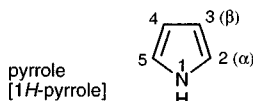
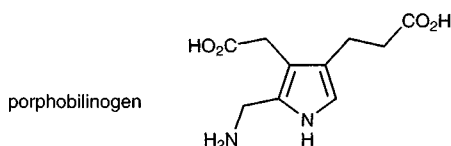


13 Pyrroles: reactions and synthesis

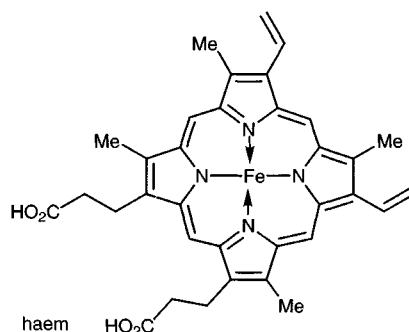
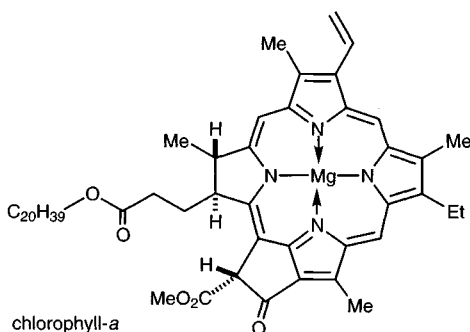


Pyrrole¹ and the simple alkyl pyrroles are colourless liquids, with relatively weak odours rather like that of aniline, which, also like the anilines, darken by autoxidation. Pyrrole itself is readily available commercially, and is manufactured by alumina-catalysed gas-phase interaction of furan and ammonia. Pyrrole was first isolated from coal tar in 1834 and then in 1857 from the pyrolysate of bone by a process which is similar to an early laboratory method for the preparation of pyrrole – the pyrolysis of the ammonium salt of the sugar acid, mucic acid. The word pyrrole is derived from the Greek for red, which refers to the bright red colour which pyrrole imparts to a pinewood shaving moistened with concentrated hydrochloric acid.

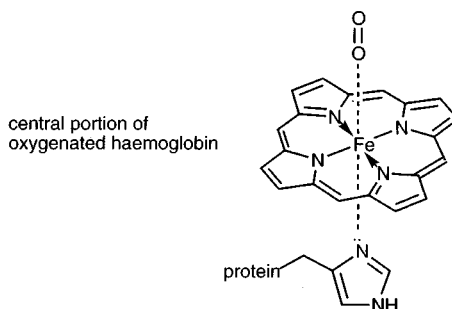
The early impetus for the study of pyrroles came from degradative work relating to the structures of two pigments central to life processes, the blood respiratory pigment haem, and chlorophyll, the green photosynthetic pigment of plants.² Such degradations led to the formation of mixtures of alkylpyrroles. Chlorophyll and haem are synthesised in the living cell from porphobilinogen, the only aromatic pyrrole to play a function – a vitally important function – in fundamental metabolism.^{3,4}



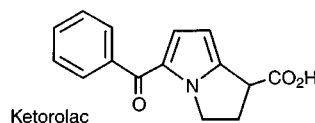
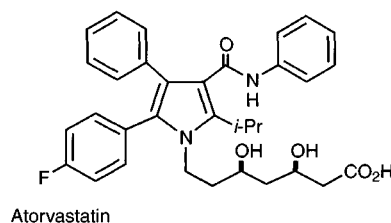
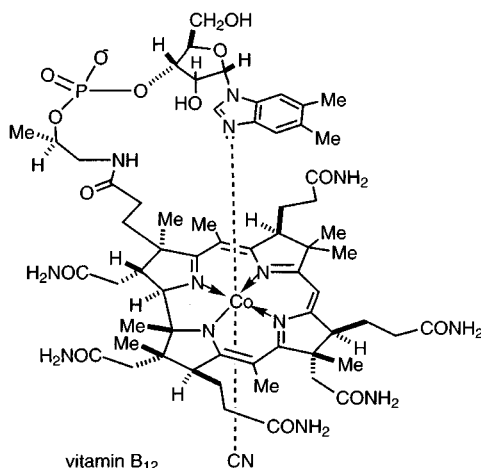
Ultimately, all life on earth depends on the incorporation of atmospheric carbon dioxide into carbohydrates. The energy for this highly endergonic process is sunlight, and the whole is called photosynthesis. The very first step in the complex sequence is the absorption of a photon by pigments, of which the most important in multicellular plants is chlorophyll-*a*. This photonic energy is then used chemically to achieve a crucial carbon-carbon bonding reaction to carbon dioxide, in which ultimately oxygen is liberated. Thus, formation of the by-product of this process, molecular oxygen, allowed the evolution of aerobic organisms of which man is one.



Haemoglobin is the agent which carries oxygen from lung to tissue in the arterial blood-stream in mammals; it is made up of the protein globin associated with a prosthetic group, the pigment haem (also spelt heme). The very close structural similarity of haem with chlorophyll is striking, suggesting a common evolutionary origin. In oxygenated haemoglobin, the iron is six-coordinate iron(II) with an imidazolyl nitrogen of a protein histidine residue as ligand on one side of the plane of the macrocycle, and on the other, molecular oxygen. Haem without the ferrous iron is called protoporphyrin IX and the unsubstituted macrocycle is called porphyrin. Haem is also the active site of the cytochromes,⁵ which are enzymes concerned with electron transfer.



Another porphobilinogen-derived system is vitamin B₁₂,⁶ the structure of which is significantly different, though related to chlorophyll and haem. The parent, unsubstituted macrocycle is called corrin.



Ketorolac, an analgesic and anti-inflammatory agent, is equal to morphine sulfate on a weight-to-weight basis for the alleviation of post-operative pain. Atorvastatin lowers cholesterol levels.

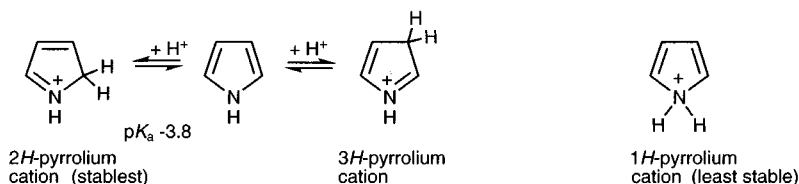
13.1 Reactions with electrophilic reagents⁷

Whereas pyrroles are resistant to nucleophilic addition and substitution, they are very susceptible to attack by electrophilic reagents and react almost exclusively by substitution. Pyrrole itself, *N*- and *C*-monoalkyl and to a lesser extent *C*, *C'*-dialkylpyrroles, are polymerised by strong acids so that many of the electrophilic

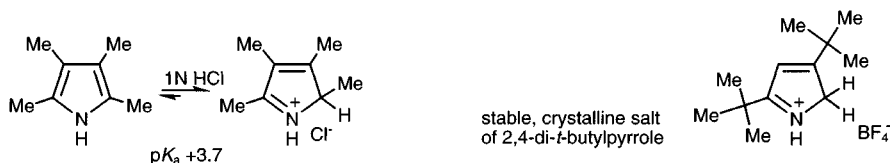
reagents useful in benzenic chemistry cannot be used. However, the presence of an electron-withdrawing substituent such as an ester, prevents polymerisation and allows the use of the strongly acidic, nitrating and sulfonating agents.

13.1.1 Protonation

In solution, reversible proton addition occurs at all positions, being by far the fastest at the nitrogen, and about twice as fast at C-2 as at C-3.⁸ In the gas phase, mild acids like C_4H_9^+ and NH_4^+ protonate pyrrole *only* on carbon and with a larger proton affinity at C-2 than at C-3.⁹ Thermodynamically the stablest cation, the 2*H*-pyrrolium ion, is that formed by protonation at C-2 and observed $\text{p}K_{\text{a}}$ values for pyrroles are for these 2-protonated species. The weak *N*-basicity of pyrroles is the consequence of the absence of mesomeric delocalisation of charge in the 1*H*-pyrrolium cation.

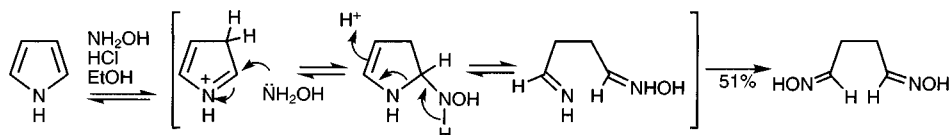


The $\text{p}K_{\text{a}}$ values of a wide range of pyrroles have been determined:¹⁰ pyrrole itself is an extremely weak base with a $\text{p}K_{\text{a}}$ value of -3.8 ; this, as a 0.1 molar solution in normal acid, corresponds to only one protonated molecule to about 5000 unprotonated. However, basicity increases very rapidly with increasing alkyl substitution, so that 2,3,4,5-tetramethylpyrrole, with a $\text{p}K_{\text{a}}$ of $+3.7$, is almost completely protonated on carbon as a 0.1 molar solution in normal acid (*cf.* aniline, which has a $\text{p}K_{\text{a}}$ of $+4.6$). Thus alkyl groups have a striking stabilising effect on cations – isolable, crystalline salts can be obtained from pyrroles carrying *t*-butyl groups.¹¹



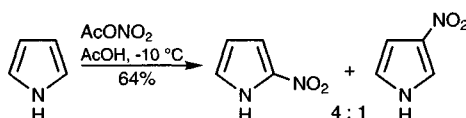
13.1.1. Reactions of protonated pyrroles

The 2*H*- and 3*H*-pyrrolium cations are essentially iminium ions and as such are electrophilic: they play the key role in polymerisation (section 13.1.8) and reduction (section 13.8) of pyrroles in acid. In the reaction of pyrroles with hydroxylamine hydrochloride, which produces ring-opened 1,4-dioximes, it is probably the more reactive 3*H*-pyrrolium cation which is the starter.¹² Primary amines, RNH_2 , can thus be protected, by conversion into 1-*R*-2,5-dimethylpyrroles (section 13.18.1.1), the protecting group being removable by this reaction with hydroxylamine.¹³

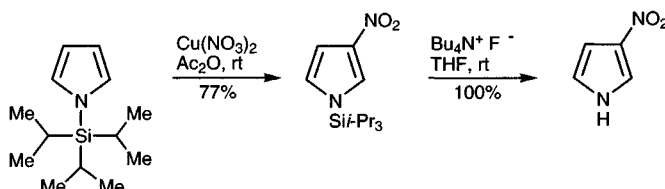


13.1.2 Nitration

Nitrating mixtures suitable for benzenoid compounds cause complete decomposition of pyrrole, but reaction occurs smoothly with acetyl nitrate at low temperature, giving mainly 2-nitropyrrole. This nitrating agent is formed by mixing fuming nitric acid with acetic anhydride to form acetyl nitrate and acetic acid, thus removing the strong mineral acid. In the nitration of pyrrole with this reagent it has been shown that C-2 is 1.3×10^5 and C-3 is 3×10^4 times more reactive than benzene.¹⁴

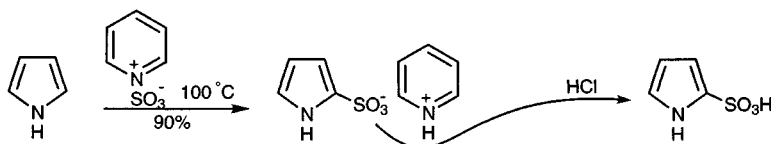


N-Substitution of pyrroles gives rise to increased proportions of β -substitution, even methyl causing the $\beta:\alpha$ ratio to change to 1:3, the much larger *t*-butyl actually reverses the relative positional reactivities, with a $\beta:\alpha$ ratio of 4:1,¹⁵ and the intrinsic α -reactivity can be effectively completely blocked with a very large substituent such as a triisopropylsilyl (TIPS) group, especially useful since it can be subsequently easily removed.¹⁶

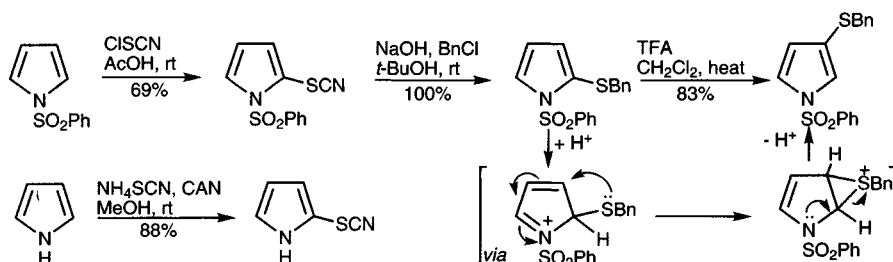


13.1.3 Sulfonation and reactions with other sulfur electrophiles

For sulfonation, a mild reagent of low acidity must be used: the pyridine-sulfur trioxide compound smoothly converts pyrrole into the 2-sulfonate.¹⁷



Sulfonylation of pyrrole¹⁸ and thiocyanation of pyrrole¹⁹ or of 1-phenylsulfonylpyrrole²⁰ also provide means for the electrophilic introduction of sulfur, but at lower oxidation levels.

