

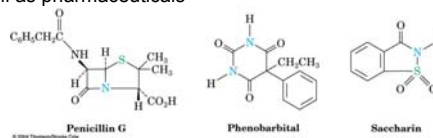
## Heterocyclic Compounds

- **Definition:** **Heterocyclic compounds** are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic

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## Heterocycles

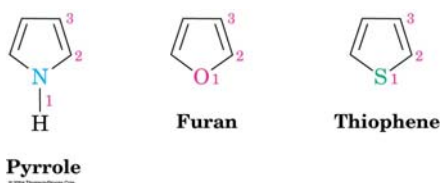
- Cyclic organic compounds are carbocycles or heterocycles
  - Carbocycle rings contain only carbon atoms
  - Heterocycle rings atoms in addition to carbon (N,S,O are common)
- Heterocycles include many important natural materials as well as pharmaceuticals



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## Five-Membered Heterocycles

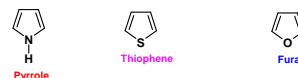
- Pyrrole, furan, and thiophene are common five-membered unsaturated heterocycles
- Each has two double bonds and N, O, or S



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## Five-Membered Heterocycles

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



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## Aromatic Heterocycles

- Aromatic heterocyclic compounds are those that have a heteroatom in a ring and behave in a manner similar to benzene in some of their properties (i.e. react by electrophilic aromatic substitution).
- Furthermore, these compounds comply with the general rule proposed by Huckel.

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## Aromatic Heterocycles

- Erich Hückel, a German physical chemist recognized in the early 1930s through MO calculations that cyclic planar molecules with a closed loop of 2,6,10,14,18,22.....  $\pi$ -electrons in a fully conjugated system should be **aromatic**.
- This finding is called the  $(4n+2)$   $\pi$ -electron rule. Conversely, monocyclic planar molecules with  $4n$   $\pi$ -electrons are said to be **antiaromatic**.

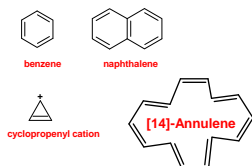
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## Aromaticity

- For a molecule to be aromatic it must:
  - Be cyclic
  - Have a  $p$ -orbital on every atom in ring
  - Be planar
  - Posses  $4n+2$   $p$  electrons ( $n = \text{any integer}$ )



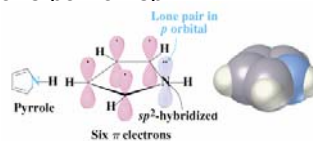
Erich Hückel



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## Structures of Pyrrole, Furan, and Thiophene

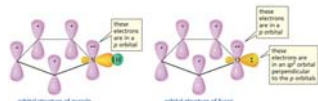
- Pyrrole, furan, and thiophene are aromatic (Six  $\pi$  electrons in a cyclic conjugated system of overlapping  $p$  orbitals)
- In pyrrole  $\pi$  electrons come from C atoms and lone pair on  $sp^2$ -N



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## Structure and Aromaticity

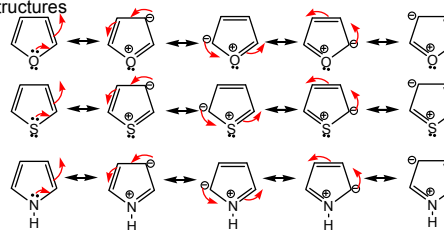
- Pyrrole furan and thiophene are aromatic because:
  - they fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity,
    - thus the grading of aromaticity is in the order of: furan < pyrrole < thiophene < benzene
    - this order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



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## Structure and Aromaticity

- They tend to react by electrophilic substitution due appearance of  $-ve$  charge on carbon atoms due to delocalization as shown in the following resonance structures



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## Structures of Pyrrole, Furan, and Thiophene

- However, the extent of aromaticity (as determined by resonance energies, see below) for these compounds is different from that of benzene (which undergoes electrophilic substitution reactions) .
  - Resonance Energies (experimental and theoretical values):
    - Furan 88  $\text{KJmol}^{-1}$
    - Pyrrole 100  $\text{KJmol}^{-1}$
    - Thiophene 130  $\text{KJmol}^{-1}$
    - Benzene 151  $\text{KJmol}^{-1}$
- Thus the order of aromatic character of these three heterocycles is as follows:  
Thiophene > pyrrole > Furan
- This order is consistent with the order of the electronegativity values

