FIVE MEMBERED AROMATIC HETEROCYCLES
Electrophilic aromatic substitution reaction of five membered aromatic heterocycles

The Substitution is regioselective to the $\alpha$ position; when these positions are occupied, the $\beta$-position is substituted.
WHY?
The +ve charge is better resonance stabilized when the substitution is at the \( \alpha \)-position than at \( \beta \)-position.

A more stable intermediate carbocation having 3 resonance forms.

only 2 resonance forms
Common reactions of pyrrole, furan, and thiophene

The following reaction are common to the three five membered aromatic heterocycles.

A. Electrophilic Aromatic Substitution

Electrophilic aromatic substitution reaction is easy and is preferred at α-position; also easy at β-position.
B. Substitution at α-position via α-lithiated Intermediates

\[
\begin{align*}
\text{Z} & \quad \text{H} \quad \text{n-BuLi} \quad \text{Li} \quad \text{E}^{+} \quad \text{E} \\
\downarrow & \quad \downarrow & \quad \downarrow & \quad \downarrow & \quad \downarrow
\end{align*}
\]

\( \text{Z} = \text{O, S, NR} \)

C. Vilsmeier-Haack reaction

Vilsmeier reaction (Vilsmeier-Haack reaction) allows the formylation (addition of -CHO) of heterocyclic molecules. The formylating agent, chloroiminium ion, is formed in situ from N,N-dimethylamide and POCl₃.
Vilsmeier-Haack reaction

1. $\text{H}_2\text{NCONH}$
2. $\text{POCl}_3$
3. $\text{H}_2\text{O}$

$Z = \text{O, S, NH}$

Example

1. $(\text{CH}_3)_2\text{NCHO}$
2. $\text{POCl}_3$
3. $\text{H}_2\text{O}$

Reduction

Oxidation
Mechanism

Chloroiminium ion

H₂O
The reaction of electron rich heterocycles with formaldehyde and primary/secondary amine forming an amino alkylated heterocyclic compound is called the Mannich reaction.

$Z = O, S, NH$
Mechanism
Furans are volatile, fairly stable compounds with pleasant odours. Furan itself is slightly soluble in water. It is readily available, and its commercial importance is mainly due to its role as the precursor of the very widely used solvent tetrahydrofuran (THF).
By analogy with benzene, furan undergoes reactions with electrophilic reagents, often with substitution. However, it can also react by addition and/or ring-opening depending on reagent and reaction conditions.
Electrophilic Aromatic Substitution Reaction

- **Furan**
  - Nitration
    - $\text{CH}_3\text{CO}_2\text{NO}_2$
    - Product: $\text{NO}_2$
  - Sulfonation
    - Pyridine, $\text{SO}_3$
    - Product: $\text{SO}_3\text{H}$
  - Friedel Crafts acylation
    - $(\text{CH}_3\text{CO})_2\text{O}, \text{BF}_3$
    - Product: $\text{C} = \text{O}$

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Furan can be halogenated at α-position. Bromination and iodination are easy to control as only one halogen atom adds to furan. In the case of chlorination, di-substitution has been known to occur.

\[
\text{Br}_2 \quad \text{dioxane} \quad \text{Cl}_2 \quad -40 \, ^\circ\text{C}
\]

\[
\begin{align*}
\text{Br} & \quad \text{+} \quad \text{Cl} & \quad \text{Cl} \\
\text{variable yields}
\end{align*}
\]
Acylation

Acetyl groups in the presence of phosphoric acid (or a Lewis acid) add at $\alpha$-position of furans.

In general, position 2 ($\alpha$-position) is more reactive than position 3. When position 2 is blocked, $\beta$-acylation can proceed smoothly.
Metalation

n-Butyllithium in hexane metalates furan in the 2-position, while excess of reagent at higher temperature produces 2,5-dilithiofuran.
Addition reactions

Furans yield the corresponding tetrahydrofurans by catalytic hydrogenation.

In some addition reactions, furans behave as 1,3-dienes. For example, furan reacts with bromine in methanol in the presence of potassium acetate to give 2,5-dimethoxy-2,5-dihydrofuran by a 1,4-addition:
Ring-opening reactions

Furans are protonated in the 2-position, and not on the O-atom, by BRÖNSTED acids:
Thiophene prefers reactions with electrophilic reagents. Additions and ring-opening reactions are less important than with furan, and substitution reactions are dominant.

Some additional reactions, such as oxidation and desulfurization, are due to the presence of sulfur and are thus confined to thiophenes.
Electrophilic substitutions

Thiophene reacts more slowly than furan but faster than benzene. Substitution is regioselective in the 2- or in the 2,5-position.
Reactions with nucleophilic reagents

\[
\begin{align*}
\text{H}_2\text{SCH}_3 & \quad \text{n-BuLi} \quad \rightarrow \quad \text{H}_2\text{SCH}_3 \text{Li} \\
& \quad \text{Br}_2/\text{H}_2\text{O}, \text{r.t.} \quad \rightarrow \quad \text{H}_2\text{SCH}_3 \text{MgBr} \\
& \quad \text{Mg}/\text{Et}_2\text{O} \quad \rightarrow \quad \text{H}_2\text{SCH}_3 \text{MgBr} \quad \text{1. CO}_2 \quad \rightarrow \quad \text{H}_2\text{SCH}_3 \text{CO}_2\text{H} \\
& \quad \text{H} = \text{CH}_2 \quad \rightarrow \quad \text{H}_2\text{SCH}_3 \text{OH} \\
\end{align*}
\]
Oxidation

Thiophenes are oxidized by peroxy acids to give thiophene 1,1-dioxides:

\[
\begin{align*}
\text{R-} & \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{Thiophene} & \quad \xrightarrow{\text{Oxidation}} \quad \text{Thiophene dioxides}
\end{align*}
\]
Pyrrole reacts with sodium, sodium hydride or potassium in inert solvents, and with sodium amide in liquid ammonia, to give salt-like compounds:

\[
\text{Pyrrole} + \text{NaH} \rightarrow \text{Pyrrole sodium} + \text{H}_2
\]

\[
\text{Pyrrole} + \text{CH}_3\text{MgI} \rightarrow \text{Pyrrole-MgI} + \text{CH}_4
\]

\[
\text{Pyrrole} + \text{n-BuLi} \rightarrow \text{Pyrrole-Li} + \text{n-BuH}
\]
Electrophilic substitution reactions on carbon

Nitration

\[
\text{AcONO}_2 \quad \text{Ac}_2\text{O} / -10^\circ\text{C}
\]

\[
\begin{align*}
\text{N} & \quad \text{H} \\
\text{H} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{H} \quad \text{NO}_2 \quad (51\%) \\
\text{H} & \quad \text{N} \quad \text{NO}_2 \\
\text{H} & \quad \text{N} \quad \text{NO}_2 \quad (13\%)
\end{align*}
\]
Halogenation

SOCl₂ (1 mole)
Et₂O/ 0 °C

SOCl₂
(4 moles)

Br₂, EtOH
0 °C

KI/ AcOH
aq EtOH/ H₂O₂