Oxidations of Alcohols

Oxidation = Addition of O-atoms (or other electronegative atoms such as Br_2), or removal of H-atoms.
Reduction: *vice versa*.

Alcohol oxidation outcome depends on the type of alcohol:

Prim. alcohols	**aldehydes**	**carboxylic acids**
Secon. alcohols	**ketones**	
Tert. alcohols		

Usually, the oxidation of the aldehyde to the carboxylic acid is faster than is the oxidation of the primary alcohol to the aldehyde. Aldehydes usually cannot be made from primary alcohols.

Oxidation with Chromium(VI)

Reagents:

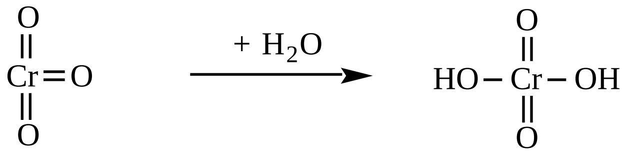
The reactive species: chromic acid, H_2CrO_4
CrO_3 // dilute H_2SO_4
$K_2Cr_2O_7 = K_2O + 2\ CrO_3$ // dilute H_2SO_4
$Na_2Cr_2O_7 = Na_2O + 2\ CrO_3$ // dilute H_2SO_4

Jones reagent: CrO_3 // dilute H_2SO_4. Dripped into acetone solution of the organic compound that is to be oxidized.

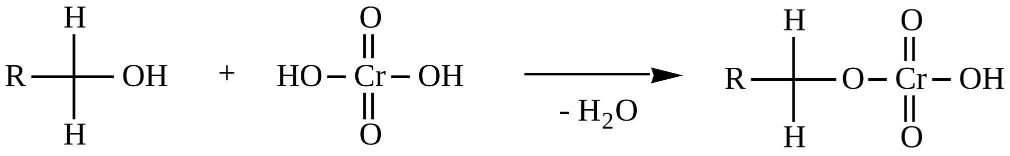
These reagents are Cr(VI) and they all are yellow or yellow-orange and they are being reduced to green Cr(III).

Mechanism for Oxidation with CrO_3

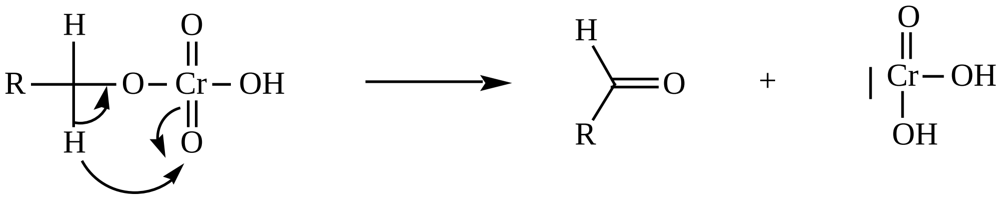
Step 1: Form chromic acid by addition of water to CrO_3



Step 2: Alcohol and chromic acid form an **inorganic ester** via **condensation** (loss of water).



Step 3: Transfer of one H-atom from the alcohol head-C to a chromate oxygen. This is the oxidation step! Cr(IV) is now Cr(IV).



Oxidation with PCC: Aldehydes from Alcohols

PCC = Pyridinium chlorochromate = combination of pyridine (azabenzene), HCl, and CrO_3. HCl protonates the pyridine and the chloride coordinates to the CrO_3, CrO_3Cl^-.

Used **in dichloromethane solution**. This is the key, in the absence of water the overoxidation of aldehyde to carboxylic acid does not occur.

Example: Propanol to propanal.

Derivatives of Alcohols

Alkoxides

Deprotonation with Strong Bases

The simple hydrides all are strong bases: LiH, NaH, KH
LDA = lithium diisopropylamide LiN(*i*-Pro)$_2$
BuLi = buthyl lithium (comes as *n*- and *t*-BuLi)
The reaction of any of these strong bases with alcohols yields complete alkoxide formation.

