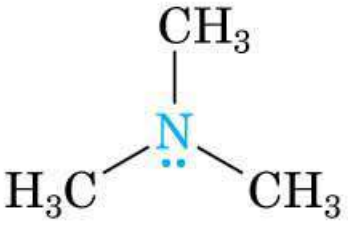
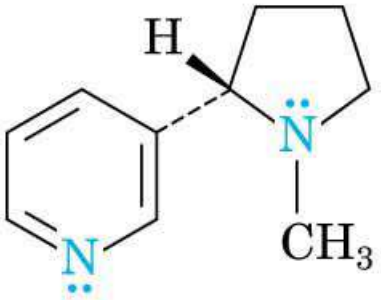
Amines & Phenols

Part 1

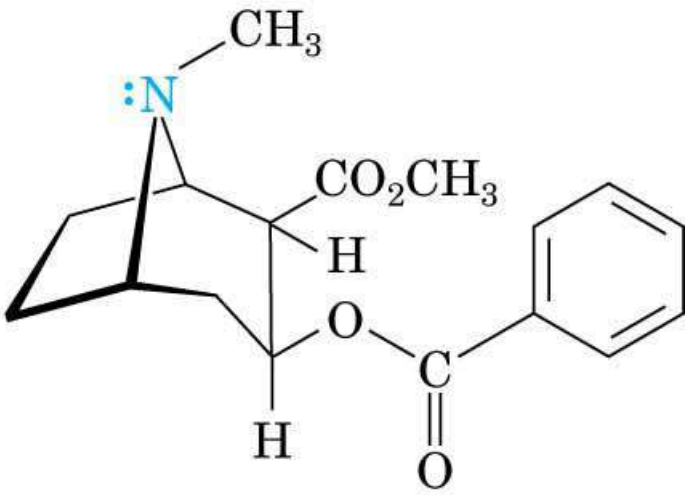
Amines – Organic Nitrogen Compounds



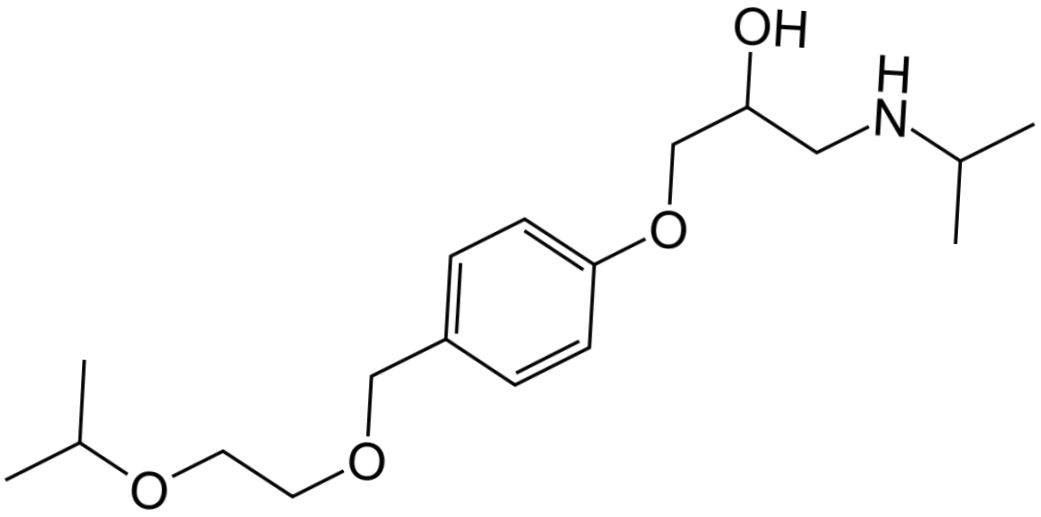
Trimethylamine



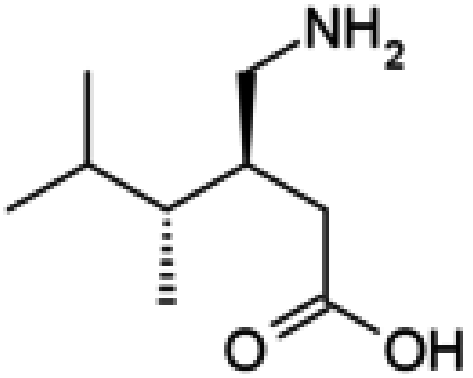
Nicotine



Cocaine

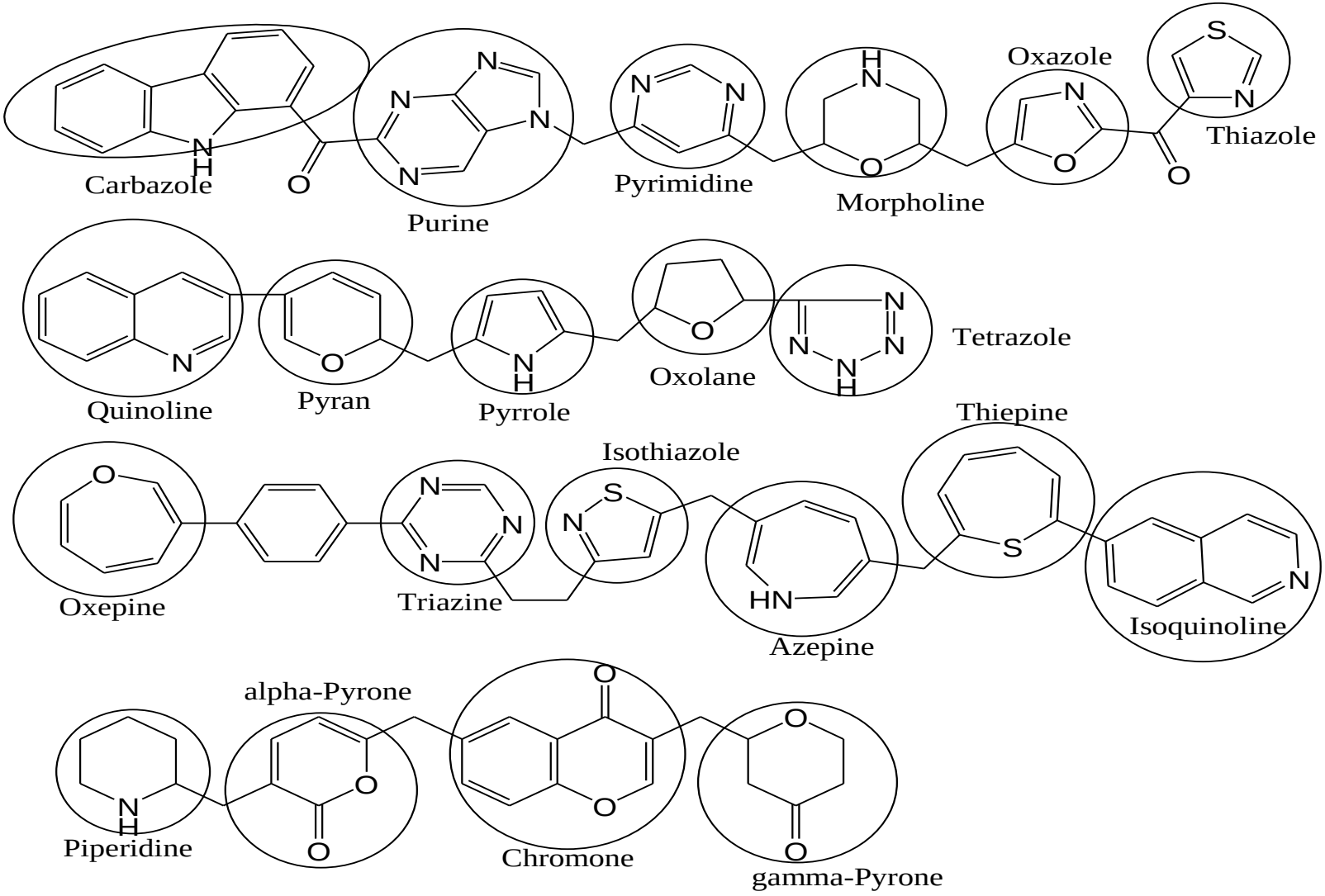


Concor

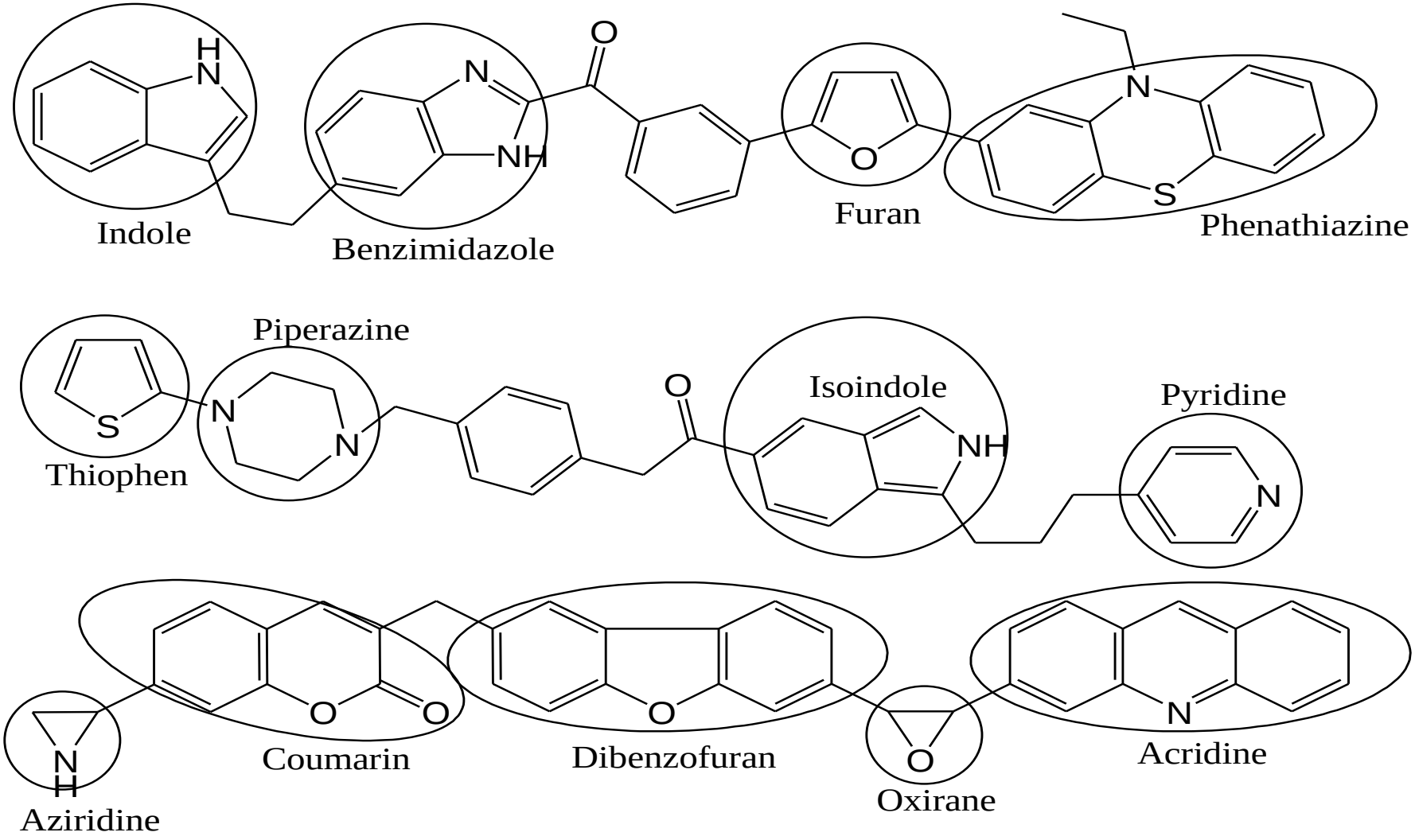


Pregabalin

Very common heterocyclic nucleus in pharmaceutical compounds

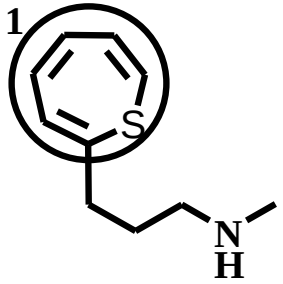


Very common heterocyclic nucleus in pharmaceutical compounds

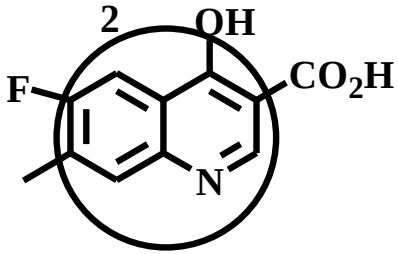


In each of the following arbitrary compounds, give the name for each circled heterocyclic nucleus