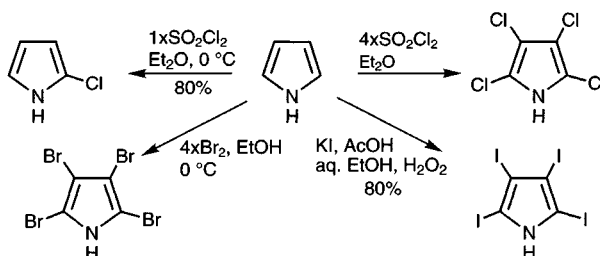


Acid catalyses rearrangement of sulfur substituents from the α -position (kinetically-controlled substitution) to give β -substituted pyrroles^{20,21} (see also section 13.1.5); the scheme above shows a reasonable mechanism for this

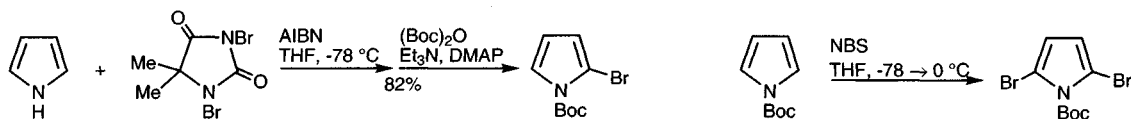
transposition, though work on acid-catalysed rearrangement of arylthioindoles revealed a more complex sequence.²²

13.1.4 Halogenation

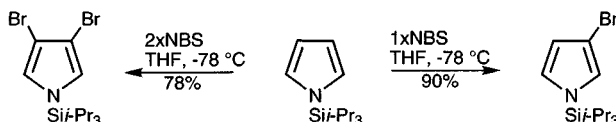
Pyrrole halogenates so readily that unless controlled conditions are used, stable tetrahalopyrroles are the only isolable products.²³ Attempts to monohalogenate simple alkylpyrroles fail, probably because of side-chain halogenation and the generation of extremely reactive pyrrolylalkyl halides (section 13.12).



2-Bromo- and 2-chloropyrroles, unstable compounds, can be prepared by direct halogenation of pyrrole.²⁴ Using 1,3-dibromo-5,5-dimethylhydantoin as brominating agent, both 2-bromo- and 2,5-dibromopyrroles can be obtained, the products stabilised by immediate conversion to their *N*-*t*-butoxycarbonyl derivatives.²⁵ Conversely, bromination of *N*-Boc-pyrrole with *N*-bromosuccinimide gives the 2,5-dibromo derivative.²⁶

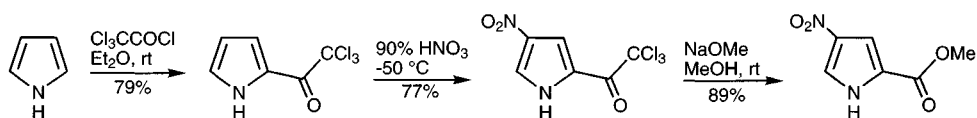


N-Triisopropylsilylpyrrole monobrominates and monoiodinates cleanly and nearly exclusively at C-3, and with two mol equivalents of *N*-bromosuccinimide dibrominates, at C-3 and C-4.^{16,27}

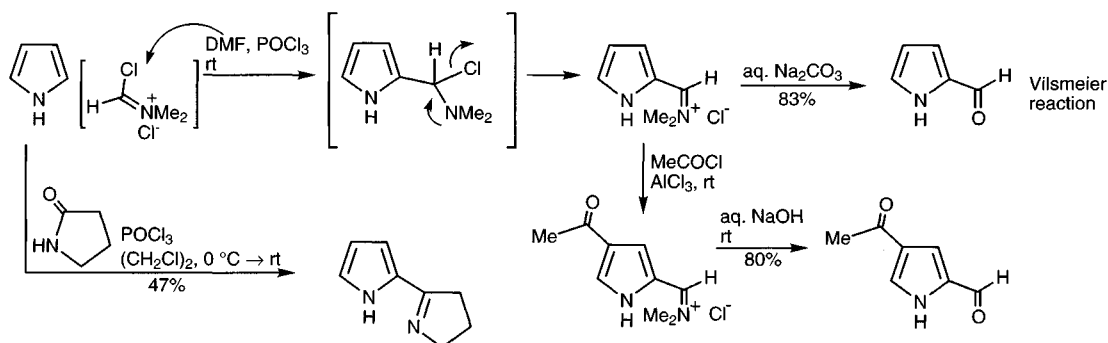


13.1.5 Acylation

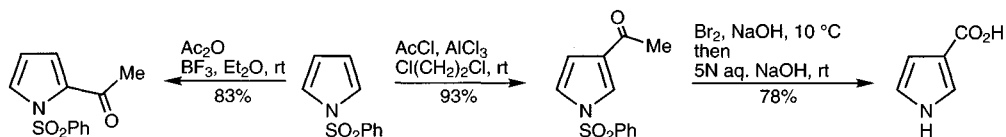
Direct acetylation of pyrrole with acetic anhydride at 200 °C leads to 2-acetylpyrrole as main product together with some 3-acetylpyrrole, but no *N*-acetylpyrrole.²⁸ *N*-Acetylpyrrole can be obtained in high yield by heating pyrrole with *N*-acetylimidazole.²⁹ Alkyl substitution facilitates *C*-acylation, so that 2,3,4-trimethylpyrrole yields the 5-acetyl derivative even on refluxing in acetic acid. The more reactive trifluoroacetic anhydride and trichloroacetyl chloride react with pyrrole efficiently, even at room temperature, to give 2-substituted products, alcoholysis or hydrolysis of which provides a clean route to pyrrole-2-esters or -acids.³⁰ Strong electron-withdrawing (*meta*-directing) substituents at a pyrrole α -position tend to override the intrinsic pyrrole regioselectivity and further substitution takes place mainly at C-4 as illustrated, not the remaining α -position.³¹



Vilsmeier^{32,33} acylation of pyrroles, formylation with dimethylformamide/phosphoryl chloride in particular, is a generally applicable process.³⁴ As shown below, the actual electrophilic species is an *N,N*-dialkyl chloromethyleneiminium cation.³⁵ Here again, the presence of a large pyrrole-*N*-substituent perturbs the intrinsic α -selectivity, formylation of *N*-tritylpyrrole favouring the β -position by 2.8:1 and trifluoroacetylation of this pyrrole giving only the 3-ketone,³⁶ the use of bulky *N*-silyl-substituents allows β -acylation with subsequent removal of the *N*-substituent.³⁷ The electrophilic species produced by the combination of dimethylformamide with pyrophosphoryl chloride is more bulky and leads to increased proportions of β -attack on *N*-substituted pyrroles.³⁸ The iminium salt intermediates under Vilsmeier conditions, before hydrolysis, can be neatly utilised for further Friedel Crafts substitution. The substituent is strongly *meta* directing, thus leading to 2,4-diacylated pyrroles.³⁹ Where a cyclic secondary amide is used, hydrolysis does not take place and the isolated product is a cyclic imine.⁴⁰

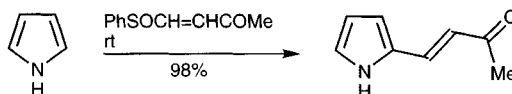


Acylation of 1-phenylsulfonyl pyrrole, with its deactivating *N*-substituent, requires more forcing conditions in the form of a Lewis acid as catalyst, the regioselectivity of attack depending both on choice of catalyst and on the particular acylating agent as illustrated below.⁴¹ The use of weaker Lewis acid catalysts leads to a greater proportion of α -substitution. Regioselectivity of Friedel-Crafts acylations, depending on the strength of the Lewis acids employed, also extends to pyrroles with electron-withdrawing/stabilising groups, like esters, on carbon.⁴² Lewis acid catalysed acylation of 3-acylpyrroles, easily obtained by hydrolysis of 1-phenylsulfonyl-3-acylpyrroles, proceeds smoothly to give 2,4-diacylpyrroles;⁴³ Vilsmeier formylation of methyl pyrrolyl-2-carboxylate takes place at C-5.⁴⁴ Oxidation of 3-acetyl-1-phenylsulfonylpyrrole⁴⁵ or hydrolysis and detritylation of 3-trifluoroacetyl-1-tritylpyrrole are each efficient routes to pyrrole-3-carboxylic acid.



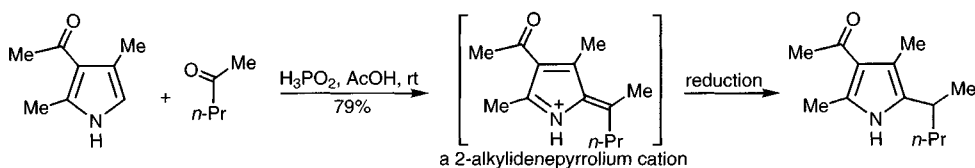
13.1.6 Alkylation

Mono-C-alkylation of pyrroles cannot be achieved by direct reaction with simple alkyl halides either alone or with a Lewis acid catalyst, for example pyrrole does not react with methyl iodide below 100 °C; above about 150 °C a series of reactions occurs leading to a complex mixture made up mostly of polymeric material together with some poly-methylated pyrroles. The more reactive allyl bromide reacts with pyrrole at room temperature, but mixtures of mono- to tetraallylpyrroles together with oligomers and polymers are obtained. Alkylations with conjugated enones carrying a leaving group at the β -position proceed smoothly, usefully producing mono-alkenylated pyrroles.⁴⁶

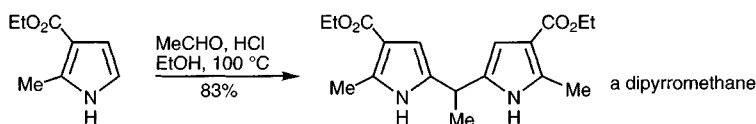


13.1.7 Condensation with aldehydes and ketones

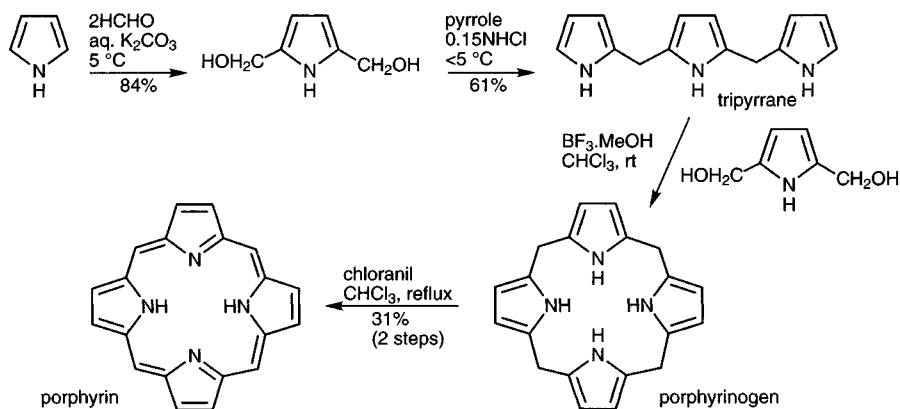
Condensations of pyrroles with aldehydes and ketones occur easily by acid catalysis but the resulting pyrrolylcarbinols cannot usually be isolated, for under the reaction conditions proton-catalysed loss of water produces 2-alkyldenepyrrolium cations which are themselves highly reactive electrophiles. Thus, in the case of pyrrole itself, reaction with aliphatic aldehydes in acid inevitably leads to resins, probably linear polymers. Reductive trapping of these cationic intermediates produces alkylated pyrroles; all free positions react and as the example shows, acyl and alkoxy carbonyl substituents are unaffected.⁴⁷ A mechanistically related process is the clean 4-chloromethylation of pyrroles carrying acyl groups at C-2.⁴⁸



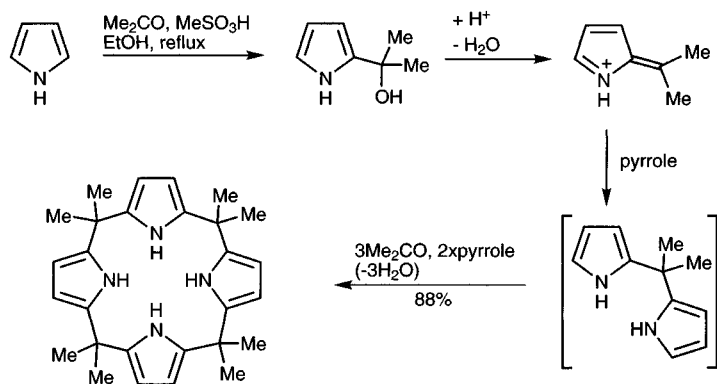
Syntheses of dipyrromethanes have usually involved pyrroles with electron-withdrawing substituents and only one free α -position, the dipyrromethane resulting from attack by a second mol equivalent of the pyrrole on the 2-alkyldenepyrrolium intermediate.⁴⁹



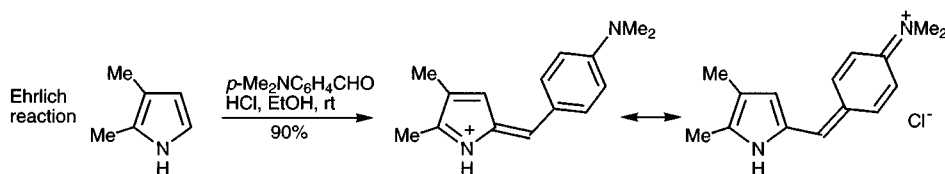
However, conditions have been established for the production and isolation of bis(pyrrol-2-yl)methane itself from treatment of pyrrole with aqueous formalin in acetic acid;⁵⁰ from reaction with formalin in the presence of potassium carbonate a bis-hydroxymethylation product is obtained.⁵¹ This reacts with pyrrole in dilute acid to give tripyrrane and from this, as the scheme shows, reaction with 2,5-bis(hydroxymethyl)pyrrole gives porphyrinogen which can be oxidised to porphyrin.



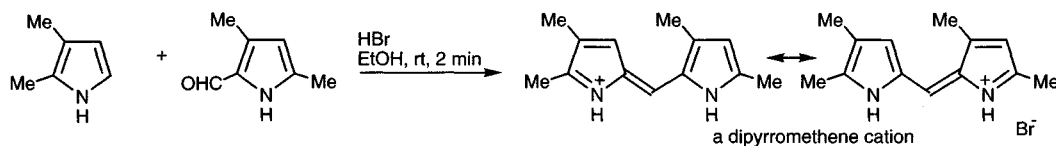
Acetone, reacting in a comparable manner, gives a cyclic tetramer directly and in high yield, perhaps because the geminal methyl groups tend to force the pyrrole rings into a coplanar conformation, greatly increasing the chances of cyclisation of a linear tetrapyrrolic precursor.⁵²



Condensations with aromatic aldehydes carrying appropriate electron-releasing substituents produce cations which are sufficiently stabilised by mesomerism to be isolated. Such cations are coloured: the reaction with *p*-dimethylaminobenzaldehyde is the basis for the classical Ehrlich test, deep red/violet colours being produced by pyrroles (and also by furans and indoles) which have a free nuclear position.

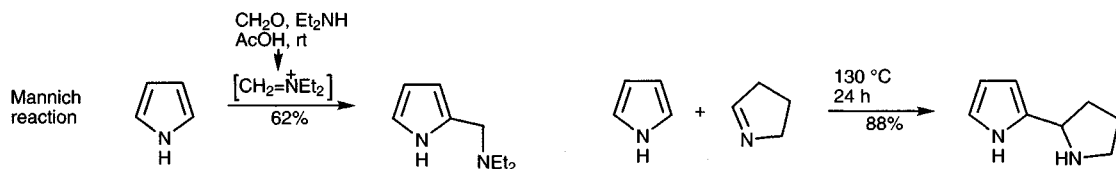


Analogous condensations with a pyrrole aldehyde lead to mesomeric dipyrromethene cations, which play an important part in porphyrin synthesis. Under appropriate conditions one can combine four mol equivalents of pyrrole and four of an aromatic aldehyde to produce a tetra-aryl substituted porphyrin in one pot.⁵³

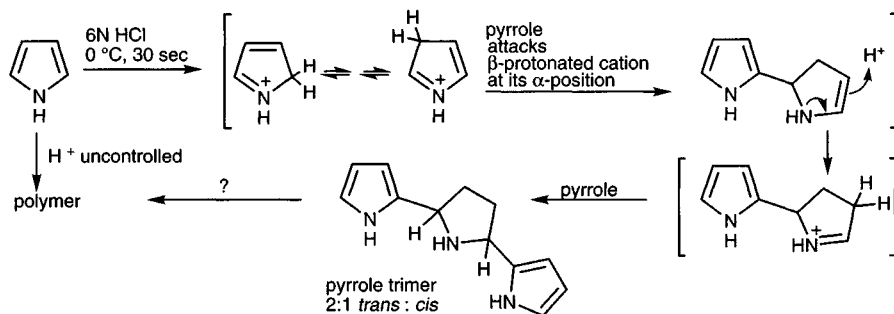


13.1.8 Condensation with imines and iminium ions

The imine and iminium functional groupings are, of course, the nitrogen equivalents of carbonyl and *O*-protonated carbonyl groups, and their reactivity is analogous. The Mannich reaction of pyrrole produces dialkylaminomethyl derivatives, the iminium electrophile being generated *in situ* from formaldehyde, dialkylamine, and acetic acid.⁵⁴ There are only a few examples of the reactions of imines themselves with pyrroles; the condensation of 1-pyrroline with pyrrole as reactant and solvent is one such example.⁵⁵

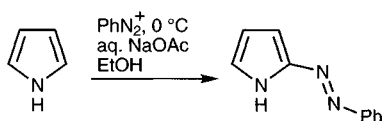


The mineral acid-catalysed polymerisation of pyrrole involves a series of Mannich reactions, but under controlled conditions pyrrole can be converted into an isolable trimer, which is probably an intermediate in the polymerisation. The key to understanding the formation of the observed trimer is that the less stable, therefore more reactive β -protonated pyrrolium cation is the electrophile which initiates the sequence attacking a second mol equivalent of the heterocycle. The dimer, an enamine, is too reactive to be isolable, however the trimer, relatively protected as its salt, reacts further only slowly.⁵⁶



13.1.9 Diazo-coupling⁵⁷

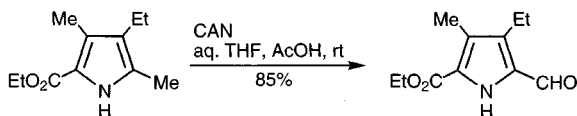
The high reactivity of pyrroles is illustrated by their ready reaction with benzenediazonium salts. Pyrrole itself gives a mono-azo derivative by reacting as a neutral species below pH 8, but by way of the pyrrol anion (section 13.4), and 10⁸ times faster, in solutions above pH 10. In more strongly alkaline conditions 2,5-bisdiazo derivatives are formed.



13.2 Reactions with oxidising agents⁵⁸

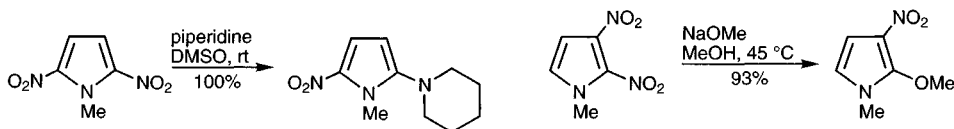
Simple pyrroles are generally easily attacked by strong chemical oxidising agents, frequently with complete breakdown. When the ring does survive, maleimide derivatives are the commonest products, even when there was originally a 2- or 5-alkyl substituent. This kind of oxidative degradation played an important part in early porphyrin structure determination, in which chromium trioxide in aqueous sulfuric acid or fuming nitric acid were usually used as oxidising agents. Hydrogen peroxide is a more selective reagent and can convert pyrrole itself into a tautomeric mixture of pyrrolin-2-ones in good yield (section 13.17.1).

Pyrroles which have a ketone or ester substituent are more resistant to ring degradation and high yielding side-chain oxidation can be achieved using cerium(IV) ammonium nitrate with selectivity for an α -alkyl.⁵⁹

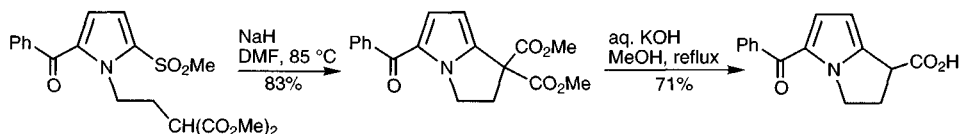


13.3 Reactions with nucleophilic reagents

Pyrrole and its derivatives do not react with nucleophilic reagents by addition or by substitution, except in the same type of situation which allows nucleophilic substitution in benzene chemistry: the two examples below are illustrative.⁶⁰



A key step in a synthesis of Ketorolac involves an intramolecular nucleophilic displacement of a methanesulfonyl group activated by a 5-ketone.⁶¹

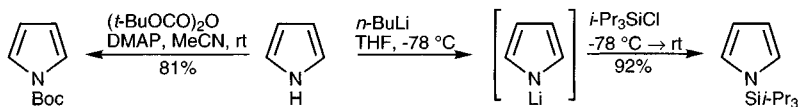


13.4 Reactions with bases

13.4.1 Deprotonation of *N*-hydrogen

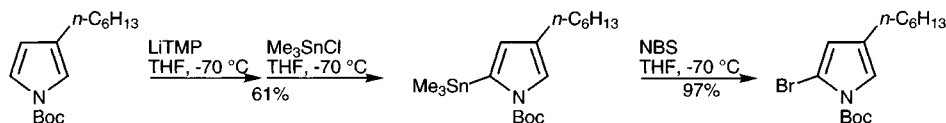
Pyrrole *N*-hydrogen is much more acidic (pK_a 17.5) than that of a comparable saturated amine, say pyrrolidine ($\text{pK}_a \sim 44$), or aniline (pK_a 30.7), and of the same order as that of 2,4-dinitroaniline. Any very strong base will effect complete conversion of an *N*-unsubstituted pyrrole into the corresponding pyrrol anion,

perhaps the most convenient being commercial *n*-butyllithium in hexane exemplified below by the preparation of 1-triisopropylsilylpyrrole, however reactions at nitrogen can proceed *via* smaller, equilibrium concentrations of pyrrol anion as in the formation of 1-chloropyrrole (in solution) by treatment with sodium hypochlorite⁶² or the preparation of 1-*t*-butoxycarbonylpyrrole.⁶³



13.4.2 Deprotonation of C-hydrogen

The C-deprotonation of pyrroles requires the absence of the much more acidic *N*-hydrogen i.e. the presence of an *N*-substituent, either alkyl⁶⁴ or, if required, a removable group like phenylsulfonyl,⁶⁵ carboxylate,⁶⁶ trimethylsilylethoxymethyl,⁶⁷ or *t*-butylaminocarbonyl.⁶⁸ Even in the absence of chelation assistance to lithiation, which is certainly an additional feature in each of the latter examples, metallation proceeds at the α -position. Deprotonation of *N*-methylpyrrole proceeds further, amazingly easily, to a dilithio derivative, either 2,4- or 2,5-dilithio-1-methylpyrrole depending on the exact conditions.⁶⁹ Lithiation of 1-*t*-butoxycarbonyl-3-*n*-hexylpyrrole occurs at C-5, avoiding both steric and electronic discouragement of the alternative C-2 deprotonation.⁷⁰

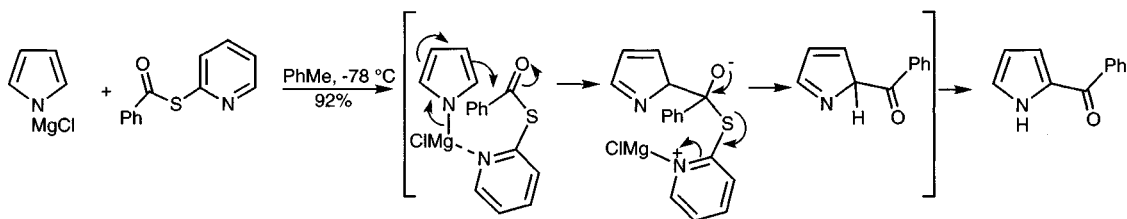


13.5 Reactions of *N*-metallated pyrroles

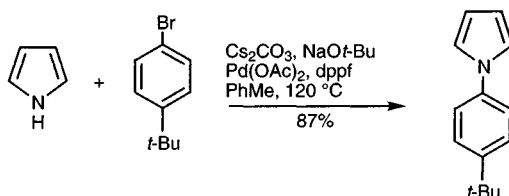
13.5.1 Lithium, sodium, potassium, magnesium, and zinc derivatives

N-Metallated pyrroles can react with electrophiles to give either *N*- or C-substituted pyrroles: generally speaking the more ionic the metal–nitrogen bond and/or the better the solvating power of the solvent, the greater is the percentage of attack at nitrogen.⁷¹ Based on these principles, several methods are available for efficient *N*-alkylation of pyrroles including the use of potassium hydroxide in dimethylsulfoxide,⁷² or in benzene with 18-crown-6,⁷³ thallous ethoxide,⁷⁴ using phase-transfer methodology,⁷⁵ or of course by reaction of the pyrrol anion generated using *n*-butyllithium. The thallium salt acylates⁷⁶ and the potassium salt arylsulfonylates⁷⁷ efficiently on nitrogen. *N*-Acylpyrroles can be reduced to *N*-alkylpyrroles using borane.⁷⁸

