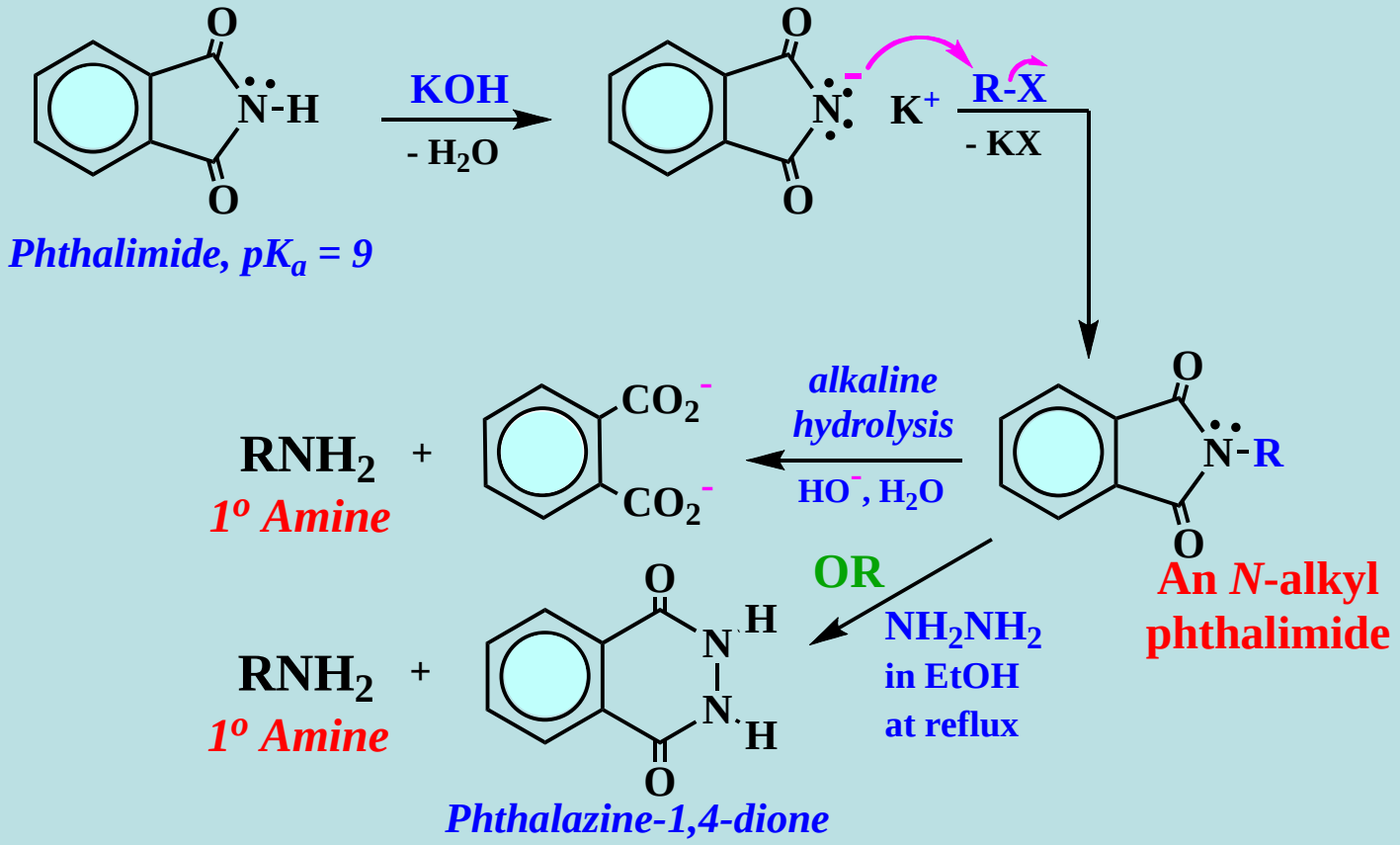
The Gabriel Synthesis of 1º Amines (S. Gabriel, 1887)

The Gabriel synthesis is a good choice when 1º amines are desired.

This synthesis utilizes the anion of phthalimide as a nucleophile in S_N2 reaction with alkyl halides. Alkaline hydrolysis of the *N*-alkylated phthalimide yields the 1º amine free of 2º and 3º amines.

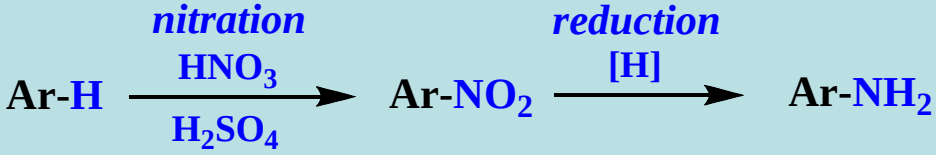


The alternative of using hydrazine, NH_2NH_2, to release the 1º amine often gives superior results.

The Synthesis of Amines by Reduction Methodologies

Reduction of Nitro Compounds

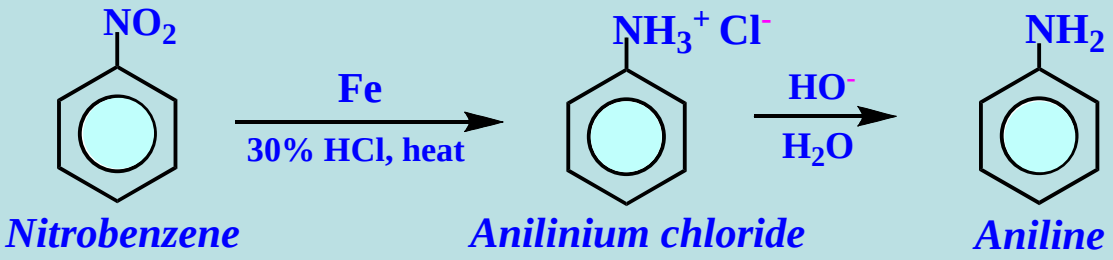
Anilines may be prepared by reduction of nitrobenzenes. The overall synthetic sequence begins with nitration of the starting arene.



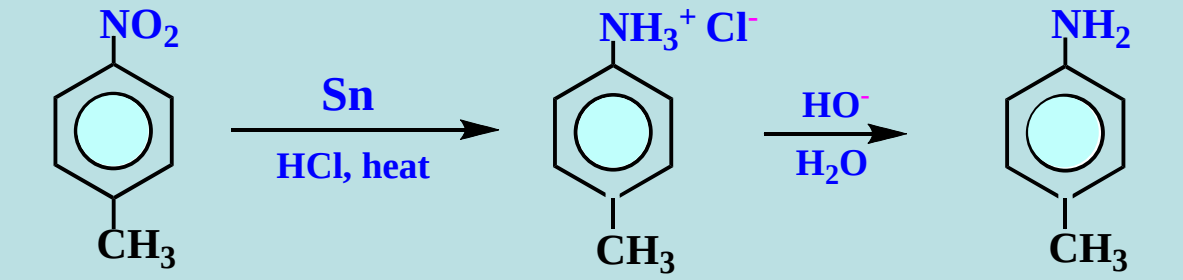
The Dissolving Metal Reduction of Nitrobenzenes to Anilines

These reactions use metals such as iron, zinc and tin and typically are carried out at reflux in hydrochloric acid solution, sometimes with added acetic acid to help dissolve the aromatic compound.

EXAMPLE



A SECOND EXAMPLE

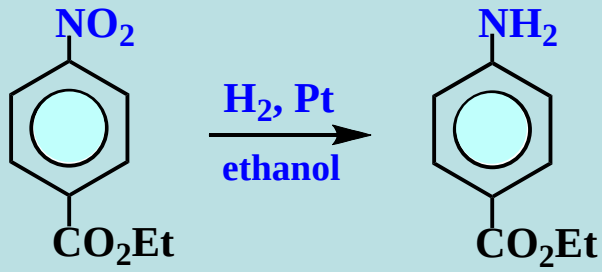


p-Nitrotoluene

p-Toluidine

Catalytic Hydrogenation of Nitroaromatics

Anilines may also be prepared by catalyzed reaction of pre-formed hydrogen with nitroaromatics:

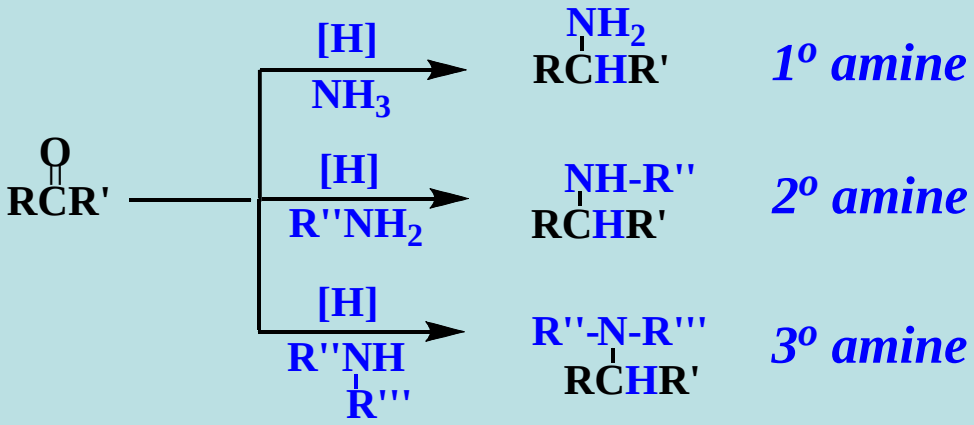


Ethyl *p*-nitrobenzoate

Ethyl *p*-aminobenzoate

Reductive Amination

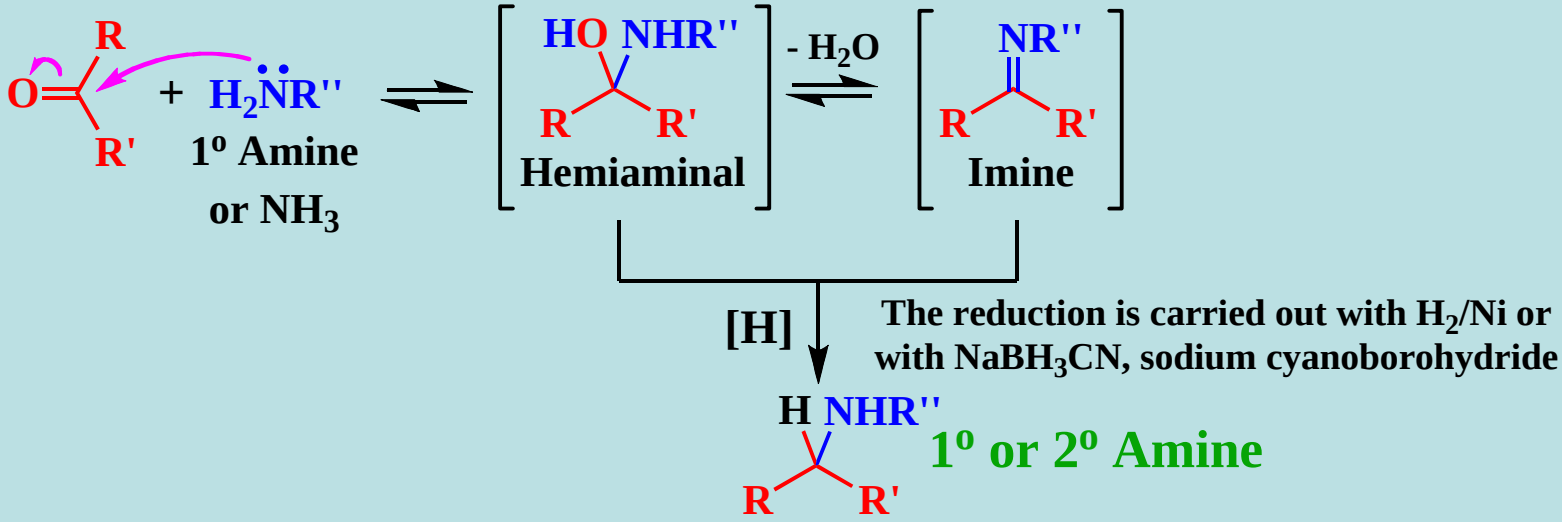
Aldehydes and ketones can be converted into amines by catalytic or chemical reduction in the presence of ammonia or a 1º or 2º amine. The overall synthetic schemes are these:

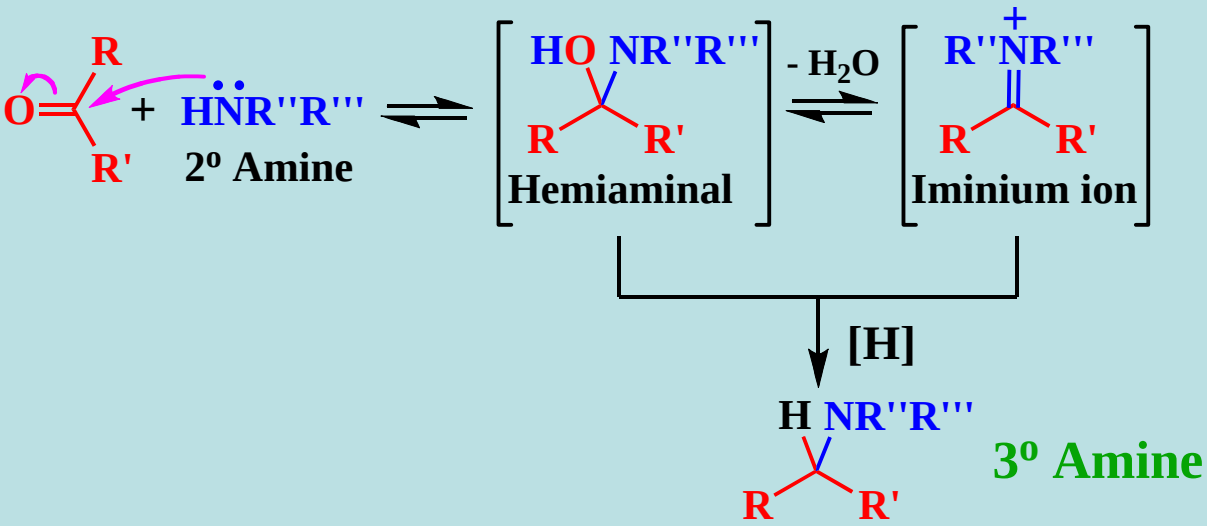


These conversions can alternatively be viewed as reductive alkylations of the starting amines.

A Mechanism for Reductive Amination

Reductive amination involves addition of the amine to the carbonyl followed by reduction via the immediate aminal or its dehydration product, an imine.





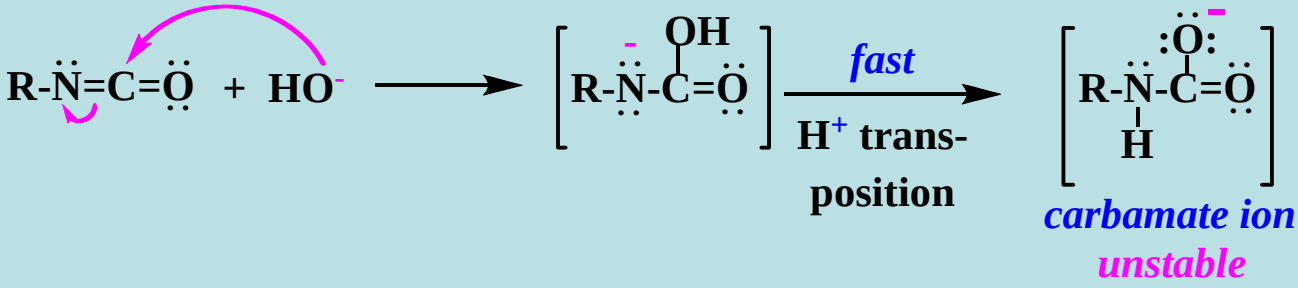
The Hofmann Rearrangement: Amines from Primary Amides

Primary amides are converted into amines by loss of the carbonyl group in aqueous basic solutions of Br_2 or Cl_2.

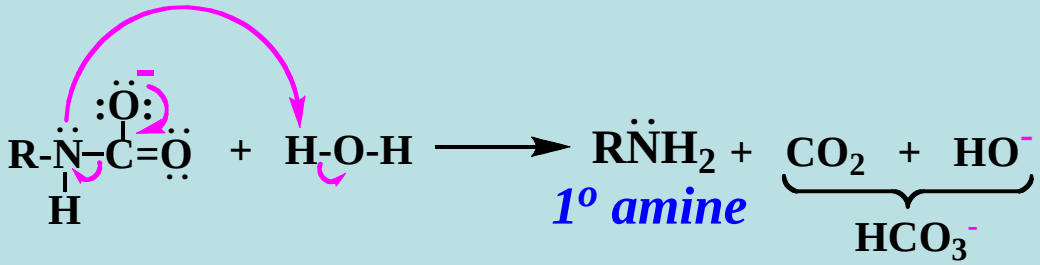
The Hofmann rearrangement of 1º amides provides 1º amines exclusively, with no contamination from 2º or 3º amines. This reaction also can be useful for shortening a carbon chain, which explains why it is sometimes referred to as a Hofmann degradation.

