

## Lab 5A • 01/30/12

[lab report format, calculations, and due dates]

Carbonyl peaks are often the second most identifiable functional group in IR. Alcohols give that nice, big, characteristic broad – OH peak; carbonyls tend to give a very characteristic sharp peak, in the high 1600 – low 1700 range.

[spectral analysis]

Synthesis problems

The first one might have been the most difficult because it did require recognizing a variation to a reaction that we learned. The first problem involves taking a ketone and making what almost would look like a halohydrin, something that's got an oxygen on one carbon and right next door, a bromine. How do you put both of those functional groups on at the same time? [One attempt would be to take] Br<sub>2</sub>, making a dibromide, and somehow reacting one or the other, but that's kinda tough to do. It turns out, though, that if you take an alkene and react it with bromine and, not water, but an alcohol, that the alcohol will add in the same way that water would. So in order to get both of those functional groups on at the same time, all you really need to do is add the alcohol to the alkene by using bromine. So bromine is attacked first, makes the cyclic intermediate, then the alcohol attacks, pushes the ring open. What that does mean is if we back up retrosynthetically one step, we need an alkene and we need that alcohol. The alcohol can be synthesized easily. If you take the ketone and react it with either lithium aluminum hydride or sodium borohydride, either one, and then follow it with acid work-up. That'll get you the alcohol. In reducing an aldehyde or a ketone, sodium hydride is not a good choice. That's because the boron in sodium borohydride or aluminum in lithium aluminum do participate in the mechanism. From the alcohol, we could continue on to make the alkene, which there are a couple of different ways you could go about that. Since there's only one alkene that could possibly be formed, dehydration might not be a bad route to take in this case. There is the reagent POCl<sub>3</sub>; that could be used to dehydrate as well. Or, instead of dehydration, we could try to do an elimination, which –OH itself is not a leaving group, so you can't eliminate directly. But, you could, for example, convert it into an alkyl halide first – for example, using thionyl chloride – and then doing an elimination using a strong, hindered base. Once you get those two pieces, then you react the alkene with the alcohol at the same time you react with bromine, and that gets you the product. Sodium hydride is usually used when you want H<sup>-</sup> as a base. For example, when we're deprotonating alcohols to make alkoxides; there we wouldn't use lithium aluminum hydride, although technically you could, but it would be a waste of the reagent.

If I wrote the mechanism out, it would look like this. First, the bromine gets attacked, and optionally, some people show an arrow coming back to the alkene to highlight the fact that you do end up with a bridged intermediate. It's exactly that kind of intermediate that I mentioned when we did the epoxide opening; this is that same situation where we have a three-membered ring that's strained, and it's going to be the bond to the secondary carbon that's weaker because of the potential to form the more favorable positive charge. The alcohol, if you make that the solvent, it out-populates the bromine, so instead of bromine attacking, it's the alcohol. Then there's just one final step where you get deprotonation.

Second problem. That one might have been the most annoying problem, because you probably came up with all kinds of answers that got you close to the right answer, but the problem is, how do you deal with the deuterium. Let me show you a couple of things that won't work. If you tried to do just plain hydration, using D<sup>+</sup> and water, the deuterium is going to the least-substituted position, because that's what happens in a Markovnikov addition anyways. [Additionally,] since you form a secondary carbocation, you get carbocation migration, so the –OH group's not even going to end up where you want it to. That route just doesn't work. What about the oxymercuration-demercuration version of it? You could start with mercury acetate; let's see what you would get that far. Mercury acetate in water, water adds to the more substituted position; but the mercury acetate ends up at the least substituted position. Even if we reduced it with a deuterium agent, the deuterium's gonna still end up in the wrong place; at least the alcohol's in the right place, though. But if I did follow through and did the the step two with lithium aluminum deuteride, you get the wrong product. Same thing happens with borane: in that case, if you tried to do hydroboration, that would get you completely the wrong answer. You could make the alcohol and then dehydrate it to make the alkene to the more substituted position and then use borane, because that's going to put the alcohol in the right place; but in that case, the deuterium would still go to a different carbon. So how in the world can you get a deuterium on to the same place as where an alcohol is going to form? What other way do you know to make an alcohol, besides from an alkene? What about from a ketone? The way you reduce a carbonyl, a hydrogen attacks the carbon, pushes open the carbonyl bond, gives you an alcohol. What if you had deuterium attack the carbonyl instead? Then that would give you the deuterium at exactly the right place. So, you need an alcohol to then oxidize to the ketone to reduce it right back down again. You should be aware that aldehydes and ketones are often starting materials for alcohols.

How could we have done this? We don't know a way of going directly from this alkene to the ketone so we're going to need the alcohol first. We don't want the alcohol to rearrange, so it can't be dehydration. There's two ways to get there. The direct way is to do oxymercuration-demercuration.

Technically, we could get there another route. If we use MCPBA, we'll make an epoxide. You could use lithium aluminum hydride to pop open an epoxide. Hydride would attack at the less substituted position, leaving the alcohol at the more substituted position, which, once we neutralize, we get the product that we want, that secondary alcohol. Once we have the alcohol, we can then oxidize using Jones' reagent, aqueous chromium trioxide. That gets us the ketone. Now, if we use lithium aluminum deuteride or sodium borodeuteride and reduce, it puts the deuterium in the right place, and we get the alcohol. Just to show you you can introduce deuterium different places – this is not the answer we want – what would happen if I used sodium borohydride, followed by D<sup>+</sup>? In the product, the hydrogen and deuterium shown would swap places. Since it's lithium aluminum hydride, the hydride would attack the carbonyl bond, but since I used D<sup>+</sup> as the neutralizing agent, the deuterium would end up on the alcohol.

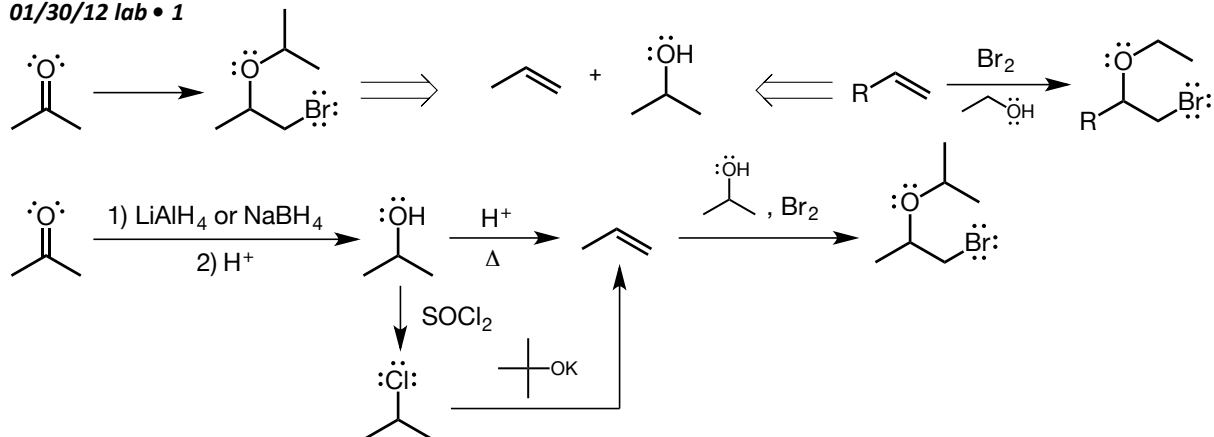
There is a longer route that would work to get you that alcohol. First, react it with Br<sub>2</sub>; makes the vicinal dihalide. React that with two equivalents of a strong base like sodium amide; that makes the alkyne. Using a mercury catalyst in acidic conditions, it puts an alcohol, but it puts the alcohol where an alkene is, which means it would tautomerize, so you would get the ketone.

Third. To convert an alcohol into a vicinal dihalide. Part of the point of this sample problem was to [get at the fact that] if you end up with two functional groups right next door to each other, it probably came from an alkene, an alkyne, or an epoxide, because those are all functional groups that bridge two carbons, and we have a functional group that shows up at two different carbons. A dihalide comes from an alkene, just by reacting with Br<sub>2</sub>. Ignoring stereochemistry, I could make a dihalide if I just had an alkene. Because this is a symmetric alcohol, there's only one product you would get if you tried to dehydrate, it would be perfectly fine to dehydrate here, and then once you have that alkene, just react with bromine. This would make a vicinal dihalide with anti addition, meaning that the two groups would be oppositely pointed from each other, which in this ring case means you'd end up with a trans compound. Because the double bond is planar, you would have gotten enantiomers of that trans compound. If we had to worry about stereochemistry, you'd need to know what stereochemistry would result. You don't know how to isolate one enantiomer from another, so in a synthesis that does make enantiomers, don't worry about the fact that you have enantiomers. What if I had shown you that I wanted to take this alcohol and specifically make a case where the Br groups are both pointed the same way as each other? Not much of a problem; we just have to be sneaky. We still dehydrate; we still use Br<sub>2</sub> – but Br<sub>2</sub> with water. You'll make enantiomers (I'm only showing one of them) but the bromine and –OH group would end up opposite to each other. But since PBr<sub>3</sub> causes inversion of configuration anyways, it would make the alcohol pop around and give us the right stereochemistry. So regardless of what the stereochemistry was, we have a way of getting there. Could we use something like HBr, where the alcohol would get protonated, and then a bromine could come in and kick the alcohol off? Yes, it is possible, except in that specific case you might get the same reaction to occur but in an S<sub>N</sub>1 style, where the alcohol would get protonated, a carbocation would form, and then the halide would come in to attack. It could in theory work, but you might get a mixture of products; if it were a primary position, then use, that's the way it would occur.

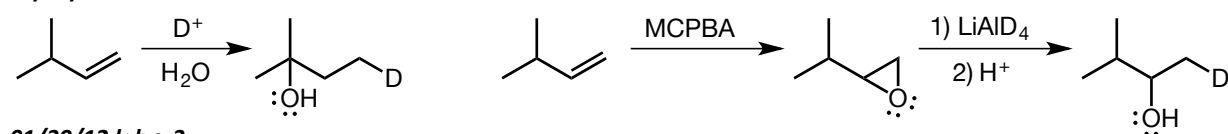
Last one. The reason for showing you this problem is to highlight one of the few ways that we've learned to make a carbon-carbon bond. Making or breaking carbon-carbon bonds is really important in synthesis. I can use an alkyne to make a new carbon-carbon bond. Imagine that we had these two pieces: something with a leaving group, and an alkyne salt (an acetylide ion). That does S<sub>N</sub>2; afterwards you would still have the triple bond, but you could just hydrogenate to get rid of that. Question is: how could we make a leaving group like that, at that correct position? Notice that that would be anti-Markovnikov from the perspective of the original compound. There's two ways you could go about it. One, the modified borane reagent where you put two alkyl groups on the borane; follow that up by oxidative work-up. It initially forms an enol, puts an alcohol at the less substituted position. But because it's also an alkene, it's enol, it tautomerizes, and we end up with an aldehyde. That aldehyde we could then reduce to make an alcohol. We could [instead] have tried to get to the alkene. Since this alkyne can't make a cis or trans alkene – there only one group on either side of the alkyne – we get two choices: we could have done hydrogen with Lindlar's catalyst or sodium in ammonia. They both would have made the same alkene, which then you could react with regular borane and work it up to make that same alcohol. Once we make the alcohol, we need a leaving group – above I showed bromide, you could use tosyl chloride, make a tosylate instead. The alkyne, you deprotonate. That forms the acetylide salt. Throw those two compounds together, it makes the six-carbon alkyne, which you can hydrogenate to make hexane.

Structures

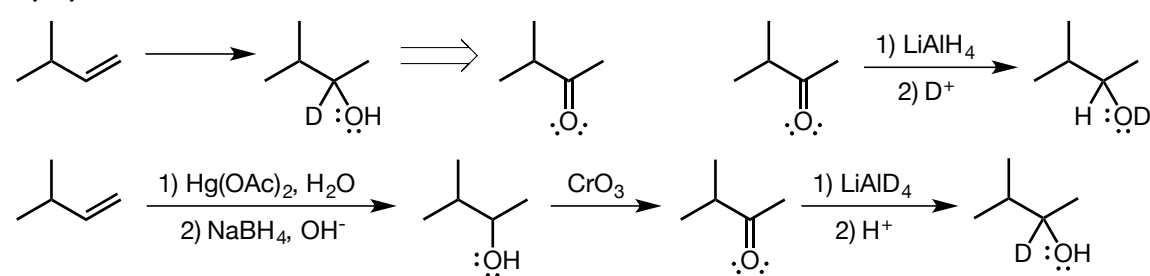
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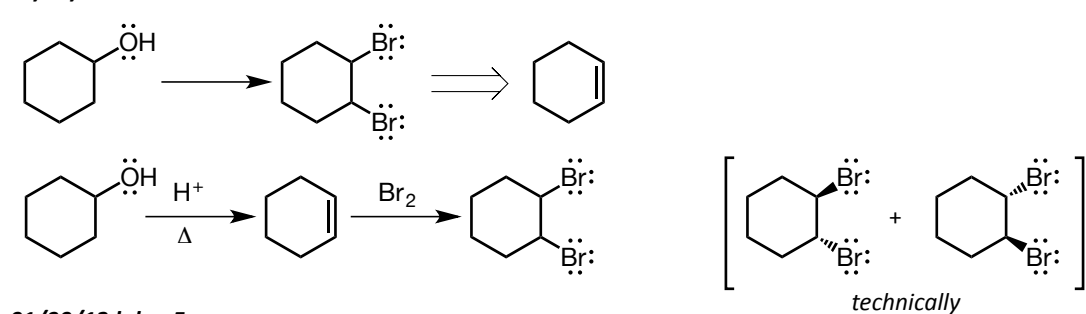
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