

Alkyl Halide Reactions Cheat Sheet

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1 Definitions

1.1 Halogen

Halogen just refers to group 7 elements in the periodic table.

1.2 Nucleophiles

A nucleophile is a chemical species that form bonds by donating an electron-pair. Nucleophiles are electron-pair donors. You can think of nucleophiles as electron haters, so they want to donate their electrons away.

1.3 Organic halides (RX)

Organic halides are organic compounds that contain one or more halogen atoms. The $C - X$ bond is longer and hence weaker as you go down the periodic table. The $C - X$ bond is polarised, and organic halides are often good starting materials in **nucleophilic substitution and elimination**.

1.4 Polar protic solvents

Polar protic solvents are polar solvents that have at least 1 hydrogen that is connected directly to a particular electronegative atom, such as $O-H$, $N-H$ and are capable of forming hydrogen bonds with the solute. Water is an example of a polar protic solvent.

1.5 Polar aprotic solvents

Polar aprotic solvents are polar solvents that are unable to form hydrogen bonds with the solute. Examples include, acetone, chloroform, dichloromethane, ether, HMPA, DMSO, DMF and CH_3CN .

1.6 Alpha carbon (α -carbon)

The alpha carbon is the **first** carbon atom that attaches to a functional group, like a halogen group.

1.7 Beta carbon (β -carbon)

The beta carbon is the second carbon atom that attaches to a function group, like a halogen group. The beta carbon atom is always the adjacent carbon atom to the alpha carbon atom.

1.8 Zaitsev's rule

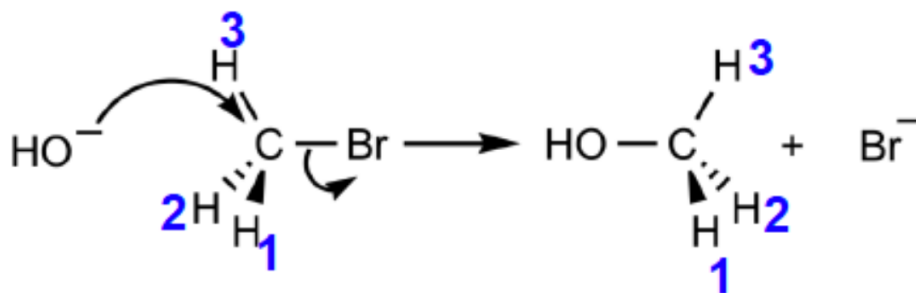
Zaitsev's rule states that the major product is the one with the **more substituted** double bonds.

1.9 Hoffman's rule

Hoffman's rule states that the major product is the one with the **less substituted** double bonds.

2 Nucleophilic substitution: S_N2 reactions

S_N2 reactions are single step, and the S stands for substitution, N stands for nucleophilic, and 2 stands for bimolecular.



- Configuration is **inverted** at the carbon where substitution occurs.
- The formation of the new bond and the breaking of the old bond happens **simultaneously**.

The nucleophile attacks from the back side as the halogen simultaneously leaves from the front side. It is a one-step process.

There are 4 factors that affect S_N2 reactions:

1. Steric effects
2. Nucleophilic strength
3. Leaving group effects
4. Solvent effects

2.1 Steric effects

The rate of S_N2 nucleophilic substitution reaction **increases** as the steric hindrance **decreases**. This is because it is much easier for the nucleophile to perform the backside attack when there are less bulky groups blocking the carbon atom.

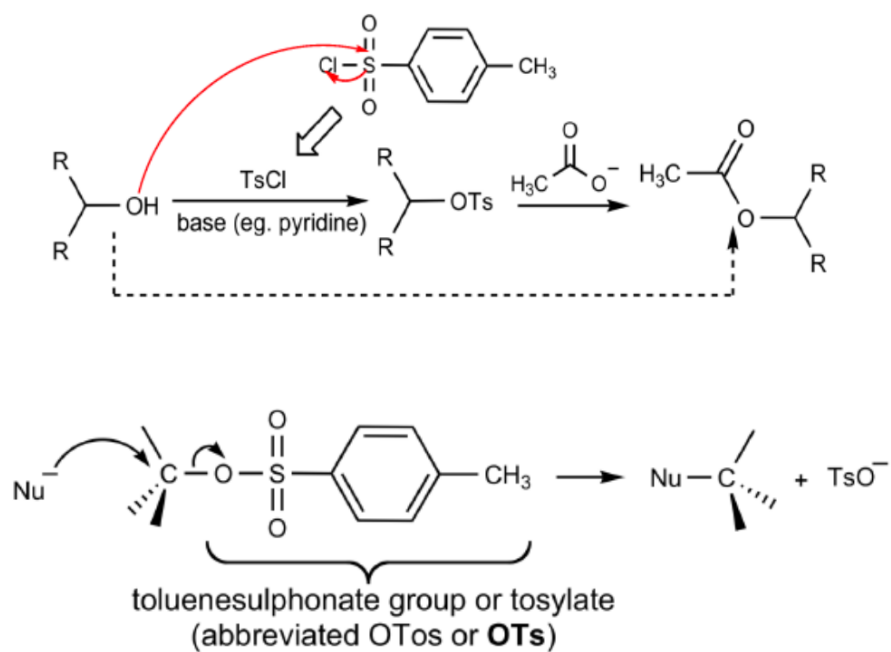
2.2 Nucleophilic strength

- Nucleophilic strength decreases across the same row (left to right) in the periodic table.
- Nucleophilic strength increases down the same group in the period table (in polar protic solvent).
- Negative charge increases the nucleophilic strength.

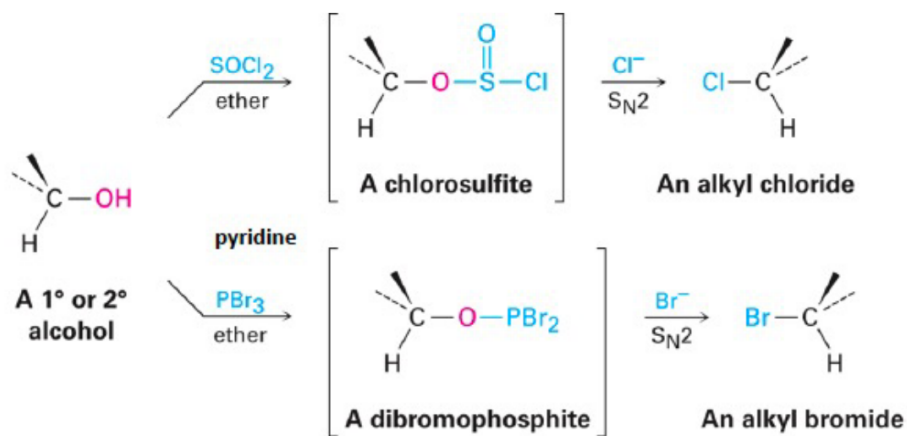
2.3 Leaving group effects

- The more stable the negatively-charged leaving group, the better the leaving group.
- Weak bases are usually good leaving groups as the negative charges are stabilised.
- Bulky groups are often good leaving groups due to **resonance stabilisation**.
- If a leaving group is very basic or small, it does not undergo the S_N2 reaction (e.g. alkyl fluoride, alcohols, ethers and amines do not undergo S_N2 reactions).
- However, you can activate alcohols to make them better leaving groups.

2.3.1 Conversion of alcohols to tosylate



2.3.2 Conversion of alcohols to alkyl halides

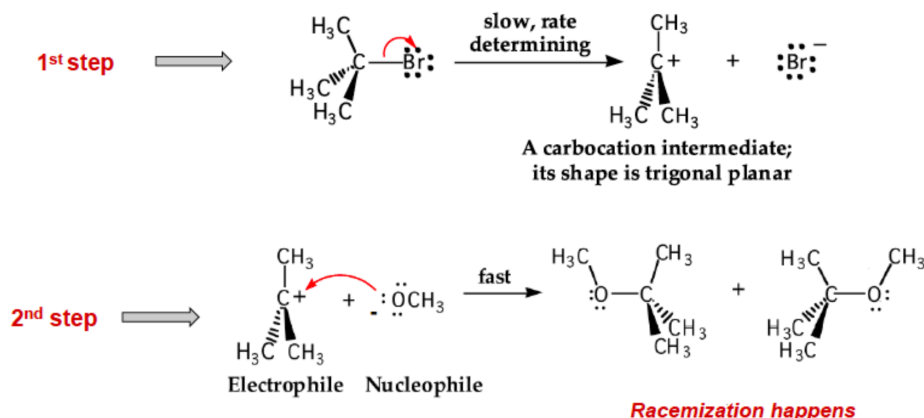


2.4 Solvent effects

- Polar protic solvents form *H*-bond with the anion, which **lowers the reactivity** of the nucleophile.
- Polar aprotic solvents **increase the reactivity of the nucleophiles** by stabilising the cation. They do not undergo hydrogen bonding with the anions.
- Hence **polar aprotic solvents** are better for S_N2 reactions.

3 Nucleophilic substitution: S_N1 reactions

S_N1 reactions have two steps, and the *S* stands for substitution, *N* stands for nucleophilic, and 1 stands for unimolecular.



- In the first step of the S_N1 , the leaving group departs to generate a carbo-cation. The step is the slow step, or the rate-determining step.
- The intermediate is **planar**, and hence the **chirality** is lost.
- In the second step, the nucleophile attacks the carbo-cation. The product is a **racemic mixture** with 50% of each enantiomer.

There are 3 factors that affect S_N1 reactions:

1. Substrate effects
2. Leaving group effects
3. Solvent effects

3.1 Substrate effects

- Alkyl halides that can generate more **stable carbo-cations** are more reactive in the S_N1 pathway.
- **Sterically bulky substituents** are preferred for S_N1 reactions, which is the opposite of S_N2 reactions.

3.2 Leaving group effects

- Good leaving groups facilitates S_N1 reactions, which is the same as S_N2 reactions.

3.3 Solvent effects

The solvent influences the **transition state** and the **intermediate carbo-cation**.

- Polar solvents can stabilise the C^+ in the transition state.
- Polar protic solvents could also stabilise the leaving group.
- Hence, polar protic solvents are ideal for S_N1 reactions.

3.4 Nucleophilic strength

Nucleophilic strength of the nucleophile is **not crucial** as the nucleophile is not involved in the rate determining step. Often, the nucleophile is the solvent itself.

4 S_N2 versus S_N1

| | S_N1 | S_N2 |
|-----------------|-----------------------------|------------------------|
| Electrophile | $CH_3X > 1^\circ > 2^\circ$ | $3^\circ > 2^\circ$ |
| Nucleophile | Strong, unhindered base | Often the solvent |
| Rate | 2^{nd} order | 1^{st} order |
| Solvent | Polar protic | Polar aprotic |
| Leaving group | Weak base | Weak base |
| Stereochemistry | Inversion of configuration | Racemic mixture formed |

5 Elimination

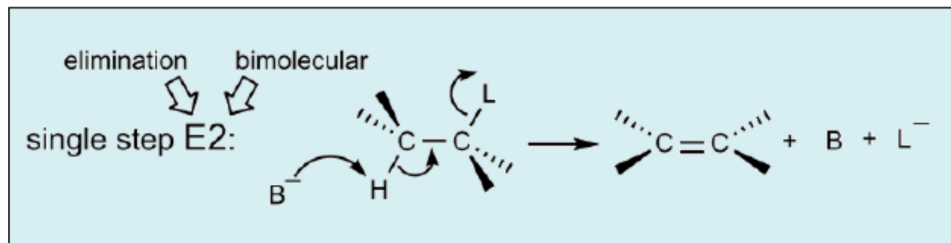
- Elimination reactions compete with nucleophilic substitution reactions in alkyl halides.
- The nucleophile acts as the **base** by plucking the H atom on the **beta carbon atom**.
- **Alkenes** are the result of elimination reactions.

There are 2 types of elimination reactions:

- E2 mechanism
- E1 mechanism

5.1 E2 mechanism

In the E2 mechanism, the breaking of the $R-L$ and $C-H$ bonds is simultaneous. The E2 mechanism is analogous to S_N2 reactions. The E stands for elimination and the 2 stands for bimolecular. The rate for the E2 mechanism is 2nd order.



- The E2 mechanism is a single step reaction with the adduct " $Nu-H-C-X$ " as the intermediate scaffold.
- Nucleophiles attack the $\beta-H$ bond to initialise the elimination.
- E2 occurs in the presence of **strong bases** like OH^- or RO^- .
- Tertiary alkyl halides are good substrates for E2, which is unlike S_N2 .

5.1.1 Stereochemistry

E2 occurs through an **anti-periplanar geometry** of the hydrogen atom bonded to the beta carbon and the halogen group. Basically, the hydrogen atom must be 180° away from the halogen, or the hydrogen atom must be on the opposite side of the halogen group.

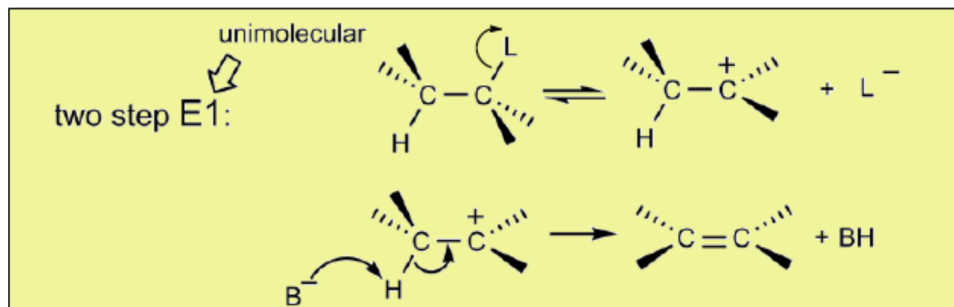
This anti-periplanar requirement makes **E2 reactions stereospecific**. This means the stereochemistry of the product is controlled by the stereochemistry in the starting compound.

5.1.2 Reaction in cyclohexyl halides

- The hydrogen atom and the leaving group should align **trans-diaxial** to be anti-periplanar.
- An **equatorial** leaving group **cannot** undergo elimination via the E2 mechanism.
- So conformation matters in the E2 mechanism.

5.2 E1 mechanism

In the E1 mechanism, the breaking of the $R-L$ bond generates a carbocation. The base then extracts the proton. The E1 mechanism is analogous to S_N1 reactions. The E stands for elimination and the 1 stands for unimolecular.



- E1 occurs with a **weak base** and under **acidic or neutral** conditions (similar to S_N1)
- There is no anti-periplanar requirement for H and X .
- The E1 product often accompanies the product of a S_N1 reaction.
- There are no geometric requirements for E1, which means E1 can take place in any conformation of the cyclohexane ring.

5.3 Zaitsev's rule for elimination

- Elimination often gives a mixture of products when there is more than $\beta-H$.
- The major product is the one with the **more substituted** double bonds.

There are exceptions to the Zaitsev's rule when the base is **bulky**. The base cannot extract the hydrogen atom on the more substituted carbon atom due to **steric hindrance**, and thus the major product is the one with **less substituted** double bonds. One example of such a base is tert-butoxide, $C(CH_3)_3O^-$.

6 E2 and E1 comparison

| | E2 | E1 |
|-----------------------|---|--|
| Rate law | Bimolecular (depends on the concentration of both the substrate and the base) | Unimolecular (depends on the concentration of the substrate) |
| Barrier | None | Formation of carbo-cation $3^\circ > 2^\circ \gg 1^\circ$ |
| Requires strong base? | Yes | No |
| Stereochemistry | Leaving group must be <i>anti</i> to the hydrogen removed | No requirement |

7 Summary of S_N and E

| Substrate carbons | Poor Nu/weak base (acidic H_2O or ROH) | Good Nu & weak base ($N, S, Se, Cl, Br, I, NC^-, N_3^-, S^-, Se^-, AcO^-$) ^a | Good Nu & strong base (N^- & O^-) | |
|--------------------------|--|--|---|-------------------------------|
| | | | Non-bulky (RO^-) | Bulky ($t-BuO^-$, DBU, DBN) |
| Methyl H_3C-L | N.R. | S_N2 | S_N2 | S_N2 |
| Primary (unhindered) | N.R. | S_N2 | S_N2 | E2 |
| Primary (hindered) | N.R. | S_N2 | E2 | E2 |
| Secondary | S_N1 or slow E1 | S_N2 | E2 | E2 |
| tertiary | S_N1 or E1 | S_N1 or slow E1 | E2 | E2 |

L = good leaving groups: halides; tosylates. ^a: reacting atom in nucleophiles are highlighted in red.

8 Determining the mechanism of alkyl halide reactions

8.1 Step 1

Identify the type of carbon atom attached to the halogen atom.

8.1.1 Primary halides (1°)

Primary halides can only undergo **S_N2** and **E2**.

8.1.2 Secondary halides (2°)

Secondary halides can undergo all alkyl halide reactions, so they can undergo **S_N1** , **S_N2** , **E1**, and **E2**.

8.1.3 Tertiary halides (3°)

Tertiary halides can only undergo **S_N1** , **E1**, and **E2**.

8.2 Step 2

Identify the attacking group or the nucleophile.

8.2.1 Weak nucleophile and weak base

Examples include acidic H_2O , ROH , or any neutral molecule in general. The possible mechanisms for this situation are **S_N1** and **E1**.

8.2.2 Weak nucleophile and strong base

Examples include bulky nucleophiles like $t\text{-BuO}^-$, DBU, and DBN. The only possible mechanism in this situation is **E2**.

8.2.3 Strong nucleophile and weak base

Examples include small nucleophiles like N , S , Se , Cl^- , Br^- , I^- , NC^- , N_3^- , S^- , Se^- , and AcO^- . The only mechanism for this situation is **S_N2** .

8.2.4 Strong nucleophile and strong base

Examples include non-bulky nucleophiles like RO^- . The possible mechanisms for this situation are **S_N2** and **E2**.

8.3 Step 3

Identify the solvent.

8.3.1 Polar protic solvent

Examples of polar protic solvents include water and alcohols. They favour S_N1 and $E1$ reactions, and disfavour S_N2 reactions.

8.3.2 Polar aprotic solvent

Examples of polar **aprotic** solvents include acetone, ether, HMPA, and DMSO. Generally the solvents with names in capital letter are polar **aprotic** solvents. They favour S_N2 reactions.

8.3.3 Heat

When there is heat, the mechanism is highly likely to be $E1$.