Reactive Intermediates: Carbene and Nitrene

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Lecture – 15

Reaction of Carbene (Contd.)

Hello everybody, welcome to my course Reactive Intermediates Carbenes and Nitrenes. So, in my last classes, we were discussing about various type of reactions that is associated with carbene. We have discussed addition reactions; we have discussed insertion reaction; we have discussed different type of nucleophilic addition towards the carbine. And in the last class, we have discussed different type of rearrangement reaction ok. And in the rearrangement reactions, we have understand that how that once the carbene generated even though there are possibility of as for example that CH insertion, then still there is a if there is no beta hydrogen how that carbene can proceed with the rearrangement reactions.

Again today we will continuing, continue with this rearrangement reactions. One very important reaction is there that we will discuss first then we will proceed ok. So, one of the most common feature in these type of carbenes that is they are generally adjacent to a carbon carbonyl group ok. So, the carbenes which is forming if that is adjacent to a carbonyl group, then what will happen ok, so under this rearrangement conditions that we will see. In general it has been seen that if there is alpha diazoketone ok, so under thermal or photolytic condition that we will give the ketenes ok. And this is called is a very famous rearrangement, this is called Wolff rearrangement ok.

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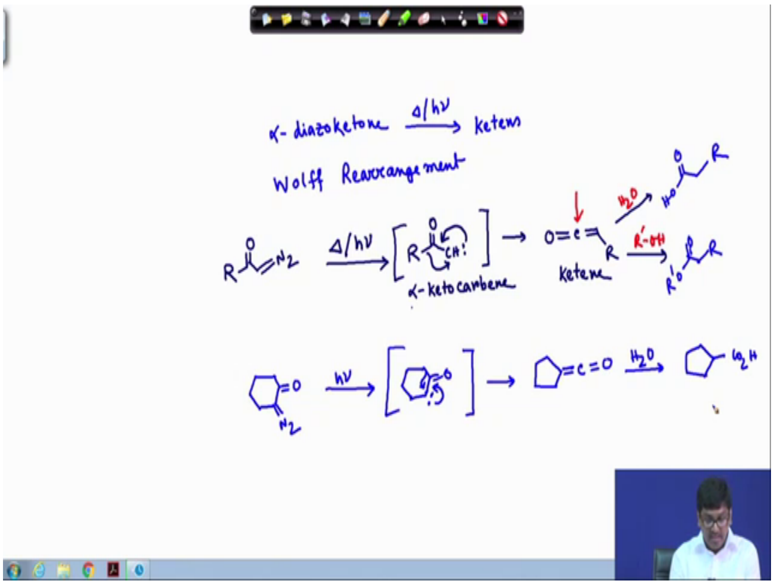

So, what we said that if we take the substrate as alpha diazoketone ok, now under thermal or photolytic condition, what it will form. It will generate the carbene. We know these things that during the preparation of carbenes or the generation of carbenes, we have learned this ok. Now, this is the alpha keto carbene ok. Now, if we have this alpha keto carbine, the rearrangement can happen ok. And if these rearrangement happen, then what it will generate? It will generate the corresponding carbene will give you the corresponding ketene ok.

So, we are starting from these alpha diazoketone and that is finally generating the ketene. Now, this ketene is ready for different type of reactions, different nucleophiles can attack to this centre ok. And once it will react, it will give different type of products as for example, if you treat with water, the product will be the corresponding carboxylic acid. Or if it attacks with alcohol ok, then what will happen if it attacks with alcohol, this will be corresponding ester ok. So, as for example here R prime, so this will be the corresponding ester ok.

So, in this way, we can generate the ketene from alpha diazo this ketone and that can proceed this of the generation of this ketene that can proceed to carboxylic acids or esters. So, this is called the Wolff rearrangement. This particular rearrangement is called Wolff rearrangement, where ketene is forming ok.

So, once we have this Wolff rearrangement, now let see if you take these particular substrate, these diazo ketone compound as the carbene precursor. So, this will generate the corresponding carbene. And once it will generate the carbene under photolyt condition ok. So, what it will form? So, and fine and once it will form these here in these case you see there the ring contraction is happening that means we have started from six member. Now, after this rearrangement, this Wolff rearrangement these become five member, having this ketene. Now, this one in presence of water will give the corresponding carboxylic acid ok. So, here you see that we have started with six member ring and we are ending with a five member ring having this carboxylic acid.

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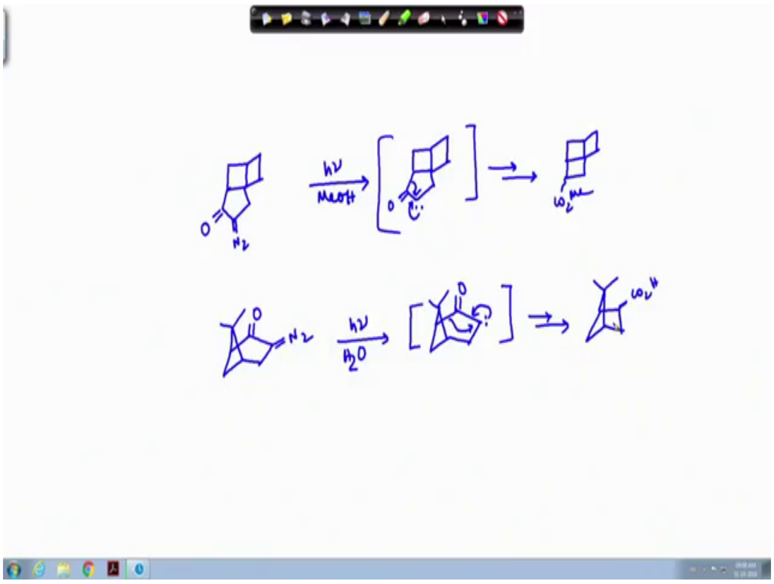

Similarly, if we take this fused one, fused ring as the substrate ok; so, this alpha diazo ketone if we take and under again photolysis and here methanol is there as a nucleophile. So, what it will form, it will form as you have already mention that first it will generate the corresponding carbine. And now, there will be the Wolff rearrangement and once it will do the Wolff rearrangement then it will generate the corresponding carbene and I am not going into detail of that and once that will generate the carbene. After that the methanol will attack to it and finally, the product will be again, here we have started with five memebered ring. Now, it will ring contractions will happen and we will get the four membered ring.

See, this is a very interesting product. Because there are three four memebered ring that is fused and with a ester moiety. So, we have started 4 4 5, but we came as a 4 4 4 ok. Next, if we take a compound bicyclic compound, this alpha diazo ketone ok. So, this is have been the corresponding (Refer Time: 09:03) with dimethyl group. Now again, under photolytic condition, then here water is as a necleophile. So, as per our previous experience, we can simply make here alpha the corresponding carbene.

And once this carbene then this one will migrate obviously, here if you see these bond that is associated with another two carbon carbon bond and where these bond possibility of migration of these bond is lower, because, here associated with on one carbon as well as two hydrogens ok. So, in these case so, these particular bond and migrate and the migrating attitude will be higher here and that will give the after that the nucleophilic attack of this water to the ketene moiety will give the five membered ring from here, and overall the product will be ok. So, this is the five membered ring with a carboxylic acid.

All these cases whatever I have shown here you see that we have started from more number of ring, but, at the end we are decreasing and the ring number is decreasing. And overall if you start from six membered, we are getting five membered. If we start from seven membered, we are getting six membered.

Now, one of the most important synthetic applications of this Wolff rearrangement, we will see that and what is that. If we consider this Wolff rearrangement, then we are starting from these alpha diazoketone and that is converting into the corresponding ketene and different type of nucleophiles are attacking.

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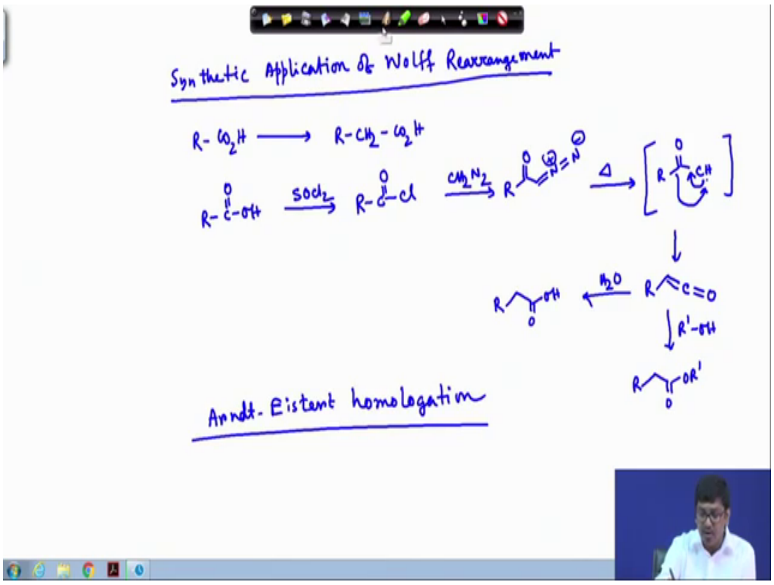

Synthetic Application of Wolff Rearrangement

Arndt-Eistent homologation

So now, if we start with a carboxylic acid and we were to see the most important synthetic applications of Wolff rearrangement ok. So, if we want to see that let say we have started with this carboxylic acid. Now, one carbon homologation of this carboxylic acid is the main synthetic application of Wolff rearrangement. As per example, if you start from here we are getting finally this one ok.

So, how we are doing that? If we take this carboxylic acid, then we can in presence of thionyl chloride or oxalyl chloride ok, we can make easily this acid chloride once we have generated that then in presence of diazo methane that is that will react with this electrophilic centre and give you the corresponding alpha diazoketone compound ok.

So, we can write over here fine. Now, if you have this, once it is there, now this is ready to generate our desired carbene precursor. So, under thermal conditions again, now there it will form ok. And this can go for this Wolff rearrangement to give the ketene moiety ok. Now, if we have the water as a nucleophile, then actually what we are getting we are getting the corresponding carboxylic acid with one carbon extra.

Similarly, if you take R prime OH that means alcohol as the nucleophile, then we will get the corresponding ester with one carbon more ok. So, we are starting from a carboxylic acid or we are and after that we are ending into one carbon homologated carboxylic acid or its corresponding ester and this is happening through the Wolff rearrangement this is a one of the beautiful application of Wolff rearrangement where one carbon homologation is possible from its corresponding carboxylic acid and this is called Arndt-Eistert homologation ok. This method is called Arndt-Eistert homologation fine. So, in this way we can simply take one carboxylic acid and we can increase into its one carbon homologation to get the corresponding carboxylic acid or the corresponding ester fine.

We will now see one of its applications of this Arndt-Eistert synthesis. Synthesis of grandisol. What is this grnadisol? This is a experiment from a paste of cotton boost and these actually creating a lot of problem in this harvesting of this cotton. So, synthetically its application in agriculture field is enormous, because if we can synthesize this compound, then actually we can use these to attract these type of lot of paste ok. So, the paste that is generating these pheromone. So, we can attract those pastes and then we can eliminate them from the field, so that is one of the important application for this type of pheromone that if we can synthesize them.

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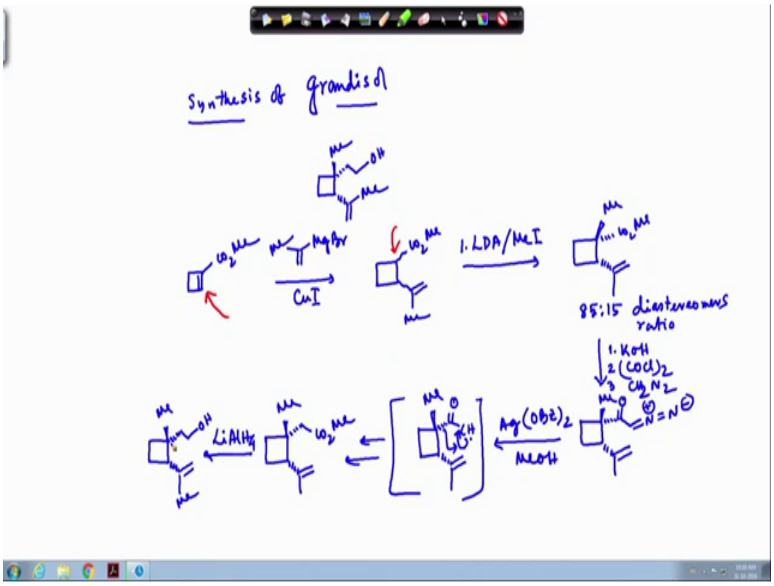

Now, what is this structure. So, it is having this cyclobutane ring and two stereogenic center ok. So, this is a x pheromone from paste of cotton (Refer Time: 17:15), and its name is grandisol ok; so, the precursor that has been taken from this cyclobutane derivative. After that its conjugate addition from this grignard reagent in presence of copper 1, the attack will happen over here, this 1,4 addition ok. Once this will happen, then the product will be the 1, 4 addition product and ok.

So, once we have this, then in presence of ldithium diisopropylamide one very strong base, and the electrophile here is this methyl iodide we have used for the methylations. And the overall product will be see this is the here this is the most acidic proton over here. So, what it will do this base that will pick up the proton from here ok. Once it will pick up the proton, after that that can again attack to the corresponding electrophile. And in that case, definitely that attack will be definitely that attack will be the corresponding guided attack. And once it will be the guided attack, then this will give you the product of this one ok.

So, once it will give this (Refer Time: 19:24) center then actually here the ratio of diastereomer 85 is to 15 ok. So, we have given this obviously the other diastereomer also will form, but this will predominant. And once, it has been synthesized then the corresponding hydrolysis, basic hydrolysis with KOH potassium hydroxide, so the ester will be its corresponding carboxylate. And after that the acid chloride followed by diazo methane treatment, we will give this corresponding alpha diazo ketone ok.

So, now we have this alpha diazo ketone, it can be in presence of silver salt, and methanol is here as a nucleophile, so that can give the one carbon homologation, because here you see now this will generate ok. So, once this will generate. So, again this will some kind of Wolff rearrangement will happen, I am not going into detail of this. But overall once this will generate this ketene moiety, then the methanol will attack. And once the methanol will attack, after that it will give the corresponding one carbon homologated ester ok.

So, what it will form after the ketene and corresponding methanolic attack, then it will form the one carbon homologated ester ok. Now, we have these ester, these can be now treated with lithium aluminum hydride. And in presence of lithium aluminum hydride, this will give the corresponding primary alcohol which is actually our target molecule ok.

So, in this way, you start from a very basic cyclobutane moiety, and then followed by different-different reactions. First this conjugate addition conjugated addition, then this say generation of this (Refer Time: 22:43) center. And after that the formation of this alpha diazo ketone, followed by this Wolff rearrangement, and the attack of this methanol will give this one carbon homologation. And finally, the reduction with lithium aluminum hydride will give the alcohol. So, this is a beautiful example about this Arndt-Eister synthesis.

So, these are different type of rearrangements that we have seen in our last discussion, last two discussions. Now, there are two reactions. I will discuss that are in very much important for the carbene chemistry-1 is called Reimer-Tiemann reactions ok. So, other reactions from carbenes among that Reimer-Tiemann reactions is very important ok.

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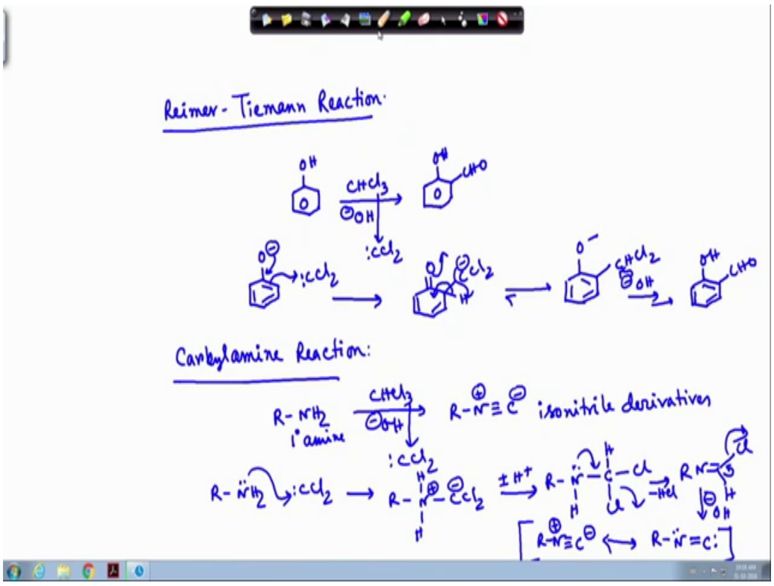

So, what is this reaction? In these case actually the starting material is the phenol ok. So, phenol to its corresponding ortho formylations; that means, we will get phenol to salicylaldehyde in presence of chloroform under basic medium. So, that itself tells that chloroform under this basic medium will generate the carbene species and that will react with these phenol to give the final compound that is the salicylaldehyde.

So, what is the starting material here? So, the starting material here is the phenol and ok. So, in these case, this is the specifically the ortho substitution is happening through this dichloro carbene. One of the important reason behind these could be the electrostatic interactions when these phenoxide forms. And in presence of that these when the sodium hydroxide or potassium hydroxides that generated this phenoxide that will form; and after that this dichlorocarbene that will give this corresponding ion pair they are due to these electrostatic interactions that actually facilitating these ortho substitution ok.

So, what could be the mechanism? The mechanism could be presence of base these phenoxide, and then from here it can generate the carbene ok. So, this dichlorocarbene it can react. So, this will give ok. Now, this can pick up this two proton ok. So, overall ok, then the corresponding hydroxide attack; and further once this hydroxide will attack liberate, and finally that will give the corresponding salicylaldehyde as the final product. So, this will attack over here, and one it will liberate that c l minus. And after that this will give you the final compound that is the salicylaldehyde ok.

And another reactions in these aspect with the carbene considering the carbene reactions. If you not say that particular reactions it will not complete that is called carbylamine reaction ok. So, in this case, the carbylamine reactions, the starting material is one degree amine or primary amine ok. And again in presence of chloroform under basic medium that gives the foul smelling isonitrile derivatives ok, so these isonitrile derivatives ok.

So, here also it will generate these dichlorocarbene, and obviously, this R NH 2 that can react nucleophilic attack to this dichlorocarbene. And once it will give that so it will be this species ok, then you can make plus minus H plus; that means, this H plus can go over here. And over all what you will get ok, now nitrogen has this lone pair. So, you can go out then overall what you will get that once it will go out.

So, basically that will give ok. Now, this can nicely generate in presence of acid sorry in presence of basic medium ok. So, this can generate the corresponding isocyanide ok. So, we have started there are two different type of reactions which is important for carbenes one is called Reimer-Tiemann reactions.

And another one is called carbylamine reactions. In case of Reimer-Tiemann reactions, we have used this phenol which has been converted into salicylaldehyde in presence of chloroform and sodium hydroxide or potassium hydroxide. Whereas, in case of cabylamine reactions, we have started with one degree amine that we will convert into its isonitrile derivatives and that is also going via this dichlorocarbene species. So, with these I am finishing the various reactions of carbene.

Thank you.