Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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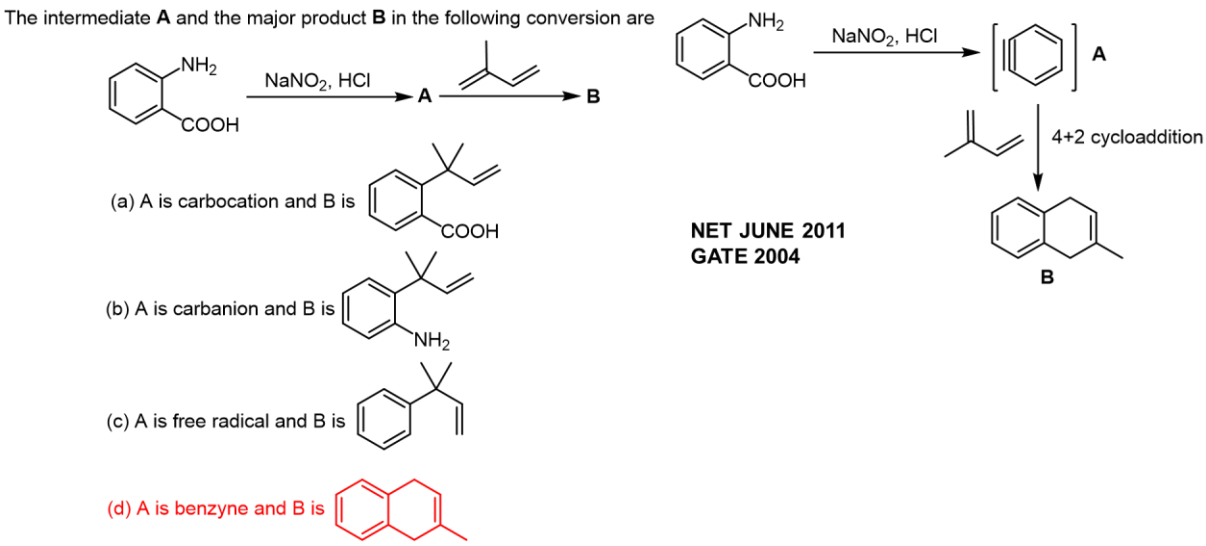
Lecture 31: Benzyne question answer discussion

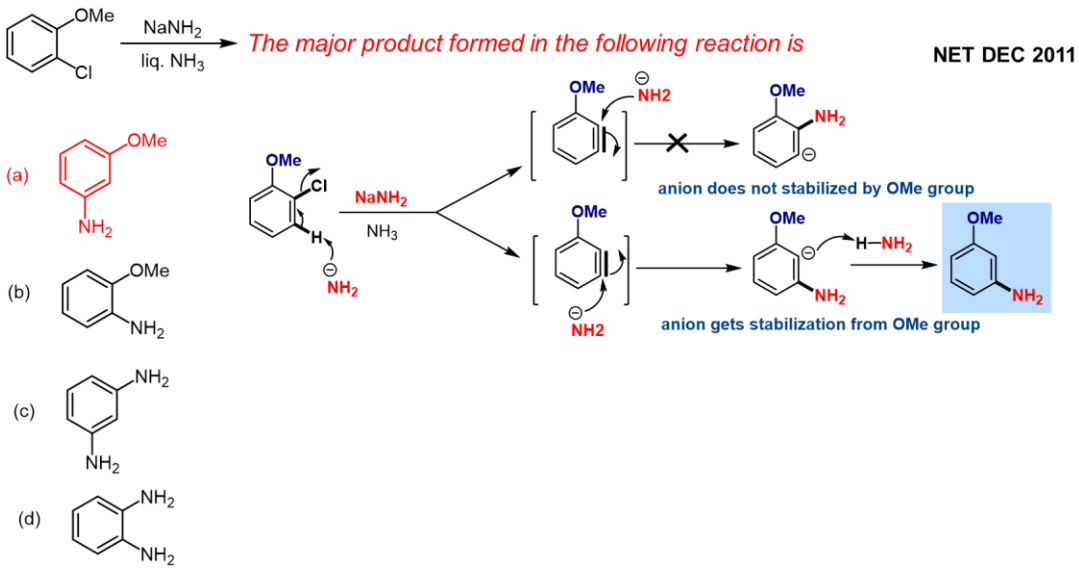
Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. So, last three classes I was talking about benzyne. In the today's class, I decided to solve some of the previous year questions. So, that you can see some of the summary what you have learned in the last three classes. So, let us talk about with the first question. So, let us I think in this particular question what they are asking? Starting from anthranilic acid, if you treat with $NaNO_2$, HCl, what will be happen? What will be your A and now if you treat with this diene what will be your B? Let us recall what you have learned.

