

Chapter 20 Amines-part 2

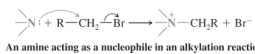
Reactions of Amines

- ◆ Lone pair on the nitrogen directs the chemistry of amines

Acid-Base Reactions

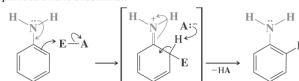


Alkylation



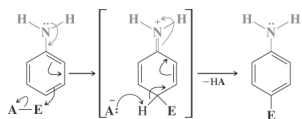
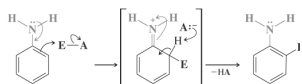
- ◆ The nitrogen lone pair can also make a carbon nucleophilic by resonance

Electrophilic Aromatic Substitution



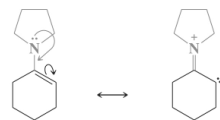
Amines can also activate carbons to be nucleophilic

1. Electrophilic Aromatic Substitution



The amino group acting as an activating group and as an ortho-para director in electrophilic aromatic substitution

2. Enamines have a nucleophilic carbon

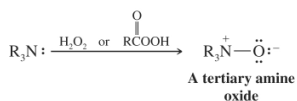


Alkylation or acylation occurs mostly at carbon rather than nitrogen

Oxidation of Amines

➔ Primary and secondary amines undergo *N*-oxidation, but useful products are not obtained because of side-reactions

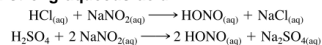
➔ Tertiary amines undergo clean *N*-oxidation



(Will use later for the Cope Elimination reaction)

Reactions of Amines with Nitrous Acid

◆ Nitrous acid (HONO) is prepared *in situ* by reaction of sodium nitrite with a strong aqueous acid

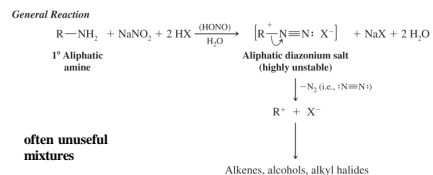


1. Reaction of Primary Aliphatic Amines with Nitrous Acid

● Primary amines undergo *diazotization*

➔ The unstable *diazonium salts* decompose to form carbocations

➔ The carbocations react further to give alkenes, alcohols and alkyl halides

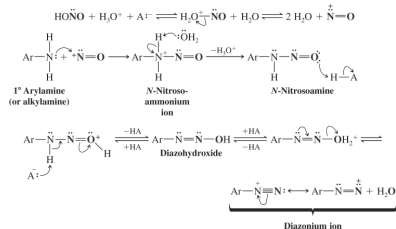


Reaction of Primary Arylamines with Nitrous Acid

◆ Reaction of primary arylamines with nitrous acid results in the formation of relatively stable arenediazonium salts (below 5°C!)

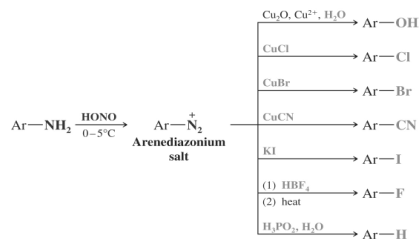


● This reaction occurs through the intermediacy of an *N*-nitrosoamine



Replacement Reactions of Arenediazonium Salts

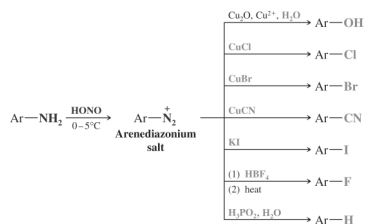
◆ Aryldiazonium salts react readily with various nucleophilic reagents to give a wide variety of aromatic compounds



Finally – a way to do “nucleophilic substitutions” on a benzene ring!

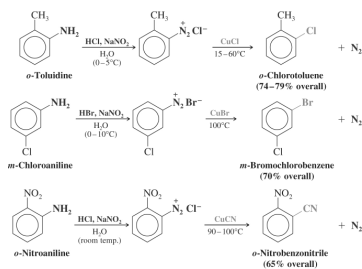
Replacement Reactions of Arenediazonium Salts

- The aryldiazonium salt is made from the corresponding arylamine
- The arylamine can be made by reduction of a nitroaromatic compound



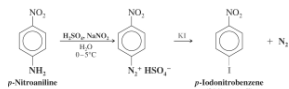
Sandmeyer Reaction: Replacement of Diazonium Ion by Cl, Br or CN

- ♦ Mechanism of the Sandmeyer reaction is not well-understood but is thought to occur via radicals



• Replacement by -I

- ➔ Reaction of arenediazonium salts with potassium iodide gives the aryl iodide



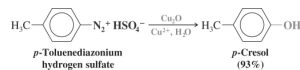
• Replacement by -F

- ➔ A diazonium fluoroborate is isolated, dried and heated until it decomposes to the fluoroaromatic product



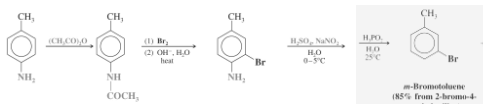
• Replacement by -OH

- ➔ An aryl diazonium salt is placed in aqueous solution with a large excess of cupric nitrate and then treated with cuprous oxide



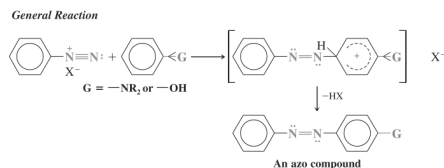
Replacement by Hydrogen: Deamination by Diazotization

- ◆ An arenediazonium salt can react with hypophosphorous acid (H_3PO_2) to replace the diazonium group with a hydrogen atom
- ◆ This reaction can be used to remove an amino group that was important early in a synthesis as an ortho, para director
 - ➔ Example: *m*-Bromotoluene cannot be made directly from either toluene or bromobenzene
 - ★ *N*-acetylation is used to reduce the activating effect of the amine



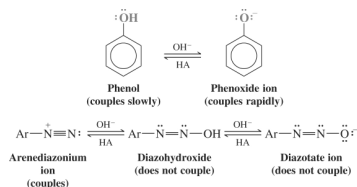
Coupling Reactions of Arenediazonium Salts

- ◆ Arenediazonium ions react as electrophiles with highly reactive aromatic compounds such as phenol and aromatic tertiary amines
- ◆ Called a *diazo coupling reaction*

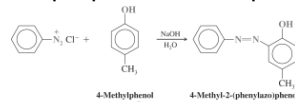


Coupling Reactions of Arenediazonium Salts

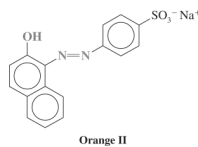
- ◆ Coupling with phenol occurs best in slightly alkaline solution
 - Generates a phenoxide ion that couples more rapidly
 - If the solution is too alkaline, a nonreactive diazohydroxide is produced



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



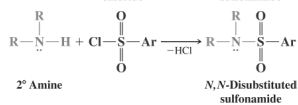
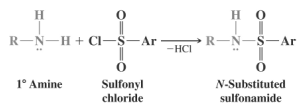
- ◆ Azo compounds are commonly used as dyes
 - Highly conjugated and absorb light in the visible region
 - Eg, Orange II from 2-naphthol and sulfanilic acid



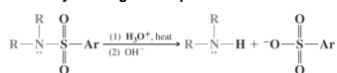
Polar groups can bind the dye to fibers of wool or cotton

Reactions of Amines with Sulfonyl Chlorides

- ◆ Primary and secondary amines react with sulfonyl chlorides to produce **sulfonamides**



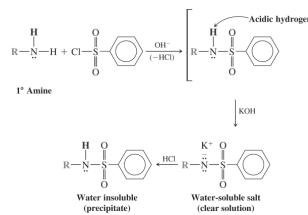
- ◆ Reverse reaction by heating with aqueous acid



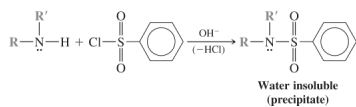
The Hinsberg Test

- ◆ Test to distinguish between 1°, 2° and 3° amines
- ◆ An amine and benzenesulfonyl chloride are mixed with aqueous potassium hydroxide; the reaction is acidified in a second step.

1. A benzenesulfonamide from a primary amine is soluble in basic solution, but precipitates upon acidification

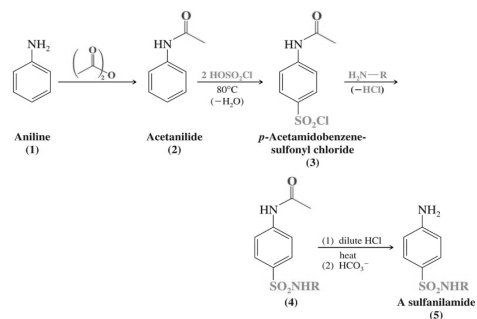


2. A secondary amine forms a precipitate directly because an *N,N*-disubstituted sulfonamide remains insoluble in basic solution (There is no acidic hydrogen in an *N,N*-disubstituted sulfonamide)



3. A tertiary amine will not react to form a sulfonamide, but will dissolve upon acidification

Synthesis of sulfa drugs = sulfanilamides



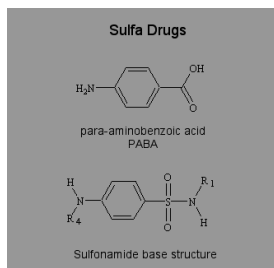
Mechanism of Sulfa Drugs as Antimetabolite

All cells need folic acid

Mammals can absorb from diet

Bacteria must synthesize from PABA

Sulfa drugs interfere



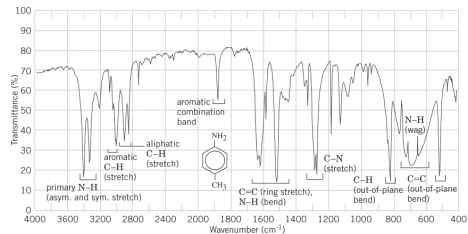
Analysis of Amines

◆ Chemical Analysis

- Distinguished by their ability to dissolve in dilute aqueous acid
- Wet litmus paper will indicate the basicity of an amine
- The Hinsberg test can be used to distinguish among primary, secondary and tertiary amines

◆ Infrared Spectra

- Characteristic N-H stretching vibrations in the 3300-3555 cm^{-1} region
- Primary amines give 2 absorptions (from symmetric and asymmetric stretching); secondary amines give one absorption



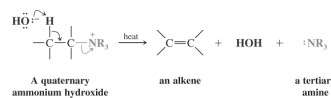
◆ ^1H NMR

- Primary and secondary amines have broad, uncoupled N-H peaks at δ 0.5-5
- N-H protons will exchange with D_2O and disappear from the ^1H spectrum
- Protons on carbons adjacent to the nitrogen appear at δ 2.2-2.9

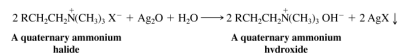
Eliminations Involving Ammonium Compounds: Hofmann Elimination

- ◆ An E2-type reaction occurs when a quaternary ammonium hydroxide is heated

- An amine is a relatively good leaving group

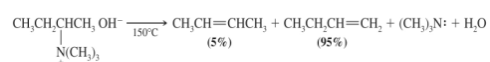
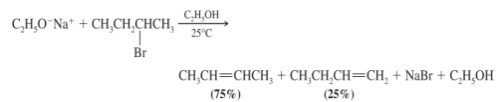


- A quaternary ammonium hydroxide is made from a quaternary ammonium halide using silver oxide



◆ Hofmann elimination gives the least substituted double bond

- Origin of the Hofmann rule
- Least substituted alkene is called the Hofmann product



The Cope Elimination

- ◆ Tertiary amine oxide will undergo elimination to the alkene when heated
- ◆ Made from tertiary amines by reaction with hydrogen peroxide
 - Cyclic transition state needs to syn elimination

