

Lecture 4B • 01/17/12

We had two synthesis problems that I had given to you at the end of class last time and I had asked you to work on those. How many of you have had the chance to work on those synthesis problems. [admonition that you won't have someone looking over your shoulder helping you during an exam, so do the problems that are suggested] First problem was a chiral alcohol that I wanted you to convert into an alkyl azide. I had even told you that it's the reagent sodium azide that you're going to need to do this synthesis. This really had just one important synthetic stumbling point that you needed to consider, which is this: N_3^- , that's a fairly strong nucleophile, which means, especially given that this is a primary substrate, means $\text{S}_\text{N}2$ is the only thing that's going to happen. $\text{S}_\text{N}1$ just can't happen on a primary substrate. $\text{S}_\text{N}2$ occurs with inversion of configuration, doesn't it? That means we've got to be very careful about what we make the alcohol into as far as a leaving group, because if, for example, we used thionyl chloride to make a leaving group, thionyl chloride itself occurs by a mechanism that causes inversion of configuration. if you then followed that up with sodium azide, you're then going to end up with an alkyl azide that's the wrong stereochem. With what you've learned, the most direct correct answer would have been to use tosyl chloride, because when tosyl chloride reacts, it does not affect the carbon-oxygen bond. No inversion happens here, so that when you do use sodium azide, when now you do get inversion, you do get the correct stereochemistry. That is, in fact, the answer to this synthesis: first converting it to a leaving group but doing so without inverting the stereochemistry, so making it into a tosylate, and then, turning the tosylate into an azide. Another answer that could have worked, if you thought it through, is if you had used tosyl chloride to start with. You could have then done the Finkelstein reaction to make the iodide, because that's another $\text{S}_\text{N}2$. If you did thionyl chloride, which causes inversion, then the Finkelstein reaction, which causes inversion, and then you did the sodium azide attack, which causes inversion, three wrongs make a right in this case.

Let's look at the second problem. That was to convert an alcohol that was at a more substituted position somehow into an alkyl chloride that was at a less substituted position. We're going to have a more method approach to synthesis. One of the first things that you will normally look for is how many carbons are there in the carbon framework, because making or breaking carbon-carbon bonds turns out to be one of the most important synthetic events that can occur. None of that happens here; we start with seven carbons, we end with seven carbons; we're only transforming functional groups. But have you learned any reactions that can directly convert something in a more substituted position into something that winds up at a less-substituted position? Have you learned any one-step reactions like that? No. You've learned the reverse. If you had an alcohol at the end of this molecule, we might be able to come up with a mechanism to show carbocation migration. But carbocations would not want to migrate this way, because this is going from more to less favorable. So, one common trick that we're going to see that we can use is to make the position of the functional group apparently shift like this, we need an intermediate where the functional group itself involves two carbons. Do we know any intermediates like that? Of course we do. What if we had an alkene that at some point or another connected those two carbons. That might give us access to some way to change the substituent position. Alkynes sometimes can be used as intermediates, and epoxides, they also bridge two carbons; remember that an epoxide is a cyclic ether. One of these three intermediates might have been appropriate in this case. Let's do this retrosynthetically; maybe if we have a picture of an alkene in our minds, can we somehow get this molecule into being an alkene. Doing this retrosynthetically, if I had this chloride, do we know any other molecule that we could have used to make this particular chloride? An alcohol – a primary alcohol; that would have been an easy conversion. What reagent could we have used to go from the alcohol to this chloride? Thionyl chloride. We still then have the problem of how do we somehow involve both carbons so we can have this position of functional group switch occur. Is there a way that we could have made a double bond that went from the tertiary carbon here to the primary? Or is there any way that an alkene like that could have made an alcohol with the $-\text{OH}$ group on the less-substituted position? If we do hydroboration-oxidation, that purposely makes the less-substituted alcohol. So yes, if we had this alkene, we could have used borane•THF, followed by hydrogen peroxide and hydroxide, and that would have made the less-substituted alcohol. Do we know a way of making this particular alkene from the alcohol directly? We haven't covered it yet, but there is one more dehydration reaction we haven't discussed. Ignoring that, even, the version of dehydration we did learn, that was cationic using an acid catalyst, doesn't that dehydration usually favor the thermodynamically more-favored alkene? Would this be the most favorable alkene possible from that particular alcohol? No, but is there a way we can cause the less-favorable alkene to be made? If we do an elimination with a bulky base, meaning the thing right before here wasn't the alcohol itself, maybe we had a tosylate even – doesn't really matter what our leaving group was as long as we had some leaving group there. Then we would have used a hindered base to cause the kinetic product to form. To get from the alcohol to this point, all that would have required is tosyl chloride. So now, in the forward direction, we took that original alcohol, reacted it with tosyl chloride, we made the leaving group. We use a bulky, hindered base to cause the less-favored alkene to form; then it react with borane and then hydrogen peroxide to make the less-substituted alcohol, which then we could turn into a chloride. Why did I want to form an alkene? Because how else am I going to get from a more-substituted to a less-substituted position? I need some reaction pathway to allow me to switch the places where the functional group shows up. One way you can do that is through an alkene, because an alkene connects both of the carbons involved.

