Principles of Organic synthesis
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Lecture 3: Base-Catalysed Carbon-Carbon Bond Formation

Welcome you all to Principles of Organic synthesis. At present, we study base-catalyzed carbon-carbon bond formation. So far we have seen two lectures in this topic. The first lecture focused on Aldol reaction. In the second lecture, we studied Perkin reaction, Claisen condensation and Thorpe reaction. In this lecture, we study the reaction of enolate with alkyl halides and α,β-unsaturated carbonyl compounds.

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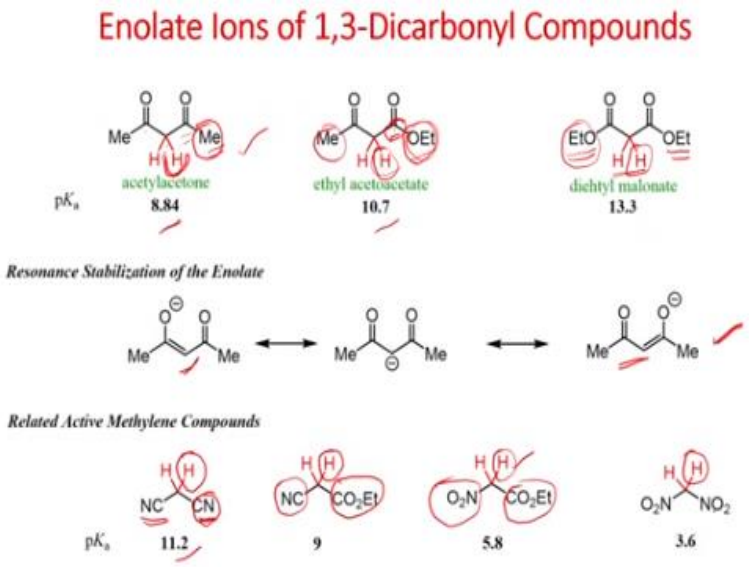

This slide shows the pKa of the hydrogens. When you look at acetylacetone, pKa of this hydrogen is 8.84. When you replace one of the methyl groups with an ethoxy group, the pKa value of the hydrogen is increased to 10.7. This is because the electrophilicity of the carbonyl group is reduced. When you replace the other methyl group with an another ethoxy group, the pKa of the hydrogen is further increased to 13.3 because both sides you have the less electrophilic carbonyl groups.

Here the resonance stabilization of an enolate of acetylacetone is shown, when you deprotonate it generates the carbanion, which can be stabilized by the carbonyl group.

Some related active methylene compounds are showing here. This methylene is bonded with the two electron withdrawing nitrile group and the pKa of the hydrogen is 11.2. You can replace one of the nitrile groups with an ester group, now the pKa is reduced to 9, this is because ester is more electron withdrawing compared to nitrile. Therefore, the acidity of the hydrogen is increased. If you replace the nitrile further with the nitro group, the methylene hydrogen is more acidic, because this is strong electron withdrawing group and pKa of the hydrogen is 5.8. When you replace the ester group with a nitro group the acidity of the hydrogen is further increased and the pKa of the hydrogen is further reduced to 3.6.

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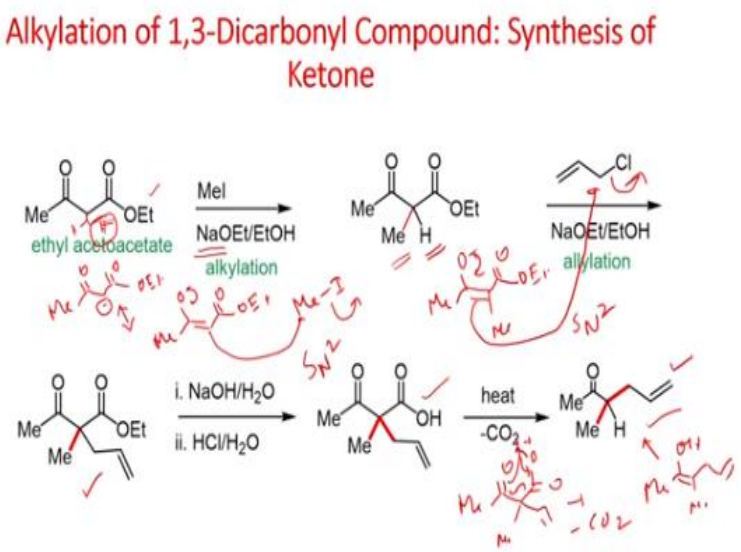