We have learned that if you treat with $NaNO_2$, HCl with anthranilic acid, what is going to happen? Think about it. What is going to happen? In this particular reaction, you have amine and you have this aniline and you have the acid. So, you can definitely think about a reaction using $NaNO_2$, HCl which is going to generate the HNO_2 and it is going to form this corresponding diazonium chloride from this. So, we know that the first thing going to happen, it is going to form a diazonium chloride. But it is not going to stay there because once you form this, what you have learned here that from the acid, proton will be abstracted also going to form this minus. So, there will be a decarboxylation going to happen which you can learn in the two-step formation of carbanion or you can write something like that. So, you end up making a benzyne. So, starting from anthranilic acid, we have already learned. So, it is going to form this type of zwitterion species. So, your A will be a benzyne and, then what is your next thing now once benzyne see this diene. So, what reaction you have? can you recall from the lecture number, I think we have talk in the lecture number 2. So, this is an important pericyclic reaction So, you can think about that it is going to take part in a [4+2] cycloaddition reaction. Once you are going to take part in a [4+2] cycloaddition, it is going to end up the product B. So, the benzyne act as a dienophile. So, you have a diene and dienophile that will take part in a [4+2]. So, that will be B.



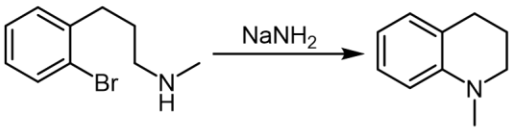
In this particular problem let us try to think about first. So, what is going to happen? If you treat with $NaNH_2$ and liquid ammonia with this particular compound. So, we have taught this type of question in the lecture number 1 that once you have this scenario, where you treat with this compound where you have a corresponding chlorine or corresponding fluorine or corresponding bromine what you have seen that this in presence of strong base, it is going to abstract this proton from here. So, and, then going to form a minus and, then there will be a after forming minus, there will be elimination. So, that is going to end up forming the corresponding benzyne, but it is not going to end here because you have form a benzyne that is fine, but what is the next thing going to happen. But then you have to understand, you have already a nucleophile in the reaction. you already have this liquid ammonia so that means, you already have a nucleophile in the reaction. That means, if you have a nucleophile in the reaction, then this benzyne is going to get attacked with a nucleophile. Now, there is two different position it can attack. It can attack in this position or it can attack in this particular position. We have already discussed that and, you can find this type of problem was discussed in Clayden books. Now, what is going to happen if nucleophile comes from here? It is going to generate a carbanion. So, you end up generating two different carbanions. One could be like this or if we attacking from here then it is going to generate a carbanion. So, there could be a what is happening here? There is a meta versus. So, let me write down that one. You are attacking here. You are generating a carbanion here. So, ortho versus meta-attack. So, if you are attacking with the NH_3. So, you can write a NH_2 here. Because that will at the beginning, it will be NH_3. I think, you can write NH_3 and then plus, but that will be coming this minus is going to take the proton out. So, now the question come what is going to happen here? There are two possibilities. So, here the OMe has a inductive effect. If that is having an inductive effect, what is going to happen? It is going to stabilize this carbon and more compared to this. So, that is how

you see the meta-attack will be favorable. If meta-attack is favorable then we are end up getting to this particular product that will be the answer for this question.



Then another important question here, you start from this particular compound, you treat it with the $NaNH_2$. So, what will be your product in this reaction. Now, once you think there is a $NaNH_2$ and in your starting material, you have a C-Br bond, you should immediately start thinking about this is a base not only base this is a strong base. So, one thing you might said, there will be a N- going to be abstracted. So, this it going to abstract the proton from there, but that is not the only thing going to happen. So, what is going to happen? It can do other things also because you have learned about that if you have a C-Br bond and this is going to. So, this the acidity of this proton will be high. So, the $NaNH_2$ can able to abstract this proton to generate a carbanion here and then, what is going to happen? It is going to generate this carbanion then; it is going to go for this. I think we have shown here, it is going to go for the cleavage of this C-Br bond. So, the bromine will get out from here and generate a benzyne. Now what is going to happen? There is a N- waiting here. This can attack to the benzyne, from this minus which can take a proton to get to the corresponding product. So, the question comes the reactive intermediate involved in the following reaction is. So, they can ask two different questions from here. They can either ask what will be the product? or they can ask what type of question like that. Then what type of intermediate this reaction is going through? A carbocation you might think a carban ion, but that is not the right answer. It will be an aryne.

