

Lecture 5A • 01/27/12

Quiz 1 answers

Mechanism problem 1. You had four different reagents you were suppose to react with this starting material. We did start with a chiral alcohol that reacts first with PBr₃, followed by the sulfur analog of sodium hydroxide, followed by sodium hydride, and, finally, bromomethane. PBr₃, that is one of the reagents we learned for converting an alcohol into a leaving group. In this case, the phosphorus is very delta positive, so the alcohol attacks the phosphorus and, at the same time, bromide gets kicked off. We have an oxonium ion. Now that I've written the full structure once, I'll abbreviate PBr₂, make it a little easier to write. Deprotonation occurs, and then, the bromide that was kicked off comes back to kick the OPBr₂ off. At that point, because it's like an S_N2 style attack, we are going to end up with inversion of configuration. That has a leaving group, so it's going to be able to react with the next reagent. Remember that sulfur, when compared to oxygen, if you're looking at two equivalent molecules that only differ by the fact that they have sulfur versus oxygen, sulfur's actually the better nucleophile. This could very easily undergo an S_N2 reaction, in one step, and that means that again you're going to have inversion of configuration. What do we have next? Sodium hydride. Just like an alcohol can get deprotonated, thiols can get deprotonated, so hydride pulls a hydrogen off. We make the sulfur equivalent of an alkoxide, which is not as basic, which in turn means the thiol is easier to deprotonate than an alcohol; this compound ends up not as basic as an alkoxide, but again, much more nucleophilic than the equivalent oxygen compound, so very easily will participate in an S_N2 reaction. Since we have methyl bromide around, that's one of the best possible substrates to do an S_N2 reaction; that will get attacked by the sulfur, then here is our final product.

The second problem was straight out of lecture; it was an oxidation. Deuterium is not a carbon; this seems to be a common mistake that is popping up. Deuterium is not a carbon, so is that a primary, secondary, or tertiary alcohol? It's a secondary alcohol. It will oxidize but When you asked if it was under anhydrous conditions, I couldn't comment, because it didn't matter if it was under anhydrous conditions, cause secondary alcohols can't be overoxidized, so the worst that's going to happen is it's going to oxidize to a ketone. Very technically, if equilibrium can be established, it will be established. We're going to make a ketone; some of you may then realize that if we have aqueous conditions, couldn't that ketone form a hydrate? Yes, technically, reversibly in solution, it would. But as far as an isolatable product, hydrates are not favorable normally. So even if we are in aqueous conditions and even if there's acid around, the expected product is an aldehyde or ketone, leave it as the aldehyde or ketone, don't continue to take it through to the hydrate. Because it's reversible, because it's not favorable, if you then tried to isolate the product, it would revert back to the aldehyde or, in this case, the ketone.

Let's see the mechanism for this. You were given the abbreviation PCC, which you did need to know is pyridinium chlorochromate. Now that I've written the structure this first time, I'm going to abbreviate using 'pyr'. I'll do a step-by-step attack. So we open the chromium-oxygen double bond, then it reforms; don't forget about the pyridinium that's floating around. Positively-charged oxygen, which gets deprotonated. Then we have our chromate ester. Since pyridine as a solvent was used, and it's the conjugate base of pyridinium that's part of PCC, it logically is the species most like to cause the oxidation at this point. If you just used 'B' for base as a general term, that would have been perfectly correct, but if you showed pyridine, that also would be correct. It pulls off deuterium, which is just another form of hydrogen, causing the chromium to be kicked off (that's the oxidation step right there), and you end up with acetone as the product.

