# Loudon Chapter 10 Review: Alcohols & Thiols
**Jacquie Richardson, CU Boulder – Last updated 3/9/2021**

Alcohols (ROH) and thiols (RSH) have many reactions in common with alkyl halides, but they don't do everything exactly the same. The main difference between this and alkyl halide chemistry is that unlike halides, hydroxide ($^-$OH) is a bad leaving group because it's a strong base. The first few reactions involve converting the $^-$OH into a good leaving group, which allows them to do most of the reactions out of Ch. 9.

Acid-Catalyzed Eliminations
One way to convert the hydroxide to a good leaving group is to protonate it to $-OH_2^+$. This way, once it dissociates, it leaves as a neutral, stable H_2O molecule instead of a strongly basic OH^-. If you use H_2SO_4, there's not really a good nucleophile around so the most likely outcome is elimination.
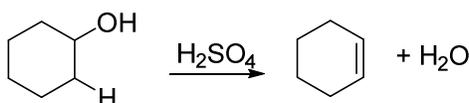

This reaction is exactly like hydration of alkenes but in reverse:
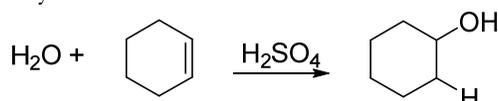
Since both reactions are catalyzed by acid, how do we control which direction is favored? We have to take advantage of Le Châtelier's principal: having more water present will drive the reaction towards the alcohol side, but having less water present will drive it towards the alkene side. We can remove water by using a strong, concentrated acid like H_2SO_4 or H_3PO_4 and adding it directly to the alcohol, with no water or solvent involved. We can also distill off the alkene as it forms, so that it's no longer in the presence of water.

The mechanism for dehydration of alcohols is exactly the same as the mechanism for hydration of alkenes, but in reverse. If you look at each intermediate, you should recognize it as an intermediate from hydration.
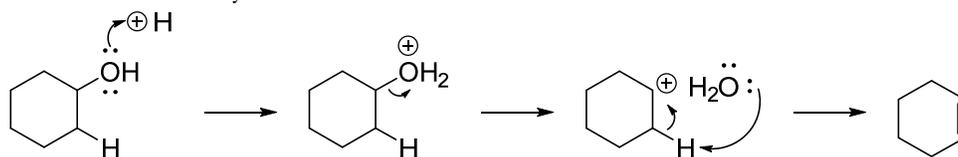
This mechanism also closely resembles the E1 mechanism we saw in Ch. 9, with the difference that the OH group needs to be protonated before it can dissociate. Just like in other E1 reactions, more substituted alcohols react faster, carbocation rearrangements are a possibility, and the regiochemistry follows Zaitsev's rule:
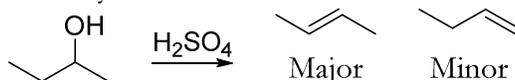
Converting Alcohols to Alkyl Halides or Pseudohalides
There are three different ways to convert halogens to alkyl halides or "pseudohalides". Some work better under certain conditions.
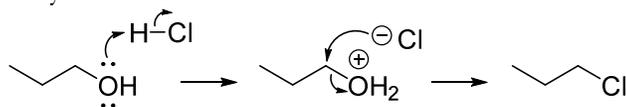1. React with HX – this looks a lot like S_N1/S_N2, but just like acid-catalyzed elimination, you need to protonate the OH to make it leave.

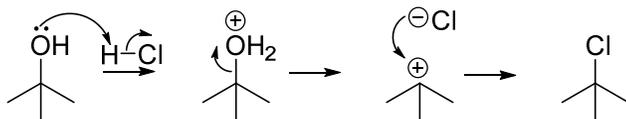Since this is under protic conditions, the larger halogens are better at this reaction. This goes by S_N2 for primary alcohols:
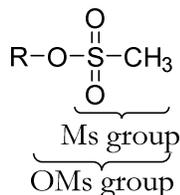

It goes by S_N1 for secondary and tertiary. Again, remember to check for carbocation rearrangement if it's S_N1.
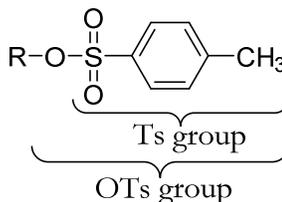

2. The most widely applicable method, and usually the best choice during a synthesis, is to convert the alcohol to a sulfonate ester.
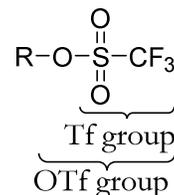
| An alkyl mesylate (methylsulfonate) contains a mesyl (Ms) group	An alkyl tosylate (p-Toluenesulfonate) contains a tosyl (Ts) group	An alkyl triflate (trifluoromethanesulfonate) contains a triflyl (Tf) group

This creates a group that acts so much like a halogen that sulfonate esters are often referred to as pseudohalides. This is because their leaving group ability is about the same as a halogen – the pKa of the $^-OS(O_2)R'$ group is in the same range. Mesyl and tosyl are about as good as bromide, and triflyl is slightly better - about as good as iodide.

