Heterocyclic Chemistry
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Lecture - 39
Bicyclic Polyheteroatomic Heterocycles

Good morning. In this class I will cover a big topic, I should say large topic synthesis of bicyclic polyheteroatomic heterocyclic.

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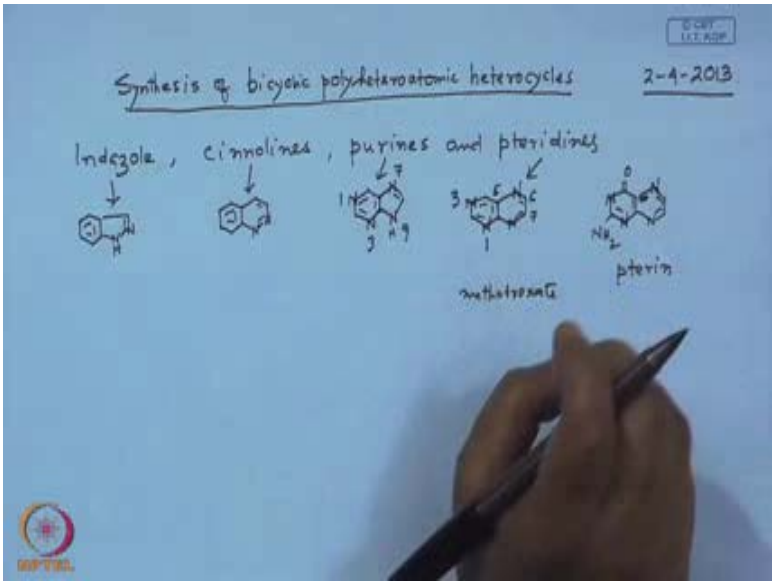

It is a worst area or worst ((Refer Time: 00:38)) area I should say. And in this topic I have selected only few important nuclei namely one is indazole; then other could be cinnolines. Then, third one is well known to many of you is known as purines; and the forth one is known as pteridines. So, I have selected only 4 of them under the category of bicyclic polyheteroatomic heterocycles. And before we start I think we should be able to know the structures; the first one as a named says it has to be six membered as a five membered and just like Indole.

So, we can say two as a Indole. So, this is indalone; cinnolines also are very similar to indazoles. But the second ring is a six membered ring and all of you know purine consist of a five membered ring and a six membered ring; five member ring is a fused with a six membered ring and five membered ring is imidazole. And then the other one is

pyrimidine. So, this is an important nucleus all of us know; and then next most important is again a six member six member. But in these case you have a pyrimidine ring system; and then you have 2 nitrogens on this sides. And this is so this is actually pteridines; this is pteridines this is actually cinnolines, and this is indazoles. And some of you probably also know a kind of a nucleus which is pretty familiar in organic chemistry; it is a six member again, six member with Pyrimidine nucleus, ketone up here and N H 2. And this nucleus also is commonly encountering heterocyclic chemistry; this is known as pterin.

So, you have to know all these things; these are very important nuclei I mean most of them either biologically active or they are found somewhere in a pharmaceutical, formulations. And of course they are of continued research; means there are potential applications of all these nuclei as we will go we will see. And among these heterocycles I think this third or fourth one also is important terms of the nomenclatures; the numbering systems. I do not know how many of you know the numbering system; in case of purine the numbering starts from a particular nitrogen unlike the conventional IUPAC numbering these 2 systems will have a different kinds of numbering they do not belong to these IUPAC rules. And that is because of the historical reasons like say I mean why naphthalene is naphthalene it could have been benzo benzene or something like that. But historically it has been named as naphthalene and that name has been written by IUPAC.

Similarly, purine nucleus all of us know many of the nucleic bases, nucleic acid bases would have this sort of nucleus. And the numbering starts from pyrimidine nitrogen that means six member and one; and then it goes to 2 and 3 then this one 5 is say 4, 5, 6 and then third nitrogen is seventh, 8 and 9. So, this is the you have to remember nothing can be done. And then let us go to the other one; other one is what pteridines. Pteridine also is a very important nucleus as we will go will see. And in fact very briefly I can say pteridine is found in anybody knows pteridine found with this wings of the butterflies. So, this is coloring material actually this is pigment; this due to this pyridine nucleus. And it is in these case the numbering starts from here these this nitrogen I mean there is no logic.

But again it has been retained and it has been excepted; so 1, 2, 3, 4 and 1, 2, 3, 4, 5 right; this was this should be 5 and this nitrogen is not number though. So, actually this carbon is number. So, that the 6, 7 and this so this is how the numbering goes and this nucleus is also a pretty important; because of many important occurrence. For example,

it is found in metho it is found in methotroxate is nothing but it is a commercially available anticancer drug. So, likewise also these are found in molybdenum 4 factors pretty important enzyme. So, that is there like say pteridine sorry pterin why define pterin? Pterin actually is found in spinach is nothing but

Student: ((Refer Time: 06:53))

Any kind of ((Refer Time: 06:53)); I should not say ((Refer Time: 06:57)) any kind of. So, but there are that means they are important as we will see we will have more examples; then also me chemical behavior also peculiar. For example, this pteridine is solvable pentane or hexane as well as what? Normally those molecules which are soluble in organic solvent not soluble in inorganic solvent etcetera but in these case it is true ok. Let us look at some of the synthetic aspects of let us say indazoles.

