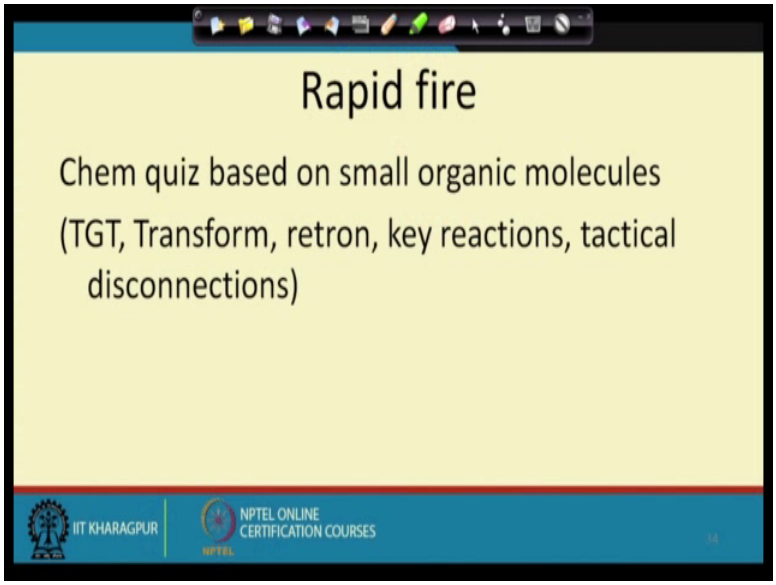
**A Study Guide in Organic Retrosynthesis: Problem Solving Approach**

**Prof. Samik Nanda**
**Department of Chemistry**
**Indian Institute of Technology, Kharagpur**

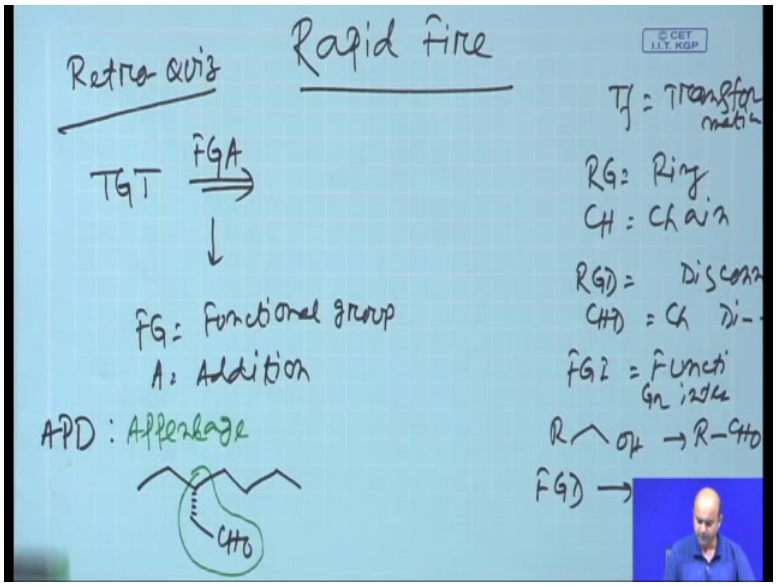
**Lecture – 03**
**Introductory Remarks and Some Rapid Fire Quiz**

(Refer Slide Time: 00:18)




So, welcome back students. So, as we basically continued throughout our discussion, and today what we are going to do we will be trying to do a rapid fire round to basically test your knowledge.

(Refer Slide Time: 00:24)




And this rapid fire round is basically based on some of the quiz chemical quiz and it is basically based on small organic molecules, and how you can solve those transformation. I gave them name as a retro quiz, which are basically based on retro quiz. Now, it during the starting this retro quiz we will talk about different terminologies, probably you are familiar with this terminology which is called TGT - the target molecule.

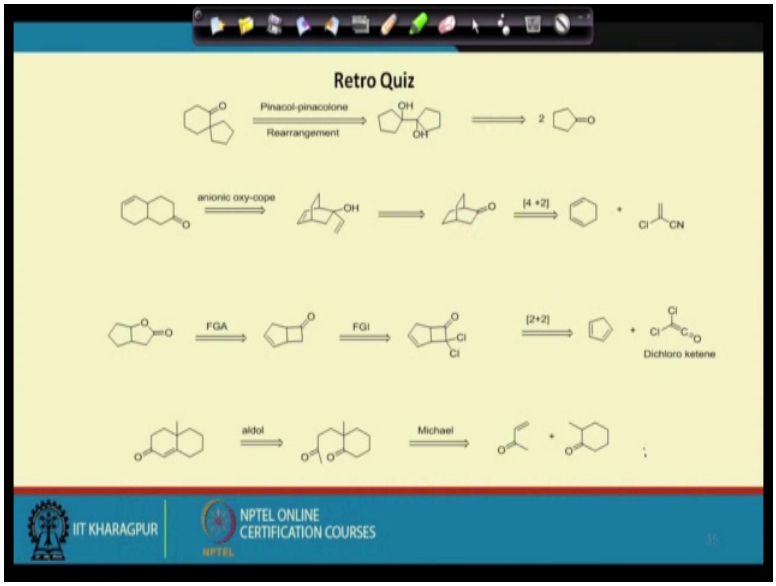
Now, I am trying to put some abbreviation which you may not heard it, it is called FGA FGA stands for functional group functional group functional group, any functional group can be called as a FG, A stands for addition. So, if your transformation is gives a functional group addition in the target molecule that is called a GA. And you can also abbreviate it different other terminologies let us say TF stands for transformation stands for transformation. Any potential chemical reaction can be called as transformation. RG, RG stands for ring if your target molecule having a ring is called RG. CH, CH stands for chain sometimes if you have a cyclic chain then the molecule is called chain RG is there.

Now, if you say RGD which stands for ring disconnection; D stands for disconnection. If you have CHD, so chain disconnection. So, these are the common terminologies you can be we will be often using. TGT all of you know target this terminology is called FGI is called functional group interconversion let us say you are having a alcohol you are making it aldehyde, so that is basically give you a functional group interconversion it is called FGI functional group interconversion. So, there are other terminologies like

functional group D stands for functional group disconnection or functional group deletion those are the points.

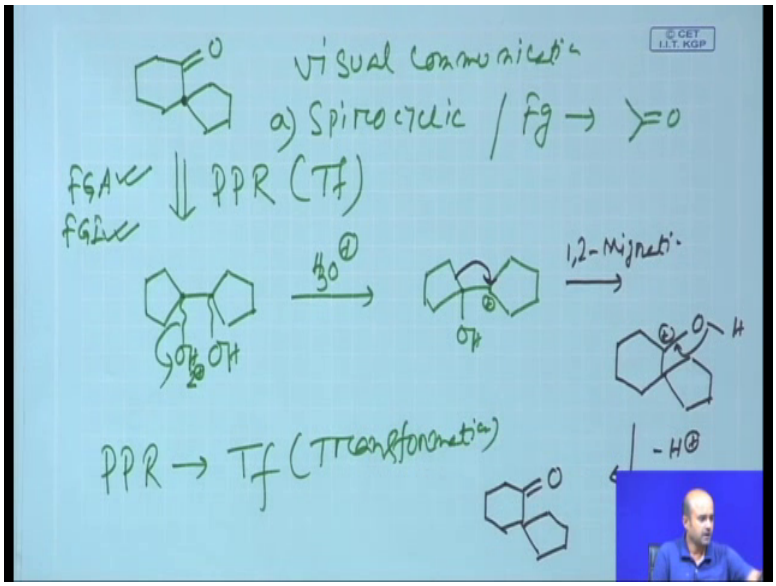
One terminology is for all of you are not familiar is called appendage. Now, what are appendages, appendages sometimes are called to such groups, which are basically hanging through a linear chain. Let us say this is a linear chain and this particular group which is hanging though this linear chain is called the appendage. So, CH 2 CH O, which is hanging here is called appendage. So, appendage are basically good point of disconnection. So, normally we will try to figure it out those different things in our retro quiz or rapid-fire quiz.

(Refer Slide Time: 03:30)




Start the game.

(Refer Slide Time: 03:34)




The very beginning we have a molecule which basically you can see it see the molecule it is a basically a cyclopentane and a cyclohexane based compound, it is a spirocycle compound. So, and as I said you start with a start a visual dialogue with this molecule or visual communication. Now, what is said it is said that this molecule is having a spirocycle structure; spirocycles are nothing basically having a good spirocyclic structure a cyclic connectivity good cyclic connectivity, this point the spirocycles. Then the functional group content functional group content FG content is having a only a carbonyl group ketone nothing else fine.

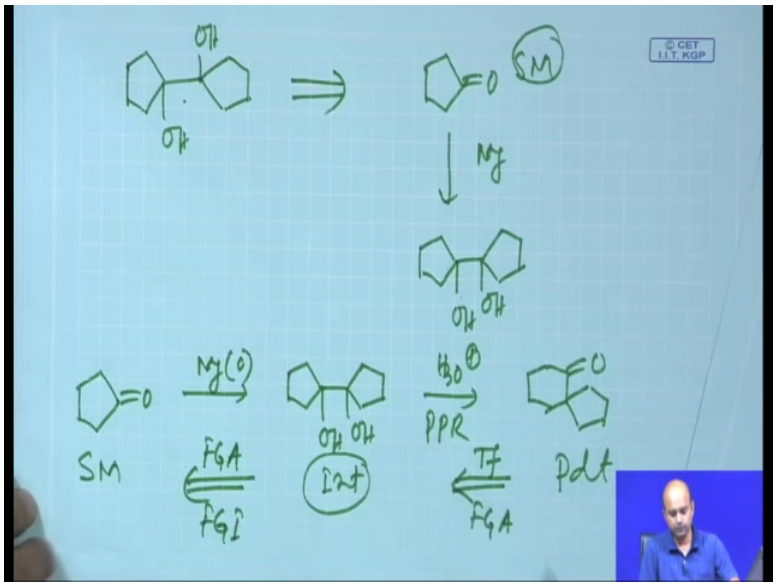
Eventually as I said if you are familiar with certain reaction this retro will be very straight forward to you. How? The site says that a pinacol pinacolone rearrangement PPR. Now, what is PPR? PPR probably all of you know pinacol-pinacolone rearrangement is a very conventional organic synthesis transformation. Now, PPR is basically transformation, it is a transformation. And also you can call it as a functional group addition or functional group interconversion because this is the starting material you are starting with. You do a pinacol pinacolone rearrangement I will be coming what is pinacol pinacolone rearrangement. And then this starting compound is having a diol functionality diol, but the final compound you are not having it, you are having ketone. So, you can call it as a functional group interconversion as well as functional group addition, because a new functional group has been introduced.

So, pinacol pinacolone rearrangement is a very interesting rearrangement which basically takes part in presence of mineral acid, you subjected this compound is a mineral acid one of the OH group will undergo elimination by a water I mean water elimination takes place and basically you will getting a carbonium ion here. So, this OH we said so you will be getting a carbonium ion here, and this carbonium ion will undergo 1-2 migration one of these things will basically migrate. So, this is 1, 2-migration. And after 1, 2-migration you will basically get.

Let us see the structure now. So, this green bond migrates to this carbocation is of definition centre then what you get you basically get a cyclohexane system and a cyclopentane system with a OH and H 2 division centre fine. So, next is simple H plus removal to neutralize the charge, you will get the target molecule. So, I said this is very simple, because if you are familiar with the pinnacle pinacolone rearrangement, your job is half done or even 90 percent done.

So, pinacol pinacolone rearrangement is the crucial reaction, PPR reaction is a crucial reaction or we will often use the terminology transformation, it is a transformation it is the transformation, we will be using it, transformation. And the conventional retro pathway or the retro arrow, this is the retro arrow retro arrow we are often used. You see in the slide here retro arrow it is the retro arrow, we often used. Retro arrow is the main thing. Now this particular starting material as I said particular starting material how we can make it the diol.

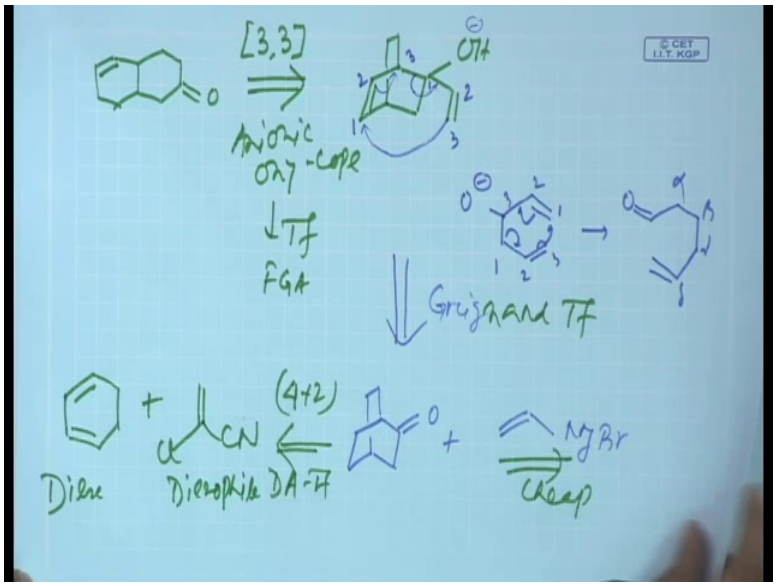
(Refer Slide Time: 07:39)




This diol eventually can be made from a simple commercially available cyclopentanone. To do an another retro by putting cyclopentanone. Cyclopentanone if you react with magnesium simple magnesium that will basically give you a radical-radical coupling, and then you will get this diol which you can find in the standard textbook. So, this is the chief starting material. So, your entire pathway will now having this picture, we start with cyclopentanone, do a magnesium mediated coupling, you get this diol, this is your forward pathway as I am saying, then you do a pinacol pinacolone rearrangement which is PPR, and then finally, you get the your target molecule.

So, this is the entire pathway it is a three steps pathway. Your starting material, this is one of the intermediate and this is the final product. And these arrows are basically forward arrow, but when you write the retro pathway you start with these you give a backward arrow something like this and you come to the starting material. Here you put a transformation, which is called pinacol pinacolone rearrangement or you can call FGA functional group addition. Here is the intermediate again you can call FGA, because initial starting material having ketonel; the intermediate which is having diol it is a FGI functional group addition or even you can call it as functional group interconversion. So, this is the simplified version of a retro synthetic pathway we will try to follow throughout out discussion and that will basically should not be too much complicated we will try exercise this practice throughout our course work.

(Refer Slide Time: 09:42)



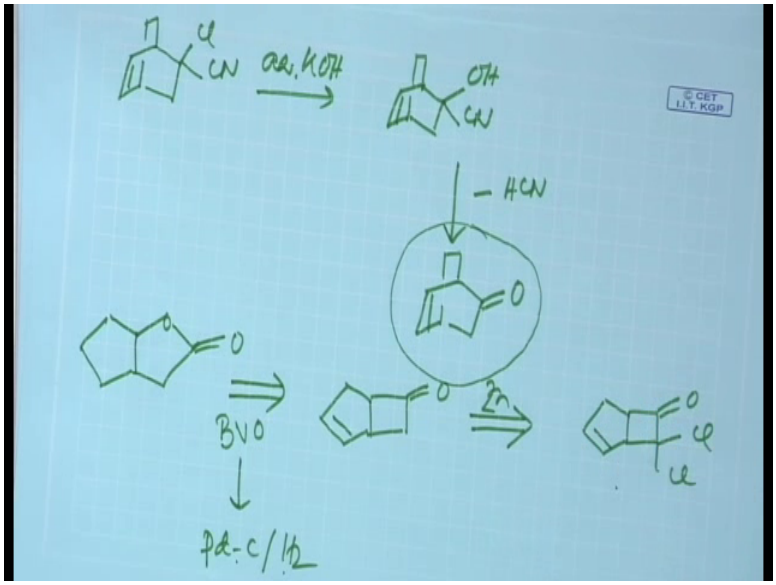

So, we will try to have a little bit complex molecules, let us come to a molecule which is bit complex it is a bicyclic molecule I said it is a bicyclic molecule and as I said this it is basically to test your knowledge. Now, if you are familiar with a reaction named as anionic oxy-cope, this should not be a problem to you. So, I said draw a retro arrow and now the slideshow will basically give you a things. Now, I am not sure whether you are quite familiar with this particular transformation, but it is basically a unique transformation which basically based on a 3, 3-sigmatropic rearrangement which named as anionic oxy-cope rearrangement oxy-cope.

So, this is a unique transformation. So, you can call this retro as a transformation based things or is an it is a FGA, FGI, because functional groups in the final product and the intermediate has been rapidly changed. Now what is anionic oxy-cope rearrangement it says anionic oxy-cope rearrangement is nothing it is a 3 to 3-sigmatropic rearrangement you try to find it out the network. It is a one, it is a two, it is a three, it is a one, it is a two, it is a three. So, anionic oxy-cope rearrangement is something like this where you have a o minus, you did to the base then basically your entire things this pi this one, two, three this sigma bond and pi bond will try to react and finally, you will basically get a product something like this. So, this is your main structural viewpoint yeah. So, basically it is alpha, beta, gamma, delta, so this kind of compounds you will finally, get in this entire pathway.

Now, you see here. So, once this it will become O minus here then the pathways start taking place basically having this things come here and this go back here. So, you need to redraw a structure, redraw a structure or to get this product. Finally, this will basically give you the target as we said, it is anionic oxy-cope rearrangement. Try to practice it in your home, or when you have time, fine.

Now, this intermediate which we have just drawn here is also not a commercially available. So, you need to make it. Now, this seems to be pretty simple you can have a some simple reaction by a vinylic magnesium bromide with this ketone. So, a simple grignard reaction simple grignard will able to give you this kind of transformation simple grignard reaction grignard transformation fine. This is commercially available cheap material. Now, this ketone you need to make. We will do another retro. Now, see the retro which was given in the slide is based on a Diesl-Alders transformation cycloaddition. Now, what we exactly do you basically start with a dien, it is a 4 plus 2 cycloaddition reaction or you can say Diesl-Alders transformation it is a dien, and in a dienophile which is the main criteria for Diesl-Alders reaction.

(Refer Slide Time: 13:31)




So, you start with this dien, and you do a 4 plus 2 cycloaddition reaction. And eventually what we will get we basically get a compound, we just drawn in this way. So, it is 4 plus 2 cycloaddition. Now, you need to convert this compound the corresponding ketone. How you can do it, it is basically says that if you can use a aquas K OH. So, eventually

this will give to a replacement of the chlorine with the OH as an nucleophilic partner. Now, this compound is a cyanohydrin, it is a cyanohydrin which instantly releases HCN because cyanohydrin it is a normally unstable and finally, you will come back or you can generate the parent ketone. So, this is the main way you can generate the parent ketone.

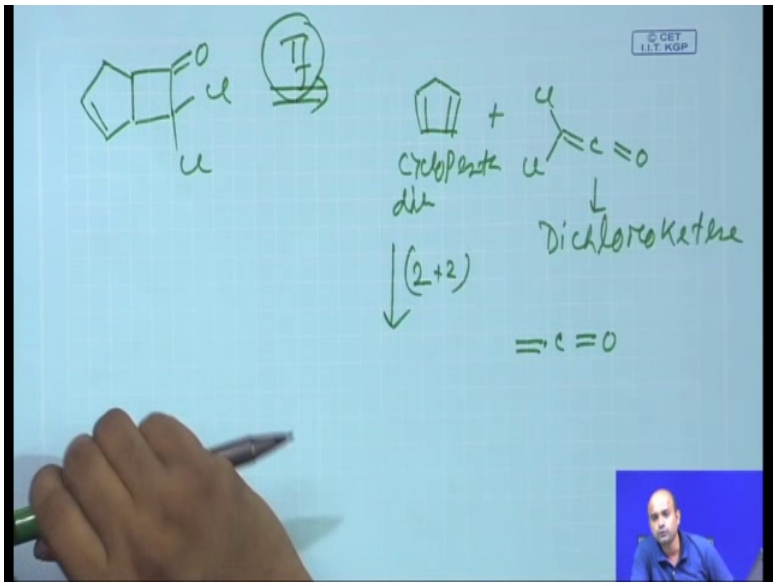
So, what is the transformation we used here, we used is anionic oxy-cope, we used anionic oxy cope here, and then we also used a Diesl-Alders cycloaddition reaction to get this particular kitchen this ketone. And this ketone is basically very useful as a starting material. And then you can do a vinyl magnesium bromide reaction, which we have already discussed and then you can anionic oxy-cope.

So, the quiz number three or you see this is the target molecule where you can see the structure of this particular compound is basically this is a target molecule. Now, the target molecule, if you give a functional group analysis it is basically internal ester which will nothing is a lactone, it is a lactone, we say it is a lactone fine. So, what are the steps basically you want to have it, you want to have a these kind of things. So, initial target molecule I said this one. So, now, I do a retro by putting something else. We put a double bond here, why I put the double bond that will be quite clear after sometime. So, it means that you just need to do a two transformation, this is a four member ketone. Now, four member ketone can undergo a ring expansion reaction to give a five member lactone, if you know this transformation which is called as a Baeyer-Villiger oxidation.

So, Baeyer-Villiger oxidation will basically give you a four member ketone to a parent lactone - five member lactone. This double bond is required because this double bond we need you can basically reduce this double bond by paradigm charcoal hydrogen to get the target molecule fine. For the target molecule, you do not have a double bond unsaturation. So, next retro is very interesting and it is all based on the specific transformation and that should be clear why you put the double bond here.

We used a alpha-alpha dichloroketone compound as the starting precursor. Now, see that this is known that if you subject this alpha-alpha dichloroketone with the zinc metallic zinc, the dechlorination occurs to give you this target molecule intermediate which undergoes Baeyer-Villiger oxidation reaction and the paradigm charcoal hydrogenation to give you the target molecule. Now, why you have chosen this as a starting material this as a starting material, we can explain it in the next slide.

(Refer Slide Time: 17:35)

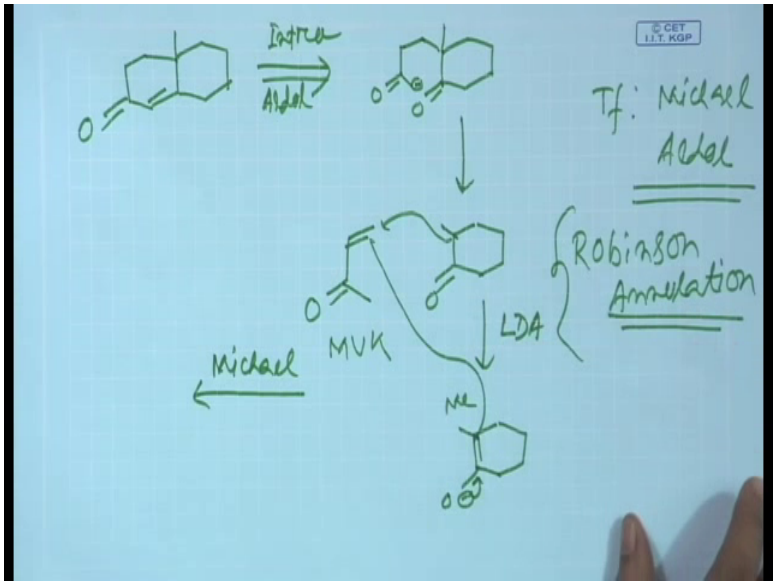



So, what it says that, if you have a intermediate whose structure is something like this you basically can disconnect in a different way. You can do a disconnection based on a 2 plus 2 reaction which is not very popular, but still some of the dienophiles give a 2 plus 2 reaction. Now, this compound is a cyclopentadiene, which all of us know cyclopentadiene cyclopenta diene. This compound is dichloroketene ketene are specific compounds which is having this kind of functional group this is name as ketene. Now, ketene can undergo two plus two cycloaddition under thermal condition by a simple chemical logic we know that two plus two reaction can occur under light, but ketene has a specific molecular orbital alignment, which allows the ketene can undergo 2 plus 2 cycloaddition this information you just keep it as you in your memory

So, then if you undergo 2 plus 2 cycloaddition reactions ketene, you get this compound. And then you do a dechlorination as discussed earlier do a Baeyer-Villiger reaction. So, particularly if you do not know this reaction, which is its transformation probably your entire pathway. So, that is what I am saying more and more transformation you know or more and more knowledge based information you know you will be quite familiar to design a efficient pathway. So, this pathway basically says like three step pathway. You see the pathway, it is a three step pathway you start with ketene, sorry start with ketene then take the cyclopentanine is a one step then you do a dechlorination here. Once you get the intermediate you do a dechlorination here then you do a Baeyer-Villiger oxidation

and finally, paradigm (Refer Time: 19:52) hydrogenation that basically gives you the final product. So, our next will be having some further quiz.

(Refer Slide Time: 20:11)



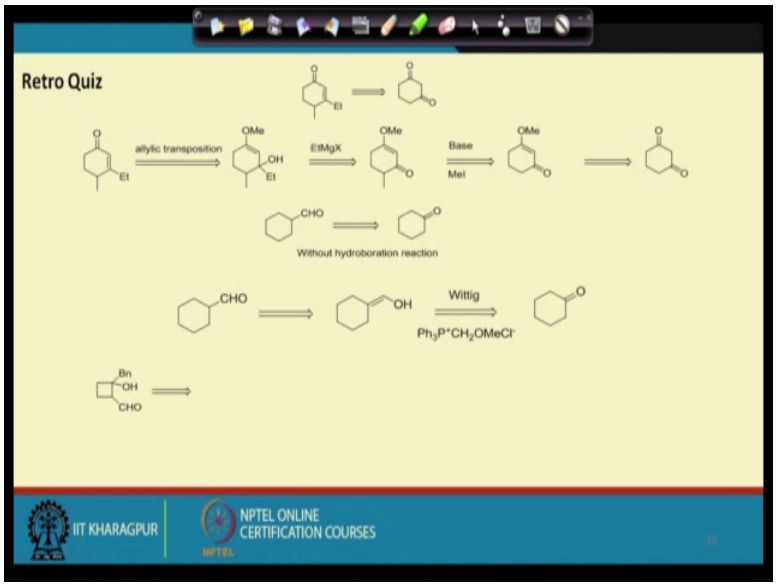

So, the next quiz which was basically a similar kind of a problem the target molecule is a bicyclic compound, see its structure, it is pretty simple bicyclic compound. It is a bicyclic compound; it is a bicyclic compound. Now, a simple chemical analogy you can devise a retro which will basically will give you a very well known reaction which is named as Robinson-Annulation or is a Michael Aldol reaction. Now, you can basically have a intramolecular Aldol version intra Aldol reaction, it is a intra Aldol reaction. Now, what is this reaction it is basically undergoing a this minus will add up to the electrophilic ketone and final dehydration to give you with the product fine. So, you need to basically make this compound.

Now, this compound is what is a one, two, three, four, five, 1-5-dicarbonate species and we see it is structural features this compound can easily be synthesized if you have starting material something like this and a Michael acceptor something like this. So, what is this the two methyl cyclohexanone and it is a methyl vinyl ketone. So, if you subject this compound to methyl ketone to a base normal base like LDA or something like that you basically have N all generated by extracting this hydrogen. Now, this is basically the nucleophilic point. So, this nucleophile will now attack to this Michael acceptor like this these things will attack to this Michael acceptor both the way you can write. You can put

a free carbon ion you can put a analyte now once this Michael reaction. So, Michael reaction is the key transformation Michael reaction. So, you basically get the product as I have drawn here then Aldol.

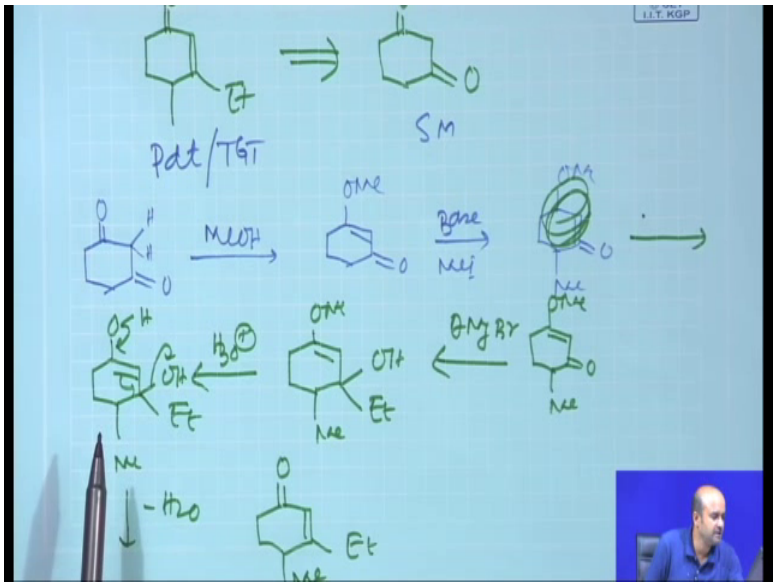
So, the main hydrolysis synthesis transformation what we used we used a Michael reaction followed by a Aldol reaction and these entire reaction sequences was named as Robinson Annulation. Sir Robinson who is who made a significant contribution in the field of organic synthesis and annulation annul means forming ring, ring forming reaction. So, annulations are very useful reaction where you have a possibility of forming ring you can use annulation reaction this is simplified version of annulation reaction, but this usually follows a Michael as well as Aldol transformation based on the overall pathway.

(Refer Slide Time: 23:17)




So, we will go back or we will basically continue our discussion with other quiz. There are couple of a interesting quizzes now throughout this entire course work we will talk about more about these quizzes. So, throughout this quiz is basically your doubts will be cleared and whenever some new transformation we are talking about I will try to cover the mechanism for individual transformations.

(Refer Slide Time: 23:43)




Let us talk about these things. This is a cyclohexanone based compound if you see the target molecule is having a cyclohexanone, this is a ethyl group and the starting material was taken a or proposed a 1-3-cyclohexanone dien. Normally in many cases, I will give you the starting material. So, you can basically design the pathway. I said product or target molecule and starting material is this one. So, the pathway or the transformation what normally we will use here it is as a very interesting, you see the pathway or we will do a forward synthesis here. Sometimes we need to do a forward synthesis. Take this compound as a starting material. Now, this compound is having high acidic hydrogens. So, good to treat with simple methanol, this compound will analyze this compound will analyze and you basically get a this things.

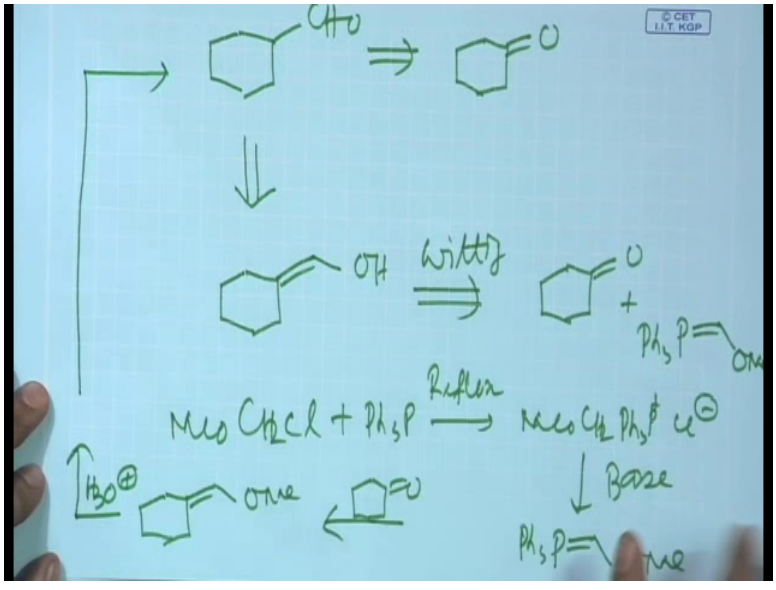
Now, as I said the target molecule having a methyl appendage or methyl substitution at this here methyl substitution in this point methyl substitution in this point, now that is very important, so methyl group is here. So, you need to introduce this methyl group in the early stage of synthesis. So, you put a base, you put a base and methyl iodide here, that basically give you a methyl thing with a OMA fine. So, then what you need to do you basically to do some important reaction to introduce the ethyl group and that was the main highlight of the reaction of the entire course.

So, the structure was a little bit wrong, you can basically have a structure something like this double bond O methyl will be here and there is a OME here fine. So, now you do a

ethyl magnesium bromide to introduce the ethyl group, this is alpha beta unsaturated ketone. So, ethyl magnesium bromide will basically make a attack here to give you a tertiary alcohol, your methyl is here fine. Now, this is basically a vinylic ether and you have a quaternary alcohol. So, if we just subject to this compound with a acid, first the vinyl methyl ethyl will hydrolyze to give you OH. Now, this OH would not sit idle. What we will try to do, it will basically try to undergo some kind of elimination type of reaction to this. And basically eventually water elimination will lead you the target molecule.

This reaction is pretty interesting and this is often regarded as allylic transposition reaction means that this is a allylic double bond. This allylic double bond is basically migrating or transposed, so transposed means changing the position. So, this double bond is coming from here to here that is why it is called allylic transposition. Now, how it happens is basically you are having a O methoxy, you are hydrolyzing it and then there a hydrolysis will basically give you the vinylic alcohol OH which is prone to elimination of water molecule and then you are having this double bond isomerization or double bond transposition. Means double bond has changed its original position to a another position so that is the one of the assignment. And you are basically trying to have a new reaction which is quite unique because we need to know some important reactions.

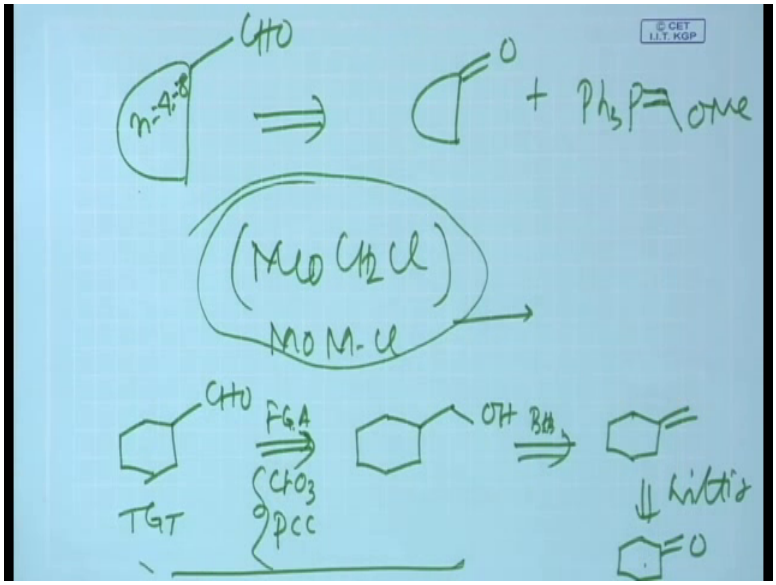
(Refer Slide Time: 28:15)



Next one is pretty simple. We will stop today's discussion after having this one. This one I says your target molecule is something like a cyclohexanecarboxaldehyde, but what you I said you have a prerequisite, you cannot use hydroboration reaction that basically puts your selection a little bit in dilemma. So, what you can think about is there are many other ways, definitely there are many other ways. Now, we will do a retro we will do a retro and we devise that if you can have this kind of vinylic alcohol which can instantly tautomerizes to this fine.

Now, this vinylic alcohol, how you can get we will be using a potentially Wittig transformation by starting from a cyclohexanone with a Wittig elite Ph 3 P double bond chome. Now, this wittig elite can be instantly generated from a compound called methoxy methyl chloride plus triphenylphosphine, you do a reflex just do a reflex you basically will get Meo CH 2 Ph 3 plus Cl minus. You treat with a base that will basically this Wittig elite. And this Wittig elite will react here with cyclohexanone. So, it will react with cyclohexanone and what you will get you will basically get a first step vinylic ether standard Wittig reaction. The vinylic ethers are prone to hydrolysis you just put a mineral acid that will basically give you a vinylic alchohol which instantly tautomerize to the corresponding cyclohexanone aldehyde.

(Refer Slide Time: 30:10)




So, in nutshell any of this these kind of retro, you can basically figure it out something like this. Let us say you have a ring, you want to make this kind of compound. I said this

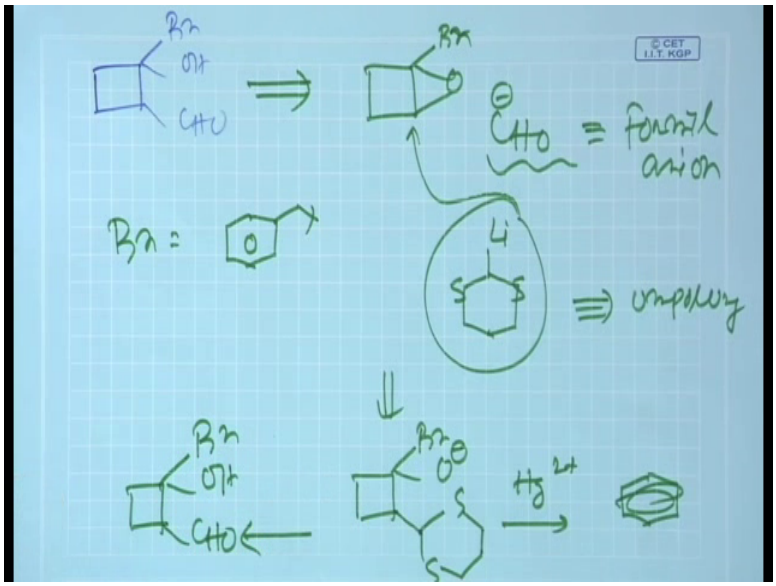
is a ring means n, n could be 4 to 7 or 8, I mean four member ring, seven member ring eight member ring. The retro will be something like this you start with corresponding cyclohexanone, which are very cheap very cheap, and then use a Wittig reaction based on this kind of Wittig elite. Now, this Wittig elite is easily available or you can even make it by starting from a compound called methoxy methyl chloride, it is called MOM chloride abbreviated as MOM chloride.

So, this MOM chloride wittig you can use it to get a very nice way of introducing a carboxy aldehyde group, carboxy aldehyde group, but eventually you are not using a Wittig reaction you are not using a Wittig reaction that was the prerequisite I said sorry without the hydroboration reaction. We cannot use the hydroboration reaction. Now, if the standard route I said you can use with the hydroboration reaction then we do the center route. You start with a starting material you initial was the retro says if you have this starting material which is a functional group addition simple oxidation and then you do hydroboration starting from this compound and then you have a wittig route starting from cyclohexanone.

So, this is a standard route. You can basically make your routes available. So, cyclohexanone Wittig, you get the here. You do a hydroboration means boron Thf you get cyclohexylmethanol functional group addition by simple oxidation let us say chromium trioxide or PCC pyridinium chlorochromate or our oxidizing agent, you are coming here. So, that basically, but we are giving a prerequisite in this particular problem. You cannot use hydroboration reaction. So, if hydroboration reaction has to be avoided then you can use the MOM chloride Wittig, the MOM chloride wittig which just now discussed.

It says hydroboration can be used then definitely you can think about the final route which we have just discussed. Start with cyclohexanone, do a Wittig, get the corresponding hexocyclic methenine compound hydroboration and then you come back to the oxidation and get that target molecule. So, you do a functional group addition here. The transformation which we used we used a Wittig transformation, you we used a hydroboration we used a oxidation. In the original problem we used simply a Wittig reaction and a hydrolysis, so that is it. So, those kind of certain thinking are essential to devise a pathway and stay focused whatever was required from you, so that will be basically give you the entire pathway.

(Refer Slide Time: 33:46)




We will probably try to have a similar kind of problem. Let us see how the next problem comes. Next problem if it comes then you can discuss. Next problem is a very simple one. We will try to give it a little bit faster it is basically a cyclobutane containing compound, we say Bn OH CHO, we do a retro very straightforward we say that the compounds if you have a epoxite and a Formil anion. Now, Bn stands for benzyl this group Bn is basically benzyl as a benzyl group. Now, sometimes can you have this kind of species, which are called synthetic equivalents, it is basically Formil anion. Now, we will talk those spaces in the subsequent sections.

Now, the synthesis which was devised here basically we will have similar kind of pathway if you have a one three (Refer Time: 34:37) derivative with the lithium species which all of us know. And this can basically give you a umpolung, umpolung species where the charge has been reversed. And if you have a umpolung species which can attack to these epoxite that will basically give you the desired product after you remove this 1, 3-dithiane group by a mercury mediated hydrolysis that will give you the final product. So, I am sorry this is the basically the cyclobutane based product and finally, the product which is you get Bn OH CHO.

So, in the next class, we will basically talking about some of the again retro quizzes and then you will then try to deep or submerge into the real problem throughout this entire coursework, we will talk about this approach. We take a some targets and we try to figure

it out what is the transformation available. If you would know the transformation, you would not explain the mechanism otherwise normally try to explain the mechanism for an unknown transformations I assume that some transformations which you do not know.

So, again see you in the next week, have a good time.