A Green Chemistry Module

Nucleophilic Aromatic Substitution

Presidential Green Chemistry Challenge Award
**S_NAr Mechanism - addition / elimination**

**ADDITION**

\[ \text{Nu} \quad \text{slow} \quad \rightarrow \quad \text{Meisenheimer Complex} \quad \text{Resonance Stabilized} \]

**ELIMINATION**

\[ \text{Nu} \quad \text{fast} \quad \rightarrow \quad \text{Product} + \text{LG}^{-} \]

**Common Activating Groups for NAS**

- CF₃, CN, CHO, COR, COOH, Br, Cl, I

**Resonance Stabilization of the Intermediate Anion**

[The Meisenheimer Complex]
Benzyne Mechanism - elimination / addition

**ELIMINATION**

**ADDITION**

Step-wise formation of Benzyne

[Diagram showing the benzyne mechanism with step-wise formation and elimination/addition pathways]
Evidence for the Benzyne Mechanism

Trapping in Diels/Alder Reaction

Substrate Modification – absence of $\alpha$ hydrogens

Isotopic Labeling
$S_{N1}$ Mechanism

RDS (rate determining step)

Aryl Cation

slow
$S_{NR1}$ Mechanism

Initiation

\[ \text{electron donor} \]

Chain Propagation Steps

1. \[ \text{I} \]

2. \[ \cdot \] + \[ \text{I}^- \]

3. \[ \text{NH}_2^- \]

4. \[ \text{I} \]

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Brown Chemistry Route to 4-ADPA

**Electrophilic Aromatic Substitution**

![Chemical reaction diagram for electrophilic aromatic substitution](image)

**Nucleophilic Aromatic Substitution**

![Chemical reaction diagram for nucleophilic aromatic substitution](image)

4-ADPA
Atom Economy of the Traditional Chemistry

<table>
<thead>
<tr>
<th>Reagent formula</th>
<th>Reagent FW</th>
<th>Utilized Atoms</th>
<th>Wt</th>
<th>Unutilized Atoms</th>
<th>Wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 C₆H₆</td>
<td>78</td>
<td>6C, 4H</td>
<td>53</td>
<td>2 H</td>
<td>2</td>
</tr>
<tr>
<td>2 Cl₂</td>
<td>70</td>
<td>-------------------</td>
<td>0</td>
<td>2 Cl</td>
<td>70</td>
</tr>
<tr>
<td>3 HNO₃</td>
<td>63</td>
<td>1 N</td>
<td>14</td>
<td>1 H, 3 O</td>
<td>49</td>
</tr>
<tr>
<td>4 C₃H₇NO</td>
<td>121</td>
<td>6 C, 6 H, 1 N</td>
<td>92</td>
<td>1 C, 1 O, 1 H</td>
<td>29</td>
</tr>
<tr>
<td>5 K₂CO₃</td>
<td>98</td>
<td>-------------------</td>
<td>0</td>
<td>2 K, 1 C, 3 O</td>
<td>98</td>
</tr>
<tr>
<td>6 H₂</td>
<td>2</td>
<td>2 H</td>
<td>2</td>
<td>----------------</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>432</td>
<td>12C, 12H, 2N</td>
<td>161</td>
<td>2C, 4H, 2C, 2K, 7O</td>
<td>248</td>
</tr>
</tbody>
</table>
Brown Chemistry
Nucleophilic Aromatic Substitution for Chlorine

- Large amount of chlorine storage and handling
- Waste stream components: inorganic salts and organics
- Large amounts of water consumed
- Heavy metal catalyst
Nucleophilic Aromatic Substitution for Hydrogen

General Mechanism
Flexsys Route to 4-ADPA

Base-Promoted Coupling Reaction

Base-Promoted Coupling Reaction

\[
\text{[Nitrobenzene] + [Aniline]} \xrightarrow{\text{Base}} \text{[4-ADPA]}
\]
**Flexsys - Anaerobic Oxidation to 4-NDPA**

```
intramolecular  simultaneous reactions  intermolecular
```

4-NODPA

4-ADPA

4-NDPA

H₂ over Catalyst
**Flexsys - Intermolecular Oxidation Pathway**

Diagram: A reaction pathway involving the intermolecular oxidation of a molecule, leading to the formation of 4-NDPA and Azobenzene. The reaction involves the oxidation of a nitro group (NO₂) to a nitroso group (NO) and the addition of an amino group (NH₂) to another molecule.
Atom Economy of the Flexsys Chemistry

Reagent Formula | Reagent FW | Utilized Atoms | Wt | Unutilized Atoms | Wt
--- | --- | --- | --- | --- | ---
1 C₆H₆ | 78 | 6 C, 4 H | 76 | 2 H | 2
2 HNO₃ | 63 | 1 N | 14 | 1 H, 3 O | 49
3 C₆H₇N | 93 | 6 C, 6 H, N | 92 | 1 H | 1
4 H₂ | 2 | 2 H | 2 | -------- | 0
TOTAL | 236 | 12C, 12 h, 2 n | 184 | 4H, 3O | 52
Green Chemistry Advantages for Nucleophilic Aromatic Substitution for Hydrogen

- **Reduction in chemical waste generation**
  - elimination of
  - 74% of organic waste
  - 99% of inorganic waste

- **Eliminates use of chlorine**

- **Reduction in waste water**
  - more than 97% savings

- **Eliminates use of xylene**
  - a SARA chemical

- **Improves process safety**
  - lower reaction temperatures