Introduction to Alcohols and Ethers

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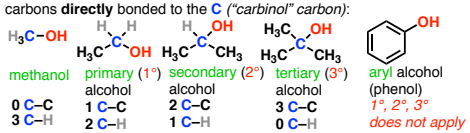
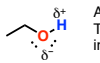
Alcohols

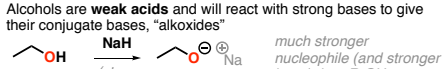
Alkyl *("aliphatic")* alcohols are classified by the number of carbons **directly** bonded to the C *("carbinol" carbon)*:



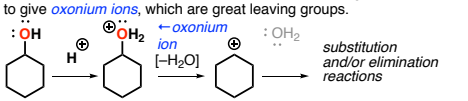


Alcohols have relatively high boiling points. The hydroxy group (OH) is **polar** and can participate in **hydrogen bonding**.

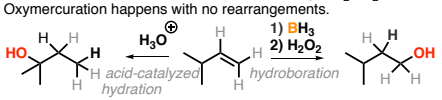
Alcohols are **weak acids** and will react with strong bases to give their conjugate bases, "alkoxides"



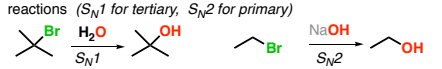
Alcohols are also weak bases and will react with strong acids to give *oxonium ions*, which are great leaving groups.



Alcohols can be synthesized from alkenes via hydroboration, acid-catalyzed hydration, or oxymercuration ($HgOAc_2$ / H_2O) Oxymercuration happens with no rearrangements.



They can also be synthesized from alkyl halides via substitution reactions *(S_N1 for tertiary, S_N2 for primary)*

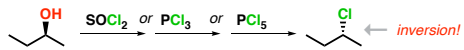


Conversion of Alcohols to Good Leaving Groups

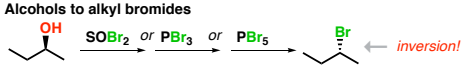
The hydroxide group (HO^-) of alcohols is a strong base and a poor leaving group. Converting the OH to a halogen or "sulfonate" (e.g. OTs or OMs) greatly facilitates substitution & elimination reactions.

Alcohols to alkyl chlorides using $SOCl_2$, PCl_3, or PCl_5

Note that these reactions proceed with *inversion* of stereochemistry.



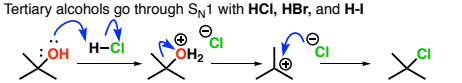
Alcohols to alkyl bromides



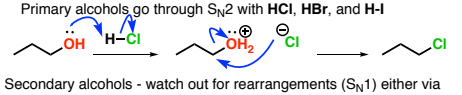
Note that some courses teach that $SOCl_2$ gives *retention* and $SOCl_2$ plus base (e.g. pyridine) gives inversion. *Check with your teacher!*

Alcohols to alkyl halides by using acids

Tertiary alcohols go through S_N1 with **HCl, HBr,** and **H-I**



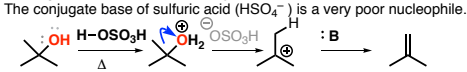
Primary alcohols go through S_N2 with **HCl**, **HBr**, and **H-I**



Secondary alcohols - watch out for rearrangements (S_N1) either via hydride or alkyl shifts. H_2SO_4 will generally give alkenes via E1.

Alcohols to Alkenes with H_2SO_4 or H_3PO_4

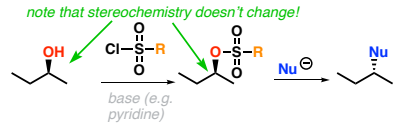
Heating alcohols with H_2SO_4 or H_3PO_4 usually leads to elimination. The conjugate base of sulfuric acid (HSO_4^-) is a very poor nucleophile.

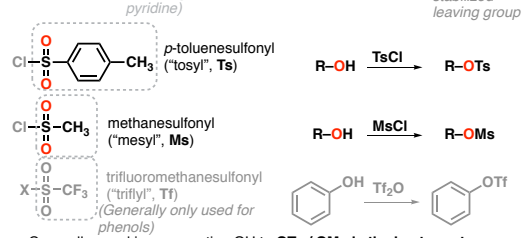


With secondary alcohols, **rearrangement** through hydride or alkyl shifts is very common. Watch out!

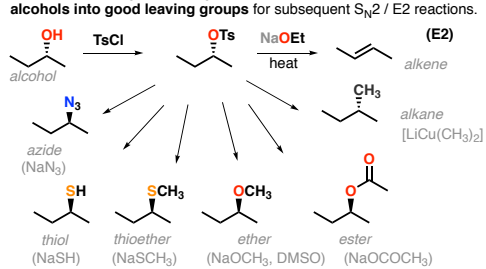
Alcohols to tosylates and mesylates ("sulfonate esters")

Like halides, sulfonates RSO_3^- are great leaving groups. Note that the stereochemistry of the C–O doesn't change (unlike $SOCl_2$ or PBr_3)



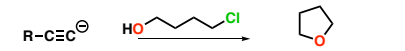


Generally speaking, converting OH to **OTs / OMs is the best way to convert alcohols into good leaving groups** for subsequent S_N2 / E2 reactions.

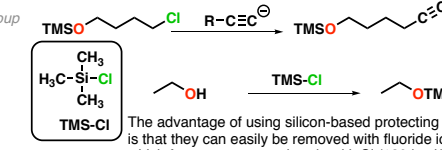


Alcohol protecting groups

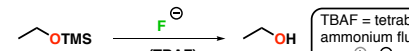
The weakly acidic OH group can interfere with various reagents like this attempted S_N2 with acetylide that instead deprotonates OH



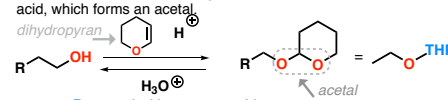
This can be prevented if the OH is "protected" with a blocking group ("protecting group") like trimethylsilyl (TMS)



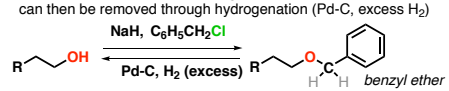
The advantage of using silicon-based protecting groups is that they can easily be removed with fluoride ion, which forms very strong bonds with Si (130 kcal/mol)



Another protecting group for alcohols is tetrahydropyranyl (THP). This can be formed by treating an alcohol with dihydropyran and acid, which forms an acetal.

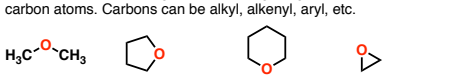


Benzyl ethers are installed through a Williamson ether reaction and can then be removed through hydrogenation (Pd-C, excess H_2)



Ethers

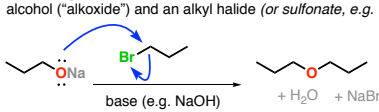
An **ether** is a functional group containing oxygen bonded to two carbon atoms. Carbons can be alkyl, alkenyl, aryl, etc.



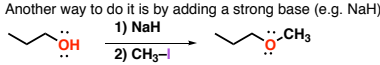
Ethers have lower boiling points than alcohols. The O–C bond is not as polarized as an O–H bond, so there is no hydrogen bonding.

Synthesis of ethers

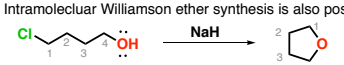
The Williamson ether synthesis is by far the most important method for forming ethers. It is an S_N2 reaction between a deprotonated alcohol ("alkoxide") and an alkyl halide *(or sulfonate, e.g. OTs or OMs)*



Another way to do it is by adding a strong base (e.g. NaH) to an alcohol

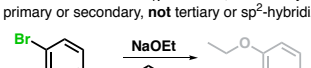


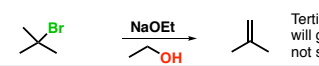
Intramolecluar Williamson ether synthesis is also possible.



What doesn't work?

