three aminopyridines are all more basic than pyridine itself and form crystalline salts by protonation at the ring nitrogen. The α - and γ -isomers are monobasic only, because charge delocalisation over both nitrogen atoms, in the manner of an amidinium cation, prevents the addition of a second proton. The effect of the delocalisation is strongest in 4-aminopyridine (pK_a 9.1) and much weaker in 2-aminopyridine (pK_a 7.2). Delocalisation is not possible for the β -isomer which thus can form a di-cation in strong acid (pK_{a1} 6.6 and -1.5).¹⁵⁷



Whereas alkylation, irreversible at room temperature, gives the product of kinetically controlled attack at the most nucleophilic nitrogen, the ring nitrogen,¹⁵⁸ acetylation gives the product of reaction at a side-chain amino group. The acetylamino pyridine which is isolated probably results from side-chain deprotonation of an *N*-acetylpyridinium salt followed by side-chain *N*-acylation, with loss of the ring-*N*-acetyl during aqueous work up as shown below.



As in benzene chemistry, electron-releasing groups facilitate electrophilic substitution, so that, for example, 2-aminopyridine undergoes 5-bromination in acetic acid even at room temperature; this product can then be nitrated, at room temperature, forming 2-amino-5-bromo-3-nitropyridine.¹⁵⁹ Chlorination of 3-aminopyridine affords 3-amino-2-chloropyridine.¹⁶⁰ Nitration of aminopyridines in acid solution is also relatively easy, with selective attack of 2- and 4-isomers at β -positions. A study of dialkylaminopyridines showed nitration to take place by attack on the salts.¹⁶¹

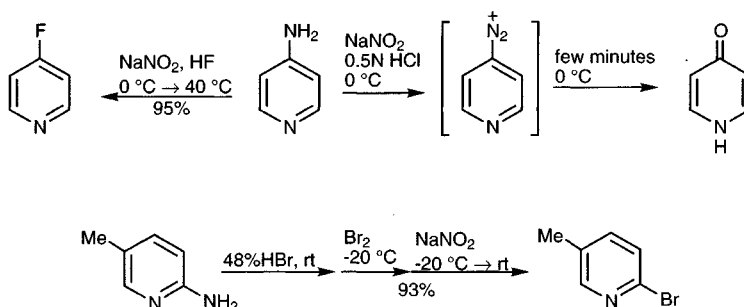


Whereas previously some *C*-alkylations of aminopyridines had been reported under very vigorous conditions, now a much milder alkylation results from reaction of 2-aminopyridines with 1-hydroxymethylbenzotriazole (section 26.3) in the presence of acid. One must assume that this *C*-substitution is made possible by a

reversible ring-*N*-alkylation.¹⁶² The products of such alkylations display all the characteristics of benzotriazole derivatives for further manipulation (section 26.3).

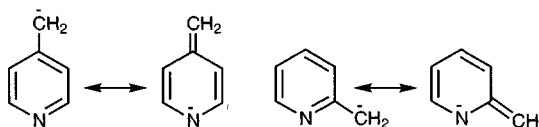
5.10.3.2 Reactions of the amino group

β -Aminopyridines give normal diazonium salts on reaction with nitrous acid, but with α - and γ -isomers, unless precautions are taken, the corresponding pyridones are then produced *via* easy hydrolysis,¹⁶³ water addition at the diazonium-bearing carbon being rapid.¹⁶⁴ With care however, this same susceptibility to nucleophilic displacement can be harnessed in effecting Sandmeyer-type reactions, without the use of copper, of either 2- or 4-aminopyridines.^{163,165,166}

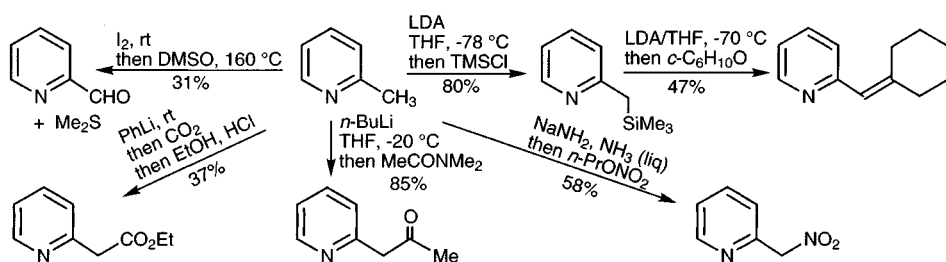


5.11 Alkylpyridines

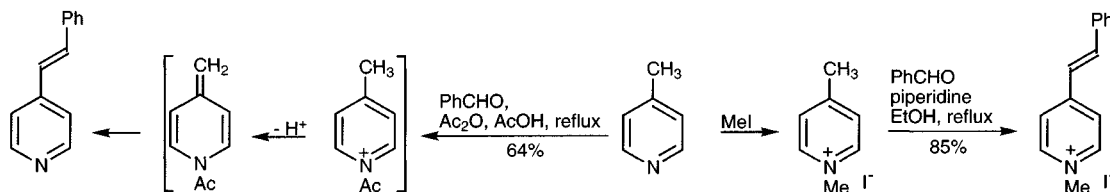
The main feature of the reactivity of alkylpyridines is deprotonation of the alkyl group at the carbon adjacent to the ring.¹⁶⁷ Measurements of side-chain-exchange in methanolic sodium methoxide, 4:2:3, 1800:130:1,¹⁶⁸ and of $\text{p}K_{\text{a}}$ values in tetrahydrofuran¹⁶⁹ each have the γ -isomer more acidic than the α -isomer, both being much more acidic than the β -isomer, though the actual carbanion produced in competitive situations can depend on both the counterion and the solvent. Alkylolithiums selectively deprotonate an α -methyl where amide bases produce the more stable γ -anion.¹⁷⁰ The much greater ease of deprotonation¹⁷¹ of the α - and γ -isomers is related to mesomeric stabilisation of the anion involving the ring nitrogen, not available to the β -isomer for which there is only inductive facilitation, but deprotonation can be effected at a β -methyl under suitable conditions;¹⁷² the difference in acidity between 2- and 3-methyl groups allows selective reaction at the former.¹⁷³



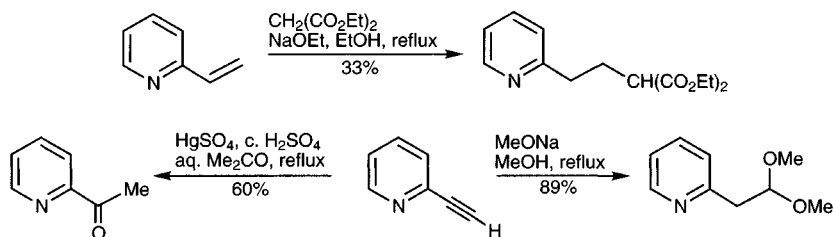
The 'enamine' anions produced by deprotonating α - and γ -alkylpyridines can participate in a wide range of reactions,¹⁷⁴ being closely analogous to enolate anions. Similar side-chain carbanion formation is seen in *ortho*- but not *meta*-nitrotoluene. Side-chain metallation of 2-*t*-butylcarbonylamino-4-methylpyridine proceeds at room temperature.¹⁷⁵



In the quaternary salts of alkylpyridines, the side-chain hydrogens are considerably more acidic and condensations can be brought about under quite mild conditions, the reactive species being an enamine;¹⁷⁶ side-chain deprotonation of *N*-oxides can also be achieved, though it can be complicated by ring deprotonation at C-2.¹⁷⁷



A further consequence of the stabilisation of carbanionic centres at pyridine α - and γ -positions is the facility with which vinylpyridines,¹⁷⁸ and alkynylpyridines, add nucleophiles, in Michael-like processes (mercury-catalysed hydration goes in the opposite sense¹⁷⁹). Complimentarily, pyridin-2-yl- and 4-ylethyl esters, sulfides or sulfones can serve as protecting groups, being readily and mildly removed by pyridine nitrogen quaternisation (iodomethane), causing elimination of the vinylpyridinium salt.¹⁸⁰

