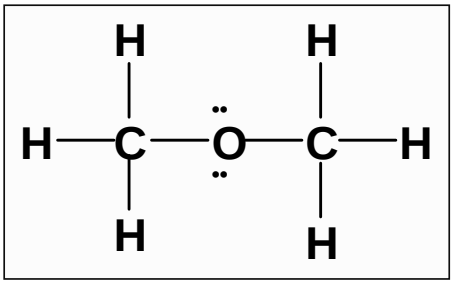
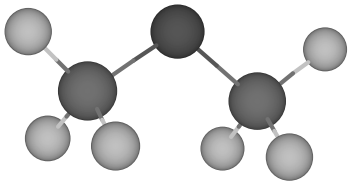
Ethers, Sulfides (omit), and Epoxides

Chapter 11

Structure

- The functional group of an ether is an oxygen atom bonded to two carbon atoms.
  - In dialkyl ethers, **oxygen is *sp*^{3} hybridized** with bond angles of approximately 109.5°.
  - In dimethyl ether, the C-O-C bond angle is 110.3°.



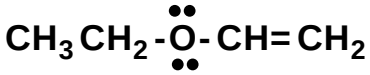


Structure

– In other ethers, the ether oxygen is bonded to an sp^2 hybridized carbon.

– In ethyl vinyl ether, for example, the ether oxygen is bonded to one sp^3 hybridized carbon and one sp^2 hybridized carbon.

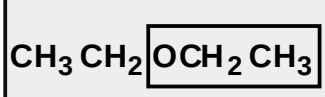
Ethoxyethene
(Ethyl vinyl ether)



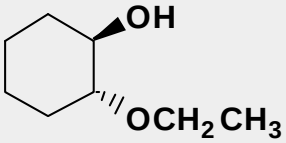
Nomenclature

- IUPAC: the longest carbon chain is the parent.

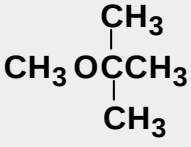
  Name the OR group as an alkoxy substituent.
- **Common names:** name the groups bonded to oxygen in alphabetical order followed by the word **ether**.



Ethoxyethane
(Diethyl ether)



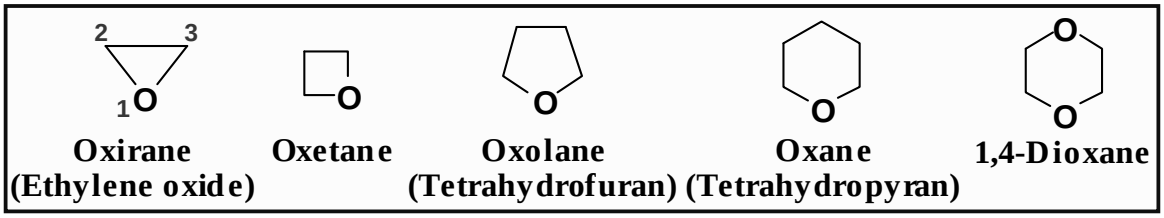
***trans*- 2-Ethoxy-cyclohexanol**



2-Methoxy-2-methylpropane
(*tert*- Butyl methyl ether)

Nomenclature

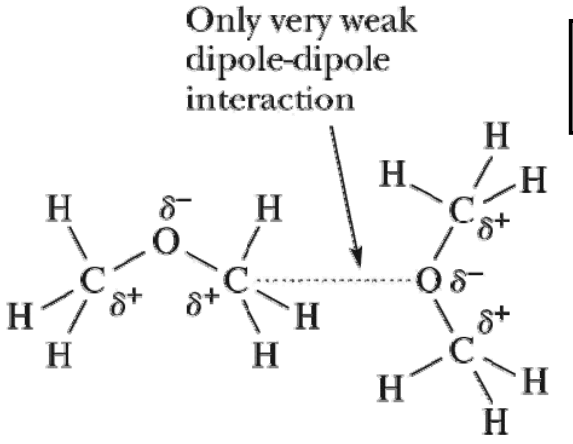
- Although cyclic ethers have IUPAC names, their **common names are more widely used.**
  - IUPAC: prefix ox- shows oxygen in the ring.
  - The suffixes -irane, -etane, -olane, and -ane show three, four, five, and six atoms in a saturated ring.



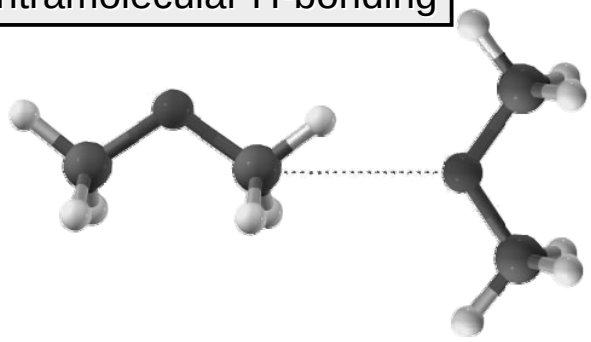
Oxirane (Ethylene oxide) **Oxetane** **Oxolane (Tetrahydrofuran)** **Oxane (Tetrahydropyran)** **1,4-Dioxane**

Physical Properties

- Although ethers are polar compounds, only weak **dipole-dipole** attractive forces exist between their molecules in the pure liquid state.

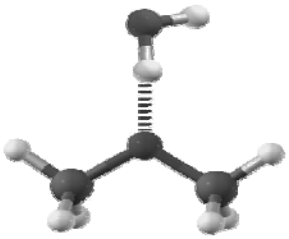


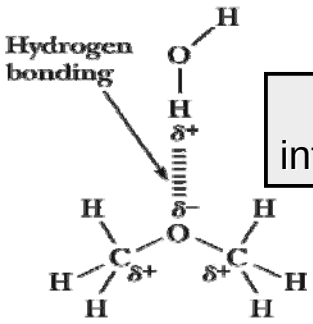
Note bene: there is NO intramolecular H-bonding



Physical Properties

- **Boiling points** of ethers are
  - lower than alcohols of comparable MW.
  - close to those of hydrocarbons of comparable MW.
- Ethers are hydrogen bond acceptors.
  - They are **NOT** soluble in H_2O, but
  - They are more soluble in H_2O than are hydrocarbons..

