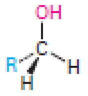
Chapter III : Alcohols, carboxylic and amine functions

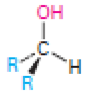
I. Alcohols; Phenols ; Etheroxides

I.1. Alcohols

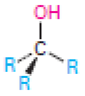
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbon substituents bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol

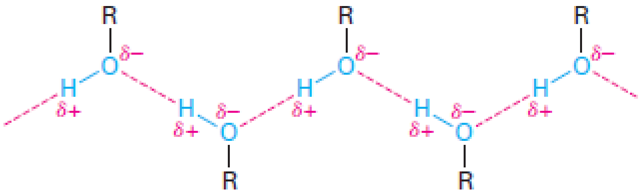


A secondary (2°) alcohol

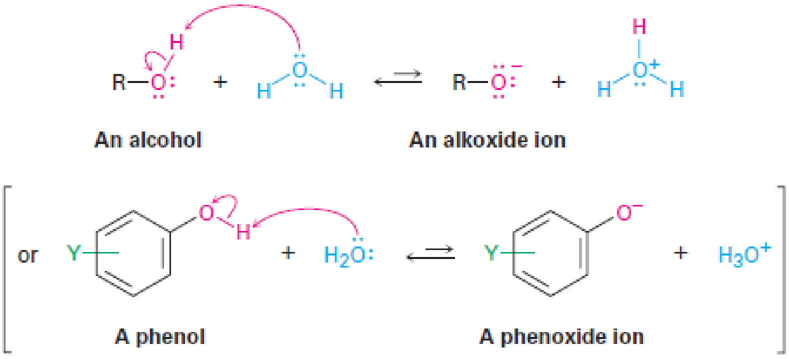


A tertiary (3°) alcohol

Alcohols, phenols, and ethers can be thought of as organic derivatives of water in which one or both of the hydrogens have been replaced by organic parts: H-O-H becomes R-O-H, Ar-OH, or R-O-R′. Thus, all three classes of compounds have nearly the same geometry as water. The C-O-H or C-O-C bond angles are approximately tetrahedral 109° in methanol and 112° in dimethyl ether, for instance the oxygen atoms are sp3 hybridized.



As weak acids, alcohols and phenols dissociate to a slight extent in dilute aqueous solution by donating a proton to water, generating $\mathbf{H_3O^+}$ and an alkoxide ion ($\mathbf{RO^-}$) or a phenoxide ion ($\mathbf{ArO^-}$).



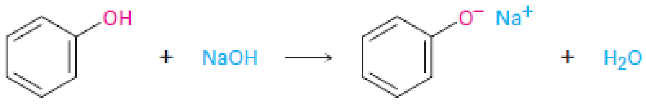
An alcohol

An alkoxide ion

A phenol

A phenoxide ion

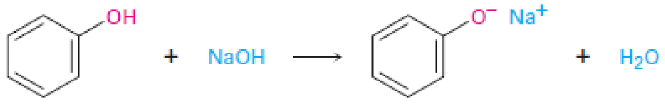
Phenols are about a million times more acidic than alcohols and are therefore soluble in dilute aqueous NaOH.



Phenol

Sodium phenoxide (sodium phenolate)

Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized by the aromatic ring. Sharing the negative charge over the ring increases the stability of the phenoxide anion and thus increases the tendency of the corresponding phenol to dissociate.



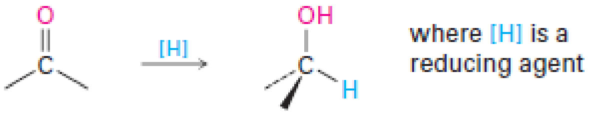
Phenol

Sodium phenoxide (sodium phenolate)

I.1.2. Synthesis of alcohol

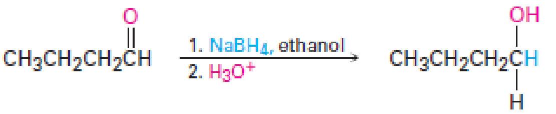
I.1.2.1. Reduction of Carbonyl Compounds

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane, reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.



A carbonyl compound **An alcohol**

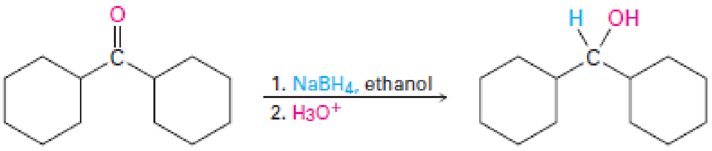
I.1.2.2. Aldehyde reduction



Butanal

Butan-1-ol (85%)
(a 1° alcohol)

I.1.2.3. Ketone reduction



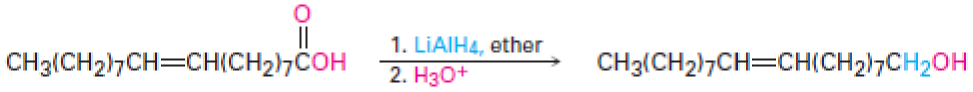
Dicyclohexyl ketone

Dicyclohexylmethanol (88%)
(a 2° alcohol)

I.1.2.4. Reduction of Carboxylic Acids and Esters

Esters and carboxylic acids are reduced to give primary alcohols.

I.1.2.5. Carboxylic acid reduction

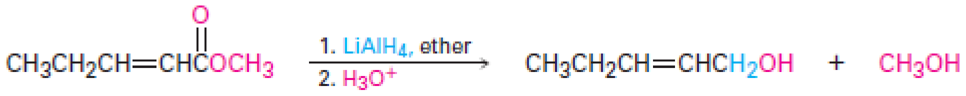


$$CH_3(CH_2)_7CH{=}CH(CH_2)_7\overset{\overset{O}{\|}}{C}OH \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4,\ ether} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

Octadec-9-enoic acid
(oleic acid)

Octadec-9-en-1-ol (87%)

I.1.2.6. Ester reduction



$$CH_3CH_2CH{=}CH\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4,\ ether} CH_3CH_2CH{=}CHCH_2OH + CH_3OH$$

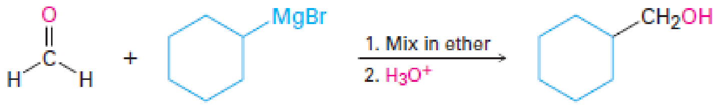
Methyl pent-2-enoate

Pent-2-en-1-ol (91%)

I.1.2.7. Grignard Reactions of Carbonyl Compounds

Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium, react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do.

