Introductory Organic Chemistry - II
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Lecture 16
Tutorial - 2 Part- 01

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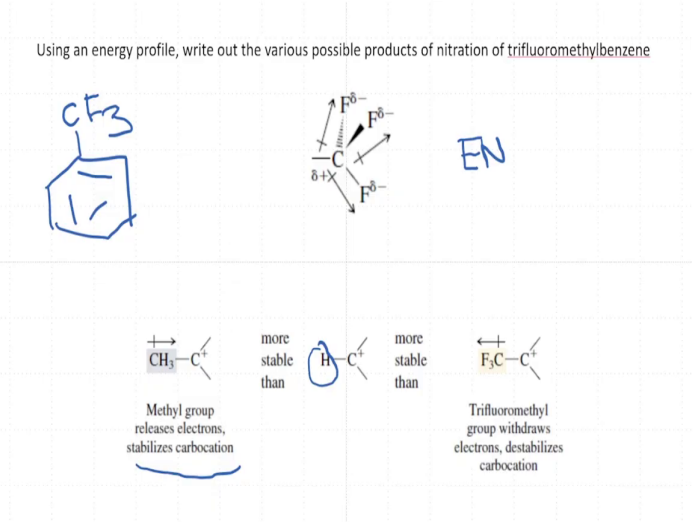

Using an energy profile, write out the various products of nitration of trifluoromethyl benzene. So, trifluoromethyl benzene has a trifluoromethyl group. So, we see here that fluorine is highly electronegative, so it is going to pull electrons through induction. And so, any group that is attached to a CF_3 group is going to be electron deficient.

So, the example that we can look at is that if I compare a regular secondary carbocation such as this, and if instead of hydrogen, I put in a CH_3 group, the CH_3 group is electron-donating, and this stabilizes the carbocation substantially in the form of donating electrons and delocalizing the positive charge. Whereas, the trifluoromethyl group withdraws electrons and destabilizes the carbocation.

So therefore, the trifluoromethyl group is considered as a fairly strong electron-withdrawing group. Now, when it comes to nitration of trifluoromethyl benzene, what we are talking about is if I take this compound and expose this to the standard nitration conditions, what are the possible products.

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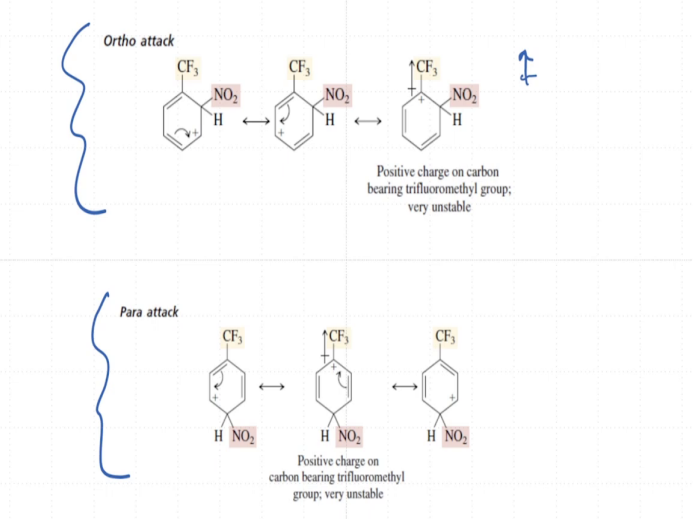

Now, let us consider the first situation which is the ortho-substituted compound. So, here once the attack happens, there is going to be a positive charge that develops right next to this attacking carbon. And you can delocalize this carbocation by pushing electrons in the following manner. So, there is one structure that you will clearly see here, where the CF_3 group is directly attached to the carbon bearing the positive charge. So, therefore, the ortho attack will lead to a situation where the intermediate is somewhat unstable.

If you consider the para-attack, similarly, when the nitro groups react with this carbon, there is going to be a positive charge that is immediately developing here, which can then delocalize and go into this resonance form, wherein the CF_3 is directly attached to the positive charge. So, this again leads to a less unstable or less stable situation. So, both ortho and para-attack is going to give you a very unstable intermediate.

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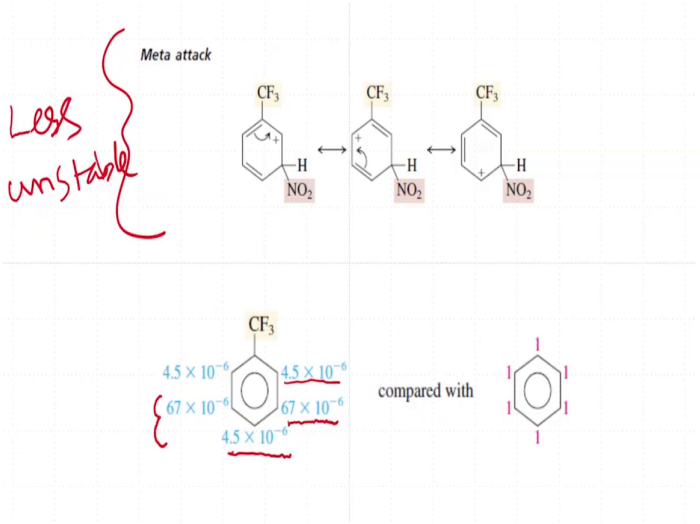

