Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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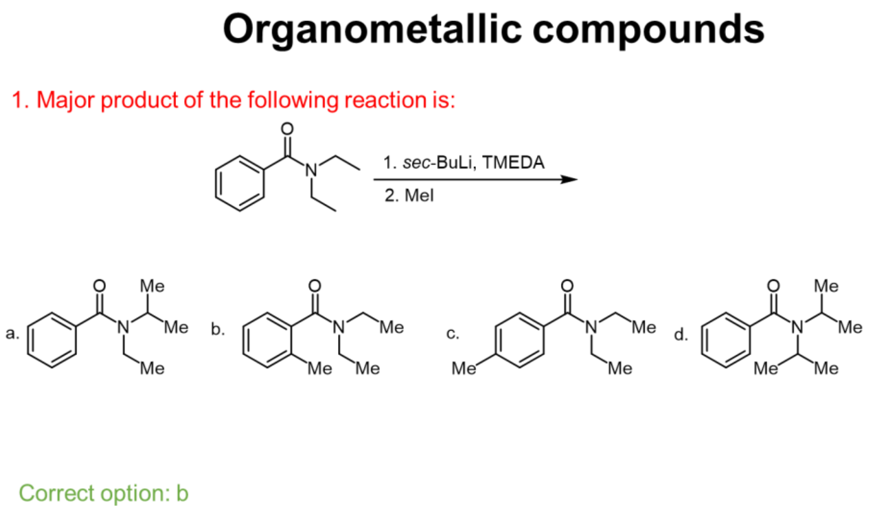
Lecture 58: Tutorial 3

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last two classes i talked about some of the problems from the from all the different section which i covered in this class. So i already covered the problems from the carbocation and then also from the carbene nitrene. In the today's class I am going to focus in some of the problem from carbanion and also from the Grignard and organolithium. So, those are also can be considered as a like some sort of a carbanion. So let's talk about the problems. So the first problem is again I think these are the problems came all the different competitive exams.

Here what we are seeing here we can see there is a amide linkage here and you are treating with sec-BuLi with a TMEDA and then there is a electrophile methyl iodide. So, if you remember I think I talk about directed lithiation correct and at that time I also talk about that if you have some sort of a directing group. attached with the aromatic ring if you can say directing group then what that can do now if the directing group has some sort of a group which can coordinate with your which can be a Lewis basic character. So, that which can coordinate with your lithium then when you have the R-Li which could be sec-butyl lithium, tert-butyllithium.

So, that can allow the lithiation to be happen to the next proton. So, this R is actually R minus correct So, you can think about this as a minus and this is as a plus. So, this can able to take this proton and generate a corresponding carbanion. And also I talk about there are several different reacting groups correct. So, this is one of the example of similar problems.

And now if you treat with a electrophile then you will be able to introduce a electrophile So, in this problem what is happening you have a carbonyl with this a So, here you can think about this can chelate with your lithium and the corresponding sec-BuLi, this can able to take this proton generate a carbanion. And now, if you treat with methyl iodide what is going to happen? So, it is get rid of the iodine that can act as a electrophile to introduce a methyl group. So, this is acting as a directing group to introduce methyl in the ortho position of this amide. Now, if you look into all the different answer we can find only the answer B which has the correct structure which is showing the introduction of methyl group in this position. So, you can see that is the correct answer for this problem.



Organometallic compounds

1. Major product of the following reaction is:

Correct option: b

So, let's move into the next problem again this is from the Grignard chemistry. So, I already talk about lot about the Grignard chemistry and one of the important thing if you remember I talk about different type of Grignard chemistry primary, secondary, tertiary. And one thing I mention that professor Nochev's group developed one important chemistry that if you want to go for a magnesium So, we have learned about the organo-lithium can be I think you have already previously seen that if you have this corresponding bromide then if you use a n-BuLi through metal halogen exchange, we already talk about this we spend lot of time talking about this type of reaction. ok. So, so this is a so using organolithium you are doing a metal halogen exchange, but this can be also done using Grignard reagent ok.