Let's cover oxidation. I'm going to show you a special form of oxidation first, because primary alcohols versus secondary alcohols, they can potentially form different products. Let me give you the overview first. If we have a secondary alcohol and – without worrying about the specific conditions – if I just say that we have oxidation that can occur, a secondary alcohol can oxidize to a ketone. A primary alcohol, if you use the right conditions, you can oxidize it up to an aldehyde.

But, depending on your point of view, if you use the right or wrong conditions, aldehydes themselves can be further oxidized to create a carboxylic acid. Let me show you a reagent that can be used to stop at the aldehyde first, so this is selective oxidation of primary alcohols. The reagent that we use is PCC, pyridinium chlorochromate. We'll do this in steps. Pyridinium comes from this cyclic compound called pyridine. Pyridine is a very common solvent; it does have some toxicity to it, but it is a very widely-used solvent. It's a relative of benzene [the major difference being the nitrogen incorporated into the ring]. Nitrogens on organic compounds are usually bases; they may not be strong bases, but they often can become protonated. If we add a hydrogen to pyridine, then we make this positively-charge nitrogen ion that is the pyridinium ion. Chlorochromate is the following. Chromate is chromium that has [four] oxygens around it; chloro- means to substitute, so this is chlorochromate. Put the two ions together and that's the compound PCC. You will be allowed to an abbreviation for pyridinium so you don't have to write either the word or the compound over and over and over again, but you do need to know what the structure of PCC is. And, you need to know it's name so in case I only give you the abbreviation, you'd recognize what PCC is.

How does PCC react? The pyridinium ion is just a very weak acid, so it could be used as a source of protons, but it does not do the job of oxidation itself; instead, it's the chromium. These types of reactions can have some environmental consequences. [discussion of erin brockovich and hexavalent chromium] This chromium reagent is so reactive because it's much like the sulfur that we've seen in tosyl chloride and thionyl chloride: having some central atom that's connected to a bunch of electronegative groups. Notice that we also have a chlorine, so this is going to be almost exactly like a reaction involving tosyl chloride, where that chromium center's going to get attacked, and somewhere along the way, chlorine's going to get kicked off as a leaving group. Before, I've been showing attacks on these kinds of compounds with the carbonyl opening up and then simultaneously collapsing back again for attack. Setting myself up for a discussion in the future, I'm going to show it as two separate steps this time around, so I'm going to show it like this: first time out, I'll write the whole structure, to be an example of what you could do in your own mechanisms. Here's the chlorochromate which, you do need to initially show, is complexed with pyridinium. First step of the mechanism looks like tosyl chloride reacting: the alcohol attacks the chromium, which causes one of the double bonds from chromium to open. Notice how I've abbreviated here: I just wrote pyr+ to represent the pyridinium ion. After you've represented the full structure one time, you can abbreviate it in this way as well. Initially, there's a bunch of bonds to the chromium, and here's the logic behind what happens: we've got this negatively-charged oxygen that's really got nowhere to go, except to go right back and attack chromium again, which in theory could kick the alcohol right back off; it would be as if the reaction was just happening in reverse. But, if and when that negative charge does reattack the chromium, it is possible to kick the chlorine off instead, because chlorine's a good leaving group. So, we end up with this kind of intermediate, which will become deprotonated.