Fill-in-the-blank

We started with a chiral alcohol that reacted with something, followed by sodium azide, to make an alkyl azide. Notice that, overall, there is one but only one inversion of configuration that occurs. If we used PBr₃ like in the first synthesis problem, we would have had double inversion occur, because we would have had inversion with the PBr₃, and then when sodium amide attacks this primary center, that's an S_N2 reaction, and so you'd have another inversion. But in this process, we only have a single inversion overall. What would have been the best single reagent to put here? Tosyl chloride, because it does not affect that carbon-oxygen bond; it just affects the oxygen-hydrogen bond, so it preserves the stereochemistry. What if you put tosic acid? The acid is just a source of H⁺, so it would not form a tosylate; you absolutely must have the chloride [in order to form a tosylate]. If you had been allowed to use two reagents, you could have done PB₃ or SOCl₂, followed by the Finkelstein reaction, using sodium iodide, because that would have been two inversions, and this is one of those cases where two wrongs make a right. So, if you do the double inversion, you get back your original stereochemistry again, like you had used tosyl chloride, and then the single inversion due to the sodium azide would have given you the product that you wanted. But, since you only had one blank, the answer was tosyl chloride.

The other one. What would happen if we put this in tosic acid with heat? It's going to be a dehydration reaction. But, do you think that keeping the four-membered ring is likely if there's any way at all for that ring strain to be relieved? Whether you form a carbocation, or just somehow that water group gets kicked off, if we did end up with that carbocation, wouldn't it be great if the ring could open in a ring-expansion carbocation shift, much like the one that we did as a problem in lecture. If that occurs, we end up with this compound, which, if we do show it, could dehydrate and make cyclopentene.

Let's flip over to the synthesis problems. These are problems in which you start out with a particular carbon framework, and you're allowed to use that source of carbon, but as your only source of carbon, and you can use whatever other reagents that you might want. This is where a road map might be kind of useful. If you put an alcohol in the middle of a piece of paper, you can take all of the reactions that you learn and a large number of them go through an alcohol as an intermediate. Another way to say it is: you can make the alcohol an intermediate in an awful lot of reactions. Think of all of the reactions that make an alcohol: S_N2 using hydroxide; oxymercuration-demercuration of an alkene; hydration of an alkene; hydroboration-oxidation; making a halohydrin; making a geminal diol (a hydrate); reduction of aldehydes and ketone – we have quite a number of reactions, don't we. What about reactions of alcohols? Oxidation to make an aldehyde, a ketone, or a carboxylic acid; conversion into a leaving group; dehydration to make an alkene. Put an alcohol in the middle of a piece of paper and see how many reactions leading from it you can figure out, and how many reactions leading to an alcohol you can make. These problems are simpler problems in that they're just functional group transformations. The way it works is kinda like a puzzle piece. Look at the product we have, an aldehyde: how many ways do you (currently) know how to make an aldehyde? Just one – oxidizing an alcohol. So if you wanted to, you could work this problem retrosynthetically where you look and say, what could have made an aldehyde? An alcohol. Is there a way that you could have taken the starting material to make an alcohol? Yes, and S_N2 reaction. The answer in this case would be just a two-step synthesis. This is the way you would need to write your synthesis answers: you show the reagent and you show what results from that reagent; you then show the next reagent and results from that next reagent.

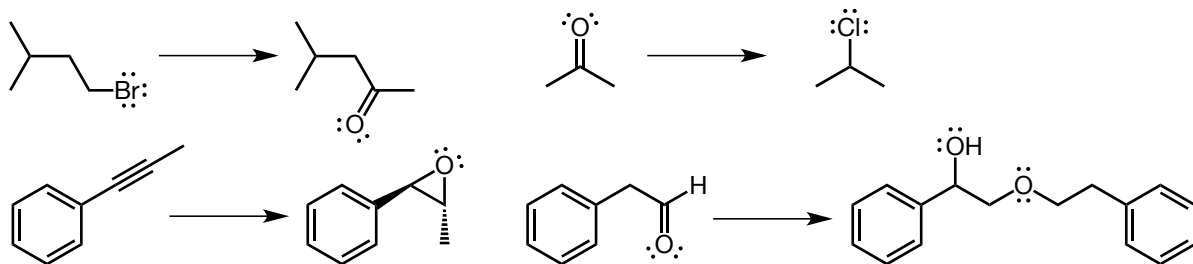
Second problem. Do you know a reaction that goes directly from a ketone to an alkyl chloride? No, but what compounds do you know that you could make an alkyl chloride from? An alcohol. Do you know a way to convert this ketone into an alcohol? Yes – again, a demonstration of using an alcohol as an intermediate. For making the alcohol, we could use either lithium aluminum hydride or sodium borohydride – you can't use sodium hydride; although it is a source of hydride, the reactivity is a bit different – followed by H^+ , to show that there's a follow-up set of conditions – work-up, it's often called. After that, we could have an alcohol, which since it's a secondary alcohol, without modification, we can show thionyl chloride doing that transformation. Tosyl chloride will make the tosylate, not the chloride. If you use tosyl chloride followed by sodium chloride, that would have been allowable. HCl should also have worked, the only problem you would have in real life is whether you would get dehydration.

