Heterocyclic Chemistry
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Lecture - 38
Synthesis of Quinolines and Isoquinolines

Good morning. So, todays lecture I will cover the Synthesis of Quinolines and Isoquinolines. All of you know the Quinolines and Isoquinolines belong to defused heterocycles in which one of the rings is benzene other is pyridine.

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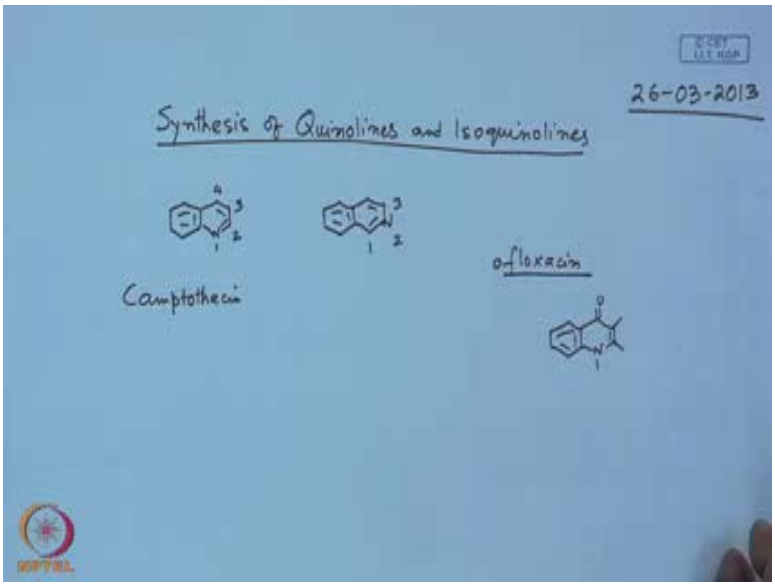

And, there are basic structures are written in a manner where nitrogen occupies position 1 in Quinoline. And Isoquinoline is a having the nitrogen at the position number 2. So, all of you know the numbering starts from 1, 2, 3, 4 this way in case of isoquinoline 1, 2 and 3. And this nuclear is very important in the pharmaceutical industry as well as natural products chemistry. And also many of you know that quinine is a natural product in which quinoline moiety is found. And isoquinoline also is a nucleus where which can be found in a very famous natural product it is little difficult to visualize. But it is there in the structure of morphine it is not exactly the aromatic 1 but it is a hydro aromatic 1ok.

So, likewise then there are other molecules like camptothecins it said quinoline alkaloid. I will just write the name structure you can find out from the Google camptothecins it

belongs to an Indole alkaloid. And there are other pharmaceutical industries, pharmaceutical compounds like chloroquine, primaquine they are belong to the quinoline group of compounds. Then, one more I think very important class of antibiotic which is known as floxacin. I do not know how many of you know or not floxacin, for floxacin actually again it belongs to quinoline nucleus or it contains quinoline nucleus. But more precisely it contains this quinoline nucleus. And this very powerful antibiotic next to beta lactams the floxacin are very useful into life many of you also have heard of I mean this is floxacin normally the parent 1 they will that is more popular in the market much ofloxacin.

And, some of you probably have heard of norflox t z this is a very common medicine norflox t z what is that t z is tinidazole means, it is again heterocyclic molecule it is an azoles derivative. And norflox means, norfloxacin. Norfloxacin means, basically the say ofloxacin with 1 less carbon. So, that means; the combination of the tinidazole and the floxacin. So, that means; what I am trying to say let this sort of compounds are very useful especially Quinolines and Isoquinolines. Quinolines is a more known all of you knows some of the synthetic compounds are antimalarials right like, chloroquines, primaquines and there. And then isoquinoline in addition to the morphine in which the isoquinoline is their there are other molecules called papaverine, barbarian, alkalytes many alkalytes also will have this isoquinoline moiety. But most cases though they are not aromatic partly aromatic, partly non-aromatic, that means; this nitrogen contain part is non-aromatic. But any cases in all of the cases the synthetic strategies are very similar strategies.

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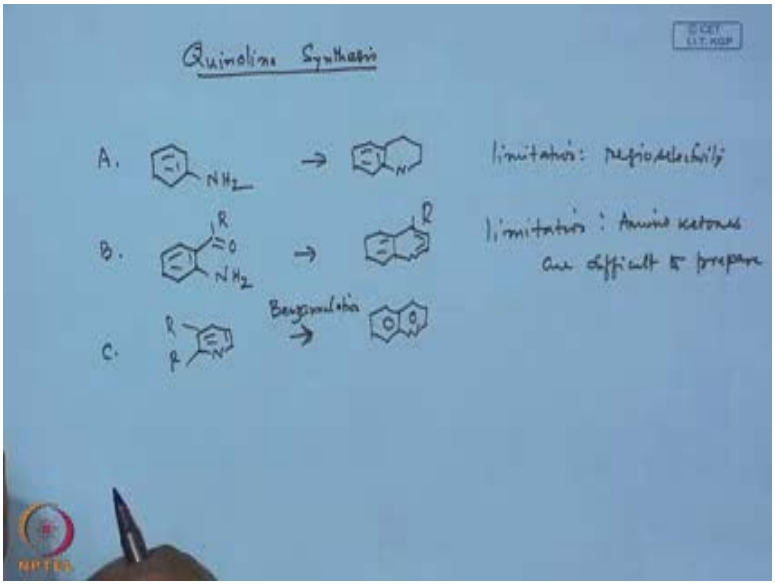

Let us begin with quinoline and I am sure some of you know some of this is but will have one or two few or one or few new synthesis. So, how do we approach? If you write the structure we can very quickly visualize that the retro synthesis requires cleaves in the vicinity of nitrogen, that means; quinoline can be broken into this airline right. So, this is one of this ways that means; you just elaborate airline and then make quinoline. So, this is one of this approaches then second approach is I think many of you know second approach is would be also a very similar in these case it is a disubstituted once orthodose substituted right. And so we can go to the quinoline moiety again ok. And what is the third possibility there are other.

So, these are the 2 major possibilities and in fact, both are worked out. And there is a limitation here limitation what is the limitation? Is Regio selectivity right because if you have a substitution in the aromatic ring, and depending on the situation you can have different regioisomers. And in these case what could be the limitation here, the second case both the substituent now in ortho positions. So, the inherent limitations present in the first approach that means, a first approach can be avoided by fixing the substituent already in the benzene ring.

But there is a limitation, the limitation is that the amino ketones compounds are difficult to make amino ketones right. So, like say if amino ketones are difficult to prepare so but the depending is all depends of the situation which we want. And in some cases the

reaction conditions also is very important. The third approach could be is not that well known though what is the third approach could be guess? So, we have 2 important possible third approach could be you start form a pyridine nucleus right you start from pyridine nucleus. And well of course; you have to have a disubstituted pyridine. And then you can elaborate and this into the pyridine.

But it is the not many examples in this category very few category here normally that is adopted it is called benzannulation made basically, what do you do you do the ring contraction and right. And the fourth category as well so the so these are all the fourth category there is many other things. That means; you can obviously simultaneously you can do intermolecular Diels- Alder reactions. And construct both the rings together so but those are not the very popular.

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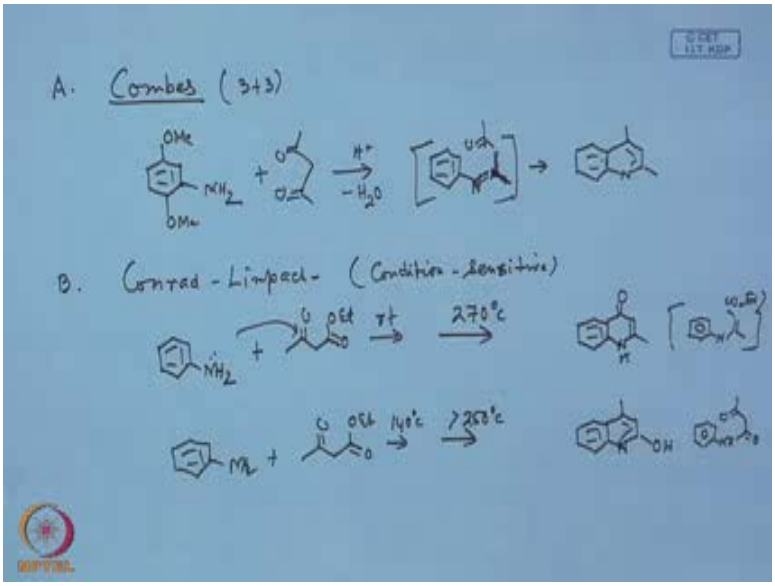

Once, I think many of you know one of the approaches or other methods I think we should know by the name combes synthesis. What it is? You can without knowing the I mean, so it is basically the mode 1, mode A I should say. And when I say mode A, that means; the starting material is mono station basically aniline derivative. And the example I am showing you here, requires a methoxy groups. And there the other starting material could be at the commonest one in heterocyclic chemistry right. So, 1, 2, 3; so you have 3 component that means; this is 3 plus 3. Then obviously, the other reacting component should be the corresponding 1, 3-diketones. Then the reaction conditions I you workout

this reaction mechanism what you will find? First will form the enamine and then in the presence of acid of course, mild acid sometime heating is good enough.

So, it will have any intermediate shift base that sorry nitrogen here and this and then of course; within in the presence of little acid. So, this would give you the condensation product which is 1, 2, 4 disubstituted quinoline. So, likewise; there are other ways is a very similar to this combes there is a method called Conrad right. Conrad and few other names Conrad limpach right nor etc. But we should not remember this I think but what is the important here, again a mono substituted benzene, that means; aniline derivative. But what is the other substrate here, other substrate is again a beta keto ester you say a beta keto that means; once a diketo compounds.

And, this is a pic villa reaction though many of you know this is conditions sensitive. This reaction is very condition sensitive that means; there are 2 different conditions. So, in under 2 different conditions you get 2 different products both are regio isomeric just see the differences what is the differences? In the first case you will be getting the 4 quinoline. And the second case you will be getting 2 quinoline which is essentially, 2 hydroxyl, 4 methyl, quinoline same product difference guess? I can tell you in these cases the first is room temperature you just let it for sometimes and left to heat. And then second step you heat at the high temperature around 270 degrees centigrade. And then next example, just heat this mixture to at so low temperature first then high temperature again about 250 degree centigrade.

