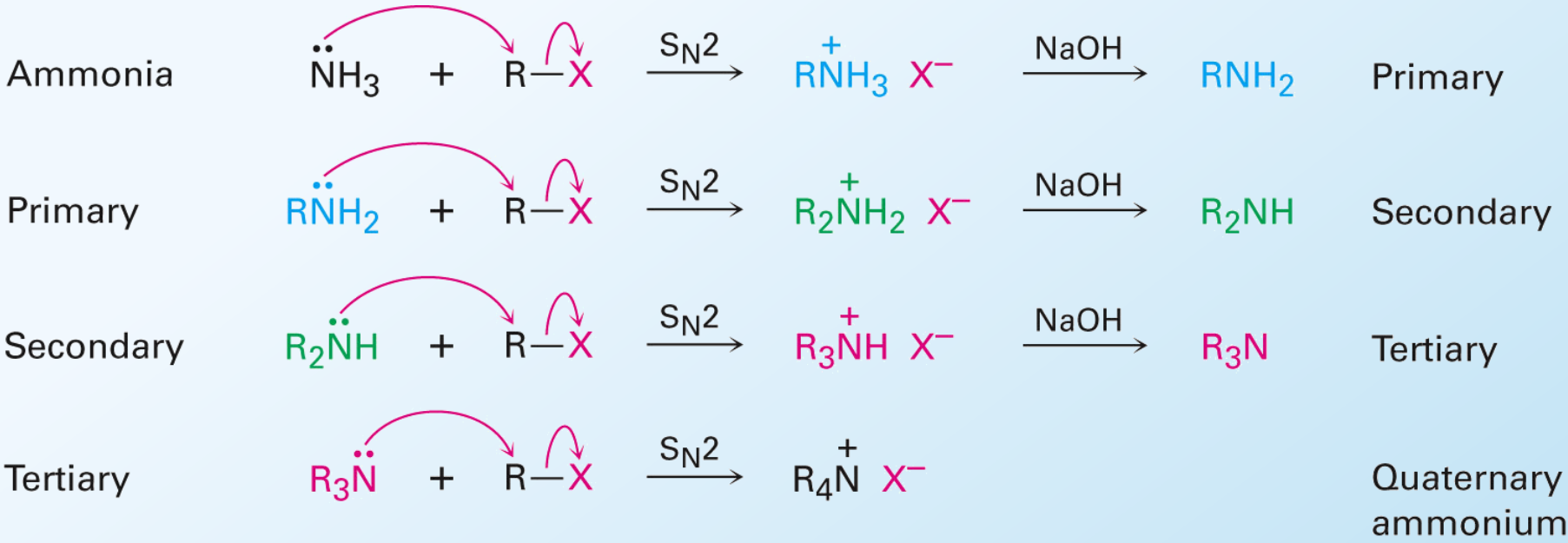
Amines
Synthesis and Reactions

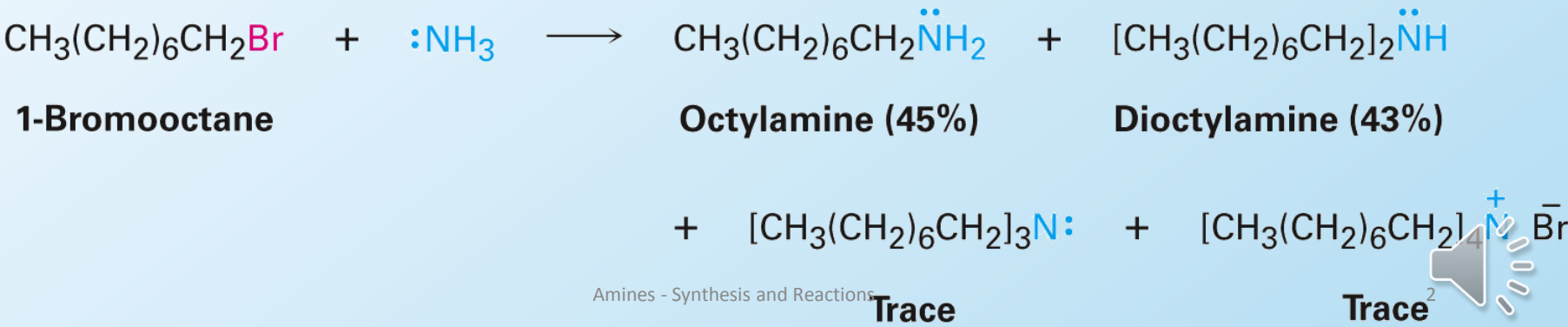
Dr. Sapna Gupta

Synthesis of Amines – S_N2

1) From Ammonia Using S_N2

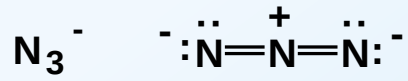


- Drawback is that multiple alkylations can occur

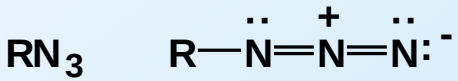


Synthesis of Amines– Using Azide

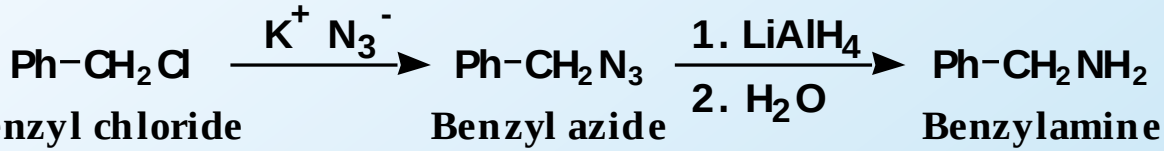
2) Using azide



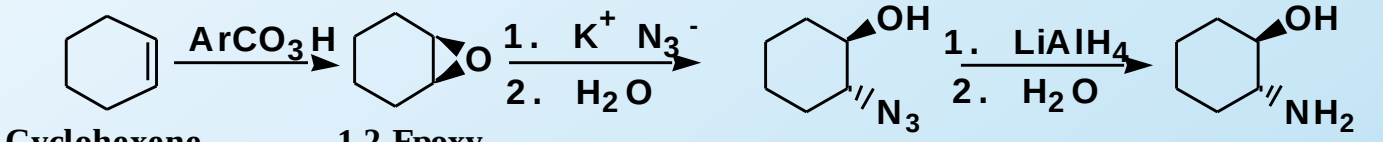
Azide ion
(a good nucleophile)



