

Lecture 6B • 01/26/12

[Quiz 1]

You started out with a chiral alcohol that you reacted with four reagents: first PBr_3 , second SH^- , then sodium hydride, then methyl bromide. First portion of the mechanism, phosphorus tribromide. In this case, the oxygen attacks the phosphorus, kicking off a bromide, in a process that looks kinda like $\text{S}_\text{N}2$. Since I showed the full structure once, I can just say PBr_2 to simplify my writing. We have an oxonium ion that's going to deprotonate, and then that OPBr_2 is going to be kicked off by bromide. At this point, since this portion is like $\text{S}_\text{N}2$, there is going to be inversion of stereochemistry. We now have an alkyl halide. Sulfur is a much better nucleophile than oxygen, if you're comparing two molecules that are identical other than the fact they have sulfur versus oxygen. This very easily going to undergo an $\text{S}_\text{N}2$ reaction, which again undergoes inversion of configuration. Third step, sodium hydride: I had given the hint to remember that sulfur's in the same column as oxygen, so a sulfur-hydrogen bond is going to act a lot like an oxygen-hydrogen bond. Sodium hydride is going to pull that hydrogen off [of the sulfur]. Final reagent is methyl bromide – not even a primary, less than that, it's just a methyl substrate, one of the best things to be attacked in an $\text{S}_\text{N}2$ reaction. Sulfur attacks the carbon, kicking off the bromine, and there is our final product.

The second mechanism was oxidation using PCC and pyridine. Two comments: one, deuterium is not carbon; is this a primary, secondary, or tertiary alcohol? Secondary. Some of you had accidentally interpreted this as a tertiary alcohol because of there being three things attached to the carbon. But it's not just how many things are attached that determine whether it's primary, secondary, or tertiary; it's how many carbons are attached. Since we only have two carbons that are attached, it's a secondary alcohol. I didn't need to comment on whether this is under anhydrous conditions, because whether you have anhydrous or aqueous conditions, you can't oxidize a secondary alcohol past a ketone. So one you've gone through the reaction once, it's not going to be able to do anything else, unless you assume there was water, and unless you assume a hydrate would form, which is possible because if equilibrium can happen it will happen. So even though it's not like for a hydrate to want to form, quite technically if you had water around, the ketone that we're going to be showing here could react and form a hydrate. That would not be the major product in solution. When you have an oxidation like this, if there's water around, you wouldn't need to show the hydrate formation, unless it's really going to get overoxidized. For most aldehydes and ketones, it's a fraction of a percent of it that will at any one moment convert into the hydrate. Let's see the mechanism once:

[We have] pyridinium chlorochromate. The chromium gets attacked. [The carbonyl bond opens as a result;] subsequently, one of the negatively charged oxygens collapses back to kick the chlorine off. We do have pyridinium floating around as a counterion. We still have the oxonium ion, so we'll have deprotonation. We now that the chromate ester, which is going to get deprotonated. Pyridine is generally the solvent used in this kind of reaction. If you don't want to have any potential for some strange form of side reaction, especially an acid-base one, it makes sense to have pyridinium along with the pyridine. It would be pyridine that would be the base that would remove the proton. Pyridine can remove that deuterium; deuterium's the same as hydrogen, it's just a different form of hydrogen. There would be a kinetic effect. There is what is known as the kinetic isotope effect, which is where we could make some judgement of the mechanism of a reaction by replacing key hydrogen or hydrogens with deuterium and see how that would affect the reaction rate. Deuterium is just another form of hydrogen, so even though you're going to have a different reaction rate – because you have a deuterium hooked up to the carbon, it's heavier than hydrogen, it's got a different bond strength than hydrogen, but not enough different to drastically affect how it's going to react. Pull the deuterium off. The pair from the bond kicks back to the oxygen, which kicks off the chromium, and we end up with acetone.

