Lecture 2A • 01/11/12

Review: conversion of an alcohol to an alkyl chloride, and conversion of an alcohol to a sulfonate.

For review, I'll take this chiral alcohol and show that if we do use thionyl chloride, we end up with an alkyl chloride, but with inversion of configuration. If instead, if we use tosyl chloride, tosyl chloride forms a tosylate without touching the carbon-oxygen, and therefore we end up with retention of configuration. There's two more reactions that I want to show you, one of which is very similar to the thionyl chloride reaction, in that we're going to make an alkyl halide and it's going to happen with inversion of configuration. That would be with the reagent phosphorus tribromide (PBr3). Phosphorus tribromide, you can imagine, is quite reactive, because you've got these three electron withdrawing groups on the phosphorus. Note that since phosphorus is in the same column as nitrogen on the periodic table, it is going to have this lone pair, so don't forget it. First step of the reaction is going to be very similar to thionyl chloride in that because that phosphorus is very delta positive, the delta negative oxygen on the alcohol is going to end up attacking it. Unlike the thionyl chloride mechanism, since there's no double bond present, we'll immediately have a bromide that's kicked off as a response. This oxonium ion will deprotonate, and then the bromide that just got kicked off is going to end up coming back and kicking the OPBR2 group off because it ends up being a good leaving group. That will happen simultaneously, so it's an Sn2-style reaction, which means it's going to cause the formation of an alkyl bromide, but with inversion of configuration.

There's one last reaction which is really nothing more than a plain Sn2 reaction. This is called the Finkelstein reaction. The reaction is to take an alkyl bromide or chloride, react it with sodium iodide in acetone, in order to from an alkyl iodide. The fact that I'm specifying acetone as a solvent should be a big red flag that acetone is important in this reaction. Why? Because this is a reaction based on equilibrium and based on solubility tricks. More than equilibrium, it's Le Châtelier's principle. Sodium iodide is soluble, to some degree, in acetone, but sodium chloride and sodium bromide are not. In principle, iodide and bromide could keep displacing each other in solution, but, if the bromide comes off, it ends up becoming insoluble in the acetone, and so it's not really able to react and further. You have sodium iodide as the reagent, you have sodium bromide as a product, and it ends up forming a precipitate. Because of that, it pulls the reaction to the right, which favors the formation of the alkyl iodide. There are some other approaches to making alkyl iodides directly, but they're usually more extreme in condition, so this will be our main method we use to get to alkyl iodides. Sodium iodide is soluble in acetone, while sodium bromide and sodium chloride are not. As this reaction procedes, sodium bromide or sodium chloride precipitate out of solution, which prevents bromide or chloride from re-attacking the alkyl iodide as it's formed. Using a solubility trick to help pull the reaction forward.

We use thionyl chloride to make an alkyl chloride; PBr3 to make an alkyl bromide; take those alkyl chlorides or bromides, react them with sodium iodide to make an alkyl iodide; and then we have the formation of a tosylate.

Let's move on to the next reaction – alkylation, which means adding an alkyl group to something. We're going to alkylate an alcohol to make an ether. In fact, the reaction I'll show you first usually goes by the name Williamson ether synthesis; it's really just another form of Sn2. Before the synthesis itself, I need to show you how to make a good, strong nucleophile out of an alcohol, because an alcohol is non-ionic. This dissociation I just showed – an alcohol giving off a hydroxide – is something that almost never happens; it's just not a favorable process. Whenever you see an alcohol, do not visualize that as having hydroxide. Alcohols are essentially neutral compounds. They're not terrible acidic, but they do have hydrogens that can be forced off and therefore become ionic compounds, which makes them basic, strong nucleophiles.

There's two easy ways to do that. One is to use the compound sodium hydride. In most compounds, hydrogens has a formal charge of 0 or +1 and, generally, an oxidation state of 1. This is one of those exceptions, though, because hydrogen is more electronegative than sodium. On the periodic table, it's hydrogen, then lithium, then sodium in that first column. Electronegativity increases up and to the right of the periodic table, so since hydrogen's directly above sodium, it is more electronegative than sodium. Really, that acts as a source of H–. H– tends to not be nucleophilic, but it is basic. You react it with an alcohol and it very cleanly ends up forming an alkoxide. The general term for RO– is alkoxide. Some simple names of alkoxides: if you have methanol, the name gets shortened a bit to methoxide. If you have ethanol that's deprotonated, it's ethoxide. Another way to make an alkoxide is to react it simply with sodium metal. Sodium acts as a reducing agent, and it reduces hydrogen. What you can end up with is an alkoxide, but you have to be a little bit careful, because what you also end up with is hydrogen gas. If we want to balance the equation. Since it is a redox reaction, since it's a radical reaction, not a mechanism that you need to worry about, but it is a reagent you need to worry about. Either of these reagents could be used for producing an alkoxide, which we can then use in an Sn2 reaction to make an ether.

For example, if I start with t-butanol, react it with sodium hydride, and then if I threw something in like methyl bromide, a very unhindered substrate, it does a rapid Sn2 reaction and makes an ether. A brief word about nomenclature of ethers: there's the common names, where all you do is name the alkyl groups that are part of the ether itself. For example, this compound that's got two ethyl groups, this is diethyl ether. If you had something that was asymmetric, this can be called methyl ethyl ether. In terms of systematic nomenclature, there is no such thing as an ether functional group ending. Instead, it's viewed as an alkane that has an alkoxy substituent. What you do is you identify the longer and the shorter chains.

The shorter chain becomes the substituent. So we would name this compound 1-ethoxybutane. Systematically, there's not a special ether functional group ending. If you see a compound with the word ether in it, it's a common name.

We used t-butanol, or 2-methylpropan-2-ol, did an Sn2 reaction on bromomethane, and we made 2-methoxy-2-methylpropane. There's some synthesis strategy involved. In fact, this is going to be our first foray into what is known as retrosynthesis. Retrosynthesis means we start at the end, we look at what product we make, and we try to come up with some different potential pathways that might have gotten us to that product. Here's exactly the type of situation that I'm talking about: let's say that we wanted to make this t-butyl methyl ether. We know that this could be made by an Sn2 reaction, so we take a step backwards. This kind of arrow that I've just shown is referred to as a retrosynthetic arrow, which means you're not showing reagents or anything like that, you're showing what was there before the reaction happened. In this case, it's only a one-step reaction, but we're going to see that retrosynthesis is a technique we can use to synthesize much more complicated molecules. Here's the point of focusing on this as the product: if we pulled these compounds apart, we could have wondered whether the might have been synthesized from exact the set of molecules that we used up above. Or, in theory, if we didn't know any better, couldn't we maybe have used methoxide and t-butylbromide? If we didn't know any better, we might say that the methoxide kicks off the bromide, and we make exactly the same ether. But no, we can't, why not? It's a tertiary substrate, so you can't do a direct Williamson ether synthesis, a direct Sn2-style reaction, because Sn2 is not possible on tertiary substrates.

What you could potentially do, although you end up in real life making a big mess, is you could try to do cationic joining.

To review, there's two ways we just saw to make alkoxides: using sodium metal, or using sodium hydride. Once you have the alkoxide, you can do an Sn2 reaction to make an ether – the only thing that we have to consider in terms of synthesis is whether that reaction is possible. If I give you a target ether, you do have to use a little bit of logic to figure out which way should it have been synthesized.

