Lecture 1B • 01/10/12

[welcome and syllabus]

Our first lecture is going to be on alcohols and ethers.

Alcohols. When I was learning o-chem, my o-chem instructor had this story he told once that, imagine you were on a desert island out in the middle of nowhere, except that somehow you had this fantastic chemical synthesis facility, except for the fact that you only had five sources of carbon that you could use for anything you might need to make to live out the rest of your life. The instructor said, what would those five compounds be? Because you'd want something that would be really useful, that you could make anything out of. His answer was, well, all five of them would be alcohols, the major one of which, if you're stuck on a desert island, would be ethanol, which, if you're not familiar, is the active ingredient in alcoholic beverages. Why would he joke that the five alcohols would be what you'd want to have for starting materials? Because, if you were to draw an alcohol in the middle of a piece of paper, you're going to find that, by the end of 12C, we'll know methods for converting that alcohol, in one or two steps, for the most part, into every other functional group. And then the reverse is true as well; most of the functional groups, with a small number of steps, can be converted into an alcohol. So in a larger synthesis, it's not uncommon for an alcohol to be one of the main synthetic intermediates; if not one of the intermediates, then one of the primary reagents to generate other functional groups from. That's, in fact, what we're going to start the quater with, because we played a lot with alkyl halides, we learned about Sn1, Sn2, E1, E2. Wouldn't it be great if we could take an alcohol and make it be useable in one of these substitution or elimination reactions. An alcohol itself doesn't have a good leaving group. The first set of reactions we're going to see is to turn an alcohol into an alkyl chloride, an alkyl bromide, an alkyl iodide, and, what's my other favorite type of leaving group that we learned? Sulfonates, like tosylates, so we'll learn how to make tosylates as well.

Before we do that even, though, I want to review the types of pieces of information that you'd want to put on flash cards. [pep talk about flash cards]

How exactly you get this information on the card is kinda up to you, although generally what I recommend is, the mechanism I put on one side of the card, and the other pieces of information I usually put on the other. First thing is, what is the synthetic utility of a reaction; in other words, what does it make? I already mentioned that one of the things we're going to do today is to convert an alcohol into an alkyl halide, and there'll be different reactions that we do for alkyl chlorides, bromides, and iodides. So, the synthetic utility might be: to convert an alcohol into alkyl chloride.

Generally, for a particular type of reaction, there are some characteristic set of reagents. So, the second thing you need to know are what are the particular reagents for a reaction. Along with that, there may be certain reaction conditions that might need to be obeyed. For example, hydroboration can't be done in the presence of water; it would totally kill off the borane. Grignard reaction, same type of thing, it can't be done in the presence of water or, technically, oxygen or carbon dioxide; they would all cause decomposition of the reagent involved. Some reactions have to be done with heat, some can't be done with heat. Some have to be done with light; some can't be done with light. Those are the types of things you would put under conditions.

The most important of these things that you need to know is mechanism. The first three of the items would be more the type of thing you'd encounter on a fill-in-the-blank problem. Then there is the type of problem where you have mechanism, which is the full step-by-step mechanism for a reaction. There will occasionally be reactions were we don't see a mechanism for, either because it's not known or it's too complicated for the level of this course. We're going to generally use mechanism to be able to describe two other aspects of a reaction, which are: what happens in terms of stereochemistry ... and there's stereochemistry in a couple of different forms: if you already have a stereocenter that the reaction ends up affecting, then maybe it'll be something like an Sn2 reaction, where you have inversion of configuration, or it'll be something like an Sn1 reaction where you have loss of configuration, or maybe, it'll be like what we see today, where you end up with retention of configuration; that's one form of stereochemistry. Another form would be something like alkene reactions. Would it be a reaction like bromination, where the first bromine ends up making a ring on one face of the double bond, which therefore causes the second bromine to attack from the opposite face; that's calle anti addition. Or, maybe you'd have something like hydrogenation, where you could take an alkyne and make a specifically cis alkene; that's a form of of syn addition. Those are the types of stereochemical concerns that we might have. Many of those we can get from the mechanism of a reaction.

Along with stereochemistry, then, is regiochemistry: where does something end up. Sometimes, there aren't regiochemical concerns. For example, when we learn reductions of ketones and aldehydes, that reduction always happens where the ketone is. Maybe it's something like addition to a double bond, where you have this Markovnikov addition principle, where the stability of the intermediate influences where the eventual attack is going to occur on that molecule. Those are the types of things that we worry about with regiochemistry.

In principle, every reaction we learn, you need to know all of these items for. But, don't just go blindly memorizing these things. If you can remember a mechanism, you can use that mechanism to figure out stereochemistry and regiochemistry.

