Amines

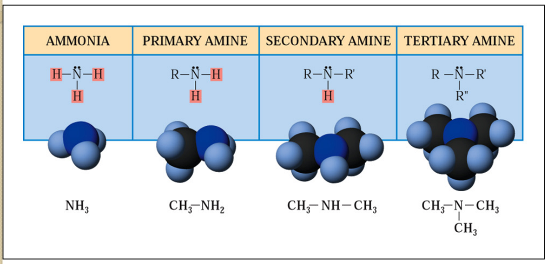
Amines

- Amines are compounds and functional groups that contain a basic nitrogen atom with a lone pair.
- They are organic derivatives of ammonia, in which one, two, or all three of the hydrogens of ammonia are replaced by organic groups

Amines

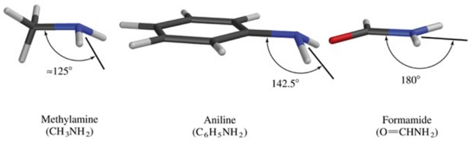
- Amines are organized into three subcategories based on the number of carbon atoms adjacent to the nitrogen
  - **Primary (1°) amines**—Primary amines arise when one of three hydrogen atoms in ammonia is replaced by an alkyl or aromatic group.
  - **Secondary (2°) amines**—Secondary amines have two organic substituents (alkyl, aryl or both) bound to the nitrogen together with one hydrogen.
  - **Tertiary (3°) amines**—In tertiary amines, nitrogen has three organic substituents.

Classification of Amines



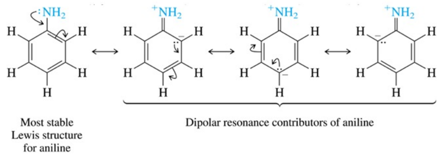
Structure and bonding

- The nitrogen of alkylamines is sp^3 hybridized and tetrahedral.



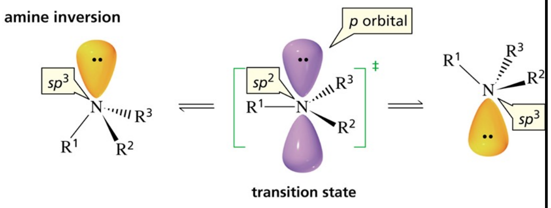
Structure and bonding

- The nitrogen of arylamines (aniline) is slightly flatten, reflecting resonance interactions with the aromatic ring.



Structure and bonding

- The lone-pair electrons on nitrogen allows an amine to turn "inside out" rapidly at room temperature



Basicity of Amines

- Amines are basic because they possess a pair of unshared electrons, which they can share with other atoms.
- These unshared electrons create an electron density around the nitrogen atom.
- The greater the electron density, the more basic the molecule.
- Groups that donate or supply electrons will increase the basicity of amines while groups that decrease the electron density around the nitrogen decrease the basicity of the molecule.

Basicity of Amines

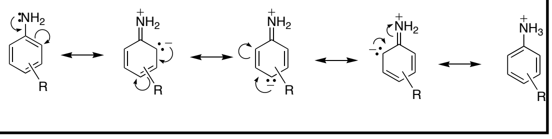
- Basicity of Amines: Amine Salts
- The greater the basicity of an amine, the weaker the acidity of its conjugate acid, the cation in its salts.

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]} \qquad pK_a = -\log K_a$$

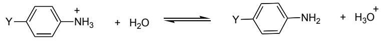
Basicity of Amines

- Arylamines are much less basic than alkylamines.
- The lone pair of electrons on the nitrogen of aniline are conjugated to the π-electrons of the aromatic ring and are therefore less available for acid-base chemistry.



