Lecture 1A • 01/09/12

[welcome and syllabus]

Our first lecture today is going to be converting alcohols into leaving groups. A large part of last quarter was devoted to nucleophilic substitution and elimination reactions which have alkyl halides or alkyl sulfonates as their substrates. We're going to learn how to make alkyl halides and alkyl sulfonates today.

Let me do a little bit of review. [harping about study habits]

Flashcards : there are six pieces of information you want to make sure that you have on your flashcards. There are six things that in one way or another you should stick on each flashcard for each reaction that you're going to learn. What's the first one we always discussed? Something called the synthetic utility, which means what does the reaction do. Today's synthetic utility is going to be to convert alcohols to some kind of leaving group. We'll learn a reaction to make an alkyl bromide, an alkyl chloride, an alkyl iodide, and an alkyl sulfonate. So there's four reactions that you learn today.

The next thing: reagents. Many times you can identify a reaction just by the unique reagents that are used in that reaction. Sometimes, a reaction might have a specific set of conditions that you have to follow as well. For example, hydroboration-oxydation: borane is incredibly reactive to practically anything that's got a lone pair, so you can't have oxygen or water around for a borane reaction. If you're doing bromination, there's some types of bromination where you do want light; there's some types of bromination where you can't have light. Those types of things would be listed under conditions.

Probably the most important of these is mechanism, because this is a mechanism-based course. You're going to use mechanism to explain why certain things happen in a reaction. Two things in particular that we're going to use mechanism to describe are stereochemistry – stereochemistry from a couple of different perspectives: if we're talking about a chiral center, we could talk about whether the stereochemistry of that center is maintained, so whether we have retention of configuration, or does it get inverted like in an Sn2 reaction, or does it get scrambled as in an Sn1 reaction, which would be loss of configuration. It could also mean the stereochemistry of a double bond. If we have something like hydrogenation where the two hydrogens add to the same face of the double bond, that is a syn addition. Versus, if we have something like vicinal dihalide formation from Br2: one bromine adds to one face, one adds to the other, because the second one comes around to attack from the opposite side from where the ring formed with the first bromine. It's anti addition, it's another example of stereochemistry.

Aside from stereochemistry, we also have regiochemistry. If it's a carbocation-based mechanism, it means we're likely going to have carbocation rearrangement. If we had something like oxymercuration-demercuration, where we have a cation but not a carbocation, then maybe we won't have rearrangement. If we had something like elimination, you know there's different types of double bonds you might be able to form from one substrate, so which one of those forms, that's also a regiochemical consideration.

These six items are what you need to know for each reaction.

Let's go into the reactivity of alcohols.

My organic chemistry teacher that I had when I was at Rice made a joke about alcohols when he first started teaching them. He said that, if you were stranded on a desert island that had a full synthesis lab, but only had one type of starting material, one source of carbon, what functional group would you want? If you had five compound for your source of synthesis, what would they be? He said all five of them would be alcohols, the largest one of which, he would say, should be ethanol – for dealing with the fact that you're stuck on an island with nothing except a synthesis lab. If you're not familiar, ethanol is the active ingredient in alcoholic beverages. But why, other than trying to make a joke, would he say that you'd want all of those to be alcohols? Because you can create almost every single functional group out of an alcohol, and many functional groups, in turn, can be converted back into being alcohols. One exercise we may do later this quarter is to put an alcohol in the middle of a sheet of paper and to think of every reaction you know to convert and alcohol off into another functional group, and then trace that back with a reaction to get back to an alcohol. At some point, you're going to see that nearly every functional group is able to do it. That's why alcohols are such useful starting materials. They're also commonly available from biological sources, so there are many unusual alcohols we get just by harvesting a plant source, for example.

Let's remind ourselves about the nomenclature of alcohols. If we have a plain, unbranched alcohol, with only just one -OH group on it, what is the functional group ending we use for an alcohol? -ol. And most of the time, we have to say where the position of that functional group is, because we could easily have an isomer, where we would have the same number of carbons, but the alcohol itself at a different position. How would I name the first compound? There's actually two ways to do it. The older style was put the position number in front of the number of carbons. So butane would be this compound if we had four carbons; the -ane ending we drop and turn into butan-ol.

