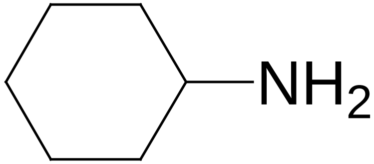
台灣大學開放式課程

有機化學乙

蔡蘊明　教授

※ Nomenclature

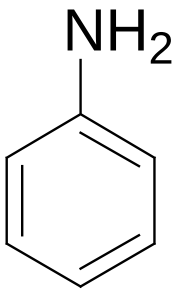
RNH_2	primary amine
R_2NH	secondary amine
R_3N	tertiary amine
$R_4N^+X^-$	quaternary amine salt

CH_3NH_2	methylamine or methanamine
	cyclohexylamine or cyclohexanamine

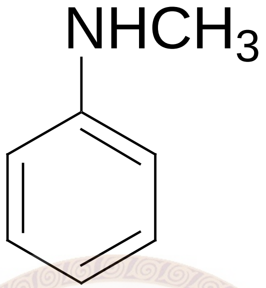
$CH_3NHCH_2CH_3$	ethylmethylamine or *N*-methylethanamine
Et_3N	triethylamine or *N,N*-diethylethanamine
$H_2NCH_2CH_2OH$	2-aminoethanol

amino group

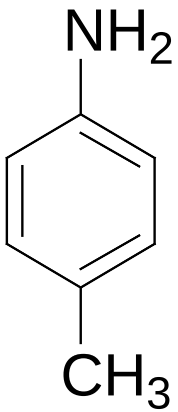
✓ Arylamines



aniline
(benzenamine)

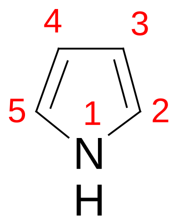


N-methylaniline

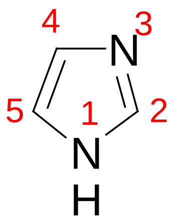


p-toluidine

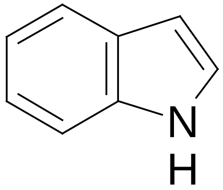
✓ Heterocyclic amines



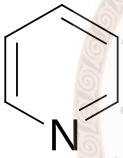
pyrrole
(1-azacyclopenta-2,4-diene)



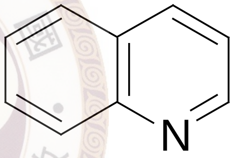
imidazole



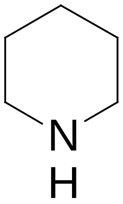
indole
(1-azaindene)



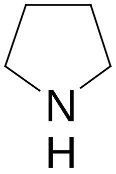
pyridine



quinoline



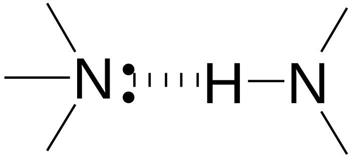
piperidine



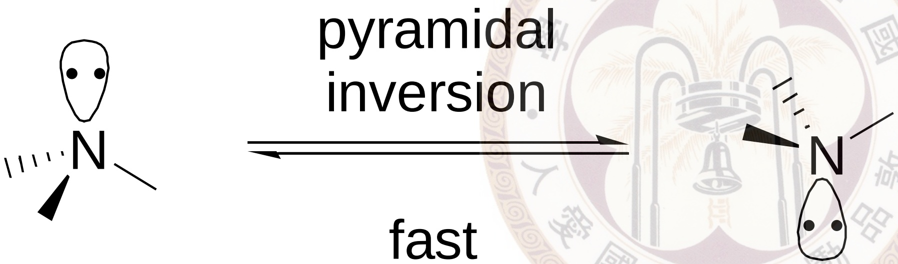
pyrrolidine

※ Physical properties and structures

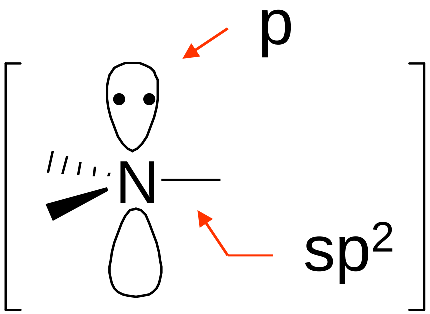
Polar, water soluble when small



Hydrogen bonding possible



enantiomeric



TS for inversion

separable quaternary ammonium salt

※ Basicity

$$RNH_2 + H_2O \overset{K_b}{\rightleftharpoons} R\overset{+}{N}H_3 + OH^-$$

	NH_3	CH_3NH_2
pK_b	4.47	3.36

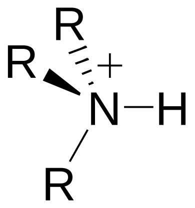
electron donating
⇨ increases basicity

Gas phase basicity:

$$(CH_3)_3N > (CH_3)_2NH > CH_3NH_2 > NH_3$$

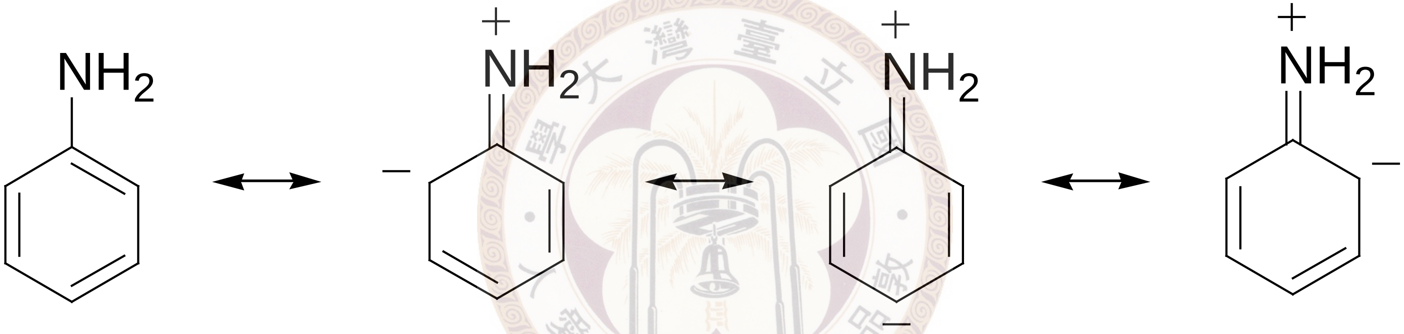
Solution phase:

$$(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N > NH_3$$

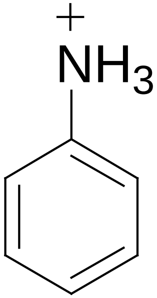


← less solvation stabilization
(steric effect)

pK_b 3.36 9.42



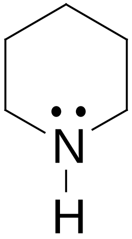
Lone pair delocalized into the π system



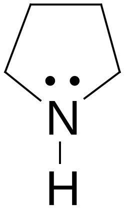
Lone pair no longer exists

✓ Basicity of heterocyclic amines

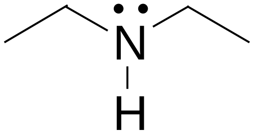
pK$_a$ of corresponding aminium ion



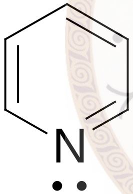
piperidine
11.20



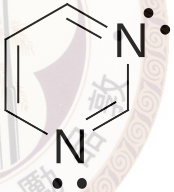
pyrrolidine
11.11



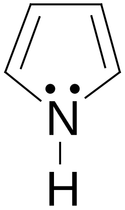
diethylamine
10.98



pyridine
5.23

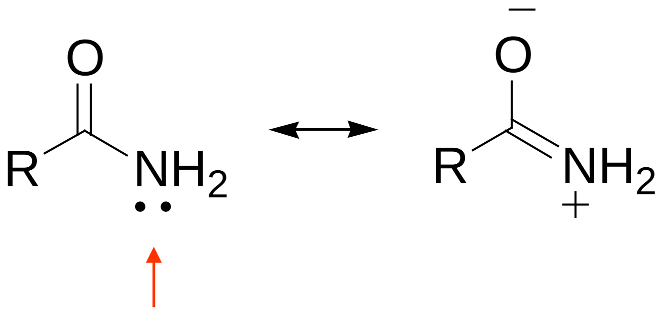


pyrimidine
2.70

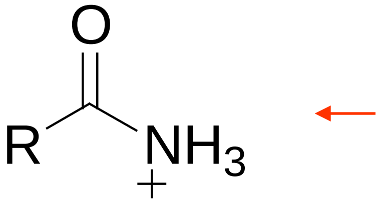


pyrrole
0.40

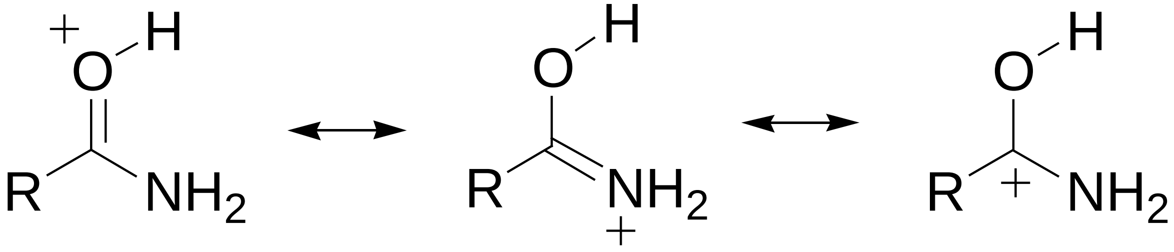
✓ Amides



Basically neutral
Strong amide resonance makes the lone pair unavailable

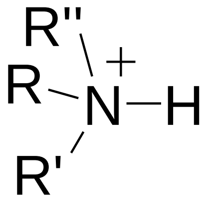


Lost amide resonance completely



better

◎ Aminium salt and quaternary ammonium salt



aminium salt

$CH_3CH_2\overset{+}{N}H_3\ Cl^-$ ethylaminium chloride

$Et_4N^+\ Br^-$ tetraethylammonium bromide

$$\Big\downarrow \text{Ag}_2\text{O, H}_2\text{O}$$

$AgBr\downarrow\ +\ Et_4N^+\ OH^-$ tetraethylammonium hydroxide

↑ strong base as NaOH

◎ Acidity of amines

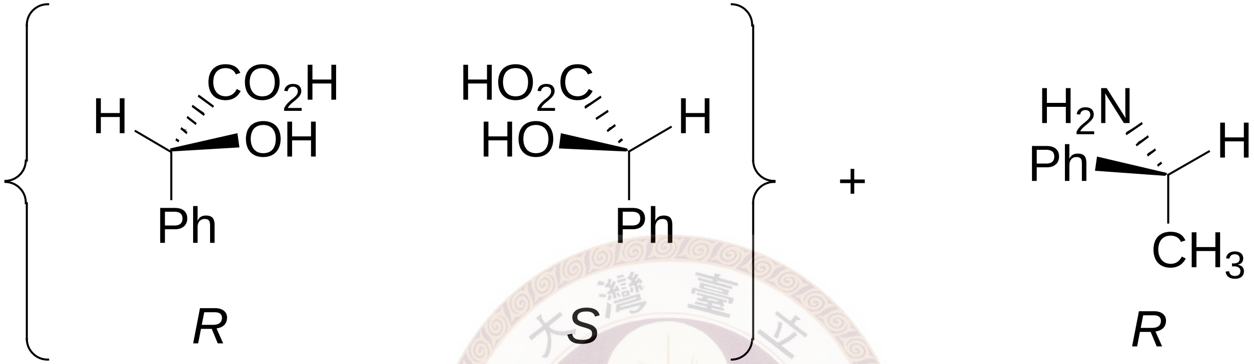
$$Pr_2NH + n\text{-}BuLi \longrightarrow Pr_2N^- Li^+ + \text{Butane}$$

pK_a ~40

lithium
diisopropylamide
(LDA)

pK_a ~50

※ Amines used as resolving agents



↓

(*R*)-acid♦(*R*)-amine salt + (*S*)-acid♦(*R*)-amine salt

↖ diastereomers ↗

separable by fractional recrystallization

↓ HCl/H_2O

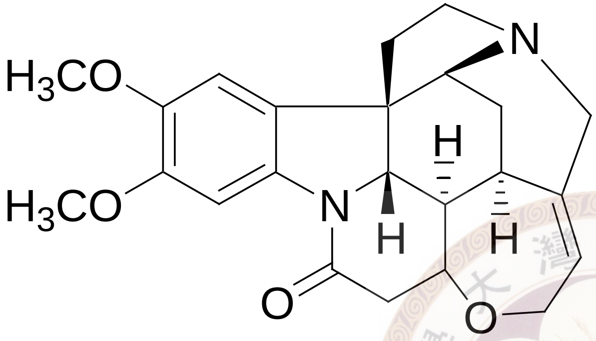
(*R*)-acid + (*R*)-aminium salt
(in aqueous solution)

↓ HCl/H_2O

(*S*)-acid + (*R*)-aminium salt
(in aqueous solution)

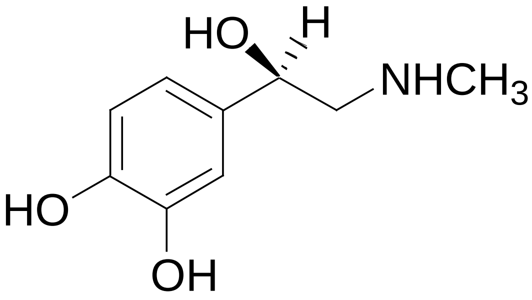
Naturally occurring optically active amines can be used as resolving agents

例

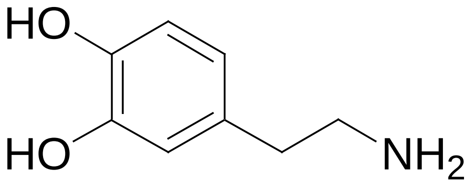


(–)-brucine

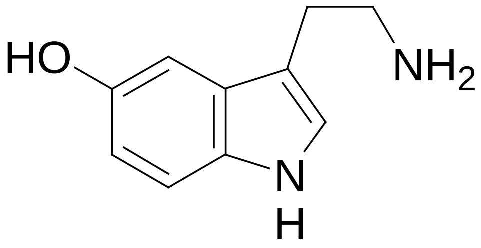
馬錢子鹼



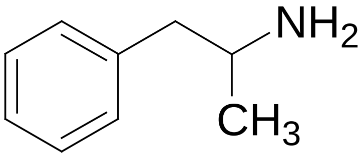
epinephrine
(adrenaline)



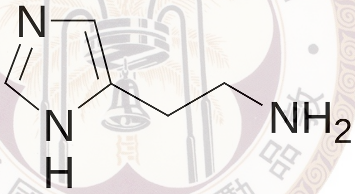
dopamine



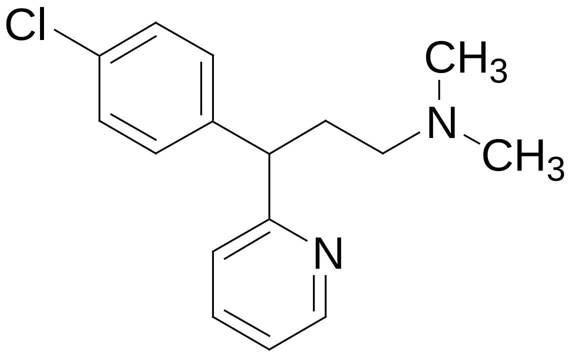
serotonine



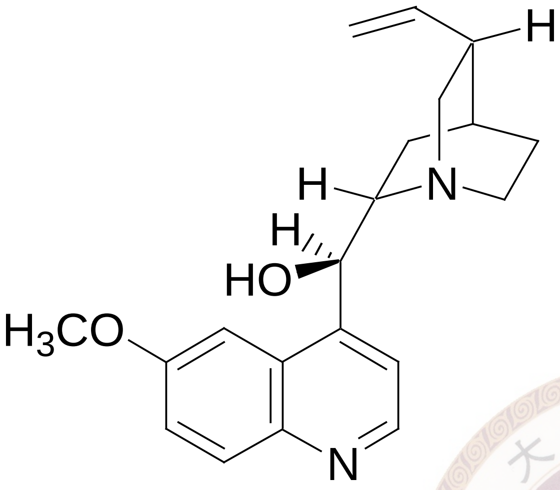
amphetamine



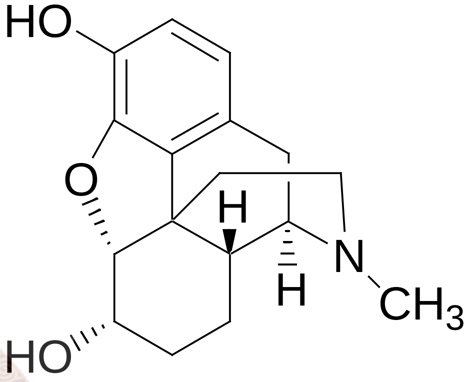
histamine



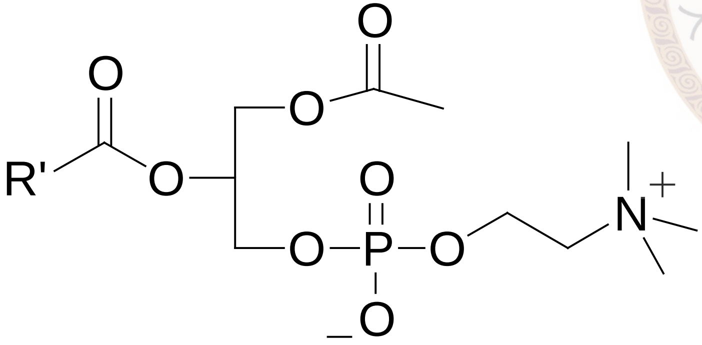
chlorpheniramine
(an antihistamine)



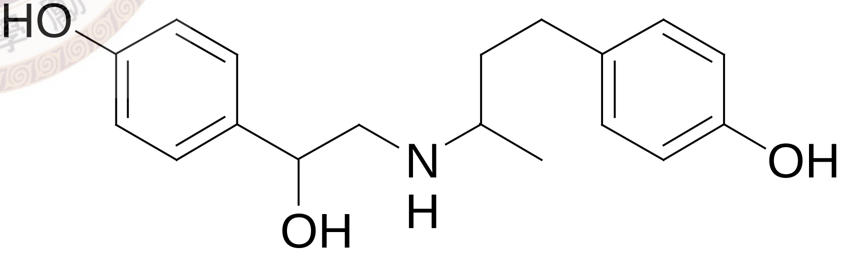
(-)-qunine



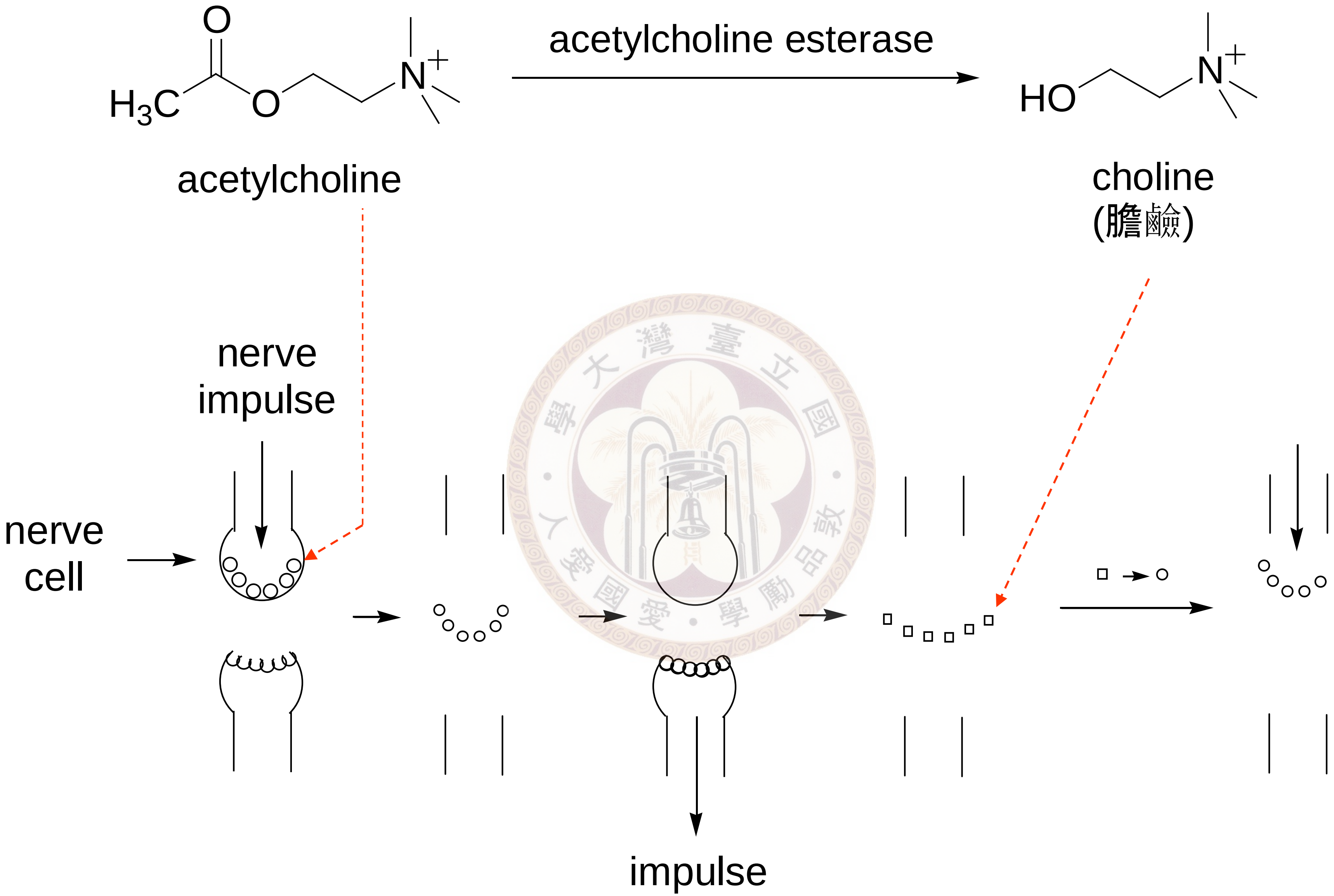
morphine



lecithins
(卵磷脂)



ractopamine



acetylcholine esterase

acetylcholine

choline
(膽鹼)

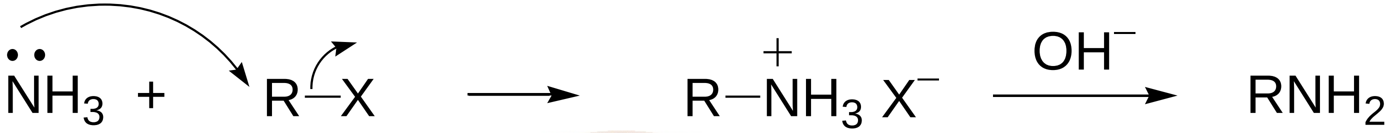
nerve impulse

nerve cell

impulse

※ Preparation

◎ Via substitutions



$$\ddot{N}H_3 + R-X \longrightarrow R-\overset{+}{N}H_3\ X^- \xrightarrow{OH^-} RNH_2$$

Problem:

multiple alkylations

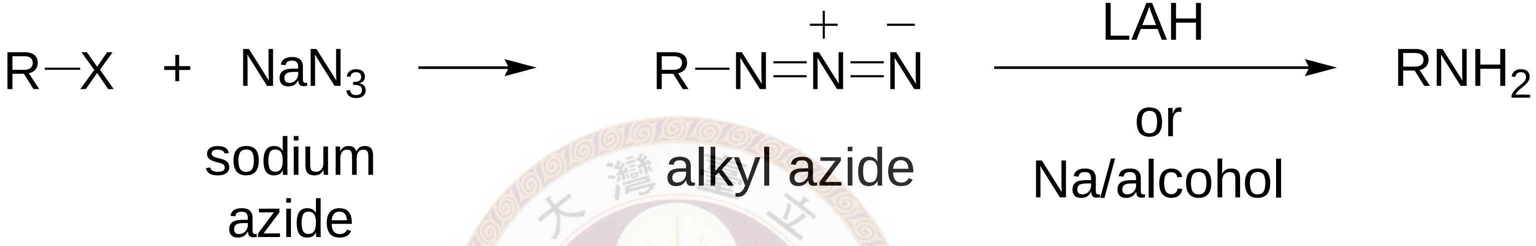
$$RNH_2 + R\text{-}X \xrightarrow{OH^-} R_2NH$$

$$R_2NH + R\text{-}X \xrightarrow{OH^-} R_3N$$

$$R_3N + R\text{-}X \xrightarrow{OH^-} R_4\overset{+}{N}\ X^-$$

Some solutions:

- ✓ Use excess amine to stop at mono-alkylations
- ✓

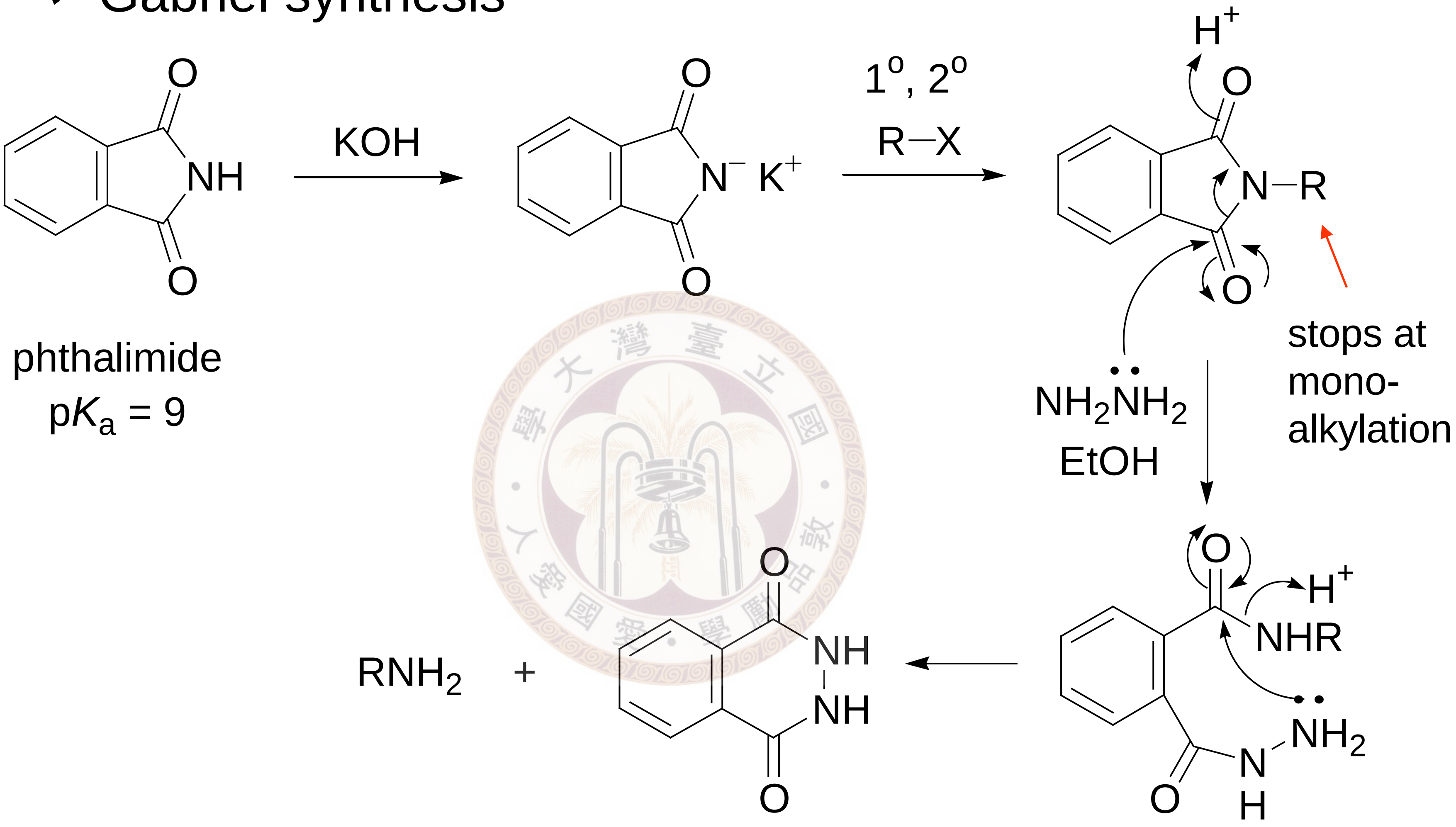


$$R{-}X + NaN_3 \longrightarrow R{-}N{=}\overset{+}{N}{=}\overset{-}{N} \xrightarrow[\text{or Na/alcohol}]{\text{LAH}} RNH_2$$

sodium azide

alkyl azide

✓ Gabriel synthesis



phthalimide

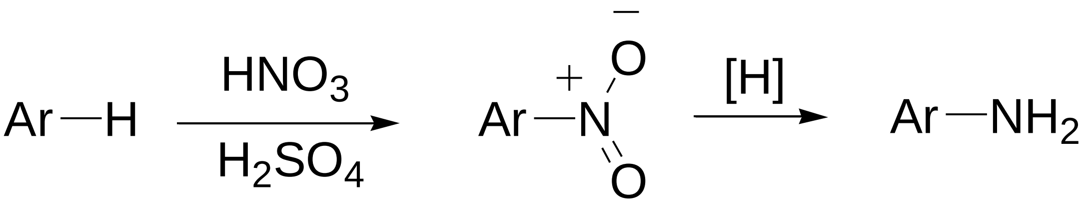
pK_a = 9

stops at mono-alkylation

phthalazine-1,4-dione

◎ Via reduction

✓ From nitro compounds



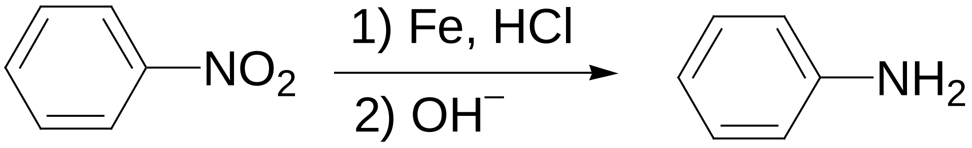
condition

H_2/Ni

or 1) Fe, HCl; 2) OH^-

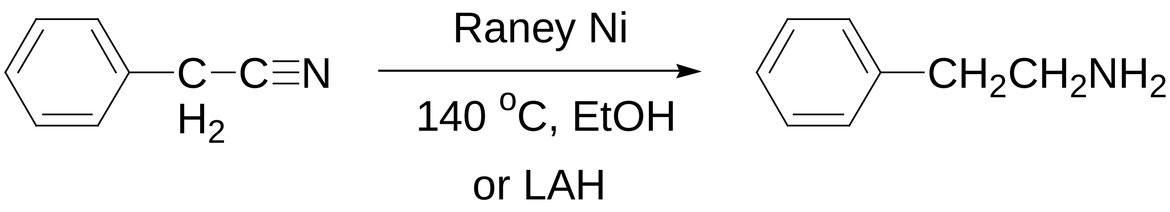
or 1) Zn, AcOH; 2) OH^-

or 1) Sn, HCl; 2) OH^-

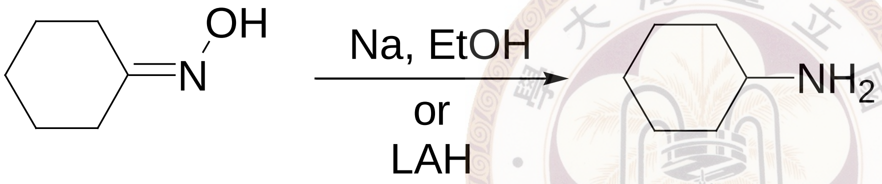


97%

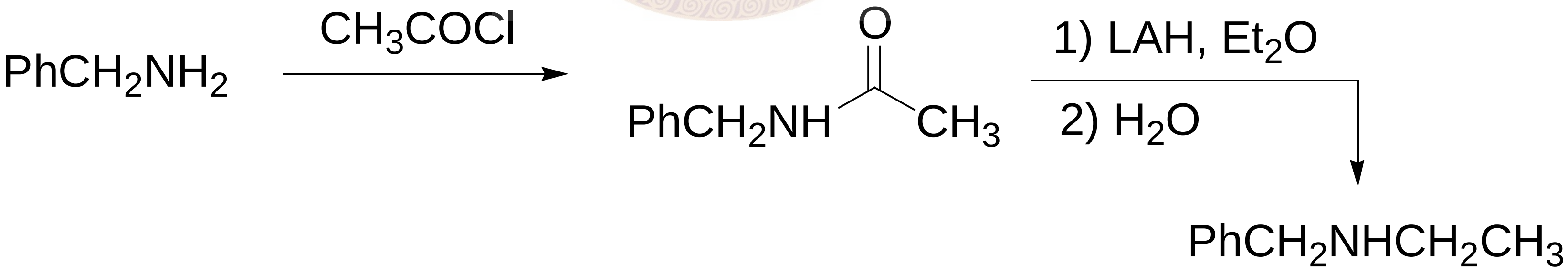
✓ From cyanide



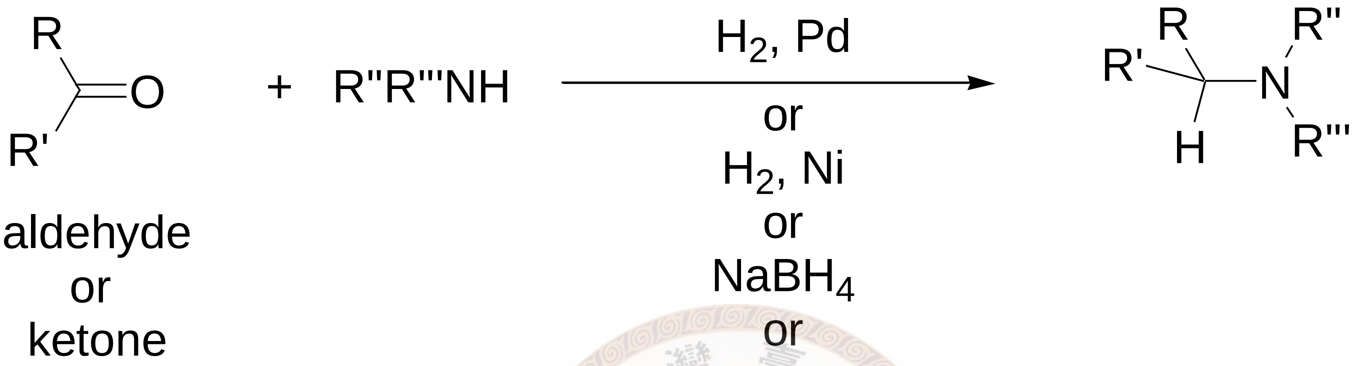
✓ From oximes



✓ From amides



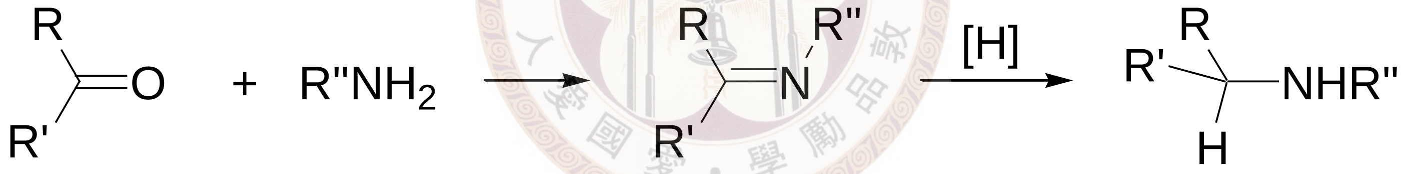
★ Reductive amination



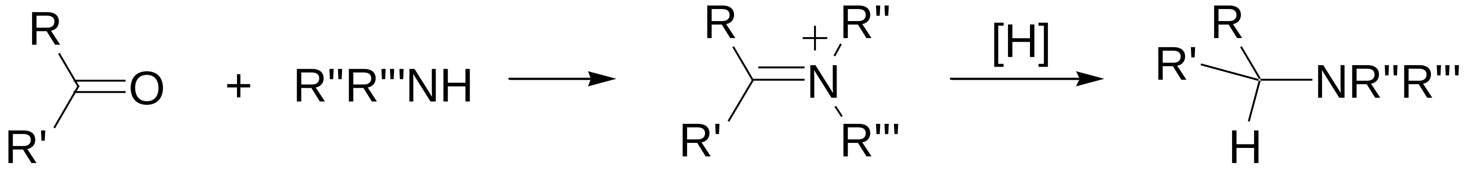
aldehyde
or
ketone

H_2, Pd
or
H_2, Ni
or
$NaBH_4$
or
$NaBH_3CN$ at pH ~3

Mechanism:

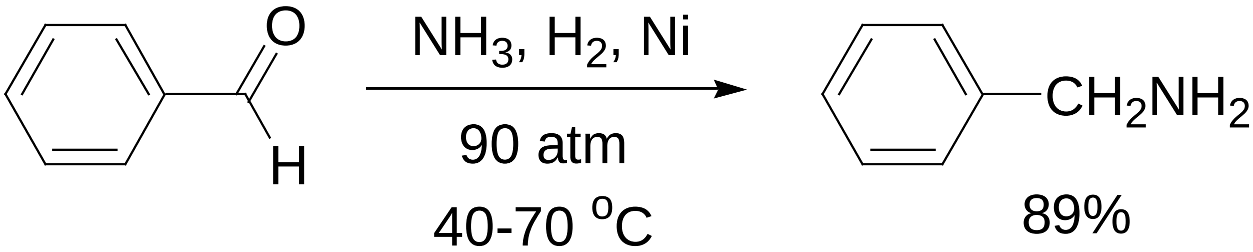


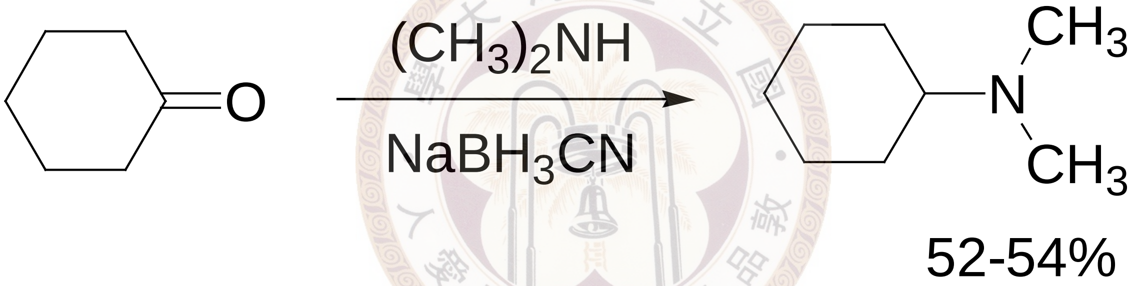
imine
(Schiff base)



iminium ion

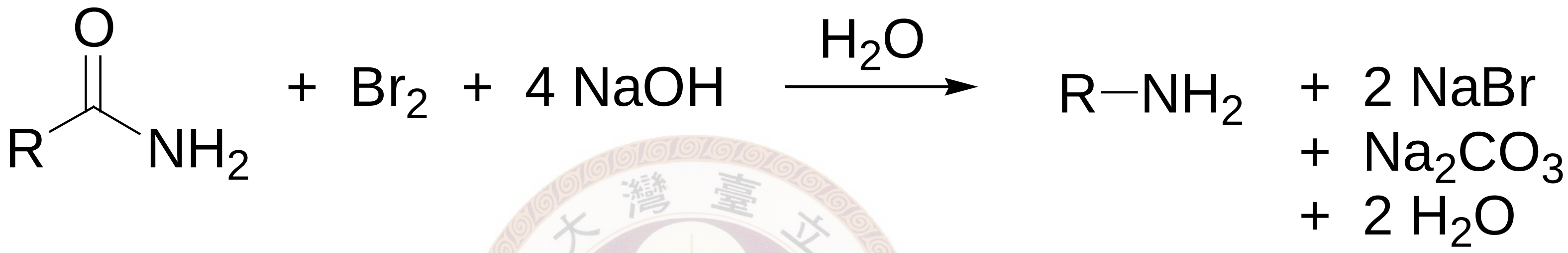
例


O
H
NH_3, H_2, Ni
90 atm
40-70 °C
CH_2NH_2
89%

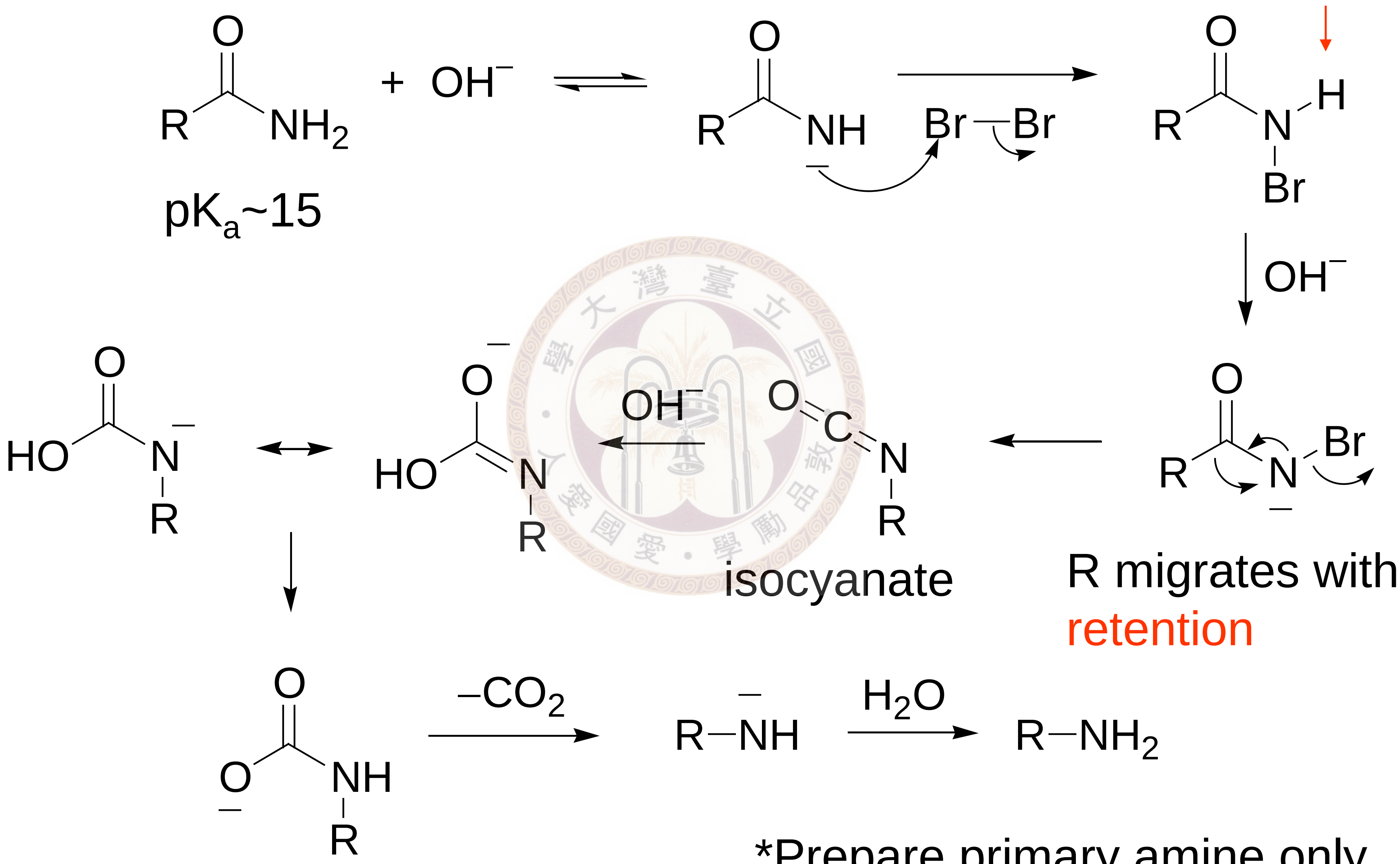

O
$(CH_3)_2NH$
$NaBH_3CN$
N
CH_3
CH_3
52-54%

◎ Through rearrangements

✓ Hofmann rearrangement (Hofmann degradation)



Mechanism:



more acidic

pK_a~15

isocyanate

R migrates with retention

*Prepare primary amine only

※ Reactions of amines

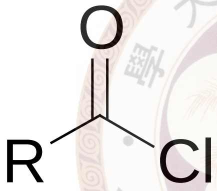
◎ Substitution reaction

Amines are good nucleophiles

— better than oxygen compounds

reacts with R-LVG

or



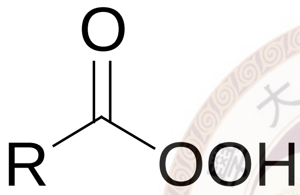
$RCOCl$

◎ Oxidation of amines

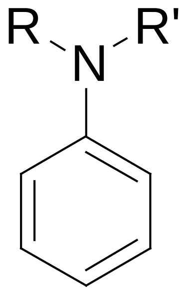
$$R_3N \quad + \quad H_2O_2 \quad \longrightarrow \quad R_3\overset{+}{N}-\overset{-}{O}$$

tertiary amines

or



a tertiary amine oxide



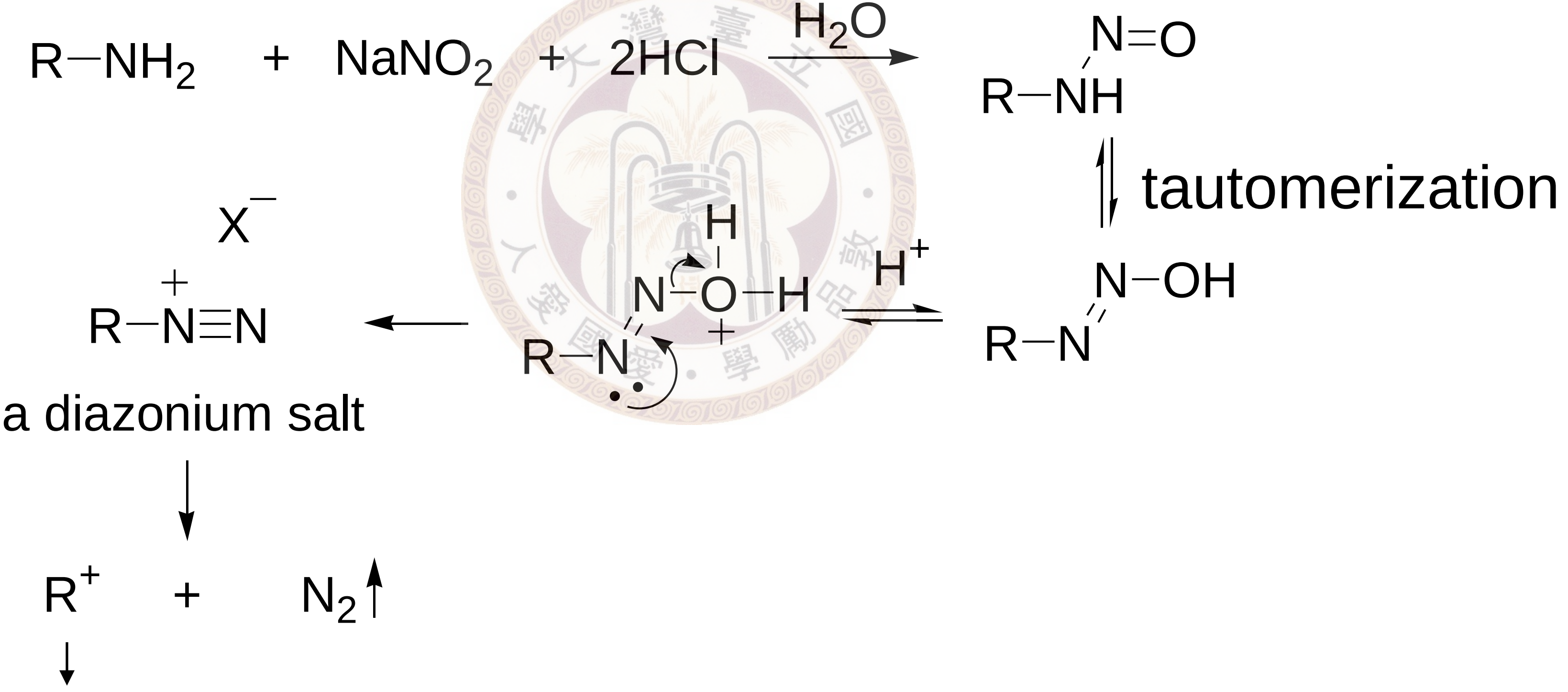
← Electron rich, oxidize the ring easily

◎ Reaction with nitrous acid (HNO_2)

$$NaNO_{2\,(aq)} + HCl_{(aq)} \rightarrow HO\text{-}N{=}O_{(aq)} + NaCl_{(aq)}$$

sodium nitrite (H_2SO_4) (Na_2SO_4)

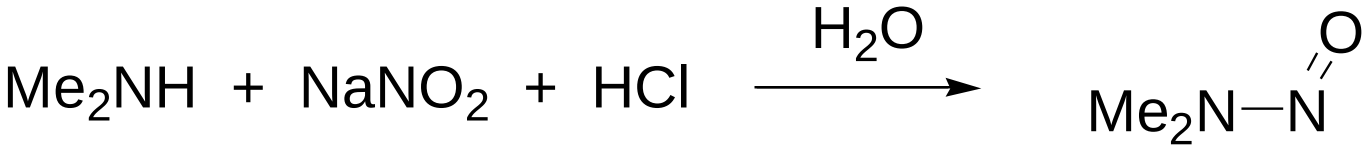
✓ 1° Aliphatic amines



Alkenes, alcohols, alkyl halides

→ Not useful for 1° amines

- ✓ 2° Aliphatic amines



$$Me_2NH + NaNO_2 + HCl \xrightarrow{H_2O} Me_2N{-}N{=}O$$

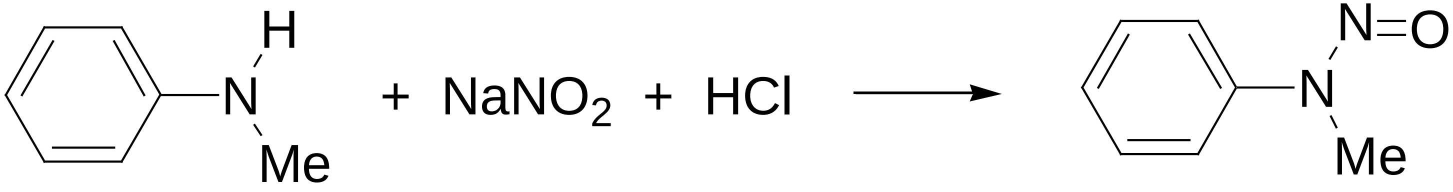
N-nitrosodimethylamine
(yellow color)
strong carcinogen

- ✓ 1° Aryl amines

$$Ar{-}NH_2 + NaNO_2 + HX \longrightarrow Ar{-}\overset{+}{N}{\equiv}N \; X^-$$

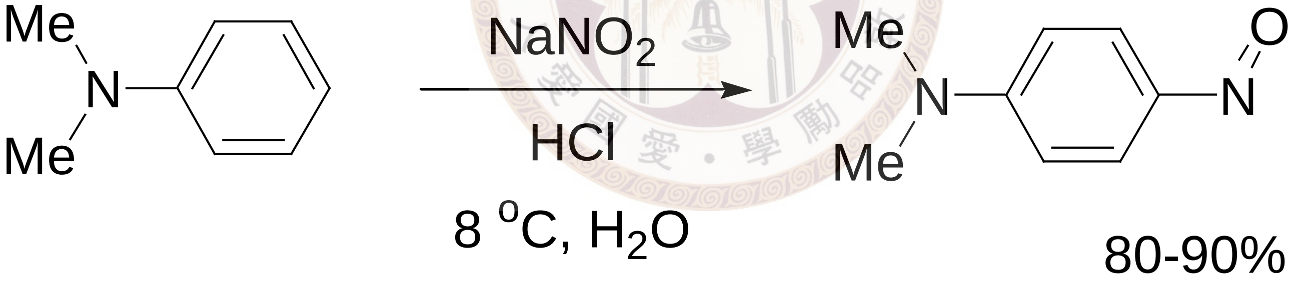
arenediazonium salts
more stable
decompose at higher T

✓ 2^o Aryl amines



yellow color

✓ 3^o Aryl amines



◎ Reactions of arenediazonium salts

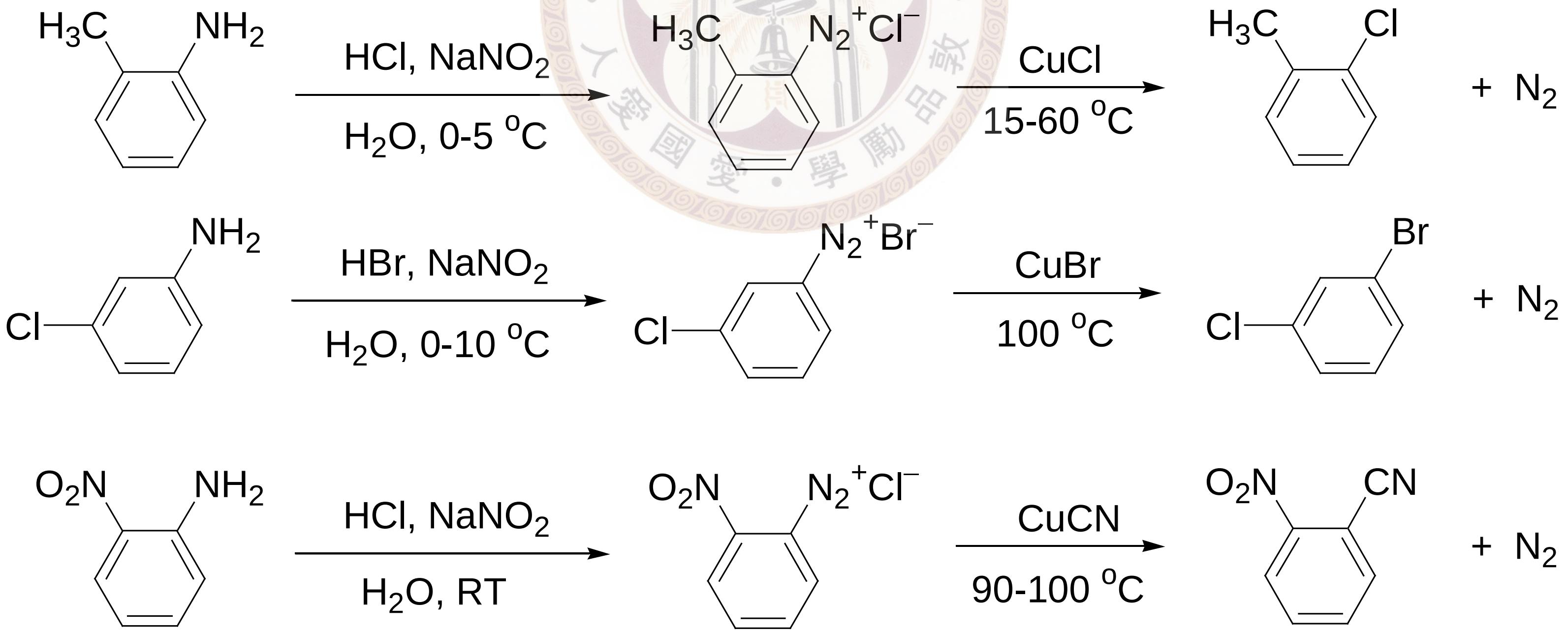
✓ The Sandmeyer reaction

$$Ar{-}N_2^+ \xrightarrow{CuCl} Ar{-}Cl$$

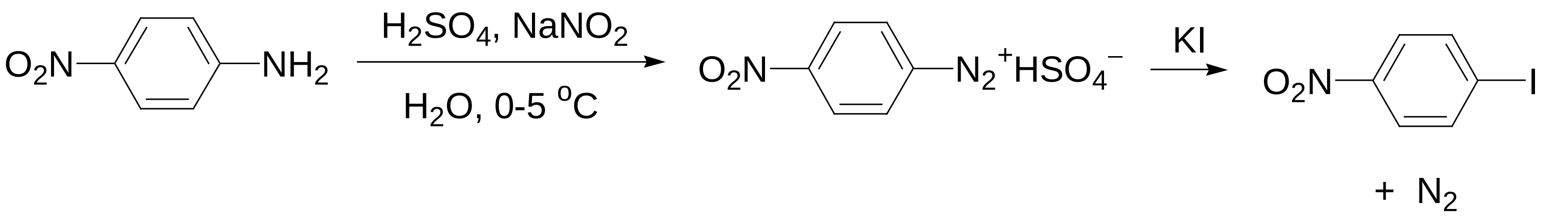
$$Ar{-}N_2^+ \xrightarrow{CuBr} Ar{-}Br$$

$$Ar{-}N_2^+ \xrightarrow{CuCN} Ar{-}CN$$

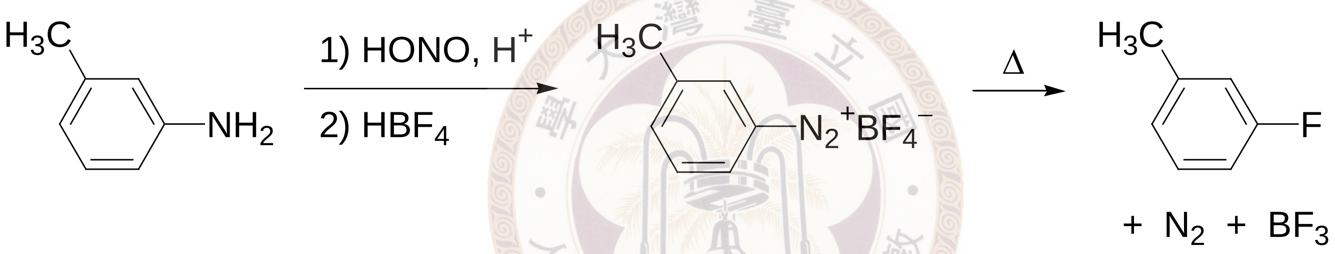
例



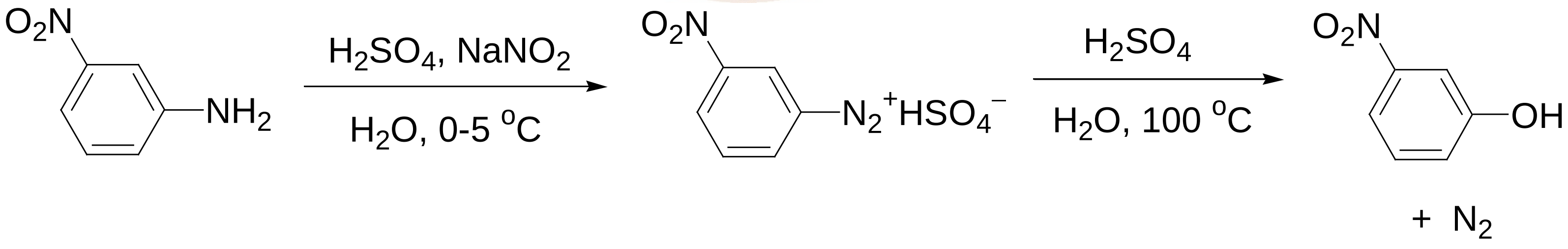
✓ Aryl iodides



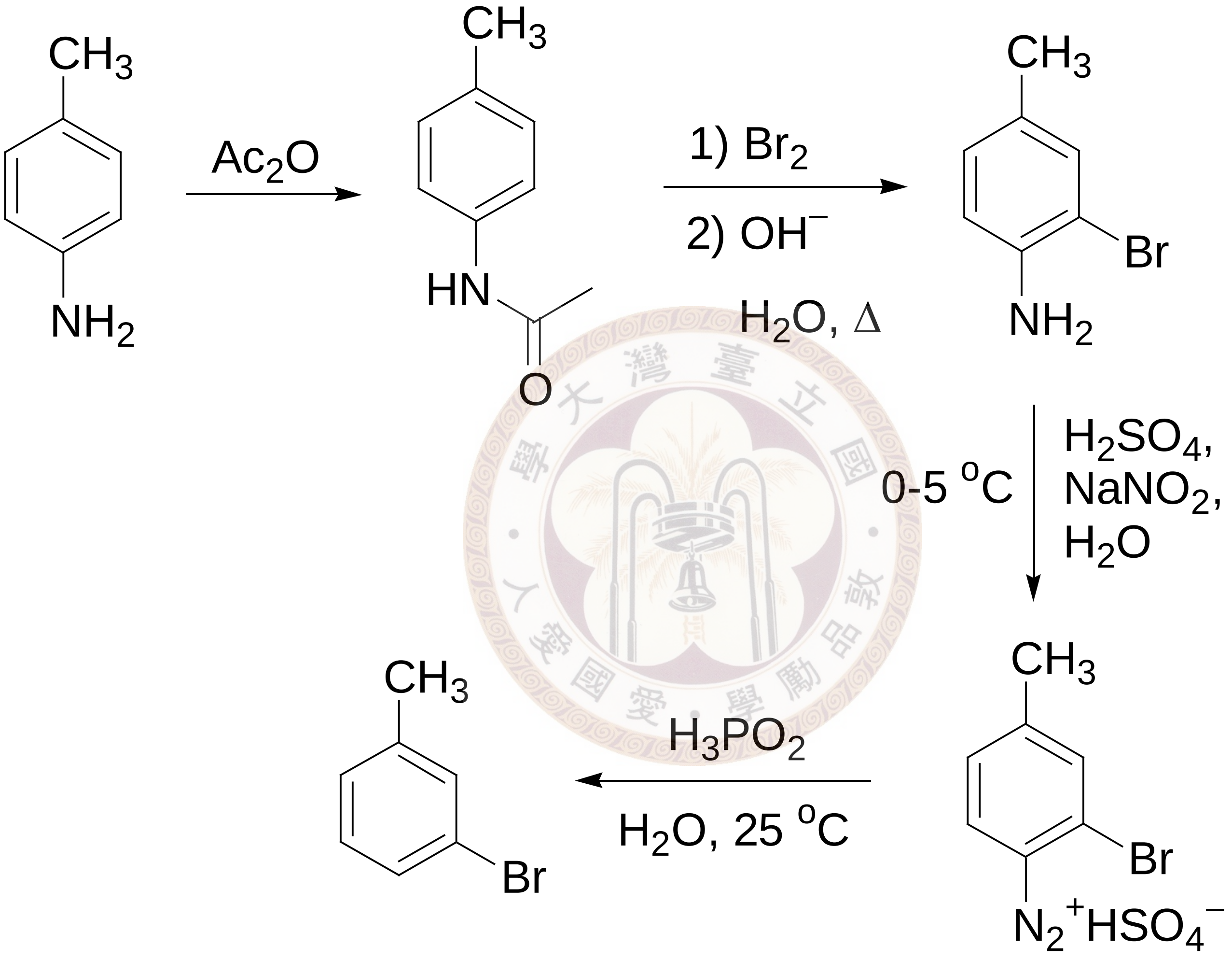
✓ Aryl fluorides



✓ Phenols

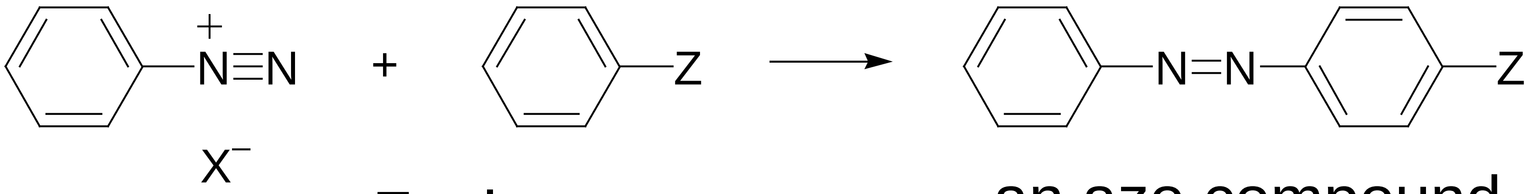


✓ Deamination



H_3PO_2 hypophosphorous acid

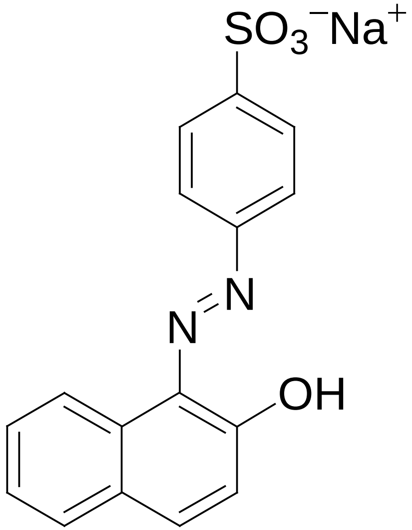
✓ Coupling reactions



Z: electron
donating group

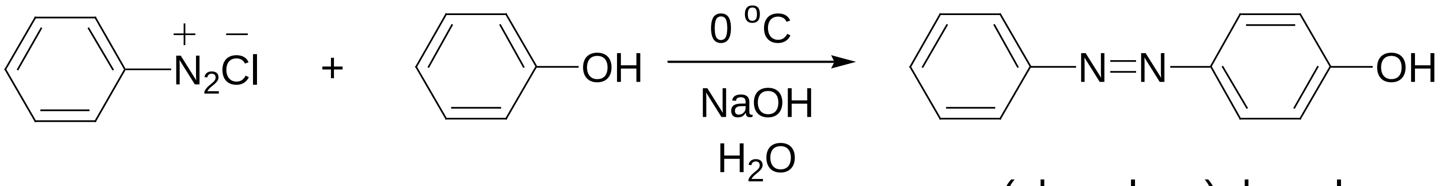
an azo compound
colored (azo dyes):
with highly conjugated
π system

例

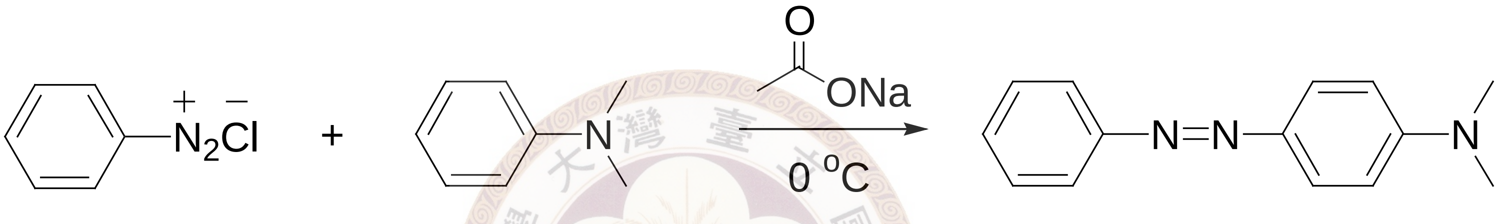


orange II

例

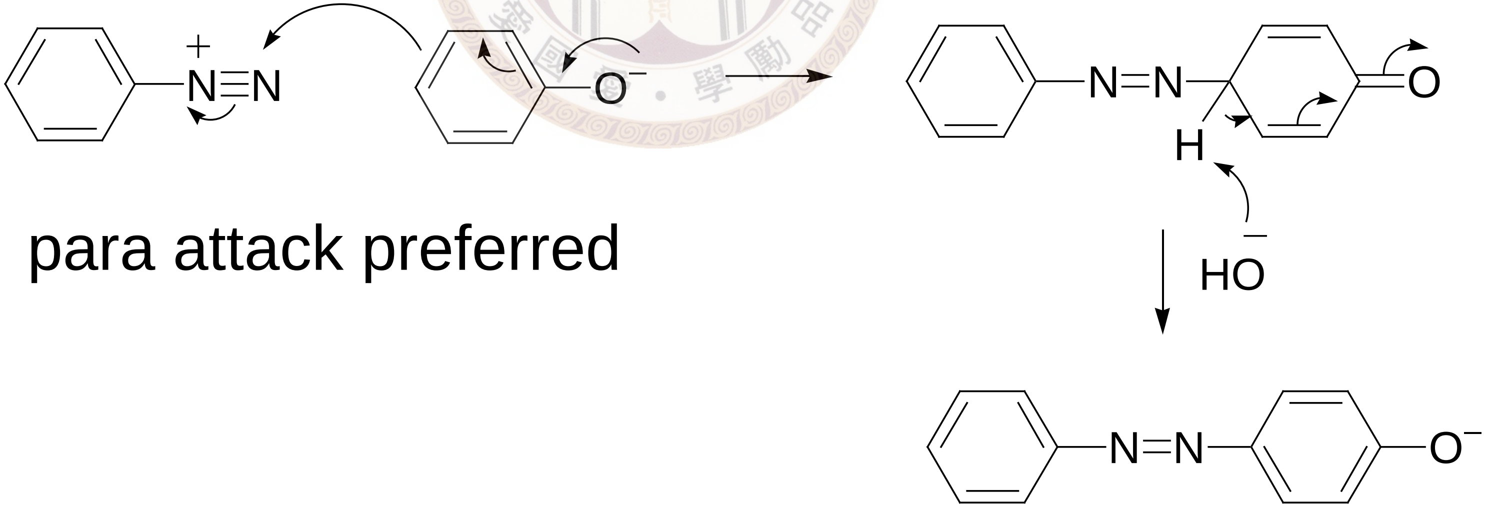


p-(phenylazo)phenol
orange color



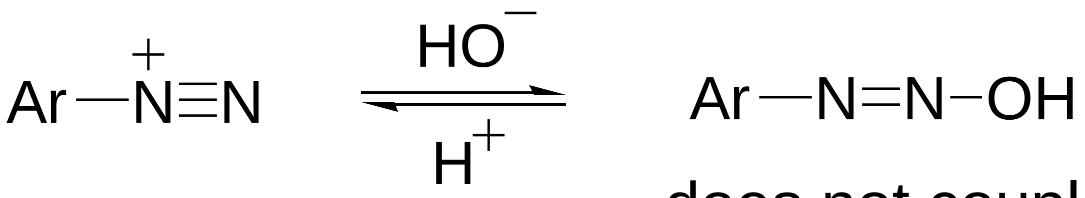
yellow color

Mechanism:



para attack preferred

If too basic:



$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N} \underset{H^+}{\overset{HO^-}{\rightleftharpoons}} \mathrm{Ar{-}N{=}N{-}OH}$$

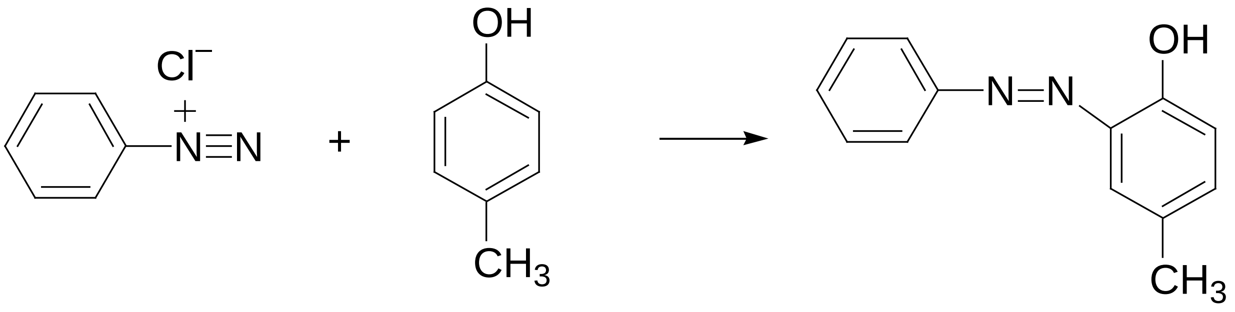
does not couple

For arylamines: pH 5-7 is preferred

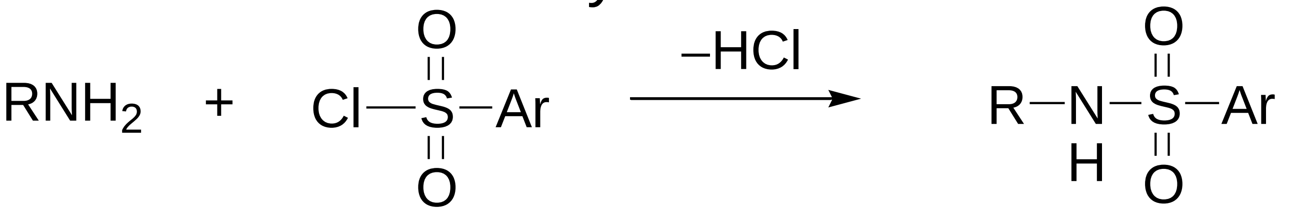
If too acidic:

does not couple

Ortho coupling also possible

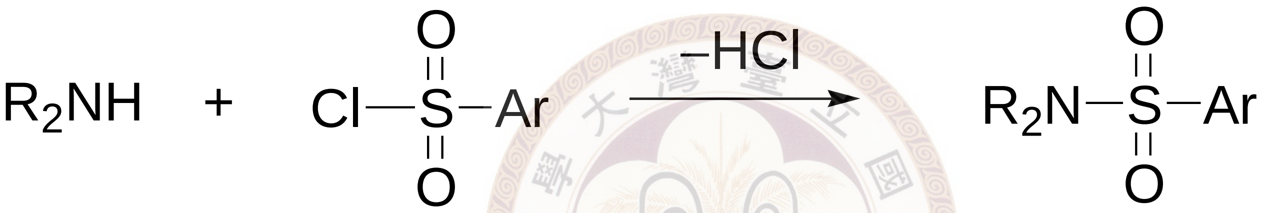


◎ Reactions with sulfonyl chlorides

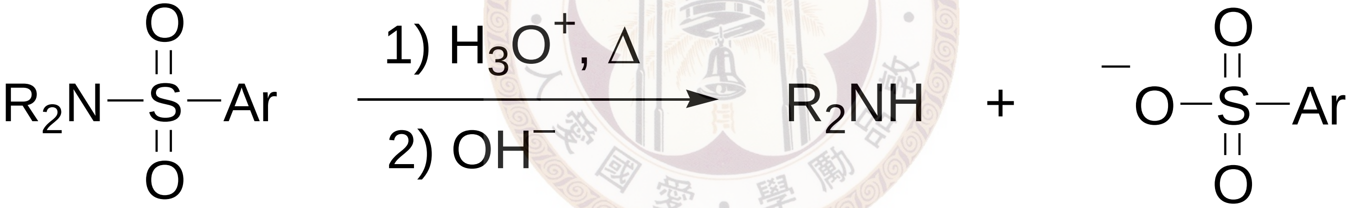


$$RNH_2 + Cl-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar \xrightarrow{-HCl} R-\underset{H}{N}-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar$$

a sulfonamide

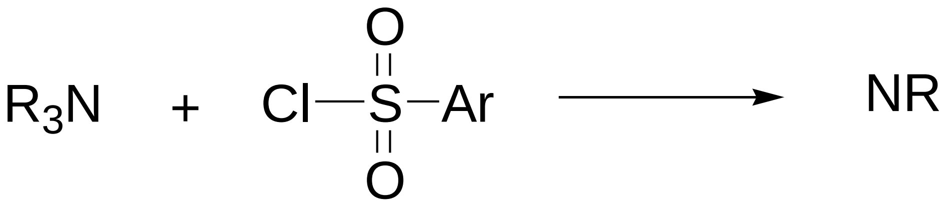


$$R_2NH + Cl-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar \xrightarrow{-HCl} R_2N-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar$$



$$R_2N-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar \xrightarrow[\text{2) } OH^-]{\text{1) } H_3O^+,\ \Delta} R_2NH + {}^-O-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar$$

The sulfonyl group can be used as a protecting group

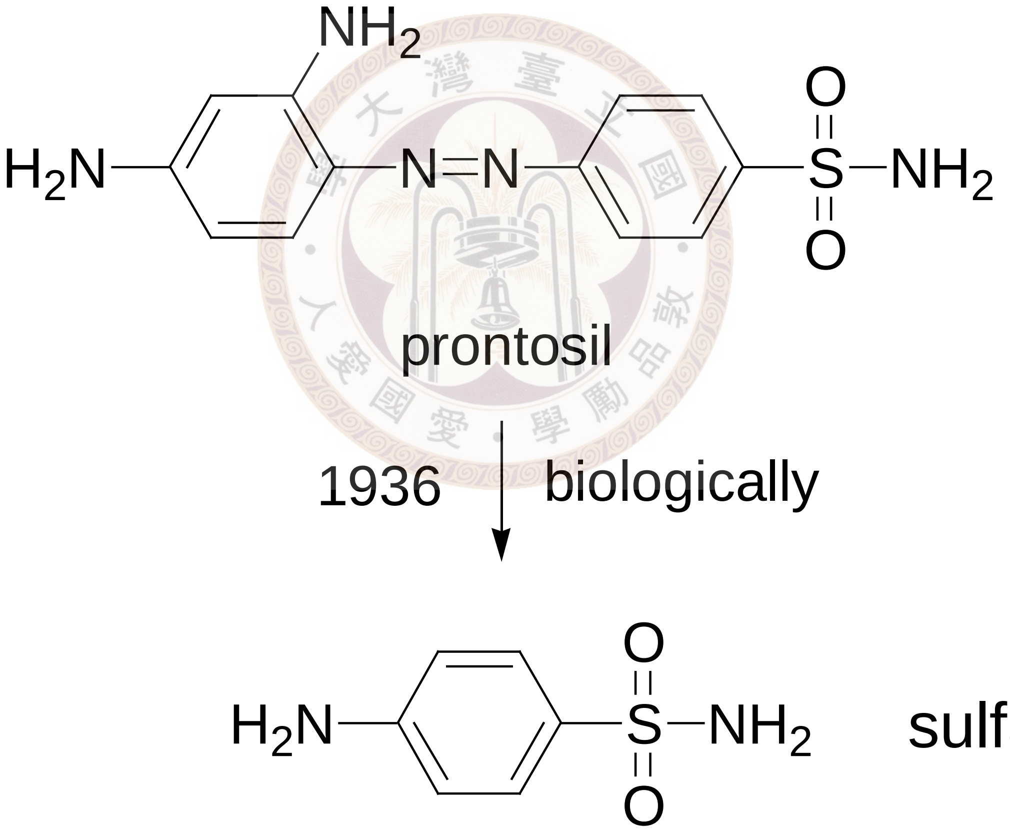


$$R_3N + Cl-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Ar \longrightarrow NR$$

※ The sulfa drugs

Paul Ehrlich Chemotherapy

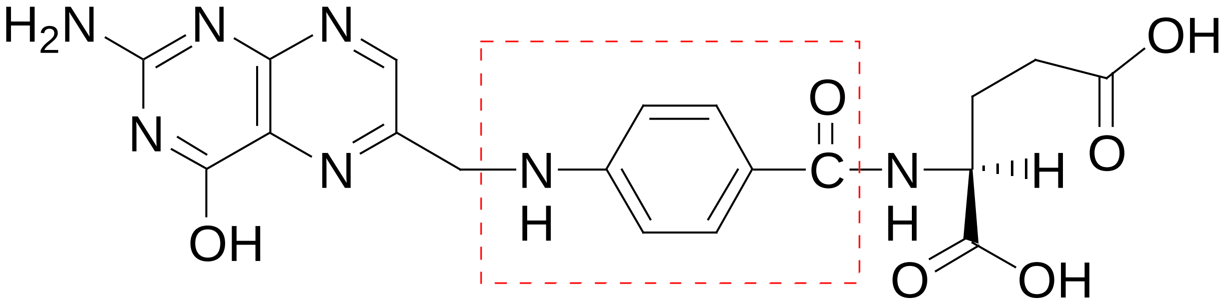
Gerhard Domagk 1935



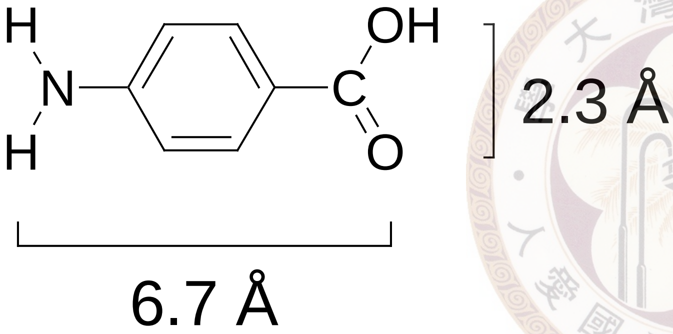
prontosil

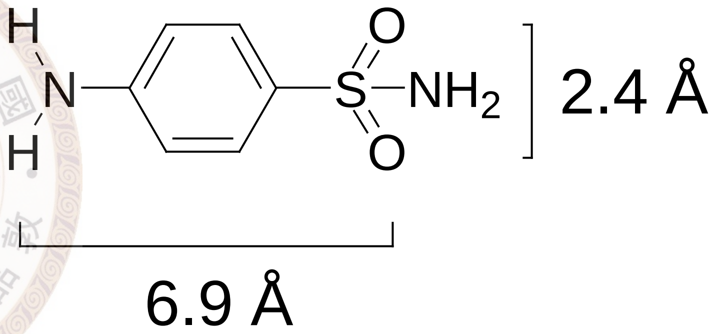
1936 biologically

sulfanilamide

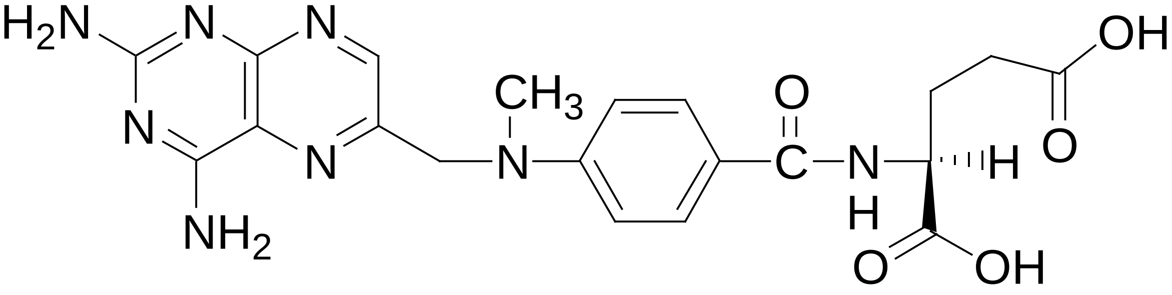


folic acid



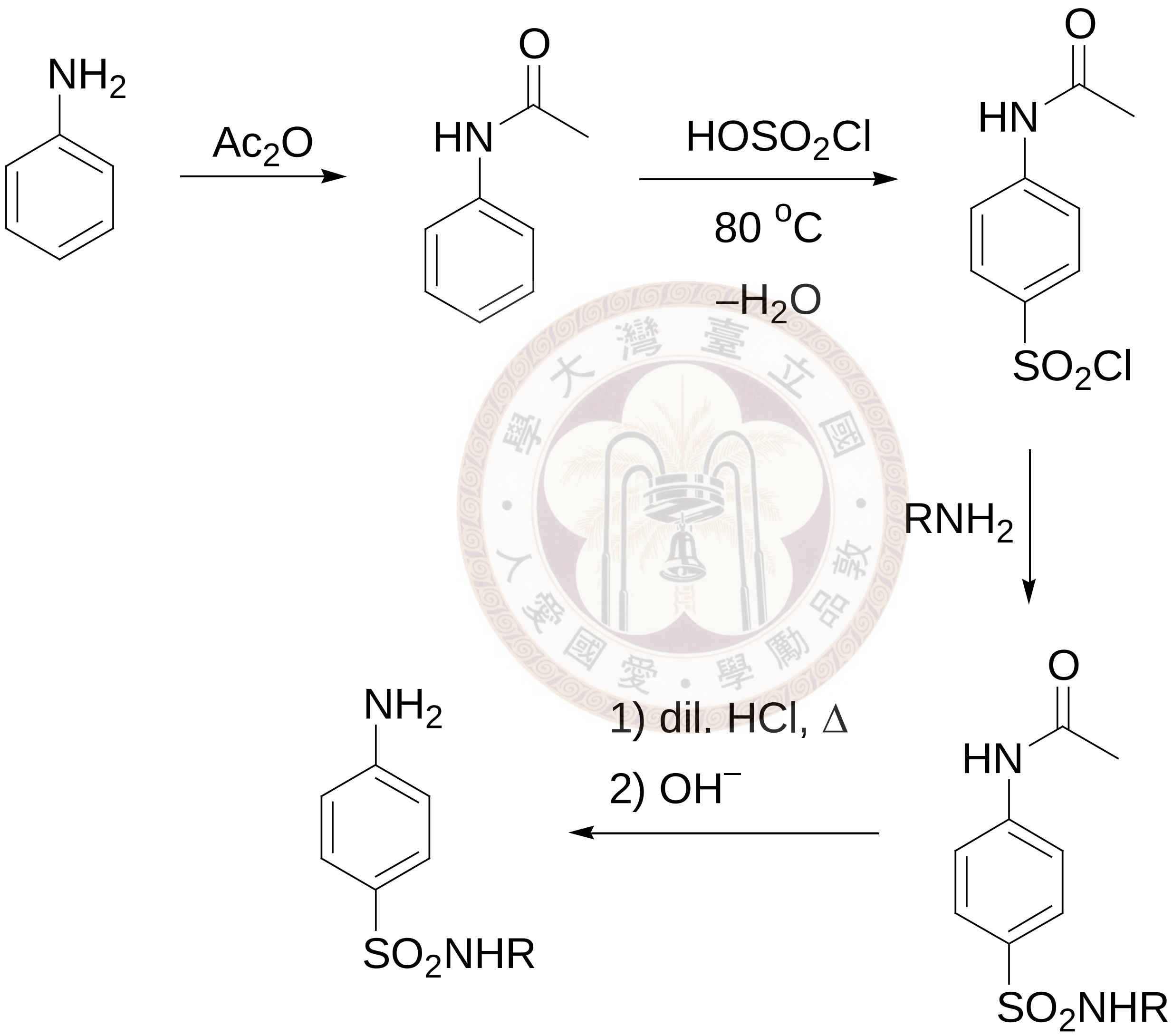


Folic acid is important in cell division



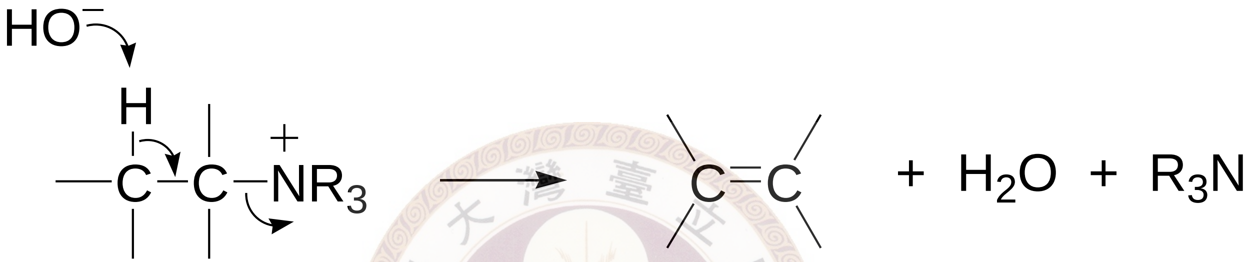
methotrexate:
anti-cancer

◎ Preparation of sulfa drugs

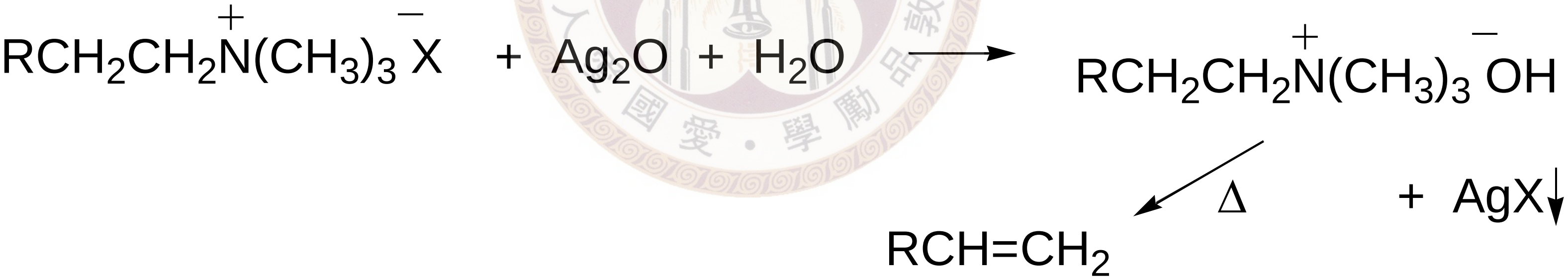


※ Ammonium compounds

The Hofmann elimination



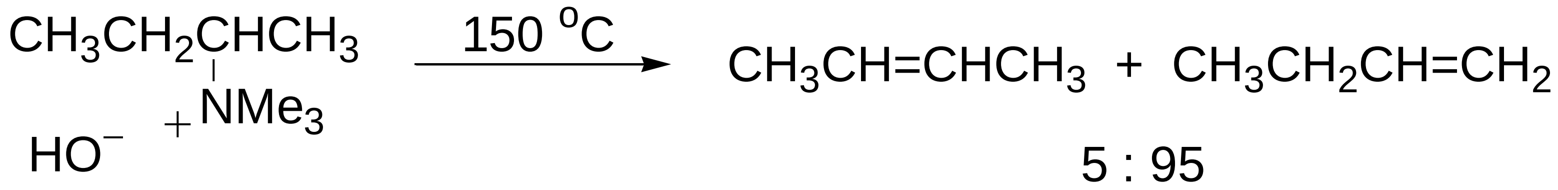
$$\mathrm{HO^-} + \mathrm{H{-}\overset{|}{C}{-}\overset{|}{C}{-}\overset{+}{N}R_3} \longrightarrow \mathrm{C{=}C} + H_2O + R_3N$$



$$RCH_2CH_2\overset{+}{N}(CH_3)_3\,\overset{-}{X} + Ag_2O + H_2O \longrightarrow RCH_2CH_2\overset{+}{N}(CH_3)_3\,\overset{-}{O}H + AgX\downarrow$$

$$RCH_2CH_2\overset{+}{N}(CH_3)_3\,\overset{-}{O}H \xrightarrow{\Delta} RCH{=}CH_2$$

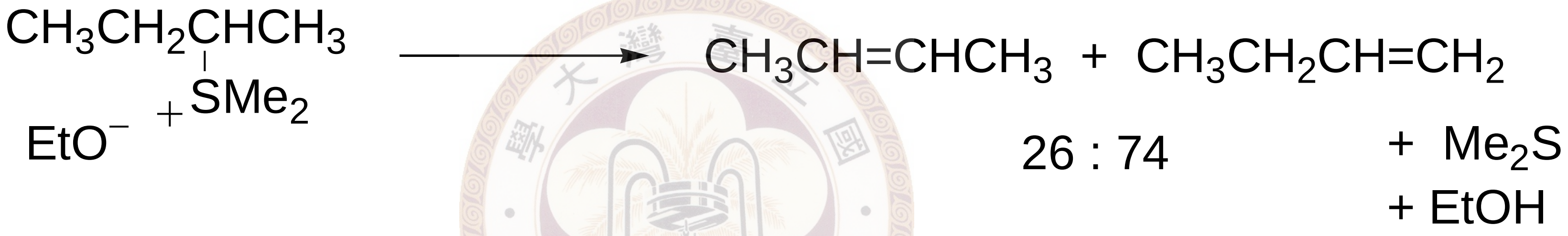
✓ Regiochemistry: The Hofmann elimination



$$\underset{HO^- \quad \overset{+}{N}Me_3}{CH_3CH_2\underset{|}{C}HCH_3} \xrightarrow{150\ ^{o}C} CH_3CH=CHCH_3 + CH_3CH_2CH=CH_2$$

5 : 95

cf.



$$\underset{EtO^- \quad \overset{+}{S}Me_2}{CH_3CH_2\underset{|}{C}HCH_3} \longrightarrow CH_3CH=CHCH_3 + CH_3CH_2CH=CH_2 + Me_2S + EtOH$$

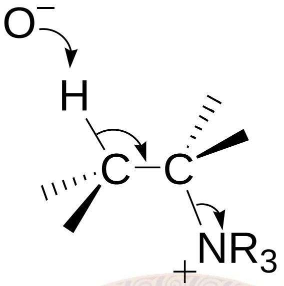
26 : 74

$$\underset{Br}{CH_3CH_2\underset{|}{C}HCH_3} \xrightarrow{NaOEt}$$

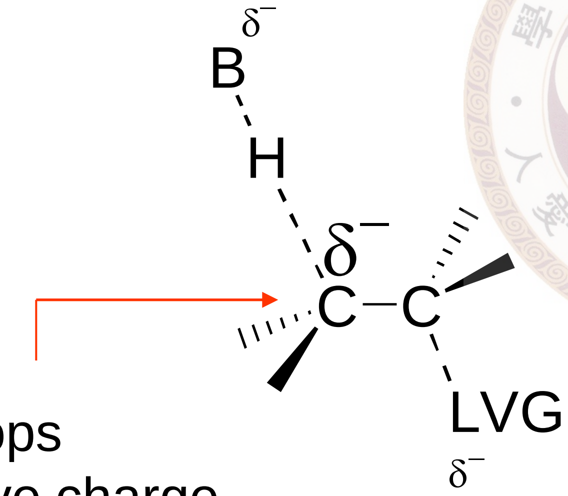
75 : 25

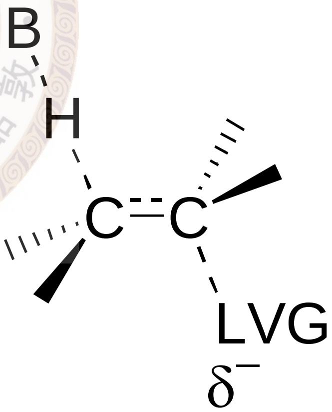
Reason:

Basic requirement for elimination – anti-periplanar



Further consideration



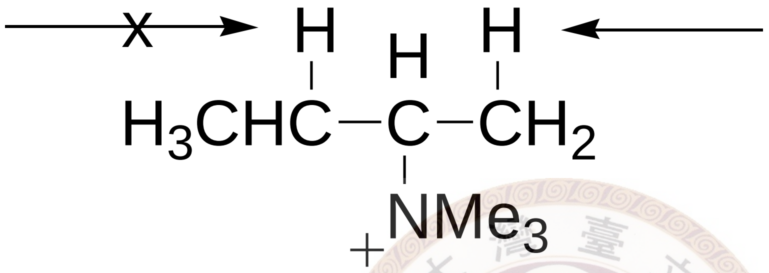


Develops
negative charge
on this carbon ⟹ Carbanion like

Alkene like transition state
→ Zaitsev orientation
gives more stable compound

*Carbanion stability

$1^o > 2^o > 3^o$



$H_3CH\overset{H}{C}-\underset{\overset{+}{N}Me_3}{\overset{H}{C}}-\overset{H}{C}H_2$

preferred

※ Spectroscopy

IR: N-H stretching 3300-3550 cm^{-1} (br)

^{1}H NMR

N-H δ 1-5 depends on concentration

	CH_3NR_2	RCH_2NR_2	R_2CHNR_2
δ	2.2	2.4	2.8

MS