I.1.2.8. Formaldehyde reaction

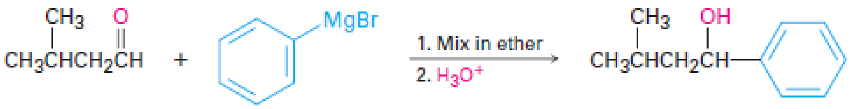


Formaldehyde

Cyclohexyl-
magnesium
bromide

Cyclohexylmethanol (65%)
(a 1° alcohol)

I.1.2.9. Aldehyde reaction

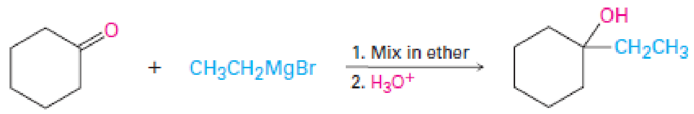


3-Methylbutanal

Phenylmagnesium
bromide

3-Methyl-1-phenyl-
butan-1-ol (73%)
(a 2° alcohol)

I.1.2.10. Ketone reaction

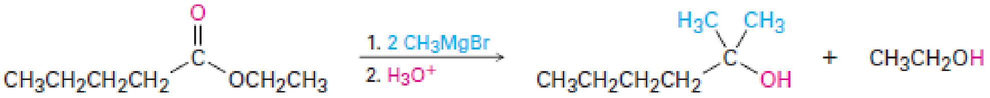


Cyclohexanone

Ethylmagnesium
bromide

1-Ethylcyclohexanol (89%)
(a 3° alcohol)

I.1.2.11. Ester reaction



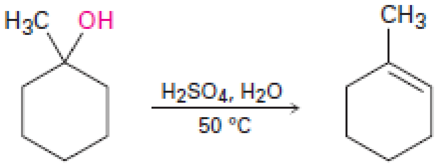
Ethyl pentanoate

2-Methylhexan-2-ol (85%)
(a 3° alcohol)

I.1.3. Reactivity of alcohol

I.1.3.1. Dehydration of Alcohols

Alcohols undergo dehydration—the elimination of H_2O—to give alkenes. A method that works particularly well for secondary and tertiary alcohols is treatment with a strong acid.

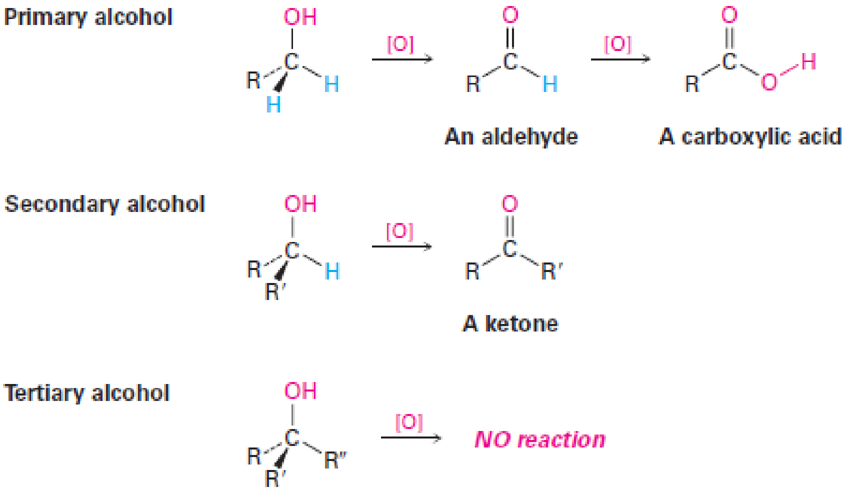


1-Methylcyclohexanol **1-Methylcyclohexene (91%)**

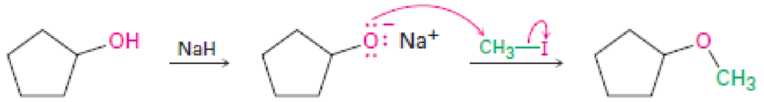
I.1.3.2. Oxidation of Alcohols

Perhaps the most valuable reaction of alcohols is their oxidation to yield carbonyl compounds the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols yield aldehydes or carboxylic acids, and secondary alcohols yield ketones, but tertiary alcohols don't normally react with oxidizing agents.

Older methods were often based on **Cr(VI)** reagents, such as **CrO_3** or **$Na_2Cr_2O_7$**, but the most common current choice for preparing an aldehyde from a primary alcohol in the laboratory is to use a periodinane **HIO_4**.



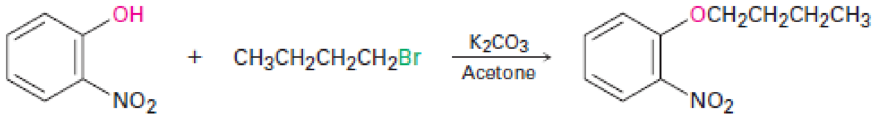
I.1.3.3. Conversion into Ethers



Cyclopentanol **Alkoxide ion** **Cyclopentyl methyl ether (74%)**

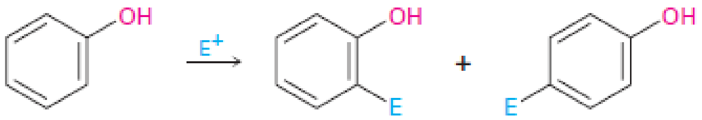
I.1.4. Reactivity of phenol

I.1.4.1. Alcohol-Like Reactions of Phenols

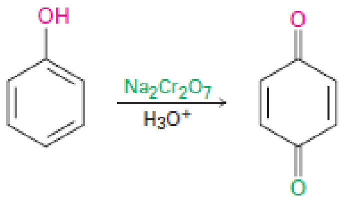


o-Nitrophenol 1-Bromobutane Butyl *o*-nitrophenyl ether (80%)

I.1.4.2. Electrophilic Aromatic Substitution Reactions of Phenols

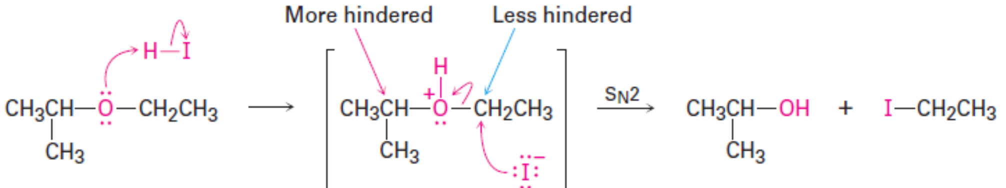


I.1.4.3. Oxidation of Phenols: Quinones



I.1.5. Reactivity of ethers

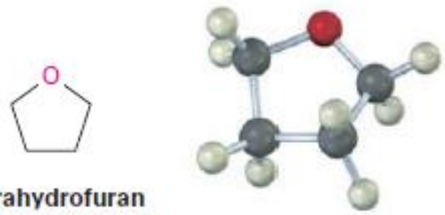
Ethers are unreactive to most common reagents, a property that accounts for their frequent use as reaction solvents. Halogens, mild acids, bases, and nucleophiles have no effect on most ethers. In fact, ethers undergo only one general reaction—they are cleaved by strong acids such as aqueous HI or HBr.