Now, when you consider the meta-attack, you will find that the ortho position, I mean right next to it, is a positive charge. Once you delocalize it, you are going to get a positive charge over here. And now, when the next delocalization can happen, and where there is a positive charge here. So, in none of these resonance forms, the CF_3 is directly next to the positive charge.

Therefore, this structure is less unstable compared to the other two structures. Now, if I calculate, if I try and understand the rates at which these are going to react. When compared to benzene, assuming that the relative rate is 1, the ortho position reacts at a rate of 4.5×10^{-6}

So, that is about a million-fold slower. The meta position is going to react about 10-fold faster than the ortho position, and the para position is going to react at the same rate as the ortho position. So therefore, it is not like the meta position is highly stable, it is just that the substitution at meta is a little bit faster than that of ortho and para and therefore, the meta product dominates.

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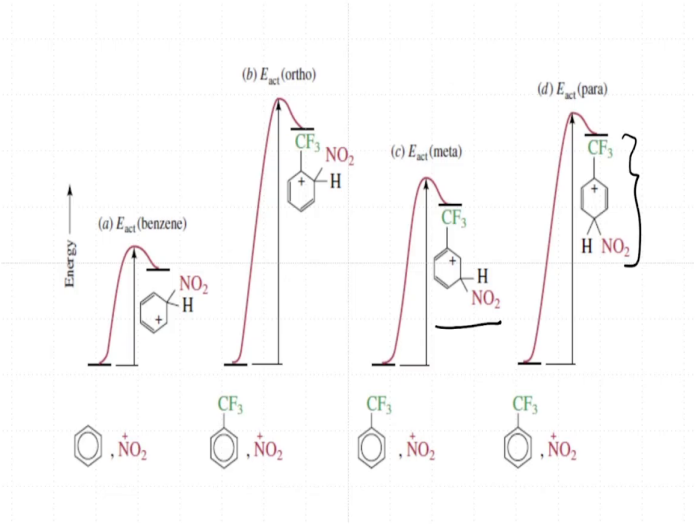

Now, coming to the energy profile. So, if we consider a regular benzene ring to form the nitration of the benzene ring, so we already know that this is the activation energy and this is going to be the complex that is formed. Now, when we consider the CF_3 group, electrophile is Nitro. When it attacks at the ortho position, there is going to be a positive charge right next to the CF_3.

And this is going to contribute to the lack of stability of this and therefore, with respect to benzene, one can imagine that this energy is going to be higher. Similarly, in the para, we already discussed that one of the resonance forms has a positive charge next to the CF_3 and therefore, this also is going to be quite unstable. Lastly, when we consider the meta, the meta intermediate is somewhat more stable when compared to the ortho and para. And therefore, the barrier to cross the meta is lower than that of ortho and para.

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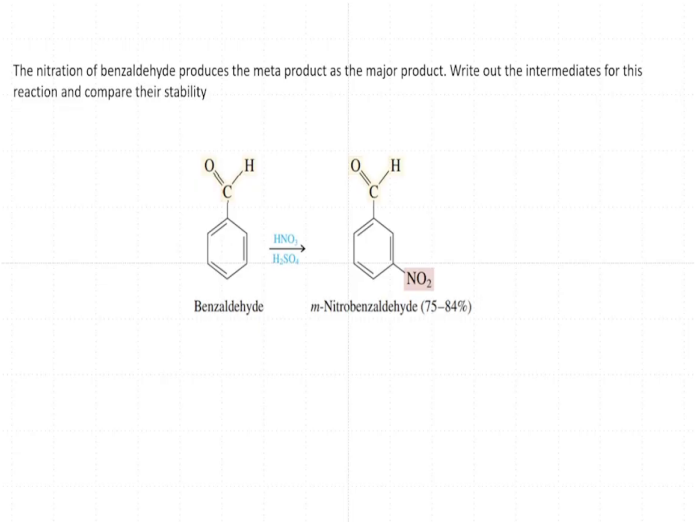

The nitration of benzaldehyde produces the meta product as the major product. Write out the intermediates for this reaction and compare their stability. So, here in this question, benzaldehyde is reacted with HNO_3, H_2SO_4 and the meta-nitro product is the major product.

