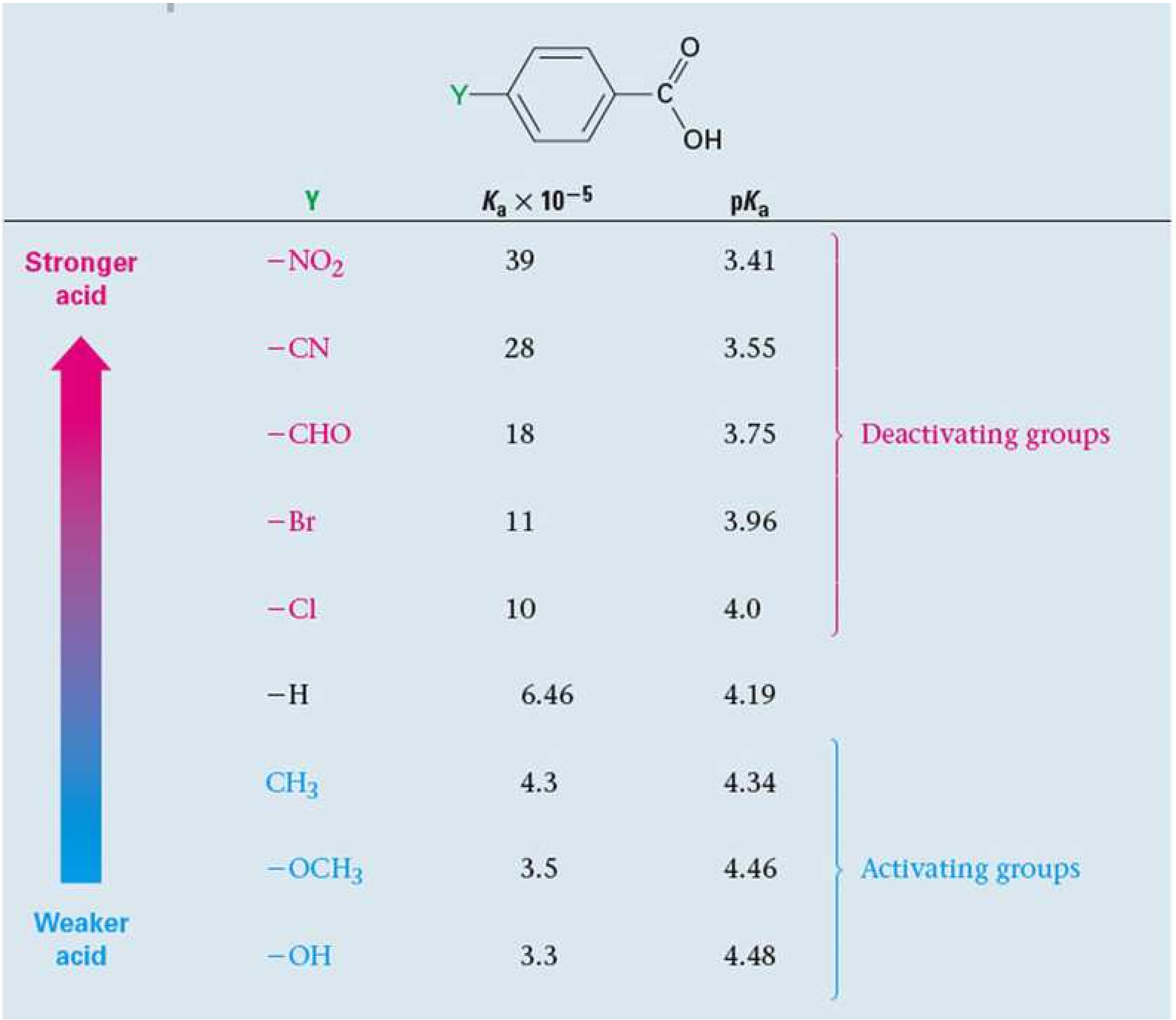
다섯째주

Carboxylic Acids and Nitriles (1)

