

## 11. MICHAEL ADDITION

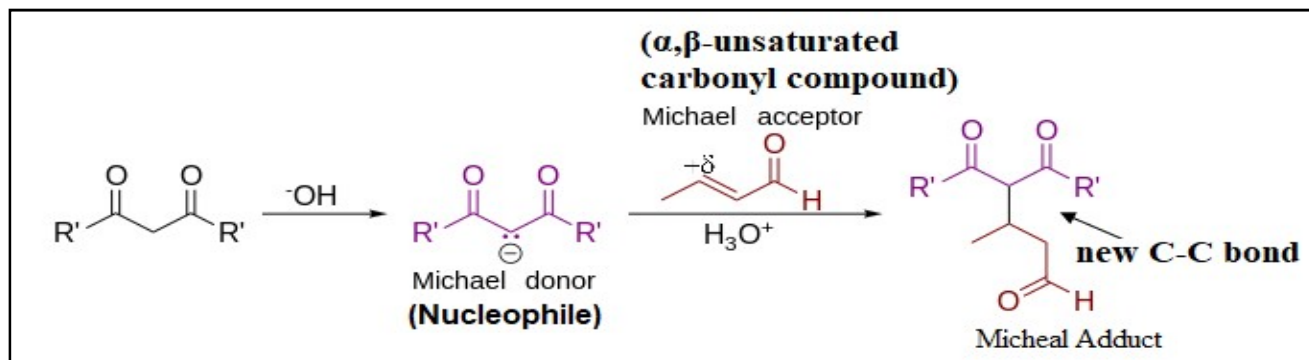
The Michael addition (Michael reaction) is a **nucleophilic addition** reaction involving the addition of a **carbanion** to an  **$\alpha, \beta$ -unsaturated carbonyl compound** through a 1,4-addition mechanism, occur in the **presence of base** to form a **new carbon-carbon bonds** (Michael adduct)

**Substrate** : Michael donor ( $\text{Nu}^-$ ) & Michael acceptor ( $\alpha, \beta$ -unsaturated Carbonyl comp.)

**Reagent** : Base (Sodium ethoxide)

**Product** : Michael adduct (new C-C bond)

Michael donor + Michael acceptor  $\xrightarrow{\text{Base}}$  Michael adduct



Michael reaction (Michael 1,4 addition) is the conjugate addition reaction between a Michael donor (carbanion/ $\text{Nu}^-$ ) and a Michael acceptor ( $\alpha, \beta$ -unsaturated carbonyl comp.) to produce a Michael adduct (new carbon-carbon bond at the acceptor's  $\beta$ -carbon)

### Components of the Micheal reaction

**Michael donors:** Nucleophile is called the Michael donor.

Eg: Acyl groups, cyano groups, active methylene group etc.

**Michael acceptors:** Electrophile is called the Michael acceptor.

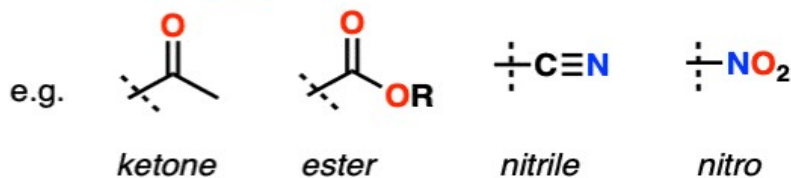
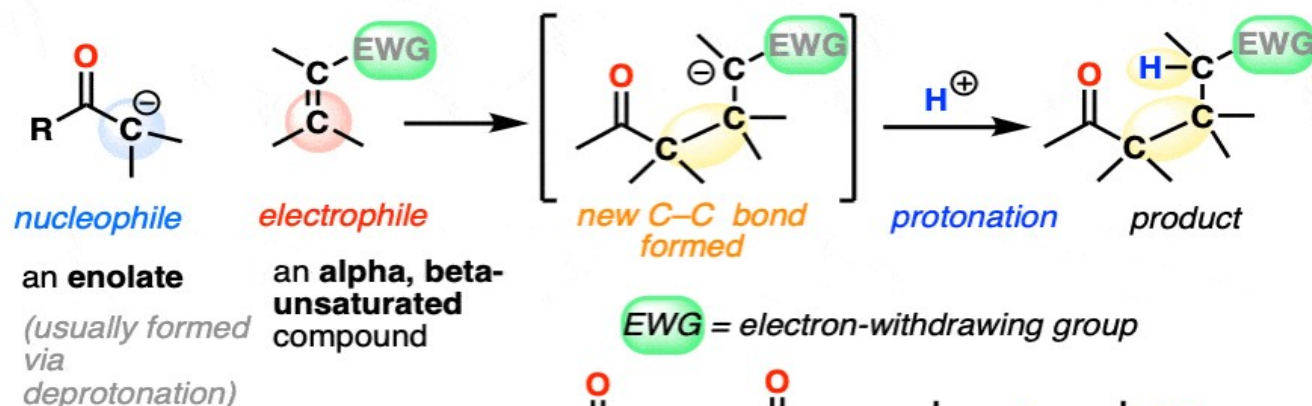
Eg:  $\alpha, \beta$ -unsaturated ketones, esters, nitriles, sulfones, Vinyl ketones, alkyl acrylates, acrylo nitrile, fumarates etc. can act as Michael acceptors.

