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

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Lecture 26

Reactive Functionalities: Enediynes (contd), Allenes and Ketenes

Hello, 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 a new set of reactions which are called cycloaromatization reactions. What was that?

Cycloaromatization reactions are reactions which lead to, first of all it is cycle, it leads to a new cycle a cyclic network that is number one and number two is that the cyclic network that is generated has aromatic character. So, that is why it is called cycloaromatization that means, it is a cyclic process, it is the cyclisation leading to the creation of a new aromatic ring.

Bergman cyclization is the first of this class of reactions. There are many reactions where you can, where you can change the alkene alkyne part and replace it by allene, isocyanate, diamide, ketene allene, etc all these things. And depending on that variation, you have different name reactions that are there for this cycloaromatization reactions. But our point of discussion is Bergman cyclization.

And Bergman cyclization gives gives a route to generate 1, 4 benzene 1, 4 diradicals which are also called the para-benzynes. This para-benzynes are basically primarily they exist in the diradical form and that is why they abstract the atom like hydrogen if they are available from a from a source which is already there present in the system.

But in absence of a hydrogen donor and in presence of excess of a nucleophilic reagent like ortho-benzynes, which is dominated by nucleophilic addition, parabens benzynes also can undergo nucleophilic addition, like if you take an enediyne and treat with lithium halide excess of lithium halide then it has been found that the halide on an ion attacks the whatever diradical is generated that para-benzyne moiety and then the anion can be added from from one of the side the other side is then generating, generating another anion and then that abstract the hydrogen.

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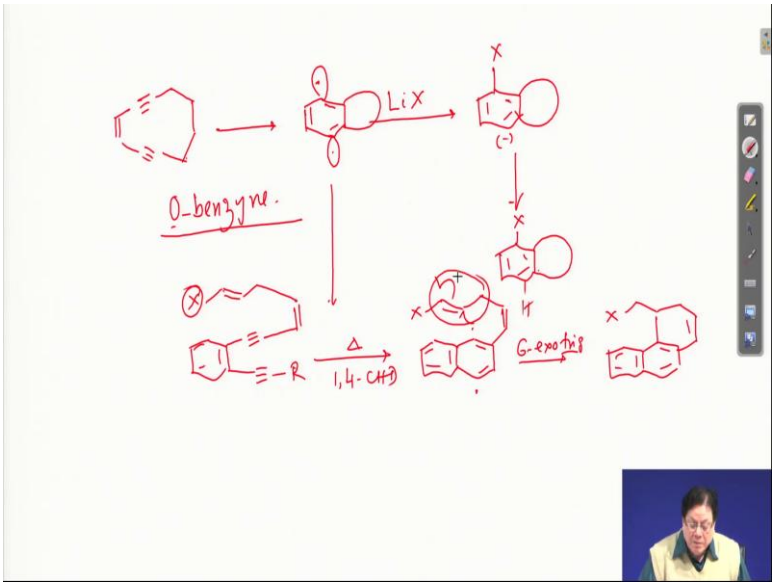

Like let me show you the whatever I am saying is basically, that this is the diradical, but the anion can add if you have lithium sorry this is the other network lithium halide then what happens? The halide adds from one side so, you get X and, on this side, you get minus and then that will be quenched by a proton source. So, you get, the basic thing is that you get addition of an anion like the ortho-benzyne chemistry. So, para-benzynes can be forced to undergo an ionic addition like the ortho-benzyne chemistry.

Now, these diradicals can can be exploited to make different different types of skeletons, they can be trapped intramolecularly or even intermolecularly by you know the radicals can add to the double bond very easily. So, if you take a system like this, if you take a system like this, the X may be an electron withdrawing group and do this cyclization heat it, in presence of a hydrogen donor like 1, 4 CHD, then what will happen?

Then you first generate this diradical and then that will be intramolecularly trapped, because this radical now can add to this double bond in a, in an exo-trig fashion This is in this case it is 6 6 6 exo-trig you know that that is allowed by Baldwins rule and ultimate product after hydrogen after quenching with the hydrogen atom from the source that is 1,4 CHD, you will get this type of skeleton.

So, this is a very good way of making new carbon carbon bonds and getting different types of skeletons. There are many examples of this type of trapping of the radicals to get various type of skeletons including helicons, Bergman cyclization can be utilised to form the helicons by trapping with a, if the trapping moiety is another aromatic ring then what you will get? You will get helicon moiety.

Now, what is the utility? Why as I said, this enediynes have attracted lot of attention in the last 30 years after their discovery. Remember Bergman cyclization was discovered in the early 70s. But, these enediynes as natural compounds came out only in the 1980s and some of these natural compounds are are extremely potent anti-cancer agents and their mechanism of biological action is nothing but formation of the diradical and these diradical then abstracts hydrogen if it is generated in a biological medium in the inside a cell.

Then there are many macromolecules inside the cell biomacromolecules like the nucleic acids and nucleic acids have lots of potential hydrogen donors are there because it has got a sugar moiety. So, the hydrogen can be abstracted from the nucleic acid as a result of the nucleic acid breaks. So, there is complete breakage of the nucleic acid like the DNA. So, that is the reason why they show their anti-cancer activity.

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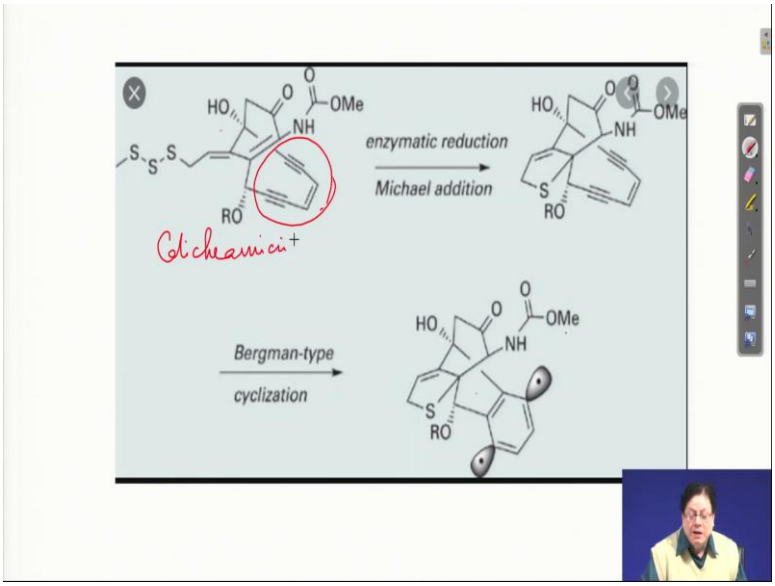

One example is shown here that it is a very complicated system that you have this enediyne this is a natural compound. So, you have this enediyne functionality and then by suitable mechanism we will not go into any details of this because this is not a biochemistry course, but remember that this enediyne functionality can be utilised to form the diradical and this diradical can abstract hydrogen from the two strands of the two complementary strands of DNA and the result is that the DNA strand is broken.

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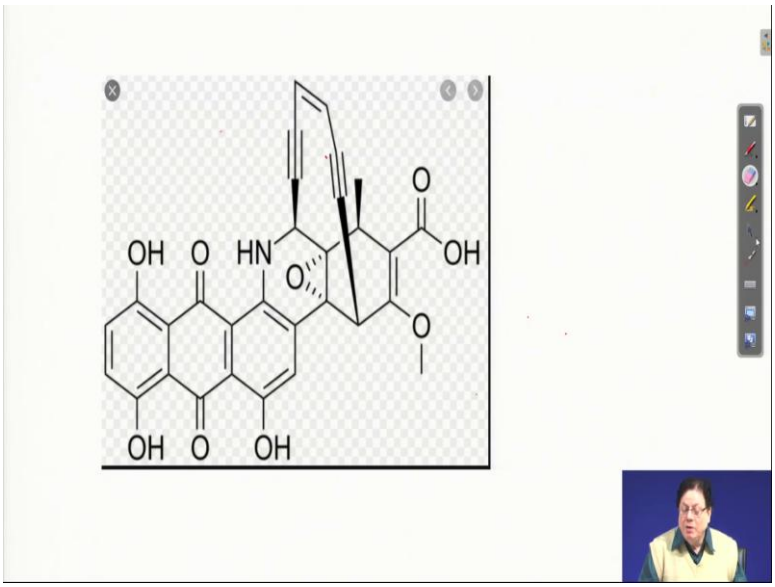

So, this is one compound which is known as calicheamicin and then there is another one which is also dependent on this Bergman cyclization that is called dynamicin. These are some of the natural products that are being developed, some are some are already in the market, the calicheamicin based dynamicin people are trying to utilise it for making it to the market as an anti-cancer agent.

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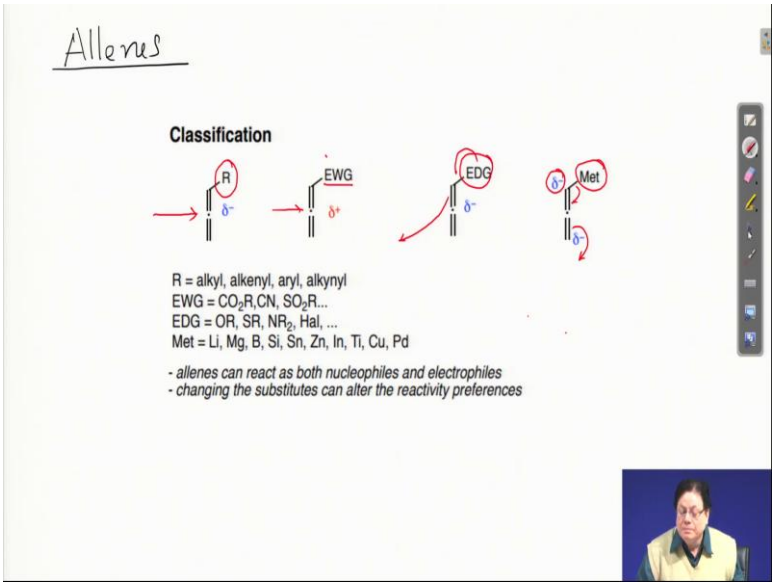

Now, let us I think that enediyne chemistry and the para-benzyne we have we have some glimpse of the type of chemistry that it can it can undergo. First of all, again to summarise that para we started with the aryne chemistry and we thought and we want to restrict it to the para-aryne or the para- benzyne specifically chemistry and para-benzynes exists mainly in the

1, 4 diradical form and these 1, 4 diradical can be generated by a reaction which is called Bergman cyclization and that is a subclass of what is broadly known as cycloaromatization reaction.

And these 1, 4 diradicals are powerful DNA cleaving agents, that is their biological activity. However, they are also powerful in forming carbon carbon bonds in synthetic chemistry, like I showed one intramolecular trapping via a 6 exo-trig process, then there are trapping with aromatic rings to form helicons that example, we have not given. So, I think that is more or less that the chemistry of the arynes. It is a big chapter there are many examples but we are not going into that.

The other type of reactive molecules, very similar to alkynes are the allenes and then you have the ketenes because I promised that we will cover these allenes and ketenes just will highlight some of the important ones, important chemistry which are not very well taught, which are not taught much in the undergraduate syllabus. We will talk about that.

Now in the allene chemistry, allenes are you know two double bonds which are not conjugated, cumulated double bonds but not conjugated. And how do you know that you have an allene functionality in a molecule? Their IR is quite unique, but the most unique is the is the chemical shift of this carbon of the central carbon, that is C 13 the central carbon has a distinct chemical shift which comes more than 200 ppm.

Now, this allene moiety can be can be a donor or can be an acceptor, depending on this R which is nothing unusual because if you have a double bond that also the double bond can be electron deficient or the double bond can be electron rich both are possible. So, different types of allenes are there and depending on R you have this character build up.

If it is attached to an electron withdrawing group, then the central carbon will be attacked by a nucleophile because that becomes delta plus. If it is an electron donor group then electron flows like this and now it will it will act as a nucleophile. And if you have a metal attached to the terminal position, then what happens you have a you have a delta negative character here at this carbon or you can have a delta negative character at the other terminal. So, depending on different types of substituents you have different types of reactivity of the allene moiety.

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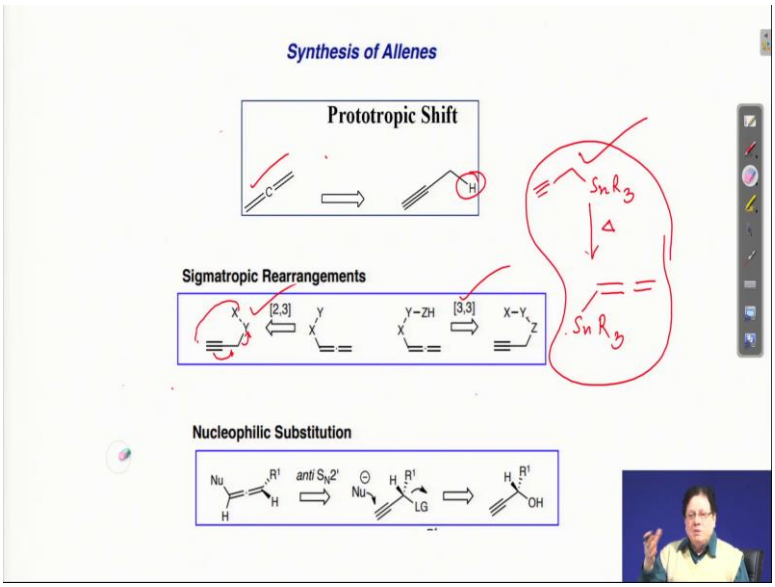

How the allenes are made? There are different ways to make the allenes, one is by isomerization of acetylene alkyne from alkyne you can make the allenes by phototropic shift that is possible that you take this alkyne and then you do 1, 3 shift and that goes to the allene and or you can have this hydrogen replaced by a metal, you can have a metal which can also do this shift and convert it to an allene species.

An example is that if you have a tin compound, a propargyl tin compound then if you heat that what happens, it goes into the allenyl tin compound. That is very well known, we will come back to the utility of this propargyl system in a minute. Let us complete what are the general strategies to make the allenes?

One is this prototrophic shift or shift involving metals 1, 3 shift involving metals 2, 3 sigma tropic rearrangement like if you have again you start with an, see when you make the allene one interesting point is your starting material is always an alkyne. So, you are basically isomerizing an alkyne into an allene.

So, one way is shift prototrophic shift or shift of metal and then sigma tropic shift 2,3 sigma tropic shift as is shown here, that X Y then CH2 then the triple bond. So, it is a it could be a shift like this. So, this is a 2, 3 sigma tropic shift or you can have a 3, 3 sigma tropic shift that is also possible.

And the other option is that if you start with the propargylic system, and then with the leaving group at the propargylic carbon, then by adding a nucleophile which adds at the terminal alkyne. And then you can get basically you are having a very good leaving group here and

you add a nucleophile. So, it is a Sn to prime reaction. So, then you get an allene moiety. So, these are some of the typical ways to make the allene molecules.

Today we will just talk about one reaction, which is a radical based chemistry that can generate terminal allenes, that can generate terminal allenes, that means you put a terminal allene functionality onto an R group by this process and this is what is the reaction is what is called an allene transfer reaction. Basically, you are transferring a three carbon moiety and during the transfer the three carbon moiety becomes an allenic moiety and gets attached to your target substrate.

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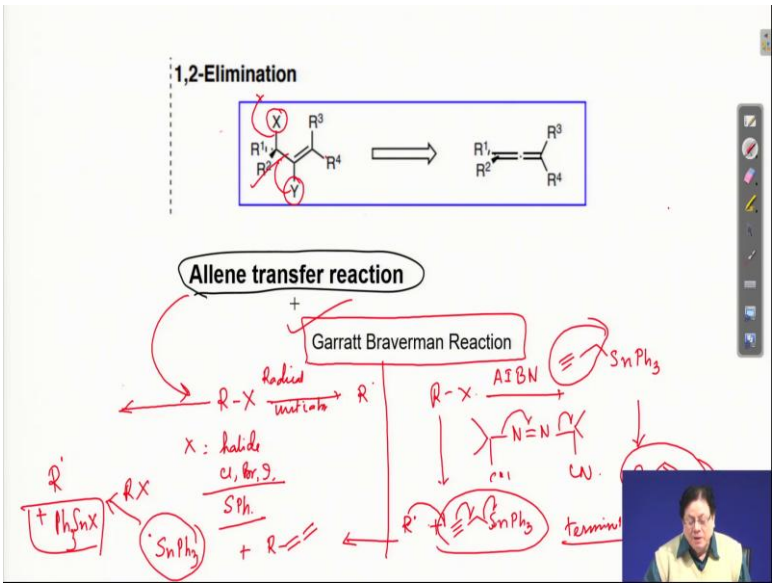

Now, what is that reaction? Let me, there is another method which is obviously the well-known one that is again by 1, 2 elimination like I told you in alkyne the traditional method was to do two sequential 1, 2 elimination.

Here if you take an alkyne already a double bond is present and if you have a halogen suitably substituted at the propargyl at the allylic position like here the allylic position then you can do this if Y is hydrogen then you can do this elimination and get the allene. That is the most traditional way of making the allene.

I wanted to talk about this allene transfer reaction. So, what is this reaction? The reaction is that you take an alkyl halide RX, X could be halide but not fluoride, it could be chloride bromide or iodide or it could be sulphur based like Sph okay. Now these compounds are well known to generate R dot in presence of an initiator, radical initiator, in presence of a radical initiator it generates R dot.

And then if you want to replace X with H, you know that you have to add tributyltin hydride which actually delivers the hydrogen but that goes via the radical mechanism, you need a little bit of initiator which forms this, which forms ultimately leads to the formation of the R dot and then that is abstracted by the, that reacts with the tin hydride to form the RH and generates another tin radical.

So, here in allene transfer reaction, what is done you take RX you have the initiator, initiator is a compound which is called AIBN Azobisisobutyronitrile AIBN, I will write the structure azo, two methyl's and then cyanide and cyanide. So, this actually can upon heating so, this reaction takes place nitrogen eliminates and it forms this isobutyronitrile radical, that is the initiator.

So, if you take AIBN RX and these compounds the one I just wrote earlier, this propargyl tin compound. Then what happens? You get this whole propargylic system gets transferred to R replacing X and when it is transferred it is converted isomerized to the allene moiety. So, you get the terminal allene. So, this is what is allene transfer reaction, terminal allene.

And what will be the mechanism? The mechanism is very simple, first of all RX, RX in presence of initiator generates R dot and then that reacts with this propargyl tin compound and it does Sn prime type of reaction, but it is single electron sorry. So, just a second that we have to be particular, we have to be particular with the, with the arrows because this is now, we are talking about a single electron attack by a radical.

So, now, that will be a single electron movement, this will be a single electron movement and that will be a single electron movement. So, you get the transfer of the propargyl to the R but the in the process, this is isomerized to the allene and what you end up creating is this Sn Ph3 radical.

Now this, see initial reaction started by this AIBN, radical initiator, you need tiny amount. The reaction has started and, in the process, you are generating each allene transfer will generate one equivalent of this SnPh3 radical. So, this tin radical now reacts with RX to generate R dot plus Ph3 SnX. And now this R dot again reacts with the propargyl tin compound and forms the allene moiety. So, this is a beautiful synthesis of terminal allenes by a radical best chemistry. There is another reaction where these allene moieties are involved, Garratt Braverman reaction.

The slide I showed you many reactions of cycloaromatization I showed but I quickly I just showed the slide but I never discussed that, what I said, that the cycloaromatization different cycloaromatization reactions can occur if you try to replace the alkyne part with similar functionalities like allene, isocyanide, ketene etc. So, basically Garratt this reaction which is known as Garratt Braverman cyclization it was discovered in just mid-70s, mid 70s and it is again a very similar type of reaction that what we call Bergman cyclization.

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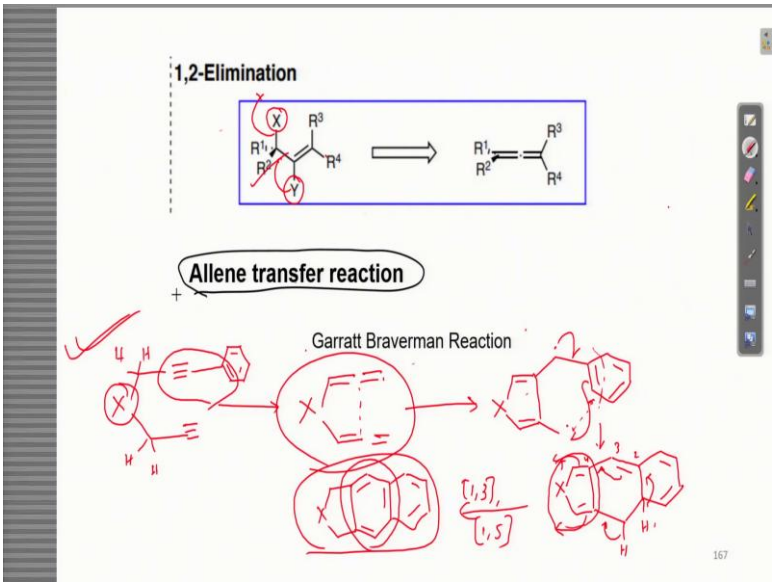

Here these you start with, in case of Bergman cyclization you start with enediynes, in case of Garrett Braverman cyclization you start with a Bis-propargyl system like this, a Bis-propargyl system. And if you do, if you treat that X is an electron withdrawing group, so, that makes these hydrogens very acidic. And in presence of a base, what will happen?

This will now be converted into the Bis-allene, Bis-allene and once it is forming Bis-allene then what happens? It undergoes cycloaromatization like this, this type of diradical is formed. So, it is, see it is nothing different from Bergman cyclization only thing your starting material is different.

Again a 1, 4 diradical has been formed. There are many debates about this reaction whether it is a diradical pure diradical or not, but that is always there even in Bergman cyclization that is there. Obviously, that will be, it cannot be fully diradical depending on the structural elements other other functionalities that are attached to the alkyne moiety, the different types of chemistry can be generated, different types of intermediates can be there.

Only one example I want to show you, that if this one of the propargyl hand has a, has either an aromatic system or just a double bond like this, this double bond is present, then what happens? Then you have the two radicals there and you have this aromatic ring. Again, I repeat, you do not need the complete aromatic ring. What you basically need is this double bond, via these double bond what will happen? That these two radicals can now basically communicate with each other via this double bond and result is that you form a diamagnetic species.

So, they actually are self-quenching process, it is a self-quenching process, the self-quenching has taken place with the participation of this double bond. If this double bond is not present, then self-quenching is a little difficult because you are forming a four membered ring, first of all, whether the distance is optimal or not, whether they are in close contact. But if you have this double bond which will which is a facilitator basically. So, via this double bond, you formed an intermediate like this, because you have to be, you have to be you have to remember that this double bond benzyne aromaticity is lost while doing this type of cyclization.

And so, basically, we are now talking about two types of, two cyclization processes. First of all, this is one cyclisation and this is another cyclization. And however, the overall process is known as the Garrett Braverman cyclization. So, you get this and then it will definitely, it will undergo tautomerization to regain the, to regain the aromaticity.

Now, there are different types of products which are possible. First of all, that this tautomerization can end up going up to this point and there is another tautomerization, this is 1, 3 hydrogen shift that is that is 1, 5; 1, 1; 2,3,4,5. So, there is 1,3 and 1, 5 shift. Now, you why that is so? Because you, if it is a sub sulphur then you have a thiophene ring. On the other hand, if there is only 1, 3 shift, then you have this saturated, it is a it is a saturated ring, it is not a purely benzene ring, but you have the aromaticity coming from the thiophene.

On the other hand, if you do both 1,3 and 1, 5 shift, what will happen, that instead of the thiophene ring having aromaticity that is replaced by aromaticity of the benzene rings. I think you can appreciate that this will have higher resonance energy and so, the ultimate product will be something like this.

So, this is another very interesting piece of chemistry, it happens if you have Bis-allenes, then Bis-allenes can undergo a very similar type of cyclization which is there in case of Bergman cyclization. So, a new cycloaromatization reaction forming this five membered heterocycles

which is actually aromatic, that is why this is called the initial product is a leads to a cyclic network which is aromatic. So, that satisfies the the definition of cycloaromatization.

But then, if you have a double bond attached to one of the alkyne terminals, then via this double bond, the via the participation of this double bond, the two radicals can quench each other and the final product is that you get the aromaticity of the thiophene is replaced by a newly formed benzene ring.

So, lot of, why this is important reaction? Because as I told you from the very beginning, even from the start of this reactive molecules, reactive intermediates, that the one moto of synthetic organic chemistry is to make carbon carbon bonds and the more number of carbon carbon bonds you make in a single reaction that reaction will be more attractive like Diels–Alder reaction, you know, it is extremely attractive, you form two carbon carbon bonds.

And there are other factors of course, which is which makes Diels–Alder reaction very attractive like it is an atom economy process, means you are not losing anything diene dienophile, they add together. It is a reagent free process. So, many of these favourable attributes are there for Diels–Alder reaction.

In Garrett Braverman reaction, you see, again you are forming two carbon carbon bonds in a single reaction. And then of course, the other important factor which I did not mention, but Diels–Alder is the yield of the product, which is also very high in case of Diels–Alder reaction and it is usually free from side products. Garrett Braverman reaction is also very similar to that it forms two carbon carbon bonds and it is also a very high yield in reaction.

So, so, we have done the allene, we are now let us see the what is we want to just have a quick glance at the, at the ketene ring chemistry. Ketenes, we know that they are they are involved in many reactions as intermediates, which you are aware of.

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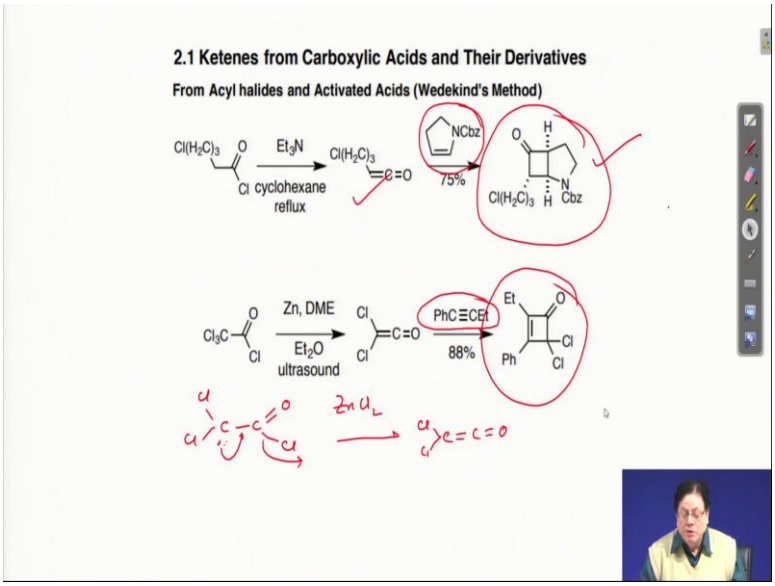

But I will just talk about only one type of one example of ketene chemistry, is the is the reaction is the 2 plus 2 cycloaddition, which is also true in case of allene, you know, allenes, ketenes, isocyanates having cumulated double bonds, they are, they can undergo 2 plus 2 cycloaddition which is otherwise thermally forbidden.

If you want to dimerize ethylene, it is not possible thermally because 2 plus 2 cycloaddition is not thermally allowed. However, if you have these type of cumulated double bonds, which you already know that ketenes, allenes, isocyanate, etc. They can participate in the 2 plus 2 cycloaddition.

So, one so, many examples of ketene chemistry which actually relies on the cycloaddition chemistry. How do we generate the ketenes? That is the first one because ketenes are usually unstable, they are reactive intermediates. So, you generate ketenes in C2 and then react with the, with your other counterpart which is another alkene part because you want to do the 2 plus 2 cycloaddition.

One way of generating ketene is to take an acyl halide. An acyl halide, if you add a base like triethylamine, then what will happen? There will be elimination of HCl 1, 2 elimination and that 1, 2 elimination gives rise to ketene, sorry, gives rise to ketene and then if you do this reaction in presence of this alkene cyclic in with this dihydro pyrrole, then what will happen? There will be 2 plus 2 cycloaddition and you get very interesting network a 4, 5 fused network very, very interesting framework from synthetic point of view.

You can also take instead of the alkene you can take alkyne that also can add in a 2 plus 2 fashion. So, which the example is shown here that here it is elimination of a acyl HCl from acyl halide, this reaction, this is trichloroacetyl chloride if you add zinc then what will happen, zinc will, one of the chlorine will be will be removed and what will happen that you will get a system so, zinc donates the two electrons and you have Cl Cl. So, one Cl leaves as zinc chloride.

So, this zinc 2 plus so, that donates the two electrons to this carbon and then these electrons can come back and pick out the chloride. So, that makes that dichloroketene. And then if you add this acetylenic compound there is 2 plus 2 cycloaddition and you form this cyclobutanone framework. So, these are some standard chemistry of of ketenes.

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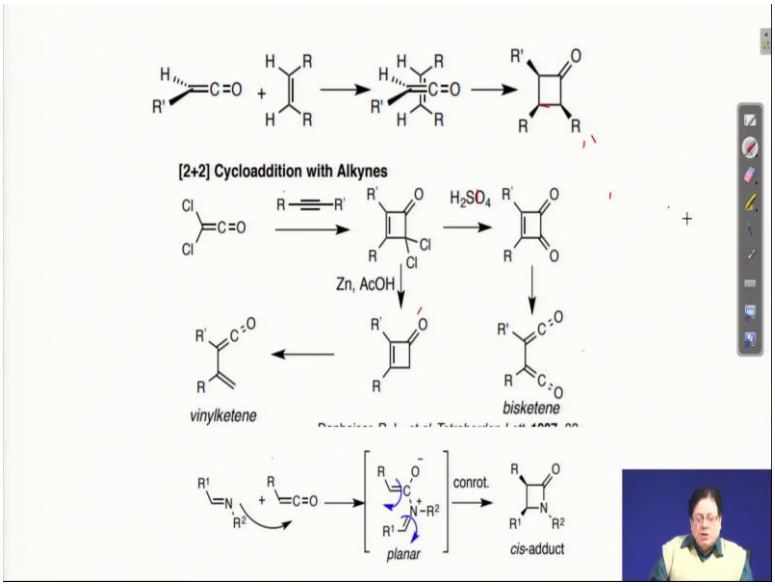

The other reaction which I wanted to tell you, which is also very similar to 2 plus 2 cycloaddition. However, there is a debate whether the reaction is really a 2 plus 2 reaction or a or a stepwise process because you know pericyclic reactions are concerted processes whereas when you cannot meet the rules of the pericyclic reaction then the reaction had to take a stepwise stepwise fashion, had to go in a stepwise fashion.

Now, there is a reaction which is called the Staudinger synthesis, the Staudinger synthesis. This is not Staudinger reaction there are Staudinger actually developed chemistries one is Staudinger reaction which is basically reduction of an azide with triphenylphosphine, and the azide goes to the amine, that is Staudinger reaction.

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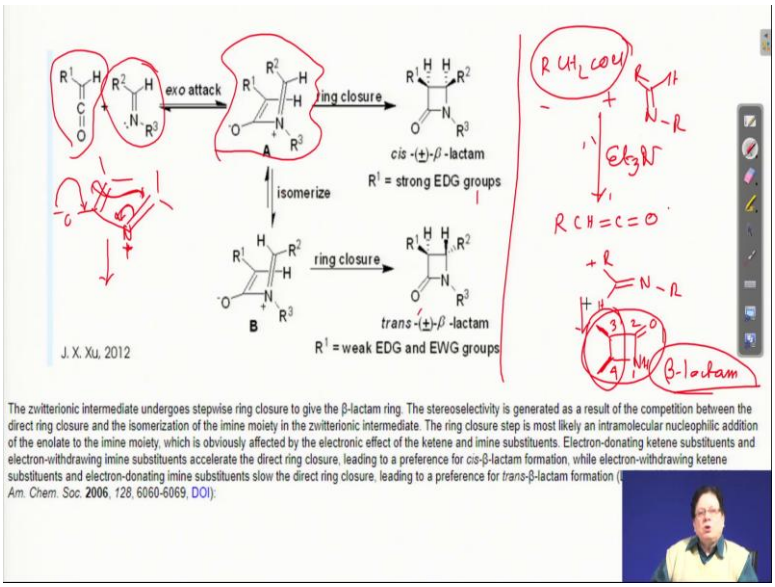

What we are talking about today is Staudinger synthesis and what is Staudinger synthesis? Staudinger synthesis is let me see, yes, it is shown here, what you have in Staudinger synthesis is that you take an acid chloride R CH2 COCl and you take an amine. You take an amine and you add a base like triethylamine. So, what will happen?

I already told you that acid chloride can undergo 1, 2 elimination and form the ketene and then once the ketene is formed, then you have ketene and you have the amine. And if you do a 2 plus 2 cycloaddition, then what you will get is basically a four membered ring with the nitrogen and the carbonyl. This is a famous ring present in many antibiotics like penicillin. So, this is what is called beta lactam.

So, staudinger synthesis is nothing but synthesis of beta lactam moiety by a formal 2 plus 2 cycloaddition. I used this word formal because apparently it is not a just straight cut 2 plus 2 cycloaddition. The mechanism involves the first the as the ketene is formed then the amine nitrogen attacks the carbonyl carbon and you get an intermediate like this.

Now, if the subsequent step, subsequent step can be what? Subsequent step can be, can be a, basically now you have a you have a system which looks like this nitrogen and this. Now, you can have this is another pericyclic reaction. This is which is called an electro cyclic reaction. So, you can have an electro cyclic ring closure, electro cyclic ring closure and that is it is four electron. So, it will be conrotatory. So, that is one possibility.

So, if the cyclization is very facile, then is very facile, then you get one type of stereochemistry of the beta lactam. On the other hand, if you slow down this subsequent step,

because some people believe that it is actually not a conrotatory ring closure, what happens is that if it is slowed down, then this undergoes a kind of attack like this, which is of course, violating the Baldwin's rule because it is an endo-attack in a four membered ring.

But however, Baldwin's rule sometimes is not applicable to these charged species like this iminium ions. But anyway, many people believe that this is the mechanism that it is a it is an endo-attack by the enolate. So, either conrotatory or the enolate, whatever it is, the rule is that if the cyclization is very fast, then you get if you are starting immune is like this, the structure is this then you get cis beta lactam.

On the other hand, if you can slow down the cyclisation by having appropriate appropriate control of the electronic character of these substituents, electron donor, electron acceptor character of the substituents, if you can slow down the process, then what happens there is chance of isomerization and it can isomerize and you can get the trans beta lactam in the process.

What is cis beta lactam? What is trans beta lactam? That is the relation between these. So, these so, this is one, that is two, that is three, that is four. So, these 3, 4 substituents whether they are cis or trans that depends on the reactivity, that depends on how fast is the second cyclization is taking place.

Just to again summarise, Staudinger synthesis is nothing but the addition of, is the reaction between an asyl halide and an imine in presence of a base. The mechanism it gives cis beta lactam or it can give trans beta lactam as the major product. In, the mechanism is not straightforward 2 plus 2 cycloaddition although it looks like a formal 2 plus 2 cycloaddition but the mechanism is is that the mechanism is basically the the imine attacking the ketene, the ketene is generated from the asyl halide and then the the imine amine collapses into the beta lactam either by a conrotatory electro cyclic ring closing process or by an endo cyclic attacked by the enolate.

If the cyclization, second step is very fast you get good control of the stereoselectivity of the reaction, if it is very slow then that you can see isomerization and you can get a mixture of cis-trans and obviously, if there is isomerization possible trans is more stable, because it is free of the steric effect. So, 1, 2 trans relationship is more more stable. So, you can get trans as the major product. So, that is the Staudinger synthesis.

So, that actually finishes up our this topic that we have covered the alkyne chemistry, we have covered the aryne chemistry, we have covered the allene chemistry and finally we have covered the the ketene chemistry and we have discussed this Staudinger reaction, synthesis. I think with that, let me conclude this topic the topic of chemistry of these reactive organic systems, molecules or intermediates. Thank you very much.