III. Heterocyclic Compounds
22. Furan, Pyrrole and Thiophene: Electrophilic Substitution Reaction

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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 : Electrophilic Substitution Reactions
2. Metallation Reaction / Deprotonation Reaction
Furans, Pyrroles and Thiophenes – Electrophilic Substitution

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

$\begin{align*}
X &= \text{NH} \quad \text{4:1} \\
X &= \text{O} \quad \text{6:1}
\end{align*}$
Furans – Electrophilic Substitution

Nitration of Furans

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

Bromination of Furans

- Furan reacts vigorously with Br$_2$ or Cl$_2$ at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature
Furans – Electrophilic Substitution

**Friedel-Crafts Acylation** of Furan

\[ \text{Furan} + \text{Ac}_2\text{O}, \text{SnCl}_4, \text{H}_3\text{PO}_4 \text{cat.} \rightarrow \alpha:\beta \ 6800:1 \ \text{Me} \]

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

**Vilsmeier Formylation** of Furan

\[ \text{Furan} + \text{Me}_2\text{NCO}, \text{POCl}_3, \text{0 to 100 }^{\circ}\text{C} \rightarrow \text{Me} \]

**Mannich Reaction** of Furans

\[ \text{Furan} + \text{CH}_2\text{O}, \text{Me}_2\text{NH.HCl} \rightarrow \text{CH}_2\text{=}\text{NMe}_2 \rightarrow \text{Furan} \]

\[ \alpha:\beta \ 66\% \text{ NMe}_2 \]
Thiophenes – Electrophilic Substitution

Nitration of Thiophenes

\[
\text{AcONO}_2 \rightarrow \text{AcONO}_2
\]

- Reagent AcONO\(_2\) generated \textit{in situ} from c-HNO\(_3\) and Ac\(_2\)O

Halogenation of Thiophenes

\[
\begin{align*}
\text{Br}_2, \text{Et}_2\text{O}, \\ 48\% \text{ HBr}, \\ -10 \rightarrow 10 \degree \text{C}
\end{align*}
\]

- Occurs readily at room temperature and even at \(-30 \degree \text{C}\)

\[
\begin{align*}
\text{Br}_2, \text{Et}_2\text{O}, \\ 48\% \text{ HBr}, \\ -25 \rightarrow -5 \degree \text{C}
\end{align*}
\]

- Careful control or reaction conditions is required to ensure mono-bromination

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Pyrroles – Electrophilic Substitution

Nitration of Pyrroles

\[
\text{Pyrrole} \xrightarrow{\text{AcONO}_2, \text{AcOH}, -10 \, ^\circ\text{C}} \begin{array}{c}
\text{Pyrrole} \\
\text{NO}_2 \\
\text{51%}
\end{array} \quad \begin{array}{c}
\text{Pyrrole} \\
\text{NO}_2 \\
\text{13%}
\end{array}
\]

• Mild conditions are required (c-HNO\(_3\) and c-H\(_2\)SO\(_4\) gives decomposition)

Vilsmeier Formylation of Pyrroles

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\xrightarrow{\text{POCl}_3} \quad \begin{align*}
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{OPCl}_2 \\
\text{H} & \quad \text{H}
\end{align*}
\xrightarrow{\text{K}_2\text{CO}_3 \text{aq.}} \quad \begin{align*}
\text{Me} & \quad \text{Me} \\
\text{NMe}_2 & \quad \text{H}
\end{align*}
\]

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Pyrroles – Porphyrin Formation

- The extended aromatic 18 $\pi$-electron system is more stable than that having four isolated aromatic pyrroles
Furans, Pyrroles Thiophenes – Deprotonation

**Metallation**

\[
\text{Bu}^- \xrightarrow{n-\text{BuLi}} \text{Bu}^- + \alpha \gg \beta
\]

\[
X = \text{O} \quad pK_a^a (\text{THF}) \quad X = 35.6
\]

\[
X = \text{NR} \quad pK_a^a (\text{THF}) \quad X = 39.5
\]

\[
X = \text{S} \quad pK_a^a (\text{THF}) \quad 33.0
\]

**Deprotonation of Pyrroles**

Free pyrroles can undergo \( N \) or \( C \) deprotonation.

- Large cations and polar solvents favour \( N \) substitution.
- A temporary blocking group on \( N \) can be used to obtain the \( C \)-substituted compound.
Control of Regioselectivity in Deprotonation

![Deprotonation Reaction Diagram]

Common directing groups: CO$_2$H(Li), CH$_2$OMe, CONR$_2$, CH(OR)$_2$

Synthesis of $\alpha,\alpha'$-Disubstituted Systems

![Synthesis Diagram]

Use of a Trialkylsilyl Blocking Group

![Blocking Group Diagram]
Furans – Synthesis of a Drug

Preparation of Ranitidine (Zantac®) Using a Mannich Reaction

- Furfural is produced very cheaply from waste vegetable matter and can be reduced to give the commercially available compound furfuryl alcohol.
- The second chain is introduced using a Mannich reaction which allows selective substitution at the 5-position.
- The final step involves conjugate addition of the amine to the $\alpha,\beta$-unsaturated nitro compound and then elimination of methane thiol.

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THANK YOU