Hydrolysis of Isocyanate to Obtain an Amine

Isocyanates undergo nucleophilic addition reactions at the electropositive carbon center.

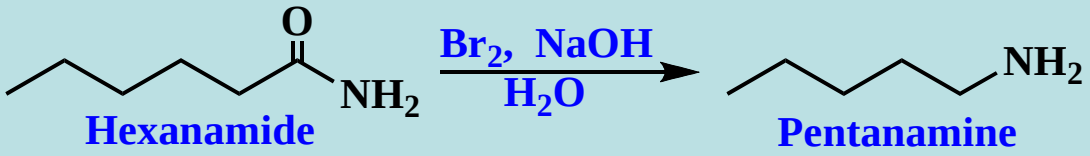


decarboxylation of carbamate anion

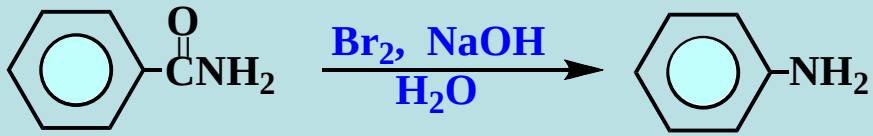


Some Features of the Hofmann Rearrangement

the migrating group may be alkyl or aryl

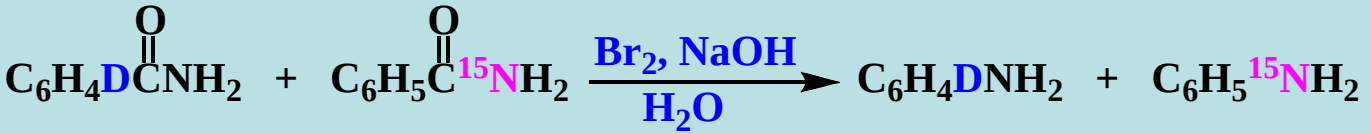


Hexanamide — Pentanamine



Benzamide — Aniline

the rearrangement is intramolecular

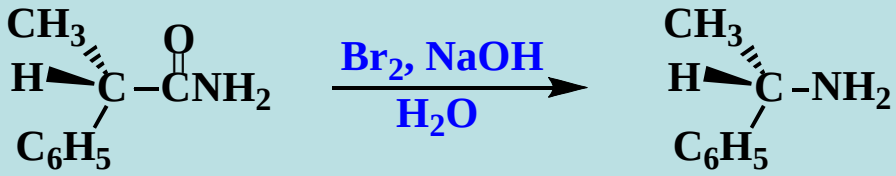


A double label experiment

No crossover of isotope labels

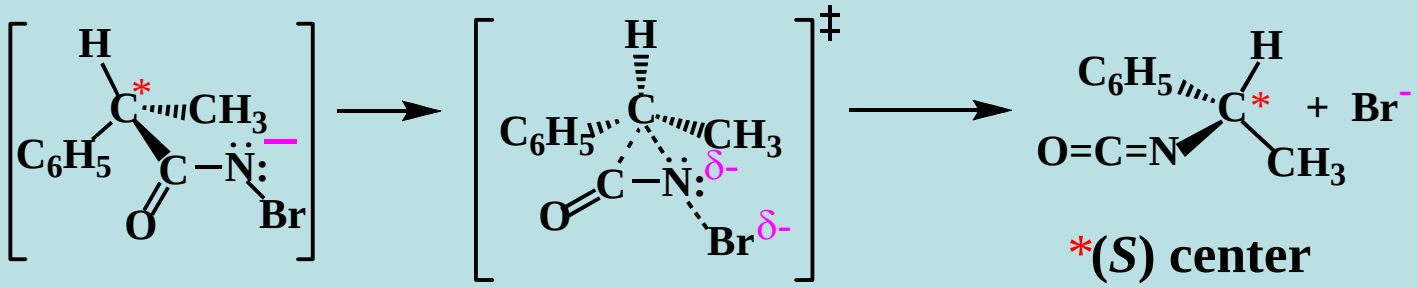
stereocenters migrate <u>with retention</u>

[That is, neither complete inversion nor racemization is observed.]



(*S*)-(+)-2-Phenylpropanamide **(*S*)-(-)-1-Phenylethanamine**

The evidence suggests that the migrating group never becomes detached.

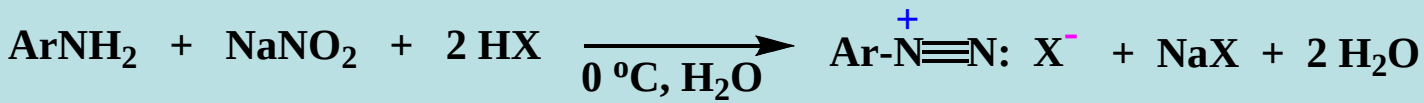


(*S*) center** ***transition state ***(*S*) center**

Reactions of 1º Arylamines with Nitrous Acid

This most important reaction of amines with nitrous acid yields aryl diazonium ions, which have many replacement reaction uses in organic synthesis.

Aryl diazonium salts can be prepared and manipulated at 0 ºC:



sodium nitrite

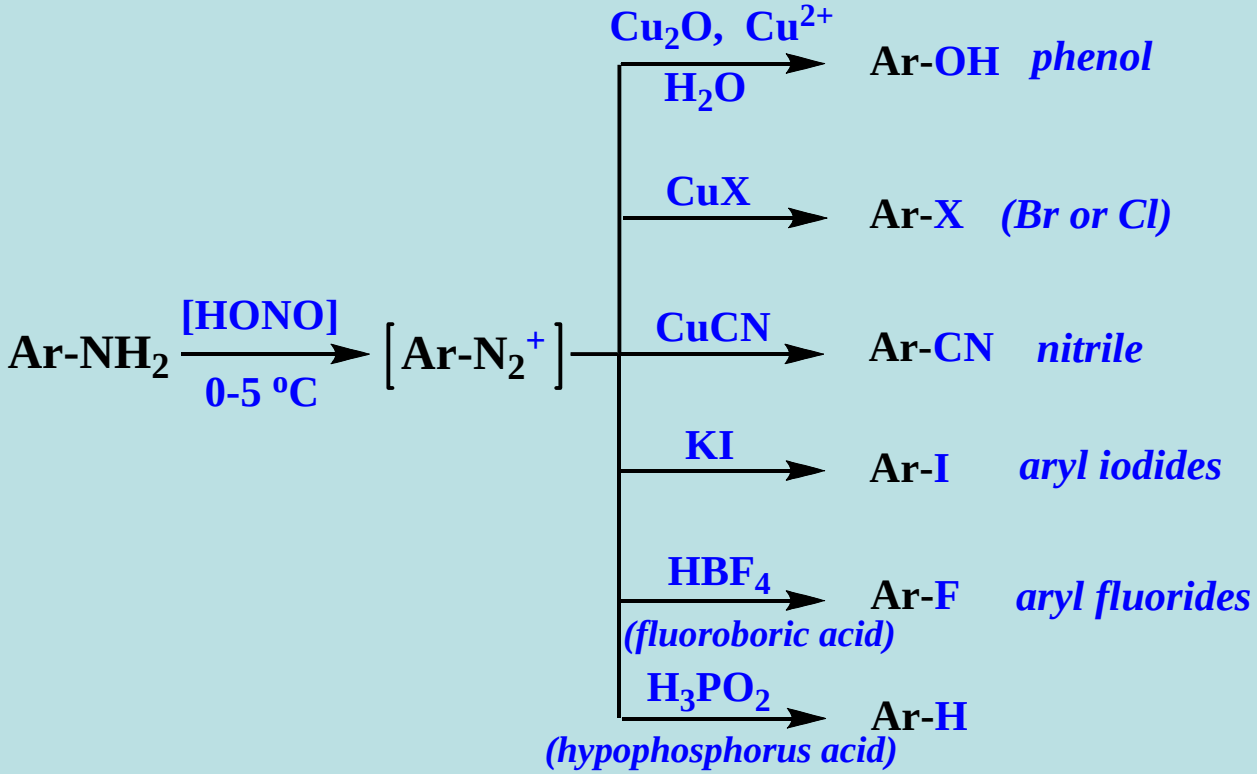
aryl diazonium salt

(stable below 5 ºC)

Note: Many dry aryl diazonium salts are explosive. Therefore, these compounds are typically not isolated but prepared and then used in the same solution.

