

5.3: PREPARING ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
 - a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
 - b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
 - c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
 - a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
 - b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
 - c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

STUDY NOTES

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.5.

The “new” method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.9, which you might now wish to review.

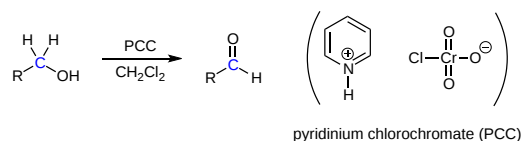
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

FORMATION OF ALDEHYDES

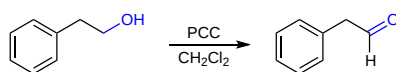
OXIDATION OF 1° ALCOHOLS TO FORM ALDEHYDES (SECTION 17.7)

PCC

Pyridinium chlorochromate (PCC) is a milder version of [chromic acid](#). PCC oxidizes alcohols one rung up the [oxidation ladder](#), from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids.

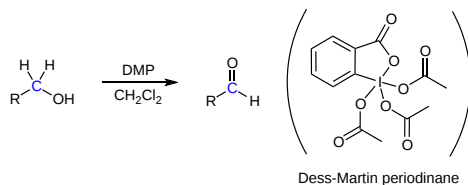


Example oxidation of a primary alcohol to an aldehyde

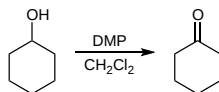


DESS-MARTIN PERIODINANE (DMP)

PCC is being replaced in laboratories by Dess-Martin periodinane (DMP), which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983. Similar to PCC, it oxidizes primary alcohols to aldehydes without continuing the oxidation to a carboxylic acid. It can also be used to oxidize secondary alcohols to ketones.

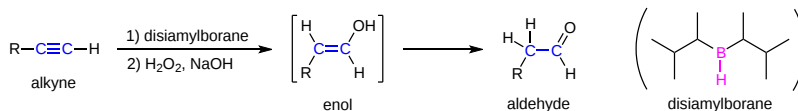


Example oxidation of an alcohol to a ketone using DMP

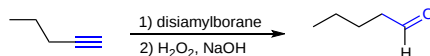


HYDRATION OF AN ALKYNES TO FORM ALDEHYDES (SECTION 9.5)

Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. This can be accomplished by hydroboration-oxidation reactions.

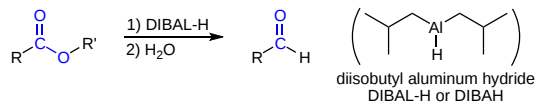


Example reaction of a terminal alkyne with disiamylborane followed by oxidation with hydrogen peroxide and hydroxide converting 1-pentyne to pentanal.



HYDRIDE REDUCTION OF ESTERS TO FORM ALDEHYDES (SECTION 21.8)

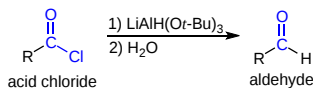
Various hydride sources allow for the partial reduction of some carboxylic acid derivatives to form aldehydes. These reactions are usually carried out at low temperatures (-78 °C) to prevent over reaction with the aldehyde product.



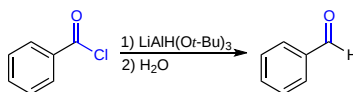
DIBAL-H reduction of methyl benzoate to benzaldehyde

HYDRIDE REDUCTION OF ACID CHLORIDES TO FORM ALDEHYDES (SECTIONS 21.6)

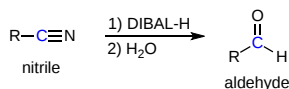
Reduction of acid chlorides to aldehydes requires hydride reagents with reduced reactivity as lithium aluminum hydride will continue reducing to the primary alcohol.



Example reduction of an acid halide to form an aldehyde



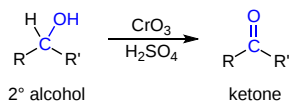
HYDRIDE REDUCTION OF A NITRILE TO FORM ALDEHYDES



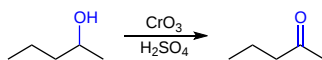
FORMATION OF KETONES

OXIDATION OF 2° ALCOHOLS TO FORM KETONES (SECTION 17.7)

Oxidation of 2° alcohols to form ketones typically uses Jones reagent (CrO_3 in H_2SO_4) but many other oxidizing agents can be used.