Now, let us see the reaction of some of the carbonyl compounds. Let us start with ethyl acetoacetate, when you react with sodium ethoxide it can deprotonate this hydrogen to generate the enolate, which can undergo S_N2 reaction with methyl iodide to give methyl derivative. This further deprotonates to give the enolate, which leads to S_N2 alkylation with allyl chloride to give the di-alkylated compound. This compound can be hydrolyzed using aqueous NaOH to give the carboxylic acid. When you heat, decarboxylation takes place to give the keto derivative as the product.

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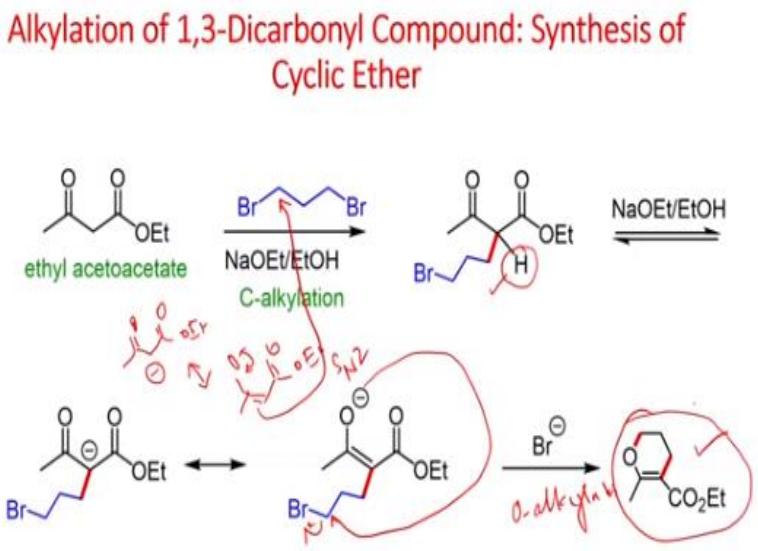

Now, let us look at the reaction of ethyl acetoacetate with 1 3-dibromopropane. As we have seen above, the substrate undergoes reaction with the base to form the enolate, which leads to substitution with 1,3-diboromopropane to give the alkyl derivative. Further deprotonation can form the enolate, which leads to O-alkylation to produce the cyclic ether. In this reaction, C-alkylation followed by O-alkylation is involved to produce the cyclic ether as the product.

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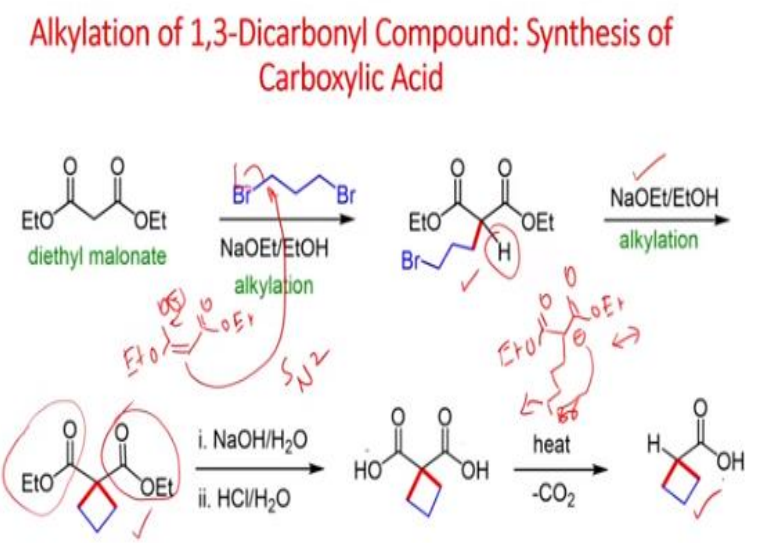

