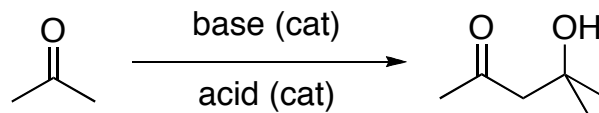


## ALDOL CONDENSATION

Condensation is a reaction between two or more molecules that leads to the formation of a larger molecule and an elimination of a smaller molecule (usually water). Aldol condensation refers to reactions that involve carbonyl-containing compounds, *i.e.*, aldehydes and ketones, which yield  $\beta$ -hydroxy carbonyl products – aldol (aldehyde+alcohol). If both partners in the condensation processes are the same – the reaction can be referred to as *self-condensation*. An example of self-condensation is shown in Scheme 1.



Scheme 1

The aldol reactions are catalyzed by either an acid or a base. The reason for such ambivalent nature stems from the ability of

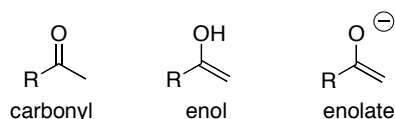
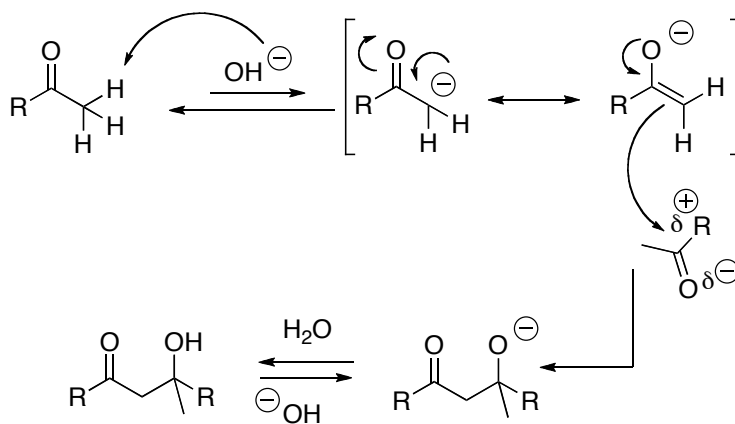


Figure 1

carbonyl compounds to act either as electrophiles or as nucleophiles. In either case, an enol or enolate ion act as nucleophilic species (Figure 1), which react with the electrophilic center of the carbonyl compound. The detailed mechanism of a base-catalyzed aldol condensation is shown in Scheme 2.

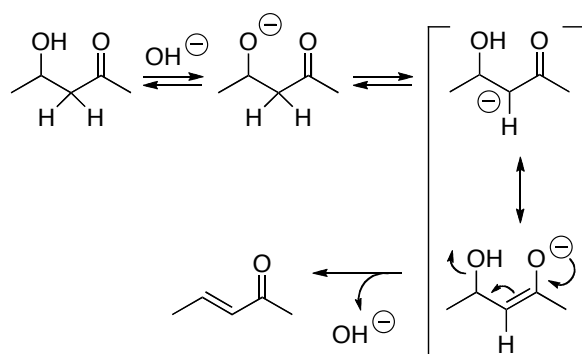
The reaction starts with a formation of the enolate ion species, upon abstraction of a proton from acetone (not that in this step acetone is acting as an acid) by a base, *i.e.*,  $\text{OH}^-$ . Enolate is stabilized via resonance: the negative charge can be stabilized due to the close proximity of the carbonyl moiety. Once the enolate ion is formed, it can act as a nucleophile towards the electrophilic center of another molecule of acetone. Once the condensation product is formed, it can get protonated at the work-up step to yield 5-hydroxy, 5-methyl-pentan-2-one.



Scheme 2

Acid-catalyzed aldol reaction proceeds in a similar manner. One notable distinction from the base-catalyzed aldol condensation is that in the first step, acetone will act as a base that accepts a proton, which leads to the formation of the enol. This enol can now react as a nucleophile.

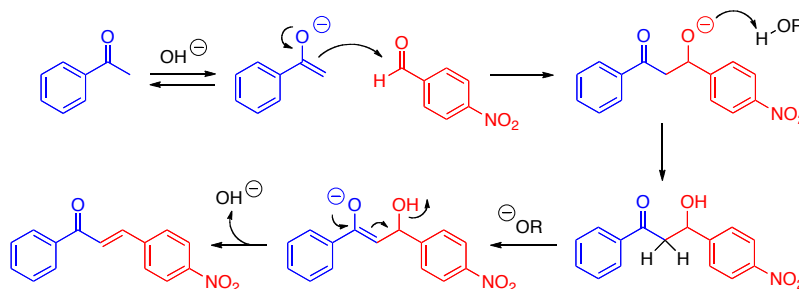
The aldol products are very susceptible to a dehydration reaction, *i.e.*, the loss of water. The dehydration of aldol products can take place under both acidic and basic conditions. This



Scheme 3

process is fairly facile, since the loss of water leads to a product (enone) that is stabilized by conjugation. Therefore, for the synthesis of  $\beta$ -hydroxy carbonyl products elevated temperature and excess of the base/acid should be avoided to prevent the dehydration step. Otherwise, aldol reaction followed by the dehydration presents a convenient, one-pot preparation of enones, which are valuable synthons in various organic transformations. The mechanism of the base-catalyzed dehydration step is shown in Scheme 3.

