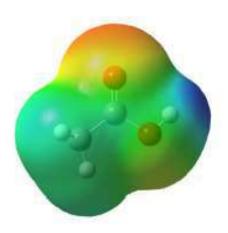
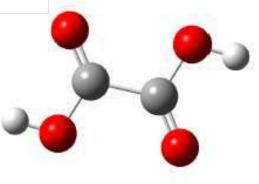


# Chapter 10: Carboxylic Acids and Their Derivatives

Done by: Khalid Awadallah





## Carboxylic acids

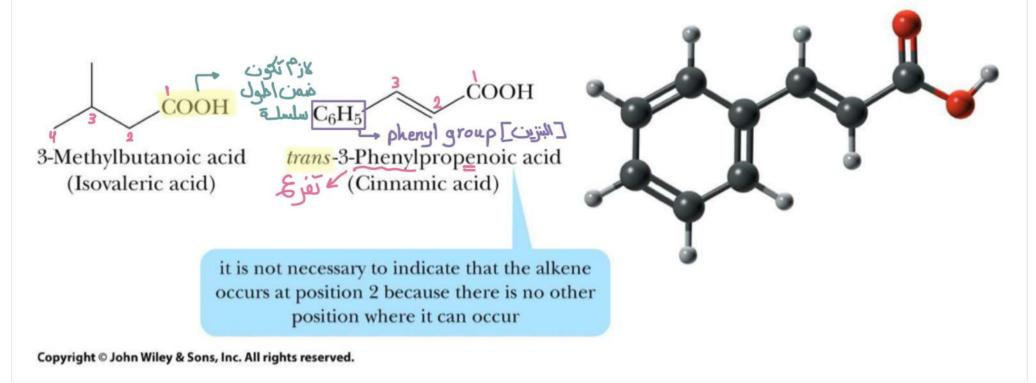
They contain a carboxyl group : COOH – C– OH

The carboxyl group must be terminal on the chain

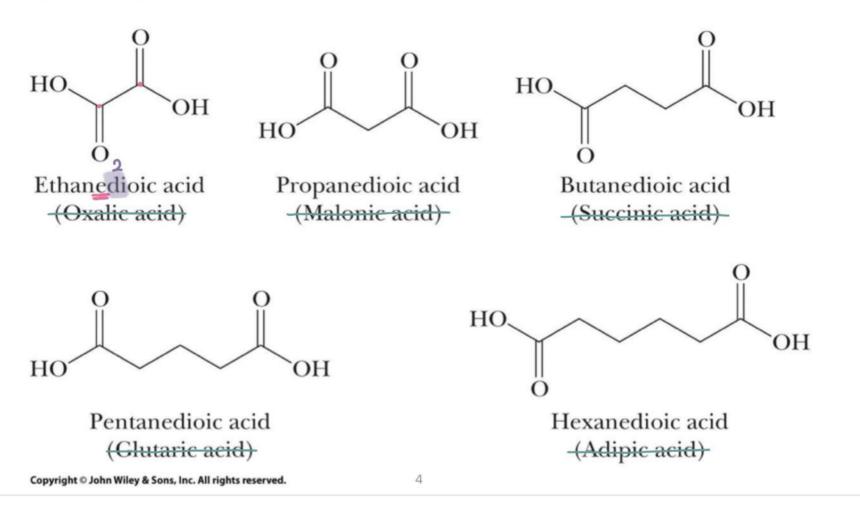
بنسبد <u>ام بمجموعات أخرى م</u> Acid derivatives : 1)Amides (NH2) 2)Esters (OR) 3)Acyl halides (X) 4)Anhydrides (COOR) بالنسبة للمشتقات من الحموض الكربوكسيلية عندي 4 انواع: تلخيص السلايد انو عنا عشان نحكى انو هاد 1)الامينات المركب حمض كربوكسيلي لازم يتوافر 2) الاستر شغلتين 3) الاسيل لازم يكون عندي مجموعة كربوكسيل 4) الانهايدر إيد ٤) لازم تكون مجموعة الكربوكسيل طرفية كيف بنحصل عليهم ؟ بنبدل ال OH بالمجمو عات المكتوبة فوق

هون الفكرة اني بدل ع وجود الكربوكسيل في المركب في التسمية اني بحكي oic acid بنهاية الاسم طبعا اذا كان الchain عبارة عن الكين او يحتوي على رابطة ثنائية بين ذرتى كريون بنسميه الكين بعدين بتطبق قاعدة ال ioc acid

- IUPAC names: drop the -e from the parent alkane and add the suffix -oic acid, Alkanoic acid
  - If the compound contains a carbon-carbon double bond, change the infix -an- to -en-.

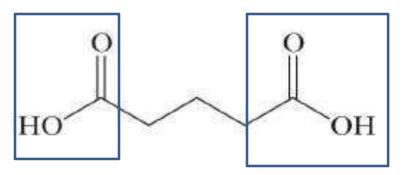


- Dicarboxylic acids: add -dioic acid to the name of the parent alkane containing both carboxyl groups.
- There is no need to use numbers to locate the carboxyl groups; they can only be on the ends of the chain.



هون بحكيلي كيف بنسمي لما يكون عندي مجموعة كربوكسيل عكل طرف ببساطة بخليها dioic acid وبخلي ال e-تبعت الالكان

We might have a carboxyl group at each end so the way to name them is -dioic acid



Note that in the dioic acid example the –e from the alkane nomenclature remained and this only happens in dioic examples

This is a : Pentanedioic acid

Note that a ring structure is different than an aromatic structure

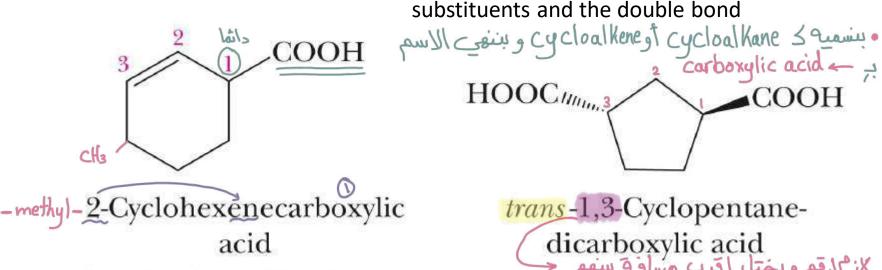
carboxylic acid

#### If the carboxyl group is bonded to a ring, name the ring compound and then add the suffix

Note that we use # to locate the

HOOC

-carboxylic acid



Note that the first C atom is NOT the one forming the carboxyl group as we treat the carboxyl group as a substituent (only in ring structures)

trans-1,3-Cyclopentanedicarboxylic acid لازمارقم وبختاراقرب مسافة بسهم ح Note that u can have more than 2 carboxyl groups in ring structures while u can NOT have more than 2 in chain structures