Deprotonation with Alkalimetals

Alcohols react with alkalimetals to form alkoxides and H_2.
The rate of reaction depends on R in ROH and decreases in the order

R = H >> Me > primary > secondary > tertiary

<u>Example 1:</u> Fast formation of the ethoxide

$$2\ CH_3CH_2OH\ +\ 2\ Na\ \text{------>}\ 2\ CH_3CH_2O^-Na^+\ +\ H_2$$

<u>Example 2:</u> Slow reaction with 2-methyl-2-propanol even with K (used to destroy K in lab)

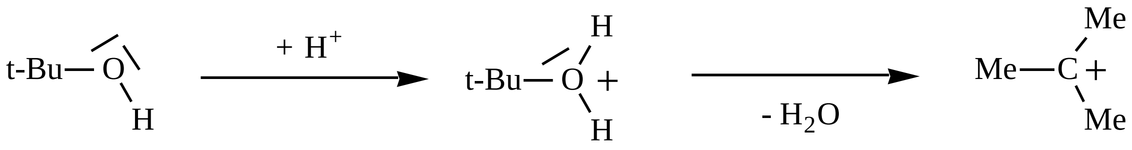
$$2\ (CH_3)_3COH\ +\ 2\ K\ \text{------>}\ 2\ (CH_3)_3CO^-K^+\ +\ H_2$$

Acid-Catalyzed S_N and E Reactions of Alcohols: Alkyloxonium Ions

Principle

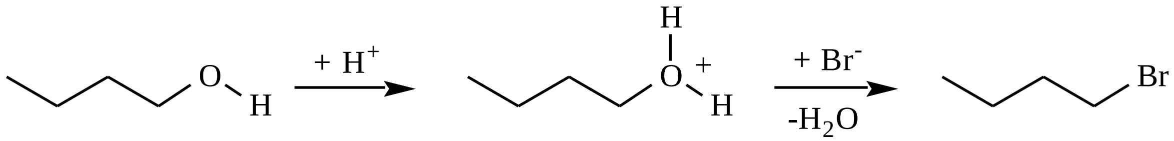
The hydroxyl group is a poor leaving group.

Protonate the hydroxyl group — that is form the alkyloxonium ion — and use water as a very good leaving group. This step is used in substitution and elimination reactions and in both types (uni- end bimolecular).



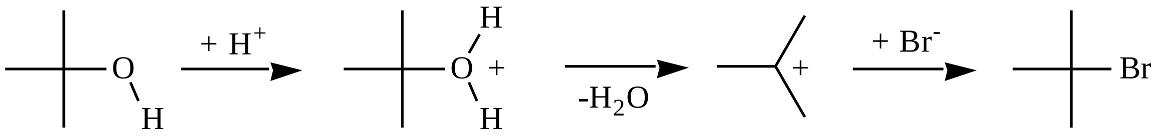
Application 1: Primary Halides from Alcohols

Why is this important? Remember that the primary halides are hard to make by radical chain halogenation. So, now we make the primary alcohol (e.g. from an aldehyde by reduction) and then do a clean S_N2 with Hbr.



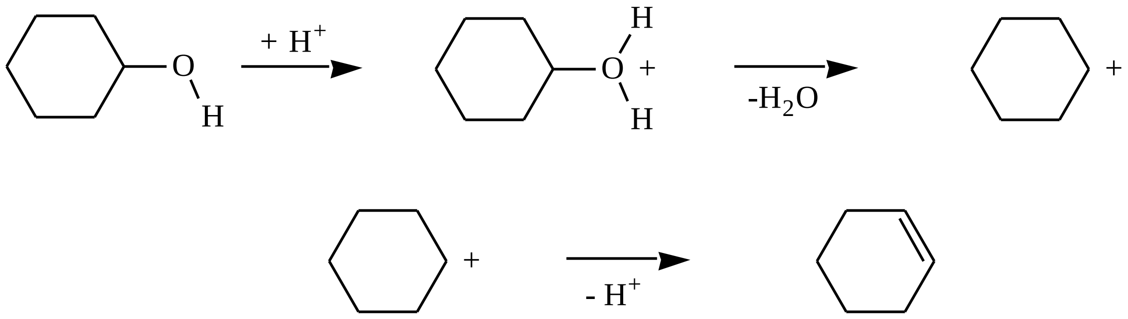
Application 2: Tertiary Halides from Alcohol

Use HBr as the acid. The proton catalyzes the water elimination. The bromide is a good nucleophile and does the substitution. In this case, the reaction is S_N1.



Application 3: Acid-Catalyzed Elimination

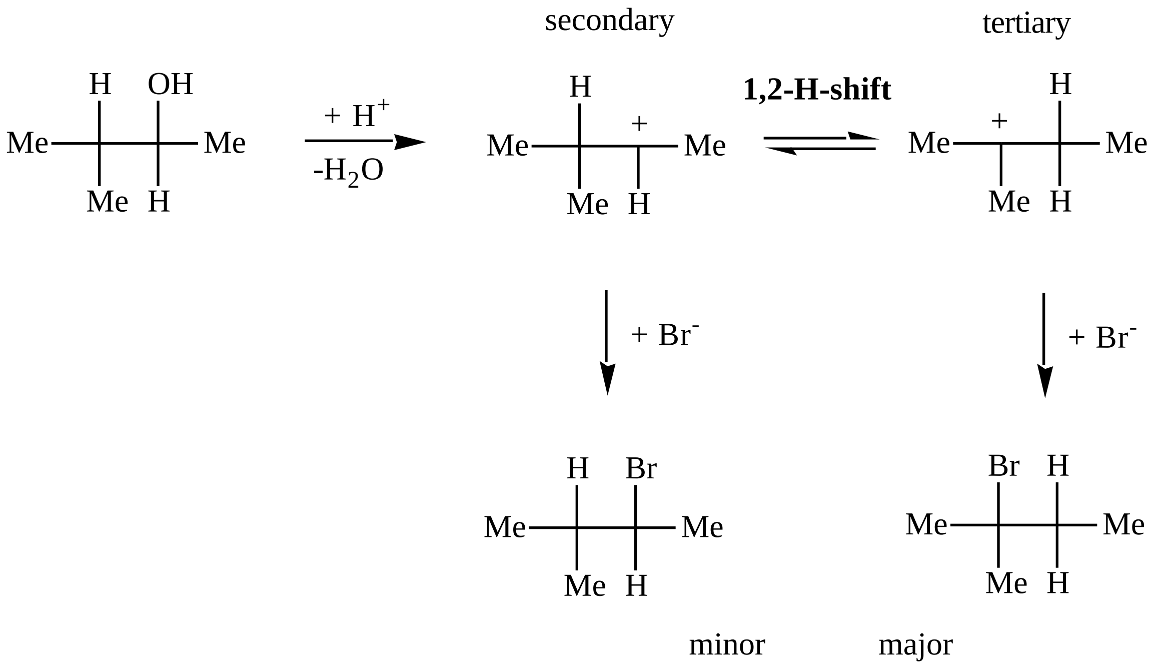
Use H_2SO_4 as the acid at 130 ˚C. The proton catalyzes the water elimination. The sulfate is a not such a good nucleophile and does not do the substitution. This reaction is E1.



Carbocation Rearrangements

The Classical Example for **Hydride Shift**:
Secondary to Tertiary in S_N1

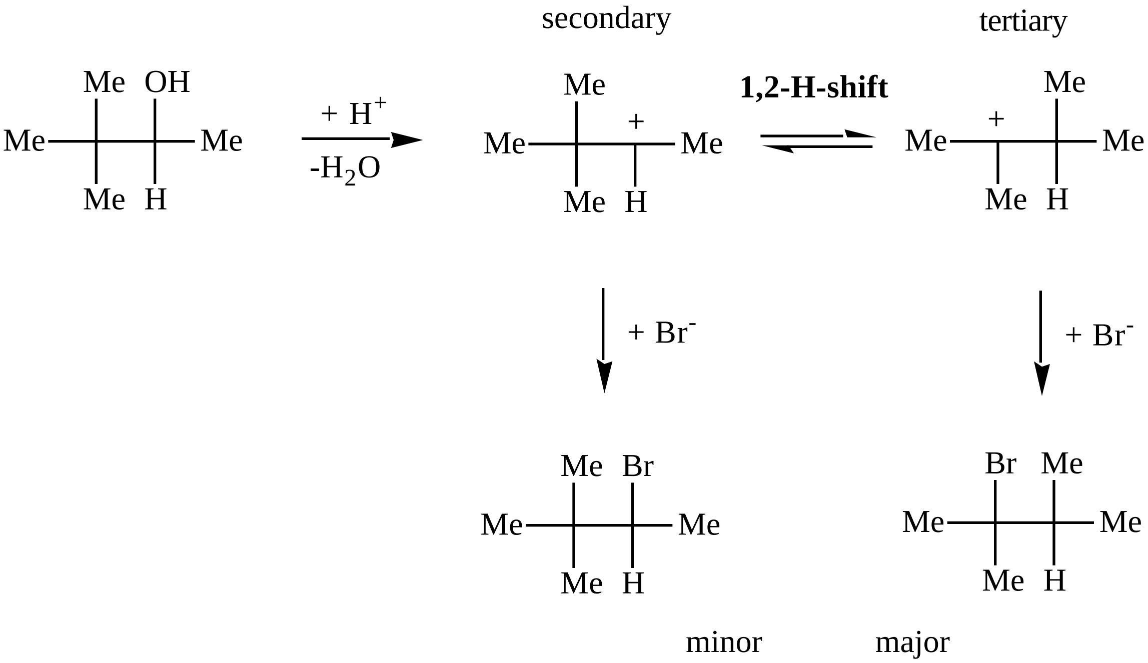
The acid-catalyzed dehydration of 3-methyl-2-butanol leads to a secondary carbocation. This cation can undergo a **hydride shift** to form the thermodynamically more stable tertiary carbocation. Hence, the reaction of HBr with 3-methyl-2-butanol yields two products and the major product is the one that was generated by the rearrangement.



The Classical Example for **Alkyl Shift**:

Secondary to Tertiary in S_N1

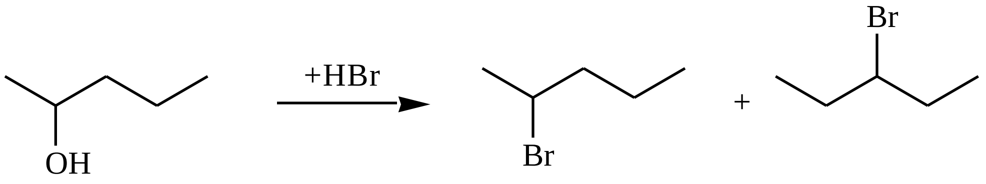
The acid-catalyzed dehydration of 3,3-dimethyl-2-butanol leads to a secondary carbocation. This cation **cannot** undergo a **hydride shift** but it **can** undergo a **alkyl shift** to form the thermodynamically more stable tertiary carbocation. Hence, the reaction of HBr with 3,3-dimethyl-2-butanol yields two products and the major product is the one that was generated by the rearrangement.



This is very much the same as the previous H-shift example. The alkyl shifts happen when the H-shifts can't help.

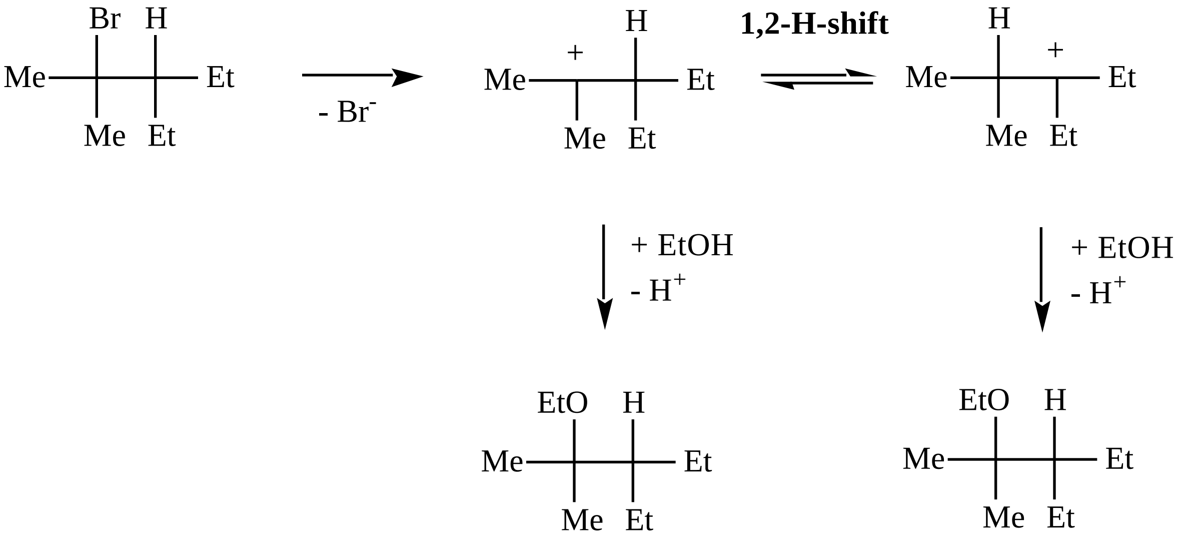
Secondary to Secondary Rearrangements in S_N1

Equilibrium may form between several secondary carbenium ion.



Note that alkyl shifts won’t work in such a case because they would have to produce a primary carbocation and nothing would be gained!

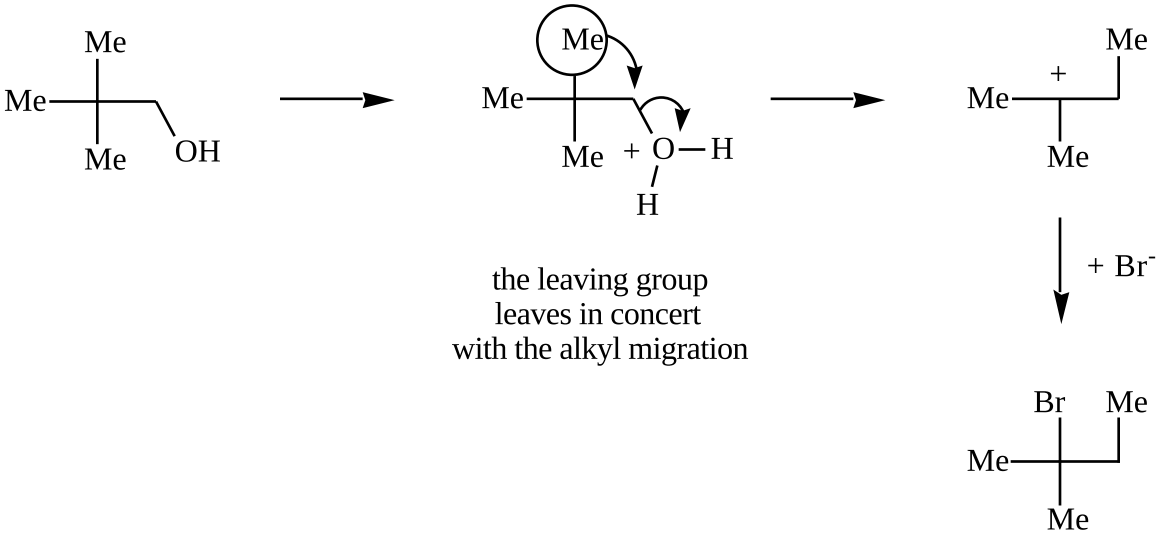
Tertiary to Tertiary Rearrangements in S_N1: Solvolysis of an alkylbromide



About Rearrangements Involving Primary Carbocations

This is very rare and it is not expected to happen! The primary substrates do not react via a unimolecular reaction. So we do not expect a cartion to be formed in the first place. And this is right. There is however way for such substrates to realize *de facto* rearrangements.

The rearranging alkyl group acts as the nucleophile in the S_N2 reaction that kicks out the leaving group. The product of that S_N2 reaction is the rearranged carbenium ion which then adds a nucleophile.



the leaving group
leaves in concert
with the alkyl migration

Organic and Inorganic Esters of Alcohols

Ester = Condensation product between an acid and an alcohol.

