Lecture 16
Still More Carbonyl Chemistry

March 24, 2019
Thanks to the Orbitals
Ok...let’s do some synthesis as a “warm up”
The Wittig Reaction

\[
\begin{align*}
\text{R} & \quad \text{C} = \text{O} \\
\text{R'} & 
\end{align*} + \quad \text{(C}_6\text{H}_5\text{)}_3\text{P} - \text{C} & : \\
\text{R} & \quad \text{C} = \text{C} & : \\
\text{R'} & 
\end{align*} + \quad \text{(C}_6\text{H}_5\text{)}_3\text{P} : & \text{O}:
\]

“ylide”
Preparation of Ylides

The ylid is made in a two step process. The first step is a nucleophilic substitution reaction that forms a phosphonium salt.

\[
(C_6H_5)_3P\cdot \cdot \cdot + \text{CH}_A\text{BX}(C_6H_5)_3P\cdot \cdot \cdot + \text{X}^-
\]
In the second step, the phosphonium salt is treated with a strong base in order to remove a proton from the carbon bonded to phosphorus.

\[
\begin{align*}
(C_6H_5)_3P & \quad \text{+ base} \\
C & \quad \text{H} \\
\text{B} & \quad \text{base} \\
\rightarrow & \\
(C_6H_5)_3P & \quad \text{+} \\
\quad & \quad \text{C} : \\
\quad & \quad \text{B} \\
\quad & \quad \text{H} \quad \text{+ base} \quad \text{H}
\end{align*}
\]
Mechanism

Step 1

\[
\begin{align*}
R & \quad R' \\
A & \quad B \\
C & \quad \text{P(C}_6\text{H}_5)_3
\end{align*}
\]

\[
\begin{align*}
R & \quad R' \\
A & \quad C \\
B & \quad \text{P(C}_6\text{H}_5)_3
\end{align*}
\]
Mechanism

Step 2

\[
\text{R} \quad \begin{array}{c}
\text{C} \\
\text{R'}
\end{array} + \quad \begin{array}{c}
\text{C} \\
\text{A}
\end{array} + \quad \begin{array}{c}
\text{C} \\
\text{B}
\end{array}
\]

\[
\begin{array}{c}
\text{R} \\
\text{R'}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{A}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{B}
\end{array}
\]

\[
\text{P(C}_6\text{H}_5)_3
\]

\[
\text{R} \quad \begin{array}{c}
\text{C} \\
\text{R'}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{A}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{B}
\end{array}
\]

\[
\text{P(C}_6\text{H}_5)_3
\]

Chemistry 328N
Triphenylphosphine oxide

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{P(C}_6\text{H}_5\text{)}_3 & \quad \text{P(C}_6\text{H}_5\text{)}_3
\end{align*}
\]

This substance is very stable
Nearly insoluble in many solvents, i.e. pentane
Oral, mouse: LD50 = 1380 mg/kg;
Wittig Reaction

- More examples

\[
\text{Ph}_3\text{P} - \text{CHCH}_3 + \text{Ph}_3\text{PO} \rightarrow \text{PhCH} = \text{CCH}_3 + \text{Ph}_3\text{P}=\text{O}
\]

87% Z isomer

Don’t plan to control the E/Z ratio…you get generally get a mixture
The Wittig Reaction

- See... sometimes you can control it
- we won’t try to do that in this class
- You can learn this in the graduate synthesis class
- The reaction has broad “scope”

\[
\text{Ph}_3\text{P} - \text{CHCOCH}_2\text{CH}_3 + \text{CH}_2=\text{C}(\text{Ph})-\text{CH}_2\text{CO}_2\text{H} \rightarrow \text{Ph}_3\text{P}=\text{O} + \text{Ph}-\text{CH}=\text{CH}_2-\text{CH}_2\text{CO}_2\text{H}
\]

100% E isomer
An Example: Write the structure of the products

\[
\text{Cyclopentanone} + \left[ \begin{array}{c}
\text{Phenyl}
\end{array} \right]_3 \xrightarrow{\text{reaction}} \text{Product Structure}
\]
Synthesis..
benzene and 3 carbon starting materials
Synthesis
Oxidation and Reduction

- Aldehydes are oxidized to carboxylic acids by a variety of oxidizing agents and it is possible to do some selective reduction reactions.
- To calculate the oxidation state, assume that oxygen is “always” -2 and hydrogen is “always” +1.

<table>
<thead>
<tr>
<th></th>
<th>CH₄</th>
<th>CH₃OH</th>
<th>H-C-H</th>
<th>H-C-OH</th>
<th>O=C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>-4</td>
<td>-2</td>
<td>0</td>
<td>+2</td>
<td>+4</td>
</tr>
<tr>
<td>Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reduction

- Aldehydes can be reduced to $1^\circ$ alcohols and ketones to $2^\circ$ alcohols. In addition, the C=O group can be reduced to a $-\text{CH}_2-$ group.

<table>
<thead>
<tr>
<th>Aldehydes</th>
<th>Can be Reduced to</th>
<th>Ketones</th>
<th>Can be Reduced to</th>
</tr>
</thead>
</table>
| $\ce{O} \ \ 
\ce{RCH} \rightarrow \ce{RCH_3}$  | $\ce{RCH_2 OH}$ | $\ce{O} \ \ 
\ce{RCR'} \rightarrow \ce{RCHR'}$ | $\ce{OH}$ |
|           |                  |         | $\ce{RCH_2 R'}$    |
Metal Hydride Reduction

- The most selective reagents for the reduction of aldehydes and ketones are NaBH₄ and LiAlH₄
  - both are sources of hydride ion, H:\(^-\), a very powerful nucleophile

```
Na⁺ | H-B-H
H   | H
Sodium borohydride

Li⁺ | H-Al-H
H    | H
Lithium aluminum hydride (LAH)

H⁻⁺
Hydride ion
```
The key step in metal hydride reduction is transfer of a hydride ion to the C=O group to form a tetrahedral carbonyl addition compound.
Closer look at borohydride reductions

B-O bond is much stronger than B – H bond
This is the driving force for the reaction…
NaBH$_4$ Reduction

- Reductions with NaBH$_4$ are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol

\[
\text{RCH} + \text{NaBH}_4 \xrightarrow{\text{CH}_3\text{OH}} \text{RCH}_2\text{OH}
\]
Examples: Sodium Borohydride

Aldehyde

\[
\text{O}_2\text{N} \quad \text{CH} \quad \text{O} \quad \text{NaBH}_4 \quad \text{methanol} \quad \text{CH}_2\text{OH}
\]

Ketone

\[
\text{H} \quad \text{OH} \quad \text{NaBH}_4 \quad \text{ethanol}
\]
Lithium aluminum hydride

\[ \text{LiAlH}_4 \]

- More reactive than sodium borohydride
- Cannot use water, ethanol, methanol, etc., as solvents
- Diethyl ether and THF are the most commonly used solvent
- This is a dangerous but useful reagent

\[ \text{RCCH}_3 + \text{LiAlH}_4 \rightarrow \text{RCCH}_2\text{H}_3 + \text{LiAlH}_3 \]
Examples: Lithium Aluminum Hydride

Aldehyde

This is “overkill”…just use safer NaBH₄

Ketone

1. LiAlH₄
diethyl ether

2. H₂O
neither NaBH₄ or LiAlH₄ will reduce isolated double bonds

1. LiAlH₄
diethyl ether

2. H₂O
Selectivity in Reduction

- LiAlH$_4$ reduces *any* and all carbonyl compounds to the corresponding alcohols

- NaBH$_4$ *only* reduces aldehydes and ketones
Catalytic Reduction

- Catalytic reductions are generally carried out from 25° to 100°C and from 1 to 5 atm H₂.
- Carbon-carbon double bonds can be selectively reduced using Rhodium catalysts.

