

Lab 2B • 04/17/12

Chem 12B final – synthesis problems

[types of problems : synthesis, mechanism, fill-in-the-blank, nomenclature, pKa, short answer, theoretical][ACS exam]

First problem, you had a cyclic molecule with a side-chain. The big, fat hint that was given for this problem was: what kind of functional group was it? We've got two oxygens attached to the same position, so it's either an ketal, acetal, hemiketal, hemiacetal; we know it's not a hydrate cause that would have to be two -OH groups attached to that point. There is a hydrogen here as well, so that means it's either a hemiacetal or an acetal. The fact that both of the oxygens have R groups attached to it means it is an acetal, which under acid hydrolysis means this is going to reverse back to something that has a carbonyl – specifically, an aldehyde. If we look at the carbon framework, there are five carbons, exclusive of the other bit that's attached to the oxygen out here. If we take this compound and subject it to acid and water, then this ring is going to unfold. The position where the two oxygens are attached, that becomes a carbonyl, which means it's an aldehyde. There are five carbons in that aldehyde, plus you do have an oxygen at the other end, which will not disconnect during opening; that means you get an omega-hydroxyaldehyde – plus, there's this ethanol that's spit off. We need that because if we look at the product, we can identify that there's a five-carbon fragment that is functional on both ends, just like the hydroxyaldehyde, and then we have a two-carbon fragment.

Since there is a carbon-carbon bond that's formed between them, then what reaction seem the most obvious to try to perform in this case? A Grignard reaction, because the only carbon-carbon bond forming reactions we discussed were the Wittig and the Grignard reaction. Wittig, though, makes a double bond instead of an alcohol, and given that that alcohol is in the middle of the molecule, we'd have a very difficult time after a Wittig reaction selectively putting the hydroxy group at one position or the other. However, if we did the correct form of Grignard reaction, then the hydroxy group automatically ends up in the right place. But what's the big gotcha in this problem? We have an alcohol on the same molecule that has the carbonyl that we would want to attack. If we look at that, we know that this is the carbonyl that needs to be attacked because of where the -OH group ends up. The -OH group always ends up where the carbonyl was. [If the hydroxy group was one more position over,] that would mean that this molecule was the Grignard reagent that you had to attack an oxidized molecule to form the right product; [it would be] the backwards problem. Here, we're going to make a Grignard reagent out of the more obvious molecule, ethanol; that means we're going to have to use a protecting group on this other one, so that this alcohol does not just simply neutralize the Grignard reagent.

It was optional which protecting group that you could use, cause you had both DHP and a silyl chloride; I'll show [the silyl chloride]. TBDMS chloride is the one I had recommended, only because it's bulkier than simply trimethylsilyl chloride, less prone to hydrolysis. Separately, we need a halide out of the alcohol; we could use PBr₃, for example; then, react it with magnesium and diethyl ether in order to make the Grignard reagent. Combine the two together: you have to be careful how you notate this next part, because after the reaction, we need to deprotonate the alkoxide that's formed. If I put H⁺ on the arrow I've just written, though, that means that H⁺ is reacting at the same time as both of these reagents, which, of course, that would just kill off the Grignard reagent. If you're taking a short cut, you need to do something like this where you show protonation as separate step. Once you do protonate, if you use a strong enough acid, you can both knock off the protecting group and protonate the alcohol that just got formed by the Grignard reaction. At the end here, you could have used dilute acid; you would have been able to retain the protecting group, and then you could have followed that up with TBAF, tetrabutylammonium fluoride. Or, if you used DHP and made the tetrahydropyranyl ether, then, again, if you use acid and water in case, then you would have protonated the alkoxide and knocked off the THP group.