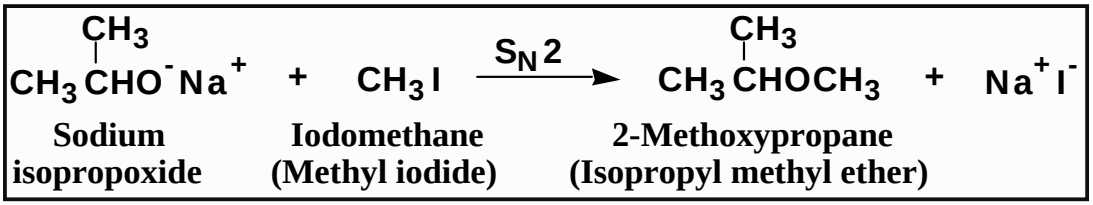


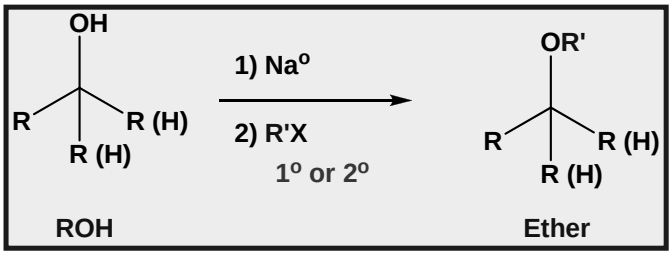


Note bene: there IS intermolecular H-bonding

Preparation of Ethers

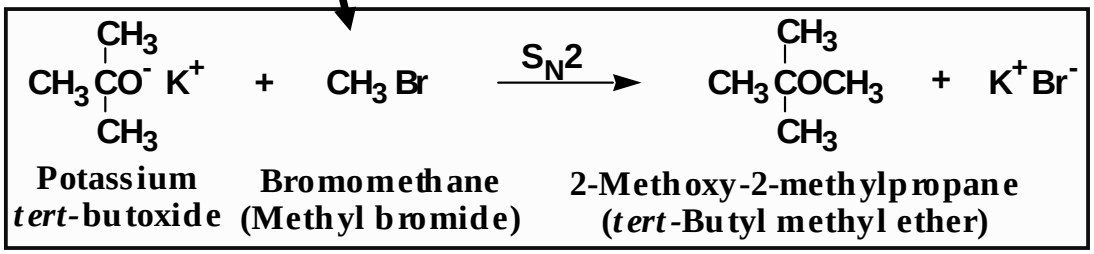
- **Williamson ether synthesis:** Ether synthesis by the S_N2 displacement of halide, tosylate, or mesylate by alkoxide ion.





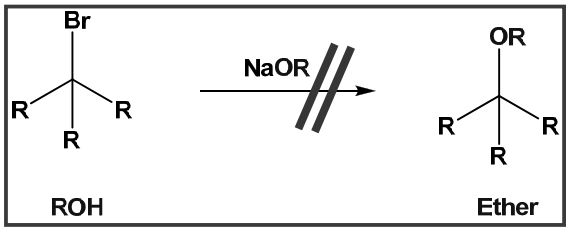
Preparation of Ethers

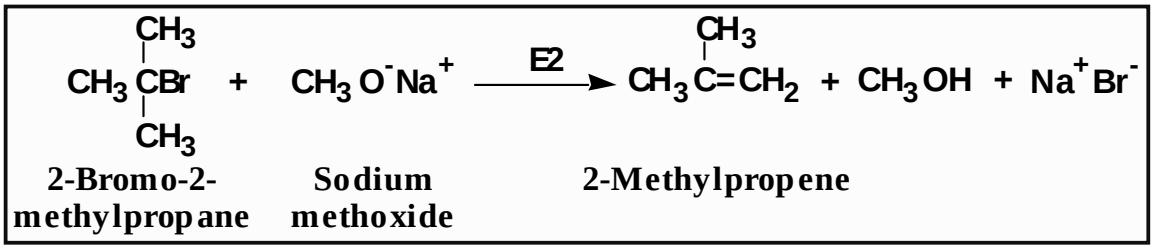
- Yields are highest with methyl and 1° **halides**,
- lower with 2° halides (competing β-elimination)



Preparation of Ethers

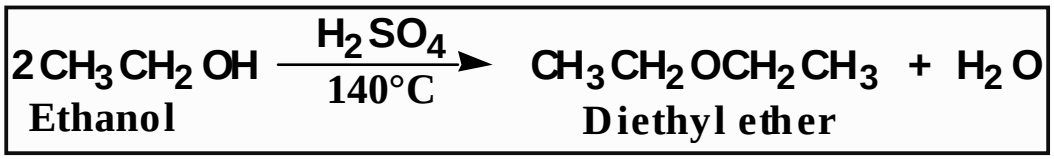
reaction fails with 3° halides (β-elimination only).

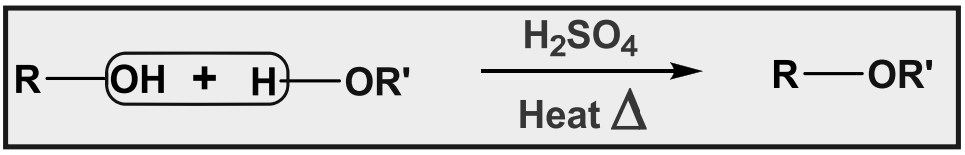




Preparation of Ethers

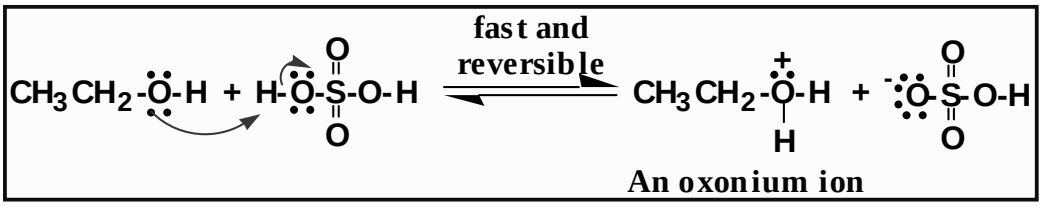
- **Acid-catalyzed dehydration of alcohols**
  - Diethyl ether and several other ethers are made this way on an industrial scale.
  - A specific example of an S_N2 reaction in which a poor leaving group (OH^-) is converted to a better one (H_2O).



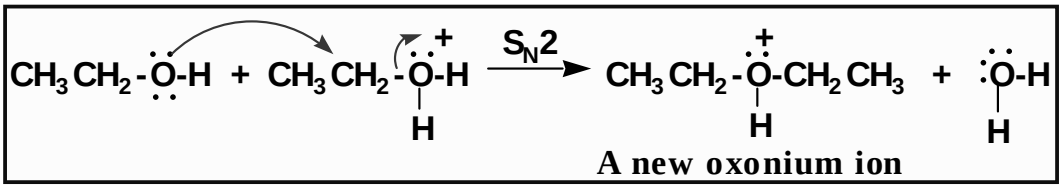


Preparation of Ethers

- **Step 1:** Proton transfer gives an oxonium ion.

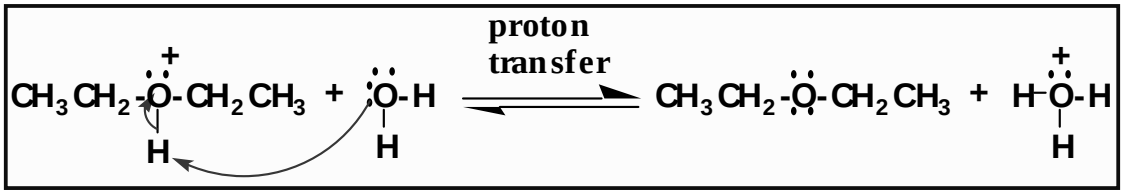


- **Step 2:** Nucleophilic displacement of H_2O by the OH group of the alcohol gives a new oxonium ion.



