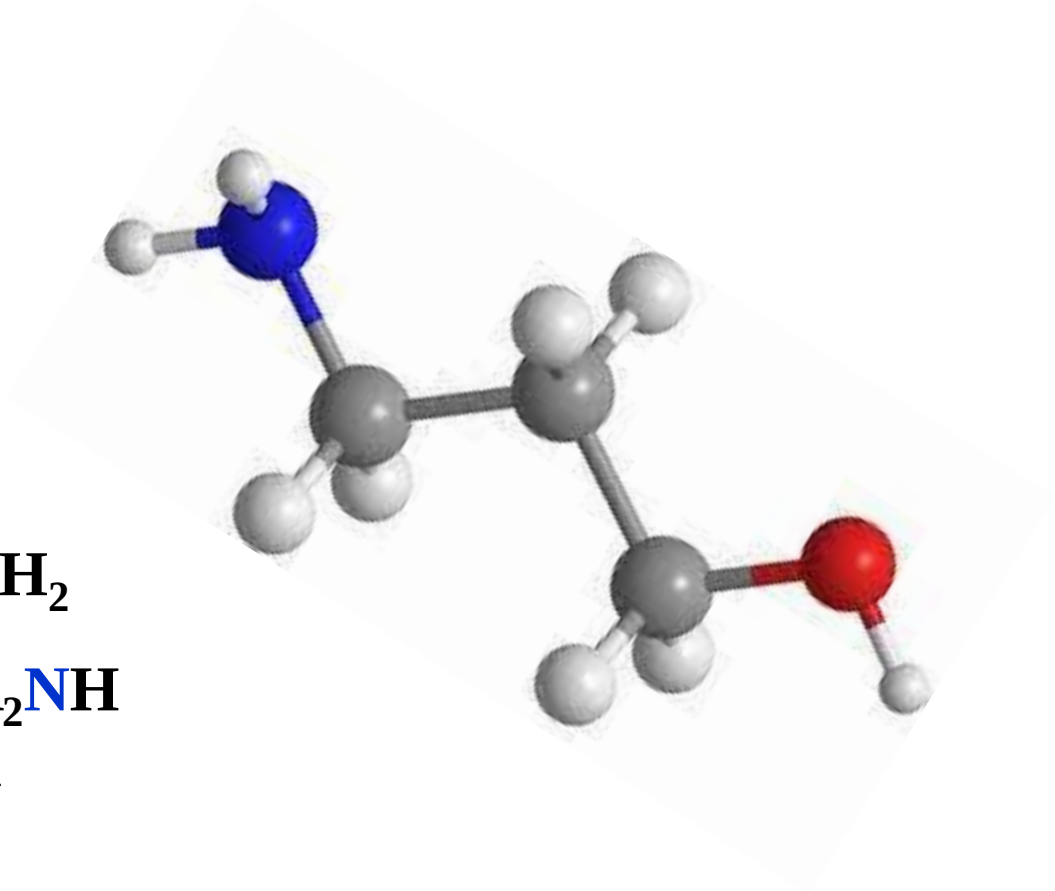
Chapter 14 : Amines



1° (primary amine) RNH_2

2° (secondary amine) R_2NH

3° (tertiary amine) R_3N

4° (quaternary amine salt) R_4N^+

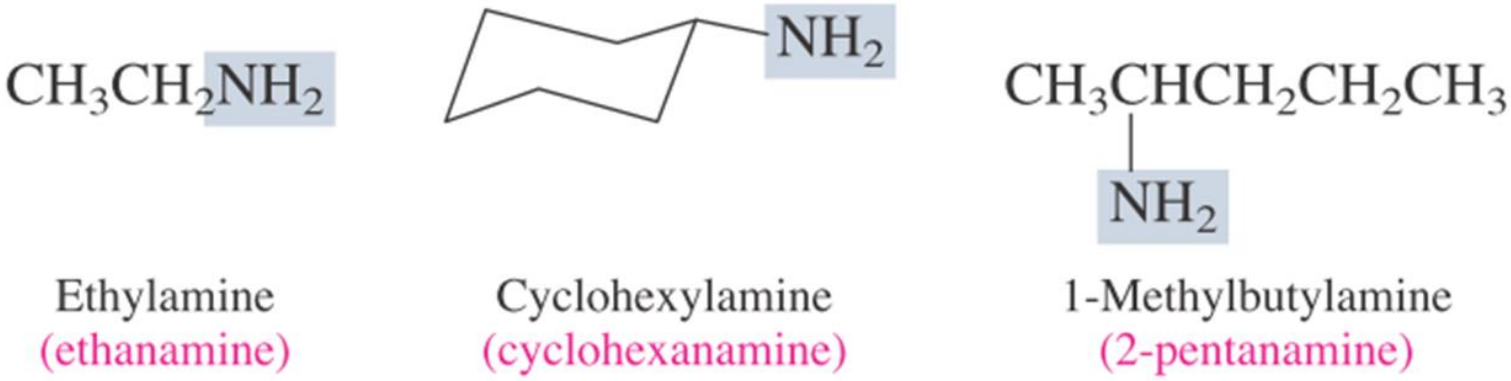
Primary Amine

- **Common name:**

Alkylamines -When primary amines are named as **alkylamines**, the ending –amine is added to the name of the alkyl group that bears the nitrogen.

- **IUPAC system:**

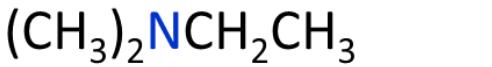
Alkanamines – The suffix -e of the parent alkane replaced by –amine.



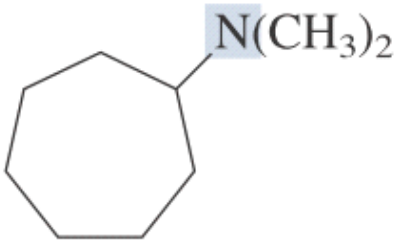
Secondary and Tertiary Amine

- Secondary and tertiary amines are named as **N-substituted derivatives of primary amines.**
- The parent primary amine is taken to be the one with **the longest carbon chain.**
- The prefix N- is added as a locant to identify substituents on the amino nitrogen as needed.

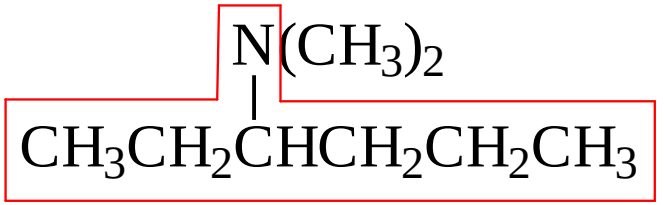
N-Methylethylamine



N,N-dimethylethylamine

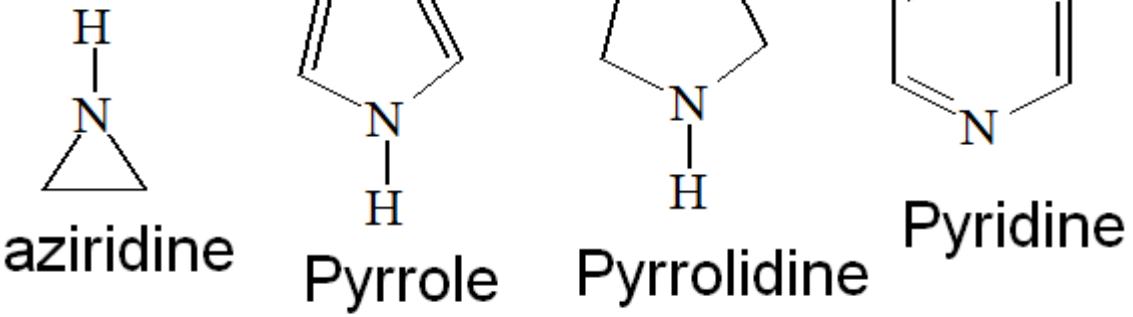


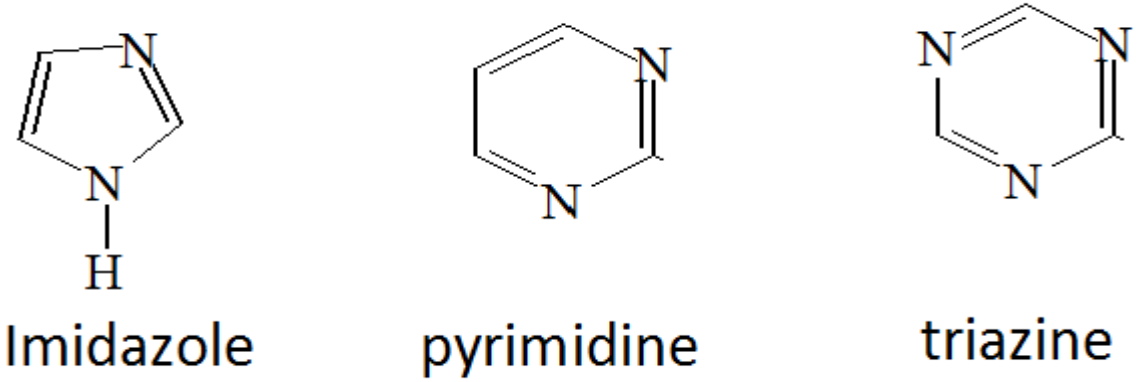
N,N-Dimethylcyclo-heptylamine



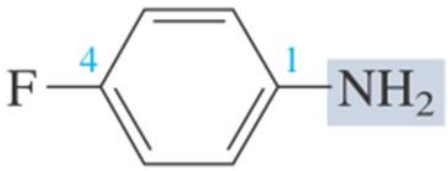
N,N-dimethyl-3-hexanamine

Some Common Nitrogen Containing Heterocycles

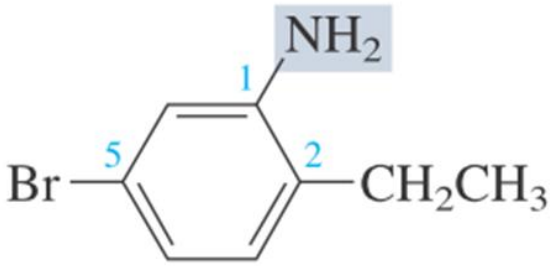




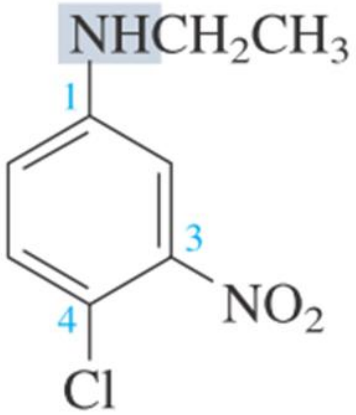
Aniline.



p-Fluoroaniline



5-Bromo-2-ethylaniline



4-Chloro-*N*-ethyl-3-nitroaniline
(a secondary amine)

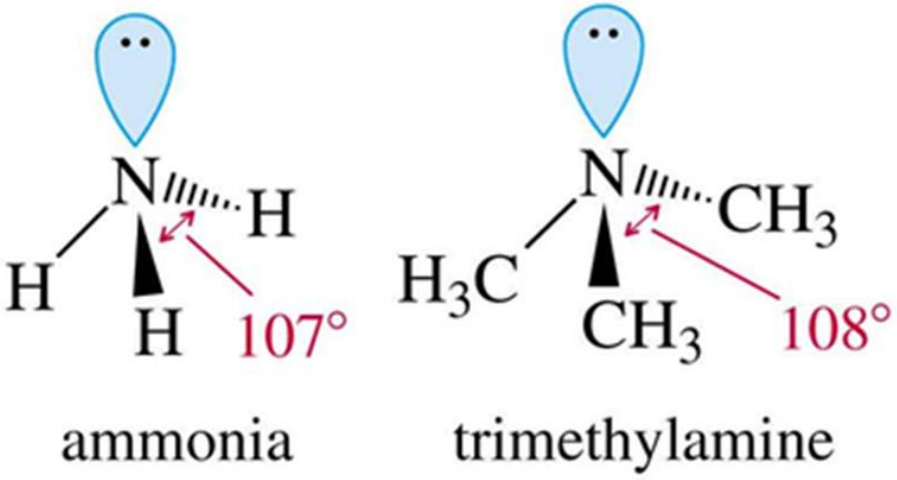
IUPAC Priority of Amine

- Among the various functional groups discussed in the text, -NH_2 is one of the **lowest in order of precedence**.

