

## Alcohols II

**Reading:** Wade chapter 11, sections 11-1- 11-9

**Study Problems:** 11-42, 11-46, 11-47, 11-49, 11-52, 11-54

### **Key Concepts and Skills:**

- Predict the products of the reactions of alcohols with oxidizing and reducing agents.
- Predict the products of the reactions of alkoxide ions.
- Know how to form 1°, 2°, and 3° alkyl halides from 1°, 2°, and 3° alcohols.

### **Lecture Topics:**

#### **I. Oxidation of alcohols**

The hydroxyl functional group is very versatile and can be converted into almost any other functional group. Oxidation reactions convert alcohols into carbonyl compounds.

**Oxidation** is a gain of O, loss of H<sub>2</sub> (or a gain of O<sub>2</sub>, X<sub>2</sub>)

**Reduction** is a gain of H<sub>2</sub> or H<sup>-</sup> or a loss of O or O<sub>2</sub>. It can also be a loss of X<sub>2</sub>

Consider the following changes in oxidation state at carbon:

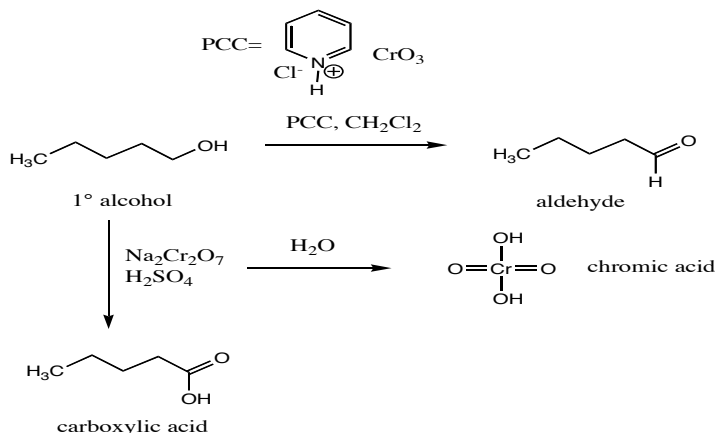
R-CH<sub>3</sub> → R-CH<sub>2</sub>-OH (gain of O) → R-CH=O (loss of H<sub>2</sub>) → R-C(=O)OH (gain of O)

RR'CH<sub>2</sub> → RR'CHOH (gain of O) → RR'C=O (loss of H<sub>2</sub>)

RR'R''CH → RR'R''COH (gain of O)

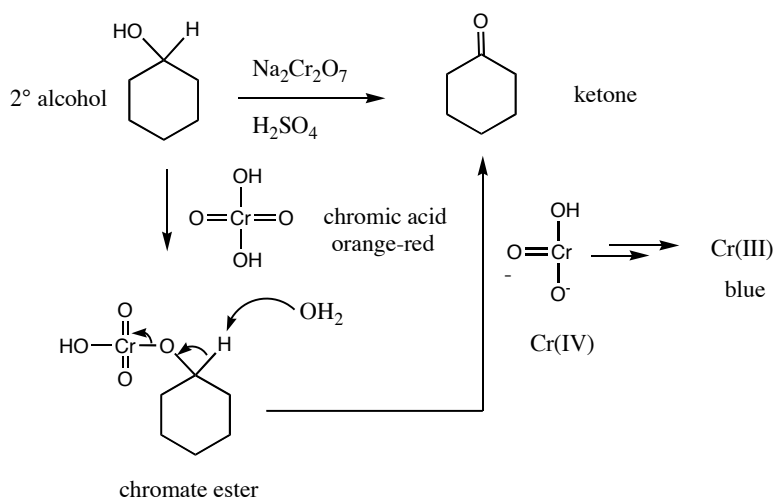
#### **Oxidation of 1° alcohols to aldehydes and carboxylic acids**

Primary alcohols may be oxidized to aldehydes by the reagent pyridium chlorochromate (PCC), which is a mild oxidizing agent. In contrast, sodium dichromate in sulfuric acid, a strong oxidizing agent that produces chromic acid in situ, oxidizes alcohols all the way to carboxylic acids:



#### **Secondary alcohols can be oxidized to ketones**

Chromic acid generated in situ from acidic sodium dichromate allows formation of ketones from 2° alcohols. All chromium oxidations are thought to involve formation of an intermediate chromate ester. The reaction progress for chromic acid oxidations can be monitored by observing the color of solution: chromic acid (Cr (VI)) is red-orange, while the reduced Cr(III) species that is produced after oxidation is blue.

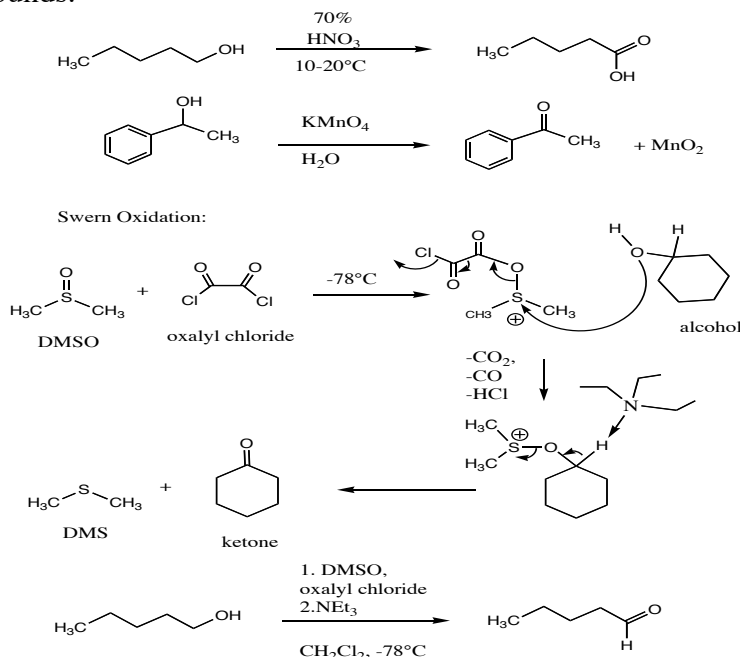


### Tertiary alcohols are not oxidized under these conditions

Tertiary alcohols lack carbinol hydrogen atoms that can be abstracted for oxidation to take place (see mechanism above). Thus, under the conditions outlined above, no oxidation of tertiary alcohols takes place.

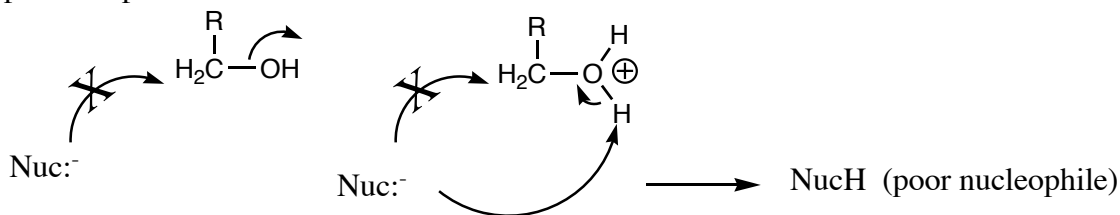
### Alternative oxidizing agents

Collins reagent ( $\text{CrO}_3$ -pyridine) and Jones reagent ( $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , acetone) are milder reagents than chromic acid for oxidizing 2° alcohols to ketones.  $\text{KMnO}_4$  and nitric acid are very strong oxidants which oxidize 2° alcohols to ketones and 1° alcohols to carboxylic acids. The **Swern** oxidation is by far the mildest method for transforming 1° alcohols into aldehydes and 2° alcohols into ketones. Mixing DMSO and oxalyl chloride produces an activated intermediate to which an alcohol and a tertiary amine (triethyl amine) are added. The entire process takes place at  $-78^\circ\text{C}$  and affords high yields of carbonyl compounds:



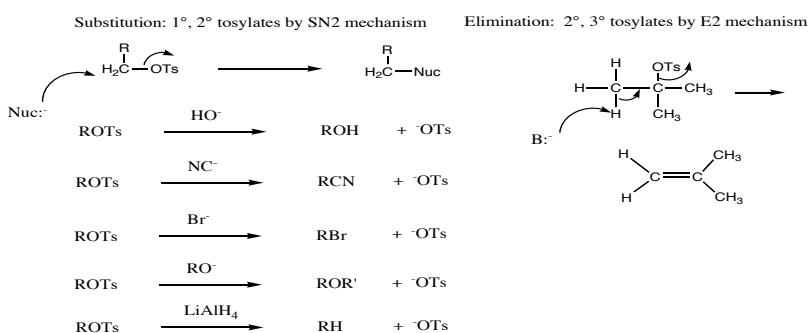
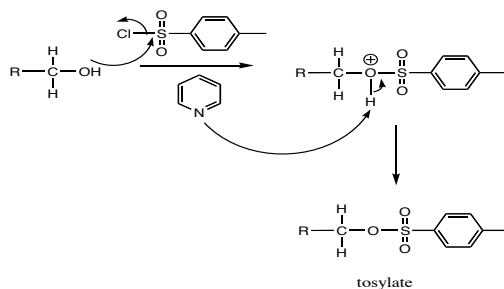
## II. Alcohols as Nucleophiles and Electrophiles

Alcohols themselves are weak nucleophiles, but they can be converted into strong nucleophiles (alkoxide ions) by deprotonation. Alcohols themselves are weak electrophiles because hydroxide ion is a poor leaving group. Protonation of alcohols in acid generates a good leaving group, water; however, under the acidic conditions required to generate this leaving group, most good nucleophiles (eg, ones which are negatively charged,  $\text{Nuc}^-$ ) are converted into poor nucleophiles,  $\text{NucH}$ . Thus, nucleophilic substitution of alcohols in acidic media is in most cases (except for halogenation) not a practical process.

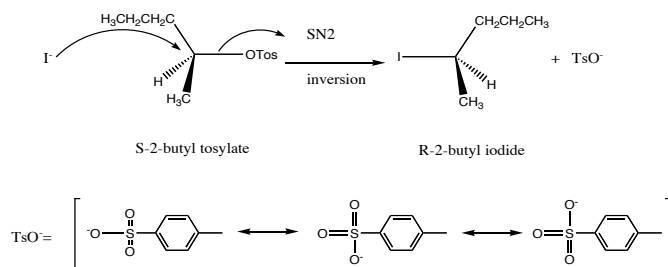


### Toluenesulfonate esters

Alcohols can be converted into excellent leaving groups by transformation into toluenesulfonate esters by treatment with tosyl chloride in pyridine. Tosylates are excellent leaving groups that undergo efficient substitution and elimination reactions with nucleophiles and bases in an analogous fashion to alkyl halides.

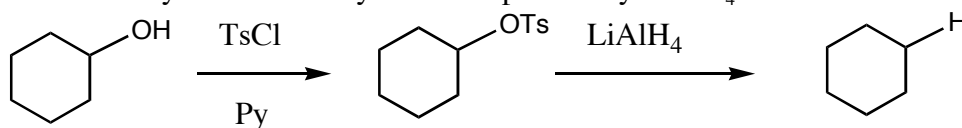


The  $\text{S}_{\text{N}}2$  mechanism with tosylates is stereospecific, with inversion of configuration observed. The reason that tosylates are such good leaving groups is that  $\text{TsO}^-$  ion is very stable due to resonance delocalization of the negative charge over multiple oxygens.



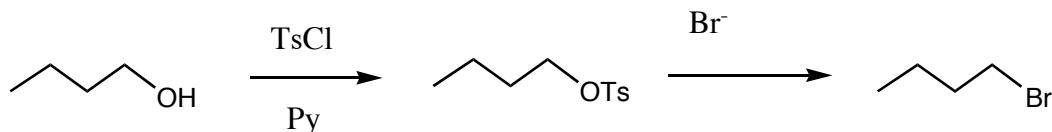
### Reduction of alcohols

The most practical method for reduction of alcohols to alkanes is by hydride displacement of tosylates. This may be accomplished by  $\text{LiAlH}_4$ .



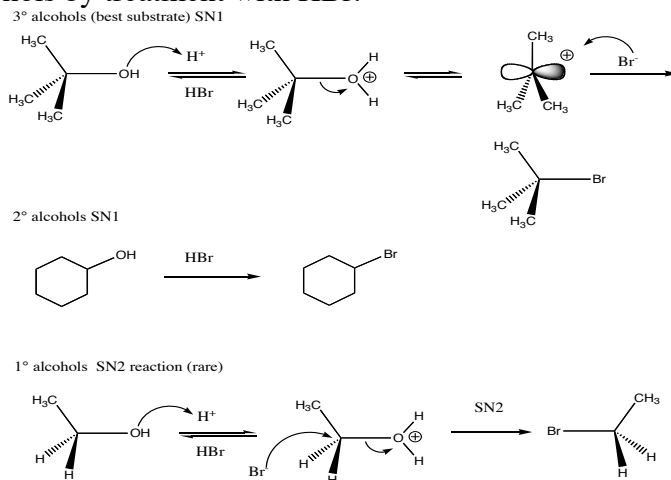
### III. Formation of halides from alcohols

Halides can be formed from tosylates by  $\text{SN}_2$  displacement of  $1^\circ$  and  $2^\circ$  tosylates:



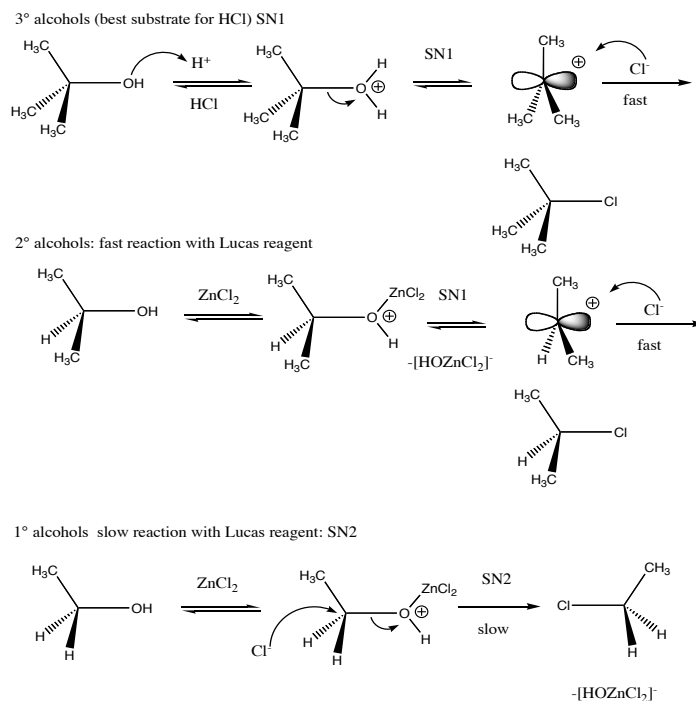
### Formation of alkyl bromides by treatment of alcohols with H-X

This process works well for tertiary alcohols because protonation of the alcohol facilitates ionization to the stable carbocation. Since halides like bromide ion are sufficiently nucleophilic even in acidic media, simple alkyl bromides can be formed efficiently from  $1^\circ$ ,  $2^\circ$ , and  $3^\circ$  alcohols by treatment with  $\text{HBr}$ :



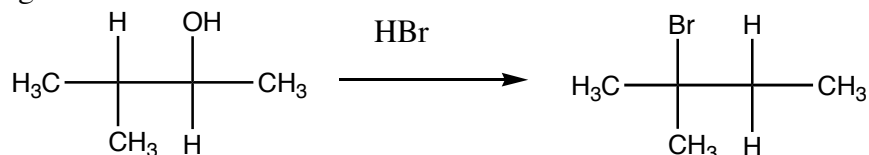
Only tertiary alcohols can be converted to the corresponding alkyl chlorides by  $\text{HCl}$ ; chloride is not as good a nucleophile as bromide, so  $\text{ZnCl}_2/\text{HCl}$  (Lucas reagent) is used to convert  $1^\circ$  and  $2^\circ$  alcohols to chlorides. The  $\text{ZnCl}_2$  forms a strong complex with  $\text{O}$ , assisting ionization and preventing return of  $\text{H}_2\text{O}$  so that chloride can effectively compete as a nucleophile. Tertiary and secondary alcohols react fast with Lucas reagent because of

rapid formation of an intermediate carbocation; primary alcohols react slowly because SN2 reaction is taking place.



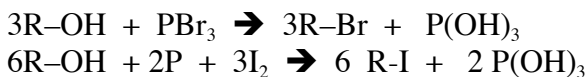
### Iodination

Most alcohols do not react with HI to give alkyl iodides. The acidic methods outlined above, which for the best substrates (3°, 2° alcohols) proceed through the intermediacy of carbocations, are prone to rearrangements and eliminations as side reactions. Consider the following:

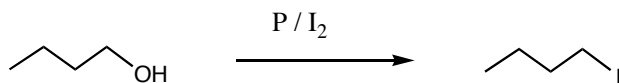
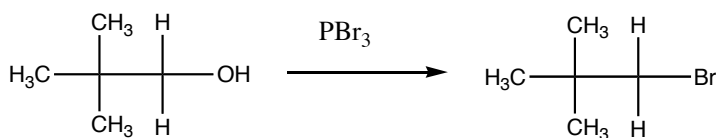


### Alternative Methods of Halogenation: Phosphorous Halides

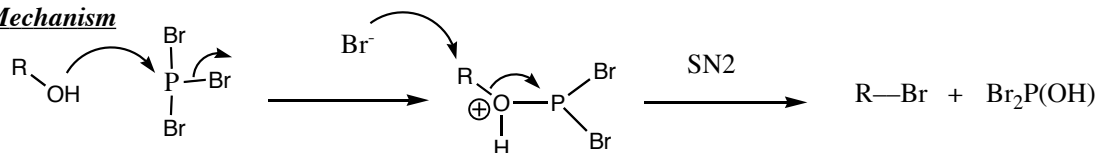
Treating 1° or 2° alcohols with phosphorous halides PBr<sub>3</sub> and PI<sub>2</sub> results in good yields of conversion to the corresponding alkyl bromide and iodides, respectively.



Note: this method does not work for 3° halides, since reaction proceeds by SN2 inversion. Reaction of the alcohol with the phosphorous reagent makes an activated alcohol intermediate that undergoes SN2 inversion with halide ion.

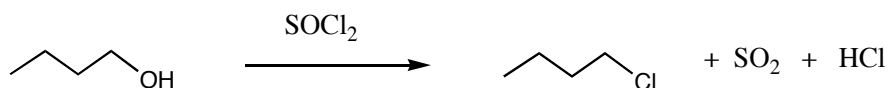


**Mechanism**

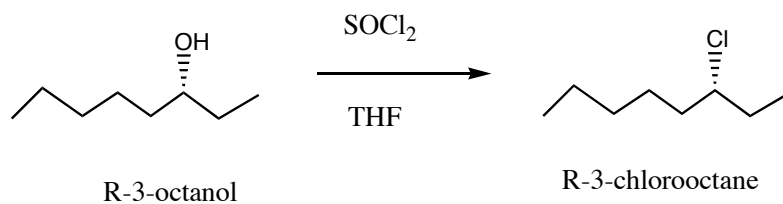
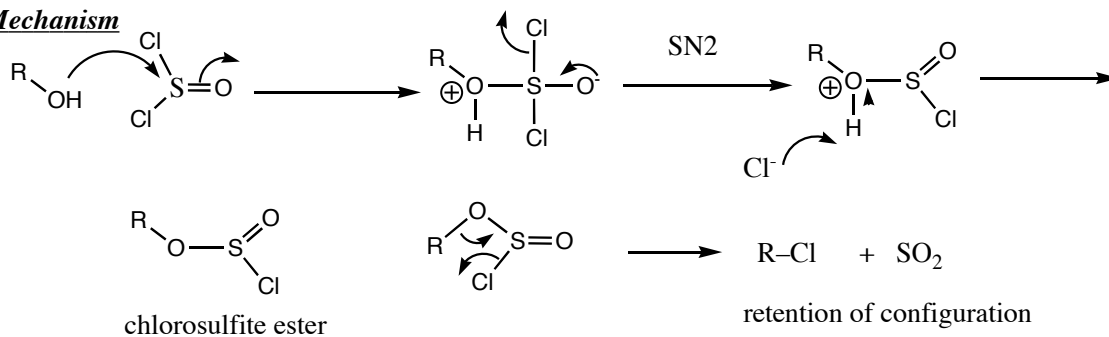


since an SN2 reaction is taking place, only 1° and 2° halides work well!

For forming 1° and 2° chlorides, the reagent of choice is SOCl<sub>2</sub>, which reacts with alcohols to form a chlorosulfite ester. Retention of configuration is observed in many cases, but not all:



**Mechanism**

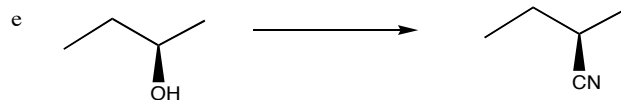
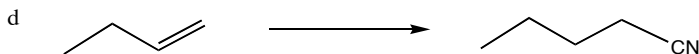
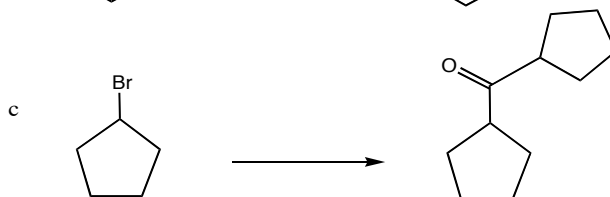
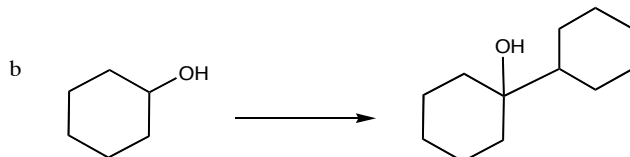
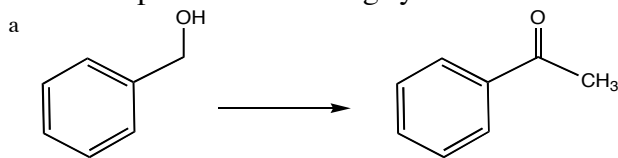


Best reagents for halide formation depending on substitution of the alcohol:

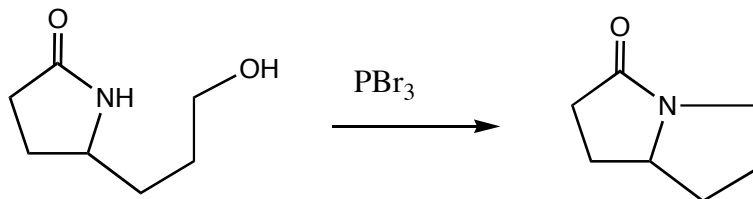
	<u>Alcohol</u>		
<u>halide</u>	1°	2°	3°
chloride	SOCl <sub>2</sub>	SOCl <sub>2</sub>	HCl
bromide	PBr <sub>3</sub>	PBr <sub>3</sub>	HBr
iodide	P/I <sub>2</sub>	P/I <sub>2</sub>	HI

Additional Problems for practice:

1. Show how to accomplish the following synthetic conversions:



2. Propose a mechanism for the following transformation:



3. Design a preparation of the following molecules from the indicated starting materials:

