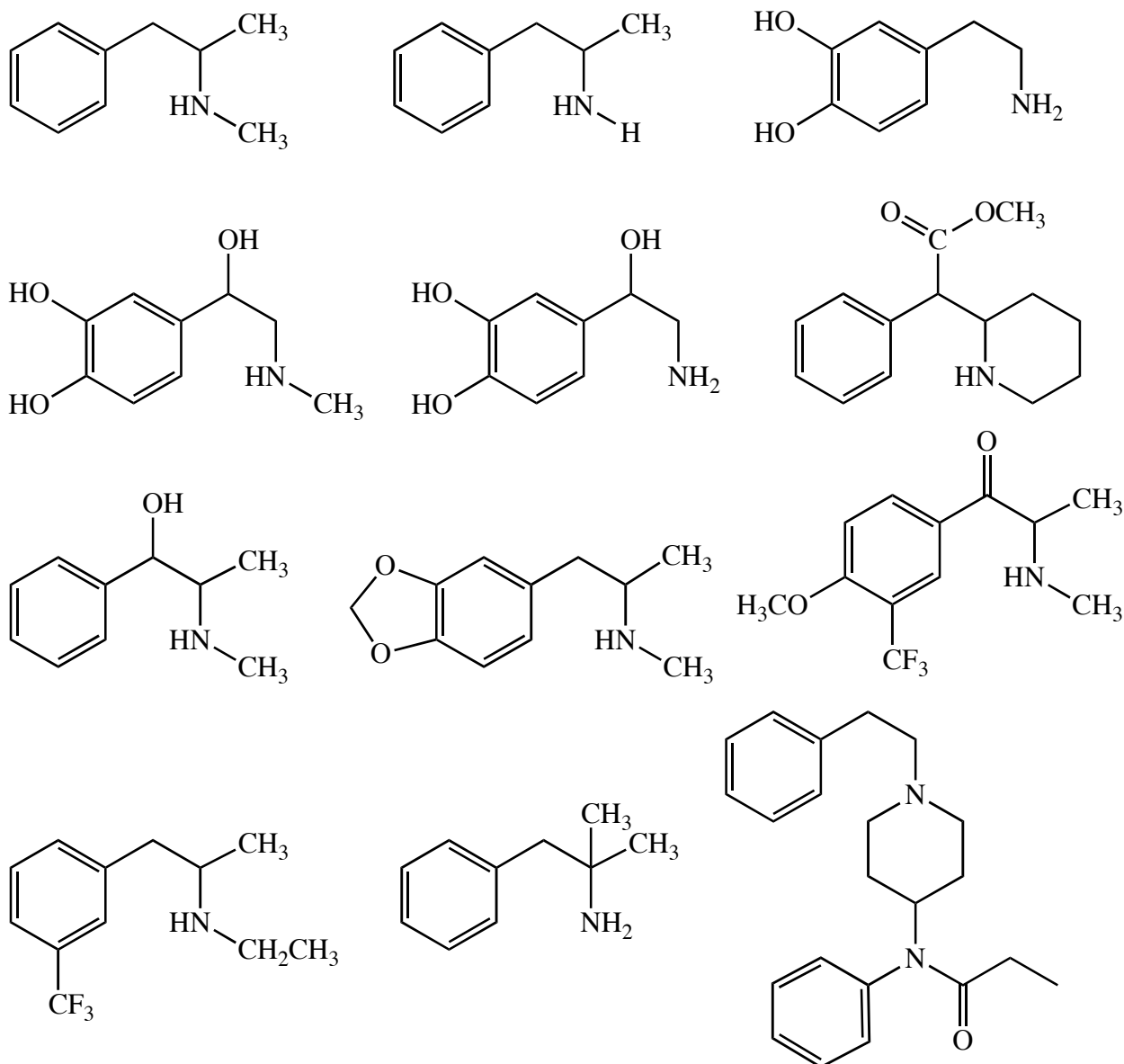


Lecture Notes
Chem 51C
S. King

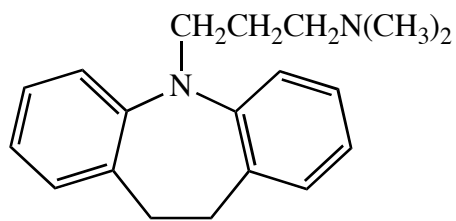
Chapter 25 Amines

Amines are widely found in nature. Many plants synthesize complex amines called alkaloids, some of which have medicinal or poisonous properties.