Substituent Effects on Acidity

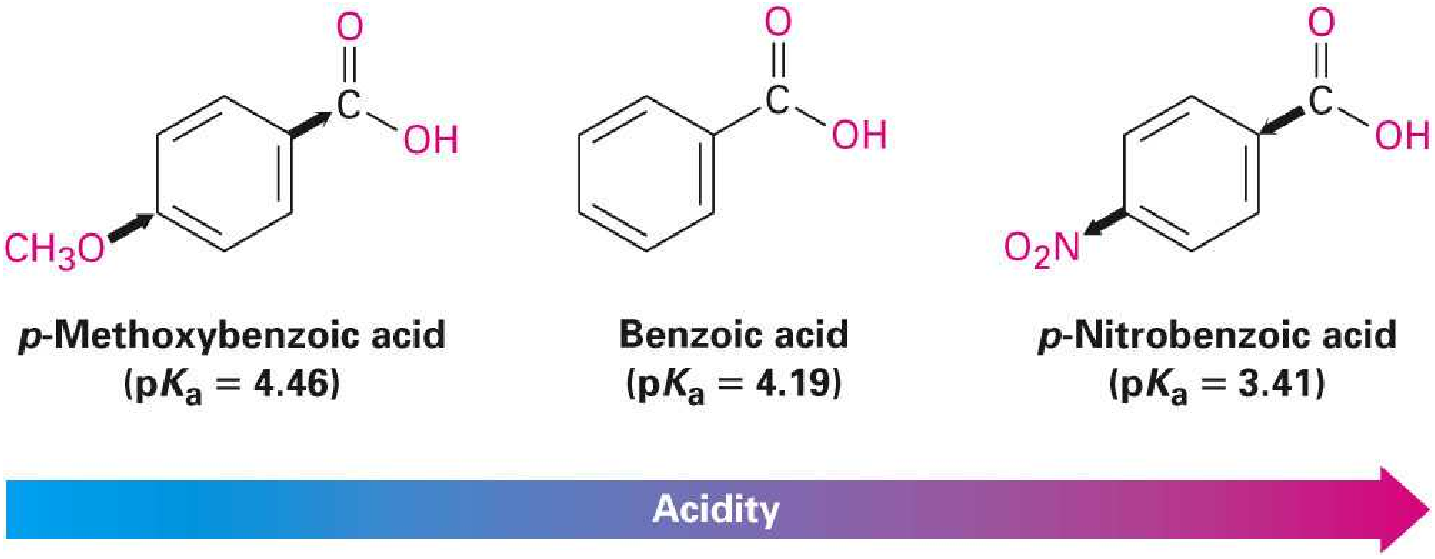
p-Substituted Benzoic Acids의 산도에 치환기 효과



	Y	$K_a \times 10^{-5}$	pK_a	
Stronger acid	$-NO_2$	39	3.41	Deactivating groups
	$-CN$	28	3.55	
	$-CHO$	18	3.75	
	$-Br$	11	3.96	
	$-Cl$	10	4.0	
	$-H$	6.46	4.19	
	CH_3	4.3	4.34	Activating groups
	$-OCH_3$	3.5	4.46	
Weaker acid	$-OH$	3.3	4.48	

Aromatic Substituent Effects

- An electron-withdrawing group (-NO_2) increases acidity by stabilizing the carboxylate anion, and an electron-donating (activating) group (OCH_3) decreases acidity by destabilizing the carboxylate anion
- We can use relative pKa's as a calibration for effects on relative free energies of reactions with the same substituents

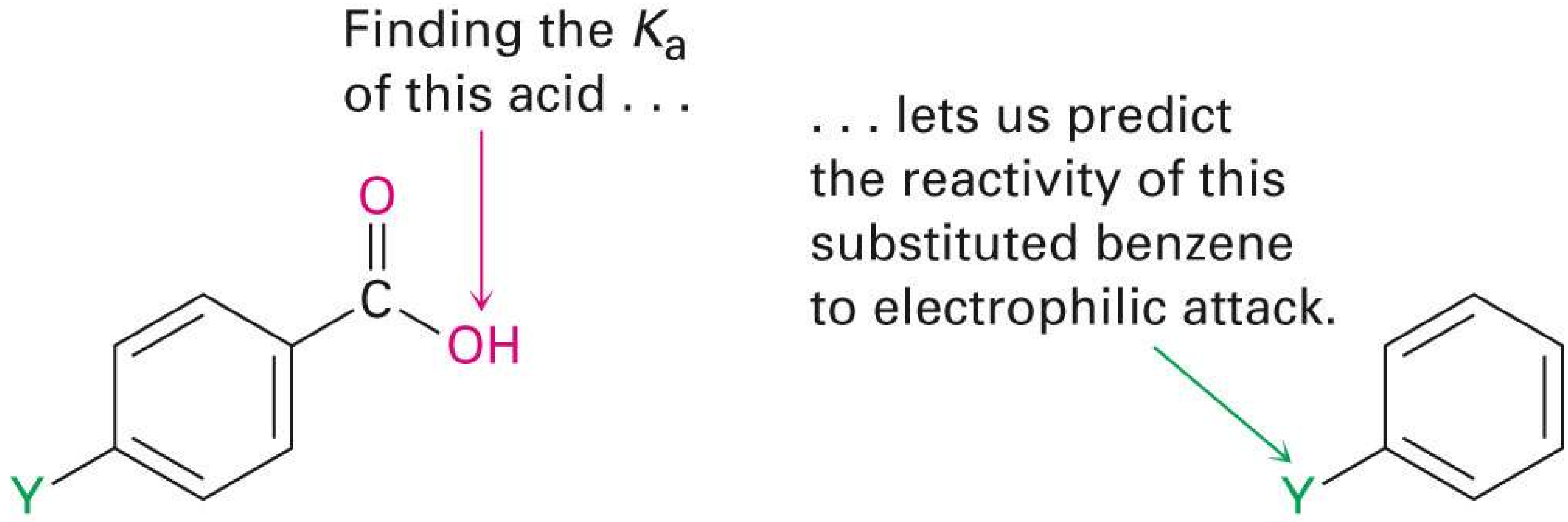


p-Methoxybenzoic acid
($pK_a = 4.46$)

Benzoic acid
($pK_a = 4.19$)

p-Nitrobenzoic acid
($pK_a = 3.41$)

Aromatic Substituent Effects

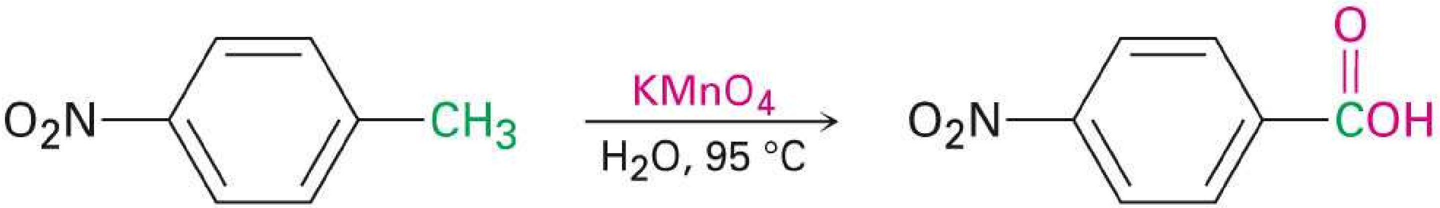


Finding the K_a of this acid . . .

