Principles of Organic Synthesis
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Lecture 11 - Aliphatic Carbon-Nitrogen Bond

Welcome you all to Principles of Organic Synthesis. At present, we study aliphatic C-N bond formation. In this topic, so far we had one lecture where we studied the principles for the aliphatic C-N bond formation, following that we studied the Ritter reaction where if you have the alcohol or alkene, they can be converted to the carbocation that can be reacted with nitrile to give amide.

We have also seen the use of cobalt based catalyst for the transformation of allylic alcohol to the corresponding allylic amides. We have also then seen some example for the substitution reaction.

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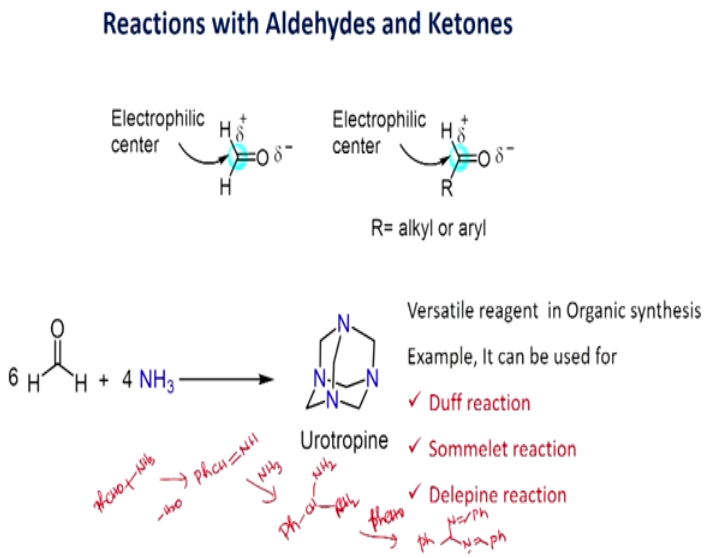

In this lecture, we will study the reaction of aldehydes and ketones with amines. As all of you know very well, aldehyde readily undergoes reaction with amine to give imine. If you have an excess amine, the imine can further react to give the addition product. For example, if you look at here the reaction of formaldehyde with ammonia is shown. In this reaction 6 molecules of formaldehyde undergo condensation with 4 molecules of ammonia where you will be able to generate the hexamethylenetetramine as a product. This is similar to adamantane structure.

Similarly, when you react benzaldehyde with ammonia, which also undergo readily reaction to give imine that can further react with ammonia. In this way, you will be able to generate this di-amine as a product. This can further react with benzaldehyde to generate the Schiff base as a product. So whenever you have the amine that can be readily reacted with aldehyde to form the imine. The imine can undergo further reaction to give the addition product.

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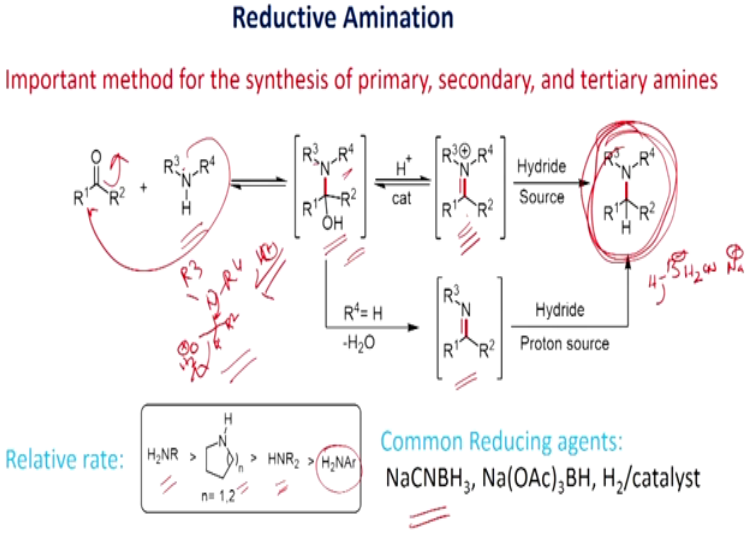

Now let us look at some applications. The reaction of a carbonyl compound with amine is shown here. When you react the carbonyl compound with amine, you will be able to get the addition compound. It can protonate in the presence of acid to form the hydronium ion, which can lose a water molecule to give the imine. It can be reduced using sodium borohyride, sodium cyanoborohydride, sodium acetoxy borohydride or hydrogenation to generate the alkyl amine as the product.

Now let us look at the relative rate of the reactivity of amines shown here. Primary amine is more reactive compared to secondary amine. Cyclic amine is more reactive compared to acyclic amine, which is more reactive comparing to aryl amines. Aliphatic amines are more reactive compared to aryl amines.