Fill-in-the-blank problems

First fill-in-the-blank problem was related to $\text{S}_\text{N}2$. You had a chiral alcohol reacting with something, followed by sodium azide, in order to make a chiral alkyl azide. One method [of forming leaving groups from alcohols] can lead to inversion of stereochemistry of an alcohol, which means once it undergoes $\text{S}_\text{N}2$ you flip it back again. But there's another method, where you can have the stereochemistry retained. Two other methods – making a chloride from thionyl chloride and a bromide from PBr_3 – those cause an initial inversion, and then if you're going $\text{S}_\text{N}2$, you'll have a reinversion. Tosyl chloride and the Finkelstein reaction effectively preserve stereochemistry. In the case of tosyl chloride it's because the carbon-oxygen bond doesn't get involved in the first place, and in the case of the Finkelstein reaction it's because, usually, if you're starting with an alcohol, you first make a bromide, which causes inversion, then you make the iodide, which again causes inversion. If you had something like tosyl chloride, which didn't change the stereocenter, then when you do $\text{S}_\text{N}2$, you're going to get inversion, means this exactly what happened here, which means the answer to this problem is tosyl chloride or mesyl chloride or any other sulfonyl chloride. If we used tosic acid, won't work; tosic acid won't do anything to an alcohol except possibly dehydrate it if you're at high temperatures; you must have [tosyl] chloride in order for that reaction to work.

What about the second one? Second one was an alcohol reacting with tosic acid and heat. It is true that primary carbocations that are terribly unfavorable, but you can, with enough heat and acid, dehydrate a primary alcohol. But if you were going to try to dehydrate this primary alcohol, there's going to be something interesting that happens.

Initially, protonation occurs; with enough heat, you could drive water off, forming a carbocation – yes, it is true that primary carbocations aren't favorable. But if we had an alkyl shift, couldn't we make a more stable carbocation? You might respond back and say no, what if we do a hydride shift? Because if we get a hydride off of this tertiary position into the primary, that's going to make a tertiary carbocation. Yes it is, but you got a four-membered ring there, [so there will be ring expansion instead]. Once [the ring expands], then hydrogen can be eliminated, making cyclopentene.

Nomenclature

First nomenclature question involved a diketone that has an alkoxide substituent. As far as which direction to number the chain from, if you started from the righthand side, the alkoxide gets a 2, but it's not the more important functional group, it's just a substituent. Since the ketone's more important, it would get the lower number if we start from the left, so we are, in fact, going to number from the left. We do have a stereocenter, so let's figure out whether it's R or S. We have oxygen versus carbon with anything attached to it, versus carbon with just hydrogens attached. It is S. Since there's only one stereocenter, we don't need a number with that, we just say S. We have a single substituent, 5-ethoxy; there's no other substituent, so we go to the main part of the name, hex; in all names, you have either an, en, or yn that is part of the name; you do not drop that because it shows what kind of unsaturated hydrocarbon. So after hex, before the one, there's an, there has to be. Because there are two ketones, we're going to use an 'e' there. So this is (S)-5-ethoxyhexane-2,4-dione. Ethers don't have their own functional group ending; they're always just substituents.

Second problem. This had an aldehyde and an alcohol. I didn't write that position with a dash or a wedge, so it is impossible to determine whether it's R or S. Don't worry about that position when naming the compound. [But,] when would you not worry about stereochemistry? You will see sometimes structures written purposely ambiguously because it might not matter. There's only one nameable stereocenter here; let's figure out its configuration. It does require the use of phantom atoms, since we have a double bond there. Effectively, on the lefthand side, we have [O, O, H], because of the doubling of the double bond that we do; on the righthand side, we have [O, C, H]. [O, O, H] is more important than [O, C, H], so the aldehyde's more important than the alcohol, then the methyl group, so this is R. We have two substituents; the substituents are named in alphabetical order. Once you have substituents, there's no priority order, it's numerical order. The 'h' in hydroxy comes before the 'm' in methyl. This is a four-carbon compound, so it's butanal.

The last nomenclature problem had a little of everything on it, except an alkene or an alkyne. This was to see if you remembered that an aldehyde is more important than a ketone, and therefore the ketone's going to be named as oxo, as substituents, so there's a total of three substituents on this molecule. Notice that there's a functional group at every position, so this also was to see if you recognized that because the aldehyde's more important, that's where the numbering starts. Remember that prefixes like di-, tri-, tetra- don't get alphabetized, so this compound is 4-hydroxy-2,3-dioxobutanal. The 'd' in 'di' doesn't get alphabetized, that's why the 'o' in 'oxo' still comes second.