Replacement Reactions of Aryl Diazonium Salts

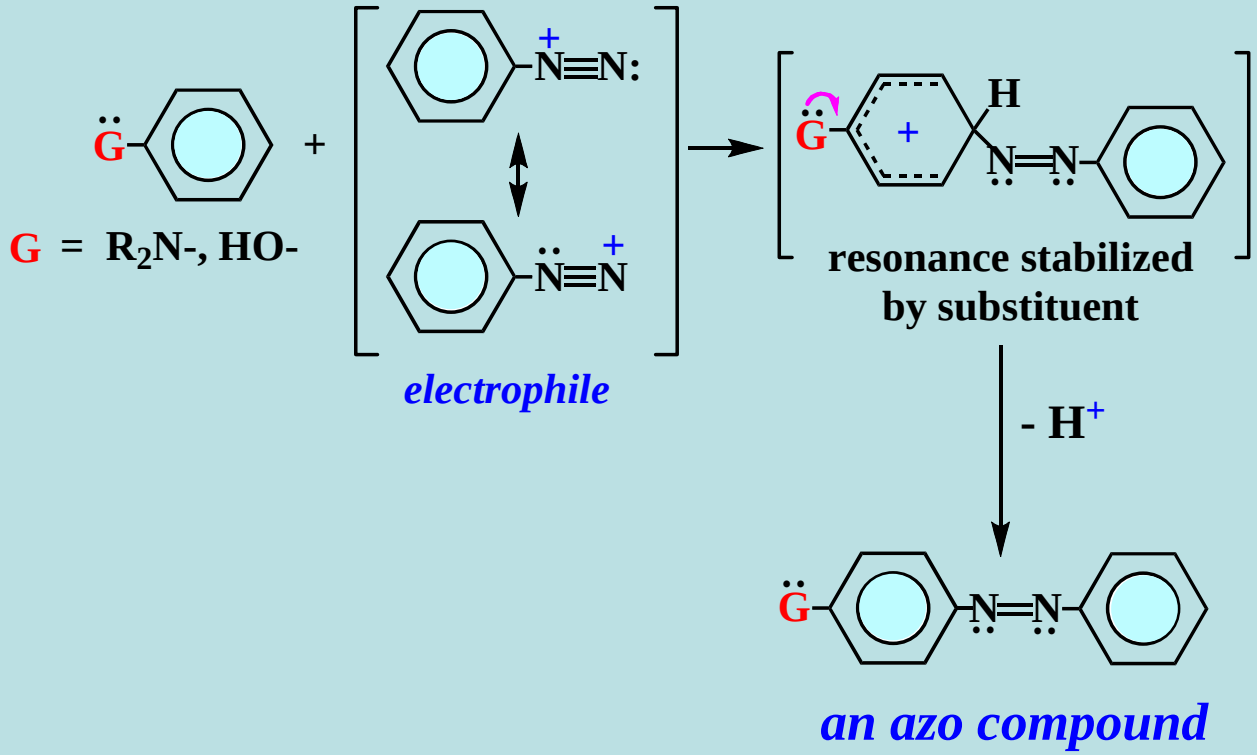
Reaction of aryl diazonium salts with various reagents results in replacement of the diazonium group by other groups.



Coupling Reactions of Aryldiazonium Salts

Aryldiazonium ions are weak electrophiles that react with electron-rich aromatics such as phenols and *N*,*N*-disubstituted aryl amines to give azo compounds.

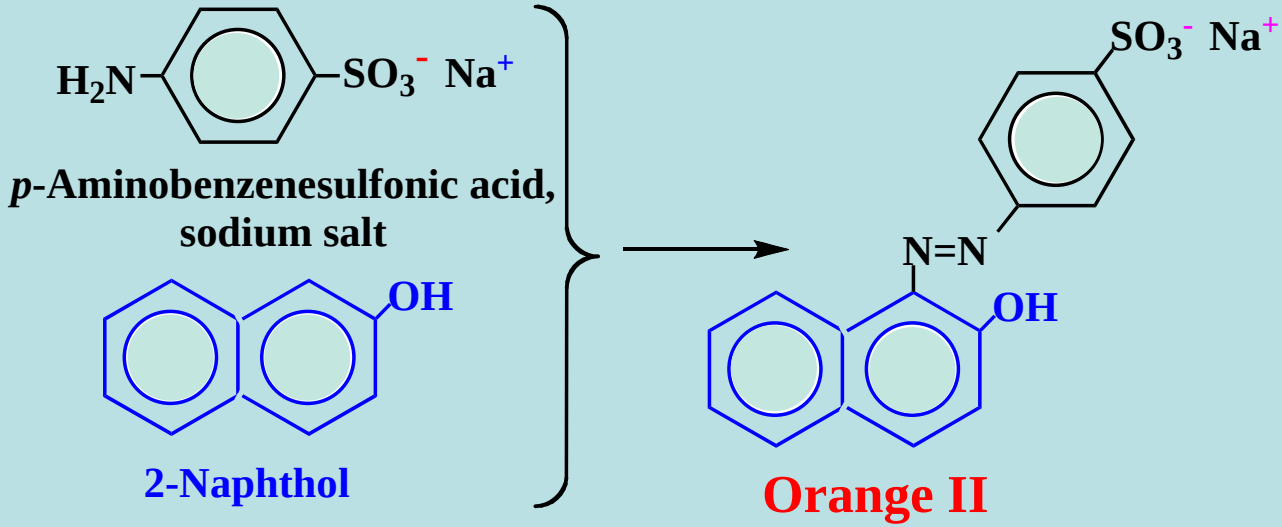
Electrophilic aromatic substitution



an azo compound

Azo Dyes

Azo compounds are typically intensely colored because of their extended π-electron systems that absorb radiation in the visible region. They are used commercially as dyes. Substituent groups such as $-SO_3^-\ Na^+$ are introduced to make them water soluble and to promote their binding to polar fibers (wool, cotton, or nylon).

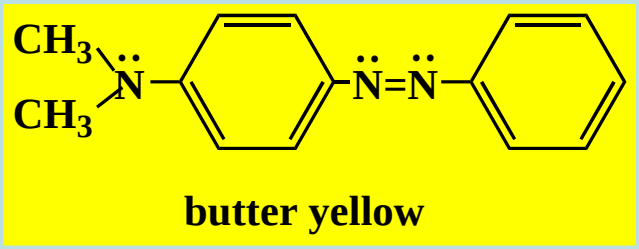


A particularly brilliant example

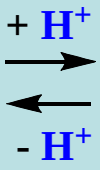
Azo Dyes as pH Indicators

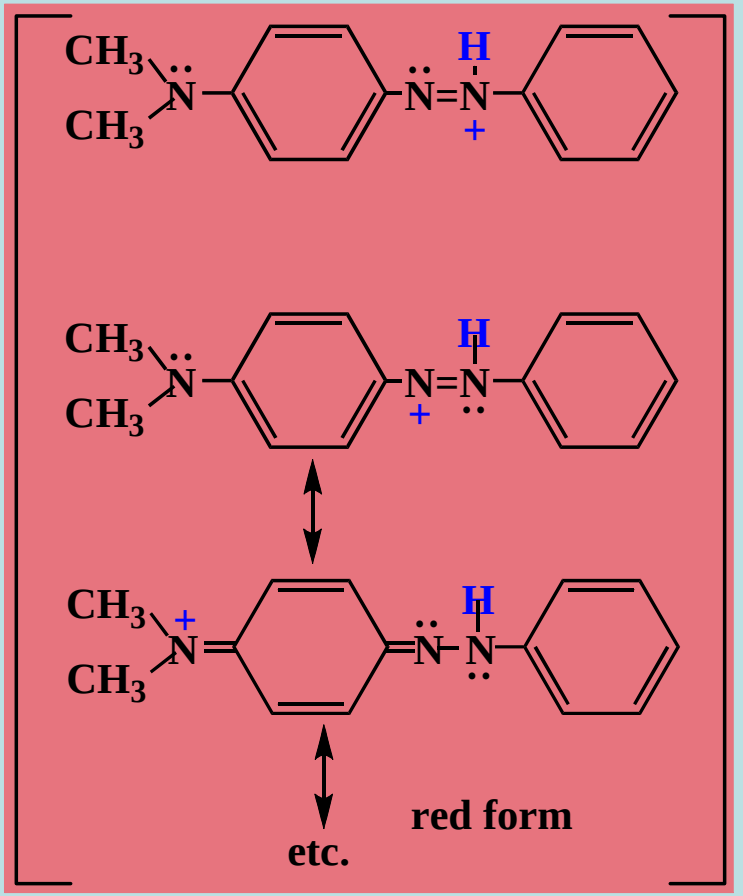
Azo dyes are used as pH indicators because their π-electron systems change dramatically between the free base and conjugate acid forms, leading to different colors for the two forms.

