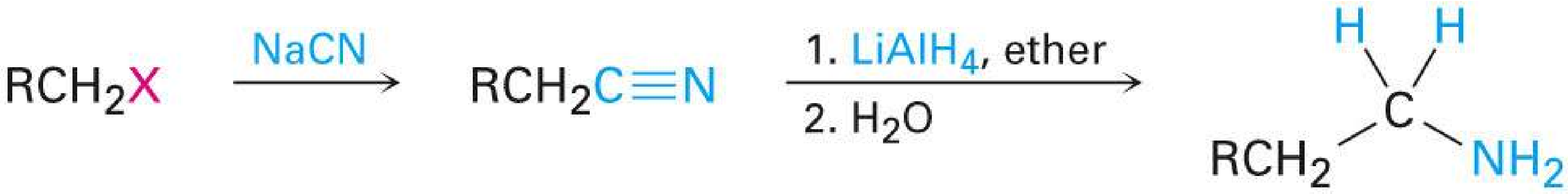
열세번째주

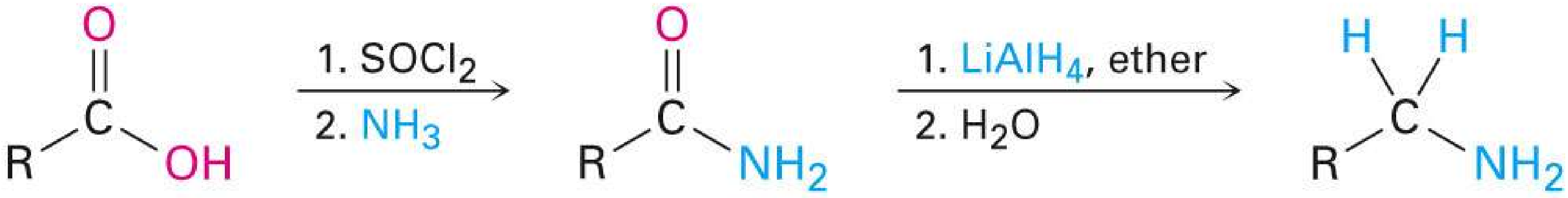
Amines and Heterocycles (2)

Synthesis of Amines



Alkyl halide

1° amine

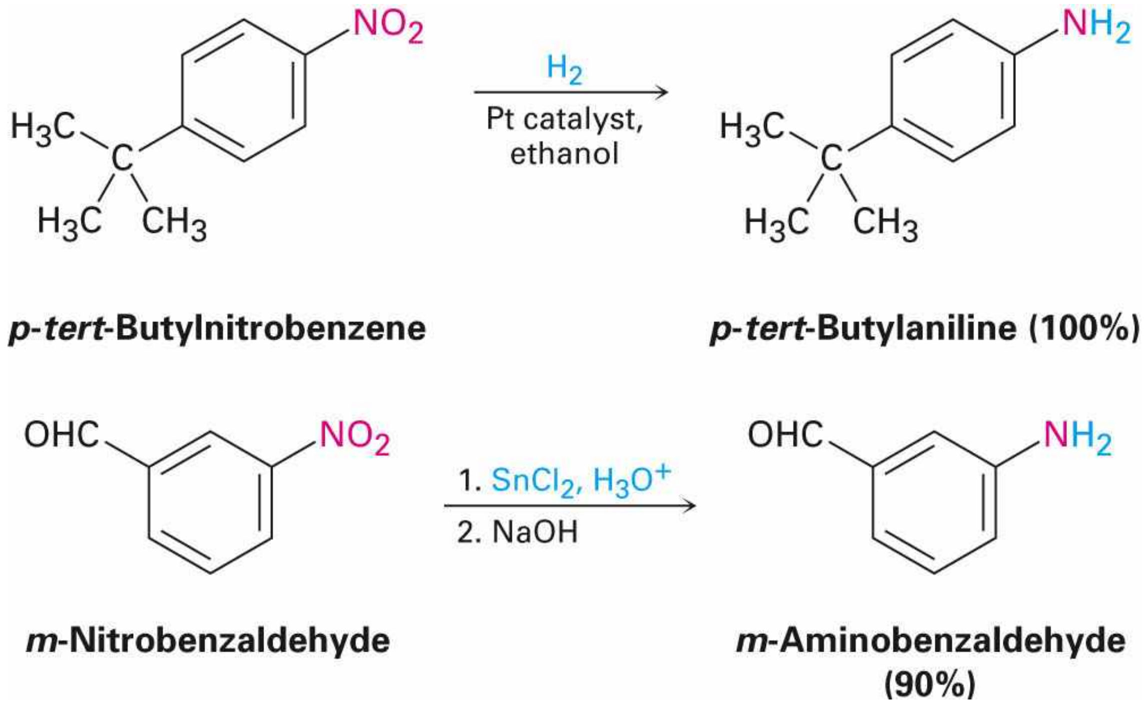


Carboxylic acid

1° amine

Synthesis of Amines

- 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



***p-tert*-Butylnitrobenzene**

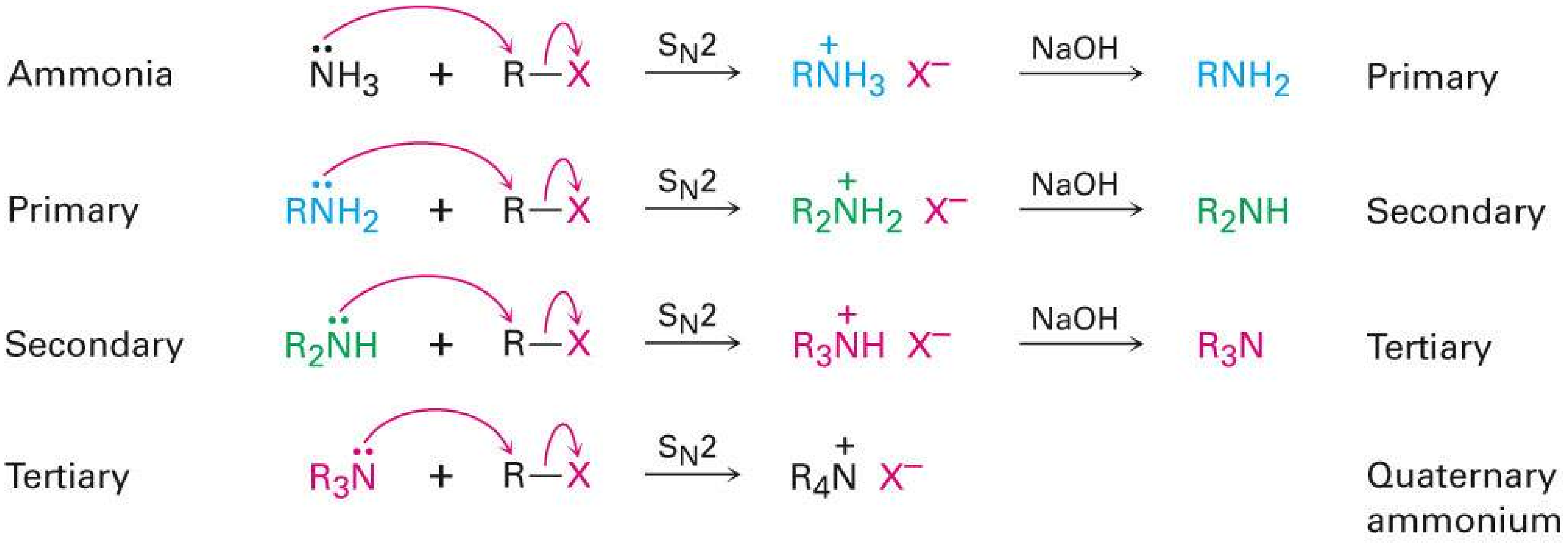
***p-tert*-Butylaniline (100%)**

***m*-Nitrobenzaldehyde**

***m*-Aminobenzaldehyde (90%)**

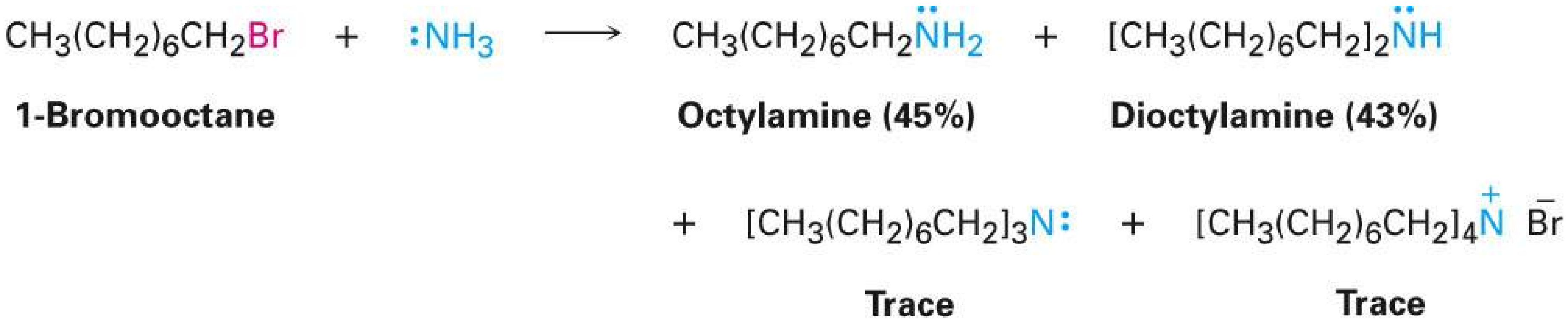
S_N2 Reactions of Alkyl Halides

- Ammonia and other amines are good nucleophiles



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



$$CH_3(CH_2)_6CH_2Br + :NH_3 \longrightarrow CH_3(CH_2)_6CH_2\ddot{N}H_2 + [CH_3(CH_2)_6CH_2]_2\ddot{N}H$$

$$+ [CH_3(CH_2)_6CH_2]_3N: + [CH_3(CH_2)_6CH_2]_4\overset{+}{N}\ \overset{-}{Br}$$

1-Bromooctane

Octylamine (45%)

Dioctylamine (43%)

