Principles of Organic synthesis
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Lecture 4: Formation of Aliphatic Carbon-Carbon Bonds: Acid Catalysed Reactions

Welcome you all to aliphatic carbon-carbon bond formation using acid as a catalyst.

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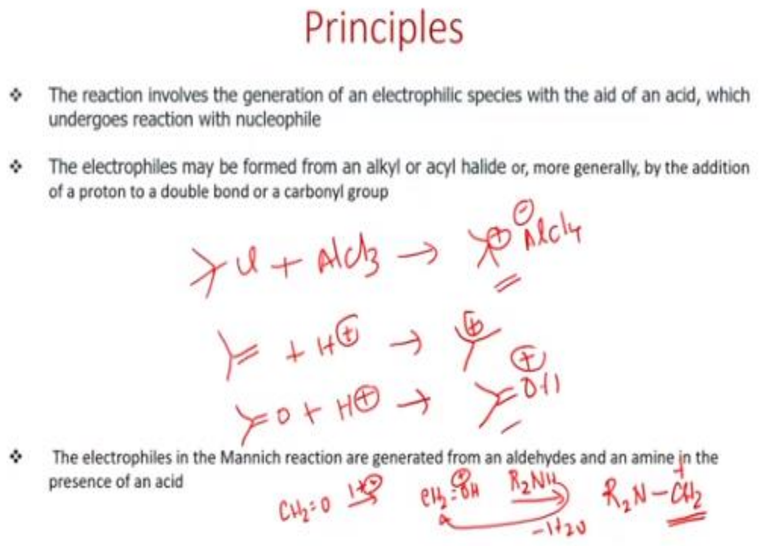

Principles

- The reaction involves the generation of an electrophilic species with the aid of an acid, which undergoes reaction with nucleophile
- The electrophiles may be formed from an alkyl or acyl halide or, more generally, by the addition of a proton to a double bond or a carbonyl group
- The electrophiles in the Mannich reaction are generated from an aldehydes and an amine in the presence of an acid

This slide shows the principles of acid-catalyzed carbon-carbon bond formation. The reaction involves the formation of electrophilic species using acid as the catalyst, which undergoes reaction with the nucleophile. The electrophile can be formed from acyl halide or by the addition of proton to a double bond or a carbonyl group. For example, if you have a tert-butyl halide, when you treat with aluminum(III) chloride, you can generate carbocation, which can undergo reaction with nucleophile. The other example is a carbonyl compound, for example, acetone, which can undergo reaction with acid to give a protonated species, which is more electrophilic and can undergo reaction readily with the nucleophile. Another example, Mannich reaction, where aldehyde with amine gives an iminium ion, which acts as an electrophile.

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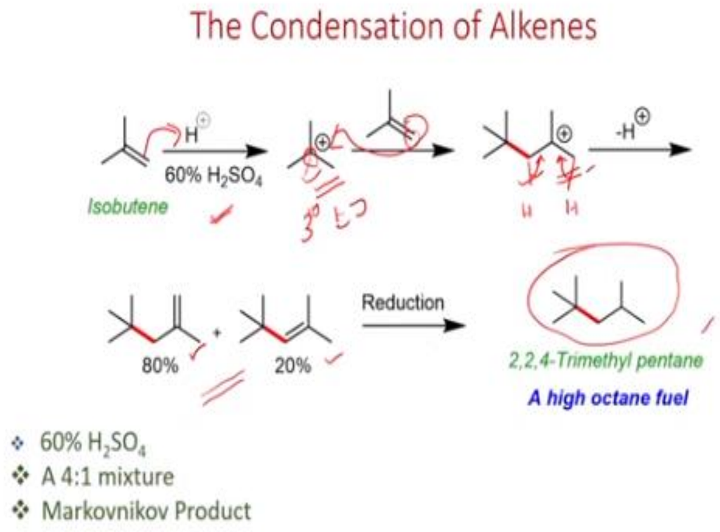

The Condensation of Alkenes

- 60% H_2SO_4
- A 4:1 mixture
- Markovnikov Product

Here the reaction of an alkene is shown. For example, when you react isobutene with 60% H_2SO_4, *tert*-carbocation forms, which reacts with isobutene to give a *tert*-carbocation that loses a proton to give a 4:1 mixture of alkenes as the products. These are reduced to 2,2,4-trimethyl pentane, which is a high octane fuel.

