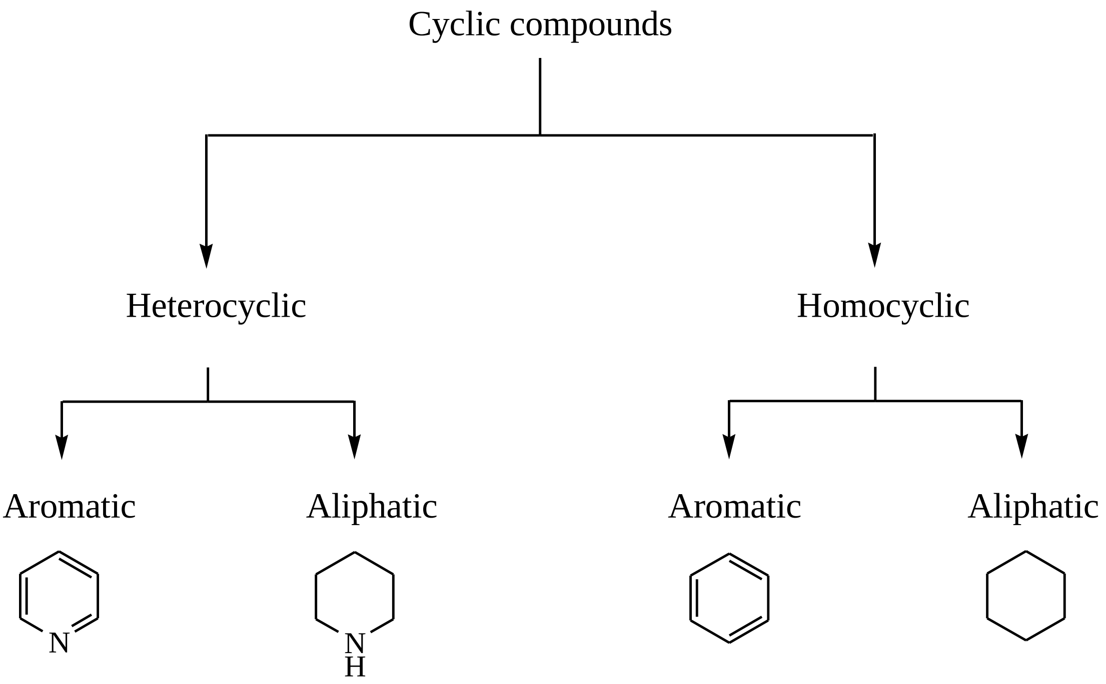
1) Heterocyclic compounds :

A heterocyclic compound is one that contains a ring made up of more than one kind of atoms (like O , S , N) beside carbon atoms.
The most important rings are the five – and six – membered heterocycles.

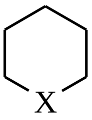
The following scheme illustrates the classification of cyclic compounds:



Heterocyclic compounds may be classified into two types:

1- The aliphatic heterocycles: which are the cyclic analogues of amines, ethers, esters and thioesters, their properties are influenced by ring strain. They react largely like their aliphatic analogues.

e.g.

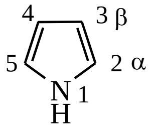


X= O ⟹ oxane reacts as dialkyl ethers
X= S ⟹ thiane reacts as dialkyl sulfides
X= NH ⟹ piperdine reacts as secondary aliphatic amines

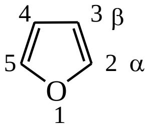
2- The aromatic heterocycles: which shows aromatic behavior as in benzene. These compounds follow the Huckel's rule which states that " cyclic conjugated and planar systems having (4n+2) π electrons are aromatic ", these compounds can be classified into two types:

a- This type is the same as in cyclopentadiene with replacing (CH_2) group by hetero atom like (O , S , N), in which the unshared pair of electrons will be a part of the aromatic sextet.

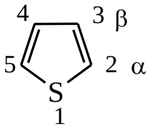
e.g.:



Pyrrole

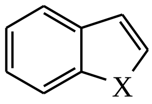


Furan

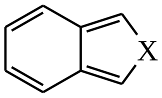


Thiophene

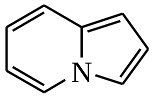
Monocyclic system



X= NH Indole
X= O Benzofuran
X= S Benzothiophene



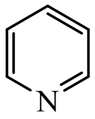
Isoindole
Isobenzofuran
Isobenzothiophene



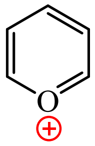
Indolizine

Bicyclic system

b- The second type is the same as in benzene with the replacement of (- CH_2=) unit by hetero atom like (N) as in pyridine, or (O) atom as in pyrylium salts.

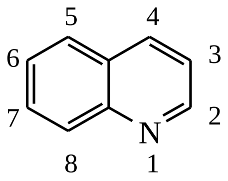


Pyridine

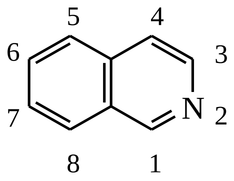


Pyrylium cation

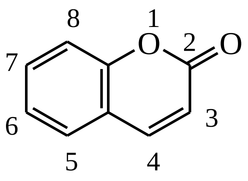
As in five membered heterocycles; six membered heterocyclic compounds may exist as monocyclic system as mentioned above or as bicyclic system as the following:



Quinoline

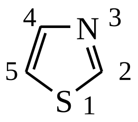


Isoquinoline

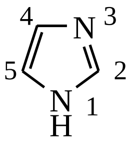


Coumarin

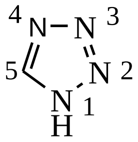
Furthermore heterocyclic compounds may contain more than one hetero atom which could be of the same type or different type, and here again they could be five or six membered ring system which either mono or bi cyclic systems.



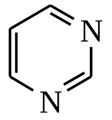
Thiazole



Imidazole

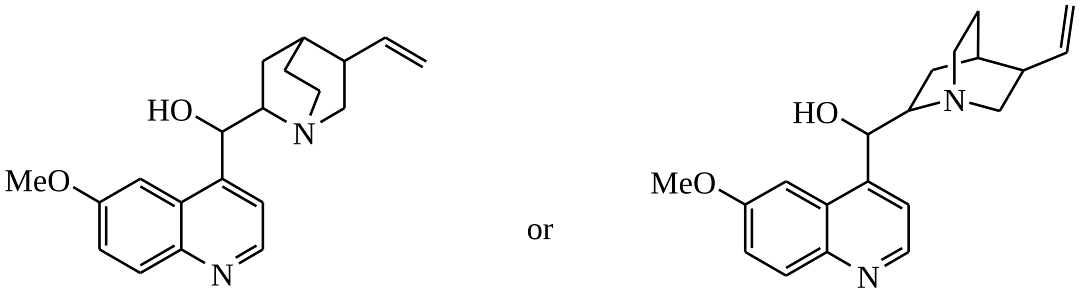


Tetrazole



Pyrimidine

Significance: Two third of all organic compounds are aromatic heterocycles. Most pharmaceuticals are heterocycles like quinine which used as antimalarial drug.



Quinine

Many heterocyclic compounds occur naturally and are actively involved in biology e.g. nucleic acids (purine and pyrimidine bases), vitamins (B_1, B_2, B_3, B_6 and C), penicillins, chlorophyll ……..etc.

The study of hrterocyclic chemistry is a vast and expanding area of chemistry because of their applications in medicine, agriculture and other fields.

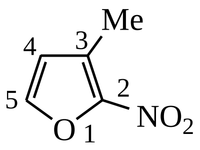
2) Systematic nomenclature of heterocyclic compounds:

The derivation of systematic name is based on its structure. The IUPAC rules allow two nomenclatures. The Hantzsch – Widman method is recommended for three – to ten – membered ring system.

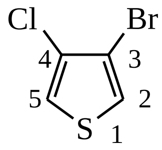
For larger ring heterocycles, replacement nomenclature should be used.

Simply, in five membered ring system numbering start from the hetero atom and proceed in a manner that the substituents takes the lowest possible number. (note: substituents names should be written alphabetically).

e.g.

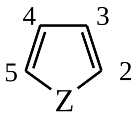


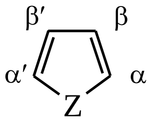
3-methyl-2-nitro furan



3-bromo-4-chloro thiophene

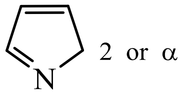
Latin letters can be also used instead of numbers to indicate the substituent position:



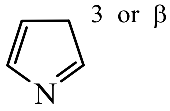


Z= O, S, N

Nomenclature of these compounds is also depend on the position of the double bonds, for example pyrrole exist in two tautomeric forms *2H*-pyrrolenine and *3H*-pyrrolenine:

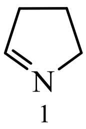


2H-pyrrole

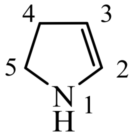


3H-pyrrole

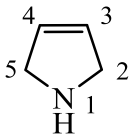
Furthermore partially saturated dihydropyrroles are called pyrrolines, three of these namely Δ^1 – , Δ^2 – and Δ^3 – pyrrolines are possible. The fully saturated pyrrole is designated as pyrrolidine.



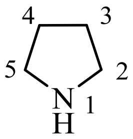
Δ^1–pyrroline
or
3,4-dihydro-2H-pyrrole



Δ^2–pyrroline
or
4,5-dihydro-1H-pyrrole



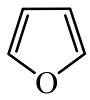
Δ^3–pyrroline
or
2,5-dihydro-1H-pyrrole

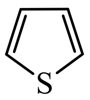


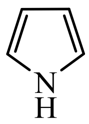
pyrrolidine

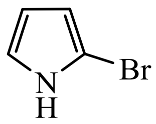
Note: (Δ) refer to the double bond position.

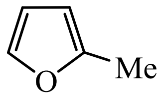
General examples:

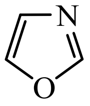

Furan

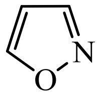

Thiophene

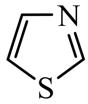

Pyrrole

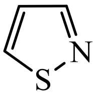

2-Bromo pyrrole

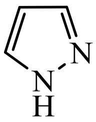

2-Methyl furan

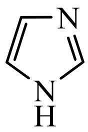

Oxazole

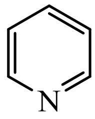

Isoxazole

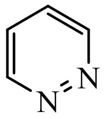

Thiazole

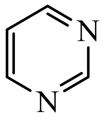

Isothiazole

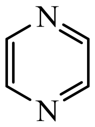

Pyrazole

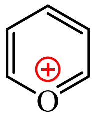

Imidazole

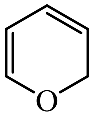

Pyridine

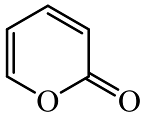

Pyridazine

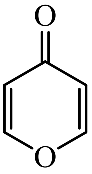

Pyrimidine


Pyrazine


Pyrylium cation


2H-pyrane

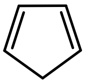

α or 2- pyrone


γ or 4- pyrone

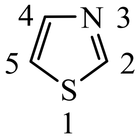
On the other hand the replacement method can be summarized as the following:

a- The hetero atom is indicated by a prefix:
O= oxa , S= thia , N= aza

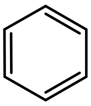
b- *Position and prefix for each hetero atom are written in front of the name of the corresponding hydrocarbon.*
This is derived from the heterocyclic system by replacing every hetero atom by CH_2, CH or C:



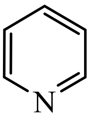
Cyclopentadiene



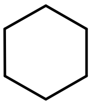
1-Thia-3-azacyclopenta-2,4-diene



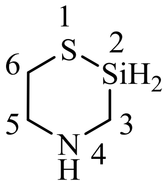
Benzene



Azabenzene



Cyclohexane



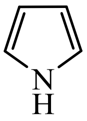
1-Thia-4-aza-2-silacyclohexane

Sequence and numbering follow the rules in Hantzch – Widman method in which:

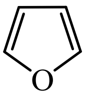
1) The hetero atom sequence:
   O > S > Se > Te > N > P > As > Sb > Bi > Si ……
2) Numbering start from the hetero atom taking in our account the above sequence.

3) Five – membered rings:

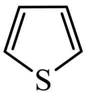
The simplest five – membered heterocyclic compounds are pyrrole, furan and thiophene, each of which contains a single hetero atom.



Pyrrole



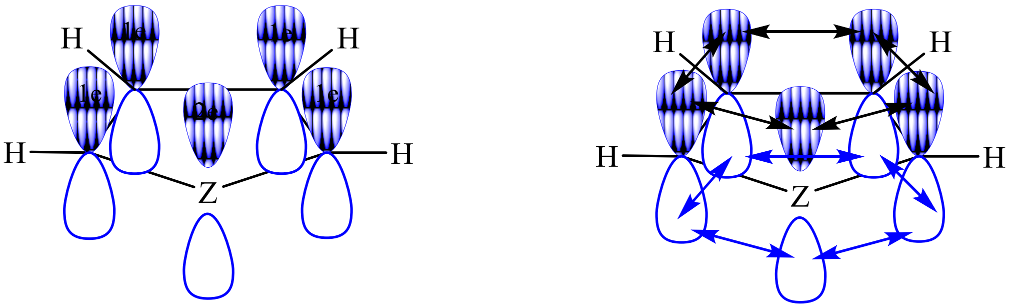
Furan



Thiophene

If we examine the structure for these compounds we can find that they consist of five membered planar aromatic ring system, since the (*p*) orbital of each of oxygen, nitrogen or sulfur possess an unshared pair of electrons that overlap with the (π) orbital's resulting in the formation of two electronic clouds (π clouds) one above and one below the plane of the ring as in benzene figure (1).

Note: *the π clouds contain a total six electrons, the aromatic sextet.*



(a) (b)

Z= NH, O or S

Figure (1): five membered heterocyclic molecule. (a) Two electrons in *p* orbital of hetero atom; one electron in *p* orbital of each carbon. (b) overlap of *p* orbitals to form π bonds.

