**Principles of Organic Synthesis**
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**Lecture 12**
**Aliphatic Carbon-Nitrogen Bond Formation**

Welcome you all to Principles of Organic Synthesis. At present, we study the aliphatic C-N bond formation. So far, we had two lectures in this topic. In this lecture, we will study the reaction of nucleophilic nitrogen with electrophilic carbon. In the second part, we will focus on the reaction of electrophilic nitrogen with nucleophilic carbon.

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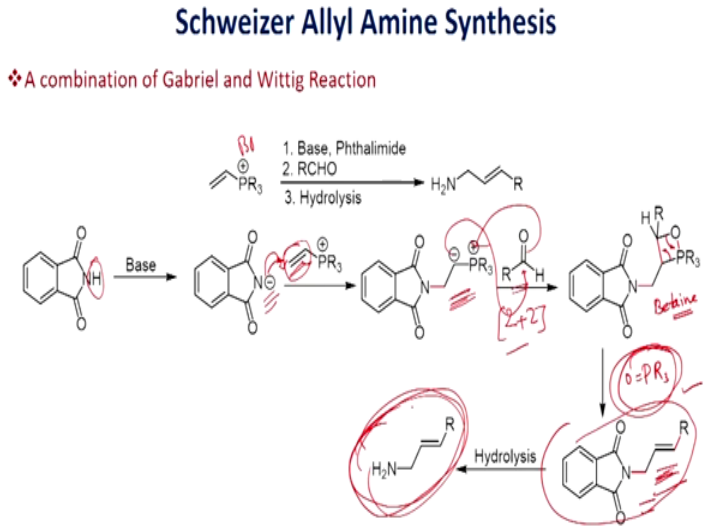


Here the synthesis of allylamine is shown. Phthalimide with base produces the anion, which reacts with vinyl phosphonium salt to give the ylide. [2+2]-Cycloaddition with aldehyde produces betaine, which loses phosphine oxide to give N-allyl phthalimide that on hydrolysis produces allylamine.

If you look at the reaction, it involves 3 steps. First, the base deprotonates to generate the anion, which undergoes addition with the double bond to give the phosphonium ylide. Reaction with aldehyde gives the betaine, which loses phosphine oxide to yield the allyl imide that is hydrolyzed to allylamine.

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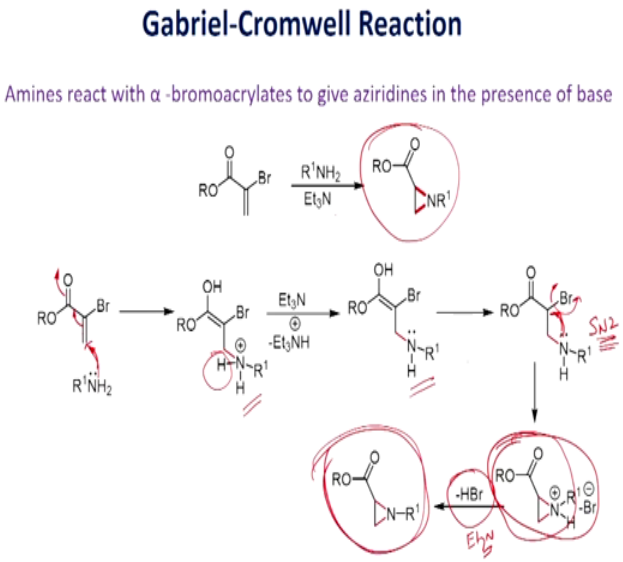


Here the reaction of α-bromoacrylate with amine is shown. Amine undergoes conjugate addition with α-bromoacrylate to give the salt, which leads an intramolecular $S_N2$ reaction to give the activated aziridine.

So if you have α-bromoacrylate, which can be reacted with amine in the presence of base to give aziridine.

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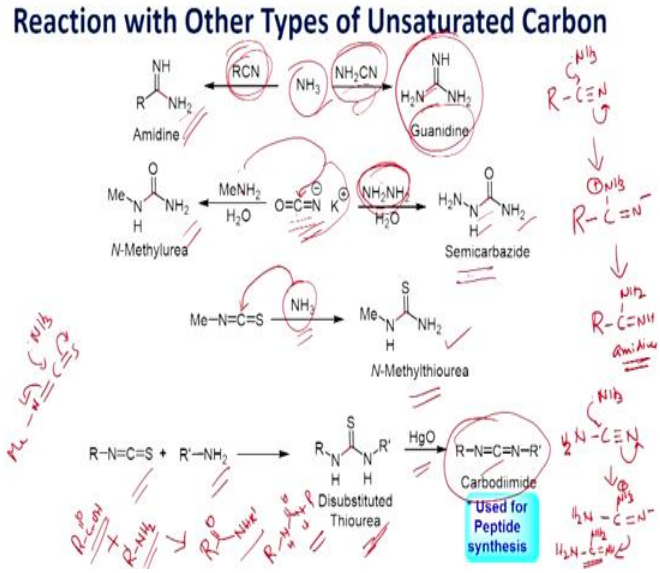

Here the first example involves the addition of ammonia with nitrile to produce amidine. Similarly, cyanimide with ammonia gives guanidine. The next example involves the addition of methylamine with potassium isocyanate to provide N-methyl urea. While the reaction with hydrazine produces semicarbazide. In these reactions, basically you add a nitrogen nucleophile to an electrophilic carbon to make a C-N bond.