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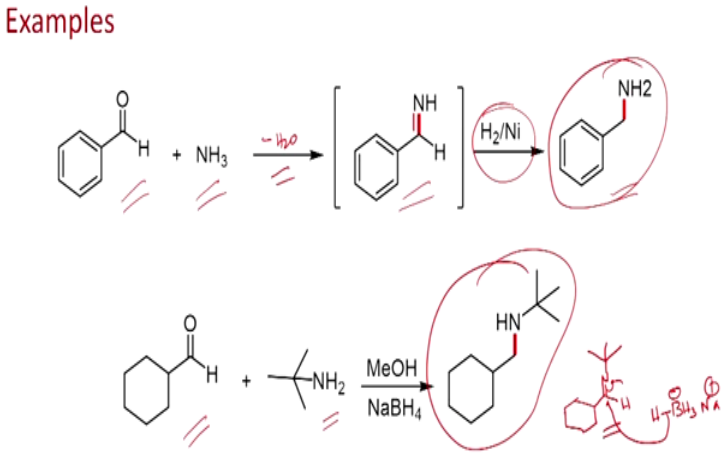

Here the reaction of benzaldehyde with ammonia gives imine, which is reduced using hydrogen in presence of nickel catalyst to gives benzylamine.

The other example involves the reaction of cyclohexanecarbaldehyde with *tert*-butylamine. The imine is reduced in-situ in by sodium borohydride to give the amine.

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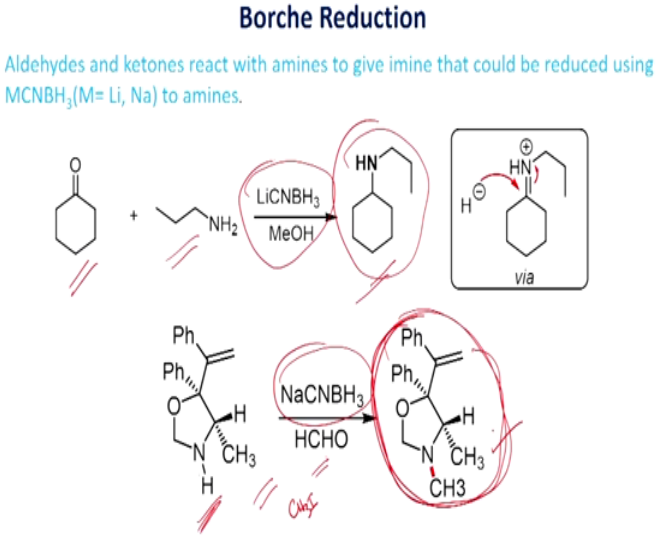

Now let us look at some more examples. The reaction of cyclohexanone with propylamine gives imine, which is reduced in situ by lithium cyanoborohydride to provide n-propyl cyclohexylamine as the product.

The next example involves the reaction of formaldehyde with the cyclic secondary amine. The imine is reduced using sodium cyanoborohydride. In this way, you will be able to introduce n-methyl group in secondary amine nitrogen.

So if you want to do N-methylation, the best approach is, you can react with formaldehyde to form the imine, which can be reduced to amine. Alternatively, if you have secondary amine, you can try to react with methyl iodide. By substitution reaction, you will be able to form the n-methyl derivative, and the best approach is the reaction with the formaldehyde that can be reduced in the reaction medium to give N-methylamine derivative as the product.

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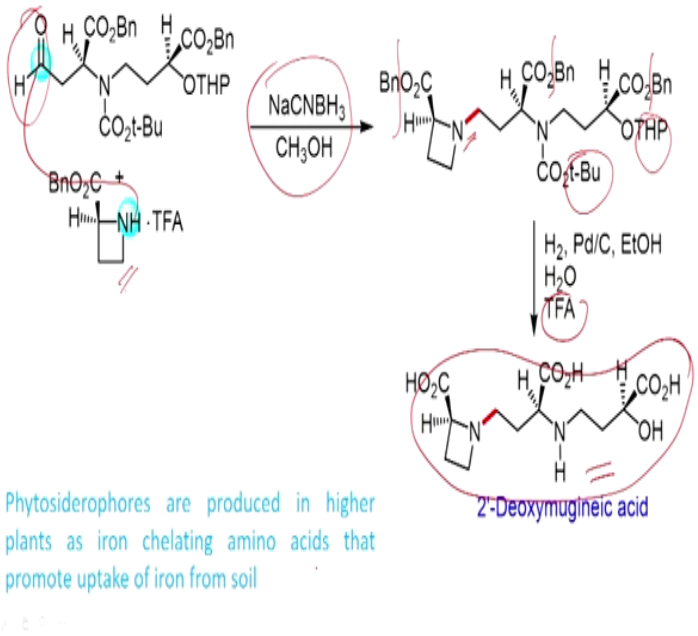

Here the synthesis of the amino acid starts with the secondary cyclic amine. It reacts with aldehyde to give the imine, which can be reduced in the reaction medium using sodium cyanoborohydride into amine. When you do hydrogenation using palladium/charcoal, the benzyl group is deprotected. Similarly, the reaction using TFA can deprotect t-butyl as well as THP to produce 2-deoxymugineic acid. It is produced in higher plants as iron chelating amino acids that promotes uptake of iron from the soil.

