Principles of Organic synthesis
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Lecture 10
Carbon-Nitrogen Bond Formation

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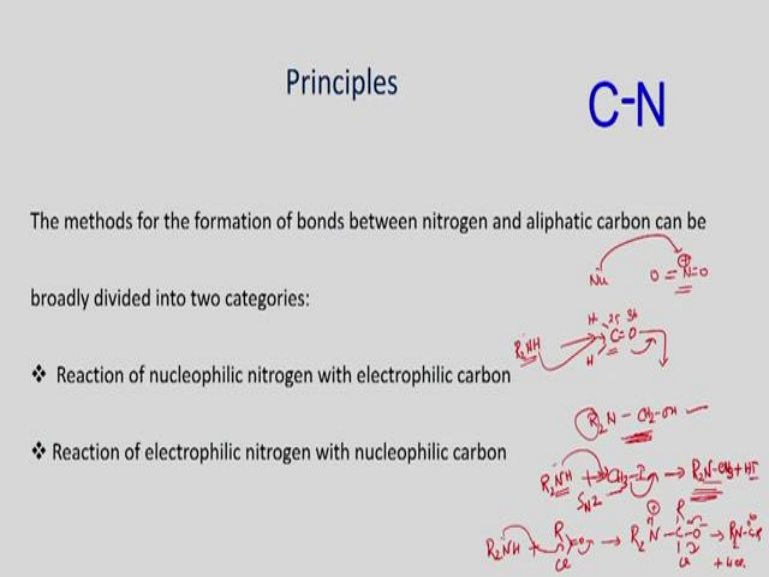

Welcome you all to principles of organic synthesis. So far, we had nine lectures where we studied the formation of aliphatic carbon-carbon bonds. In the first module, we saw the use of base as a catalyst. Then, we saw the reaction using acid as a catalyst. At the end, we saw the use of organometallic reagents.

Today, we will start the construction of C-N bond. This is an important transformation. If you want to make heterocyclic compounds, for example, having nitrogen atom, this is one of the efficient approaches.

The principles for the carbon-nitrogen bond formation is here shown. As you can see, if the nitrogen is nucleophilic enough, it can undergo an addition reaction with electrophiles. Let us look at formaldehyde, the carbon is electrophilic because the bond pair is polarized towards oxygen (electronegativity oxygen is 2.5). Thus, when you have the nucleophilic nitrogen, it can undergo addition reaction. For example, if you react with the amine, it can lead to the addition reaction. Depends on the substituent, if it is hydrogen, it can lose water molecule to give the Schiff base as the product. Similarly, if you react with methyl iodide, which can undergo S_N2 reaction. The other example involves acid chloride, which can react with amine to give amide as the product via addition followed by elimination of HCl. These are the some of the examples for the reaction of nucleophilic nitrogen with electrophilic carbons.

On the other hand, if the nitrogen is electrophilic, it can undergo reaction nucleophile. For example, let us take NO_2^+ where the nitrogen is electrophilic. Therefore, whenever you have the nucleophile, which can undergo addition reaction to give the addition product.

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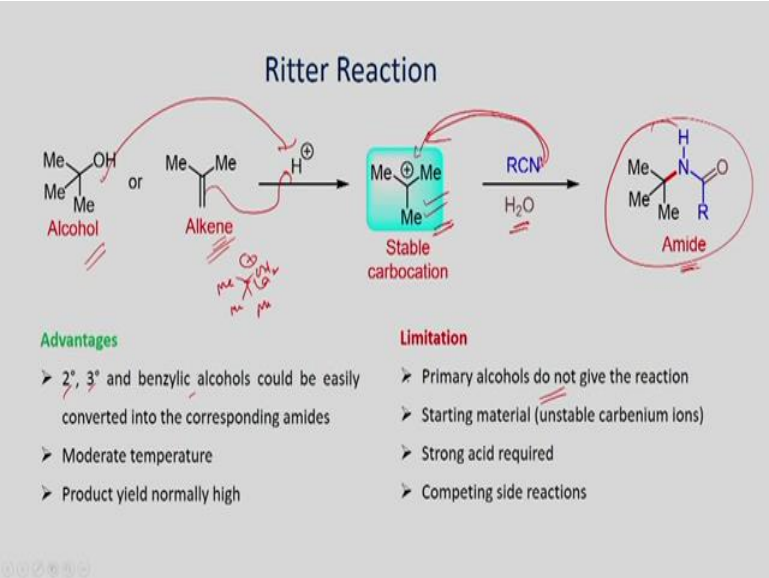

Now let us look at the Ritter reaction. If you have the tertiary alcohol or substituted alkene, which with acid can form a carbocation. The carbocation can undergo addition with nitrile to form an ammonium ion, which when you do the work up using water, it will be converted to amide.

