Introductory Organic Chemistry II
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Indian Institute of Science Education and Research, Pune
Module 08
Lecture 57
Rearrangements - Part 4

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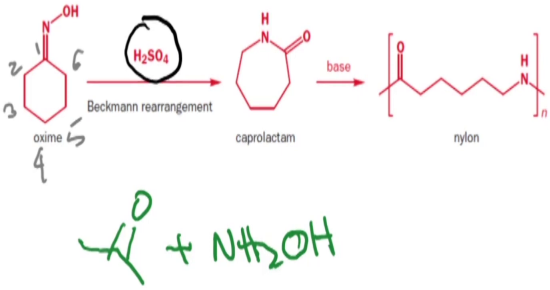
BECKMANN REARRANGEMENT



So, the next rearrangement that we will be looking at is the Beckmann Rearrangement. And this Beckmann Rearrangement occurs when we start with an oxime. And we all know that an oxime can be produced by reacting ketone with hydroxylamine, usually in the presence of an acid, and that is going to give you this oxime product.

And when you treat this oxime with an acid, such as H_2SO_4, it undergoes a rearrangement to produce caprolactam. And caprolactam is a very important industrial reagent that is used to produce nylon, as you know nylon is a polymer that is very widely used. And so, this is an industrially very important reaction. Now let us look at the mechanism of this reaction.

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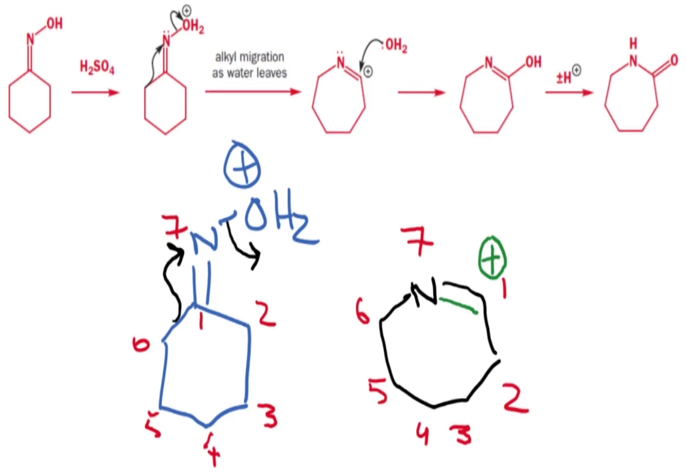

So, as we would expect in the presence of an acid, one of the groups is going to get protonated. So, if the hydroxyl group gets protonated, then you would end up with this protonated water, or OH_2^+, and which is an excellent leaving group. So, you can imagine that this nitrogen-oxygen bond can break and this breaking can coincide with the migration of this carbon-carbon bond to the nitrogen.

So once this carbon-carbon bond migrates, you end up with this type of a carbocation. So, what I am going to do now is I am going to sort of go through this step a little bit in detail, so that we understand this. So, what I will do now is I will just draw out this key step here, so that it is easy for us to follow. So, this contains cyclohexane ring. And so, I am just going to number this so that we understand this migration better.

So, if you just number this, let us just call this 1, 2, 3, 4, 5, 6. I am just going to call this nitrogen as 7. And so, what has been suggested is that this is going to leave and that is going to be accompanied by the carbon-1, 6 bond breaking and moving towards the nitrogen. So, now I am going to draw out this 7-membered ring.

So, and let me just continue the numbering the way we have drawn it, so nitrogen is 7. And there is a new bond between carbon-6 and carbon-7, 5, 4, 3, 2, 1. And this bond between carbon-1 and nitrogen still remains and the valency of carbon-1 is not satisfied, and you end up with a positive charge on this nitrogen as shown here.

So, it is important that you understand the way in which this migration occurs and the way in which the leaving group leaves. So, please learn how to number carbons and nitrogen and oxygen so that you can keep track of what is going on. And then subsequently, water attacks this positively charged species here and it forms this OH, which can then undergo a tautomerism kind of reaction to give you the final amide.

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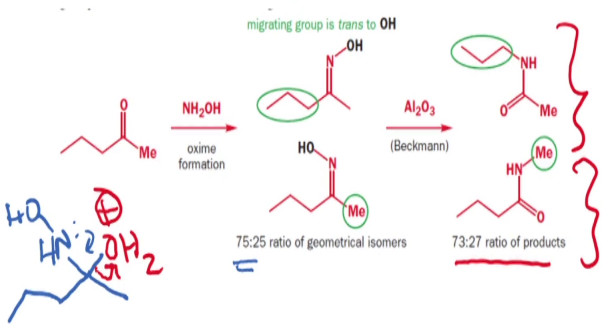
WHICH GROUP MIGRATES?



So now the question is, which group migrates? So, in order to understand this, let me just draw this oxime in the following manner. So, when ketone reacts with hydroxylamine, if it is a symmetrical ketone, you get only one product. But if it is asymmetrical ketone, you end up getting a mixture of geometrical isomers. So, one of the isomers, the hydroxyl group is far away from the larger group, and the other one, the hydroxyl group is far away from the smaller group.

So, the key step here in the oxime formation is this reaction where the lone pair on nitrogen comes in and kicks out water. So, this occurs in a way in which the more stable product dominates. So, if you see here, the ratio between these two products here is 75 to 25, where the larger group is far away from the hydroxyl group or trans. And the minor isomer, which is 25 percent is where the methyl group is trans to the hydroxyl group.

The important result here is that when you add a Lewis acid such as Al_2O_3, the migration occurs or the rearrangement occurs in such a manner that the ratio of these two is maintained that is, you start with 75 to 25 and you end up with a nearly identical ratio of products. Keep in mind that if this propyl group migrates, then you end up getting this propyl amine based derivative and if the methyl group migrates then you get this methyl amine-based derivative.

So, this mapping of the products is very useful because it helps us understand whether there is any possibility of an intermediate or anything that has been formed. So, if this Beckmann Rearrangement occurs in a stepwise manner that is first this bond breaks, or first this bond breaks and then there are two fragments which are produced and then they recombine to give you the product, then all bets are off, the ratio can be anything, but since the ratio of the oxime isomers is maintained in the product, it seems like the group that is trans to the hydroxyl group migrates.

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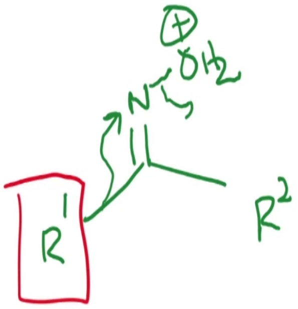

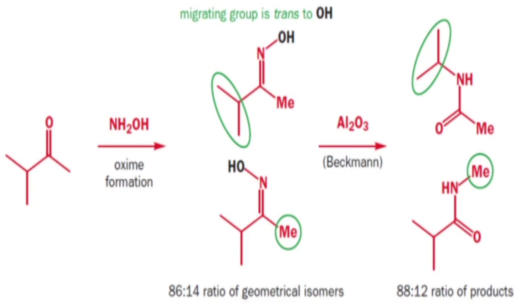

So, the way we understand this is that this nature of this group here is not really important. What is more important is which group is going to be trans to the leaving group. So, I will give you one more piece of evidence to support this. So, when you start with isopropyl methyl ketone and react it with hydroxylamine, you get like an 86 to 14 ratio of these two products, again the trans to the hydroxyl group is more favoured and that is the isomer that is produced in greater quantity.

And when you react this with the Al_2O_3, you end up with the same ratio almost the same ratio at 88 to 12 where the isopropyl group migrates compared to a methyl group. If you remember we discussed during the Baeyer-Villiger Oxidation, where the isopropyl group had a much better propensity to migrate when compared to a methyl group. So, that does not hold good here, what is more important is that the isopropyl group is trans to the leaving group.

And if there was some way to completely convert this group to this, then you will find that the methyl migration is the exclusive product. So, in the case of the Beckmann Rearrangement, what is more important is which group is going to be trans to the leaving group, which is the water. Now, let us move on to the next rearrangement.

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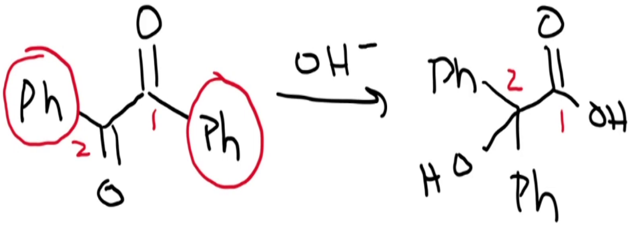
BENZILLIC ACID REARRANGEMENT



This is called the Benzilic Acid Rearrangement. So, if you look at this structure here, this is a 1,2-diketone. So, I will just number this is 1, 2, and when you react this with hydroxide ion, you end up getting a product such as this where you know the carbon-1, which is just a ketone, and now forms a carboxylic acid and carbon-2 which had a ketone now has an alcohol. And clearly one of this phenyl group or this phenyl group migrates of this reaction. So, the mechanism of that we propose for this reaction is as follows.

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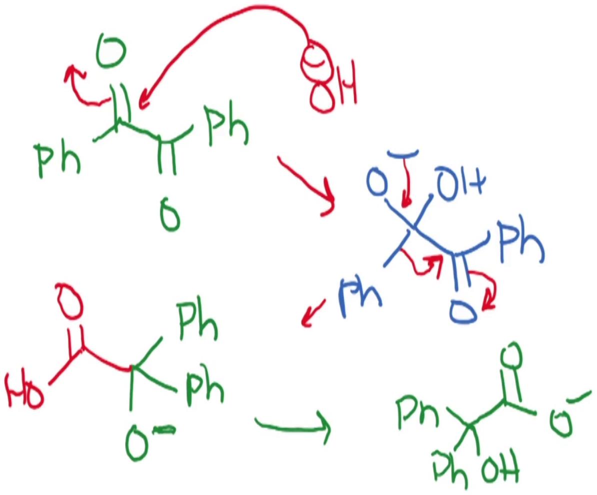

So, you have this PhC=OC=OPh, and the first step is the addition of hydroxide ion and the hydroxide ion can attack either of these carbonyl compounds, but let us say it attacks this one, then the product that is, or the intermediate that is formed is the following, you have PhCO$^-$(OH)C=OPh. And now, we need to keep in mind that the product formed has two phenyl groups attached to the same carbon.

So, there has to be some sort of migration that occurs. And so, the migration that we can propose is the following, the collapse of this tetrahedral intermediate and this phenyl ring here can actually migrate to this carbonyl and open up this carbonyl in this following manner. So, the product that is formed in this case would be C double bond O OH so that is from this part.

And now the second carbon over here, this OH is now going to be, I mean C double bond O is going to become O minus and a phenyl ring is here, and the phenyl ring is here. And subsequently, this is a strong base and this is a good acid. And so, this is going to rearrange and give you the desired product, which is $(Ph)_2C(OH)C{=}OO^-$. So, this is called the Benzilic Acid Rearrangement. And this product that is shown here is benzilic acid.

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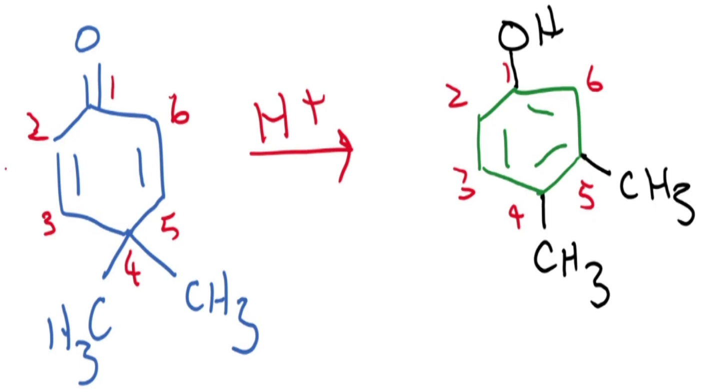
DIENONE-PHENOL REARRANGEMENT



Let us move on to the next rearrangement which is called the Dienone-Phenol Rearrangement. This is called a dienone because it is a ketone, which is attached to two olefins. And in the presence of an acid, it undergoes a rearrangement to give you a phenol. So now, let us just number these carbons over here so that we can understand what is going on 1, 2, 3, 4, 5, and 6. So if you see here, this is 1, 2, 3, 4, 5, and 6, so the carbon-1, which used to be a ketone has now become a phenol. And carbon-4 used to have two methyl groups, it has only one, and carbon-5 which used to have a hydrogen now has a methyl group.

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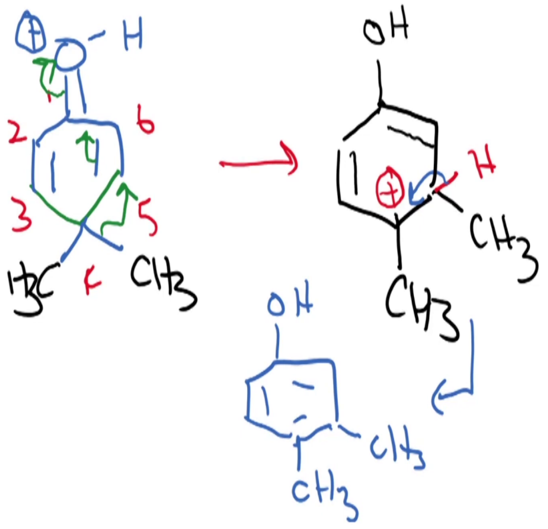

So now in order to address the mechanism, let us consider the following. So, the most straightforward thing for us to do is to just simply protonate this carbonyl. So, you have OH plus. And now, the important part here is to understand that the carbon-4 has only 1 methyl group and carbon-5 in the product has 1 methyl group. So, what is going to happen is that you are going to have the migration of this methyl to carbon-5, so this has to move here.

So, if this moves here, then what can happen is that this double bond migrates here, and it neutralizes this, or it breaks this carbonyl bond to form OH. So, let me just write out this product. So again, please be very systematic in your approach, and make sure that the arrows are being pushed in the correct manner. So, this is a CH_3, there is a CH_3, so one of the CH_3 remains here.

And now on carbon-5 is the next methyl group that we have now migrated it to, and there is a bond between carbon-1 and carbon-6, a double bond, this double bond between carbon-2 and carbon-3 remains intact, and the OH remains as OH. Now, the only point to note here is that there used to be a hydrogen on carbon-5, which continues to be there.

And now this acquires a full positive charge because the methyl has now migrated out. Now, you can imagine that there is going to be a loss of a proton to give you the final product, which is the phenol. So, it is a fairly straightforward rearrangement for us to consider. And this is called the Dienone-Phenol Rearrangement.

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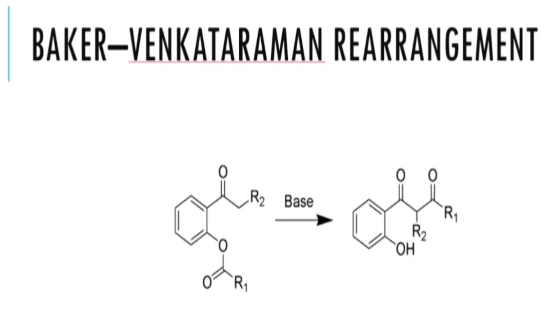

BAKER–VENKATARAMAN REARRANGEMENT

Now, let us move on to the next rearrangement which is called the Baker–Venkataraman Rearrangement. And this rearrangement involves a carbonyl compound and a base. So, what we would expect here is that again, this is the ketone part here and there is an ester here and in the presence of a base this ester bond seems to be broken and this carbonyl part of the ester is moved to this carbon next to the ketone.

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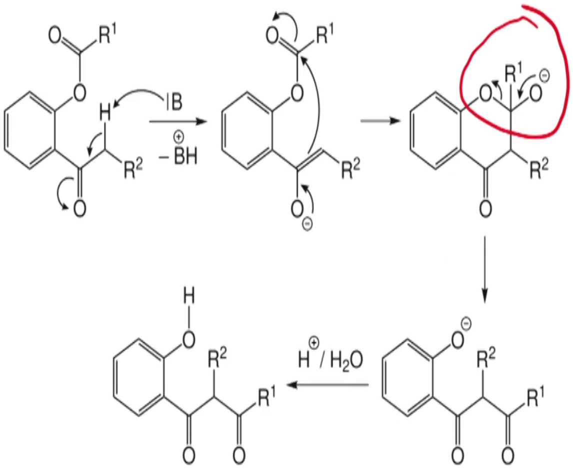

So as with any carbonyl compound, we would expect that there will be an enolate produced. So, the first step of the mechanism is that the base is going to abstract this hydrogen and produce this enolate. And now the enolate has an opportunity to react in an intramolecular fashion with this ester and it produces this tetrahedral intermediate as shown here, this tetrahedral intermediate can further collapse and kick out this phenoxide ion.

And in the process, the acyl group has migrated to this carbonyl position over here. And then subsequently acquiring a proton gives you the desired product. So again, please keep in mind that the important step here for us to understand is that when we start any mechanism that we look at for rearrangements we need to look at, go through the basics and we generate the enolate as we always do, and then this attack on the carbonyl compound has to be the step that is involved because this group ends up on the enolate.

And so there has to be a carbon-carbon bond that is formed. The only unique thing here is this collapse of this intermediate which happens in an intramolecular fashion and generates the phenolate.

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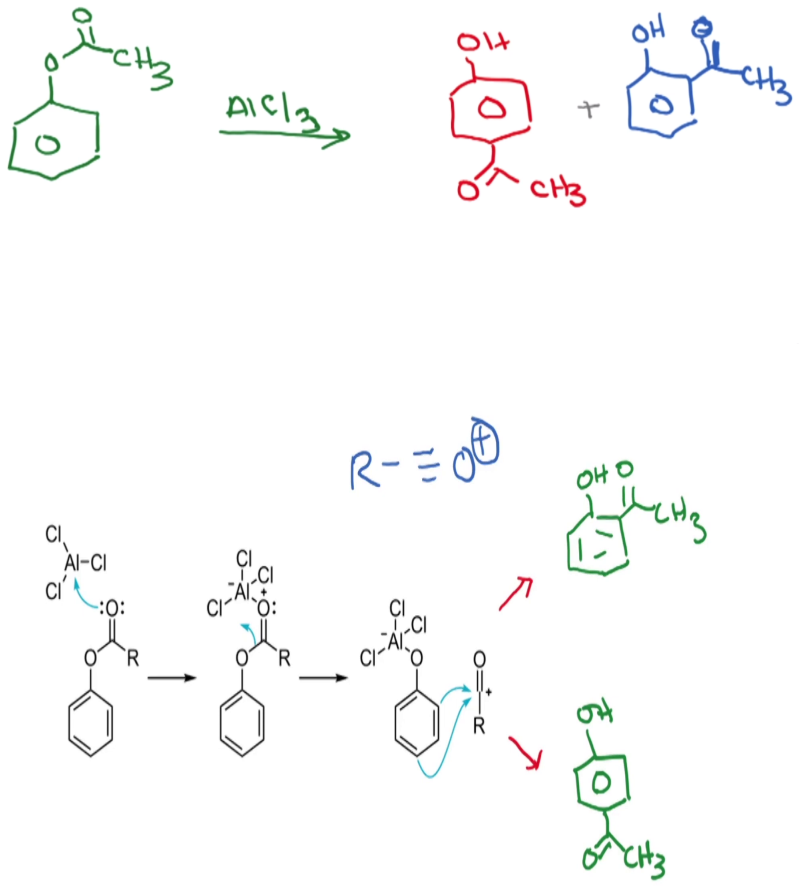
FRIES REARRANGEMENT



The next rearrangement that we are going to look at is the Fries Rearrangement. So, the Fries Rearrangement, what happens is that you can you start with acetyl phenol and react it with aluminium chloride and you invariably get one or more products such as these, wherein the the acetyl group here ends up in the ortho or the para position.

And so, clearly there is a migration of this acetyl group which is going to be probably linked to an electrophilic aromatic substitution. So, this follows us to look at the mechanism in the following manner. So, the mechanism of the reaction is as follows. So, aluminium chloride we know is a Lewis acid, so it is going to coordinate with the carbonyl carbon.

And then subsequently there is a loss of this carbonyl carbon to produce, we have already looked at this, so you produce an intermediate such as this. And this intermediate is now in a great position to react through the ortho position or the para position to give you the corresponding acetylated compound. So, this is like a Friedel Crafts acylation, which we have already looked at in detail in this course.

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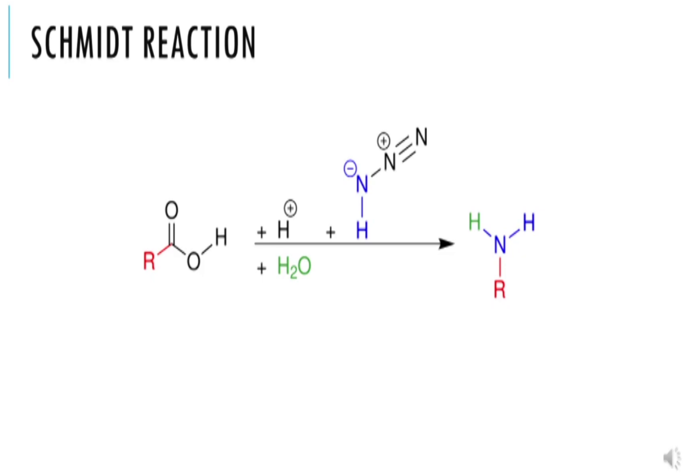
SCHMIDT REACTION

Now, the next reaction is the Schmidt Reaction. So, here you start with a carboxylic acid and in the presence of this HN_3 which is Hydrazoic acid you end up with an amine. So, if you see here the R group here is now attached to RNH_2. So, this is a very interesting transformation because this allows for us to convert carboxylic acids to amines. And clearly there is going to be a loss of carbon probably through CO_2.

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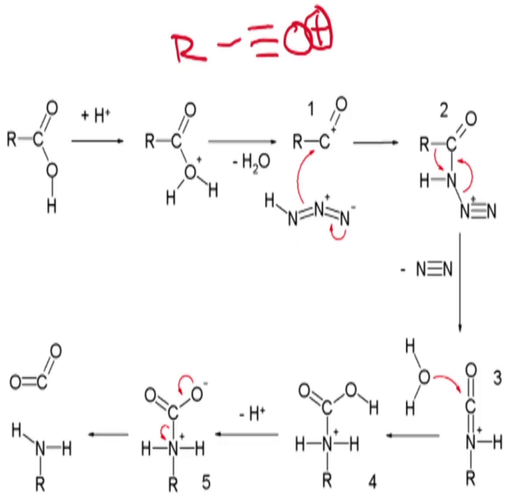

And so, we look at the mechanism. So, the carboxylic acid is in the presence of H^+ forms this protonated carboxylic acid which can lose water to produce an intermediate such as this, which we have already looked at in the previous Friedel Crafts reaction. And now, the interesting reaction here is between the azide and this carbonyl compound.

So, the azide as you know is an excellent nucleophile. So, it attacks through one of the nitrogens as shown here and produces this quasi-amide type of compound which can then subsequently lose nitrogen. So, this kind of a rearrangement, we are already familiar with. So, this is like almost like the Beckmann Rearrangement where the carbon-carbon bond migrates to nitrogen.

And now, the only difference here is that this carbon-carbon bond after it migrates results in the loss of N_2 and once N_2 is gone, it produces this type of isocyanate type of an intermediate which then reacts with water to give you an intermediate such as this which then loses CO_2 to give you the amine. So, the important step here is this rearrangement that happens after reaction of the azide with the carbonyl compound.

Now that we are familiar with this functional group of cyanate let us look at this functional group in a little bit of detail.

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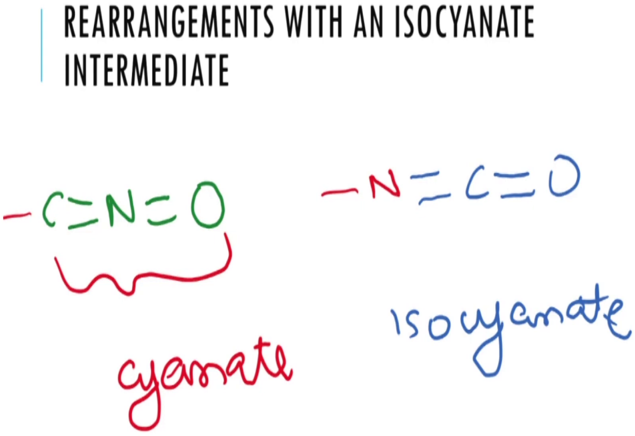
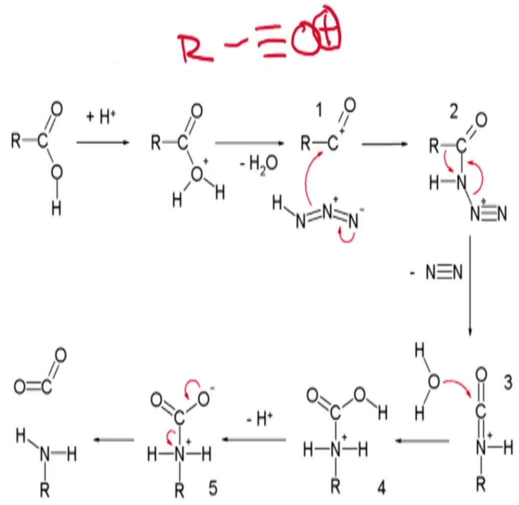


REARRANGEMENTS WITH AN ISOCYANATE INTERMEDIATE

$-\underbrace{C=N=O}$ $\quad -N=C=O$

cyanate $\quad$ isocyanate



So, isocyanate rather, so this functional group is called a cyanate functional group, where you have C double bond N double bond O. You can also have flipping of the carbon and nitrogen or swapping of the carbon and nitrogen and this type of group is called the isocyanate. There are a few rearrangements which we will look at including this, which involve the isocyanate.

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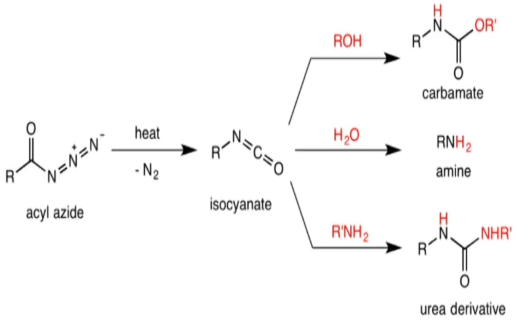
CURTIUS REARRANGEMENT



And the first of this is called the Curtius Rearrangement. So, where you have acyl azide, when you heat it up, you lose nitrogen to produce an isocyanate and isocyanate can react in many ways. For example, isocyanate is basically like a carbonyl compound that can react with an alcohol to produce carbamate. This carbon is now bound to this oxygen here.

If it reacts with water, it can get hydrolyse to form an amine. And if it reacts with an amine, then it can form what is known as a urea; urea is basically C double bond O flanked by 2 nitrogens. So therefore, this Curtius Rearrangement is a very powerful way for you to convert carbonyl compound into multiple derivatives that are very useful.

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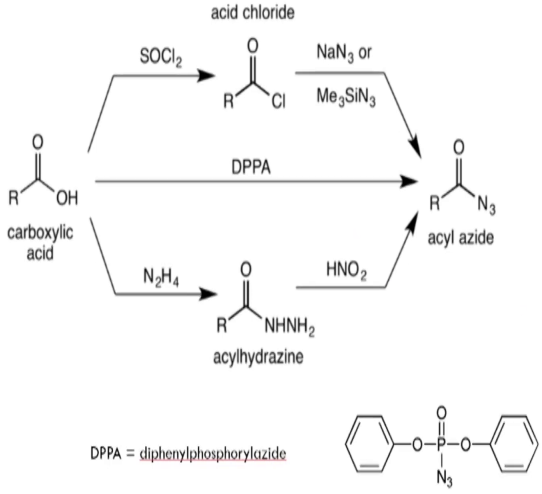

So, the way in which you generate this acyl azide is you start with a carboxylic acid, and you can react it with $SOCl_2$ and produce an acid chloride. And subsequently the reaction of the acid chloride with sodium azide or trimethylsilyl azide gives you the acyl azide. You can also do this reaction by reacting it with the diphenylphosphoryl azide, whose structure is shown here.

And the last way to produce an acyl azide is to react it with hydrazine, which will give you this acyl hydrazine and then you react it with the HNO_2, which if you recall is going to form diazonium type of intermediate and the diazonium and azide are quite similar because N double bond N double bond N that is azide and whereas the diazonium is N triple bond N. So, you are going to generate the acyl azide.

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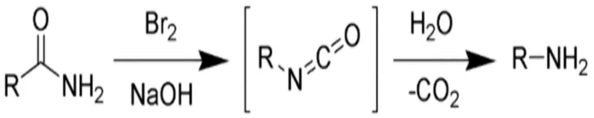
HOFMANN REARRANGEMENT



The next rearrangement that we are going to look at is the Hoffmann Rearrangement. And the Hofmann Rearrangement also involves isocyanate. And this is one of the standard and very famous rearrangement. It is also called the Hoffmann-Bromamide reaction. So here you react an amide with bromine and you end up with an amine. And it goes through an isocyanate intermediate.

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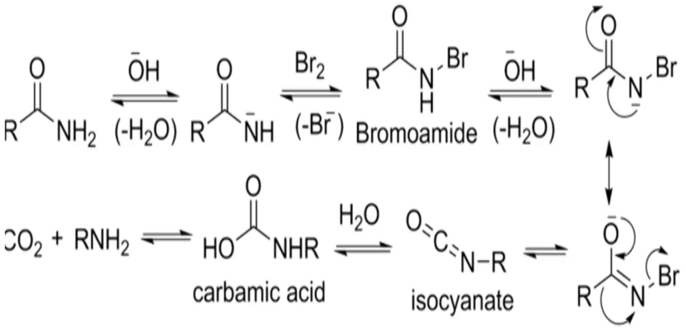

So, let us look at the mechanism. So, in the presence of a base, this RC=ONH$_2$ forms RCO NH$^-$, which is a nucleophile and can react with bromine. The loss of bromide to give you what is known as a bromoamide. And the bromoamide can again undergo deprotonation to give you N minus.

And here is where very interesting reaction happens. So, this N minus can donate its electrons here, and open up the carbonyl compound to produce this kind of an intermediate. And now comes the migration step when the O minus forms a C double bond O, the R can migrate over here and Br minus can be lost. So, this migration again, involves the loss of a bromide and the breaking of carbon-carbon bond to form a carbon-nitrogen bond.

So, you will see the similarities in many of these rearrangements. So once the isocyanate is produced, it reacts with water and forms carbamic acid, which can subsequently lose CO_2 to produce the amine. So, this is similar to the previous rearrangement that we looked at.

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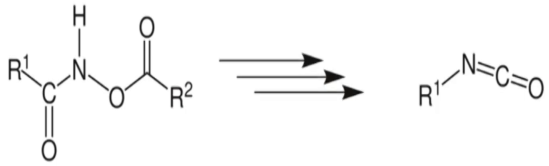
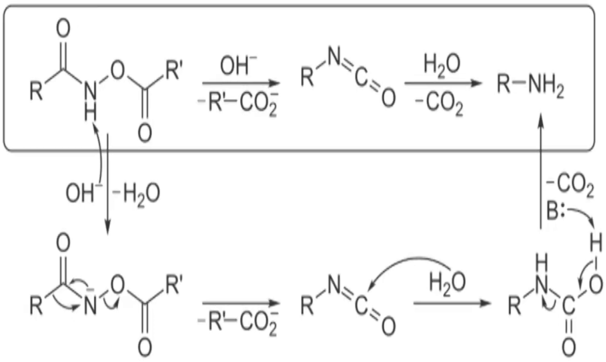
LOSSEN REARRANGEMENT





The last rearrangement that we are going to look at in the series is the Lossen Rearrangement, where again, it involves the formation of an isocyanate. And this isocyanate is produced using this intermediate as shown here. Now, let us look at this reaction. So, this is again, very similar to the bromoamide and the other isocyanate-based reactions.

So, in the presence of hydroxide ion, the amide proton undergoes deprotonation. And then it produces this kind of a N minus. And now again, this N minus moves in here. And there is a migration of the nitrogen and loss of $RCOO^-$, so if you lose $RCOO^-$ over here, you end up with isocyanate. And isocyanate can subsequently react with water to give you carbamic acid, which then loses CO_2 to produce the amine. So, these are a bunch of these rearrangements that are going through an isocyanate type of intermediate.