

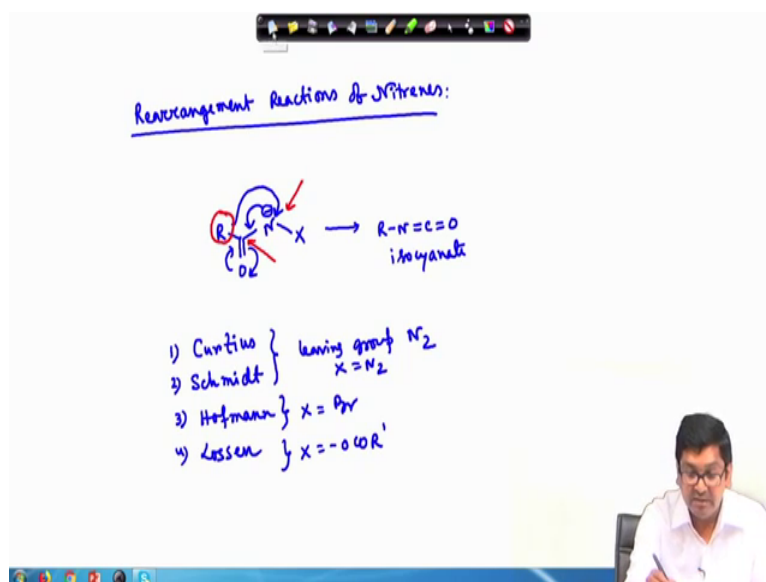
Reactive Intermediates: Carbene and Nitrene
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Lecture – 20
Reaction of Nitrene (Contd.)

Hello everybody, welcome to the last part of my topic that is Reactive Intermediates Carbenes and Nitrenes. From our last classes what we have seen, we have discussed that various type of reactions associated with the nitrenes. We have seen that the reactions with the nitrenes with olefins or alkynes that is the addition reactions that we have seen. After that we have discussed various type of insertion reactions; that mean, the electron deficient nitrene species how it can be inserted into a carbon hydrogen bond and different type of reducing activity that also we have discussed.

Today in the last topic we will discuss our last lecture we will discuss that the various type of rearrangement reactions that is associated with nitrenes.

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So, what we will learn today? We will learn the rearrangement ok, rearrangement reactions of nitrenes ok.

So, now we have seen in case of carbines, there are certain rearrangements that is happening with the carbine species; one of them that is very important that is called Wolff rearrangement. In this case it has also found for the nitrenes that similar type of rearrangements are possible with nitrenes species also and all these rearrangements there here the migration occurs to electron deficient nitrogen center that means, that 1 to shift of an atom or group from the adjacent carbon to the electron deficient nitrogen center that happens and that is quite similar like a carbons and in this way these rearrangements happens.

Now, if the leaving groups due to these migrations some groups that will be act as a leaving group, they will be different in different reactions, according to that different rearrangement names came. So, if we see that for carbons that Wolff rearrangement how it works, that will clear that in case of nitrene, how these reactions are proceeds. One of the most prominent intermediate in these type of reactions that generates commonly is isocyanate.

If we see the rearrangement in general, so this will happen in this way then this 1 to migration if you see, this is the adjacent carbon, this is the adjacent carbon and these associated group or atom that will be migrated to the electron deficient nitrogen centers over here and overall what it will give, it will give this isocyanate species.

And what we got for these nitrenes species various type of rearrangements are possible for this basically, the rearrangements with the electron deficient rather electron deficient nitrogen species, we will not say that these reactions are directly going through nitrenes, but in general this is going through electron deficient nitrogen species we will see that how these reactions will work. As per example there are 4 different type of rearrangement reactions we will discuss today one is called Curtius reactions.

Next that is called Schmidt reaction, number 3 is that Hofmann reaction, Hofmann rearrangement reactions ok, 4 is called Lossen reactions. So, courteous rearrangements, Schmidt rearrangement, Hofmann rearrangement and Lossen rearrangement those these 4 type of reactions that is associated with the electron deficient nitrogen species.

So, in that case, so, in these 4 type of reactions for these first 2 cases here the leaving group is leaving group is nitrogen whereas, in this case; that means, here x equals to

So, these are the basic differences between these 4 type of reactions though these are in general passing through similar type of reactions pathway, but these are overall difference for this 4 type of reactions.

Curtius Rearrangement

$$R-\overset{\overset{O}{\parallel}}{C}-OH \xrightarrow{ClCO_2Et} R-\overset{\overset{O}{\parallel}}{C}-O-C(=O)OEt \xrightarrow{N_3^-} R-\overset{\overset{O}{\parallel}}{C}-ON_3 \xrightarrow{(PhO)_2P^+N_3^-} R-CO_2H$$

$$R-\overset{\overset{O}{\parallel}}{C}-NH-NH_2 \xrightarrow[HO^-]{NaNH_2} R-\overset{\overset{O}{\parallel}}{C}-N=N-N \xrightarrow{N_2} R-N=C=O \xrightarrow[\text{R'OH}]{\text{nucleophiles}} R-\overset{\overset{O}{\parallel}}{C}-OR'$$

Concerted Process

~~$R-\overset{\overset{O}{\parallel}}{C}-NH-NH_2$~~

As per example all these type of product starting materials that will eventually leads to the leads to this acyl azide ok. How these reactions can happen that first you can trace to it this chloro ethyl formate and this will give first you the mixed anhydride ok. And then you can treat with some azide source and that will give you this acyl azide ok.

Similarly, this thing this you can get from the diphenylphosphoryl azide that is and you can start from carboxylic acid that directly we will give you this acyl azide compound with the reaction of this diphenylphosphoryl azide ok. Additionally you can start from

this hydroxy hydrogene derivative to the corresponding acyl azide in presence of sodium nitrite under acidic conditions that we will also give you this acyl azide.

Now, this is a nice precursor to generate the desired isocyanate intermediate through this way ok. So, now, sorry you can draw in this way ok. So, ok, so now, this 1 to migrations can happen to liberate the nitrogen and give you this isocyanate derivative ok.

And now, various nucleophiles can react as per example. So, water as per examples alcohol and give you this can attack over here and then finally, you will get this desired product, it could be acid and in if it is acids then sorry if it is a water then the decarboxylation. So, we will give you finally, the corresponding amines.

So, in this way various type of nucleophiles can react with this isocyanate and give you different products ok. Now in these type of reactions whether they are going via discrete nitrene species or the reaction is these migration is concerted to form the isocyanate intermediate. To know that various type of control experiments were carried out. As for example, if the reactions were done in crossover experiment, then there is no mixed product formed.

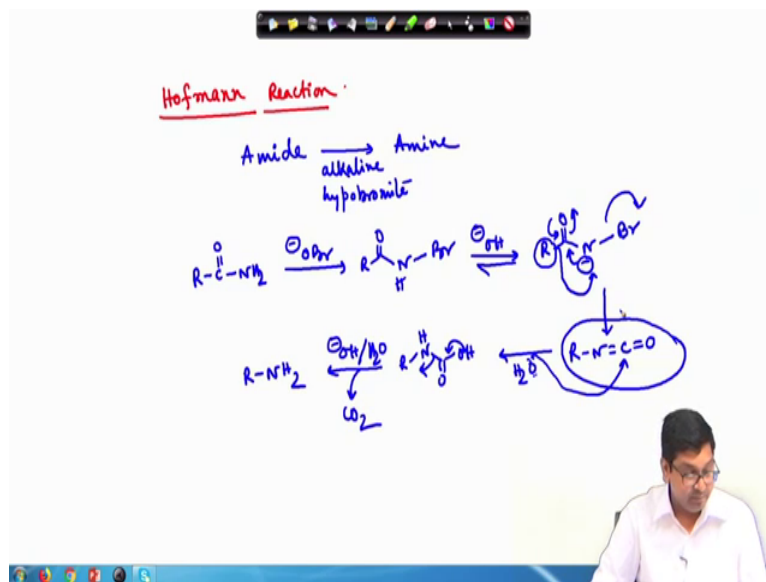
These proves that this reaction is not going through the discrete nitrene species. Number 2, there if the reactions was carried out in presence of water, then there is no formation of this particular this one $R-C(=O)-NHOH$ ok. This proves also that this reactions is not forming the discrete nitrene spaces. So, this has not formed ok.

So, this way you can prove that this 1 to migration is happening through concerted manner ok. Additionally it has been found that if this I R group this is chiral then what happens then, this if this is chiral after migration also want to migration also they retain their configuration; that means, this reaction is definitely happening through concerted manner ok.

So, this is overall we can say that this reactions is concerted process and that has been proved as there is no crossover experiment products and there is no formation of this $R-C(=O)-NHOH$ that shows that these reactions are happening in concerted manner ok.

Next we will see the another type of reaction that is we have discussed that one initially that that is called Hofmann reaction. Hofmann rearrangement reactions So, Hofmann reaction ok.

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So, in case of Hofmann rearrangement reactions the starting material is amide and the end product will be amine ok.

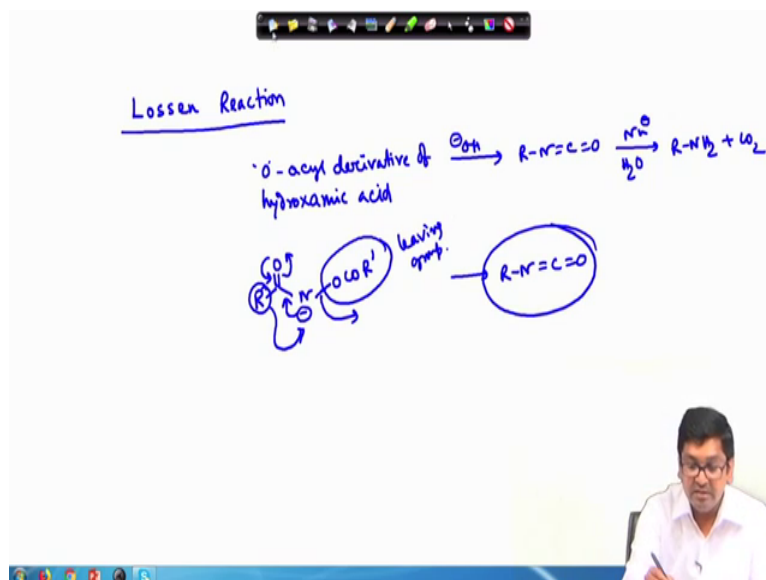
So, in this case, in spite of acyl azide here it will start from the amide group and the reagent is alkaline hypo bromide ok. So, if you start from the corresponding amide, in presence of hypo bromide it will pick up one proton and then to it will generate this intermediate. And then in presence of base this will pick up another proton ok.

Now, this 1 to migration will happen and bromine will be liberated. And in this case again what you will get? You will get the very important isocyanate intermediate and then water if nucleophile then it will attack, can attack to this electrophilic center and give this intermediate which again in presence of condition, basic condition this will eliminate the carbon dioxide and give the corresponding amine ok.

So, so, the starting material here is in case of Hofmann reaction is amide and the end product is the corresponding amine. And if you see here, here also as I mentioned previously the main intermediate that is forming the isocyanate and then it leads to the corresponding amine. So, the difference actually here is both cases this 1 to migrations

are happening, but in case of Curtius there is the leaving group was nitrogen; whereas, here it is the corresponding bromide ok.

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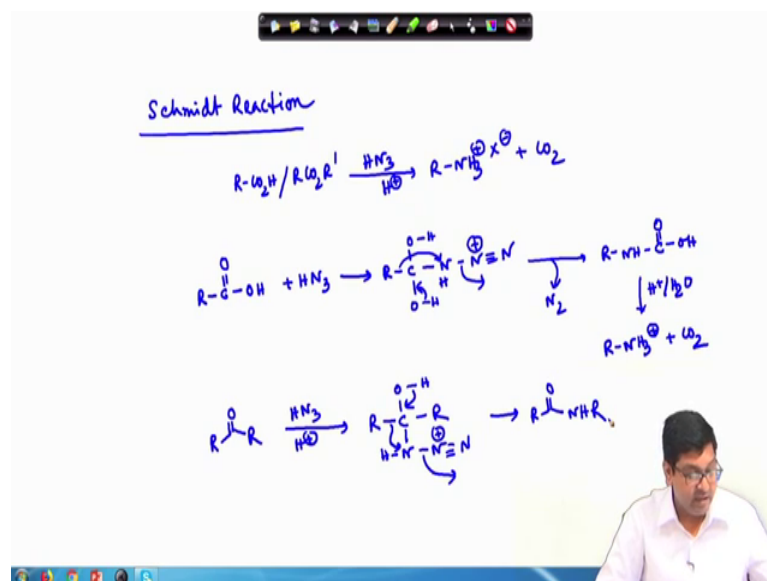


Next we will see the third type of rearrangement reactions that is we can call like a Lossen reaction ok. This is also similar like Hofmann reactions, but only in this case in spite of bromide here as the leaving group is this o acyl derivative of the corresponding hydroxamic acid ok. So, as for example, here if we take this o acyl derivative of hydroxamic acid that will give the in presence of base, the corresponding isocyanate through this 1 to migration and finally, in presence of various nucleophile like water here this will give the amine plus carbon dioxide ok. Only thing is here the difference with the Hofmann is that here this o acyl derivative of this hydroxamic acid is the starting material and in this case the leaving group is this one, this is the leaving group ok.

So, in this case also this 1 to migrations can happen to the leaving group as the o acyl derivative ok. And what it will generate from here? It will generate this isocyanate derivative fine. So, whatever we have seen this Curtius, Hofmann and Lossen they are basically the basic mechanism where this 1 to migration is very important as it happens in case of Wolff rearrangement in carbon ok.

Next we will learn another very important reactions that is called Schmidt reaction.

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This is more like the Curtius reactions because in this case of Schmidt reaction Schmidt rearrangement reactions rather in this case also it was more similar like a Curtius type of reactions because, in this case also the leaving group is nitrogen ok. So, the starting material is either the carboxylic acid or the ester. In presence of hydrogenic acid and the different acid in many cases it is dilute sulfuric acid and in that case it will give the corresponding amine ok.

So, we can see that that carboxylic acid in presence of hydrogenic acid that gives the corresponding amine and carbon dioxide ok. So, this is the overall Schmidt reactions. In these case also the leaving group is nitrogen and the main reaction happening through this 1 to migrations. So, if we see the reaction mechanism ok, so this gives this intermediate and once this generated then this 1 to migration can happen and nitrogen can liberate. So, what you will get? So you will get this carbamic acid ok.

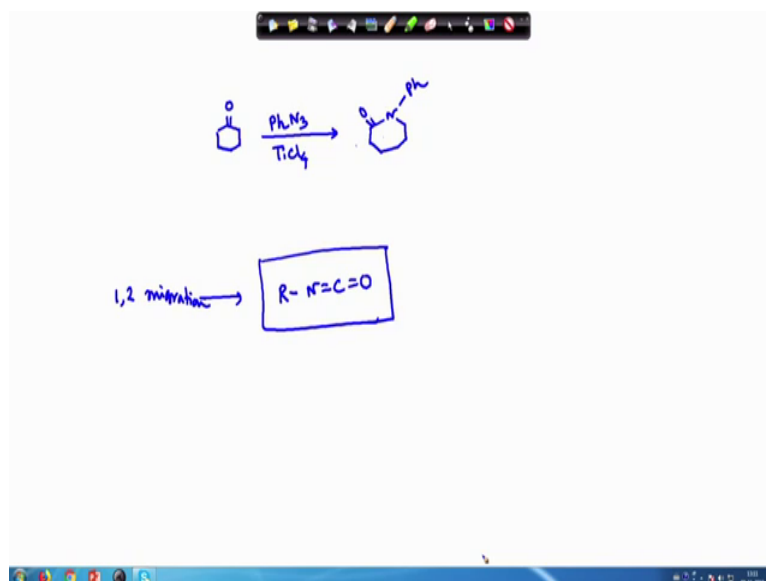
So, once you will get this carbamic acid, then in acidic conditions, this will give your desire amine compound ok.

This in these Schmidt reactions, this hydrogenic acid that can again react with the ketones also. As per example, if you take this ketone as a starting material in the place of carboxylic acid then in presence of this hydrogenic acid, under acidic medium this will generate this intermediate and once it will generate then again this is now ready for this

one to migration, then nitrogen can be liberated and overall what you will get? You will get the corresponding amide ok.

So, if you start from carboxylic acid that will give you the corresponding amine and if you start from the ketones you will get the corresponding amides fine.

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As for example, if we see, if it is the ketones like cyclic ketone then, like cyclohexanone if it is cyclohexanone in presence of phenyl azide I mean this aryl azide and TiCl₄ as the Lewis acid then overall what you will get? The product will be the corresponding lactam, sorry definitely in this case the ring size will increase because due to the 1 to migration as this is a cyclic starting material. So, due to 1 to migrations the ring member that will be increased by number 1; that means, if it is here 6 member ring it will becomes like a 7 member ring.

So, in this case 1, 2, 3, 4, 5, 6, 7; so, this will be the corresponding lactam product ok. So, whatever we have seen all these cases one very important intermediate that is forming that is called that isocyanate ok. And how this is coming all these cases this one is coming through the corresponding 1 to migration which is nothing, but similar like in Wolff rearrangement in case of carbenes and what happened, all these cases when this isocyanate forms after that this nucleophile can react and that gives the desired target product.

Another important aspects for all this type of nitrene associated reactions rather this deficient nitrogen center associated reactions are like all these cases the starting materials are in principle they are different. As per example in case of Curtius case this what is that that acyl azides that is the starting material and the leaving group is the nitrogen.

Similar like in case of Schmidt reactions also that in presence of these carboxylic acid or ketones they are the that will also generate in presence of this hydrogenic acids that will give you this corresponding intermediate, which eventually will give this isocyanate and then finally, that will give this product ok. And in this case what we have found that, in this case these during the Schmidt reactions when it is a keto compound that gives the corresponding amides ok.

So, these are the overall type of different type of reactions associated with the nitrenes and for Hofmann, sorry for Hofmann reactions what is the leaving group here in case of Hofmann's, the leaving group is bromide ok, but it also passes through this isocyanate intermediate ok.

And in case of Hofmann the starting material is the amide and after one carbon degradation you are getting and the desired product that is the amine compound and or for Lossen reactions what we found? In case of Lossen reactions which is similar to like a Hofmann reactions in that case also the leaving group is the o acyl derivative starting materials which we will finally, give you this isocyanate derivatives to and ready for the different nucleophilic attack ok.

So, these are the overall different type of reactions that is associated with the electron deficient nitrogen species ok. Now if we do the summary of these nitrenes what we found, this is a monovalent nitrogen species and this is isoelectronic with carbenes and contain 6 number of electrons. These are highly reactive and generally nucleophilic sorry generally electrophilic in nature as their electron deficient species and these they can be singlet or triplet.

And obviously, due to their electronic nature different their electronic structure, their reactivity are different than carbons and it has been found that this nitrogen center that is in triplet that is sp hybridized whereas, the nitrogen center in singlet that is sp^2

hybridized and like carbons nitrenes also gives various type of reactions like addition reaction insertion reaction rearrangement reaction etcetera.

So, overall these are all aspects we have discussed in this course that is the reactive intermediates carbines and nitrenes. We have discussed they are all type of starting from their generation, their characteristics, their reactivities and various type of reactions both for carbines as well as nitrenes. Hope you have enjoyed this course and we will learn a lot about carbines and nitrates.

Thank you very much.