In those instances when the carbonyl compounds are different, the aldol condensation can be referred to as *cross-condensation*. Under these conditions, a mixture of 3 products might be expected. In order to obtain a clean reaction, which is leading to the production of only one product, the carbonyl compounds should be carefully chosen. The idea is quite simple – by having one carbonyl component that can easily be converted into an enolate and by making one partner very electrophilic (or unable to undergo an enolization), it might be possible to achieve a selective cross-condensation, and avoid self-condensation reactions. For example, a base-catalyzed aldol condensation between acetophenone, and 4-nitrobenzaldehyde (Scheme 4).

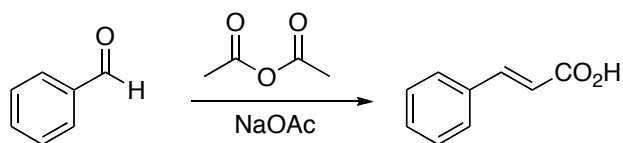


Scheme 4

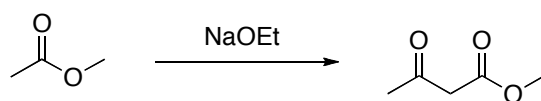
The benzaldehyde cannot undergo the enol tautomerization, simply because it does not have an  $\alpha$ -hydrogen. In addition, this aldehyde is very electrophilic, due to the electronegative effect of the nitro-group. Thus, acetophenone is the only carbonyl compound that can react with the base, *i.e.*,  $\text{OH}^-$  or  $\text{OR}^-$ . The subsequent steps, leading to the formation of the enone are similar to the processes of the aldol condensation described in Scheme 3.

There are other types of base-catalyzed condensations that involve carbonyl compounds. Several important examples are shown in Scheme 5. Mechanistically, all these reactions rely on the generation of a nucleophile, and subsequent attack on the electrophilic carbon of the carbonyl moiety; in many cases, elimination of a good leaving group takes place to produce compounds with enhanced stability due to conjugation paradigms

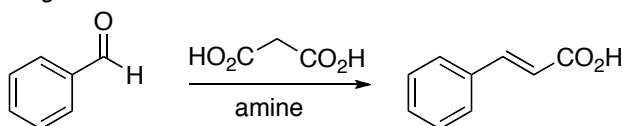
*Perkin condensation*



*Claisen condensation*



*Knoevenagel condensation*

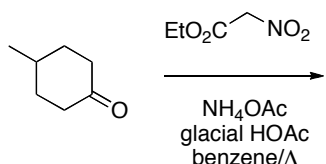
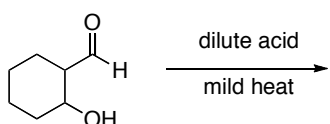
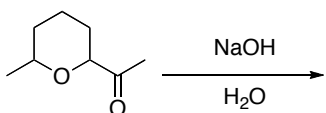
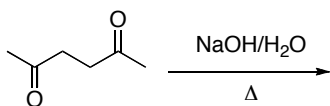


Scheme 5

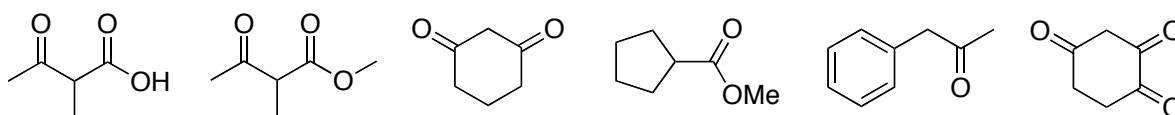
## PROBLEMS

Some questions are based on the material covered in the lecture

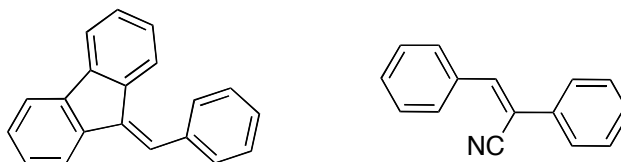
1. Provide the major products of the following reactions:



2. Write all possible products of the reaction between acetophenone and p-anisaldehyde, and indicate which one is going to be the major one and why?
3. 2-Pentanone can undergo a self-condensation aldol reaction. Write all possible products.
4. Identify the most acidic and the least acidic hydrogens in each of the following compounds:



5. Suggest the reagents for the synthesis of the following compounds:



6. A student was supposed to carry an aldol reaction between benzaldehyde and acetone, in ethanolic solution of NaOH. However, after adding benzaldehyde to NaOH the student went to ask the instructor about grading on the last report. After the chat was over, the student came back to add acetone, but noticed that a white precipitate was formed in the reaction flask. What is the precipitate and how did it form? (Hint: Cannizzaro reaction).
7. Would you expect any self-condensation products to be forming in this week's experiment (next page)? Briefly explain why yes or why no.