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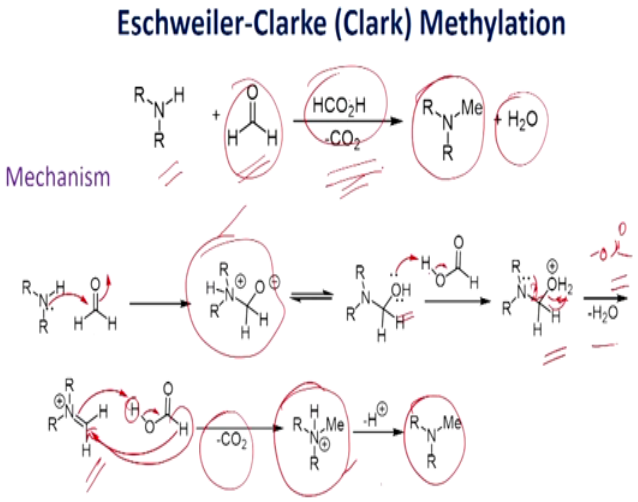

In the previous reactions aldehydes react with amine to give imine, which is reduced in the reaction or separately using hydride or hydrogen in the presence of nickel or palladium based catalyst.

Alternatively, if we have the amine that can be reacted with aldehyde to form the imine, which can be reduced using formic acid to alkylamine, where you generate water as a by-product. The mechanism is here shown. Amine with formaldehyde gives the addition compound, which undergoes protonation using formic acid. Removal of water provides an iminium ion, which is reduced by formic acid to give N-methyl amine as the product.

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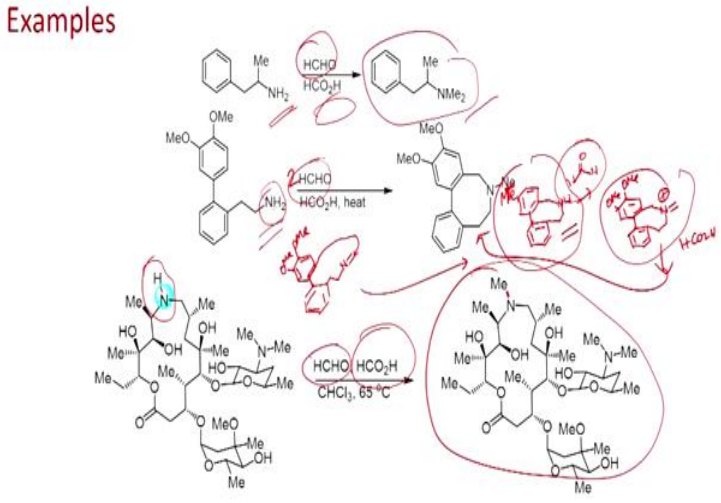

This slide shows some more examples for the transformation of amine to n-methyl amines. The first example involves the reaction of primary amine with formaldehyde in the presence of formic acid to produce dimethylamine.

The next example involves the reaction of primary amine with formaldehyde to produce imine, which undergoes an intramolecular aromatic electrophilic substitution to give the cyclic secondary amine. Which further reacts with formaldehyde to give imine that is reduced by formic acid to produce N-methyl amine derivative as the product.

In the other example, the macrocyclic secondary amine reacts with formaldehyde to give imine that is reduced using formic acid to give the n-methylamine as a product. So this one of the effective routes if you want to introduce methyl group.

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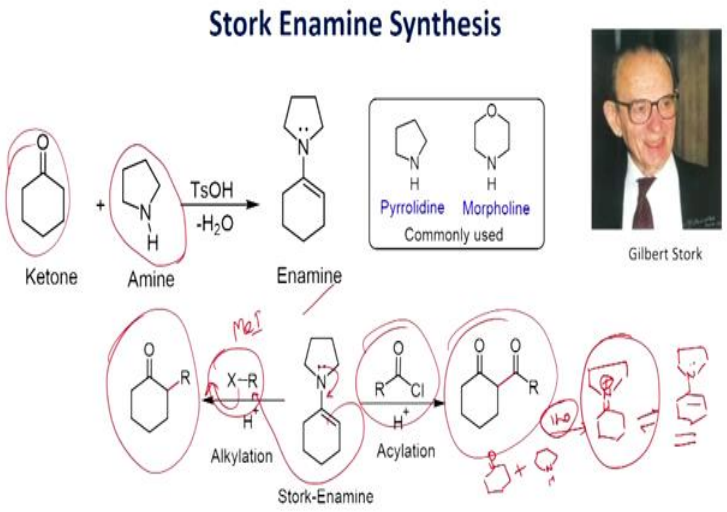

So far we have seen the formation of imine and their reduction to amines. Now let us see the application of Stork enamine synthesis. In this reaction, the carbonyl compound undergoes condensation with secondary amine to give enamine. Here the reaction of pyrrolidine with cyclohexanone gives the enamine, which undergoes a substitution or addition reaction. For example, if you react with methyl iodide, which leads to a substitution reaction. This way you will be able to introduce an alkyl group. On the other hand, if you react with an acid chloride, you can carry out acylation to produce 1,3-diketone as the product.