. . . lets us predict the reactivity of this substituted benzene to electrophilic attack.

Carboxylic Acids의 합성

- Oxidation of a substituted alkylbenzene with $KMnO_4$ or $Na_2Cr_2O_7$ gives a substituted benzoic acid.
- 1° and 2° alkyl groups can be oxidized, but tertiary groups are not.

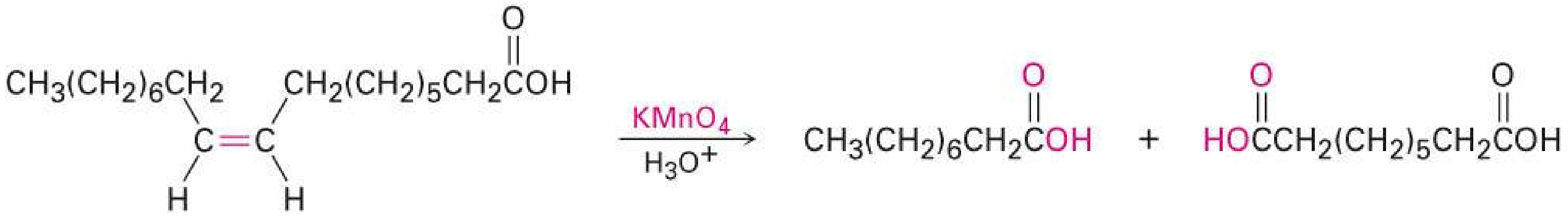


p-Nitrotoluene

p-Nitrobenzoic acid (88%)

Alkenes로 부터 합성

- Oxidative cleavage of an alkene with $KMnO_4$ gives a carboxylic acid if the alkene has at least one vinylic hydrogen



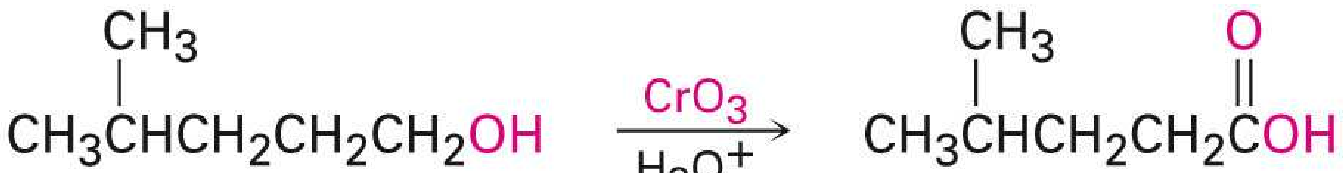
Oleic acid

Nonanoic acid

Nonanedioic acid

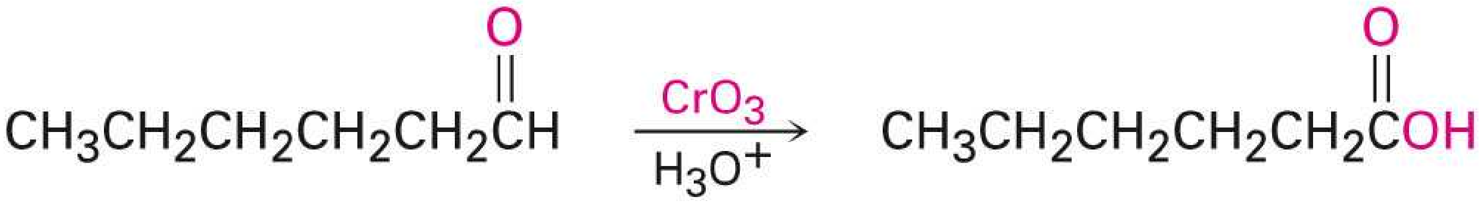
Alcohols로부터 합성

- Oxidation of a primary alcohol or an aldehyde with CrO_3 in aqueous acid



$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2CH_2OH \xrightarrow[H_3O^+]{CrO_3} CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

