A Study Guide in Organic Retrosynthesis: Problem Solving Approach.

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Lecture – 60
Concluding Remarks

Welcome back students. As discussed in this earlier lecture today, basically will be the final, lecture of this entire course work and today what we are trying to do? I will, I have picked up a molecule medium sized natural product as a target molecule and we will try to explore all our acquired knowledge. So, that your main idea or take home message should be if you are given a target, how you should approach the molecule from, it is, initial perspective means.

First start with a visual dialogue, then, do the psycho biology of the synthesis or psycho analysis of the synthesis; means your visual thing will start at the beginning, want to see the molecule then try to apply all the tools, which you have already acquired. Tools mean; you apply transformation based strategies, a functional group based strategies, starting material based strategies try to analyse the key structural features in the given molecule.

If there are some stereochemistry's involved that is very important, then if the molecule is topologically unique, try to analyse it is topology and then try to figure it out, whether topological based strategies will be of any help then finally, do the forward synthesis and, and try to complete the story. So, the molecule which I am now going to discuss the molecule structure first I am going to write it down the structure of the molecule basically.

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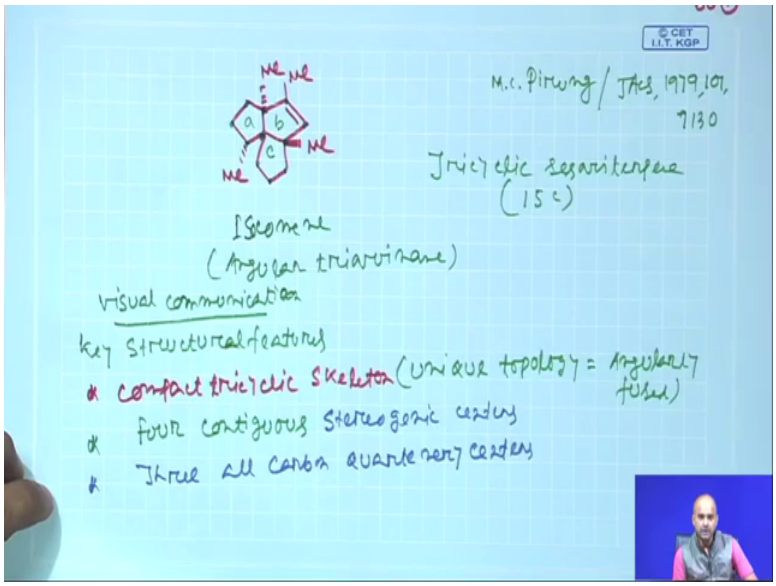

We have already discussed similar kind of structure is angular triquinane, triquinane. We says triquinane is a very interesting framework or a topology, topology based framework, which is very, very much abandoned in the nature and this particular angular triquinane is a unique class of natural product and I was seeing structural features. The molecule is named as isocomene, isocomene, isocomene. It is a angular triquinane. It falls in the class of angular triquinane, the molecule does not have any active functionality, except a Olefinic unsaturation the synthesis, which I am going to discuss is first reported by Professor Michael Pirung in a Jacs paper.

If you want the paper, I can send it to you. It was done in 1979 quite long ago. Now, this particular molecule as I said, if you count the number of carbon it is a tricyclic sesquiterpene, sesquiterpene. You often says, they contains a 15 carbon in it is framework. Now, start counting it 1 1 2 3 4 5 6 7 8 9 10 11, then you have this 4 methyl, which counts for say 15. Now, as I said, initially start the visual communication, visual communication, with your molecule visual communication means; your visual dialogue initially, I said you need to find it out, what are the key structural element in this given molecule or key structural features.

Now, if you see structural features, I will try to write it out. This molecule has a compact tricyclic, I will write it down compact tricyclic skeleton, but the tricyclic skeleton has a unique topology. Having a unique topology means it is angularly fused. Now, what is the

topology; is angularly fused, angularly fused the a b 2, ring is linearly fused with this series angularly featured with every ring is angularly fused, that topology is pretty important. Now, the next part, I am saying four contiguous, four contiguous carbon, which basically stereogenic, stereogenic. Basically, we are not going to discuss about the stereogenic stereochemical strategies, but if you see, what are those is the 1 2 3 4. Now, contiguous means, they are basically kind of continuous, they are continuous array is a continuous, four contiguous. You can say stereogenic centre ok.

Then you are having three quaternary, three, all carbon quaternary centre. You see this 1, this 2, this 3, this is also contiguous three, all carbon quaternary centres. So, these are the main structural features, which will, be seeing in this molecule and, from the very beginning, you can say that as there is no active functionality, probably some type of, redundant functionality, you have to think about. Anyway, we will, try to analyse, how this, things can be done.

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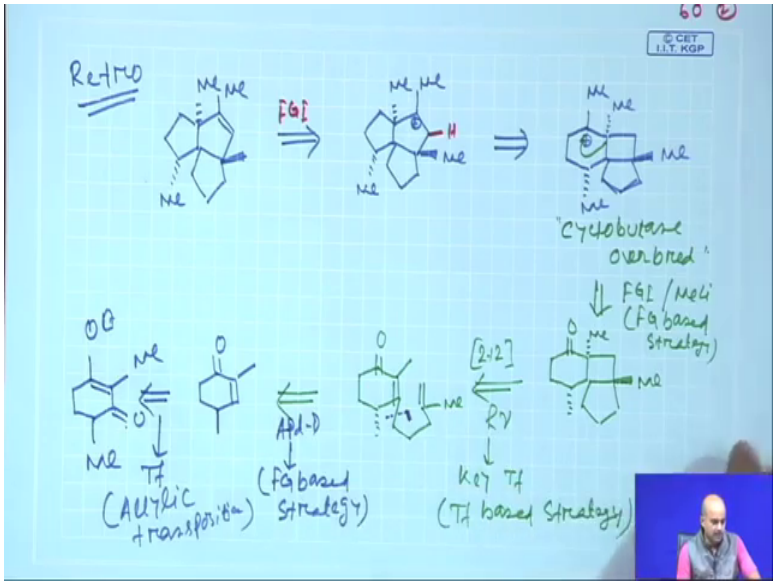

So, now coming to the retro, coming to the initial retro we first, start doing a, doing a mental analysis by the information, which was given to us at this moment. So, the starting material sorry, the target will first. Write it again. The target is basically, basically complex. It is not that easy target, it is not that easy target, because there is absolutely no functional group. So, initially I am saying that as this target, it is the only active functional group is methyl functionality.

Probably this, olefinic sorry, this olefinic unsaturation can be created by the simple elimination reaction, which all of us quite familiar. The stereochemistry part is basically, will keep it as it is. Why I am saying that if you are having this 3 degree carbony amine, which can eliminate this hydrogen. So, this is basically a F G I, simple F G I; so normal elimination ok, now fine.

Now, this carbonyl amine, this carbonyl amine, how you can generate a 3 degree carbonyl amine absolutely stable, there is no issue. So, if you can put some O H or something. Here, it is possible, it is definitely possible, but what we say this five member, five member, five member, this particular array, probably seems to be little bit complicated structure.

Normally five member, though five member ring containing starting materials, are easily available, but as we have generated a 3 degree carbonyl amine, we just wondering, if this kind of carbonyl amine can also be generated, by some, by some, by some rearrangement or some migration. So, now, we are trying to guide you through another reaction, which I am now basically, focusing I am just opposing the retro as the synthesis was reported by Professor Pirung. We are trying to exactly follow the retro, which he has, he has devised.

Now, professor Pirung says, if you have, this kind of carbonyl amine this also 3 degree. Now, this is a six member ring, fused with a four member ring, angularly fused with a five member ring. Now, what was proposed, if this carbonyl amine is generated in the reaction mixture is a four member ring. So, a cyclobutane overbred. So, now, you try to apply your topology based strategies, this cyclobutane overbred, overbred. So, a topology is coming into picture, we said that in the overbred intermediate, you create some intermediate, which will be definitely strained.

Now, if it undergoes a one to migration here, you will get the, another 3 degree carbonyl amine, but the strain of four member ring has been released fine. So, you get this 5 5 5 system. Now; obviously,, what will give you this four member ring access. Now, four member as we said, we already discussed at the most elegant way to access four member rings is 2 plus 2 cyclo addition reaction fine, we will now, try to analyse how it can be done. Now, I was saying that if you having this particular compound in the beginning, you just do a F G I through a methyl lithium addition. So, take this ketone do a methyl

lithium addition, then do the quarter elimination. So, this is F G I functional group inter conversion. So, your functional group based strategies is applicable ok.

Now, we are trying to analyse the by saying that a retro 2 plus 2 would be probably feasible. Now, what I am saying? I am saying that ok, if you have compound like this olefin and then I am, draw it in this way. Now, if you have this compound a substituted cyclohexanone system, you can easily do a 2 plus 2 reaction. Now, what is this? This is your key transformation. So, your transformation based strategies is coming into picture fine. Now, I am saying that ok. So, you are almost close or something like that.

So, next, I am saying that, this particular appendage. This particular appendage, you can easily constructed, if you have a compound like this, this particular compound, if you have a just putting a appendage with this. Now, this is basically a appendage based discussion, which is also we covered in the functional group based strategies F G based strategies appendage. How to disconnect by simple F G based strategies now, I saying that ok. This particular compound, this particular compound, you can easily, easily I mean, you can basically, do this entire, entire conformation by, if you having a this, this particular 1 3 dike tone derivative and you do a Grignard reaction.

Now, this kind of allylic transposition, we have already, already talked about. This is a very unique transformation, if you remember, earlier we talked about this allylic transposition. Allylic transposition means, the allylic double bond has been kind of rearranged this from this. Here, it basically rearranged to here with this incoming nucleophile and then simplifying the starting material, you can then try to figure it out that, this would be easily start from this 1 3 cyclohexanedione.

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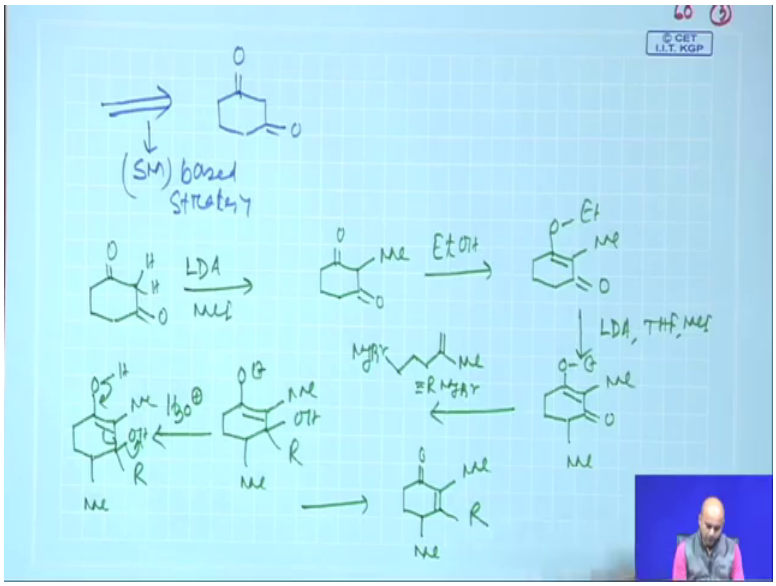

So, this is basically a starting material based strategy, starting material based strategy. So, now we will try to analyse how this start starting material can be related to the intermediate initially, if you see a methyl group has to basically, introduced here. So, we try to do we will just use a L D A methyl iodide, because most acidic hydrogen's are here; so the first methyl which is introduced in this way. So, this compound is 1 3 diketone.

So, it will be seems to be tautomerized and will exist in particularly this kind of enol ether, this is known ok. Now, this enol ether; now, you see the structure, this, there should be another methyl, which needs to be introduced at this carbonyl. So, again we will be doing another round of L D A T H F and methyl iodide. Now, you will be getting this compound. So, two methyl group has been introduced, now your allylic transposition has to taken place. Now, the particular appendage, which you need to introduce will be having, just go back to the earlier page, we will find that you basically need this appendages.

So, what we try we will take a Grignard something like this and you add two particularly this things. Now, we will say that this Grignard we, we write it as a R M g B r to explain the mechanism to you. So, here is the O E t, here is the methyl, here is the methyl, the Grignard is now, O H R R is the entire group.

Now, I am saying this allylic transposition, you just react with a acquas acidic workup, the vinylic ether will be first hydrolysed to give you O H, you have a methyl. Here you have a methyl, here you have a O H and R. Now, this vinyl ether will now, tend to rearrange it is double bond to give you a ketone, whose structure is this, methyl is there, this double bond is there, this R.

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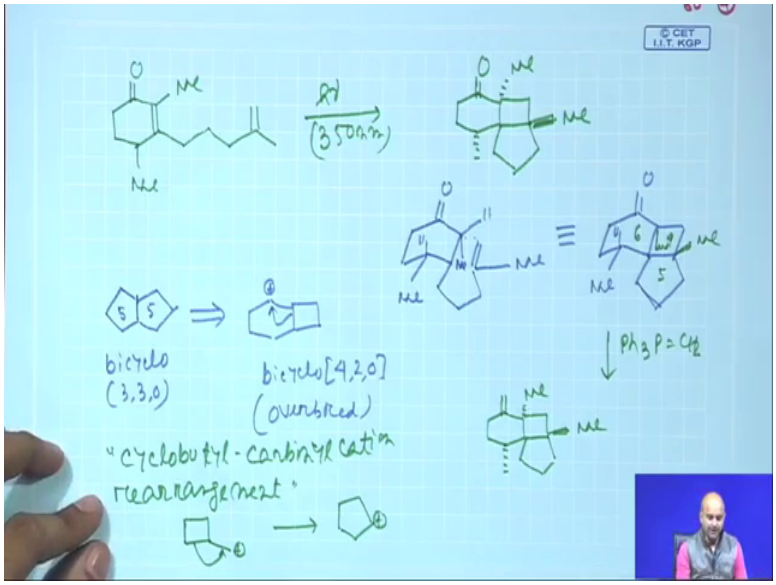

So, now this is your allylic transposition. So, now we will again writing the particular intermediate, which we got. Now, this intermediate, if you now draw this, structure, let us draw it in this way. There are 3 methyl double bond, this things.

So, things are now ready for this cyclo addition reaction. Now, this cyclo addition reaction, it was done in a H nu a 350 nanometre light source was used. It is found that the cyclohexanone, the relative stereochemistry of this particular product, which you obtain after this cyclo addition is basically, this one, this one. Now,,, we are just trying to analyse, how this stereochemistry?.

You might get, I am saying that the, the parent cyclohexane might exhibit in this conformational behaviour, because this is a half chair kind of thing and then you are having this, this, this, this and then this double bond and then your, the methyl. This methyl and this methyl is a pseudo equatorial, pseudo actial. So, this methyl is seems to be the below and this methyl seems to be this way.

Then this is 2 plus 2 takes place, and finally, the stereochemistry of this cyclic product, which you will get. The methyl is below the plane, hydrogen is here. Now, close this ring in this way and then try to figure it out, the cyclopentane ring. Now, where you say that the transition state will be trying to have this methyl below and this methyl will be above in this cyclobutane ring, to avoid the steric interaction in the t s.

So, this stereochemistry also you can explain in terms of, ground state conformation energy and then. So, you have this overbred, it is kind of overbred your basically; so this topology linear 6 4. So, 6 4 and 5, this topology you have been basically, created fine, your next part will be quite easy. So, next, what we do? You do a simple wittig reaction. So, wittig reaction will basically giving you everything remains same, this is your methyl a x o cyclic double bond will be just created right.

Now, before this final step of this reaction I will, try to give you a another thing, if you see the target molecule were basically having a five member, five member in the linear fashion. So, this structure is a having a topology bicyclo 3 3 0 3 3 0. Now, what you are saying that this particular topology can be, can be constructed, if you having a this carbonyl amine, which is now bicyclo 4 2 0 4 2 0. We are saying that this is overbred. So, this is overbred and this is having a straight four member ring. It will basically, undergo 1 2 rearrangement. Now, these particular rearrangements sometimes refer referred as cyclobutyl, cyclobutyl carbinyl cation rearrangement.

So, this particular cyclobutyl, cyclobutyl carbinyl, cyclobutyl carbinyl rearrangement. So, it basically says that, if you having a system like this, it will tend to rearrange to give you a more stable cyclo pentyl cation. So, we are almost finishing stage of the synthesis.

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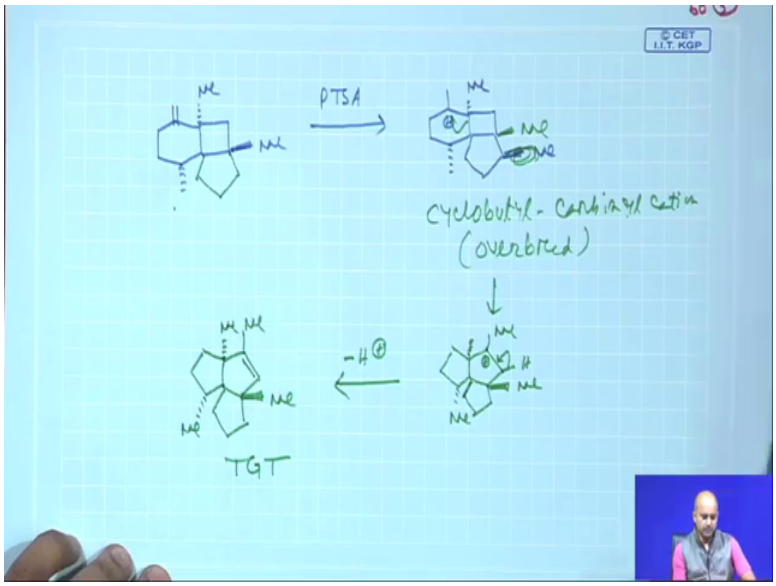

Now, we will again draw the structure of the wittig intermediate, which we obtained. Now, this x o cyclic double bond is here and your overbred is basically here. Now, we will be doing the standard cyclobutyl carbinyl cation rearrangement. So, this compound was just subjected to a little bit acid, simple acid probably not too strong acid, patronic sulphonic acid and it is found that initially you get this this methyl, remain same. All the, that is stereochemistry remains similar. Now, this is what this, you just now explained is a cyclobutyl cyclobutyl carbinyl cation.

So, this cation is a overbred is basically, overbred is a overbred and this will basically migrate to here and if it migrates, you will basically get the cyclopentene pentane system. So, now, you try to figure it out, you will get the cyclopentane system and this cyclopentane system will now having this. This one is the ring fused here, no sorry. This methyl is not here, this is basically here ok.

This structure is I did not write it ok, it just small mistakes. So, then you will get this angular methyl here and this methyl you get this things and you get this methyl fine. So, a cyclobutyl system is undergoing rearrangement to, to a cyclo pentane based system. So, strain has been released, the only thing is now, your elimination, this elimination. Now, takes place and then you basically get the final product. Your methyl is here, your double bond and this methyl.

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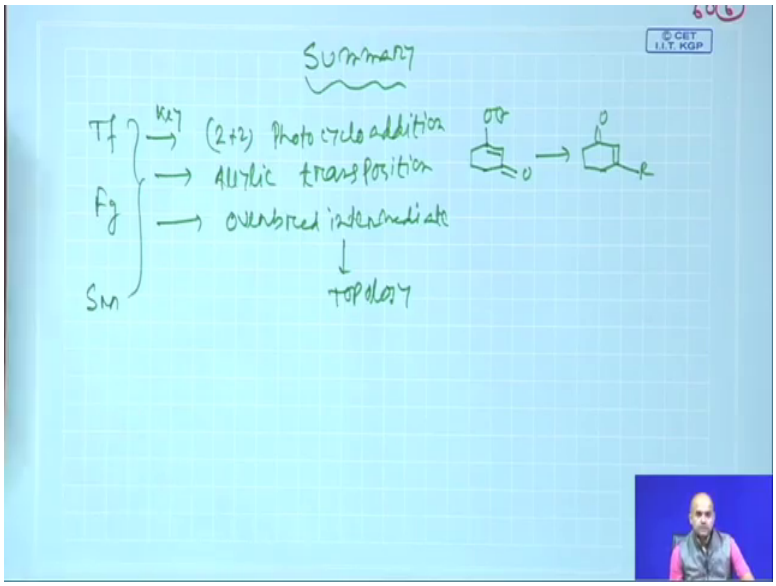

So, target molecule now, has been achieved. Now, in, if you try to do the summary of the whole synthesis, summary of the whole synthesis, write transformation functional starting material, which are this things, we always combine. So, transformation what we used, the key transformation a 2 plus 2 photo cyclo addition it. It was absolutely useful before that you basically, used this allylic transposition system. Allylic transposition of these kind of vinylic ether to give you a, target molecule, something like this.

These are transposition, we used and we also used this, overbred based intermediate overbred intermediate, which will falls into the class of topology and in addition, we, was explained the stereochemistry, which a gives you a, gives you final access of this target molecule; so now, as we are having relatively few minutes left.

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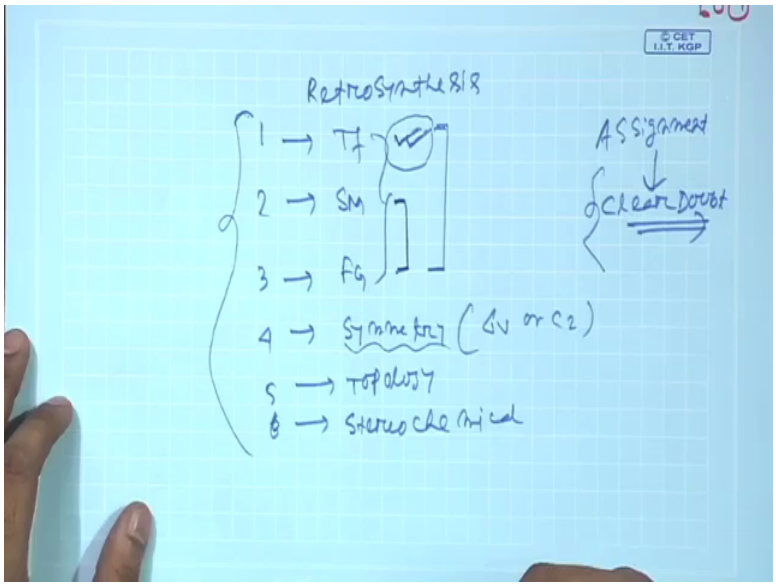

So, this particular retrosynthesis, if you can now, try to formulate. There are six guidelines as you say starting transformation, starting material functional group, which will always combined in three aspects. The symmetry will be coming into picture, when you dealing with the symmetrical molecule and we said mainly sigma V or C 2 is very important.

Now, C 2 is also very important, when you talking about a C 2 symmetric molecule. We explained today, core response and dimension strategy topology. Topology is absolutely important for cyclic molecule and the molecule, which you have just now, discussed, isocomene as a unique topology and finally, stereochemical strategies is very important, when you are trying to make the molecules in enantio selective or enantio pure fashion.

So, you basically need to be muster or all this six different aspects. Now, to gain enough control of your, entire design or entire pathway, you basically need to know what are the transformations or unique transformation. Standard transformation are known in the literature or textbooks, but sometimes very unknown transformation, but in this, in this lecture, we talked about some reaction like demio reaction, barton nitrite ester photolysis reaction.

Those reaction probably are not explained in detail, in many textbooks, those are very important transformation. Now, starting material and functional group, you basically have a close analysis of the functional group in a given molecule then try to correlate the

starting material and then basically, transformation is your linking point between starting material and functional group that is what we said a same T f and F G should be in a combinative fashion. Symmetry will always come into picture. Symmetry has a nice aspects and as we, discussed symmetry controlled reaction.

We have been discussed topology is a very unique feature, stereochemistry definitely the core features, but you need to be master on the topic, because stereochemical phenomena, to have a deep understanding, you need to visualize as the molecule in a three dimensional way and what are the governing factors to dictate that whether you are creating a when you are creating a new stereo centres? What will be the absolute configuration of the newly generated stereo centres. So, try to follow the entire lectures, as entire lecture I have gone through a standard writing methods. There might be some minor mistakes, which I may have over looked.

So, if you find some mistakes, you just,, try to point it out that sir you did some mistake. I will be happy to rectify those things, because it happen sometimes, human error comes and we do some mistake, because entire part I am just drawing it. So, in the drawing process may be I do some mistakes, try to do solve the assignments. The assignments solving will basically, help you to boost your confidence even, even if you see that entire course work. We just, followed the tradition of a assignment solving approaches, we give you couple of assignments or problems then to solve those problems.

What are the essential knowledge you required sometimes? Some of the reactions I may not discussed in detail about that mechanism, because time is not there, but I have given you enough hint, when it sometimes I may not write something, but I talk little bit more words. So, try to, try to listen what I said and then the key words, based on the key words or key transformation, which you have written may be the Stetter reaction. The mechanism was not explained in detail, but Stetter reaction, if you can give a search in the, standard search engine Google or Wikipedia, you will get the information.

So, those information will basically help you and as it is a, 30 hours course definitely, it is a kind of condensed course. So, you have absolutely, no control of the time sometimes, many important reactions. We have to over look due to time constraint. So, that is why assignment solving will help you, to give you a very assignments, which will be, which

will be provided, to you and try to solve those assignments and if you have doubt we can clear the doubts, doubt clearing, doubt clearing is a very important session.

So, any doubts you can always get it, get it clarified by me or you can consult your respective teachers, who will be helping you to clarify the doubts, but as I am saying the synthetic, the only synthesis chemistry or synthetic chemistry or particularly principles of amine synthesis retro synthesis is, absolutely or immensely important subject, if you want to excel, want to explore further dimensions, further horizons in this particular field, go through the lecture notes, go through the, assignments and try to get more information from outside sources.

There are plenty of sources as I said syn archive is a very good source to give you a firsthand information and if you start liking this particular subject I will be very happy, because, my and then coming for the exam purpose, this, exams like all India based competitive exams NEET GATE JAM all those exams, probably. If you start solving their question papers, you, download their question papers for last 10 years, try to solve it. Particularly this organic synthesis based problems, if you have doubts, you can just go through the lecture notes. If the question answer was given is fine otherwise, try to solve it based on your knowledge, which you gained through this course work.

Now, again, I will stop it with this particular word (Refer Time: 35:13) synthesis, such a discipline you can basically, love it or hate it, but you cannot ignore it. So, have a good time, have a safe time, till then goodbye.

Thank you.