Only the ‘e’ gets dropped, because the ‘a’ part says that we only have single bonds present. The alcohol is at the one position, so yes, this could be named 1-butanol. The newer way to do it is to put the position number right before where the functional group is. So, butan-1-ol. Why is it 1? Because you number the chain from the point of most important functional group. In this case, we only have one functional group on the molecule, so that automatically establishes where to number. We’ll do a couple of examples of polyfunctional molecules in just a minute.

The second molecule, we still would number to give that functional group as low a number as possible, so this would give us the molecule 2-butanol or butan-2-ol. I prefer the newer style, but if correctly do the older style, you won’t be marked wrong. Most texts and most chemicals are still labeled the old way, but you will see this new method as well.

There’s a couple of cases where you don’t need the position numbers. For example, there is no such thing as ethan-2-ol, because from either end, if you try to number it, the only way that you get the lowest number is to give the alcohol position 1. That case is just ethanol, no numbers, just like the one-carbon would be methanol. There’s one more case that you could lump together, and that’s if you only have one functional group on a cyclic molecule. That functional group automatically gets position 1, so this would just be cyclohexanol.

Let’s see when we have more than one alcohol present. Which end would we number from in this case? From the right; why? Because we get the number one. If we started from the left, then the first alcohol we encounter we get the number two instead. Well, one is lower than two, so we pick the route that gets us the lowest number the first possible place. But we have a stereocenter, don’t we? R or S? R, correct. Why? Because the oxygen of the alcohol is the most important thing in that stereocenter; the carbon chain to the right is a carbon chain, as opposed to just the plain methyl group on the left, so priority 1, 2, 3, so this is R. There are no other substituents, we we would name the main part of the molecule, but this is a diol, isn’t it? So, notice, butan-, you keep the -an- part of the word, because that means that it is fully saturated. The common mistake is to do something like butdiol, not even put the -an- in there, but the -an- part for an alcohol never goes away. It can change, as we will see in another example in a moment. Now that ‘e’ is there because we’re about to put a consonant after it. Where are the alcohols located? Well, they’re at positions 1 and 3. Now notice that since we only have one stereocenter, we did not actually need to put a position number for that stereocenter; it’s automatically understood. Then we round this off with a diol; the ‘di’ is because of two alcohols.

One last example, then we need to get to some mechanisms. What if we had an alkene and an alcohol at the same time? I’ll make this this a simple example where we don’t have E or Z or cis or trans possible for the alkene, since it’s at the end of the molecule, and I also made it where we have no stereocenter. Which end do we number from, the left or the right? Why? An alcohol is a more important functional group that any carbon-based functional group. So alcohols are more important that alkanes, alkenes, or alkynes. So therefore, we’re going to give 1 to the alcohol and 4 to the alkene. There are no substituents, so we name the parent as it is. This is pent, but it’s not a pentane. Here’s we’re going to switch to ‘en’. Why? Because we have an alkene. Pent-4-en-1-ol.

Before we get to the mechanisms, let’s remind ourselves: why is it that alcohols are poor substrates for nucleophilic substitution and elimination? Because the hydroxide that that would turn into if we could kick the –OH group off, that’s basic, and good leaving groups are conjugate bases of strong acids. Water’s not a strong acid at all; it’s a neutral compound. So, in other words, –OH doesn’t want to come off the molecule. That’s why we want to make, if you want to make alcohols useful in one way, you want to turn it into a leaving group.

