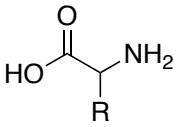
CHAPTER 22: Amines

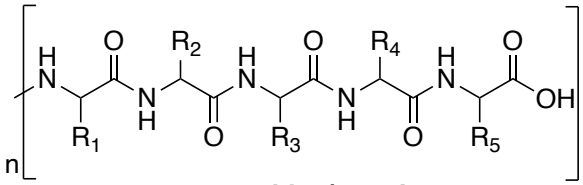
Based on notes by JRZ updated 4/18/2022

Amines are Biologically Important

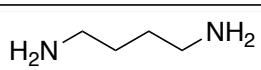
Amino acids are the basis of all peptides and proteins. These are the tissue building blocks and nature's catalysts (enzymes) in biological systems. Amine functional groups have marketed biological activity, from being very foul smelling compounds from degrading flesh to impacting neural chemistry.



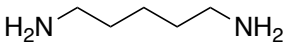
amino acids



peptides/proteins

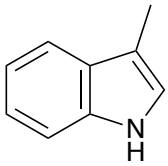


putrescine



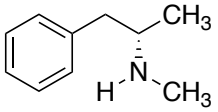
cadeverine

foul smelling constituents from rotting flesh

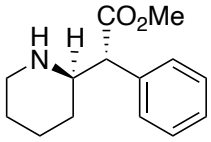


3-methyl-1H-indole
aka. skatole

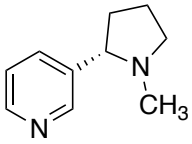
Some biologically active compounds



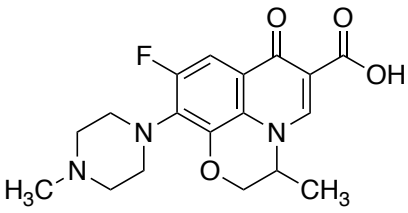
methamphetamine



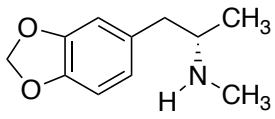
Dexmethylphenidate (ritalin)



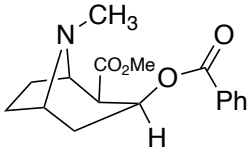
nicotine



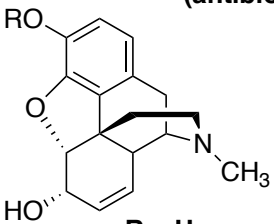
ofloxacin (antibiotic for anthrax treatment)



ecstasy (MDMA)



cocaine



R = H: morphine
R = CH_3: codeine

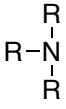
Amine Substitution

Primary, secondary, and tertiary amines refer to the amount of alkyl substitution on the Nitrogen atom (not the carbon as is the case with other functional groups).

