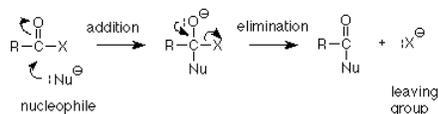


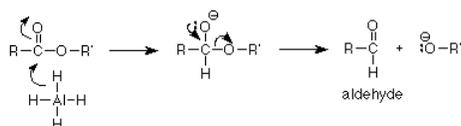
## 1.10: Carboxylic Acid Derivatives - Alpha Carbon Reactions

### Reduction of Esters - Lithium Aluminum Hydride

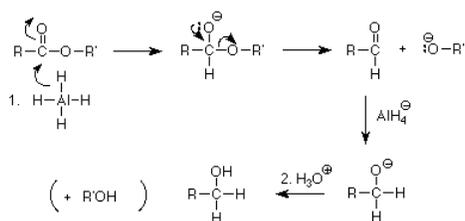
We've seen that carboxylic acid derivatives react with nucleophiles to give substitution products in which the leaving group is replaced by the attacking nucleophile.



This same pattern describes the first steps in the reaction of esters with lithium aluminum hydride and Grignard reagents, but in both cases the reaction proceeds further because the first product formed also reacts with the reagent. For an example, let's look at the reduction of an ester with lithium aluminum hydride.



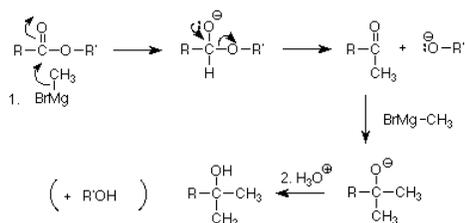
When the "hydride ion" ( $\text{H}^-$ ) from lithium aluminum hydride replaces the  $\text{OR}'$  group of the ester, an aldehyde is formed. We've already seen that an aldehyde is reduced by lithium aluminum hydride, so it comes as no surprise that the aldehyde is immediately reduced to a primary alcohol. In fact, the aldehyde is more electrophilic than the ester, so as soon as a few molecules of aldehyde are formed, they are attacked by the hydride in preference to the ester. The reaction is completed by the later addition of aqueous acid to protonate the  $\text{O}^-$  atoms.



The result is that esters are reduced by lithium aluminum hydride to primary alcohols in which the ester carbon has become the alcohol carbon. Sodium borohydride is not reactive enough to carry out this reduction. This is a useful way to make primary alcohols.

### Reaction of Esters with Grignard Reagents

A very similar process occurs when an ester reacts with a Grignard reagent. Remember that the Grignard reagent serves as a source of carbon nucleophiles. We can use the same pattern as worked for the lithium aluminum hydride reduction by replacing the " $\text{H}^-$ " with the " $\text{C}^-$ " from the Grignard reagent. Here's an example in which the Grignard reagent is methylmagnesium bromide:



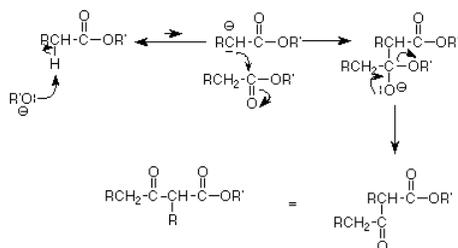
Here the first product is a ketone in which the  $\text{OR}'$  group of the ester has been replaced by the alkyl group of the Grignard reagent. This ketone is immediately attacked by another molecule of the Grignard reagent. After neutralization with aqueous acid the product is an alcohol in which the two identical groups attached to the alcohol carbon are from the Grignard reagent. If the R group of the ester is a carbon group this will be a tertiary alcohol.

In both these cases, we've combined a the general pattern for carboxylic acid derivatives, substitution of the nucleophile in place of the leaving group, with a pattern which applies to aldehydes and ketones, to arrive at "double" reaction. The first part is substitution and the second part is addition. We can't stop the reaction halfway, because aldehydes and ketones are more reactive than esters, so the aldehydes and ketones gobble up the reagent faster than the esters.

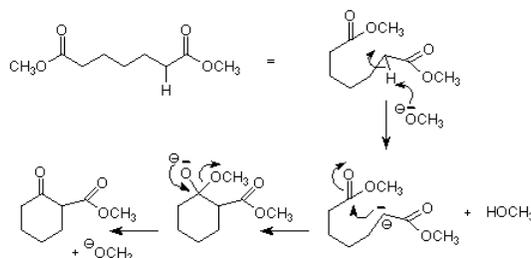
## Claisen and Dieckmann Condensations

We spent some time on the aldol condensation when we were studying aldehydes, and we learned that the alpha C-H bonds of aldehydes and ketones can be attacked by base to form enolates. The same thing can occur with esters, although we need to be very specific about the identity of the base we use -- it needs to be the same as the OR' (alcohol derived) portion of the ester. (Consider what would happen if the base and the OR' group were different. The base would attack the carbonyl carbon and would replace the OR' group. A new and unwanted product would appear. If the base is the same as the OR' group, attack by the base on the carbonyl carbon results in no net change and keeps the reaction simpler.)

The first step in such a reaction is strictly analogous to making an enolate from an aldehyde. This is followed by attack of the nucleophilic alpha carbon of the enolate on the carbonyl carbon of a second molecule of the ester. Again, this is strictly analogous to the situation in the aldol reaction, and it has resulted in a nucleophilic addition to the carbonyl carbon. As is typical for carboxylic acid derivatives, the next step is loss of the leaving group, so that the carbonyl group which has been added to shows up as a ketone. (Since the newly-formed ketone is in a beta position relative to the ester functional group these compounds are called beta-keto-esters.) This overall reaction is called the Claisen condensation after Ludwig Claisen, a prominent German organic chemist of the late 19th and early 20th centuries.



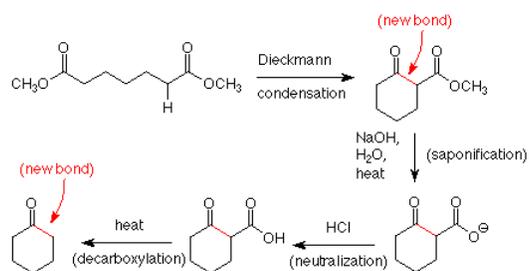
When there are two ester groups on the same carbon chain (a **diester**), the enolate formed at the alpha carbon atom of one ester group can react with the carbonyl carbon of the other ester group.



The resulting Claisen condensation makes a ring of carbon atoms. If this ring has five or six carbons in it, it forms readily. This (*intramolecular* variation of the Claisen condensation is called the Dieckmann condensation. Since many organic compounds which occur in nature have five or six membered rings, the Dieckmann condensation has been widely used in synthesis.

## Decarboxylation and Ketone Synthesis

Notice that both the Claisen condensation and its Dieckmann condensation variant make a compound we can call a *beta-keto-ester*, that is, an ester with a keto group on the carbon two atoms away from the carbonyl carbon. Such beta-keto-esters can be hydrolyzed to beta-keto-acids by base-promoted hydrolysis ([saponification](#)) and acidification. The beta-keto-acids readily lose a molecule of carbon dioxide when heated to form a ketone. This means that a Dieckmann or Claisen condensation can be followed by a hydrolysis-decarboxylation step to form a ketone. This gives us a way to make ketones. Notice that the new carbon-carbon formed in this sequence is one which joins a carbonyl carbon to one of its alpha carbons. Here's an example of the use of this synthetic sequence of reactions to make cyclohexanone:



We'll look at some of the details of the saponification reaction next time.

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