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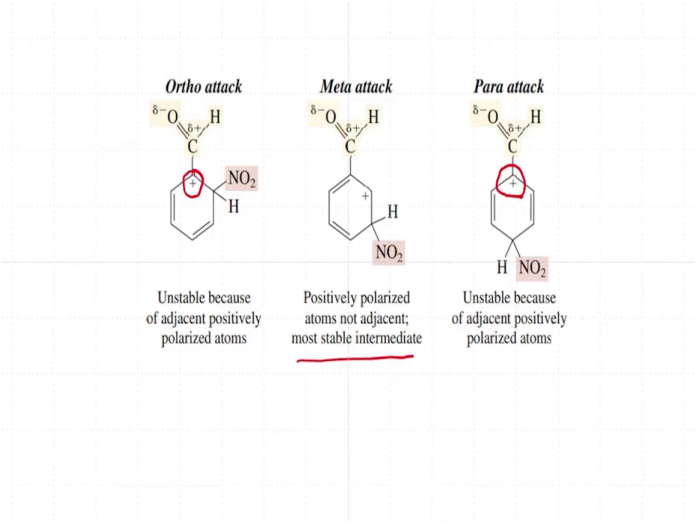

So, we already know that the aldehyde is going to be electron-withdrawing. And so, when we look at the three intermediates that are possible for ortho, meta, and para, just like the trifluoromethyl example or the other previous examples that we have taken, we need to consider the resonance form, where if there is a positive charge right next to the electron-donating or electron-withdrawing group that is going to be more important. So,

clearly, this positive charge here right next to the aldehyde is going to be unstable. And therefore, the ortho attack is not favoured.

Similarly, when you look at the para-nitro substituent, the positive charge again right next to the aldehyde and therefore, this intermediate also is less stable. However, in the meta-attack, the positive charge does not have an opportunity to interact directly with the carbonyl carbon and therefore, it becomes the more stable intermediate.

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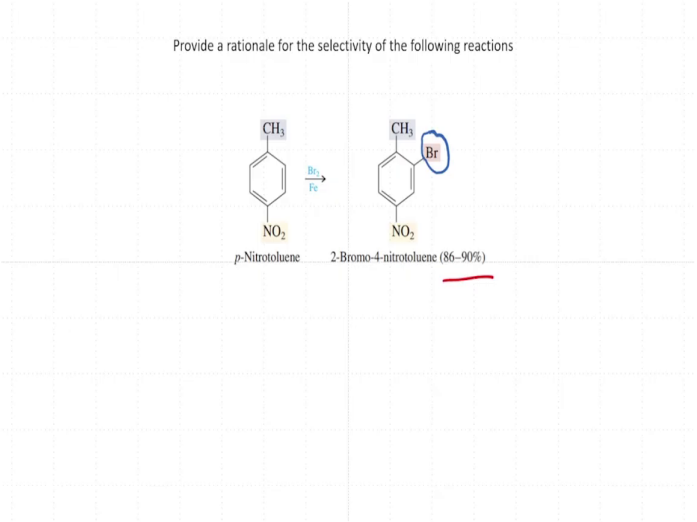

Provide a rationale for the selectivity of the following reactions. The first example here is the bromination of 4-Nitrotoluene. And it gives this product exclusively in about 86 to 90 percent yield. In order to address this problem, the strategy that we would adopt is to find out what kind of groups are ortho, para directing and what are meta directing.

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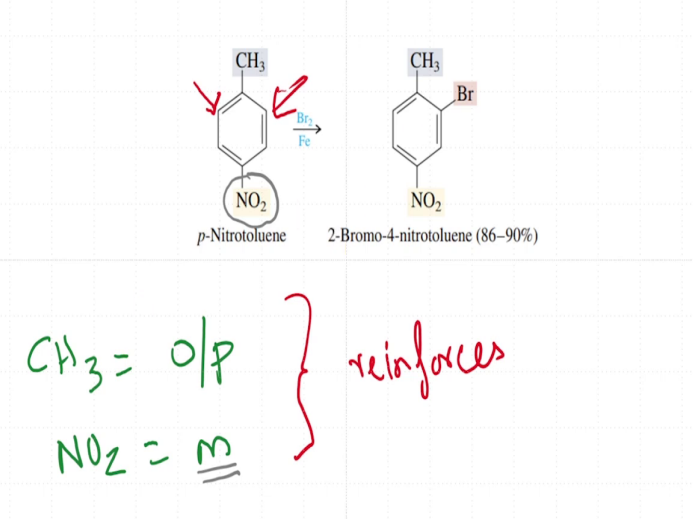

So, to begin with, let us look at the methyl group. The methyl group is clearly ortho, para directing and therefore, the two red arrows as shown here are going to be the preferred positions for attack. The nitro group on the other hand is going to be meta directing and also it is going to be directing the bromination at the positions as shown by the arrow.

Now, given that the methyl group is an electron-donating group and its effect on the aromatic ring is greater, it is likely that this is going to dominate. But what is important here is that the nitro group does not hinder the attack of bromination because the nitro group is also meta directing. So therefore, in this particular case, if the two groups reinforce each other and the bromination exclusively happens at this position, which is ortho to the methyl group.