What you're going to see is a lot of commonality between mechanisms, particularly when we get to reactions of the carbonyl: there's cationic mechanism, there's anionic mechanisms, and many of them look almost like each other, or very, very similar. So, it's better to learn the patterns. Last quarter it might have been all memorization since everything was new, but you're going to see a lot of things that look just like pieces of mechanism we learned last quarter.

Let's revisit briefly the nomenclature of alcohols. We'll do just a few simple examples for today. An alcohol, in general, has what characteristic functional group ending to it? -ol. So, all alcohols that have just alcohols in them are going to end in -ol. For most alcohols, we have to say where the alcohol is positioned, because this is a form of butanol, but this is a form of butanol as well. How do we number a simple alcohol like this, where it's the only functional group on the molecule? Start at whichever end is going to give the alcohol the lowest possible number. For the first compound, we start from the left or the right? The right, because the –OH group is at the end on the right. There are two ways to name this: the old style is to put the position number in front of the number of carbons; in other words, it would be named 1-butanol. For clarity sake, there's been a change, where the position number got moved to right before whatever substituent or functional group that number was trying to describe. I greatly prefer the second style, because to me it is more systematic, however since so many texts and chemicals are still labeled with the old style, if you use the old style naming, you won't get marked off for it as long as you're doing it correctly. If this is butan-1-ol, then this next one we would number from the left, because from the left we would get the number 2 instead of the number 3, so this would be either 2-butanol or butan-2-ol.

Most of the time you need these position numbers, but there's three easy examples of cases where you wouldn't use numbers. That's if it's not possible to have an alternate number. For example, ethanol: whether you put the –OH group on the left carbon or the right carbon, it automatically makes it carbon number 1, because it's only two carbons long. Because there's no ambiguity, that's why the number is not needed. Similarly, if we only had one carbon, then there's no need to number it. Another similar case is if you have a cyclic compound that only has one alcohol on it, one of the most important functional group on it. In that case also, since that would automatically be assigned the position 1, we can leave the 1 out, so it's just called cyclohexanol.

Let's see a couple of slightly more complicate example. Let's see what would happen if we did have two alcohols on a molecule. This doesn't have any substituents, so this is a butanediol. We put the prefix di- in there to show that there's two alcohols, and we do have to name where the alcohols are located. So would I number this compound from the left or the right? Again, from the right. It does not matter overall how big the numbers are, it's the very first number you write down that that needs to be as small as possible. From the left, the first number we would get is 2, from the right, the first number we get is 1. 1 is lower than 2, and that's why we number from the right. This is butane-1,3-diol. Notice that the -ane ending is still there. When you're using -ol, the only thing that it replaces is the 'e' in the word, so you don't get rid of the -an because that 'an' shows that it is saturated. A very minor spelling rule for naming compounds is when do you use an 'e' and when do you not use an 'e'. In this case, we use an 'e' because there's consonants coming up. Notice the di- that's here, which is used because we have two alcohols on that molecule. There is one thing that I've left out, though: is it R or S? R. There's our most important functional group. Automatically, this is the second most-important functional group because it's got carbon that's attached to anything besides hydrogen, versus, this least-important – other than the hydrogen – group, because there's only hydrogens attached to that position. So the priorities go clockwise, so that is R. Since we only have the one stereocenter, you don't need to use numbers with it, so this complete name is (R)-butane-1,3-diol, or (R)-1,3-butanediol.

Last example for today, is what if you do have an alkene with an alcohol? There is an order of priority, and what is it? What's more important, and alkene or an alcohol? An alcohol. All of the hydrocarbons are less important that alcohols, aldehydes, ketones, any of the functional groups we're learning this quarter. That means that it's going to be numbered, in this case, from the right, to give the –OH group the lower number instead of the alkene. There are no substituents, so we'd name the molecule just with its core name. Notice that it's a terminal alkene, so it's not even any cis/trans that we need to worry about. No stereocenters. So this is a five-carbon compound, so it's pent-, but it does have an alkene. This is where that 'an' part of the ending changes; it becomes 'en' to show that we do have unsaturation. At the 1 position, we then have an alcohol. We don't use an 'e' after the 'n' because there's already a vowel coming. This is its full name: pent-4-en-1ol. This is why I prefer the newer style of naming, because there's no confusion as to what the 4 refers to, what the 1 refers to. If we had yet another alcohol, it would be pentenediol. If there was no alkene, then it would be pentanediol; the 'an' would still be there.

Let's move on to some reactions now.

The first reaction I want to show you involves the molecule $SOCl_2$, thionyl chloride, which has this structure to it. Notice the lone pair on sulfur; that's probably the most missed part of that molecule's structure. That sulfur-oxygen bond has somewhat the reactivity like a carbon-oxygen bond, primarily due to the fact that it's polarized. Which of the two ends of that bond, would you say, is more negatively charged? What's the most electronegative element in that compound? Fluorine's the most electronegative element; what's the second most electronegative element? Oxygen. So, oxygen's going to be negatively charged – partially negatively charged. That means the sulfur's going to be very positively charged, because aside from the sulfur-oxygen double bond, you have these two electronegative chlorines also pulling electron density away.