Next problem. This one you had an alkene, which is reminiscent of the structure in a set of compounds known as terpenes. Terpenes have this five-carbon framework which – if you're really creative and imaginative – you could imagine a little stick figure with two legs and then the head at the other end. Depending on how different isoprene units, how these five-carbon units align with each other – either head-to-tail, head-to-head, or in a cycle – they produce things like menthol, that you find in mints, lavender, all these different derivatives from plants, fragrances, all the way up to big huge molecules like cholesterol. We have this five-carbon that somehow is mixed with this aldehyde to form a ketone, but one that is deuterated. There's a note here: where did a carbon-carbon bond form, and how? That gets at the approach that I would normally recommend that you'd take for synthesis problems. What I normally do is circle where the carbon framework of each reactant shows up in the product. If we look at the structure of the reactant, we have a five-carbon fragment that's got that split in it. We could find that same five-carbon fragment in the product. Of course, the only thing left over is a two-carbon fragment, which we've got here. We see that there's a new carbon-carbon bond, and we originally started with an alkene which was functional at two positions, and you can see that we end up with something that's functional at two position – in one case, we end up with a ketone, in the other, it's that new carbon-carbon bond.

But notice that where the carbon-carbon bond forms is not where the oxygen is. If we did a Grignard reaction, the oxygen of that product ends up where the carbonyl had been, but it's not here.

But, there was one other functional group we talked about that [could react with Grignard reagents]; what was that other functional group? An epoxide. An epoxide, if you attack it with a really basic reagent, then due to sterics, it attacks at the less-substituted position, pushes the ring open, and you end up with the oxygen one carbon away – exactly like what we've got here. So we've got two issues – one, we need an epoxide, which there's a one-step way and a two-step way to get that from the alkene; second, though, there's this deuterium. You might remember I showed you these two reactions: if we had a regular aldehyde that we reduced with a regular reducing agent, we would make an alkoxide first, which if we threw deuterated acid at it, you could end up with a deuterated alcohol, where the deuterium itself is on the oxygen. But, we also saw that we could flip the sequence of hydrogen versus deuterium being introduced to the molecule. In other words, if we used sodium borodeuteride, then the deuterium ends up attached to the carbon instead. Then, if we just acidify normally, we end up with a regular alcohol, but then on the carbon has been substituted with a deuterium – that's exactly what we need in this problem, because we need a Grignard reagent, and we need the Grignard reagent to react at the same position where the deuterium was at.

We have alcohol at that correct position, two steps away, then, from being that Grignard reagent. React it with PBr_3 or thionyl chloride, something to make a halide, and then magnesium and ether to make the Grignard reagent. Separately, we take the alkene, and we could do one of two things: we could react it with MCPBA, meta-chloroperoxybenzoic acid, or MMPP, magnesium monoperoxyphthalate – they're peroxyacids and, in a concerted mechanism, make the epoxide. There's also this trick that we could do where we could make the halohydrin first, use bromine and water, to make a halohydrin, which upon treatment with sodium hydride does an intramolecular $\text{S}_\text{N}2$ and gets us the epoxide as well. That epoxide, we then react with the Grignard reagent; we end up with the alkoxide on the inside of where the attack occurred; we've made the new carbon-carbon bond; we have the deuterium in the right place. We treat it with acid to get the alcohol out, and then any form of oxidizing agent we use would bring that to the ketone. Secondary alcohols cannot be oxidized to carboxylic acids, so it doesn't matter if we use chromium trioxide or PCC.

Let to the fill-in-the-blank problems now. First problem, you had an epoxide that reacted with something to form a molecule that had both an alcohol and an ether. This problem gets at the two ways that we learned that epoxides can be opened – one under cationic conditions, one under anionic conditions. Under cationic conditions, the attack occurs at the more substituted position, because of the greater ability to form a potential positive charge. But under basic conditions, attack would occur at the less-substituted position, because of sterics. Now look at where the -OH group ends up: it ends up at the less-substituted position, which means the attack occurred at the more-substituted position. You also notice that stereochemistry is inverted at that more substituted position, which is exactly what you would expect in cationic ring opening. Since it's cationic, that means that you must use an alcohol with an acid catalyst. If you said sodium methoxide, followed by H^+ , no, because that would cause attack at the less-substituted position. If you had H^+ and sodium methoxide together, without a 1 and a 2, it's technically correct, but it's still wrong in a sense because the methoxide would react with the H^+ to make the methanol, which, then, would do the correct reaction. [ether and alcohol were switched for other section]

The next one: we have a ketone, but we also have a ketal – two oxygens, each with an R group, both attached to the same carbon that has no hydrogen. Reacts with first a Grignard reagent, followed by water, acid, and heat. I did have a caveat here that said the product must be isolatable. To jump straight to the point, yes, you have a ketone; yes, a ketal, in theory, can make a hydrate under acid and water conditions, but it's not isolatable, not in most cases. If you carried the reaction too far, all the way to the hydrate, then it was considered incorrect. What was the point of this problem? To recognize that the ketal doesn't react, that it's a protecting group for the ketone it can turn into; but we do have an exposed ketone that will react. You get one substitution, then when you hydrate the molecule, you'll break open the protecting group, getting a ketone, so the product would be this. Or, because of the acid and heat, you could dehydrate.

Next one: we had something reacting with a Wittig reagent – a single-carbon Wittig reagent. The product did have both an alkene and an alcohol, but the alcohol was really just to throw you off the track, cause all that really matters is how did the alkene form. Break it apart, one side of it only has that one carbon that would have come from reaction with the Wittig reagent. What must have been there instead was a carbonyl, so the answer in this case looked the same, except with the addition of an oxygen at the end of the double bond.

Next reaction, one of the simplest: a chiral alcohol reacting with something to make a chiral chloride with opposite stereochemistry. The only answer for that was thionyl chloride. [why can't tosyl chloride do the same? why does the chloride kicked out not come back and attack]

Next problem: what kind of functional group is this? This is an imine, which means we have a carbon-nitrogen double bond, which upon hydration you get back a ketone or aldehyde. Since there's not hydrogen on that double bond, that means it is going to be a ketone. Since it's deuterated acid and water that's being used, when you open the product up, aside from the carbonyl, you also have an amine. That amine, because of the reagents used, will have deuterium on it.

Next problem starts with [an] unknown substrate reacting with a three-carbon Grignard reagent. This is a little bit different than a standard Grignard reaction because instead of doing protonation afterwards, you react it with an alkyl halide.

Think of it this way: if you had a Grignard reaction that you didn't quench, then you'd have an alkoxide, which is a nucleophile in S_N2 reactions. This is an excellent substrate for S_N2 reactions. If you look at the product, the methyl group ends up on the oxygen. To analyze the problem further, then, we look at the Grignard reagent used; it had three carbons in it, only three carbons. There's the only three-carbon fragment that would not include the carbonyl. Pull both of those alkyl groups off, reform the carbonyl, and that meant the starting material had to be butane-2-one – four-carbon compound with the carbonyl on the second of the carbons.

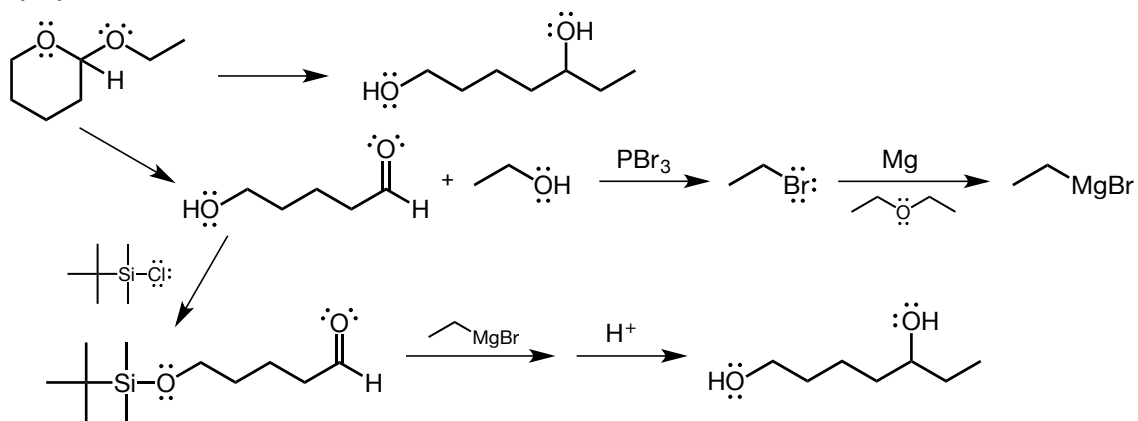
Anisole [differs from anisaldehyde by a carbonyl]. This reacts with something to make an acylated anisole. We only learned one acylation reaction, which was Friedel-Crafts acylation, which requires an acyl halide that we know how to synthesize. An acyl halide plus a Lewis acid, the most common of which being aluminum trichloride.

Final problem: something reacts with an two equivalents of PCC – the only reason I put [that] there was to see if you might read water by mistake, but this doesn't mention water – in pyridine to make this hydroxyoxoaldehyde. Two equivalents means for every molecule that you started with, two equivalents were consumed. The only way that two equivalents must have been used is if two things got oxidized. We have two carbonyls, so that means the starting material would have had to have been a triol, cause recognize that tertiary alcohols would not have been affected by an oxidizing agent and is not formed by an oxidizing agent. The answer I was expecting was this: the aldehyde came from a primary alcohol; the ketone came from a secondary alcohol; and, of course, there's the tertiary alcohol that had not reacted in the first place.

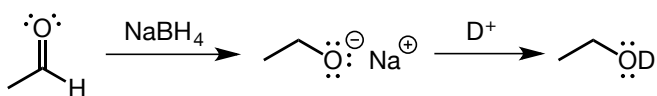
[lab directions]

Structures (remaining structures identical to lab 1A)

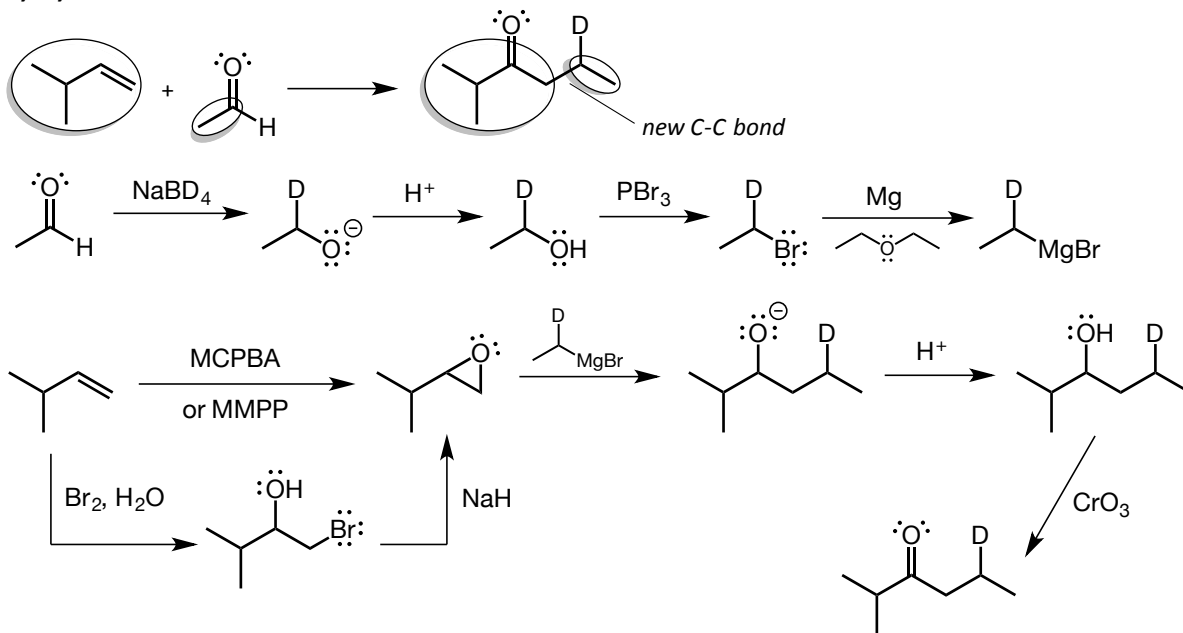
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