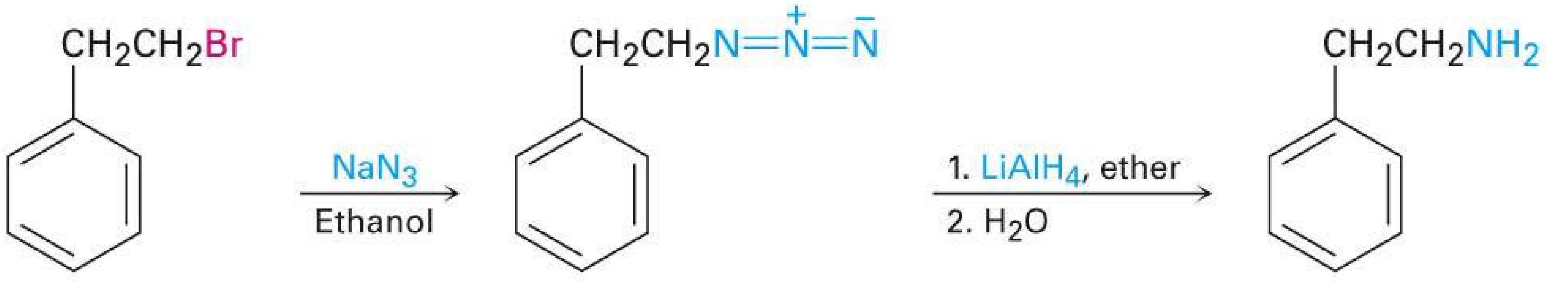
Trace

Trace

Selective Preparation of Primary Amines:

the Azide Synthesis

- Azide ion, N_3^- displaces a halide ion from a primary or secondary alkyl halide to give an alkyl azide, RN_3
- Alkyl azides are not nucleophilic (but they are explosive)
- Reduction gives the primary amine



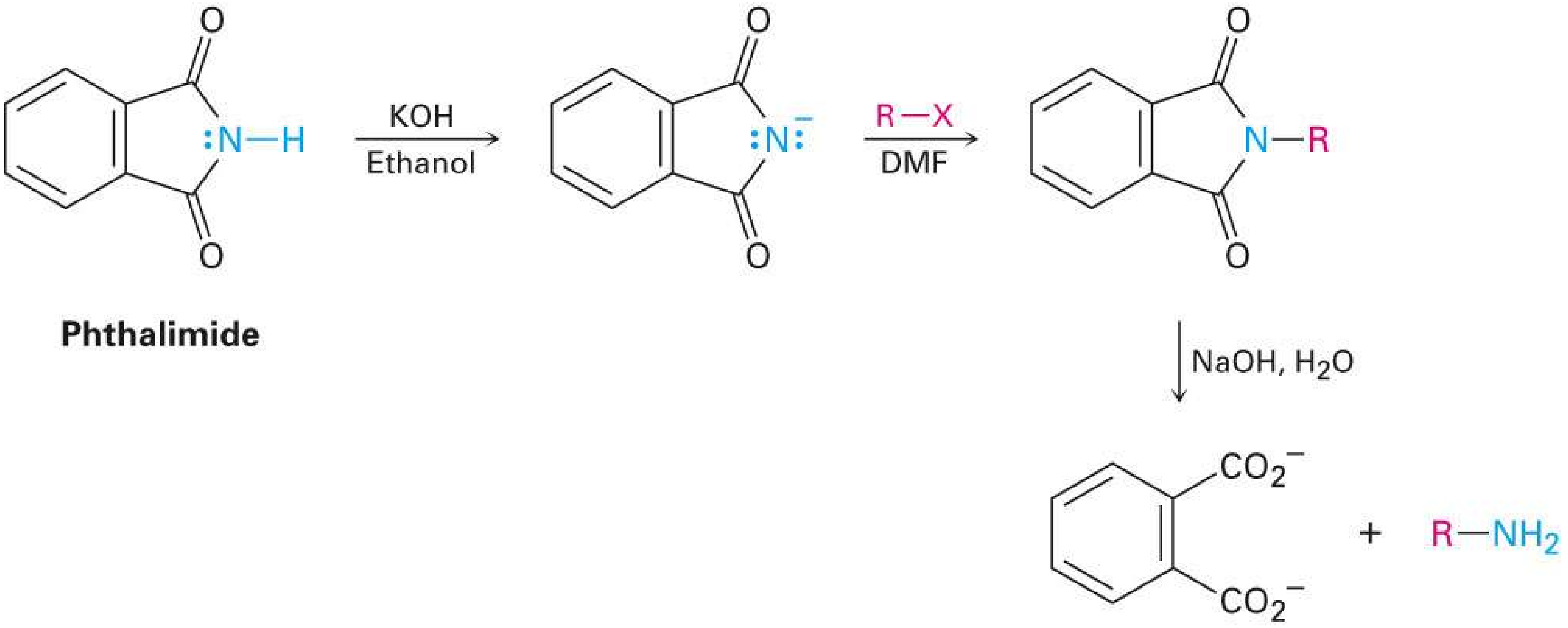
1-Bromo-2-phenylethane

2-Phenylethyl azide

2-Phenylethylamine (89%)

Gabriel Synthesis of Primary Amines

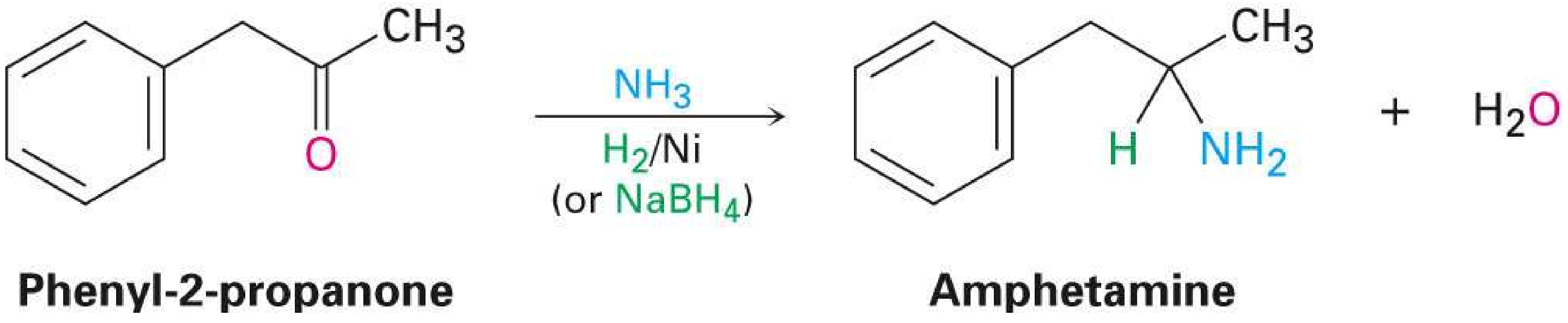
- A *phthalimide* alkylation for preparing a primary amine from an alkyl halid e
- The N-H in imides (—CONHCO—) can be removed by KOH followed by alkylation and hydrolysis



Phthalimide

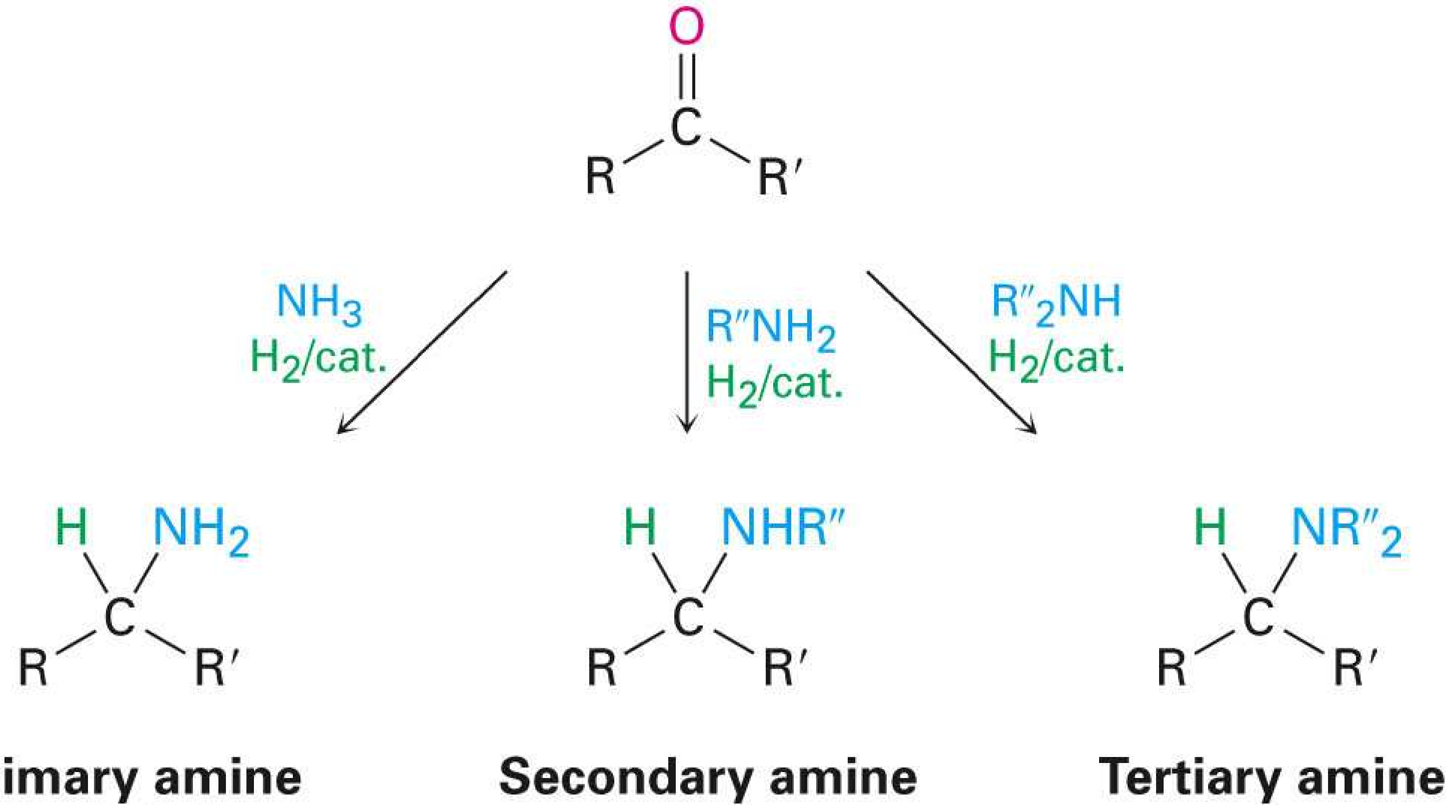
Reductive Amination of Aldehydes and Ketones

- 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

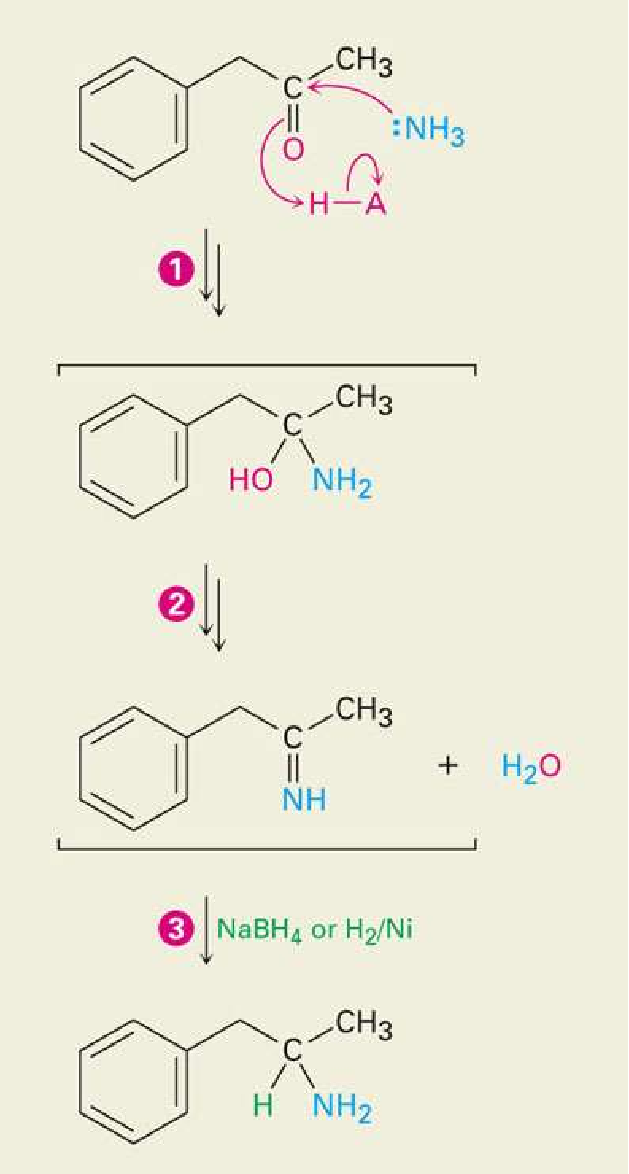


Mechanism of Reductive Amination

1. Ammonia adds to the ketone carbonyl group in a nucleophilic addition reaction to yield an intermediate carbinolamine.

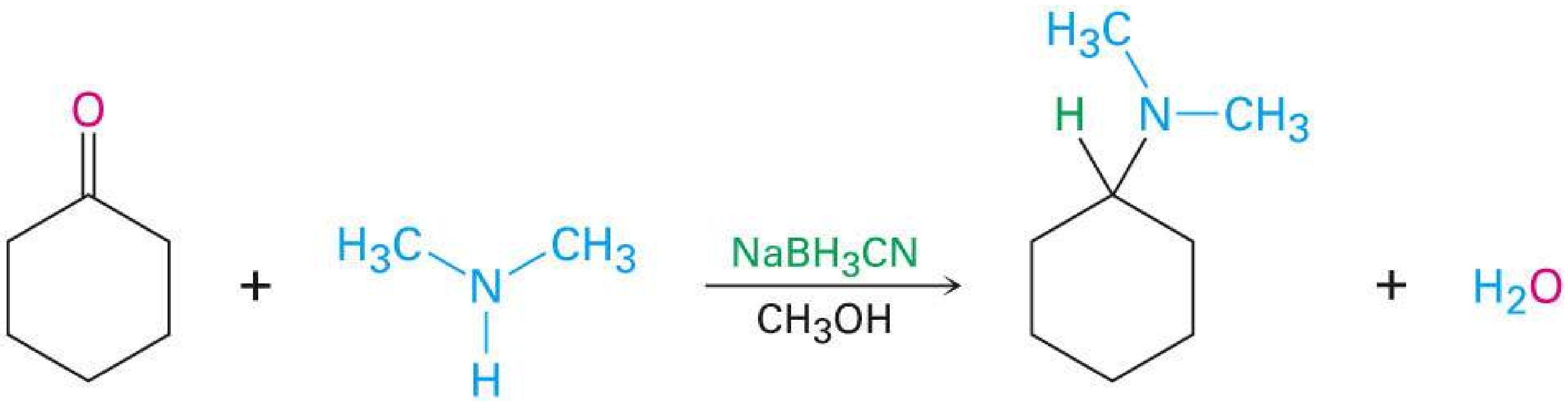
2. The carbinolamine loses water to give an imine.

3. The imine is reduced by NaBH4 or H2/Ni to yield the amine product.



Reducing Step

- Sodium cyanoborohydride, $NaBH_3CN$, reduces C=N but not C=O
- Stable in water



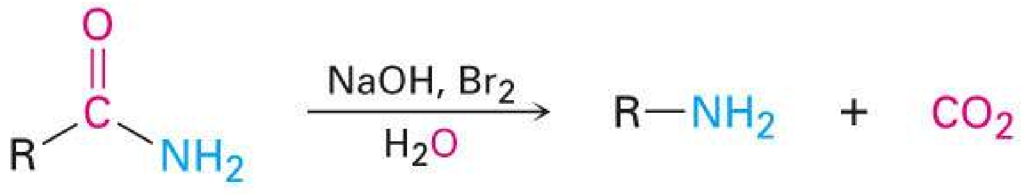
Cyclohexanone

***N,N*-Dimethylcyclohexylamine (85%)**

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

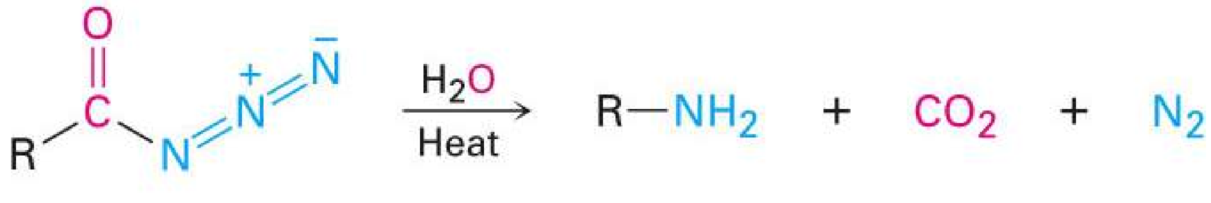
Hofmann rearrangement



An amide

- $RCONH_2$ reacts with Br_2 and base
- Gives high yields of arylamines and alkylamines

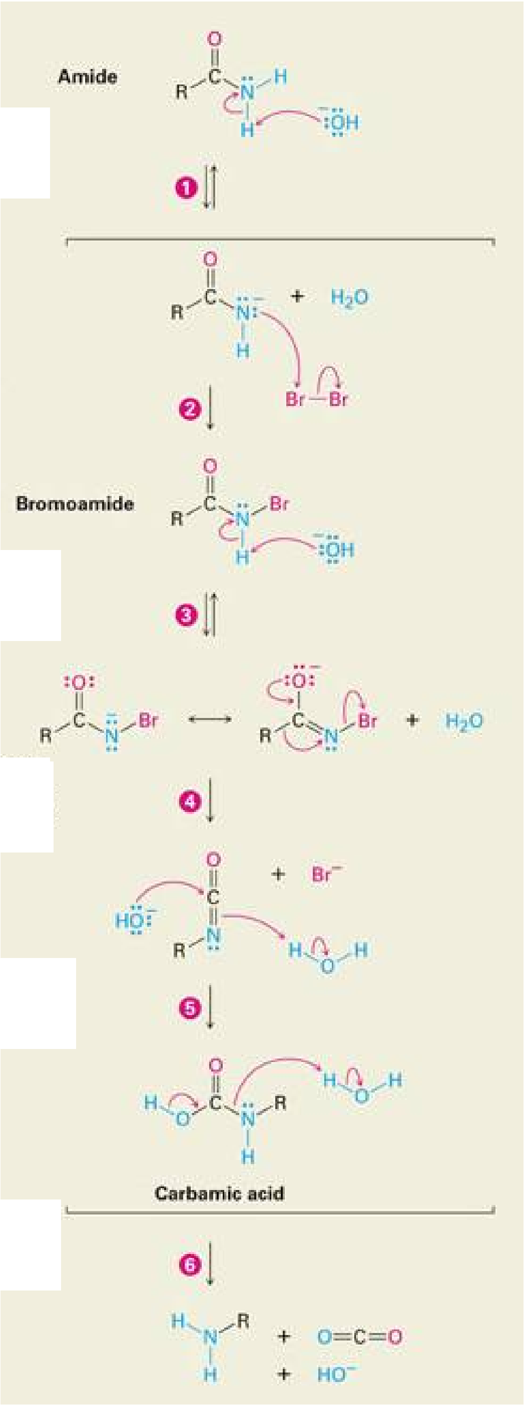
Curtius rearrangement



An acyl azide

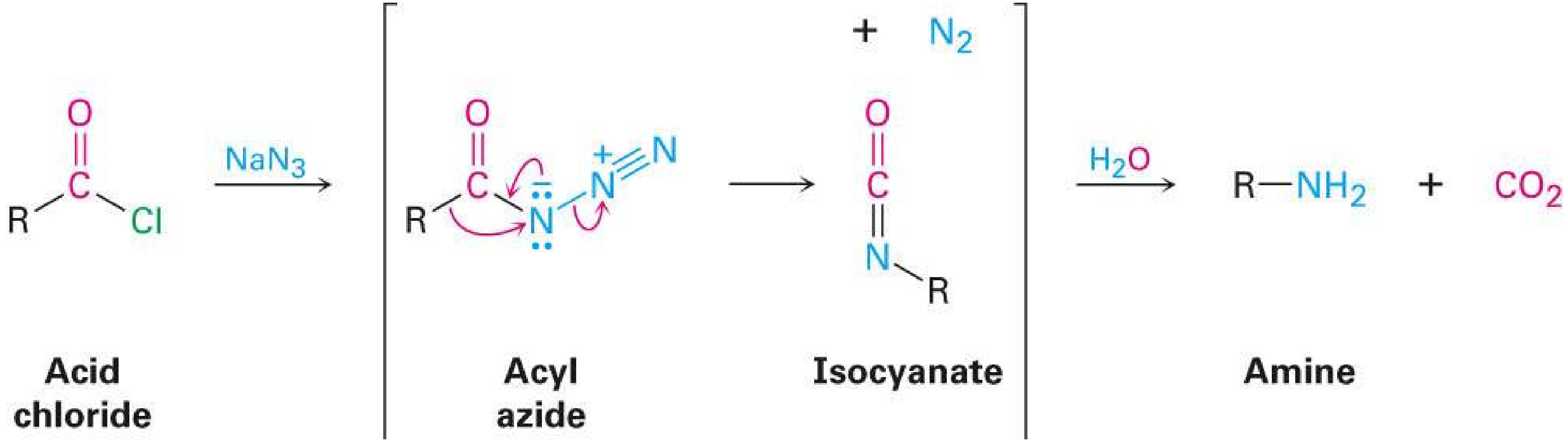
Hofmann Rearrangement

1. Base abstracts an acidic N-H proton, yielding an amide anion.
2. The anion reacts with bromine in an α-substituted reaction to give an N-bromoamide.
3. Abstraction of the remaining N-H proton by base gives a resonance-stabilized bromoamide anion…
4. … which rearranges when the R group attached to the carbonyl carbon migrates to nitrogen at the same time the bromide ion leaves.
5. The isocyanate formed on rearrangemnet adds water in a nucleophilic addition step to yield a carbamic acid.
6. The carbamic acid spontaneously loses CO2 to give an amine.



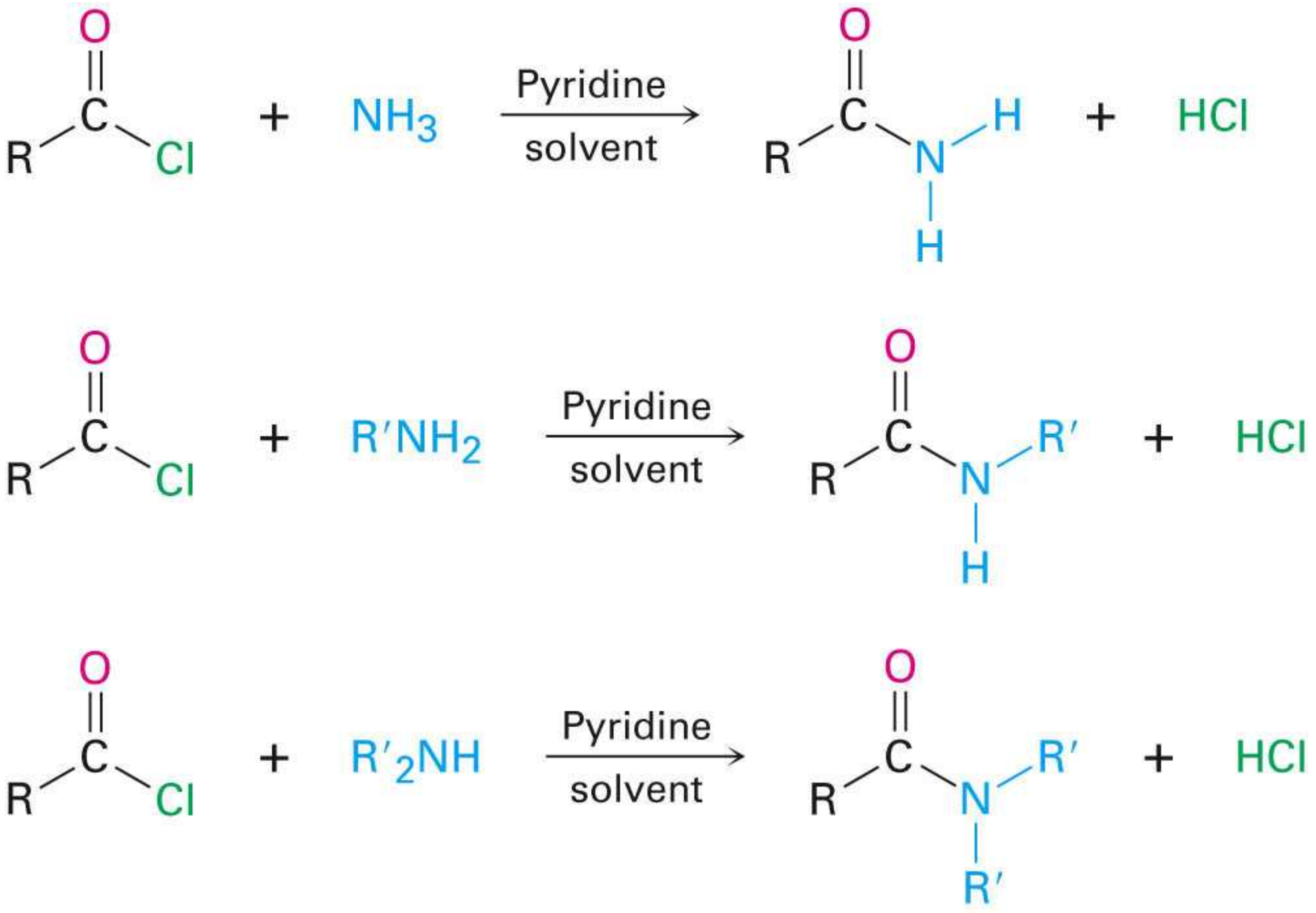
Curtius Rearrangement

- Heating an acyl azide prepared from an acid chloride
- Migration of —R from C=O to the neighboring nitrogen with simu ltaneous loss of a leaving group



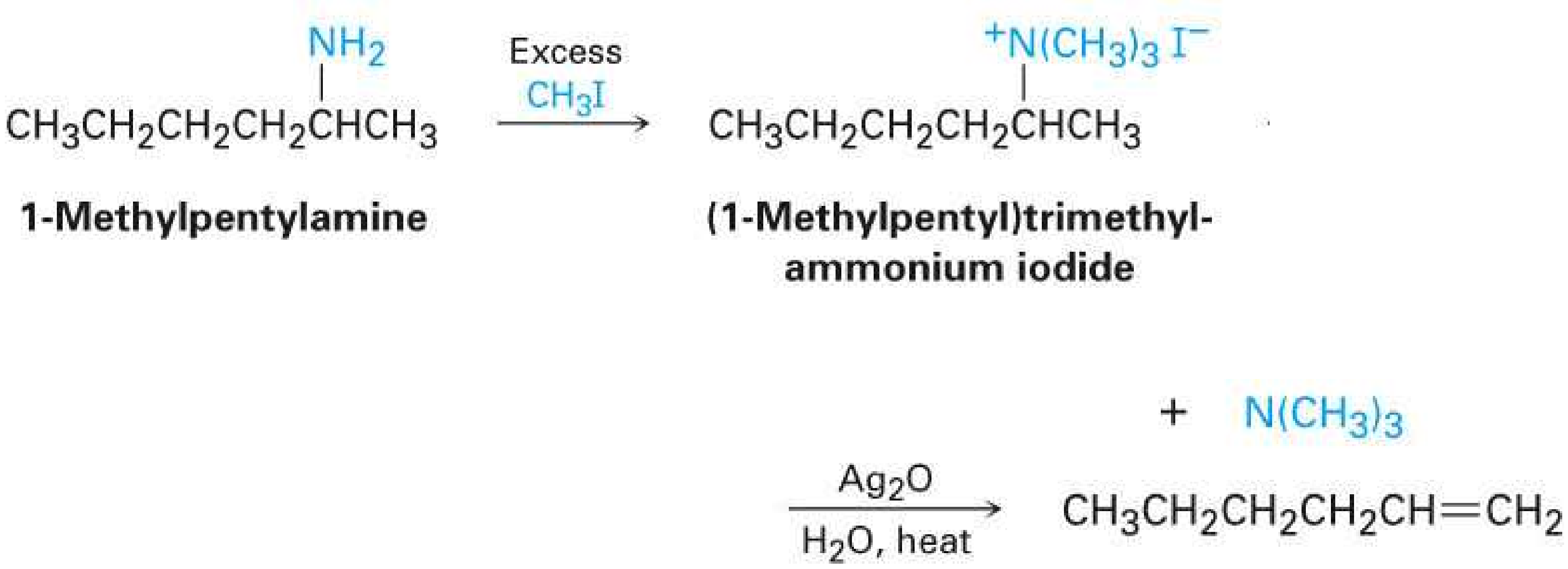
Reactions of Amines

- Alkylation and acylation have already been presented



Hofmann Elimination

- Converts amines into alkenes
- NH_2^- is very a poor leaving group so it converted to an alkylammonium ion, which is a good leaving group



$$CH_3CH_2CH_2CH_2\overset{NH_2}{C}HCH_3 \xrightarrow[]{\text{Excess } CH_3I} CH_3CH_2CH_2CH_2\overset{^+N(CH_3)_3\ I^-}{C}HCH_3$$

1-Methylpentylamine

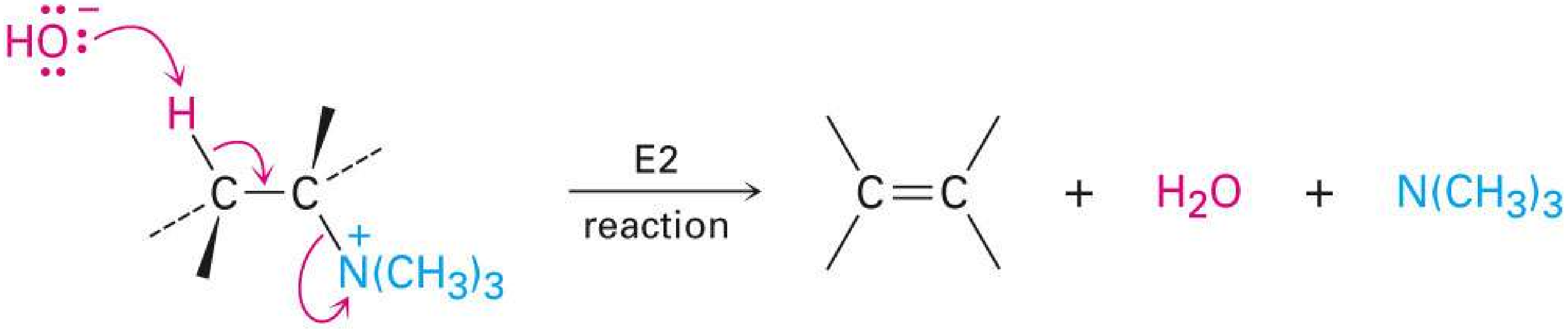
(1-Methylpentyl)trimethylammonium iodide

$$\xrightarrow[H_2O,\ \text{heat}]{Ag_2O} CH_3CH_2CH_2CH_2CH{=}CH_2 + N(CH_3)_3$$

1-Hexene (60%)

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



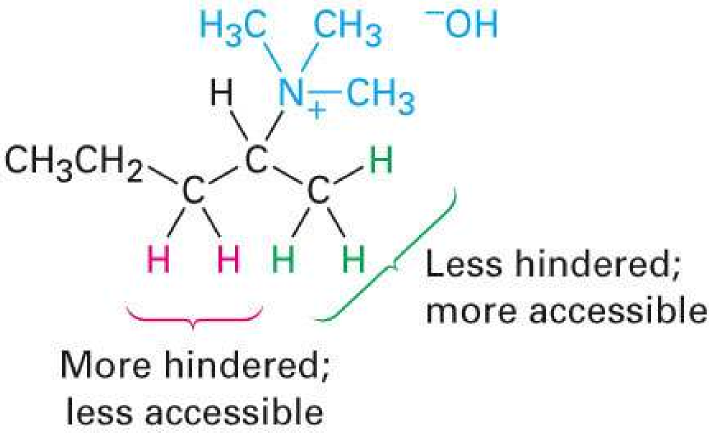
Quaternary ammonium salt

Alkene

Orientation in Hofmann Elimination

- 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**

Steric Effects Control the Orientation



(1-Methylbutyl)trimethylammonium hydroxide

$$\downarrow$$

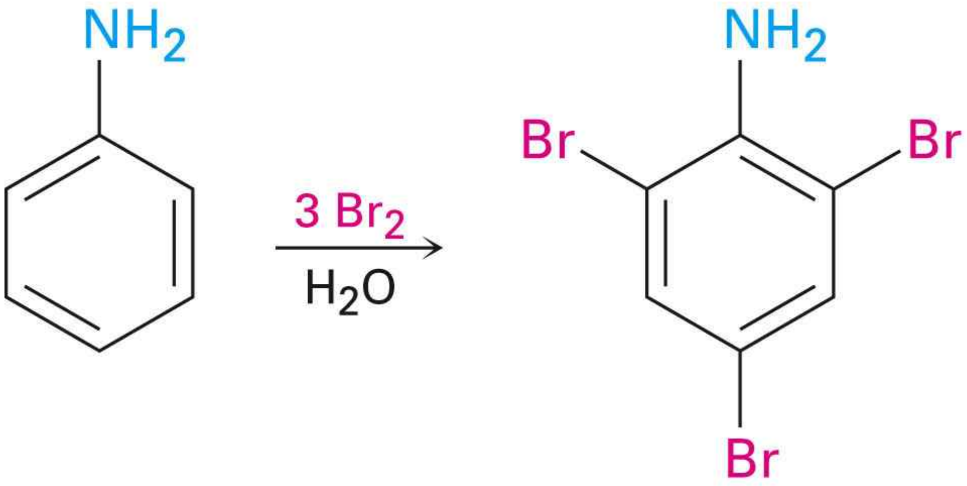
$CH_3CH_2CH_2CH{=}CH_2$ + $CH_3CH_2CH{=}CHCH_3$

1-Pentene
(94%)

2-Pentene
(6%)

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

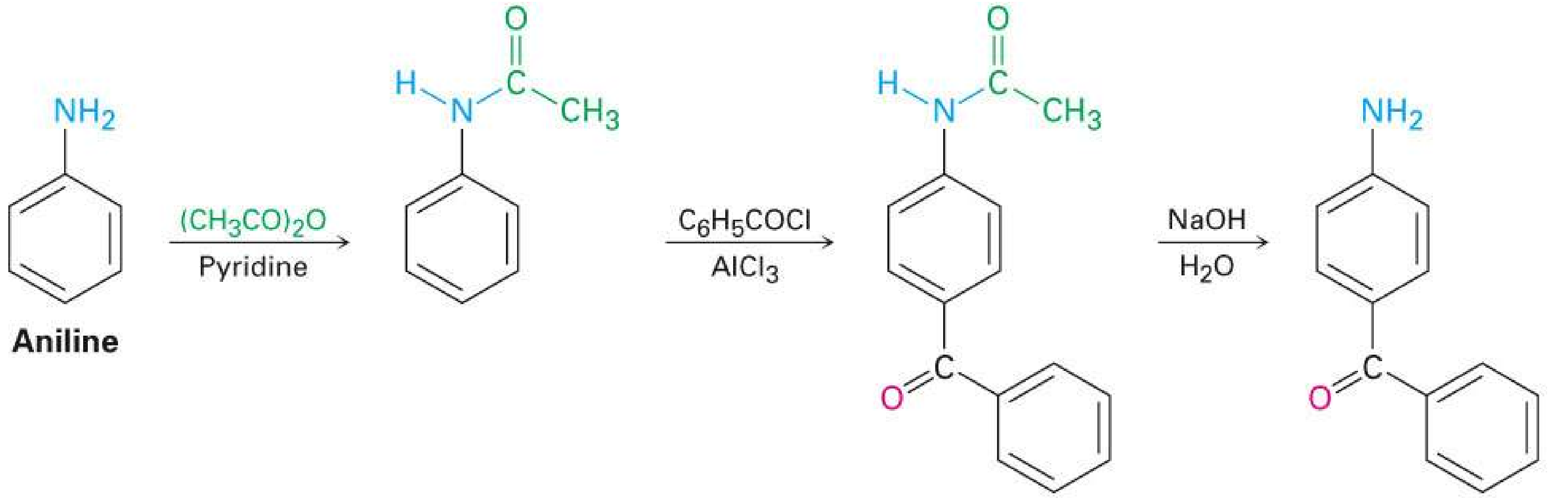


Aniline

2,4,6-Tribromoaniline (100%)

Arylamines Are Not Useful for Friedel-Crafts Reactions

- The amino group forms a Lewis acid–base complex with the $AlCl_3$ catalyst, preventing further reaction
- Therefore we use the corresponding amide

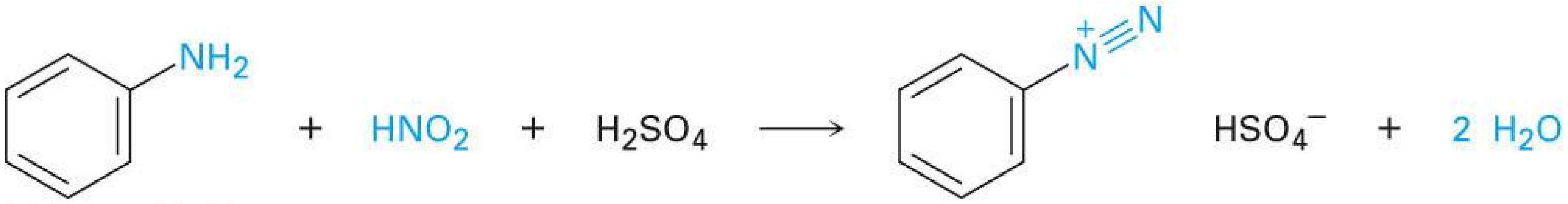


Aniline

4-Aminobenzophenone (80%)

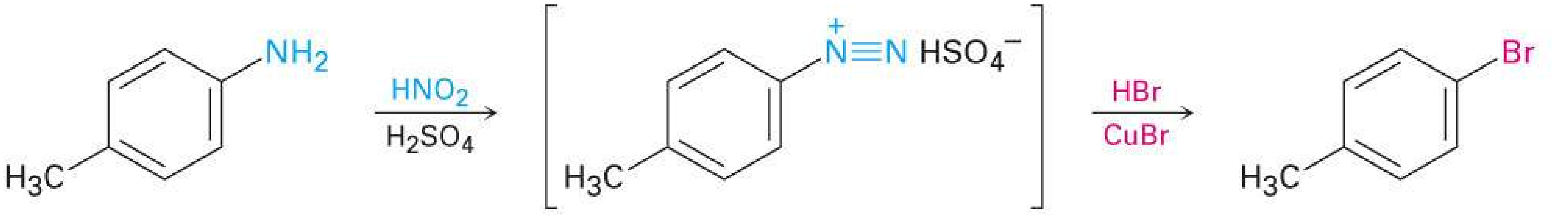
Diazonium Salts: The Sandmeyer Reaction

- Primary arylamines react with HNO_2, yielding stable arenediazonium salts



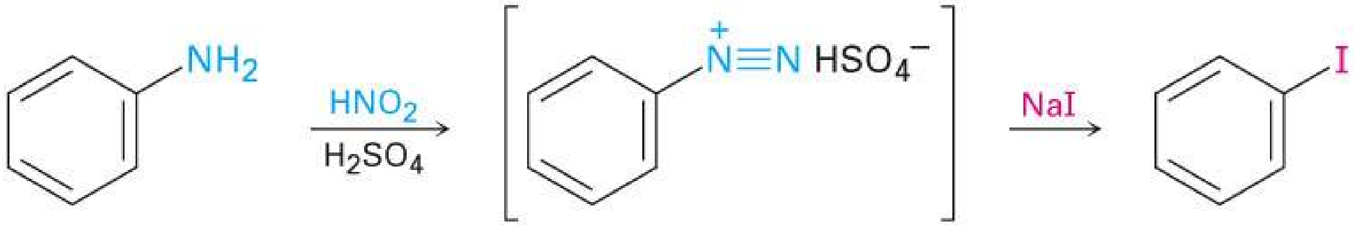
Uses of Arenediazonium Salts

- The N_2 group can be replaced by a nucleophile



p-Methylaniline

p-Bromotoluene (73%)

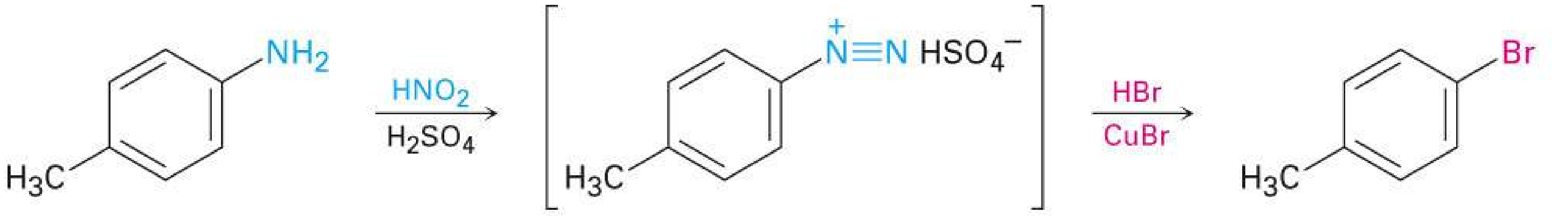


Aniline

Iodobenzene (67%)

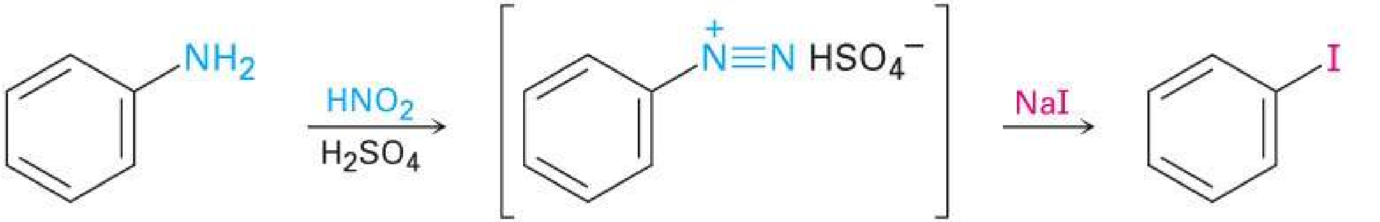
Preparation of Aryl Halides

- 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



p-Methylaniline

p-Bromotoluene (73%)

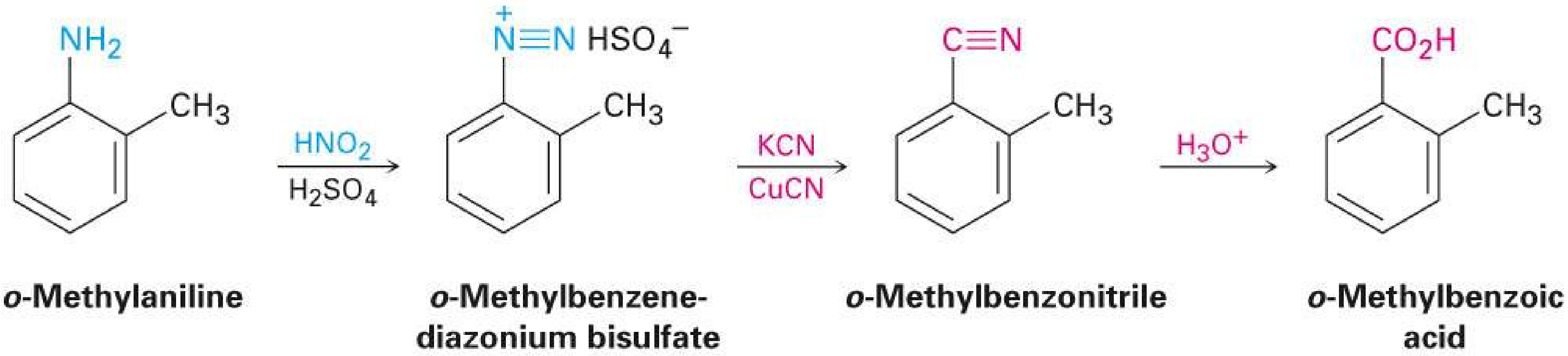


Aniline

Iodobenzene (67%)

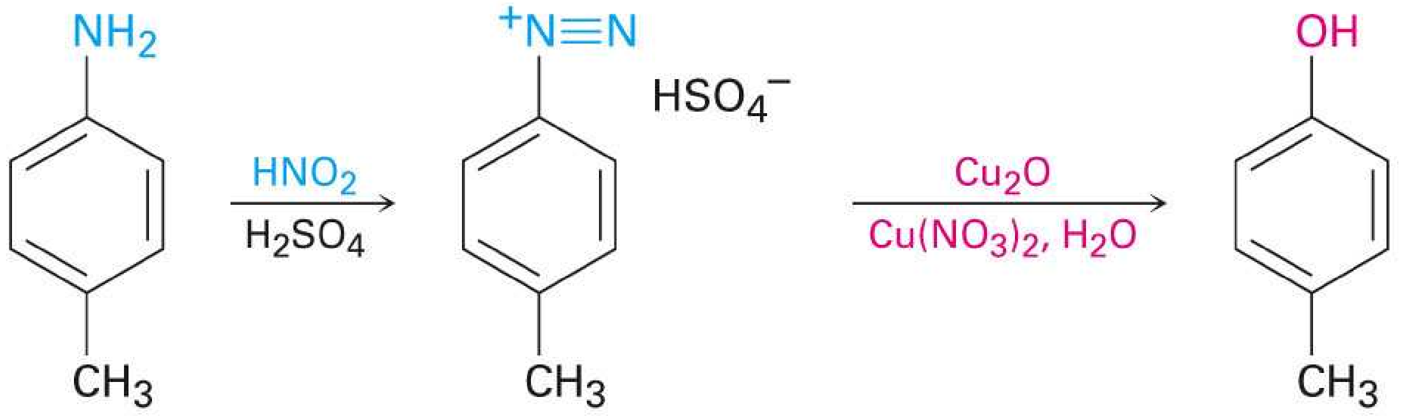
Aryl Nitriles and Carboxylic Acids

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



Formation of Phenols (ArOH)

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

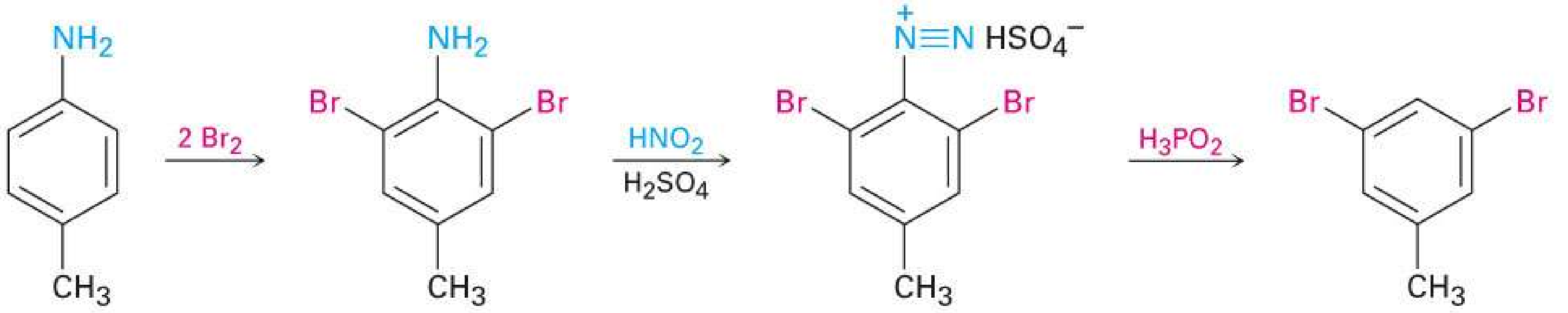


***p*-Methylaniline**
(*p*-Toluidine)

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

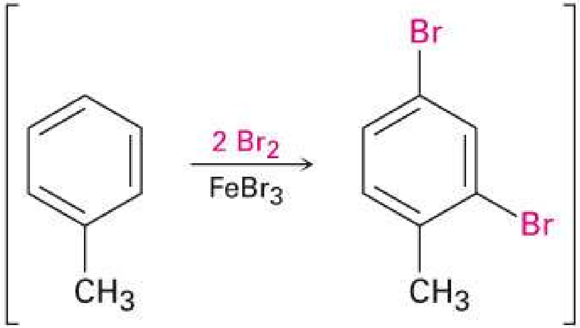
Reduction to a Hydrocarbon

- By treatment of a diazonium salt with hypophosphorous acid, H_3PO_2



p-Methylaniline

3,5-Dibromotoluene

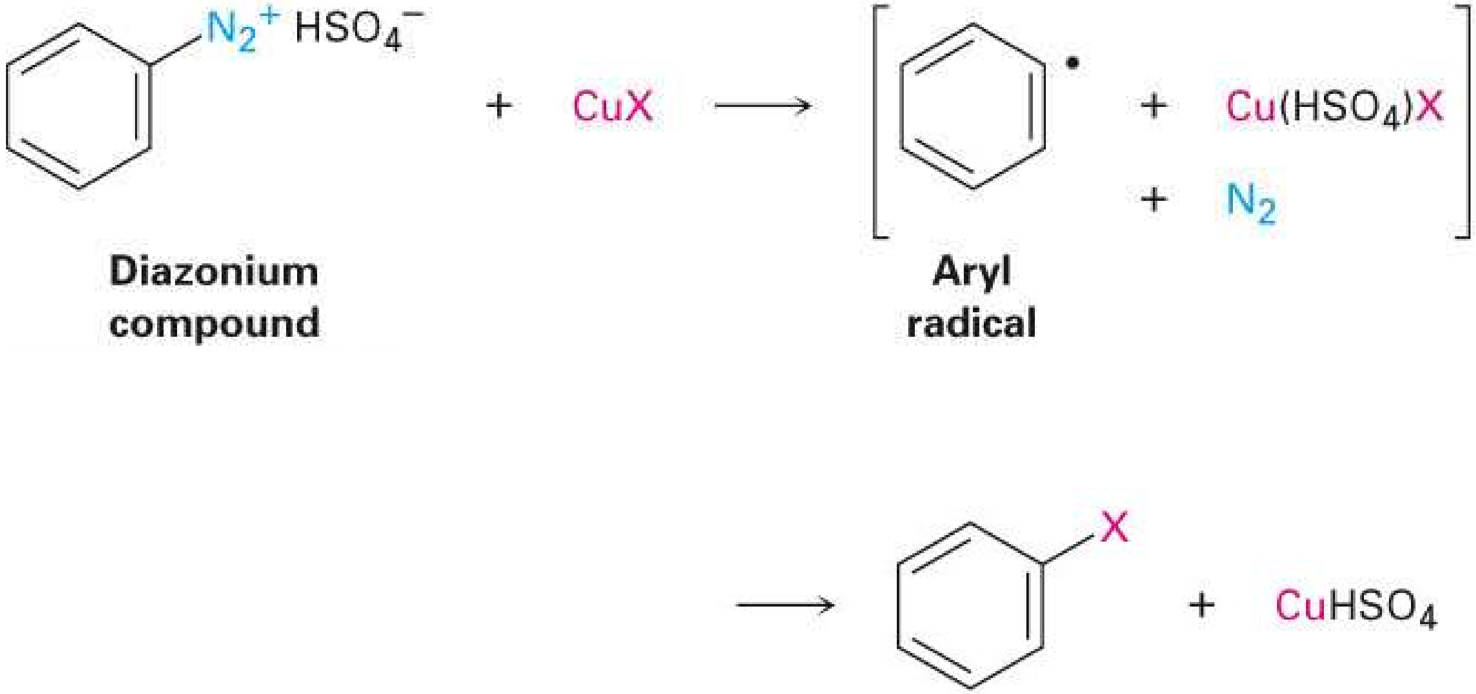


Toluene

2,4-Dibromotoluene

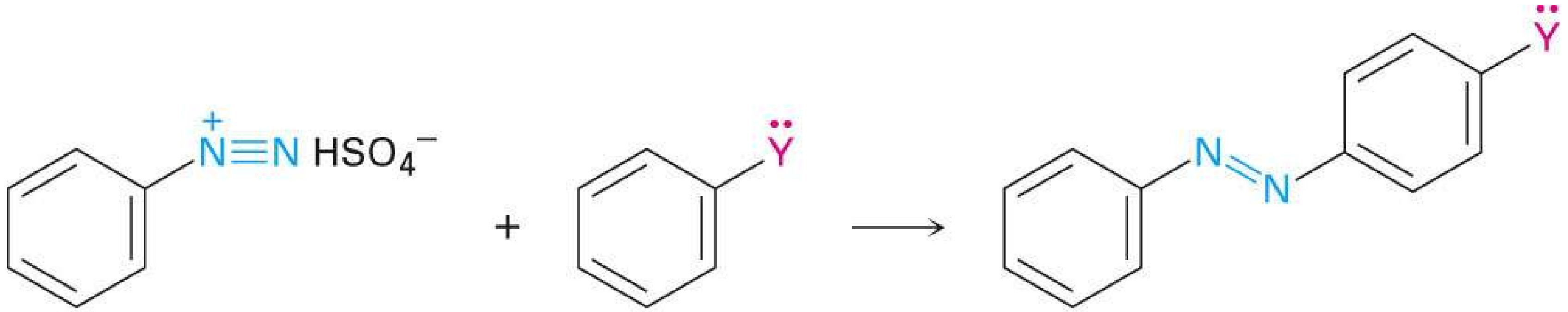
Mechanism of Diazonium Replacement

- Through radical (rather than polar or ionic) pathways



Diazonium Coupling Reactions

- Arenediazonium salts undergo a coupling reaction with activated aromatic rings, such as phenols and arylamines, to yield brightly colored azo compounds, Ar—N=N—Ar′

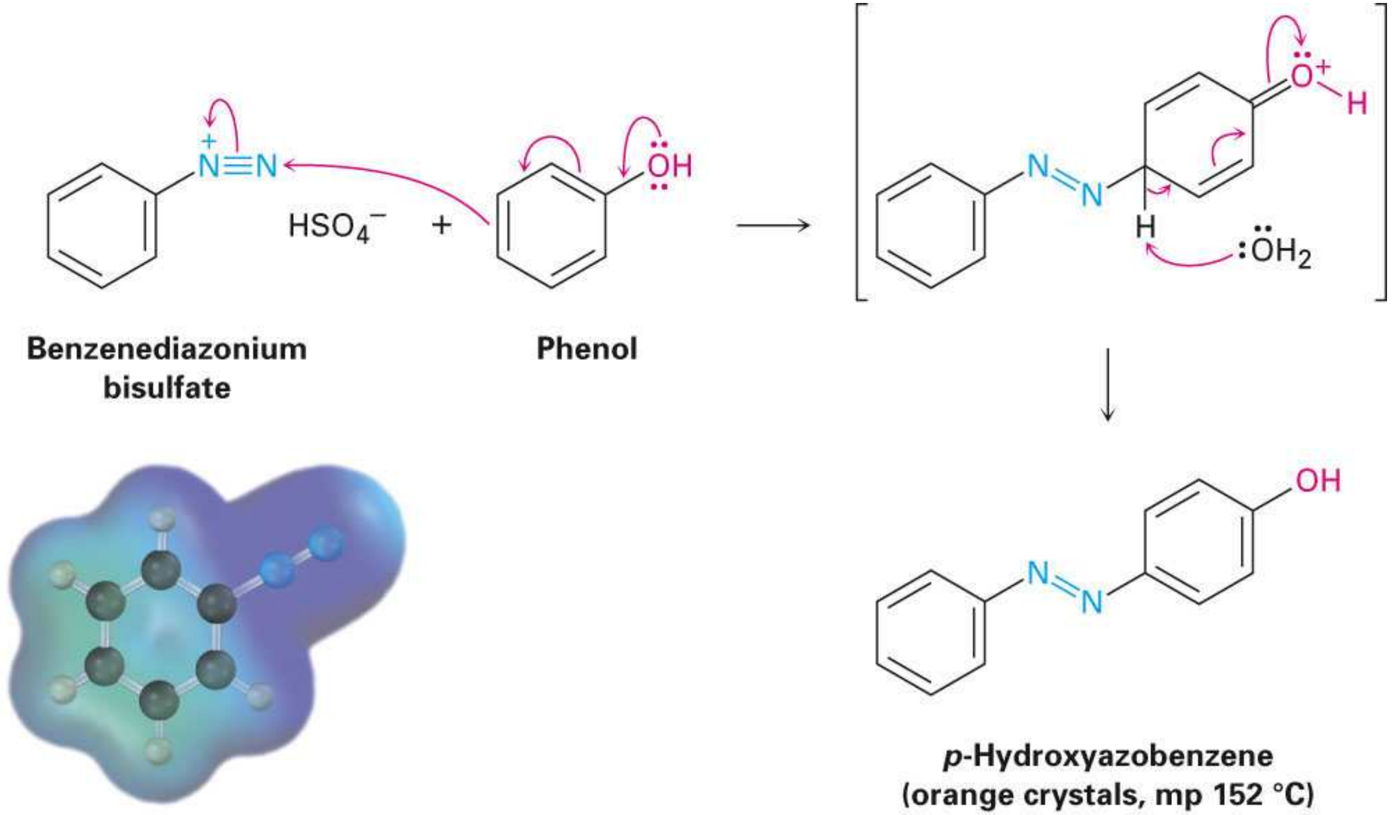


An azo compound

where Y = $-OH$ or $-NR_2$

How Diazonium Coupling Occurs

- The electrophilic diazonium ion reacts with the electron-rich ring of a phenol or arylamine
- Usually occurs at the para position but goes ortho if para is blocked



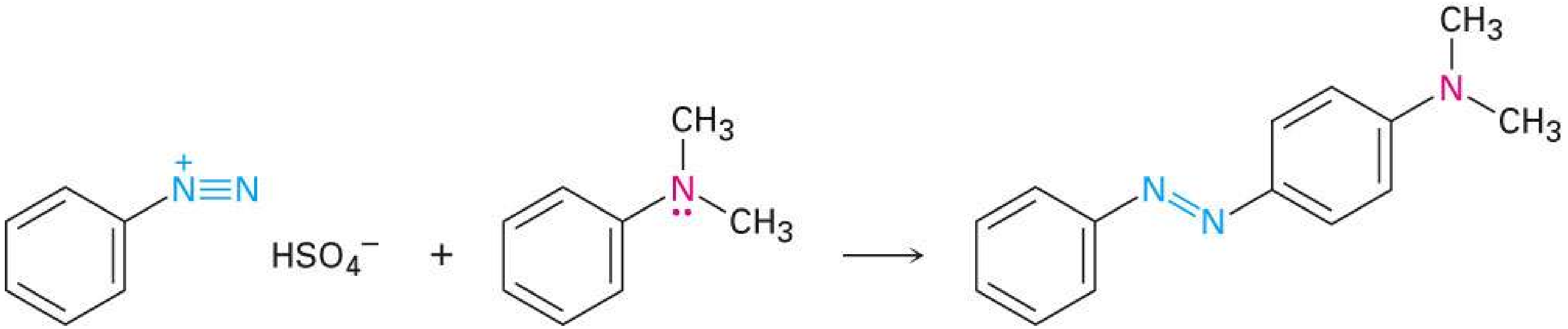
Benzenediazonium bisulfate

Phenol

***p*-Hydroxyazobenzene (orange crystals, mp 152 °C)**

Azo Dyes

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



Benzenediazonium bisulfate

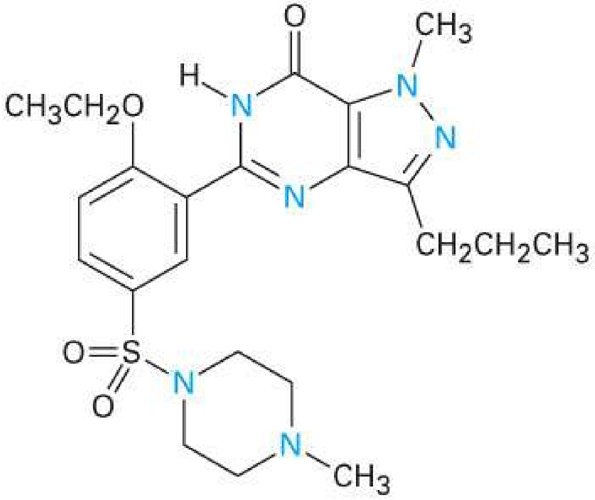
***N,N*-Dimethylaniline**

***p*-(Dimethylamino)azobenzene (yellow crystals, mp 127 °C)**

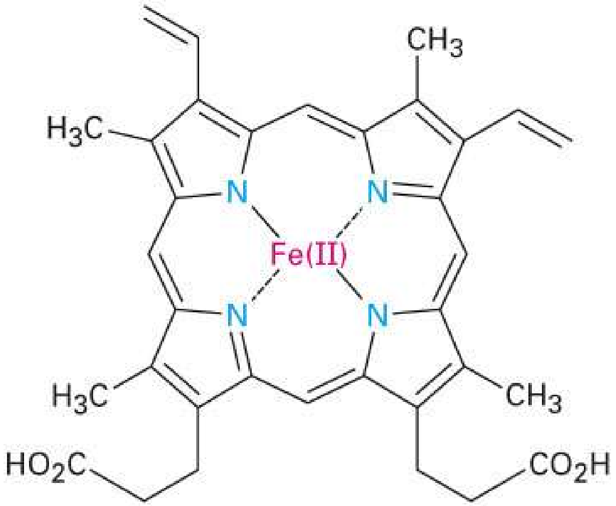
Heterocycles

- A heterocycle is a cyclic compound that contains atoms of two or more elements in its ring, usually C along with N, O, or S

Pyridoxal phosphate
(a coenzyme)



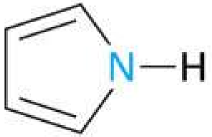
Sildenafil
(Viagra)



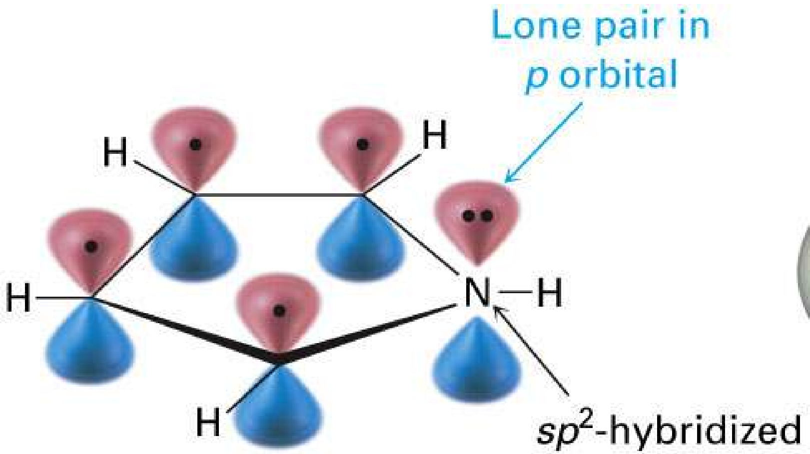
Heme

Pyrole and Imidazole

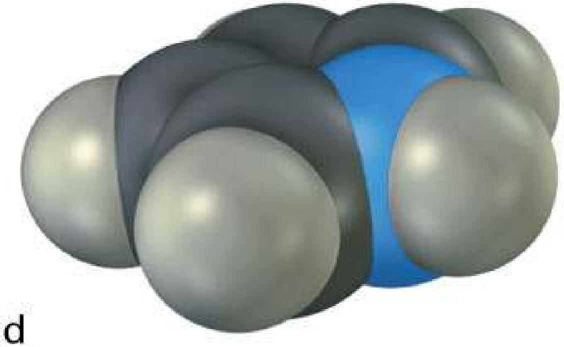
- Pyrole is an amine and a conjugated diene, however its chemical properties are not consistent with either of structural features



Pyrrole

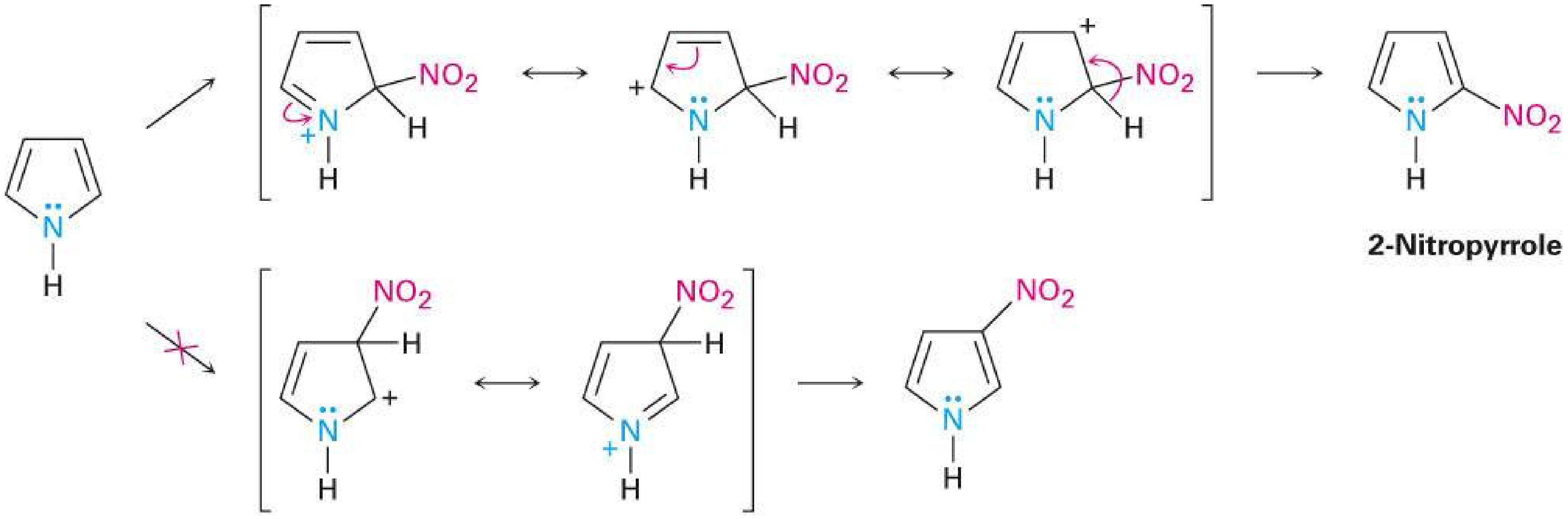


Six π electrons



Chemistry of Pyrrole

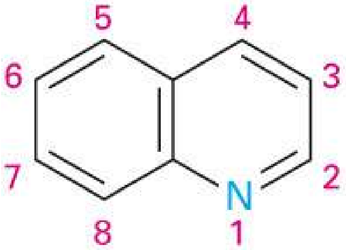
- Electrophilic substitution reactions occur at C2 b/c it is position next to the N
- A more stable intermediate cation having 3 resonance forms
- At C3, only 2 resonance forms



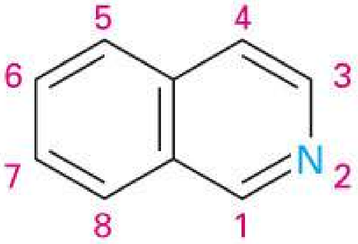
2-Nitropyrrole

3-Nitropyrrole
(NOT formed)

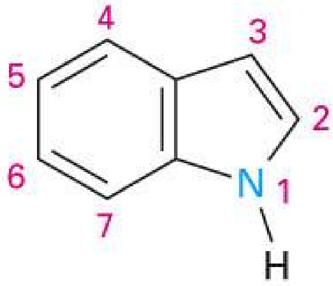
Polycyclic Heterocycles



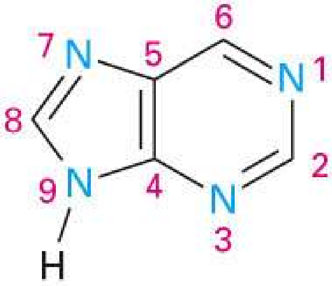
Quinoline



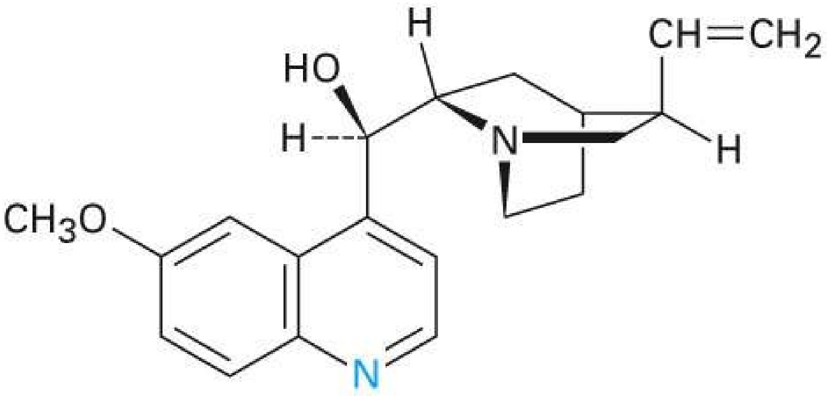
Isoquinoline



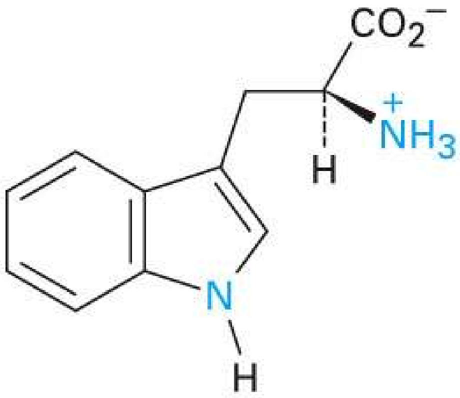
Indole



Purine



Quinine
(antimalarial)



Tryptophan
(amino acid)

Adenine
(DNA constituent)