Last time we ended with the following problem:

Draw a mechanism to explain the formation of both products:

\[
\text{HBr/H}_2\text{O} \rightarrow \text{H}_3\text{C} \quad \text{Br}\text{Ph}
\]

The first product comes from straightforward substitution of the OH group. But how do we get the second product?

It looks like the phenyl group has migrated. However, the phenyl group actually goes through a three-membered ring intermediate during the migration step:

That’s all I want to discuss about carbocation rearrangements and neighboring group participation. For the next three classes, we are going to cover carbonyl chemistry. Hopefully much of this is a review for most of you.

Today we are going to discuss aldehydes and ketones, next time we will talk about reactions of aldehydes and ketones, and in the third class we will talk about carboxylic acids, esters, and amides.

**Aldehydes** – The general structure of an aldehyde is shown below:

\[
\text{RCHO}
\]

These compounds are very sensitive and reactive, mostly because they are intermediate in oxidation state between an alcohol and a carboxylic acid.

\[
\text{ROH} \xrightarrow{\text{oxidation}} \text{RCHO} \xrightarrow{\text{reduction}} \text{RCH}_2\text{OH}
\]

We are going to talk about three ways to make them: Oxidation, reduction, and ozonolysis.

1. Oxidation: When we talk about oxidation, you should keep in mind that you will have to carefully control the reaction conditions so that you don’t end up over-oxidizing your alcohol all the way to a carboxylic acid. One way to form aldehydes selectively is by using Swern oxidation. The overall reaction is shown below:
The mechanism for the oxidation is shown below:

**Step 1:** Production of dimethylsulfonium chloride as a key intermediate

![Chemical reaction diagram](image)

**Step 2:** The dimethylsulfonium chloride then attacks the alcohol oxygen, to generate an intermediate that is deprotonated by base and forms a sulfur ylide. The sulfur ylide then abstracts a proton, and forms the desired carbonyl compound and dimethyl sulfide.

![Chemical reaction diagram](image)

An interesting side note is when we think about the best way to draw DMSO (dimethyl sulfoxide), you have two possible resonance forms:

![Resonance forms of DMSO](image)

The first one is completely neutral, with no formal charges on any part of the molecule, whereas the second structure has two charges. Based on your previous chemistry classes, you probably think that the first structure is by far the most stable, although this is not necessarily the case. There are a number of molecules that are actually more stable as zwitterions (double ions), compared to their neutral form.

One other example of this, which we will talk about in detail later in the semester, is squaraine. Squaraine dyes have the general structure shown below:

![Squaraine structure](image)

There is a central 4-membered ring core (that is where the name “squaraine” comes from), and two electron-rich aromatic rings. It turns out that the most stable resonance form of the squaraine compound is actually an ionic version:
This is relatively easy to explain. Oxygen is very electronegative, so it doesn’t mind having a negative charge. And the central cyclobutene ring with a +2 charge is actually an aromatic ring system. According to Hückel, as you may recall, aromatic rings have 4n+2 pi electrons. The most common example is benzene, which has six pi electrons (4n+2 with n = 1). This is a case of an aromatic ring system of 4n+2 electrons with n=0.

Back to Swern oxidation: This is a fairly environmentally-friendly way to oxidize alcohols, because you do not use any heavy metals and do not produce toxic byproducts. There are other ways to form aldehydes by oxidation, including using chromium (VI) reagents like potassium dichromate and pyridinium chlorochromate (PCC, structure shown below):

2. Reduction: You can also form aldehydes by reducing a variety of compounds, but here again you have to be careful that you do not over-reduce it all the way to an alcohol. One way to do this is by using diisobutyl aluminum hydride (DIBAL) to reduce esters and nitriles to aldehydes.

Ester reduction:

\[
\begin{align*}
\text{DIBAL, } -78^\circ\text{C} \quad &\quad \text{Al}((\text{Et})_2) \quad \text{H}_3\text{O}^+ \\
\text{OR} \quad &\quad \text{OR'} \\
\longrightarrow &\quad \text{R} \quad \text{H} \\
\longrightarrow &\quad \text{R} \quad \text{H} \\
\end{align*}
\]

Oxidizes an ester to an alcohol.

Nitrile reduction:

\[
\begin{align*}
\text{DIBAL, } -78^\circ\text{C} \quad &\quad \text{Al}((\text{Et})_2) \quad \text{H}_3\text{O}^+ \\
\text{R} \quad \text{N} \quad &\quad \text{R} \quad \text{H} \\
\longrightarrow &\quad \text{R} \quad \text{H} \\
\end{align*}
\]

Oxidizes a nitrile to an aldehyde.

Using DIBAL allows you to stop the reduction at the aldehyde, whereas lithium aluminum hydride would reduce all of these molecules to the corresponding alcohols.

3. You can also form aldehydes from alkenes by using ozonolysis. The overall ozonolysis reaction is shown below:

\[
\begin{align*}
\text{O}_3, -78^\circ\text{C} \quad &\quad \text{O} \\
\longrightarrow &\quad \text{CH}_2\text{CH}=\text{CH}_2 \\
\text{O}_{3}, -78^\circ\text{C} \quad &\quad \text{CH}_2\text{CH} \quad \text{(CH}_3)_2\text{S} \\
\longrightarrow &\quad \text{CH}_2\text{CH} \quad \text{CH}_2\text{CH} \\
\end{align*}
\]

The mechanism of the ozonolysis reaction is interesting, and involves the formation of two different cyclic intermediates:
The first cyclic intermediate is called an ozonide, which then undergoes a retro cycloaddition to generate two new compounds that form another five membered ring, called a trioxolane. Reduction of the trioxolane gives two carbonyl products. Ozonolysis is used just as often to form ketones as well, starting from a more substituted alkene. The dimethyl sulfide is used to reduce the trioxolane to the final carbonyl products.

OK that concludes today’s discussion of aldehydes. Let’s now discuss how to form ketones, whose general structure is shown below:

Ketones are much less sensitive than aldehydes, because it is much harder to over-oxidize or over-reduce a compound (would have to involve breaking a C-C bond). Here are a few ways that you can make ketones:

1. Ketones can also be made from ozonolysis, if you start from a more highly substituted alkene:

2. They can also be made via Friedel Crafts acylation. The overall reaction is shown below:

As you may remember from the first time you heard of Friedel-Crafts reactions, there are really two different reactions: Friedel-Crafts alkylation and Friedel-Crafts acylation.

F-C alkylation involves the addition of an alkyl carbocation to an aromatic ring using a Lewis acid like FeCl₃. The reaction is shown below:

The problem with this reaction is that you form a number of different products (with multiple R groups attached):
A F-C acylation, in contrast, only gives you one product:

\[
\text{Ar} + \text{R-Cl} \xrightarrow{\text{AlCl}_3} \text{Ar-R} + \text{Ar-Cl}
\]

This difference in reactivity is because when you do the initial acylation reaction, the substituted aromatic ring product is de-activated from further additions (because of the electron-withdrawing acyl group). When you do an F-C alkylation, the resulting substituted aromatic ring is more activated towards further addition reactions because it now has an electron-donating alkyl group attached to it. This is a pretty good method to form aromatic ketones.