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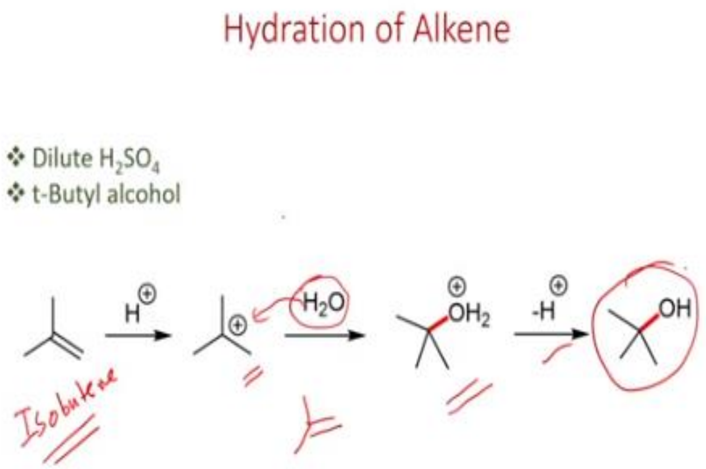

Hydration of Alkene

- Dilute H_2SO_4
- t-Butyl alcohol

However, when you react isobutene with dilute H_2SO_4, *tert*-butanol is formed. As above, isobutene undergoes reaction with acid to give a *tert*-carbocation, which reacts with water to produce *tert*-butanol as the product. Thus, concentration of H_2SO_4 is important in the reaction.

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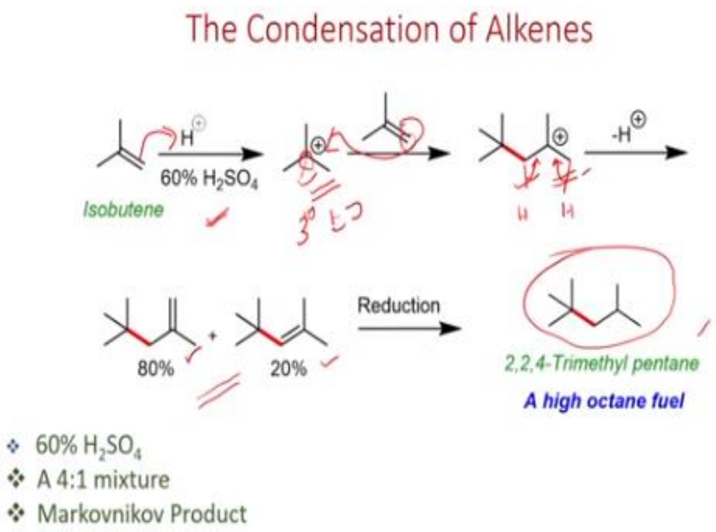

The Condensation of Alkenes

- 60% H_2SO_4
- A 4:1 mixture
- Markovnikov Product

Thus, in 60% H_2SO_4, the condensation of isobutene takes place to give an addition product, while, in dil. H_2SO_4, isobutene undergoes reaction with water to give a tertiary butanol.

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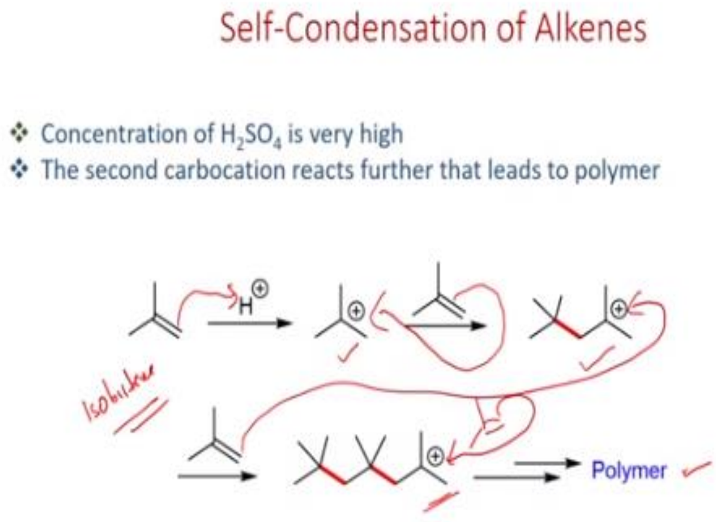

Self-Condensation of Alkenes

- Concentration of H_2SO_4 is very high
- The second carbocation reacts further that leads to polymer

On the other hand, if you use concentrated H_2SO_4, isobutene undergoes polymerization via *tert*-carbocation. Thus, the concentration of the acid plays a crucial role.