Next major topic is dehydration reactions

Dehydration reaction is one way we can convert an alcohol into an alkene. Let's say that we have a compound like this: 2-methylbutan-2-ol. You use a strong acid source and heat, and, preferably, if you could remove water as this happens, you're going to drive this reaction into being an alkene. Let's see the mechanism for this reaction. You had a strong acid source, the only logical thing that can happen at first is for the alcohol to become protonated. Of course, that alcohol, once it becomes protonated, becomes an oxonium ion, which is super acidic. It would be logical that that proton might just fall right back off. In other words, this is a reversible reaction step. There are some general trends with cationic versus anionic reactions. We had some introduction to that last quater. Many, many cationic reactions, particularly acid-catalyzed reactions, are reversible reactions. Exactly like this kind of situation, where, yes, maybe in the presence of an acid, the only thing that logically could happen is for an oxygen to get protonated, but it doesn't necessarily like to be protonated. That proton will hop on and off and on and off and on and off ... until at some point, maybe instead of the hydrogen coming off, the carbon-oxygen bond breaks instead, which would form a carbocation. This would be a relatively favorable example of this because you are making a tertiary carbocation. Due to hyperconjugation, the more alkyl groups that you have around a carbocation, the more stable that carbocation is going to be.

This is an intermediate that can undergo either Sn1 or E1. But if we're using heat, and if we're drying away water, then you can favor the E1 elimination. The next step is for a hydrogen to be removed, and for the pair of the electrons that was in that bond to collapse back to the carbocation, making the alkene. You absolutely cannot use hydroxide to show the removal of this hydrogen, because if you're in acidic conditions, how can hydroxide exist? We're going to learn a lot functional groups where half of the reactions are in acidic conditions, half of them are in basic conditions. You just have to make sure that you don't suddenly switch from one set of conditions to another during a reaction mechanism. Notice that this is really just the reverse reaction of hydration of an alkene. Based on the principle of microscopic reversibility, which says that every step of the reaction in the forward direction, if it's the most favorable, it's exactly the same as the steps in the reverse reaction, just in reverse. Then, if a hydrogen coming off is the last thing that happens to make the alkene, the first thing that happens is the alkene reacts with H+. It's going to form the most stabilized carbocation, and in this case if we want to influence and force the production of an alcohol, we would add water. Notice that that's the next step in reverse, that water had come off. Once the water is put on, we again have an oxonium ion, which would want to deprotonate. That gets us back to the alcohol. So hydration of alkenes and dehydration of alcohols are only just reverse reactions of each other. Dehydration is favored by using heat and removing water as the reaction occurs. That removal of water is, again, an example of Le Châtelier's, and hydration is favored by adding water. Both reactions involve an acid catalyst.

[description of side arm to remove water]

Notice which alkene I produced in this reaction. Why did I choose this product? Because this is the more thermodynamically stable molecule. There is a competition between kinetics and thermodynamics.

For example, in E2 eliminations, if you had a big bulky base, that could make a less-favored alkene form, but if you had a small base, then the more thermodynamically-favored product will form. That's because a big, bulky base, there's a kinetic issue going on, where otherwise it's controlled by thermodynamics. Since this is a reaction involving heat, the more thermodynamically-stable alkene is normally produced by this simple acid-catalyzed dehydration. Internal, versus terminal, alkenes are more stable; more substituents (internal versus terminal), and trans versus cis. Let's see where this principle of forming the most thermodynamically stable molecule shows up. What is this TsOH? Tosic acid – p-toluenesulfonic acid. Why am I using tosic acid here? The conjugate is not nucleophilic, it's cheap, it's a solid, which means it's easy to be handled, and, a strong acid. It's a great catalyst, because it is a cheap solid, it is a strong acid, and the conjugate is non-nucleophilic. That therefore means no side reactions are going to occur with this. Sulfuric acid could be an oxidizing agent; hydrochloric acid, chlorine could end up being a nucleophile; nitric acid, also an oxidizing reaction. If we want something that's a strong acid, but without other consequences, this is a good one to use. Sometimes if I'm lazy and I don't care, I'll just say H+. Realize it can't just be any acid; you have to worry about potential side reactions. If I show a source of H+, I'm usually going to use tosic acid. In real life, that's what we used as an acid catalyst.

