Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach

Professor Amit Basak
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture 31

Radical Mediated C-C Bond Formation(continued)

Hello, everybody. Welcome to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. Last few lectures we have been discussing the chemistry of carbon centred radicals. So, today we will continue on that what is still remaining on that aspect.

One important point is how do you really know that a reaction involves a radical as an intermediate. That means, we need to know how to detect the existence of a radical. Now, there are many methods, but the most direct approach is to do a spectroscopic determination and that is by electron spin resonance or electron paramagnetic resonance.

You know that a single electron has one type of spin and in a magnetic field there can be, it can be aligned or it can be opposed. So, you can do this inter-conversion and then see the energy that is required to do that. So, that is the spectroscopic means, which is which is called EPR or ESR.

Now, there is a sometimes what happens that some of these radicals are extremely short lived, their half Life is very low and then in many cases also like an enzymatic reaction where there is an active site and if the reaction that the enzyme catalyses involve a radical sometimes it is difficult to detect the presence of that radical which is buried inside the active site. So, in those cases EPR or ESR may not be applicable.

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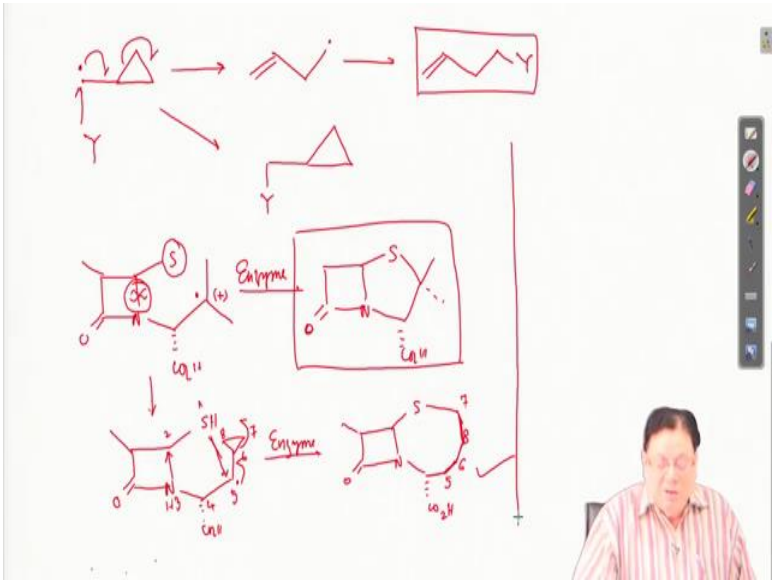

So, what is the other alternative? Now, there is a indirect chemical method which is which involves something what is called a radical clock, that means a clock which shows the existence of a radical and that is basically that if you have a radical generated adjacent to a cyclopropyl system, a cyclopropane system and if you are generating a radical, then the there is a spontaneous, extremely rapid ring opening of the cyclopropane. So, you will get something like this.

So, when you see that you are trying to do a reaction at a carbon and you are ending up the product suppose you are trying to do a reaction with Y and instead of getting this one the directs the product where it is supposed to act, supposed to react you may get a small amount of that, but along with that, you are always you always see the existence of another product which is the ring opening product.

This so, the formation of this product immediately tells you that that possibly the reaction is going through a radical. This radical cyclopropane based cyclopropyl methyl radical, this is this has been exploited to unravel the mechanism of many reactions where there is direct observation by direct observation of the EPR signal is not possible.

One example I can tell you that there was a debate in the reaction of a where a carbon sulphur bond is formed to form a bicyclic network like this. Incidentally this framework is what is present in many of the beta lactam antibiotics. So, there was a there is an enzyme which does this reaction and there was a debate that whether this carbon sulphur bond goes via a radical or it goes via a cation.

So, these are the two possible possibilities, anion was ruled out because you are you have a nucleophile. So, you can rule out the existence of an anion at that centre. However, this radical and and this cation are certainly the possibilities. So, what was done? The experiment that was done was basically make a make a substrate incidentally the enzyme also does the formation of these carbon nitrogen bond.

So, basically you start your reaction from an acyclic compound like this, acyclic compound like this and then the enzyme first closes this bond and then subsequently this bond. And we are talking about the formation of this carbon sulphur bond that whether it involves a radical or a cation.

So, the experiment that was done that basically instead of this dimethyl, instead of this gem-dimethyl sorry yes, instead of this gem-dimethyl you can take alternate substrates like you can put a cyclopropyl. If you put a cyclopropyl then what will happen? If it is a radical as I said the radical will immediately open up and what you will get in the end is a product which is the ring size will be much more.

What will be the ring size? Now you can tell this is 1, 2, 3, 4, 5, 6, 7, 8. So, the ring size is suppose I put a number 1, 2, 3, 4, 5, 6, 7, and 8. So, now you have a connection between sulphur so basically this radical will now, the sulphur will react to the radical at see 7. So, that will be 7, then 7 will be connected to 8 and 8 will be connected to 5, sorry 8 will be connected to 6, 6 will be connected to 5, and 5 will be connected to 4. So, this is the product that will end up.

So, this is this is the product. So, ring expansion product that you will get and indeed this was obtained. So, that was one of the early evidence that this reaction goes via a radical. So, that is how about the detection? How you detect the radicals.

Now, let us again go back and start proving that how the radicals are generated. I have already given you possibly one method which is a tin hydride-based method, that will take an alkyl halide or you can take a alkyl thiosulphide SPh or an alkyl selenide, and if you add tributyltin hydride, the reaction goes via a radical pathway.

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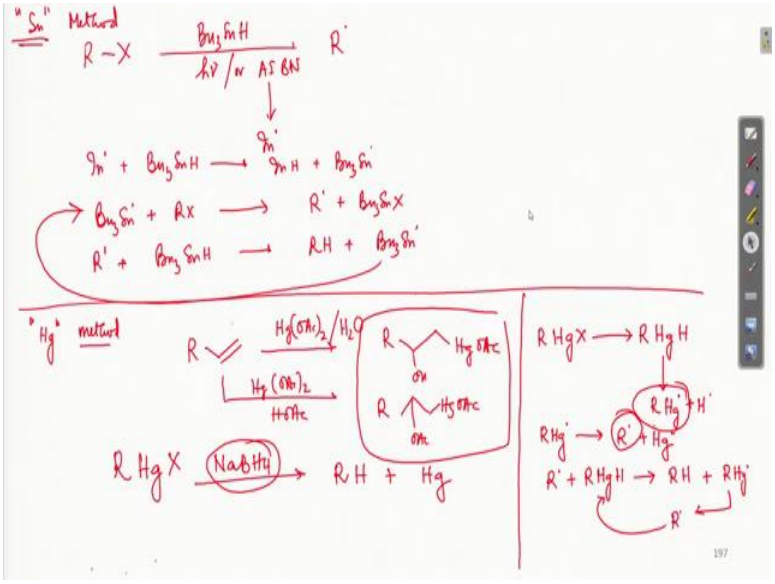

So, let us now talk about how many different ways one can generate radicals. So, our first method is RX and Bu3 SnH. So, that is called the tin method. So, that is the tin method for generation of radical. And this reaction requests either h nu or you can utilise AIBN. So, that will generate R dot.

Then you have something what is called, before we go on to that, again I remind you, what is the mechanism of this reaction that AIBN gives the initiator radical and that initiator radical reacts with tributyltin hydride and that forms the tributyltin radical and tributyltin radical then reacts with RX and then you get R dot plus tributyltin halide and then R dot reacts with tributyltin hydride to form RH plus Bu3 Sn dot and this Bu3 Sn dot then carries out the reaction and the chain propagation happens. Now, this is the mechanism of tin hydride. So, that is the tin method.

Now, there is another called the marketing method. The marketing method is basically that you start with a with an alkene and you know you have done you know what is mercuration oxymercuration demercuration reaction. And that means the double bonds are prone to addition by mercury sols, like if you take Hg OAC twice and if you take say water. Then what happens? You have R OH here and this is Hg OAC.

Or if you take Hg OAC in acetic acid then you will get, we will get R sorry this is your OAC and that will be your Hg OAC. Now, let us call this as R Hg X, where X can be acetate, X can be halide, also mercury chloride, all these are possibilities. So, we call this as in general RHgX.

Now, if you reduce RHgX with sodium borohydride, then what happens? You get RH plus mercury. So, metallic mercury comes out and the result is that RHg bond is broken and that is replaced by hydrogen. So, RH. Now the mechanism of this reaction again it involves a radical first of all RHgX by sodium borohydride or you can take other borohydride like trimethoxy sodium borohydride. So, different versions of borohydrides are available. So, you can take that and but the basis is that they are hydride transfer agent, they are reducing agent.

So, first that will be reduced to RHgH. Now, RHgH this alkyl mercury hydride are very unstable compounds. So, they decompose even if it is tiny extent, but the decomposed like this RHg dot plus H dot. So, that happens under the normal thermal condition, not to a great extent, but a tiny amount of this reactions that you need for the whole reaction to follow in a radical, in a radical chain process.

So, what happens? As soon as RHg dot is formed that will also not be very stable. So, that will be R dot plus mercury. So, basically you are now making the alkyl radical. So, this alkyl radical now will react with RHgH. Remember you have sociometric amount of sodium borohydride. So, you have sociometric amount of alkyl mercury hydride. So, a tiny amount of that decomposes into RHg dot plus H dot and RHg dot then subsequently decomposes to the alkyl radical and mercury, metallic mercury.

And this R dot then reacts with the remaining RgH that alkyl mercury hydride and forms RH plus RHg dot. So, you see the same thing which is responsible for propagating propagation of the chain that is regenerated. So, RHg dot then decomposes into R dot and the reaction follows in a the chain propagates like this. So, that is the other way of generating radicals. Now, there is a this these are the two methods the mercury and the tin method. Now, let us see what are the other methods. The third method is what is called the boron method. The boron method employs triethylborane in presence of oxygen.

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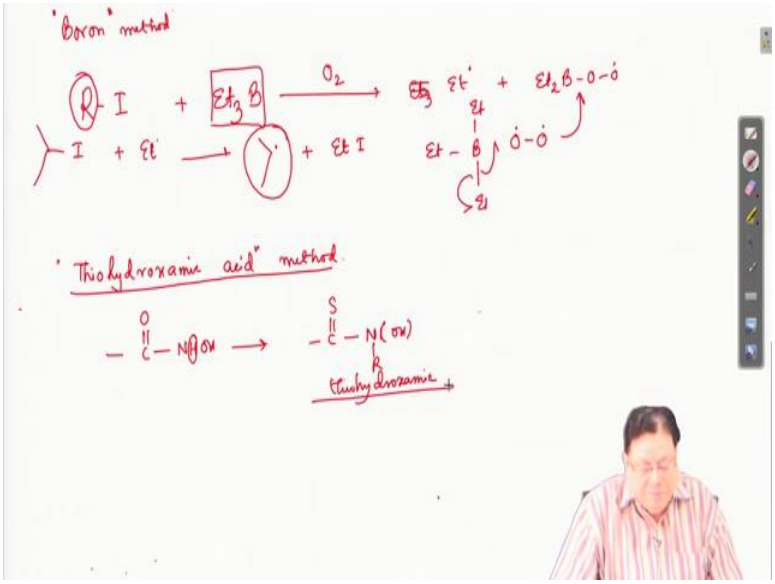

So, suppose you have you have you have an alkyl I am sorry, you have an alkyl halide RI and you add triethylborane and do the reaction in presence of oxygen. That is quite interesting because when you do the radical reactions like the team method or the mercury methods specially the tin method. So, that the radicals because you are making the radicals for a purpose that either you want to make a new carbon carbon bond like the amino acid example, I showed yesterday then the C glycosides that I also have shown you that how the bromo sugar the bromo sugar moieties can be converted into C glucosides or glycosides. So, you have a purpose.

Now, the radicals you know that if there is oxygen that is present, oxygen itself is a, is a diradical, it is a it is a triplet. So, that can react with the whatever radical, alkyl radical that is produced. So, you can basically divert the reaction in an oxidative pathway, that means via the oxygen. So, generally you carry out these reactions in deoxygenated solvents like benzene is one typical solvent. So, you deoxygenate benzene to remove all the oxygens. If there is oxygen, then what you see is the reduction of the yield of the intended product as well as formation of side product, that is by reaction of the oxygen.

Moreover, the initiator is also that can be quenched in the presence of oxygen, because you need initiator from time to time. It is not that sometimes what happens you add the initiator, the reaction starts, but after some time the reaction stops. So, you have to intermittently add the initiator in in few cases. So, now, we are talking about the boron method. So, what is the boron method? That in triethylborane and oxygen, what happens? Triethylborane in presence of oxygen generates sorry generates an ethyl radical plus diethyl boron peroxy radical. So,

basically what is happening? That you have triethylborane, you have this oxygen, one electron each.

Now, to form a boron oxygen bond you need one electron from one of the boron ethyl bond. Again, that should be only one electron shift. So, you get this plus the ethyl radical. Now, if you are suppose this is your this R is an isopropyl iodide. So, then isopropyl radical is certainly more stable than ethyl radical. So, now the reaction will take place between ethyl radical and isopropyl iodide and with the formation of isopropyl radical and ethyl iodide. And then whatever carbon carbon bonds that is in your mind you can try to make those with the help of this isopropyl radical.

So, this is the boron method, will give examples of everyone of all these processes. I think the tin one we have already given few examples. We will start with the mercury one and then the boron. And finally, the one I want to also like to mention is that there is a method which is called thiohydroxamic or thiohydroxamic acid method, thiohydroxamic acid method.

What is thiohydroxamic acid? You know what is hydroxamic acid CO NH OH. So, what is thiohydroxamic acid? That will be any substance which will contain, H is not mandatory which contains N OH and that could be R. So, this is your thiohydroxamic acid. And I will show you how thiohydroxamic acid can be utilised to form an alkyl radical. So, let us start with the examples. First the mercury method. How the mercury method has been utilised to make useful compounds. There are plenty of examples in the literature. I will just show one or two very interesting examples.

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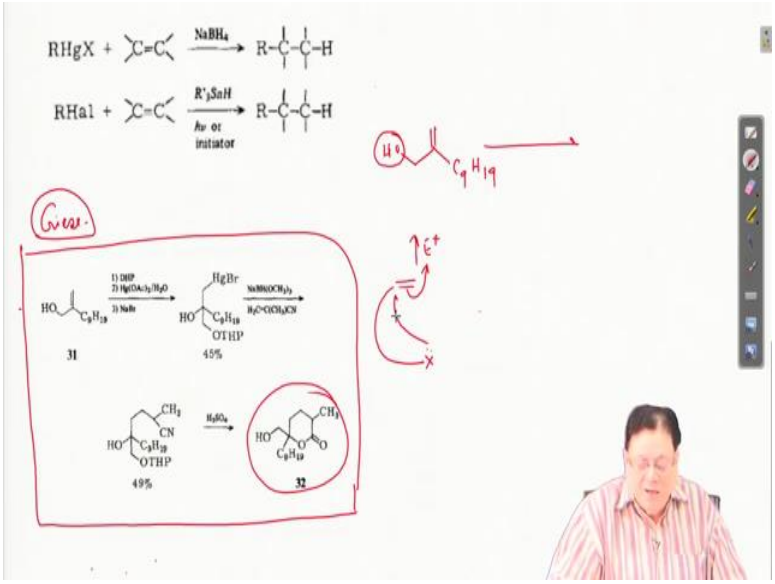

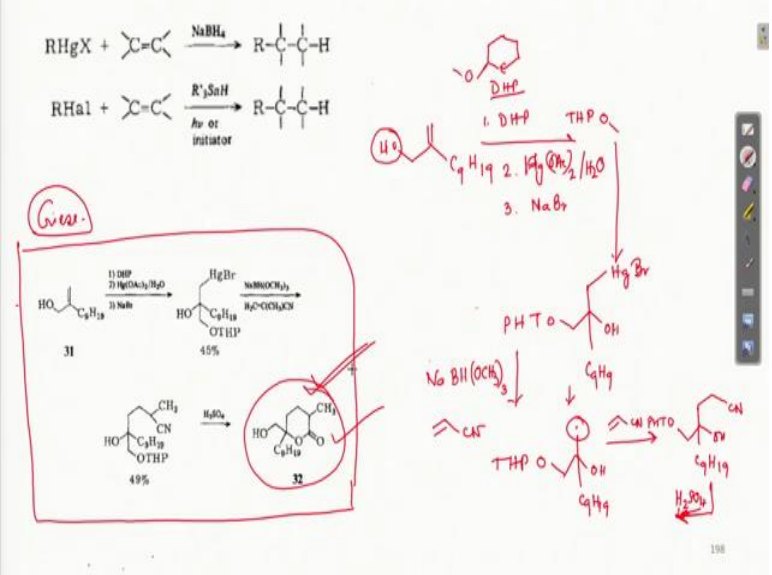

One is sorry, it is an ally sorry it is here. Let me utilise this slide. So, look at this what is depicted here. This is the synthesis of an antibiotic lactone, it is very small molecule and with the help of this carbon carbon bond forming reactions under radical conditions. Giese a German scientist, he was he is a pioneer of this development of radical chemistry especially the mercury method. So, with very few steps he could make this lactone and how how could he achieve that?

He started with an allyl alcohol containing the required side chain. The required sidechain here is C9 H19. This is the Alkyl the nonyl side chain. So, C9, C9 alkyl group and an allyl okay. So, first what happened? That you add first you protect this hydroxy, because if you do not protect the hydroxy, what will happen? If you do not protect the hydroxy, then hydroxy will participate.

You know, if you have a double bond and if you have a nucleophile somewhere and if you want to add a electrophile here, then what happens? The X participates form a ring and like if I like exo-trig fashion the electrophile is added. So, in order to suppress that you have to protect this hydroxy, otherwise this hydroxy could form an epoxide if you want to do mercuration on this double bond.

So, first you protect the hydroxy with a protecting group called tetrahydropyranyl protecting group. It is a THP, it it is it comes off under mild acid conditions. And it is also protecting group has has two aspects, first of all how to do the protection and then how to do the deprotection.

The protection is done with what is called DHP, the reagent dihydropyran and when the alcohol that you want to protect adds to this double bond, so, the double bond will not be there that will be called a tetrahydropyranyl derivative. So that is what is called a THP derivative. So, this dihydropyran on reaction with an alcohol in presence of, again that is an acid catalysed but you should not have water at all.

So, anhydrous condition, so you get OTHP group and the THP can be taken off by adding aqueous acid. So, let us first see that, first it is the protection. The OH, reaction in DHP. So, the first reagent is DHP and the second reagent in sodium. What is they are using? Ag sorry, Ag OAC twice and water and the third one is sodium bromide. So, what happens here?

First of all, OH is this is THP and then you have this double bond it adds in a markovnikoff way. So, you have a OH first of all this C9 that is there H19 you have OH here and you have this Ag OAC. When you add sodium bromide that is basically displacement of this acetate. So, initially the acetate is formed, but then you are replacing this acetate with the bromide, with the possibility that the bromide reacts better than the acetate, when you do the radical formation.

So, the next step as as you have got this alkyl mercury bromide system, now, you add sodium borohydride, in this case we should stick to whatever the literature says trimethoxy sodium borohydride. And you also add an acuril or nitrile. What is the purpose of sodium trimethoxy sodium borohydride, is to generate a radical at this position. So, you generate a radical or THP and then a radical here and this will have C9 H19 and this will have the OH and then this radical is obviously a nucleophilic radical and nucleophilic radical and that will add to an electron deficient alkene.

Remember last time what we have said, that for an electron for a nucleophilic radical, it is better to employ an electron deficient alkene, so, that you get very good yield of the product. So, you get OTHP and then this adds to the cyanide. So, you have this cyanide added the carbon carbon bond formation is done then this is OH and this is C9 H19. So, this is the product.

You remember that how did you suppress the formation of the telomere. The telomere is suppressed because of the change of the character of the radical that is that is generated after one addition to the acrylonitrile. This is a nucleophilic radical, but the radical centre that is generated here will be electrophilic because adjacent to a cyanide. So, that will be reluctant to

add to acrylonitrile. So, you end up delivering the hydrogen at this radical. So, that is the initial product.

And then what you have to do? You have to do hydrolysis with aqueous H2SO4. So, H2SO4 does a few things. First of all, OTHP becomes OH and then the cyanide becomes CO2H. So, now there will be a lactonization CO2H and OH that will form, so, it will be actually quite concentrated H2SO4, because you are doing lactonization.

So, lactonization will happen with this there are two OH's remember, this OH and that OH, but this way it will form a delta lactone which is obviously more stable than the participation of this OH, that is not only a tertiary OH, that is one difficulty. The other is that it will form a gamma lactone. So, ultimately what you end up is the delta lactone and that is that is the natural compound which is an antibiotic. So, this is a nice demonstration of the utilisation of the mercury method and then I create carbon carbon double bond and finally get important molecules.

So, let us see what is the next one. The next one should be the boron method, one example of the boron method. Remember that I told you that radicals are usually orthogonal to many of the natural functionalities. It adds it preferentially adds to a double bond carbon carbon double bond, but then it does not want to add to a carbonyl, because of the strength of the carbon carbon bond.

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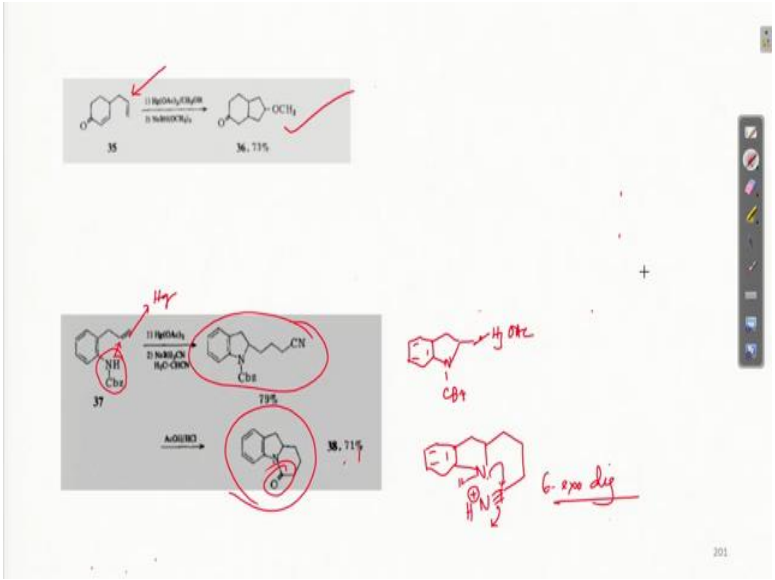

So, what else? These are some before we go into that, there are some other examples of the mercury method which can come as problems in assignments, very similar problems. The

formation of this bicyclic network very quickly we can brush through that if you have this enone and then this allyl group and you add mercuric acetate and methanol.

So, now what will happen? Methanol will obviously it will be a markovnik of addition, methanol add here, mercury will add here, and then when we generate radical here that will undergo a 5 exo-trig cyclization. So, ultimately you will get this product. The yield is pretty good that is 73 percent.

Then another example that is you have this amine allyl amine derivative. Allyl amine derivative, it is a benzene-based allyl amine derivative. So, what happens? That this is a nucleophile. So, when you do mercuration here as I said I gave an example that if there is an internal nucleophile then you get the internal nucleophilic attack and the mercuration takes place at the terminal carbon.

So, exactly that what happens? The nitrogen attacks this end and this takes up the mercury. So, you get the intermediate that you will get will be something like this, Cbz is a protecting group and this is the radical. This is the mercury first, sorry, this is the mercury acetate. Then you add sodium borohydride and sodium cyanoborohydride in this case and acrylonitrile.

So, your final product will be something like this, because you have this, actually you will achieve the formation of the carbon carbon bond and for the reasons that is already known to you that telomore formation will be suppressed because of the changeover of the radical character. And then as soon as you get this cyano compound you can now hydrolyze it and if you hydrolyze then Cbz will fall off, that is a protecting group and the cyanide will be converted to the acid and what you will get? You will get a basically formation of an amide. So, this is the final product.

Here the mechanism will be slightly different like you can, it will not be going via the carboxylic acid. What it will involve possibly what it would involve and that will be nitrogen and then you have this cyanide. So, you have C triple bond N. So, that will be protonated and then the nitrogen with H. So, nitrogen will undergo cyclization in this fashion. So, it will be a 5 it will be a 6 exo-dig cyclisation.

And ultimately the imine that will be formed will be hydrolyzed to the ketone. So, it is not a hydrolysis of the cyanide because you should remember that hydrolysis, direct hydrolysis of cyanide to carboxylic acid requires much stronger conditions. Here it is an internal attack on to the cyanide.

So, that is the that is that ends the the mercury method. And we have seen how the mercury method can be utilised in making various skeletons of importance. Many of these heterocyclic skeletons are part of the natural product or part of the biomolecules which are having important biological activity. Thank you very much.