The Chemistry of Heterocycles

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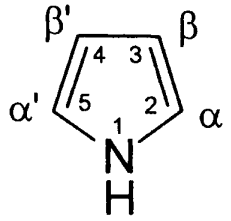
The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

5.12 Pyrrole

[A] The univalent radical derived from pyrrole is known as pyrrolyl. All atoms of the pyrrole molecule lie in a plane and the ring forms an almost regular pentagon.

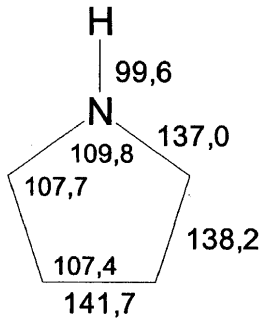


The ionization potential was found to be 8.23 eV. The electron is derived from the HOMO, π_3. The dipole moment is 1.58 D. In contrast to furan and thiophene, the heteroatom represents the positive end of the dipole.

This could be due to the fact that the heteroatom in pyrrole possesses only one nonbonding electron pair, whereas in furan and thiophene, there are two.

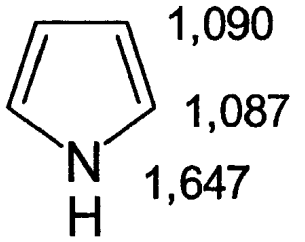
As for furan and thiophene, the chemical shifts in the NMR spectrum are to be found in the region typical for aromatic compounds. The chemical shift for the NH proton depends on the solvent used.

UV (ethanol)	^{1}H-NMR ($CDCl_3$)	^{13}C-NMR (CH_2Cl_2)
λ (nm) (ε)	δ (ppm)	δ (ppm)
210 (4.20)	H-2/H-5: 6.68	C-2/C-5: 118.2
	H-3/H-4: 6.22	C-3/C-4: 109.2



Structure of pyrrole
(bond lengths in pm, bond angles in degrees)

Pyrrole is aromatic. Like furan and thiophene, it belongs to the π-electron excessive heterocycles because the electron density on each ring atom is greater than one:



An acceptable mean value for the empirical resonance energy of pyrrole would be 100 kJ mol^{-1}. The aromaticity of pyrrole is thus greater than that of furan but less than that of thiophene. The value of 22.2 kJ mol^{-1} for the DEWAR resonance energy also fits this picture.

If the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, then the grading of aromaticity, i.e. furan < pyrrole < thiophene < benzene, is correctly reflected by PAULING'S electronegativity values for oxygen (3.5), nitrogen (3.0) and sulfur (2.5).

[B] Pyrroles undergo many reactions, the most important of which are described below.

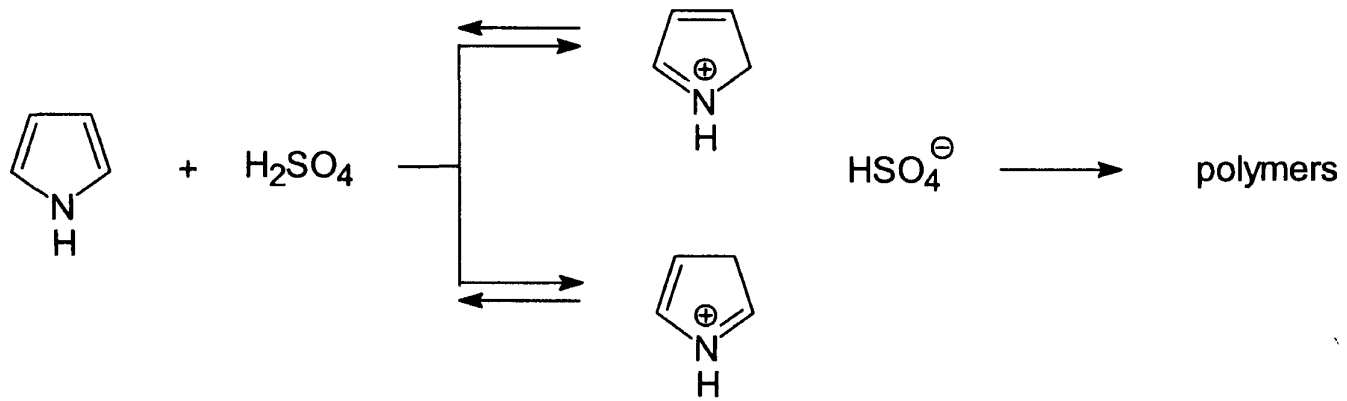
Acid-base reactions

The pyrrole molecule possesses the NH group typical of secondary amines. The basicity of pyrrole, pK_a = -3.8 for the conjugated acid is, however, much less than that of dimethylamine (pK_a = 10.87).

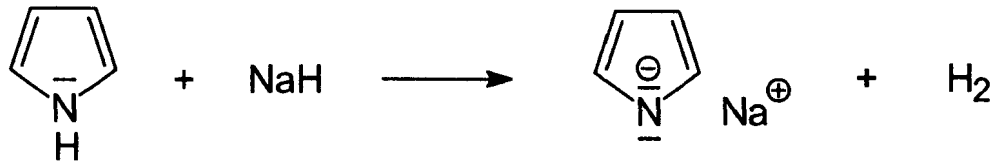
This large difference is due to the incorporation of the nonbonding electron pair of the N-atom into the cyclic conjugated system of the pyrrole molecule.

The protonation, moreover, does not occur on the N-atom, but to the extent of 80% on C-2 and of 20% on C-3.

A consequence of the loss of the cyclic 6 π-system is rapid polymerization of the generated cations.

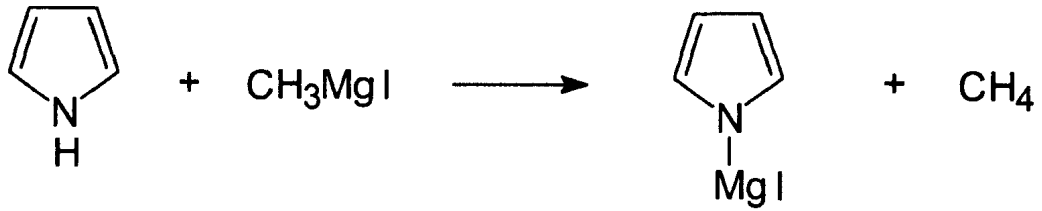


By analogy with secondary amines, pyrrole proves to be an NH acid, pK_a = 17.51. For this reason, pyrrole reacts with sodium, sodium hydride or potassium in inert solvents, and with sodium amide in liquid ammonia, to give salt-like compounds:

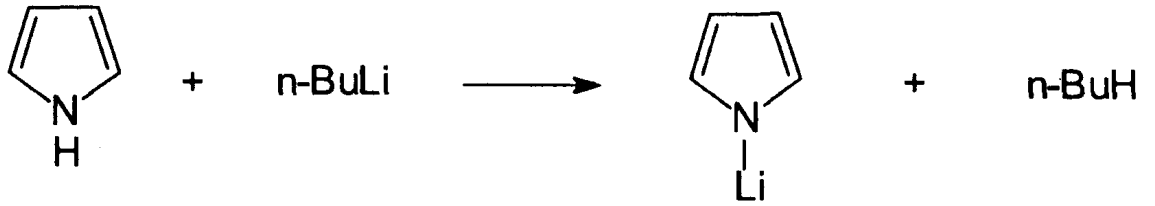


pyrrole sodium

The presence of 'active hydrogen' in pyrrole can also be detected with methylmagnesium iodide according to ZEREWITINOFF:



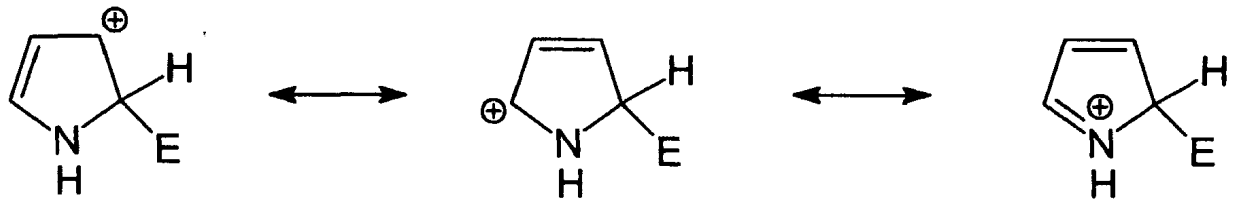
n-Butyllithium reacts in an analogous manner:



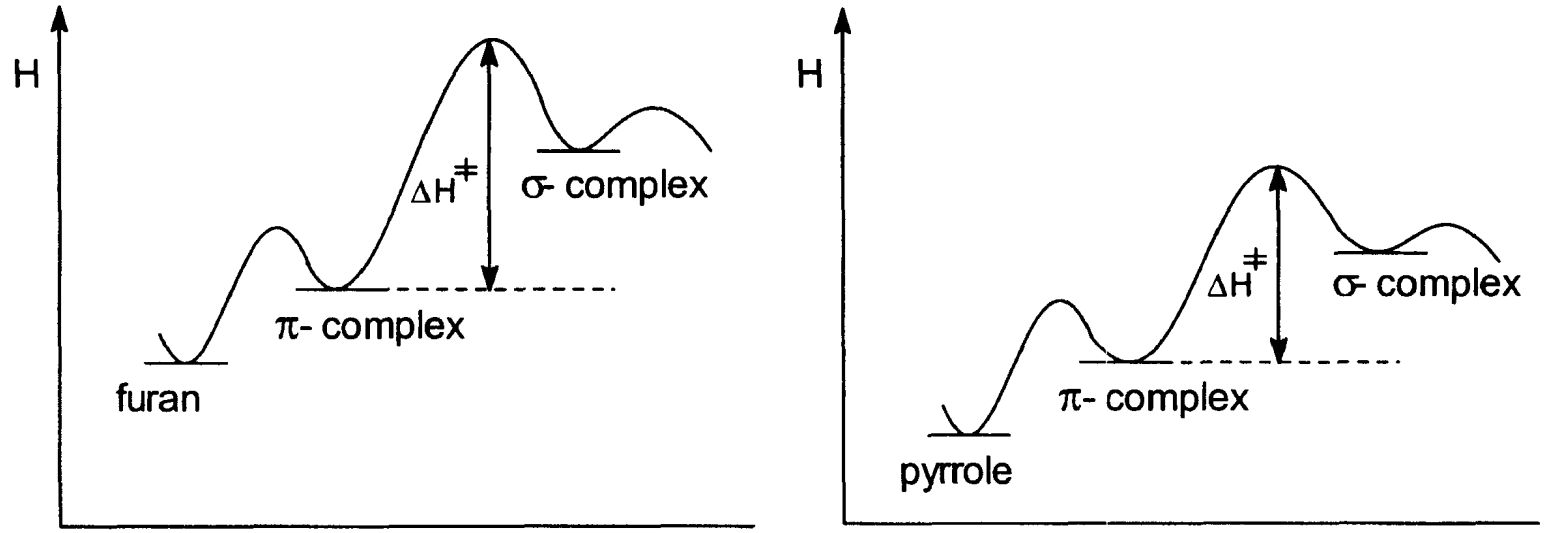
Electrophilic substitution reactions on carbon

Pyrrole reacts in electrophilic substitution reactions about 10^5 faster than furan under similar conditions. This is in spite of the fact that its resonance energy is greater than that of furan; it should, therefore, react more slowly.

This postulates that in the case of pyrrole, the σ-complex is especially stabilized by a carbenium-iminium mesomerism:



As a consequence, ΔH^* for the rate-determining step could become lower than that for furan. On the other hand, differences in the stability of the π-complexes could also influence ΔH^*.



Energy profile of the formation of the π- and σ-complex in the electrophilic substitution of furan and pyrrole

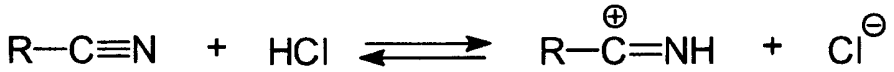
In most electrophilic substitution reactions, pyrrole is preferentially attacked at the α-position. This regioselectivity also depends on whether the reactions are carried out in **solution** or in the **gas** phase.

Pyrrole reacts with *N*-chlorosuccinimide to give 2-chloropyrrole. However, with SO_2Cl_2 or aq. NaOCl, one obtains 2,3,4,5-tetrachloropyrrole. *N*-Bromosuccinimide forms 2-bromopyrrole, and bromine forms 2,3,4,5-tetrabromopyrrole.

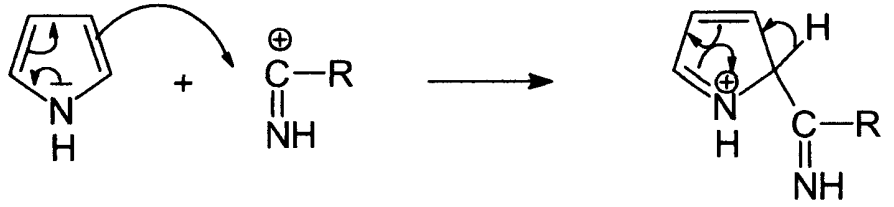
Pyrroles are nitrated with HNO_3 in acetic anhydride at -10 °C to yield 2-nitropyrroles.

Concentrated sulfuric acid causes polymerization of pyrroles, but at 100 °C, pyridine-SO_3 complex provides the corresponding pyrrole-2-sulfonic acids.

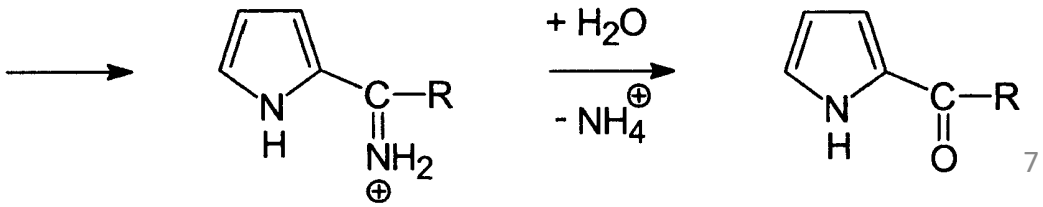
Alkylation of pyrroles proves to be problematic because the usual LEWIS acid catalysts initiate polymerization.



