Reactions of alkyl halides (S_N2, S_N1, E2, E1, E1CB)

There are two general reactions of alkyl halides; *Substitution* and *Elimination*:

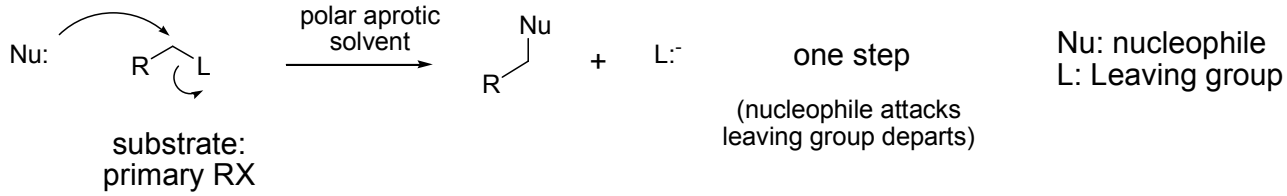
a. Substitution (Nu + R–L → Nu–R + L^-)

Two steps:

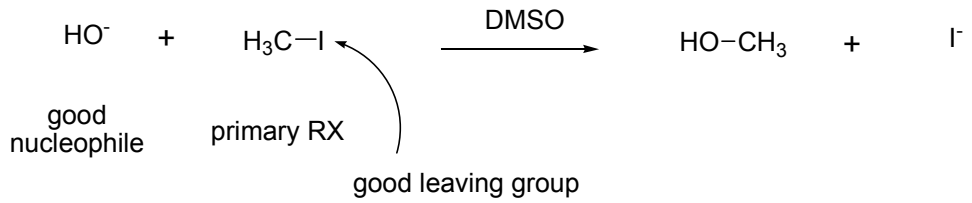
- ***Nucleophilic attack***
- ***Departure of the leaving group***

i. S_N2 (Bimolecular **N**ucleophilic **S**ubstitution; *concerted* **one-step** mechanism)

- ***Nucleophilic attack and departure of the leaving group take place at the same time (one step concerted mechanism)***



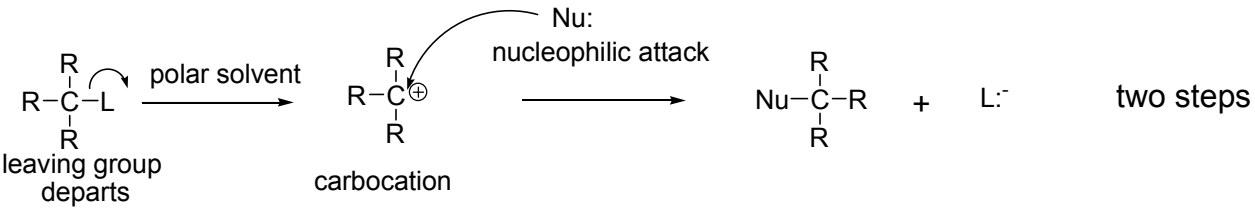
Example:



ii. S_N1 (Unimolecular **N**ucleophilic **S**ubstitution; **two-step** mechanism)

Two step mechanism:

- ***Departure of the leaving group to form a carbocation***
- ***Nucleophilic attack on the carbocation***



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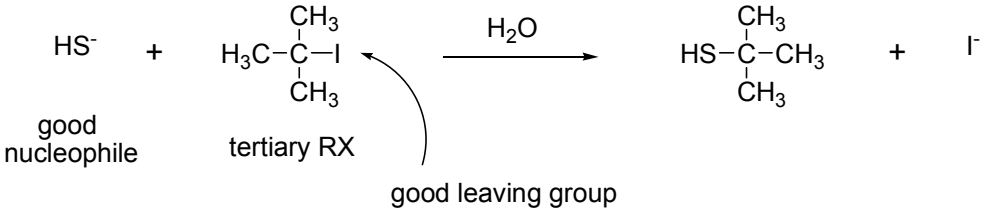


b. Elimination

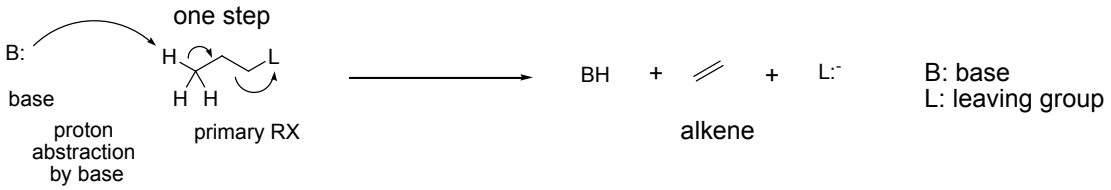
Three steps:

- ***Deprotonation by a base***
- ***Formation of C-C double bond***
- ***Departure of the leaving group***

i. **E2** (*concerted* **<u>one-step</u>** elimination)

- ***Deprotonation by a base, formation of C-C double bond and departure of the leaving group take place at the same time (one step concerted mechanism)***

E2 occurs when an alkyl halide (usually secondary or tertiary) is treated with a strong base such as HO^-, RO^- such as CH_3O^-, $CH_3CH_2O^-$, $(CH_3)_3O^-$
(*t*-butoxide n the form potassium *t*-butoxide ***$(CH_3)_3O^-$ K+ or*** *sodium t*-butoxide ***$(CH_3)_3O^-$ Na+***))



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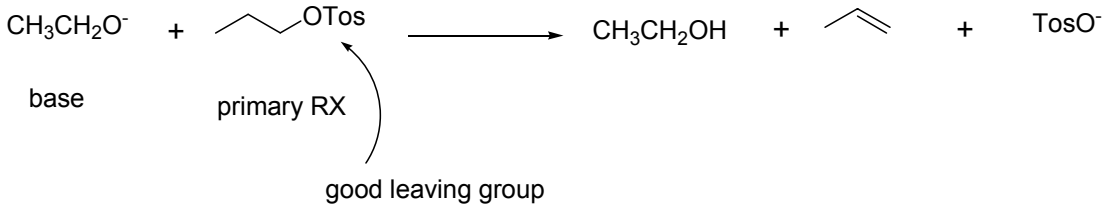
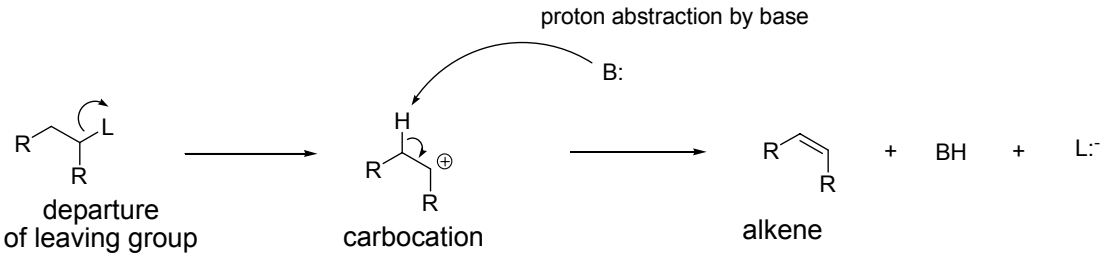


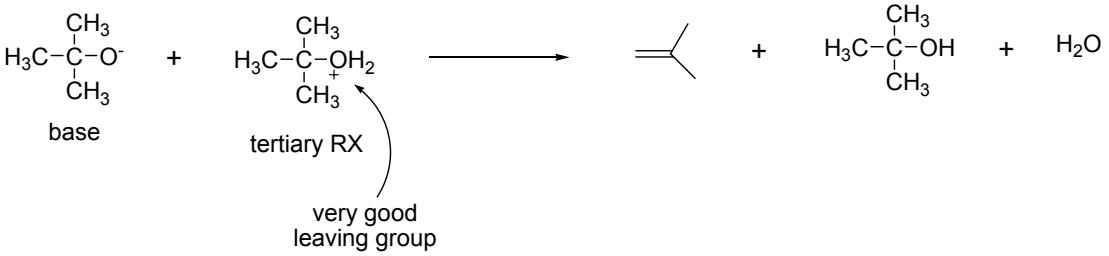
ii. **E1** (**<u>two-step</u>** elimination)

Two steps:

- *Departure of the leaving group*
- *Then proton abstraction by the base followed by formation of the C-C double bond*



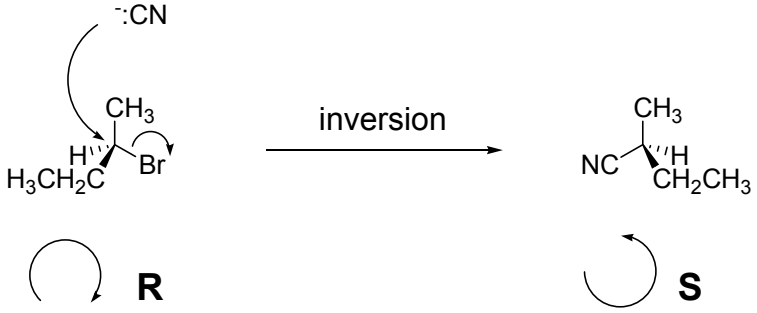
Example:



1. S_N2

- ***Nucleophilic attack and departure of the leaving group take place at the same time (one step concerted mechanism)***

- Second order kinetics
  Rate = *k* [Nu][RX]
- Takes place with inversion of stereochemistry



- Players: Nucleophile, Substrate (alkyl halide), Leaving group, Solvent

i. ***Nucleophile*** ***(more nucleophilic than basic, small and strong)***

Examples:

Species	Nucleophilicity
NC^-	**Excellent**
HS^-	**Excellent**
I^-	**Excellent**
CH_3S^-	**Excellent**
N_3^-	**Excellent**
RO^- Example: CH_3O^-	**Good**
HO^-	**Good**
Br^-	**Good**
N_3^-	**Good**
NH_3	**Good**
NO_2^-	**Good**
Cl^-	**Fair**
$CH_3CO_2^-$	**Fair**
F^-	**Fair**
CH_3OH	**Fair**
H_2O	**Fair**

ii. ***Substrate*** ***(must be sterically accessible; no steric bulk/hinderance)***

Order of Reactivity:

Methyl substrate >> primary substrate >>> secondary substrate

Tertiary alkyl halides are not reactive at all in SN2 reactions.

Branching and increasing the carbon chair decrease the rate of the SN2 reaction.

For example:

Butyl bromide is less reactive than ethyl bromide. 2-Bromo-2-methylpropane is less reactive than 1-bromopropane

iii. Leaving Group

Weak bases that best stabilize the negative charge. Anions (conjugate bases) of strong acids are the best leaving groups.

Leaving Group	Efficiency	Acid	pK_a
I^-	Good	HI	–10
Br^-	Good	HBr	–9
Cl^-	Good	HCl	–7
RSO_2O^- *Example*: $TosO^-$	Good	RSO_3H	–6.5
H_2O	Good	H_3O^+	–1.7
F^-	bad	HF	+ 3.2
HS^-	bad	H_2S	+ 7.0
NC^-	bad	HCN	+ 9.2
HO^-	bad	H_2O	+ 15.7
RO^-	bad	ROH	+ 16-18
NH_2^-	bad	NH_3	36

iv. Solvent

Polar Aprotic (no O–H or N–H bonds) solvents (no solvation of the nucleophile) are the best (the solvents that do not destabilise the nucleophile)

Examples: DMSO, DMF, CH_3CN, HMPA

Polar protic solvents (such as H_2O, alcohols, NH_3) slow down S_N2 reactions *via* solvatio

2. S_N1

- First order kinetics

Rate = *k*[RX]

Two step mechanism:

- ***Departure of the leaving group to form a carbocation***
- ***Nucleophilic attack on the carbocation***

- Generally recemisation occurs. The first step involves departure of the leaving group thus forming an intermediate carbocation. The carbocation will not be chiral anymore since it is trigonal planar. In the second step, the nucleophile can attack the positive carbon from either side leading to both enantiomers. Therefore the product will be a mixture of R/S enantiomers which will then be racemic.
- Players:

i. Nucleophile (must be nucleophilic but not basic) (see table above)

ii. Substrate: **must be sterically inaccessible, sterically bulky/hindered)** the substrate that gives the most stable carbocation is the best

Order of Reactivity:

3º alkyl substrate > 2º alkyl substrate ≈ allylic substrate ≈ benzylic substrate

iii. Leaving group: as before

iv. Solvent: must be ***Polar*** and of high dielectric polarization to stabilize the carbocation intermediate (examples H_2O, CH_3OH, CH_3CH_2OH)

R	**S_N2**	**S_N1**
CH_3	Fast with good Nu and good L	No
Primary	Fast with good Nu and good L (slowed down when there is branching)	No
Secondary	Slow (can work with high conc. of good Nu in polar aprotic solvent)	Slow (can work with good leaving groups in polar protic solvents)
Tertiary	No	Fast with good leaving groups in polar protic solvents

3. E2

- ***Deprotonation by a base, formation of C-C double bond and departure of the leaving group take place at the same time (one step concerted mechanism)***

E2 occurs when an alkyl halide (usually secondary or tertiary) is treated with a strong base such as HO^-, RO^- such as CH_3O^-, $CH_3CH_2O^-$, $(CH_3)_3O^-$
(*t*-butoxide n the form potassium *t*-butoxide ***$(CH_3)_3O^-$ K+ or*** *sodium t*-butoxide ***$(CH_3)_3O^-$ Na+***))

- Second order kinetics

Rate = *k* [B][RX]

- **Zaitsev's rule** applies: the ***most stable*** alkene predominates

- Players:

i. Base (Strongly Basic, weakly nucleophilic): a ***strong base*** such as **alkoxides (RO^-)**, **potassium t-butoxide (K^+ ^-O*t*-Bu**)

ii. Substrate

Order of Reactivity:

Methyl halide >> primary alkyl halide >>> secondary alkyl halide

4. E1

- First order kinetics

Rate = *k*[RX]

- **Zaitsev's rule** applies: the ***most stable*** alkene predominates

Two steps:

- *Departure of the leaving group*
- *Then proton abstraction by the base followed by formation of the C-C double bond*

- Players

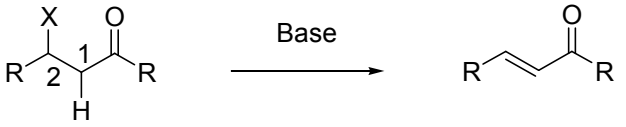
i. **Base (weakly basic)**: a weak *base* such as H_2O will work
ii. **Substrate**: the substrate that gives the most stable carbocation is the best

Order of Reactivity:

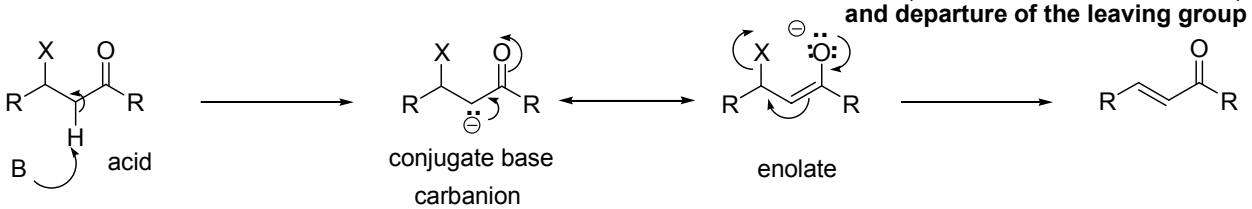
3º alkyl halide > 2º alkyl halide ≈ allylic alkyl halide ≈ benzylic alkyl halide > 1º alkyl halide

5. E1CB

When the leaving group is two carbons away from a carbonyl group



reformation of C-O double bond, formation of new C-C bond, and departure of the leaving group



conjugate base

carbanion

enolate

proton abstrcation by the base

carbanion which resonates to an enolate (resonance stabilisation)