This forms the real intermediate, which is known as a chromate ester. An ester is when you take a carboxylic acid and react it with an alcohol of some sort so that instead of a carboxylic acid, instead of having an -OH group attached to the carbonyl, you have an -OR group attached to the carbonyl. This changes the reactivity of that compound quite drastically, because in the original carboxylic acid, it is an acid, because it has a proton that can come off relatively easily because the ion that would form has delocalization. Well there is no ion that can easily form from an ester; esters do have some of the behavior of carboxylic acids. This is a carbon ester; what's a chromate ester? Notice that you still have this central atom that's got double bonds on it, and hanging off of that is another -OR group. That's why it's called a chromate ester, because it's got the chromium core, but it still has an -OR group that's hanging off of it. What's so special about these chromate esters? Why bother making one? Because of the reactivity of chromium. Chromium originally starts out in a +6 oxidation state, and chromium is a very good at [getting reduced] in general. How is it going to get reduced? With a little help. Not worrying about what the base is, a base can come along and help the removal of a proton on the same carbon as where the oxygen is. In all of the elimination reactions we've done in the past, it's always involved the hydrogen that is one carbon away from the leaving group. That is still true in this case, but it's because oxygen is not the leaving group; chromium is. The reason it happens is because chromium is able to be reduced here. So, hydrogen gets removed; the pair of electrons in that bond attacks oxygen, which causes the oxygen-chromium bond to break; chromium is being reduced. I prefer to just skip what happens to the chromium afterwards. PCC can be used in anhydrous conditions to make an aldehyde from a primary alcohol.

But having said that, let me show you this side reaction. Because if there's any water around, even if you're using the reagent PCC - I should emphasize this fact: I showed you this reaction with PCC because it is an anhydrous reagent, it's ionic but not water-based. Even if you use the same PCC, though, if you have water around, you're defeating the reason that you'd use PCC, but you would still, therefore, have this side reaction. Overoxidation will occur. Why will it occur? If we have water around, couldn't we form a hydrate? That's what happens. Here's an important point about equilibrium: even if only .1% of .1% of .1% of the product forms at equilibrium, if there's an equilibrium, that means that little itty bitty amount of product will form. Let's look again to see what the product of a hydrate is, and we'll take this product that we just made to see exactly what side reaction would occur. Remember that there's this acronym POAD that we use for hydration: protonate, open, attack, deprotonate. Protonate - there's only one place a hydrogen it makes sense for it to go, which is on the oxygen. Open - the only bond that can easily open, other than the reverse reaction of the hydrogen falling off, is for the carbonyl to open up. Please be careful because that is a resonance step, not a reaction step, so make sure you're using resonance arrows and brackets like this. The next step is attack - which since we're forming a hydrate, it's going to be attack of water, which makes a vicinal diol, which goes through a final deprotonate step.

Now we've made the hydrate. Even if we were in PCC, this side reaction would happen. This is a [geminal] diol, but that still means it's an alcohol. So just like the first time around, this alcohol can now attack the chromium. Which means the same sequence of steps occurs – one of the oxygens with the negative charge can collapse back down to finish forming the chromate ester. You initially have a protonated intermediate, an oxonium ion, which is going to deprotonate again in order to make something that is neutral. This is the same mechanism; it's happening again on the same molecule only because the hydrate formed. We've made the hydrate, the hydrate formed that chromate ester, now the elimination that causes this oxidation happens again. Something pull off the hydrogen; that pair of electrons can collapse back to oxygen, which causes a pair of electrons to go back to chromium, making chromium the oxidizing agent, and oxidizers get reduced. The product we end up with is now a carboxylic acid. Although forming a hydrate is often thermodynamically unfavorable, if an equilibrium can occur, it will occur. Therefore, some proportion of hydrate will always form. As soon as that hydrate forms, it instantly is able to become oxidized, which is why this carboxylic acid forms as a product. Formation of a hydrate is often thermodynamically unfavorable. However, the formation is a reversible equilibrium process, and if it can happen, which means if water's present, it will happen, even if only a trace of hydrate forms at any one time. As so as the hydrate does form, it can instantly become oxidized, which is why carboxylic acids can form from alcohols if water's present. Some aldehydes just naturally decompose in air to become carboxylic acids.

We'll keep two distinct sets of conditions that we'll use to describe the oxidation of primary alcohols. One is exactly this set of PCC and, we use the solvent pyridine often in these oxidations. I'll use this as the set of reagents to mean there's no water. In a reaction like this, then, if you're using PCC, that might be the reagent; the condition then would that it must be anhydrous. Since PCC is kinda a waste if you do have water around, then chromium(IV) trioxide can be a reagent that's used in aqueous conditions. Certain combinations of water and chromium trioxide are referred to as the Jones reagent. [mention of Swern oxidation]

