

# **Advance Organic Synthesis and Reaction Mechanism**

**Lect.1**

## **Rearrangements**

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*Rearrangements and Neighboring Group Effects*  
*Nonclassical Ions*  
*Intramolecular nucleophilic attack*

Carbonium ions can rearrange through migration of an organic group or a hydrogen atom, with its pair of electrons, to the electron-deficient carbon.

When an electron-deficient carbon is generated, a near-by group may help to relieve this deficiency.

It may, of course, remain in place and release electrons through the molecular framework, inductively or by resonance or it may actually carry the electrons to where they are needed

The *most important class of molecular rearrangements* is that involving *1,2-shifts* to electron-deficient atoms.

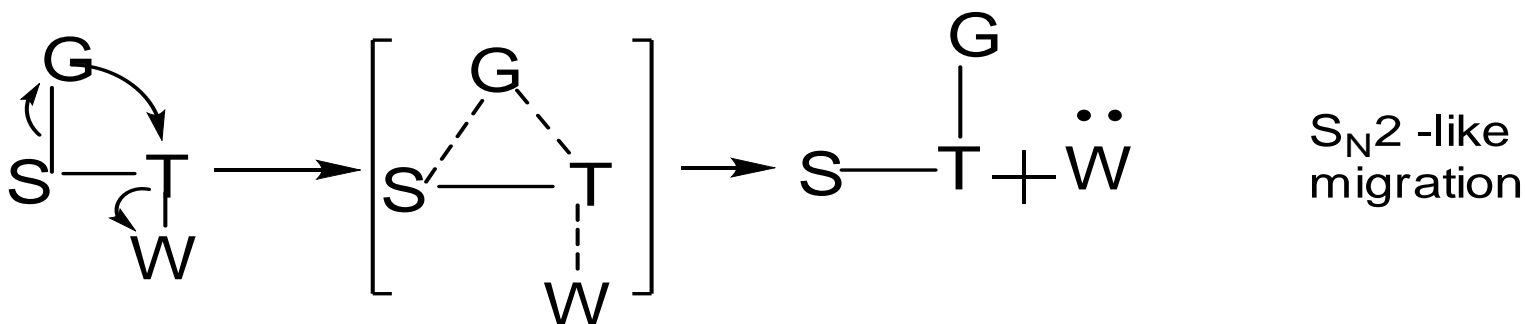
An *electron-deficient carbon* is most commonly *generated* by the departure of a *leaving group* which takes the bonding electrons with it.

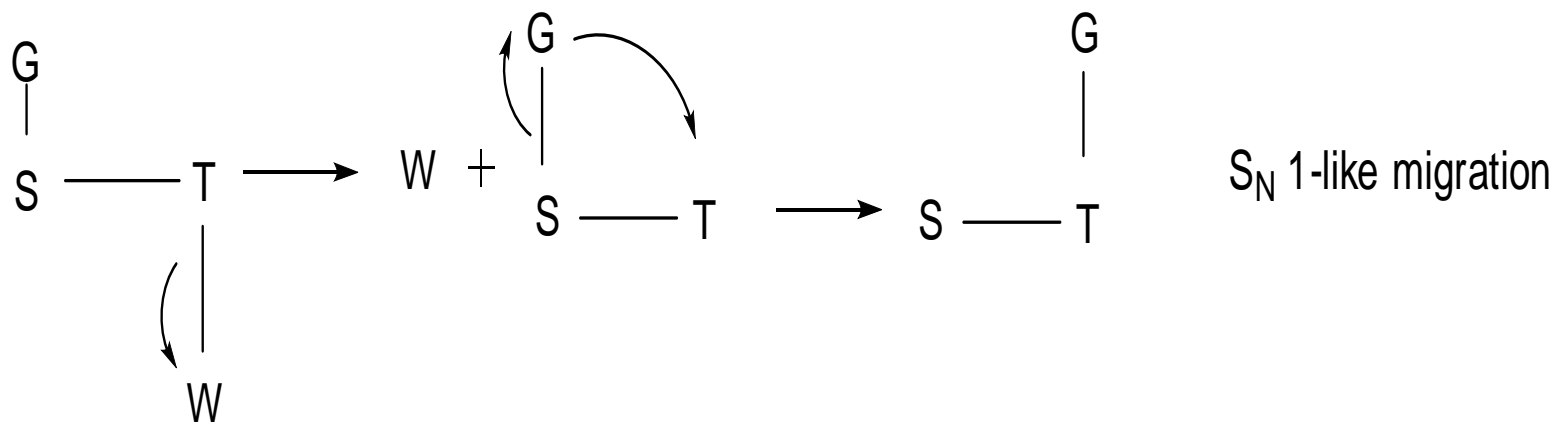
The *migrating group* is a Nucleophile, and so a rearrangement of this sort amounts to *intra-molecular nucleophilic substitution*.

Now *Nucleophilic substitution* can be of two kinds, SN2 and SN1

Exactly the same possibilities exist for a *rearrangement*:

it can be SN2-like, with the *migration group* helping to push out the *leaving group* in a *single step reaction*; Or it can be SN1-like, with the *migrating group* waiting for the departure of the *leaving group* before it moves.





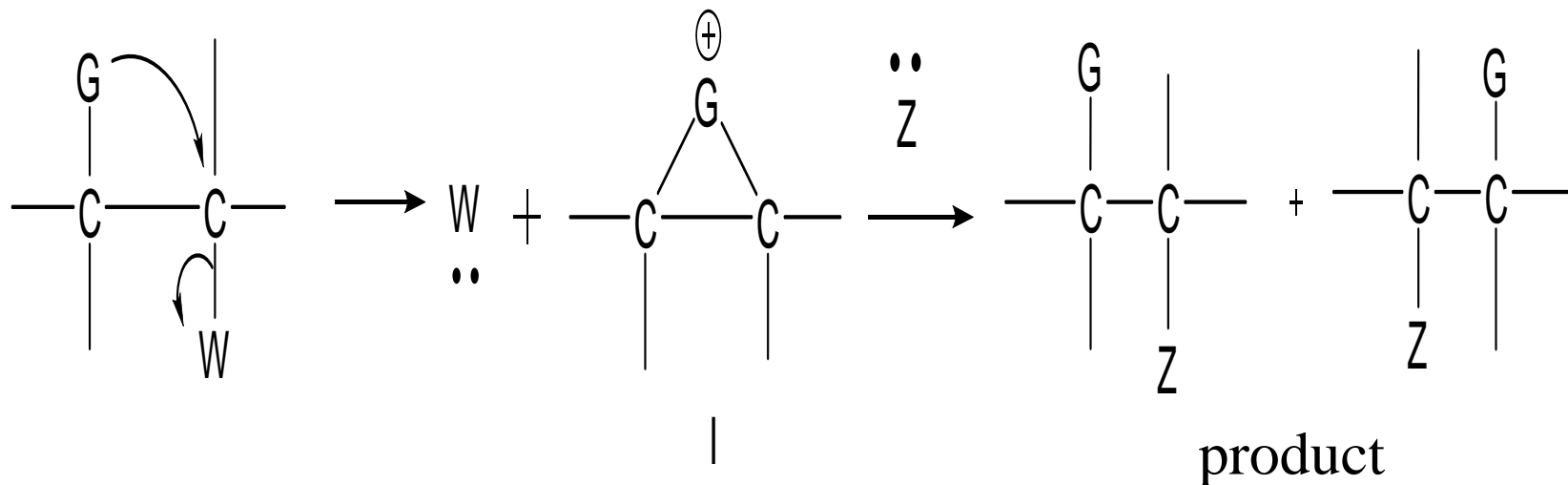
This matter of timing of ***bond-breaking*** and ***bond making*** is of major concern in the study of rearrangements.

The term ***anchimeric assistance*** (Gr., anchi + meros, adjacent parts) is often used to describe the help given by ***a migrating group*** in the expelling of a ***leaving group***.

*Neighboring group effects involve the same basic process as rearrangement*

Which is *Intramolecular effects* exerted on a reaction through direct participation—that is, through movement to within bonding distance—by a group near the reaction center.

