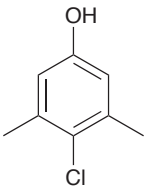
Alcohols and Phenols

Klein, D. (2012). Alcohols and Phenols. En *Organic Chemistry* (pp. 591- 600). USA: Wiley.

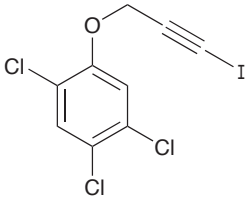
MEDICALLYSPEAKING

Phenols as Antifungal Agents

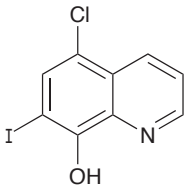
Many phenols and their derivatives exhibit topical antifungal properties. These agents are believed to interfere with the cell membrane function of fungi. The following are just a few examples.



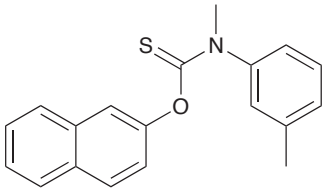
para-Chloro-*meta*-xylenol



Haloprogin

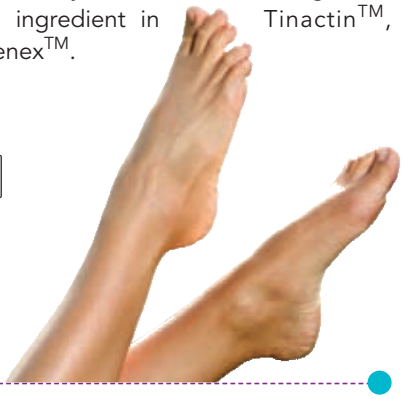


Clioquinol



Tolnaftate

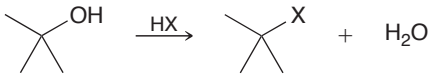
These compounds, as well as many others, are used in the treatment of athlete's foot, jock itch, and ringworm. Tolnaftate is the active ingredient in Tinactin™, Odor Eaters™, and Desenex™.



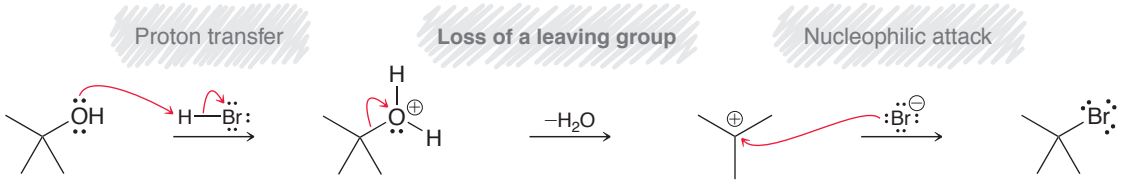
13.9 Reactions of Alcohols: Substitution and Elimination

S_N1 Reactions with Alcohols

As seen in Section 7.5, tertiary alcohols will undergo a substitution reaction when treated with a hydrogen halide.



We saw that this reaction proceeds via an S_N1 mechanism.

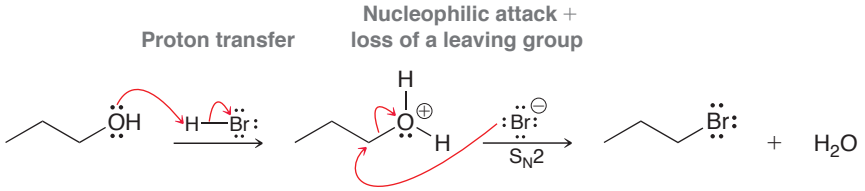


Recall that an S_N1 mechanism has two core steps (loss of leaving group and nucleophilic attack). When the starting material is an alcohol, we saw that an additional step is required in order to protonate the hydroxyl group first. This reaction proceeds via a carbocation intermediate and is therefore most appropriate for tertiary alcohols. Secondary alcohols undergo S_N1 more slowly, and primary alcohols will not undergo S_N1 at an appreciable rate. When dealing with a primary alcohol, an S_N2 pathway is required in order to convert an alcohol into an alkyl halide.

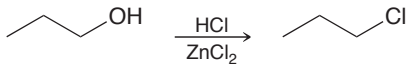
S_N2 Reactions with Alcohols

Primary and secondary alcohols will undergo substitution reactions with a variety of reagents, all of which proceed via an S_N2 process. In this section, we will explore three such reactions that all employ an S_N2 process.