![Chemical Reaction Diagram](image)
Hydrogenolysis of benzylic carbonyls

- Palladium catalysis of hydrogenation reduces only benzylic C-O bonds to methylene groups.
- Benzyl ethers, aldehydes and alcohols are also reduced to the corresponding methylene group.
Clemmensen Reduction

- Refluxing an aldehyde or ketone with amalgamated zinc in concentrated HCl converts the carbonyl group to a methylene group.
- Limitations…??

\[
\text{OH} \quad \text{C(CH}_2\text{)}_5 \text{CH}_3 \quad \xrightarrow{\text{Zn(Hg), HCl}} \quad \text{OH} \quad \text{CH}_2(\text{CH}_2\text{)}_5 \text{CH}_3
\]
Wolff-Kishner Reduction

- If aldehydes or ketones are refluxed with hydrazine and KOH in a high-boiling solvent, the reaction converts carbonyls into methylenes.

\[
\text{KOH, H}_2\text{NNH}_2, \Delta \Rightarrow
\]

![Chemical structure diagram showing the Wolff-Kishner reduction process.](image)
Hexavalent chromium compounds (including chromium trioxide, chromic acids, chromates, chlorochromates) are toxic and carcinogenic.
Chromic acid is often made "in situ" (that is, in the reaction flask) through the addition of acid to sources of chromium (such as chromate salts). The large number of possible chromium sources (and acids!) can make this confusing, but it is chromic acid that is the active reagent.
Oxidation at Benzylic Positions

\[ \text{H}_2\text{SO}_4, \text{K}_2\text{CrO}_4 \rightarrow \text{Heat} \]

KMnO4 in Base also works
Selective Chromate Oxidations

- Chromic acid and heat Oxidizes benzylic positions bearing at least one hydrogen to acids.

- Jones Reagent ($H_2CrO_4$ in acetone) takes primary alcohols to acids and secondary alcohols to ketones...The acetone keeps the reaction cool. Jones oxidation does not oxidize benzylic positions even with a hydrogen.

- PCC (pyridinium chlorochromate) is weaker yet, it only oxidizes primary alcohols to aldehydes (!) and secondary alcohols to ketones.
The Jones Oxidation Examples

H₂SO₄

H₂CrO₄, Acetone

OH

H₃C

O

C

H

H₃C

OH

H₃C

O

C

H

H₃C

OH

H₃C

O

C

H

H₃C

OH

H₃C

O

C

H

H₃C
PCC Oxidations

\[ \text{C}_5\text{H}_5\text{N} + \text{HCl} + \text{CrO}_3 \rightarrow [\text{C}_5\text{H}_5\text{NH}][\text{CrO}_3\text{Cl}] \]
Selectivity!!?

CH₄  CH₃OH  H–C–H  H–C–OH  O=C=O
-4    -2    0       +2       +4

Oxidation

Reduction
Selective Oxidation Reactions

- **Jones Reagent** ($\text{H}_2\text{CrO}_4$ in acetone) takes primary alcohols to acids and secondary alcohols to ketones

- **The Tollens’s Test**  $\text{Ag(NH}_3\text{)}_2\text{OH}$…the silver mirror reaction is a qualitative test for aldehydes and an efficient but expensive way to make acids form aldehydes
Tollens Test

\[ 2 \text{AgNO}_3 + 2 \text{NaOH} \rightarrow \text{Ag}_2\text{O(s)} + \text{H}_2\text{O} + 2 \text{Na}^{+1} + 2 \text{NO}_3^{-1} \]

\[ \text{Ag}_2\text{O(s)} + 4\text{NH}_3 + \text{H}_2\text{O} \rightarrow 2\text{Ag(NH}_3)_2^{+} + 2\text{OH}^{-} \quad \text{(Totally Dissolved)} \]

\[ 2(\text{Ag(NH}_3)_2^{+} \text{OH}^{-}) + R\text{COO}^{-} + \text{NH}_4^{+} + \text{H}_2\text{O} + 3\text{NH}_3 \]
Examples

\[
\text{H}_2\text{CrO}_4, \text{Acetone} \quad \rightarrow \quad \text{H}_2\text{SO}_4 \quad \rightarrow \quad \text{H}_2\text{CrO}_4, \text{Acetone} \\
\text{Ag(NH}_3)_2 \text{OH} \quad \rightarrow \quad \text{Ag}^0
\]
Ok...more synthesis

From benzene, any thing with less than 3 carbons, and any other reagents that do not become part of the structure.