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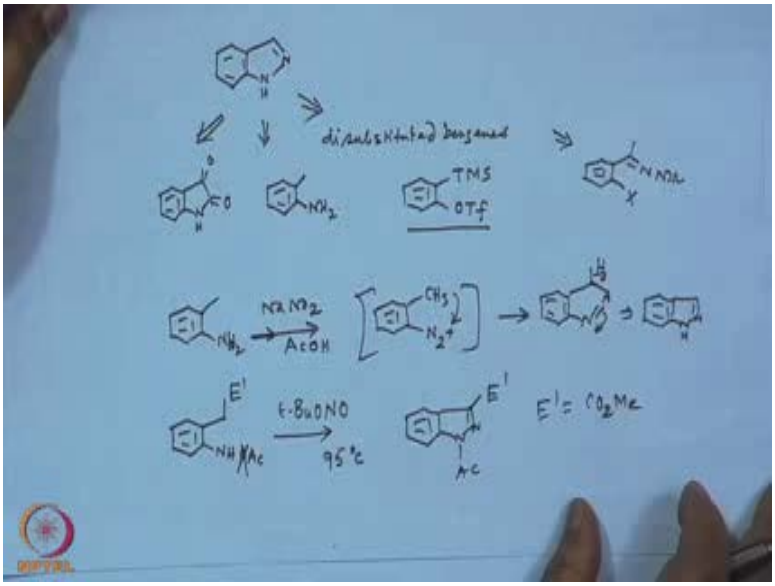

Indazoles I mean there are of course hypothetically one can write so many methods, so many approaches. But the known approach is all of them would starts from a disubstituted benzene derivative all of them. And there are about 6 or 7 methods but today we will talk about only 2 of them or rather may be 3 of them; one of these ways to starts from Isatin I think all of us know now; Isatin is a Indole kind of nucleus with a 2 keto groups; one amide and this thing you can starts from there. The other that is also pretty popular is pretty interesting too also; it starts from orthocor divine kind of thing. So, this is another way and third approach again quite interesting is very interesting in

the sense; because this sort of copy is quite useful. So, this is I think by looking at the structure we can see there is a when I write this the number the right one it something suite come to your mind; what is it, any idea?

So, but any case all the will have let us say I mean sort of hetero disubstituted benzene type of compounds likewise there are amine. So, you can think about anything for example you can think about corresponding let us say hydrazone; and then do something to get to the compounds. Then, you can also have nitrobenzaldehyde, ortho nitrobenzaldehyde; so like these you can think about this. But all of them involve the 1, 2 disubstituted compounds. And actually third one is important as I said it is a precursor of benzyne; if you use let us say cesium fluoride or potassium fluoride or tetrabutylammonium fluoride it first the fluoride attacks the TMS group; and then it induces the loss of triplet. So, it is a nice important precursor at the room temperature. So, we will see how to make use of it in these synthesis of indazoles; the one that is mechanistically important is the middle one; that is a second one. What we will see if a Toulidine kind of molecule is treated with sodium nitrite in presence of in presence of acetic acid; so acetic acid is a basically solvent.

So, one would expect the expectation is pretty obvious right; and say we will have a diazonium kind of salt diazonium salt. But this diazonium salt is does not exist in that way; it is interestingly cyclizes to as if it forms in negative charge here; and then attacks the diazo group. And so you will have attacks the diazo group. So, you will have obviously this kind of intermediate and that eventually tautomerizes to the indazole. So, this is quite interesting that means diazo compound which is not belief to participate in the intermolecular reaction; this in intermolecular reaction should be diazo compound ok.

Likewise just one more example probably I can give you just one step you can get to this indazole derivative. For example, you begin with again it is a orthotoluidine; that means you will have to have a substituent here. And I think now so is pretty similar only thing in these case N H is protected as sorry A C. And then to carry out the reaction all of you know what is the substitute of sodium nitrite in organic solvent; substitute of sodium nitrite that means nitro setting reagent in organic solvent. All of you know you have studied in B sc one of them is amyl nitrite amyl sorry amyl nitrite; other one is butyl nitrite; in these case it is the one you have shown here tertiary butyl nitrite is a basically

source of N O plus. So, it is equivalent to and in this case it is solvent I have missed; but the temperature require is around 90 degree centigrade. And as in analogy the previous example one can write this structure here is an n acetyl indazole; and of course, E 1 all of us know E 1 stands for this methyl ester right in our case.

So, like this you can I mean nicely get an access to these indazole derivatives; the second method that I would like to talk about I think the one example is good enough to demonstrate the utility of isotene right.

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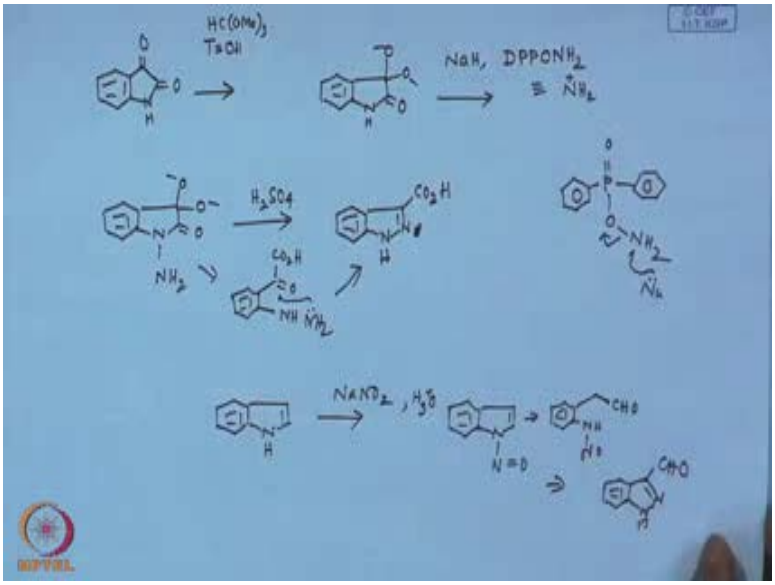

If you recall in one of the last classes we have talked about the use of isotene in the synthesis of anybody remembers; isotene is a very useful component, there are so many multiple process uses of isotenes. And in one of the classes we have talked about actually it is used any synthesis of quinoline.

Student: ((Refer Time: 13:53))

The structure demands is quinoline; so quinoline synthesis. In these case if you treat with para toluene sulphonic acid and methyl format is I think all of us know what is the answer, what is the answer? It would because there are 2 kinds of which are ketones one is amide; other is the just ketones. So, it would undergo Ketalization. The next thing that is done is sodium hydride and then one new reagent is used that is called DPPONH 2;

what is it? It is nothing but is a source of this is equivalent to you can say N H 2 plus like N H 2 C l. So, similarly this is equivalent to N H 2 plus.

So, you can guess what is the impossible reaction there is only one abstractable hydrogen which is sitting at nitrogen. So, this should aminate this nitrogen and you will have this ketal as it is. And by the way you have to remember the structures also of this one DPPONH 2 is nothing but is a phosphenyl hydroxyl amine. So, that means it has to be like this. And so diphenyl so I think the as the name says it should be diphenyl right diphenyl alphabet is phosphenyl; this is o and hydroxyl amine this is the structure. So, when you nucleophile attacks this nitrogen and this diphenyl phosphonate proof is coming out as the leaving room is a pretty useful one. What is the next reaction?

The next reactions one would expect you just if you boil with sulfuric acid in these one you can get a nice kind of rearrangement. And eventually it will give you this indazole with a carboxylic acid at the 3 position; carboxylic acid is 3 position. I do not have to explain to you right sorry hydrogen is up here I do not have to explain; actually under the acidic conditions it undergoes what hydrolysis right. So, hydrolysis would give you N H and basically phenyl hydrazine and a keto here and a carboxylic acid.

So, just hydrolysis of the ketal and the hydrolysis of the amide that will give you the; and then this one would undergo cyclizations to this. In this way so this is a nice I mean the basic clean kind of synthesis. Let me give you there are other kinds just in these contest let me just quickly, let you know an interesting reaction I do not know whether you should be able to predict the product of this reaction. Let us say Indole all of us know is a famous nucleus; then this sodium nitrite also is a famous reagent right famous reagent. So, in the presence of acid you get the new compound. So, what could be the structure?

Student: nitrosation.

Nitrosation fine; then what?

Student: ((Refer Time: 18:05))

Amorphous. So, presumably it will I mean it can Indole all of us know it can undergo nitrosation at the 3 position or nitrogen there are 2 possibilities. But with nitric acids in heard one; so you can expect a n nitrosation right; and then what? You see you have

actually I should have written here in dilute acid; so that means you have water in it. So, if you actually enamine if you hydrolyze enamine the Indole means basically enamine right if you hydrolyze what you are expected to get is N H here and N O. And in these case what you will be getting here aldehyde; enamine means hydrolysis would give you the corresponding starting metal the corresponding secondary amine and the aldehyde and ketone.

Now, you can guess previous example compound with the previous example means in last slide we have shown that ortho ((Refer Time: 19:20)) with sodium nitride it gives you the indazole. So, you have with an ester group there you can end up with an ester pyrazole, indazole. So, this would immediately cyclizes to it will cyclizes to the indazole here. And then so basically you will get the 3-formyl indazole; just like the previous example when you see this ((Refer Time: 19:53)) the sodium nitride it gives the indazole ok. So, then let us look at one more reaction I think that would suffice for the synthesis of indazole like say if you this is the benzyne route.

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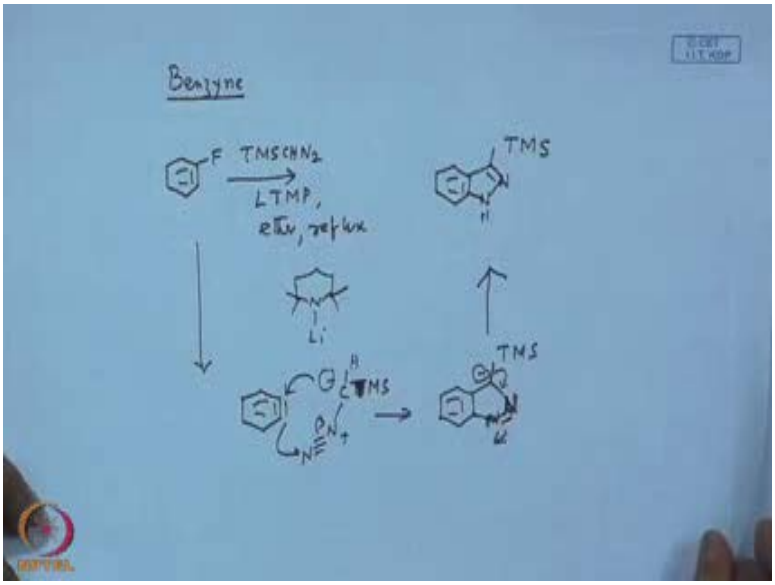

I think that is the way it should be known benzyne; if you treat with fluoro benzene with TMS diazomethane. TMS diazomethane means equally substitute of the diazomethane; and then LTMP in ether reflux; ether reflux means basically 35 degree centigrade. And in one step you will be getting these indazole derivative. So, indazole derivative and here TMS is TMS indazole; by the way recently I have come across repentant actually

describing indazoles for the use of treatments of diabetics; that means there are pretty useful.

Now, I think all of you know what does LTMP stands for? We talked about that in fourth year it lithium tetramethyl piperine diet.

Student: lithium tetramethyl piperine diet.

Like LDA lithium di isopropyl amide id; so it is basically a base, hinder base with this. What is the mechanism? Mechanism is it goes to it goes to benzyne here and then in the presence of the strong base you get the lithium and this diazonium salt here. And this diazo compound right; this is TMS. So, one can think about this electron movement to benzene as an electro acceptor; and this is neutralize and then you have one hydrogen up here. And so it will now the form this nucleus sorry double bond and then TMS. And in the presence of the excess base it will form this amine; this negative charge here. And then negative charge of course isomerizes to upon work up. So, I mean this is a fairly method that in the next example what I will see rather the most popular benzyne precursor these days; most popular benzyne precursor.

