Heterocyclic Chemistry
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Lecture - 36
Oxazole, Imidazole & Thiazole Synthesis

Good morning. Today's topic is something different I taken up actually 3 topics together is a reverse topic. Today's topic is synthesis of Oxazole, Imidazoles and Thiazoles is a huge group of molecules in heterocyclic chemistry. And let me just go back that last time what we talked about actually we talked about Thiophene. So, thiophene chemistry like any other 5 member rings we have seen the retrosynthesis, and it demands use of sulfur containing compounds. And I think the most striking once Lawessons reagent. And other one is sulfur dichloride which has been used for the synthesis of thiophene as well as similar compound has been useful the synthesis of ((Refer Time: 01:31)) offence.

Todays topic again as the name says is little different and so long had been talking about pyrrole furan thiophene. Now, we have start it to talk about poly at hetero atomic, hetero cycles well if you say; so then you can actually think about more than 15 to 20 different heterocyclic compounds, heterocyclic classes of compounds. For example, in addition to the those. I would mentioned you can think about 1,3- dioxolane, 1, 3- dithiane sulfonate then pyrazoles, isothiazolones, isoxazoles in a then triazoles could be 1, 2, 3, 1, 2, 4 all combinations then tetrazoles. So, likewise; there are actually then you can also think about the dihydro derivatives like pyrrole, pyrrolidine. So, similarly; you know all these heterocycles can be also sub classified in to their corresponding dihydro compounds. So, there are too many things.

But basically we will be talking today only the aromatic once this oxozoles and imidazoles and thiazoles all of you know they pretty useful. Oxazole has different kind of exercise yes, they appear in a natural products macro cycles. Similarly, imidazoles for you know one of the commonest amino acid contains imidazole right.

Student: Histidine.

Very good Histidine and thiozole of course, thiozole is famous for vitamin B 1 right. Many of you probably have come across thiazolium salts in this organic synthesis as in substitute for the potassium cyanide right.

Student: ((Refer Time: 03:35))

Benzene condensation more generally it is actually assign a condensation. So, you have all kinds of that actually molecules then imidazoles we have talked about oxazoles. So, there are plenty of methods; so what I will do I will just go through the oxazoles first and see some of the recent development also in this area.

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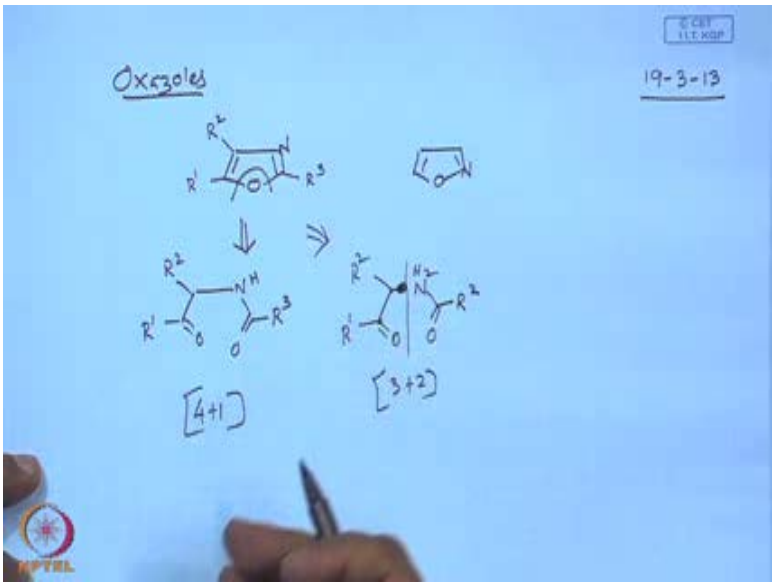

So, let us look at the structure in most cases the structures are like what? Structures are 1, 3 dispositions means; we talk about oxazole we will have structure of this kind where you have 5 members ring. So, all of you know by now know joule means; basically refers to the 5membered heterocycles. So, we know do not have any kind of word like iso or something like, prefix. Then you can think about the 2 hetero atoms are in 1, 3 positions.

So, when we talk about isoxozoles it would be appearing like this. So, basically nitrogen and oxygen are side by side. So, this is known as isoxozole; so like a Imidazoles. So, Imidazoles will have 1, 3-dinitrogen, 1, 2-dinitrogen. But it is not the isoimidazole it

should be pyrazole. But if you have sulfur nitrogen together that should be also known as isothiazoles. So, the Imidazoles systems you do not have any iso Imidazoles.

Now, our job is to see the synthesis; so what should we start from. Let us say will assume that we have all kinds of the substituents R 1, R 2, R 3 right. So, as usual our additive synthesis could be of many kinds, many possibilities. But so far, I think you have understood that we normally rely upon 2 important modes what is the important mode? One is the actually 4 plus 1, another is 3 plus 2 that is it. And that 2 you can also little bit more specific by when I say 4 plus 1, that means; the your bond session should be around the heteroatom ok. So, that means; one can think about a ketone of this kind ketone here, on this kind. And then here is a ketone of this that is it.

If you want to be little more pre size; so what you have to do? You have to do this hydro nitric cleavages in the beginning we talked about at water to across the multiple bond then you break open. So, that would give rise to the sort of compounds, that means; if you want to will may be if you have understood we will comeback that. But this hydro nitric cleavages one of the best approach to the synthesis of the heterocyclic molecules. That means, you break open and the heterocyclic molecule by hydrolysis. Then condense back to this that would be a synthesis that is the probably one of the methods of choice.

And, now this is one of the otherwise possibly could be you can just think about here, what you can think about you can start from here. So, 2, 3, that means; you can think about something like this R 1, R 2. And third atom could be 1, 2, and 3. So, it could be something like this right. Something like this it could be N H 2 for here; something like this one of this could be ok. So, there are ways. But we look at this one first one, that means; 4 plus 1, that means; this 4 plus 1. And this is 3 plus 2 mode of course; there are many more 3 plus, 3 modes.

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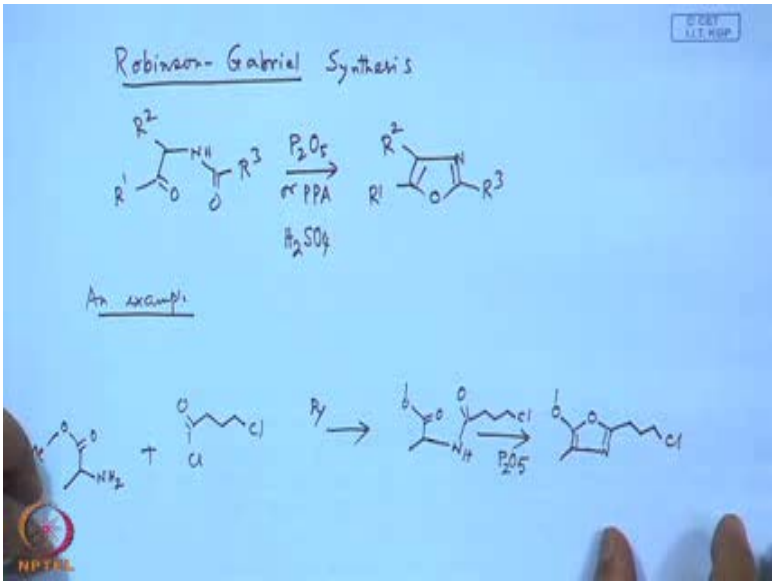

Let us begin with the first one which is known as Robinson-Gabriel synthesis. Robinson the famous and lessons of the same person and he extensively work on heterocyclic chemistry and this is known as Gabriel synthesis. So, what can I do? So, he said basically acylamino compounds the same thing what you wrote before. And now; in the polar mode then we have to reach the target here with Imidazoles. Now, we have to find out the reagent as before I said you have to examine the either the mechanism if you are comfortable with the mechanism or you can just evaluate the oxidation number identify the oxidation numbers ok.

And, I hope all of you recall this oxidation number method finding of the oxidation number method the left hand side what is the oxidation number? 4 right 1, 2, 3, 4, 5 minus 1, and 4. The right hand side you have 1, 2, 3, 4, 5 minus 1, 4. So, that means you have to only choose, that means oxidation number did not change. So, that means you have to either acetal base in this particular example what have to do you have to chosen acid. Because you want to do condensation and that to in dehydative acid, means; dehydative acid means would which you acid oxides which. So, the preferably the first choice would be P 2 O 5 or this is also quite often use in heterocyclic chemistry. Because somewhat innocent this is P P A; Polyphosphoric acid.

And, for this particular transformation also sulfuric acid has been used ok. And this mode of reaction pretty versatile. Now, just let us take an example basically an example

from a somewhat special literature. Let us say we want to make oxazole of this kind say you say functionalize one. You have chlorine substituents somewhere then you have methoxy substituent and this nitrogen here in the oxazole and the methyl group. Now, so what can you think about so how do you make this molecule? If you go back you can just in analogy the previous one. I have just inverted the structure just to make a little confused. So, what you have to do again 4 plus 1 retrosynthesis; so what you have to do then you have to take this is a carbonyl here, then nitrogen sorry carbon here then up here is nitrogen right.

This should be N H then there should be carbonyl up here and you have 1, 2, 3 and a chloride right. 1, 2, 3 am I right 1, 2, 3, 4, 5. So, that means; now, we can guess and what should be the next starting material is pretty easy at this level we can find out what should be the starting material. So, this one, that means; this one actually proceeds through this Robinson-Gabriel synthesis you just put phosphorus phenoxide that would give you this one. So, different between this now, we can instead of the R you can actually accommodate O M E that is the advantage. So, what is this if you now break open what will find? We will find something like this; so it is a chloro acid chloride all of us know between the 2 chlorines and the one is more reactive than the other which one?

Student: ((Refer Time: 13:07))

Attach to the carbonyl; so acid chloride is more reactive. So, and the other portion if you look at is pretty well known to all of you right. So, we have to basically begin with an ester now, begin with an ester here methyl group and N H 2 what is it? Not really running. So, methyl alaninate; so that means you see here although is a very highly functionalized oxazole; you can with little systematic approach you can produce this molecule. So, likewise; I will convince, that means; each of this strategies will have sort of a dissection of this molecule in to 4 plus 1 or 3 plus 2 most cases. And then you go on proceeding with different substrates and reagents.

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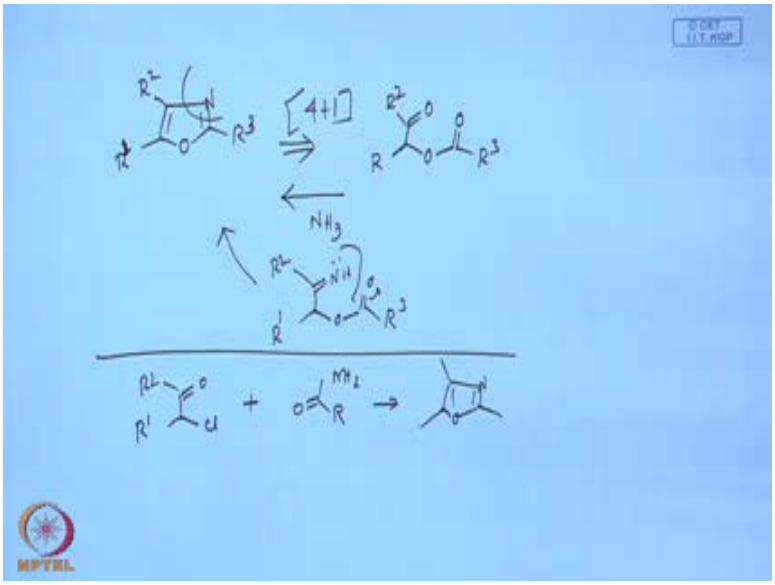

Next one could be let us say have an oxazole once again I am writing the same thing same old thing here. So, R let us say R 3, R 1, R 3 and this nitrogen here. Now, you want to let us say you want to again breaking to this is a 4 plus 1 way. So, how did it look like it will look like this that means; you cannot have these imines. So, will have hydroxyl then here and once again right. So, what you have to know here oxygen right R 3 and R 2 and R 1 right that is it. I mean just pullout this 1 atom by breaking 2 atoms. So that, you can break open in to 4 plus 1. Now, you can what can I do? That means; if you look at this structure it is nothing. But this alpha if you block this it will look like an alpha hydroxyl ketone. And the hydroxyl has been acetylated so easily melt there how so you get back to the rather or I should or you can say do the synthesis you have to put nitrogen.

So, and the obviously the important source of nitrogen this just like a in previous case you had eliminated water right, in this case you also you can eliminate water. But you can put this nitrogen first form of imine. And then cyclises; so if you have a system like this it first forms this imine here hydroxyl. And then so R 1, R 2, R 3 and under this reaction conditions actually aromatization is driving force. So, one can think about the formation of this oxazole system so ok. So, there are other methods also similarly, one can so that means; here you have an hydroxyl ketone there are methods where we can use corresponding halogen compound. Let us say x and R here R 1, R 2 and then you can

treat with corresponding phenyl amide corresponding amide and you get to this oxazoles systems ok.

So, you can that means you have all kinds of permutations combinations on there. But the one that is a little sophisticated. So, that means basically as I said before you have to identify you have to break you have to do little synthesis on the conventional way or this hydrolysis way or hydriodic way. Then you have to choose the right starting material that is it. And it is just like under goes to the furan synthesis 1, 4-diketone has been condensed to the corresponding furan even additional hetero atoms. So, it gives to the poly hydromatic, poly hetero atomic, hetero cycles. And I will skip some of them regular once.

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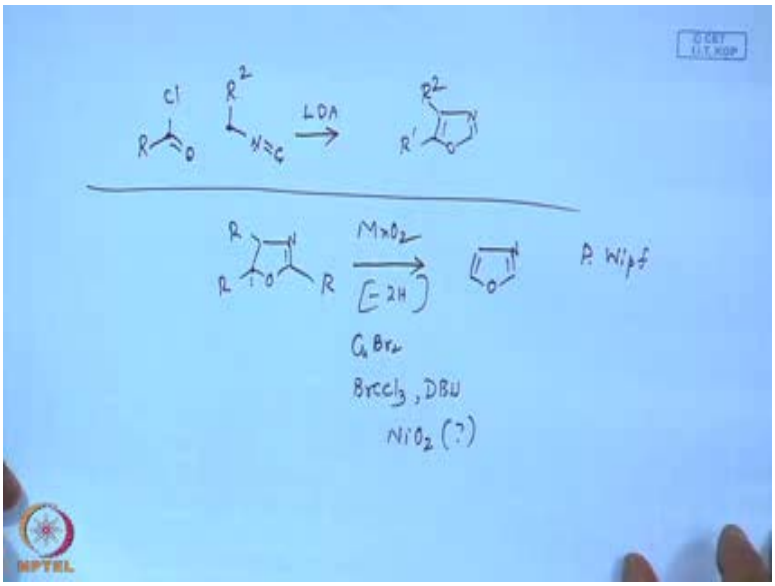

Let us look at the other possible substrates. For example, this one of the recent one actually starts from alpha, Diageo, carbonyl compounds. So, in this case you have this Diageo compounds. Let us say R 1 again R 2 and then you can guess what else to be done this is alpha, Diageo, ketone. So, again this now, unlike this amino carbonyl compound which acts as a nitrogen-carbons-carbons source. In this case Diageo compounds many of you know it is a basically precursor of the corresponding carbine. So, that means this will oxygen-carbon and carbon; so it is a basically 3 atom sin than. Then other that means oxazole what you have to choose 1 more carbon nitrogen system here and this.

That means, this should be link to this carbon-nitrogen and this oxygen should be linked to this one. So, eventually once again you will get the same kind of oxazole here I will not write the Rs we can write. But only thing that again you have to choose the catalyst what is the catalyst? You can think of the conventional once is heat. And then occasionally copper triplates all these things are used. But more sophisticated one more model one is not really disodium tetra acetate ok. Let us now, one of the most famous development in heterocyclic chemistry in recent years is due to Van leusen.

So, what you remember about Van leusen? Anybody remembers about the Van leusen? Van leusen has developed a pyrrole synthesis. So, that is pyrrole synthesis based upon the reagent known as tosmic tosylmethyl isocyanide and tosmic methyl isocyanide is equivalent to C N C. So, that is why remember C N C carbon-nitrogen-carbon. And Tosyl group, methyl and isocyanide, nitrogen and this. So, this is now; extensively used in fact; so that means; say basically simple for carbon-nitrogen. And carbon now; if you let us say so the retrosynthesis on a small molecule like this with 1 substituent.

So, what you can think about you can how do I just cleave actually it basically requires 2 components 3 and plus 2. So, tosmic actually serves as the 3 atom component; so that means; you have to break open only this much. So, this one comes from tosmic; so obviously is very simple. I mean; if you in the way; so what should be the starting metal? So, this one is tosmic and other one is what? Aldehyde otherwise in this case of course, it is aldehyde that is it. So, if you have tosmic and the corresponding aldehyde and the reaction is so easy. And by the by reaction conditions are very easy you just add potassium carbonate, attach some potassium carbonate eventually you get this compound. And this reaction is pretty general now; if you recall in the case of pyrrole synthesis what you needed anybody remember?

For the pyrrole synthesis you needed alpha, beta unsaturated ketones sorry alpha, beta unsaturated esters. So that, would gives you the corresponding pyrrole; so that means; carbon-carbon multiple bond. So, in this case you have carbon-oxygen multiple bond plus tosmic. And the other possible, other one say little not that regularly used because it of some other reasons one can also think of a 2 atoms in term like acid chloride. And then one more C N C it is not really tosmic it is kind of it. I mean, it is kind of it tosmic you can say in this case the sulphone is not there; so it is isocyanide that is it. And here

you have this carbon-nitrogen-carbon again a C N C and you have an carbon-oxygen multiple bond.

Difference between the previous one the tosmic portion had a living room that is; tosyl group in this case there 2 carbons, 2 atoms in concerning acid chloride is having a living room that is the chloride that is it. I means, you have basically inter change the living rooms. And the obviously the previous case it was sodium carbonate and potassium carbonate. But this isocyanides are not that as acetic acid tosmic; so you have just stronger based normally it used L D A. So, and as usual one can go to the corresponding oxazole ok.

And, then last one I think probably would be the may one of the finest synthesis is an oxazoline synthesis first what you do you take oxazoline like, oxazoline means? Any idea oxazoline is dihydrooxazole there is a that means; you have nitrogen here and this right. And let us say R here let us say again R I think I will now; write R 1, R 2 all these things. Now, this is one of this realistic approach just 2 oxazoles reason being I can you can do this oxidation, that means; dehydrogenations. So, how can you do the dehydrogenation? How can you do? That means; you can if you remove the 2 hydrogen you can get to this sort of compound. And this is pretty made popular by Peter Wipf he is pretty well known scientist and a university principle, and here extensively dark on this mode of oxazole preparations ok.

Now, the question of how to remove these 2 hydrogen? That means, is this dehydrogenation process that means; you have to have sufficient knowledge about the dehydrogenation. What are the methods you know of one of this methods is principle involves p d q for example, p d q paradigm charcoal; so the commonest one in organic chemistry. But heterocyclic chemistry has some limitations you can used all the oxidizing agents used in the normal chemistry organic chemistry in heterocyclic chemistry partly. Because of the susceptible of the hetero atoms to the oxygen oxidations. For example, nitrogen many of you know nitrogen under goes of very easy oxidation with hydrogen peroxide quickly M C P B A oxidization nitrogen corresponding oxides.

So, that means you have some limitations in this example actually the use M n o 2. And there are actually limited options or one can use cupric bromide start impress first this

again oxidizing agent. The other one this is Bromotrichloromethane and D B U Bromotrichloromethane how does it do? Actually it first brominates this hydrogen first then D B U all of you know is best. So, it hydrogen and I am not sure actually in my notes actually there is a question mark probably you have seen somewhere also with nickel peroxide probably I am not sure. Now, the question is how to make this oxazoline? Then oxazoline there are once again oxazoline how do you make? This can be made from amino alcohols pretty easily amino alcohols ok.

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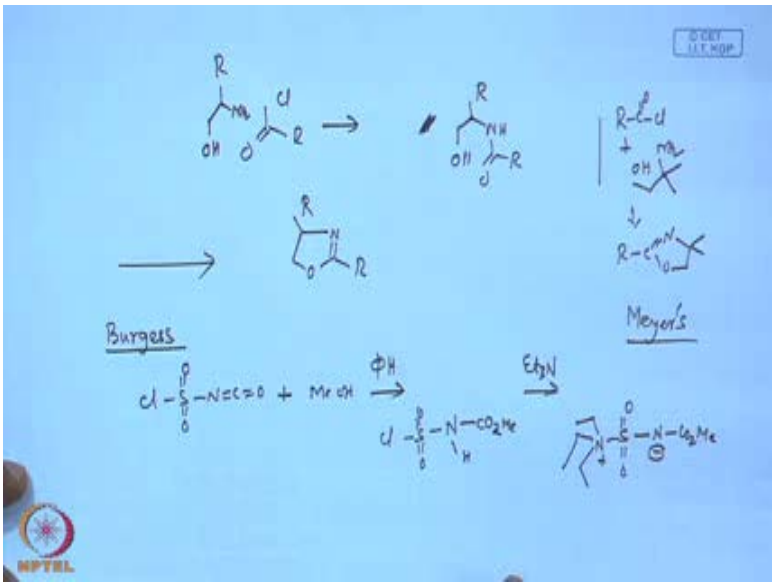

And, if you take acid chloride for example, acid chlorides and then amino alcohols like this. And then mix them; so I think there are reasons why particular this synthetic mode is chosen any idea? Because this sort of amino alcohols are readily available from epoxides and amino acids if you reduce the carboxylic acid you can go to the this. And then epoxides can be re open to amino alcohols. So, that is the reason why then if you mix them with the presence of base obviously what you will be getting, you will be getting here N H carbonyl and R here ok.

There are cases like if you want to produce let us say ((Refer Time: 29:25)) oxazoline many of you probably know purdeys right acid chloride plus again an amino alcohol. And it has little bit difference you have 2 methyl groups here, is just mix them together you get directly oxazoline you do not have to anything else here. So that, you will be getting, we will straight way getting the reactions are sources asylum. And many of you

know this is directive group in ortho locations is also activates the corresponding C H alpha to this group. So, there are well known in call sometime people this is known as actually Meyers scheme, Meyers chemistry you can say now problem is here. How to cyclize, that means; once again is a position of what is this next step, that means; this is a next step would be the cyclization right. So, you have to do a cyclization here; so how do you do the cyclization?

If you have cyclization like K 2 O 5 but this is not you have free O H group here. So, P 2 F H is good if you have the carbonyl compounds. Then I intra molecular cyclization dehydrations are pretty good. But if you have this free alcohol K 2 O 5 is not good because it make all kinds of rearrangements this thing, that thing. So, you have to a method which would be very selective for only for dehydration. And I will nothing let you know one of the reagents it is very popular. And now a days it is commercially available also in fact; I came to know that day before yesterday that is also commercially available is pretty famous reagent burgers reagent but just burgers ok.

Burgers reagent and if you type in googles at least you will find my name there reason being in 2001 we wrote an article on this. But this reagent in organic synthesis we did not know that it would be becomes; so popular year before last. Now, all this chemical is now marketing it is nothing but it is a mixture of chlorosulfonyl isocyanate I think I will write this Chlorosulfonyl isocyanate plus methanol ok. And then one more step you get the solid nice crystalline. And it nothing but is a dehydrating agent and what are the reactions? Actually, solvent of course, benzene; so what is the product you can expect there are 2 reactive centers have a isonade center you have sulfonil chloride center of course, within the 2 which one is more likely to the more reactive ?Which one?

Student: ((Refer Time: 32:39))

Very good. So, at least in fact before I wrote this note I thought it would be acid chloride. But when I looked up literature actually I will found it is more reactive. So, methanol first reacts with isocyanides. And so obviously what you will find it should be the methanol convert this carbonyl part to ester. And this is N H and then you have the sulfonyl chloride part of here. Now, what does it do here now; this is next step is basically kind of a ((Refer Time: 33:15)) kind of things. So, here now; triethylamine displaces this chloride part and the chloride fixed up this hydrogen form the carbonite

unit. So, it forms basically nitrogen minus here nitrogen plus is a sustain kind of a molecule it looks but preparation is pretty easy.

And, so this I mean if you again go to the literature almost every month you will see one article on where a burgers agent has been use for the dehydration in this case it is a in fact; simple alcohol. For example, many of you probably do not know for dehydration of primary sorry primary alcohol to corresponding alkynes. What method to do use? For ethanol concentrated sulfuric acid perfectly all right. But for all other practical organic chemistry research especially; sulfuric acid is not a welcome reagent right. Because it is very restrict one. So, what else you do would you which one?

Student: ((Refer Time: 34:32))

Jantec formation, but nobody uses you will not you just over cross the organic chemistry lab nobody uses it. Because it requires very high temperature in fact; in our lab

Student: ((Refer Time: 34:44))

200 degrees centigrade; so if you go beyond 200 degree centigrade nobody uses this in my lab there is a machine like nobody is using it. I told that is a plus ((Refer Time: 34:55)) long back we used to carry out the reaction at minus sorry at 500 degree centigrade. But other day I suggested someone to make use of it he did not that means; it is not very comparable for us. So, what else what are the other methods do you know of aluminum oxide there are not very reliable in principle is ok. But that also require very high temperature I am talking about the primary alcohols, tertiary alcohols very easy.

Let us say if you have a tertiary alcohol you want to do dehydration let us see butanol to butaline how do you do? Simple iodine is good enough just iodine is reflux you will get the butaline. But the primary it is not; so that is the reason this progressive reagent is very good one as per you can do this dehydrations this ok.

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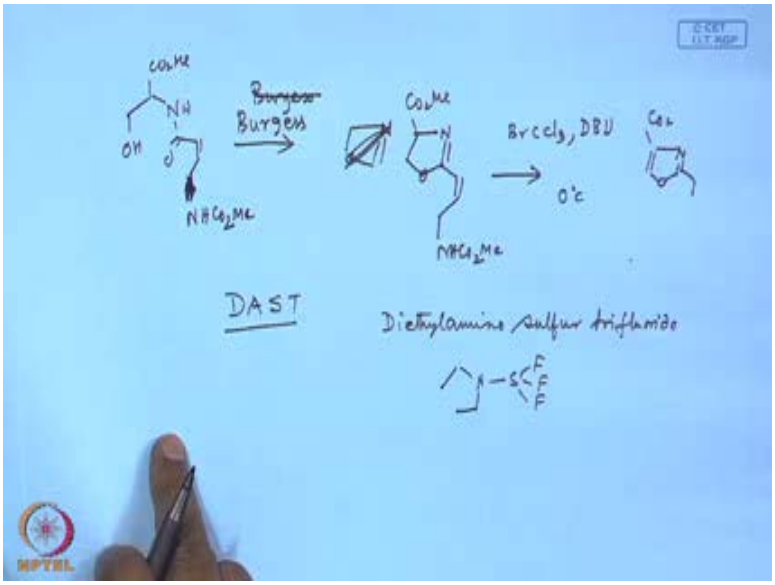

And, so what peter with did I will tell you will just taken alcohol and aryl amino alcohol here; He first made I now you see this molecule here is a little complex here this is nitrogen this is carbonate unit ok. Now; so you use burgers reagent why burgers reagent? Because you have; so many functional group here esters you have, that means; you have amines here. That means; if this amine can undergo intra molecular cyclization etc. But the burgers reagent is so; unique it will form this oxazole here sorry oxazoline and the ester here. And then the rest of the things remain as it is without any problem you can get to this oxazole in systems here.

And, then this you have to introduce double bond. So, what you have to do you have to bromotrichloromethane and D B U. And this reaction is done at 0 degree centigrade to corresponding re aromatize one I will not write this rest of the things. So, you cannot write; so is this one so; you can use burgers reagent or I will introduce to you to another kind of a reagent I think this is for advance level the sometime it is required let us say this is a reagent called dust. I do not know how many of you know dust? I mean, no dust actually one should know actually we often one this part of the chemistry.

But this chemistry is very useful fluorine chemistry especially for the organic chemistry and medical chemist, fluorine chemistry is very useful. Because you can pull the biosystems by replacing hydrogen by fluorine next to hydrogen fluorine is the tiniest atom in the predictable right. So, most of the enzymes and this bacteria pulled if you put

a plus take demand is pretty close to hydrogen. So, how do you convert it? Let us seen primary once again primary alcohol to corresponding fluoride there are not many methods dust is one of the finest methods. So, finest reagent you see her e it is nothing but the names tells you diethyl amino, sulfur trifluoride. So, here you have 3 fluorides, the 3product fluoride items, nitrogen and that is it. And this is a providing agent it converts alcohol to the corresponding fluoride we did use once to convert 3 hydroxyl halide to corresponding ((Refer Time: 39:30)) and also it acts as a dehydrating agent like, that means; it could be substitute for this.

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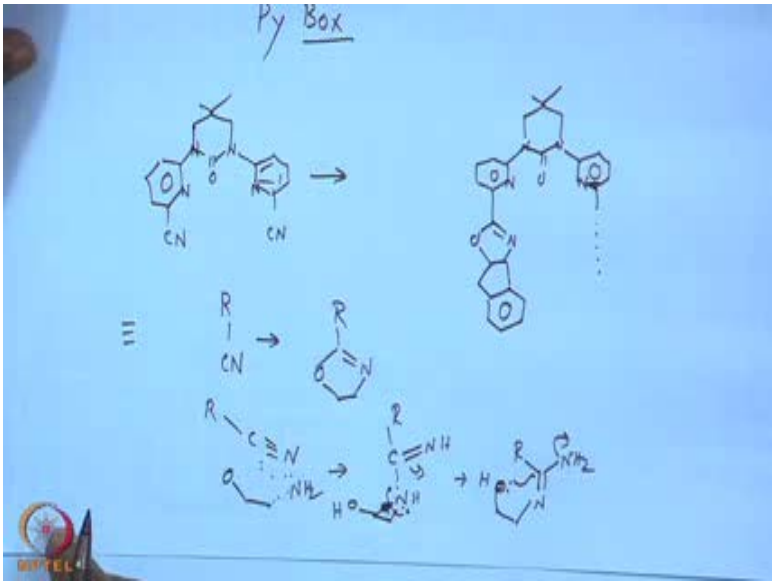

So, adjust a now quickly we will have kind of test for this sort of cyclizations into big molecule many of you know that is a class of reagent call Py box right boxy agent what is that box reagent? Box reagent nobody no you must know especially I cannot excuse Vivekananda.

Student: ((Refer Time: 40:37))

Oxazoline not oxazolidine no oxazoline, oxazolidine is different. No, there are 2things oxazole is 2 double bond oxazoline is 1 double bond oxazolidine is no double bond; so oxazoline ok. And I will just give you puzzle here this is molecule has been May synthesized in 2009 someone try to convert this. Now, we have enough of the background on iso sorry, oxazole synthesis. Now, suggest me how to convert this into nitrogen-nitrogen here you have this pyridine ok. Now, the cyanide has to be converted

to oxazoline right. And this oxazoline again it is link to a 5 member ring and the. And then I think I will not write because it is a Bis compound and the other part remains as it is. So, you have to write this other part and here this is again Indian system right.

So, this is equivalent to basically you have R C N and you have to convert this R C N into oxazoline that is it. So, what can I do? We have talked about; so many things right. Actually, by looking at; so what should be the mode the synthesis cyanide the way I have written actually what you can see cyanide would serve as a 2 atoms((Refer Time: 43:12)) so that means; you have to choose the 3 atom; so 3 atom right.

So, what are what is that 3 atom that is what do you have look at that means; the cyanide should be looking like this. Then you have to have an oxygen up here this and now you have to fill in the blank here guess? So, the heterocyclic chemistry only the guess of the rights starting materials that means; a group which would be a nucleophile at the same time which could also live the system right.

Once again because if I if you recall this sort of systems actually sign amines attach the cyanide in heterocyclic system the plenty of cases to form the corresponding imine. And the corresponding just I will only write this part. Then I will come back to the; so what will you see you will see something like this right. Then eventually it amine eventually it will migrate. So, I am just only write the part structure I will give you the final answer later. So, we will have now; N H 2 up here; so you have 2 carbon atom sorry, 2 carbon atoms. Now, you can have one more you have oxygen up here. And then under this reaction conditions it will expels this amine. And then eventually we got this; what this is the, I mean formulation.

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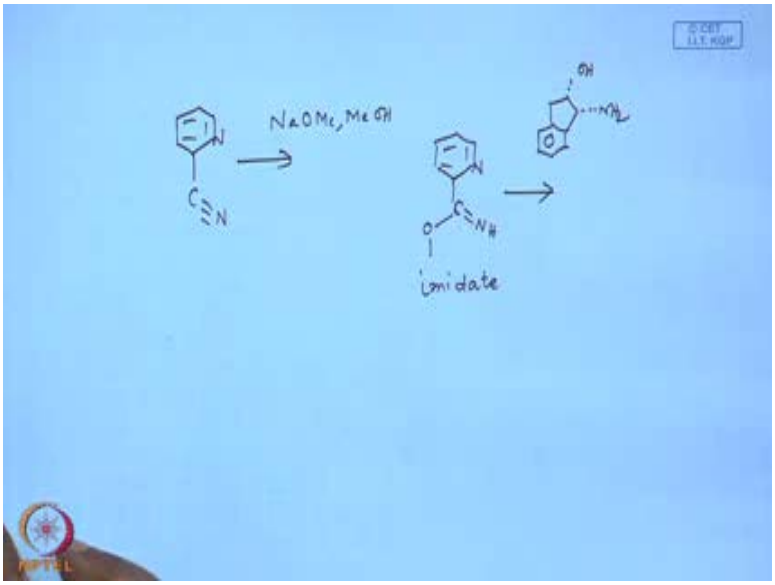

Now, let us see actually answer is like this. So, they had this pyridine unit, cyanide and then they reaction often we do not study though. But is a very useful reaction by the by very useful reaction. And the also it refreshes your memory on pyridine chemistry. So, what is this product here? So, all of us know pyridine under goes ((Refer time: 46:06)) reaction this thing, that thing, that means; it undergoes nucleophilic addition at the 2 positions. But you see here, cyanide is so reactive and cyanide reaction probably often we do not read this. But actually it converts this cyanide 2 this one what is the name? What is the name of the functional group? Immediate like carboxylates, immediate ok. Pretty useful.

I mean you can just you know do in the lab takes acetonitrile add H C L dry H C L no if you have just H C L you will get the hydrolysis of cyanide to the corresponding carboxylic acid. Dry H C L and methanol you get the immediate hydrochloride corresponding hydrochloride to be obtain ok. Then and this one this aminol; so this aminol is used which is obtain from the corresponding, that means; Indian system. And this is a chemical compound is a starting material for N T H i drug in Indian veal ok. So you just mix them together I mean; just dichloromethane no nothing, no reagent nothing it will from the corresponding oxazoline. So, there is pretty fine chemical reaction.

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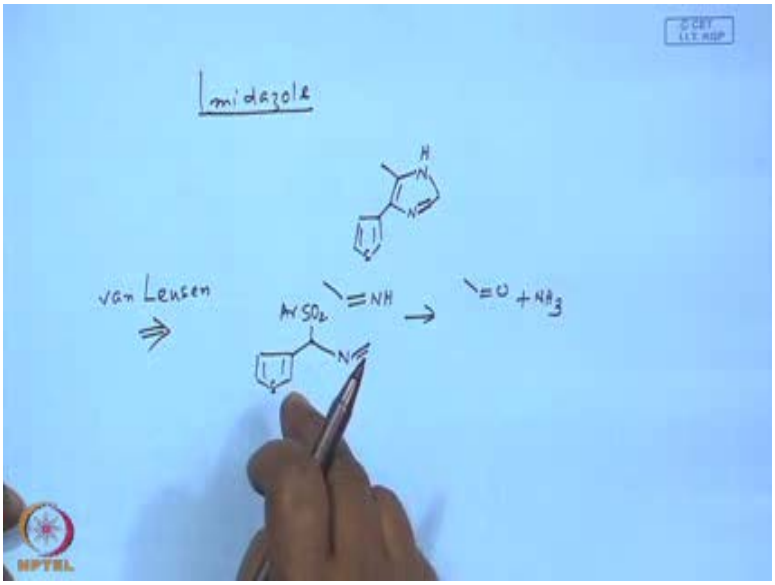

And, so let me quickly just go to one more synthesis; so that means; all these sort of synthesis would be very similar for Imidazoles also Imidazoles But I will only take up one which is very popular to me at least the that means; how to make Imidazoles the way you have broken down this molecules into 4 plus 1 and 2 plus sorry, 3 plus 2. So, these are the modes and the one I will be talking about today now is pretty mass similar to this van leusen method ok. Let us say we want to produce Imidazoles on these structures here and in this case you have thiophene many units. So, how do you make this is nitrogen N H. Now, how do you make this? Ok. And in this case there are 2 heterocycle molecule of course, the one, that is; the Robastone.

So, you do not you start with a Robastone between the 2, that is; a Imidazoles and thiophene all of us know the little bit of the chemistry part chemistry thiophene is petty robust means; is not that reactive Imidazoles are petty reactive it has it under goes oxidation, it undergoes protonation hydrolysis everything. I mean; faster than any other heterocyclic like thiophene. So, you have to take a thiophene derivative then use van leusen method. So, how do you make this; so what are the reagents, that means; so what are what are the synthons? Van leusen means; what I said C N C that means; you begin with thiophene then C N C that is it. And of course; one of this carbon is cyanide other carbon contains sulphone or in this tosyl and that is then you have this.

So, eventually you just to the mechanism there you can go to this right. What are the 2component systems? 2 components system should be C double bond nitrogen in this case it is imine. So, how do you get this imine from this ketone and ammonia, in fact; this particular compound has been synthesis starting from the corresponding van leusen reagent then the aldehyde and ammonia. So, I mean if you just systematically proceed this synthesis of this other examples, I will not give you even from the corresponding Glyoxolic acetone. So, you can make a similar Imidazoles derivative.

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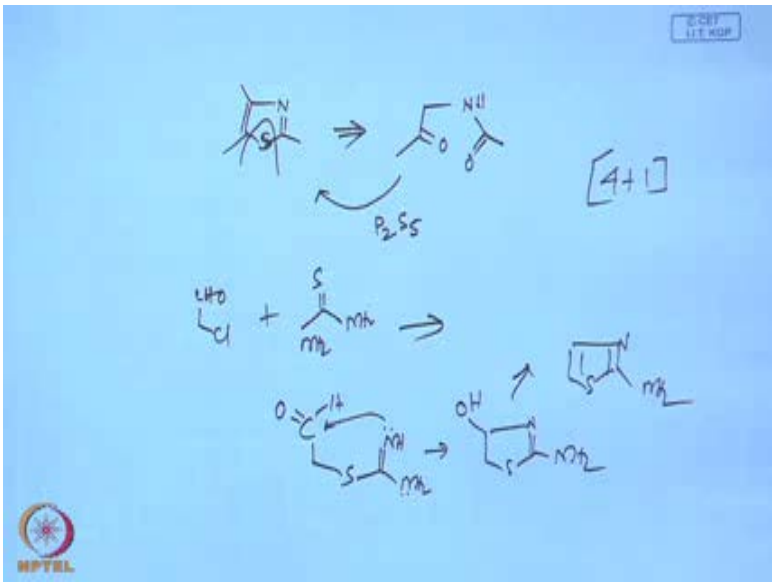

And, the last example would be I think thiazoles right. Once again is analogs to oxazoles; so you have and you have all again different the same protocol of this little synthesis. And what can I do here let us say 4 plus 1, that means; you have to break open this molecule and extract the sulfur out, that means; you are starting material should be of this kind N H. And here you have oxygen here and this that is it. So, what is the, what should be the reagent? The reagent would be P 2 S 5 or people write P 4 S 10. So that means; and then this situation demands you can sue lavas in agent. But I have not come across like this. So, this is basically 4 plus 1 mode right.

Now, there are other methods also, you can just go on to and but you have to see especially, the thiazole chemistry you have to see the ability of the starting materials. In this case what you can see basically acyl amino ketones that you have seen before in the case of oxazole synthesis is pretty easy. There are other ways to look at the thiophene

chemistry is sulfur source is commonly thioacetamide, thioamides one of them. And other sulfur source is ((Refer Time: 52:43)) ok.

So, for example; I will just give you 1, 3 plus 2 for example, if you take chloroacetaldehyde and thiourea. So, what you expect thiourea say you have to think about this thing, that is; sulfur is a soft nucleophile. So, it is likely that it would replace this and so sulfur would attack this one right. And then O H sulfur then this is nitrogen and this N H 2. And then of course, then what is then what you will be getting you will be getting this amino thiazoles. So, that means; this is there are 2 important modes 1 is that this Gabriel synthesis which involves the use of P 2 S 5 other is the basically the methods which use thiourea are corresponding thioamides also.

There are other methods there are plenty of other methods. But basically these are the 2 different kinds of the methods one best on the sulfurs, sulfur items and other sulfur source like P 2 S 5. And there are cases of course; I mean other common sources could be carbon disulfide. So, depending on the then there are for example; thiazole how you make thiazole other method could be isocyanides also could be isocyanides sorry, thioisocyanate.

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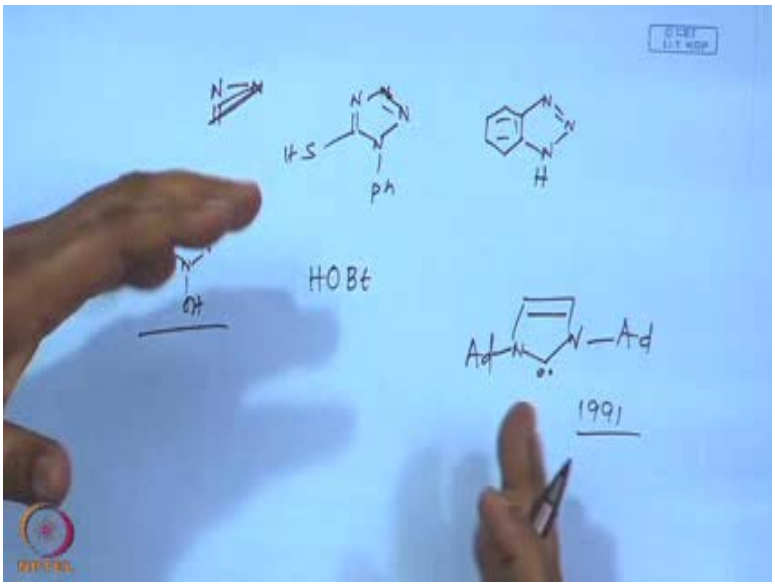

And, lastly I think probably you can think about how to make this molecule some of you probably know this is a tetrazole nitrogen-nitrogen. And then this; so it is a tetrazole here and this reagent is pretty useful in early synthesis. So, how do you make it? Any idea?

Student: ((Refer Time: 55:30))

t m s, t m s not really actually, that is; actually it has been made in commercially sodium azide and phenyl thioisocyanate likewise; many of you probably know this reagent right. How to make this reagent? what is it known as benzotriazole how to make?

Student: ((Refer Time: 56:01))

Ortho phenyl diamine ((Refer Time: 56:09)) and now you have tell me how to and what is this reagent? Is a famous reagent in penetrate chemistry very good H O B t what is it what is the full form hydroxybenzotrazole good. So, you know; so this is made form ortho phenyl diamine. Now, how do you make this? This is hydrogen. So, basically hydrogen is replace by oxygen O H. I will tell you the clue is that the reagents are readily available you can get those chemicals anywhere in our lab. I mean; any under graduate college also, what could be the starting material this is how basically we have to think about see, heterocyclic chemistry.

I mean; if you try to remember or memorize you will be lost. Because so many, things to remember. But best thing to just because you know retrosynthesis, you know little bit about the ability of the starting materials and the reagents and the chemistry. So, we can formulate our own kind of actually these methods. So, what is the method you suggest for making this molecule? Think about it. I will give you the answer is ortho chloro nitrobenzene and hydrogen. Ortho chloro nitrobenzene you will get anywhere nitrogen ok. And last point in this class I have to just one more point I think many of you know N H C right. Heterocyclic carbines, that means; carbines I mean; when study the chemistry people is to tell us our teachers tell us that carbines are not very stable.

But in 1991 there was a scientist in industry name ((Refer Time: 58:31)) have you heard of the name ((Refer Time: 58:33)) he was an chemist of course, working in industry he discovered something new. But he said carbine can be stored in a bottle for months we know what it is? What is the structure? The structure is again these Imidazoles. And this carbine is stable free form anything and it you can store in a bottle that was published in 1991 that has given. But too many, many carbines now, so all of us know now re carbines n s c n heterocyclic carbines etc. And that means; basically and the starting material obviously what should be the starting material. Starting material is

corresponding imidazole, imidazolium salt then if you has sodium hydride in D M S O you can get the free carbine.