The VILSMEIER-HAACK formylation leads to the formation of pyrrole-2-carbaldehyde in good yield.



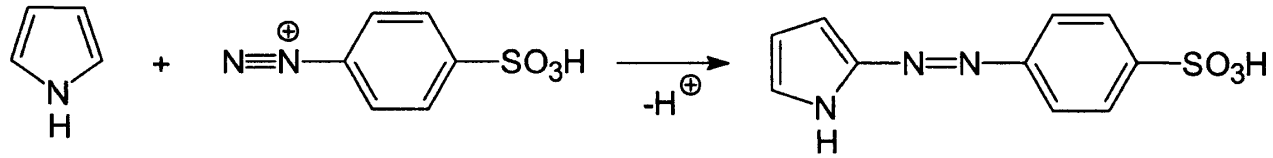
The HOUBEN-HOESCH acylation (reaction with nitriles in the presence of hydrogen chloride) provides 2-acylpyrroles:



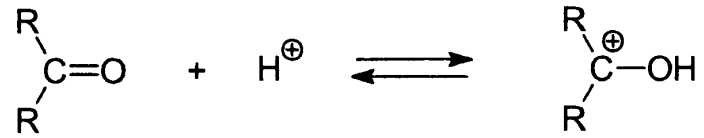
The mechanism of this reaction is illustrated in order to show the low-energy iminium structure of the σ-complex. 2-Acylpyrrole is only formed after the ketimimum salt is hydrolyzed with water.

The **unusually** high reactivity of pyrrole towards electrophiles is demonstrated by two further reactions which are not observed in furan or in thiophene:

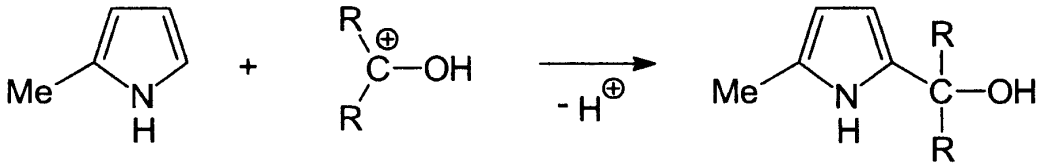
• Pyrroles react with arene diazonium salts to give azo compounds, e.g.:

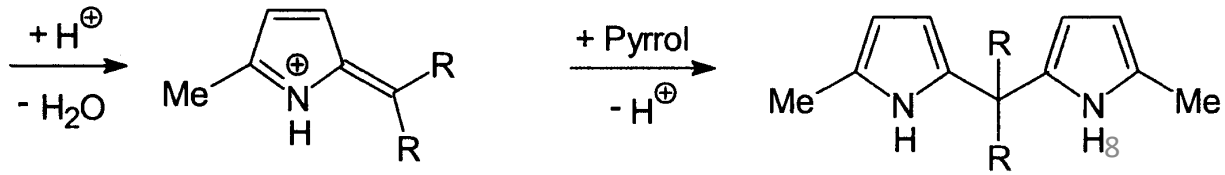


Pyrrole couples even faster than *N*,*N*-dimethylaniline. With 2,5-disubstituted pyrroles, coupling occurs in the 3-position.

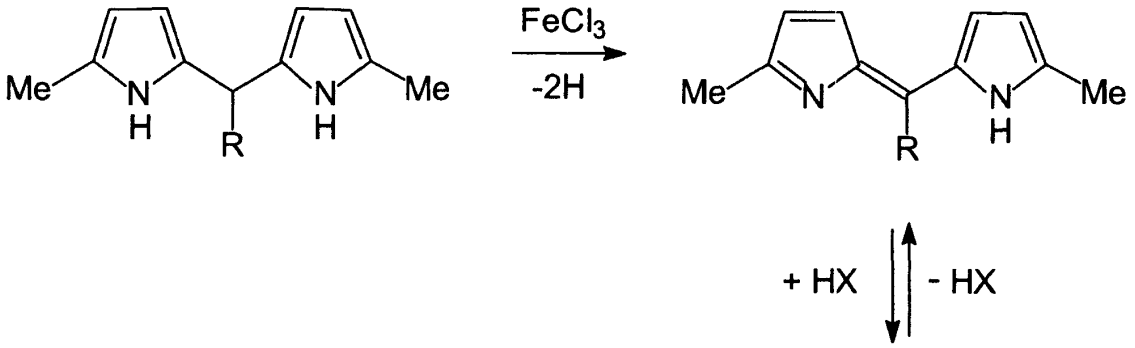


• Pyrroles undergo hydroxymethylation in the 2-position with carbonyl compounds in the presence of acid. The products react further to give dipyrrolylmethanes:

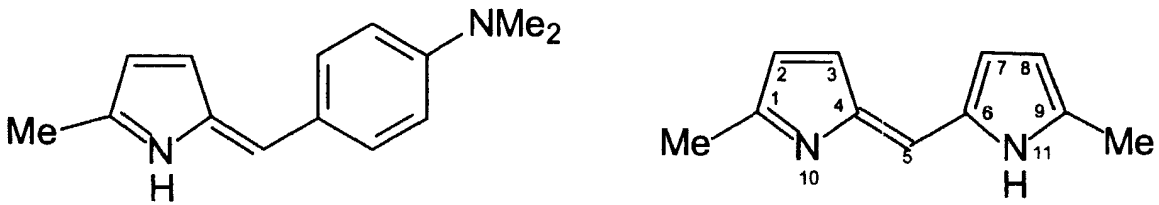




In the case of aldehydes, iron(III) chloride oxidizes the dipyrrolylmethanes to give colored pyrrolyl(pyrrol-2-ylidene)methanes, which are converted by acids into symmetrically delocalized protonated salts:



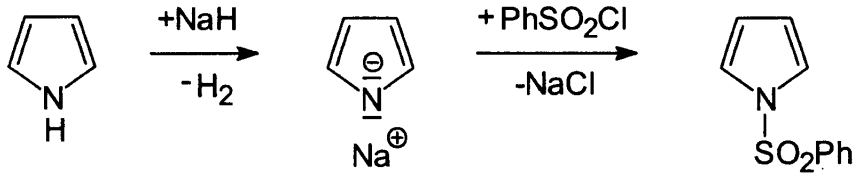
With EHRLICH'S reagent, i.e. a solution of 4-(dimethylamino)benzaldehyde in hydrochloric acid, the reaction proceeds to give only the purple-colored azafulvenium salt:



From 2-methylpyrrole and formaldehyde, orange-colored pyrrolyl(pyrrol-2-ylidene)methane is formed, which is unsubstituted in the 5-position. In acid-catalyzed reactions with carbonyl compounds, pyrroles behave similarly to phenols, which give diphenylmethanes via hydroxymethyl compounds.

