Chapter 7: Alkyl Halides and Nucleophilic Substitution

SN2 Reaction

Mechanism:

Notes:

- One step reaction
- Order of reactivity: Methyl > Primary > Secondary > Tertiary
- Stereochemistry: Inversion of configuration at stereogenic center (because of backside attack)
- Better leaving group = faster reaction
- Favors: Strong nucleophiles
- Favors: Not-sterically-hindered alkyl halides
- Favors: Polar aprotic solvents (cannot hydrogen bond)

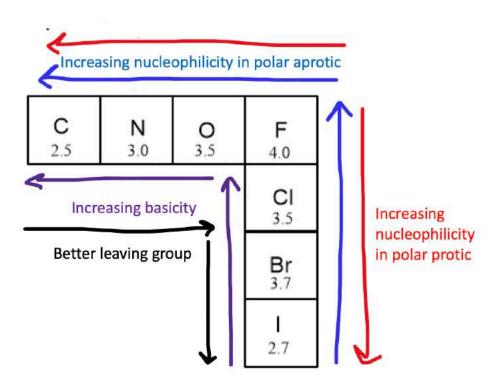
SN1 Reaction

Mechanism:

Notes:

- Two step reaction
- Order of reactivity: **Tertiary** > **Secondary** > Primary > Methyl
- Stereochemistry: Racemization (because the carbocation is planar)
- Better leaving group = faster reaction
- Favors: Weak nucleophiles
- Favors: Sterically hindered alkyl halides
- Favors: Polar protic solvents (can hydrogen bond)

Important Trends



Chapter 8: Alkyl Halides and Elimination Reactions

E2 Reaction

Mechanism:

Notes:

- One step reaction
- Order of reactivity: **Tertiary** > **Secondary** > **Primary**
- Stereochemistry: antiperiplanar arrangement of H and X
- Better leaving group = faster reaction
- Favors: Polar aprotic solvents, strong bases
- Products follow Zaitsev rule (more substituted alkene is the major product)

E1 Reaction

$$CH_3$$
 + HO CH_3 + HO CH_3

- Two step reaction
- Order of reactivity: **Tertiary** > **Secondary** > Primary
- Stereochemistry: Trigonal planar carbocation intermediate
- Better leaving group = faster reaction
- Favors: Polar protic solvents, weak bases
- Products follow Zaitsev rule

Chapter 9: Alcohols, Ethers, and Epoxides

Preparation of Alcohols

Mechanism:

Notes:

• SN2 mechanism

Preparation of Alkoxides

Mechanism:

Preparation of Ethers (Williamson Ether Synthesis)

• SN2 mechanism

Preparation of Epoxides

Mechanism:

Alcohol Dehydration: Secondary and Tertiary

+ H3O+ + -OSO3H

Notes:

- E1 mechanism
- Zaitsev rule applies (the most substituted product is the major product)
- Carbocation rearrangements are possible

Alcohol Dehydration: Primary

Mechanism:

base here can be H₂O, OSO₃H, or other weak Lewis base

Notes:

- E2 mechanism
- Zaitsev rule applies

Other Reagents to Form Alkenes: POCI3 and Pyridine

$$\begin{array}{c|c}
 & \downarrow & \\
 & C - C - \\
\hline
 & H & OH
\end{array}$$

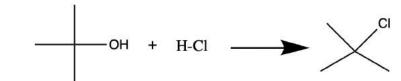
$$\begin{array}{c|c}
 & POCI_3 \\
\hline
 & pyridine
\end{array}$$

$$\begin{array}{c|c}
 & C = C \\
\hline
 & POCI_3
\end{array}$$

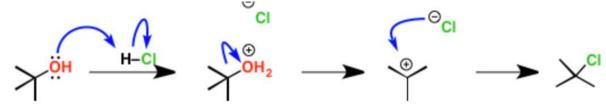
Notes:

• E2 mechanism

Alkyl Halides Formation from Alcohols: Secondary and Tertiary



Mechanism:



Notes:

- SN1 mechanism
- Carbocation rearrangements are possible

Alkyl Halides Formation from Alcohols: Primary

Mechanism:

Notes:

• SN2 mechanism (inversion of stereochemistry)

Other Reagents to Form Alkyl Halides: SOCI2 and PBr3

$$R-OH + SOCI_2 \xrightarrow{pyridine} R-CI$$
 $R-OH + PBr_3 \longrightarrow R-Br$

Notes:

• SN2 reaction, both reagents will lead to inversion of stereochemistry

Reaction with Alkyl Tosylates

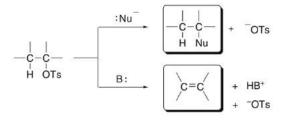
$$R-OH + CI - \overset{O}{\overset{\parallel}{S}} - \overset{O}{\overset{\parallel}{C}} - CH_3 \xrightarrow{pyridine} R-O - \overset{O}{\overset{\parallel}{S}} - \overset{O}{\overset{\parallel}{C}} - CH_3$$

$$R-OTs$$

First step:

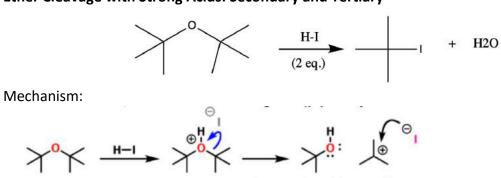
• Note: Stereochemistry is retained

Second step:



- Substitution is carried out with strong: Nu⁻, so the mechanism is S_N2.
- Elimination is carried out with strong bases, so the mechanism is E2.

Ether Cleavage with Strong Acids: Secondary and Tertiary



Notes:

• SN1 mechanism

nucleophile

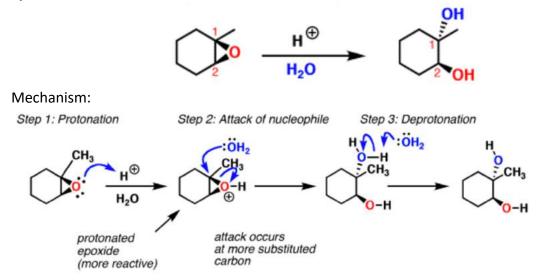
Ether Cleavage with Strong Acids: Primary

Mechanism:

Notes:

SN2 mechanism

Epoxide Reactions with Acids



Notes:

- SN1/SN2 mechanism
- Attacks at the more substituted carbon
- Backside attack = inversion of configuration

Epoxide Reactions with Strong Nucleophiles

- SN2 mechanism
- Attacks the less substituted carbon
- Backside attack = inversion of configuration

Chapter 10: Alkenes

Hydrohalogenation

Mechanism:

Notes:

- Carbocation rearrangements are possible
- Markovnikov's rule is followed (H bonds to less subbed carbon, X bonds to more subbed carbon)
- Stereochemistry: Syn (added to same sides) and anti (add to opposite sides) addition

Hydration

$$H_2SO_4$$
 H_2SO_4
 H_0
 H_1

Mechanism:

Addition of water to alkenes

Notes:

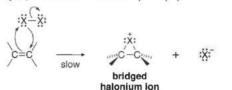
- Carbocation rearrangements are possible
- Markovnikov's rule is followed
- Same mechanism if using alcohol instead of water to make ethers
- Stereochemistry: Syn and anti-addition occur

Halogenation

$$C = C + X - X - C - C - X \times X \times X_2 \text{ is added.}$$
This π bond is broken. vicinal dihalide

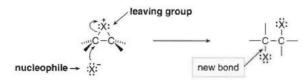
Mechanism:

Step [1] Addition of the electrophile (X^+) to the π bond



- Four bonds are broken or formed in this step: the electron pair in the π bond and a lone pair on a halogen atom are used to form two new C-X bonds. The X-X bond is also cleaved heterolytically, forming X⁻. This step is rate-determining.
- The three-membered ring containing a positively charged halogen atom is called a **bridged halonium ion**. This strained three-membered ring is highly unstable, making it amenable to opening of the ring in the second step.

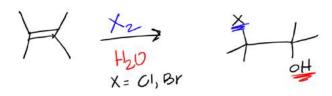
Step [2] Nucleophilic attack of X-



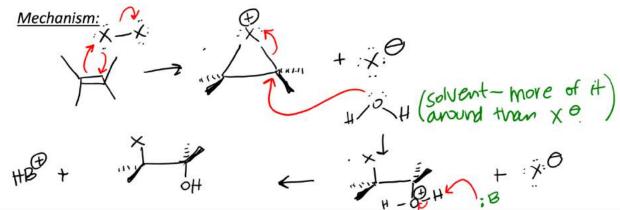
 Nucleophilic attack of X⁻ opens the ring of the halonium ion, forming a new C – X bond and relieving the strain in the three-membered ring.

- Halogen attacks most subbed carbon in halonium ion
- No carbocation rearrangements
- Stereochemistry: anti-addition

Halohydrin Formation

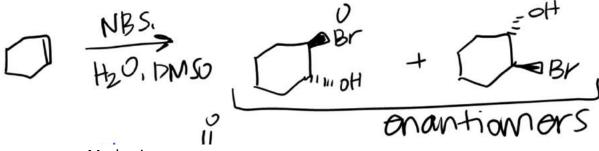


Mechanism:



Notes:

- H2O attacks more subbed carbon (recall acid-catalyzed ring opening of an epoxide)
- No carbocation rearrangements
- Stereochemistry: Anti-addition
- Special reagent: NBS



Hydroboration-Oxidation

Mechanism:

Notes:

- You only need to know the hydroboration step, not the oxidation step
- Anti-markovnikov (OH is added to less subbed carbon)
- No carbocation rearrangements
- Syn-addition
- Retention of configuration
- Same mechanism as 9-BBN

Chapter 11: Alkynes

Preparation of Alkynes

Mechanism (2nd step):

Hydrohalogenation

Mechanism:

Addition of first equivalent:

Addition of second equivalent:

Notes:

- Markovnikov's rule is followed
- The carbocation will form on the more substituted or resonance-stabilized carbon

Halogenation

Part [1] Addition of X2 to form a trans dihalide

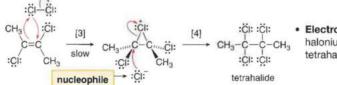
$$\begin{array}{c} : \ddot{\text{Ci}} - \ddot{\text{Ci}} : \\ \text{CH}_3 - \text{C} = \text{C} - \text{CH}_3 & \begin{array}{c} [1] \\ \text{slow} \end{array} \\ \text{CH}_3 & \begin{array}{c} \vdots \ddot{\text{Ci}} : \\ \text{C} + G \end{array} \\ \begin{array}{c} \text{C} + G \end{array} \\ \text{CH}_3 & \begin{array}{c} \vdots \ddot{\text{Ci}} : \\ \text{C} + G \end{array} \\ \begin{array}{c} \text{CH}_3 & \vdots \ddot{\text{Ci}} : \\ \text{CH}_3 & \vdots \ddot{\text{Ci}} : \end{array} \\ \begin{array}{c} \text{nucleophile} \\ \end{array}$$

bridged halonium ion

bridged halonium ion

- Two bonds are broken and two are formed in Step [1] to generate a **bridged halonium ion.** This strained threemembered ring is highly unstable, making it amenable to opening of the ring in the second step.
- Nucleophilic attack by Cl⁻ from the back side forms the trans dihalide in Step [2].

Part [2] Addition of X2 to form a tetrahalide



 Electrophilic addition of Cl⁺ in Step [3] forms the bridged halonium ion ring, which is opened with Cl⁻ to form the tetrahalide in Step [4].

Notes:

- Anti-addition
- Halogens will attack the more substituted or resonance-stabilized side

Hydration

Mechanism:

$$H_{2}O + H_{3}O^{3}H \longrightarrow H_{3}O^{4} + D = 0$$

$$CH_{3} \longrightarrow CH_{3} + H_{2}D \longrightarrow H_{3}D \longrightarrow H_{2}D \longrightarrow H_{3}D \longrightarrow H_$$

Notes:

- Markovnikov's rule is followed
- Unstable enol
- End product is a ketone
- Acid-catalyzed

Hydroboration-Oxidation

Mechanism:

Notes:

- Anti-markovnikov
- Unstable enol
- End product is aldehyde (if it's a terminal alkyne) or ketone

Formation of Acetylide Anions

$$R-C\equiv C-H$$
 + :B $R-C\equiv C$: + HB^+

Typical bases used are NaNH2 and NaH

Acetylide Anion Reactions with Alkyl Halides

• SN2 if primary alkyl halide, secondary or tertiary alkyl halide = E2

Acetylide Anion Reactions with Epoxides

$$H-C \equiv C: - \qquad [1] \stackrel{O}{\longrightarrow} \qquad H-C \equiv C-CH_2CH_2OH$$

- SN2 mechanism
- Acetylide attacks the less substituted carbon on the epoxide

Chapter 12: Oxidation and Reduction

Reduction of Alkenes

$$R-CH=CH-R \xrightarrow{H_2} Pd/C \xrightarrow{H} H H$$

$$R-C-C-R$$

$$H H$$

$$H H$$

$$Alkane$$

• Syn addition occurs

Reduction of Aldehydes

Reduction of Ketones

• Stereochemistry: Racemic mixture

Reduction of Alkynes

$$R-C \equiv C-R \qquad \begin{array}{c} 2 \text{ H}_2 \\ \hline \text{Pd-C} \end{array} \qquad \begin{array}{c} H & H \\ R-C-C-R \\ H & H \\ \text{alkane} \end{array}$$

- 2 equivalents of H2 are required
- 4 new C-H bonds are formed

$$R-C \equiv C-R \qquad \begin{array}{c} H_2 \\ \hline Lindlar \\ catalyst \end{array} \qquad \begin{array}{c} R \\ C=C \\ H \\ cis \ alkene \end{array}$$

• Syn addition occurs = cis alkene product

$$R-C \equiv C-R \qquad \begin{array}{c} Na \\ NH_3 \end{array} \qquad \begin{array}{c} R \\ C=C \\ H \\ R \\ trans \ alkene \end{array}$$

• Anti-addition occurs = trans alkene product

Reduction of Alkyl Halides

$$R-X \xrightarrow{[2] H_2O} R-H$$
alkane

- SN2 mechanism
- Attacks the less substituted carbon if attacking epoxides

Epoxidation

Mechanism:

Notes:

- One step reaction
- Syn addition
- Reaction is stereospecific (syn alkene = cis product, trans alkene = trans product)

Syn Dihydroxylation

- Cis products
- Stereochemistry: Racemic mixture (but for the example above the products are identical)

Trans Dihydroxylation

- Trans products
- Stereochemistry: Racemic mixture
- Step 2 can also use KOH instead of sulfuric acid and water

Oxidative Cleavage of Alkenes

$$\rightarrow$$
 \rightarrow 03 \rightarrow 0 + 0 \rightarrow

Oxidative Cleavage of Alkynes

$$\begin{array}{c} R-C\equiv C-R' \\ \text{internal alkyne} \end{array} \xrightarrow{ \begin{array}{c} [1] \ O_3 \\ [2] \ H_2O \end{array} } \begin{array}{c} R \\ C=O \ + \ O=C \\ HO \end{array} \xrightarrow{ \begin{array}{c} R' \\ OH \\ \text{carboxylic acids} \end{array} \end{array}$$

Oxidation of Alcohols

Chapter 15 Radical Reactions

Halogenation of Alkanes

CH₃CH₃ + Cl₂
$$\xrightarrow{hv \text{ or } \Lambda}$$
 CH₃CH₂Cl + HCl

Mechanism:

Initiation

Step [1] Bond cleavage forms two radicals.

- Homolysis of the weakest bond in the starting materials requires energy from light or heat.
- Thus, the CI CI bond (ΔH° = 242 kJ/mol), which is weaker than either the C C or C H bond in ethane (ΔH° = 368 and 410 kJ/mol, respectively), is broken to form two chlorine radicals.

Propagation

Steps [2] and [3] One radical reacts and a new radical is formed.

$$\begin{array}{c} \text{product} \\ \text{CH}_3\dot{\text{CH}}_2 + \vdots \ddot{\text{CH}}_2 \ddot{\text{Ci}} \vdots \xrightarrow{[3]} & \text{CH}_3\text{CH}_2 - \ddot{\text{Ci}} \vdots & + \cdot \ddot{\text{Ci}} \vdots \\ \end{array}$$

Repeat Steps [2], [3], [2], [3], again and again.

- The Cl⁻ radicals abstract a hydrogen atom from ethane (Step [2]).
 This forms H Cl and leaves one unpaired electron on carbon, generating the ethyl radical (CH₃CH₂).
- CH₃CH₂: abstracts a chlorine atom from Cl₂ (Step [3]), forming CH₃CH₂Cl and a new chlorine radical (Cl⁺).
- The CI⁻ radical formed in Step [3] is a reactant in Step [2], so Steps [2] and [3] can occur repeatedly without an additional initiation reaction (Step [1]).
- In each propagation step, one radical is consumed and one radical is formed. The two products—CH₃CH₂Cl and HCl—are formed during propagation.

Termination

Step [4] Two radicals react to form a σ bond.

 To terminate the chain, two radicals react with each other in one of three ways (Steps [4a, b, and c]) to form stable bonds.

- Must be Br2 or Cl2
- Chlorination is faster and less selective than bromination = 2+ products
- Bromination = 1 product (most substitued carbon is chosen)
- Stereochemistry: Racemic mixture

Radical Addition of HBr to an Alkene

Mechanism:

Step 1: Initiation

Initation (step 2) - formation of bromine radical



Step 2: Addition of bromine radical to alkene

Abstraction of hydrogen from H-Br to give addition product

Step 3: Termination

Notes:

 Bromine gets added to the less substituted side (vs adding to the most substituted side with only H-Br)

Chapter 16: Conjugation, Resonance, and Dienes

1,3 Diene Electrophilic Addition

- Markovnikov's rule is followed
- Kinetic product: 1,2 product. More formed at lower temperatures
- Thermodynamic product: 1,4 product. More formed at higher temperatures

Diels-Alder Reaction

Mechanism:

Notes:

- Reaction is one-step (concerted)
- Diene must be in s-cis conformation
- Trans diene = no reaction
- Stereochemistry is retained

• (ie. If the dienophile was trans, product will be trans)

Chapter 17: Benzene and Aromatic Compounds

Huckel's Rule

Aromatic compound

- A cyclic, planar, completely conjugated compound that contains $4n + 2\pi$ electrons (n = 0, 1, 2, 3, and so forth).
- An aromatic compound is more stable than a similar acyclic compound having the same number of π electrons.

Antiaromatic compound

- A cyclic, planar, completely conjugated compound that contains $4n \pi$ electrons (n = 0, 1, 2, 3, and so forth).
- An antiaromatic compound is less stable than a similar acyclic compound having the same number of π electrons.

A compound that is not • aromatic

 A compound that lacks one (or more) of the requirements to be aromatic or antiaromatic.

not completely conjugated

Examples of aromatic compounds with 6 π electrons (17.8) benzene pyridine pyrrole cyclopentadienyl anion tropylium cation Examples of compounds that are not aromatic (17.8)