Butter yellow, a dye once used to color margarine, is red below pH 3 (in the conjugate acid form) and yellow at and above pH 4 in the free base form).



butter yellow

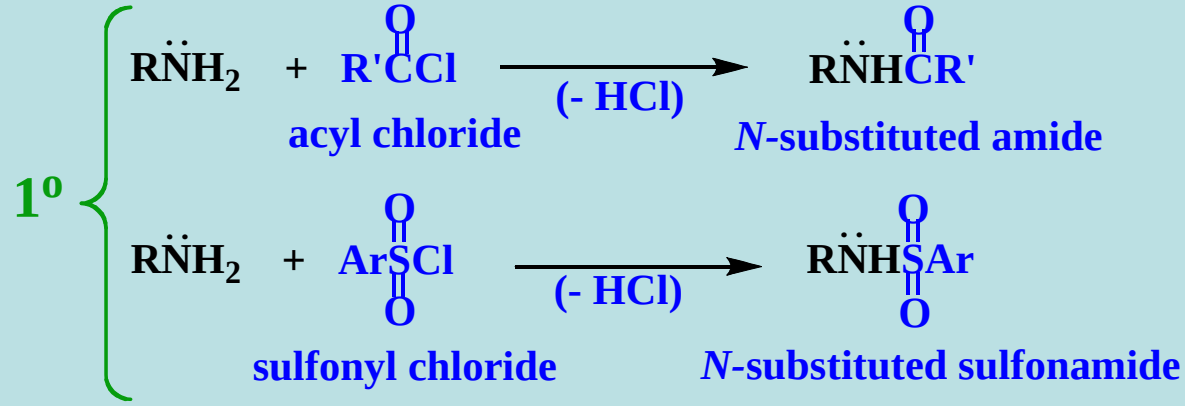




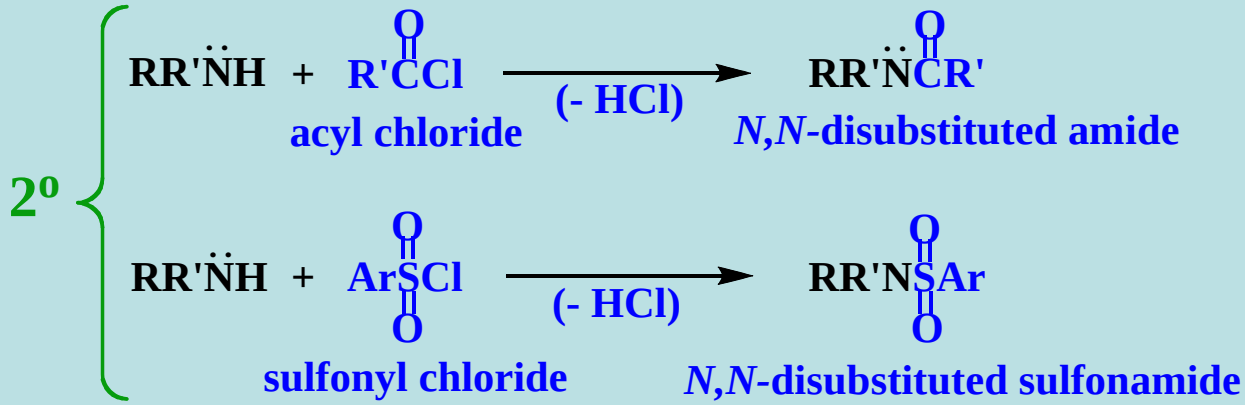
Protonation on the azo function is energetically favored because it produces a cation with more resonance stabilization than the cation produced by protonation on the amino nitrogen.

Reactions of Amines with Sulfonyl Chlorides

Primary and secondary amines react readily with sulfonyl chlorides just as they do with acyl chlorides:



Similarly,



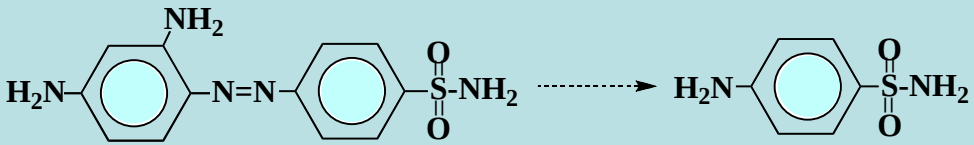
Tertiary amines do not give stable products.

Discovery of Sulfanilamide

Between 1909 and 1935, thousands of chemicals, including many dyes, were screened for activity. Very few "magic bullets" were found until a desperate father tried to save the life of his sick daughter in 1935.

Gerhard Domagk was a doctor employed by a German dye manufacturer (I. G. Farbenindustrie) when his daughter contracted a streptococcal infection. She became very ill and was near death when in one final desperate act, Domagk gave her a dose of a dye called prontosil. It was selected because tests at I. G. Farben had shown that prontosil inhibited the growth of streptococci in mice. The child recovered and a new generation of chemotherapeutics was discovered.

In 1936, Ernest Fourneau of the Pasteur Institute in Paris showed that prontosil breaks down in the human body to produce sulfanilamide, the active agent.



prontosil ***sulfanilamide***

the first sulfa drug

In the following years, many thousands of structural variations of sulfanilamide were synthesized in the search for additional drugs.

Analysis of Amines

Infrared Spectroscopy

1º and 2º Amines show sharp, characteristic absorption bands between 3300-3500 cm^{-1} from N-H stretch. 1º Amines show two bands (symmetric and asymmetric stretches) while 2º amines show a single band. 3º Amines have, of course, no such bands.

Proton NMR Spectroscopy

N-H proton signals may appear anywhere between δ 0.5-5. The signals may be broad and are influenced by solvent, concentration and other factors. Because of rapid proton exchange among nitrogen atoms, N-H protons usually do not spin-spin couple to H on adjacent carbon atoms. They are best detected by adding D_2O, which results in exchange of N-H for N-D, with disappearance of any N-H signals.

Protons on the α carbon of an aliphatic amine are deshielded and absorb typically at δ 2.2-2.9.

^{13}C NMR Spectroscopy

The α carbon of an aliphatic amine is somewhat deshielded, appearing typically at δ 30-60.

MS Spectra of Amines

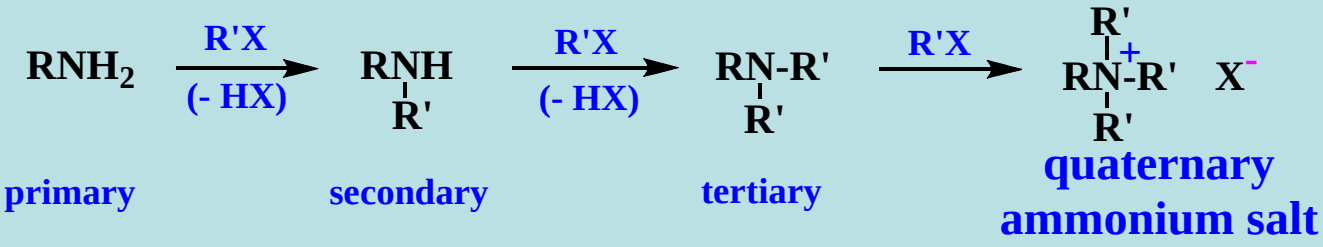
If there is an odd number of nitrogen atoms present, the molecular ion peak has an odd number mass. Cleavage between the α and β carbons is a common mode of fragmentation.

The Hofmann Elimination

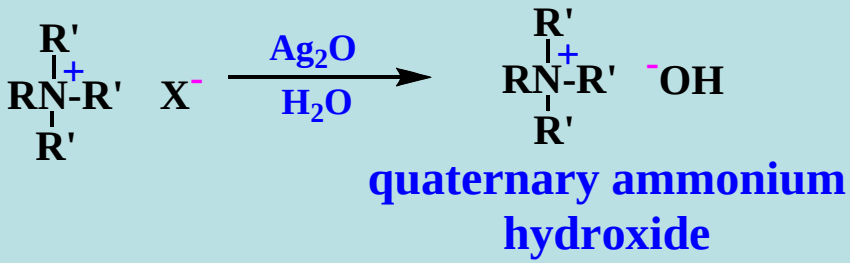
The starting material for Hofmann elimination reactions is a quaternary ammonium hydroxide.

Quaternary Ammonium Hydroxides

Exhaustive *N*-alkylation converts amines into quaternary ammonium salts:



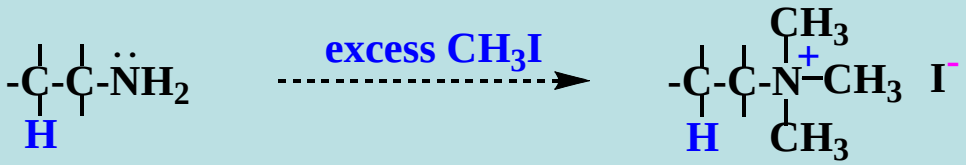
Treatment of a quaternary ammonium halide with an aqueous solution of silver oxide (actually AgOH), precipitates AgX and yields a solution containing the quaternary ammonium hydroxide.



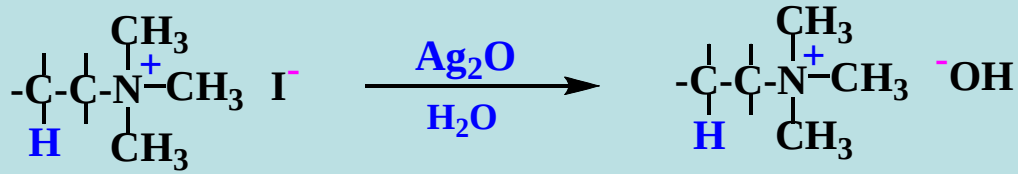
The Hofmann Elimination

In the late 19th century, the prominent German-born chemist, August W. von Hofmann (1818-1895) , discovered that quaternary ammonium hydroxides on heating undergo an elimination reaction to produce an alkene. Hofmann made many important contributions to organic chemistry as a professor at the Royal College of Chemistry in London.

In the traditional Hofmann elimination, a primary amine with a β-H is exhaustively methylated to give a trimethylalkylammonium salt:

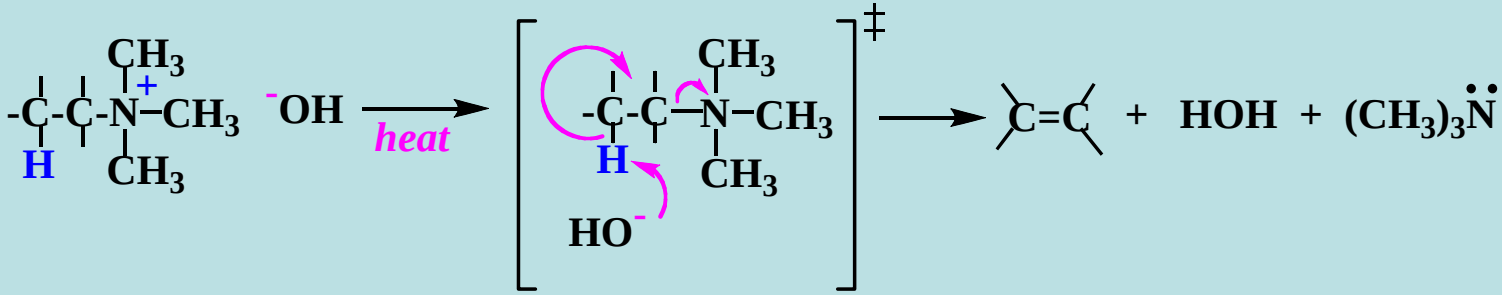


Treatment with aqueous silver oxide produces the hydroxide salt:

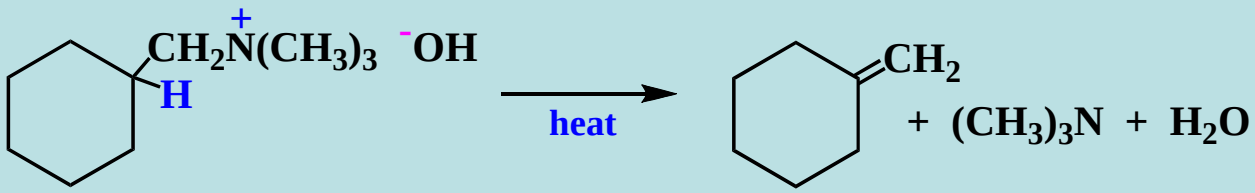


Hofmann Elimination, An E2 Reaction

The 4º ammonium hydroxide is stable and may be isolated and purified. When it is heated in the solid state or in solution to around 200 ºC an E2 reaction occurs. The availability of a β-H is, of course, a requirement for this reaction, and a trialkylamine (here trimethylamine) is the leaving group.



An Example



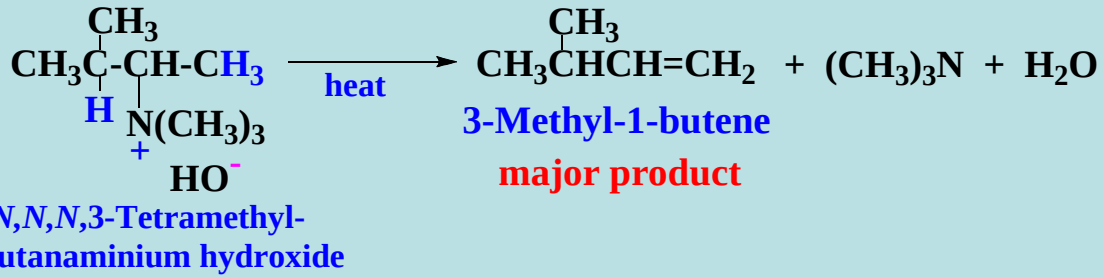
Cyclohexylmethyltrimethyl-ammonium hydroxide

Methylenecyclohexane

Regioselectivity in the Hofmann Elimination

In quaternary ammonium hydroxides that have two or more nonequivalent β-H's, the major product results from abstraction of the more or most acidic β-H. This is what is called the Hofmann rule. Since alkyl groups are electron-donating relative to H, a β-H is more acidic the fewer alkyl substituents are on the carbon to which it is attached.

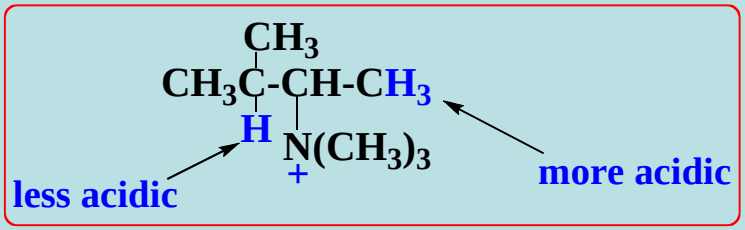
EXAMPLE



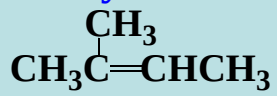
N,N,N,3-Tetramethyl-2-butanaminium hydroxide

3-Methyl-1-butene

major product

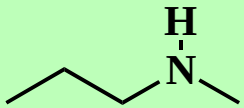


Recall that in eliminations involving neutral substrates, e. g., an alkyl bromide, the major product is that predicted by the Zaitsev rule: the most heavily substituted (the most stable) alkene possible. For example, if the leaving group above were bromide instead of $(CH_3)_3N$, the major product would involve loss of the alternative β-H and be 2-methyl-2-butene.

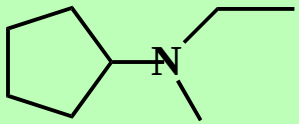


Quiz 20.01

Provide both common and IUPAC names for these amines.



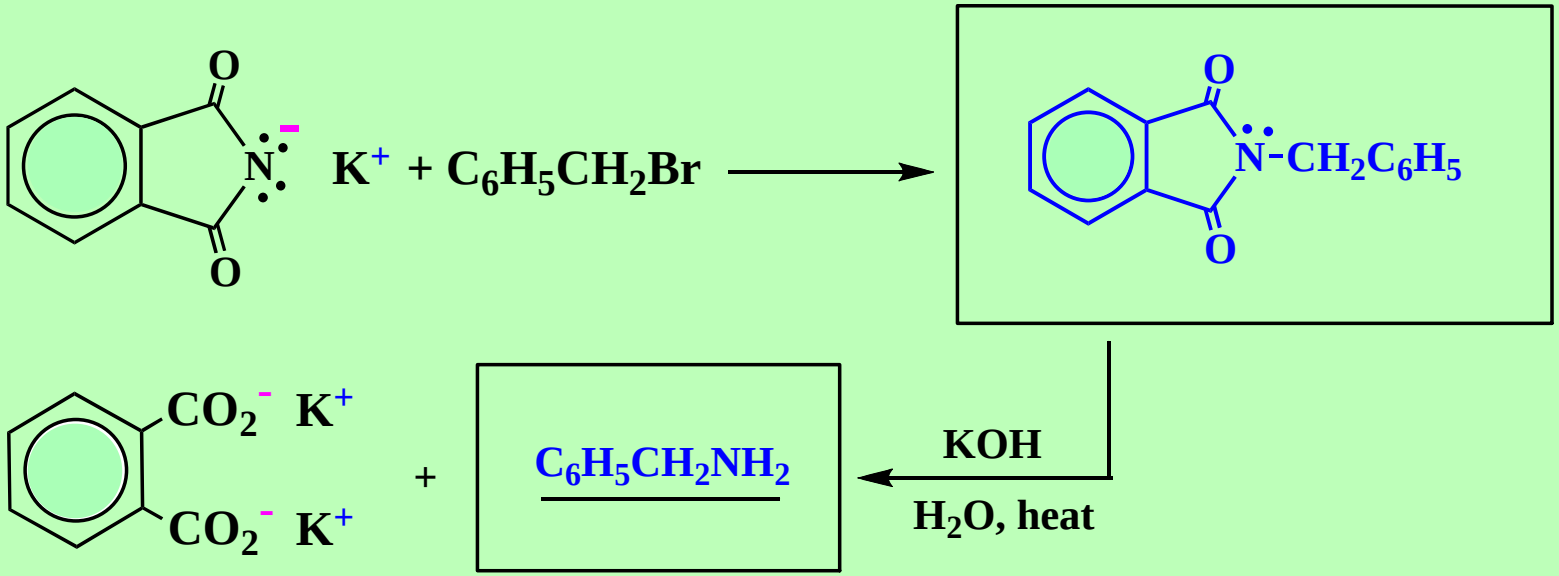
Methylpropylamine
***N*-Methylpropanamine**