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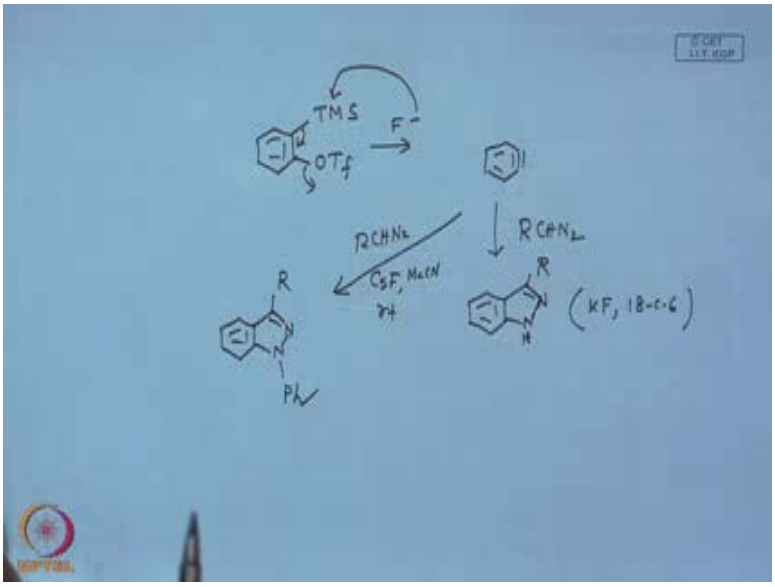

What I have said before the most popular one is the TMS here; and o triplet. What does it do? If you treat with a fluoride reagent so fluoride goes to TMS and then comes out. So, eventually you will be getting this sort of a neutral basic conditions benzyne information.

Now, if you treat this with let us say RCHN 2 I mean apparently I mean unless you know I mean we cannot think of this indazole formation. So, like the previous example here under this under the condition you will be getting this indazole formation with N H here double bond and R; this is a pretty fairly general method. The only condition that you have the but it is condition sensitive; condition sensitive means this is obtained if you have this potassium fluoride and of course 18-c-6 crown ether. So, if you use then you will get this. But if you have different kind the same kind of substrate but the reagent is little different this is cesium fluoride. And which suppose to generate more nucleophilic carbon ion; more nucleophilic carbon ion and the other condition is methyl's cyanide that is acetone nitrile and room temperature. What do you expect? You will expect a very similar compound but not exactly the one we have we have seeing in the right hand side.

So, in guess since we have been talking about these indazoles; we will be getting the indazoles here and R will be R. And this N will be linking something else this is one of serious by product in the reactions or you can you can get as the major product provided you monitor the reaction rather than optimize the reaction. And what could be the byproduct, guess? Just basically if you have little mechanistic approach we can quickly come up with the byproduct you will be getting here; nitrogen would be link to a group. What could be? Phenyl that means at the end you will have nitrogen minus here that minus will add to another benzyne nucleus; that is how it will work. And let us go to the next one.

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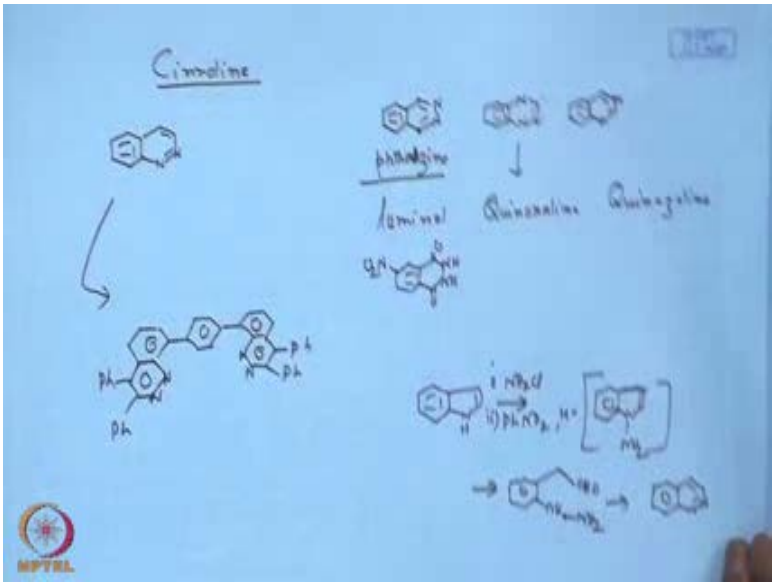

Next one is cinnoline right; cinnolines what is it? It is very similar to indazoles but this second ring is a six membered ring is this. I think before that I should also tell you some of the other analogous nucleus. For example did I do not know whether if I have told you or not there is a nucleus; for example like this there are like this there is a nucleus which will be looking like this. There is a nucleus which will that means all these are basically diatomic bicyclic in compounds this. So, that means right how many of you can recognize these 3 nuclei by name the right hand side? Synolyne you see it is 1, 2 nitrogen; any guess? This is an important nucleus again phthalazine why because most of the phthalic acid will have a carbon up here carbon up here. And it comes a hydrazine so phthalic acid hydrazine.

So, and the many of you know phthalates are pretty useful this luminal have you heard of the term luminal? How many of you heard of have you heard of luminal are its very important molecule; you can do it in lab is a nitro corresponding I mean I roughly remember it is a it obtain from the corresponding phthalic anhydride and isonitro is somewhere here is a nitro. Why it is luminal? Because if you tautomerize if this is hydroxy here and hydroxy here. If you treat with hydrogen peroxide and little bit of iron you know what happens is an example of chemi luminescence; you can see the light you can do it. And this I have done it once when I was a graduate student; it persist for at least half a minute or minute you can see the nice luminescence. And so and then this one what is the name this is a quinoxaline; and this one is has a very similar name quinazoline. I do not know how to remember this one but I can see that phthalazine because you would have 2 carbons here like phthalic acid. And quinoxaline it has a way to remember this portion comes from oxalic acid; the that these 2 carbons here.

