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

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Lecture 25

Reactive Functionalities: Chemistry of Alkynes(contd), Arynes and Enediynes

Hello, everyone. Welcome back to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. In the last lecture you have been introduced to some reactive organic molecules and the functionality that we have selected are the, is the triple bond. So, we are discussing some of the newer aspects of chemistry of alkyne.

So, we have seen some new methodology, how the alkynes can be prepared, namely, the use of Seyforth Gilbert reagent and which was followed by an improved version by Ohira Bestman reagent and then we discussed the reactivity of alkynes in forming carbon carbon bonds and the reaction that we discussed first was the Pauson Khand reaction, Pauson Khand reaction and then you were introduced to a 2 plus 2 plus 2 cycloaddition, which basically trimerization of alkyne to benzene systems.

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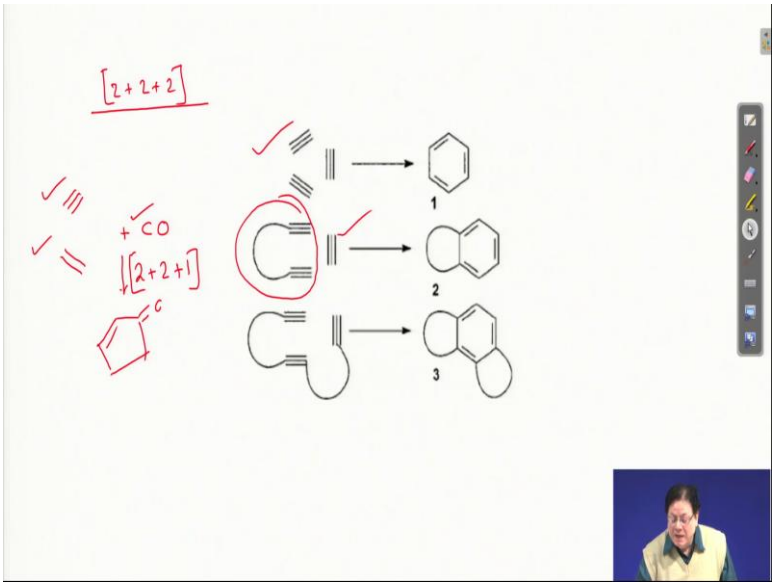

So, this slide, the slide that is here, this is nothing but the 2 plus 2 plus 2 cycloaddition. Earlier it was much more difficult to to achieve good yields for this reaction, but later on with the advancement of organometallic chemistry, so, new catalysts were developed and now, today this reaction gives quite decent yield considering the fact that there are three carbon carbon bonds that are formed in this reaction.

Now, if you look carefully into this reaction, the reaction should have been highly favoured because you are forming an aromatic system. However, it has got a huge activation barrier. So, there lies the importance of catalysts and Peter Vuillard, he developed one catalyst which was the cobalt-based catalysts and that can give good yields, good, very good yields of these benzenoid systems.

Now, the reaction can be intramolecular, completely intramolecular like the the first one then it could be partially intramolecular that in one, one of the substrate has two acetylene moieties and the other one is separate. And so, that is partially intra, partially intramolecular in the sense that these two acetylenes are reacting in an intramolecular fashion and these acetylene counter part is reacting in a intermolecular way and you can have the completely intramolecular version of this reaction as is shown here. I think this is the endpoint of the last the slide this lecture that was delivered last time.

Now, remember the analogous type of reaction is the Pauson Khand reaction which is basically again the three components one is alkyne and other is alkene and the third component is carbon monoxide and that gives cyclopentenone. So, if you try to describe it, this should be 2 plus 2 plus 1 addition. So, this is Pauson Khand reaction and this is cyclotrimerization 2 plus 2 plus 2.

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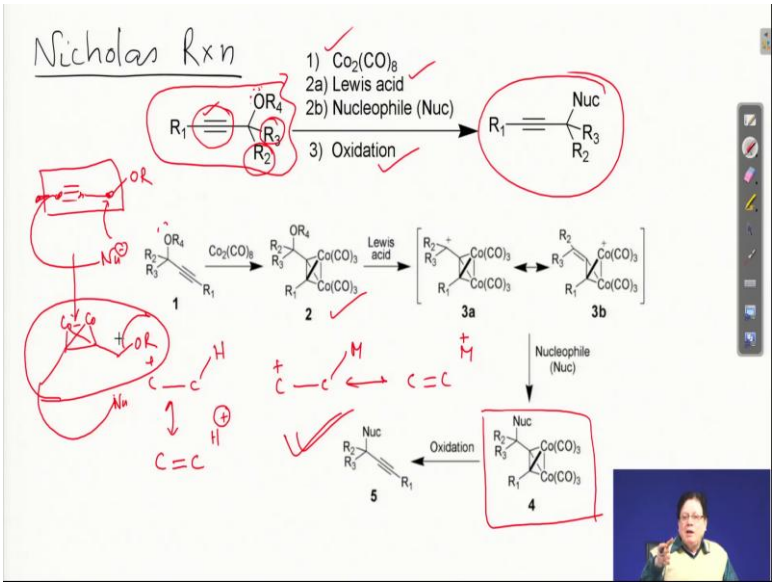