4-Methyl-1-pentanol **4-Methylpentanoic acid**

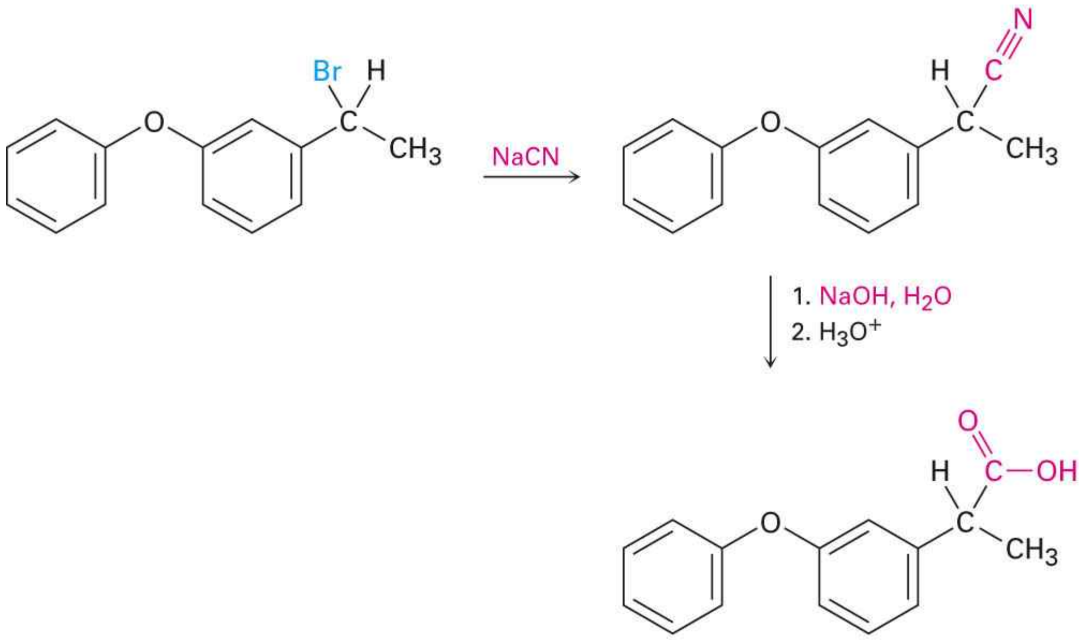


$$CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[H_3O^+]{CrO_3} CH_3CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

Hexanal **Hexanoic acid**

Nitriles의 가수분해

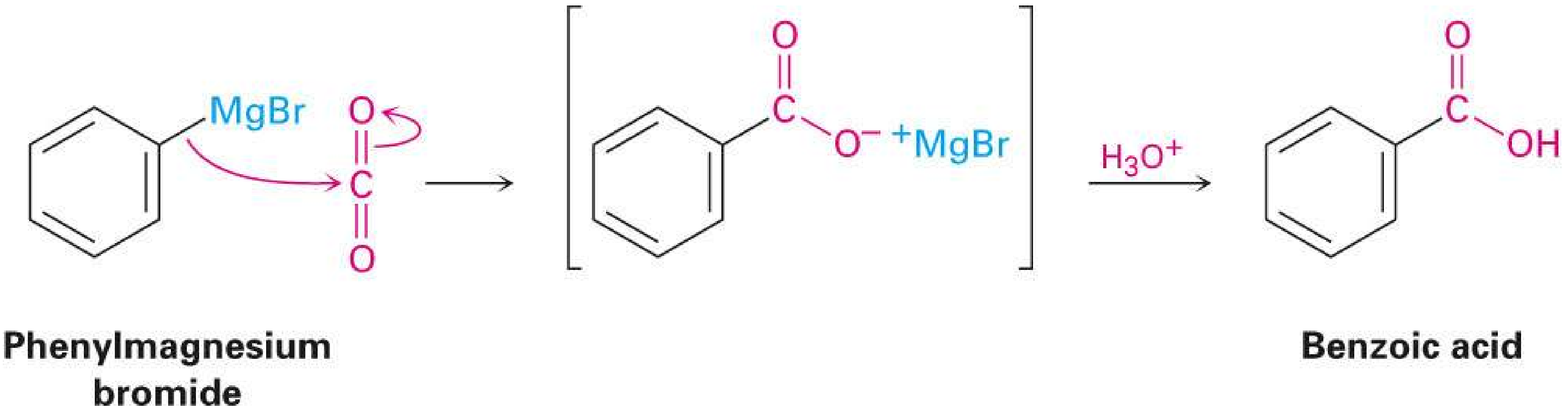
- Hot acid or base yields carboxylic acids
- Conversion of an alkyl halide to a nitrile (with cyanide ion) followed by hydrolysis produces a carboxylic acid with one more carbon (RBr → RC≡N → RCO_2H)
- Best with primary halides because elimination reactions occur with secondary or tertiary alkyl halides



Fenoprofen
(an antiarthritis agent)