So, what you make it out from this reaction that means; from amine to this beta keto ester. Actually, it first I think one first case it is pretty easy at room temperature what is the reaction possible? This is shift base formation, that is; the faster reaction shift base formation. Then it forms a shift base with this ketone then isomerizes to enamine. And then when you heat it undergoes cyclizition. So, that means; then in this case the intermediate is this 1 and this ester here. And the second case this just by warming or at 40 degree centigrade or heating what you do you we know what this shift base formation instead this amine now, directly reacts with the ester directly reacts with the ester. So, what you will find it first forms this corresponding amide and then you have this other part.

So, this is the basically the intermediate. So, these are the 2 actually, that means; there are other cases also you will see as heterocyclic chemistry is very peculiar under the different reaction conditions. You will get different kinds of the product, different kind of regioisomers all this things. So, and reaction condition is very important.

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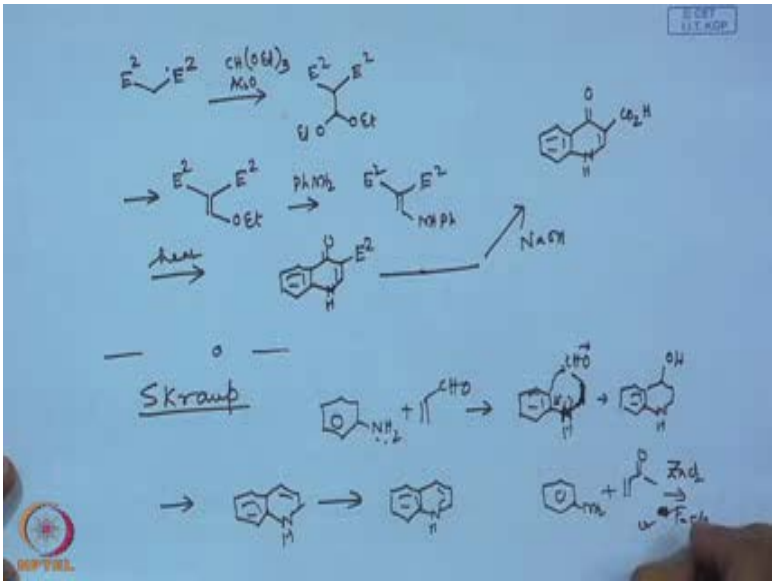

Let us look at one more example, probably that would tell you the how do you make norfloxacin? For example, norfloxacin if you remember the structural norfloxacin it is a quinoline derivative in these case. So, that was an honored method so that gives you the quinoline 4-oxoquinoline. And or other quinoline derivative now norfloxacin will have again the same kind of thing this quinoline derivative. But we have an acid here so obviously, I mean the substituents if you fallow these ((Refer Time: 15:04)) what you have to do, you have to take I would say I think you know my convention E 2 what does it mean? Ethyl ester.

So, Diethyl malonate then if you react with ethyl ortho format in the presence of acetic anhydride can you guess what is the product? See all of us have studied dimethyl malonate reactions. With most of the cases this alkali medium reactions alkali sorry not alkali bees medium, bees mediated reactions sodium said do this alkylation etc. But this is somewhat, like acidic conditions in these case that means; acidic anhydride is sufficient to inlise diethyl malonate. So, that means; this middle carbon becomes nucleophilic. And in ethyl ortho format also under the presence of acid it forms

oxyamine eventually what it you will form this E 2. So, you will get this of this sort of kittles. And then it goes to in the again all of know this presence of acetic anhydride lose ethanol to for methyl acetate that is the driving force.

So, you get the ethoxy methylene diethyl malonate and this was chemical actually was largely used by company called Bengali unity. I do not know how many of you know or not Bengali unity at least those who are from Kolkata would be knowing there is a place Bengali did near Moula-Ali. And just opposite industry called I mean these are all passed Garia of Bengal though Bengali unity is to produce lot of p h d s in those days. And it produce m e t in as one of these anti what is that m e t is n t m e v medicine anti if you have the dysentery then you can anti what anti dysentery that is better anti dysentery anti forgotten.

Then actually, they used to also produce this anti ((Refer Time: 17:57)) this 2 of this quinine derivatives quinoline derivatives like chloroquine, primaquine. And one of these intermediaries would be of this kind this quinoline derivative. And they use to use lot amount of this one just very briefly, however; I tell you that the industry is gone now is closed. And they use to produce lot of in fact; some of professors were in Science College from that institution. And in fact; one of the factory members also was teaching almighty purpose for some time. So, I mean some of them also went to almighty for point out producing that means; it was so I mean well known. So, I mean whether stable institutions as per the research as well as the industry is concern any case. So, they use to make this sort of compound.

Now, of course, once you have this if you react with aniline and there is a reaction all of us know Michel addition followed by elimination which will give you this right. And then just simply heat. So, if you heat what you will get you will get this, that is; quinoline derivative that is; it 4-quinoline derivative and this ester here and ester here. And then if you use of course, sodium hydroxide mild conditions there are 2 groups this was this amide group can also break. But under control conditions with sodium hydroxide you can go to the corresponding acid derivatives without much problem. And then what are the methods based on only aniline utilization of aniline derivatives all of you know there is a method called SKraup synthesis.