Similarly, ammonia adds to methyl isothiocyanate to produce N-methyl thiourea. The next example involves the reaction of amine with alkyl isothiocyanate to give disubstituted thiourea, which with HgO produces carbodiimide that we use as the coupling reagent in peptide chemistry. For example, if you have amine and carboxylic acid, you will be able to form amide. Similarly, carboxylic acid can be coupled with alcohol to give ester. Basically carbodiimide removes water and converts to urea derivative. We will study the application of carbodiimide in detail in the synthesis of peptides.

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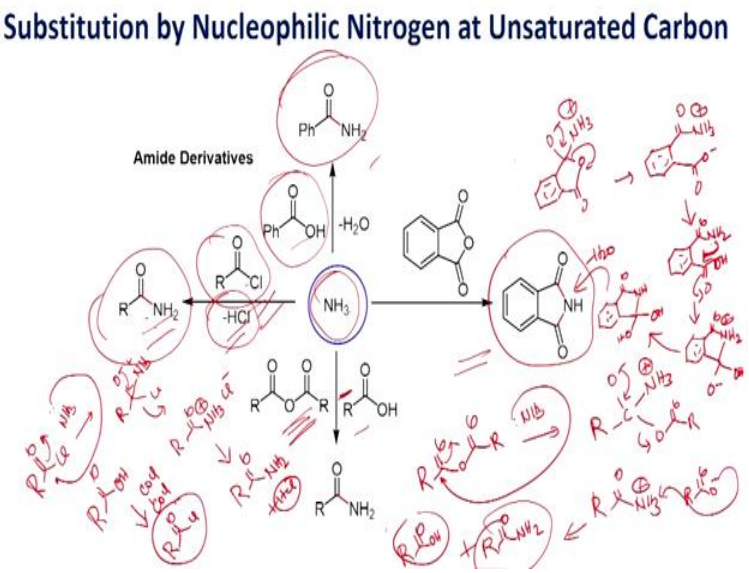


Here the reaction of ammonia with a variety of carbonyl systems is shown. If you look at the reaction of benzoic acid with ammonia, you will be able to form benzamide by the removal of water. However, the reaction of amine with aliphatic carboxylic acid is difficult as it forms salt. The best way is you can convert the carboxylic acid to acid chloride, which can be readily reacted with ammonia to generate the amide.

In place of acid chloride, you can use acid anhydride. It can also readily react to give the amide, where it generates carboxylic acid as a byproduct. For example, phthalic anhydride with ammonia produces phthalimide. First, the reaction of ammonia with phthalic anhydride produces benzamide derivative, which undergoes intramolecular condensation with carboxyl group to produce the imide.

Similarly, ammonia reacts with acyclic acid anhydride to produce amide along with one equiv of carboxylic acid via an addition followed by the removal of the carboxylic acid. Some carboxylic acids can be condensed with ammonia under heating to product the amide. Therefore, whenever we have the amine or ammonia that can undergo reaction with carbonyl systems like acid chloride, acid anhydride or carboxylic acid to give the amide as a product.

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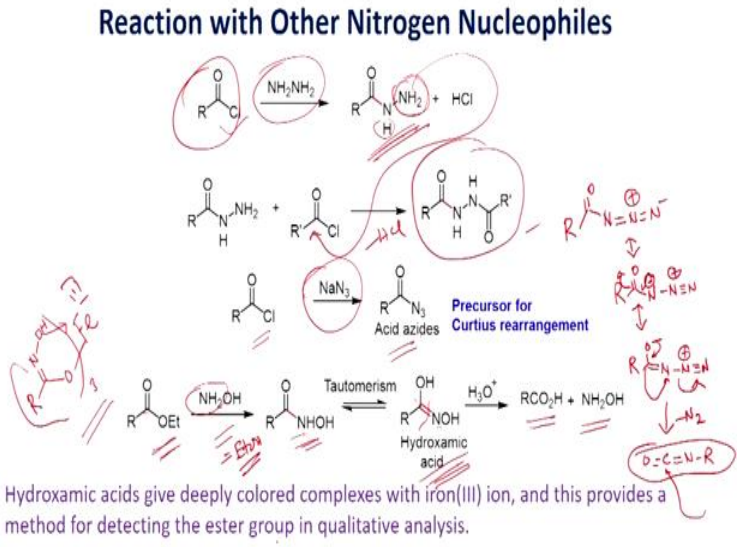


In addition to ammonia, you can also add other nitrogen nucleophiles. For example, if you look at here, you have the acid chloride, which can be reacted with hydrazine to provide the amide derivative. The reaction involves two equiv of acid chloride with one equiv of hydrazine to give the amide derivative.

The next example involves the reaction of acid chloride with sodium azide to provide acyl azide. This is the precursor for the Curtius rearrangement. When you heat, it leads to rearrangement to produce isocyanate.