For example, when you react tertiary butanol with acid, you will protonate to form the hydronium ion. This can lose a water molecular to form tertiary carbocation. Similarly, isobutene can add to proton when we treat with acid to produce the tertiary carbocation. Once you form the stable tertiary carbocation, which can readily undergo reaction with lone pair of the nitrogen of nitrile to form the iminium ion. Which can be added with water where water acts as a nucleophile and the iminium ion acts as the electrophile to give the amide as the product.

Using this method, secondary, tertiary and benzyl alcohols can be converted to the amides. On the other hand, if you have the primary alcohols, which are required vigorous reaction conditions and produce the by-products.

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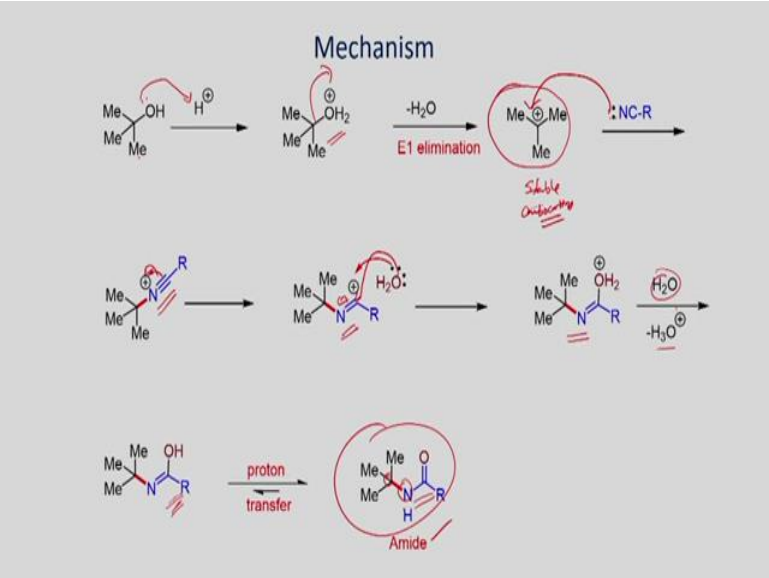

Mechanism of the reaction of tertiary alcohol is shown here. Protonation of the OH group can generate the hydronium ion, which loses water molecule to give the tertiary carbocation. Which can react with the nitrile to form the salt that will be converted to the iminium ion. Addition of water molecule can produce the enol. which will be converted to the amide. So if you have the tertiary alcohol, it can be readily converted to the amide at moderate temperature using acid and where you make a new C-N bond between the carbon of alcohol and nitrogen of the nitrile.

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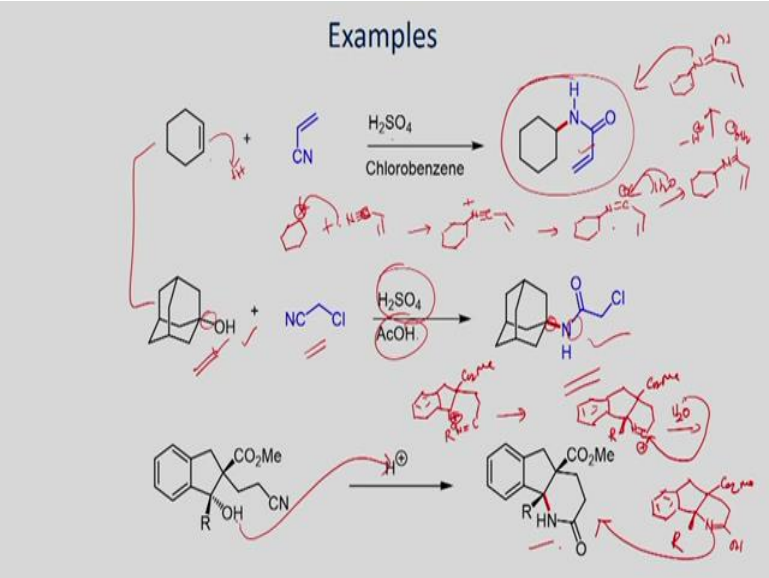

Let us see some more examples. The first one involves the reaction of cyclohexene with acrylonitrile using acid to give the amide. The alkene first forms the secondary carbocation, which reacts with acrylonitrile to give the iminium ion that can add with water to produce the enol. This can be converted to amide as the product.

Similarly, the tertiary alcohol can be readily reacted with nitrile compound in the presence of sulphuric acid in acetic acid medium to generate the amide. This way you can make a C-N bond between the nitrogen of nitrile and the carbon of the tertiary alcohol. These are the examples for the intermolecular reaction.

The third example involves an intramolecular reaction. When you do the protonation, you will be able to form the benzylic carbocation. Which can undergo intramolecular reaction with the nitrile to form an iminium ion. Addition of water molecule can lead to the formation of the amide as the product.