The reactive intermediate inolved in the following reaction is



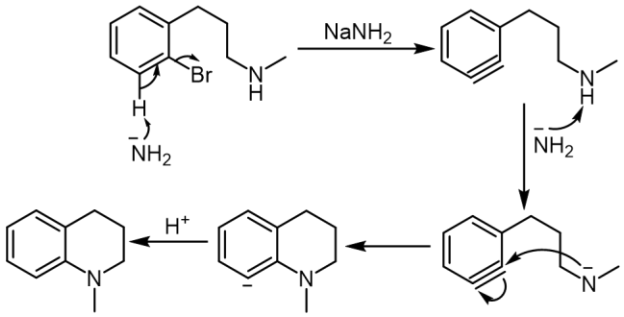
NET JUNE 2013

(a) a carbocation

(b) a carbanion

(c) a free radical

(d) an aryne



So, anthranilic acid treatment with iso-amyl nitrite furnishes a product which display a strong peak at 76 in its mass spectra. The structure of the product is- So, I think I have already discussed this thing at the beginning that once you are having a benzyne and you are going for a mass spectra, we have already learned that the benzyne which is forming from anthranilic acid. So, anthranilic acid, once it is treated with the iso-amyl nitrite, if it is a treating with sodium nitrite or it is treating with isoamyl nitrite, it is going to form this diazo here and once there is this type of zwitterionic species it going to get rid of the CO_2 and N_2 to get to the corresponding benzyne. And once the benzyne is there as I told you and there is no other partner for coupling that benzyne can self dimerize. So, that is happening. In a mass spectrum, you can see there is a dimerization happening. Now, once you take this type of compound in mass spectrum there is a plus and a minus. This bond getting cleaved, there is a plus and a minus. So, you can see think about the phenyl having that total mass will be for in case of phenyl ring, it is 78. So, if you have a you are missing these two hydrogens once you come to this type of species or in the benzyne what you have seen? In case of benzyne or the species I am talking here both cases what is going to happen? They are missing these two hydrogens. So, they are 76. You are seeing a peaks at 76 that means, what they are saying in the mass spectrum. You end up making actually this particular compound. So, that will be the actually the correct answer. So, if you see the other option also, in all other options none of them is showing anything related to benzyne. And also, if you try to count the mass the 76, you cannot able to count from any of this other options.

Anthranilic acid, treament with iso-amyl nitrite furnishes a product which displays a strong peak at 76 (m/e) in its mass spectrum. The structure of the product is

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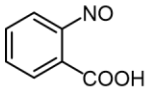
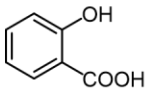
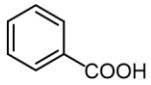
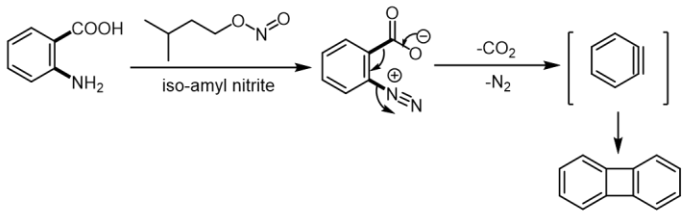
(a)

(b) 

(c) 

(d) 



So, this type of question comes in often in the exam. So, you might see this is a question which is came not only in the NET December you have seen this type of question comes in the gate several times. So, you start with the 1-bromo-2-fluorobenzene, they are not going to give you the entire thing. They will tell you that starting from this 1-bromo-2-fluorobenzene if you take furan in the presence of one equivalent of magnesium that is all going to be given here. So, if I am in your place, first thing is, I have to draw the 1-bromo-2-fluorobenzene. So, let us draw that. So, this will be your 1-bromo-2-fluorobenzene. So, now if you think about 1-bromo-2-fluorobenzene and they have given furan. and they have given a magnesium. So, let us think about that if you have a magnesium and furan, there is nothing going to happen. They cannot react each other. But once you have a 1-bromo-2-fluorobenzene and you have a magnesium that this can form the corresponding Grignard reagent. And once that is going to form the Grignard reagent what is going to happen? We have already learned that this C-F going to cleave and it is going to form this corresponding benzyne. So, now if you form a benzyne, you have already made a corresponding dienophile. Now you have this corresponding diene which is the furan. So, once you think about furan, you should always think about this is a very good diene. So, this is going to take part in a [4+2] cycloaddition. So, I think I have taught this in the pericyclic reaction part which will be in the lecture number 2 where I talk about this type of reaction that if you have a benzyne and if you have a furan, it is going to take part in a [4+2] cycloaddition to form this type of product. So, now if you see this the option is given here, all these options are given here this is the option now the option C will be the right option.

