Chapter 10

Synthetic Uses of Substitution and Elimination Reactions

How to use these reactions (S_N1, S_N2, E1, and E2) to make organic compounds?

10.1 Substitution Reactioins

S_N2 is more commonly used than S_N1 for the preparation of organic compounds

⇒**Disadvantages of S_N1;** Loss of stereochemistry and or Rearrangement because carbocation in involved in the rxn

⇒**S_N2 can also accompanied by elimination reactions;** To decrease the elimination, minimize the steric hindrance and/or **decrease the basicity of Nü.**

The effect of substrate;

1. Primary carbon;only S_N2 is possible

2. Secondary carbon; S_N2 is possible when Nü is weak base, while with strong base E2 can be accompanied

⇒ use S_N1

3. Tertiary carbon; no S_N2, use S_N1 for any rate

10.2 Preparation of alcohols

1. From S_N2 using hydroxide ion (a strong Nu and a strong base)

R-L = 1^o alkyl halides

R-L = activated 2^o alkyl halides (allylic, benzylic, or adjacent to a carbonyl group)

However $^{-}$OH is seldom used for unactivated 2^{o} alkyl halides and never used 3^{o} alkyl halides due to the elimination. Therefore

2. From S_N1 using water (weak base) with heating; solvolysis reaction or hydrolysis reaction.

ex)

Preparation of alcohols

1. S_N2; strong basicity of Nü elimination is accompanied
2. S_N1; yield is not high

3. Use synthetic equivalent, acetate, instead of hydroxide

lower basicity (due to resonance), still reasonable Nü.

Then elimination can be minimized ($S_N2 > E2$)

10.3 Preparation of Ethers

1. Williamson synthesis; alkoxide with alkyl halide

Strong base; similar to hydroxide, therefore the same rules are applied.

1. 1^{o} alkyl halides and activated 2^{o} alkyl halides are OK.
2. unactivated 2^{o} alkyl halides are seldom used and 3^{o} alkyl halides are never used due to the elimination

Preparation of alkoxides

1. alcohols (alkyl); use sodium metal (very strong base)

2. phenols; use hydroxides or carbonate (weaker base than sodium metal. Because phenols are nore acidic than alkanols

Examples of Williamson ether synthesis

Preparation of asymmetrical ethers

⇒ Use two different Williamson ether syntheses

Example

elimination can be accompanied.

+ more sterically hindered

better strategy

2. Ether preparation for 2^o alkyl halides or 3^o alkyl halides using alcohols not alkoxide

(1) **ethanolysis; S_N1**

(2) **using strong acids and alcohols; S_N2**

Mechanism

3. preparation of cyclic ethers

(1) Possible by intermolecular rxn.

(2) 3-, 5-, 6- membered rings can be prepared

(3) Both S_N1 and S_N2 mechanisms can be used

Examples

mechanism

10.4 Preparation of esters

⇒ **Using carboxylate salts with 1° or 2° substrate.**

⇒ **As carboxylate salts are only weakly basic, Eliminations are not problem.**

Examples

10.5 Preparation of alkyl halides

1. **Using alcohols with 1° or 2° substrate. As –OH is a poor leaving group, it must be converted into a better leaving group**

Conversion of -OH to -OH_2^+ thorough protonation

⇒ **Halogen acids protonate the –OH and provide nucleophile.**

⇒ **Favor S_N1, while S_N2 is possible for 1° substrates unless a resonance-stabilized carbocation is formed.**

⇒ **Stronger acids, HBr and HI work alone**

⇒ **weaker acid, HCl, are used together with a Lewis acid such as $ZnCl_2$**

Examples

Conversion of the alcohol (OH) into a sulfonate ester (OTs or OMs).

⇒ **Requires two steps**

Example

2. Using alcohols with $SOCl_2$, PBr_3, or PI_3; one step reaction.

⇒ **Using sulfonyl chloride ($SOCl_2$);** generally via S_N1 mechanism for 2°and 3° substrates or S_N2 mechanism for 1° substrates.

Examples

mechanism

⇒ **Using PBr_3 and PI_3;** rxn mechanism is similar to that using thionyl chloride.

Examples

3. S_N2 reaction using one halogen as the leaving group and different halide ion as the nucleophile

⇒ It is a equilibrium reaction. We need a driving force to shift the equilibrium.

Example

⇒ NaI is soluble in aceton, while NaBr and NaCl is insoluble.

10.6 Preparation of amines

1. **Ammonia and unhindered amines are good nucleophile, therefore S_N2 mechanism is possible with alkyl halides or sulfonate esters**

⇒ **Disadvantage; multiple alkylation**

Example

⇒ **nucleophilicity; ammonia < 1° amine < 2° amine**

while 3° amine is not a strong nucleophile because of steric effect

2. Gabriel synthesis; better method to prepare primary amines

⇒ Using a phthalimide; not very basic or nucleophilic

not basic or nucleophilic because of the resonance structure

Example

⇒ KOH is used to remove –H (pk_a value of phthalimide is 9.7)

mechanism

10.7 Preparation of Hydrocarbon

- ⇒ **S_N2 mechanism (reactions with only 1^o and 2^o carbon) using a hydride ion (H^-)**
- ⇒ **Source of the hydride ion; lithium aluminium hydride and sodium borohydride**

General rxn

Examples

10.8 Formation of C-C bonds

- ⇒ Larger compounds can be made.
- ⇒ S_N2 mechanism using a carbanion (carbon anion)

General rxn

1. Using cyanide ion;

- ⇒ High yields for 1^o substrate.
- ⇒ For 2^o substrate, yields are lower due to competing elimination

Examples

2. Using acetylide anion

⇒ **Generated by treating 1-akyne with a very strong base**

$pK_a = 25$ **very strong base** **less strong base**

⇒ **acetylide anoins still strong bases and strong nucleophiles.**

⇒ **High yields for 1^o substrate.**

⇒ **For 2^o substrate, major rxn is elimination**

10.9 Phosphorus and Sulfur Nü

⇒ S and P comp’ds are weaker bases but better Nü’s compared with O and N compunds.

(S and P are larger than O and N)

⇒ Excellent yields from S_N2 mechanism

⇒ Both 1^o and 2^o substrate can be employed in the substitution reaction without elimination.

10.10 Ring opening of Epoxides

- ⇒ $^{-}$OH and $^{-}$OR are both strongly basic, therefore they are very poor leaving groups.
- ⇒ Generation of a leaving group from them; through protonation. See chap 8 for alcohols.

This rxn requires more vigorous condition than that for the alcohol.

Therefore not commonly used.

Epoxide (cyclic ether) can be used for the substitution rxn because it is unstable due to a ring strain.

Under basic or neutral conditions

⇒ S_N2 mechanism

Why S_N2 ?

1. two reactants are involved.
2. nucleophile reacts at less hindered carbon.
3. inversion of configuration.

2. Under acidic conditions

⇒ **mechanism between S_N1 and S_N2**

Why?

1. Stereochemistry; S_N2

⇒ The nucleophile attacks the side opposite the leaving group, then a phase inversion happens.

2. Regiochemistry; S_N1

⇒ The rxn occurs at the more hindered carbon.

mechanism between S_N1 and S_N2

Possible transition state

More stable;pheny group stabilize the positive charge of the carbon

10.11 Elimination of Hydrogen Halides

(dehydrohalogenation)

⇒ **Preparation of Alkene; rxns of alkyl halides with strong bases or of sulfonate esters with strong bases.**

⇒ **strong bases; NaOH, KOH, NaOEt, KOMe, *tert*-butoxide (*t*-BuO- for less hindered substrate if not S_N2) etc.**

Examples

10.12 Preparation of alkynes

- ⇒ by elimination of two molecules of HX.
- ⇒ very strongly basic codntions are employed; KOH at high temperatures or using sodium amide (very strong base).

Examples

One step

pK_a ~ 38

pK_a ~ 25

More basic than acetylide anoin

Two step

⇒ **using vinyl chloride at very basic conditions.**

Examples

10.13 Dehydration

- ⇒ rxn of an alcohol with a catalytic amount of sulfuric or phosphoric acid.
- ⇒ generally the rxns follows E1 mechanism; 3° alcohols are more reactive then 2° alcohols.
- ⇒ One of the few cases in which E1 is favored over S_N1; because there are no good Nü in the rxns (HSO_4^- and $H_2PO_4^-$ are not very nucleophilic)

Examples

mechanism

The acid is regenerated. Therefore only catalytic amount of acid is needed.

The limitation of dehydration ⇒ carbocation rearrangements.

Zaitsev’s isomeric mixtures

10.14 Elimination to form C=O bonds; oxidation

1. Oxidation; a loss of electrons or an increase in oxygen content
2. Reduction; a gain in electrons or an decrease in oxygen content.

Oxidation of alcohols

⇒ To oxidize alcohols, the hydrogen on the oxygen should be replaced by some leaving groups

⇒ leaving groups; metals in high oxidation state such as chronium in the +6 oxidation state (see table 9.10)

⇒ after oxidation the metals are reduced to lower oxidation state.

mechanism

Useful oxidizing reagents

10.15 The strategy of organic synthesis

⇒ **retrosynthetic analysis**

Example; synthesis of

⇒ **2^{o} alkyl halide in route A ; elimination is possible with a strong acid.**

⇒ **Route B is acceptable.**

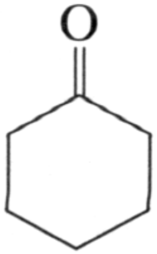
1. preparation of alkoxide

2. preparation of cyclopentanol

3. preparation of final product

Example; synthesis of $CH_3CH_2{-}C{\equiv}C{-}CH_2CH_2CH_3$ from $H{-}C{\equiv}C{-}H$

Example; synthesis of



from an alkyl halide