SKraup synthesis requires none the classical one requires aniline Glyceraldehyde and one synthesize sulfuric acid concentrated sulfuric acid what else a nitro benzene and concentrated sulfuric acid glycerin gives the Acrolein. So, acrolein it gives acrolein that means; alpha, beta unsaturated ketones. So, in a ketones and then it undergoes Michel addition then in the presence of acid it undergoes kind of reaction. And then in the presence of I think all of you know right I will not write this. So, you will go to this is nitrogen here and this right. And then this would like enamine it will undergo the intermolecular kinds of reactions. So, eventually what you will get, you will get this hydroxyl derivative. And this would give you the what? Dihydro quinoline. And in the presence of

Student: nitrobenzene

Nitrobenzene but there is other modifications some time people use iodine also iodine also is an oxidizing agent. So, eventually you get this is fairly well known. And there are I will show you one example today. But other variation could be you can take just instead of this the classical one you can take aniline. And any kind of alpha, beta unsaturated ketones or methyl, phenyl, ketones you can think about other lose acid like zinc chloride or even zinc chloride or even ferric chloride. So, the fate is same; so just fallow this mechanism you will go to the substituted quinoline derivative.

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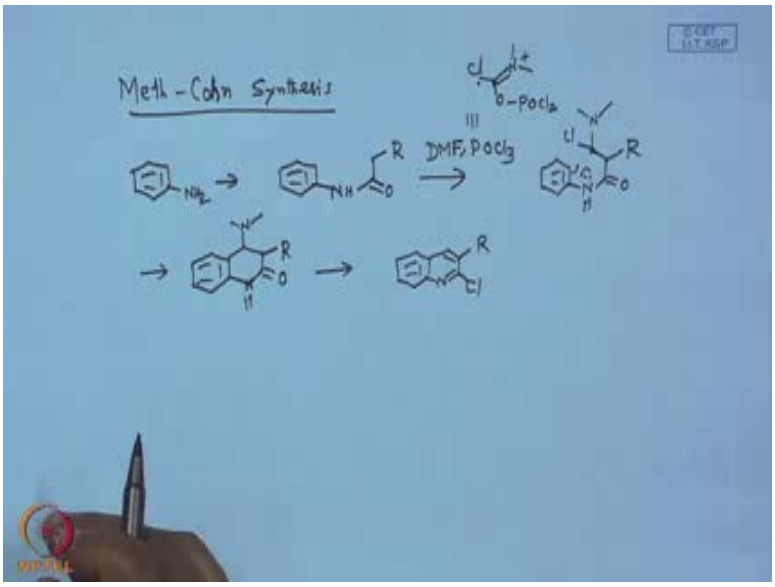

There is one more other one more on the basis of the utilization of aniline, that is; little that is; that has a name called Meth-Cohn synthesis it is starts from again aniline. But step wise manner you develop the quinoline synthesis take the aniline first then do the Acylation standard protocol. Acylation means, you will have this corresponding acidic anhydride and this. Now, D M F and P O C l 3 this is a ((Refer Time: 22:41)) reagent means; it is equivalent to if you know what is that equivalent to D M F so that means; nitrogen right. And this is chlorine right.

Student: O P O C l 2.

O P O C l 2; so O-P O C l 2, right. Yes, so basically oxygen of D M F displaces 1chlorine from the P O C l. So, this is very active Electrophile, that is; very active electrophile. So, you have a living group here, at the chlorine. So, any nucleophile goes to here, attack this nitrogen of this carbon, alpha carbon here. Then on the return you will lose chlorine. So, eventually is a basically 1 carbon homologation. So, in this case it is initially giving a 1 carbon homologated product which is so what you can see right. Now, you can write so this is 1 carbon this one is the additional carbon here, and then you have chlorine. So, under the reaction conditions of course, then you have aniline means it is sort of enamine kind right is basically enamine kind of thing.

And, it will undergo electrophilic substitution, intermolecular, electrophilic substitution reactions with nitrogen here and there, and then this right. And of course, you are missing R here and R here what next? I think all of us can guess P O C l 3 also in heterocyclic chemistry is a very famous reagent for the for other than.

Student: ((Refer Time: 24:48))

If you have this amide linkage if I with N H you can readily convert this into corresponding alpha-chloro compounds. I say you have an amide here, in the with the treatment of this what you can do as if you can analyze And to the hydroxyl that is hydroxyl is now, that means; phenyl. For example, phenyl also can be converted to corresponding chloro compound of course, under the dusty conditions to this. But with an amide getting converted to the corresponding chloro compound is very easy this is standard practice. And we also do in all level and then of course, under the reaction conditions. Since, it is an acetic chloride right acid so amine comes out. And so you straight way get the corresponding chloro derivative this.