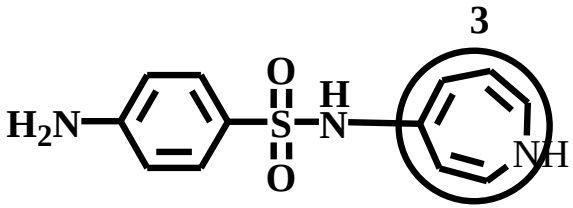
a]



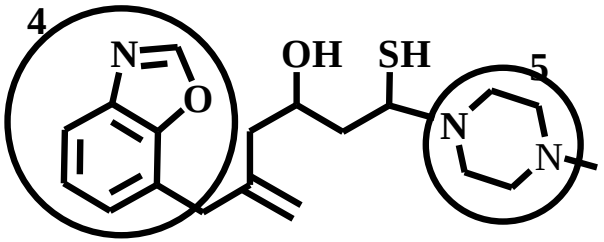
b]



c]

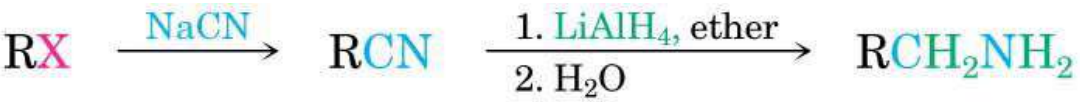


d]

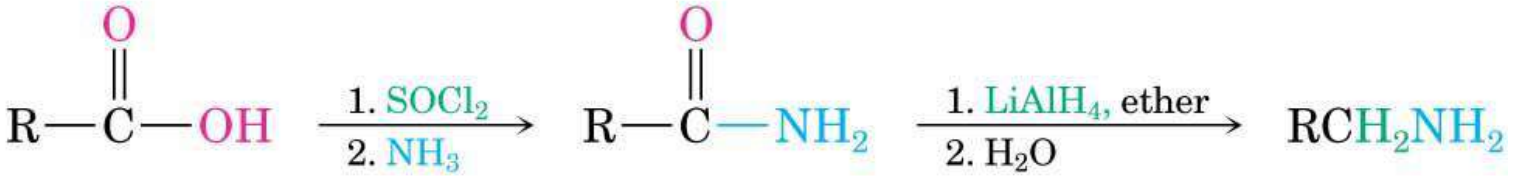


Synthesis of Amines

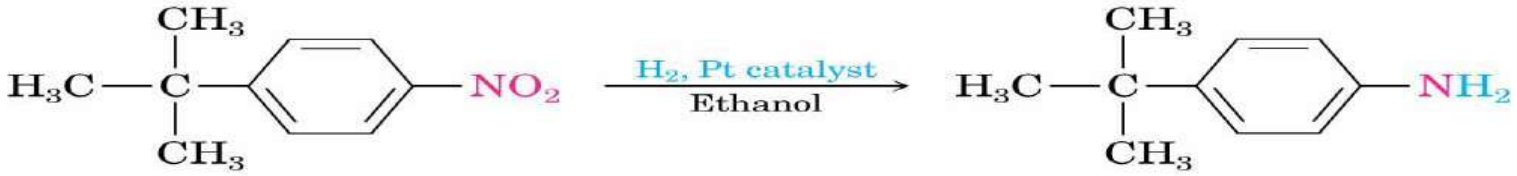
- **Reduction of nitro compounds, nitriles and amides**



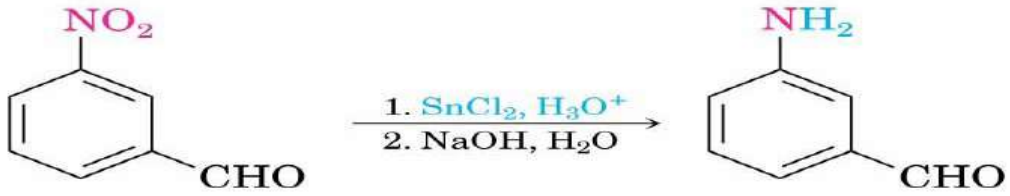
Alkyl halide **1° amine**



Carboxylic acid **1° amine**



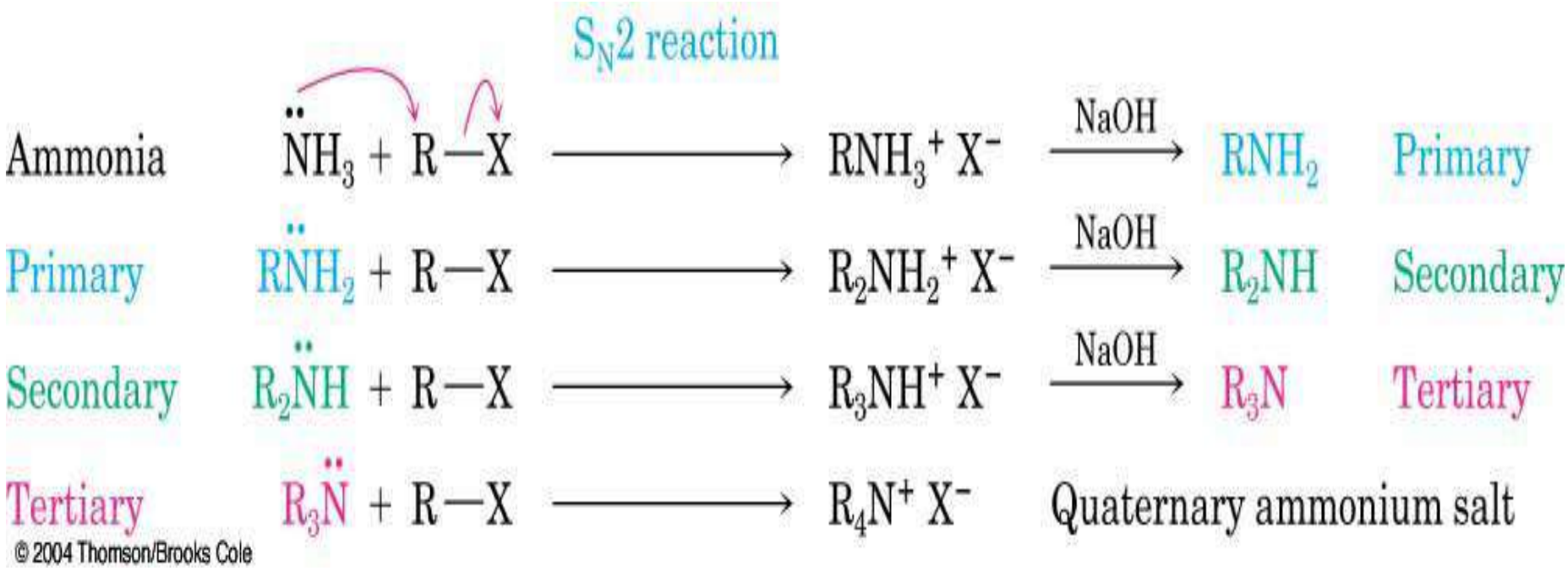
***p-tert*-Butylnitrobenzene** ***p-tert*-Butylaniline (100%)**



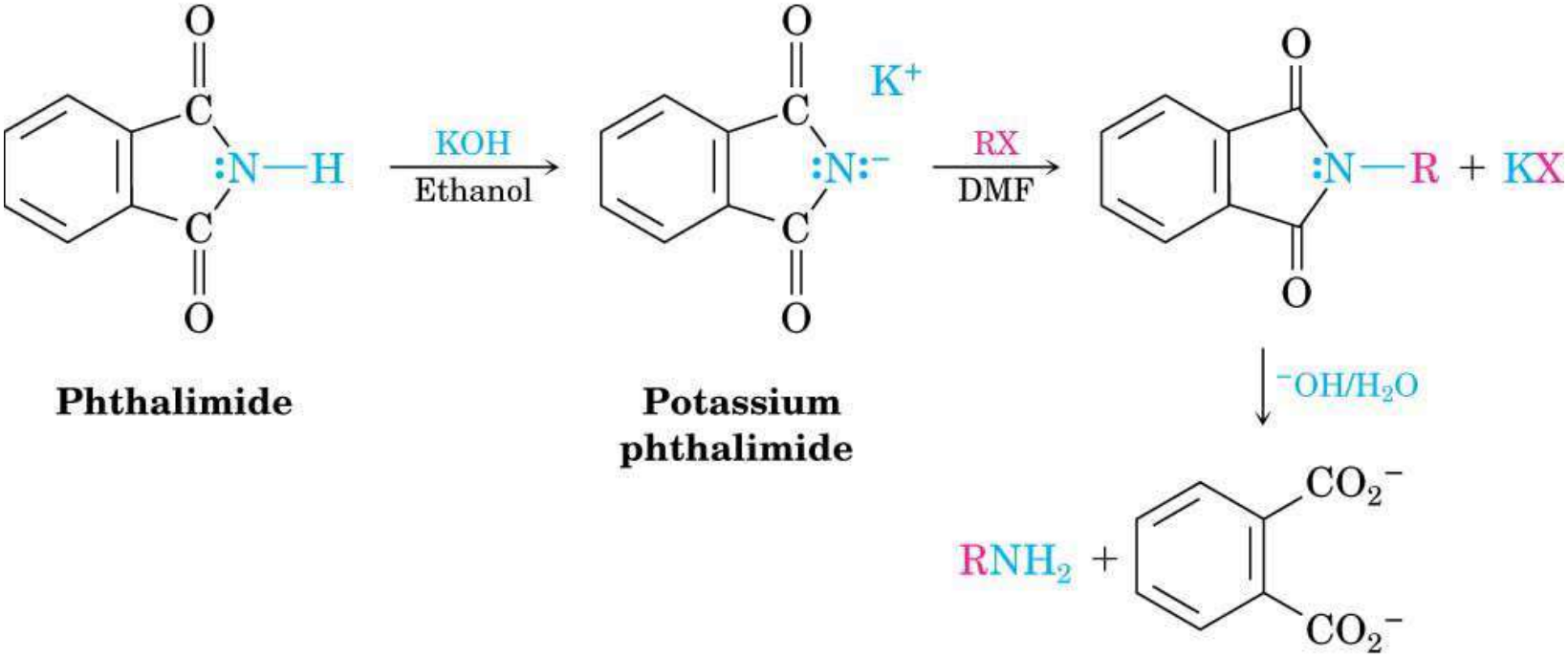
***m*-Nitrobenzaldehyde** ***m*-Aminobenzaldehyde (90%)**

SN2 Reactions of Alkyl Halides

- **Ammonia and other amines are good nucleophiles (uncontrolled)**

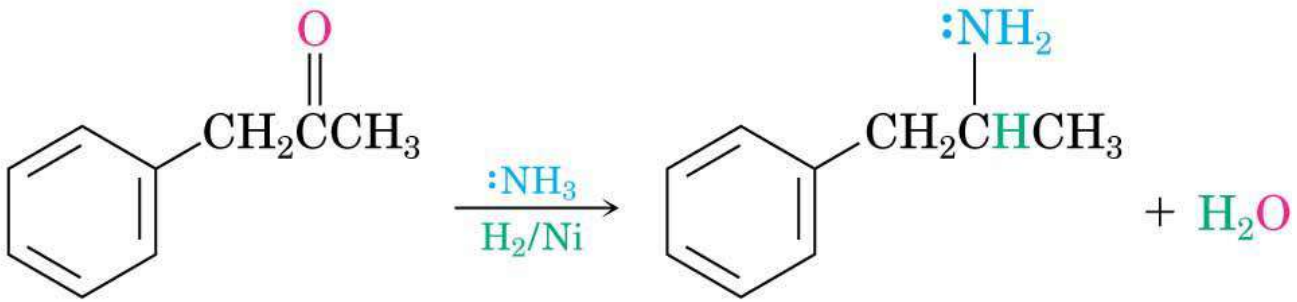


Gabriel Synthesis of Primary Amines



Reductive Amination of Aldehydes and Ketones

- **Treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent**

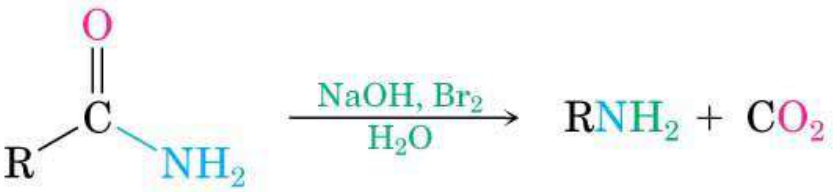


Phenyl-2-propanone **Amphetamine**

Hofmann and Curtius Rearrangements

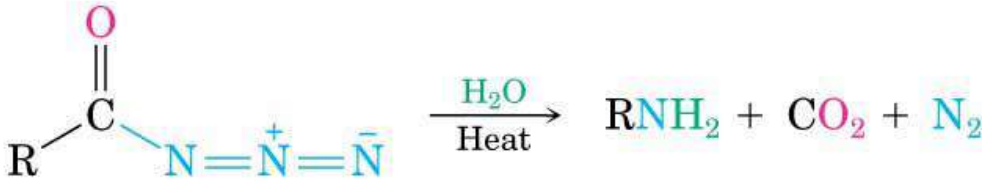
- Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the Hofmann rearrangement and the Curtius rearrangement

Hofmann rearrangement

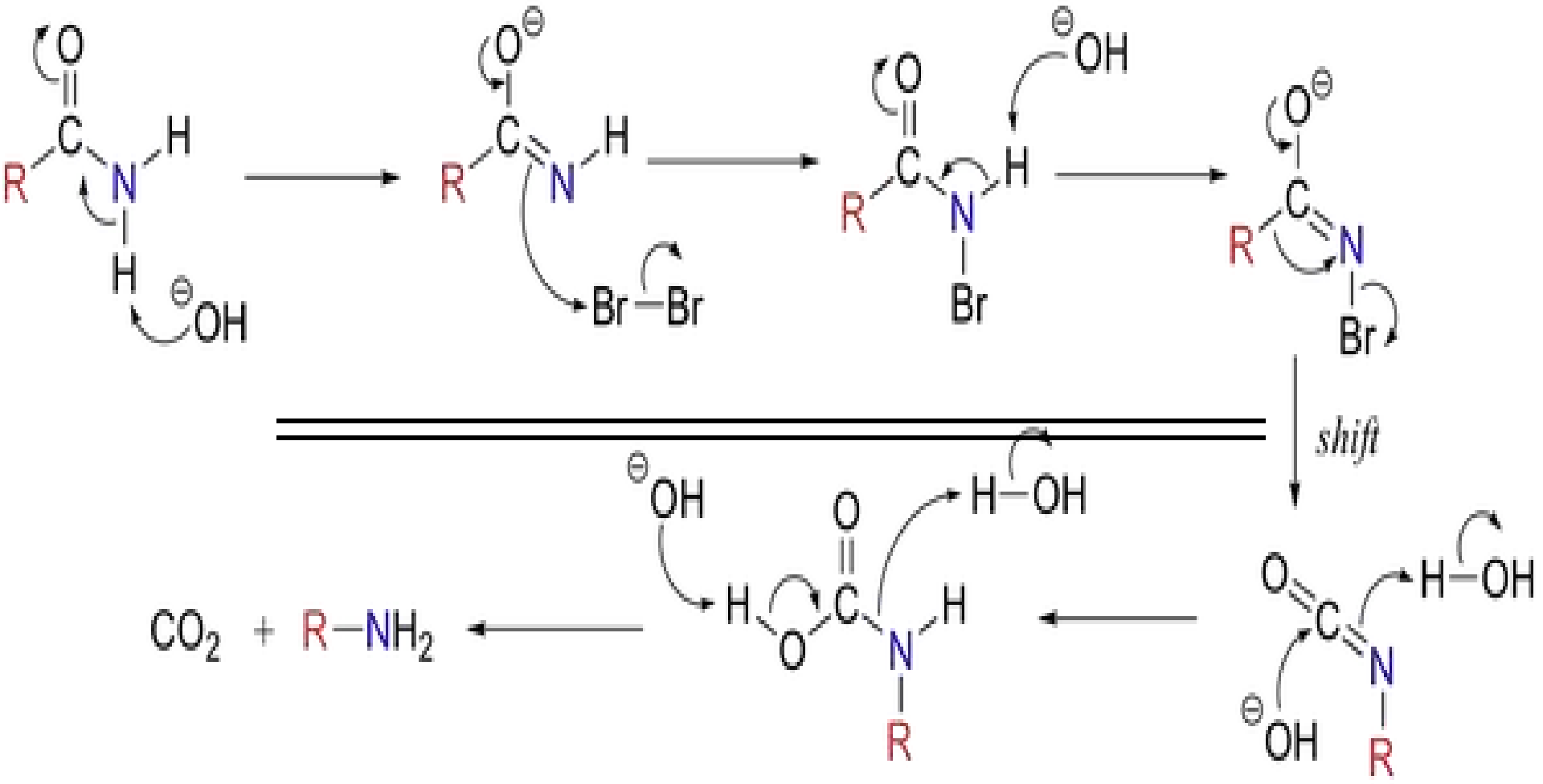


An amide

Curtius rearrangement

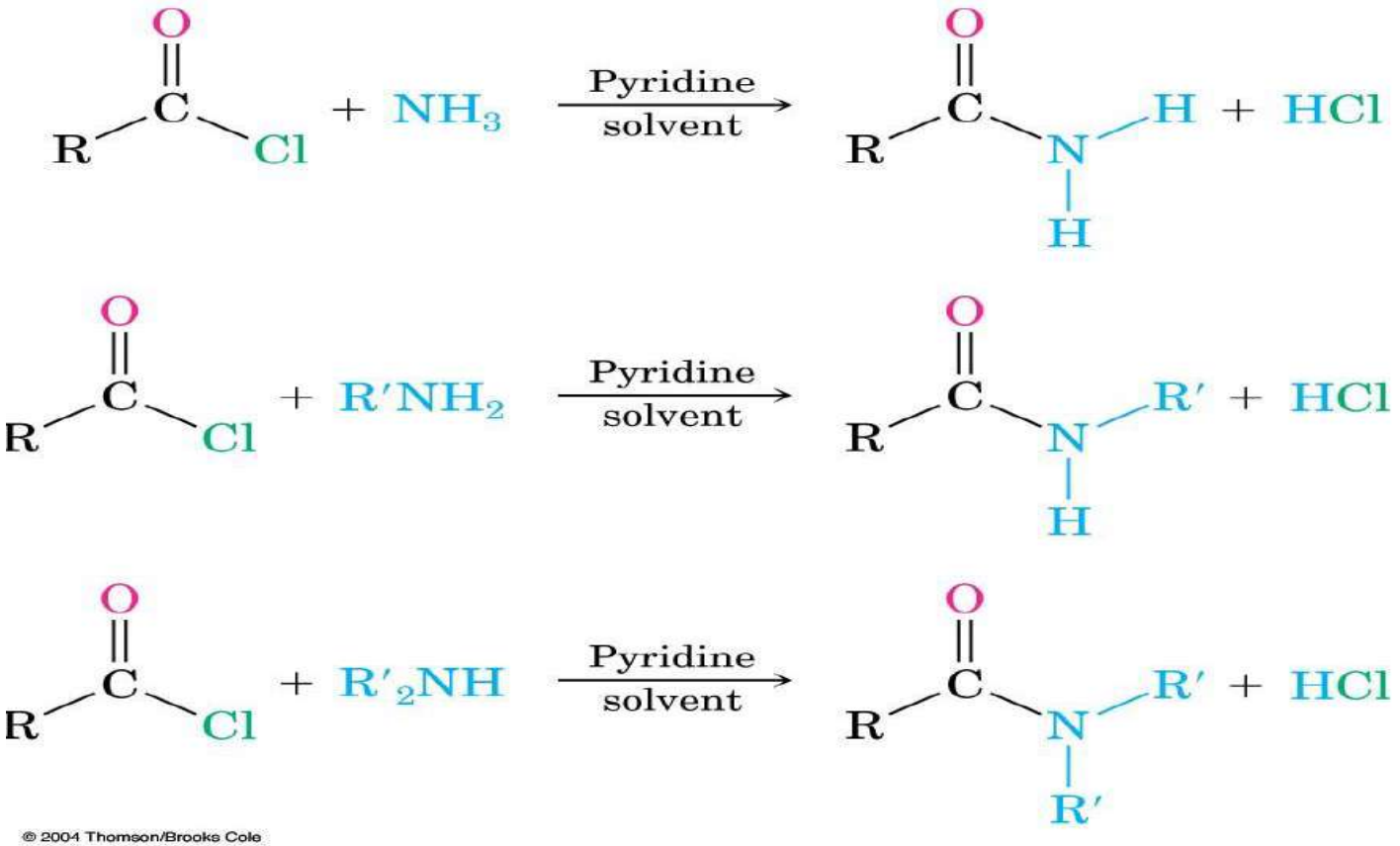


An acyl azide


shift
CO2 + R–NH2

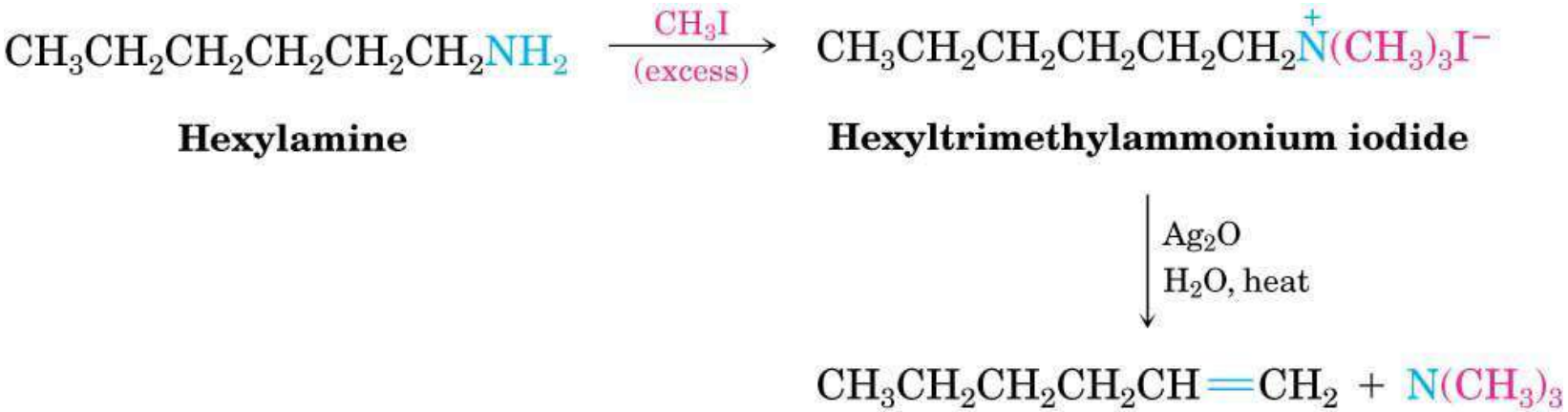
Reactions of Amines

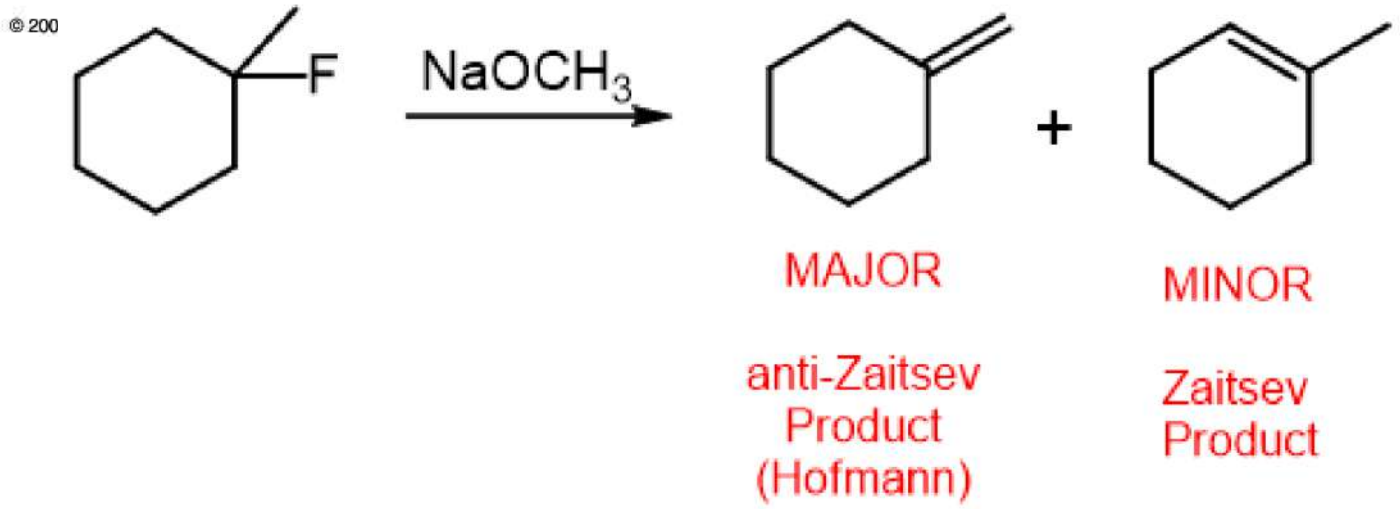
- **Aminolysis of carboxylic acid derivatives**



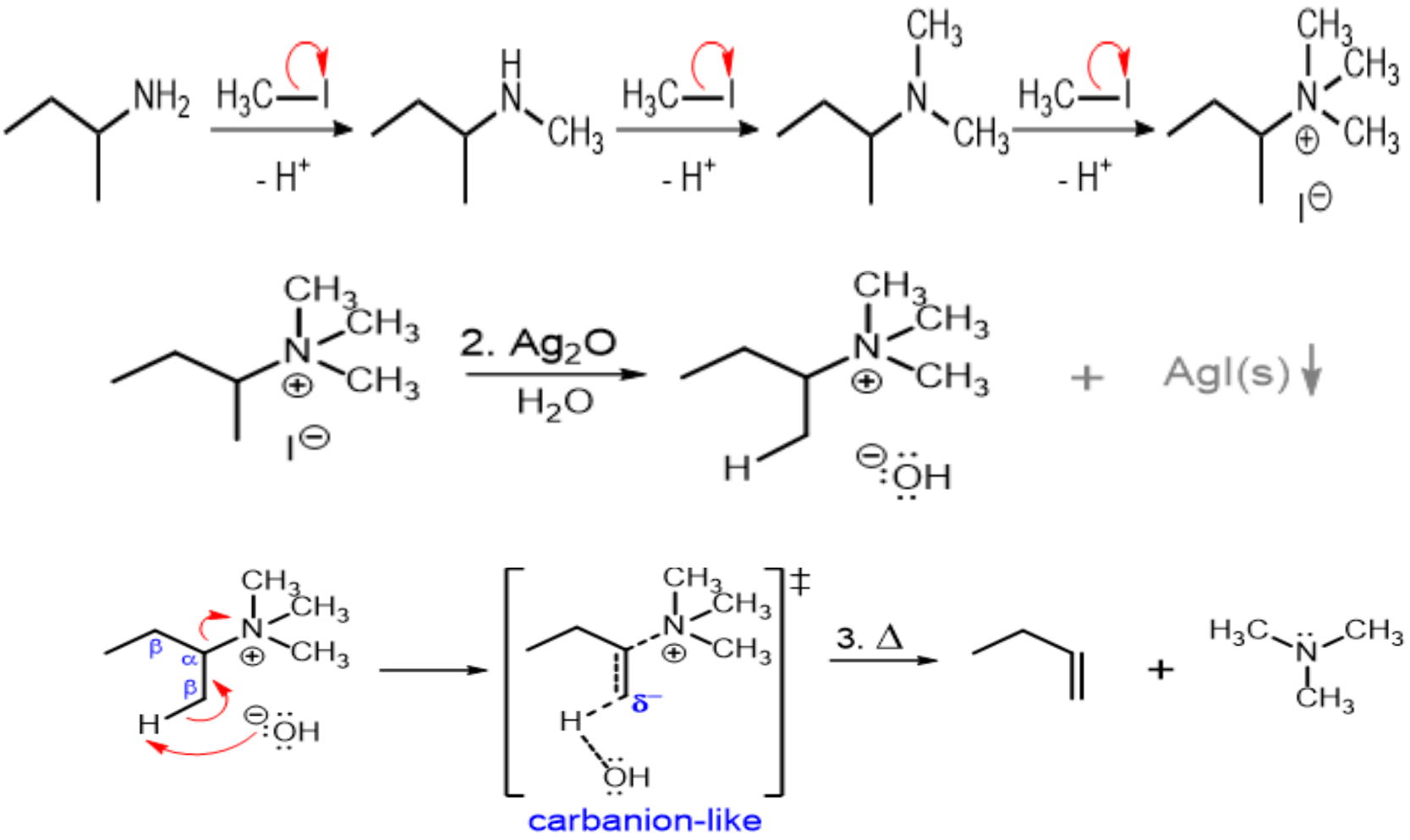
Hofmann Elimination

- **What is the difference between Hofman and Zaitseves alkene?**





Hofmann Elimination Mechanism



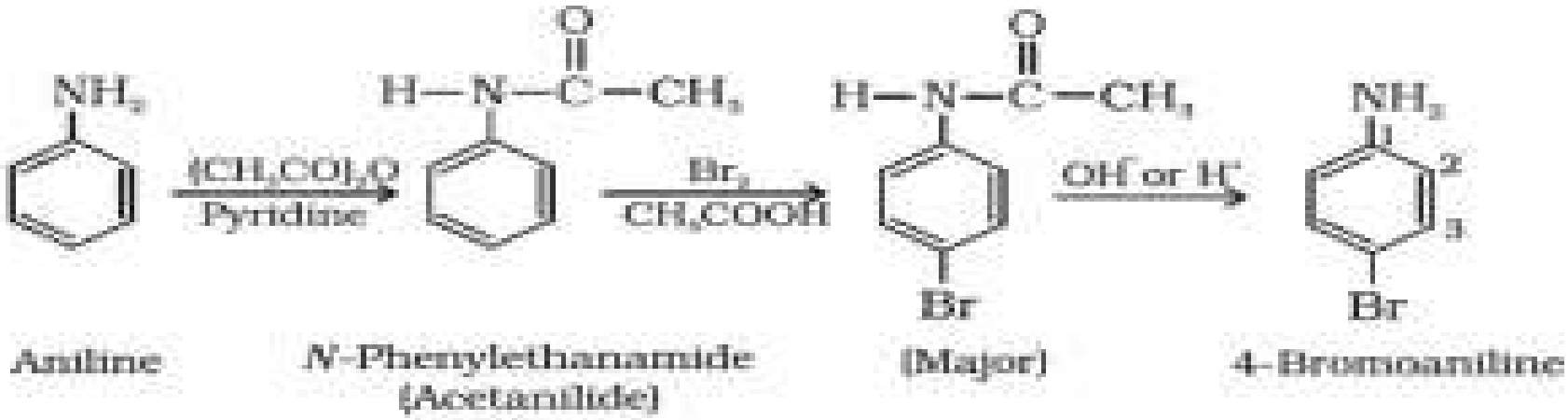
Part 2

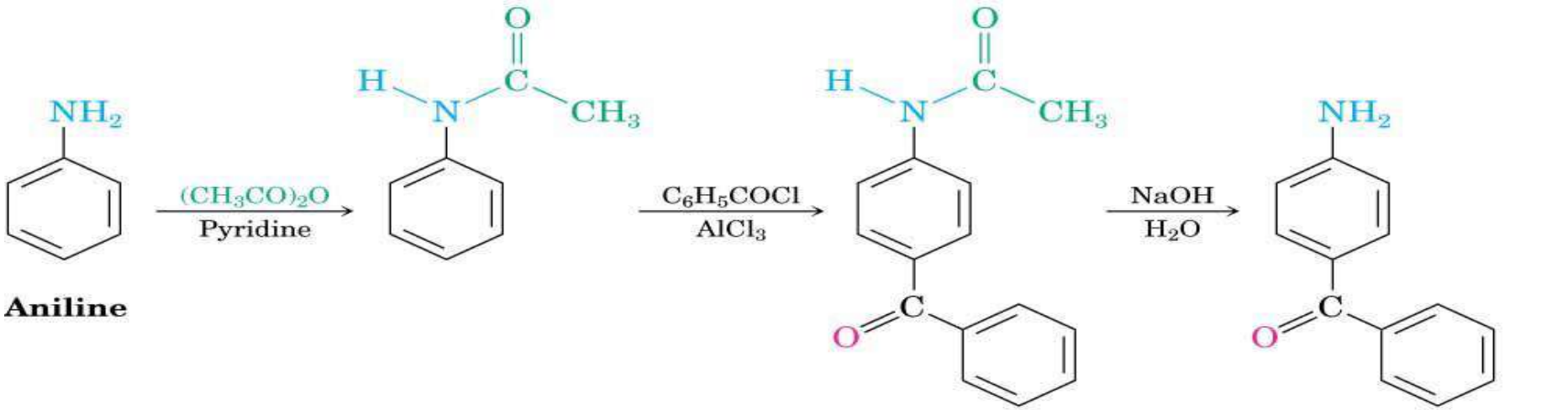
Reactions of Aryl amine

Amino substituents are strongly activating, ortho- and para-directing groups in electrophilic aromatic substitution reactions.

Reactions are controlled by conversion to amide then back to amine

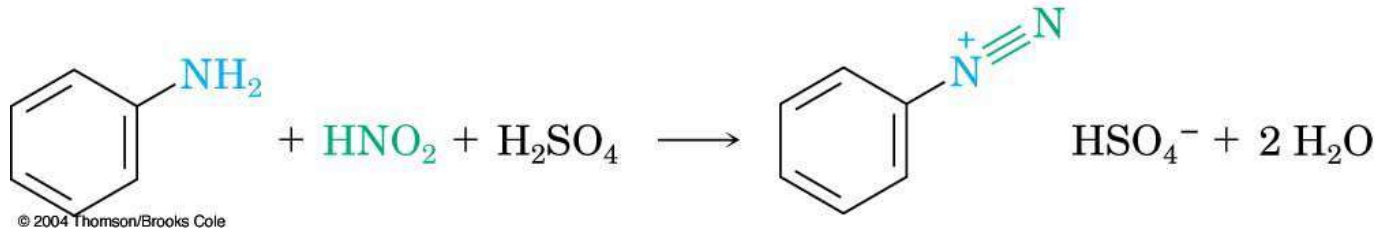
Reactions of Arylamines





Diazonium Salts

- **Primary arylamines react with HNO_2, "Nitrous acid" yielding stable arenediazonium salts**



Mechanism: Formation of Diazonium Ions From Aromatic Amines

Step 1: Addition to nitrosonium ion

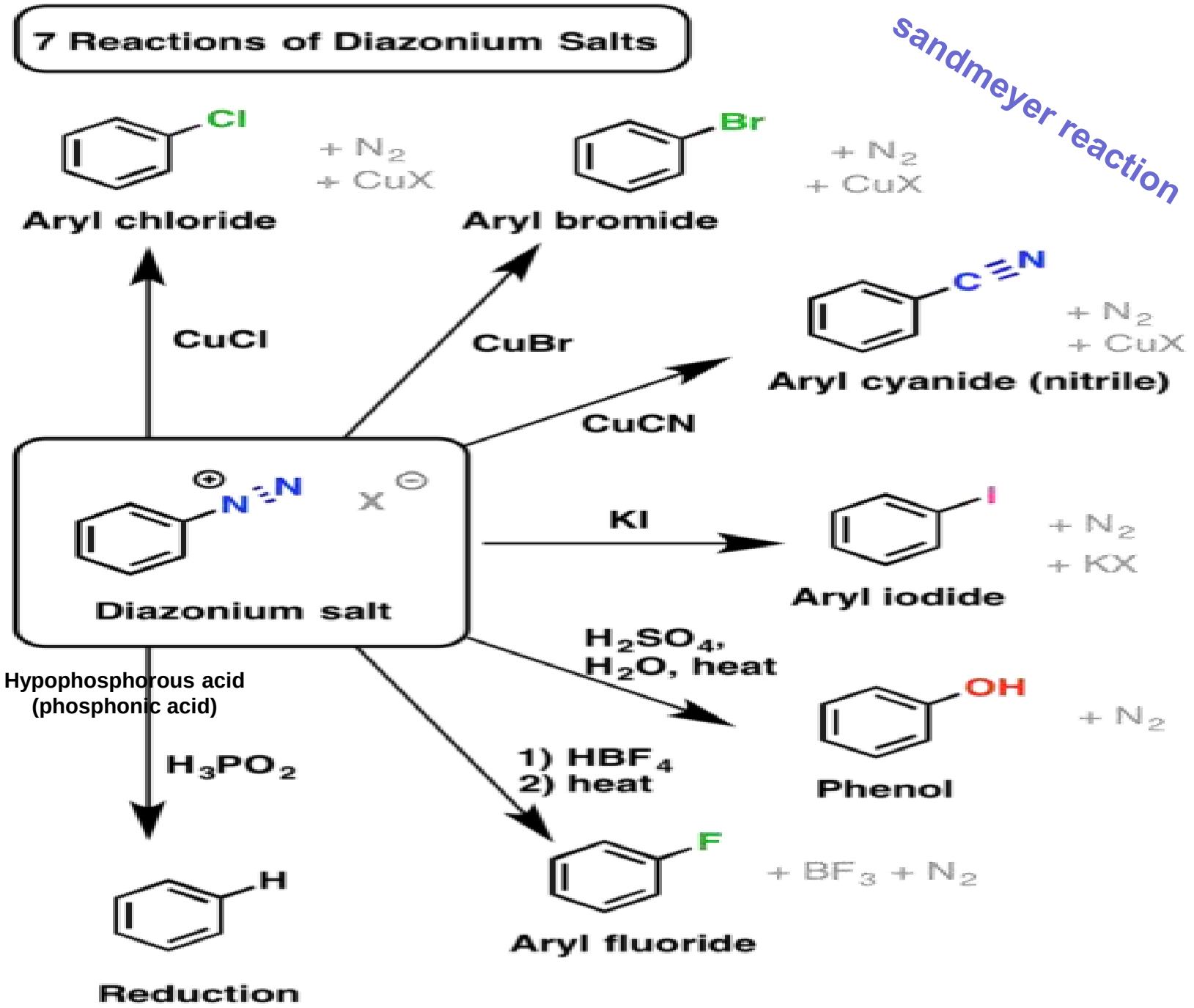
Step 2: Proton Transfer

Step 3: Proton Transfer

Step 4: Elimination of H_2O

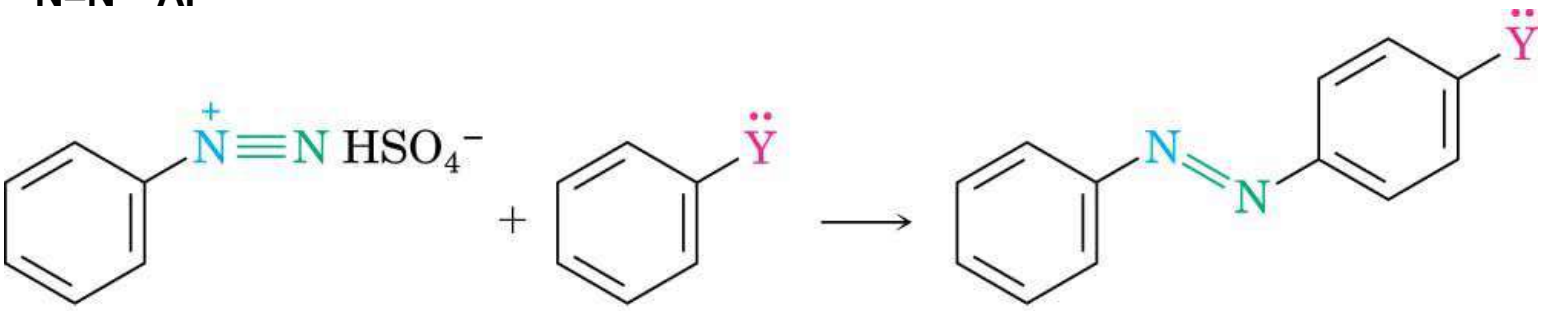
Diazonium salt

+ H_2O


7 Reactions of Diazonium Salts
sandmeyer reaction
Cl
+ N2
+ CuX
Aryl chloride
Br
+ N2
+ CuX
Aryl bromide
CuCl
CuBr
CuCN
N
C
+ N2
+ CuX
Aryl cyanide (nitrile)
N N
X
Diazonium salt
KI
I
+ N2
+ KX
Aryl iodide
H2SO4,
H2O, heat
OH
+ N2
Phenol
Hypophosphorous acid
(phosphonic acid)
H3PO2
1) HBF4
2) heat
F
+ BF3 + N2
Aryl fluoride
H
Reduction

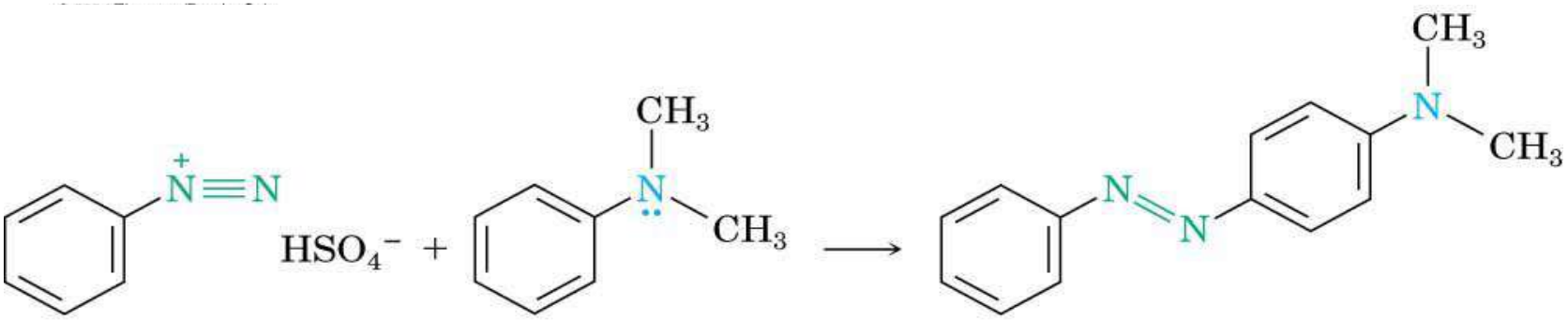
Diazonium Coupling Reactions
Azo dyes

- **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′**



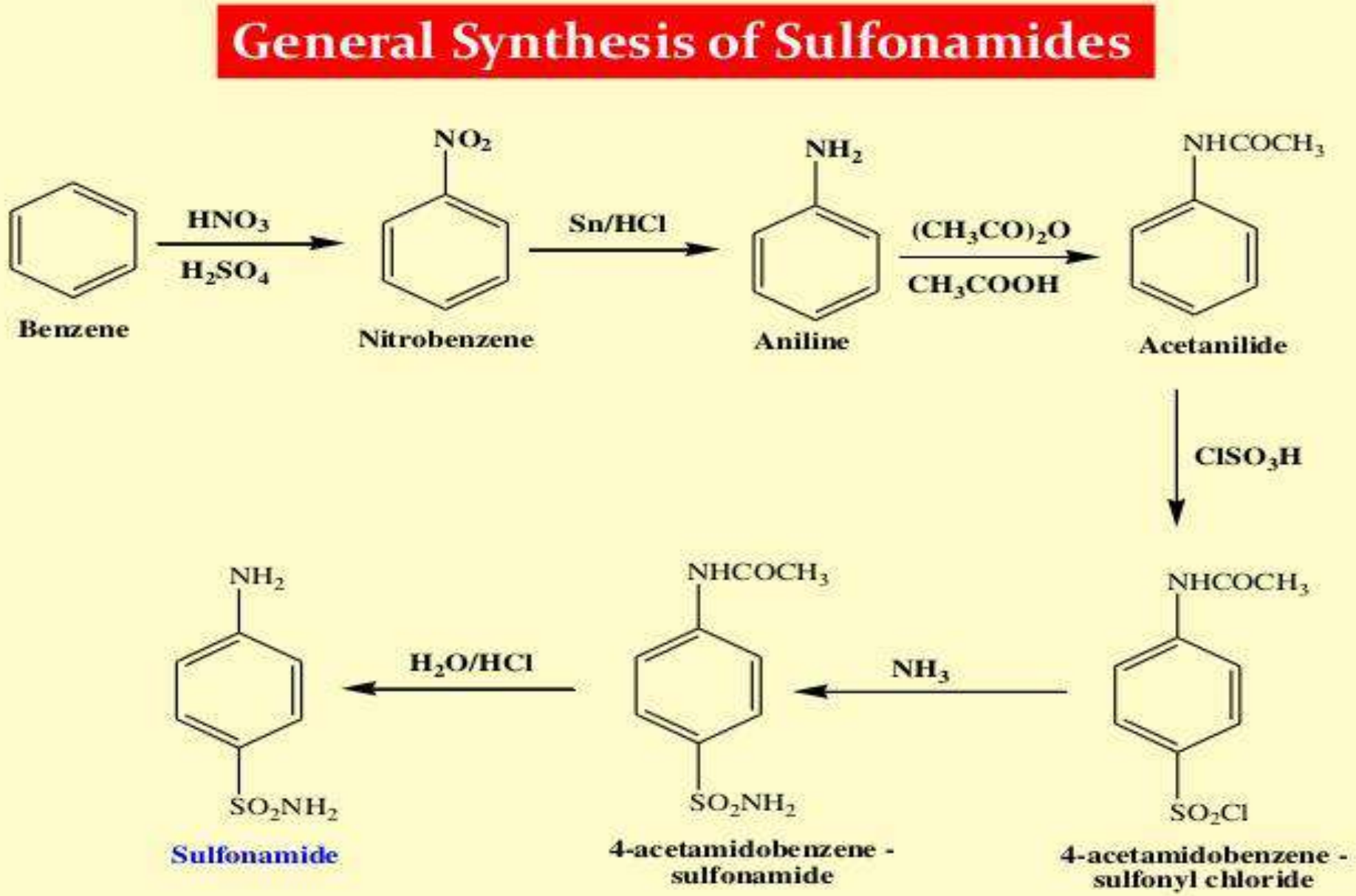
An azo compound

where Y = –OH or –NR_2

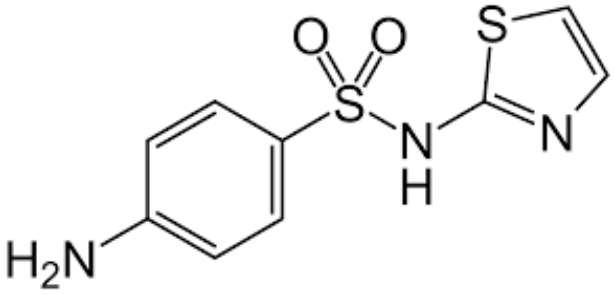


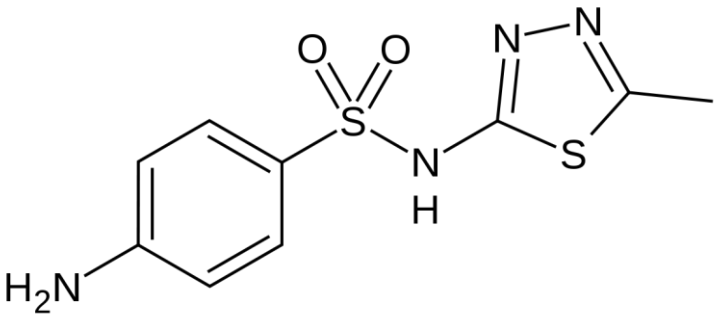
Benzenediazonium bisulfate | ***N,N*-Dimethylaniline** | ***p*-(Dimethylamino)azobenzene (yellow crystals, mp 127°C)**

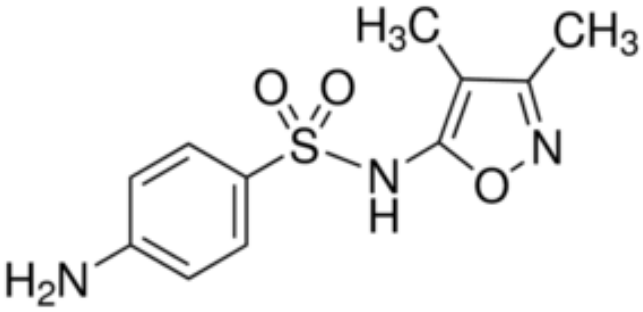
Sulfa drugs

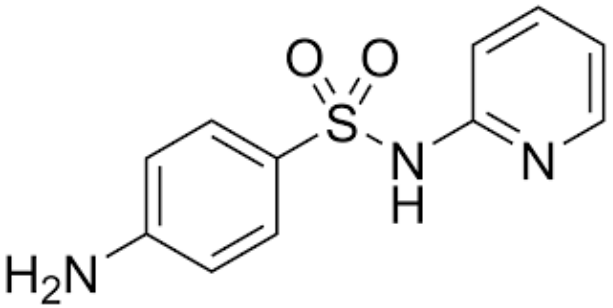

General Synthesis of Sulfonamides
Benzene
HNO3
H2SO4
NO2
Nitrobenzene
Sn/HCl
NH2
Aniline
(CH3CO)2O
CH3COOH
NHCOCH3
Acetanilide
ClSO3H
NHCOCH3
SO2Cl
4-acetamidobenzene - sulfonyl chloride
NH3
NHCOCH3
SO2NH2
4-acetamidobenzene - sulfonamide
H2O/HCl
NH2
SO2NH2
Sulfonamide

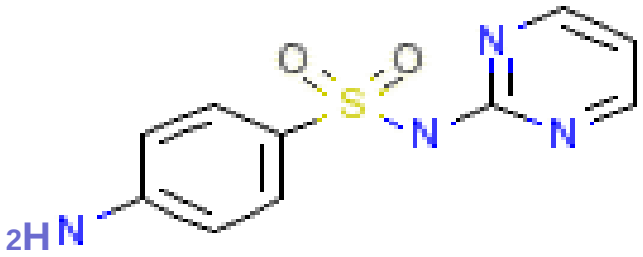
Examples for some Sulfa drugs



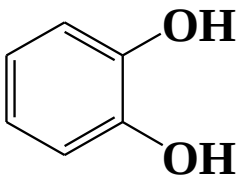




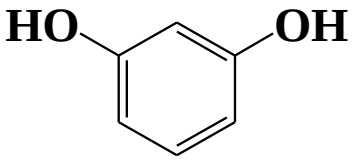




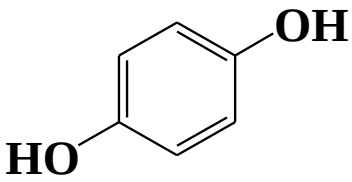
Phenols Ar-OH



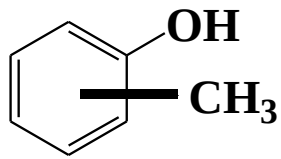
Catechol



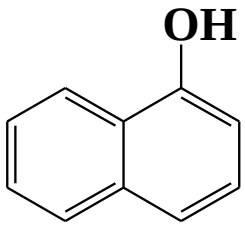
Resorcinol



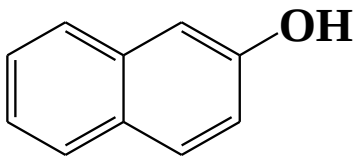
Hydroquinone



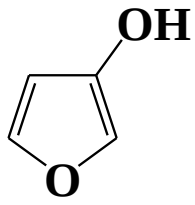
Cresol



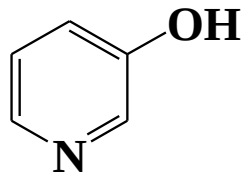
α–Naphthol



β–Naphthol



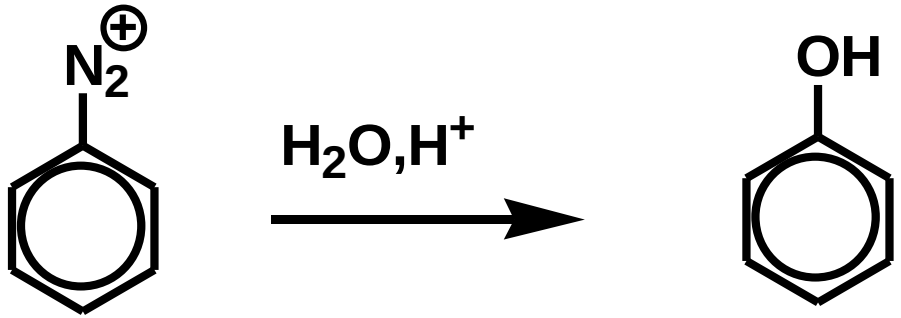
Furan-2-ol



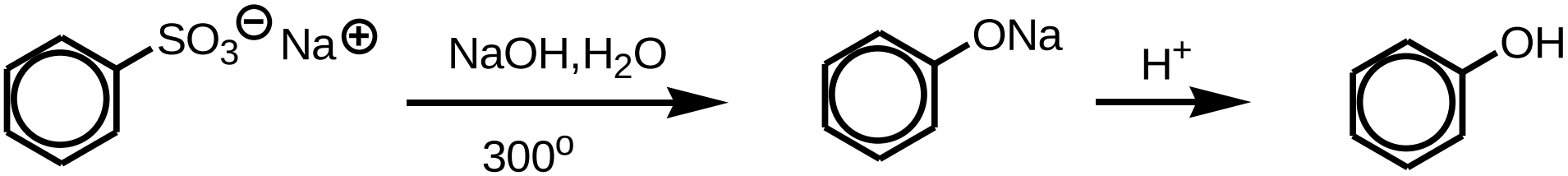
Pyridin2
-ol

phenols, syntheses:

1. **From diazonium salts**

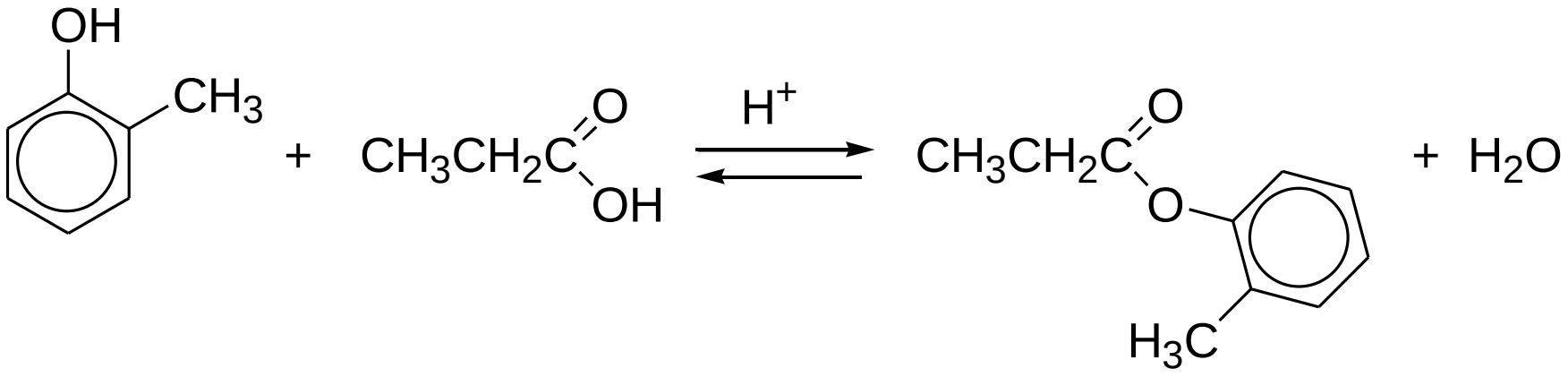


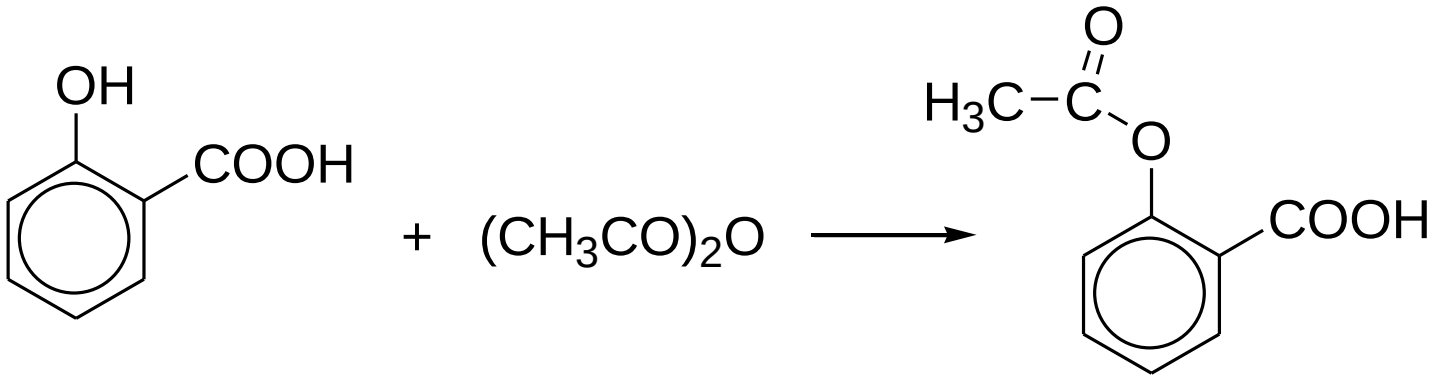
2. **Alkali fusion of sulfonates**



Reactions of phenol

1) Ester formation (Phenolysis)

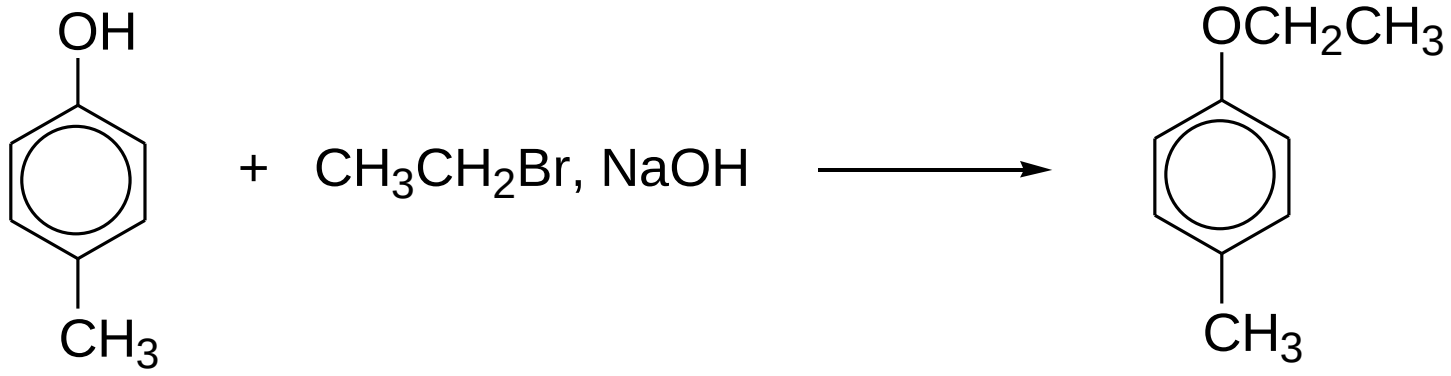




salicyclic acid

aspirin

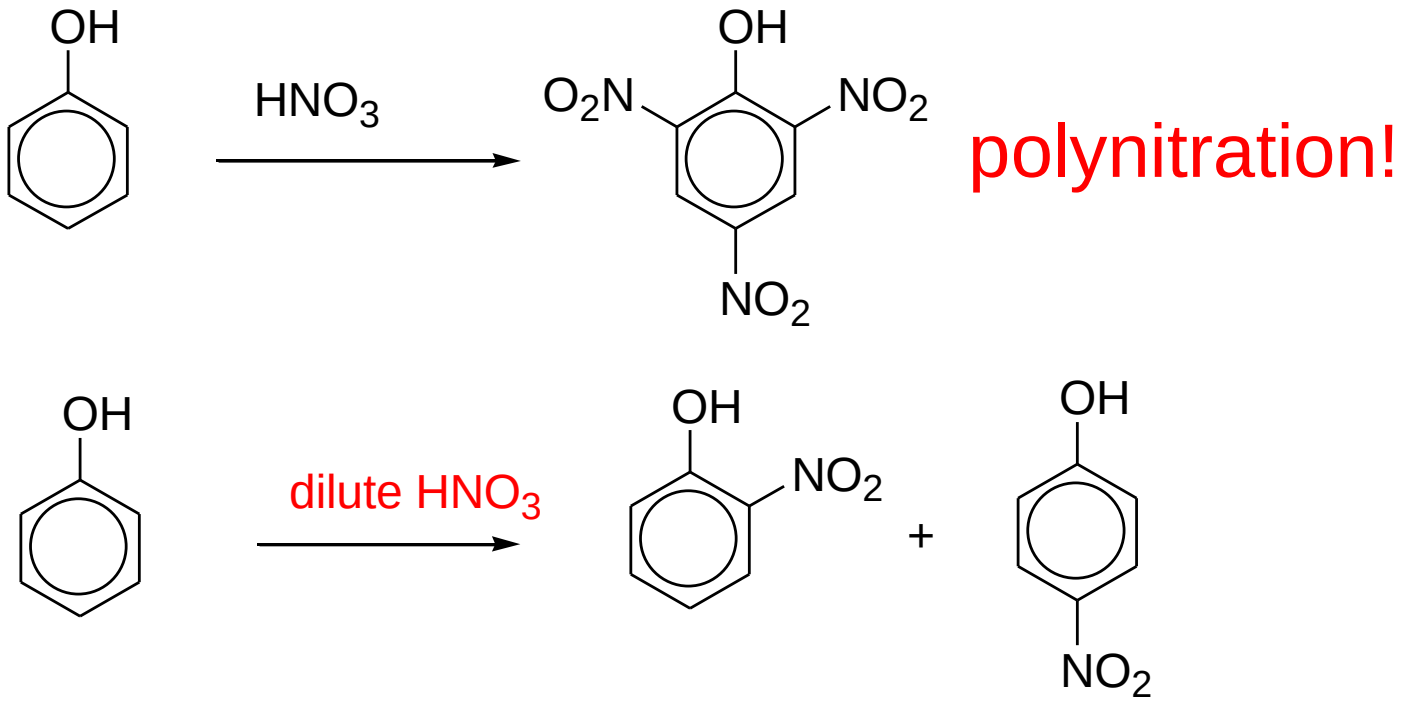
2) Ether formation (Williamson Synthesis)



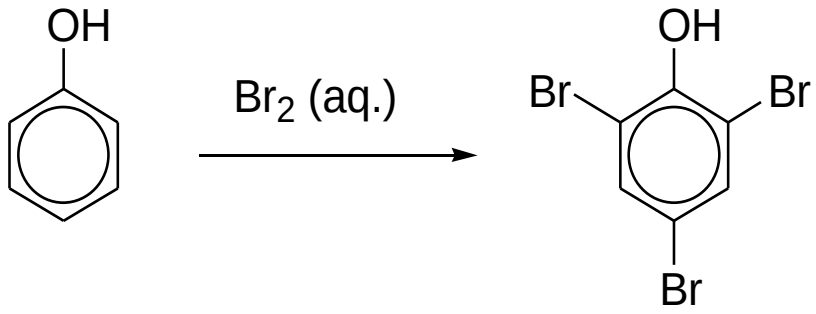
3) Electrophilic Aromatic Substitution

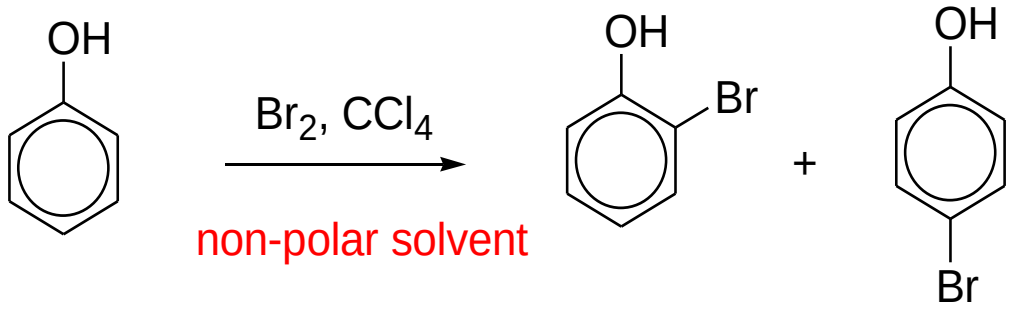
The –OH group is a powerful activating group in EAS and an *ortho/para* director.

a) nitration

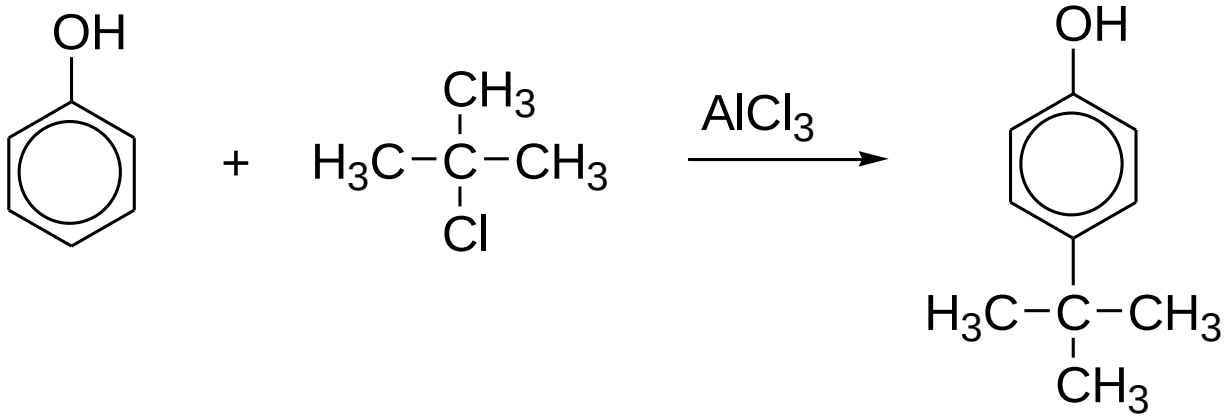


b) halogenation

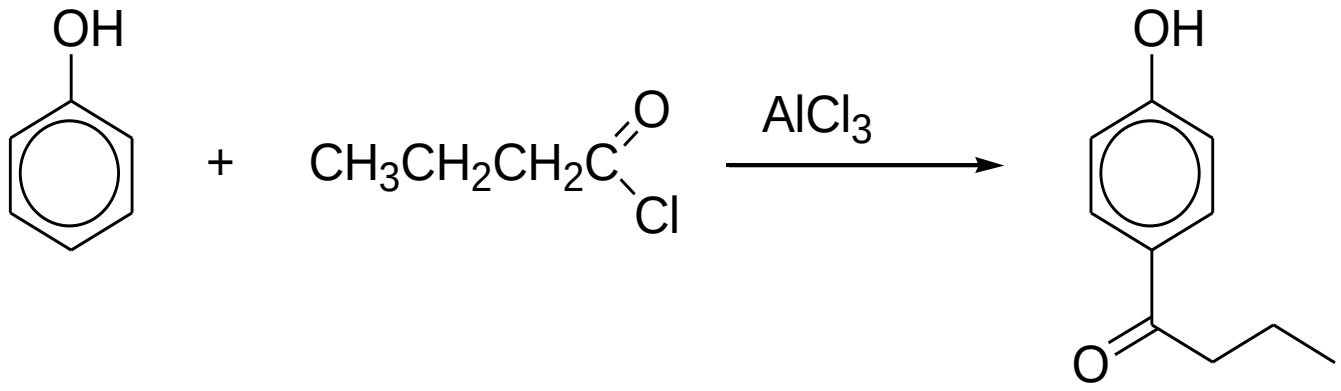




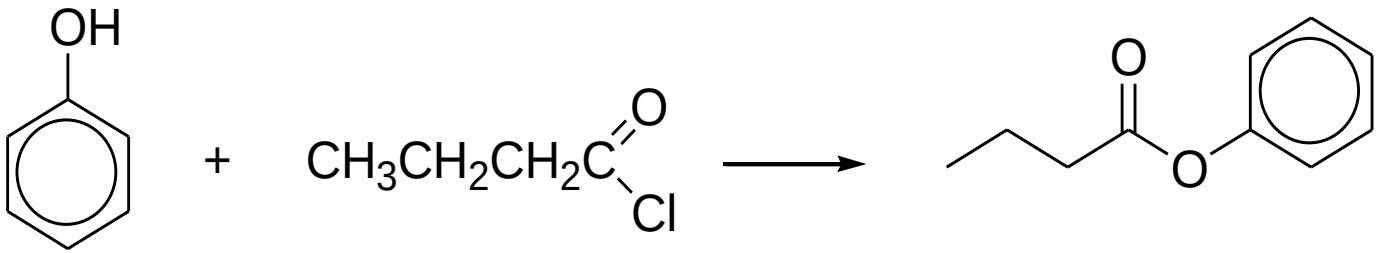
c) Friedel-Crafts alkylation.



d) Friedel-Crafts acylation

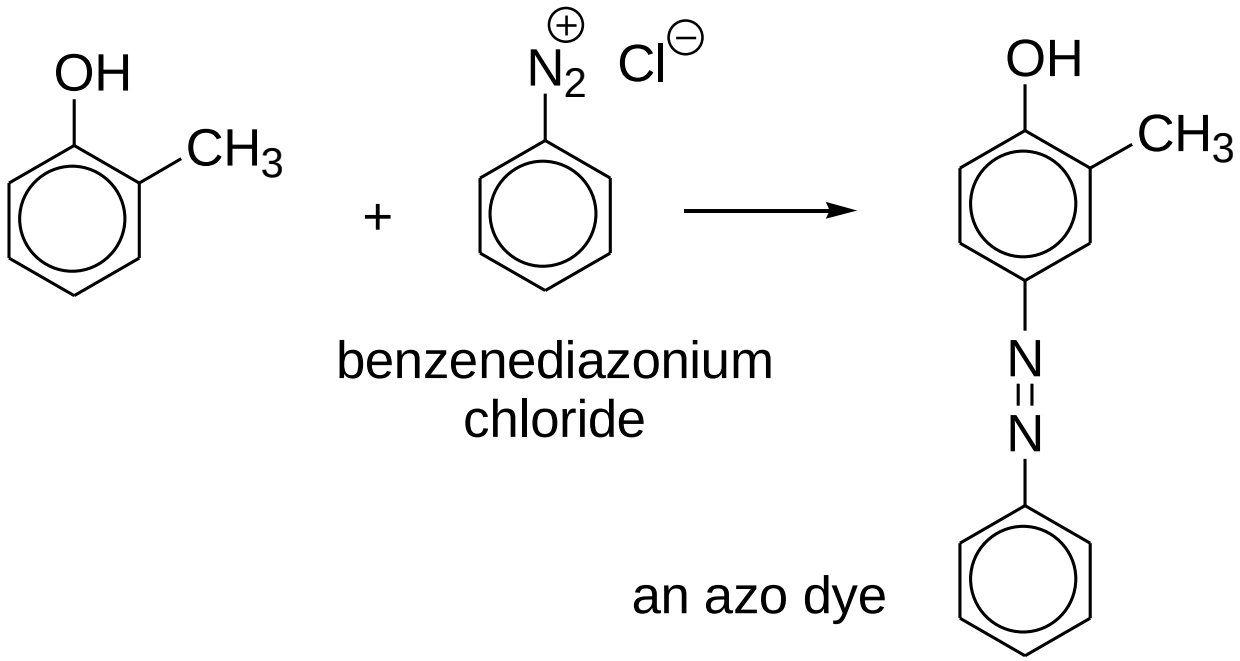


Do not confuse FC acylation with esterification:

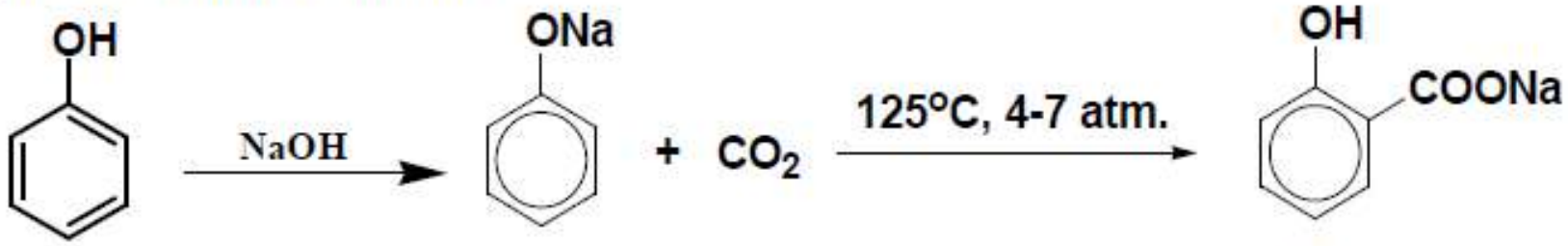


4) coupling with diazonium salts

(EAS with the weak electrophile diazonium)

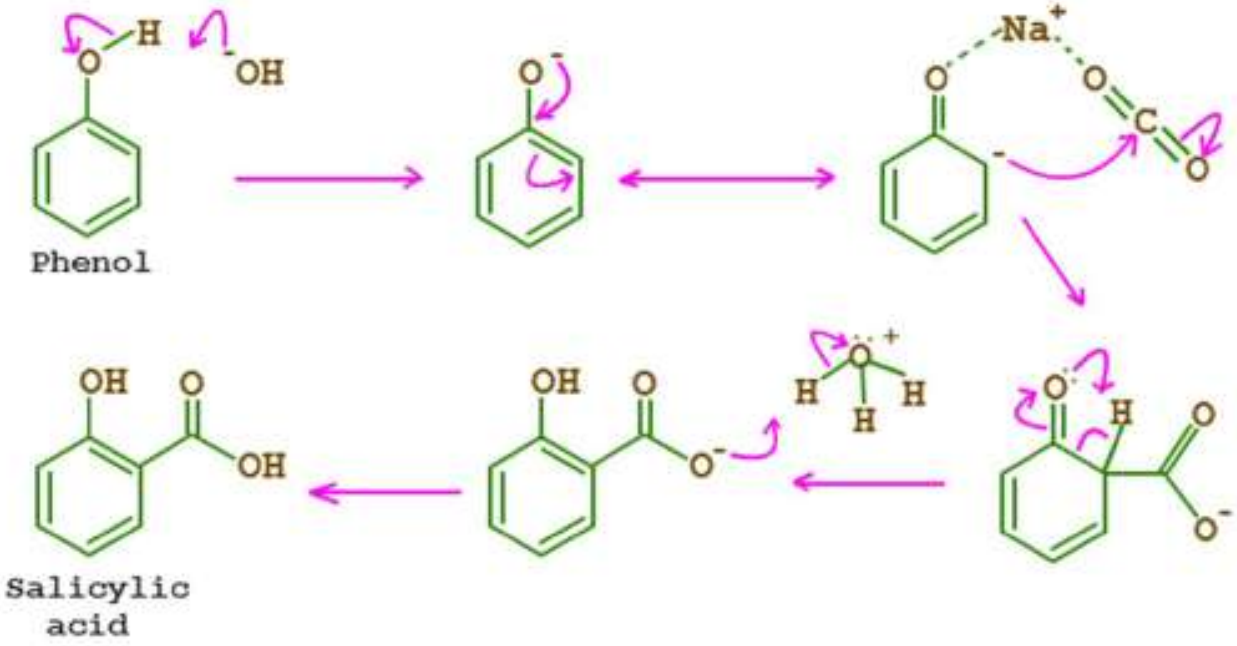


5) kolbe-schmitt reaction

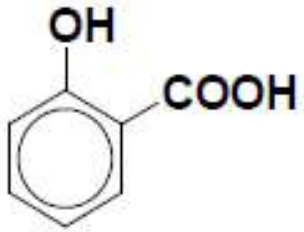


sodium salicylate

Mechanism

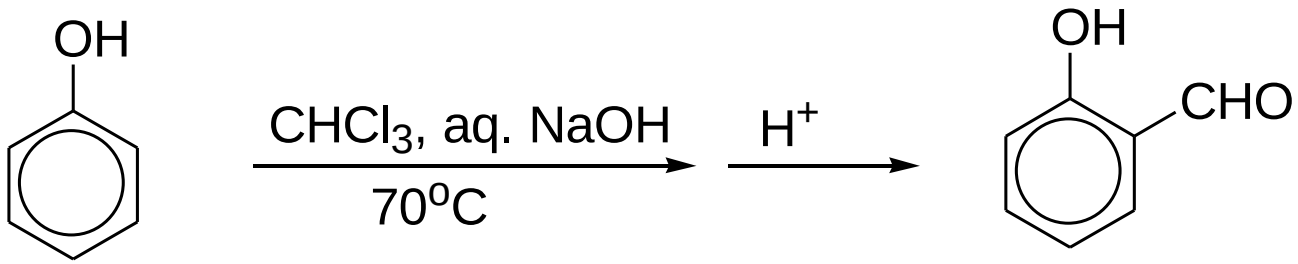


H^+



salicylic acid

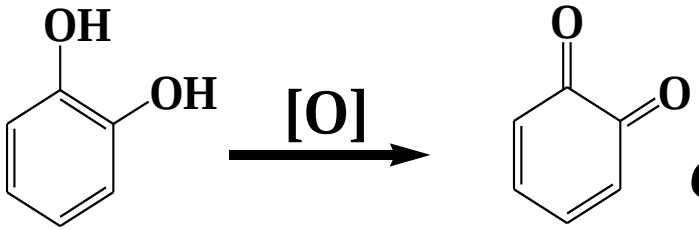
6) Reimer-Tiemann reaction



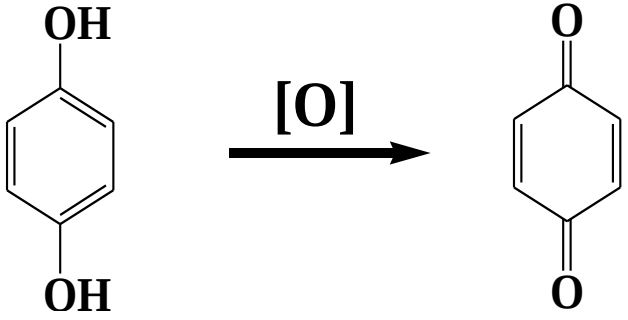
salicylaldehyde

The salicylaldehyde can be easily oxidized to salicylic acid

7) Oxidation



***O*-Benzoquinone**



***P*-Benzoquinone**

O= Ag_2O, $K_2Cr_2O_7$, $KMnO_4$

& Fremy's salt $(KSO_3)_2NO$