A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 23
Fg based Strategy (Contd.)

Students welcome back. So, we basically discussing functional group based strategies, and we have discussed that how you can use several synthetic equivalents; we mainly talked about how formyl anions are chosen as a synthetic equivalents to introduce a CHO functional group in couple of couple of molecular structure.

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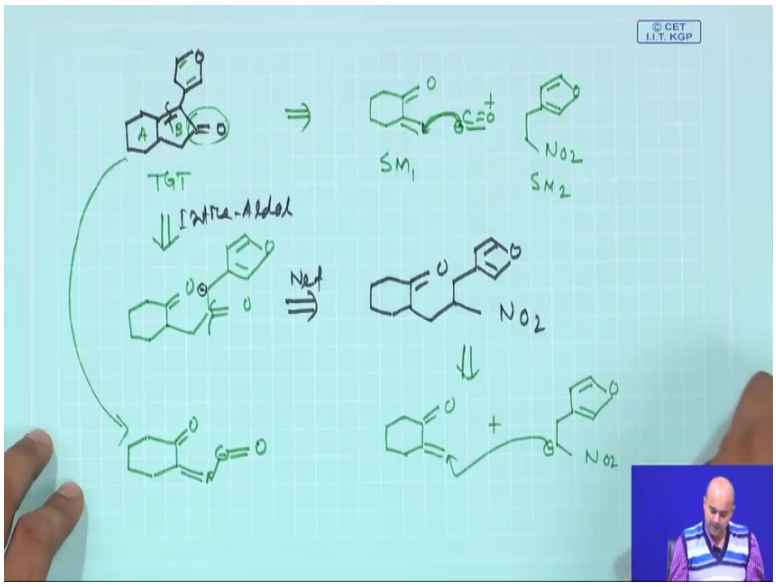

So we will try to continue our, discuss on the same point. Now here today the initial problem which we will try to focus it is based on little bit different thing see the structure very carefully, then we will try to give you how this molecule can be constructed. Now this part this molecule is having A 3 substituted furan is a furan ring, and here this is bicyclic compound. So, is having a ring A 6 member, ring B 5 member and; obviously, I will give you the starting material I say the starting material also will be giving to you.

The starting material which have given to you it is a starting material, which is not very popular starting material and the other starting material which is a is giving to you a furan based compound. Now as the starting material was giving to you your job is almost simplified, starting material 1, starting material 2. Now you try to correlate that how this

2 starting material can be assembled or how this target can be skeletally disconnected. So, that tool of this starting material can be arrived.

Now we will try to do a retro pathway we say this molecule as it is having a alpha beta unsaturated or not a exactly alpha beta unsaturated, it is this part is alpha beta unsaturated. So, we can basically construct through a intra molecular aldol dehydration, which is always over is our prefer pathway and the disconnection should now give you 1 2 3 4, a 1 4 dicarbonyl species where the remaining part of this molecule will be similar. So, we just disconnect it here, and you see this is a goes to a intra aldol.

Now, you say that this carbonyl adjacent to a furan system, as well as adjacent to a alpha carbonyl can undergo this intra molecular aldol. Now see the starting material which was giving to you. A starting material which was given to you, now basically we are trying to figure it out how this starting material can be assembled to give you the required target, now I said Nef reaction is known to you fine. So, if you do a Nef reaction here you get this carbonyl. So, particularly this disconnection was done with this Nef per formation.

Now, you are almost very close, and now you see if you have this starting material with the furan part CH 2 CH 2 NO 2, we say the carbon ion can be easily generated to undergoing a Michael type of reaction, isn't it? Now in reality in terms of synthetic equivalents probably this reaction what synthetic equivalents we have used, we have basically used a synthetic equivalents something like, if you now do a disconnection here you see that we have used a synthetic equivalents, this synthetic equivalents which is basically adding here, isn't it to give you CH 2 CO, and the remaining part might be similar.

Now, this is synthetic equivalents which is coming from a this nitro basis through a Nef reaction which we already talked about.

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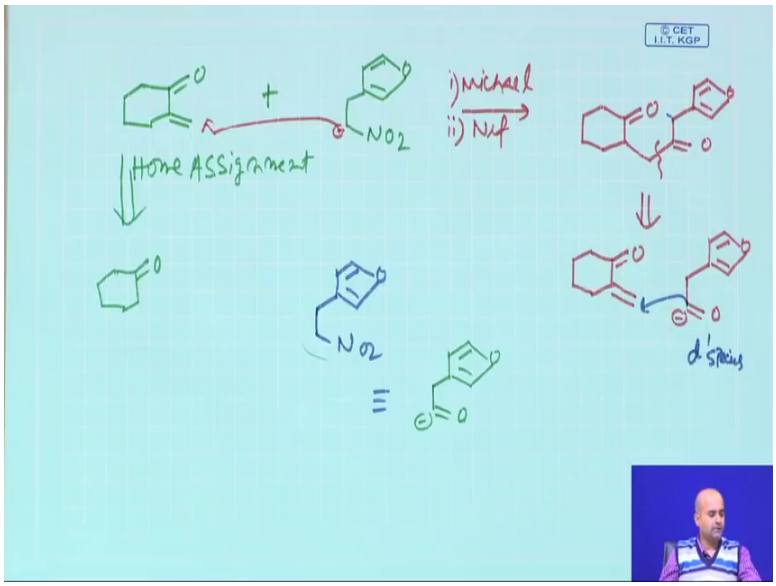

So now, you go to the forward synthesis pathway and find that this is a very excellent demonstration, I will give you a home assignment that how the starting material you can synthesise from cyclohexanone how this compound you can make ok.

Now, coming to our problem we react this compound with a starting material which is available to you in this form. And now you say that if you observe the target molecule we are basically using this C O as synthetic equivalents, and trying to put a Michael reaction with this C O minus here. So, this C O this C double 1 O is undergoing a Michael reaction, here is not it is undergoing a Michael reaction here. So, this is the synthetic equivalent which is really coming from this furan derived nitro species this nitro species now reacts here, in a Michael fashion and then you do a I write Michael followed by Nef both are done together. So, what basically you will get you basically get, isn't it?

Now, I will show you what exactly the synthetic equivalents we have used here, now do a disconnection here, the synthetic equivalents what basically we have used here, isn't it? This synthetic equivalents which is basically a d 1 species d 1 species which we used here, now as I said this is not commercially available this we have been generated with the help of this nitro species and thanks goes to the Nef reaction. We know that C nitro bond can be clipped to corresponding and can be converted to corresponding carbonyl compound with the help of this Nef reaction. So, we can start with the starting material with the help of a synthetic equivalent something like this, and then you simply do a

aldol kind of dehydration. So, this is a complex synthetic equivalents, and in terms the entire this starting material can be now figure it out as a synthetic equivalents of this species yes. So, this is the real intermediate, and this is the reagent which is acting as a synthetic equivalent of this particular species.

So, your synthetic equivalent based problems can be solved in this way, and always is skeletal disconnection is pretty much required. Next 1 will try to explore a similar kind of problem.

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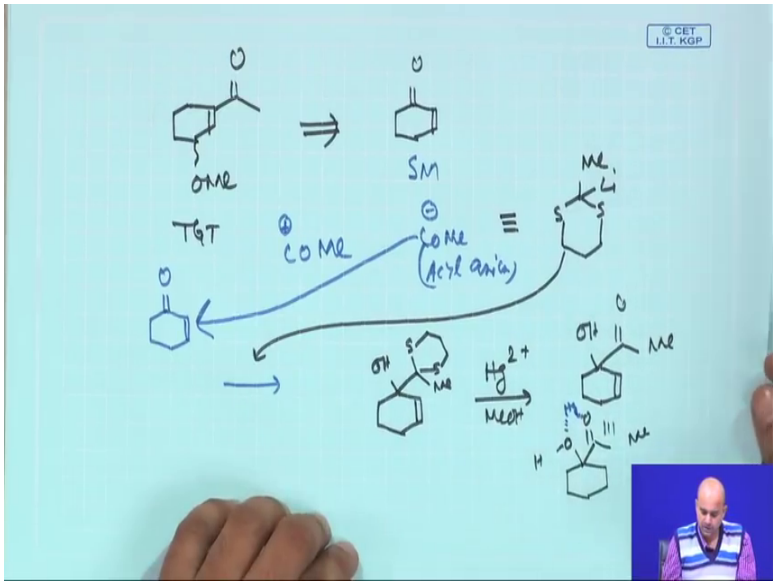

But this is bit unusual; bit unusual, will be using a functional group inter conversion using a umpolung species, the target molecule which was given is this 1. It is a alpha beta unsaturated ketone having 1 in having a O methoxy the starting structure or precursor which was given tio you cyclohexanone. If you try to correlate what are the extra functional group was added to the compound starting material is this one, you have added a extra CO Me group is not it, CO Me group and then we have added a extra O methoxy here, now what is said that you have this starting material. see you basically need to do a need to add CO Me. Now the CO Me it could be a positive CO Me or could be a negative CO Me means Me CO minus a acyl anion or a acyl cation. So, this is the acyl anion which is the umpolung.

Now, if you see this compound is basically is a Michael acceptor is a 1 4, as well as is 1 2. So, this molecule can only accept there is no donor side except this 1, but this

synthetic this part pole is untouched, because if you see this 1 2 3, this CH 2 this 3CH 2 remains untouched. So, probably you need some kind of this CO Me species which attack either 1 2 or 1 4 fashion, we will try to figure it out how it takes place.

Now, this CO Me species you can basically generate from a acetaldehyde, which is put it as a 1 3 dithiane. So, you pick up this hydrogen by lithium, and now react this species with this cyclohexanone in 1 2 fashion. Basically you will get a compound whose structure will be this a methyl is there this is the thing, now what is it your CO Me additions somehow was done, but only thing is your double bond was kind of a migrated or rearranged with an insertion of a O methoxy group. We will try to figure it out this sulphur was will be not there, we will make sure that first sulphur goes up. So, basically you get a OH CO Me with this compound.

Actually reality on this mercury mediated 1 3 dithiane depression was done, methanol was used as a solvent, and as mercury was still there this starting material seem to have a intermediate, which basically chilates with this mercury to this alcohol oxygen as well as, this carbonyl oxygen we will draw this structure more clearly in the next slide or next piece of paper.

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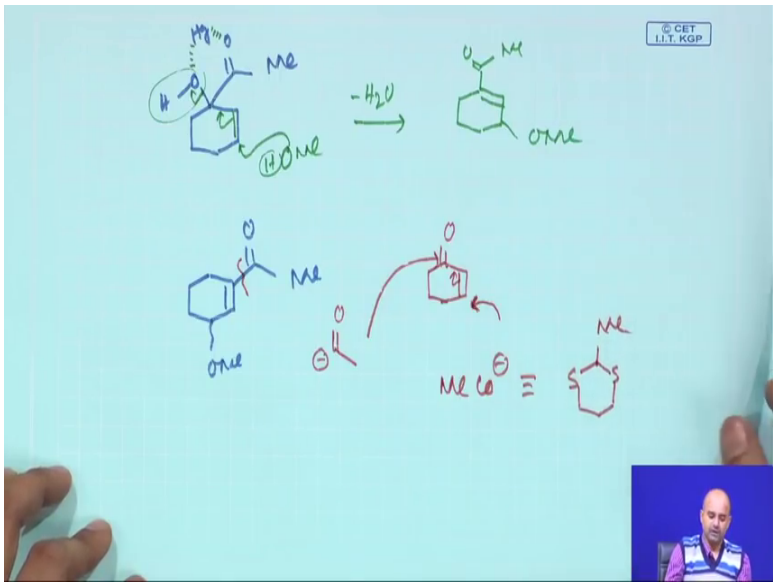

We say once this 1 3 dithiane group deported, we basically have a compound something like this. In the mercury was forming a chilate a 5 member chilate, or chilate and then your double bond is here. Now this methanol is basically acting as a nucleophile, now as

this chilate was done the electrophilicity of this center was correspondingly enhanced, and then methanol was attacking in a kind of Michael fashion not exactly Michael fashion. And that basically triggers up the elimination of this water molecule, this is O H and this H basically is kind of a methanolysis takes place, and then you see this compound basically generating a methanol O methoxy attacks here and this hydrogen and this O H goes off as water.

So, basically you are having a nucleophilic attack on methanol. And now the target which was initially given to you is these things, the starting material which was also given to you is a cyclohexanone. So, what exactly we did we just do a acyl anion umpolung chemistry. Now this acyl anion umpolung chemistry was normally first reacted in a 1 4 fashion.

Now, this 1 4 fashion sorry 1 2 fashion; 1 2 fashion the 1 2 attack was done here, and then once this 1 2 attack was done, then this tertiary alcohol was reacting with this mercury which was used for the removal of this 1 3 dithiane. And then methanolysis takes place methanolysis methanol basically attacks here, this allylic double bond basically migrates. So, this is the main synthetic transformation and you actually need a Me CO minus. So, which has been generated from this particular acetaldehyde 1 3 dithiane is bit unusual to visualise, but sometimes it gives you a very nice interesting chemistry.

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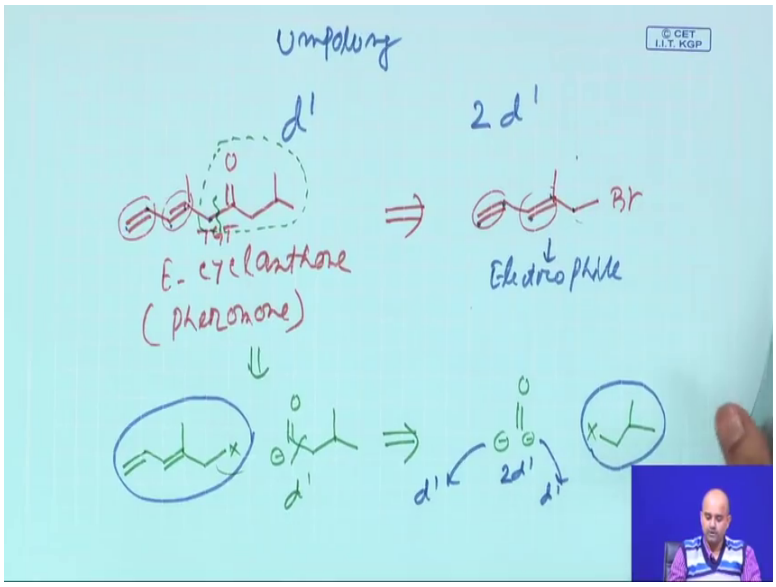

We will just try to hub little bit more example on this umpolung species, what we say that is this species are basically a d 1 species, or a 2 d 1 species. Next then we will talk about a problem which will basically highlight that how this umpolung chemistry was used in the synthesis of some natural products, this particular compound is a natural product it is name is E-cyclanthone, it was used as a pheromone.

Pheromones are basically chemical compounds, which are being secreted by some certain insects, and they are acting as a chemical messengers which helps them to communicate with 2 insects or 2 primates, they are basically secreted by those insects, and they have a strong aroma this compounds are volatile in nature, and they are acting as a chemical messenger. So, you have to talk in the chemical way you secrete some chemicals which then gives the signal.

Now, this particular natural product or cyclanthone will now do the retro. The starting material was given to you for your analysis. I set the starting material which will be provided to you as this one. Now as I am doing a functional group based approach; so use the starting material having allelic bromo, in the final target having a carbonyl compound as main core functionality and 2 olyphenic bonds are there, but the starting material to olyphenic bonds are also there. So, these 2 starting olyphenic double bonds remain same in the target molecule. So, no need to change anything because methyl is there only thing is this CH 2 is there so, up to this part 1 2 3 4 5, 1 2 3 4 5 up to this part the starting material is providing to you basically need to add this entire part to a starting material to access the target molecule.

Now, you see this allylic bromide can be a very good electrophile is not it. Now if we do the retro we say that we will make this connection here. So, basically you can think about. So, if you having a this synthetic equivalents and your starting material was available to you is simple electrophile you can easily construct a carbon carbon bond, now this particular synthetic equivalents can now, it is basically a d 1 species it can also be further it synthetically disconnected as discussed earlier by a by this bond. So, this is a 2 d 1 species means this end is 1 d 1, this end is 1 d 1, and this is your 1 electrophile, this is your 1 electrophile, which has been supplied to you.

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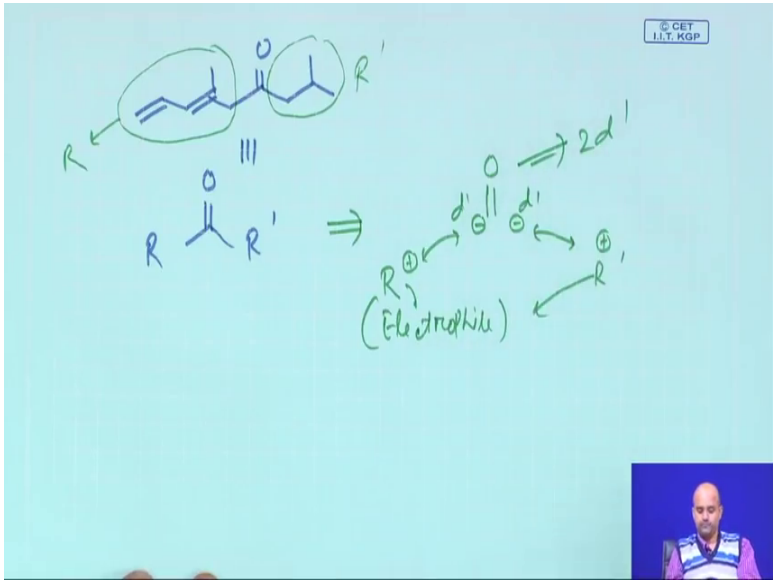

So, in principle this molecule which was given to you will now, write the molecule in a different way, which as this molecule can be simplified as R, R prime.

Now, this part is the R I say and this part is the R prime to disconnection now, can be basically based on a minus, a minus which is a R plus and R prime plus. So, is a basically a electrophile electrophile both the things are electrophile. So, what we need to do this is a d 1 at this end d 1 at this end. So, altogether this is a 2 d 1 species. So, now, finalize the end game of the synthesis.

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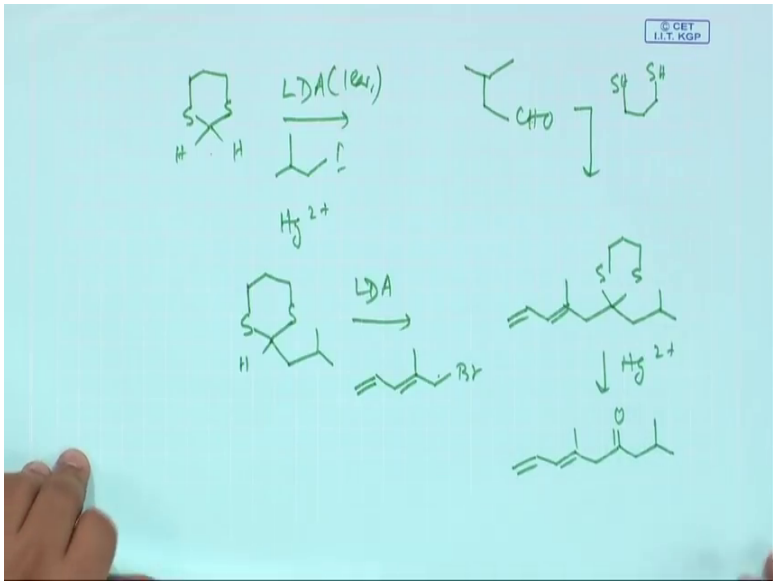

Now we will start from a starting material which is already known or available to all of us formaldehyde 1 3 dithiane. As a first we will do a LDA 1 equivalent and we use a isobutyl iodide, and then do a mercury plus so, initially we will basically get this isobutyl CHO or other way you do not put the mercury here, you first do the synthesis like this you put keep this hydrogen. Now put another equivalent of LDA, and your another electrophile, which was given to you which is having this structure. So, then you will basically get sulphur and then your this things.

So, now you simply do a Hg 2 plus to close the final synthesis is not it, or if you have started the earlier way formaldehyde 1 3 dithiane LDA 1 equivalent isobutyl iodide Hg 2 plus you end up with here, now here you react with again a 1 equivalent of formaldehyde 1 three dithiane to get this isobutyl dithiane, 1 3 dithiane abstract with 1 equivalent of LDA and react with this you end up here, and then do the marker immediate reproduction. So, by this way this kind of synthetic equivalents will always help you to give you a very nice flavour. Now we always talked about this dithiane chemistry.

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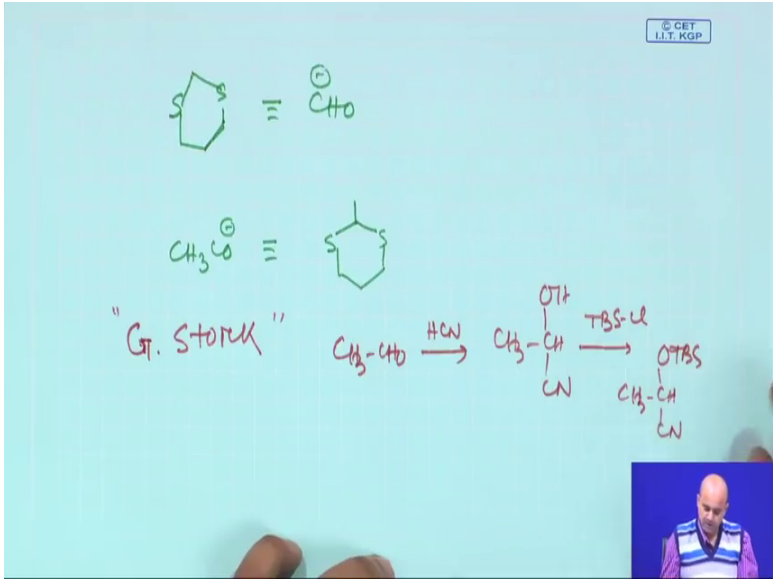

Now are they are any other ways to generate this kind of species I said this is a nice equivalent of formyl anion. Now if I talk about a acetyl anion what are the species you can think about this is already known that this species you can use it.

Now, in this case is quite witting tribute to remember a great organic scientist named Gilbert stork. Now Gilbert stork was using this chemistry of O protected cyanohydrin,

what is this if you have acetaldehyde you react with HCN to get this corresponding cyanohydrins. Now cyanohydrin as I said they are very unstable, you put it this cyanohydrin with a selectively protecting group t b s chloride or this free alcohol. So, this alcohol is now protected as a O TBS CN.

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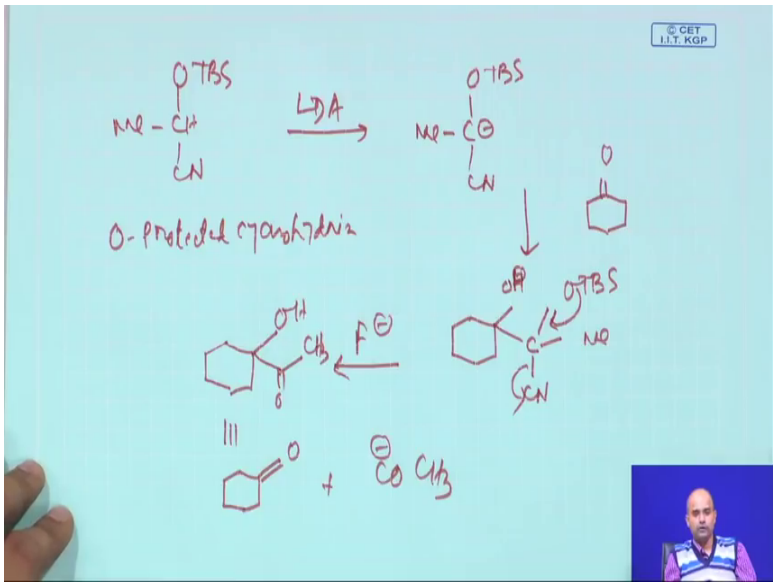

Now this compound is now named as methyl O TBS CN it is called O protected cyanohydrins. Now this compound is treat with a base cyanide with a (Refer Time: 25:57) group we basically get a minus here O TBS. Now this compound now act as a umpolung and here, now if you react with a electrophile like cyclohexanone initially basically you will get O minus C CN methyl your O TBS, everything is fine if you just put a quench with simple methanol you will get a OH plus also.

Now, this oxygen silicon bond can be normally clipped, and here this oxygen silicon bond was normally clipped by some silicon some fluoride species, and then that basically keeps in this way and gives you this. So, in reality at the end we basically get a this compound, now what is this retro this retro is nothing a carbonyl plus a acyl anion. So, acyl anion has been reality in really generated from a O (Refer Time: 27:19) protected cyanohydrins, which is also earlier used very much and professor Gilbert stork was the main pioneer to invent up this O (Refer Time: 27:26) protected cyanohydrins, and normally this is also a very good source of umpolung in addition to your conventional 1 3 dithiane reagent.

So, probably next week we will be talking about something else. So, synthetic equivalents this is the very preliminary discussion we have covered, we will try to cover more of synthetic equivalents, when you talk about a condensed lecture on synthetic equivalents in the final part of our discussion. So, till then goodbye, have a good time.