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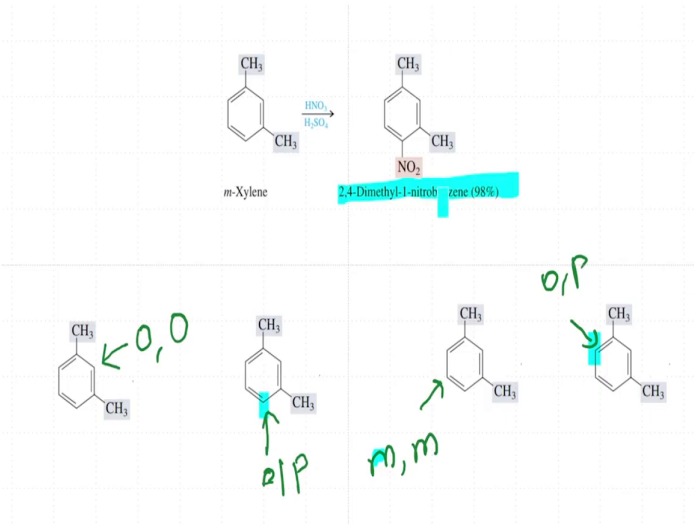

In the next example, we are going to look at m-xylene and where the nitration occurs on m-xylene. So, in the case of m-xylene, it produces this product here that is 2,4-Dimethyl-1-nitrobenzene in 98 percent yield. So, again the approach here that we need to take is to write out the structure and find out what each of those groups, each of those positions here, what is going to be the nature of the directing group, directing ability. So, both methyl groups here are ortho, para directing.

So, if for the first position as shown here, this substitution here would occur if both the methyl groups are ortho-directing. Similarly, if one of them is ortho directing and the other one is para directing, this is going to be preferred. And substitution will happen here if both the groups are meta directing, that is if a substitution happens here it is meta to both the methyl groups. And lastly, this substitution here is going to be ortho to one of the methyl groups and para to the other methyl group.

Notice that this hydrogen here is essentially identical to this hydrogen because they both are ortho as well as para to the methyl group. So, basically, we have three choices here. And one can conclude that the meta directing or the meta substitution is unlikely given that the methyl group is ortho, para directing. And now between these two choices, we would prefer this one here.

And the reason for that is that there is some steric hindrance that happens when you have substituent at the ortho position, that is you have two substituents at the ortho position. And

therefore, the attack on this carbon is unlikely. So, this model helps us explain the excellent yield of 2,4-Dimethyl-1-nitrobenzene in this reaction.

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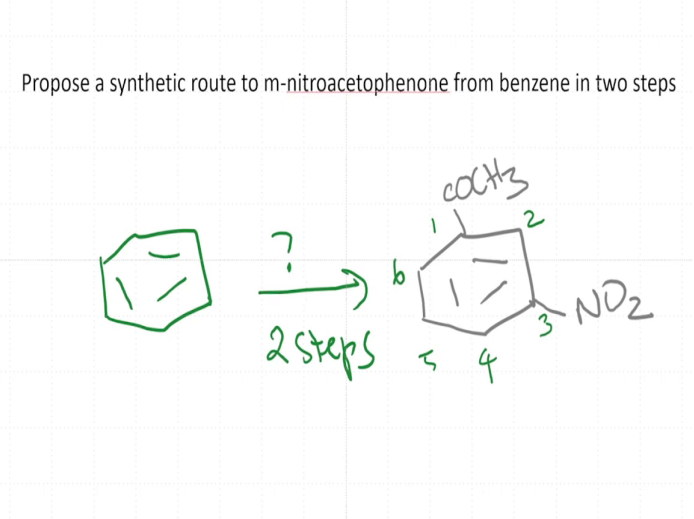

The next problem, we are looking at proposing a synthetic route to m-Nitroacetophenone from benzene in two steps. So, m-Nitroacetophenone is this structure and the nitro group is in the meta position. And how do you make this from nitrobenzene?

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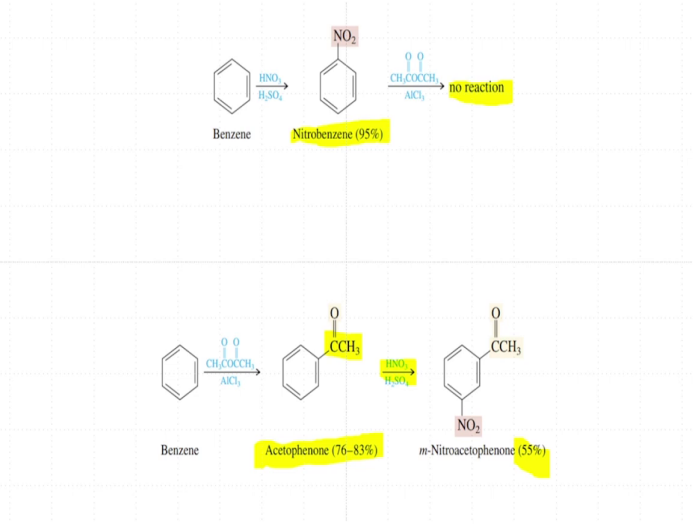