Let's see what the mechanism of this reaction would be. Based on what we saw above, what would be the first step of the reaction? So alcohol attacks H+. We form water. What would happen next? Water comes off. What kind of carbocation did I just make? Wouldn't it really prefer being a tertiary carbocation? So it does become one. This is an alkyl shift. Essentially, you can think of this as hyperconjugation gone wild. Hyperconjugation is the fact that the sigma bond, the one that's being shown migrating here, can provide some electron density into the carbocation to stabilize it. What if instead of just stabilizing it, the whole bond just moves. That's what happens. That creates a tertiary carbocation that's now more stable. If the most thermodynamically-stable product would want to form from this, what hydrogen would I now show being removed to finish the dehydration? There, because that would make an alkene that has four substituents on it, so that is the one that is going to form as the major product. There is this idea that even if at the very first instance the most stable thermodynamic product is not the one formed first, if you leave it sitting around in these reaction conditions long enough, the fact that it's a reversible reaction means that it can go back and forth between different alkenes and alcohols until eventually it ends up at the one that's the most stable.

At this point, not hydroxide; again, you're in acidic conditions, so if you're using something to show the removal of a proton, it needs to be water itself. So this is an E1 elimination. Notice that I did switch and use just a forward arrow arrow at one point, but that is just because I went from a secondary to a tertiary carbocation. Technically, it is reversible, but it's going to be highly favored to the right, because that's the more stable carbocation. So the end product is this alkene, which might not be immediately evident from the starting material that we had. This is my way of broadcasting that you really gotta watch out for this kind of situation. Rearrangements in cationic reactions are common, and, sometimes, directly exploited. For example, what do you think happens in this case? You're probably going to guess that there's some kind of rearrangement. This is ring expansion. Why? Because this four-membered ring is strained, so if and when it has the opportunity to expand, it will. Let's see how that occurs. These are the conditions for dehydration, so it's going to start out the same way. Notice that, at this point, we're not doing multiple reactions; we're just seeing one reaction, but some of its various regiochemical consequences. So alcohol gets protonated; we end up with water as a leaving group, so it comes off. Now, we have a secondary carbocation, but we also have this strained ring. Relieving that strain is enough of a driving force to exchange one secondary carbocation with another; let me number my carbons so you can see this better. It's technically reversible, but not. [note that numbers are not nomenclature numbers] Bond shifted from position one to position 5, which means when I go back and write the carbocation in, it's going to be at position one. So there's our ring expansion. To finish the reaction off, the double bond forming towards the methyl group is more favored because it makes a more substituted alkene, so that's the hydrogen that's more likely to be removed, so we'll show that last elimination step. So we end up with a cyclopentene, not a cyclobutene or some other four-membered ring compound.

There's one more rearrangement that I want to show you. It's such a classic reaction. It's known as the pinacol rearrangement. Pinacol is this particular alcohol. It is a vicinal diol, so let's see what happens when one of these types of vicinal diols is dehydrated. Same conditions that we've been using so far: acid catalyst in heat. Same first reaction step: one of the alcohols get protonated and turns in water, which leaves. So we already have a tertiary carbocation, but what if we did have a methyl shift occur? Let's see what we would get if one of these next-door methyl groups moves over. You might be asking, how do we know this kind of thing is going to happen? When it's energetically favorable for it to happen. Let's see why this might be favorable. After that shift occurs, notice what we have: we technically, in some senses, only have a secondary carbocation. But don't we have an oxygen right next door? And that oxygen has a lone pair that it's not hyperconjugation that can go on, it's conjugation; that lone pair can delocalize. That's just a resonance structure, in fact. At this point, we now have a protonated carbon, which is, like an oxonium ion, extremely acidic, so it can deprotonate, and we end up with a ketone.

