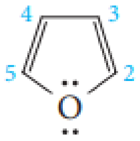
CH-2-I

Five-membered Heterocycles

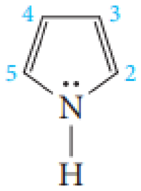
Pyrrole, Furan and Thiophene

Five Membered Heterocycles-Introduction

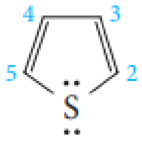
- The main reason for the study of pyrrole came from the work on the structure of haem; the blood respiratory pigment, and the chlorophyll; the green photosynthetic pigment of plants.
- Thiophen does occur in plants in association with polyacetylenes with which they are biogenetically closely linked.
- Furan occurs widely in secondary plant metabolites, especially in terpenoids.
- Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum.



furan
(bp 32°C)



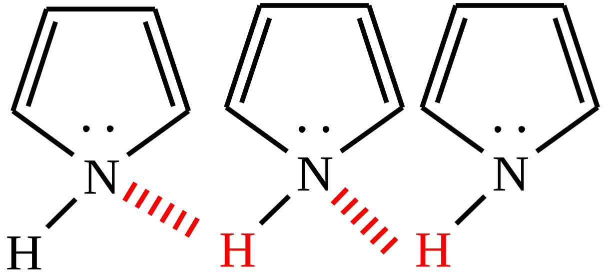
pyrrole
(bp 131°C)



thiophene
(bp 84°C)

General Characteristics

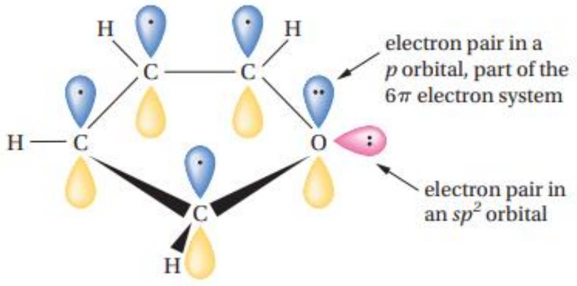
- Pyrrole, thiophene and furan are colorless liquids of boiling points 131°, 84° and 32° respectively.
- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



Structure and Aromaticity

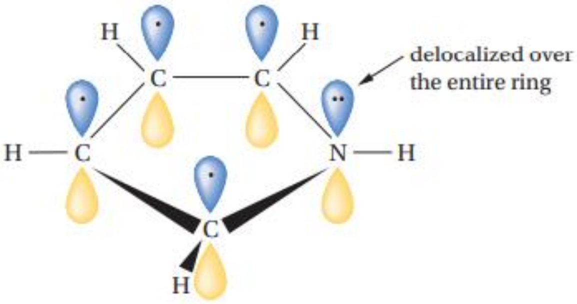
- Pyrrole, furan and thiophene are aromatic because:

1) they fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, thus the grading of aromaticity is in the order of: furan < pyrrole < thiophene < benzene this order is consistent with the order of electronegativity values for oxygen (3.44), nitrogen (3.04) and thiophene (2.56).



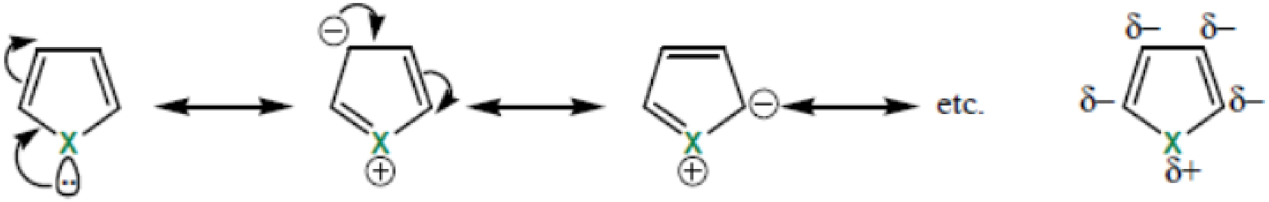
electron pair in a *p* orbital, part of the 6π electron system

electron pair in an sp^2 orbital



delocalized over the entire ring

2) They tend to react by electrophilic substitution due appearance of –ve charge on carbon atoms due to delocalization as shown in the following resonance structures.



Structure and Aromaticity

- The order of aromatic character of these three heterocycles compared to benzene is as follows:

Benzene > Thiophene > pyrrole > Furan

This order is consistent with the *resonance Energies and* order of the electronegativity values.

- In comparison to benzene the order of reactivity in electrophilic substitution is as follows:

Pyrrole > Furan > Thiophene > Benzene

- Eelectrophilic substitution on furan requires very mild non acidic conditions (acids may induce polymerization or ring opening), however, for thiophene the acidity is less critical since it is stable to aqueous minral acids but not to 100 % strong acids or Lewis acids such as $AlCl_3$.

- Regioselectivity: The 2 & 5 (α) positions are more reactive than 3 & 4 (β) Positions, as in pyrrole the intermediate results from electrophilic attack at C2 can be stabillized by three resonance structure while the intermaediate results from the attack C3 is only satbilized by two resonance structures.

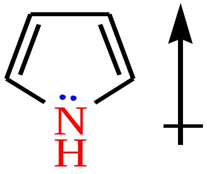
Evidences of aromatic character in pyrrole

1) All ring bonds are intermediates between single and double bonds.

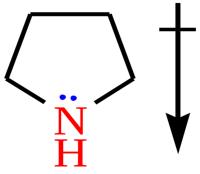
2) It tends to react by electrophilic substitution.

3) Its exceptional lack of basicity and strong acidity as a secondary amine compared to the aliphatic analog (pyrrolidine). This can be explained on the basis of participation of N lone pair in aromatic sextet (see the previous resonance structures) thus the dipole moment of pyrrole compared with pyrolidine is reverted and thus protonation occurs at carbons not at N.