So, we could consider two different routes. The first route that we can take or we could suggest is the nitration of benzene, which will give us nitrobenzene. And this reaction works really well. The next step is a Friedel-Crafts acylation reaction which can be tried with acetic anhydride and aluminium chloride. However, we observed no reaction or we expect that there will be no reaction because the nitro group is highly deactivating. On the other hand, if we

take the other route, that is we first do the Friedel-Crafts acylation and produce acetophenone from benzene, this yield is also pretty okay, which is about 75 to 80 percent.

And then we follow it by nitration. The acetophenone, the acetyl group, although is electron-withdrawing, we have already looked at it, and it is not as strong an electron-withdrawing group as a nitro group. And therefore, this reaction can occur. And although the yield is not that great, it is still something that can move forward and give you the desired product. So, between the two choices, this reaction occurs preferentially, this second scheme is preferred.

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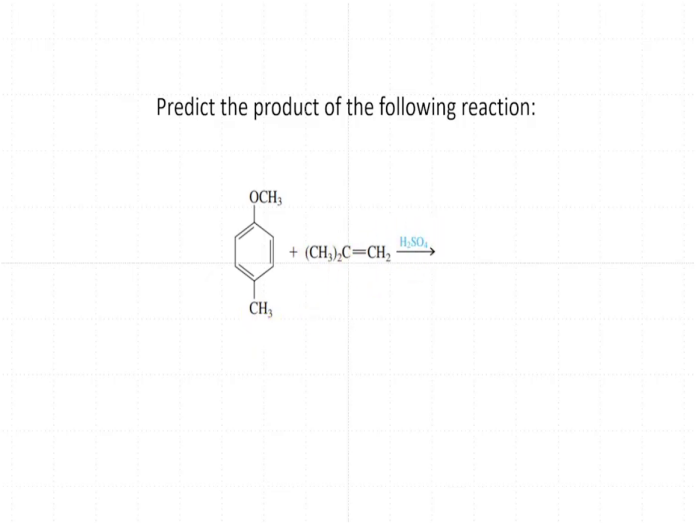

Predict the product of the following reaction. So here, we are dealing with a competition between methoxy group and methyl group and the reaction with this olefin in the presence of H_2SO_4. So, as you would have correctly guessed, they are predicted.

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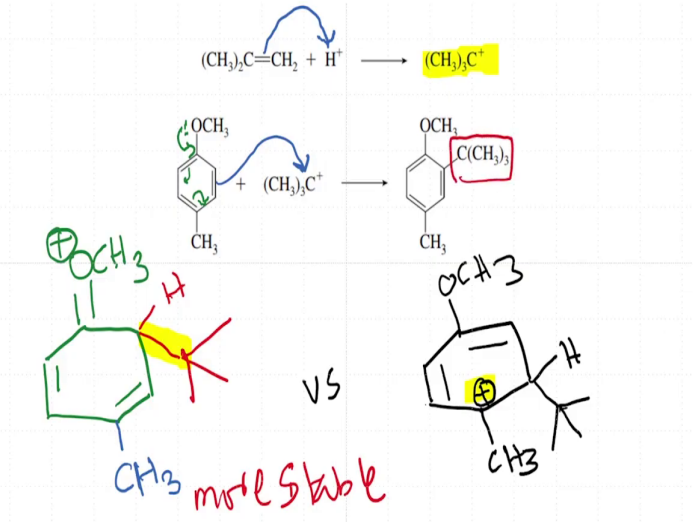

The olefin is going to get protonated and it is going to produce a tertiary carbocation as shown here. Now, you have two choices, this methoxy group you know the electrons from the O oxygen can enter the benzene ring through conjugation. And it can react with tertiary butyl carbocation to give you an intermediate such as this, so there is a new bond that is being formed. And there is going to be a full positive charge on the oxygen. This is one choice.

And the other choice is the reaction of this double bond with the same tertiary butyl carbocation, which results in the formation of this intermediate. Now, if I have to compare the stability between this intermediate and this intermediate, clearly this one is more stable, and you know the involvement of the electronegative or a lone pair from oxygen is very important. And also, the stabilization by this group is far more than the methyl group. So, it is not surprising therefore that this is the exclusive product that is formed under these circumstances.