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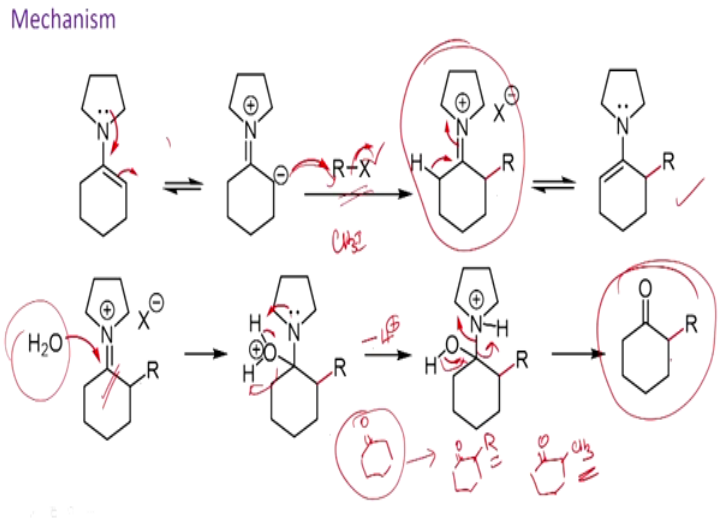

Let us see the mechanism. If you have an alkyl halide, enamine can undergo the substitution reaction. So you will be able to get the substitution product. Hydrolysis of the iminium ion can produce the alkylated ketone as the product.

So if you have the ketone, you can try to readily react with secondary amine to produce the enamine, which can be readily reacted with the electrophile to give the substitution product. Here cyclohexanone is converted to 2-alkyl cyclohexanone. For example, if you react with methyl iodide, you will be able to generate 2-methyl cyclohexanone.

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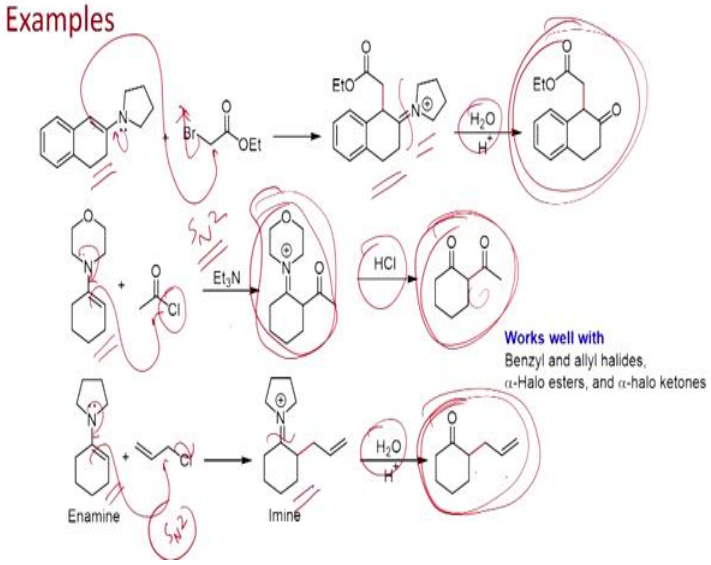

Here the reaction of enamine with α-bromoester gives the substituted product. Hydrolysis of the iminium ion produces the alkylated ketone as the product.

The next example involves the reaction of the enamine with an acid chloride. As we have seen, you can readily react to introduce the acyl group. Hydrolysis of the iminium ion using HCl gives the 1, 3-diketone as the product.

The third example involves the reaction of enamine with allyl chloride. As we have seen, you can readily react via S_N2 pathway to give iminium ion. Which by hydrolysis is converted to allylic cyclohexanone.

So the enamine can be readily reacted with alkyl halide, acid chloride or allyl halide via substitution to give the corresponding substituted compound. The resultant iminium salt can be converted to the corresponding keto derivatives by hydrolysis.