The next example involves the reaction of ester with hydroxylamine to produce amide derivative, which tautomerizes to hydroxamic acid. Which is under hydrolysis converted to carboxylic acid and hydroxyl amine. This experiment is used in qualitative analysis to find out the presence of the ester functional group as hydroxamic acid gives deep color complex with iron(III) salts.

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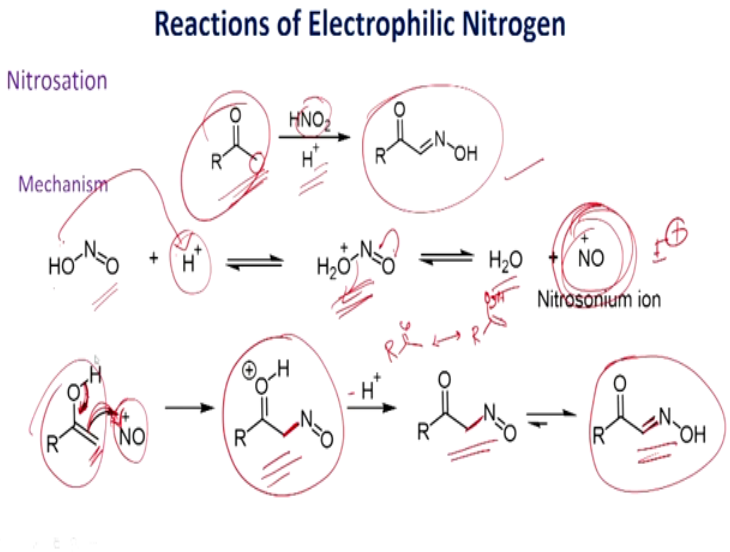


So far we have studied the reaction of nucleophilic amine with electrophilic carbon. Now, we are going to look at the reaction of electrophilic nitrogen with nucleophilic carbon. Look at here, the reaction of $HNO_2$ with ketone gives oxime as the product. If you look at the mechanism, $HNO_2$ protonates and loses a water molecule to give nitrosonium ion. Which leads to an addition reaction with enol of the ketone to give the oxime.

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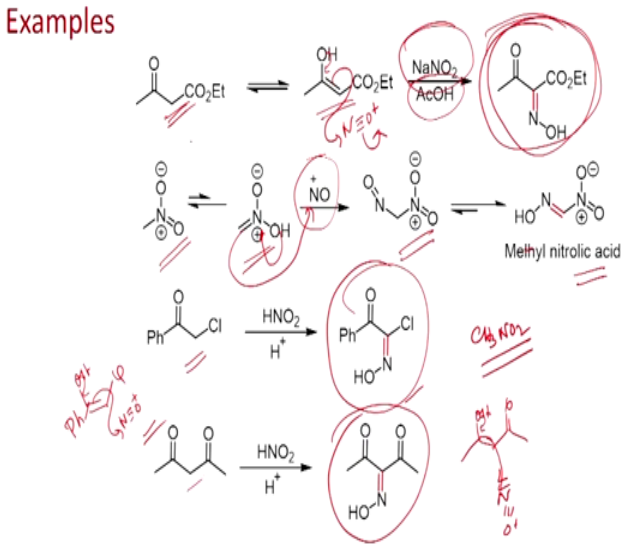


Some more examples are here given. Ethyl acetoacetate reacts with $NaNO_2$ in acidic medium to form the oxime. As just we have seen, ethyl acetoacetate converts to enol in acidic medium, while $NaNO_2$ in acidic medium produces nitrosonium ion. The enol reacts with the *in situ* generated nitrosonium ion to produce the oxime as the product.

The next example involves the reaction of nitromethane with nitrosonium ion to afford methyl nitrolic acid. Similarly, α-chloroacetophenone undergoes reaction nitrosonium ion to produce oxime derivative, while acetyl acetone proceeds reaction with nitrosonium ion to give the respective oxime derivative. In these reactions, the carbonyl compounds enolize, which act as the nucleophile and react with nitrosonium ion that acts as the electrophile.

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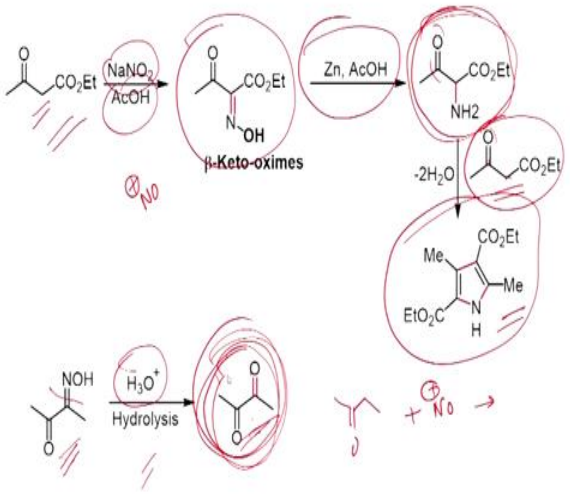


The next example involves the reaction of ethyl acetoacetate with $NaNO_2$ in acetic acid to produce oxime, which is reduced using zinc in acetic acid to yield the amine derivative. It further reacts with ethyl acetoacetate to give tetrasubstituted pyrrole as the product. The next example shows the transformation of ethyl methyl ketone to 2,3-butanone. Enol of the ketone adds to the nitrosonium ion to produce the oxime, which is converted to 1,2-diketone by hydrolysis.

