Chapter 19
Ketones and Aldehydes

17.1-17.4, 17.6-17.18, 17.20-23 (in chapter, help to understand materials); 17.24-69

18.1-18.90.

Oxidation of Secondary Alcohols to Ketones

- Secondary alcohols are readily oxidized to ketones with sodium dichromate ($\text{Na}_2\text{Cr}_2\text{O}_7$) in sulfuric acid or by potassium permanganate ($\text{KMnO}_4$).
Ozonolysis of Alkenes

The double bond is oxidatively cleaved by ozone followed by reduction.

- Ketones and aldehydes can be isolated as products.
Friedel–Crafts Reaction

\[
\text{R–C–Cl} + \text{G} \xrightarrow{(1) \text{AlCl}_3 \text{(2) H}_2\text{O}} \text{G–C–R} + \text{G–C–R}
\]

R is alkyl or aryl; G is hydrogen, an activating group, or a halogen.

- Reaction between an acyl halide and an aromatic ring will produce a ketone.
Hydration of Alkynes

The initial product of Markovnikov hydration is an enol, which quickly tautomerizes to its keto form.

Internal alkynes can be hydrated, but mixtures of ketones often result.
Oxidation of Primary Alcohols to Aldehydes

Pyridinium chlorochromate (PCC) is selectively used to oxidize primary alcohols to aldehydes.

Copyright © 2010 Pearson Prentice Hall, Inc.
Hydroboration–Oxidation of Alkynes

- Hydroboration–oxidation of an alkyne gives anti-Markovnikov addition of water across the triple bond.
Summary: Ketone preparation

1) Oxidation of Secondary Alcohols

\[ \text{ROH} \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{RCR} \]

2) Ozonolysis of Alkenes

\[ \text{R=C=CR} \xrightarrow{1) \text{O}_3, 2) \text{DMS}} \text{RCR} + \text{O=CR} \]

3) Acid-catalyzed Hydration of Terminal Alkynes

\[ \text{R=CR} \xrightarrow{\text{HgSO}_4, \text{H}_2\text{O}} \text{RCR} \text{ (Markovnikov)} \]

4) Friedel-Crafts Acylation

\[ \text{Cl-CR} \xrightarrow{\text{AlCl}_3} \text{RCR} \]

Chapter 19
Summary: Aldehyde preparation

1) Oxidation of Primary Alcohols

R<sub>OH</sub> \[\xrightarrow{\text{PCC, CH}_2\text{Cl}_2 \text{ or DMP, CH}_2\text{Cl}_2 \text{ or 1) DMSO, (COCl)}_2 \text{ 2) Et}_3\text{N}}\] R<sub>CH</sub>

2) Ozonolysis of Alkenes

R<sub>H</sub>H \[\xrightarrow{1) O_3 \ 2) \text{DMS}}\] R<sub>CH</sub>+ R<sub>CH</sub>

3) Hydroboration-Oxidation of Terminal Alkynes

R≡\[\xrightarrow{1) \text{BH}_3, \text{THF} \ 2) \text{H}_2\text{O}_2, \text{NaOH}}\] R<sub>H</sub>H

Anti-Markovnikov
Nucleophilic Addition

- A strong nucleophile attacks the carbonyl carbon, forming an alkoxide ion that is then protonated.
- Aldehydes are more reactive than ketones.
Nucleophilic Addition: Mechanism

Basic condition:

No formation of strong acid

Acidic condition:

No formation of strong base
Nucleophile covered in Chapter 19

Oxygen

\[ \text{H}_2\text{O} \]

\[ \text{R}\cdot\text{O}\cdot\text{H} \]

\[ \text{H-O-O-H} \]

Sulfur

\[ \text{H-S-S-H} \]

\[ \text{R-S-S-H} \]

\[ \text{H-S-S-H} \]

Nitrogen

\[ \text{H} \]

\[ \text{N} \]

\[ \text{R-N} \]

\[ \text{R-N} \]

Hydrogen

\[ \text{\textcircled{2}AlH}_4 \]

\[ \text{\textcircled{2}BH}_4 \]

Carbon

\[ \text{\textcircled{2}C=\text{N}} \]

\[ \text{Ph}^+\text{P=\text{C}}\text{\textcircled{2}}\]

\[ \text{Ph}^+\text{P=\text{C}}\text{\textcircled{2}}\]

\[ \text{Ph}^+\text{P=\text{C}}\text{\textcircled{2}}\]

\[ \text{Ph}^+\text{P=\text{C}}\text{\textcircled{2}}\]
Hydration of Ketones and Aldehydes

In an aqueous solution, a ketone or an aldehyde is in equilibrium with its hydrate, a geminal diol.