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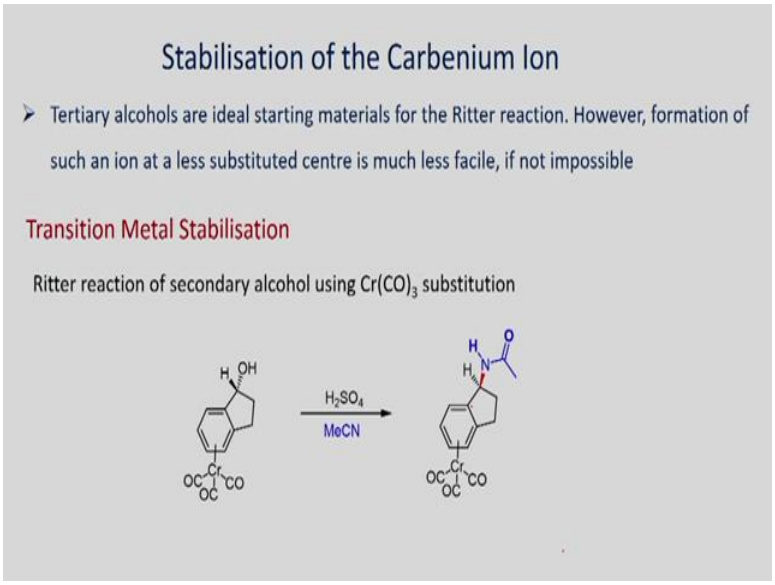

Here an example is shown where the reaction of the indanol bearing chromium tricarbonyl with an acetonitrile in the presence of sulphuric acid gives the corresponding amide as the product. In this substrate, chromium tricarbonyl stabilizes the carbocation intermediate to facilitate the reaction.

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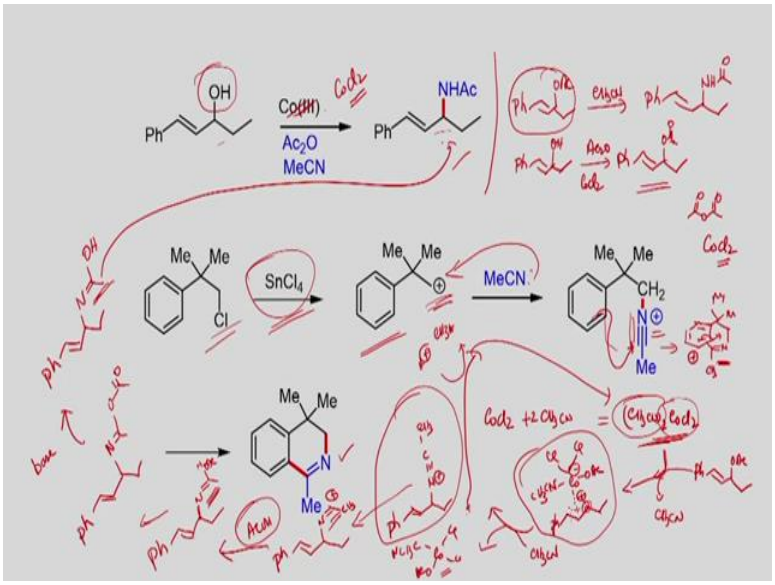

This slide shows the reaction of allylic secondary alcohol to amide. In this reaction, first the allylic alcohol is converted to acetate, which further reacts with acetonitrile to give the amide as a product. If you look at the mechanism, the alcohol reacts with acetic anhydride using cobalt(II) chloride to give the allyl acetate as the product. Which with cobalt chloride in the presence of acetonitrile form the allyl cobalt complex. Intramolecular transfer of acetonitrile gives the iminium ion, which can react with acetic acid to give the acetate. Base hydrolysis can produce the enol, which can isomerize to acetamide as the product. Thus, cobalt(II) chloride first acts as a Lewis acid to convert alcohol to acetate, which further reacts with cobalt(II) chloride to form the allyl complex, in which acetonitrile reacts to give the substituted iminium ion, which is further converted to amide.

The next example involves the reaction of the alkyl chloride with tin(IV) chloride to produce the primary carbocation. Which undergoes reaction with acetonitrile to give the nitrilium ion that reacts with aromatic ring via electrophilic substitution to give the bicyclic compound.

