

Organic Chemistry, 6th Edition
L. G. Wade, Jr.



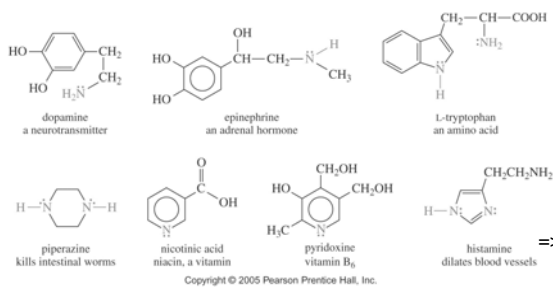
Chapter 19 Amines

Jo Blackburn
Richland College, Dallas, TX
Dallas County Community College District
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Introduction



- Organic derivatives of ammonia.
- Many are biologically active.



Biological Activity



- Neurotransmitters: dopamine
- Bioregulators: epinephrine
- Vitamins: niacin, B₆
- Alkaloids: nicotine, morphine, cocaine
- Amino acids

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Classes of Amines



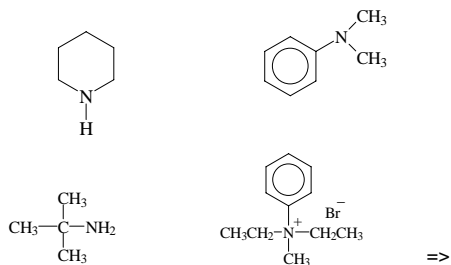
- Primary (1°): one C-N bond, 2 N-H bonds.
- Secondary (2°): two C-N bonds, 1 N-H bond.
- Tertiary (3°): three C-N bonds, no N-H bond.
- Quaternary (4°): four C-N bonds, nitrogen has a + formal charge.

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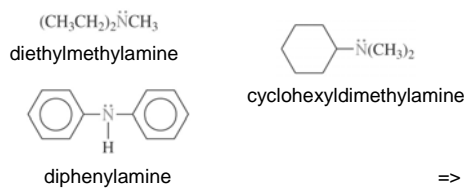
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Classify:



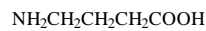
Common Names

Name the alkyl or aryl groups bonded to nitrogen, then add suffix *-amine*.

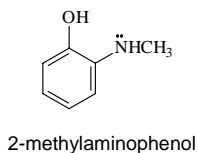


Amine as Substituent

- On a molecule with a higher priority functional group, the amine is named as a substituent.

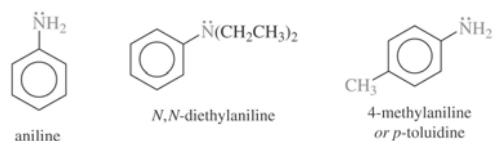


γ -aminobutyric acid or
4-aminobutanoic acid



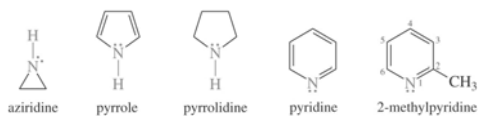
Aromatic Amines

Amino group is bonded to a benzene ring.
Parent compound is called aniline.



Heterocyclic Amines

The nitrogen is assigned the number 1.

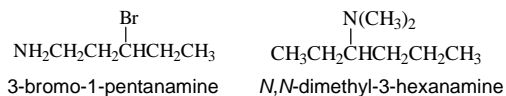


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IUPAC Names

- Name is based on longest carbon chain.
- -e of alkane is replaced with -amine.
- Substituents on nitrogen have *N*- prefix.

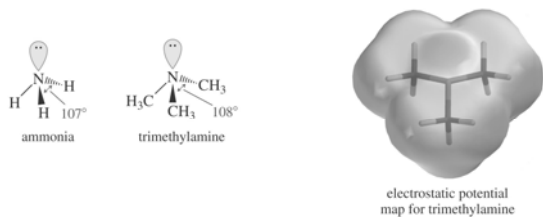


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Structure of Amines

Nitrogen is sp^3 hybridized with a lone pair of electrons in an sp^3 orbital.



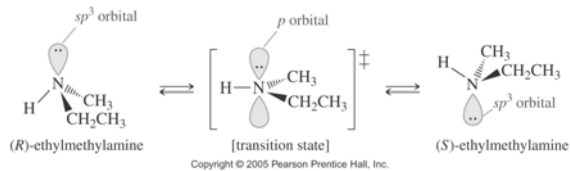
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Chirality of Amines¹

Nitrogen may have 3 different groups and a lone pair, but enantiomers cannot be isolated due to inversion around N.

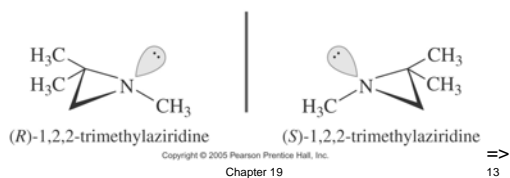


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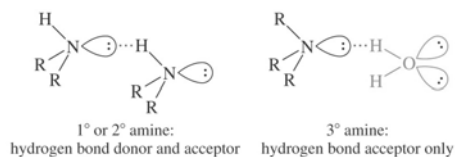
Chiral Amines

- Amines with chiral carbon: 2-butanamine.
- Quaternary ammonium salts with four different groups bonded to nitrogen.
- Amines in which the nitrogen is restricted in rotation so it cannot interconvert.



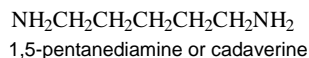
Boiling Points

- N-H less polar than O-H.
- Weaker hydrogen bonding.
- Tertiary amines cannot hydrogen bond.



Solubility and Odor

- Small amines (<6 C) soluble in water.
- All amines accept hydrogen bonds from water and alcohol.
- Branching increases solubility.
- Most amines smell like rotting fish.

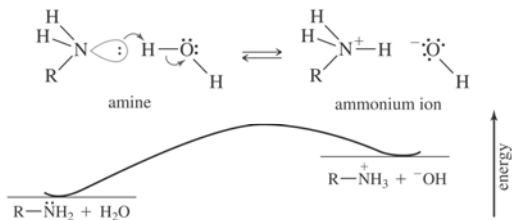


Basicity of Amines

- Lone pair of electrons on nitrogen can accept a proton from an acid
 - Aqueous solutions are basic to litmus.
 - Ammonia $pK_b = 4.74$
 - Alkyl amines are usually stronger bases than ammonia. Increasing the number of alkyl groups decreases solvation of ion, so 2° and 3° amines are similar to 1° amines in basicity.
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Energy Diagram

Alkyl groups are electron-donating and stabilize the cation.

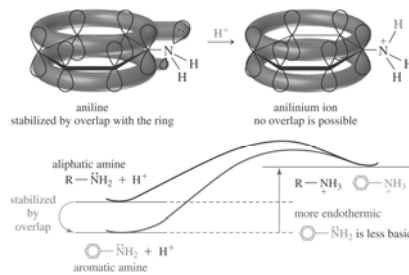


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Resonance Effects

Any delocalization of the electron pair weakens the base.



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Hybridization Effects

Electrons are held more tightly in orbitals with more s character, so those compounds are weaker bases.



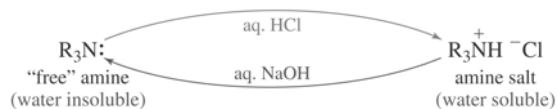
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Amine Salts

- Ionic solids with high melting points
- Soluble in water
- No fishy odor

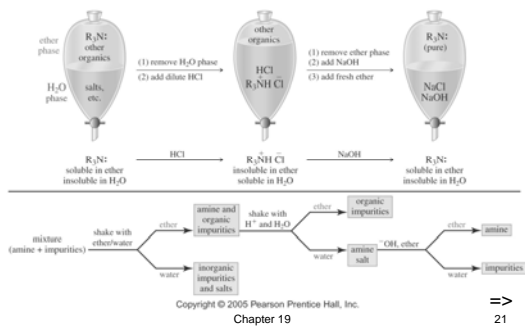


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Purifying an Amine



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Phase Transfer Catalysts



Mechanism:

1. Aqueous phase



2. Organic phase

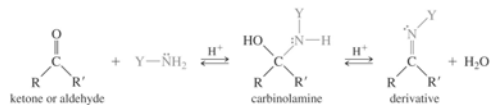


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Reactions with C=O

Ammonia and primary amines react with carbonyls to give an imine (Schiff base).



Y = H or alkyl gives an imine (Schiff base)
 Y = OH gives an oxime
 Y = NHR gives a hydrazone

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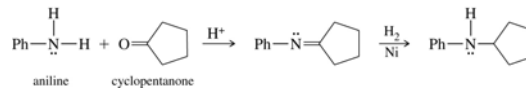
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SOLVED PROBLEM 19-5

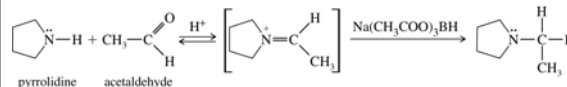
Show how to synthesize the following amines from the indicated starting materials.
 (a) *N*-cyclopentylaniline from aniline (primary) (b) *N*-ethylpyrrolidine from pyrrolidine

Solution

(a) This synthesis requires adding a cyclopentyl group to aniline (primary) to make a secondary amine. Cyclopentanone is the carbonyl compound.



(b) This synthesis requires adding an ethyl group to a secondary amine to make a tertiary amine. The carbonyl compound is acetaldehyde. Formation of a tertiary amine by $\text{Na}(\text{AcO})_2\text{BH}$ reductive amination involves an iminium intermediate, which is reduced by (sodium triacetoxyborohydride).



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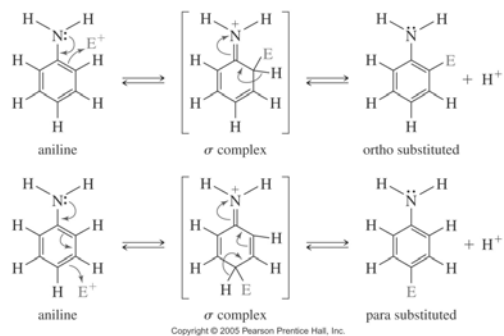
Electrophilic Substitution of Aniline

- -NH_2 is strong activator, o -, p -directing.
- May trisubstitute with excess reagent.
- H^+ changes -NH_2 to -NH_3^+ , a *meta*-allowing deactivator.
- Attempt to nitrate aniline may explode.

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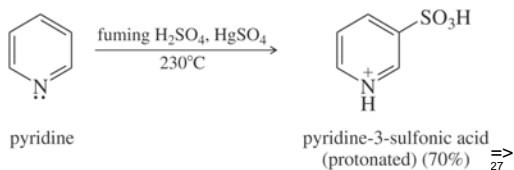
Aniline Substitution



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Electrophilic Substitution of Pyridine

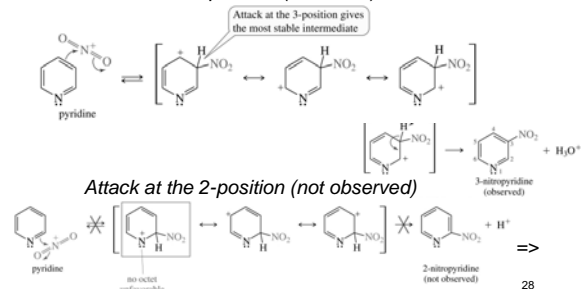
- Strongly deactivated by electronegative N.
- Substitutes in the 3-position.
- Electrons on N can react with electrophile.