**Michael Adduct:** The product formed in the Michael addition reaction is called Michael adduct, new carbon-carbon bond.

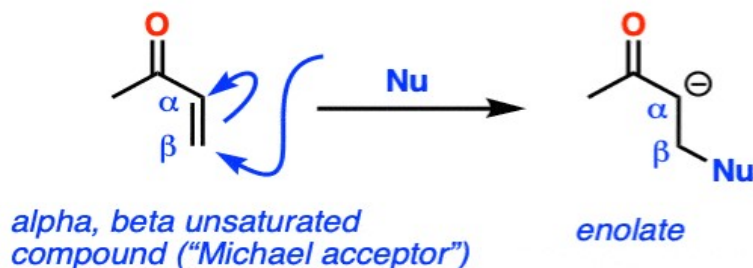
## The Michael Reaction (sometimes "Michael Addition")

• addition of an **enolate** (*nucleophile*) to an **electrophilic** alkene conjugated to an electron withdrawing group (EWG)

Form	Break
C-C	C-C (pi)
C-H	C-H



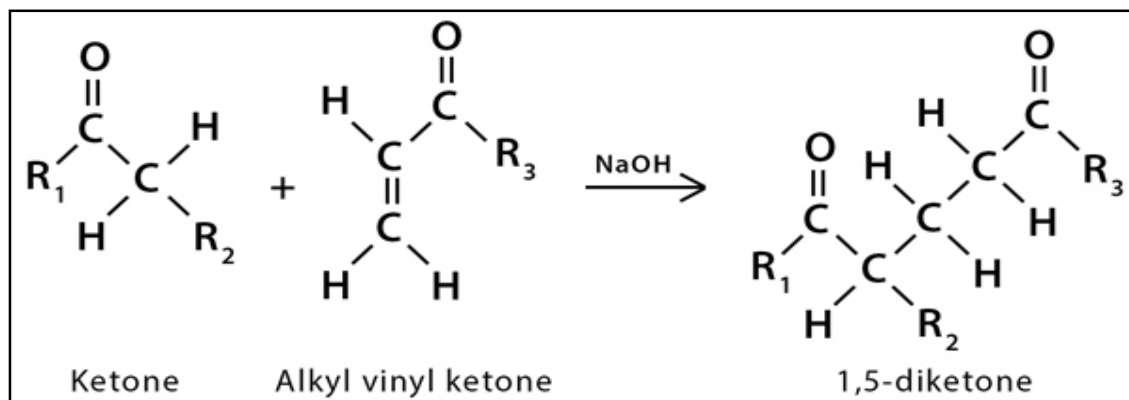
**Conjugate addition** is the general name for addition of a nucleophile to the beta position of alpha,beta-unsaturated compounds.

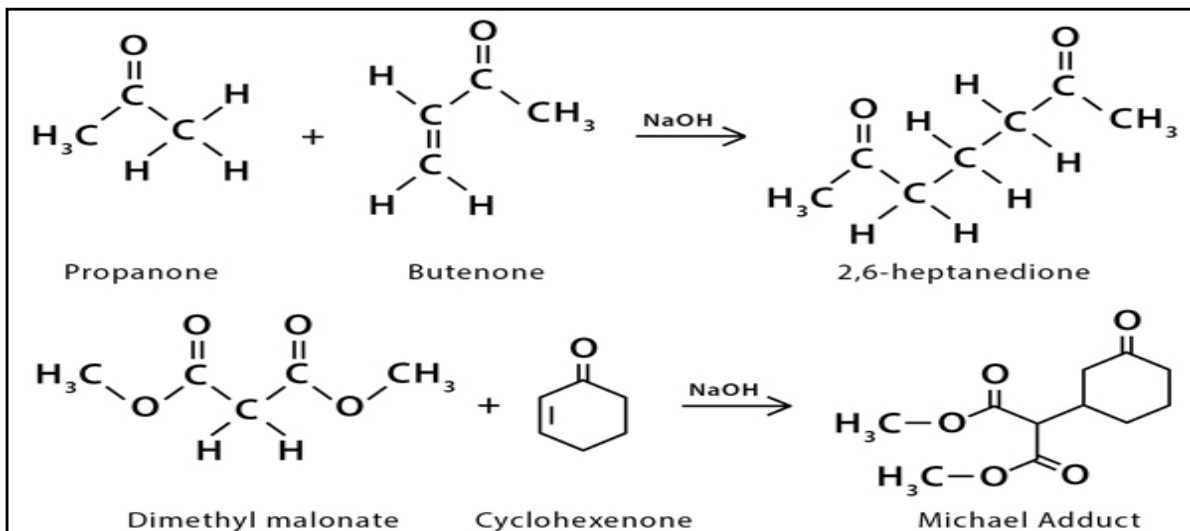


### Typical nucleophiles for conjugate addition

- enolates
- thiols (RSH), thiolates  $RS^{\ominus}$
- enamines
- amines
- organocuprates ( $R_2CuLi$ )

