Heterocyclic Chemistry
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Lecture - 30
Pyrrole Synthesis I

Good morning. Today's class is first of synthesis, truly synthesis classes. See, Heterocyclic synthesis can be divided in many different classes, subclasses. But what I have done, I have structure the course in a fashion; where, first I will talk about the five-membered heterocycles and then obviously the six-membered. And then if time permits then we talk about the fused once; fused heterocycles. Like, say Pyrrole pyridine or furuno pyridine, those sort of things. Then that means the first class which I have titled is the Pyrrole one in which we will be talking about only the Pyrrole synthesis.

And, Pyrrole synthesis is such a first area, it can be divided into actually two classes; could be even more, but I have restricted to only two classes. And in these one, what I will do; I will select some of the important Pyrrole synthesizes. And then talk about one by one; the most conventional once, would be talked little later. Like many of you know, in case of Pyrrole synthesis there are three well studied or whether well known synthesis.

One is paal-knorr synthesis as a knorr synthesis and hand synthesis. So, we will be talking about those little bit later. And then among the five-membered, let say Pyrrole, pyridine; sorry Pyrrole, furan and thiofin, many of you know the Pyrrole is actually more abundant both in nature as well in as synthetic materials. So, there are if you go through the literature, you will find almost every year there is a new synthesis coming up. Say, lot of people are innovating lot of methods.

So, but if you go to a recent review in chemical review by Evergen; one scientist name as Evergen. And he has written an article of 130 pages only on heterocyclic synthesis and with more than 800 references. So, it is very difficult; actually to keep track up all these developments, ok. So, what we will do, we will do this basic once; the once which are more frequently used in organic chemistry. And just let us look at the complexity of the synthesizes actually.

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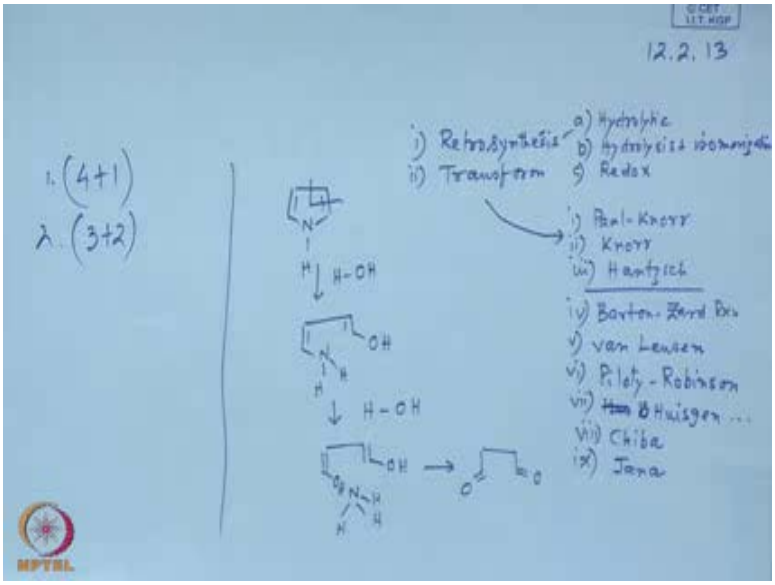

The first one, if you look at the Pyrrole nucleus and try to construct Pyrrole nucleus or a substitute nucleus, so where do we start from? Traditionally, there are two ways to start from. What are the two ways? Number 1, is Retro synthesis, right. All of us, because we have been trying to organize this kind of synthesis by retrosynthesis the other way; these are the two ways. Where to start? Let us, I give you an unknown problem and I say that, ok you synthesize this molecule. Then you have to start your thinking.

There are two ways, one is Retro synthesis; other is, which one is the other? Other best possible rather best possible is the Transform base. So, start form base. Because if I just try to show you the Retro synthesis; Retro synthesis is not really, that easy. And most often practicing scientist what would they do? They go by the transform. Initially, they will do the Retro synthesis, but when they get lost they will try to do synthesis. Let us say just very briefly, how many ways can you retro synthesize your Pyrrole nucleus? Guess?

Student: ((Refer Time: 04:39))

No, how many I mean, just give me a number; that I can break this nucleus in 5 different ways, 3 different ways, 10 different ways, 20 different ways, give me a number. That means what I am trying to say that the retro synthesis is very complex; very complex. Our if you, any idea how many ways? Actually, I have a note, I will just show you. I do not know whether you can see or not this is 18 right; 18 different ways. But I can write

more; so that means we are lost. So, which one to? For example, but if you have attended my synthesis class, if you remember, but my first clue about the retro synthesis is the first clue about the retro synthesis is, anybody remember? Hydrolytic cleavages.

So, what do you do? You just choose any one bond; especially, one that is attached to a heteroatom; just hydrolyze it. That means, at one point you have to add hydrogen, other point you have to OH; result would be and then of course, the cleavage. And so then you have to have, little bit of this idea about this electronegativity. For example, when I write the first step right, hydrogen can go to this nitrogen as well as carbon; but all of us know nitrogen is more electronegative. So, it will pick up this hydrogen. So, that means then we now restrict this choice to just one; this hydrogen should be on this side and ways on the other side. So, you break the bond here, right. And then rest remains as it is.

So, let us talk about one more. Again, if you do so what we will see. Again, you have one hetero; all of us know this innols. Innols they rapidly isomerizes to the aldehyde; so will not touch that. And then you have one more here bond, carbon nitrogen bond; so will break them then. What about the, at the hydrogen we had will keep them; then the new hydrogen should be placed and then new OH should be replaced here. New OH replaced here.

Now, all of us know this tautomerism and what you will find? You will find, that is nothing but succinaldehyde, nothing but succinaldehyde, right. So, this is one of the best way of looking at retro synthesizes. Instead of going all possible, say in a nucleus; let say how do I generate the all these. First we go by the number of the bonds. For example, I can click one, I can click one bond here, then second bond here, third bond, forth bond, fifth bond; so like these number of bonds.

Then, what we can do? We can have a simultaneous cleavages; means, at a point you can click both the bond together. Then 3 bonds together, 4 bonds together; all possible combinations. Then there are two more important bonds are like, you can have an ring expansion. Let us say if you have to make a 5 membered ring; so you start from 4 membered ring or 3 membered ring. Then expand the ring system, ring contraction. That is also pretty popular way of making the Pyrrole ring systems. If you have sorry pyridazine; pyridazine nucleus you can just contract it other ways. So, you can make the Pyrrole ring systems. So, there are ways; I mean not only these typical bond cleavages,

this thing, that thing you can. But I think the best way to look at the retro synthesis of the heterocycle is the way that hydriodic cleavages.

Next thing that one should think about hydriodic cleavages plus isomerisation. Isomerisation of the normally, isomerisation is the functional groups or the double bonds; this is one of these ways to look at. And the third one vice versa; isomerisation forward by a hydrolysis or hydrolysis forward by isomerisation; this is one of these. Third could be third kind of the transform is the Redox; either you oxidized or reduce all these things. But these are the, if you want to go by these retro synthesis; here, very broad. Now, if you go to the transform based, I think we have already talked about, right. The conventional once is paal-knorr and the next one is brood-knorr and third one is hantzsch, right; hantzsch thing. These are the three conventional once.

And, the latest one I think we start from here, for the fourth one then will go back to the time permits. Therefore, this is a very useful one, this is call Barton-zard reaction; barton-zard reaction. And then there is one call Van Leusen Pyrrole synthesis. Likewise there are many more, I think may be one should also know Piloty Robinson synthesis. Piloty Robinson synthesis there are many more. I think again it depending on the time may be we will talk about little bit of this Huisgen synthesis. Then we have huisgen synthesis; then there are many other I think may be will these are the little bit of this specialized once; chiba scientist of Singapore. And then there are many, many, many you can go on; I mean I have selected only those which are very popular. And this is my prediction though it may not be true but I have added this one Jana.

Jana is a actually he is from Jadavpur university Umasish Jana; I do not know whether you have heard of him a lot. He has published paper in 2011, if the time permits you should talk about that, you should learn about it. You say very unique synthesis though it has been published in JOC and it is likely to be a well sighted method. So, if the time permits we will talk about this. But as a whole, what I says that means the most successful approach; most successful approach. If you see, if we classify by the number of the atoms, first one is basically this 4 1 kind of cyclisation. 4 1 means you have a 4 atom species and 1 atom species like the paal-knorr one. This is a most successful one, and then other successful one of course 3 plus 2.

So, these are the two, I mean so you can think about I mean there are all possible ways of looking at Retro synthesis. But when it comes to Pyrrole, you can concentrate on this two numbers 4 plus 1 and 3 plus 2. When it is 4 plus 1 means paal-knorr, 3 plus 2 means the knorr and hantzsch; even Barton, van-leusen like all these, all these are basically. Then piloty is little different, huisgen is again 3 plus 2, chiba again 3 plus 2, Jana is different. It is 1 plus 1 plus 1 plus 1 plus 1. He has combined all these chemicals together as you will see and then put little bit of the ferric product, nothing else; very unique. He has 4 different starting material and as just added 10 percent ferric chloride and reflux regard; all well substituted Pyrrole well defined Pyrrole; we will talk about that. And let us begin with Barton-zard reaction ok.

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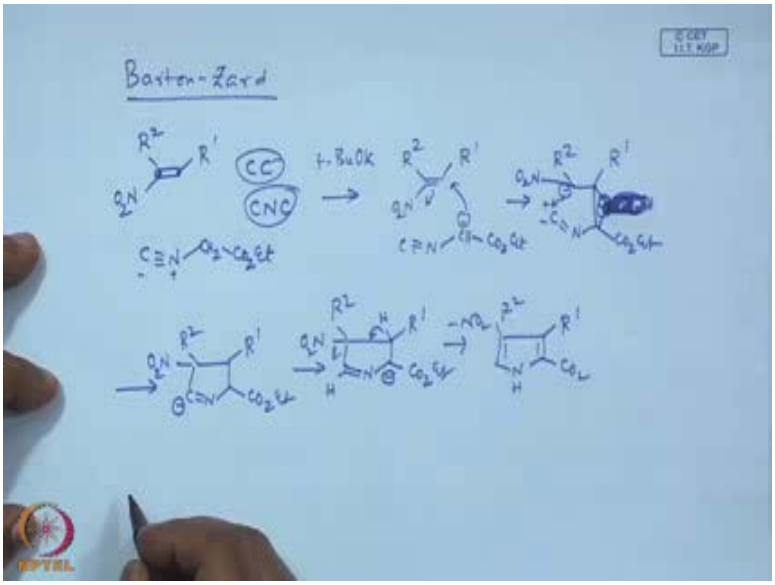

So, when I say so many of you know what Barton is right, which Barton? He died only 10 years ago from England d h r Barton; d h produce well known scientist zard, samir zard is one of his students. So, what he has developed; once again when I talk about a new synthesis of Pyrrole, you have to keep it in your mind either 4 plus 1 or 3 plus 2 mostly of course.

And, this is basically belongs to 3 plus 2. So, when I say 3 plus 2; that means you have to think about 3 atom component and 2 atom component. In his case 2 atom component is, that is what you have to remember. In his case 2 component is a nitroalkene. That means, these 2 are the contributing atom; the other one obviously it should be C N C component.

That means, when I say this is actually C C component, 2 atom and the other component is C N C; that is what you have two sign.

That means, you have to choose a starting material but it will provide a carbon followed by nitrogen followed by carbon and that is the trick there. And in his case it is a this C actually comes from isocyanide and these, the third one is comes from this acid group and the staring material is so with this one, guess. You understand what it is? It is Ethyl isocyanoacetate. Ethyl isocyanoacetate is not a cyanide, isocyanide. And isocyanide very briefly I can tell you how to make it, where is it to make is start form glycine hydrochloride; then boil with methyl format. It keeps the n formalization; if time permits I will give you the reaction and then do the dehydration. Dehydration, there are about 10 different ways but the most commonly the used method is p o c l 3 and triethylamine. So, that is very easy to make, anyone can make it.

So, that means the only this one; this nitroalkenes, any case. Then if you is a base obviously most commonly used base is little strong base is required potassium tertiary butoxide. All of you can guess, what happens. So, actually base has a function to deprotonate of the most acidic hydrogen. In these case the acidic hydrogen that would be picked up is the one between ester and the isocyanide group. And then all of us know that Michael addition reaction is one of the fastest reaction. So, it will undergo Michael addition, what does it do? It creates a new carbon ion. So, eventually what will have is a new bond here and then C right N and this is a carbon here and this is minus. And many of you know, I think the way one should write this isocyanide is basically a carbon means is a plasma center at the minus center, right.

So, this plasma and minus forms a bond here; mistake, yes, there is a mistake, right. There is a mistake; actually this would be ester, then what? Now, we have a 5 membered ring C bond N, this is the ester here R 1, R 2, right. Now, the negative charge is here and sorry here also you have to have a nitro group here, the nitro group here, right. What next? You can think off. It is an exchange deprotonation, intramolecular deprotonation. So, all intramolecular this is the deprotonation would take place.

That means, this here, this hydrogen would be coming and anion would be forming here, right. Anion would be forming here, Co 2; then R 2 and No 2. So, next there is I mean all kinds of the deprotonation take would be taking place and eventually there would be a

loss of nitrous acid. So, eventually what you will be getting? I mean you can do all kinds of this isomerisation, all the steps and eventually you will get the loss of No 2 minus and R 1 and R 2.

So, what do you see here? There are things to be remembered. What is this? I mean what is new here? New here, isocyanide is taking place into 3 plus 2 cycloaddition reactions. And then this what interesting here; whether what is you have to remember? Often we do not see loss of No 2. No 2 is often is a, is an activating group; it activates the alpha position, right. Assist the, increase the acidity of the alpha hydrogen. But in this case, it is basically activating a double bond; that means making a olefin as micro acceptor. At the same time No 2 also serving as a living group; that is what you have to remember. And this reaction is very useful and the last step is abbreviated I mean you can do all kinds of proton dislocation and elimination and all these things. And now what will, just we will see an example. I mean how powerful this synthesis is.

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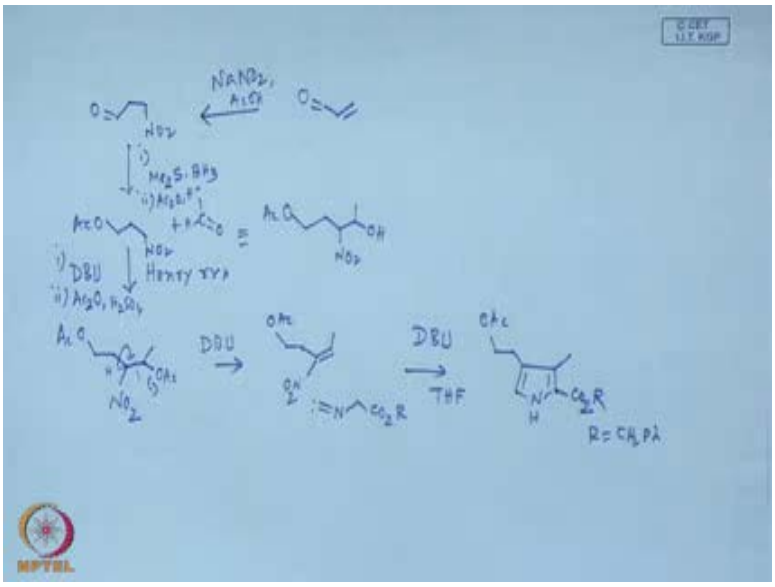

If you look at a target molecule for example, in this case the target molecule is a once again a Pyrrole here. Then I will write just simply R. In this R is equal to here is benzyl, in this a particular example. Then and you have a 2 carbon and acetate here let us say. And now if you are given a synthesis or synthetic problem of this kind; so first thing you recognize that it has a Pyrrole nucleus.

Then, you think about there are other ways; if you do not you have you have forgotten the reactions, then you try to develop your own retro synthesis. If you remember something about this, then you go by this. Let say as I said 4 plus 1 or 4 plus 2. But 4 plus 1 you have to remember, 4 plus 1 is little more restricted towards 2 phi by substituted Pyrroles. Especially, when you are substituted polynor is very good; so that is transform base approach. The other one, what do you see just if you go back to the earlier slide, you will see; Barton gives what? Mainly 3 4; because your nitroalkene has a substituent, that would be giving the substituent at the 3 and 4 positions.

So, we see that structural features here and also the isocyanide, if you recall the Barton reaction that it provides carbon nitrogen carbon. So, that means at some point you have to have a nitroalkene here. So, that means the nitroalkene that has to be, that is to be made is some kind of right; this one. Then you have acetate; so you have this methyl here nitro. And then nothing else, this is your isocyanide, ethyl isocyanide or in this case is this one that is it; and this is isocyanide. So, that means it boils downs to the preparation of an nitroalkene, methyl nitroalkene. So, what is this? Now, you need a base. In the previous example, I gave you the base; tertiary butoxide. Now, I see give you a base that this is also possible with DBU as a base. That means, you do not have to have an inorganic base, organic base is sufficient ok.

Now, this one, nice now, nitroalkene; how do you make nitroalkene? Those who are familiar with the very nice reaction though again and known reaction starts with h. So, what you have to do? You have to make a compound of this kind; then you have to have a living group here, somewhere. And in this case the living group is this. Mind it, and you have a two, we have one more acetate here; one more acetate here. So, how do you make this? What is the critical bond, you make? This one. So, then if you have a substrate of this kind, let us say the beta-acetoxy nitro compound. So, in the presence of base and again the base is nothing but DBU; so you can have e 1 c b kind of reactions. That means, hydrogen is picked up, nitro is an alcohol hydrogen of nitro compounds is very acidic; I mean, almost acidic as aldehydes even more acidic.

So, it loses acetate group and eventually you get this one. But how do you get this nitro acetate compounds? There is a reaction many of you know; there is a reaction known as Henry reaction. Have you heard of Henry reaction? It is nothing but is an aldol condensation, aldol condensation of nitro compounds; aldol nitro compounds. And in

this case what do you do? You take this nitro and then react this with acetaldehyde; that is it. Once again, in the presence of base and what is the base here? The base is DBU. So, DBU serve you lot of purposes. And right so this is equivalent to what? When you do this reaction actually; so what you will have? This is nitro and in this case I will have basically aldol condensation.

So, in aldol condensation two components are the aldehydes or Ketones. But in this case one of them is aldehyde, other is the nitro compound. And this is O, AC. So, that means after this aldol you get this one. Then actually you have to use a reagent, this acetic anhydride; to activate the OH group, to make it a better living group. And how do you do? Acetic anhydride and then what else? Pyridine; that is the commonest one. But also you have to know, in these case if pyridine it might leads to many thing.

Because you know that it can also straight way give you the corresponding nitroolefin another things. So, you have to restrict these; that means, the by new choice acetic anhydride and sulfuric acid. This is I think most of am not talked about but this is one of the nicest way of doing it. What do you do? In case of acetic anhydride pyridine, you activate OH groups right with loss of hydrogen etcetera, etcetera. But by using sulfuric acid actually you are activating the acetic anhydride.

So, sulfuric acid proton protonates the acetyl oxygen and mix these formation of acetyl cation easier. So, this is the, there are two ways one can make. So, that means that eventually gives this one. But then what next? How to make this one? In that means, basically, when I talk about synthesis at the end of the synthesis, you have to reevaluate synthesis on the basis of availability of the starting material. This is the most active; I mean we often ignore this aspect in synthesis. But that is the most important aspect of synthesis. That means, you have to make use of easily available starting material. In that case, the synthesis would be the better one. When I talk about that Janas Pyrrole synthesis, what he has done? He has taken all these readily available staring materials; then used reaction that is enough to give you particular molecule ok.

So, you have to keep it in mind. Your starting materials should be readily available, easily available. So, to make this one; so one can think about what is it? It is a basically 3 carbon aldehyde and nitro compound; 3 carbon aldehyde and nitro compound. So, how

do we get it? Say in alcohol, right. So, I mean no one can reduce this, we reduce this with how do you reduce? Chemo selectively; this aldehyde group keeping the nitro intact.

Student: ((Refer Time: 29:38))

I have no idea it whether it was or not; but any other suggestion? You have two reducible groups, nitro and aldehyde. And I possibly would work but again not readily available though. You have to have cheaper reagent. In these case, it is a borane dimethyl sulfide complex; sulfide complex. Of course, next step is acetic anhydride; acetic anhydride and acid. This borane dimethyl sulfide complex, this called ((Refer Time: 30:28)) right. I told you in the fourth year class; who was he? Varun kumar mandal M.Sc from IIT kharagpur KGP in 1971. And but next thing; we are still one step above from the competition of the synthesis ok.

How do you make this easily, this nitro aldehyde for a very easily available staring material. Without wasting time, let us see. Yes, Carolyn readily available, commercially available; but what do you do? But you have to choose the other starting material, other reactant. So, simple, right; only thing you have to add that means as if we have to do a little bit of the Michael addition; where nitro No 2 minus would be serving as the Michael donor and nothing. And you will not believe is the reaction is so simple; you take sodium nitrate and acetic acid, nothing else, the reaction is very simple. That means, sodium nitrate also can undergo Michael addition to Michael Caroline ok. So, as a whole you see here is the Pyrrole has been eased by the use of Barton zard reaction. Let us look at one more reaction one more reaction this also very powerful reaction, very powerful reaction.

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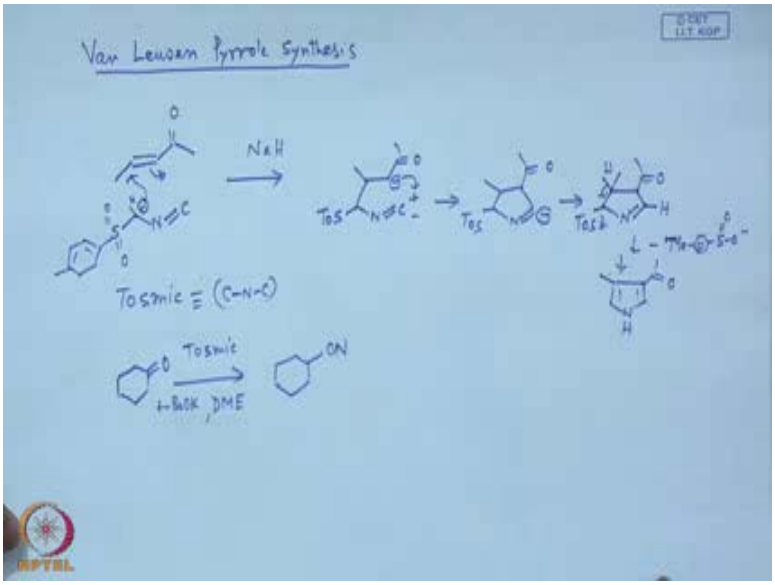

So, the next one we talk about is Van Leusen Pyrrole synthesis. This is a very, is very similar though is again the mode is 3 plus 2; mode is 3 plus 2 and very similar. So, like the previous one, what you need is a double bound, activated double bound; so it has to be alpha beta unsaturated something like this, right. So, in previous case also but you had in nitro group here, in the place of acetyl group. Then other one again a C N C, C N C fragment, C N C carbon nitrogen carbon fragment; what is it? That means here, nitrogen here and I think the way I have written it seems like it is an isocyanide. And then this is the trick and valuation probably I am not sure, I think is scientist I am not sure ok.

Now, what you he see here, what is it? It is a tosyl group. See, this is CH 2 group, methyl and isocyanide. So, this is known as, this is popularly known as you will find any where Tosmic; tosyl methyl isocyanide. What is it? It is equivalent to C N C fragment; like the one before, right. And if you use sodium hydride in this case, what is expected? That this, the one this hydrogen that is activated at methylene hydrogen and would be deprotonated sodium hydride. Then same old thing Michael addition taking place; so you will be getting a new carbon ion. That means, and I will just write Tosyl group. We have a carbon ion here, right and isocyanide means plus and minus. So, it will form a new bond here and this so is a 5 membered ring now.

Now, this carbon is minus right and here you have this proselyte here. So, then you can go on it will, you will have olefin here and this is nitrogen at some point it will this be

like this, tosyl here. This is hydrogen and then I mean so on, so on. You can just basically, loose the minus what? Methyl, then this is benzene and what you will be getting? You will be getting this minus methyl at this is phenyl sulfinate. This is sulfinate not sulfone; the sulfinate. And then isomerisation etcetera; eventually you will get, if you do the isomerisation, you will get this Pyrrole here. I think there is a methyl group here and methyl group here, that is it.

So, it is very similar to the Barton and zard reaction, what is the difference? Difference is that the C N C component carries the living group, in this case tosyl group. In the previous one, what the nitro group and this; that was this nitro group that was in the 2 atom component. But in this case, the living group is in 3 atom component and in the place of nitro, it is the sulfone. And this is nice way of doing it and the outcome is very similar to Barton zard reactions. What do you see here, that you are getting a 3, 4 disubstituted Pyrrole ring system.

And, something little more not heterocycle, this compound is very useful tosmic. I do not know whether you know or not. In general is a very useful compound, in carbon chemistry. Let say if you have a ketone of this kind and you do, try to do the homologation and put a cyanide here. How do you do? This is actually known as Van Leusen reaction, the previous one is called Van Leusen Pyrrole synthesis; in this case this is known as Van Leusen reaction.

This is very simple trick. Just basically you are adding a carbon; adding a carbon mind it. You started with an isocyanide and you are ending up in the cyanide and in the all these things are going away including your methylene group etcetera, etcetera. And is nothing but tosmic and I think DME; DME is a solvent in this case, dimethoxy ethane and potassium tertiary butoxide, so very useful, very useful reactions. You want to add a carbon, one to the carbonyl group and this is one of the ways up to maintain it. So, let us see; that means both the reactions are very similar. Now, let us look at one more reaction.

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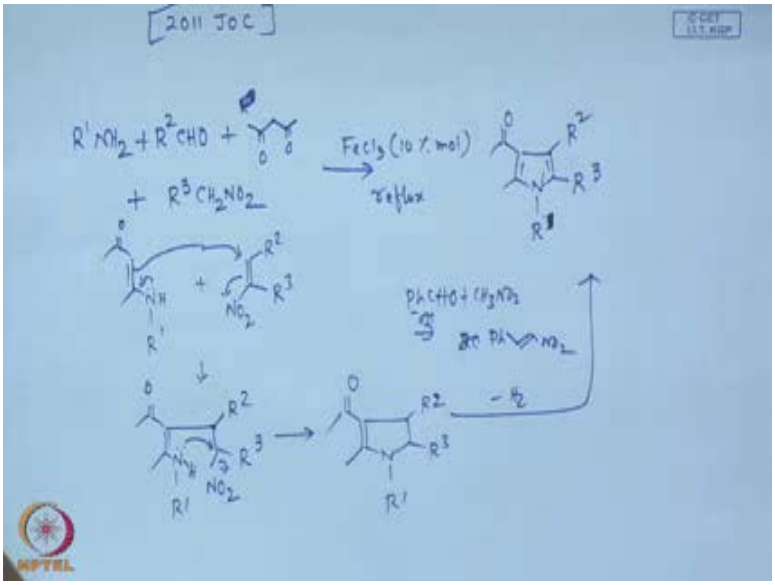

One more reaction that what I said this was done by Mercies Jana, and what he has done you will see, I mean is pretty interesting. I mean all kinds of the starting materials we think about in organic chemistry, aldehyde and then I think I will make it acetyl acetone; what else? One more thing. So, it is a 4 component reaction; there is 4 different starting material and the reaction is done in one part and this nitro compound. So, the previous two synthesis also were invert in nitro compound and this one. Ferric chloride only 10 percent; 10 mole percent of the starting materials and the net result is in one, just reflux by the way; just reflux no solvent. I think nitro compound is given large little excess what you get? This is one and a sorry this is R 1 and this is R 3 and this is R 2; this is R 1 you see here it super seeds the all these Pyrrole synthesis.

And here made some than 20, 30 different Pyrroles by this method; and the trick is very similar. What is the trick? Again, you can just classify this method into 3 plus 2 systems although officially it looks little more complicated. But it is basically when I said that means memorize this reaction if you consider this as a 3 plus 2 reaction; that is pretty easy.

So, how do we get this 3 plus 2? What are the first reaction? You can think off let us say. First reaction is think off if you have a 4 component reactions of the like this; I mean you have to just mentally makeup your mind to decide which one of the, is the fastest reaction. Normally, if you have an amine and alcohol sorry aldehyde is seeds based

formation is if; but that two again equilibrium. That means, often the shift base this is r n equilibrium with the aldehydes or the ketenes. So, you have to have a reactions which will be irreversible at the best irreversible is the reaction that is your Henry reaction; means the reactions aldehyde and the nitro compounds. So, aldehydes and the nitro compound that means that would produce what? R 3 and right is it not; you just take a aldol condensation; this aldehyde and the nitro compound to be producing this like.

Let us say if you take benzaldehyde for example, to just refresh your mind take benzaldehyde and nitro methane. And in presence of base I think this is H S right; it gives you nitrostyrene. Nitrostyrene is very easy to make described in googles book; nice green compound you can make it in one day. So, that means is a must fast reactions.

What next? So, we have seen that these two would be reacting obviously than the other two are left out right. So, amine and beta keto di ketone, 1, 3 di ketone; what is it reaction anybody can guess, anybody can guess? The way I have written here I can write beta keto di ketone is a very, very fast reaction; you can do in just half an hour's time; take acetylacetone all of you have right some point; take acetyl acetone dissolve in ether add little bit of aqueous ammonia what do you guess?

Student: in amino ketone.

In amino ketone very easy just shake it in a funnel. And just extract it you check the anomer; you see what it is? It is nothing but this is in amino ketone; and in these case is this one that is it. So, if you and what else, what is the next step that in amine all of us know under say a nucleophile; so nitro alkene is an accept Michael acceptor.

So, eventually what you will be getting here R 1; I mean you can do the all kinds of the other mechanism do this one; R 2, in these case R 3. And this is nitro and this is hydrogen, right what else? That means, Michael addition taking place all these things. Then again isomerisation they all these things eventually you get a basically addition of the 2 components. What next you can expect, what next?

Student: ((Refer Time: 45:57))

Nitrogen will attack.

Student: ((Refer Time: 45:59))

Right. So, that means you have to decide actually in these case this nitro also is a good leaving group; that you have been seeing that right. So, getting this nitro and this is R 3, this is R 1, R 2; this is R 1. Then you have everything here what next sort of area oxidation kind of things. So, dehydrogenation will give rise to this one, dehydrogenation loss of hydrogen that you will get this. So, is a very good reaction actually there are examples of this kinds go to the will quickly look at one more reaction.

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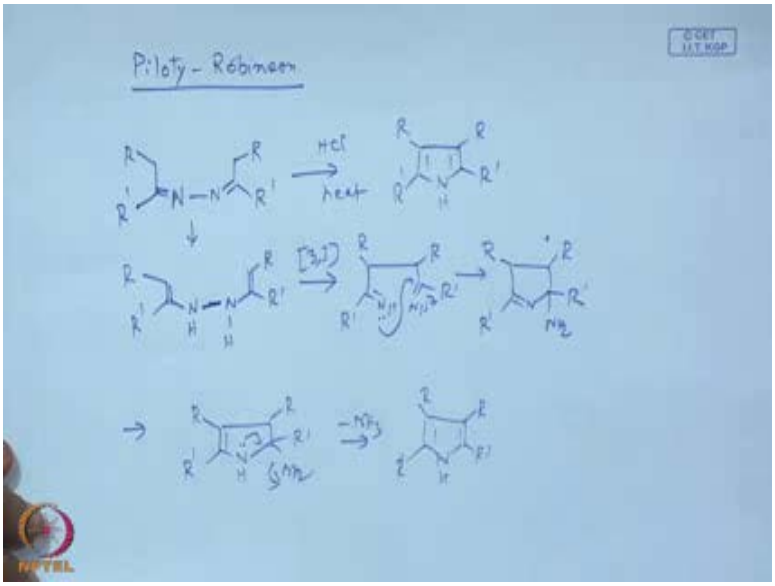

And, this reaction is known as piloty Robinson reaction. What it is? Piloty Robinson reaction piloty of course he published this reactions around 1910. And then there is a person this is one of the very few ladies though; if you are interested in lady scientists discovering organic reactions, you have to go to accounts of chemical research. And I want to that article eventually found that this robinson is not the true robinson have you heard of robinson before?

Student: ((Refer Time: 47:40))

Robinson this wife actually; he is not the Robinson himself Robinson's wife. And that article actually describe that is one of the very few lady discovers organic reactions. Actually reaction was discovered long back and the original one is nothing but if you take hydrogene. For example, hydrogene and let us take ketone what do you expect? So, if you have let us say you have a ketone and of this kind take the take hydrogene condensed just heat it, I heat them together. And what will see?

Student: condensation reaction.

Condensation if get hydrazone. But many of you probably do not know if the proportion is not really taking care of actually you get dihydrazone. That means, you will be getting this kind of molecule dihydrazone. And in fact it happened with it we try to make one the benzophenone hydrazone once upon a time. But we could see that both the nitrogens are condensed obviously; and this quite obvious right once it is condensed and the other side also if the material is available. And what they did the first to adjust simply to HCL and heat HCL and heat. And of course the product is here is this one Pyrrole is Pyrrole; that is it that 2 things to be learned is very similar to many of you know ((Refer Time: 49:24)) synthesis right is very similar. In these case what is happening here you are getting this isomerisation two enamine right this is well known; isomerisation to enamine.

Then, I think all of you can just by looking at this structure you can make out. What would be the next step, what would be the next step? Pretty easy.

Student: ((Refer Time: 49:56))

Very good. So this quite obvious right ((Refer Time: 50:01)) so matrix that means this this bound would migrate. That means, so what you will be getting is this N; this is now NH, now again NH R1. So, this is now will have 3 sigma trophy R and R here and R prime. What next?

Student: nitrogen will attack.

Nitrogen will attack that means this nitrogen will attack; what you will get is a imine; then this would be N H 2, R here, R prime, R prime, R and R here right and R. Now, what is quite important here this then goes to again enamine NH 2, R prime, R and in these case R double bond. What next? I think all of us know that this nitrogen germinal nitrogens they do not two nitrogens of the same carbons are not very comfortable; one of them has to lose, one of them has to depart the molecule. And so you basically you get a loss of ammonia. So, you go to this product that we written before and this is this one R and R. And what do you see in the only striking about this that reaction loses ammonia. That means, loss of ammonia in heterocyclic chemistry is very commonly encounter; I mean ammonia is not a good NH 2 is not a good leaving group. But when you have a

driving force like aromatization of this kind; then you can expect leaving group property of there are other molecules. So, I mean this can be in fact very recently I just in 2009 or so there is an paper in organic letters. And what they have done?

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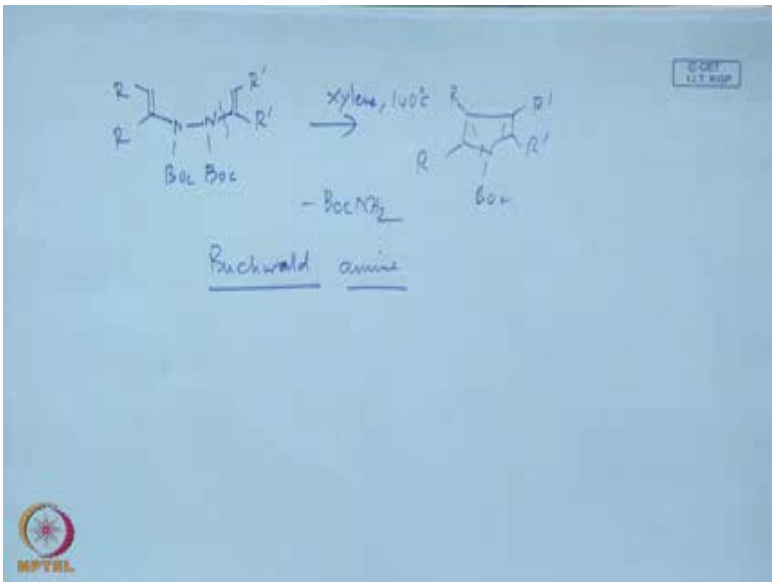

They have taken very similar compound; but in these case the R both the R primes in a different on the one side and both the R are in other side, and the BOC derivative tertiary butyl oxy carbonyl. And what you have to do? You have to take xylene and then of course xylene boiling point is around 140 degree simply heat it. And you will be getting the corresponding BOC protected Pyrrole; mind it in these case what you are losing here actually? You are not losing the ammonia; what you are losing? Boc amide. So, what is the merit of the synthesis? Now, you see you have well define di hydrozole; the previous one was symmetrical one means all these R and R they are the molecule symmetrical. But in these case you can separately add 2aliphatic components by reaction known as I think many of you have a heard Buchwald yes, Buchwald amination.

This is a very famous reaction now Buchwald amination; it involves actually copper catalyst. So, if you start from an ido compound and hydrazine BOC protected hydrazine you can do this new carbon nitrogen bond. So, likewise there are many more reactions. And I think summary what I said; next class what will be talking about how to convert this alkyne percussion to Pyrrole synthesis; open chain compound with triple bond. And next one more very famous style of making Pyrrole molecules; remember any body

remembers; to start when you started the lecture we said that this Pyrrole synthesis can be classifieds number one; one is the conventional once, other is not; so conventional like this Barton-Zard valentino may be Jana; and this one piloty robinson there are many more; so I have chosen this.

Then, other 2 categories of synthesis that would involve basically transition metal catalyst isomerisation, cycloisomerization means you have to have an alkynes or alkenes and you have somewhere at a nitrogen; then you cyclise it. So, that mode is a very useful mode we will talk about in the next class. And also there is there is an approach based on ring contraction; you take pridgens do the written contractions. Then you do pyridine molecule, ethoxide etcetera you can do photolytic ring contractions, alkynes. And the third one is a special that starting from ((Refer Time: 55:34)) compounds also very similar to this reaction. But in that case the starting material ((Refer Time: 55:40)) compounds, so will talk about those in the next class.