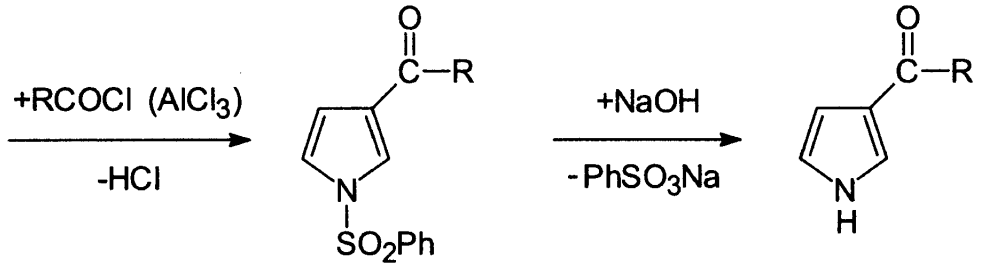
Electrophilic substitution reactions on nitrogen

Pyrrole sodium and pyrrole potassium yield 1-substituted pyrroles with haloalkanes, acyl halides, sulfonyl halides as well as with chlorotrimethylsilane. On the other hand, 2-methylpyrrole is obtained from pyrrol-1-ylmagnesium iodide and methyl iodide.

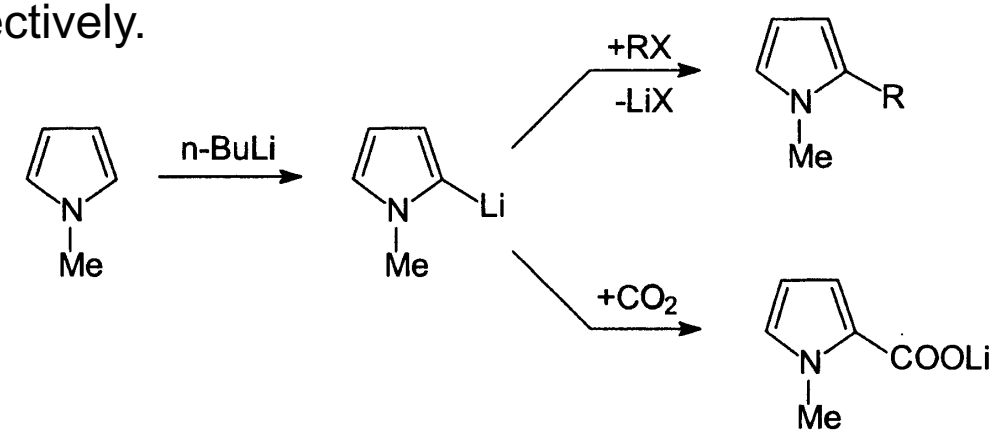


1-Acylpyrroles add lithium organic reagents to the carbonyl group.

1-Phenylsulfonylpyrrole undergoes FRIEDEL-CRAFTS acylation with substitution in the 3-position. 3- Acylpyrroles are obtained from pyrrole as follows:



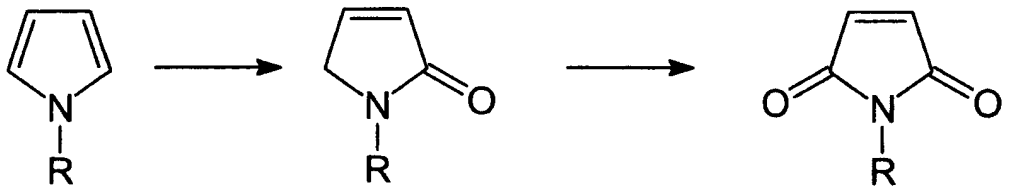
n-butyllithium effects the lithiation of pyrroles in the 1-position. If this position is blocked by a substituent, then 2-lithiopyrroles are formed regioselectively.



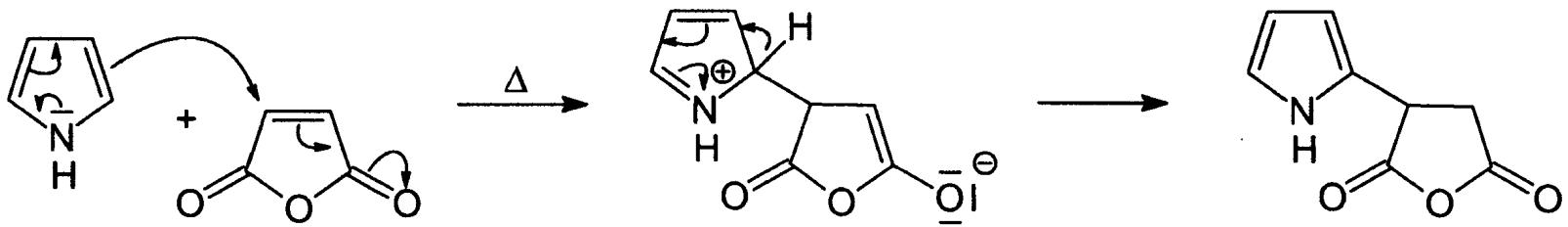
Addition reactions

Hydrogenation of pyrroles to pyrrolidines by RANEY nickel proceeds only under pressure and at high temperatures.

Autoxidation of pyrroles, as well as oxidation with hydrogen peroxide, can be considered addition reactions. Attack of O_2 or H_2O_2 occurs first at the 2-position and then at the 5-position, resulting finally in the formation of maleimide or *N*-substituted maleimide:

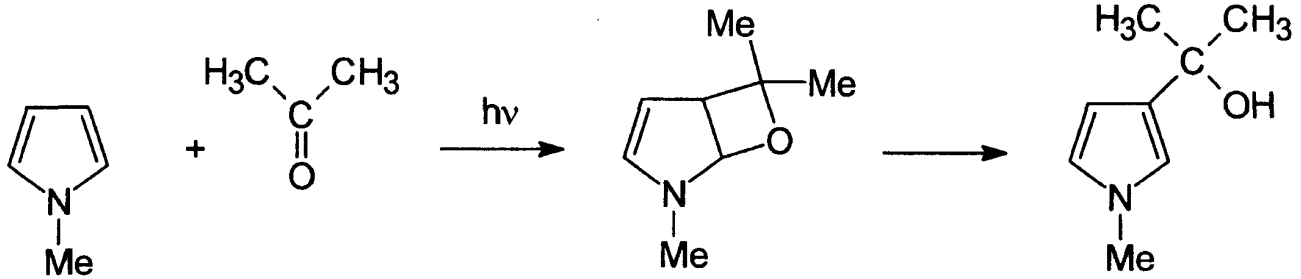


The great reactivity of pyrrole towards electrophiles is the reason why the reaction with maleic anhydride does not result in a DIELS-ALDER addition but in an electrophilic substitution.

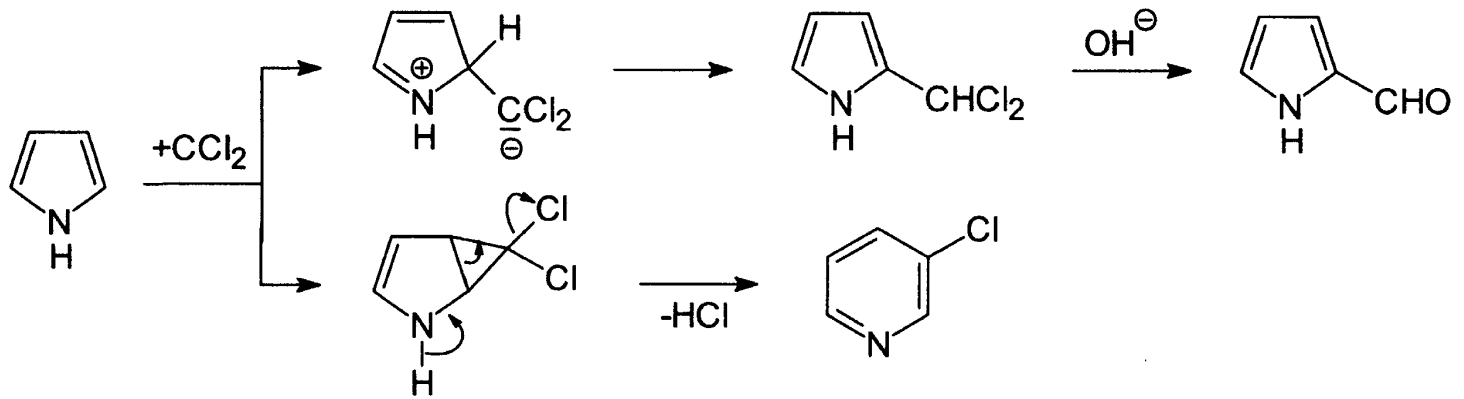


This reaction can also be regarded as a MICHAEL addition of pyrrole to maleic anhydride. Some substituted pyrroles undergo a [4+2] cycloaddition with acetylene dienophiles, e.g. 1-(ethoxycarbonyl)pyrrole with acetylene dicarboxylic ester.

Among the [2+2] cycloadditions, the PATERNO-BUCHI reaction with pyrroles has been investigated. The oxetanes isomerize to give 3-(hydroxyalkyl)pyrroles under the reaction conditions:



A well-established cycloaddition of pyrroles is the [2+2] cycloaddition with dichlorocarbene. This is in competition with the REIMER-TIEMANN formylation:



Under strongly basic conditions (generation of dichlorocarbene from chloroform and potassium hydroxide), electrophilic substitution of pyrrole by dichlorocarbene dominates, leading eventually to pyrrole-2-carbaldehyde.

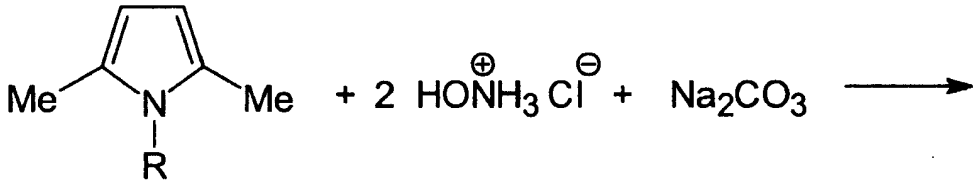
In a weakly basic medium (generation of dichlorocarbene by heating sodium trichloroacetate), the [2+1] cycloaddition prevails. The primary product eliminates hydrogen chloride to give 3-chloropyridine.

Ring-opening reactions

The opening of the pyrrole ring leads to clean reactions in only a few cases, because BRÖNSTED as well as LEWIS acids initiate polymerization, and strong bases cause only salt formation.

Hydroxylamine hydrochloride and sodium carbonate in ethanol react with pyrroles to dioximes of 1,4-dicarbonyl compounds:

Pyrrole itself yields the dioxime of butandial and ammonia.

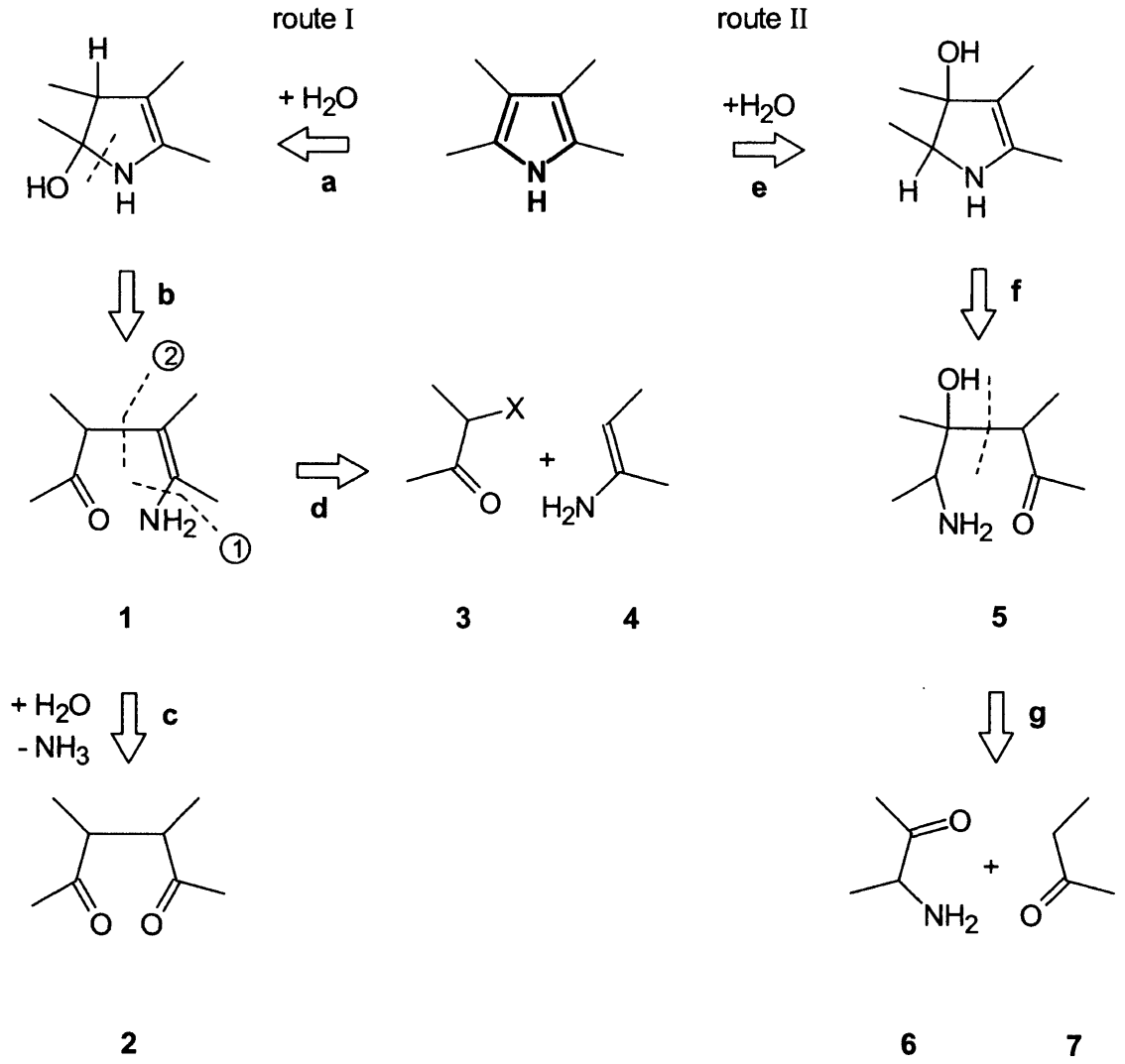


[C] Concerning its *retrosynthesis* pyrrole exhibits the function of a double enamine and can, therefore, be dissected retroanalytically in two ways (**I**/**II**), analogously to furan.