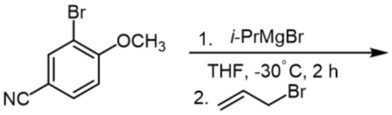
So, this discovery is a very important discovery because lot of the reaction if you think if you have n-butyllithium there are very reactive, but the Grignard was not that reactive compared to the lithium. So, you can able to tolerate lot of different functional I think I mentioned during that time that if you want to use some sort of a functional group like cyanide or ester or carbonyl. So, now, we are talking about this type of substrate. So, here if you treat with n-BuLi what is going to happen it will go for metal halogen exchange, but it will attack to the cyanide also. So, that is why the idea is if you use some sort of a hindered Grignard like something like isopropyl magnesium bromide, then it can go for a.

The Grignard reagent can also go for a metal halogen exchange and it can allow you to generate the corresponding and these reactions happens at some sort of low temperature less than -10, -20°C around that temperature this reaction happen it can allow you to generate corresponding Grignard reagent here and keeping this cyanide and other functional group intact. ok. And now once you treat with the corresponding electrophile this is the allyl bromide then this Grignard can go to attack here to get rid of the corresponding bromide and you will be able introduce the corresponding. So, again I think one of the advantages of using this Grignard method over the organolithium is that this meta halogen exchange happening the low temperature where it is not attacking the corresponding cyanide. So, that is remaining intact you are able to generate the corresponding Grignard and you can do some sort of a reaction with the corresponding electrophile some sort of S_N2 type reaction with the electrophile to get to the corresponding product.

So, now if you look into the all the different answer, we can see this cannot be the right answer the bromine is there neither this one. So, this one looks the correct answer where the bromine was replaced with the allyl group. So, this is the correct option here.

Organometallic compounds

2. Major product of the following reaction is:



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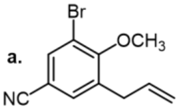

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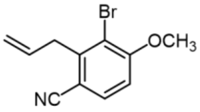

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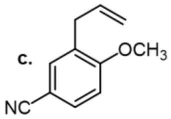

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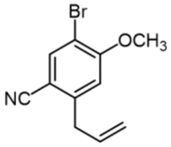


Correct option: c

So, moving further in this problem what we are seeing here let us first look into. So, we can see clearly there is a diene here and then you have some sort of-$OCOCH_2CH_3$.

So, it is not a acetate you have a ethyl group here now if you treat with LDA. So, if you remember I talk about LDA and I talk about this is a strong base use for several deprotection reaction there is two isopropyl group and then it is the N-Li. So, this can able to if you see in this particular compound this is the proton which is acidic. So, LDA can able to go for the deprotonation and it is going to generate and then what you are treating with after the LDA that means, once you generate the lithium you are treating with -TBDMS chloride. So, that can take you all the way to the corresponding.

So, let me just wiped this part which you do not need here you already. So, what is going to happen here we end up forming -OTBDMS. And now what we are doing after the first step we are treating this, with this compound. So, you can see there is a good this diene is electron rich and you have a dienophile. So, which reaction you have learned So, there is a 4π-2π.

So, this is a [4+2] cycloaddition. So, you are giving this dienophile and heat. So, that can take you to the [4+2]. Now, the question comes is these are not the symmetrical neither the diene or the dienophile. So, there is a possibility of different type of regioisomer.

So, question comes now once this the Diels Alder happening which side of the diene is more electron rich and which side of dienophile is electron deficient those two part going to combine. So, now if you look into the electron density wise this oxygen can give the lone pair electron density here and this can give more electron density on to this particular carbon. As well as once you have a electron withdrawing group this is the carbon will be electron deficient. That means, this is the two part going to be combined. You can able to find out from the co-efficient of of this particular carbon from there also you can see this will be the highest co-efficient I have here the this will be the lowest co-efficient in terms of electron withdrawing group.

