Al-Mustaqbal University College
Department of Pharmacy

Organic Chemistry

Lec 8

Reaction of Five-Membered Heterocyclic Compounds

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# Reactivity Order in Five-Membered Heterocycles

- The reactivity of five-membered heterocycles towards electrophiles <u>depends (1) on the electron availability on the ring carbon atoms or (2) mesomerically electron release from the heteroatom and (3) the greater stabilization of transition state.</u>

- The order of reactivity in five-membered heterocycles is :

  pyrrole > furan > thiophene > benzene (for comparison).

- <u>The greater reactivity of pyrrole towards electrophiles is attributed to the greater electron releasing ability of trivalent nitrogen (when linked by three bonds) making ring carbon atoms electron rich and to the greater stabilization of transition states involving positive charge on the tetravalent nitrogen atom</u>

(i)   (ii)
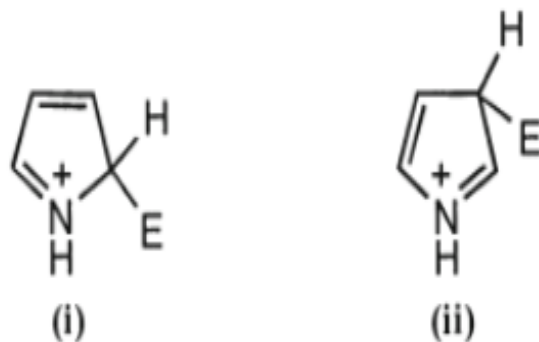
- Furan is also reactive (although less than pyrrole) towards electrophiles (preferably at C-2) and the reason is the same as for pyrrole. Since oxygen is more electronegative than nitrogen and withdraws electrons from the ring carbon atoms, the positive charge is less readily accommodated by oxygen atom than by nitrogen atom. The transition state with oxygen atom positively charged resulting from the electrophilic attack on furan is, therefore, less stable than that of pyrrole. Thus, furan is less reactive towards electrophiles than pyrrole as phenol is less reactive than aniline.

(i)   (ii)
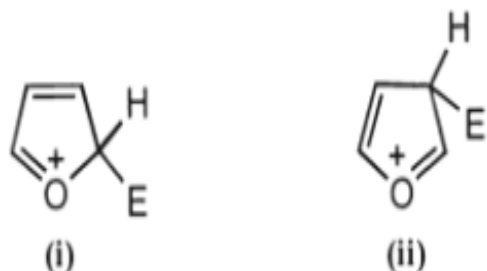
- Thiophene is less reactive than even furan towards electrophiles. The sulfur atom is less electronegative than the oxygen atom and therefore withdraws electrons less readily from the ring carbon atoms. Moreover, +M effect of sulfur (mesomeric electron release from sulfur) is smaller than that of oxygen because of not effective overlapping of differently sized p-orbitals of carbon and sulfur than in carbon and oxygen. The relative reactivity of thiophene and furan can be shown by the following reaction in which nitration with mild nitrating agent occurs only in furan nucleus at C-2
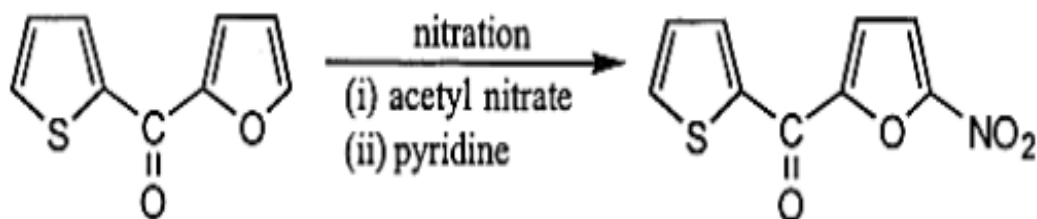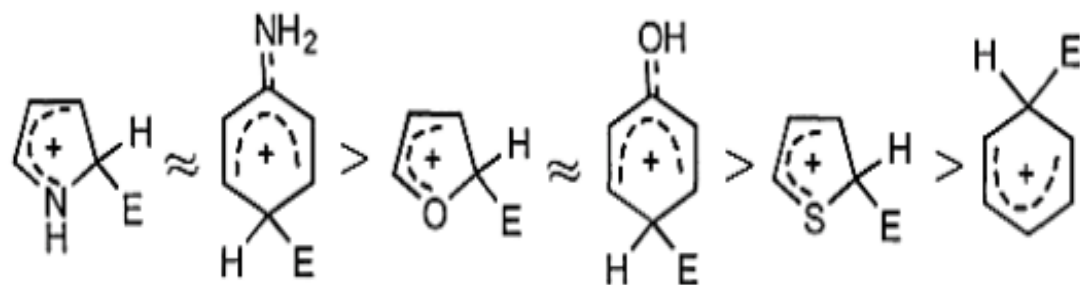
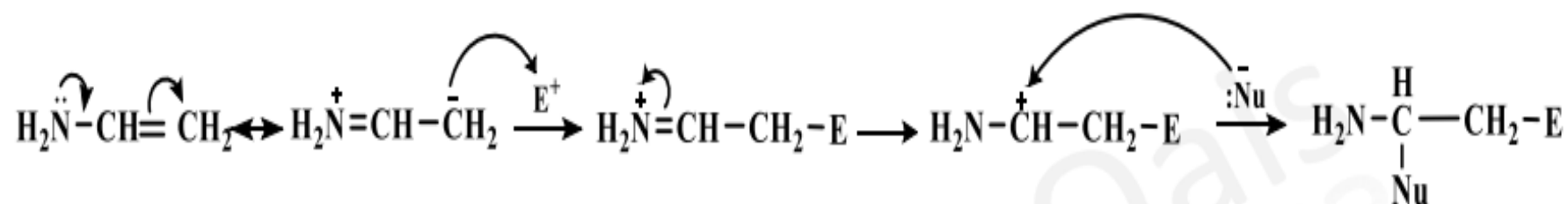# Reactivity Comparison with Benzene

The electrophilic substitution in thiophene is much easier than in benzene. Thiophene is brominated 109 times more rapidly than benzene which, in turn, is 103-107 times more reactive than pyridine. <u>Thus, benzene is much less reactive than the five-membered heterocycles towards electrophiles</u>. The reactivity depends on:

(i) The stabilization energy and
(ii) The stability of transition state.

<u>The lower reactivity of benzene towards electrophiles is attributed partly to the greater resonance stabilization energy of benzene. The higher energy of the transition state of benzene than the structurally related transition states of five-membered heterocycles is also responsible for the lower reactivity of benzene</u> . The stability order of the transition states has been observed to be as follows

Effect of Aromaticity on Reactivity

$$H_2\ddot{N}-CH\!=\!CH_2 \longleftrightarrow H_2\overset{+}{N}\!=\!CH-\overset{-}{C}H_2 \xrightarrow{E^+} H_2\overset{+}{N}\!=\!CH-CH_2-E \longrightarrow H_2N-\overset{+}{C}H-CH_2-E \xrightarrow{:\overset{-}{N}u} H_2N-\underset{Nu}{\overset{H}{\underset{|}{\overset{|}{C}}}}-CH_2-E$$

Electrophilic addition in acyclic system

$$X = NH, O, S \qquad (i) \qquad\qquad (ii) \qquad\qquad (iii)$$
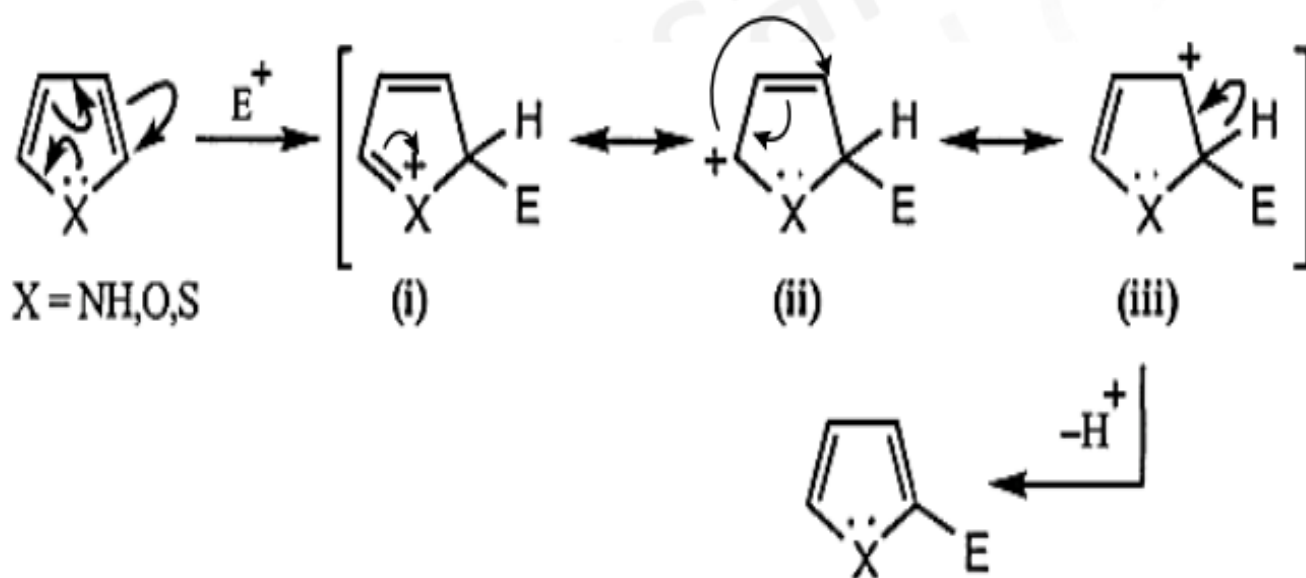
Electrophilic substitution in heterocyclic system

- Thus, in both the systems; acyclic and heterocyclic, the first step is the same and involves an electrophilic attack, but in the second step acyclic conjugated system instead of losing a proton is attacked by a nucleophile at the positively charged carbon atom providing addition product.

summary

. Pyrrole, furan, and thiophene undergo electrophilic substitution, preferentially at C-2:

• Pyrrole > furan > thiophene > benzene   **(Reactivity)**

• Thiophene is the most aromatic in character and undergoes the slowest reaction

• Pyrrole and furan react under very mild conditions

• The aromaticity order in these heterocycles depends on the electronegativity of the heteroatom : **$0 > N > S$** and, therefore, the aromaticity follows the order as :

Thiophene > Pyrrole > Furan.

And the extra stabilization of thiophene is attributed to the expansion of valence shell of sulfur by using d-orbitals in hybridization.

- α-Substitution favoured over β-substitution more resonance forms for intermediate and so the charge is less localised (also applies to the transition state)

- Some β-substitution usually observed – depends on X and substituents

$$X = NH \quad 4:1$$
$$X = O \quad 6:1$$

Resonance Stabilization:

(i)   (ii)   (iii)   (iv)   (v)
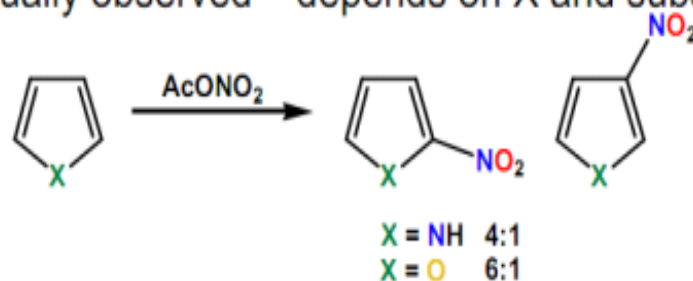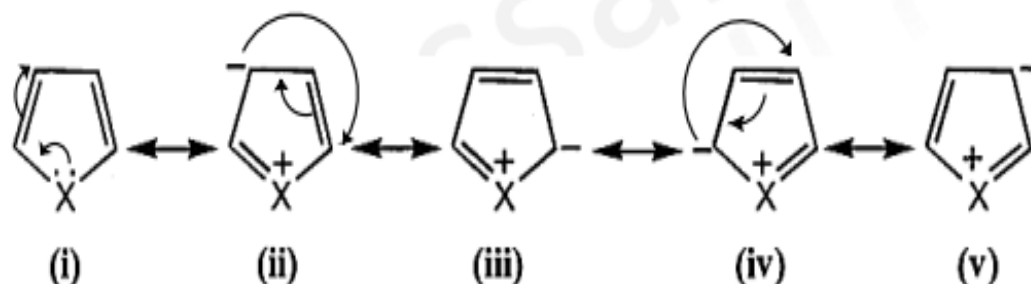
Resonating structures of five-membered heterocycles with one heteroatom

(vi)   (vii)   (viii)
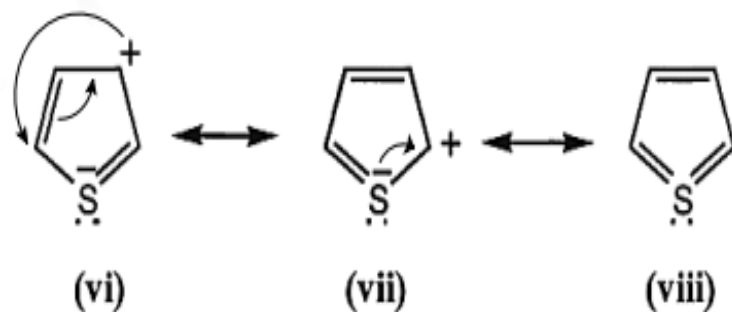
Additional resonating structures of thiophene

The lone pair associated with the heteroatom is involved in the aromatic sextet and is delocalized over

The lone pair associated with the heteroatom is involved in the aromatic sextet and is delocalized over the ring carbons. The stabilization energies of these heterocycles (87.69 kJ/mol for pyrrole, 66.81 kJ/mol for furan and 121.10 kJ/mol for thiophene) are approximately half of the value of benzene because only one uncharged resonating structure contributing to the resonance hybrid is possible in these heterocycles as compared to two uncharged resonating structures for benzene. The extra stabilization of thiophene is attributed to the expansion of valence shell of sulfur by using d-orbitals in hybridization.

General mechanism of electrophilic substitution in the five-membered heterocycles
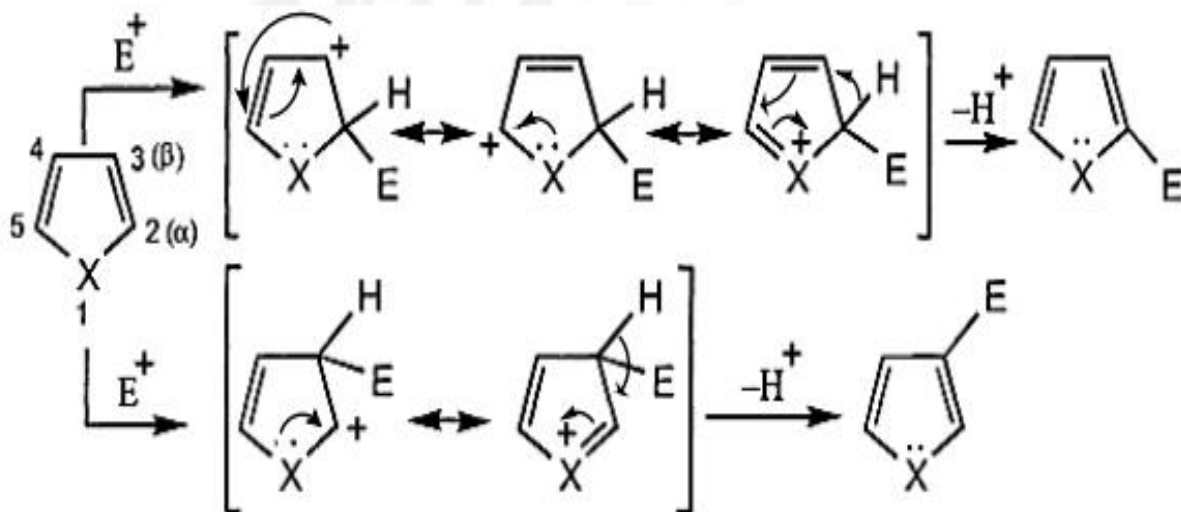
Reactions of Five-Membered Heterocycles :

Reactions of Pyrroles: Reactions with Electrophilic Reagents

Whereas pyrroles are resistant to nucleophilic addition and substitution, they are very susceptible to attack by electrophilic reagents and undergo easy *C*-substitution. Pyrrole itself, *N*- and *C*-monoalkyl- and to a lesser extent *C,C'*-dialkyl-pyrroles, are polymerised by strong acids, so that many of the electrophilic reagents useful in benzene chemistry cannot be used. However, the presence of an electron-withdrawing substituent, such as an ester, prevents polymerisation and allows the use of the strongly acidic, nitrating and sulfonating agents.

Orientation

(i) The substituents attached to the nitrogen atom of pyrrole (**position-1**) do not have an appreciable effect unless they are bulky or strongly electron releasing or electron-withdrawing substituents. The presence of bulky group exerts steric hindrance and directs electrophilic attack at the **position-3**. The proportion of **3-substitution** increases with increasing steric effect of the substituent at the **position-1**.

(ii) Electron-releasing substituents at **carbon-2** of the pyrrole ring facilitate electrophilic substitution at the **position-5 (C-5)**, while the presence of substituent at **carbon-3** causes substitution at the **position-2 (C-2).**

(iii) Electron-withdrawing substituents at **carbon-2** result in electrophilic substitution at **both carbon-4 and carbon-5**, but the ratio depends upon the -M effect of the substituent as the proportion of **4-isomer** increases with effect. The presence of electron-withdrawing substituent at **carbon-3** facilitates the attack of electrophile at **carbon-5**.

1- Nitration:

Nitrating mixtures suitable for benzenoid compounds cause complete decomposition of pyrrole, but reaction occurs smoothly with acetyl nitrate at low temperature, giving mainly 2-nitropyrrole. This nitrating agent is formed by mixing fuming nitric acid with acetic anhydride to form acetyl nitrate and acetic acid, thus removing the strong mineral acid. In the nitration of pyrrole with this reagent, it has been shown that C-2 is 1.3×10^5 and C-3 is 3×10^4 times more reactive than benzene.[13] A combination of PPh_3, $AgNO_3$ and Br_2 also produces a comparable mixture of nitro-pyrroles.[14]

(Mixture of nitric acid + acetic anhydrde) acetyl nitrate

$$(CH_3-CO)_2O + HNO_3 \longrightarrow CH_3COONO_2^+ + CH_3COOH$$

(CH₃CO)₂O

$CH_3-C(=O)-ONO_2$

NO_2

NO_2

R   R   R

O_2N

$+ CH_3-C(=O)-ONO_2$ (CH₃CO)₂O

$COCH_3$ O_2N $COCH_3$

H   H   H

NO_2 O_2N

$+ CH_3-C(=O)-ONO_2$ (CH₃CO)₂O

R   R   R O_2N R

H   H   H   H
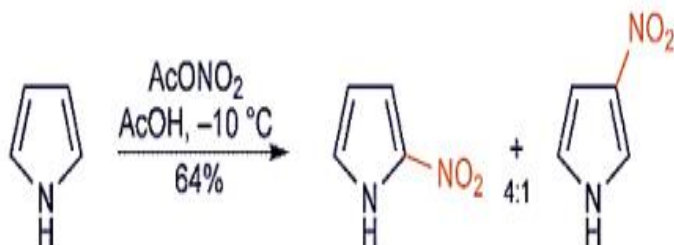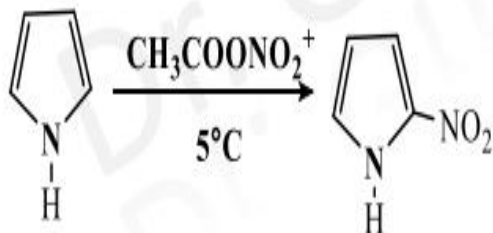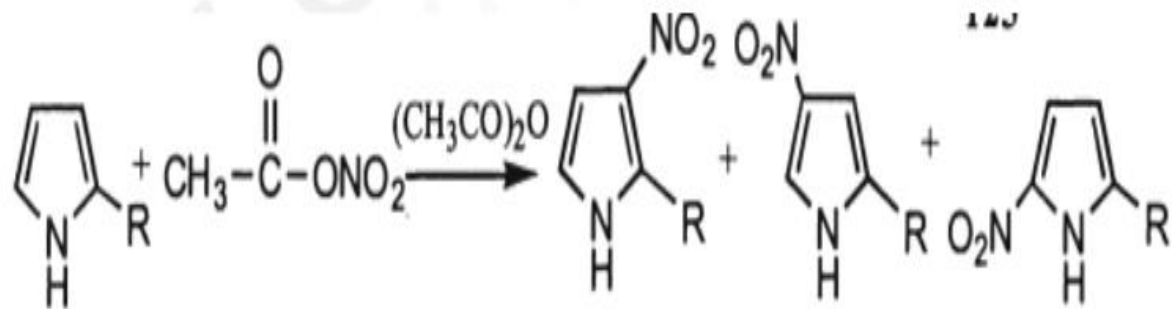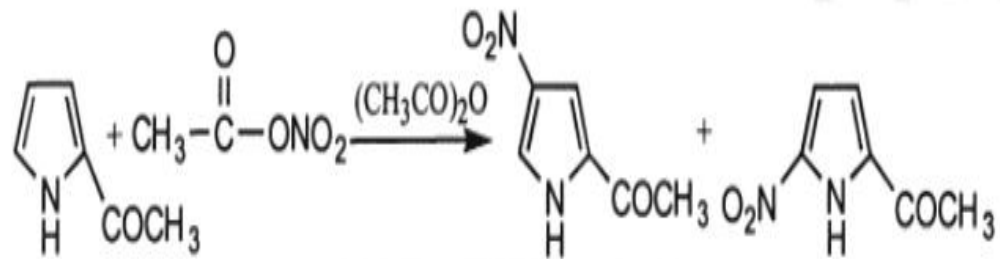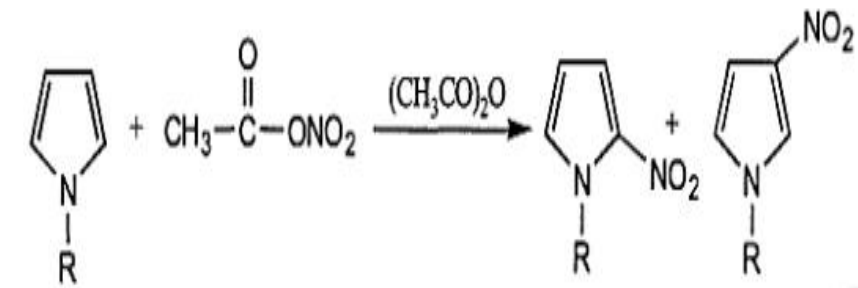
2- Sulfonation :

Pyrrole and its N- and C-alkylpyrroles cannot be sulfonated under ordinary conditions as these are polymerized by concentrated sulfuric acid. These are, therefore, sulfonated by mild sulfonating agent (pyridine-sulfur trioxide) of low acidity. The reaction of pyrrole with pyridine-sulfur trioxide complex at 100°C, a 90% yield of the corresponding pyrrole-2-sulfonic acid is obtained, after acidification.
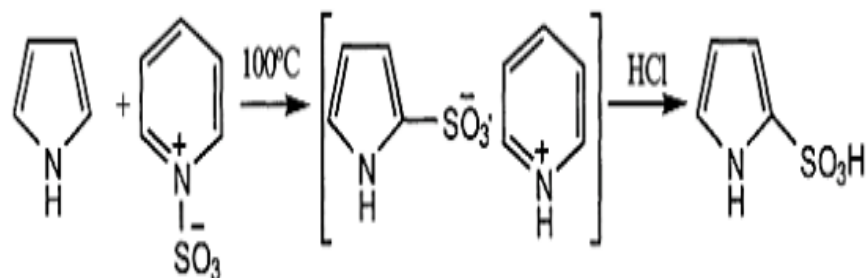
Pyrroles substituted with electron- withdrawing substituents require vigorous reaction conditions (chlorosulfonic acid, cone. sulfuric acid and oleum). If both the a-positions are blocked, the sulfonation occurs at the β-position
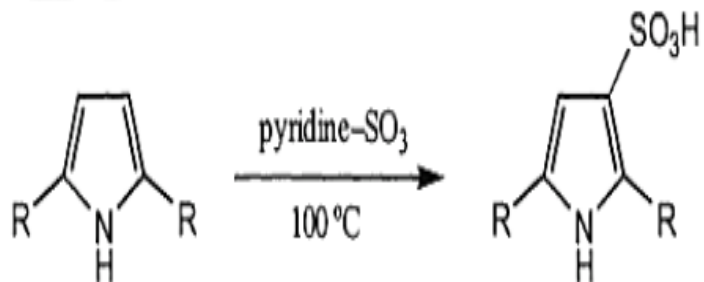
3- Halogenation :

The high reactivity of pyrrole ring system causes it to undergo halogenation at all the strongly activating positions. The special reagents with mild conditions are, therefore, required for the halogenation of pyrroles.
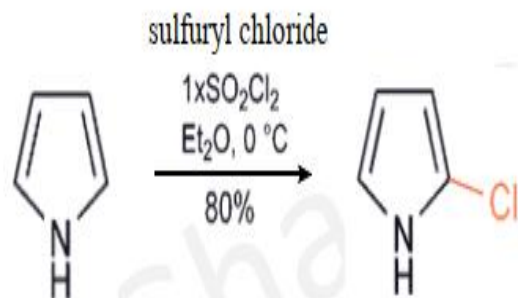
Note:
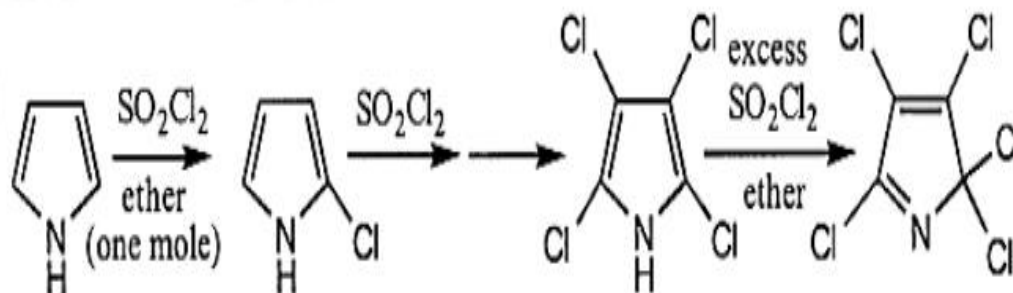
- Bromination of pyrrole with bromine in acetic acid gives 2,3,4,5-tetrabromopyrrole
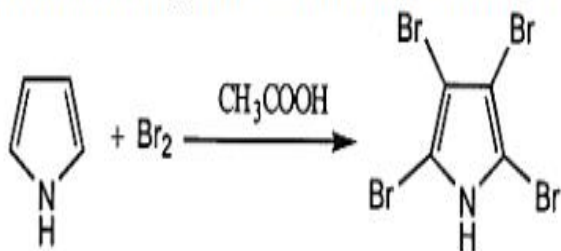
- pyrrole substituted with electron-withdrawing substituent undergoes bromination providing monobrominated pyrroles
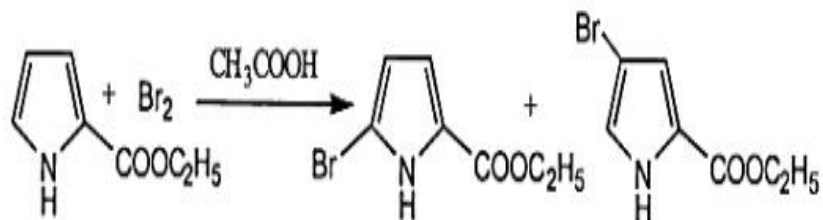
- with bromine in carbon tetrachloride, 3-bromopyrrole is obtained by the isomerization of thermodynamically less stable 2-bromopyrrole

pyrrole   2,3,4,5-tetrabromopyrrole
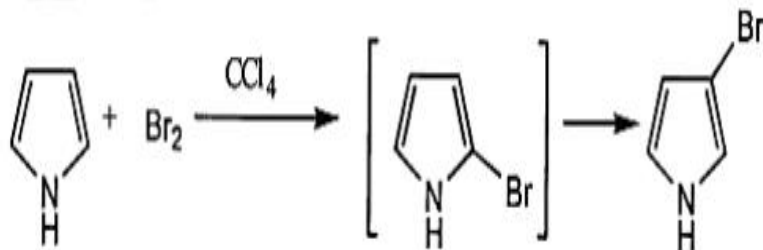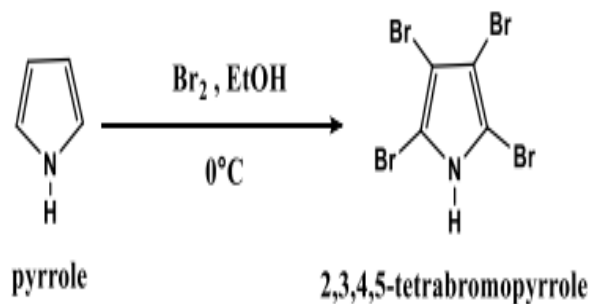
Although unstable compounds, 2-bromo- and 2-chloropyrrole (also using SO_2Cl_2) can be prepared by direct halogenation of pyrrole with the N-halo-succinimides

N-Bromo succinamide
(N.B.S)
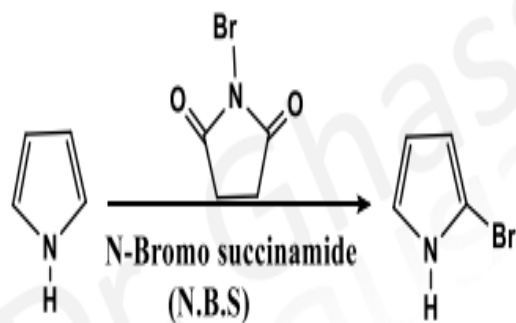
- Iodination of pyrrole with iodine in aqueous potassium iodide provides tetraiodopyrrole.
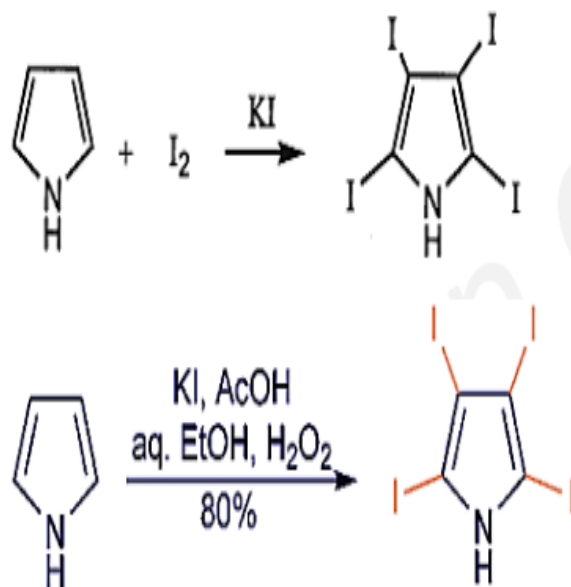
- Iodination of pyrrole substituted with electron-withdrawing substituent at the position-2 results in substitution at the position- 4.
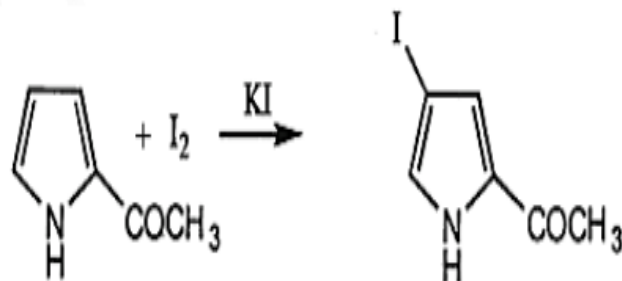
4- Friedel-Crafts Acylation:

Typical electrophilic reactions, such as nitration, halogenation with a Lewis acid (as a 'carrier'), **Friedel-Crafts C-alkylation and -acylation, that work well with benzene, cannot be applied to pyrrole, because heating with strong acids, or a Lewis acid, destroys the heterocycle. However, milder conditions can sometimes be used.**

Direct acetylation of pyrrole with acetic anhydride at 200 °C leads to 2-acetylpyrrole as main product, together with some 3-acetylpyrrole, but no *N*-acetylpyrrole.[32] *N*-Acetylpyrrole can be obtained in high yield by heating pyrrole with *N*-acetylimidazole.

or pyrrole with acetic anhydride in the presence of sodium acetate provides N-acylpyrrole

2-acytal pyrrole
90%

3-acytal pyrrole
10%
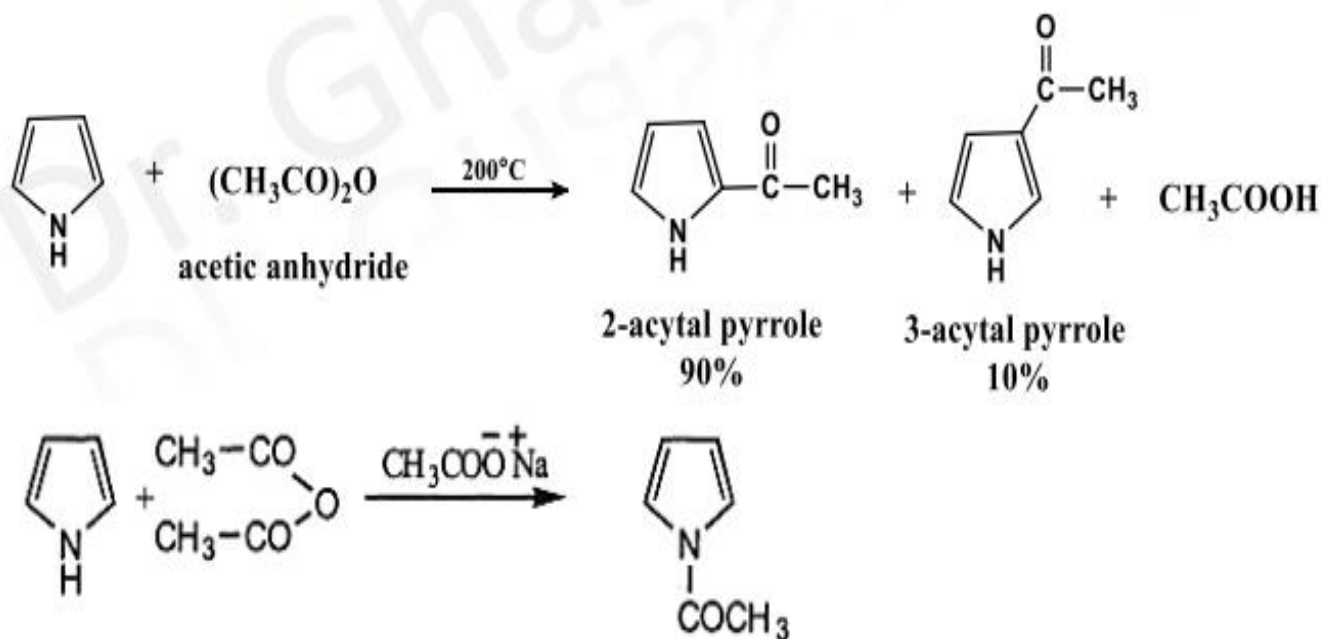
> N-Acylpyrroles can be obtained by the reaction of alkali metal salt of pyrroles with an acyl halide
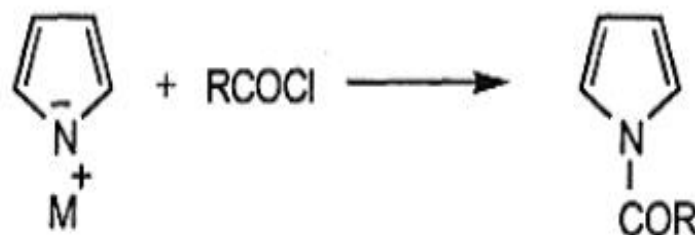
5- Vilsmeier reaction :

The Vilsmeier reaction (reagents: POCl3, and N, N-dimethylformamide) gives 2-formylpyrrole

2-formylpyrrole

(1*H*-pyrrole-2-carbaldehyde)
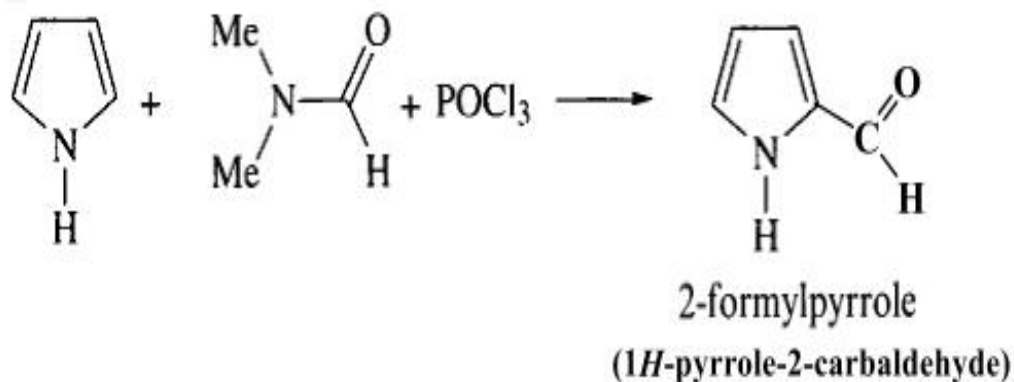
6- Friedel-Crafts Alkylation:

Because of high reactivity of the pyrrole ring, Friedel-Crafts alkylation of pyrrole with alkyl halides and highly reactive allyl- and benzyl halides results in polyalkylation under milder conditions. Therefore, it is not possible to obtain monoalkylated product.

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

poly-mthylated pyrroles
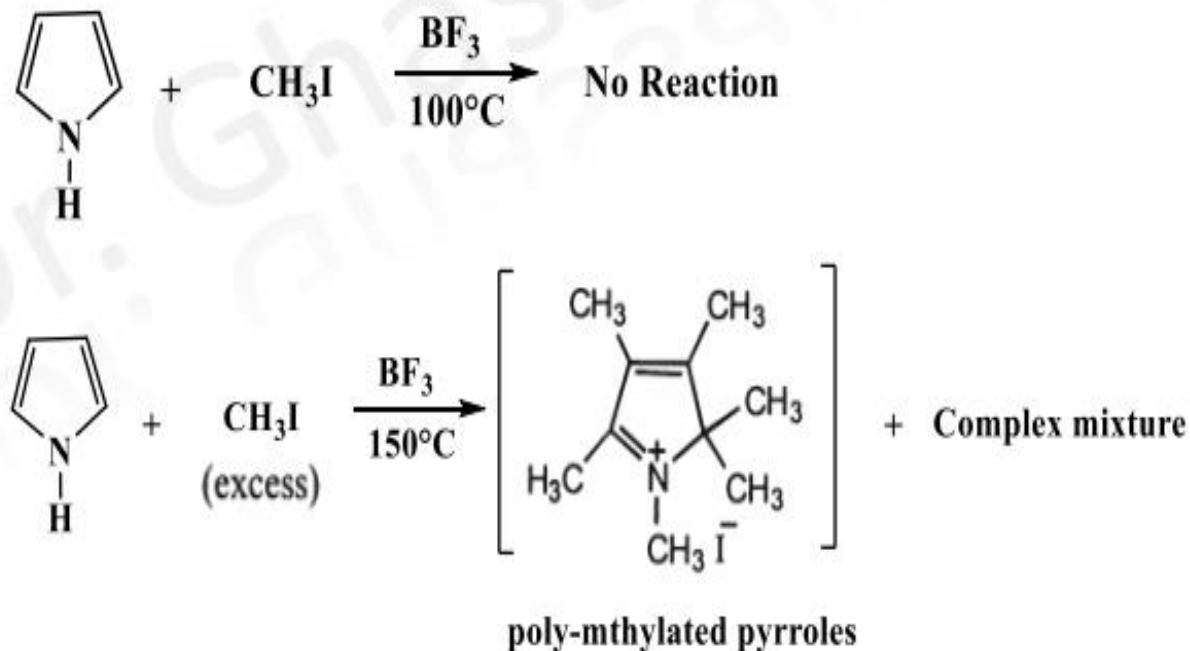
➤ The reactivity of pyrroles substituted with electron-withdrawing substituents towards Friedel-Crafts alkylation is decreased because of co-ordination of substituent with Friedel-Crafts catalyst. The reaction of ethyl pyrrole-2-carboxylate with alkene in the presence of Lewis acid results in the formation of 4-isopropyl- and 4,5-diisopropyl- derivatives

ethyl 4,5-diisopropyl-1*H*-pyrrole-2-carboxylate
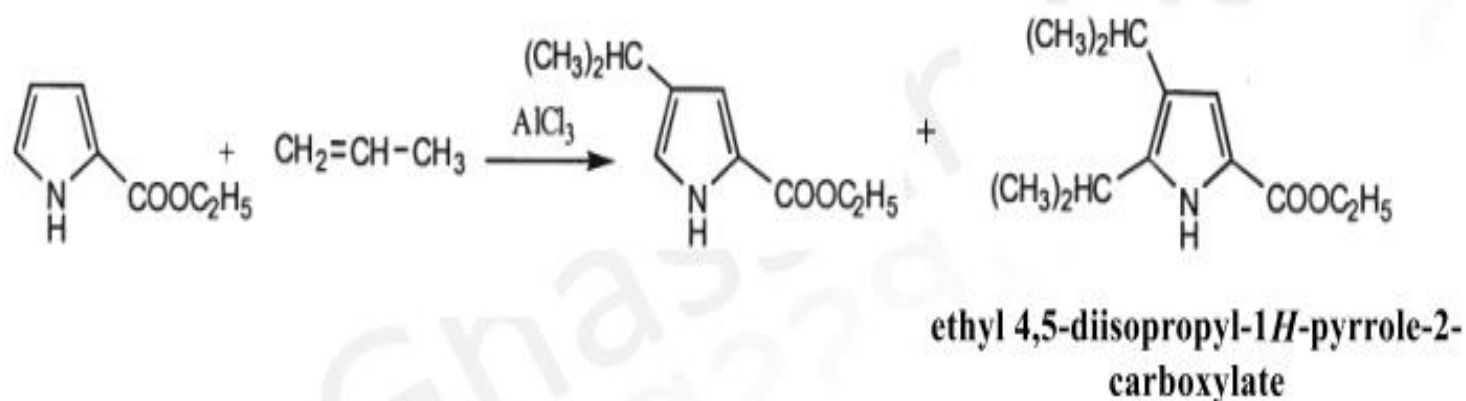
➤ Friedel-Crafts alkylation of pyrrole Grignard reagent produces 2-alkylpyrrole via 1-alkylpyrrole involving Hofmann-Martius type rearrangement
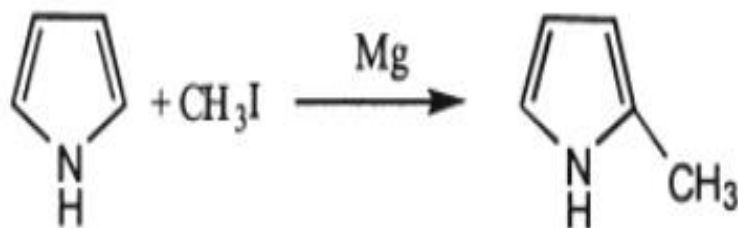
7) Hydroxymethylation (Mannich Reaction)

Pyrrole undergoes Mannich reaction with formaldehyde and primary or secondary amine in the presence of an acid with the introduction of functionalized alkyl group at the α-position. However, if both the a-positions $(\alpha, \acute{\alpha})$ are substituted, the substitution then occurs at a free β-position. The reaction is considered to involve electrophilic attack of iminium electrophile which is produced in situ from the reaction of formaldehyde with amine in the presence of an acid. The product of Mannich reaction (Mannich base) is synthetically useful as it undergoes a number of transformations providing important compounds.
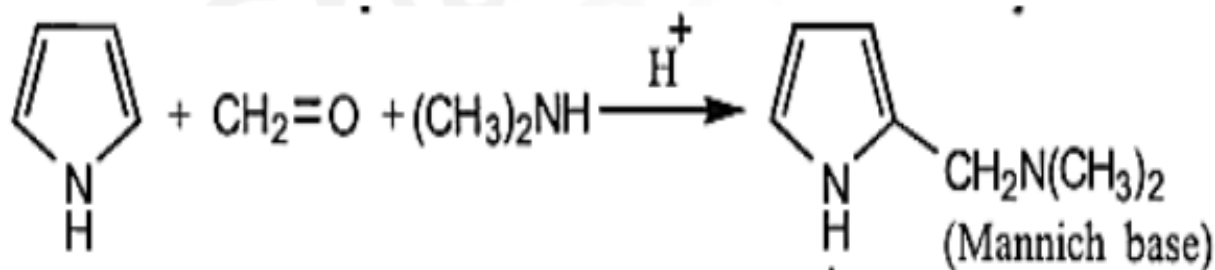
8) Diazo Coupling

Pyrrole undergoes diazo coupling reactions very readily with benzenediazonium salts providing 2-aza- or 2,5-bis(aza)- pyrroles depending on the reaction conditions. The rate of the reaction is faster in an alkaline media as it involves pyrrolyl anion and results in the formation of 2,5-bis(aza)-pyrrole
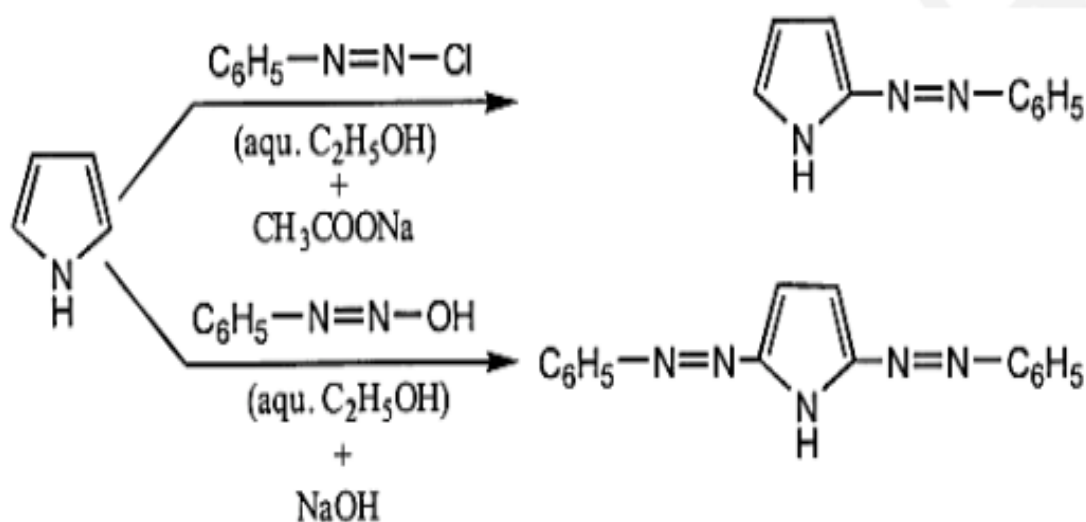
> If both the α-positions are occupied, diazo coupling occurs at the B-position
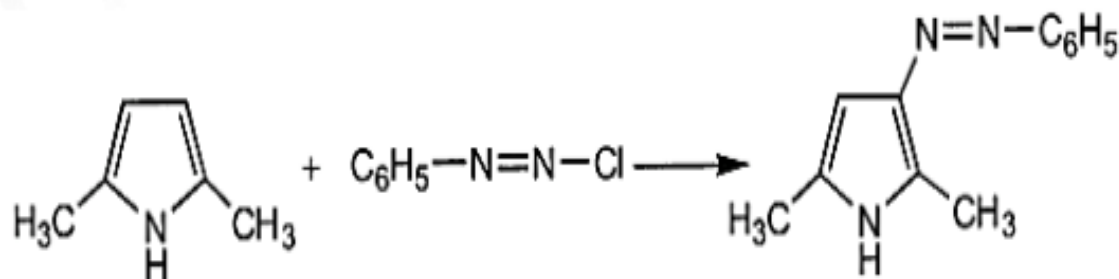
2) Sulfonation

Furan and its simple alkyl - derivatives are decomposed by the usual strong acid reagents, but the pyridine – sulfur - trioxide complex or dioxane can be used, and provides 2-sulfonic or 2,5-disulfonic acid depending on the reaction conditions, disubstitution of furan occurring even at room temperature. However, furan substituted with an electron-withdrawing substituent at the position-2 can be sulfonated by oleum with the formation of 5-sulfonic acid derivative.

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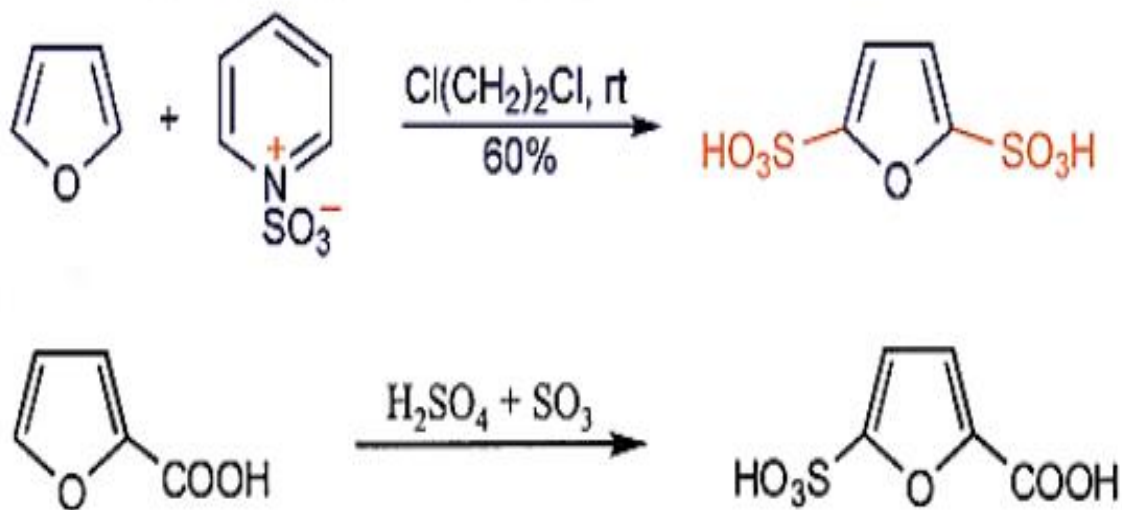
3) Halogenation

Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products, but does not react at all with iodine. Controlled conditions, the milder conditions are required for the formation of monobromo- and monochloro-furans. Bromination of furan by bromine in dimethylformamide at room temperature – smoothly produce 2 - bromo - or 2,5 - dibromo - furans. dioxane-dibromide (Br2 + dioxane) at -5°C gives 2-bromofuran
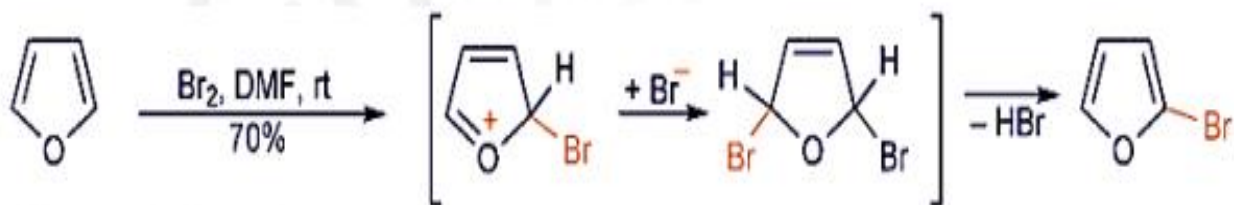
Mechanism:
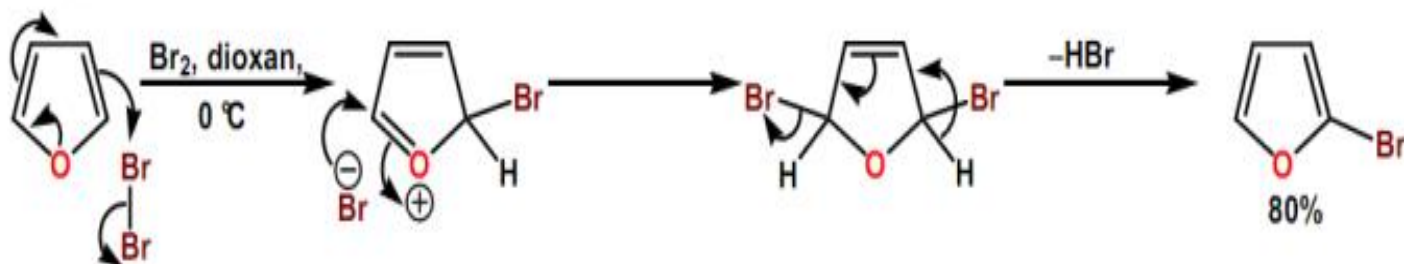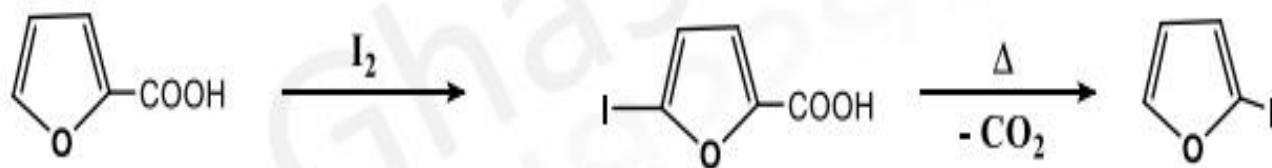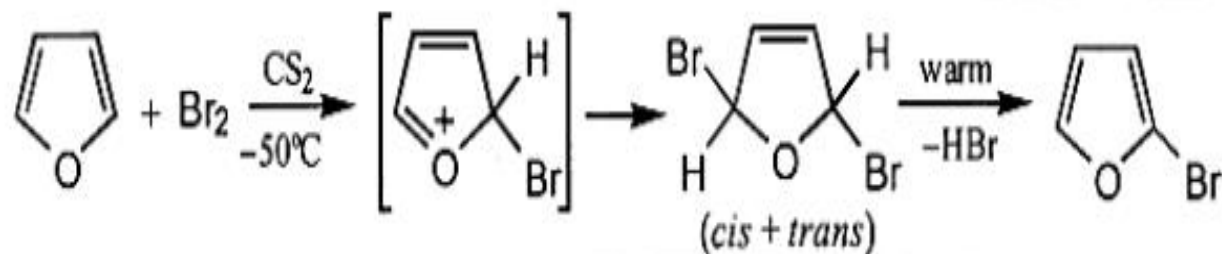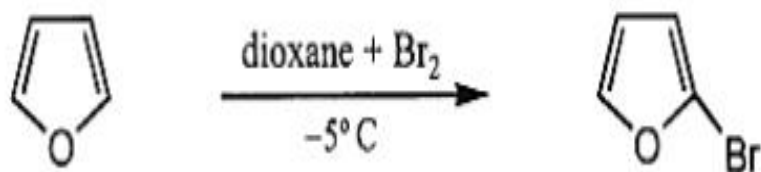
في هذا المثال تكون عملية الهلجنة للفيوران بشكل غير مباشر

Note:

Bromination of furan substituted with an electron-withdrawing substituent at the position-2 generally provides 5-bromo derivative involving an electrophilic substitution mechanism.
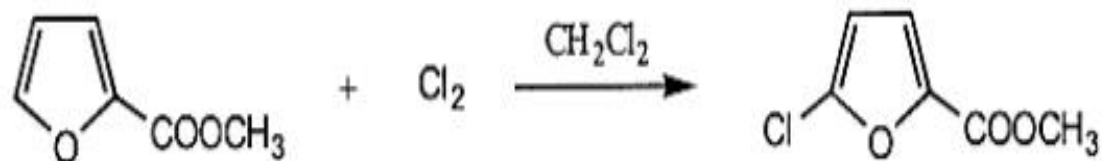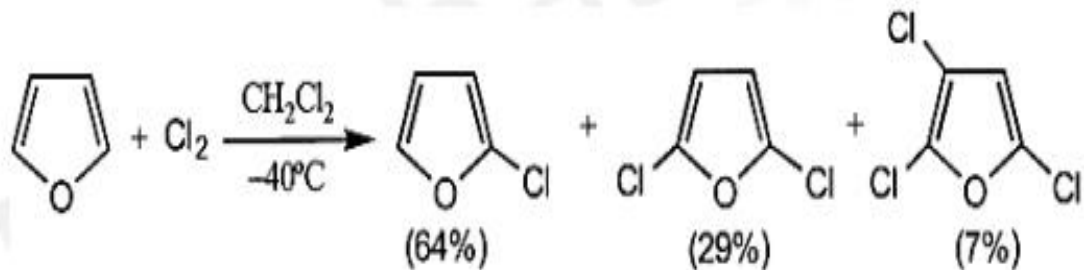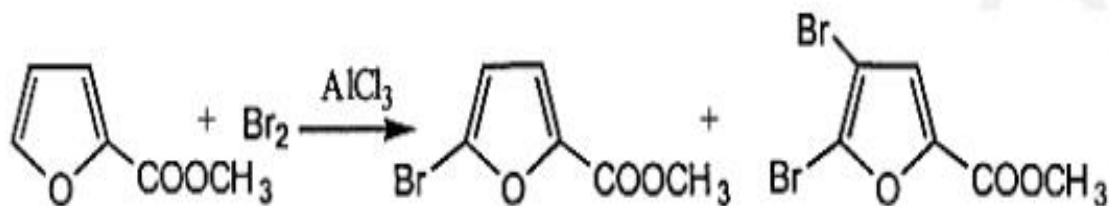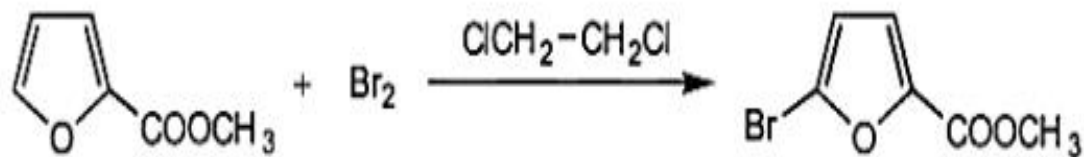
4) Friedel-Crafts Acylation

The acylation of furan with acid anhydrides in the presence of mild catalysts such as phosphoric acid or boron trifluoride etherate results in exclusively 2-acylfuran. The acylation of furans can be performed also with acetyl p-toluene sulfonate or Ac 20-SnC14, although trifluoroacetic anhydride does not require any catalyst.

α:β 6800:1
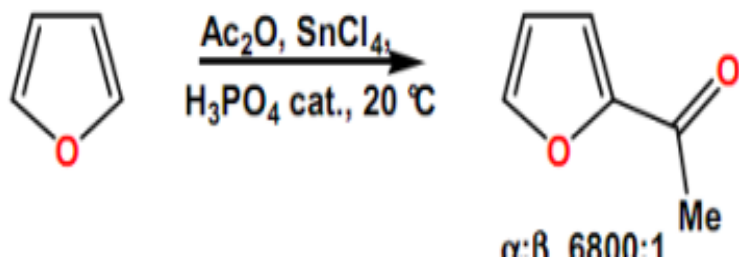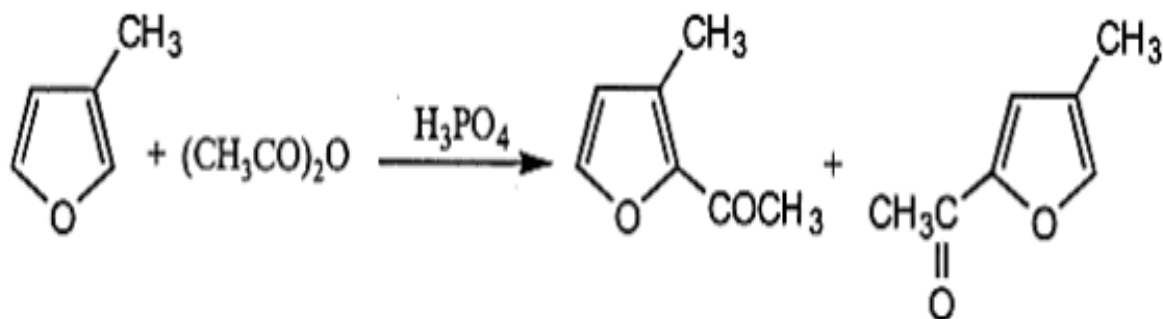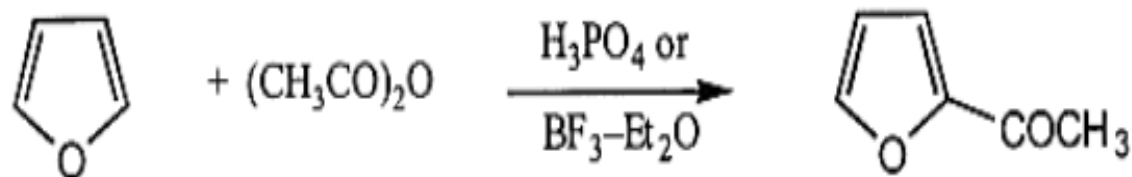
• Blocking groups at the α positions and high temperatures required to give β acylation

H_3C—furan—CH_3 + $(CH_3CO)_2O$ $\xrightarrow{SnCl_4}$ product with $COCH_3$

Me-furan $\xrightarrow[\substack{BF_3.Et_2O,\ 0\ °C \\ 30\%}]{(i\text{-}BuCO)_2O}$ product

furan-$COOCH_3$ + $(RCO)_2O$ $\xrightarrow{BF_3-Et_2O}$ $R-\overset{O}{\underset{\parallel}{C}}$-furan-$COOCH_3$
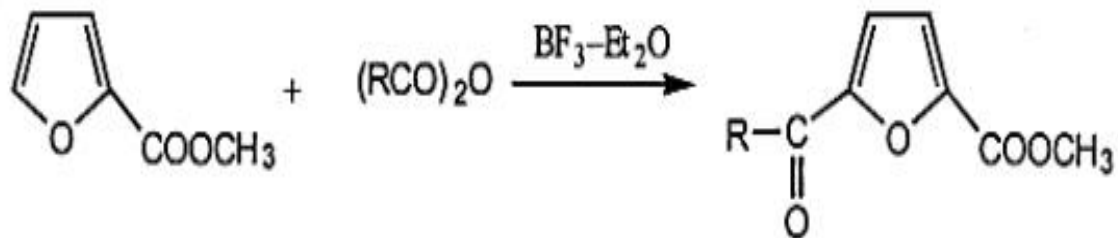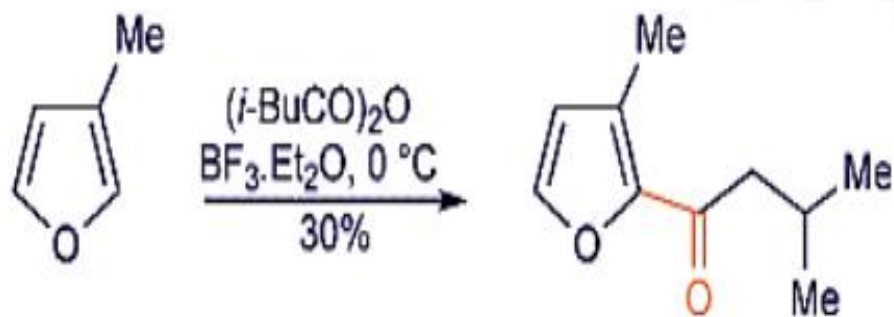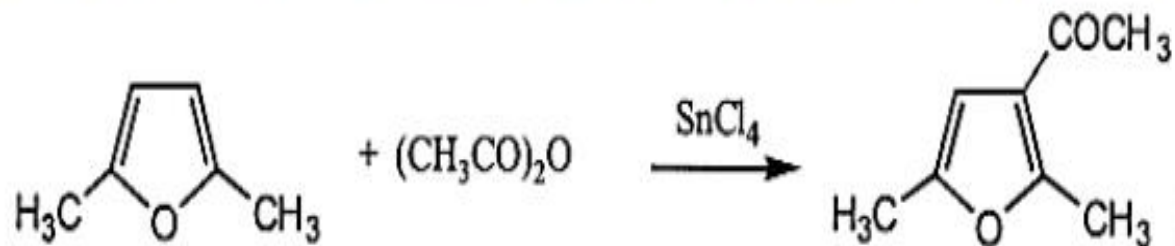
5) Vilsmeier reaction :

► Vilsmeier formylation of furans is a good route to α-formyl-furans

DMF = N, N-dimethylformamide
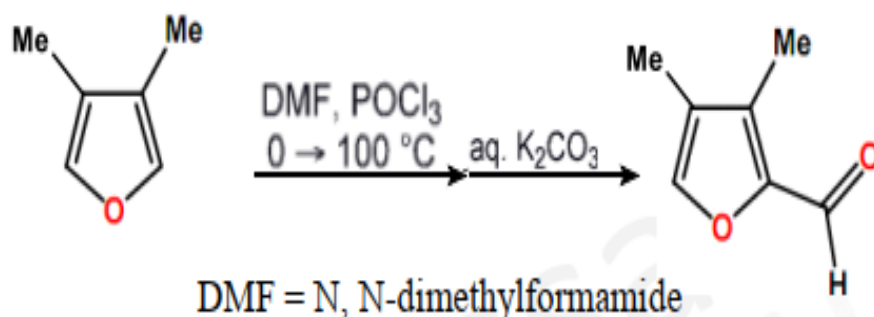
6) Friedel-Crafts Alkylation

Furan does not undergo Friedel-Crafts alkylation. The catalysts required in Friedel-Crafts alkylation affect polymerization because of the acid sensitivity of furan. The alkylation is affected by alkenes at the position-2 in the presence of mild catalysts (phosphoric acid or boron trifluoride)
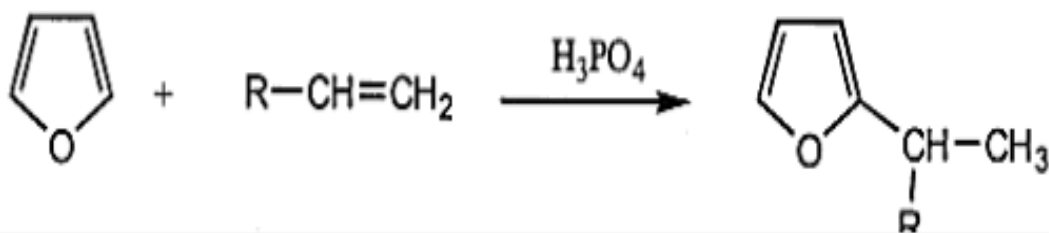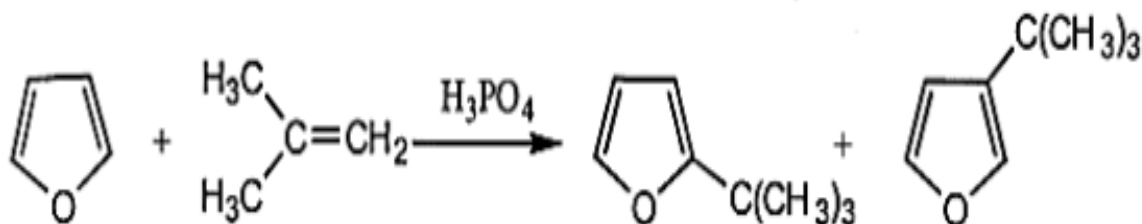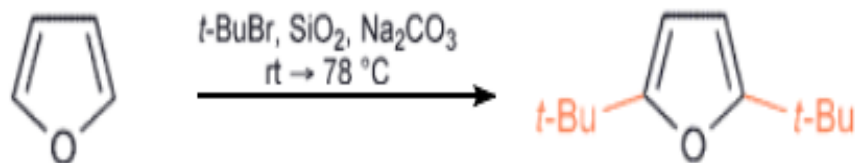
3-alkylated (tert-butylation) furans

Note:

furans substituted with electron-withdrawing substituents at the position-2 undergo Friedel-Crafts alkylation at room temperature providing a mixture of alkylfurans
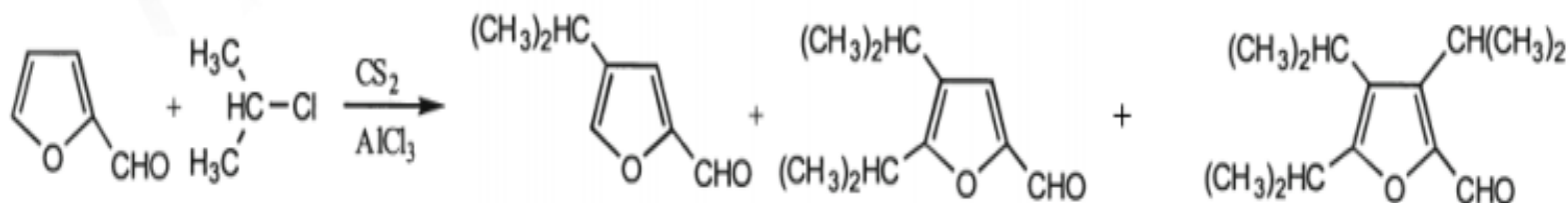
7) Reactions with Diazonium Salts

Furan undergoes phenylation rather than diazo coupling on reaction with benzenediazonium salts.
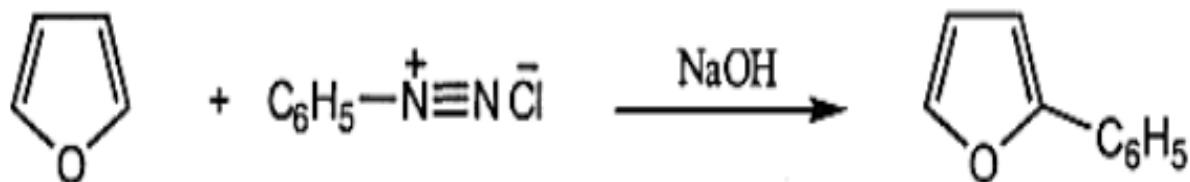
Thiophenes: Reactions

1) Nitration:

Thiophene undergoes nitration predominantly at an α-position with the formation of 2-nitrothiophene, when treated with mild nitrating agent, acetyl nitrate [mixture of fuming nitric acid and acetic anhydride], at 10°C. Although small amount of 3-nitrothiophene is also obtained, the selectivity in nitration decreases with the strong nitrating agents.

يدخل مركب الثايوفين تفاعل النيترة بسهولة
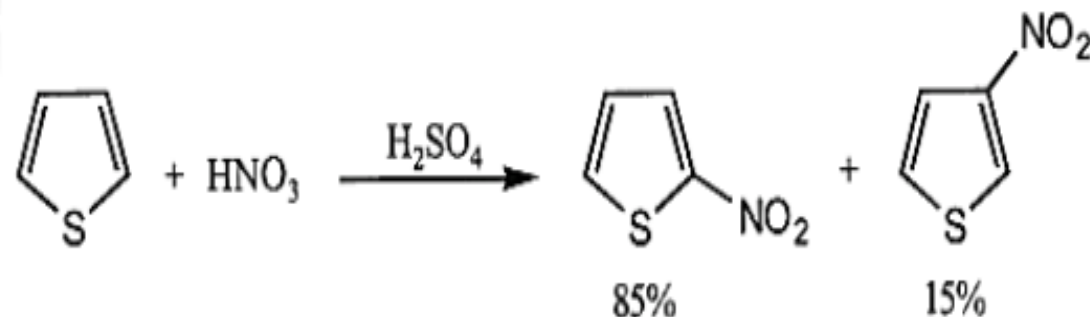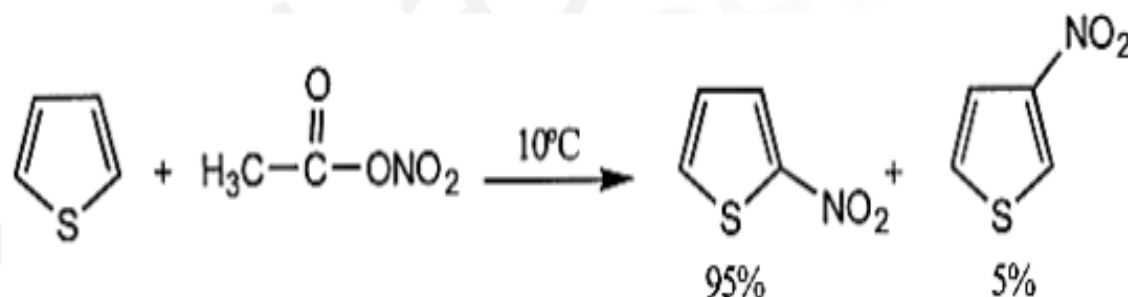
- The nitration of thiophenes substituted with electron-releasing substituents (with +I effect) at C-2 provides 3-nitro- and 5-nitrothiophenes. But when the substituent is with considerable steric hindrance, the nitration occurs exclusively at C-5
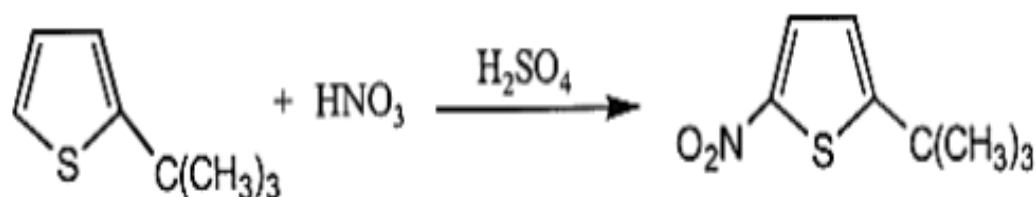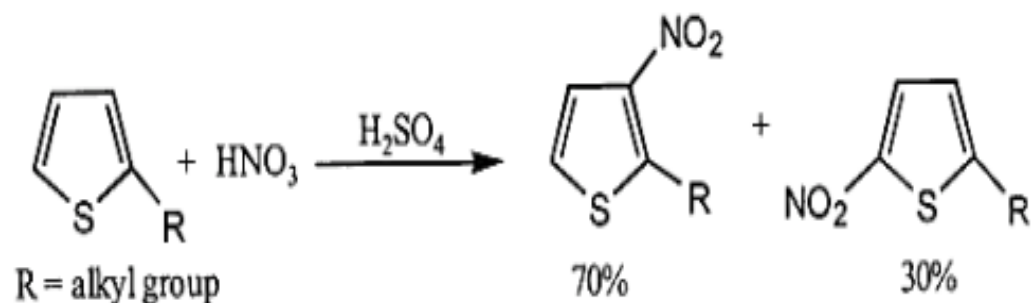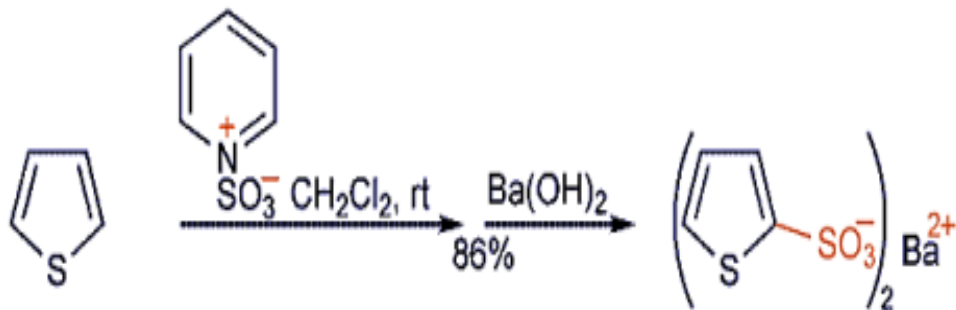

- Thiophenes with electron-withdrawing substituents at C-2 undergo nitration at the C-4 and C-5 positions providing 4-nitro- and 5-nitro derivatives
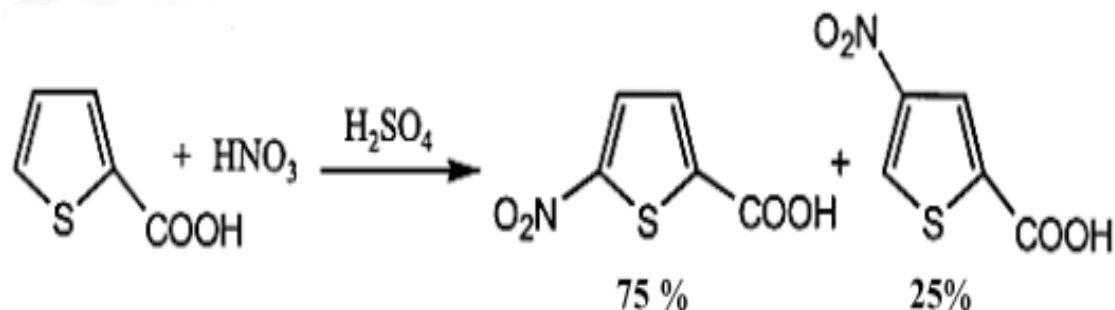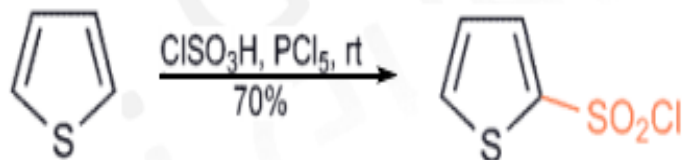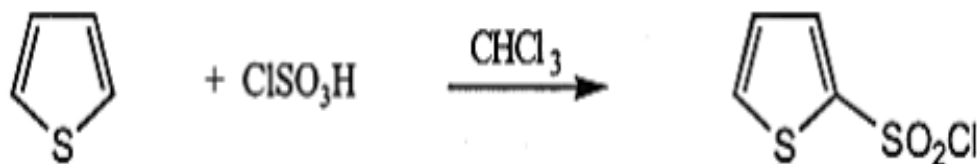
- ➤ Thiophenes substituted with electron-releasing substituents (+M effect) involve nitration at the a- and 13-positions , but in halothiophenes nitration takes place exclusively at C-5 (α-position)
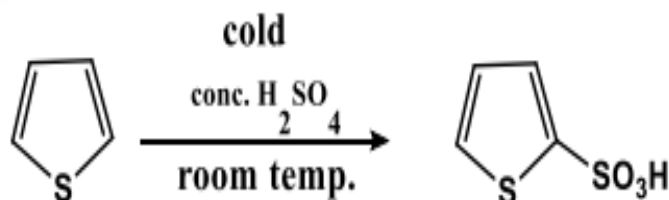

80%   20%
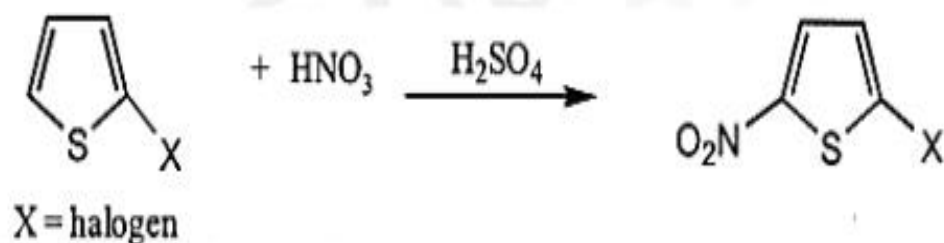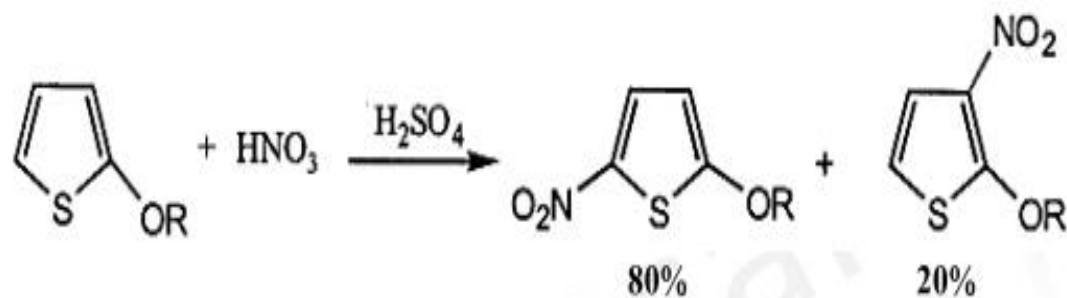
X = halogen

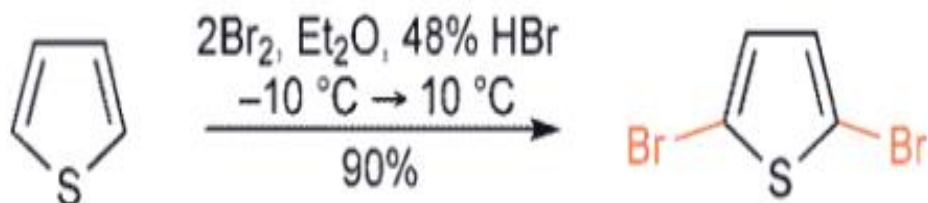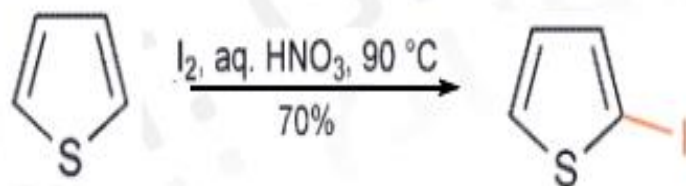> The reaction of thiophene with chlorosulfonic acid affords thiophene-2-sulfonyl chloride 467 in low yield
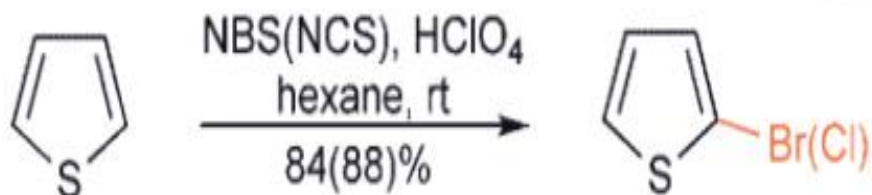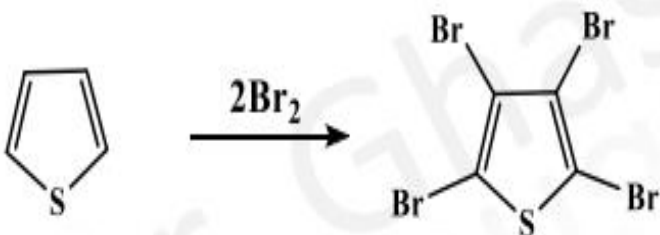

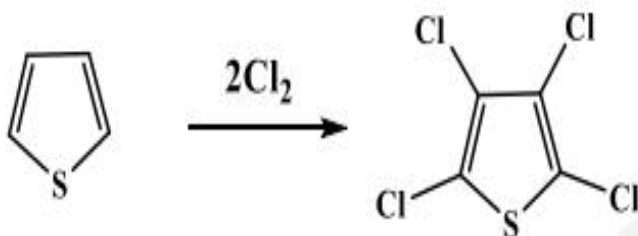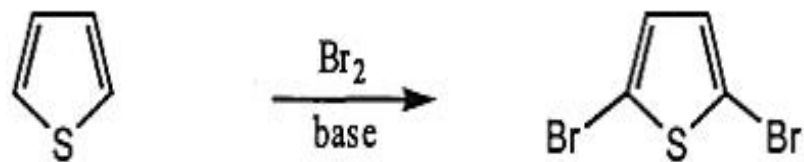

يمكن ان يدخل مركب الثايوفين تفاعل السلفنة من خلط الثايوفين مع حامض الكبريتيك المركز البارد

# 3) Halogenation:

Halogenation of thiophene occurs very readily at room temperature and is rapid even at − 30 ° C in the dark; tetrasubstitution occurs easily.   The rate of halogenation of thiophene at 25 ° C is about 10 8 times that of benzene.   2 - Bromo - , 2 - chloro -   and 2 - iodothiophenes   and 2,5 - dibromo - and 2,5 - dichlorothiophenes   can be produced cleanly under various controlled conditions. Controlled bromination of 3 - bromothiophene produces 2,3 - dibromothiophene.

$$\text{NBS(NCS), HClO}_4$$
$$\text{hexane, rt}$$
$$84(88)\%$$

$$\text{I}_2\text{, aq. HNO}_3\text{, 90 °C}$$
$$70\%$$

$$2\text{Br}_2\text{, Et}_2\text{O, 48\% HBr}$$
$$-10\text{ °C} \rightarrow 10\text{ °C}$$
$$90\%$$

يعاني الثايوفين عملية هلجنة متعددة احادي وثنائي وثلاثي ورباعي مع الكلور او البروم

N-Bromo succinamide
(N.B.S)
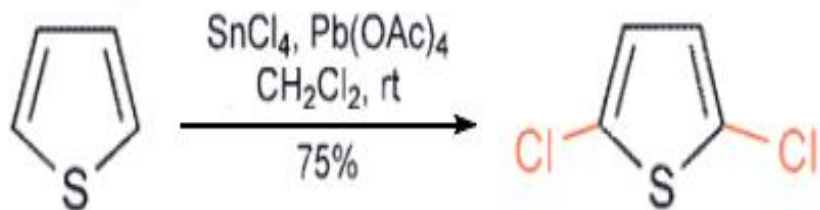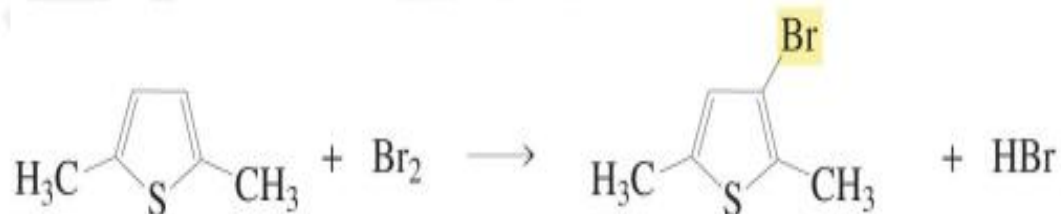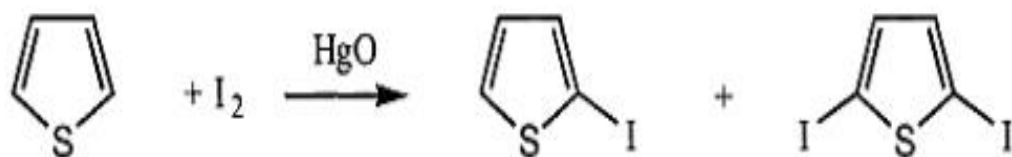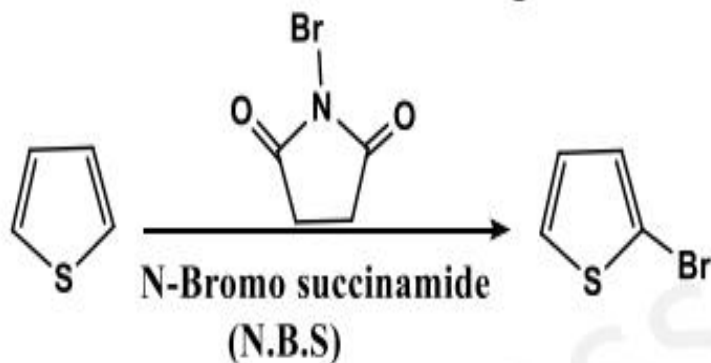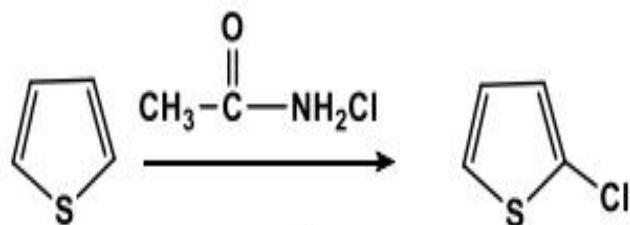
3-bromo-2,5-dimethylthiophene

Note:

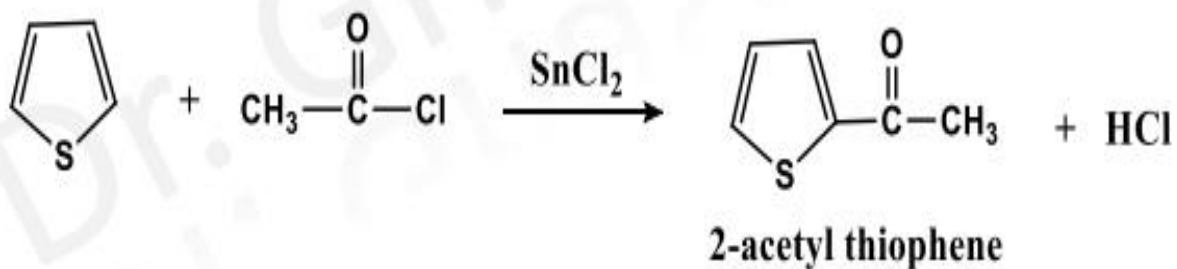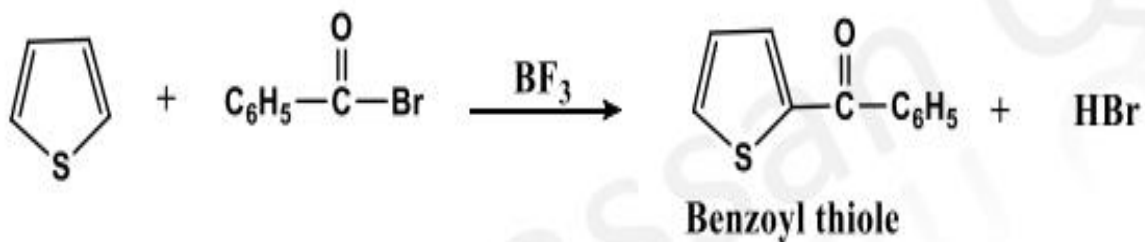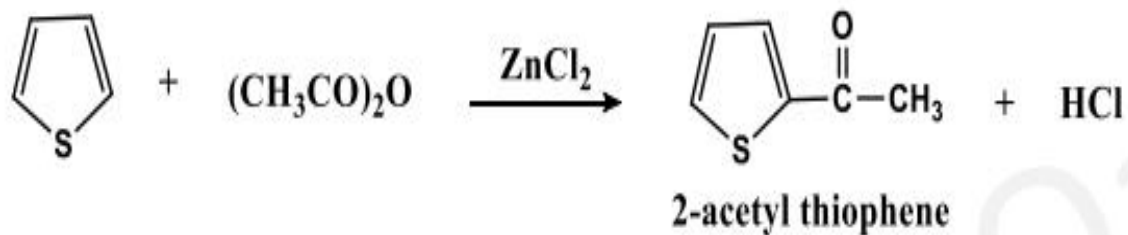If both positions adjacent to the heteroatom are occupied, electrophilic substitution occurs at C-3:

4) Friedel-Crafts Acylation:

Thiophene is polymerized when treated with acetyl chloride in the presence of aluminium chloride, but undergoes acylation exclusively at an a-position ($\alpha : \beta = 200 : 1$) when acylated by acid anhydrides in the presence of phosphoric acid or by acid chlorides in the presence of stannic chloride. The reactivity of α-position in thiophene is much higher than that of the β-position towards acylations and therefore leads to the α-substitution selectively.
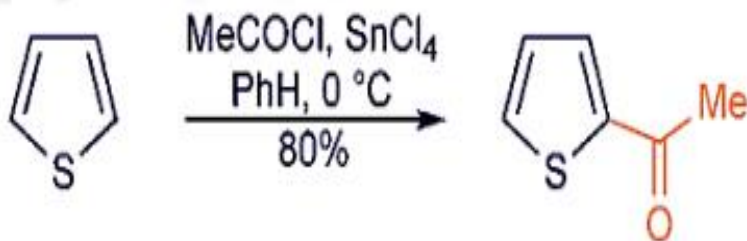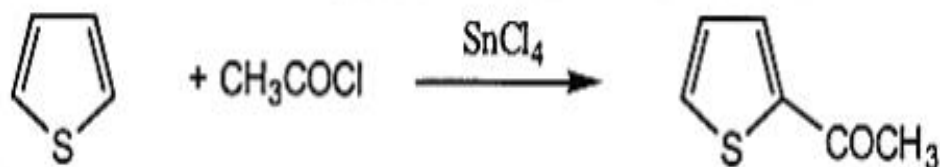
هنا لايستخدم AICI3 كعامل مساعد في عملية الاسيلة للثايوفين الغير معوض لانه يعطي بوليمر لذلك يستعاض عنه بعامل مساعد اخر مثل ZnCL2, SnCl4, BF3

Thiophene + $(CH_3CO)_2O$ $\xrightarrow{ZnCl_2}$ 2-acetyl thiophene + HCl

Thiophene + $C_6H_5-\overset{\overset{\displaystyle O}{\|}}{C}-Br$ $\xrightarrow{BF_3}$ Benzoyl thiole + HBr

Thiophene + $CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-Cl$ $\xrightarrow{SnCl_2}$ 2-acetyl thiophene + HCl

> the acylation of 2-acylthiophenes in the presence of Lewis acid occurs at the position-4 probably because of co-ordination of Lewis acid with oxygen of an acyl group
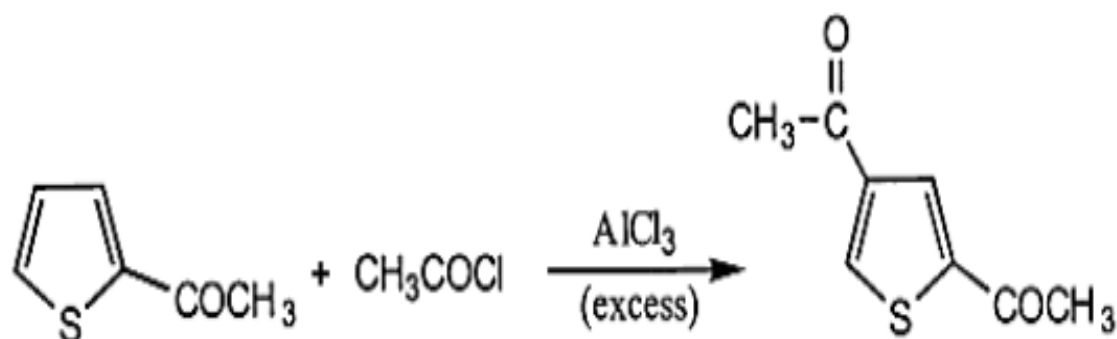

> Thiophenes substituted with electron-releasing substituents such as methyl-, tert-butyl- or thiomethyl- at the position-2 undergo acylation exclusively at the position-5 (α-substitution)


R = CH₃, (CH₃)₃C, SCH₃
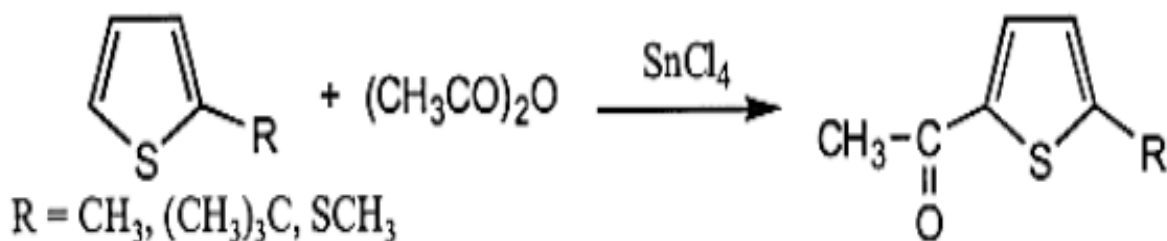
5- Vilsmeier reaction :

Vilmseier formylation of thiophene leads efficiently to 2-formylthiophene,[34] comparable substitution of 3-phenylthiophene gives 2-formyl-3-phenylthiophene,[35] the regioselectivity echoed in the Vilsmeier 2-formylation of 3-methylthiophene using N-formylpyrrolidine[36] (2-formyl-4-methylthiophene can be produced by lithiation   then reaction with dimethylformamide[37]).


475
(major product)

476
(minor product)
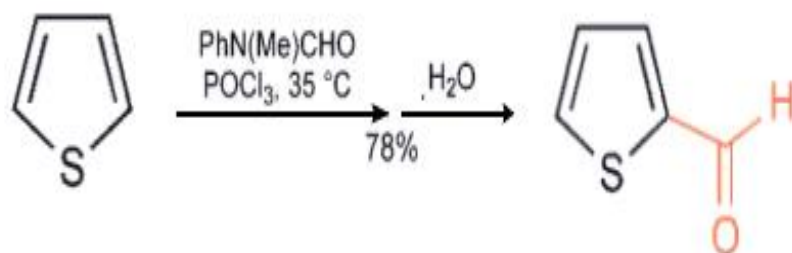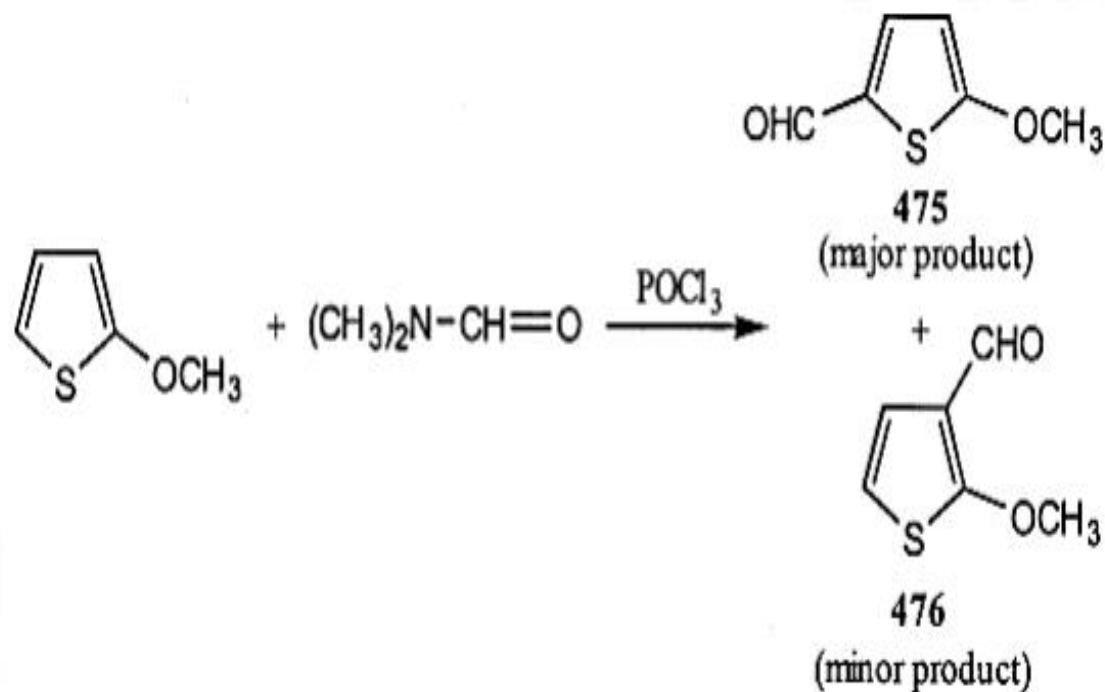
6) Friedel-Crafts Alkylation:

Alkylation of thiophene under Friedel-Crafts conditions results in polyalkylation and polymerization probably because of the successive protonation and electrophilic substitutions. However, alkylation of thiophene with alkenes in the presence of phosphoric acid or boron trifluoride gives a mixture of α-and β-isomers . The poor a-selectivity is due to the indiscriminate attack of highly reactive carbonium ion at the α- and β-positions during alkylation. The α-selectivity is not effected in the alkylation of thiophenes if substituted with either methyl-, tert-butyl-, or thiomethyl- at the position-2. But electron-withdrawing substituents at the position-2 have considerable effect and favour alkylation predominantly at the position-4 because of the swamping catalyst effect

$R = CH_3, (CH_3)_3C, SCH_3$
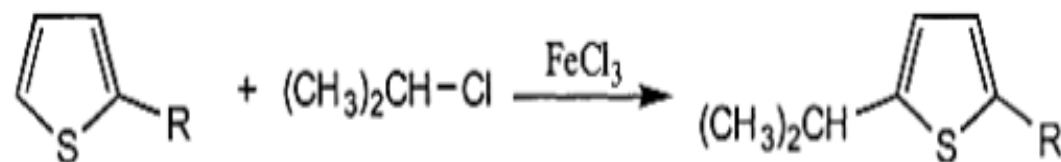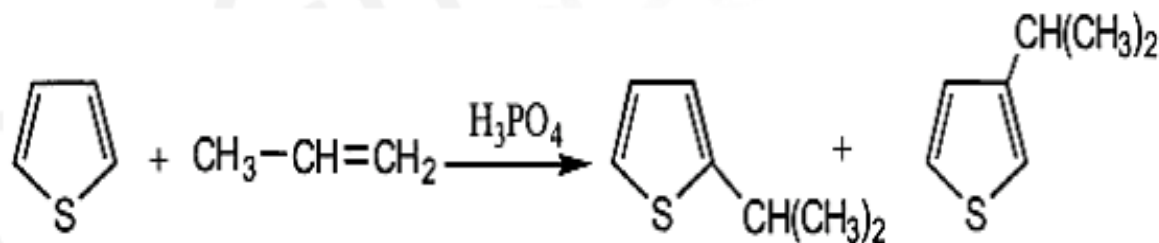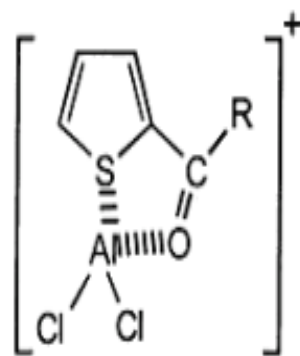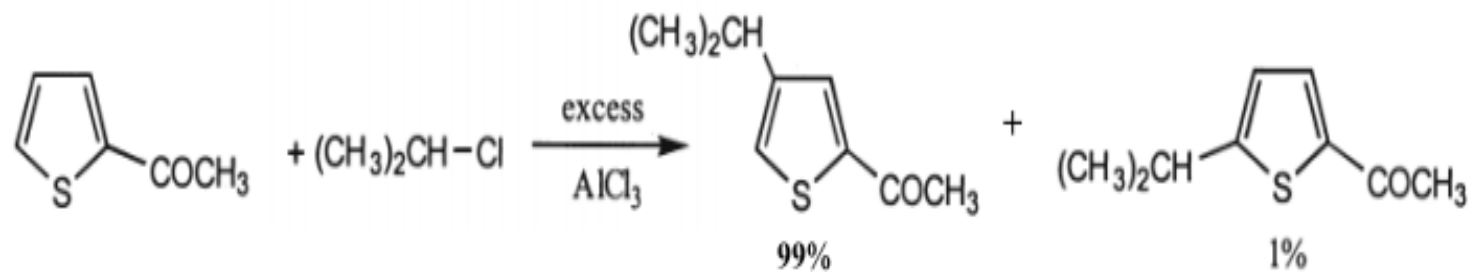
(swamping catalyst effect)

7) Reactions with Diazonium Salts

Thiophene is not sufficiently reactive to diazo coupling and undergoes arylation rather than coupling reaction when treated with diazonium salts under alkaline conditions and produces 2-aryl- or 2,5-diarylthiophene probably by the mechanism depicted in. However, 2-methyl-, 2-tert-butyl-, 2-phenyl- and 2,4-dimethyl-thiophenes with diazonium salts under acidic conditions result in the formation of coupled products involving normal coupling at the position-2

$R^1 = CH_3 \quad R^2 = H$
$R^1 = C(CH_3)_3 \quad R^2 = H$
$R^1 = C_6H_5 \quad R^2 = H$
$R^1 = CH_3 \quad R^2 = CH_3$