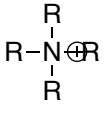
ammonia

1°

2°



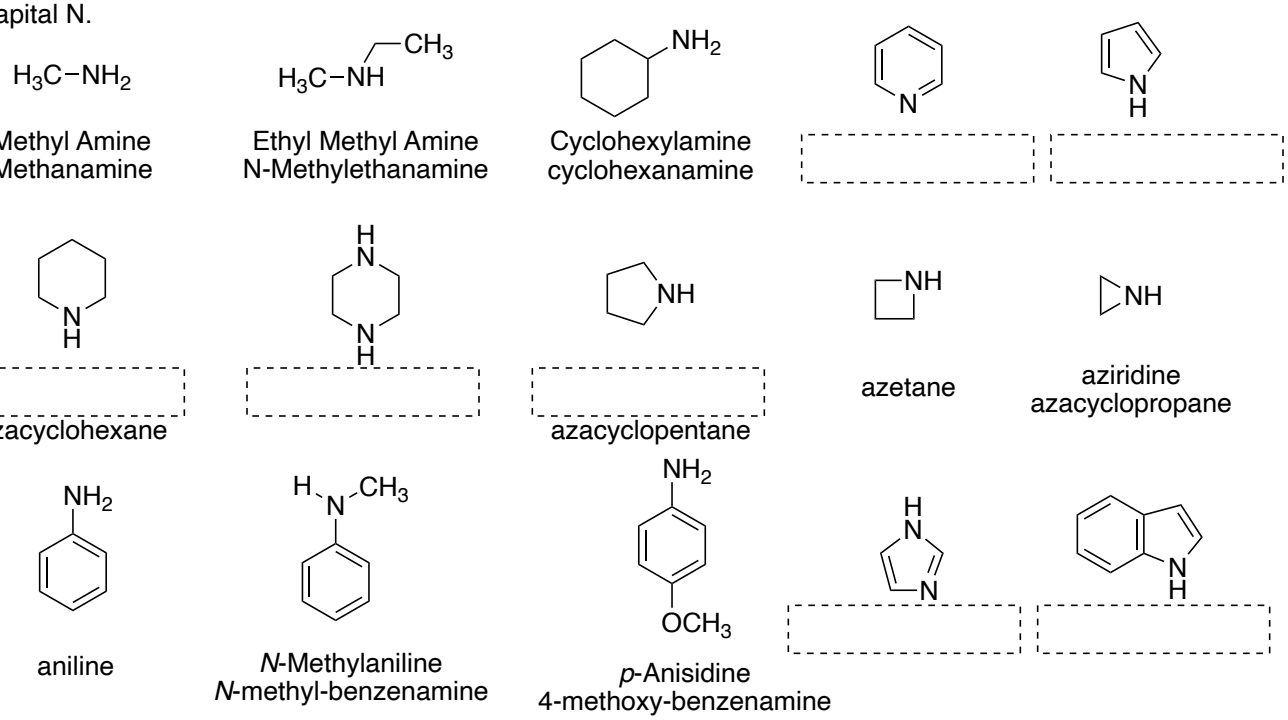
3°



4° quaternary ammonium salt

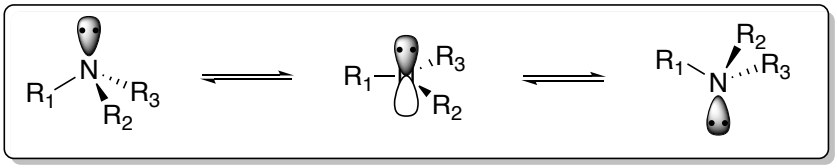
Amine Naming

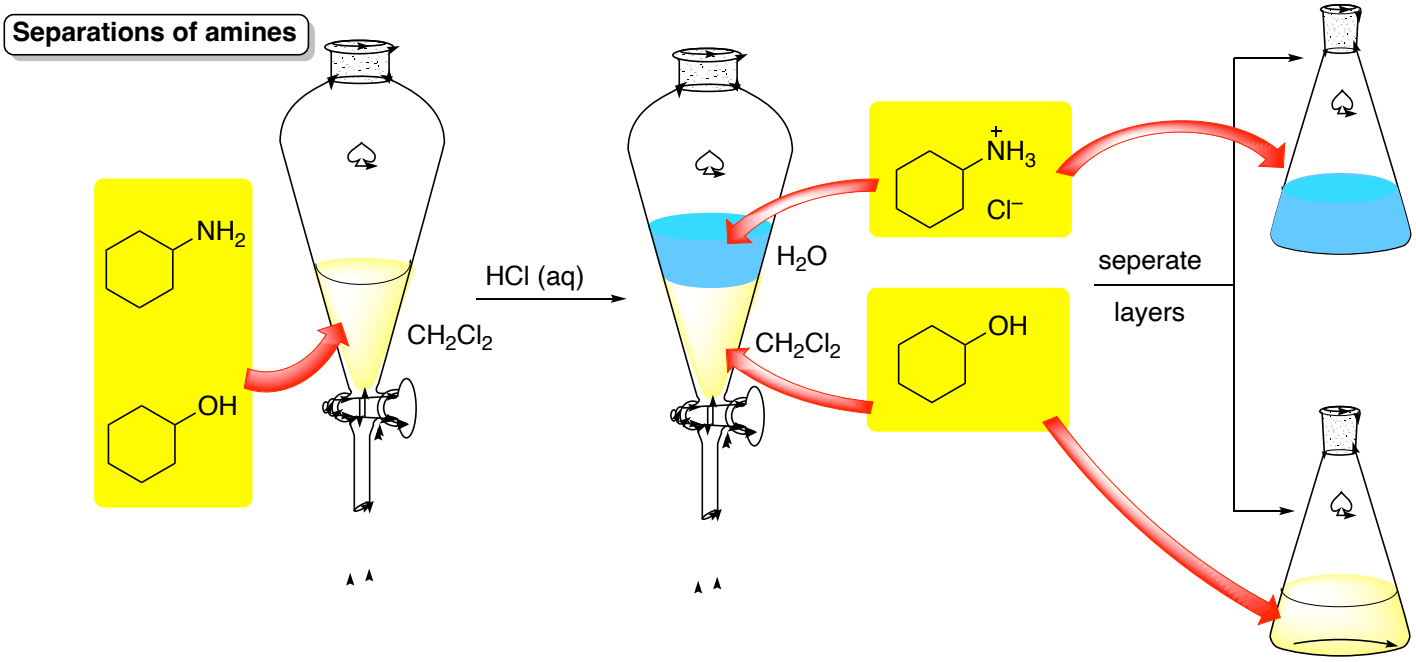
There are several ways to name amines, depending on what you call the substitutent and what you call the parent. Also, when necessary, substituents on the nitrogen are indicated with a capital N.



