Lab 1A • 04/09/12

[class structure]
[pre-labs – reason; format; hazards; waste]
[lab safety – lab goggles; clothes; shoes; spare set of clothes; food/drink; eyewash stations; earthquake safety and exits; health services; emergency phone]
[lab safety – pre-existing conditions; considerations if pregnant; lab cleanliness; chemical handling and storage; secondary containment]
[lab books]
[types of problems – synthesis; mechanism; fill-in-the-blank; theoretical; nomenclature; pKa values]

Answers to Chem 12B final

Synthesis problems

[obsessive of charges and lone pairs]

This problem had a big, huge hint to it, which is what? What functional group is this? What functional group is it? It's an acetal. How do we know that? Because we have two oxygens connected to the same carbon. The only five functional groups that have that are hydrates, hemiacetals, hemiketals, acetals, and ketals; it has to be one of those things to have two oxygens connected. We look and see that, on each oxygen, there's an R group attached. That means it's going to be either an acetal or a ketal. How do we tell the difference between the two? The fact that we also have a hydrogen on that same carbon where the two oxygens are joined. Once this is exposed to water and acid, it's going to decompose and make a carbonyl-containing compound. Let's do a structure analysis. We have a five-carbon fragment, and we have a two-carbon fragment. Notice I haven't even written the product down yet, cause that first hint about what is the functional group, is even more important in this case. Let's follow that first, and then I'll show you what the product was. Let's look at that five-carbon fragment again. One end has the two oxygens connected; that's where the carbonyl used to be, because in any of these types of reactions, making ketals or acetals, the carbonyl starts out wherever both oxygens end up at. That means we're going to have a five-carbon aldehyde. What's at the other end, though? There's just an oxygen attached there, but it's on the same molecule, which means you end up with it in your product. That is one of the products: 5-hydroxypentanal. But, it's not the only thing, because there was also ethanol in that original acetal. These really are our two starting materials. What was the given product? 6-hydroxyheptanal.

Let's now analyze the carbon backbone. Here's that five-carbon piece; here's that two-carbon piece. Of course, we have a new carbon-carbon bond. There's only a limited number of ways we had learned to make carbon-carbon bonds. You could use sodium nitride and make a nitrile; you could use an acetylide ion, alkylate an alkyne. Or, more likely, a Grignard reaction or a Wittig reaction. Which of the two seems more likely in this case? Grignard, because Grignard makes single carbon-carbon bonds. A Wittig reaction would not be the best choice, because we couldn't control where the -OH group ends up afterwards. Because there was a route that did definitely give you only one product, you did need to come up with that. What two things do we need for a Grignard reaction? A carbonyl to be attacked, and a Grignard reagent. How do we know how to make which out of what? Look where the product's -OH group is: wherever the alcohol ends up is where the carbonyl started. The -OH group ends up on the two-carbon fragment, that means that two-carbon fragment needs to be converted into something with an aldehyde. We're going to do a divergent synthesis, meaning we're going to take these two materials we got from the same source but split them into separate containers. The ethanol, we're going to oxidize so we can get that carbonyl. If I only wanted an aldehyde, though, what oxidizing reagent should I use? PCC, under anhydrous conditions. That will give us ethanal, which we'll come back to later.

Look at the five-carbon fragment. At one end, we still have the aldehyde; the other end, though, we made the new carbon-carbon bond. That means we're gonna want to go back and take the alcohol from that five-carbon fragment and turn it into a Grignard reagent. We can't turn an alcohol directly into a Grignard reagent, can we; what do we need? We need an alkyl halide, because magnesium doesn't react with alcohols; it reacts with halogens. Bromides are my default in synthesis because they're more reactive than chlorides, but I could have used thionyl chloride at this point instead [and] make a chloride. Once I have the bromide, can I make the Grignard reagent? No. Why not? Because the compound would just react with itself. You have a carbonyl on the very molecule you're trying to make the Grignard reagent from, so you have to protect it first. You can protect it with the very alcohol that you just made up above. So, ethanol and acid source, we'll make another acetal – not the original one, of course, one that has a bromine available this time. That bromine we can convert into a Grignard reagent using magnesium and ether. Recall that you have to have THF, diethyl ether, or something like it that can complex with the magnesium, otherwise the Grignard reagent won't form. Once you make the Gringard reagent, we throw ethanal at it. If you show that aldehyde and that acetal Grignard reagent and H+ all togehter, it's wrong, because that means throw all the reagents together at the same time. The Grignard reagent's just killed off by the H+. You've gotta be careful in your notations. H+ has to be its own separate step, after the Grignard reaction happens. What happens with that H+? Two things: when the Grignard reaction first occurs, you're going to have an alkoxide.

Part of the point of acid work-up is to get the product alcohol out that you wanted. But, the acetal is also sensitive to acid and water, and so the same step that you reprotonate the molecule will also knock off the protecting group, which means you got the product. If you did protonation with a gentle acid and then used TBAF, that is not the protecting group in this case; it is H+ [and water that should be used].

Let's go to the next one. In the second synthesis, we have a five-carbon fragment and a two-carbon fragment. We end up with seven, so again that's a good thing because that just means all we've done is formed a new carbon-carbon bond. Let's see if we can figure out where. Look at the shape of that five-carbon fragment; that is reminiscent of what is called an isoprenoid, from isoprene, [which is a term associated with terpenes,] which are classes of biological compounds that are synthesized from structural units that look like that. If you have bit of imagination, you can imagine that those are two legs that some kind of head or something [is] walking around on, so we talk about whether things are connected head-to-tail, [tail-to-head], head-to-head, or however. But take lots of common compounds like methnol, the stuff that gives mint its flavor, or lavanduol, the stuff that gives lavender its scent, or cholesterol – [a] huge molecule that after multiple, multiple rounds can be generated from starting materials like that. It's a structural motif that we'll see again.

That five-carbon fragment we can find in the product. It looks like we've again identified our five-carbon fragment, our two-carbon fragment, so we again have identified where the new carbon-carbon bond is. This is very similar to the previous problem, where, most like, it looks like we want to do a Grignard reaction, which again means we need a carbonyl source and again means we need a Grignard reagent. This is a little different than the previous problem, because look at where the end carbonyl is. That's a little strange by itself, because Grignard reactions don't make carbonyls, they make alcohols, so there had to be an oxidation that went on as well. What else is unusual? That means that the aldehyde we start with is not the carbonyl that gets attacked, so we have to convert that aldehyde into a Grignard reagent. In doing so, that's how we deal with this D that's up there, deuterium. You might recall we talked about reduction using deuterated reagents. There were two possibilities that can occur: one is a reduction where you use a regular reducing agent like LiAlH4, but then follow it up with deuterated acid, D+. What that will give you is an alcohol, but with a deuterium at the alcohol position, -OD.

Another way to do it, though, to introduce deuterium is to use lithium aluminum deuteride, and then follow up with H+. You'll get a normal alcohol, but one that also has a deuterium on that same carbon – exactly what you need for this problem. Look at the product and look at what we just made. We have an alcohol that we just made that we can turn into a Grignard reagent and attack – well, attack what? We can't attack an alkene; we need a carbonyl source. The only way to put an oxygen at the end, the less substituted position of an alkene like that, that we know of – hydroboration oxidation. Take the alkene, react it first with borane, then oxidize; that gets us anti-Markovnikov addition. We have to use something like PCC without water to selectively oxidize to the aldehyde. We could take exactly what we have shown here, ethanal; reduce it with lithium aluminum deuteride, followed by H+; that gives us a deuterated alcohol with the deuteration on carbon. Use PBr3 to make the alkyl halide, which we need because we want to make a Grignard reagent, using magnesium and ether. Continuing, if you take that aldehyde, react it with the Grignard reagent that we just made, we'd get an alkoxide first. React that with a dilute source of H+, so we could reprotonate the alkoxide. Since it's a secondary alcohol, it doesn't matter which oxidizing agent I use, but I use some form of oxidizing agent to turn that alcohol into a ketone, which means we're now at the product.

Fill-in-the-blank problems

First one: an epoxide, reacts with something to make a combination alcohol-ether. The point of this question is that there are two conditions that can be used to open up epoxides: acidic conditions, basic conditions. We have an epoxide that has both a primary center and a tertiary center. Remember that, under acidic conditions, since it's the ring that gets protonated first and then destabilizes the rest of the molecule. Attack would occur at the tertiary center under acidic conditions. But notice, the tertiary center here did not change stereochemistry; all that happened is you end up with an alcohol, because the ring had been pushed open at the less substituted position. That only occurs under basic conditions. That means there's only one right answer: sodium methoxide, followed by acid work-up. If you did not put your 1)/2)s in, then what you're saying is react sodium methoxide with H+, and the combination put with the epoxide. Since the combination would make methanol, you get a different product. You need the H+, because otherwise you're going to end up with a negatively-charged molecule; you don't end up with something neutral. You need base attack, and then you need to acidify afterwards.

Next one. Notice that this is not an ester. An ester has a carbonyl, yes, and a single-bond oxygen, but to the same carbon; there's one carbon between those two things here, so this is an acetal on one side, a ketone on the other. You react that with methylmagnesium bromide, a Grignard reagent, followed by acid and water. The point of this problem was to see whether or not you try to react the acetal, because acetals are protecting groups against Grignard reactions, so the carbonyl, the lefthand side of the molecule's gonna react; the righthand side's not. After the first step, here's what, potentially, we would have. You can see on the lefthandside, we have a new methyl group that's attacked; that's why we have the alkoxide also. Acid and heat, those conditions, the acetal can't tolerate, so the acetal's going to fall apart. If you counted your carbons properly, this is again example of a five-carbon aldehyde that has the hydroxy group at the end, but also has a methyl and hydroxy group one position in.

If you made a hydrate, there was a note that said the product must be isolatable, and hydrates are not isolatable, not normally. You might have dehydrated, but you had to be careful because if you made an alkene on the same carbon as an alcohol, tautomerization occurs.

Something reacts with a Wittig reagent to make an alkene – exactly what we expect. The way to analyze these in reverse is to notice, in this particular case, we only have a one-carbon Wittig reagent. That one carbon is what formed a new alkene. Chop that alkene up and put a carbonyl there, that's what the original starting material was. The -OH was really there just to throw you off; it didn't do anything in this reaction.

Next one: something reacts with this chiral secondary alcohol to make a chiral alkyl halide, but of reverse stereochemistry – of course, that's thionyl chloride.

Next one was a classic from a previous year: this is what kind of functional group? It is an imine, it is a carbon-nitrogen double bond; those come from aldehydes or ketones. Open this structure up – it's another five-carbon compound. Where the carbon-nitrogen double bond used to be, you have a carbon-oxygen double bond, but that nitrogen's part of the same molecule, so it doesn't just disappear, it's at the end. Since we had deuterium, not hydrogen, it's ND2. Why? Cause there's no hydrogen to get it from, so you can't have NH2.

Something reacts with a three-carbon Grignard reagent and methyl bromide [in sequential steps] to make 3-methoxy-3-methylhexane. First thing to recognize is that the methyl group on oxygen came from the methyl bromide, cause after a Grignard reaction, you have an alkoxide. If you throw an alkyl halide at that – before you do acid workup, you have an alkoxide, which means you can do Williamson ether synthesis. Once we've accounted for that methyl group, we need to go back and look at the Grignard reaction part of it. There's a three-carbon fragment that's been added on; if we look at this, here's those three carbons right here. Pull that out of the structure, what do we have left? Butan-2-one. That has four carbons, the Grignard had three; that gives us the seven total (minus the methyl group that's on the oxygen).

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Two more. What's its name? Anisole. What can put an acyl group on there? Friedel-Crafts acylation, which uses acetyl chloride. It had to be the chloride, not an aldehyde. Technically, there are other functional groups that would work. With the acetyl chloride, you need either iron(III) trichloride or aluminum trichloride, some strong kind of Lewis acid.

The last reaction: something reacting with PCC – technically, two equivalents, which means if you have one mole of starting material, you use two moles of PCC. The product was this: 4-hydroxy-3-oxopentanal. PCC is an oxidizing agent; two equivalents were used; we have two carbonyls, so the original material was this – a triol. Since there's PCC but no water, the primary alcohol was turned into an aldehyde. Regardless of conditions, the secondary alcohol turns into a ketone, and [a] tertiary alcohol can't react.

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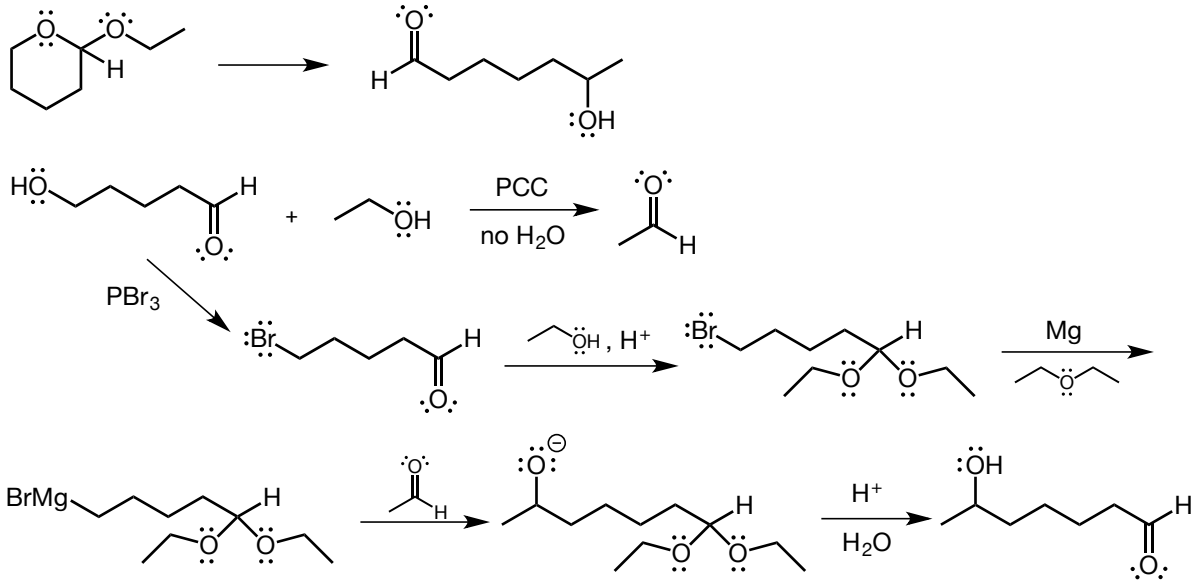
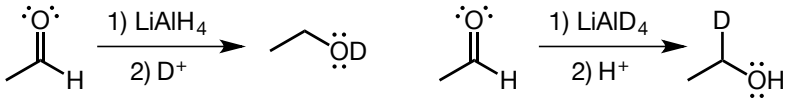
Structures

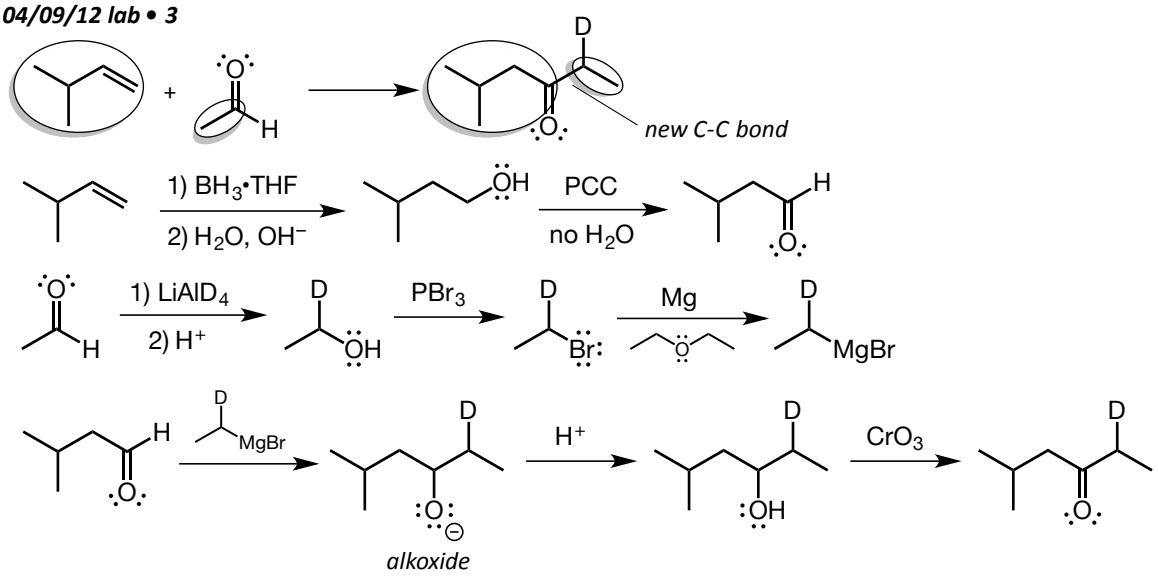
04/09/12 lab • 1

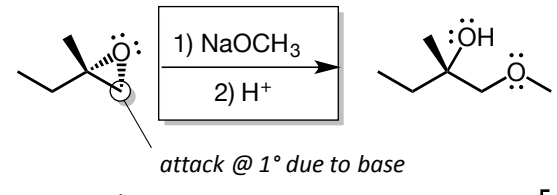


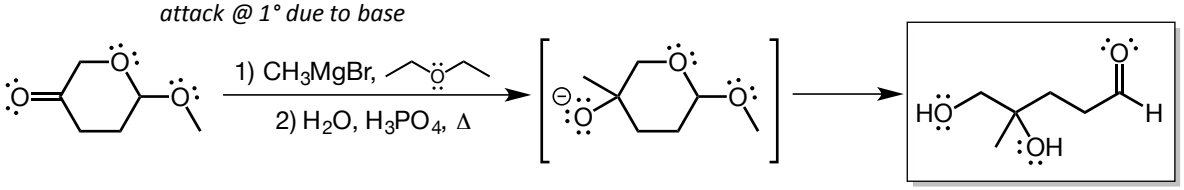
04/09/12 lab • 2

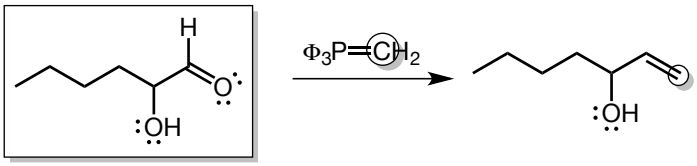


04/09/12 lab • 3

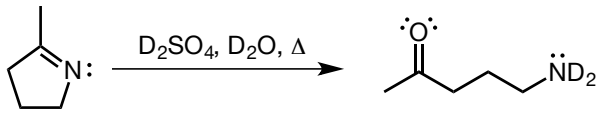


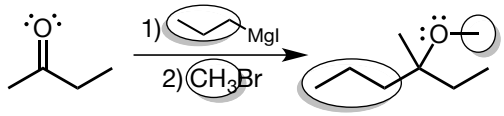

1) NaOCH3
2) H+
attack @ 1° due to base

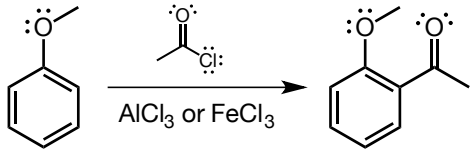

1) CH3MgBr,
2) H2O, H3PO4, Δ

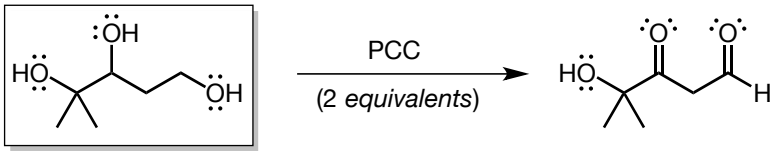

Φ3P=CH2


SOCl2


D2SO4, D2O, Δ


1)
MgI
2)
CH3Br


AlCl3 or FeCl3


PCC
(2 equivalents)