So, that way you can remember that actually it comes in quinoxaline; so that ox come from probably there. And so but today will be talking about just a N H as an example of the polyhetero automatic this Synolyne. Synolyne of course will have 1, 2 nitrogen's of this kind and as usual they are found in many compounds with antitumor properties. And then there are some semiconducting material for example, the one I am writing now has nice n type semiconducting properties; this one is you have lot of phenyl here and there lot of phenyl's. So, then of course Synolyne means you have to have nitrogen; so 2 nitrogen; 1, 2 nitrogen here. And then phenyl up here is a symmetrical one linked with a benzene ring system you do not have to write; just I mean see most of the aromatic

compounds will have some material properties, electron optical property, optoelectronic properties or conducting nature.

Now, how to make our case is how to make it? One of the classical ways to get into this sort of or access this sort of material is ring expansion of Indole again Indole. Now, if you treat this with NH2Cl and nitrobenzene in the presence of heat; I think this is the first step; and this is second step. And you can guess what happen? It first forms this again this n nitroso sorry n amino right n amino; and then this is like a this an enamine part. So, enamine part and then that would hydrolyzed to this hydrazine. So, this is basically one way of making the like previous example is a hydrazine here and this is this aldehyde. Then, that sis base formation aromatization all these things eventually will give you the Synolyne. So, this is the one way of doing it; the other way is the could be this quite interesting; what are the other possibilities again is disubstituted aniline derivative.

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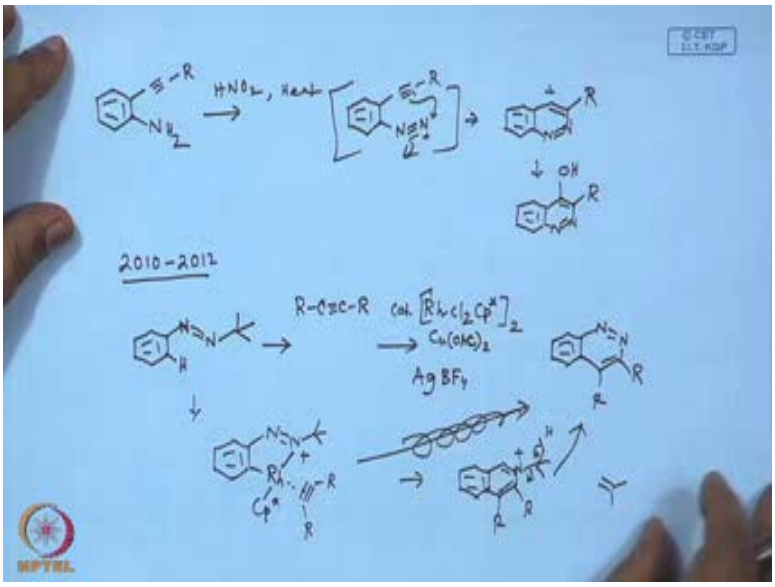

So, benzene derivative; you take this one then you have to have necessary carbon that is it. So, what is the linkage here? That would permit the formation of the Synolyne nucleus; you see you have to have 2 carbon and little bit of the unsaturation. Because to comply with the oxidation level of the final product right. And in this case it is this alkyne; see throughout the heterocyclic chemistry if we have a amine and a carbonyl.

And if we do not have a carbonyl then you substitute the carbonyl within alkyne precursor; this is the quickest way of thinking heterocyclic synthesis ok.

Now, this is so if this compound is treated with let us say nitrous acid and maybe I mean; let us say nitrous acid and heat probably then quite interestingly. So, what you will expect? You will expect right so diazonium salt. And then although apparently these two are quite far apart; but it would cyclize to this nucleus. So, that means plus sign is here; this is R, nitrogen and this. And depending on this reaction condition you can get O H here but in these case you will be getting O H; and if you have a concentrated nucleophile like chlorine, bromine, iodine. So, you can also have incorporation of this halogen's here in the presence of the carbonium ion. So, these are the two way of doing it.

But the recent once recent one could be just I think this I do not have the reference; it is published somewhere between 2010 and 2012 is a quite interesting, you starts from this azo compound. So, azo compound all of us know azo compounds are useful as what? Dyes what else; basically are dyes in food diazoles, most of the food dyes available in the market they are actually azo compounds.

So, now if you treat this with alkyne disubstituted alkyne let us say R here. And in presence of rhodium catalyst in these case the rhodium catalyst is rhodium C l 2 dichloro and then C p star this is belief to be in dimeric state. And this is catalyst; then equivalent amount of oxidant is required; often I think many of you know the cupric acid is one of the I mean cheapest or rather cheap oxidizing agents and then something else. So, this see all these organometallic chemistry would involve lot of actually optimization studies, formulations. But if you know the little bit of the mechanism if you know the mechanism you can come up with the right combinations. I mean non-chemist can also do chemistry something like this non-chemist can also do something. But they will have to just do ((Refer Time: 35:28)); but we do little bit of intelligently right judiciously.

So, we use little intelligent guess; so and what is the intelligent guess? This whole reaction conditions or reagent conditions are missing one of the reagent; you can guess what could be the reagent? Essential product is now Synolyne right. So, here is R, here R here what could be the missing reagent? I mean I have shown this hydrogen up here. So, this hydrogen has to be abstracted organometallic chemist people say that it is C H

activation; see this is a very popular term these days. If you can do a C H activation you are doing something great. But I am in organic chemist so what I look at I look at a simple electrophillic substitution reaction reactions only but with the metal now.