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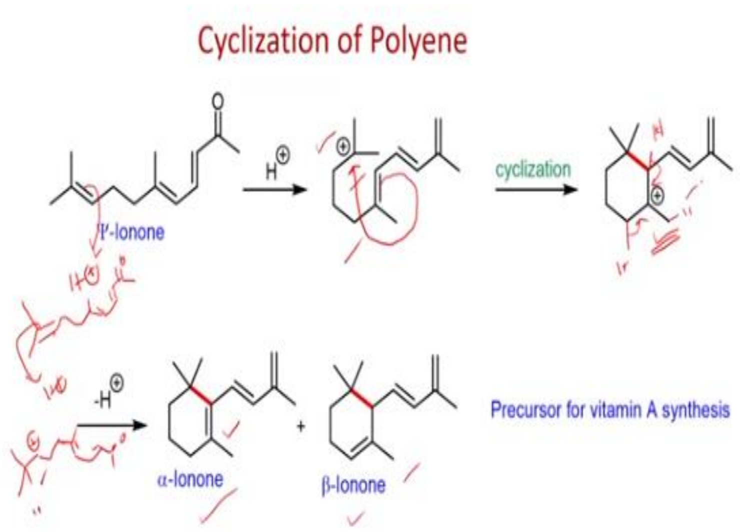
Cyclization of Polyene

Precursor for vitamin A synthesis

So far we have seen acid catalyzed intermolecular reaction of isobutene. Now let us see an acid catalyzed cyclization of polyene. For example, when you treat ψ-ionone with an acid, it undergoes cyclization to produce a mixture α– and β-Ionones is observed. This can be explained as follows:

Protonation of the double bond can form form a tert-carbocation, which can react with double bond intramolecularly to produce a six membered cyclic compound with a tert-carbocation. Removal of the proton can produce a mixture α- as well as β-ionones. β-Ionone is precursor to synthesis vitamin A. So, this is a very useful reaction.

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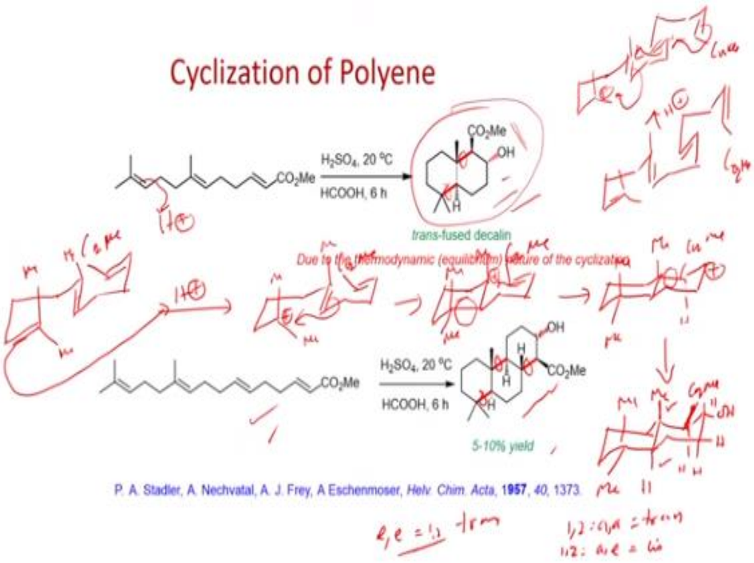

Cyclization of Polyene

P. A. Stadler, A. Nechvatal, A. J. Frey, A Eschenmoser, *Helv. Chim. Acta*, **1957**, *40*, 1373.

Now, let us look at these examples. This is also a triene, when you react with sulfuric acid at room temperature, the formation of *trans*-decalin is observed. However, when you increase the number of double bonds, the yield is reduced. The formation of *trans*-decalin can be explained as follows:

Protonation of the double bond can form a *tert*-carbocation, which can cyclize to a *tert*-carbocation. The latter can lead to an intramolecular cyclization to produce a secondary carbocation. The formation of the bicyclic system takes place via a tandem C-C bond formation of the carbocation with the double bond. The stereochemistry can be explained through the six membered chair conformation. The resultant secondary carbocation can react with water to produce the bicyclic alcohol as the product.

Similarly, the tetraene can cyclize to give the tricyclic alcohol via the formation of carbocation and reaction with double bond.

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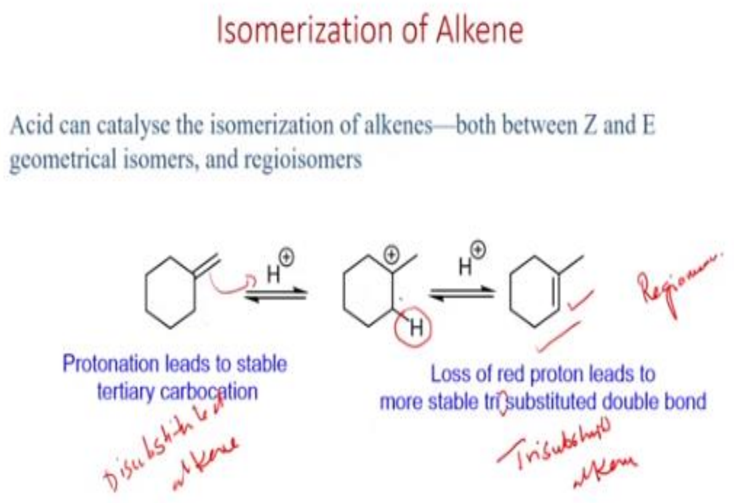