Amine Structure

Amines are sp^3-hybridized and tetrahedral with the lone pair taking up one of the four positions. Amines are inherently chiral; however, they undergo rapid inversion at room temperature (requires the same energy as rotation around an sp^3–sp3 bond). Thus, they are always racemic.



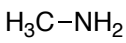
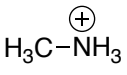
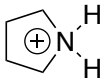
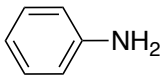
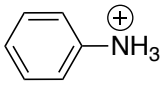
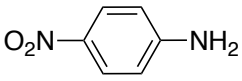
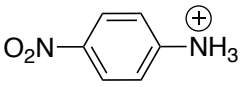
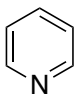
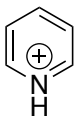
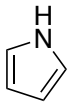
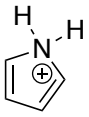
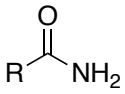
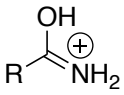


Amines are Good Bases

Amines are very good bases - more basic than oxygen-containing compounds like alcohols or water. One way to measure the base strength is to look at the pK_a of the protonated amine (conjugate acid). The weaker the acid is, the stronger was the base that generated it.

NH_4OH is a base

NH_4Cl is an acid

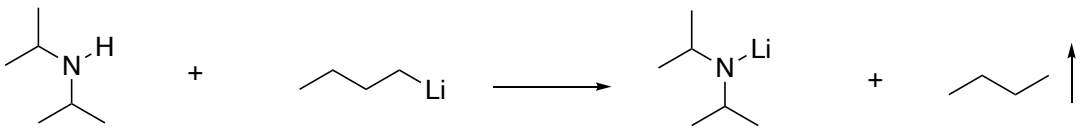
AMINE	AMMONIUM	pK_a (ammonium)
		9.3
		10.8
		11.2
		11.0
		4.6
		1.0
		5.3
		0.4
		-1

Note that the conj. acid of aliphatic amines have a pKa ~10

Note aniline is less basic than Et_3N

Amines are very poor acids

But they can be deprotonated with very, very strong bases like butyl lithium. For example, this is how chemists prepare LDA.

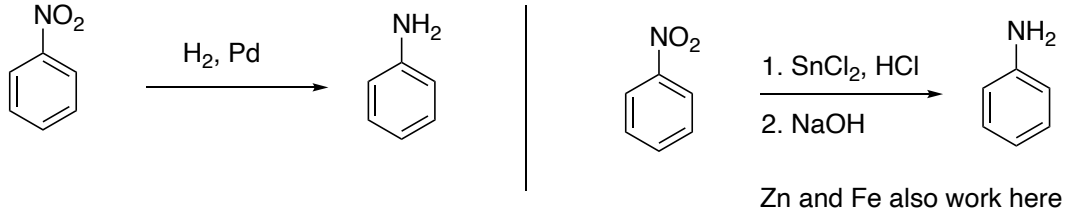


Lithium DiisopropylAmide
(LDA)

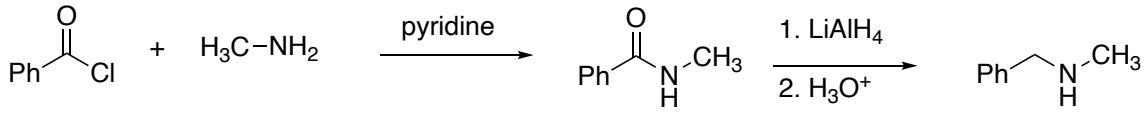
Note the term amide as applied here is a deprotonated amine

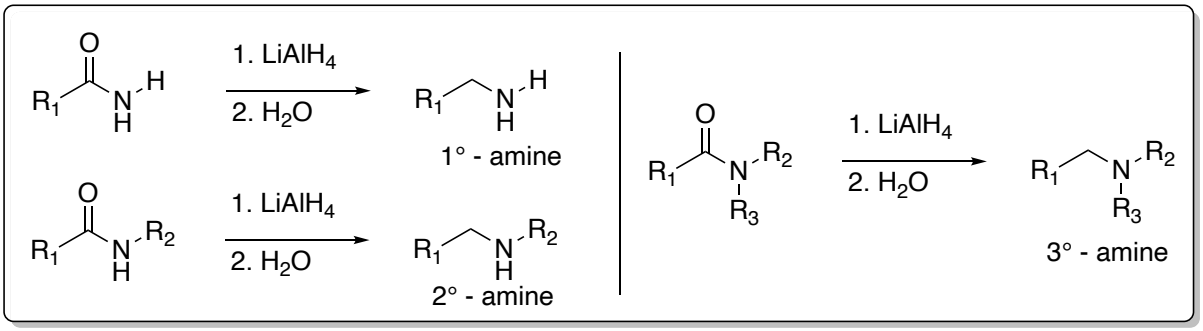
Preparation of Amines - From previous chapters

Aromatic nitro compounds can be reduced to afford anilines and amides can be reduced to form amines.