R-C(O)-**OH** + **HO**-R' <==> R-C(O)-O-R' + $\mathbf{H_2O}$

Organic Ester = Carboxylic acid and alcohol
Inorganic Ester = Inorganic acid and alcohol

Often the ester is made not directly from the acid but with the use of an **acid halide**. An acid halide is the derivative of the acid in which an OH group has been replaced by a halogen.

R-C(O)-**OH** + **HO**-R' <===> R-C(O)-O-R' + $\mathbf{H_2O}$
R-C(O)-**X** + **HO**-R' <===> R-C(O)-O-R' + **HX**

Inorganic acids have OH groups and can formally react just like the organic acids (e.g. replace the OH by the OR). Again, most usually the inorganic ester is made not directly from the acid but with the use of an **acid halide**. The example shows sulfonates.

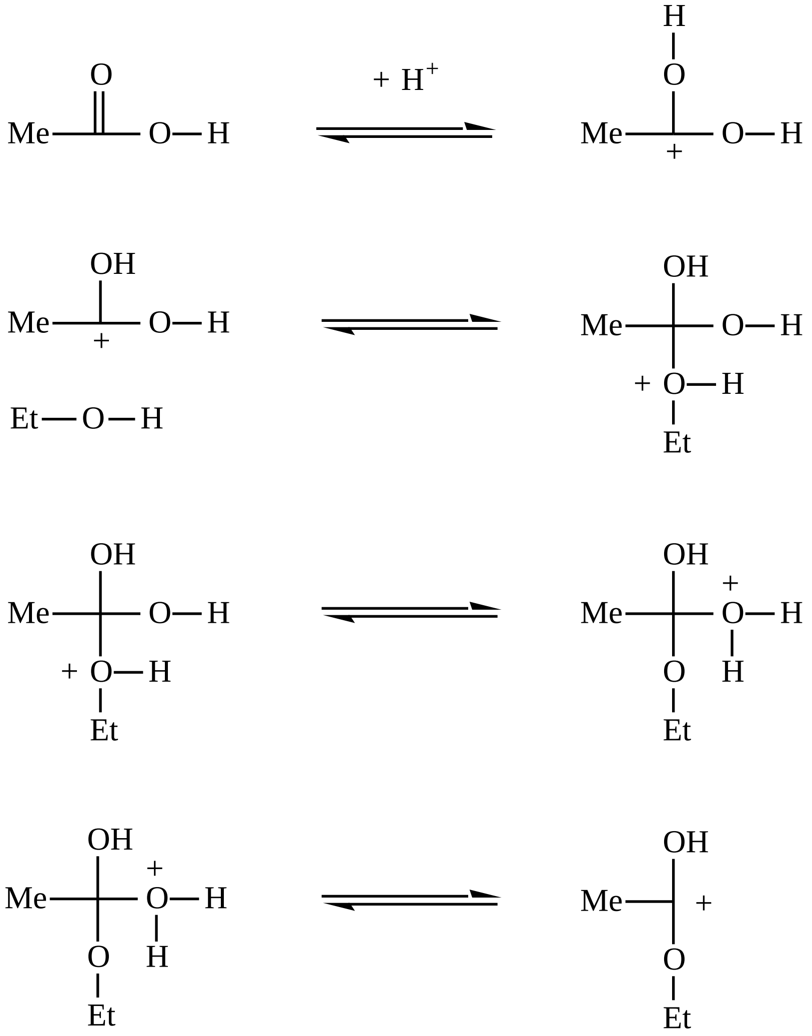
R-SO_2-**OH** + **HO**-R' <===> R-SO_2-O-R' + $\mathbf{H_2O}$
R-SO_2-**X** + **HO**-R' <===> R-SO_2-O-R' + **HX**

<u>Examples of Inorganic Acids:</u> Chromic acid make chromates. Phosphoric acid make phosphates. Sulfuric acid makes sulfates. Sulfonic acids make sulfonates.