Let us look at this substrate. When you do deprotonation using sodium ethoxide, you can form carbanion which can undergo intermolecular C-alkylation. Further deprotonation and intramolecular C-alkylation can give the cyclobutane derivative. Hydrolysis of the ester group using aqueous NaOH can give the dicarboxylic acid derivative. One of the carboxylic acid group can lead to decarboxylation on heating to produce the cyclobutane carboxylic acid.

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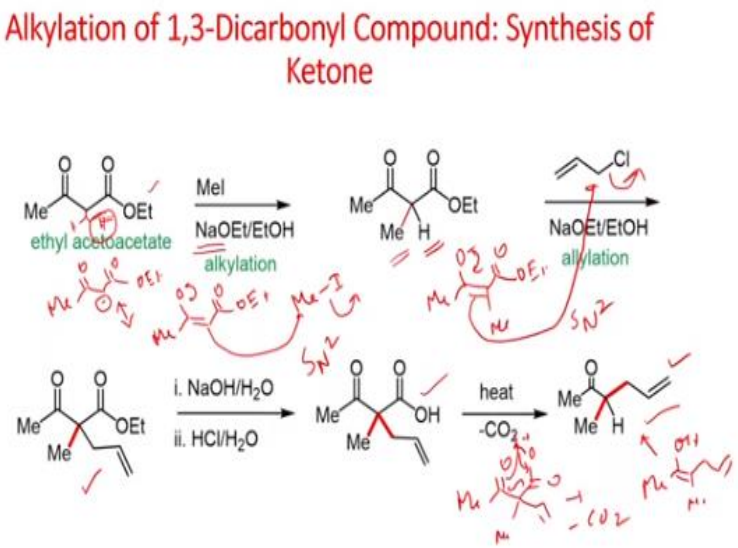

So far, we have seen the intermolecular reactions of two different alkyl halides with ethyl acetoacetate. Next, we saw the alkylation of ethyl acetoacetate with 1,3-dibromopropane to give the cyclic ether via intermolecular C-alkylation followed by an intramolecular O-alkylation.

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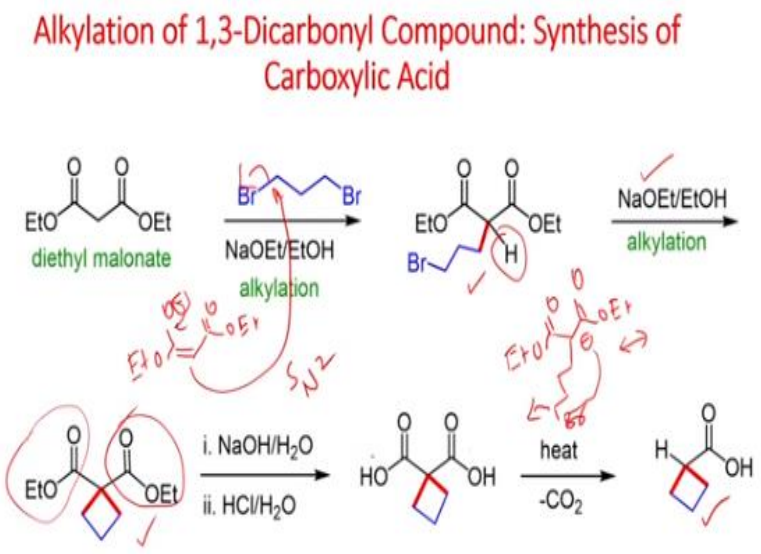

Then, we have seen the reaction of diethyl malonate with 1,3-dibromopropane, which involves inter- followed by intramolecular C-alkylation to give cyclobutane derivatives.

