

9.8: THE CLAISEN CONDENSATION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate a Claisen condensation reaction.
2. write a detailed mechanism for a Claisen condensation reaction or its reverse.
3. identify the product formed in a given Claisen condensation reaction.
4. identify the ester and other reagents needed to form a given β -keto ester by a Claisen condensation reaction.

KEY TERMS

- Claisen condensation reaction

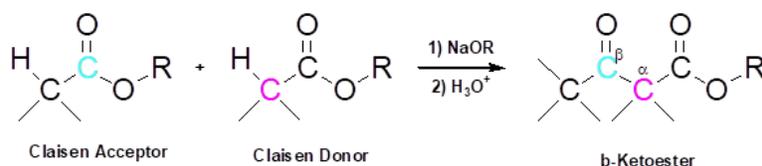
STUDY NOTES

You have already seen that ethyl acetoacetate-type compounds are very useful in organic syntheses. Any reaction which results in the formation of these compounds will also be of importance. In the next section, you will see how the range of β -keto esters that can be prepared by this method is extended through the use of two different esters as starting materials.

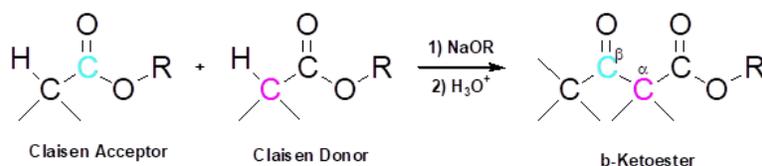
CLAISEN CONDENSATION

Because esters commonly contain both α -hydrogens and a carbonyl bond, they can undergo a reversible condensation similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol reaction, one ester acts as a Claisen enolate donor (nucleophile) while a second ester acts as the Claisen acceptor (electrophile). During the reaction a new carbon-carbon is formed to produce a β -keto ester product. This reaction is considered a condensation because it eliminates a small alcohol as an unwanted side-product.

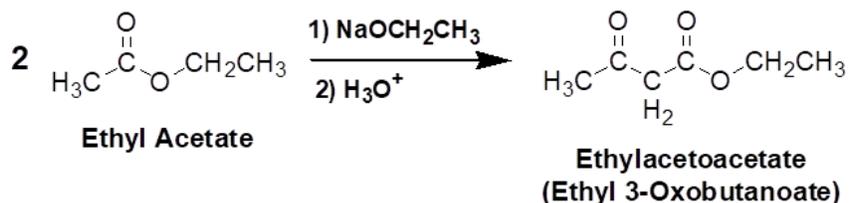
GENERAL REACTION



PREDICTING THE PRODUCT OF A CLAISEN CONDENSATION



EXAMPLE

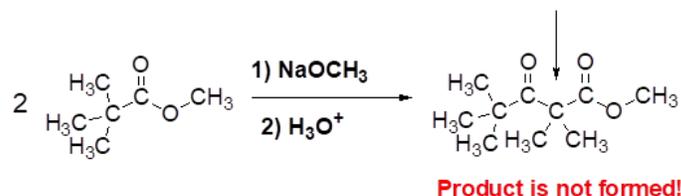


Although they may appear similar, there are a number of fundamental differences between an aldol and Claisen condensation. During the mechanism of the reaction, the formed tetrahedral alkoxide intermediate is not protonated to form an "aldol" type product. Rather, the alkoxide intermediate will reform the $C=O$ carbonyl bond and eliminate a ($-OR$) leaving group to produce a nucleophilic acyl substitution product.

Claisen condensations cannot use a hydroxide for the reaction base due to the possibility of ester hydrolysis. Also, to prevent transesterification side products, the alkoxide base typically has the same alkyl group as alkoxy group present in the ester starting material.

Lastly, the β -keto ester products of Claisen condensation can be acidic enough to be deprotonated by the reaction's base during the final steps of the mechanism. This means the base is not catalytically regenerated during the reaction and a full equivalent of base is required. The β -keto ester condensation products are removed from the equilibrium by this deprotonation, which causes the reaction to be driven forward by Le Chatelier's principle. This concept is so important that a Claisen product will not form unless it contains an alpha hydrogen acidic enough to react completely with the reaction base. This requires that the ester starting materials have at least two alpha-hydrogens for a Claisen condensation product to form. One is removed to form an ester enolate and the second is removed to drive the reaction forward.

