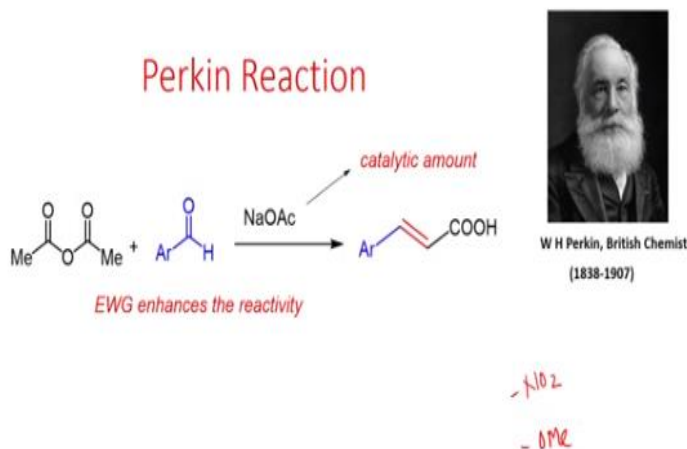


Principles of Organic synthesis
Professor: T. Punniyamurthy
Department of Chemistry.
Indian Institute of Technology Guwahati
Lecture 2: Base-Catalyzed Carbon-Carbon Bond Formation

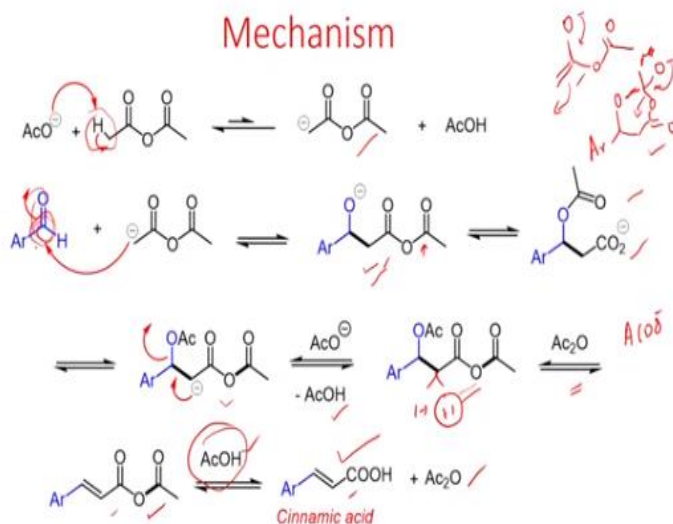
Welcome you all to Principles of Organic Synthesis. In the first lecture, we studied base catalyzed carbon-carbon bond formation. In continuation, in this lecture, we will study Perkin reaction, Claisen condensation and Thorpe reaction. The scheme for the Perkin reaction is shown here.

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Aromatic aldehyde undergoes condensation with acid anhydride in the presence of base to give cinnamic acid. You need a catalytic amount of base for this transformation. If you have electron withdrawing group in the aromatic ring, for example, nitro group the reaction is facilitated. On the other hand, if you have electron donating group like methoxy group, the reaction is slowed.

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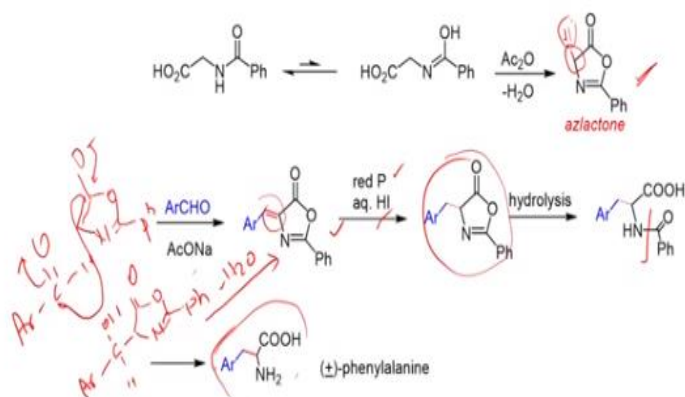


The mechanism for this reaction is shown here. Deprotonation of the acidic hydrogen of acetic anhydride gives carbanion, which can be stabilized by the carbonyl group. The carbanion can then react with aldehyde to give an addition product, which can undergo intramolecular acyl transfer via cyclic transition state to give a carboxylate. Acylation of the carboxylate with acetic anhydride can give anhydride derivative, which can undergo E1_{cB} elimination followed by hydrolysis to produce cinnamic acid.