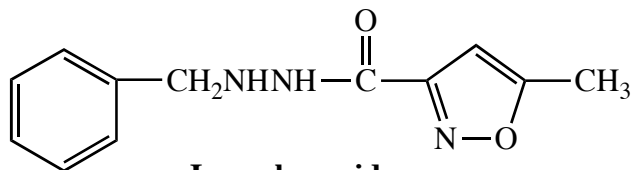
Some famous amines:



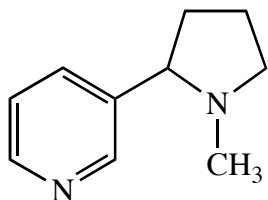
Some Famous Heterocycles:



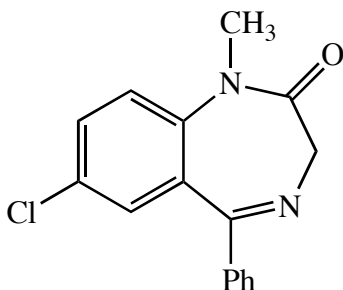
Imipramine
a tricyclic antidepressant



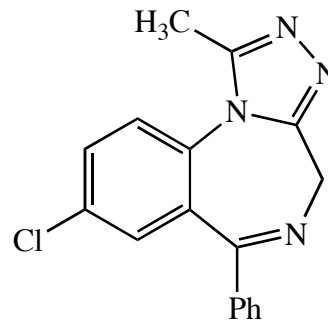
Isocarboxazid
a monoamine oxidase inhibitor