An alkyl azide



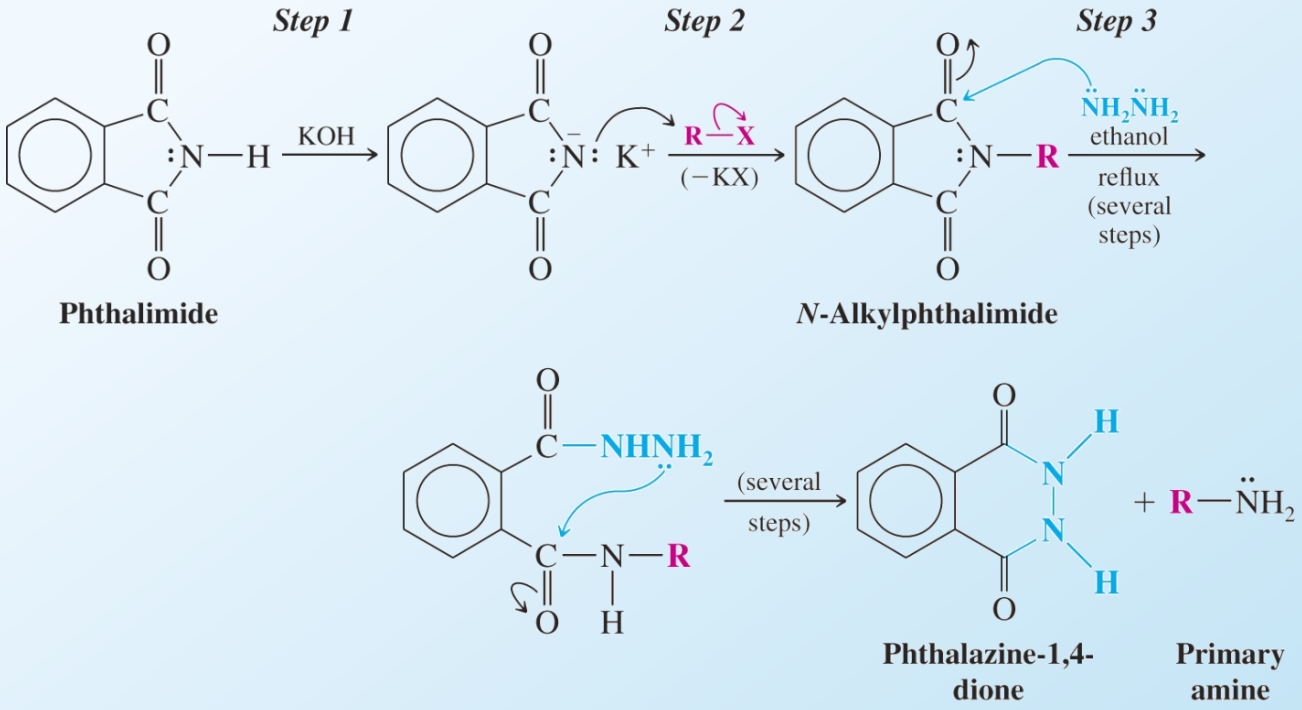
Benzyl chloride — Benzyl azide — Benzylamine



Cyclohexene — 1,2-Epoxy-cyclohexane — *trans*- 2-Azido-cyclohexanol (racemic) — *trans*- 2-Amino-cyclohexanol (racemic)

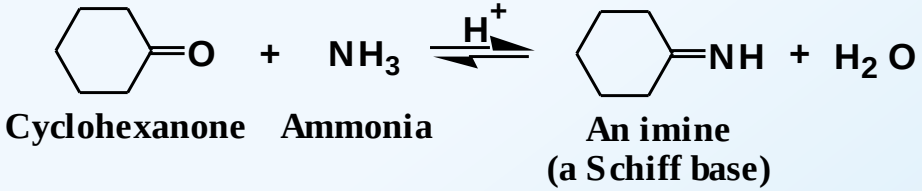
Synthesis of Amines – Gabriel (for 1º)

3) Gabriel synthesis, pthalimide, for primary amines



Synthesis of Amines – Reductive Amination

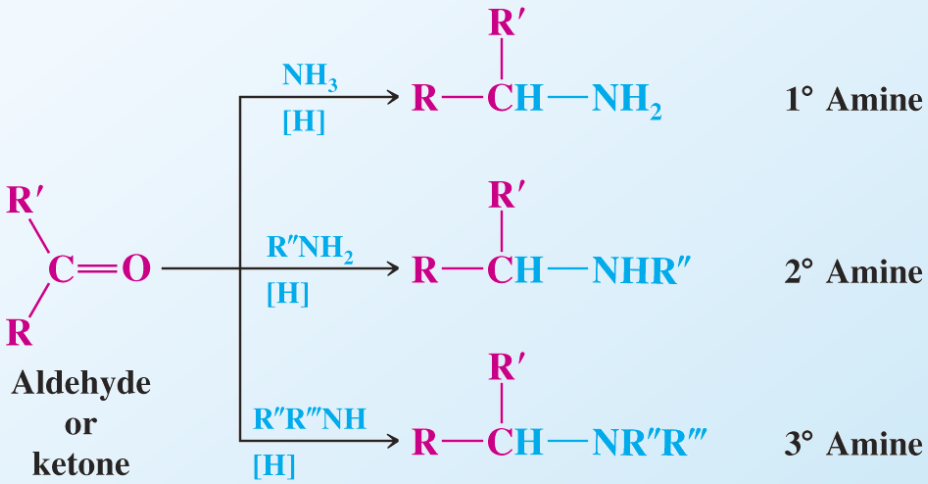
4) Reduction of imines from aldehydes and ketones



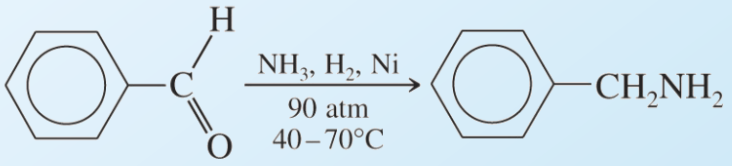
Cyclohexanone Ammonia

An imine
(a Schiff base)

General Reaction

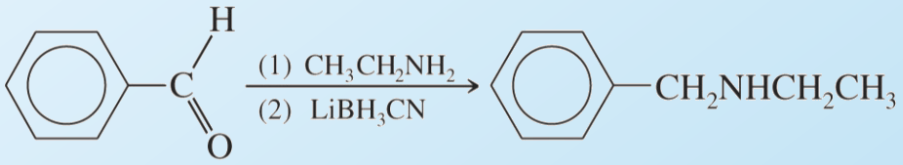


Examples



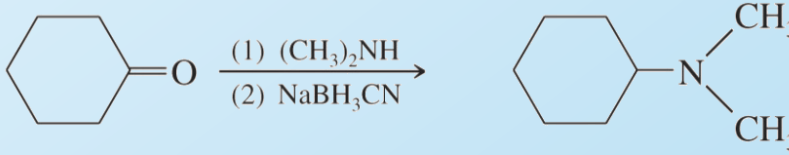
Benzaldehyde

Benzylamine
(89%)



Benzaldehyde

N-Benzylethanamine
(89%)



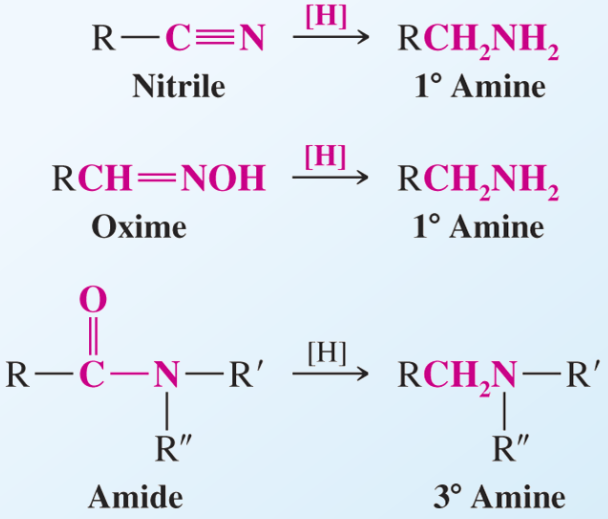
Cyclohexanone

N,*N*-Dimethylcyclohexanamine
(52–54%)

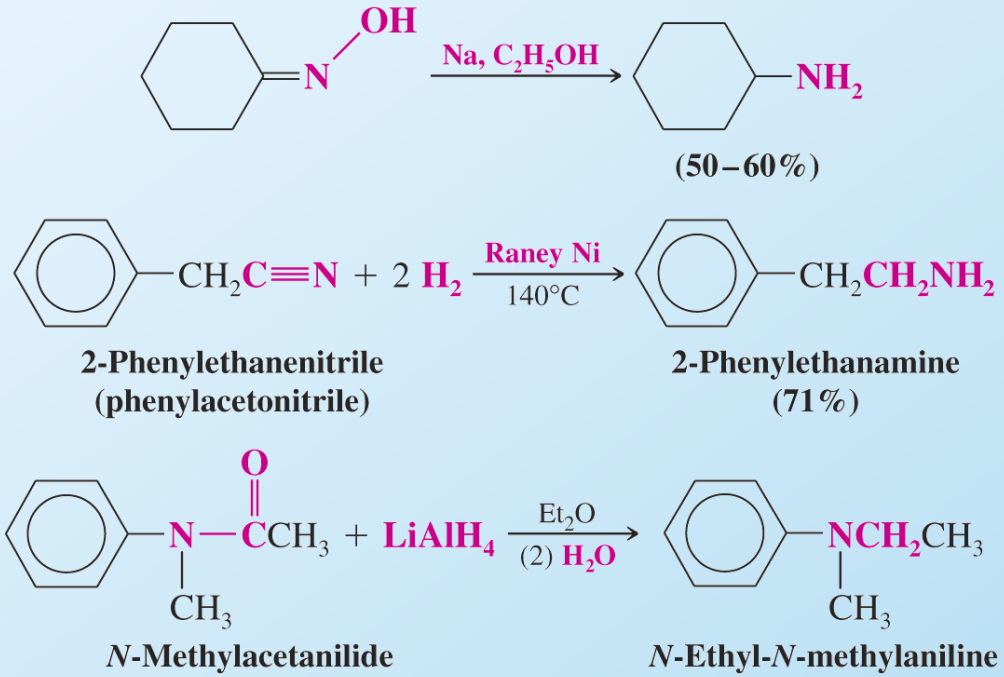
Synthesis of Amines– Reduction

5) From reduction of nitriles, oximes and amides

General Reactions



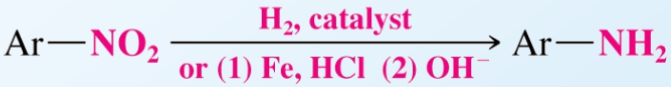
Examples



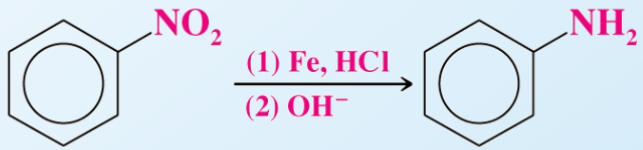
Reduction of Nitro Group and Hoffman Rearrangement

6) From reduction of nitrobenzene

General Reaction



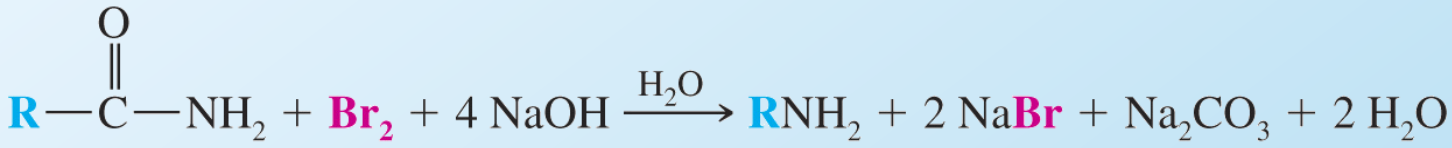
Specific Example



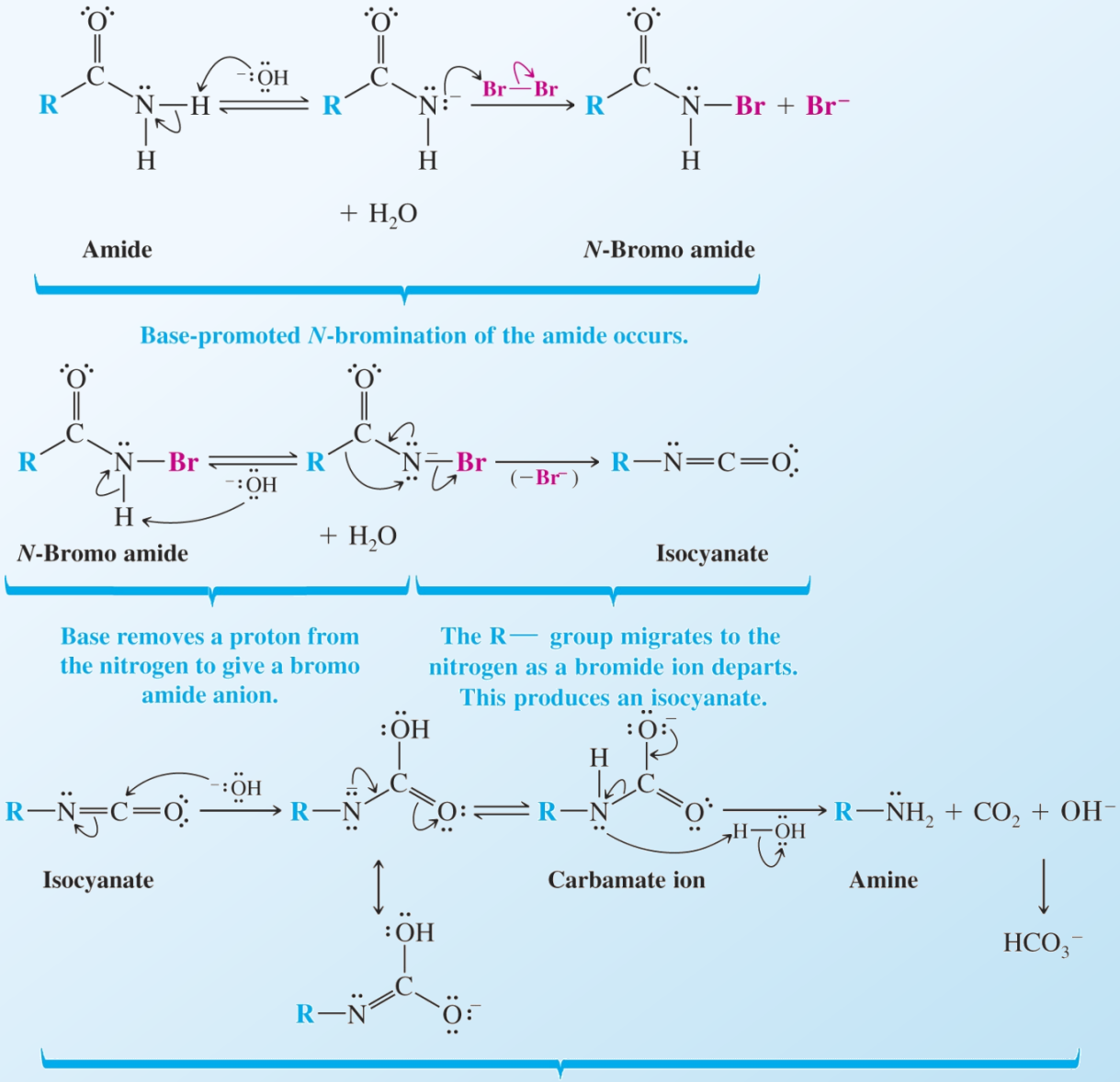
(97%)

7) Hoffman Rearrangement: This is for 1° amines only. Start with an amide, treat it with Br_2 and NaOH.