I'd like to review [cationic and anionic ring opening of an epoxide] briefly and [give] a little more detail about each of those. We covered MCPBA as one way to [synthesize epoxides], we talked about making a halohydrin as an intermediate to get to an epoxide. Cationic ring opening. I want to write out how you would represent those reagents by synthesis. The question has also come up what conditions should [be listed] for this type of reaction. If it's cationic, what's one of the things that you've got to have around? An acid catalyst. Tonic acid is usually going to be the one I suggest to use. What else also goes with this? What types of compounds would be used in the ring opening? Alcohols, or, technically what else could be used? What's the smallest non-carbon alcohol? Water. Water acts much like an alcohol; it's got an –OH group; it only has a hydrogen besides that but that's why it does react like an alcohol. So, we'll say ROH or H₂O. I'll show the product as if it was ROH. Focusing on the regiochemistry. Where will the –OH group when the ring opens end up, on the more or the less substituted carbon? The less substituted position. Remember the intermediate that gets formed here: we have an oxonium ion that has to get pushed open. [This reaction is similar to] bromination, where we have a cyclobromonium ion and then oxymercuration-demercuration where we form a cyclomercurinium ion.

This ring is unstable, and, unlike the way I've drawn it, it's deceptive, it's not an equilateral triangle; one side is not the same length as the other. That's because the more substituted carbon does a better job at handling a positive charge if the positive charge forms. There is stereochemical evidence to show that that ring does not open ahead of time. How do we know that that ring doesn't open by itself? If it did, you really would form a carbocation, which means two things could happen: carbocation rearrangement; and, the carbocation could be attacked from either face. We don't see that in the product mix (at least appreciatively), which means that that ring stays a ring until something comes and pushes the ring open. Then, we have to go back and say, why would it end up attacking at the more substituted position? Because, if something's attacking at the same time the ring's opening, that feels like an S_N2 reaction, and in S_N2 reactions, kinetics controls the reaction. Attack at a primary position is much faster for S_N2 and a secondary or tertiary position. That's because this is not a normal S_N2 case. That ring is so strained; imagine that you had an oxygen connected by two rubber bands to two carbons and you pull on that oxygen; one of the rubber bands is weaker than the other. Then, if you have something that's going to come along and possibly interact with one of those rubber bands, the weaker one is going to be the one that likely breaks.

Same thing here – the lefthand bond to the more substituted position is longer and weaker because if you had that bond break the carbocation that forms would be more stable. That's why we end up with this form of regiochemistry.

How's everything different with the anionic reaction? What would I write down, not for mechanism, but for synthesis? An alkoxide. Acid and alkoxide, in that order? So alkoxide and then acid. Do I need a 1/2? Yes, I absolutely do. An alkoxide with acid would react to make an alcohol and never touch the epoxide ring, unless you have more acid and then you're back to a cationic ring opening. What you've got to show is an alkoxide, or hydroxide, reacting with the ring, followed by H⁺. Notice what I'm going to say here: not tosic acid. Tosis acid would work; it would do nothing wrong. But it's a waste. The reason that we normally use tosic acid as an acid catalyst, meaning that we need just a small quantity of H⁺, you need just a little pinch of tosic acid, that's good enough. Here, after the first step of the reaction, you use an alkoxide to make an alkoxide. You pop the ring open using an alkoxide; you make an alkoxide because of the oxygen that just opened, so you have to neutralize it with acid. Why use tosic acid if you do neutralization. You still need to be care what acid you use; we're soon going to start seeing what happens when we have multiple functional groups. Let's say that I through strong, concentrated sulfuric acid in this. It might work in this case, but what if there's an alkene on the molecule as well? That alkene could react, so in real life, you'd use a very dilute solution of acid so that it just barely neutralizes everything without causing some sort of side reaction. That's something to think about as we go into the future. Discussing regiochemistry, if I imagine that an alkoxide reactions, it's sterics that control the reaction, so now you will get substituted at the less-substituted position. So the –OH gets pushed to the more substituted position.

This is not quite reality. Epoxides actually have a litte more complicated behavior than this. [The problems here will be carefully designed so that with the epoxide] you're choosing between a primary and a tertiary center. There is some squirrely behavior that can happen when you have a secondary center versus a primary.

There's two other reagents that do this anionic ring opening. One of those reagents is lithium aluminum hydride. If you had an epoxide, synthetically, you'd write it lithium aluminum hydride, followed by acid workup. A plain H⁻ gets involved; it attacks, pushes open the ring. Notice there's now only one functional group that results: the alcohol. Since the second step is the addition of acid, I'm allowed to show H⁺ here. This is a reduction, because previously, both carbons were connected to the oxygen, so both carbons used to have higher oxidation states, but on the end carbon, oxygen got replaced by hydrogen, so its oxidation state goes down by two. Mechanistically, though, it's the same as what you saw above; it's just hydrogen instead of hydroxide or an alkoxide.