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Mechanism for Electrophilic Substitution

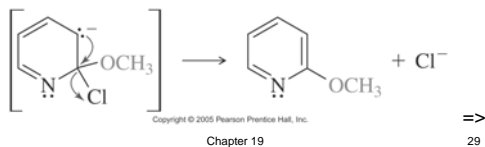
Attack at the 3-position (observed)



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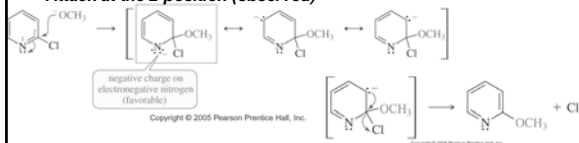
Nucleophilic Substitution of Pyridine

- Deactivated toward electrophilic attack.
- Activated toward nucleophilic attack.
- Nucleophile will replace a good leaving group in the 2- or 4-position.

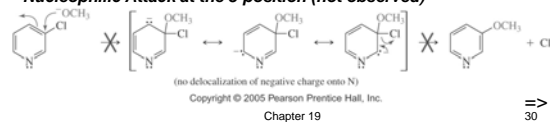


Mechanism for Nucleophilic Substitution

Attack at the 2-position (observed)

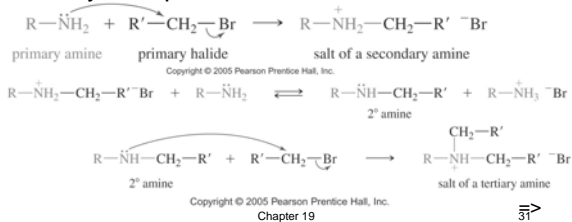


Nucleophilic Attack at the 3-position (not observed)



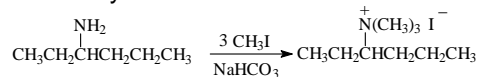
Alkylation of Amines

- Amines react with 1° alkyl halides via the S_N2 mechanism.
- Mixtures of the mono-, di-, and tri-alkylated products are obtained.

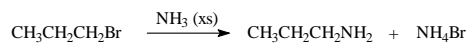


Useful Alkylations

- Exhaustive alkylation to form the tetraalkylammonium salt.



- Reaction with large excess of NH₃ to form the primary amine.

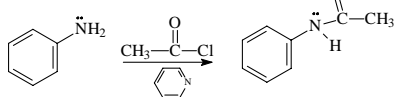


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Acylation of Amines by Acid Chlorides

- Amine attacks C=O, chloride ion leaves.
- Product is amide, neutral, not basic.
- Useful for decreasing activity of aniline toward electrophilic aromatic substitution.



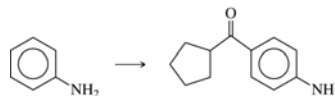
to remove HCl

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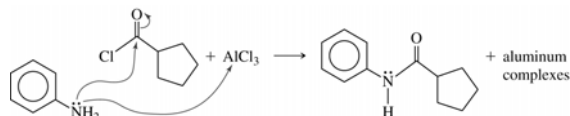
SOLVED PROBLEM 19-1

Show how you would accomplish the following synthetic conversion in good yield.



Solution

An attempted Friedel-Crafts acylation on aniline would likely meet with disaster. The free amino group would attack both the acid chloride and the Lewis acid catalyst.



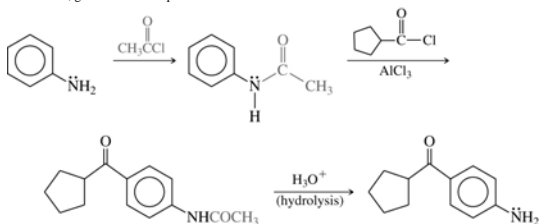
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SOLVED PROBLEM 19-1 (continued)

Solution (continued)

We can control the nucleophilicity of aniline's amino group by converting it to an amide, which is still activating and ortho, para directing for the Friedel-Crafts reaction. Acylation, followed by hydrolysis of the amide, gives the desired product.