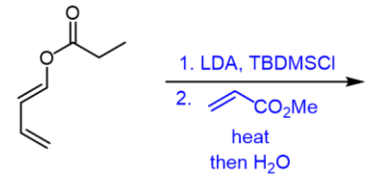
So, they are going to get combined and then that can able to form the one of the other things when one of the Diels Alder Reaction happening they are approaching in the same phase. So, you end up getting to this particular diastereomer. So, after formation of this what we are doing we are treating this also. So, again I think if you look into this particular compound now you can see that there is a 1, 2, 3 and again other will be 1, 2, 3. Now if I can draw them properly we can clearly see a possibility of a [3,3]-sigmatropic rearrangement.

So, under heat the [3,3]-sigmatropic shift going to occur. Cleavage of this carbon oxygen bond formation of carbon oxygen double bond. We already talked about and then one of the important thing if you see this [3,3]-sigmatropic arrangement is happening where this new bond formation is also happening from the same phase where the oxygen bond was there so that means you end up so you will have you end up as -COOOTBDMS and you will have a methyl here and then there is a ester here. So, now what is going to happen if you look into all the different options, you do not find these options and again then they put water and of course, in this reaction there is a possibility that this -OTBDMS is going to get deprotected. And if it is getting deprotected then what is going to happen this can convert to the corresponding acid.

So, now if you look into all these different examples, these are in the 1,2,3 position in the 1,4 positions. So, if you look into all the answer this is the only answer where you can see these are in the 2, 3, 4. Of course, one thing going to happen there is a new bond going to form between this which we missed here. I think you can see here when the claisen rearrengement is happening there is a new bond formation happening between 1 and 2. So, this is going to be the correct product here.

Organometallic compounds

3. Major product of the following reaction is:



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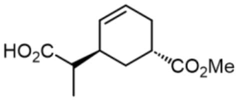

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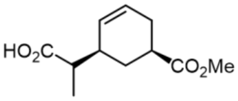

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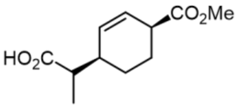

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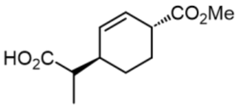


Correct option: c

So, there is couple of things happening first you can see deprotonation then there is a [4+2] and then there is a claisen rearrengement. again you can see the this is the current of option here . So, moving further this is a very interesting problem here we can see there is a 5,5 fused ring with where the 2 Hydrogen in the cis it is first hitting with a LDA or minus 50°C with then giving phenyl selenium chloride. And then again LDA minus 50°C with methyl iodide. So, what will be the structure A and then if you do this with H_2O_2 and 50°C what will be the structure B.

So, let's start about first thing what will be the structure of A. Again to understand this I think I am going to use this model to describe these things very nicely. So, first thing is that in this reaction first step is happening a deprotonation. Once you use this LDA this is going to abstruct this proton to generate a carbanion. this can generate a carbanion and then this will make a corresponding enolate.

Now, if you try to look into the model. So, let's look into the model for a second to understand how this reaction, which phase the electrophile going to approach. So, can you focus on the model? So, we are trying to understand in this particular cases you can see these are the two hydrogens they are in the above phase and I am talking about you already form a double bond here between these two carbon because you form the enolate. Now, the question comes that when you are going to trap a electrophile. The electrophile can come from this phase the top phase or it can come from the bottom phase.

Now, you can clearly see that if you are coming from the bottom phase what are the interaction it has to act. These are the carbon carbon bonds of the other cyclopentane ring these are actually going to be put a steric-interactions with the upcoming nucleophile. Because these are see if you look into the model you can see there is some sort of a cavity here in the bottom side. So, once something is approaching through the cavity it is actually getting interacted with this particular another cyclopentane ring you can see here. So, these are actually that's why the nucleophile when it is approaching here in this direction Sorry a electrophile when it is coming in this side it is getting a steric hindrance.