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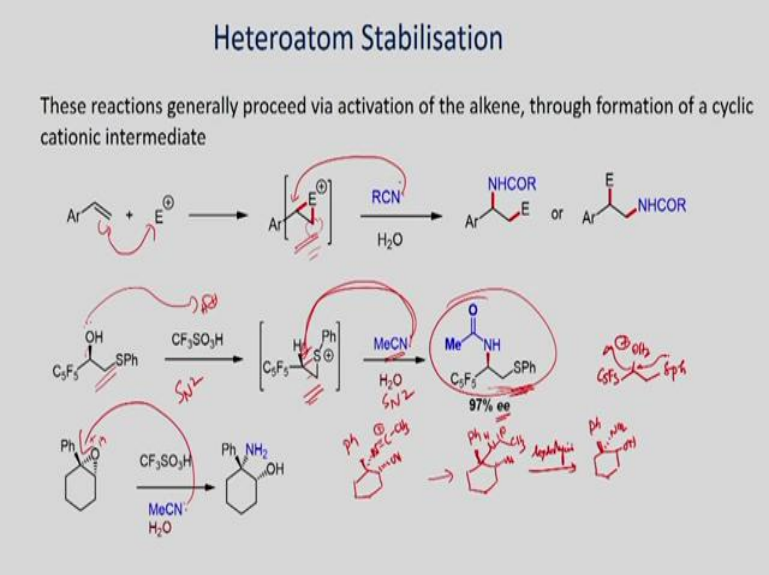

Here are the reactions that involve the stabilization by heteroatoms. The first example involves the reaction of styrene with electrophile to give the cyclic cation intermediate. Which reacts with nitrile at benzylic as well as less hindered carbon to give a mixture of amides.

The next example involves the reaction of the optically active secondary alcohol with acetonitrile using trifluoromethanesulphonic acid. In the reaction, the removal of water molecule is facilitated by the S_N2 substitution of neighbouring SPh. The cation intermediate undergoes reaction with acetonitrile via S_N2 pathway to produce the amide with retention configuration.

The other example involves the opening of epoxide with acetonitrile followed by hydrolysis to give the amino alcohol as the product. In this reaction, the epoxide is protonated, which then undergoes the nucleophilic ring opening with acetonitrile to give the nitrilium ion. Reaction with water can form the amide that can be converted to amine by hydrolysis.

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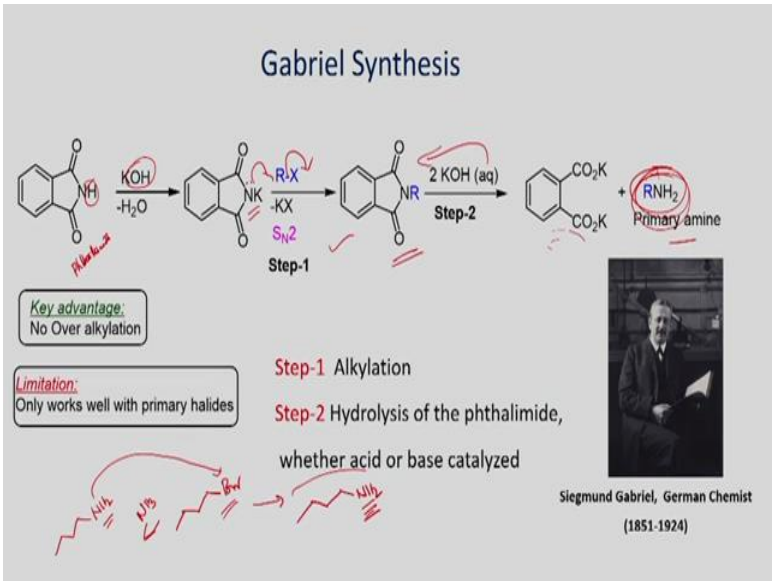

Now let us look at amination of alkyl halide. If you want to make primary amine from alkyl halide, one of the efficient approaches is the Gabriel synthesis. You have to start with phthalimide. Deprotonation using base can give the salt, which can undergo S_N2 reaction with alkyl halide to N-alkyl phthalimide. Treatment with two equiv of aqueous KOH cam give the primary alkyl amine as the product.

On the other hand, if you react alkyl bromide with ammonia, it will produce prmary alkyl amine, which can further react with alkyl halide to give dialkyated product. The dialkylated product can also further react with alkyl halide to give trialkyl amine. Thus, if you want selectively the primary alkyl amine Gabriel synthesis is one of the best methods.

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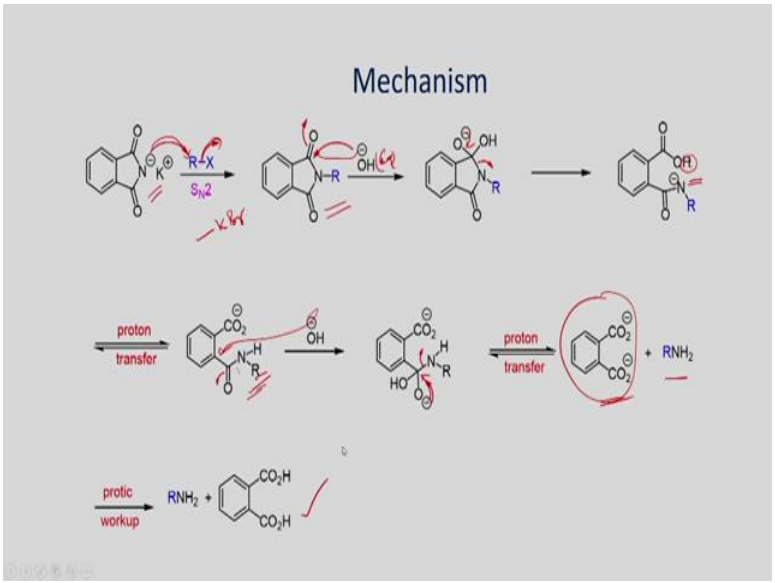

