Lecture 14B • 02/21/12

Synthesis problem. You have two starting materials – you have ethanol and then this five-carbon combination ketone/alkene. Somehow you had to end up with something that had a total of nine carbons. We're going to do the same thing that we did with the previous round of synthesis problems: let's start with the carbon framework first. We have a five-carbon fragment, three carbons of which are involved in functional groups. We can see that there's a functional group at the second carbon in, where the ketone is, and in the product we can identify a similar five-carbon piece that also has some functionality at the second position. Then, we also have a new carbon-carbon bond that includes the end carbon of the five-carbon piece, which would correspond to one of the two carbons of the double. It looks like we've got here two Grigard-type reactions, two carbon-carbon bond forming reactions. The only complication here is the fact that there's no alcohol at one of the new positions of the carbon-carbon bond; we have a double bond instead at the other one. Part of this simple, part of this tricky, because the Grignard part of it itself you hopefully more easily recognize. Can we get up to this molecule somehow. The really tricky part of this question is: can you get one Grignard reaction with out the other happening, because what are you going to do if you have two different alcohols, one that you just need to completely get rid of, and then the other one that you need to eliminate somehow. There's some sneakiness here as well, because: what kind of alcohol would form in the position where the ketone started? Tertiary. So after a Grignard attacks that carbonyl, you end up with a teritary alcohol. Can tertiary alcohols be oxidized? No. Looking at the alkene, alkenes can't react directly with Grignard regents, so we're going to have to do something to convert it into a carbon source of some sorts. Or, there is going to be a reaction that could also allow us to do another style of what looks like a Grignard, but instead of having to have a carbonyl, you could have just an alkyl halide. It's not an Sn2 mechanism, but it's an alternate organometallic route. With what we've learned up through so far, though, one could imagine that we could try to put the functional group here at the end of the alkene – we've already seen hydroboration-oxidation as a way to do that. We could then turn that into an aldehyde, which we could do a Grignard reaction on. What kind of alcohol would that be, though, if we did make an aldehyde and then attack it? The alcohol that you produce would be a secondary. Can you oxidize secondary alcohols? Yes. Can you oxidize tertiary alcohols? No. So here's the sneaky part of this sequence. We'll do both Grignard reactions, because we'll be able to take advantage of the fact that one position is a secondary versus a tertiary; we'll be able to do it like this.

First, if we want to do two Grignard reactions at once, we need to get the alkene to be something that can be attacked by a Grignard, so we need an aldehyde. First, borane and THF, followed by hydrogen peroxide and sodium hydroxide. That'll make a terminal alcohol, which we can then oxidize with PCC and pyridine to form the aldehyde. We're doing a Grignard reaction; we need a Grignard reagent. Since I tend to make alkyl bromides, I'll do so here, using PBr3. React with magnesium in ether, that'll make our Grignard reagent. I'm going to throw a two in front of here; you take two equivalents of the Grignard, plus this aldehyde/ketone, combine them. We'll initially get a dialkoxide, which we could work up with acid to make the dialcohol. Here's where the sneakiness comes in: if you oxidize with Jones reagent, one of the alcohols stays an alcohol, because it can't be oxidized; the other alcohol that can be oxidized turns into a ketone. Now I'm going to use the same trick that we used in a previous example. If I react with hydrazine, followed by sodium hydroxide, that's the Wolff-Kishner reduction. Base won't do anything to the alcohol, so the only thing that happens is we lose the ketone. Now, if we turn it into a leaving group, and then do an elimination, we might get an isomer because we can't guarantee which way elimination's going to occur, we could get the alkene.