See the next slide for mechanism of this reaction. (You don't have to know the mechanism for exam.)

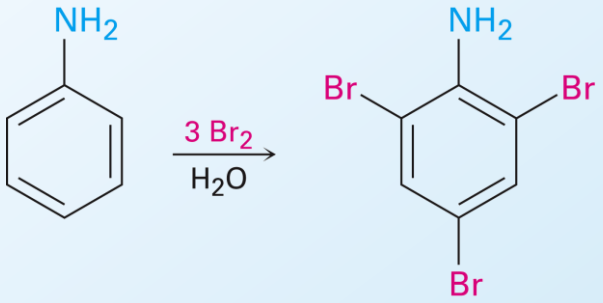


Hoffman Rearrangement - Mechanism



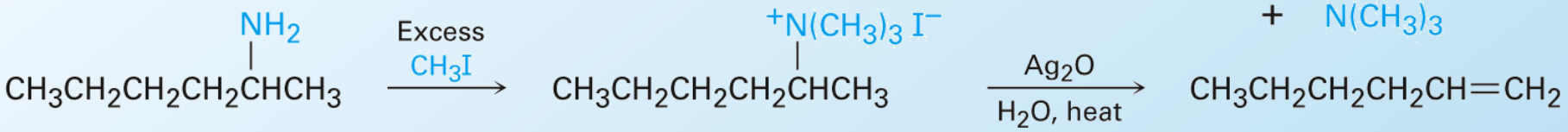
Reaction of Amines

1) Electrophilic reaction of aniline



Aniline **2,4,6-Tribromoaniline (100%)**

2) Hoffman Elimination: NH_2^- is a poor leaving group, but it can be converted to an alkylammonium ion which is a good leaving group. Because of its bulkiness, the product is usually the anti-Zaitsev's product (less stable alkene)



1-Methylpentylamine **(1-Methylpentyl)trimethyl-ammonium iodide** **1-Hexene (60%)**

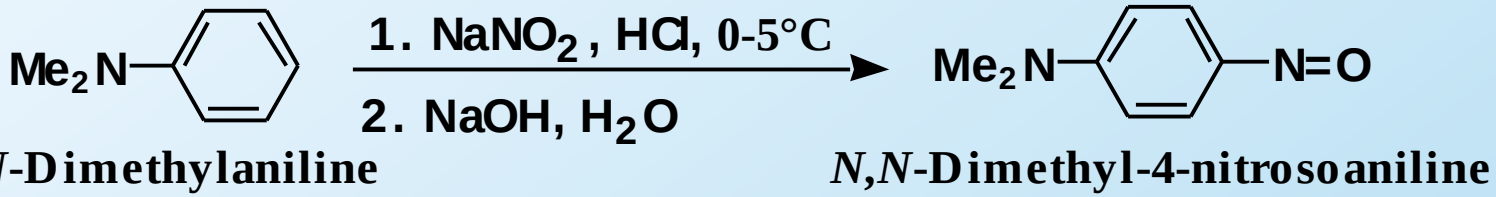
Reaction of Amines – Nitrous Acids

- Nitrous acid, a weak acid, is prepared by treating sodium nitrite, $NaNO_2$,with H_2SO_4 or HCl.

$$HCl_{(aq)} + NaNO_{2(aq)} \longrightarrow HONO_{(aq)} + NaCl_{(aq)}$$

$$H_2SO_4 + 2\ NaNO_{2(aq)} \longrightarrow 2\ HONO_{(aq)} + Na_2SO_{4(aq)}$$

- In its reactions with amines, nitrous acid:
  - participates in proton-transfer reactions.
  - is a source of the nitrosyl cation, NO^+, a weak electrophile.
- Reaction with 3° amines: These do not react with nitrous acids.

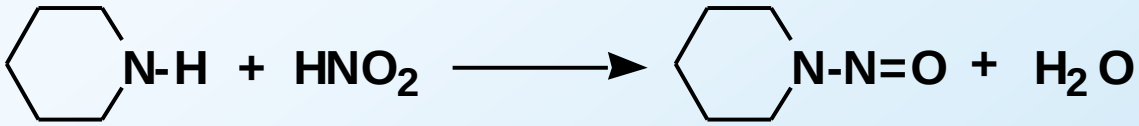


N,*N*-Dimethylaniline

N,*N*-Dimethyl-4-nitrosoaniline

Reactions of Amines – Nitrous Acid with 2° Amines

2° Aliphatic and aromatic amines react with NO+ to give N-nitrosamines.