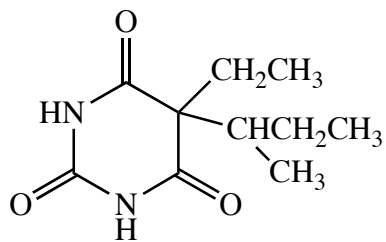
Nicotine



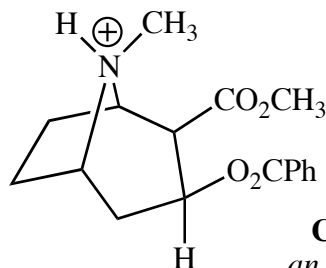
Diazepam (Valium)
a benzodiazepine



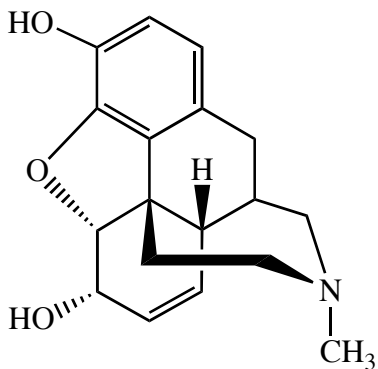
Aprazolam (Xanax)
a benzodiazepine



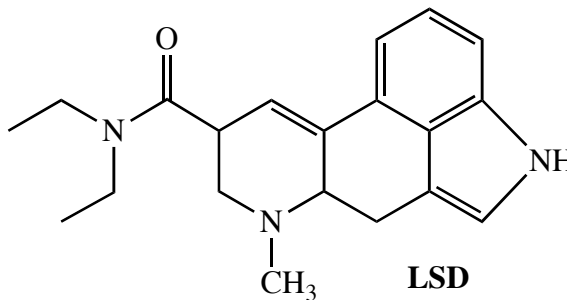
Secobarbital (Seconal)
a barbiturate



Cocaine
an anesthetic



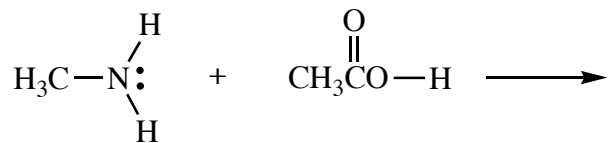
Morphine
a narcotic



LSD
a hallucinogen

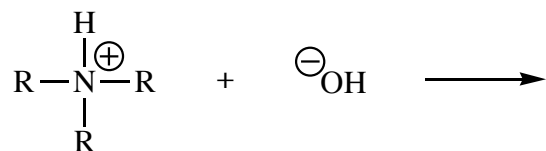
I. Acid and Base Properties of Amines

A. Reaction of an Amine as a Base:

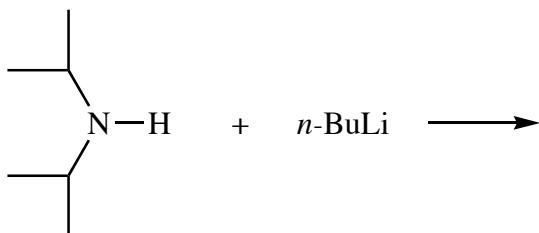


B. Reaction of an Amine as an Acid:

Ammonium ion acts as an acid:



- Amines can also be deprotonated by *very* strong bases to make amides (not to be confused with amide derivatives of carboxylic acids)



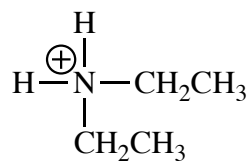
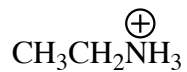
Substituent Effects on Amine Acidity and Basicity:

The basicity of an amine depends on its structure. Factors that effect acidity basicity:

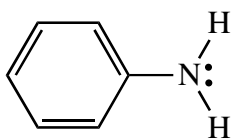
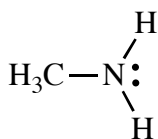
1. the effect of alkyl substitution
2. inductive effects
3. resonance effects

☛ **TEST YOUR KNOWLEDGE:**

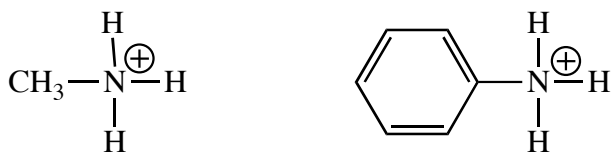
Q1: Which is the most acidic compound? Which is the least acidic?



Q2: Which amine is the most basic?

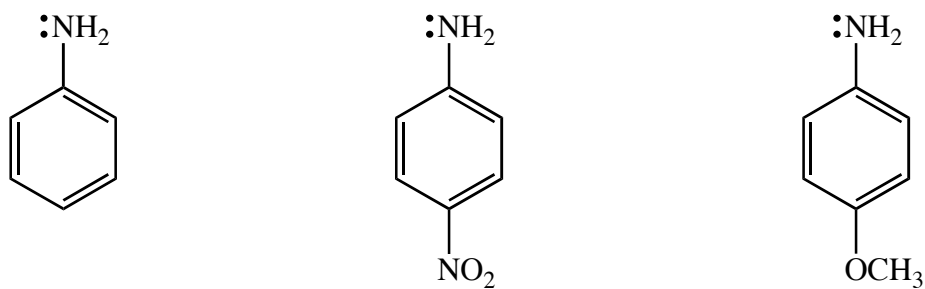


Q3: Which amine is more acidic?

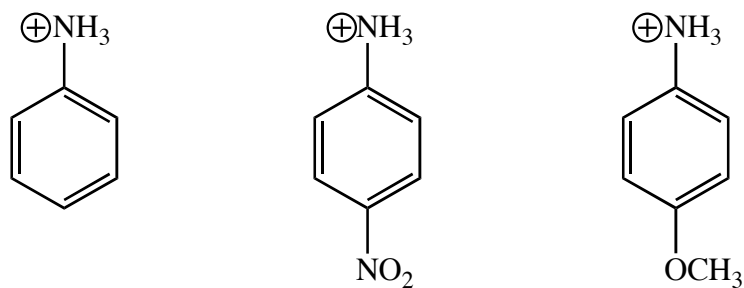


Always look at the conjugate base! If the conjugate base is more stable, then the compound is more acidic.

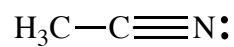
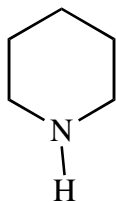
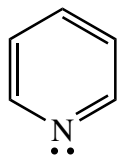
Q4: Which amine is more basic?