عنا هون اول اشي لازم نراعيه بالتسمية هو ال parent وهاد الجدول بوضحلنا مين الى اله الاولوية

	TABLE 12	TABLE 12.1 Increasing Order of Precedence of Six Functional Groups			
	Functional Group	Suffix	Prefix	Example of When the Functional Group Has Lower Priority	
Highest priority	Carboxyl	-oic acid	1 <del></del>		
Q	Aldehyde	-al	oxo-	<u>3-Oxo</u> propanoic acid	H 3 2 COOH
3	Ketone	-one	охо-	3-Oxobutanal	
(J	Alcohol	-ol	hydroxy-	4-Hydroxy-2-butanone	HO 4 3 2 1 O
E	Amino	-amine	amino-	2-Amino-1-propanol	3 2 1 OH
Lowest priority	Sulfhydryl	-thiol	mercapto-	2-Mercaptoethanol	HS 2 1 OH

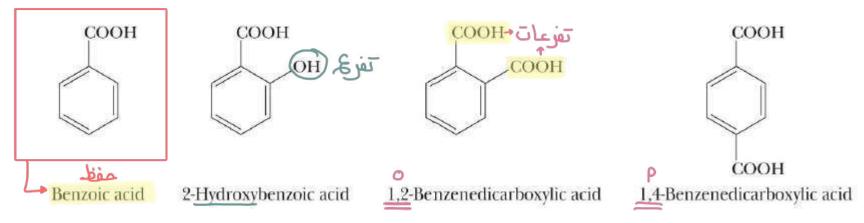
مثلا عندي كربوكسيل و كحول ف بعطي الاولوية للكربوكسيل لانه دائما هو الاعلى من حيث الاولوية ف بصفي ك تسمية في المثال السابق : hydroxy carboxylic acid الفكرة انو اذا لقيت مركب يحتوي على مجموعتين وظيفيات ف بعطي الاولوية لل parentيكون اللي اعلى في الجدول

هون معطيك كيف تسمي المركبات الاروماتية الي بتختلف عن الحلقات زي ما حكينا بالسلايد القبل وكيف انو ال benzoic acid هو ابسطها

Benzoic acid is the simplest aromatic carboxylic acid

We use # to locate the substituents or we may use the o,m,p nomenclature, بقراستخدمهم هون

We don't use # only if we have 1 substituent and that's when there is only 1 carboxyl group



## Physical properties of Acids

They are acidic => pKa = 5

They are more acidic than alcohols

②The form strong H-bonds especially with each dimer  $R \xrightarrow{0} H-bonds H-0$   $R \xrightarrow{R} R$  0-H H-bonds 0  $R \xrightarrow{0-H} H-bonds 0$ Alcohols

other

They have high BP,MP=> higher than eq. MW alcohols

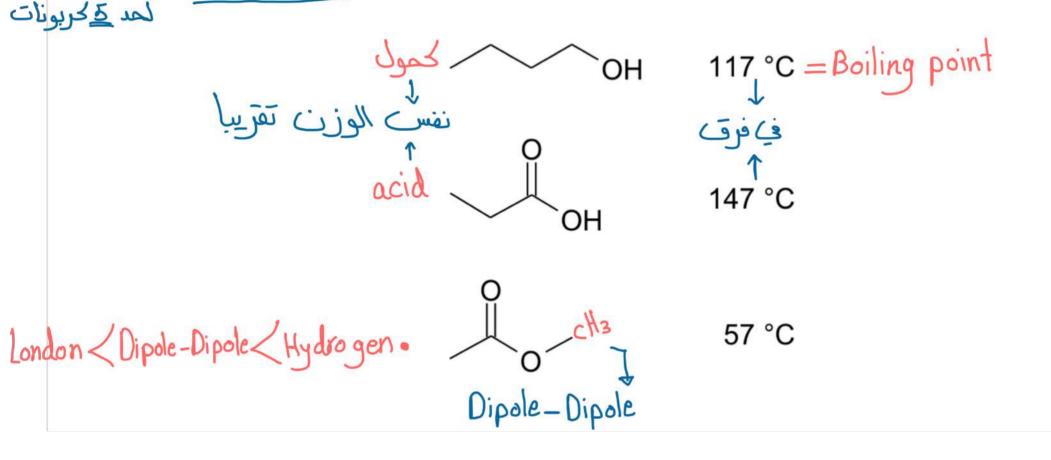
They are very soluble in polar protic solvents

هون الفكرة انو بحكيلك عن خصائص الحموض الكربوكسيلية الفزيائية : انو هي 1) اكثر حمضية لانها اكثر استقرارا ( الشرح بالسلايد الجاي ) 2) وبتعمل روابط هيدروجينية تابعة لل 3 IMF) وعندها درجة غليان وانصبهار اعلى من الكحول اللي عندها نفس الكتلة الذرية 4) وانها قوية الذوبان في المحاليل ال polar proticزي الكحول والماء

# **Physical Properties of Acids**

#### This produces:

- 1. High BP & MP, higher than equivalent weight alcohols
- 4 -2. Very soluble in polar protic solvents like water or alcohols



# Physical properties of Acids

هون بغض النظر عن تفاعل تكوين الكوكسايد بس لما نيجي نشوف هون بنلاقي انو فش عندي resonance حيث انو عندي شحنة مثبتة في مكانها (localized) وال resonance مقترنة بال stability برضو ال stability علاقتها طردية مع ال acidity