So, we have a chloride ((Refer Time: 36:41)) reaction; we have a alkyl chloride in this case we have rhodium chloride. So, and but in this alkyl chloride can be activated by aluminum chloride, rhodium chloride can be activated by yes; no guess silver tetrafluoroamide. All of us know it can pull the chlorine; silver has a strong affinity towards chlorine or halogens. So, it pull the chlorine so rhodium plus. That means, eventually what you will be getting here as an intermediate you will be getting an organo rhodium right organo rhodium. And that would be that would be having a halogen here right. But then there you have a second nitrogen that can also displace the intramolecular link. So, one halogen is replaced by benzene nucleus, other halogen is replaced by nitrogen. And then what is left C p star left. So, this is this intermediate.

Now, you have an organometallic rhodium complex; then all of us know that you have organometallic, you have the ((Refer Time: 37:52)). So, there is a pi complex formation; then once you have pi complex formation oxidative addition, reductive elimination so all these processes would proceed. Then, eventually you have cupric acid that would oxidize the rhodium again; and then you will enter it to the catalytic cycle. So, eventually you will get to this one.

And, this is a pretty general one actually what happens in between when the reaction is over or rather towards the penultimate stage; what you will be getting here R and this and this is synolium salt; because you have a tertiary butyl group. Then, all of us know these tertiary butyl groups are pretty because of the carbonium stability; it will do you lost as a isobutylene or if you have let us say you do not have the enough chloride. So, you would have if you had enough chloride you would have obtain tertiary butyl chloride right. So, that means you will get the ((Refer Time: 39:02)). Now, how do you know this the mechanism operating very simple to test this; what you can do?

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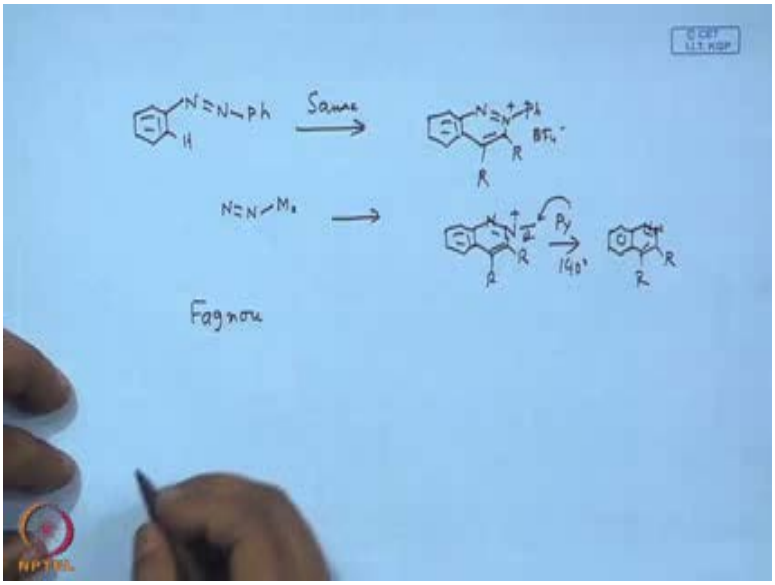

You just change the substrate change the substrate here you will have just take instead of the tertiary butyl group you take phenyl; and the reaction same reaction conditions right. So, what would be expecting now cinnolinium salt here you will be expecting cinnolinium salt but the phenyl group here that is it. And the corresponding the ((Refer Time: 39:40)) in this case may be ((Refer Time: 39:43)); and this is R here, R here, R here. So, this is a kind of test that means the tertiary butyl that synolium salt is first formed. And then separately in one case if you have a methyl for example, if you have very similar compound with methyl here. Then, you will be getting the corresponding methyl salt right the rest remains as it is; and you will get this methyl salt here. Bu, that can be simply I think just heated with pyridine at 140 degree centigrade. So, we can get the demethylation done and isopyridine attacking this methyl group here; neutralizing the nitrogen.

So, you will get to the free sinolines. So, these are all pretty useful one actually this work is pattern after a scientist name many of you probably know any of you heard of this person Fagnou is a Canadian scientist organic chemistry. And very unfortunate very unfortunate he died at the age of 35; he publish so many JACS paper before 35. And people were thinking that there would be a really could scientist but he died at the age of 35 or 40 may be below 40 for sure. Because of anybody knows this story Swine flu; have you heard of Swine flu, Tami flu Swine flu few years ago it was in the news Swine flu.

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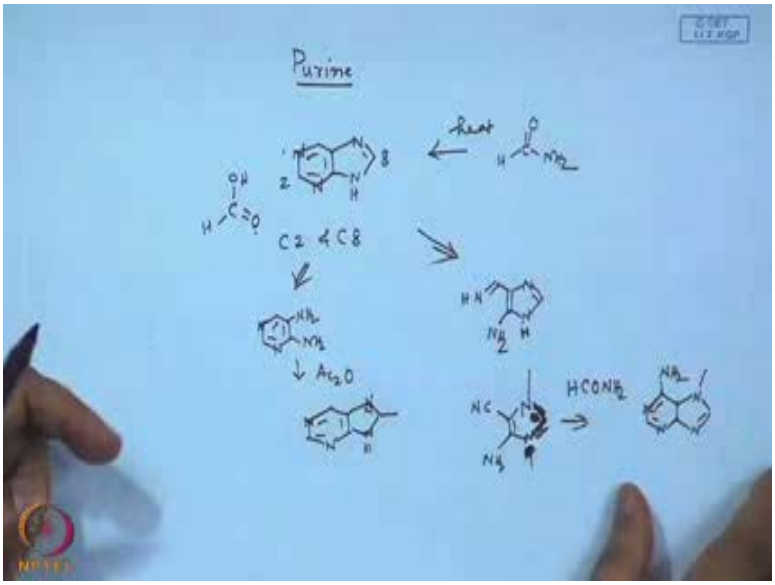

And, so let us talk about bit of purine. So, purine let us say how would you let us say purine all of us know is an imidazole and pyrimidine. We have to remember also the numbering right; you have by the way you have to at least purine pteridine you can forget about. But pyridine purine you have to remember for pyridine sorry for purine you have to remember the numbering system; and so how can you make it? And what is the starting point? The starting point here if you remember this is one, this is two; you have to look at two c 2 and c 8; what does it tell you? So, this is how we actually when you are start with a heterocyclic molecule you have to look at the structural features first. Structural features do you see any pattern, do you see any similarity, do you do you see any similarity between the c 2 carbon and an existing starting material or other popular starting material? If you remember in the first few classes in organic synthesis I talk about only oxidation reduction this thing that thing. And at the end of fourth year only we have learned oxidation, reduction that is fine. But that is a very important guideline though a very powerful guideline for any synthetic chemistry ok.