Basicity of Amines

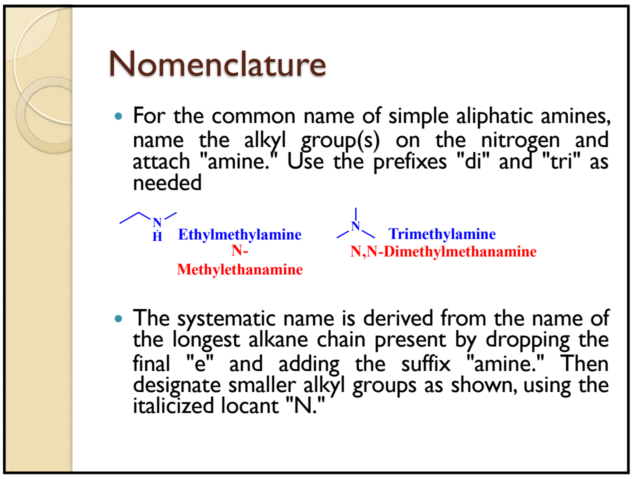
- Electron-donating substituents ($-CH_3$, -OH, $-OCH_3$) make the substituted aniline more basic than aniline itself (the pK_a of the anilinium ion is higher than 4.6)
- Electron-withdrawing substituents (-Cl, $-NO_2$) make the substituted aniline less basic than aniline itself (the p*K*a of the anilinium ion is lower than 4.6)



Y=	p*K*a		
$-NH_2$	p*K*a= 6.2	↓	less acidic (more basic)
$-OCH_3$	p*K*a= 5.3		
$-CH_3$	p*K*a= 5.1		
-H	p*K*a= 4.6		
-Cl	p*K*a= 4.0		
$-CF_3$	p*K*a= 3.5		more acidic (less basic)
-CN	p*K*a= 1.7		
$-NO_2$	p*K*a= 1.0		

Nomenclature

- In the IUPAC system of nomenclature, functional groups are normally designated in one of two ways.
- The presence of the function may be indicated by a characteristic suffix and a location number.
- This is common for the carbon-carbon double and triple bonds which have the respective suffixes ene and yne.
- Halogens, on the other hand, do not have a suffix and are named as substituents, for example: $(CH3)_2C{=}CHCHClCH_3$ is 4-chloro-2-methyl-2-pentene.



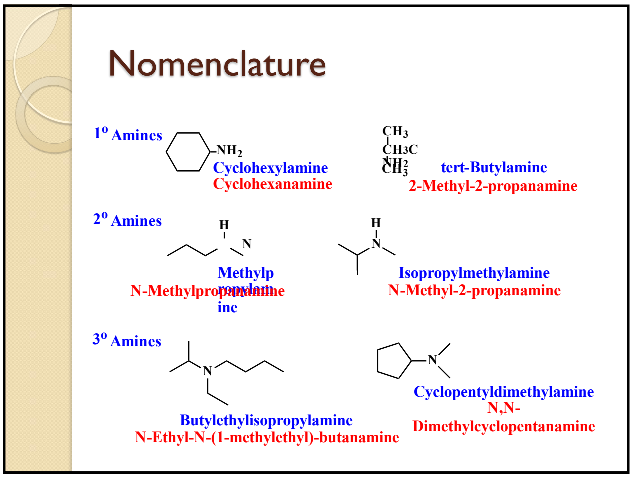
Nomenclature

- For the common name of simple aliphatic amines, name the alkyl group(s) on the nitrogen and attach "amine." Use the prefixes "di" and "tri" as needed

Ethylmethylamine
N-Methylethanamine

Trimethylamine
N,N-Dimethylmethanamine

- The systematic name is derived from the name of the longest alkane chain present by dropping the final "e" and adding the suffix "amine." Then designate smaller alkyl groups as shown, using the italicized locant "N."



Nomenclature

1^o Amines

Cyclohexylamine
Cyclohexanamine

tert-Butylamine
2-Methyl-2-propanamine

2^o Amines

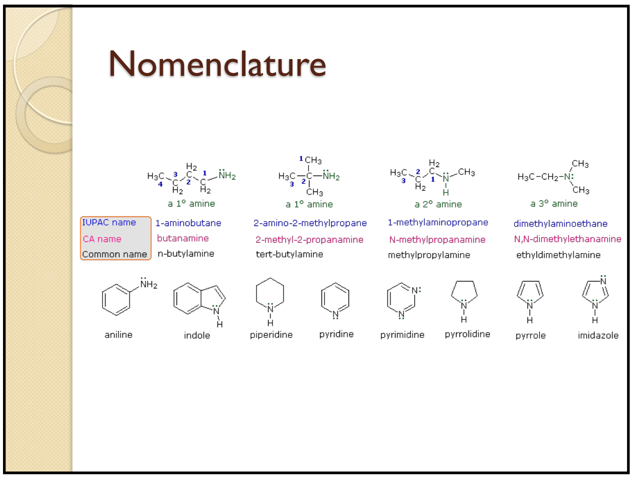
Methylpropylamine
N-Methylpropanamine

Isopropylmethylamine
N-Methyl-2-propanamine

3^o Amines

Butylethylisopropylamine
N-Ethyl-N-(1-methylethyl)-butanamine

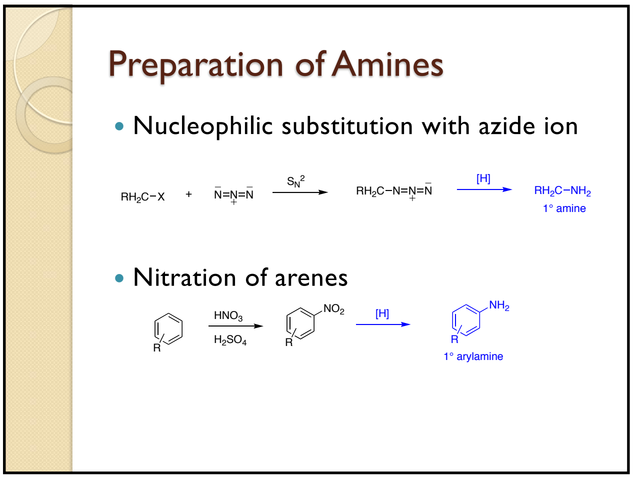
Cyclopentyldimethylamine
N,N-Dimethylcyclopentanamine



Nomenclature

	a 1° amine	a 1° amine	a 2° amine	a 3° amine
IUPAC name	1-aminobutane	2-amino-2-methylpropane	1-methylaminopropane	dimethylaminoethane
CA name	butanamine	2-methyl-2-propanamine	N-methylpropanamine	N,N-dimethylethanamine
Common name	n-butylamine	tert-butylamine	methylpropylamine	ethyldimethylamine

aniline indole piperidine pyridine pyrimidine pyrrolidine pyrrole imidazole



Preparation of Amines

- Nucleophilic substitution with azide ion

$$RH_2C{-}X \quad + \quad \bar{N}{=}\underset{+}{N}{=}\bar{N} \xrightarrow{S_N2} RH_2C{-}N{=}\underset{+}{N}{=}\bar{N} \xrightarrow{[H]} RH_2C{-}NH_2$$

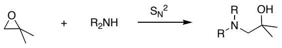
1° amine

- Nitration of arenes

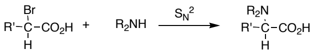
1° arylamine

Preparation of Amines

- Nucleophilic ring opening of epoxides with NH_3



- Nucleophilic substitution of α-halo acids with NH_3

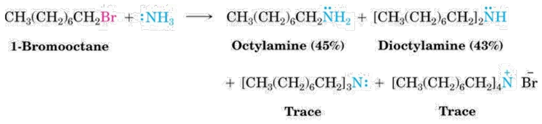


- **From alcohols**
  - Industrially significant amines are prepared from ammonia by alkylation with alcohol

$$ROH + NH_3 \rightarrow RNH_2 + H_2O$$

Preparation of Amines

- Preparation of Amines by Alkylation of Ammonia



$$CH_3(CH_2)_6CH_2Br + :NH_3 \longrightarrow CH_3(CH_2)_6CH_2\ddot{N}H_2 + [CH_3(CH_2)_6CH_2]_2\ddot{N}H + [CH_3(CH_2)_6CH_2]_3N: + [CH_3(CH_2)_6CH_2]_4\overset{+}{N}\ \overset{-}{Br}$$

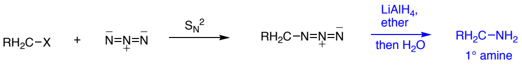
1-Bromooctane; Octylamine (45%); Dioctylamine (43%); Trace; Trace

Preparation of Amines

Preparation of Amines by Reduction

- Alkyl azides, nitriles, amides, and nitroarene can be reduced to the corresponding amines.

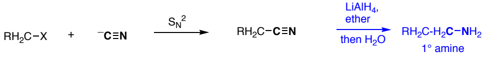
LiAlH$_4$ reduces alkyl azides to 1° amines



$$RH_2C{-}X + \bar{N}{=}\underset{+}{N}{=}\bar{N} \xrightarrow{S_N2} RH_2C{-}N{=}\underset{+}{N}{=}\bar{N} \xrightarrow[\text{then } H_2O]{LiAlH_4,\ \text{ether}} RH_2C{-}NH_2$$

1° amine

- LiAlH$_4$ reduces nitriles to 1° amines



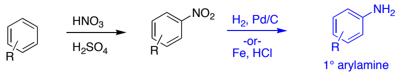
$$RH_2C{-}X + {}^{-}\mathbf{C{\equiv}N} \xrightarrow{S_N2} RH_2C{-}\mathbf{C{\equiv}N} \xrightarrow[\text{then } H_2O]{LiAlH_4,\ \text{ether}} RH_2C\text{-}H_2\mathbf{C}{-}\mathbf{N}H_2$$

1° amine

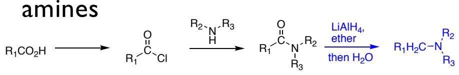
Preparation of Amines

Preparation of Amines by Reduction

- Nitroarenes are reduced to anilines

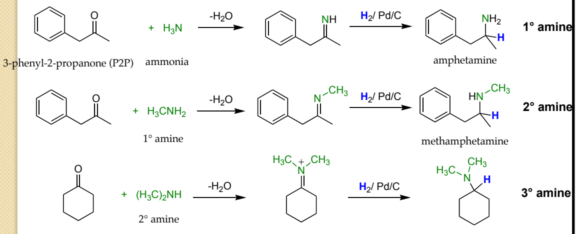


- LiAlH$_4$ reduces amides to 1°, 2° or 3° amines



Reductive Amination

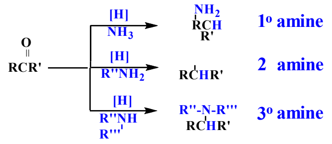
- Imines and iminium ions are easily reduced to amines.



iminium ion

Reductive Amination

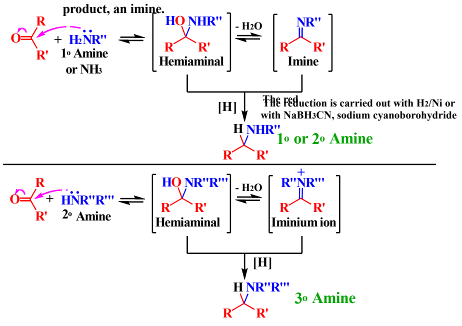
- Aldehydes and ketones can be converted into amines by catalytic or chemical reduction in the presence of ammonia or a 1^0 or 2^0 amine. The overall synthetic schemes are these:



Reductive Amination

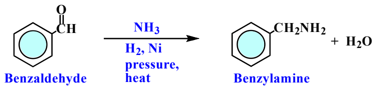
A Mechanism for Reductive Amination

Reductive amination involves addition of the amine to the carbonyl followed by reduction via the immediate aminal or its dehydration product, an imine.

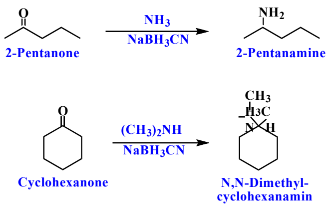


The red The reduction is carried out with H$_2$/Ni or with NaBH$_3$CN, sodium cyanoborohydride

Reductive Amination



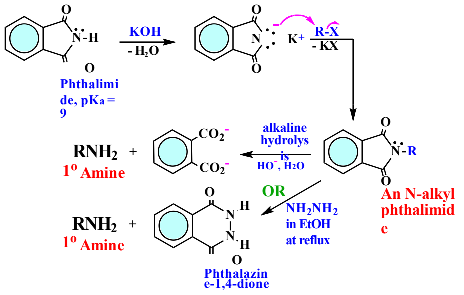
Amination of aldehyde OR alkylation of ammonia



The Gabriel Synthesis

- The Gabriel synthesis is a good choice when primary amines are desired.
- This synthesis utilizes the anion of phthalimide as a nucleophile in S_N2 reaction with alkyl halides.
- Alkaline hydrolysis of the N-alkylated phthalimide yields the primary amine free of secondary and tertiary amines.

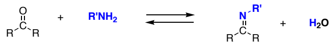
The Gabriel Synthesis



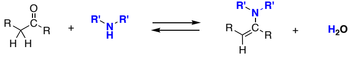
The alternative of using hydrazine, NH2NH2, to release the primary amine often gives superior results.

Reactions of Amines

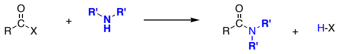
- Reaction of ammonia and 1° amines with aldehyde and ketones to afford imines (w/ loss of H_2O)



- Reaction of 2° amines with aldehyde and ketones (w/ an α-proton) to afford an enamine (w/ loss of H_2O)



- Reaction of ammonia, 1°, and 2° amines with acid chloride, anhydrides and esters to afford amides.

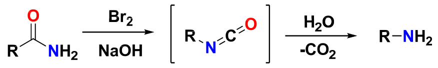


Hoffmann Bromamide reaction

- When an amide is treated with bromine in an aqueous or ethanolic solution of sodium hydroxide, degradation of amide takes place leading to the formation of primary amine.
- This reaction involving degradation of amide and is popularly known as Hoffmann bromamide degradation reaction.

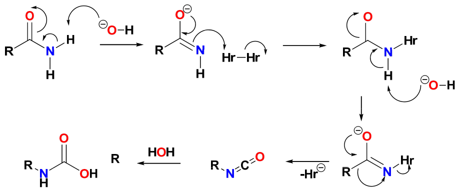
Hoffmann Bromamide reaction

Reaction Scheme



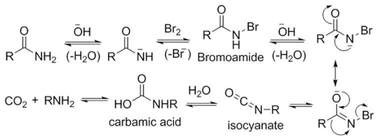
Hoffmann Bromamide reaction

Mechanism of Hofmann Rearrangement

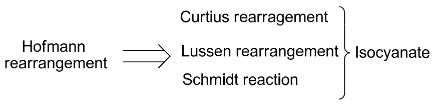


Hoffmann Bromamide reaction

- Base abstracts an acidic N-H proton, yielding an anion.
- The anion reacts with bromine in an α-substitution reaction to give an N-bromoamide.
- Base abstraction of the remaining amide proton gives a bromoamide anion.
- The bromoamide anion rearranges as the R group attached to the carbonyl carbon migrates to nitrogen at the same time the bromide ion leaves, giving an isocyanate.
- The isocyanate adds water in a nucleophilic addition step to yield a carbamic acid (aka urethane).
- The carbamic acid spontaneously loses CO2, yielding the amine product.



Similar Reactions

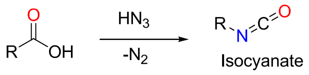


Hofmann rearrangement

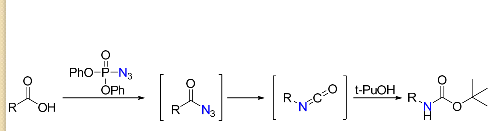
Curtius rearrangement
Lussen rearrangement
Schmidt reaction

Isocyanate

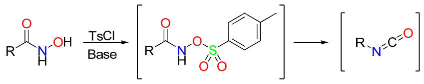
Schmidt Reaction



Curtius Rearrangement

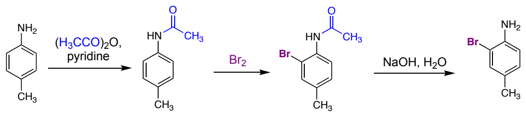


Lossen Rearrangement



Electrophilic Substitution

- The amino group is a strongly activating, ortho/para director; however, it is largely incompatible with Friedel-Crafts reactions.
- Electrophilic aromatic substitution of phenyl acetamides (amides of aniline): The acetamide group is still activating and an ortho/para director.



Electrophilic Substitution

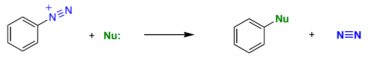
- The acetamides acts as a protecting group for the arylamine
- Anilines are so activated that multiple substitution reactions can be a problem.
- The reactivity of the acetamide is attenuated so that mono-substitution is achieved.
- The acetamide group is compatible with the Friedel-Crafts reactions

Nitrosation of Arylamines

- Reaction of aniline with *nitrous acid* leads to an aryl diazonium cation, which are value precursors to other functional groups.

$$NaNO_2 + H^+ \rightarrow HONO$$

- Aryl diazonium salts react with nucleophiles in a substitution reaction. N_2 is one of the best leaving groups.



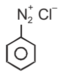
Diazonium Salts

The diazonium salts are represented by general formula $ArN_2^+X^-$, where Ar stands for the aryl group and X may be any anion such as

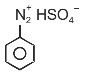
$Cl^-, Br^-, HSO_4^-, BF_4^-$ etc.

Nomenclature

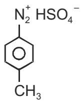
obtained by adding the suffix diazonium to the parent compound and is further followed by the name of the anion, e.g.



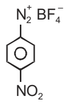
Benzene diazonium chloride



Benzene diazonium hydrogen sulphate



p - toluene diazonium hydrogen sulphate



p -nitrobenzene diazonium fluoroborate

Diazonium Salts

Preparation of diazonium salts

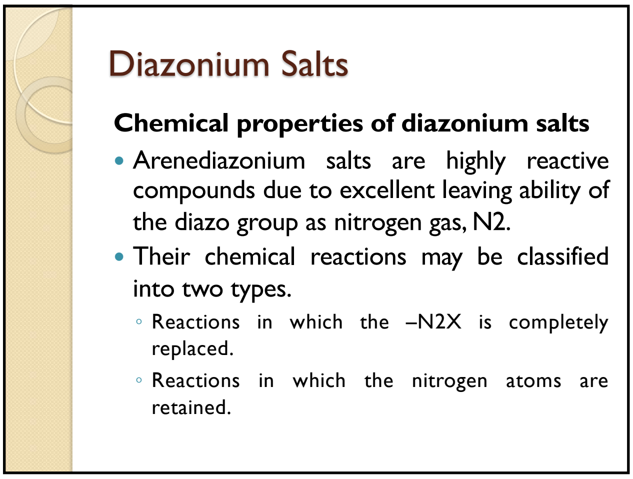
1. Obtained by treatment of primary aromatic amine dissolved in cold aqueous mineral acid with sodium nitrite.

   The conversion of primary amine into a diazonium salt is called **diazotisation**.

$$\underset{(1^\circ \text{ Aromatic amine})}{Ar-NH_2} + NaNO_2 + 2HX \xrightarrow{\text{Cold}} \underset{(\text{A diazonium salt})}{Ar-N\equiv N^+X^-} + NaX + 2H_2$$

2. Nitrite esters formed from alcohols and nitrous acid are also used to generate diazonium salt on treatment with aromatic primary amines.

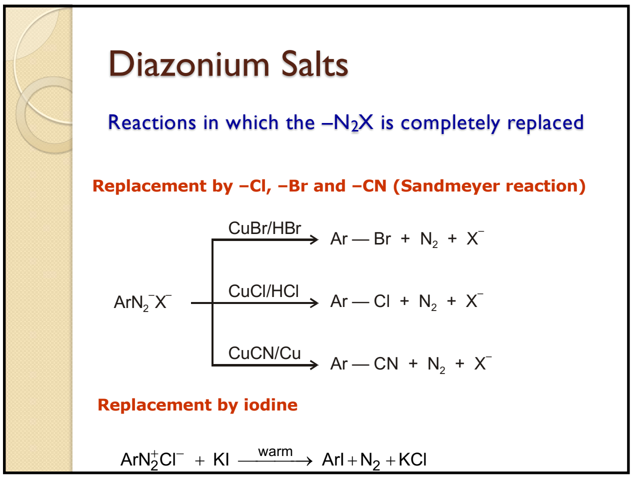
$$C_5H_{11}-O-N=O + HCl + C_6H_5NH_2 \xrightarrow{273\text{–}278\text{ K}} C_6H_5\overset{+}{N}\equiv NCl^- + C_5H_{11}OH + H_2$$



Diazonium Salts

Chemical properties of diazonium salts

- Arenediazonium salts are highly reactive compounds due to excellent leaving ability of the diazo group as nitrogen gas, N2.
- Their chemical reactions may be classified into two types.
  - Reactions in which the –N2X is completely replaced.
  - Reactions in which the nitrogen atoms are retained.



Diazonium Salts

Reactions in which the –N_2X is completely replaced

Replacement by –Cl, –Br and –CN (Sandmeyer reaction)

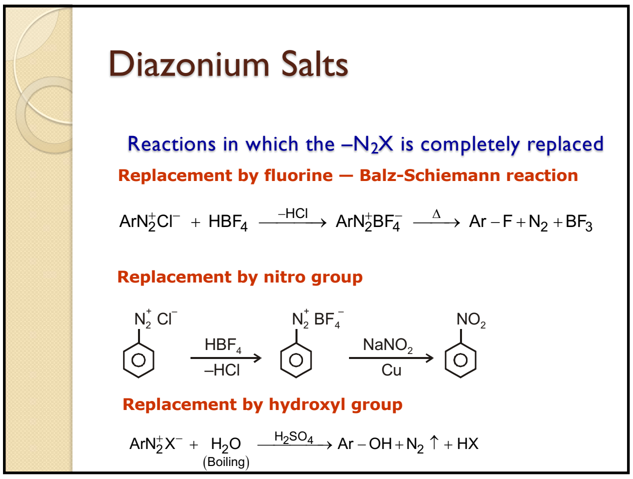
$$ArN_2^-X^- \xrightarrow{CuBr/HBr} Ar-Br + N_2 + X^-$$

$$ArN_2^-X^- \xrightarrow{CuCl/HCl} Ar-Cl + N_2 + X^-$$

$$ArN_2^-X^- \xrightarrow{CuCN/Cu} Ar-CN + N_2 + X^-$$

Replacement by iodine

$$ArN_2^+Cl^- + KI \xrightarrow{warm} ArI + N_2 + KCl$$



Diazonium Salts

Reactions in which the –N_2X is completely replaced

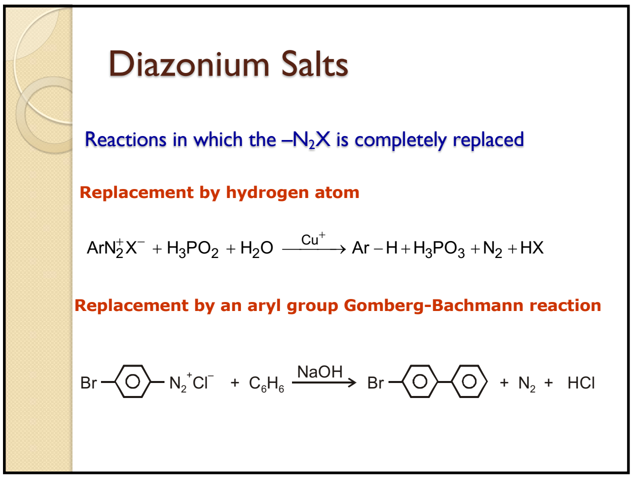
Replacement by fluorine — Balz-Schiemann reaction

$$ArN_2^+Cl^- + HBF_4 \xrightarrow{-HCl} ArN_2^+BF_4^- \xrightarrow{\Delta} Ar-F + N_2 + BF_3$$

Replacement by nitro group

Replacement by hydroxyl group

$$ArN_2^+X^- + \underset{(Boiling)}{H_2O} \xrightarrow{H_2SO_4} Ar-OH + N_2\uparrow + HX$$



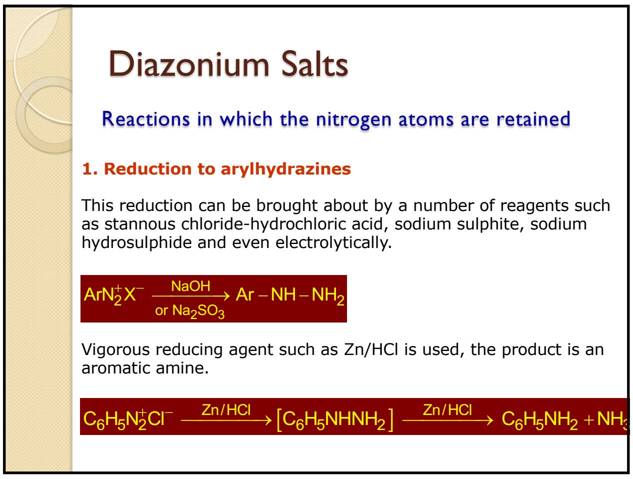
Diazonium Salts

Reactions in which the –N_2X is completely replaced

Replacement by hydrogen atom

$$ArN_2^+X^- + H_3PO_2 + H_2O \xrightarrow{Cu^+} Ar-H + H_3PO_3 + N_2 + HX$$

Replacement by an aryl group Gomberg-Bachmann reaction



Diazonium Salts

Reactions in which the nitrogen atoms are retained

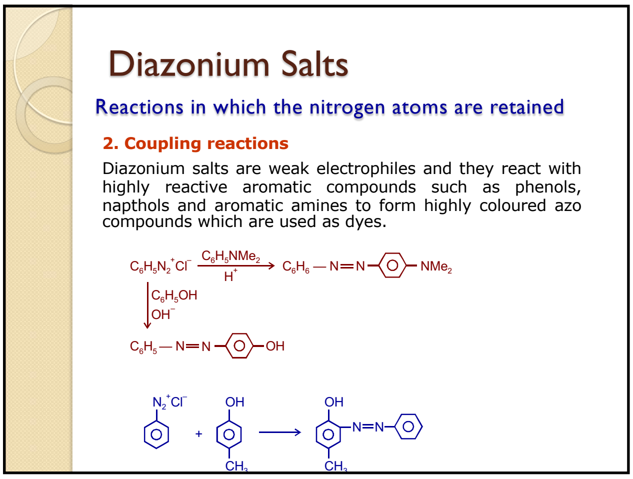
1. Reduction to arylhydrazines

This reduction can be brought about by a number of reagents such as stannous chloride-hydrochloric acid, sodium sulphite, sodium hydrosulphide and even electrolytically.

$$ArN_2^+X^- \xrightarrow[\text{or } Na_2SO_3]{NaOH} Ar-NH-NH_2$$

Vigorous reducing agent such as Zn/HCl is used, the product is an aromatic amine.

$$C_6H_5N_2^+Cl^- \xrightarrow{Zn/HCl} [C_6H_5NHNH_2] \xrightarrow{Zn/HCl} C_6H_5NH_2 + NH$$

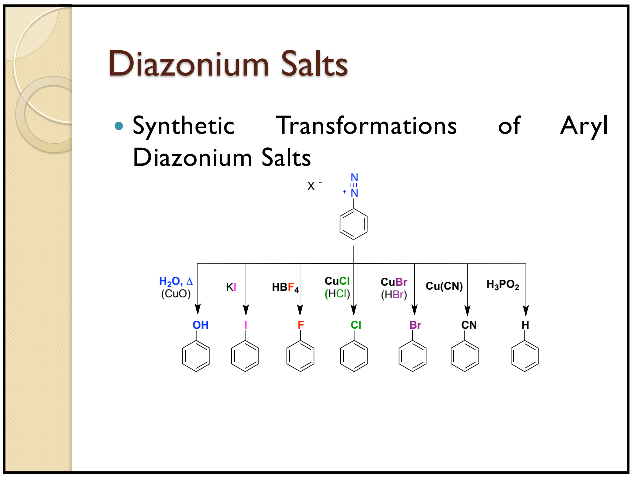


Diazonium Salts

Reactions in which the nitrogen atoms are retained

2. Coupling reactions

Diazonium salts are weak electrophiles and they react with highly reactive aromatic compounds such as phenols, napthols and aromatic amines to form highly coloured azo compounds which are used as dyes.



Diazonium Salts

- Synthetic Transformations of Aryl Diazonium Salts