يمكن عجقتكم 😳

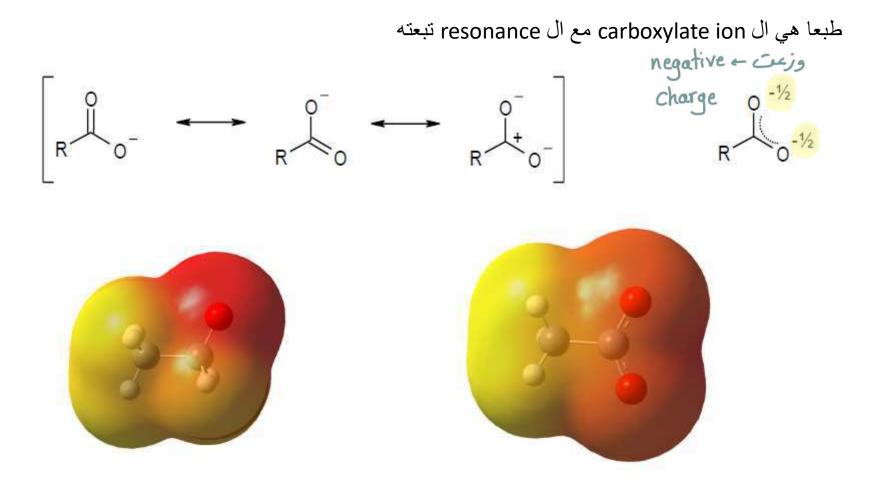
الحموضة

الملخص انو لما يكون

عندي resonance بتزيد

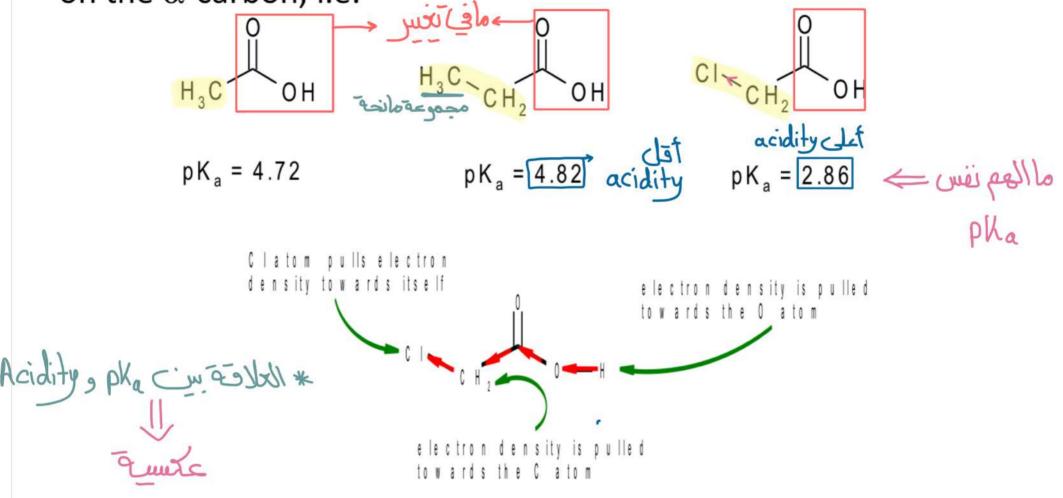
$$R - O + H - H^{+} R - O = R^{+} R^{+} R^{+} R^{-} Q^{+} R^{+} R^$$

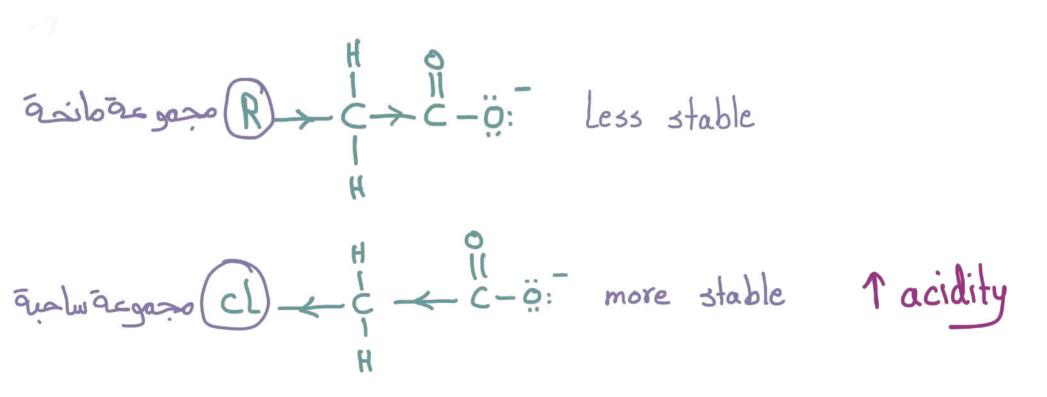
### Carboxylate ion



# **Physical Properties of Acids**

The pK<sub>a</sub> can also be affected by *inductive processes* from groups on the  $\alpha$ -carbon, i.e.

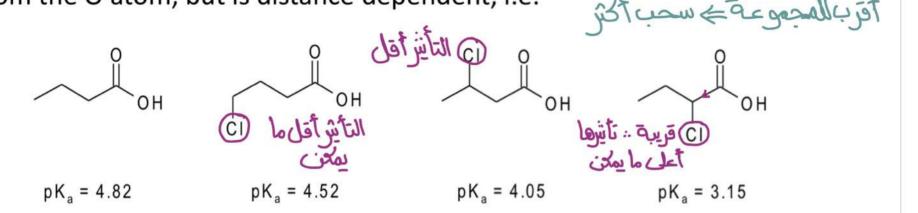




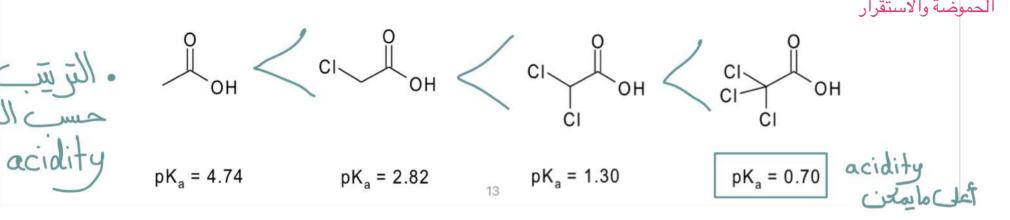
عطية السحب والإعلاء بتكون عن طريق > Inductive effect

# **Physical Properties of Acids**

This helps stabilize the conjugate base by shifting the charge density away from the O atom, but is distance dependent, i.e.