Let's skip to the fourth problem. You should start with the number of carbons for any synthesis problem. Notice that the carbon framework of the starting material can be found in the product – it just happens to be found twice. Notice also that where the functional group is on the starting material, there is functionality in the product at the same relative position; the only thing that's a little odd, possibly, is where did we get this third bit of functionality from? Well, there are two functional groups that we have learned (three really) that involve two different carbons: an alkene – which that mean also alkynes – and epoxides as well. [One example of a reaction of an alkene that products two functional groups at the same time is] making a halohydrin. We've also used epoxides [to make two functional groups at the same time] – opening epoxides would [often] result in a molecule that has two functional groups right next to each other. In fact, this looks like the type of thing you could get from an epoxide, because if you open an epoxide with an alcohol or an alkoxide – either cationic or anionic conditions – you're going to get an ether and an hydroxide right next to each other in the product. An epoxide is going to be the most likely intermediate in this problem.

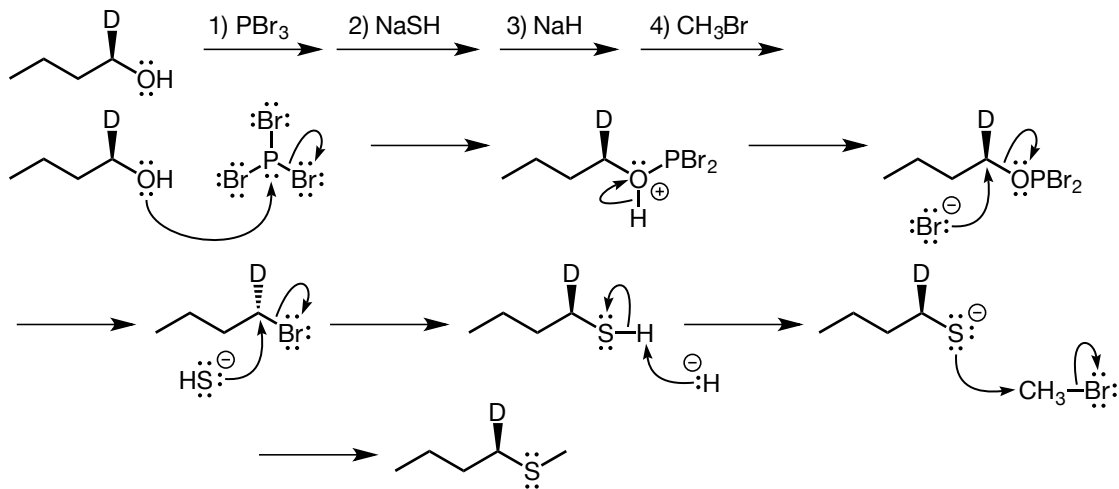
How do we make an epoxide? What functional group could you make an epoxide from? An alkene. Can we get an alkene directly from an aldehyde? No, but what could we get it from? An alcohol. Can we make an alcohol from an aldehyde? Yes we can, so let's start there. I'll use sodium borohydride this time to make the alcohol. If we wanted to do a nice, clean elimination, we could make it a leaving group first – I'll use tosyl chloride – which then I could do an elimination with. Once I make the alkene, I could then use MCPBA to make the epoxide. Notice that, in a previous step, I already made the alcohol I would want to use, either directly in a cationic ring opening, or to make an alkoxide to do an anionic ring opening. Based on the position of the $-OH$ group in the product, which form of attack am I going to want to do – anionic or cationic? The base one, the anionic one, because the ether ends up at the less substituted position, which is something that would happen if sterics were controlling, which is something that happens in the base version of the reaction. To get that alkoxide, I'll separately use some of the alcohol from above. We deprotonate using sodium hydride. We combine the two of these products – we did divergent synthesis, where we used one reagent in two different ways, and we did convergent synthesis, where we made two things and then later combined them together. At first we'll get an alkoxide, once we initially open up the epoxide ring, and then, gentle H^+ to get us to the product.