Pyrrol Grignard reagents, obtained in solution by treating an *N*-unsubstituted pyrrole with alkyl Grignard, tend to react at carbon with alkylating and acylating agents, but sometimes give mixtures of 2- and 3-substituted products with the former predominating,⁷⁹ *via* neutral, non-aromatic intermediates. Clean α -acylation can be achieved for example with bromacetates⁸⁰ or, as exemplified below, using 2-acylthiopyridines (section 5.10.2.4) as acylating agents.⁸¹



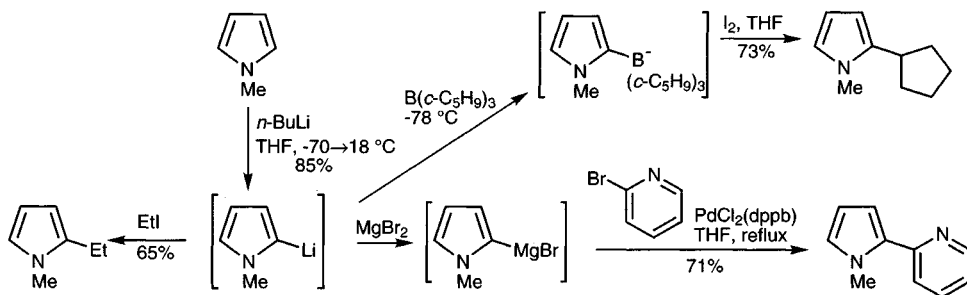
N-Arylation of pyrroles can be achieved by conversion of 1-lithiopyrroles into the corresponding zinc compounds and then reaction with aryl bromides using palladium(0) catalysis⁸² or by direct reaction of the pyrrole with an aryl halide in the presence of base and the palladium catalyst.⁸³



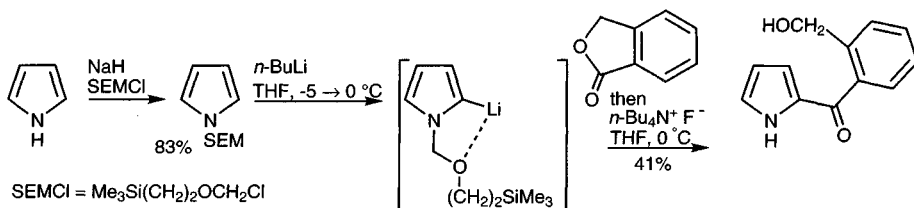
13.6 Reactions of C-metallated pyrroles

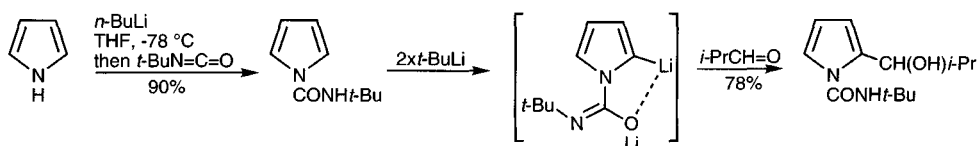
13.6.1 Lithium derivatives

Reactions of the species produced by the lithiation of *N*-substituted pyrroles are efficient for the introduction of groups to the 2-position, either by reaction with electrophiles^{64–68} or by coupling processes based on boron or palladium chemistry.⁸⁴

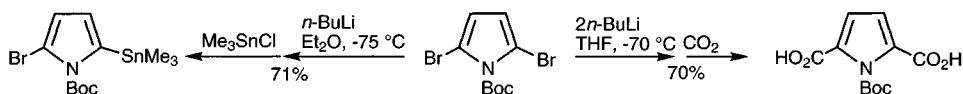


Some examples where removable *N*-blocking groups have been used in the synthesis of 2-substituted pyrroles, *via* lithiation, are shown below.

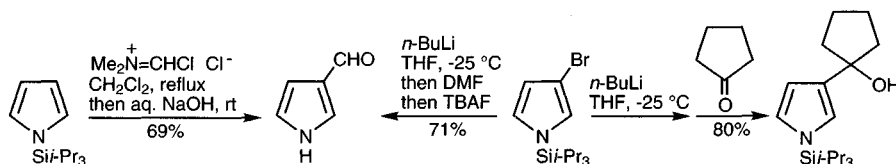




Metal/halogen exchange on 2-bromo-1-*t*-butoxycarbonylpyrrole and on its 2,5-dibromo counterpart proceed normally and the mono- or dilithiated species thus produced react with the usual range of electrophiles, as illustrated below.^{25,26}

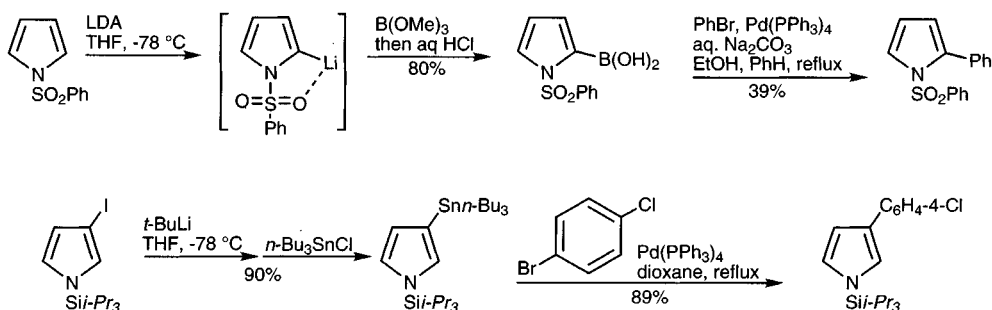


Metal/halogen exchange using 3-bromo-*N*-triisopropylsilylpyrrole very usefully allows the introduction of groups to the pyrrole β -position and can complement direct electrophilic substitution of *N*-triisopropylsilylpyrrole (see sections 13.1.2 and 13.1.4).



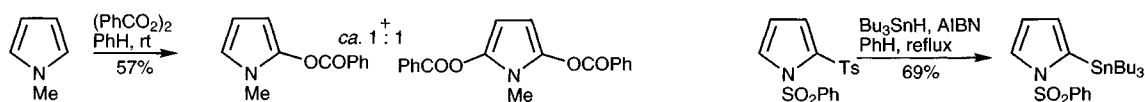
13.6.2 Palladium-catalysed reactions

Pyrrolylstannanes and boronic acids can be synthesised and utilised in the standard manner. The examples below show palladium(0)-catalysed coupling to an aromatic halide.⁸⁵



13.7 Reactions with radical reagents

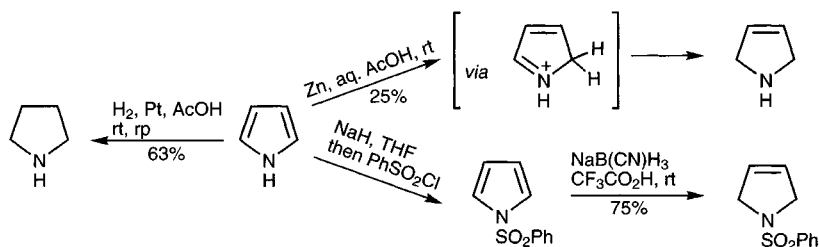
Pyrrole itself tends to give tars under radical conditions, probably by way of initial *N*-hydrogen abstraction, but some *N*-substituted derivatives will undergo preparatively useful arylations, with attack taking place predominantly at an α -position.⁸⁶ More efficient routes to arylpyrroles depend on transition metal-mediated coupling processes (see section 2.7.2.2). *N*-Methylpyrrole is attacked by electrophilic benzoyloxy radicals at its α -positions.⁸⁷



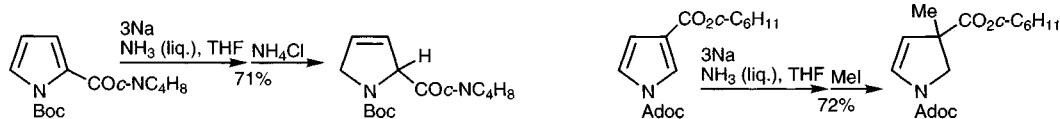
Radical substitution of hydrogen⁸⁸ or of toluenesulfonyl⁸⁹ at an α -position are processes which will no doubt be developed further in future.

13.8 Reactions with reducing agents

Simple pyrroles are not reduced by hydride reducing agents, diborane, or alkali metal/ethanol or /liquid ammonia combinations, but are reduced in acidic media, in which the species under attack is the protonated pyrrole. The products are 2,5-dihydropyrroles, accompanied by some of the pyrrolidine as by-product.⁹⁰ Reduction⁹¹ of pyrroles to pyrrolidines can be effected catalytically over a range of catalysts, is especially easy if the nitrogen carries an electron-withdrawing group, and is not complicated by carbon–heteroatom hydrogenolysis and ring opening as is the case for furans.

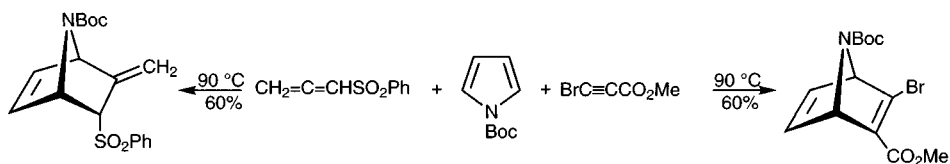


Birch reduction of pyrrole carboxylic esters and tertiary amides gives dihydro derivatives; the presence of an electron-withdrawing group on the nitrogen serves both to remove the acidic *N*-hydrogen and also to reduce the electron density on the ring. Quenching with an alkyl halide produces alkylated dihydropyrroles.⁹²

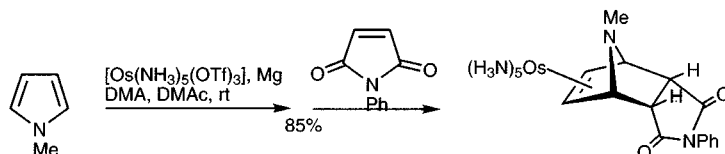


13.9 Electrocyclic reactions (ground state)

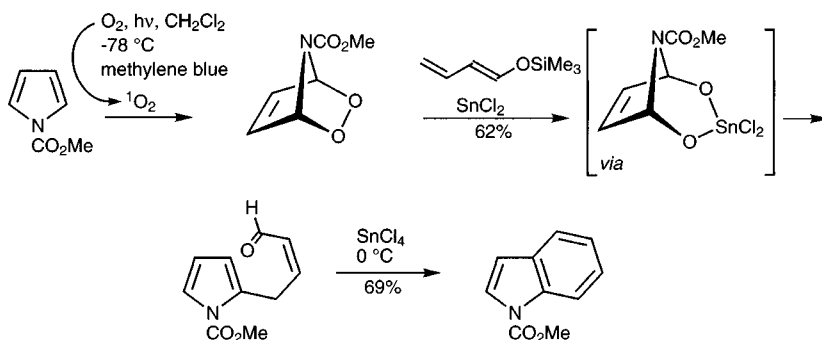
Simple pyrroles do not react as 4π components in cycloadditions – exposure of pyrrole to benzyne for example leads only to 2-phenylpyrrole, in low yield.⁹³ However *N*-substitution, particularly with an electron-withdrawing group, does allow such reactions to occur,⁹⁴ thus adducts with arynes were obtained using 1-trimethylsilylpyrrole.⁹⁵ Whereas pyrrole itself reacts with dimethyl acetylenedicarboxylate only by α -substitution, even at 15 kbar,⁹⁶ 1-acetyl- and 1-alkoxycarbonylpyrroles give cycloadducts,⁹⁷ addition being much accelerated by high pressure or by aluminium chloride catalysis.⁹⁸ The most popular *N*-substituted pyrrole in this context has been its *N*-*t*-butoxycarbonyl (Boc) derivative: the reactions shown below illustrate this.⁹⁹



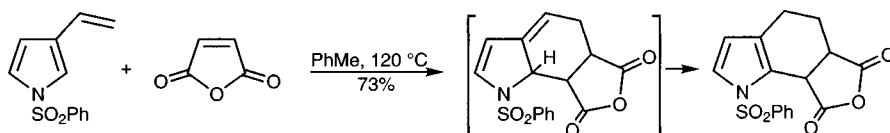
A completely different device to encourage pyrroles to react as dienes is their conversion into osmium complexes;¹⁰⁰ in this way even traditional dienophiles will react under mild conditions as shown below; adducts can be subsequently obtained by oxidative destruction of the metal complex.¹⁰¹



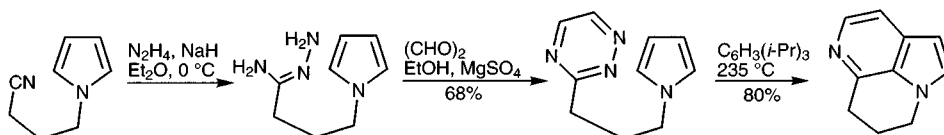
A process which has proved valuable in synthesis is the addition of singlet oxygen to *N*-alkyl- and especially *N*-acylpyrroles¹⁰² producing 2,3-dioxo-7-azabicyclo[2.2.1]-heptanes which react with nucleophiles, such as silyl enol ethers, mediated by tin(II) chloride, generating 2-substituted pyrroles which can be used, as shown, for the synthesis of indoles.