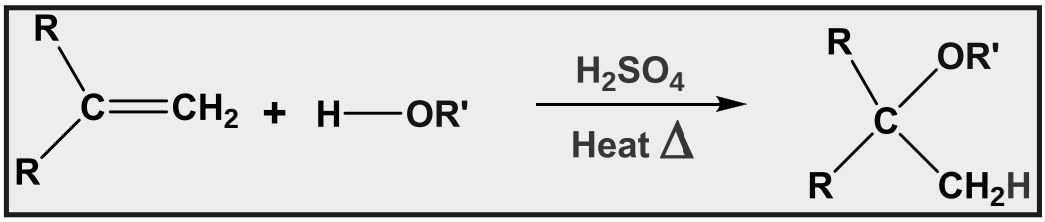
Preparation of Ethers

Step 3: Proton transfer to solvent completes the reaction.



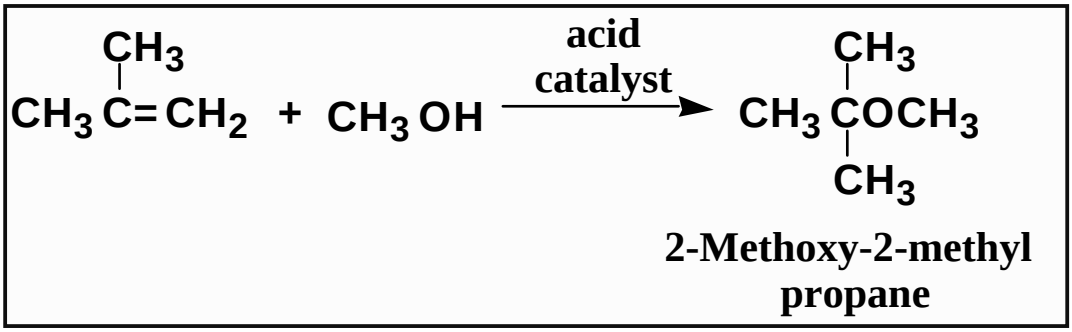
Preparation of Ethers

- Acid-catalyzed addition of alcohols to alkenes
  - Yields are highest using an alkene that can form a stable carbocation and
  - using methanol or a 1° alcohol that is not prone to undergo acid-catalyzed dehydration.



Preparation of Ethers

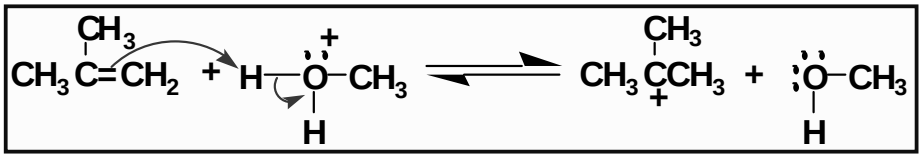
1. Use an alkene that can form a stable carbocation (2^o or 3^o)
2. Use a 1° alcohol (that is not prone to undergo acid-catalyzed dehydration).



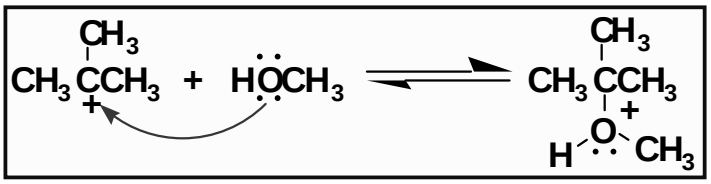
2-Methoxy-2-methyl propane

Preparation of Ethers

– **Step 1:** Protonation of the alkene gives a carbocation.

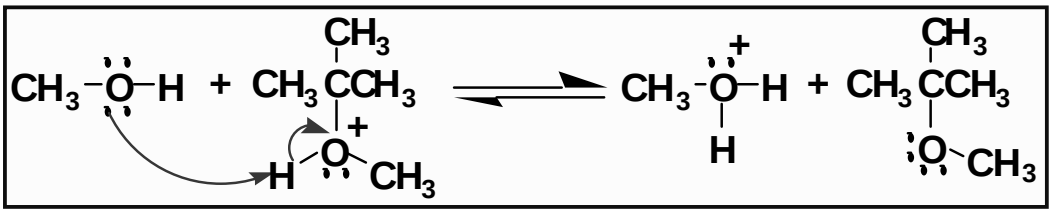


– **Step 2:** Reaction of the carbocation (an electrophile) with the alcohol (a nucleophile) gives an oxonium ion.



Preparation of Ethers

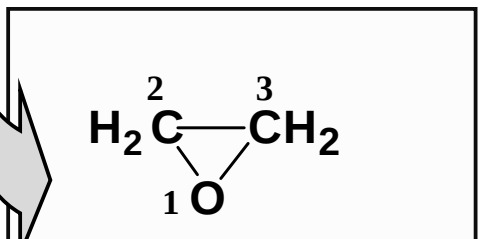
Step 3: Proton transfer to solvent completes the reaction.



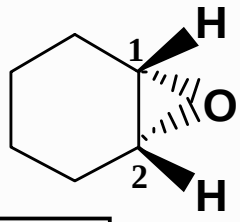
Epoxides

- Epoxide: A cyclic ether in which oxygen is one atom of a three-membered ring.
  - Simple epoxides are named as derivatives of oxirane.

Where the epoxide is part of another ring system, it is shown by the prefix epoxy-.



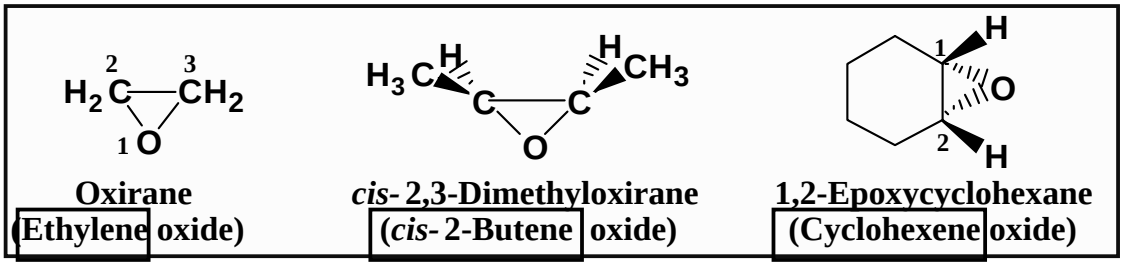
Oxirane
(Ethylene oxide)



1,2-Epoxycyclohexane
(Cyclohexene oxide)

Epoxides

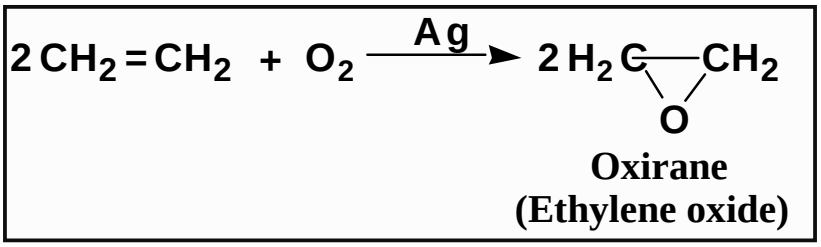
- Epoxide: A cyclic ether in which oxygen is one atom of a three-membered ring.
  - **Common names** are derived from the name of the **alkene** from which the epoxide is formally derived.

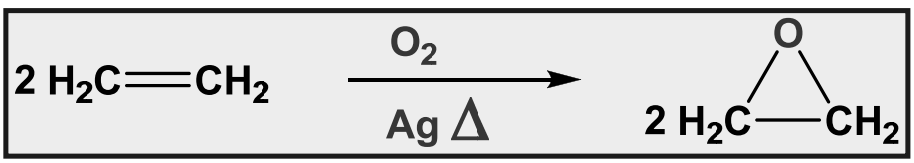


Oxirane (Ethylene oxide) | ***cis*-2,3-Dimethyloxirane (*cis*-2-Butene oxide)** | **1,2-Epoxycyclohexane (Cyclohexene oxide)**

Synthesis of Epoxides

- Ethylene oxide, one of the few epoxides manufactured on an industrial scale, is prepared by air oxidation of ethylene.

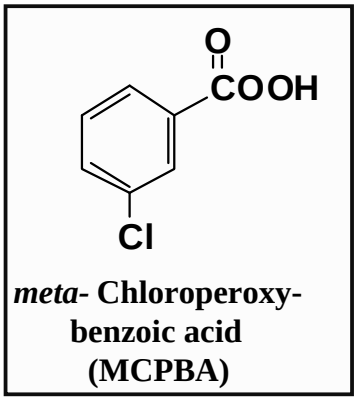




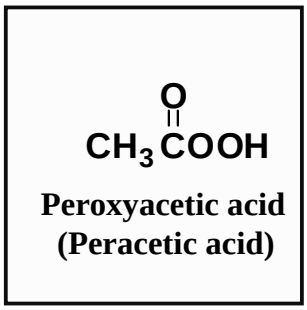
procaine

Synthesis of Epoxides

- The most common laboratory method is oxidation of an alkene using a **peroxycarboxylic acid (a peracid).**



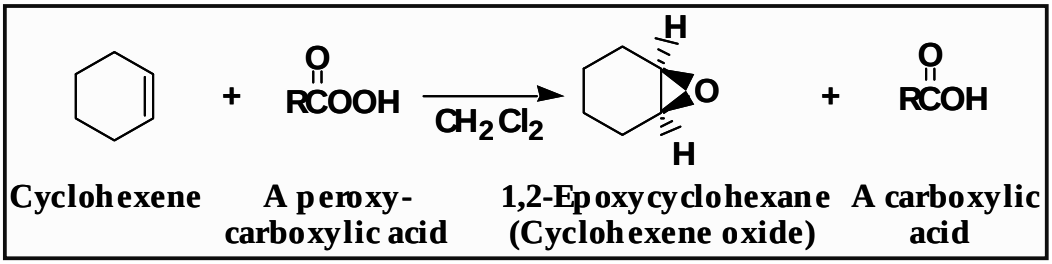
***meta*- Chloroperoxy-benzoic acid (MCPBA)**



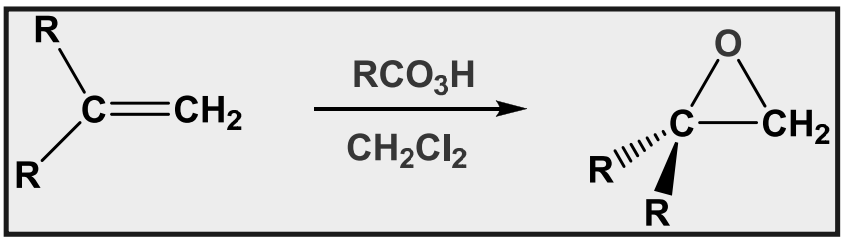
Peroxyacetic acid (Peracetic acid)

Synthesis of Epoxides

- Epoxidation of cyclohexene

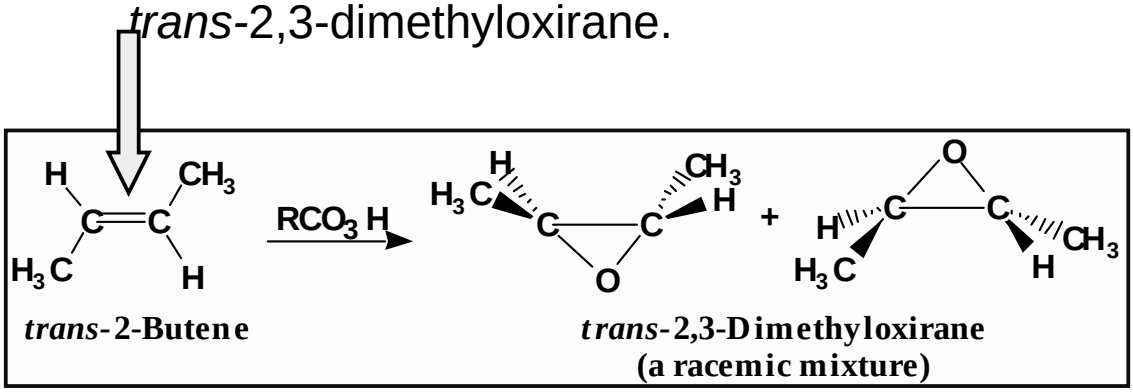


Cyclohexene | **A peroxy-carboxylic acid** | **1,2-Epoxycyclohexane (Cyclohexene oxide)** | **A carboxylic acid**



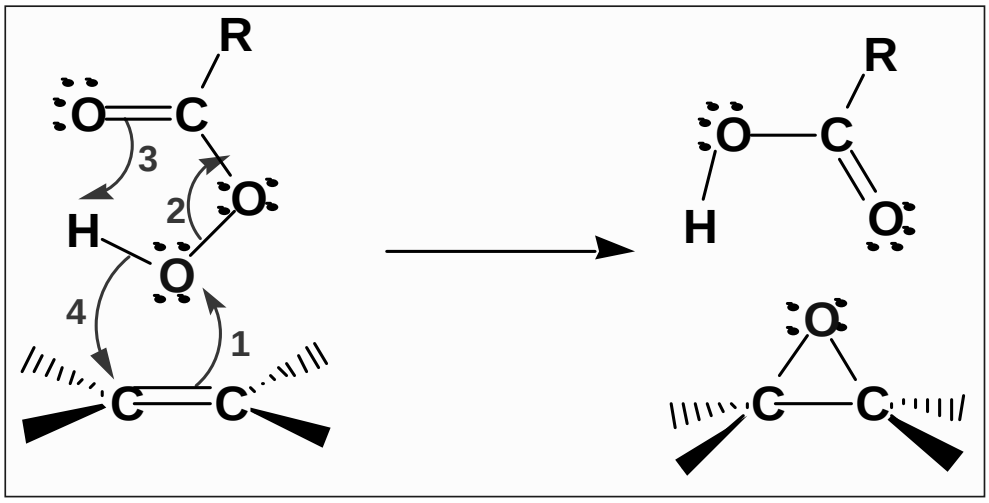
Synthesis of Epoxides

- **Epoxidation is stereospecific:**
  - Epoxidation of *cis*-2-butene gives only *cis*-2,3-dimethyloxirane.
  - Epoxidation of *trans*-2-butene gives only *trans*-2,3-dimethyloxirane.