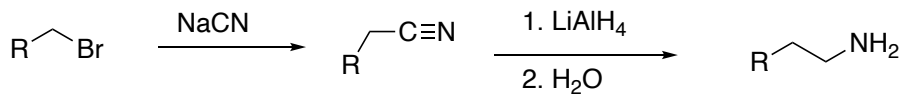


Make an amide, then reduce:

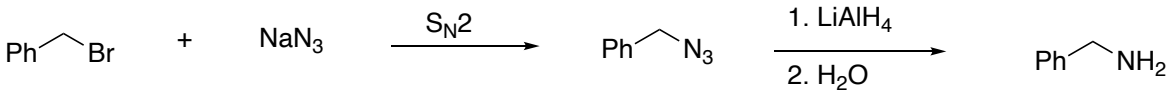




Reduce a nitrile to a primary amine:

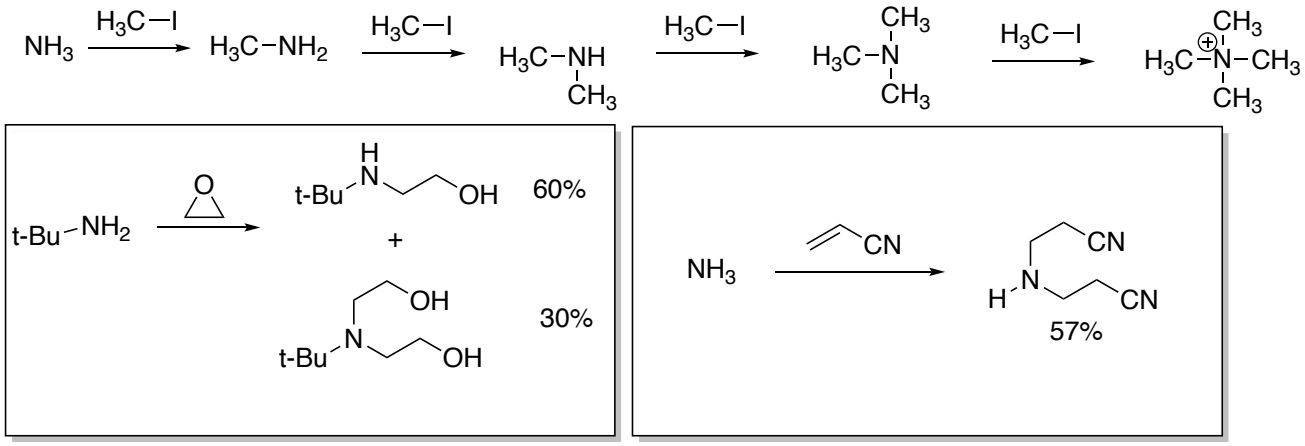


Use azide as a nucleophile, then reduce:



Alkylation of amines

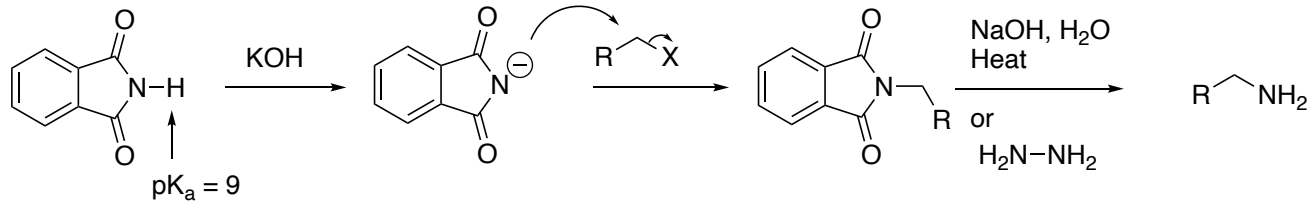
Amines are very good nucleophiles. Too good as a matter of fact. It is difficult to stop the reaction at just one alkylation.