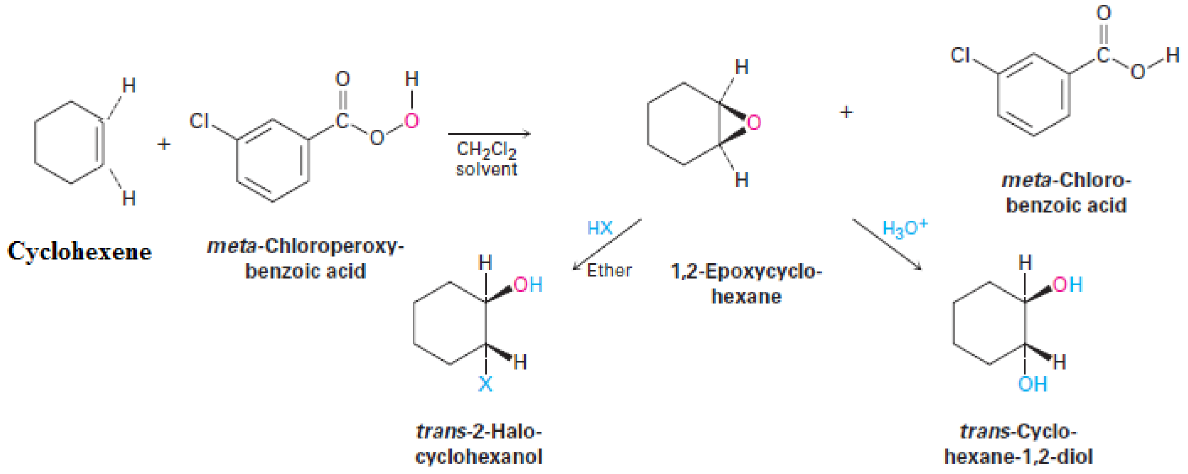
Ethyl isopropyl ether Isopropyl alcohol Iodoethane

I.1.6. Cyclic ether

For the most part, cyclic ethers behave like acyclic ethers. The chemistry of the ether functional group is the same whether it's in an open chain or in a ring. Thus, the cyclic ether tetrahydrofuran (**THF**) is often used as a solvent because of its inertness.

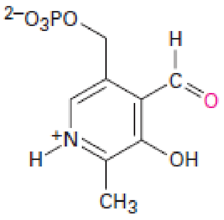


Tetrahydrofuran

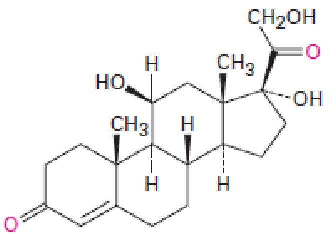


II. Acid; Aldehydes; Ketones

There are many different kinds of carbonyl compounds, but we'll begin our coverage by looking at just two: aldehydes (RCHO) and ketones (R_2CO). In nature, many substances found in living organisms are aldehydes or ketones. The aldehyde pyridoxal phosphate, for instance, is a coenzyme involved in a large number of metabolic reactions, and the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.



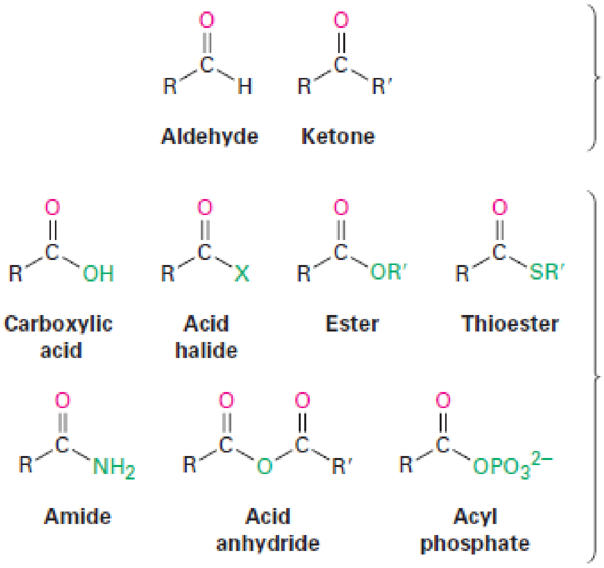
Pyridoxal phosphate (PLP)



Hydrocortisone

II.1. The nature of carbonyl compounds

It's useful to classify carbonyl compounds into two general categories based on the kinds of chemistry they undergo. In one category are aldehydes and ketones; in the other are carboxylic acids and their derivatives.

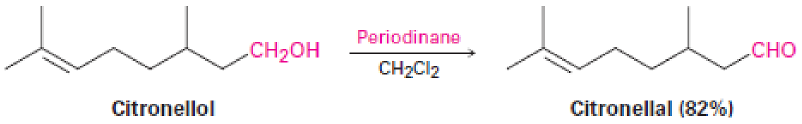


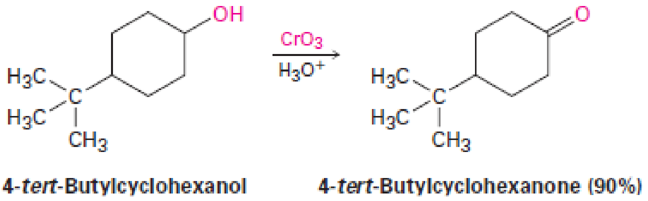
The –R′ and –H in these compounds *can't* act as leaving groups in nucleophilic substitution reactions.

The –OH, –X, –OR′, –SR, $-NH_2$, –OCOR′, and $-OPO_3^{2-}$ in these compounds *can* act as leaving groups in nucleophilic substitution reactions.