Using this method, you can make substituted cinnamic acids. As I mentioned earlier, if we have electron withdrawing substituent in the aryl ring, the reaction is accelerated, which may be due to an increase of the electrophilicity of the carbonyl group. On the other hand, if you have electron donating group, it can reduce the electrophilicity of the carbonyl group that slows the reaction.

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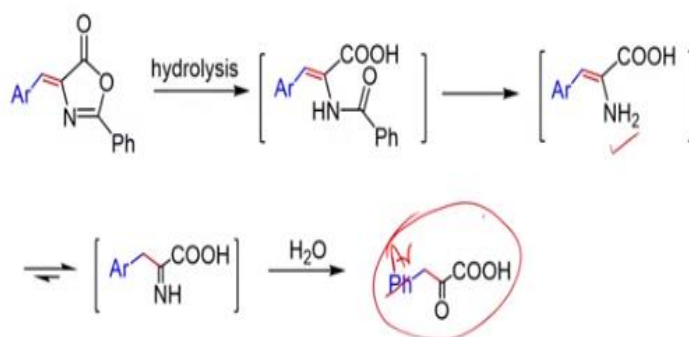
α-Amino Acid Synthesis



Benzyl protected glycine with acetic anhydride gives azlactone. When you react with sodium acetate, which can deprotonate the active methylene hydrogen. The resultant carbanion can react with aromatic aldehyde to give the addition product, which can lead to dehydration. Reduction of the double bond using red phosphorus and aqueous hydrogen iodide can give the benzyl derivative that can be converted into carboxylic acid. If you do further hydrolysis and deprotect the benzyl group that can lead to the formation of substituted phenylalanine.

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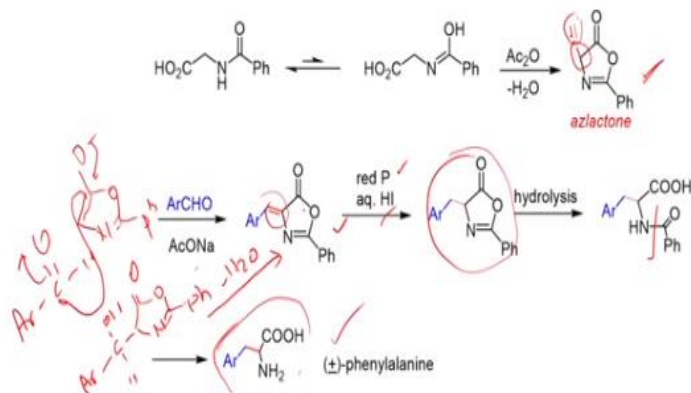
α-Keto Acid Synthesis



You can also do hydrolysis of the intermediate to give α-keto carboxylic acid.

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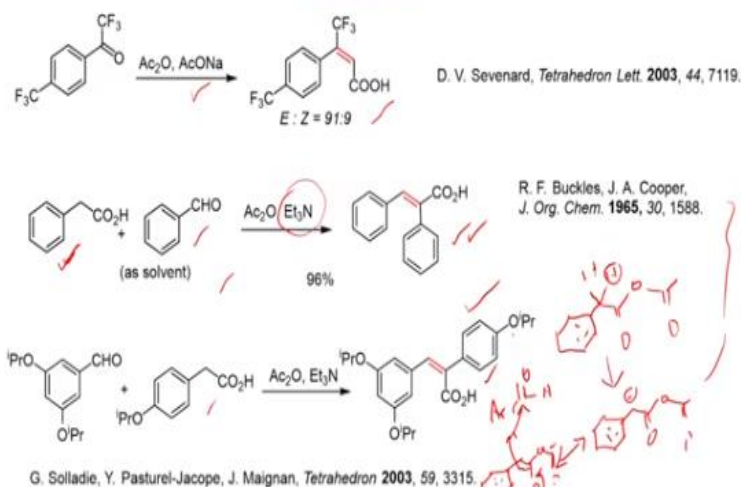
α -Amino Acid Synthesis



This protocol basically involves the aldol reaction. Deprotonation of azlactone produces carbanion, which undergoes addition with aromatic aldehyde to give aldol that can dehydrate to give the condensation product. Which can further convert to phenylalanine. Alternatively, you can do hydrolysis to get the α -keto carboxylic acid.

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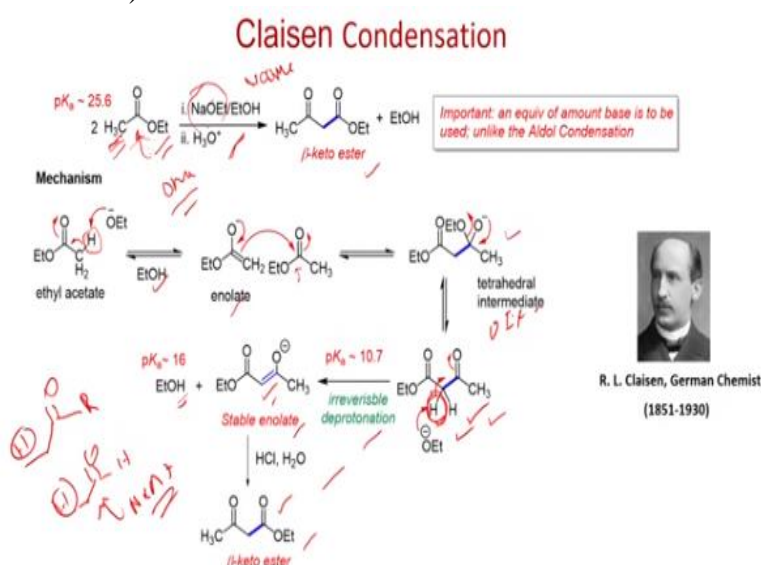
Examples



The first example involves the reaction of ketone with acetic anhydride using sodium acetate to give the substituted cinnamic acid with $E : Z$ ratio 9 :1. The next example involves the reaction of phenylacetic acid with benzaldehyde to give substituted cinnamic

acid. The third example involves the reaction of the substituted benzaldehyde with the substituted phenylacetic acid in the presence of triethylamine to give substituted cinnamic acid. The last two examples show the use of triethylamine for the preparation of substituted cinnamic acids.

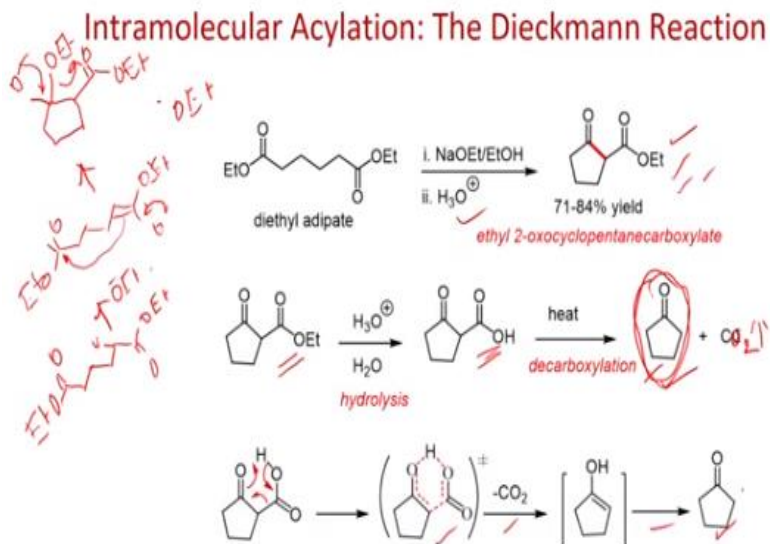
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Here the reaction of EtOAc is shown. EtOAc can be reacted using NaOEt in EtOH to give β -keto ester. Here we have to use NaOEt because in case if it undergoes addition reaction with the substrate the starting material will remain intact. So the EtO^- group can deprotonate the α -hydrogen to give EtOH, the enolate then undergoes addition with the carbonyl group of another ester. The tetrahedral intermediate is then converted into β -keto ester.