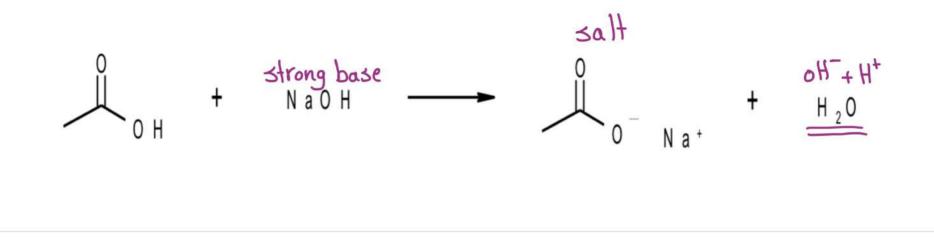
The effective is cumulative so the greater the number of electron هون تأثير عدد الذرات الي بتسحب الشحنة بعيدا عن ذرة الاكسجين الي عليها الشحنة عشان تزيد



# **Formation of Salts**

A salt is an ionic compound containing the conjugate base of an acid and a group I or II metal.

They are generated by treating an organic acid with NaOH or KOH, the OH<sup>-</sup> combines with the acidic proton in a neutralization reaction to form water. The conjugate base and metal ion form an ionic solid, i.e.



### Resonance + inductive effects

(1)

(2)



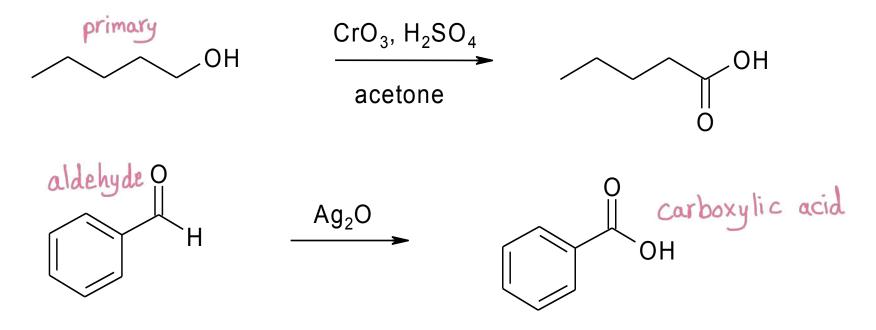
هون عندي اللهي مهم حكى عنه الدكتور اللي هو انو فيهم عنده حموضة اكثر ؟ هسا اول اللهي مجموعة الامين (NH2)بتعمل توجيه meta والكربوكسيل بتعمل توجيه ortho para واذا بتتذكروا ب شابتر 4 انو احنا ما بنحط المجموعات ع اساس الاولوية والاولوية هون للكربوكسيل ف الكربوكسيل زي ما قلنا بوجه ortho para ف الي بصير عندك في (1) انو وانا ما عندي direct بصير عندك بالاخر انو => (1) عندها بس inductive effect بصير عندك بالاخر انو => (1) عندها بس inductive effect (2) عندها الما زاد ال resonance وفرق هيك عندها ال inductive effect طبعا احنا قلنا كل ما زاد ال sonance وال inductive effect (2)

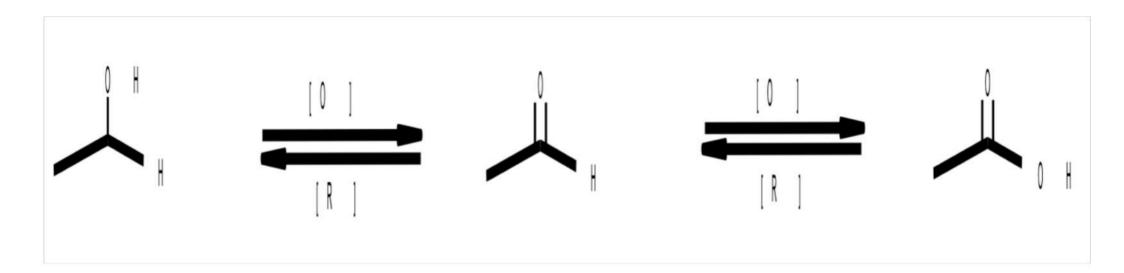
# **Preparation of Acids**

There are a number of ways to create carboxylic acids:

**1.** Oxidation of 1° alcohols or aldehydes:

Common reagents include;  $CrO_3$ ,  $H_2SO_4$  in acetone (Jones' reagent), KMnO<sub>4</sub>, HNO<sub>3</sub>, and for aldehydes Ag<sub>2</sub>O, i.e.