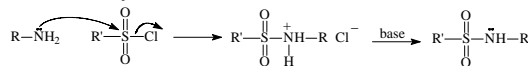


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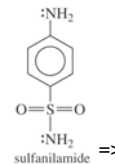
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Formation of Sulfonamides

- Primary or secondary amines react with sulfonyl chloride.



- Sulfa drugs are sulfonamides that are antibacterial agents.

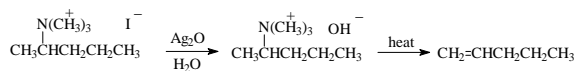


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Hofmann Elimination

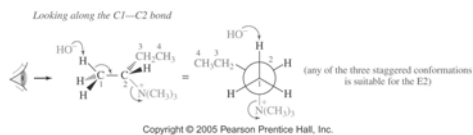
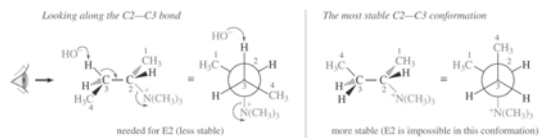
- A quaternary ammonium salt has a good leaving group - a neutral amine.
- Heating the hydroxide salt produces the least substituted alkene.



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E2 Mechanism

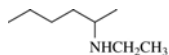


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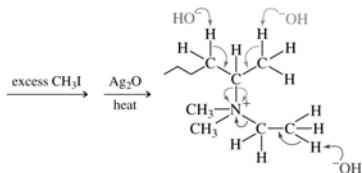
SOLVED PROBLEM 19-2

Predict the major product(s) formed when the following amine is treated with excess iodomethane, followed by heating with silver oxide.



Solution

Solving this type of problem requires finding every possible elimination of the methylated salt. In this case, the salt has the following structure:



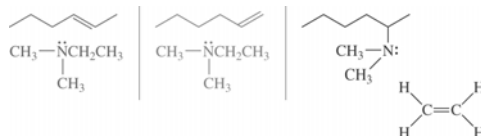
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SOLVED PROBLEM 19-2 (continued)

Solution (continued)

The green, blue, and red arrows show the three possible elimination routes. The corresponding products are



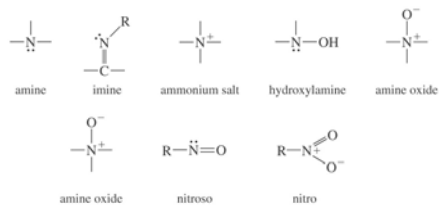
The first (green) alkene has a disubstituted double bond, the second (blue) alkene is monosubstituted, and the red alkene (ethylene) has an unsubstituted double bond. We predict that the red products will be favored.

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Oxidation of Amines

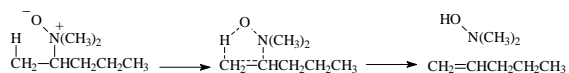
- Amines are easily oxidized, even in air.
- Common oxidizing agents: H_2O_2 , MCPBA.
- 2° Amines oxidize to hydroxylamine (-NOH).
- 3° Amines oxidize to amine oxide (-N⁺-O⁻).



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Cope Elimination

Amine oxides undergo elimination to form the least substituted alkene under milder conditions than the Hofmann reaction.

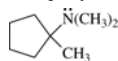


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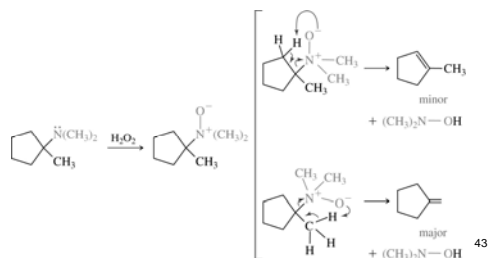
SOLVED PROBLEM 19-3

Predict the products expected when the following compound is treated with H_2O_2 and heated.



