



Mixed Aldol Condensations

Carbonyl condensation reactions take place between two carbonyl groups and involve a combination of nucleophilic addition and α -substitution steps. The reaction demonstrates how a carbonyl group can be used as a source of both nucleophiles and electrophiles. Mechanistically, the reaction proceeds via formation of an enolate anion (the *nucleophile*) from one of the carbonyl groups. This anion is the nucleophile for a nucleophilic addition to the C=O of the second carbonyl group (the *electrophile*). The general mechanism is shown in Figure 1.

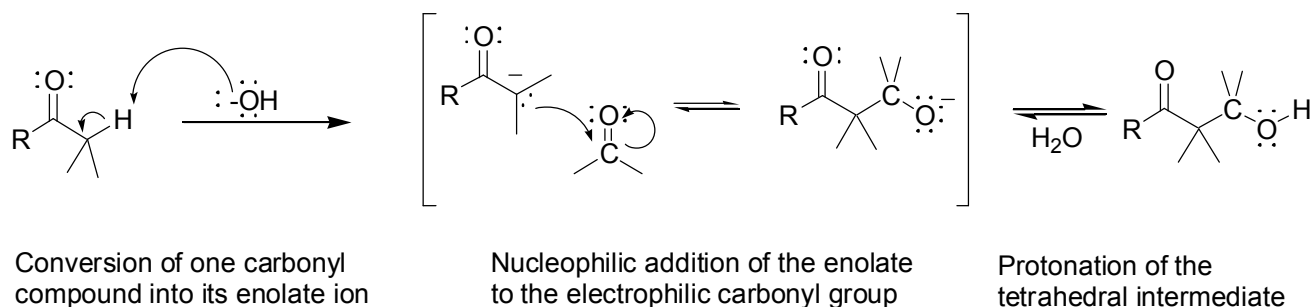
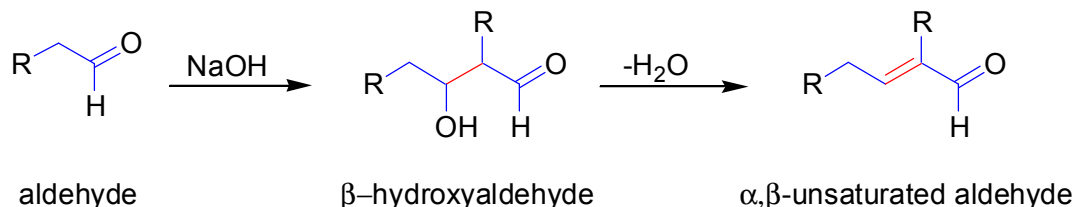


Figure 1. General mechanism of a carbonyl condensation reaction.

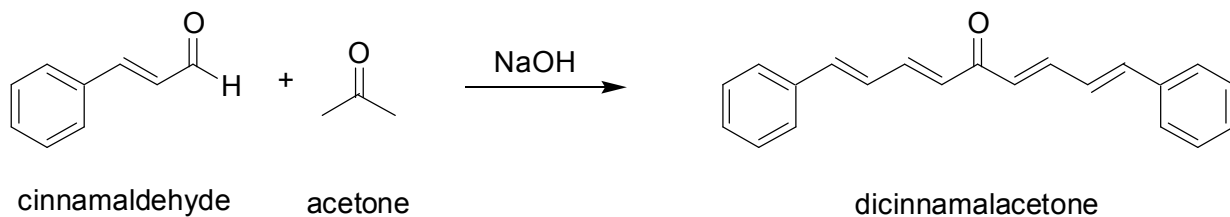
All kinds of carbonyl compounds, including aldehydes, ketones, esters, amides, anhydrides, and nitriles, undergo condensation reactions. See McMurray, 5th Ed., Chapters 22 and 23 for a more detailed discussion.

In this experiment, you will investigate the aldol condensation and its application to the synthesis of β -hydroxyaldehydes and ketones as well as α,β -unsaturated aldehydes and ketones.