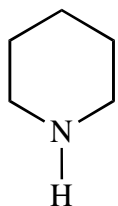
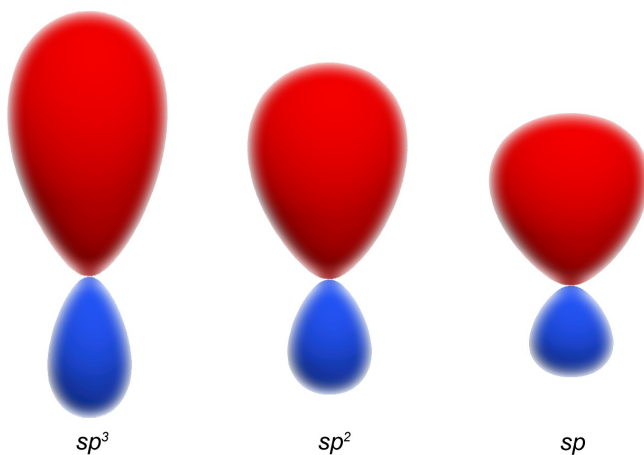
Look at the pK_a 's of the conjugate acids:



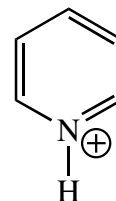
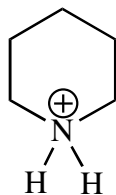
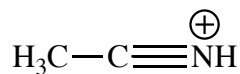
Q5: Which nitrogen is the most basic?



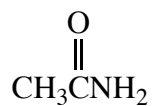
- electrons are held more tightly in orbitals with more “s” character.



This is a large effect. Compare the pK_a 's of the conjugate acids:



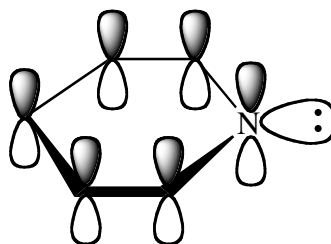
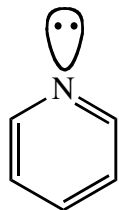
Q6: Which is the most basic?



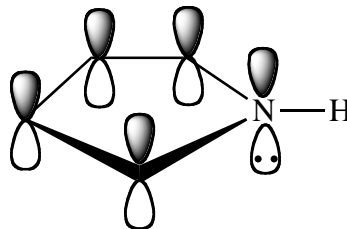
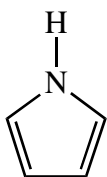
II. Acidity & Basicity of Aromatic Heterocycles

When considering acidity & basicity of aromatic heterocycles, keep in mind:

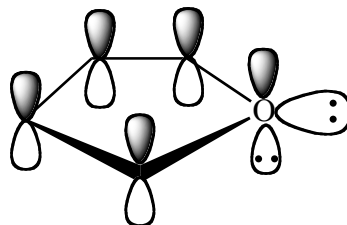
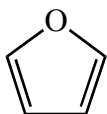
- *If N: is part of a double bond, then the lone pair is **not** part of the aromatic π -system.*



- If N: is **not** part of a double bond, then the lone pair **is** part of the aromatic π -system.

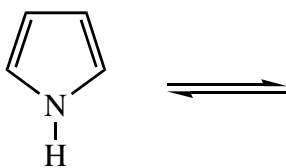


- If oxygen is part of an aromatic ring, **only one lone pair** is part of the aromatic π -system.



Look @ pyrrole:

Q. Do you expect pyrrole to be very basic?



Q. What about deprotonation of pyrrole?



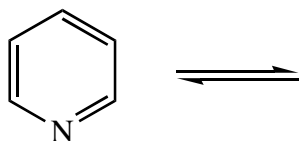
Compare the pK_a of pyrrole with that of ammonia:

Q. Why is pyrrole more acidic than ammonia?

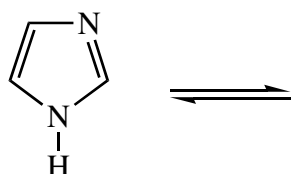
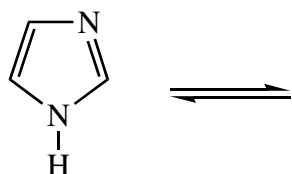
A.

