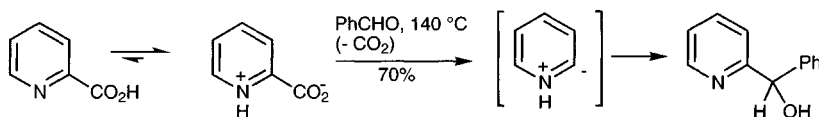


picolinic acids also undergo easy decarboxylation.¹⁸⁴ The process can also be carried out by heating a silyl ester of picolinic acid in the presence of a carbonyl electrophile.¹⁸⁵

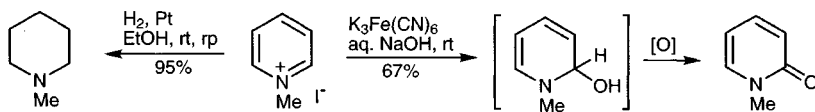


5.13 Quaternary pyridinium salts

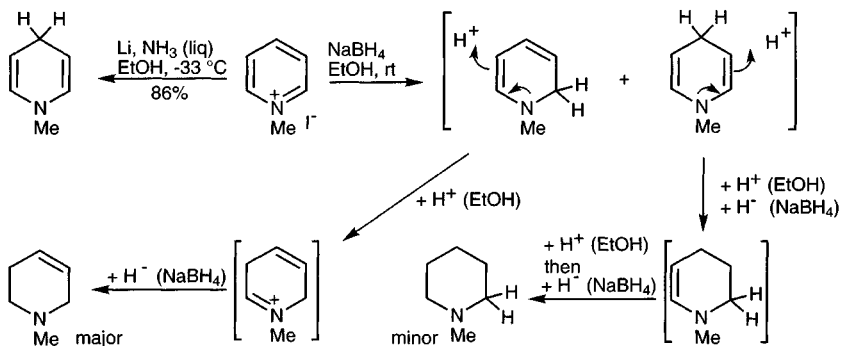
The main features of the reactivity of pyridinium salts are (i) the greatly enhanced susceptibility to nucleophilic addition and displacement at the α - and γ -positions, sometimes followed by ring opening and (ii) the easy deprotonation of α - and γ -alkyl groups (see also section 5.11).

5.13.1 Reduction and oxidation

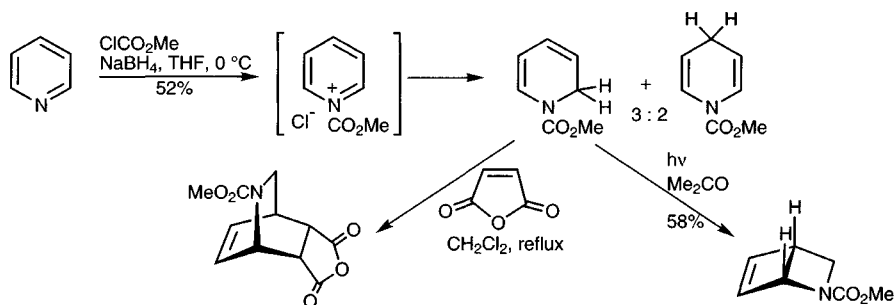
The oxidation of pyridinium salts¹⁸⁶ to pyridones by alkaline ferricyanide is presumed to involve a very small concentration of hydroxide adduct. 3-Substituted pyridinium ions are transformed into mixtures of 2- and 6-pyridones, for example oxidation of 1,3-dimethylpyridinium iodide gives a 9:1 ratio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



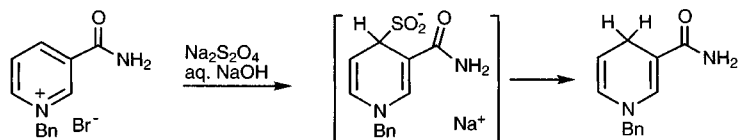
Catalytic reduction of pyridinium salts to piperidines is particularly easy; they are also susceptible to hydride addition by complex metal hydrides¹⁸⁷ or formate,¹⁸⁸ and lithium/ammonia reduction.¹⁸⁹ In the reduction with sodium borohydride in protic media the main product is a tetrahydro-derivative 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



N-Acyl, particularly *N*-alkoxy- or *N*-aryloxycarbonylpyridiniums can be reductively trapped as dihydro-derivatives by borohydride;¹⁹² no further reduction occurs because the immediate product is an enamide and not an enamine and therefore does not protonate under the conditions of the reduction.¹⁹³ The 1,2-dihydro-isomers, which can be produced essentially exclusively by reduction at -70°C in methanol, serve as dienes in Diels-Alder reactions. Irradiation causes conversion into 2-azabicyclo[2.2.0]hexenes; removal of the carbamate and *N*-alkylation gives derivatives which are synthons for unstable *N*-alkyldihydropyridines, and convertible into the latter thermally.¹⁹⁴

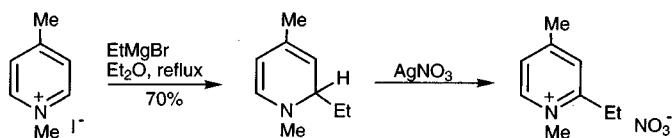


The easy specific reduction of 3-acylpyridinium salts giving stable 3-acyl-1,4-dihydropyridines using sodium dithionite is often quoted, because of its perceived relevance to nicotinamide coenzyme activity; the mechanism involves addition of sulfur at C-4 as its first step, as shown below.¹⁹⁵ 1,4-Dihydropyridines are normally air-sensitive, easily rearomatised molecules; the stability of 3-acyl-1,4-dihydropyridines is related to the conjugation between ring nitrogen and side-chain carbonyl group (see also Hantzsch synthesis, section 5.15.1.2). However, even simple pyridinium salts, provided the *N*-substituent is larger than propyl, or for example benzyl, can be reduced to 1,4-dihydropyridines with sodium dithionite.¹⁹⁶



5.13.2 Organometallic addition

Organometallic reagents add very readily to *N*-alkyl-, *N*-aryl- and with important synthetic significance, *N*-acylpyridinium salts. In the simplest cases, addition is to an α -carbon; the resulting 2-substituted-1,2-dihydropyridine can be handled and spectroscopically identified, with care, but more importantly can be easily oxidised to a 2-substituted pyridinium salt.¹⁹⁷

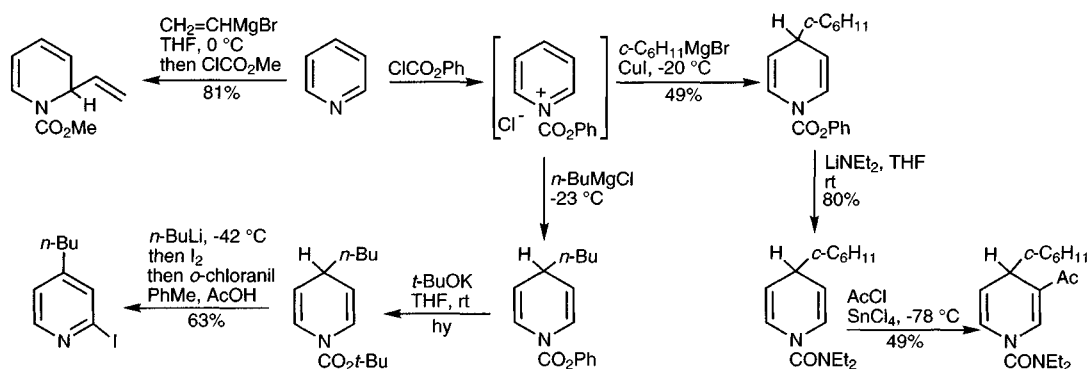


The great significance of the later discovery, that exactly comparable additions to *N*-acylpyridinium cations, generated and reacted *in situ*, is that the dihydropyridines which result can be further manipulated if required and that during rearomatisation

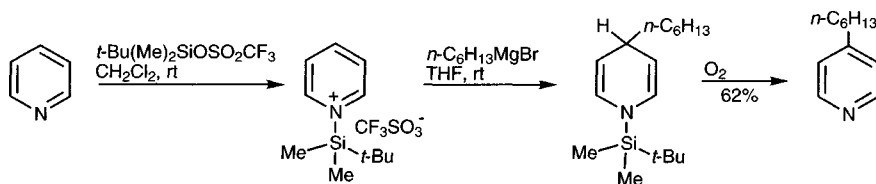
the *N*-substituent can be easily removed to give a substituted pyridine. It is worth noting the contrast to the use of *N*-acylpyridinium salts for reaction with alcohol, amine nucleophiles (section 5.1.1.7) when attack is at the carbonyl carbon; the use of an *N*-alkoxycarbonyl pyridinium salt in the present context aids this discrimination.

Generally, organometallic addition to *N*-alkoxy- or *N*-aryloxycarbonylpyridinium salts¹⁹² takes place at both 2- and 4-positions,¹⁹⁸ however higher selectivity for the 4-position can be achieved using copper reagents.¹⁹⁹ Indole as the neutral molecule, reacts with *N*-benzoylpyridinium chloride at C-4,²⁰⁰ but its anion will add to *N*-methylpyridinium salts having acyl groups at C-3 either at C-6 or at C-4 depending on the solvent.²⁰¹ High selectivity for the 2-position is found in the addition of phenyl,²⁰² alkenyl and alkynyl organometallics,²⁰³ including ethoxycarbonylmethyl²⁰⁴ and alkynyl²⁰⁵ tin reagents.

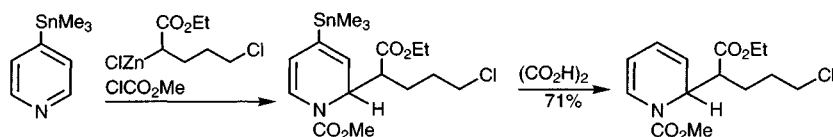
Examples of the further manipulation of dihydropyridines produced by the methods described above include introduction of substituents at a β -position, by acylation of the enamide,¹⁵⁰ and at an α -position, *via* 2-lithiation, each of which is illustrated below.¹⁵⁰



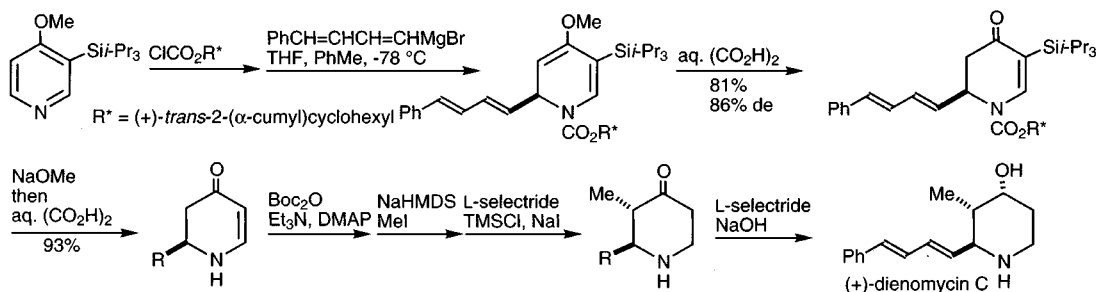
Silylation at nitrogen with *t*-butyldimethylsilyl triflate, generates pyridinium salts which, because of the size of the *N*-substituent, react with Grignard reagents exclusively at C-4;²⁰⁶ montmorillonite-catalysed addition of silyl enol ethers to pyridines has a comparable effect in producing 1-trimethylsilyl-1,4-dihydropyridines carrying an acylalkyl substituent at C-4.²⁰⁷



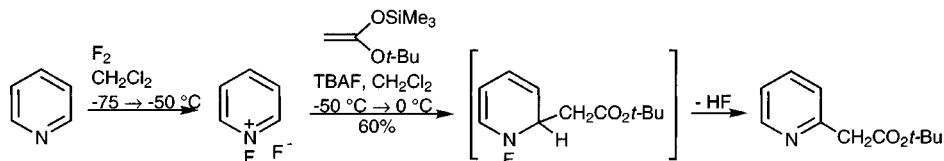
4-Substituents direct attack to an α -carbon;^{208,209} the use of a removable 4-blocking group – trimethyltin in the example below – can be made the means for the production of 2-substituted isomers.²¹⁰



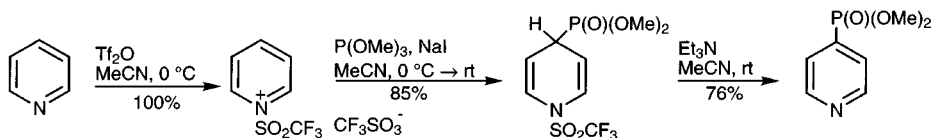
The use of chiral chloroformates such as that derived from *trans*-2-(α -cumyl)cyclohexanol allows diastereoselective additions to 4-methoxypyridine. The introduction of a tri-*i*-propylsilyl group at C-3 greatly enhances the diastereoselectivity. The products of these reactions are multifunctional chiral piperidines which have found use in the asymmetric synthesis of natural products.²¹¹



Some nucleophiles add to *N*-fluoropyridinium salts to give dihydropyridines in which elimination of fluoride occurs *in situ* to give the 2-substituted pyridine, thus avoiding the need for a dehydrogenation step. The main disadvantages of this method are that the preparation of the pyridinium salts require the use of elemental fluorine and that some carbanions give only modest yields due to competitive reactions such as C-fluorination. However, silyl enol ethers do react efficiently; stabilised heteronucleophiles (phenolate, azide) can also be used. Addition to *N*-fluoropyridinium salts shows a strong preference for attack at an α -position.²¹²

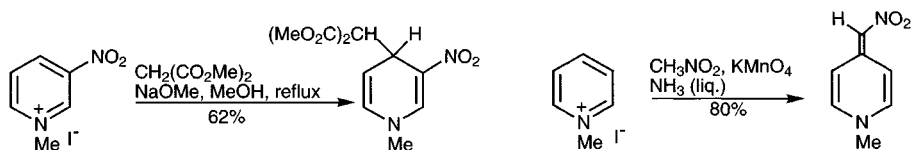


In a similar way, pyridine phosphonium salts and phosphonates can be prepared by reaction of trivalent phosphorus compounds with the more accessible *N*-trifluoromethanesulfonyl pyridines, when trifluoromethanesulfinate is the leaving group from nitrogen; attack is normally at C-4 as illustrated below.²¹³



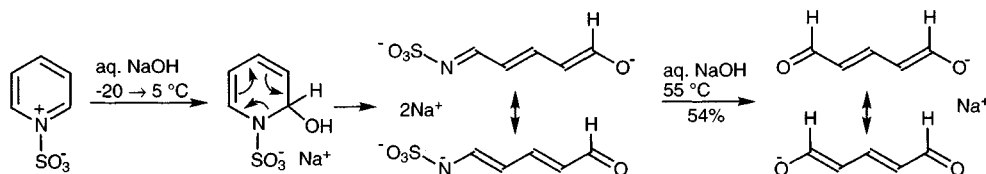
5.13.3 Other nucleophilic additions

There are a variety of examples of other nucleophiles adding to *N*-alkylpyridinium salts. A study²¹⁴ of reversible additions to 3-cyano-1-methylpyridinium iodide showed α -attack to be kinetically favoured but the γ -adduct to be the more thermodynamically stable. Similarly, in thermodynamically-controlled processes, 1-methyl-3-nitropyridinium gives products resulting from addition at C-4 in which again there is stabilising conjugation between ring nitrogen and 3-substituent.²¹⁵ Products of γ -addition, even in 1-methyl- or -phenylpyridinium iodides, lacking a conjugating 3-substituent, can be trapped via attack by added oxidant as illustrated.²¹⁶

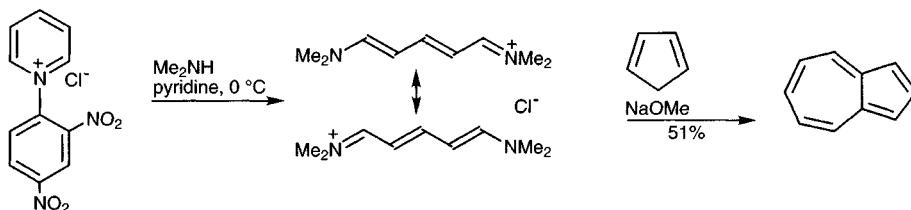


5.13.4 Nucleophilic addition followed by ring opening²¹⁷

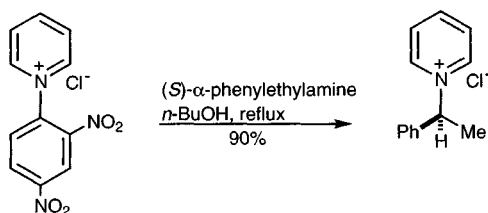
There are many examples of pyridinium salts, particularly, but not exclusively, those with powerful electron-withdrawing *N*-substituents, adding a nucleophile at C-2 and then undergoing a ring opening. Perhaps the classic example is addition of hydroxide to the pyridine sulfur trioxide complex, which produces the sodium salt of glutaconaldehyde as shown below.²¹⁸



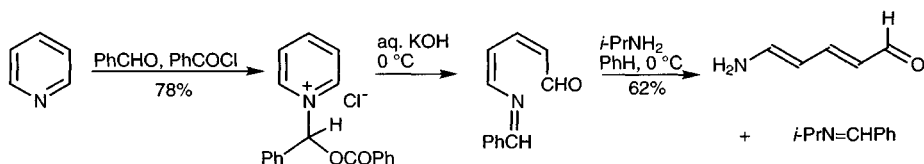
Another well known example is a synthesis of azulene which utilises the bis dimethylamine derivative of glutaconaldehyde produced with loss of 2,4-dinitroaniline from 1-(2,4-dinitrophenyl)pyridinium chloride (Zincke's salt).²¹⁹



The reaction of such pyridinium salts with primary amines, including amino acid esters is a useful synthesis of chirally-*N*-substituted pyridinium salts.²²⁰



As a final example of nucleophilic addition then ring opening, it has even been possible to isolate the ring-opened 'hydrate' of pyridine, by reaction with benzaldehyde and benzoyl chloride, as shown below.²²¹



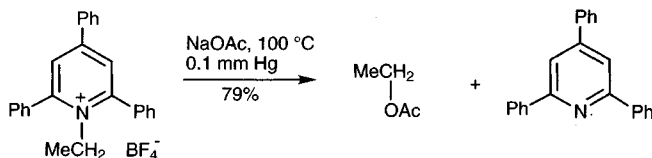
5.13.5 Cyclisations involving an α -position or an α -substituent

It is often possible to achieve cyclisation of pyridinium salts, in which the ring closure involves an α -substituent or the electrophilic nature of the α -position (see also section 5.1.1.8) and gives a neutral product – sections 25.1.2, 25.2.1, 25.2.2, and 25.2.3 give examples.

5.13.6 N-Dealkylation

The conversion of *N*-alkyl- or -arylpseudopyridinium salts into the corresponding pyridine, i.e. the removal of the *N*-substituent, is generally not an easy process, however triphenylphosphine²²² or simply heating the iodide salt²²³ can work for metho-salts. 1-Triphenylmethyl-4-dimethylaminopyridinium chloride²²⁴ and 1-trialkylsilylpyridinium triflates²²⁵ are isolable and relatively stable salts; *O*-tritylations and *O*-silylations involving transfer of trityl or trialkylsilyl from the positively charged nitrogen in such salts are usually carried out without isolation using mixtures of 4-dimethylaminopyridine (DMAP) with chlorotriphenylmethane or, for example, chloro-*t*-butyldimethylsilane.²²⁶

Pyridinium salts corresponding to 2,4,6-trisubstituted pyridines, which must be prepared by reacting a primary amine with 2,4,6-trisubstituted pyrylium perchlorate (see section 8.1.2.2) are attacked by a variety of nucleophiles with transfer of the *N*-substituent to the attacking reagent and as such are convenient alkylating agents,²²⁷ and, recalling that the precursor to the pyridinium salt is the primary amine, the sequence also represents the overall transformation of a primary amine into a variety of derivatives.



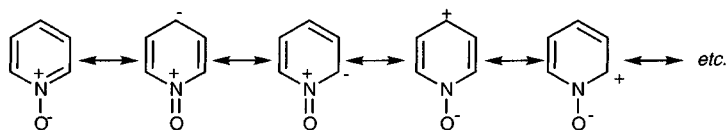
5.14 Pyridine *N*-oxides²²⁸

The reactions of pyridine *N*-oxides are of great interest,²²⁹ differing significantly from those of both neutral pyridines and pyridinium salts.

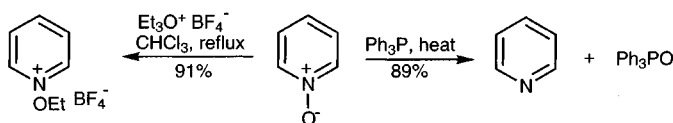


A striking difference between pyridines and their *N*-oxides is the much greater susceptibility of the latter to electrophilic nitration. This can be understood in terms of mesomeric release from the oxide oxygen, and is parallel to electron release by oxygen and hence increased reactivity towards electrophilic substitution in phenols and phenoxides. One can find support for this rationalisation by a comparison of the dipole moments of trimethylamine and its *N*-oxide, on the one hand, and pyridine and its *N*-oxide, on the other: the difference of 2.03 D for the latter pair is much smaller than the 4.37 D found for the former. The smaller difference signals significant contributions from those canonical forms in which the oxygen is neutral and the ring negatively charged. Clearly, however, the situation is subtle, as those

contributors carrying formal positive charges on α - and γ -carbons suggest a polarisation in the opposite sense and thus an increased susceptibility to nucleophilic attack too, compared with the neutral pyridine, and this is indeed found to be the case. Summarising: the *N*-oxide function in pyridine *N*-oxides serves to facilitate, on demand, both electrophilic and nucleophilic addition to the α - and γ -positions.

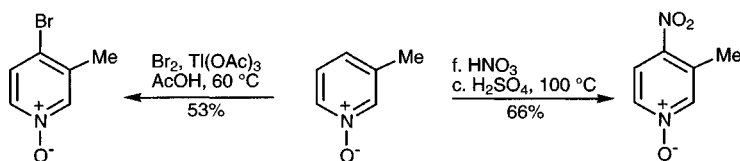


Many methods are available for the removal of oxygen from *N*-oxides, samarium iodide, chromous chloride, stannous chloride with low-valent titanium, ammonium formate with palladium, and catalytic hydrogenation all do the job at room temperature.²³⁰ The most frequently used methods have involved oxygen transfer to trivalent phosphorus²²⁸ or divalent sulfur.²³¹

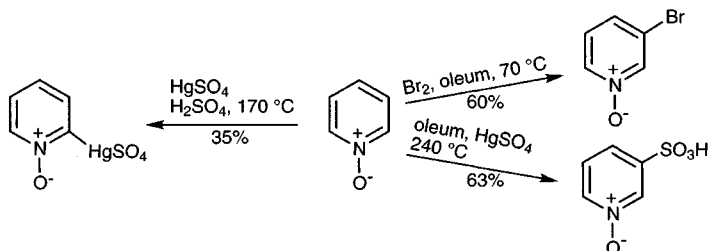


5.14.1 Electrophilic addition and substitution

Pyridine *N*-oxides protonate and are alkylated at oxygen; stable salts can be isolated in some cases.²³² Hot aqueous sodium hydroxide treatment of alkoxy pyridinium salts produces aldehydes corresponding to the alkoxy substituent.²³³



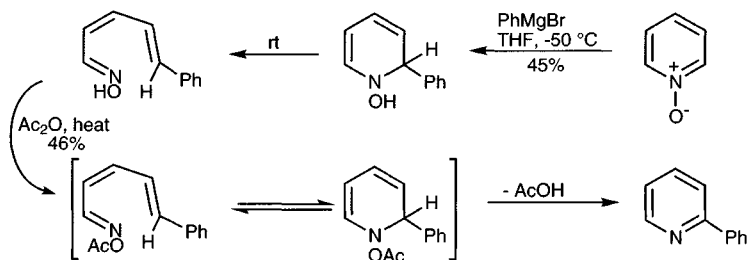
Electrophilic nitration and bromination of pyridine *N*-oxides can be controlled to give 4-substituted products²³⁴ by way of attack on the free *N*-oxide.²³⁵ Under conditions where the *N*-oxide is *O*-protonated, substitution follows the typical pyridine/pyridinium reactivity pattern thus, in fuming sulfuric acid, bromination shows β -regioselectivity,²³⁶ mercuration, however, takes place at the α -position.²³⁷



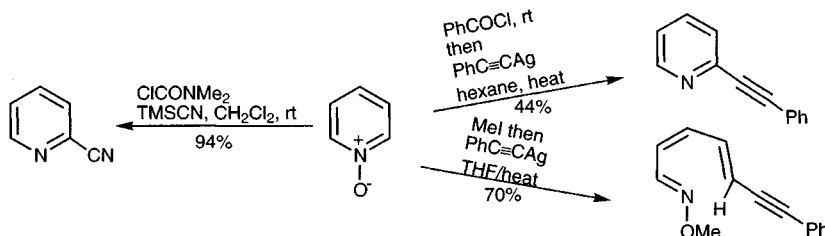
5.14.2 Nucleophilic addition and substitution

The *N*-oxide function enhances the rate of nucleophilic displacement of halogen from α - and γ -positions. The relative rates $4 > 2 > 3$ found for pyridines are echoed for the *N*-oxides, but interestingly altered to $2 > 4 > 3$ in methiodides.²³⁸

Grignard reagents add to pyridine *N*-oxide forming adducts, which can be characterised from a low temperature reaction, but which at room temperature undergo disrotatory ring opening, the isolated product being an acyclic, unsaturated oxime. Heating with acetic anhydride brings about rearomatisation, *via* electrocyclic ring closure rendered irreversible by the loss of acetic acid.²³⁹



Comparable addition/ring openings can be observed with 1-alkoxypyridiniums,^{240,241} however prior acylation at the *N*-oxide oxygen before addition of alkyl or aryl Grignard or acetylide leads through to 2-substituted-pyridines.^{241,242}

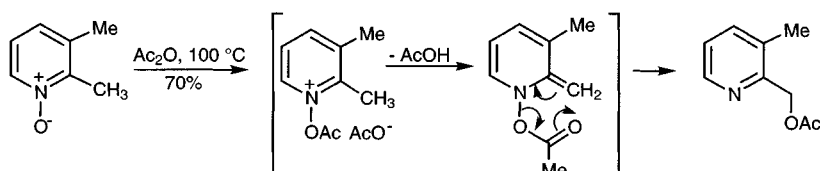


Very clean conversions of pyridine *N*-oxide into 2-cyanopyridine depend on prior conversion of oxide into silyloxy or carbamate,²⁴³ and displace earlier methods which utilised *N*-alkoxypyridinium salts.²⁴⁴

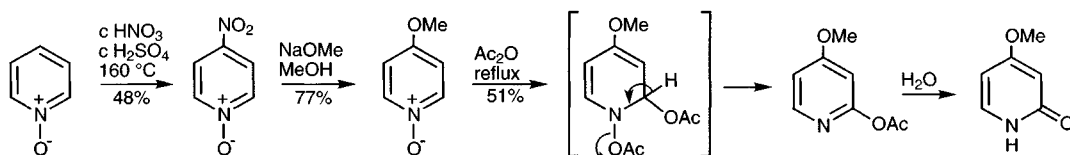
5.14.3 Rearrangements

A range of synthetically useful rearrangements convert pyridine *N*-oxides into variously substituted pyridines in which an α -(γ)-position, or an α -substituent has been modified.

2-Methylpyridine *N*-oxides react with hot acetic anhydride and produce 2-acetoxymethylpyridines; using trifluoroacetic anhydride permits reaction at room temperature with fewer by-products.²⁴⁵ Repetition of the sequence affords 2-aldehydes after hydrolysis.²⁴⁶ The course²⁴⁷ of the rearrangement would seem to be most simply explained by invoking an electrocyclic sequence, as shown below.



In the absence of a 2-substituent, reaction with thionyl chloride or with acetic anhydride leads to the formation of 2- and 4-chloro- or 2-acetoxypyridines. Mechanistically, electrophilic addition to oxide is followed by nucleophilic addition to an α - or γ -position, the process being completed by an elimination.²²⁸ The sequence below shows an example and also illustrates other aspects of *N*-oxide chemistry discussed above.²⁴⁸



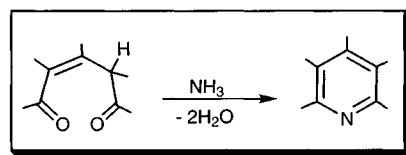
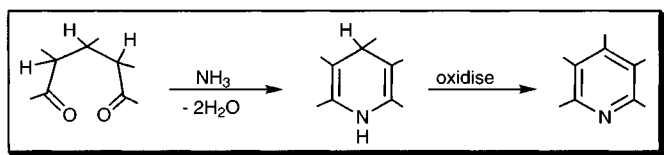
5.15 Synthesis of pyridines

5.15.1 Ring synthesis

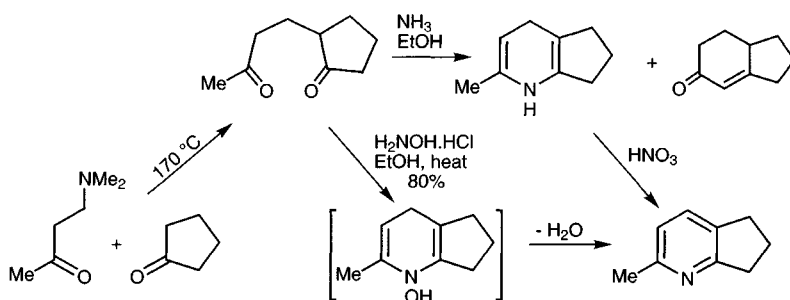
There are very many ways of achieving the synthesis of a pyridine ring; the following section describes the main general methods.

5.15.1.1 From 1,5-dicarbonyl compounds and ammonia

Ammonia reacts with 1,5-dicarbonyl compounds to give 1,4-dihydropyridines which are easily dehydrogenated to pyridines. With unsaturated 1,5-dicarbonyl compounds, or their equivalents (e.g. pyrylium ions) ammonia reacts to give pyridines directly.

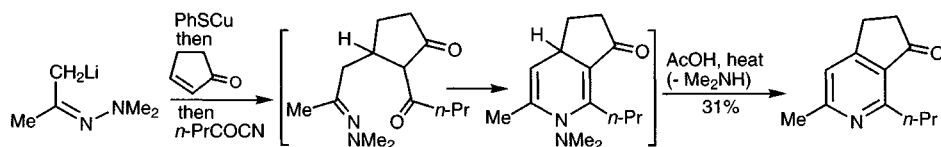


1,5-Diketones are accessible *via* a number routes, for example by Michael addition of enolate to enone (or precursor Mannich base²⁴⁹), by ozonolysis of a cyclopentene precursor, or by reaction of silyl enol ethers with 3-methoxyallylic alcohols.²⁵⁰ They react with ammonia, with loss of two mol equivalents of water to produce a cyclic bis-enamine, i.e. a 1,4-dihydropyridine, which is generally unstable but can be easily and efficiently dehydrogenated to the aromatic heterocycle.

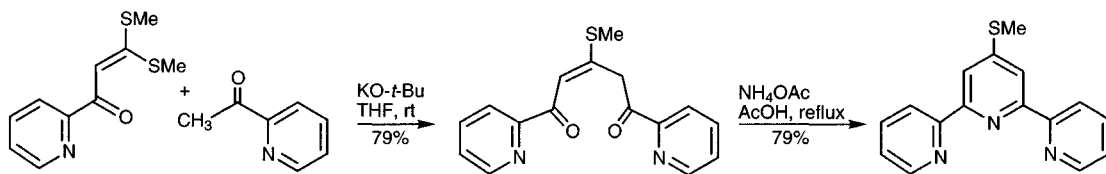


The oxidative final step can be neatly avoided by the use of hydroxylamine,²⁵¹ instead of ammonia, when a final 1,4-loss of water produces the aromatic heterocycle. In an extension of this concept, the construction of a 1,5-diketone

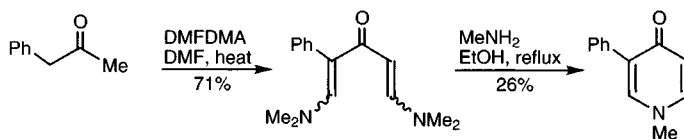
equivalent by tandem Michael addition of dimethylhydrazone anion to an enone, then acylation, has loss of dimethylamine as the final aromatisation step.²⁵²



It follows, that the use of an unsaturated 1,5-dicarbonyl compound will also afford aromatic pyridine directly; a number of methods are available for the assembly of the unsaturated diketone, including the use of pyrylium ions or 2-pyrones²⁵³ (see chapter 8) as synthons, or the alkylation of an enolate with a 3,3-bis(methylthio)-enone.²⁵⁴

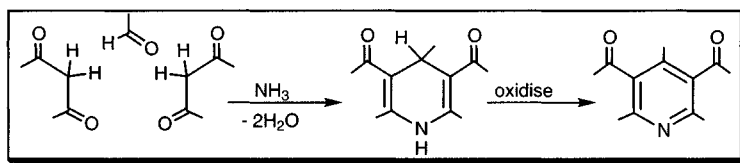


When one of the carbonyl carbons is at the oxidation level of acid (as in a 2-pyrone, section 8.2) then the product, reflecting this oxidation level, is a 2-pyridone.²⁵⁵ Similarly, 4-pyrones (section 8.2) react with ammonia or primary amines to give 4-pyridones²⁵⁶ and similarly the bis-enamines which can be obtained directly from ketones by condensation on both sides of the carbonyl group with dimethylformamide dimethylacetal, produce 4-pyridones on reaction with primary amines.²⁵⁷ When one of the 'carbonyl' units is actually a nitrile, then an aminopyridine results.²⁵⁸



5.15.1.2 From an aldehyde, two equivalents of a 1,3-dicarbonyl compound, and ammonia

Symmetrical 1,4-dihydropyridines, which can be easily dehydrogenated, are produced from the interaction of ammonia, an aldehyde, and two equivalents of a 1,3-dicarbonyl compound which must have a central methylene.

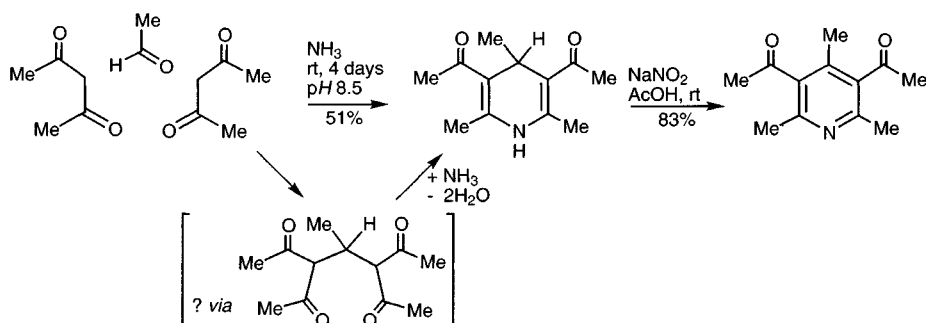


The Hantzsch synthesis²⁵⁹

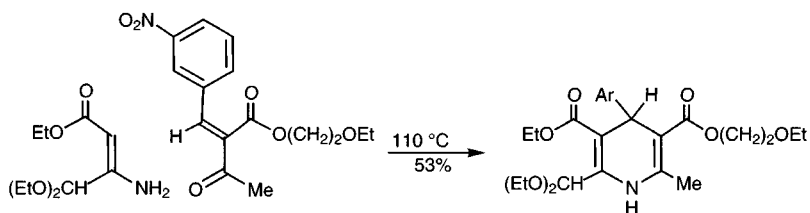
The product from the classical Hantzsch synthesis is necessarily a symmetrically substituted 1,4-dihydropyridine since two mol equivalents of the one dicarbonyl component are utilised, the aldehyde carbonyl carbon becoming the pyridine C-4. The precise sequence of intermediate steps is not known for certain, and may indeed

vary from case to case, for example the ammonia may become involved early or late, but a reasonable sequence would be aldol condensation followed by Michael addition generating, *in situ*, a 1,5-dicarbonyl compound.

The 1,4-dihydropyridines produced in this approach, carrying conjugating substituents at each β -position, are stable, and can be easily isolated before dehydrogenation; classically the oxidation has been achieved with nitric acid, or nitrous acid, but other oxidants such as cerium(IV) ammonium nitrate, copper(II) nitrate on montmorillonite, and manganese dioxide on bentonite also all achieve this objective smoothly.²⁶⁰

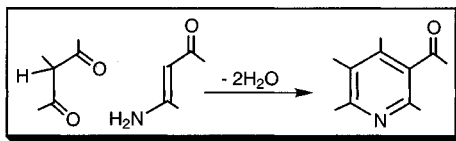


Unsymmetrical 1,4-dihydropyridines can be produced by conducting the Hantzsch synthesis in two stages, i.e. by making the (presumed) aldol condensation product separately, then reacting with ammonia and a different 1,3-dicarbonyl component, or an enaminoketone, in a second step.²⁶¹



5.15.1.3 From 1,3-dicarbonyl compounds and 3-amino-enones or -nitriles

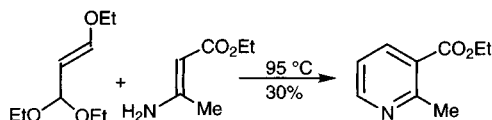
Pyridines are formed from the interaction between a 1,3-dicarbonyl compound and a 3-amino-enone or 3-aminoacrylate; 3-cyano-2-pyridones result if cyanoacetamide is used instead of an amino-enone.



This approach, in its various forms, is probably the most versatile and useful since it allows the construction of unsymmetrically substituted pyridines from relatively simple precursors. Again, in this pyridine ring construction, intermediates are not isolated and it is difficult to be sure of the exact sequence of events.

3-Amino-enones or 3-amino-acrylates can be prepared by the straightforward reaction of ammonia with a 1,3-diketone or a 1,3-keto-ester. The simplest 1,3-dicarbonyl compound, malondialdehyde, is too unstable to be useful, but its readily

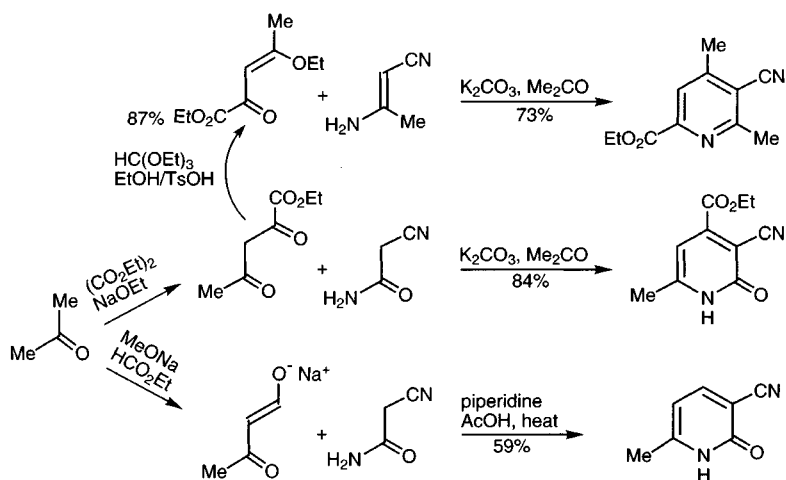
available acetal enol ether can be used instead, as shown below.²⁶² Vinamidinium ($R_2NCH=CR'/CH=N^+R_2$) salts will serve as synthons for substituted malondialdehydes or unsaturated keto-aldehydes in these syntheses.²⁶³



The Guareschi synthesis

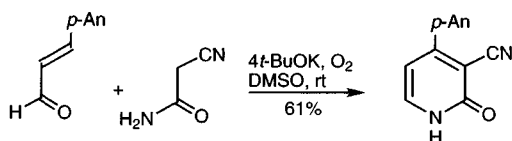
The variation which makes use of cyanoacetamide as the nitrogen-containing component leads to 3-cyano-2-pyridones, from which the carbonyl group and/or the cyano group can be subsequently removed.

Providing the two carbonyl groups are sufficiently different in reactivity, only one of the two possible isomeric pyridine/pyridone products is formed *via* reaction of the more electrophilic carbonyl group with the central carbon of the 3-amino-enone, 3-aminoacrylate, or cyanoacetamide.^{264,265}



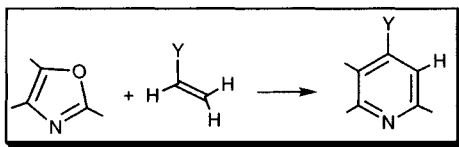
Variations include the use of yne-ones, when conjugate addition of the cyanoacetamide controls the regiochemistry of reaction,²⁶⁶ and 3-alkoxy-enones (i.e. the enol ethers of 1,3-diketones) when comparably, the initial Michael-type interaction dictates the regiochemistry.^{264,267} Using $H_2NCOCH_2C(NH_2)=N^+H_2Cl^-$ instead of cyanoacetamide gives 2-aminopyridine-3-carboxamides²⁶⁸ and using $H_2NCOCH_2NO_2$ instead of cyanoacetamide produces 3-nitro-2-pyridones.²⁶⁹

Successful ring closure to produce pyridines and pyridones can also be carried out with starting materials at a lower oxidation level, with *in situ* dehydrogenation by air or added oxygen, i.e. instead of using a 1,3-dicarbonyl component, an α,β -unsaturated ketone/aldehyde is employed, as illustrated below.²⁷⁰

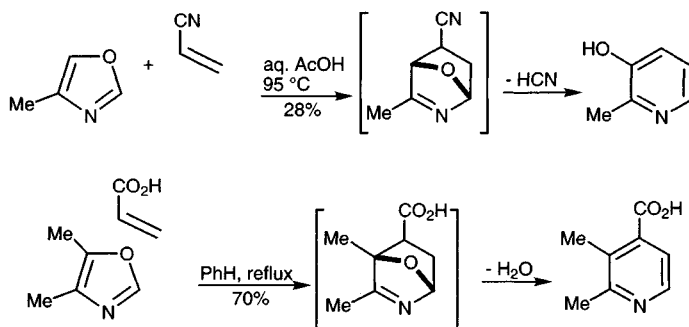


5.15.1.4 By cycloadditions

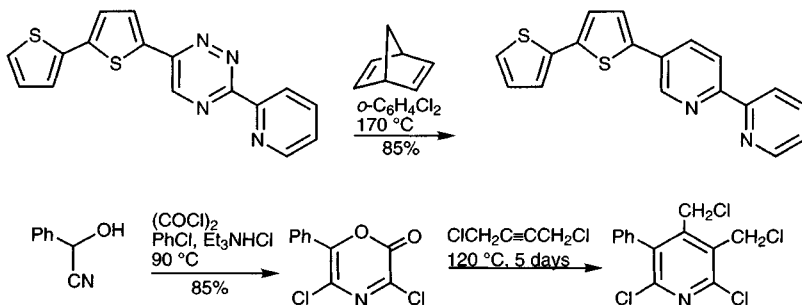
Various electrocyclic additions, with subsequent extrusion of a small molecule have been used to construct pyridines: addition to oxazoles is one of these.



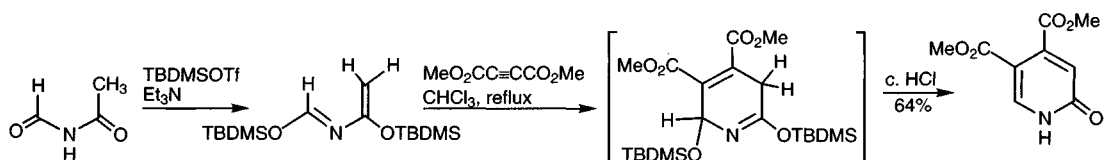
A number of 6π cycloadditions, some with inverse electron-demand, have been developed into useful means for the construction of pyridines. Historically, the first of these was the addition of a dienophile to an oxazole; sometimes the oxazole oxygen is retained (giving 3-hydroxypyridines) and sometimes it is lost, as illustrated below.²⁷¹



1,2,3-²⁷² and 1,2,4-Triazines, acting as inverse electron-demand azadienes, add to enamines and thus, following extrusion of nitrogen and loss of amine, a pyridine is produced (see section 25.2.1).²⁷³ 1,2,4-Triazines will also react with other dienophiles: reaction with ethynyltributyltin for example gives 4-stannylpyridines;²⁷⁴ norbornadiene is useful as an acetylene equivalent;²⁷⁵ oxazinones can also be used as the 'diene' component.²⁷⁶



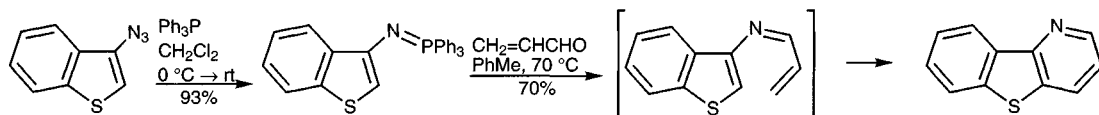
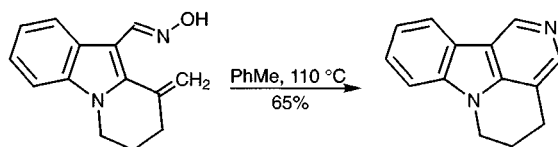
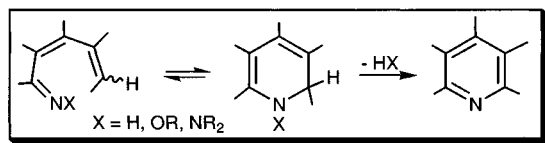
The *O,O'*-bis-*t*-butyldimethylsilyl derivative of an imide serves as an azadiene in reaction with dienophiles; 2-pyridones are the result, following desilylation.²⁷⁷



5.15.1.5 By thermal electrocyclisations

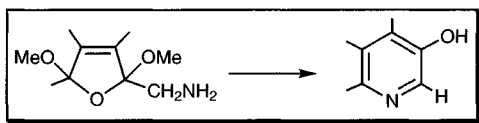
From 1-aza-1,3,5-trienes

Electrocyclisation of 1-aza-1,3,5-trienes generates dihydropyridines which can be oxidised to pyridines. If an oxime or hydrazine derivative is used, elimination of water or an amine *in situ* gives the pyridine directly. This method is particularly useful for fusion of pyridines to other ring systems and is illustrated by the examples below.²⁷⁸

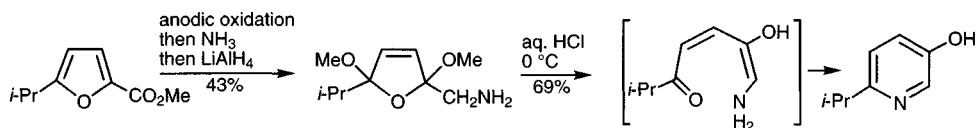


5.15.1.6 From furans

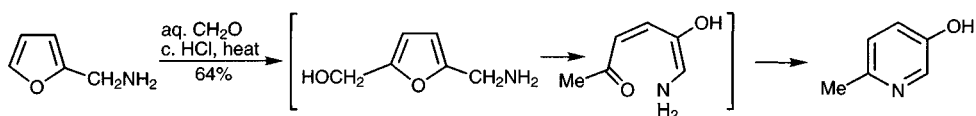
2-Furfurylamines, can be converted *via* ring-opening ring-closure sequences, for example through 2,5-dimethoxy-2,5-dihydrofurans, into 3-hydroxypyridines.



Ring-opening and reclosure processes using furans include several significant methods for the construction of pyridines. 2,5-Dihydro-2,5-dimethoxyfurans (see section 15.1.4) carrying as side-chain an aminoalkyl group, give rise to 3-hydroxypyridines.²⁷⁹

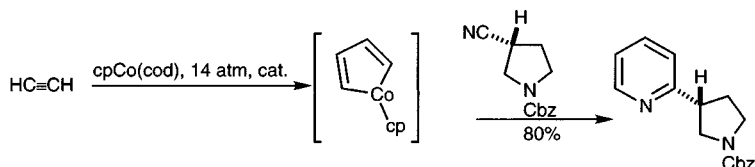


Furfurylamines react with formaldehyde, directly,²⁸⁰ (or with an aromatic aldehyde *via* 5-lithiation after *N*-protection²⁸¹) to give 3-hydroxy-6-substituted pyridines.



5.15.1.7 Miscellaneous methods

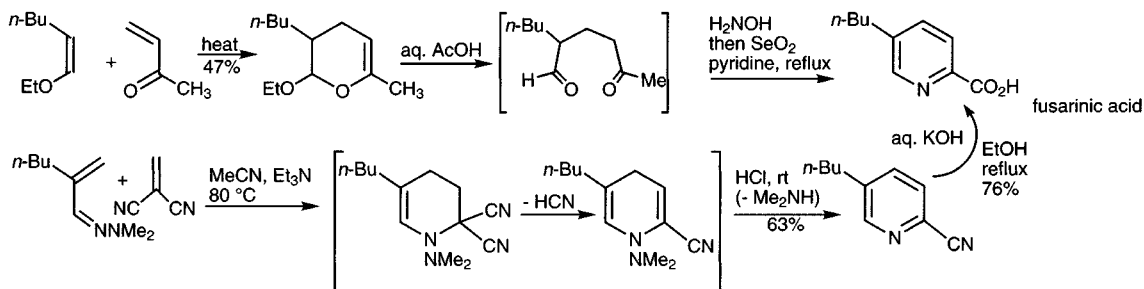
Many alkylpyridines are manufactured commercially by chemically complex processes which often produce them as mixtures. A good example is the extraordinary *Chichibabin synthesis*, in which paraldehyde and ammonium hydroxide react together at 230 °C under pressure to afford 52% of 5-ethyl-2-methylpyridine; so here, four mol equivalents of acetaldehyde and one of ammonia combine.²⁸² Also of commercial significance is the cobalt-catalysed interaction of a nitrile and acetylene.²⁸³



5.15.2 Examples of notable syntheses of pyridine compounds

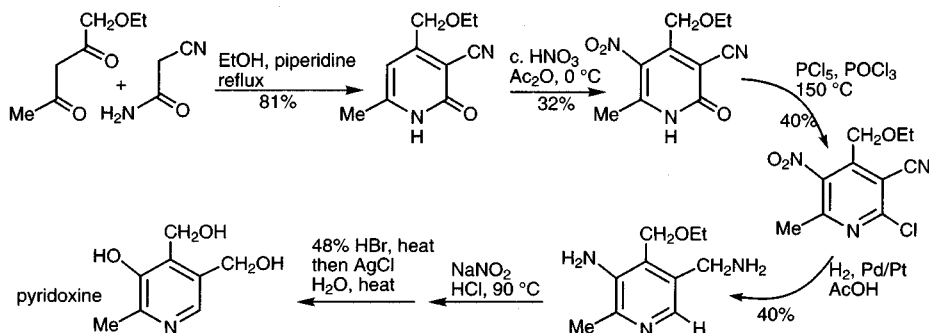
5.15.2.1 Fusarinic acid

Fusarinic acid is a mould metabolite with antibiotic and antihypertensive activity. Two syntheses of this substance employ cycloadditions, the earlier²⁸⁴ as a means to produce a 1,5-diketone, and the second²⁸⁵ to generate a 1-dimethylamino-1,4-dihydropyridine.



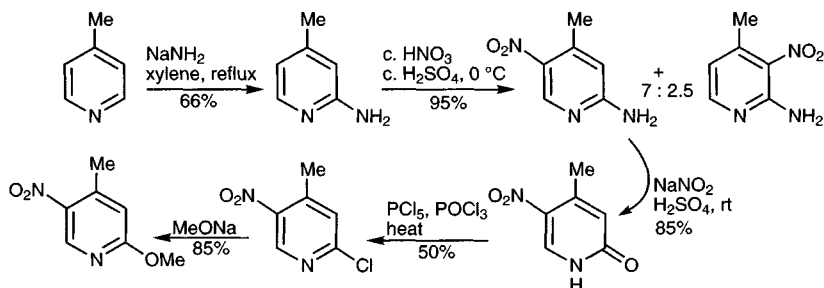
5.15.2.2 Pyridoxine

Pyridoxine, vitamin B₆, has been synthesised by several routes, including one which utilises a Guareschi ring synthesis, as shown below.²⁸⁶



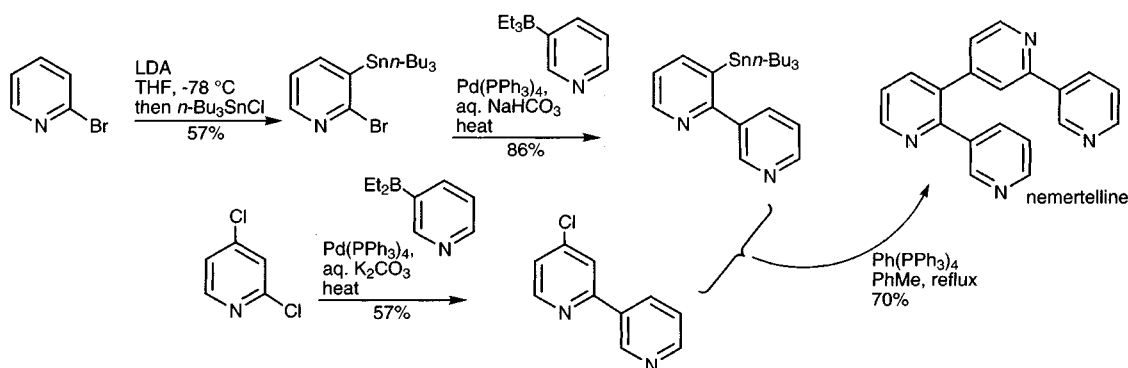
5.15.2.3 2-Methoxy-4-methyl-5-nitropyridine

2-Methoxy-4-methyl-5-nitropyridine is an intermediate used in a synthesis of porphobilinogen (section 13.18.3.1).



5.15.2.4 Nemertelline

The total synthesis of nemertelline, a hoploemertinin worm toxin, illustrates the use of metallation and palladium-catalysed couplings.²⁸⁷



Exercises for chapter 5

Straightforward revision exercises (consult chapters 4 and 5)

- In what way does pyridine react with electrophilic reagents such as acids and alkyl halides?
- What factors make it much more difficult to bring about electrophilic substitution of pyridine than benzene?
- How do pyridines compare with benzenes with regard to (i) oxidative destruction of the ring and (ii) reduction of the ring?
- Give two examples of pyridines reacting with nucleophilic reagents with substitution of a hydrogen.
- What are the relative reactivities of bromobenzene, 2-bromopyridine, 3-bromopyridine towards replacement of the halide with ethoxide on treatment with NaOEt?
- How could one generate 2-lithiopyridine?
- What would result from treatment of 3-chloropyridine with LDA at low temperature?

- (h) Draw the main tautomeric forms of 2-hydroxypyridine (2-pyridone), 3-hydroxypyridine and 2-aminopyridine.
- (i) How could one convert 4-pyridone cleanly into 1-ethyl-4-pyridone?
- (j) What would be the result of treating a 1 : 1 mixture of 2- and 3-methylpyridines with 0.5 equivalents of LDA and then 0.5 equivalents of MeI?
- (k) Draw the structure of the product(s) you would expect to be formed if pyridine were reacted successively with methyl chloroformate and then phenyllithium.
- (l) In pyridine *N*-oxides, both electrophilic substitution and nucleophilic displacement of halide from C-4 go more rapidly than in pyridine – explain.
- (m) Describe two important methods for the synthesis of pyridines from precursors which do not contain the ring.
- (n) What compounds would result from the following reagent combinations: (i) $\text{H}_2\text{NCOCH}_2\text{CN}$ (cyanoacetamide) with $\text{MeCOCH}_2\text{COMe}$; (ii) $\text{MeC}(\text{NH}_2)=\text{CHCO}_2\text{Et}$ (ethyl 3-aminocrotonate) with $\text{MeCOCH}_2\text{COMe}$; (iii) $\text{PhCH}=\text{O}$, $\text{MeCOCH}_2\text{COMe}$, and NH_3 ?

More advanced exercises

1. Suggest a structure for the products: (i) $\text{C}_7\text{H}_8\text{N}_2\text{O}_3$ produced by treating 3-ethoxypyridine with f. $\text{HNO}_3/\text{c. H}_2\text{SO}_4$ at 100°C , (ii) $\text{C}_6\text{H}_4\text{BrNO}_2$ produced by reaction of 4-methylpyridine first with $\text{Br}_2/\text{H}_2\text{SO}_4/\text{oleum}$ then with hot KMnO_4 .
2. Deduce a structure for the product $\text{C}_9\text{H}_{15}\text{N}_3$ produced by reacting pyridine with the potassium salt of $\text{Me}_2\text{N}(\text{CH}_2)_2\text{NH}_2$.
3. Deduce structures for the product formed by (i) reacting 2-chloropyridine with (a) hydrazine $\rightarrow \text{C}_5\text{H}_7\text{N}_3$, (b) water $\rightarrow \text{C}_5\text{H}_5\text{NO}$; (ii) 4-nitropyridine heated with water at $60^\circ\text{C} \rightarrow \text{C}_5\text{H}_5\text{NO}$.
4. Deduce structures for the products formed in turn by reacting 4-chloropyridine with (i) sodium methoxide $\rightarrow \text{C}_6\text{H}_7\text{NO}$, A, this with iodomethane $\rightarrow \text{C}_7\text{H}_{10}\text{INO}$, then this heated at $185^\circ\text{C} \rightarrow \text{C}_6\text{H}_7\text{NO}$, isomeric with A.
5. Treatment of 4-bromopyridine with NaNH_2 in NH_3 (liq) gives two products (isomers, $\text{C}_5\text{H}_6\text{N}_2$) but reaction with sodium methoxide gives a single product, $\text{C}_6\text{H}_7\text{NO}$. What are the products and why is there a difference?
6. Write structures for the products to be expected in the following sequences: (i) 4-diisopropylaminocarbonyl pyridine with LDA then with benzophenone, then with hot acid $\rightarrow \text{C}_{19}\text{H}_{13}\text{NO}_2$; (ii) 2-chloropyridine with LDA then iodine $\rightarrow \text{C}_5\text{H}_3\text{ClNI}$; (iii) 3-fluoropyridine with LDA then with acetone $\rightarrow \text{C}_8\text{H}_{10}\text{FNO}$; (iv) 2-bromopyridine with butyllithium at -78°C then chlorotrimethylstannane $\rightarrow \text{C}_8\text{H}_{13}\text{NSn}$.
7. A crystalline solid $\text{C}_9\text{H}_{11}\text{BrN}_2\text{O}_3$ is formed when 2-methyl-5-nitropyridine is reacted with bromoacetone, subsequent treatment with NaHCO_3 affords $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$ – deduce the structures and write out a mechanism.
8. When the salt, $\text{C}_9\text{H}_{13}\text{N}^+ \text{I}^-$ produced by reacting pyridine with 1,4-diiodobutane is then treated with Bu_3SnH in the presence of AIBN, a new salt, $\text{C}_9\text{H}_{12}\text{N}^+ \text{I}^-$ is formed, which had ^1H NMR signals for four aromatic protons. Suggest structures for the two salts and a mechanism of formation of the latter.
9. Deduce a structure for the product, $\text{C}_6\text{H}_{11}\text{NO}_3$, produced by exposing 4-methyl-2-pyridone to the following sequence: (i) irradiation at 310 nm, (ii) $\text{O}_3/\text{MeOH}/-78^\circ\text{C}$ then NaBH_4 .

10. Write structures for the compounds produced at each stage in the following sequence: 4-methylpyridine reacted with $\text{NaNH}_2 \rightarrow \text{C}_6\text{H}_8\text{N}_2$, this then with $\text{NaNO}_2/\text{H}_2\text{SO}_4$ at $0^\circ\text{C} \rightarrow \text{rt} \rightarrow \text{C}_6\text{H}_7\text{NO}$, then this with sodium methoxide and iodomethane $\rightarrow \text{C}_7\text{H}_9\text{NO}$ and finally this with $\text{KOEt}/(\text{CO}_2\text{Et})_2 \rightarrow \text{C}_{11}\text{H}_{13}\text{NO}_4$.
11. Nitration of aniline is not generally possible, yet nitration of 2- and 4-aminopyridines can be achieved easily – why?
12. When 3-hydroxypyridine is reacted with 5-bromopent-1-ene a crystalline salt, $\text{C}_{10}\text{H}_{14}\text{NBrO}$ is formed. Treatment of the salt with mild base gave a dipolar substance $\text{C}_{10}\text{H}_{13}\text{NO}$ which on heating provided a neutral, non-aromatic isomer. Deduce the structures of these compounds.
13. Give an explanation for the relatively easy decarboxylation of pyridine-2-acetic acid; what is the organic product?
14. Suggest a structure for the product, $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ resulting from the interaction of 4-vinylpyridine with diethyl acetamidomalonate ($\text{AcNHCH}(\text{CO}_2\text{Et})_2$) and base.
15. Write structures for the products of reacting (i) 2,3-dimethylpyridine with butyllithium then diphenyldisulfide $\rightarrow \text{C}_{13}\text{H}_{13}\text{NS}$; (ii) 2,3-dimethylpyridine with NBS then with $\text{PhSH} \rightarrow \text{C}_{13}\text{H}_{13}\text{NS}$ isomeric with the product in (i).
16. Write structures for the isomeric compounds $\text{C}_7\text{H}_6\text{N}_2\text{O}$ (formed in a ratio of 4:3) when 3-cyanopyridine methiodide is reacted with alkaline potassium ferricyanide.
17. Predict the sites at which deuterium would be found when 1-butylpyridinium iodide is reduced with NaBD_4 in EtOH forming (mainly) 1-butyl-1,2,5,6-tetrahydropyridine.
18. Deduce structures for the final product, and intermediate, in the following sequence: pyridine with methyl chloroformate and sodium borohydride gave $\text{C}_7\text{H}_9\text{NO}_2$, then this irradiated gave an isomer which had NMR signals for only two alkene protons – what are the compounds?
19. When pyridine *N*-oxide is heated with c. H_2SO_4 and c. HNO_3 a product $\text{C}_5\text{H}_4\text{N}_2\text{O}_3$ is formed; separate reactions of this with PCl_3 then $\text{H}_2/\text{Pd-C}$ produces $\text{C}_5\text{H}_4\text{N}_2\text{O}_2$ and $\text{C}_5\text{H}_6\text{N}_2$ sequentially. What are the three products?
20. Write a structure for the cyclic product, $\text{C}_{18}\text{H}_{21}\text{NO}_4$, from the reaction of ammonia, phenylacetaldehyde ($\text{PhCH}_2\text{CH}=\text{O}$), and two mol equivalents of methyl acetoacetate. How might it be converted into a pyridine?
21. 2,3-Dihydrofuran reacts with acrolein to give $\text{C}_7\text{H}_{10}\text{O}_2$; reaction of this with aq. $\text{H}_2\text{NOH}/\text{HCl}$ gave a pyridine, $\text{C}_7\text{H}_9\text{NO}$: deduce structures.
22. What pyridines or pyridones would be produced from the following combinations of reactants: (a) $\text{H}_2\text{NCOCH}_2\text{CN}$ (cyanoacetamide) with (i) $\text{EtCOCH}_2\text{CO}_2\text{Et}$; (ii) 2-acetylcyclohexanone; (iii) ethyl propiolate; (b) $\text{MeC}(\text{NH}_2)=\text{CHCO}_2\text{Et}$ (ethyl 3-aminocrotonate) with (i) but-3-yne-2-one; (ii) $\text{MeCOC}(\text{CO}_2\text{Et})=\text{CHOEt}$.
23. When the sodium salt of formyl acetone ($\text{MeCOCH}=\text{CHO}^- \text{Na}^+$) is treated with ammonia a pyridine, $\text{C}_8\text{H}_9\text{NO}$ is formed. Deduce a structure and explain the regiochemistry of reaction.

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