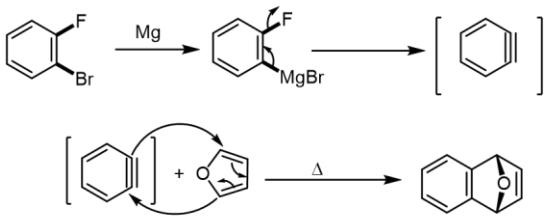
The reaction of 1-bromo-2-fluorobenzene with furan in the presence of one equivalent of Mg gives- **NET DEC 2014**

(a)

(b)

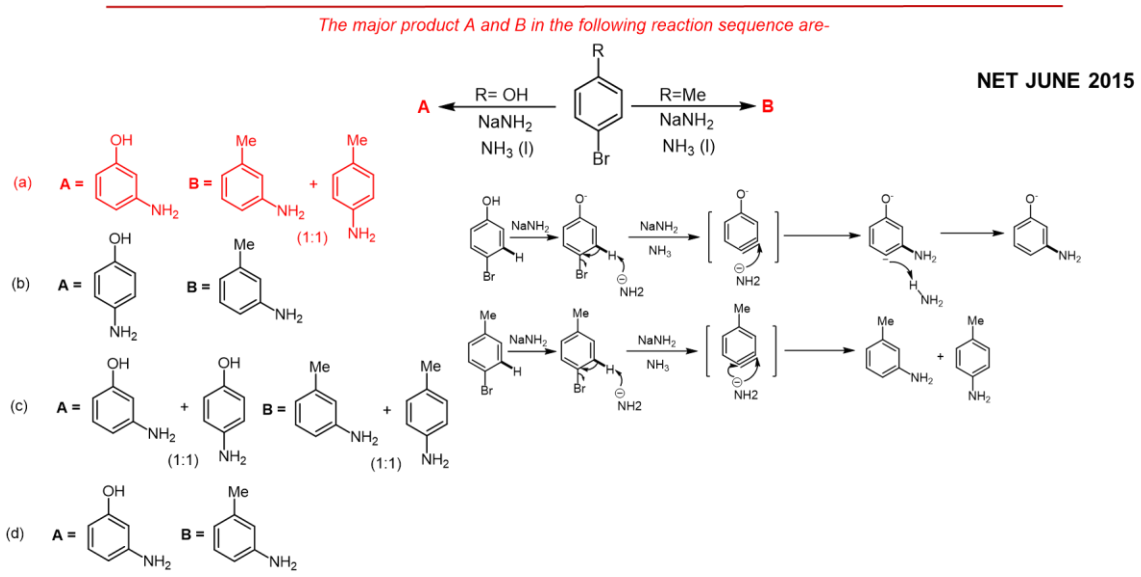
(c)

(d)



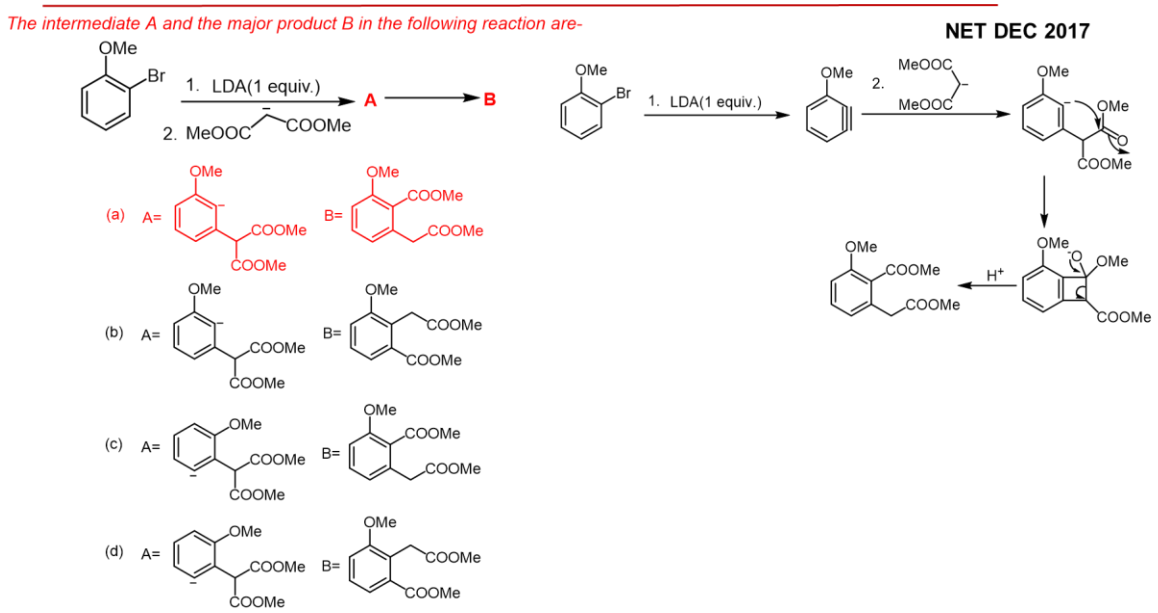
So, this is another question the major product A and B in the following reaction sequence. So, these types of questions where you see there will be a genaration of benzyne and there will be $NaNH_2$ and liquid NH_3, they are asking this type of question again and again in several different type of exam. So, we should be ready with this type of question. One of the important facts is about R. I think I taught you that depending on R, will be electron donating or electron withdrawing. You will see it two different set of attack. Some cases if you have a -I effect, you have seen the meta depending on the benzyne going to form. If it is an *ortho* versus a *para* you will see different type of attack going to be happen. So, let us start with this compound first. So, it is not a methoxy. is say actually a OH group here. So, what will be the difference between a methoxy and a OH group that is the important things here, because first things I think OH proton will be abstracted by $NaNH_2$ to make a O- correct. So, once you have a O- and now it is going to take the proton. So, it can take proton from this side or that side both are same correct. It going to end up generating this corresponding benzyne. So, now, once it is generating a benzyne, you have to think about the O-. So, O- is not having any type of inductive effect. So, it will try to have a, it is a electron rich species. So, it will try to see the carbanion as far as possible. So, if you want to put the carbanion as far means, there is a two option. If you attack from the meta position then the carbon will be in the para position, it will be the far from the O-. So, that is how this will be the product which you going to see as a major product here, once you are generating this O- species. So, that will be your answer A. Now, what will be answer B? Once you have a methyl group, I think, I already covered that if you have a methyl group then, there is two different possibility that it can form this benzyne. So, first it will form this corresponding benzyne, now the benzyne can have a attack from the para position or meta position. I told you in generally in case of the methyl, as methyl has a inductive effect or it has a +I effect and it is not that strong. So, what is going to happen? In case of methyl, there is also a steric effect which also sometime make a factor for this type of preference. So, in case of methyl, I told you there is not much preference for this type of attack. So, you will see there will be attack happening from the para position or happening from the meta position

