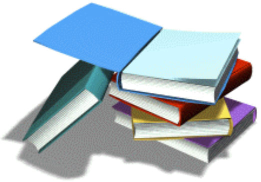
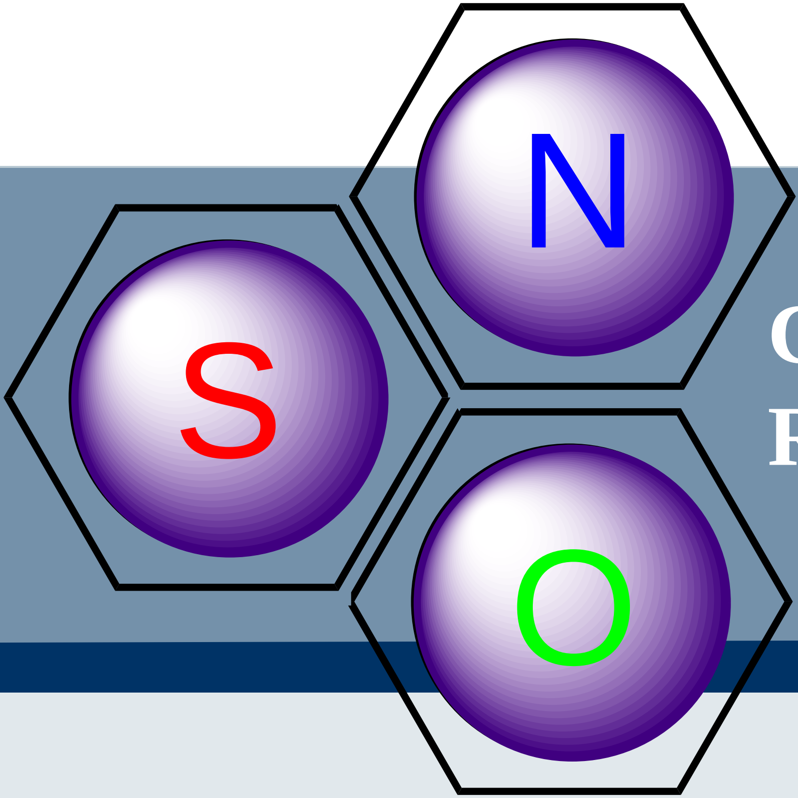


Heterocyclic Chemistry

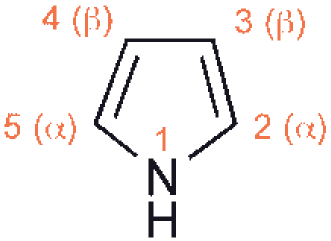


Chapter 10:Pyrroles, Reactions and Synthesis

M. R. Naimi-Jamal

Pyrroles: Reactions and Synthesis

- Based On: J. A. Joule & K. Mills’s Heterocyclic Chemistry



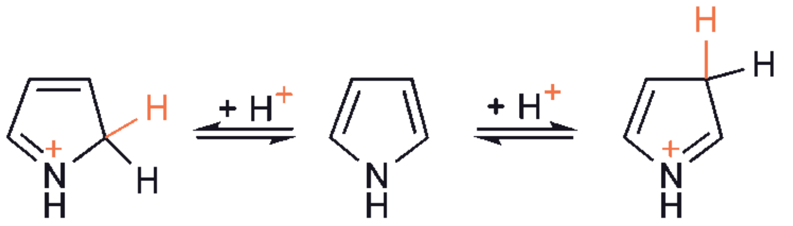
pyrrole
1*H*-pyrrole

Pyrrole 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, the chemistry of 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.

Reactions with Electrophilic Reagents

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. In the gas phase, mild acids like C4H9+ and NH 4+ protonate pyrrole only on carbon and with a larger proton affinity at C-2 than at C-3. Thermodynamically, the stablest cation is the 2H-pyrrolium ion, formed by protonation at C-2 and observed pK_{aH} 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.



2*H*-pyrrolium cation
(most stable)

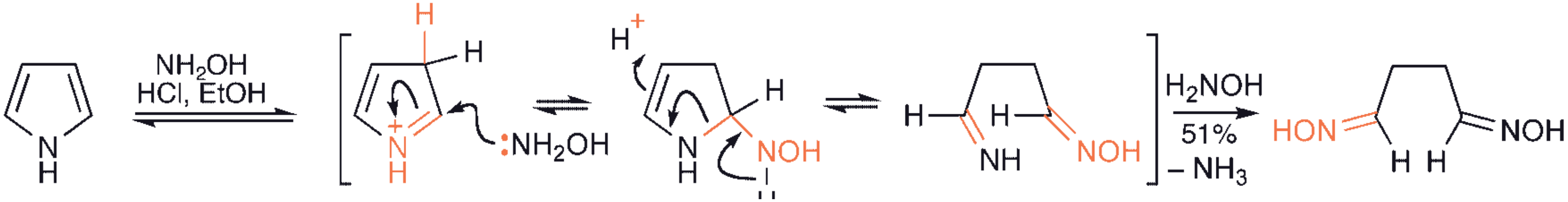
3*H*-pyrrolium cation

1*H*-pyrrolium cation
(least stable)

Reactions with Electrophilic Reagents

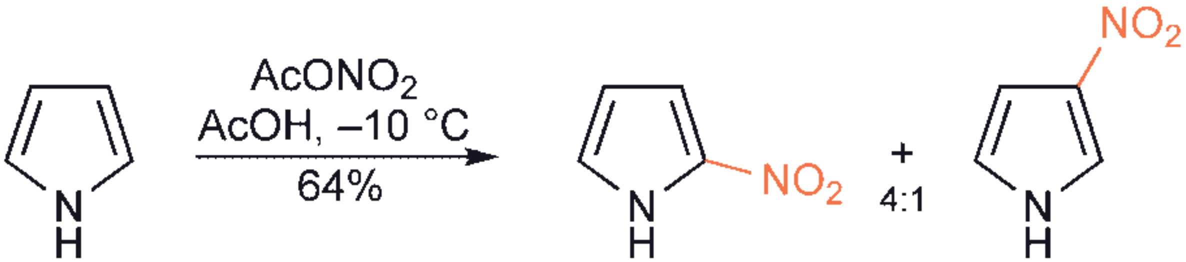
Reactions of Protonated Pyrroles

The 2*H*- and 3*H*-pyrrolium cations are essentially iminium ions and as such are electrophilic: they play the key role in polymerisation (see 16.1.8) and reduction (16.7) 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 that is the starter.[10] Primary amines, RNH_2, can be protected, by conversion into 1-R-2,5-dimethylpyrroles (16.16.1.1), recovery of the amine being by way of this reaction with hydroxylamine.[11,12]



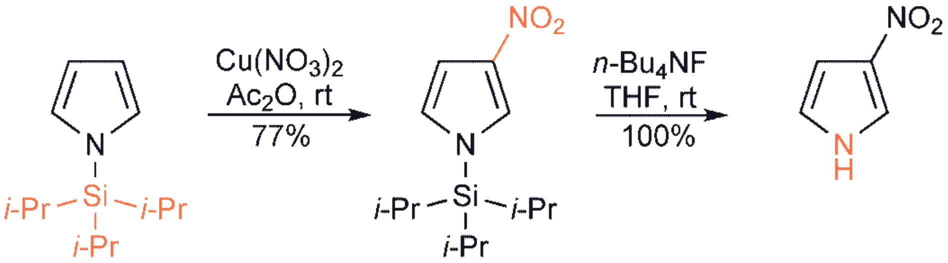
16.1.1.2 Nitration

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.[13] A combination of PPh_3, $AgNO_3$ and Br_2 also produces a comparable mixture of nitro-pyrroles.[14]



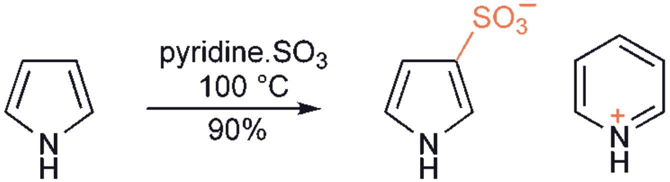
For preparation of 3-NO2:

N-Substitution of pyrroles gives rise to increased proportions of β-nitration, even an *N*-methyl producing a β:α ratio of 1:3, and the much larger *t*-butyl actually reverses the relative positional reactivities, with a β:α ratio of 4:1.[15] 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]



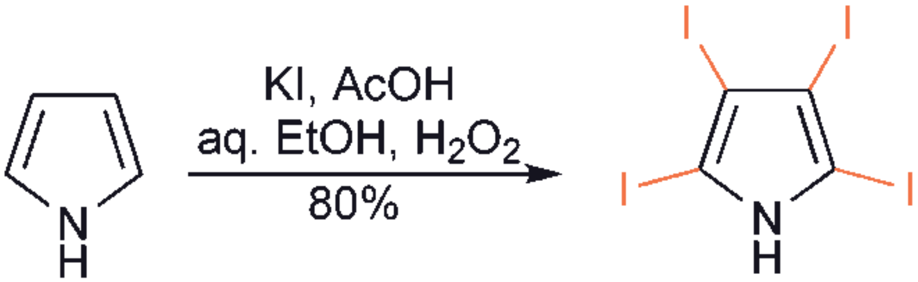
16.1.1.3 *Sulfonation and Reactions with Other Sulfur Electrophiles*

For sulfonation, a mild reagent of low acidity must be used: the pyridine–sulfur trioxide compound smoothly converts pyrrole into a sulfonate initially believed to be the 2-isomer,[17] but subsequently shown to be pyrrole-3-sulfonic acid.[18] It seems likely that this isomer results from reversibility of the sulfonation, and the eventual formation of the more stable acid. Chlorosulfonation of 1-phenylsulfonylpyrrole is clean and an efficient route to pyrrole 3-sulfonic-acid derivatives.[19]



16.1.1.4 Halogenation

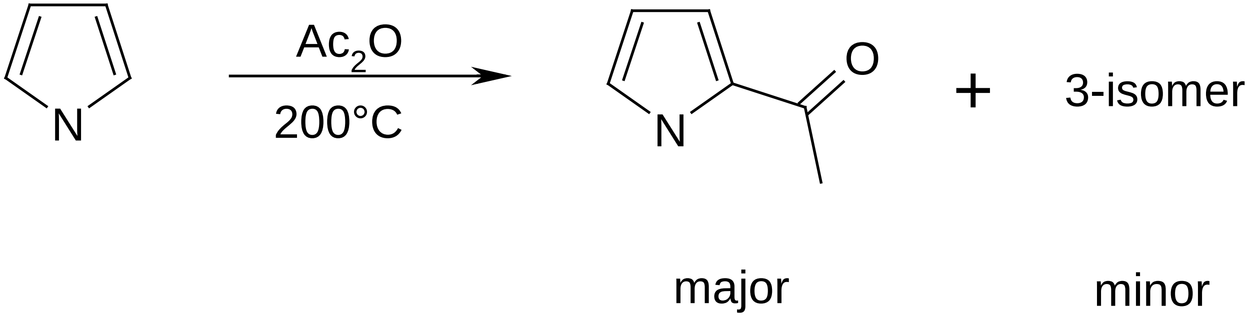
Pyrrole reacts with halogens so readily that unless controlled conditions are used, tetrahalo-pyrroles are the only isolable products, and these are stable.[24] Attempts to mono-halogenate simple alkyl-pyrroles fail, probably because of side-chain halogenation and the generation of extremely reactive pyrryl-alkyl halides (16.11).



Although unstable compounds, 2-bromo - and 2-chloropyrrole (also using SO_2Cl_2) can be prepared by direct halogenation of pyrrole with the *N - halo – succinimides*.

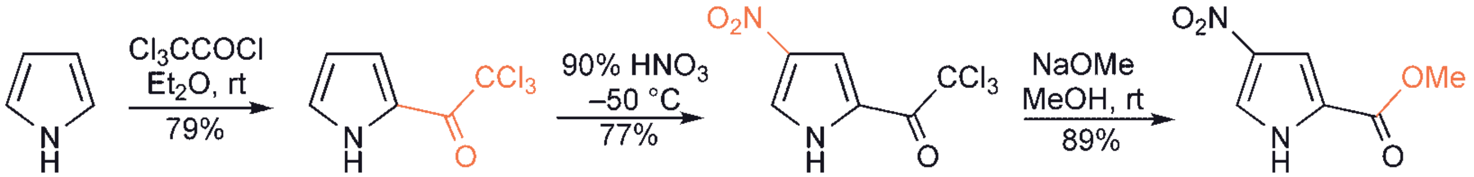
Acylation

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*.

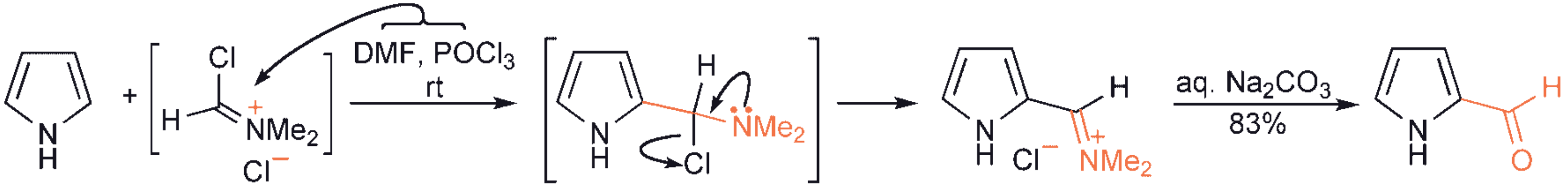


Acylation

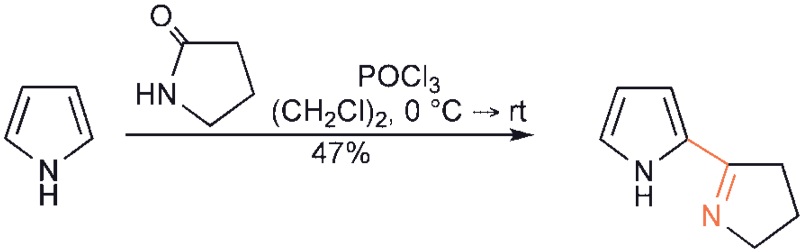
The more reactive trifluoroacetic anhydride and trichloroacetyl chloride react with pyrrole efficiently, even at room temperature, to give 2 - substituted products, alcoholysis or hydrolysis of which provides a clean route to pyrrole - 2-esters or -acids.



Vilsmeier acylation of pyrroles



The Vilsmeier reaction

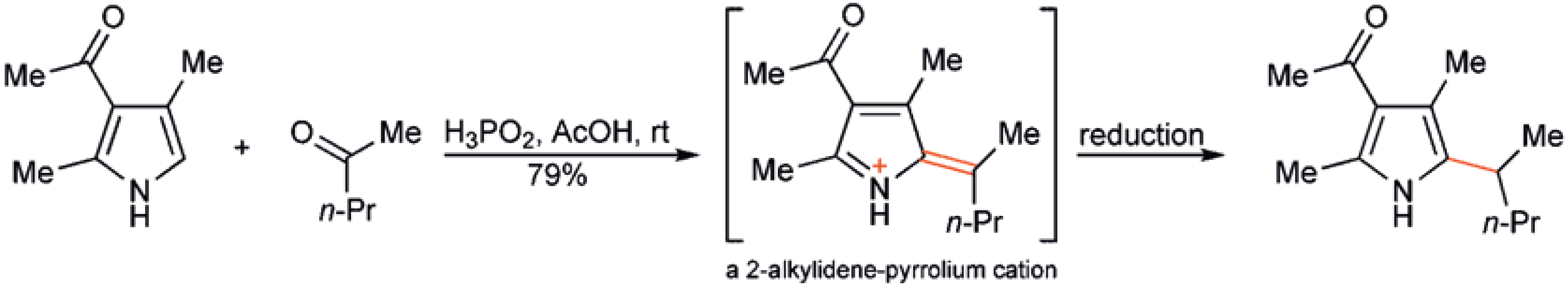


Alkylation

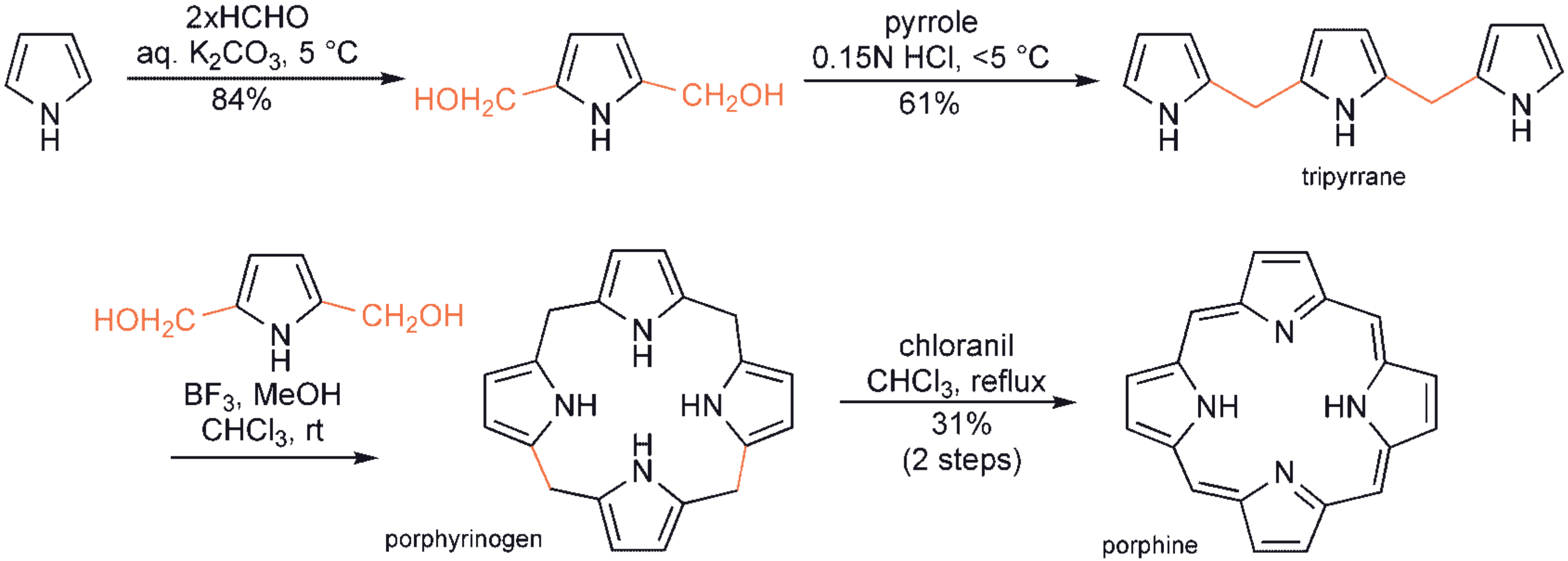
Mono -C-alkylation of pyrroles cannot be achieved by direct reaction with simple alkyl halides, either alone or with a Lewis - acid catalyst, for example pyrrole does not react with methyl iodide below 100 ° C; above about 150 ° C, a series of reactions occurs leading to a complex mixture made up mostly 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 tetra - allyl - pyrroles together with oligomers and polymers are obtained.

16.1.1.7 Condensation with Aldehydes and Ketones

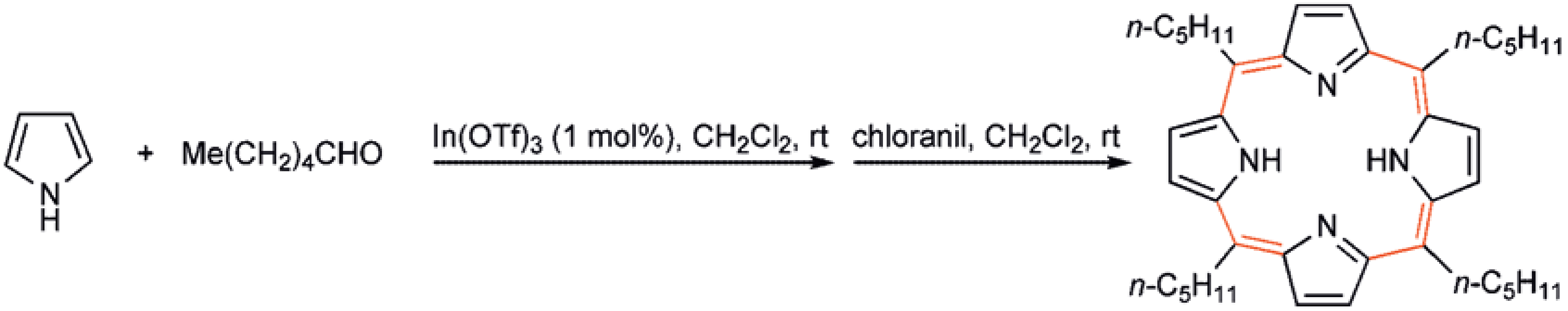
Condensations of pyrroles with aldehydes and ketones occur easily by acid catalysis, but the resulting pyrrolyl-carbinols cannot usually be isolated, for under the reaction conditions proton-catalysed loss of water produces 2-alkylidene-pyrrolium cations that are themselves reactive electrophiles. Thus, 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, producing alkylated pyrroles, can be synthetically useful, however all free positions react; acyl and alkoxycarbonyl-substituents are unaffected.[53]

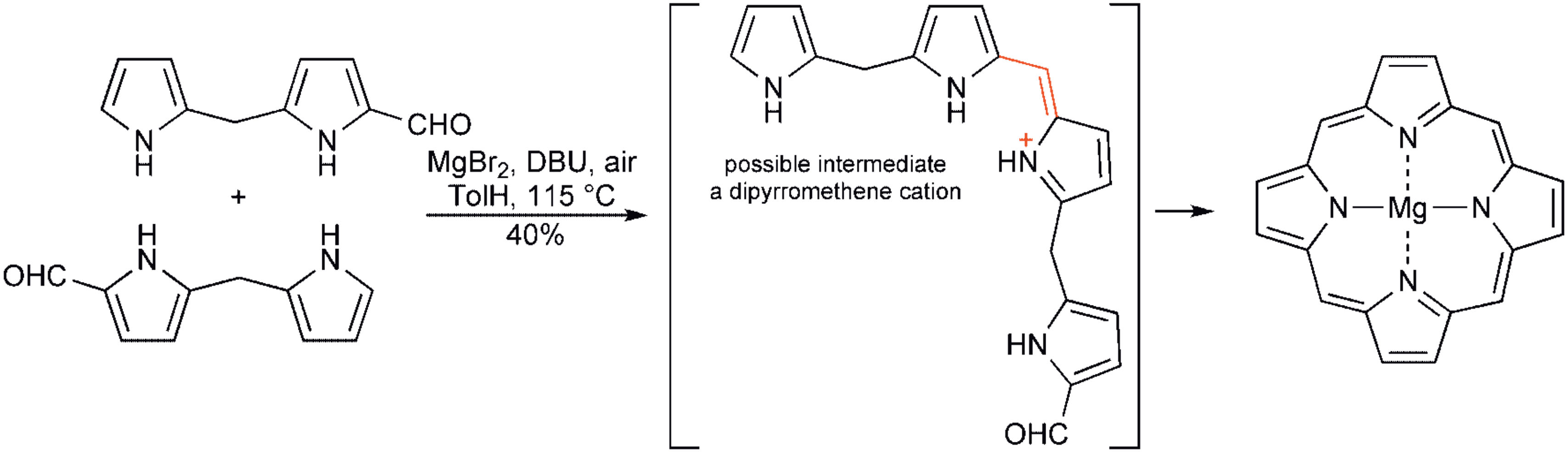


The simplest dipyrromethane, bis(pyrrol-2-yl)methane, can be obtained directly from pyrrole with aqueous formalin in acetic acid; reaction in the presence of potassium carbonate allows 2,5-bis-hydroxymethylpyrrole to be isolated. This diol reacts with pyrrole in dilute acid to give tripyrrane and from this, reaction with 2,5-bis(hydroxymethyl)pyrrole gives porphyrinogen, which can be oxidised with chloranil (2,3,5,6 –tetrachloro-p-benzoquinone) to porphine, the simplest porphyrin.



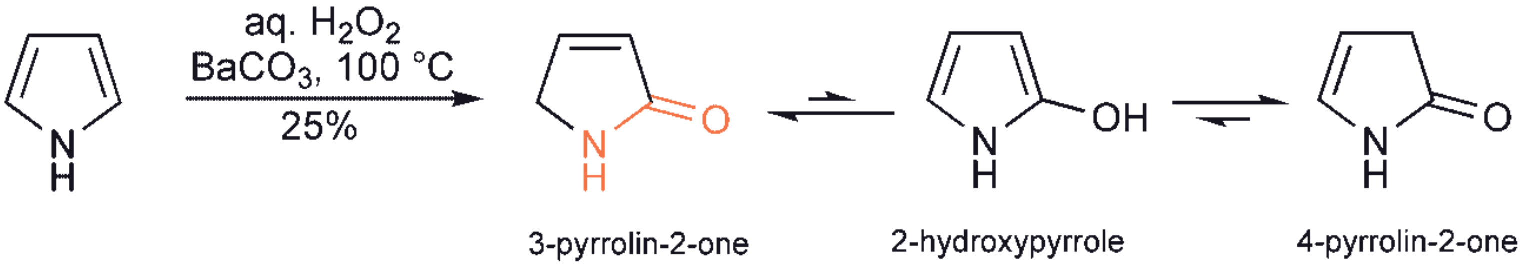
Other examples:



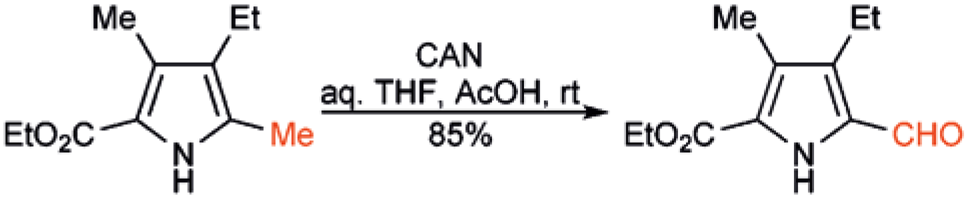


Reactions with Oxidising Agents

Simple pyrroles are generally easily attacked by strong oxidising agents, frequently with complete breakdown. Hydrogen peroxide is a more selective reagent and can convert pyrrole itself into a tautomeric mixture of pyrrolin-2-ones in good yield.

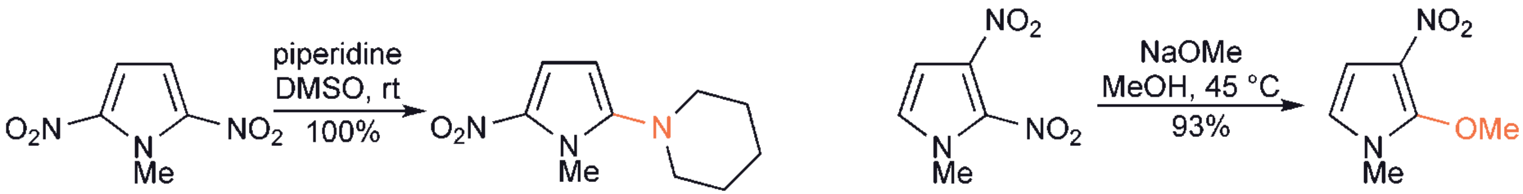


Pyrroles which have a ketone or ester substituent are more resistant to ring degradation and high-yielding side-chain oxidation can be achieved using cerium(IV) ammonium nitrate, with selectivity for an α-alkyl.[66]

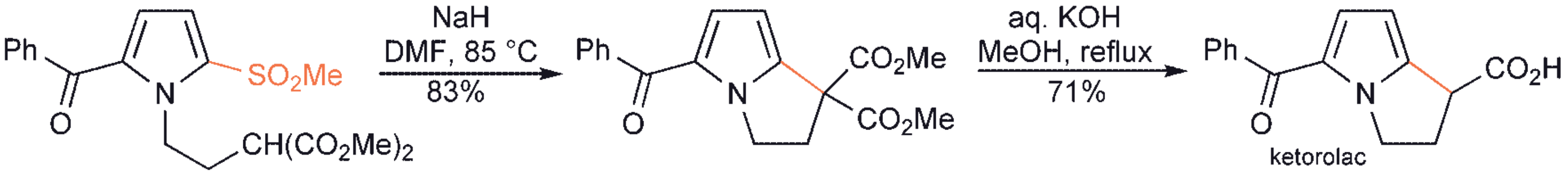


Reactions with Nucleophilic Reagents

Pyrrole and its derivatives do not react with nucleophilic reagents by addition or by substitution, except in the same type of situation that allows nucleophilic substitution in benzene chemistry, i.e. where the leaving group is *ortho or para to an electron - withdrawing group: the two examples below are illustrative.*



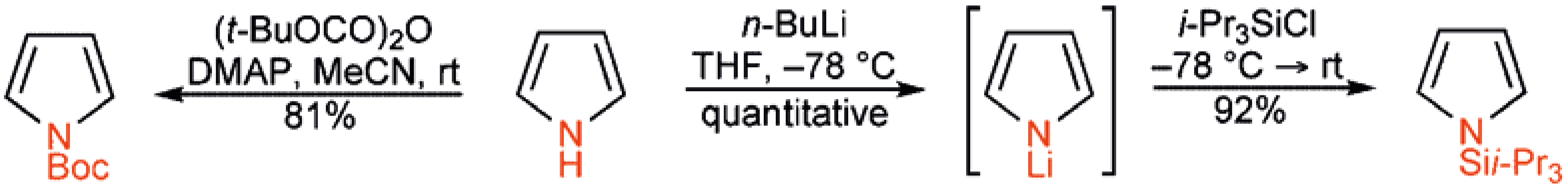
A key step in a synthesis of ketorolac, an analgesic and anti-inflammatory agent, involves an intramolecular nucleophilic displacement of a methanesulfonyl group activated by a 5-ketone.



Reactions with Bases

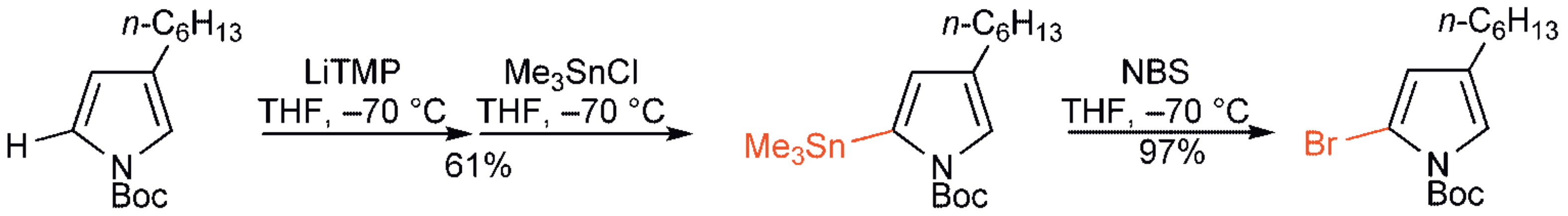
Deprotonation of N - Hydrogen and Reactions of Pyrryl Anions

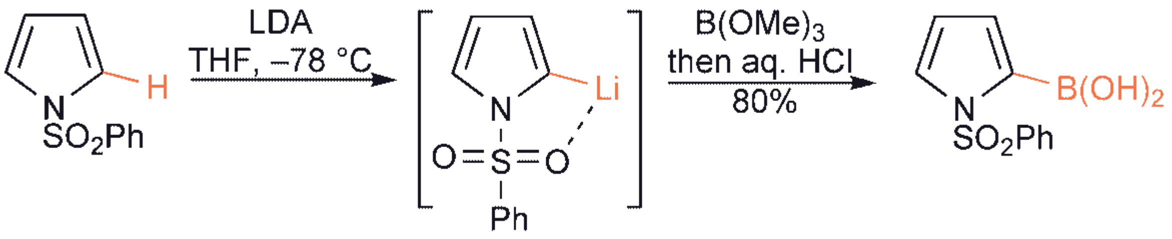
Pyrrole N-hydrogen is much more acidic (pKa 17.5) than that of a comparable saturated amine, say pyrrolidine (pKa ~ 44), or aniline (pKa 30.7), and of the same order as that of 2,4 - dinitroaniline. Any very strong base will effect complete conversion of an N-unsubstituted pyrrole into the correspon-ding pyrryl anion, perhaps the most convenient being commercial n-butyllithium solution. The pyrryl anion is nucleophilic at nitrogen and thus provides the means for the introduction of groups onto pyrrole nitrogen, for example using alkyl halides.



Direct Ring C – H Metallation

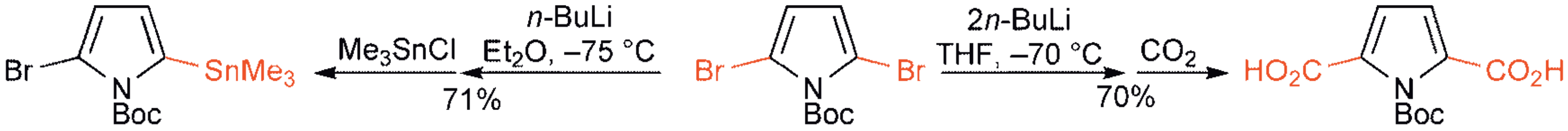
The C-lithiation of pyrroles requires the absence of the acidic N-hydrogen, i.e. the presence of an N-substituent.





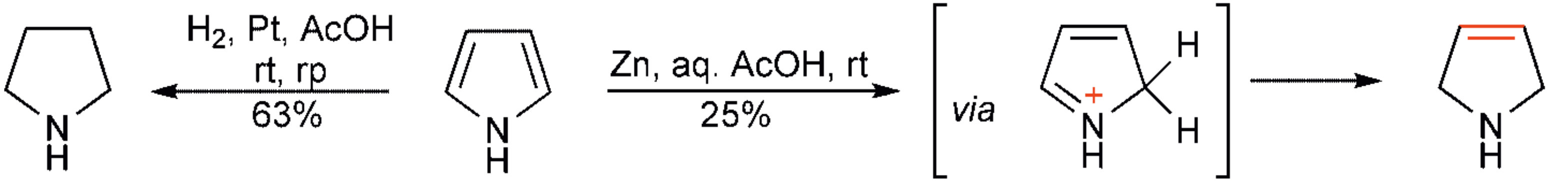
Metal – Halogen Exchange

Metal–halogen exchange on *N*-protected-pyrroles can provide access to either 2- or 3-lithio-pyrroles. Thus, for example, 2-bromo-1-*t*-butoxycarbonylpyrrole and its 2,5-dibromo-counterpart give monolithiated reagents and from the latter, even a dilithiated species can be generated.[30]



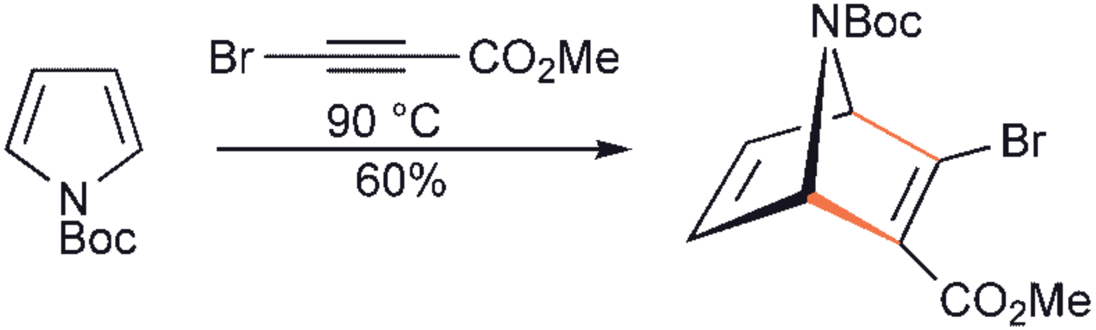
Reactions with Reducing Agents

Simple pyrroles are not reduced by hydride reducing agents or diborane, 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.



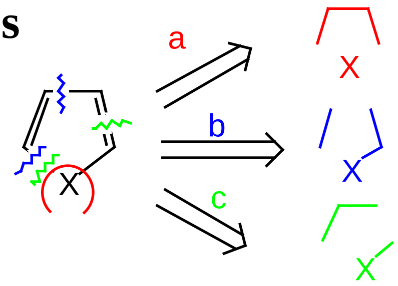
Electrocyclic Reactions (Ground State)

Simple pyrroles do not react as 4 π components in Diels – Alder cycloadditions: exposure of pyrrole to benzyne, for example, leads only to 2-phenylpyrrole, in low yield. However N - substitution, particularly with an electron - withdrawing group, does allow such reactions to occur,

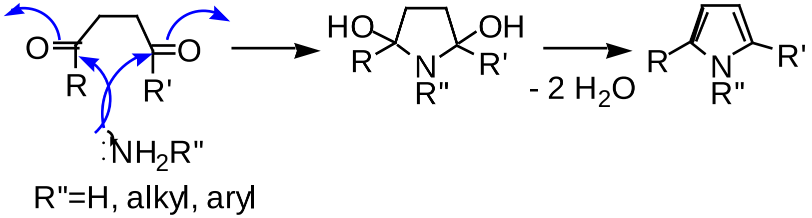


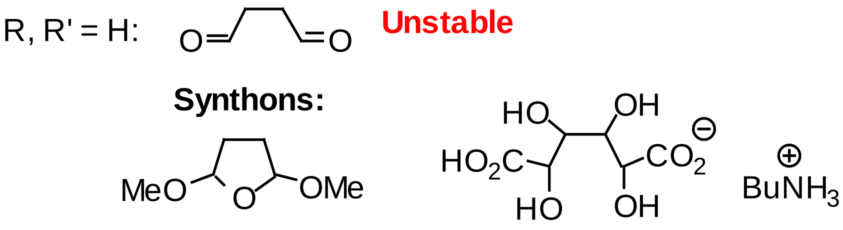
Synthesis of Pyrroles and Indoles

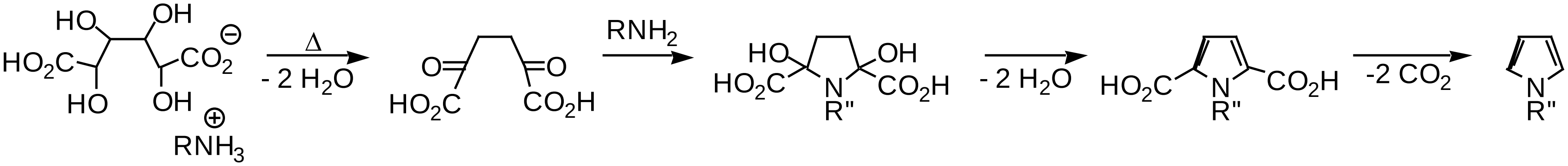
Carbonyl condensations (c.f. chapt. 3) - Pyrroles



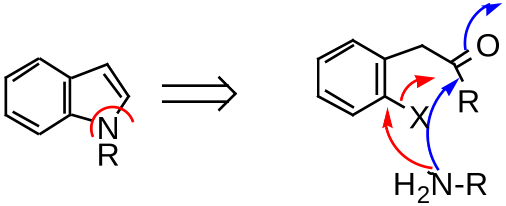
Strategy a; Paal-Knorr synth.





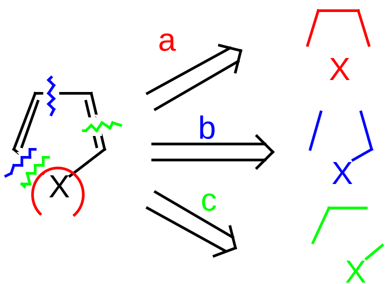


Not useful for indoles

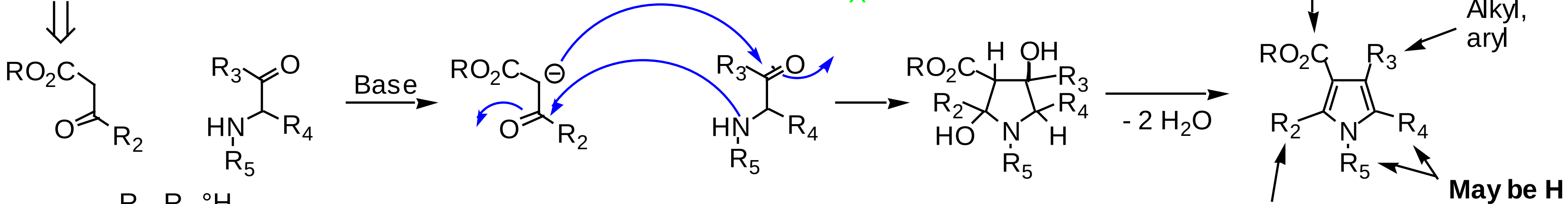


Would require
Nu.Ar subst.

Strategy b; Knorr synth.



Neccesary for easy enolization



R_2, R_3 °H

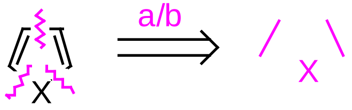
Can be removed; hydrol., decarbox.

Alkyl, aryl

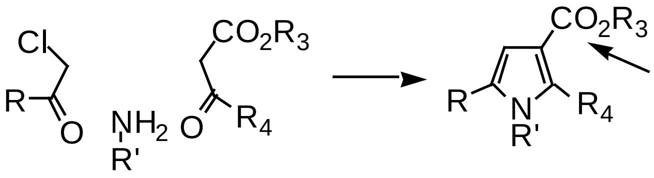
May be H

If R_2=CO_2R
Can be removed; hydrol., decarbox.

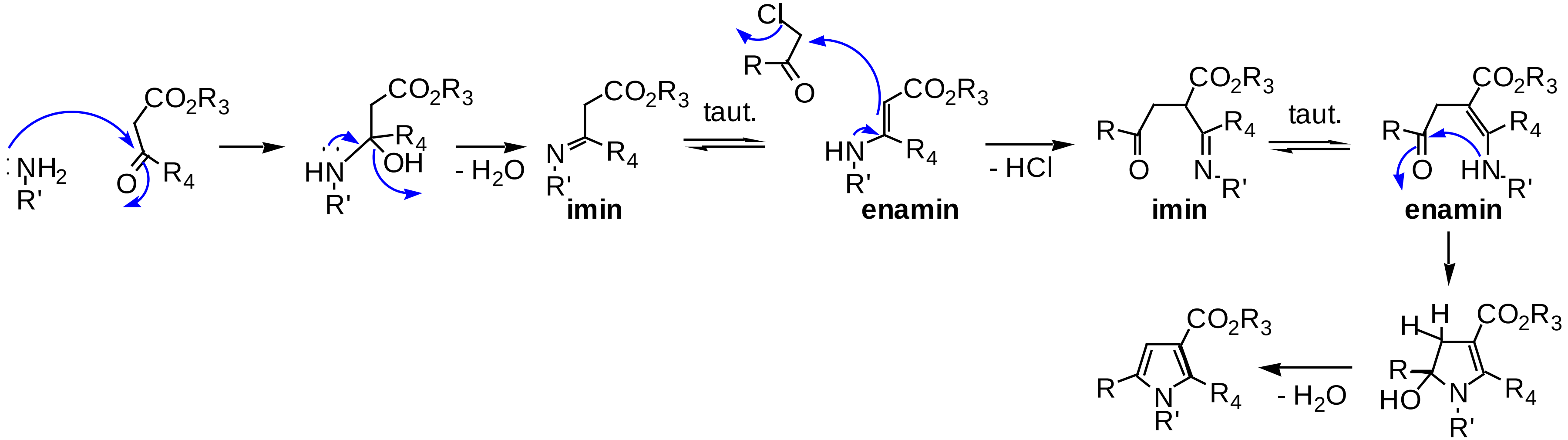
Strategy a and b combined; Hantzsch synth.



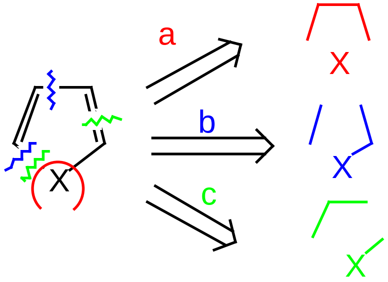
R, R_4: alkyl, aryl
R': H, alkyl, aryl

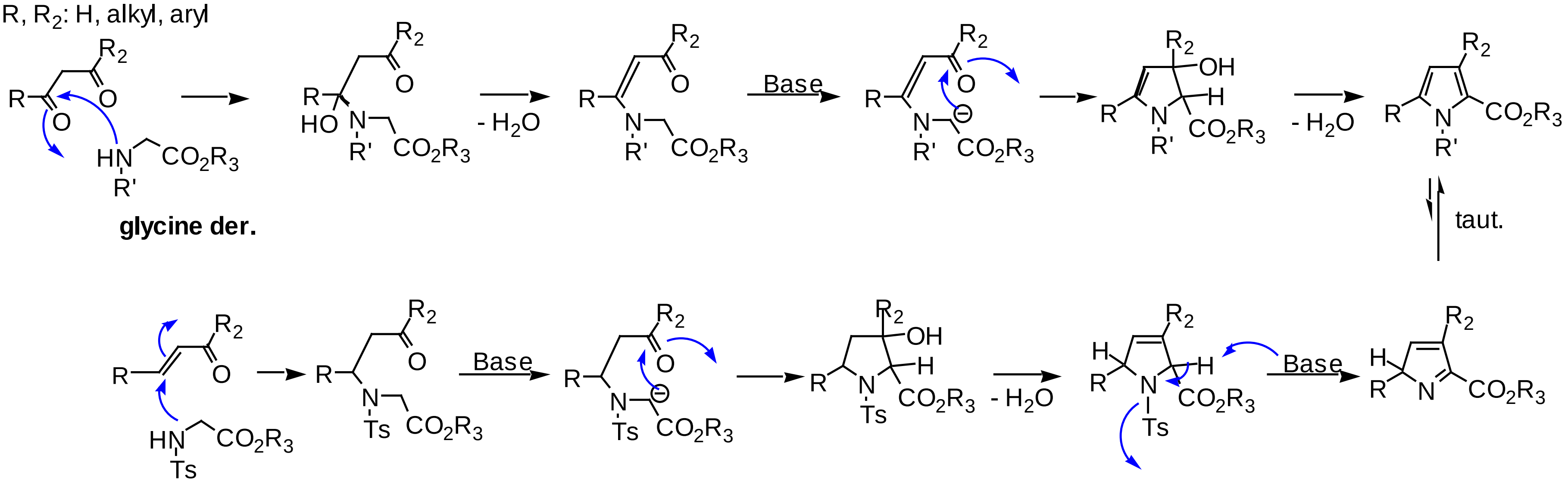


May be removed; hydrol, decarbox.

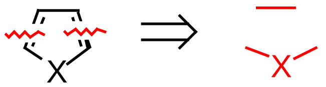


Strategy c


X
a
b
c
X
X
X


R, R2: H, alkyl, aryl
glycine der.
- H2O
Base
- H2O
taut.
Base
- H2O
Base
R
R2
O
HN
R'
CO2R3
HO
N
OH
H
Ts
HN

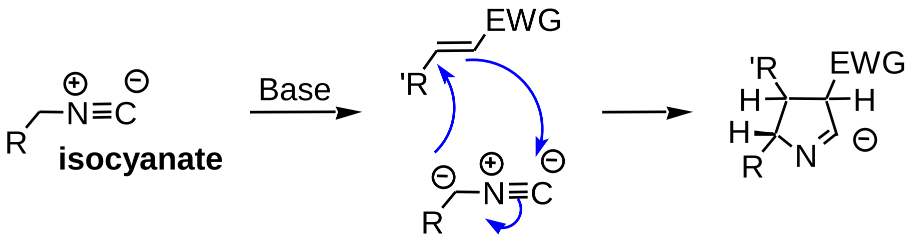
Cycloadditions with 1,3-dipoles (c.f. chapt. 3)



alkene / alkyne

1,3-dipole

Reaction with isocyanide

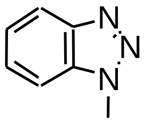


R=Ts (TsMIC)
R=Benzotriazolyl (BetMIC)
R=-CO_2R

EWG= NO_2, COR

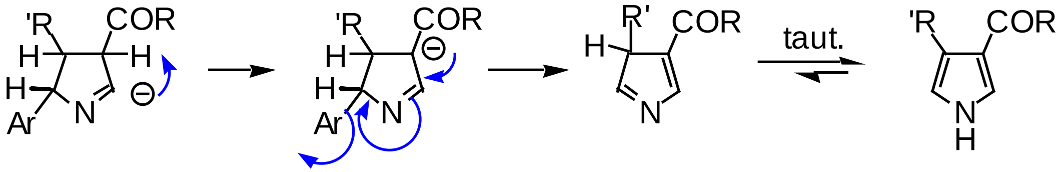
MIC: methyl isocyanate

Bet:



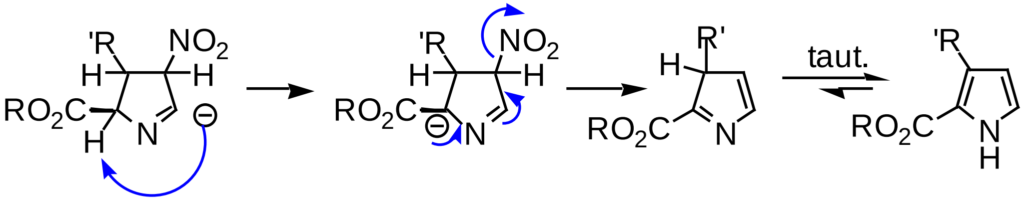
Alt. I; van Leusen synth.

R: Ts or Bet (Good leaving groups)
EWG: -COR

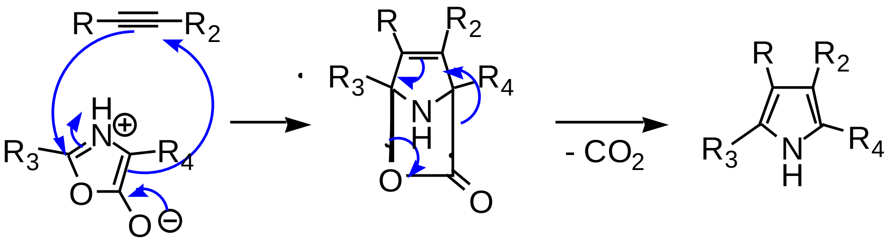


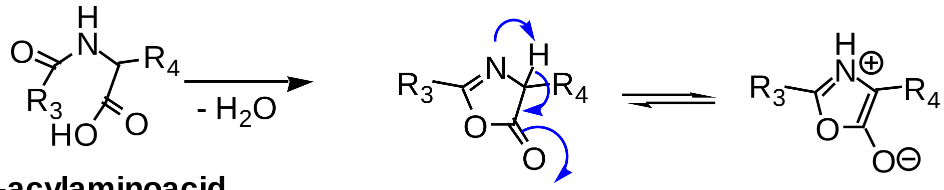
Alt. II; Barton Zard synth.

R: -CO2R
EWG: -NO_2



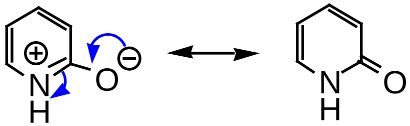
Reaction with mesoionic oxido-oxazoliums





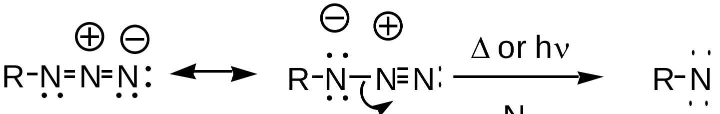
N-acylaminoacid

Mesoionic:
Zwitter ion -
no uncharged
res. form



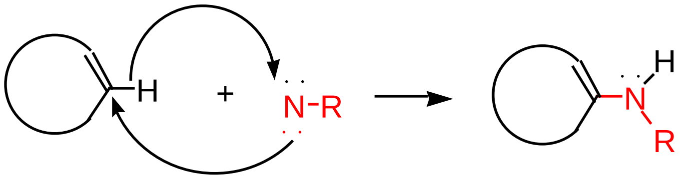
Not mesoionic

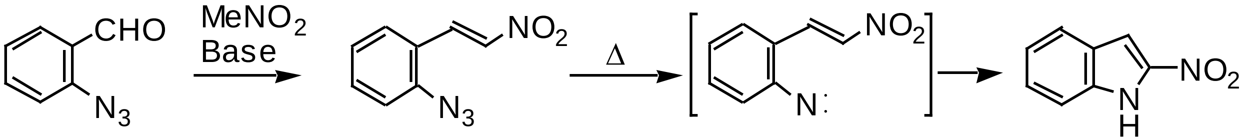
Reaction with nitrenes



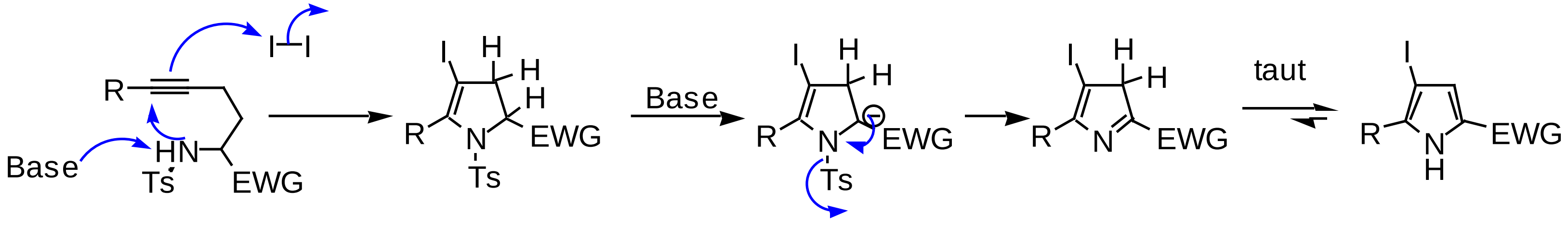
azid
(1,3-dipol)

Nitren





Synthesis from aminoalkynes



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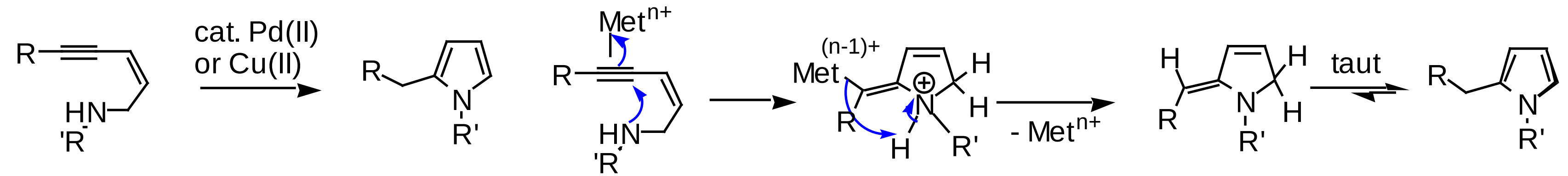

R: alkyl, alkenyl