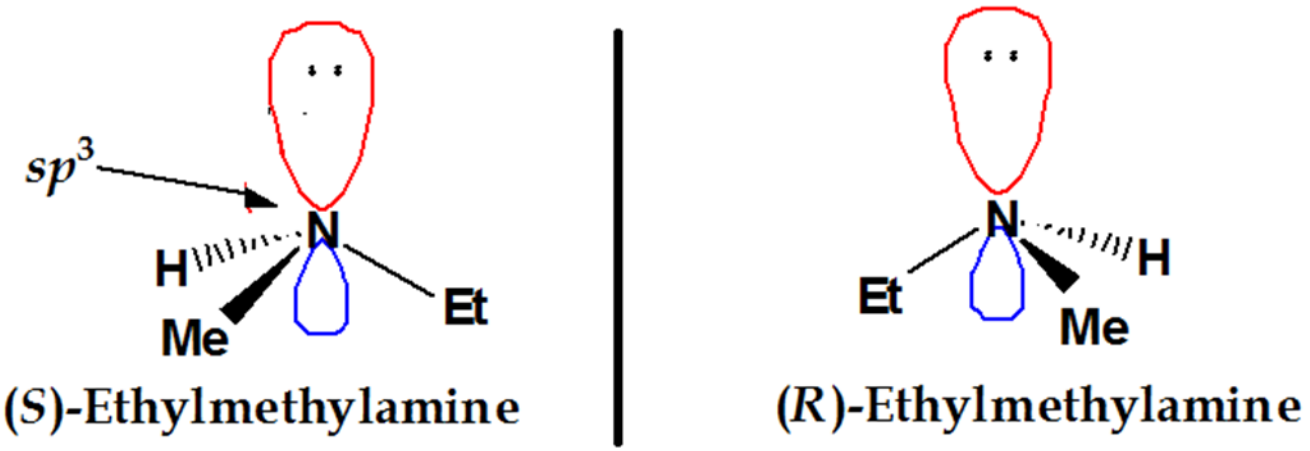
$H_2NCH_2CH_2OH$
2-Aminoethanol

$H_2NCH_2CH_2CH_2CO_2H$
4-Aminobutanoic acid

- Amines have an sp^3 hybridized nitrogen with **a lone pair of electrons in an *sp*^{3} orbital.**

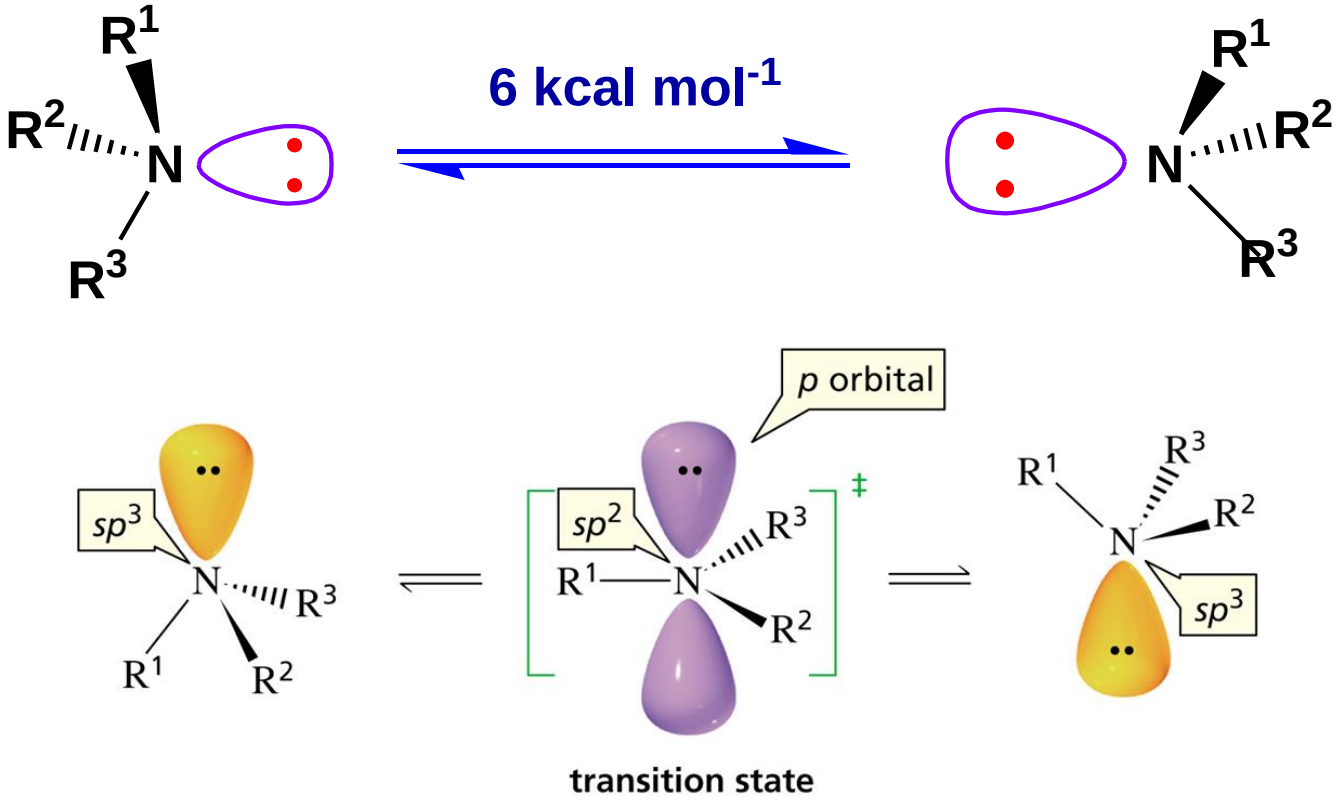


- In principle, **acyclic tertiary amines** with three different groups can be envisage to be **chiral** (i.e., **nitrogen as a stereocenter**).



THE ENANTIOMERS CANNOT BE ISOLATED.
Why???

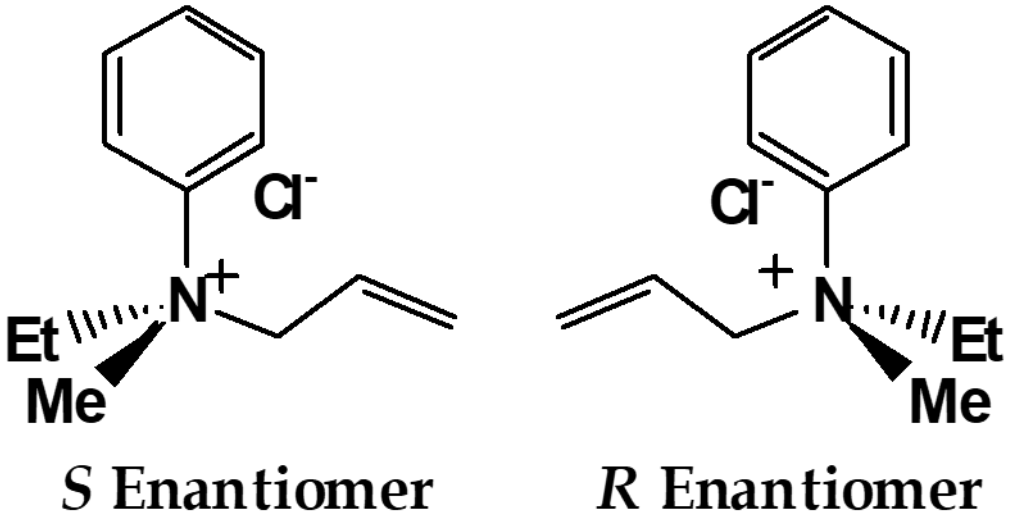
- **Rapid pyramidal inversion of the amine nitrogen** prevents isolation of the enantiomers except where the nitrogen is part of a ring or has other geometrical constraint



Enantiomers that cannot be resolved-Rapid Interconversion

- Quaternary Amines – CHIRAL:

Pyramidal inversion is not possible with quaternary ammonium ions, and their salts can be resolved.



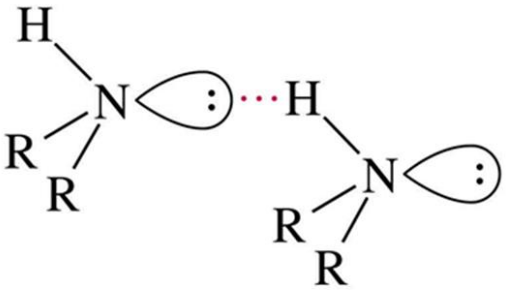
S Enantiomer *R* Enantiomer

Physical Properties

- POLARITY: Alcohol > **Amines** > Alkane

$CH_3CH_2CH_3$	$CH_3CH_2NH_2$	CH_3CH_2OH
Propane	Ethylamine	Ethanol
bp −42°C	bp 17°C	bp 78°C

- 쌍극자 – 쌍극자 상호작용과 수소 결합 (일차 및 이차 아민의 경우에만)



1° or 2° amine:
hydrogen bond donor
and acceptor

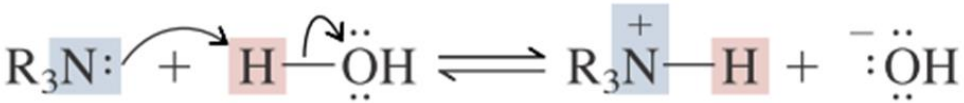
이성질체성 아민 중에서,
일차 아민이 끓는점이 가장 높고
삼차 아민이 가장 낮다.

$CH_3CH_2CH_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3N$
Propylamine	*N*-Methylethylamine	Trimethylamine
(a primary amine)	(a secondary amine)	(a tertiary amine)
bp 50°C	bp 34°C	bp 3°C

Basicity of Amines

- 모든 아민은 약염기이고, 아민의 수용액은 염기성:

  질소는 양성자에 고립 전자쌍을 줄 수 있기 때문이다. 또한 이러한 성질로 아민은 **친핵체**이다.



$$K_b = \frac{[R_3NH^+][HO^-]}{[R_3N]} \qquad \text{and} \qquad pK_b = -\log K_b$$

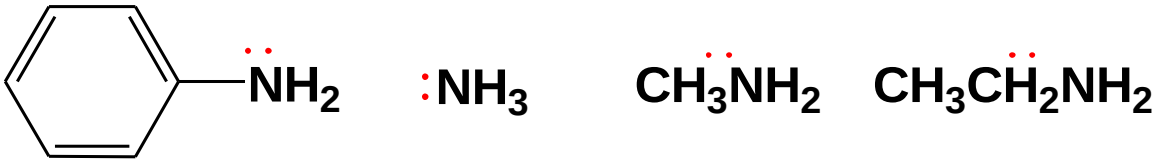
아민의 $K_b = 10^{-3}$ to 10^{-4}

- 아민 염기도의 가장 중요한 관계:

1. 알킬아민은 암모니아보다 약간 센 염기.

2. 알킬아민의 염기도는 크게 차이가 나지 않음:
   알킬 기의 수가 증가하면 이온의 용매화가 감소하므로 2° 및 3° 아민은 염기도가 1° 아민과 비슷.

3. 아릴아민은 암모니아와 알킬아민보다 훨씬 약한 염기.

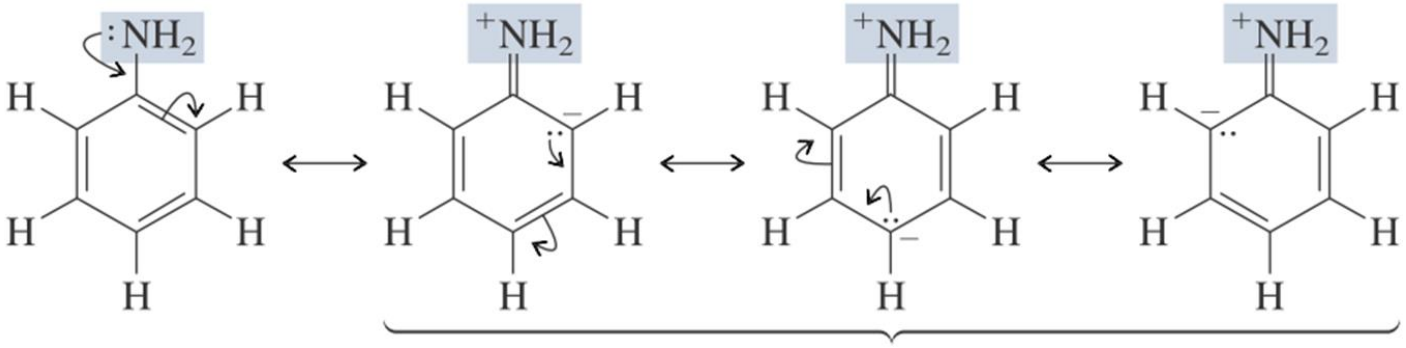


pK_b	9.42	4.74	3.36	3.25

염기도 증가

- 아릴아민은 암모니아와 알킬아민보다 훨씬 약한 염기:

  질소의 고립쌍 전자가 방향족 고리에 비편재화되므로 산과 반응할 전자가 감소함.

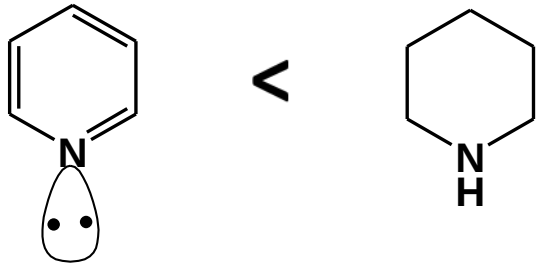


- 질소 원자의 염기도에 영향을 주는 요인

공명 효과

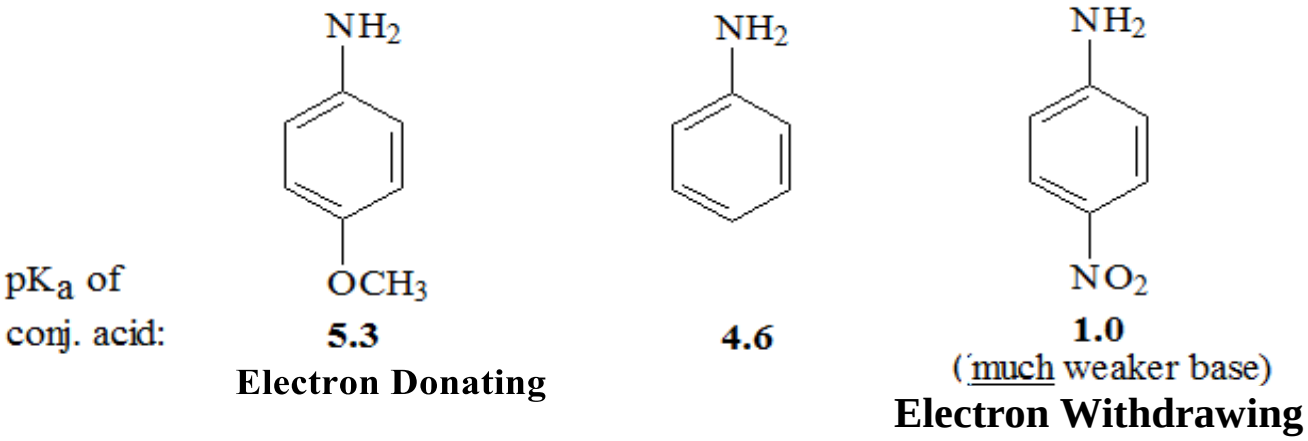
pK_b ~15 < 2.73

혼성화 효과

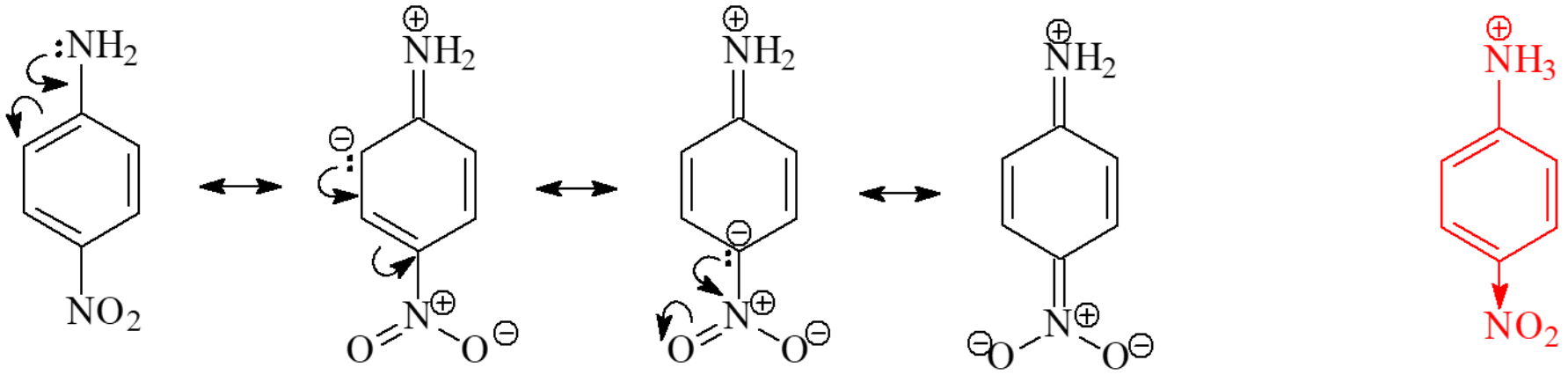


pK_b ~8.75 < 2.88

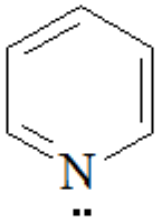
- 아닐린의 염기도와 치환기 효과



공명은 짝산을 안정화시킴. 전자 당김 기는 불안정화시킴.



Basicity



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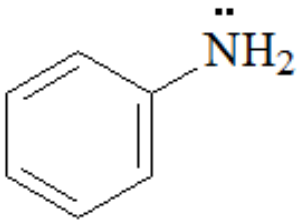

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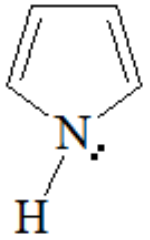


pK_a =

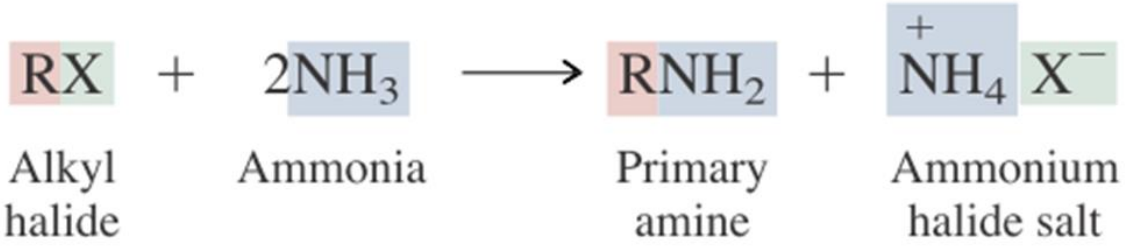
pyridine
5.2

aniline
4.6

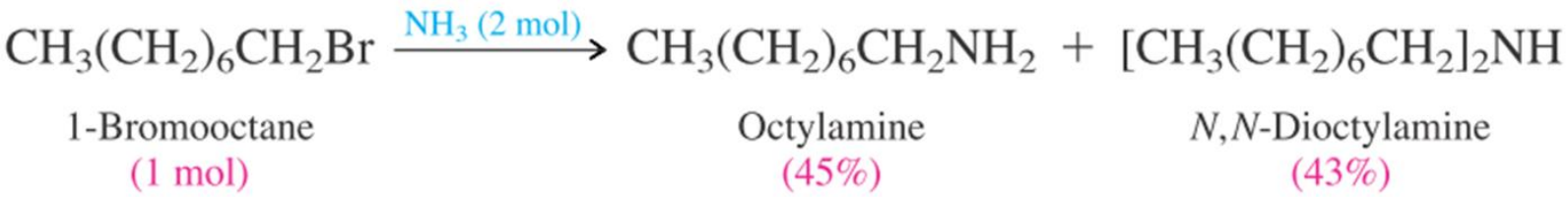
pyrrole
0.4

- **Pyridine**은 산과 반응할 고립 전자쌍이 있으므로 **<u>가장 센 염기이다</u>**.
- **Aniline**은 고립 전자쌍이 공명에 의하여 방향족 고리로 비편재화되므로 **<u>더 약한 염기이다</u>**.
- **Pyrrole**은 **<u>가장 약한 염기인데</u>** 고립 전자쌍이 방향성을 이루기 위한 6 π 전자의 일부분이 되어야 하고 따라서 산과는 반응할 여유가 없기 때문이다.

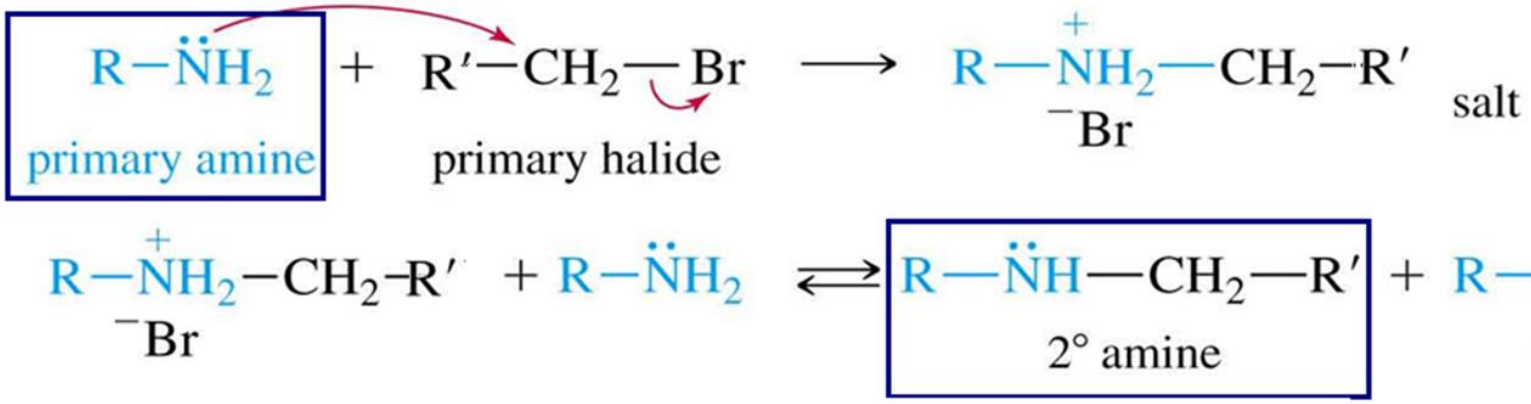
By Alkylation of Ammonia



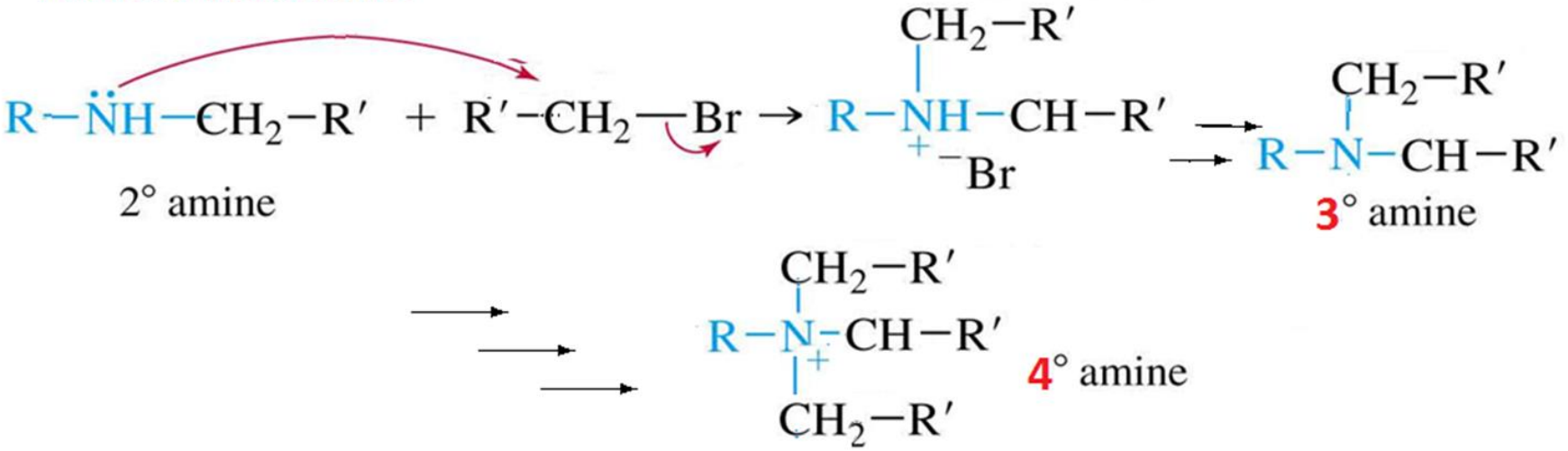
- 실제 반응– 다알킬화 반응 생성물
- 알킬아민의 S_N2 반응성이 암모니아 보다 더 크므로.
  일반적으로, 다알킬화 반응 생성물의 혼합물이 얻어짐.



반응 메커니즘



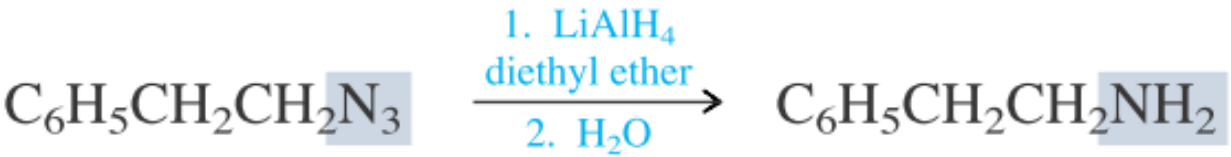
Further Reactions



By Reduction

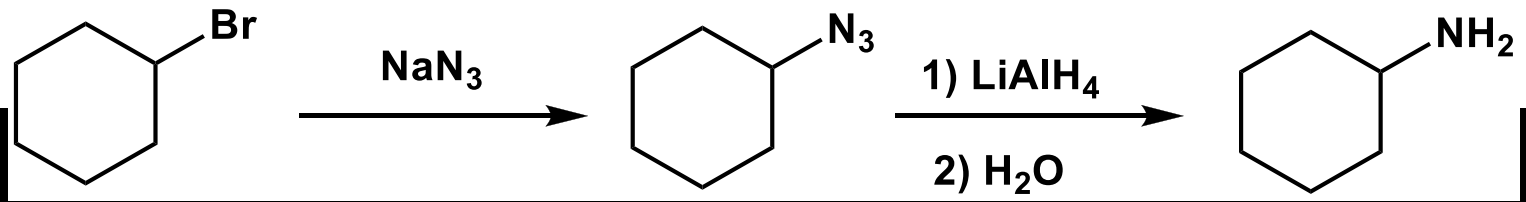
- **Reduction of Alkyl azide** – lithium aluminum hydride or catalytic hydrogenation

Alkyl azide — Primary amine

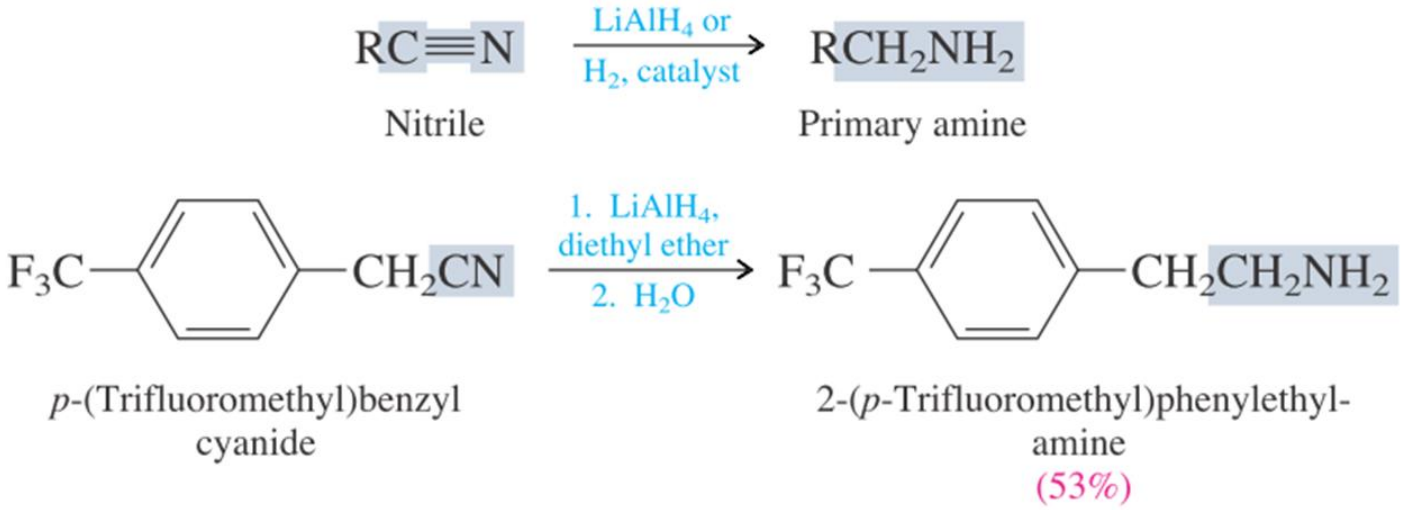


2-Phenylethyl azide — 2-Phenylethylamine (89%)

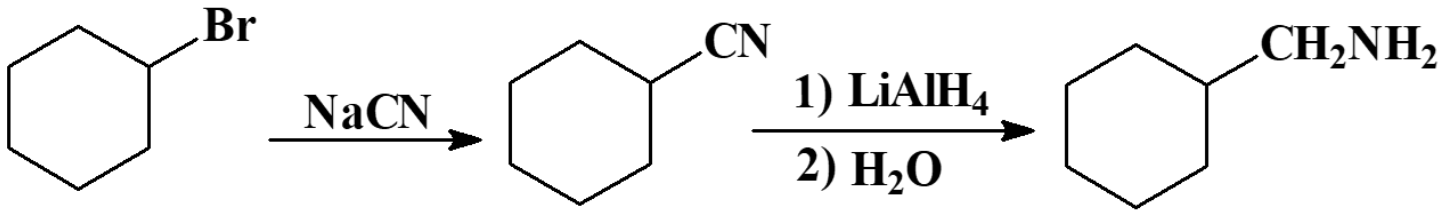
- **Remember: Azide can be prepared by S_N2 Reaction between alky halide and sodium azide.**



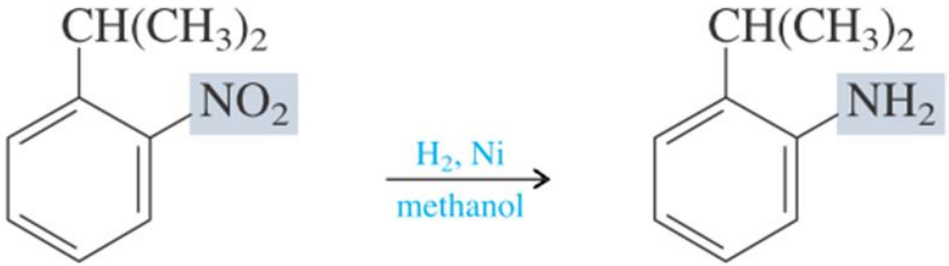
Reduction of Nitriles to Primary amines



- **Nitrile**은 알킬 할라이드와 **NaCN**의 S_N2 반응으로 얻는다.

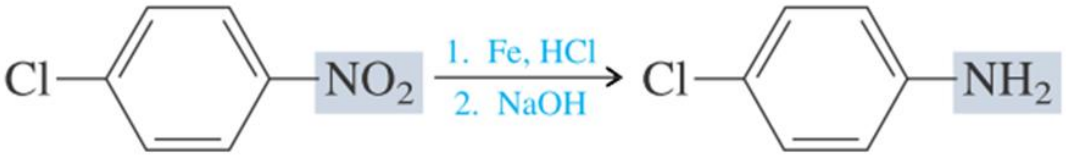


Reduction of Nitro to Primary amines



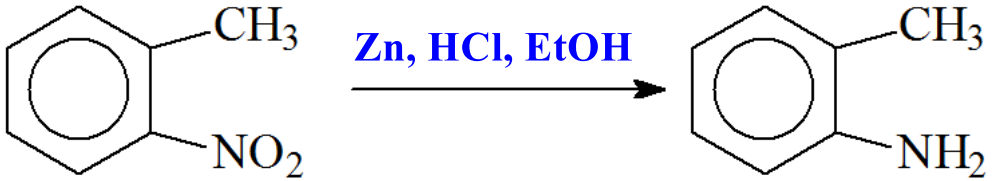
o-Isopropylnitrobenzene

o-Isopropylaniline
(92%)



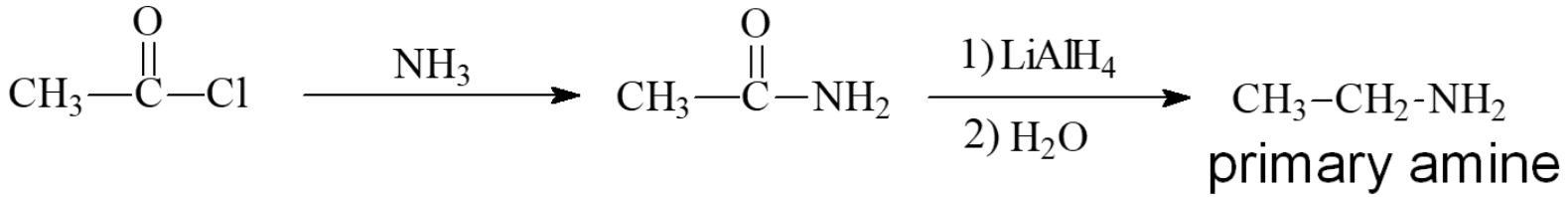
p-Chloronitrobenzene

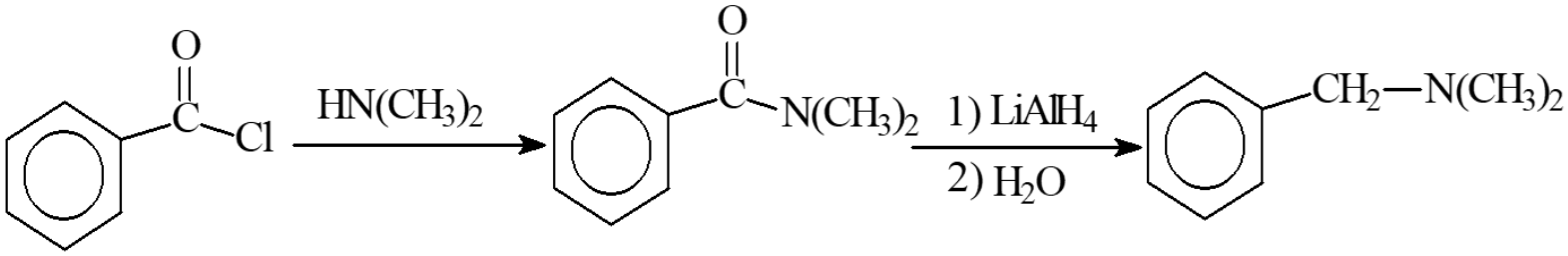
p-Chloroaniline
(95%)



Reduction of Amides

- 아마이드에서
  - ✓ 암모니아는 1° 아민을 만듦.
  - ✓ 1° 아민은 2° 아민을 만듦.
  - ✓ 2° 아민은 3° 아민을 만듦.

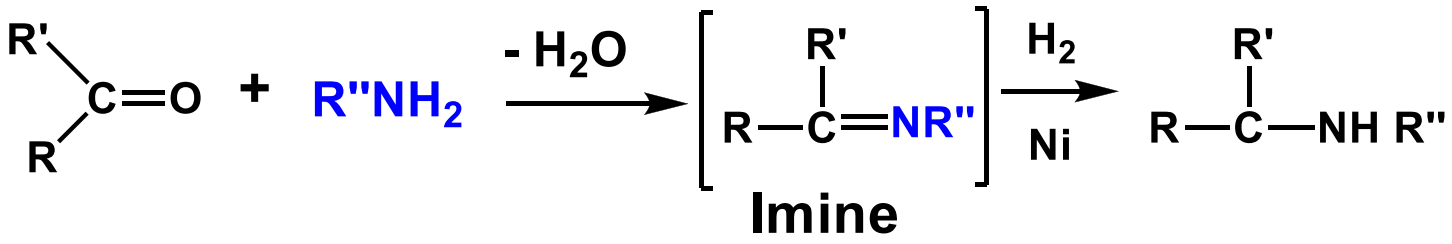




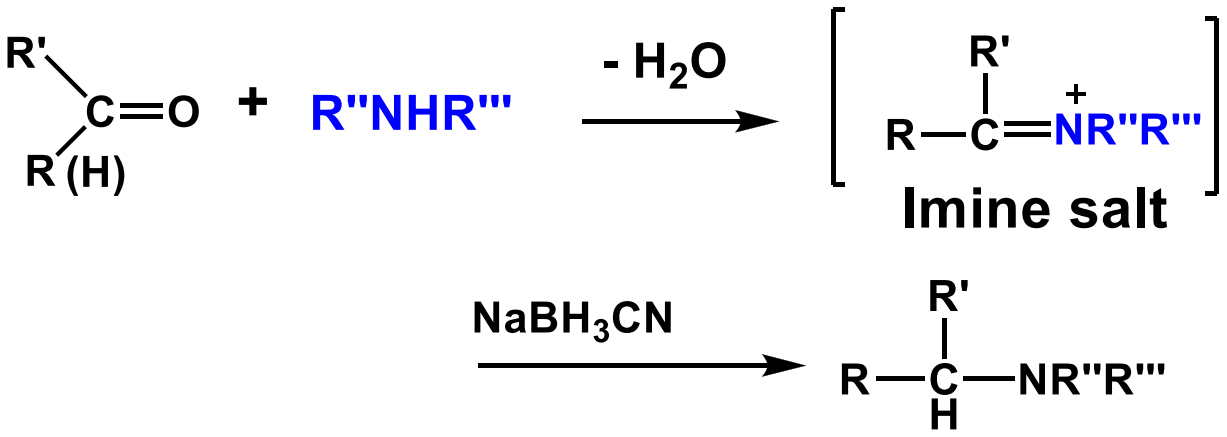
Amide is less reactive than amine.

Reduction of Imine

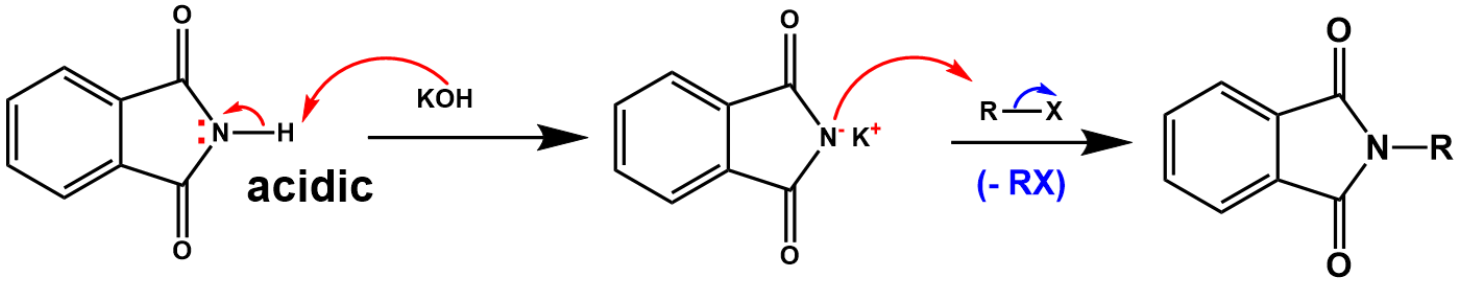
- **Primary amine gives secondary amine**



- **Secondary amine gives tertiary amine**

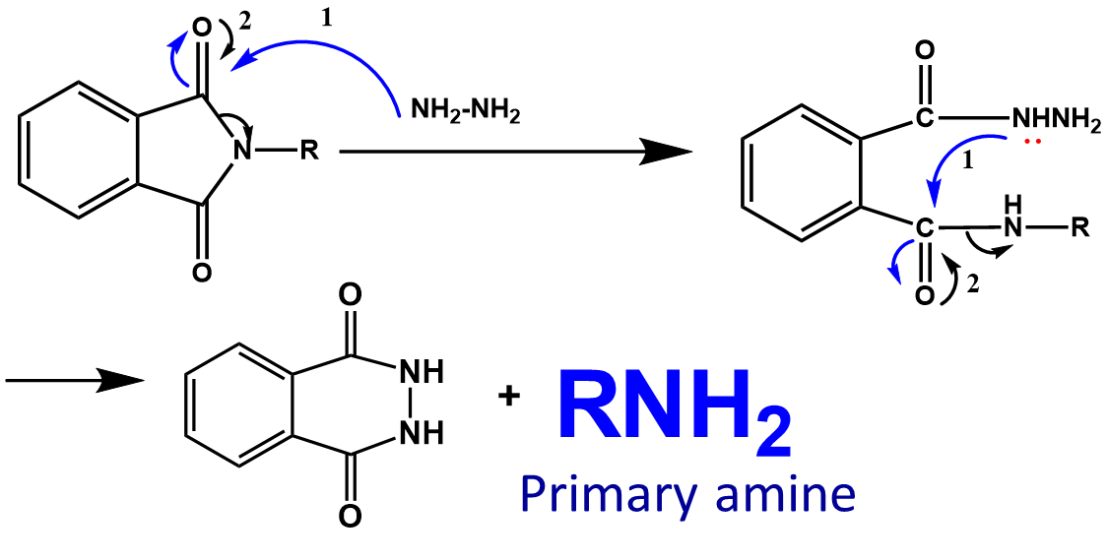


Gabriel synthesis – Primary Amine



Phthalimide

Nucleophile substitution reaction with alkyl halides



+ RNH_2

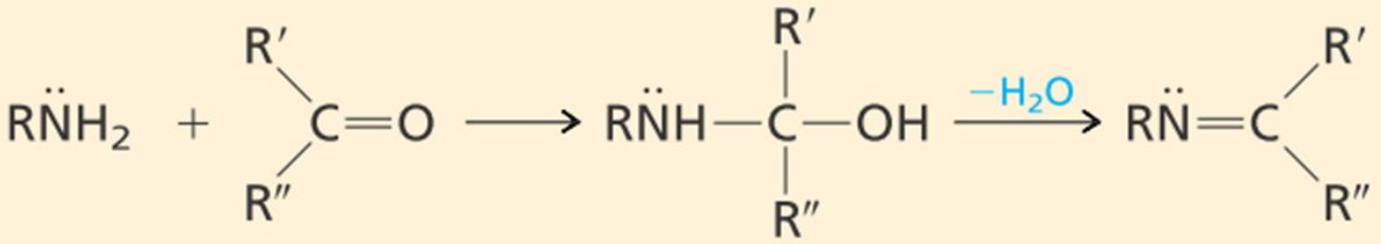
Primary amine

Siegmund Gabriel	
Born	7 November 1851 Berlin, Germany
Died	22 March 1924 (aged 72) Berlin, Germany
Nationality	German
Alma mater	University of Heidelberg
Known for	Gabriel Synthesis
Scientific career	
Institutions	University of Berlin

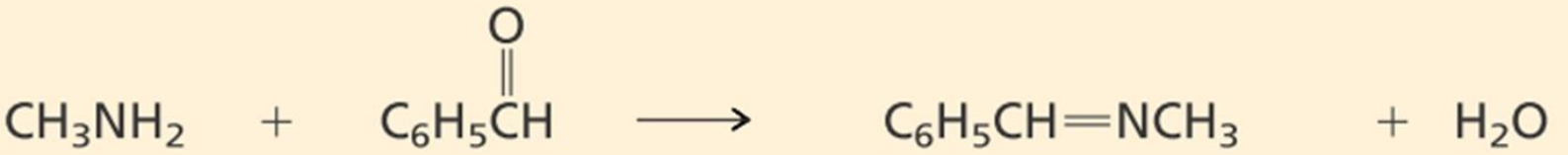
One of Gabriel's most significant contributions to organic chemistry was made in 1887, when he discovered the Gabriel Synthesis with his partner James Dornbush. The Gabriel Synthesis is a reaction which synthesizes pure primary amines, involving the reaction of potassium phthalimide with an alkyl halide, followed by hydrolysis. The Gabriel Synthesis was adapted by Gabriel in 1889 to a procedure for the preparation of amino acids.

Reaction of primary amines with aldehydes and ketones

General Equation and Specific Example

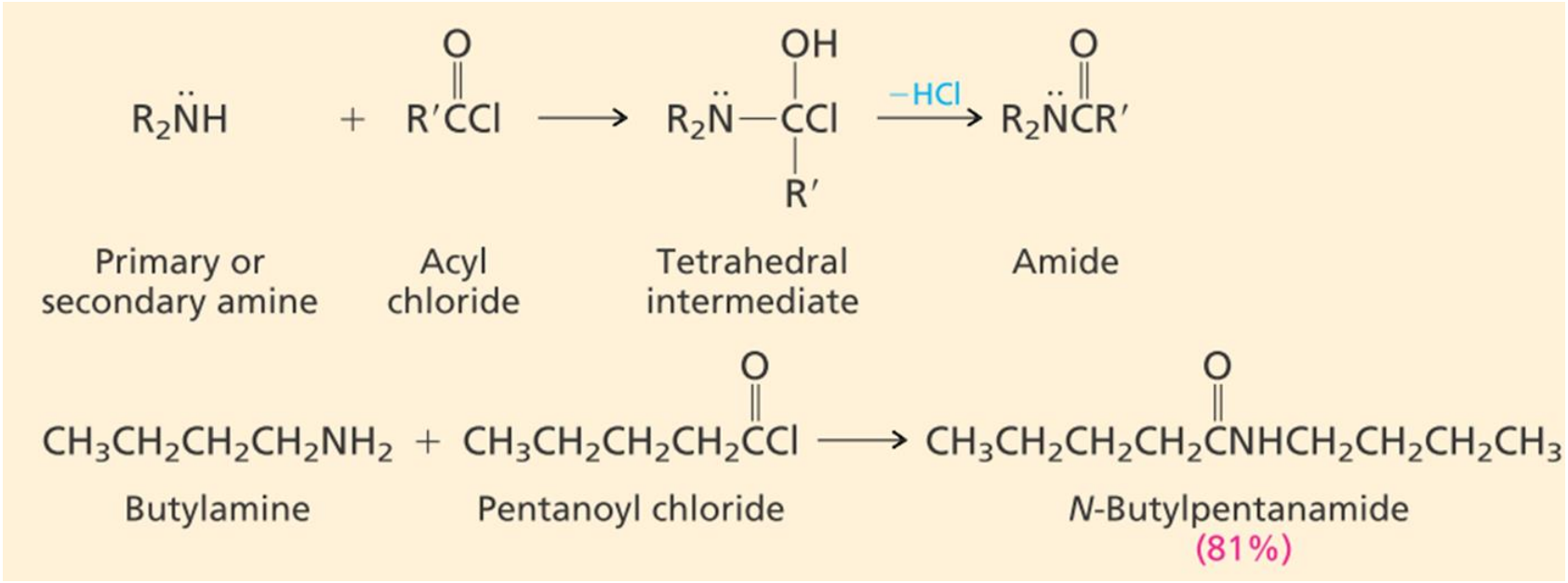


Primary amine | Aldehyde or ketone | Carbinolamine | Imine



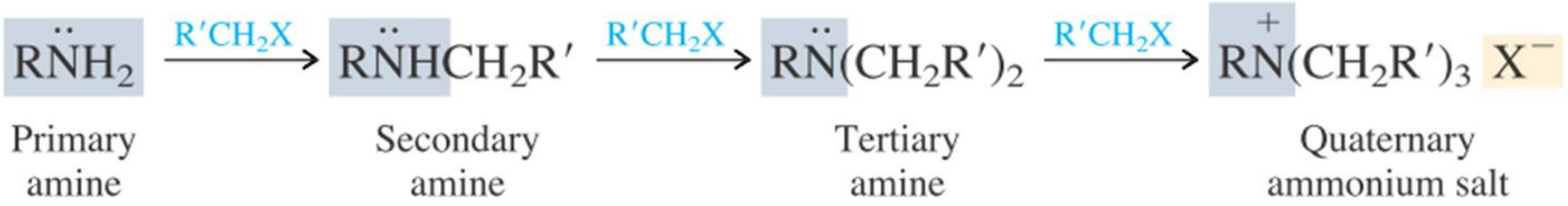
Methylamine | Benzaldehyde | *N*-Benzylidenemethylamine (70%) | Water

Reaction of amines with acyl chlorides

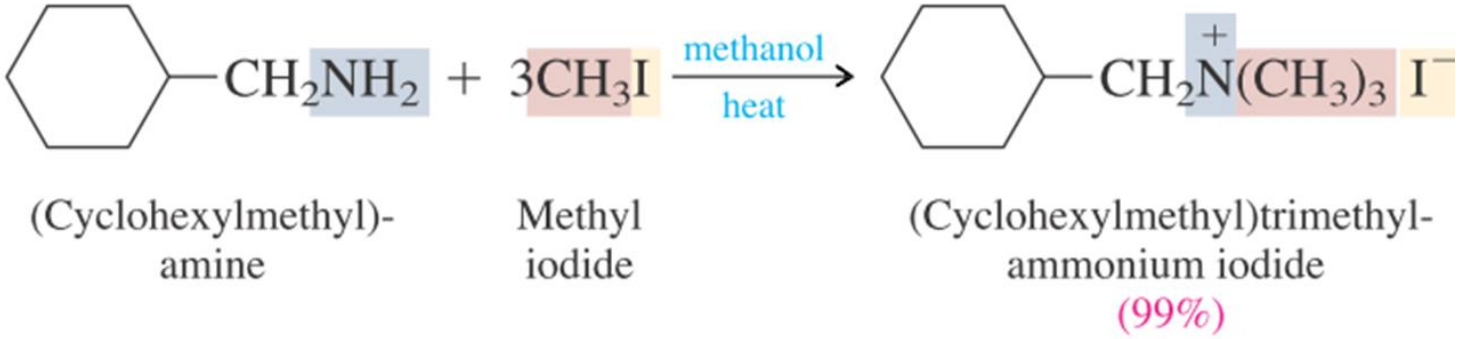


Reaction of amines with alkyl halides

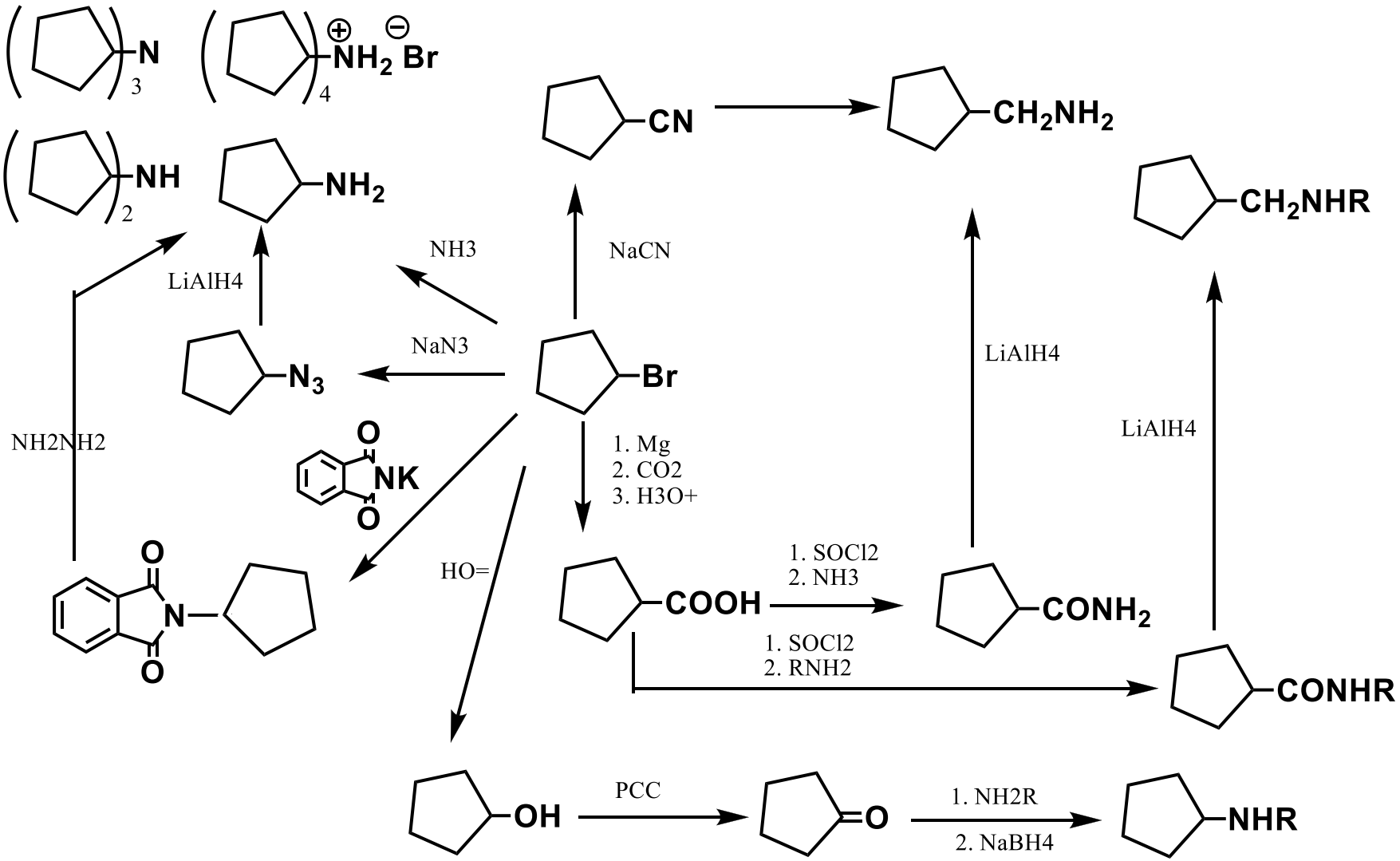
- Problem with polyalkylation- **Product More Reactive**



- Good for preparing quaternary ammonium salts

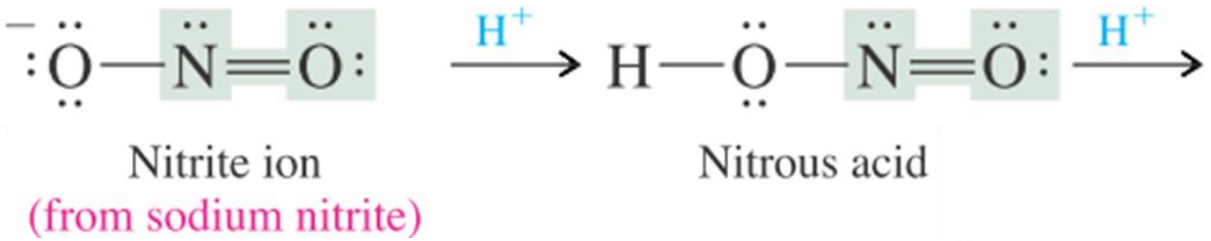


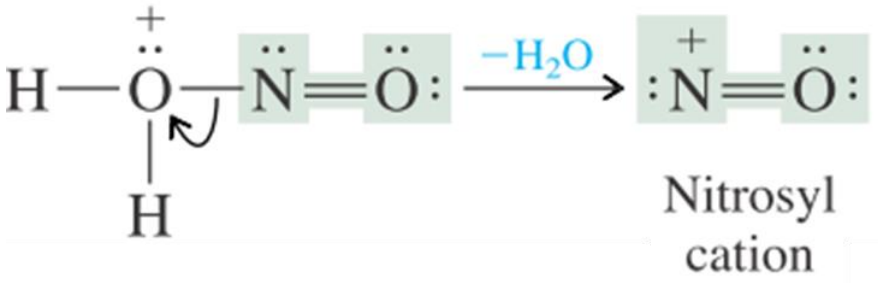
Functional Groups Inter-conversion for the synthesis of Amine



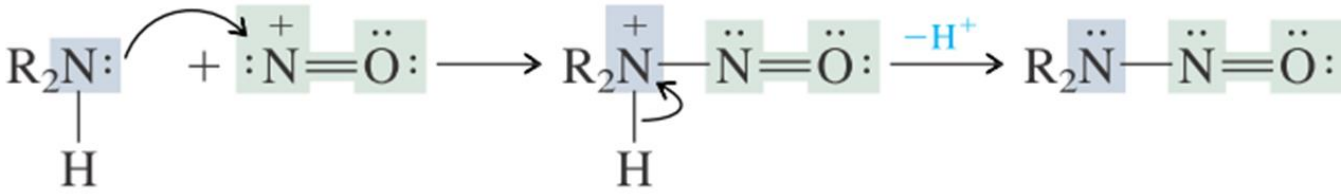
Nitrosation of Amines

- **Generation of nitrosyl cation**

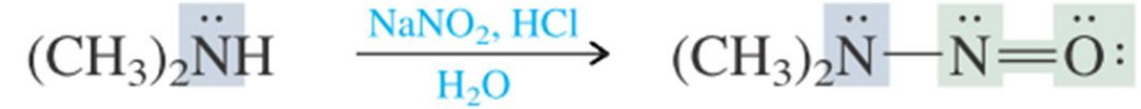




- **Nitrosation of secondary amines from nitrosyl cation - formation of nitroso compound**



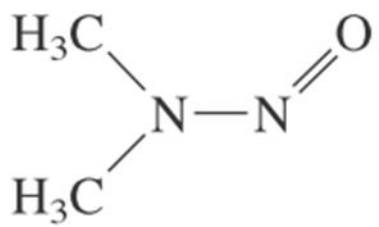
Secondary alkylamine | Nitrosyl cation | *N*-Nitroso amine



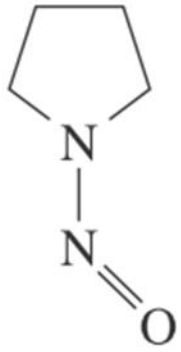
Dimethylamine

N-Nitrosodimethylamine (88–90%)

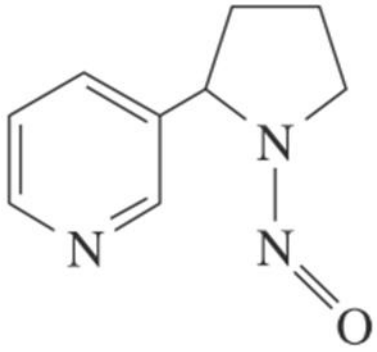
나이트로소아민은 알려진 발암물질



N-Nitrosodimethylamine
(formed during tanning of leather; also found in beer and herbicides)

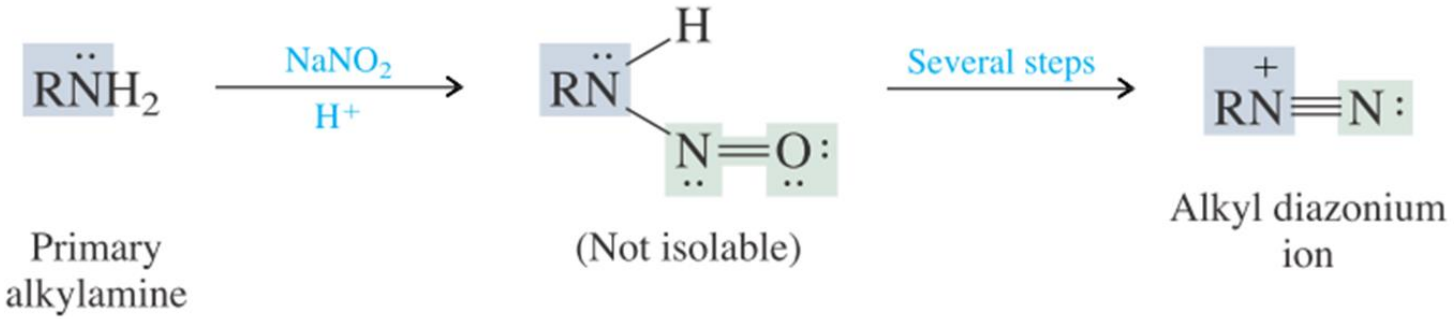


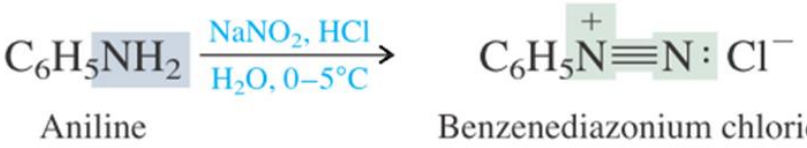
N-Nitrosopyrrolidine
(formed when bacon that has been cured with sodium nitrite is fried)

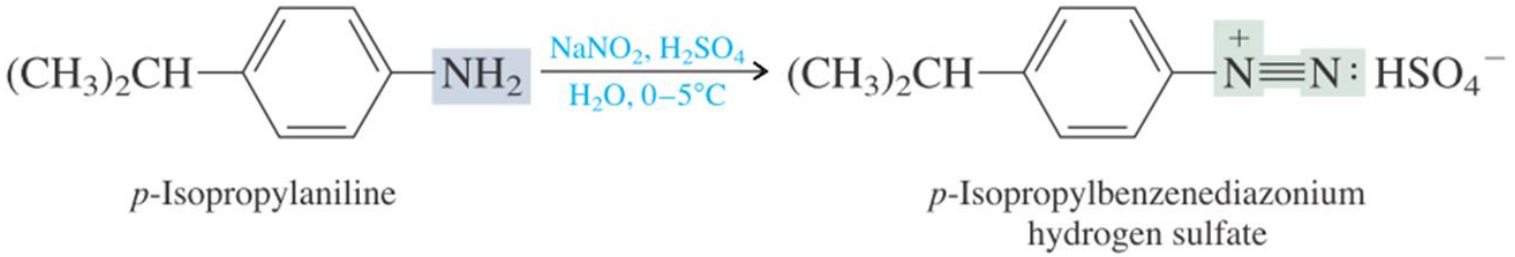


N-Nitrosonornicotine
(present in tobacco smoke)

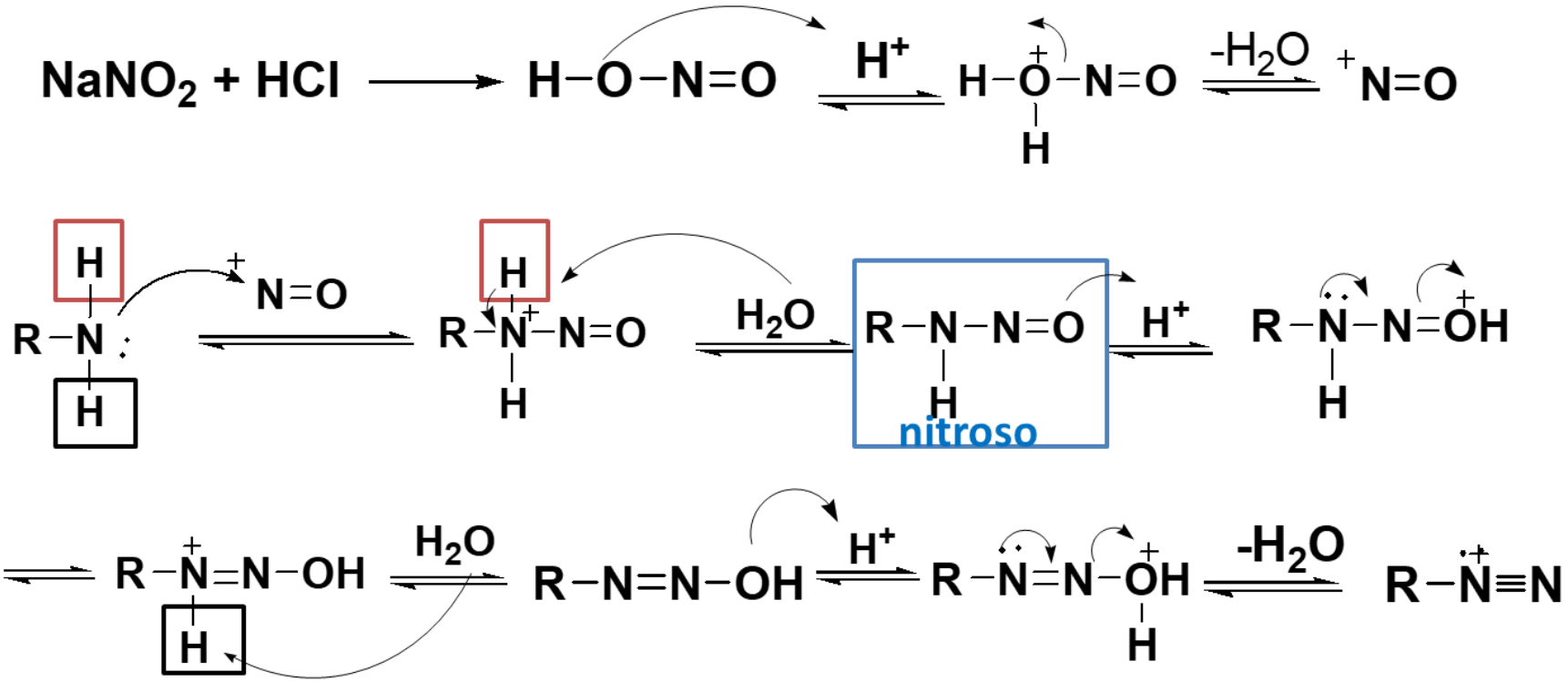
- **Nitrosation of primary amines from nitrosyl cation - formation of diazonium salt (via nitroso-intermediate)**







Overall Mechanism of Diazotization

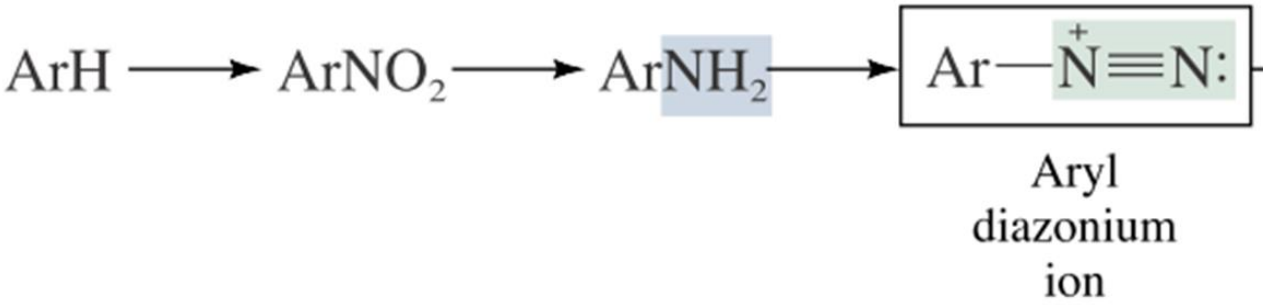


- **N-nitrosamines are carcinogens formed in foods by reaction of nitrite with secondary amines, often in the form of amino acids.**

✓ 절인 고기: 아질산 염이 들어 있고 pH가 약 5이므로 대부분의 아질산 염은 NO_2^- (99%)로 존재. 또한 절인 고기에는 NO_2^- 와 반응하는 바이타민 C를 첨가하므로 아민의 나이트로소아민으로의 변환이 억제된다.

✓ 위장에서: HCl 때문에 주위가 산성 환경이므로 (pH=2) 섭취한 아질산 염은 **아민의 나이트로소화 반응을 일으켜서 나이트로소아민 (발암물질)이 생긴다**. 나이트로소화 반응은 아민의 농도가 낮거나 (예: 저단백질 식단, 발효 식품 무섭취) 바이타민 C 농도가 높으면 (예: 과일을 많이 먹음) 느리다.

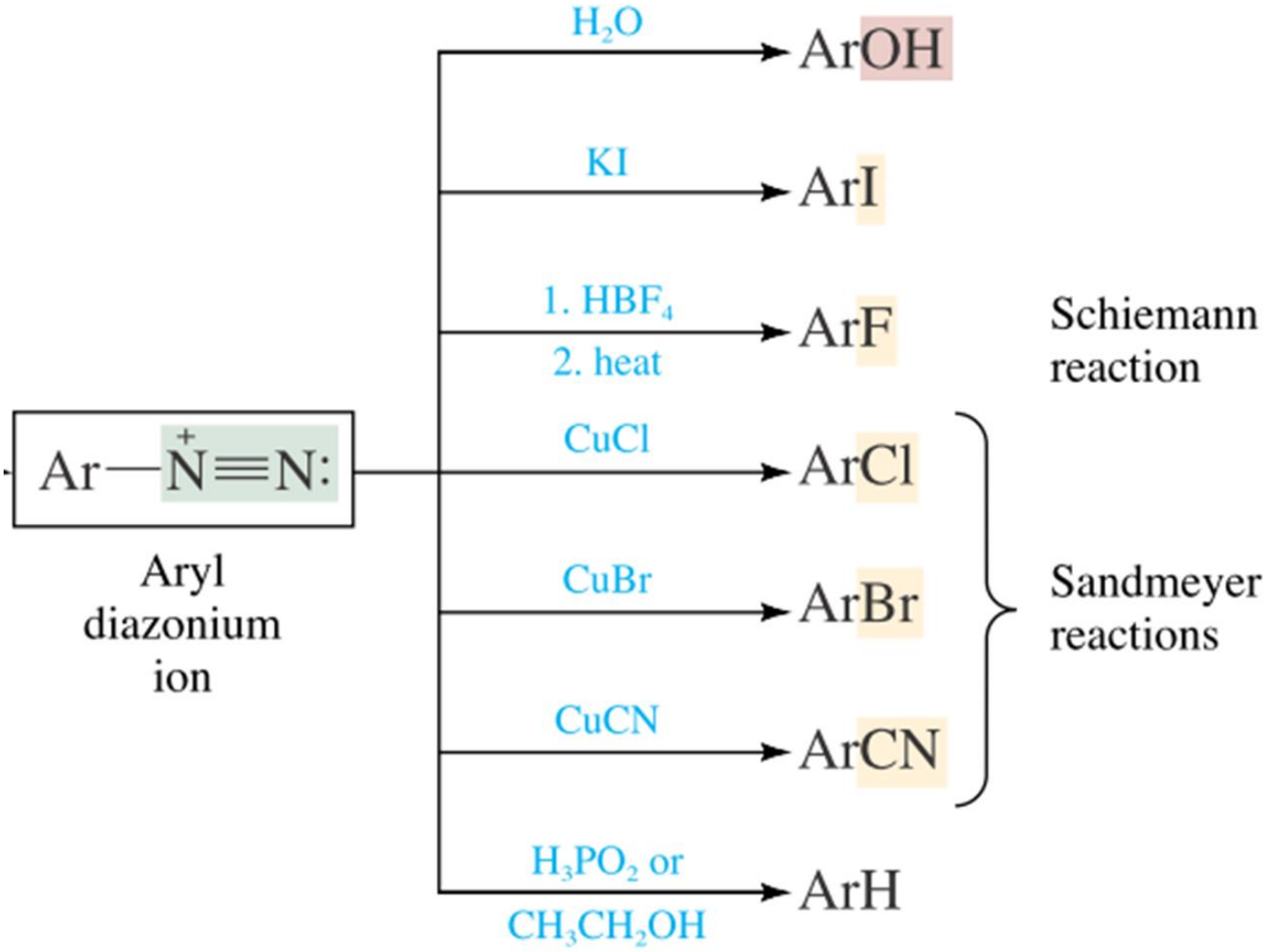
Aryl Diazonium Salt을 이용한 합성



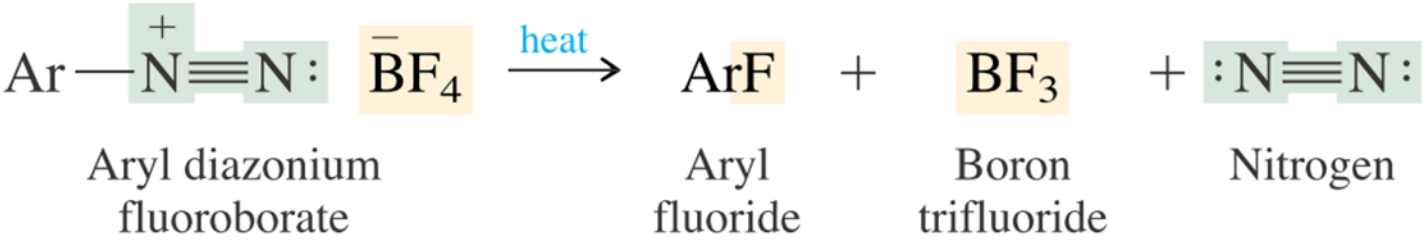
- 합성 유기 화학 에서 아릴 다이아조늄 염의 가치 두 가지는:

1. 플루오로, 아이오도, 사이아노, 하이드록실 기 같이 얻기 어려운 치환기를 벤젠 고리에 쉽게 도입

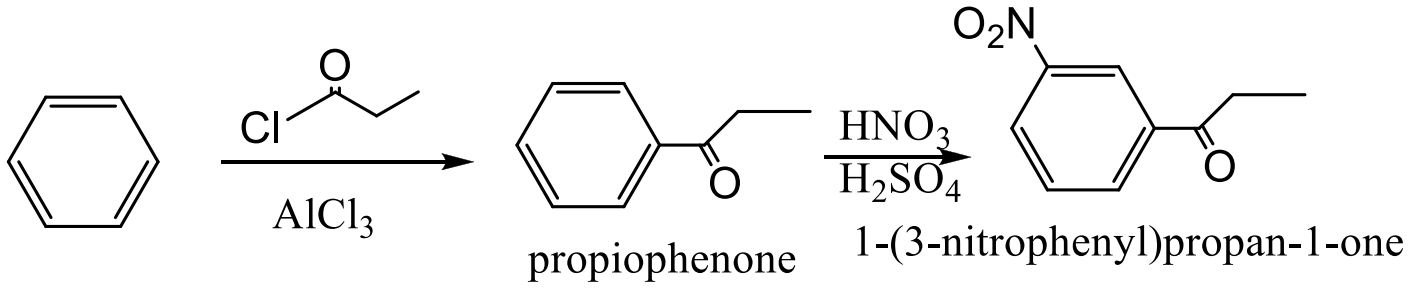
2. 친전자성 방향족 치환 반응으로는 직접 얻을 수 없는 화합물을 얻을 수 있음

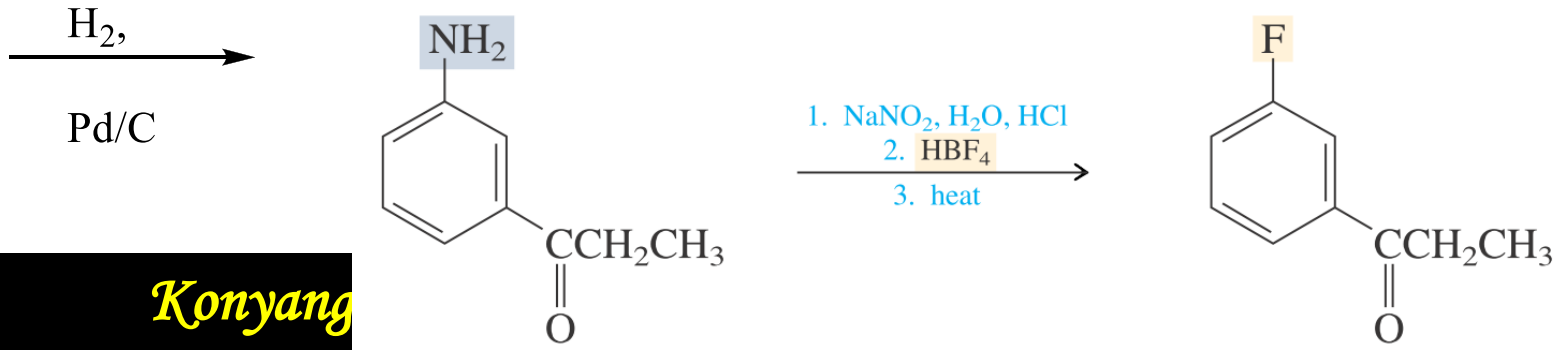

H_2O
ArOH
KI
ArI
1. HBF_4
2. heat
ArF
Schiemann reaction
Ar—$\overset{+}{N}\equiv N$:
CuCl
ArCl
CuBr
ArBr
Sandmeyer reactions
CuCN
ArCN
Aryl diazonium ion
H_3PO_2 or
CH_3CH_2OH
ArH

- **Schiemann reaction - Aryl fluorides**

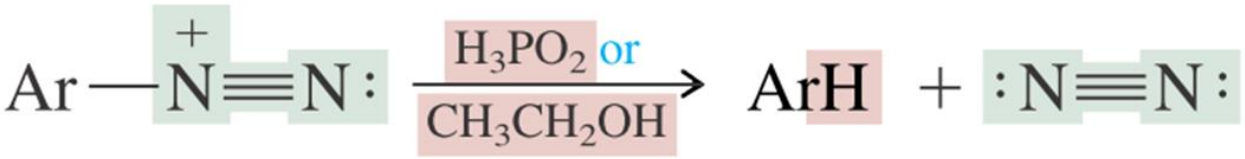


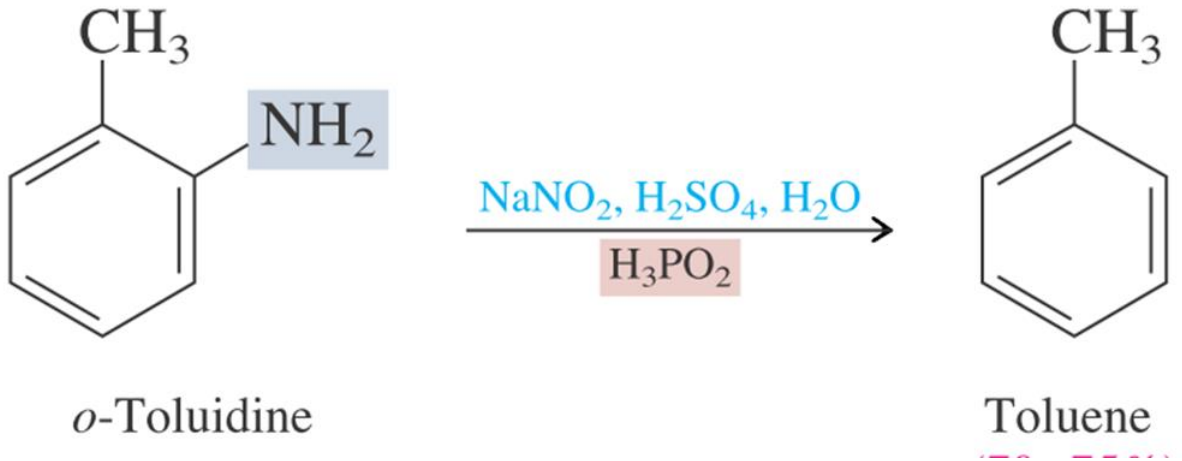
Design synthesis of m-fluoropropiophenone from benzene





- **Reductive Deaminations via Diazonium Salts**

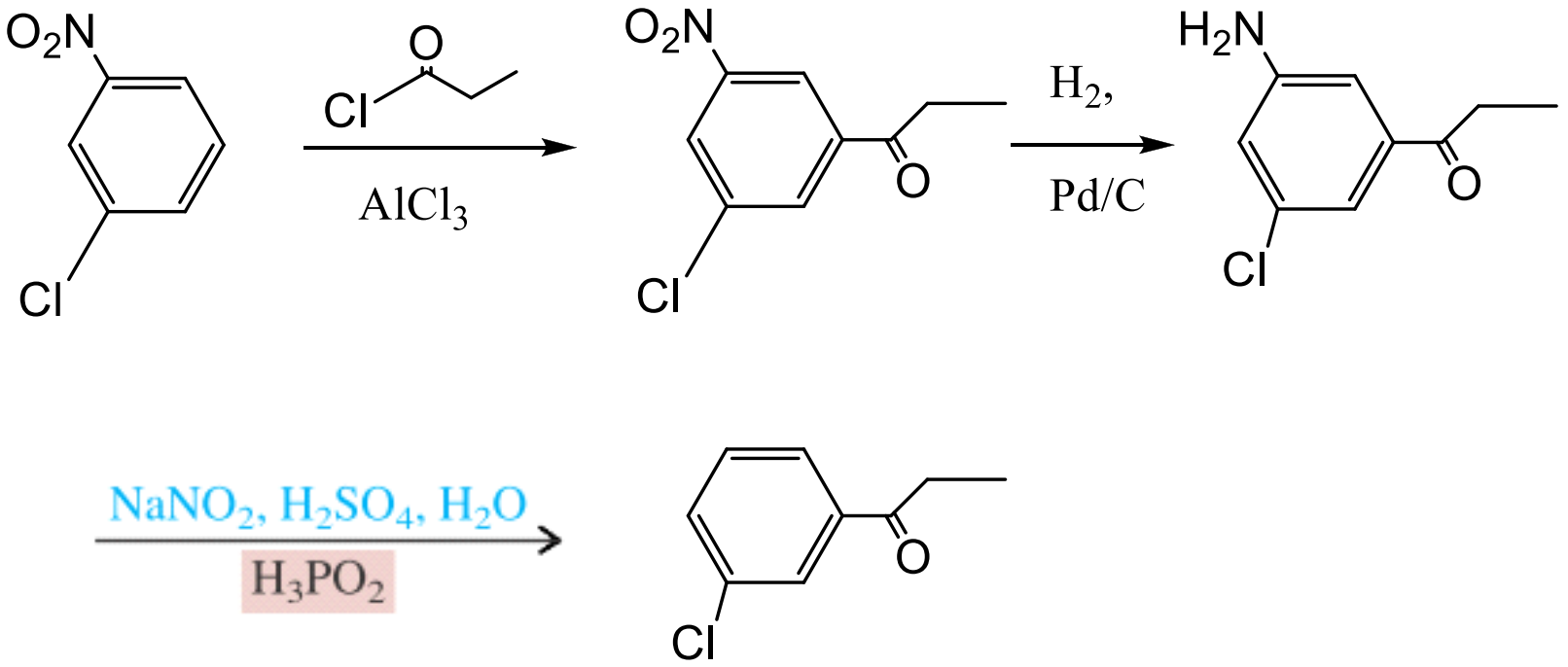




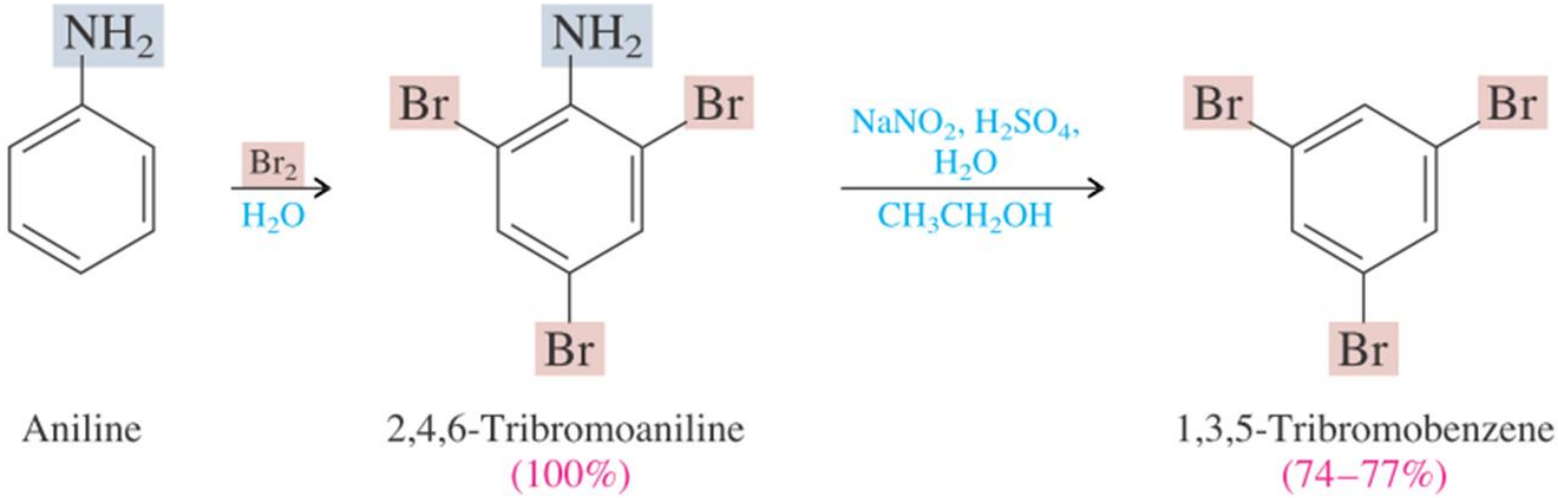
o-Toluidine

Toluene

- 다이아조늄 염의 환원적 아미노제거 반응: 응용



- 아미노 기를 이용한 ortho, para 치환 및 다이아조늄 염의 환원적 <u>아미노제거 반응</u>



Aniline

2,4,6-Tribromoaniline
(100%)

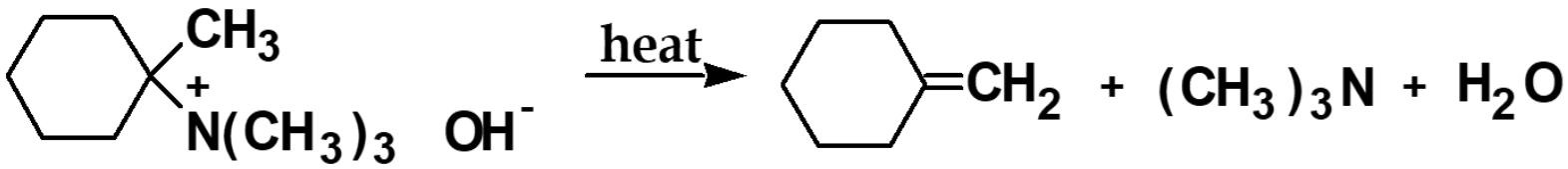
1,3,5-Tribromobenzene
(74–77%)

- **Summary: Reaction with Nitrous Acid**

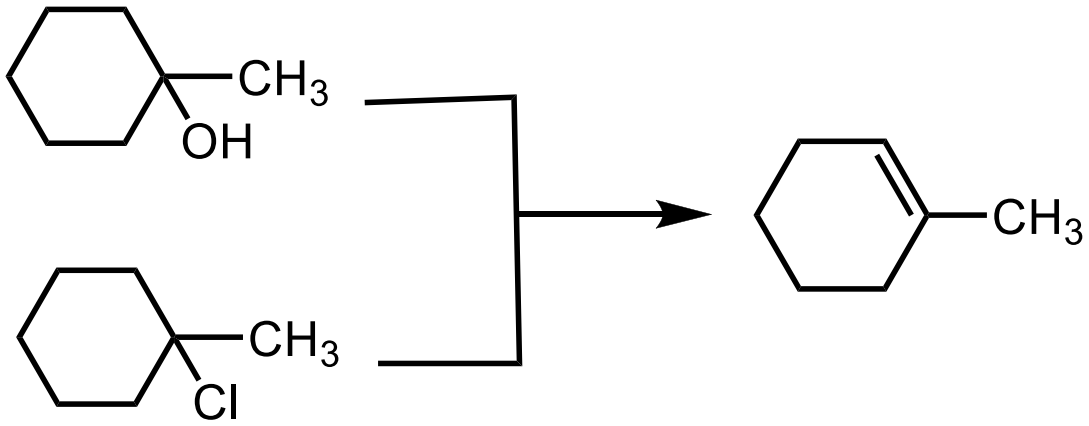
  - ✓ 1° 아민은 다이아조늄 염, $R\text{-}N^{+}{\equiv}N$을 생성
  - ✓ 2° 아민은 실험동물에서 암을 일으키는 것으로 알려진 *N*-나이트로소아민, $R_2N\text{-}N{=}O$을 생성
  - ✓ 알킬 다이아조늄 염은 매우 불안정하나, 아렌다이아조늄 염은 합성에서 널리 쓰임

Hofmann Elimination

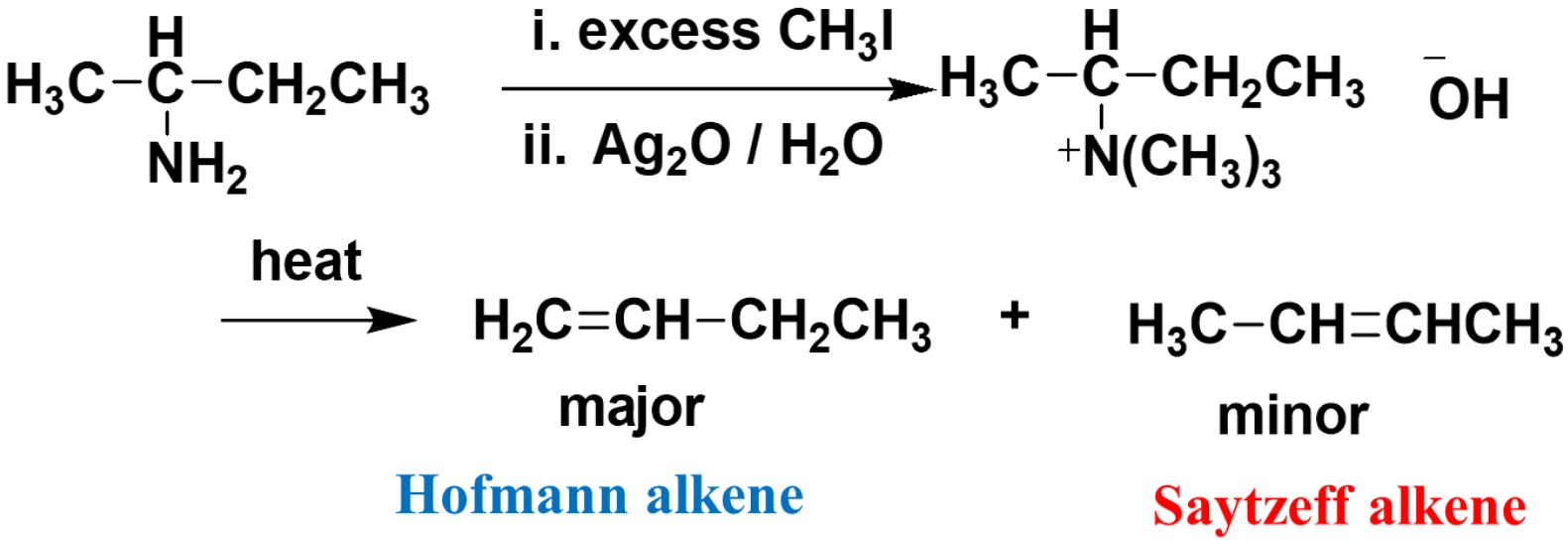
- **Hofmann's rule:** Elimination that occurs preferentially to give the least substituted alkene as the major product.



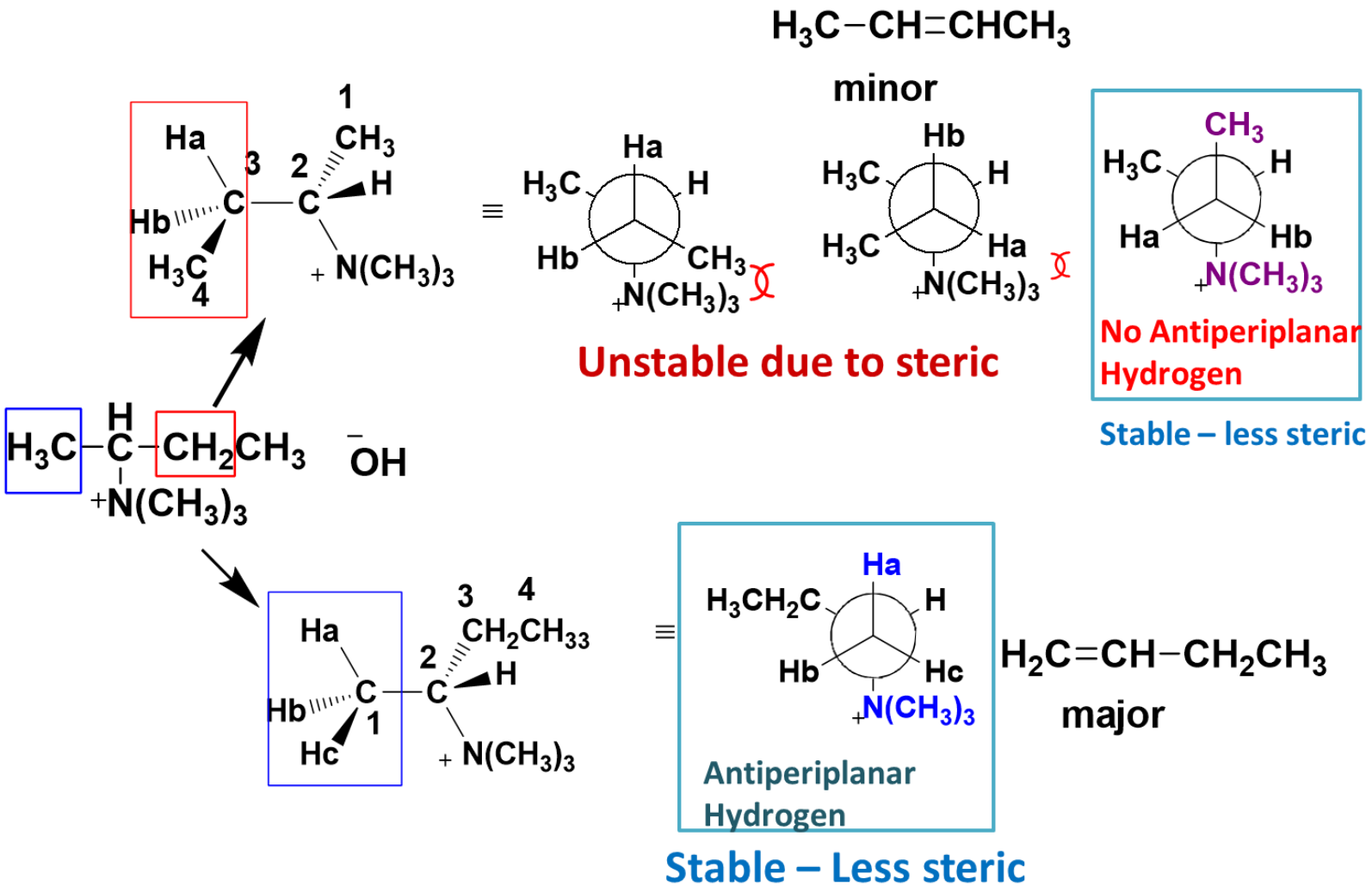
Elimination of halogen or alcohol give the more substituted alkene

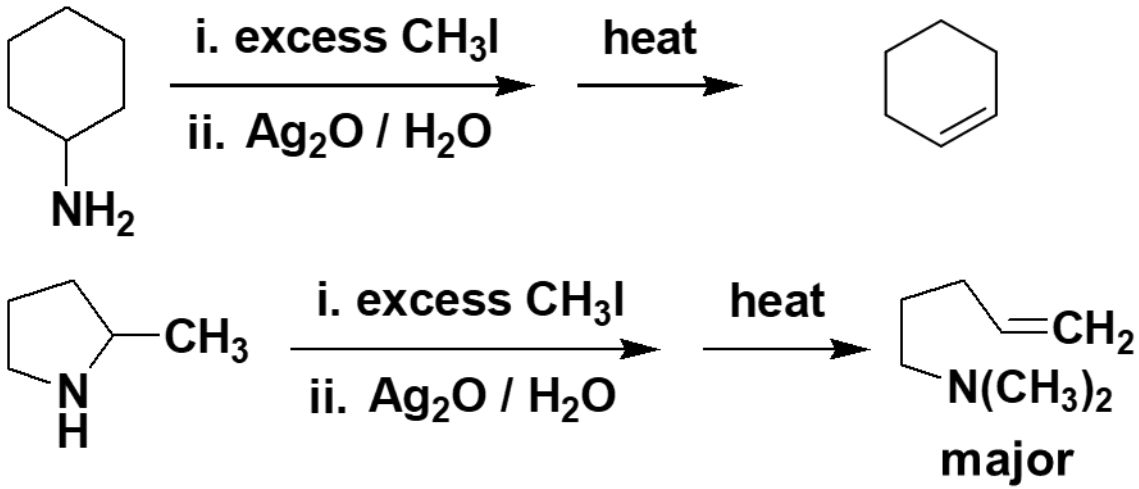


- **Synthesis of Quaternary Ammonium salt and Hofmann Elimination**



- **The Hofmann rule-Newmann Projection - anti-coplanar elimination**




i. excess CH_3I
ii. Ag_2O / H_2O
heat
NH_2
CH_3
N
H
i. excess CH_3I
ii. Ag_2O / H_2O
heat
CH_2
$N(CH_3)_2$
major