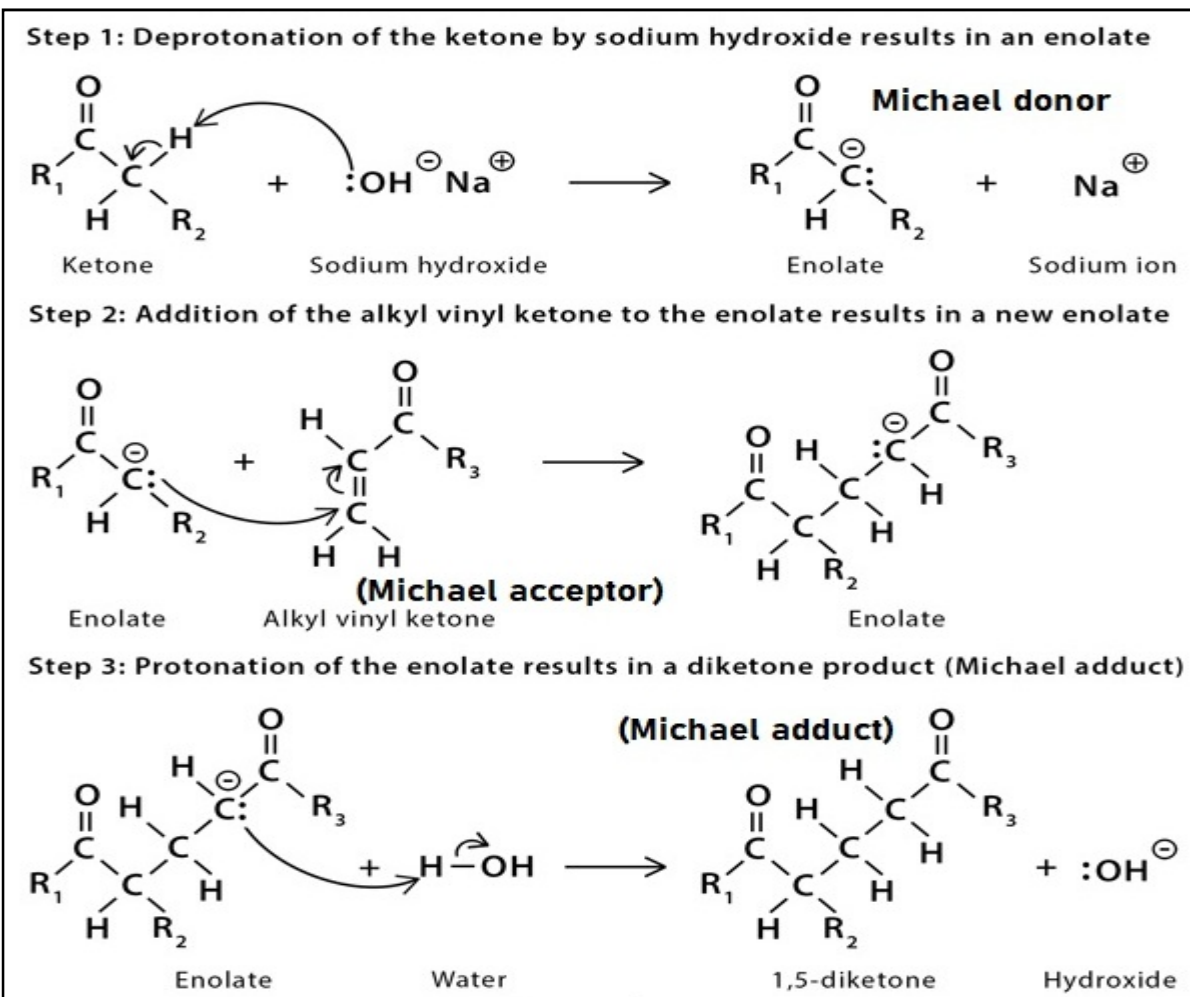
### Examples of Michael addition reaction,





## Mechanism of Michael Addition

- I. Deprotonation of the starting material to give an enolate
- II. Conjugate addition (1,4-addition) of the enolate to an electrophilic alkene
- III. Protonation of the resulting enolate