So, think about what the structure of an alcohol is. There are two main ways an alcohol will react. What do you guess one of them is? What about that hydrogen? What is a rough pKa value for this alcohol? What about the pKa of water? 15.7. And in solution, alcohols have about the same acidity as water does. Primary alcohols have a pKa of round about 16, which means that hydrogen can be pulled off comparatively easily, easier than a lot of just plain hydrocarbons. So one form of reaction of alcohols that we'll see later is for that hydrogen to react. But, if you think about polarity, the oxygen there is partially negatively charged, because it is the most electronegative element. If we threw these two molecules – thionyl chloride and this alcohol – together, what could you imagine the opening first step might logically be? For the oxygen to attack the sulfur; for the partially negatively-charged atom to attack the partially positively-charged atom. That's exactly what happens. There are multiple ways to write this mechanism, and we'll discuss later on why or why not to do some of these different ways I'm showing you. To keep things simple for today, I'm going to show you the mechanism in this way. If that oxygen attacks the sulfur, then something has to give, and it would make sense that that sulfur-oxygen bond might break, because that would look like something that might even happen during resonance. But once that bond opens, you end up with a negative charge sitting there, which is pretty basic. Well, if you have a negative charge on the oxygen, wouldn't it be simple if it were to just come back and reattack sulfur, and kick chlorine off at the same time? So this is a a kind of wrap-around mechanism. Is this the way it really works? There is some evidence for that sulfur-oxygen bond being kicked open, but just like there might be evidence showing that chlorine being directly kicked off. I'm bring this to your attention that this might change, but this is the easiest way to present the mechanism. What we get initially is a positively-charged intermediate, because both molecules had been neutral, and even though the sulfur's going to lose something in this process (a chlorine) and therefore remain neutral, the oxygen now has three bonds to it, so it's going to initially be positively charged. Do you know what the proper term is for a positively-charged oxygen ion is? Oxonium ion. Oxonium ions that have hydrogens are usually very, very acid, on the level of sulfuric acid acidic, so we'll rapidly have a deprotonation. I'm a little lazy about my hydrogens, because yes, there could be something in solution that's removing this hydrogen, but it doesn't matter what it is. In the past, when I used to worry more about it, I found that I would always telling students, "don't worry about that; don't worry about that", so at some point I decided to just stop writing it, because it's not important. What's important is that hydrogen comes off. Number 1 mistake made in o-chem, though, is writing the arrow towards the hydrogen. Remember that these mechanism arrows show where electrons go, not atoms. So the bond is breaking and leaving its lone pair on oxygen, which gets us a neutral molecule now.

But, this thing that we just created, this whole thing, turns out to be a really good leaving group. And with the way the reaction is done, that chloride that's still sitting around in solution is able to continue to react and push that off as a leaving group. Part of the reason this does end up being a good leaving group is what happens after it comes off. So I'm not going to show just the Sn2 part, and this really is an Sn2 style mechanism – chlorine attacking, simultaneously the oxygen coming off. But instead of it just coming off, that pair of electrons from the carbon-oxygen bond can swing around and attack sulfur, just as before causing this wrap-around mechanism, during which another chlorine comes off. You end up with two products in this case: an alkyl chloride (that's the point of this reaction); but you also make the by-product sulfur dioxide. In mechanisms in which we cause the expulsion of either carbon dioxide, sulfur dioxide, or nitrogen (N2), those are usually thermodynamically very favorable events.

How about we write out those six aspects of a reaction, so you can write your flash cards. Synthetic utility: it is to convert an alcohol into an alkyl chloride. What are the reagents used? The principal one is thionyl chloride; there are sometimes some bases we include to help the reaction along, but a little too much detail for the first day of the quarter. What conditions must this be done under? We can't have any water, cause water has an –OH group on it, just like an alcohol does, so water would just directly react with and decompose the thionyl chloride. Mechanism, we have up above. I'm going to skip number 5 for the moment and come to regiochemistry. Essentially, I could say there's none, cause it only happens where the functional group is; there are not possibilities; wherever the functional group was is where it ends up being. Instead of none, I might say, no change. Let's back up to this last item: the stereochemistry of the overall reaction. Look at the reaction mechanism, and tell me, in the first step, does anything happen to the carbon-oxygen bond? No. So, if there was a stereocenter there, nothing would happen to it in the first step. The second step, that's just hydrogen coming off of the oxygen; definitely doesn't have anything to do with the carbon-oxygen bond. What about that last step? It's inversion, because it really is an Sn2 reaction. That means that this overall process occurs with inversion, which is really important, because the reason to do this reaction is to turn an alcohol into something with a leaving group. If you then did a real Sn2 reaction after that, you'd invert the stereochemistry a second time, which would mean, overall, you'd have an alcohol with a stereocenter that's the same when you get done with your multistep synthesis. Well, what if you didn't want that? Then you've gotta be aware that this does cause inversion.