to generate the carbanion either in the meta position or in the para position. So, you end up getting both the product. So, you will end up getting a mixture of these two products. So, that will be the answer B and this will be the answer A. So, your option A is the correct one.



So, let us talk about this particular problem. So, started with this particular compound you have this methoxy group and a bromo and you treated with LDA correct. So, once you think about treating with LDA to this compound, what is going to happen? So, they are asking what will be your A and then once you treat with this particular compound, what is going to happen? So, now you can think about that first thing once you treat with LDA, what is going to happen here? Again, you see if you have a C-Br bond, this is the proton is activated one. So, this is going to be deprotonated So, it is going to form this carbanion, finally it is end up forming this benzyne. So, now what is going to happen? So, now we have learnt that if you have base already in the medium and if you have this dimethyl malonate what is going to happen here? That is going to abstract this acidic proton here and now if you have a nucleophile ready to attack. So, this is going to attack to the benzyne again. There are two different positions, it can attack. I always told you if you have a methoxy group, it is going to attack to the meta position to generate the anion in the ortho position. So, that means, this is the attack going to be favorable. So, this is going to be attack here that can generate and then you have this minus here. So, what is going to happen? This carbanion now going to attack here as I told you, it going to form first this O- here. So, you can see I think we have already drawn the mechanism for you. It is going to form this O-. So, let us try to write down the rest of the things here. I think we have already written in this particular position you can see after the attacking here you are going to form this. Then once it is forming, the next thing I told you always, there will be cleavage of this particular bond. It is a strain ring; it is going to get cleaved to relief the strain. So, that will end up giving you this sort of a product. So, what is

happening in these particular cases we are seeing some sort of insertion happening that in this particular compound you have this COOME in one carbon and then the CH_2COOME going to the other one. So, that is end up forming, this is a product. So, what is your A?

