A GENERAL SUBSTITUTION REACTION

A GENERAL ELIMINATION REACTION

<table>
<thead>
<tr>
<th>NUCLEOPHILES</th>
<th>ELECTROPHILES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Alkyl Halides, RX</td>
</tr>
<tr>
<td></td>
<td>(Not aryl or vinyl)</td>
</tr>
<tr>
<td>Okay</td>
<td>Activated Alcohols, ROH₂, ROSCl, ROPBr₂, ROTos</td>
</tr>
<tr>
<td>Poor</td>
<td><em>Add these to your N&amp;E list</em></td>
</tr>
</tbody>
</table>

LEAVING GROUP CONSIDERATIONS
(Same idea as considering the stability of a conjugate base)

<table>
<thead>
<tr>
<th>Good leaving groups:</th>
<th>Bad Leaving Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigger is better!</td>
<td>Neutral or resonance-stabilized leaving groups are good.</td>
</tr>
</tbody>
</table>

SOLVENTS

<table>
<thead>
<tr>
<th>Polar, aprotic</th>
<th>Polar, protic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SUBSTITUTION REACTIONS: $S_N1$ vs. $S_N2$

All of the following substitution reactions proceed as shown (there may be some elimination products as well, but we'll worry about that later). At first glance, the products of substitution reactions are the same whether they go by $S_N1$ or $S_N2$ mechanism but there are a couple factors that stand out. Use the following steps to determine whether the reaction occurred by $S_N1$ or $S_N2$ mechanism.

1. **Substitution of the alkyl halide**:  
   - Methyl or primary alkyl halides proceed by $S_N2$.  
   - Tertiary alkyl halides proceed by $S_N1$.  
   - Secondary alkyl halides can go either way, depending on the solvent – go to step 2.

2. **Solvent (skip unless secondary alkyl halide)**:  
   - Aprotic solvents will favor $S_N2$.  
   - Protic solvents will favor $S_N1$.

3. **Stereochemistry**:  
   - A single chiral product must have come from an $S_N2$ reaction.  
   - A racemic mixture must have come from an $S_N1$ reaction.

---

(1) $\text{I} \xrightarrow{\text{NaOCH}_3, \text{DMSO}} \text{OCH}_3$

(2) $\text{I} \xrightarrow{\text{CH}_3\text{OH}} \text{OCH}_3$

(3) $\text{I} \xrightarrow{\text{NaOCH}_3, \text{Acetone}} \text{OCH}_3$

(4) $\text{Br} \xrightarrow{\text{OCONa, DMSO}} \text{O} \xrightarrow{\text{CO}}$

(5) $\text{I} \xrightarrow{\text{CH}_3\text{CO}_2\text{H}} \text{O} \xrightarrow{\text{O}}$

(6) $\text{Br} \xrightarrow{\text{Me}_2\text{NH, Acetone}} \text{NMe}_2$

(7) $\text{Cl} \xrightarrow{\text{H}_2\text{O}} \text{OH}
ELIMINATION REACTIONS: E1 vs. E2

The products of an elimination reaction, whether by E1 or E2, almost always look identical. The difference is that the E1 mechanism occurs with weak bases and the E2 mechanism occurs in the presence of strong bases. Also, there are stereochemical concerns in the E2 mechanism.

Use the examples of weak and strong bases to determine the products of each reaction.

Strong bases (E2) – Alkoxides, Hydroxide

Weak bases (E1) – Water, Alcohols, Carboxylates

1. \[
\begin{align*}
\text{Cl} & \quad \text{KOT-Bu} \\
\text{t-BuOH} & \\
\end{align*}
\]

2. \[
\begin{align*}
\text{Cl} & \quad \text{NaOCH}_3 \\
\text{CH}_3\text{OH} & \\
\end{align*}
\]

3. \[
\begin{align*}
\text{Cl} & \quad \text{KOT-Bu} \\
\text{t-BuOH} & \\
\end{align*}
\]

4. \[
\begin{align*}
\text{Cl} & \quad \text{CH}_3\text{CO}_2\text{Na} \\
\text{CH}_3\text{CO}_2\text{H} & \\
\end{align*}
\]
SUBSTITUTION AND ELIMINATION REACTIONS:

$S_N^1$ vs. $S_N^2$ vs. E1 vs. E2 vs. NR

Below are reactions of alkyl halides with nucleophiles and/or bases. Some reactions will give only one product; others will give a mixture. Recall the specific conditions required for only one reaction mechanism to be favored (except for E1).

<table>
<thead>
<tr>
<th>$S_N^1$ – tertiary alkyl halide</th>
<th>$E_1$ – (always a mixture with Substitution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_N^2$ – methyl alkyl halide</td>
<td>$E_2$ – potassium tert-butoxide, KOt-Bu, KOC(CH$_3$)$_3$</td>
</tr>
</tbody>
</table>

If any one of those conditions is not met (for example, a secondary alkyl halide), determine whether the reagent is a nucleophile (substitution), base (elimination), or both.

Look out for non-leaving groups!

1. \[
\begin{align*}
\text{CH}_3\text{I} \quad \text{NaCl} & \quad \text{Acetone (S}_N^2) \\
\end{align*}
\]

2. \[
\begin{align*}
\text{CH}_3\text{F} \quad \text{KOt-Bu} & \quad \text{t-BuOH} \\
\end{align*}
\]

3. \[
\begin{align*}
\text{PhCH}_2\text{Br} \quad \text{CH}_3\text{OH} & \\
\end{align*}
\]

4. \[
\begin{align*}
\text{PhCH}_2\text{Br} \quad \text{NaOCH}_3 & \quad \text{CH}_3\text{OH} \\
\end{align*}
\]

5. \[
\begin{align*}
\text{cyclohexylI} \quad \text{KOt-Bu} & \quad \text{t-BuOH} \\
\end{align*}
\]

6. \[
\begin{align*}
\text{cyclopentylI} \quad \text{HBr} & \\
\end{align*}
\]

7. \[
\begin{align*}
\text{CH}_3\text{I} \quad \text{NaCl} & \quad \text{Acetone} \\
\end{align*}
\]