With ketones, the equilibrium favors the unhydrated keto form (carbonyl).
Mechanism of Hydration of Ketones and Aldehydes

- Hydration occurs through the nucleophilic addition mechanism, with water (in acid) or hydroxide (in base) serving as the nucleophile.
Formation of Acetals

\[
\text{aldehyde} + 2 \text{R’} \text{-OH} \xrightleftharpoons{H^+} \text{R’O-CH-OR’} + \text{H}_2\text{O}
\]

\[
\text{ketone} + 2 \text{R”} \text{-OH} \xrightleftharpoons{H^+} \text{R”O-CH-OR”} + \text{H}_2\text{O}
\]

Copyright © 2010 Pearson Prentice Hall, Inc.
Mechanism for Hemiaceetal Formation

- Must be acid-catalyzed.
- Adding $\text{H}^+$ to carbonyl makes it more reactive with weak nucleophile, ROH.
In most cases, hemiacetal is not stable.

But hemiacetal is stable, when 5 or 6-member ring formed.
Acetal Formation

\[
\text{CH}_3\overset{\text{O}}{\text{O}}\overset{\text{O}}{\text{O}}\overset{\text{H}}{\text{H}} \quad \xrightleftharpoons{\text{H}^+} \quad \text{protonation, loss of water} \quad \xrightleftharpoons{} \quad \text{resonance-stabilized carbocation} \quad + \text{H}_2\text{O}
\]

hemiacetal

Copyright © 2010 Pearson Prentice Hall, Inc.

\[
\text{CH}_3\overset{\text{O}}{\text{O}}\overset{\text{O}}{\text{O}}\overset{\text{O}}{\text{O}}\overset{\text{H}}{\text{H}} \quad \xrightleftharpoons{} \quad \text{attack by methanol} \quad \xrightleftharpoons{} \quad \text{acetal} \quad + \text{CH}_3\overset{\text{O}}{\text{O}}\overset{\text{O}}{\text{O}}\overset{\text{O}}{\text{O}}\overset{\text{H}}{\text{H}}
\]

Copyright © 2010 Pearson Prentice Hall, Inc.
Cyclic Acetals

Addition of a diol produces a cyclic acetal.

The reaction is reversible.

This reaction is used in synthesis to protect carbonyls from reaction.
Acetals as Protecting Groups

- Hydrolyze easily in acid; stable in base.
- Aldehydes are more reactive than ketones.
The acetal will not react with NaBH$_4$, so only the ketone will get reduced.

- Hydrolysis conditions will protonate the alcohol and remove the acetal to restore the aldehyde.
Formation of Imines

- Ammonia or a primary amine reacts with a ketone or an aldehyde to form an imine.
- Imines are nitrogen analogues of ketones and aldehydes with a C≡N bond in place of the carbonyl group.
Mechanism of Imine Formation

Acid-catalyzed addition of the amine to the carbonyl compound group.

Acid-catalyzed dehydration.

Copyright © 2010 Pearson Prentice Hall, Inc.
Other Condensations with Amines

\[ \text{C} = \text{O} + \text{H}_2\text{N} - Z \xrightarrow{\text{H}^+} \text{C} = \text{N} - Z + \text{H}_2\text{O} \]

<table>
<thead>
<tr>
<th>$Z$ in $Z-NH_2$</th>
<th>Reagent</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\text{H}$</td>
<td>$\text{H}_2\text{N} - \text{H}$ ammonia</td>
<td>$\text{C} = \text{N} - \text{H}$ an imine</td>
</tr>
<tr>
<td>$-\text{R}$</td>
<td>$\text{H}_2\text{N} - \text{R}$ primary amine</td>
<td>$\text{C} = \text{N} - \text{R}$ an imine (Schiff base)</td>
</tr>
<tr>
<td>$-\text{OH}$</td>
<td>$\text{H}_2\text{N} - \text{OH}$ hydroxylamine</td>
<td>$\text{C} = \text{N} - \text{OH}$ an oxime</td>
</tr>
<tr>
<td>$-\text{NH}_2$</td>
<td>$\text{H}_2\text{N} - \text{NH}_2$ hydrazine</td>
<td>$\text{C} = \text{N} - \text{NH}_2$ a hydrazone</td>
</tr>
<tr>
<td>$-\text{NHPH}$</td>
<td>$\text{H}_2\text{N} - \text{NPH}$ phenylhydrazine</td>
<td>$\text{C} = \text{N} - \text{NPH}$ a phenylhydrazone</td>
</tr>
<tr>
<td>$-\text{O}$</td>
<td>$\text{H}_2\text{N} - \text{NH} - \text{C} - \text{NH}_2$ semicarbazide</td>
<td>$\text{C} = \text{N} - \text{NH} - \text{C} - \text{NH}_2$ a semicarbazone</td>
</tr>
</tbody>
</table>