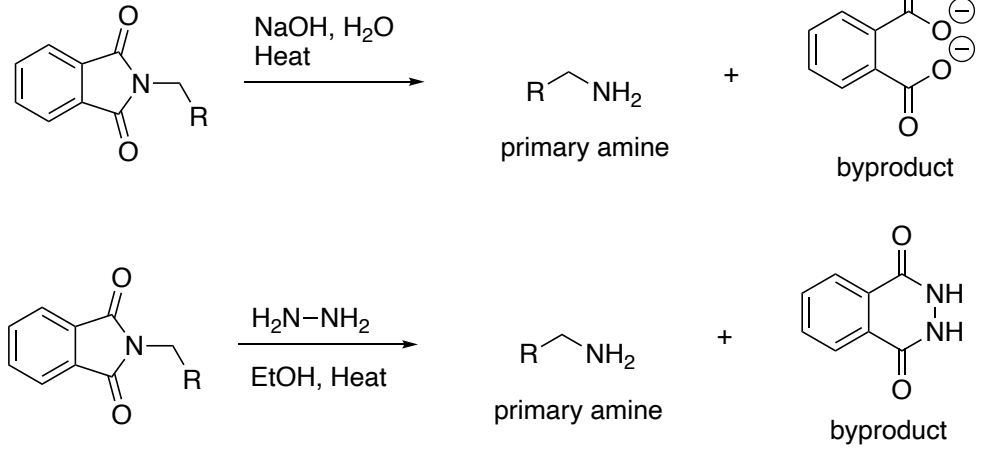
Controlling the Alkylation of Amines

In order to avoid problems with over alkylation, there are several strategies that can be undertaken.

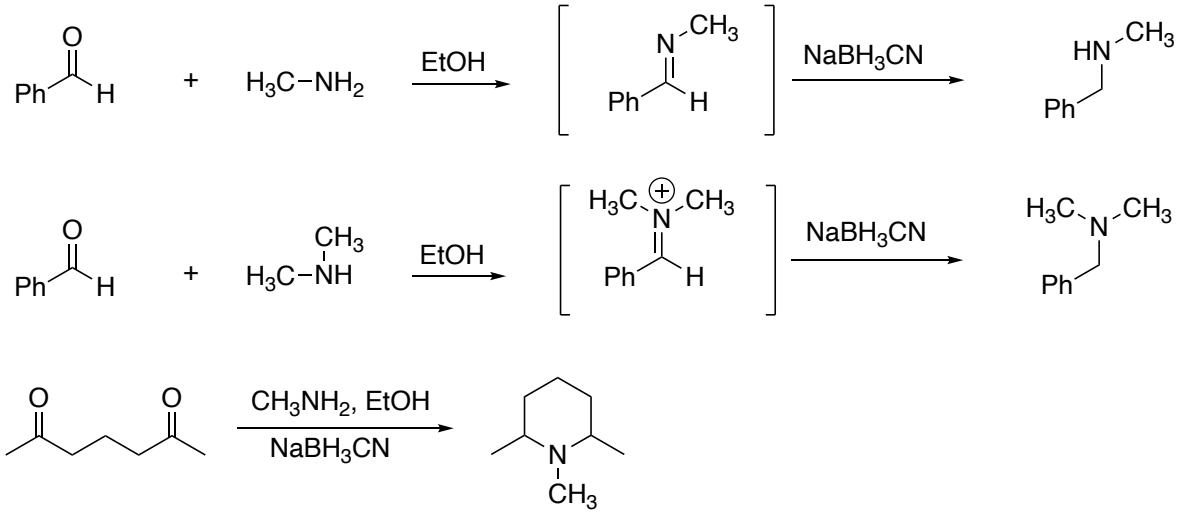
Use Phthalimide as a Nucleophile, then deprotect (Gabriel Synthesis):



Conversion of phthalimide to amine:



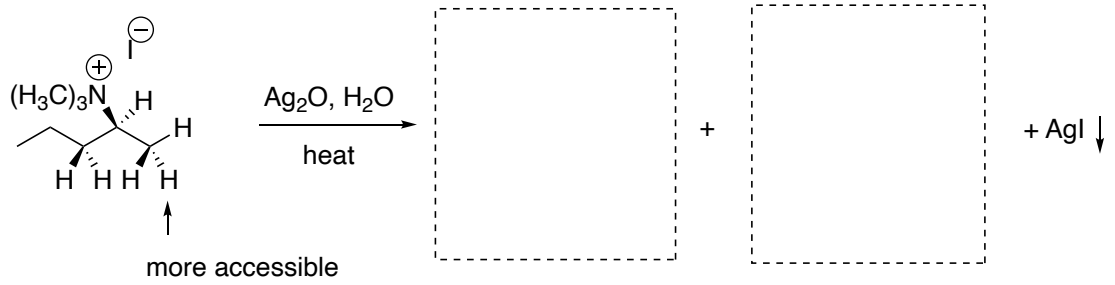
Reductive Amination with Amine and Aldehyde



$NaBH_3CN$ (derived from $NaBH_4$) is very effective for reductive aminations.
H_2/Pd can be substituted for $NaBH_3CN$
Note imines reduce faster than ketones, aldehydes, and before enamines can form