Formation of Organic Esters via "Esterification"

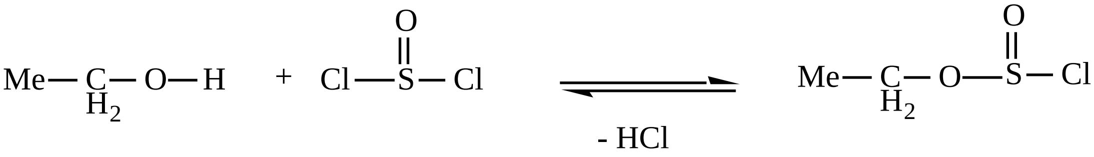
Acid-catalyzed reaction of alcohol with carboxylic acid. The mechanism is illustrated for acetic acid and ethanol. The reaction will be discussed in detail in Chemistry 212.

Step 1: Protonate the carbonyl-O of acetic acid.
Step 2: Add the alcohol-O and make an alkyloxonium ion.
Step 3: Proton transfer to one of the hydroxyl-O.
Step 4: Eliminate the hydroxyl group as water.
Step 5: Deprotonate at OH. (not shown)

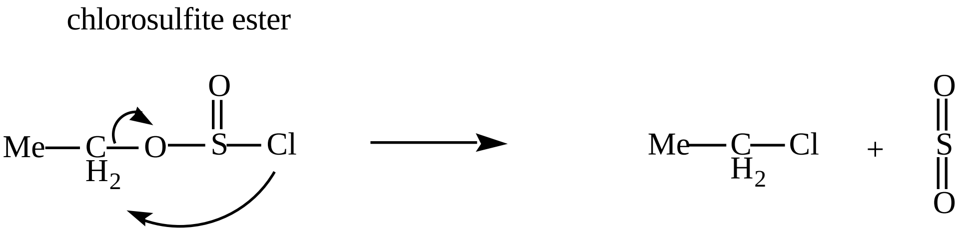


Thionyl Chloride in Chloroalkane Synthesis

Thionyl chloride is $O{=}SCl_2$. The dichloride of **sulfurous** acid $O{=}S(OH)_2$ (note the contrast to sulfuric acid which is H_2SO_2). Thionyl chloride reacts with alcohols to form an inorganic ester under HCl elimination.



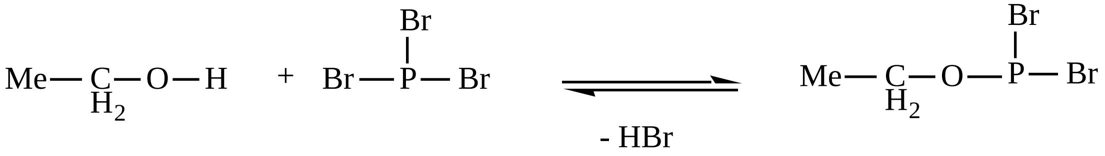
The HCl generated then initiates a bimolecular nucleophilic substitution of the inorganic ester. This ester is a very good leaving group because it forms SO_2 and HCl.



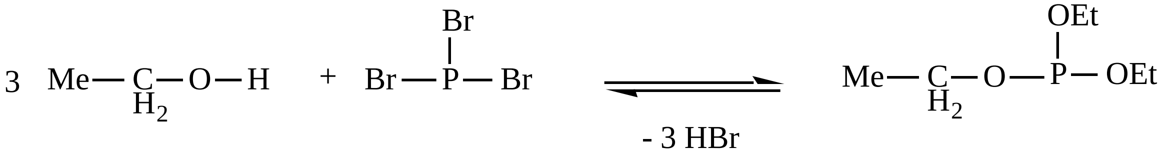
The chloride attack is intramolecular. Chiral alcohols show retention.

Phosphorus Tribromide in Bromoalkane Synthesis

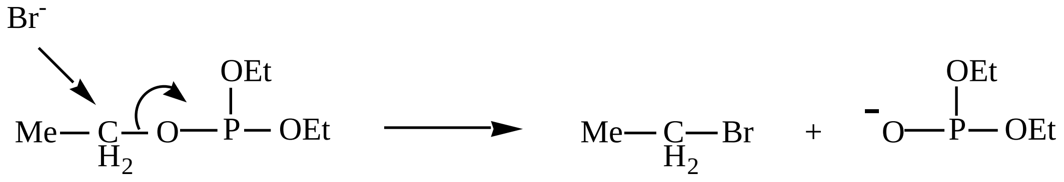
Phosphorous tribromide is PBr_3. The tribromide of **hypophosphorous** acid $P(OH)_3$ or $HP(O)(OH)_2$. Phosphorous tribromide reacts with alcohols to form an inorganic ester under HBr elimination.