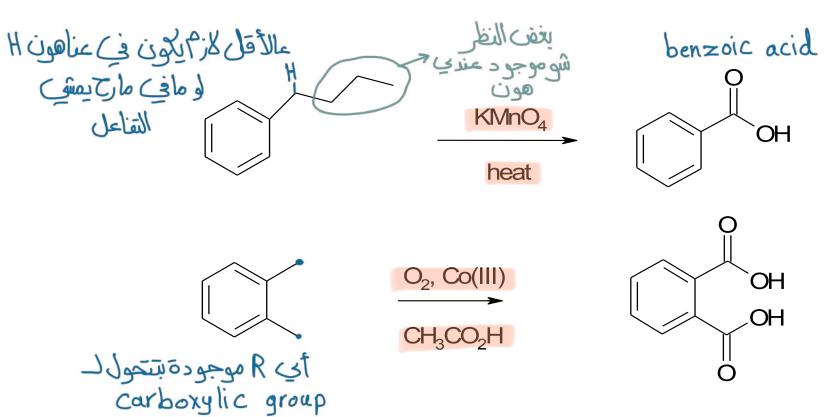




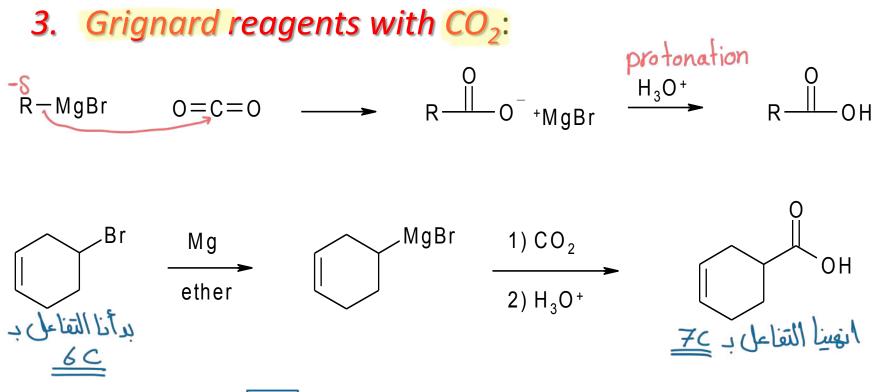
# **Preparation of Acids**

#### 2. Oxidation of aromatic alkyl side chains:

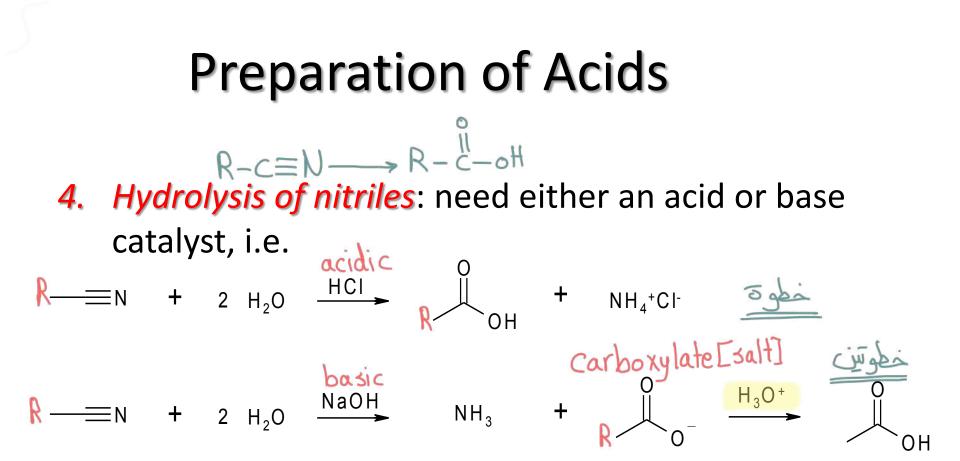
Common reagents include;  $KMnO_4$ , commercially:  $O_2$ , Co(III) in  $CH_3CO_2H$ , i.e.



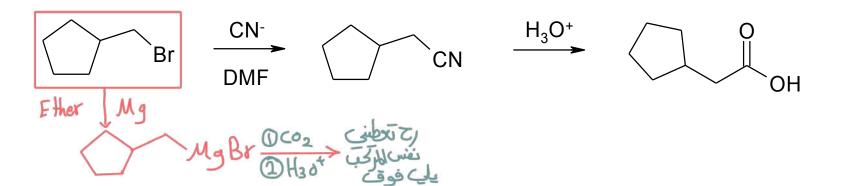
# **Preparation of Acids**



Note: the acid is one carbon atom longer than the Grignard reagent.

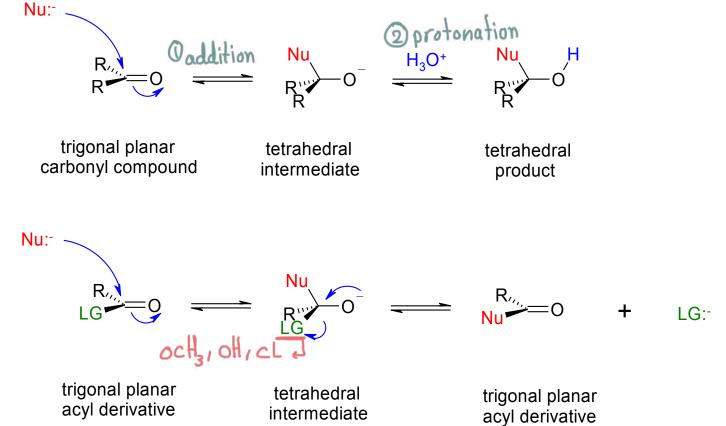


Note: the nitrile can be made from an alkyl halide, i.e.



# **Nucleophilic Acyl Substitution**

In contrast to aldehydes and ketones, which react by *nucleophilic* (acyl) *addition*, carboxylic acids (and derivatives) react by *nucleophilic acyl substitution*, i.e.



R-c-oH , Nu O addition

 $\begin{array}{c} \stackrel{:}{\scriptstyle 0} \stackrel{:}{\scriptstyle 0}$ 



ملخص تفاعلات تحضير الحمض

العوامل المساعدة	المتفاعلات	الطريقة	
Jones' reagent KMnO4 HNO3	Primary alcohol	Primary alcohol oxidation	
Ag2O	Primary aldehyde	Primary aldehyde oxidation	
KMnO4 with heat =1eq O2,Co(III) in CH3CO2H= 2eq	Aromatic alkyl side chain	Aromatic alkyl side chain oxidation	
H3O+ in step 2 to protonate carboxylate ion	Grignard+CO2	Grignard + CO2	
Either acidic or basic catalyst	<b>CN+2H2O</b>	Nitrile hydrolysis	