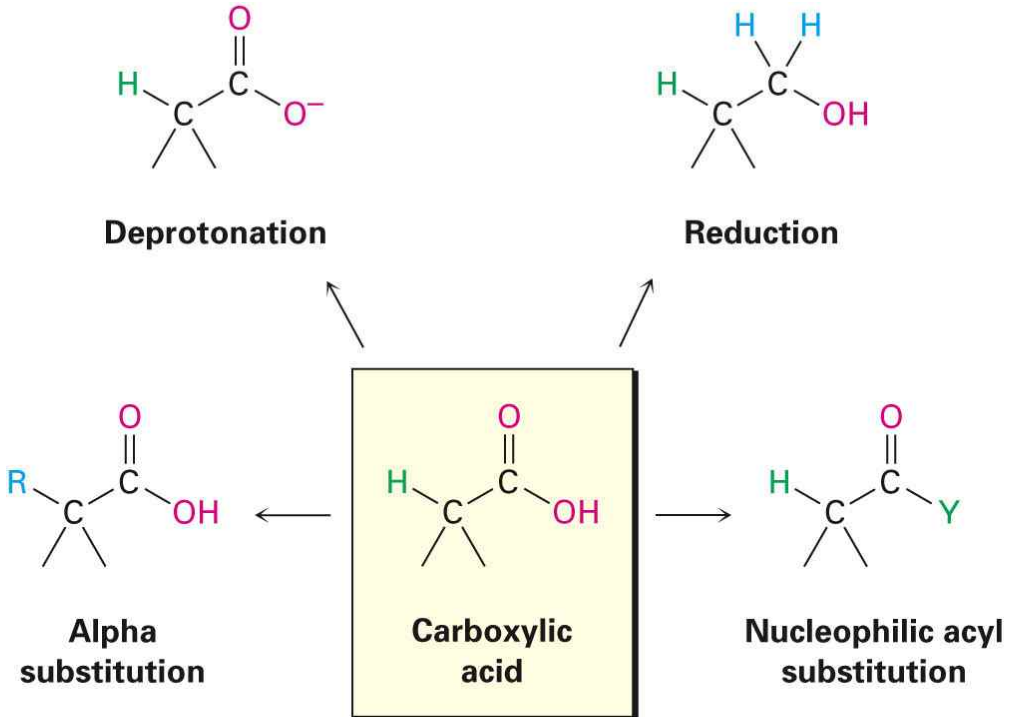
Carboxylation의 Grignard 반응

- Grignard reagents react with dry CO_2 to yield a metal carboxylate
- Limited to alkyl halides that can form Grignard reagents
- The organomagnesium halide adds to C=O of carbon dioxide
- Protonation by addition of aqueous HCl in a separate step gives the free carboxylic acid



Carboxylic Acids 반응

- Carboxylic acids transfer a proton to a base to give anions, which are good nucleophiles in S_N2 reactions
- Like ketones, carboxylic acids undergo addition of nucleophiles to the carbonyl group
- In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones



Nitriles

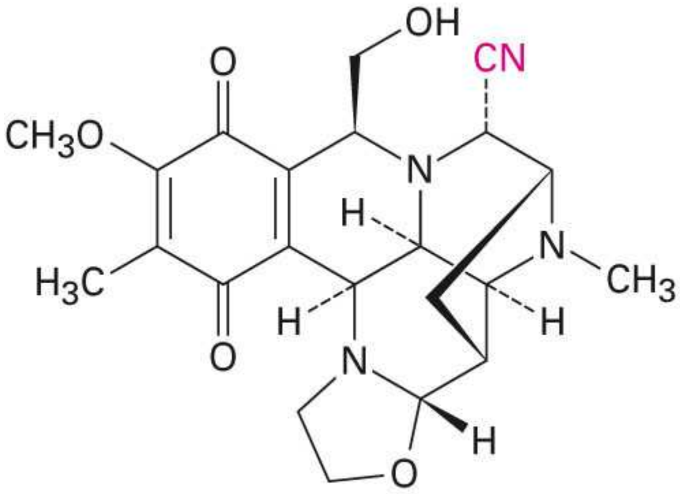
- Nitriles and carboxylic acids both have a carbon atom with three bonds to an electronegative atom, and contain a π bond
- Both both are electrophiles

$R-C\equiv N$

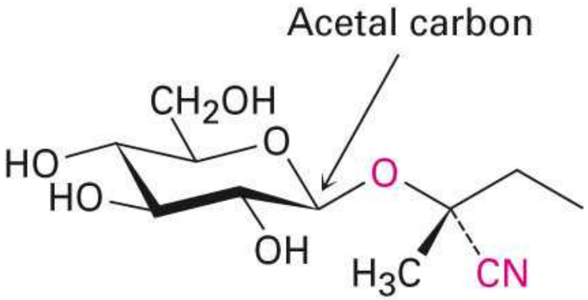
A nitrile—three bonds to nitrogen

An acid—three bonds to two oxygens

자연에 존재하는 **Nitriles**



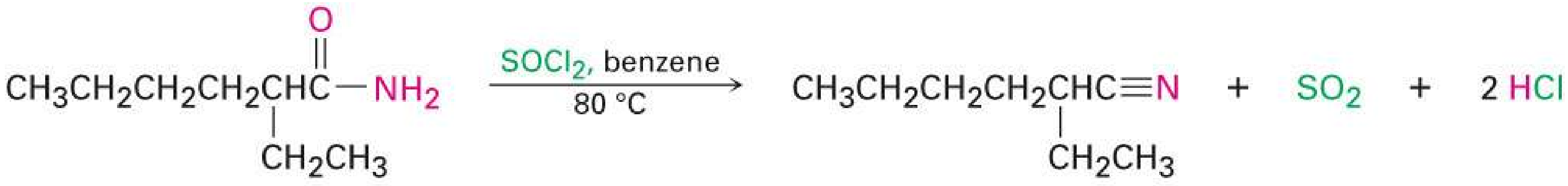
Cyanocycline A



Lotaustralin
(a cyanogenic glycoside)

Nitriles 제조 : Dehydration

- Reaction of primary amides $RCONH_2$ with $SOCl_2$ or $POCl_3$ (or other dehydrating agents)
- Not limited by steric hindrance or side reactions (as is the reaction of alkyl halides with NaCN)