Copyright © 2010 Pearson Prentice Hall, Inc.
Formation of Enamines

\[
\text{Ketone} \xrightarrow{[H^+]} \text{Amine}
\]

Secondary amine

Primary amine

\[
R\text{NH}_2 \rightarrow R\text{NH}_2\text{OH} \rightarrow R\text{NH} + \text{OH}_2 \rightarrow R\text{N} + \text{NRH} \rightarrow R\text{N}
\]

Secondary amine

Chapter 19
Wolff–Kishner Reduction

- Forms hydrazone, then heat with strong base like KOH or potassium tert-butoxide.
- Use a high-boiling solvent: ethylene glycol, diethylene glycol, or DMSO.
- A molecule of nitrogen is lost in the last steps of the reaction.
Wolff–Kishner Reduction Mechanism

\[
\text{OHH}_2 + \text{NH}_2\text{NH}_2 \xrightarrow{\text{Hydrozine}} \text{H}_2\text{N}-\text{N} = \text{N} \xrightarrow{\text{KOH/H}_2\text{O}} \text{Heat} \rightarrow \text{N}_2 + \text{N}_2
\]
Hydrolysis of Acetals, Imines and Enamines

- The same intermediates with the formation of acetals, imines and enamines, but in reverse order.
- Occurred under acidic condition not basic.
Sulfur Nucleophiles

\[
\text{O} + 2 \text{RSH} \xrightleftharpoons{[\text{H}^+]} \xrightarrow{\text{[H}^+\text{]}} \text{RS}_{\text{SR}} + \text{H}_2\text{O}
\]

Thioacetal

\[
\text{O} + \text{H-S-S-H} \xrightleftharpoons{[\text{H}^+]} \xrightarrow{\text{[H}^+\text{]}} \text{S}_{\text{SS}} + \text{H}_2\text{O}
\]

Cyclic thioacetal

\[
\text{S}_{\text{SS}} \xrightarrow{\text{Raney Ni}} \text{H}_{\text{HH}}
\]

Cyclic thioacetal

- mechanism is analogous to acetal formation
Clemmensen Reduction

\[ \text{Ph-CHOCH}_2\text{CH}_3 \xrightarrow{\text{Zn(Hg)}} \text{Ph-CH}_2\text{CH}_2\text{CH}_3 \] 

\[ \text{Cyclo-C-CHOCH}_2\text{H} \xrightarrow{\text{Zn(Hg)}} \text{Cyclo-C-CH}_2\text{CH}_3 \]
Ketone/aldehyde to alkane

Clemmensen Reduction: **Acidic condition**

\[ \text{R}-\text{R} \quad \overset{\text{Zn(Hg), HCl, Heat}}{\rightarrow} \quad \text{H}-\text{H} \]

Wolff-Kishiner Reduction: **Basic condition**

\[ \text{R} \quad \overset{\text{Hydrozine, } \text{H}_2\text{N}-\text{NH}_2}{\rightarrow} \quad \text{H}_2\text{N} \cdot \text{N} \quad \overset{\text{KOH/H}_2\text{O, Heat}}{\rightarrow} \quad \text{R} \quad + \quad \text{N}_2 \]

Raney Nickel catalyzed Desulfurization: **Acidic condition**

\[ \text{O} \quad + \quad \text{H-S-S-H} \quad \overset{[\text{H}^+]}{\leftrightarrow} \quad \text{S-S} \quad \overset{\text{Raney Ni}}{\rightarrow} \quad \text{H}-\text{H} \]

Chapter 19
Reduction Reagents

- Sodium borohydride, \( \text{NaBH}_4 \), can reduce ketones to secondary alcohols and aldehydes to primary alcohols.
- Lithium aluminum hydride, \( \text{LiAlH}_4 \), is a powerful reducing agent, so it can also reduce carboxylic acids and their derivatives.
Sodium Borohydride

\[
\text{R} \backslash \text{R(H) \rightarrow NaBH}_4 \rightarrow \text{R} \backslash \text{R(H)}
\]

