**Heterocyclic Chemistry**
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**Lecture - 32**
**Indole Synthesis I**

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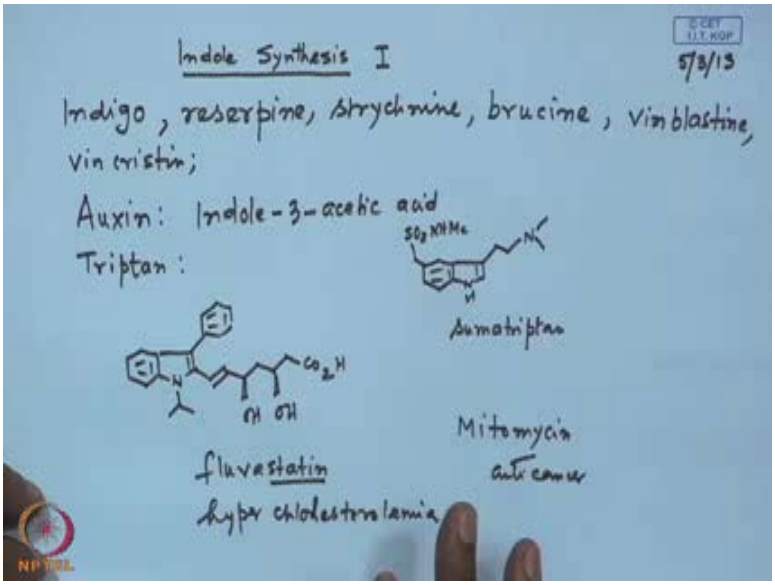


Good morning. Today the lecture title is Indole synthesis. Indole synthesis is a very important topic, so that is why it is divided into 2 parts - number one today. And tomorrow we will talk about the second part of the lecture, and why it is important? Because there are so many important Indole compounds are there, both natural as well as synthetic. And consequently there are many important, many famous Indole syntheses are known in the literature; I mean like pyrrole; what you have seen there are more than 60 pyrrole syntheses. In Indole also is closely parallels pyrrole synthesis. But number is little less; it is a many 2 dozens of very famous Indole synthesis are known in the literature.

So, what I will do today? I will just basically give you the glimpses of may be 3 or 4 different Indole synthesis. And before that let me just tell you little bit of about the importance of the Indole compounds. Because as I said because they are very important. So, how they are important as natural products they are important, and then you have to know little bit of the important compounds; let us say. What are important Indole

compounds? There are 2 different kinds what I said natural and synthesis. Let us say among the natural Indoles; what are the important Indoles do you know of that you have to just bit of you have to think about it. What is the natural Indoles? You think do you know of at least you have to have 12 different or let us say 10 different natural Indoles. I think what comes to my mind.

Student: Indigo.

Indigo. What else talking about natural Indole compounds. What?

Student: ((Refer Time: 02:51))

Tell me the name. You have to tell me the name.

Student: ((Refer Time: 02:57))

Good, reserpine.

Student: Mescaline.

Mescaline is not I do not think this is an Indole alkalide. But you check reserpine and then strychnine; strychnine which is a heterocyclic compound.

Student: ((Refer Time: 03:18))

Then, brucine many of you know; strychnine and brucines they are used for optical resolution, chiral resolution and very asymmetric bases. Then what else; I am talking about the natural once reserpines, strychnine, brucine then what else vinblastine. Then vincristin they are all vinblastine and vincristin they are commercially used as ((Refer Time: 03:59)); they are actually dimeric Indole kind of alkaloids. And they are commercially used in for treatment of cancer. So, they are all different kinds of these natural; then there are more than 10 different Indole synthetic Indoles are known. And the common is to one of course benzophenone, auxin right auxin. What is it? Auxin is a planned grow thermal is a very one of this very simple Indole derivative.

Indole 3 acetic acid is a planned is a class of planned the member of the plant go to thermal auxines. Then there are so many thing like say there is a class call triptan. What is it? Triptan is a again a class of synthetic drugs which are used for the treatment of

migraine. And I think all of us know what is migraine? I do not know some of you will be having migraine what is the what is the meaning of migraine?

Student: ((Refer Time: 05:15))

Right is a headache. So, the structure would be very similar means similar to Indole acetic acid. So, you have the Indole moiety and at 3 position you have something these. Then other positions also will have substituent; let us say in these case this is a sulphonamide; and this one has a name call sumatriptan. So, likewise you know there are few more actually there is one more call rizatriptan which is marketed by mark; again for the treatment of these. Then there are medicines for treatment of hypertension and then also there is a drug for lowering the cholesterol level in human being. And which is would be looking like again a 3, 4 disubstituted pyrrole. Why I am writing all these things; I think you have to know the importance you know otherwise I mean even today people have been developing synthetic methods does not being; there are so many natural alkaloids I mean alkaloids are all natural; so many bi active natural alkaloids are known.

And, of course they are many synthetic compounds are known; this one for example, as a name called fluvastatin I think by now what is the meaning of the statin means basically all these drugs belonging to this class would provide the cholesterol level. That means, segment for it is used for the treatment of hyper cholestero lemia. So, that means treatment hyper cholestero lemia ok.

So, that means reduce is and so then there are also very I mean quite few more famous drugs. For example, mitomycin so why I am you have to remember some of the names not all the names; but some of the name. Mitomycin is a very famous term and use to again it is an anticancer drug. And because of all these because of the importance of these compound there are so many Indole synthesis. When you talk about the Indole synthesis I think these in our class because there are so many; so you have to just you have to classify and sub classify.

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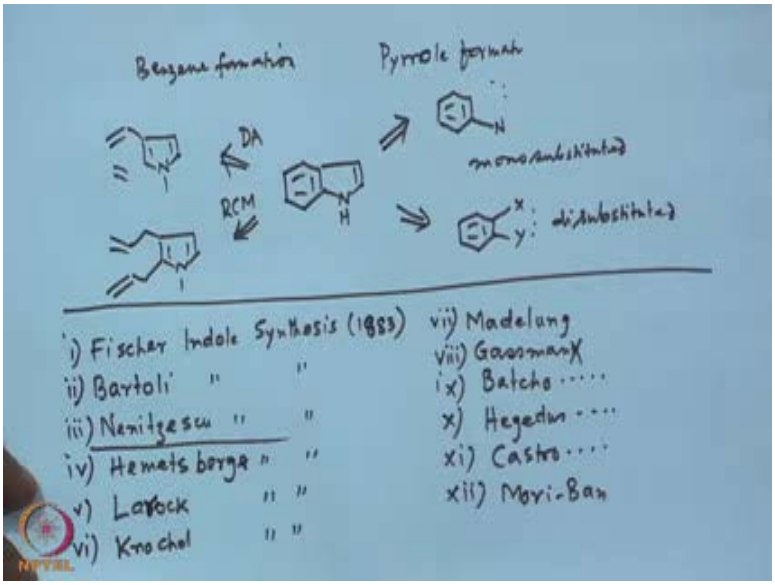


If you take just let us say if you take the nucleus; so like pyrrole if you remember pyrrole if you do the bisection sorry dissection of the molecules or do the retro synthesis; you can come up with more than 20 different methods. So, Indole how many methods you can come up with many, many… So, what we will do actually we will take up only important ones not the those one not the not very popular; like say. For example, what you can do? The way one can think about that so something like this; that means you have to have a aniline derivative or mono substituted benzene. So, you can start from mono substituted benzene right you can then of course there are ways to look at; so one can also let us say x and y. So, you can start from a disubstituted benzene derivative right; so these are the two. Because from the structure you can make out that you can build up a ring here and you a build up a ring here; so 5 member ring.

That means, basically these two retro synthesis reflects the formation of five member pyrrole ring system. What are the other possibilities? Other possibilities could be that you start with a pyrrole derivative now; you have learned we have learned pyrrole right, so Pyrrole derivatives. Now, one can think about let us say Diels-alder kind of thing let us say if you have a vinyl kind of pyrrole you can do the Diels-alder. So, you can make the benzene derivative there is one of the ways one can think about then other possibility. What are the other possibilities? So, right hand sides basically represents the formation of the pyrrole. So, this is a pyrrole formation and then this is a mode where you can form

the benzene ring formation. Then other possibilities one can think about these are the these days which is more popular right.

So, you can think about what is it? The substrate is design for a reaction many of you know RCM metathesis reaction. So, you can think about this RCM here, Diels-alder here; then I mean you can go on breaking this molecule in the way you think about. And one can think about constricting both the pyrrole and the benzene ring together by the intermolecular reactions. So, you have different kinds of mode. And today as I said there are more than 20 different very famous Indole synthesis are known in the literature.

So, what I will do; I will probably talk about 6 or 6 not many 6 or 7. And of course, the first thing that comes to your comes to our mind is what are the methods? I think we limited we limit our discussions to maximum 10 different methods; today may be 5 or 3 to 5 and tomorrow rest. First thing that comes to our mind is Fischer Indole; Fischer Indole synthesis; even today people are using Fischer Indole synthesis. And this was one of the earliest methods discovered when it was discovered in 1883. So, it was discovered in 1883.

So, you see it is more than 100 years old; more than 100 some people still developing very, very the develop method or improve method of the Indole synthesis. Then the next thing that probably we would like to take up there is a reaction call Bartoli Indole synthesis. Then we can take up one more these are all which are often used Nenitzescu Indole synthesis; then this is my order of priority by the way. Then the next one could be Hematsberger Indole synthesis and then there are I think many of you know there is a scientist call Larock Indole synthesis. And then there are there is a synthesis called knochal Indole synthesis. So, these are all different I think we will take up all these in order. Then if there are some classics one for example many of people are know some of them. So, that is so we made take them up in the next class; what else do you know?

Student: madelung.

Madelung. So, we will take up madelung next time; and also we will tell you why even people are still interested in modifying the classical classics one or classical ones madelung synthesis. Then this is not often use both though Gasman pyrrole synthesis gas sorry 1 m gasman pyrrole synthesis. Then I am just I have just picked up some of these Batcho pyrrole synthesis; then there is an organometallic chemist known as hegedas; so

hegedas Indole synthesis. And I mean you can go on like say Castro Indole synthesis; then twelfth one could be Mori-ban Indole synthesis. So, likewise I mean I have a few more I think ((Refer Time: 14:37)) Indole synthesis is there is also quite well known book Indole synthesis; then sugasawa Indole synthesis. So, that means so I have a list of 15 here it could be more even ok.

So, but let us look at only let us say 3 or fourth day; and that means Fischer Indole synthesis, Bartoli and nenitzescu probably we will I think we will stop probably here today. And when you talk about this I think if you just look at the top; we will ignore the left hand side means Diels-alder and RCM they are not that very popular. So, that means our concentration would be focused on this pyrrole ring formation.

So, in the last class we talked about the pyrrole ring. So, we will see also look at the pyrrole synthesis but normally using heterocyclic chemistry what I said before is that the all these synthesis or syntheses are govern by the 2 key factors. What are the two key factors? Let us say which synthesis would you study or which synthesis would you do research on there are some thing I mean; so there are only there are only 2 factor key factors in a synthesis especially in heterocyclic chemistry. What are the 2 key factors?

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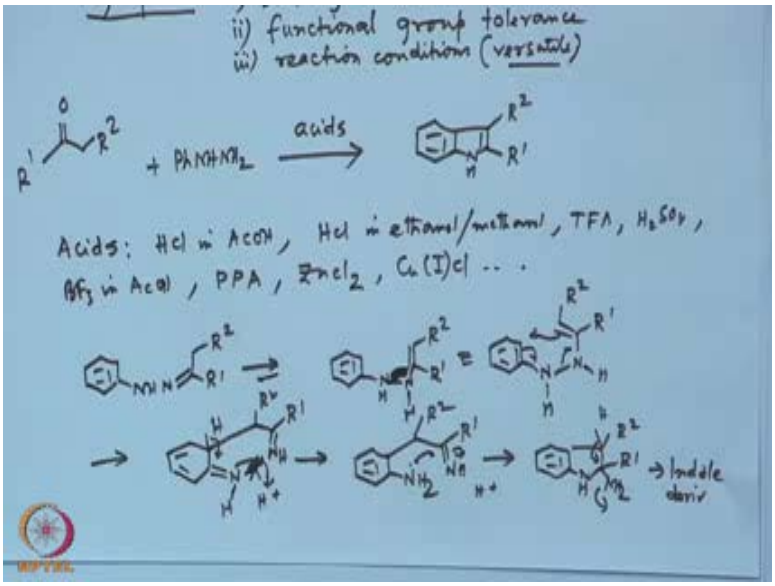


I told you during the pyrrole synthesis

Student: ((Refer Time: 16:14))

No key factors; I mean that makes a synthesis very popular like say what I said Paul-knorr synthesis; where I say even today people are using it, people have used that Paul knorr synthesis for the manufacture of Lipitor that the commercial drug. So, it is a very old synthesis; that means basically the one of the key factors is the starting material. So, this starting material should be very easy that is important; starting materials that is so you have to that is why when I divided the synthesis I said pyrrole formation. That means, your starting material must be benzenoids unlike not the pyrrole compound. So, the pyrrole compounds are difficult to make, benzene compounds are easier to make. Then what next? Another important factor functional group.

Student: ((Refer Time: 17:32))

No. Functional group tolerance I think you know the meaning right what is the meaning? Means if you when you are doing the key transformations the other pendent functional group should be remaining intact. So, there should not be affected. So, these are two important factors in most organic synthesis. And then in certain cases of course the other things chemistry part also is important. But when you talk about the text book chemistry and it is the functional groups and the reaction conditions also. Third factor of course I mean you can just add basically the easy reaction, friendly reaction conditions. So, this is also an important are versatile and versatile reaction conditions.

So, this versatile and friendly reaction conditions; so these are the 3 important factors. Now, today what I said that it was discovered in 19 sorry 1883 and even today this is a very popular. Because the many of us know that one of the starting materials in case of Fischer Indole synthesis is hydrazine right is hydrazine; the other one is other is a ketone right. So, you have ketones and hydrazines and both are very readily available.

So, that is it is in why Fischer Indole synthesis is very popular. Third one of course all of us know the other points; reaction conditions. What is the reaction conditions, what is the Fischer Indole synthesis? Reaction condition is not necessarily acids and what is the product? So, product is you say Indole and what you will see? You will find is a disubstituted Indole derivative this is the commonest one ok.

So, that means it is this satisfies that the starting materials are readily available; ketones and hydrazines; functional group tolerance we have not seen so for yet. But reaction condition is versatile and friendly when I say friendly that means what are the possible

acids? Acids could be simple HCL say HCL in acetic acid; this is one of these even HCL in ethanol or methanol you can see here trifluoroacetic acid even sulfuric acid also could be used; of course it is at low percentage. Then BF 3 in acetic acid I mean you can then you can use more often now use this PPA, polyphosphoric acid. And the one more commonest acid catalyst is zinc chloride sometime cuprous chloride also used as the Lewis acidic conditions.

So, you have a wide varieties of the acids available for the reaction conditions. And that is reason I think this is I think probably second organic reactions on which a book is completely devoted to. What is the other reactions for which one complete text book is devote? For example, there is a book on only Fischer Indole synthesis published in 1992 by Wyle. So, tell me one more reaction which should be very famous and for which a book can be written.

Student: ((Refer Time: 21:31))

No, one reaction. So, we learnt so much organic chemistry right just tell me one good reaction for which big volume of text book can be written.

Student: ((Refer Time: 21:57))

Very good. Diels-alder reaction yes I think he is right; Diels-alder reaction. So, let us say coming back to this Indole. So, I think many of you know what is the mechanism? Mechanism is so is again you start with a mono substituted right mono substituted benzene derivative that is hydrazine; so all of us know in the presence of ketone it under goes hydrogen formation. What next? This is also very important what next? Under the influence of acid it under go sorry it under goes isomerization right isomerization or let us say let us rewrite.

So, R 1 and R 2 right; so all of us know under goes isomerizations to form the corresponding sorry hydrogeno compound; so hydrogeno alkene. And I think many of us know now next in the presence of acid and presence of acid. So, I mean one can write the acid here also straight way you can say that this can undergo 3, 3 sigma tropic rearrangement. So, what we will have? So, R 1, R 2 and you have hydrogen up here and then you have a new bond now right. And this is there is a hydrogen up here and in the presence of one of this acid catalyst.

So, you can acetate I just write that this would this which hydrogen here. And so this would again it will form and aniline kind of derivative right. So, R 1 and R 2 and I think rest many of you know what happens again in the presence of acid. So, there is a loss of ammonia in the process of the condensation; so it will give you an intermediate. So, amino you can say amino Indole derivative as the intermediates and this is NH here. And then subsequently you will have this loss of ammonia in the again in the presence and what we will get? We will get the Indole derivative. So, this is the standard protocol.

Then, you have all kinds of now but you have to very carefully look at actually the reaction intermediate. So, what is first one is the hydrazine, second one how do you describe the second this intermediate? After isomerization you get the intermediate of this kind right the one I am pointing two. How do you describe this derivative? I mean that means the substrate what I will say it is a n phenyl hydrazine; n it is not a hydrazone this one is n vinyl hydrazine.

That means, if you can make a substrate which would be looking like an n vinyl hydrazine the reaction would take place without any problem. So, that is what you have to about. I mean you do not have to have an hydrazone all the time just say simple vinyl hydrazine also is susepectable to undergo this Indole synthesis. Let me give you a quick variant is a properly useful variant.

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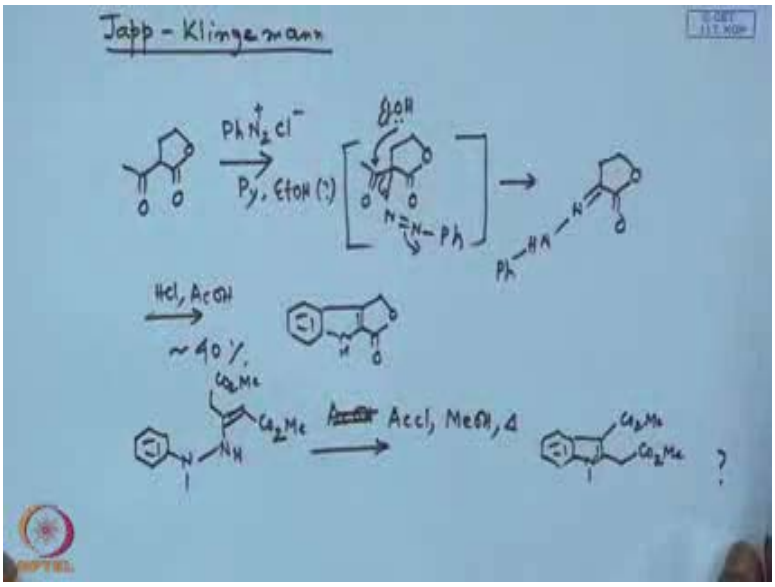

Let us say of the Fischer Indole synthesis this is known as Japp-klingemann Indole synthesis; what is it? I think that if you look at the reaction would be if the you see and this reaction is done in our lab almost routinely. We starts from a compound of this kind is that is acetyl-gamma-butyrolactone is a pretty cheap compound. Then we had these 2 phenyldiazonium chloride phenyldiazonium chloride; can you guess what will happen in the presence of course the catalyst is pyridine; pyridine I think ethanol water I guess. I remember I think ethanol also is there; I have I am not sure and some catalyst and the solvent system is there. What do you think, what can be the first reaction product any guess? All of us know right that we have studied in B sc diazo coupling reaction; if a reaction if a substrate response to diazo coupling reaction. So, conclusion is that the this unknown sample is phenol right. What else?

Student: ((Refer Time: 27:59))

Primary amine; fine aromatic primary amine and in aliphatic case.

Student: ((Refer Time: 28:13))

Right.

Student: ((Refer Time: 28:15))

No, ((Refer Time: 28:16)). So, that means nothing but say beta keto ester kind of thing; beta keto ester all of us know it exist in the form of the ((Refer Time: 28:26)). So, it will undergo diazo coupling reaction; so diazo coupling reaction. And what you will find? You will find acetate here nitrogen and this is phenyl. But this is not your isolated group, this is not isolated; but the presence of pyridine and sodium ethoxide it undergoes or let us say de alkoxy carbonations.

So, you can think about this ethoxide or ethanol is perfectly all right; and what we will find? We will find this reaction would proceed to give you the one you wanted. That means, what you get is basically hydrazone; that means now the hydrazone is formed at the alpha position of the lactole; alpha position lactole. And in presence of again the standard protocol HCL in acetic acid.

So, you will nicely get this Indole derivative without much problem although yield is not very good it is approximately 40 percent. But this one this hydrazone formation is more

than 90 percent sometimes; 100 percent. But you see here this is a basically the modification of and there are plenty of examples; so I will not give you. But now I will just give you one more possible kind of thing; let us see whether you can predict this product similar to this; not exactly same thing. But let us say if you begin with a substrate this is a olefin here right; and then I have one more ester group, there are 2 ester groups.

And, if you reflects with acetic sorry acetyl chloride, methanol and then heat; and what you get a product; can write the structure of the product? First of all you have to identify the reaction conditions what is the reaction and then substrate; what is the reaction condition? Acetyl chloride methanol and heat. What is the reaction condition? Quick you have to give what is it is a reagent of is a combinational reagent. What is the reagent? That would cause the reaction; reagent means chemical agent that would cause the reaction right, promote the reaction. What is the reagent? Quick; all of you most of you are ((Refer Time: 31:50)). You have to do; how to ((Refer Time: 31:57)) in lab.

Student: ((Refer Time: 32:02))

Ammonium chloride and sulfuric acid right; ammonium sulfur HCL comes out that is the standard way of producing. But if you want to produce HCL in organic medium, how do you do in acetyl chloride and methanol. Then that would actually the it will form methyl acetate and HCL; so it is nothing but HCL in ethanol. So, that is one of the conditions for Fischer Indole synthesis. And what is to do this then what we have recognized that Fischer Indole synthesis it is not necessarily the hydrazone you have to take. What you have to take one of the other possibility is.

Student: ((Refer Time: 32:42))

Vinyl hydrazine. So, in these case what you see here there is a vinyl group; so obviously then you can write the structure of the product right; you note an again this reaction is done in our lab. And this is I mean our lab means I mean we repeated rather we do not need we are not the first time we are not the first ((Refer Time: 33:02)). And this the product is now I said an Indole di ester; so like this you know you can modify these the basic Fischer Indole synthesis the way you want; let me take you to one more quick one.

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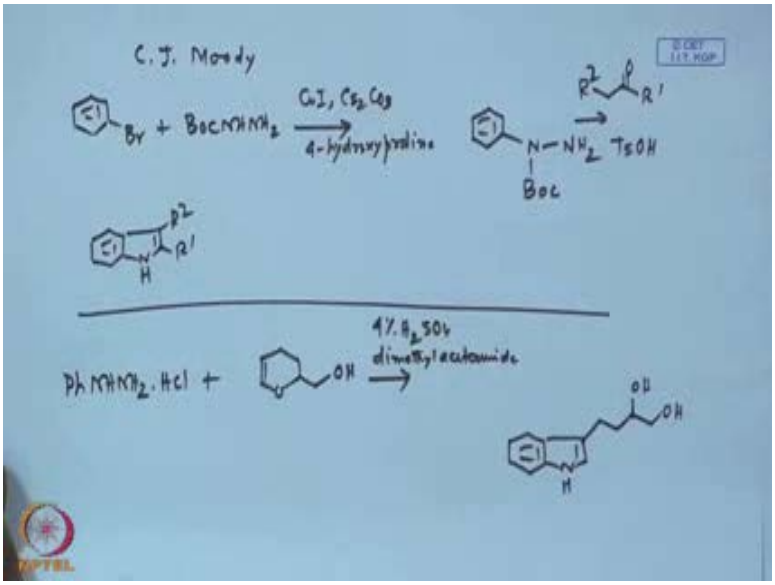


Let us say this is made by Christopher moody C. J moody only very recently in 2010 or 11; what he did he started with a bromo compound. Because hydrazines are not that easy to make all time. So, then you take a BOC hydrazine all of you know the meaning right BOC. Who does not know BOC? All of you know fine.

So, then under these conditions you take cuprous iodide and cesium carbonate. Then there is a that amine like and of course, this is 4 hydroxy proline that is or you can use ((Refer Time: 34:17)) proline, 1, 10 ((Refer Time: 34:19)) proline also can be used; just to solubilize the copper part. So, what can you guess? So, actually bromine is displaced and with nitrogen, one more nitrogen right. So, the you get the hydrazine derivative; so hydrazine derivative. But you have to know which nitrogen would be link to the phenyl ring; any idea, any guess? The one with BOC or without BOC; that is what one would think so. But in these case that is reason I ask this question it is this one BOC; reason being carbonyl compound right you have caesium carbonate which is a base. So, it will pickup that hydrogen; so make nitrogen minus. So, nitrogen minus verses N H 2 obviously all of us know nitrogen minus would be more nucleophilic in nature.

So, that means once you have this then you can do this one. So, again let us say R 2 and R 1 ketone; and obviously the answer is answer so this in these case the reaction condition is like acid, toxic acid para toluene sulfuric acid. And the product is straight way you get this 1, 2 disubstituted Indole. So, is just a small modification thought but

what he did he could develop a new kind of hydrazine source; I mean I can go on write this. I think may be just this is a very important aspect I think the next example is a small variation. Let us say with this much of background let us I will stop here for may be half a minute; and you have to tell me the product you know.

Let us say the condition is like this hydrazine often hydrochloride and then what you see here is a pyran derivative now; it is a pyran derivative. And then we have this is an example of the tolerance of the functional group; you see very interesting functional group tolerance. And reaction condition is 4 percent sulfuric acid and then other solvent is dimethyl dimethylacetamide; when I say dimethylacetamide mean; n, n dimethylacetamide ok.

So, write down the intermediate or the product whichever let us see in half a minute. It is an example of Fischer Indole synthesis; I mean for us it is pretty easy right without looking at I can just write down at least this much. Because it is an example of Fischer Indole synthesis; so Indole has to be there. And Fischer Indole synthesis what are the key intermediates? Hydrazone and vinyl hydrazone. So, these are the key intermediates.

So, if you can identify the vinyl hydrazine and hydrazone just connect this nitrogen and remove all of the nitrogen; that takes care of the formation of the. So, this is how or you can just simply sit down and do this little bit of the manipulations; do I need to wait or just give anybody? Let me just quickly ask you the question whether it would produce the 2 substituted Indole or 3 substituted Indole; 2 substituted or 3 substituted.

Student: ((Refer Time: 38:46))

No.

Student: Number three carbon.

Number three carbon. So, you workout the mechanism it would be looking like this. Then finally, I have one more question to ask you.

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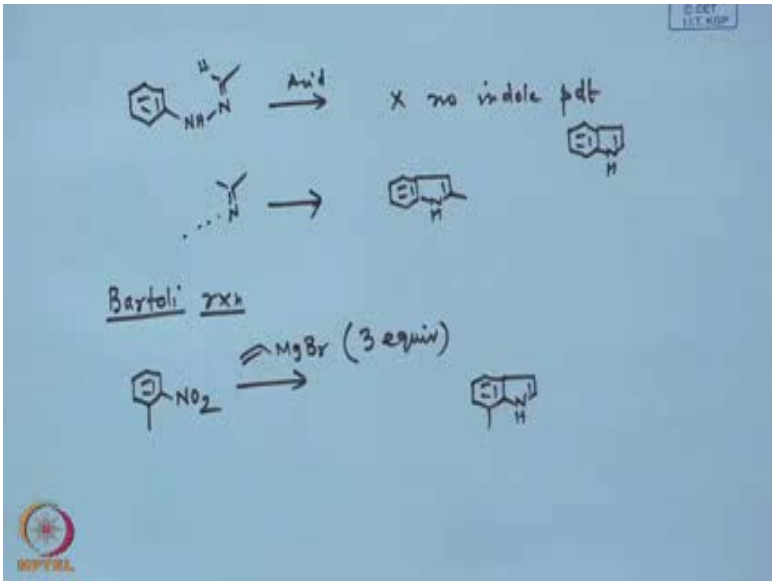


And, this let us say this is an I will this is an exceptionally exceptional case. Let us say if you begin with hydrazine then condense with let us say acetaldehyde; acetaldehyde means this one right. So, you get acetaldehyde hydrazine and try to do the Fischer Indole synthesis and Fischer Indole synthesis does not go; means there is no Indole product. But if you do let us say acetone for example, in the same thing if you begin with acetone; so what we will get? We will get the 2 substituted Indole, 2 methyl substituted Indole under say similar conditions; did I make it clear to you the difference between the 2 reactions; one is acetaldehyde derived hydrazone, other is acetone derived hydrazone. In one case you get this product a fell in good yield, the other case now no Indole product is found. Who can tell me the answer, why the top one does not go that is the basis of the next reaction. So, what I will be talking about.

Student: ((Refer Time: 40:44))

No, one cyclizes loss of ammonia in presence of we have a acid; all of us know acid will scavenge ammonia that is not a problem at all; see most of an the reaction felts in if the cyclization does not proceed. Once you have a cyclic structure you can do all kinds of manipulations. So, that is reason when we had you have answer, what is your name I forgot Sushita good.

Student: ((Refer Time: 41:19))

Very right, right very good, good. I think he know the answer. See, if you remember when you talked about that 2 kinds of the intermediates; hydrazone and vinyl hydrazone. The vinyl hydrazone is not sufficiently stable because you do not have a methyl group there; in the case in the here you have a methyl substituent which stabilizes the double bond through hyper conjugation.

So, that hyper conjugative stability is not there from the corresponding vinyl hydrazine. So, the what I mean to say that means is easy to make substituted Indoles but it is not easy to make unsubstituted Indole. So, that is the reason why the Bartoli reaction is pretty useful, Bartoli reaction. So, you can say or Bartoli synthesis; what is it simply is a once again what you see here the previous example hydrazine derivative; in this case you have nitro derivative. And often also you have to think about often it is an ortho substituted often ortho substituted.

Then, if you take vinyl magnesium bromide; once again normally it is used in excess as we will go on and see the reaction conditions or the reaction mechanism you will see. Then it is readily necessary with one equivalent you can get product. And what we will get? We will get so 2, 3 unsubstituted Indole derivative; in this case what was expected? It was just is a plane Indole right in the first case. So, what you see here the 2 and 3 positions are unsubstituted and mechanistically what it does? You can sit down I can just outline the intermediates probably.

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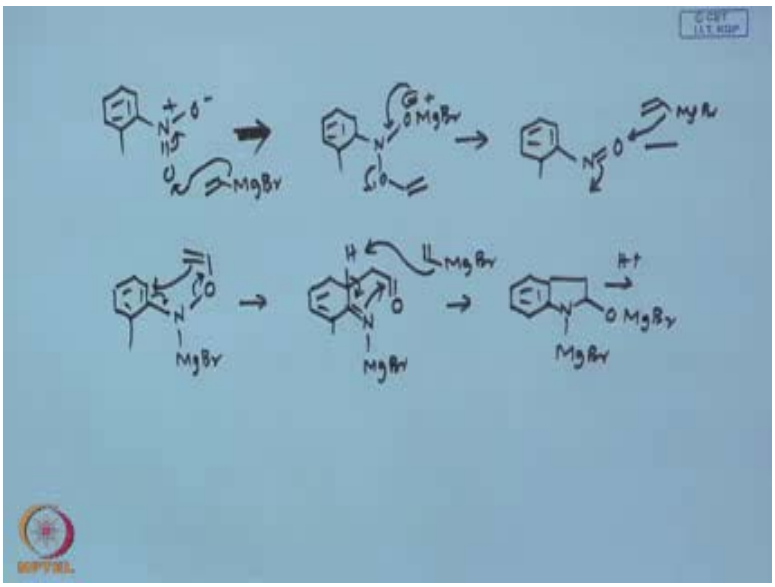

So, quite interestingly all of us know this nitro would be written like this. Now, this vinyl magnesium bromide all of us know these are all nucleophilic in nature ((Refer Time: 43:54)) reaction takes place here this vinyl carbon ion attacks and this nitrogen plus is neutralize. And then magnesium is I link to this oxygen minus. So, what you will find? You will find something like this right. So, and then what? Then it collapses to form let us all of us know this is minus and plus; so it collapses to form nitroso benzene. So, essentially one of the just ignore this methyl here and what we will get you will? You will get this nitroso benzene.

So, that means the first equivalent of vinyl magnesium bromide is reducing the nitro compound to the nitroso; what next? And we can again take this vinyl magnesium bromide. So, it will now sort of an inverse because of this benzene ring at inversely. So, what you will get? You will get nitrogen up here then oxygen and now something like this right. And this nitrogen minus would be neutralized with magnesium bromide; what next? I think you can guess what it is right, what next?

Student: ((Refer Time: 45:30))

Louder.

Student: ((Refer Time: 45:34))

Sigma tropic rearrangements; it is sigma tropic rearrangements. So, that means you will get the 3 sigma tropic rearrangements; and what next? Then you have see that means that this is the second one, third one now all of us know the Grignard is sufficiently basic in nature also. So, one would expect kind of proton abstraction followed by cyclization. So, what you will be getting? You will getting this Indole now; Indole and here would be the again magnesium now would be shifted to this then again magnesium. And then of course if you do this acid treatment you lose water here and then N H is free. So, eventually you get to this compound; so what you see here this is a very way of making it. So, what you have to do? You have to take vinyl magnesium bromide which are readily available so likewise.

And, you have a nitro compounds, aromatic nitro compounds are pretty easy to make. But there is only one limitation; actually the limitation is that it has to have an ortho substitute; if you do not have an ortho substitute the reaction would not go. It can give

rise to all kinds of the complications; many of you know this nitro compounds undergo substitution reaction; we will talk about that sometime later. And so lastly I think this is a pretty very useful reaction though very useful reactions.

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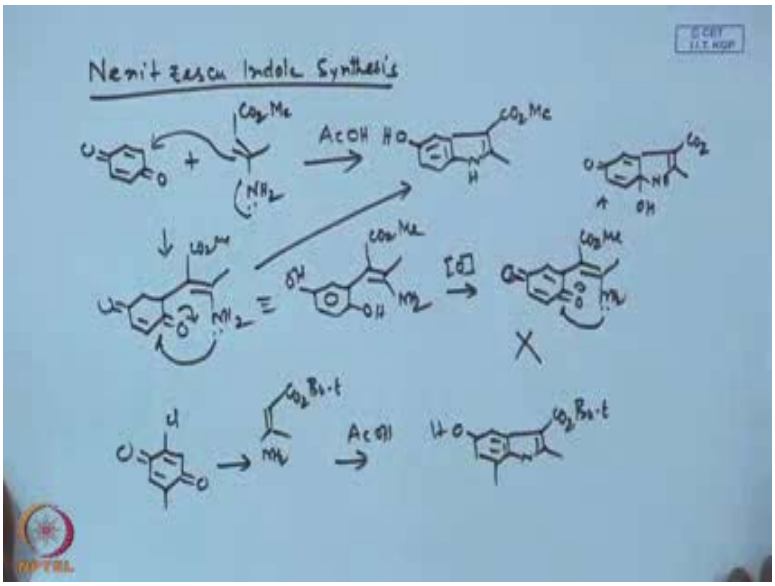


And, pretty easy to make Nenitzescu Indole synthesis is a very famous one; once again. And why? Because is because the starting metals are pretty easy to get and one of the starting material is like say Quinone and this is a must in case; this is a common starting material is for all Nenitzescu reactions. The other one is something like this what is it, any guess? What is the how do you describe the starting material? See, the again in the first merit of this lecture I said the starting materials are important in heterocyclic chemistry.

Student: ((Refer Time: 48:39))

Right. But that is fine.

Student: ((Refer Time: 48:42))

That is very good. But so but how do you describe this; name subclass of the compound is not a bit ((Refer Time: 48:51)) is an amino; what? So, actually it is called enamino ester. So, this is if you do not have an ester that is basically in amine right; amine is attaches to the alkene; so in inamine, so inamino ester. So, if you have inamino ester this and simply just is a such a simple reaction though by the way very simple reaction. Once

you have to write quinone and just as Karthik says that you take beta keto ester ammonia. And then you get to this product without much problem; and just take in a separating funnel and it will be aqueous ammonia and shake it. And you will get this compound very easy to make of course it is commercially available.

Now, take that compound benzoquinone that is also readily available mix them in acetic acid and heat it for sometime is immediately you get this Indole derivative. So, Indole derivative but only drawback or usefulness whatever you say I think it is an usefulness. Because what you will be getting? You will be getting this one O H; so hydroxy Indole. So, you what are the things you have to remember here Nenitzescu reactions require benzoquinones as a starting material and in amino ester.

And, the product is a hydroxy unlike the previous 2 synthesis. And the mechanistically one can what is the mechanism? Mechanistically one will see here; what is the mechanism first step that is important; a good beginning is important; there are 2 possibilities. Then N H 2 can undergo condensation with carbonyl group that is a possibility or inamines can undergo michael addition; there are 2 possibility between the two if you remember I have been telling you between the 2 which one is more favor faster?

Student: ((Refer Time: 50:59))

Sis base yes sis base but it is a benzoquinone sis base. Normally the sis base formation would require acid by acetic acid is not that sufficiently acidic? So, Michael addition is one of the one of the first right but in this case it is not a purely sis base reaction. So, Michael addition would undergo a first probably.

And, if you do so you will have the intermediate like this right which is equivalent to what? Hydroquinone which is equivalent to hydroquinone right these; then it undergoes air oxidation. So, once again you will get an ketone and this inamine and this ester and here. What next I think next is pretty easy so it will undergo cyclization right. So, cyclization double bond ketone here you will have O H, N H the methyl group here right and this is something wrong O H right. Anything wrong? There is a mistake I can guess if you have write oxidation level etcetera, I think this would not should not be incorporated; it should be like say I think.

Now, we can straightway put this here that quinone can be tautomerize to the ketone right. And then you can straightway go to this one loss of this is not oxidation is not oxidation required. If you look at then sit down and see the oxidation number calculation you will find oxidation is not a requirement here.

So, any case; so this is now I mean just may be one more example probably I will give you rather just to show you the group tolerance. For example, if you begin with the n highly substituted quinone of this kind and then take this inamino ester. And in this case tertiary butyl ester and the reaction condition is pretty easy; acetic acid etcetera. And what you will get? You will get this hydroxy Indole derivative once again. So, that means and you can keep it in mind; that hydroxy is disposed para to the nitrogen. And you will be getting the corresponding this tertiary butyl ester and this one pretty easy.

So, only restriction is to get the right kind of the benzoquinone that is; so summery quick summery. So, what you have to know? First thing you have known the Indole compounds are very important. So, you have to name you have to remember at least 10 different important Indole compound; synthetic and natural. Then there are above dozens of Indole disynthesis but you have to learn in the for this class how many?

Student: ((Refer Time: 55:26))

6, 5 or 6. Today we have talked about 3 of course the most famous one is Fischer Indole; then it has different kinds of the variants one of the Japp-klingemann, other is the moody variant. So, like this there is a variant of the book ward variant also we have not talked about. But that basically essentially involves the synthesis of hydrazine, the next one was Bartoli. So, you have to remember the starting material nitro compound and the vinyl magnesium or the basically Grignard reagent.

Then only drawback it used in 3 equivalents of the last one Nenitzescu; easy to operate, easy to carry out perform the reaction; that is not then starting metals are pretty once again not very expensive the benzoquinone. So, you have to have right benzoquinone and the reaction conditions are very you have to only acetic acid and boil it. And end product is hydroxy Indole and this hydroxy Indole is para to the nitrogen that is it. So, we have learned only 3 of the Indole synthesis, and next we will talk about the other 3.