

Lecture 7B • 01/27/12

Let's start on the synthesis problems. The first two problems are really supposed to be examples of simple transformations. If you put an alcohol in the middle of a piece of paper, because you can use alcohols to make a large variety of functional groups, a large of functional groups make alcohols. For example, name off some reactions that you know that produce alcohols as a product: S_N2 on alkyl halides; S_N1 on alkyl halides; cationic and anionic ring opening of an epoxide – there is an ether that might be formed, but you make an alcohol at the same time; hydroboration-oxidation; oxymercuration-demercuration; hydration of alkenes; making a hydrate. What about reactions of alcohols? Making an alkyl chloride; PBr_3 to make an alkyl bromide; making a tosylate; oxidation to make an aldehyde, ketone, or carboxylic acid; alkylation, doing the Williamson ether synthesis; dehydration to make an alkene; if it was a halohydrin, to make an epoxide. Several of these problems are to show that alcohols are often very useful intermediates in synthesis problems. Flashcards – you've learned all this stuff about the different colors of your palette that you could use to paint – the idea being that you've got these different things you could use to do synthesis; but you need to start using them and recognizing the common patterns. That's what these first two problems are for.

Do you know a way to go directly from an alkyl halide to an aldehyde? Have you learned a reaction to make an aldehyde? Oxidation. So if we had an alcohol, we could make the aldehyde. Do we know a way of making the alcohol from this alkyl halide? Sure we do, it's an S_N2 reaction. I've shown this retrosynthetic arrows in class before. What the retrosynthetic arrow is for is for logic, for you to solve this problem to figure out what could have been the step right before. But, when you do write out your answers to these synthesis problems, it needs to be written as synthesis – write out the first substrate, show the reagent that would be used to do the transformation (reagent or reagents), you show what you get immediately after than first reactant, then you show the next set of reagent or reagents. In this case, it would be PCC and pyridine. Methylene chloride can also be used as a solvent or cosolvent in this reaction. Chromic acid cannot be used because it would cause overoxidation. Here we have to use PCC in anhydrous conditions because we want the aldehyde, not the carboxylic acid. After PCC/pyridine, this is the product we would get. It's just a two-step transformation. It may look easy, but the reason for showing you this is so you can get used to this easy to conversion.

Let me show you that mechanism for CrO_3 . The Jones reagent is chromic acid, water, and sulfuric acid. Sulfuric acid acts as a catalyst, you could say. What happens initially is chromium trioxide – this chromic acid is in a source of H^+ . One of the chromium-oxygen double bonds opens up. We've got formally a positive charge on the chromium now, which gets attacked by whatever alcohol may react with it. Because this is usually going to be used for secondary alcohols – or if you did want to overoxidize a primary alcohol – I'm going to show you the mechanism with a secondary alcohol. So it attacks in, and from this point forwards, it's virtually identical to the mechanism you learned with PCC. The only difference is now that we're in an acidic environment, instead of an O^- with some sort of counterion there, you just an $-OH$ group coming off of the chromium. The same progression will occur where deprotonation of that oxygen happens, and then elimination occurs. Since we don't have truly a base, we use what's closest to it – water – to show the proton being removed, kicking off chromium just like with PCC, and producing, in this case, our ketone. If you have a primary alcohol, it would overoxidize, because these are aqueous conditions.

The second synthesis problem was to go from a carbonyl-containing compound back to just an alkyl halide. Do you currently know any ways to directly do this reaction, to go directly from a carbonyl to an alkyl halide? The answer is no, there's not a direct way, but if we reduce, what are we going to make? An alkoxide initially, then you've got to neutralize it to get the alcohol. Then, you could use thionyl chloride, or we could use, in some circumstances, hydrochloric acid – the only caveat with that is that if you have high temperatures, with an acid you could get dehydration, or if you have any mechanism that goes by a carbocation, you carbocation rearrangement. Based on what we've learned so far this quarter, the cleanest sequence of steps would be this. To do reduction, which you could use either lithium aluminum hydride or sodium borohydride, as aldehydes and ketones will react with both. Sodium hydride would not work in this case, and that's because the aluminum or boron of these reducing agents participates partly in the reaction, which makes the reagent different than sodium hydride. Think of sodium hydride as just a source of basic H^- , whereas these reagents are really a source of reducing H^- . There is a work-up step. Immediately after the reaction you technically don't have an alcohol, you have an alkoxide, because you're in an extraordinarily basic environment. To isolate the alcohol, we have to add acid. Doing the 1/2 combo will get the alcohol. Because the work-up step almost always follows a reaction, it's ok to show me the 1/2 like this, you don't have to show me the alkoxide as an intermediate. Then, I'll show thionyl chloride being our reagent that could make the chloride.

