

Lecture 13A • 02/22/12

This problem was almost an accidental problem. I was looking at that original ketone and thinking: how could I do two different Grignard reactions. You notice that in one case, we end up with an alkene where a ketone used to be, so you could imagine that maybe a Grignard occurred and then either an elimination or a dehydration. But on the other end, there's no functional group there. [But,] this is a good problem because you have to exploit a trick to get it to work, because if I were to create a functional group like an aldehyde where I could do a Grignard here, we'd get one alcohol here, but, if I didn't do some form of protection, this ketone would also react, which would also put an alcohol here. How could we deal with this situation where we've got an alcohol there, an alcohol there, but only one of them we want to dehydrate. The trick is: what kind of alcohols are formed?

Let's analyze this carbon backbone so that we could see that a Grignard approach would probably be the best approach. We're going to learn another reaction that we could use that would be an easier way to get the same product. Analyzing the carbon framework, I've got a five-carbon fragment that has a functional group at the second position in, and then a double bond, which I'm going to circle the end of that double bond, because we have changes that occur at exactly both of those locations that we could identify in the product. Here's a five-carbon fragment that has a functional group at the second position and the fifth position. We see that there's two new carbons added to each of those positions, and so that would correspond to something coming from ethanol. A Wittig reaction is not really appropriate for the lefthand side, for the ketone, because, at least for the original product that I have shown, that wouldn't be what you'd get from a Wittig, because the Wittig adds a carbon and the carbon-carbon double bond forms to that new carbon; here, we have the double bond pointed towards the interior, which that indicates some kind of elimination or dehydration's going to go on. Since you don't know how to control one versus the other, that's why I said or, because you have this other byproduct that's going to be formed. There's a two-carbon fragment, then we have the other two-carbon fragment over there. Again, looks like a Grignard.

Let's do the two Grignards, and then let me show you the trick that can be done. First, let's get what we need for the Grignard at the end of the molecule; let's get that aldehyde. To get there, we'll do hydroboration-oxidation, cause that'll put a functional group at the end of the molecule, and then we could oxidize with PCC. That's the carbonyls; then we need the Grignard reagent. We could start with ethanol, make a halide, make the Grignard reagent. Then we take that carbonyl source and react it with two equivalents of that Grignard reagent. That'll completely react both carbonyls. We'll initially end up with a double alkoxide, which we could then protonate. If we did this approach, you might say: what about protecting groups? Can we protect, somehow, a secondary versus a tertiary alcohol? Possibly, but it's something beyond the level of this course. Could we eliminate one alcohol versus the other? The secondary alcohol, in terms of elimination, might be a little bit less reactive than the tertiary, because the tertiary carbocation would be easier to form instead of a secondary, but that might be a tricky transformation to pull off.

Here's another thought: what happens if we through the Jones reagent at this? What happens to the tertiary alcohol? Nothing. What happens to the secondary alcohol? You make a ketone out of it, which means if you use hydrazine and then sodium hydroxide and heat, we can do the Wolff-Kishner reduction and get rid of that ketone. Very sneaky, because we take advantage of the fact that one of these alcohols can be oxidized, the other can't. To finish it up then – and this is the part that's a bit unsatisfactory – we could attempt an elimination to get our product. The main ideas to take from this are to analyze the carbon framework – could you at least figure out where a Grignard reaction needed to happen, even if you couldn't quite figure how to make the right one happen at least the way that you wanted to. This is another example of using the Wolff-Kishner reduction to get rid of a carbonyl.

You could take the alkene, turn it into the alcohol. We could protect the ketone, make a Wittig reagent; that would survive; do the Wittig reaction, then hydrogenate the alkene that forms, then go back and do a Grignard on this position.

[quiz 2]

Problem 2, mechanism problems. First one was butanal reacting with ethanol and acid. This was the class protonate-open-attack-deprotonate mechanism. Protonate – this is not the imine case. [In this case, it's not likely the] alcohol will attack the carbonyl first. Alcohols are not very basic, so there's not really any good driving force to having an alcohol attack and push open the carbonyl. In this case, it really is protonate first, and then whatever else you want to show. It is possible to combine the open and attack steps, because the opening of that carbonyl, that's just resonance; if it's resonance, it doesn't matter where you write it, really. In fact, some people write the carbonyl bond as being the thing that attacks H⁺ directly – again, because it's a resonance structure, so it doesn't really matter which way you write it. Whether you show the opening by itself or whether you show this combo, both would be ok. The one advantages of showing it this combined way, it reduces the number of times you have to write everything. After that attack, we'll have a deprotonation occur. We're now at the halfway point; this is a hemiacetal. In either a hemiacetal or acetal, you're going to have two oxygens attached to the same carbon. For a hemiacetal, one oxygen has an R group; for the acetal, both oxygens have an R group. In all those cases, there's a hydrogen attached to the common carbon. A hemiacetal is similar to a hemiketal, in that usually they're not isolatable; usually, they're not favorable, so the reaction's not likely to stop here.

We'll go through another cycle of protonate – in this case forming water, which'll act as a leaving group. It will open up. At this point, a carbonyl is not likely to form; this is not the case of an imine. Nitrogen is able to have a lone pair delocalize and then, if you start out with a primary amine, deprotonate. Here, this won't happen because the oxygen, if you formed that carbonyl, couldn't be stabilized, so instead, an alcohol comes along and attacks. Then again, we have one last deprotonation step.

The other mechanism problem. What functional group is this? An imine. Where do imines come from? Aldehydes or ketones. When you're given this, and you're also given the hint that maybe something was happening in reverse, the reverse of being an imine would be to form the imine, from the aldehyde or the ketone. Once you realized that, then you've got to come up with a mechanism that will get you back to that aldehyde or ketone. You realized that, since I had also highlighted the fact that we're in acidic conditions, the only logical step was for the nitrogen to attack hydrogen. If you showed the double bond attacking hydrogen, that would have been fine too; that's conserving steps, combining the resonance step in just like the previous mechanism. Realize that the carbon where the double bond is, it's got a hydrogen already, and it's not likely to take a second hydrogen and leave a positive charge on nitrogen by nitrogen not having an octet. In other words, because nitrogen is more electronegative than carbon, it's more likely that you're going to get carbon plus, not nitrogen plus. If you weren't sure which way to open the bond, that's why you were given the hint that this is a reverse reaction. If you look at [formation of an imine], one of the last things that happens is a lone pair coming from nitrogen to make the carbon-nitrogen double bond, which is why in reverse, it's the carbon-nitrogen bond that opens up to the nitrogen. There should be a plus charge [on nitrogen], and the double bond opens to the nitrogen.

Since water is one of the reagents, water can now come in and attack; then, we have deprotonation. What is the name of this functional group? Carbinolamine. The reason I point this out is that [a] carbinolamine is the nitrogen equivalent of a hemiacetal or a hemiketal; it's that halfway point, it's that stopping off point to getting all the way to an isolatable product, so it won't stop here is the point I'm making. The nitrogen will again get protonated. Then, remember the goal is to get to an aldehyde or a ketone. The way we're going to do that is for the carbon-nitrogen bond to break. If that doesn't make sense, then look at the reaction in the forward direction and you'll see that there's a nitrogen that, in forward direction, would be attacking, so in the reverse direction, like what we're doing, it opens up. Part of the justification for why it's able to open up is because it forms a carbocation right next door to an oxygen. Even though that's a primary carbocation, it's stabilized by resonance. A deprotonation can occur, which means we end up with the aldehyde. If you compare the product I just wrote with what we started with, we could see both contain five carbons. You can seek it's the nitrogen that wrapped around to make the imine with the carbonyl. Once you've seen the answer, you could easily go back and say of course that makes sense.

Fill-in-the-blank problems. First one was unusual. It was a multiblack fill-in-the-blank. Something reacts with triphenylphosphine to make an intermediate, which reacts with butyllithium to make yet one more intermediate, that reacts with cyclobutanone to make a product. This question, you had to recognize, was a Wittig reaction. If you know it's a Wittig reaction, you know that the cyclobutanone is going to become the four carbons I just circled in the product. But that means that we have three more carbons that somehow get added in. That means that in all three boxes there, you're going to have a three-carbon chain: but what kind of three-carbon chain? If this is a Wittig reaction, then the step right before the end, you have to have the Wittig reagent, which you could write in one of two ways: you could write [it] as this octet-expanded phosphorus, or you could write it as the zwitterion, having the positive on phosphorus, negative on the carbon right next door. The negative on that carbon comes from deprotonation; that is the point of the butyllithium. One step right before, then, is the tetraalkylphosphonium salt. Real life reagents, you can't take a cation and put it in a bottle, an anion and put it in a bottle; it has to be a compound, a combination of some important cation, but with a counterion present. You really should have showed bromide, chloride, iodide, tosylate, something else that would have come from the leaving group, because that's what the triphenylphosphine would have reacted with, is some form of leaving group. It didn't have to be bromide, but since I wrote bromide along with the phosphorus in the next step, that's why I put bromide as my leaving group in the first place.

The last one was the one that had that note about organometallic on it. This was a Grignard reaction, [but the reagent is not just Mg and ether]. The question wasn't asking you to synthesize a Grignard reagent, it was seeing if you could recognize that's what you needed. It turned out [for a similar problem] there were two answers that were possible, just as there are two answers possible in this case. The carbon where the alcohol is is where the carbonyl used to be, or used to have to be. The new carbon-carbon bond forms to where the Grignard reagent is; it has to be either one side or the other. That means we could analyze this two ways: it could have been phenylmagnesium bromide, just the benzene portion of it, reacting with a four-carbon aldehyde. It had to be an aldehyde because you don't want any alkyl groups, other than the four-carbon group where the alcohol ends up. That's one possibility. It could have also been: cut one carbon off the chain, make that the Grignard reagent. If you look where I've circled, the new carbon-carbon bond, there would be three carbons; there's your three carbons. It would then have to attack not benzene, but benzaldehyde. There was one more answer. The other answer is to use an epoxide, cause if you use a two-carbon fragment, and if you used a ketone or an aldehyde, it wouldn't give you the right structure. But, remember, for an epoxide, it attacks at the less-substituted position, so the alcohol would end up exactly where we need it. That's a Grignard reagent, that counts as an organometallic, so this would have also been a correct answer.

[exam review]

[POAD – acetals, ketals, hemiacetals, hemiketals, imines, enamines, carbinolamines, oximes, hydrazones, hydrates, and cyanohydrins]

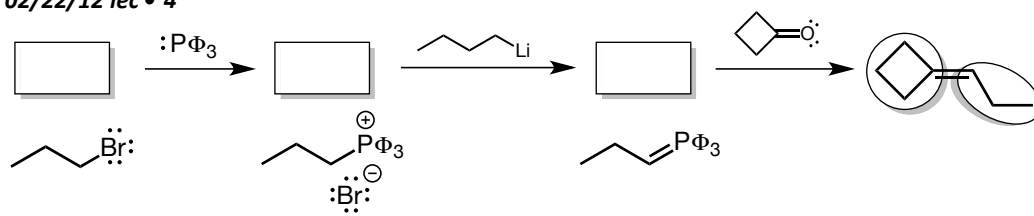
[reactions of carbonyls – Wittig, Grignard, Wolff-Kishner reduction]

[protecting groups – DHP, TBDMSCl, ketals and acetals for carbonyls]

[types of amines]

[tautomerization – mechanism and why it occurs]

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