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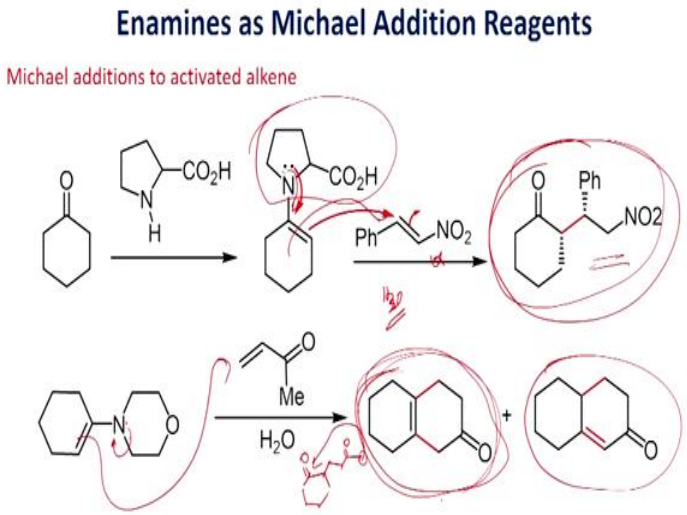

The next example involves the reaction of enamine with an activated alkene via Michael addition to produce the addition product. As we have seen, the auxiliary can be removed by hydrolysis to produce the substituted cyclohexanone.

The next example involves the reaction of methyl vinyl ketone, as we have seen again, it can undergo addition reaction via Michael addition. The resultant product can be converted into bicyclic ketone via aldol reaction using base or acid.

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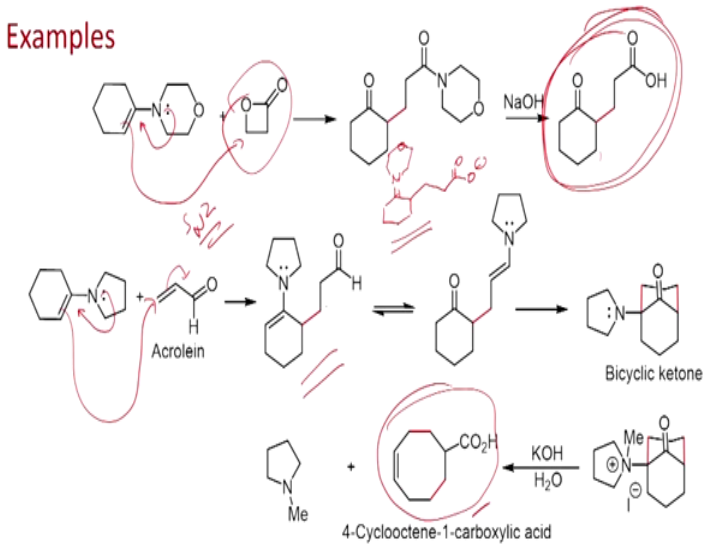

Similarly, enamine can be reacted with lactone via the nucleophilic ring opening. The base hydrolysis can produce the carboxylic acid as the product. For example, the reactive four

membered lactone undergoes nucleophilic ring opening to give the amide, that can be further converted to carboxylic acid derivative.

Next example involves the reaction of acrolein via Michael addition to produce the addition product. Which can undergo further reaction to produce the bicyclic ketone, which on treatment with methyl iodide provides amine salt. This rearranges to cyclooctene carboxylic acid and N-methyl pyrrolidine.

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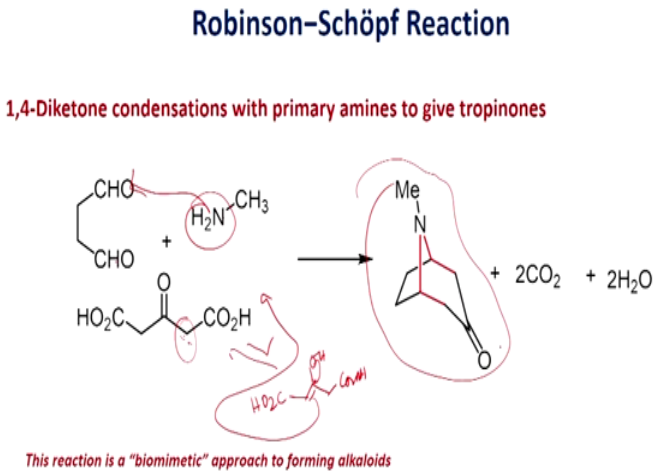

Here the coupling of succinaldehyde with methylamine and acetonedicarboxylic acid is shown. In the reaction, the amine first undergoes condensation with CHO group to give an imine. Which undergoes addition reaction with the enol of succincarboxylic acid to produce the addition product. As above, the resultant secondary amine can further react with CHO group to produce an iminium ion, which can undergo addition reaction with the keto enol to give the bicyclic dicarboxylic acid. Dearboxylation can produce the bicyclic ketone as the product. Thus, the reaction involves a double Mannich reaction followed decarboxylation.