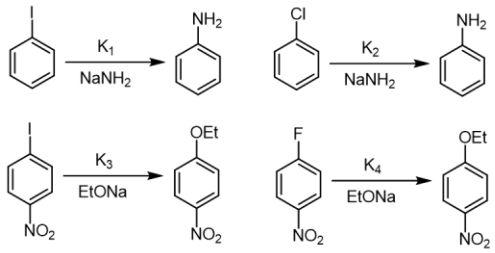


So, your A answer will be, out of this all this answer if you look into it. I think you can clearly see this is the answer where there will be negative formation here that will be the correct answer here because first thing what they are giving, they are giving LDA and this compound together. So, that will be the A and then, your B will be when it will be after the reaction is over and going to finally, a insertion product which is this one. I have already discussed in the part 3 about insertion. So, now, the question I think I already talked about that I think this is an again important topic, as I was telling, you will see a lot of problem using this $NaNH_2$ and corresponding iodobenzene or chlorobenzene or bromobenzene. So, in these particular cases what they are asking? They are asking about the different rate. So, what is the correct order for the following reaction. So, you have this K_1, K_2 here then, K_3 and K_4. If you remember, I talk about this thing that this thing what generally depend on, it is actually depending on that first thing if you are generating. So, if you have a weak bond there, if you have a scenario here, first thing is in these particular cases if you are generating a carbanion here, in this case then it is going to easy to get rid of this corresponding iodine which is shown here. Because in every case what is happening? You are going to end up generating a corresponding benzene. So, in general the order will be this iodo bromo chloro because this is the elimination order and because the bond between C-I will be the weaker one compared to the C-Br or the compared to the C-Cl correct. So, here what is going to happen the K_1 will be greater than K_2. So, that is kind of understandable that if you compare between the K_1 and K_2. now the K_1 will be the greater than K_2. So, now come to the example here. So, here, what is going to happen in this particular cases? You have a nitro group here and you have a iodo here and in both the cases you have a nitro and iodo group. What is going to

happen? There will be iodo going to be replaced by the OEt group and here in case of fluoro the similar thing is happening. So now what is happening? As this reaction going through formation of this corresponding carbanion because once you are using a sodium ethoxide that is not that strong base like a sodium amide which is very strong. So what is going to happen in that cases, you have to understand there is another important factor of this type of reaction. So here, what is happening? This type of reaction is going via some sort of ipso substitution correct. So that means in case of the sodium ethoxide, it is actually attacking here, is shown in the because you have a nitro group which is shown here. So, it is going for some sort of ipso substitution because it cannot able to abstract this proton. So, it is attacking here first for ipso substitution and, then it is going for elimination. It is just a elimination happening of this X group. So, here the order of reactivity will be fluoro chloro bromo versus iodo. So, that means the K_4 will be greater than K_3. So, that is how you are end of. So, your correct answer will be B.

NET JUNE 2018

The correct order of rates for the following reaction is



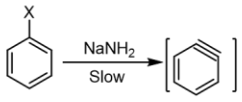
(a) $K_1>K_2$ and $K_3>K_4$

(b) $K_1>K_2$ and $K_4>K_3$

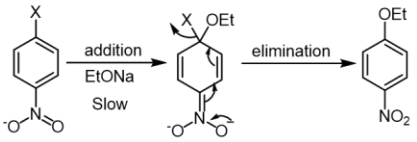
(c) $K_2>K_1$ and $K_3>K_4$

(d) $K_2>K_1$ and K_4 and K_3

Here two type reaction K_1 and K_2 follow elimination addition and K_3 and K_4 addition elimination reaction.



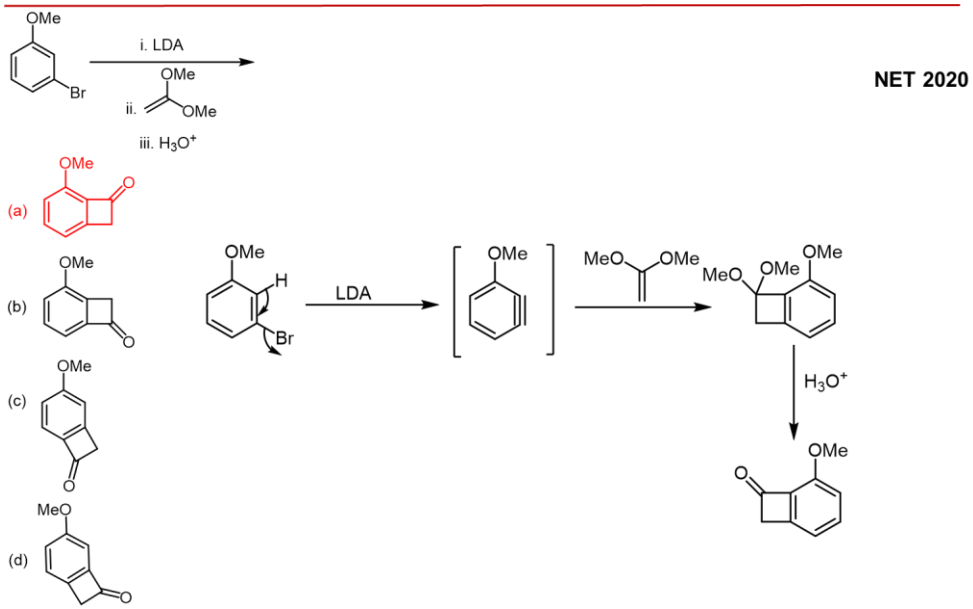
Here the order of halogen reactivity I > Br > Cl > F and here elimination of halogen is rate dermining step.
So $K_1 > K_2$



Order or reactivity of halogen F > Cl > Br > I and here addition of nucleophilec is rate dermining step.
So $K_4 > K_3$