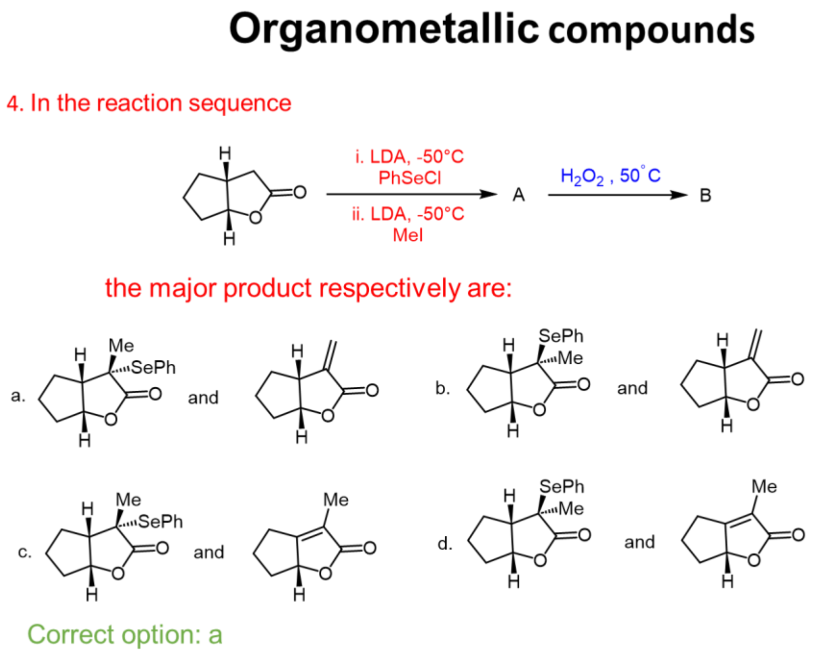
But if it is coming on the top side of it then there is only these 2-hydrogen which is getting interaction otherwise you can see this is the double bond there is no other interaction it is actually. So, that is why the electrophile will prefer to come from this top phase. So, that is the most preferable approach. So, let's go back to the problem again. So, if that is the case what is going to happen here? After the enolate formation So, it is going to form, it is going to trap the selenium Ph.

So, it is first form the enolate and then it is going to trap. So, this will be your first thing then what is going to happen, you give again LDA. If you give LDA again then the proton here this is going to be abstracted generate a carbanion here and you again able to make another enolate and you have this selenium Ph. Now, again once you treat with another electrophile what is going to happen you treat with methyl iodide. Again the approach of the methyl will be from the top phase again if you do not want to get the steric interaction when it is come from the through the cavity.

So, it will better to approach from the top phase. So, in that case what is going to happen you end up generating this particular product. So, again your methyl will be up and selenium will be down. So, this will be your compound A. Now, what is going to happen if you treat with H_2O_2? Once you take this compound and treat with H_2O_2.

So, let's draw the structure which is going to be the compound A. So, it is going to convert. So, you have at the beginning SePh, H_2O_2 is going to oxidize it. It is going to oxidize the corresponding selenium because this part will be remain unreacted, but what is going to happen here? You have a selenoxide and now once you have a selenoxide what is going to happen now you can think about this type of reaction here where if you remember that if you have a methyl group here and think about this three proton and then the selenoxide you can think about as a O minus selenium plus this will be able to take this proton form a double bond and this will eliminate. So, there will be syn elimination going to happen which will end up generating this exocyclic olefin.

So, what is going to happen at the end you have got this is your A. So, let's look for what is the A compound would look like I think we can see here also look like our product in option C also has the product, but now if you compare that the option B then we can only see in this particular problem we are having this exocyclic olefin. So, that means the option-a is the correct option here.



Organometallic compounds

4. In the reaction sequence

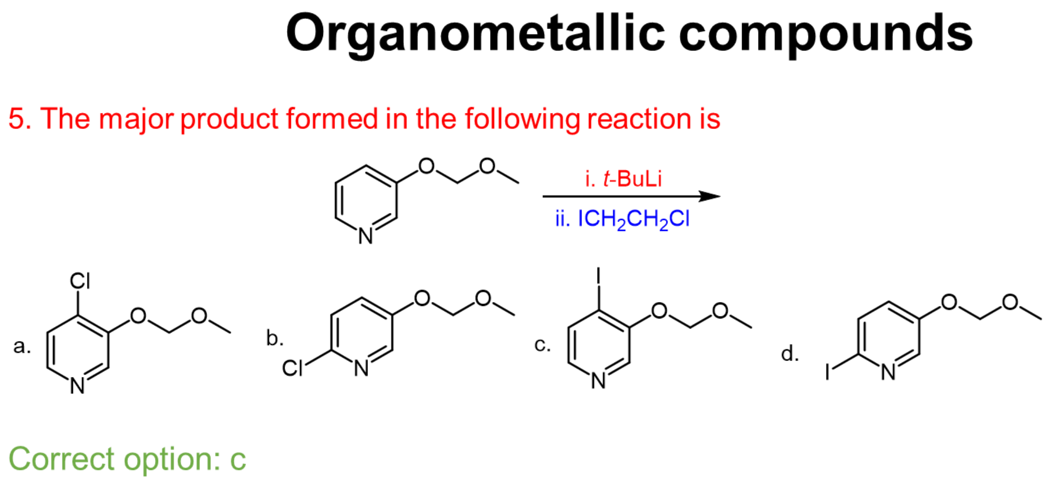
the major product respectively are:

Correct option: a

Let us move into the the next problem. So, here again what we are seeing we are seeing a pyridine and then we are seeing a MOM protection of this corresponding 3 hydroxy group you are treating with t-BuLi and then you are treating with ICH_2CH_2Cl So, here what is going to happen if you have that.

Again now we can understand that once you have a t-BuLi and once you have a pyridine what is going to happen the t-BuLi can abstract the proton from the pyridine and generate a some sort of a carbanion. Now we have to understand that there is a again if you have I think in the previous classes when I was talking about the pyridine one thing I have clearly mentioned that once you talk about the abstraction of this 3 different proton and the rate of abstraction if this is 1 this is 72 this is 700. So, formation of carbanion in case of pyridine in the 4 position is the most preferred one. So, here also instead of the 2 position that means in these cases you will see that the -MOM protection group can able to act as a directing group here. So, that the tributyl minus can able to take this proton generate a corresponding carbanion.

And then once you treat with this corresponding ICH_2CH_2Cl it will be taking the corresponding iodine and going to convert to It can iodinate in this position So, now if you look into all the different product, that is not the product and the only cases when you come to the c, you can see this is the chiral structure Again this is another you know very similar question of that you know the directed lithiation. So, we have learned directed lithiation at the beginning you can see in case of benzene ring you will not able to find a difference, but once you come to the pyridine then the C 4 carbon is more stable than the C 2.



Organometallic compounds

5. The major product formed in the following reaction is

$$\xrightarrow[\text{ii. } ICH_2CH_2Cl]{\text{i. } t\text{-BuLi}}$$

a. b. c. d.

Correct option: c

This is a unsymmetrical scenario here we are we are talking about directed lithiation. Again there are several problem come from directed lithiation in the in the competitive exams. So, that is why I brought several different questions.

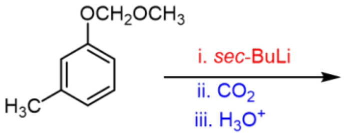
This is again another -MOM protection and you have the -CH3 group here. So, let's try to understand again you are using a Sec-BuLi and CO_2 as electrophile and you are treating with the H_3O plus to protonate. So, if you try to write from this structure we can clearly understand there is two different possibilities correct. One is it can bind with a lithium for that and if you see this is R and this can able to take this proton to generate a carbanion. So, there is a possibility number one or there is another possibility here.

So, now in these two possibility which carbon will be forming, because once you can decide that you can get the answer right. Now, if you look these two different transition state where it is forming, you can clearly understand that in this particular case if you give them B and this is A in case of B what is happening because of the presence of this methyl group there is a steric interaction there is when it is going to because it has to go through a chelation model. So, for the for the chelation with the oxygen is very important for this directed lithiation. Now, if there is a group like -CH_3 which is not really if you instead of -CH_3 if you have a -OCH_3 then that can also take part in the chelation.

But -CH_3 group cannot take part in the chelation. So, it kind of act as a kind of steric. So, it can actually have a sterically, in a steric interaction that will not allow you to form this as a major one you will get the other one where it is forming in this position is the major one. And if this is the major one then from there if you treat with CO_2 what is going to happen? You end up introducing CO_2 minus and you have a -CH_3 here and now once you give H_3O plus you will able to get to the corresponding product. Now, if you look into the all the different options we can clearly see option-a, is not possible option-b, is not possible only in case of option-c we can see that is the correct structure So, the option-c is the correct answer.

Organolithium reagents

6. The major product formed in the following reaction is:



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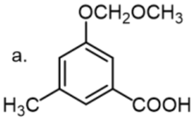

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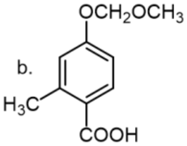

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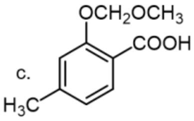

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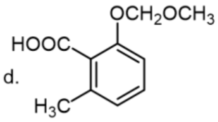


Correct option: c

Again there is a another important problem always comes in the exam the where I think this is the example of you take a carbonyl compound you take tosylhydrazine and ethanol and then you treat with excess butyllithium and finally you use DMF. So, there could be a several different variation in this type of questions, but if you see the first two reagent can directing you what you are going to form. Now, the last one could be DMF could be other different electrophile based on that you will get a different product. So let's try to understand.

So this is an example of a Shapiro reaction. I think I already talked about Shapiro reaction when I talk about lithium chemistry. If you forgot please go back to that notes. So let's try to understand what you are going to get in this particular reaction. So which will be your product.

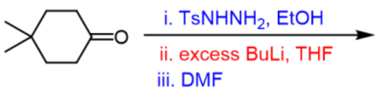
So let's try to draw the mechanism of this reaction. So what you have learned that if you have a hydrazine and you have a carbonyl compound the first thing is formation of hydrazone. So once you have -$TsNHNH_2$, the tosylhydrazine going to form the so there will be loss of water you are using ethanol as a solvent in this reaction I am sure nobody has any doubt up to this. and then now what you are doing we are treating n-BuLi excess. So, once you have a n-BuLi the first thing is you can see in this molecule this is the NH proton is the acidic one. So, there will be deprotonation of that N minus Ts if you have a more n-BuLi So, next this will be the acidic proton.

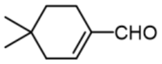
So, this will be taken by the n-BuLi to generate the corresponding carbanion. This will come back this will form a nitrogen nitrogen double bond get rid of the tosyl the nitrogen minus and double bond here, this minus will come back and cleave this carbon nitrogen bond. So, you have already a lithium plus in the medium. So, you can write as a carbanion or you can write as a vinyl lithium either way is fine, but once you have this corresponding lithium, vinyl lithium if you treat with DMF.

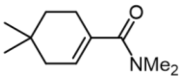
The structure of DMF. So, lithium is going to attack to the carbonyl group and it will come back and get rid of the NMe_2 to get to this product. So, the carbon will get out there will be a CHO going to introduce and there will be double bond here. So, now if you look into all the different options I can see the option number a is the correct structure, but the b or the c or the d do not have the correct structure. So, the a is the correct answer here.

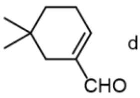
Organolithium reagents

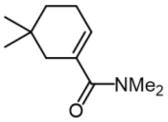
7. The major product formed in the following reaction sequence is:



a. 

b. 

c. 

d. 

Correct option: a

So, now we are going to talk about what is the major product A and B in the following reaction sequence

So, if you look into this particular compound by looking into the compound. I can see this compound can be called as a 1,3-dicarbonyl compound if you can 1, 2, 3. So, it is a 1,3-dicarbonyl compound you treat it with 2 equivalent of LDA. So, let's try to understand first what is happening here. So, I think we have already learned before that if you have a 1,3-dicarbonyl compound then the proton in between this carbon is the highly acidic one because it is having two different electron withdrawing group . So, if you give a base LDA it is going to abstract that proton and form the corresponding carbanion and you can write that.

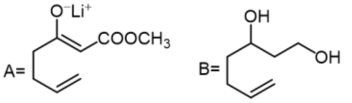
Now, if you treat with one more equivalent of LDA which is the next acidic proton this is the acidic proton, the CH_3 carbon correct, -CH_3 attached with the carbonyl group. So, now, if you treat with another LDA this will go for a deprotonation of this proton to generate another carbanion here. you can write it like this also as enolate form . So, now, if you have dienolate form and you treat with allyl bromide what is going to happen how it will trap with electrophile. Now, if you try to write that down that you have electrophile here you can think about this will, this minus will come back and this can able to react because these are in a conjugation.

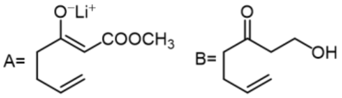
So, you will be able to form this will be a compound A of course, once you have O minus you can write lithium plus and if you look into all the different options you can see in this option also has the correct structure and of course, here also you see find a correct structure option both in option a and b, we can see the a is Now, what will happen if you treat lithium aluminum hydride and H_3O plus? Again instead of writing this in the enolate form we can also write it you can also if you get a proton here because it will not going to stay at the end of the reaction it once you quenched the reaction it will convert to this compound. Now, if you take this compound treat with lithium aluminum hydride again I talk about lithium aluminum hydride when I talk about hydride reduction in organoboron part. So, that this is a very reactive one it is going to reduce both the ketone and the ester. In case of ester it is going to reduce twice because first if you do reduction of the ester it is going to generate corresponding aldehyde It will go for further reduction because aldehydes will be more reactive than ester it will go all the way to the corresponding primary alcohol. So, you will get and this ketone is going to reduce to the corresponding secondary

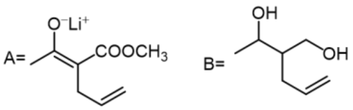
So, you will have a secondary alcohol and a primary alcohol here. Now if you look into the different answer of a and b We can see in case of a and this looks the correct answer, but if you go to the option b, this does not looks the correct answer because the carbonyl will be also reduced here. So, the option a is going to be the correct answer here.

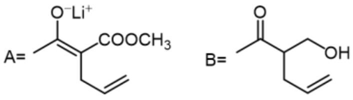
Organometallic compounds

8. The major product A and B in the following reaction sequence are

(a).


(b)


(c)


(d)


Correct option: a

The major product formed in the following reaction is. So, the again there is three different reaction happening first they using LDA to abstract a proton. So, that should form some sort of enolate then they are treating with this $ICH_2CH_2CH_2Cl$ again it is a alkyl halide happening.

So, after enolization there will be alkylation and then you are treating with methyl magnesium bromide and then H_3O plus ok coinciding with the acid. So, let us see how this. So, if you look into this particular compound which proton will be acidic proton if you give a base of course this side of carbon will have a double bond. So, this these protons which is next to the carbon will be the acidic proton one of them will be abstracted once you give LDA. So, we can understand if you give LDA is going to form this corresponding enolate.

Now, you treating with ICH_2CH_2Cl. So, of course, this is the alkylation going to take place. So, if you write CH_2I and then $CH_2CH_2CH_2Cl$. 1, 2, 3, 4, there are 1, 2, 3, there are only 3. So, this is a Cl here.

So, this is going to come back and go for SN2 reaction. See that alkylation happening first and now what you is happening. So, this is going to be your A. So, now, if you look into the all the different options here we can clearly see in option-a, this is cannot be right. The one here also cannot be right because the iodine will be better leaving group.

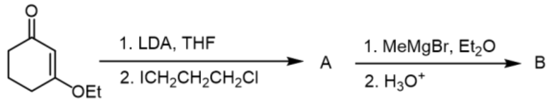
So, this option seems the correct option. Now, we have to also consider what will be the option-b. Again once you got a now if you treat with methyl magnesium bromide, what is going to happen if you treat with methyl magnesium bromide? We know that methyl magnesium bromide is a hard reagent. So, it is going to react with your carbon compound that will and then that will generate this O minus and methyl here and you have this corresponding Cl here. And now what you have done once you take this compound all the way you have O minus methyl and -OEt you give H_3O plus some dilute HCl. Once you give dilute HCl there is couple of things going to happen one is that this will be -OH and then you have a methyl of course, this part will get protonated.

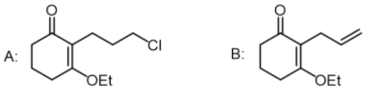
So, this will get protonated here once you have I think you can think about that this -OEt can able to take a proton like and it can be hydrolyzed. I think first thing going to happen let's leave this first. So, once you have a this one we cannot find any answer we can see in this answer there is a double bond here. So, let us think if you have this -OH and methyl here we are bringing a double bond and here you are bringing a carbonyl that means, what is going to happen this vinyl ether in presence of a H_3O plus, it is going to hydrolyze to the corresponding ketone. So, your vinyl ether going to convert to the corresponding carbonyl group here and now you have a -OH and a methyl So, this can get protonated and these are the protons going to be the acidic.

So, this can eliminate it can able to convert to a very similar to the corresponding aldol type reactions like where you have a carbonyl group and an elimination happen to get to the corresponding condensation product So, this will be the your the correct product which is going to form that is your B . Now, if you look into the answer of course, this is the going to be the correct answer. So, option-c, is the correct option here.

Organometallic compounds

9. The major product formed in the following reaction is:



(a)


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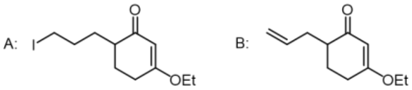
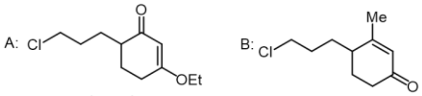


(c)


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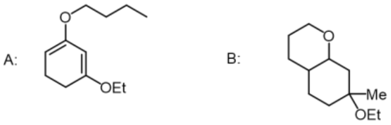


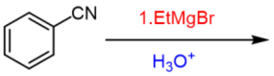
Correct option: c

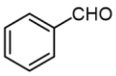
The major product formed in the following reaction. So, here you have this corresponding -CN group where the Grignard is going to get attacked.

So, you have this phenyl with a where your ethyl magnesium bromide going to attack on the carbon N-MgBr and you will have a ethyl Now of course, once you have a H_3O plus this can protonate this and as well as once it can take you to the NH and then also once you have a H_3O plus This is a imine, this is from iminium and going to hydrolyze to all the way to the corresponding ketone. So this will be the your product. So, you can see this is not the correct option, this is going to be the correct option here option-b. So, if you treat with the aryl cyanide in Grignard you will end up getting to the corresponding ketone. So, you can see option-b is the correct option.

Organometallic compounds

10. The major product formed in the following reaction:



a.


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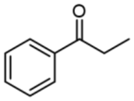
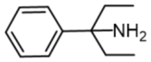
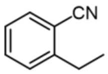


c.


d.


Correct option: b

Again in this particular part i talk about some of the problem from organolithium and also from the carbanion and also i will encourage you to practice more problem and if you have any other queries of course you can come back in the chat So thank you so much for coming to the class and i am going to see you in the next class thank you.