Cyclopentylethylmethylamine
***N*-Ethyl-*N*-methylcyclopentanamine**

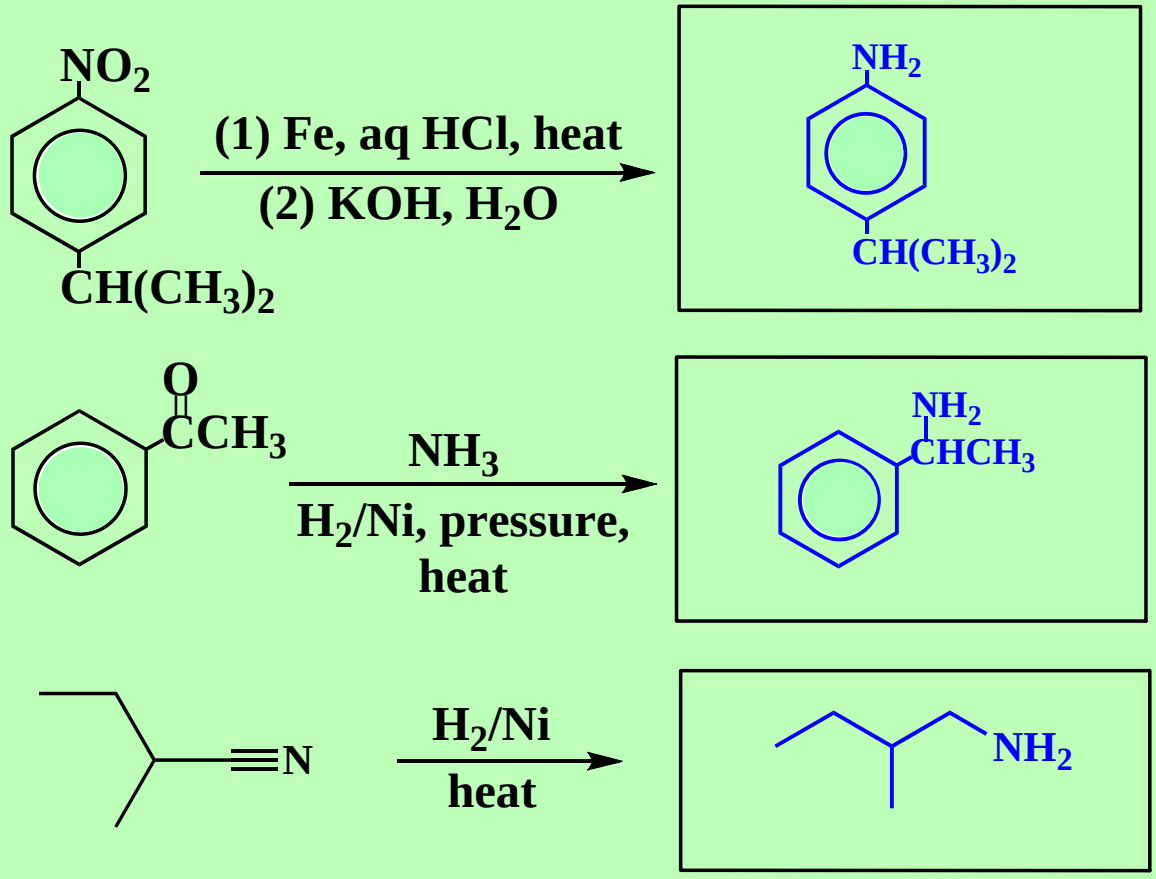
Quiz 20.02

Provide the missing structures in the reaction scheme below.



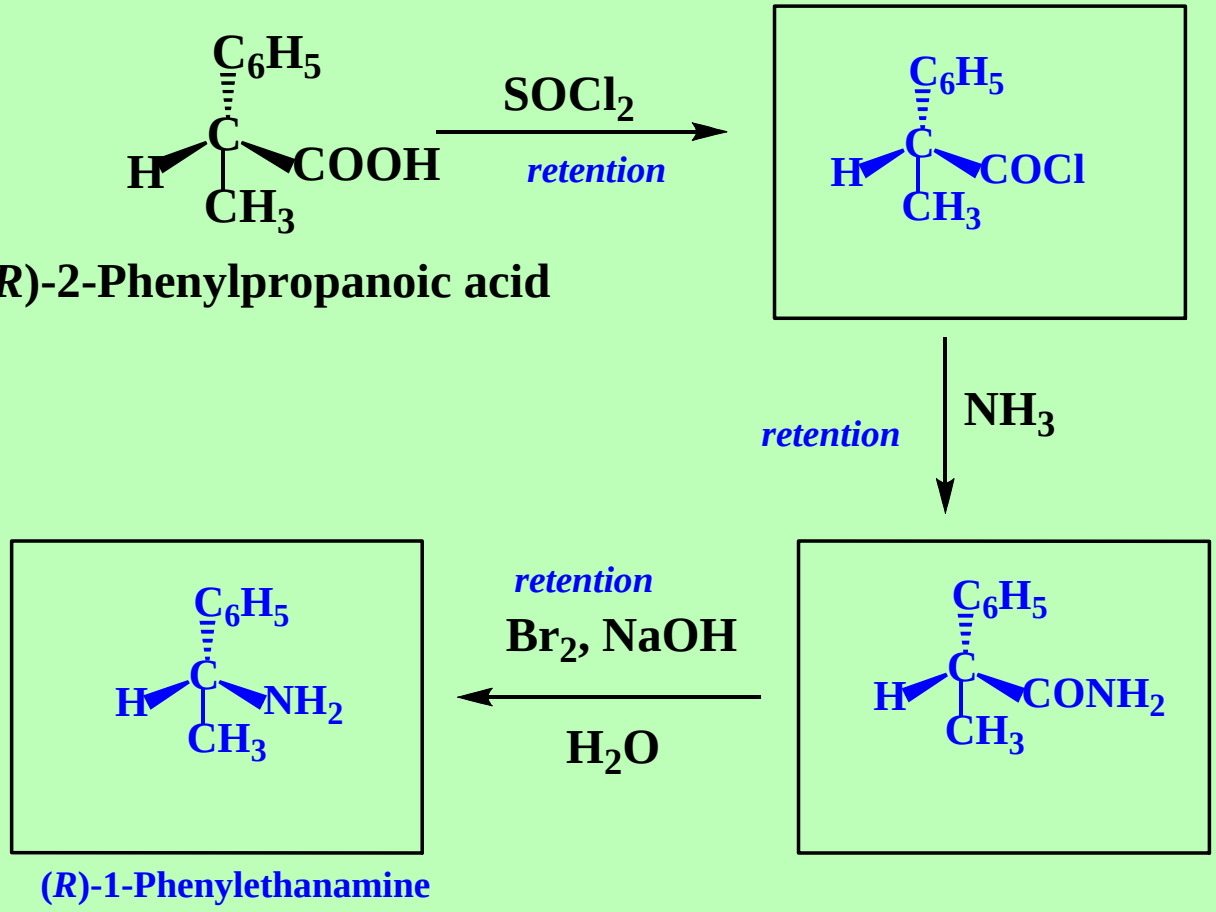
Quiz 20.03

Provide the structures of the products of the following reactions.



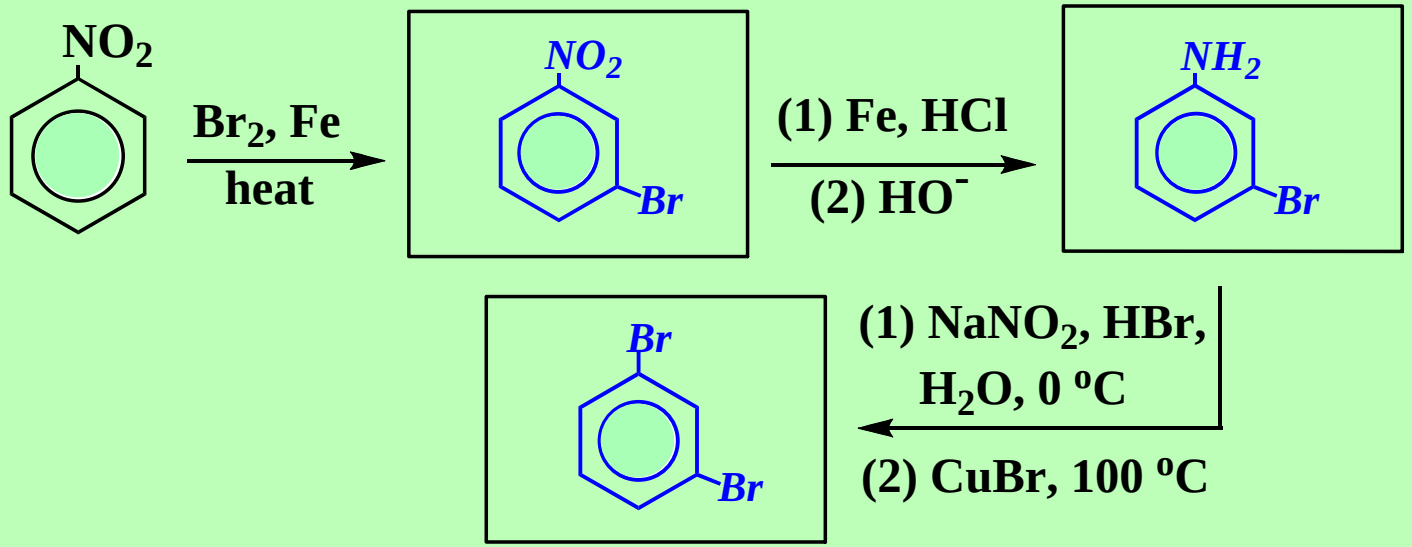
Quiz 20.04

Provide the missing structures in the following scheme.



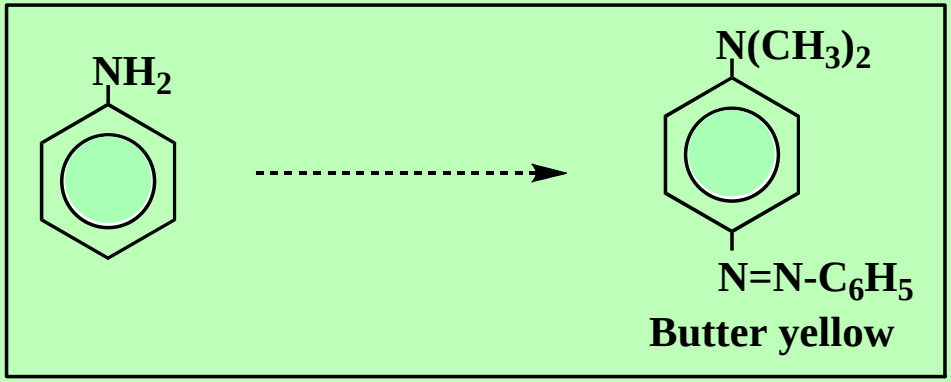
Quiz 20.05

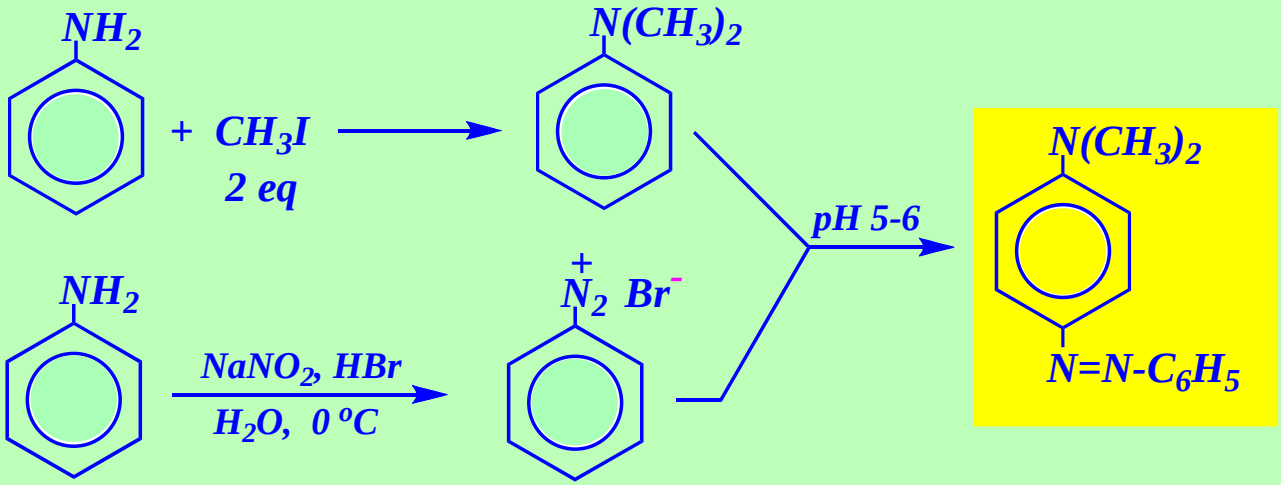
Provide the missing structures in the scheme below.



Quiz 20.06

Design a synthesis of the dye butter yellow from aniline.

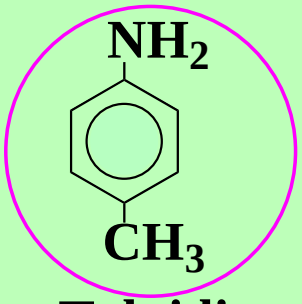




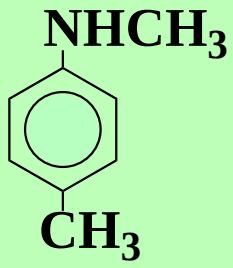
Quiz 20.07

An unknown amine is one of the three compounds below. When the Hinsberg test is run, the unknown amine dissolves completely in the Hinsberg reagent ($C_6H_5SO_2Cl$, KOH, H_2O), but a solid is formed when acid is added and the solution pH is adjusted to 7.

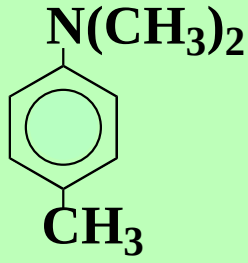
Circle the structure of the unknown amine.



***p*-Toluidine**



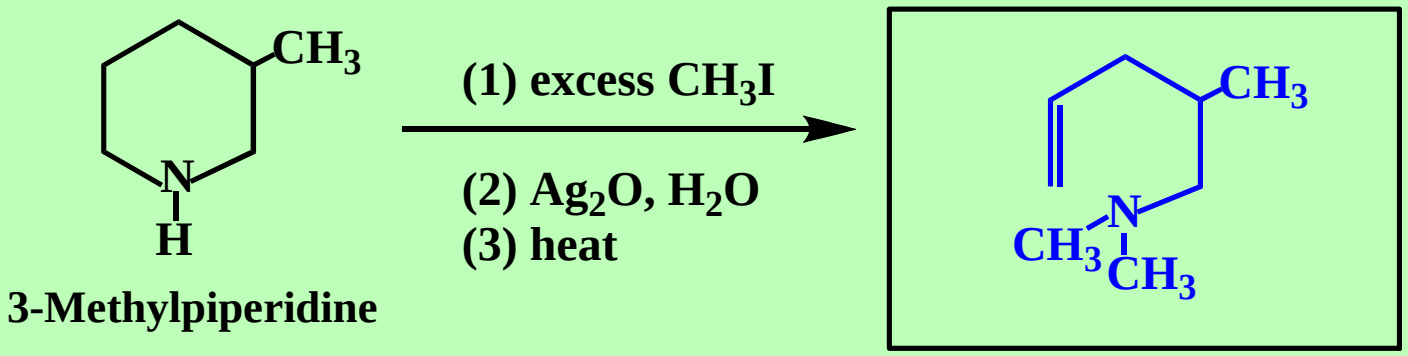
***N*-Methyl-*p*-toluidine**



***N*,*N*-Dimethyl-*p*-toluidine**

Quiz 20.08

Exhaustive methylation of 3-methylpiperidine, followed by treatment with aqueous silver oxide and heating, yields an amine product, $C_8H_{17}N$. What is its structure?



3-Methylpiperidine

$C_8H_{17}N$