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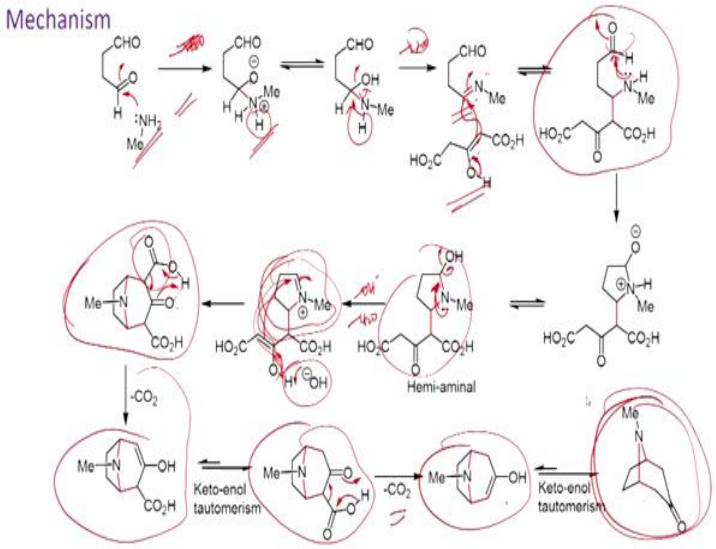

The mechanism is here shown. CHO group first undergoes condensation with methylamine to generate an imine, which leads to an addition reaction with enol to give the secondary amine derivative. As above, the secondary amine can further undergo intramolecular condensation with the CHO group to give the iminium ion intermediate. Which can undergo intramolecular addition reaction with enol to give the bicyclic compound. Decarboxylation produces the bicyclic ketone.

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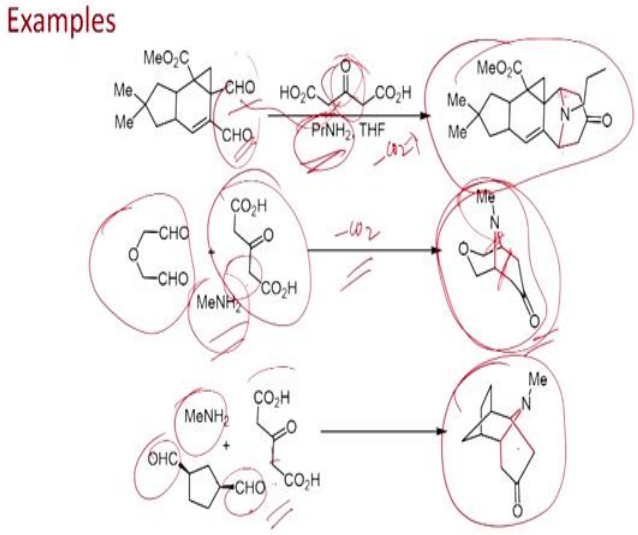

Here three component coupling of propylamine with dialdehyde and acetonedicarboxylic acid produces the fuzed heterocyclic scaffold via the double Mannich reaction. One of the CHO groups undergoes condensation with propylamine to form the imine. That imine can undergo

reaction as just we have seen with the enol of the acetonediarboxylic acid. The resultant secondary amine can further undergo the intramolecular condensation with another CHO group to give the iminium ion. Intramolecular addition with enol that can be generated from the keto diarboxylic acid can give the fuzed heterocyclic scaffold.

Similarly, the next example involves the coupling of methylamine with dialdehyde and acetonedicarboxylic acid followed by decarboxylation to produce the bicyclic ketone bearing ether and amine functional groups. The next example involves the three-component coupling of the dialdehyde, methylamine and acetonedicarboxylic acid followed by decarboxylation to give the tricyclic ketone. Thus, Mannich reaction provides a powerful synthetic tool for the coupling of amine, aldehyde and enol to give complex heterocyclic compounds that are important in medicinal science.

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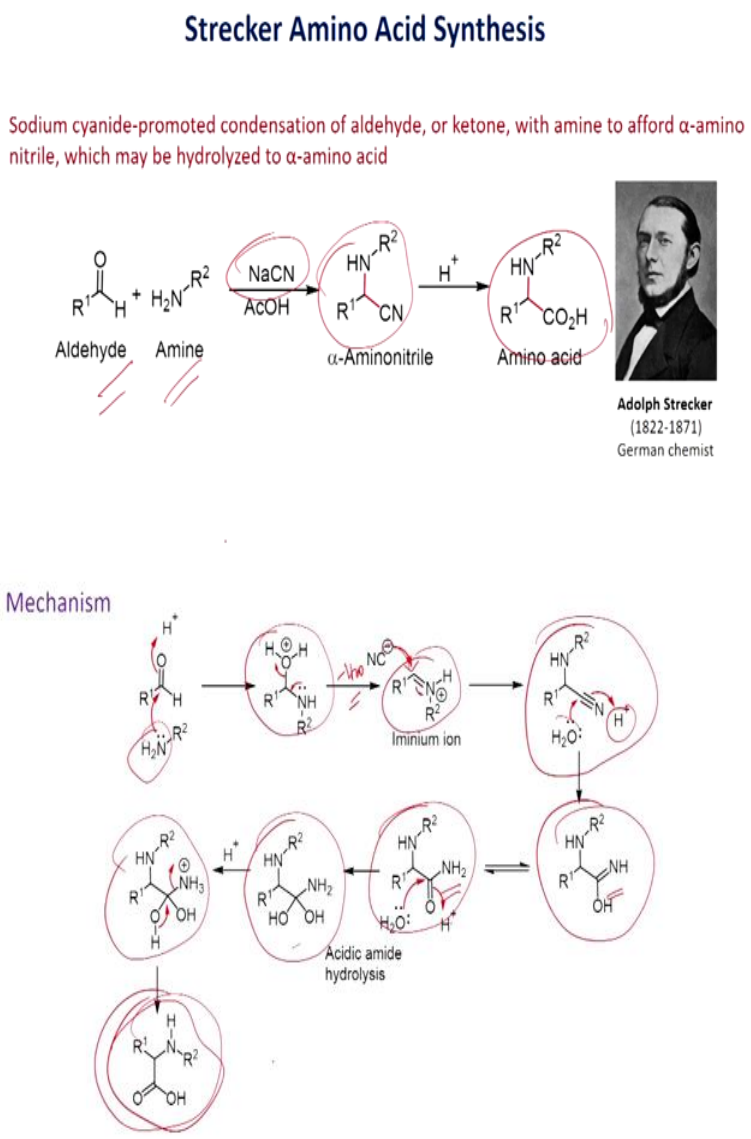