Delocalization of the π electrons stabilizes the ring, thus the resonance energy for furan is 23 Kcal/mole while thiophene and pyrrole 31 kcal/mole. Thus the resonance energy will follow the sequence:

Benzene 36 > Pyrrole and Thiophene 31 > Furan 23

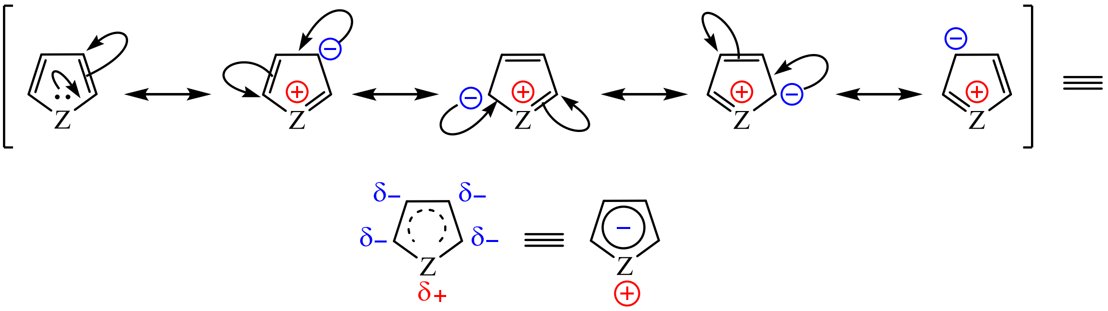
Aromatic properties for these compounds compared with benzene will be as the following:

Benzene > Thiophene > Pyrrole > Furan

Since benzene is a homocyclic compound and there is no differences in electronegativity between ring atoms, as in hetero aromatic systems.
Thus as the electronegativity of the hetero atom increase, the contribution of the unshared pair of electrons will decrease, hence the aromaticity (aromatic character) will decrease. So thiophene has more aromatic properties than pyrrole and furan respectively.

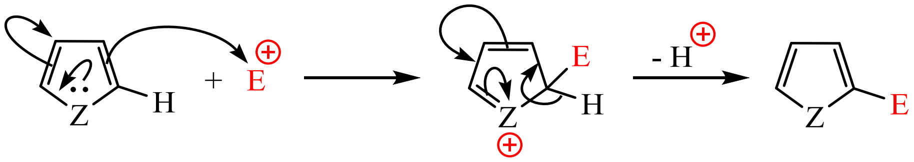
Electronegativity: $\overleftarrow{\text{O (3.44) > N (3.04) > S (2.58)}}$

Delocalization will produce a resonance hybrid structures as the following:



Z= NH, O or S

These compounds are reactive toward electrophilic reagents (like aromatic compounds) and this due to the contribution of the lone pair of electrons at the hetero atom (O, S or N) by mesomeric effect as the following:



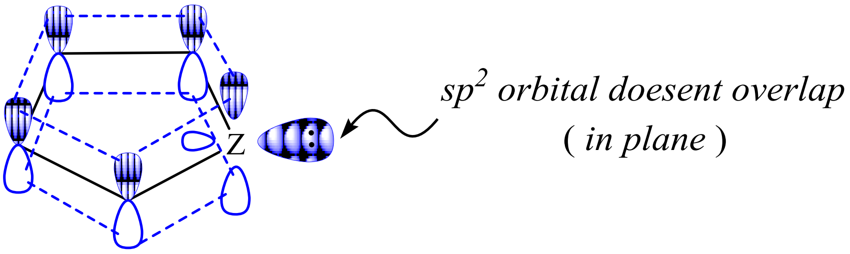
(Electrophilic Substitution)

The reactivity sequence will be as following:

Pyrrole > Furan > Thiophene > Benzene

***Notes*:**

a) *Pyrrole is more reactive than furan since the resonance energy is higher.*
b) *Thiophene is less reactive than furan towards electrophilic substitution due to the p electrons of sulfur are in 3p orbital which overlap less effectively than the 2p orbital of N or O atoms with the 2p orbital of carbon.*
c) *The nitrogen atom has only one lone pair of electros, while both of oxygen and sulfur have two lone pair of electrons.*
d) *As the number of lone pair increase the donation is decreased.*
e) *The second lone pair of electrons is placed in the sp^2 hybrid orbital in plane with no chance to overlap as the following:*

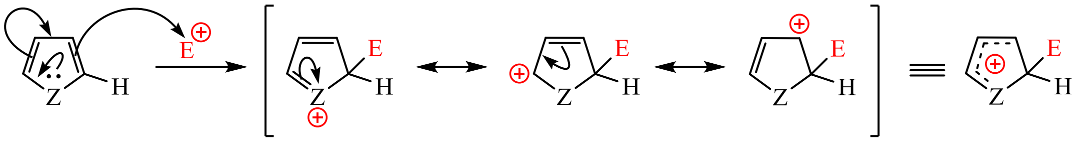


4) Relative reactivity of α- and β- positions:

As we learned from our previous study that (electron donating groups EDGs) on benzene ring direct the incoming electrophile to (*o* – *p*) positions, while (electron withdrawing groups EWGs) direct to (*m*).

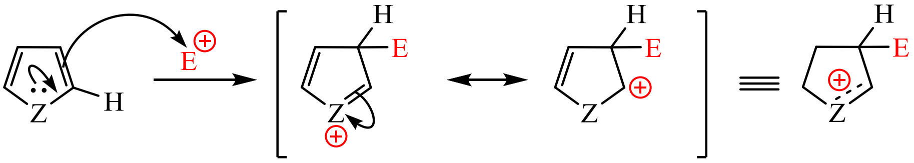
In heterocyclic system the hetero atom play a role in the direction of the incoming electrophile in the electrophilic substitution reactions as the following:

1) Attack at C2 or α:



more stable (I)

2) Attack at C3 or β:



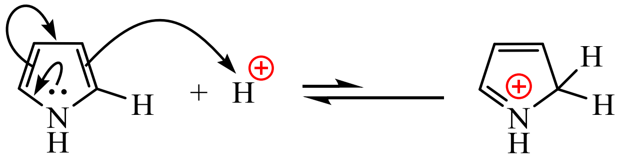
less stable (II)

Attack at position 2 yields a carbocation that have a three hybrid structures, while attack at position 3 yields a carbocation with two hybrid structures only, thus attack at position 2 is preferable than that at position 3, since the developing positive (+ve) charge is accommodate by three atoms of the ring instead of by only two.

5) Pyrrole:

Pyrrole have been discovered for the first time by Anderson in (1857). It is a colorless liquid, b.p.= 129°C and its odor like chloroform.

Pyrrole is nonbasic compared to ordinary amines, since the lone pair of electrons on nitrogen is tied up by conjugation.

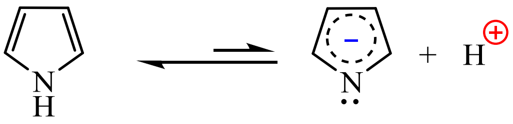


pKa= - 4.4

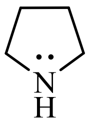
*<u>**Note:**</u> very strong acid is required to affect protonation.*

On the other hand, pyrroles are not only very nonbasic, they are in fact relatively acidic.

Clearly we can see that pKa for pyrrolidine = 35 as in amines while in pyrrole = 16.5, this increasing in acidity is due to the change from *sp*^{3} to *sp*^{2} hybridization and the delocalization of the negative (-ve) charge.



Thus pyrrole is very weak base compared with pyrrolidine and even pyridine as shown below:



(1)

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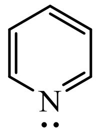

(2)

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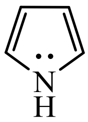
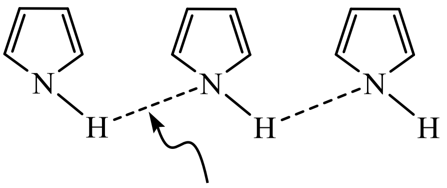


(3)

1) The lone pair of electrons is free i.e. like aliphatic amines.
2) The lone pair doesn’t involve in resonance.
3) The lone pair is tied up by conjugation.

Pyrrole can form intermolecular hydrogen bonding, thus it possess boiling point higher than thiophene 84°C and furan 32°C which cannot form these bonds:



(an intermolecular hydrogen bonding)

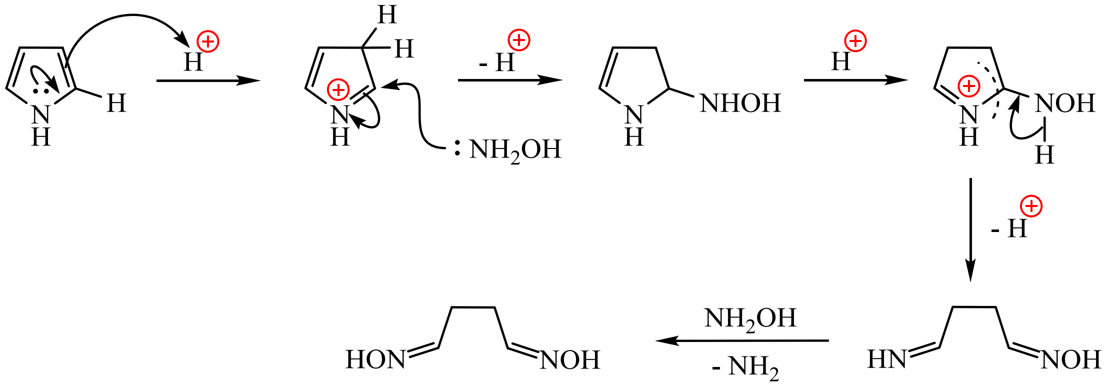
5.1) Chemical properties and reactions of pyrrole:

Pyrrole resist nucleophilic substitution or addition reactions, but it react with electrophilic reagents (electrophilic substitution reactions), furthermore it shows some acidic and basic properties (amphoteric) as mentioned previously.

5.1.1) Ring opening of pyrrole:

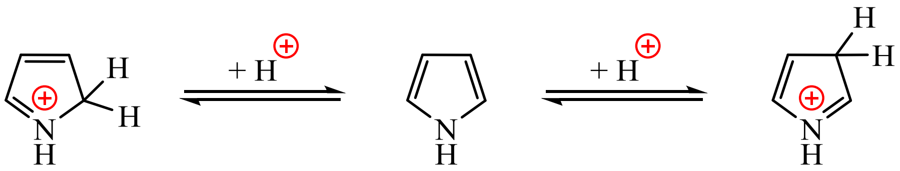
Pyrrole ring doesn't open easily by its treatment with acids or bases at room temperature.

But reaction of pyrrole at its boiling point with alcoholic hydroxylamine will give the dioxime of succinaldehyde.



5.1.2) Addition reactions:

Pyrrole has aromatic properties due to the presence of the lonepair of electrons that complete the aromatic sextet, on the other hand this lone pair made pyrrole act as very weak base pKa= - 4.4

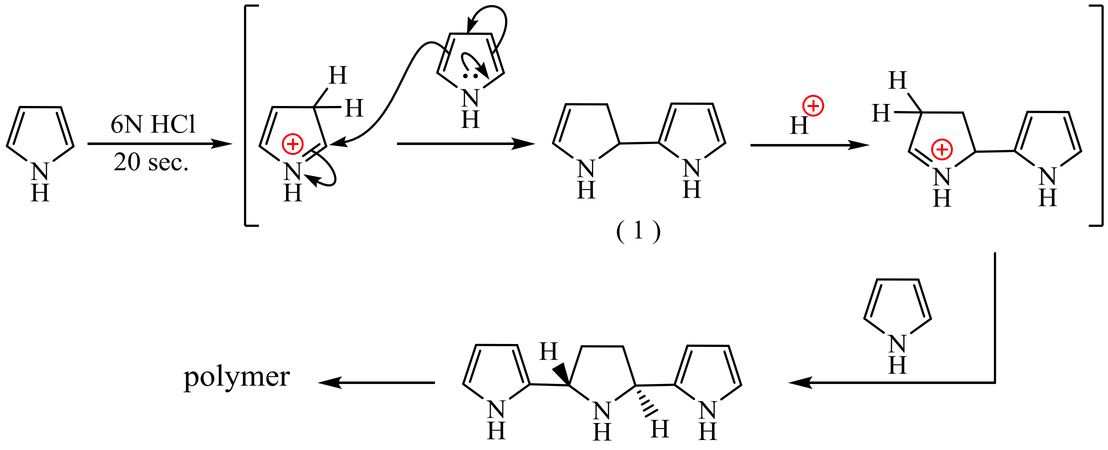


H2- pyrrolium cation

H3- pyrrolium cation

Protonation doesn’t occur on the nitrogen atom but 80% on C-2 and 20% on C-3.

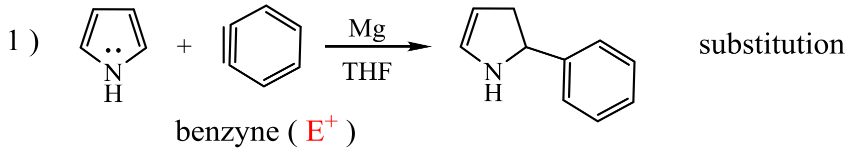
Treatment of pyrrole with (6 N HCl) at 0°C for 20 sec. produce crystalline material (2) that formed from electrophilic addition of H3-pyrrolium cation to pyrrole molecule to give (1) which protonated at 4 position followed by addition to another pyrrole molecule to give the final product:

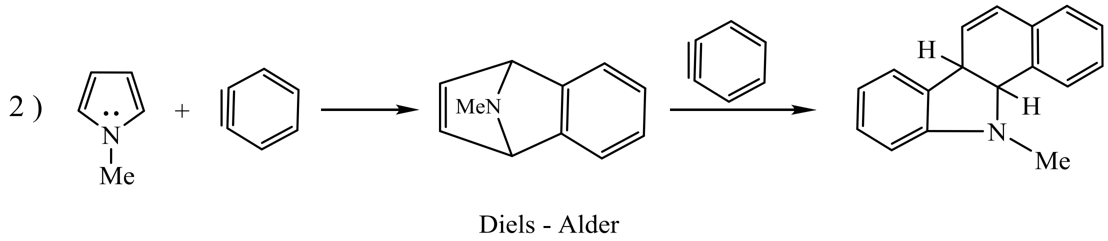


(2)

***Note**: strong acidic conditions will lead to polymerization.*

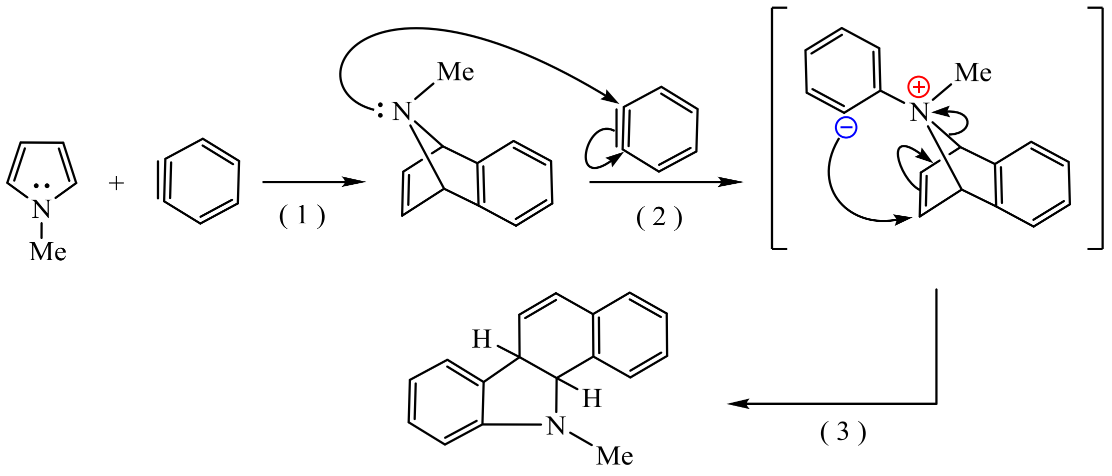
A few examples shows that pyrrole can react as a diene especially when the nitrogen atom substituted by alkyl group.