One other reagent that behaves very similarly. There's a sneaky way we can add a carbon-carbon bond here. That's using an acetylide ion. You might remember these from last quarter when we discussed the acidity of alkynes – the fact that an alkyne hydrogen is more acidic than an alkene one that's more acidic than an alkane. Relatively easier to deprotonate an alkyne, but you still need made something that's really basic. The average pKa value of an alkyne is 25; an alcohol, 16 – 18. If you deprotonated an alcohol and deprotonated an alkyne, alkyne's more basic. So if you can get an alkoxide to pop this epoxide ring open, this will also pop the ring open. Be care about the way that you draw triple bonds. I've circled the carbon the new bond got made to; notice, therefore, I've got a line going from the triple bond to that carbon. That's because, on either side of that triple line, those positions are carbons themselves; if I did not draw the connector, then what I really would have been showing is this carbon being replaced by that carbon. That's not what happens; you form a bond there. For some reason, maybe because of the odd way that triple bonds look, it often confuses students writing answers down. In real life, you'd do this as a 1/2, where you do the acetylide ion first, and then H⁺ following afterwards, so you finish up exactly the same way.

I'm going to show you an example synthesis problem. What is this? You're given a carbon fragment – in this case, just an alkane – an you have to provide the sequence of steps that would be able to convert that alkane into the target product. How in the world are we going to get between the two? Maybe we can make an alcohol and an alkene. Do you know any reaction to make an alcohol or an alkene directly from an alkane? What is the one and only reaction you've learned to convert an alkane into anything useful? Free radical halogenation. [use of flashcards] So far, if we were painters, we've only been worried about how we made the paint, but we haven't done any painting yet. That's the transition we're making here. We've learned all of these reactions, but so what? What do you do with them? You make molecules. The one and only reaction you know is free radical halogenation – bromine and light, bromine because it's more selective than chlorine. You get mainly the more-substituted bromide. Do we know any reaction that could take that bromide to an alcohol? Sn2. Do we know any reaction that could be made to make an alkene? E2. Do we know any reaction that could make an alkyne? Not directly, but if we did do an E2 reaction to make the alkene, there is a two-step process to go from an alkene to an alkyne – bromine without light or water to make the vicinal dihalide; a double elimination with sodium amide [gives] us the alkyne.

Notice that all of these [molecules] so far have three carbons in them, but somehow we end up with a product that has six carbons. Did I just show you in the step up above a new way of making a carbon-carbon bond, by using an alkyne to attack an epoxide. I could get an epoxide if I took the same alkene and, in a separate pot from the bromine, react it with MCPBA. This is an example of what you would call divergent synthesis, where your reaction pathway splits. You take one substance and use it two different ways. An alkyne won't directly react with an epoxide; first, we have to deprotonate it, which we can use yet another sodium amide to do that deprotonation.

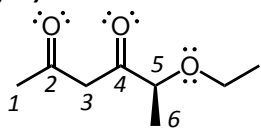
Now if we simply take those two compounds – the epoxide and the acetylide ion – we could do now what's called convergent synthesis, where you separately make two complicated molecules and then, at the last moment, through them together to make an even more complicated molecule. Initially, we have an alkoxide, which if we use dilute (dil) H^+ , we can make an alcohol. But that's not what the product's supposed to be; it's supposed to be an alkene, a cis alkene, which means the last step is Lindlar's catalyst and hydrogen. You can study this and say, ok, each one of those steps makes sense; how in the world am I supposed to know to do that whole thing, though?

cationic epoxide ring-opening

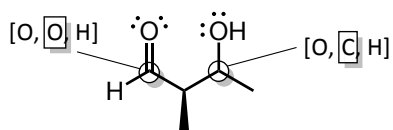
anionic epoxide ring-opening

Structures (remaining structures identical to lecture 4A)

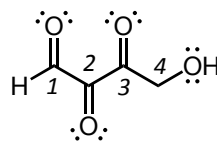
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(S)-5-ethoxyhexane-2,4-dione



(R)-3-hydroxy-2-methylbutanal



4-hydroxy-2,3-dioxobutanal