The fourth one uses elements of both of these two problems and presents a more complicated structural case. If you look at reaction, I started with what you could characterize as a two-carbon fragment with a benzene ring hanging off of it, eight carbons total. You end up with a product that has a whole lot more carbon, but if you look at it carefully, you notice that it's really two sets of the same type of carbon structure that we started with – two carbons that's got a benzene ring hanging off of it. We're going to start doing more reactions that can form carbon-carbon bond and break carbon-carbon bonds, so it's going to make examination of the carbon structure a much more important thing in your synthesis problems. It's important to note that it looks like two units of the same starting material – which we would hope would be true because I told you you could only use the starting material in your synthesis.

On top of that, you'll notice that where the functional group starts on that original compound, we have functionality on the same places on the product – except, we also have a third functional group, a third place where there is functionality; that's the alcohol. This is the more difficult problem because you had recognize in order to make this product, we had to go through a functional group that involved two of the carbons. Whenever you do see two functional groups right next door to each other, where you might have only started with one, that indicates you probably when through either an alkene, an alkyne, or an epoxide, because those are all three functional groups that bridge two carbons, and that gives you a way of somehow possibly functionalizing both carbons. For example, with an alkene, we could make a bromohydrin, a halohydrin, an –OH on one group and a bromine on the other. For epoxides, if we do cationic or anionic ring opening, we're going to get a functional group in two different places. This is a synthetic example of trying to use one of those things as an intermediate.

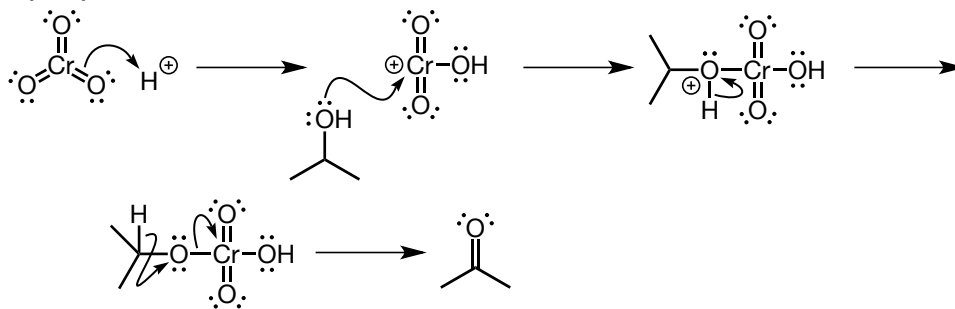
Based on the type of product here, which one of those three – alkene, alkyne, or epoxide – do you think is going to be our main synthetic intermediate? Epoxide. The epoxide answer is correct, because we end up with an ether and an alcohol. Why does it appear that it opened up under basic conditions? The –OH itself ends up at the more substituted position, which means what ever opened the ring attacked at the less substituted position, which is what happens when kinetics matter, which is what happens when you are doing basic conditions. Because you have two functional groups right next door to each other, that's why you should recognize that as being from an alkene, an alkyne, or an epoxide. From there, I got down to an epoxide because this is the type of structure you would get when an epoxide opens – an ether and an alcohol. Finally, this is basic conditions for opening because of where the ether ended up (or where the alcohol ended up). Do we know a way of making an epoxide directly from an aldehyde? Not directly. What functional group do we know we can make an epoxide from? Alkene, or, technically, a halohydrin, which also would have come from an alkene. Do we know a way to make this aldehyde directly into an alkene? No. How do we know how to make alkenes? From an alcohol. Can we make an alcohol from this aldehyde? Yes we can. Let's start with that. Lithium aluminum hydride or sodium borohydride – because it's the far safer reagent, when possible I almost always list sodium borohydride. Technically, I could dehydrate this molecule, but just to show a clean example of elimination, I'm going to turn it into a leaving group first using tosyl chloride, and then using potassium t-butoxide, or some other hindered base, to perform the elimination. This is a common sequence of steps as well, a very common type of transformation. We are going to learn a way to go directly from a ketone or aldehyde to an alkene. From here, we need the epoxide. If I want to do the one-step version, it would be MCPBA. We need an alkoxide, because if you're doing anionic ring opening, you need a base. We already made the alcohol that would be appropriate for the alkoxide. This would be an example of divergent synthesis – you make one compound that you use two different ways. This alcohol I use to make an alkene, but, separately, I could deprotonate it to make the alkoxide. Put the two together, the two separate things I make, and that would be called convergent synthesis – making two separate things, putting them together to make a more complicated molecule. Immediately after that step, I don't yet quite have the product; I've opened up the ring but I still have a (different) alkoxide. At the very end, just add H⁺, you'll protonate that alkoxide and you'll get the product. There are such things called as one-pot syntheses, which is kinda the goal of synthetic chemistry, where you can just pour in a bunch of stuff and out comes this magic molecule. Almost whenever you're doing divergent synthesis, it's got to be two different pots.