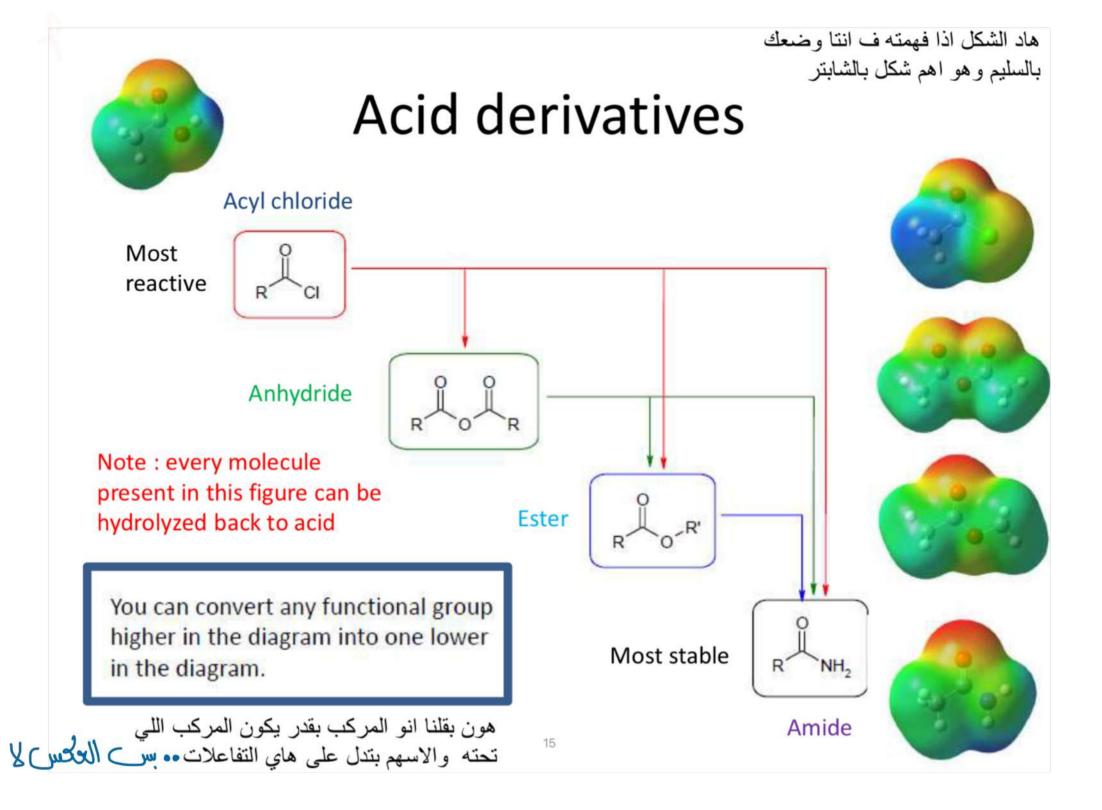
# **Acid Derivatives**

The -OH group of the acid has been replaced by another functional group.

All of the derivatives can be hydrolyzed back to the carboxylic acid.

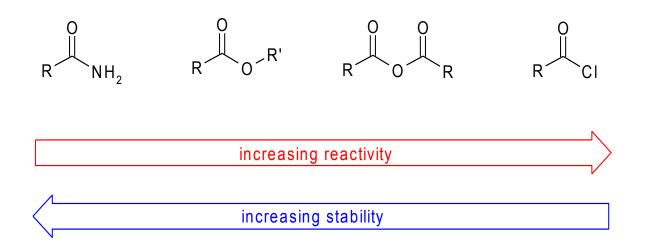
Types of derivatives:

- **1**. *Esters*: R-CO<sub>2</sub>-R'
- 2. Acyl halides: R-CO-Cl
- **3.** Anhydrides: R-CO<sub>2</sub>CO-R
- **4.** Amides: R-CO-NH<sub>2</sub>



# **Nucleophilic Acyl Substitution**

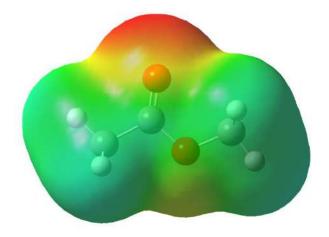
The reaction proceeds by a substitution since the acid / derivative has a leaving group in place of an H atom or alkyl group of the aldehyde or ketone, neither of which is a good leaving group. The relative reactivity of the derivatives depends on the leaving group ability, i.e.



### Esters

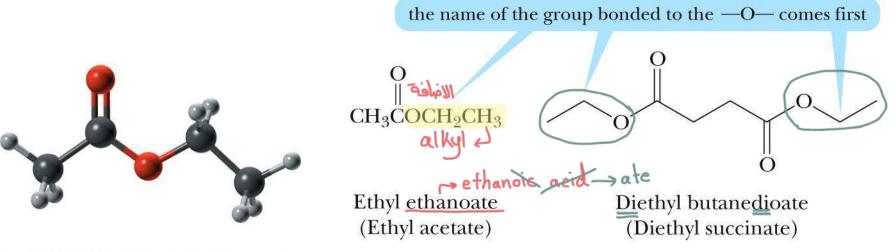
The –OH of an acid has been replaced by a –OR' from an alcohol.  $OH \xrightarrow{\text{II}} OR$ 

Very common compounds in nature and a wide variety are produced commercially.



### Esters

- The functional group of an ester is an acyl group bonded to -OR or -OAr.
  - Name the alkyl or aryl group bonded to oxygen followed by the name of the acid.
  - Change the suffix -ic acid to -ate.



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# **Preparation of Esters**

The most common method is a "Fisher esterification".

The general reaction is:

water.

$$R \xrightarrow{0} 0 H + R' \xrightarrow{-0} 0 H \xrightarrow{catalyst} R' \xrightarrow{-0} R' + H_2 0$$

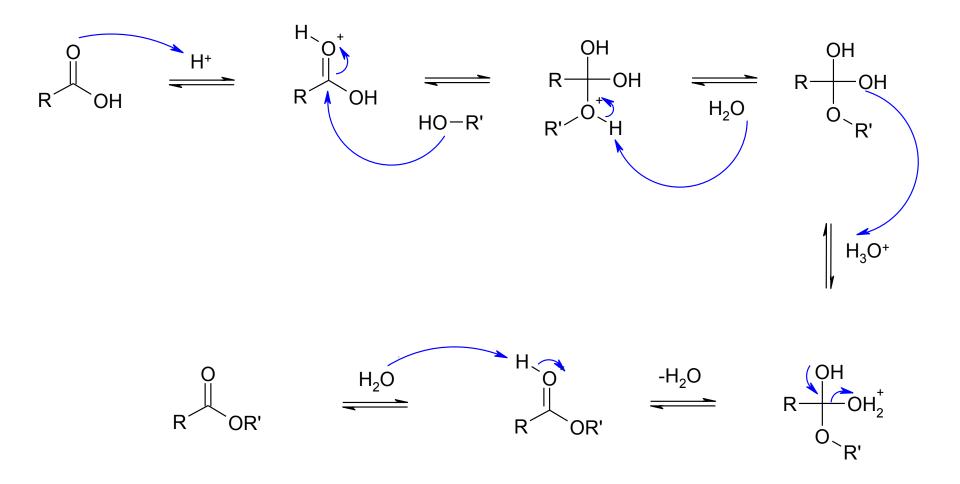
Note: you need an acid catalyst.

it is an equilibrium reaction, to drive it forward use excess alcohol or acid, or distill off the ester or

بماجة الفي الملع واحدمن products لحتى يوشي التقاعل باتجاه واحد

### **Preparation of Esters**

The mechanism:



# **Preparation of Esters**

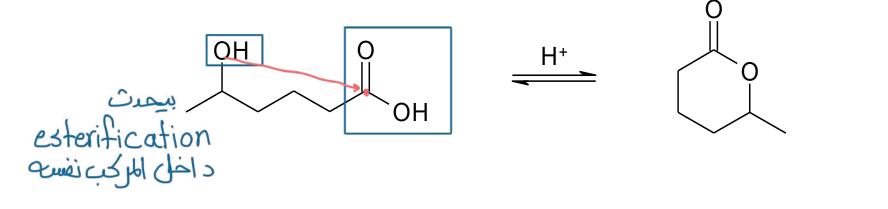
#### Note:

- i. Every step is reversible so the entire reaction is reversible
- ii. The –OR' comes from the alcohol, i.e. it is a nucleophilic attack by the alcohol O atom on the carboxylate C atom (this is confirmed by radioisotopic labeling).
- iii. Substitution occurs rather than addition as we generate a very good leaving group, a water molecule.