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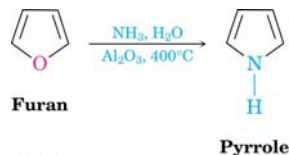
## Structures of Pyrrole, Furan, and Thiophene

- As O is more electronegative than N and S , it provides the two electron necessary for the aromatic sextet less easily, and in consequence furan is less aromatic than pyrrole and thiophene
- Element                      O      N      S
- Electron negativity      3.44   3.04   2.58
- For the same reason pyrrole is less aromatic than thiophene which resonance energy is higher than that of furan and pyrrole and about the same as in benzene.
- Therefore thiophene resemble benzene rather than furan or pyrrole in many of its reactions but it is more reactive and less stable.

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## Pyrrole

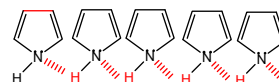
- Commercially from coal tar or by treatment of furan with ammonia over an alumina catalyst at 400°C.



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## General Characteristics

- Pyrrole, furan and thiophene are colorless liquids of boiling points 126°, 32°, and 84° respectively.
- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



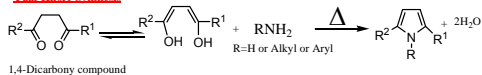
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## Synthesis of Pyrrole

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

Generally substituted pyrrole may be synthesized through the cyclization of 1,4-diketones in combination with ammonia (NH<sub>3</sub>) or amines. The ring-closure is proceeded by dehydration (condensation), which then yields the two double bonds and thus the aromatic π system. The formation of the energetically favored aromatic system is one of the driving forces of the reaction.

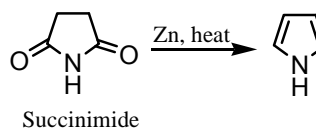
#### Paal-Knorr Synthesis



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## Synthesis of Pyrrole

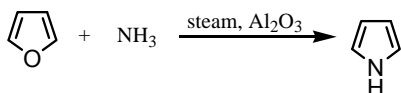
- 2) Pyrrole is obtained by distillation of succinimide over zinc dust.



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## Synthesis of Pyrrole

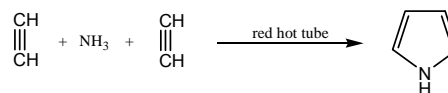
- 3) By heating a mixture of furan, ammonia and steam over alumina catalyst



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## Synthesis of Pyrrole

- 4) By passing a mixture of acetylene and ammonia over red hot tube.

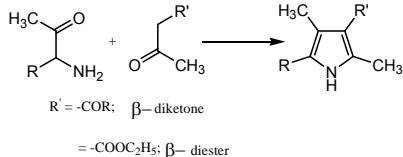


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## Synthesis of Pyrrole

### 5) Knorr-pyrrole synthesis:

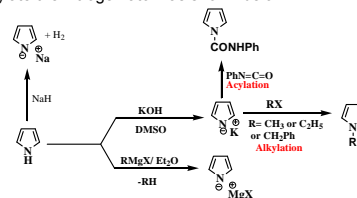
This involves the condensation of  $\alpha$ -amino ketones with a  $\beta$ -diketone or a  $\beta$ -ketoester to give a substituted pyrrole.



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## Acidic Properties of Pyrrole

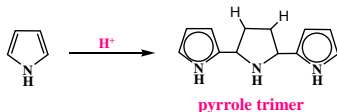
- Due to participation of N lone pair in aromaticity, pyrrole has exceptionally strong acidic properties for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodium amide in liquid ammonia, to give salt-like compounds which can be used to alkylate or acylate the nitrogen atom as shown below:



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## Sensitivity of Pyrrole to acids

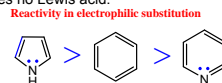
- Pyrrole is sensitive to strong acids.
- This is due to protonation occurs at one of C-3 and the resulting protonated molecule will add to another unprotonated pyrrole molecule this continues to give pyrrole trimer.
- This reaction is considered as electrophilic addition to pyrrole



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## Electrophilic Substitutions

- As expected for aromatic compound, pyrrole can react by electrophilic substitution.
- In comparison to benzene pyrrole is more reactive thus the substitution is easier and milder reagents can be used.
- The increased reactivity is a result of resonance which pushes the electrons from the N-atom into the ring making the C-atoms of pyrrole ring more electron rich than in case of benzene. In fact pyrrole resembles most reactive benzene derivatives (phenols and amines).
- Consequently, there are some modifications in usual electrophilic reagents, for instance, sulphonating and nitrating reagents have been modified to avoid the use of strong acids (induce polymerization). Also reaction with halogens requires no Lewis acid.

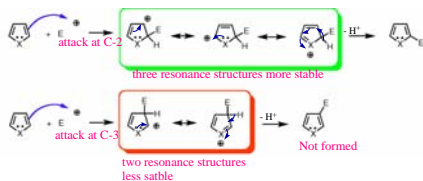


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## Electrophilic Substitution

### Orientation

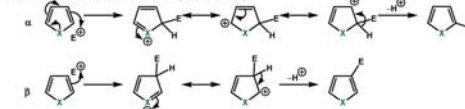
- Electrophilic substitution normally occurs at a carbon atoms instead of at the nitrogen as explained before.
- Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).
- This is due to attack at C-2 gives more stable intermediate (it is stabilized by three resonance structure) than the intermediate resulted from C-3 attack (it is stabilized by two resonance structure).



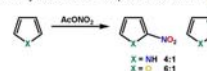
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## Electrophilic Substitutions

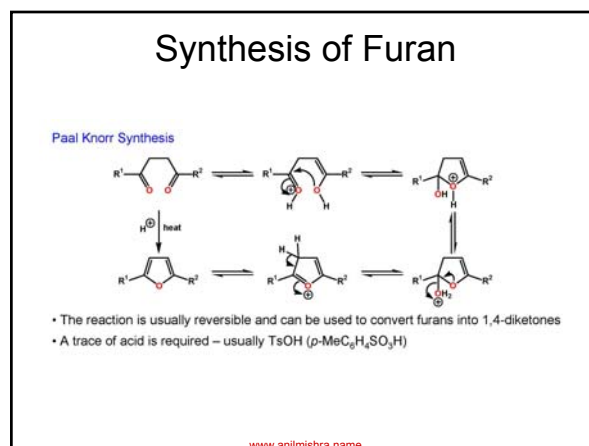
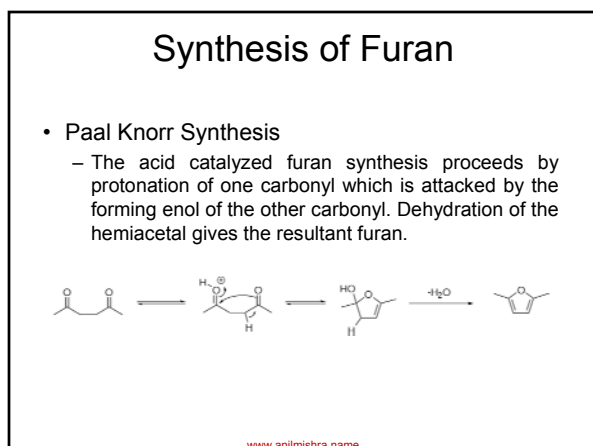
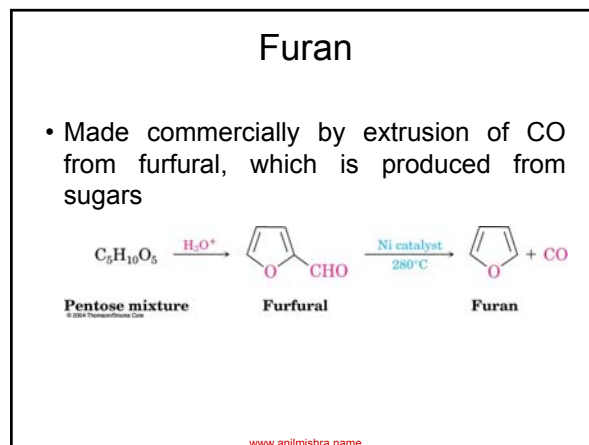
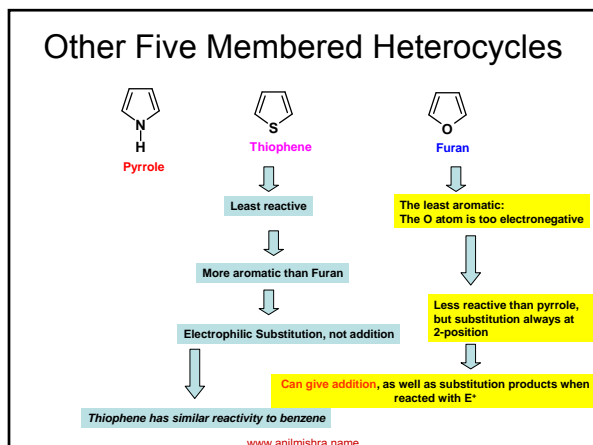
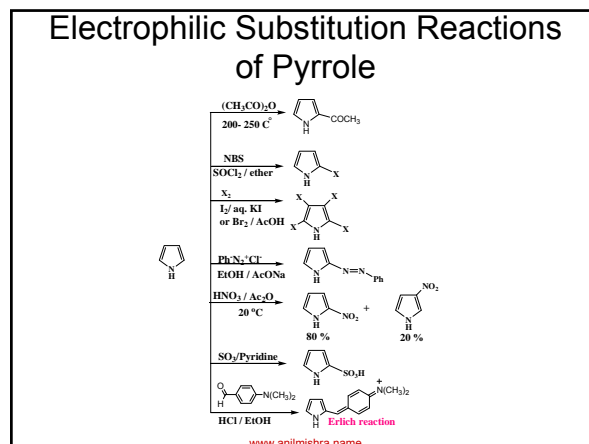
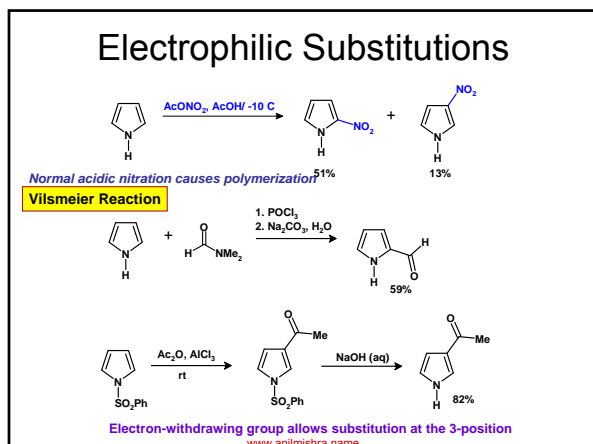
### Electrophilic Substitution – Regioselectivity



- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- $\alpha$ -Substitution favoured over  $\beta$ -substitution more resonance forms for intermediate and so the charge is less localised (also applies to the transition state)
- Some  $\beta$ -substitution usually observed – depends on X and substituents

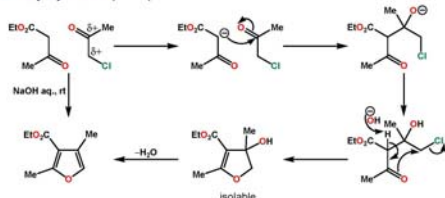


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## Synthesis of Furan

### Feist-Benary Synthesis ("3+2")

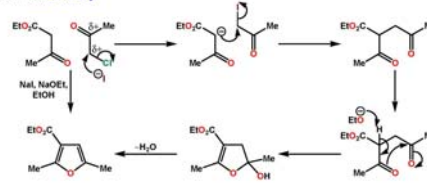


- The product prior to dehydration can be isolated under certain circumstances
- Reaction can be tuned by changing the reaction conditions

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## Synthesis of Furan

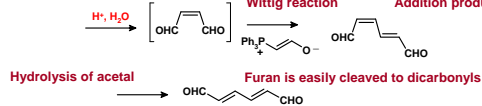
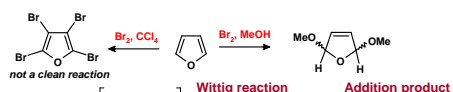
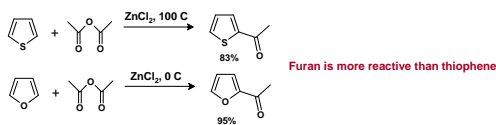
### Modified Feist-Benary



- Iodide is a better leaving group than Cl and the carbon becomes more electrophilic
- The **Paal Knorr** sequence is followed from the 1,4-diketone onwards
- The regiochemical outcome of the reaction is completely altered by addition of iodide

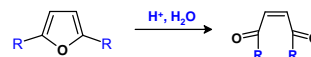
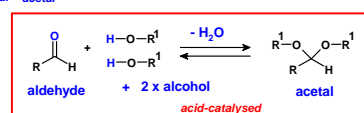
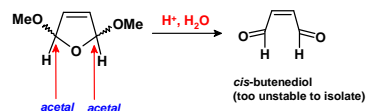
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## Reactions of Furan



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## Reactions of Furan

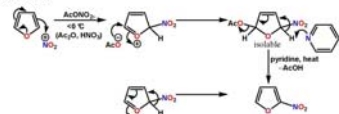


Furan is a source of 1,4-dicarbonyls in Organic Synthesis

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## Reactions of Furan

### Nitration of Furans



- Nitration can occur by an addition-elimination process
- When  $\text{NO}_2\text{BF}_4$  is used as a nitrating agent, the reaction follows usual mechanism

### Bromination of Furans

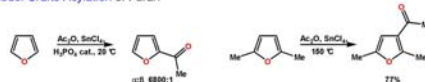


- Furan reacts vigorously with  $\text{Br}_2$  or  $\text{Cl}_2$  at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature

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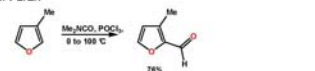
## Reactions of Furan

### Friedel-Crafts Acylation of Furan

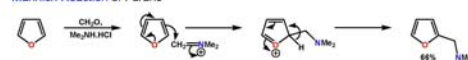


- Blocking groups at the  $\alpha$  positions and high temperatures required to give  $\beta$  acylation

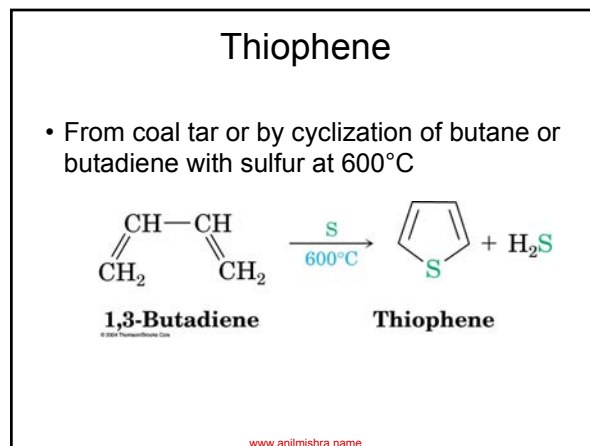
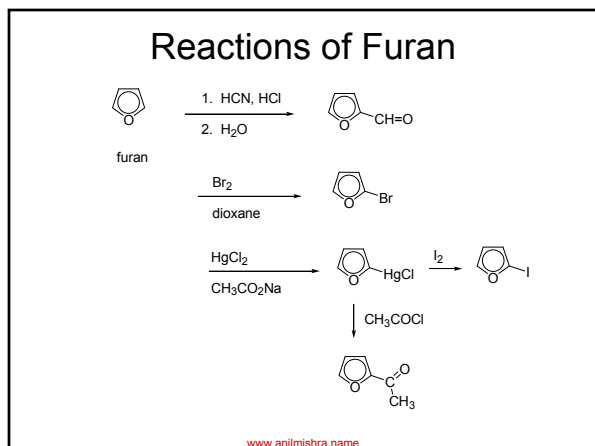
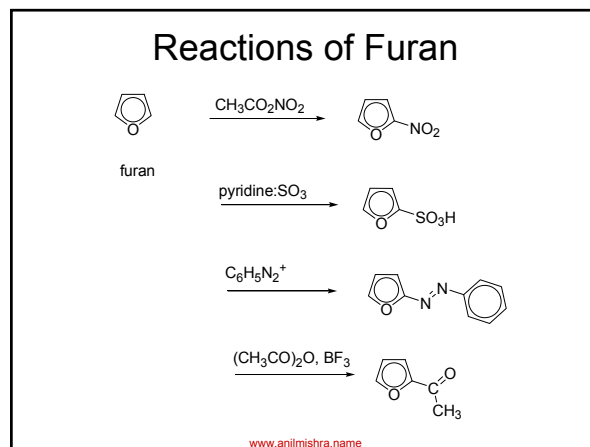
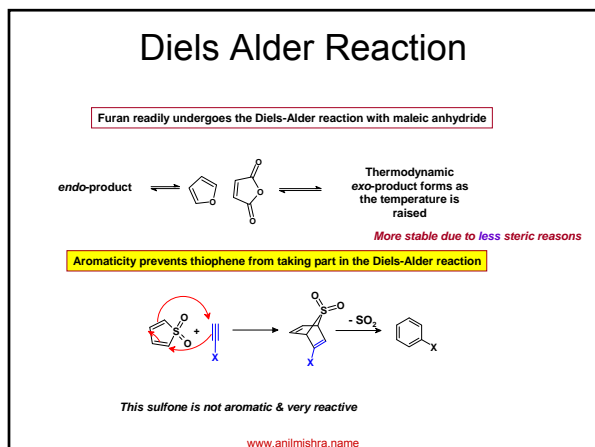
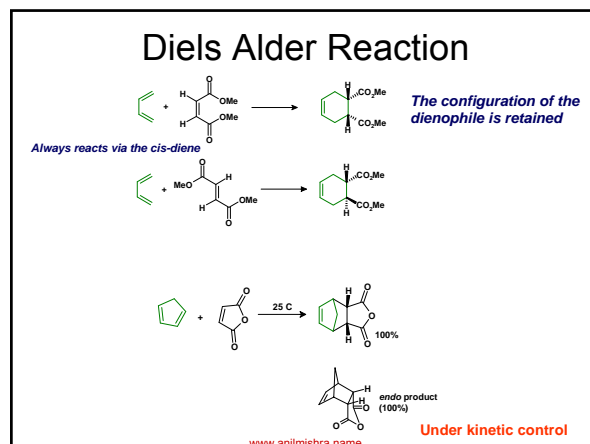
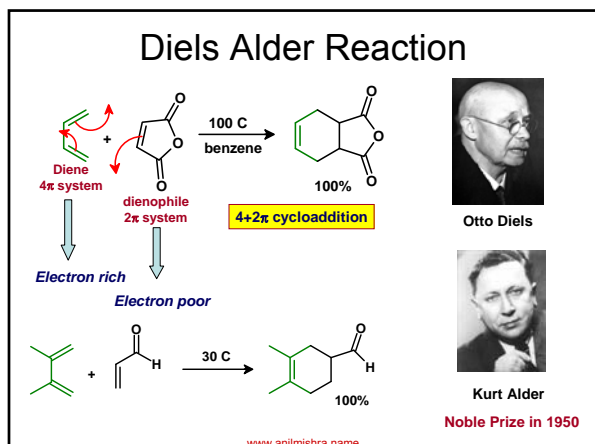
### Vilsmeier Formylation of Furans



### Mannich Reaction of Furans



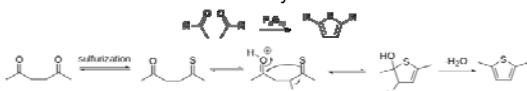
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## Synthesis of Thiophene

- Paal Knorr Synthesis

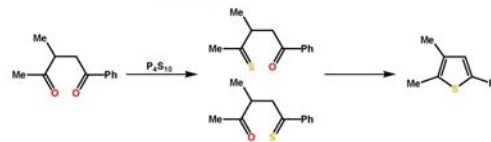
– Thiophene synthesis is achieved via a mechanism very similar to the furan synthesis. The initial diketone is converted to a thioketone with a sulfurizing agent, which then undergoes the same mechanism as the furan synthesis.



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## Synthesis of Thiophene

Synthesis of Thiophenes by Paal Knorr type reaction ("4+1")

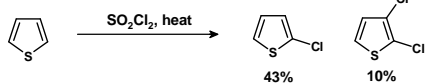
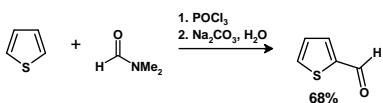
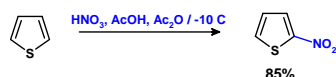


• Reaction might occur via the 1,4-bis-thioketone

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## Electrophilic Substitutions

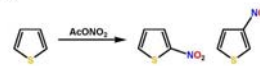
Avoid concentrated mineral acids or strong Lewis acids, e.g.  $AlCl_3$



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## Reactions of Thiophene

Nitration of Thiophenes



• Reagent  $AcONO_2$  generated *in situ* from  $c-HNO_3$  and  $Ac_2O$

Halogenation of Thiophenes

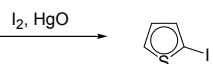
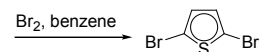
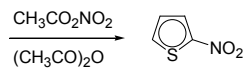
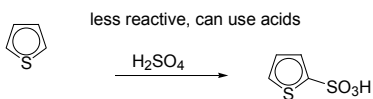


• Occurs readily at room temperature and even at  $-30\text{ }^\circ\text{C}$

• Careful control of reaction conditions is required to ensure mono-bromination

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## Reactions of Thiophene



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