Route **I** (after retrosynthetic operations of an enamine hydrolysis **a**-**c**) yields 1,4-dicarbonyl compounds as potential starting materials, which should produce pyrroles by cyclocondensation with NH_3.

When the intermediate **1** i.e. γ-keto enamine is treated according to step **d**, a bond cleavage different from that leading to **2** is possible.

This reversal of an enamine alkylation gives rise to α-halocarbonyls **3** and enamines **4** and thereby suggests alternative starting materials:

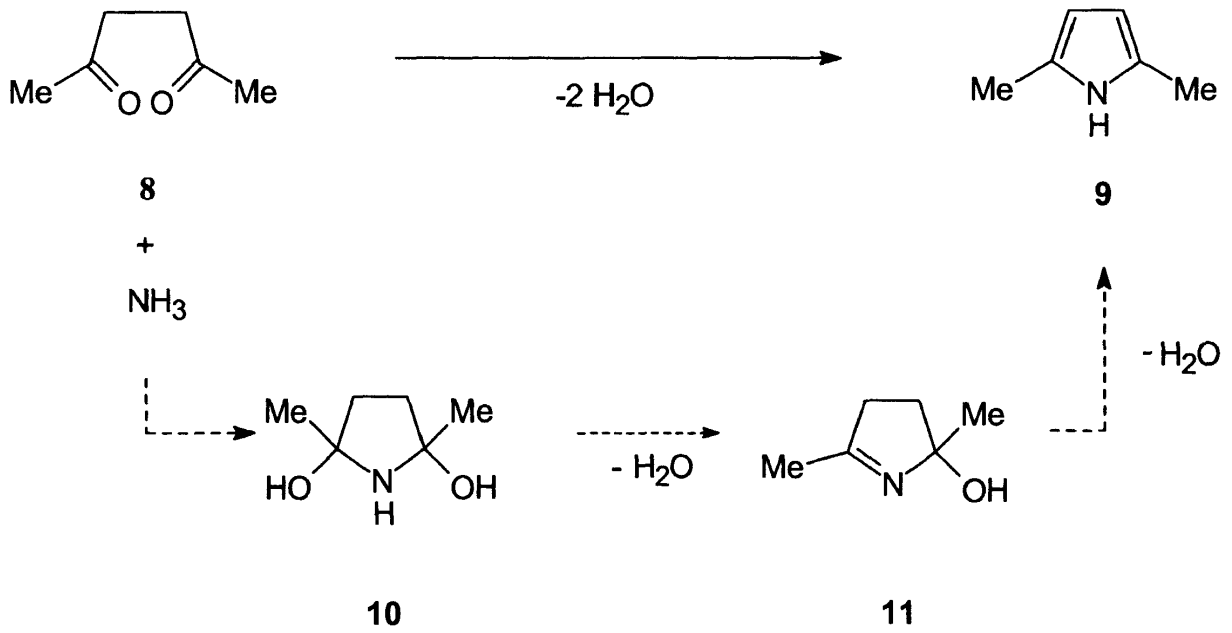


Retrosynthesis of pyrrole

After H_2O addition and enamine hydrolysis (**e** / **f**), route **II** leads to the γ-amino aldol intermediate **5**. Aldol fission follows (retroanalysis step **g**) resulting in the formation of α-amino carbonyl compounds **6** and methylene ketones **7**.

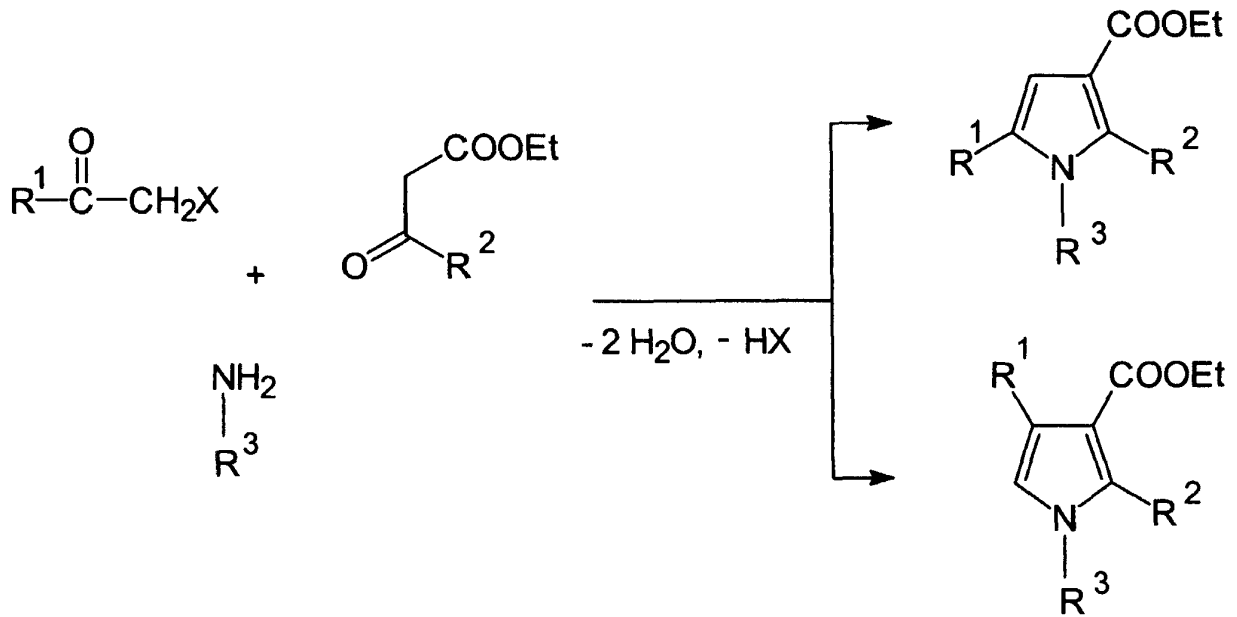
These are possible starting materials for the synthesis of pyrroles.

(1) The Paal-Knorr synthesis, in which 1,4-dicarbonyl compounds are treated with NH_3 or primary amines (or with ammonium or alkylammonium salts) in ethanol or acetic acid, leads to 2,5-disubstituted pyrroles, and is universally applicable. For instance, hexane-2,5-dione **8** reacts with NH_3 to yield 2,5-dimethylpyrrole **9**:



The primary step leads to the double hemiaminal **10** which, by stepwise H_2O elimination, furnishes the pyrrole system **9** via the imine **11**.

(2) α-Halocarbonyl compounds react with β-keto esters or β-diketones and ammonia or primary amines to give 3-alkoxycarbonyl- or 3-acyl-substituted pyrrole derivatives, respectively (Hantzsch synthesis):

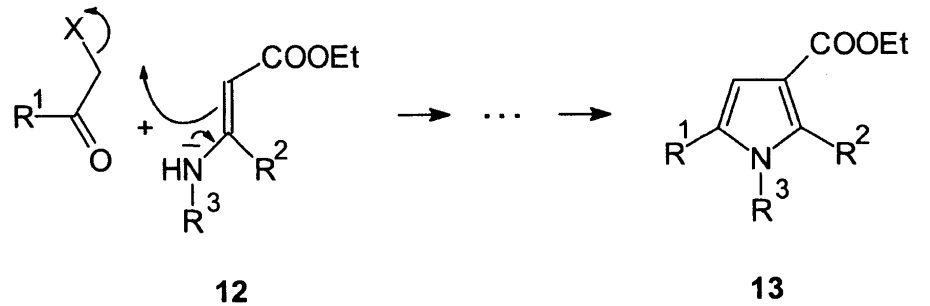


The regioselectivity depends on the substituents in the starting material but gives mainly the 1,2,3,5-tetrasubstituted pyrrole. Exhaustive investigations show that β-keto esters react with ammonia or amine to give a β-aminoacrylic ester (**12**) as a primary step.

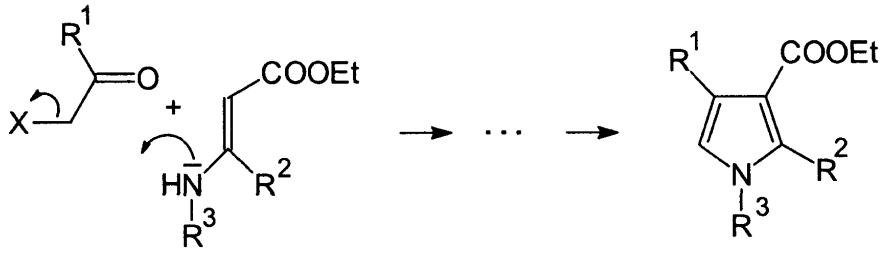
C-Alkylation of the enamine function in **12** by the haloketone produces the 1,2,3,5-substituted pyrrole **13**, while *N*-alkylation leads to a 1,2,3,4-substituted pyrrole **14**:

(3) α-Amino ketones undergo cyclocondensation with β-keto esters or β-diketones to give 3-alkoxycarbonyl- or 3-acyl-substituted pyrroles **15** (Knorr synthesis).

The KNORR synthesis also proceeds via β-enaminone intermediates **16**.



12 **13**



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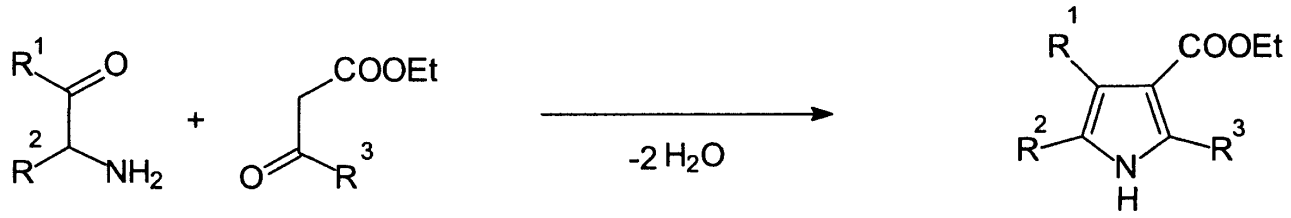

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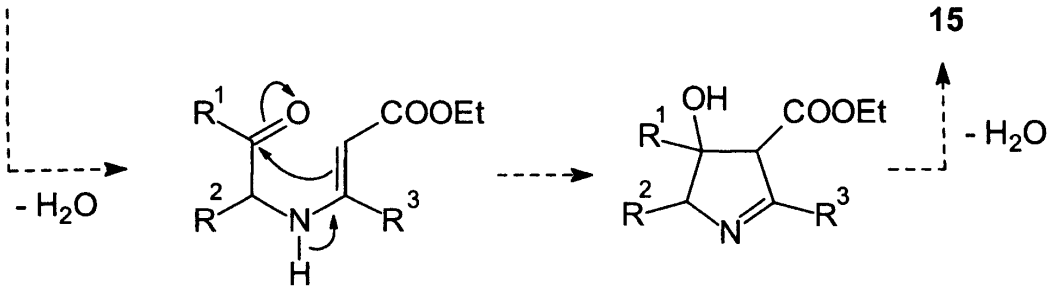
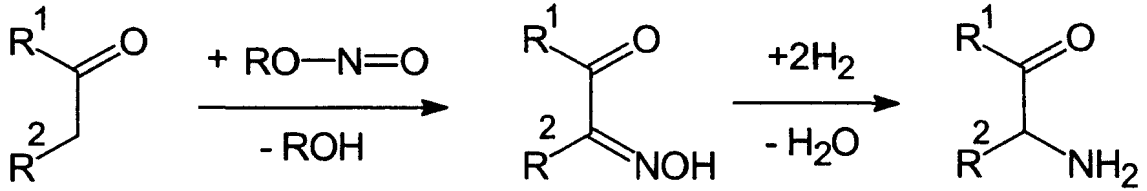


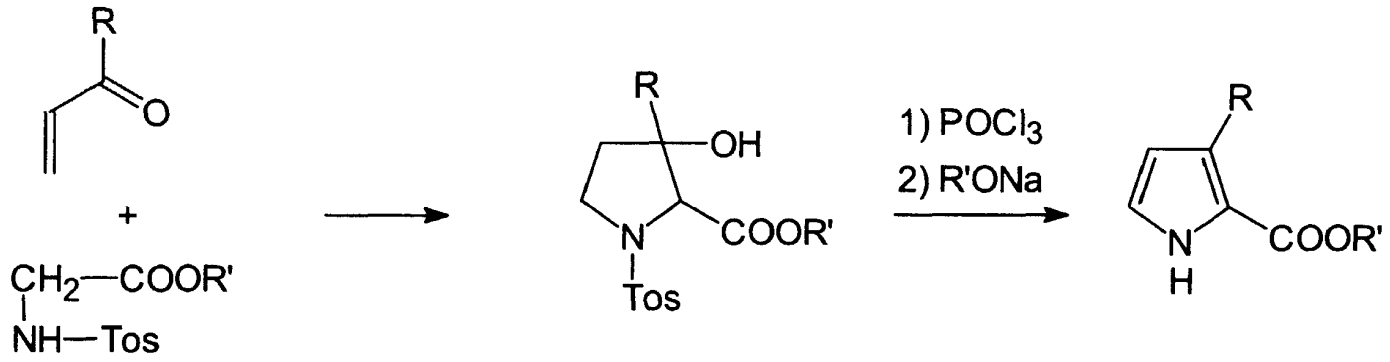
16

Frequently, the α-amino ketones are not employed as such but generated in situ by reduction of α-oximino ketones. The latter are obtained by nitrosation of ketones with alkyl nitrites in the presence of sodium methoxide:



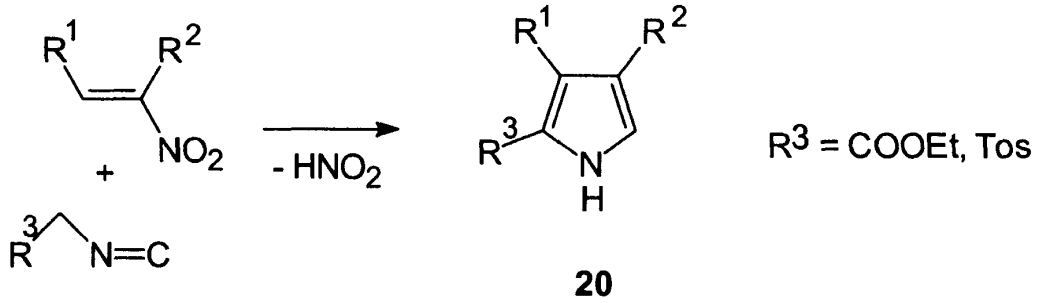
(4) 3-Substituted pyrrole-2-carboxylic esters **19** are synthesized from *N*-tolylsulfonyl glycine ester **17** and vinyl ketones (*Kenner synthesis*).

By MICHAEL addition and intramolecular aldol addition, they first yield pyrrolidine-2-carboxylic esters **18**. These are converted into pyrroles by successive H_2O and sulfmic acid eliminations.



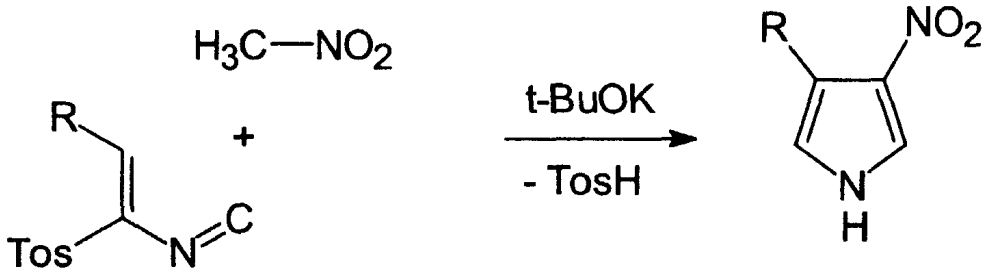
17 **18** **19**

(5) Cyclocondensation of nitroalkenes with CH-acidic isocyanides in the presence of bases leads to the formation of trisubstituted pyrroles **20** (*Barton-Zard synthesis*):



20

The first step of this reaction is a MICHAEL addition of isocyanide to the nitroalkene. Cyclization and elimination of HNO_2 follow. On the other hand, α,β-unsaturated isocyanides and nitromethane yield 3-nitropyrroles **21**.

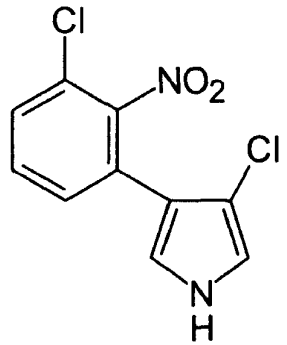


21

[D] Pyrrole was first isolated from bone oil, but also occurs in coal tar. It can be prepared by the dry distillation of the ammonium salt of D-galactaric acid (mucic acid).

Pyrrole is a colorless liquid with a characteristic odor reminiscent of chloroform, of mp -24 °C and bp 131 °C. It is slightly soluble in water and turns brown quickly in air.

The pyrrole ring, although not very common in nature, occurs in some very important natural products. A few antibiotics contain a pyrrole ring, one of the simplest is pyrrolnitrin **22**:

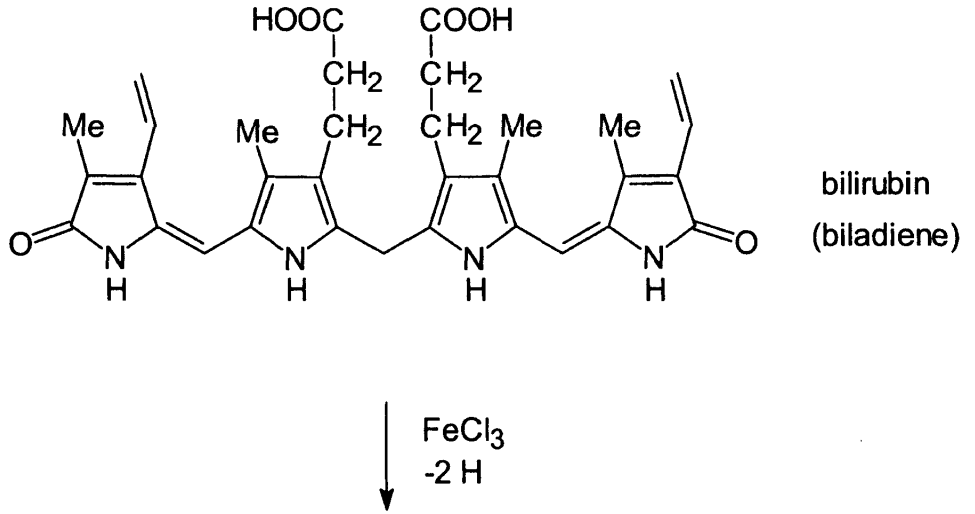


22

The biologically important tetrapyrroles contain four pyrrole rings, which are linked by CH_2 or CH bridges. One differentiates between linear tetrapyrroles (bilirubinoids) and cyclic tetrapyrroles (porphyrins and corrins).

Bilirubinoids are colored compounds occurring in vertebrates, in some invertebrates and even in algae. They are formed by the biological oxidation of porphyrins. The most important representative is the orange-colored bilirubin.

It occurs in the bile and in gallstones and is excreted in the feces and in urine. Bilirubin was first isolated by STAEDELER (1864) and can be purified via its crystalline ammonium salt. It is oxidized to blue-green biliverdine by iron(III) chloride:

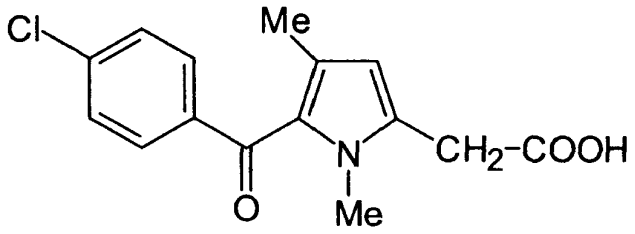


bilirubin
(biladiene)

biliverdine
(bilin)

The corresponding unsubstituted compounds are known as biladiene and bilin.

A number of pharmaceuticals are derived from pyrrole, e.g. the analgesic and anti-inflammatory zomepirac **23** [5-(4-chlorobenzoyl)-l,4-dimethylpyrrol-2-ylacetic acid]:



23

Polymers and copolymers of pyrrole are used as organic conductors for special purposes, e.g. in photovoltaic cells.