Lactones \_\_\_\_\_ cyclic esters

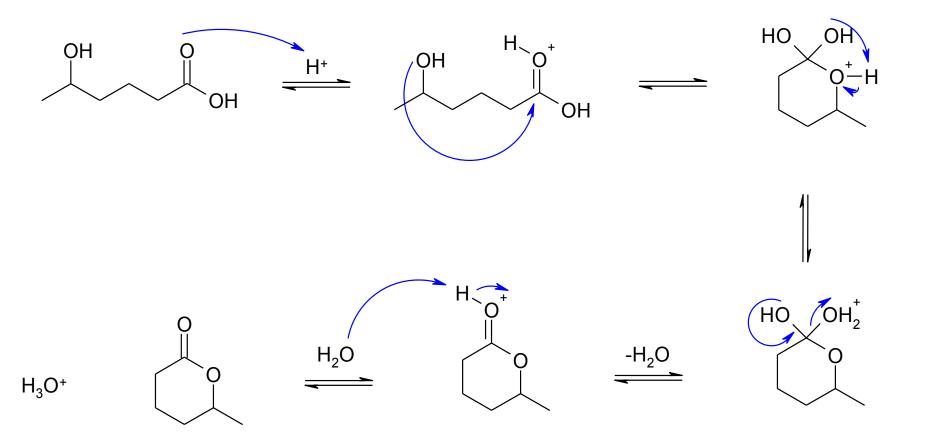
**Lactones** are cyclic esters made from  $\gamma$  or  $\delta$  hydroxy acids.

Common reaction produces a 5 or 6 membered ring which are stable, i.e.



### Lactones

Mechanism:

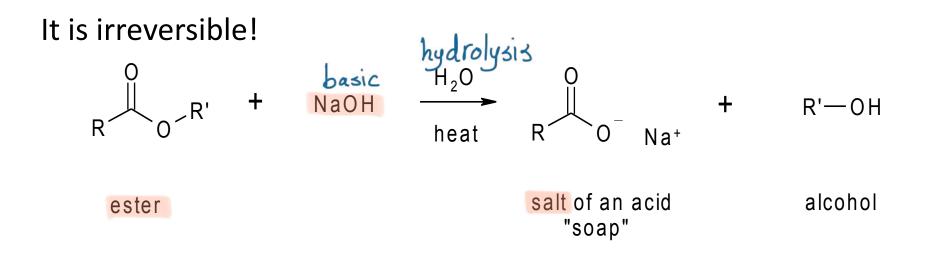


Saponification = base hydrolysis

Generally done on esters but acids work also.

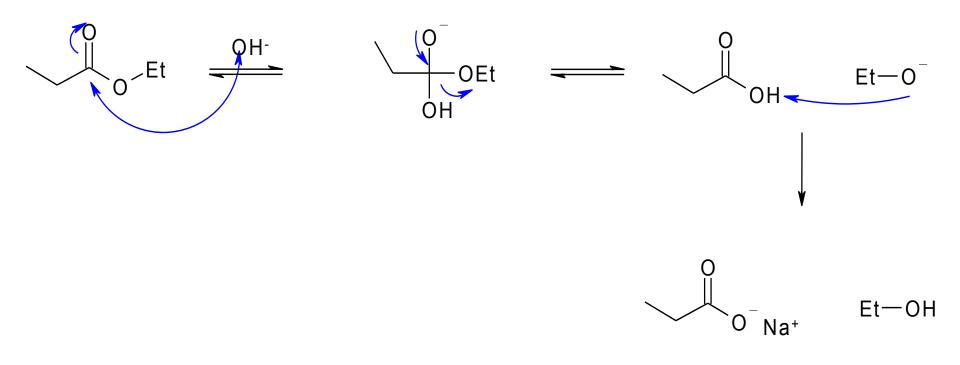
Used to make soap (or in structure determination to remove the alcohol group).