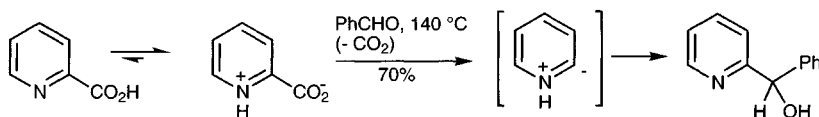


In considering reactions of side-chain halides, it is significant that calculations, supported by mass spectroscopic measurements, showed that pyridyl-2-cations are stabilised significantly by overlap with the coplanar nitrogen lone pair.¹⁸¹

5.12 Pyridine aldehydes, ketones, carboxylic acids and esters

These compounds all closely resemble the corresponding benzene compounds in their reactivity because the carbonyl group cannot interact mesomerically with the ring nitrogen. The pyridine 2- (picolinic), 3- (nicotinic), and 4- (isonicotinic) acids exist almost entirely in their zwitterionic forms in aqueous solution; they are slightly stronger acids than benzoic acid. Decarboxylation of picolinic acids is relatively easy and results in the transient formation of the same type of ylide which is responsible for specific proton α -exchange of pyridine in acid solution (see section 5.1.2.1).¹⁸² This transient ylide can be trapped by aromatic or aliphatic aldehydes in a reaction known as the Hammick reaction.¹⁸³ As implied by this mechanism, quaternary salts of

picolinic acids also undergo easy decarboxylation.¹⁸⁴ The process can also be carried out by heating a silyl ester of picolinic acid in the presence of a carbonyl electrophile.¹⁸⁵

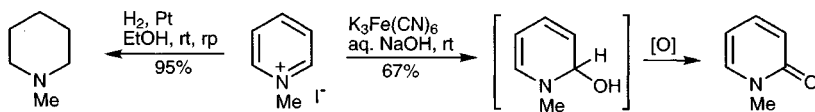


5.13 Quaternary pyridinium salts

The main features of the reactivity of pyridinium salts are (i) the greatly enhanced susceptibility to nucleophilic addition and displacement at the α - and γ -positions, sometimes followed by ring opening and (ii) the easy deprotonation of α - and γ -alkyl groups (see also section 5.11).

5.13.1 Reduction and oxidation

The oxidation of pyridinium salts¹⁸⁶ to pyridones by alkaline ferricyanide is presumed to involve a very small concentration of hydroxide adduct. 3-Substituted pyridinium ions are transformed into mixtures of 2- and 6-pyridones, for example oxidation of 1,3-dimethylpyridinium iodide gives a 9:1 ratio of 2- and 6-pyridones.



Catalytic reduction of pyridinium salts to piperidines is particularly easy; they are also susceptible to hydride addition by complex metal hydrides¹⁸⁷ or formate,¹⁸⁸ and lithium/ammonia reduction.¹⁸⁹ In the reduction with sodium borohydride in protic media the main product is a tetrahydro-derivative with the double bond at the allylic, 3,4-position. These cyclic allyl amines are formed by initial hydride addition at C-2, followed by enamine β -protonation and a second hydride addition. Some fully reduced material is always produced and its relative percentage increases with increasing *N*-substituent bulk, consistent with a competing sequence having initial attack at C-4, generating a dienamine which can then undergo two successive proton-then-hydride addition steps. When 3-substituted pyridinium salts are reduced with sodium borohydride, 3-substituted-1,2,5,6-tetrahydropyridines result. Care must be taken to destroy amine-borane which can be present at the end of such reductions.¹⁹⁰ When 1,4-dihydro-1-methylpyridine and 1,2-dihydro-1-methylpyridine are equilibrated using strong base, the former predominates to the extent of approximately 9:1.¹⁹¹