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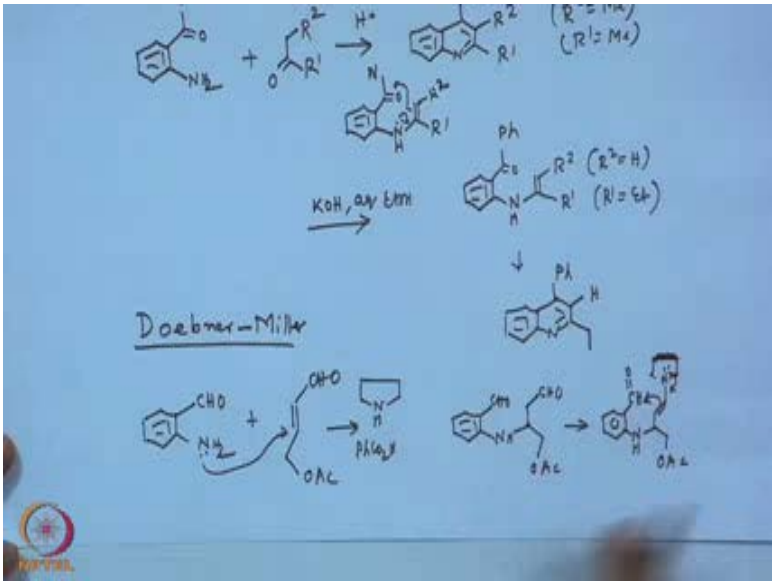

Let us very quickly look at one more pretty powerful reaction, very powerful reaction probably this is. I think the next mode that is I think will write the mode B what it is mode B, means; so almost always your starting material should be N H 2 and ortho substituent is fixed. So, in this case it is normally the ketone and commonly the ketone. And then not is the other requirement is pretty easy what is other requirement? If you want to build up a quinoline nucleus from the starting material which is already fixed. So, this is a donor that means; nucleophile this is acceptor that means; you have to have a compound which will have an acceptor and a donor that is it.

Now, you have to choose the reaction conditions let us say this is R 1, R 2 here. In the presence of acid what you do, what you expect, you will be expecting a reaction of this kind reason being in the presence of acid what you will see? You will see formation of enamine. Because of the all of us know first it forms amine right ketone and amine first form amine. And then in the presence of acid it undergoes isomerization to corresponding enamine. So, of course, then once you have enamine and then all of us know enamine is nucleophile. So, it would undergo nucleophilic addition to the intermolecularly to the ketone. And in this case you will have this phenyl up here and this R 1 this is R 2; so eventually you go to this compound.

Now, under this or with the same set of starting materials if you just change the reaction conditions. And just use a K O H and aqueous ethanol the reaction is little different,

though reaction is little different what happens in these case you get and enamine here. I think I what are you say here in these case R 2 is hydrogen. Whenever, you have hydrogen of here R 2 hydrogen. And let us say an R O and R 1 is ethyl this is a case that means; you get the less substituted enamine in the presence of see in acid means you have strong equilibrium strong. I mean very first equilibrium in the presence of base you do not have a ((Refer Time: 29:14)) and it will produce a only the less substituted once. And the product that would be formed here, then it would be something like I think best thing would be to write is the P h here. And this one would be this ethyl group here and the R 2 is hydrogen at the hydrogen ok.

So, in brief that means; in this case I should write R 2 is let us see methyl here, and R 1 is methyl here. So, whenever you have an unsymmetrical ketone so there is likelihood that you can alter the reactions force and to get 2 different substituted products. Now, there is a simple variations of these, there is a variation many of you know I guess Doebner- miller what is it? Again; so the best thing to follow in heterocyclic chemistry what I said before is the starting material. So, we have been talking about the mode 2the starting material is ortho disubstituted aniline. So, that means; in this case let us say you have aldehyde. So, is very similar if you look at this reaction intermediate here it is just like an enamine.

So, in these case; so what is done here, and since; alpha, beta unsaturated aldehyde the example I have picked up this is an reaction intermediate used for competition preparations. And use pyrroline base in the presence of benzoic acid and you can guess what could be the product? The product is the first you see here the mechanistically what you can see it undergoes Michel kind of addition N H this then you have aldehyde right. So, this is an aldehyde and acid acetate and this aldehyde what next? I think you can guess pyrrolidine between the 2 aldehyde all of us know the 1 would be more reactive than the other, which one aliphatic aldehyde right sorry this is pyrrolidine aliphatic aldehyde. So, it will form the enamine now, you have the existing aldehyde here. So, it would undergo again intra molecular nucleophilic addition right.

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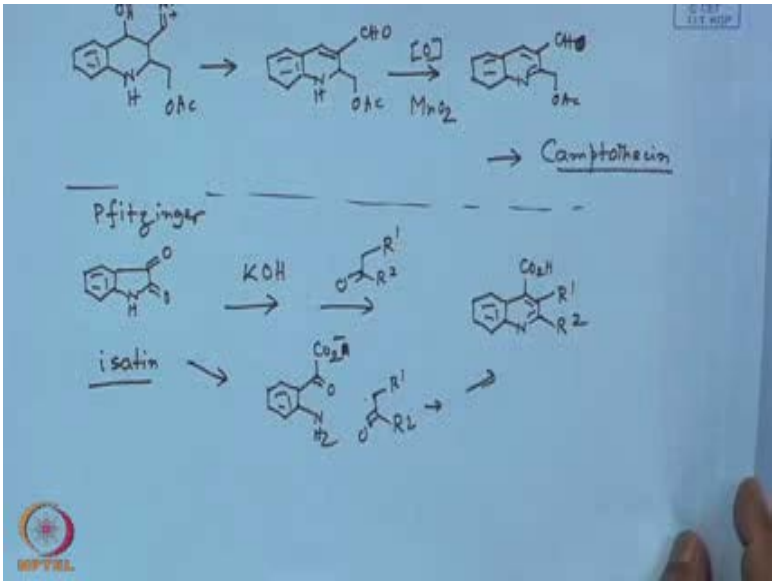

And, this would give you quinoline nucleus of course, this would be iminium salt. And the aldehyde becomes O H this is N H and this right this would be this. And of course, in presence of this acid benzoic is sufficiently good enough to activate this O H group you get the double bound up here. And this pyrrolidine is hydrolyzed N H and this is O H. Then you have to dehydrogenate it so that, you can get the corresponding quinoline derivative I. And so you have to do this oxidation up here and but this is again a matter of choice. I mean; what is kind of oxidizing agent should be using in this case what kind of oxidizing agent you do not have many though. What are the possible oxidizing agents?

In the previous case coloring case you have seen nitrobenzene iodine. So, that means; you have to use mild oxidizing agent you can use metal, acid, oxone i b x all these things i b x also causes dehydrogenations. But in these example, which has been used is mechanics dioxide. And why does it go this is an intermediate for come to ((Refer Time: 34:37)) right. And what is it? It is an antitumor acolyte very popular acolyte if you just go to the research you will find a plenty of references. And is use clinically for the treatment of certain cancers. And in all about departments somebody does research on this right, and also got in award recently by presenting this work ok. So, next thing next also is a pretty interesting one I do not know whether you know or not this molecule is pretty famous molecule and pretty cheap what is it?

Student: ((Refer Time: 35:23))

Right, good how did you know? Is a very cheap 100 gram bottle 100 may be something. But if you do just is a very interesting mechanistically first boil with alkali then you begin with ketone of course, with alpha hydrogen. And what you get end up with nice cleanly, very nice reaction; so what we get is clean product like this. And so you said trisubstituted quinoline what is the name? Pfitzinger quinoline synthesis; so once again the starting material is an ortho disubstituted aniline derivative. So that is what that is how you have to remember? But it is based on this and mechanically quite interesting what does it do? We have K O H can hydrolyze this amide K O H can also break open this one to diketones right like, holly bowen reaction just adds ways, adds the carbonyl. And then break opens this carbon- carbon bound but in these case what is happening here it is hydrolyzing the hetero bounds.

So, obviously that means; you will have N H 2 the other portion becomes now, this top carbonyl remains as it is. And this then 1 that is that was connected to this amide will have linkage like this that means; in this case of course, it is a salt here. Then you can guess right this is now typical. Now, once you have this will basically it is a variation of the Fred lender method. The previously the method to what the mode B is known as the Fred lender where you have this amine ortho substituted aniline derivative. So, essentially what you are doing here, for you are making an ortho substituted aniline derivative. Then once you have this then you have an nucleophile and electrophile that means amine goes to this carbonyl. And this active methylene goes to the another carbonyl. So, eventually you will go to this compound and so that is; so may be will if the time permits will come back to this sort of example, may be somewhat later.

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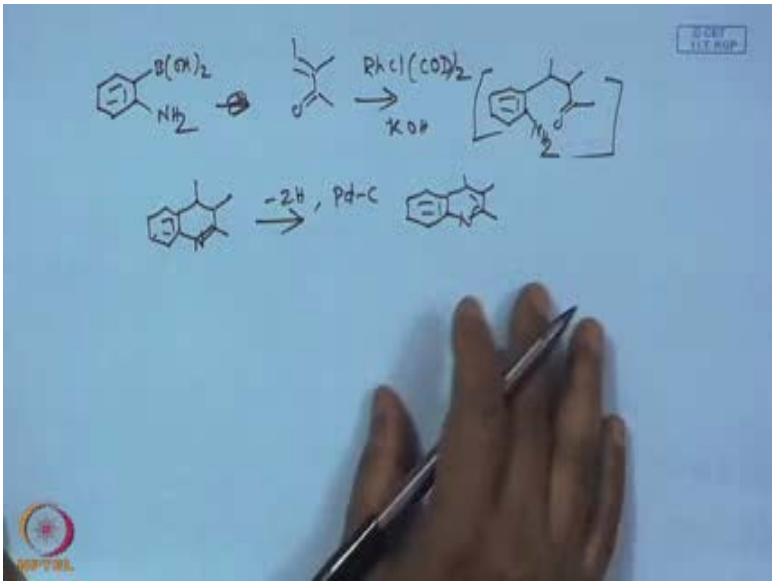

And, then what is the other possibility you have not talk much the third mode that is so is a mode called benzannulation mode right benzannulation there are not many examples. And this has been published from our department what would you will see you start with pyridine derivative Then the it is an ortho substituted aldehyde and then alkynes treat this with auric chloride thin chloride and in the presence of acetylene dicarboxylate. So, what will be getting again you will be getting trisubstituted quinoline but all the substituents now are in the benzene ring that means; here you will have ketone, you have ester here, you have ester here. This is a sometimes it is known as this is sometime is a very popular in aromatic chemistry it is sometime it is known as Yamamoto Masao Benzannulation.

That means; if you have let us say benzene derivative of course, what you will get you will be getting the corresponding naphthalene compound. And this is very fascinating reaction what is the mechanism? Any idea mechanism goes like this that means; this oxygen lone pair oxygen attacks this alkynes. And this of course, all of us know the role of auric chloride. What is this role? You see all these days you will see that gold catalyst reactions many people wherever you go to this conference somewhere in abstracts at least one of them would be on the gold catalyzing reaction. Simply, because these alkynes are easy to make by reactions are all of us know. And then if you can activate the alkyne the previously we had very limitations to activate this alkynes only with marking sulfate and iodine.

Now, it is gold catalyst or gold catalyst many you can solubilize gold in organic solvent with the help ((Refer Time: 41:01)) so you can carry out many important organic reactions with gold. And thus you can also activate this alkyne and that is what is happening here. So, what do you do you let us say this oxygen now right. And let us see if I am try if I can make it and this is plus here. And this is there all right that oxygen loan pair attacks this s p carbon and which is activated by this gold now you have these acceptors. So, what you see here may be I think I made a mistake which one what is not there ok. Now, what you see here this is a Diene system

So, this is diene I think I was right. This is; so you want E 2 say, if you see this portion is a diene system. So, it will undergoes a typical 4 plus 2 cycloaddition reaction oxygen here this is P h. And then you have this double bound E 1, E 2 right. And so you will have what? Right and this one will have A u negative and C l 3 right. So, in during the work up probably; so if you just break open this one it becomes carbonyl; and so will have O H this is E 1 right. Then this becomes P h then this is A u C l minus and E 1 right. Now, this minus means then the catalyst should come out so it will come out and O H is lost.

So, sufficiently that means; what will be getting you will be getting the corresponding but this ok. So, it is a nice example of basically benzannulation nice example of benzannulation but that can be extended to this. And then very recently just one more example, I will tell you based on this disubstituted you see is a very recent addition it is nothing to do with this it is example, of Friedlander synthesis or I should say variation of this cloud synthesis. And this is recent once what it begins with; it begins with again an ortho disubstituted aniline derivative. But eventually it is reacted with an alpha, beta unsaturated ketones of this kind. And the reaction takes place in the presence of rhodium chloride and C O D rhodium chloride.

And, what does it do, you say typical Michel addition kind of things. So, many of you know boronic acid means what? It is an electrophile or nucleophile. Boronic acid is actually is a metal, boron is a metal so that means; just like a sort of a grignard reagent so grignard reagent. So, it will but in these case it will undergo 1, 4 addition. So, you will get this sort of cyclic compounds here and as an intermediate. So, this is an intermediate and under the presence of base that potassium hydroxide it gives a dihydro quinoline.

And, of course, all of you know at the next step is to basically dehydrogenate. So, dehydrogenate, dehydrogenation can be done with palladium charcoal. And one can have well defined quinoline derivative with 3 different substitutions or substituents in this pyridine nucleus. Pyridine that means; in summary you have what let us say quinoline after the quinoline we have 2 different, 3 different approaches first is mono substituted aromatics, that means; aniline derivatives, then ortho disubstituted derivatives and then benzene accommodation mode. So, these are the 3 different modes and then you have all different variants and different names different variants. And the last one is talked about that requires a boronic acid derivative.

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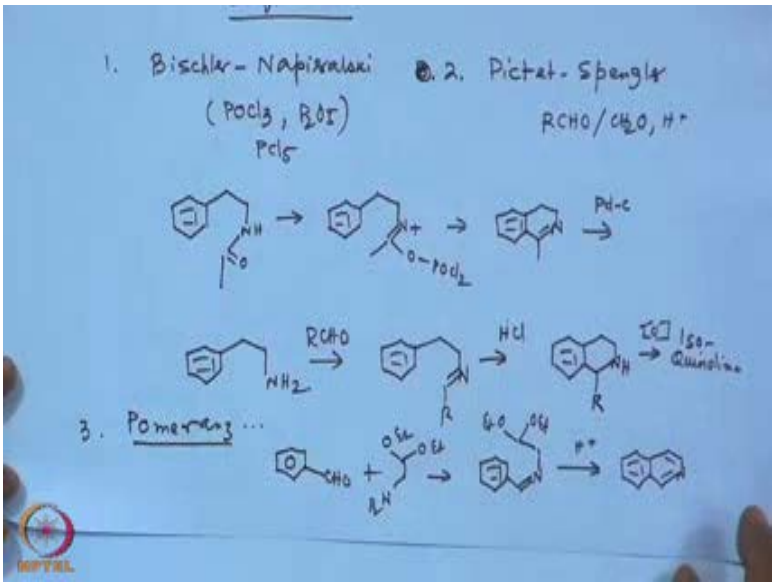

And, let us look at the next one next topic is isoquinoline. Once again isoquinoline could be I think we have only 2 I think I should say 2 different methods for isoquinoline which are very popular. And what are the 2 methods for the first one Bischler-napieralski and second one; so these are the 2 basically that they are not many; so they are pretty similar and pictet spengler synthesis. And there is one more that is also very similar but all of them actually start from a mono substituted compound. Bischler-napieralski what does it so you have to only remember bischler-napieralski goes to P O C l 3 bischler-napieralski PO C l 3 or P 2 O 5? And this one actually requires an aldehyde or a form aldehyde in presence of acid that is it.

So, whenever you see the P O C l 3 something like that means; it have to have a carbonyl compound. And normally what do you do here N H and a carbonyl and this N H then nitrogen has to be there. So, that means; this easier to remember all isoquinoline methods will have mono substituted benzene derivative with nitrogen aprendiz in case of dessler it is an amide. And the other case picketed sprinkler it is a basically amine. So, this is how easy to remember then when you have an amide. So, the likely reagent to be use phosphorus oxy chloride phosphorus pent oxide in fact; also you can use P C l 5 also depending on the situation you can use.

And, all of you know this method goes through these reaction is the corresponding this right iminium salt. So, as usual if you are using P O C l 3; so it should be P O C l 2 and this is right. And then typical intermolecular fill cups kind of cyclizition electrically substitution reaction and will get the dihydro quinoline. And then aromatization or dehydrogenation that could be done by palladium this is typical procedure. Only thing you have to remember in case of regio chemical confusion you can change over the course of the reactions by you know varying the reagents? For example, in at least I remember in one case if you have P O C l 3 used. Then you have get a compound and if you just substitute P O C l 3 by P 2 O 5 you will get a different regioisomer not different regioisomer mixture of regioisomer.

Let us say if you are I do not remember exactly. But there are cases you just from changing other changing reagent you can get the desired product in 100 percent it. And this sprinkler is very similar. So, method and which would require in these case would be amine right. So, instead of the amide here your amine but you are having a lesser number of carbons. So, if you begin with this has the plan amine; so you have to have this now shift base. So, you have to have shift base and to activate shift base of course, what you have to do? You have to use acid in this case you have the example, I have been looking at it uses hydrochloric acid. So, at once again typical electrophilic substitution reaction and you will get this. Now, what? Is the difference in the previous example, you had the dihydro quinoline. Now, we are getting a tetra hydro quinoline method is same next is to basically oxidize to the quinoline derivative oxidize. So, what you get, you get the corresponding quinoline derivative ok.

Student: ((Refer Time: 52:09))

Sorry, isoquinoline derivative good isoquinoline derivative ok. So, I mean there are other ways like see the few are interested I can just write may be one more method is there that is all are very similar though. In these case what you do you first form the shifts base then you cyclize sorry the first i mean have this required side chain. Then you form shift base and cyclize the next one that is known as Pomeranz. And some synthesis what it does actually, in these case you begin within aldehyde instead of these this amine derivatives you take the aldehyde. And then you protected amine and protected amine is taken. So, as usual aldehyde and amine when hit at together shifts base right. Now, you have this shifts base and the kettle and of course, again all of us know both the shifts base and the metals are activated by acids.

So, then you can straight way go to this quinoline difference. So, there are that means; if you take this as a third method there are differences seen bischler-napieralski you get the dihydro quinoline. And pickled sprinkler you get the tetra hydro isoquinoline sorry, isoquinoline. And pomaranz you get the direct to the quinoline derivative.

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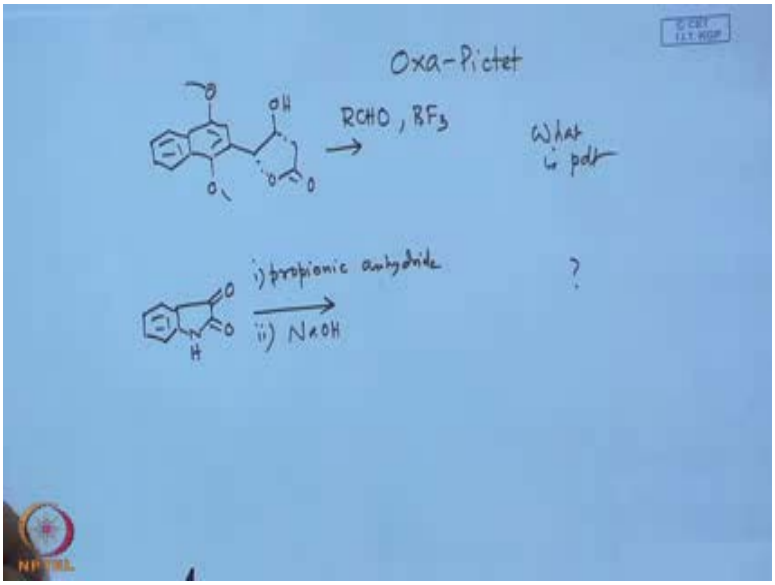

So, I think we have a verb out in most of the methods just quickly and see if you can write this structure of this product here, just an exercise. We begin with a compound which has known nitrogen in it is a lactones then you have O H of here. And then reacted with aldehyde in presence of B F 3. So, what is the product guess? So, but it belongs to the topic we had been talking about ok. I will give you just since we have one more

minute I will give one more product and the this has some relation to our lab. So, hope fully would be able to write the structure propionic anhydride first we just at room temperature and treat this with. Then you get a compound and you get a quinoline derivative what is the product? I gave you an example right, an example Fred lender example I will give you the hint for the first one can you guess there is no nitrogen.

So, this reaction is known as Oxa-Pictet method. Let us see we can except this in example fine; so you have to the next one also pretty easy. So, before you leave I think you have to work it out. So, any case; so we have I think we have talked about most of the important methods for the synthesis of quinoline and isoquinoline ok. What we have done we have not actually talked about one other method which you have already known before in the context of 4 plus 2 cycloaddition reactions. What is the method? Anybody remembers we talked about a method for making quinoline derivatives.