ORGANIC SYNTHESIS: ALDOL CONDENSATION REACTION

TECHNIQUES REQUIRED:

Filtration (Vacuum), Recrystallisation, Melting Point Determination, Yield calculation

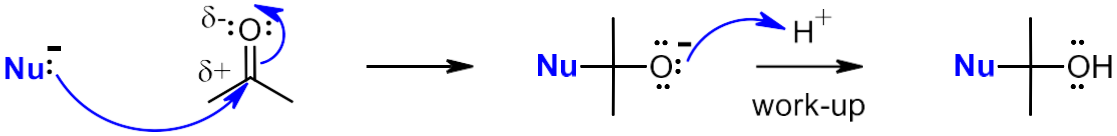
OTHER DOCUMENTS: Experimental Procedure, Report template

INTRODUCTION

Most of the techniques in this procedure are standard, common but important techniques that were first encountered in Chem 351 laboratories. However, we recommend that you review the techniques links at the top of this page because we expect you will know how to use them during your in-person laboratory session. As part of your preparation, make sure to watch this YouTube video of someone doing this reaction. https://www.youtube.com/watch?v=yfy57Gc8VfM Pay attention to the various steps of the procedure, especially the vacuum filtration and the discussion of the mechanism.

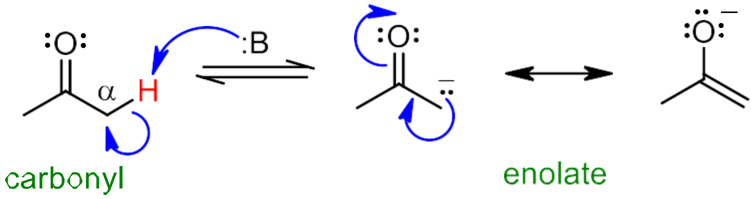
Aldehydes and ketones are very important functional groups[1] in organic chemistry primarily because of the diversity of the reactions that they undergo. They are closely related to each other, sharing some common ground. There are two important but contrasting reactivity patterns for these systems:

- Aldehydes and ketones have **electrophilic character** at the carbonyl C (see δ+ below) and therefore react with **nucleophiles** ultimately undergoing what is described as nucleophilic addition[2]:



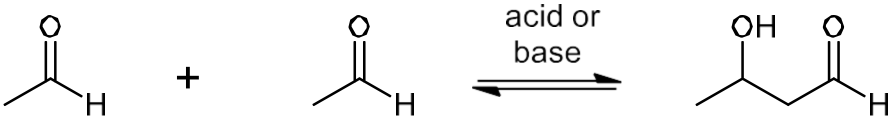
Nucleophilic Addition under **BASIC** conditions with stronger nucleophiles

- Treatment of aldehydes and ketones with a suitable base (*i.e.* strong enough) can lead to the formation of a **nucleophilic species** that are called enolates[3] (review this in acidity/basicity from Chem 351). Enolates typically undergo reaction as a carbon nucleophile with **electrophiles** such as alkyl halides or even other carbonyl systems. In order for a base to be able to react with a carbonyl containing compound to form an enolate, there must be an H atom on the C atom **adjacent** to the C=O group in the aldehyde or ketone. This leads to the formation of a resonance stabilised enolate which makes these C-H bonds on the α-carbon (typical pKa 16-20) much more acidic than simple alkane sp^3 C-H bonds (typical pKa 50+)



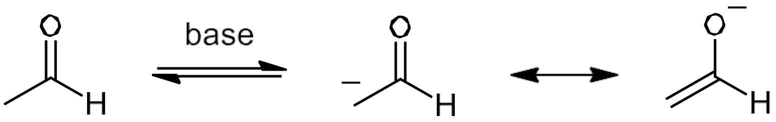
This laboratory activity on the “aldol condensation reaction” involves both of these aspects of aldehyde and ketone reactivity.

In an "*aldol addition*" reaction, an enol or more commonly the more nucleophilic enolate of an aldehyde or ketone reacts with a second aldehyde or ketone forming a **new carbon-carbon bond**. This makes the aldol reaction an important reaction for organic synthesis. Originally, the ***aldol reaction*** used ethanal (see below) and therefore the product contained both an **ald**ehyde and an alcoh**ol** functional group; thus it became known as the **aldol** reaction.



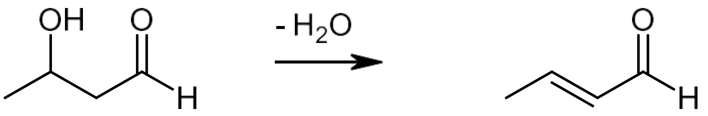
As shown above, aldehydes and ketones typically undergo nucleophilic addition reactions. The aldol reaction demonstrates how carbonyl compounds can react as electrophiles or nucleophiles depending on the reaction conditions and what other species are present. Alcohols are similar in that respect (can you think of examples to illustrate that ?). The aldol reaction requires an aldehyde or ketone that contains at least one α-hydrogen (the α-hydrogen is on the carbon **adjacent** to the C=O group) since the α-hydrogen is required in order to form the enol or enolate.

In the base-catalysed aldol reaction, the relatively acidic hydrogen on the α-carbon (typical pKa 16-20) is deprotonated by a base to form the enolate. The enolate reacts as a carbon nucleophile that can then react with the electrophilic carbonyl carbon of another aldehyde or ketone molecule. Depending on the strength of the base used, the extent of deprotonation can be controlled. If a strong base is used (such as lithium diisopropylamide, LiN(CH(CH$_3$)$_2$)$_2$ = LDA, approx. pKa = 36), then deprotonation is quantitative (100%). If weaker bases such as hydroxide or alkoxides (approx. pKa = 15) are used, then there is equilibrium deprotonation (*i.e.* only a small amount of enolate is present at any one time).

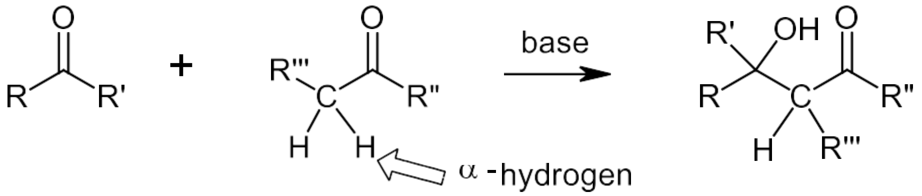


enolate resonance contributors

The equilibrium for the aldol reaction can lie in the direction of reactants or products, depending on their structure and the reaction conditions. The aldol product can often undergo elimination of water (*i.e.* dehydration) to give an α,β-unsaturated aldehyde or ketone, that contains a conjugated carbonyl group. The overall process is then referred to as an "***aldol condensation***".

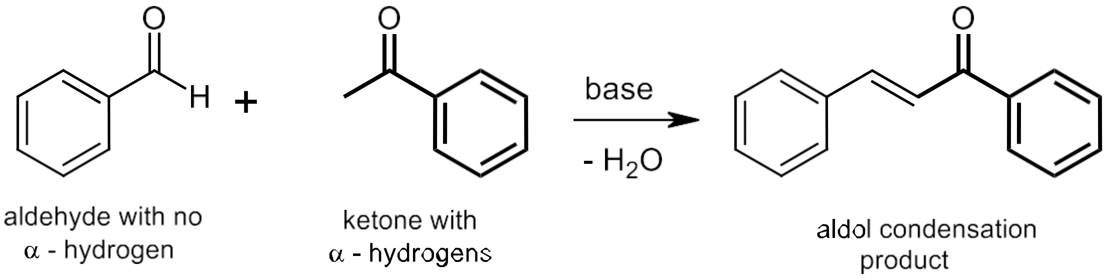


The example using ethanal shown above only involves one starting material and is therefore referred to as a "self condensation". "Mixed" or "crossed" aldol condensations occur when two different molecules containing carbonyl groups are combined. Intramolecular versions of these reactions are also possible.

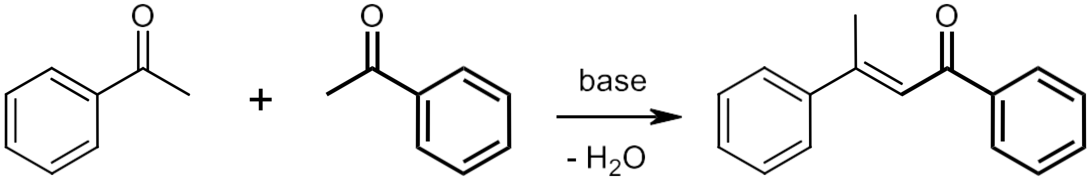


A generic mixed aldol reaction where two different carbonyl-containing molecules are mixed together.

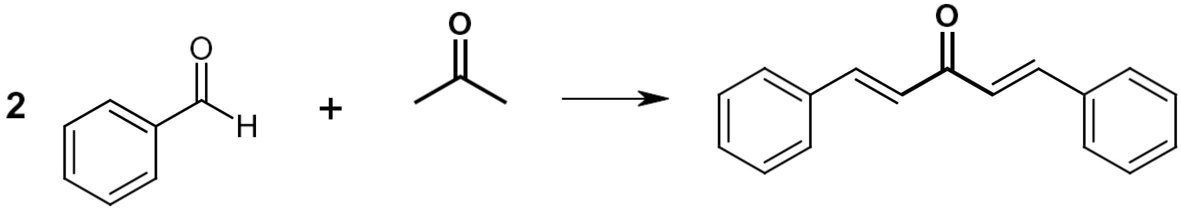
In terms of the scope of the reaction, the R-groups can be alkyl, aryl or H. This ability to join different aldehydes and ketones together with some degree of control is what gives this process its synthetic value. Typically, a mixed aldol condensation is only practical if one of the compounds has no α-hydrogens – thus only one enol or enolate is generated and so there is only a single nucleophile formed. The mixed aldol reaction typically occurs between an aldehyde that has no α-hydrogens, and a ketone. Thus, the nucleophile is generated solely from the ketone. The aldehyde is usually more reactive towards nucleophiles than the ketone, further reducing the possibility of the ketone undergoing unwanted self-condensation. Minimizing any unwanted self-condensation of the ketone can also be achieved by taking care with the order in which the reagents are added. In the example below, the ketone would be added to a mixture containing the aldehyde and the base. This means that the ketone enolate forms in the presence of excess aldehyde.



In contrast, prolonged contact between the ketone and base in the absence of the aldehyde can result in self-condensation of the ketone (in this case an unwanted side reaction).



In this experiment you will be reacting two equivalents of benzaldehyde with propan-2-one, according to the following general scheme:



This product can be used as a sunscreen as the conjugated system including the aromatic, alkene and carbonyl units create a chromophore that allows the molecule to absorb high energy uv radiation and so preventing the uv radiation from damaging the cells in the skin.

REFERENCES

1. Organic Chemistry On-Line Learning Center Chapter 17, “Aldehydes and Ketone. Nucleophilic Addition to C=O” https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch17/ch17-0.html
2. Organic Chemistry On-Line Learning Center Chapter 17 “Nucleophilic Addition” https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch17/ch17-3-0.html
3. Organic Chemistry On-Line Learning Center Chapter 18; “Enols and Enolates” https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch18/ch18-0.html