

Lecture 2B • 01/12/12

We covered three different reactions for converting alcohols into leaving groups. One was to turn an alcohol into an alkyl chloride, that was using thionyl chloride. Second reaction was using tosyl chloride; the primary difference between those two reactions is one of stereochemistry. An inversion of stereochemistry does occur if you use thionyl chloride, because it does affect the carbon-oxygen bond, but because forming a tosylate does not touch the carbon-oxygen bond, only the oxygen-hydrogen bond, there's no change in stereochemistry there. We then saw phosphorus tribromide that reacts very similarly to the thionyl chloride; you get an alkyl bromide instead, but it also has inversion of configuration.

The last reaction is not a new mechanism, it is just an S_N2 reaction, it's called the Finkelstein reaction. Really this works, in a sense, off of Le Châtelier's principle. In solution, in theory, sodium iodide can displace bromide, but sodium bromide can displace iodide, so you can have an S_N2 reaction that goes back and forth and back and forth and back and forth. Except, sodium iodide is somewhat soluble in acetone, while sodium chloride and sodium bromide are not. So, in fact, one of the things that we get out of this as a by-product is sodium bromide, which, again, is not soluble in acetone and therefore precipitates out and is no longer part of the reaction mixture, so there's no reverse reaction possible. Because of this solubility trick, it allows this reaction to be pulled forward, which means you can get the alkyl iodide. Sodium iodide is soluble, while sodium chloride and sodium bromide are not. The products of the reaction are therefore favored, due to the precipitation of the sodium halide. I'll rephrase it this way: the products of the reaction are favored due to the continuous removal of the sodium halide from solution. [admonition to make flashcards]

Let's move to the next flavor of reaction, which is alkylation. Alkylation means to add an alkyl group. It's a reaction that we can do with alcohols in order to make ethers. In fact, if the normal anionic version of a reaction is performed, that's often called the Williamson ether synthesis. Before I can present this reaction, I need to show you have to form the reagents for this reaction, which are alkoxides. The Williamson ether synthesis is really nothing more than another kind of S_N2 reaction. An alkoxide, that is an anion in which you have an alkyl group attached to an oxygen. In fact, it is short for 'alkyl oxide'. Oxide, as the ion, would be -2 ; put an alkyl group on it, that's how it becomes a -1 charge. How do we name alkoxides? Well, kinda like parent name 'alkoxide', it's some group followed by the oxide ending. So, so if we had CH_3 , it has the shorter name methoxide. If we had something longer, two carbons, ethoxide. Notice it's one of the few exceptions to what we've seen so far: the 'an' part of the name is dropped in this case.

How can we synthesize these? There's two ways. One involves the molecule sodium hydride. If you think about the periodic table, you have hydrogen at the top left corner, down below it is lithium, down below it is sodium. So sodium, being lower than hydrogen on the periodic table, which is more electronegative, hydrogen or sodium? Hydrogen, cause as you go up and to the right on the periodic table, that's where you have higher electronegativity. Since hydrogen's more electronegative than sodium, then this is one of those rare exceptions where hydrogen does act as if it was negatively charged. In fact, the rules of oxidation state – the ones I always make fun of – one of the rules is hydrogen is $+1$, except when it's part of a metal hydride. Let me write the name of this out, in fact. Sodium hydride. Hydrides are generally not that nucleophilic due to poor orbital overlap, but they are very basic. An alcohol is somewhat acidic; it's far more acidic than an alkane, an alkene, or an alkyne, but it's not acidic – acidic enough, though, that the hydride can pull off the hydrogen. The rough pK_a value for an alcohol is 16-18, 16 in solution for a primary alcohol, 18 for a tertiary alcohol. The pK_a of water is 15.7. Alcohols are just slightly less acidic than water (in solution). The hydride will simply pull a hydrogen off; you'll get hydrogen gas as a by-product, plus you'll get the sodium alkoxide.

There's another way to do the same type of process, which is instead of using sodium hydride as a reagent, you just use sodium metal, which, to write a balanced version of that reaction, two molecules of the alcohol react with solid sodium, in order to form two of the alkoxide plus, again, hydrogen gas. There's no mechanism you need to learn for this because it's a redox reaction. Much like the reduction of an alkyne, you have sodium as a source of electrons. One hydrogen gets one electron; the other hydrogen gets the other. Or, you could say the oxygens get it which release the hydrogen and they end up forming hydrogen gas. Easy reaction: you take the alcohol; throw it in a beaker; take a small chunk of sodium, carefully stir it up for a while. Sodium is less reactive in an alcohol than water, so you have to be careful with the reaction, but it's still a clean way to make an alkoxide.

How can you react these alkoxides? It's a type of S_N2 reaction. We could start, for example, with something like t-butanol, react it with sodium hydride in order to make sodium t-butoxide, and then follow it up with a simple S_N2 reaction. For example, if you had a great substrate like bromomethane, bromine would be very easily displaced. In this case, even though the t-butoxide is big and bulky, there's no elimination possible, so we'll get substitution, and we'll get this ether product.

A quick comment on ether nomenclature. Ethers are not given a special functional group ending. What they are instead viewed as are alkanes that have alkoxides on them. There is a common set of nomenclature. There are a lot of historical or alternative ways to name functional groups. Ethers are one of those that have commonly-appearing common names. Some examples: the ether that you use normally in the lab, that has two ethyl groups attached to the oxygen, so it's called diethyl ether. You might have something like methyl ether ether. In other words, you simply name the two alkyl groups that are attached to the oxygen.

Systematically, though, what we do is identify the longest alkyl chain and we make that the main chain of the compound. We then name any of the alkoxides as substituents. A very quick example of that: let's say that we had this five-carbon compound. Four of the carbons on one side, one on the other, therefore the longer chain is the parent chain, and then this is the shorter chain, so it's the substituent. It's at the 1 position of that longer chain, so it is called 1-methoxybutane.

We've seen how to make alkoxides: sodium hydride or sodium metal. We've seen that they can do $\text{S}_{\text{N}}2$ reactions. But one other thing that we need to talk about is synthetic considerations. You might imagine that this molecule that I had made, what if maybe there was some other way to make it. I want to give this to us as our first little baby example of a concept known as retrosynthesis. Retrosynthesis is this idea: we have some target molecule that we want to synthesize. We would hope that we could find a set of reagents that we could do a small number of transformations to in order to be able to make this product. What we can do is try to step backwards: if this the end of the story, we're trying to click back a frame and see what molecules might have just come together to make this last molecule. From there, if we have it broken up into a few small pieces, in turn, we think how could we have made these pieces. You step backwards and backwards and backwards until you can arrive to starting materials that are usable, that you can either buy or easily synthesize. We'll talk more about retrosynthesis once we've learned a few more reactions. The way that it's often represented is to use what is known as a retrosynthetic arrow. Loosely, then, you could say that we're showing products and aiming back at which reagents made them. Reason I'm showing you this is as an example is we can disconnect this ether – that term disconnect shows up a lot if you're talking about retrosynthesis. Disconnect the ether and we end up with exactly the alkoxide and the alkyl bromide that we saw originally. But, not knowing anything about this reaction, if all we were doing was playing around blindly with atoms on paper, couldn't we in theory also represent this reaction as the t-butyl halide instead getting attacked by a methyl alkoxide; we could imagine alkoxide kicks off the bromide to make the same product. But this is exactly why I want to give this example because one of these sets of reagents would work, the other set you would only get by-products. Why is it that that second set won't work? Too bulky; $\text{S}_{\text{N}}2$ is not possible on a tertiary substrate. There are often multiple ways to make an ether using the Williamson ether synthesis, but you have to be careful to consider what kind of substrates and nucleophiles are involved. In this, you would get $\text{E}2$, elimination. Often an ether can be produced in more than one way. However, the type of substituent and base used must be taken into consideration. There is sometimes a cationic mechanism that can be used to circumvent this problem.

Next, dehydration. Let me start off with a fairly simple example of this mechanism. We'll take 2-methylbutan-2-ol and react it with some kind of acid catalyst. If we did have some strong acid source in solution, really what is the only logical first step that can occur? The -OH group attacks an H^+ , because C-H and C-C bonds really aren't polar enough for anything with an acid to happen, but because the oxygen has that lone pair, that's why something can happen. Oxonium ions are usually (if they have hydrogens) very, very, very acidic, on the level of sulfuric acid acidic. It might make sense that the only logical thing to happen is for the hydrogen to hop onto the -OH group, but then, the reverse reaction – notice I have used a reversible arrow here – the reverse reaction is also extraordinarily likely. In real life, this protonation/deprotonation happens rapidly, reversibly, and repetitively. The idea is that, at some point, instead of the hydrogen immediately falling back off, what if now the fact that we have water, water leaves as a leaving group instead. Turns out that that's just as reversible as well, but once we get to this carbocation, instead of water just coming back to attack, what if instead it pulls off a neighboring hydrogen? In other words, this turns into a style of $\text{E}1$ elimination, giving us an alkene. A big, huge, important note here: notice that I must use water as what I show being used to remove the hydrogen. That's because if you're in acidic conditions, there is no appreciable trace of hydroxide around. Of course that's logical, but you'll find that we'll have this dualism in reaction pathways that we study. We're going to talk about cationic reactions that mostly involve acids and we're going to talk about anionic reactions that mostly involve bases. Many times, similar products may result just by two different pathways, [so you must avoid] starting out with an acid pathway and then suddenly switch to a base one, which is impossible without a switch in reagents. When you're in acid, H^+ and water is all that you can say exists, in terms of things related to water. If you're in base, there's no such thing as H^+ ; it's water or -OH .

I've written this as a completely reversible reaction, which means we could view this as a reaction from last quarter, just in reverse; that would be hydration. If the last step of dehydration is for a proton to come off, the first step of hydration is for the proton to re-add to the double bond. Then, because we have a carbocation, if we had water around, then water can attack the carbocation, which would form that oxonium ion and deprotonation could occur to get us back to the original alcohol. If hydration and dehydration are just reversible reactions of each other, how could we influence this to force one or the other product to form? Take the product out. If we were doing dehydration, water's a product, remove the water from solution. You might remember that we had this one experimental set-up where you were doing a distillation, but instead of just going up and down in some sort of reflux column, you had a sidearm where some of that condensation dripped down into. The point of that was, in most cases when we're doing a reaction where the organic layer is the less dense layer, is the one on top, then as that reflux is going on and some of it condenses into the sidearm, the water's going to settled down on the bottom, and that water, as it accumulates because it's more dense, it'll push the solution that's reacting back into the reaction flask. Over time, then, you're pulling water out, preventing it from being able to react and, therefore, effectively using Le Châtelier's principle to pull this reaction forward. If you want to dehydrate something, it's normally done at high temperatures while removing water. If you want to hydrate something, you flood it with water; generally, it again uses higher temperatures. Notice that in both of these types of reactions, it is involving an acid catalyst.

Let me summarize a little bit of this: hydration of an alkene and dehydration of an alcohol are just reverse reactions of each other. Dehydration is favored at high temperatures using the removal of water. Hydration is favored by adding water. Both reactions involve an acid catalyst.

You can't view water as H^+ and $-OH$, just as you can't view an alcohol as being $-OH$ and R^+ . That dissociation is not favorable. Yes, it's true that in neutral water you have tiny, tiny proportions of each of these, but nowhere near enough in concentration so that we could call it H^+ or $-OH$, unless it truly was an acidic solution or a basic solution. If you have water, you cannot say H^+ and $-OH$, you can only say water. For hydration, you have to have water, and an acid catalyst. For removing it, there's a piece of glassware called a Dean-Stark apparatus that you usually use in situations where you want to reflux and remove water at the same time.

Acid-catalyzed dehydration generally favors the thermodynamically-favored alkene. The role of kinetics versus thermodynamic came up last quarter when we were talking about $E2$ reactions. In $E2$ reactions involving small bases, that's where Zaitsev's rule applies, where the more thermodynamically-stable product tends to form. More thermodynamically stable means more substituted, means internal versus terminal, and it also means trans versus cis formation. But, what if we did have a reaction where you did have a bulky base? Particularly if you were at a cold temperature, because at cold temperatures, if you have multiple reactions possible, they're each going to have a different activation barrier. At cold temperatures, there's not enough energy to just be able to cross any which barrier you might want to, only the easiest to cross is the one that is likely to happen, which means that kinetics are controlling the reaction.

You know need to know what my favorite acid catalyst is. What is it? Tonic acid. Tonic acid is what would be produced if you took tosyl chloride and subjected it to just plain water. Full name: p-toluenesulfonic acid, or tonic acid for short. Why is it that tonic acid is used as a catalyst? What are some of the reasons? It's cheap, it's a strong, organic-soluble acid, it's easy to be handled, and the conjugate is non-reactive, it is non-nucleophilic. A cheap, easily-handled organic solid; it's a strong acid, and the conjugate is non-reactive. Let's draw a mechanism of an example of a dehydration of an alcohol, where the product we might get might be exactly matching the structure of the alcohol that we begin with.

Let's take 3,3-dimethylpentan-2-ol and react it with tonic acid. The logical first step of the reaction is going to be that the alcohol gets protonated. We make water, which is a viable leaving group, so water leaves; again, technically reversible. We end up forming a secondary carbocation. Secondary carbocations are ok, but they're not anywhere near as good as tertiary carbocations. Wouldn't it be great if somehow we could make a tertiary carbocation out of this molecule. Turns out that it does. One whole methyl group will shift next door. You've heard of hydride shifts or carbocation migration, but not only is this [alkyl shift] an effect you need to know about, it's sometimes exploited in synthesis, to have these sophisticated shifts occur. [This is how nature often produces] biological molecules like estrogen or other cholesterol-style molecules. They all can be formed from a molecule called squalene through a sequence of very complicated, multiple carbocation shifts. We're later going to talk about an orbital molecular orbital description of this what's called sigmatropic rearrangement, this alkyl shift.

Let's see what happens as far as the products are formed. We started out with 2 methyl groups on one carbon, but now we have the methyl groups on different carbons. Notice that we now have gone from a secondary to a tertiary carbocation. It's because we get to a much more favorable carbocation that this shift does occur. Now, at this point, removal of that tertiary hydrogen I just drew would make the most stable alkene because it would make the one with the most substituents. The major product of this reaction is going to be 2,3-dimethylbutene. I'm going to put in parentheses the reversible arrow involving the alkyl shift, because it is technically reversible, but it's much more favorable for the forward process to happen, to make the tertiary carbocation.

Let me show you one last mechanism. This cyclic molecule can be dehydrated just like the other examples that we've seen so far. Let's walk through the mechanism. Protonation forms water; water leaves; we end up with a secondary carbocation. We could, in theory, have a hydride shift occur to make a tertiary carbocation, but, what do you know about four-membered rings? They're strained. Instead of the hydrogen moving over, what if part of the ring shifted over? Let me number this compound so we can better see this shift. These are not nomenclature numbers, they're just position numbers. I'm showing that the bond from carbon 4 that used to be at position 1 now goes to position 5. It's technically reversible, but it's not really wanting to be reversible. We end up with this intermediate – a five-membered ring. I've labeled the carbons so you could see what ended up where. Because carbon 1 did have a bond but now it's lost the bond, it now has the carbocation. Now, at this point, we could have water pull off a hydrogen, and so the product we end up is 1-methylcyclopentene. This kind of phenomenon is known as ring expansion. There's several examples of this. Pinacol rearrangement.

Finkelstein rxn

NaI is soluble in acetone, while NaBr and NaCl are not. The products of this rxn are favored due to the continuous removal of NaCl or NaBr from solution by precipitation.

Alkylation

Williamson ether synthesis – S_N2
Alkoxides – “alkyl oxide”

Ether nomenclature:

Often, an ether can be produced in more than one way; however, the type of substrate and base used must be taken into consideration.

Dehydration of alcohols

Hydration of an alkene and dehydration of an alcohol are just reverse rxns of each other. Dehydration is favored at high temperatures and the removal of water as it's formed (Le Châtelier's); hydration is favored by adding water. Both rxns involve an acid catalyst. [Dean-Stark trap] Acid-catalyzed dehydration normally favors the most thermodynamically favored alkene (most substituents; internal versus terminal; trans vs cis).

H₂O ≠ H⁺ -OH

Structures

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