Vinylpyrroles take part in Diels-Alder processes as 4π components;¹⁰³ this reactivity is best controlled by the presence of a phenylsulfonyl group on the pyrrole nitrogen as illustrated below, the presumed initial product easily isomerising in the reaction conditions to reform an aromatic pyrrole.¹⁰⁴

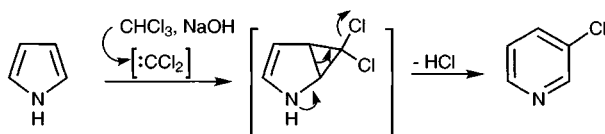


Intermolecular examples of pyrroles serving as 2π components in cycloadditions are very rare, however in an intramolecular sense tricyclic 6-azaindoles have been produced effectively where the 4π component is a 1,2,4-triazene (section 25.2.1).¹⁰⁵

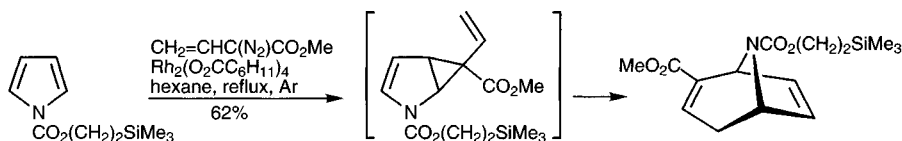


13.10 Reactions with carbenes and carbenoids

The reaction of pyrrole with dichlorocarbene proceeds in part *via* a dichlorocyclopropane intermediate, ring expansion of which leads to 3-chloropyridine.^{106,107} There are relatively few (section 14.1.2) reported isolable cyclopropane-containing adducts from pyrroles – 1-methoxycarbonylpyrrole¹⁰⁸ or *N*-acylpyrroles.¹⁰⁹ 1-Methylpyrrole with ethoxycarbonylcarbene gives only substitution products.¹¹⁰

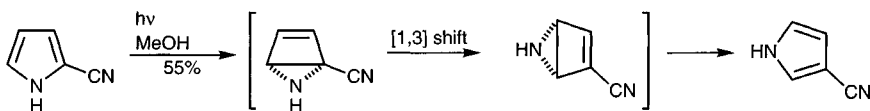


More useful regimes involve the interaction of pyrroles with electron-withdrawing groups on nitrogen with carbenoids generated from diazoalkanes and rhodium(II) compounds; in the example shown below, addition of a vinyl carbene produces a cyclopropanated intermediate which undergoes a Cope rearrangement neatly producing an 8-azabicyclo[3.2.1]octadiene – the ring skeleton of cocaine.¹¹¹



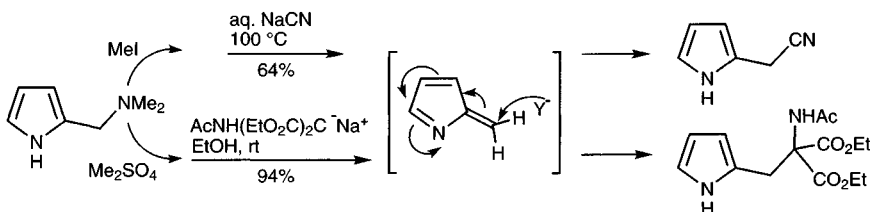
13.11 Photochemical reactions¹¹²

The photo-catalysed rearrangement of 2- to 3-cyanopyrroles is considered to involve a 1,3-shift in an initially-formed bicyclic aziridine.¹¹³



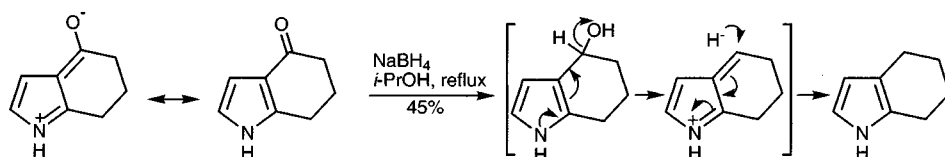
13.12 Pyrrol-C-X compounds

Pyrroles of this type, where X is halogen, alcohol, alkoxy, or amine, and especially protonated alcohol or alkoxy, or quaternised amine, easily lose X generating very reactive electrophilic species. Thus ketones can be reduced to alkane, *via* the loss of oxygen from the initially formed alcohol (cf. section 13.1.7), and quaternary ammonium salts, typified by 2-dimethylaminomethylpyrrole metho-salts, react with nucleophiles by loss of trimethylamine in an elimination/addition sequence of considerable synthetic utility.¹¹⁴

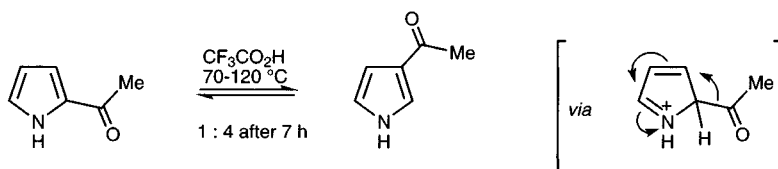


13.13 Pyrrole aldehydes and ketones

These are stable compounds which do not polymerise or autoxidise. For the most part, pyrrole aldehydes and ketones are typical aryl ketones, though less reactive – such ketones can be viewed as vinylogous amides. They can be reduced to alkylpyrroles by the Wolff-Kishner method, or by sodium borohydride *via* elimination from the initial alcoholic product.¹¹⁵ Treatment of acylated 1-phenylsulfonylpyrroles with *t*-butylamine-borane effects conversion to the corresponding alkyl derivatives.¹¹⁶

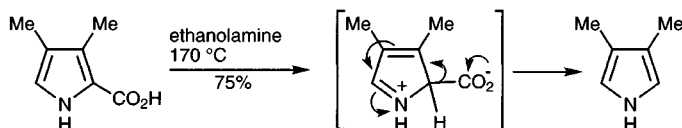


β - and α -Acylpyrroles can be equilibrated one with the other using acid; for *N*-alkyl-*C*-acylpyrroles, the equilibrium lies completely on the side of the 3-isomer.¹¹⁷

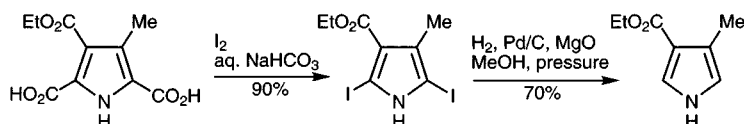


13.14 Pyrrole carboxylic acids

The main feature within this group is the ease with which loss of the carboxyl group occurs. Simply heating¹¹⁸ pyrrole acids causes easy loss of carbon dioxide in what is essentially *ipso* displacement of carbon dioxide by proton.¹¹⁹ This facility is of considerable relevance to pyrrole synthesis since many of the ring-forming routes (e.g. see sections 13.18.1.2 and 13.18.1.3) produce pyrrole esters, in which the ester function may not be required ultimately.

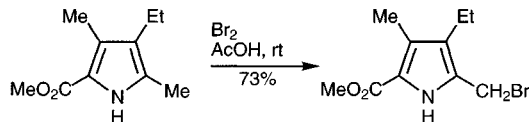
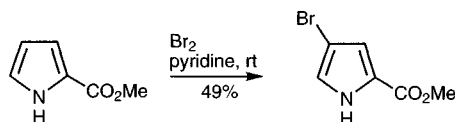


Displacement of carboxyl groups by other electrophiles such as halogens¹²⁰ or under nitrating conditions, or with aryl diazonium cations occurs more readily than at a carbon carrying hydrogen.



13.15 Pyrrole carboxylic acid esters

The electrophilic substitution of these stable compounds has been much studied; the *meta*-directing effect of the ester overcomes the normally dominant tendency for α -substitution.¹²¹



An ester group can also activate side-chain alkyl for halogenation, and such pyrrolylalkyl halides have been used extensively in synthesis.¹²² Cerium(IV) triflate in methanol can be used for the analogous introduction of methoxide onto an alkyl side chain.¹²³

The rates of alkaline hydrolysis of α - and β -esters are markedly different, the former being faster than the latter, possibly because of stabilisation of the intermediate by intramolecular hydrogen bonding involving the ring hetero-atom.¹²⁴

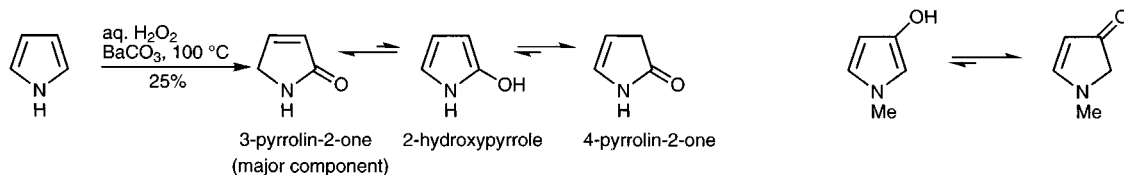
13.16 Halopyrroles

Simple 2-halopyrroles are very unstable compounds whereas 3-halopyrroles are relatively stable, as indeed are 2-halopyrrole ketones and esters. Chemical manipulation of halopyrroles is best achieved with an electron-withdrawing substituent on nitrogen. Pyrrole halides have typical aryl halide reactivity being inert to nucleophilic displacement but undergoing exchange with *n*-butyllithium and palladium-catalysed couplings.¹²⁵ Pyrrole halides undergo catalytic hydrogenolysis, which has allowed the use of halide as a blocking substituent.

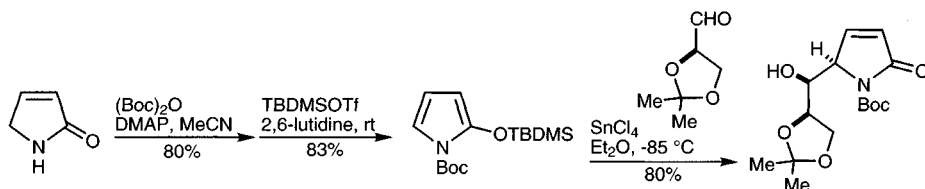
13.17 Oxy- and aminopyrroles

13.17.1 2-Oxypyrroles

2-Oxypyrroles exist in the hydroxyl form, if at all, only as a minor component of the tautomeric mixture which favours 3-pyrrolin-2-one over 4-pyrrolin-2-one by 9:1.¹²⁶



After *N*-protection, silylation produces 2-silyloxypyrroles which react with aldehydes to give substituted 3-pyrrolin-2-ones.¹²⁷

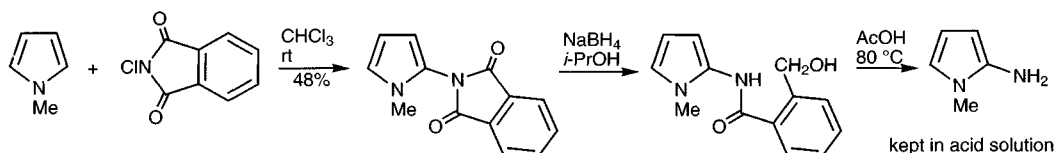


13.17.2 3-Oxypyrroles

3-Oxypyrroles exist largely in the carbonyl form, unless flanked by an ester group at C-2 which favours the hydroxyl tautomer by intramolecular hydrogen bonding.¹²⁸

13.17.3 Aminopyrroles

Aminopyrroles have been very little studied because they are relatively unstable and difficult to prepare.¹²⁹ Simple 2-aminopyrroles can be prepared and stored in acidic solution.¹³⁰

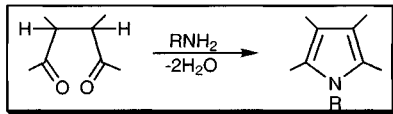


13.18 Synthesis of pyrroles^{7,131}

13.18.1 Ring synthesis

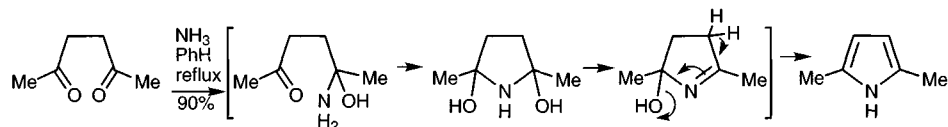
13.18.1.1 From 1,4-dicarbonyl compounds and ammonia or primary amines¹³²

1,4-Dicarbonyl compounds react with ammonia or primary amines to give pyrroles.