No Acidic Alpha Hydrogens

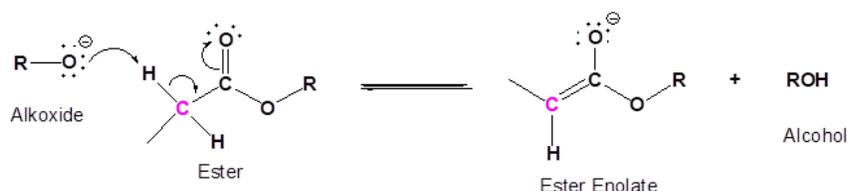


MECHANISM

The Claisen condensation mechanism is analogous to the ester saponification reaction seen in [Section 21.6](#).

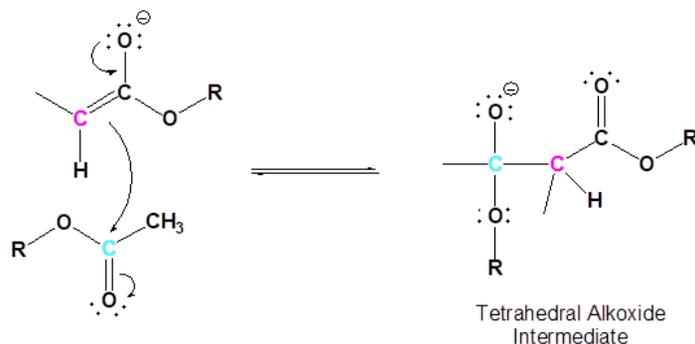
1) ENOLATE FORMATION

The mechanism starts with the alkoxide base removing an alpha-hydrogen from the ester to form a nucleophilic ester enolate ion.



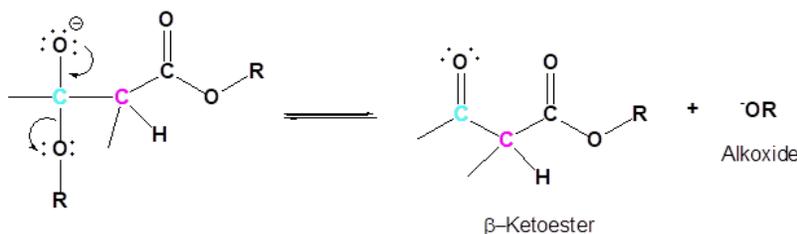
2) NUCLEOPHILIC ATTACK

The enolate nucleophile adds to the carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



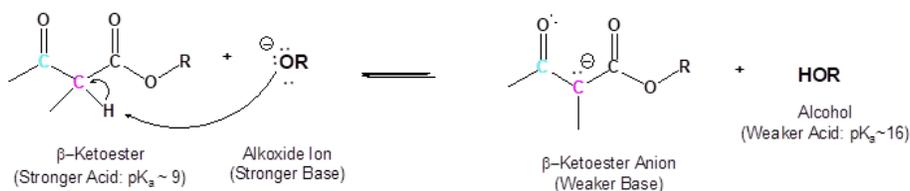
3) REMOVAL OF LEAVING GROUP

The alkoxide then reforms the carbonyl, eliminating the $-OR$ leaving group to form a β -ketoester.



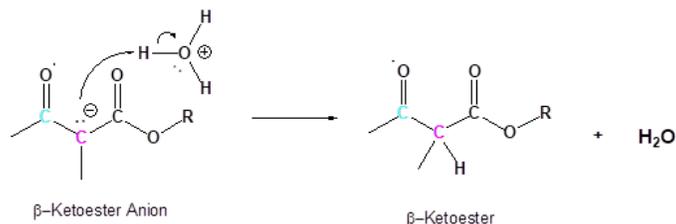
4) DEPROTONATION

The acidity of β -ketoesters ($pK_a \sim 9$) is high enough to allow them to be completely deprotonated by alkoxide bases (pK_a of an alcohol ~ 16) to form a second enolate. This makes the equilibrium of this step very favorable, which is enough to drive the whole reaction towards the product.