Mechanism of the Gabriel synthesis is here shown. Deprotonation of phthalimide with base can give the salt, which can undergo S_N2 substitution with alkyl halide to give N-alkyl phthalimide. Treatment with two equiv of aqueous potassium or sodium hydroxide can give the primary alkyl amine and phthalic acid. So Gabriel synthesis is a good method if you want to convert a primary alkyl halide into the corresponding primary alkyl amine as the product.

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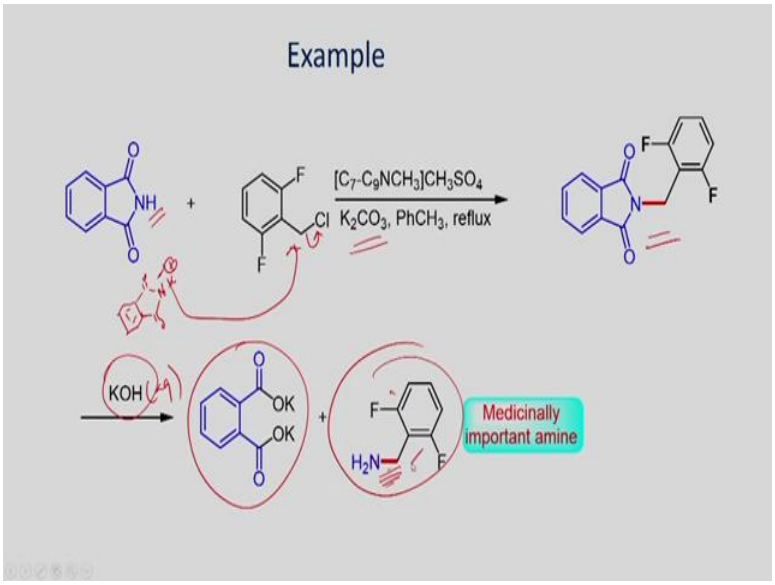

Here an example is shown for the construction of 2,6-difluorobenzylamine. Coupling of the 2,6-difluorobenzyamine with phthalimide in the presence of base can produce N-2,6-difluorobenzyl phthalimide. Hydrolysis using two equiv of aq KOH can produce the target 1,6-difluorobenzylamine and potassium salt of phthalic acid.

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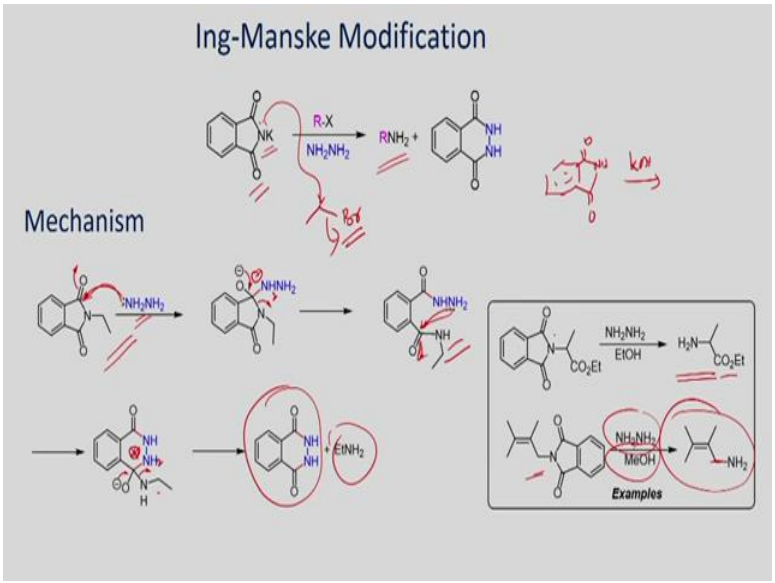

N-Alkyl phthalimide can also be reacted with hydrazine to generate the primary alkyl amine, which is known as Ing-Manske modification. The mechanism follows: for example, if you react potassium salt of phthalimide with ethyl bromide, you will be able to form N-ethyl phthalimide vis S_N2 reaction. Addition of reaction of hydrazine can generate the ethyl amine.

Here two examples are shown. The first one shows the reaction with hydrazine to produce α-amino ester. The next example involves the reaction of N-allyl phthalimide with hydrazine to produce allyl amine.

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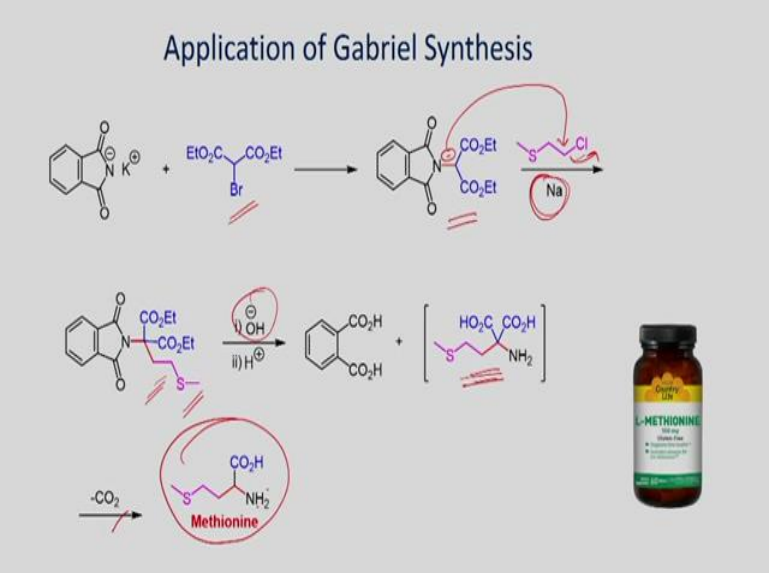

Here an application of Gabriel synthesis is shown for the preparation of methionine. As we have seen, when you react phthalimide salt with diethyl malonate bearing bromo substituent, you will be able to form the substituted compound. Which can undergo reaction with sodium to form carbanion, that can lead to S_N2 reaction with the chloro derivative bearing thioether to give N-alkyl phthalimide. Treatment with an excess aq KOH will be produce methionine via hydrolysis of phthalimide as well as the esters followed decarboxylation.

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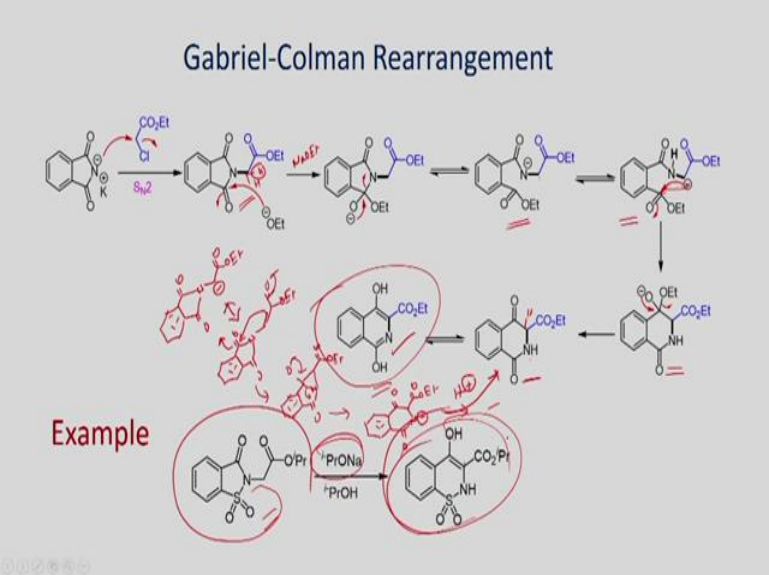

Here the Gabriel-Colman rearrangement is shown. When you react ethyl chloroacetate with potassium salt of phthalimide, you will be able to get the S_N2 substituted derivative. Addition of ethoxide ion to imide carbonyl group can produce the ring opened ester derivative. Proton shift to nitrogen ion can generate the carbanion, which can be stabilized by the ester group. Intramolecular cyclization with the ester group can form the lactam. Which can convert to the isoquinoline derivative.

Alternatively, the ethoxide can deprotonate the acidic hydrogen to generate carbanion, which can be stabilized by the ester group. Intramolecular addition to imide carbonyl group can produce a three membered cyclic intermediate, which can open up since it is strained to form the lactam that will be converted to the isoquinoline.

In the example given, as above, the alkoxide ion can deprotonate the acidic hydrogen and the carbanion can lead to addition followed by ring expansion to give the bicyclic sulphone derivative.

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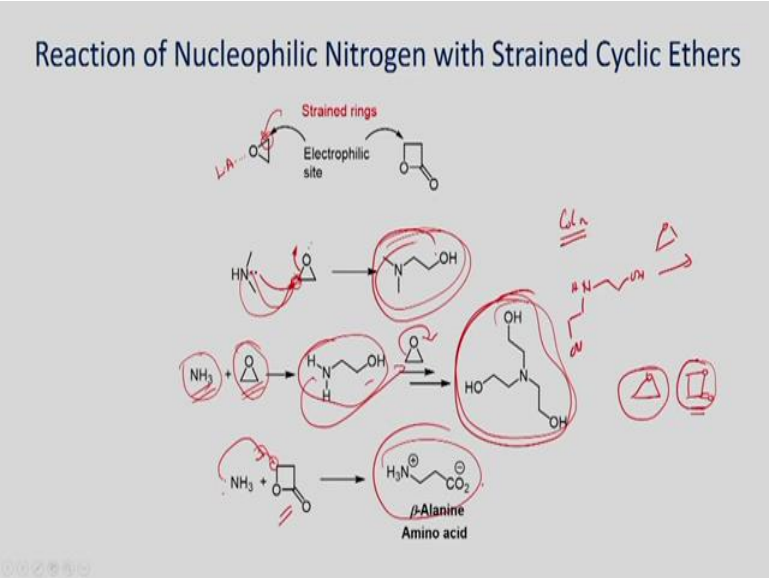

The reaction of strained ring molecules is here given. You can readily activate epoxide a well as lactones using Lewis acid. Chelation of the Lewis acid with epoxide or lactone can make the carbon more electrophilic, which can react with nitrogen nucleophile via nucleophilic substitution to give the ring opened products.

In the first example, the secondary amine opens epoxide to give amino alcohol. The reaction can be facilitated using Lewis acid like colbalt(II) chloride or cobalt(II) complex as the catalyst. The cobalt catalyst can make chelation with epoxide oxygen and can activate the carbon as more electrophilic. So that the dimethyamine can readily open the epoxide to produce the amino alcohol as the product.

The next example involves the reaction of ammonia with ethylene oxide. The reaction shows the reaction one equiv of ammonia with three equiv of epoxide to produce the tertiary amino alcohol as the product.

The third example involves the opening of lactone with ammonia to produce β-alanine. Since the product exists as zwitterion, which does not further react with another molecule of lactone to produce di or trisubstituted amino derivative.

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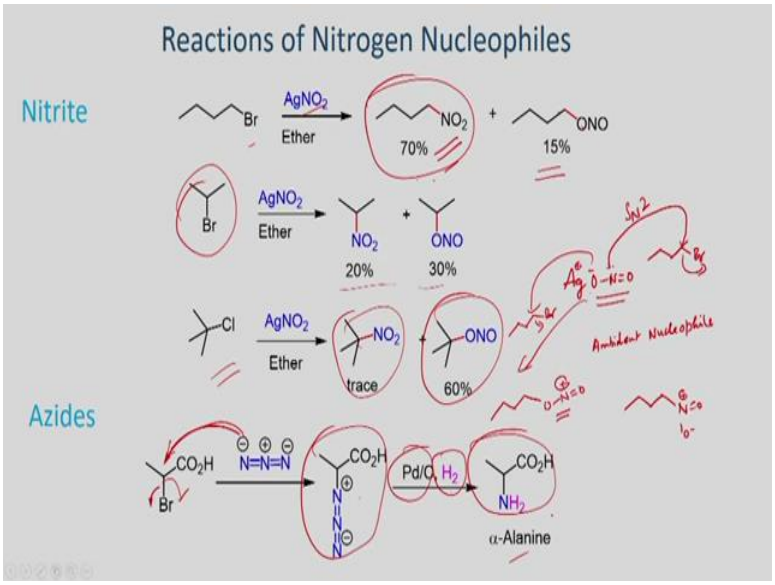

Here the substitution reactions are shown. The reaction between alkyl halide and silver nitrite produces a mixture of products due to ambident nature of NO_2 (nitrogen as well as oxygen act as the nucleophile).

The next example involves the reaction of azide ion with α-bromopropionic acid via nucleophilic substitution. Reduction of the azide substituent using palladium/charcoal produces α-alanine as the product

So here we have seen the nitrite as a nucleophile if you have alkyl halide it can undergo substitution reaction to give the alkyl nitrite as the product. Similarly, if you have azide ion that also can act as a nucleophile and can undergo substitution reaction with alkyl bromide or alkyl iodide to give the corresponding substituted alkyl azide as a product. This alkyl azide can be further reduced using palladium/charcoal in the presence of hydrogen to give amine derivative as a product.

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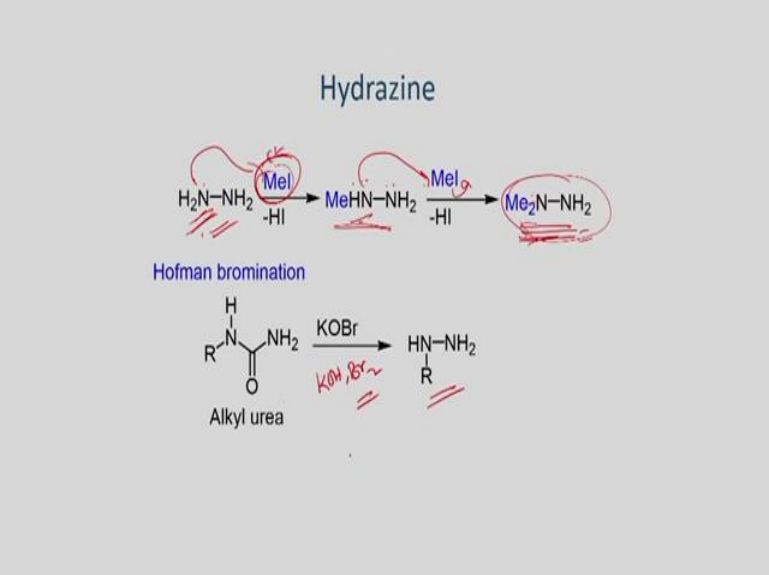

Here the reaction of hydrazine with alkyl iodide is shown. The reaction of between hydrazine and methyl iodide gives monomethylhydrazine. Since the methyl substituted nitrogen is more nucleophilic, it further reacts with an another equiv of methyl iodide to produce the respective dimethylhydrazine as the product.

The next example involves the selective preparation of monoalkylated hydrazine. This can be accomplished by the reaction of alkyl urea with potassium hydroxide and Br_2 (KOBr). It gives monoalkylhydrazine as the product through Hoffman bromination.

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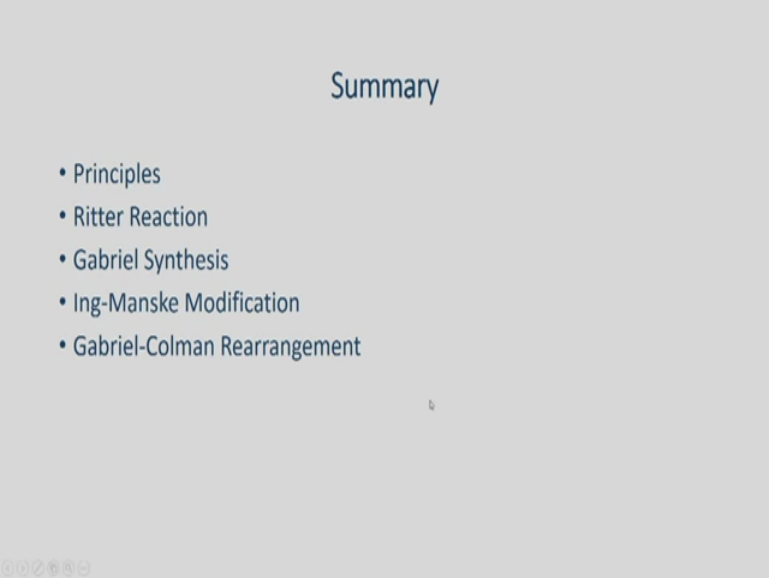

In summary, so we have seen several approaches for the construction of C-N bond. We have seen the principles of the reaction of nitrogen nucleophiles with carbon electrophiles. For example, if you have an amine that can react with the carbonyl compound like formaldehyde where the carbonyl group acts as an electrophile.

Then, we have seen the substitution reaction of methyl iodide. Further, acid chloride can undergo substitution via addition followed by removal of HCl to produce amide.

Alternatively, if you have the nitro group, which can act as an electrophile. In principle if you have a nitrogen nucleophile which can react with carbon electrophile to make C-N bond. On the other hand, if you have the nitrogen electrophile, which can react with carbon nucleophile to give C-N bond.

We have seen the Ritter reaction, which works well with tertiary alcohol as well as substituted alkene. In the presence of acid, they can convert to carbocation, which reacts with nitrile to give the amide. We have also seen cobalt-catalyzed allylic alcohol to allylic amide via allylic acetate formation.

We have seen the Gabriel synthesis for the preparation of primary alkyl amine from alkyl halide and phthalimide. The reaction involves nucleophilic substitution followed by removal of the phthalic acid. We have seen the application of the reaction for the synthesis of methionine. We can also use of hydrazine in place aqueous KOH for the formation of alkyl primary amine from N-alkyl phthalimide. This is called Ing-Manske modification.

We have seen Gabriel-Colman rearrangement for the preparation of isoquinoline derivatives. Subsequently, we studied the ring opening of epoxides and lactones with amines to produce amino alcohol as well as amino acids.

We have then seen alkylation of hydrazine as well as rearrangement of monoalkyl urea to monoalkylhydrazine using potassium hypobromite, with this we conclude this lecture. Thank you very much.