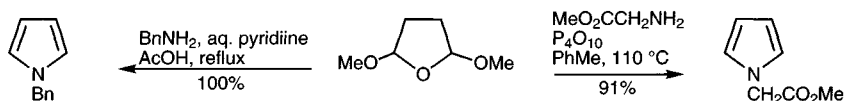


Paal-Knorr synthesis¹³³

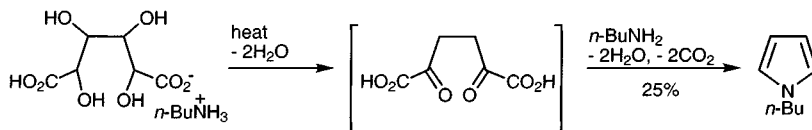
Pyrroles are formed by the reaction of ammonia or a primary amine with a 1,4-dicarbonyl compound¹³⁴ (see also 15.14.1.1). An alternative to the use of ammonia for the synthesis of *N*-unsubstituted pyrroles by this method employs hexamethyldisilazide with alumina.¹³⁵ Successive nucleophilic additions of the amine nitrogen to the two carbonyl carbon atoms and the loss of two mol equivalents of water represent the net course of the synthesis; a reasonable sequence¹³⁶ for this is shown below using the synthesis of 2,5-dimethylpyrrole¹³⁷ as an example.



The best synthon for unstable succindialdehyde, for the ring synthesis of *C*-unsubstituted pyrroles, is 2,5-dimethoxytetrahydrofuran (section 15.1.4),¹³⁸ or 1,4-dichloro-1,4-dimethoxybutane obtainable from it.¹³⁹ 2,5-Dimethoxytetrahydrofuran will react with aliphatic and aromatic amines, amino esters, arylsulfonamides, trimethylsilylethoxycarbonylhydrazine,¹⁴⁰ or primary amides to give the corresponding *N*-substituted pyrroles.¹⁴¹

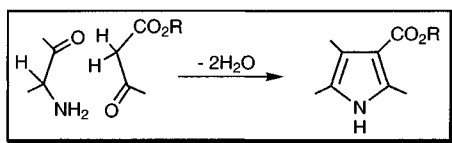


A still useful synthesis of *N*-substituted pyrroles, which consists of dry distillation of the alkylammonium salt of mucic or saccharic acid,¹⁴² probably also proceeds by way of a 1,4-dicarbonyl intermediate. The overall process involves loss of four mol equivalents of water and two of carbon dioxide, and may proceed as shown.



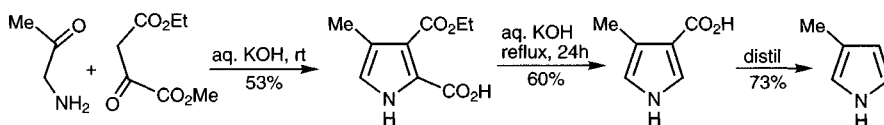
13.18.1.2 From α -aminocarbonyl compounds and activated ketones

α -Aminoketones react with carbonyl compounds which have an α -methylene grouping, preferably further activated, for example by ester, as in the illustration.

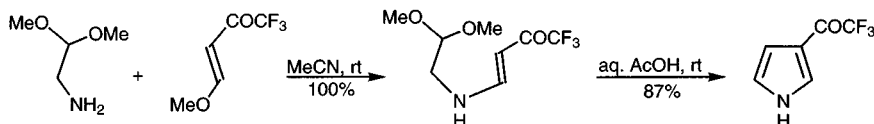


Knorr synthesis

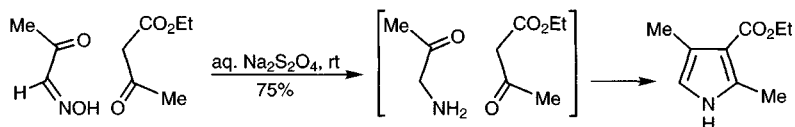
This widely used general approach to pyrroles, utilizes two components: one, the α -aminocarbonyl component, supplies the nitrogen and C-2 and C-3, and the second component supplies C-4 and C-5 and must possess a methylene group α to carbonyl. The Knorr synthesis works well only if the methylene group of the second component is further activated (e.g. as in acetoacetic ester) to enable the desired condensation leading to pyrrole to compete effectively with the self-condensation of the α -aminocarbonyl component. The synthesis of 4-methylpyrrole-3-carboxylic acid and therefrom, 3-methylpyrrole illustrates the process.



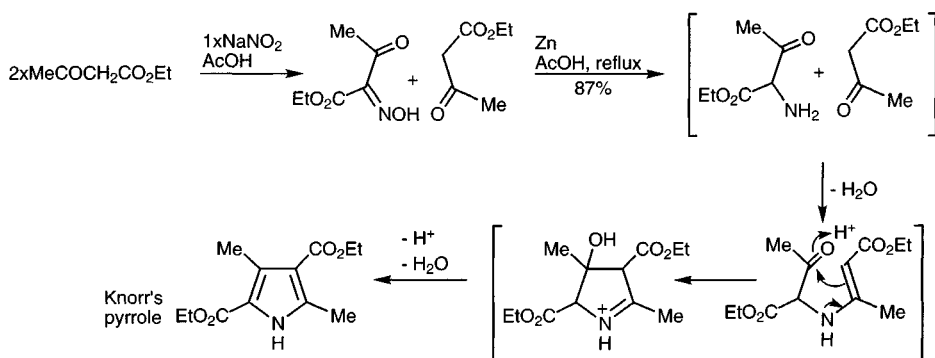
Since free α -aminocarbonyl compounds self-condense very readily producing dihydropyrazines (section 11.13.3.1), they have traditionally been prepared and used in the form of their salts, to be liberated for reaction by the base present in the reaction mixture. Alternatively, carbonyl-protected amines, such as aminoacetal ($\text{H}_2\text{NCH}_2\text{CH}(\text{OEt})_2$), have been used, in this case with the enol ether of a 1,3-diketone as synthon for the activated carbonyl component.¹⁴³



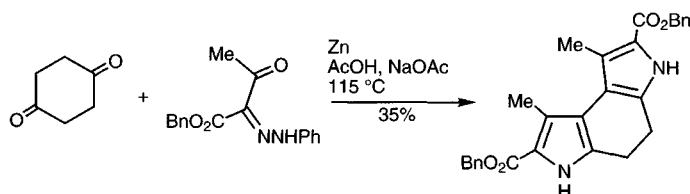
A way of avoiding the difficulty of handling α -aminocarbonyl compounds is to prepare them in the presence of the second component, with which they are to react. Zinc–acetic acid or sodium dithionite¹⁴⁴ can be used to reduce oximino groups to amino while leaving ketone and ester groups untouched.



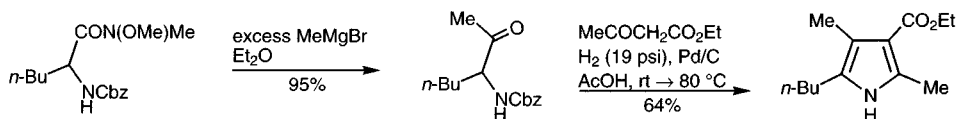
In the classical synthesis, which gives this route its name, the α -aminocarbonyl component is simply an amino-derivative of the other carbonyl component, and it is even possible to generate the oximino precursor of the amine *in situ*.¹⁴⁵



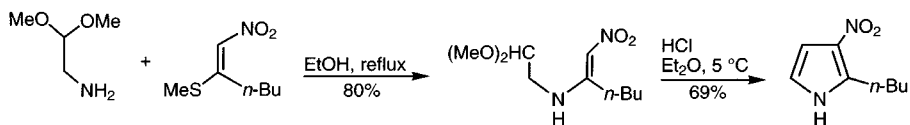
It is believed that in the mechanism, shown for Knorr's pyrrole, an N–C-2 bond is the first formed, which implies that the nitrogen becomes attached to the more electrophilic of the two carbonyl groups of the other component. Similarly, the C-3–C-4 bond is made to the more electrophilic carbonyl group of the original α -aminocarbonyl component, where there is a choice. There are many elegant examples of the use of this approach; an interesting example in which two pyrrole rings are formed using a phenylhydrazone as precursor of the α -aminocarbonyl component is shown below.¹⁴⁶



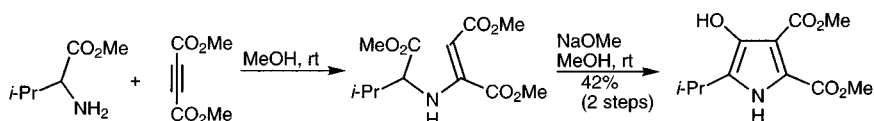
Modern alternatives for the assembly of the α -aminocarbonyl component include the reaction of a 2-bromoketone with sodium diformamide producing an α -formamido-ketone,¹⁴⁷ and the reaction of a Weinreb amide of an *N*-protected α -amino acid with a Grignard reagent, then release of the *N*-protection in the presence of the second component, as illustrated below.¹⁴⁸ Hydride reduction of the Weinreb amide of an *N*-protected α -amino acid gives *N*-protected α -amino-aldehydes for use in this approach.¹⁴⁹



Bis(methylthio)nitroethene reacts with organocuprates, aryl or alkyl groups displacing one methylthio group. These products react with aminoacetal, as the α -aminocarbonyl synthon, to give intermediates which ring close to 2-substituted-3-nitropyrroles.¹⁵⁰

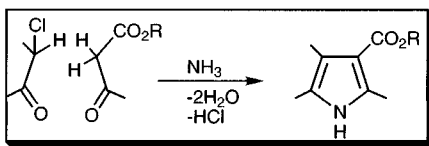


Finally in this category, the enamines produced by addition of an α -amino ester to dimethyl acetylenedicarboxylate form 3-hydroxypyrroles by Claisen-type ring closure.¹⁵¹



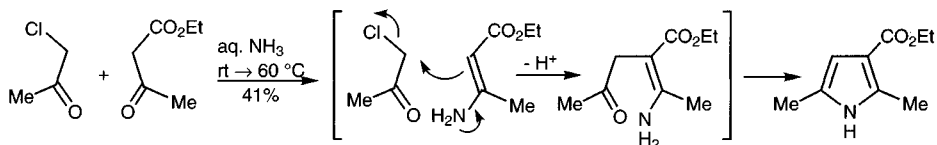
13.18.1.3 From α -halocarbonyl compounds

An alternative strategy for combining a pair of two-carbon units employs an α -halocarbonyl compound, a β -keto-ester, and ammonia.



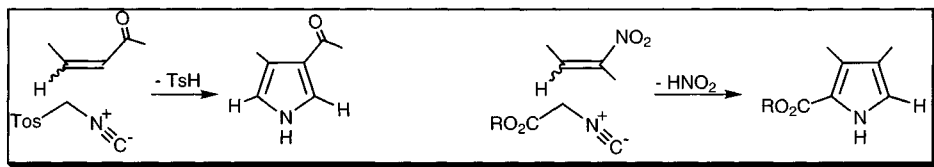
Hantzsch synthesis

In this modification of the Feist-Benary synthesis of furans (section 15.14.1.4), ammonia or a primary amine, is incorporated. The pyrrole is probably formed by initial interaction of ammonia (or a primary amine) with the β -ketoester, the resulting β -aminocrotonate then being alkylated by the halo-ketone or -aldehyde.¹⁵²



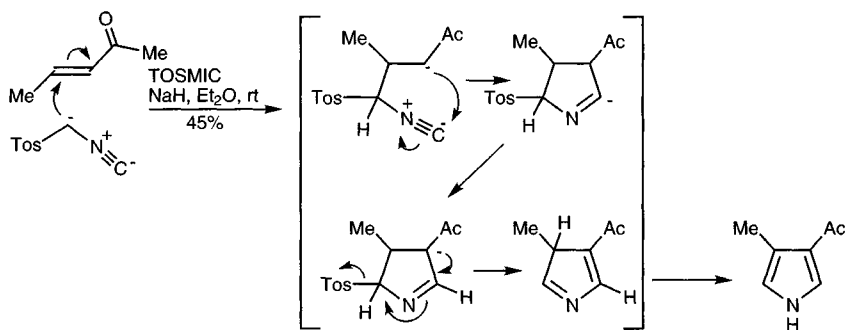
13.18.1.4 From tosylmethylisocyanide and α,β -unsaturated esters or ketones and from isocyano acetates and α,β -unsaturated nitro compounds

Tosylmethyl isocyanide anion reacts with α,β -unsaturated esters, ketones, or sulfones with loss of toluenesulfonate. Isocyanoacetates react with α,β -unsaturated nitro compounds with loss of nitrous acid.



