Heterocyclic Chemistry
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Lecture - 33
Indole Synthesis II

Good afternoon, so in the last class we talked about several Indole Ssynthesis, this is the last class on Indole Synthesis, not a last class of the heterocyclic chemistry. So, last time we talked about, what three different methods, one was Fischer indole synthesis, another was, no. What is the second one?

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Bartoli synthesis, third one ((Refer Time: 00:52)) and what I said on the basis of the starting material you should remember, because that is the very easy. For example, when I say Fischer indole means, it starts with hydrogen derivaties and then, next thing what you should remember, the most common intermediates. For example, Fischer indole synthesis forming the most common intermediates could be vinyl hydrogen. So, then you can, if you know the intermediates then, you just formulate your own synthesis.

On the basis of that, there are so many variants, one of the variant Jap Klingman method, so where you can make hydrogen by different way. Second variant could be ((Refer Time: 01:53)), he has made this BOC protected hydrogen derivative. So, like wise, there are many more, Buckvalt also has produced variant, so similarly Bartoli is very easy to remember. He requires nitro benzenes, nitro alkenes and vinyl grignard, not any kind of gignad, again a vinyl grignard, that was a vinyl hydrogen and vinyl grignard.

And third category was on basis of this Renijesco, Renijesco requires the benzo quinones and inamino ketones, so this is how you have to remember. So, there are many more methods, I think we will talk about today one very important indole synthesis, which is not really listed in the books, most of the books while very few books would list. As you will go on see, that it is very powerful reaction, there are little bit, there are very little problems of course.

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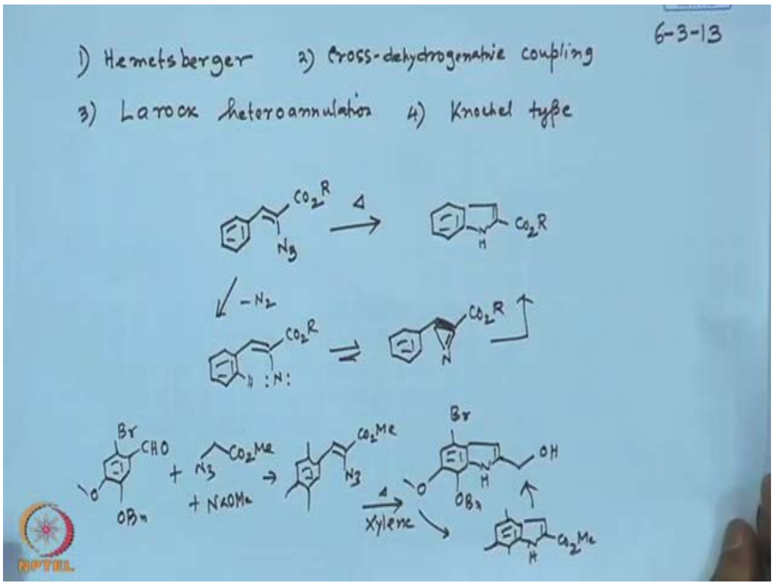

And so, this afternoon we will talk about mainly three, so the one that is called Hemetsberger, this is one we will talk about. And then, second one probably we will talk about, how do we say, let us say cross dehydrogenatic coupling and third one that probably we talk about is again a very powerful is called Larocx heteroannulation, which is again one can say indole synthesis by Larocx method. And the fourth one that, if time permits we will talk about again, so this would be there is no name, but I think I will write knockel, not really knockel, knockel type synthesis.

So now, as we go on again I said, you have to identify the starting material then, the little bit of mechanism then, the applications. And so, let us begin with this Hemmetsberger, so what does it do, actually it requires beta azido styrene. So that means, if you write the structure this way, what do will see here, the adjacent position is the alpha, so this is beta, beta azido styrene. And if you heat it, not very at temperature, just at less than 200 degree Centigrade.

So, what you are likely to get, you are likely to get a product, which is nothing but, in one that means, sort of like a neutral conditions, you can get to the product here, this is indole, that is it. So, and what is the mechanism, mechanism is that, it is suggested it looses nitrogen and of course, once azide looses nitrogen that means, what you will be getting, you will be getting these nitrine intermediate. So, like abine and nitrine and of course, one can nitrine but then, what happens, there are nitrine, what are the other possible reactions with the nitrine?

Student: Insertion

Insertion, I think the very first thing that want to talk about is the isolation, because isolation requires only very little changes in this caritor. So, infact this is suggested and it has been verified as you will see later that, it gives you a molecule of this kind, so which is nothing but, azidine, so azidine derivative you get. And so, then of course, if you recall this azidine derivative has a propensity to under go rearrangement, what kind of rearrangement?

Student: ((Refer Time: 07:14))

Piety mass like that, not exactly though, so that means, that can under go this one and this is the suggested mechanism and probably it is accepted. You can also question, why not directly nitrine under go insertion to this carbon hydrogen bond of this benzene ring systems, all that possibilities ruled out as you will go on see next example. We will see, there are quite a few variance of this, where you can starts from azidine and you can go on making this indole, simply because azidines are very readily available from simple starting material like oxygen, you can make azidines pretty easily without much problem.

And so, let us begin with example and like say, if you are suppose to make indole derivative for example, where you will have indole and two position will have is hydroxy methyl group and bromo here and this benzyl protecting group and O with it. That means, heavily substituted indole derivative, you have 1 2 3 4 substitute, so how do you make it, any guess. That means, if you look at the top one, one would make a vinyl kind of azite or aziodo styrene you can make.

So, what kind of aziodo styrene you will take, you will not take that means, if you just do the little bit of the disconnections, you will find that, you need a aziodo styrene, an aziodo styrene with a CH 2 OH functional group. But, at the same time, you have to think about, whether that is really required or not. If you want to know the methods of how to make the aziodo styrene, you will see that little difficult to make, number 1.

Number 2, if you begin with CH 2 OH group, during the decomposition of the azide, there is a likely hold that, this will not undergo nitrine insertion on the other side, instead of being giving this azadine intermediates. So, in this case, top one you have an ester group, so there was no possibility of insertion of the right hand side, on the ester side. But, if you think about CH 2 OH here, you can think of an insertion reaction with the nitrine.

So, essentially in this case, what has been done, this has been obtain from the corresponding ester derivative and this aldehyde. So, take the aldehyde here and then, azido ester in this case, this azido ester pretty very is to make, so take then, sodium ethoxide or methoxide, ethoxide then, typically what you will find, you will find just like a alcohol type of condensation. So, you will get this azido esters and then what, just simply again heat in xylene solution.

So, you get this corresponding indole that is, this one without any much problem and so, you been have these methyl ester here and of course, once you know that of methyl ester is there then, it is pretty easy to reduce this to corresponding alcohol. So, this is very straight forward then, what is the problem then, just only small limitations is there, any body who knows about the limitations of the azides. What could be the limitations, you see here, just the preparation is pretty easy.

If you have azido acetate, you can do sort of an alcohol type, you can get the vinyl azide, so all these problems are very easy, but this reaction is little tricky that is it. But, that is not the serious problem, the problems is at loss in production, because it is known that, most cases this azido compounds are explosives. So, whenever you do reactions with azides, you have to be very careful, you do not know when it explodes.

In small quantity of course, I mean we have been doing overcome this, but so far, you have not come across any problem, but it is reported that, one should be very careful about this. But, merits of this method is that, you dont have to make azide so that means, you can bypass it, because we know the reaction mechanism. What was the reaction mechanism, azides when decomposes, it forms the azidine. So, azidine can made alternatively by, atleast I know that, two different very convenient method.

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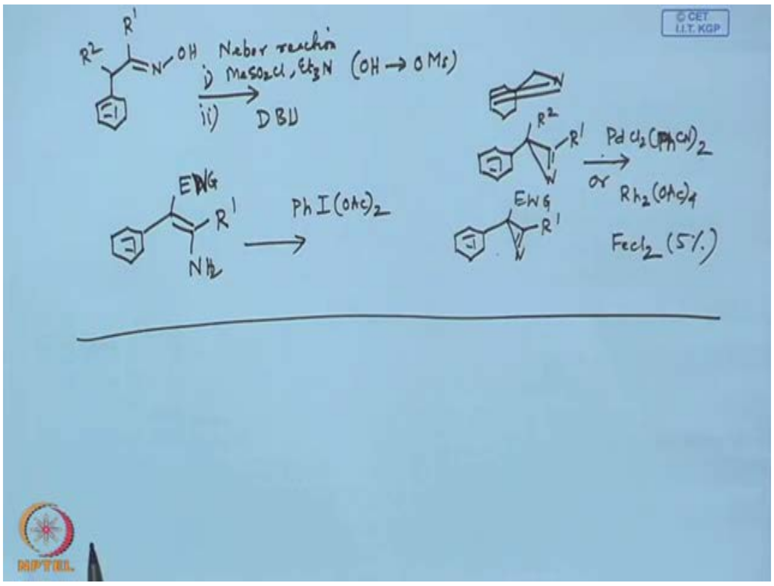

For example, the one where to make is to make an oxen, so if you begin with an oxen here, all of us know how to make oxen, the corresponding ketone and hydroxide and hydrochloride, so very good reaction and it is a standard reaction for derivative ketone. So, that is not a problem then, you do Neber reaction, what is the Neber reaction, Neber reaction is nothing but, the first step, you make this methyl derivative that means, methane sulphonyl chloride and triethyl amine.

So, I think I dont have to write the intermediate, it converts the OH group to OMS, so this basically OH is converted to OMS. And then, second step, if you do a DBU, so what you will be getting, you will be getting the corresponding azidine, so you will be corresponding getting 1 2 nitrogen here double bond and this R 1 and R 2. So, you get this azidine of course that means, you can bypass the demerits of the Hemmetsberger procedure.

Alternatively, there is another way of lookinig at, one just take, let us say you have something like this, R 1 and let us say electron withdrawing group and NH 2. So, how do you make it, it is an inamino ester, in the last class we talked about it, this inamino ester are required in the reaction of ((Refer Time: 14:55)), so easy to make beta 2 ester kind of things then, ammonia that would give this.

So, the same starting material if it is reacted with a reagent, which is written as this one, phenyl iodinium diacetate. Phenyl iodinium diacetate is very useful reagent and for last may be 10 years, we have been continuously using this reagent and this belongs to a class of the agent known as, guess?

Student: ((Refer Time: 15:30))

Hypervalent iodine reagent, there are plenty of reagents based on this, why hypervalent, normally iodine is conceal to be monovalent. In this case divalent, there are multivalents also all of you know, but most cases the trivalent iodine reagent is powerful oxidizing agent and mild and selective. So, depending on the situation, you can make use of it, there are many many uses, you will see one more use also towards the end of the lecture plus it is innocent, the by product is iodo benzene.

That means, does not cause any decomposition of the products or the as the starting materials, so that way basically, but it is dioxidizing agent. So, what do you get, once again what you get is the basically, you will get this substituted azidine here and electron withdrawing group here. So that means, you can have all kinds of azidines, now what you will find that, the azidines again can be converted to indole, you have already as you seen before, by simply heating it.

But, you dont have to heat at high temperature, people have been using different catalyst now. For example, the one recently use this peradium chloride and then, there is a acetonitryl complex, those who are working with peradium complex you will see is very stable complex with two aceto nityrl, in this case, benzo nitryl. So, it forms nice complex and this complex is very soluble also in organic solvent. So, with this complex, you can decompose this azodine directly to the indole.

Similarly, there are or you can use I think the one that is used to generate carbene from diazocompound, what is this dirhodium tetraacetate, this is very nice again complex, is basically what it does, it lowers the temperature of the decompositions of this azidines or azides and it generates nitrines and carbenes at milder conditions. And then, the latest one, I think latest one is pretty interesting, it has been published in 2010 and what do you add is nothing but, ferrous chloride and that too with only 5 percent.

So, you see here the trend here, that was the palladium expensive then, rhodium little I mean, almost equally expensive, but ferrous chloride is very cheap, you walk into this lab and find out the ferrous chloride. And at low temperature, just around 80 degree

Centigrade, you can decompose and get the indole. That means, this is a very powerful method with regard to the starting material, you can either use azides or you can azidines and that azidines can be obtained from the inamino acetones or azidines.

And for decomposition or for the rearrangements, you have many options, different kinds of the catalyst and these things and then, so what next. That means, again going back little bit to the last class, so we had only two different kinds of methods, general methods one is mono substituted benzene, other is the di substituted benzene. The third and fourth category, where you can make the benzene derivative is not really very popular. And so, this one you can see here, this is a mono substituted one, there are other OH also to look at.

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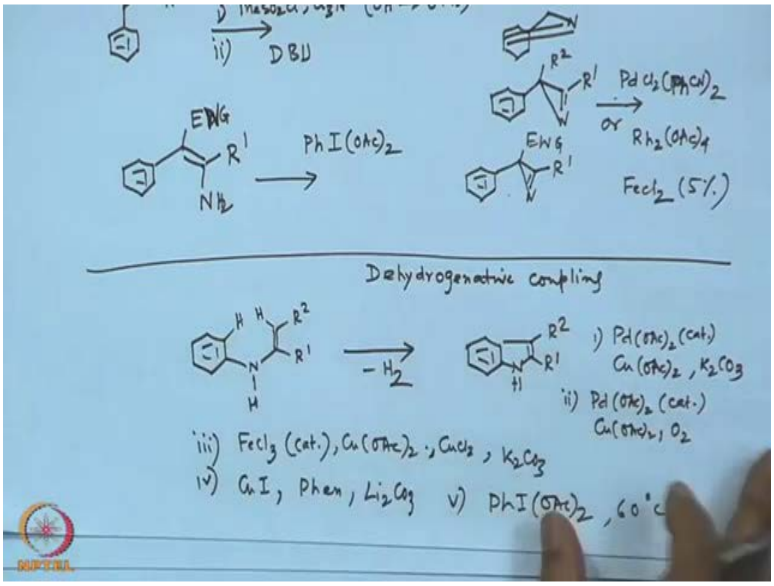

For example, if you take inamine kind of thing, inamine kind of thing here, if you take ketone, straight way make this inamine and so, what you can guess, how do you make indole form here. So, what is the reason would you like to use, if you just take the atom balancing, if you do the little bit of atom counting, what you will find, it actually revokes two of this indicated hydrogens. So, that is reason, this is known as dehydrogenetive, this is what very recently we used, dehydrogenetive coupling.

Dehydrogenetive coupling that means, minus 2 hydrogen, so you end up with the corresponding indole derivative, so in principles, it looks pretty good and so easy. And inamine formation you take from ketones and little bit of isolations and then, you will get this cinamine done. But of course, you have only limited choice, but I cannot say so, because by now it is known that there are more than eight different catalytic systems are found to be useful and most of them are published in good journals.

And, but basically what you need, you need either palladium based catalyst or copper based catalyst, I think all of you can agree that palladium has a tendency to under go C paradation reaction. C paradation reaction means, like any paradium chemistry reaction what you do, let us say first thing have learned last year that, all the cross coupling reaction would involve palladium. Why, because palladium undergo first insertion, insertion between the carbon halogen bond and goes on reaction with another carbon to form carbon palladium linkages.

So, in this case, I think I will give you the possible catalyst then, I will tell you how to see the mechanism. Let us say, all are very similar, but and only they differ little in their composition for example, the very first one, the popular one is palladium acetate. Paradium acetate and this of course, this expensinve, so you have to use catalytic amount and the stoichiometric catalyst could be then copper, because copper acteate is cheaper and all of us know, you need also base, because eventually acetic acid is excess would come out.

So, in this case, the base that is used is potassium carbonate this is one, let us say second one, you will see once again it is little better in the sense that, you use palladium once again catalytic amount. And then, cupric acetate, this again catalytic amount then, what is the stoichiometric oxidant or what do we call terminal oxidant is oxygen itself. So that means, second one is a better one, third one is little different and ferric chloride, once again it is a catalytic amount then, cupric acteate.

So, all possible combinations are there then, with cupric chloride and then, has to have a base here. So, forth one I mean, once again the previous one was palladium acetate, cupric acetate oxygen, you can skip cupric acetate, all different combionation, basically you have do little bit of the trial and error. And the one that is little uncommon, here is a cuprous iodide and phen all of you know and in this case, lithium carbonate, because it is more soluble in organic solvents.

So, what is phen?

Student: ((Refer Time: 25:25))

But, not 9 10, I suppose it is 1 10, phen has to be 1 10 not 9 10, so like this and I think there are many more combinations. I think I will stop here and of course, the one more very popular one is this one, phenyl addendum diactate, this is also has been used and that too add at very low temperature at 60 degree Centigrade. So, you have all kinds of the options and mechanistically I mean, obviously if you look at the mechanism.

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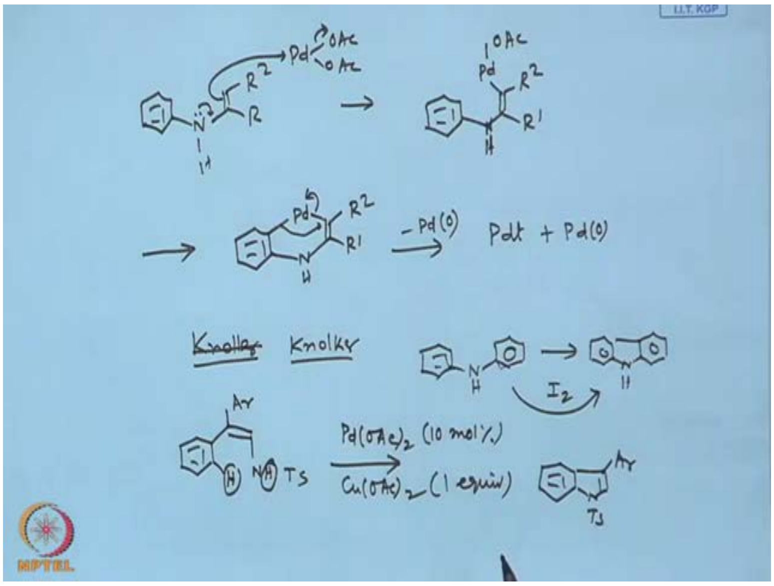

So, what is the first step, the first step would involve palladation, palladation of a that means, hydrogen here, let us say you have palladium acetate and all of us know, how to shift the arrows from inamine, so it goes to pardium. And so, what you will see then, what the rearrangement, so what you will be getting, you will be getting R 1 R 2 and here would be palladium acetate, all of us know. And I mean, I just skip the second step that is, the loss of hydrogen from the position swap palladium is attach, just like a aromatic elimination substitution reaction.

So, hydrogen is lost and then, you get this, so palladium is now incorporated to the beta position respect to the nitrogen and and what is next, these are all the standard protocol. What is expected now, what is next step, so these are all typical organ metallic mechanism I mean, there would be many more. Organic metallic chemist would do all kinds of things ((Refer Time: 27:18)) and insertion, substitution, all these things, but organic chemist skips all those steps, basically we just very quickly go to the final product

So, what is the next step, next step is the insertion of palladium between carbon and hydrogen I mean, there are so many carbon hydrogen of course, the one that is aromatic one CH 2. So, what you will find, you will find, so something like this would found, this is R 1 R 2 and hydrogen and this. So, and then that means, then of course, acetic acid comes out then, you have all kinds of elegants here and by now, all of you know what is the next step?

Student: Reductive elimination

So, reductive elimination and that means, it will go like this and this, so once you have reduction elimination of palladium, 0. So, what you will get, you will get the product palladium 0 and then, there palladium has to be recycled. Recycle means, has to be converted into divalent palladium, so in oxidising agent. What is oxidising agent, as you will see on the list, in one case it is cupric acid, other case cupric acid and oxygen and oxygen will be activated to hydrogen peroxide, their oxidize this palladium to pelladium 0.

So, all kinds of techniques are there then, ferric chloride different kinds of oxidizing agent, but in the certain cases, the reactions are bad, some reactions are very good depending on the situation and you have to be little expert in finding out the optimum conditions. But, in organic chemistry often we do, what we do, we just keep on optimizing different thing without knowing little bit of these thing. So, but any case, this method of, but unfortunately for example, I will not tell you the exact problem, long back we had a similar problem, we could not solve the problem.

And we could not solve the problem, may be in few months time, we will again take up the problem, exactly this very similar problem, only thing that R 1 R 2 were member of a cycle. So, you could not connect them, but someone in fact, many of you know, he is very heterocyclic chemist Knolker, he has done this thing very easily without much problem. He has used cupric acetate and phenyl hydrogen acetate and got the carbogen derivative without much problem.

That means, in this case, the other side also is a cycle, but he could get to this carbogen derivative with this. Few years ago I mean, one could also convert this simply with iodine, iodine is an oxidizing agent for all practical problems, because it gets converted to iodide. So, if you just mix them together, at high temperature it can give you the carbogen. But, in principle, there are many methods available and what you will see here, I will give you one more example, it is again starting from mono substituted one.

But, in this case, this inamine is little different though, so again it is an inamine though, now nitrogen is not link to the aromatic ring system. So, you have an hydrogen here that means, circled hydrogen, this circled hydrogen and there are two different kinds of hydrogen. So, if you have proper oxidizing agent and it should undergo dehydrogenetic cross coupling or we call cross dehydrogenetic coupling.

So, once again this combination is palladium acetate, cupric acetate and this is 10 more percent, 10 more percent means, catalytic. And this is one equivalent cupric acetate and of course, without saying one can write the corresponding indole derivative. So that means, this example tell you very useful reaction, the useful way of looking at the...

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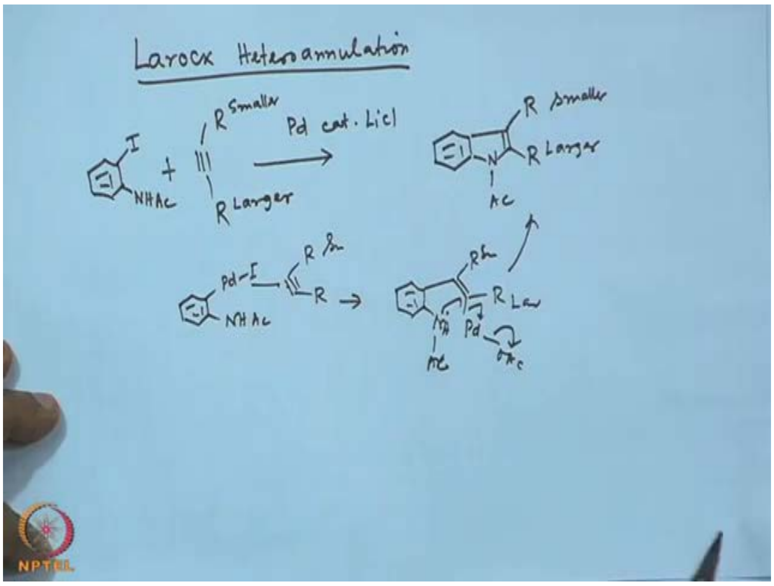

Now, next one, this has been very popular these days, this is known as Larock hetero annulation and what is the meaning of annulation, formation of a new ring, formation of minimum two new bonds. In this case, you are incorporating one hetero atom into the new ring, so that is the reason, it is known as heteroannulation. And what is the starting material, in this case it is the just one was in sort of like a intra molecular reactions. But, in this case, the Larock annulation of named itself says that, actually it shoud be an intra molecular reaction.

Normally, annulations are intra molecular reactions that means, you have to have two different component and in this case, one of the component is let us say like this that menas, alkynes. One of the component is alkyne and then, other component is, now for a change it is disubstituted benzene derivative that means, iodo acetanalyde, iodo aniline kind. So, one kind of one class is iodo aniline, other kind is this alkynes, by the by this alkynes are known as or classified as internal alkyne, it is not a terminal alkyne, terminal alkyne means hydrogen is free, so internal alkyne.

And what is again the catalyst is palladium based catalyst and often little bit of sodium chloride, lithium chloride is used many of you know, because it is easier to substitute reagent with a chlorine and the palladium. And advantage that you get aniline derivative, so disubstituted aniline derivative, 2 3 disubstituted aniline derivative in one single part. Now that means, if you have a symmetrical alkyne, there is no problem, but if you have let us say, if you have two different group, one is large of course, other is smaller one.

Then, you will have different problems, the two position could be with larger, other one could be smaller. So, there are you have possibility of regio isomer formation. Fortunately, this method is very regio selective means, it gives only one isomer exclusively and if you know little bit of the reaction mechanism, you can predict which one would form. That means, with a larger would be at the two position or three position, but any case that is the reason why, this method has been become very popular, because it is one part, regio selective, the substitution tolerance are very high.

So, guess which one, between the two R groups, which one would be the larger one, often you see when you go to this typical electrophilic, nucleophilic, substitution reaction, etcetera is follow a mechanism. But, if you want to just change the orientation etcetera then, you go the organo metallic compound. So, organo metallic compounds gives sort of counter thermodynamic product for example, many of you know, if you have internal double bond, you can shift shift it to the terminals of an alkene by using an organo metallic compound.

What is that, there are methods you have an internal olefin, you want to shift it to the terminals of carbon chain, you do hydro boration with bulky group then, keep on heating, because of the bulk, it will go to the end then, you use one more alkene, where this boron would be transferred to this second alkene. So, like this you know, so similarly most of the organo metallic reactions are sensitive to staring effect because of that, this R larger would be in a particular positions and giving rise to the particular regio isomer.

I will give you the answer, let us say if you can make out and almost always the larger group would end of in the position 2. So obviously, the other option is, this is the smaller one and mechanistically, should I write mechanistically one can quickly think about that palladium has a job to under go oxidative addition. So, if you have palladium 0, you undergo oxidative addition then what, palladium because of the iodine, here electrophilic in nature.

So, one would expect that, polar corrector would dictate this orientation of acetylene, but in this case, because it is metal templeted reaction, so eventually this larger group should be higher from the thing and it will under go insertion the way larger here and are here smaller one. So, I mean, you can say first it forms the complex and then, this is smaller one and here, we have a palladium, etcetera R larger then, NH, acetate and then of course, the palladium undergoes reductive eliminations.

So, this is how that means, basically during this insertion, it is oriented in the such a manner that, actually the smaller one would be link to the benzene ring system. So that means, it is a powerful reaction, it is one part reaction, starting materials are very simple alkynes, all this ortho anilines, ortho iodo anilines can be easily made. If you have proper substitution, you can just simply adding iodine to the aniline, you can get the corresponding iodo compound, because anilines are very activated.

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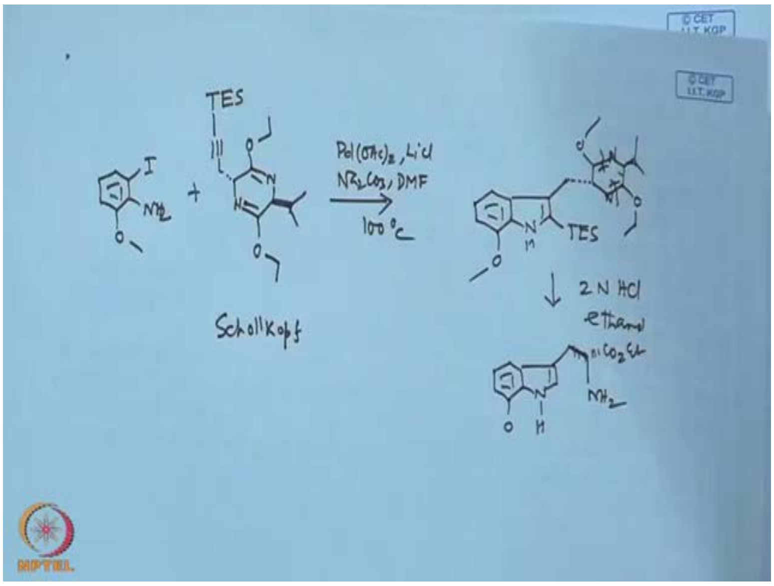

I will just give you one example, that would tell you this importants of this reaction and it can accommodate all kinds of the substituents here, like you have aniline, oxygen here. And then, this is chiral auxiliary, I do not know whether you know or not, it is chilar auxiliary, where you will have this ethoxy on both the sides then, you have iso propyl group here and TES. Let us say, this is chiral auxiliary, reaction conditions palladium acetate, lithium chloride then, sodium carbonate and DMF 100 degree Centigrade.

So, both the substrates satisfy the requirements, one is iodo aniline then, other one is internal alkyne and now you have to decide, see here triethyl silyl group and on the other end of this alkyne, you have CH 2. So, between the two, which one is larger, I think all of us would agree silicon, silicon is a triably substituted, so it is a larger group. And this other auxiliary which is known as actually, is a very famous one Schollkopf, is called Schollkopf auxiliary.

This is a must auxiliary, it can produce amino acid and it is obtained from, if you look at this substitutes here, this portion comes from valine, the other portion comes from the lysine. And this amine portion, it depends on effected, silicon motif depends on effected and in one part what you will be getting, you will be getting this indole derivative here and this one alkyne portion and this is triethyl silyl portion. And then, you have this group here then, nitrogen, both the nitrogen are with respect to each other in these 1 and 4 positions.

Then, you have this isopropyl side chain and this etyl side chain, ethoxy side chains, that is it and it could have been the other wise, but as I said already, that this larger group would be attach to the C 2 position. So, you will have rise this one, this linkage and what next and if you just treat with the two normalised Hcl in ethanol and what will find of course, the indole ring is very stable, there are three things which take place here, actually hydrolysis.

So, hydrolysis would give you this ester here, this is NH 2 and of course, this one that means, it hydrolyse this heterocycle, that pyralgin derivative, hydolyse this shift base that means, hydrolysis would give you this ester here. And on this side, basically this would be valine, the other should be this that means, basically hydrolysis would take place in amine position.

So, one side will generate this amino group and other side ester group, it is nothing but, it is a ((Refer Time: 45:15)) derivative and under the same condition, decyclization take place. So, this is nice way of getting this optically active ((Refer Time: 45:23)) derivative. And so, what else, one more style of getting indole derivative, which is well known, that also starts from this alkyne derivatives.

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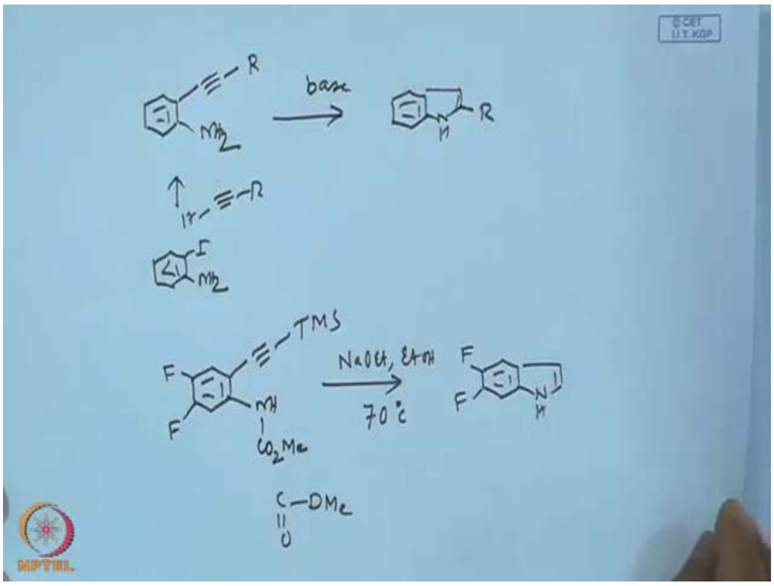

So, alkyne derivatives here again something like this, if you have and this NH 2 is a very popular one, what have to do, just basically use base and you straight away go to the product here. That means, this alkyne derivatives all of us know, can obtained by solo plate coupling from the corresponding iodo compound. So that means, you can make use of terminal alkyne, so that mean, iodo aniline, you can separately do this solo plate coupling and then, you can get to this one.

And then, this cycliation can be achieved by use of different basis different like the one example I will tell you, it is quite need to see that, how this alkyne can be converted to corresponding indole derivative. Here, you have fluorine substituents and mind it, it is a base, sodium ethoxy ethanol and of course, ethanol is there means, temperature is not very high, only 70 degree Centigrade. And once again in one part, you get to the corresponding indole derivative and that too 2 3 unsubstituted indole derivative.

So, what you see here, the three things are happening, one is cycliation, if this nitrogen minus is attacking this alkyne, so undergoing cycliation. Second thing that is going decyclization, third thing that is taking place is known as alkoxy decarbonylation that means, CO O amine. So, in this case, methoxy decarbonylation more prescribely, methoxy group and decarbonation taking place, so you get to this one. And this has been known, there are in most cases either ethoxide, sodium ethoxide, ((Refer Time: 48:24)) are very recently...

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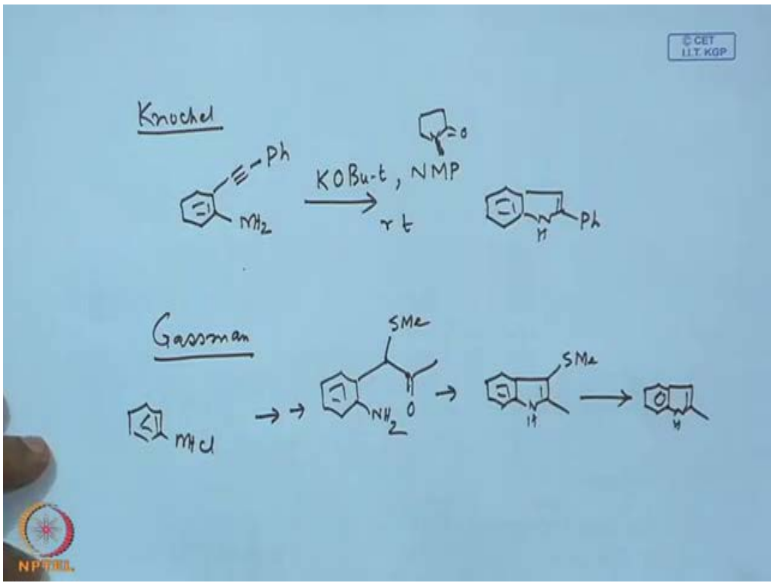

What I said is knochel type, actually Pal Knochel, Germen scientist, what he did, his protocol is very similar, but he could again published in a good journal, only doing a small change in the reaction condition. What was it, it is a potassium tertiary butoxide and NMP, what is it, n methyl pyrrolidone, again a heterocyclic, so it is a high boiling solvent, so high boiling solvent this. And of course, the product is the corresponding indole derivative.

So, what is the difference between the previous one and this one, in the previous case, we are sodium ethoxide, ethanol and 70 degree Centigrade and latest one, only have a lower down the temperature. So, and that means, this is a good achievement, just lowering down the temperature and why it is so, because what is the job of the NMP, NMP actually solubalize all this alkoxides, it can ethanol does not dissolve this alkoxide, but here it can solubalize in this alkoxide and hence, you can accelerate the reaction.

So, there are other reactions in there are many other kinds of reactions, I have already told you before, there are name like castro reactions again starting from this iodo anilines then, you have palladium catalyst cycliations of allele anilines then, there are other also call ma indole synthesis then, cacchi indole synthesis. So, like wise many, but the most popular one what we learned is still there in the text book though and that is known as gassman indole synthesis

So, I think you will find this gassman indole synthesis both in Gricke's book and Joule's book, but just very briefly what it is, it is nothing but, it again starts from aniline. And I will just tell you only this much, you generate something like this, amino kind of ketone and here you will have, where they make the substrate introduces an asemi group at this particular position. This is a sort of a kind of, you can say intra molecular form of shifting.

I mean, I can go on talking about it, it starts from actually something like this then, you do this the corresponding disulphide, this disulphide under condition it form the sulponium salt, this under goes. Then, in the presence of dithalamine, it forms an carbonan and just like ((Refer Time: 52:08)) reaction, it undergoes incorporate the ortho position. And of course, once you have substrate like this and then, rest is quite easy, just simply heating it, you will end up in indole derivative with an asemi group.

Of course, the next one is...

Student: ((Refer Time: 52:36))

No, but you have to do sulfur here, how do sulfur, this thunder protocol is raney nickel, if it is raney nickel, sulfur is knocked off. And so, you product with this and the last one, last one is what.

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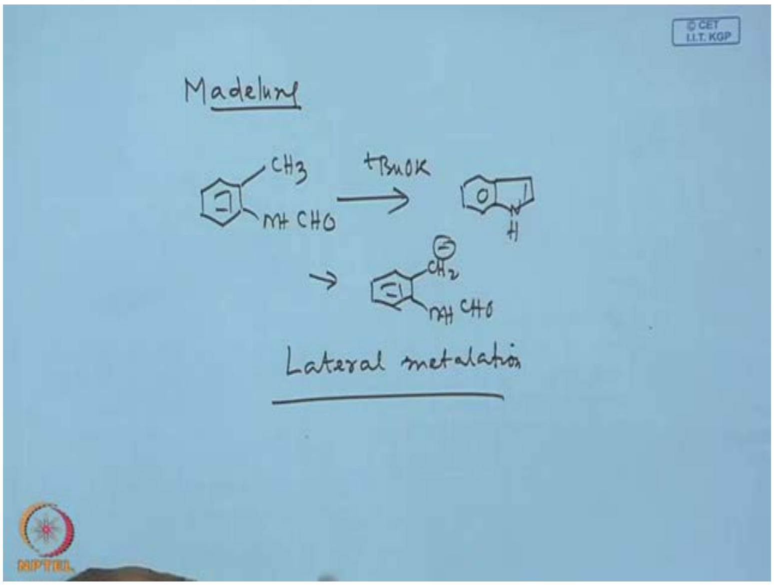

Last one is madelune synthesis, what is madelune synthesis, madelune synthesis is again a something like this, you have to have a CH 3 group here, NH and this thing, what it does, actually you have to use a strong base. So, potassium tertiary butoxide and ortho toulene can be formulated in the presence of formic acid and you get the formile derivative, informile or toulene. So, in the presence of strong base, so what you will get, you will get the corresponding indole derivative.

Mechanistically, what is mechanism, this reaction forms a annon, NH and this AHO, so that means, this annon formation is I think we call it, lot of people have this name is called lateral metallism. Lateral metallism means, basically lateral means, side wise that means, side chain, side chain metallism and more precisely, it is benzylic metallation. And latest development is, in these area if you use n butyl lithium, reaction can be run at 20 degree Centigrade, otherwise these reaction has to be carried out at let us say 200 degree Centigrade.

So, there is a major change now and I have a paper with me, the same person known as Bartoli, do you remember Bartoli indole synthesis. Bartoli in 1990, he has modified the metal procedure, he has use di lithio compounds and instead of using a formyl group, he has introduce this ester here and then, converted them to corresponding indole derivative. That is little more versatile, because you can make use of any kind of ester to introduce the substitutes at two position.

So that means, all these some of the old methods also are still useful, but and among the new methods, which are the new let us say, so far, we have described six or seven different indole synthesis we talked about, which one thing is more versatile. So, in the last class, we talked about three, Fischer then, Bartoli and ((Refer Time: 55:45)). So, in the last class, Fischer indole is more versatile probably and the next most versatile could be, I think Larock.