So, do you see any similarity between the c 2 carbon and with any particular starting material? Let us say what are the starting material you can think of methanol, ethanol; one carbon right one carbon symptom; so called symptom methanol, formaldehyde, formic acid all these things right. And all these actually but if you see at c 2 actually it has some resembles with formic acid right or formaldehyde; formic acid. If you just take it out because see basically this one instead of nitrogen you put oxygen here; in these

case sorry its formic acid take this carbon out instead of nitrogen you put oxygen here and the in the place nitrogen. So, that means the c 2 matches the oxidation level of formic acid.

And, similarly c 8 also matches the level of oxidation level of the formic acid. That means, one of the important starting materials could be that means you have a C H up here and the two heteroatoms. So, this can be obtained from formic acid or the corresponding derivatives; this also can be formic acid derivative by the way historically if you see if you take Formamide I did not get this I mean you may you have to work it out. You can get you just simply heat it you get the purine is a nice way of looking at to this purine synthesis; the other approaches could be there are 2 approaches. Now, you can let us say there are 2 approaches one could be just you start with the imidazole right imidazole. And the corresponding disubstituted imidazole sorry disubstituted imidazole; the other could be disubstituted pyrimidine that is it.

So, these are the 2 ways. Now, how do you real life how do you do? Let us say if you treat with simply treat with acetic anhydride you will get is a methyl substituted purine. And mechanistically basically sis base condensation; so likewise I will give you example up here. Let us say in these case sorry in these case it should be if you break this it would be N H 2 here and this one could be N H this right. Then, to give another example I think just quickly I just write example on this system you take imidazole and let us say if you have cyano here. And then N H 2 instead of the imine there sorry I made a mistake here this is 5 membered ring and double bond up here. And then of course what I said c 2 is equivalent to formic acid in this case if you use for Formamide.

So, you will get the substituted purine right you have an extra amine group that would incorporate one N H 2 group here N H 2 group here ok this sorry this I think we made a mistake somewhere here or the sorry I think this starting material is something just correct the starting material this should be amine here; and methyl group here, methyl group then nitrogen and this. Basically I mean so easy to remember there are 2 ways to remember you start with imidazole one and is this. And either you break at in fact these days you know if you can also come up with this starting metal very easily; how do you just write the structure in ((Refer Time: 47:20)) use delete; once you put delete automatically you will generate these sort of structures ok. So, that is and last item that is to be talked about.

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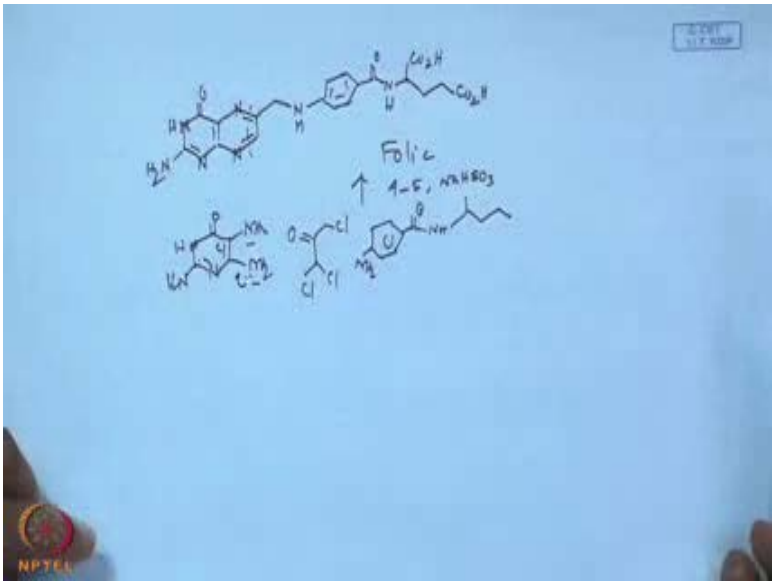

Let us say I will write the structure right; you have to tell me the name; this structure the heterocyclic nucleus that is here is N H 2 what is the heterocyclic nucleus the way I have written, any guess? To start with I have told you the very first slide; what is the heterocycle?

Student: ((Refer Time: 48:08))

Pterin it is called pterin right it is called pterin; so pterin. And then it has a name I think many of you have studied medicinal chemistry or PABA right PABA; para aminobenzoic acid. And then this one let us see how many of you know this amino acid.

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

Glutamic acid. So, I think all of you glutamic acid right. So, that means you have 3 important components and what is the name of the whole molecule?

Student: Folic acid.

Folic acid; and what is it use for?

Student: ((Refer Time: 49:01))

Vitamin is very important actually B two alpha; B complex.

Student: ((Refer Time: 49:10))

Vinyl fine. But if you have this deficiency of folic acid actually you will have lot of complications. I mean I have a list I think I can tell you I can read out it can lead to diarrhea, it can lead to anemia, it can lead to shortness of breath; you know is important though important many of you probably not know; but at least I had been benefited. Because of I mean is a prescription by a doctor and I was having a deficiency of vitamin D. But many doctors said no you have blood sugar; then one skin specialist said no you might be having a vitamin D deficiency I was treated; I mean I recovered in just in weeks time while I suffer for 2 years before that. So, that means the general I mean important how do you make it?

So, now how do you make it? Once again it is you just look at the structure here; so pterin nucleus is obtainable from the corresponding amine. And so like say this case diamine here right; and the other portion all of us know this is a basically peptide derivative we can say peptide derivative. So, you have all these things and this is amine here; and in the middle you can see now we are organic chemist we can think about right. But you have to differentiate these 2 nitrogen's see when you breakdown this folic acid you will have it this nitrogen and this nitrogen; between the two if you just apply your nucleophilicity knowledge, acidity knowledge all these resonance save this thing. One of them is more nucleophilic which one is more nucleophilic guess between the two underlined see N H 2 group top or bottom one.

Student: ((Refer Time: 51:16))

Top or bottom of course answer could be either top or bottom; but what you see here right. So, that means lone pair is now directed towards the carbonyl that means this is not available the top one is available. So, you put a carbonyl there that is it carbonyl there C H 2 C l and then but you have to differentiate here also. How do you differentiate put 2 carbonyl 2 chlorine atoms all of us know the gem chlorine is equivalent to an aldehyde. So, that way just that is it and by the way this reaction is so easy to carry out just p H 4, p h 4 to 5 and this is an antioxidant you can say; it is stops the oxidations sodium bisulphide just heat it you get folic acid. So, that means with proper design one can do this folication synthesis very easily.

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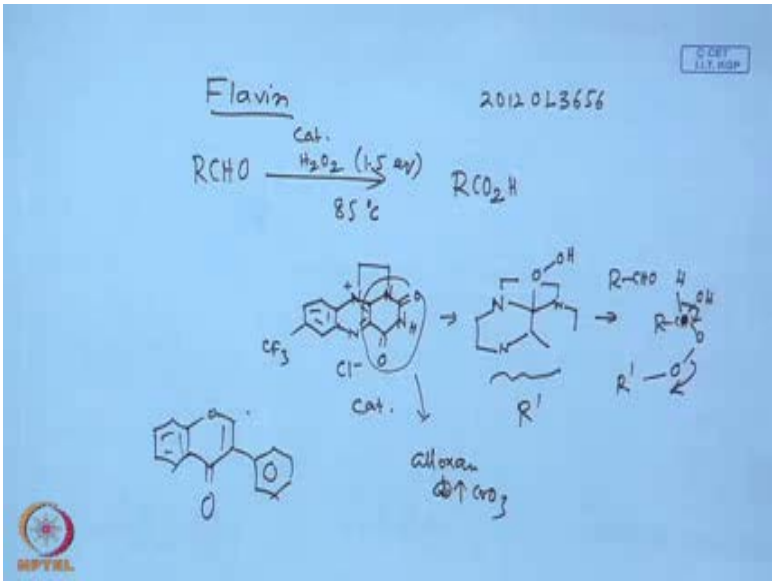

And, then last one this is an important topic though many of you probably have heard Flavin right; what is it? Flavin is again a pteridine derivative; so is a benzo pteridine derivative. And that means it is nitrogen up here is that means and then this portion is basically pteridine derivative this N H here, carbonyl. And N is and I am just writing only one specific one because this is pretty useful; this chloride minus this has been man prepared very recently. And what is used for? So, actually is a nice catalyst for oxidation suppose you begin with an aldehyde begin with an aldehyde so use this CAT.

That means, is a catalytic amount and what else I mean to get to the carboxylic acid. And it has been apply to many compounds this is published in; so it is call Flavin catalyzed oxidation is a is a kind of a green catalyst. We have hydrogen peroxide it is green reagent; there is no metal here right there is no metal; here this is in published in 2012 there are other papers but latest one is this one. So, you can go to it and see is quite interesting. And so what you have to do you have to just use 1.5 equivalent of hydrogen peroxide not much 1.5 equivalent. So, hydrogen peroxide and probably you have to heat it at some temperature obvious you have to heat it at 85 degree centigrade. And the catalyst amount that is required is very little only this one only 2.5 mole percent. So, we can go to this and what is the intermediate? Intermediate is basically a I think I will just write only the part structure; hydrogen peroxide undergoes nucleophilic addition first nucleophilic addition; first to get this hydroperoxide.

Now, this hydroperoxide goes to react with aldehyde to form hemiester. So, hydrogen peroxide and let us say R prime; that means this one. So, this portion is R prime and then all of us know that under this since peroxy linkages are weak linkages. So, it releases this. So, oxidation done again and then it then it can be under the reaction conditions, it can be the cyclic to the corresponding chloride; the reaction condition that is basically this HCL. And how to but our topic this was is a nice example of this an example of heterocyclic being used as a catalyst for the oxidations of organic compounds. And how to make it? Again do the simplifications you start from Alloxan actually this portion actually comes from Alloxan I think. So, let us say yes Alloxan actually it comes from Barbituric acid some people say Barbituric acid. What is a Barbituric acid anybody knows, how do you make it? Barbituric acid is a condensation product of diethyl malonate and urea.

So, if you oxidize that with chromium peroxide you will be go to this compound. So, I think that is all about we have to talk about. So, what is the thing you have to remember though summary of the class. First of all we have to remember the structure of the important nucleus; indazole is an easy to remember because 1, 2 nitrogen so likewise Synolyne, quinazoline, quinoline all these things they are pretty typical and pretty well known heterocyclic molecules. Then, between the purine and pteridine you have to remember the numbering system of the purine. Because it occurs in many places right all these nucleic acid most of the nucleic acid bases will have purine nucleus.

Pteridine is important because of folic acid; and what else and in the presence in the anticancer drug, methotroxate. And of course pteridine also is found in Flavin right. And then you have to make a difference between Flavin and flavones though there is a very commonly used word call flavones. How many of you know, what is flavone? Flavone green tea people say green tea is having flavone nucleus; anybody knows what is chromone? Chromone is something like this; and chromone it could be of many kinds right. Chromones it could be of many kinds like these right flavone is nothing but if I have forgotten I think it is in 2 position or 3; that may be on this side also sorry it is a phenyl chromone carbon pretty.