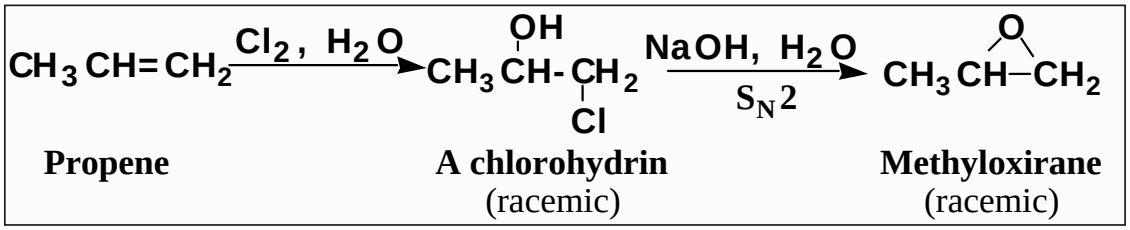
Synthesis of Epoxides

- A mechanism for alkene epoxidation.

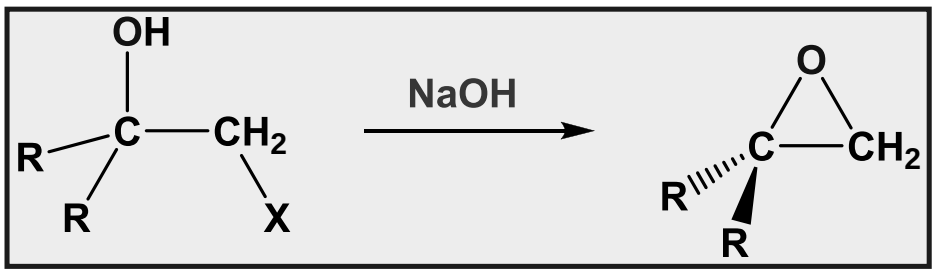


Synthesis of Epoxides

- Epoxides are also synthesized via **halohydrins**.

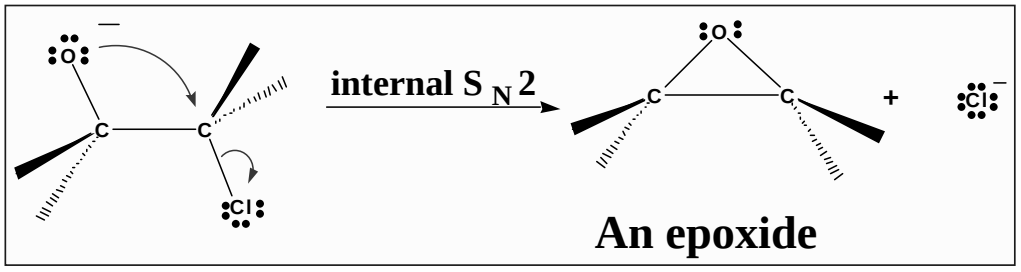


Propene | **A chlorohydrin** (racemic) | **Methyloxirane** (racemic)



Synthesis of Epoxides

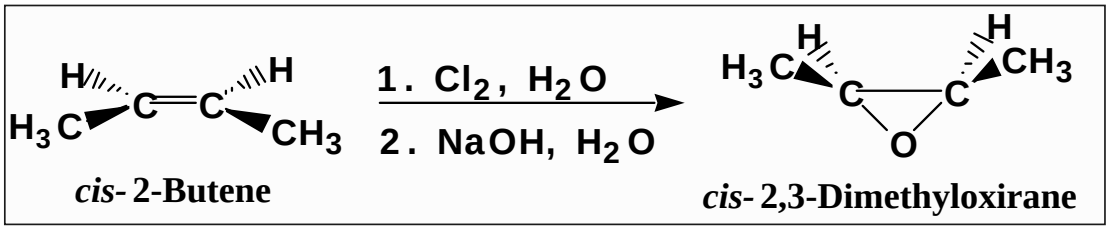
The second step is an internal S_N2 reaction.



Synthesis of Epoxides

– **Halohydrin formation** is both **regioselective** and **stereoselective**; for alkenes that show *cis,trans* isomerism, it is also **stereospecific**.

– Conversion of a halohydrin to an epoxide is **stereoselective**:

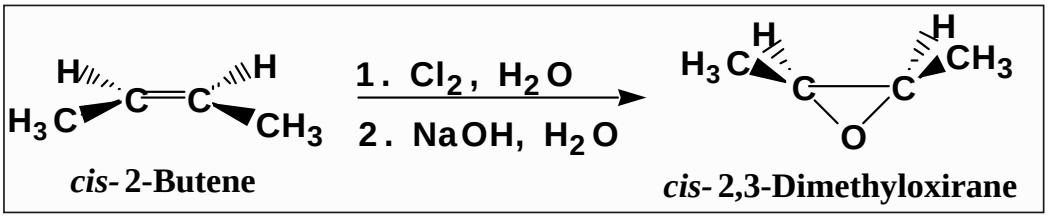


cis-2-Butene

cis-2,3-Dimethyloxirane

Synthesis of Epoxides

- Problem: Account for the fact that conversion of *cis*-2-butene to an epoxide by the halohydrin method gives only *cis*-2,3-dimethyloxirane.

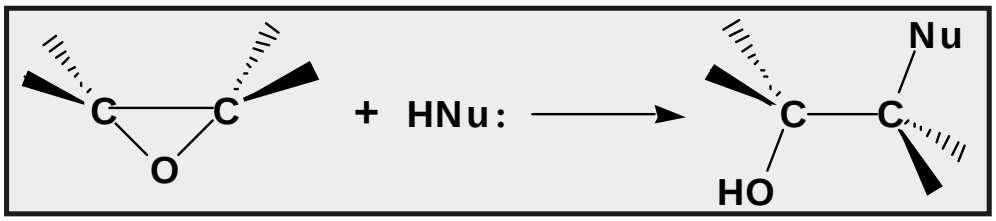


cis-2-Butene

cis-2,3-Dimethyloxirane

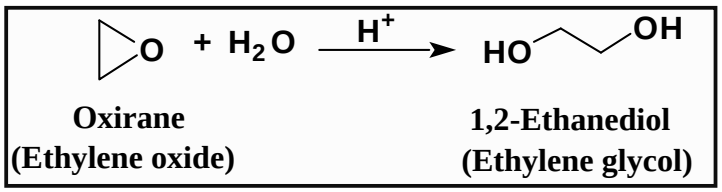
Reactions of Epoxides

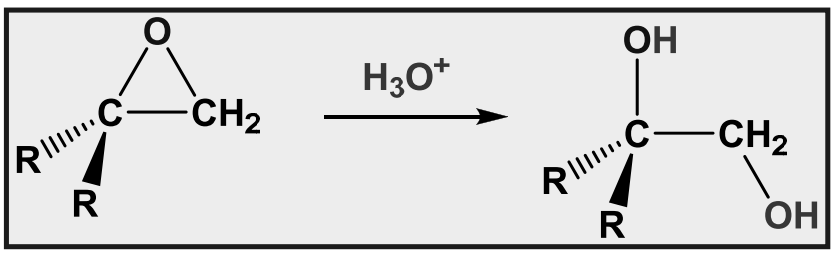
- Ethers are not normally susceptible to attack by nucleophiles.
- Because of the strain associated with the three-membered ring, epoxides readily undergo a variety of ring-opening reactions.