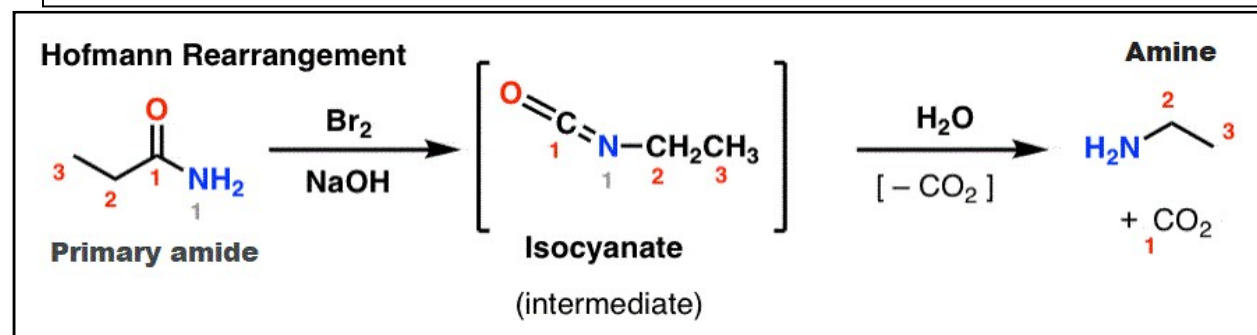
## 12. HOFFMAN REARRANGEMENT

The Hofmann rearrangement (Hofmann degradation) is the reaction of a **primary amide** with a **halogen** (chlorine or bromine) in strongly **basic** (NaOH/KOH) aqueous medium, to a **primary amine**, through an isocyanate intermediate.

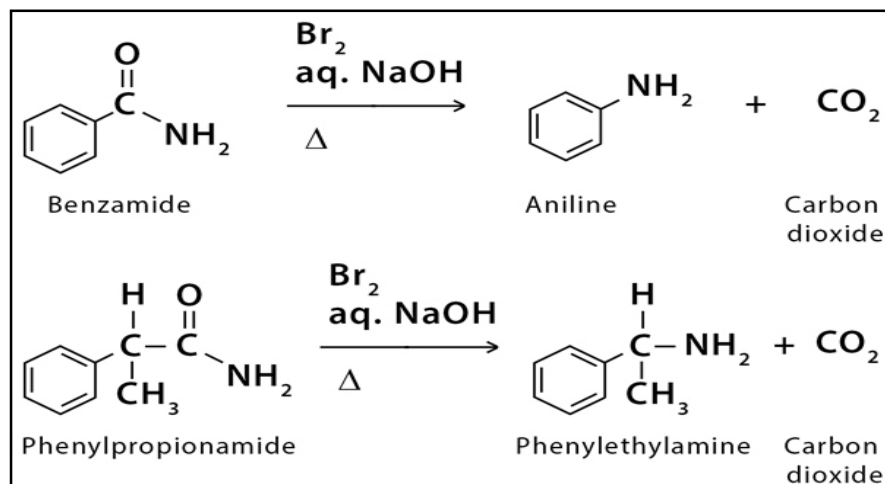
**Substrate** : 1° Amide

**Reagent** : Halogen in alkaline medium

**Product** : 1° Amine



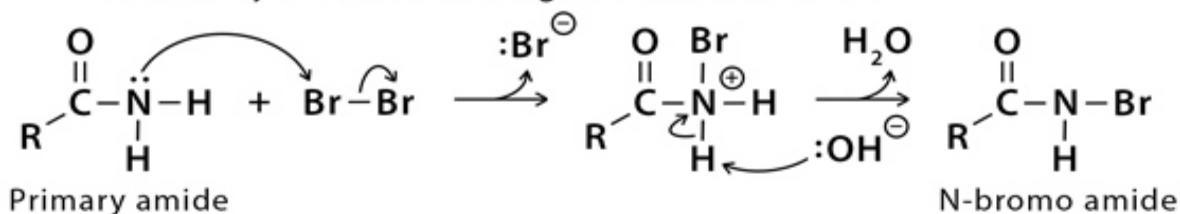
- Reaction of a **primary amide** to a **primary amine**.
- The reaction involves oxidation of the nitrogen followed by rearrangement of the carbonyl and nitrogen to give an isocyanate intermediate.
- The reaction can form a wide range of products, like alkyl and aryl amines.
- Hofmann rearrangement can be used to prepare anthranilic acid from phthalimide.



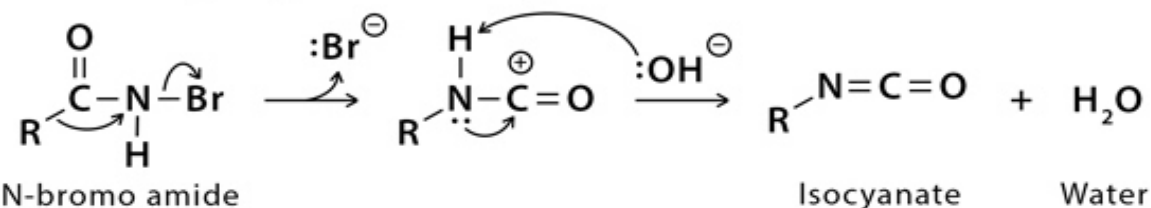
## Mechanism of Hofmann Rearrangement

An 1° amide is treated with bromine and aqueous sodium hydroxide (NaOH). Upon heating, an intermediate isocyanate is formed (**migration of alkyl group from C to electron deficient N atom**). When water is added, the isocyanate loses carbon dioxide and forms 1° amine.