Isomerization of Alkene

Acid can catalyse the isomerization of alkenes—both between Z and E geometrical isomers, and regioisomers

Protonation leads to stable tertiary carbocation

Loss of red proton leads to more stable trisubstituted double bond

Now, let us look at the isomerization of exocyclic to internal alkene. When you treat the exo-cyclic alkene with acid, you form a tertiary carbocation that can lose a proton to give the more substituted internal alkene, which is more stable. Therefore, the isomerization takes place when you react with acid, you will be able to form the tri-substituted alkene as a product.

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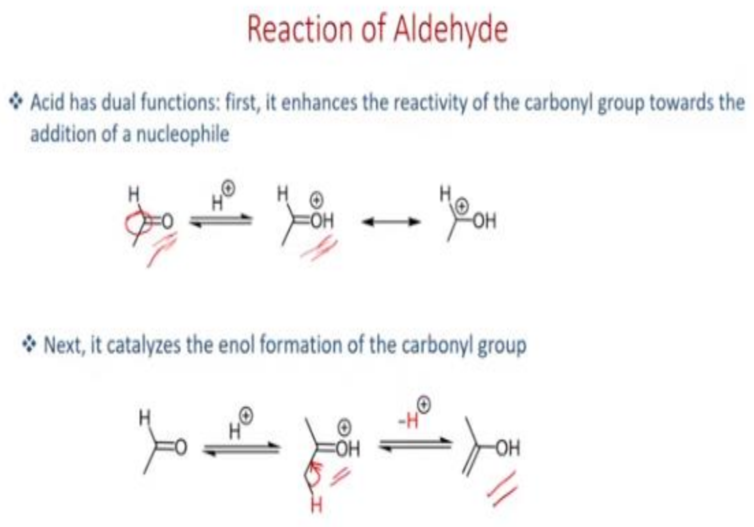

Reaction of Aldehyde

- Acid has dual functions: first, it enhances the reactivity of the carbonyl group towards the addition of a nucleophile

- Next, it catalyzes the enol formation of the carbonyl group

So far, we have seen the reaction of alkenes. Now let us see few examples for the reaction of aldehydes and ketones. Here the dual role of acid is shown. Protonation of the carbonyl group of the aldehyde gives the more electrophilic species. Similarly, acid can also facilitate to formation of enol, which can act as a nucleophile in form a carbon-carbon bond.

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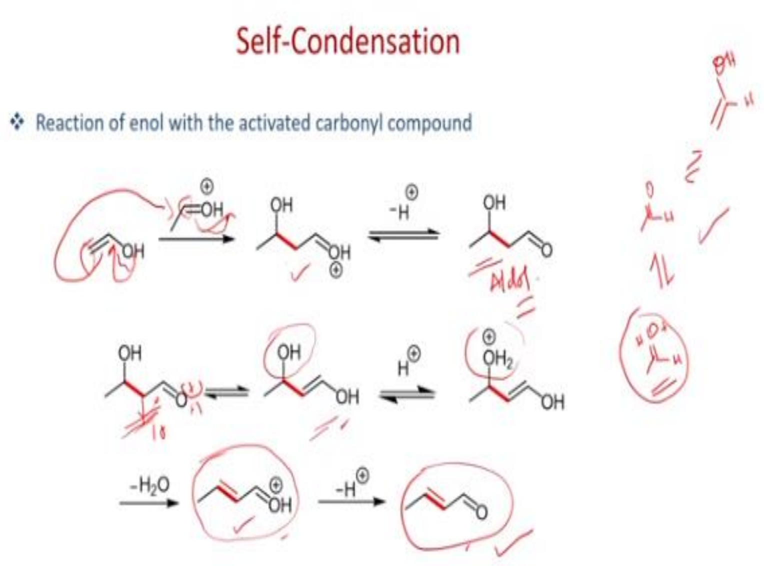

Self-Condensation

❖ Reaction of enol with the activated carbonyl compound

Here the acid catalyzed aldol reaction of acetaldehyde is shown. Protonation of the carbonyl group of acetaldehyde gives the more electrophilic protonated species. Which reacts with enol (acts as a nucleophile), which can be formed using the acid as the catalyst. So acid plays dual role in the reaction. First, increases the electrophilicity of the carbonyl group by protonation. Then, it also helps to form enol, which acts as the nucleophile. Protonation of aldol OH group followed by dehydration can give the α,β-unsaturated aldehyde, which is known as crotonaldehyde. The overall reaction is known as aldol condensation.

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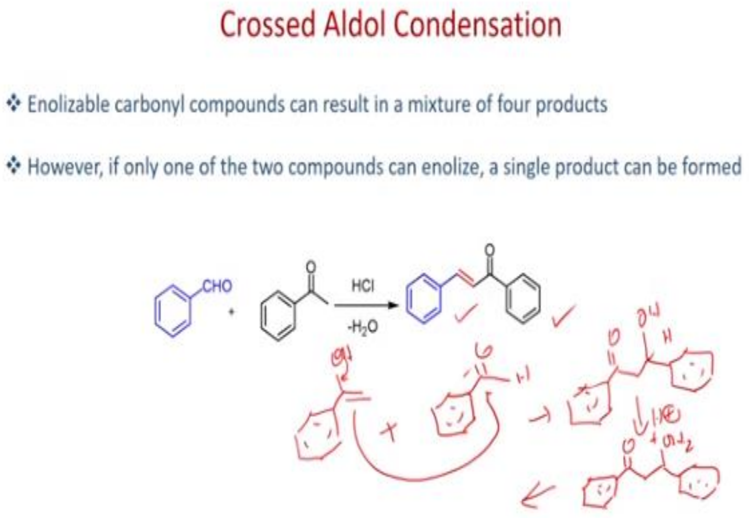

Crossed Aldol Condensation

- ❖ Enolizable carbonyl compounds can result in a mixture of four products
- ❖ However, if only one of the two compounds can enolize, a single product can be formed

Here the reaction of acetophenone with benzaldehyde is shown, which is known as the cross-aldol condensation (reaction between two different substrates). Acetophenone can form enol, which acts as a nucleophile, while benzaldehyde is protonated and acts as an electrophile. Addition reaction can give the aldol, which can undergo dehydration to give the α,β-unsaturated ketone as the product.

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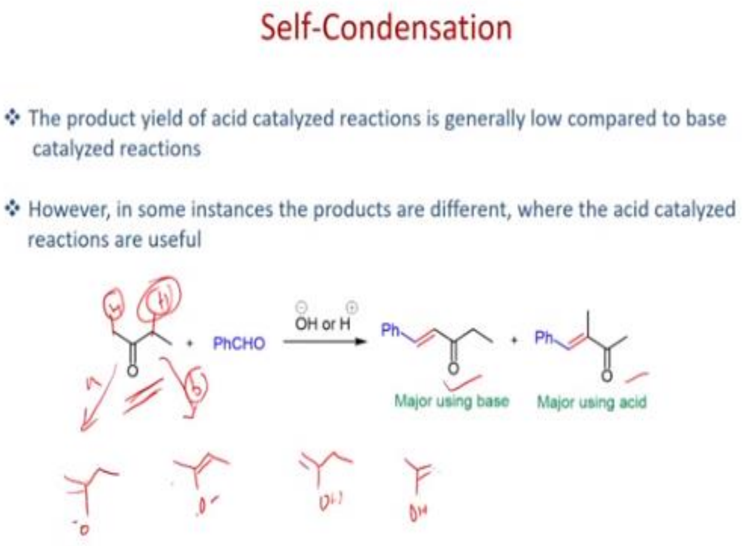

Self-Condensation

- ❖ The product yield of acid catalyzed reactions is generally low compared to base catalyzed reactions
- ❖ However, in some instances the products are different, where the acid catalyzed reactions are useful

Now, let us look at the reaction of benzaldehyde with ethyl methyl ketone. The product formed using acid is different from that employing base. Acid catalyzed aldol is thus useful sometime to avail different product in comparison to the base catalyzed reaction.

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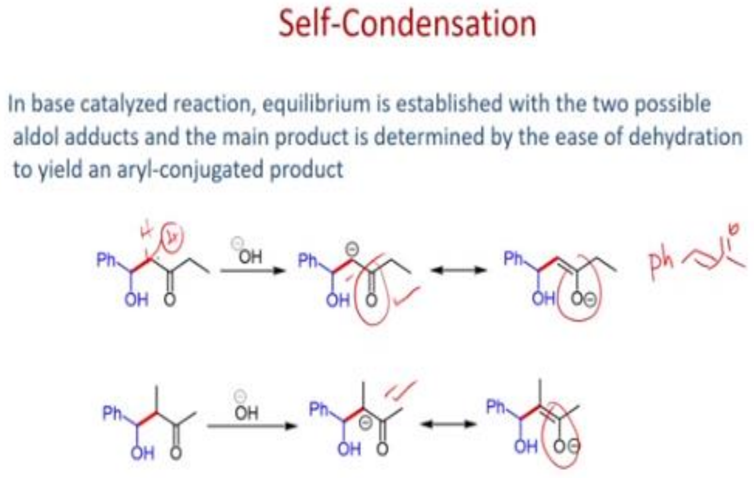

Self-Condensation

In base catalyzed reaction, equilibrium is established with the two possible aldol adducts and the main product is determined by the ease of dehydration to yield an aryl-conjugated product

Now, let us look at here. Enolates (methyl and ethyl groups) with benzaldehyde produces two types of aldols, which exit in equilibrium. Deprotonation of methylene hydrogen of the aldol is more favored (Ist example) that can lead to ease dehydration compared to the deprotonation of methyl methylene hydrogen (2nd example) and subsequent dehydration to give the conjugated product. Thus, the formation of the methylene anion of the aldols is crucial in the base catalyzed reaction.

On the other hand, when you use acid as the catalyst, you can form two types of enols, which exist in equilibrium in the reaction medium. The more substituted enol (ethyl group) is more favored compared to less substituted enol (methyl group.) Thus, the aldol formed using the former is more compared to the latter. In acid catalyzed reaction, the formation of carbon-carbon bond is thus crucial (aldol), whereas in base catalyzed reaction, the formation of anion of the aldol is critical. These are responsible for the difference in the formation of the aldol products.

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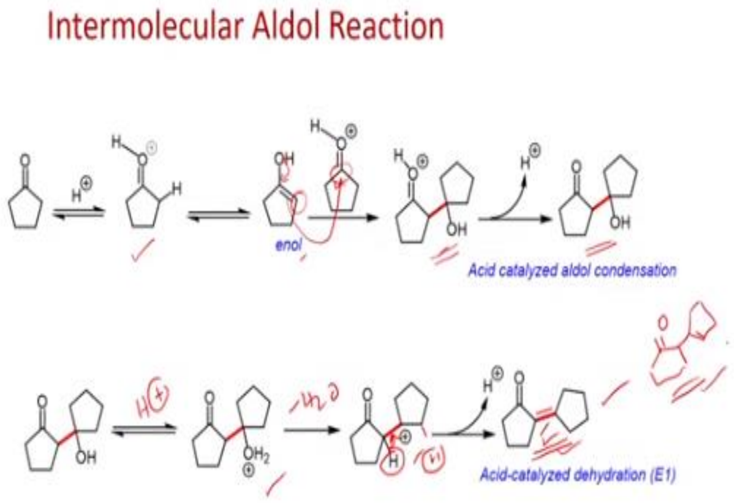
Intermolecular Aldol Reaction

Now, let us look at the acid-catalyzed intermolecular aldol reaction of cyclopentanone. As we have seen above, cyclopentanone can form enol, which can undergo addition with another protonated cyclopentanone to give the aldol, which can undergo acid-catalyzed dehydration to give the α,β-unsaturated compound.

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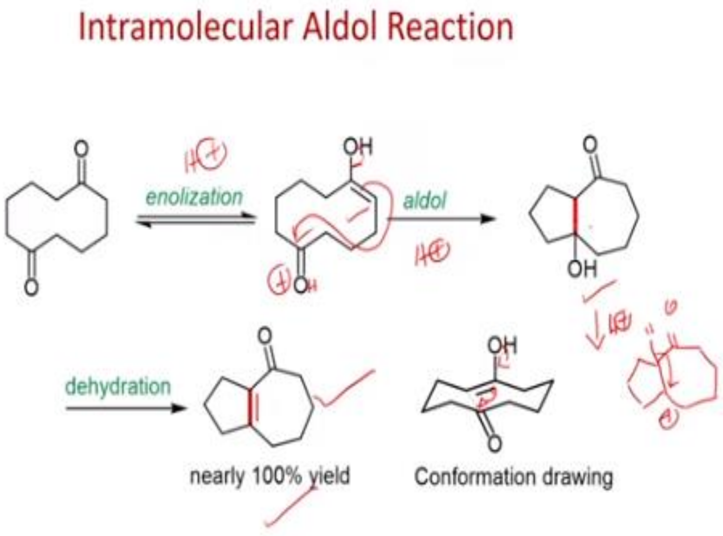

Intramolecular Aldol Reaction

Now, let us look at the intramolecular aldol reaction of the diketone. One of the keto groups undergoes enolization and the other is protonated. Intramolecular addition gives the bicyclic aldol, which readily undergoes dehydration to give α,β-unsaturated bicyclic ketone as the product. The formation of the bicyclic compound can be understood from the above drawn conformation.

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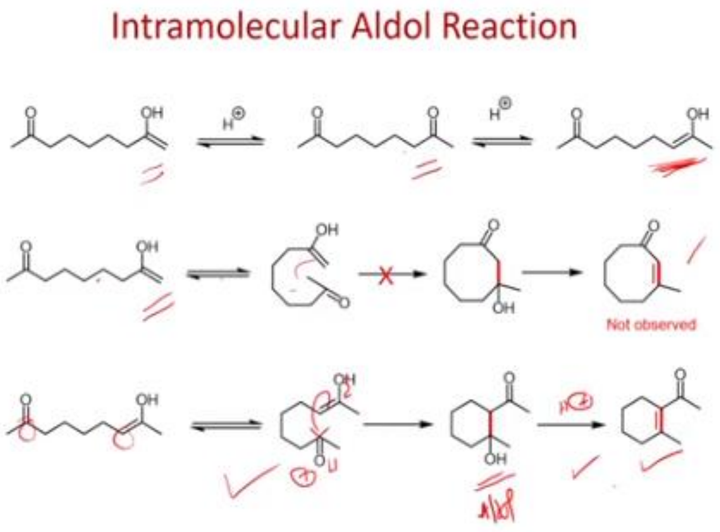

Intramolecular Aldol Reaction

The next example is an intramolecular aldol reaction of linear diketone. As above, one of the keto group undergoes enolization and other is protonated. Intramolecular addition leads to six membered aldol, which undergoes dehydration to give the α,β-unsaturated carbonyl compound. The formation of six membered cyclization is favored compared to eight membered one.

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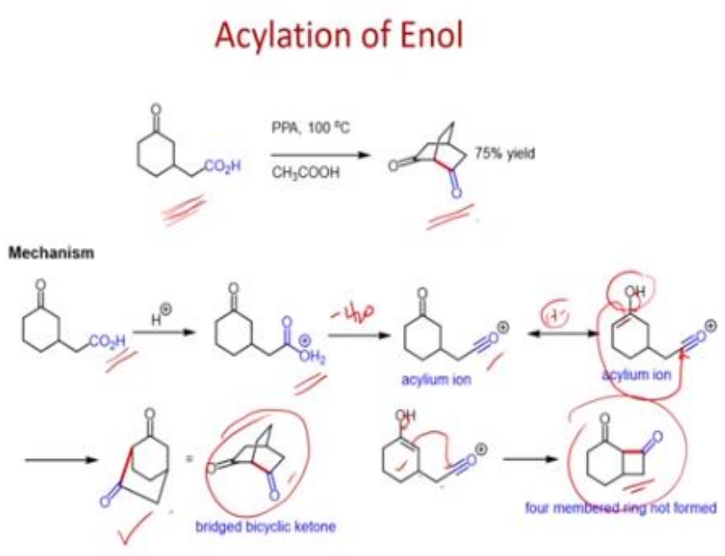

Acylation of Enol

Now, let us look at an intramolecular acylation of enol. In the presence of polyphosphoric acid, the carboxylic acid undergoes protonation and dehydration to give an acylium ion, which undergoes addition reaction with enol to produce the bridged bicyclic ketone as the product. Four membered ring formation is not favored due to strain.

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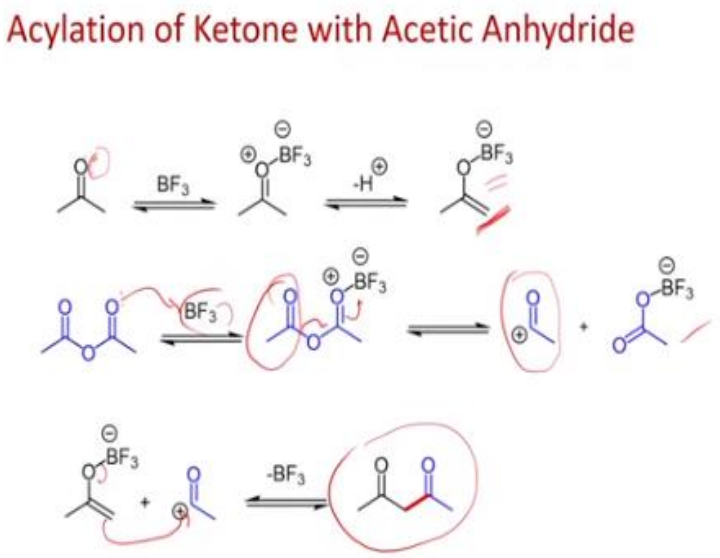

Acylation of Ketone with Acetic Anhydride

Here Lewis acid catalyzed acylation of acetone with acetic anhydride is presented. Lewis acid with anhydride can form the acylium ion, which can readily react with enolate of acetone to give acetyl acetone as the product.

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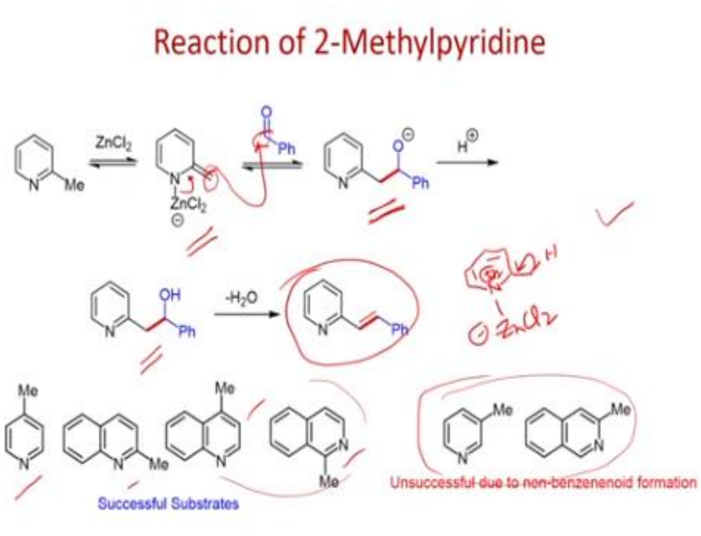

Reaction of 2-Methylpyridine

This slide shows the acylation of 2-methylpyridine in the presence of Lewis acid. Chelation of ZnCl$_2$ with 2-methyl pyridine can form methylene derivative, which can react with benzaldehyde to give addition product. Since the reaction is performed under acidic condition, the product leads to dehydration to give the conjugated product. The reaction can be extended to 4-methylpyridine, 2- and 4-methylquinolines and 1-methylisoquinoline.

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Summary

- Reaction of Alkenes
- Aldol condensation
- Application to synthesis of cyclic compounds
- Acylation of Ketones
- Reaction of 2-methylpyridine with aldehyde

In summary, we have seen the activation of carbonyl group like aldehydes and ketones with acid, it can protonate the carbonyl group and enhance the electrophilicity. For example, reaction of acetaldehyde to give the aldol product, which can undergo further reaction dehydration to give the α,β-unsaturated aldehyde. Subsequently, we have some examples for inter- and intramolecular aldol reactions that can lead to cyclic compounds.

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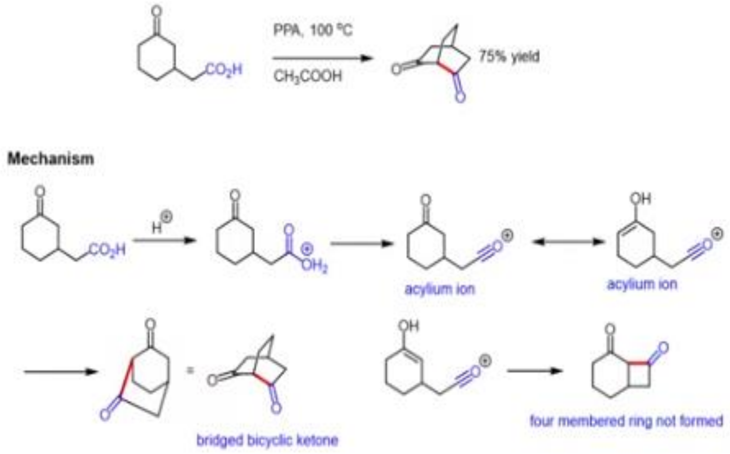
Acylation of Enol



Then we have seen the acylation of ketone using carboxylic acid as the acylating agent using phosphoric acid as a catalyst.

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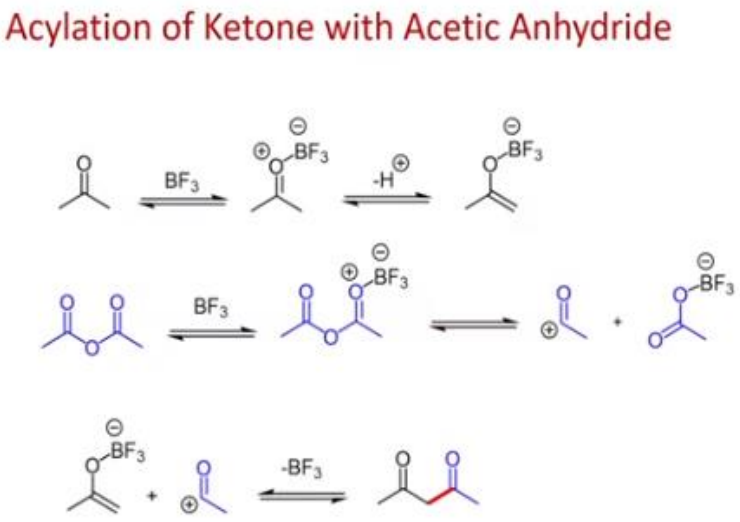

Acylation of Ketone with Acetic Anhydride

Finally, we have the acylation of 2-methylpyridine with benzaldehyde in the presence of $ZnCl_2$ as the catalyst.

With this we conclude this lecture. Thank you very much!