III. Heterocyclic Compounds
21. Furan, Pyrrole and Thiophene : Methods For Synthesis

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Heterocyclic Compounds  
Classification and nomenclature, Structure, aromaticity in 5-numbered and 6-membered rings containing one heteroatom; Synthesis, reactions and mechanism of substitution reactions of: Furan, Pyrrole (Paal-Knorr synthesis, Knorr pyrrole synthesis, Hantzsch synthesis), Thiophene, Pyridine (Hantzsch synthesis), Pyrimidine, Structure elucidation of indole, Fischer indole synthesis and Madelung synthesis), Structure elucidation of quinoline and isoquinoline, Skraup synthesis, Friedlander’s synthesis, Knorr quinoline synthesis, Doebner-Miller synthesis, Bischler-Napieralski reaction, Pictet-Spengler reaction, Pomeranz-Fritsch reaction 
Derivatives of furan: Furfural and furoic acid.

Coverage: 
1. Furan, Pyrrole and Thiophene : Methods For Synthesis
Furans, Pyrroles and Thiophenes – Structure

Structure

- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures

- Electron donation into the ring by resonance but inductive electron withdrawal

- O and S are more electronegative than N and so inductive effects dominate
Furans – Synthesis

Paal Knorr Synthesis

- The reaction is usually reversible and can be used to convert furans into 1,4-diketones
- A trace of acid is required – usually TsOH (p-MeC₆H₄SO₃H)
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.
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
Thiophenes – Synthesis

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

- Reaction might occur via the 1,4-\textit{bis}-thioketone
Thiophenes – Synthesis

Paal Knorr Synthesis (“4+1”)

- Ammonia or a primary amine can be used to give the pyrrole or $N$-alkyl pyrrole
Pyrroles – Synthesis

Knorr Pyrrole Synthesis (“3+2”)

- Use of a free amino ketone is problematic – dimerisation gives a dihydropyrazine

- Problem can be overcome by storing amino carbonyl compound in a protected form
- Reactive methylene partner required so that pyrrole formation occurs more rapidly than dimer formation

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Pyrroles – Synthesis

Liberation of an Amino Ketone in situ by Oxime Reduction

\[
\text{EtO}_2\text{C} \quad \begin{array}{c} \text{Me} \\ \text{N} \\ \text{OH} \end{array} \quad \xrightarrow{\text{Zn, AcOH or Na}_2\text{S}_2\text{O}_4 \text{aq.}} \quad \text{EtO}_2\text{C} \quad \begin{array}{c} \text{Me} \\ \text{N} \\ \text{H} \end{array}
\]

Preparation of $\alpha$-Keto Oximes from $\beta$-Dicarbonyl Compounds

\[
\text{EtO} \quad \text{O} \quad \text{O} \quad \xrightarrow{\text{NaNO}_2, \text{H}^+} \quad \text{EtO} \quad \text{O} \quad \text{O}
\]

\[
\text{EtO} \quad \text{O} \quad \text{O} \quad \xrightarrow{\text{H}_2\text{O}, \text{N}=\text{O}} \quad \text{EtO} \quad \text{O} \quad \text{O}
\]

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Pyrroles – Synthesis

One-Pot Oxime Reduction and Pyrrole Formation

Hantzsch Synthesis of Pyrroles (“3+2”)

- A modified version of the Feist-Benary synthesis and using the same starting materials: an α-halo carbonyl compound and a β-keto ester