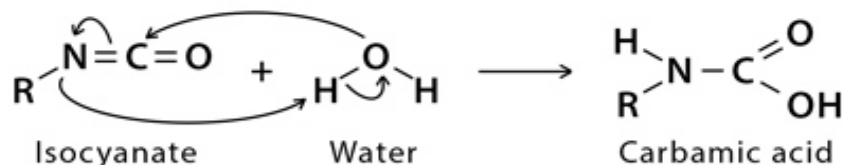
**Step 1:** Breakage of N-H and the formation of N-Br in the presence of sodium hydroxide resulting in n-bromo amide



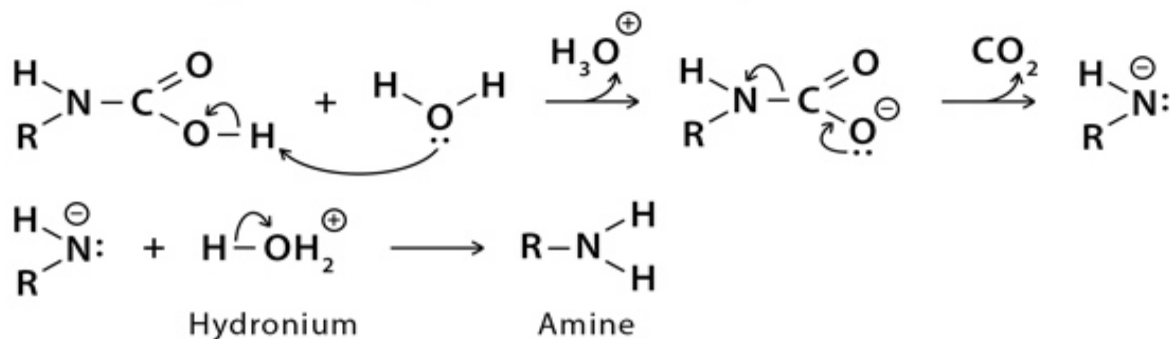
**Step 2:** Migration of a carbon atom to displace the bromide group on the adjacent nitrogen followed by deprotonation of the N-H bond giving a neutral isocyanate



**Step 3:** Attack on the isocyanate by water followed by proton transfer resulting in an unstable carbamic acid



**Step 4:** Thermal degradation of the carbamic acid releasing carbon dioxide gas resulting in an amine after protonation

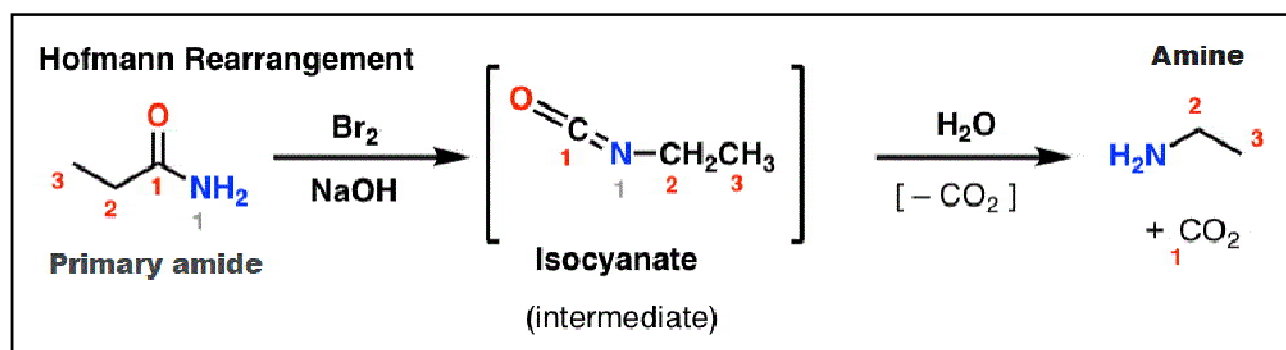


### 13. MIGRATION TO ELECTRON DEFICIENT NITROGEN

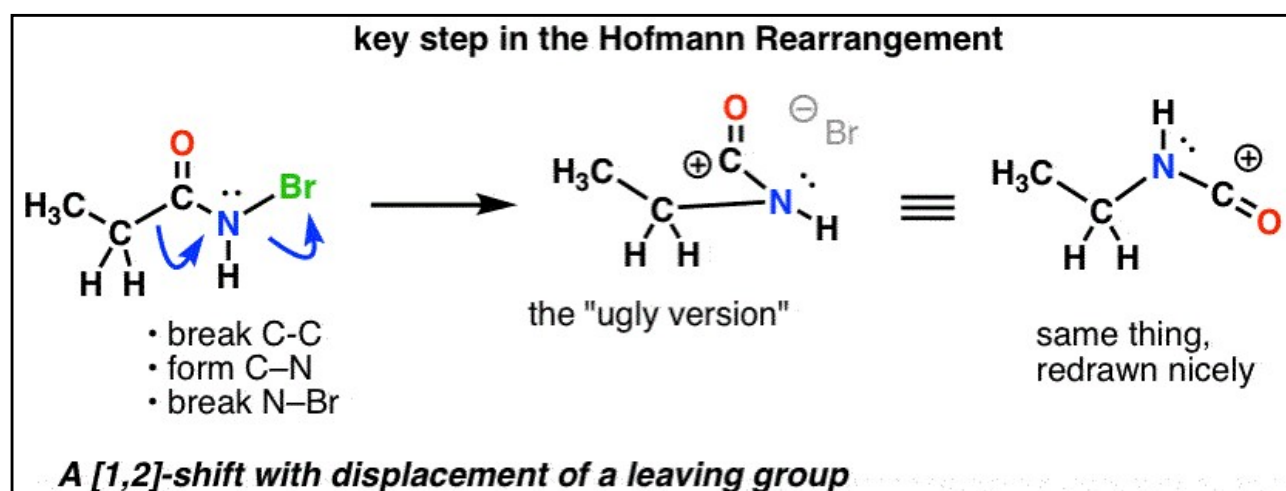
The key step in the Hofmann and Curtius rearrangements is **migration of a carbon atom to displace a leaving group on adjacent nitrogen**.

The driving force for these rearrangements is also an electron deficient atom but because of the trivalency of nitrogen.

In the **Hofmann rearrangement**, an **amide** is treated with bromine and base (usually NaOH or KOH). Upon heating, an intermediate **isocyanate** is formed, which is not isolated. In the presence of water, the isocyanate loses carbon dioxide ("decarboxylates") to give an **amine**.

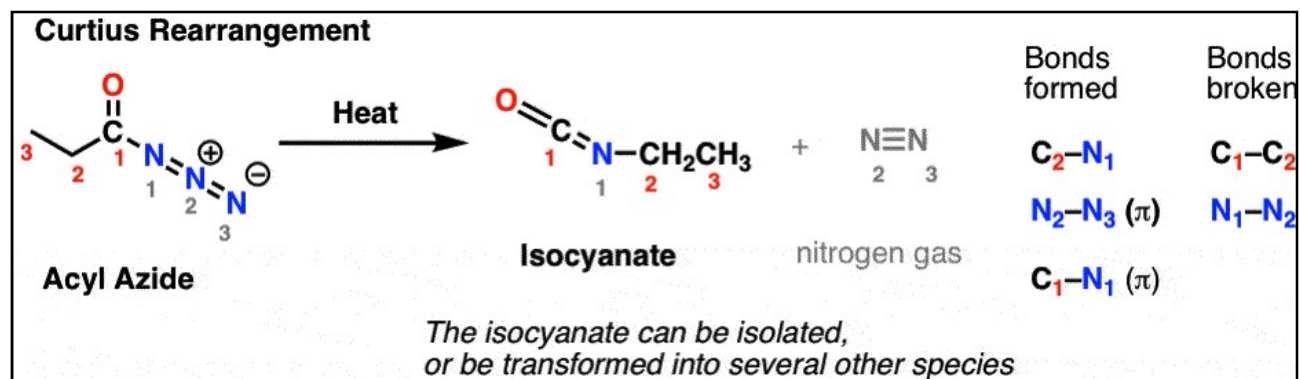


Here's the key step in the Hofmann, where heating results in **breakage of the C-C bond, formation of C-N, and breakage of N-Br**, ie. **ALKYL GROUP IS MIGRATED FROM C TO ELECTRON DEFICIENT N ATOM**.

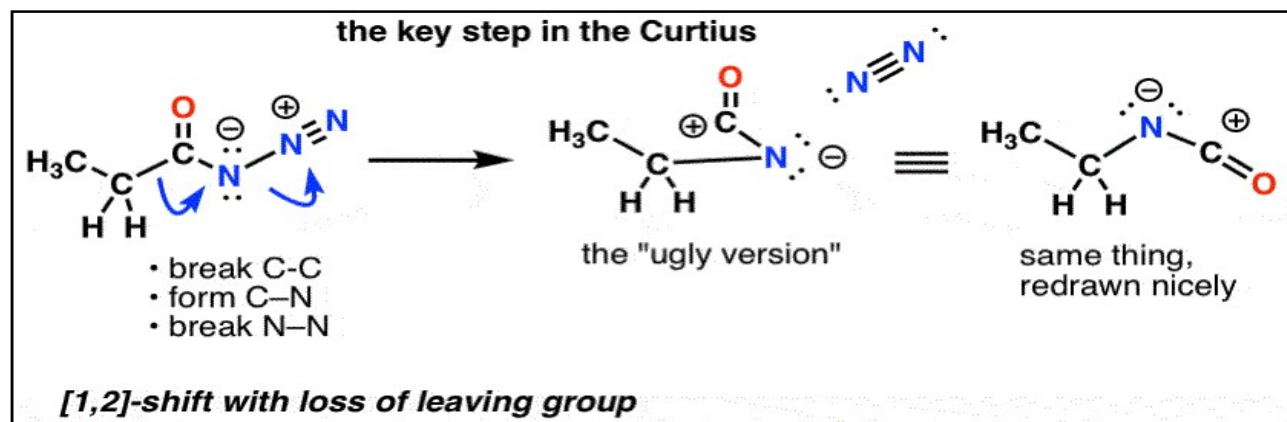


(For Mechanism, refer page no. 510)

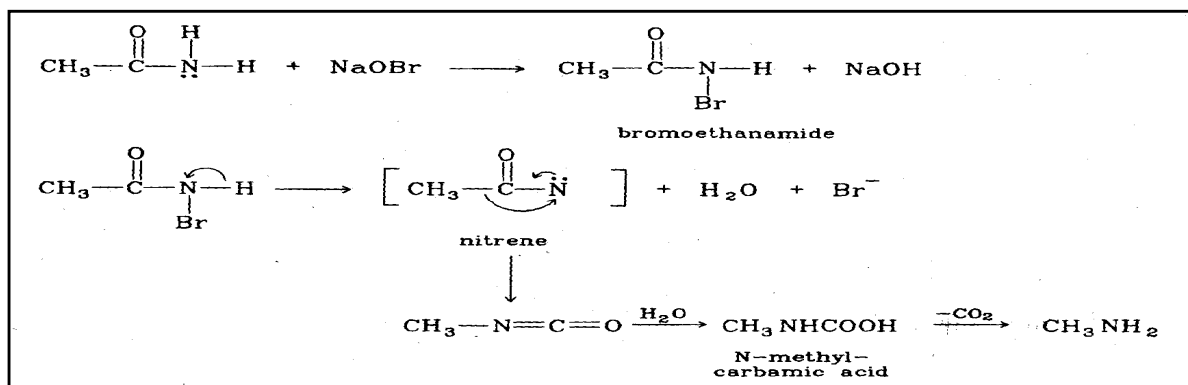
In the Curtius rearrangement, an acyl azide is heated, and an isocyanate is formed. In the Curtius, the isocyanate can be isolated, but is usually transformed further into other species such a carbamate, a urea, or to an amine.



In the Curtius, heating the acyl azide results in rearrangement. The leaving group is nitrogen gas ( $N_2$ ). Here also ALKYL GROUP IS MIGRATED FROM C TO ELECTRON DEFICIENT N.



**Another Eg:**



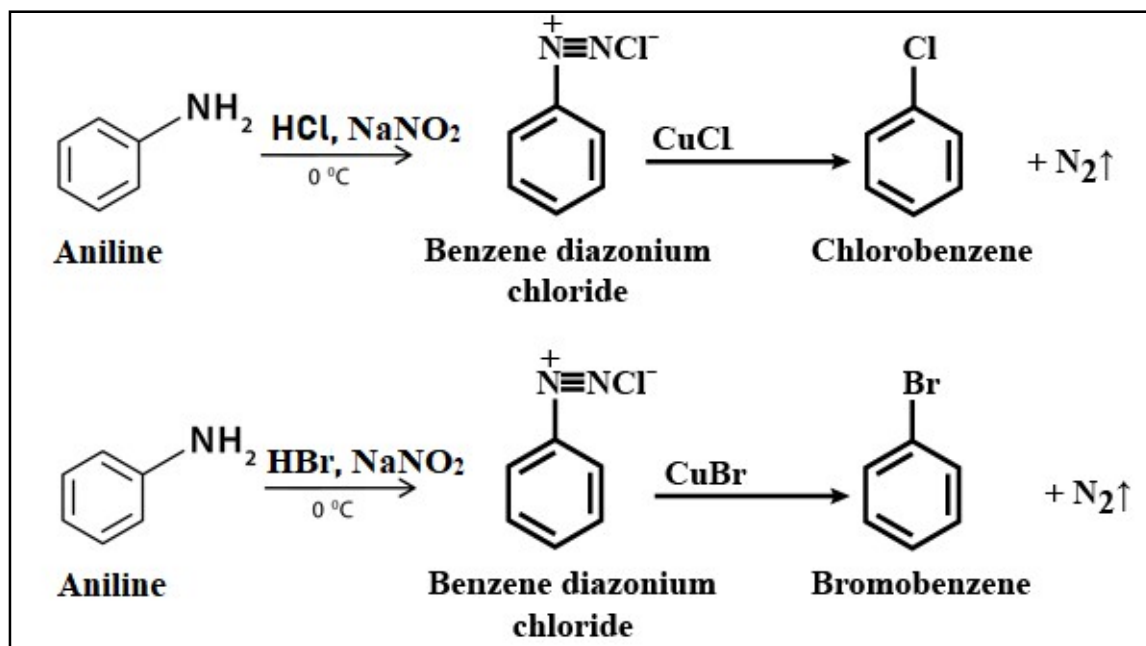
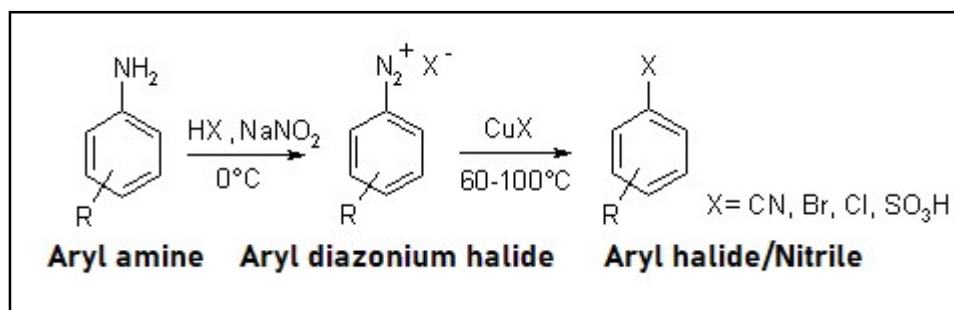
## 14. SANDMEYER'S REACTION

Sandmeyer reaction is a type of radical-nucleophilic aromatic substitution reaction, used to synthesize **aryl halides** from **aryl diazonium salts** using **copper salts** as reagents or catalysts.

**Substrate** : Aryl diazonium salts

**Reagent** : copper salts (copper (I) halide like chloride, bromide or iodide ions)

**Product** : Aryl halides

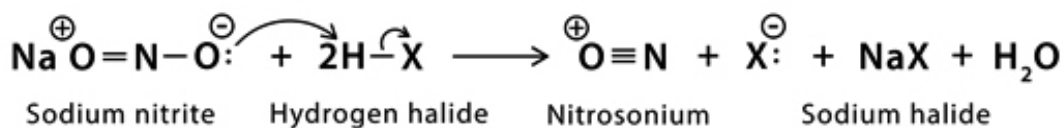


✚ The Sandmeyer reaction provides a method through which one can perform unique transformations on benzene, such as halogenation, cyanation, trifluoromethylation and hydroxylation.

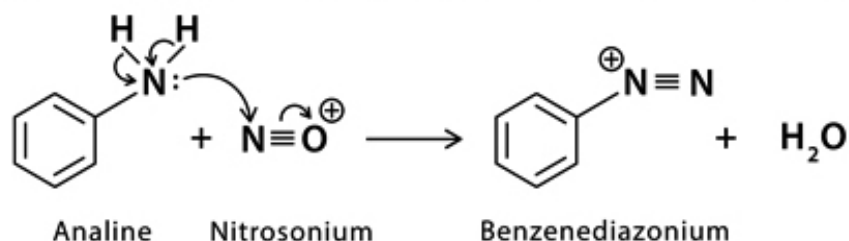


## Mechanism of Sandmeyer Reaction

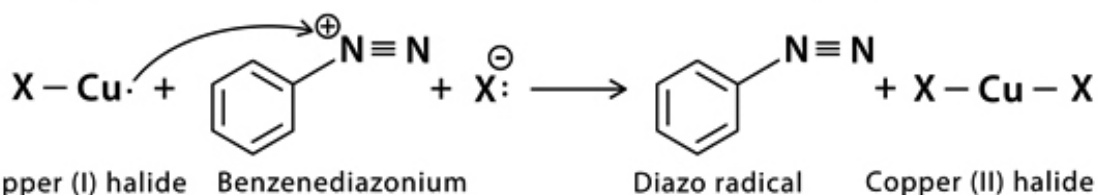
Step 1: Protonation takes place twice during which sodium nitrite reacts with hydrogen halide to form nitrosonium and halide ions



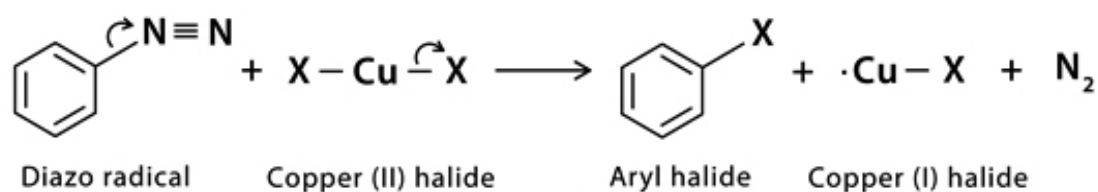
Step 2: Conversion of amine into diazonium salt by the electrophilic nitrosonium



Step 3: Single electron transfer from copper to the diazonium and from halide to copper (I) halide ion to form a neutral diazo radical and copper (II) halide



Step 4: Release of nitrogen gas by the diazo radical to form an aryl radical which reacts with the copper (II) halide to regenerate copper (I) halide catalyst and form the final aryl halide product



## Applications of Sandmeyer Reaction

- Halogenation                      - Synthesis of aryl halides
- Cyanation                            - Synthesis of benzonitriles
- Trifluoromethylation - Synthesis of aryl compounds having trifluoromethyl group and are used as pharmaceuticals