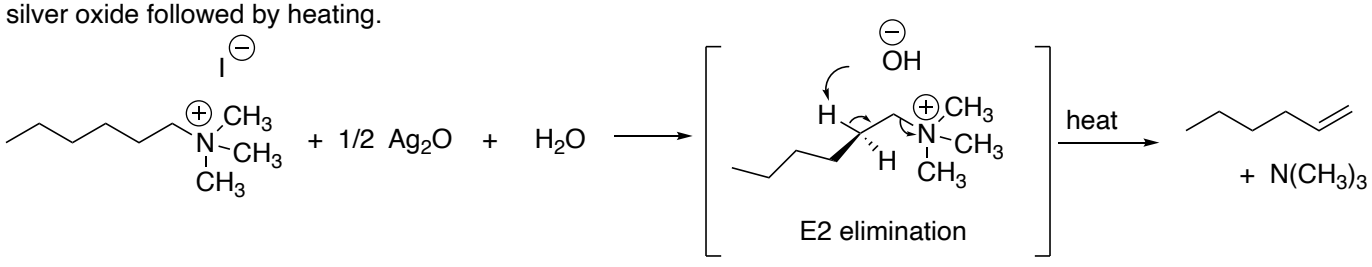
Eliminations: Hofmann Elimination

Amines can undergo eliminations too, like alcohols and alkyl halides, however they cannot eliminate directly. First, the amine must be converted into a good leaving group by exhaustive methylation (using methyl iodide), creating an ammonium ion that can leave as a neutral amine.



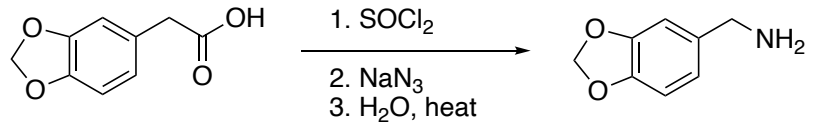
The Hofmann elimination prefers the least substituted alkene. This is mostly due to the sterics of the quaternary ammonium ion.

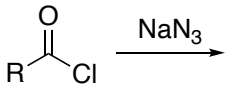
Elimination of the quaternary ammonium salt generally takes place by the E2 mechanism, which requires a strong base. To provide the base, the quaternary ammonium iodide is converted to the hydroxide salt by treatment with silver oxide followed by heating.



Curtius Rearrangement (not in book)

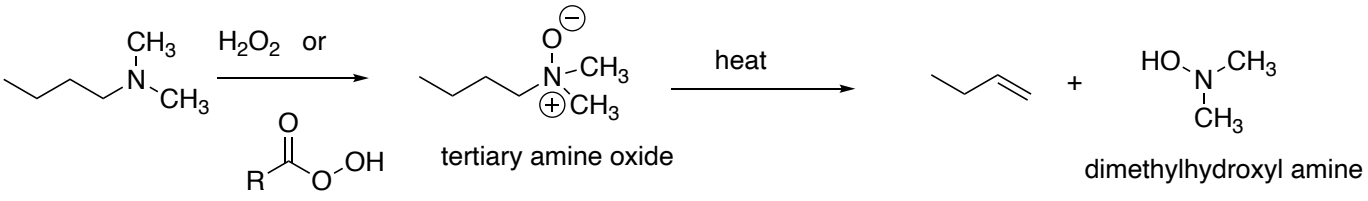
An acid chloride reacts with azide ion to give an acyl azide, which undergoes Curtius rearrangement when heated.



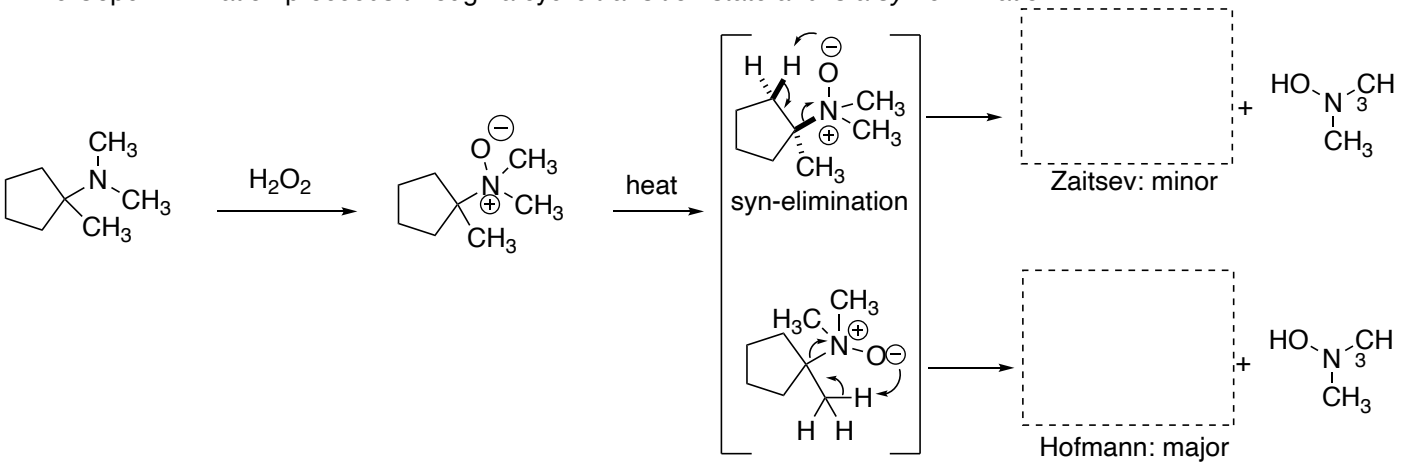


*N_2 serves as the leaving group!