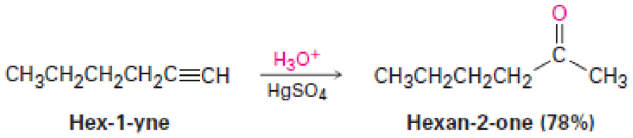
II.2. Synthesis of aldehydes and ketones

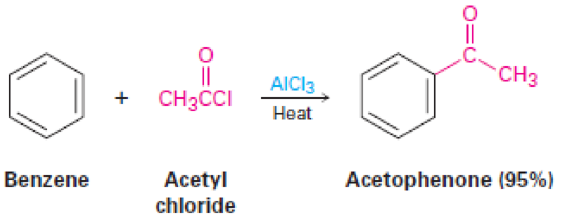
Primary alcohols are oxidized to give aldehydes, and secondary alcohols are oxidized to give ketones. A periodinane oxidizing agent in dichloromethane is often chosen for making aldehydes, while CrO_3 and $Na_2Cr_2O_7$ in aqueous acid are frequently used for making ketones.





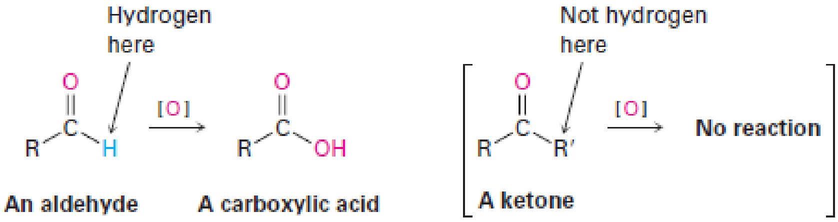
Other methods we've seen for preparing ketones include the hydration of a terminal alkyne to yield a methyl ketone and the Friedel–Crafts acylation of an aromatic ring.





II.3. Reactivity of aldehydes and ketones

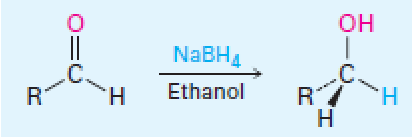
II.3.1. Oxidation of aldehydes



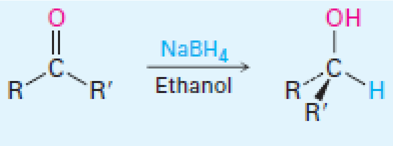
II.3.2. Nucleophilic addition reaction

1. Reaction with hydride reagents to yield alcohols

(a) Reaction of aldehydes to yield primary alcohols

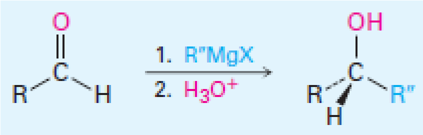


(b) Reaction of ketones to yield secondary alcohols

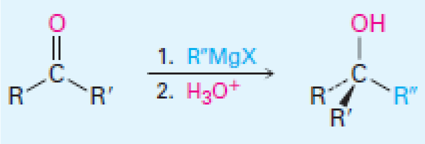


2. Reaction with Grignard reagents to yield alcohols

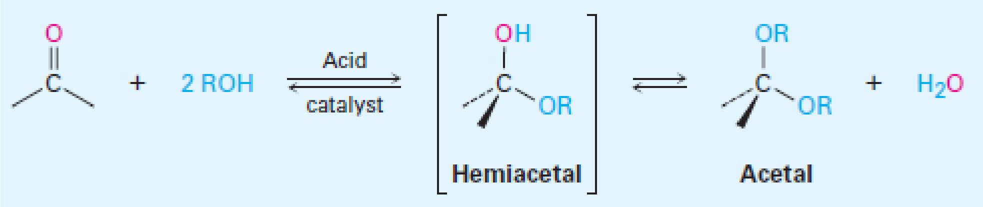
(a) Reaction of aldehydes to yield secondary alcohols



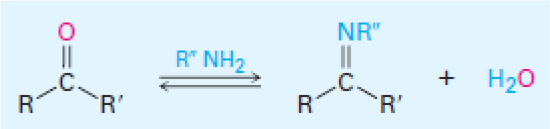
(b) Reaction of ketones to yield tertiary alcohols



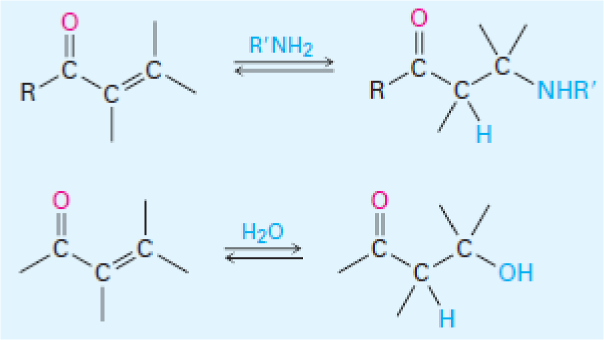
3. Reaction with alcohols to yield acetals



4. Reaction with amines to yield imines

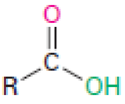


5. Conjugate (1,4) nucleophilic addition reaction



III. Carboxylic Acids

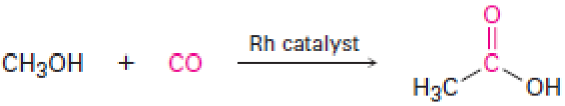
Carboxylic acids and their derivatives are the most abundant of all organic compounds, both in the laboratory and in living organisms.



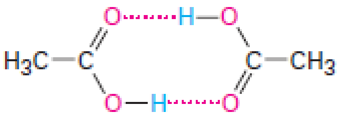
Carboxylic acid

Carboxylic acids are everywhere in nature. Acetic acid, CH_3CO_2H, for instance, is the principal organic component of vinegar.

Approximately 5 million tons of acetic acid are produced each year worldwide for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.



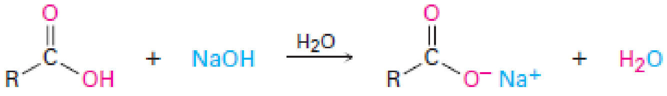
Like alcohols, carboxylic acids form strong intermolecular hydrogen bonds. Most carboxylic acids, in fact, exist as dimers held together by two hydrogen bonds.



Acetic acid dimer

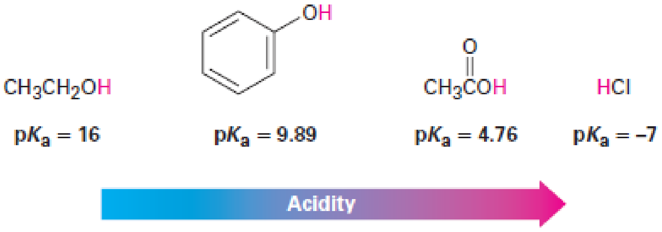
III.1. Acidity of carboxylic acid

The most obvious property of carboxylic acids is implied by their name: carboxylic acids are acidic. Acetic acid, for example, has Ka = **$1.75 \text{ x } 10^{-5}$** (**pKa = 4.76**). In practical terms, a Ka value near 10^{-5} means that only about 1% of the molecules in a 0.1 M aqueous solution are dissociated. Because of their acidity, carboxylic acids react with bases such as NaOH to give watersoluble metal carboxylates, $RCO_2^- Na^+$.



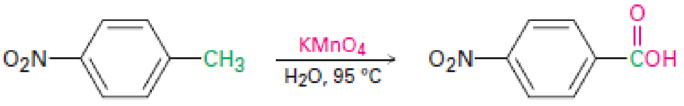
A carboxylic acid (water-insoluble) A carboxylic acid salt (water-soluble)

Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The **Ka** of ethanol, for example, is approximately **10^{-16}**, making ethanol a weaker acid than acetic acid by a factor of **10^{11}**.



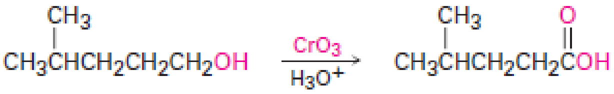
III.2. Synthesis of carboxylic acid

A substituted alkylbenzene can be oxidized with $KMnO_4$ to give a substituted benzoic acid.



p-Nitrotoluene p-Nitrobenzoic acid (88%)

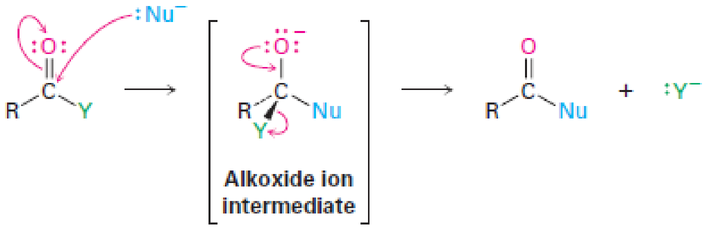
Primary alcohols and aldehydes can be oxidized with aqueous CrO_3 or $Na_2Cr_2O_7$ to give carboxylic acids.



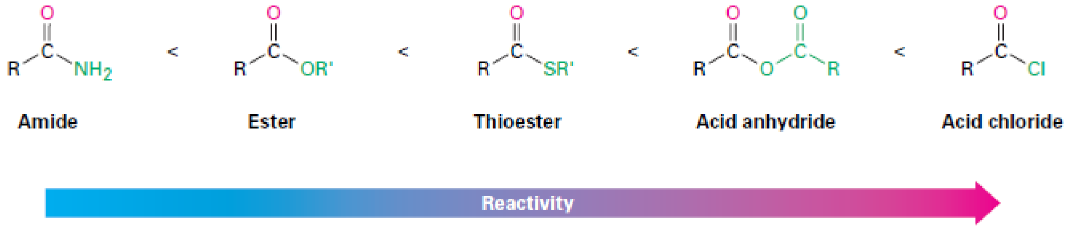
4-Methylpentan-1-ol 4-Methylpentanoic acid

III.3. Nucleophilic acyl substitutions reactions

III.3.1. Carboxylic acid derivative: nucleophilic acyl substitution

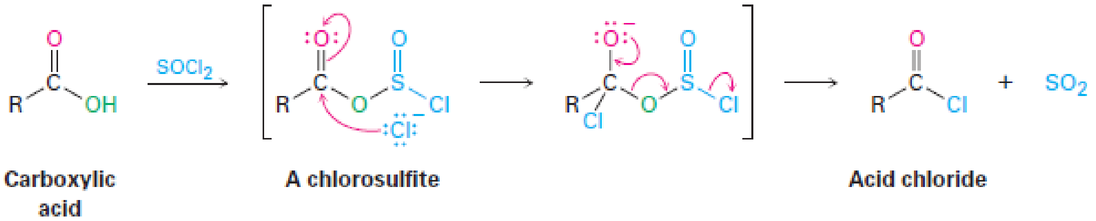


A consequence of these reactivity differences is that it’s usually possible to convert a more reactive acid derivative into a less reactive one.

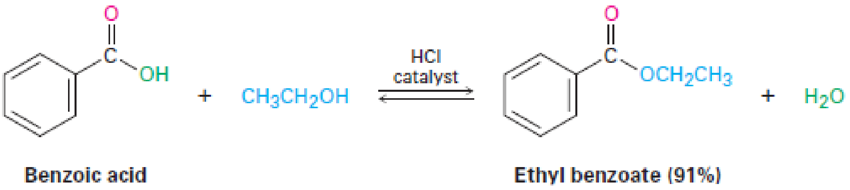


III.4. Reactivity of carboxylic acid

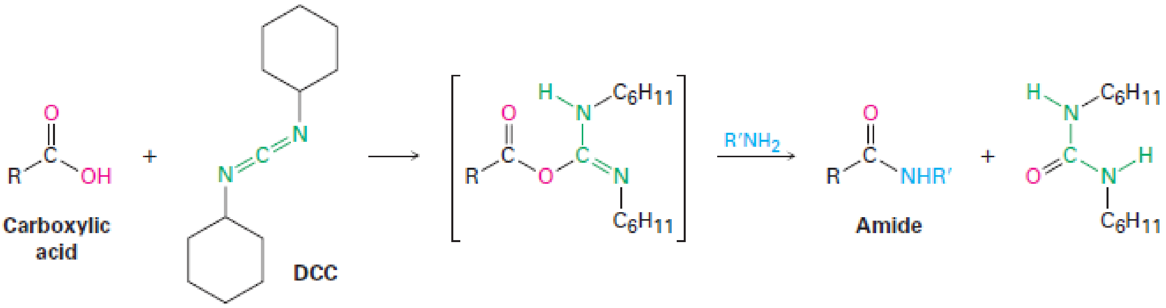
III.4.1. Conversion of Acids into Acid Chlorides



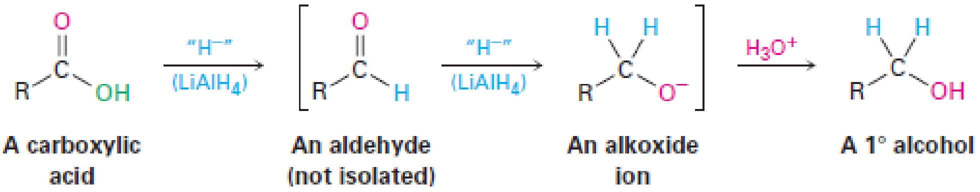
III.4.2. Conversion of Acids into Esters



III.4.3. Conversion of Acids into Amides



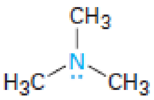
III.4.4. Conversion of Acids into Alcohols



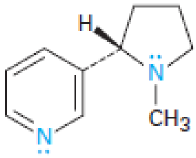
IV. Amines

Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water.

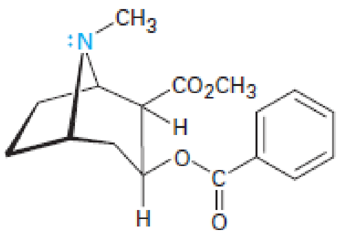
Amines occur widely in both plants and animals. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the South American coca bush.



Trimethylamine

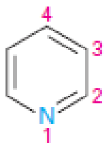


Nicotine

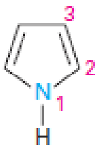


Cocaine

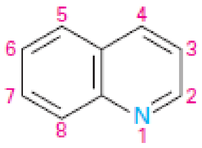
Heterocyclic amines compounds in which the nitrogen atom occurs as part of a ring are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.



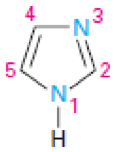
Pyridine



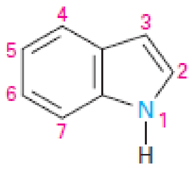
Pyrrole



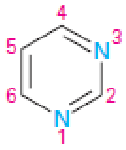
Quinoline



Imidazole



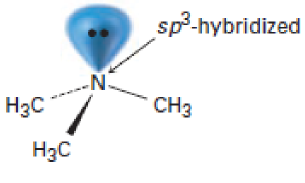
Indole



Pyrimidine

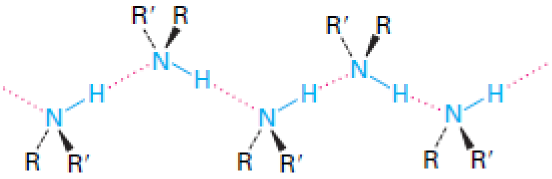
IV.1. Structure and properties of amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp3-hybridized, with the three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C-N-C bond angles are very close to the 109° tetrahedral value 108° in trimethylamine, for example.



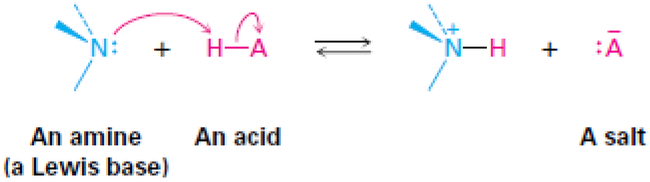
Trimethylamine

Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight.

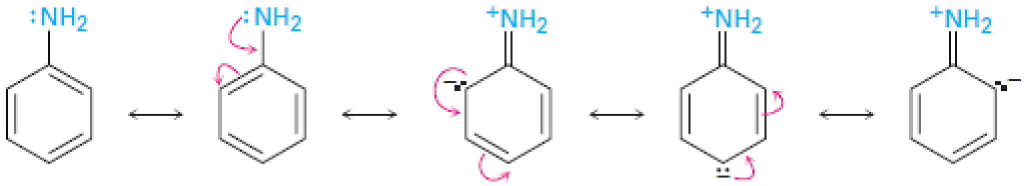


IV. 2. Basicity of amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They therefore react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions.

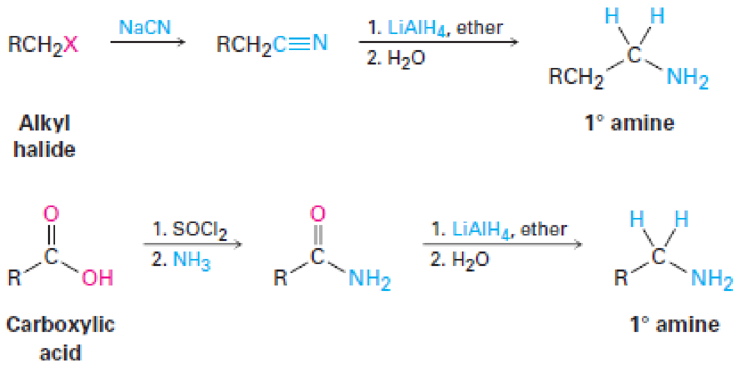


The decreased basicity of arylamines relative to alkylamines is due to the fact that the nitrogen lone-pair electrons in an arylamine are shared by orbital overlap with the p orbitals of the aromatic ring through five resonance forms and are less available for bonding to an acid.



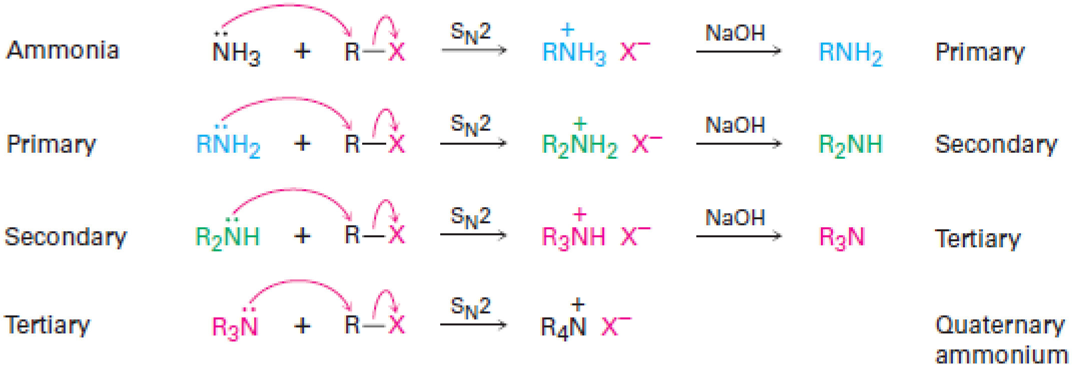
IV. 3. Synthesis of amines

The two-step sequence of SN2 reaction of an alkyl halide with cyanide ion, followed by reduction, is a good method for converting an alkyl halide into a primary amine having one more carbon atom than the original halide.