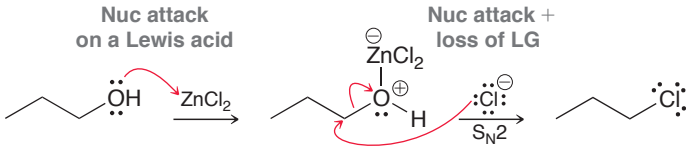
1. Primary alcohols will react with HBr via an S_N2 process.



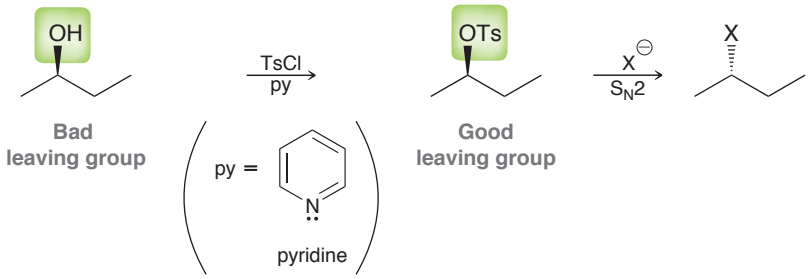
The hydroxyl group is first protonated, converting it into an excellent leaving group, followed by an S_N2 process. This reaction works well for HBr but does not work well for HCl. To replace the hydroxyl group with chloride, $ZnCl_2$ is used as a catalyst.



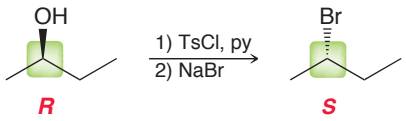
The catalyst is a Lewis acid that converts the hydroxyl group into a better leaving group.



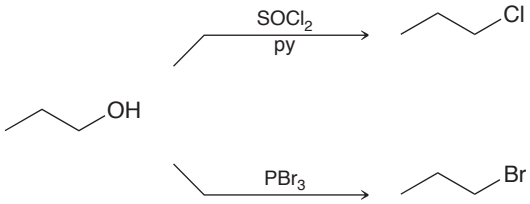
2. As seen in Section 7.8, an alcohol can be converted into a tosylate, followed by nucleophilic attack.



Using tosyl chloride and pyridine, the hydroxyl group is converted into a tosylate group (an excellent leaving group), which is susceptible to an S_N2 process. Notice the stereochemical outcome of the previous reaction. The configuration of the chirality center is not inverted during formation of the tosylate, but it is inverted during the S_N2 process. The net result is inversion of configuration.

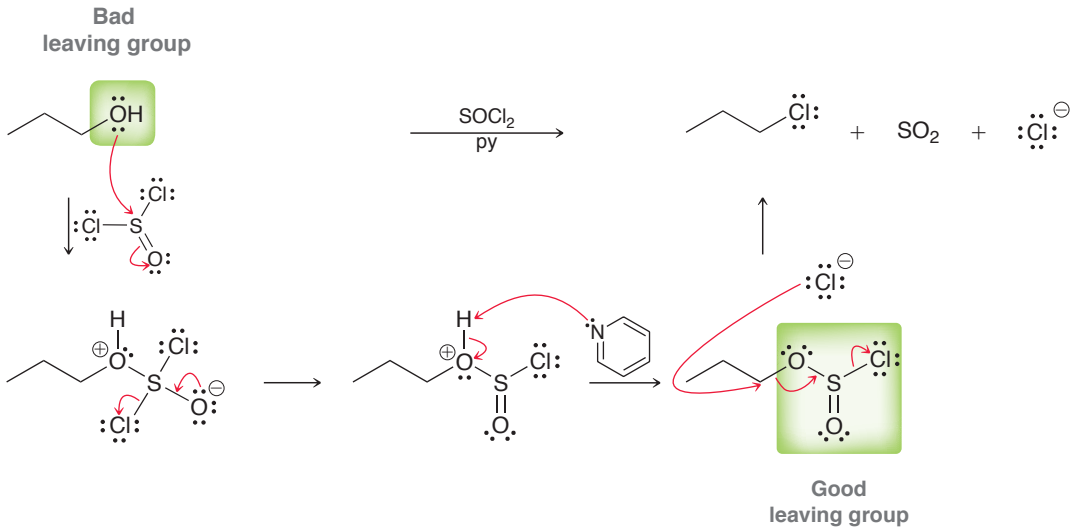


3. Primary and secondary alcohols react with $SOCl_2$ or PBr_3 via an S_N2 process.



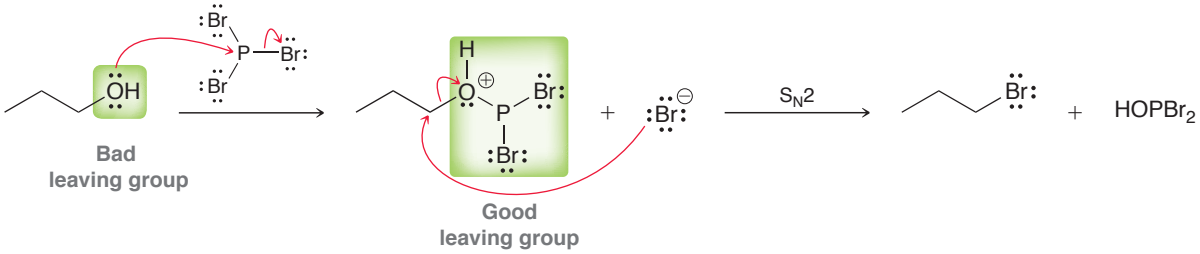
The mechanisms for these two pathways are very similar. The first few steps convert a bad leaving group into a good leaving group, then the halide attacks in an S_N2 process (Mechanism 13.6).

MECHANISM 13.6 THE REACTION BETWEEN $SOCl_2$ AND AN ALCOHOL



The reaction mechanism for PBr_3 has similar characteristics, including conversion of the hydroxyl group into a better leaving group followed by nucleophilic attack (Mechanism 13.7).

MECHANISM 13.7 THE REACTION BETWEEN PBr_3 AND AN ALCOHOL



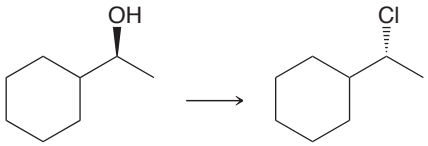
Notice the similarity among all of the S_N2 processes that we have seen in this section. All involve the conversion of the hydroxyl group into a better leaving group followed by nucleophilic attack. If any of these reactions occurs at a chirality center, inversion of configuration is to be expected.

SKILLBUILDER

13.6 PROPOSING REAGENTS FOR THE CONVERSION OF AN ALCOHOL INTO AN ALKYL HALIDE

LEARN the skill

Identify the reagents you would use to accomplish the following transformation.



SOLUTION

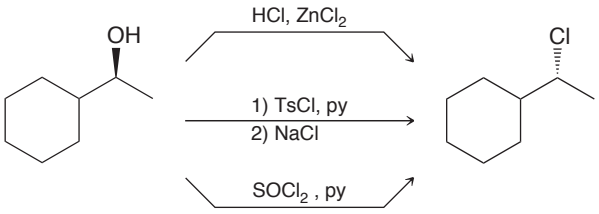
This transformation is a substitution process, so we must decide whether to use S_N1 conditions or S_N2 conditions. The key factor is the substrate. The substrate here is secondary, so either S_N1 or S_N2 could theoretically work. However, we don't have a choice in this case. The transformation requires inversion of configuration, which can only be accomplished via S_N2 (an S_N1 process would give racemization, as we saw in Section 7.5). In addition, the substrate would likely undergo a carbocation rearrangement if subjected to S_N1 conditions. For both of these reasons, an S_N2 process is required.

STEP 1 Analyze the substrate.

STEP 2 Analyze the stereochemical outcome and determine whether S_N2 is required.

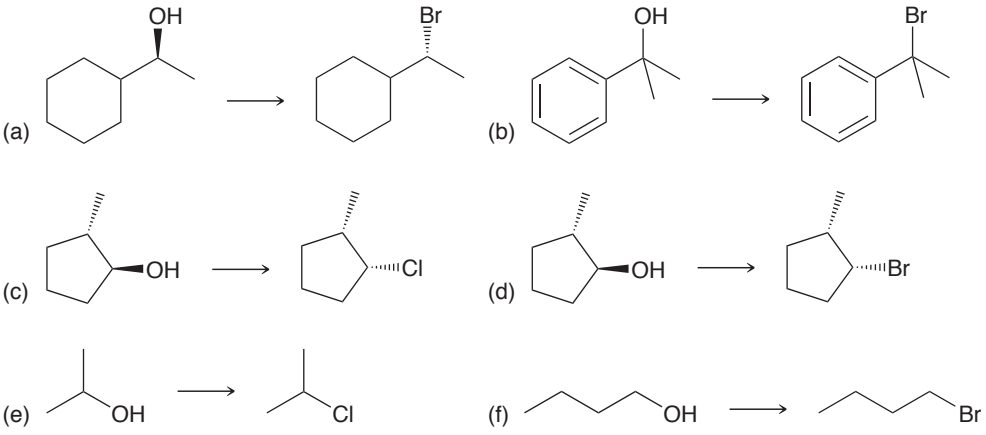
We saw three different reagents for performing an S_N2 process. With all three, the hydroxyl group is converted into a better leaving group, followed by nucleophilic attack. Any of the three methods can be used.

STEP 3 Identify reagents that achieve the process determined in step 2.



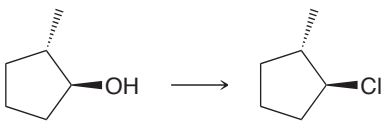
PRACTICE the skill

13.19 Identify the reagents you would use to accomplish each of the following transformations.



APPLY the skill

13.20 Identify the reagents you would use to accomplish the following transformation.



need more **PRACTICE?** **Try Problems 13.35a–c, 13.44f, 13.52r**

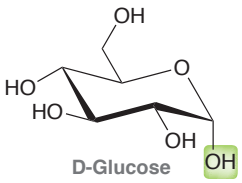
PRACTICALLYSPEAKING

Drug Metabolism

Drug metabolism refers to the set of reactions by which drugs are converted into other compounds that are either used by the body or excreted. Our bodies dispose of the medications we ingest by a variety of metabolic pathways.

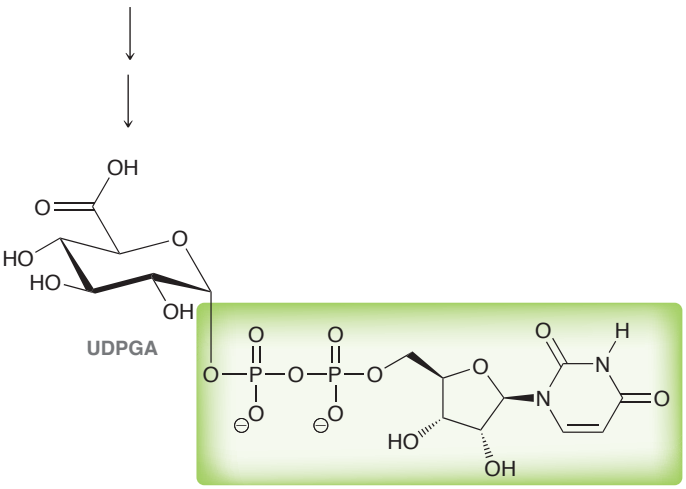
One common metabolic pathway is called glucuronic acid conjugation, or simply glucuronidation. This process is very similar to all of the S_N2 processes that we investigated in the previous section. Specifically, a bad leaving group (hydroxyl) is first converted into a good leaving group, followed by nucleophilic attack. Glucuronidation exhibits the same two key steps.

1. Formation of UDPGA (uridine-5′-diphospho-α-D-glucuronic acid) from glucose involves conversion of a bad leaving group into a good leaving group.



D-Glucose

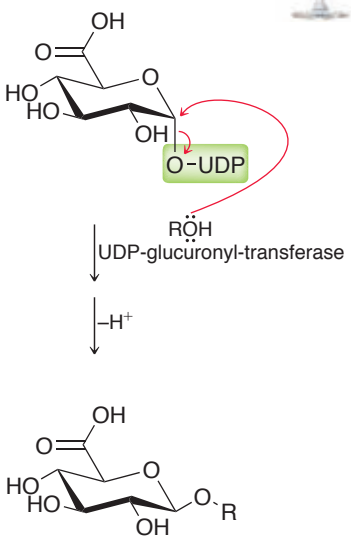
Bad LG



Good LG (called UDP)

UDPGA is a compound with a very good leaving group. This large leaving group is called UDP. In this transformation, one of the hydroxyl groups in glucose has been converted into a good leaving group.

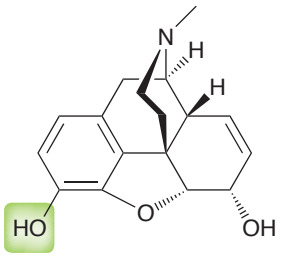
2. Next, an S_N2 process occurs in which the drug being metabolized (such as an alcohol) attacks UDPGA, expelling the good leaving group.



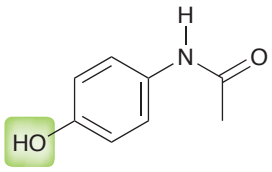
***β*-Glucuronide**

This S_N2 process requires an enzyme (a biological catalyst) called UDP-glucuronyl transferase. The reaction proceeds via inversion of configuration (as expected of an S_N2 process) to produce a β-glucuronide, which is highly water soluble and is readily excreted in the urine.

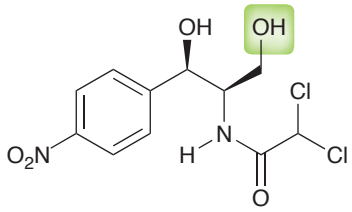
Many functional groups undergo glucuronidation, but alcohols and phenols are the most common classes of compounds that undergo this metabolic pathway. For example, morphine, acetaminophen, and chloramphenicol are all metabolized via glucuronidation:



Morphine
An opiate analgesic used to treat severe pain



Acetaminophen
An analgesic (pain-relieving) and antipyretic (fever-reducing) agent, sold under the trade name Tylenol™

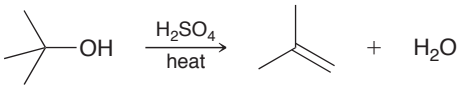


Chloramphenicol
An antibiotic used in eye drops to treat bacterial conjuctivitis

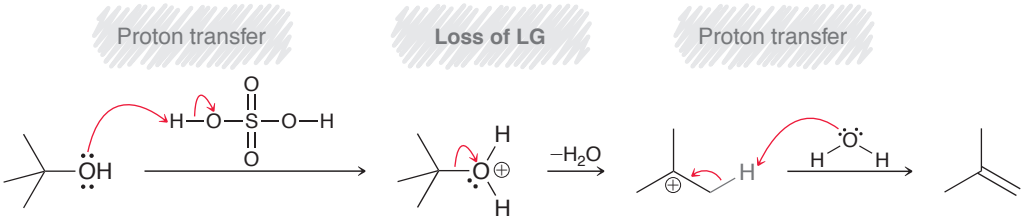
In each of these three compounds, the highlighted hydroxyl group attacks UDPGA. Glucuronidation is the main metabolic pathway by which these drugs are eliminated from the body.

E1 and E2 Reactions with Alcohols

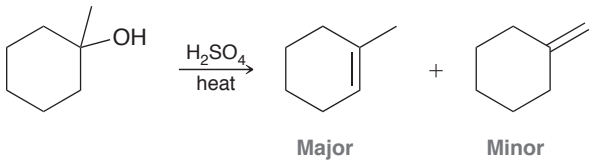
Recall from Section 8.9 that alcohols undergo elimination reactions in acidic conditions.



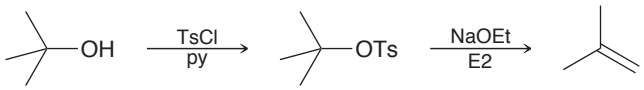
This transformation follows an E1 mechanism:



Recall that the two core steps of an E1 mechanism are loss of a leaving group followed by a proton transfer. However, when the starting material is an alcohol, an additional step is first required in order to protonate the hydroxyl group. This reaction proceeds via a carbocation intermediate and is therefore best for tertiary alcohols. Also recall that elimination generally favors the more substituted alkene.



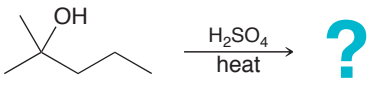
This transformation can also be accomplished via an E2 pathway if the hydroxyl group is first converted into a better leaving group, such as a tosylate. A strong base can then be employed to accomplish an E2 reaction.

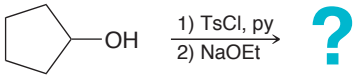


The E2 process also generally produces the more substituted alkene, and no carbocation rearrangements are observed in E2 processes.

CONCEPTUAL CHECKPOINT

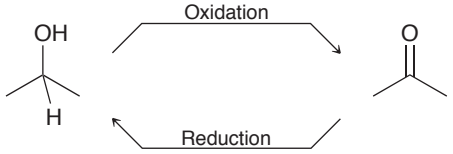
13.21 Predict the products for each of the following transformations.

(a) 

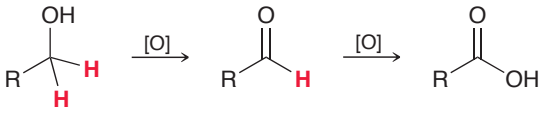
(b) 

13.10 Reactions of Alcohols: Oxidation

In Section 13.4, we saw that alcohols can be formed via a reduction process. In this section, we will explore the reverse process, called **oxidation**, which involves an increase in oxidation state.



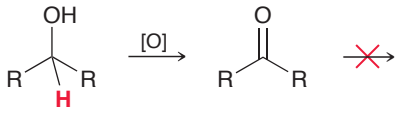
The outcome of an oxidation process depends on whether the starting alcohol is primary, secondary, or tertiary. Let's first consider the oxidation of a primary alcohol.



Primary alcohol Aldehyde Carboxylic acid

Notice that a primary alcohol has two protons at the α position (the carbon atom bearing the hydroxyl group). As a result, primary alcohols can be oxidized twice. The first oxidation produces an aldehyde, and then oxidation of the aldehyde produces a carboxylic acid.

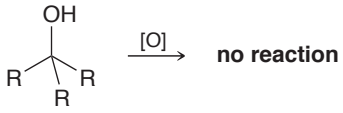
Secondary alcohols only have one proton at the α position so they can only be oxidized once, forming a ketone.



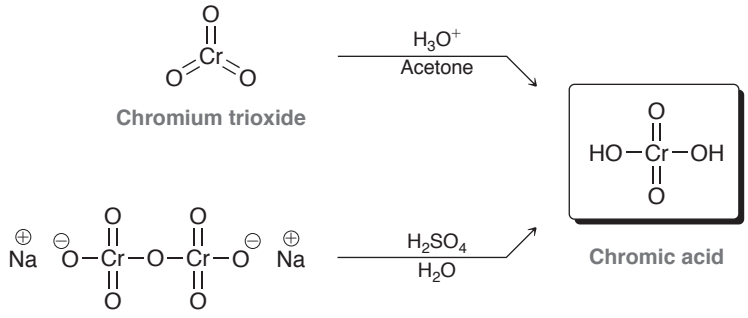
Secondary alcohol Ketone

LOOKING AHEAD
For an exception to this general rule, see Section 20.11, where we will learn about a special oxidizing reagent that can oxidize a ketone to form an ester.

Generally speaking, the ketone is not further oxidized. Tertiary alcohols do not have any protons at the α position, and as a result, they generally do not undergo oxidation:



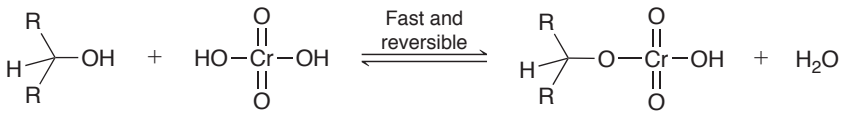
A large number of reagents are available for oxidizing primary and secondary alcohols. The most common oxidizing reagent is chromic acid (H_2CrO_4), which can be formed either from chromium trioxide (CrO_3) or from sodium dichromate ($Na_2Cr_2O_7$) in aqueous acidic solution.



The mechanism of oxidation with chromic acid has two main steps (Mechanism 13.8). The first step involves formation of a chromate ester, and the second step is an E2 process to form a carbon-oxygen π bond (rather than a carbon-carbon π bond).

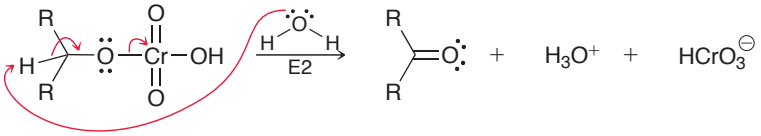
MECHANISM 13.8 OXIDATION OF AN ALCOHOL WITH CHROMIC ACID

STEP 1



Chromate ester

STEP 2

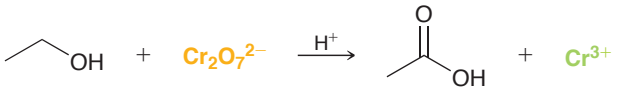


Chromate ester

PRACTICALLYSPEAKING

Breath Tests to Measure Blood Alcohol Level

Ethanol is a primary alcohol. Therefore, ethanol will react with potassium dichromate in acidic conditions to produce acetic acid.

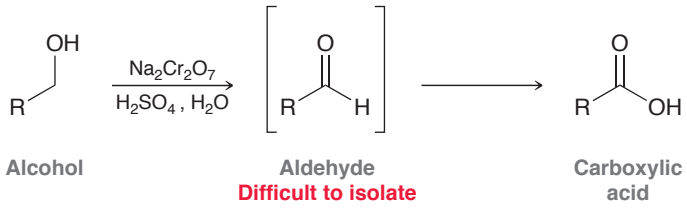


Ethanol | Reddish orange | Acetic acid | Green

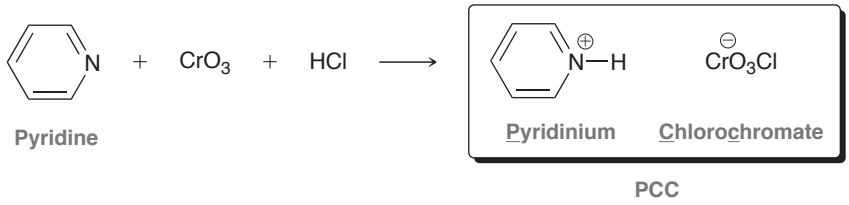
In the process, ethanol is oxidized, and the chromium reagent is reduced. The new chromium compound is a different color, and therefore, the progress of the reaction can be monitored by the color change from reddish-orange to green. This reaction formed the basis for many of the early breath tests that assessed the level of blood alcohol. Breath tests that utilize this reaction are still commercially available. The test consists of a tube, where one end is fitted with a mouthpiece and the other end has a bag. The inside of the tube contains sodium dichromate that is adsorbed onto the surface of an inert solid, such as silica gel. As the user blows air through the tube and fills up the bag, the alcohol in the user's breath reacts with the oxidizing agent in the tube, and a color change occurs. The extent of the color change gives an indication of the blood alcohol content.

The Breathalyzer™ is based on the same idea, but it is more accurate. A measured volume of breath is bubbled through an aqueous acidic solution of potassium dichromate, and the change in color is measured with an ultraviolet-visible (UV-VIS) spectrophotometer (Section 17.11). Contrary to popular belief, it is not possible to beat the test by sucking a breath mint or rinsing with a breath freshener. These techniques might fool a person, but they won't fool the potassium dichromate.

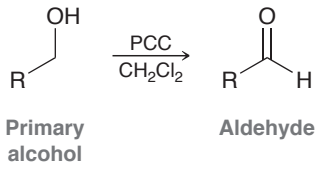
When a primary alcohol is oxidized with chromic acid, a carboxylic acid is obtained. It is generally difficult to control the reaction to produce the aldehyde.



In order to produce the aldehyde as the final product, it is necessary to use a more selective oxidizing reagent, one that will react with the alcohol but will not react with the aldehyde. Many such reagents are available, including pyridinium chlorochromate (PCC). PCC is formed from the reaction between pyridine, chromium trioxide, and hydrochloric acid.

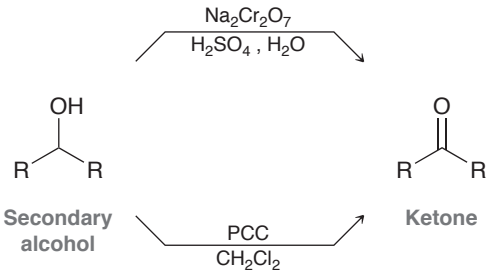


When PCC is used as the oxidizing agent, an aldehyde is produced as the major product. Under these conditions, the aldehyde is not further oxidized to the carboxylic acid.



Methylene chloride (CH_2Cl_2) is typically the solvent used when PCC is employed.

Secondary alcohols are oxidized only once to form a ketone, which is stable under oxidizing conditions. Therefore, a secondary alcohol can be oxidized either with chromic acid or with PCC.



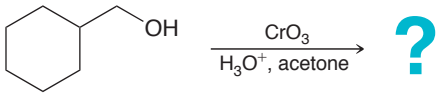
Sodium dichromate is less expensive, but PCC is more gentle and often preferred if other sensitive functional groups are present in the compound.

SKILLBUILDER

13.7 PREDICTING THE PRODUCTS OF AN OXIDATION REACTION

LEARN the skill

Predict the major organic product of the following reaction.

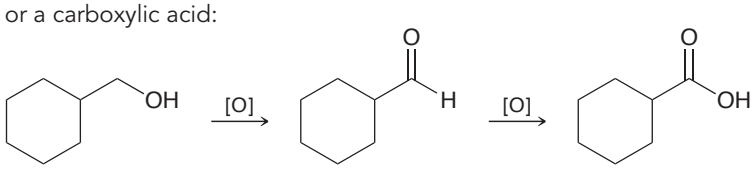


SOLUTION

In order to predict the product, identify whether the alcohol is primary or secondary. In this case, the alcohol is primary, and therefore, we must decide whether the process will produce an aldehyde or a carboxylic acid:

STEP 1 Identify whether the alcohol is primary or secondary.

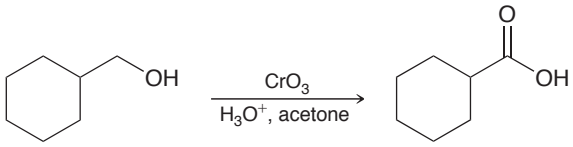
STEP 2 If the alcohol is primary, consider whether an aldehyde or a carboxylic acid is obtained.



Aldehyde **Carboxylic acid**

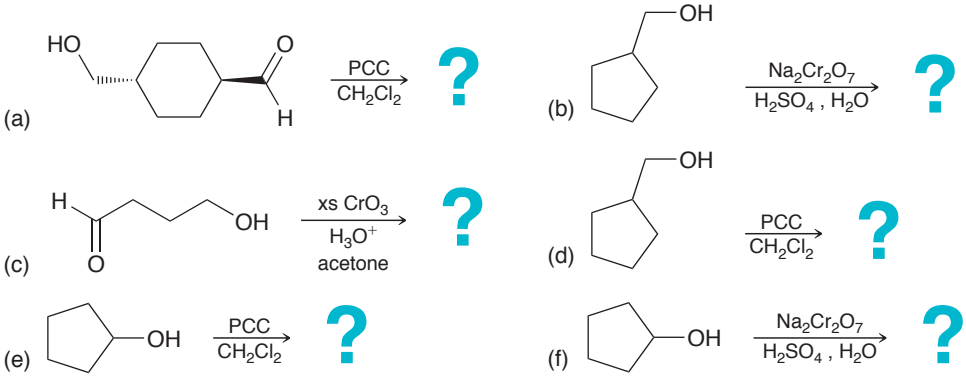
The product is determined by the choice of reagent. Chromium trioxide in acidic conditions forms chromic acid, which will oxidize the alcohol twice to give the carboxylic acid. In order to stop at the aldehyde, PCC would be used instead.

STEP 3 Draw the product.



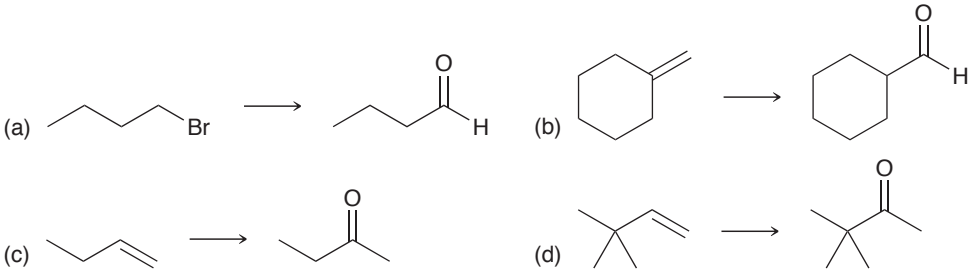
PRACTICE the skill

13.22 Predict the major organic product for each of the following reactions.



APPLY the skill

13.23 Propose a synthesis for each of the following transformations.



need more **PRACTICE?** **Try Problems 13.35e–f, 13.37, 13.48**