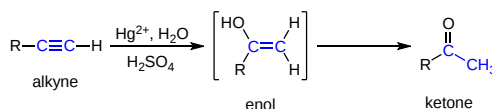


Example oxidation of a secondary alcohol to a ketone

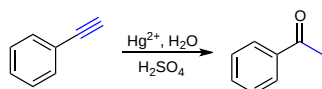


HYDRATION OF ALKYNES TO FORM KETONES (SECTION 9.4)

The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.

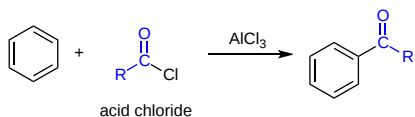


Example reaction of an alkyne with Hg^{2+} , H_2O , and H_2SO_4 to give a ketone

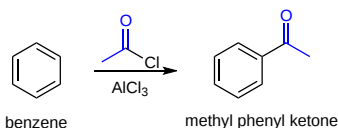


FRIEDEL-CRAFTS ACYLATION TO FORM A KETONE (SECTION 16.3)

Aromatic ketones can be synthesized through Friedel–Crafts acylation of an aromatic ring with an acid chloride. Aluminum chloride (AlCl_3) is used as a Lewis acid catalyst.

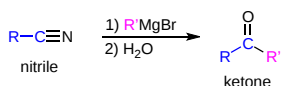


Example of Friedel-Crafts acylation to form a ketone from benzene.

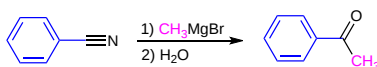


REACTION OF GRIGNARD REAGENTS WITH NITRILES TO FORM KETONES (SECTION 20.7)

Grignard reagents can attack the electrophilic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.

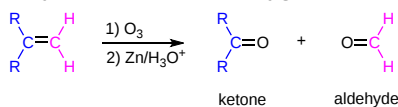


Example of Grignard addition to a nitrile to give a ketone.

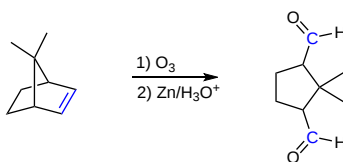


ALKENES CAN BE CLEAVED USING OZONE (O_3) TO FORM ALDEHYDES AND/OR KETONES (SECTION 8.8)

Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen.

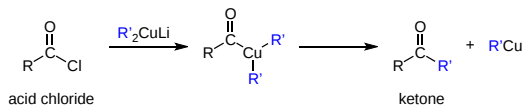


Example ozonolysis of an alkene to form aldehydes.

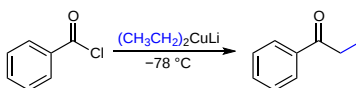


ORGANOCUPRATE REAGENTS CONVERT ACID CHLORIDES TO KETONES (SECTION 21.4)

An important reaction exhibited by lithium alkylcopper reagents (Gilman Reagents), is the nucleophilic addition to acid chlorides. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference is exploited to allow for a single nucleophilic addition to form a ketone.



Example of organocuprate addition to an acid chloride to generate a ketone.



? EXERCISE 5.3.1

What reagents would be required to prepare hexanal from the following starting materials?

- $CH_3CH_2CH_2CH_2CH_2CH_2OH$
- $CH_3CH_2CH_2CH_2CH_2CH=CH_2$
- $CH_3CH_2CH_2CH_2CO_2CH_3$
- $CH_3CH_2CH_2CH=CH_2$

Answer

- Dess–Martin periodinane or PCC in CH_2Cl_2
1. O_3 , 2. Zn/H_3O^+
1. DIBAL 2. H_2O
1. BH_3 2. $H_2O_2/NaOH$; 2. Dess–Martin periodinane or PCC

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