I wanted to talk about secondary alcohols and tertiary alcohols. Even if we use the conditions of overoxidation, even if we have water present, the only thing that we'll get when we oxidize a secondary alcohol is a ketone. There's no carboxylic acid; why not? Let's write the structure down of what it would look like, if such a critter could form. What's wrong with this picture? Five bonds to carbon; it can't exist. So it doesn't particularly matter which set of reagents you use for a secondary alcohol. Tertiary alcohol – no reaction. Why not? Can't do it; same problem – you'd end up with five bonds to carbon. So you have your summary right here – primary alcohols can form aldehydes or carboxylic acids, depending on your conditions; secondary alcohols can only form ketones, you can't form an aldehyde because there'd automatically be two R groups there, so you'd form a ketone, which can't, in the normal way, oxidize. There are other reagents, including other chromium reagents, that can cause other forms of oxidation. In particular, potassium permanganate does a lot of other aggressive types of oxidations, but they often cause carbon-carbon bonds to break. Notice that this particular oxidation doesn't change the carbon framework of a molecule at all; all it's doing is playing with functional groups. To finish off the review, the tertiary alcohol, for similar reasons as to why a ketone doesn't overoxidize, you can't even oxidize a tertiary alcohol because you can't make enough bonds to carbon.

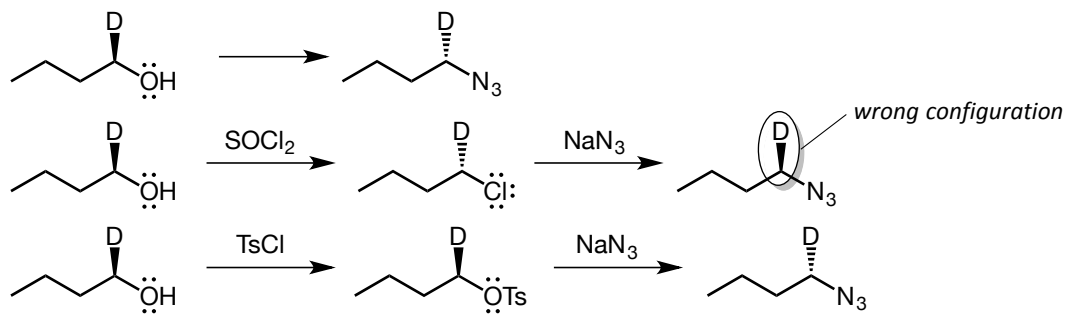
Selective oxidation of 1° alcohols

PCC – pyridinium chlorochromate – PCC can be used in anhydrous conditions to make an aldehyde. *If there is any water around, "over" oxidation will occur.

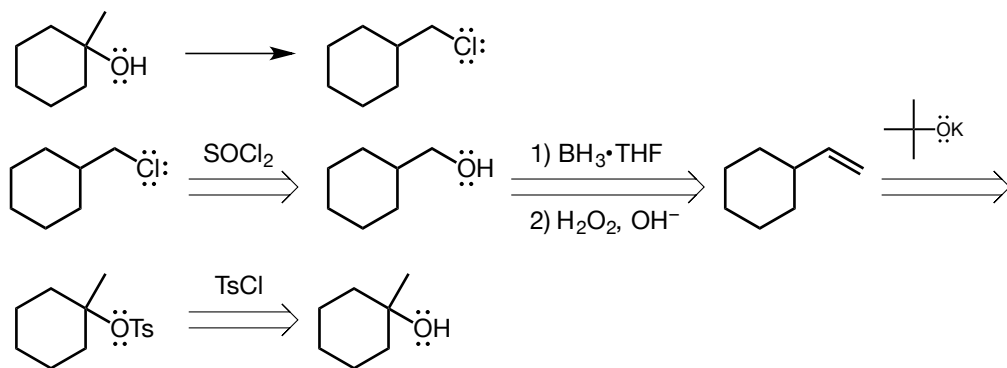
Formation of a hydrate is often thermodynamically unfavorable. However, the formation is a reversible equilibrium process, and if it can happen (if water is present), it will happen, even if only a trace of hydrate forms at any one time. Once the hydrate forms (even briefly), it can become oxidized, which is why oxidation of 1° alcohols can lead to the formation of carboxylic acids.