Solution

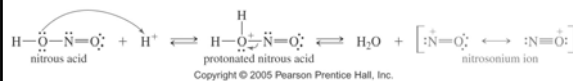
Oxidation converts the tertiary amine to an amine oxide. Cope elimination can give either of two alkenes. We expect the less hindered elimination to be favored, giving the Hofmann product.



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Nitrous Acid Reagent

- Nitrous acid is produced *in situ* by mixing sodium nitrite with HCl.
- The nitrous acid is protonated, loses water to form the nitrosonium ion.



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Reaction with Nitrous Acid

- 1° Amines form diazonium salts, $R-N^+ \equiv N$.
- Alkyldiazonium salts are unstable, but arenediazonium salts are widely used for synthesis.
- 2° Amines form *N*-nitrosoamines, $R_2N-N=O$, found to cause cancer in laboratory animals.

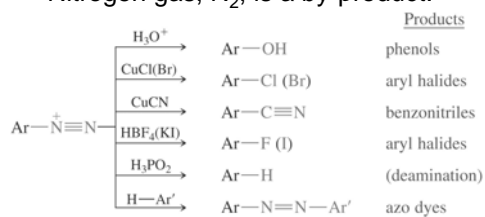
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Arenediazonium Salts

- Stable in solution at $0^\circ - 10^\circ C$.
- The $-N \equiv N$ group is easily replaced by many different groups.
- Nitrogen gas, N_2 , is a by-product.



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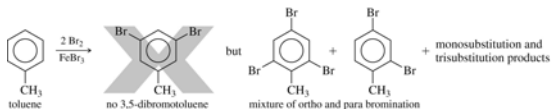
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SOLVED PROBLEM 19-4

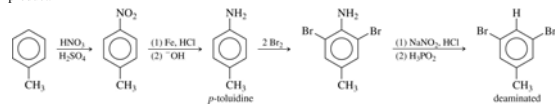
Show how you would convert toluene to 3,5-dibromotoluene in good yield.

Solution

Direct bromination of toluene cannot give 3,5-dibromotoluene because the methyl group activates the ortho and para positions.



Starting with *p*-toluidine (*p*-methylaniline), however, the strongly activating amino group directs bromination to its ortho positions. Removal of the amino group (deamination) gives the desired product.



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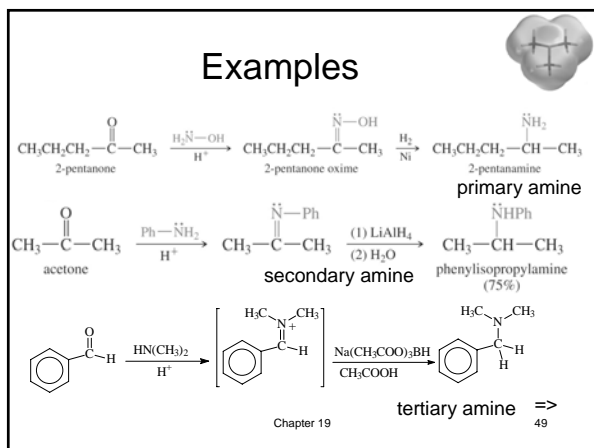
Synthesis by Reductive Amination

- To produce a 1° amine, react an aldehyde or ketone with hydroxylamine, then reduce the oxime.
- To produce a 2° amine, react an aldehyde or ketone with a 1° amine, then reduce the imine.
- To produce a 3° amine, react an aldehyde or ketone with a 2° amine, then reduce the imine salt.


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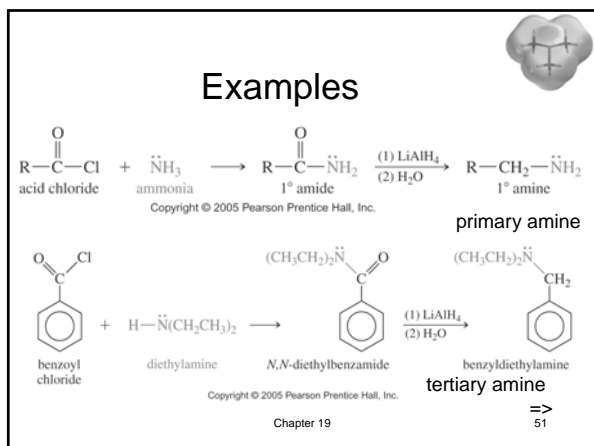
Acylation-Reduction




- An acid chloride reacts with ammonia or a 1° amine or a 2° amine to form an amide.
- The C=O of the amide is reduced to CH₂ with lithium aluminum hydride.
- Ammonia yields a 1° amine.
- A 1° amine yields a 2° amine.
- A 2° amine yields a 3° amine.

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Direct Alkylation (1°)



- Use a large excess (10:1) of ammonia with a primary alkyl halide or tosylate.
- Reaction mechanism is S_N2.

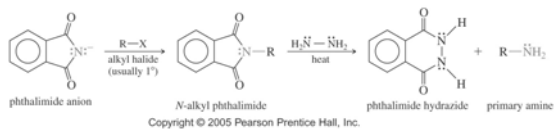
$$\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NH}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 + \text{NH}_4\text{Br}$$

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Gabriel Synthesis (1°)

- Use the phthalimide anion as a form of ammonia that can only alkylate once.
- React the anion with a good S_N2 substrate, then heat with hydrazine.

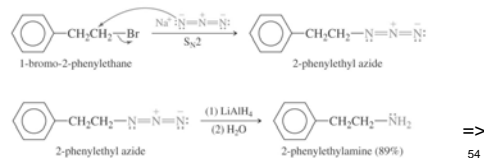


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Azide Reduction (1°)

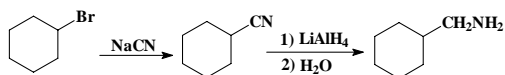
- Azide ion, N₃⁻, is a good nucleophile.
- React azide with unhindered 1° or 2° halide or tosylate (S_N2).
- Alkyl azides are explosive! Do not isolate.



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Nitrile Reduction (1°)

- Nitrile, -C≡N, is a good S_N2 nucleophile.
- Reduction with H₂ or LiAlH₄ adds -CH₂NH₂.

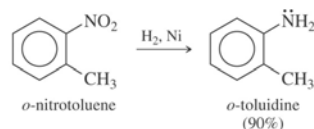


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Reduction of Nitro Compounds (1°)

- -NO₂ is reduced to -NH₂ by catalytic hydrogenation, or active metal with acid.
- Commonly used to synthesize anilines.

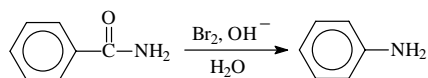


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Hofmann Rearrangement of Amides (1°)

In the presence of a strong base, primary amides react with chlorine or bromine to form amines with one less C.

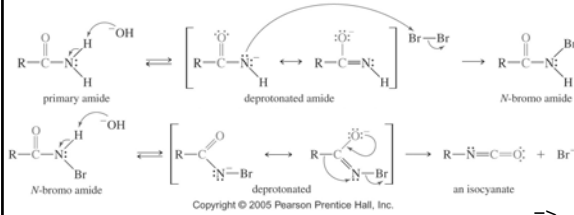


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Hofmann Mechanism (1)

- N-H protons of amide are abstracted.
- Rearrangement forms an isocyanate.



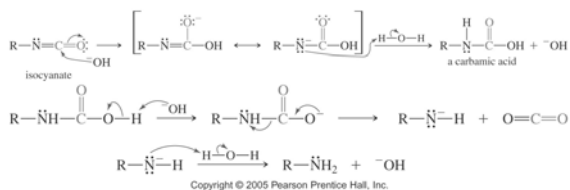
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Hofmann Mechanism (2)

Isocyanate reacts with water to form carbamic acid, which loses CO₂.



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End of Chapter 19

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