# Heterocyclic Chemistry
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## Lecture - 33
## Indole Synthesis II

Good afternoon. So, in the last class we talked about several indole synthesis. This is the last class on indole synthesis; not an last class of the heterocyclic chemistry. So, last time we talked about, what? 3 different methods; one was fizzle indole synthesis, another was? No, what is the second one? Battalion synthesis. Third one ((Refer Time: 00:53)) ok. And, what i said on the basis of the starting material you should remember.

Because thats the very easy. For example, when I say fizzle indole means, it starts with hydrogen derivities and then next thing what you should remember, the most common intermediates. For example, fizzle indole synthesis for most common intermediates could be phenyl 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 is jap klingman method. So, where you can make it hydrogen by different way. Second variant could be matheson kristopher matheson he has made this boc protected hydrogen divergent.

So, like wise there are many more buckalto also has produced variant. So similarly, battoli. Battoli is very easy to remember nitro benzenes, nitro alkynes, algenes and gignad phenyl not any kind of gignad again a phenyl gignad that was a phenyl hydrogen and phenyl gignad and, third category was on basis of ((Refer Time: 02:33)) we requires the what? banjo kuonoles and inamino akitones 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 bookswhile very few books would list as you will go on see that it is very powerful reaction. There are little, there are very little problems of course.

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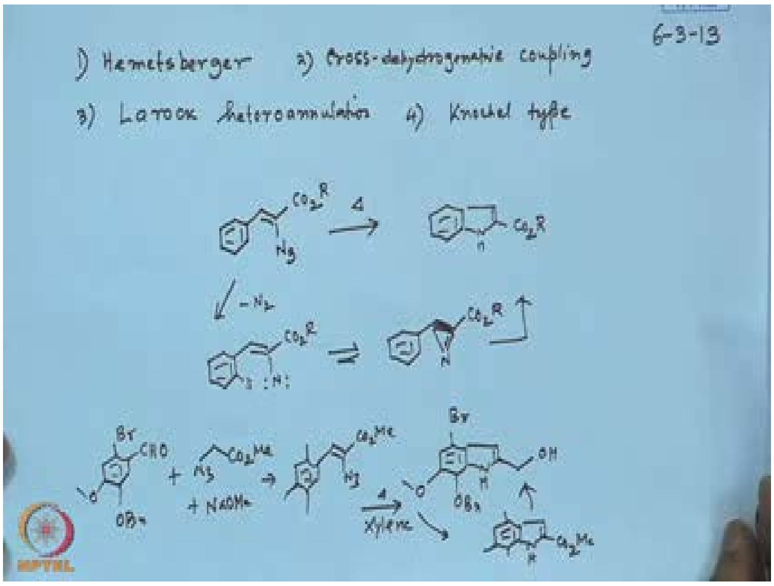

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1) Hemetsberger 2) Cross-dehydrogenative coupling

3) Larock heteroannulation 4) Knochel type

And, so this afternoon we will talk about mainly 3. So, the one that is called himmets burger, is one we will talk about. And, second one probably we 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 heteroanulation, which is again one can say indole synthesis by larocx method. And, the fourth one that it depend it time permits will talk about again this would be, there is no name. But I think I will how is that I will write knockel not really knockel, but knockel type synthesis. 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 hemmets burger, 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 azodo styrene. And, if you heat it not very at temperature just at less than 200 centigrade. So, what you are likely to get you a product which is nothing, but in one salt of like a neutral conditions. You can get to the product here this is indole that is it.

So right, and what is the mechanism? The mechanism is that suggest it, it looses nitrogen so it looses nitrogen and of course,once it looses azoide, the azoid looses nitrogen that means, what you will be getting? We will be getting this nitrine intermediate. So, like albene and nitrine and of course, one can nitrine right and, 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 isomerization. Because isomerazation requires only very little changes in this couritane. So, infact this is suggested, and it has been very pite as you will see you 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? 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 only; you can also question, why not directly nitrine under go insertion to this carbon hydrogen bond of this benzene ring system, 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 or from simple starting material like oxygen. You can make azidines without much problem.

And, let us begin with example, and like say if you are suppose to make an indole derivative. For example, where you will have indole and 2 position will have is hydroxi methyl group and bromo here. And, then this benzyl protecting group and 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 1 would find out, 1 would make a phenyl kind of azite or, aziodo styrene you can make right.

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 C H 2 O H 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, how to make the aziodo styrene you will see that little difficult to make number 1. Number 2; if you begin with C H 2 O H group during the decomposition of the azide, there is a likely hold that this it will undergo nitrine insertion on the other side, instead of being instead of giving this azadine intermediates. So, in this case top one you have an ester group there was no possibility of insertion of the right hand side on the ester side. But think about C H 2 O H 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 here then we call azido ester in this case; this azido ester is very easy to make. So take, then sodium ethoxide or methoxide then typically what you will find? You will find just like a algal 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 will have these methyl ester here.

And of course, once you know that of methyl ester is there, then it is very easy to reduce this to corresponding alcohol. So, this is very straight forward then, what is the problem then? That is 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 very easy if you have azido acetate. You can do salt of an albaltype, you get the phenyl azide. So, all this problems are very easy, but this reaction is little tricky thats it. But that is not the serious problem, the problems is at classical production. Because it is known that most cases this azido compounds are explosives azides are explosive.

So, whenever you do reactions with azide; you have to be very careful. In small quantity of course, I mean we have been doing to over come this so, for you have not come across any problem. But it is report it let, I want should be very careful about this thing. But merits of this method is that you dont have to make azid; 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. You know atleast, I know that 2 different; very convenient methods.

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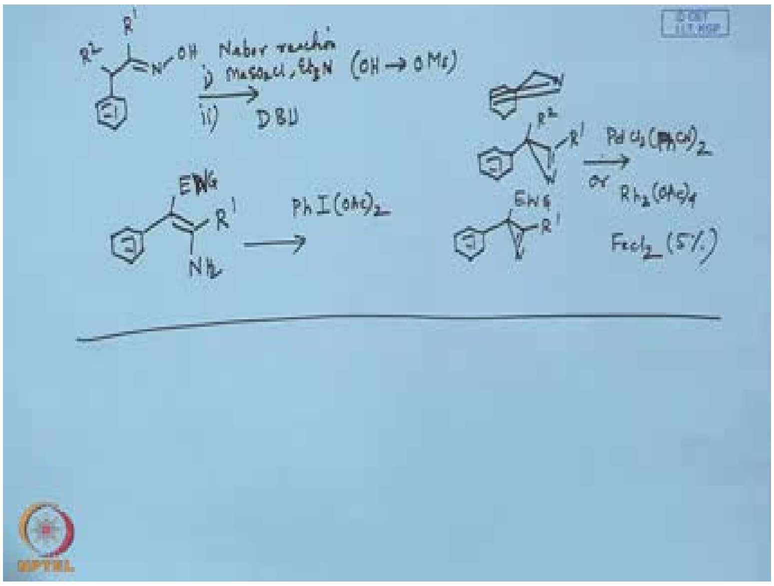

For example, the one where to make an oxen. So, if you begin with an oxen here like oxen all of us know how to make oxen right, the corresponding acetone and hydroxide and hydro chloride so very good reaction and it is a standard reaction for derivatizing ketone. So, that is not a problem, then you do neber reaction.What is neber reaction? Neber reaction is nothing but the first step you make this methyl derivative, that is methane sulphorine chloride and triethylamine. So, I think I dont have to write the intermediate, it converts O H group to O M S right. So, this basically O H is converted to O M S.

And then, second step if you do D B U so, what you will be getting? You will be getting corresponding azidine sorry, 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 by pass the demerits of the hemmets burger procedure alternatively. That is a another way of look at, one just take let us say you have something like this R 1 and electron withdrawing sorry, electron withdrawing group N H 2. So, how do you make it is an inamino ester in the last class we talked about it right.

This inamino ester required can be reaction of ((Refer Time: 14:55)) beta to ester kind of things, then ammonia that would be given. So the same starting material, if it is reacted with a reagent which is written as this one; phenyl iodinium dy acetate is very useful reagent. And, for last, may be what 10 years you have been continuously using this reagent, and this belongs to a class of the agent known as; guess?

Student: Hyper panan iodine reagent.

Very good. Hyper panan iodine reagent, there are plenty of reagents based on this. Why hyper panan? Normally iodine is concedered to be monovalent, in this case divalent, pentavalent are also all of you know. But most case in the trivalent agents are powerful oxidizing agent and mild and selective. So, depending on the situation you can make use of it. There are many uses; you will see one more use also towards the end of the lecture, plus it is innocent the by product is advoingine.

So, that means does not cause any decomposition of the products.All the starting material that is why this very easy. But it is nice oxidizing agent and, so what do you get? Once again what you get is the basically; this you will get, this azidine substituted azidine here and electoral withdrawing group. So, that means you can have all kinds of azidines now, what you will find? That the azidines again you know can be converted to indole; you have already as you seen before by simply heating it.

But you do not 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 acetolytel complex right; those who are working with peradium complex, you will see is very stable complex with 2 aceto nitrail sorry, so in this case benzo nitrile. 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 anidine sorry indole.

Similarly, there are or R you can use, I think the one that is use to generate carbine from dyzocompound. What is this di rodium; what, di rodium tetra acetate, this is very di rodium tetra acetate is very nice again complex is basically what it does? It elevates the temperature of the decompositions of this azidines or, azides. And, it generates nitrines and carbines milder conditions. And, then the latest one I think latest one is very interesting, it has been published in 2010. And, what do you add is nothing but ferrous chloride and, that to with only 5 percent.

So, you see here the trend here, that was the peradium expensive sodium 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 use azidines. And, that azidines can be obtain from the inamino ketones or the oxens. And, they decompose for decomposition for the rearrangements, you have many options, different kinds of the catalyst and this things. And, then so what next, this that means again going back to the little bit to the last class. So, we had only there are 2 different kinds of methods; right general methods. 1 is mono substituted benzene, other is the di substituted benzene, the third and fourth category the where you can make the benzene derivative is not really very popular. So, in this one you can see here, this is a mono substituted one there are other wise also to look at.

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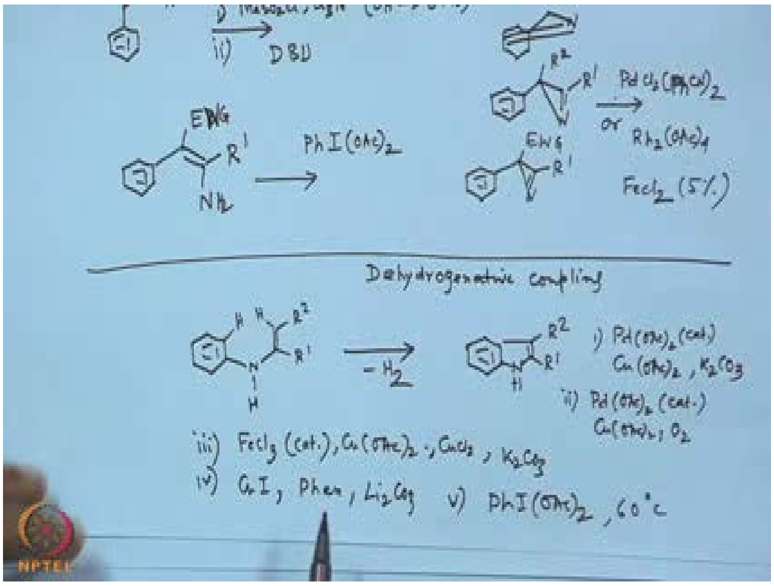

For example, if you take enamine kind of thing here, if you take acetone straight way make this enamine. And, what you can guess? How do you make indolphone here; so, what is the reason would you like to use? If you just take the atom balancing, if you do the little bit of atom counting. What you will find? It actually removes 2 of this indicated hydrogens. So, that is reason this is known as dehydrogenetive, this is a what very recently used, dehydrogenetive coupling that means minus 2 hydrogen. So, you end up with the corresponding indole derivative.

So, in principles looks very good right, and so easy anenamine formation; you take from acetones and little bit of isolations. And, then you will get this anenamine done. Well, but of course, you have only limited choice but I cannot say so. But because by now it is known, other more than 8 different catalytic systems are found to be useful. And, an most of them are published in good generals. 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 hygene and tendency to under go c paradation reaction.

Means likes any palladium chemistry reaction, what you do? Let us say first thing you have learned last year, all the cross coupling reaction would be involved paradium; why? Because palladium under go first insertion between the carbon halogen bond; and, then it goes on reaction. Another carbon bond, carbon to form carbon paradium 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 the differ little in their composition. For example, very first one the popular one is palladium acetate.

And, this of course, this is expensinve. So, you have to use catalytic amount and the strechumatis catalyst could be copper. Because copper acetate is cheaper. And, all of us know you need also base, because eventually acetic acid acid etc 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 cupling acetate this again catalytic amount then what is the stretuatic oxidant or what do we call terminal oxidant is oxygen it self. 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 be a has to have a base here right. So, forth one I mean once again, the previous one was palladium acetate, cupric acetate oxygen you skip cupric acetate. All different combionation basically you have do little bit of the trial and error. And the one little un common here is a cupric iodide and phen right phen all of you know, and this case lithium carbonate because it is more soluble in organic solvents so, what is phen?

Student: 9 10.

Not 9 10, it is not 9 10; I suppose it is 1 10. Phen has to be 1, 10 right, not 9, 10. I think fine, 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 dictate. This is also has been used and that to very low temperature at 60 degree centigrade. So, you have all kinds of the options and mechanistically obviously mechanistically if you look at the mechanism.

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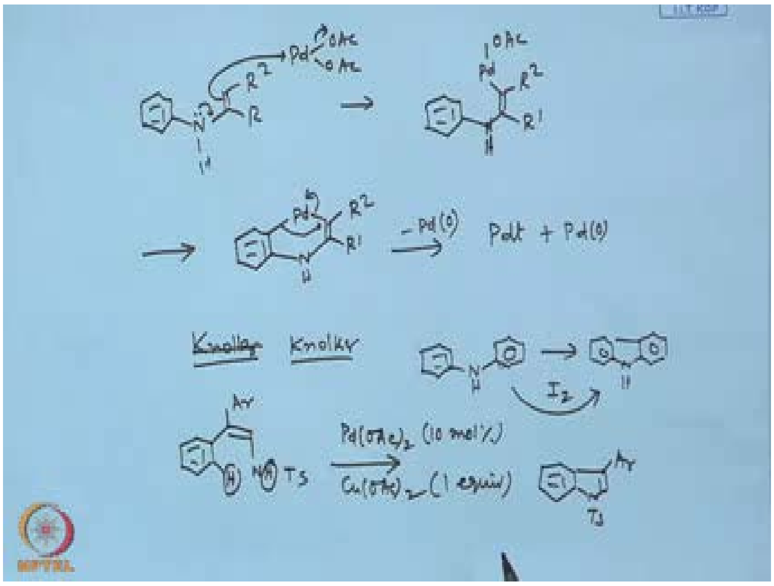

So, what is the first step? the first step would involve palladation of a that means hydrogen here. Let us say you have palladium acetate right, and all of us know how to shift the arrows from enamine; so it goes to palladium and so, what you will see? Then, what the rearrangement? So, what you will be getting? you will be getting R 1, R 2 and here would be palladium acetate right all of us know. And, I mean I just skip the second step, that is the loss of hydrogen from the position of hydrogen in the palladiun is attack right, just like a aromatic substitution reaction. So, hydrogen is lost and then, you get this so palladium is now in cooperated to the beta position respect to the nitrogen. And, what is next?

These are all the standard protocols; what is expected now? What is next step? So, these are all typical organ metallic mechanism, I mean there would be many more organ metallic chemistry would do all kinds of things then pi complexion and insertion, substitution all this thing. 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 paradium between carbon hydrogen. I mean, there are so many carbon hydrogens. Of course, the one that is aromatic one C H 2. What you will find? You will find so something like this would found, this is R 1, R 2 and hydrogen and this right. So, and then that means; then of course, acetic acid comes out. Then you have all kinds of elegant 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 paradium 0 and then, there palladium has to be recycled. Recycle means has to be converted into divalent palladium so, need an oxidizing agent. What is oxidaizing 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 that oxidizes this palladium to peradium 0. So, all kinds of techniques there then ferric chloride different kinds of oxidizing agent; but 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 do what we do, we just keep on optimizing different thing know without knowing little bit of these thing right. 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. And, we could not solve the problem may be in few months time we will again take up the problem exactly this is very similar problem, only thing that R 1, R 2 where member of a cycle. So, you could not connect them but someone in fact many of you know, he is very heterocyclic chemist right. Knolker, he gave here he has done this thing very easily without much problem.

He has used cupric acetate and phenyl hydrogen acetate and got the carbazole derivative, without much problem that means; one in this case the other side also is a cycle but he could get to this carbazole derivative. Few years ago, I mean one also, who just that means 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 high temperature it can give you the carbazole. But there in principle, there are many methods available; and what you will see here I will just I will give you one more example, its again starting from mono substituted one, but in this case this phenamine is little different though.

So, again it is enanmine though, now nitrogen and not link to the aromatic ring system. So, you have an hydrogen here that means circled hydrogen, this circled hydrogen and they are 2 different kinds of hydrogens. So, if you have proper oxidizing agent and it should under go de hydro genetic cross coupling or, we call cross go de hydro geneted coupling. So, once again this combination is palladium acetate cupric acetate and this is 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; it is very useful reaction, the useful way of looking at the.

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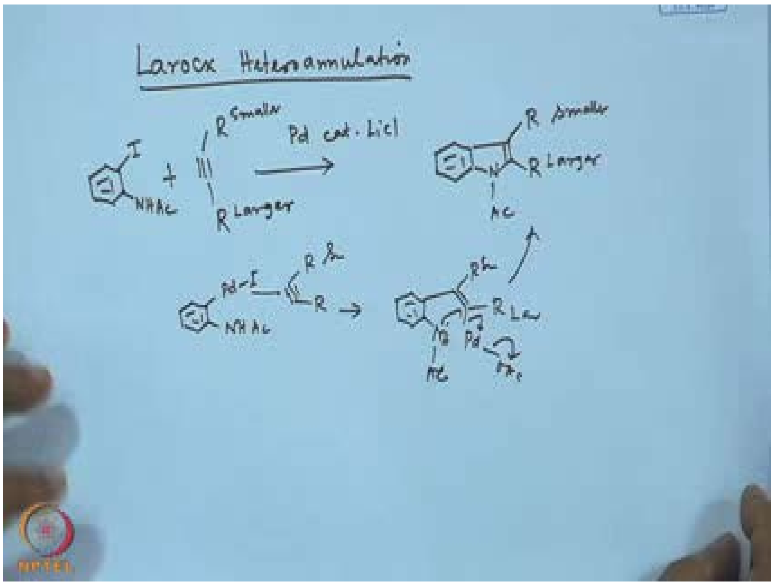

Now, next one this has been very popular these days; this is known as Larock hetero annulation right, and what is the meaning of annulations?

Student: Formation of a new ring.

Formation of new ring with minimum 2 new bonds; in this case, you are incorporating one hetero atom into the new ring. So, that is the reason is known as hetero atom 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 will larock annulations; the name itself says that it actually it shoud be intra molecular reaction. Normally, annulations are intra molecular reactions; that means, you have to have 2 different components. And, in this case, one of the component is; let us say like this alkynes, and then other component is now for a change it is now is di substituted benzene derivative that means iodole ((Refer Time: 33:48)) So, one kind of one class is idole elegant, other kind is this alkynes by the by this alkynes are known as are classified as internal alkyne right. It is not a terminal alkyne; terminal alkyne means hydrogen is free.

So, internal alkyne and what is again catalyst is palladium base catalyst and often little bit of sodium chloride, lithium chloride is used. Many of you know, because it is easier to substitute elegant with a chlorine and the palladium. And, advantage that you get aniline derivative; di substituted aniline derivative. 2 3 di substituted aniline derivative in one single part fine. Now, that means if you have a symmetrical alkyne there is no problem. But if you have, let us say if you have 2 different books; one is large of course, other is smaller one. Then, you will have different problems; the 2 position could be larger, other one could be smaller. So, there are you have possibility of regio isomer formation.

Fortunately, this method is very regio selective mean, 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 2 position all 3 position. But any case that is the reason why, this method has been become very popular. Because it is one part, it is regio selective, it has it can tolerate or the substitution tolerates are very high.

So, guess? which one between the 2 r books, which one would be the larger one? See in the often, you see when you go to this typical ((Refer Time: 36:29)) substituted reaction etc you follow a mechanism. But if you want to change the orientation etceara. Then, you go the oregano metallic compound. So, organo metallic compounds gives sort of counter thermo dynamic product for example, many of you know if you have internal double bond you can shift it to the terminals of an alkene, by using an oregano metallic compound right.

What is that? There are methods, you have an internal alifil. You have shift it to the terminals of chain 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 borone would be transferred to this cycle alkene. So, like this you know so similarly, most of the oregano metallic reactions are sensitive to starring effect. Because of that, this R larger would be in a particular position and, giving lifes 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 jump to under go oxodation right. So, if you have palladium 0, you under go oxygen de addition then what, palladium because of the iodine here electro folic in nature right. So, one would expect that polar connector 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 means the larger here and, r here smaller one.

So, I mean you can say first forms the complex and, then this is smaller one. And, here we have a palladium etc. R larger then, N H acetate and then of course, the palladium undergoes reductive eliminations. So, reductive elimination so, this is how basically the 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. This ortho anilines,ortho idol anilines can be easily made. If you have proper substitution, you can just simply adding iodine to the aniline, you can get the corresponding idol compound. Because anilines are very activated. I will just give you one example that would tell you this importance of this reaction.

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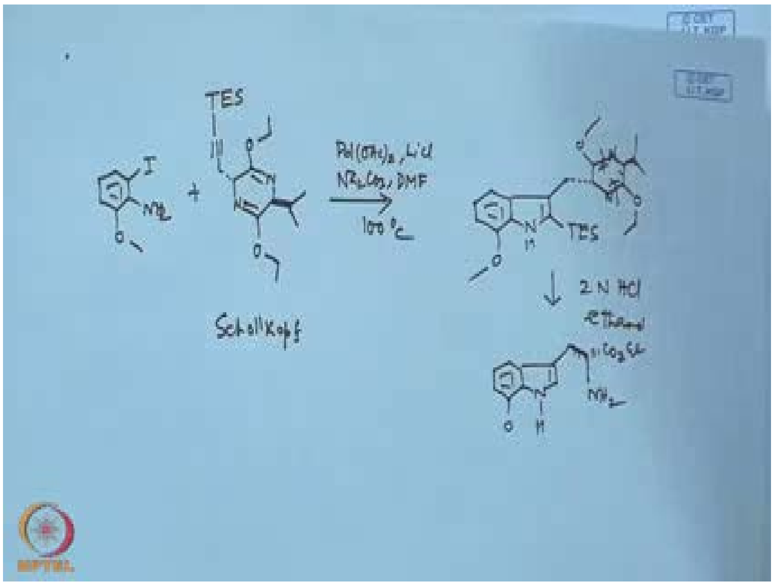

If you and it can accommodate all kinds of the substituents here, like you have aniline, oxygen here and, then this is cyler auxiliary. I do not know whether you know or not it is cyler auxiliary, where you will have this ethaxy on both the sides. Then, have iso propel group here and, T E S let us say, this is a kyler auxiliary reaction conditions, palladium acetate, lithium chloride then, sodium carbonate and D M F 100 degree centigrade. So, both the substrates satisfy the requirements, one is ido aniline then other one is alkyne internal alkyne. And, now you have to decide, see here triethyl homily group and, on the other end of this alkyne you have C H 2. So, between the 2 which one is larger?

I think all of us would agree silicon right, silicon is a tri homily substituted with the larger group. And, this other auxiliary whish is known as actually is a very famous one schollkopf this called scholkopf auxiliary; this is a must auxiliary is called produce amino acid, it can produce amino acid. And, it is obtained from; if you look at this substitutes here, this portion comes from hyaline this proportion comes from the glysine. And, this amine portion revence on effected, silicon motive revence on effected and, in one part what you will be getting? You will be getting aniline sorry indole derivative here.

And, this one terminal sorry alkyne portion and, this is triethyl silal 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 iso propel sitezen and this etyl sitegen, ethoxy sitegen that is. It and it could have been the other wise, as I said already is that this larger group would be attest to the C 2 position so, you will have rise this one this linkage.

And, what next? and if you just treat the 2 normal H C L in ethanol and, what will find? of course, the indole ring is very stable there are three things; we take place here actually hydrolysis. So, hydrolysis would give you this amino group here, ester here, this is N H 2 and of course, this is 1. That means, hydrolise this heterocycle that pyralgine derivative hydolyne is shift base means hydrolysis would give you this ester here. And, on this site this would be basically, this would be hyaline, the other should be this. That means basically hydrolysis would take place in amine position and, one side will generate this amino group and, other side ester group nothing but it is ((Refer Time: 45:15)) derivative; and at the same condition are deciliztion take place. So, this is nice way of getting in this optically active tiptop hen derivative.

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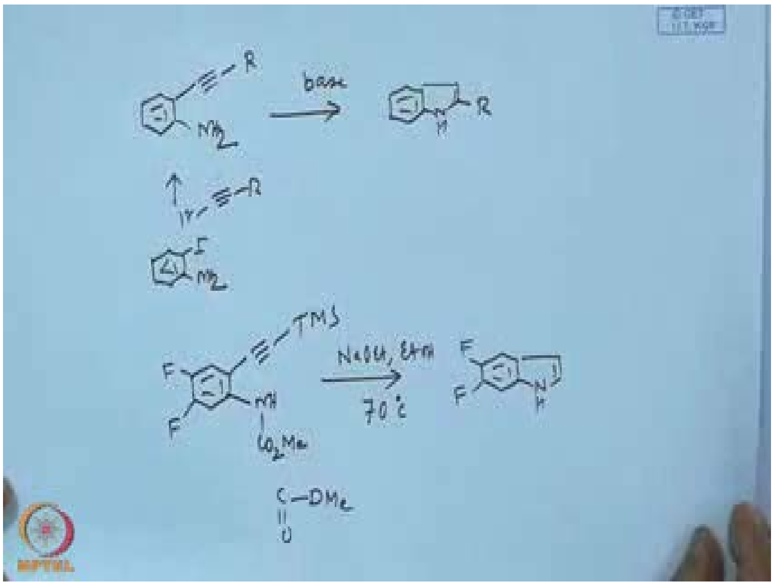

And, so what else, one more style of getting indole derivative which all that also starts from this alkyne derivatives. So, alkyne derivatives here, again something like this if you have and this N H 2 and very popular one. What have to do? Just basically use base and you straight way go to the product here, that means; this alkyne derivatives of all of us know, can obtain by solo acid coupling from the corresponding iado compound. So, that means you can make use of terminal alkyne right.

That means, iado analine, you can separately do this solo acid coupling and then you can get to this one and this cycliation can be achieved by use of different basis. Like the one example I will tell you, it is quite need to see that, how this is alkyne can be converted to corresponding indole derivative here. You have phenols sorry fluorine substituents and mind it is a base sodium ethnocide ethanol.

And, of course ethanol 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 to 2 3 un substituted indole derivative. So, what you see here the 3 things are happening; 1 is cyclication, if this nitrogen minus is attacking this alkyne so under go in cyclication. Second thing that is going decilization. Third thing that is taking place is known as alkaxi de carbonation. That means, C O O amine; so, this is are a in this case methoxy de carbonations more prescribely methoxy group and, de carbonation taking place so, you get to this one. And this has been known there are in most cases ((Refer Time: 48:23)) are very recently.

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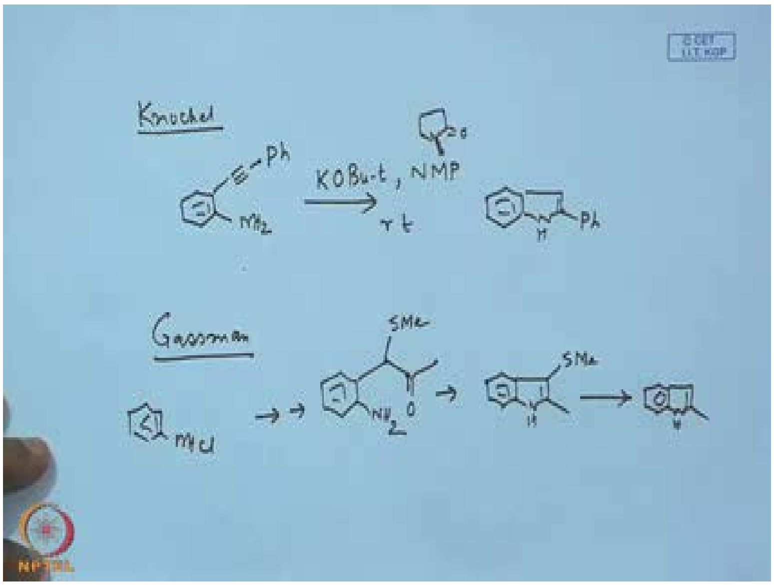

What I said is knocel type, is knocel actually pal knocel germen scientist; what he did? his protocol is very similar, but he could again published in a good journal only doing a small change in the reaction condition. What was it? It is a potassium trisoly bitoxide and N M P. What is it? N methyl payrolledenole. Agin a heterocyclic right, so it is high veiling solvent. And of course, the product is the corresponding indole derivative. So, what is differ? And, 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 low down the temperature.

So, and that means this is a good achievement thet is lowing down the temperature so, and why it is so? Because what is the job of the N M P? N M P is actually solubalize all this alkoxides it can sodium ethixde, ethanol does not dissolve this alkoxide; but here it can solubalize in this alkoxide. And, hence this 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 reaction, again starting from this iado anilines then, you have palladium catalyse cycliations of allele anilines then, there are other also call ma indole synthesis then, cacti indole synthesis. So, like wise many, but the most popular one what we learned still they are in the text book and, that is known as gasman indole synthesis.

So, I think you will find this gasman indole synthesis both in grickes book and, jules 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 a ketone and, here you will have where they make the substrate introduces an a semi group at the this particular position. This is a sort of a kind of, you can say intra molecular pomarar shifting, I mean I go on talking about it. It starts from actually something like this, then you do this the corresponding di sulphide, under condition it form the sulponium salt, this under go.

Then, in benzenes of tri ethylamine it forms an carbogen and just like somanode houser reaction. It under goes in corporation and ortho position. And of course, once you have substrate like this, then rest is quite easy just simply heating it you will end of indole derivative with an a semi group. Of course, the next one is no, but you have to demon sulpher here. How do sulpher this thunder protocol is which renanicule. If you an renanicule sulpher is not of and so you product with this.

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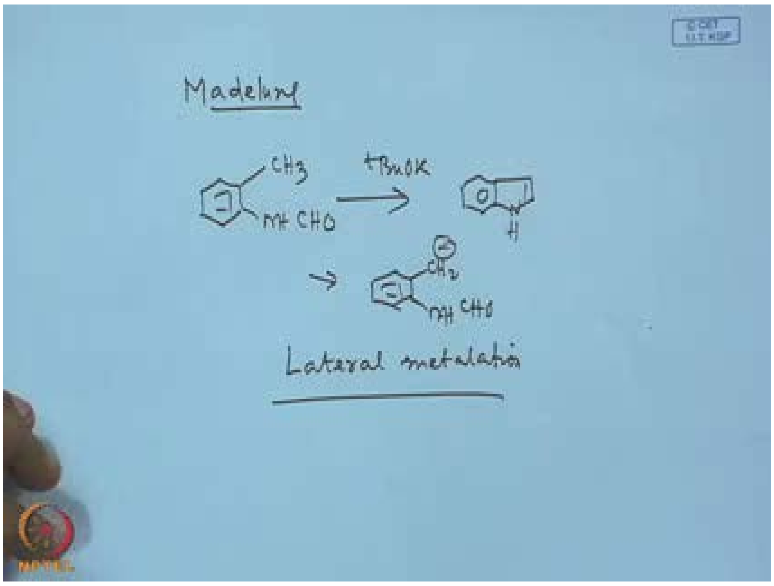

And, the last one is what? Last one is madulane synthesis. what is madulane synthesis? Madulane synthesis is again, a something like this right you have to have a C H 3 group here, N H and this thing. What it does actually? You have to use a base, strong base so potassium trosli bitoxide and ortho toloidine can be formulated in the presence of acetic acid. And, you get the formile derivative in formile altolatine. 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 anine here, N H and this C H O. So, that means this anine formation is I think we call it lot of people have this name is called lateral metallation.

It is known as lateral metallation. Lateral metallation means basically, lateral means side wise that means side chain, side chain metallation. And, more precisely it is benzylic metallation. And, latest development is in these area, if you use enbito lithium reaction can be run at 20 degree centigrade, other wise these reaction has to be carried out and, 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 batoli right, do you remember batoli indole synthesis? batoli in 1990, he has modified the metal procedure. He has use di lithio compound and instead of using a formyle group, he has introduce this ester here and then in converted.

Them 2 corresponding indole derivative thats little more versatile. Because you can make use of any kind of ester to introduce the substituted 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 for we have described 6 or 7 different indole synthesis we talked about right. Which one is thing would more versatile? So in the last class we talked about three pheser then batoli and lenities crew. So, in the last class fissle indole is more versatile probably and the next most versatile could be I think larook but it has.