

Hoffman Rearrangement

Hofmann Rearrangement (Hofmann Degradation)

Introduction:

- Hofmann rearrangement is an organic reaction where a primary amide ($R-\text{CONH}_2$) is converted into a primary amine ($R-\text{NH}_2$) with one carbon atom less.
- This reaction is useful for degrading carbon chains or preparing amines from amides.
- The reaction involves the use of halogens (Br_2 or Cl_2) and a strong base (usually NaOH or KOH).
- A key feature of this reaction is that the carbonyl carbon is lost as CO_2 .

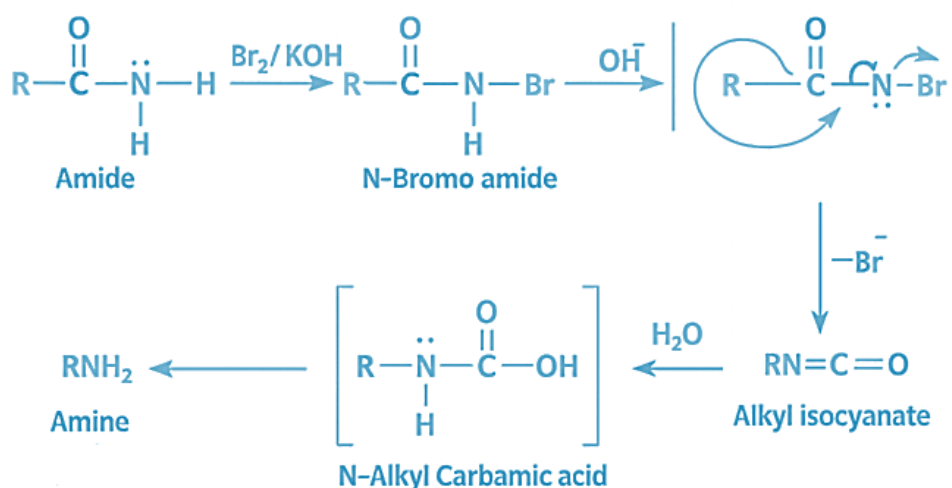
General Reaction:



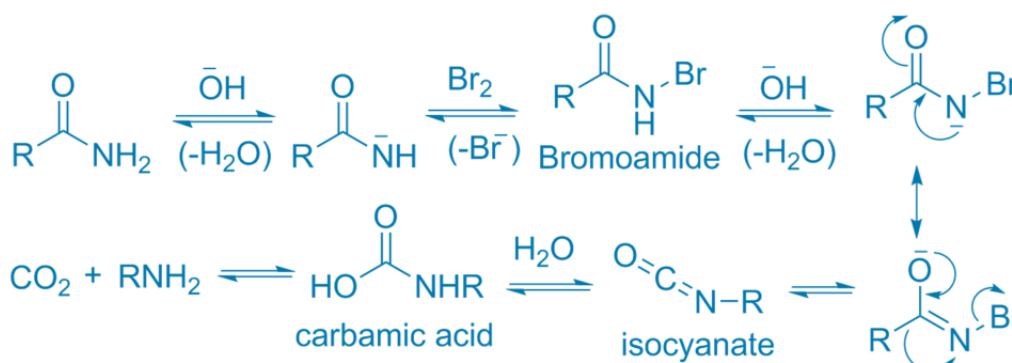
- $R-\text{CONH}_2$ = Primary amide
- $R-\text{NH}_2$ = Primary amine (product, with one carbon less)

Mechanism:

- The Hofmann rearrangement proceeds through several distinct steps.
- The key transformation is the migration of the R group from carbon to nitrogen, accompanied by loss of CO_2 .



OR



1. Halogenation of Amide (Formation of N-haloamide):

- The base deprotonates the amide nitrogen to form a resonance-stabilized anion.
- This anion reacts with Br₂ to form N-bromoamide.



2. Deprotonation and Rearrangement:

- Base deprotonates the N-Br amide to form a dianion (negative on nitrogen).
- This leads to rearrangement: the R group migrates from the carbon to nitrogen through a concerted mechanism, and the carbonyl carbon becomes an isocyanate (R-N=C=O).



3. Hydrolysis of Isocyanate:

- The isocyanate is unstable in aqueous solution and hydrolyzes to form a primary amine and carbon dioxide.



Stereochemistry:

- The Hofmann rearrangement proceeds via a concerted mechanism, meaning the R group migrates with retention of configuration if it is a chiral center.
- Therefore, if the migrating group is chiral, its stereochemistry is usually preserved.
- No new stereocenters are formed during the rearrangement.

Applications:

1. Synthesis of Primary Amines:

- Especially useful for synthesizing aniline derivatives and aliphatic primary amines with one carbon less.

2. Preparation of Heterocycles:

- Used in synthesis of heterocyclic compounds like indoles, quinolines, and others.

3. Peptide Modification:

- Can be applied to modify peptides or amino acids for synthetic purposes.

4. Pharmaceutical Chemistry:

- Used to prepare drugs or intermediates where amine groups are required.

5. Degradation of Amino Acids:

- Helps in structural elucidation by removing one carbon from the molecule.

Migration to Electron Deficient Nitrogen (as part of rearrangement reactions)

Introduction:

- This topic refers to a key mechanistic step observed in rearrangement reactions, where a substituent group migrates from one atom (usually carbon) to a nitrogen atom that is electron-deficient, typically during a rearrangement process such as Hofmann rearrangement, Curtius rearrangement, or Lossen rearrangement.
- Electron-deficient nitrogen usually arises when nitrogen is bonded to an electron-withdrawing group (e.g., -C=O in amides, -N_3 in azides, or halogens).
- The migration step is typically part of a concerted mechanism that forms a reactive intermediate like isocyanate.