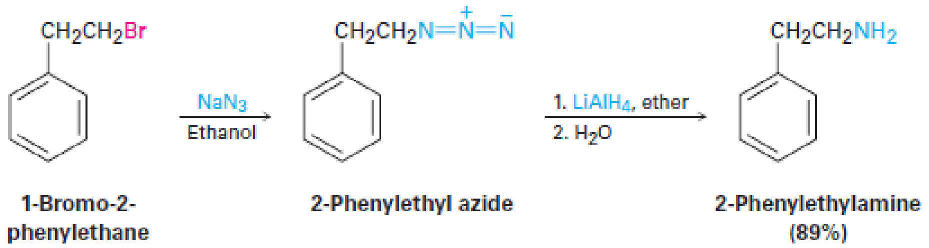


IV. 3.1. SN2 Alkylation Reactions of Alkyl Halides

Ammonia and other amines are good nucleophiles in SN2 reactions. As a result, the simplest method of alkylamine synthesis is by SN2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides, yielding quaternary ammonium salts, $R4N^+X^-$.

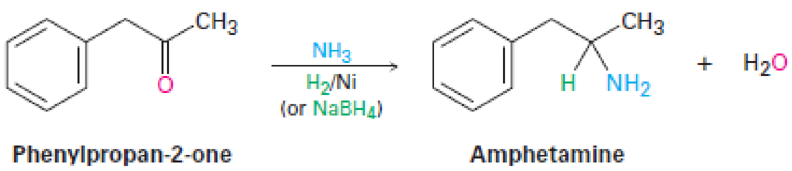


A better method for preparing primary amines from alkyl halides is to use azide ion, N_3^-, as the nucleophile rather than ammonia. The product is an alkyl azide, which is not nucleophilic, so overalkylation can't occur. Subsequent reduction of the alkyl azide with $LiAlH_4$ then leads to the desired primary amine.

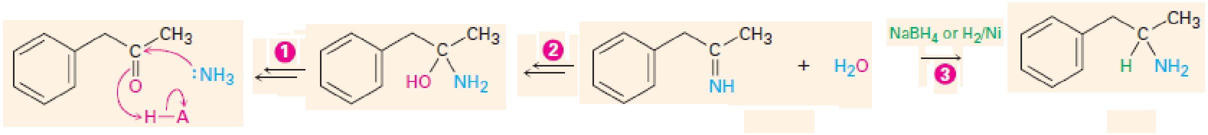


IV. 3.2. Reductive Amination of Aldehydes and Ketones

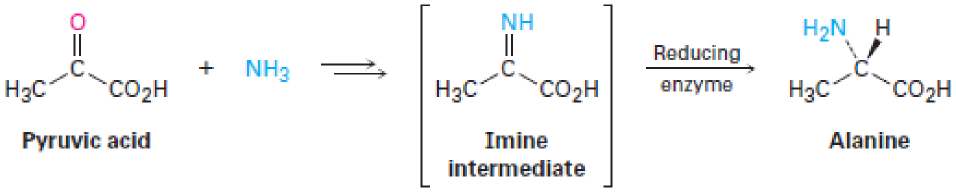
Amines can be synthesized from an aldehyde or ketone in a single step by reaction with ammonia or an amine in the presence of a reducing agent, a process called reductive amination.



IV. 3.2.1. Mechanism

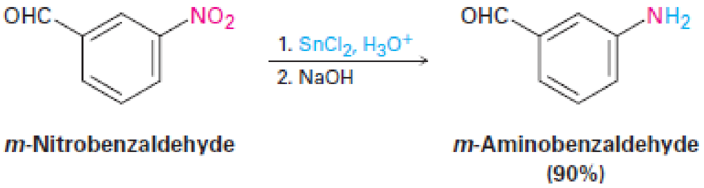


The amino acid alanine, for instance, arises by reaction of pyruvic acid and ammonia to give an intermediate imine that is then enzymatically reduced.



IV. 3.3. Reduction of Nitrobenzenes

The reduction step can be carried out in different ways, depending on the circumstances. Catalytic over platinum works well but is sometimes incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds. Iron, tin, and stannous chloride ($SnCl_2$) in aqueous acid are also effective.

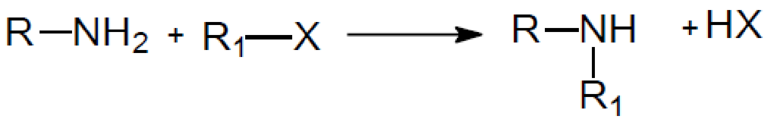


IV.4. Reactivity of amines

IV.4.1. Protonation

$$CH_3\text{-}NH_2 + HCl \longrightarrow CH_3\text{-}NH_3^+\,Cl^-$$

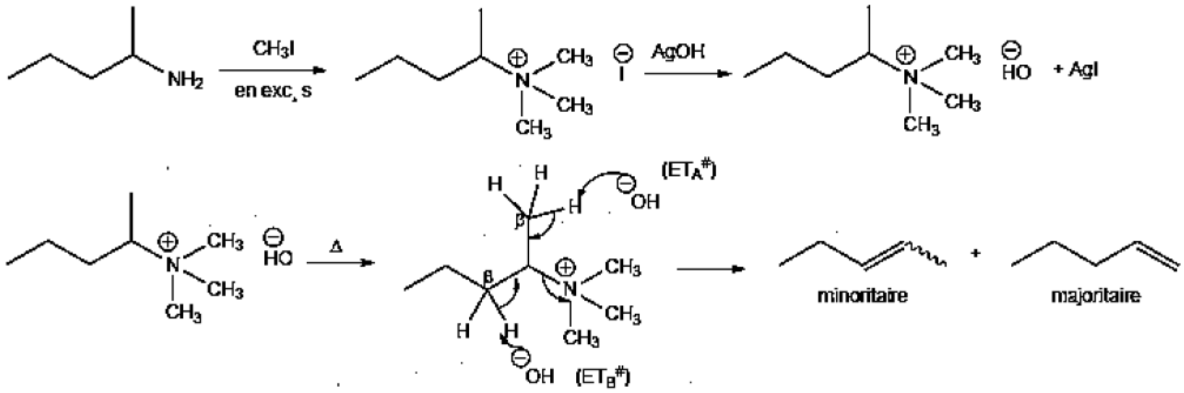
IV.4.2. Alkylation by halogenated derivatives