Reactions of Epoxides

- Acid-catalyzed ring opening
  - In the presence of an acid catalyst, such as sulfuric acid, epoxides are hydrolyzed to glycols.



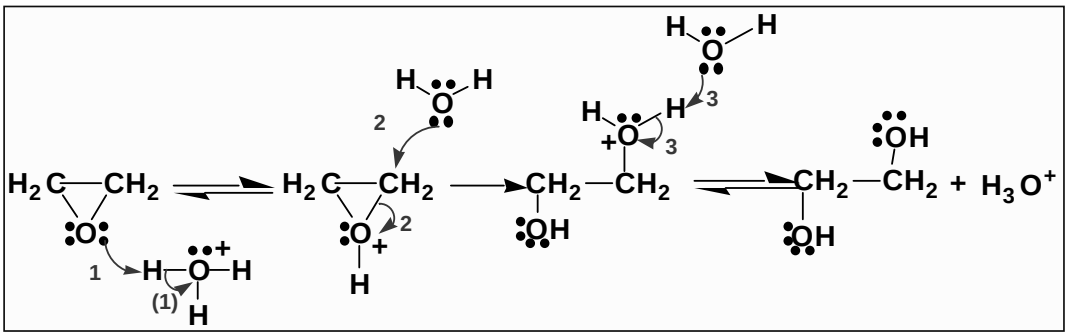


Reactions of Epoxides

Step 1: Proton transfer to oxygen gives a bridged oxonium ion intermediate.

Step 2: Backside attack by water (a nucleophile) on the oxonium ion (an electrophile) opens the ring.

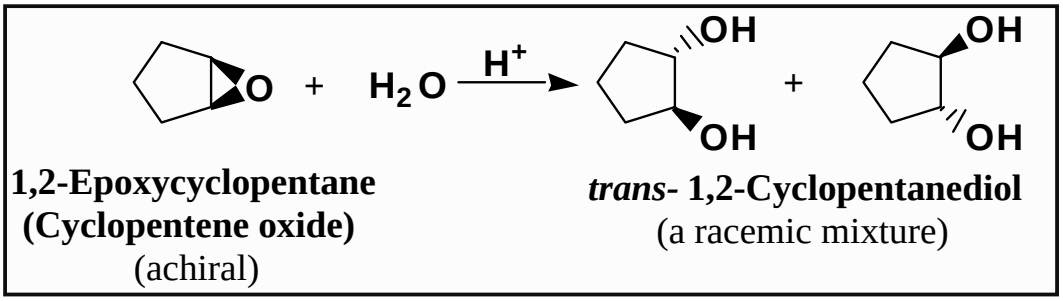
Step 3: Proton transfer to solvent completes the reaction.



Reactions of Epoxides

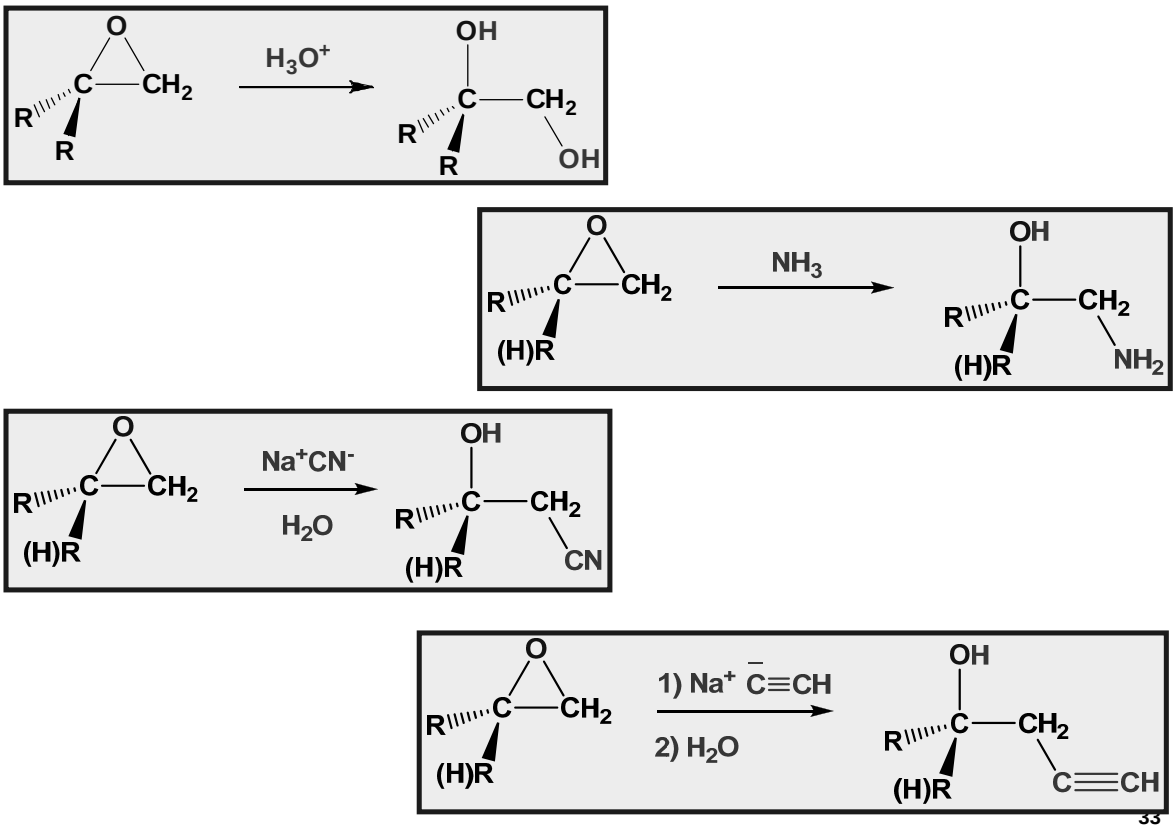
Attack of the nucleophile on the protonated epoxide shows anti stereoselectivity.

– Hydrolysis of an epoxycycloalkane gives a *trans*-1,2-diol.



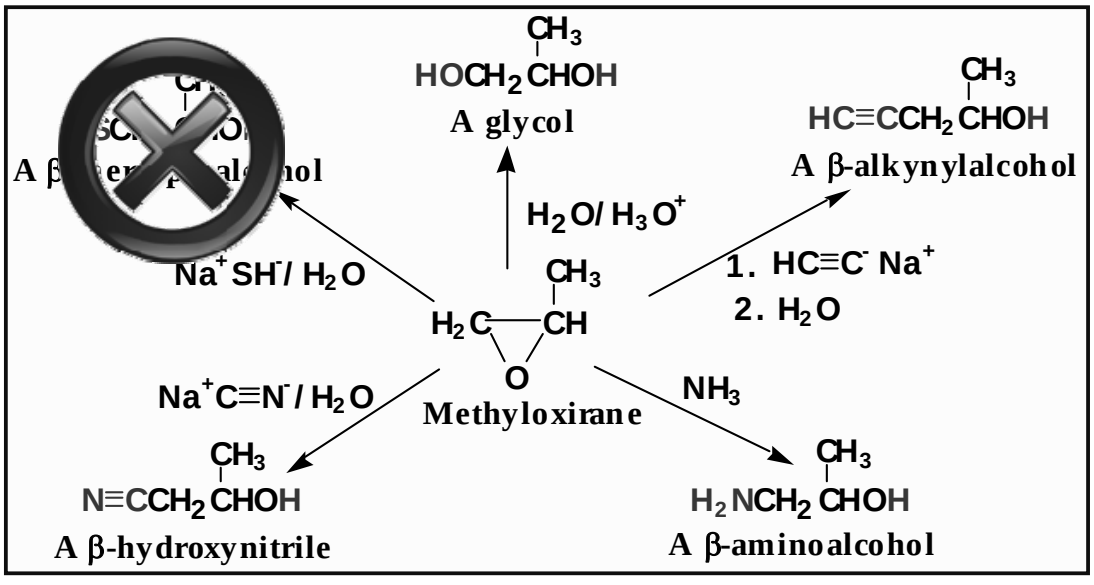
1,2-Epoxycyclopentane (Cyclopentene oxide) (achiral)

***trans*- 1,2-Cyclopentanediol** (a racemic mixture)

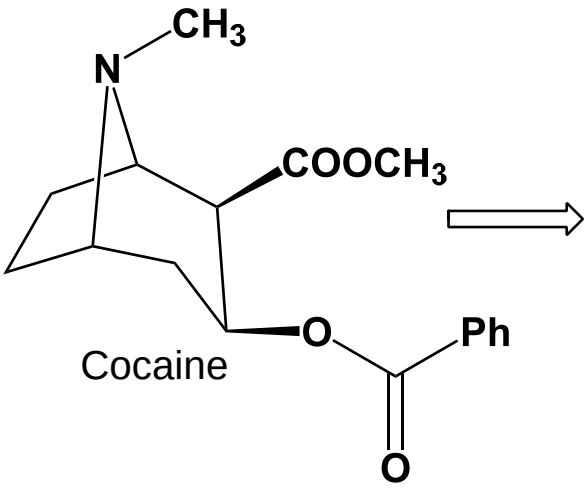


Reactions of Epoxides

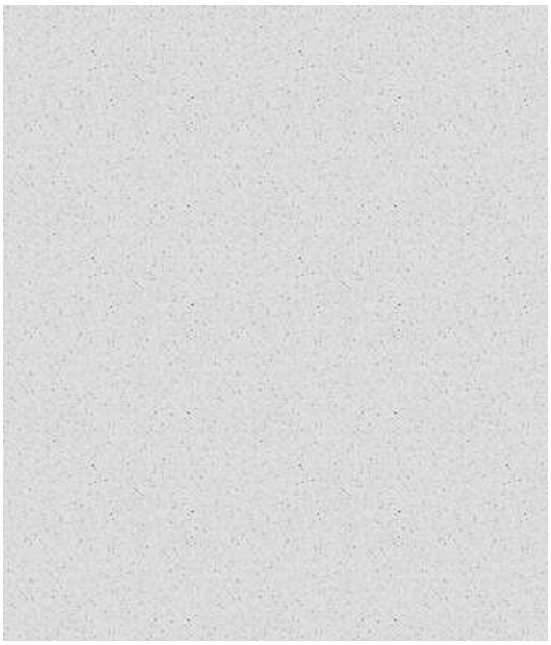
The value of epoxides is the variety of nucleophiles that will open the ring and the combinations of functional groups that can be prepared from them.



Medicinal Chemistry



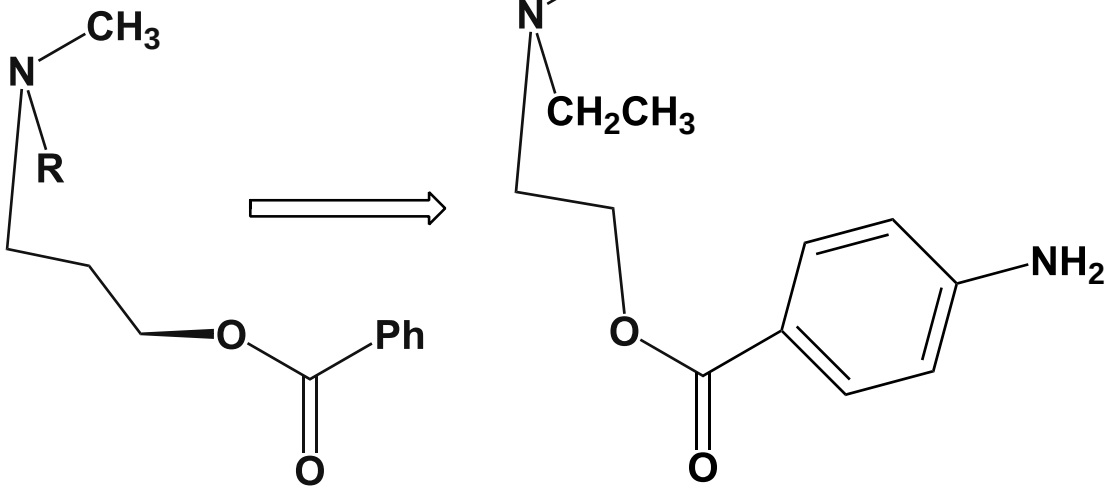
Cocaine

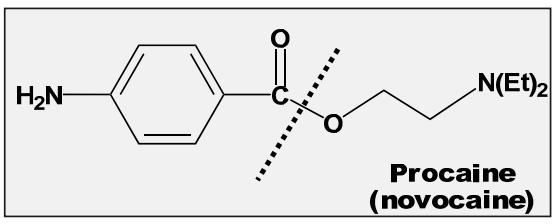


Topical anesthetic (local)
CNS stimulant

NOT exam material

Medicinal Chemistry





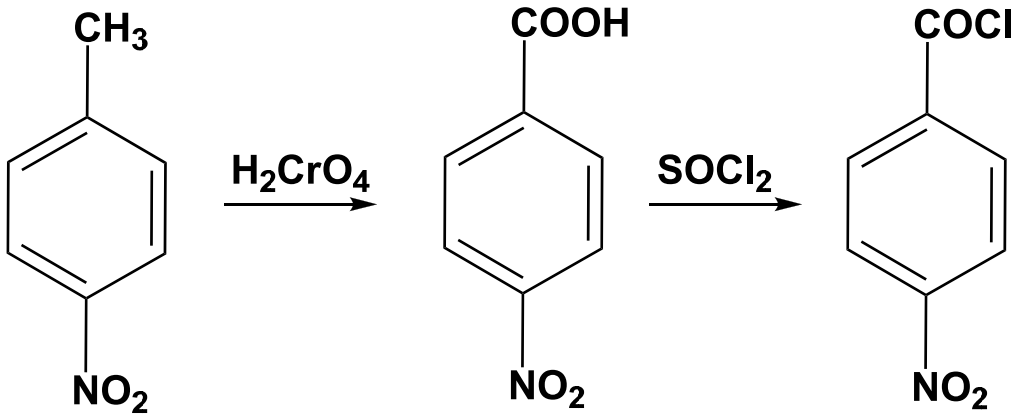
Alkanolamines

(Ethanolamines)

Procaine

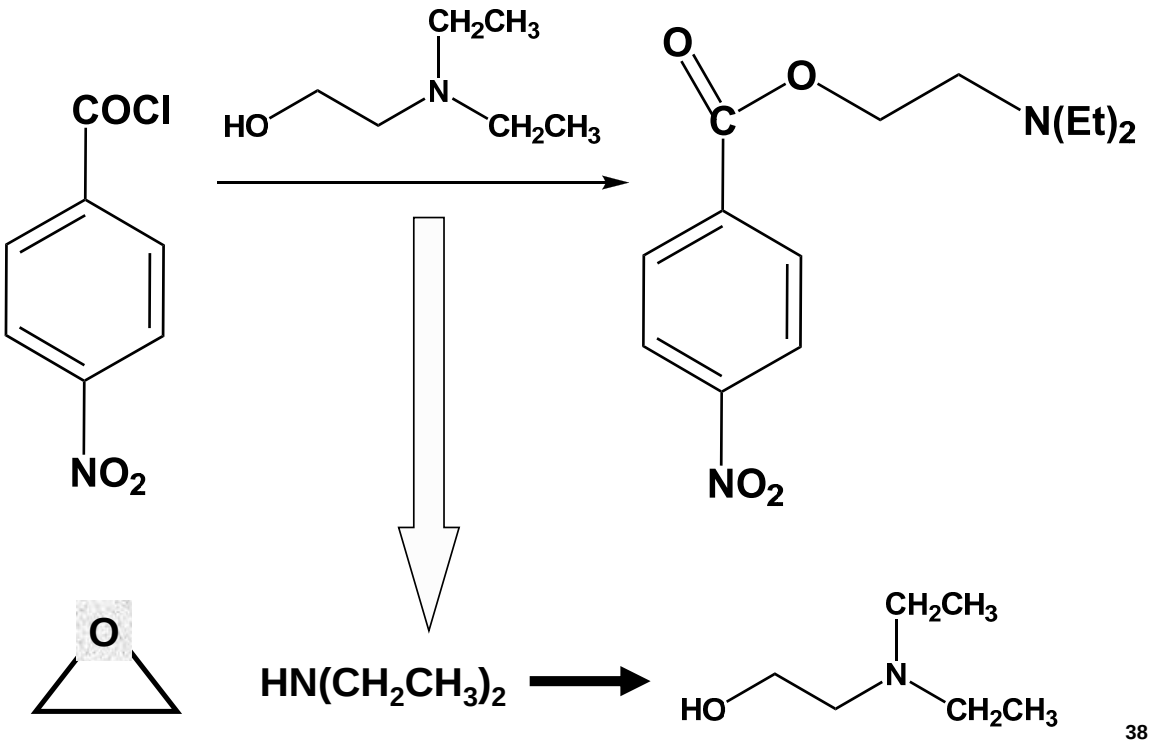
Medicinal Chemistry

Synthesis of Procaine



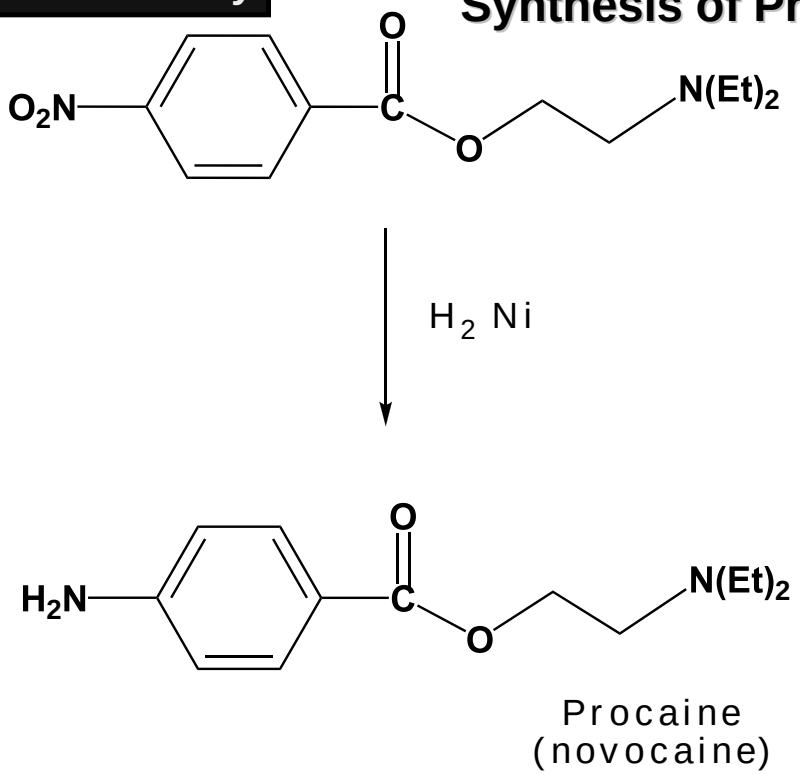
Medicinal Chemistry

Synthesis of Procaine



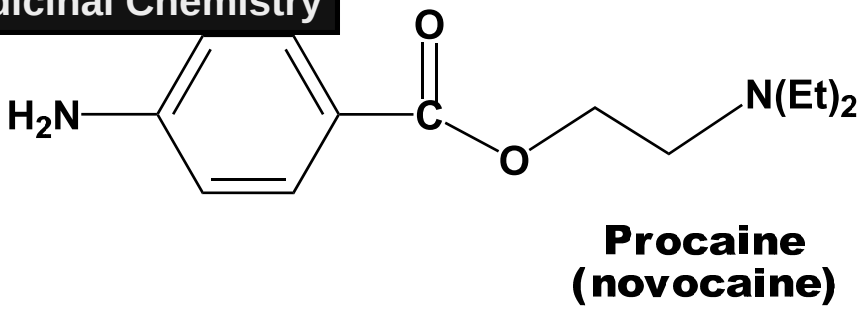
Medicinal Chemistry

Synthesis of Procaine

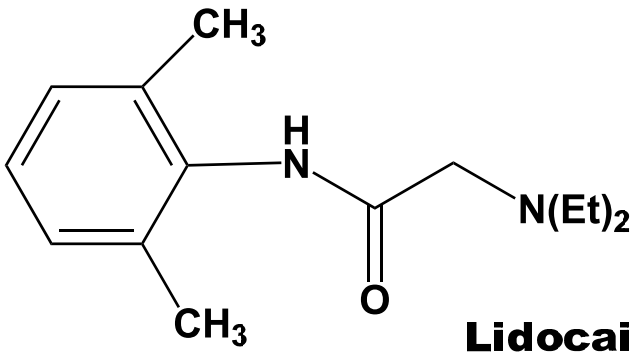


Procaine
(novocaine)

Medicinal Chemistry



Procaine
(novocaine)



Lidocaine

Xylocaine®