This reaction can be repeated until all P-Br bonds are replaced by the bonds to the alcohol. This leads to the **triester**.

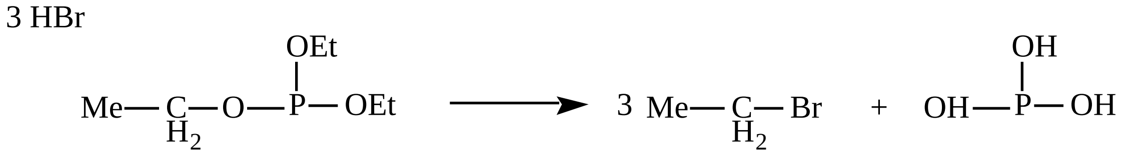


The HBr generated then initiates a bimolecular nucleophilic substitution of the inorganic ester. This ester is a very good leaving group. Only the first nucleophilic attack is shown. The other two esters groups can be attacked in the same way and the overall reaction is shown below.



$$\mathrm{Br^-} + \mathrm{Me{-}CH_2{-}O{-}P(OEt){-}OEt} \longrightarrow \mathrm{Me{-}CH_2{-}Br} + \mathrm{{}^-O{-}P(OEt){-}OEt}$$

Overall reaction:



$$3\ \mathrm{HBr} \quad \mathrm{Me{-}CH_2{-}O{-}P(OEt){-}OEt} \longrightarrow 3\ \mathrm{Me{-}CH_2{-}Br} + \mathrm{OH{-}P(OH){-}OH}$$

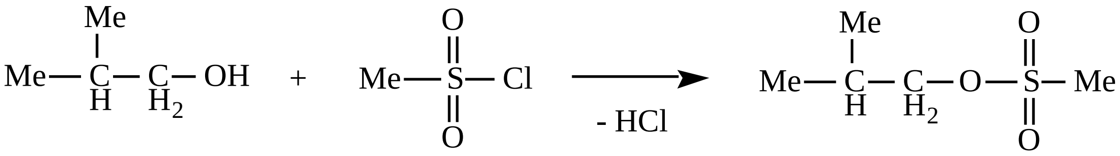
Alkylsulfonates in Substitution Reactions

Sulfonates are good leaving groups in S_N (and E) reactions.

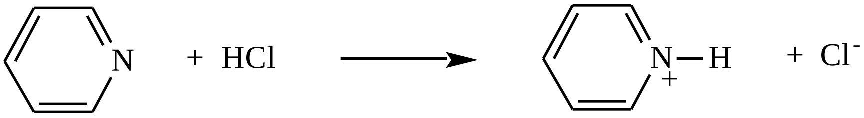
Sulfonates are best prepared by reaction of an alcohol with a **sulfonyl chloride**.

The reaction generates HCl and pyridine is used to capture the HCl before it can do an S_N (and E) reactions. The pyridine binds the HCl forming pyridinium chloride.

Example: 2-methyl-1-propanol and Mesyl chloride (methanesulfonyl chloride)



$$\mathrm{Me{-}\overset{Me}{\underset{H}{C}}{-}\underset{H_2}{C}{-}OH} + \mathrm{Me{-}\overset{O}{\underset{O}{S}}{-}Cl} \xrightarrow[\text{- HCl}]{} \mathrm{Me{-}\overset{Me}{\underset{H}{C}}{-}\underset{H_2}{C}{-}O{-}\overset{O}{\underset{O}{S}}{-}Me}$$



The sulfonates are very well suited for the preparation of **iodides** and of **mercaptanes**.

Example 1: Mesylate of 1-propanol reacts with iodide

Example 2: Tosylate of 2-propanol reacts with EtS^-