Chapter 11
Reactions of Alcohols

Summary Table

<table>
<thead>
<tr>
<th>R—OH</th>
<th>type of reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—OH</td>
<td>Dehydration</td>
<td>alkenes</td>
</tr>
<tr>
<td>R—OH</td>
<td>Oxidation</td>
<td>aldehydes, ketones</td>
</tr>
<tr>
<td>R—OH</td>
<td>Substitution</td>
<td>alkyl halides</td>
</tr>
<tr>
<td>R—OH</td>
<td>Reduction</td>
<td>R—H</td>
</tr>
</tbody>
</table>

Oxidation

- Easy for inorganic salts
  - \( \text{CrO}_4^{2-} \) reduced to \( \text{Cr}_2\text{O}_3 \)
  - \( \text{KMnO}_4 \) reduced to \( \text{MnO}_2 \)
- Oxidation: loss of \( \text{H}_2 \), gain of \( \text{O}, \text{O}_2, \text{or X}_2 \)
- Reduction: gain of \( \text{H}_2 \) or \( \text{H}^- \), loss of \( \text{O}, \text{O}_2, \text{or X}_2 \)
- Neither: gain or loss of \( \text{H}^+, \text{H}_2\text{O}, \text{HX} \)

Oxidation of 2° Alcohols

- 2° alcohol becomes a ketone
- Reagent is \( \text{Na}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4 \)
- Active reagent probably \( \text{H}_2\text{CrO}_4 \)
- Color change: orange to greenish-blue

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{CH}_3 & \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7 / \text{H}_2\text{SO}_4} \text{CH}_3\text{CCH}_2\text{CH}_3
\end{align*}
\]
Oxidation of 1° Alcohols

- 1° alcohol to aldehyde to carboxylic acid
- Difficult to stop at aldehyde
- Use pyridinium chlorochromate (PCC) to limit the oxidation.
- PCC can also be used to oxidize 2° alcohols to ketones.

3° Alcohols Don’t Oxidize

- Cannot lose 2 H’s
- Basis for chromic acid test

<table>
<thead>
<tr>
<th>Oxidize</th>
<th>Product</th>
<th>Reagent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2° alcohol</td>
<td>ketone</td>
<td>chromic acid (or PCC)</td>
</tr>
<tr>
<td>1° alcohol</td>
<td>aldehyde</td>
<td>PCC</td>
</tr>
<tr>
<td>1° alcohol</td>
<td>acid</td>
<td>chromic acid</td>
</tr>
</tbody>
</table>

Other Oxidation Reagents

- Collins reagent: Cr₂O₃ in pyridine
- Jones reagent: chromic acid in acetone
- KMnO₄ (strong oxidizer)
- Nitric acid (strong oxidizer)
- CuO, 300°C (industrial dehydrogenation)
- Swern oxidation: dimethylsulfoxide, with oxalyl chloride and hindered base, oxidizes 2° alcohols to ketones and 1° alcohols to aldehydes.

Biological Oxidation

- Catalyzed by ADH, alcohol dehydrogenase.
- Oxidizing agent is NAD⁺, nicotinamide adenine dinucleotide.
- Ethanol oxidizes to acetaldehyde, then acetic acid, a normal metabolite.
- Methanol oxidizes to formaldehyde, then formic acid, more toxic than methanol.
- Ethylene glycol oxidizes to oxalic acid, toxic.
- Treatment for poisoning is excess ethanol.

Alcohol as a Nucleophile

- ROH is weak nucleophile
- RO⁻ is strong nucleophile
- New O-C bond forms, O-H bond breaks.

Alcohol as an Electrophile

- OH⁻ is not a good leaving group unless it is protonated, but most nucleophiles are strong bases which would remove H⁺.
- Convert to tosylate (good leaving group) to react with strong nucleophile (base)
Formation of Tosylate Ester

\[ \text{p-toluenesulfonyl chloride (TsCl, “tosyl chloride“)} \rightarrow \text{ROTs, a tosylate ester} \]

SN2 Reactions of Tosylates
- With hydroxide produces alcohol
- With cyanide produces nitrile
- With halide ion produces alkyl halide
- With alkoxide ion produces ether
- With ammonia produces amine salt
- With LiAlH4 produces alkane

Summary of Tosylate Reactions

Reduction of Alcohols
- Dehydrate with conc. H2SO4, then add H2
- Tosylate, then reduce with LiAlH4

Reaction with HBr
- -OH of alcohol is protonated
- -OH2+ is good leaving group
- 3° and 2° alcohols react with Br+ via S_N1
- 1° alcohols react via S_N2

Reaction with HCl
- Chloride is a weaker nucleophile than bromide.
- Add ZnCl2, which bonds strongly with -OH, to promote the reaction.
- The chloride product is insoluble.
- Lucas test: ZnCl2 in conc. HCl
  - 1° alcohols react slowly or not at all.
  - 2° alcohols react in 1-5 minutes.
  - 3° alcohols react in less than 1 minute.
Limitations of HX Reactions

- HI does not react
- Poor yields of 1° and 2° chlorides
- May get alkene instead of alkyl halide
- Carbocation intermediate may rearrange.

Reactions with Phosphorus Halides

- Good yields with 1° and 2° alcohols
- PCl₃ for alkyl chloride (but SOCl₂ better)
- PBr₃ for alkyl bromide
- P and I₂ for alkyl iodide (PI₃ not stable)

Mechanism with PBr₃

1. Step 1: Displacement of bromide ion, forming an excellent leaving group.
2. Step 2: S_N2 attack on the alkyl group.
   - P bonds to -OH as Br⁻ leaves
   - Br⁻ attacks backside (S_N2)
   - HOPBr₂ leaves

Reaction with Thionyl Chloride

- Produces alkyl chloride, SO₂, HCl
- S bonds to -OH, Cl⁻ leaves
- Cl⁻ abstracts H⁺ from OH
- C-O bond breaks as Cl⁻ transferred to C

Dehydration Reactions

- Conc. H₂SO₄ produces alkene
- Carbocation intermediate
- Saytzeff product
- Bimolecular dehydration produces ether
- Low temp, 140°C and below, favors ether
- High temp, 180°C and above, favors alkene

Dehydration Mechanisms

- OH → H₂O → alkene
- H₂SO₄ → SO₂ → HCl → alkene
- CH₃OH → H₂O → CH₃OCH₃
Unique Reactions of Diols

- Pinacol rearrangement
- Periodic acid cleavage

Pinacol Rearrangement
- Pinacol: 2,3-dimethyl-2,3-butanediol
- Dehydration with sulfuric acid

Periodic Cleavage of Glycols
Same products formed as from ozonolysis of the corresponding alkene.

Esterification
- Fischer: alcohol + carboxylic acid
- Tosylate esters
- Sulfate esters
- Nitrate esters
- Phosphate esters

Fischer Esterification
- Acid + Alcohol yields Ester + Water
- Sulfuric acid is a catalyst.
- Each step is reversible.
Tosylate Esters

- Alcohol + p-Toluenesulfonic acid, TsOH
- Acid chloride is actually used, TsCl

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{HO S} \overset{\text{O}}{\text{O}} \text{O} \overset{\text{O}}{\text{O}} \text{CH}_3 \overset{\text{H}^+}{\longrightarrow} \text{CH}_3\text{CH}_2\text{O}_2\text{SCH}_3 \]

Sulfate Esters

Alcohol + Sulfuric Acid

\[
\text{CHOH} + \text{H}_2\text{SO}_4 \overset{\text{H}^+}{\longrightarrow} \text{CH}_3\text{CH}_2\text{O}_2\text{SH} \]

Nitrate Esters

\[
\text{CH}_3\text{O}_2\text{H} + \text{H}_2\text{O} \overset{\text{H}^+}{\longrightarrow} \text{CH}_3\text{O}_2\text{NO}_2 \]

Phosphate Esters

\[
\text{CH}_3\text{O}_2\text{H} + \text{H}_2\text{O} \overset{\text{H}^+}{\longrightarrow} \text{CH}_3\text{O}_2\text{PO}_2\text{H} \]

Phosphate Esters in DNA

Alkoxide Ions

- ROH + Na (or NaH) yields sodium alkoxide
- RO⁻ + 1° alkyl halide yields ether (Williamson ether synthesis)

\[
\text{CH}_3\text{CH}_2\text{CH}_3 + \text{CH}_2\text{CH}_2\text{Br} \overset{\text{CH}_3\text{CH}_2\text{H}_2\text{O}}{\longrightarrow} \text{CH}_3\text{CH}_2\text{Br} \]

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