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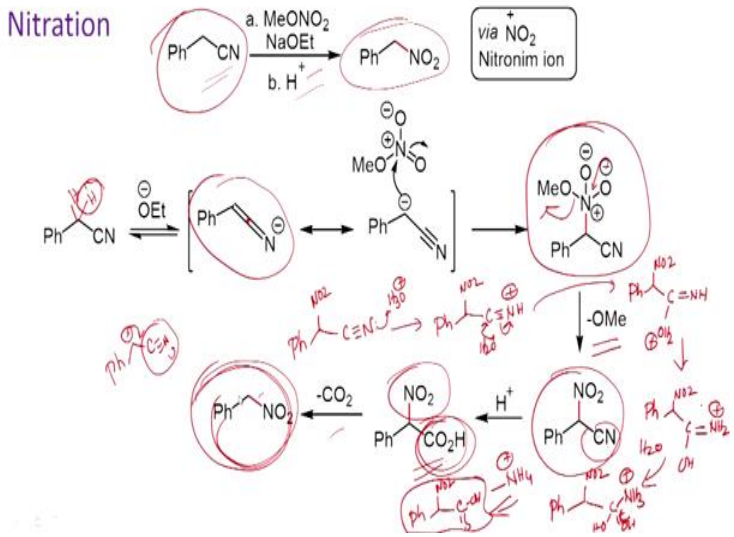

Here benzyl nitrile reacts with methyl nitrate to produce phenyl nitromethane. The reaction involves two steps. First, base deprotonates the benzylic hydrogen to produce carbanion, which is stabilized by nitrile as well as aryl ring. Carbanion reacts with methyl nitrate to give nitro compound. Hydrolysis of the nitrile substituent to carboxylic acid followed by decarboxylation gives phenyl nitromethane.

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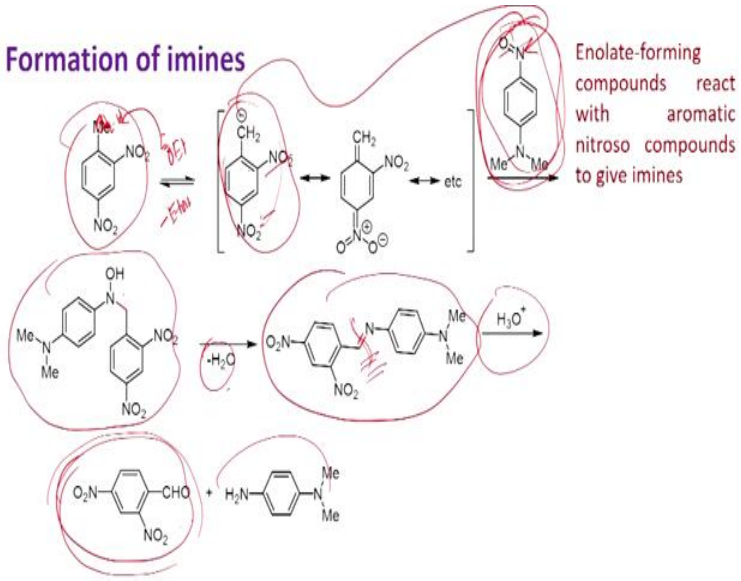


Here the transformation of 2,4-dinitrotoluene to 2,4-dinitrobenzaldhyde is shown. Deprotonation of benzylic hydrogen generates the benzylic carbanion. Which undergoes addition reaction with *N*,*N*-dimethyl-4-nitrosoaniline to give hydroxylamine derivative. It undergoes dehydration to produce the Schiff base, which is converted to 2,4-dinitrobenzaldehyde by aqueous hydrolysis.

So far we have seen several reactions. First, we have seen the reactions of nucleophilic amine with electrophilic carbon. Then, we have seen the reaction enol or carbanion to the electrophilic nitrogen

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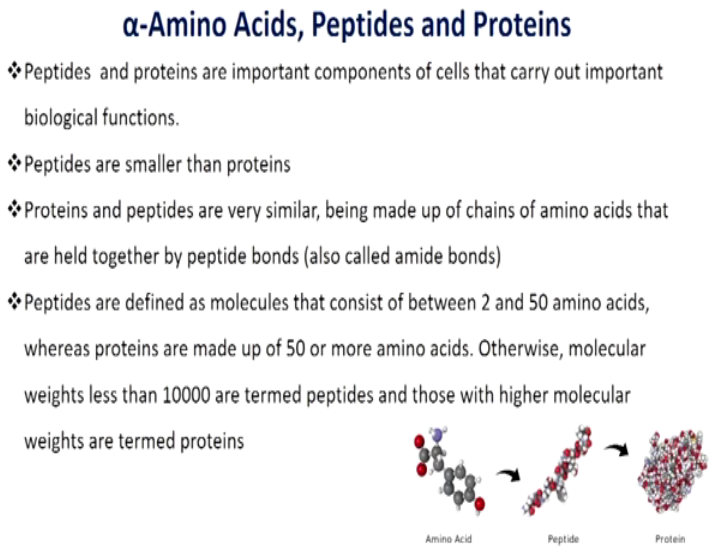


Now let us look at amino acids, peptides and proteins. All of you know very well peptides and proteins are important components of cells that carry out important biological functions. Peptides are smaller than proteins. Proteins and peptides are very similar but being made up of chains of amino acids that are held together by peptide bonds.

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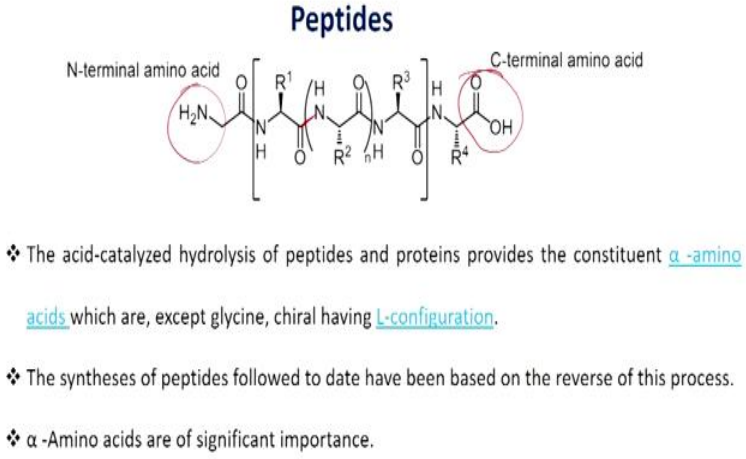


Here the structure of peptides is shown. You can see the peptide bond between the carboxylic acid and amino group of amino acid. This is called C terminal amino acid and this is N terminal amino acid.

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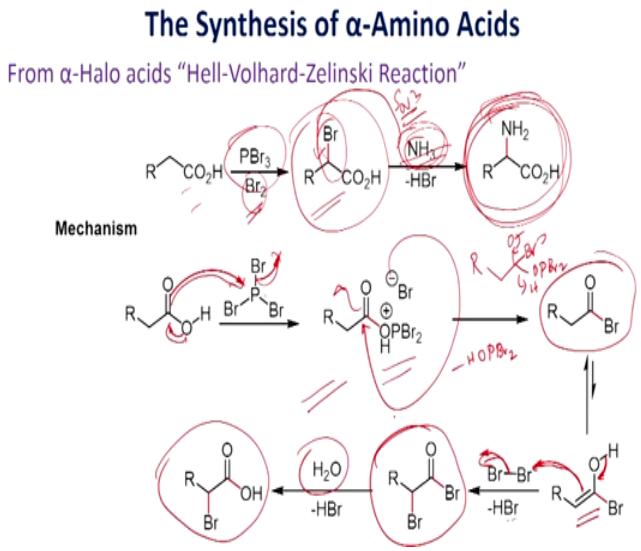


Now let us look at the synthesis of α-amino acid. As you can see here, if you have the carboxylic acid, you can do halogenation at the α-carbon. For example, if you use $PBr_3$, you will be able to form α-bromo carboxylic acid, which reacts with ammonia to form the α-amino acid.

The mechanism of the preparation of α-bromocarboxylic acid is here shown. The carboxylic acid reacts with $PBr_3$ to produce the salt. Addition reaction of brominium ion produces the acid bromide, which reacts with bromine via $S_N2$ reaction to yield α-bromo acyl bromide. Treatment with water yields the α-bromo carboxylic acid.

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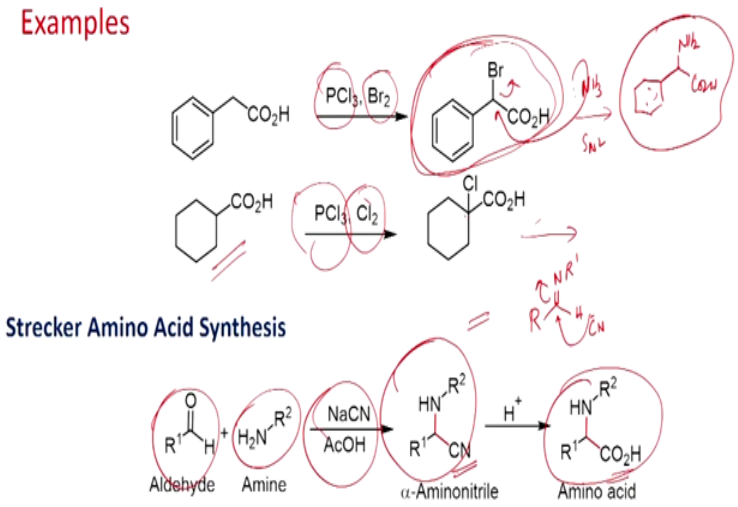


Here are some more examples. The firs one involves the reaction phenylacetic acid with $PBr_3$ to produce α-bromophenylacetic acid. Which can be reacted with ammonia via $S_N2$ to produce the corresponding amino acid. The next example involves the reaction of cyclohexanecarboxylic acid with $PCl_3$ to produce α-chlorocyclohexanecarboxylic acid, which can be reacted with ammonia to give the amino acid.

The other approach is Strecker amino acid synthesis. In the reaction, aldehyde reacts with amine to form imine. Which reacts with cyanide ion to give α-aminonitrile that is converted to α-amino acid via hydrolysis.

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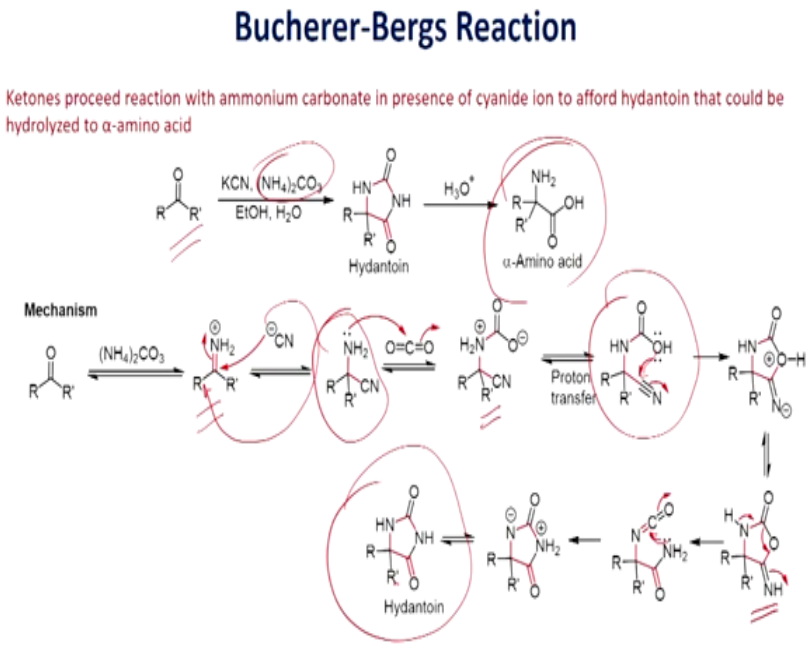


Here is an another approach for the synthesis of α-amino acid. The reaction involves the reaction of carbonyl compound with $(NH_4)_2CO_3$ and KCN to produce hydantoin, which hydrolyzes to produce the amino acid.

The mechanism starts with the condensation of carbonyl compound with ammonium carbonate to give the imine, which leads to an addition reaction with cyanide ion. α-Amino nitrile with $CO_2$ produces the addition product, which undergoes addition with nitrile to produce hydantoin via rearrangement.

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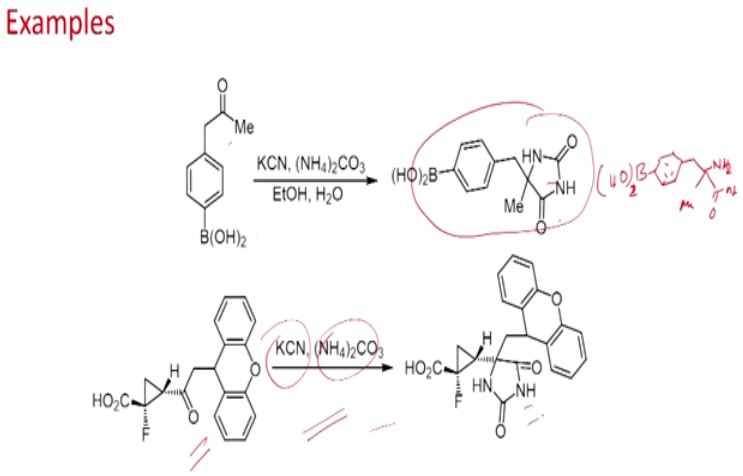


Here the first example involves the reaction of ketone with ammonium carbonate and KCN to give the cyclic compound, which can be hydrolyzed to produce the functionalized phenylalanine. Similarly, the next example produces the cyclic heterocyclic scaffold, which can be hydrolyzed to give the α-amino acid. Using these approaches highly functionalized complex α-amino acids can be prepared.

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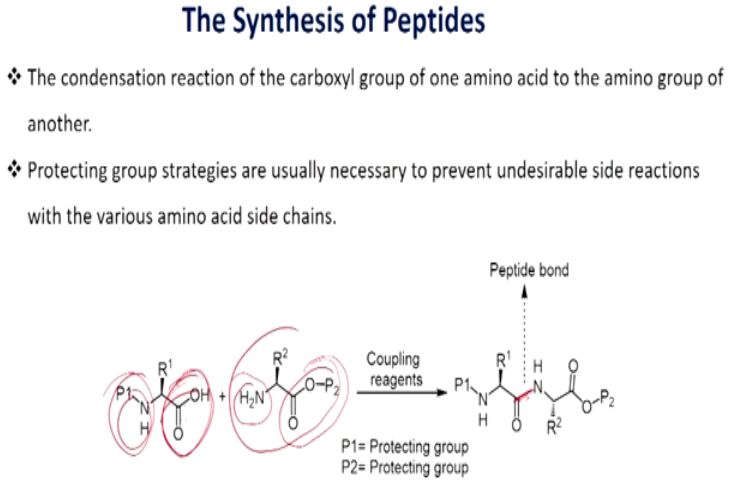

Here the peptide synthesis is shown. The free -COOH group of the N-protected amino acid couples with free -$NH_2$ of the carboxyl group protected amino acid in the presence of coupling reagent to make the peptide bond. In this way amino acids can be coupled to produce the peptide.

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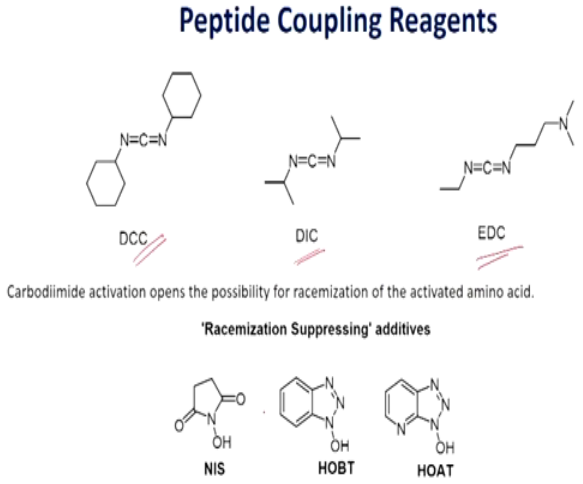


Here some of the common coupling reagents are summarized. Carbodiimides are commonly used for the coupling of carboxyl group with amino group to form the peptide bond. Sometimes optically active substrates undergo racemization during the coupling. Thus, NIS, HOBT and HOAT are used as the additives to minimize the racemization.

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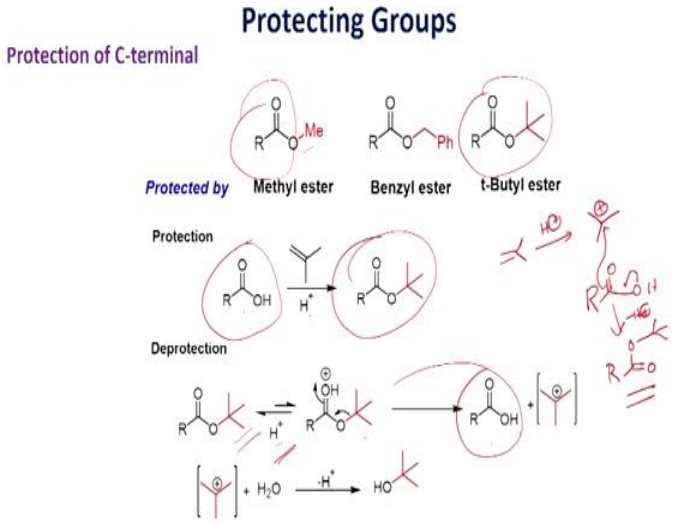


Here are some of the protecting groups of the carboxylic acid group. For example, if you have the carboxylic acid, you can convert to ester. The protection and deprotection of t-butyl group are shown. Carboxyl group reacts with isobutene to give t-butyl ester. Isobutene is converted to t-carbocation, which adds to carboxyl group to give the ester. Similarly, you can readily remove t-butyl group from ester in the presence of acid. As you can see here, protonation of the ester followed removal of t-butanol produces carboxyl group.

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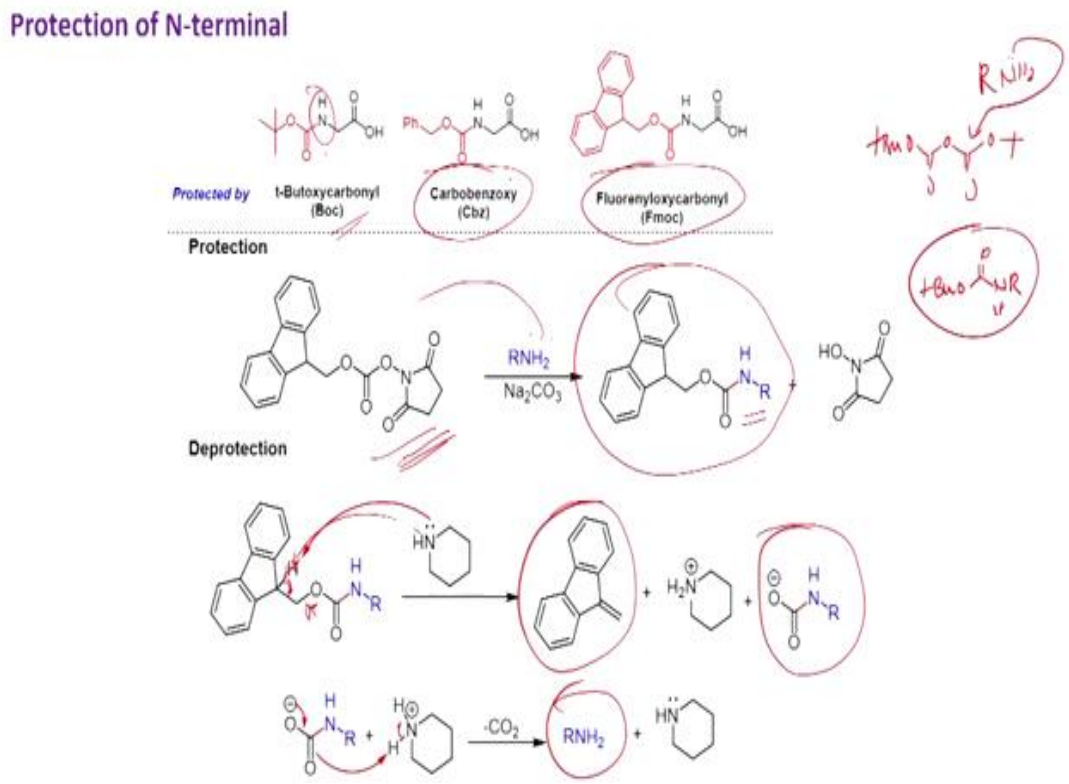


Here the common protecting groups of amino group is shown. For example, amine with di-tert-butyl dicarbonate produces t-butoxycarobnyl derivative. Similarly, amine can be protected using benzyl chloroformate to produces carbobenzoxy derivative in the presence of base. Similarly, amine with fluorenylmethyloxycarbonyl chloride produces fluoronyloxycarbonyl derivative.

The protecting groups can be readily deprotected. Boc is cleaved using TFA in $CH_2Cl_2$, while Cbz can be removed by hydrogenation using Pd/C catalysis. The removal of Fmoc is shown in the presence of piperidine. Deprotonation followed by removal of $CO_2$ gives the amine.

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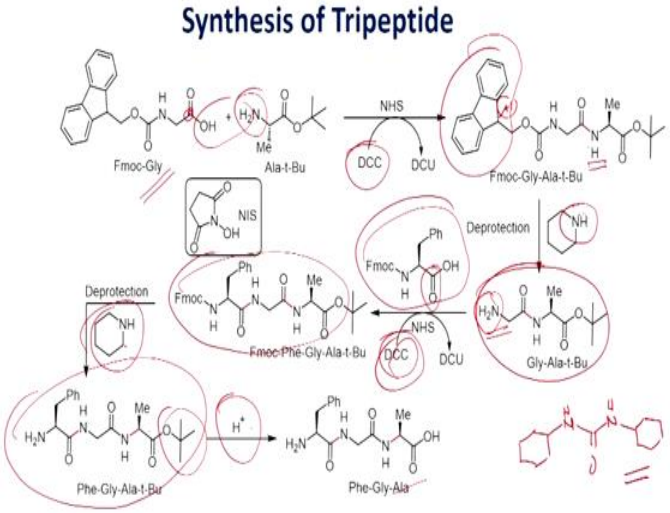


Now let us see an example for the construction of tripeptide. Fmoc-Gly couples with alanine tert-butyl ester in the presence of DCC/NHS to produce Fmoc-Gly-Ala-t-Bu dipeptide. Deprotection of Fmoc using piperidine give Gly-Ala-t-Bu, which couples with Fmoc-Phe in the presence of DCC/NHS to give Fmoc-Phe-Gly-Ala-t-Bu. Removal of Fmoc using piperidine followed by deprotection of Boc using $CF_3COOH$ produces Phe-Gly-Ala tripeptide.

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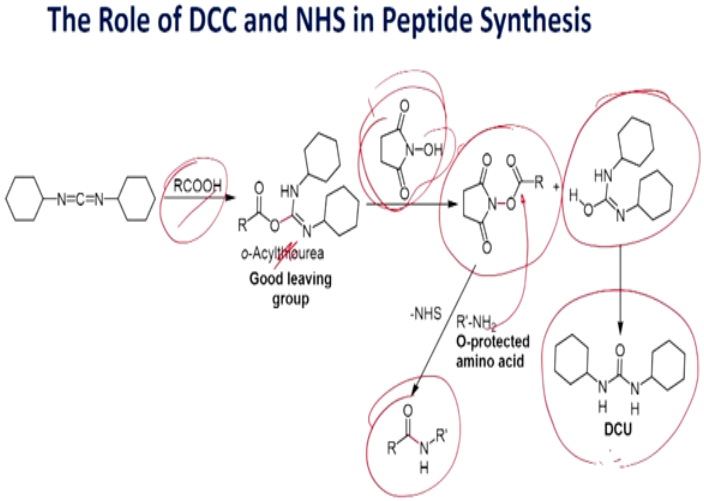


Here the role of DCC and the N-hydroxysuccinimide in peptide synthesis is shown. DCC reacts with carboxyl group to give the activated carboxyl derivative, which with N-hydroxysuccinimide gives N-hydroxysuccimide ester. This can be reacted with amino group to make a peptide bond. DCC is converted to urea.

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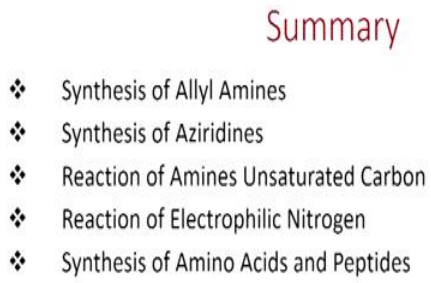


In summary, we have seen the synthesis of allylamines and aziridines. Then, we have seen the reaction of amine with unsaturated carbon. Subsequently, we have seen the reaction of electrophilic nitrogen with nucleophilic carbon. We have seen the reaction of nitrosonium and

nitronium ions. Then, we have seen the synthesis of amino acids and peptides. With these we conclude this lecture. Thank you very much.