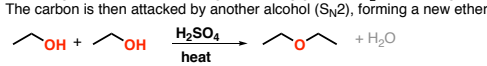
The Williamson is an S_N2 reaction, so the alkyl halide should be primary or secondary, **not** tertiary or sp^2-hybridized





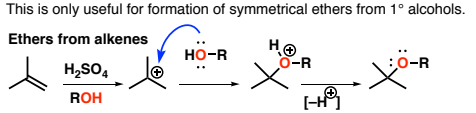
Synthesis of symmetrical ethers from 1° alcohols through dehydration

The OH group is converted to a good leaving group (OH_2) with strong acid. The carbon is then attacked by another alcohol (S_N2), forming a new ether.



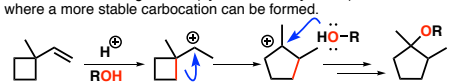
This is only useful for formation of symmetrical ethers from 1° alcohols.

Ethers from alkenes

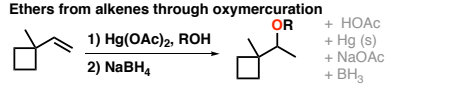


Acid leads to the formation of a carbocation, from the alkene, which is then trapped by the alcohol as solvent.

Carbocation rearrangements (hydride and alkyl shifts) can occur in cases where a more stable carbocation can be formed.



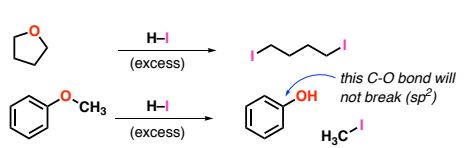
Ethers from alkenes through oxymercuration



The **key difference** is that it does **not** proceed through a carbocation, so **no rearrangements** can occur.

Reactions of Ethers

Ethers are generally unreactive functional groups and don't undergo any significant reactions except for *cleavage* with strong acid.



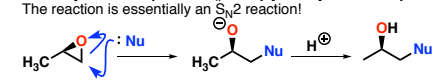
Epoxides

Opening of epoxides

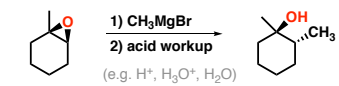
Epoxides are highly reactive towards nucleophiles due to ring strain (about 13 kcal/mol). They will react with nucleophiles under both acidic and basic conditions. However the *patterns* are different.

Opening Under Basic Conditions Is Similar To S_N2

Under basic conditions, nucleophiles will attack epoxides at the ***least sterically hindered position*** (primary [fastest] > secondary > tertiary [slowest]) The reaction is essentially an S_N2 reaction!

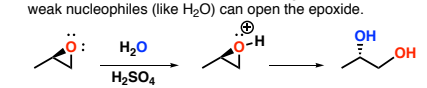


Example: reaction of epoxides with Grignard reagents

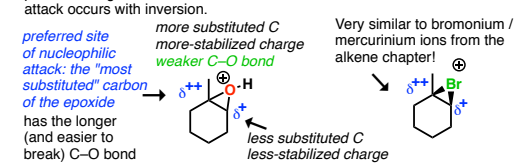


Epoxide Opening Under Acidic Conditions Occurs At The Most Substituted Carbon

Under acidic conditions, the epoxide oxygen is protonated, and weak nucleophiles (like H_2O) can open the epoxide.



The nucleophile will attack the carbon best able to stabilize positive charge - which is the **more substituted** carbon. This attack occurs with inversion.

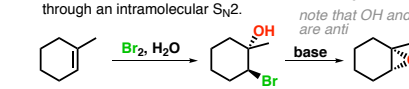


Epoxides from alkenes

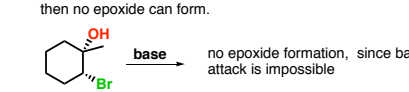
m-CPBA (*meta*-chloroperoxybenzoic acid, a peroxyacid) converts alkenes to epoxides. Other peroxyacids can be used (e.g. CH_3CO_3H)

Epoxides from halohydrins

Halohydrins (formed from alkenes with X_2 / H_2O) can form epoxides upon deprotonation of OH by base (e.g. NaH) through an intramolecular S_N2.



This is an internal S_N2 reaction which occurs with backside attack. If rotation cannot occur (such as in cyclic halohydrins) then no epoxide can form.



Practice Questions on This Material

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