Now, let us discuss some other chemistry of of this alkyne involving alkyne. I think that was already done. Let me erase this part. Today we will discuss another reaction which is called Nicholas reaction. Now, Nicholas reaction is again a cobalt mediated activation of a leaving group which is adjacent to, to an alkyne moiety, like this one the the substrate for Nicholas

reaction is can be represented by this general structure that you have an alkyne and you have a, you have a group which is represented by here OR4 and the other two substituents are the R2 and R3.

Now this being a basic centre, so, what will happen that you can make a complex with a Lewis acid where the oxygen is going to donate its lone pair to form the complex with the Lewis acid. But before that, that is a standard way of activation of of an oxygen containing leaving group either you add mineral acid by protonation you can activate or you can actually add Lewis acid to activate the the leaving group. The leaving group in this case is represented by OR4, it could be alkoxy or it could be a mesylate, a tosylate all these are possibilities.

Now, the difference here in the Nicholas reaction what happens there is an adjacent alkyne moiety, which is present. So, the reaction starts like this, that you add that the same reagent which was used in Pauson Khand that dicobalt octacarbonyl which can form a, which is basically a way to protect the acetylene. And because you can, you form the complex the organometallic complex with the acetylene moiety and you can, if required you can also remove the, the cobalt moiety and regenerate the acetylene.

So, the first step is that formation of that organometallic complex with the alkyne moiety, and then you add the Lewis acid. So, Lewis acid, the oxygen will be will be coordinating to the Lewis acid and becomes activated and what happens because of this complexation the this leaving group leaves and generating a cation at this propargylic carbon, at this propargylic carbon, which is not happening or which was much difficult to achieve, if you have that triple bond intact.

So, when you make this organometallic complex with cobalt, somehow this complex is stabilising the cation that is generated at the propargylic carbon. So, first you add this from the complex, the Lewis acid and this OR4 leaves and forms a cation and then that cation can be trapped by a nucleophile.

So, you add a nucleophile and then the nucleophile adds to the propargylic carbon and you get a, and then you remove the the cobalt from the complex by doing oxidation with several reagents' iodine is a typical one that you add iodine the complex will collapse and it will regenerate the alkyne moiety. So, this is what is Nicholas reaction.

Now, what is the, what is the beauty of this reaction? The beauty of this reaction is that if you want to do a direct nucleophilic displacement at this propargylic carbon it may not be feasible

sometimes, for various reasons. Here, because of the generation of the cation which is stabilised by the adjacent cobalt complex. So, the nucleophile, nucleophilic addition becomes very facile.

Now, let us talk about the mechanism of this reaction. As I said the first step is formation of this cobalt organometallic complex and you know that acetylene basically has two double bonds. So, one double bond, first forms the, one double bond is involved in formation of the complex, the other one is also. So, the complex is is represented by this type of structure.

So, there is a cobalt cobalt bond that was originally present and remember that during this reaction two molecules of carbon monoxide leaves, which are the bridging ligands. So, the bridging ligands leaves and instead is replaced by the alkyne moiety, the two double bonds, the two pi bonds of the alkyne moiety.

So, this is the complex and then what happens you add the Lewis acid it so, that becomes coordinated to the Lewis acid becomes activated and it leaves and formation of the cation. Now the question is the why it will form the cation? Obviously the reason has to be the stability of this cation, some extra stability of the cation which was not there when it was only alkyne.

So, what is the stability here? Because you have a carbon cobalt bond, you I told you also during discussion of Pauson Khand that these are very vulnerable bonds, they can be easily manipulated. So, what will happen, that as soon as we generate a positive charge, now, this carbon cobalt bond is very similar to hyper conjugation that, that bond will go there. So, form the double bond and instead the positive charge will now be borne by the cobalt.

The same thing happens in in hyper conjugation, the hydrogen CH bond participates. So, I can write that in hyper conjugation you have this and the resonating structure will be something like this one. Here what you have is you have C plus and then a carbon and a metal ion. So, that will, that can undergo resonance that can do resonance like, the same way like the no bond resonance or hyper conjugation.

So, because of this carbon cobalt bond, the presence at the, at the at the adjacent carbon, so, that can now participate in a no bond resonance fashion and stabilise the cation. So, that is the driving force for the formation of the cation, the extra stability. And if you have acetylene instead of the cobalt complex, that bond is much stronger and that will not participate to that significant extent to stabilise the cation.

So, the carbon metal bond is much more vulnerable, much more easily breakable and it can participate in the no bond resonance, then the nucleophile comes and attacks the the cation and you form the, the not the final product the product with this cobalt complex. Now, as I said cobalt complexation is nothing but it is a way to protect, it is a way to protect the alkyne, of course, it is not only protection here, it is also assisting the reaction.

So, one part of the cobalt complex is to protect the alkyne and the other one more importantly here in this reaction Nicholas reaction that the, it activates it activates the propargylic carbon for attack to be attacked by the nucleophile. So, that is the mechanism of Nicholas reaction.

Now, where it can be useful? It is useful in certain reactions which are difficult, like I tell you that if you want to do a cyclization reaction involving an acetylene and this OR moiety and some kind of cyclization, a nucleophile here. Now, you know the acetylene is actually is a linear shaped. So, it may so happen that this nucleophile cannot reach the centre because you know the stereo electrical requirement for displacement of this OR that it has to come from the backside. And the distance, if the size is not very big, then it may not be feasible to do this reaction.

On the other hand, when you form the complex with the cobalt, then it no longer remains, then it no longer remains that linear. So, there is a bending of this of this system. So, now, you see the bending here. Earlier it was linear, this carbon, this carbon, this carbon and the carbon attached directly, they are in one straight line. Here now, this carbon is now bent. So, there is a bending that has taken place due to this cobalt complexation and that bending may allow the nucleophile now to reach and attack this carbon.

Of course, in Nicholas reaction, this leaves forms a cation here, but however that cation with a p orbital, vacant p orbital that has to be also attacked in a particular orientation. So that maximum overlap takes place, that is the stereo electronic requirement, but that may be satisfied because of the bending of this system of the alkyne. And so that is where that is one of the utility of Nicholas reaction.

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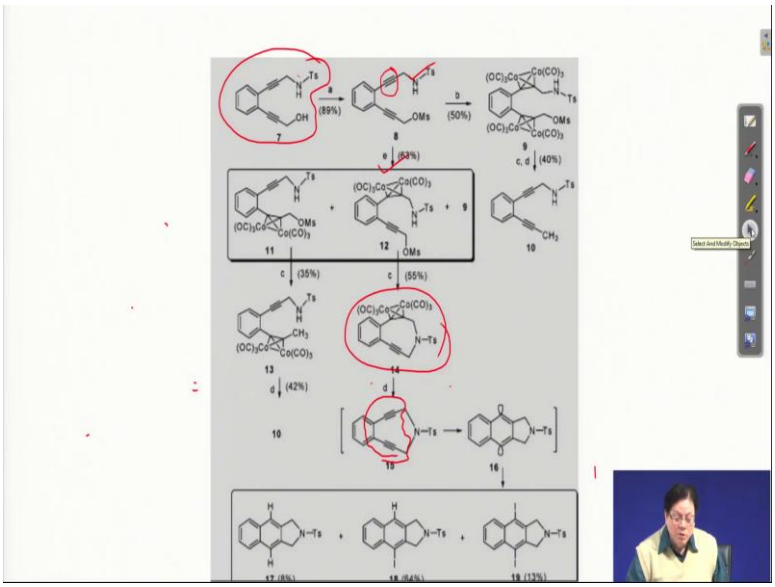

And there is an example I think, maybe the next one let us see, that where this type of bending helped the, help the cyclization process. Of course, this is a little bit complicated chemistry, but I will just simplify by showing only only one or two structures here. See, look at this molecule, if you look at this molecule this is, this is there is a OH and then you have this NH tosyl and what was being attempted was this nucleophilic some kind of nucleophilic displacement at this propargylic carbon.

Of course the, that OH has to be made into a better living group, which you can do by converting it into a mesyl group or a tosyl group. So, but what happened even if you make, even if you make a mesyl here make a good leaving group, but the reaction was not occurring. As I said, because that nitrogen cannot reach that carbon, geometrically it is not feasible, it cannot satisfy this stereo electronic requirement for the cyclization.

So, what happened actually here that if you make a complex acetylene complex at this at that cobalt complex then it it is bent like this and then the reaction can go and actually it it happened there was this formation of this cyclic network. We will come back to this example, because this is a, this is a molecule which has got certain other functionality two alkyne moieties and which is in between there is a double bond in this case a benzene ring.

So, there are these are special type of compounds, we will discuss the chemistry of those compounds later on, but right now, this is one example where Nicholas reaction has by Nicholas reaction you can achieve difficult cyclization processes. And the reason is that there is the two reasons are there, one is you can activate the leaving group by generating a cation, that is one possibility. The other is that there is a bending of the system which allow the

system to satisfy the stereo electronic requirement for this cyclization process. So, that is your Nicholas reaction, let me see what is in store for us in the next slide. Just a second.

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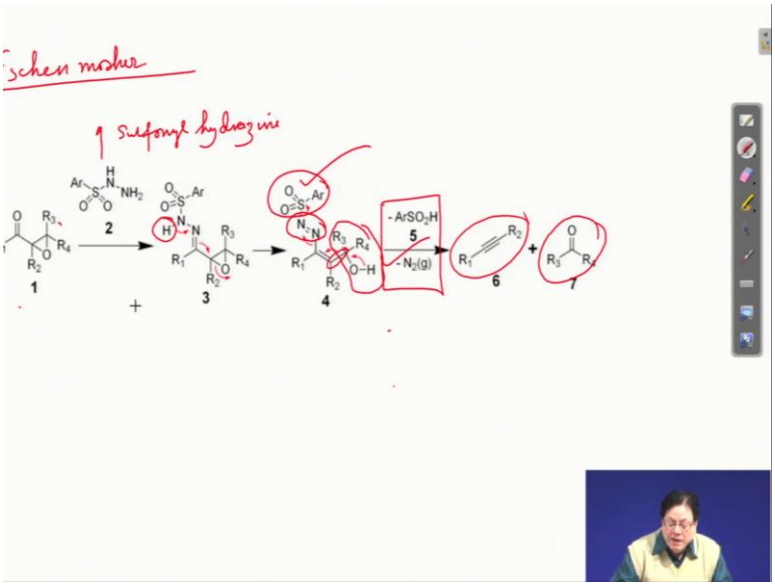

Now, let us talk about another reaction which is also very interesting involving a fragmentation reaction, where you generate an alkyne moiety. Remember, we have, the last lecture, we have seen that how alkynes can be made by this Seyforth Gilbert reagent or Ohira Bestman modification those type of chemistry we have already discussed.

There are other methods where via fragmentation route one can generate alkyne. And there is a famous reaction called Eschenmoser fragmentation. Eschenmoser fragmentation. Eschenmoser, by the way is a famous Swiss chemist and he was working at Zurich that is a famous Institute called ETH Zurich. And he developed this chemistry.

What is this chemistry all about? That he took this epoxy, alpha epoxy carbonyl system. So, an alpha epoxyketone. Now, ketones are famous for formation of hydrazone. So, if you take it is a, it is not a purely one it is a tosyl tosyl or it is a sulfonyl hydrazone, depending on here, whether it will be a tosyl or a nosyl different types of substitution can be present in the aryl group.

So, it is a sulfonyl, you can say that this is a sulfonyl hydrazine, sulfonyl hydrazine, if you add to the system that alpha epoxy carbonyl system. So, the carbonyl will form the, will form the hydrazone. And then if you treat that with a base, then what will happen? The way it has been shown by these red arrows that this hydrogen is is very acidic because it is adjacent to this the sulfonyl group as well as there is this imine functionality. And there is a relay

process, the flow of electrons, the flow of electrons take place in such a direction that ultimately it opens the epoxide, epoxide being the strained ring.

So, what will happen? The epoxide will will open and so, this electron comes here between the NN bond, this imine double bond comes here and the result is that the epoxide gets opened. The epoxide gets opened, but then that is not a stable system. What will happen now, the again the electron will flow back the way it came from it, it will, it will flow back and then while going back, it kicks out the sulfonyl, the sulfonyl group because that is a very good leaving group.

So, you can now do a reverse arrow pushing. So, electrons now come here and and then there is a what you are actually doing here, you are basically now breaking a carbon carbon single bond that is very important. Here there is a carbon oxygen bond that that got broken because it is a strained epoxide. So, the driving force is the opening of the strained epoxide.

Here the driving force is for breakage of the carbon carbon bond is basically two things, one is there is this nitrogen in the process. If you continue this arrow pushing, what will happen that you see nitrogen gas comes out and this being a good leaving group that also leaves. So, the it is a thermodynamically very feasible process, first of all nitrogen gas comes out. So, that drives the reaction to the right side, the stable nitrogen and also coupled with the fact that this is a good leaving group.

So, these two enable this molecule to fragment. Now, you see a fragmentation, fragmentation means the whole the the skeleton gots fragmented into two, one is this alkyne and another is the the resulting epoxy carbon has become a carbonyl. So, this is the, what is called the Eschenmoser fragmentation.

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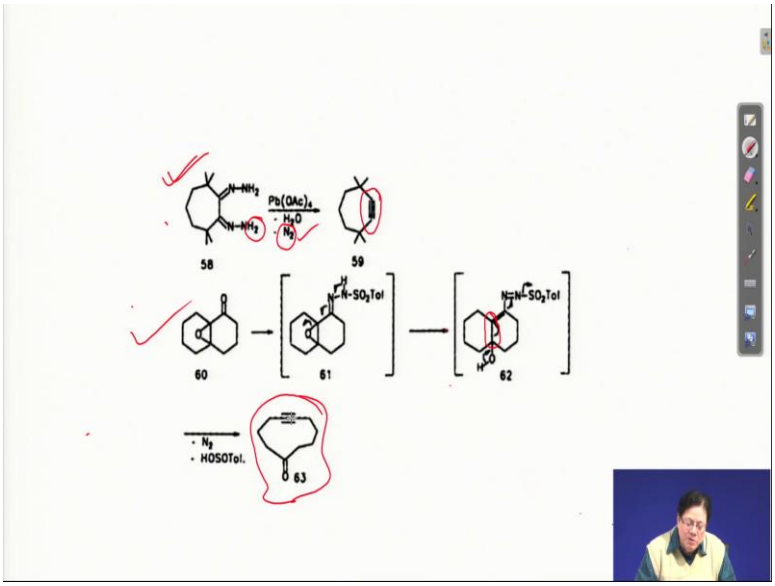

Where it can be utilised? I think I can show you another slide where it has been sorry, let me let me erase this that you can make large ring alkynes by utilising this type of reaction. So, again the starting point of the, to do the Eschenmoser fragmentation is the alpha epoxyketone. So, if you have this bicyclic, it is a decalin system. So decalone and the ring junction has an epoxy ring. So, you do the same reaction. Here, they have taken the tosyl. So, the tosyl hydrazine was reacted with this. So, you get the tosyl hydrazone.

And then the same trick that it opens up in presence of a base, it opens up and the ultimately the electron flows in this direction towards the, to assist the opening up the epoxide ring. And as the epoxide ring opens up, the again, it flows back, electron flows back with the result that nitrogen gas is eliminated. And the sulfonyl, the tosyl sulfonyl group also comes as the sulfinic acid. And so, ultimately what you get is this product, it is a large ring alkyne with a carbonyl function.

Here it is, they are not fragmented into two parts, because it is a, it is an intramolecular process, but there is definitely fragmentation that has happened. The fragmentation is this carbon carbon bond which is broken. That is, so it is again the same reaction, Eschenmoser fragmentation.

Earlier it was in an intermolecular fashion, it happened so it it was divided into two parts. But here it is basically an intramolecular process. So, the both the carbonyl and the alkyne are tied up to the same molecule. So that is a very interesting reaction.

A very similar type of reaction, not exactly the same, but similar type that you can have 1,2 Bis hydrazone, if you have 1,2 Bis hydrazone, and if you oxidise this with oxidising agents like laterite triacetate. Then what will happen? Then also it loses nitrogen, two molecules of nitrogen will come out and water will come out and finally you get alkyne moiety. This will we are leaving in store you try to do the mechanism of this reaction in your own way. But whatever you do remember there are two molecules of nitrogen that get lost in the process.

So, these are the two methods where you can make the alkyne moiety in a, in a large cyclic network, one is this Eschenmoser fragmentation and that is basically you take your bicyclic system and fragment it into a monocyclic system. The other is that you take the monocyclic system, large monocyclic system 1,2 Bis hydrazone and then oxidise it and you can get the alkyne in the process.

Now, our next topic as I said, I gave you one application of Nicholas reaction, the application was there to form a cyclic ring. And the way to do it is just to bend the alkyne via complexation with the cobalt, as well as activating the the leaving group. Either you can exploit both the parameters or you can actually in some reactions only one parameter can be utilised and not the other.

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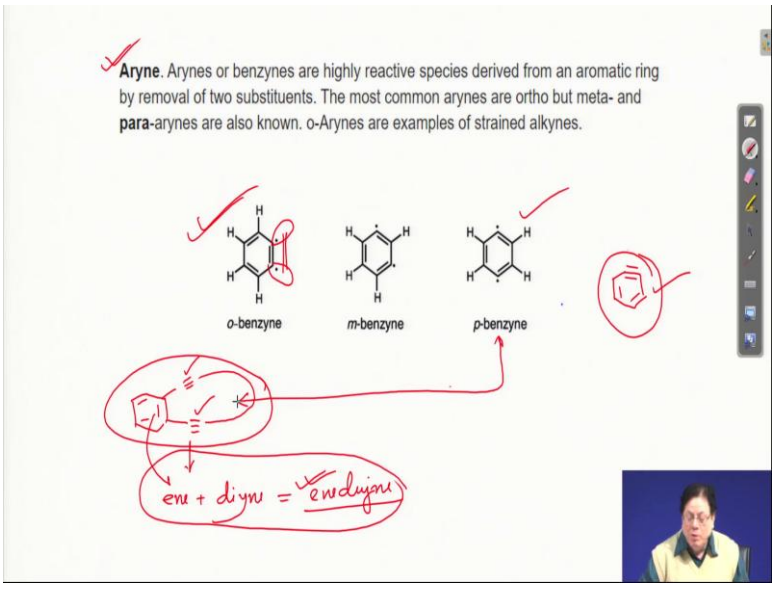

Now, let us go to that, that type of molecule which was displayed in that Nicholas reaction. There was this two triple bonds in a benzene ring. Let me draw the the basic structure at that what was used at that time, something like this. This was the basic structure and this was the ultimate cyclic network. Now, these compounds have attracted a lot of attention in the last 30

years because of some some interesting chemistry as well as biochemistry that that is involved with this type of network.

The network is nothing but that you have two alkynes which are connected via a double bond. So, these type of compound can be collectively called as this is the ene and then you have two alkyne so diyne. So, that makes it enediyne. Some people can call it diyne diyneene the other way around, but I think popularly it is known as enediyne.

When we want to discuss this chemistry of these enediyne, let us go to a more general topic from where we will ultimately come to the chemistry of these enediyne. The general topic is that we have discussed alkynes, alkynes are the the triple bonds and when you say alkynes means it is an aliphatic system and with the triple bond.

Now, the the corresponding aromatic system are are known as arynes. The arynes arynes like benzynes, you are very well, you are well familiar with the with the chemistry of benzyne, benzynes are basically formed by 1, 2 elimination in a benzene ring. And however, they are so, they are formally called arynes, although it is very difficult to to visualise or to conceptualise the existence of a triple bond in a benzene ring, because it will be, because triple bond you know that will be, that will try to be linear. So, you cannot really fulfil that geometry of the triple bond if you have a formal formal structure like this for the for the aryne.

However, these class of molecules, whatever may be the structure, whatever may be the form are collectively called aryne. So, aromatic rings with a triple bond. Now, whether that is a that is a complete triple bond or whether they are they are resonating forms of different different structures. That is a debatable thing.

So, arynes are now they are extremely reactive obviously, that will be reactive because to have accommodate a triple bond in a benzene ring is is almost impossible. They are impossible because because of the linearity. And so, what could be the, why it is so reactive? Because the the bond strength of this, the newly formed triple bond which is making the triple bond the so-called triple bond is very weak.

So, it is very easy to break that bond and that is what is the genesis of reactivity of the of the of the benzyne, but these are, when we talk about benzyne we do not, we are not very familiar by calling it ortho-benzyne actually, that should be called ortho-benzyne because

benzynes can be of different types. It could be ortho-benzyne, it could be meta or it could be para. These three are possible.

And one of the structure as I told you that it cannot be a complete triple bond. So, that is one of the resonating structure you can think of is that it is a radical diradical structure. So, this is one orbital, that is the other orbital. There may be some partial overlap between the two and that we represent in the form of a triple bond, but the best way is to make it a resonance form of various structures. One of the forms is this diradical structure.

However, diradical structure is not the or is not the dominant form in case of ortho-benzyne because you know that in ortho-benzyne they are susceptible to nucleophilic attack. So, if it is radical, then you have a problem diradical, then you have a problem to involve a nucleophile to attack one of these orbitals. So, it could be a suitor ionic structure that two two of the both the electrons are in one orbital, the other orbital is free. So that brings singlet, triplet those type of dichotomy.

Anyway, today, what we will be discussing is the chemistry of para-benzyne, para-benzyne means when the these radical two radical centres are actually 1, 4 position. So, now we define benzyne as an aromatic system, which which can exist in a diradical form if the two radicals are in 1, 2 fashion, are position 1, 2 then that is ortho-benzyne or ortho-aryne, then 1, 3 that is meta-benzyne or meta-aryne. And you have 1, 4 that is para-aryne or para-benzyne.

We will be discussing the chemistry of the para-benzyne because ortho-benzyne chemistry is well covered under the, in the undergraduate syllabus. And meta-benzyne chemistry is not that vast, but para-benzyne chemistry recently has drawn as I said, in the last 30 years, they have drawn enormous attention. That means there is a connection between these type of structure and these para-benzyne. We will see where is the connection.

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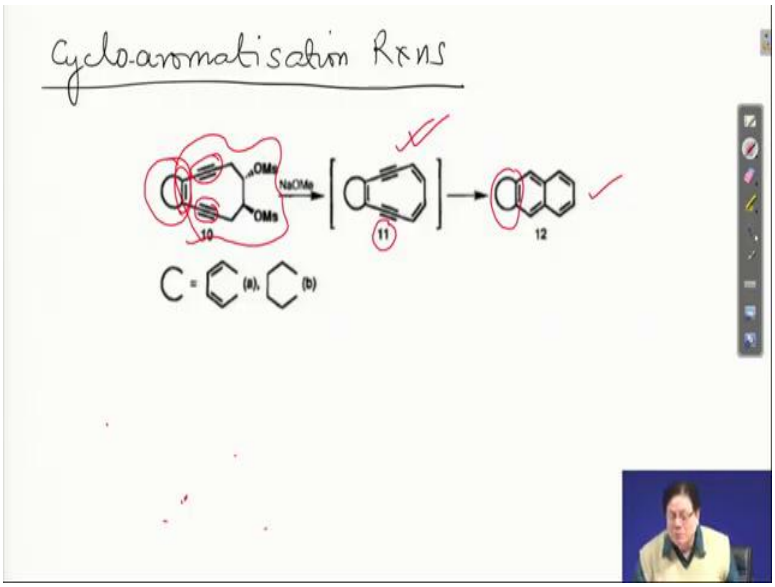

So, it all started with an example in the late 1960s. There was, there was a scientist, Masamune, who was working at MIT in USA. He, he developed this chemistry. See, he took this cyclic compound, where again you have this double bond sorry, you have this double bond and this this two alkyne moiety that means enediyne, and then it is a 10 membered ring and there are two leaving groups in the form of the methylate.

So, he took this molecule and treated with sodium methoxide, he wanted to make this type of system that means a system where a 10 membered ring with two alkynes and then three alkene moiety and wanted to study it is reactivity. Now, what happened? He could not isolate this compound, which is shown here in this structure number 11. In the in the what he ended up is the formation of a naphthalene ring and the original fused portion is always there.

So, this is the fused portion, but the, what happened to this enediyne moiety? That is now forming two naphthalene, forming two benzene rings in the formation of a, in the form of naphthalene. And so Masamune observed this and reported it, but the mechanism of this reaction was not known at that time.

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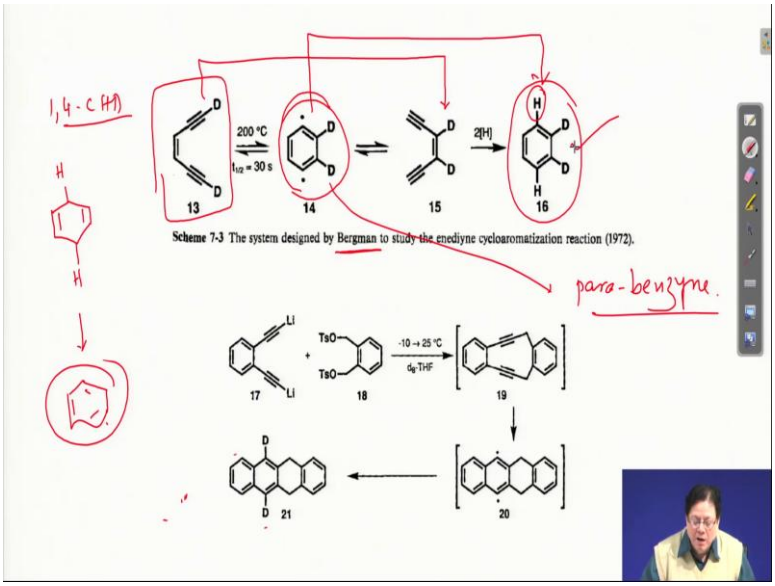

Later on, what happened? Later on, in the early 70s, a scientist whose name is R G Bergman. He again, took similar sort of system, but it is not cyclic. He took an enediyne moiety like this and he did it to a very high temperature like 200 degrees centigrade. And what he found is that two things.

First of all, if he, if he is not using any other reagent, which is which is a good hydrogen donor, so, in absence of a hydrogen donor or any atom donor, what happened is that he could isomerize this compound into the other alkyne other enediyne, where the two deuterium's are now, in the connected to the alkene part.

Earlier they were the terminals of the two alkyne moiety. But now, the two deuterium's are inside, that means they are connected to the alkene part. That is one observation. The other observation is that, if you have hydrogen, good hydrogen atom donors if you do this reaction in good hydrogen atom donors like one very good hydrogen atom donor is cyclohexadiene.

Cyclohexadiene, what happens? These two hydrogens can be donated as atoms because by this donation the cyclohexadiene will go to the aromatic benzene ring. So, there is a driving force to lose this two hydrogens. And so, if you do this reaction in presence of this, this is 1,4 cyclohexadiene. So, 1,4 CHD. Then these hydrogens will be picked up by this by this diradical and ultimately what you will get is, you will get the benzene compound. That means dideuterium benzene system.

So, two things if you do not have the hydrogen donor then you end up in isomerized, this is also isomerization but you do not get a cyclic network. So, you get just the isomer, another

linear form and in presence of the hydrogen donor, you get a cyclic network which is an aromatic ring. And this reaction that means formation of this and isolation of this aromatic ring in presence of hydrogen donors.

Bergman, saw this and then he proposed that these reaction is going through this intermediate, the diradical intermediate which we have termed as para-benzyne. So, they are, so it is going through a para-benzyne intermediate and that para-benzyne abstracts the two hydrogens from a source, if that is there. So, you get the aromatic compounds.

Now, later on there are many reactions which were discovered, which are based on alkyne or allene those type of networks are present. So, they all, the common the common thing between all these structures is that like this molecule this enediyne when you have heated it in presence of a hydrogen donor, it goes to a cyclic network which is an aromatic compound.

So, what type of reaction is this? This reaction is what is called cycloaromatization, that means, you are having a cyclization not only that, unlike other cyclization's here the newly formed ring is an aromatic, has aromatic character. So, that is why this is called cycloaromatization. There are many reactions.

However, this reaction which was discovered, which was the mechanism was shown by Bergman, this is now popularly known as Bergman cyclization and he proposed that it is going through the diradical. This is the first example of the of the cycloaromatization reaction.

However, we should not forget the fact that it was Masamune who first actually formed the naphthalene moiety from that cyclic enediyne. The only problem was that that he could not establish the mechanism. It was Bergman, who gave this mechanism and termed his reactions as cycloaromatization reactions. So that is why this is popularly known as Bergman cyclization, but just to give the due respect to, due recognition to Masamune sometimes it is also called Masamune Bergman cyclization.

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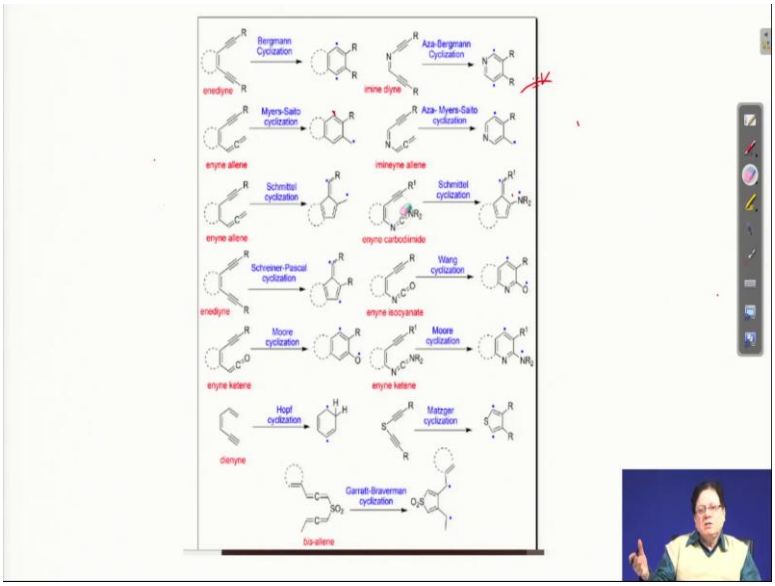

There are many examples here. I am not going to get into all those, only I want to tell you that there are, there are other type of reactions. I told you that cycloaromatization now has become a vast it is a general reaction there are many functionalities which do this, do this type of reaction that means formation of a cyclic network coupled with the fact that the cyclic network is becoming aromatic.

And what are those compounds? Let us see, what are those functionalities that are required. This is, this part I will come back little bit later. Let us, let us show you the other different type of functionalities, do not be too bothered about it. We will not go into details of any of these. But just to remember or just to show you that the cycloaromatization now can happen to many functionalities.

What is the difference between the or why are the changes from the enediyne network that you can change the alkyne into an allene moiety or you can change the alkyne into cyanide. So, all sorts of or diamides or various types of systems can be you can start from that. But remember if you look very logically that you Bergman cyclization is enediyne. So, the ene part has to be kept intact because there is no alternative for the ene part.

But alkyne, there are some alternatives. Like, alkyne triple bond can be replaced by an allene. So, you get another type of cycloaromatization or it can be replaced by a diamide, you get, you get a new reaction, a new skeleton will be formed. But remember all this cyclic networks will be aromatic or you can have ketene also instead of the alkyne. So that gives another reaction.

So, all these are basically based on changing the alkyne part into very similar sort of functionalities. And the you get different cycloaromatization reaction. So, this lecture will end here. We have just discussed the the Nicholas reaction and one application of the Nicholas reaction in using cyclization, the bent character of that we have discussed the Eschenmoser fragmentation and how alkene alkyne can be functionality can be generated in an epoxy carbonyl compound alpha epoxy carbonyl compound by the formation of hydrazone and the composition or fragmentation.

So that we have discussed then you were introduced to this para-benzyne, the benzyne type of chemistry you have already been introduced to ortho-benzyne in you under graduate course, we are not discussing that, we will discuss only the para-benzyne and we have seen the interesting way of making the para-benzyne that is the cycloaromatization reaction of enediynes which will make the para-benzynes. And we will end here. In the next lecture we will see how this para-benzynes can be utilized or what is the chemistry and biochemistry of these para-benzynes. Thank you.