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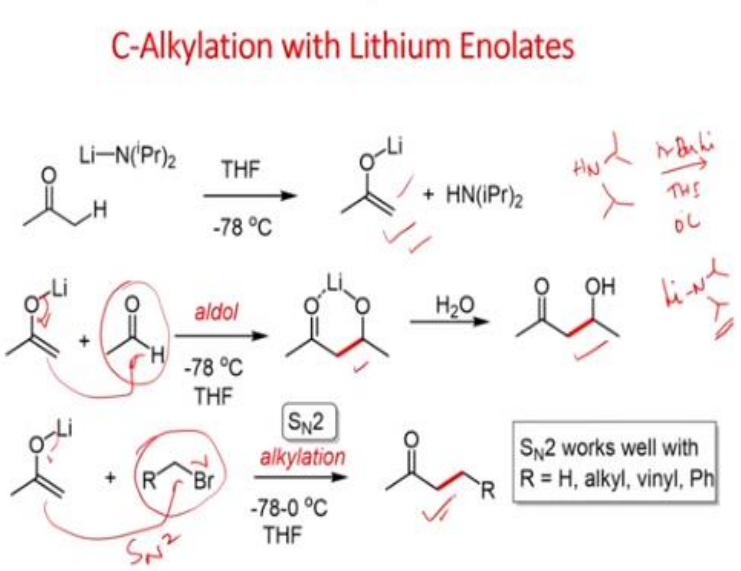

Now, let us look at the reaction of ketone. When you treat ketone with LDA at -78 °C, you can generate enolate, which can react with an electrophile. For example, if you add aldehyde, you can produce aldol product, which is well explored. Instead of aldehyde, if you add alkyl halide, it can undergo substitution via S_N2 pathway.

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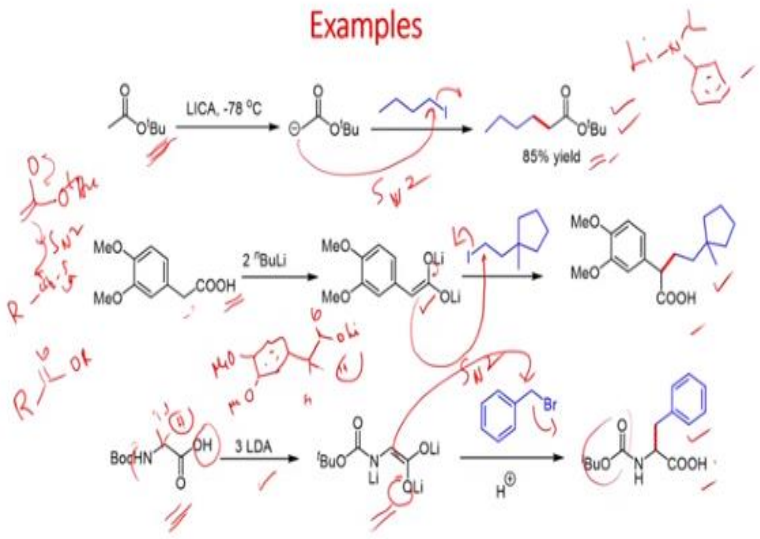

Here some examples are shown. The first example involves the coupling of ester with alkyl iodide. Deprotonation can generate the enolate, which can undergo substitution with alkyl halide via S_N2 pathway. To minimize, Claisen condensation bulkier ester group is used as the reactant.

The second example involves the alkylation of carboxylic acid. Here you have to use two equiv of lithium reagent and the enolate can be coupled with alkyl iodide to give C-alkylated compound via S_N2 pathway.

Now, let us look at this amino acid derivative. You have to use three equiv of LDA to form the enolate, which undergoes S_N2 reaction with benzyl bromide to give the C-benzylated derivative.

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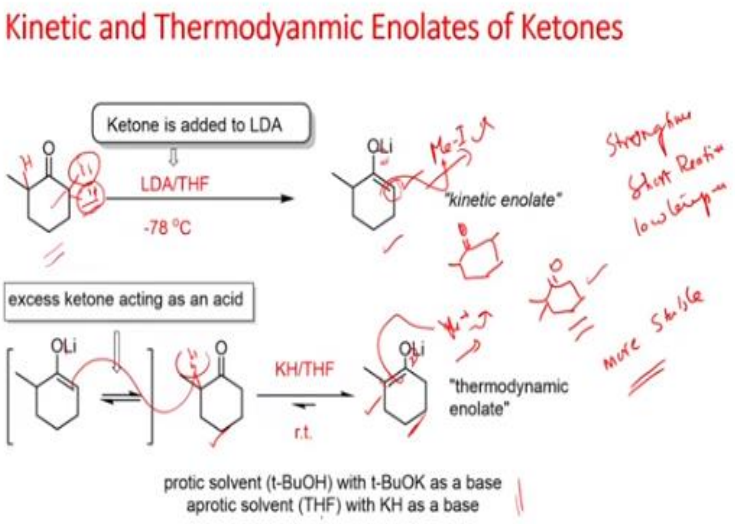

This slide shows the kinetic vs thermodynamic controlled enolate of ketone. Let us look at this ketone, where you have two kinds of hydrogens next to carbonyl group. When you react the ketone with LDA at -78 °C in THF, you can selectively deprotonate the sterically less hindered more acidic hydrogen to generate the kinetically controlled enolate, which can be selectively reacted with alkyl halide. Low temperature, short reaction time and aprotic solvent facilitate the enolate formation.

On the other hand, if you react the ketone with base like potassium hydride at high temperature, deprotonation takes place and more substituted enolate is produced, which is known as thermodynamically controlled enolate, which can be reacted with alkyl halide to give other C-alkylated compound. Protic solvent and higher temperature facilitate the formation of thermodynamically controlled enolate. So, controlling reaction conditions, you can try to selectively alkylate at different positions.

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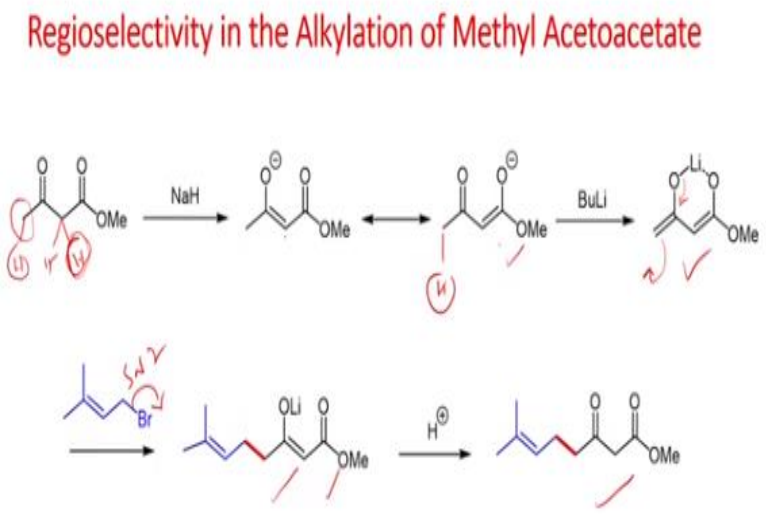

Here the regioselective allylation of methyl acetoacetate is shown. The allylation can be selectively performed at methyl instead of methylene by forming enolate as shown using NaH followed by n-BuLi. The reaction involves S_N2 pathway as we have seen earlier.

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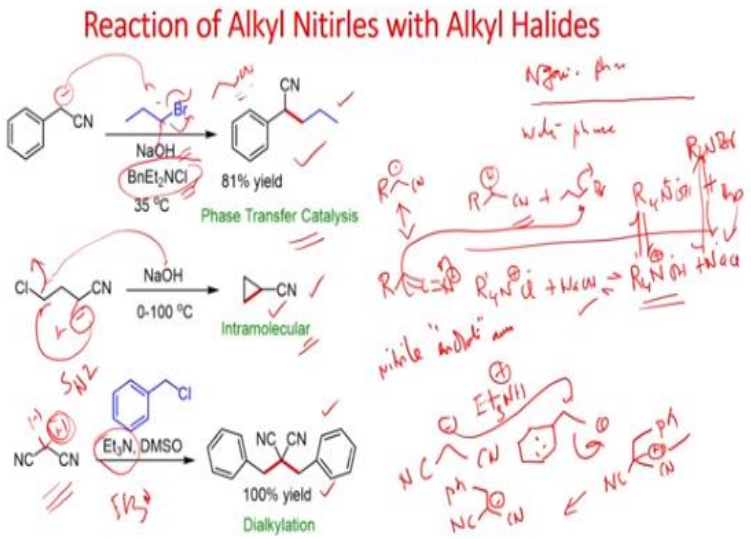

So far, we have seen the reaction of 1,3-dicarbonyl compounds and ketones. Now, let us look at the alkylation of alkyl and benzyl nitriles. The first example involves the reaction of benzyl nitrile with propyl bromide using NaOH in the presence of ammonium salt,

which acts as a phase transfer catalyst. The reaction involves biphase system, organic phase and water. NaOH reacts with amine to form ammonium salt in aqueous phase, which is soluble in organic phase and deprotonates the benzylic hydrogen.

The second example involves an intramolecular alkylation to produce cyclopropyl nitrile. There is also possibility of reaction with the sodium hydroxide to generate alcohol but that is slower compared to the intramolecular cyclization under these conditions.

The other example involves the dialkylation using benzyl bromide. Since the methylene is more acidic, weak base like trimethylamine can be utilized. The reaction takes place efficiently to give the dialkylated nitrile derivative.

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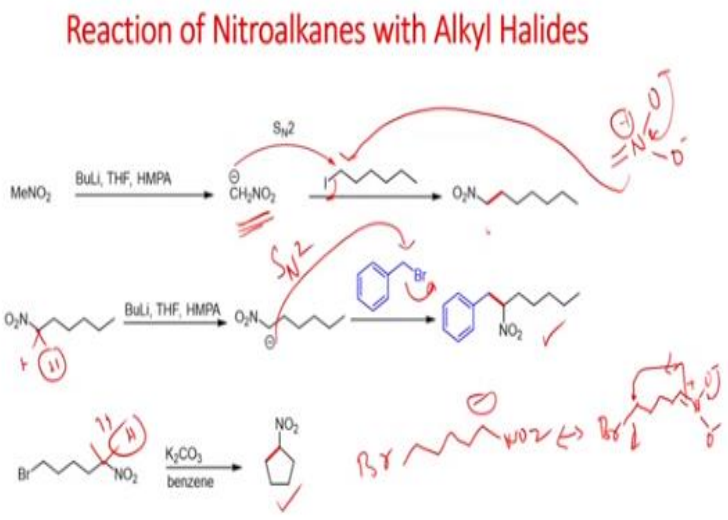

Now, let us look at the reaction of nitroalkanes. The first example involves the reaction of nitromethane with n-BuLi to produce carbanion, which undergoes substitution reaction with alkyl iodide to produce alkyl nitrate. These reaction conditions can be extended to the coupling of nitrohexane with benzyl bromide to give alkylated derivative. The next example involves the intramolecular alkylation to produce cyclopentyl nitrate in the presence of potassium carbonate.

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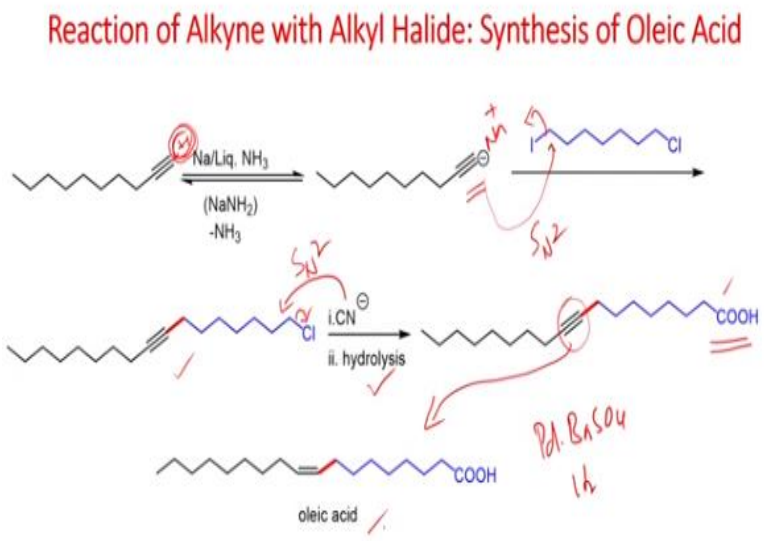

This slide shows the synthesis of oleic acid. When you react terminal alkyne with sodium in liquid ammonia, you will generate the carbanion, which can undergo S_N2 reaction selectively at the carbon bonded to iodide to give alkyl derivative. Further nucleophilic substitution using cyanide ion on the carbon bonded with chloride can give the alkyl nitrile, which can be hydrolyzed to give the carboxylic acid. Hydrogenation of triple bond with Lindar catalyst can produce the oleic acid.

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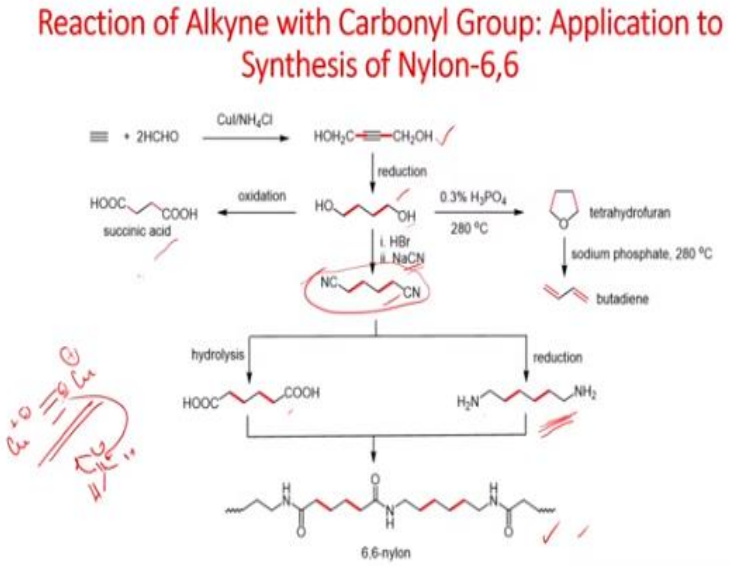

Here the reaction of alkyne with aldehyde and its application for the nylon-6,6 is covered. Acetylene with formaldehyde in the presence of copper iodide ammonium chloride produces the diol, which can be reduced to saturated diol. The diol can be converted into tetrahydrofuran using phosphoric acid and can be further converted into butadiene using sodium phosphate at elevated temperature. Similarly, the diol can also be oxidized to succinic acid.

The diol can be further reacted with HBr to produce dibromides, which can be reacted with NaCN to give dinitrile derivative. Reduction of the dinitrile derivative can produce 1,6-diaminohexane, while hydrolysis lead to the formation of adipic acid. Condensation of the diamine with dicarboxylic acid produces nylon-6,6.

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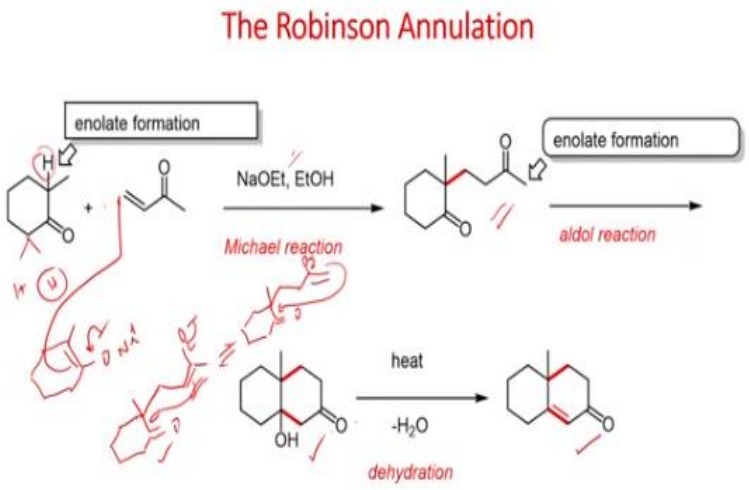

An example shown here for conjugate addition and its application for annulation. Methyl cyclohexanone with NaOEt forms thermodynamically stable enolate, which undergoes conjugate addition with methyl vinyl ketone to give 2-dialkyl cyclohexanone derivative. Deprotonation of methyl hydrogen and intramolecular 1,2-addition to carbonyl group give aldol, which leads to dehydration on heating to produce the bicyclic α,β-unsaturated ketone.

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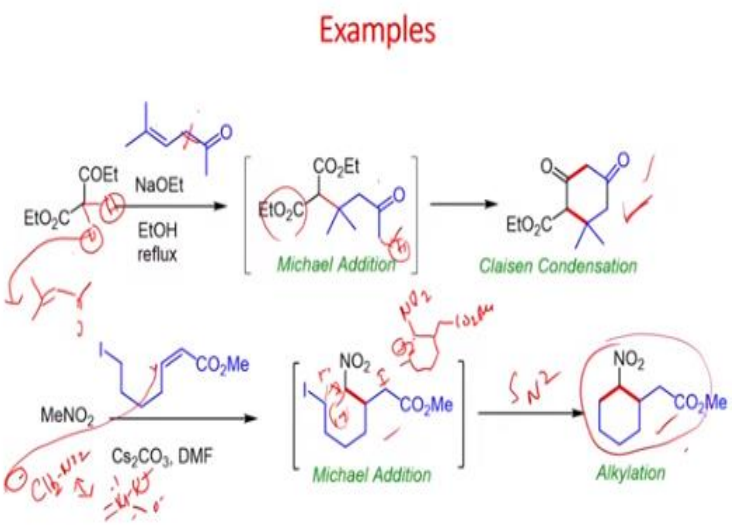

This slide has some more examples. The first example involves the reaction of diethyl malonate with methyl vinyl ketone to produce cyclic derivative. Deprotonation of the active methylene group of and subsequent conjugate addition give alkyl derivative. Further deprotonation of the methyl group and intramolecular addition to the ester group give the 1,3-dicarbonyl ester derivative.

The next example involves the reaction of nitromethane with alkenyl derivative. Deprotonation of nitromethane using Cs_2CO_3 and subsequent conjugate addition gives the addition product, which leads to deprotonation and intramolecular S_N2 reaction with carbon bonded to iodide to yield cyclohexyl derivative.

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Summary

- Alkylation of Enolates
- Kinetic vs Thermodynamic Enolates
- Alkylation of Nitriles and Nitroalkanes
- Alkylation of Alkynes
- Michael Addition

In summary, first we have seen the reaction of enolates with alkyl halides. We have mainly seen the reaction of 1,3-dicarbonyl compounds. The alkylation can be carried out by deprotonation followed by nucleophilic substitution.

Then we have seen the formation of enolate from ketone. You can generate kinetic vs thermodynamic controlled enolate by controlling the reaction conditions. If you carry out the reaction at low temperature with strong base like LDA and shorter reaction time, you can to generate kinetically controlled enolate. Alternatively, you can generate the more substituted thermodynamically stable enolate at higher temperature.

Following that we have seen the reaction of alkyl nitriles and nitroalkanes. We also have seen the reaction of terminal alkynes with alkyl halides and their application for the synthesis of oleic acid and nylon-6,6.

At the end we have seen the addition of enolate to α,β-unsaturated carbonyl compounds and their application for the cyclic compounds synthesis.

And also we have seen the addition of diethyl malonate with α,β-unsaturated carbonyl compound to give addition product which can be further reacted to cyclic derivative. We also have seen the reaction of nitroalkane with α,β-unsaturated compound, which can be again deprotonated using base that can lead to substitution to furnish the cyclic compound with this will conclude this lecture. Thank you very much.