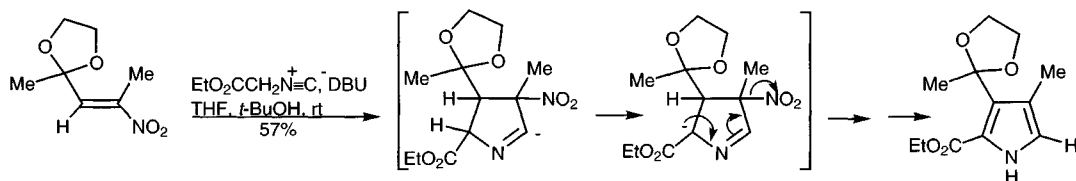
The van Leusen synthesis

The stabilised anion of tosylmethyl isocyanide (TosMIC) (or of benzotriazol-1-ylmethyl isocyanide – BetMIC¹⁵³) adds in Michael fashion to unsaturated ketones and esters, with subsequent closure onto isocyanide carbon generating the ring. Proton transfer, then elimination of toluenesulfonate generates a 3-*H*-pyrrole which tautomerises to the aromatic system which is unsubstituted at both C-2 and C-5.¹⁵⁴ Addition of the TosMIC anion to unsaturated nitro compounds gives rise to 2,5-unsubstituted-3-nitropyrroles.¹⁵⁵

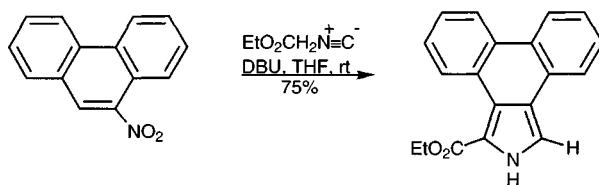


The Barton-Zard synthesis

In this approach, conjugate addition of the anion from an isocyanoacetate to an α,β -unsaturated nitro compound with eventual loss of nitrous acid, produces 5-unsubstituted pyrrole-2-esters.¹⁵⁶ This route has become very popular; the example¹⁵⁷ below shows a mechanistic sequence which can be seen to parallel that in the van Leusen synthesis. The most useful route to the α,β -unsaturated nitro compound involves the base-catalysed condensation of an aldehyde with a nitroalkane giving an α -hydroxy nitroalkane; it can alternatively be generated *in situ*, in the presence of the isonitrile, using diazabicycloundecane as base on the *O*-acetate of the α -hydroxy nitroalkane¹⁵⁸ (for an example see section 13.18.3.3).



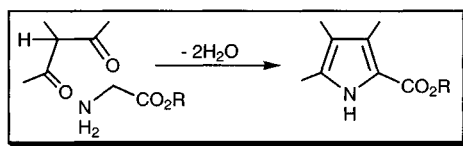
The process works even when the unsaturated nitro unit is a component of a polycyclic aromatic compound, as shown in the example below.¹⁵⁹



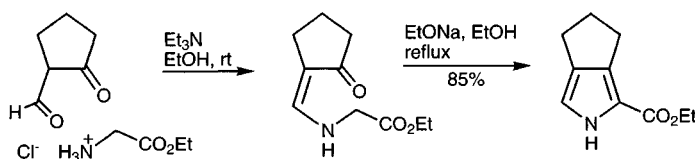
Extrapolations of this approach continue to enlarge its usefulness – α,β -unsaturated sulfones, which can be easily accessed, for example from alkenes by addition of phenylsulfonyl chloride, *S*-oxidation and then elimination of hydrogen chloride, have been reacted with isocyanacetates and isocyanonitriles to give pyrroles.¹⁶⁰

13.18.1.5 From 1,3-dicarbonyl compounds and glycine esters¹⁶¹

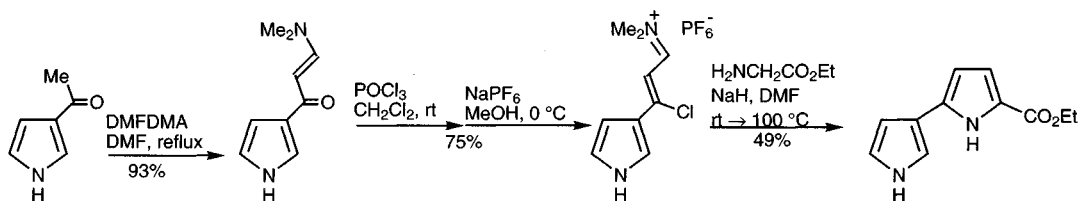
1,3-Dicarbonyl compounds, or oxidation level equivalents, react with glycine esters to give pyrrole-2-esters.



A variety of methods have been employed to effect the condensation between a 1,3-diketone and a glycine ester; perhaps the simplest is condensation using triethylamine as base to produce an intermediate enamino-ketone, this then ring closed in a second step.

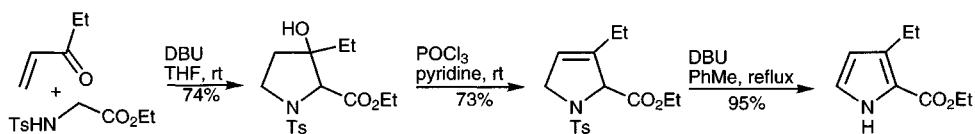


γ -Chloroiminium salts produced as shown below¹⁶² are excellent synthons for 1,3-dicarbonyl compounds and can be used in the context of reaction with glycinate.



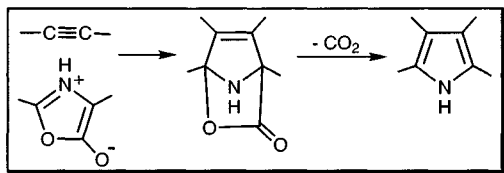
The Kenner synthesis

A related process uses a lower oxidation-level C_3 -component – an α,β -unsaturated ketone – and provides the means for achieving pyrrole oxidation level in having a tosyl group on glycine nitrogen, eliminated as toluenesulfinate later.^{163,164}

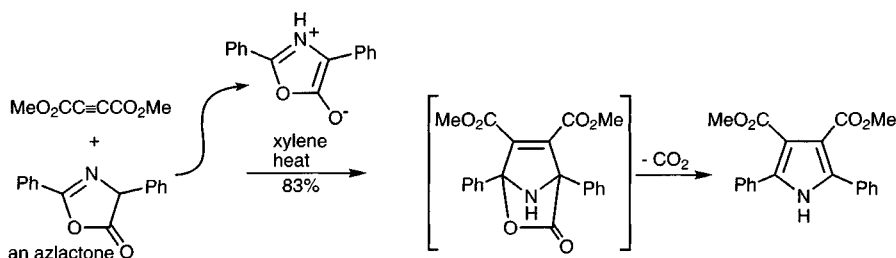


13.18.1.6 From alkynes and oxido-oxazoliums¹⁶⁵

Dipolar cycloaddition of alkynes to mesoionic oxido-oxazoliums, followed by expulsion of carbon dioxide, yields pyrroles.



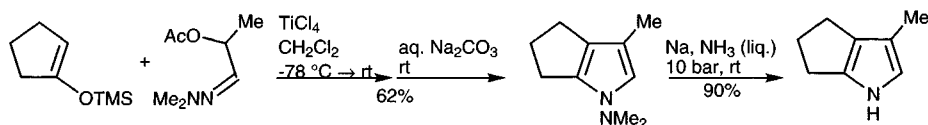
Dehydration of *N*-acylamino acids generates azlactones; these are in equilibrium with mesoionic species which can be trapped by reaction with alkynes, final loss of carbon dioxide giving the aromatic pyrrole.



13.18.2 Some new general methods

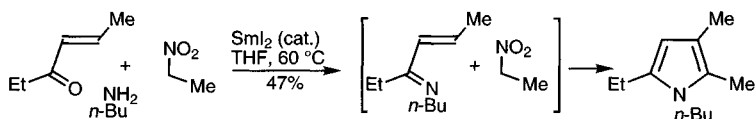
13.18.2.1 From α -acetoxy dimethylhydrazones and silyl enol ethers

Under the influence of titanium(IV) chloride, dimethylhydrazones of α -acetoxyaldehydes combine with silyl enol ethers producing 1-dimethylamino pyrroles; subsequent reduction of the *N*–*N* bond produces *N*-hydrogen pyrroles.¹⁶⁶



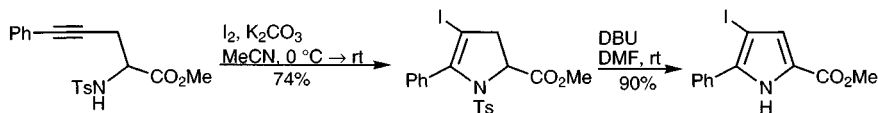
13.18.2.2 From aldehydes, amines and nitroalkanes

This route depends on the samarium-catalysed aldol-type condensation of nitroalkanes with imines generated from amines and aldehydes, all three components being incorporated into the reaction mixture at the start.¹⁶⁷



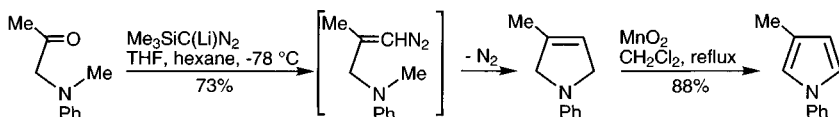
13.18.2.3 From 4-aminoalkynes and from 4-aminoalkynones

The 5 *endo dig* closure of 4-tosylaminoalkynes generates dihydropyrroles, the elimination of toluenesulfinate from which produces the aromatic system.¹⁶⁸



13.18.2.4 From 2-aminoketones through alkylidene carbenes

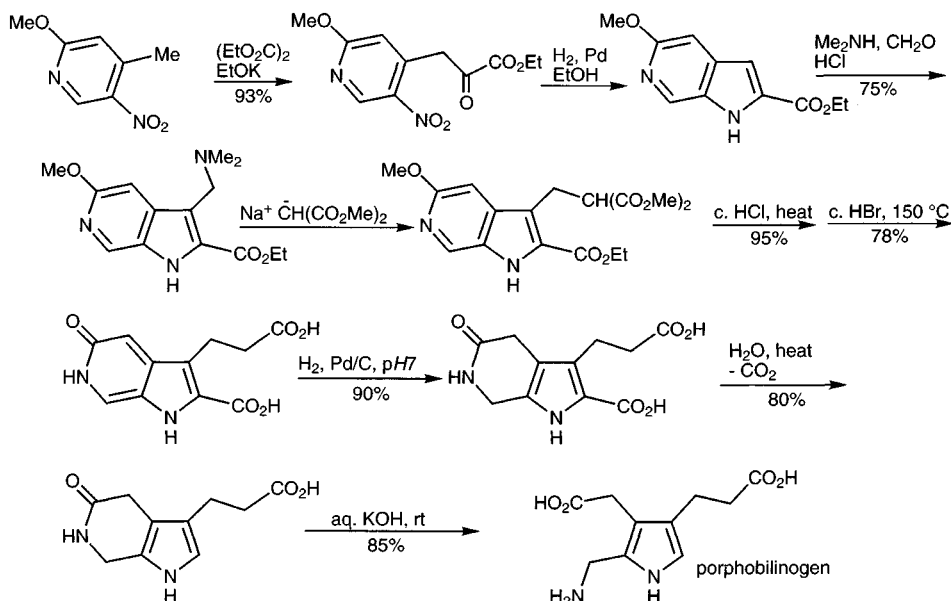
The conversion of the carbonyl group of an *N,N*-disubstituted 2-aminoketone to an alkylidene carbene leads to insertion of the carbene into one of the nitrogen substituents and the formation of a five-membered ring at the oxidation level of a dihydropyrrole. Manganese dioxide readily converts such species (or indeed pyrrolidines¹⁶⁹) into the aromatic pyrroles.¹⁷⁰



13.18.3 Some notable syntheses of pyrroles

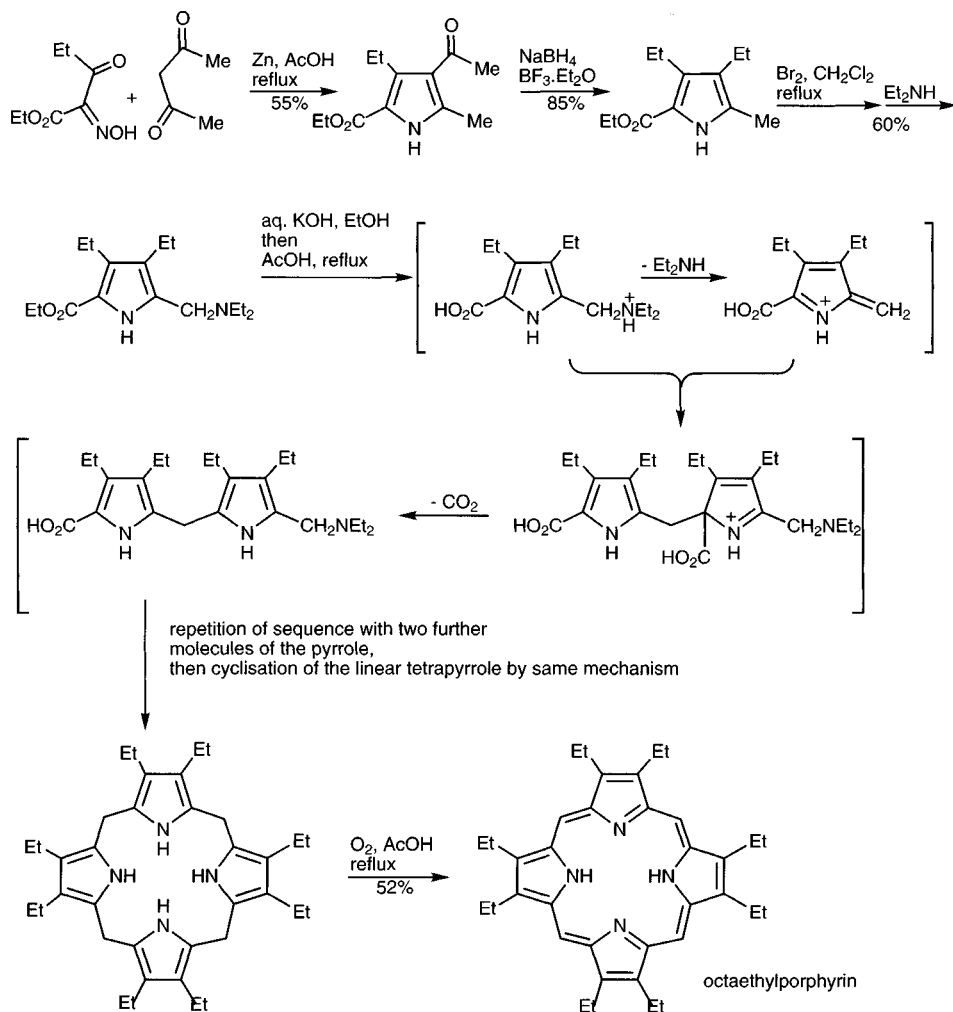
13.18.3.1 Porphobilinogen

The synthesis of porphobilinogen¹⁷¹ from 2-methoxy-4-methyl-5-nitropyridine (section 5.15.2.3) is an example of a Reissert-type synthesis (section 17.16.1.2) affording in this case a 6-azaindole as an intermediate.