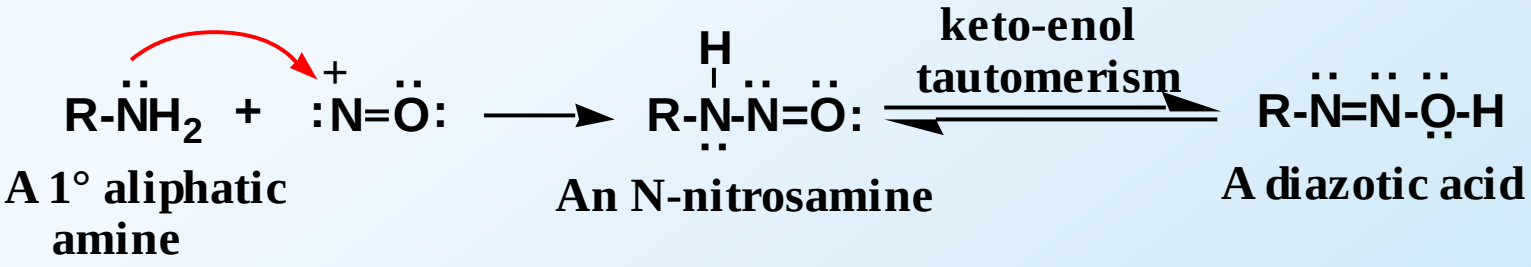


Piperidine ***N*-Nitrosopiperidine**

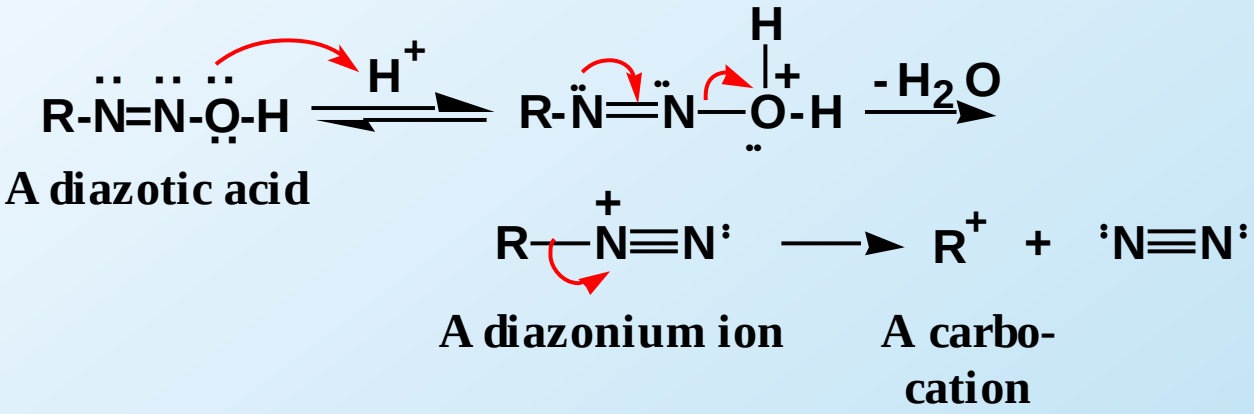
N – Nitroso amines are studied more for their toxicity.

Reactions of Amines – Nitrous Acid with 1° Amines

- Formation of a diazonium ion.
  - Step 1: Reaction of a 1° amine with the nitrosyl cation.



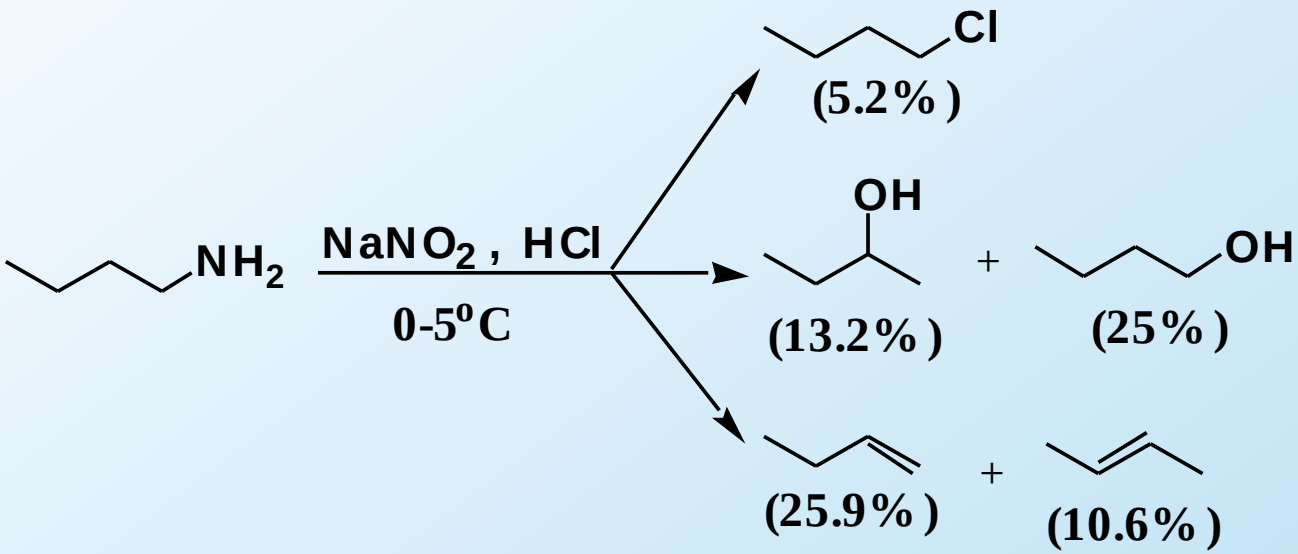
  - Step 2: Protonation followed by loss of water.



Reactions of Amines – Nitrous Acid with 1° Aliphatic Amines

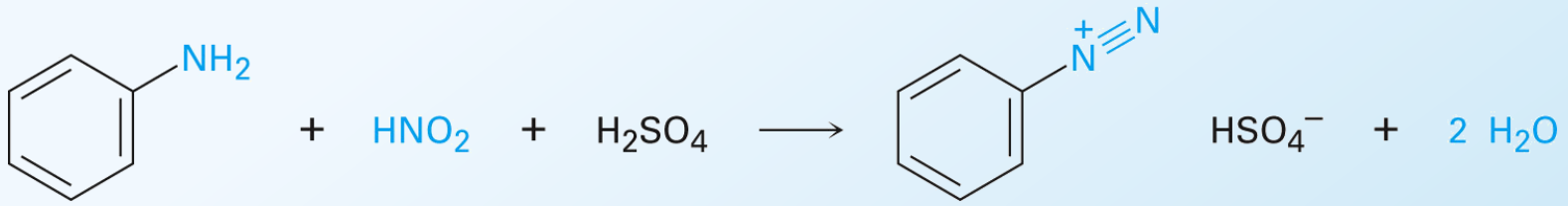
Aliphatic diazonium ions are unstable and lose N_2 to give a carbocation which can then:

1. Lose a proton to give an alkene.
2. React with a nucleophile to give a substitution product.
3. Rearrange and then react by Steps 1 and/or 2.

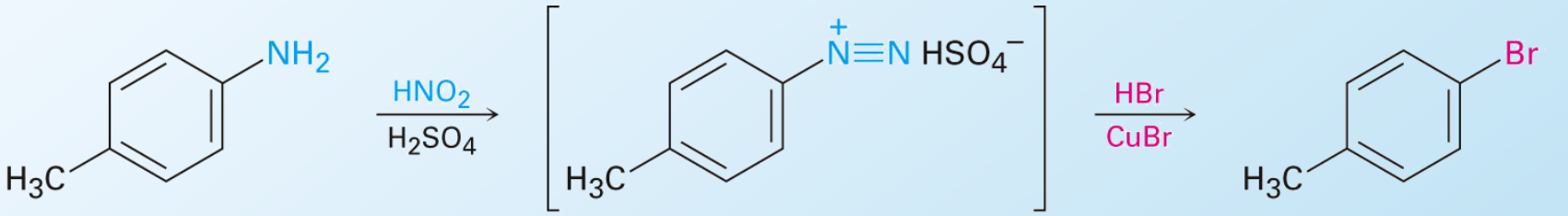


Reactions of Amines – Nitrous Acid with 1° Aromatic Amines

Primary arylamines react with HNO_2, yielding stable arenediazonium salts.



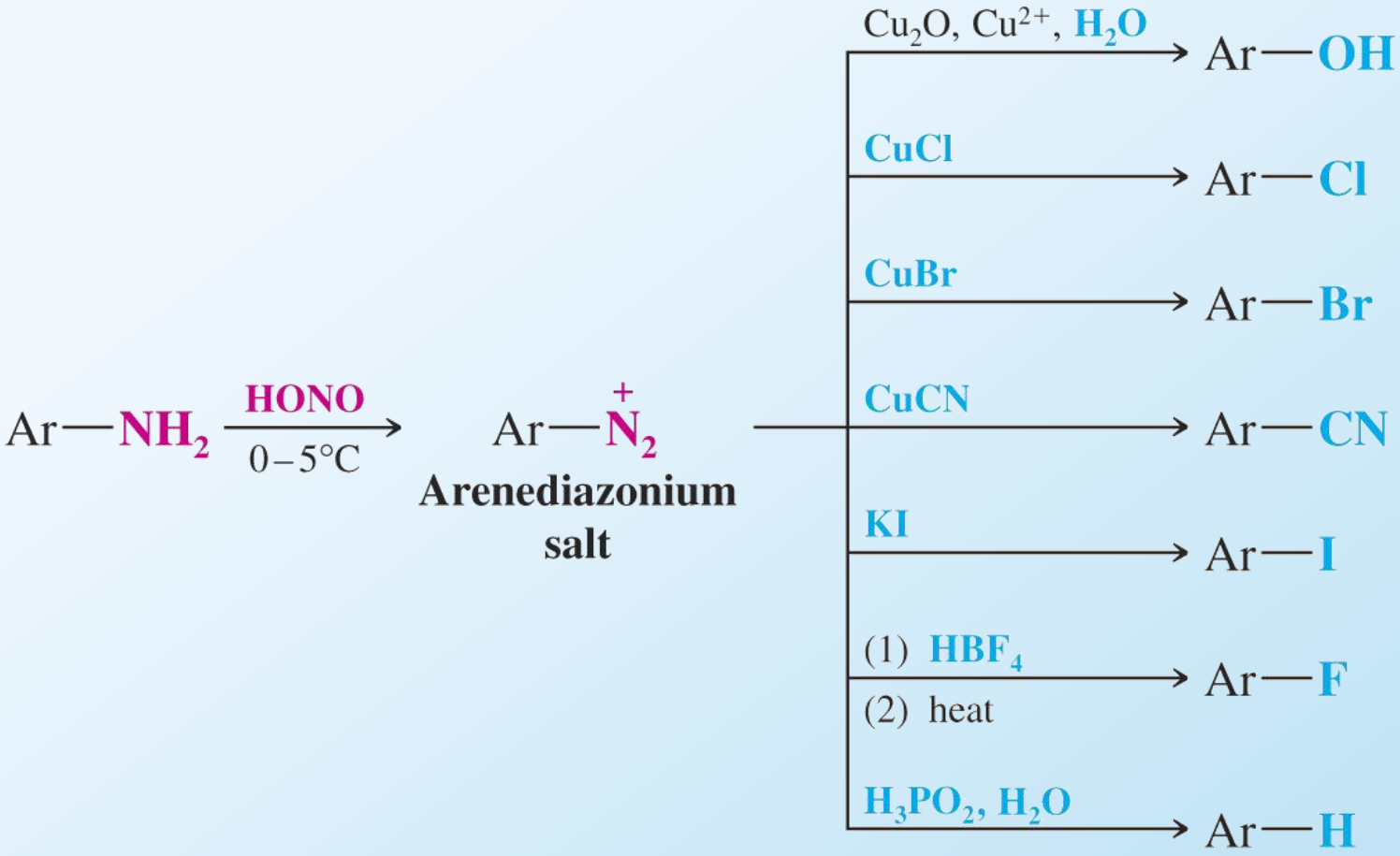
The N_2 then can be replaced by any nucleophile. This is unusual as benzene ring does not undergo S_N2 reactions.



***p*-Methylaniline**

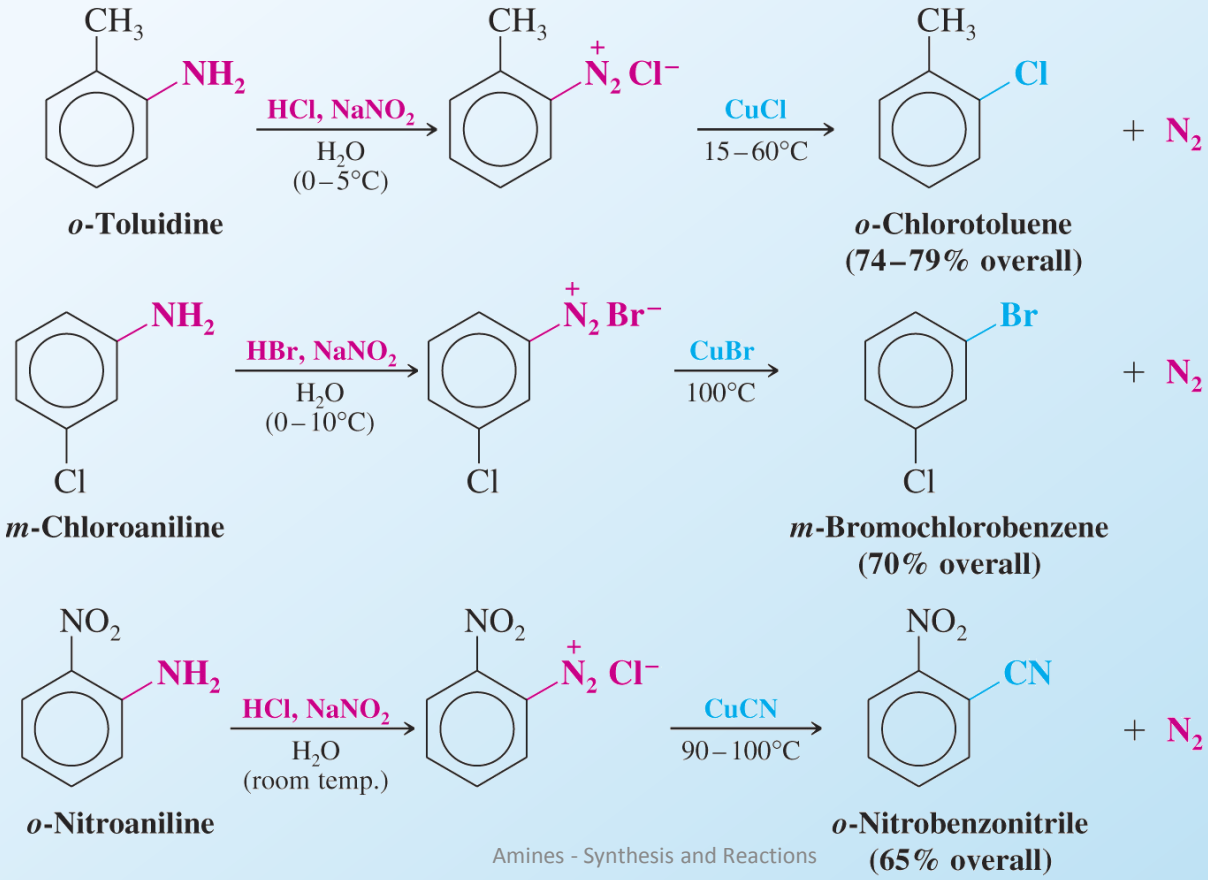
***p*-Bromotoluene (73%)**

Reactions of Amines – Nitrous Acid with 1° Aromatic Amines



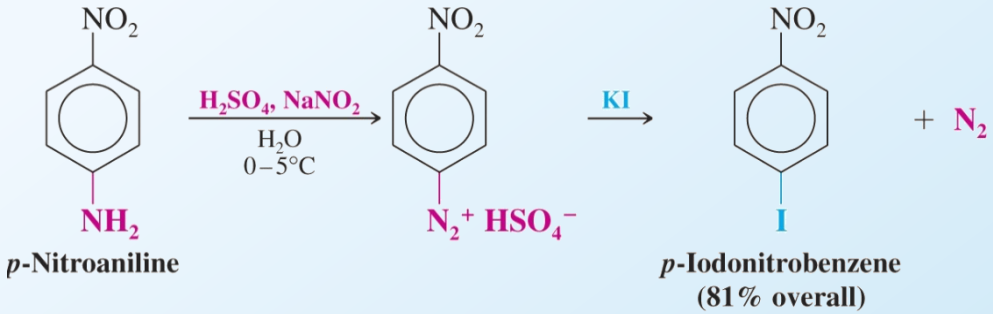
Reactions of Amines – Nitrous Acid with Aromatic Amines – Sandmeyer Reaction

- Replacement of the Diazonium Group by -Cl, -Br or -CN
- The mechanism of the Sandmeyer reaction is not well-understood but is thought to occur via radicals

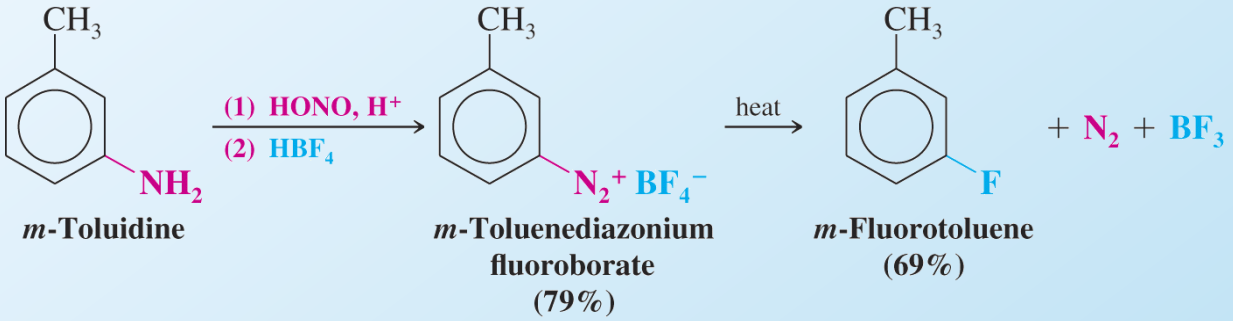


Reactions of Amines – Nitrous Acid with Aromatic Amines

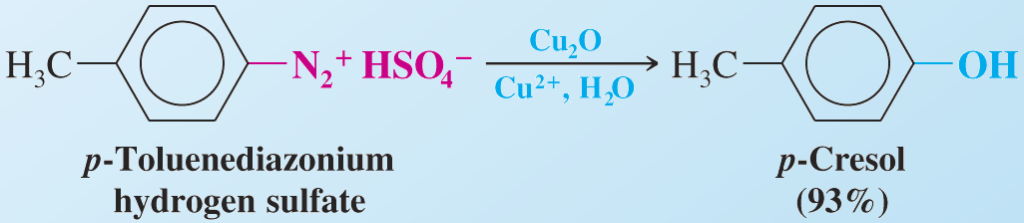
- Replacement with Iodine



- Replacement with Fluorine



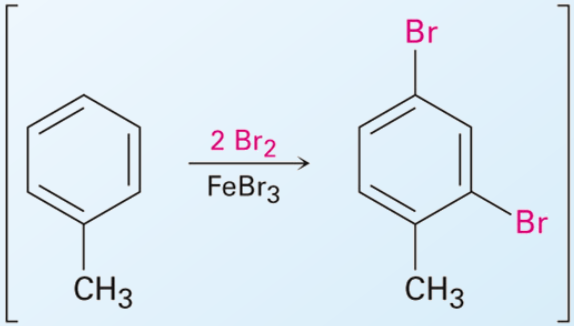
- Replacement with Hydroxide



Reactions of Amines – Nitrous Acid with Aromatic Amines – Synthetic Applications

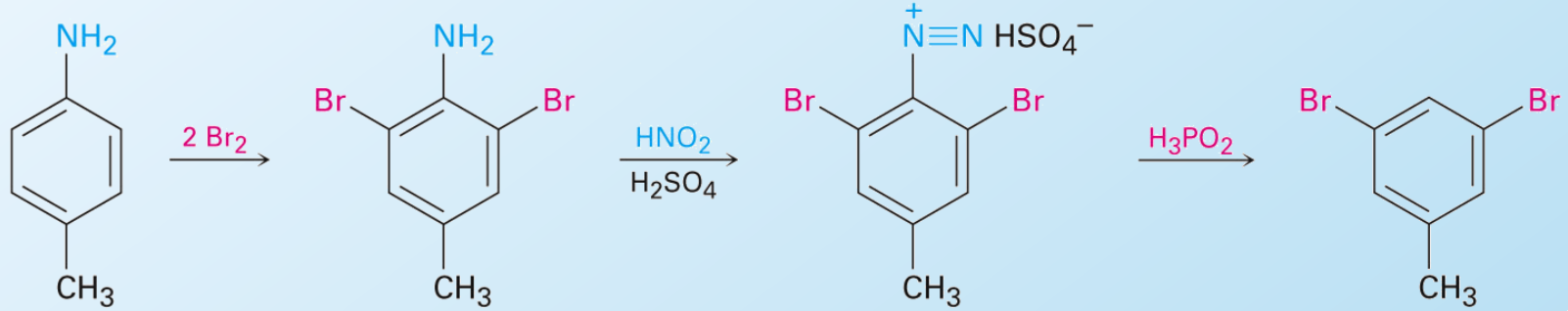
3, 5-dibromotoluene cannot be made directly from either toluene or bromobenzene.

Bromination of toluene will give o, p – substitution.



Toluene **2,4-Dibromotoluene**

However, treating p-methylaniline can be used with nitrous acid as in the following steps.

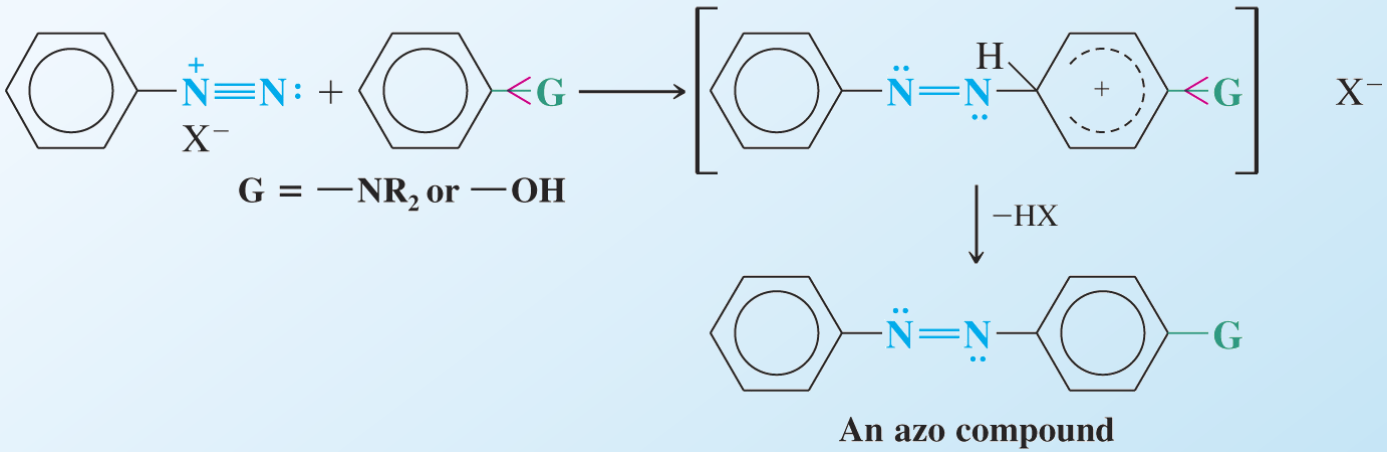


***p*-Methylaniline** **3,5-Dibromotoluene**

Reactions of Amines – Nitrous Acid with Aromatic Amines – Diazonium Coupling Reaction

- Arenediazonium ions react as electrophiles with highly reactive aromatic compounds such as phenol and aromatic tertiary amines
- The reaction is called a diazo coupling reaction

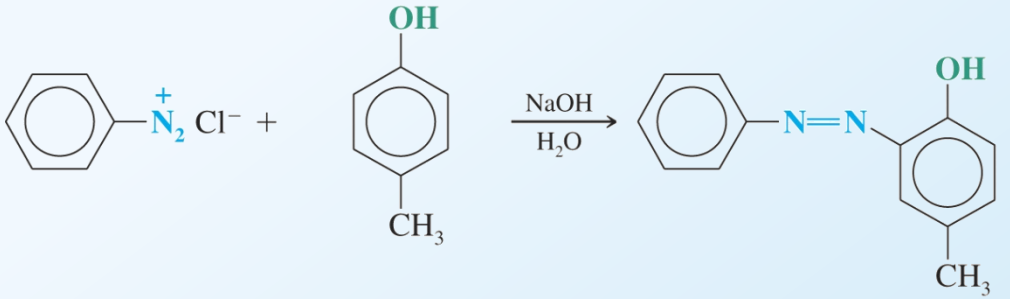
General Reaction



An azo compound

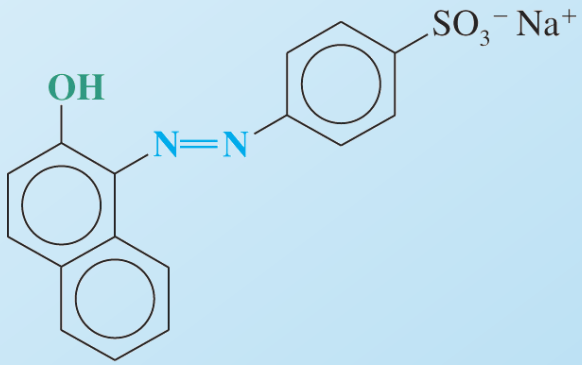
Coupling Reaction

- Phenol and aniline derivatives undergo coupling almost exclusively at the para position unless this position is blocked



4-Methylphenol (*p*-cresol) **4-Methyl-2-(phenylazo)phenol**

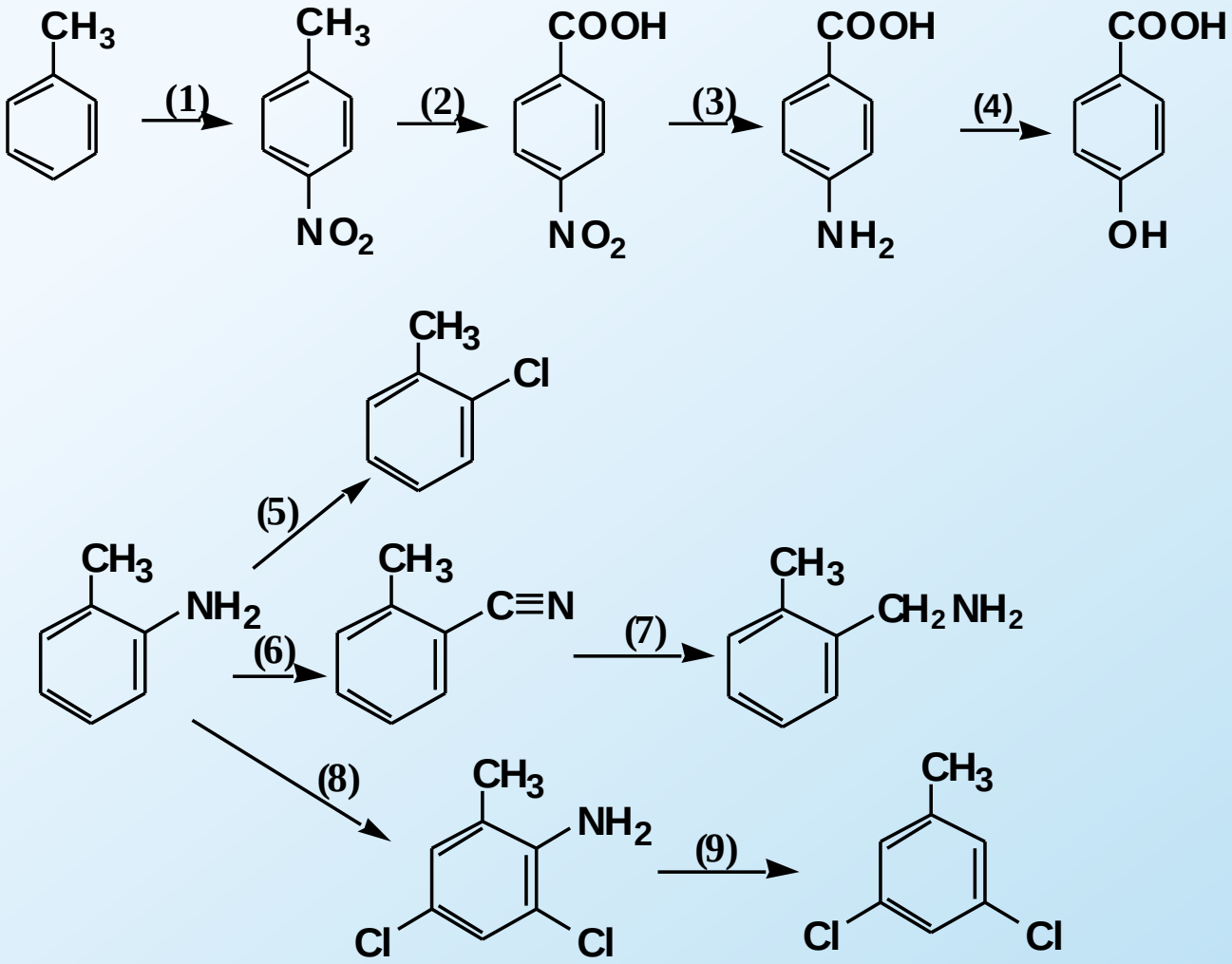
- Azo compounds are commonly used as dyes
- The azo coupling results in compounds which are highly conjugated and which often absorb light in the visible region
- The - $SO_3^-Na^+$ group is added to the molecule to confer water solubility and to link the dye to the polar fibers of wool, cotton etc.
- Orange II is made from 2-naphthol



Orange II

Problems

What reagents do you need to carry out the following reactions.



Key Concepts

- Synthesis – almost all reductions
- Reactions
- Diazonium salts
- Coupling reaction
- Aromatic synthesis