Pericyclic Reactions and Organic Photochemistry

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Module No. #07

Lecture No. #32

Photochemistry of Nitrogen compounds: Barton reaction, Hofmann-Loffler-Freytag reaction and Photo-Wolff Re-arrangement

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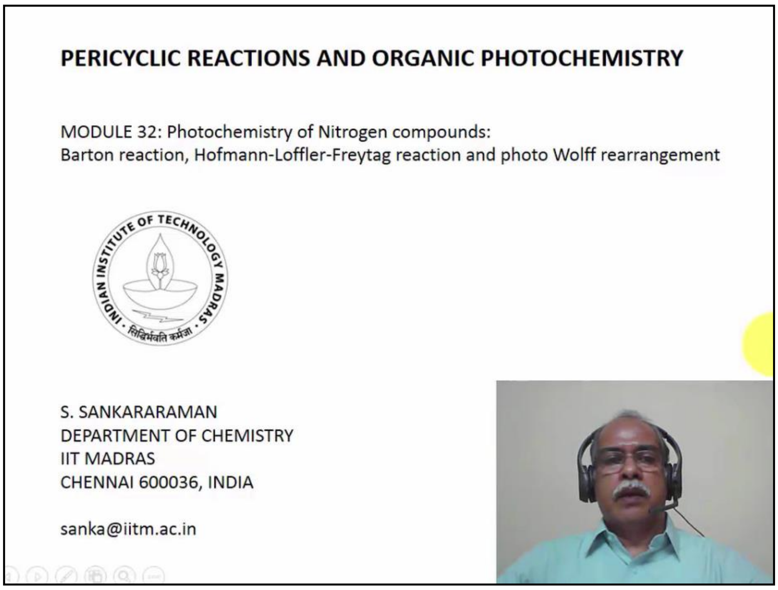

PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 32: Photochemistry of Nitrogen compounds:
Barton reaction, Hofmann-Loffler-Freytag reaction and photo Wolff rearrangement

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Hello, welcome to the online course on, Pericyclic Reactions and Organic Photochemistry. In this Module, we will consider, some interesting reactions of, Photochemistry of Nitrogen-containing molecule. This is Module Thirty-Two, of this particular course. And, in this Module, we will consider three important reactions. One is a Barton reaction. The other one is Hofmann-Loffler-Freytag rearrangement. And, the third reaction is a Photo-Wolff rearrangement.

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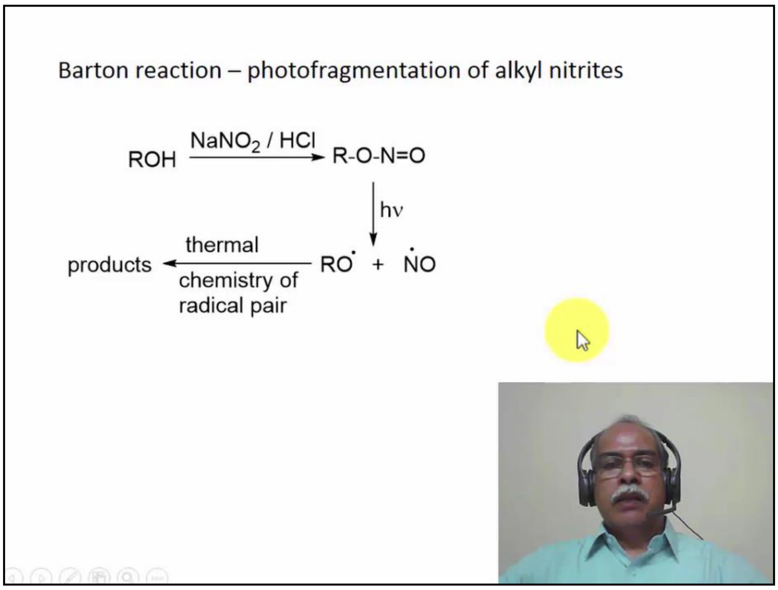

Barton reaction – photofragmentation of alkyl nitrites

$$\mathrm{ROH} \xrightarrow{\mathrm{NaNO_2\,/\,HCl}} \mathrm{R\text{-}O\text{-}N{=}O} \xrightarrow{h\nu} \mathrm{RO^{\bullet}} + \mathrm{\dot{N}O}$$

$$\text{products} \xleftarrow[\text{chemistry of radical pair}]{\text{thermal}} \mathrm{RO^{\bullet}} + \mathrm{\dot{N}O}$$

Now, the Barton reaction, is one of my favorite reactions, in the organic photochemistry, because of the ease with which, this can be done, and the utilization of this particular reaction, in remote functionalization process. Now, what is Barton's reaction? Barton's reaction, is a photochemical decomposition of an Alkyl Nitrite. This is RONO, which is a Nitrite species. This is produced, by the esterification of an alcohol with Nitrous acid, which is produced in-situ by, the reaction between, Sodium Nitrate and HCL.

So, in fact, this reaction is extremely, easy to do. All you have to do is, take an aqueous solution of Nitrous acid, which is produced in-situ by, Sodium Nitrate reaction with the HCL. Shake it up, in a separating funnel, with alcohol. And, the Alkyl Nitrate is insoluble in Water, it separates out nicely. All you have to do is, remove that layer, and distill it out under vacuum, to produce the corresponding Alkyl Nitrate. Alkyl Nitrates are usually, Yellow in color, and they have visible excitation.

So, one can actually do this reaction, also under visible light. Upon photo excitation, it produces, decomposes by fragmentation of the O-N bond, for example. In other words, this Oxygen-Nitrogen bond is cleaved, to produce an Alkoxy radical, and Nitroso radical. The recombination of these two radicals, under thermal conditions, is what the overall reaction is all about. Let us see, the overall reaction.

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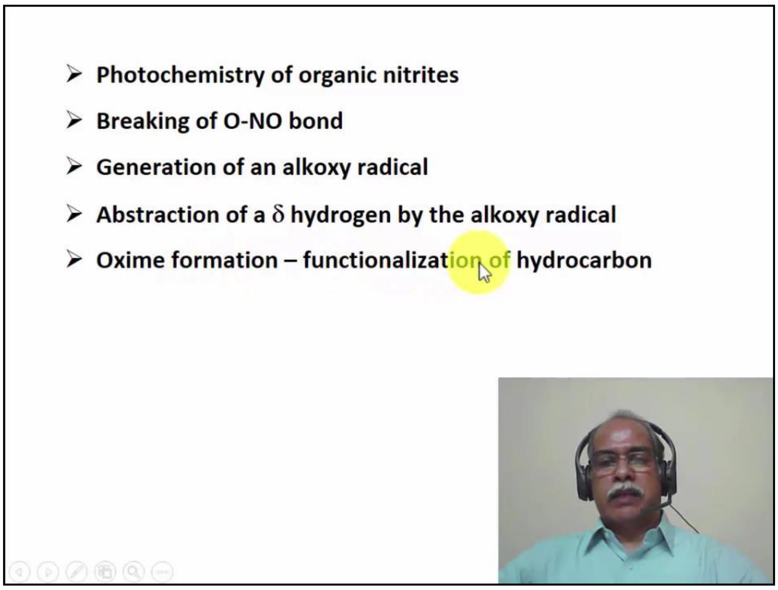

- **Photochemistry of organic nitrites**
- **Breaking of O-NO bond**
- **Generation of an alkoxy radical**
- **Abstraction of a δ hydrogen by the alkoxy radical**
- **Oxime formation – functionalization of hydrocarbon**

So, this is the photochemistry of an organic Nitrite, breaking of ONO bond, is what is producing the Alkoxy radical. Alkoxy radical, undergoes Delta Hydrogen abstraction, by the Alkoxy radical. Then, the resulting Carbon radical, is trapped by the Nitric oxide, for example, producing a Nitroso derivative, which is nothing but a, Keto Enol Tautomer of the Oxime. So, Oxime formation, which can result in the formation of the hydrolysis, to produce the corresponding Ketonic compound.

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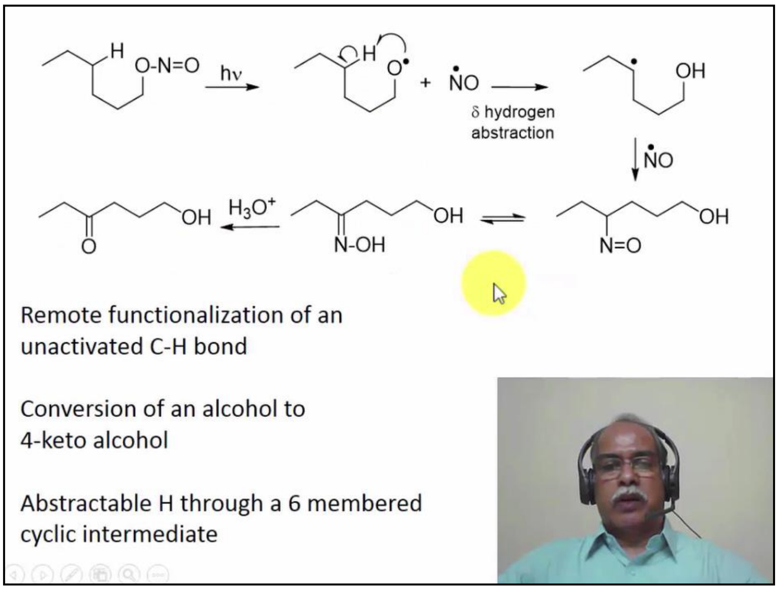

Remote functionalization of an unactivated C-H bond

Conversion of an alcohol to 4-keto alcohol

Abstractable H through a 6 membered cyclic intermediate

So, this is the overall reaction. An Alkyl Nitrite is photolyzed. An Alkoxy radical is produced, along with Nitric oxide. The Alkoxy radical, undergoes a Delta Hydrogen abstraction, in a 6-Membered Cyclic Transition state, for example, producing a Carbon centered radical. This Nitroxy radical is around, so it can combine with the Alkyl radical, to produce this C-Nitroso compound. The C-Nitroso compound, is nothing but a Tautomer of this Oxime. The Oxime can be hydrolyzed.

So, you have seen, what you have done. Take an alcohol, and converted into a Keto alcohol, for example. So, 4-Keto alcohol conversion from alcohol, is what is happening. This Hydrogen, is not particularly an activated Hydrogen. And, secondly, there are so many such Hydrogens, in this chain. It prefers, to take the Hydrogen, only from the Delta position. So, it is a remote functionalization of an un-activated CH Carbon, in a very regio specific manner.

That is the beauty, of this reaction. The fact that, this Nitrite can be easily synthesized. And, this reaction can be easily carried out, by room light photolysis, makes this synthetically very useful reaction. And, that is one of the reason, why this particular reaction, is my favorite reaction.

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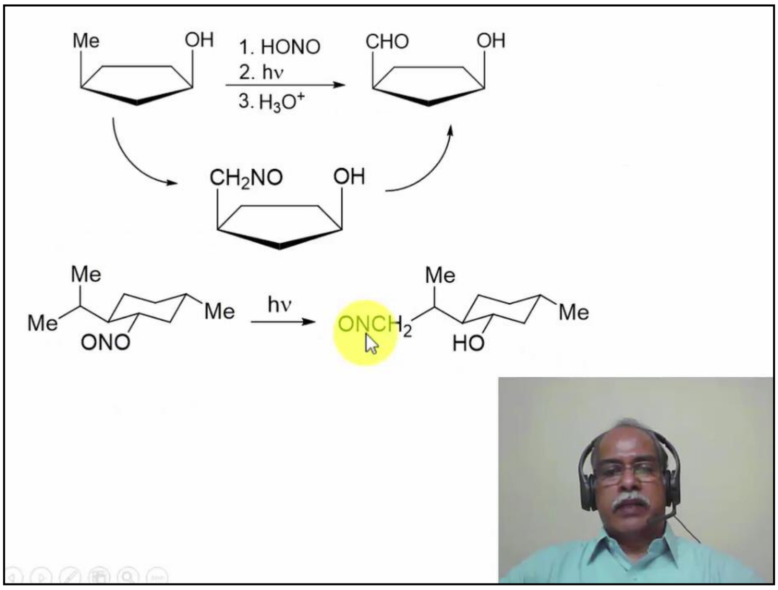

Now, here is an example of a, 1,3-Diaxial kind of a system, in this Cyclopentane derivative. So, this is 3-Methyl Pentanol Nitrite, is what is photolyzed. HNO, produces the corresponding Nitrite. Photolysis, produces the Alkoxy radical. The Alkoxy radical, has an accessible Hydrogen, in the Alpha-Beta-Gamma, Delta Hydrogen, is this particular Hydrogen. Because of the 1,3-Diaxial kind of an interaction, this is easily accessible.

The Alkoxy radical, access this Hydrogen, resulting in the formation of a CH2 radical here, and OH here. The CH2 radical, combines with a NO, that is produced, to produce the CH2NO, which is nothing but the Oxime, of this particular Aldehyde. So, Acid hydrolysis, produces the Hydroxy Aldehyde, as the final product. So, overall this reaction, has gone through the Barton’s reaction, through this formation of this particular intermediate, which is nothing but the Oxime of this particular Aldehyde, which is hydrolyzed, under acidic condition.

It is another example. This is a Menthol derivative. This is a Menthyl Nitrite, is what is given here. The Menthyl Nitrite, has an accessible Delta Hydrogen, which is this Methyl Hydrogen, for example. And, that produces the CH2NO as an intermediate, resulting in the formation of this particular compound, in the absence of any hydrolyzing agent, the Nitroso compound can be isolated, in this particular case.

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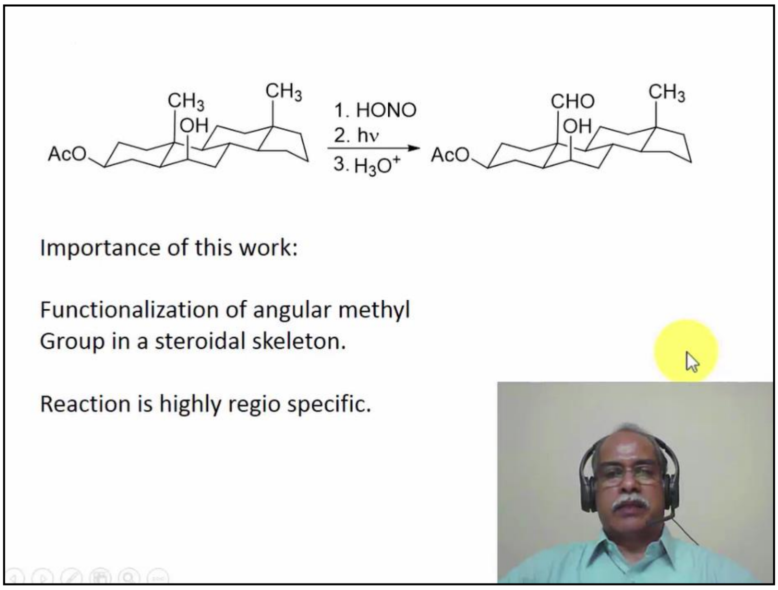

Importance of this work:

Functionalization of angular methyl Group in a steroidal skeleton.

Reaction is highly regio specific.

So, this essentially illustrates, the importance of this work. Functionalization of Angular Methyl, in a steroidal skeleton, is the overall reaction, all about. Steroidal alcohol can be converted, into the corresponding Nitrite. The Nitrite is photolyzed, to produce the corresponding Alkoxy derivative. This is the 1,3-Diaxial interaction. This Hydrogen is accessible to the Alkoxy radical, that is produced here, producing a CH2 radical, and this OH back.

And, the recombination of the Nitric oxide at this Carbon, essentially produces the Oxime, which is hydrolyzed under the condition. So, overall, if you look at the reaction, you have converted an innocuous Methyl group. In other words, unreactive Methyl group, in a very selective manner, in a regio specific manner, highly regio selective manner, into an Aldehyde, which is a very valuable Transformation.

Overall, functional group Transformation, is from a Methyl, to a CHO group. And, that too, in the presence of other Methyl groups, nothing happens. Only this Methyl, which is 1,3-Diaxial Methyl, with respect to the Alkoxy radical, that is produced, is the one, that is undergoing the reaction. That is the beauty of this reaction. So, one should appreciate the reaction itself, for its synthetic utility.

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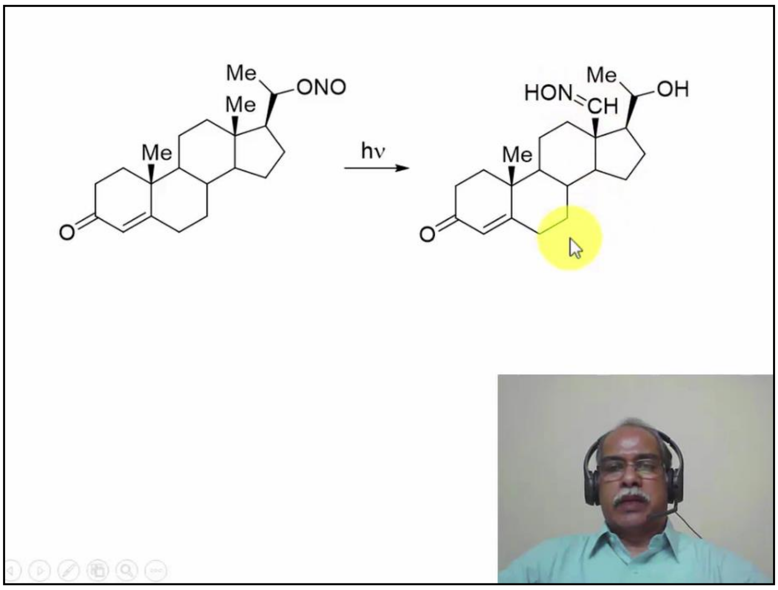

Another example. This is a Methyl, that is easily accessible here. So, the Alkyl Nitrite decomposition, under photolytic condition, functionalizes this molecule, to the corresponding Oxime. It is shown, in the Oxime stage one. Oxime can be hydrolyzed, to get the corresponding Aldehyde, in this particular case.

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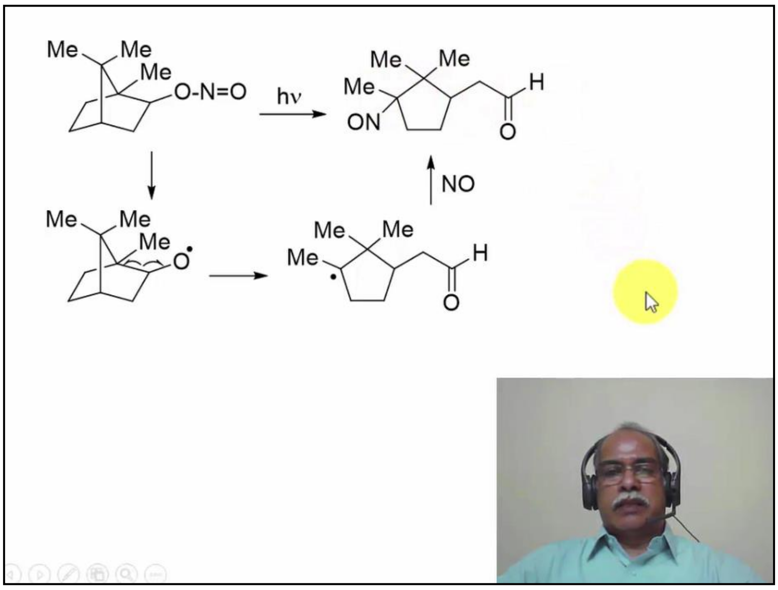

In the case, of this bicyclic derivative, the Alkoxy radical, that is produced, is unstable. So, this bond essentially fragments to undergo the, formation of the Aldehyde, and the corresponding radical. And, Nitroxide traps that particular radical, to produce the Tertiary Nitroso derivative. So, this particular example, is a fragmentative Barton rearrangement, is what is taking place, in this particular instance.

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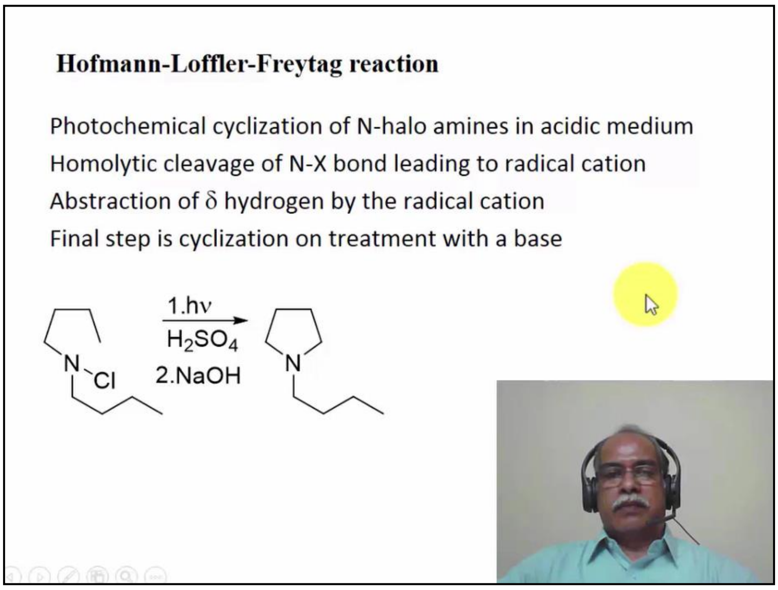

Hofmann-Loffler-Freytag reaction

Photochemical cyclization of N-halo amines in acidic medium

Homolytic cleavage of N-X bond leading to radical cation

Abstraction of δ hydrogen by the radical cation

Final step is cyclization on treatment with a base

Now, let us move on to the next reaction, which is called the Hoffman-Loffler-Freytag reaction. It is a mouthful, in terms of the names, that are involved, in this particular reaction. This is a photochemical cyclisation reaction of a, N-Halo amine. N-Halo amines can be produced, by taking the corresponding Secondary amine, and treating it with Chlorine, or taking the Secondary amine, treating it with N-Halo Succinamide kind of a reagent, one can easily produce the N-Halo derivative.

The photochemical cyclisation of N-Halo amines, in an acidic medium. So, because it is carried out in an acidic medium, most likely the protonated species, is the most reactive intermediate. The homolytic cleavage of the NX bond, in other words, the N-Halogen bond, leads to a radical cation protection.

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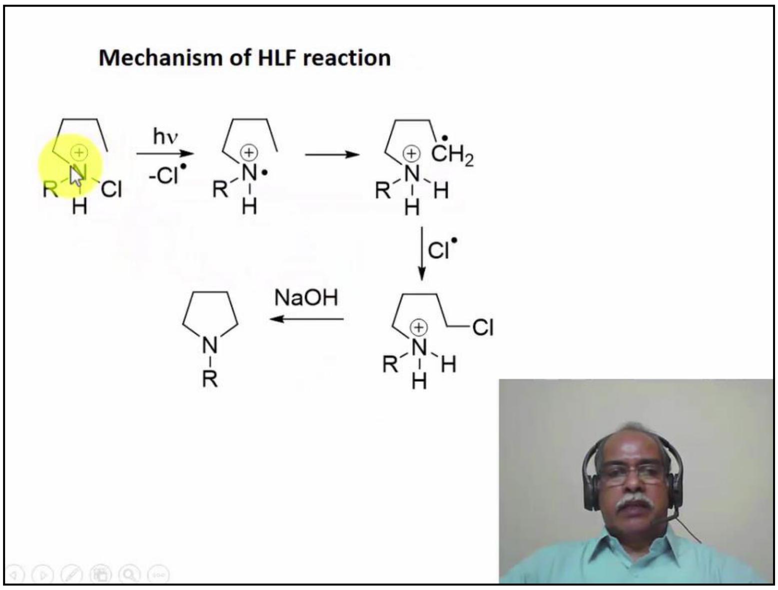

Mechanism of HLF reaction

So, this is explained in this mechanism, here. Initially, the protonated N-Chloro derivative, undergoes homolysis of the N-Halogen bond. This is the cation, to start with. When you homolyze, you are going to get a radical here, and another radical here. So, you produce a Cation radical in the process, along with the Chlorine radical. The Cation radical, now abstracts the Hydrogen from the 6-Membered Cyclic Transition state, to produce the Tertiary Ammonium salt, and an Alkyl radical.

The Alkyl radical, combines with the Chloride radical, to produce the corresponding Alkyl Chloride derivative. In the presence of a base, when you work it up, the amine that is generated, undergoes an internal Nucleophilic substitution reaction, forming a Carbon-Nitrogen bond, with a simultaneous loss of the Chloride ion, in this particular case, to produce the Cyclic amines.

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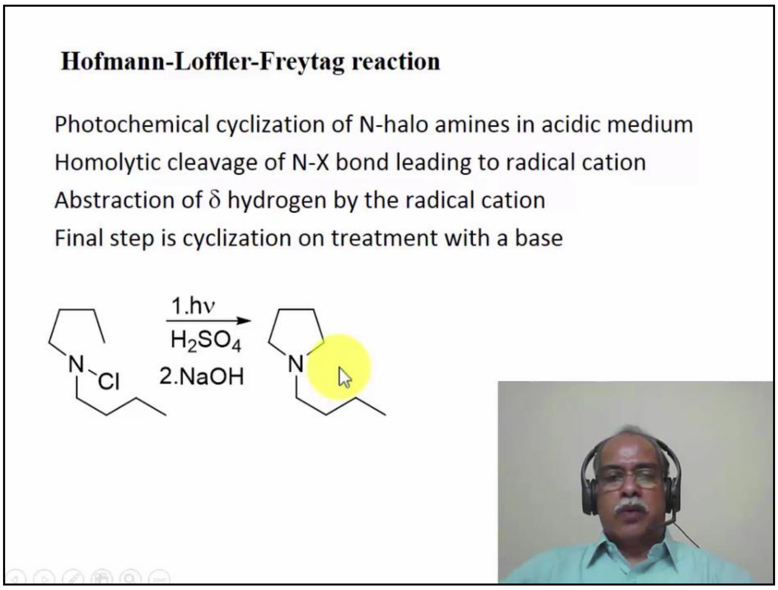

Hofmann-Loffler-Freytag reaction

Photochemical cyclization of N-halo amines in acidic medium

Homolytic cleavage of N-X bond leading to radical cation

Abstraction of δ hydrogen by the radical cation

Final step is cyclization on treatment with a base

So, this is the overall reaction. An N-Halo amine, in this particular case, Di-N-Butyl-N-Chloro amine, under acidic conditions, in the presence of Sulphuric acid, followed by work up by Aqueous Sodium Hydroxide, results in the formation of a Pyrroline derivative, which is this particular derivative. N-Butyl Pyrroline, is what is formed, in this reaction. And, the mechanism of the reaction, is shown here, very clearly.

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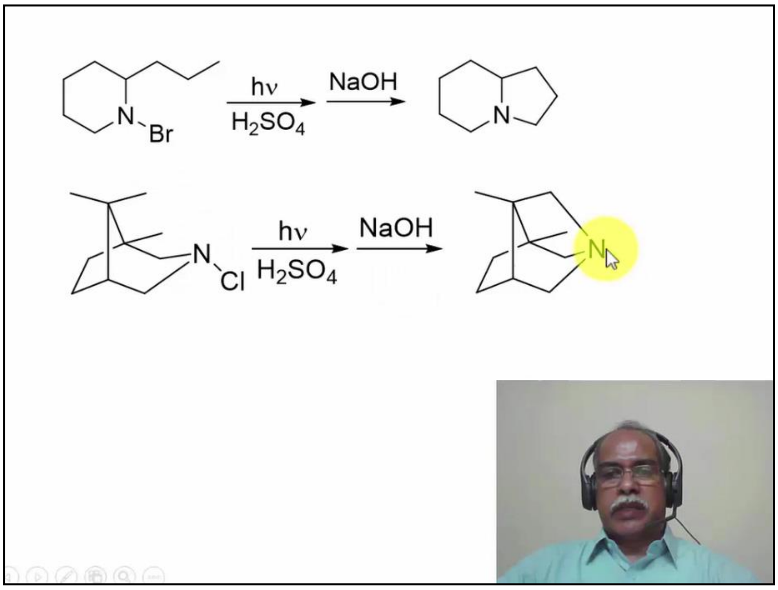

Now here, it is a N-Bromo Piperidine derivative. It undergoes, the Hydrogen abstraction, from this position here, resulting in the formation of a, Fused Bicyclic Ring system of this kind, with the Nitrogen on the ring fusion, of the system. So, in the presence of Sulphuric acid, the Protonated amine, is what is undergoing the reaction. The N-Bromo bond, is what is cleaved during the photolysis, followed by Hydrogen abstraction.

And, radical recombination of this, producing here, and Nucleophilic substitution at a 1,5 position, resulting in the formation of a 5-Membered ring. Nucleophilic substitution ring closure, of the 4-5-6-Membered rings, are very fissile. In fact, 3-Membered ring closure, is also very fissile. So, that can form the corresponding ring system, in terms of the Cyclic amine, that is being produced. If you look at this molecule, this Bridge-Head Methyl is the one, that is easily accessible, for the radical Hydrogen abstraction, for example.

So, the N-Halo bond is cleaved after protonation, and resulting in the formation of the Cation radical, which abstracts the Hydrogen from here, resulting in the formation of the bond, between the Chlorine, and the CH2CL, is produced here. Chlorine recombination at this center, will produce a CH2CL, which undergoes Nucleophilic substitution reaction, to produce the Tertiary amine, which is shown here, as the example, in this case.

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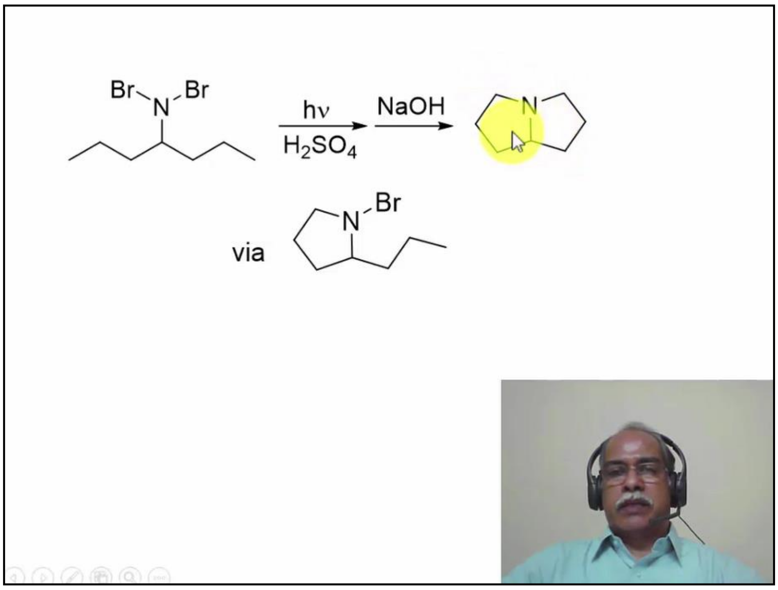

If, we have a Dibromo derivative, it can undergo double Hofmann-Loffler-Freytag cyclisation reaction. This is one cyclisation, arising from this Carbon-Bromine bond breakage. The other Carbon-Bromine bond breakage, can also lead to the other cyclisation, with the involvement of this intermediate, via this intermediate. So, initial cyclisation, produces this intermediate, which further undergo cyclisation, to produce this particular Bicyclic amine, Tertiary amine, Ring Fusion Head amine, is what is generated, in this particular instance.

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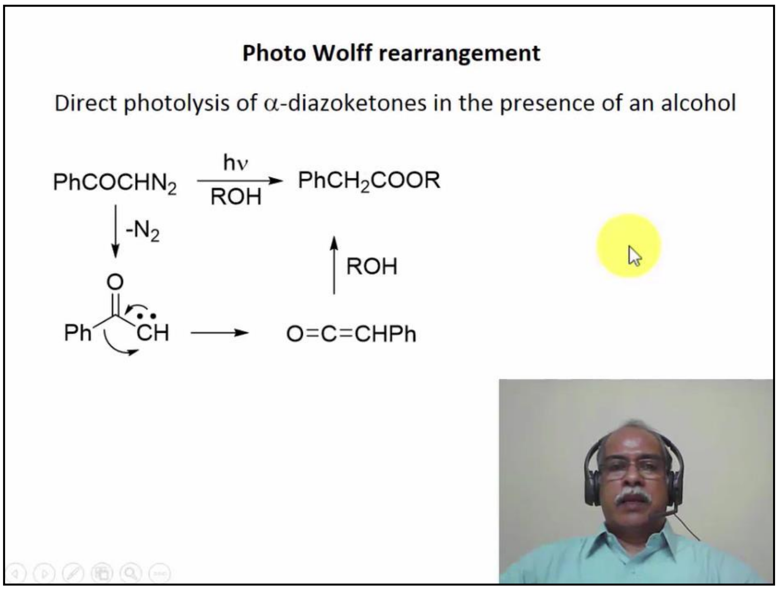

Photo Wolff rearrangement

Direct photolysis of α-diazoketones in the presence of an alcohol

Let us move on to, Photo-Wolff rearrangement. It is a direct photolysis of a Diazo Ketone, in the presence of an alcohol. So, Alpha Diazo Ketone, if you take, this is essentially coming as a part of the, onstage state synthesis homologation of the, carboxylic acid derivative. So, Acid Chloride is treated with Diazo Methane, to produce Alpha Diazo Ketone.

The Alpha Diazo Ketone, under photolytic condition, essentially produces a Ketene intermediate, through the involvement of this Carbene. The Ketene is trapped by the alcohol, to produce the corresponding esters. So, over all, you have done a homologation reaction. And, this process is known as, when it is carried out under photochemical condition, it is called the Photo-Wolff rearrangement.

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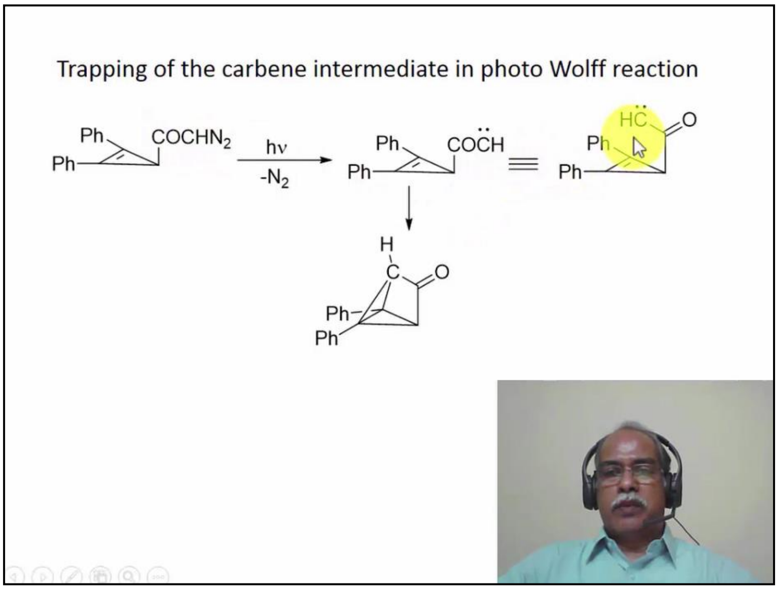

Trapping of the carbene intermediate in photo Wolff reaction

Wolff rearrangement, can also be thermally mediated, using Silver salts. But, it is easily also done, by photochemical reaction. How do we know, Carbene is formed? This is a trapping experiment. An internally built double bond, can trap the Carbene, by a cycloaddition reaction. So, the Carbene, that is generated as this particular structure, that is in close proximity with this double bond, over here.

So, cycloaddition reaction, in other words, trapping of the Carbene by the Olefin, essentially produces a 3-Membered ring. And, this molecule is produced, essentially by an internal Wolff kind of an, not a Wolff rearrangement. But, the evidence for the Carbene formation, is what is generated, in this particular experiment.

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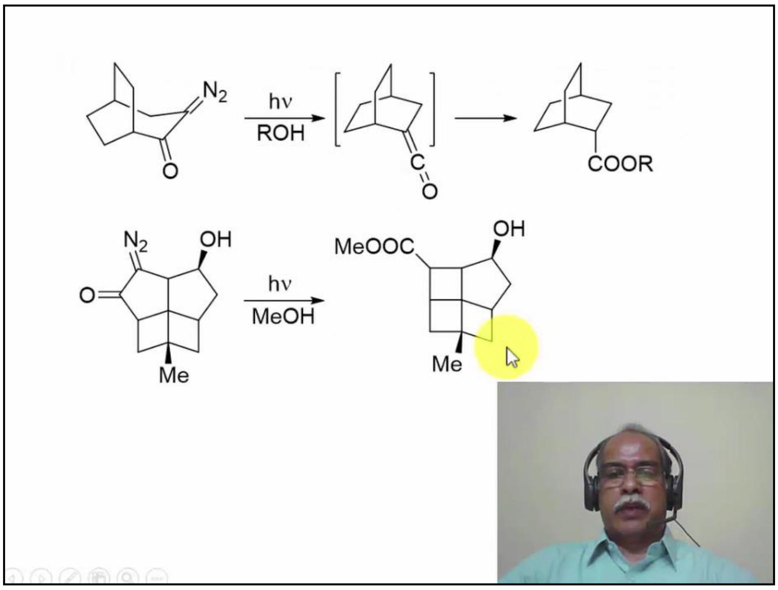

These are some synthetic examples, of the Wolff rearrangement. A 2,2,3-Bicyclic system, an Alpha Diazo Ketone, essentially undergoes Nitrogen loss, followed by the formation of the Ketene, which is trapped by the alcohol, to produce the corresponding ester, in this particular case. This is an interesting synthesis of, Fenestrine kind of a molecule. Fenestrines are molecule, which look like window.

Suppose, if you have a 4-Membered ring here, this will exactly look like a window frame, for example. So, these are interesting molecule, because the geometry at this particular Carbon, cannot be tetrahedral, if you can imagine. So, it will be a highly distorted tetrahedral kind of a geometry, is what we have. And, such molecules are interesting, from the point of view of synthesis, as well as the geometry consideration, of this particular molecule.

This molecule, is essentially produced, by a ring contraction reaction, of a Photo-Wolff rearrangement, loss of Nitrogen molecule, production of the Carbene here, and the rearrangement of the Carbene, to the corresponding Ketene. The Ketene is trapped by Methanol, to produce the ester, with the concomitant ring contraction, that is taking place. 5-Membered ring, is contracted to the 4-Membered ring, in this particular instance.

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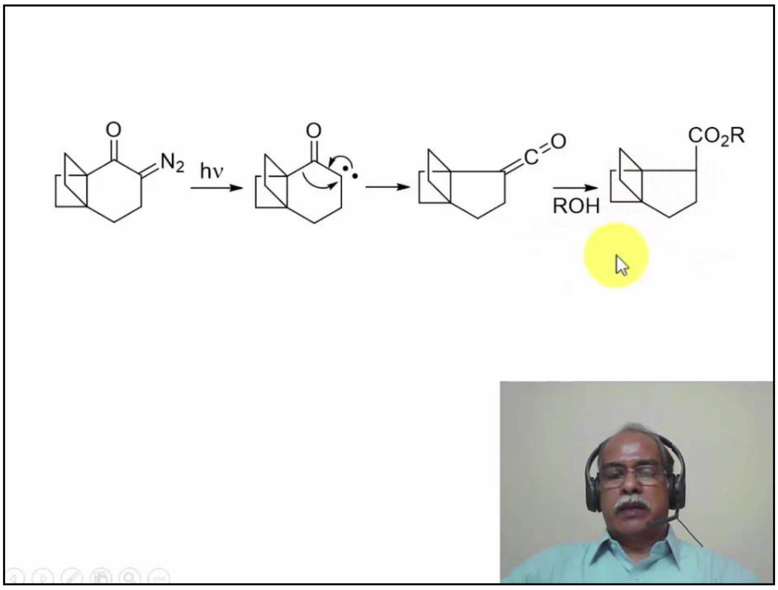

This is something, we have seen earlier. This is a double Wolff rearrangement, that is responsible for the propellane kind of a, propeller-shaped molecule. So, this is essentially obtained by, 2+2-Cycloaddition reaction of the Cyclohexenone, with the Ethylene molecule twice, for example. And, this is Alpha Diazo Transfer produces a, corresponding Alpha Diazo Ketone. And, on photolysis, it produces this Ketene, through this Carbene intermediate.

The Ketene is trapped, by the alcohol, so the ring contraction has taken place. Once again, can convert this into the corresponding Ketone, by degradation process. And, that can further undergo ring contraction reaction, by a Wolff rearrangement, producing a 2,2,2-Propeller kind of a system, in this particular instance.

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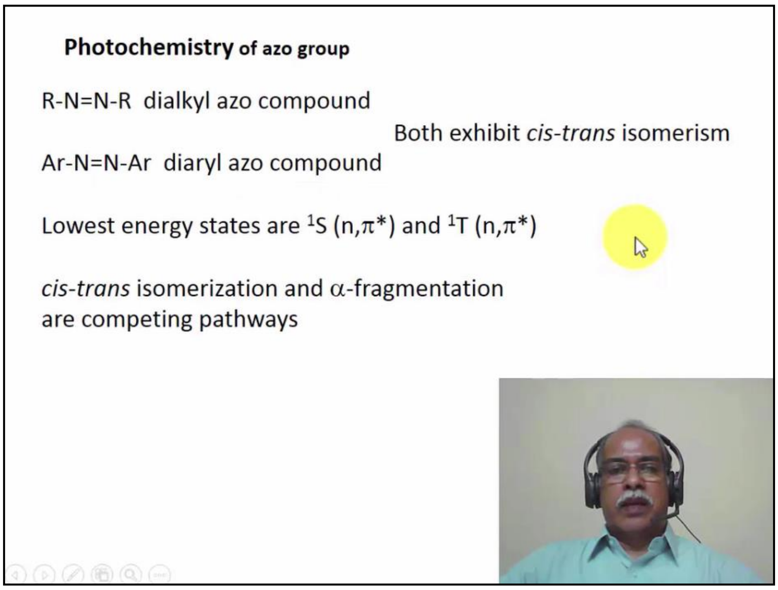

Photochemistry of azo group

R-N=N-R dialkyl azo compound

Both exhibit *cis-trans* isomerism

Ar-N=N-Ar diaryl azo compound

Lowest energy states are ^1S (n,π*) and ^1T (n,π*)

cis-trans isomerization and α-fragmentation are competing pathways

Hope, this photochemistry of Azo compound will conclude, in this particular session. The Dialkyl Azo compounds, and the Diaryl Azo compounds have, both exhibit Cis-Trans isomerism, in the ground state. In other words, the NN bond rotation energy, is very high. So, as a result of that, there is a Cis, as well as the Trans isomer, that is possible. The lowest energy states, are the first excited Singlet state, which is a N-PI-Star state, as well as the first excited Triplet state, which is also an N-PI-Star state, in this particular case.

So, the Nitrogen lone pair gets excited, to the PI-Star state of the N-double bond-N, in this particular case. So, there are two possible reaction, that can take place. The Cis-Trans isomerization, is one reaction. Alpha fragmentation, is a competing pathway, that can accompany the Cis-Trans isomerization process.

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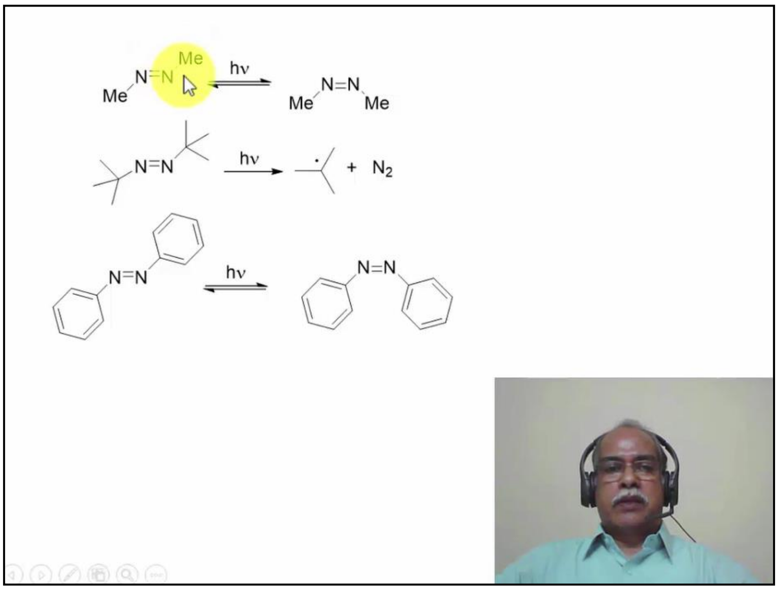

In the case of, simple Alkyl substituted derivative, one does not expect, this to undergo, an Alpha fragmentation. Because, the Alpha fragment, which is a Methyl radical, is not stable. So, the Azo Methane essentially undergoes, Cis-Trans isomerization only. On the other hand, if you have Dialkyl Azo compounds, for example, which is Di-Tertiary Butyl.

The Tertiary Butyl radical, can be stable. This can undergo disproportionation, to give Isobutane, and Isobutylene, for example. So, this is essentially undergoing a fragmentation process, whereas, this is undergoing a Cis-Trans isomerization process. In the case of Azo Benzene, for example, it known to undergo Cis-Trans isomerization, which is very useful. Earlier on, we saw the Cis-Trans isomerization of Azo Benzene, in Transporting Potassium ions, through a channel.

Remember, in the case of Olefin Cis-Trans isomerization, we discuss the Cis-Trans isomerization, of the Azo compound also, and illustrated an example of that. We have 2-Crown Ethers, are attached to the Azo Benzene moiety, which can Transport the Potassium ion, in the Cis form, but not in the Trans form. And, that was an application, of the Cis-Trans isomerization, of the Azo Benzene molecule, that was illustrated.

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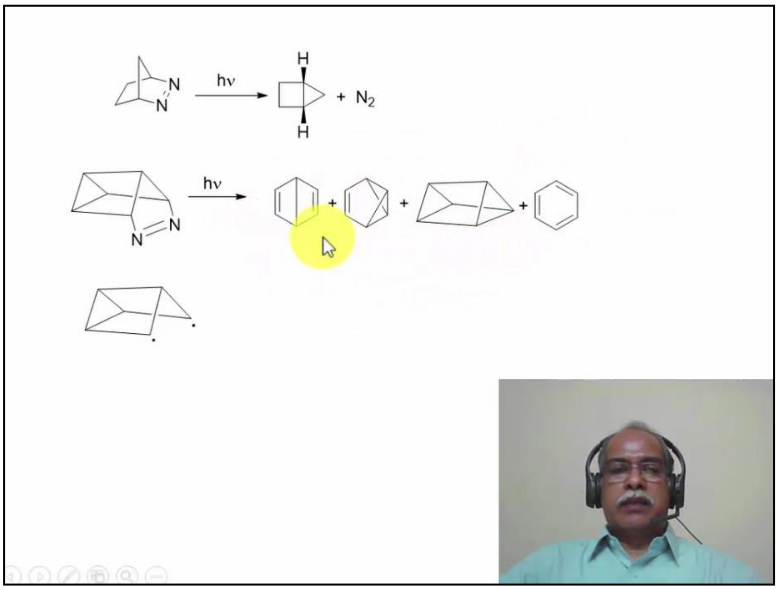

Now, in the case of Cyclic Azo compounds, the Cis-Trans isomerization is not possible obviously, because the Trans isomer will be highly constrained. So, only possible reaction, that it can undergo in the N-PI-Star excited state, is a fragmentation process of the Carbon-Nitrogen bond, producing a molecule of Nitrogen. The N-triple bond-N has a very high energy. As a result of that, the photochemical decomposition, is a highly exothermic process, of this kind, of a system.

We can see here, this is a Diazo compound, which is capable of producing, all the isomers of Benzene. This is Dewar Benzene, this is Benzvalene, this is Presamine, and Benzene itself. If the Diradical is formed, this can be rearranged to the Dewar Benzene, it can rearrange to the Benzvalene, it can simply ring close to give the Presamine, or it can undergo isomerization to give Benzene also.

So, these are some interesting examples, not synthetically very useful, because it produces a mixture of Benzene isomers. Nevertheless, from the mechanistic point of view, it illustrates that, it goes through a Diradical intermediate, of this kind.

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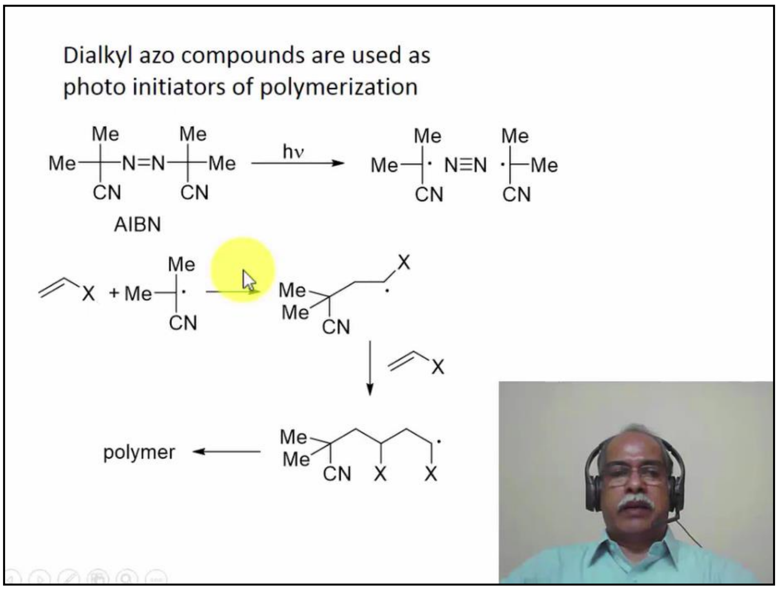

Dialkyl azo compounds are used as photo initiators of polymerization

Now, Dialkyl Azo compounds, which are bulky substituents, being present on the Nitrogen, can be used as photoinitiators, in polymerization reaction. In fact, these are free radical initiators. This is called, the AIBN, Azoisobutyronitrile. In other words, Azo, which is N-double bond-N. Iso Butyro Nitrile, is this particular. So, it is simply abbreviated as, AIBN. Upon photolysis, the Carbon-Nitrogen bonds break, a molecule of Nitrogen is produced, with the formation of a stable radical, which is this particular radical.

This radical can be stabilized, by the Cyano, as well as the Dimethyl functional group, because of hyper conjugation effect. Now, this is a radical, which is an initiator, which can initiate polymerization of Vinylic monomers, like the Vinyl acetate, or Vinyl Chloride, or Acrylate, for example, Cyanoacrylates, and so on. It can undergo an addition reaction, to produce another radical. This is the chain carrier radical. The chain career radical, further under adds the additional monomers, to produce the polymer chain.

The polymerization can produce, and it is initiated, by this particular. So, essentially, Dialkyl Azo compounds, which can actually produce, stable radicals are useful, as initiators in photo polymerization reaction. The secondary radical, that is produced is a carrier radical, for the polymerization reaction, to proceed further. So, i hope, you enjoyed this module. What we have seen, in this module, is the photochemistry of only nitrogenous compounds, starting from Alkyl Nitrate, which is Barton reaction, very useful reaction.

And, it is one of the best reactions, in organic photochemistry, for example. I like it very much. Second reaction, is a Hofmann-Loffler-Freytag reaction, which is a production of a Cyclic amine, from an Open-chain amine, through the N-Halo Open-chain amines. The third reactions, are the corresponding Diazo Wolff rearrangement, is something we saw, in this particular module.

And, finally, we concluded with the Diazo chemistry, Photochemistry of Azo compounds, is what we saw, in the final part of this particular module. Hope, you like this module. Thank you very much, for your kind attention.