



Derivatives of Carboxylic Acid

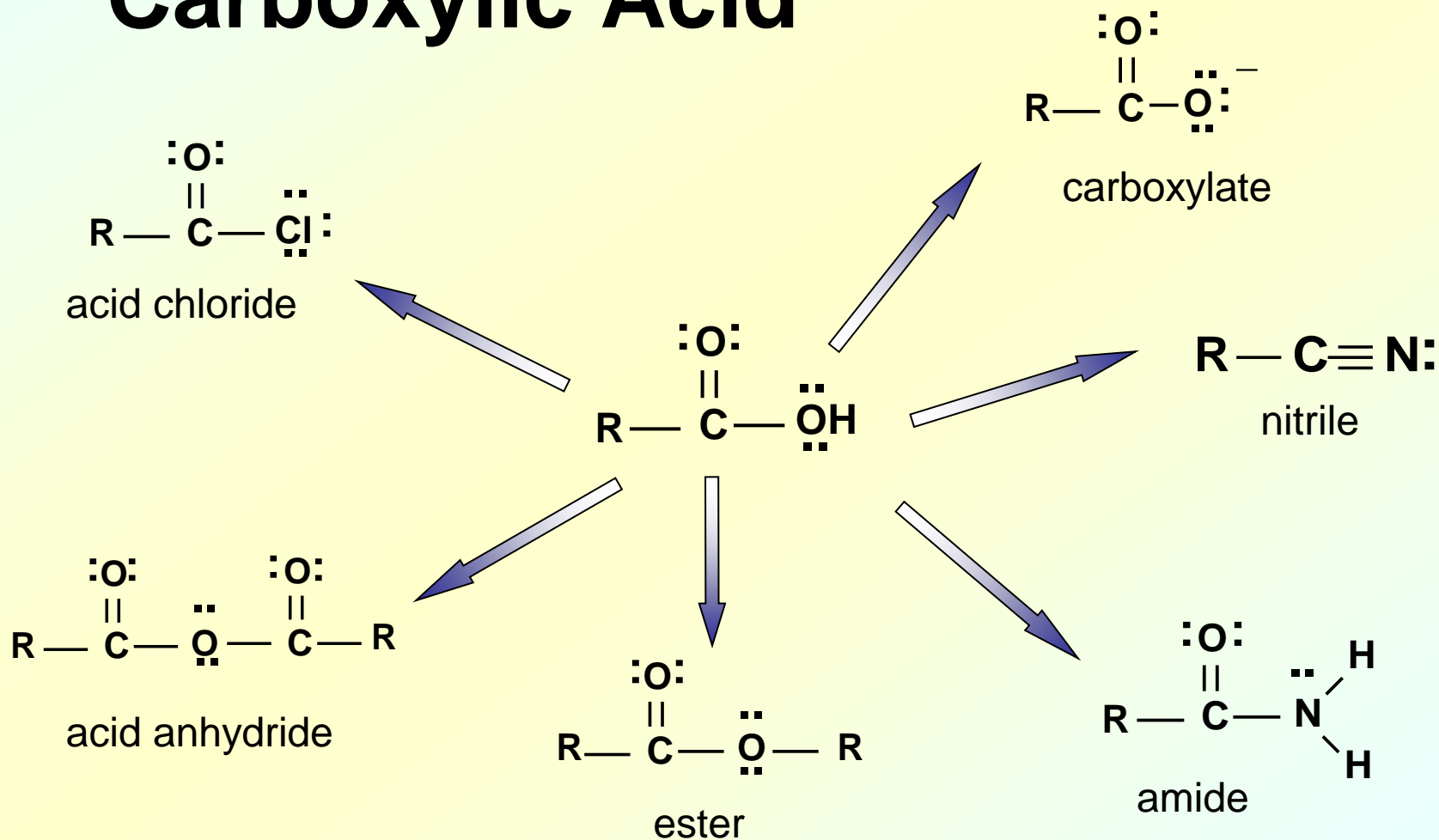
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1st Semester

College of Pharmacy, Al-Farahidi University



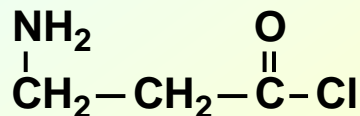
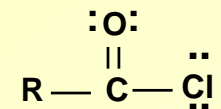
Derivatives of Carboxylic Acid



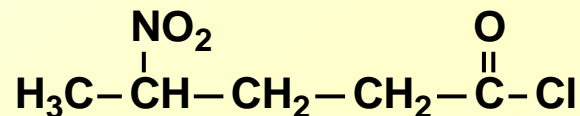
Nomenclature of Acid Halides



- IUPAC: alkanoinic acid → alkanoyl halide
- Common: alkanic acid → alkanyl halide



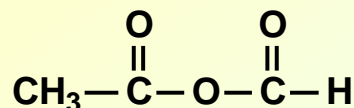
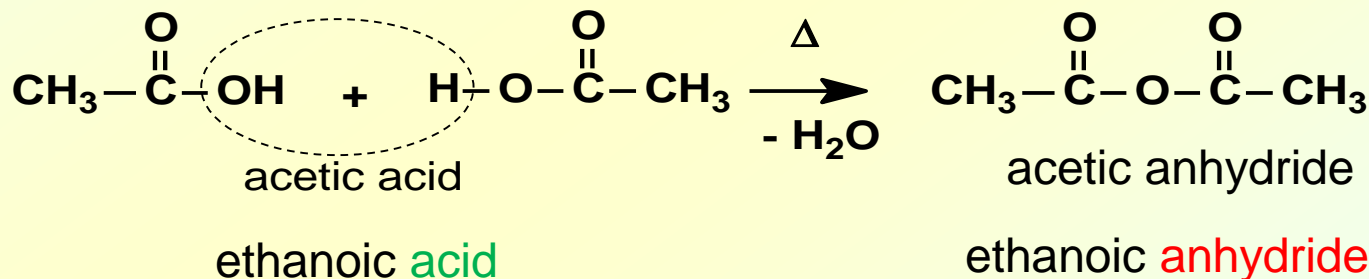
3-aminopropanoyl chloride



4-nitropentanoyl chloride

Nomenclature of Acid Anhydrides

Acid anhydrides are prepared by dehydrating carboxylic acids

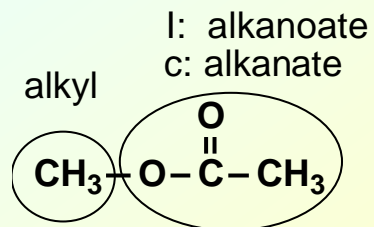
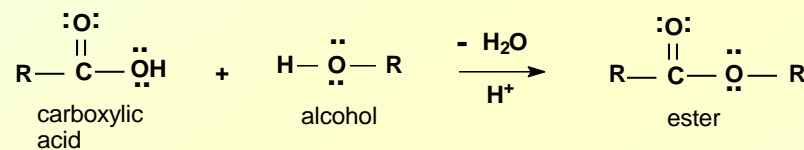


ethanoic methanoic anhydride

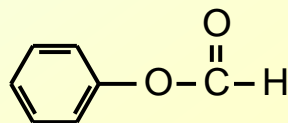
Nomenclature of Esters



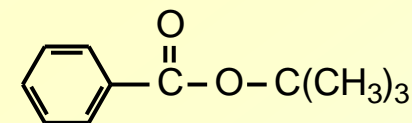
- Esters occur when carboxylic acids react with alcohols



methyl ethanoate



phenyl methanoate

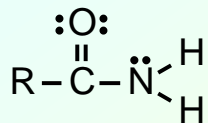


t-butyl benzenecarboxylate

Nomenclature of Amides

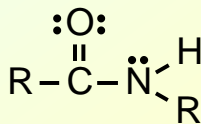


1° amide



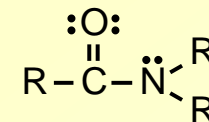
2° amide

N-substituted amide

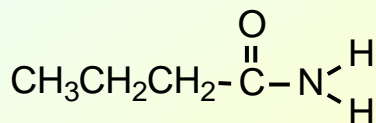


3° amide

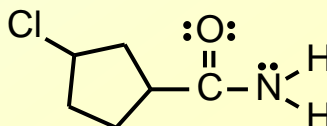
N,N-disubstituted amide



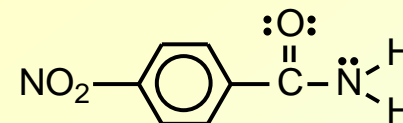
- 1° amides: 'alkanoic acid' + amide → "alkanamide"



butanamide

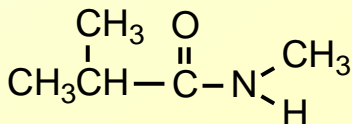


3-chlorocyclopentanecarboxamide

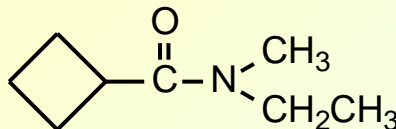


p-nitrobenzenecarboxamide

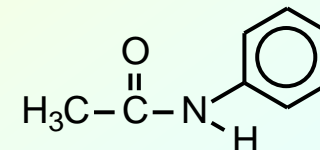
- 2° and 3° amides are *N*-substituted amides



