

Lab 8B • 02/16/12

Let's start with one of the simpler synthesis problems, which would be the conversion of butan-2-one to but-2-yne, which is just a functional group conversion. [To convert an alkene into an alkyne,] we did that by reacting the alkene with bromine, Br₂, which made a vicinal dihalide, and then we did a double elimination. Do we know of a way to go directly from a ketone to an alkene (what we need to make the alkyne). Yes, a Wittig reaction will go straight from a ketone to an alkene, but it adds carbons in the process. You notice that we start with four carbons, we end with four carbons, so Wittig would not be the right approach in this case. But, we know how to make alkenes from things like alcohols. Can we make an alcohol out of this? Easily, yes. So that's the sequence of conversions: start with the ketone, make it an alcohol; from the alcohol, we have a couple of different routes to make an alkene; from the alkene, we could then end up at the alkyne. To make an alcohol, reduction. [One very common mistake is] not putting the 1/2 in for reduction, which you have to do. If you don't put the one and two in, what that means is that sodium borohydride and H⁺ are reacting at the same time, which they would, but just with each other, you wouldn't actually get reduction, you'd just destroy the sodium borohydride. So 1/2 means first react with sodium borohydride, then, separately, react with H⁺. It's not a small detail. Same thing applies to a Grignard reaction. Remember that immediately after a Grignard reaction, all you have is an alkoxide; then you have to do that H⁺ workup to get that alcohol.

We now have an alcohol. I stated that we wanted to get an alkene from it. We could just do direct dehydration, because the internal alkene is going to be more favorable, and trans should be the most favorable of that, although it might be possible that we get some cis. It doesn't matter which one you make, because by the time you get to the alkyne, there is no stereochemistry anyways. Besides dehydration, we could turn it into a leaving group, turn it into a tosylate, for example, and then we could eliminate. But we have to eliminate with something basic, but it can't be bulky. t-Butoxide is a reagent that can cause thermodynamically unfavorable behavior. If I tried to use potassium t-butoxide, I'd make the terminal alkene instead of the internal one. Now that I'm at the alkene, it's a two-step conversion to get the alkyne: make the vicinal halide first, and then do the double elimination. So, Br₂ without light, because light would cause free-radical halogenation, which is where you just put one bromine on (if you could control the reaction). To put two bromines on side by side, that's Br₂ just by itself. The stereochemistry here does not matter, so you can do the double elimination to make the alkyne. Two equivalents are necessary because you are doing two eliminations. If all you're trying to do is deprotonate an alkyne, then you only need one equivalent of the sodium amide, because one base will remove one H⁺ from the alkyne.

[Can you go] from the ketone to some kind of alcohol and then do a double dehydration that way. There's no reaction that you know of that can go to a vicinal diol. You could make a hydrate. In the case of a primary alcohol, where we overoxidize, we can take advantage of that hydrate because the reagent that would cause the oxidation is already present. But in this case, if we tried to make a hydrate, if we then did any other step, the hydrate wouldn't be the thing that's around, because it's not favorable to be made. It turns out to be extra steps, but there is a reaction of alkenes which does produce a vicinal diol; that's the molecule osmium tetroxide. The vicinal diol, however you make it, you still would then have to go through a leaving group, because alcohols, you could dehydrate once, but notice, if you dehydrated this diol, you're going to end up at the starting material again, because after you dehydrate once, you'd make an alkene, but you'd have an alcohol on that alkene; that would tautomerize and then get you back to the ketone. So we'd have to make leaving groups, but on paper, it works, because at least you do get to the product.

