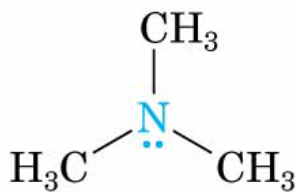


# Chapter 24. Amines

Based on McMurry's *Organic Chemistry*, 7<sup>th</sup> edition

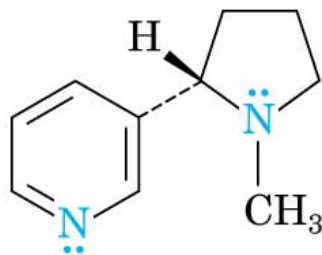
# Amines – Organic Nitrogen Compounds

- Organic derivatives of ammonia,  $\text{NH}_3$ ,
- Nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic
- Occur in plants and animals

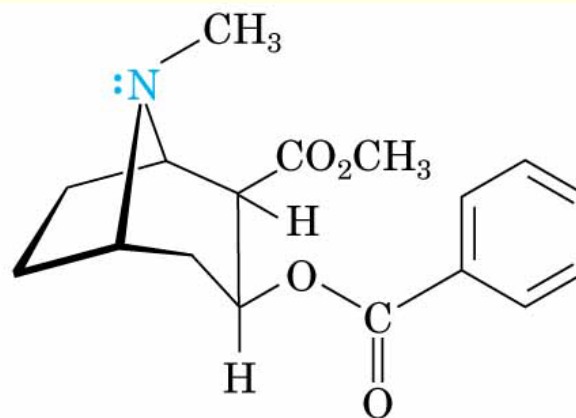


**Trimethylamine**

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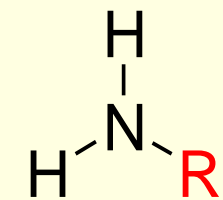
**Nicotine**



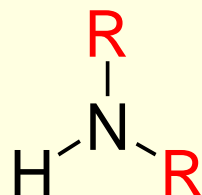
**Cocaine**

# Naming Amines

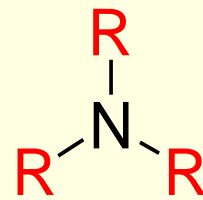
- Alkyl-substituted (alkylamines) or aryl-substituted (aryl amines)
- Classified:
  - 1° (RNH<sub>2</sub>) primary amine
  - 2° (R<sub>2</sub>NH) secondary amine
  - Tertiary amine 3° (R<sub>3</sub>N)



Primary



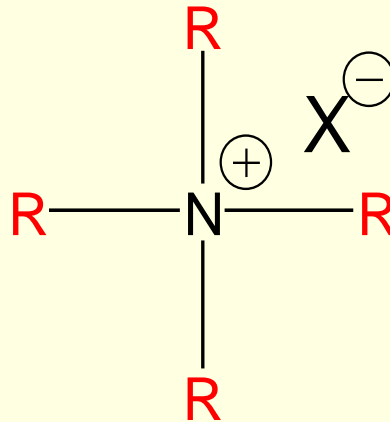
Secondary



Tertiary

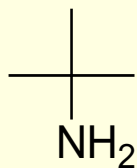
# Quaternary Ammonium Ions

- A nitrogen atom with four attached groups is positively charged
- Compounds are quaternary ammonium salts

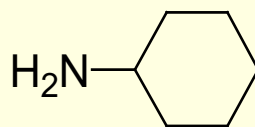


# IUPAC Names – Simple Amines

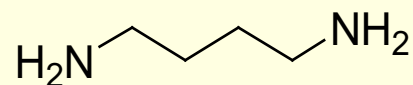
- For simple amines, the suffix *-amine* is added to the name of the alkyl substituent



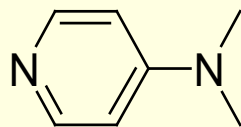
tert-butylamine



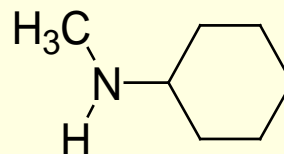
cyclohexanamine



1,4-butanediamine



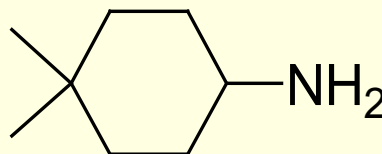
*N,N*-Dimethyl-4-aminopyridine



*N*-Methyl-Cyclohexanamine

# IUPAC Names – “-amine” Suffix

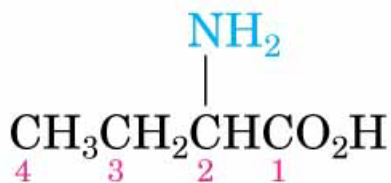
- The suffix *-amine* can be used in place of the final *-e* in the name of the parent compound



4,4-Dimethylcyclohexanamine

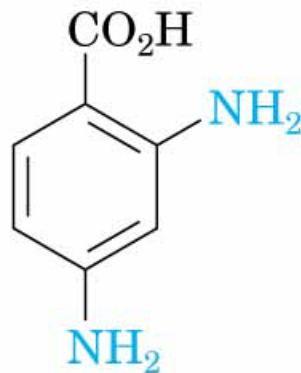
# IUPAC Names – Amines With More Than One Functional Group

- Consider the  $\text{—NH}_2$  as an *amino* substituent on the parent molecule

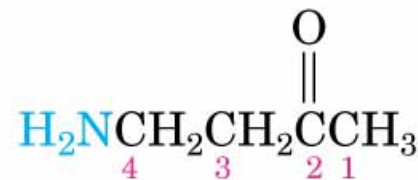


**2-Amino**butanoic acid

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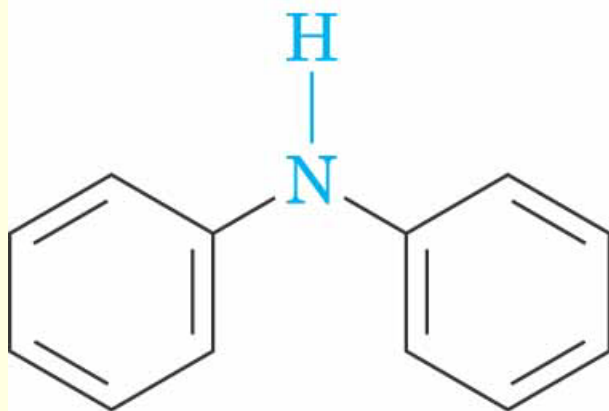
**2,4-Diamino**benzoic acid



**4-Amino-2-**butanone

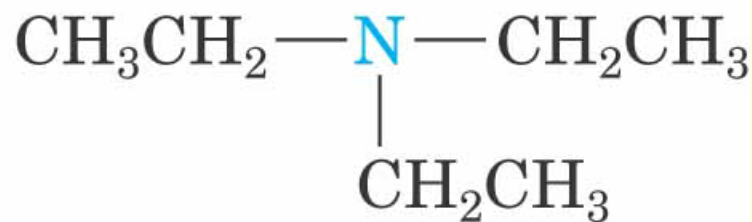
# IUPAC Names – Multiple Alkyl Groups

- Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group



**Diphenylamine**

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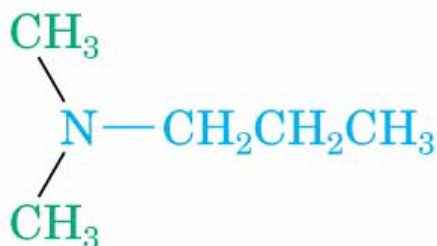


**Triethylamine**



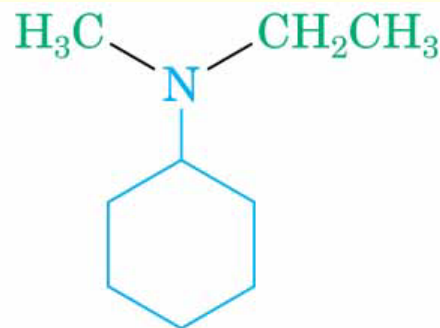
# IUPAC Names – Multiple, Different Alkyl Groups

- Named as *N*-substituted primary amines
- Largest alkyl group is the parent name, and other alkyl groups are considered *N*-substituents



***N,N*-Dimethylpropylamine**  
(propylamine is the parent name; the two methyl groups are substituents on nitrogen)

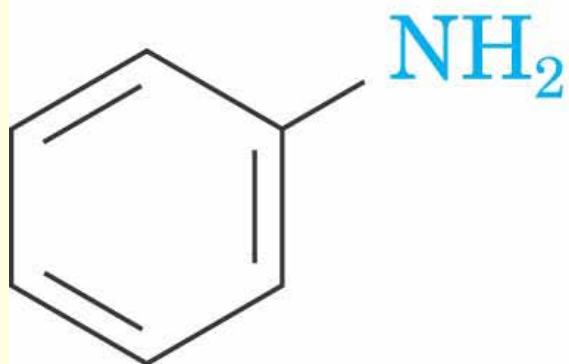
© 2004 Thomson/Brooks Cole



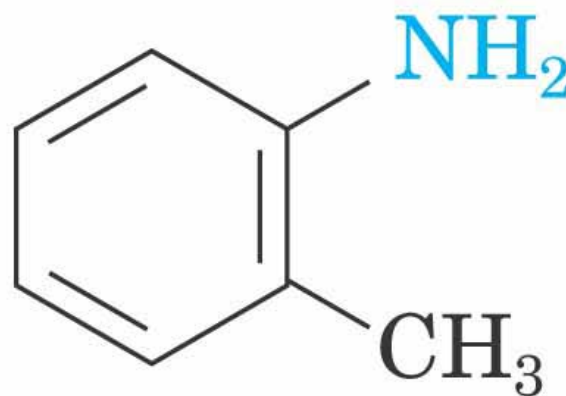
***N*-Ethyl-*N*-methylcyclohexylamine**  
(cyclohexylamine is the parent name; methyl and ethyl are *N*-substituents)

# Common Names

- Alkylamines do not have common names unless they are biological molecules
- Simple arylamines have common names