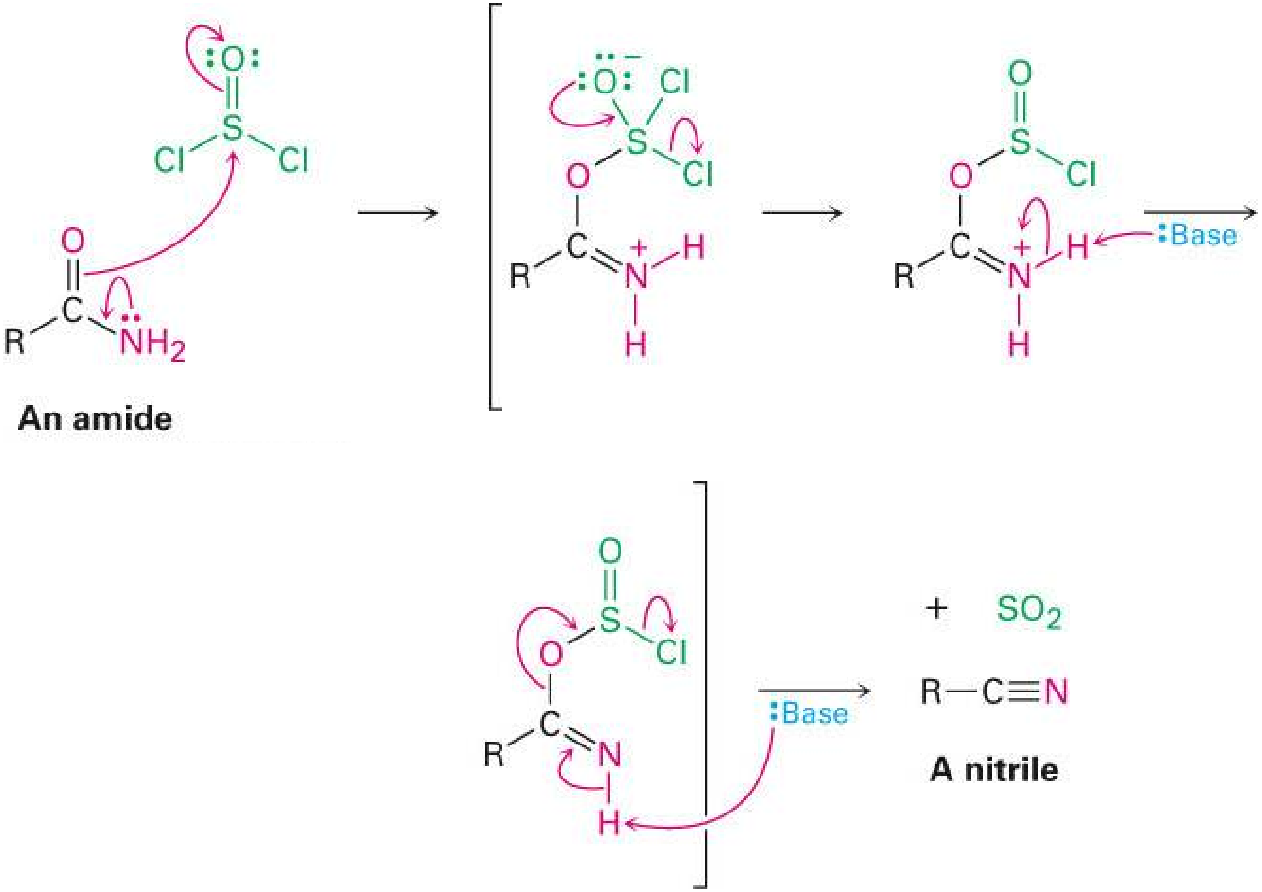
$$CH_3CH_2CH_2CH_2\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}H\overset{\displaystyle O}{\overset{\|}{C}}-NH_2 \xrightarrow[80\ ^\circ C]{SOCl_2,\ benzene} CH_3CH_2CH_2CH_2\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}HC\equiv N + SO_2 + 2\ HCl$$

2-Ethylhexanamide

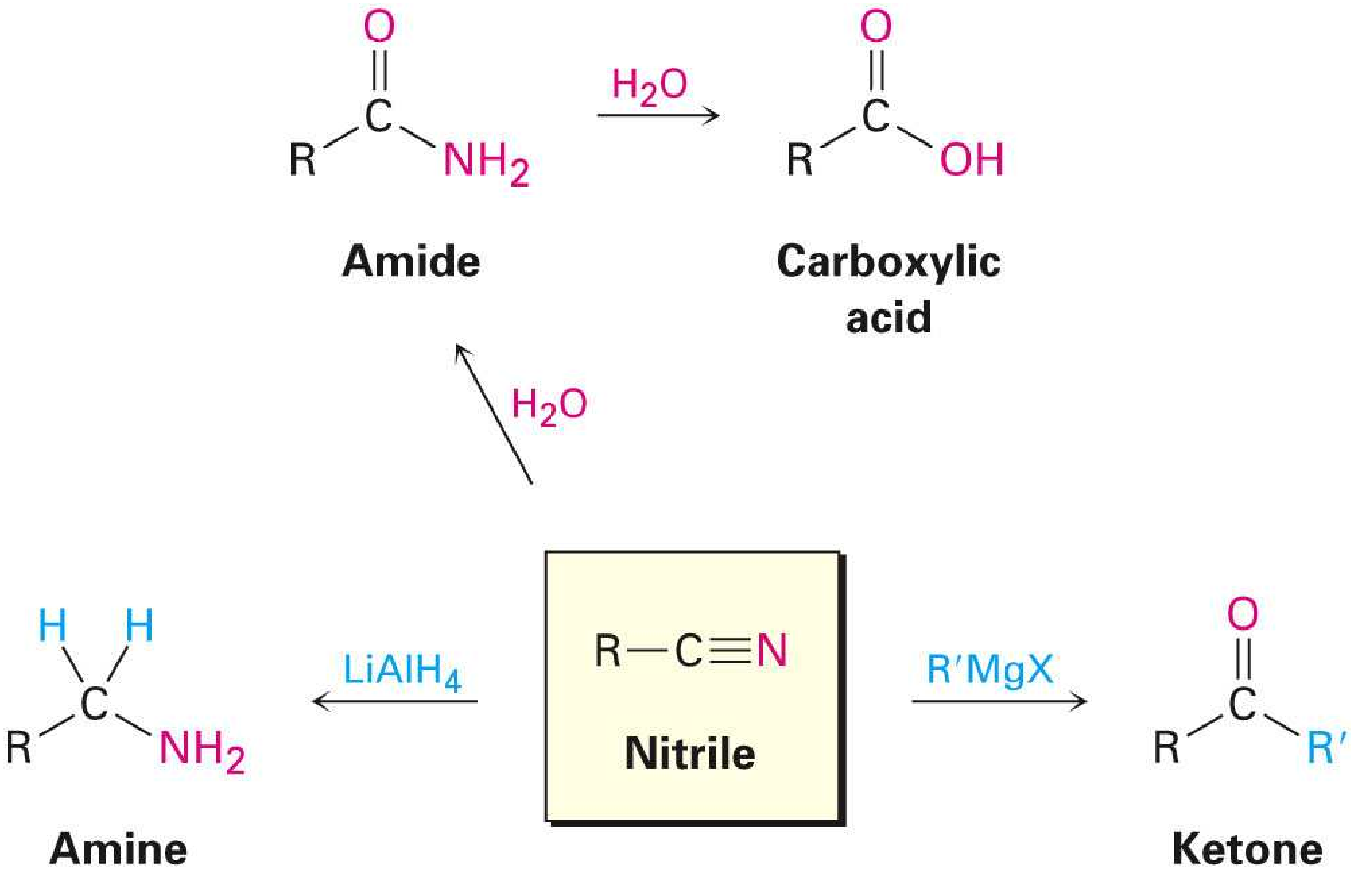
2-Ethylhexanenitrile (94%)