[answers to quiz 2][functional groups]

An acetal is some kind of functional group that derives from an aldehyde. An aldehyde is a carbonyl that's got hydrogen on one end and something on the other, either hydrogen or carbon – of course, if it's hydrogen, that's just formaldehyde, a one-carbon aldehyde, but that's possible; otherwise, we've got some kind of R group. When you make an acetal you're converting the carbonyl to a double ether; that means the hydrogen's still there. Hemiacetal means it's part ether, part alcohol; you've got one of each where the carbonyl used to be. For the acetal or hemiacetal, there has to be a hydrogen attached to that common carbon. For a ketal or a hemiketal, there can't be a hydrogen there, because a ketone doesn't have a hydrogen where the carbonyl originates.

Nitrogen always has three bonds of some sort: either a triple bond, a single and a double, or three single bonds. [imine – carbon-nitrogen double bond; enamine – carbon-nitrogen single bond attached to a carbon-carbon double bond]

For the mechanism question, the first mechanism was ethanol and butanal. That's just protonate-open-attack-deprotonate. Once you protonate that carbon, it is technically delocalized. The short cut is, if it's delocalized, we don't really have to make a separate opening step, where you're showing the resonance, because all you're doing is writing a resonance structure. You could technically show that opening at the same time you show something come in to attack. Anywhere where just resonance is involved, it doesn't really count as a step. This does save us some time writing. We'll be left with an –OH group, then there'll be a deprotonation that occurs. Remember that deprotonation, those arrows always point to the atom that's going to end up with the electrons; arrows always show where electrons go, not atoms go.

You start off with an aldehyde; what you're going to get is an intermediate, but it's normally it's not an isolatable intermediate; it's like we're in between a real product and reactants; this is the hemiacetal. Another round of reaction's going to go on. If you can't remember the sequence, the first step is to effectively stuff one molecule of alcohol on here; there's a second one that get's added in, but it has to have somewhere to go, so that place we make by reacting and getting rid of water. Water gets protonated and then leaves. At that point, we have a carbocation which, if this was nitrogen and not oxygen, nitrogen would be able to take a lone pair, delocalize, and stabilize the carbocation. We don't have that ability with oxygen, so there's no carbonyl that can form here, or if there is, you can't isolate it. The next thing that happens is another ethanol attacks, and then final deprotonation to make the acetal.

It was the second one where there was some difficulty. What is the functional group? It's an imine. Where does an imine come from? What is the one functional group that we've been talking about this whole time? Carbonyl-containing groups. Think of the context that this is going on in. What carbonyl-containing group would we have? An imine is where you take the oxygen of a carbonyl and just stuff a nitrogen in it instead; if you think about the overall transformation, the carbon-oxygen double bond turns into a carbon-nitrogen double bond. The reverse reaction's what happens, the reverse of forming an imine. How do you form an imine? Through a modified version of protonate-open-attack-deprotonate. How does that mean the imine reacts? By a modified version of protonate-open-attack-deprotonate. The reverse direction is not so modified. I then said something about this being in an acidic aqueous environment. If you couldn't remember the functional group name, if you couldn't remember the mechanism, if you couldn't understand that this was a reverse reaction, underneath everything else, we've got H+ and nitrogen, what's going to happen first? Protonation's going to occur. Not knowing anything else about what reaction this is, what happens when you protonate? You end up with the hydrogen on there. We protonate it; what's going to open? The only thing that makes sense to open is that double bond; taking the hydrogen off would be going back to where we just started from. Breaking any carbon-carbon single bond, not favorable; the double bond, that's just resonance. Attack – what do you have? Water. And then, we deprotonate. What is the name of this intermediate? A carbinolamine. A carbinolamine is functionally much the same as a hemiketal or a hemiacetal; you're halfway there, this normally can't be isolated. So, it's another round of protonate-open-attack-deprotonate.