So, coming to this problem here what is happening in this particular problem. You see, you treat with LDA first, once you treat with LDA, I already discussed that you will generate a carbanion in between this which is going to form this corresponding benzyne. And, now the question comes whatever regioselectivity you will get because once you have this, I already talked about in this [2+2] cases that if you have some sort of an enolate type of scenario where you have which can attack through this. So, it can attack through this corresponding carbon and generate this anion. So, this carbanion again has to form in this particular position which is next to this OMe, which can stabilize and now you have already formed this. So, if you have from here then we will have OMe+ and, then another OMe here. So, you can see now this minus is going to come and attack here. So, that is how you will end up getting to the this will be your major product not the other way means you can think about attacking here also at the beginning, but as you see this anion is getting stabilized that is why it is going to attack first in the meta position. This is the attack going to happen and then this is going to form and, then once you treat with

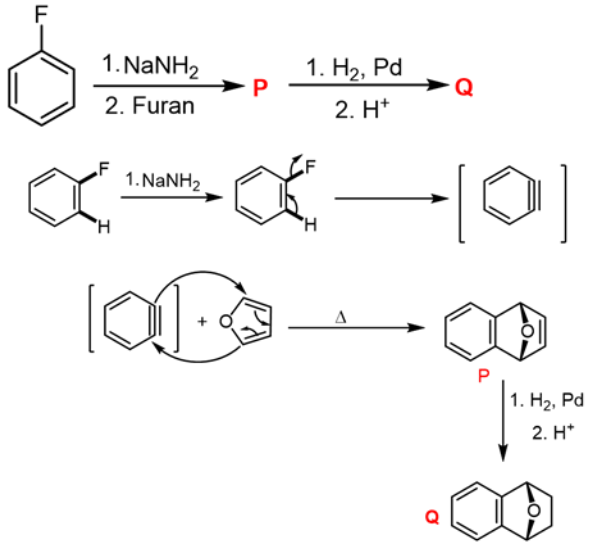
H_3O+, they have given H_3O+ in the question, it is going to form this corresponding carbonyl group correct. So, from this corresponding ketal, it is going to form the corresponding ketone.



Another question here, again the sodomide or $NaNH_2$, furan and, if you have seen this in a fluoro benzene or thing your kind of immediately started thinking about sodomide is there that means this is going to abstract this proton because this proton is the one activated is next to this fluorine. So, there will be this minus and then it is going to get rid of this fluorine to get to the benzyne then there will be a [4+2] cycloaddition I have already mentioned and, then once you form this particular compound, they are asking you to treat with palladium and carbon. So, you have hydrogen with palladium and carbon. So, this is a important condition for hydrogenation of olefin. So, here if you see this is the isolated olefin here, which is going to get hydrogenated to get to this product. So, that will be your answer that will be your Q. So, first you have a P. So, let us see what will be P. P will be after the [4+2]. So, that is your product first that is the P and that will be the Q.

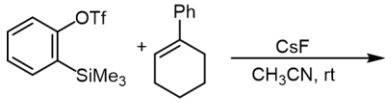
*In the following sequence of reaction, the major product **Q** is*

GATE 2005

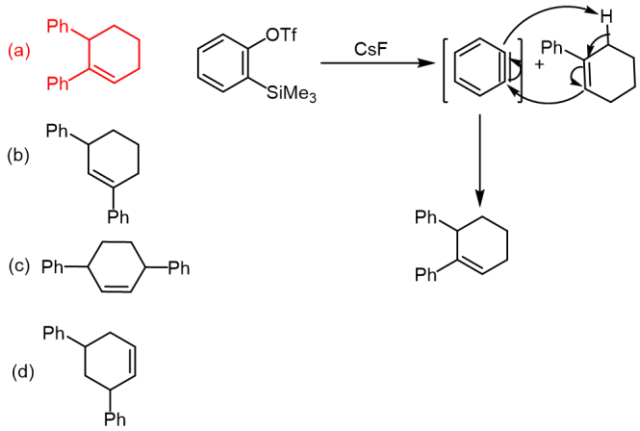


Now, this came in the gate. So, this is another important problem here. Again, they have given this particular OTf, $SiMe_3$. You can by looking into you understand this is the Kobayashi benzyne precursor in presence of cesium fluoride, it is going to form the corresponding benzyne. Now, you have this corresponding olefin having allylic hydrogen. So, if you have this allylic hydrogen, I talk about some sort of ene reaction, I already talk about during discussion in the lecture 2. So, what is going to happen? It is going to take part ene reaction. You can think about that this could be some sort of a benzyne, could be some sort of an enophile. So, in general if you think about this as a plus and minus then your understanding will be much easier. If you think about that way, then it can able to take this proton, then it is going to form the bond here and, this double bond going to attack to this side. So, if that is happening. You end up getting to this particular product because the benzyne is taking this proton forming a double bond here and this is going to attack in this particular position. So, that is ending up giving to this product.