Let's move to the next level of difficulty, which is, aside from just converting functional groups, we're going to change the number of carbons. Second problem I'd like to do is where we take that same ketone, somehow react it with an alkene to make a larger alkene. Here's the approach you should take from now on in any of these synthesis problems: look at the carbon framework of the reactants, look at the carbon framework of the products. At the moment, normally the number of carbons in the reactants should equal the product's; the only exception that we had to that was one of the synthesis problems that we had before [we we had some kind of one-carbon compound] that we reacted with itself to make a two-carbon compound that then reacted with something. [For now, you] should never end up with fewer carbons in your product than you start with. That'll change once we learn ozonolysis. Coming back to this problem, we start with four and four, we end up with eight; four plus four is eight, so that's a good sign. But besides just looking at the number of carbons, you need to look at what functional groups are present. So if we look at the first molecule, we have a four carbon fragment, yes, but it's one that has a functional group at the second carbon in. If we look at the product, we can see the same type of pattern: a four-carbon fragment that has a functional group at the second position in. We have another four-carbon fragment that has an alkene. Alkenes we've used in the past as a functional group that bridges two positions. I'm reminding us of that because we may use that as a trick later on, where, for example, we made an epoxide, we could attack at one carbon and then end up with a functional group at another. For the moment, let's just recognize that we have that second four-carbon fragment with a functional group at the terminal position, at the first carbon, which means what?

We've made a new carbon-carbon bond; we've made a new carbon-carbon antibond, so it's likely that we're going to want to do a Wittig reaction. If we need to do a Wittig reaction, we need a ketone or aldehyde, which we already have the ketone, and we need the Wittig reagent. What that really means is that we have to convert that alkene into a Wittig reagent, which means somehow we need to put a functional group at the end of the molecule.

How can we do that? Hydroboration-oxidation; that's the route we're going to take. Start with the alkene, react it with borane•THF and then oxidize. We'll make an alcohol, which then we turn in to a leaving group. React that with the triphenylphosphine; that'll get our alkyltriphenylphosphonium salt, and then use butyllithium to make the Wittig reagent. If you react the Wittig reagent directly with the ketone, then you jump directly to the product. One approach might be to do this as a Grignard reaction, but there is a concern, which is this looks like a thermodynamically favorable product – we've got three substituents on the alkene. But if the double bond was here instead, you would still have three substituents on the double bond, so it likely would be almost equal in energy. Because of that, a Grignard would probably not be the best approach.

Let's go a little more complicated. We had 3-bromopropan-1-ol and an alkene that we used to make a diol. Let's do the same type of functional group and carbon analysis. We have a three-carbon fragment, a three-carbon fragment, we end up with a six-carbon product. Three plus three makes six, so we need to somehow join the fragments together. We're making a new carbon-carbon bond. Notice that that means that carbon-carbon bond needs to be right in the middle of the molecule here. Trying to identify the fragments, I have a three-carbon fragment that has functional groups on either end. In the product, I have a three-carbon fragment that has one of those same functional groups at one end, the alcohol, and is part of that new carbon-carbon bond. We have functionality at both ends of the three-carbon fragment; [it] matches one of our starting materials. The other three-carbon fragment's gotta be the three left-over carbons. We have an alcohol at one carbon and again part of that new carbon-carbon bond at the other. The matches the fact that we have an alkene, because an alkene's got two functionalizable positions. We end up with two functional groups, but notice that we end up with the alcohol not where the new bond is formed, which means what? What are we going to use synthetically? What's a trick that we're going to have to employ. Epoxide, because of exactly what I was mentioning earlier. We make an epoxide out of this alkene, we could attack the less-substituted position, put an alcohol at the more substituted position, which would make it look exactly like the product. So we need an epoxide from this alkene, and we need a Grignard reagent from this starting material.

But, that's a problem, because as soon as we try to make a Grignard reagent out of that, it's going to neutralize itself, because alcohols are acidic, compared to Grignard reagents. That means we're going to have to use a protecting group. This problem's purpose was two-fold: one, to show the use of epoxide, because they're a little bit trickier to analyze; and two, this is an alcohol protecting group problem. You've learned two different protecting groups for alcohols so far: DHP and silyl ethers. [I'm going to use a silyl ether] The alcohol reacts with tert-butyldimethylsilyl chloride; that will make the silyl ether, which I can then react with magnesium in ether to make the Grignard reagent. Separately, I need that epoxide. Remember that there's two ways to do it: one is to just react it with a peroxyacid, for example MCPBA, or we do have the option of a two-step process, using aqueous bromine to make the bromohydrin, and then sodium hydride to do the intramolecular Sn2. We can then react it, the epoxide that is, with the Grignard reagent we just made. Initially, that's going to get us an alkoxide. We could get away with using gentle acid at this point in order to protonate the alkoxide with out destroying the silyl ether. We had talked about TBDMS versus TMS, because this one is more tolerant of slight acidic aqueous conditions. But, we don't want the protecting group any more; we do want the alcohol back, because that's what our product is. So, instead of trying to be gentle about it, you just say acid, implying a stronger or more concentrated acid; that will both protonate the alkoxide and remove the protecting group, hydrolyze it.

Let's go on to what turns out to be another example of a protecting group problem. We have a ketone that has a halogen on it reacting with an aldehyde – methanal, also called formaldehyde – and we create a molecule that has both a ketone and an aldehyde on it. Let's do the same analysis again: four-carbon fragment, functional groups at the two and four position. In the product, we could identify a four-carbon fragment that has a functional group at the two and a new carbon-carbon bond at the four position. That matches structurally what we have in the original starting material. Then, we have a one-carbon fragment, which would be where that aldehyde comes from, so it would seem to make sense that we would need to make the Grignard reagent out of the four-carbon material, attack formaldehyde, and reoxidize the formaldehyde. But that's a problem, because we have a ketone, so as soon as we try to make the Grignard reagent out of it, it would react with itself. This is a carbonyl protecting group problem, which means we need to make a ketal. You can use, technically, any alcohol, but i'm going to keep on using the same one that I've used in problems, which is ethylene glycol. Take the ketone, react it with ethylene glycol and a little acid. That'll make a ketal. React that with magnesium and ether, and that makes the Grignard reagent. We already have a target carbonyl compound, the formaldehyde, so we react it with the formaldehyde. That get's us an alkoxide. Similar to previous problem, we need don't need to protecting group any more. We need to also get the alcohol from the alkoxide, so why not add acid – and technically water – to do both. That almost looks like the product. The last thing that we need to do is oxidize the alcohol to become the aldehyde.

Let's do the second-hardest problem. [mistake] [You have] a compound that has six carbons in it, but five of them are in a ring, one of them is separate. I wanted you to make a product that had six carbons in it, but all in a row. But, what I meant to give you was this, with an alcohol in it. Let's see if we can figure out why that would have been what I wanted to have you work on. We have what kind of functional group here? Not an ester this time, because there's no carbonyl. It's an acetal. If it's an acetal, that means there used to be a carbonyl right there. When I say hidden C=O, that means when you unfold this, when you decompose this, you're going to make a carbonyl at that position. What else do you have? Four more carbon attached. You still also have that oxygen attached; when this opens up, you're going to end up with an alcohol at the end of the molecule.

If we had a carbonyl at one end, an alcohol at the other, and five carbons total in length; look at what should have been the product; carbonyl, five carbons, with an alcohol at the end. What the problem's intention was then was to take the methanol that will also get spit off here and use that to perform a Grignard reaction. That would have been the way to add one more carbon to it.

We still can solve this problem, even though I forgot to write the alcohol. We still are going to need to start out the same way, cause we need the five carbons and the sixth one to put together. We're still going to do a type of Grignard reaction. The one complication is going to be: how do we get rid of an alcohol? If you react this with acid and water, two cycles of protonate-open-attack-deprotonate later, we have this omega-hydroxyaldehyde. We want to get rid of that alcohol before we do anything else, so that'll be the first thing that we tackle. Let me also point out that the other thing spit off in this is methanol. If you can't see this transformation, it's not unusual; rings confuse students every year. It would be excellent practice for you to try the mechanism on this to see if you could get to the product I've shown you. Let's see how we're going to get rid of that alcohol. One idea: convert that alcohol into a leaving group and then eliminate it. [be careful writing the product; make sure number of carbons is correct] I have a carbon-chlorine bond here. In a hurry, what [you might] do is get rid of the chlorine [by just leaving] out of your structure, but if you still have the bond line that's there, if you just take the chlorine label off of the paper, that means that there's a carbon there instead, so you inadvertently added another carbon. A bond line to a heteroatom disappears if that heteroatom disappears. We are at the alkene. How does that help us at all? Hydrogenate.

Another creative method: take the alcohol, again make it a leaving group[, more specifically, a halogen]. React it with magnesium, make it a Grignard reagent. Then, do exactly what normally you would not do: react it with water. If we're going to that, though, we gotta do something else before we can do that; you gotta protect it. Same problem as above: if we have a carbonyl there, we're trying to make a Grignard reagent out of it, it's just going to react with itself. So, protect it, then make the Grignard out of it. Now just react it with acid and water. Yes, we'll kill off the Grignard reagent – which is exactly what you want because that means there'll be no more functional group at that position. It's exactly one of those normally bad reactions that you hopefully addressed on your lab quiz, but now we want it to happen because we want to get rid of that alcohol. Kinda a sneaky way of doing it.

There's a third method, which required the sneakiest thinking. Essentially, the problem is we want to get rid of the alcohol. But, why do we have to get rid of the alcohol? Because what we really want is just a five-carbon aldehyde. An alcohol can become an aldehyde, can't it? What if we flipped the problem around, then. What if we say I want to get rid of the aldehyde so that I can turn the alcohol into the functional group that we need. What if we react it with this, hydrazine. What kind of functional group will a hydrazine produce from an aldehyde? A hydrozone. Hydrozones and oximes are similar functional groups. Why does this help us out? Because if you react this with base and heat, you'll just reduce off the carbonyl – the Wolff-Kishner reduction. Now we only have one functional group, which is what we want. We oxidize it with PCC, we get our five-carbon aldehyde. No matter which one of those methods – of if you even thought of some other methods – no matter which way we go, once we're there, we can now put the pieces together. Methanol reacts with something, maybe PBr₃, to make a leaving group, a halide specifically, which then reacts with magnesium and ether to make a Grignard reagent, which we could then react with the aldehyde. We form an alkoxide initially; we can reprotonate it by adding acid; and then oxidize, which since it's a secondary alcohol, we might as well use the Jones' reagent.

The last problem. What I wanted to do was create a problem where you had to use two different functional groups. Let me show you why I had thought this might end up being a double protecting group problem. It looks like it's just some sort of Grignard. If we could oxidize this alcohol, attack it with a one-carbon Grignard reagent, that would get us the product. The problem is, I have an aldehyde and a ketone, yes the aldehyde is more reactive than a ketone, but I'm guessing that it might be hard to target the aldehyde versus the ketone for a reagent as strong as the Grignard reagent. If you have an aldehyde and a ketone, you can protect the aldehyde versus the ketone, but that's a different set of conditions; those are cationic conditions. That's one issue. A solution to that might be to protect this alcohol first, so it's no longer in the equation; protect the ketone by reducing it and protecting that alcohol; pop off the first protecting group; oxidize up that alcohol, and then you can do that Grignard reaction. What I realized at some point was that means not only do you need to know about protecting groups, but you need to know which protecting groups are compatible with which reagent conditions, which is a level of sophistication beyond the level of this course.

But, if you look at this again, there is a way you can solve this problem with what you know already. You might look at this and say we really would like to have an aldehyde here to attack so the alcohol ends up in the right place. Is that the only way we can end up with the alcohol in the right place? What if we did what might look more obvious: make this a Grignard reagent, which means we're still going to have to protect that carbonyl; attack a carbonyl we could make out of this. Let me do that much of it and let me show you there how we could then get to the answer that we want. Protect the carbonyl; make an alkyl halide out of it, then a Grignard reagent. Separately, we need to take that methanol, oxidize it using PCC and pyridine, we get the aldehyde, which we could combine with the Grignard reagent, and then acidify, to get one more carbon on there and now we have the alcohol. But it's in the wrong place – so we move it. We turn it into a leaving group; eliminate; and then oxymercuration-demercuration will put the alcohol back in the right place.

Structures – Identical to those from lab 9A (02/15/12)