Amides의 Dehydration 기전

- Nucleophilic amide oxygen atom attacks $SOCl_2$ followed by deprotonation and elimination

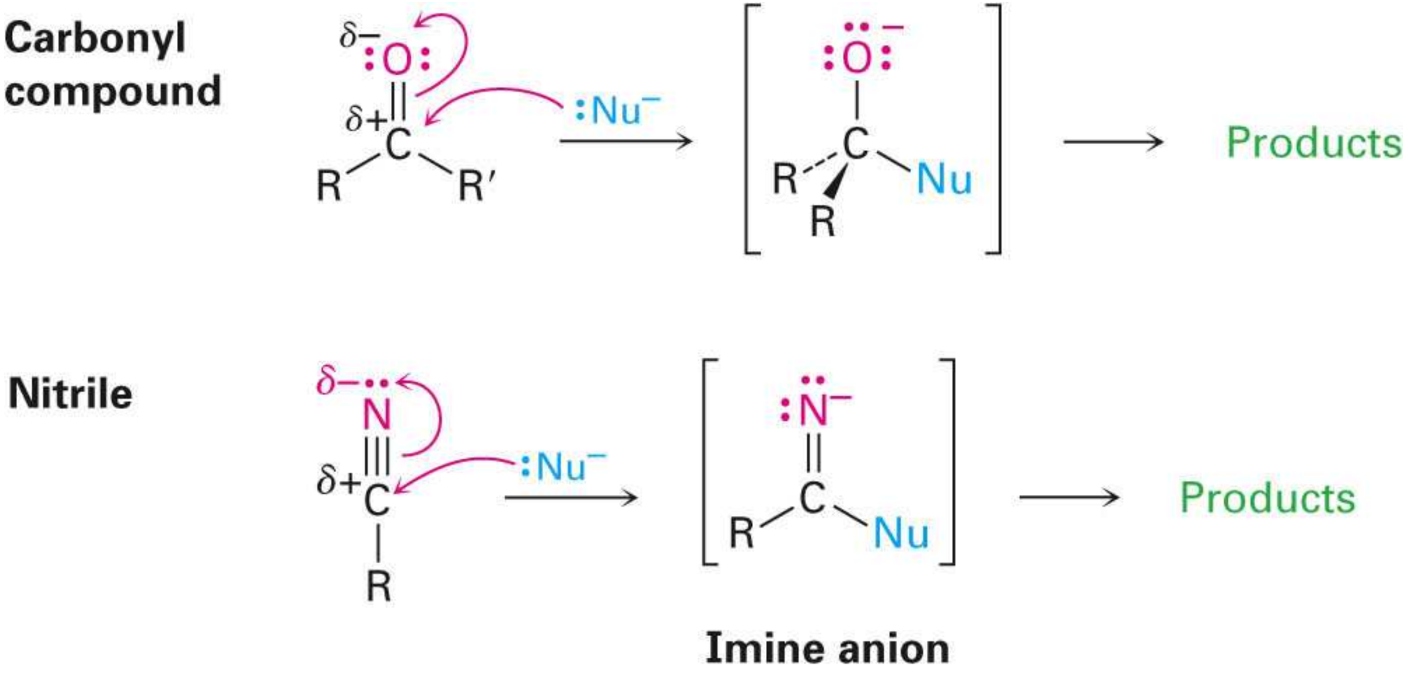


Nitriles의 반응 (1)



Nitriles의 반응 (2)

