Aldol Condensation*

Mary McHale

This work is produced by The Connexions Project and licensed under the
Creative Commons Attribution License †

1 Experiment 2: Aldol Condensation Reaction

1.1 Objective

The purpose of this laboratory exercise is to introduce the concept of the Carbon-Carbon bond forming reaction and the basic mechanism of the aldol condensation reaction.

1.2 Background Information

A useful carbon-carbon bond-forming reaction is known as the Aldol Reaction or Aldol Condensation. It is an example of electrophilic substitution at the alpha carbon in enols or enolate anions. Traditionally, it is the acid- or base-catalyzed condensation of one carbonyl compounds with the enolate/enol of another, which may or may not be the same, to generate a β-hydroxy carbonyl compound—an aldol. It is reversible in nature. The reaction may occur between two molecules of aldehyde, two molecules of ketones or one molecule of aldehyde and a molecule of ketone. When two different carbonyl compounds react, it is known as mixed aldol/ Crossed aldol condensation.

Reactions in which a larger molecule is formed from smaller components with the elimination of a very small by-product such as water are termed Condensations. Hence the following examples are properly referred to as aldol condensations. The dehydration step of an aldol condensation is also reversible in the presence of acid and base catalysts. Consequently, on heating with aqueous solutions of strong acids or bases, many α, β-unsaturated carbonyl compounds fragment into smaller aldehyde or ketones, a process known as the retro-aldol reaction. Below, a few examples of aldol condensation reaction are:

*Version 1.3: Oct 4, 2007 4:21 pm -0500
†http://creativecommons.org/licenses/by/2.0/

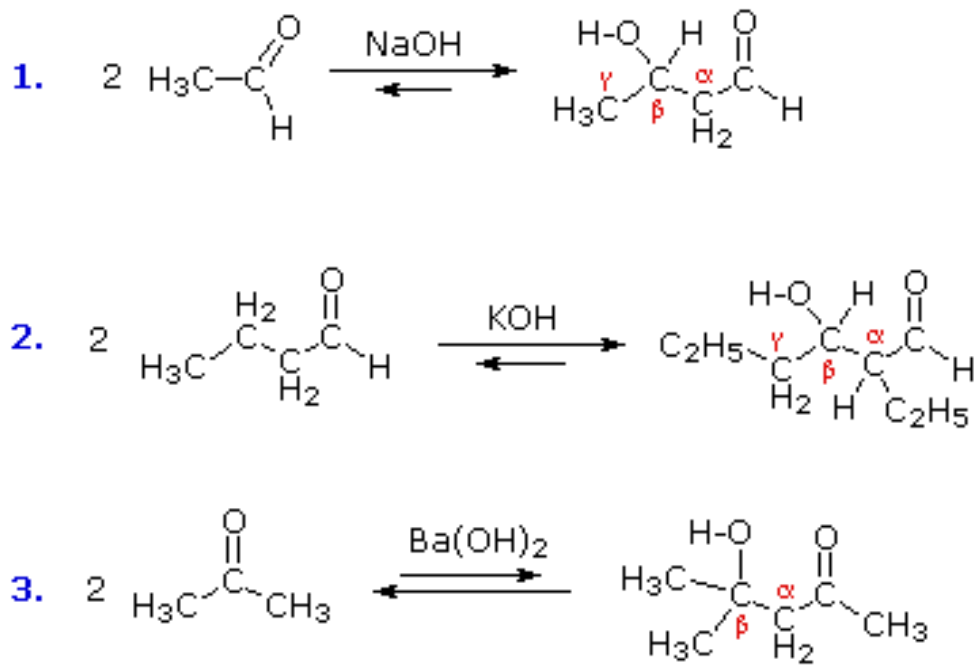


Figure 1

The product has both a carbonyl and an alcohol group; since the chemistry was initially developed with aldehydes the name "Ald-ol" (aldehyde-alcohol) was coined and has been applied to the reaction that forms it. For aldol condensation, the presence of α-H (acidic hydrogen atom) atom is necessary. In the absence of α-H atom, it can undergo the Cannizaro reaction. Aldol condensation involves the following steps in the mechanism:

1. Addition phase:

(a) Formation of an enol or enolate anion.

(b) Nucleophilic addition

(c) Proton transfer

2. Dehydration phase (If strong base/acid or some heat is applied)

Using acetone as an example:

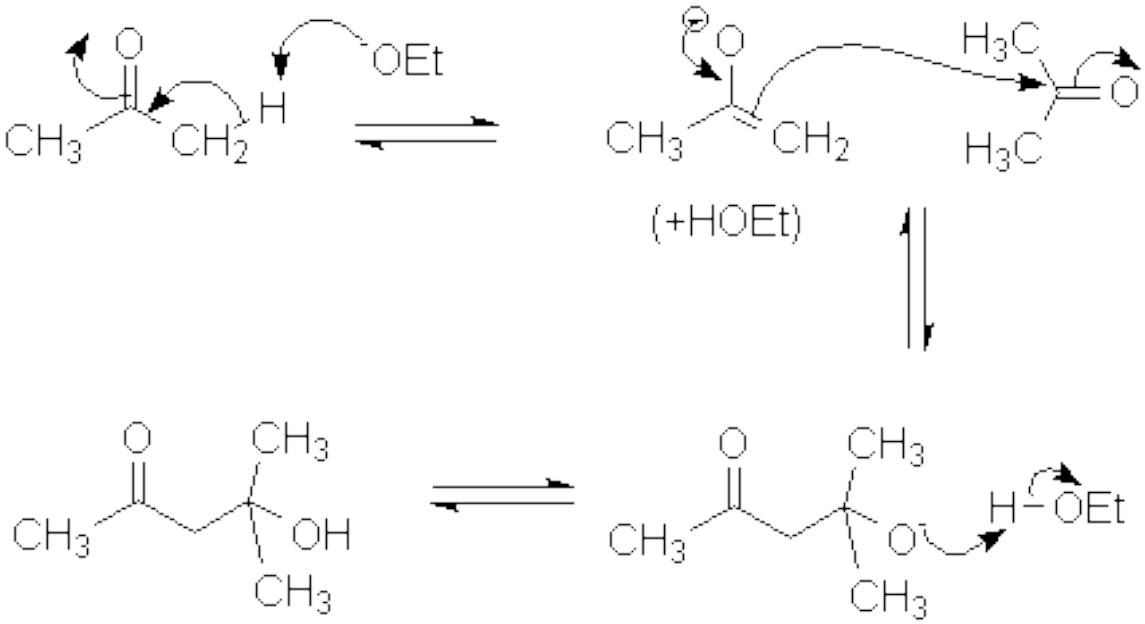


Figure 2

Step 1: An acid-base reaction occurs first. Ethoxide functions as a base and removes the acidic [U+F061]-hydrogen giving the reactive enolate.

Step 2: The nucleophilic enolate attacks another molecule of acetone at the electrophilic carbonyl C in a nucleophilic addition type process[1] giving an intermediate alkoxide.

Step 3: An acid-base reaction. The alkoxide deprotonates a solvent molecule (here ethanol) creating hydroxide and the β[U+F02D]hydroxyaldehydes or aldol product is formed.

There is little difference mechanistically between an acid or base catalyzed mechanism but examples of both have been given for completeness.

In next figure, the actual carbon-carbon bond formation has shown in different color for simplicity.

[1] http://library.tedankara.k12.tr/carey/ch17-3.html

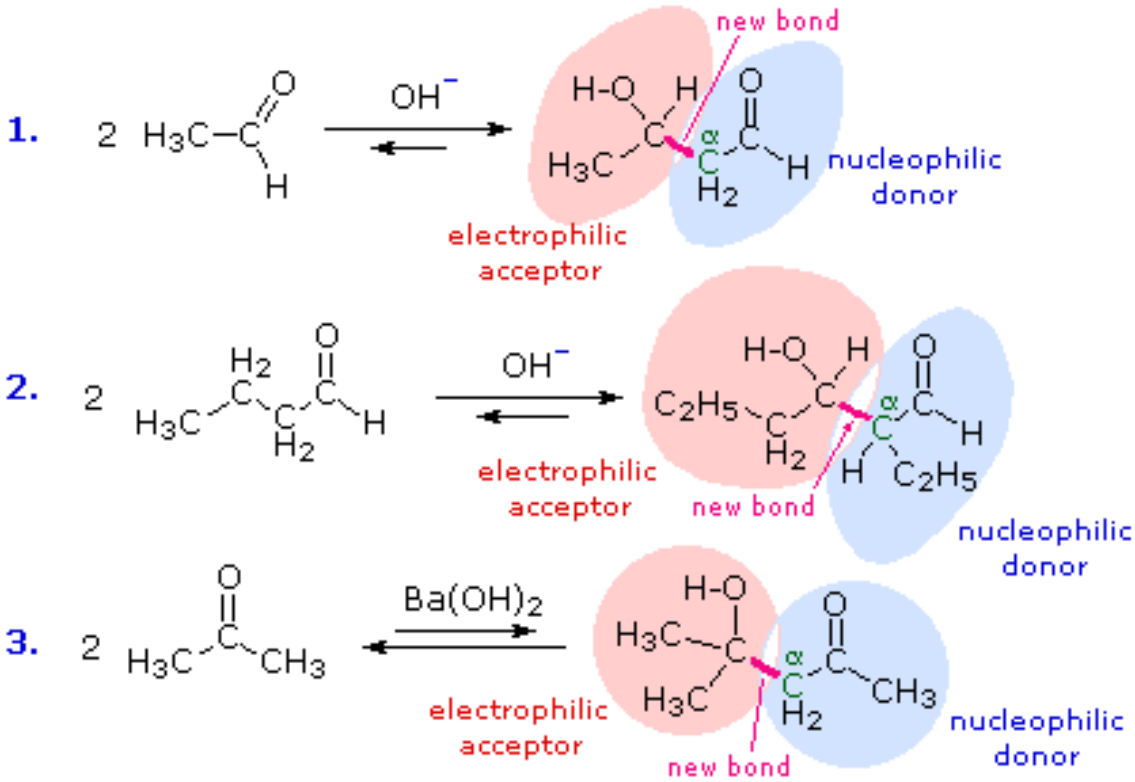


Figure 3

Acid catalyzed reaction mechanism:

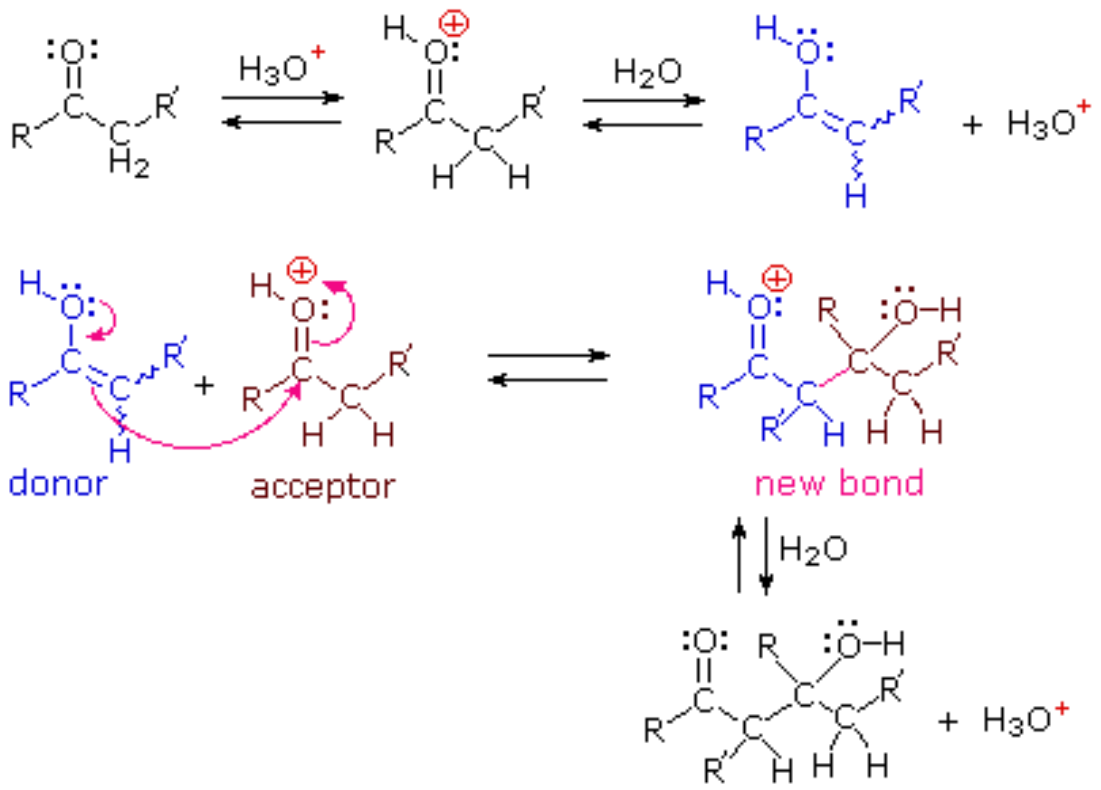


Figure 4

Base catalyzed reaction mechanism:

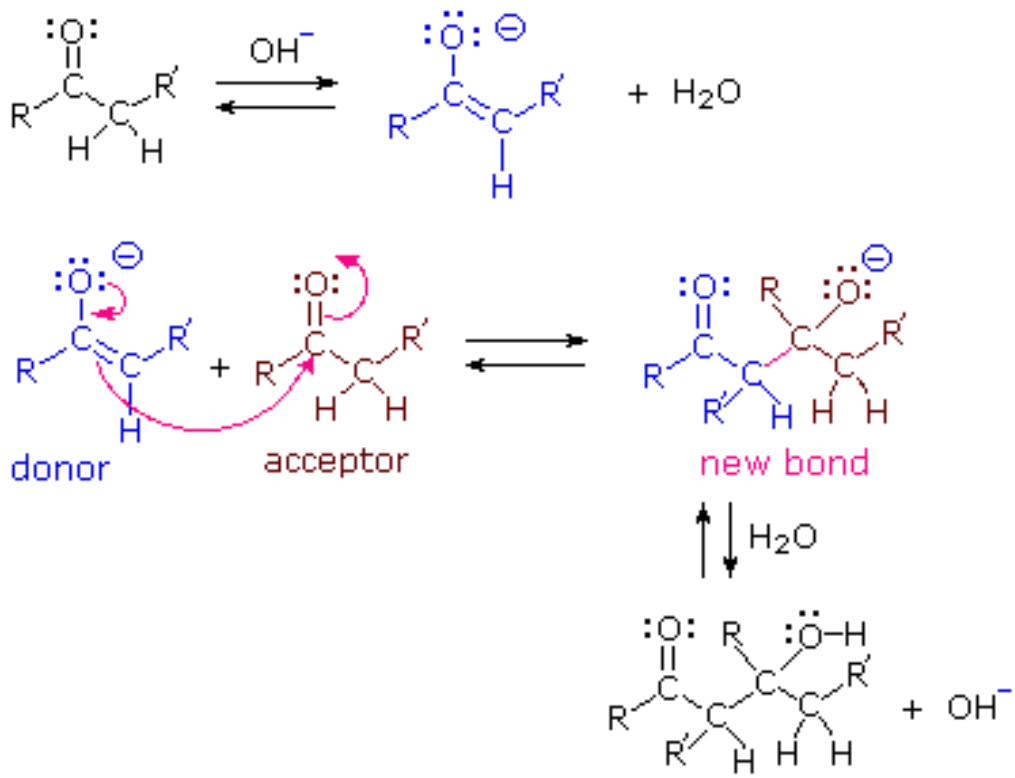


Figure 5

From the mechanism it is clear that presence of electron withdrawing group in acceptor molecule facilitates the reaction and vice versa.

1.3 Some Important Facts:

1. The reaction involves an enolate reacting with another molecule of the aldehyde.
2. Remember enolates are good nucleophiles and carbonyl C is electrophiles.
3. The products of these reactions are β[U+F02D]hydroxyaldehydes or aldehyde-alcohols = aldols.
4. The simplest aldol reaction is the condensation of ethanal.

Question: Why isn't the simplest example of an Aldol the condensation of methanal?

Answer: These Aldol products can often undergo dehydration[2] (loss of water) to give conjugated systems (an elimination reaction[3])

[2] http://library.tedankara.k12.tr/carey/ch5-2.html
[3] http://library.tedankara.k12.tr/carey/ch5-4.html

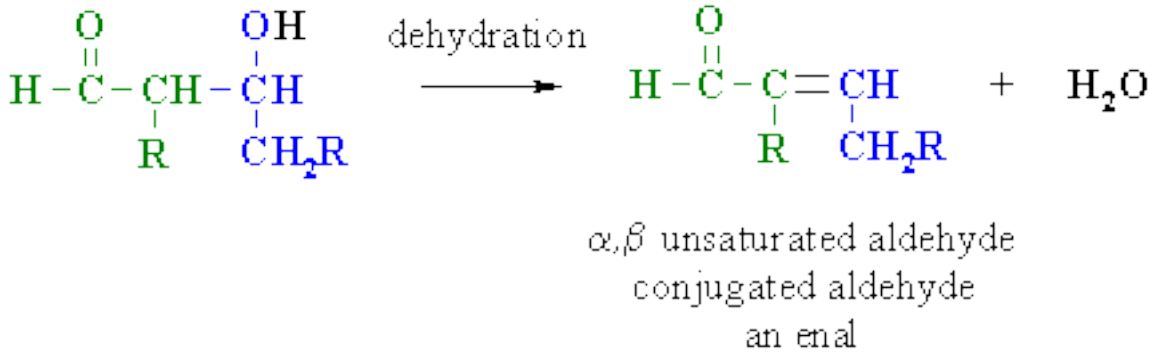


Figure 6

To recap, Aldol condensation depends mainly on two factors:

1. Acidity of α-H atom (hydrogen atom present next to carbonyl center)
2. Reactivity of carbonyl compounds

Here is an example to explain the above facts:

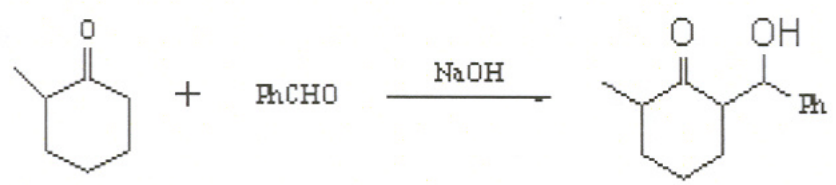


Figure 7

In methyl cyclohexanone two different types of acidic proton is present next to carbonyl center. Due to steric and electronic reasons, one proton is more acidic than the other; whereas benzaldehyde doesn't have any acidic proton. This is an example of Crossed aldol condensation. Depending on the position of hydroxyl group you can get a mixture of diastereomeric products. The dehydration step of an aldol condensation is also reversible in the presence of acid and base catalysts. Consequently, on heating with aqueous solutions of strong acids or bases, many α, β-unsaturated carbonyl compounds fragment into smaller aldehyde or ketones, a process known as the retro-aldol reaction.

The condensation is usually pushed to completion by dehydration; in some contexts the dehydration may be assumed to be part of the aldol condensation itself.The base-induced elimination is normally not seen with alcohols other than with aldols. This reaction probably proceeds via formation of an enolate, followed by loss of water molecule; formation of the, ß-unsaturated ketone makes up for the poor leaving group ability of

hydroxide. (Of course, with acid catalysis the dehydration follows the normal protonation/loss of water/loss of proton mechanism.) Either acid- or base-catalyzed dehydration is helped by increased temperature.

Several observations are necessary at this point.

1. All of the reactions shown above are reversible. You should be able, on your own to predict where each of the equilibria shown above should lie (is K > 1 or is K < 1?) 2. You should be able to predict how changes in structure will change the position of the equilibrium. (Examples: more or less bulky R groups in the ketone; ketones vs. aldehydes; electronic effects for electron-donating and electron-withdrawing groups.) 3. You should notice that the outcome of a mixture of carbonyl compounds depends on their structure: if there is no proton, no enolate can form and a cross-aldol condensation is possible. If both can form enolates, and both carbonyl groups are of similar reactivity, mixtures of products will result.

In this lab condensation between acetophenone and 4-nitrobenzaldehyde will take place. The reaction scheme as follows:

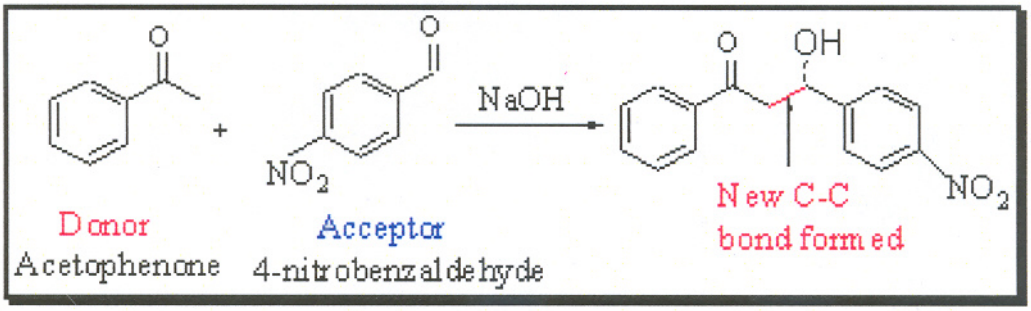


Figure 8

"Green Chemistry" is important from an environmental point of view. It requires fewer amounts of solvent and chemicals thought to be harmful to the environment. Though there are some possible drawbacks like (a) Low yield, (b) Slow reaction and (c) Increase in reaction cost, still we need to endeavor to keep our environment clean.

Exercise 1 Enter the letter of any compound that does not meet the structural requirements for the aldol condensation:

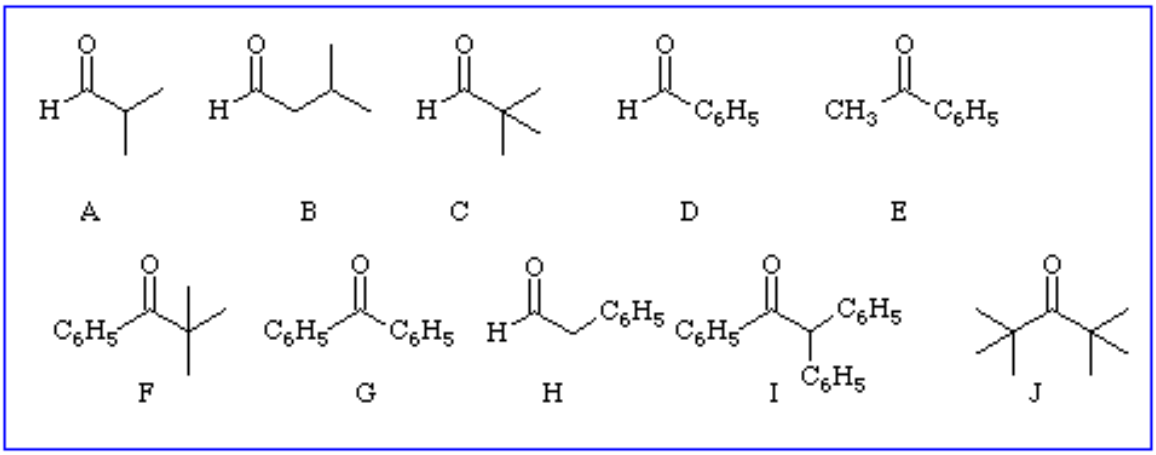


Figure 9

Answer: C, F etc. . . . . (Convince yourself)
Exercise 2 Write the letter of any β-hydroxyaldehyde or β- hydroxyketone?

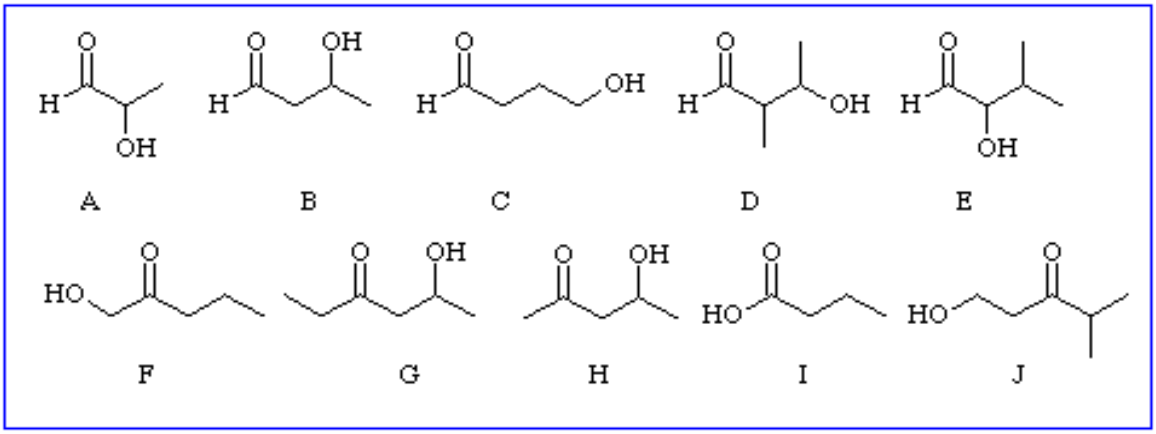


Figure 10

Answer: B, D etc. . . . . (Convince yourself)
Exercise 3 Each of the following compounds was prepared by an aldol condensation followed by dehydration. In each case, select the structure of the starting material from the list of choices in the box below.

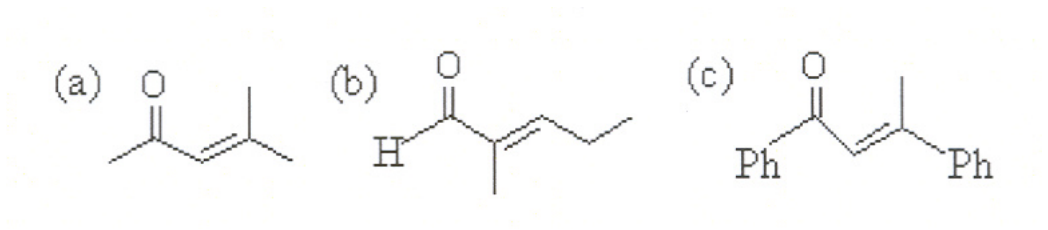


Figure 11

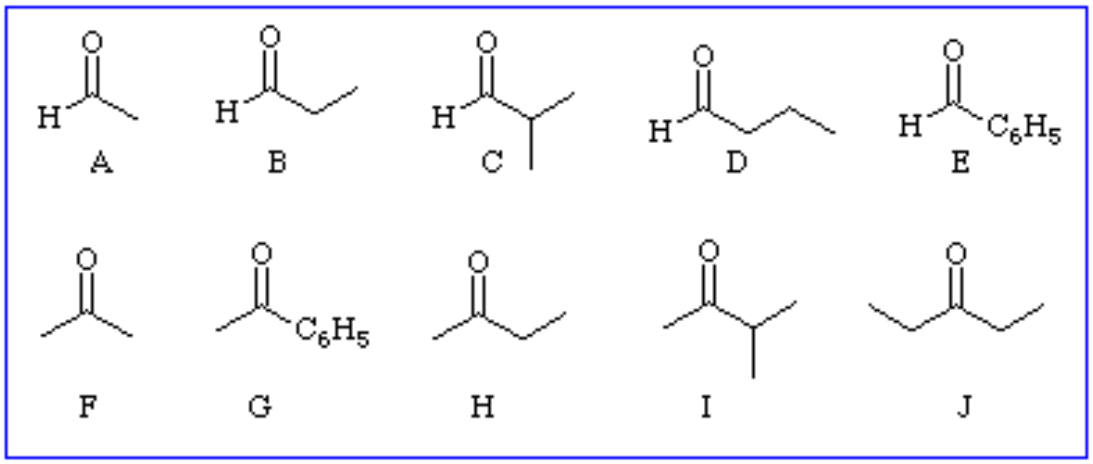


Figure 12

Answer: (a) FF (b) BB (c) _ _? _ _ (Convince yourself)

Exercise 4 Each of the following compounds was prepared by a crossed aldol condensation followed by dehydration. In each case, select the structures of the starting materials from the list of choices in the box above. Enter the letter of the compound that serves as the nucleophilic component followed by that of the electrophilic component. For example, the nucleophilic component used to prepare the first compound is A, while the electrophilic component is F.

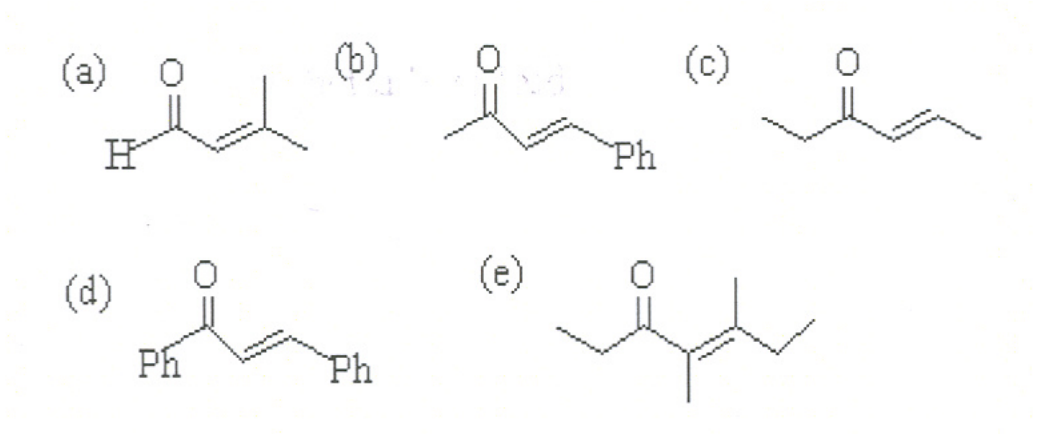


Figure 13

Answers: (a) AF (b)

2 Pre-Lab 2: Aldol Condensation (Total 10 points)

Click here[4] for the Pre-Lab

Name(Print then sign): _____

Lab Day: _____Section: _____TA_____

This assignment must be completed individually and turned in to your TA at the beginning of lab. You will not be allowed to begin the lab until you have completed this assignment.

1) Is this reaction acid or base catalyzed? Why do you need to use 1.0 M HCl at the end of the experiment? (2 points)

2) What is the role of p-nitro group in 4-nitrobenzaldehyde during the ALDOL reaction? What do you think would happen to the yield of the product if p-methoxy group was present instead of p-nitro group? (2 points)

3) Benzaldehyde (PhCHO) cannot undergo "ALDOL" reaction by itself in presence of strong base (KOH)- Why? (1 point)

4) Write the major product of the following reactions, if there is no product specifies it. (1+2+2 = 5 points)

[4] http://cnx.org/content/m15204/latest/image9.jpg/

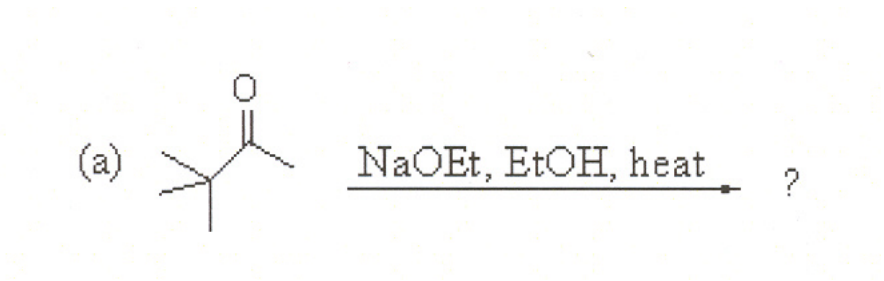


Figure 14

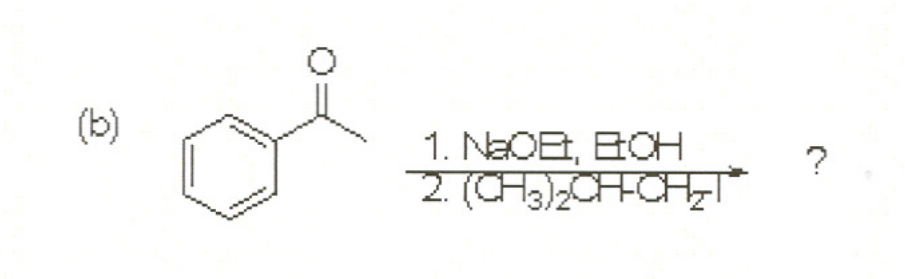


Figure 15

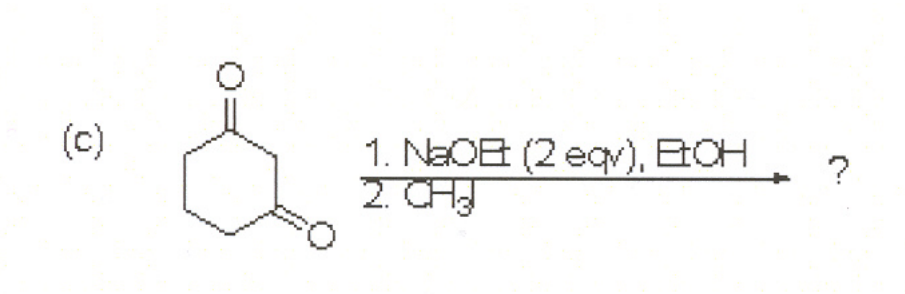


Figure 16

2.1 Grading

You will be assessed on:

- Completion of Pre lab questions.
- Write-up in your Lab Notebook (see Appendix:1 Lab Notebook Guidelines[5])
- Completion of Report questions.
- TA evaluation of lab procedure.

2.2 Materials Required

Equipment Chemicals

- Water Bath 4-nitrobenzaldehyde
- Stir bar Acetophenone
- Round bottom flask (10mL) Sodium hydroxide
- Funnel HCl (1.0 M)
- Beaker Ethanol
- Glass rod (for recrystalization) Filter paper

Safety

Wear gloves all the time, especially when working with NaOH and HCl. Keep safety glasses at all the times.

2.3 Experimental Procedure

You will be assigned either procedure A (traditional experiment procedures) or procedure B (green chemistry experiment procedures). Comparison of two methods: Give percent yield and melting point temperatures to the TA so that they can be written on the board and you can then collect everyones'data.

2.4 A. Traditional Experiment Procedure

Pre-heat your water bath to 60-70 °C.

1. Place a stir bar and 0.4 g of 4-nitrobenzaldehyde, 0.3 g of acetophenone and 0.10 g of sodium hydroxide in a 10 mL round bottom flask. NOTE: Acetophenone is a liquid with a density of 1.03 g/mL. Add 3.5 mL of 95% ethanol and heat the reaction mixture to 60-70 °C while stirring for 20 minutes. Do not overheat your product otherwise you will polymerize your sample.

Add 5 mL of ice-cold 1.0 M HCl, stir, and cool in ice for 10 minutes. If a semi-solid forms, you may need to continue stirring the cold mixture for a few minutes. Isolate the product by filtration with a funnel, and wash with 1-2 mL of water.

1. Scrape the crude product into a 30 mL beaker, add a magnetic stir bar, 1 mL of 95% ethanol, and heat with stirring at 70-80 °C. Add additional ethanol, 10 drops at a time, until the solids have dissolved. Cool to room temperature, and scrape the inside of the flask with a glass rod to induce crystallization. Once crystallization has begun, cool in ice for ten minutes, isolate your product by filtration on a Hirsch funnel, and wash with 1 mL of ice cold ethanol. Dry for 5 minutes in the funnel, then scrape onto a filter paper and let dry for 10 minutes.
2. Obtain the mass, melting point and IR of your recrystallized product.

Caution

Sodium hydroxide is hygroscopic in nature. Cap the vial immediately after every use. Do not over heat in step 3, over heating may cause a black tar substance that is due to the decomposition of your product to form.

[5] http://cnx.org/content/m15204/latest/file:///var/local/Chem%20215/Aldol/notebook.html

2.5 B. Green Chemistry Experimental Procedure

Pre-heat your water bath to 60-70 °C.

1. Place a stir bar and 0.4 g of 4-nitrobenzaldehyde and 0.3 g of acetophenone in a 10 mL round bottom flask. NOTE: Acetophenone is a liquid with a density of 1.03 g/mL. Weigh out 0.10 g of sodium hydroxide and crush into a powder with a spatula or the flat bottom of a 5 mL conical vial. Add the powdered NaOH to the 10 mL round bottom vial with the other reagents. Grind the "semi-solid" mixture with a glass stirring rod at 60-70 °C until thoroughly mixed, and continue grinding for a further two minutes. Wait 5 minutes, and then grind again for two more minutes. Repeat for three more cycles of grinding and waiting.
2. After grinding the reaction mixture for a total of ten minutes, add 5 mL of ice-cold 1.0 M HCl, stir, and cool in ice for 10 minutes. If a semi-solid forms, you may need to continue stirring the cold mixture for a few more minutes. Isolate the product by filtration on a Hirsch funnel, and wash with 1-2 mL of water.
3. Scrape the crude product into a 30 mL beaker, add a magnetic stir bar, 1 mL of 95% ethanol, and heat with stirring at 70-80 °C. Add additional ethanol, 10 drops at a time, until all the solids have dissolved. Cool to room temperature, and scrape the inside of the flask with a glass rod to induce crystallization. Once crystallization has begun, cool in ice for ten minutes, isolate your product by filtration on a Hirsch funnel, and wash with 1 mL of ice-cold ethanol. Dry for 5 minutes in the funnel, then scrape onto a watch glass and allow it to dry for 10 minutes.
4. Obtain the mass, melting point and IR of your recrystalized product.
5. One sample will be taken for NMR studies.

Caution

Carefully grind the NaOH. Do not add ethanol in the first step. Ethanol is required only during recrystalization.

3 Report Questions:

(Total 30 points)

Click here[6] for the Report Form

Note: In preparing this report you are free to use references and consult with others. However, you may not copy from other students' work (including your laboratory partner) or misrepresent your own data (see honor code).

Name(Print then sign): _____

Lab Day: _____Section: _____TA_____

1. Illustrate the complete chemical mechanism between 4-nitrobenzaldehyde, acetophenone and sodium hydroxide. (6 points)

2. Show your theoretical and percent yield calculations for the reaction. (4 points)

3. The melting point of your recrystallized product is: _____(2 points)

4. What significant IR stretches is seen and what functional groups do they correspond to? (4 points)

5. A NMR spectrum will be provided of the product. Assign each peak with a proton from your structure. Can you see any impurities? (6 points)

6. Which method (Traditional or Green chemistry) did you think was most successful and why? (3 points)

7. Write the major product of the following reactions: (2+1+2=5 points)

[6] http://cnx.org/content/m15204/latest/AldolReport07.doc

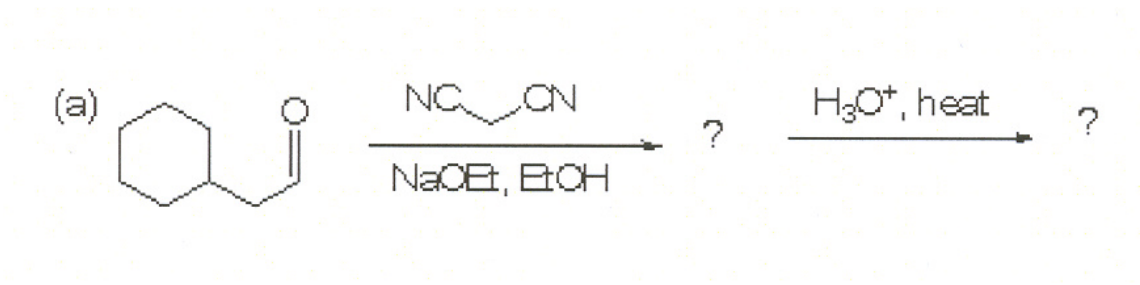
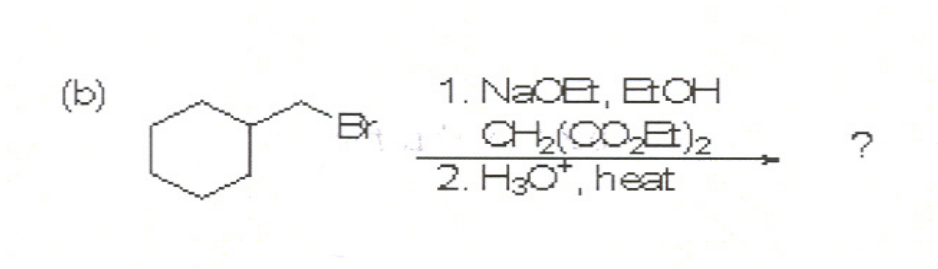

(a)
NC CN
NaOEt, EtOH
?
H3O+, heat
?

Figure 17


(b)
Br
1. NaOEt, EtOH
CH2(CO2Et)2
2. H3O+, heat
?