Look @ Pyridine:

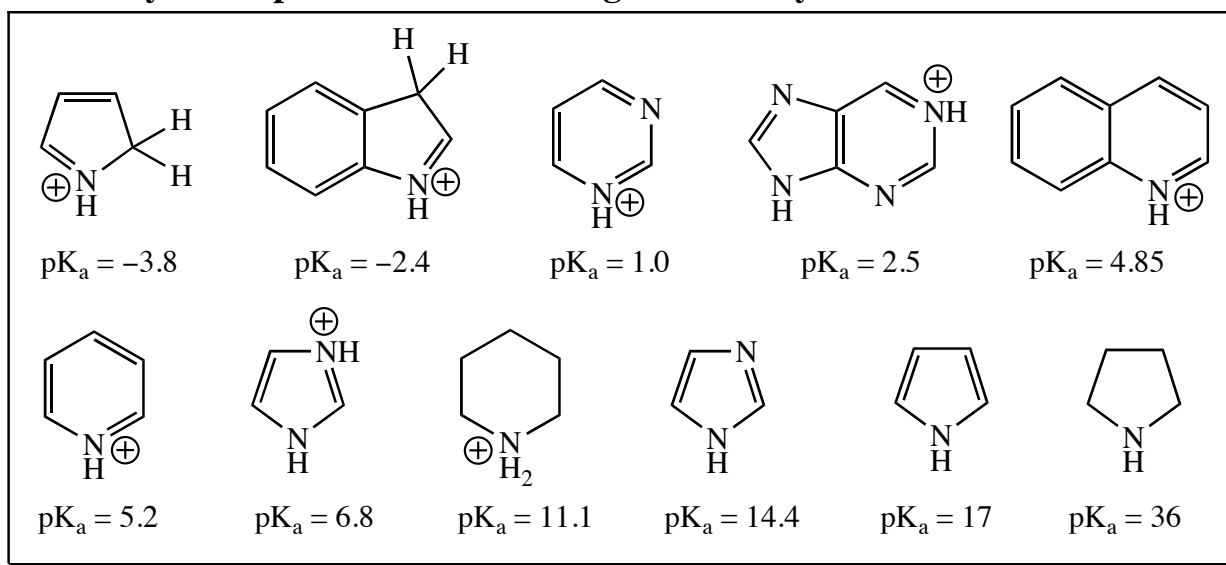
Q. Would you expect pyridine to be very basic?



Predict the relative acidity and basicity of imidazole (reactions of imidazole as an acid or base are important in many biological systems):



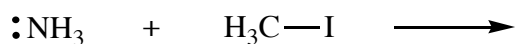
Summary of the pK_a of Several Nitrogen Heterocycles:



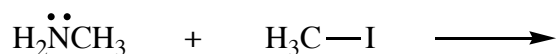
III. Preparation of Amines

A. Alkylation of Amines

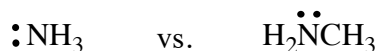
Amines are good nucleophiles and can react with primary alkyl halides to give alkylated ammonium halides. This is an S_N2 reaction so 3° halides don't work and 2° give mostly elimination reactions.



☞ Big Problem: *Overalkylation!*



Compare nucleophilicity:



Even if only 1 equivalent of CH_3I is used, you will get mixtures!

Solution:

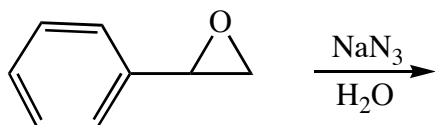
- Use a very large excess of NH_3
- Use alternative methods shown below.

B. Reduction of Azides - *Another Route to Primary Amines*



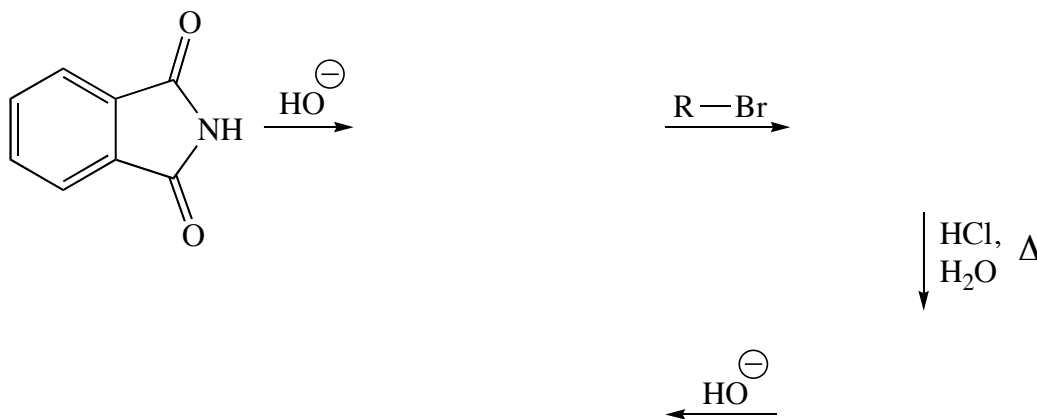
Advantages of using azide rather than ammonia to make primary amines:

Example:



C. Hydrolysis of an Imide: The Gabriel Synthesis

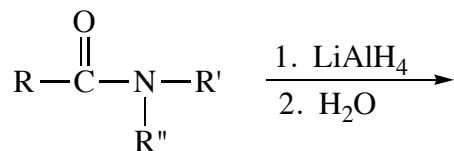
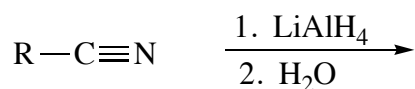
An imide is a compound with two acyl groups bound to nitrogen. The Gabriel synthesis, which converts alkyl halides into primary amines, involves hydrolysis of an imide.



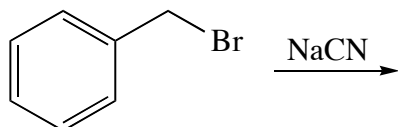
- The Gabriel Synthesis only gives one product, and therefore is a great way to synthesize primary amines.

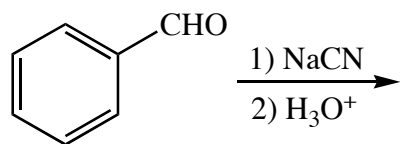
D. Reduction of Carbon-Nitrogen Double & Triple Bonds

1. Reduction of Amides & Nitriles

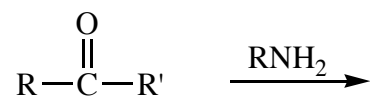


Reduction of nitriles provides a route to two types of β -phenethyl amines:

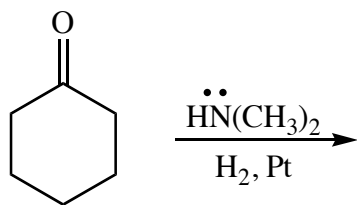




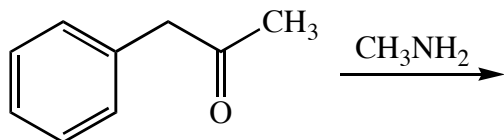
2. Reductive Amination - Reduction of Imines and Iminium ions:



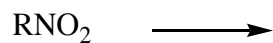
Example 1:



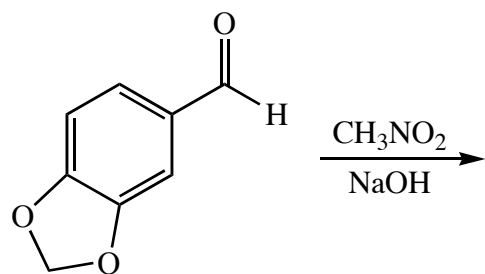
Example 2: Reductive Amination to make speed:



E. Reduction of Nitro Compounds



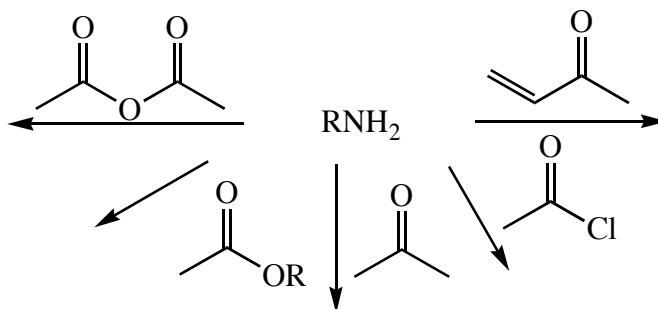
A great way to make β -phenethylamines is the **Henry Reaction** (*similar to the aldol reaction*):



Mechanism:

IV. Reaction of Amines

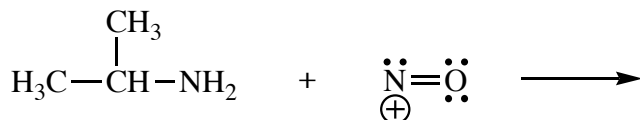
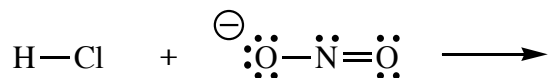
A. Amines are good nucleophiles