**Aniline**



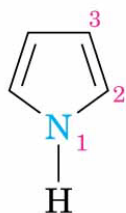
***o*-Toluidine**

# Common Names of Heterocyclic Amines

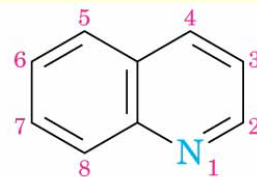
- If the nitrogen atom occurs as part of a ring, the compound is designated as being heterocyclic
- Each ring system has its own parent name



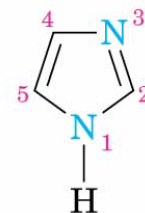
**Pyridine**



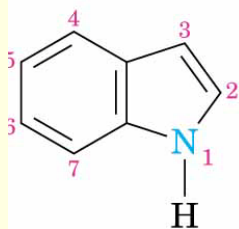
**Pyrrole**



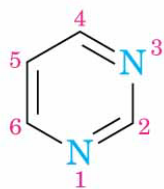
**Quinoline**



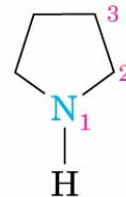
**Imidazole**



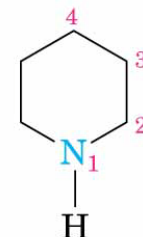
**Indole**



**Pvrimidine**



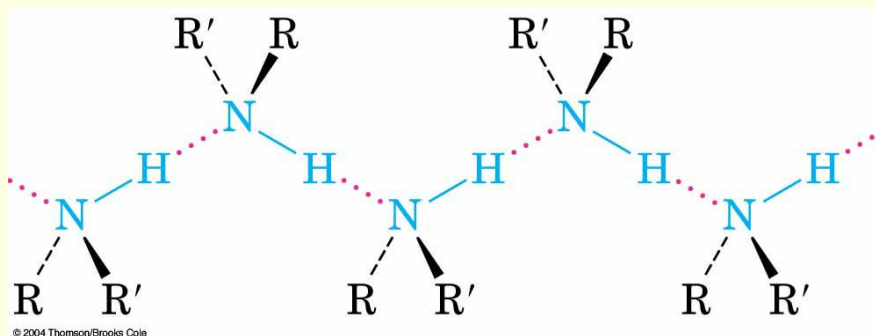
**Pyrrolidine**



**Piperidine**

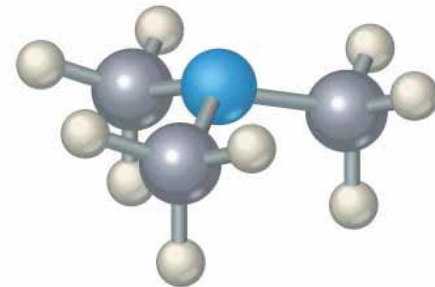
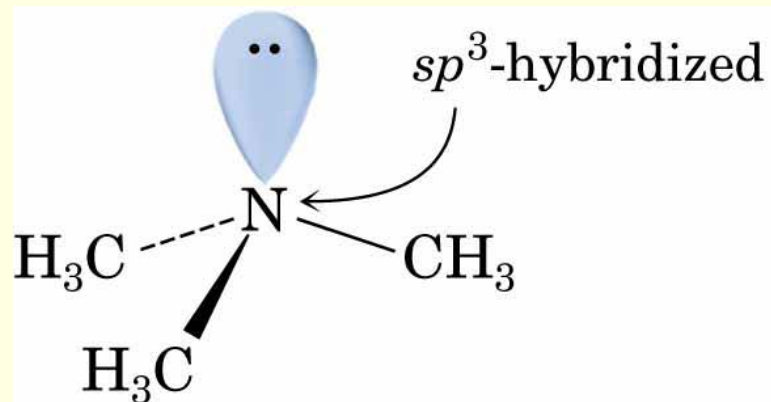
# Amines Form H-Bonds

- Amines with fewer than five carbons are water-soluble
- Primary and secondary amines form hydrogen bonds, increasing their boiling points



# Structure and Bonding in Amines

- Bonding to N is similar to that in ammonia
  - N is  $sp^3$ -hybridized
  - C–N–C bond angles are close to  $109^\circ$  tetrahedral value



**Trimethylamine**

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# Properties and Sources of Amines

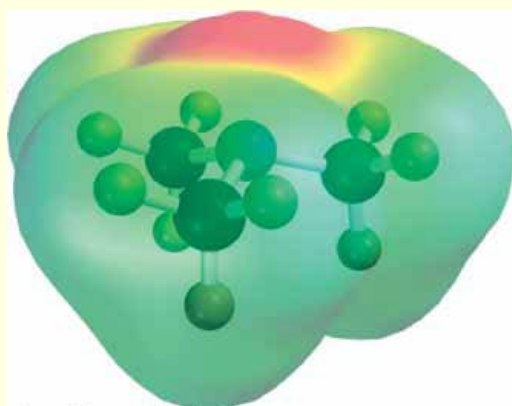
- Simple methylated amines from reaction of  $\text{NH}_3$  with  $\text{CH}_3\text{OH}$  and alumina catalyst
- Yields a mixture of monomethylated, dimethylated, and trimethylated products that are easily separated by distillation



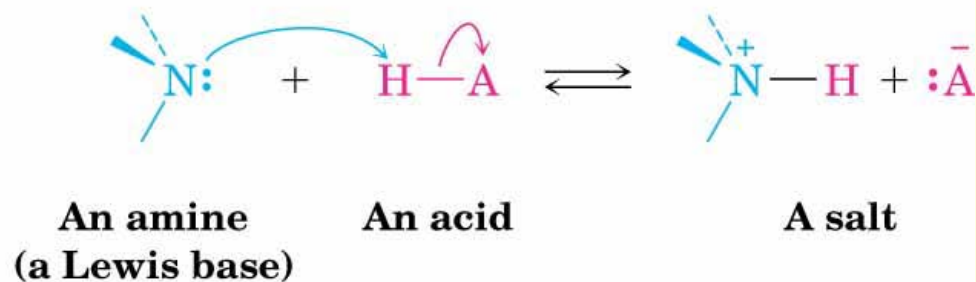
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# Basicity of Amines

- The lone pair of electrons on nitrogen makes amines basic and nucleophilic
- They react with acids to form acid–base salts and they react with electrophiles



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# Relative Basicity

- Amines are stronger bases than alcohols, ethers, or water
- Amines establish an equilibrium with water in which the amine becomes protonated and hydroxide is produced
- The most convenient way to measure the basicity of an amine ( $\text{RNH}_2$ ) is to look at the acidity of the corresponding ammonium ion ( $\text{RNH}_3^+$ )

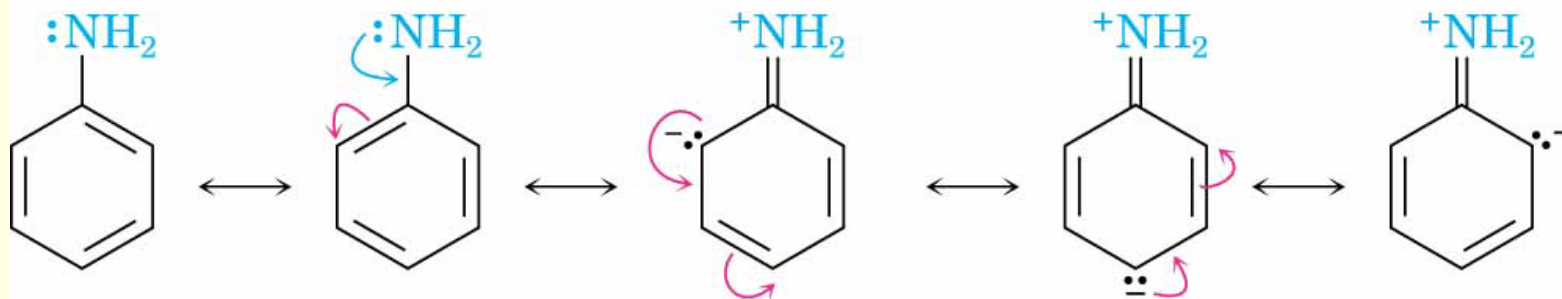


$$\text{p}K_a = \text{pH} - \log \left( \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]}\right)$$



# Basicity of Substituted Arylamines

- The N lone-pair electrons in arylamines are delocalized by interaction with the aromatic ring  $\pi$  electron system and are less able to accept  $H^+$  than are alkylamines



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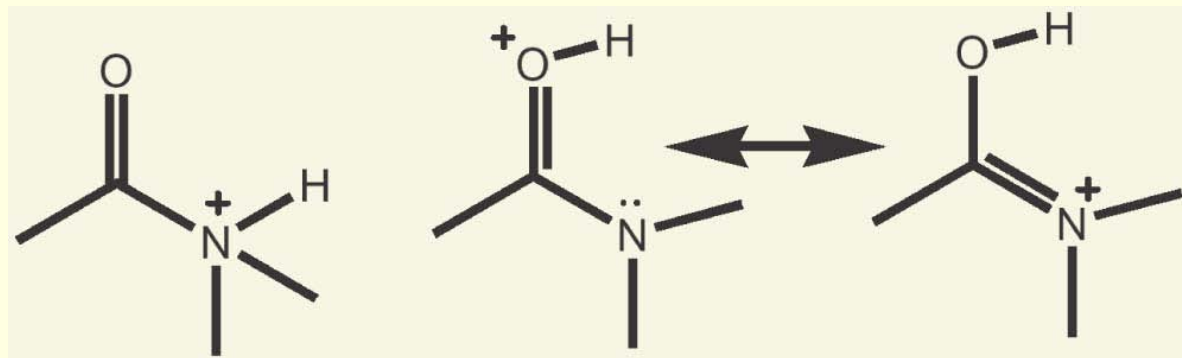
# General Patterns of Basicity

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- Table 24.1:  $pK_a$  values of ammonium ions
- Most simple alkylammonium ions have  $pK_a$ 's of 10 to 11
- Arylamines and heterocyclic aromatic amines are considerably less basic than alkylamines (conjugate acid  $pK_a$  5 or less)