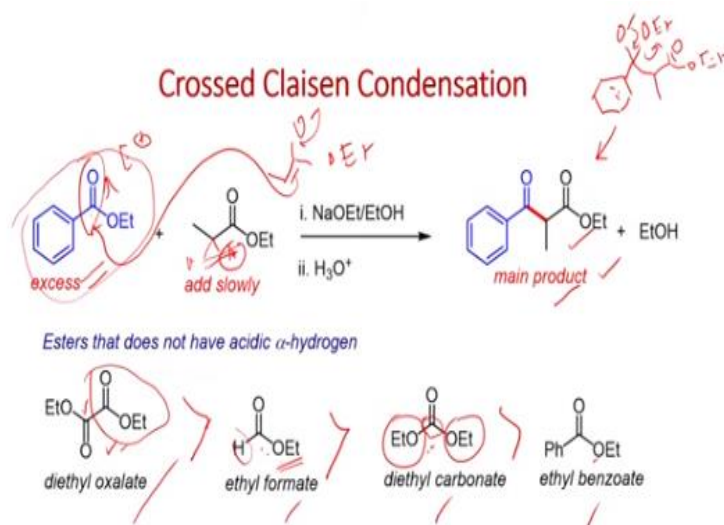
If you compare with the aldol reaction that we studied in lecture one, where we use a catalytic amount of strong base. In contrast, here you have to use stoichiometric amount of base. This is because the ester α -hydrogen is less acidic compared to the aldehyde or ketone α -hydrogen.

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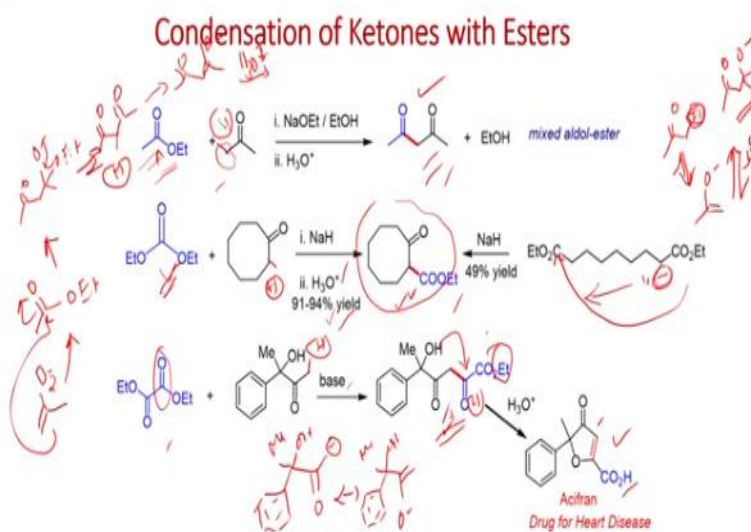
Just we have seen the reaction of EtOAc in the presence of NaOEt to give β -keto ester. This slide shows an intramolecular reaction. For example, here we have diethyl adipate, which can be converted into oxocyclopentanecarboxylate using NaOEt in EtOH. When you do hydrolysis, it will be converted to carboxylic acid, which can decarboxylate to give cyclopentanone, through the cyclic transition state. This is one of the efficient methods to make cyclic ketone.

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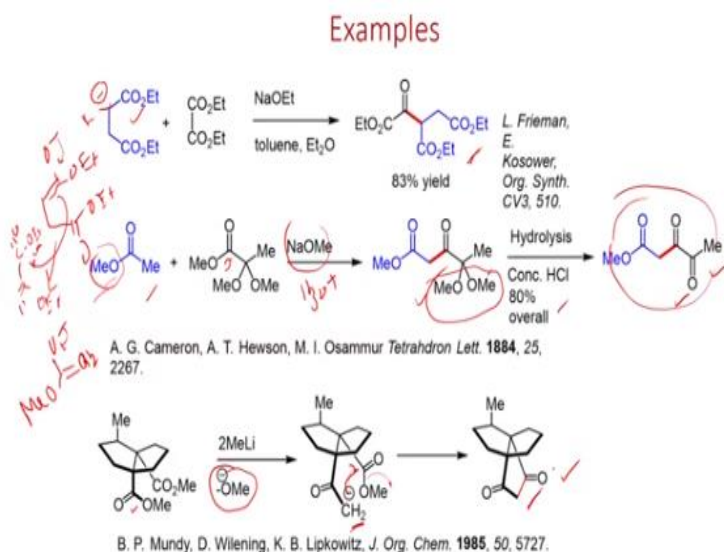
This slide shows an example for crossed Claisen condensation. Here you take two different esters, which can lead to the formation of up to four compounds. In the reaction of ethyl propionate with ethyl benzoate, β -keto ester forms as only product. If you use one of the esters as an electrophile that doesn't have the α C-H bond, which cannot undergo deprotonation. The other ester can form the enolate in that case you can try to produce a single product. Please see here the order of electrophilicity of the some of the esters which don't have the α -hydrogen.

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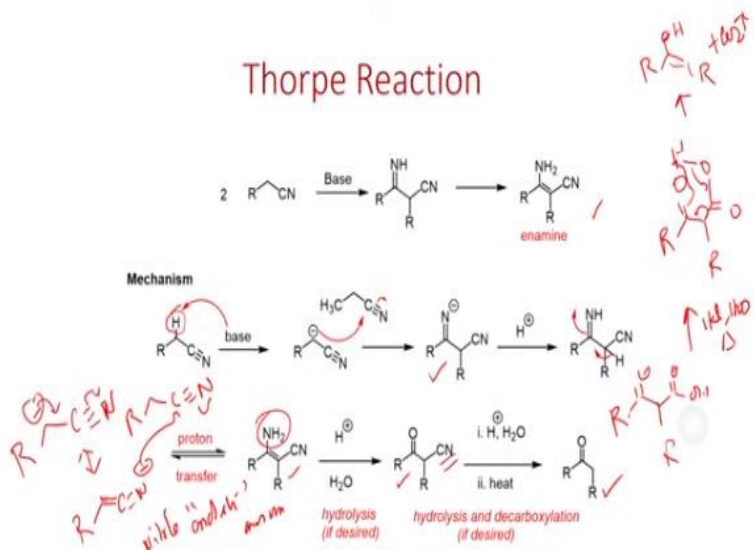
Here the reaction of acetone with ethyl acetate is shown. This reaction can be carried out using NaOEt in EtOH to give the enolate that can be converted to acetyl acetone by aqueous work up. The second example involves acylation of the enolate. The reaction of ethyl carbonate with cyclooctanone gives the β -keto ester. In another example using diethyl oxalate, you can couple with enolate that can be produced through deprotonation of the ketone using base. This can be further converted to cyclic ether by acid hydrolysis..

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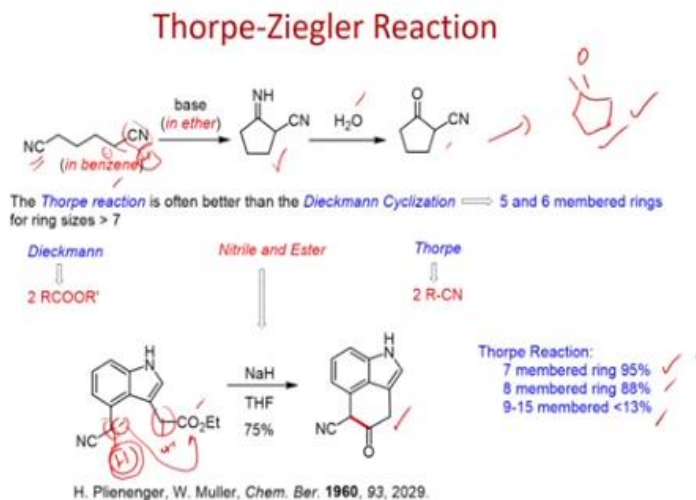
This slide shows some examples of the reaction of esters. The first example involves the reaction of the diethyl oxalate with diethyl succinate. When you react diethyl succinate with sodium ethoxide you can generate carbanion by deprotonation, which can undergo reaction with the diethyl oxalate to give the addition product. The second example involves the reaction of ester that contains acidic α -hydrogen with another ester, which does not have the acidic α -hydrogen. The third example involves an intramolecular reaction. In this reaction, 1,2-addition of methyl lithium with ester gives ketone that undergoes deprotonation using methyl lithium to give an enolate. The latter reacts intramolecularly with the ester to give 1,3-diketone. In this reaction, methyl lithium first acts as a nucleophile to undergo addition reaction to produce ketone and then acts as a base to deprotonate of acidic methyl group hydrogen to produce enolate.

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Just we have seen reaction of esters. Now let us look at the reaction of alkyl nitrile. When you react alkyl nitrile with base, you can generate nitrile enolate, which can undergo addition reaction with another molecule nitrile group to give the addition product that can be converted to carbonyl compound via enamine. Mechanism of this reaction shown here. Deprotonation of the acidic hydrogen can generate nitrile enolate, which can undergo reaction with another molecule nitrile functional group. The enamine can be hydrolyzed to yield the carbonyl compound.

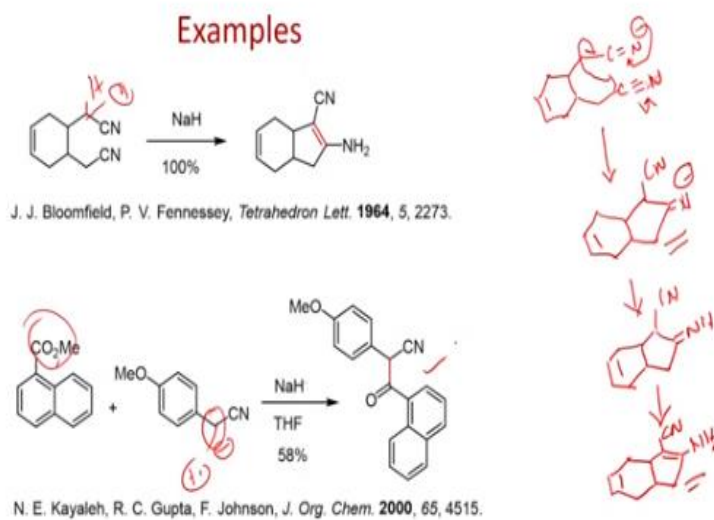
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Now, let us look at the intramolecular cyclization of the dinitrile substrate. The reaction is to be carried out by controlling the concentration of the reaction mixture. This is to minimize the intermolecular reaction. Deprotonation can lead to the formation of carbanion that can undergo intramolecular addition with the nitrile group to give the cyclic nitrile derivative that can be converted to cyclopentanone by hydrolysis. This is also a powerful reaction to make the cyclic ketone and works very well if you want to make five or six membered ring. The intramolecular cyclization of diester is known as Dieckmann Cyclization, whereas the reaction of nitrile substrate is called as Thorpe reaction. Both work very well if you want to make five and six membered rings. For larger rings like seven or eight membered rings, dinitrile substrate works well compared to diester.

The last example shows the reaction of alkyl nitrile with alkyl ester. Deprotonation of this acidic hydrogen generates carbanion, which undergoes intramolecular reaction with ester group to give the condensation product.

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Two examples are shown here. The first involves an intramolecular reaction of the dinitrile derivative. Deprotonation of the acidic hydrogen using sodium hydride can give carbanion, which can undergo addition reaction with the nitrile group to give imine,

which exists in the form of enamine. The second example involves reaction between benzyl nitrile with naphthyl ester group to give the condensation product.

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Summary

- ❖ Reaction between aromatic aldehydes and acid anhydrides
- ❖ Reaction between two esters
- ❖ Intramolecular cyclization of diesters
- ❖ Acylation of ketones
- ❖ Reaction between two alkyl nitriles

In summary, we have seen the reaction of aromatic aldehydes with acid anhydrides in the presence of base to make cinnamic acid. We have seen the reaction of benzaldehyde with acetic anhydride, you can also vary the acid anhydride instead of acetic anhydride. If you have electron withdrawing group in the aromatic ring, the reaction is efficient due to an increase of the electrophilicity of the carbonyl group of the aldehyde. On the other hand, if you have the electron donating group, it reduces the electrophilicity of the carbonyl group of the aldehyde, and the reactivity is decreased.

Then, we have seen the reaction of esters using base to give β -keto ester. We have seen the reaction of ethyl acetate to give the β -keto ester. This reaction is similar to Aldol reaction. Perkin reaction is also similar to Aldol reaction because you generate the enolate from the acetic anhydride and in this case of Claisen condensation, one of the ester should have the α hydrogen, which undergoes a deprotonation to form carbanion. Intramolecular reaction provides an efficient route to make cyclic ketone.

Then, we have seen the reaction of ketones with the different esters which don't have acidic α hydrogen.

Then, we have seen the reaction of alkyl nitrile using base. This reaction can be carried out in the presence of the catalytic amount of base. One of the alkyl nitrile α -hydrogen is deprotonated to give the nitrile enolate, which undergoes addition with nitrile group of

another alkyl nitrile to give the enamine, which can be further converted into cyclic ketone by hydrolysis. Similarly, the nitrile can be converted to carboxylic acid by hydrolysis. Once you have the carboxylic acid, which can be converted into ketone by decarboxylation using acid hydrolysis under heating.

Then we have seen the reaction between alkyl nitrile and esters. With this, we conclude the lecture. Thank you very much.