Principles of Organic Synthesis
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Lecture 23
Molecular Rearrangements
Halogen, Oxygen, Sulfur and Nitrogen Migration

Welcome you all to Principles of Organic Synthesis. Presently, we study the molecular rearrangements. So far, we had one lecture where we studied the Wagner-Meerwein, pinacol and benzilic acid rearrangements, and Arndt-Eistert synthesis. This lecture will have three parts: 1st part will focus on the migration of halogen, oxygen and sulfur functional groups, second part will cover the migration towards the electron deficient nitrogen and third part will focus on the migration to electron deficient oxygen.

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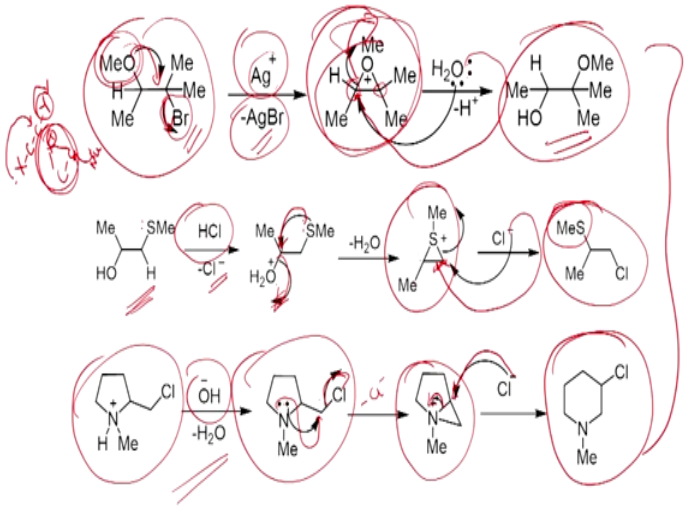

First example shows oxygen migration. When we react the alkyl bromide bearing methoxy group in the neighboring carbon with aqueous silver salt, the neighboring methoxy group assists to depart the leaving bromide via S_N2 pathway. The resultant oxonium ion undergoes nucleophilic substitution with water at the less substituted carbon via S_N2 pathway to produce the alcohol, where the methoxy group migrates to the adjacent carbon.

Second example shows sulfur migration. Protonation followed by the neighboring thiomethyl group participation to expel the leaving group gives the reactive sulfonium ion vis S_N2 pathway. Chloride anion reacts at the less substituted carbon vis S_N2 pathway to yield alkyl chloride with 1,2-shift of thiomethyl group.

Third example shows chloride migration. Deprotonation using hydroxide ion gives 2-(chloromethyl)-1-methylprrolidine, which undergoes S_N2 reaction to produce the bicyclic ammonium ion. Substitution with chloride ion at the more substituted carbon yields 3-chloro-1-methylpiperidine.

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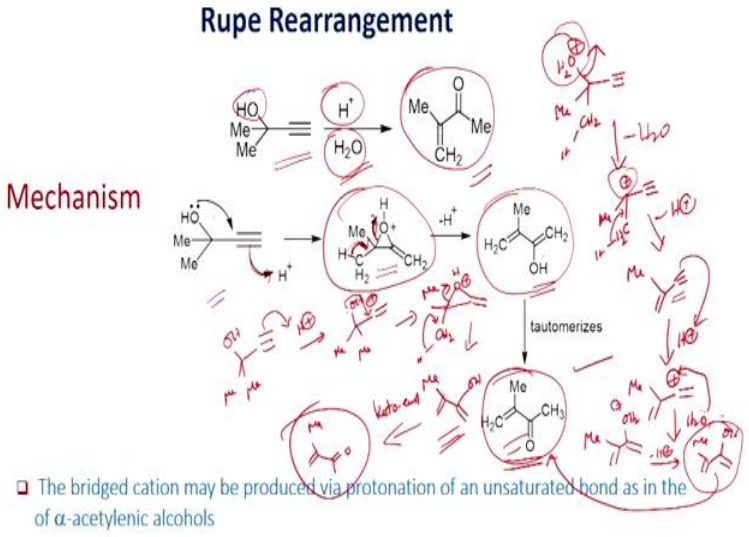

Now let us look at the acid-catalyzed reaction of propargyl alcohol, which is known as the Rupe rearrangement. Neighboring hydroxyl group adds to the triple bond to give the olefinic oxonium ion, which opens up to give the conjugated enol, which converts to methyl vinyl ketone vis tautomerization.

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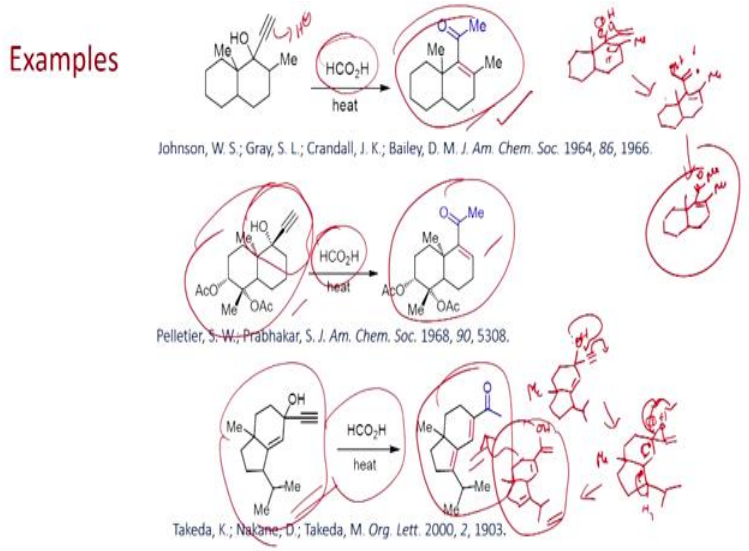

Here are three examples for the Rupe rearrangement. The reactions utilize the bicyclic propargryl alcohols, which undergo rearrangement using formic acid under heating to produce the vinyl ketone. As we have seen above, intramolecular addition of the neighboring hydroxy group to the triple bond followed by the ring opening and isomerization produce the products.

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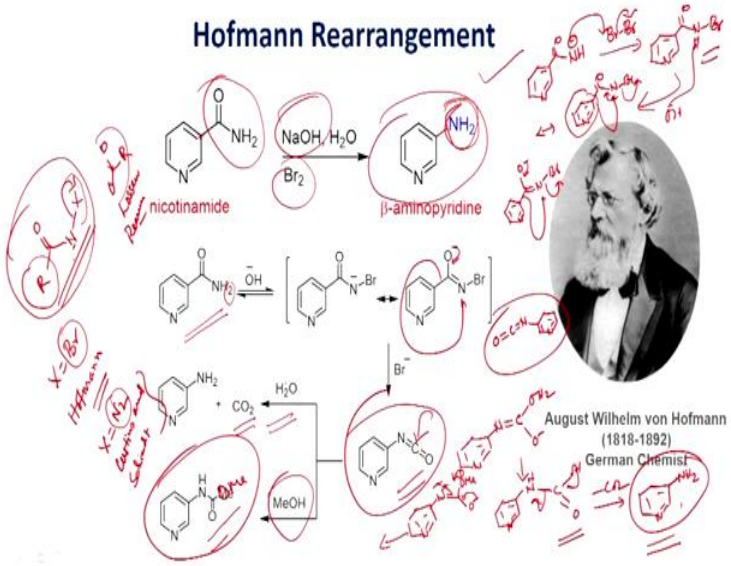

Now let us look at the migration to electron deficient nitrogen. Of them, Hofmann, Curtius, Schmidt and Lossen rearrangements involve isocyanate intermediate. In Hofman rearrangement, amide converts to amine using NaOH and Br_2. For example, nicotinamide can be converted to 3-aminopyridine. Deprotonation followed by substitution with Br_2 and rearrangement gives the isocyanate, which with water gives amine. Similarly, it can react with methanol to give methyl pyridin-3-ylcarbamate.

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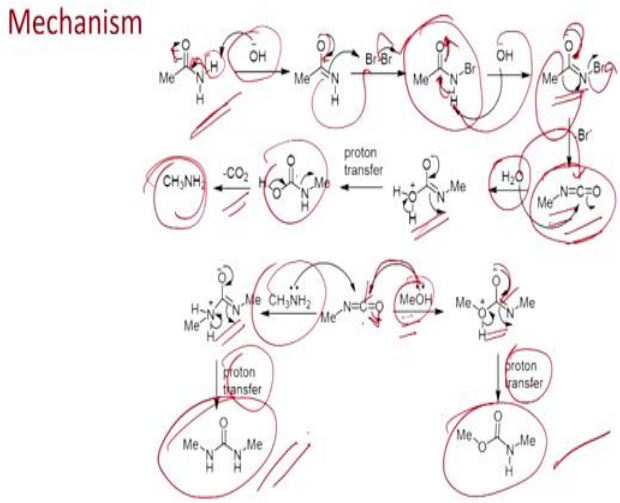

Let us look at the reaction of acetamide. Deprotonation followed by substitution with Br_2 and rearrangement gives methylisocyanate. It can be reacted with water to produce methylamine. Similarly, the isocyanate can react with methylamine to yield 1,3-dimethylurea, while the reaction using methanol furnishes methyl methyl carbamate.

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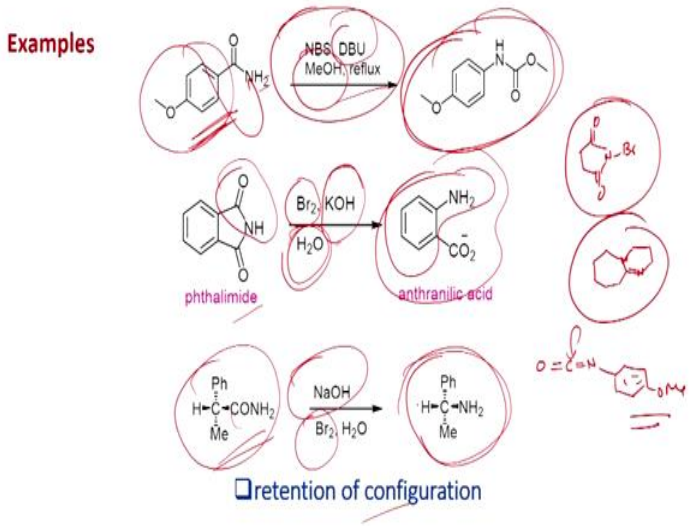

The combination of NBS and DBU converts arylamide to arylisocyanate, which can react with methanol to give N-(aryl)methyl carbamate. Similarly, phthalimide with KOH/Br_2 gives anthranilic acid. The amide bearing chiral center at α-carbon reacts with NaOH/Br_2 to give chiral amine with retention configuration.

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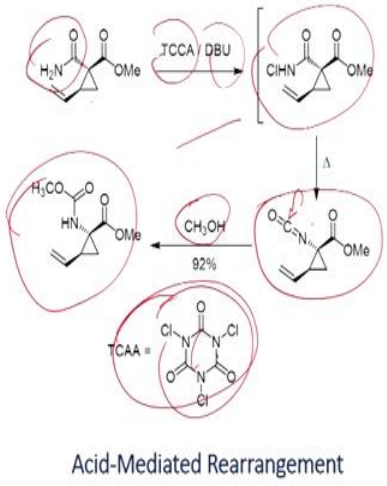

The amide bearing vinylcyclopropane reacts with ICCA in the presence of DBU to give the cyclopropylisocyanate, which reacts with methanol to produce the carbamate.

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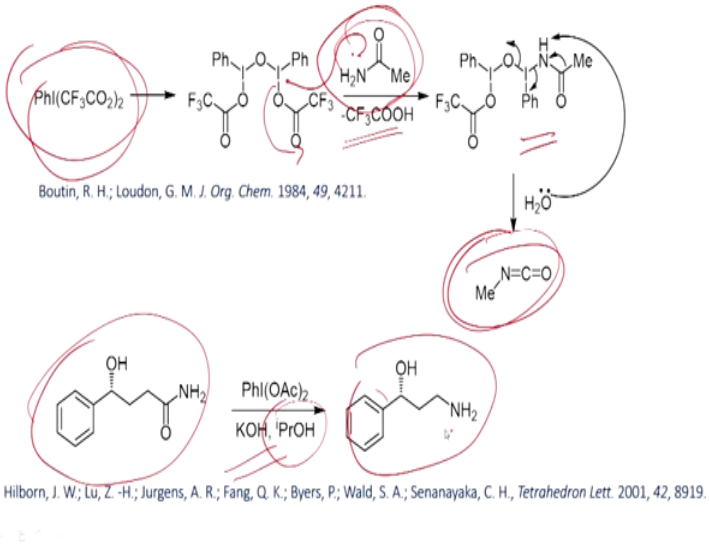

Here iodobenzene trifluoroacetate converts to anhydride, which reacts with acetamide via substitution followed by rearrangement to give methylisocyanate. Similarly, the chiral amide with iodobenzene diacetate and base produces chiral isocyanate, which can be converted to chiral amine.

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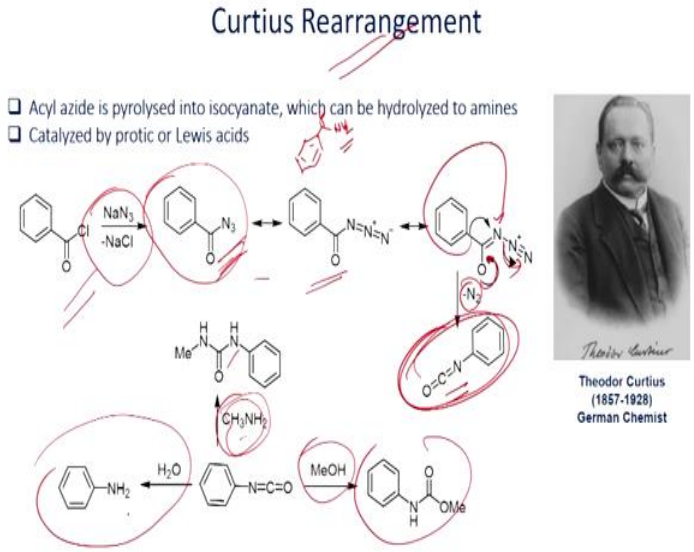

Now let us look at the Curtius rearrangement. Acid chloride with NaN_3 gives acyl azide, which rearranges to isocyanate. As we have seen in the Hofmann rearrangement, isocyanate

can react with a variety of nucleophiles. For example, benzoyl chloride with NaN_3 gives benzoyl azide, which rearranges to phenyl isocyanate. It can be reacted with water to give aniline. The reaction using MeOH produces the carbamate, while methylamine reacts to give the urea derivative.

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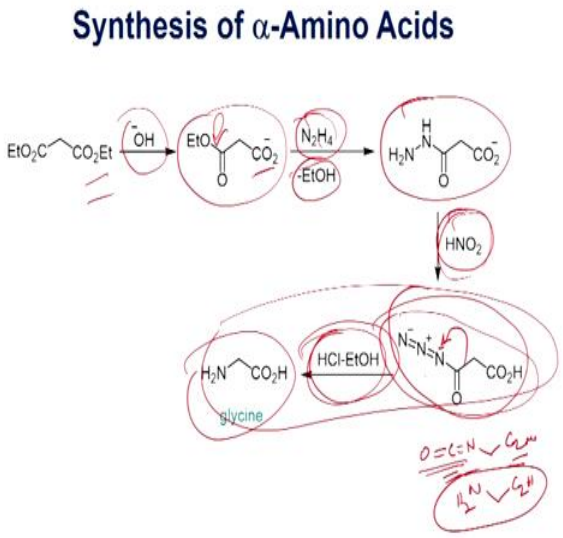

Let us see the application for the preparation of glycine. Diethyl malonate with hydroxide ion produces carboxylic acid derivative, which reacts with hydrazine to give the acylhydrazine derivative. Diazotization using HNO_2 gives the acyl azide that rearranges to the isocyanate, which converts to glycine. Similarly, we can utilize the Curtius rearrangement to prepare other amino acids.

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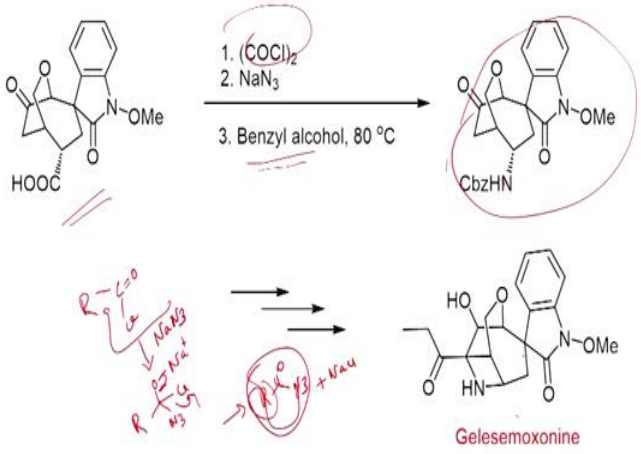

Curtius rearrangement finds wide applications. For an example, the complex molecule bearing amide, ether, keto and carboxyl groups can be reacted with oxalyl chloride to produce acid chloride that can be reacted with NaN_3, which rearranges to isocyanate and reacts with benzyl alcohol. It is an intermediate for the multistep synthesis of medicinally important gelesemoxonine.

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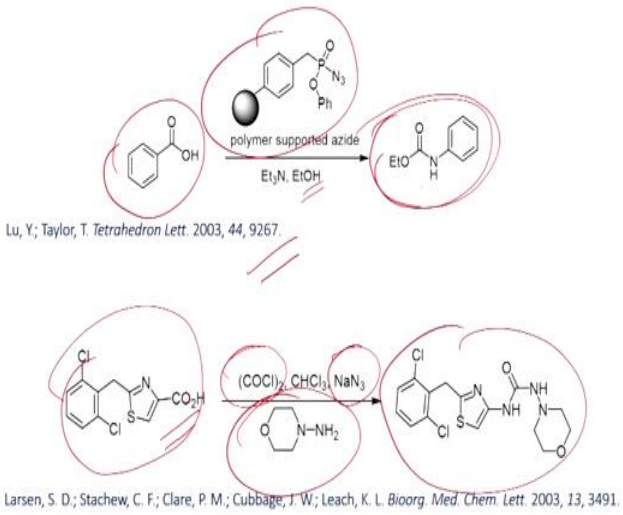

Here first example involves the reaction of benzoic acid with polymer anchored organic azide to produce isocyanate that reacts with ethanol to give the carbamate. The next example bearing carboxyl group reacts with oxalyl chloride to give acyl chloride that reacts with NaN_3 to produce isocyanate, which reacts with 4-aminomorpholine to yield the urea derivative.

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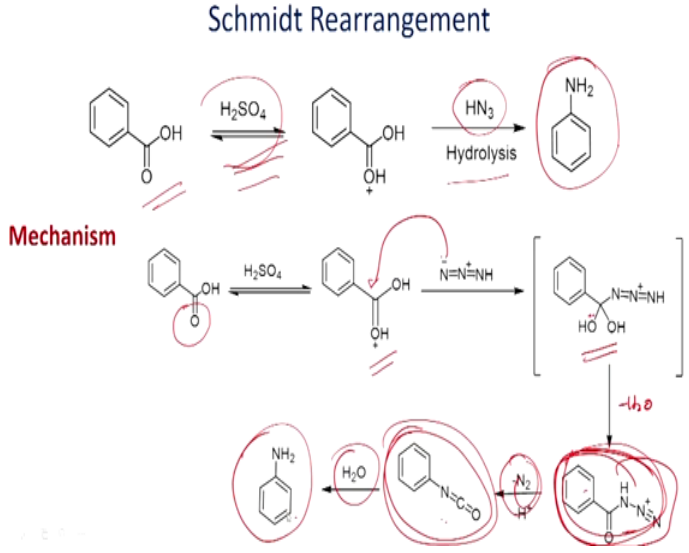

Now let us focus on the Schmidt rearrangement. For example, protonation of benzoic acid followed by the addition reaction of hydrazoic acid and removal of water molecule gives the acyl azide. It rearranges to isocyanate that can be reacted with water to give aniline.

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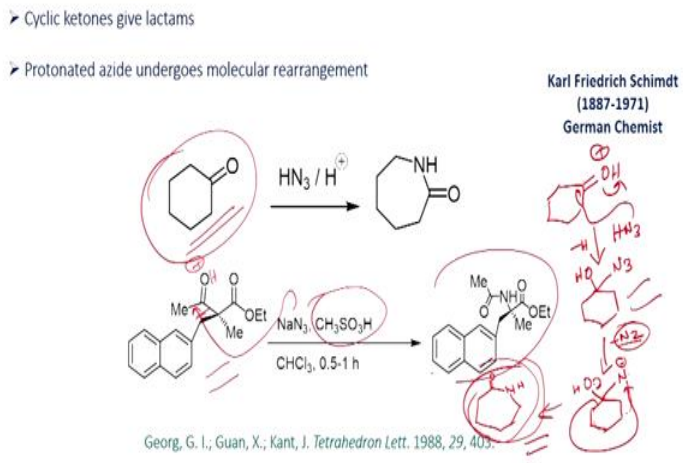

Using this approach, cyclohexanone can be converted to caprolactam. Protonation of the keto group followed by addition of hydrazoic acid and rearrangement gives the lactam, which is precursor for the nylon-6 synthesis. Similarly, the keto group of the β-ketoester protonates that undergoes addition reaction with NaN_3, which rearranges to the acetamide. The reaction condition is mild and the ester group is intact.

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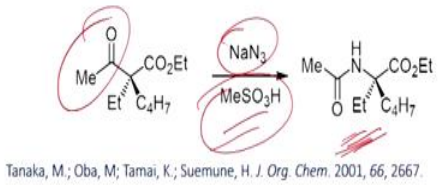

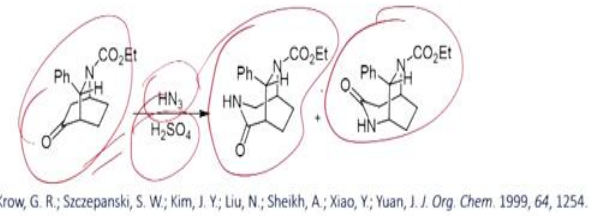

Similarly, the β-ketoester rearranges using NaN_3 and methanesulfonic acid to produce the amide. Further, the bicyclic ketone can be reacted with hydrazoic acid in the presence of sulfuric acid to produce a mixture of the bicyclic lactams.

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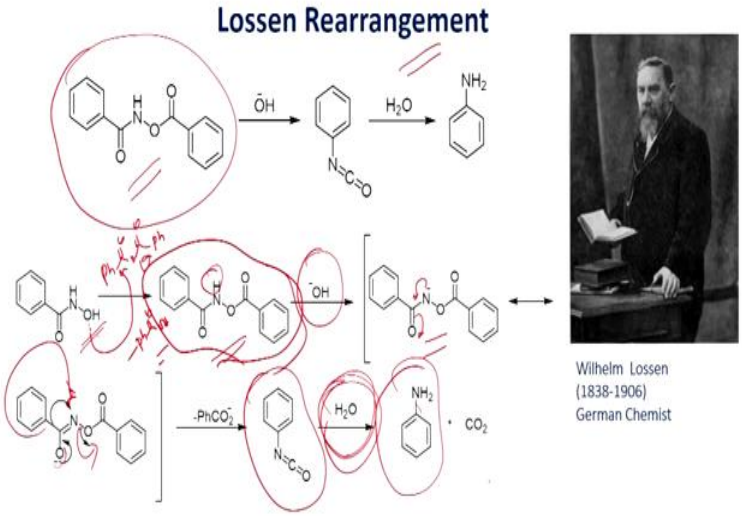

Now let us look at the Lossen rearrangement that involves the transformation of hydroxamate ester to isocyanate using hydroxide, which reacts with nucleophile. For example, hydroxamic acid with benzoic anhydride produces N-(benzoyloxy)benzamide. Deprotonation using hydroxide followed by elimination of benzoate gives phenyl isocyanate, which undergoes addition reaction with water to produce aniline.

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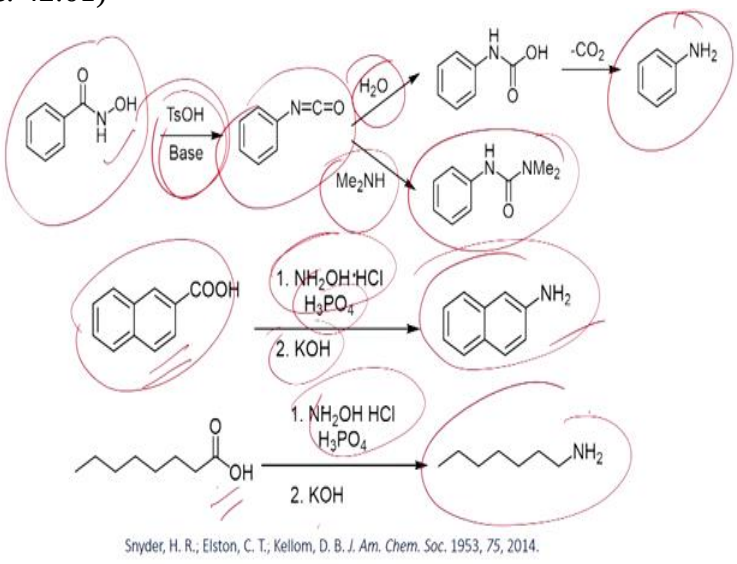

Benzhydroxamic acid converts to phenyl isocyanate using TsOH/base, which reacts with water to give aniline, while the reaction with dimethylamine yields urea. Similarly, 2-naphthoic acid with hydroxyl amine produces hydroxamic acid, which converts to isocyanate using hydroxide. Reaction with water produces 2-naphthylamine. These reaction conditions are found to be effective for the transformation of octanoic acid to octylamine.

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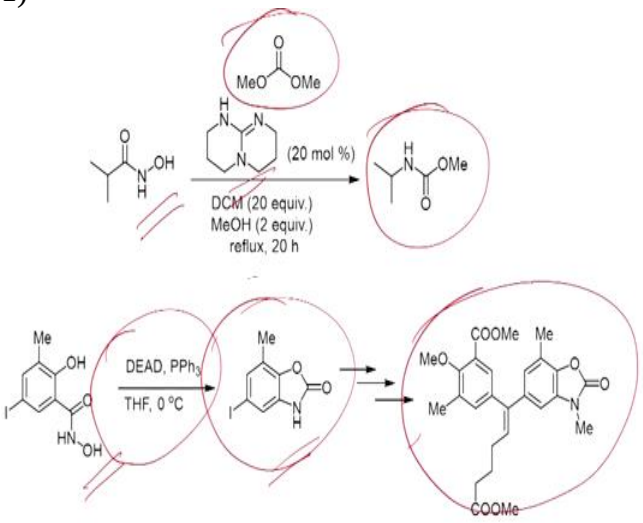

Access to bioactive molecule having anti-HIV properties via Lossen rearrangement

Isopropyl hydroxamic acid with dimethyl carbonate in the presence of the organic base gives isopropyl isocyanate that can be reacted with methanol to produce the carbamate. Similarly, the aryl hydroxamic acid with DEAD and PPh_3 produces the isocyanate, which reacts with hydroxy group to produce the oxazolone that has been converted to anti-HIV agent.

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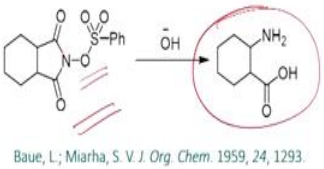
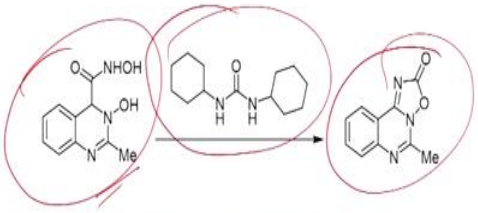


Baue, L.; Miarha, S. V. *J. Org. Chem.* 1959, *24*, 1293.



Bergman, J.; Lindstriim, J.-O. *Tetrahedron Lett.* 1976, *17*, 3615.

Here the first example with hydroxide opens up to give hydroxyamic acid that converts to isocyanate. Reaction with water gives 2-aminocyclohexanecarboxylic acid, whereas the next example focuses on the reaction of heterocyclic hydroxyamic acid with DCC to produce isocyanate that reacts with N-hydroxyl group to produce the heterocyclic framework. So far we have seen the Hofmann, Curtius, Schmidt and Lossen rearrangements. In these reactions, the rearrangement takes place to electron deficient nitrogen.

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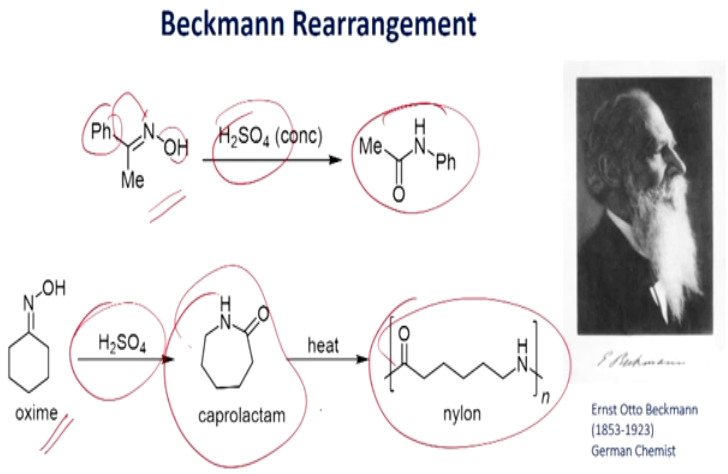

Now let us focus on the Beckmann rearrangement, which involves the transformation of oxime to substituted amide. For example, acetophenone oxime rearranges to acetanilide in the presence of sulfuric acid. Similarly, cyclohexanone oxime produces caprolactam using sulfuric acid, which is an important transformation as it is the substrate precursor to make nylon-6.

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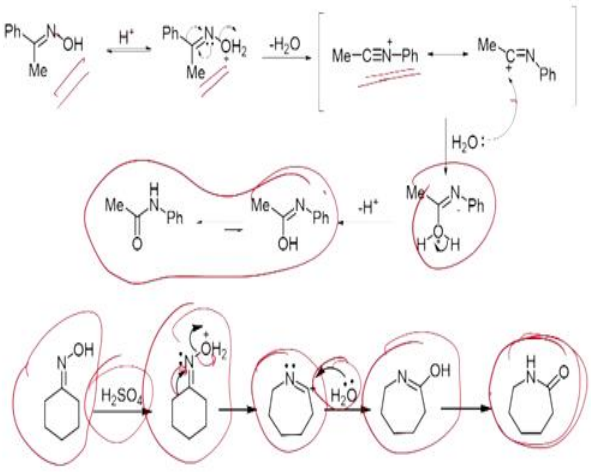

Protonation of the acetophenone oxime followed by anti-periplanar substituent migration to the expulsion of the leaving group produces the nitrilium ion. Solvolysis of the imidate produces acetanilide. Similarly, cyclohexanone oxime protonates and the migration of the carbon anti-periplanar to the leaving group produces the cyclic nitrilium ion. Solvolysis of the imidate give caprolactam.

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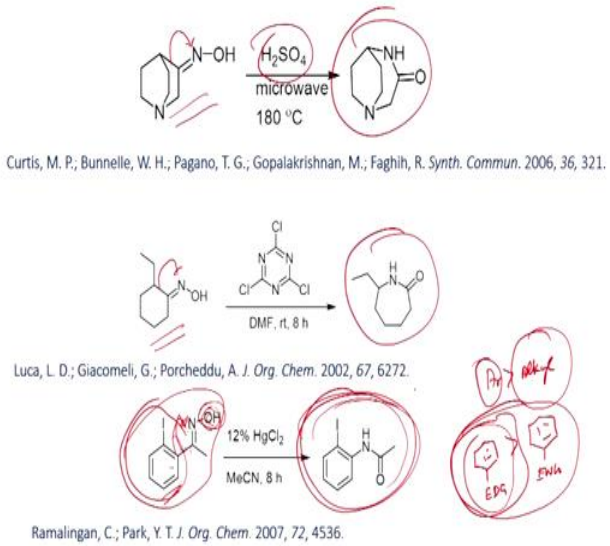

The first example shows the rearrangement of the ketoxime to lactam using sulfuric acid under microwave condition. The tertiary carbon migrates to the nitrogen to produce the nitrilium ion, which under solvolysis gives the lactam. Similarly, 2-ethylcyclohexanone oxime rearranges under mild conditions using 2,4,6-trichloro[1,3,5]triazine at room temperature. The next example shows the rearrangement of 2-iodoacetophenone oxime to 2-iodoanilides in the presence of dilute sulfuric acid.

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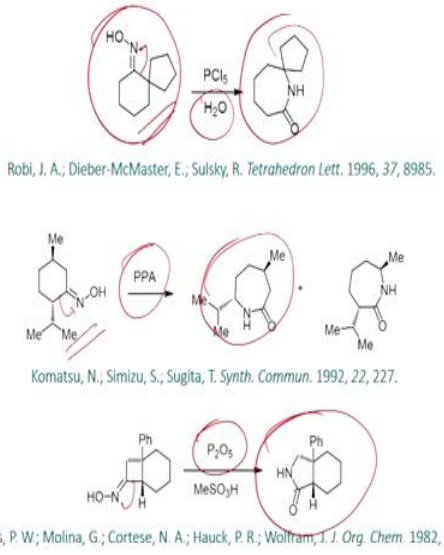

Here the spirocyclic ketoxime rearranges to spirocyclic lactam in the presence of PCl_5. Similarly, menthone oxime rearranges to a mixture of caprolactam derivatives in the presence of polyphosphoric acid. Further, the bicyclic ketoxime converts to the lactam utilizing P_2O_5 in the presence of methanesulfonic acid. So far, we have seen the migration to electron deficient nitrogen. Now let us cover the migration to electron deficient oxygen.

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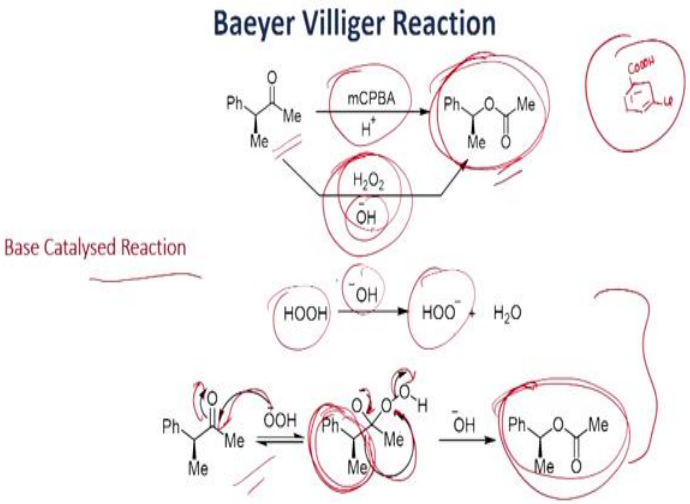

Ketone oxidizes to ester, while the cyclic ketone oxidizes lactone using peroxyacid or peroxide, which is known as the Baeyer-Villiger reaction. Let us see the hydroperoxide mediated oxidation of the ketone, which uses base as a catalyst. Addition to carbonyl group followed by migration of the electron rich carbon to the electron deficient oxygen with the expulsion of the hydroxide produces the ester as the product. Since the hydroperoxide anion is more nucleophilic compared to hydroxide anion, the addition to carbonyl group is favoured that can lead to the rearrangement.

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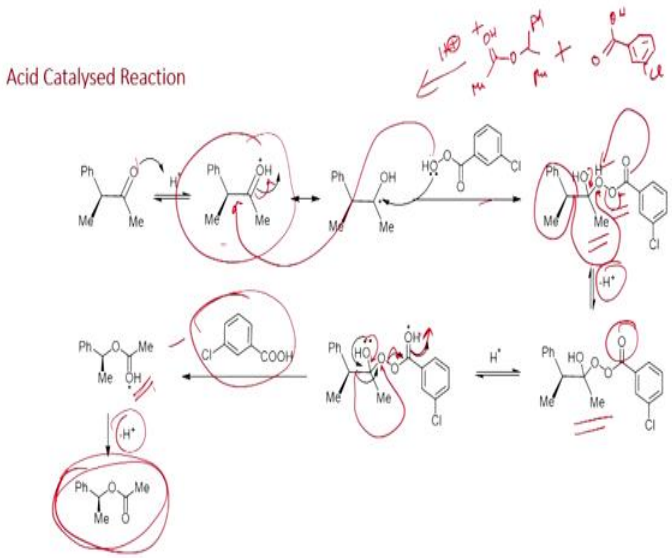

Now let us see the mechanism of m-CPBA-mediated oxidation. Protonation of the carbonyl group followed by addition of peroxyacid and migration of the electron rich carbon to the electron deficient oxygen results in the formation of the ester.

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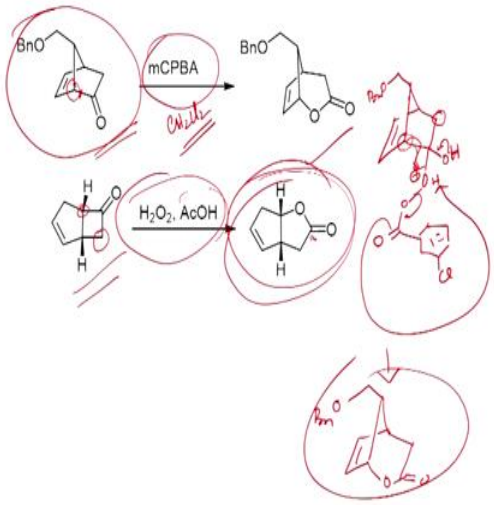

Here the first example covers the reaction of bicyclic ketone to lactone using m-CPBA. The oxygen inserts in between the more substituted carbon and carbonyl group as the more substituted carbon migrates to the oxygen.

The next example involves the combination of hydrogen peroxide and AcOH to oxidize the cyclic ketone to lactone. The oxygen insertion takes place between the more substituted carbon and the carbonyl group.

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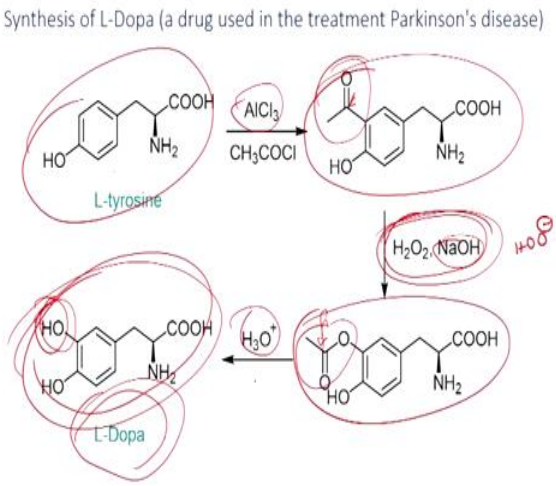

Here is the application of Baeyer-Villiger oxidation for the synthesis of L- dopa. Lewis acid catalyzed acetylation of L-tyrosine with acetyl chloride produces the ketone, which reacts with hydrogen peroxide/NaOH to give the ester that converts to L-Dopa by hydrolysis.

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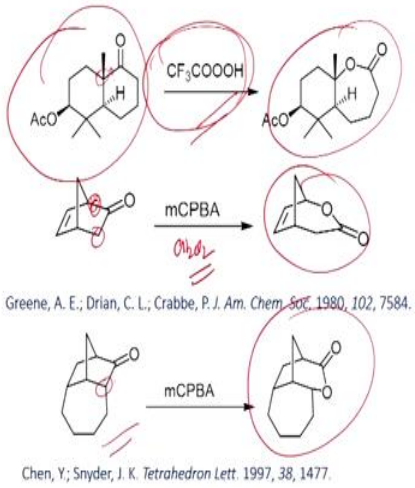

First example involves the use of trifluoroperacetic acid to oxidize diketone to lactone. The stereochemistry of the quaternary carbon that migrates is intact, while the second example utilizes m-CPBA for the oxidation of the bicyclic ketone to lactone. The double bond is intact and no epoxidation is observed. The third example involves the oxidation of cyclic ketone to lactone employing m-CPBA.

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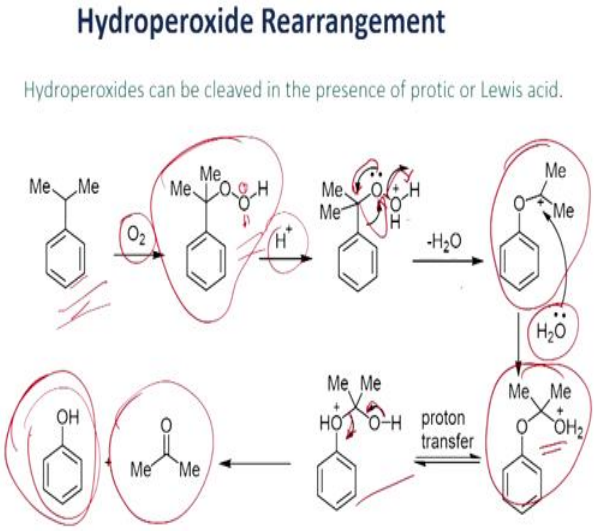

Now let us look at the hydroperoxide rearrangement for the industrial production of phenol. Cumene with oxygen produces the cumene hydroperoxide. Protonation and migration of aryl ring with the electron deficient oxygen gives the oxonium ion. Addition of water followed by proton transfer facilitates the formation of phenol and acetone.

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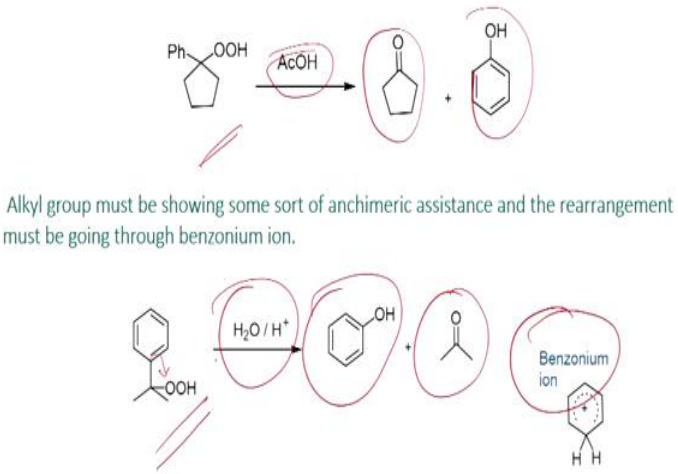

The first example involves the protonation and rearrangement of hydroperoxide using AcOH to produce phenol and cyclopentanone. The second example shows the rearrangement of the cumene hydroperoxide to give phenol and acetone.

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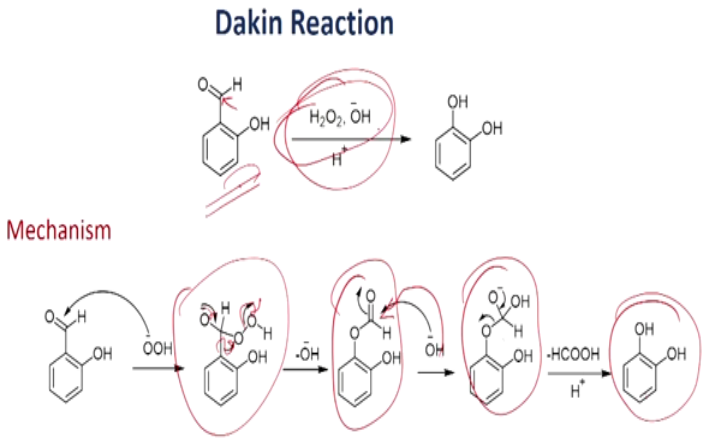

Oxidation of salicylaldehyde with hydrogen peroxide in the presence of base gives catechol, which is known as the Dakin reaction. Addition of hydroperoxide to aldehyde followed by migration of the aryl ring to the electron deficient oxygen and alkaline hydrolysis gives the catechol,

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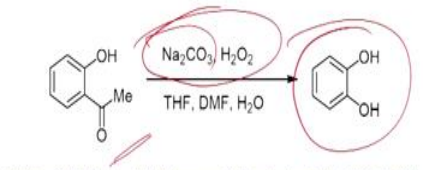
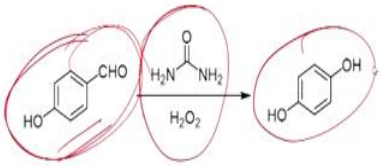


Kabalka, G. W.; Reddy, N. K.; Narayana, C. *Tetrahedron Lett.* 1992, *33*, 865.



Varma, R. S.; Naiker, K. P. *Org. Lett.* 1999, *1*, 189.

The first example involves the oxidation of aryl methyl ketone to catechol using hydrogen peroxide in the presence of sodium carbonate. The next example shows the oxidation of 4-hydroxybenzaldehyde with urea hydrogen peroxide to produce hydroquinone.

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In summary, we have seen examples for the migration of oxygen, sulfur and halogen atoms to electron deficient carbon.

Then, we have seen the rearrangement to electron deficient nitrogen. The Hofmann, Curtius, Schmidt and Lossen rearrangements involve isocyanate as the common intermediate. We

have then seen the rearrangement of oxime to amide or lactam, which is known Beckmann rearrangement.

Finally, we have covered the Baeyer-Villiger and hydroperoxide rearrangements, where the migration takes place on the electron deficient oxygen. With this we conclude this lecture. Thank you very much.