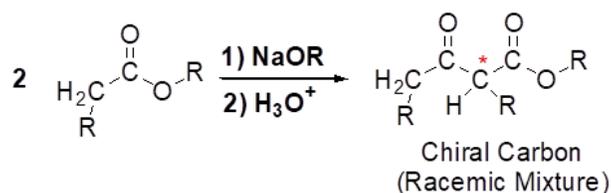
5) PROTONATION

The enolate is protonated in an acid work-up to form the neutral beta-ketoester product.



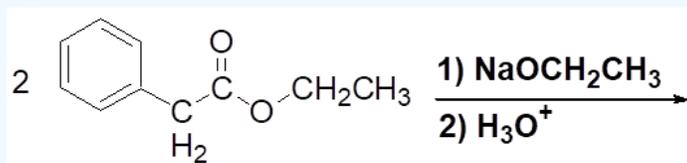
Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction which means it will most likely form a chiral carbon. The fact that the alpha-carbon is temporarily converted to an enolate in the last step of the mechanism means that a racemic mixture of enantiomers will form.



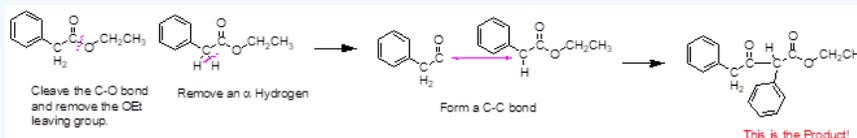
? WORKED EXAMPLE

Draw the products of the following reaction:



Answer

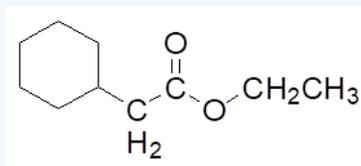
Analysis: Remember to consider each start ester separately.



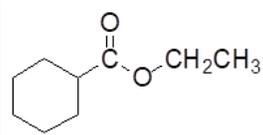
? EXERCISE 9.8.1

Please draw the products if the following molecules were to undergo a Claisen condensation.

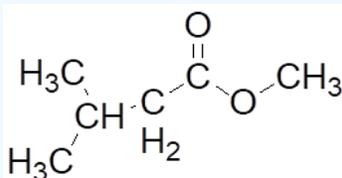
a)



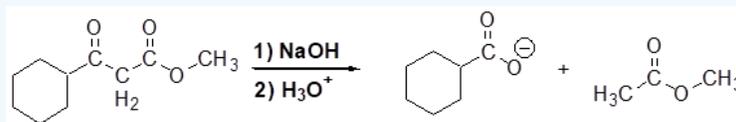
b)



c)

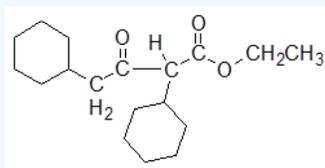


2) The beta-keto ester product of a claisen condensation can under hydrolysis with Sodium Hydroxide as shown in the reaction below. Please draw a curved arrow mechanism to explain how the products are formed. Also, explain why the ketone functional group preferably reacts with hydroxide instead of the ester.

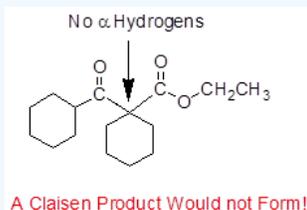


Answers

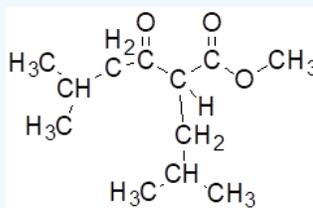
a)



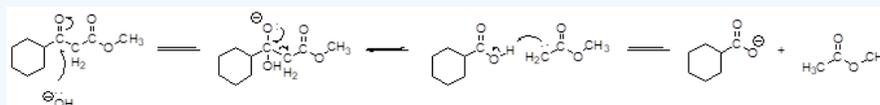
b)



c)



2) The carbonyl of the ketone is more likely to be attacked by the hydroxide nucleophile because is more reactive than the ester's



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