Structures

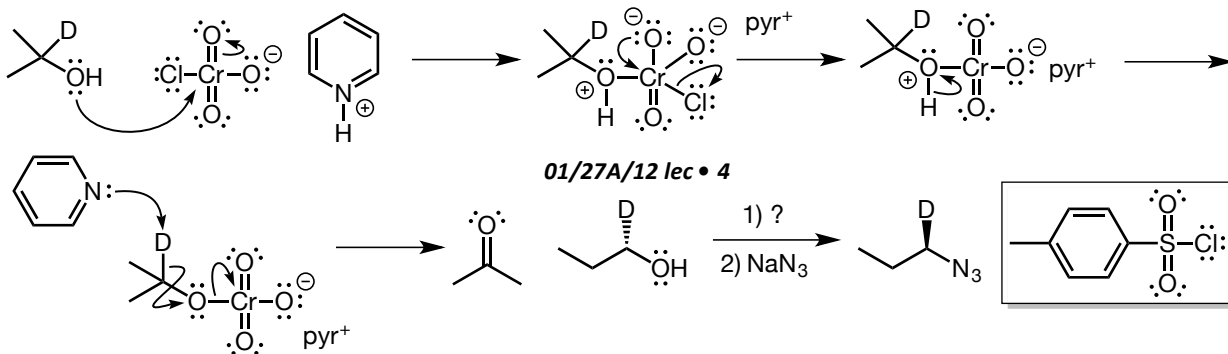
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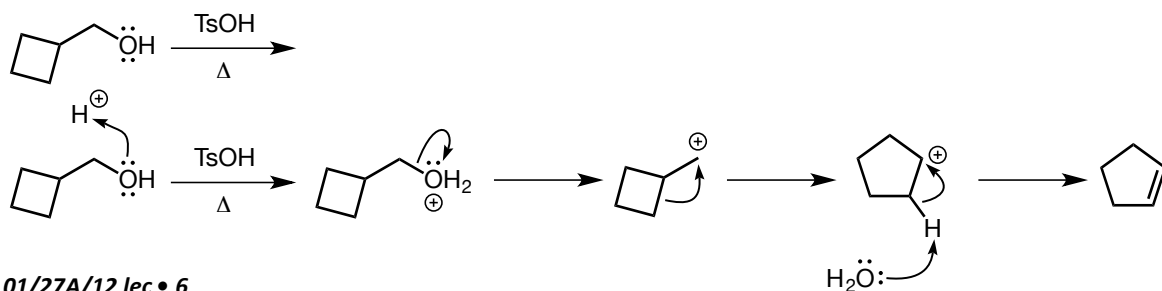


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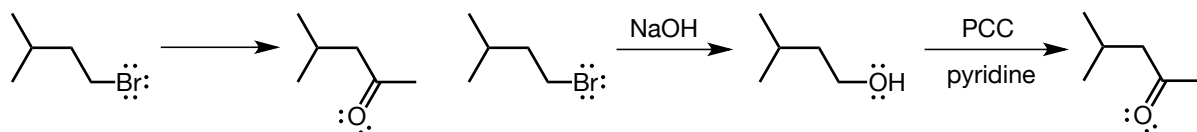


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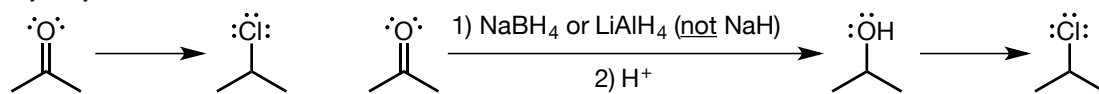
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