The neighboring group, acting as an *Internal Nucleophile*, attacks carbon at the reaction center; the leaving group is lost, and there is formed a bridged intermediate (1) usually a *cation*. This undergoes attack by an *external nucleophile* to yield the product.



If the *Neighboring group* is to form a **bridged cation**, it must have electrons to form the extra bond. These may be *unshared pairs* on atoms like sulfur, nitrogen, oxygen, or bromide; pi electrons of a double bond or aromatic ring; or even, in some cases, sigma Electrons.

## *Neighboring group participation (NGP)*

Groups remote from a reaction centre can participate in substitution reactions –Neighboring Group

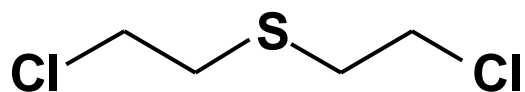
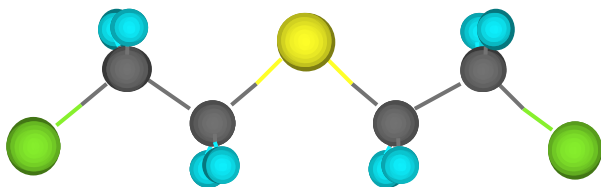
Participation (NGP)(or Anchimeric assistance):–lone pairs of electrons, typically on N, O, S or Hal atoms interact with electron deficient/cationic centers



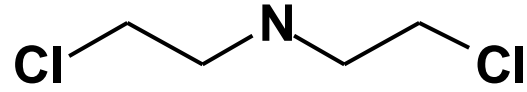
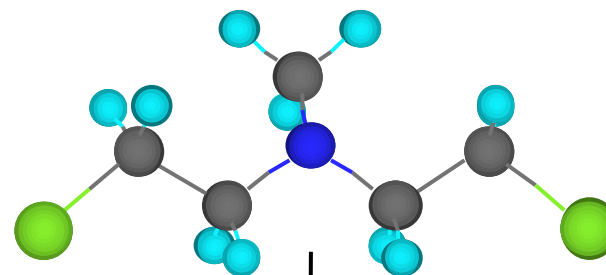
# Neighboring Group Effect

- **Mustard gases**

- contain either S-C-C-X or N-C-C-X

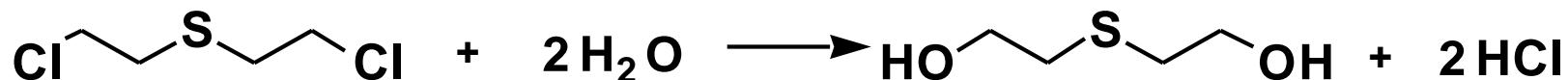


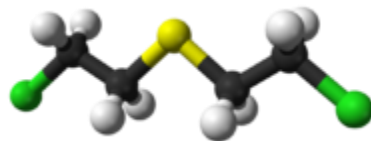
**Bis(2-chloroethyl)sulfide**  
(a sulfur mustard gas)



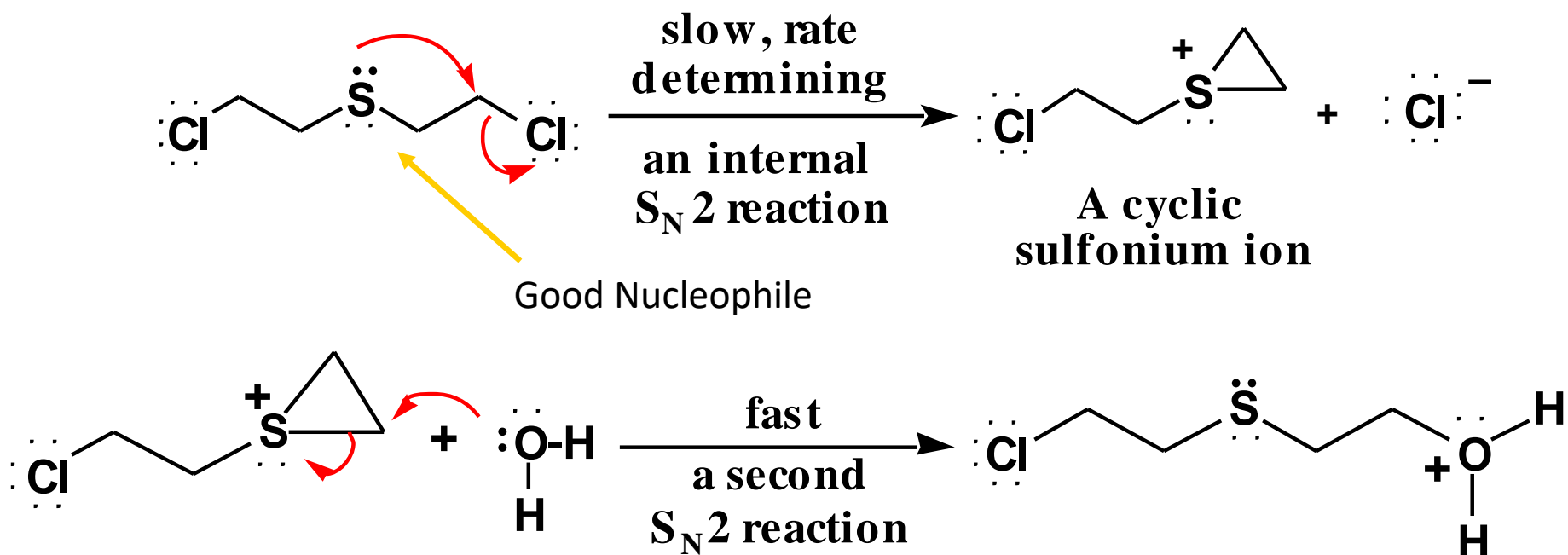
**Bis(2-chloroethyl)methylamine**  
(a nitrogen mustard gas)

- **What is unusual** about the mustard gases is that they **undergo hydrolysis rapidly** in water, (a very poor nucleophile).





- The reason is **Neighboring group participation** by the adjacent heteroatom

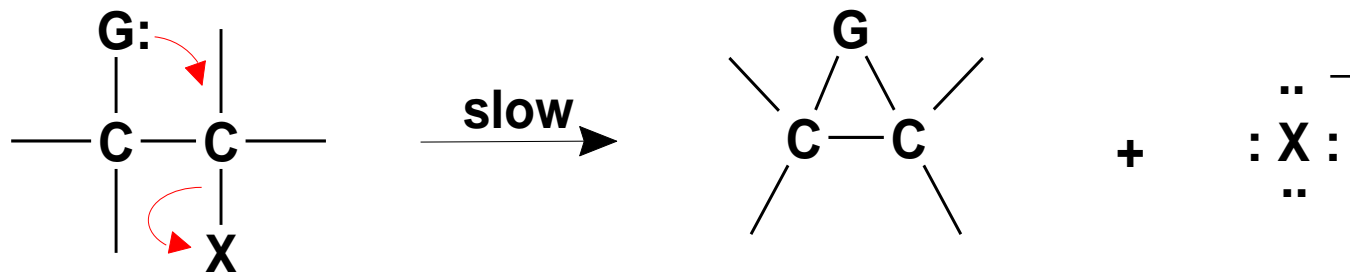


- proton transfer to "solvent" completes the reaction

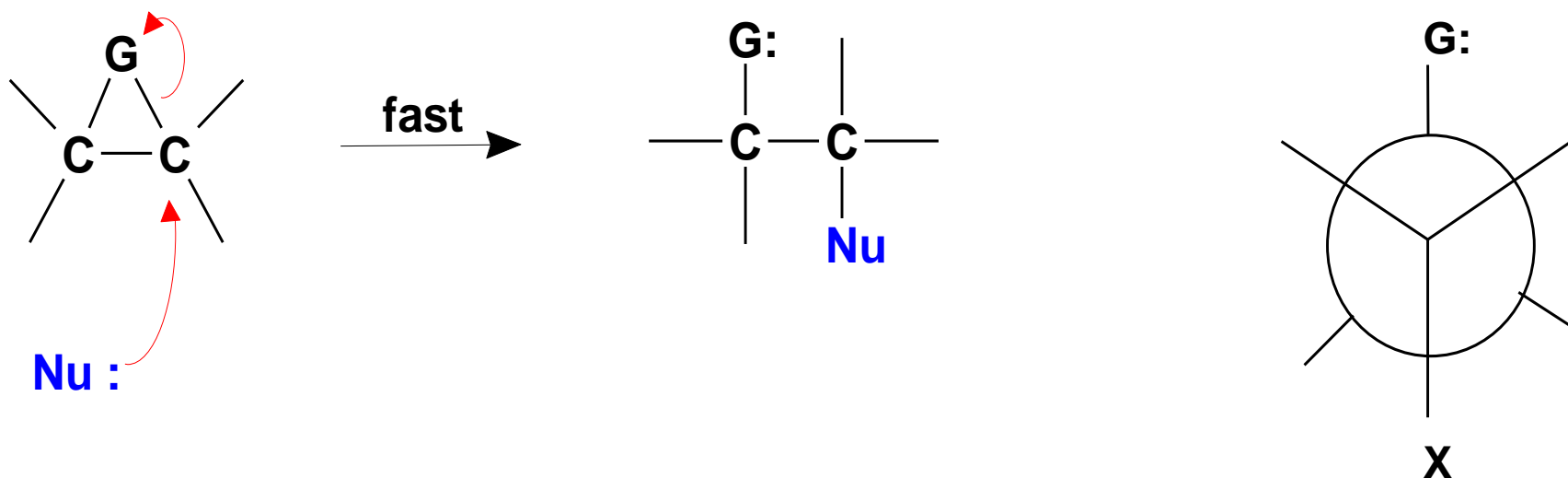
# Neighboring Group Participation

Internal  $S_N2$  reaction followed by an external  $S_N2$  reaction

1)

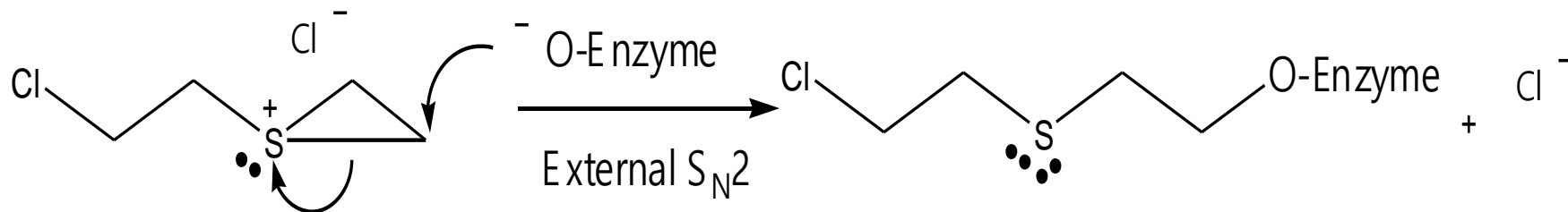
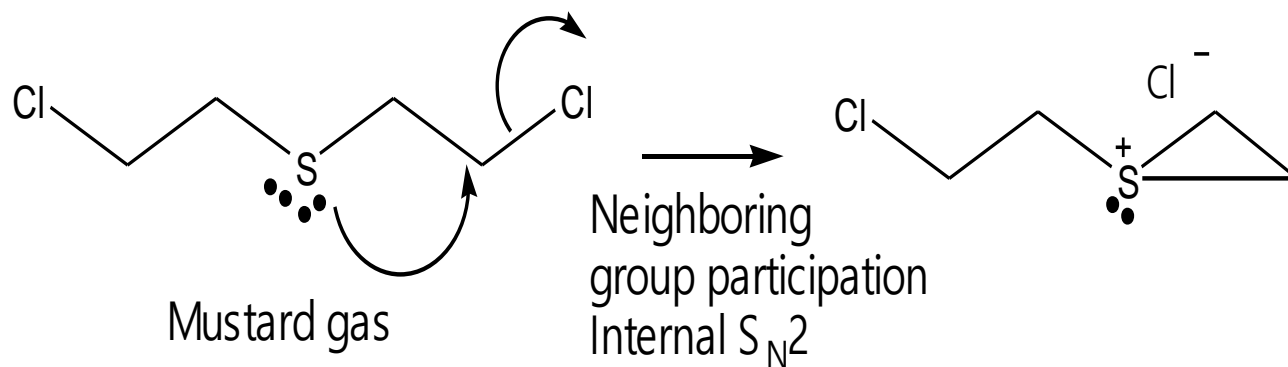


2)



# Mustard gas

- Mustard gas is a substance that causes tissue blistering (a vesicant). It is highly reactive compound that combines with proteins and DNA and results in cellular changes immediately after exposure. Mustard gas was used as a chemical warfare agent in World War I by both sides.



## **Neighboring group participation:**

- Enhanced rate of reaction
- Retention of configuration

# REARRANGEMENTS ON HETEROATOMS

Rearrangement occurs in many organic reactions.

Rearranged products result from the thermodynamic stability aspect.

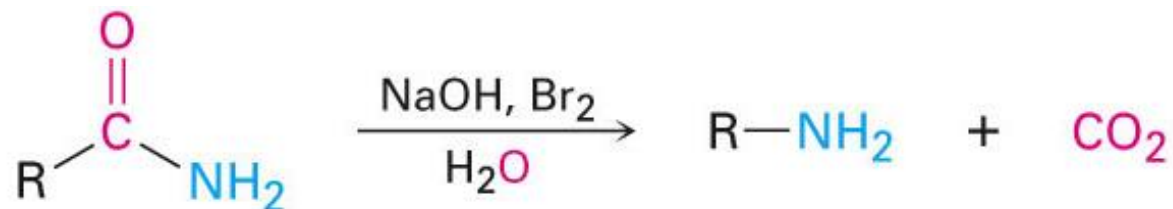
The widely used rearrangements are those which take place on the carbonium ions.

Wagner-Meerwein rearrangement is undoubtedly the best example of this kind.

*Rearrangements on heteroatoms such as oxygen and nitrogen* in organic compounds are best illustrated by those of Hofmann and Beckmann. Cope and Claisen rearrangements are among the most well-known pericyclic reactions (**reactions with cyclic transition states**) governed by the Woodward-Hoffmann rules.

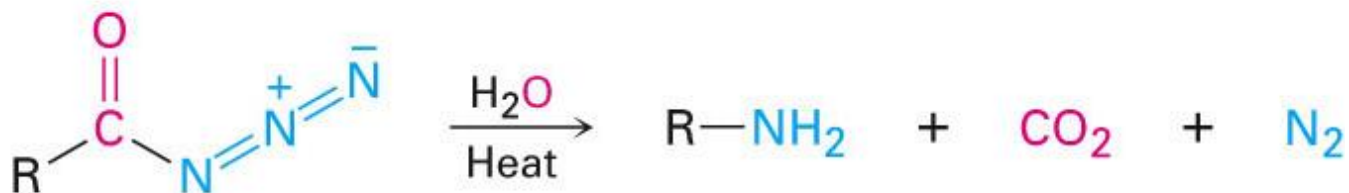
# Hofmann and Curtius Rearrangements

## Hofmann rearrangement



An amide

## Curtius rearrangement



An acyl azide

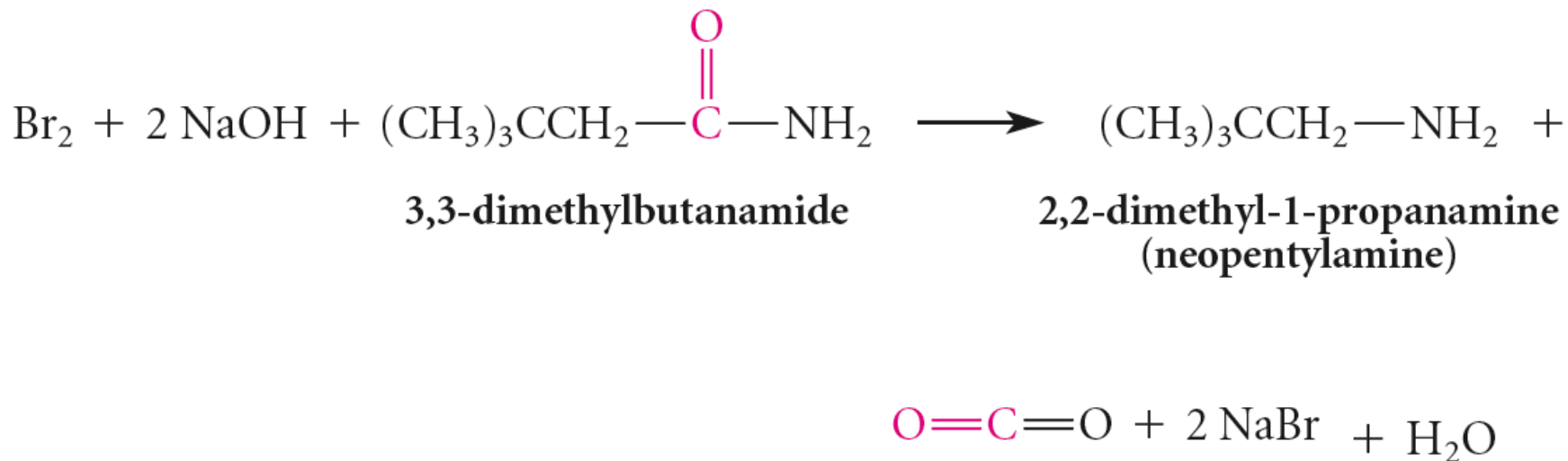


# Hofmann rearrangement

In 1882 A. W. Hofmann found that the reaction of amides with bromine in basic solution afforded products with one carbon less than the starting amide. This latter aspect of the reaction, often called *Hofmann degradation* makes this rearrangement a distinct reaction in synthesis. It is interesting to note that the *Hofmann degradation* yields products with retention of configuration.

# The Hofmann Rearrangement

- Sometimes called the **Hofmann hypobromite reaction**
- $\text{Cl}_2$  is sometimes used in place of  $\text{Br}_2$
- A primary amide is the required starting compound



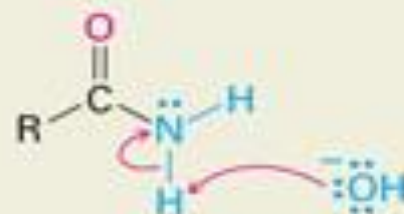
# *Hofmann rearrangement. Migration to electron-deficient nitrogen*

Treatment of amides with bromine in basic solution gives an amine with **loss of the carbonyl carbon**.

## ***The Mechanism of Hofmann rearrangement***

1. formation of an *N-bromo amide*
2. conversion of the *N-bromo amide to an isocyanate*
3. hydrolysis of the isocyanate

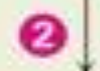
Amide



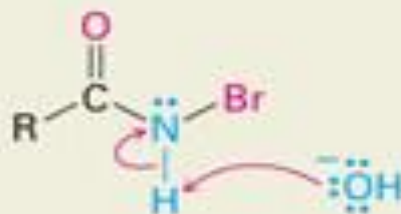
- 1 Base abstracts an acidic N-H proton, yielding an amide anion.



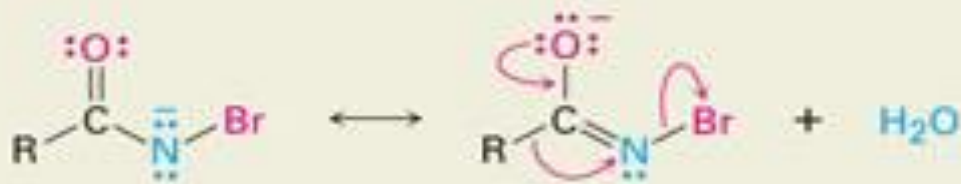
- 2 The anion reacts with bromine in an  $\alpha$ -substitution reaction to give an *N*-bromoamide.



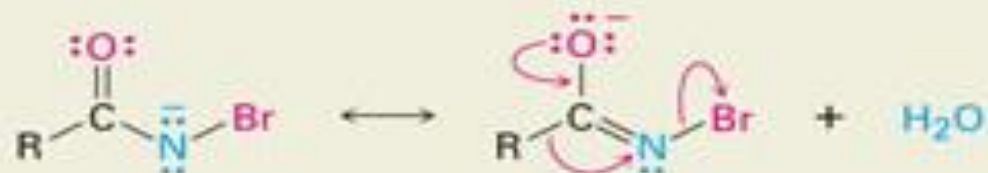
Bromoamide



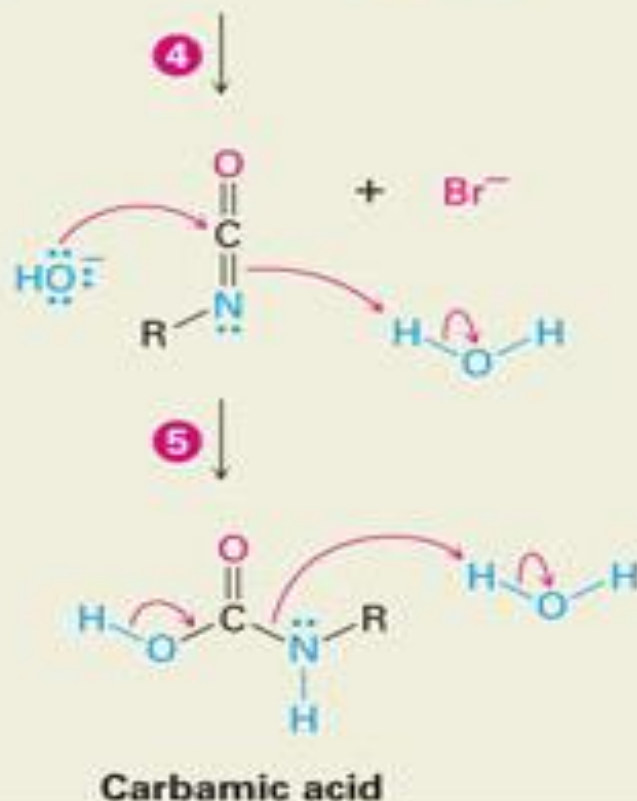
- 3 Abstraction of the remaining N-H proton by base gives a resonance-stabilized bromoamide anion . . .



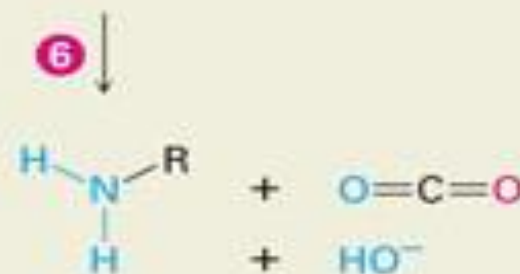
- 4 . . . which rearranges when the R group attached to the carbonyl carbon migrates to nitrogen at the same time the bromide ion leaves.



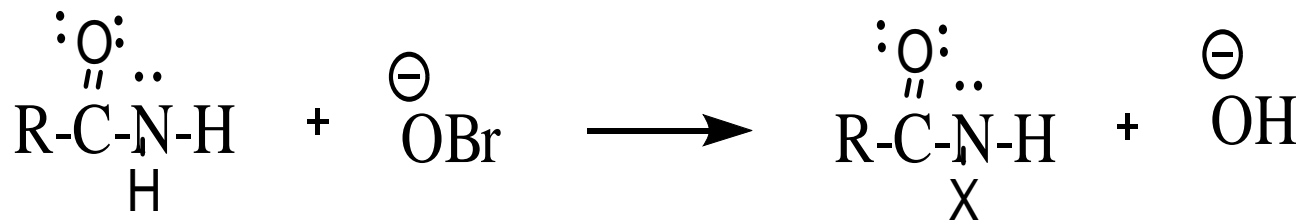
- 5 The isocyanate formed on rearrangement adds water in a nucleophilic addition step to yield a carbamic acid.



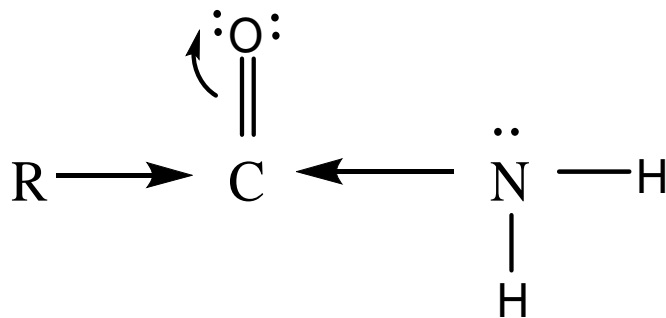
- 6 The carbamic acid spontaneously loses CO<sub>2</sub> to give an amine.

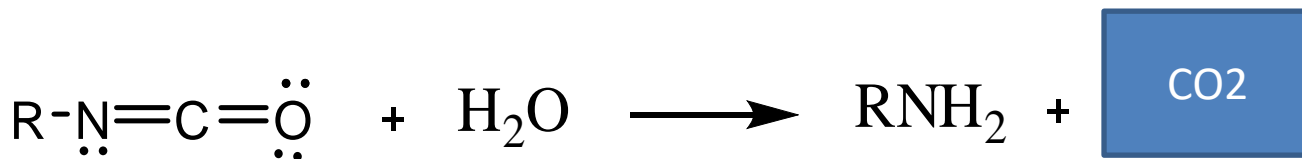
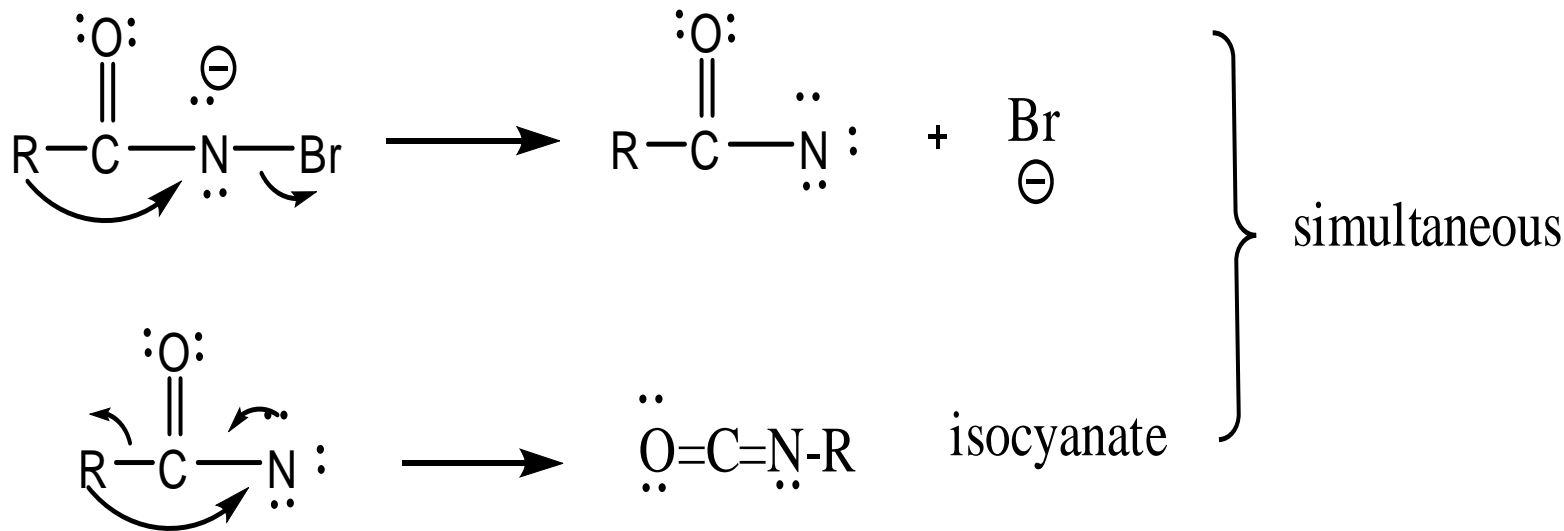
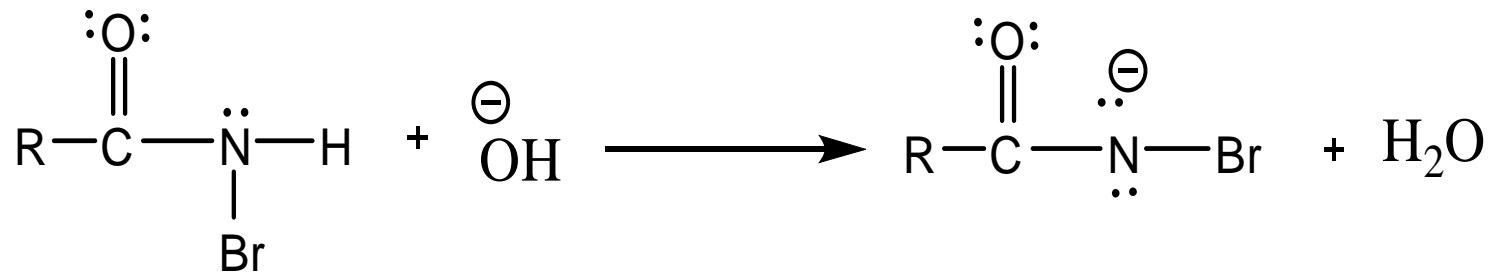


# The classical mechanism

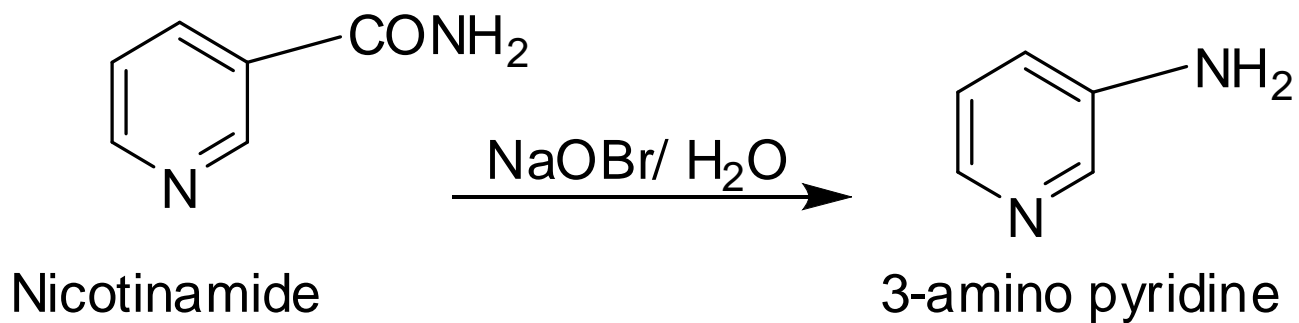
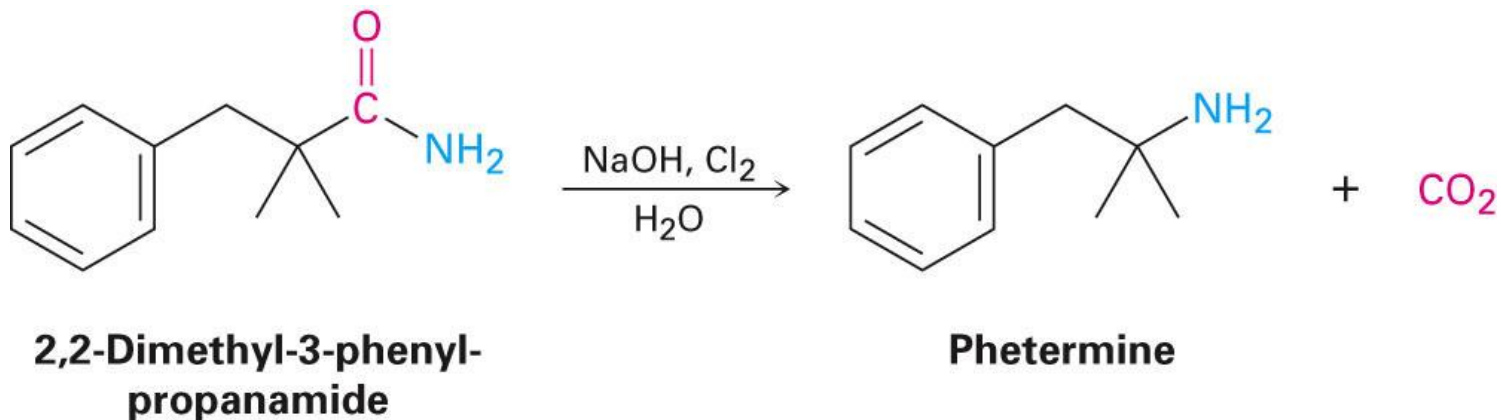


$\ominus \text{OBr}$  is more basic than  $\ominus \text{OH}$



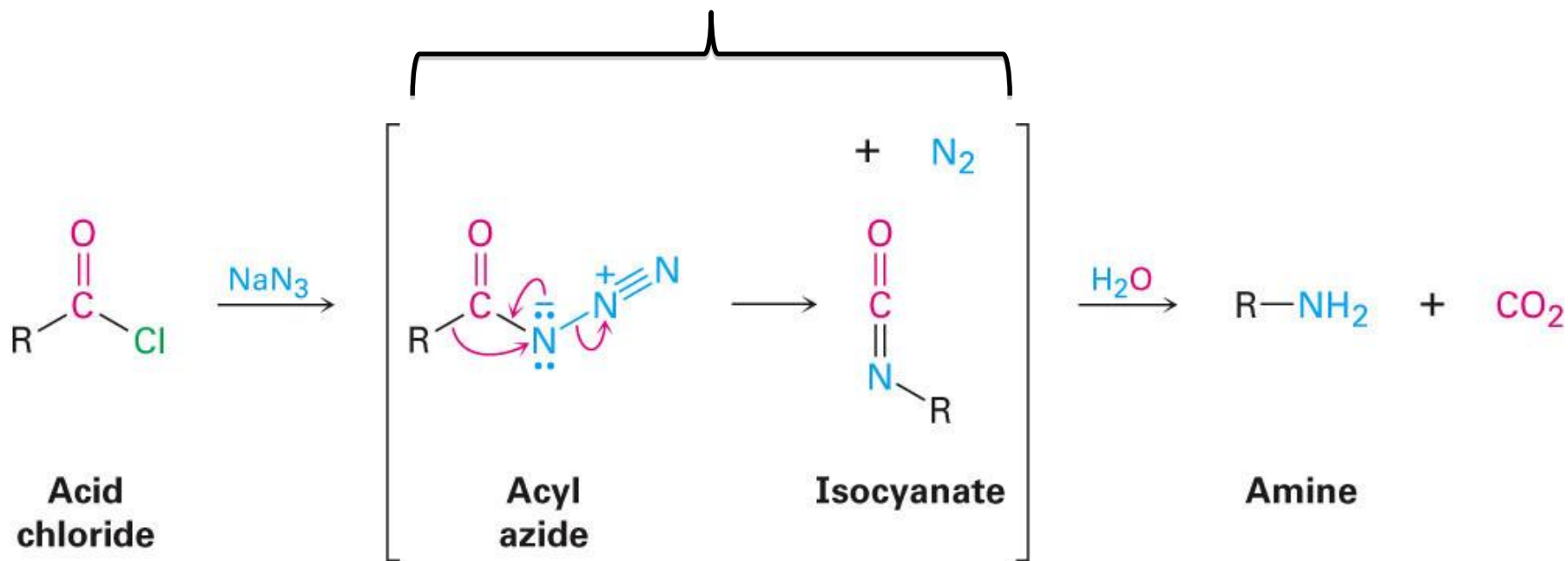


# Hofmann example:

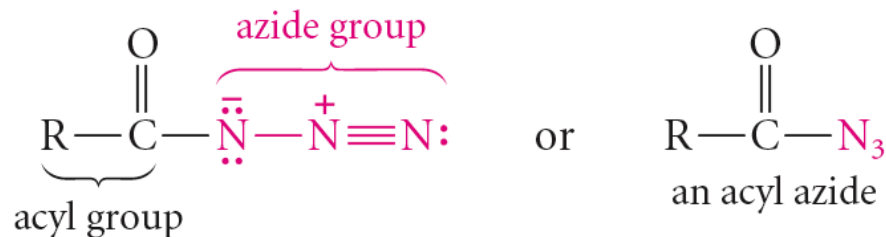




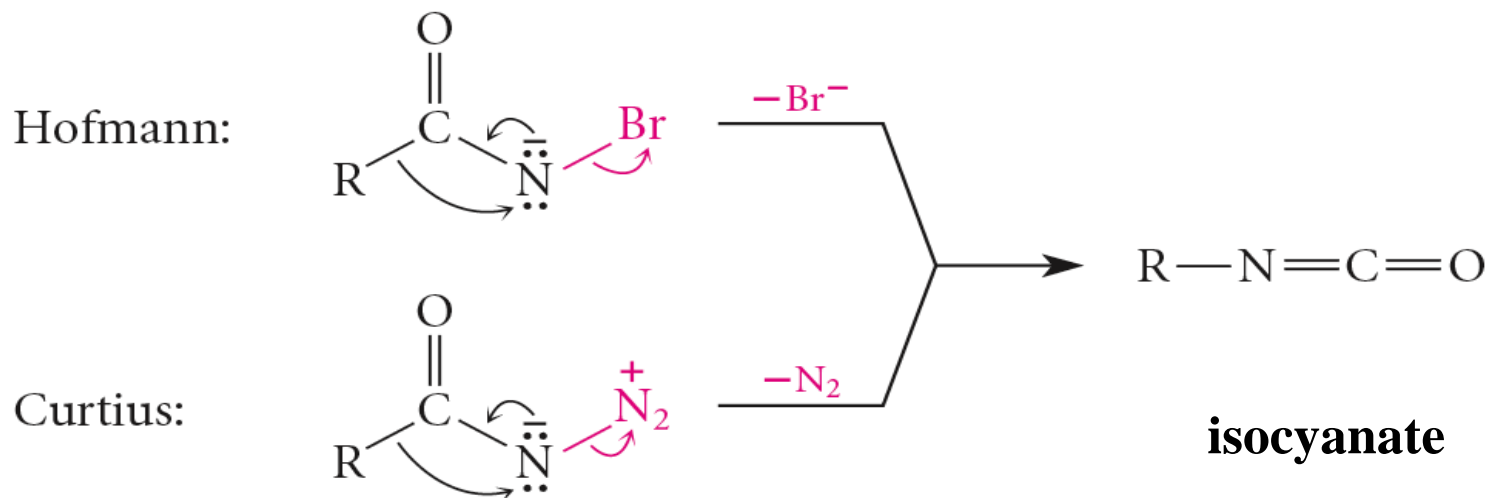
# The Curtius Rearrangement



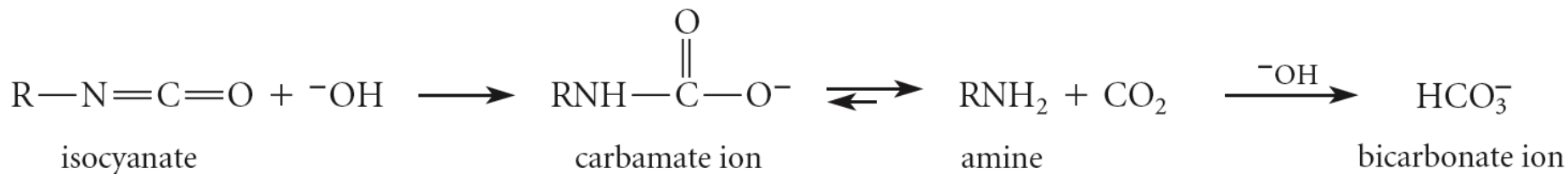
- **Acyl azides** provide access to primary amines via an **isocyanate**
- Concerted reaction



# Hofmann vs. Curtius

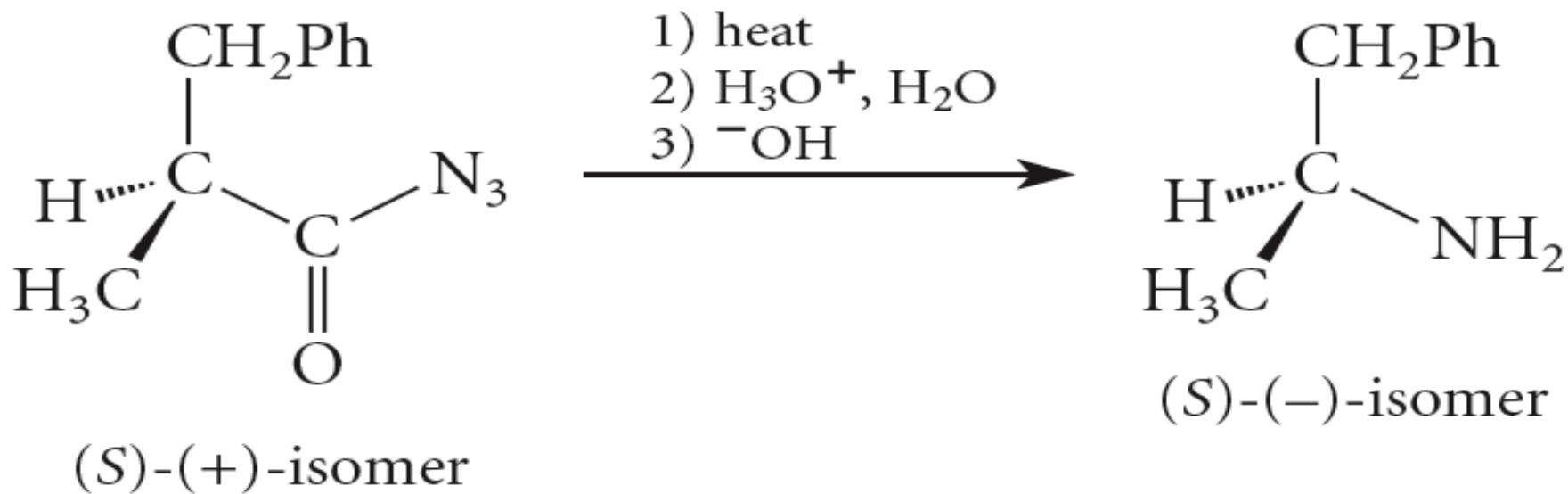


- In the Hofmann rearrangement, the isocyanate cannot be isolated as the reaction is carried out in aqueous base**

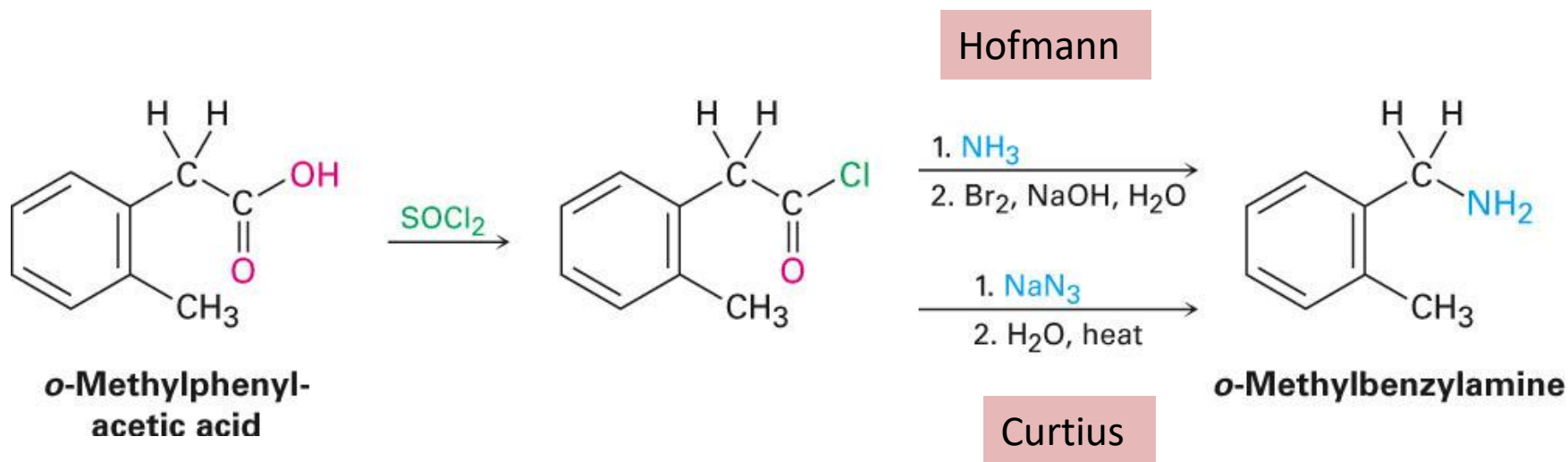


# Curtius and Hofmann Rearrangements

In both of these reactions, the alkyl group migrates with complete retention of configuration



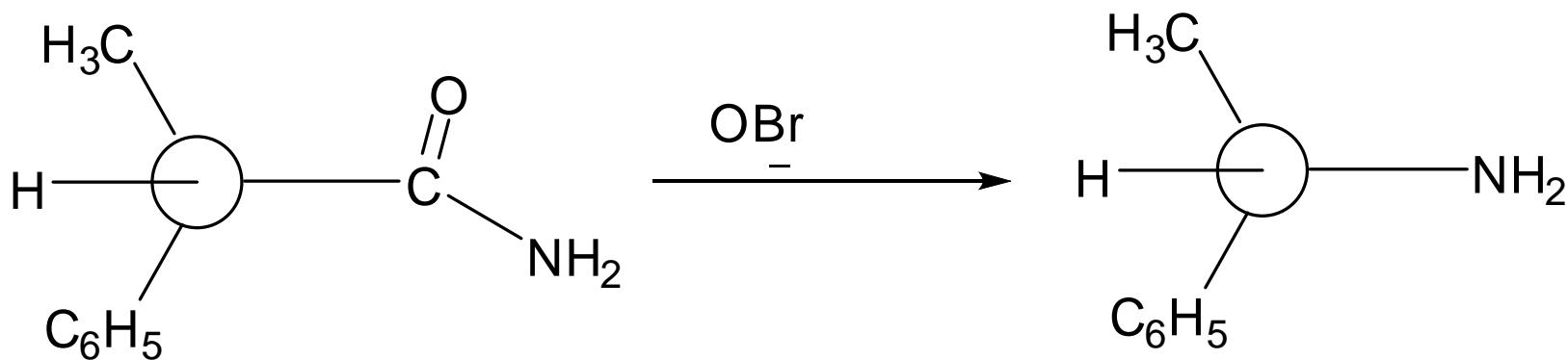
**Q1) Prepare o-methylbenzylamine from a carboxylic acid using a Hofmann rearrangement.**



**Q2) Prepare o-methylbenzylamine from a carboxylic acid using a Curtius rearrangement.**

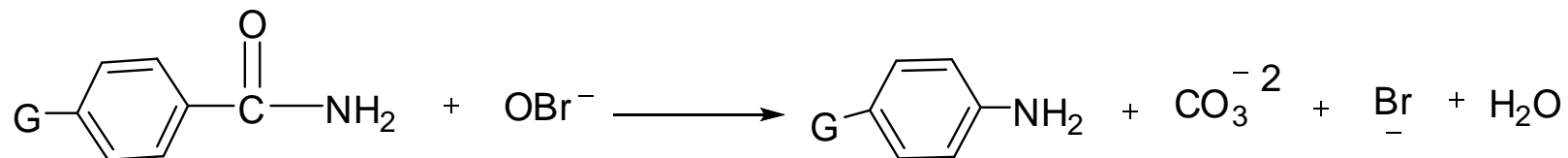
## *Hofmann rearrangement. Stereochemistry at the migrating group*

When optically active alpha-phenylpropionamide undergoes the Hofmann degradation, alpha-phenylethylamine of the same configuration and of essentially the same optical purity is obtained:



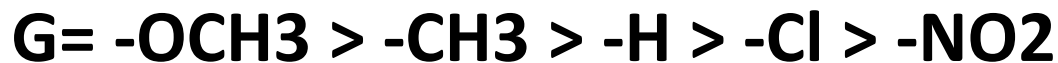
Retention of configuration

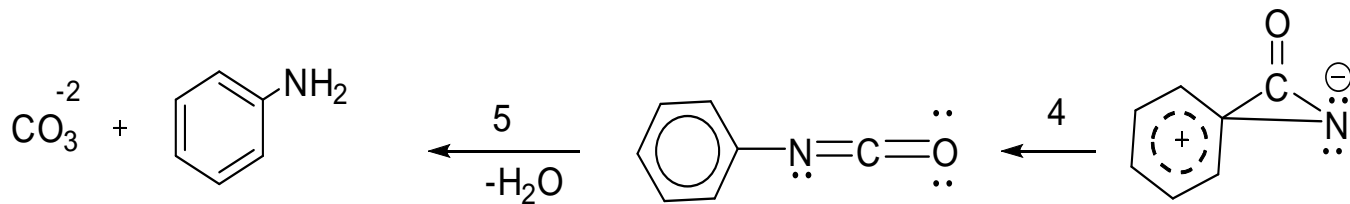
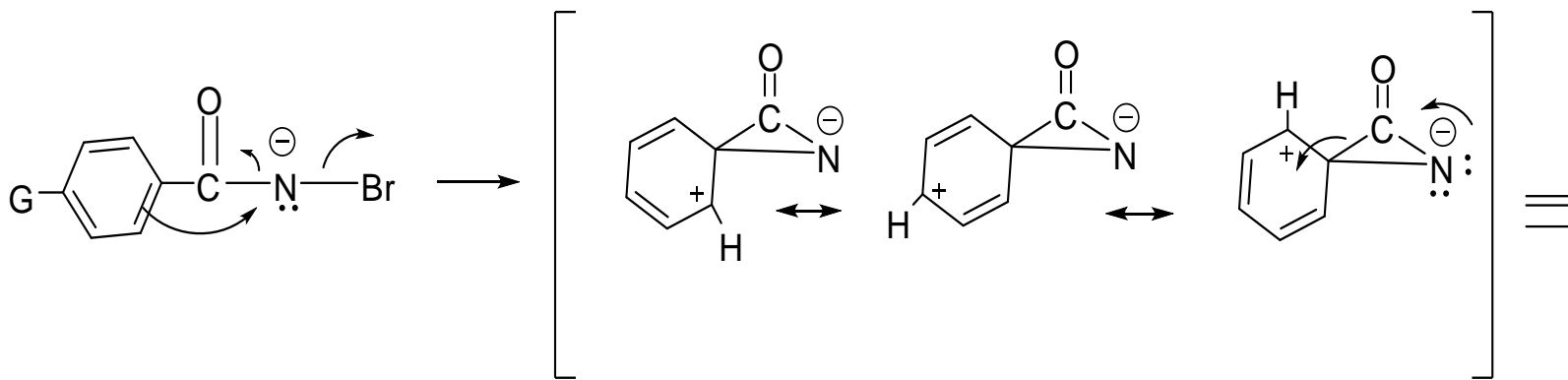
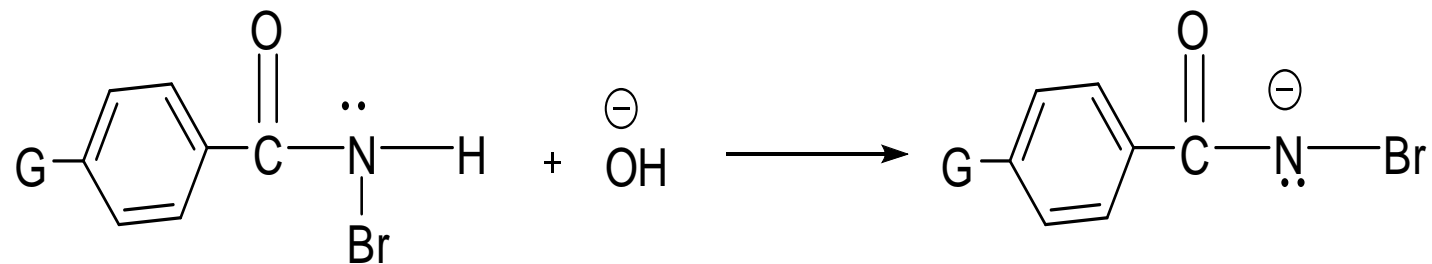
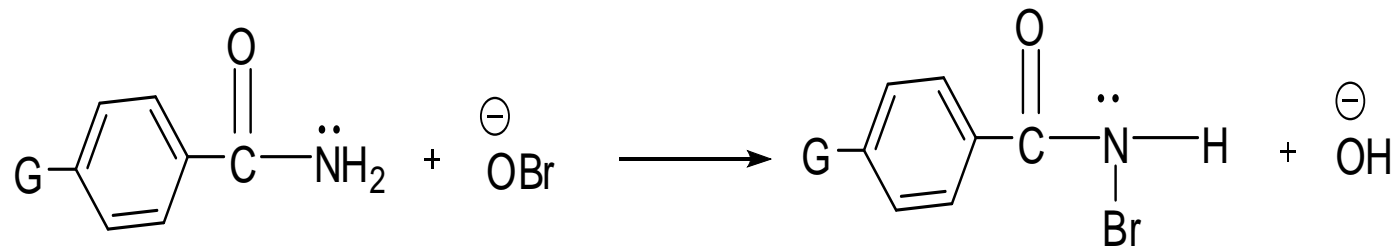
## Aryl migration : migration aptitude



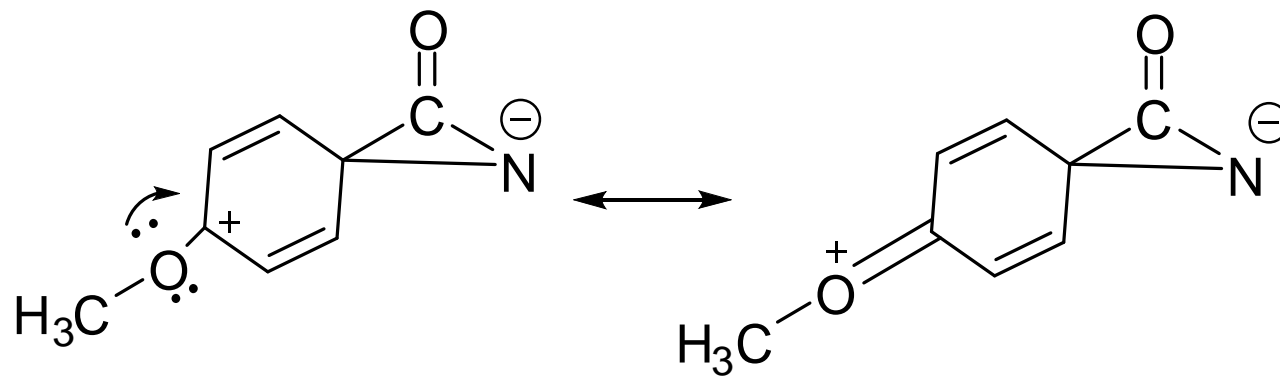
*Q) write the mechanism of the reaction*

When the migrating group is aryl, the rate of the Hofmann degradation is **increased** by the presence of **electron-releasing** substituent in the aromatic ring; Thus substituted benzamides show the following order of reactivity





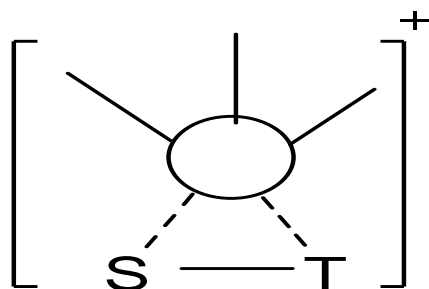
**If G is equal OCH<sub>3</sub>**





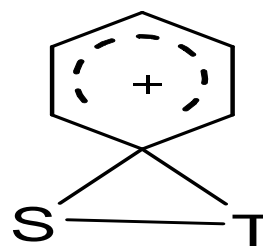
It's generally true in *1,2-shifts* that *aryl groups* have greater *Migratory aptitudes* than alkyl groups. **Why this should be so?**

Migration of an alkyl group must involve a transition state containing **Pentavalent carbon(IV)**, on the other hand migration of an aryl group takes place via a structure of the **benzenonium ion** type (V): transition state or actual intermediate, V clearly offers an easier path for migration than does IV



IV

Alkyl migration:  
pentavalent carbon



V

Aryl migration:  
benzenonium ion

**Thank you for your  
attention**