General Reaction (illustrative example - Hofmann Rearrangement):



- The key step is the migration of the R group from carbon to nitrogen as the nitrogen becomes electrophilic (electron-deficient).

Mechanism:

1. Activation of Nitrogen:

- Through halogenation or other means, the nitrogen of the amide is made electron-deficient (e.g., by converting to N-bromoamide or forming azide in other rearrangements).

2. Rearrangement Step:

- The R group attached to the carbonyl carbon migrates to the nitrogen atom.
- This is a 1,2-migration: the group migrates from the α -carbon (adjacent to carbonyl) to nitrogen.
- This step is often concerted with the loss of a leaving group (e.g., CO_2 , N_2).

3. Formation of Reactive Intermediate:

- Migration results in formation of reactive species like isocyanate, which is then hydrolyzed.

Stereochemistry:

- **Stereospecific migration:** The migrating group retains its stereochemistry if chiral.
- The migration occurs with retention of configuration because the movement is intramolecular and concerted.

Applications:

1. Key Step in Rearrangement Reactions:

- Central to many name reactions: Hofmann, Curtius, Schmidt, Beckmann, Lossen, etc.

2. Synthesis of Amines and Isocyanates:

- Essential for converting carboxylic acid derivatives to amines.

3. Pharmaceutical Applications:

- Used to synthesize intermediates for drugs via rearrangement of carboxylic acid derivatives.

4. Synthesis of Ureas and Carbamates:

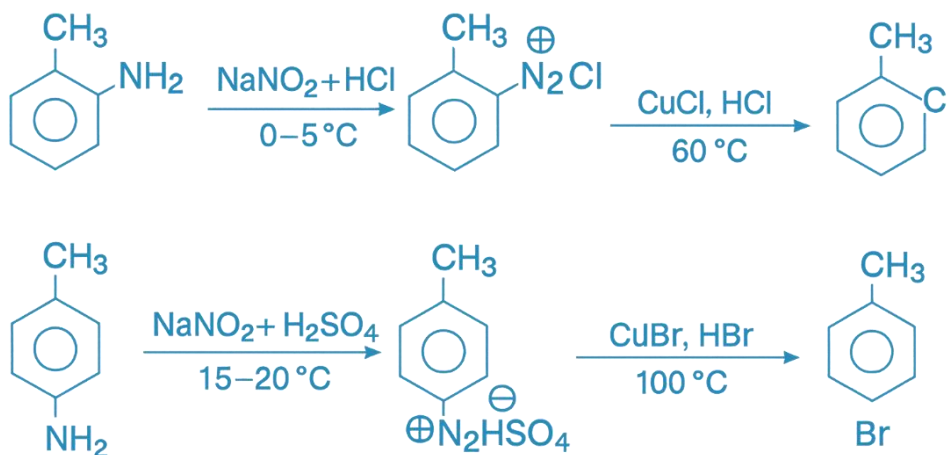
- The isocyanate intermediate can react further to form various derivatives.

Sandmeyer's Reaction

Introduction:

- Sandmeyer's reaction is a substitution reaction that involves the replacement of an aromatic diazonium group ($-N_2^+$) with a nucleophile such as halides (Cl^- , Br^- , CN^-) or hydroxide (OH^-), in the presence of copper(I) salts (like $CuCl$, $CuBr$, $CuCN$) as catalysts.
- Discovered by Traugott Sandmeyer in 1884, this reaction is widely used in aromatic substitution chemistry.

General Reaction:



- For halogenation:



- (Where X = Cl, Br, CN, etc.)

- Example:



Mechanism:

- The exact mechanism of the Sandmeyer reaction is complex and involves radical intermediates.

Here is a simplified mechanism:

1. Formation of Diazonium Salt:

- An aromatic primary amine (Ar-NH_2) is treated with NaNO_2 and HCl at $0-5^\circ\text{C}$ to form the diazonium salt ($\text{Ar-N}_2^+\text{Cl}^-$).



2. Generation of Aryl Radical:

- The Cu(I) salt (like CuCl) facilitates the formation of an aryl radical by a single-electron transfer (SET):



3. Capture of Radical by Nucleophile:

- The aryl radical reacts with a nucleophile (Cl^- , Br^- , CN^-) present in the reaction mixture, forming the substituted aromatic compound.



4. Regeneration of Cu(I) :

- Cu^{2+} is reduced back to Cu^+ , maintaining the catalytic cycle.

Stereochemistry:

- The reaction involves aryl radicals, so stereochemistry is not a concern because the substrate is an aromatic ring (planar and symmetrical).
- Since substitution occurs on sp^2 -hybridized carbon, no chiral centers are involved or formed.

Applications:

1. Aromatic Substitution:

- Replacement of $-\text{NH}_2$ with $-\text{Cl}$, $-\text{Br}$, $-\text{CN}$, $-\text{OH}$ on aromatic rings.

2. Synthesis of Aryl Halides:

- Important for making aryl chlorides, bromides, and nitriles from anilines.

3. Pharmaceuticals and Agrochemicals:

- Used to build aromatic structures found in drugs, dyes, and pesticides.

4. Synthesis of Benzonitriles:

- Introduction of a $-\text{CN}$ group via CuCN leads to precursors for carboxylic acids, amides, and heterocycles.

5. Modifying Diazonium Compounds:

- One of the few ways to convert diazonium salts into a variety of functionalized aromatic compounds.



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