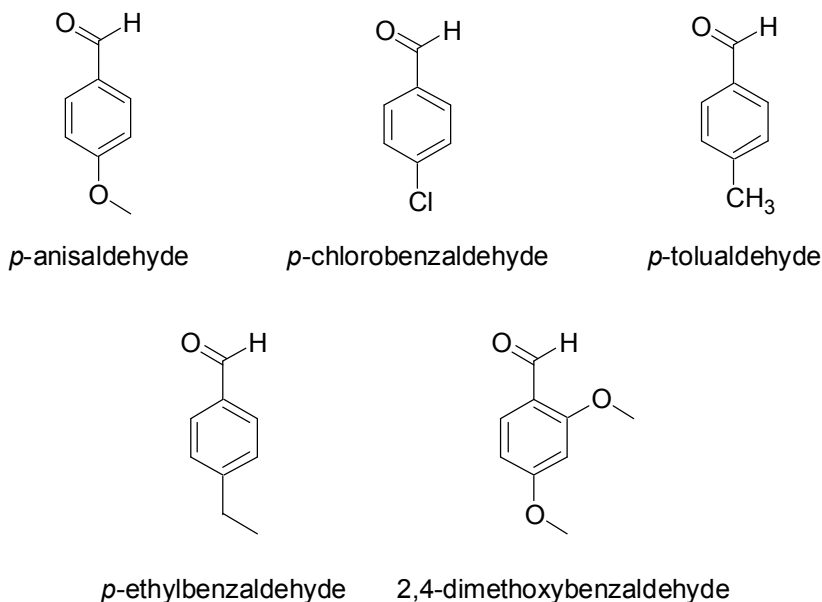
The **ALDOL CONDENSATION** is the acid- or base-catalyzed condensation of two identical molecules of an aldehyde or ketone to give the α,β -unsaturated aldehyde or ketone. In this reaction, a carbon-carbon bond is formed between the α -carbon of one molecule and the carbonyl carbon of the second. Dehydration of the corresponding aldol reaction product, a β -hydroxyaldehyde or ketone, is easily accomplished to give the desired α,β -unsaturated aldehyde or ketone. This is a versatile synthetic route to many important organic compounds.



A mixed aldol condensation reaction occurs between two different carbonyl compounds, at least one of which should be an aldehyde. This condensation is generally only practical if one of the compounds has no α -hydrogens. Thus, one compound should not be enolizable. Otherwise, up to four products can be formed. For example, a reaction between cinnamaldehyde and acetone in the presence of base (NaOH) produces 1,9-diphenyl-1,3,6,8-nonatetraene-5-one (dicinnamalacetone).



In this example, acetone has two potential sites for enol formation, thus two equivalents of cinnamaldehyde are used to give the desired product. In the first condensation step, acetone reacts with one mole of cinnamaldehyde to produce 6-phenyl-3,5-hexadien-2-one. When all the acetone is consumed, the second mole of cinnamaldehyde condenses with the 6-phenyl-3,5-hexadien-2-one to give the dicinnamalacetone.



In this experiment, each student will receive 2 g (or 2 ml) of an unknown aromatic aldehyde. You will condense the aldehyde with a ketone, purify the product, and identify the unknown aldehyde from the melting point of the mixed aldol product, Table 1. The possible aromatic aldehydes are *p*-anisaldehyde, *p*-chlorobenzaldehyde, *p*-ethylbenzaldehyde, *p*-tolualdehyde, and 2,4-dimethoxybenzaldehyde. The ketones are acetone, cyclopentanone, and cyclohexanone. Each student must prepare a minimum of two mixed aldol products for an absolute identification of their unknown aromatic aldehyde. You may choose to prepare any combination of mixed aldol products.

Table 1. Table of Melting Points of the Mixed Aldol Products

Aldehyde	Ketone		
	Acetone (°C)	Cyclopentanone (°C)	Cyclohexanone (°C)
benzaldehyde	112	192	120
<i>p</i> -anisaldehyde	131	212	159
<i>p</i> -chlorobenzaldehyde	195	225	148
<i>p</i> -ethylbenzaldehyde	125	150	127
<i>p</i> -tolualdehyde	177	238	173
2,4-dimethoxybenzaldehyde	139	187	177

Experimental Procedure:

Place 0.5 ml or 300 mg of the aldehyde and 2.5 ml of 95% ethanol in a 25 ml Erlenmeyer flask. Add 1.75 ml of 2 M KOH and swirl to mix. Add 125 : 1 of the ketone via microsyringe and swirl the mixture vigorously until precipitation is complete. If no precipitation occurs, heat the solution in a water bath until precipitation occurs. Cool the reaction mixture in an ice-water bath for ~15 minutes to ensure complete crystallization. Collect the crystals by vacuum filtration and rinse the crystals with several small portions of ice-cold 95% ethanol. Rinse the crystals with a small portion of 10% acetic acid to neutralize excess base, then rinse again with cold 95% ethanol.

To find a recrystallization solvent, test the solubility of the aldol product in toluene and 2-propanol in a small test tube. Use the better solvent to recrystallize the product at least twice. Report the final yield (g and %).

Questions

1. Write a detailed mechanism for the mixed Aldol condensation between benzaldehyde and acetone.
2. A possible side product of the reaction is self-condensation of acetone. Draw the structure of this side product. Explain how the experimental procedure is setup to minimize the formation of the side product.
3. There are a number of base-catalyzed condensation reactions that are related to the aldol condensation. Write an example for each of these “name” reactions.
 - a. the Claisen condensation
 - b. the Malonic ester synthesis
 - c. the Knoevenagel reaction
 - d. the Perkin reaction
4. Draw the structure of the expected product of the mixed aldol condensation of 3-methoxy-4-methylbenzaldehyde and acetophenone.