\( \text{aldehyde or ketone} \)

- \( \text{NaBH}_4 \) can reduce ketones and aldehydes, but not esters, carboxylic acids, acyl chlorides, or amides.
Lithium Aluminum Hydride

\[ \text{LiAlH}_4 \text{ can reduce any carbonyl because it is a very strong reducing agent.} \]

\[ \text{Difficult to handle.} \]
Carbon Nucleophiles: Grignard Reagents

1) CH₃MgBr
2) H₃O⁺
Cyanohydrin Formation

- The mechanism is a base-catalyzed nucleophilic addition: Attack by cyanide ion on the carbonyl group, followed by protonation of the intermediate.
- HCN is highly toxic.
Cyanohydrin in Synthesis

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{HO} & \quad \text{NH}_2 \\
\text{HO} & \quad \text{O} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]
The Wittig Reaction

The Wittig reaction

- The Wittig reaction converts the carbonyl group into a new C═C double bond where no bond existed before.
- A phosphorus ylide is used as the nucleophile in the reaction.
Preparation of Phosphorus Ylides

Prepared from triphenylphosphine and an unhindered alkyl halide.

Butyllithium then abstracts a hydrogen from the carbon attached to phosphorus.
Mechanism of the Wittig Reaction

Betaine formation

\[
\text{Ph}_3\text{P} \rightleftharpoons \text{C}^+: \text{H} \quad \text{R'} \quad \delta^+ \quad \delta^- \quad \text{C} = \text{O}: \quad \rightarrow \quad \text{Ph}_3\text{P} \quad :\text{O}^+ : \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{R'}
\]

ylide \quad \text{ketone or aldehyde} \quad \text{a betaine}

Copyright © 2010 Pearson Prentice Hall, Inc.

Oxaphosphetane formation

\[
\text{Ph}_3\text{P} \quad :\text{O}^+ : \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{R'} \quad \rightarrow \quad \text{Ph}_3\text{P} \quad :\text{O}^+ : \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{R'}
\]

\[
\text{R} \quad \text{R'} \quad \text{a betaine} \quad \text{oxaphosphetane}
\]

Copyright © 2010 Pearson Prentice Hall, Inc.
Mechanism for Wittig

- The oxaphosphetane will collapse, forming carbonyl (ketone or aldehyde) and a molecule of triphenyl phosphine oxide.
Wittig reaction:

\[
\begin{align*}
\text{Ph}_3\text{P} \equiv \text{H} & \quad \text{H}_3\text{C} \equiv \text{H} \\
\text{Ph} & \quad (Z)
\end{align*}
\]

How to synthesis (E)-alkene?

1) Stabilized wittig reagent

\[
\begin{align*}
\text{Ph}_3\text{P} \equiv \text{H} & \quad \text{H} \equiv \text{EWG} \\
\text{Ph} & \quad (E)
\end{align*}
\]

2) Horner-Wadsworth-Emmons (HWE) reaction

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{EtO} & \quad \text{EtO}
\end{align*}
\]

Chapter 19
Baeyer-Villiger Oxidation (oxygen insertion)

Migration rates: \( H \gg 3º\text{alkyl} > 2º\text{alkyl or Ph} > 1º\text{alkyl} > \text{Me} \)
Infrared (IR) Spectroscopy

- Very strong C═O stretch around 1710 cm\(^{-1}\).
- Additional C—H stretches for aldehyde: Two absorptions at 2710 cm\(^{-1}\) and 2810 cm\(^{-1}\).
Conjugation lowers the carbonyl stretching frequencies to about 1685 cm\(^{-1}\).

Rings that have ring strain have higher C═O wavenumber.
\[ \text{\( ^1H \) NMR Spectra} \]

- Aldehyde protons normally absorb between \( \delta 9 \) and \( \delta 10 \).
- Protons of the \( \alpha \)-carbon usually absorb between \( \delta 2.1 \) and \( \delta 2.4 \) if there are no other electron-withdrawing groups nearby.

Copyright © 2010 Pearson Prentice Hall, Inc.
Protons closer to the carbonyl group are more deshielded.
The spin-decoupled carbon NMR spectrum of 2-heptanone shows the carbonyl carbon at 208 ppm and the $\alpha$ carbon at 30 ppm (methyl) and 44 ppm (methylene).