Now let us look at the Strecker amino acid synthesis. As you can see here if you have the aldehyde, you can readily react with amine to give the imine, which can be reacted with cyanide ion to give the addition product. Once you have the addition product, which can be hydrolysed to give the α-amino acid as the product. In this way if you have the aldehyde and the amine, you can convert into α-amino acid.

The aldehyde first undergoes addition reaction with the amine, which as a nucleophile and the aldehyde as an electrophile. Once you form the hydronium ion, which can lose water molecule, as shown to form the iminium ion. Once you from the iminium ion, the cyanide ion can undergo addition reaction to form the nitrile derivative. Hydrolysis of the nitrile derivative gives the α-amino carboxylic acid.

Therefore, if you have the aldehyde and amine, you can do the condensation to form the imine that imine can be reacted with cyanide ion to give nitrile, which can be transformed to the α-amino acid as the product.

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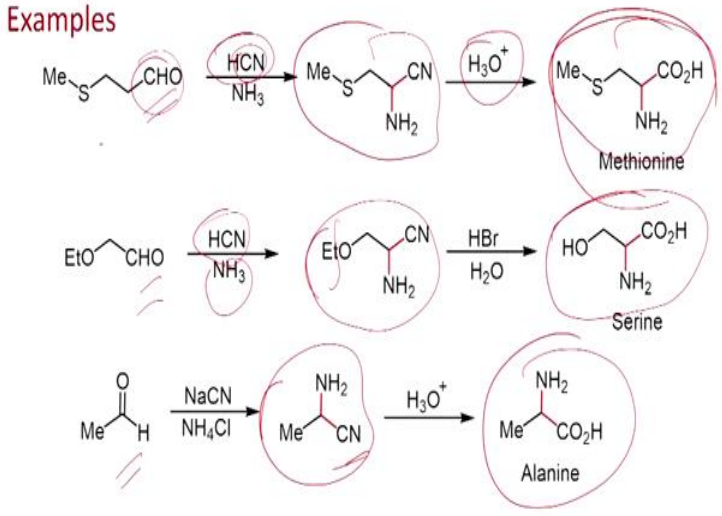

Here some examples are shown. The first example involves the reaction of the aldehyde with HCN the and ammonia. As we have seen just now, it can undergo reaction with ammonia to form the imine, which can react with the cyanide ion to give the addition product. Hydrolysis of nitrile group can produce methionine.

The second example the coupling ethoxyacetaldehyde with HCN and ammonia to produce amino nitrile derivative. Which undergoes ether cleavage as well as hydrolysis of nitrile group using aqueous HBr to serine as the product.

The next example involves the reaction of acetaldehyde with sodium cyanide and the ammonium chloride to form the amino nitrile derivative, which on hydrolysis gives the alanine. Therefore, if you have aldehyde that can be readily reacted with amine to form the imine, which can be further reacted with cyanide ion to give the nitrile derivative. Hydrolysis of the nitrile group can produce the amino acid.

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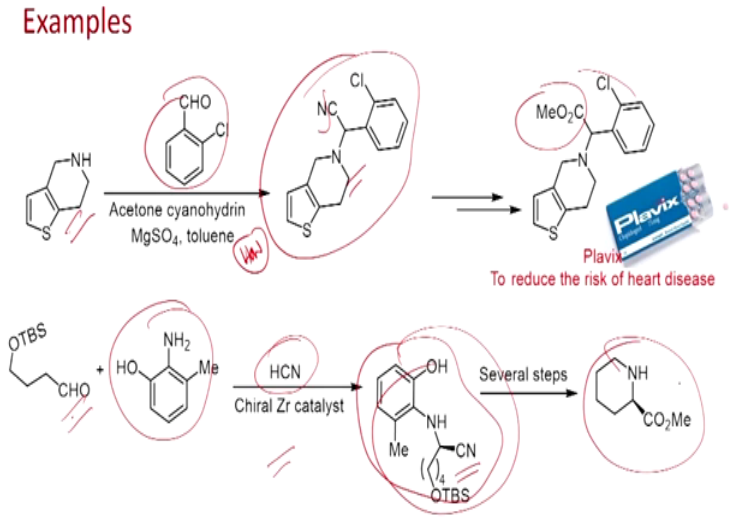