Just to have written down a specific example, if I take this alcohols, which does have a stereocenter, react it with thionyl chloride, I'll get an alkyl halide, but I'll get inversion of configuration. I love deuterium, because it's just a form of hydrogen, so that's still technically a primary reaction center, but it's a primary reaction center that's a stereocenter, cause there is deuterium instead of just hydrogen. You'll see deuterium in a lot of problems.

That's one way of making a leaving group, and this one does occur with inversion. But let's say we wanted to convert this into a leaving group where there wasn't inversion that happened. There's this beautiful little reagent that can do that. What's it look kinda like? Looks like a sulfonate; looks like a tosylate. This is what you can create tosylates from. This is para-toluenesulfonyl chloride. For short, it's called tosyl chloride.

For really short, the whole thing can be abbreviated as TsCl. So the tosyl group includes the sulfur, but not what's connected to it. If I'm showing tosyl chloride, at the same time I should show you this compound, its smaller cousin, methanesulfonyl chloride, with the short name mesyl chloride, also abbreviated MsCl. In general, this is a class of compounds known as sulfonyl chlorides. Why am I showing you these two in particular? Mesyl chloride is an inexpensive liquid; tosyl chloride is an inexpensive solid. That's why tosyl chloride is often preferred: it's very easily handleable, reacts really cleanly, smells a little bit like peanuts; for a sulfur compound, it's pretty good smelling. A very easily manipulable compound.

What kind of reaction mechanism is there? You might image that that sulfur is very delta positive, just like the sulfur in thionyl chloride was. In fact, we're going to see exactly the same style of mechanism. To make sure to show the stereochemistry, I'm going to just start with a chiral alcohol, and I'll use tosyl chloride as my example reagent. Same type of thing happens that would happen with the thionyl chloride: alcohol can attack the sulfur, causing that sulfur-oxygen bond to open. For the moment, I'm going to say it's ok to show the simultaneous collapse of that bond again, which would cause the chlorine to be kicked off. In that process, notice that the carbon-oxygen bond never gets involved. The stereocenter did not change by the attachment of that sulfonyl group. Just as before, we end up with this fairly acidic oxonium ion, which would then deprotonate. I'll go ahead and use the abbreviation now that I no longer have to show the structure of tosylate, to show that I now end up with that leaving group. Notice that this has retention of configuration. I'll let you write out the six items for this flashcard on your own.

[need to look up correct reason why no secondary attack by a halide occurs in reaction of alcohols with tosyl chloride while it does in reaction with thionyl chloride]

You're making a tosylate. It needs to be done under anhydrous conditions. Tosyl chloride's the reagent. It has no regiochemical effects, meaning the tosylate is going to end where the alcohol originally was. This reaction occurs with retention of configuration, instead of inversion [, as would be the case for thionyl chloride].

One last reaction. Very simple mechanism, involving the compound phosphorus tribromide. This is going to look identical to the reaction of a thionyl chloride. Why would you imagine that this would react that way? Phosphorus is under which element in the periodic table. This does have a complete octet because there is a lone pair there. But with three bromines on it, it does make the phosphorus fairly positively charged. So an alcohol will react with it in the same way that [it would with] thionyl chloride. In this case, though, there's no double bond, so in the first step, where the alcohol attacks, it's essentially an Sn2 style attack, where the bromine is just kicked off of the phosphorus. Since we started with a neutral alcohol, we're now going to end up with a oxonium ion, which can deprotonate. That group we just made is a good leaving group. The bromide's that still left around in solution is able to come around and attack. So the overall process was to make an alkyl bromide, but with inversion of configuration.

There is one more reaction called the Finkelstein reaction. it's just an Sn2 reaction, but its trick is that it involves a solubility trick.

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Flashcards
1) synthetic utility – what does it make?
2) reagents
3) conditions
4) mechanism
5) stereochemistry
6) regiochemistry

Alcohols

$SOCl_2$ – thionyl chloride

1) utility: alcohol –> alkyl halide
2) reagents: $SOCl_2$
3) conditions: anhydrous
5) stereochemistry: inversion of configuration
6) regiochemistry: none (no change)

sulfonyl chlorides

Due to the inclusion of a base to remove H^+, Cl^- is effectively prevented from reacting.
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Structures

Identical to those from lecture 1A (01/09/12) and 2A (01/11/12)