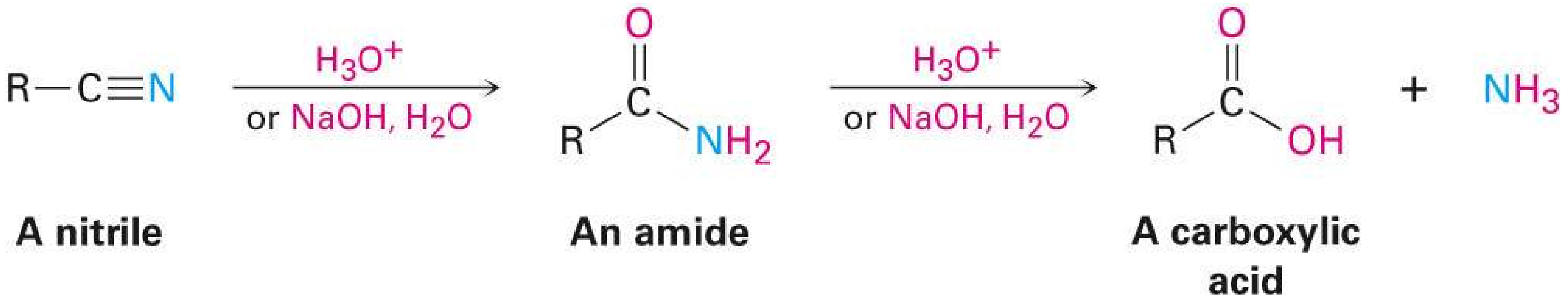
- RCºN is strongly polarized and with an electrophilic carbon atom
- Attacked by nucleophiles to yield *sp*^{2}-hybridized imine anions



Conversion of Nitriles into Carboxylic Acids

Hydrolysis (가수분해)

- Hydrolyzed in with acid or base catalysis to a carboxylic acid and ammonia or an amine



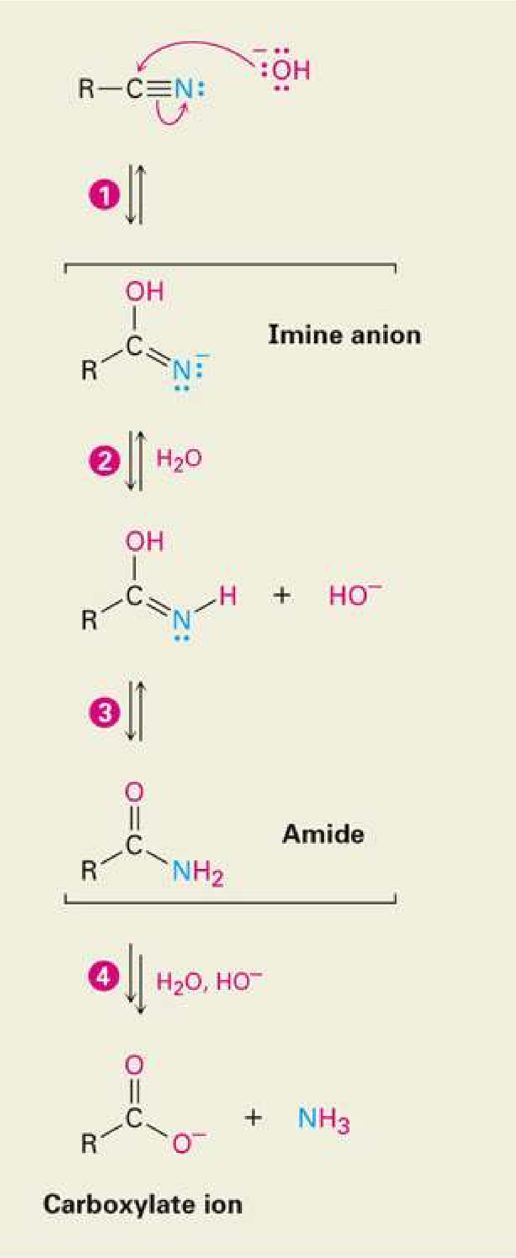
Mechanism of Hydrolysis of Nitriles

- Nucleophilic addition of hydroxide to C≡N bond

- Protonation gives a hydroxy imine, which tautomerizes to an amide

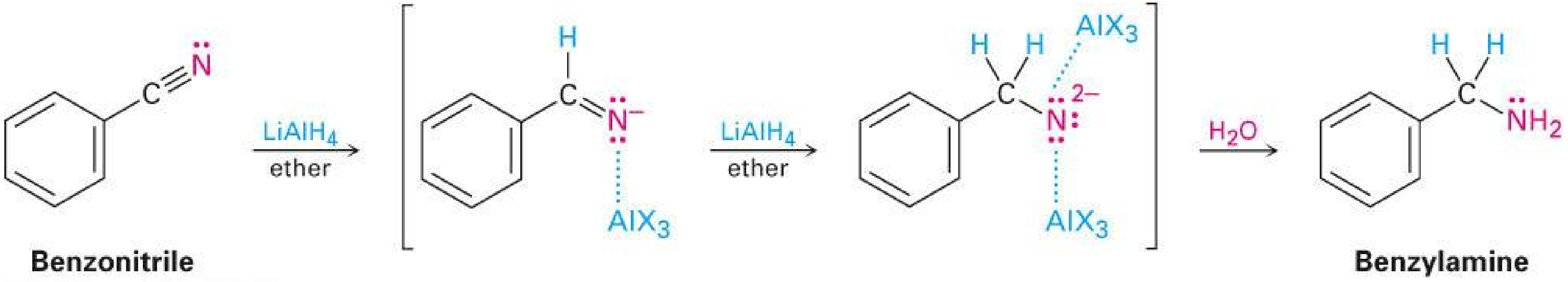
- A second hydroxide adds to the amide carbonyl group and loss of a proton gives a dianion

- Expulsion of NH_2– gives the carboxylate



Reduction: Conversion of Nitriles into Amines

- Reduction of a nitrile with $LiAlH_4$ gives a primary amine
- Nucleophilic addition of hydride ion to the polar C≡N bond, yieldis an imine anion
- The C=N bond undergoes a second nucleophilic addition of hydride to give a *dianion*, which is protonated by water



Reaction of Nitriles with Organometallic Reagents

- Grignard reagents add to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone