Principles of Organic Synthesis
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Formation of Aliphatic Carbon-Carbon Bonds: Acid Catalysed Reactions
Lecture 5

Welcome you all to the formation of aliphatic carbon-carbon bonds using acid as the catalyst. In this module, so far we had one lecture where we studied the reaction of alkenes, aldehydes and ketones. In this lecture, we will study the Mannich reaction. It involves the reaction of amine, aldehyde to give an iminium ion, which undergoes addition reaction to give β-amino derivatives.

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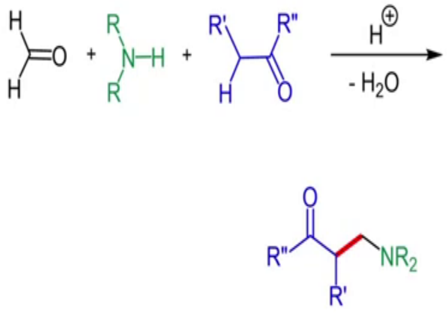
The Mannich Reaction



Carl Mannich, German Chemist
(1877-1947)

For example, secondary amine undergoes reaction with formaldehyde to give an iminium ion, which leads to addition reaction with ketone to give the β-amino carbonyl compound as the product.

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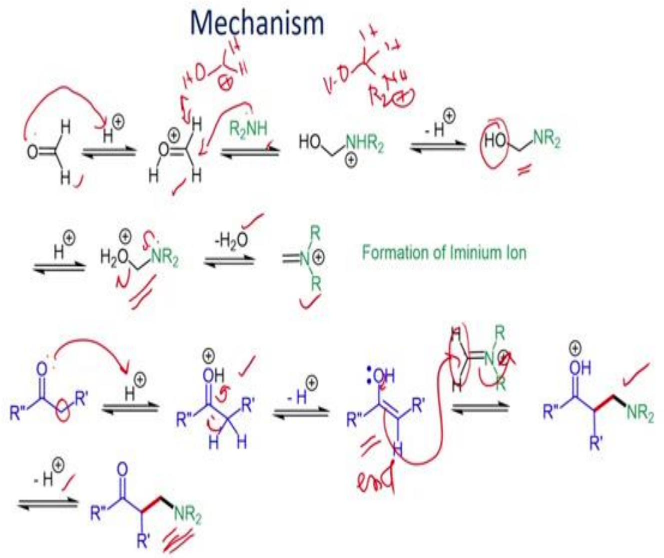

Protonation of formaldehyde followed by addition with amine gives an iminium ion. The latter acts as an electrophile and undergoes reaction with enol that can be generated from ketone as the reaction involves an acid-catalysis. The resultant product loses a proton to give β-amino ketone as the product.

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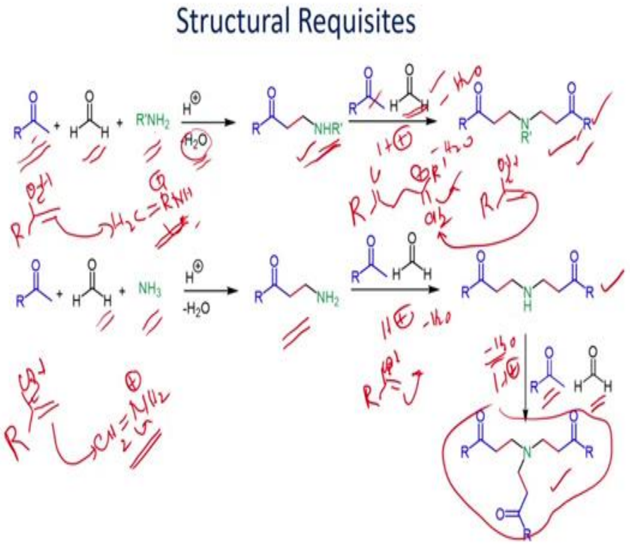

Let us look at the nature of the substrates and products. If we use primary amine, it can undergo reaction as we have seen earlier with formaldehyde to give the corresponding the iminium salt. The latter will react with the enol of ketone to give the addition compound. Since the product is secondary amine derivative, it can further react with formaldehyde to give an iminium ion. That can further react with the enol of ketone to produce the addition product (tertiary amine derivative). Thus, if you have primary amine, two equivalent of formaldehyde and enolizable ketone can react to produce the tertiary amine derivative.

You can also use ammonia in place of primary or secondary amine. As we have seen earlier, ammonia can react with formaldehyde to give an iminium ion as electrophile. This can react with enol of ketone to give primary amine derivative. The latter can further react with two equiv of formaldehydes and ketones to produce tertiary amine derivative as the product. Thus, ammonia can react with three equiv of aldehydes and ketones to produce the tertiary amine derivative as the product.

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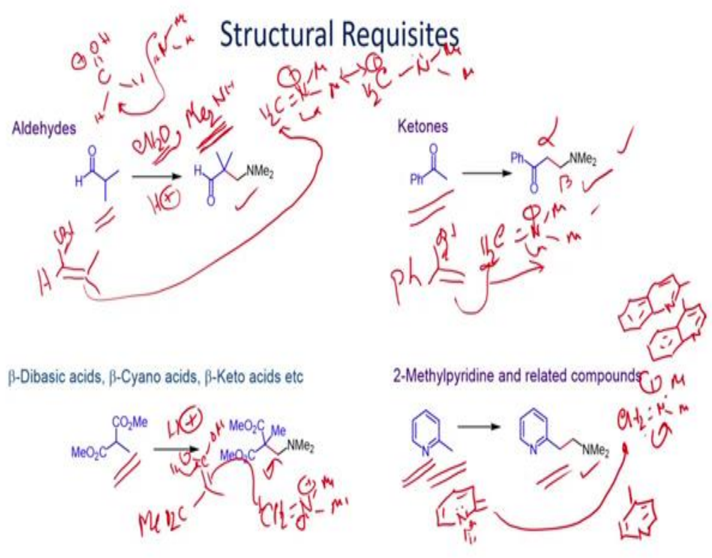

Structural Requisites

Aldehydes

Ketones

β-Dibasic acids, β-Cyano acids, β-Keto acids etc

2-Methylpyridine and related compounds

If you have enolizable aldehyde, which can be reacted with an iminium ion to give the addition product. For example, isobutyraldehyde can enolize and undergo addition reaction with iminium ion that can be generated from formaldehyde and dimethylamine.

Similarly, enalizable ketone can be reacted. For example, acetophenone can enolize and react with iminium ion that can be generated from formaldehyde and secondary amine to give the addition product.

You can also use enalizable di-ester in place of aldehyde and ketone. For example, malonate can be readily reacted with iminium ion that can be generated from formaldehyde and dimethylamine to give the addition product. Furthermore, 2-methylpyridine can be reacted with the iminium ion that can be generated from formaldehyde and dimethylamine. The reaction condition can be extended to the reaction of 4-methylpyridine, 2-methylquinoline and 4-methylquinone substrates.

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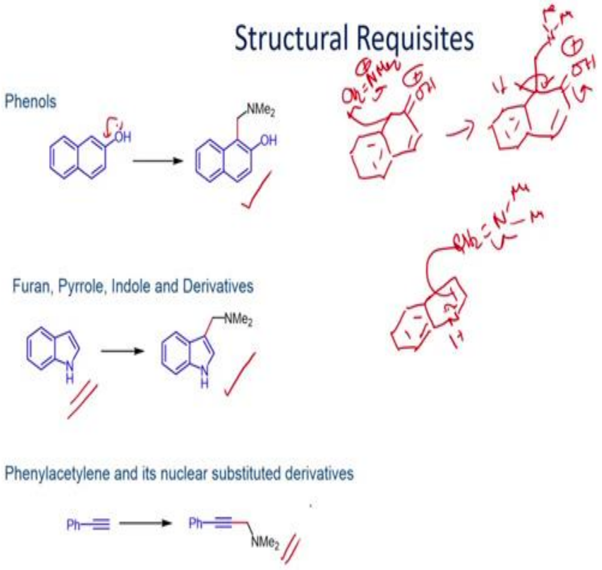

Structural Requisites

Phenols

Furan, Pyrrole, Indole and Derivatives

Phenylacetylene and its nuclear substituted derivatives

In addition, β-naphthol can be reacted with the iminium ion that can be generated dimethylamine and formaldehyde to the addition product. Similarly, furan, pyrrole and indole derivatives can be reacted. For example, indole reacts with iminium ion to give 3-substituted indole derivative as the product.

Furthermore, acetylene can undergo addition reaction with iminium salt to give the addition product. Although acetylene cannot form enol, however, it undergoes Mannich reaction to give the amine derivatives as a product. The reactions so far we have seen which use acid as catalyst to generate the iminium ion that leads to the addition reaction.

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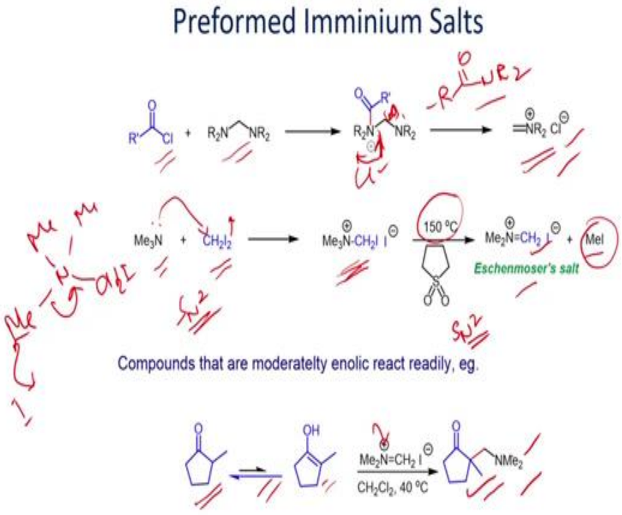

Preformed Imminium Salts

Compounds that are moderatelty enolic react readily, eg.

We can also try to make the iminium salt by substitution reaction. For example, you can react acid chloride with amine to form the salt which can lose amide to produce amine. The latter can be converted to the iminium salt.

Further, nucleophilic substitution (S_N2) of dimethylamine with diiodomethane gives salt that on heating (150 °C) releases methyl iodide to yield Eschenmoser salt, which can be reacted enaolizable compounds. For example, the partially enolizable 2-methylcyclopentane undergoes addition reaction to give the Mannich product.

So far, we have seen the nature of the amines as well as the carbonyl compounds that can be used for the Mannich reaction. Then, we have seen the formation of iminium salt and the reaction with the partially enolizable compound in the absence of acid to give the Mannich product.

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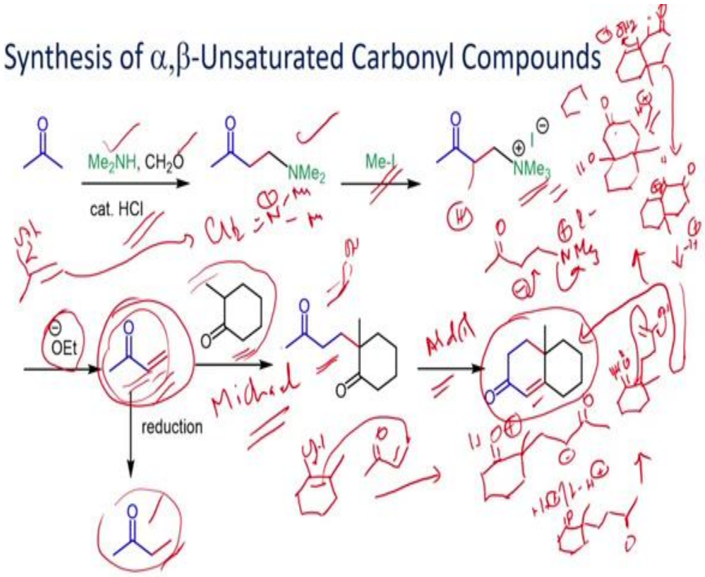
Synthesis of α,β-Unsaturated Carbonyl Compounds

Here the application of the Mannich reaction for the formation of α,β-unsaturated carbonyl compound is shown. Reaction of formaldehyde with dimethylamine gives the iminium ion, which reacts with the enol of acetone to give the addition product. This can be reacted with methyl iodide to give amine salt, which in the presence of base undergoes elimination to give the methyl vinyl ketone. This can be hydrogenated to give ethyl methyl ketone. Alternatively, it can be reacted with 2-methyl cyclohexanone via conjugate addition followed by intramolecular aldol reaction to give Robinson annulation product.

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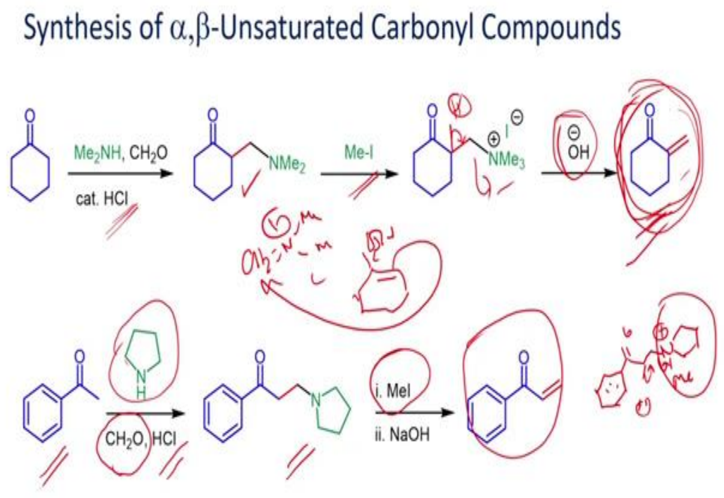

Synthesis of α,β-Unsaturated Carbonyl Compounds

Now, let us look at some more examples. Cyclohexanone can be reacted with iminium salt in the presence of acid to give the Mannich product that can be further reacted with methyl iodide to give ammonium salt. Base mediated elimination can produce α,β-unsaturated cyclohexanone.

Similarly, the acetophenone can be converted to phenyl vinyl ketone. Reaction of formaldehyde with pyrrolidine can give iminium ion, which can lead to addition reaction with enol that can be generated from acetophenone to give addition product. Reaction with methyl iodide gives ammonium salt, which can be reacted with sodium hydroxide to produce the α,β-unsaturated ketone as the product.

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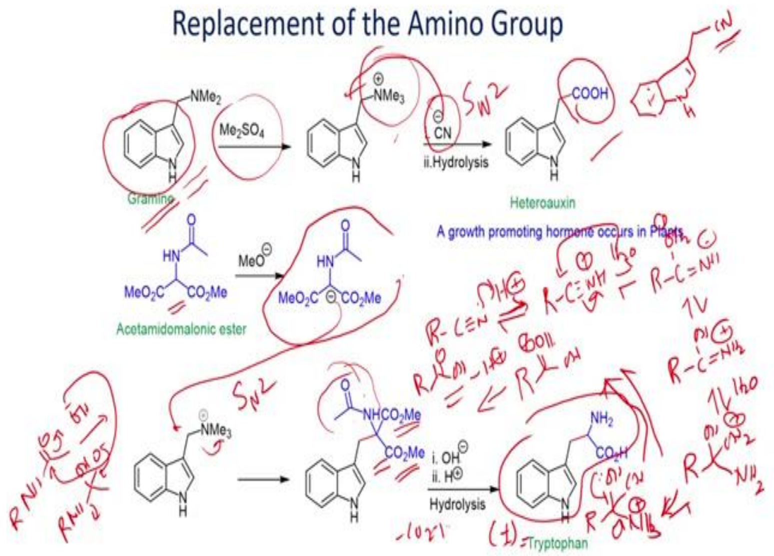

Replacement of the Amino Group

Now let us look at some other applications. When you react the Mannich base with the dimethyl sulfate, you can generate quaternary ammonium salt, which can be reacted with a nucleophile like cyanide ion by S$_N$2 pathway to give the nitrile compound.

The nitrile can be further converted into carboxylic acid by hydrolysis. Protonation followed by addition of water can give iminium ion, which can further react with water to give acetal bearing ammonium ion that can be converted into carboxylic acid.

The next example involves the deprotonation of dimethyl malonate bearing acetamide. The resultant carbanion reacts with ammonium salt bearing indole substituent via S$_N$2 pathway. The resultant product can be hydrolyzed using base as well as acid hydrolysis to remove acetyl group from amide as well as the ester group to carboxylic acid. Decarboxylation of the dicarboxylic leads to the formation of tryptophan.

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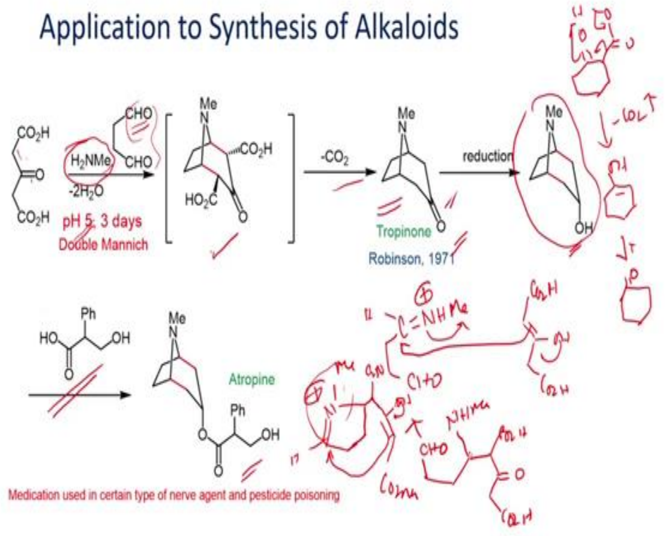

Application to Synthesis of Alkaloids

Medication used in certain type of nerve agent and pesticide poisoning

Here an application is shown for the synthesis of alkaloid. The dialdehyde reacts with primary amine and the enolizable dicarboxylic acid. When you mix the three together and leave it in acidic medium for three days, they undergo double Mannich reaction to give the bicyclic Ketone as a product. The ketone can be reduced to alcohol, which can be reacted with carboxylic acid derivative to produce atropine.

Here if you look at, primary amine undergoes condensation with one of the aldehyde groups to iminium ion, which leads to addition with the enol that you can generate from the dicarboxylic acid. The resultant Mannich base can undergo further intramolecular condensation (secondary amine with aldehyde) to form the iminium ion, which can undergo addition reaction with the enol to give the bicyclic compound. Decarboxylation can produce the bicyclic ketone, which can be reduced to give the secondary alcohols that can be reacted with carboxylic to give atropine. This is used for certain type of neuro problem as well as pesticide poisoning.

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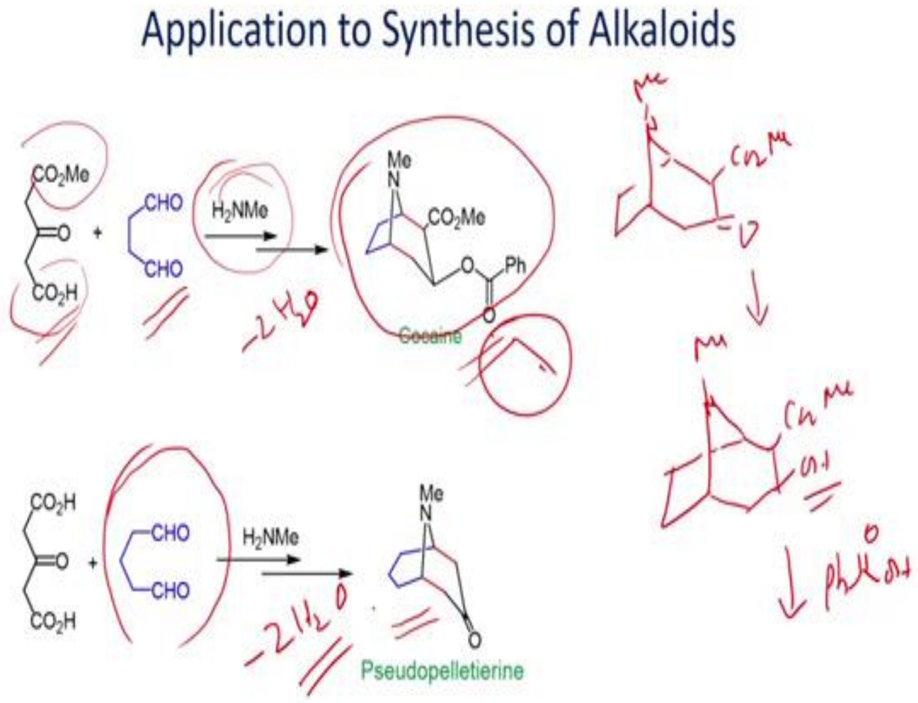

Application to Synthesis of Alkaloids

Here the synthesis of cocaine is shown. The dialdehyde can be reacted with primary amine and β-ketoester bearing carboxylic acid to produce N-containing bicyclic β-ketoester via a double Mannich reaction followed by decarboxylation. The keto group can be selectively reduced to give the secondary alcohol, which can be reacted with benzoic acid to yield the ester.

This strategy can be extended for the coupling of the dialehyde, methylamine and enolizable dicarboxylic acid to produce the double Mannich product, which can undergo decarboxylation to yield pseudopelletierine.

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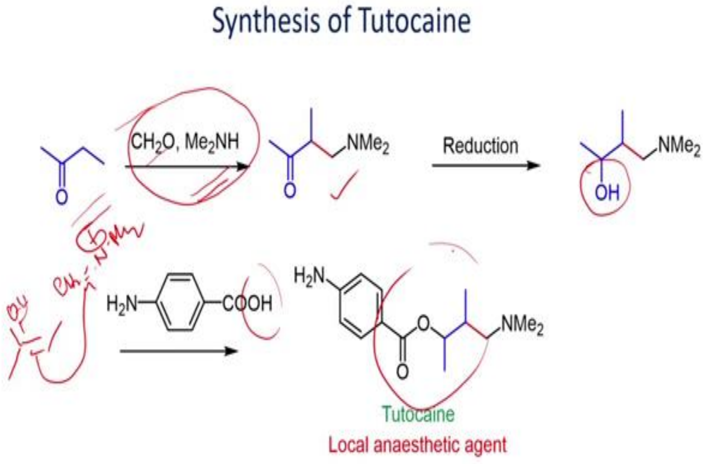

Here the application for the synthesis of tutocaine is shown. Condensation of dimethylamine with formaldehyde produces iminium ion, which can undergo addition reaction with enol of ethyl methyl ketone to give the Mannich product. Reduction of the keto group can give the secondary alcohol, which can react with benzoic acid to produce the ester.

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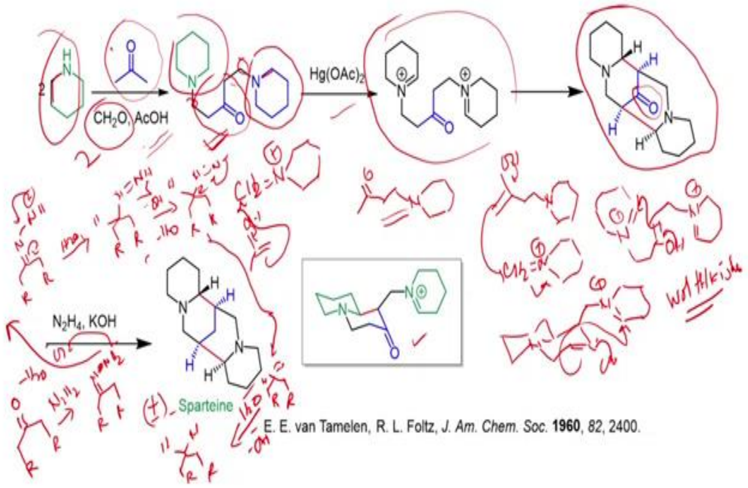
Synthesis of Sparteine



E. E. van Tamelen, R. L. Foltz, *J. Am. Chem. Soc.* **1960**, *82*, 2400.

The other application is the synthesis of sparteine. Reaction of two equiv of the secondary cyclic amine with two equiv of formaldehyde produces iminium ions, which react with one equiv of acetone in the presence of acetic acid to give β-keto diamine compound. The latter converts into the diiminium ion in the presence of Hg(OAc)$_2$ and undergoes intramolecular addition with keto enol to produce the tetracyclic N-containing compound. Wolff Kishner reduction of the ketone using hydrazine in the presence of KOH produces sparteine.

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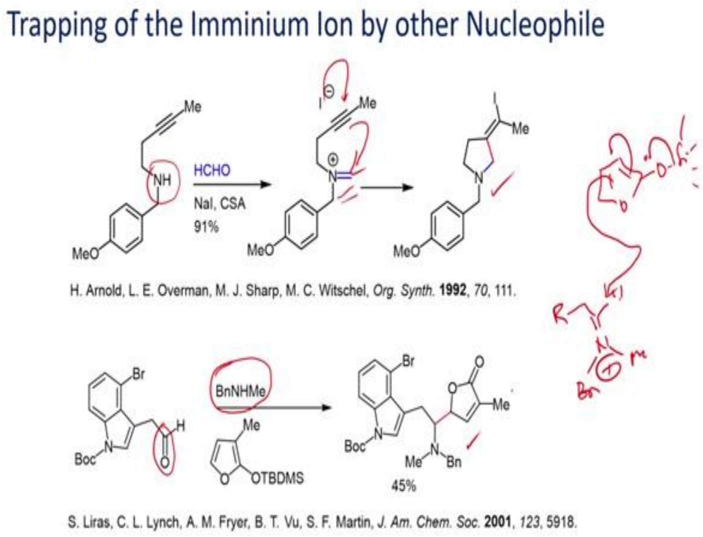

Trapping of the Imminium Ion by other Nucleophile

H. Arnold, L. E. Overman, M. J. Sharp, M. C. Witschel, *Org. Synth.* **1992**, *70*, 111.

S. Liras, C. L. Lynch, A. M. Fryer, B. T. Vu, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 5918.

This slide shows two examples for trapping iminium ion. The first one involves the reaction of secondary amine with formaldehyde to give an iminium ion that undergoes intramolecular cyclization with triple bond to give a pyrrolidine derivative bearing exocyclic double bond. The second example involves the reaction of secondary amine with aldehyde bearing indole unit to give an iminium ion, which leads to addition reaction with furyl derivative.

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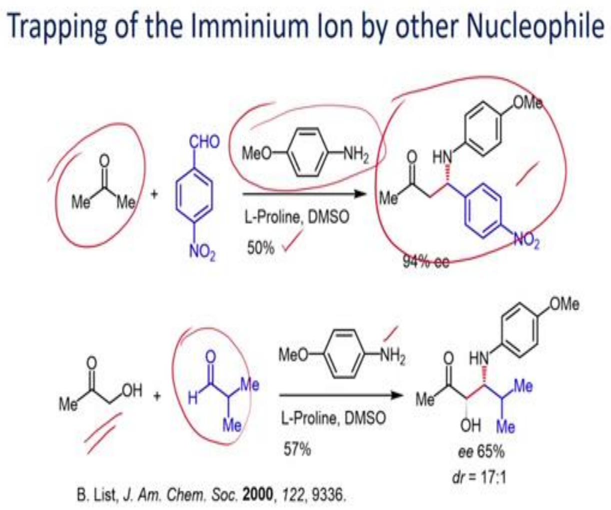

Trapping of the Imminium Ion by other Nucleophile

B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336.

Here some more examples for the trapping of the iminium ion is shown. The first example involves the reaction of *p*-anisidine with and 4-nitrobenzaldehyde to form an imine, which undergoes addition reaction of with enol of the acetone the presence of L-proline as a catalyst. This is an excellent example for the enantioselective Mannich Reaction with excellent enantiomeric excess (ee). When replace the aldehyde the selectivity is dropped. For example, the reaction *p*-anisidine with isobutryaldehyde produces imine, which leads to addition reaction with α-hydroxyacetone to produce diastereomers with moderate selectivity.

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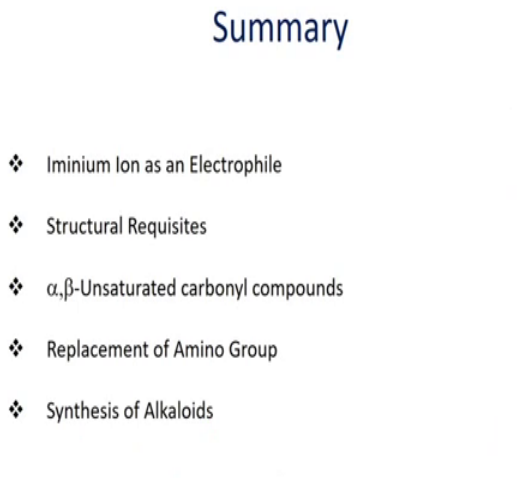

Summary

- Iminium Ion as an Electrophile
- Structural Requisites
- α,β-Unsaturated carbonyl compounds
- Replacement of Amino Group
- Synthesis of Alkaloids

In summary, first we have seen the mechanism of the Mannich reaction.

Then, we have seen the type of substrates that undergo the Mannich reaction.

Next, we have seen the application to the synthesis of α,β-unsaturated carbonyl compounds. We have also seen the preparation methyl vinyl ketone and its application for the annulation with 2-methylcyclohexanone via conjugate addition followed by intramolecular Aldol reaction.

Then, we have seen the application of sequential Mannich reactions for the syntheses of bicyclic compounds and their transformations for alkaloids.

Then, we have seen some literature examples for the trapping of the imines and their reaction with carbon nucleophiles for the construction heterocyclic scaffolds.

Finally, we have seen L-proline catalyzed enantioselective Mannich reactions, which is well explored. With these, we conclude this lecture, thank you very much.