The first reaction is an ordinary electrophilic substitution reaction, while the second reaction is combined of three steps as the following:

1) The first step is Diels – Alder reaction.
2) The second step is nucleophilic addition to benzyne.
3) The final step involve aza – Claisen rearrangement.



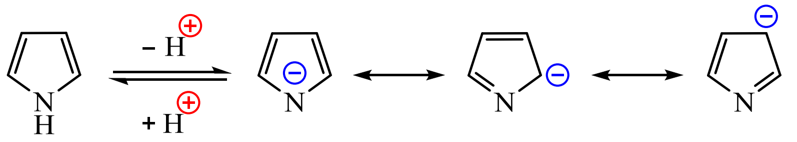
5.1.3) Substitution reactions:

Pyrrole undergoes two types of substitution reactions, the first one at the nitrogen atom while the second at one or more carbon atoms of pyrrole ring.

5.1.3.1) Substitution at nitrogen atom:

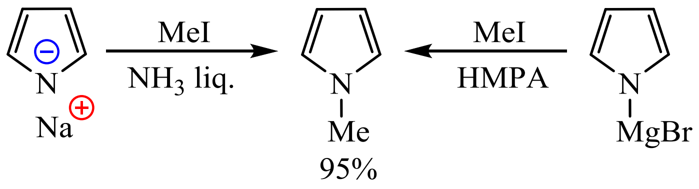
As a consequence of its weakly acidic properties, pyrrole react readily with strong bases to generate a reactive pyrrolyl anion. The aromatic properties for this anion more than pyrrole itself.

Note: Reaction of pyrrole with metals like potassium will produse the anion (pyrrolyl anion), and the hydrogen abstraction rate increase in the case of presence of (EWGs) on pyrrole ring which weaken the (N – H) bond i.e. increasing the acidity of pyrrole.



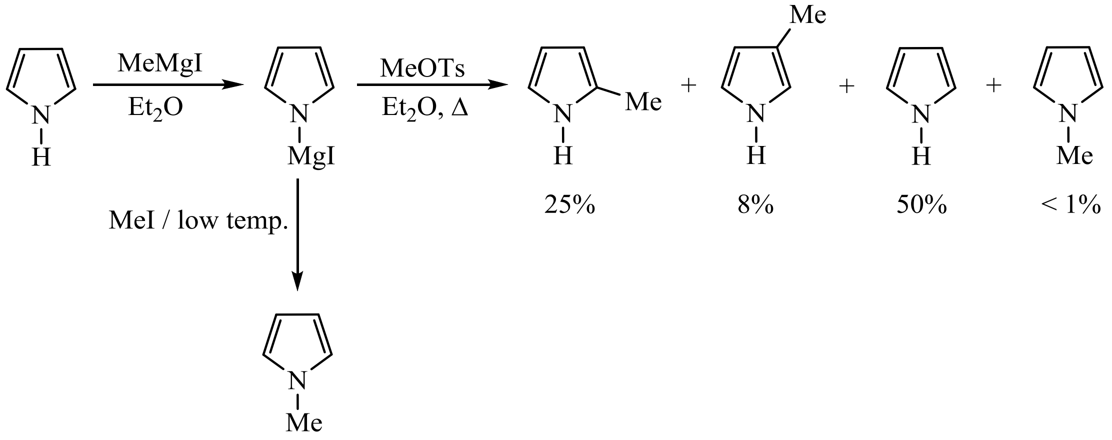
(pyrrolyl anion)

The salt used in the synthesis of substituted pyrrole (at nitrogen atom).
e.g. Reaction of pyrrolyl anion with alkyl halide produce N–alkyl pyrrole in high yield.

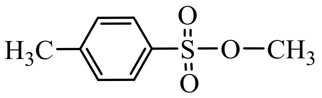


(HMPA): Hexamethylphosphoramide $[(CH_3)_2N]_3PO$, solvent for polymers, gases and organometalic compounds.

Another method that pyrrole undergoes substitution reaction at nitrogen by the reaction of pyrrole with Grignard reagent (RMgX) to produce pyrrolyl magnesium halide which react itself with alkyl halide at room temperature to produce 1-alkyl pyrrole (substitution at position 1). Increasing the temperature will cause addition at carbon atoms of pyrrole ring.

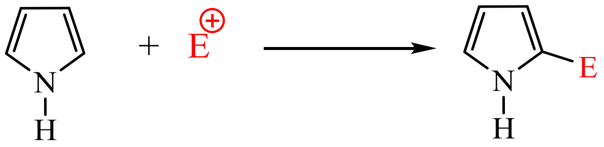


(MeOTs): Methyl p- toluene sulfonate or Methyl tosylate =



5.1.3.2) Substitution at carbon (electrophilic aromatic substitution):

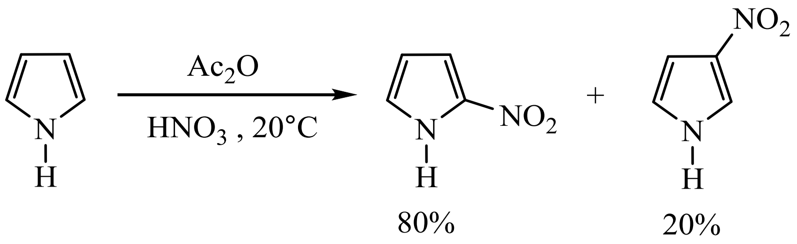
In general, pyrrole undergoes electrophilic substitution reaction at α–position as we mentioned previously. Pyrrole is much more reactive than benzene, the high reactivity of pyrrole (even furan and thiophene) makes it possible to use milder reagents comparing with those used in benzene or its derivatives, since drastic conditions will cause ring opening or polymerization, thus it is necessary to modify the usual reagents.



α C or (2&5)

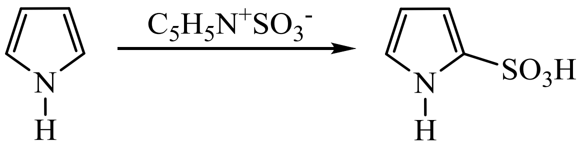
Reaction	**Electrophilic reagent**	**% yield**
Nitration	$AcNO_3$; Ac_2O (-10°C)	51
Sulfonation	$C_5H_5N^+SO_3^-$	90
Halogenation	SO_2Cl_2 / Et_2O , (0°C)	80
Acylation	Ac_2O / (150 - 200°C)	54

e.g.



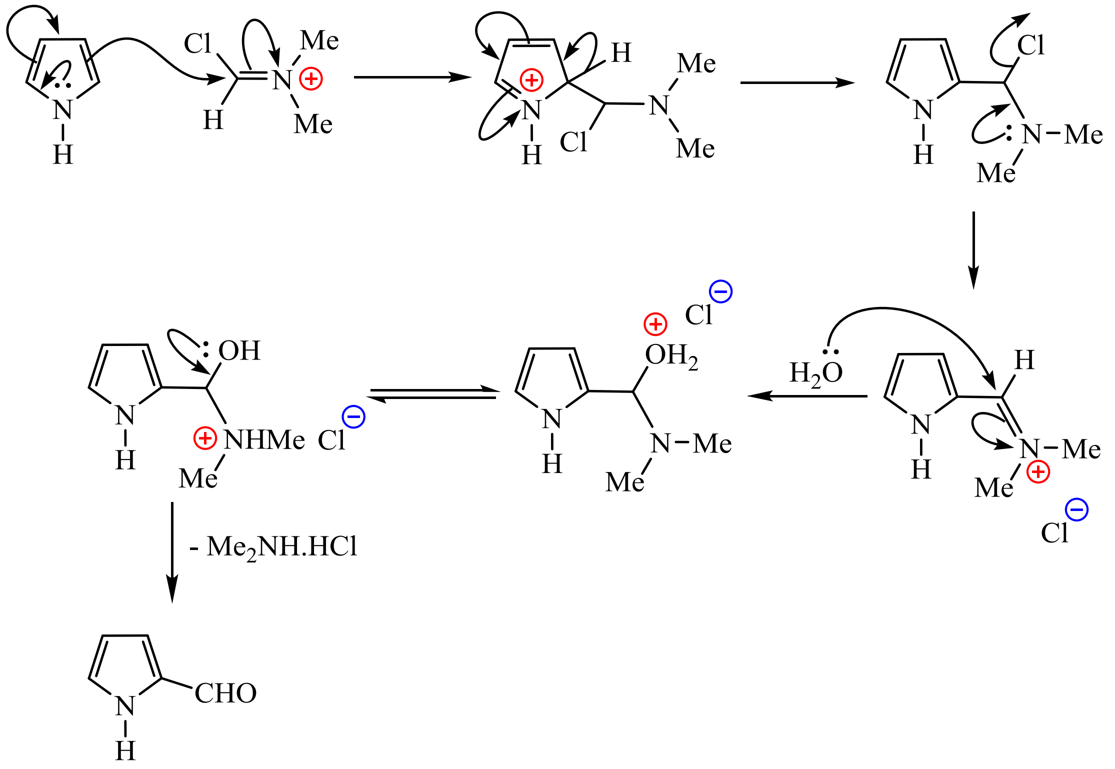
Notes:

1) *A mixture of acetic anhydride and nitric acid will produce acetyl nitrate as a nitrating agent.*
2) *A mixture of concentrated nitric acid and sulfuric acid is not used in nitration since it will lead to pyrrole polymerization.*

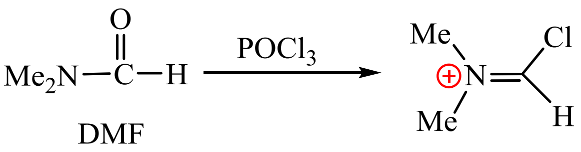


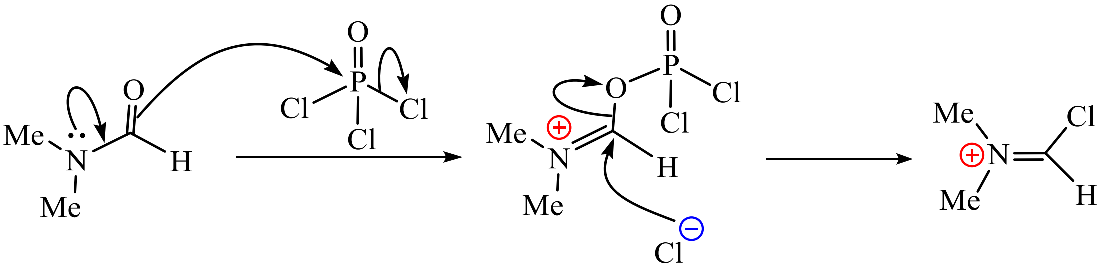
In addition to these regular electrophilic substitution reactions, pyrrole undergoes other reactions like the following:

1) Vilsmeier reaction:



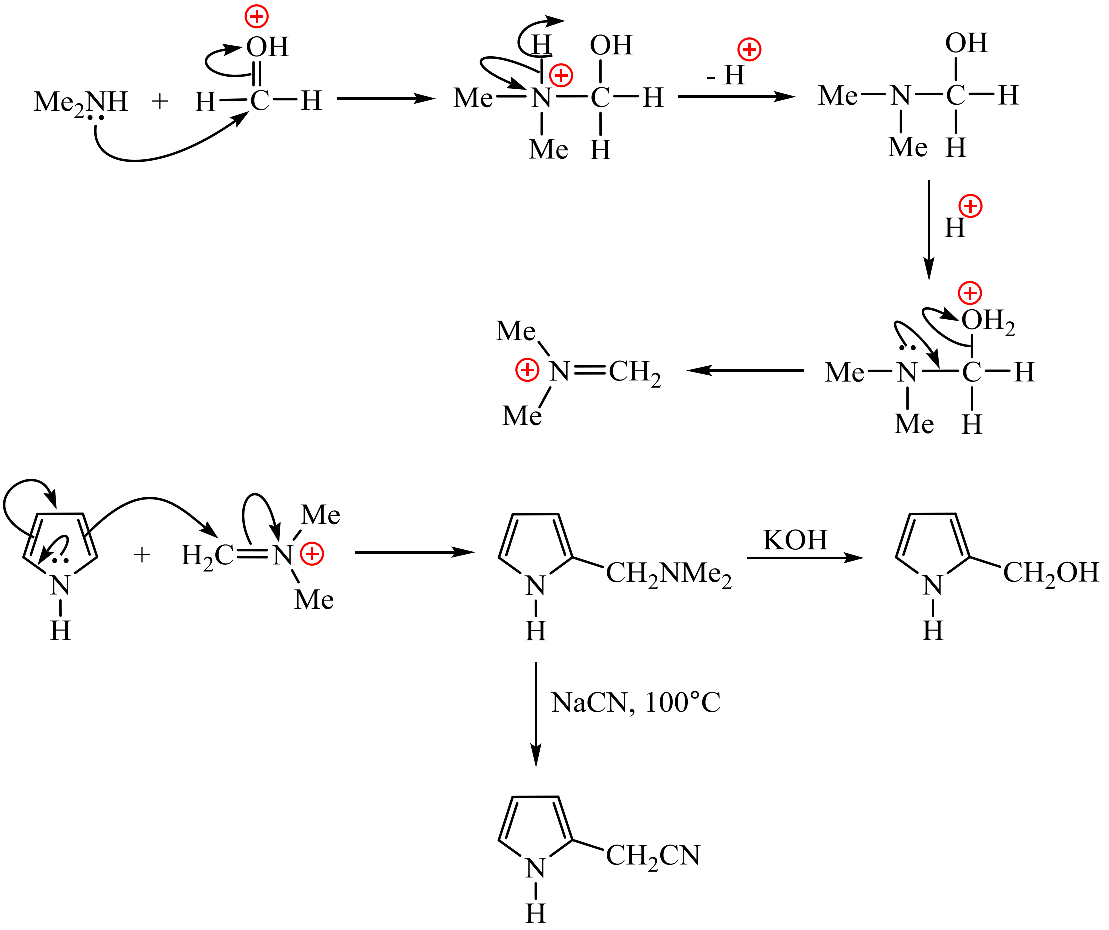
Note: *The electrophilic reagent that used in Vilsmeier reaction have been synthesized by the reaction of dimethylformamide (DMF) and phosphorus oxychloride (POCl$_3$) as the following:*





2) Mannich reaction:

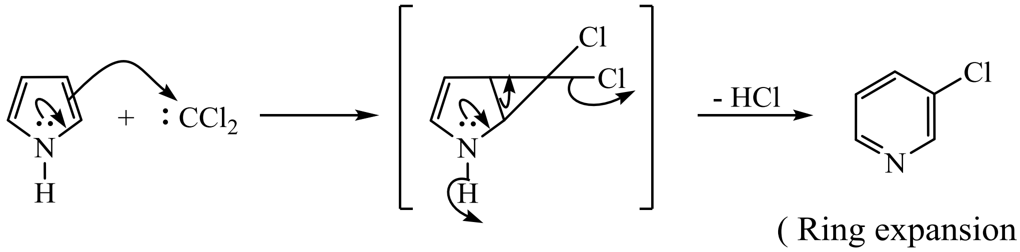
Treatement of pyrrole with formaldehyde and dimethylamine will produce pyrrole-2-methanol in the case of use of KOH, while if we use KCN, pyrrole-2-acetonitrile will formed.



3) Reimer – Tiemann reaction:

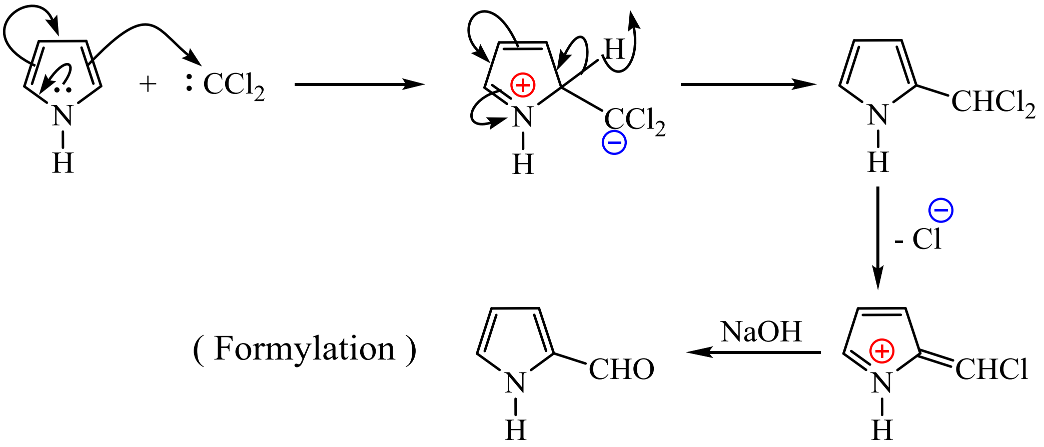
The reaction of pyrrole with chloroform in the presence of KOH (at chloroform b.p.) give a mixture of 3-chloropyridine (reaction 1) and 2-formyl pyrrole (reaction 2) as the following:

1)

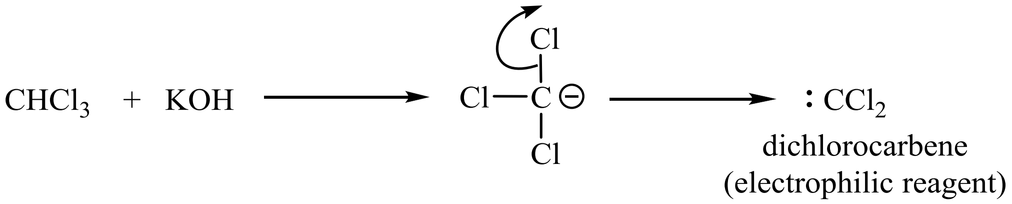


(Ring expansion)

2)



<u>Note</u>: Dichlorocarbene (:CCl_2) was generated from the reaction of chloroform with potassium hydroxide as the following:

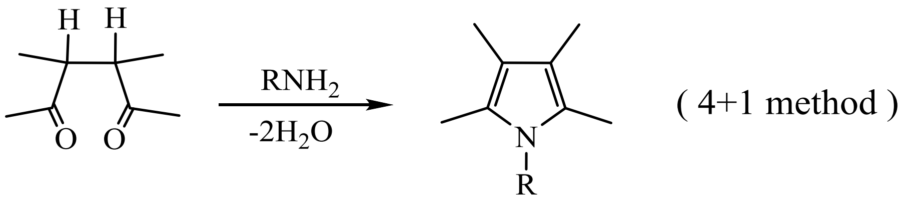


5.1.4) Synthesis of pyrrole:

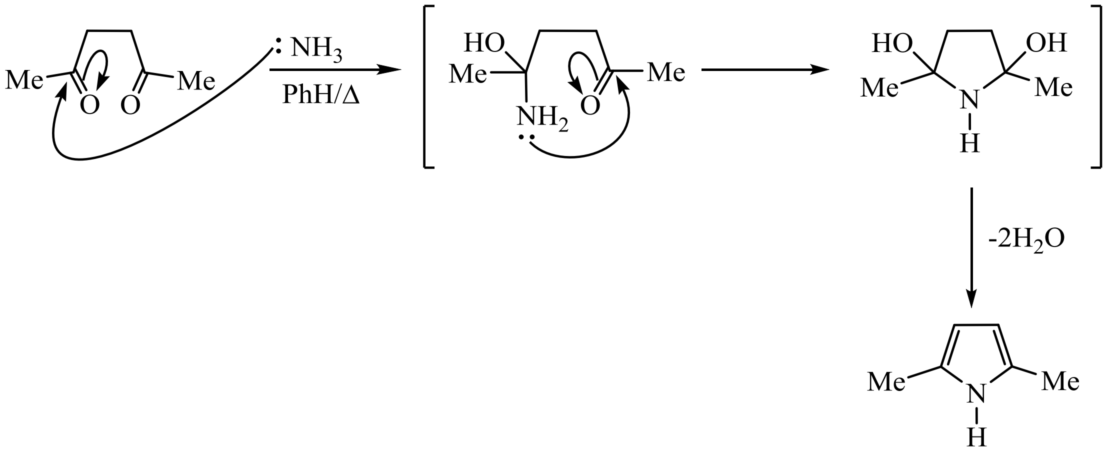
Different methods have been used to synthesize pyrrole or its derivatives from acyclic materials.

1) From 1,4-dicarbonyl compounds (Pall – Knorr synthesis):

This method involve the reaction of 1,4-dicarbonyl with ammonia or primary amines (4+1 method).



The reaction proceed through nucleophilic addition of amine at both carbonyl groups followed by loss of two water molecules. This reaction proceed in one step, without isolation of intermediates.

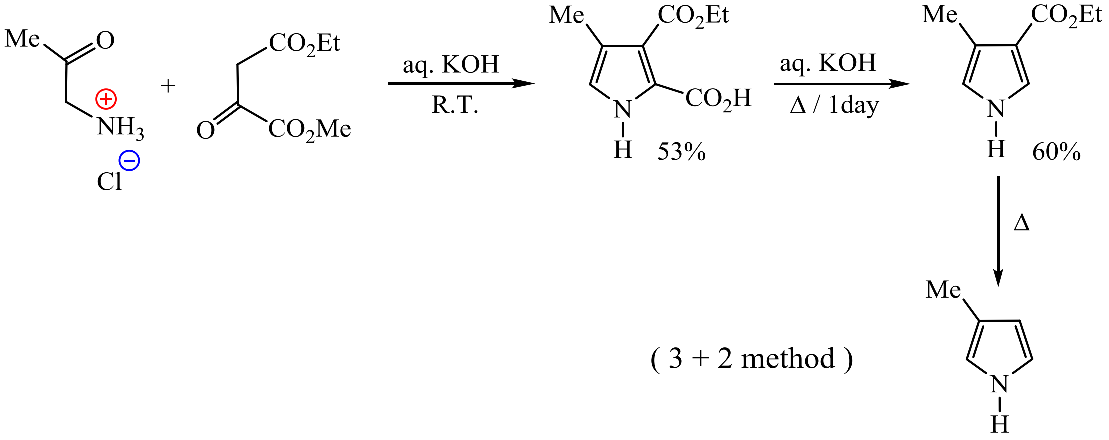


***Note**: The 1,4-dicarbonyl compound provide four carbon atoms while the primary amine provide the nitrogen atom.*

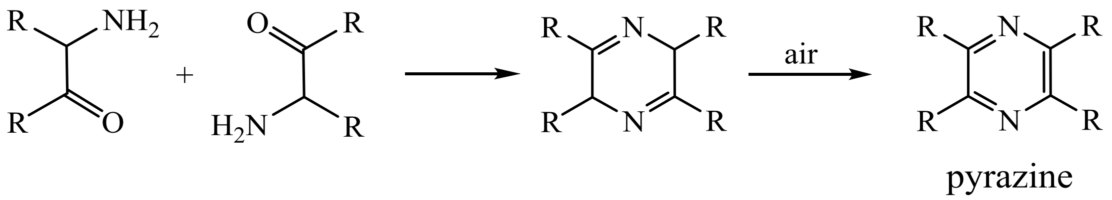
2) From α-aminocarbonyl (Knorr method):

This method is widely used to synthesize substituted pyrrole since it involve the use of two different compounds that give pyrrole with different substituents depending on starting materials.

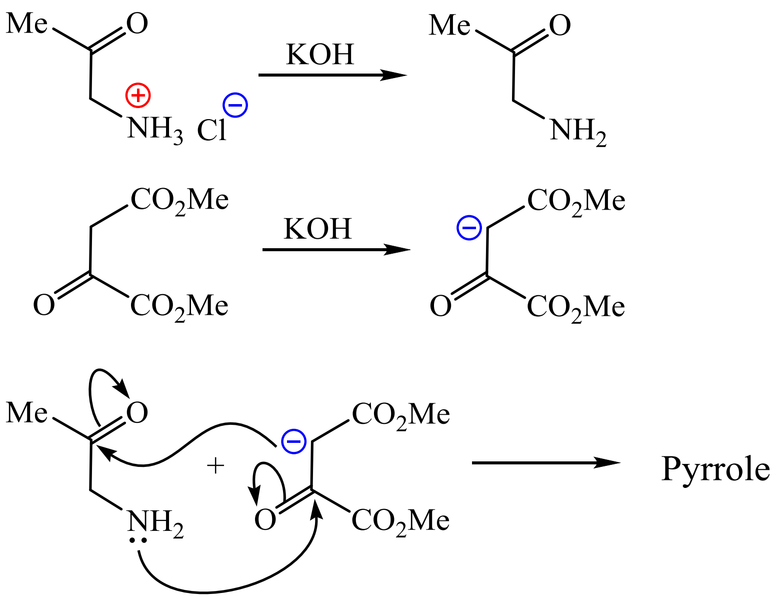
The first molecule is an α-aminocarbonyl that provide nitrogen atom and both of C2 & C3 atoms, while the second molecule is a carbonyl compound possessing α-methylene group and this provide both of C4 & C5 atoms.



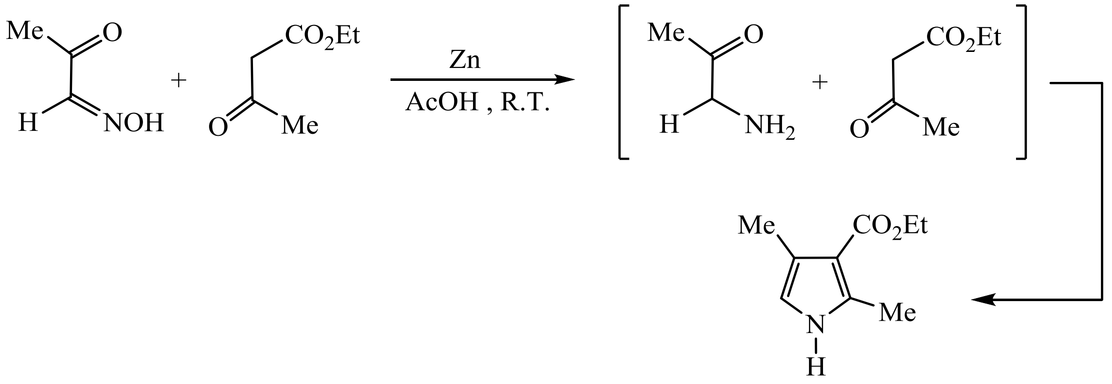
***Note**: α-aminocarbonyl compounds react with itself readily to form the dimer, thus they will be used as their hydrochloride salts. These salts when react with a base (KOH) will give the amine that react directly with the second molecule (α-methylene carbonyl compound) to form substituted pyrrole.*



<u>Note</u>: The reaction proceed faster when the α-methylene carbonyl compound contain an EWG like CO_2R group.



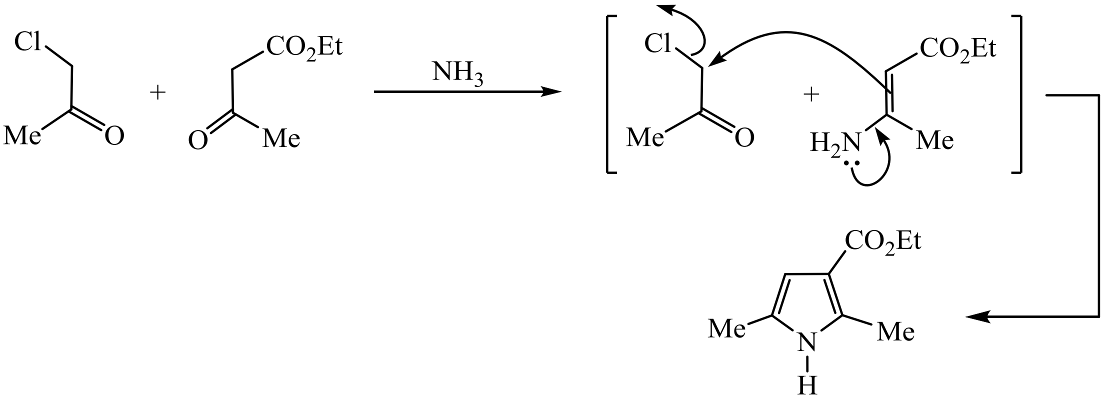
A modification for this method have been done in which the oxime was used instead of amine in the presence of zinc and acetic acid in which the oxime reduced to the proper amine then react in the same manner with the second molecule.



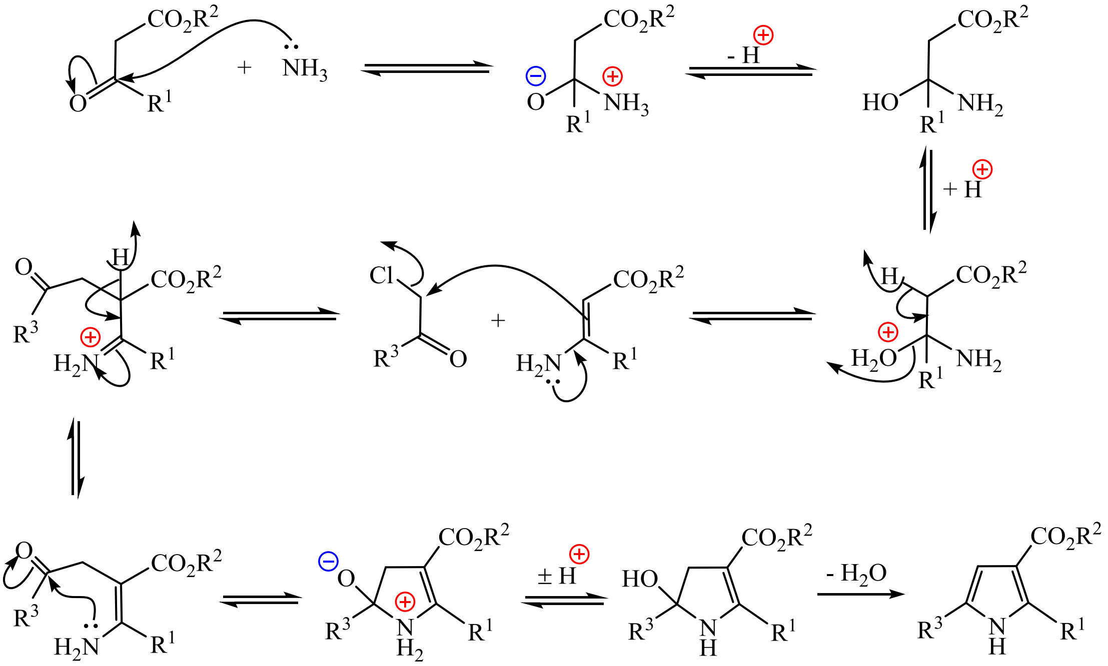
3) From α-halocarbonyl (Hantzsch method)

This method is a modified version of the Feist – Benary synthesis (that used in furan synthesis as we will see later) using the same starting materials: an α-halocarbonyl compound and a β-ketoester in the presence of ammonia.

This mean that the reaction proceed with two carbonyl compounds, one of them contain halogen atom at α-position while the other contain active methylene in the same position in the presence of ammonia.



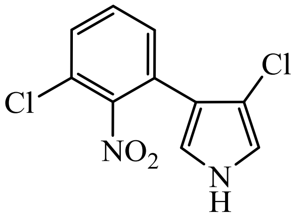
The reaction proceeds via the following mechanism:



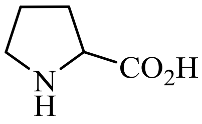
5.2) Naturally occurring pyrrole compounds:

Pyrrole itself is not naturally occurring, but many of its derivatives are found in a variety of cofactors and natural products.

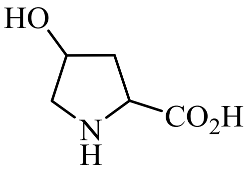
Pyrrole derivatives found in amino acids like proline and 4-hydroxyproline, furthermore pyrrole derivatives like pyrrolnitrin was used as antibiotic.



Pyrrolnitrin

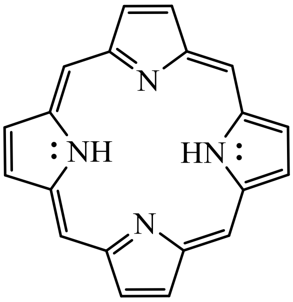


Proline



4-Hydroxy proline

Finally pyrrole found in a complicated natural products like porphyrins that consist of four pyrrole rings connected by methine group, porphyrin is the main component of heme and chlorophyll.

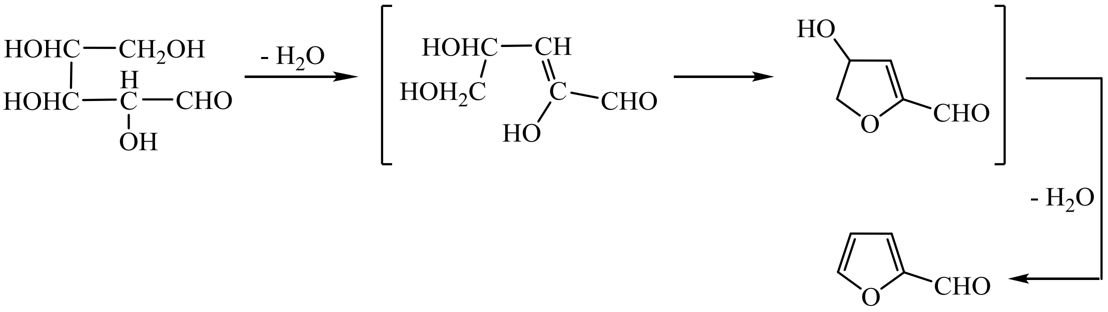


Porphyrin

6) Furan:

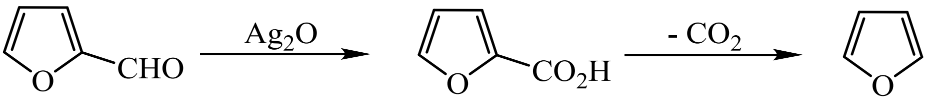
Furan is a colorless, volatile, with pleasant odor (like chloroform). Its boiling point is 31°C, and it is slightly soluble in water but soluble in common organic solvents including alcohol, ether and acetone.

Furan commercial importance is mainly due to its role as the precursor of the very widely used solvent tetrahydrofuran (THF). Furan ring exist in a large number of natural products as the main component; one of these compounds is furfural which manufactured from corn cobs and oat hulls; furthermore acid hydrolysis of polysaccharide produce the pentoses which on loss of water molecule give the furfural that used in the synthesis of polymers, pesticides, fungicides …….. etc.



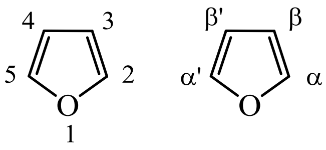
Furfural

In 1877, Baeyer convert furfural to furan via oxidation by silver oxide (Ag_2O).

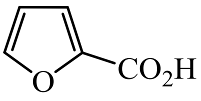


Furfural 2-Furoic acid Furan

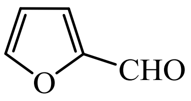
Numbering of the ring proceed with the same manner that used in pyrrole in which the oxygen atom will take number one, furthermore Latin letters α or β have been also used as the following:



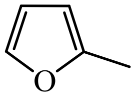
Furan



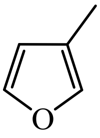
2-Furoic acid



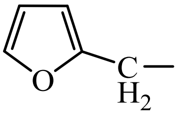
Furfural



2-Furyl



3-Furyl



2-Furfuryl

Since the electronegativity of oxygen atom is higher than nitrogen, thus the contribution of its lone pair of electrons will decrease, so the aromatic character will be less than pyrrole.

6.1) Chemical properties and reactions:

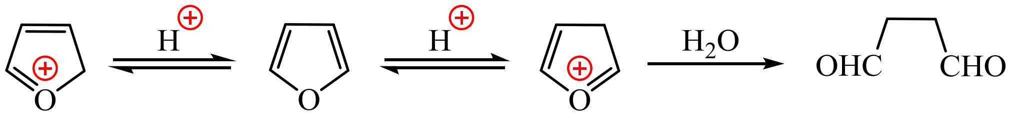
Furan ring is sensitive acidic conditions like enol ether, furthermore they undergoes addition under certain conditions at 2&5 positions like 1,3-conjugated diene. Finally they react with electrophilic reagents at 2&5 positions as in pyrrole.

6.1.1) Effect of acid on furan:

Furan and alkylated furan is more stable than enol ethers toward diluted acids since the lone pair of electrons is delocalized by resonance with π – electrons of the ring.

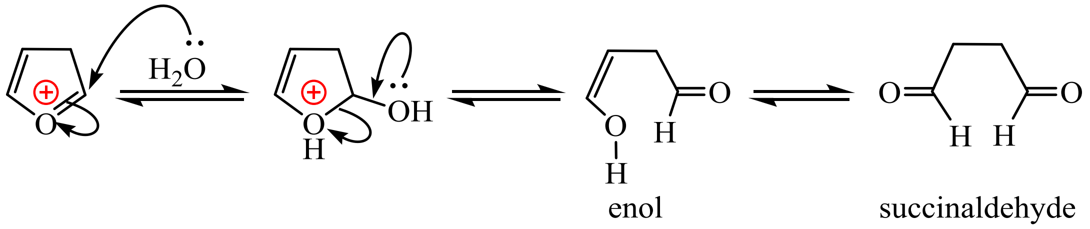
On the other hand furan ring when treated with concentrated sulfuric acid or Lewis acids will cause ring opening to give succinaldehyde or its substituents.

***Note**: Lewis acid is a chemical species that has an empty orbital which is capable to accept an electron pair from Lewis base to form Lewis adduct (like* $AlCl_3$ *).*

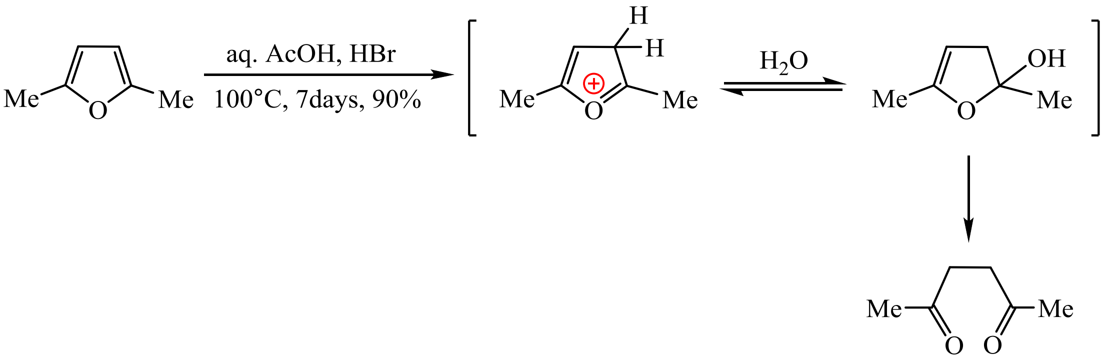


more stable (I) (α)   less stable (II) (β)   succinaldehyde

The formation of succinaldehyde will proceed as the following:

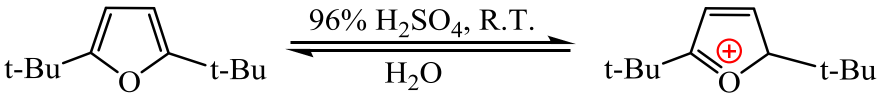


The following example explains the effect of acids in furan ring:



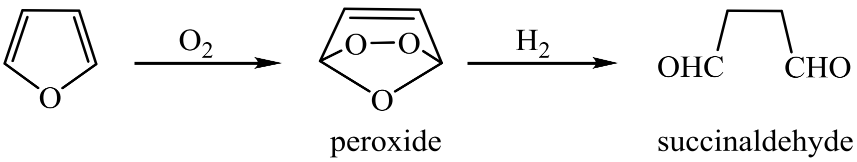
Cation (I) is more stable than (II), and this was proved from (NMR) measurement for the product that formed from the addition of sulfuric acid to 2,5-di-tert-butylfuran, the formed cation is stable at room temperature for 20 days.

Addition of water to the cation will give the starting material.



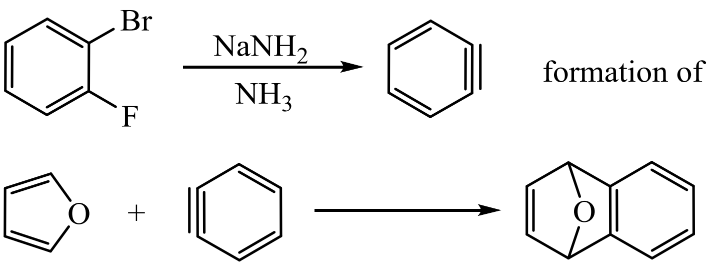
7.1.2) Addition reactions:

Furan exposure to air will oxidize it to give the peroxides (2,5-addition of oxygen to the ring). These peroxides have been isolated, and their hydrogenation produce succinaldehyde, thus furan is stabilized with small amount of hydroquinone to inhibit the formation of peroxides.



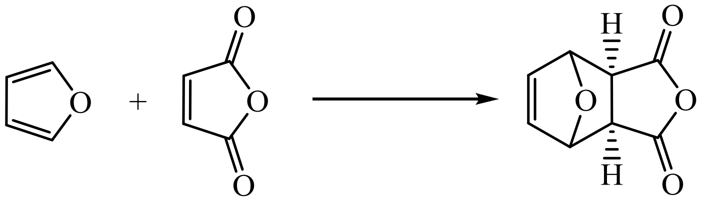
Furthermore furan react as a diene with strong dienophiles like maleic anhydride or benzyne to give Diels – Alder adduct as the following:

1)

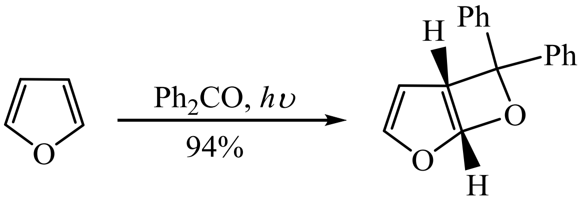


formation of benzyne

2)



Finally the photochemical reaction of furan with di-arylketones (and some aldehydes) afford the cycloaddition product, since the reaction proceeds regeoselectively to give oxetano-dihydrofurans.

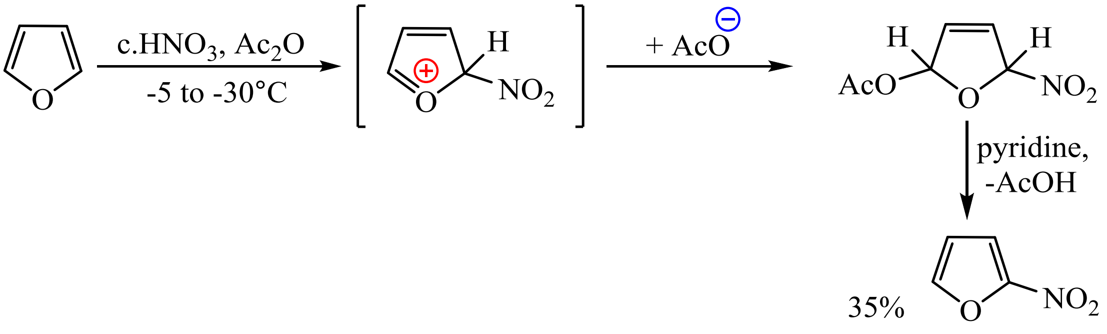


6.1.3) Substitution reaction of furan:

Furan undergoes substitution reaction in the same manner in pyrrole, in which mild conditions have been used, compared with benzene or its derivatives due to the sensitivity of the heterocyclic system toward strong acids or reagents. And here again substitution occurs at C2 or C5 atoms or both of them as the following:

6.1.3.1) Nitration:

Reaction of furan with acetyl nitrate (as a nitrating agent) give 2-nitrofuran as the following:

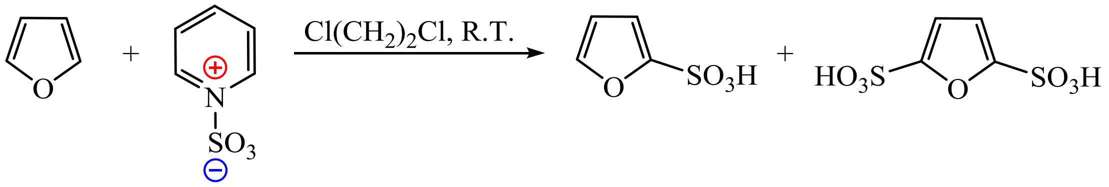


The reaction proceed to give non-aromatic adduct which followed by nucleophilic addition of acetate to the cationic intermediate at C5 atom, followed by loss of acetic acid to give the final substitution product.

Note: *Reaction of fuming nitric acid with acetic anhydride at low temperature give acetyl nitrate AcONO$_2$ as a nitrating agent.*

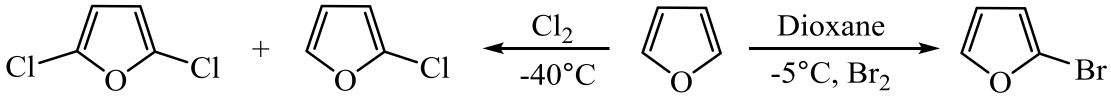
6.1.3.2) Sulfonation:

Furan and its simple alkyl derivatives are decomposed by the usual strong acids (like conc. H_2SO_4), but pyridine sulfurtrioxide (pyridinium sulfonate) complex can be used in the presence of ethylene chloride as a solvent:

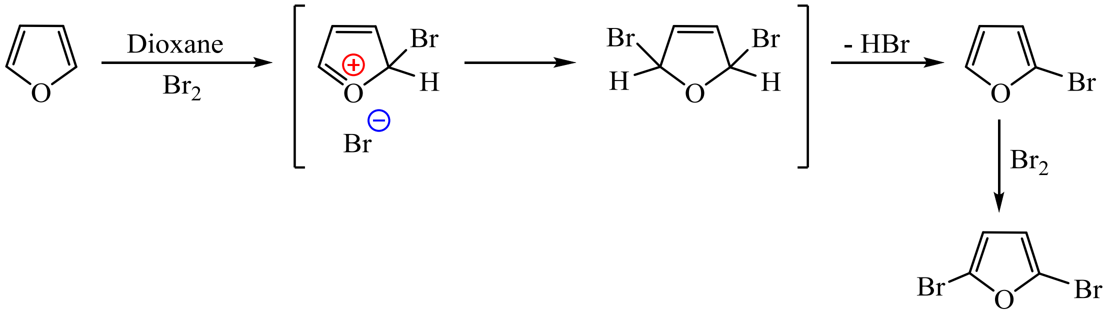


6.1.3.3) Halogenation:

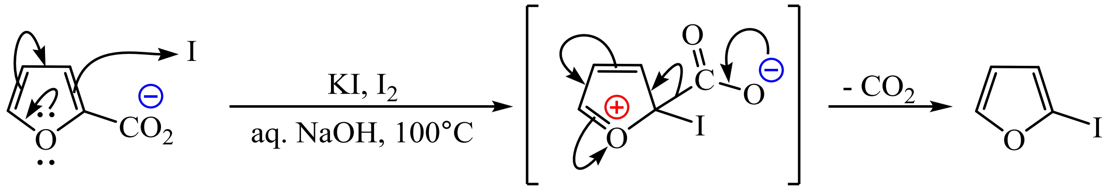
Furan react vigorously with chlorine and bromine but not iodine at room temperature resulting in polymerization due to the evolution of acids (hydrogen halides HX), thus controlled conditions should be used at low temperature (e.g. 0°C , -40°C) to give mono- or di- halo furans.



Bromination reaction proceeds as the following:



On the other hand iodine can be introduced to furan ring by reaction of substituted furan with a mixture of potassium iodide (KI) and iodine (I_2) in which the carboxyl group substituted with iodine.

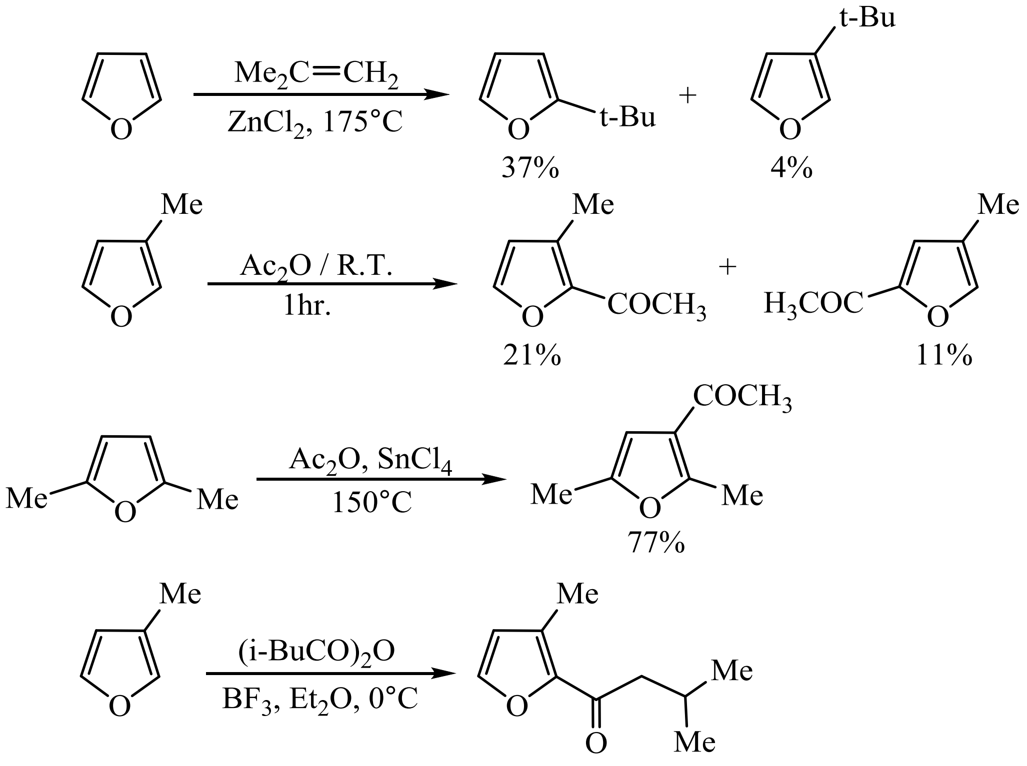


6.1.3.4) Friedel – Crafts acylation and alkylation:

Traditional Friedel – Crafts acylation or alkylation is not practicable for furan, due to the evolution of hydrogen halides that lead to polymerization. Thus olefins or acetic anhydride have been used for alkylation or acylation respectively instead of alkyl halides or acyl halides.

In these reactions Lewis acids have been used (often boron trifluoride BF_3 or zinc chloride $ZnCl_2$).

e.g.

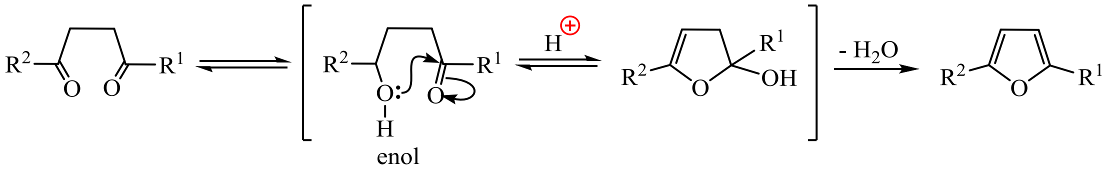


6.2) Synthetic methods:

Many routes have been used to synthesize furan ring as the following:

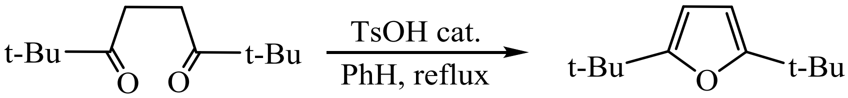
6.2.1) from 1,4-dicarbonyl compounds (the Paal – Knorr method):

In general 1,4-dicarbonyl compounds can be dehydrated with acids to give furans, since the 1,4-dicarbonyl compounds provide all of carbon and oxygen atoms for the nucleus.



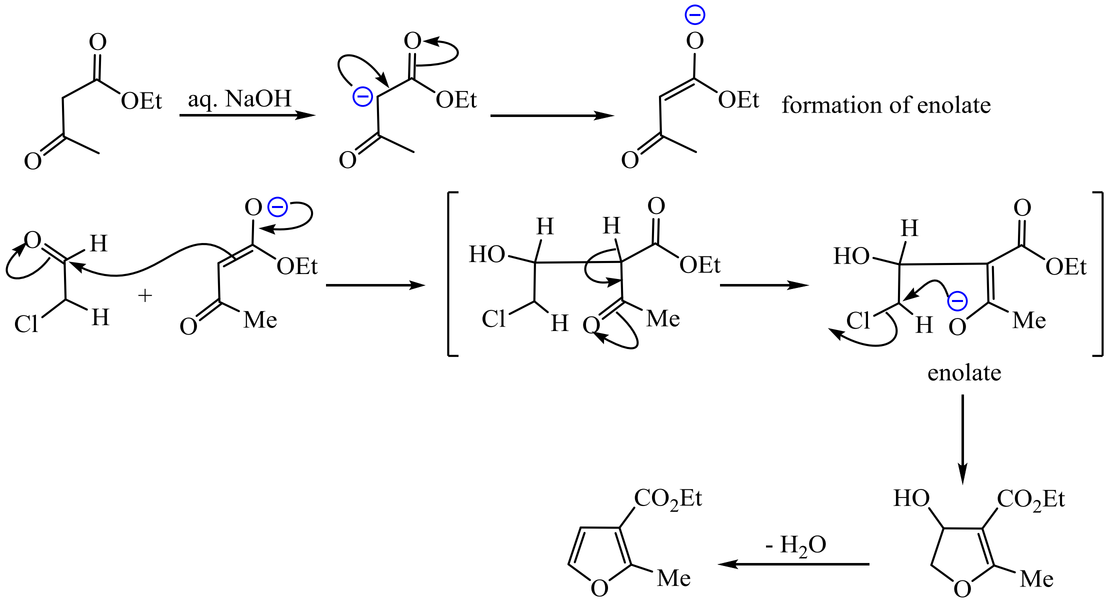
The process involve the addition of the enol oxygen of one carbonyl group to the other one followed by elimination of water.

e.g.



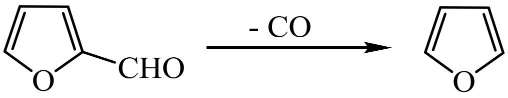
6.2.2) From α-halocarbonyl (the Feist – Benary synthesis):

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

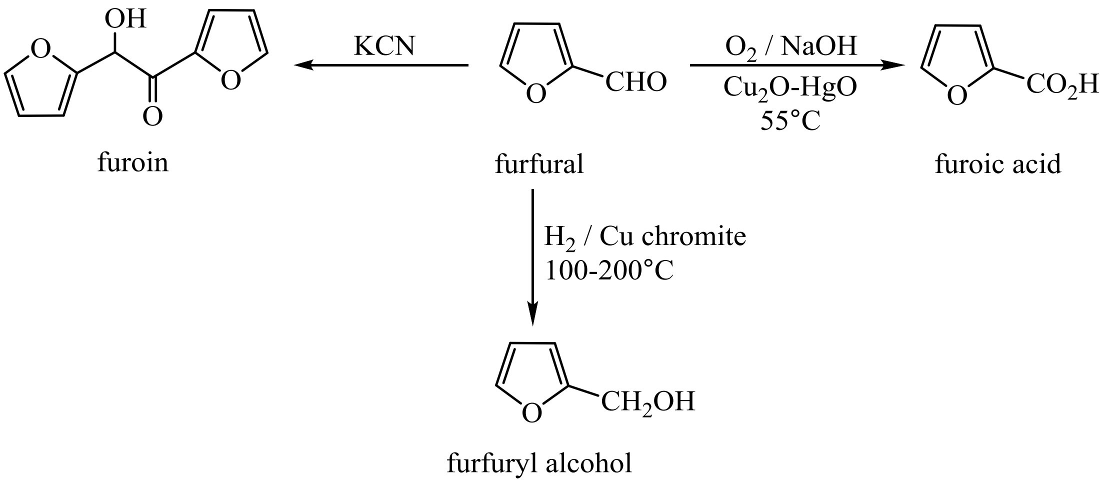


The reaction proceed initially via aldol condensation at the carbonyl of 2-halocarbonyl component; ring closure occur through an intramolecular displacement of halide by enolate oxygen.

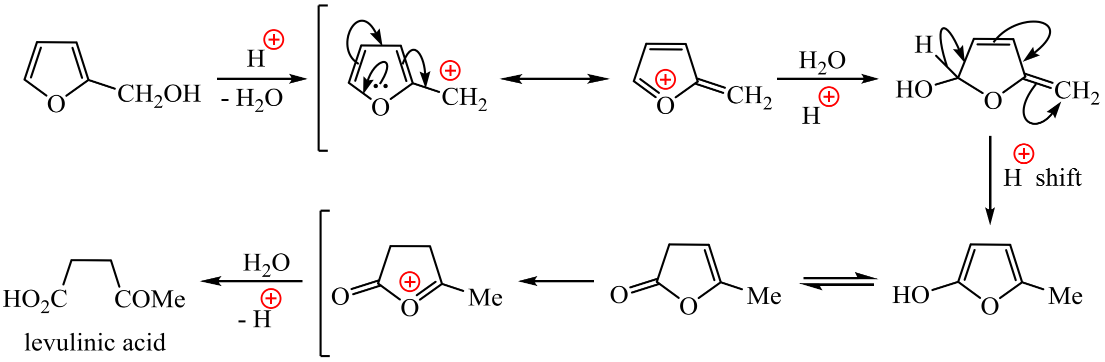
Another method for furan synthesis involve loss of carbon monoxide from furfural.



Furfural is an important furan derivative since it has been used as a precursor to synthesize a number of different important compounds as the following:

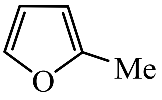


Fufuryl alcohol can be used as a precursor for the synthesis of levulinic acid as the following:

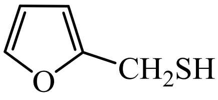


6.4) Naturally occurring furan compounds:

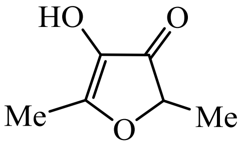
Furan ring exist in a number of naturally occurring compounds as a main component, since 2-methylfuran exist in wood oil (1), furfuryl mercaptan (furan-2-yl methan thiol) in roasted coffee (2), compound (3) in pineapple, compound (4) in potato, furthermore furacine (5) have been used as antibacterial drug.



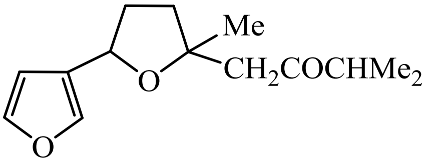
(1)



(2)



(3)



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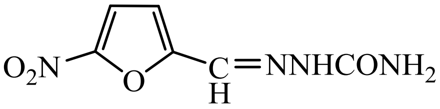
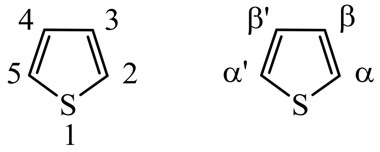


(5)

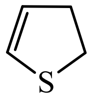
7) Thiophene:

Thiophene is a colorless liquid with a benzene like odor, it is closely resembles benzene in its chemical and physical properties. It occurs with benzene in coal tar, from which source it was first isolated in1882 as undesired compound (b.p.= 84°C while benzene 80°C).

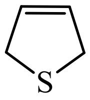
Numbering of the ring start also from the hetero atom like pyrrole and furan as the following:



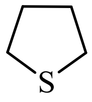
Thiophene



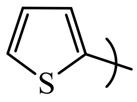
2,3-Dihydro thiophene



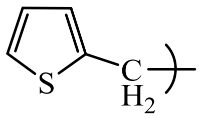
2,5-Dihydro thiophene



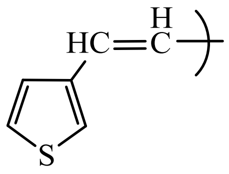
Tetrahydro thiophene



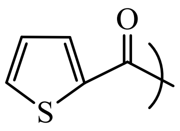
2-Thienyl



2-Thenyl



Thenylidene or
3-Thenal



Thenoyl

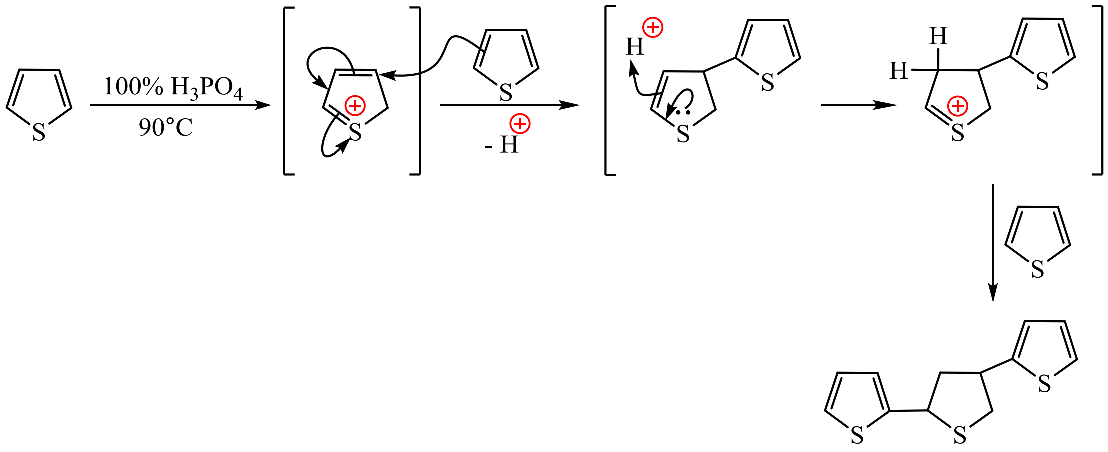
7.1) Chemical reactivity and reactions of thiophene:

As we mentioned previously, thiophene resembles benzene in most of its reactions, but it is more reactive and less stable. Thiophene undergoes reactions like furan and pyrrole at C2 or C5 positions or both of them.

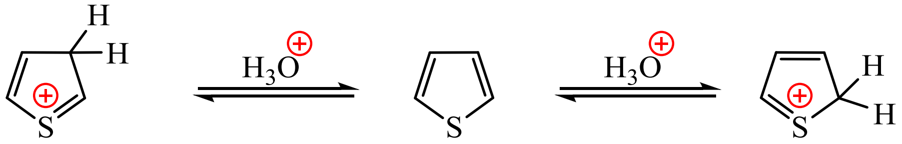
7.1.1) Effect of acids on thiophene:

Thiophene is more stable than pyrrole and furan toward acidic conditions, thus many reagents that would lead to acid – catalyzed decomposition or polymerization of furan or pyrrole can be applied successfully to thiophenes (i.e. like benzene).

The reaction of thiophene with hot concentrated phosphoric acid leads to a trimer.



The rate of proton attack at C2 atom is about 1000 times faster than at C3 atom (as the same as in benzene protonation).



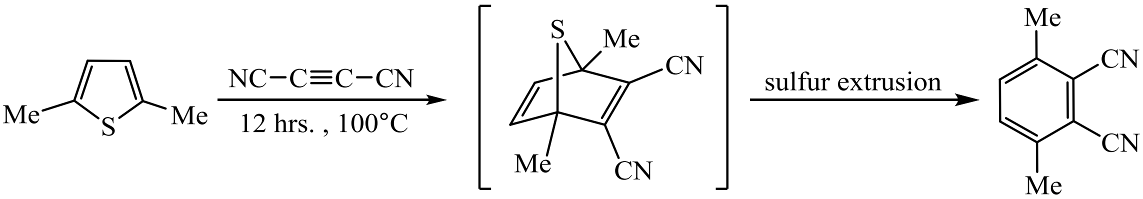
less stable cation more stable cation

Thiophene react with some Lewis acids like aluminum chloride ($AlCl_3$) to generate tars (or polymer), thus we couldn't use it in Friedel – Crafts reactions, thus we can use tin tetrachloride ($SnCl_4$) instead of ($AlCl_3$).

***Note**: Benzene that used in Friedel – Crafts reactions should be thiophene free to prevent polymerization.*

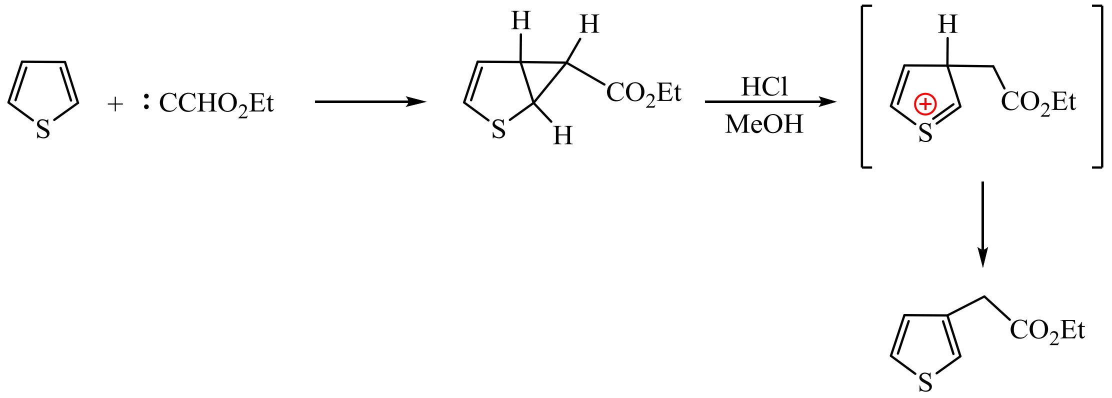
7.1.2) Addition reactions of thiophene:

Thiophene show little tendency (*due to its high resonance energy*) to react as a diene in Diels – Alder reaction. It is unreactive towards common dienophiles like benzyne and maleic anhydride, thus strong dienophiles have been used like tetrafluorobenzyne and dicyanoacetylene to give the 1,4-adduct (addition at C2 and C5 atoms).



Furthermore thiophene undergoes addition reaction at the double bond between C2 and C3 atoms when reacted with carbene (like carbethoxy carbene) to give substituted cyclopropane that on treatment with acid and methanol produce β-acetic ester of thiophen:

$N_2CHCO_2Et \longrightarrow :CHCO_2Et$ formation of carbethoxy carbene

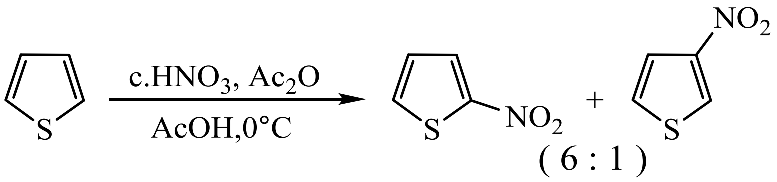


7.1.3) Substitution reaction of thiophene:

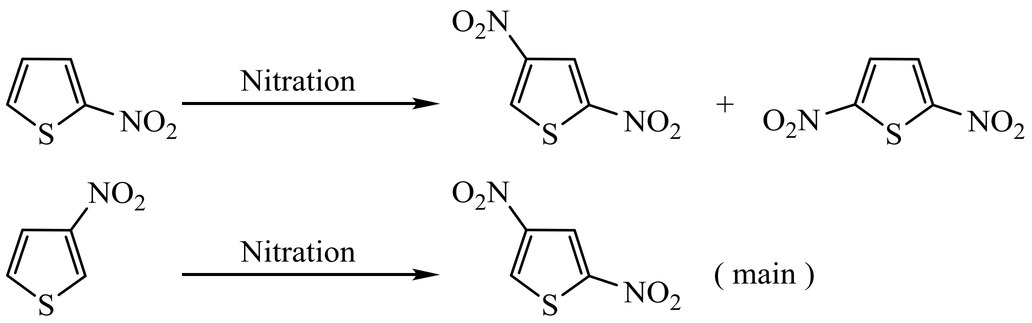
Thiophene undergoes a considerable number of electrophilic substitution reactions with greater ease (*i.e. moderate conditions can be used*) than with pyrrole or furan (even sometimes than with benzene). Substitution takes place at 2 or 5 positions or both of them.

7.1.3.1) Nitration:

Nitration of thiophene under regular conditions (that used in benzene or its derivatives) will lead to its decomposition or an explosion (*i.e. the use of a mixture of acetic acid and nitric acid will also cause an explosive reaction*), thus milder conditions should be used like acetyl nitrate to give 2- and 3- dinitro thiophene in 6:1 ratio.

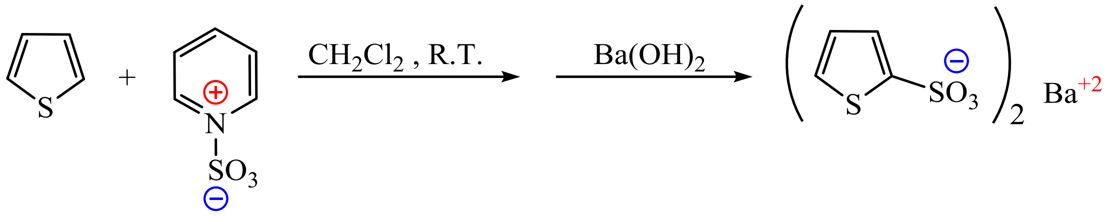


Note: *Nitration of 2-nitrothiophene and 3-nitrothiophene will proceed as the following:*

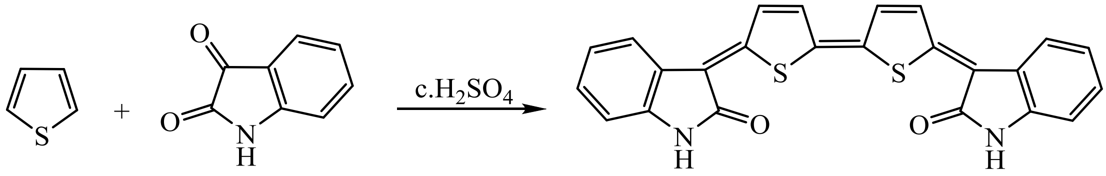


7.1.3.2) Sulfonation:

The ease of sulfonation of thiophene by sulfuric acid at room temperature lead to use this method to get rid of thiophene (as undesired component) from benzene that obtained from crude oil (petrol).

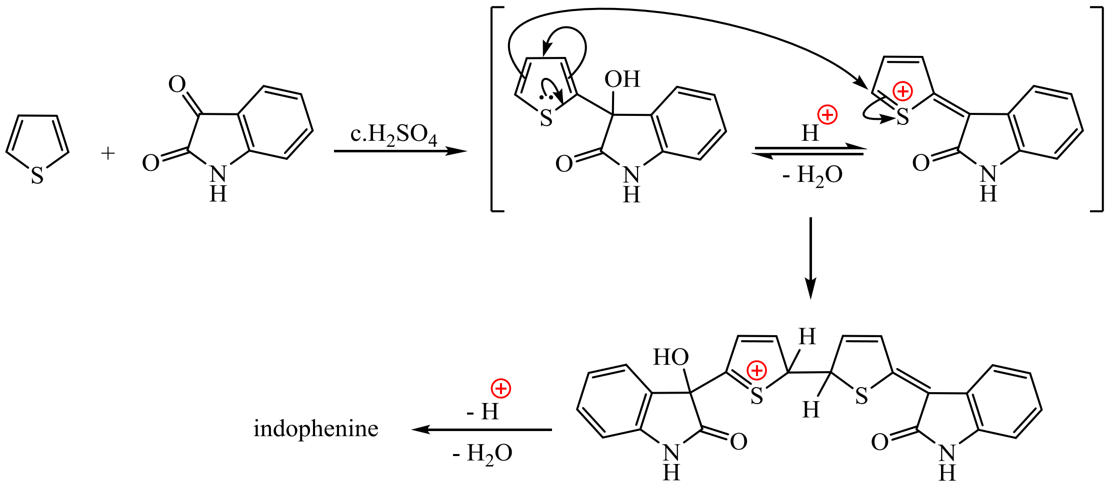


Thiophene react with isatin in the presence of sulfuric acid to give deep blue indophenine, this reaction was used as a test for the presence of thiophene in coal – tar.



isatin indophenine

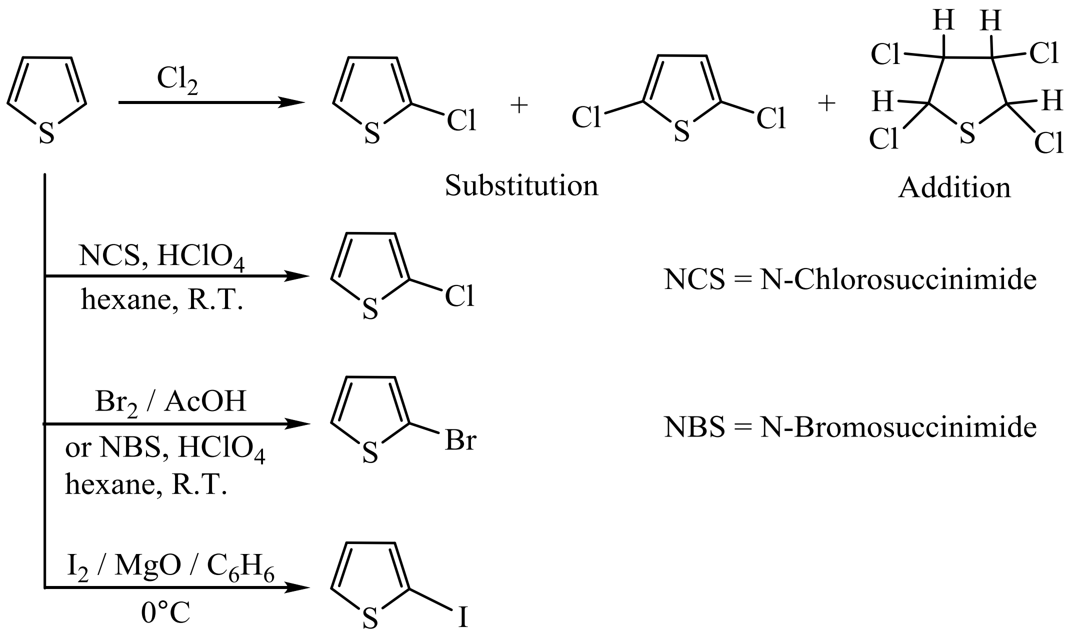
The reaction proceed as the following:



7.1.3.3) Halogenation:

Halogenations of thiophene occurs very readily at room temperature and is rapid even at -30°C in the dark, thus the rate of chlorination of thiophene is 10^7 faster than that of benzene while bromination is 10^9 at the same conditions.

Controlled reaction conditions will control the nature of the product (i.e. mono,di or tetra substituted halo thiophene).



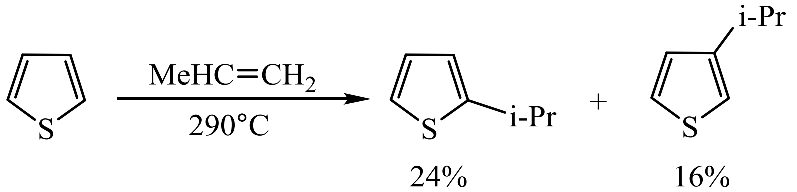
NCS = N-Chlorosuccinimide

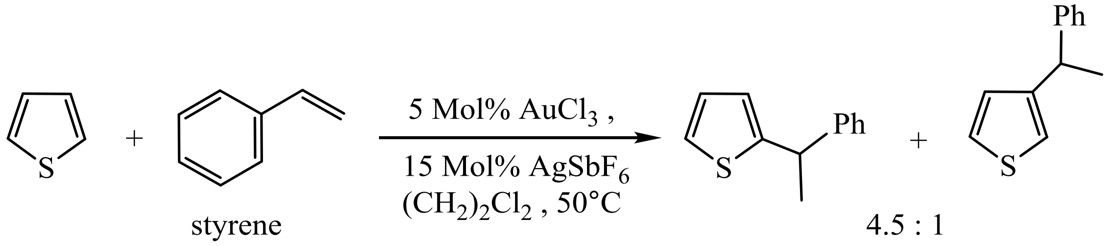
NBS = N-Bromosuccinimide

7.1.3.4) Alkylation and Acylation:

As we mentioned previously, thiophene react with some Lewis acids (like $AlCl_3$) resulting in the formation of polymerized material or tar, thus tin tetrachloride used instead or by the gradual addition of the catalyst to a mixture of thiophene and acylating or alkylating agent.

Thiophene can be alkylated at high temperature by the use of olefines, but the disadvantages of this method involve the low yield and the diversity of the products.

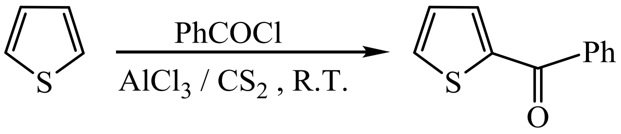


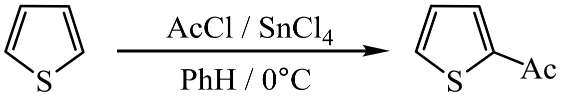


***<u>Note</u>**: $AuCl_3$ = Gold (III) chloride*

$AgSbF_6$ = Silver hexafluoroantimonate

On the other hand acylation is much more easier and produce substitution product at 2 position.





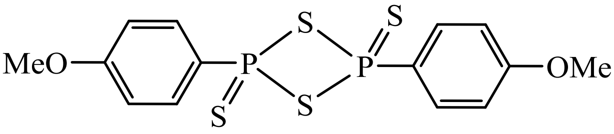
7.2) Synthetic methods:

7.2.1) From 1,4-dicarbonyl compounds and a source of sulfide (Paal – Knorr thiophene synthesis or Paal thiophene synthesis):

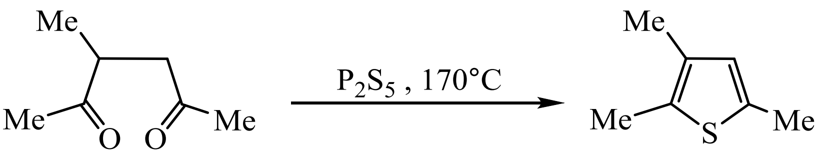
This method allows the generation of thiophene by condensation of a 1,4-dicarbonyl compound in the presence of a source of sulfur such as phosphorous pentasulfide P_2S_5 or Lawesson's reagent (LR).

***Note**: P_2S_5 present as a dimer P_4S_{10}*

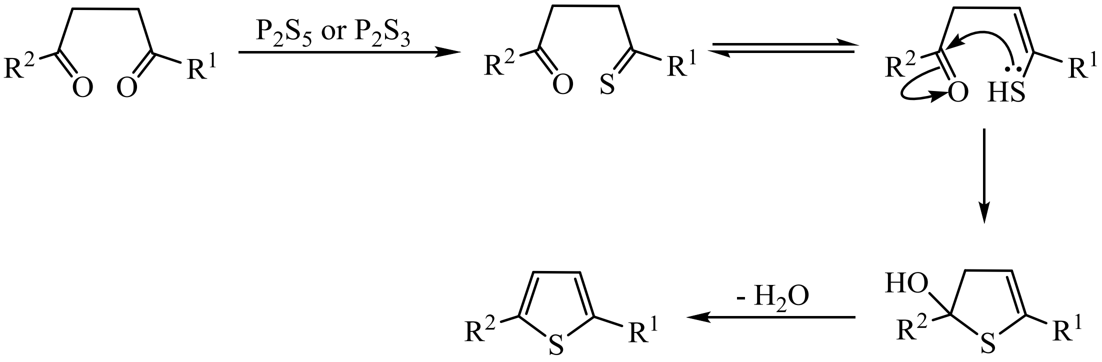
Lawesson's reagent (LR) =



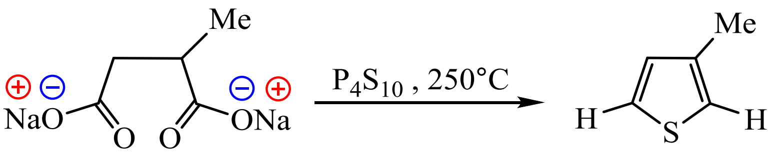
e.g.



Phosphorous pentasulfide act as sulfurizing and dehydrating agent, the reaction proceed presumably, but not necessarily via thioketone since it could proceed via bis(thioketone).



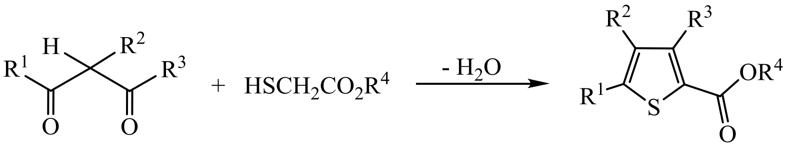
P_2S_5 or P_2S_3 reduce the carboxyl group if it was a part of 1,4-dicarbonyl compound.

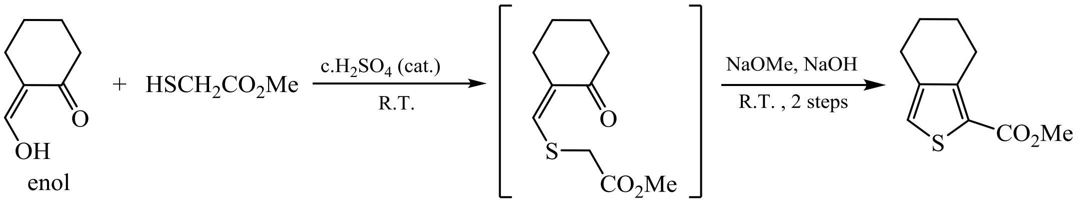


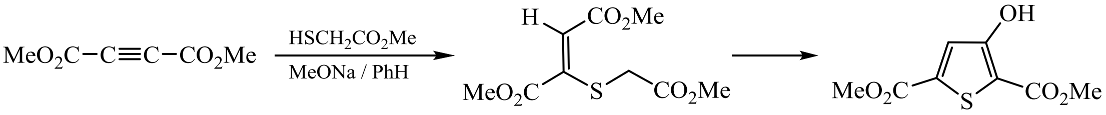
7.2.3) From 1,3-dicarbonyl compounds:

Thiophene can be prepared by the reaction of mercaptoacetic ester (thioglycolic ester) with 1,3-dicarbonyl compounds or acetylinic esters.

examples



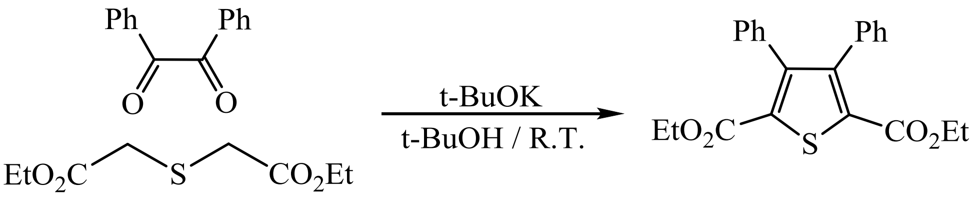




Note: *The reaction between acetylinic ester and thioglycolic ester proceed via nucleophilic addition of thiolate anion followed by cyclization through Claisen condensation.*

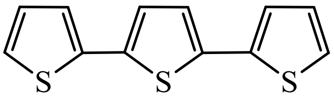
7.2.3) From 1,2-dicarbonyl compounds (the Hinsberg synthesis):

1,2-Dicarbonyl compounds condense with thio-diacetate to give substituted thiophenes. The reaction proceed through two consecutive aldol condensation with the carbonyl groups.

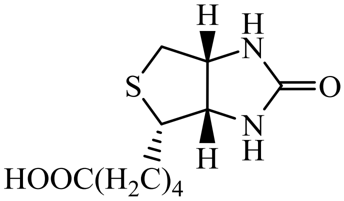


7.3) Naturally occurring thiophene compounds:

There is no clear evidences for the presence of thiophene or tetrahydrothiophene in nature inspite the fact that it do exist in different fractions of crude oil (petrol). However, thiophene derivatives exist in a number of natural products like:



α–Terthienyl
in flowers of indian marigold plant



Biotin, vitamin H