Introductory Organic Chemistry - II
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Lecture 17
Tutorial - 2 Part - 2

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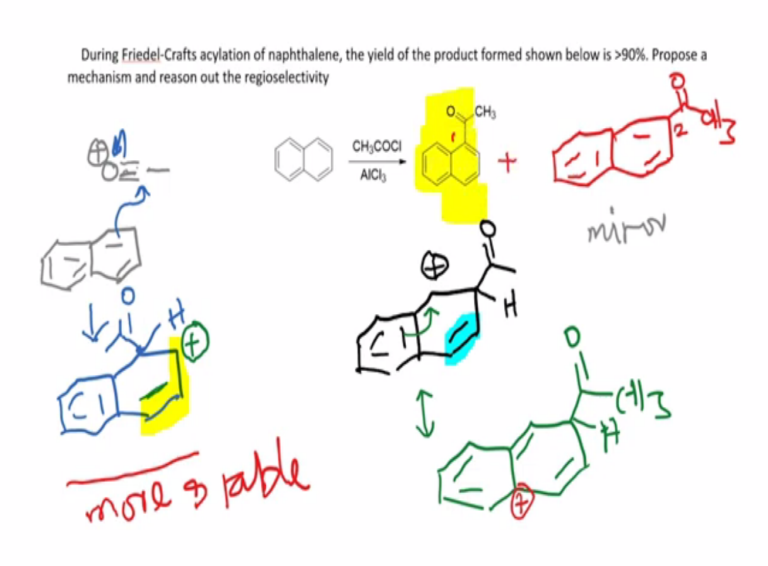

Here is the reaction of naphthalene with acetyl chloride and in the presence of aluminum chloride and it actually gives you greater than 90 percent of this compound. So, if you look at the regioselectivity of this reaction, actually there are two possible products. So, this is one, and the other one is actually the 2-substituted compound, which is as shown here. CH3C=O, so this would be position number 1, and this is actually position number 2.

So, this compound, this is the minor product over here. So, the question that is really asked here is, how do we explain this? So, the way we would explain this is let us look at the intermediate that is produced upon reaction with naphthalene. So, if I draw out naphthalene like this. And we know that the reaction happens with the acylium ion, as shown here, so the attack happens at this carbon, then there is a movement of electrons and so the resulting product that is formed is actually the one that is shown here.

So, you have the H here, and you have CH3C=O and that is hooked up with this carbon over here. And then there is a positive charge that develops here, and there is a double bond. So, if I

look at this system, I can see that there is delocalization across this allylic carbocation. Now, if I were to do the same reaction on the other position, I am just going to draw out the structure over here and you will understand the difference in stability.

So, here is the second structure as shown here. And there is a carbocation over here, and then there is the olefin over here. So, as you can see here, there is a little or no possibility of delocalization with this double bond, there is an isolated double bond, pretty much. So, any delocalization that happens will involve this benzene ring. So, once this benzene ring moves here, of course, we can draw out resonance forms where there is going to be some level of delocalization over here, but this involves the loss of aromaticity.

And therefore, any structure that is going to be significantly different instability will not contribute much to the resonance form and therefore, the stability difference between these two is quite large. So, this compound over here, this intermediate over here is more stable. And what we know from electrophilic aromatic substitution is that the stability of the intermediate contributes to the formation of or to the transition state that leads to its formation and that becomes more stable and therefore, the rate of reaction goes up. So, this helps us explain why this compound is the major product.

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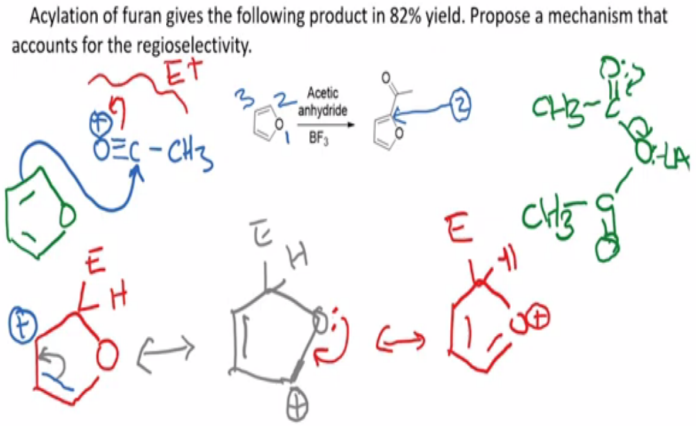

So, the next problem is understanding the reactivity of Heterocyclic compounds. And this heterocyclic compound is called Furan and Furan is, you know, one of very important heterocyclic compound that is used in the synthetic intermediate in many reactions, including to make pharmaceutically active components or drug-like molecules. So, looking at this compound, this molecule is aromatic as we all know.

Now, when you react this with acetic anhydride and BF_3, you end up with essentially a compound that is substituted at the 2-positions. So, let us get that nomenclature first straightened out. So, this 1, 2, 3 and 4 and 5 are the same as 3 and 2. So, these are the three positions that are important. And so, if you see the Friedel Crafts Acylation reaction that happens at position 2, rather than at position 3.

Now, how do we understand this? So, in order to understand this, let us first draw out Furan and react this with the electrophile. So, acetic anhydride, as all of you know, is basically $CH_3C{=}OOC{=}OCH_3$. So, this is a compound that is a precursor to the acylium ion. So, your lone pair over here can react with the Lewis acid and then it can come apart to give you the acylium carbocation.

And so, this is something that we could expect that will happen. And so, you have $^{+}O{\equiv}CCH_3$ this is the acylium carbocation or oxocarbenium ion that we are looking at. And so let us look at the situation 1 where the attack happens over here. And the bonded pair of electrons utilizes the positive charge, and you end up with an oxygen here, and I am just going to abbreviate this as E. so that it is easier for us to draw the structure.

So, this whole oxocarbenium ion is going to be called as E^+ and then when it reacts, we get E, and then there is a positive charge formed over here and this double bond remains the way it is. So, if you look at this structure, now I can draw a resonance form, wherein we have this an allylic carbocation so it can move in here, and give you a resonance form which is going to look something like this.

Oxygen is here E and H remain in the same positions, this double bond moves here, and you get a positive charge here. So, this is clearly possible and now, this is a very nice situation where you

have a lone pair on oxygen, which can move in here and it is going to give you a nice and stable oxocarbenium ion shown here. And so, if I look at the structures, I end up with three of these structures, here are the 3 resonance forms for this, and subsequently it can lose a proton to give you the product. Now, if we do the same chemistry in the other position.

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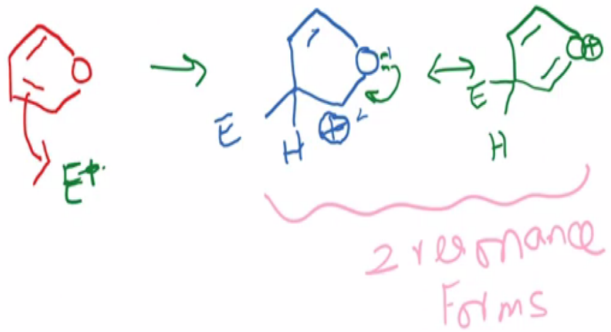

Now, if we see here, the structure as shown here will first react with E^+ and it is going to give you a compound that looks like this. So, keep in mind that this is 1, this is 2 and on the third position you have the electrophile attacking and you end up with a positive charge here. So, if we were to check this out, there can be a beautiful resonance form that can be produced here and you end up with, again, a very fairly stable oxocarbenium ion as shown here.

So, this is also fairly stable. However, if you look at the number of resonance forms here you have 2 resonance forms. And if you recall from the previous case, it actually had 3 resonance forms.

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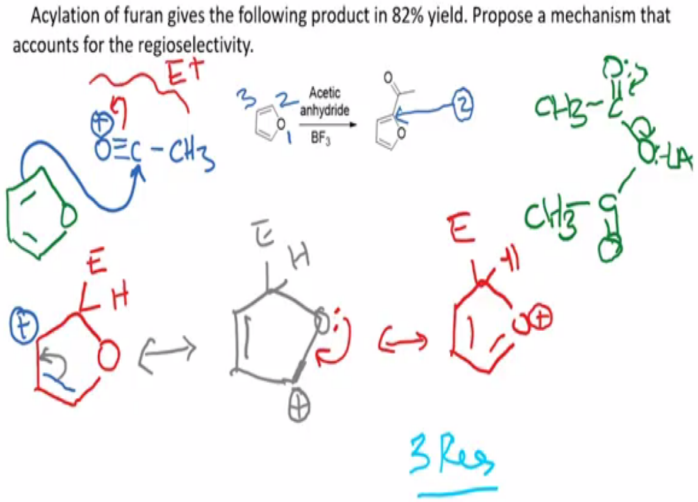

And so, therefore, having 3 resonance forms, as shown here is going to be far more preferred when compared to the situation where you have 2 resonance forms. So, which is how we can account for the high yield of this product, and regioselectivity.

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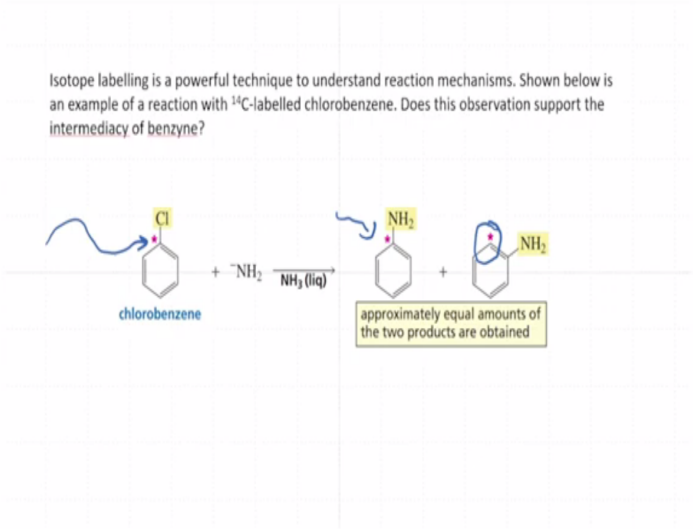

So, Isotope Labeling is a powerful technique to understand reaction mechanisms. So shown below is an example of a reaction with ^{14}C-labeled chlorobenzene. So, the question here is that,

does this observation support the formation of the benzyne? So let us look at the question a little bit in more detail. So here is chlorobenzene and if you see here, this position is labeled with carbon-14.

So, it is a very convenient way to track the presence of, or where that carbon is, or how that carbon continues to be connected in the product. So, for example, if it was a direct substitution, if we replace chlorine with NH_2, then this would be the exclusive product that is formed. But according to the observation, you have a 1:1 mixture that is almost 1 to 1 mixture of the carbon-14 label being here versus being here, which is right next to the NH_2. So, now how do we understand this or how do we explain this observation?

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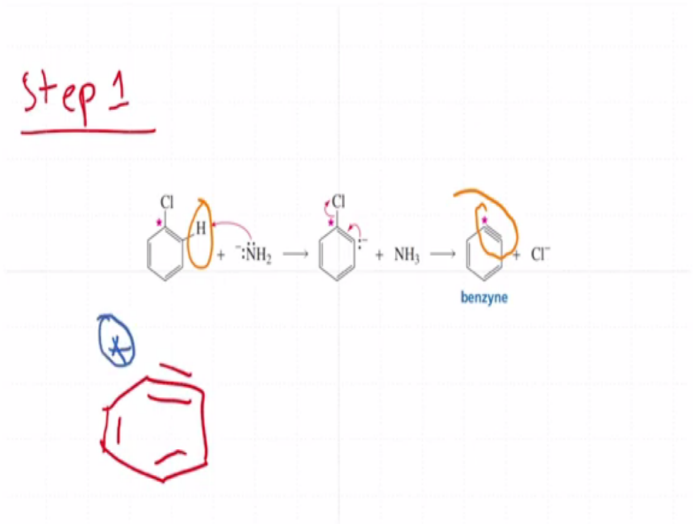

So, if you go back and look at the mechanism of the benzyne formation, what we would expect is that the first step would involve the deprotonation of the carbon next to the chlorine. And so, this is going to be pulled out. And once it is pulled out, you are going to get this carbanion, which is going to rearrange and give you the benzyne. Now, if you keep track of the label, the label starts at this position where it is on the carbon right next to the chlorine, and then subsequently, it ends up on the benzyne. So, I am just going to redraw this here. So, what we are suggesting is that the label is actually on this carbon.

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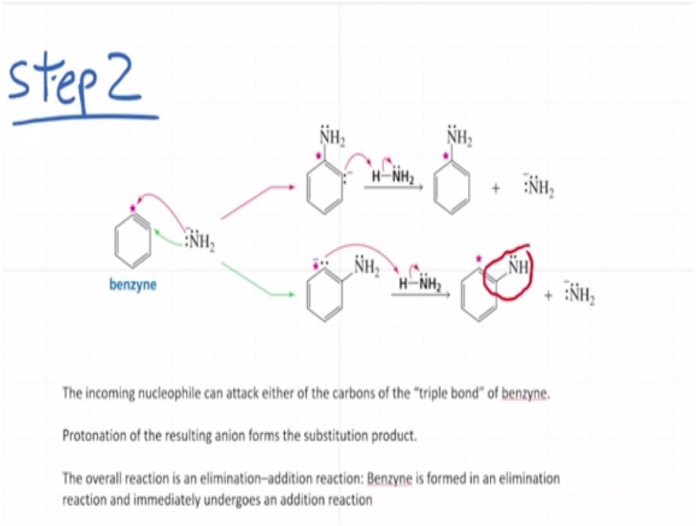

So now, in the next step, which we are all quite familiar with, the amide attacks the benzyne. So, as you can see, here, the incoming nucleophile can attack on either of the carbons of the triple bond. So, in the red case, where NH_2^- attacks on the carbon with the label, then the amine ends up attached to the carbon with the label. But in the green case, where the amide can attack on the other carbon of benzyne, so that is this carbon, then it is possible that the NH_2 will end up on the carbon which does not have the ^{14}C label.

So, as we know this is the overall reaction is an elimination addition reaction. And since there is no particular preference for the attack of one carbon over the other, what we see here is about a 50- 50 mixture of the two products. That means both these attacks are equally likely. And therefore, you see a 1:1 ratio of the products. So, the carbon-14 labeling study, therefore, is very useful in deciphering the mechanism and it suggests that the benzyne could be a possible intermediate in this reaction.

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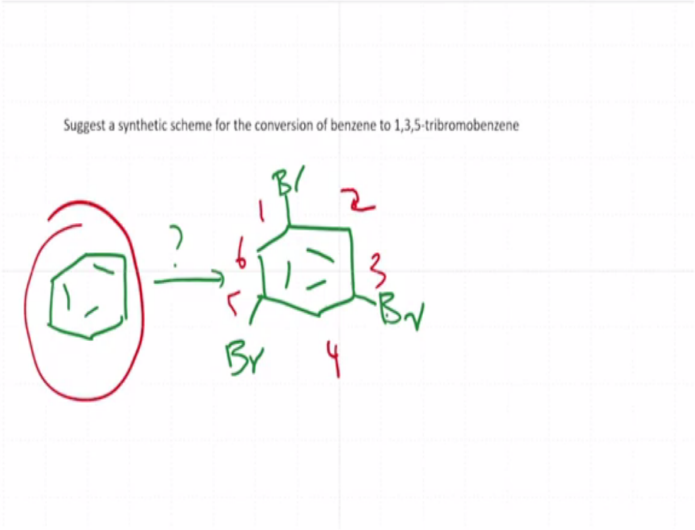

Suggests a synthetic scheme for the conversion of benzene to 1, 3, 5-tribromobenzene. So here is the reaction that we want to do, we want to convert benzene to 1, 3, 5. So if you number this 1, 2, 3, 4, 5, and 6, so, you want to prepare 1, 3, 5-tribromobenzene.

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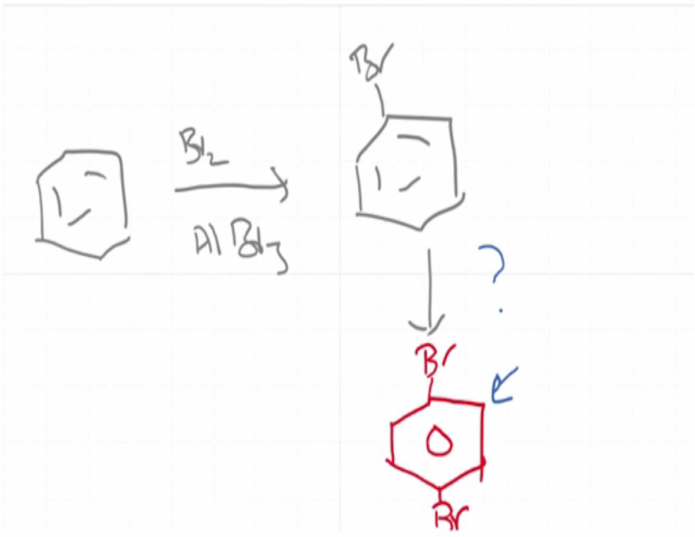

So let us now just look at straightforward bromination to begin with. So, if I start with benzene, and I use bromine and aluminum bromide, or $FeBr_3$, then I get bromobenzene, and now under

maybe heating conditions or under extreme conditions, let me do another bromination. And what is going to happen is we know that bromine is ortho para directing. So, at best you might get 1, 4-dibromo or maybe 1, 2-dibromo benzene. So, in this, using this methodology, we will not be able to get the 1, 3, 5-substituted benzene ring.

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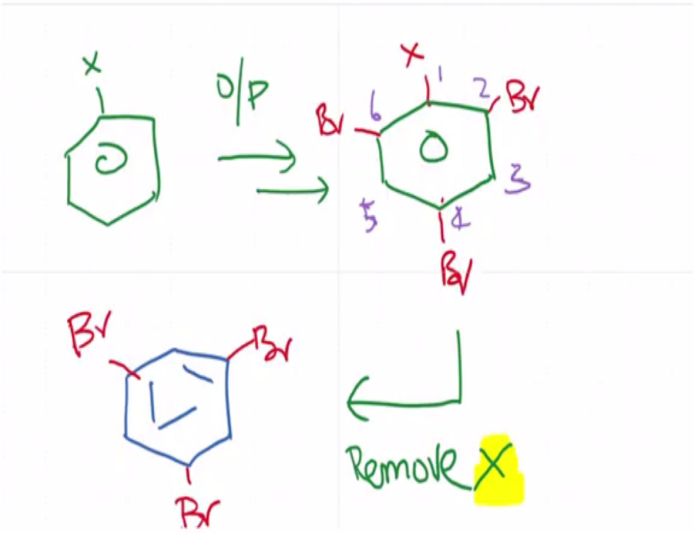

So, in order to get 1, 3, 5 one strategy that we could adopt is that if you could start with a substituted benzene compound, which we have to prepare from benzene itself. And then if that is actually ortho para directing, and if it is highly activating, then it is possible that you can prepare 1, 3, 5-tribromobenzene.

In this case it will be 2, 4, 6 after you remove the X, you are going to get 1, 3, 5. So, this numbering is just for our own convenience here. So, if you remove X here, then you get 1, 3, 5-tribromobenzene. So, therefore, this might actually be a better strategy for us to adopt if you want to convert benzene to 1, 3, 5-tribromobenzene.

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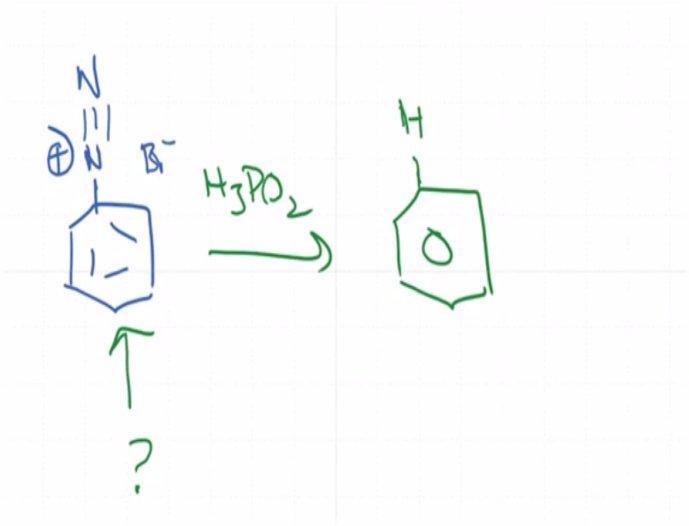

Now, we have looked at diazonium salts in our class, and diazonium salts are a very good sort of substrate for us to prepare benzene. So, if you prepare a diazonium salt, and if we react it with H_3PO_2 the product that you get is benzene. So, if we can somehow convert, therefore, this might be a good sort of protective group, or it can be a group X that can be used for conversion of X to hydrogen. So now how do we prepare diazonium salts, we prepare it from the amine.

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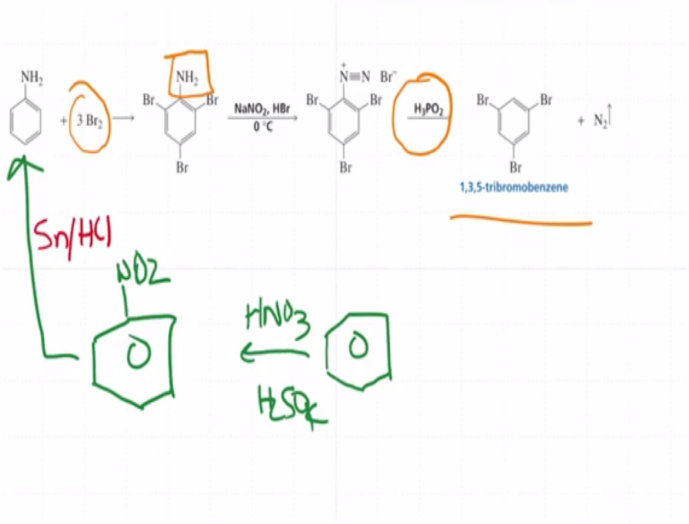

So, the strategy that we can propose is that we start with aniline. Or we can think about going from aniline. If you add bromine to aniline, we have already looked in class that you get 1, 3, 5 or 2, 4, 6-tribromo aniline. Now if you are able to diazotize and produce the diazonium salt, which can then be reacted with H_3PO_2 then the product that you would get is 1, 3, 5-tribromobenzene and of course the byproduct is nitrogen. Now, how do we convert benzene to aniline, so the way we would do this is to do a nitration on benzene to get nitrobenzene and then do a very simple reduction, which is a Tin (Sn), HCL reduction to get aniline.

So, to summarize, what the key step here is that if we convert aniline to diazonium salt, then the diazonium salt can actually be removed by adding H_3PO_2. So, this becomes a very useful way to access various regio chemical outcomes in benzene rings. So, if you in some cases, you may want to get the meta product or in some cases you want to get the ortho, para product etc. So, those can be sort of achieved by manipulating the kind of group that is being involved.

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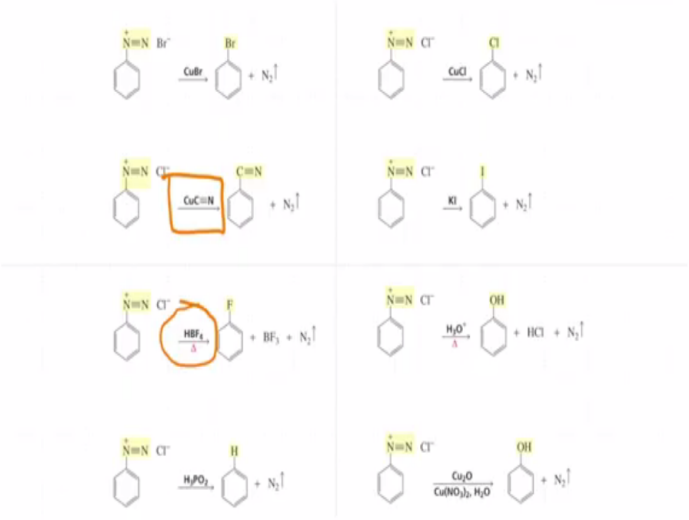

To summarize the various reactions that diazonium salts can undergo. So, if you start with the benzene diazonium salt as shown here, if we react it with the CuBr, then you get bromobenzene and nitrogen. Similarly, if you react it with copper chloride, then you get the chlorobenzene salt. and similarly with the Iodide. Now, if you react this with copper cyanide, you can actually form a

carbon-carbon bond which is very, very important in many reactions that we want to do. And so, this becomes an excellent method for us to make a carbon-carbon bond.

You can also convert it to fluoride by reacting it with the HBF_4 which is basically BF_4^- and H^+ and that is going to give you BF_3 and nitrogen as byproducts. You can also convert a diazonium salt to phenol by reacting it with aqueous acid and just know we discussed this, you can react a diazonium salt with H_3PO_2 and that nitrogen is replaced by a hydrogen. And another method to produce phenol is to react it with Cu_2O in the presence of copper nitrate. So, this is the kind of variety of reactions that diazonium salts can carry out and this becomes very useful in many of our organic synthetic procedures.

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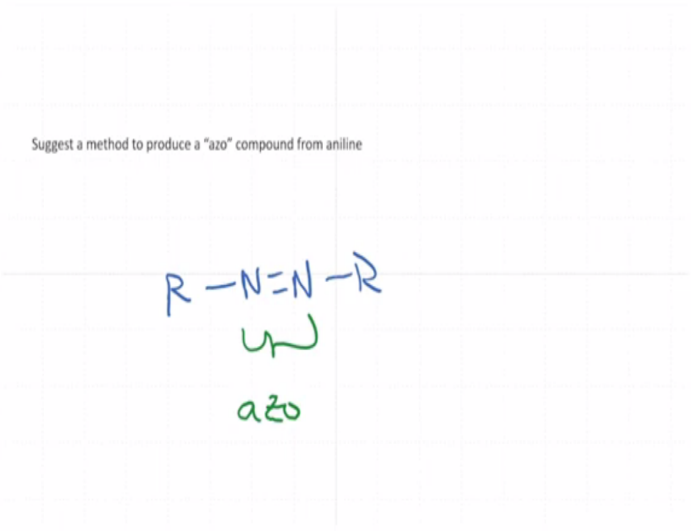

Suggest a method to produce an azo compound from aniline. So, the way we would want to, first of all let us look at what an azo compound is? So, an azo component is basically a nitrogen double bonded with nitrogen with 2 alkyl or aryl groups flanking it.

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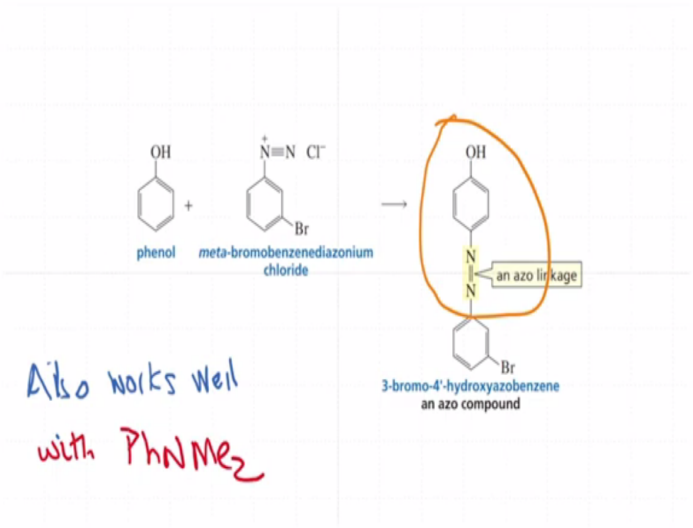

So, one of the methods by which you can produce azo linkage is to use diazonium salts. So, if we react phenol with this meta-bromo benzene diazonium chloride, then the product that you get is a diazo compound. So, clearly the nitrogen triple bond nitrogen here is involved in the reaction not in the way that we are used to, but in a very different way. So, this kind of reaction also works well with electron donating groups or electron rich benzene rings such as phenol and dimethyl aniline and so on.

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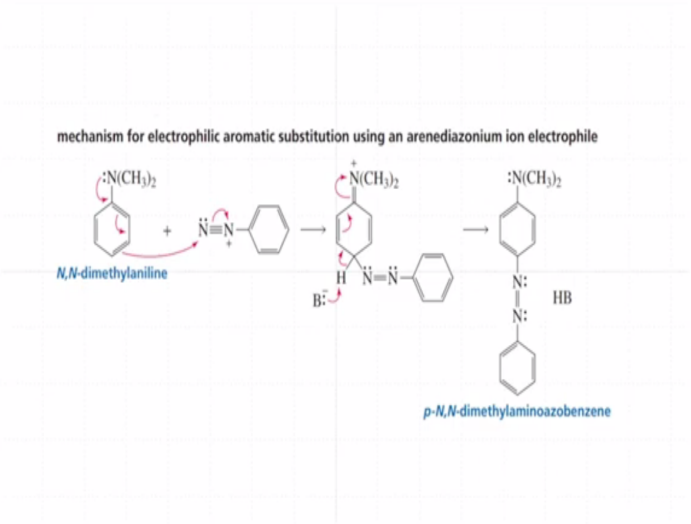

So, if we look at the mechanism with dimethyl aniline. So, what in essence happens is that your lone pair on the nitrogen can sort of move into the benzene ring and, and the benzene ring electrons can attack the diazonium salt. So, once this attack happens, then you get this diazo compound and then loss of the proton and the benzene ring is going to give you N, N-dimethylaminoazobenzene. So, these diazo compounds are actually highly colored and they become a very useful way for us to prepare dyes. A lot of dyes have diazo compounds.

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Predict the products of the following reaction, in what ratio will they be formed. So, here is another example of labeling experiment. So, we start with this chlorobenzene which is C-14 labeled and react it with sodium hydroxide water at 395 degrees centigrade. So, to put this temperature in context, the boiling point of water is 100 degrees centigrade. And we are clearly maintaining a temperature which is extraordinarily high. And so therefore, these are extreme conditions. So, we have already discussed this under extreme conditions, it is possible that nucleophilic aromatic substitution or benzyne kind of mechanism is possible.

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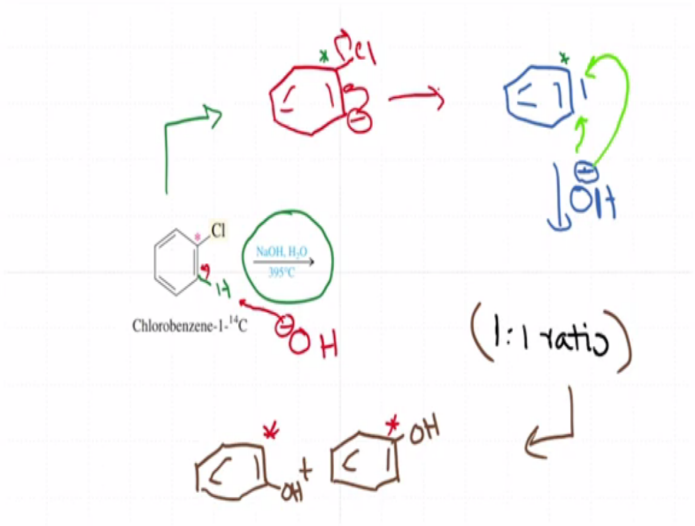

So, here this is not a substrate for nucleophilic aromatic substitution. So, therefore, you can expect that a benzyne type mechanism would occur. So, again keeping track of the carbon label, hydroxide can attack at one of the ortho positions, produce this carbon ion which can then kick out chloride and you get benzyne. And as we discussed earlier, this benzyne there is no particular preference for attack or for reaction with one carbon or the other and therefore, you would expect to get a 1:1 ratio of the two products. So, please keep track of the label when you are trying to solve these types of questions.

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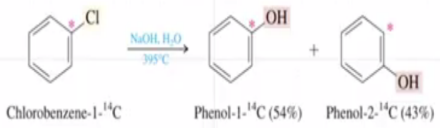

So, when you do the experiment, you get an almost 1:1 ratio, which is 54 percent of this product and 43 percent of the other product. Again, this is an example of using labeling to study the mechanism and it helps us understand the mechanism better and it also helps us to reason out what kind of intermediates are produced.