$$R{-}NH_2 + R_1{-}X \longrightarrow R{-}NH(R_1) + HX$$

IV.4.3. Elimination of Hofmann

IV.4.3.1. Mechanism

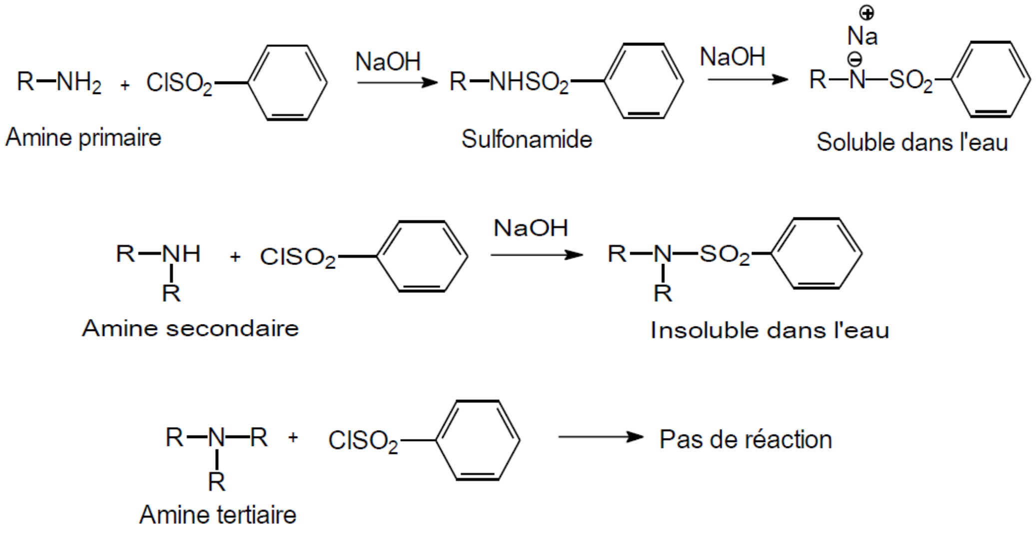


IV.4.4. Acylation

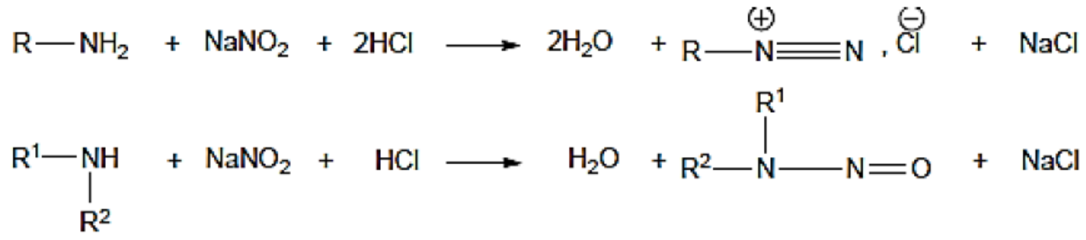
$R-C(=O)-Y + H-N< \longrightarrow R-C(=O)-N< + HY$

Y= OH, Cl, OR', OCOR

IV.4.5. Sulfonylation



IV.4.6. Action of nitrous acid

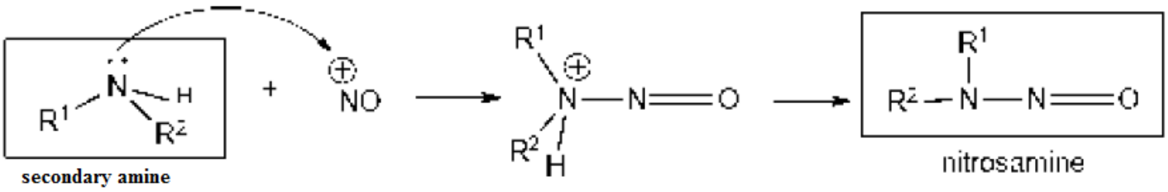


$$R-NH_2 + NaNO_2 + 2HCl \longrightarrow 2H_2O + R-\overset{\oplus}{N}\equiv N\,,\ \overset{\ominus}{Cl} + NaCl$$

$$R^1-\underset{\displaystyle R^2}{\underset{|}{NH}} + NaNO_2 + HCl \longrightarrow H_2O + R^2-\overset{\displaystyle R^1}{\overset{|}{N}}-N=O + NaCl$$

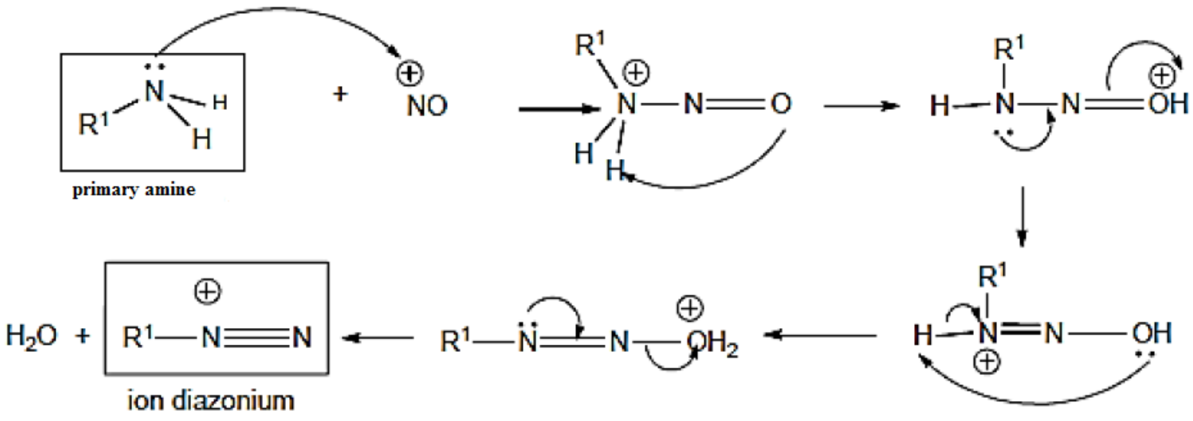
IV.4.6.1. Mechanism

IV.4.6.1.1. With secondary amine



IV.4.6.1.2. With primary amine

IV.4.6.1.2.1. primary amine to diazonium ion



IV.4.7. MANNICH reaction