Here some applications are shown. The first example involves the reaction of the secondary amine with 2-chlorobenzaldehyde. The condensation gives the imine that can be reacted with cyanide ion to give nitrile derivative. Hydrolysis followed esterification gives Plavix, which is an important drug for heart disease.

The next example involves the reaction of the aldehyde bearing silylether substituent with aniline derivative. As above, the condensation of aldehyde with amine can give the imine, which is added stereroselectivly with HCN using chiral Zr-catalyst to give optically active nitrile derivative. This has been converted into cyclic amino ester by several steps.

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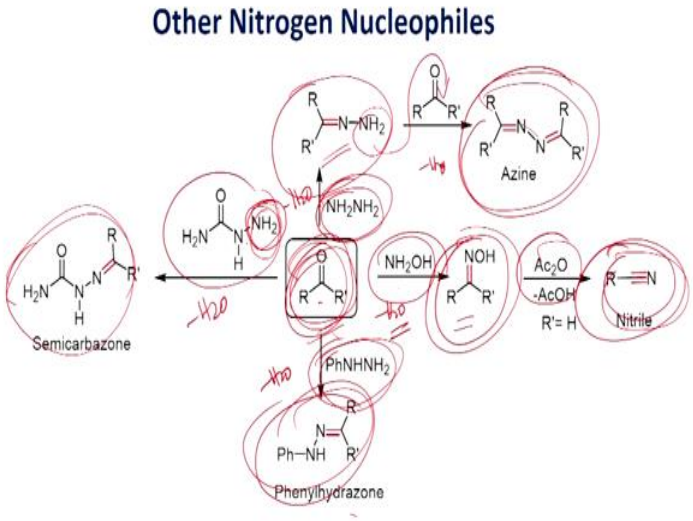

Here the reaction of carbonyl compounds with amines are shown. The first one involves the reaction of hydrazine. The condensation gives imine derivative, which can further react with another molecule of the carbonyl compound to form azine.

The next reaction involves the condensation with semicarbazide to form semicarbazone. Similarly, phenylhydrzine can undergo condensation to give phenylhydrazone via addition followed by removal of water. Likewise, hydroxylamine can undergo reaction to give oxime, which can be converted to nitrile using acetic anhydride. Therefore, if you have the carbonyl compound, you can readily react with amine to give a variety of compounds.

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Summary

- Reaction with Aldehydes
- Substitution and Addition Reaction of Imines
- Stork Enamine Synthesis
- Synthesis of Alkaloids
- Strecker Amino Acid synthesis

In summary, in the first part, we have seen the reaction of aldehyde with amines. For example, ammonia with formaldehyde give hexamethylenetetramine. Aldehyde readily undergoes reaction with amine to give the imine that depends upon the reaction conditions and nature of the substrates, they can be further reacted to give the addition product.

We have seen the transformation of the imine to amine by hydrogenation. You can use sodium cyanoborohydride and lithium cyanoborohydride, which can reduce the imine to amine. In addition, if you have the catalyst, you can reduce imine to amine by hydrogenation.

Then we have seen the formation of enamine and their application for the alkylation and acylation reactions. If you have the carbonyl compound like cyclohexanone, if you want to introduce alkyl or acyl group at the α-carbon, you can try to react with a secondary amine like pyrrolidine. You can make the imine, which can convert to enamine. Once you form the enamine, which can act as a nucleophile if you have the electrophile like alkyl halide, it can undergo substitution reaction.

On the other hand, if you have acid chloride, you can also replace the Cl, you can make the acylation at the α-carbon. If you have activated alkene, you can also do Michael addition. In this way, you can form a carbon-carbon bond. Then, we have seen the alkaloid synthesis via Mannich reaction. If you have the aldehyde and amine, they can undergo condensation to give the imine, which can be reacted with enol. We have seen the construction of variety of alkaloids using dialdehydes, acetonedicarboxylic acids and amine.

We have seen the Strecker amino acid synthesis. If you have the aldehyde, you can try to react with amine to form the imine, that can be reacted with the cyanide ion to get the addition product. Once you have the addition product, that cyanide can be converted to carboxylic acid by hydrolysis. In this way, you can try to make α-amino acids.

Then, we have seen the reaction of carbonyl compounds with different amine sources. We have seen the reaction with the hydrazine and hydroxylamine, they can be readily converted to amine derivatives. With this, we conclude this lecture. Thank you very much.