Structures

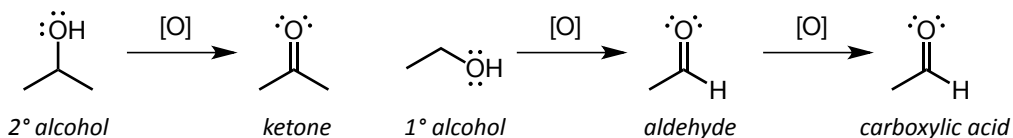
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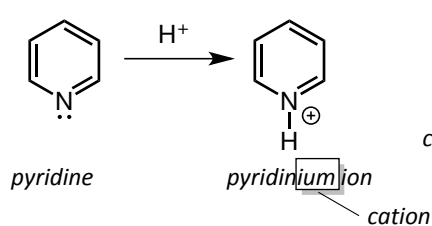
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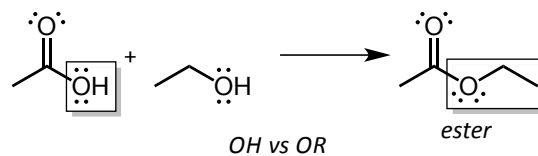
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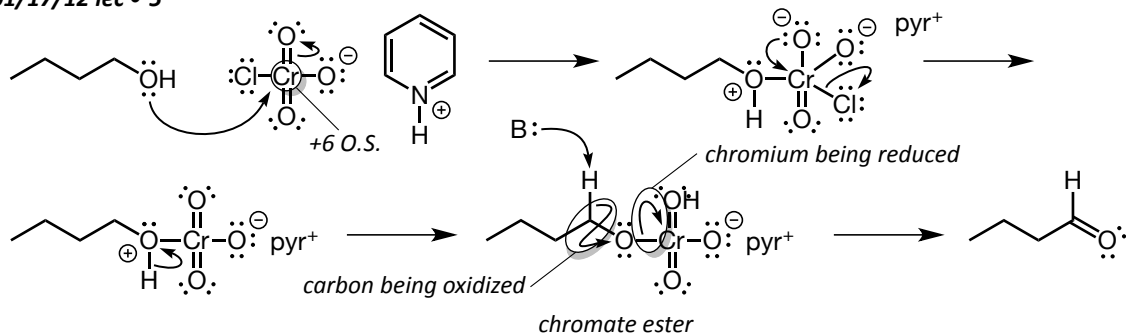
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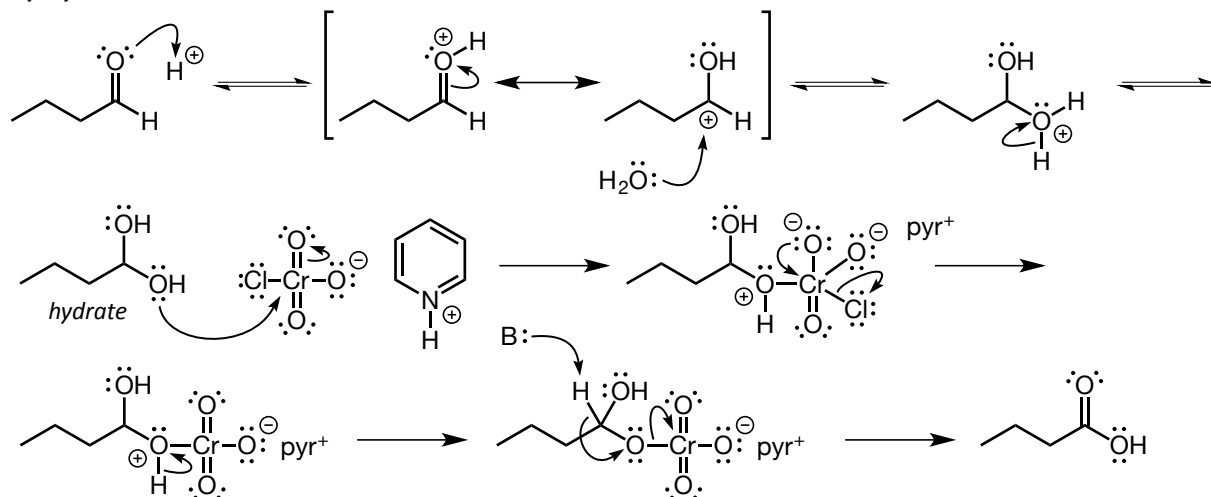
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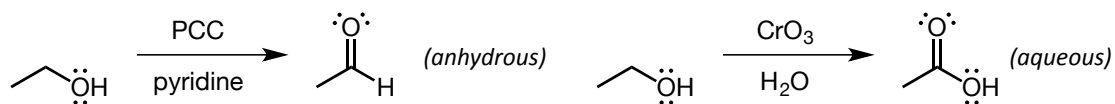
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