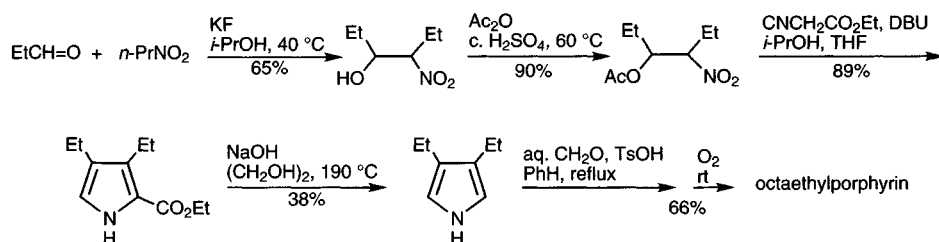


13.18.3.2 *Octaethylporphyrin*¹⁷²

This synthesis of this widely used model compound uses a Knorr sequence as the first step; the oligomerisation steps and the final cyclisation rest on side-chain reactivity of pyrrolylammonium salts (section 13.12) and the easy decarboxylation of pyrrole acids (section 13.14).

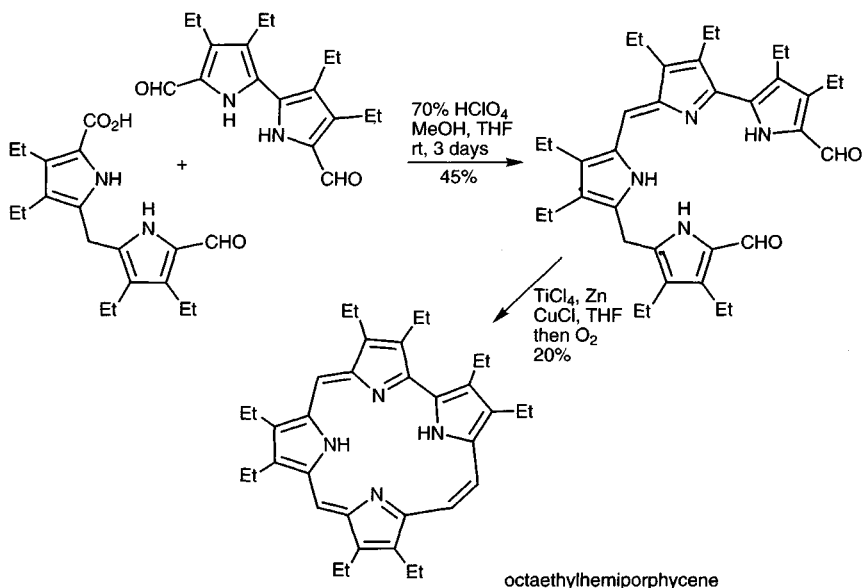
13.18.3.3 *Octaethylporphyrin*¹⁷³

In this alternative synthesis of octaethylporphyrin, a Barton-Zard sequence leads to a pyrrole 2-ester which is hydrolysed and decarboxylated.



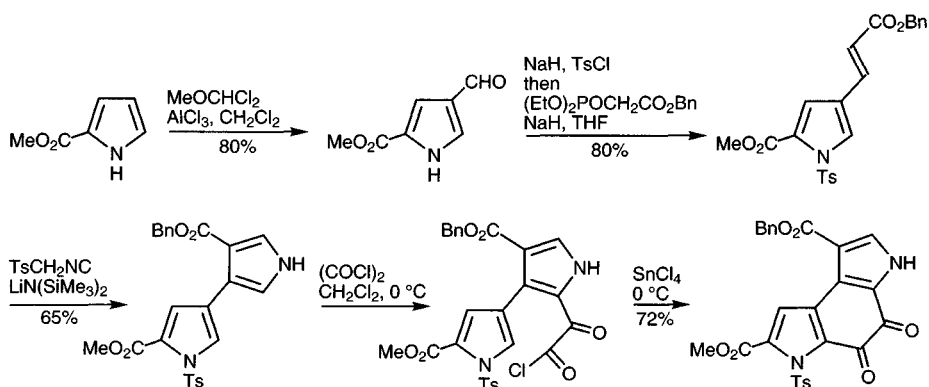
13.18.3.4 Octaethylhemiporphycene^{174,175}

All of the non-natural isomers (porphycenes) of the porphyrin ring system comprising permutations of four pyrrole rings, four methines, and having an 18 π -electron main conjugation pathway, have been synthesised. The scheme below shows the use of a MacDonald condensation¹⁷⁶ to assemble a tetrapyrrole and then the use of the McMurray reaction to construct the macrocycle.¹⁷⁷



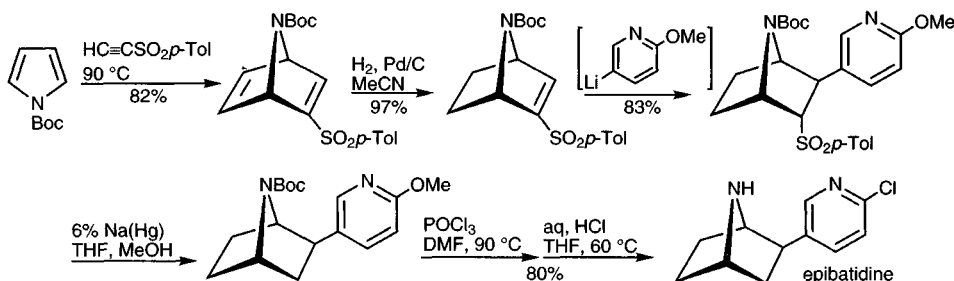
13.18.3.5 Benzo[1,2-*b*:4,3-*b'*]dipyrroles

Several ingenious approaches¹⁷⁸ have been described for the elaboration of the pyrrolo-indole unit (strictly a benzo[1,2-*b*:4,3-*b'*]dipyrrole) three of which are present in the potent anti-tumour agent CC-1065;¹⁷⁹ the approach shown here employs the method described in section 13.18.1.4 for the construction of the pyrrole nuclei.¹⁸⁰



13.18.3.6 Epibatidine¹⁸¹

Cycloaddition of *N*-Boc-pyrrole with ethynyl *p*-tolyl sulfone generated the bicyclic system; selective reduction of a double bond then conjugate addition of 5-lithio-2-methoxypyridine produced an intermediate, with the required stereochemistry, requiring only straightforward manipulations to produce epibatidine.



Exercises for chapter 13

Straightforward revision exercises (consult chapters 12 and 13)

- Why does pyrrole not form salts by protonation on nitrogen?
- Starting from pyrrole, how would one prepare, cleanly, 2-bromopyrrole, 3-bromopyrrole, 2-formylpyrrole, 3-nitropyrrole? (more than one step necessary in some cases)
- What would be the structures of the products from the following reactions: (i) pyrrole with CH_2O /pyrrolidine/ AcOH ; (ii) pyrrole with NaH/MeI ; (iii) 1-tri-*i*-propylsilylpyrrole with LDA then $\text{Me}_3\text{CCH}=\text{O}$?
- How could one produce a 3-lithiated pyrrole?
- Give two ways in which pyrrole could be encouraged to react as a diene in Diels-Alder type processes.
- How could pyrrole be converted into pyrrol-2-yl- CH_2CN in two steps?
- By what mechanism are pyrrole carboxylic acids readily decarboxylated on heating?
- Which ring synthesis method and what reactants would be appropriate for the synthesis of a pyrrole, unsubstituted on carbon but carrying $\text{CH}(\text{Me})(\text{CO}_2\text{Me})$ on nitrogen?

- (j) With what compound would ethyl acetoacetate ($\text{MeCOCH}_2\text{CO}_2\text{Et}$) need to be reacted to produce ethyl 2-methyl-4,5-diphenylpyrrole-3-carboxylate?
- (k) With what compound would TosMIC (TsCH_2NC) need to be reacted to produce methyl 4-ethylpyrrol-3-carboxylate?
- (l) With what reactants would 3-nitrohex-3-ene need to be treated to produce ethyl 3,4-diethylpyrrole-2-carboxylate?

More advanced exercises

1. Two isomeric mono-nitro-derivatives, $\text{C}_5\text{H}_6\text{N}_2\text{O}_2$, are formed in a ratio of 6:1, by treating 2-methylpyrrole with $\text{Ac}_2\text{O}/\text{HNO}_3$. What are their structures and which would you predict to be the major product?
2. Write structures for the products of the following sequences: (i) pyrrole treated with Cl_3CCOCl , then the product with Br_2 , then this product with $\text{MeONa}/\text{MeOH} \rightarrow \text{C}_6\text{H}_6\text{BrNO}_2$, (ii) pyrrole treated with DMF/POCl_3 , then with $\text{MeCOCl}/\text{AlCl}_3$, then finally with aq. $\text{NaOH} \rightarrow \text{C}_7\text{H}_7\text{NO}_2$, (iii) 2-chloropyrrole treated with DMF/POCl_3 , then aq. NaOH , then the product with $\text{LiAlH}_4 \rightarrow \text{C}_5\text{H}_6\text{ClN}$.
3. Write structures for the products formed by the reaction of pyrrole with POCl_3 in combination with (i) *N,N*-dimethylbenzamide; (ii) pyrrole-2-carboxylic acid *N,N*-dimethylamide; (iii) 2-pyrrolidone $\rightarrow \text{C}_8\text{H}_{10}\text{N}_2$, in each case followed by aq. NaOH .
4. Treatment of 2-methylpyrrole with HCl produces a dimer, not a trimer as does pyrrole itself (section 13.1.8). Suggest a structure for the dimer, $\text{C}_{10}\text{H}_{14}\text{N}_2$, and explain the non-formation of a trimer.
5. Treatment of 2,5-dimethylpyrrole with Zn/HCl gave a mixture of two isomeric products $\text{C}_6\text{H}_{11}\text{N}$: suggest structures.
6. (i) Heating 1-methoxycarbonylpyrrole with diethyl acetylenedicarboxylate at 160°C produced diethyl 1-methoxycarbonylpyrrole-3,4-dicarboxylate; suggest a mechanism and a key intermediate; (ii) deduce the structure of the product, $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$, resulting from successive treatment of 1-methoxycarbonylpyrrole with singlet oxygen then a mixture of 1-methylpyrrole and SnCl_2 .
7. Deduce structures for the products formed at each stage by treating pyrrole successively with (i) $\text{Me}_2\text{NH}/\text{HCHO}/\text{AcOH}$, (ii) CH_3I , (iii) piperidine in hot $\text{EtOH} \rightarrow \text{C}_{10}\text{H}_{16}\text{N}_2$.
8. From a precursor which does not contain a pyrrole ring how might one synthesise (i) 1-propylpyrrole; (ii) 1-(thien-2-yl)pyrrole; (iii) 1-phenylsulfonylpyrrole?
9. Reaction of $\text{MeCOCH}_2\text{CO}_2\text{Et}$ with HNO_2 , then a combination of Zn/AcOH and pentane-2,4-dione gave a pyrrole, $\text{C}_{11}\text{H}_{15}\text{NO}_3$. Deduce the structure of the pyrrole, write out a sequence for its formation, and suggest a route whereby it could then be converted into 2,4-dimethyl-3-ethylpyrrole.
10. How might one prepare (i) diethyl 4-methylpyrrole-2,3-dicarboxylate, (ii) ethyl 2,4,5-trimethylpyrrole-3-carboxylate; (iii) ethyl 4-amino-2-methylpyrrole-3-carboxylate; (iv) ethyl 3,4,5-trimethylpyrrole-2-carboxylate?

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