Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

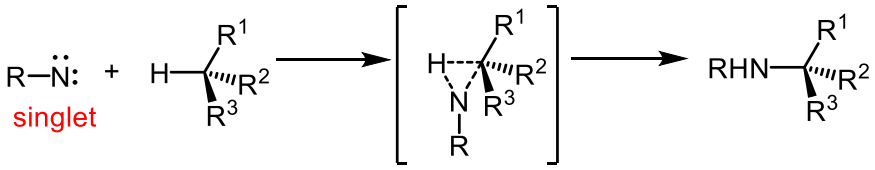
Department of Chemistry

Indian Institute of Technology, Kharagpur

Lecture 16: Nitrene

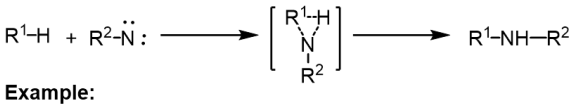
Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. So, I started talking about nitrene from the last class, I talked about different methods for the nitrene generation, I talked about their comparison with the carbene and I also talked about singlet and triplet nitrene. In today's class, I am going to talk about several other reactions like the insertion reaction and several different rearrangement reactions using nitrene. So, I am going to talk about the insertion reaction and then I am going to talk about the rearrangement reaction of nitrene. Then the 1,2 alkyl or aryl shift, these are the very important rearrangement reaction, then Curtius, Lossen, and Hofmann. I am going to talk about all of these different rearrangements with some of the examples.

So, let us start with the first thing the reaction of nitrene, and the first thing is the insertion reaction. So, we have learned about the carbene insertion reaction and I already talked about in the carbene that the reactions when happening from a singlet you have seen the reactions are very much stereospecific. That means, if you start with a chiral center that means, that particular chiral center will remain intact here, only the C-H will be replaced by NHR. That means this reaction is happening through a concerted mechanism which is the other important thing. So, this C-H insertion is happening through a concerted mechanism here. That is why this reaction is stereospecific, which means the stereochemistry will be retained. So, there will be a retention in the stereochemistry which is actually mentioned here. The reaction is inserted C-H bond in a stereospecific and a concerted pathway.

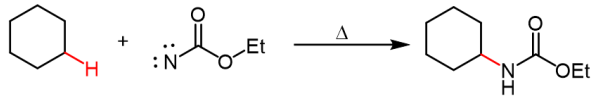


So, let us see some examples here. So, I think an example, again the same thing is mentioned here. If you generate a nitrene and if you have a saturated hydrocarbon, I have explained a very similar thing in the case of carbenes. Here you can see also that nitrene is going through a concerted pathway, it is going to generate the corresponding amine.

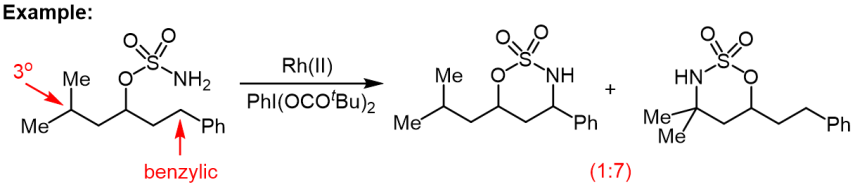
So, here again from cyclohexane this C-H bond actually getting inserted into this nitrene to form this compound. So, it is forming some sort of a carbamate after the C-H insertion.



Example:



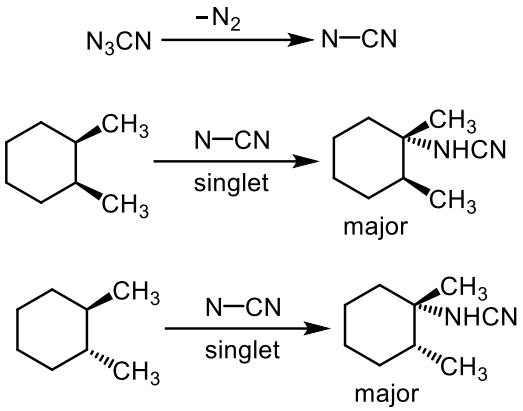
Example:



Again there is an example here. one thing if you remember when I was talking about this type of C-H insertion, I always try to show you the corresponding sort of a transition state. And in the case of carbene, you have seen how this transition state is very important because there is a steric factor sometime also getting to a dominating factor. So, there are three different types of C-H, one could be the methyl which is going to be your CH_3 going to be a primary, then you have a tertiary C-H here, then you have a benzylic C-H here.

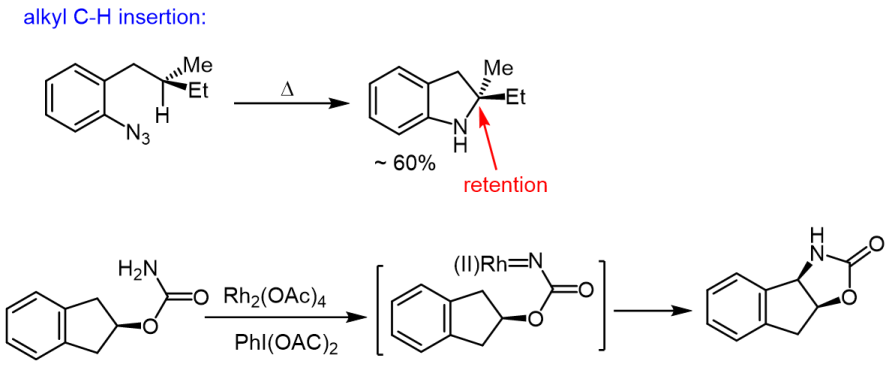
So, these are the different types of C-H are present and the reaction is happening through abstracting of this benzyl C-H is the minor product, and then abstraction from this hydrogen, the 3°- H going to be a major product. So, I think from this result we can clearly see the electronics play an important role which means the C-H insertion happening from the C-H group, how much electronically reach that is one important factor here because here it is abstracting from this one. So, this hydrogen will be more electron-rich compared to the corresponding benzylic. So, that is why you can see the abstraction is happening from this particular C-H is getting abstracted to form this product as a major product.

Then there are some other examples here, the thermolysis of cyanogen azide. So, I mentioned in the previous class that we do not see too many alkyne azides or alkyne azide from the formation of alkyne base nitrene, but from cyano, it is kind of well known that from cyanogen azide from thermolysis, it can generate the corresponding nitrene and once it is generating this nitrene which now can go for insertion. Now you can see, this is a 1,2-dimethyl cyclohexane which is *cis*. So, it is actually stereospecifically abstracting the C-H which is from here. So, it is abstracting this C-H, this C-H one as you know is a tertiary C-H, it will be electronically rich. So, it is going to abstract it in a stereospecific manner to form this product as a major product.

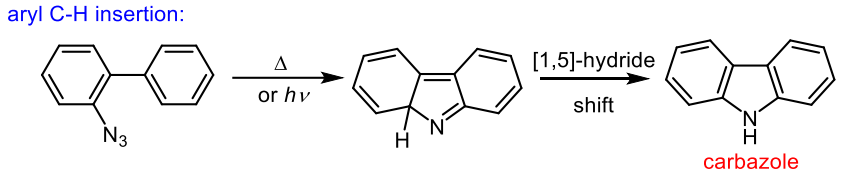


Again a very similar thing here, if you start from an *anti*-1,2-dimethyl cyclohexane, again you can see the abstraction is happening from this H here. So, it is abstracting this H. This C-H proton again the one from tertiary, electronically reach. So, it is giving a very stereospecific product because this reaction is actually happening because this is a singlet nitrene. So, if it is a singlet nitrene then the reactions will be stereospecific the C-H insertion.

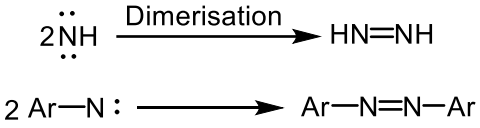
And then there is another example here. So, this is a very common example you can see in lot of time in the exam. So, this is an alkyl C-H. So, you have a chiral center here. I mentioned at the beginning that if you have a chiral center then there will be retention in the configuration after the C-H insertion happens here. So, what happens at the beginning, after the thermolysis it will go to generate the corresponding nitrene here after the expulsion of the N_2. So, this nitrene is now abstracting this C-H bond here and so there will be insertion and to form this product with a retention. There is another example here, you can also able to generate some sort of rhodium-based nitrene. So, here using the PIDA and then the rhodium tetra acetate it can generate the corresponding nitrene. Now, the nitrene is abstracting this H. You can see there are two different sides, there is a benzylic H here, it can also abstract from this side or this side they are both symmetric. So, it can abstract the H and going to form this product as a major product.



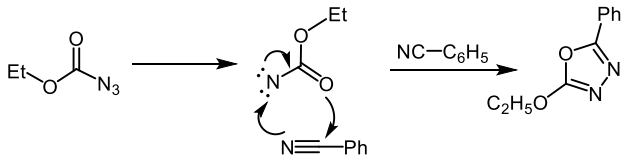
There is another example here from aryl C-H. If you are actually generating a nitrene after the heat or hv then that nitrene will going to abstract this aryl C-H. So, there will be a C-H insertion here in the nitrene to form this intermediate, and then from there a 1, 5 hydride shift. So, you can give them 1 2 3 4 5. So, there will be 1,5 hydride shifts actually end up making the corresponding carbazoles.



So, now I am going to talk about some other reaction, I mentioned at the beginning that if you go for some sort of a generation of nitrene there is one of the major things it can dimerize if you do not have anything else like if you do not have any olefin where it can able to form an aziridine then in the absence of that it can form a dimer. A very similar thing happens if you have an aryl nitrene species you can also form a dimer.

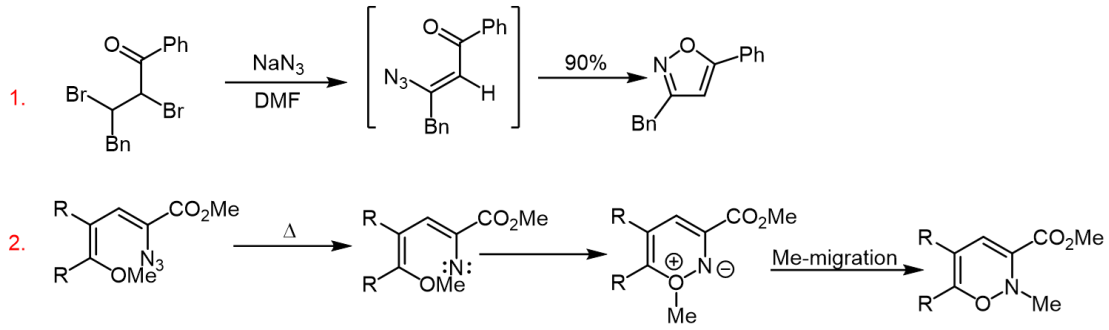


There is another thing that happens if you have this type of scenario when you have some sort of a formal group attached to the nitrene then there is a possibility because once you generate a nitrene, now you can think about them as a 1,3-dipole. because you can see there is a electron density here and to one side in the next to the oxygen there is electron density and the other side there is electron deficiency. So, this is a 1, 3 dipole going to participate with cycloaddition with the corresponding cyanide to make this oxadiazole.



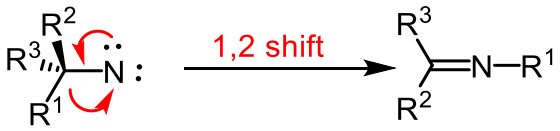
Then you can see some of the reactions with oxygen and sulfur atoms. So, we have learned about this ylide chemistry when you are talking about carbene. If you remember we talked about ylide chemistry that the oxygen lone pair of a carbonyl group interact with a carbene and then they can participate in a [3+2] cycloaddition reaction here something is going to happen. So, if starting from this reaction, if you use a sodium azide in DMF it will go for $S_N2$reactions. you can clearly see that this bromide is going to get replaced and then what is going to happen, there will be elimination to generate this compound. And now this is going to generate a nitrene. So, once it is going to generate a nitrene here. So, you can see there will be N_2 expulsion to generate a nitrene

and once it is generating nitrene the oxygen lone pair, as the nitrenes are electron deficient. So, the oxygen lone pair is going to give electron density into that empty p orbital and finally able to form this type of a heterocyclic compound.



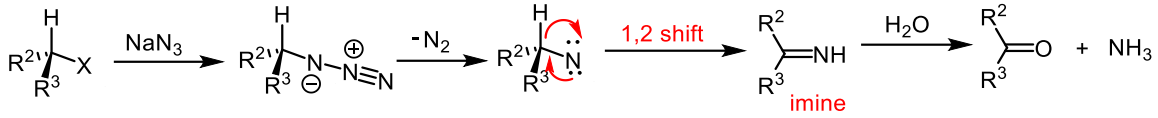
There is another example here. So, you can see again very similarly there will be first thing will be after the thermolysis or the pyrolysis, it will generate a nitrene and you have oxygen here. So, the oxygen lone pair is going to give electron density to that empty orbital here in the nitrene that will generate this type of intermediate, but you can clearly see now there is a negative charge on the nitrogen which will able to take this methyl group to release the positive charge from the oxygen to get to this type of heterocyclic compound.

Now, there will be some other reaction called the rearrangement reaction of nitrene. So, there are 1, 2 alkyl and aryl shift. So, we talk about this type of 1, 2 alkyl shift or aryl shift because of carbocation if you remember then I talked about carbanion I mentioned that the 1, 2 alkyl shift are not favorable, but the aryl shifts are favorable because of generation of the more stable carbanion. Here I am going to talk about in case of nitrene also what is going to happen? Once you have 3 alkyl groups here if your R^1, R^2, R^3 become a alkyl group. Then there will be alkyl or aryl or if you have a hydrogen alkyl. So, there could be in a different scenario. If you have hydrogen and alkyl, then there will be hydrogen shift will be happening faster than the alkyl. So, this is the rate, so, the first the hydrogen then the aryl, and then the alkyl. So, this is happening here that once this σ bond electron density is given to this empty p orbital in the nitrene, at the same time nitrene has the paired electron, it is going to transfer to the corresponding σ* orbital to get to this product.

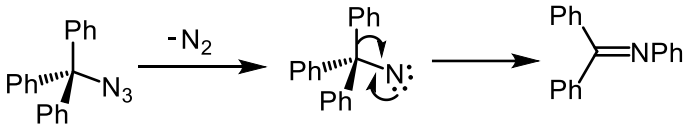


So, this method is very useful to convert alkyl halide to the corresponding carbonyl compound. So, let us see how it is happening here. So starting from alkyl halide, you can do an S_N2 reaction to get to this corresponding azide. Now, alkyl azide after the

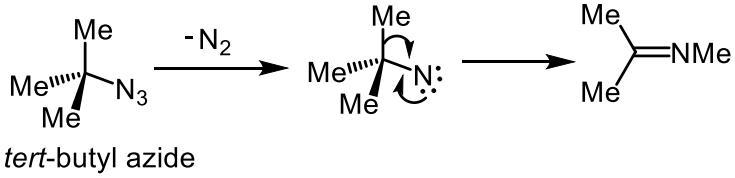
thermolysis it is going to generate the corresponding nitrene. So, there will be 1, 2 hydride shifts for this H is going to move here to generate an imine. Now, imine in the presence of H_2O can hydrolyze to the corresponding carbonyl compound. So, starting from alkyl halide you can generate a corresponding ketone using nitrene chemistry.



So, here is an example instead of the alkyl and the hydrogen you have a triphenyl. If you have a triphenyl then after the formation of this corresponding nitrene as I mentioned the phenyl group is going to get migrated. So, there will be 1, 2 aryl shift to form this corresponding imine.

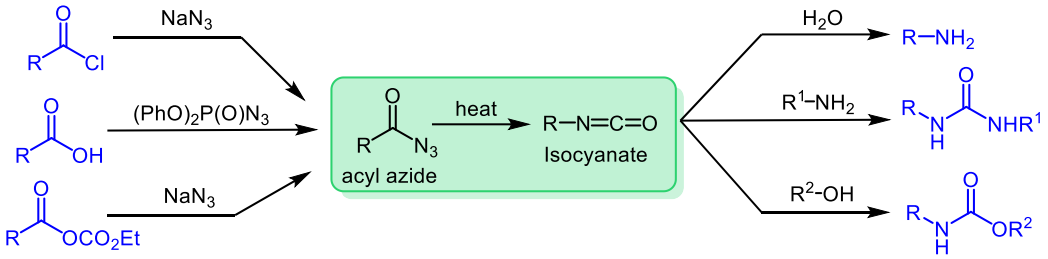


So, there is another example here if you have a trimethyl group here. If you have a trimethyl and then corresponding azide then it can form the corresponding nitrene, there will be a 1, 2 methyl shift here to generate this type of imine. So, if you have a 3-alkyl or 3-aryl that will be 1, 2-aryl or 1, 2-alkyl, but if you have hydrogen with an alkyl or hydrogen with an aryl then the shift of the hydrogen will be in the faster compared to the alkyl or aryl.



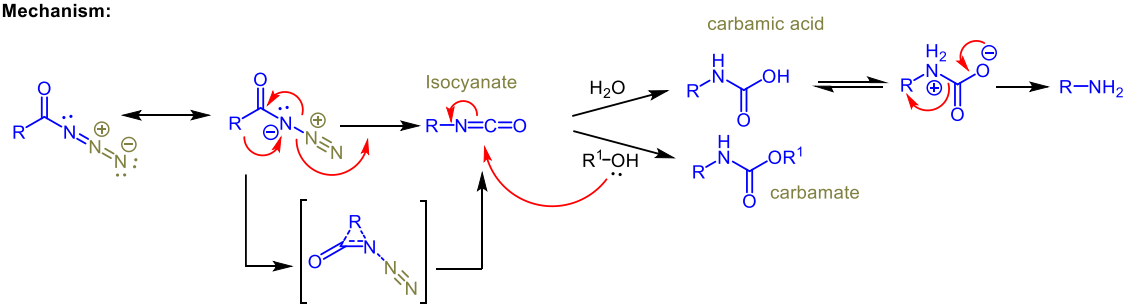
So, now I am going to talk about a very important rearrangement reaction, where there is a generation of nitrene species. So, that is called the Curtius rearrangement, it was discovered by Thedor Curtius around 1890. So, this is a very important reaction because starting from acyl azide, once you put heat it can generate the corresponding isocyanate which is a very important intermediate species. Once you treat with the H_2O, it can generate the corresponding amine once you treat with the amine it will generate corresponding urea and then once you treat with the alcohol it will generate the corresponding carbamate. This type of acyl azide is easy to make starting from

corresponding acyl chloride or corresponding acid. So, it can easily made and then you can able to generate the corresponding isocyanate and now depending on the nucleophile you choose, you can able to access a variety of compounds.



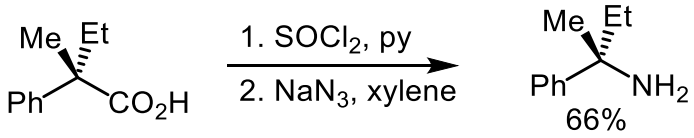
So, in this part, I am going to talk about the mechanism of the Curtius rearrangement here. So, what is happening here? you can see first thing. Once you generate the acyl azide we can try to draw the canonical structure here you can see here now this minus which is here in the azide, that can give the electron density here to make it an O-, some sort of a species here O -, and then it will come back again here and it will going to get migrated to the nitrogen and expulsion of this N_2. You know after that it can go through some sort of a transition state like this, where there is a cleavage of this carbon and the R group, there is a cleavage of this the N_2 and there is a formation of some sort of a double bond between the carbon and nitrogen which is shown here. After that it will generate the isocyanate as I said if you treat isocyanate with the water it will generate the carbamic acid.

Mechanism:

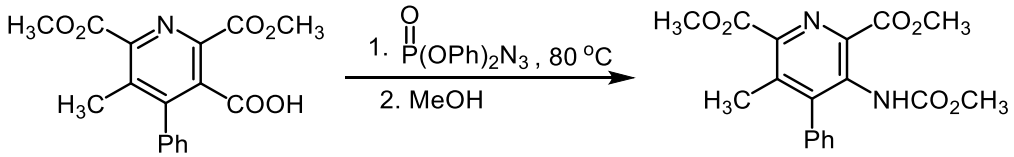


Now, there will be a decarboxylation under the presence of the heat to generate the corresponding amine after the protonation. And then if you treat with the alcohol, it will generate the corresponding carbamate. And, depending on the alcohol, you can vary different types of alcohol to get different types of carbamate here. And, most likely this rearrangement, goes through a concerted process. Although we try to show this type of arrow pushing mechanism, but this reaction, goes by a concerted mechanism to form the isocyanate.

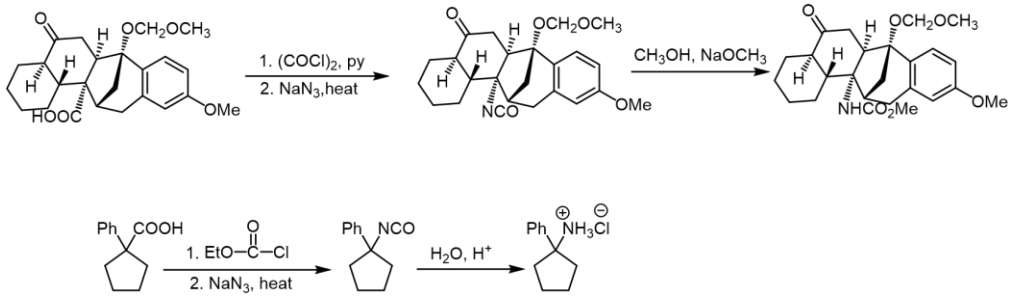
Some example here, so if you start from a chiral acid, then the configuration remain same that means, there will be retention. What about the stereochemical information there which is going to remain the same after the Curtius rearrangement. So, the first thing what you have done, they treated with the $SOCl_2$. So, that is going to pyridine and the thionyl chloride going to convert this corresponding acid to acid chloride. Now, once you treat it with the corresponding sodium azide, it will generate this corresponding α-keto azide and now in the presence of xylene and heat it is going to participate in the curtius rearrangement by forming the corresponding isocyanate and I am sure in this reaction there will be some water already present. So, as the water is present which is going to convert after it is going to the carbamic acid and then it is going to convert to the corresponding amine. So, this is a important method because you starting from a carboxylic acid in one step you can able to convert to corresponding amine.



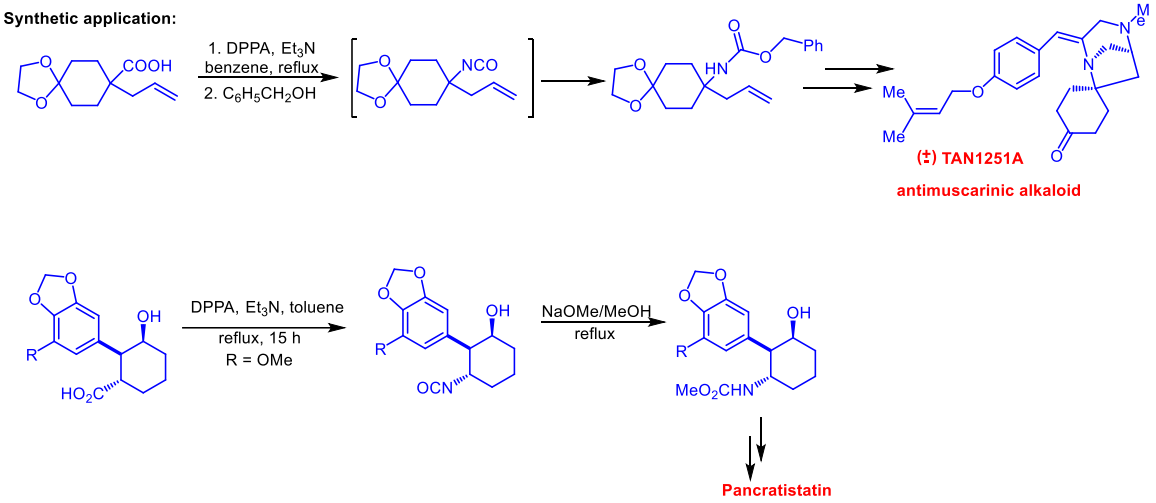
So, there is another example here starting from this type of pyridine carboxylic acid using DPPA you can able to convert this corresponding carboxylic acid to corresponding azide and then there is a heat given to this, that means this acid will convert to not only corresponding azide, it will go to corresponding isocyanate. Then there is methanol present here which is going to make the corresponding carbamate here.



There is another reaction here in this synthetic transformation you can see you have a carboxylic acid here. So, first again formation of the corresponding acid chloride, then using the sodium azide it will form the corresponding acyl azide, then under heat, it will go for a Curtius rearrangement to form the corresponding isocyanate which will once react with the methanol, it is going to form the corresponding carbamate here. So, it is a very simple thing you first convert the corresponding acid to acid chloride, then the corresponding acyl azide, and under heat it will form the isocyanate, now you choose different different nucleophiles. If you use alcohol, it will go to form the corresponding carbamate. There is another example here you have this carboxylic acid which is going to convert to acid chloride, again azide, formation of the isocyanate, in the presence of H_2O it is going to convert to corresponding amine and if you give some acid there at the end then you can isolate the amine as a protonated form as a salt.

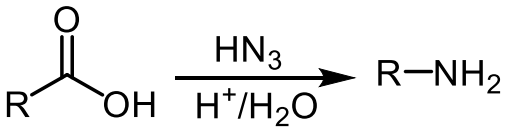


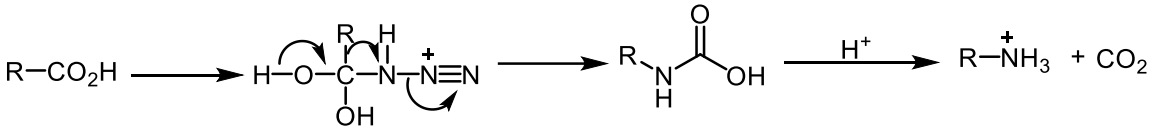
So, now there is another synthetic application again here using DPPA and triethylamine. So, this is a diphenyl phosphoryl azide that can able to convert this corresponding carboxylic acid to the azide and then the corresponding isocyanate. So, now if you choose this corresponding alcohol it will going to make this particular carbamate which you can use for further transformation to make a biological active compound. There is another example here you have a carboxylic acid, now you can see this they have a *trans* relationship and you can see the stereochemical things will be remain intact. So, you can see this will end up making this corresponding carbamate and here also you will see their relationship remain *trans*. Because you can see most of the things happening on the carboxylic acid, not the carbon attached because once the migration is happening that stereochemical information still remains retained. So, that is why, there will be a retention of the configuration. So, again I think I have explained the corresponding isocyanate first and then you can able to make the corresponding carbamate which is going to give it to this corresponding natural product.



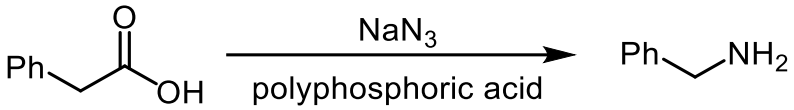
I am going to move to the Schmidt reaction here. So, the Schmidt reaction is another important reaction. So, starting from the carboxylic acid, using the hydrazoic acid it can able to convert to corresponding amine in the presence of acid and water. So now we are going to try to learn what is happening here. If you use carboxylic acid once the hydrazoic acid actually reacts to the carboxylic acid, then it is going to make this type of

species so it first going to react form this species, this is a carbamic acid. So then what is going to happen? There will be a -CO_2, so there will be decarboxylation going to happen I have already mentioned before to get to this corresponding amine. And if you have H+, it will make a corresponding amine salt.

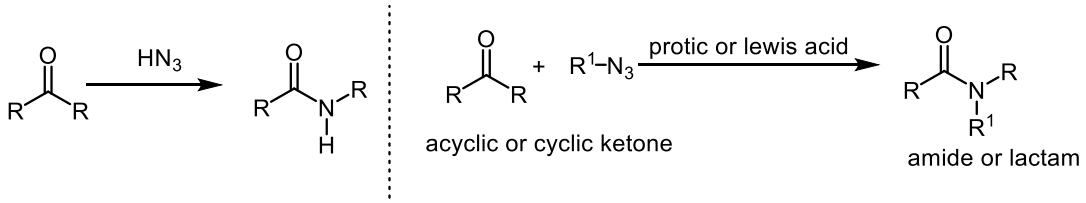


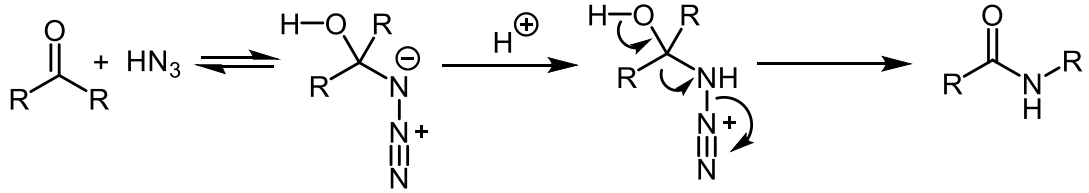


There is another example here if you have the NaN_3 and then in the polyphosphoric acid, it can able to convert to this corresponding amine. So, if you have a NaN_3 and a phosphoric acid that can generate HN_3 inside the reaction.



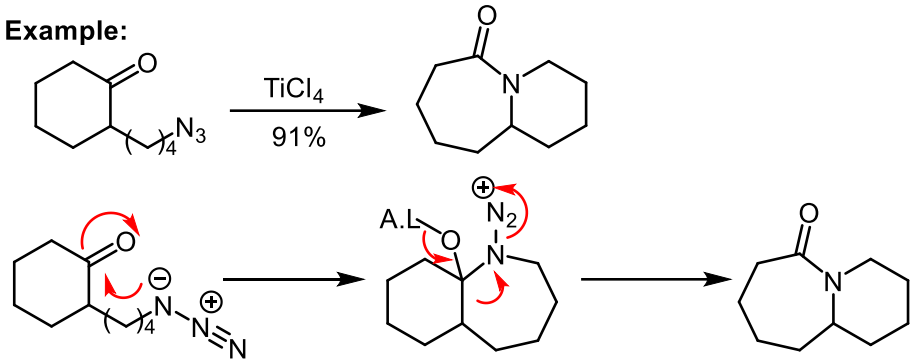
So, ketones are converted to amides when treated with hydrazoic acid. You can able to convert a ketone to corresponding amides. So, that is a very important transformation using hydrazoic acid. Again you can see in the mechanism what is happening, the nitrogen of the hydrazoic acid going to get attacked here to form this type of species after getting protonation, and then what is going to happen. This oxygen lone pair is going to push back the electron density and there will be a 1,2-shift of this R group from this carbon to the nitrogen, then elimination of the N_2 will generate this type of amide.



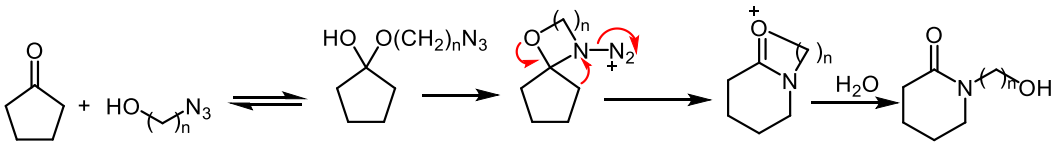


Again here is an example. It is not that always you have to be a protic acid. So, if you have some sort of a titanium tetrachloride then the reaction can also happen, but here is

an example of an intramolecular reaction you can also able to get to this corresponding lactone.



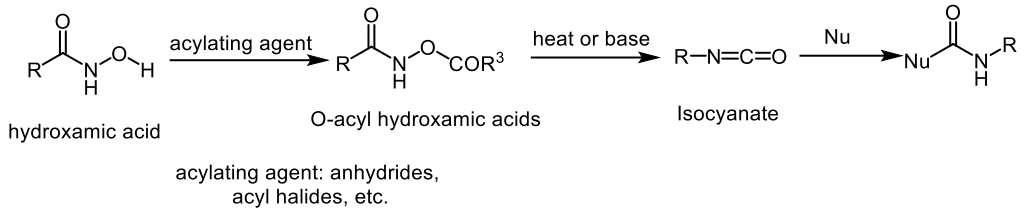
There is another example of Schmidt's reaction here. You can see there is C_4, N_3 if you treat with the titanium tetrachloride a very similar thing is going to happen, the mechanism is given. This N^- going to get attacked to the carbonyl. Then there will be a Lewis acid which is going to take with this oxygen and then it is going to come back and there will be at the end you can see this ring is getting expanded here to form this type of product. So, what is happening at the beginning? You have a 7 membered here and you have a 6. So, here is what is going to happen. So, this is going to become a 7-member and this will be a 6-member.



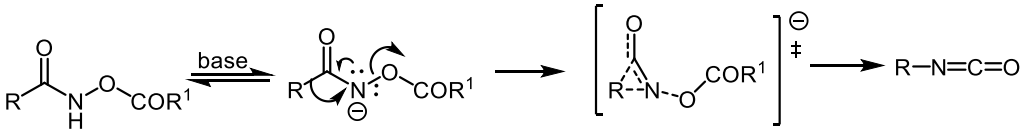
So, there is another example here. So this is a γ-hydroxy azide, when it is reacting with the carbonyl species, first, it forms this compound, it is reacting with the alcohol, and then what is happening, the nitrogen of the azide is attacking here and then it is cleaving this, going for a ring expansion to cleave this nitrogen-nitrogen bond to get rid of the N_2 to form this type of intermediate species, now the water is going to get attack here. So, water is going to attack here in this position and then after that it is going to form this some sort of a lactone again.

So, previously I talked about the Curtius rearrangement and the Schmidt reaction, now I am going to talk about the Lossen rearrangement. So, now what is going to happen? This is a conversion of O-acyl hydroxamic acid. So, starting from this O-acyl or starting from the hydroxymic acid you use a acylating agent to make this as a leaving group. So, you want to make this part as a leaving group, this can be denoted as a leaving group. So, once you have the leaving group now you become an O-acyl hydroxamic acid which in the presence of heat or in the presence of base, it is going to form the isocyanate. Now, the nucleophile can attack here as you can see very similar to the previous rearrangement

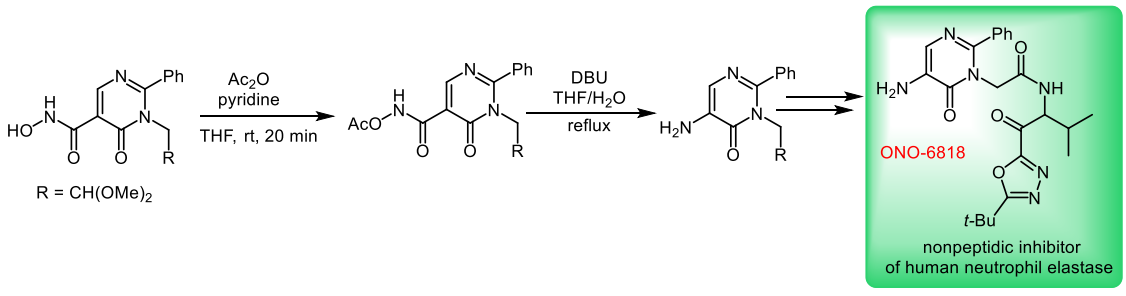
reaction and to form this corresponding product. So, this product can vary as you know starting from isocyanate depending on the nucleophile if it is water you can able to make the corresponding amine. Then if you use a corresponding alcohol you can make the corresponding carbamate and this is the mechanism again.

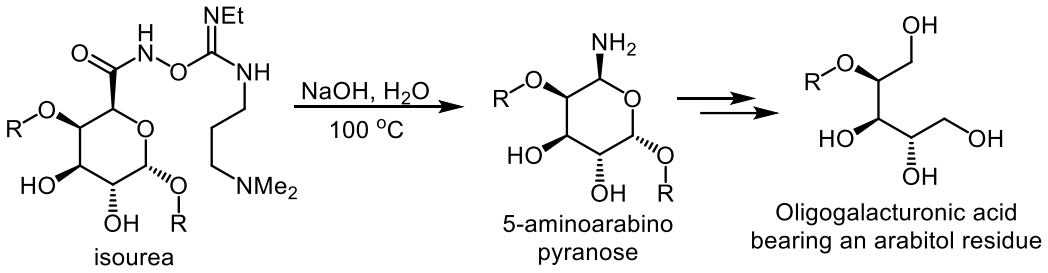


So, first, the base is going to abstract this NH and put a negative charge on the nitrogen then you use a corresponding acyl. Now what is going to happen. You can go for some sort of a mechanism like that where it can become an O- then this one gets migrated here, and this can go for a leaving group to get to some sort of a transition state to the corresponding isocyanate.

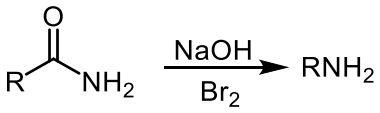


So, here is an example of Lossen rearrangement. So, what is happening? Starting from this you have the starting material already here. So, here if you use acetic anhydride and pyridine it can make it a very good leaving group. Now, just you need a base to make a deprotonation of this NH. So, that will allow this the 1,2- shift, and then you have already water. So, you are forming isocyanate which is going to treat with water to generate corresponding amine. There is another interesting example here in this molecule if you see you have this type of species here which you call isourea which is already attached to the oxygen. Again you just need a base to abstract this proton here to make N^-. Once you go for the minus this can go as a O^- it will come back and there is a 1,2-shift and then it will go for act as a leaving group. It will generate the corresponding isocyanate which can be treated with the water to generate a carbamic acid and finally, after the removal of CO_2, you will generate this corresponding amine.

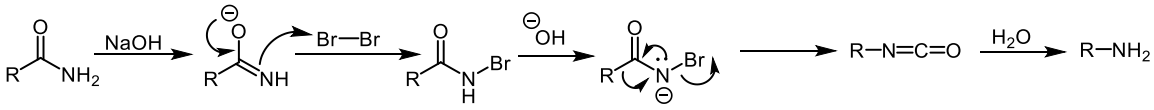




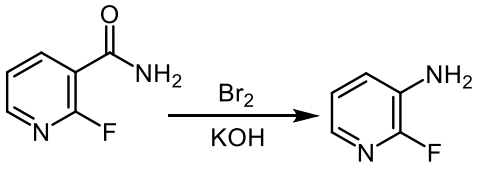
Then I am going to talk about the Hofmann rearrangement. So, this is the conversion of primary carboxyamide to the corresponding one carbon shorter amine. So, what is happening, you can see we are starting with the $RCONH_2$ to RNH_2. That means, in the end, what is happening, we are actually getting rid of this CO from the starting material to the product.



So, what is the reagent you have to use, NaOH with the Br_2. So, what is happening? The role of NaOH is to after the proton from the NH_2 forms this species, which is now what is happening, now this is going to make a N bromo species here. So, it can come back and take a bromine here. And now in presence of base it is going to take this proton to make an anion here which can go for the formation of the O-, it is going to come back and allow this 1, 2-shift. It will generate this corresponding isocyanate again and now once you treat it with water, it will generate the carbamic acid, which after the decarboxylation, will generate the corresponding amine.

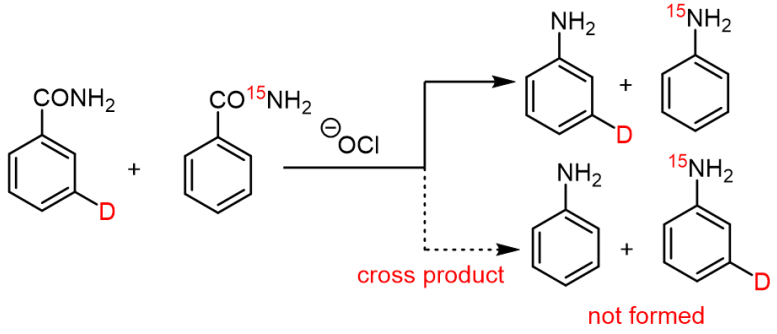


There is another example here. So what is happening, some sort of an amide you end up making to the corresponding amine. You can think about like the conversion of benzamide to corresponding aniline. I think if you think about it mechanistically this is the very similar. I think you might see this type of transformations comes in the exam. So, here is what is happening with pyridine, that is happening that with KOH and Br_2, it is actually converting into the corresponding amine.

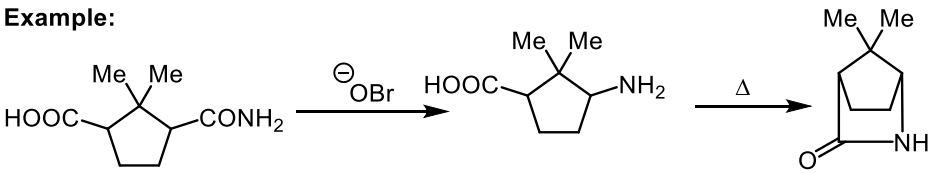


So, the Hofmann rearrangement is intramolecular or the intermolecular which means, if it is this NH_2 which is forming at the end it is coming from the other source or it is forming in the same molecule. You can test using this type of starting material. So, in one case you have a deuterium at the at the meta position, one case you have started with the 15-level nitrogen. So, what is happen at the end you end up getting this product not this set. So, what is this one telling you that this is telling me of course, this NH_2 is coming from this $CONH_2$, and in the case of the 15-level one you end up getting the aniline which is the nitrogen is 15-level. So, this is going for an intramolecular not the intermolecular.

Hofmann rearrangement is intramolecular or intermolecular?



Then there is some example of Hofmann rearrangement here. You can see in this example what is happening, you have a carboxylic acid and you have a amide here. So, it is actually interacting with the amide, abstracting this NH proton, then there is a CONHBr first and then it is going to abstract the NH proton then the formation of isocyanate, and there it will form the carbamic acid if you have a water here and then it is going to finally form the corresponding amine. So, generally, this OBr- comes from if you have a KOH and Br_2. Now after cyclization between this amine and the acid it is going to form this corresponding product.



So, one of the important fact is that if you start with this amide which is has a chiral. If you start with the chiral amide again there will be retention after the reaction. So, means what is happening as I said this group is getting migrated. So, there is no change is happening in this particular configuration. So, that configuration remain retained in the product. So, there will be a retention happening. So, what we have learned in this course?

In this part we have learned the singlet nitrene inserts into the C-H bond. So, I talk about different insertion reactions and then I talk about this 1, 2-shift of alkyl and the aryl and then I talk about the in the Curtius, Hofmann and Lossen rearrangement. And so, this is very important topic because you will see a lot of questions from nitrene is coming.

These are the references for this topic. You can able to go through the Clayden, The Advanced Organic Chemistry by Carey Sundberg and this is a very important book for reactive intermediates. Thank you so much for coming to the class. I am hoping to see you guys in the next class. Thank you.