2-methyl-*N*-methylpropanamide



N-ethyl-*N*-methylcyclobutanecarboxamide

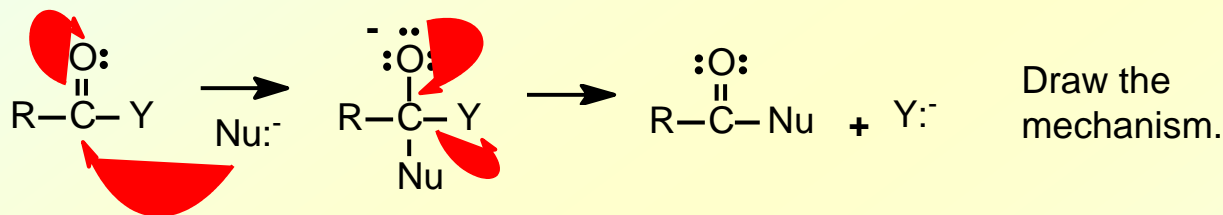
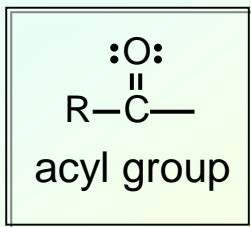


N-phenylethanamide

Nucleophilic Acyl Substitution in Acid Derivatives



- In carboxylic acid derivatives, the acyl group (RCO) is bonded to a leaving group (-Y).



- The **leaving group (-Y)** becomes a base (Y:-). The acid derivative is reactive if the base formed is weak (unreactive). Weak bases are formed from good leaving groups.
- For the carboxylic acid derivatives shown, circle the leaving group. Then draw the structure of the base formed, give its pK_b, and describe it as a strong or weak base.

| acid derivative | leaving group | pK _b | strength as base |
|--|---|-----------------|------------------|
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\ddot{\text{C}}\text{:} \end{array}$ | $\text{:}\ddot{\text{C}}\text{:}^-$ | +21 | non basic |
| $\begin{array}{c} \text{:O:} \quad \text{:O:} \\ \parallel \quad \parallel \\ \text{R}-\text{C}-\ddot{\text{O}}-\text{C}-\text{R} \end{array}$ | $\text{:}\ddot{\text{O}}-\text{C}-\text{R}$ | +9 | weak base |
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\ddot{\text{O}}-\text{R} \end{array}$ | $\text{:}\ddot{\text{O}}-\text{R}$ | -2 | strong base |
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\ddot{\text{N}}\text{H}_2 \end{array}$ | $\text{:}\ddot{\text{N}}\text{H}_2^-$ | -21 | v. strong base |

Nucleophilic Acyl Substitution in Acid Derivatives



We will study the reaction of only a few nucleophiles with various carboxylic acid derivatives and we will see that the same kinds of reactions occur repeatedly.

- **Hydrolysis:** Reaction with **water** to produce a **carboxylic acid**
- **Alcoholysis:** Reaction with an **alcohol** to produce an **ester**
- **Aminolysis:** Reaction with **ammonia** or **an amine** to produce **an amide**
- **Grignard Reaction:** Reaction with an **organometallic** to produce **a ketone or alcohol**
- **Reduction:** Reaction with a **hydride reducing agent** to produce an **aldehyde or alcohol**

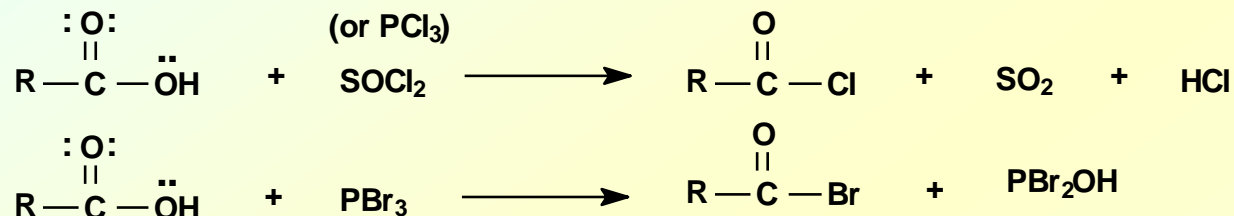
Draw the structures of the expected products of these nucleophilic substitution reactions, then circle the group that has replaced the leaving group (-Y)

| | | | | |
|--|--------------------------------------|--------------------|---|---|
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\text{Y} \end{array} +$ | $\text{H}-\ddot{\text{O}}\text{H}$ | hydrolysis | → | $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\ddot{\text{O}}-\text{H} \end{array}$ |
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\text{Y} \end{array} +$ | $\text{H}-\ddot{\text{O}}\text{R}$ | alcoholysis | → | $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\ddot{\text{O}}-\text{R} \end{array}$ |
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\text{Y} \end{array} +$ | $\text{H}-\ddot{\text{N}}\text{H}_2$ | aminolysis | → | $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\ddot{\text{N}}\text{H}_2 \end{array}$ |
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\text{Y} \end{array} +$ | $\text{R}-\text{MgX}$ | Grignard reduction | → | $\begin{array}{c} \text{:}\ddot{\text{O}}-\text{H} \\ \\ \text{R}-\text{C}-\text{R} \\ \\ \text{R} \end{array}$ |
| $\begin{array}{c} \text{:O:} \\ \parallel \\ \text{R}-\text{C}-\text{Y} \end{array} +$ | LiAlH_3-H | hydride reduction | → | $\begin{array}{c} \text{:}\ddot{\text{O}}-\text{H} \\ \\ \text{R}-\text{C}-\text{H} \\ \\ \text{H} \end{array}$ |

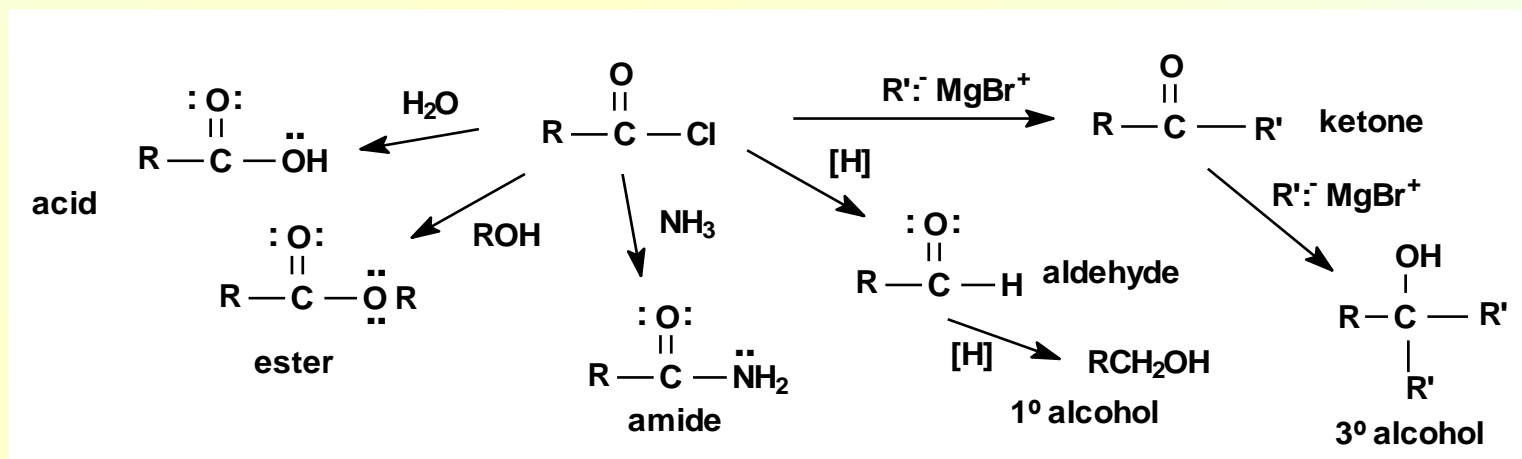
Chemistry of Acid Halides



- In the same way that acid chlorides are produced by reacting a carboxylic acid with thionyl chloride (SOCl_2), acid bromides are produced by reacting a carboxylic acid with phosphorus tribromide (PBr_3).



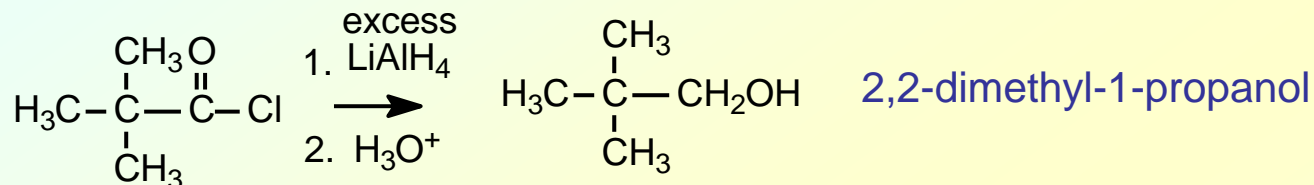
- Most acid halide reactions occur by a nucleophilic acyl substitution mechanism. The halogen can be replaced by $-\text{OH}$ to produce an acid, $-\text{OR}$ to produce an ester, $-\text{NH}_2$ to produce an amide. Hydride reduction produces a 1° alcohol, and Grignard reaction produces a 3° alcohol.



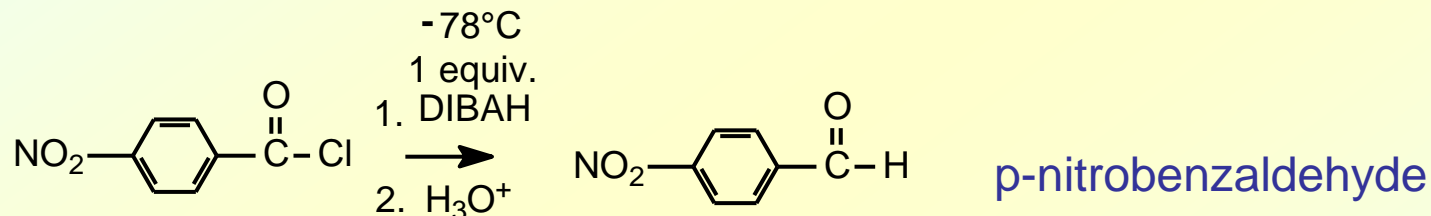
Reduction of Acid Chlorides to Alcohols



1. **With hydride** : Acid chlorides are **reduced by LiAlH_4** to produce **1° alcohols**. The alcohols can of course be produced by reduction of the carboxylic acid directly.

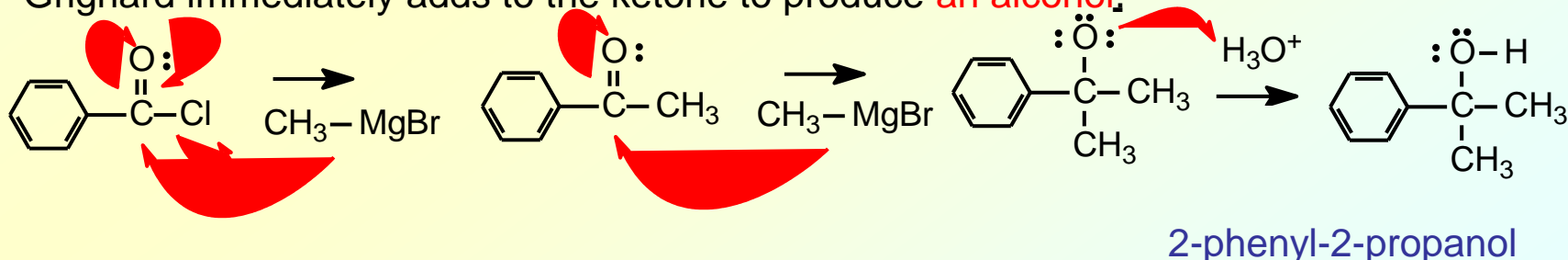


- However, the reaction will stop at the aldehyde if exactly **1 equivalent of a weaker hydride** is used, i.e., diisobutylaluminum hydride (**DIBAH**) at a low temperature (-78°C).



2. with Grignards

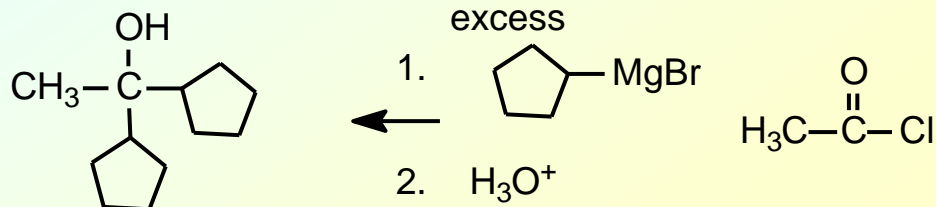
- **Grignard reagents** react with acid chlorides producing **3° alcohols** in which 2 alkyl group substituents are the same. The mechanism the 1st equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a **ketone**, and a 2nd equivalent of Grignard immediately adds to the ketone to produce **an alcohol**.



Practice Questions for Acid Chloride Reductions

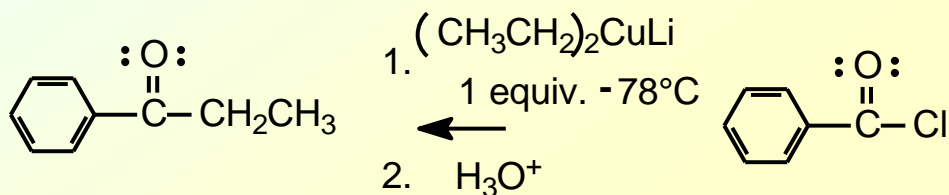


- Draw the reagents that can be used to prepare the following products from an acid chloride by reduction with hydrides, Grignards and Gilman reagent. Draw all possible combinations.

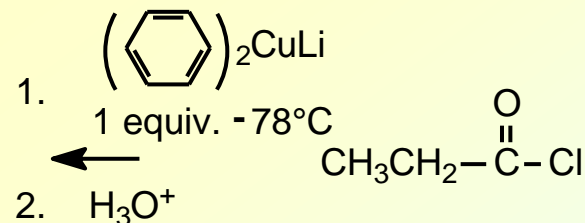


l: ethanoyl chloride

l: 1,1-dicyclopentylethanol

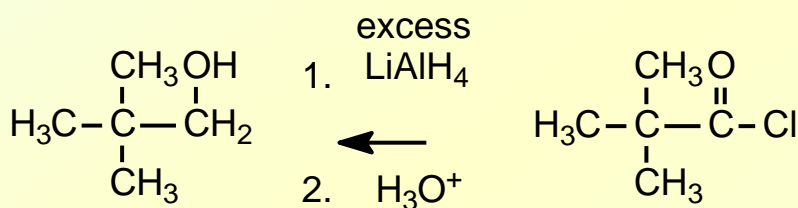


or



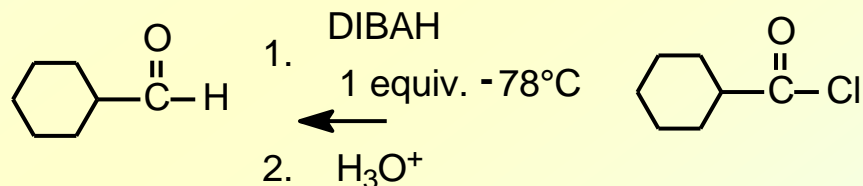
l: 1-phenyl-1-propanone

c: ethyl phenyl ketone



l: 2,2-dimethylpropanoyl chloride

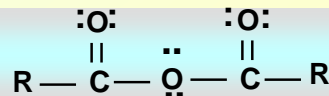
l: 2,2-dimethyl-1-propanol



l: cyclohexanecarbonyl chloride

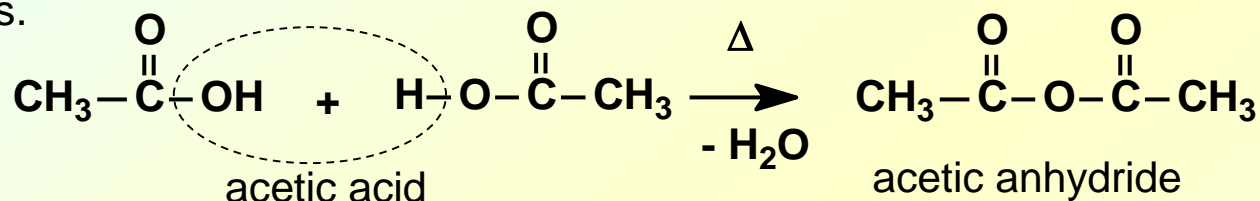
l: cyclohexanecarbaldehyde

Preparations of Acid Anhydrides

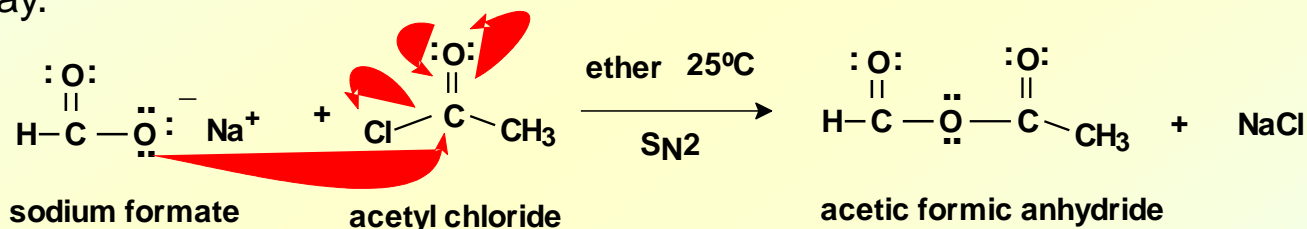


Preparation of Acid Anhydrides:

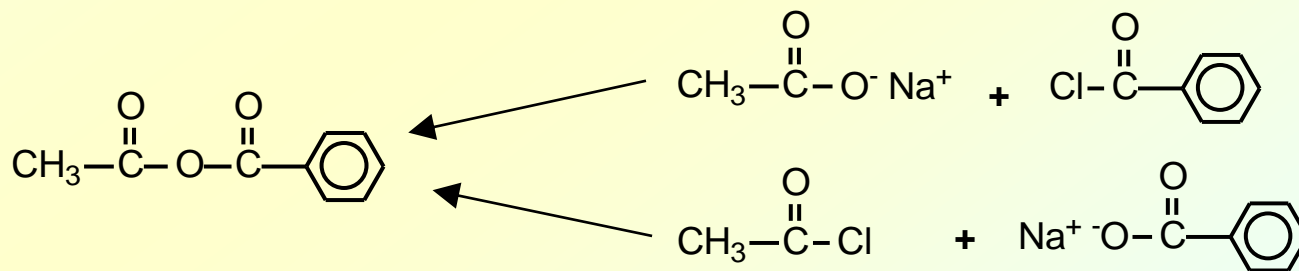
Dehydration of carboxylic acids as previously discussed is difficult and therefore limited to a few cases.



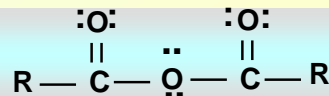
A more versatile method is by nucleophilic acyl substitution of an acid chloride with a carboxylate anion. Both symmetrical and unsymmetrical anhydrides can be prepared this way.



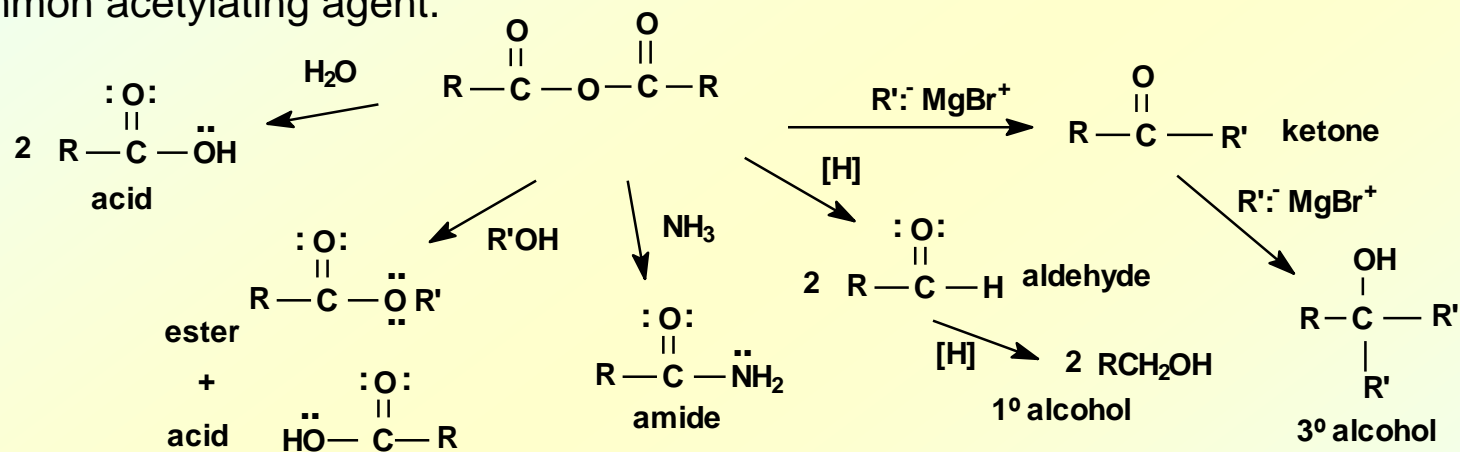
- Draw all sets of reactants that will produce the anhydride shown with an acid chloride.



Reactions of Acid Anhydrides



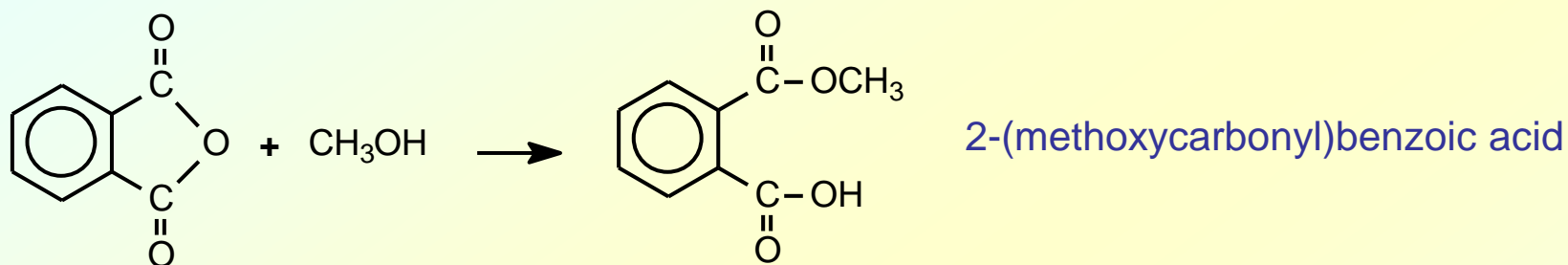
The chemistry of acid anhydrides is similar to that of acid chlorides except that anhydrides react more slowly. **Acid anhydrides** react with **HOH** to form **acids**, with **ROH** to form **esters**, with **amines** to form **amides**, with **LiAlH₄** to form **1° alcohols** and with **Grignards** to form **3° alcohols**. Note that ½ of the anhydride is wasted so that acid chlorides are more often used to acylate compounds. Acetic anhydride is one exception in that it is a very common acetylating agent.



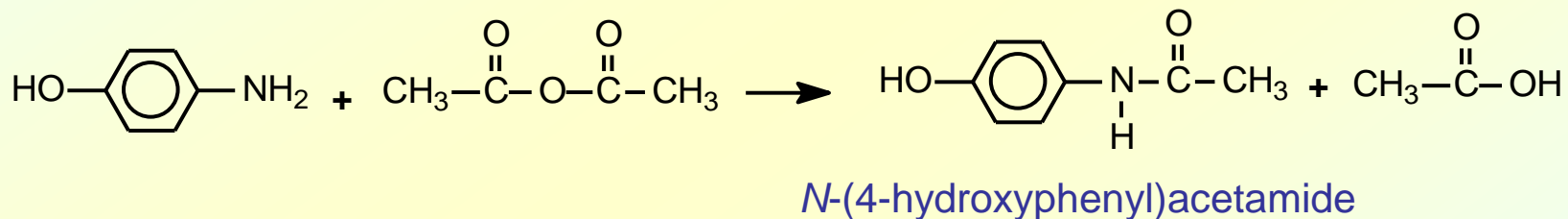
Practice Questions for Acid Anhydrides



- Show the product of methanol reacting with phthalic anhydride



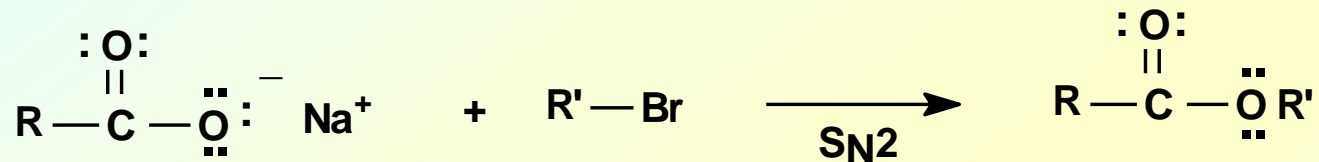
- Draw acetaminophen; formed when p-hydroxyaniline reacts with acetic anhydride



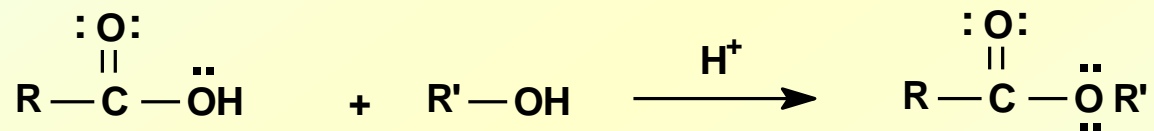
Preparation of Esters



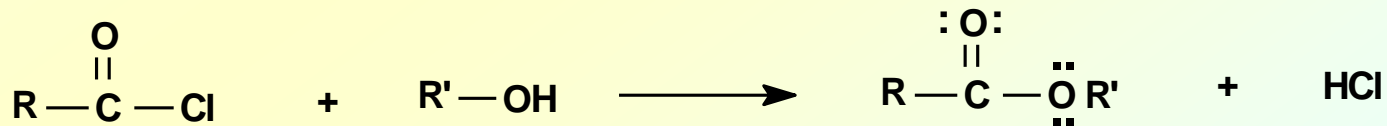
1. S_N2 reaction of a carboxylate anion with a methyl or 1° alkyl halide



2. Fischer esterification of a carboxylic acid + alcohol + acid catalyst



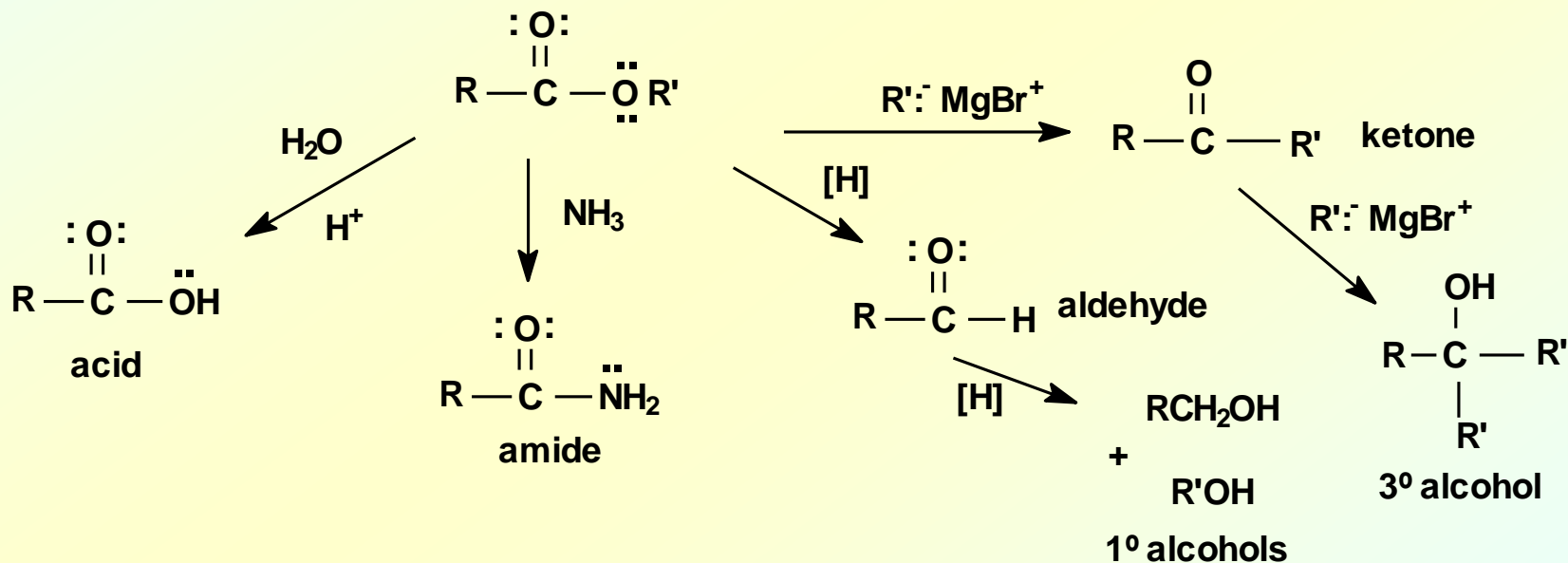
3. Acid chlorides react with alcohols in basic media



Reactions of Esters



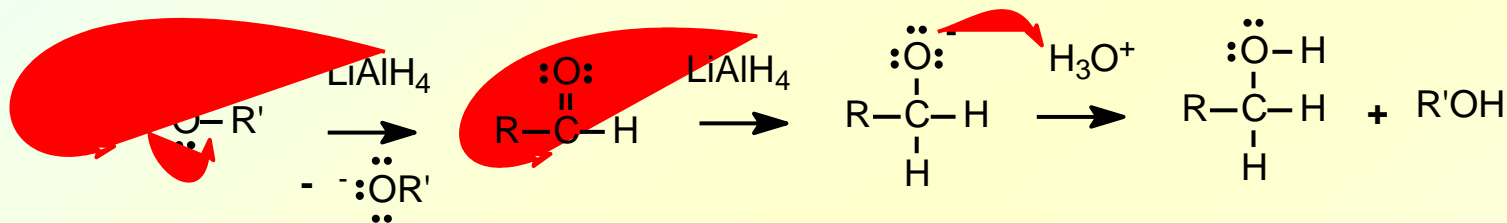
- Esters react like acid halides and anhydrides but are **less reactive toward nucleophiles** because the carbonyl C is less electrophilic. Esters are hydrolyzed by **HOH** to **carboxylic acids**, react with **amines** to **amides**, are **reduced by hydrides** to **aldehydes**, then to **1° alcohols**, and react with **Grignards** to **3° alcohols**.



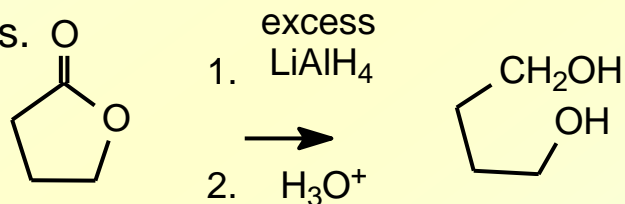
Hydride Reduction of Esters



- Esters are easily **reduced with LiAlH_4** to yield **1° alcohols**. The mechanism is similar to that of acid chloride reduction. A **hydride ion first adds** to the carbonyl carbon temporarily forming a tetrahedral alkoxide intermediate. Loss of the $-\text{OR}$ group reforms the carbonyl creating an **aldehyde** and an OR^- ion. **Further addition of H^- to aldehyde** gives the **1° alcohol**. Draw the mechanism and show all products.



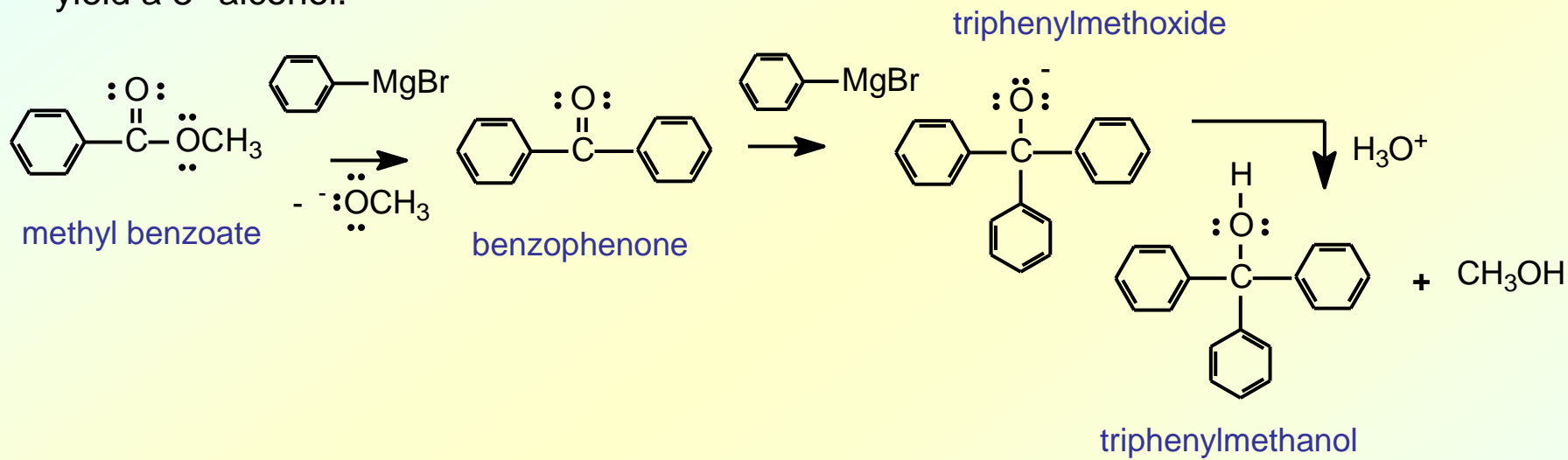
- Draw and name the products.



Grignard Reduction of Esters



- Esters react with **2 equivalents of Grignard reagent** to yield **3° alcohols** in which the 2 substituents are identical. The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard to yield a 3° alcohol.

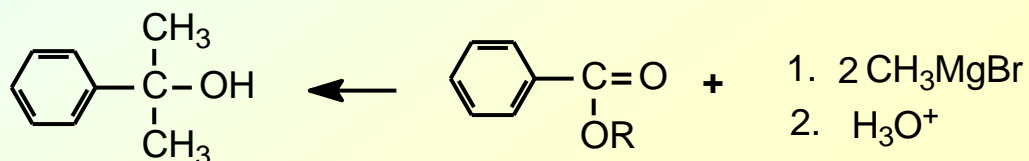


Practice with Esters

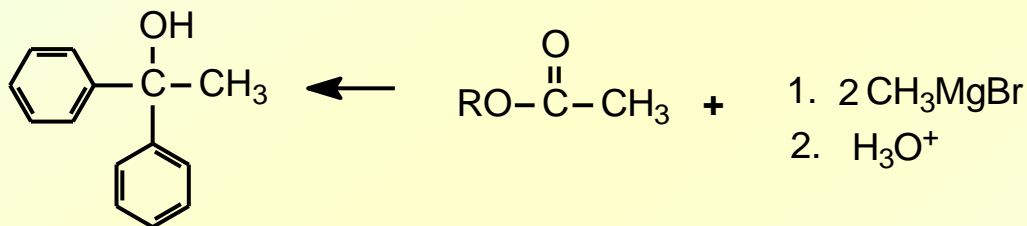


- What ester and Grignards will combine to produce the following

2-phenyl-2-propanol



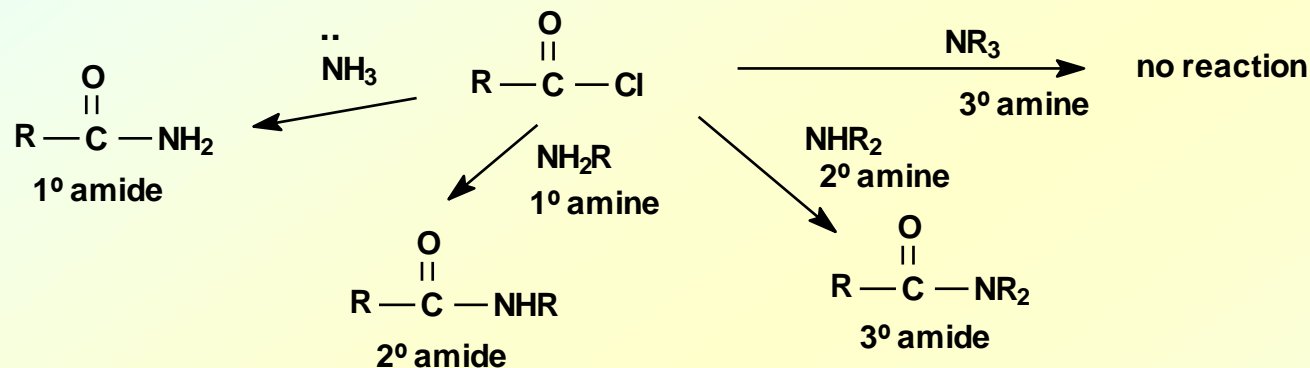
1,1-diphenylethanol



Chemistry of Amides



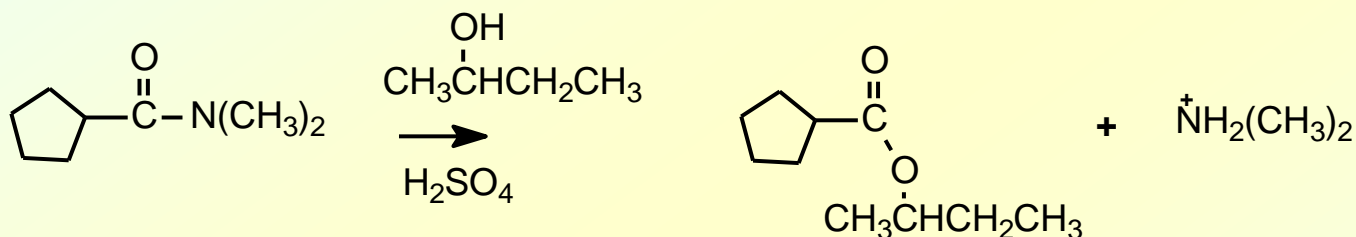
- Amides are usually prepared by reaction of an acid chloride with an amine. Ammonia, monosubstituted and disubstituted amines (but not trisubstituted amines) all react.



Alcoholysis of Amides (to Esters)



- Alcoholysis of amides occurs by the same acid catalyzed mechanism as acid hydrolysis except that the amido group of the amide is replaced with by an alcohol rather than water. Dry acid, e.g., HCl(g) or H₂SO₄ must be used otherwise water would compete with the alcohol as the nucleophile producing some carboxylic acid product in place of an ester.
- The reaction will require a long reflux period because amides are weak electrophiles and alcohols are weak nucleophiles.



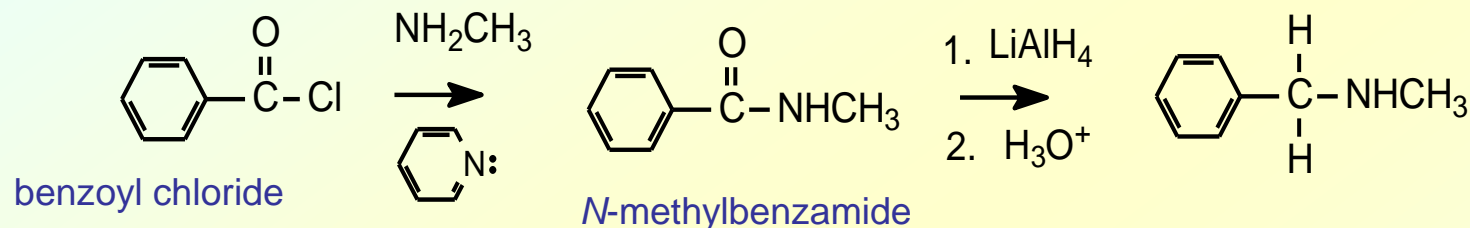
N,N-dimethylcyclopentanecarboxamide

sec-butyl cyclopentanecarboxylate

Hydride Reduction of Amides

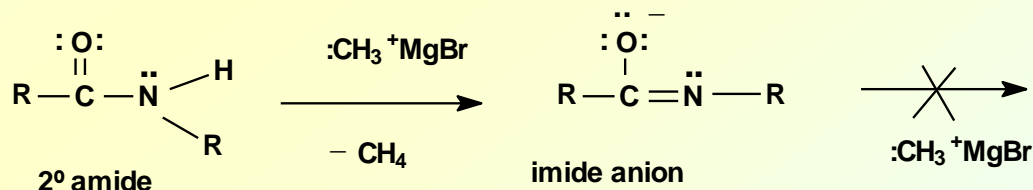


- Amides are reduced by LiAlH_4 . The product is an amine rather than an alcohol. The amide carbonyl group is converted to a methylene group ($-\text{C}=\text{O} \rightarrow -\text{CH}_2$). This is unusual.

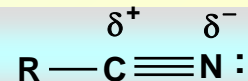


Grignard Reduction of Amides

- Grignards deprotonate 1° and 2° amides and are not reactive enough to add to the imide ion product. N-H protons are acidic enough ($\text{pK}_a = 17$) to be abstracted by Grignards.



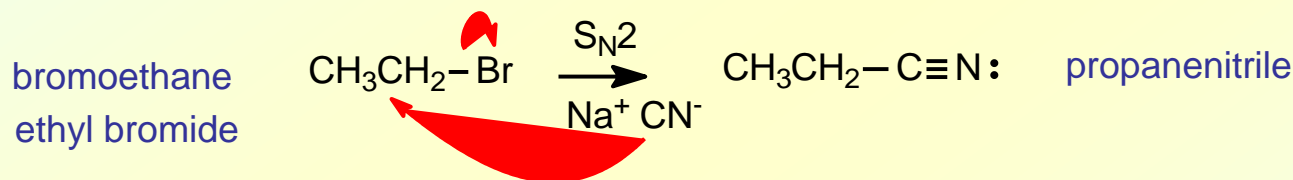
Chemistry of Nitriles



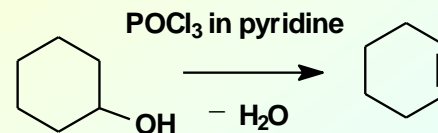
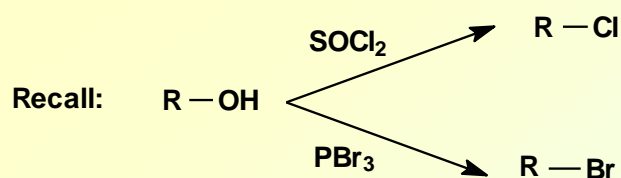
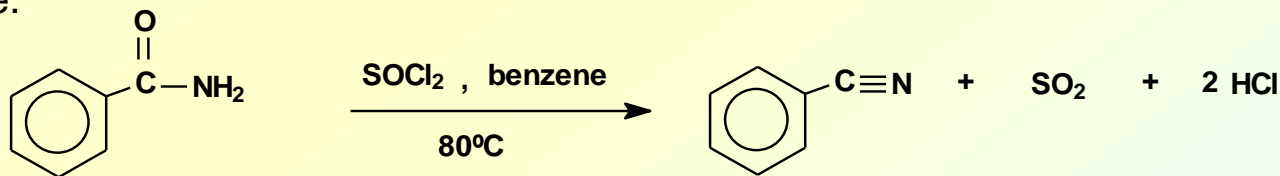
- The carbon atom in the nitrile group is electrophilic because it is bonded to an electronegative N atom and a π bond in the nitrile is easily broken, i.e., as if it were providing a leaving group.

Preparation of Nitrile:

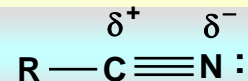
- Nitriles are easily prepared by S_N2 reaction of cyanide ion (CN^-) with methyl halides or a 1° alkyl halide. 2° alkyl halides also work but some E2 product also forms. 3° alkyl halides will result in mostly an alkene (E2) product instead of a nitrile. (pK_b of $\text{CN}^- = 4.7$)



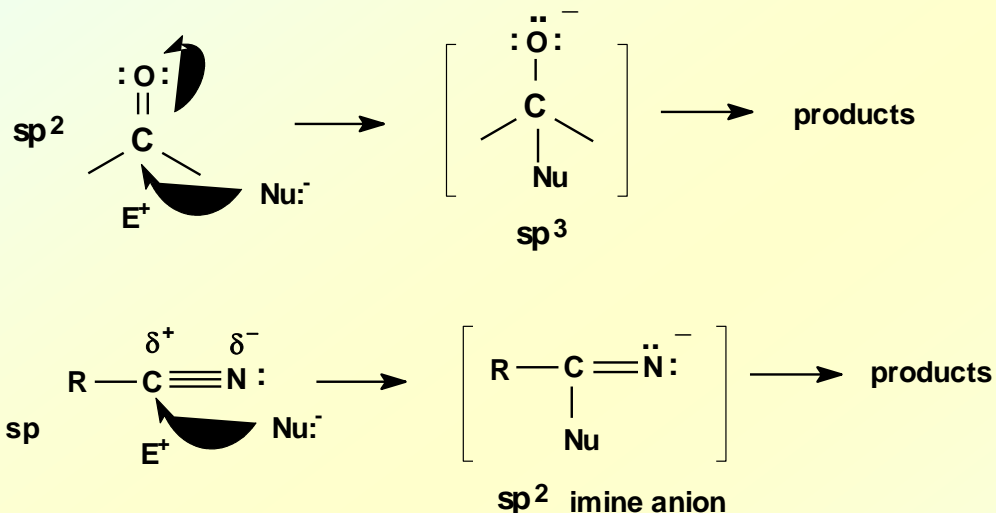
- Another method of preparing nitriles is by dehydration of a 1° amide using any suitable dehydrating agent such as SOCl_2 , POCl_3 , P_2O_5 , or acetic anhydride. Initially, SOCl_2 reacts with the amide oxygen atom and elimination follows. This method is not limited by steric hindrance.



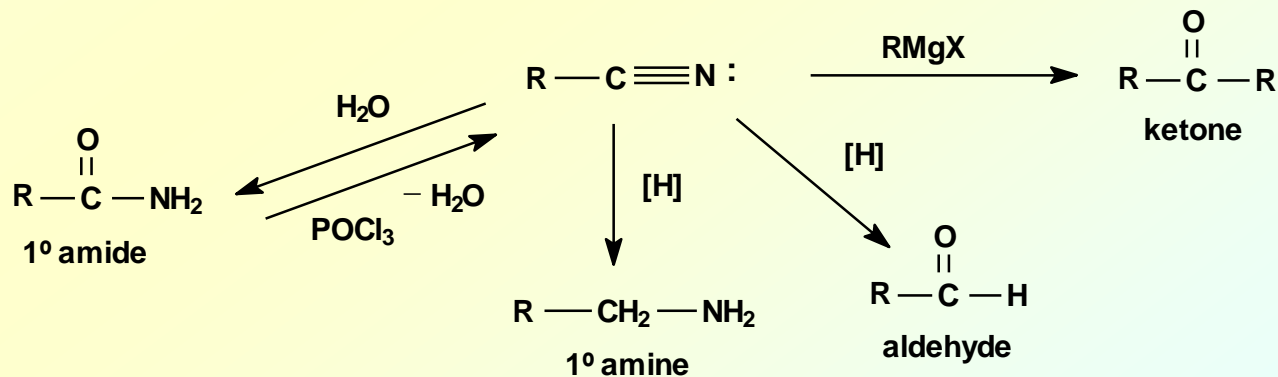
Reactions of Nitriles



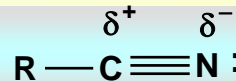
- Like carbonyl groups, the nitrile group is strongly polarized and the nitrile C is electrophilic. Nucleophiles thus attack yielding an sp² hybridized imine anion.



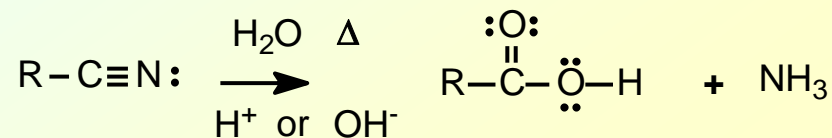
- Nitriles are hydrolyzed by HOH to amides and subsequently to carboxylic acids, reduced by hydrides to amines or aldehydes, and by Grignards to ketones.



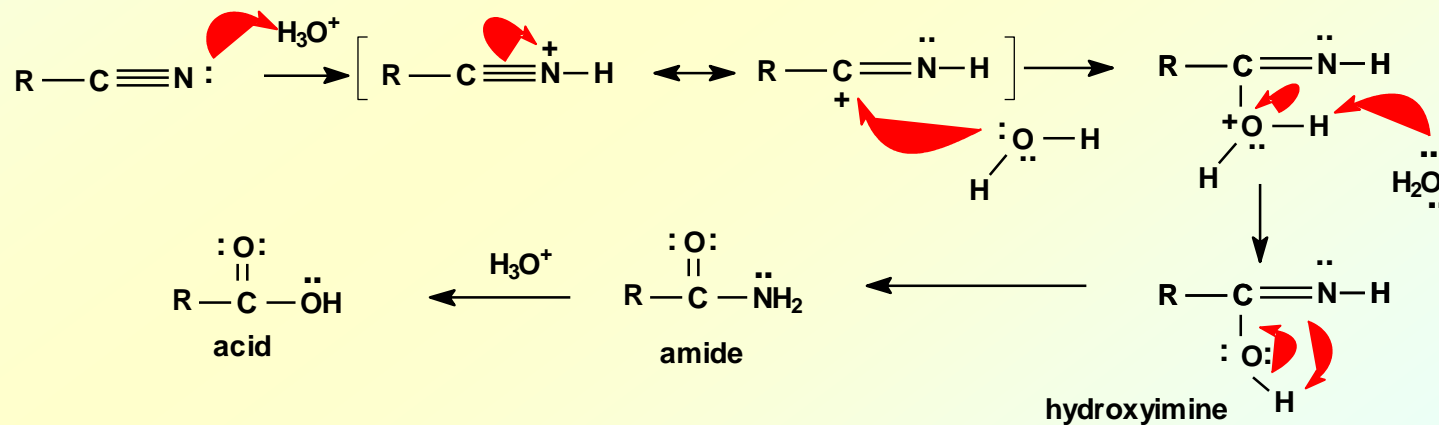
Hydrolysis of Nitriles into Carboxylic Acids



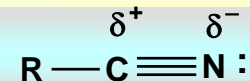
- Nitriles are hydrolyzed in either acidic or basic aqueous solution to yield carboxylic acids plus ammonia or an amine.



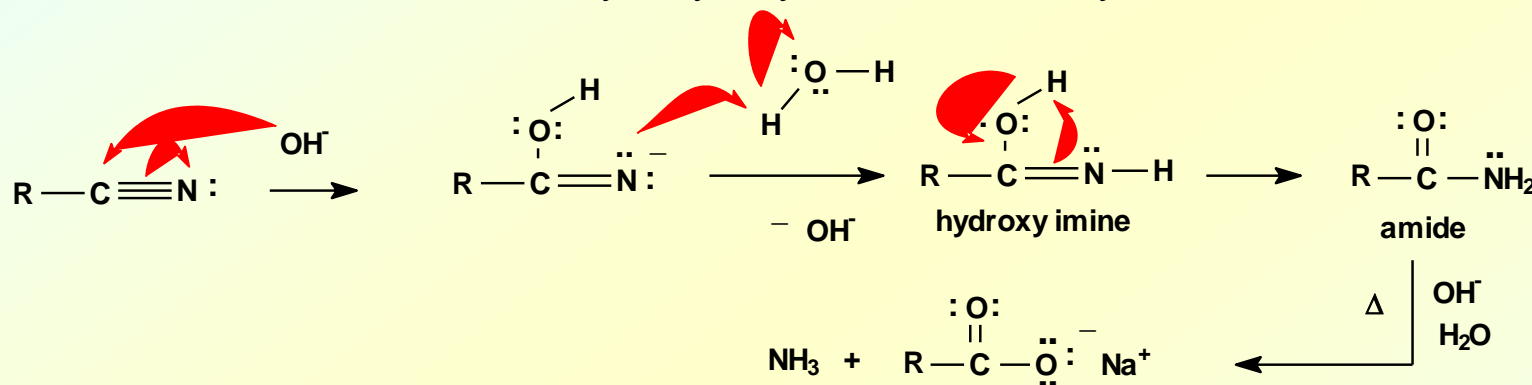
- In acid media, protonation of N produces a cation that reacts with water to give an imidic acid (an enol of an amide). Keto-enol isomerization of the imidic acid gives an amide. The amide is then hydrolyzed to a carboxylic acid and ammonium ion. It is possible to stop the reaction at the amide stage by using only 1 mole of HOH per mole of nitrile. Excess HOH forces carboxylic acid formation.



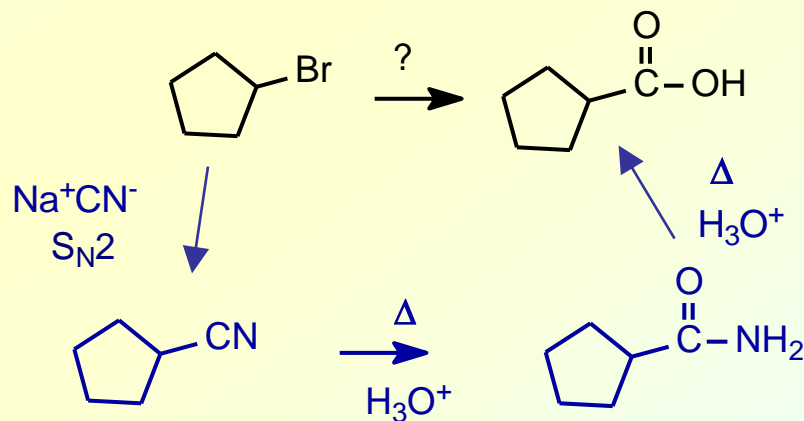
Hydrolysis of Nitriles into Carboxylate Salts



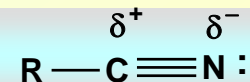
- In basic media, hydrolysis of a nitrile to a carboxylic acid is driven to completion by the reaction of the carboxylic acid with base. The mechanism involves nucleophilic attack by hydroxide ion on the electrophilic C producing a hydroxy imine, which rapidly isomerizes to an amide. Further hydrolysis yields the carboxylate salt.



- Show how the following transformation can be carried out without using a Grignard.



Reduction of Nitriles

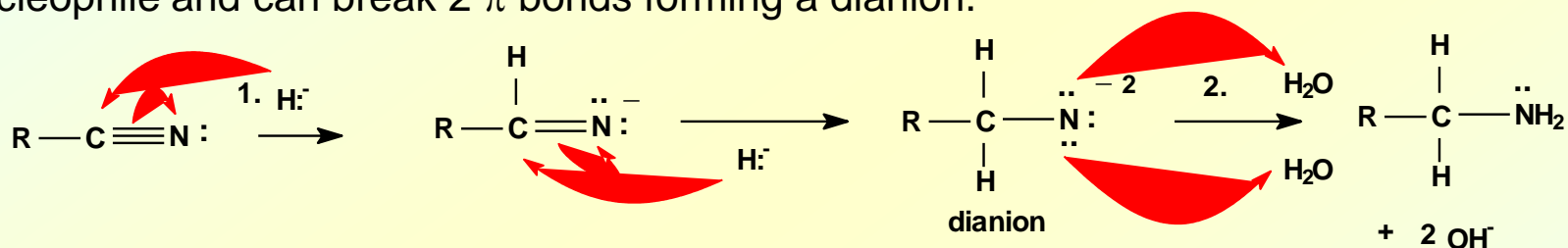


Alcoholysis of Nitriles doesn't work. Alcohols are weak nucleophiles and nitriles are weak electrophiles

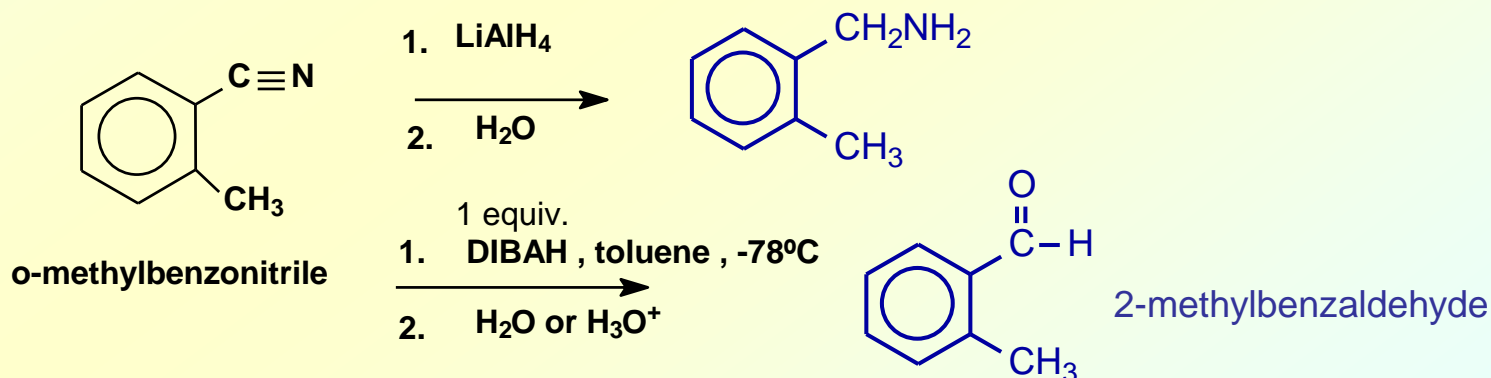
Aminolysis of Nitriles doesn't work. Amines are weak nucleophiles and nitriles are weak electrophiles.

Reduction with Hydrides:

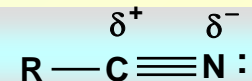
Reduction of nitriles with 2 equivalents of LiAlH_4 gives 1° amines. LiAlH_4 is a very good nucleophile and can break 2 π bonds forming a dianion.



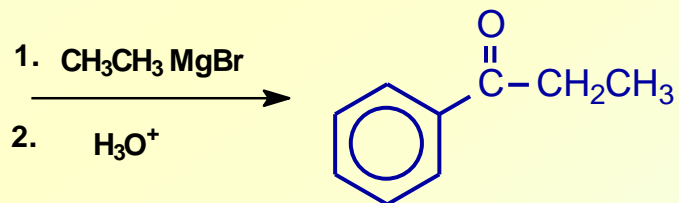
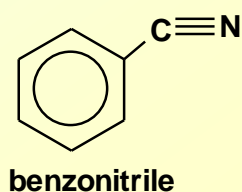
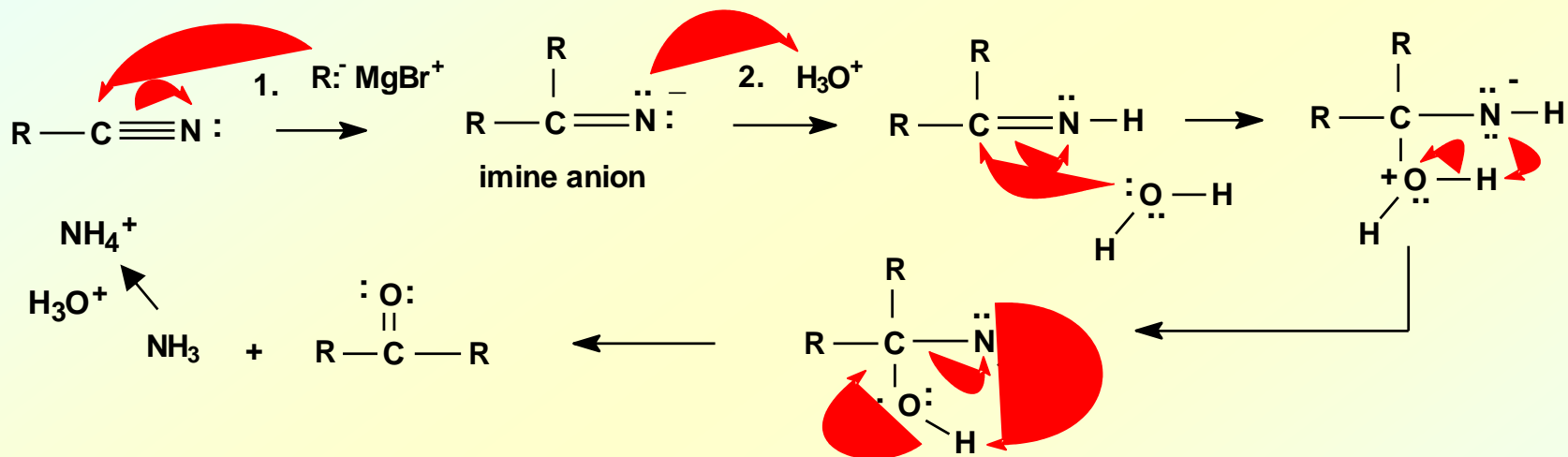
- If less powerful DIBALH is used, only 1 equivalent of hydride can add. Subsequent addition of HOH yields the aldehyde.



Reduction of Nitriles with Grignards



- Grignards add to nitriles giving intermediate imine anions which when hydrolyzed yield ketones. The mechanism is similar to hydride reduction except that the attacking nucleophile is a carbanion (R^-). Grignards are not as strongly nucleophilic as LiAlH_4 and so can only add once – a dianion is not formed.



1-phenyl-1-propanone
ethyl phenyl ketone