# Amides

- Amides ( $\text{RCONH}_2$ ) in general are not proton acceptors except in very strong acid
- The  $\text{C}=\text{O}$  group is strongly electron-withdrawing, making the N a very weak base
- Addition of a proton occurs on O but this destroys the double bond character of  $\text{C}=\text{O}$  as a requirement of stabilization by N



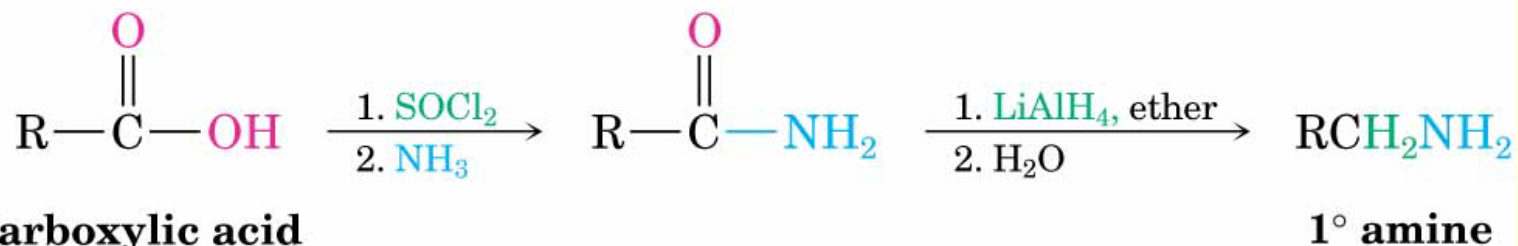
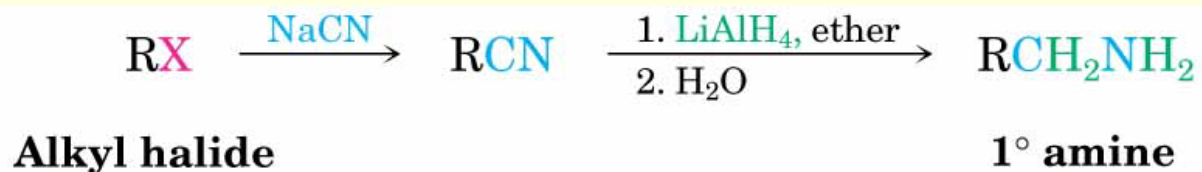
# Substituted Arylamines

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- Can be more basic or less basic than aniline
- Electron-donating substituents (such as  $\text{—CH}_3$ ,  $\text{—NH}_2$ ,  $\text{—OCH}_3$ ) increase the basicity of the corresponding arylamine
- Electron-withdrawing substituents (such as  $\text{—Cl}$ ,  $\text{—NO}_2$ ,  $\text{—CN}$ ) decrease arylamine basicity

# Synthesis of Amines

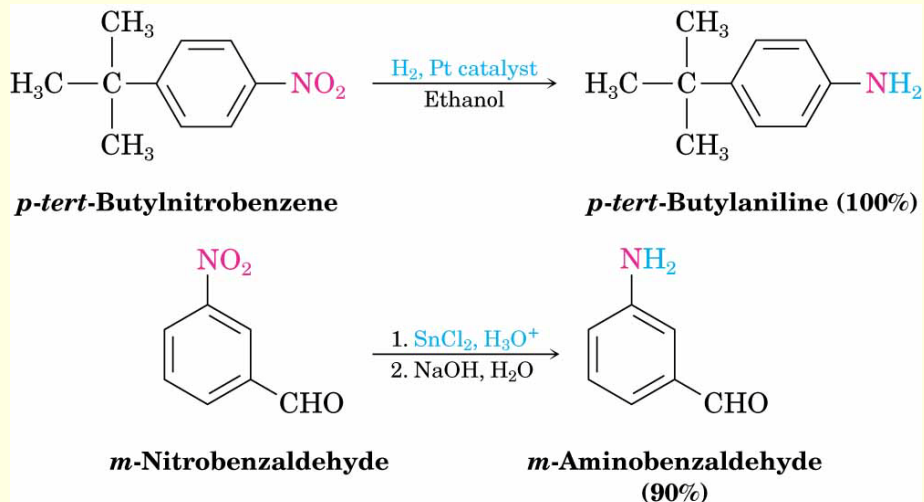
- Reduction of nitriles and amides (review)



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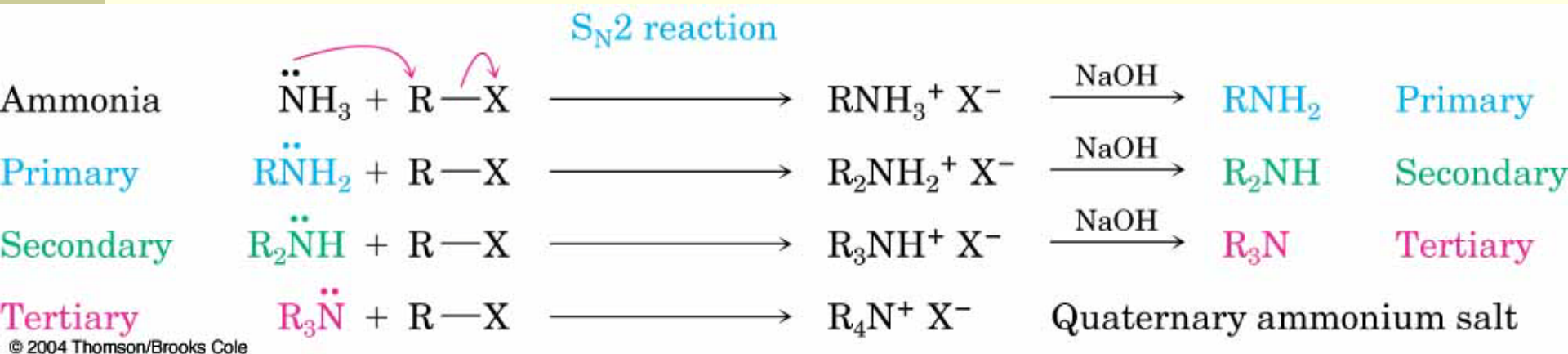
# Reduction Aryl Nitro Compounds

- Arylamines are prepared from nitration of an aromatic compound and reduction of the nitro group
- Reduction by catalytic hydrogenation over platinum is suitable if no other groups can be reduced
- Iron, zinc, tin, and tin(II) chloride are effective in acidic solution



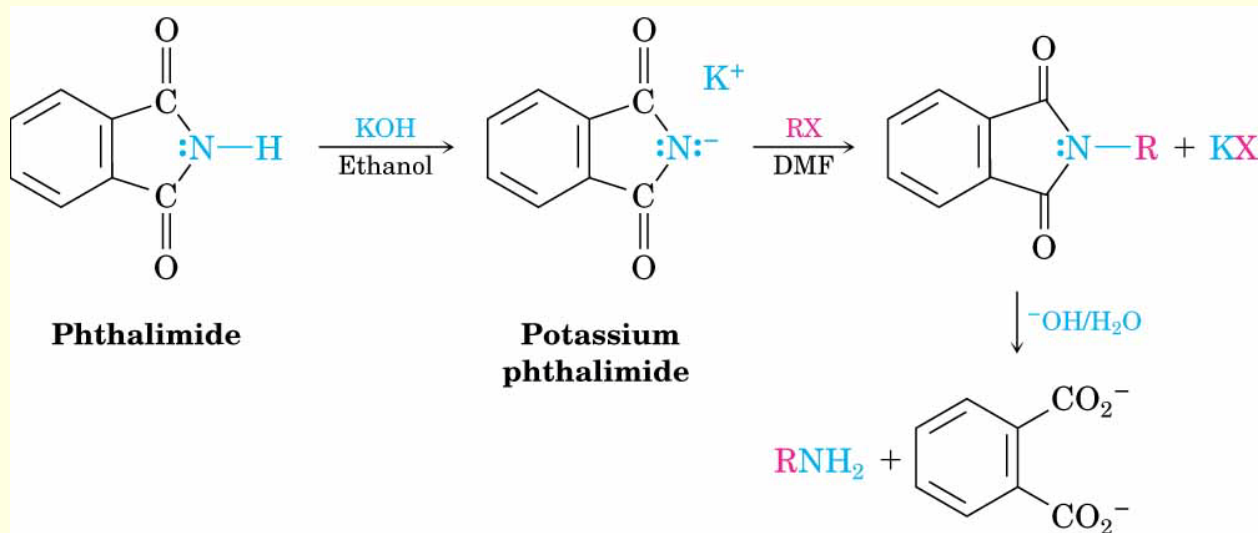
# SN2 Reactions of Alkyl Halides

- Ammonia and other amines are good nucleophiles



# Gabriel Synthesis of Primary Amines

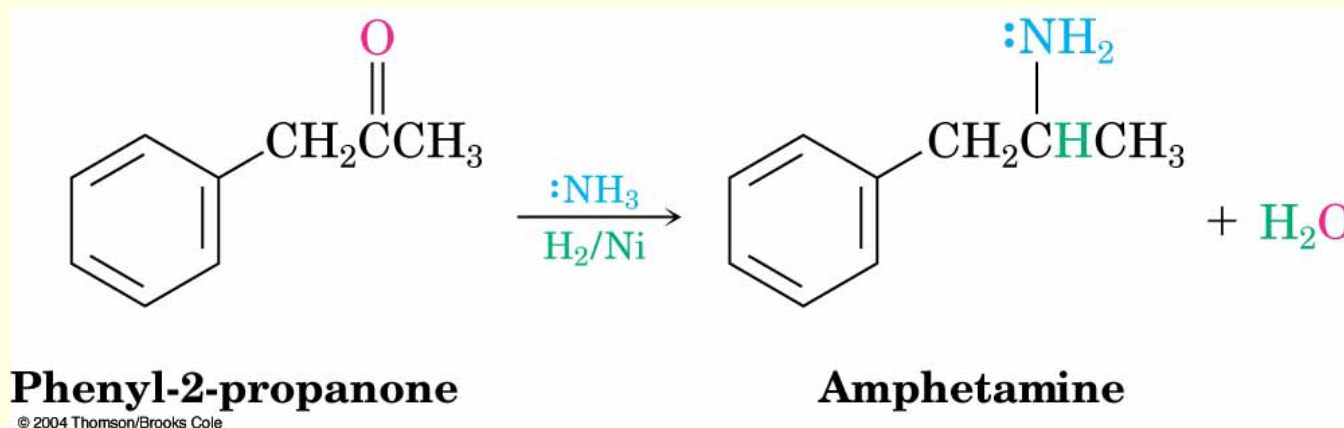
- A *phthalimide* alkylation for preparing a primary amine from an alkyl halide
- The N-H in imides ( $\text{—CONHCO—}$ ) can be removed by KOH followed by alkylation and hydrolysis