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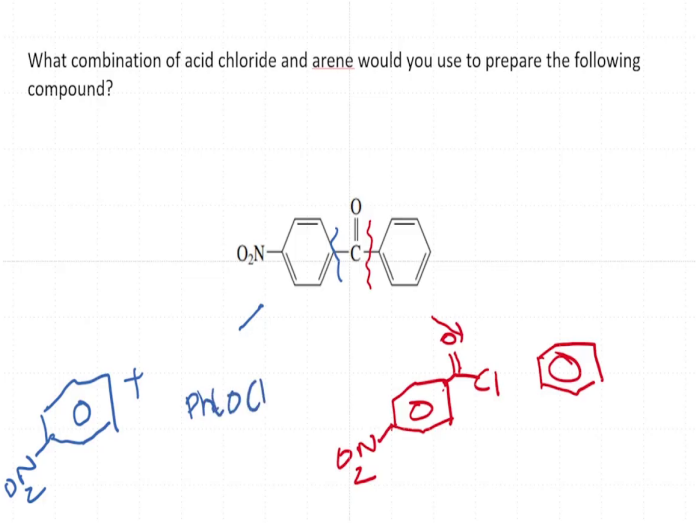

What combination of acid chloride and arene would you use to prepare the following compound? So here is another example of two choices that we could have. So, if I have to do a Friedel Crafts acylation reaction, then I am going to be breaking or I am going to be forming this bond over here. Now, if this is the bond that is going to be formed, then I would have to start with benzene and react it with 4-Nitrobenzoyl chloride.

Now, this is one choice. The second choice is that if we can break the bond as shown here, now this is going to be produced if you start with 4-Nitrobenzene and react it with benzoyl chloride. Now, let us just write out these choices on the next page.

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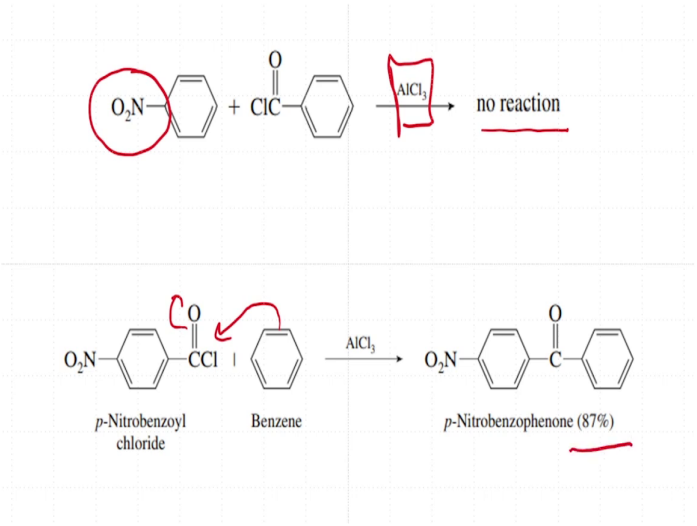

Now, when we react 4-nitrobenzene with benzoyl chloride, nitro is a very strong electron-withdrawing group, and therefore Friedel Crafts acylation reactions do not occur under these conditions. So therefore, there is no reaction that happens.

Whereas in the other scenario, where we start with 4-Nitrobenzoyl Chloride, and react it with benzene, the reacting group is actually benzene over here. And therefore, this reaction occurs without difficulty. And the yield of 4-Nitrobenzophenone is 87 percent.

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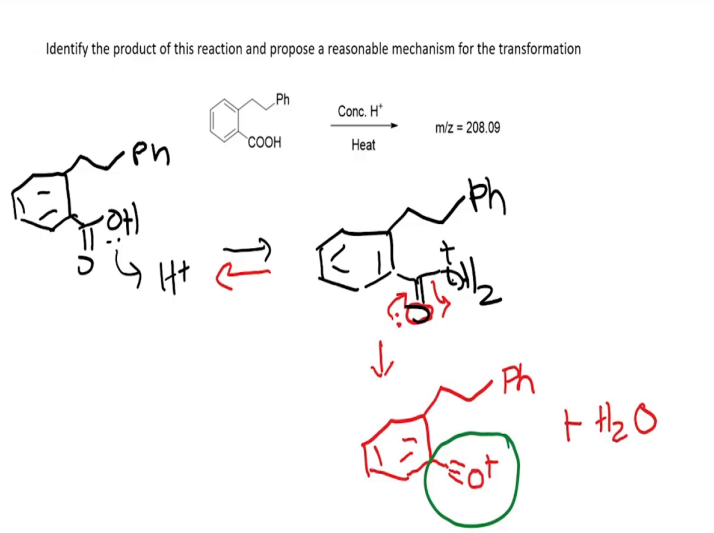

So, the problem here is to identify the product of this reaction and propose a reasonable mechanism for the transformation. So, the way we will approach this problem is to look at the major functional groups in this reaction. So, the major functional group in this reaction is actually the carboxylic acid. So, if we were to draw the structure of the carboxylic acid, and imagine what might happen to it when you heat it. So, one possibility is that they clearly get protonated.

So, you can imagine that this can pick up a proton, and it will give you the corresponding protonated OH_2^+, and the rest of the molecule might remain the same. And this protonation reaction would likely be a reversible reaction. So, it is going to go back and forth, back and forth. But since we have heated the molecule, we are heating up the reaction, it is possible that you can imagine that this lone pair comes in here and kicks out water.

So, the resulting structure that would emerge would be the benzene ring remaining intact. And you get a $C{\equiv}O^+$. And then the phenyl ring remains here and the by-product is water. So

now, depending on how reactive this molecule is, it can sometimes react again with water to give you back the starting material. But, since we are familiar with the Friedel Crafts acylation reaction, you will immediately recognize that this is the acylium ion, which is a key sort of player in the Friedel Crafts acylation reaction. So, I am just going to redraw the structure in a different format, so that it is easier for us to understand the reaction.

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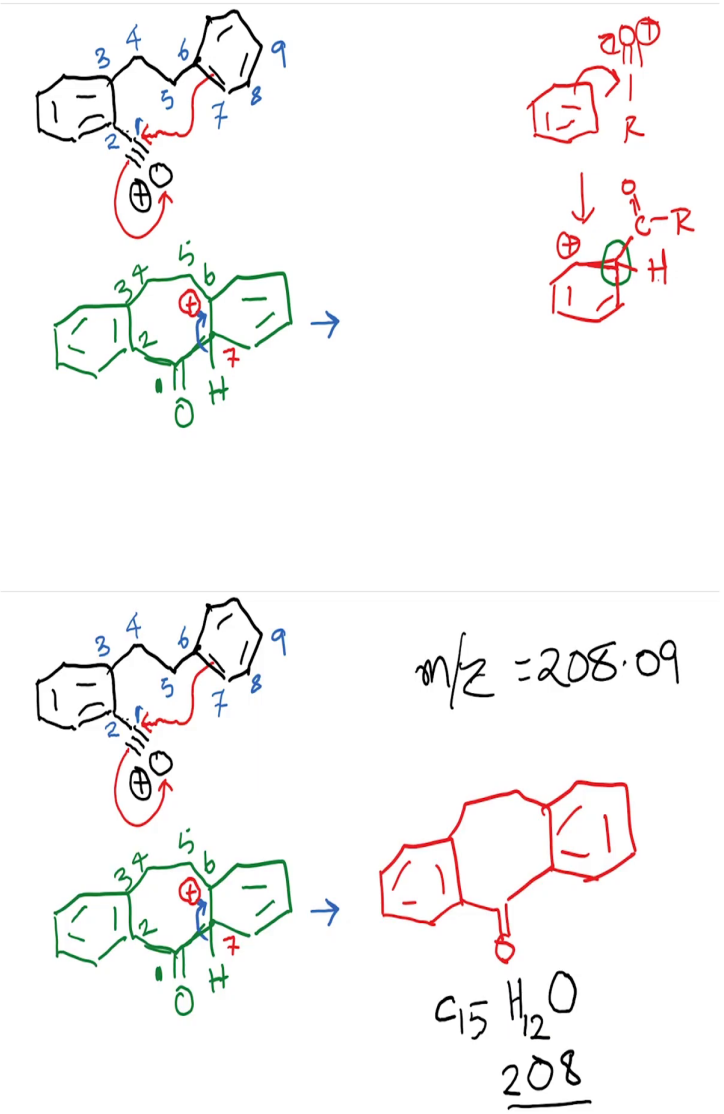

So, the benzene ring remains the way it is and your $C\equiv O^+$ is here. And now CH_2 CH_2, I am just going to draw out this benzene ring so that it becomes easy for us to follow it. So, now let me quickly number these carbons. So, I will start with the $C\equiv O^+$. So, this is number 1, carbon next to it is 2 3 4 5 6 7. So now, if these are the seven carbons. And now, of course, you can

go on numbering this further, this becomes 8 9 and then 10 and 11 are the same as 8 and 7. So this is perhaps the one good way to number it.

Of course, there could be others. But this provides us the context. So, if Friedel Crafts acylation would occur. So just to remind you, the Friedel Crafts acylation occurs in the following manner. So, you have, let us say, $RC{\equiv}O^{+}$, that is the electrophile and your compound attacks here. And it gives you a very important intermediate which is H, RC=O and there is a positive charge that ends up over here.

So, if you were to imagine that a similar situation would occur here, then the bond between carbon 6 and 7 would break and it would attack on this carbon and this bonded pair would go and end up on oxygen and neutralize it. So, the resulting molecule that would form is the benzene ring on the left remains intact. And now you will form a 7-membered ring, so let me just draw out the seven membered ring, as a new seven membered ring that is formed and the benzene ring remains the same way.

And now we need to number this. So, the bond between carbon number 1 that is over here, has the double bond, and number 2 remains the same, 3, 4 all unchanged, 5. And when we get to 6, 6 is over here. And now, the important carbon is carbon number 7. So, if you see here, this becomes a sp^3 carbon. So, carbon number 7 would be sp^3. Now, the remaining molecules are going to be the same. So, I am just going to draw out the double bond over here. So, now it forms a seven membered ring, and there is a positive charge that still remains.

And that is going to reside on carbon 6, of course, it can delocalize into this aromatic ring. But now, if we want to push arrows to regenerate aromaticity, then you would go over here and give you the final product, which is going to be the following. So, I am just going to make some space over here, so that we can use the entire sheet.

Now, the final product is going to be based on this mechanism, it is going to be this. So, now let us count the number of carbons. So, you have 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15. So, $C_{15}H_{12}O$, you can go back and know your molecular weight using this formula, and you will end up with a molecular weight of 208. And therefore, your m/z, that is going to show as per the data that is given is 208.09. So that is the answer to the first question.

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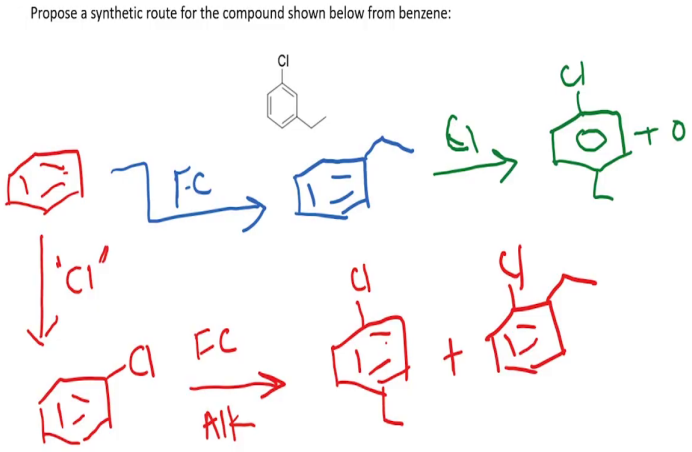

Let us move on. So here, in this case, the question is how do we synthesize this compound. So, in order to address this question, we need to, of course, start from benzene. So let us try out the first strategy, which would be to start from benzene. And then, basically chlorinate it, and you get chlorobenzene. The reagents would be chlorine and $AlCl_3$ for example. And then we do a Friedel Crafts alkylation. And that is going to give you the product that you want. But it is the regiochemistry that is going to be wrong.

So, since Chlorine is ortho, para directing, you will end up with a mixture of para plus ortho. So, this strategy clearly is not going to work. Now, let us consider the reverse situation. That is, first we do the Friedel Crafts alkylation. So, F.C. alkylation, that is going to give you ethylbenzene, and then we deck to the chlorination. And this is actually again an ortho, para directing group. And so, you are going to end up with the same mixture as shown here, plus the ortho compound. So clearly, neither of these strategies is going to work. So, we need to figure out how to do this reaction in a way that is going to give us the right regioisomer.

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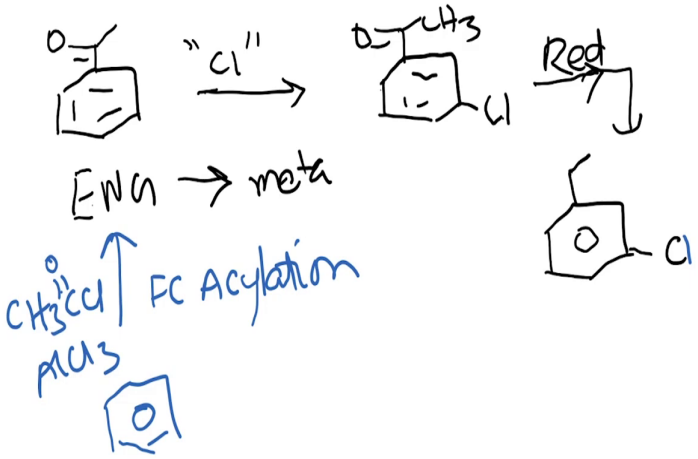

So, in order to do this, let me consider the other possibility which is to work out, let us say we start from acetophenone, and then do the chlorination and you will end up with the correct regiochemistry, which is the meta product because this is basically an electron-withdrawing group. And the electron-withdrawing groups are meta-directing. And so, you are going to end up with the meta product and then you can then just do a reduction to give you the final desired product, which is this.

Now, the way we would get to this component is fairly straightforward. We start with benzene and do a Friedel Crafts acylation. We start with $CH_3C{=}OCl$ in the presence of $AlCl_3$, that is going to give you this compound. So, one important way in which we could make this compound is through Friedel Crafts acylation as the first step. And that is going to give you acetophenone, followed by chlorination which is going to give you the meta-chloro compound. And the last step would be reduction, here you have a choice of either doing Wolff-Kishner Reduction, or Clemmensen Reduction, so this strategy will work.