The last synthesis problem. We start with an alkyne, but we end up with this epoxide. No, in order the product that I've shown you, you can't directly react an alkyne [with] an epoxide. What functional group do you know what makes epoxides? Alkenes. Do we know a way of going from an alkyne to an alkene? We two ways. If we use Lindlar's catalyst and hydrogen, we would get a cis double bond; if we used sodium in ammonia, we would get a trans double bond. Which of the two is going to give us the stereochemistry shown here? Beyond just recognizing functional groups, we do have to recognize stereochemistry. Let me show you two reactions, and this will answer the question for us. If I had a cis alkene, and I used MCPBA, MCPBA does syn addition, meaning it adds to just one face of the double bond; the two things coming up from the oxygen have to be pointed the same direction. If you start out with a cis double bond, both the benzene and the methyl group are either going to get pushed down and become dashes, or they're both going to be pushed up and become wedges. Both are going to happen, because the epoxide could add on either side, so you're going to get enantiomers. Not what we want, is it? That means we would have had to have had the trans double bond to make the product shown. So, sodium in ammonia gets us the trans double bond, which then MCPBA would give us the product. This brings up another issue: you get the product you want, plus the enantiomer; it's unavoidable. There are techniques in real life to separate enantiomers. Sometimes, unless you do have the right set of reagents, it may be unavoidable that you're going to make a mixture of stereoisomers. In a synthesis problem, if the only way you know how to get there creates an enantiomer at the same time, don't worry about it.

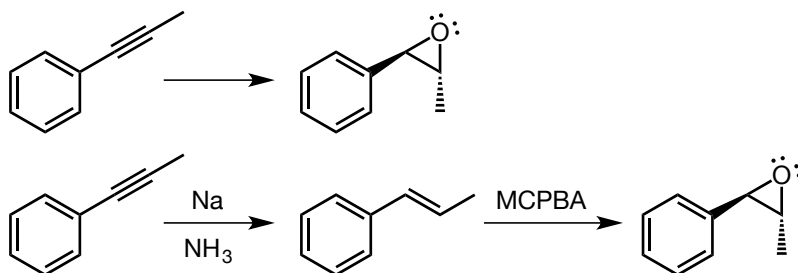
Jones Reagent – CrO₃, H₂O, H₂SO₄

Structures (remaining structures identical to lecture 4A)

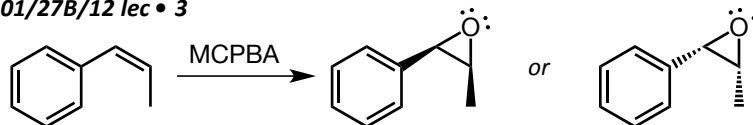
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