Introductory Organic Chemistry - II
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Lecture 14
Nucleophilic Aromatic Substitution Part 2

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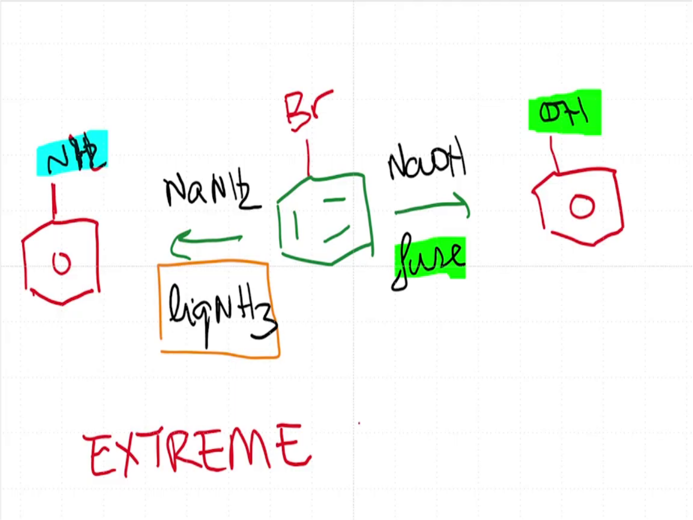

So, we discussed that nucleophilic substitution on a benzene ring is highly unlikely under the normal conditions under which we use. This reaction can however occur under fairly drastic conditions. So, when you take bromobenzene and react it with the sodium hydroxide, fuse, this means you heat it up to very high temperatures, the product that you form is phenol.

Similarly, when you take bromobenzene and react it with sodium amide in liquid ammonia the product here is aniline. So, this reaction can occur, but you need extreme reaction conditions for it to happen. And not only that the reaction mechanism is also very interesting.

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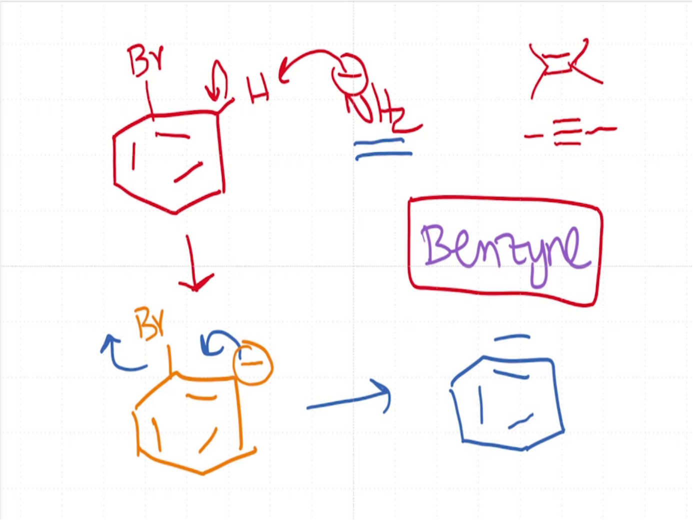

So, the proposed mechanism, the first step involves the reaction of NH_2^-, it picks up a proton and leaves behind a carbanion. And this carbanion can actually undergo a rearrangement in the following manner and produce the corresponding alkyne which is known as benzyne. So, this benzyne is the alkyne equivalent of benzene. So, as you know an olefin is usually referred to as an alkene. And when you have a triple bond, this is referred to as an alkyne. So, similarly, this is benzyne. So, benzyne intermediate is very interesting.

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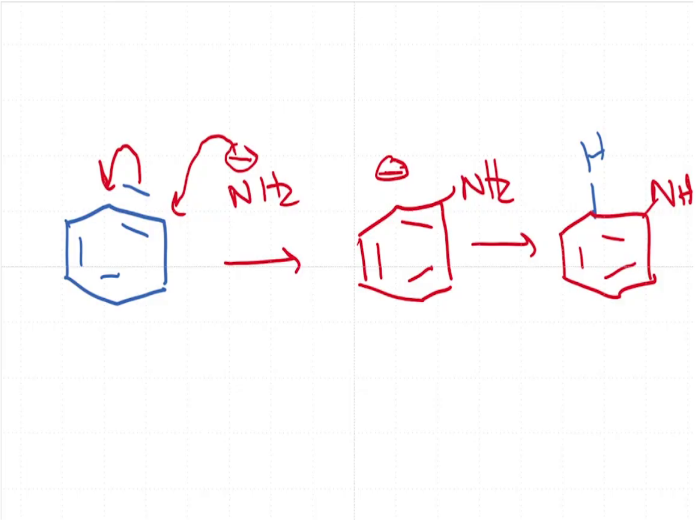

And so, this benzyne can then further react with NH_2^- and it produces the carbanion once again. And keep in mind that these are fairly extreme conditions under which this reaction can occur. And this eventually picks up a proton and gives you the final product. So, you can convert bromobenzene to aniline using sodium amide and liquid ammonia. Now, if you want to understand the structure of these benzyne compounds, what we need to see first is, let us examine the first carbanion that is produced.

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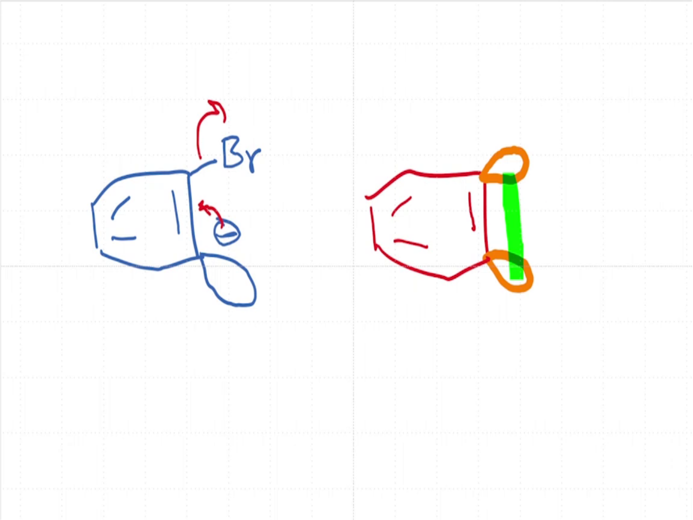

So, when you look at the structure of the first carbanion that is produced, I am going to redraw the intermediate in the following manner. So, this is the SP^2 orbital. And now when this SP^2 orbital sort of moves in here and kicks out bromide the product that is formed actually has an unconventional pi bond.

So, you already have a pi bond over here and this new pi bond is formed in the following manner. So, you have this SP^2 orbital and this SP^2 orbital and they actually overlap and give you the triple bond. So, it is not like a conventional pi bond that is formed, but it is more likely a double bond that is formed with SP^2 orbitals being overlapping with one another.

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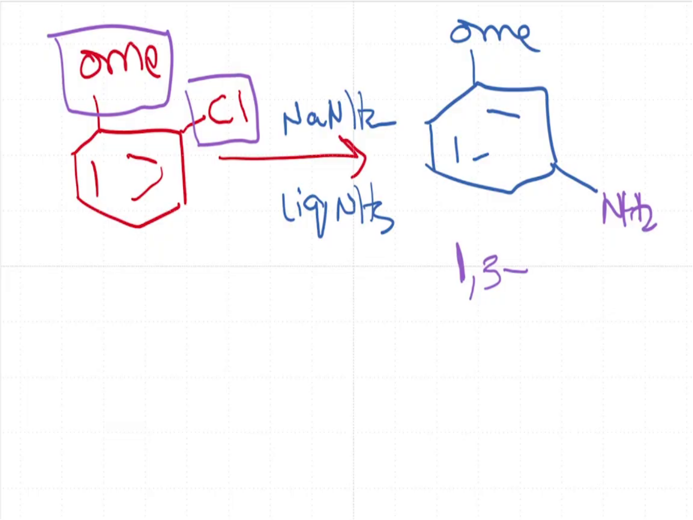

Now, the interesting question is that when you have substituted compounds, what would be the outcome. So, when you start with let us say methoxybenzene, which is basically anisole with the chloro in the 2-position. The product that is formed is actually the OMe. And what we are doing is, we are doing $NaNH_2$ in liquid ammonia and the product that is formed is the following molecule, which is 1,3- substituted product.

So, here you start with the methoxy at 1-position and chloro at the 2-position, but you end up with methoxy at 1-position and amino group at the 3-position. So, this is another piece of evidence that suggests that benzyne mechanism is actually in play. There are other pieces of evidence which are available for the formation of the benzyne.

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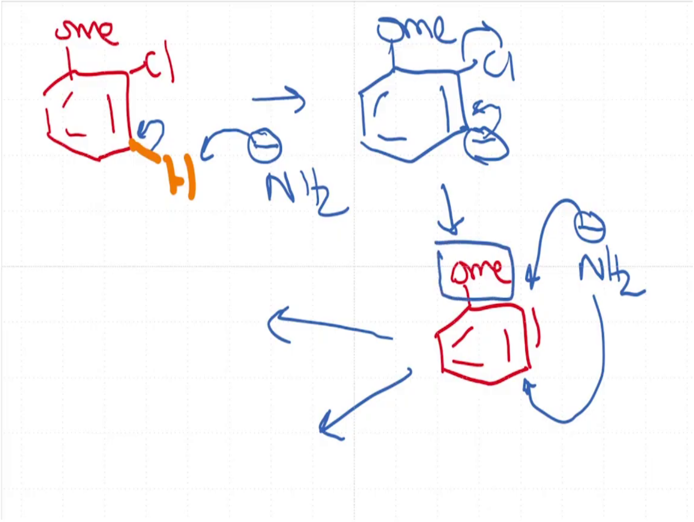

Now, let us look at the proposed mechanism for this reaction. So, the first step as we have already seen would be the, so let us keep methoxy at the 1-position, choro is at the 2-position. The first step would be the loss of this hydrogen to NH_2^- and the formation of the carbanionic intermediate. Now, the next step would be the loss of the chloride to give you the potentially key intermediate, which would be the benzyne.

Now, you have two possibilities for attack. So, this is the key intermediate. Now there are two possibilities NH_2^- can attack from this side or it can attack from here. So, this is going to give us possibly two products, wherein you have a 1,2 attack or a 1,3 attack that is with respect to the methoxy group, the attack happens either at the 2-position or at the 3-position. Now, let me just draw this intermediate once again in the next page, so that we can look at it more closely.

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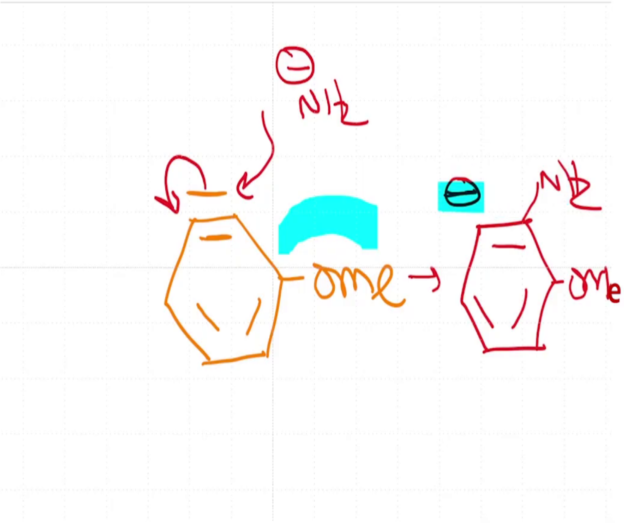

So, OMe is here, double bond is here, and here is the triple bond. So now, let us look at both the intermediates that are formed. So, NH_2^- attacks here, and the negative charge moves over here, let me just draw that out, OMe, NH_2 is here, and this negative charge is here. So, the rest of the molecule remain intact.

So, in this structure, there are a couple of issues. So, one is that there is going to be some possibility of steric hindrance in the attack because of the methyl group, so the 2-position may not be very favoured. The second issue is that the negative charge is quite far away from the methoxy group. That is, it is meta to the methoxy group. And therefore, the methoxy group does not have an electron-withdrawing inductive effect to stabilize the negative charge.

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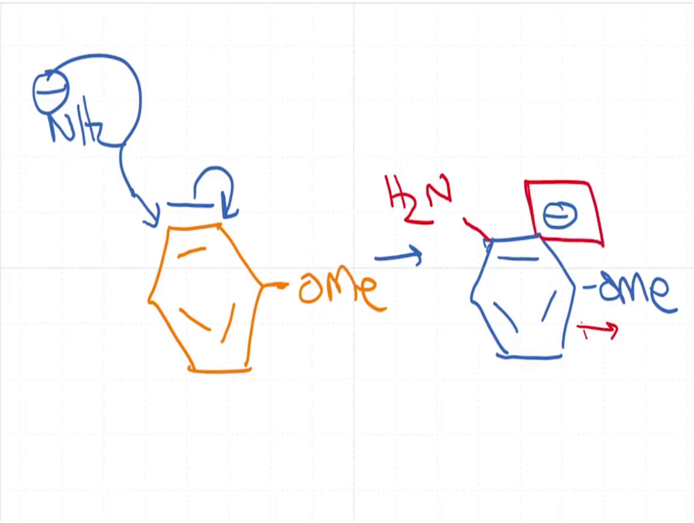

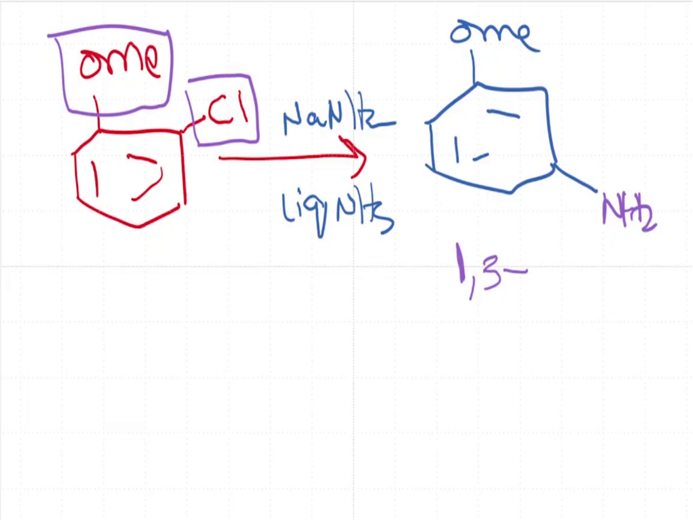

On the other hand, if the attack happens on the other carbon, so which I am going to draw again here. So, the attack happens at the 3-position, which results in the formation of the carbanion adjacent to the methoxy group. Now, we have at least solved one problem, which is of sterics. So, the methoxy group is quite far away from this position. So therefore, the attack does not necessarily have a steric hindrance.

And also, the electron-withdrawing nature of the methoxy group by induction plays a key role in stabilizing this negative charge. So, taking these two into consideration, we can help rationalize the result that we got were in the NH_2 group is actually meta to the methoxy group in the product.

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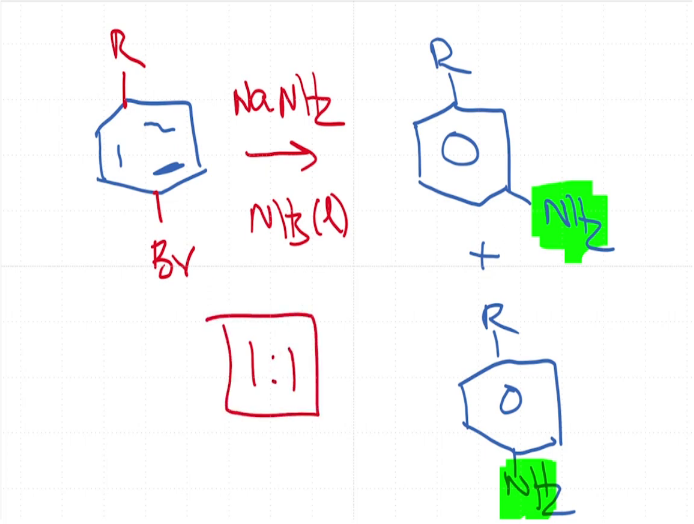

Now, let us consider another situation, where we start with, the substitution occurs in a 1,4-system. So, you have let us say R here and you have Br over here. Now, when you react it with $NaNH_2$ in ammonia, the product that you get is a 1:1 mixture of these two compounds. So, that is the 3-position, as well as the 4-position, are going to give you approximately 50 percent yield; 1:1 is the product ratio.

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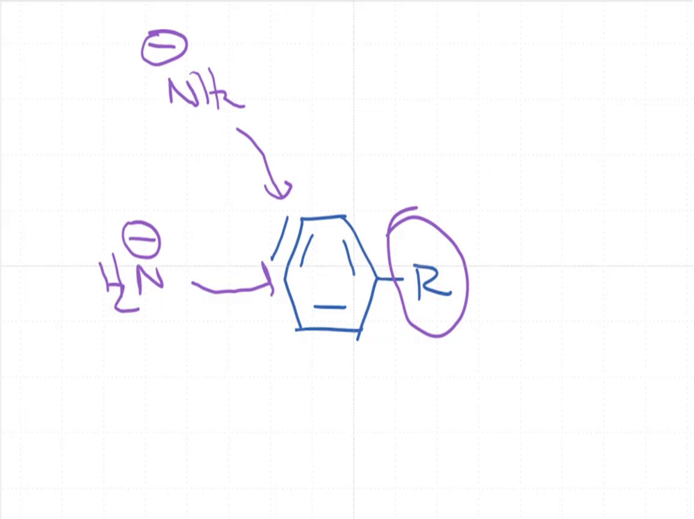

So, this is relatively easier for us to explain because if you think about it, even if you draw the intermediates, you have the benzene ring here. And now, the attack can happen from here or from here, so NH_2^- can attack here or it can attack here. So, neither of these attacks are going to be sterically hindered. So, they both are quite far away. And as we discussed, the major effect is the inductive effect of the electron-withdrawing group and that also is quite far away for these two. So, therefore, the probability of attack on this is more likely equal, and therefore, you get a 50:50 mixture of the products.

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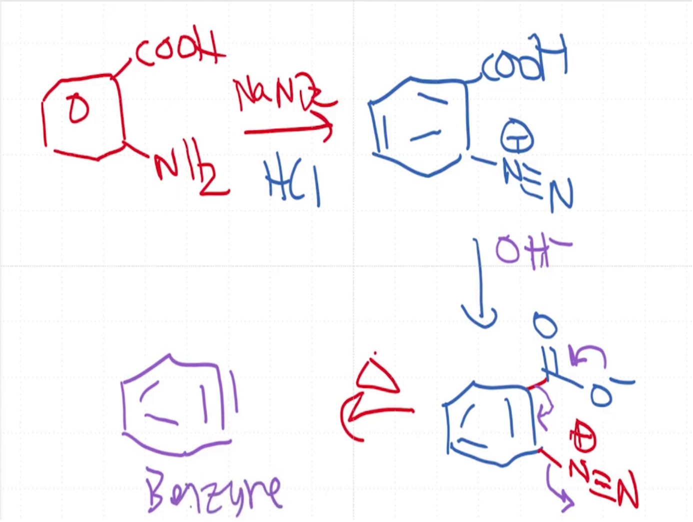

Now, lastly, we want to look at the reaction of one more piece of evidence for the formation of benzyne. So, when we start with COOH and NH_2 and do diazotization reaction on this. So, when you do $NaNO_2$ and HCl, you can produce the diazonium salt here $N\equiv N^+$, COO^-. So, if you generate this under the appropriate conditions, then what you could do is that you could then add base, OH^-.

And what it does is, it converts this carboxylic acid to the COO^-. So, you have the formation of COO^- and $N\equiv N^+$. So, now, when you heat this up to high temperatures, what can happen is that you have a loss of carbon dioxide. So, you can have a loss of CO_2 and this subsequently can move here and kick out nitrogen gas. So, the intermediate that is formed is the benzyne. So, this is a very nice way to produce benzyne. And obviously, the benzyne is not very stable.

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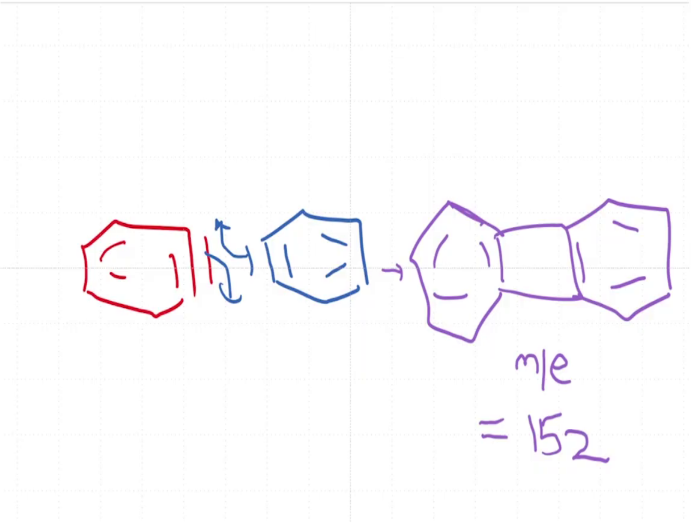

So, when you generate this benzyne under these conditions, what you do is you do a cycloaddition reaction. So, the cycloaddition reaction can happen the following manner, you can detect this in the mass spec, the cycloaddition reaction. So, you can do this the following way and the product that you get is two benzene rings fused to one another.

So, the m/e ratio that is the mass to charge ratio is 152 for this, and you do detect this in the mass spec. So, what this experiment tells you is that, the benzyne is likely an intermediate that is formed. You can also trap this benzyne using other cycloaddition reactions and it is routinely used in synthesis. So, together the formation of benzyne is a very important sort of synthetic route that helps us substitute benzene rings albeit under extreme conditions.