To install mesyl and tosyl groups, you use the acid chloride plus pyridine. Pyridine (often abbreviated as "pyr") is used to soak up the HCl that gets generated as a byproduct, and because it catalyzes the reaction.
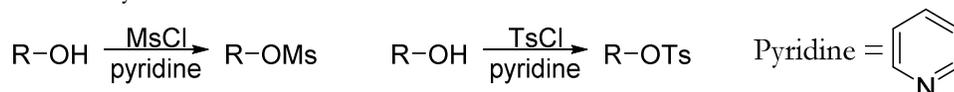
To install the triflate group, you use triflic anhydride (Tf-O-Tf or Tf_2O) plus pyridine again.
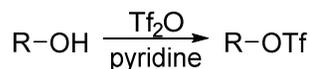

Although we don't look at the mechanism for any of these, it's important to note that the stereochemistry on R will not change during the reaction. The reaction is being done at O, not C.
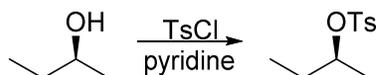

Once you have any of these three groups in place of the OH group, you can make the molecule do any of the alkyl halide chemistry from Ch. 9, exactly as if it were a real alkyl halide, and following all the same rules about which mechanism is favored when.
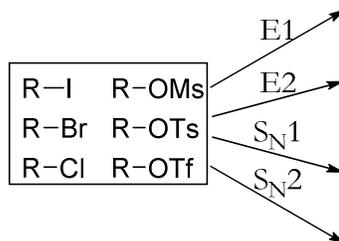
3. The third way is to use a special halogenating agent. The two options here are thionyl chloride (SOCl$_2$) to convert OH to Cl, and either triphenylphosphine dibromide (Ph$_3$PBr$_2$) or phosphorous tribromide (PBr$_3$) to convert OH to Br. The book doesn't cover PBr$_3$ because it's less popular now, due to being more hazardous and harder to work with. With SOCl$_2$, you again need pyridine to soak up the HCl byproduct.
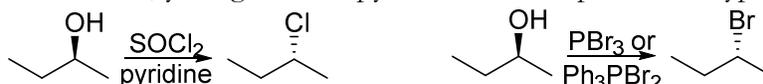

A note on stereochemistry: since both of these reactions go by S$_N$2 on the carbon, the end result is inversion of stereochemistry. This also means they work well on primary alcohols and okay on secondary, but not at all on tertiary. These are all much better methods than using HX to react with the alcohol. This is partly because they won't react with other functional groups as much – we know HX will react with alkenes to give unexpected products. They also won't undergo carbocation rearrangement. However, they are more expensive, so sometimes HX is the best choice.

The mechanism for all of these is roughly the same: the OH group attacks the other molecule, causing it to drop a halogen. This halogen then comes in and does S$_N$2 on whatever group the OH has become. We don't look at the full mechanism of how the OH attaches to the sulfur yet, because it involves S=O chemistry.
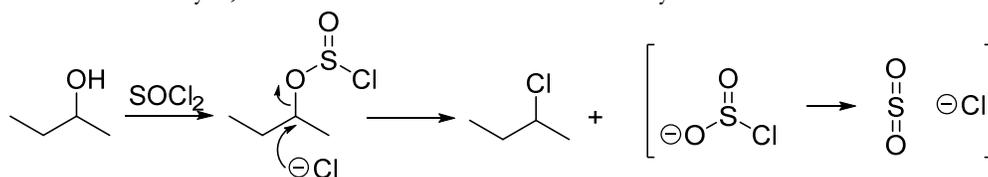
For PBr$_3$, though, the mechanism is basically S$_N$2 on phosphorous, followed by the bromide leaving group coming back in for an S$_N$2 on carbon. This creates a species that can rearrange itself to have a P=O double bond, which is very strong and favorable.
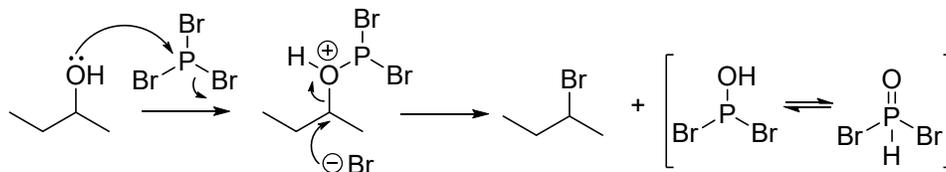
Ph$_3$PBr$_2$ does something similar, only the bromide is only ionically bonded to phosphorous to begin with the compound exists as a Ph$_3$PBr$^+$ cation, and a Br$^-$ anion. Remember that phosphorous can break the octet rule, so even though this looks strange it's still valid.
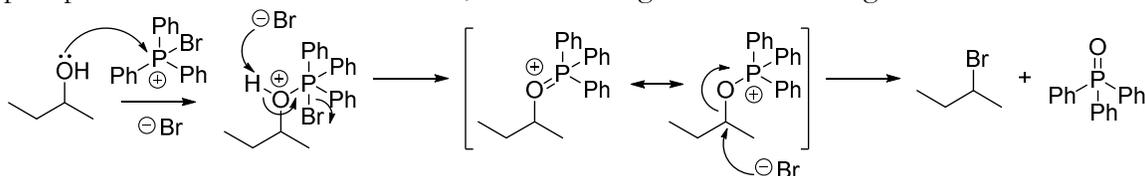
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Alkoxides
Alcohols and thiols, like water, are amphoteric. They can be protonated by an acid (as shown above), or deprotonated by a base. This is because alcohols have pKas in the range of 15-19, and thiols in the range of 10-12. Deprotonated alcohols are called alkoxides – we've already seen many examples in Ch. 9 like sodium ethoxide (NaOEt) or potassium tert-butoxide (tBuOK). The easiest way to form them is to start with the alcohol and deprotonate it with sodium hydride, NaH. This is a good choice because the byproduct that's created is H_2, which leaves the solution as a gas.

$$\text{\Large ⌁OH} \quad \text{NaH} \quad \longrightarrow \quad \text{\Large ⌁ONa} \quad \text{H–H}$$
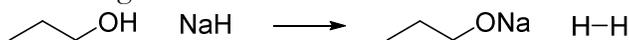
Another way to do this is by using sodium metal, Na. The mechanism for this is somewhat similar to the mechanism for Grignard formation, but we won't cover it.

$$\text{\Large ⌁OH} \quad \text{Na}^0 \quad \longrightarrow \quad \text{\Large ⌁ONa} \quad \text{H–H}$$
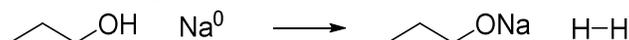
Deprotonated thiols are called mercaptides. We've also seen some of these like sodium ethyl mercaptide (NaSEt). Since these have a lower pKa, they can be made by either of the above two methods, or by reacting with an alkoxide.

$$\text{\Large ⌁SH} \quad \text{\Large ⌁ONa} \quad \longrightarrow \quad \text{\Large ⌁SNa} \quad \text{\Large ⌁OH}$$
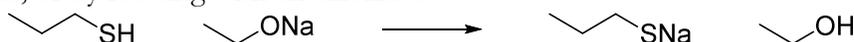
Oxidation and Reduction
In general chemistry and inorganic chemistry, redox (reduction & oxidation) involves the loss and gain of entire electrons. Redox in organic chemistry usually involves the loss and gain of electron density or partial charges. This is tracked by "formal oxidation level" (not the same thing as formal charge). If a carbon atom has bonds to less electronegative atoms like hydrogen, then it has partial negative charges and is **reduced**. If it has bonds to more electronegative atoms like oxygen, then it has partial positive charges and is **oxidized**. Remember, "LEO says GER" – **L**oss of **E**lectron density is **O**xidation, **G**ain of **E**lectron density is **R**eduction. Or you can use "OIL RIG" – **O**xidation **I**s **L**oss, **R**eduction **I**s **G**ain. We can informally categorize functional groups based on how many bonds the carbon has to atoms more electronegative than itself. All the halogens, plus oxygen and nitrogen, are more EN than carbon; most other atoms are less EN.

<div align="center"># of bonds to more EN atoms:</div>

CH_4 H_3C-CH_3 $H_2C=CH_2$	H_3C-OH H_3C-Br	(2-bond structures) CH_2Cl_2	(3-bond structures) $HCCl_3$	$O=C=O$ CCl_4
0 bonds	1 bond	2 bonds	3 bonds	4 bonds

We also have a more formal system to track partial charges on atoms, called "formal oxidation level." To find the formal oxidation level of an atom, add these numbers together:
1. For every bond an atom has to a less electronegative atom or negative charge, add -1.
2. For every bond an atom has to an equally electronegative atom or radical, add 0.
3. For every bond an atom has to a more electronegative atom or positive charge, add +1.
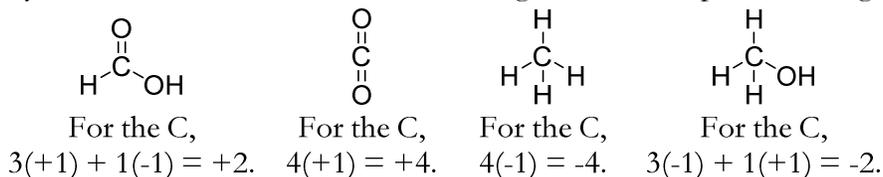
For the C,
3(+1) + 1(-1) = +2.

For the C,
4(+1) = +4.

For the C,
4(-1) = -4.

For the C,
3(-1) + 1(+1) = -2.

We can track changes on a particular atom or atoms during a reaction, to see whether the molecule as a whole is getting oxidized or reduced. The formal charge of carbon is given below for each product or reactant.

-4 → +4   Oxidation overall

0 → -2   Reduction overall
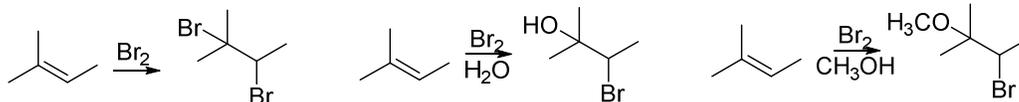
-2 → -2   Neither oxidation nor reduction
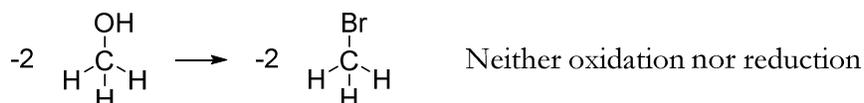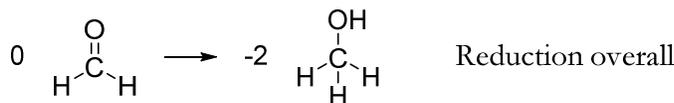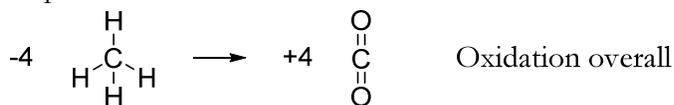
We can revisit some of the reactions we've seen previously to sort them into categories of oxidation, reduction, or neither. In this case, you need to sum up the changes across all affected carbons:
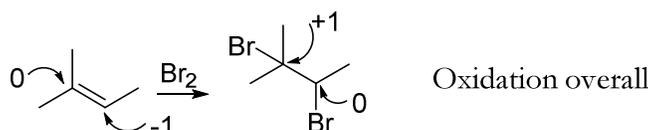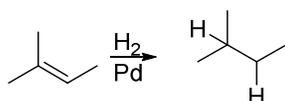
Oxidation overall

For the alkene additions we saw, the ones that add 2 non-H groups were all oxidations, the ones that add 2 Hs were reductions, and the ones that add 1 H and 1 non-H were neither.
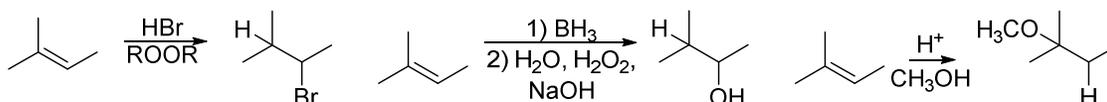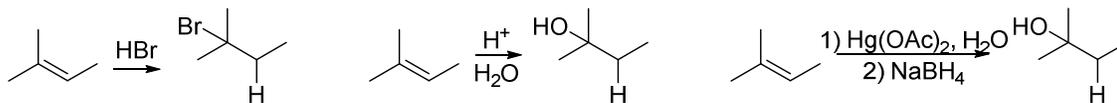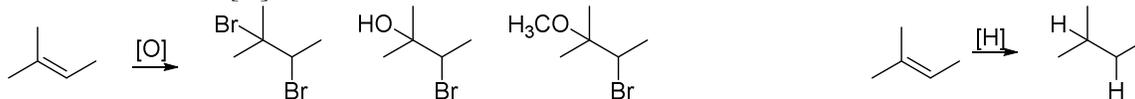
Oxidation:

Reduction:

Neither:

A general way to show that an oxidation or reduction occurs is to put "[O]" above the arrow for oxidation, or "[H]" for reduction.

Typical oxidizing agents contain high-electronegativity atoms, often bonded to each other or to a central, octet-breaking atom. Some examples are Br_2, H_2O_2, CrO_3, and O_3. Typical reducing agents contain low-electronegativity atoms, often bonded to each other or to a central, low-electronegativity atom. Some examples are H_2, BH_3, and $NaBH_4$. For example,

in Ch. 5 we saw two different workups for ozonolysis – the reductive workup (with CH_3SCH_3) and the oxidative workup (with H_2O_2).

The net oxidation or reduction must be conserved across all species during a reaction. If an alkene gets oxidized, it is because the other reagents were reduced during the reaction or vice versa. Many transition metals can exist in various different oxidation states, so to specify which it is, we use roman numerals in parentheses after the atom.

$HO-Cr-OH$ is Cr (VI) $O=Os=O$ is Os (VIII) $I-Cu$ is Cu (I)
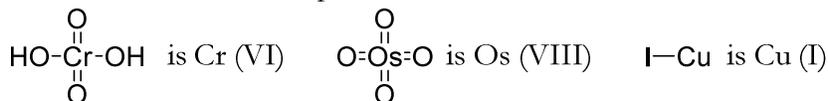
If a reaction uses Cr (VI) and produces Cr (III), we know that the chromium got reduced and so the organic molecule must have been oxidized. Since chromium's formal charge changed by 3, this would be called a "three-electron redox reaction", even though no electrons are being transferred individually.
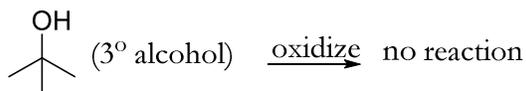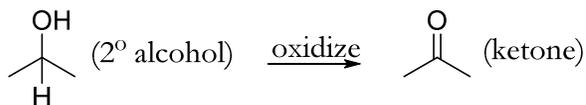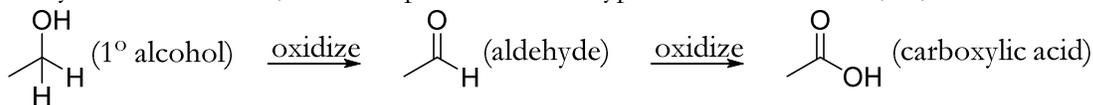
Often, even if we don't know much about what reagents to use to perform a mechanism, we can narrow it down based on whether it's a reduction, oxidation, or neither. For example, this reaction, called the pinacol rearrangement, is neither overall:
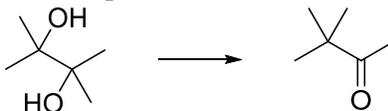
That means that neither oxidizing agents nor reducing agents are likely to make this happen. In fact, in this case, strong acid is enough to cause it to occur.

Oxidation of Alcohols

This involves changing the oxidation level of the carbon that has the OH on it, by adding more bonds to O. To do this, the C has to lose bonds to H to make room. (In a few cases, it can also lose bonds to C, but aside from one case – ozonolysis – we won't see any reactions like this for a while.) The ability of the C to get oxidized is therefore dependent on how many Hs it has to lose, which depends on what type of alcohol it is - 1°, 2°, or 3°.

(1° alcohol) → oxidize → (aldehyde) → oxidize → (carboxylic acid)

(2° alcohol) → oxidize → (ketone)

(3° alcohol) → oxidize → no reaction

There are two options available for oxidizing agents.

1. Strong oxidizers: for this, you can use many versions of chromium (VI) attached to multiple oxygen atoms, in the presence of strong acid and water. Chromate (H_2CrO_4 or Na_2CrO_4/H_2SO_4), dichromate ($H_2Cr_2O_7$ or $Na_2Cr_2O_7/H_2SO_4$), or chromium trioxide (CrO_3/H_2SO_4) will work. Potassium permanganate ($KMnO_4$) will also work but it's harsher and sometimes produces unwanted side reactions. Another way to write this is "Jones" or "Jones reagent" – this is a mixture of CrO_3, H_2SO_4, and acetone. These strong oxidizers will all oxidize up the molecule as far as possible: 1° alcohols will be become carboxylic acids and 2° alcohols will become ketones.

It's hard to stop at the aldehyde state, because if there's water present a side reaction will happen: the molecule will interconvert rapidly between an aldehyde and a hydrate. This hydrate acts just like a regular alcohol and gets oxidized further, to the carboxylic acid state.

(1° alcohol)   (aldehyde)   (hydrate)   (carboxylic acid)
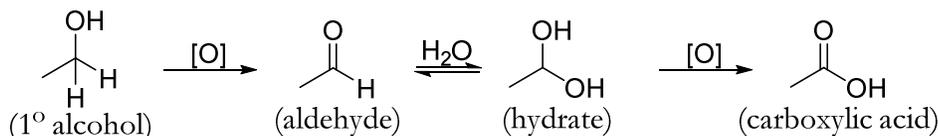
2. Weaker oxidizers: if you want to stop at the aldehyde state, you need to use special chromium (VI) reagents that work in the absence of water. These commonly use DCM as a solvent. The most common one is pyridinium chlorochromate (PCC), but pyridinium dichromate (PDC) works fine too.

pyridinium chlorochromate   pyridinium dichromate
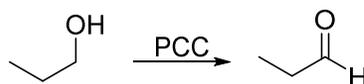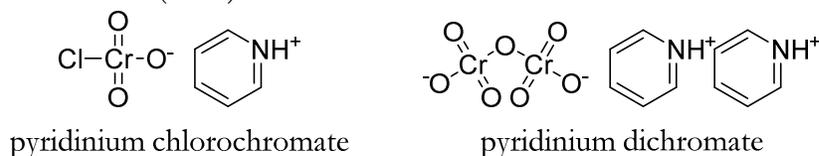
The mechanism is similar for all of these oxidizers: the oxygen forms a bond to the central atom (we won't cover the mechanism for this step), and then something deprotonates the carbon next to the oxygen in an E2-like step.
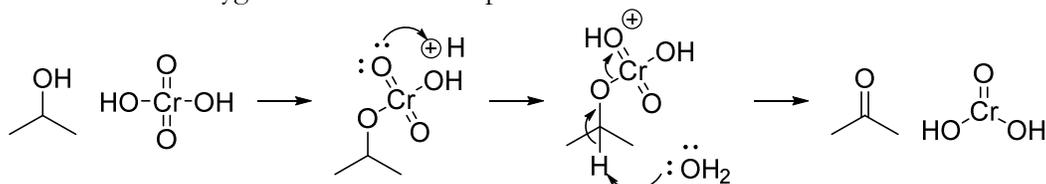
Oxidation of Thiols
This is different from oxidation of alcohols, because instead of oxidizing C by taking away Hs, we're actually oxidizing S by making it break the octet rule. There are several different oxidation states available to sulfur, but we only look at three of them – thiols, disulfides, and sulfonic acids.
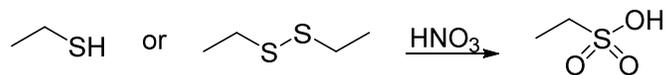
Thiol   Disulfide   Sulfonic acid
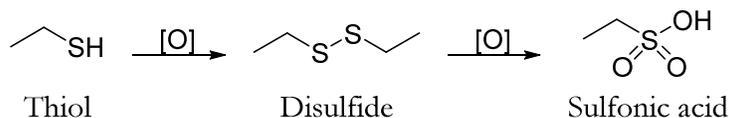
To oxidize a thiol to a disulfide, we can use a very mild oxidizer like Br_2 or I_2. This also happens very slowly in ambient air, due to oxygen itself being an oxidizer.
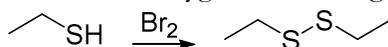
To oxidize a thiol or a disulfide to a sulfonic acid, we need a much stronger oxidizer like HNO_3 or $KMnO_4$.

Ch. 10 Synthesis Practice

Here's a synthesis problem that incorporates some of these reactions:

Make sure you track the carbons carefully here – the molecule isn't necessarily drawn with the same orientation. We need to do an anti-Zaitsev elimination, which we can only do with tBuONa, which requires us to convert the OH to a good LG (a halogen or pseudohalogen) first. From there, we do anti-Markovnikov addition of OH and then oxidize.