First reaction: let’s start with $SOCl_2$, which is the compound thionyl chloride. It has this structure to it. The thionyl is the sulfur equivalent of the carbonyl. The missed thing about thionyl chloride is the lone pair that goes on the sulfur. Where do you think the most reactive portion of this molecule is? The double bond between sulfur and oxygen? Out of those two atoms, which one do you think is going to be most likely to react with an alcohol? Well, what does an alcohol have that may want to react? There’s the hydrogen on the alcohol, which we’re going to get back to acidity later on in the quarter, but alcohols have a pKa range of roughly 16 - 18, which is a little bit less acidic than water but almost equivalent to water. But aside from the hydrogen that’s on there, there’s the lone pair on the oxygen itself. The oxygen of the alcohol: is that going to be partially negatively-charged or partially positively-charged? Why negative? Electronegativity; oxygen’s more electronegative, it’s greedy, it would have more electron density. If oxygen’s got electron density, then what about this thionyl chloride? What could you say about the sulfur and electron density? It’s partially positively, it’s partially very positive, because it’s got three quite electronegative atoms around it. In fact, that’s the rationalization to explain the first step of the reaction that will occur. There’s different ways to show this mechanism step. I’ll show you the easy way, and then we’ll get more into the story later. Let me again at least point out that the sulfur is very delta positive, and the oxygen is delta negative. The oxygen, in other words, would be acting as the nucleophile, and then the sulfur would be acting as the electrophile. Oxygen attacks the sulfur-oxygen double bond. Because of that, the sulfur-oxygen double bond is going to open up. We could argue later about whether that is its own individual step, or whether there’s actually a cascade event that occurs. For simplicity’s sake, I’m going to say that imagine that bond opens up but then collapses right back down, because you pushed that bond open, leaving a negative charge on oxygen, with it having nowhere else to go. If that negative charge were to come collapse right back down, chlorine’s a good leaving group, so it would make sense that chlorine would be kicked off at this point.

Now couldn't I just write a mechanism where I show the alcohol directly kicking the chlorine off? I could, but there is some evidence of this bond opening and closing going on. Here's the way I'm going to represent it for now. Essentially, it kinda looks like, but it's not the same as, an Sn2 reaction.

What we would end up with is an oxonium ion. If you're not familiar with that term, that means positively-charged oxygen. Any time we start out with a neutral oxygen, that's the situation that we're going to end up with. Positive charge on oxygen is oxonium ion. Usually whenever we have these types of oxonium ions, we have a very rapid deprotonation, because a positive charge on oxygen is not favorable, so a hydrogen stuck on an oxygen like that is usually as acidic as something like sulfuric acid. That comes off, and we end up with this intermediate, which then continues to react. This whole thing that we just formed is a leaving group. Since chloride is still around in solution and because of the way the reaction is performed, that chlorine is going to come back and attack the leaving group as it is formed. Here's the sequence of steps that happens there. Chlorine attacks the leaving group. That bond will end up swinging around towards the sulfur. Again, we could have that same opening and closing occur, and again, chlorine can get kicked off. Showing this complete set of steps is important because part of the driving force for this reaction is for the formation of sulfur dioxide. Forming carbon dioxide, sulfur dioxide, and diatomic nitrogen are usually three very thermodynamically-favorable events. Because you form SO2 as a by-product here, that's partly what drives this reaction along. You'll end up with an alkyl chloride, and SO2 as a by-product.

Let's briefly go over those six things that we need to know about. What is the synthetic utility? To make an alcohol into an alkyl chloride. What are the reagents? Thionyl chloride is the main reagent. We'll later get into the fact that there are some other things we throw in here to help the reaction along. Particularly, there are some bases that we could use to pull the hydrogens out. What are the conditions? Needs to be done without water, needs to be anhydrous, because the water would cause the thionyl chloride to decompose. Water is like an alcohol, so it would just merrily react with thionyl chloride the same way an alcohol would. The mechanism, that you have up above here. So let's skip to regiochemistry. Regiochemistry: none, you could say; it ends up substituting at the same position where the alcohol was originally. Stereochemistry: that's an interesting consideration. Look, for a moment, at the first step of the reaction. I did not show a chiral starting material here, but does anything happen to the carbon-oxygen bond in the first step of the reaction? No, just the oxygen attacks sulfur, correct? But the link that the oxygen had with carbon never changed. So if you had a stereocenter to begin with, it would be the same configuration. The hydrogen comes off, that has nothing to do with carbon, so again the configuration wouldn't change. But what about that last step? That's an Sn2 reaction, isn't it. Chlorine displacing that leaving group, simultaneously? Yeah, there's some other arrows that go on after that, but really, it's just a fancy version of an Sn2 reaction. What happens stereochemically in an Sn2 reaction? Inversion. So the the stereochemistry for this reaction is inversion of configuration. That's an extraordinarily important realization, because if we had some kind of chiral alcohol. Deuterium is one of my favorite atoms because I can use it to keep something still having a primary center, but still be a stereocenter, just like what I've done here. Important consideration: thionyl chloride will convert it into a leaving group, but with inversion of configuration.

What if we didn't want that, though? What if we wanted to keep the configuration? Let's say that I want to, after making the alkyl halide, react it with something like sodium azide, put yet another nucleophile on there, and let's say only at that point I wanted to invert stereochemistry? Well, turns out there's a reagent we could use to do that, a reagent that, eventually, you'll learn how to synthesize. Does this look familiar to any of you all? It's tosyl chloride. We talked about tosylates being leaving groups in an Sn2 reaction, or Sn1 reaction. This will react with an alcohol to make a tosylate. This full name is p-toluenesulfonyl chloride, or tosyl chloride for short. It has the simpler cousin, methylsulfonyl chloride, or mesyl chloride. In general, these are sulfonyl chlorides. In principal, any of them could do this type of reaction that I'm going to show you, it just happens that tosyl chloride is very widely used because it's an easily handleable, relatively safe solid; inexpensive as well, smells kinda like a can of peanuts, I don't know why, I guess the sulfur. Mesyl chlroide is similar, except it's a liquid; there are some cases where it might be preferred. Usually I'll show this reaction using a tosyl chloride.

How does the reaction work? It's going to happen very must like the mechanism for sulfonyl chloride. Yes, in o-chem there's an awful lot of memorization, but it really helps you to find patterns, particularly this quarter. Maybe last quarter, when we were just learning about alkenes and alkynes, it all seemed pretty random the different types of reactions that we were learning. But many, many of the reactions we do this quarter are all focused around carbon-oxygen single bonds, or even more so, carbon-oxygen double bonds. That carbon-oxygen double bond, in particular, has two main ways that it reacts: a cationic mechanism, or an anionic mechanism. Many of the cationic mechanisms look like each other; many of the anionic mechanisms look like each other. Same type of thing is going on here: sulfur-oxygen bond reacts in a way that a carbon-oxygen bond does. You can have a cationic mechanism or an anionic mechanism. Point being: don't just memorize, try to find the commonalities.

Let's see the first step of the reaction with an alcohol, and this time I'll start out using a chiral alcohol, so we can see right away what the stereochemical consequences will be. I'll use tosyl chloride, and I'll write the full structure out. There is an abbreviation for tosyl chloride that can be used, that I would prefer not to use in this case, but just to complete about it, what I have circled here is abbreviated Ts, so this compound could be written as TsCl. I'm not doing it in this case because then I wouldn't be able to see what happens mechanistically. Same type of thing is going to happen as what we saw with the sulfonyl chloride, because the sulfur-oxygen bond is very, very, very polarized in this case as it was previously. Same type of thing I'm going to do then: show this opening up and then collapsing back down, again kicking off a halide once that occurs.

What will we get? Just as we saw above, we'll initially get an oxonium ion, which then will deprotonate. Usually when this reaction is performed, there's some kind of base that's included that helps sop up the hydrogens that would get pulled off at this point. When a base that's neutral like that combines with hydrogen, that means it become positively charged; chloride would end up being the counterion. In other words, by including a base along with this reaction, you prevent chloride from coming back and attacking, so the reaction stops here. Due to the inclusion of a base to remove H+, chloride ends up also effectively being removed from the reaction: in other words, you don't go past the formation of this tosylate. Notice what's happened, though: we have retention of configuration, because the carbon-oxygen bond never got involved at all, because we didn't have that chlorine come back to attack.

Thionyl chloride, it's done in a way so that it encourages the chlorine to come back and attack, that's how we end up with an alkyl chloride. Here, we do it in such a way that it prevents the chloride reacting, and that's why we don't have the secondary attack and we end up instead with a tosylate.

There are two more reactions that we need to cover: one main one, involving phosphorus tribromide. The last thing we need to see is how to make an alkyl iodide, which it's not mentioned in your text, but you actually did it in a sense last quarter when you did comparative rates of different Sn1 and Sn2 reactions. This will be something called the Finklestein reaction.

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Flashcards
1) synthetic utility – what does rxn do?
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

Due to the inclusion of a base to remove H+, Cl^- ends up also being removed from rxn.

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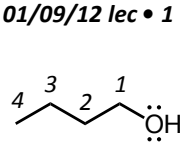
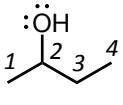
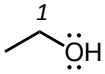


1-butanol
butan-1-ol

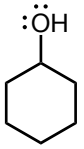


2-butanol
butan-2-ol

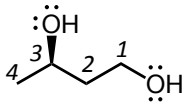


ethanol

methanol



cyclohexanol



(*R*)-butane-1,3-diol

two alcohols

saturated

due to following consonant

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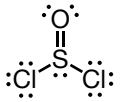
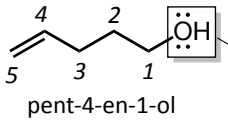


thionyl chloride



pent-4-en-1-ol

alcohol more important

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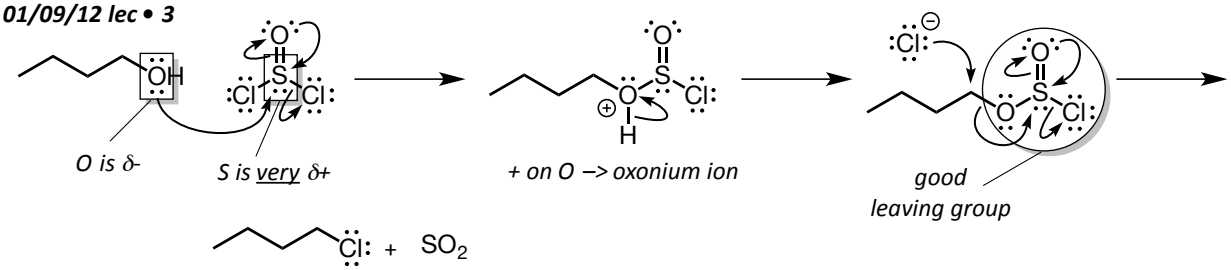

O is δ-

S is very δ+

+ on O –> oxonium ion

good leaving group

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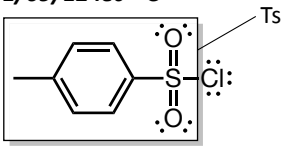
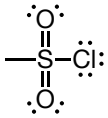


p-toluenesulfonyl chloride
tosyl chloride (TsCl)



methanesulfonyl chloride
mesyl chloride (MsCl)

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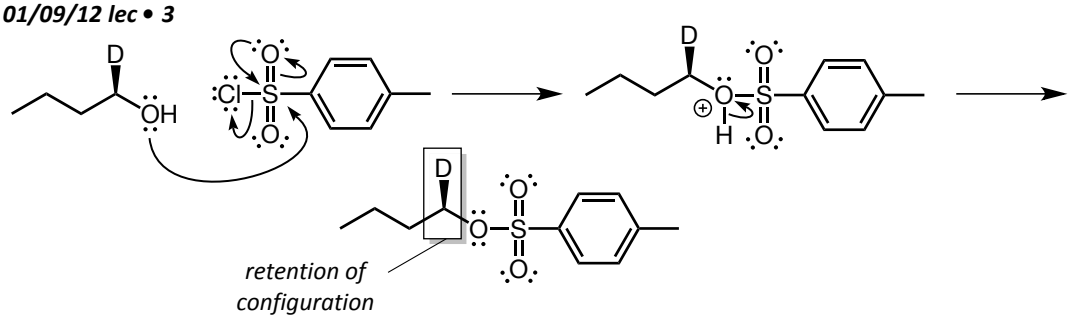

retention of configuration