Dipole moment of
pyrrole and its saturated analog

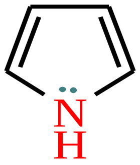


Pyrrole



Pyrrolidine

Basicity of pyrrole and its saturated analog



Pyrrole
aroamtic 2° amine

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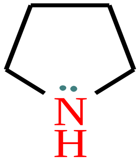
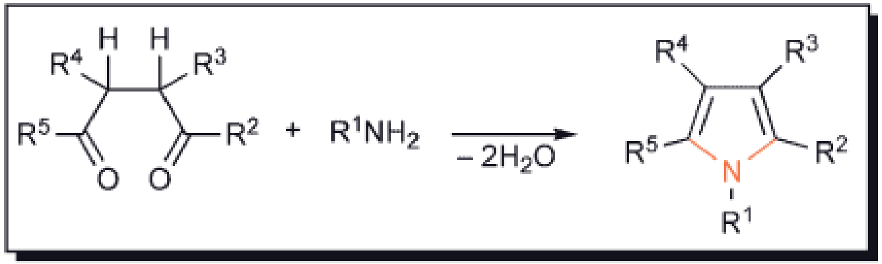


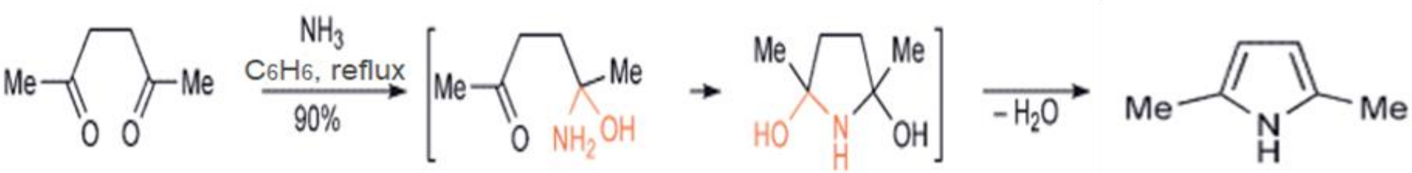
Pyrrolidin
Aliphatic 2° amine

Synthesis of Pyrrole, Furan and Thiophene

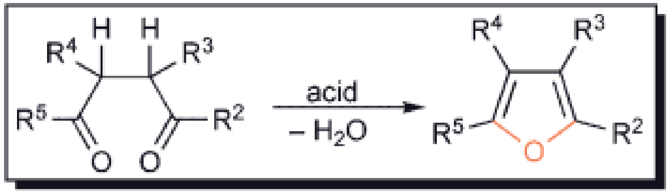
1) From 1,4-dicarbonyl compounds (Paal-Knorr Synthesis)

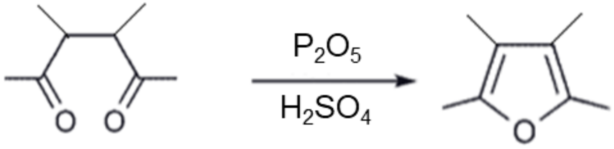
Pyrrol: 1,4-Dicarbonyl compounds can be dehydrated, with ammonia (NH_3) or amines, to form pyrrole.





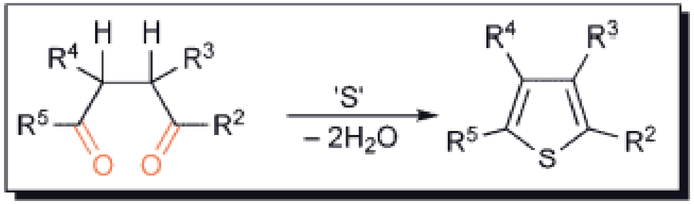
Furan: 1,4-Dicarbonyl compounds can be dehydrated, with acids, to form furans.

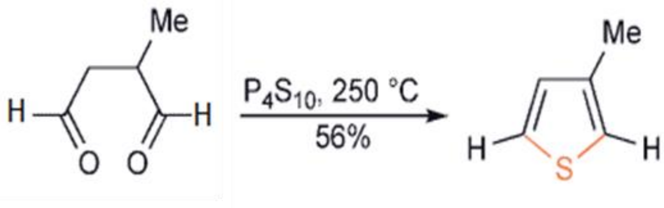




Synthesis of Pyrrole, Furan and Thiophene

Thiophene: 1,4 - Dicarbonyl compound with a source of sulfide, traditionally phosphorus sulfides, to form thiophenes.

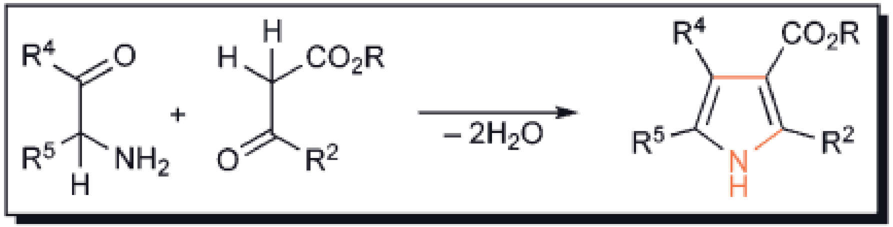


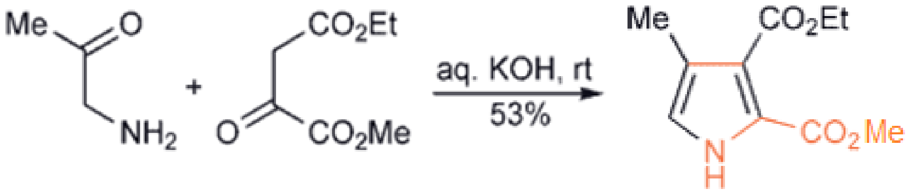


Synthesis of Pyrrole, Furan and Thiophene

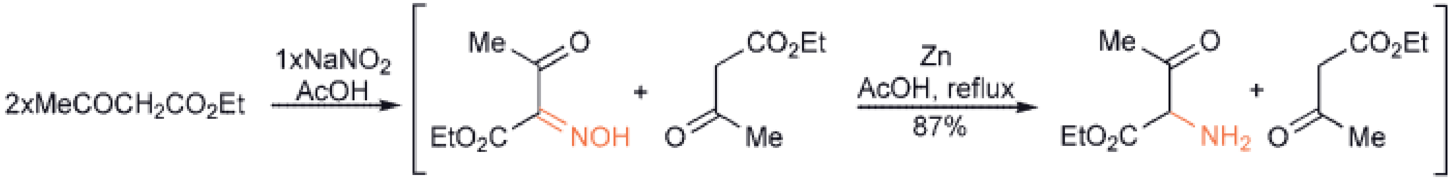
2) Knorr synthesis of Pyrrole

α - Amino - ketones react with carbonyl compounds that have an α - methylene grouping, preferably further activated, for example by ester.





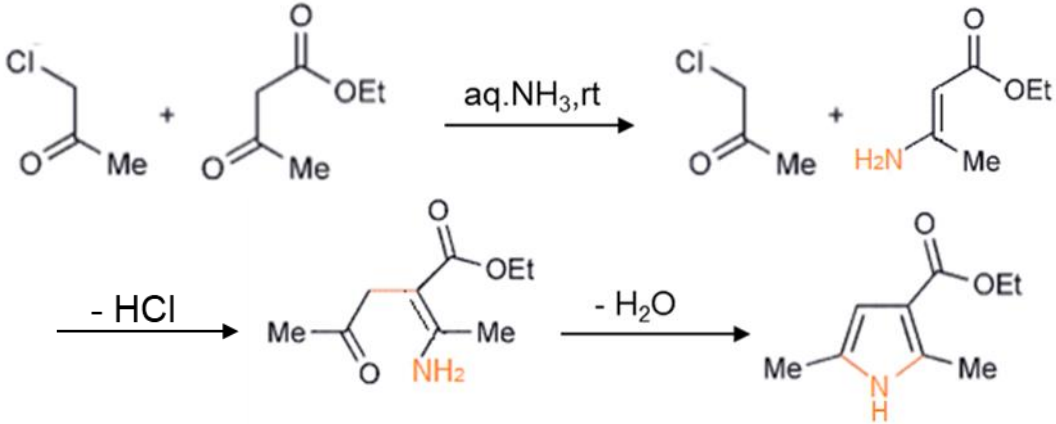
- A way of avoiding the difficulty of handling α - aminocarbonyl compounds is to prepare them in the presence of the second component, with which they are to react. Zinc – acetic acid or sodium dithionite ($Na_2S_2O_4$) can be used to reduce oximino groups to amino.



Synthesis of Pyrrole, Furan and Thiophene

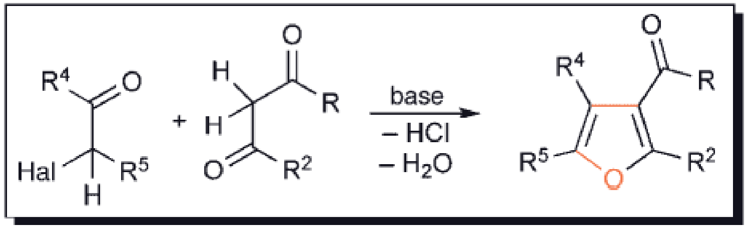
3) The Hantzsch Synthesis of Pyrrole

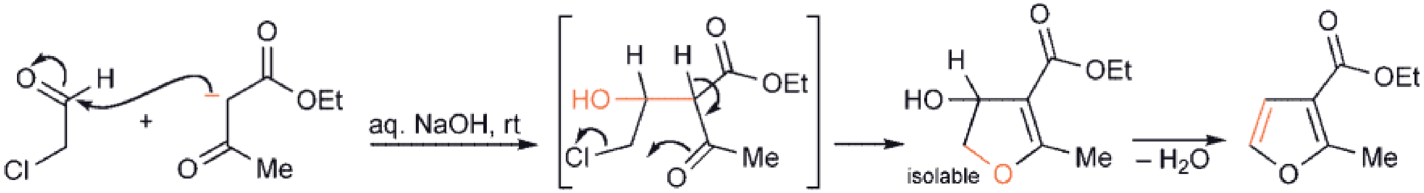
α -Halo-carbonyl compounds react with 1,3 - dicarbonyl compounds in the presence of ammonia to give pyrrole.



4) The Feist-Benary Synthesis of Furan

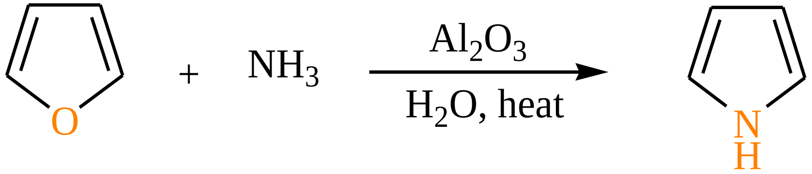
α - Halo - carbonyl compounds react with 1,3-dicarbonyl compounds in the presence of a base (not ammonia) to give furans.





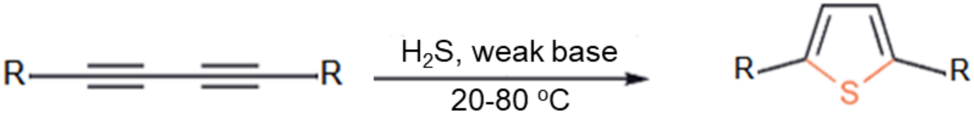
Synthesis of Furan and Thiophene

5) Synthesis of Pyrrole by heating a mixture of furan, ammonia and steam over alumina catalyst.



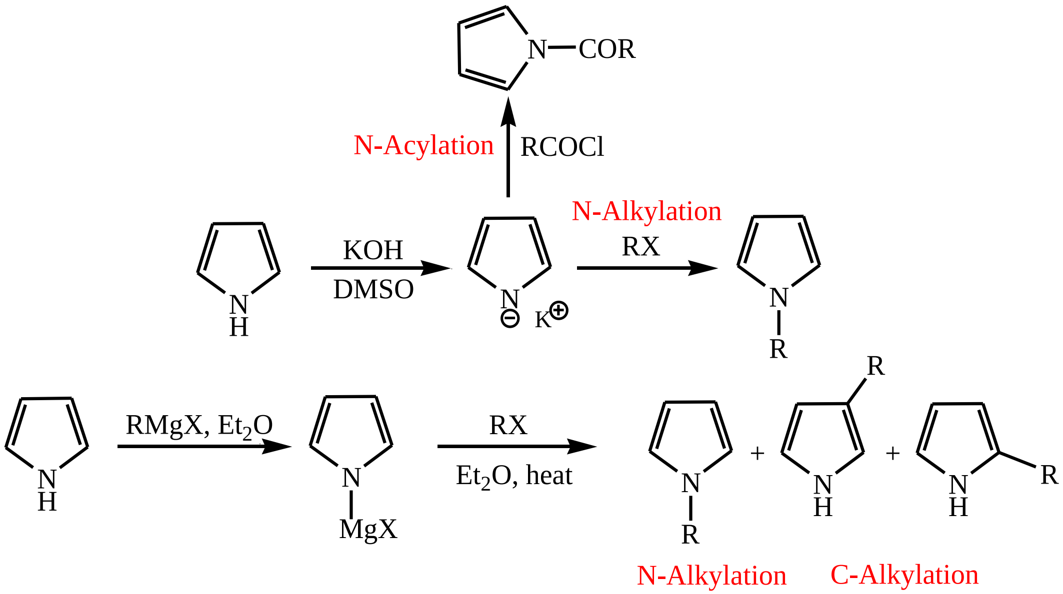
6) Synthesis of Thiophene

Conjugated diynes react smoothly with hydrosulfide or sulfide, under mild conditions to give tiophenes.



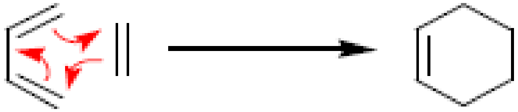
Acidic properties of pyrrole and N-metallated pyrrole

- Due to participation of N lone pair in aromaticity, pyrrole has exceptionally strong acidic properties for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodium amide in liquid ammonia, to give salt like metallated compounds.
- These derivatives can be used to alkylate or acylate pyrrole, the position of substitution may be the nitrogen, the α- or the β-carbon depending on type of metallic cation and the polarity of solvent used as shown below:

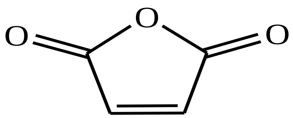


Cycloadition reactions (Diels Alder Reaction)

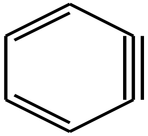
- Cycloaddition reaction is one in which two reactants add together with formation of 2 new C-C bonds at the same time to give a cyclic product e.g. Diels-Alder reaction.
- Diels-Alder reaction involves addition of a compound containing a double or a triple bond (2 π e it is Called dienophile) across the 1,4-position of a conjugated system (4π e, 1,3-diene), with the formation of a six membered ring.



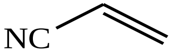
- The heterocyclic compounds can react as a 1,3-diene in D.A.reaction with reactive dienophiles (e.g. maleic anhydride, or benzyne) or with less reactive dienophiles (e.g. acrylonitrile) in presence of catalyst.



Maleic anhydride



Benzyne



Acrylonitrile

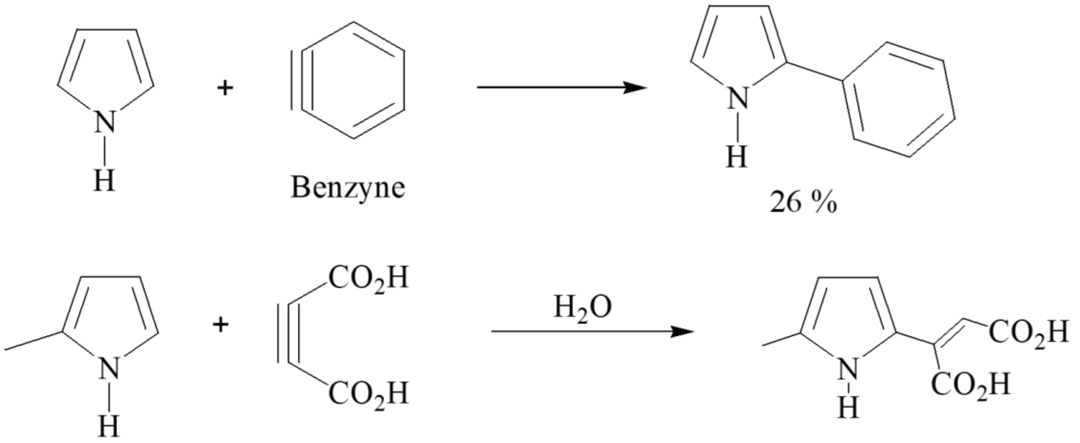
Cycloadition reactions (Diels Alder Reaction)

- The diene can be activated by EDg while the dienophile by EWg.
- Thus N-alkyl pyrrole and N-amino pyrrole are more reactive than pyrrole itself in D.A.reaction but less reactive than furan (the least aromatic 5- membered heterocycle thus the most reactive in addition) .
- The order of reactivity in D.A.reaction is as follows which is the reverse of aromaticity order:

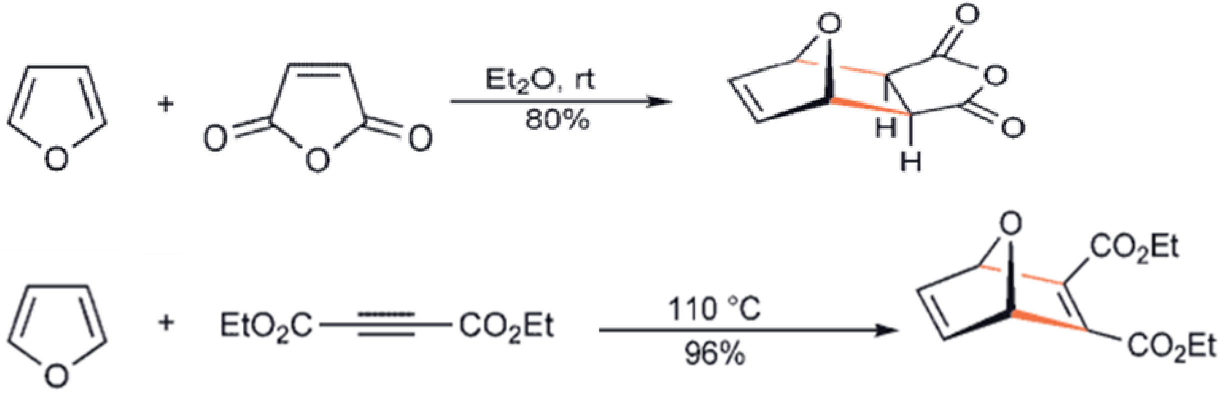
Furan > N-alkyl pyrrole > Pyrrole > Thiophene.

Cycloadition reactions (Diels Alder Reaction)

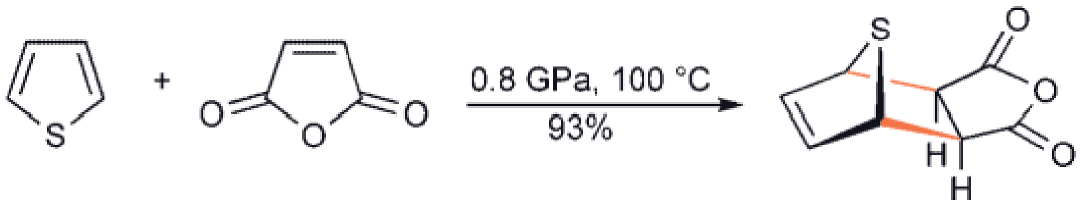
The pyrroles do not undergo easily D.A.reaction but the typical reaction is α-substitutive addition.



Furan



Thiophene

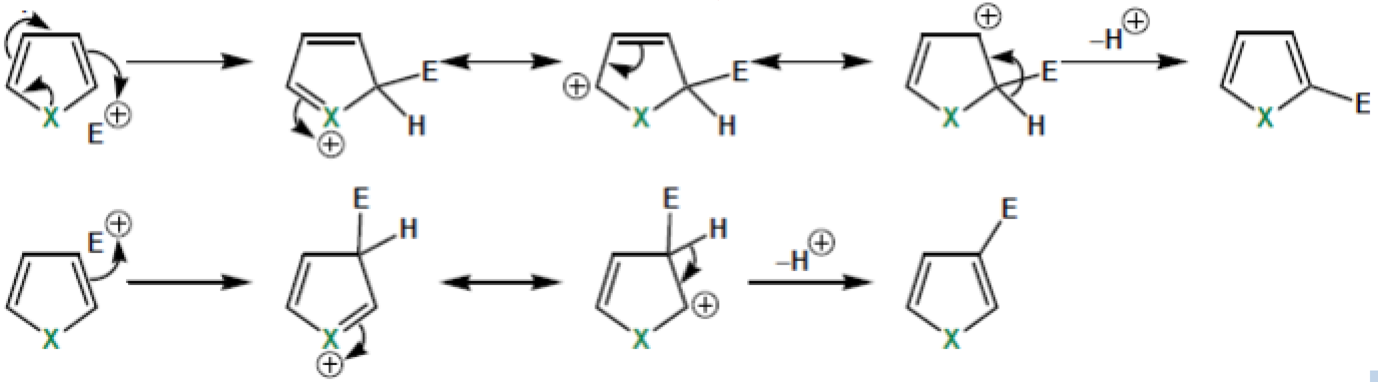


Electrophilic Substitution

- Electrophilic substitution normally occurs at a carbon atoms.

- Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).

- This is due to attack at C-2 gives more stable intermediate (it is stabilized by three resonance structure) than the intermediate resulted from C-3 attack (it is stabilized by two resonance structure).



Three resonance structures, more stable

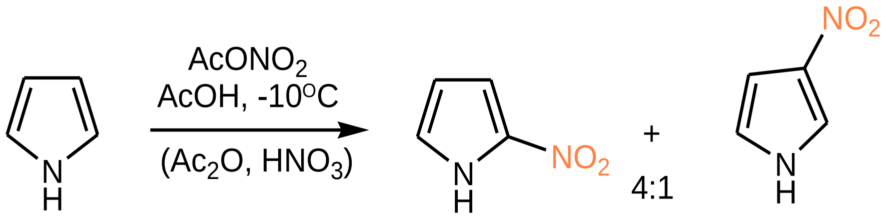
Attack at C-2

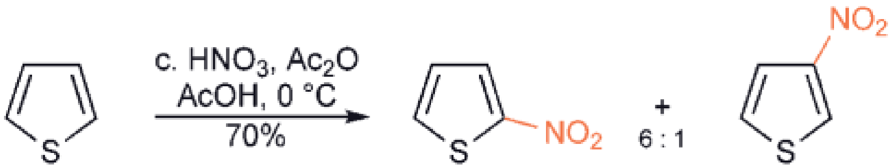
Attack at C-3

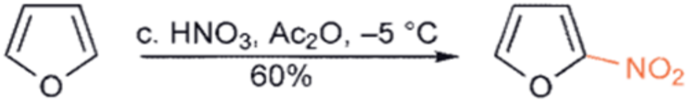
Two resonance structures, less stable

Electrophilic Substitution Reactions

1) Nitration

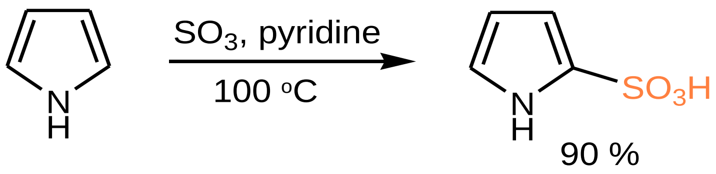


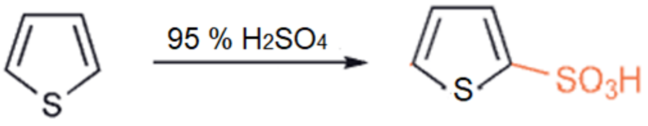


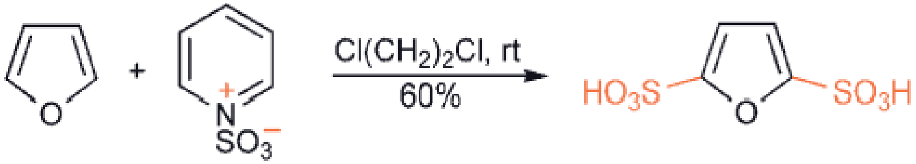


Electrophilic Substitution Reactions

2) Sulfonation

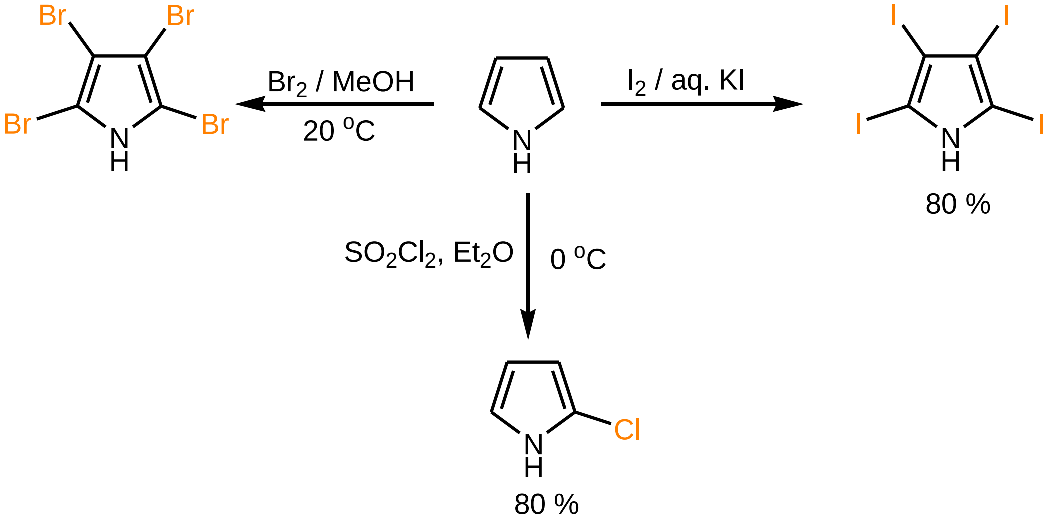


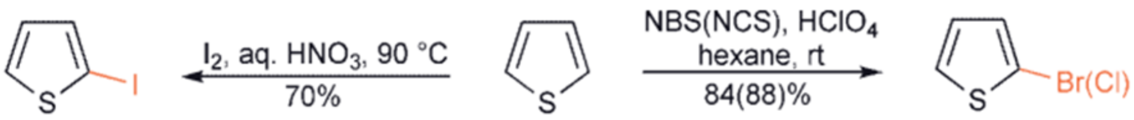




Electrophilic Substitution Reactions

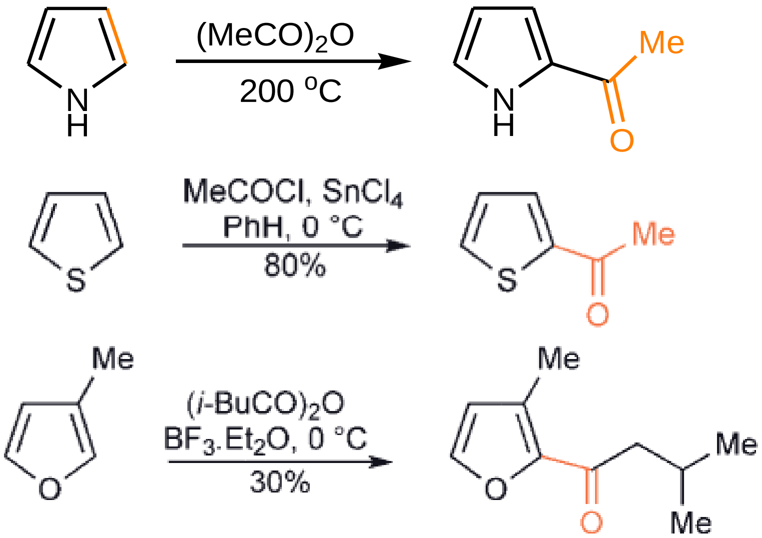
3) Halogenation





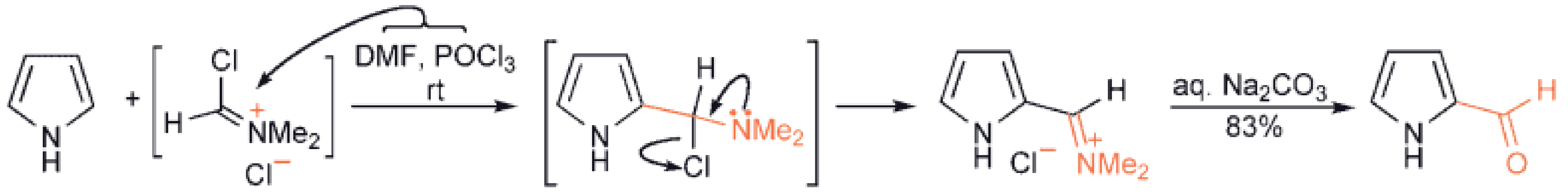
Electrophilic Substitution Reactions

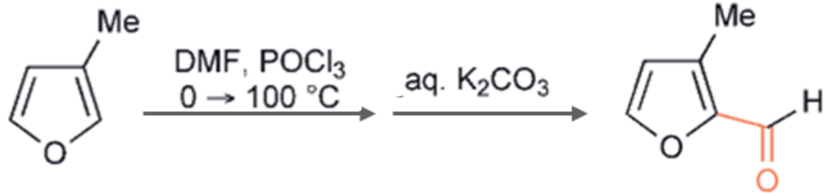
4) Friedel-Crafts Acylation (*C*-acylation)



5) Vilsmeier acylatior

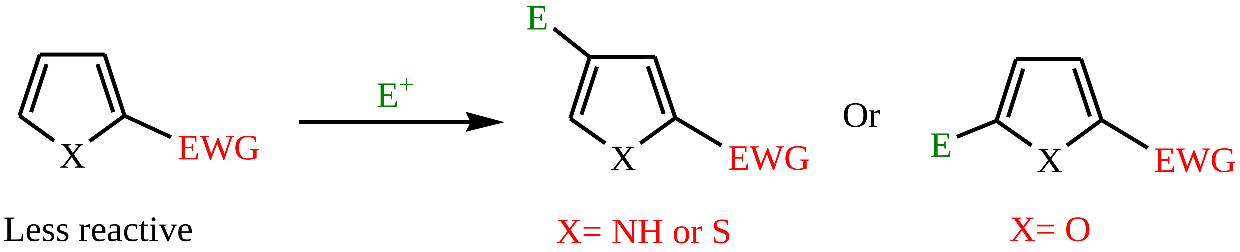
Formylation of pyrrole and furan by reacting it with dimethylformamide/phosphoryl chloride.



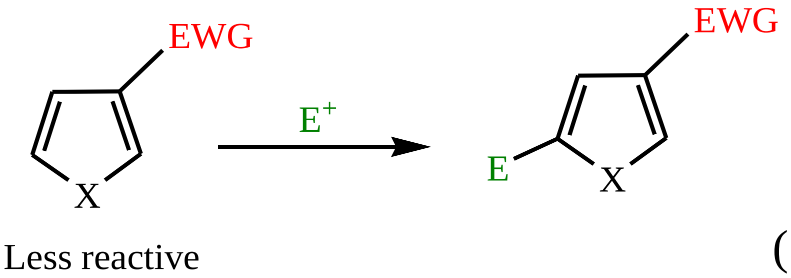


Second Electrophilic Substitution

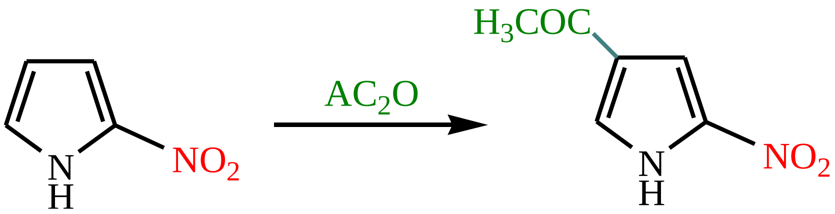
A) Monosubstituted with Electro Withdrawing group



(incoming E^+ directed to position 4 or 5)

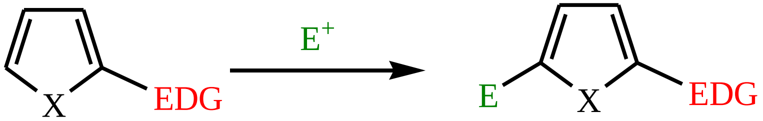


(incoming E^+ directed to position 5)



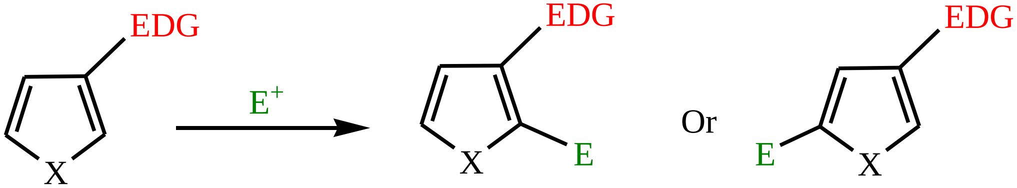
Second Electrophilic Substitution

B) Monosubstituted with Electro Donating group



More reactive

(incoming E^+ directed to position 5)



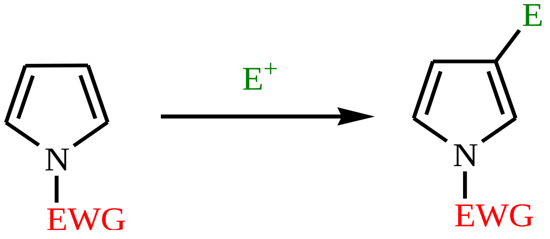
More reactive

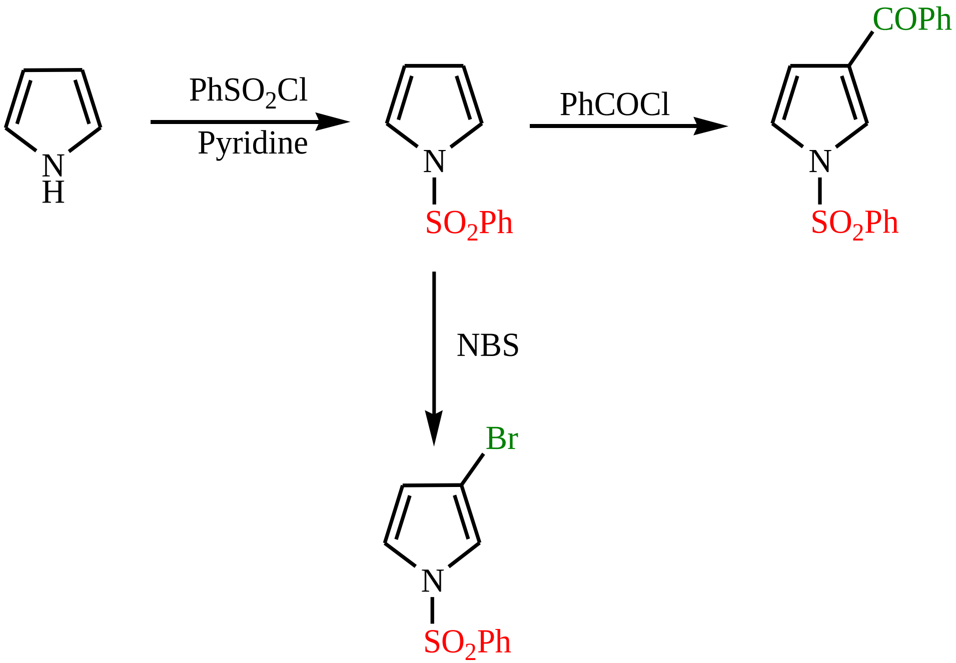
(incoming E^+ directed to position 2 or 5)

Second Electrophilic Substitution

C) N-substituted pyrrole with electron withdrawing group

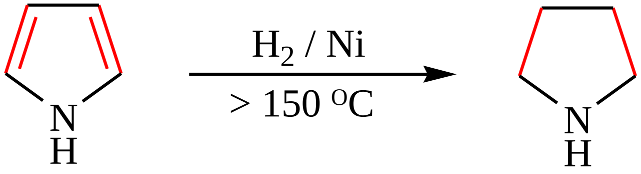
(incoming E$^+$ directed to position 3)

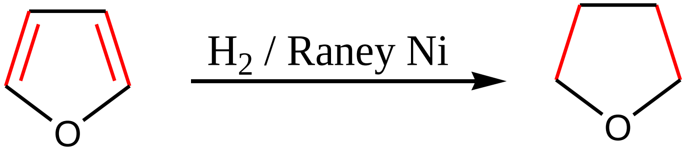


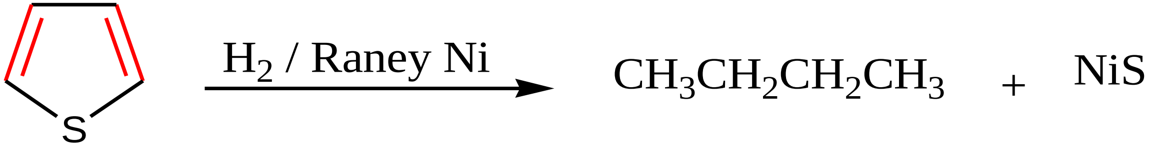


Reduction and Oxidation Reaction

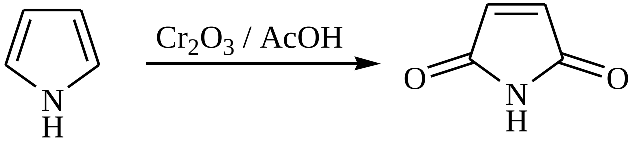
Reduction reaction

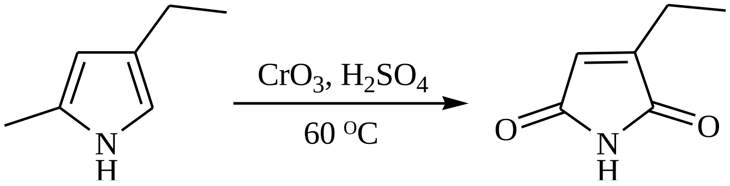






Oxidation of Pyrrole

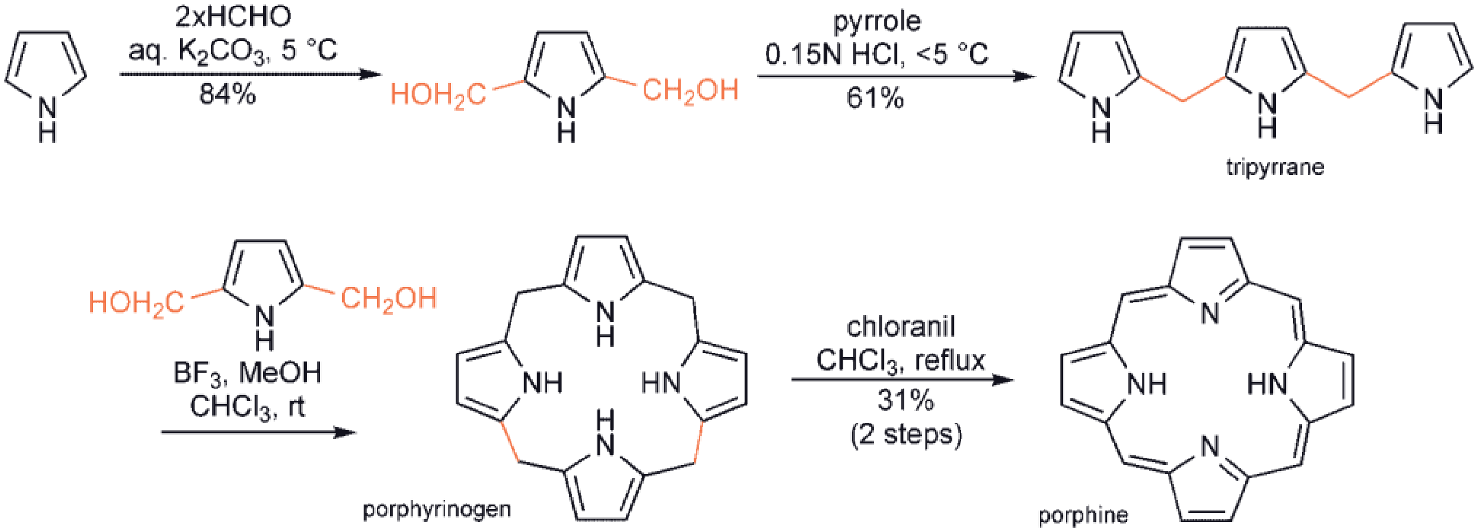


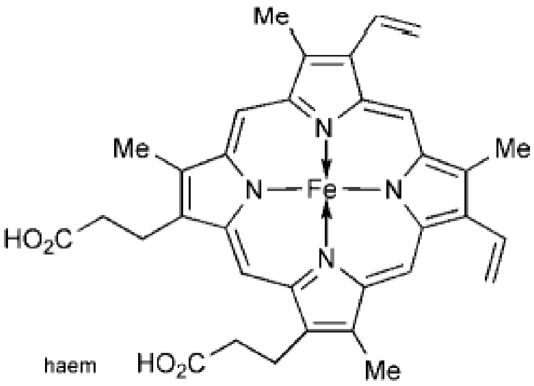


Reaction of pyrrole

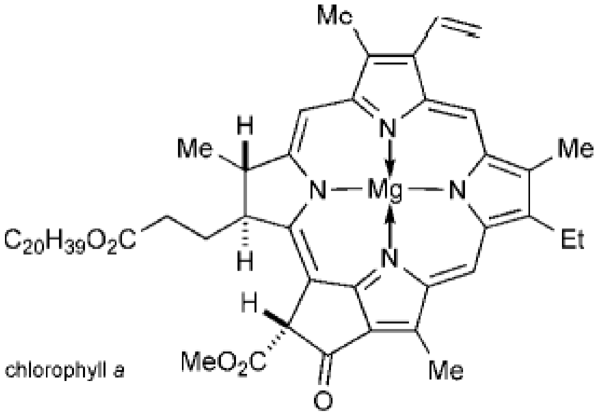
Condensation with Aldehydes and Ketones

The bis(pyrrol-2-yl)methane, can be obtained directly from pyrrole with aldehyde; 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-hydroxymethylpyrrole gives porphyrinogen, which can be oxidised with chloranil to porphine that found in many natural compounds such as haem in animal and in chlorophyll in plant.

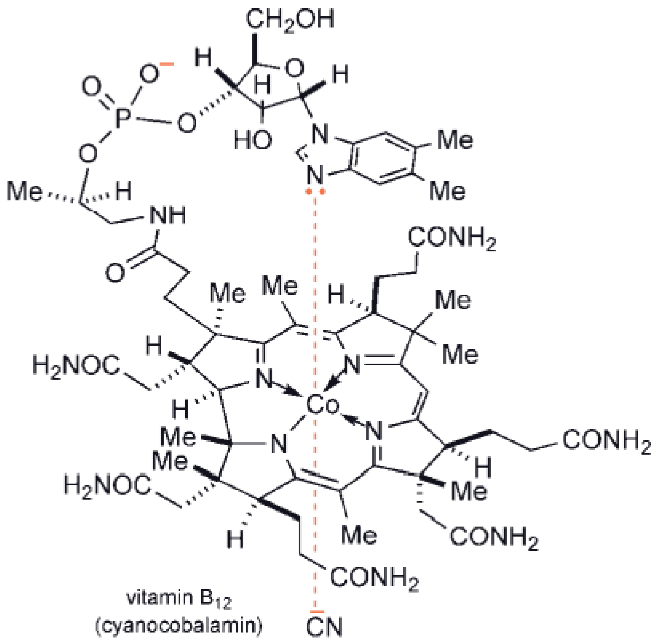




haem



chlorophyll *a*



vitamin B_{12}
(cyanocobalamin)