What get's protonated though? If we protonate the oxygen, we're going back to where we just came from, so that doesn't make sense. The only thing that would make sense that could react is the nitrogen; it gets protonated again. Something now needs to open. The carbon-nitrogen bond, there's be nothing favorable about having that break, because even if that left a neutral nitrogen, you're trying to make carbon minus, that's not favorable. You've got two possibilities: the bond breaks so that the electrons go to nitrogen, so it becomes neutral, that makes a primary carbocation, not favorable. We open the other way. You might think: how could that ring open? If you break that bond, you form a positive charge right next door to oxygen, which stabilizes that positive charge. It looks unusual, but this is exactly what happens. If you count, we have five carbons in the compound, and when it first opens, we just have a carbocation, which can undergo resonance. Our last step is deprotonation, and we end up with a combination amine/aldehyde, 5-aminopentanal; amino- is the functional group [prefix] for a NH2 substituent.

The last problem were fill-in-the-blank problems. This first one, we had something that reacts with triphenylphosphine that forms something that reacts with butyllithium that forms something that reacts with cyclobutanone to make an alkene. The key to solving this problem is you had to recognize it was a Wittig reaction. It works best to work backwards. If you look at the ketone that we've got, those four carbons of the ketone must be in the product. Whatever was not part of the ketone was part of the Wittig reagent. If there are three other carbons there, they were part of the Wittig reagent. The Wittig reagent only has one form: you have a phosphorus-carbon double bond, or, alternately, you could show it as phosphorus charge plus, carbon minus, a zwitterion. There's no lithium in that reagent, that's not a reaction that you've learned. Even if we had seen a lithium reagent, that would act as a Grignard reagent, not a Wittig reagent. The lithium in that butyllithium, that butyllithium was just there as a base; the lithium doesn't get involved or incorporated into the reagents. The step before was before you had to [de]protonate it to make the Wittig, so what you would have had then is positively-charged phosphorus, and then technically some kind of counterion; I wrote bromide only because I'm going to start with a bromide. You could have shown chloride, you could have shown iodide, you could have show tosylate, mesylate, triflate, and of the sulfonates. You can't put into a bottle a plus charge by itself or a minus charge by itself, so whenever I ask for a reagent, you need to write the whole thing out. Backing up one more step, the way that a Wittig reaction starts is by having something with a leaving group – an alkyl halide or alkyl sulfonate.

The last one, you had two boxes: one that didn't have any special notation on it, the other that said: an organometallic reagent. You make an alcohol. The organometallic part, that was a clue that this was a Grignard reaction; the organometallic reagent would therefore be a Grignard reagent. We had done a problem where we formed an alcohol, and it turns out that there were two ways we could have made it. The alcohol that's in that product had to have come from the carbonyl, and a carbon-carbon bond has to form to that carbon that the alcohol is one. What that means is that the carbon from the benzene, maybe that's the new bond, or instead, this was some benzyl substrate and it was the carbon-carbon bond the other direction that was the new carbon-carbon bond. If you pull those apart, you get two possibilities, then: one is that we had phenylmagnesium bromide as our Grignard reagent and a [four]-carbon aldehyde as our substrate; or, put one more carbon on the benzene ring, make it the aldehyde, which means you would have one less carbon, so I would need three carbons.

[Exam review – POAD, acetals, ketals, hemiacetals, hemiketals, hydrates, imines, carbinolamines, enamines; reactions of carbonyl – Wittig, Grignard, Wolff-Kisher reuction; protecting groups – DHP, tert-butyldimethylsilyl chloride, ketals and acetaols; types of amines; tautomerization; cyanohydrin

You might remember halohydrins; that's where you've got a halogen and an –OH group, so it's like part of water; that's where the hydrin part of the name comes from. Cyanohydrin means you're going to create a functional group that's part water, part cyanide – in carbon terms, that's called a nitrile. Cyanohydrins can form by reacting a carbonyl compound with HCN. Protonation can occur first; we make the resonance structure next; since we've got cyanide in solution, we can come back around and attack; and this would be the cyanohydrin.

_____

cyanohydrin

_____

Structures *(remaining structures identical to lecture 13A)*

02/21/12 lec • 1

carbinolamine