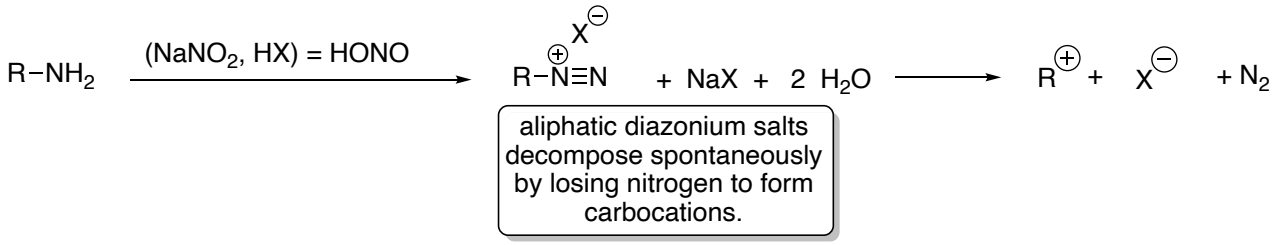
Eliminations: Cope Elimination (not in Book)



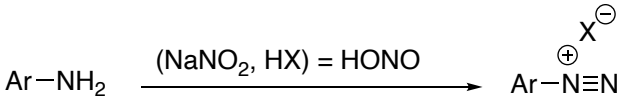
The Cope Elimination proceeds through a cyclic transition state and is a *syn*-elimination.



Reactions of Primary ALIPHATIC Amines with Nitrous Acid (HONO):

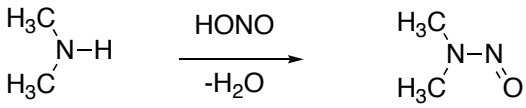


aliphatic diazonium salts decompose spontaneously by losing nitrogen to form carbocations.



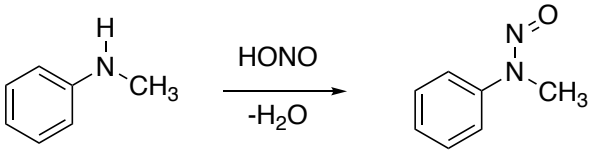
arenediazonium salt (stable if kept under 5 °C)

Reactions of Secondary Amines with Nitrous acid (HONO):



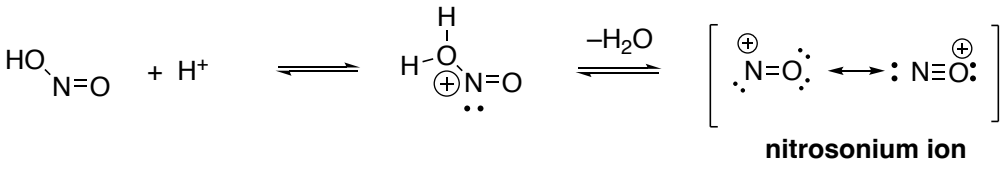
potent hepatotoxin. EPA allows 7 ng/mL

N-nitrosodimethylamine

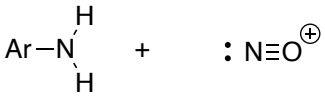


N-nitroso-N-methylaniline

Mechanism

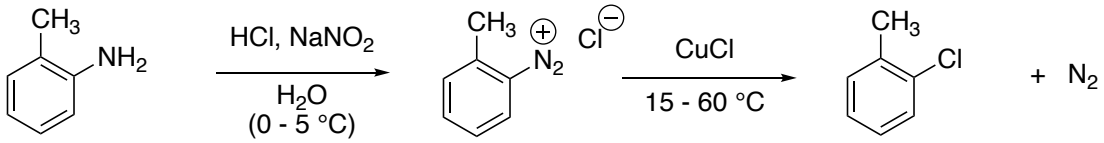


nitrosonium ion

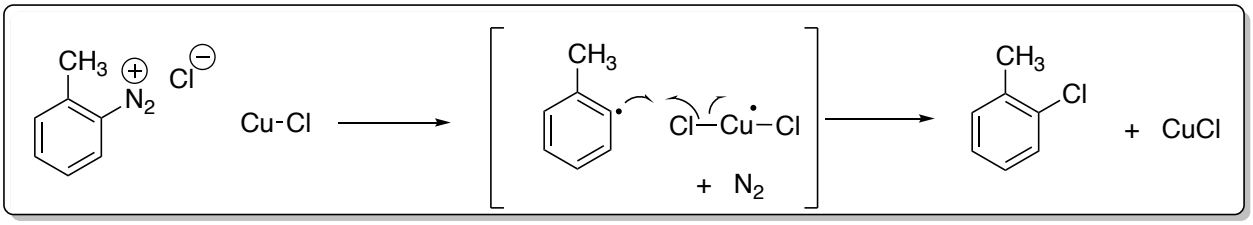


Reactions of Arenediazonium Salts

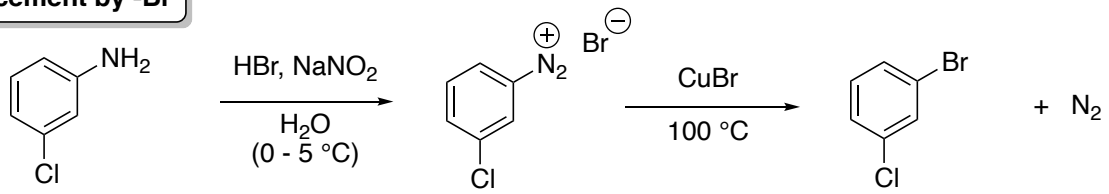
Replacement by -Cl



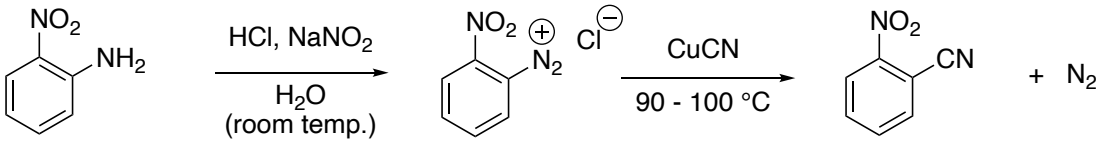
Mechanism: Radical



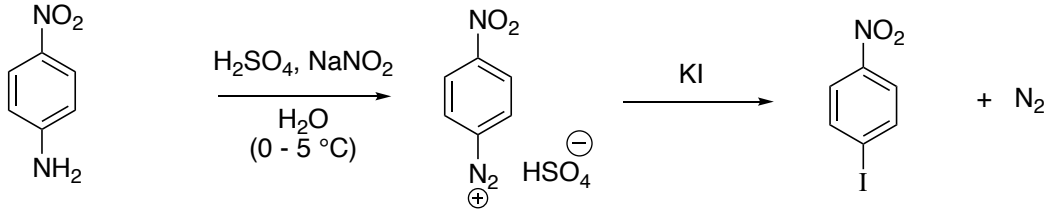
Replacement by -Br



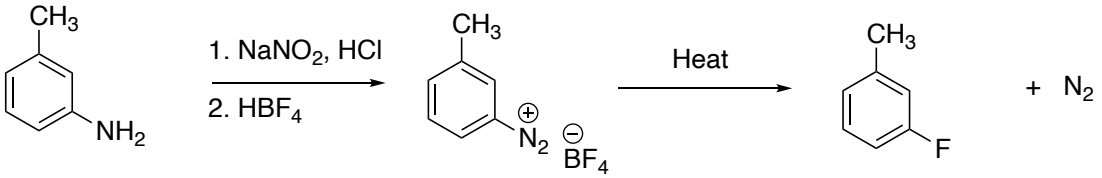
Replacement by -CN



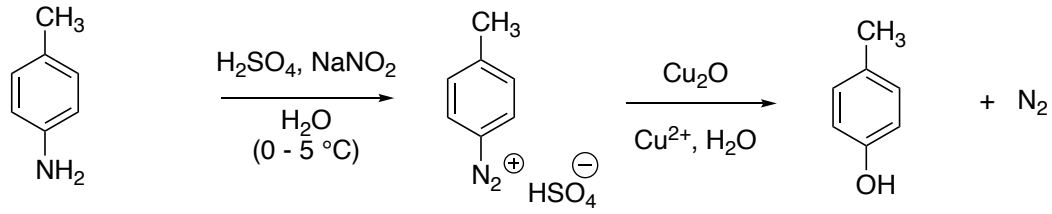
Replacement by -I



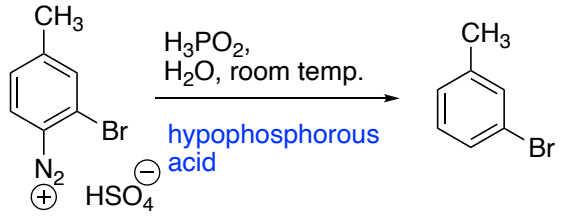
Replacement by -F



Replacement by -OH



Replacement by -H (deamination)



Coupling Reactions of Arenediazonium Salts

This is another example of an electrophilic aromatic substitution reaction. The diazonium salt is the electrophile.