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Finkelstein rxn

NaI is soluble in acetone, while NaBr and NaCl are not. As this rxn proceeds, NaBr (or NaCl) precipitates out of sol'n, which prevents Br- (or Cl-) from re-attacking the alkyl iodide as it's formed.

Alkylation

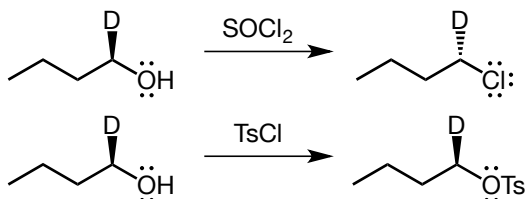Williamson ether synthesis – Sn2

synthetic strategy –> retrosynthesis

Dehydration of alcohols

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

Pinacolone

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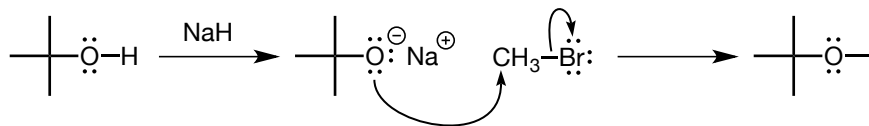
Structures

01/11/12 lec • 1

01/11/12 lec • 2
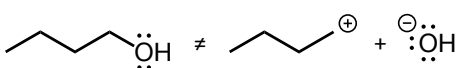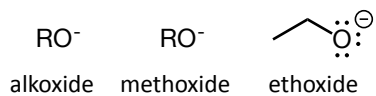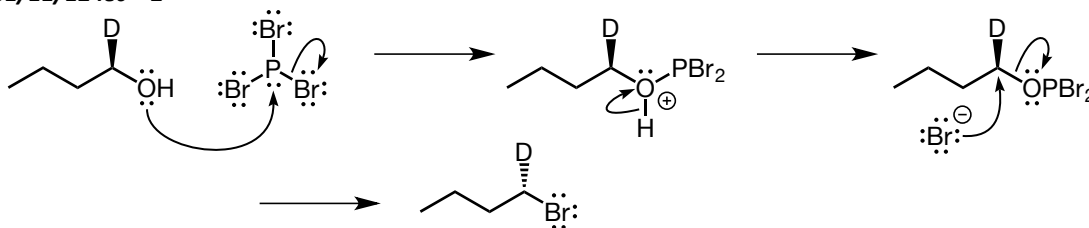
01/11/12 lec • 3
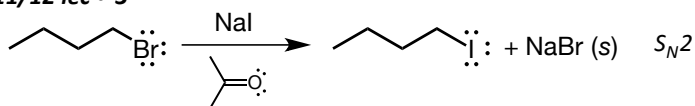
NaI, acetone → + NaBr (s) S_N2

01/11/12 lec • 4

01/11/12 lec • 6

RO⁻   RO⁻

alkoxide   methoxide   ethoxide

01/11/12 lec • 5

NaH, sodium hydride

01/11/12 lec • 7

Na (s) → 2 ... + 2 Na⁺ + H₂ (g)

01/11/12 lec • 8

NaH

01/11/12 lec • 9

common: diethyl ether   methyl ethyl ether   systematic: 1-ethoxybutane

parent chain (longer)   substituent (shorter)   substituent

01/11/12 lec • 10

retrosynthetic arrow (products –> reagents)   or   SN2 not possible for 3° substrates, so this method is not possible

Not -OH!!!!

rapidly, reversibly, repetitavely protonates
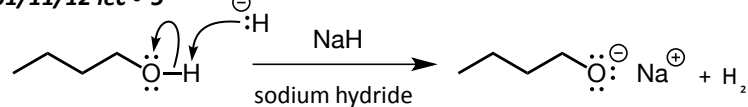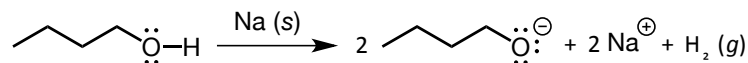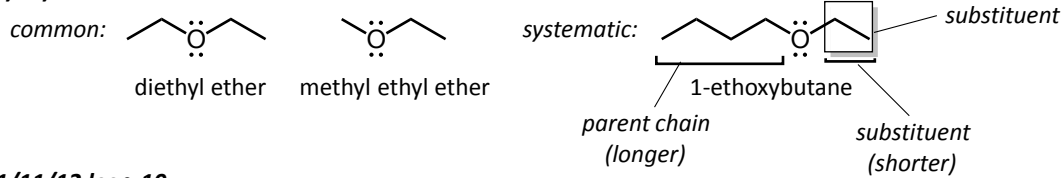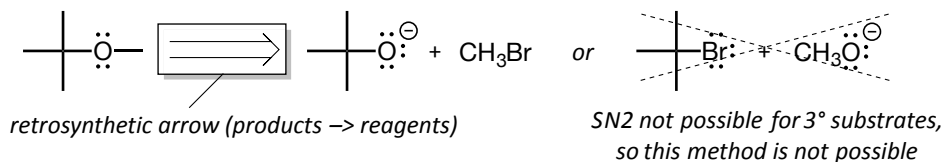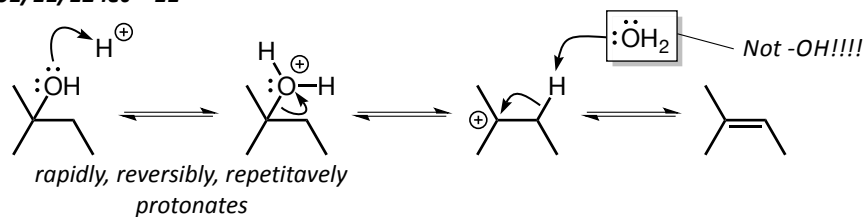
reverse reaction:

01/11/12 lec • 12

TsOH =

p-toluenesulfonic acid
tosic acid
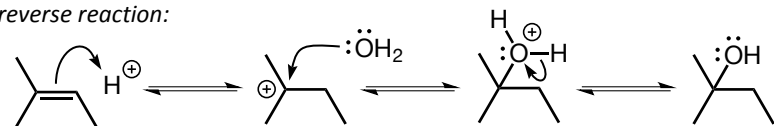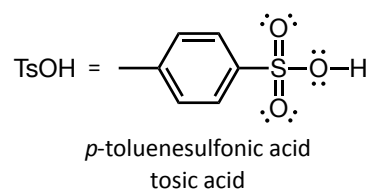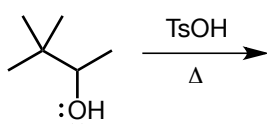
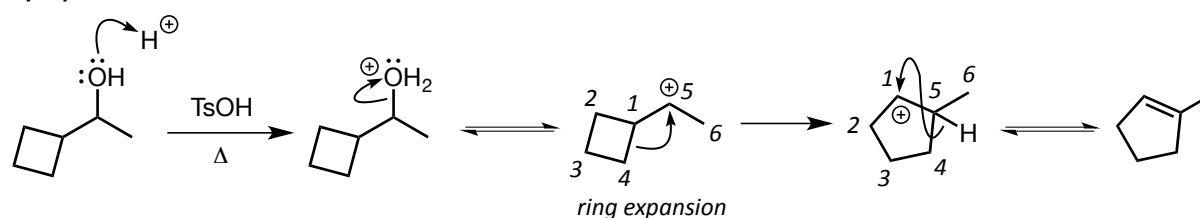*cheap, easily handled organic solid*
strong acid
conjugate is non-nucleophilic

01/11/12 lec • 13

TsOH
Δ

01/11/12 lec • 14

alkyl shift

H₂Ö:

01/11/12 lec • 15

TsOH
Δ

ring expansion

01/11/12 lec • 16

TsOH
Δ

pinacol

pinacolone