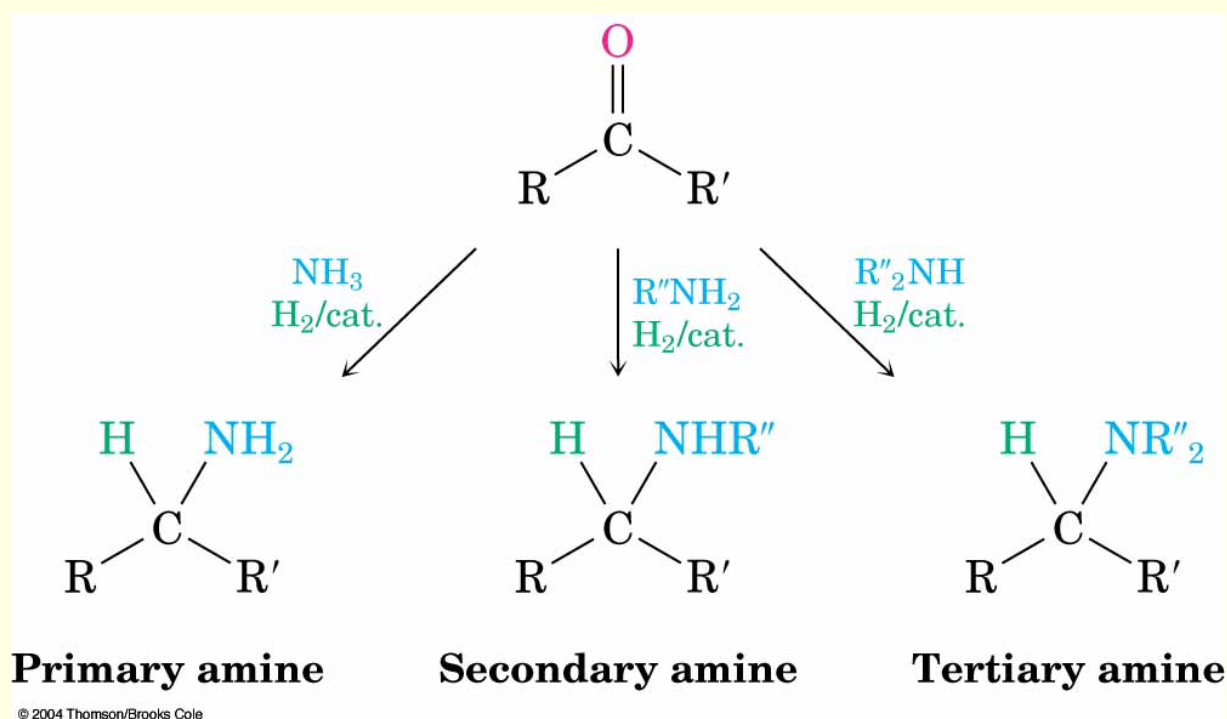
# Reductive Amination of Aldehydes and Ketones

- Treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent



# Reductive Amination Is Versatile

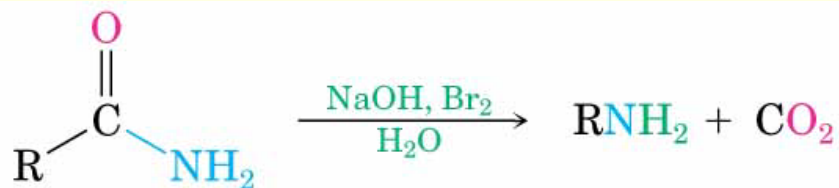
- Ammonia, primary amines, and secondary amines yield primary, secondary, and tertiary amines, respectively



# Hofmann and Curtius Rearrangements

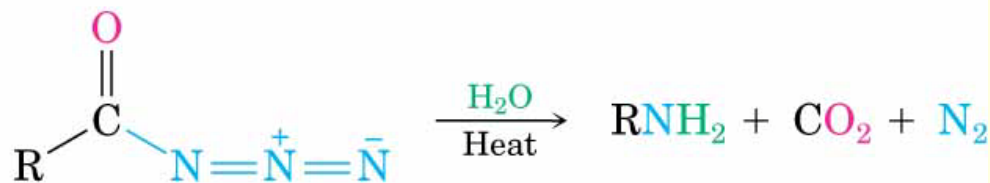
- Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the Hofmann rearrangement and the Curtius rearrangement

## Hofmann rearrangement



An amide

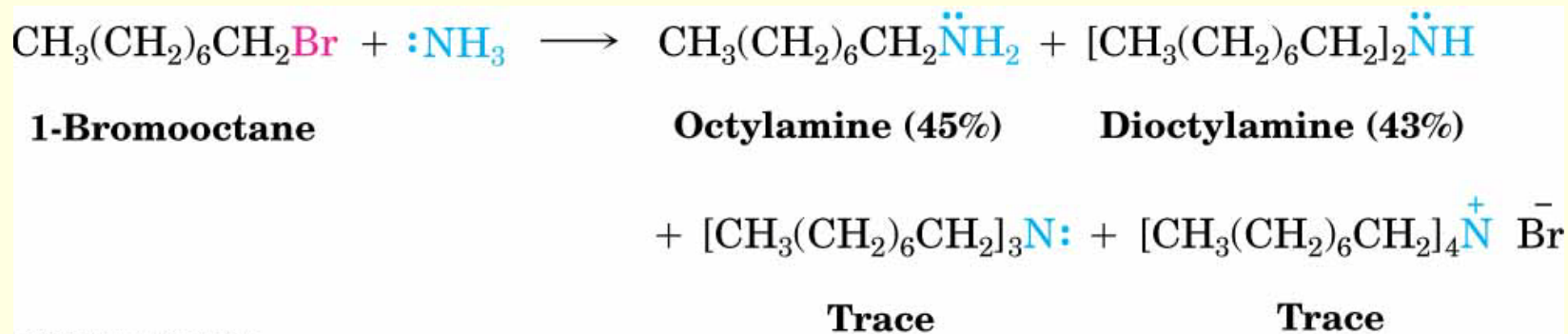
## Curtius rearrangement



An acyl azide

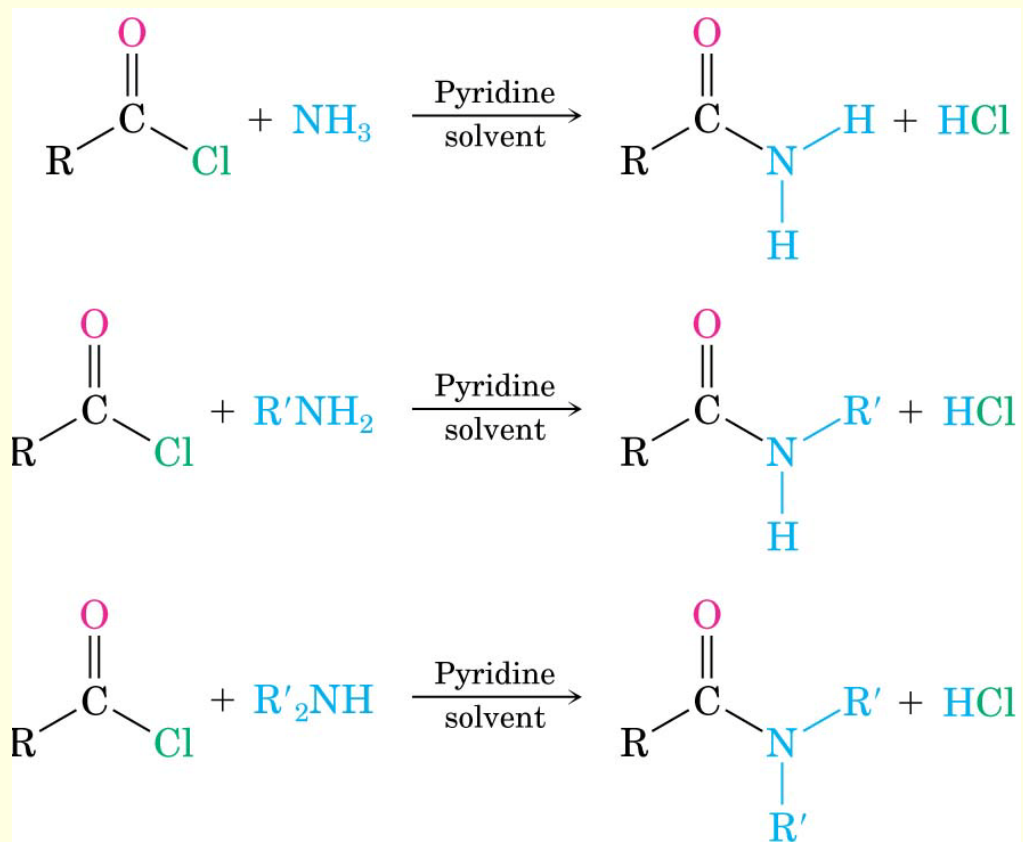
# Uncontrolled Multiple Alkylation

- Primary, secondary, and tertiary amines all have similar reactivity, the initially formed monoalkylated substance undergoes further reaction to yield a mixture of products



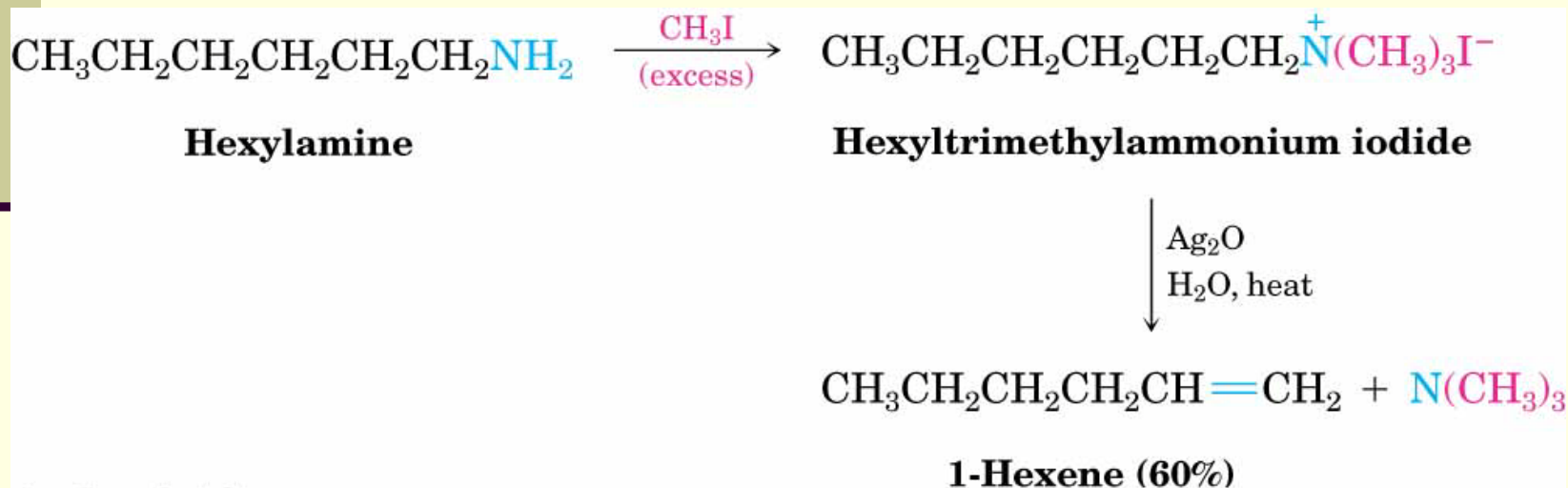
# Reactions of Amines

- Alkylation and acylation have already been presented



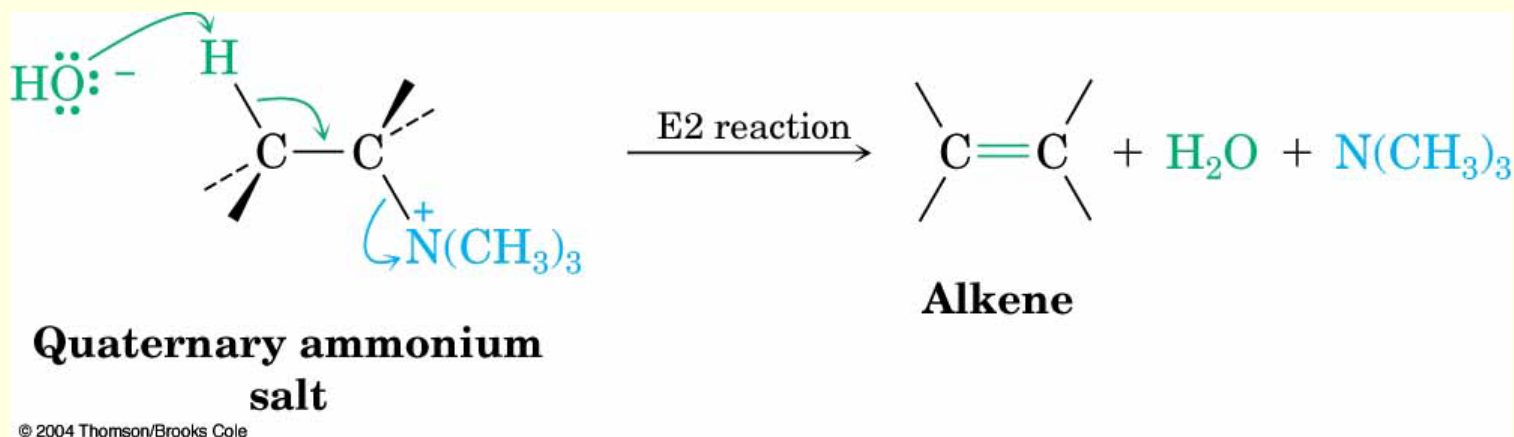
# Hofmann Elimination

- Converts amines into alkenes
- $\text{NH}_2^-$  is very a poor leaving group so it converted to an alkylammonium ion, which is a good leaving group



# Silver Oxide Is Used for the Elimination Step

- Exchanges hydroxide ion for iodide ion in the quaternary ammonium salt, thus providing the base necessary to cause elimination



# Orientation in Hofmann Elimination

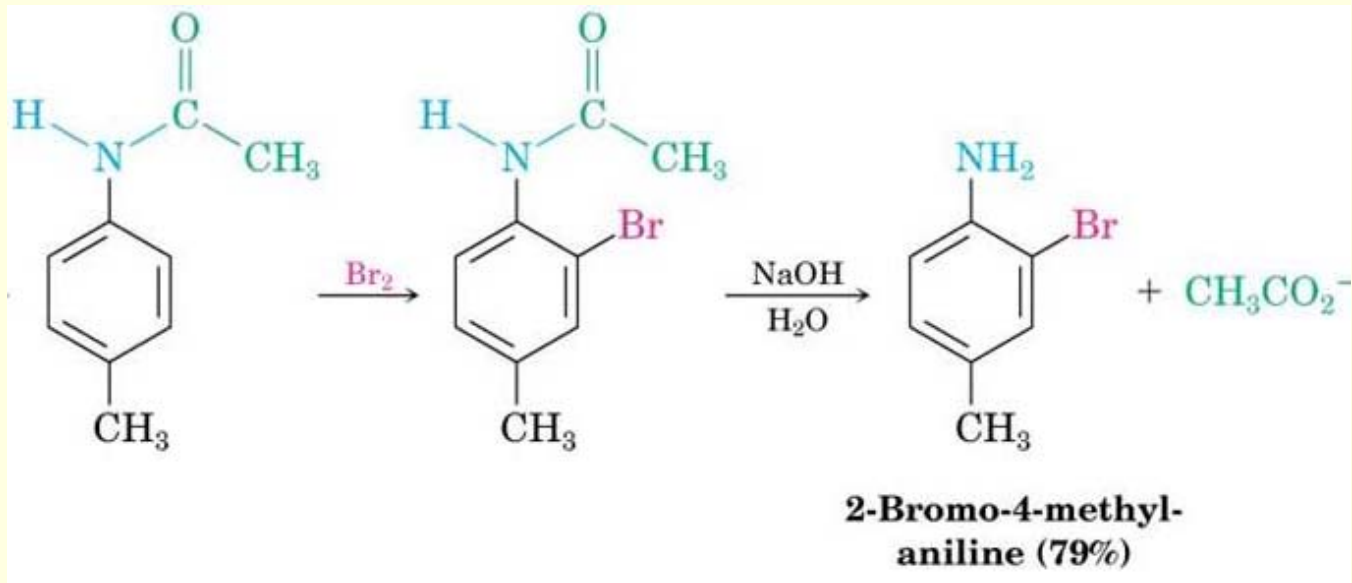
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- We would expect that the *more* highly substituted alkene product predominates in the E2 reaction of an alkyl halide (Zaitsev's rule)
- However, the *less* highly substituted alkene predominates in the Hofmann elimination due to the large size of the trialkylamine leaving group
- The base must abstract a hydrogen from the most sterically accessible, least hindered position



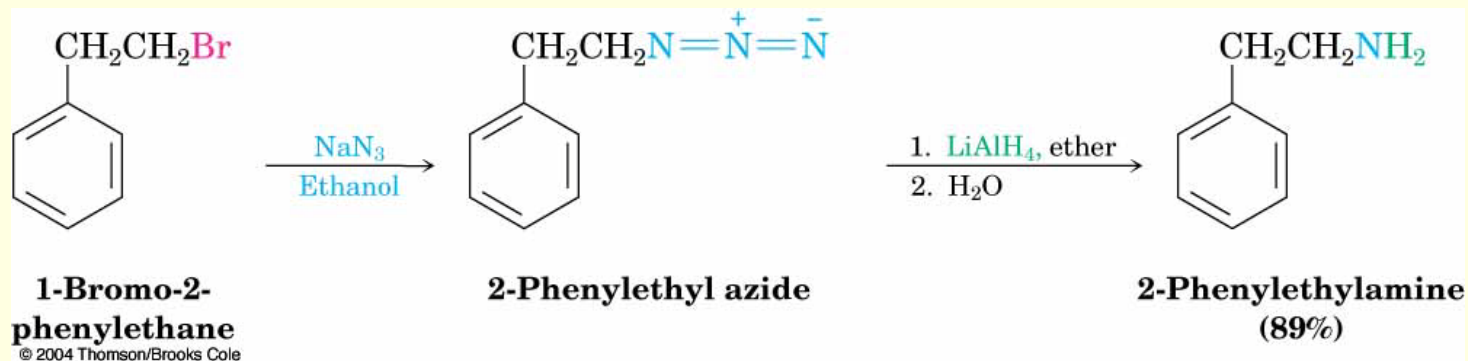
# Reactions of Arylamines

- Amino substituents are strongly activating, ortho- and para-directing groups in electrophilic aromatic substitution reactions
- Reactions are controlled by conversion to amide



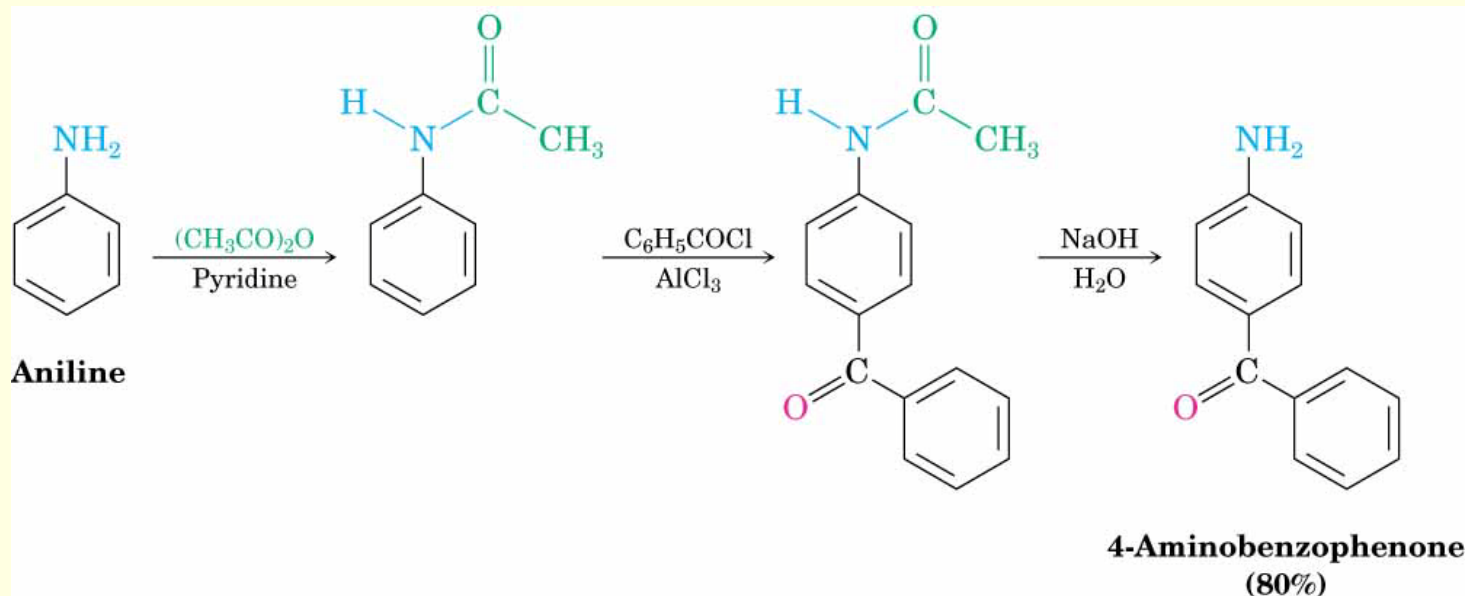
# Selective Preparation of Primary Amines: the Azide Synthesis

- Azide ion,  $\text{N}_3^-$  displaces a halide ion from a primary or secondary alkyl halide to give an alkyl azide,  $\text{RN}_3$
- Alkyl azides are not nucleophilic (but they are explosive)
- Reduction gives the primary amine



# Arylamines Are Not Useful for Friedel-Crafts Reactions

- The amino group forms a Lewis acid–base complex with the  $\text{AlCl}_3$  catalyst, preventing further reaction
- Therefore we use the corresponding amide



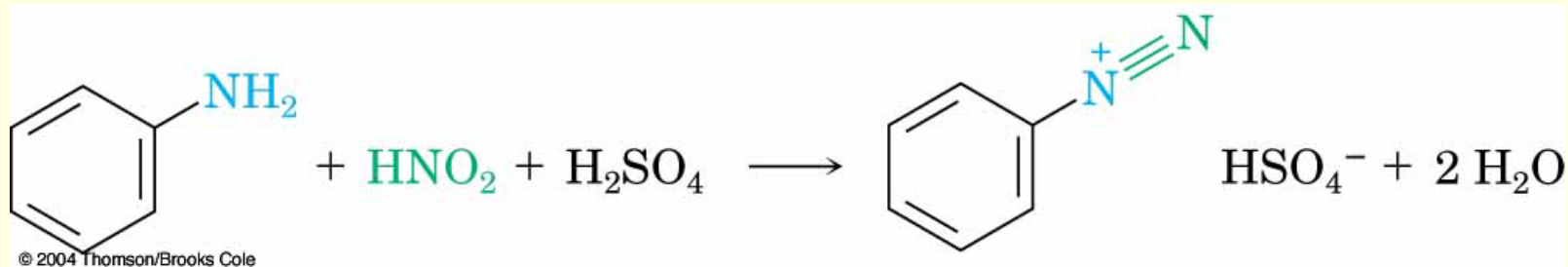
# Diverse Reactions of Arenediazonium Salts

- Sequence of (1) nitration, (2) reduction, (3) diazotization, and (4) nucleophilic substitution leads to many different products



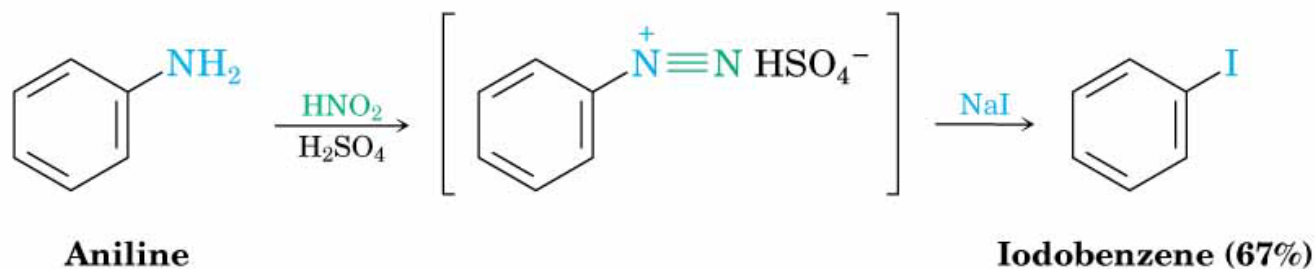
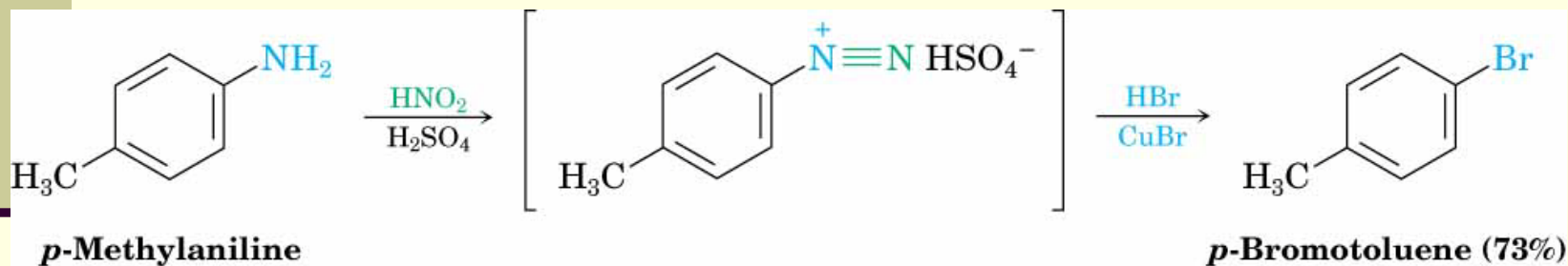
# Diazonium Salts: The Sandmeyer Reaction

- Primary arylamines react with  $\text{HNO}_2$ , yielding stable arenediazonium salts



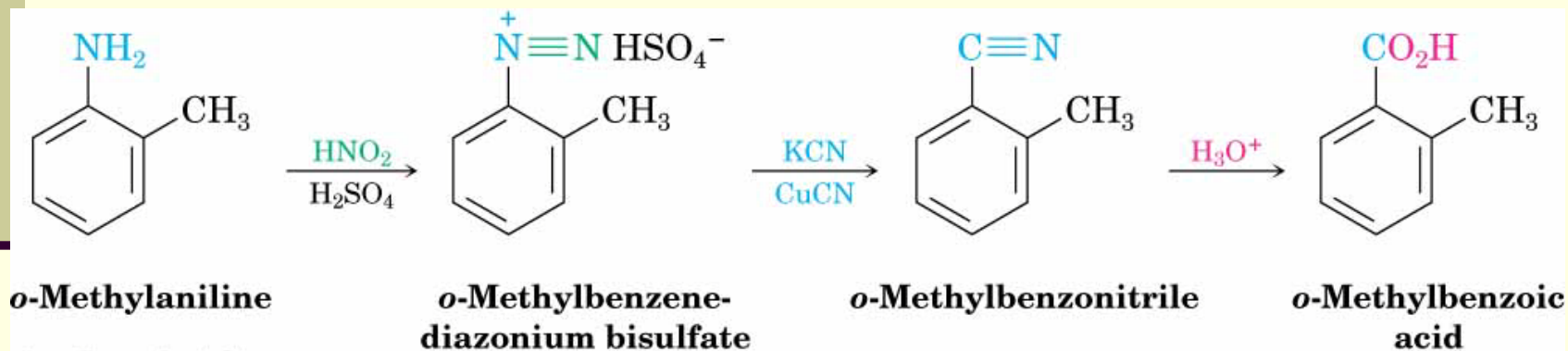
# Preparation of Aryl Halides

- Reaction of an arenediazonium salt with CuCl or CuBr gives aryl halides (Sandmeyer Reaction)
- Aryl iodides form from reaction with NaI without a copper(I) salt



# Aryl Nitriles and Carboxylic Acids

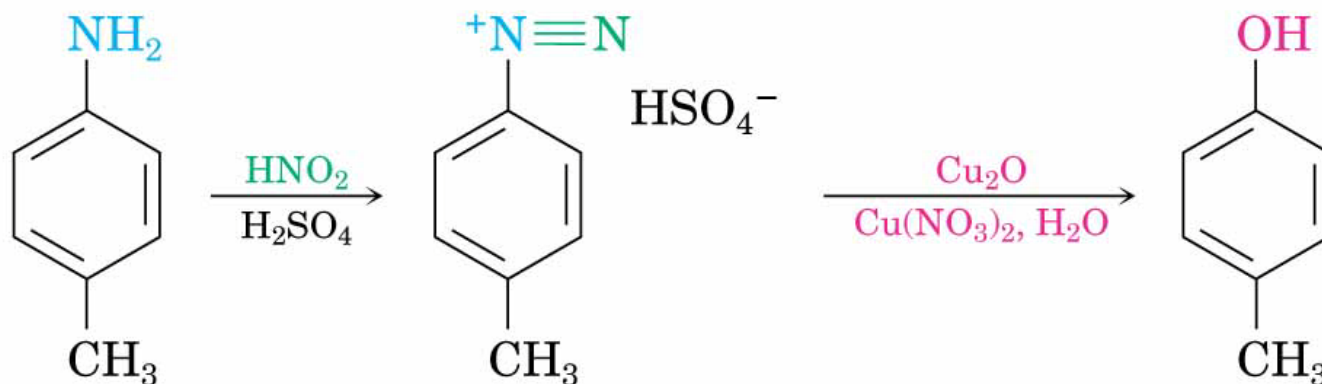
- An arenediazonium salt and CuCN yield the nitrile, ArCN, which can be hydrolyzed to ArCOOH



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# Formation of Phenols (ArOH)

- From reaction of the arenediazonium salt with copper(I) oxide in an aqueous solution of copper(II) nitrate



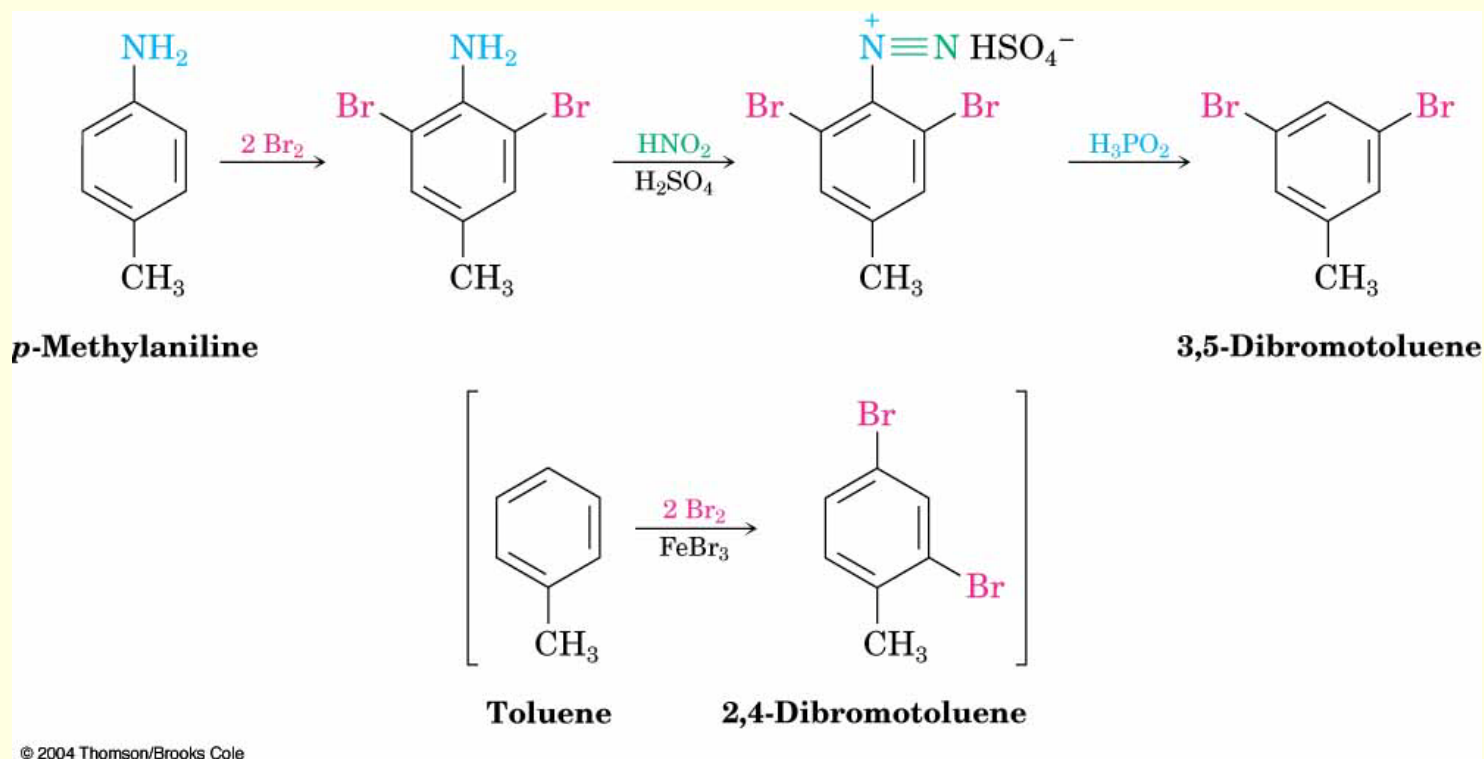
***p*-Methylaniline  
(*p*-Toluidine)**

***p*-Cresol  
(93%)**



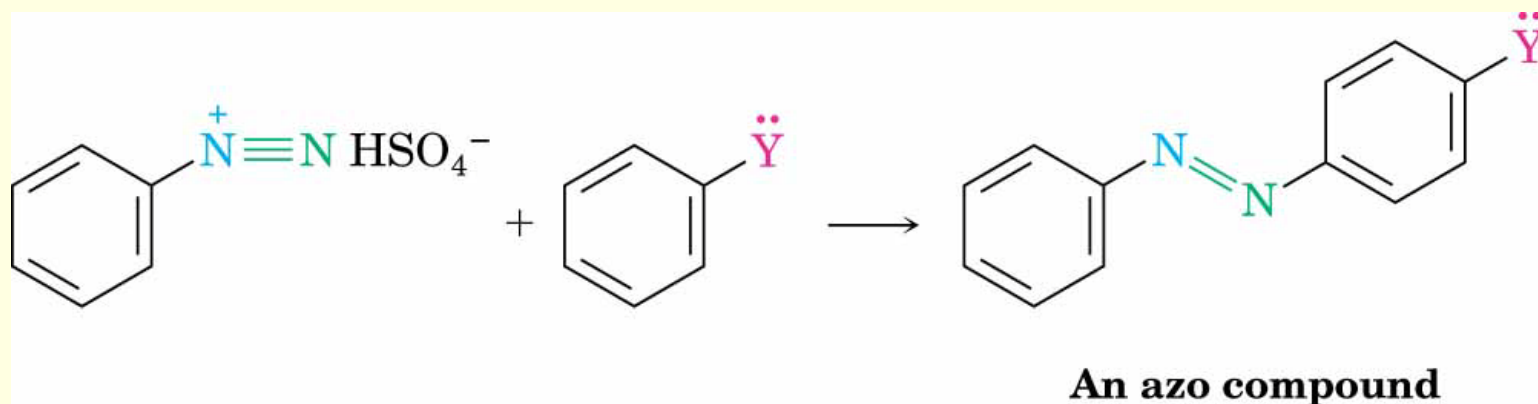
# Reduction to a Hydrocarbon

- By treatment of a diazonium salt with hypophosphorous acid,  $\text{H}_3\text{PO}_2$



# Diazonium Coupling Reactions

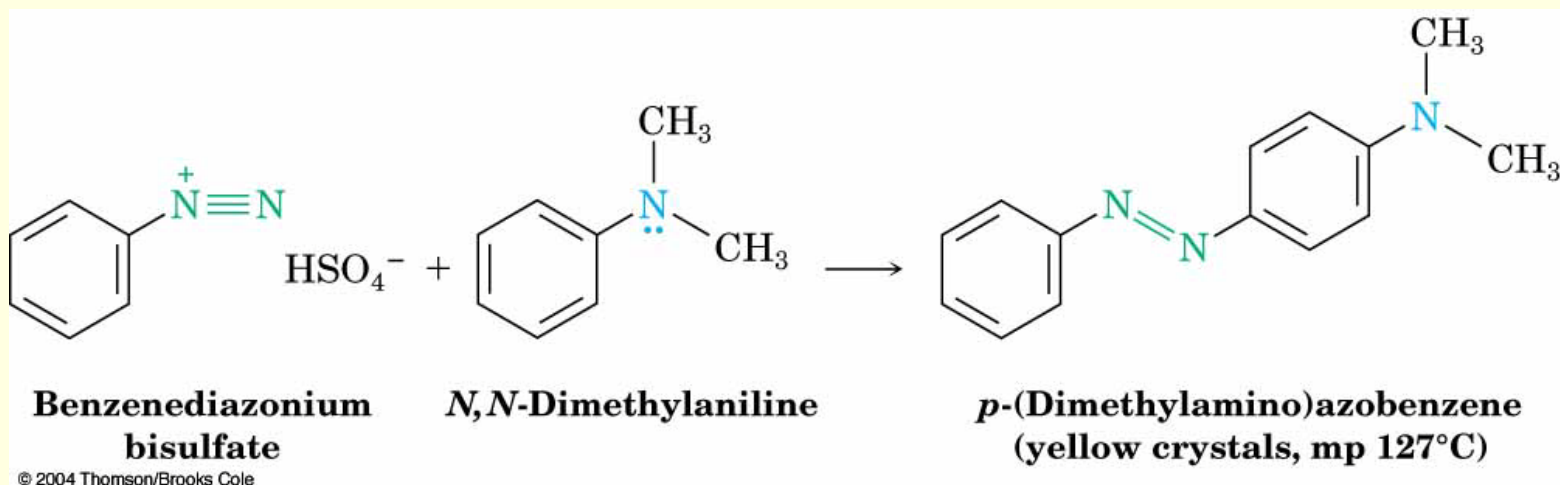
- Arenediazonium salts undergo a coupling reaction with activated aromatic rings, such as phenols and arylamines, to yield brightly colored azo compounds,  $\text{Ar}-\text{N}=\text{N}-\text{Ar}'$



where  $\text{Y} = -\text{OH}$  or  $-\text{NR}_2$

# Azo Dyes

- Azo-coupled products have extended  $\pi$  conjugation that lead to low energy electronic transitions that occur in visible light (dyes)

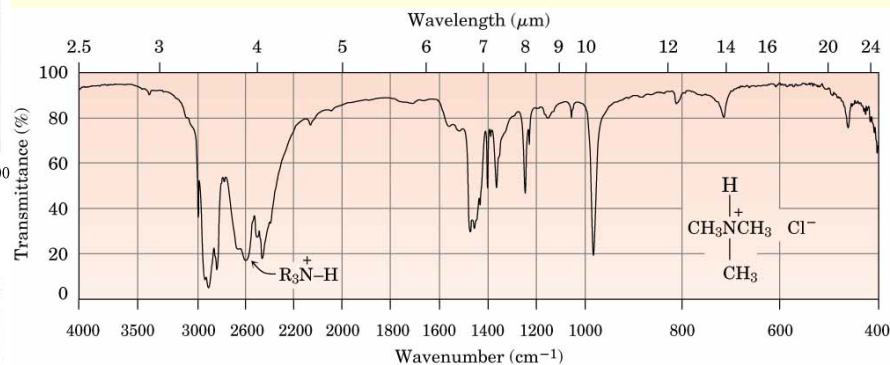
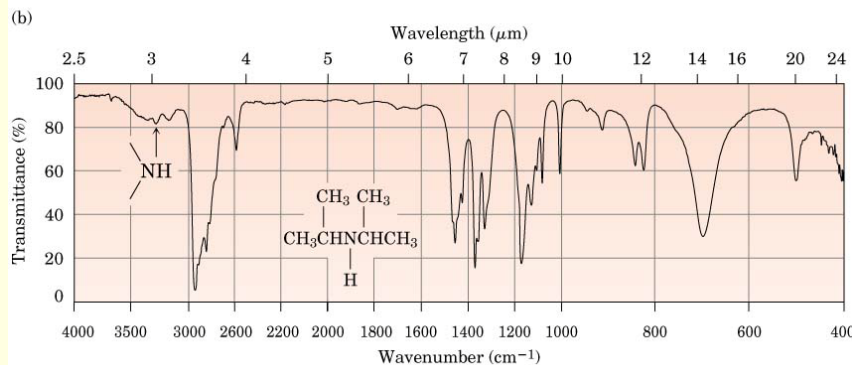
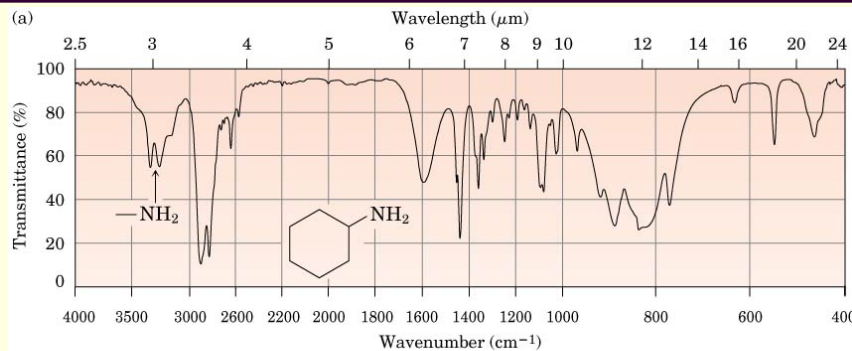


# Spectroscopy of Amines -Infrared

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- Characteristic N–H stretching absorptions 3300 to 3500  $\text{cm}^{-1}$
- Amine absorption bands are sharper and less intense than hydroxyl bands
  - Protonated amines show an ammonium band in the range 2200 to 3000  $\text{cm}^{-1}$

# Examples of Infrared Spectra

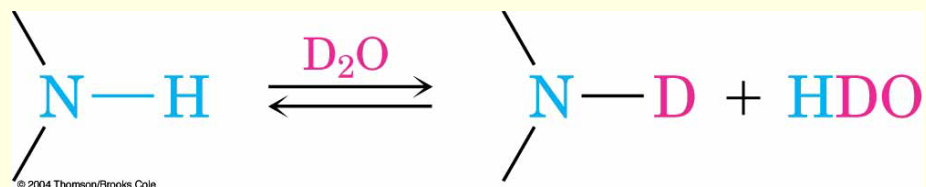


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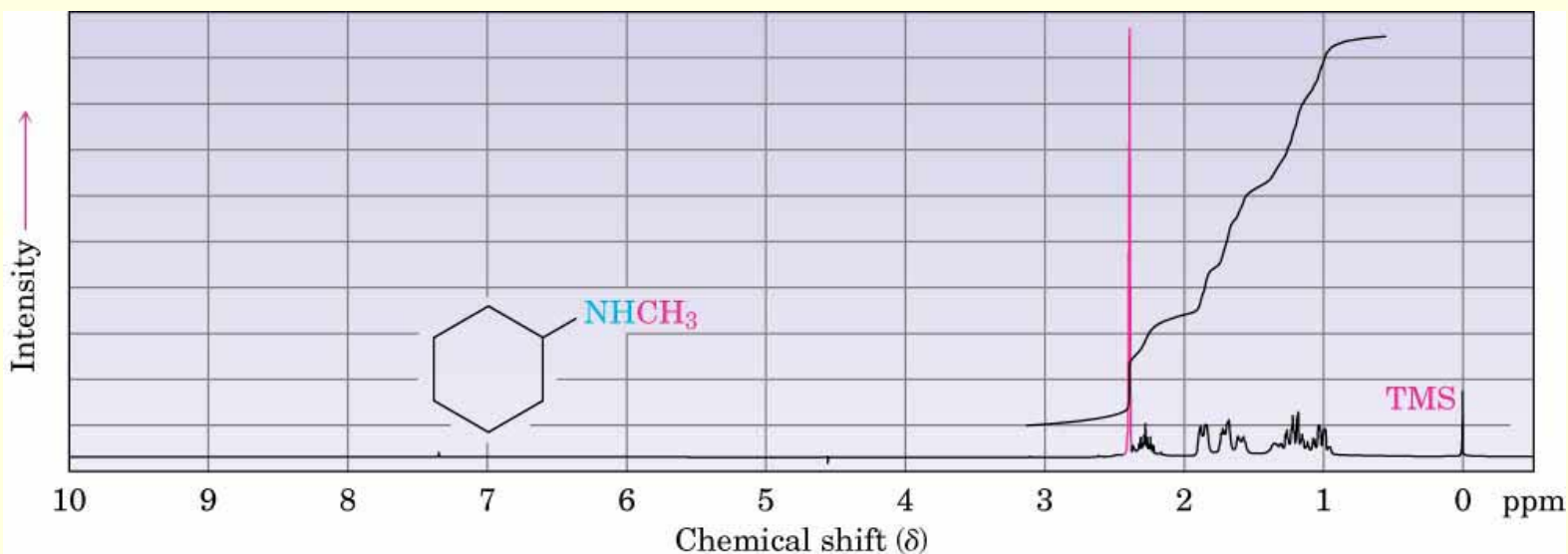
# Nuclear Magnetic Resonance Spectroscopy

- N–H hydrogens appear as broad signals without clear-cut coupling to neighboring C–H hydrogens
- In D<sub>2</sub>O exchange of N–D for N–H occurs, and the N–H signal disappears



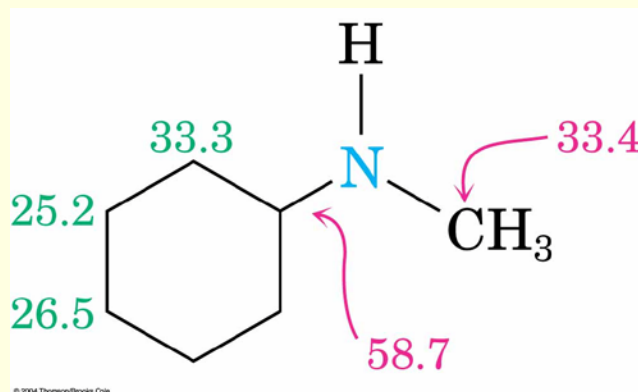
# Chemical Shift Effects

- Hydrogens on C next to N and absorb at lower field than alkane hydrogens
- *N*-CH<sub>3</sub> gives a sharp three-H singlet at  $\delta$  2.2 to  $\delta$  2.6



# $^{13}\text{C}$ NMR

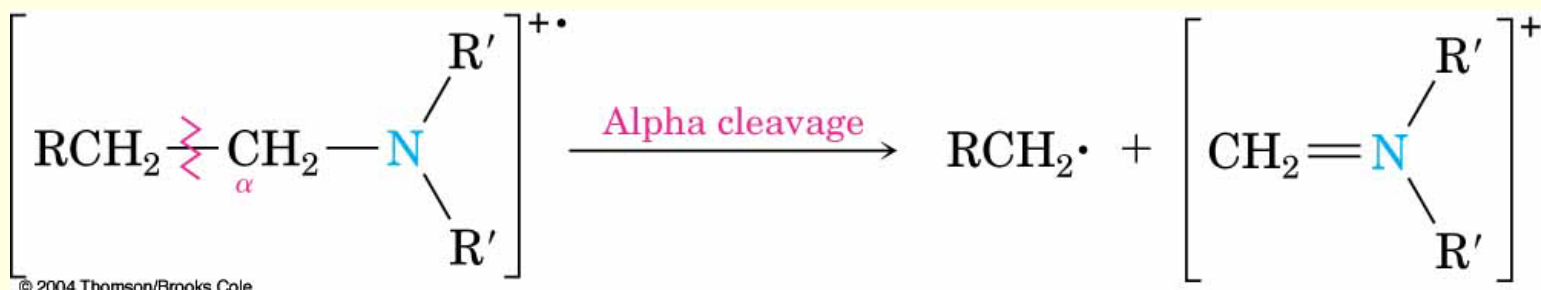
- Carbons next to amine N are slightly deshielded - about 20 ppm downfield from where they would absorb in an alkane





# Mass Spectrometry

- Since N is a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight and a corresponding parent ion
- Alkylamines cleave at the C–C bond nearest the nitrogen to yield an alkyl radical and a nitrogen-containing cation



# Mass Spectrum of N-Ethylpropylamine

- The two modes of a cleavage give fragment ions at  $m/z = 58$  and  $m/z = 72$ .