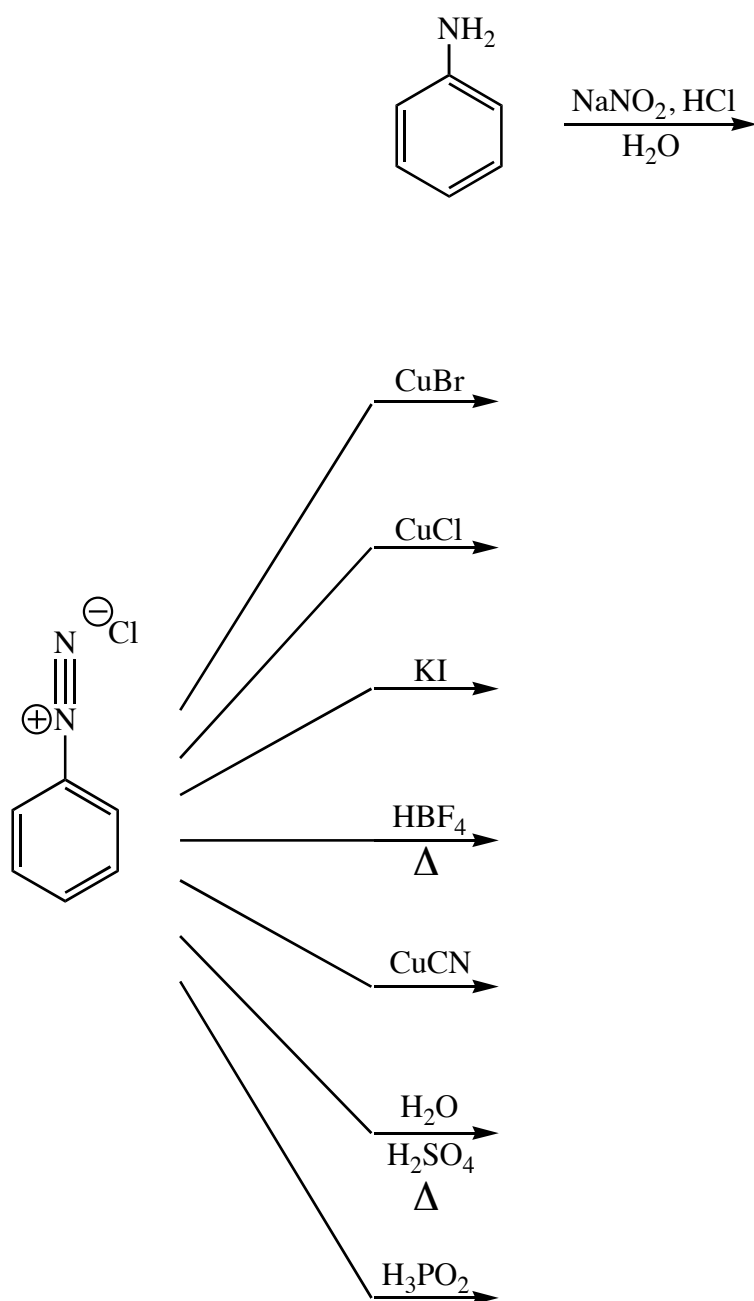
- S_N2 substitution with alkyl halides is problematic due to **overalkylation**
- Amines are also strong bases so E2 competes with S_N2

B. Reaction of 1° Amines with Nitrous Acid

Nitrous acid, HNO₂, is a weak, unstable acid generated *in situ* by treating NaNO₂ (sodium nitrite) with HCl. In the presence of acid, nitrous acid decomposes to a **nitrosonium ion**, a powerful electrophile, which reacts with 1° amines to form diazonium salts.



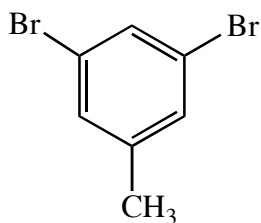
- The reaction of primary aliphatic amines with nitrous acid is not synthetically useful.
- The reaction of nitrous acid with primary aromatic amines, however *is* very synthetically useful. When aniline is allowed to react with nitrous acid, **diazotization** occurs to form an **arene diazonium salt**. This diazonium salt, has a very good L.G. (molecular nitrogen) and undergoes substitution reactions in which nitrogen is replaced by a variety of substituents:



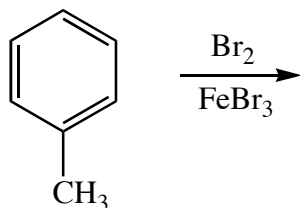
V. Using Diazonium Salts in Synthesis

The amino group can be used to direct electrophilic aromatic substitution on the ring, and can be removed through diazotization and replacement by hydrogen in a reduction reaction.

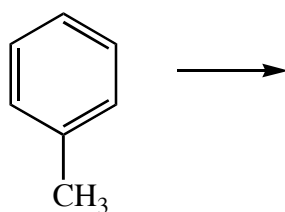
Example: Synthesize the following compound from toluene:



If toluene is brominated, you get:



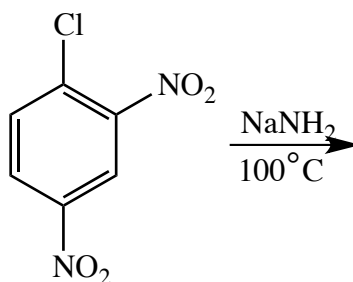
Instead:



VI. Use of Nucleophilic Aromatic Substitution to Make Substituted Aniline Rings

Background (chapter 18, 4th ed):

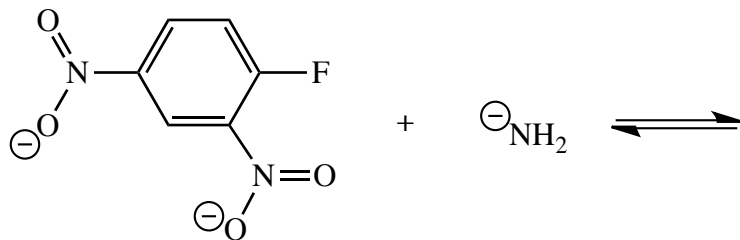
Aromatic rings do not react easily with nucleophiles. Nucleophiles *can* displace aryl halides in *highly deactivated benzene derivatives* via an addition/elimination mechanism.



Characteristics of Reaction:

- Strong nucleophile required.
- Reaction *cannot* proceed by S_N1 (formation of an aryl cation) because the EWG would destabilize this intermediate.
- Reaction *cannot* proceed by S_N2 : Like vinyl halides, aryl halides cannot achieve the correct geometry for backside displacement (aromatic ring blocks approach of the nucleophile to the back of the carbon bearing the L.G)
- Fluoride is a much better L.G. than iodide ion in this reaction.

Mechanism: Addition Elimination:



Q. Why is fluoro a better L.G. in this reaction?

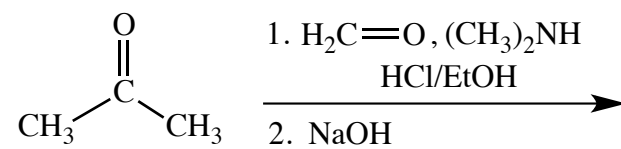
A. Two reasons:

1. **F** is more electronegative than **I**.

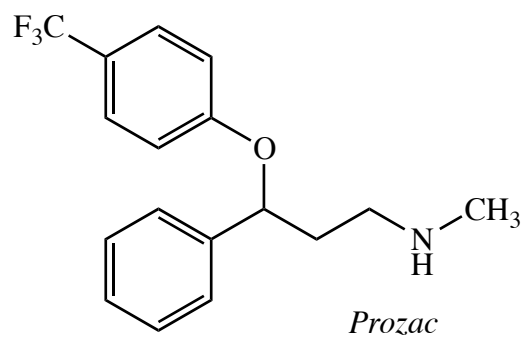
2. **F** is much smaller \therefore there is less steric hindrance to the approaching nucleophile that will bond to carbon and give a tetrahedral intermediate.

VII. Amines in Condensation Reactions: The Mannich Reaction

When an aldehyde or ketone is heated with an acid catalyst in the presence of formaldehyde and an amine, the product is a β -amino carbonyl compound.



The Mannich Reaction is used as the key step in the synthesis of Prozac[®]:



Synthesis:

