**A Study Guide in Organic Retrosynthesis: Problem Solving Approach**

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**Lecture – 08**
**Tf/SM/Fg based strategy and it is exploration**

So, we will come back. We are basically discussing transformation based strategies and last week we talked about a very important transformation (Refer Time: 00:25) reaction and you said that transformation based structural starting material based as well as functional group-based strategies are can be combined toget her. And today we will try to continue in the

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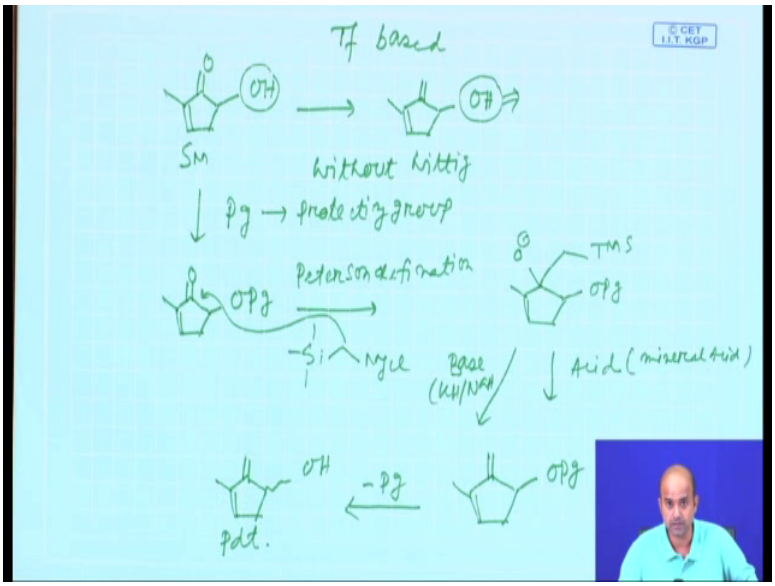


Same area transformation based strategies and the problems which I have picked up now the target is something like this you have a cyclopentanone based starting material, and I said here I give the starting material is starting material and the target I said you have to make a exocyclic methylene compound from this starting material remaining part all remain same.

Now, we said the prerequisite is you cannot use a wittig reaction. You cannot use a wittig reaction wittig reaction. All of us know. So, which you need to know some reaction some transformation without wittig and that is the beauty that there are many other transformations is available the literature where you can create carbon carbon bonds without using the wittig reaction now this particular transformation demands that your starting material having a free alcohol. So, as I said the free alcohols are normally not kept as intact. So, you can think about

protecting the free alcohol the free alcohol. So, you start with protecting the free alcohol, and as we have not discussed the protecting group chemistry 8 which will be discussing later on you just put Pg, Pg stands for protecting group we the suitable protecting group for alcohol any suitable protecting group will be discussing this things little bit later on

So, first protect the alcohol as it is a simple protecting group we put oPg. Now we said you cannot use a wittig reaction the reaction which will be here now is named as Peterson olefination. Now Peterson olefination is a similar kind of reaction a wittig type reaction now the reagent which was used here is a trimethylsilyl CH2 Ng Cl.

Now, the reaction is basically similar t m s CH2 Ng Cl means you have a t m s CH2 minus and NgCl plus. So, the first step is basically you will be oPg is here and will be getting o minus your t m s CH2 basically attach to the carbonyl here and get CH2 t m s. A situation demands next step is basically elimination of this silicone group as well as this oxygen. And this this elimination can be done in both ways you can do it a acid elimination acid mediated or base mediate elimination. Usually acid mediated elimination is simple mineral acids was used mineral acids was used. And base mediated sodium hydride or potassium hydride was usually used and the as I said the mechanism you need to find it out in the (Refer Time: 04:02) because if you focus more on the mechanism part here then will be using tracks.

So, fine eventually in the flights which I will be giving the supplementary materials we will find the mechanism there. So, peterson olefination peterson olefination will basically give you a this kind of simple elimination usually it was found that it can be undergoing acid mediated reaction as well as base mediated reaction know next what you need to do you just need to remove this Pg depending on the protecting group you can basically use the reaction condition. So, this is your now the product molecule. So, peterson olefination is a very important reaction and which will be give you the olefin without using the wittig reaction, basically making a new carbon carbon bond by using a peterson olefination is a purely transformation based approach and try to focus it out whenever you finds similar kind of target molecule give in that you need to be carbon carbon pi bond. Then you can use Peterson olefination as a suitable replacement of wittig reaction.

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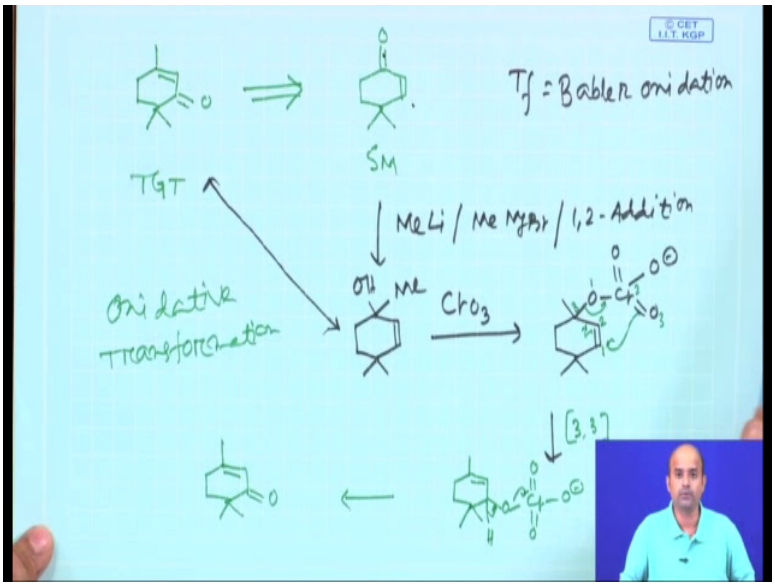


The next target was a similar kind of target again based on a transformation which is I will give you the target. This is the target molecule a target molecule. The transformation I will be also giving you the starting material you see the starting material try to correlate is how this starting material can be correlate with this final product. Now you see the starting material is a cyclohexanone derivative and the final product you have almost similar kind of structural network both this gem dimethyl groups are here, but the ketone group has been changed it is relative position from here it came into here as a starting material is here it basically comes into here to here and one extra methyl group was added.

So, the target molecule has a one extra methyl group is it this reaction if you were not familiar with suitable transformation the transformation which will be now talking about is named as Babbler oxidation, Babbler oxidation is a bit uncommon transformations now see as I said that the target molecule you have a one extra methyl group. So, you need to introduce methyl functionality the starting material is something like this.

So, we will put a methyl lithium or methyl magnesium first. Now as I said until and unless you know the Babbler oxidation this transformation is difficult to visualise. So, you first do a methyl lithium addition and you will get this corresponding grignard addition on a alphabet transformations ketone is a 1 2 addition is a 1 2 addition this compound can undergo 1 4 addition, but we have done a 1 2 addition 1 2 additions are very hard we did not do a soft addition like copper things that will promote the 1 4 audition fine.

Now, if you use try to correlate the carbonate war between the target and this intermediate everything is similar you have 3 methyl you have 3 methyl only thing is the ketone group position needs to be rearranged. Tertiaric alcohol as I said this compounds are perignot tertiaric alcohols undergo oxidation because it do not have a abstractable hydrogen here now here the Babbler oxidation is a important reaction Babbler oxidation is basically oxidative transformation where you treat a tertiary allylic alcohol with chromium based oxidizing agent. You can take simple chromium based oxidizing agent now what happens that basically gives you a initial step you will get a if put the methyl here o Cr double bond o double bond o o minus it is the which is the first intermediate.

Now, if you had a close analysis on the structure you find that this allylic double bond plays the important role is a 1 2 3 is a 1 2 3 is a kind of you just do a room temperature reaction thermal reaction with 3. 3 sigmatropic rearrangement takes place that why it is called oxidative rearrangement and then you find this oxygen is transferred from this chromium to this allylic position which is the final target molecule. So now, you do the absolute transformation what will get double bond from this position. Now has been migrated here and you get a oxygen chromium bond the remaining part remain same.

Now, see the framework has been almost achieved, the framework has been almost achieved. Now eventually you have a abstractable hydrogen here which is essential prerequisites rock to a measure oxidation now this oxidation will takes place. And now basically you will get the desired target molecule which was. So, Babbler oxidation is a very useful transformation we called it is a oxidative transformation, but the re the prerequisites is for Babbler oxidation you need to have a allylic tertiary alcohol, allylic tertiary alcohol.

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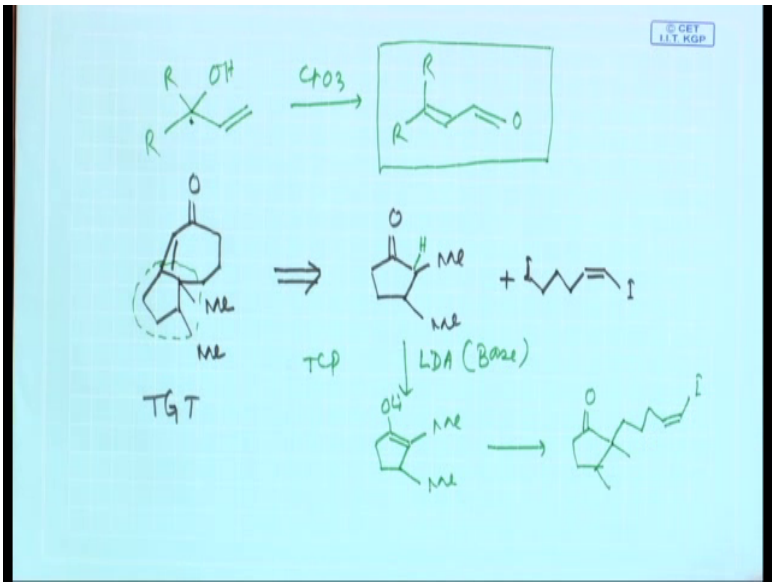


So, in terms of potential little. So, disconnection Babbler oxidation can be regarded as let us say you I am drawing a simple allylic alcohol simple R R OH this is a potentially 3 degree or tertiary ally alcohol this center is having all carbon and 1 oxygen then you subject to this reaction to chromium trioxide the Babbler oxidation the disconnection now what will get will basically get this kind of alpha beta unsaturated aldehyde through a similar kind of mechanism. So, whenever you are trying to have a alpha beta unsaturated aldehyde of this kind of structure you can try to think about it Babbler oxidation protocol. Starting from this starting material. So, Babbler oxidation was very useful for giving you alpha beta unsaturated compound depending on the reaction condition.

Now, based on the same Babbler oxidation our next problem was framed. The next problem the structure is a little bit complicated is a 5 member cyclopentane ring and then you are having it a 7 member ring, is a having a 7 member ring CH 2 CH 2 CH 3 and in addition you are having a methyl group here this is a target molecule target is bit complex, but the hint is will be using a Babbler kind of oxidation , but simplified version I will give you the starting material that what starting material will be you will using will be using a starting material this 2 3 dimethyl cyclopentanone. Which is here methyl methyl and this part the ketone group has been basically replaced.

Now, So, I will give a starting material which is similar, is a vinylic iode as well as aliphatic iode that was starting material was given to you. Now if you do a ratro now you try to

correlate this part this part is basically your this starting material and this part is CH 2 CH 2 CH 2 is CH 2 CH 2 CH 2 only thing is you need to introduce these things now. So, initially will do a lithium di isopropylamide which is the base which is the non nucleophilic base now this compound will try to abstract this hydrogen in thermodynamically controlled enolate the enolate which is most stabilized under this condition will give you this fine, and then you have a electrophile here you do a electrophilic attack out of vinylic iode and these aliphatic iode this is more active.

So, basically you will get a product methyl CH 2 CH 2 CH 2 you have a 3 carbon and then your iodo remain same. So, you get this product fine then what you need to do will basically next try to do a taking the starting material will subject it to

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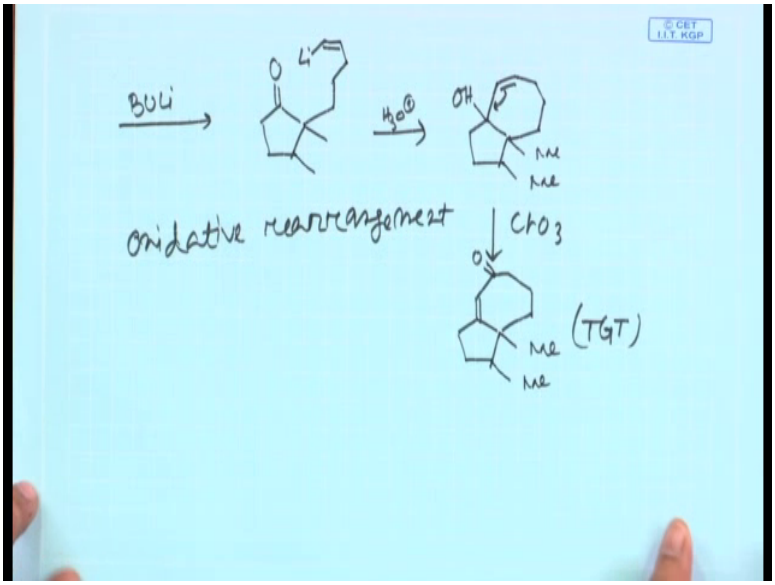


A brutal lithium treatment which will basically give you this vinylic iodo to a vinylic lithium species you put a CH 2 CH 2 CH 2 and then CH 2 CH 2 CH 2 can you try to put this vinylic lithium.

Now, this vinylic lithium will undergo intramolecular nucleophilic addition to give you the 7 member ring which was required. So now, try to draw this thing. So, after intramolecular nucleophilic attack and acidic work up you will basically get, no try to put CH 2 CH 2 CH 2 1 2 3 yes and then you have this methyl this methyl. Now potentially look to the target molecule when we have earlier discussed now what is this compound this compound is a tertiary alcohol, tertiary allylic alcohol now you subject to this Babbler oxidation by

following the similar kind of mechanism now this compound will give you the target molecule which structure is the same which is desired by us, and now basically this o chromium ester which a sigmatropic rearrangement this double bond will basically migrated here and then basically you will get a this kind of structure with this ketone now come to this allylic position 1 2 3 this things. So, this is a target molecule which was given the initial point.

So, until and unless you are quite familiar this Babbler oxidation this potentially useful transformation is by difficult, but eventually now you know the Babbler oxidation and you can now formulate the alpha beta unsaturated compound can be easily generated from tertiary allylic alcohol by oxidative transposition or transformation. So, I called this as a oxidative rearrangement or oxidative transformation oxidative rearrangement and this is the dabbler oxidation which we are a discussion. So, Babbler oxidation potentially very useful reaction and this reaction can be done in a with extreme efficiency and that will give you a good potential useful reaction. So, couple of new reactions we are basically getting familiar.

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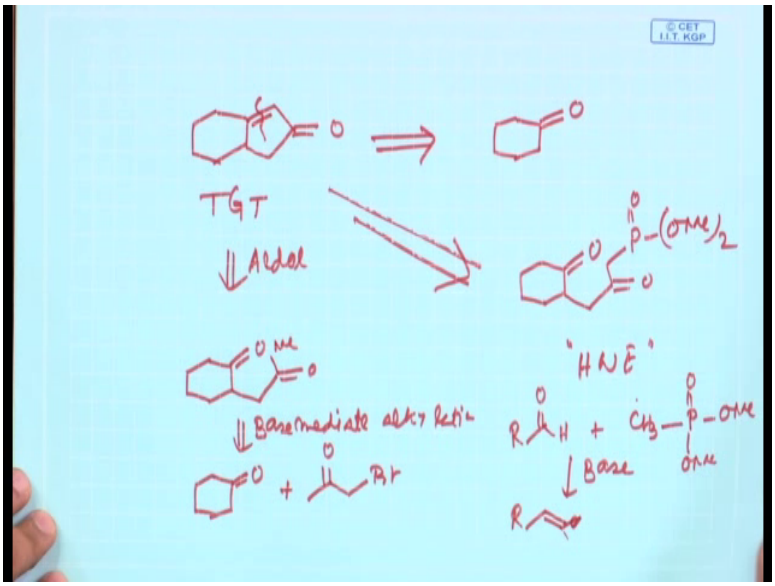


The next target. Next target was a very simplified target. Do I need to be the starting material yeah let see if I give the starting material then probably would job will be little bit easier, and I said I will be giving my starting material like cyclohexanone is a very simple straight forward approach probably has a very beginning you can think about is a alpha beta unsaturated compounds. So, is normal aldol kind of dehydration will give you the product?

So, if you do a retro something like this this is very familiar to all of you. So, you can have one of these compound as a intermediate and you can do aldol transformation find now what you need to do you need to cut down to the starting material or go back to the starting material how the starting material this is fine this you can just want to use a alkylation reaction by using monobromo acetone. You treat a basically is called a base mediated alkylation which is the main transformation base mediated alkylation.

Now, here there are other ways also other ways we can do, I said that if I give a prerequisite that you cannot use aldol reaction as a main disconnection. I have another retro which will now I will discuss and this retro is little bit adventures and then will try to find it out that how this retro is possible. We said a wittig type of reaction can also be thought about now this compound is a named as phosphonate, phosphonate and the transformation we are looking for a horner wadsworth emmons reaction a standard wittig reaction what we do, we react to aldehyde carbolic compound with a wittig right, but here will be reacting a aldehyde or carbolic compound with a phosphonate esters.

Now, phosphonate ester is basically something like these. The mechanism is in principle similar you need a carbon containing group attach to the phosphorus which is having extractable hydrogen and if the reaction occurs in presence of a base you basically get a I mean yeah, I basically get this minus attacks here and you basically get this particular olefins, but depending on the phosphonate which you choose that basically gives you what target you will be getting.

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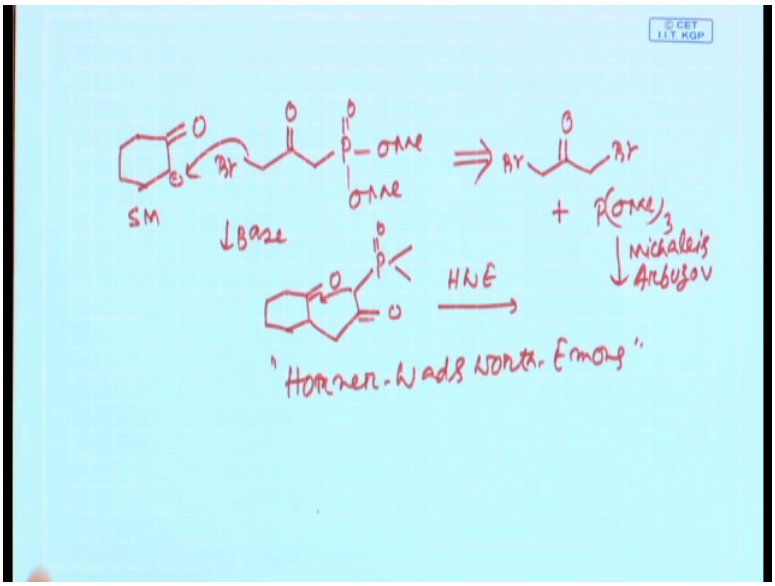


Now, let us coming to the problem which was given to you take the cyclo hexanone and if you having a phosphonate. First you do a I said if you have this starting material and this phosphonate now this phosphonate has 2-part one part is the promo part. So, first did the base it is alkylation. So, minus this comes here will give you a CH 2 these things and then your etonies there and then you are having this P double bond oMe oMe.

Now, this methylene hydrogen you can basically much more acidy as general to the ketone and the phosphonate. Now it will have undergoes intermolecular horner Wadsworth emmons reaction HWE Horner Wadsworth Eemmons reaction. So, please go to the second (Refer Time: 22:34) to have a possible mechanism of this Horner Wadsworth Emmons reaction. Then you may ask that sir how we can make this compound this also easily can be done is a purely transformations based approach and you can do it, will explain this things little bit later on this compounds can be commercially available or even you can make it the base try to make this compound is basically, start starting from this kind of compound you take this dibromo acetone and react to it tri methyl phosphite the transformation named as michaelis arbuzov reaction, michaelis arbuzov reaction you can search in the (Refer Time: 23:26) to get a idea of michaelis arbuzov reaction, but that is basically a very nice reaction and is equivalent to horner I mean this this michaelis arbuzov reaction is very good reaction which will give you the corresponding ketone phosphonate.

Now, this with this ketone phosphonate you can do a witting type of reaction which is named as Horner Wadsworth Emmons reaction. Now what are the reactions we know learnt till date we have talked about this Babbler oxidation is a very useful sapphic reaction Horner Wadsworth Emmons reaction, Peterson olefination. So, all the basically kind of a very new transformation and particular this Horner Wadsworth Emmons reaction, Peterson olefination are basically carbon carbon bond forming reaction. So, transformations based approach are basically a dealing with different kind of transformation which are key transformation key means single is transformations.

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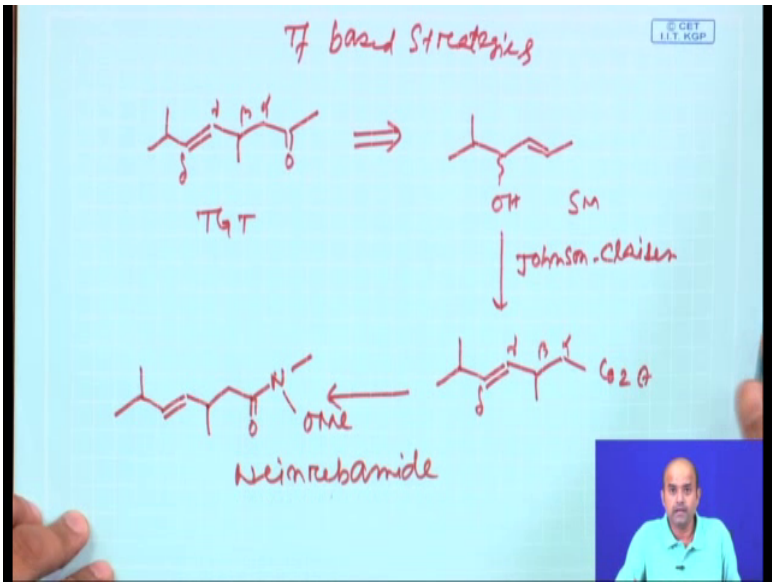


The next transformation base strategies which will be talking about is a transformation based on a very unique reaction and this I am sure all of you know it, this we have already discussed couple of times. I will giving a target something like this. And I have given you the starting material also starting material was given to you. This simple we have already discussed it if you now go back to the earlier lecture notes this is a alpha beta gamma delta unsaturated compound is basically gamma delta unsaturated compound. So, gamma delta unsaturated compound straight wise you can think about a doing a Johnson orthoester rearrangement. The starting material is a allylic alcohol starting material was given to you.

So now subject to the; our known reaction Johnson claisen rearrangement or Johnson orthoester rearrangement. It will basically give you do this reaction in your lessor time and you will find the compound which will be you will be getting is this compound. So now, what

is this? This is a alpha, beta, gamma, delta is a gamma delta unsaturated resisters now try to correlate this target molecule the target molecule only thing is you require a extra ketone methyl group.

Now, we say this esters are highly reactive if you react with Grignard reagent will basically give you access Grignard addition. So, we will be trying to convert this esters to a less reactive compound and normally do it through a amide. Now this particular amide is named as weinrub amid weinrub amid, next will be talking about a particular transformation.

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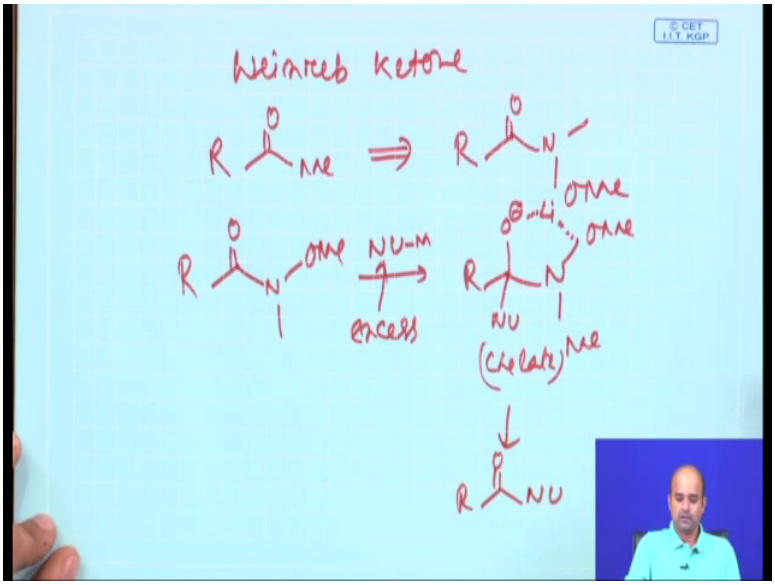


In continuation with these is a Weinrub ketone synthesis the disconnection is basically something like this we said esters are very reactive. So, you need a software regent which are less active. So, you take the corresponding amide which is now named as Weinrub amide react with a nucleophile a Grignard or something. What will get you basically get the nucleophile if it is having a middle continue in nucleophile or lithium or magnesium you will have a this kind of chelate now this chelate is exceptionally stable this chelate is exceptionally stable and that will stop the further neutrophilic addition

So, once you make this Weinrub amide this will if you use excess nucleophile does not matter it will stop the reaction. At the; this position now you basically going to this things you nucleophile will definitely here you going to be acidic work of will basically get the corresponding ketone back. So, coming to the original

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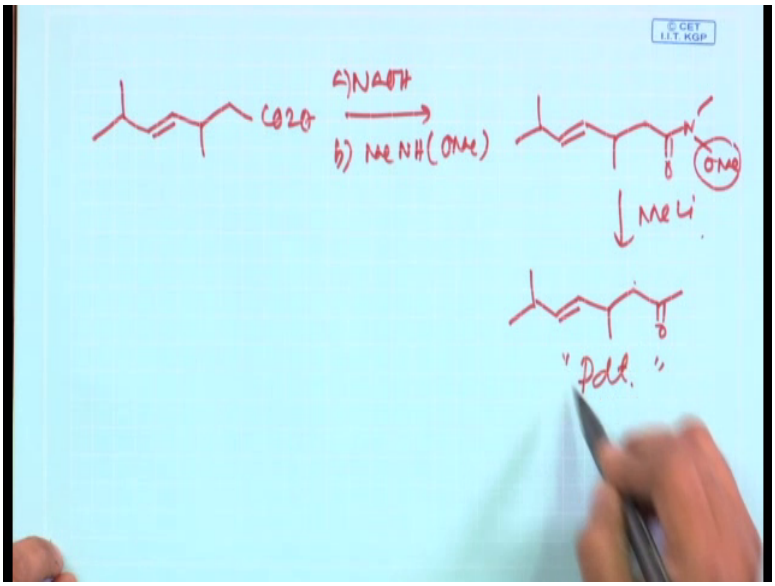


Problem which was just discussing the initial target molecule or initial intermediate of the johnson creezen thing, you getting these corresponding carboxylic acid you hydrolyse these the acid with a base and react with this NENHONE which is the Weinrub amide or Weinrub amide, you will get the corresponding Weinrub amide, you react with methyl lithium or methyl magnesium bromide you will get the target molecule.

So, that basically complete the synthesis and the final compound is again a gamma delta unsaturated target molecule which is our main target gamma delta unsaturated ketone, alpha beta gamma delta. So, weinrub kitone in this is was one of the important synthesis where you can essentially tune the reactivity of a amide esters are highly reactive that is what if your subjecting excess nucleophilic reagent like the grignard reagent to ester that will give you tertiary alcohol, ketone stop the reaction at ketone point, but if you can convert the ester to a amide mild the weinrub amide the ONE group was judiciously chosen the ONE group and that is way the ONE group has been judiciously chosen to stop the reaction at the (Refer Time: 30:05) stage no matter if you can use excess nucleophilic is like Grignard.

The reaction will stop here then you do the acidic quenching you get the one equivalent of nucleophile transferred to the corresponding carbolic compound you will get the corresponding ketone. It is next week will be back to back with more and you can discuss or you can continue our discussion based on this transformation functional as well as starting material-based strategies hope you are enjoying the lecture.

Thank you.