The major product formed in the given reaction is

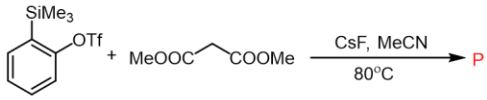


GATE 2023

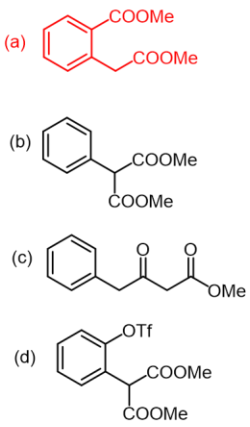


Again, very similar problem, I have already discussed which came in the gate 2022. You can think about that the very similar problem which came in the other year. You can see, it is also coming in the gate which came in the net before. So, using the Kobayashi condition, you can see first formation of the benzyne which is again, I told you this is an insertion reaction which is going to attack in this ester carbonyl. Then finally, there will be cleavage of the carbon bond which is going to form and then there will be insertion. So, this part is going to insert in this carbon and then CH_2COOMe is going to insert in this carbon.

The major product P in the following reaction is



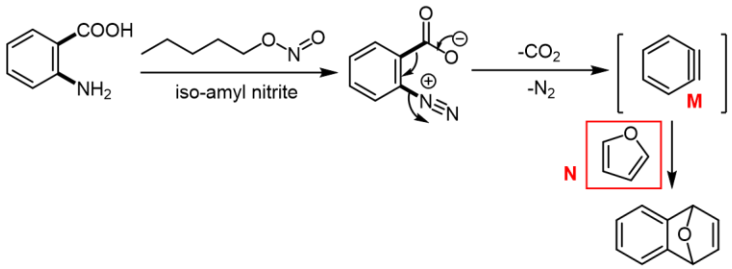
GATE 2022



Again, very similar problem, I think, starting from the anthranilic acid you are generating first M that means will be to the corresponding benzyne which is going to form then, you treat with the furan and you end up getting to this product.

Identify the structures of M and N in the following synthetic transformation

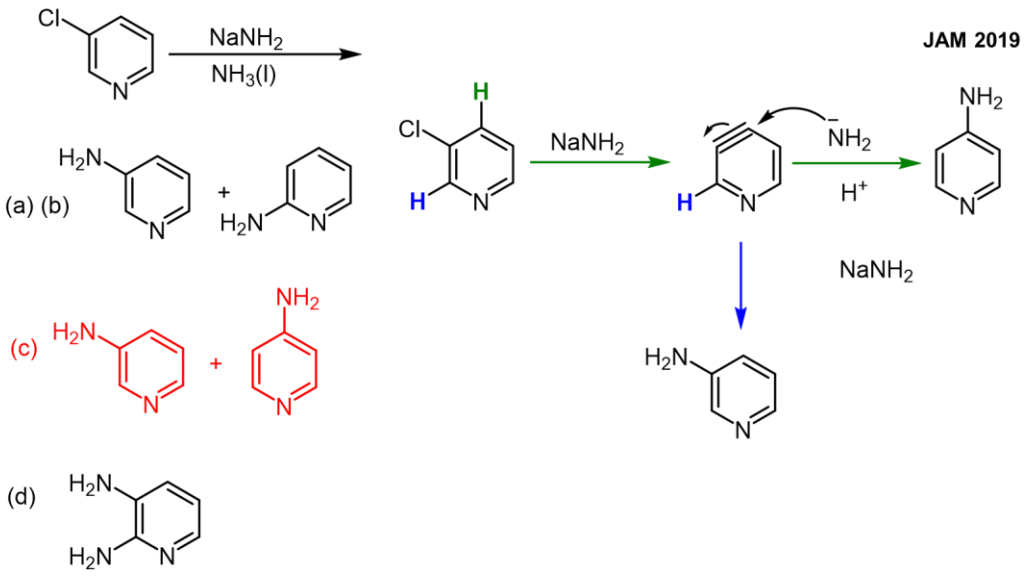
JAM 2012



Now, the question comes if you have a pyridine and if you treat with the $NaNH_2$ and ammonia, what is happening here? if you have a 3-chloropyridine. So, 3-chloropyridine what is finding out that this is the proton getting abstracted here. Once this proton is getting abstracted, it is forming this corresponding benzyne and once you have a benzyne now there is two different attacking can be possible. It can either attack from this position or it can attack from this side. Although you might think about that the attack from the C-4 will be major because of the stability and this will be minor. So, you end up getting a mixture of the product.

The correct option for the product(s) of the following reaction is

JAM 2019



Again, thank you so much for coming to the class and I am going to see you guys in the next class. Thank you.