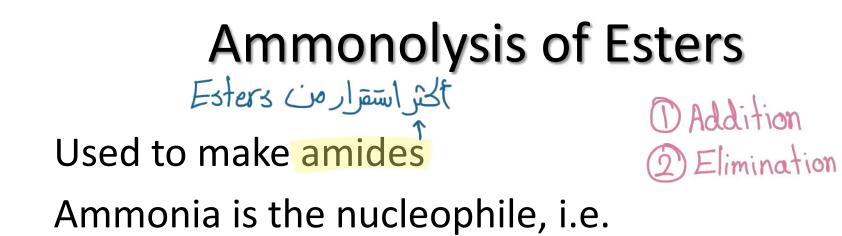
This is a base hydrolysis reaction

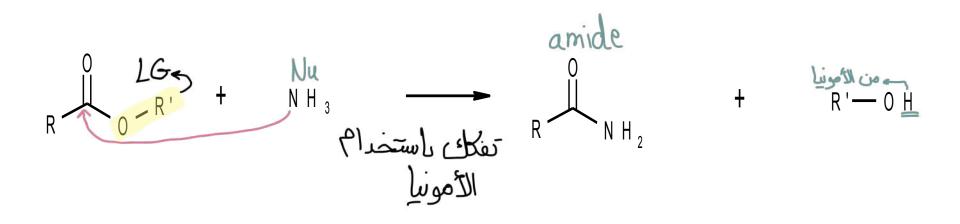


### Saponification

#### Mechanism:



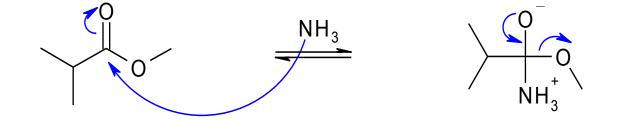


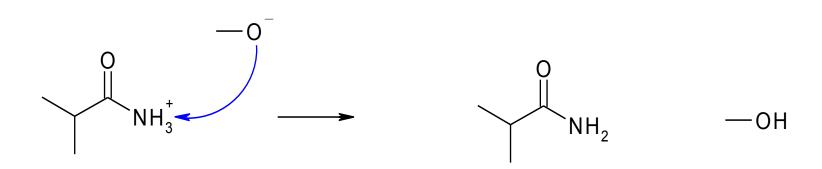


### **Ammonolysis of Esters**

ركزوا على ال general mechanism انو ال Nu بتضيف وبيطلع عندي LG

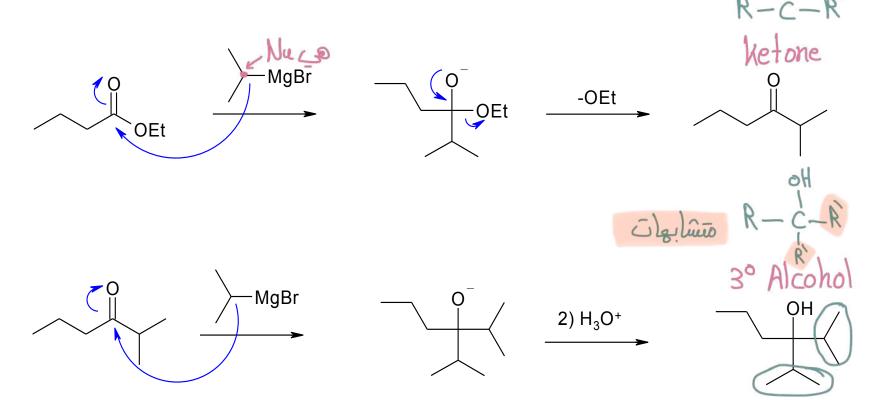
Mechanism:





#### تفاعل معمجدًا .. Ester Reactions with Grignard Reagents

Esters will react with <u>2</u> equivalents of a Grignard reagent to produce a 3° alcohol, i.e.



### **Ester Reactions with Grignard Reagents**

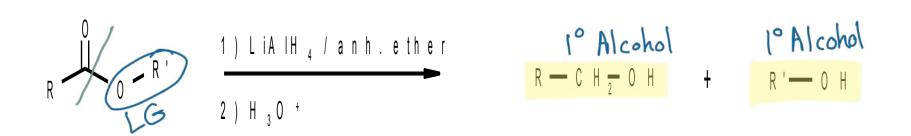
The second addition occurs since the ketone is still reactive to the Grignard reagent.

This is a good method to make 3° alcohol where two of the alkyl groups are the same.

### **Reduction of Esters**

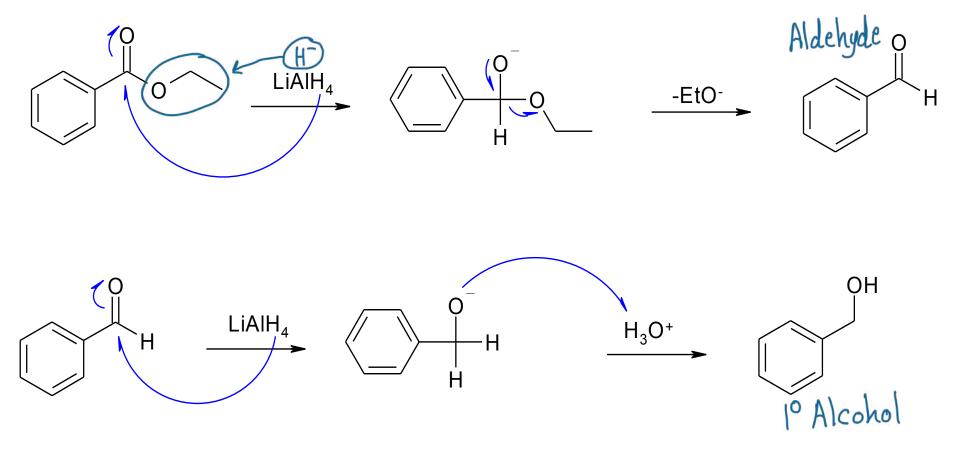
Product is a 1° alcohol.

Reagent: LiAlH<sub>4</sub> in anhydrous ether



### **Reduction of Esters**

#### Mechanism:



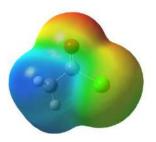
# **Reduction of Esters**

#### Note:

- You can not isolate the aldehyde as it is still reactive to the LiAlH<sub>4</sub>
- 2. LiAlH<sub>4</sub> does not reduce C=C so you can selectively reduce an acyl group without reducing a C=C  $\pi$  bond.
- ب- ما يستخدموا
  - NaBH<sub>4</sub> is not strong enough to reduce acids or acid derivatives, this allows for the selective reduction of aldehyde or ketone groups.

ملخص تفاعلات الاستر وتحضيره				
النواتج	العوامل المساعدة	المتفاعلات	الطريقة	
Ester + H2O	Acidic catalyst	Carboxylic + alcohol	Ester prep. Fisher esterification	
Cyclic ester	Acidic catalyst	Hydroxy carboxylic acid	Lactones prep.	
Soap (salt ) + Alcohol	Water + heat	Ester + NaOH	Saponification	
Amide + Alcohol	x	Ester + NH3	Ammonolysis	
Tertiary Alcohol	H3O+ To protonate 2 <sup>nd</sup> eq of Grignard	Ester + R-Mg-X	Ester + Grignard	
2eq of 2 different primary alcohol	LiAlH4 in anh.ether	Ester	Ester Reduction	

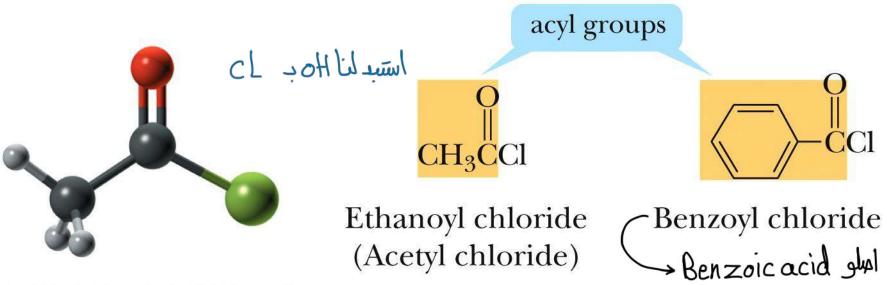
More reactive than acids or esters.



Man made compounds, they do not exist in nature.

### Acid Chlorides

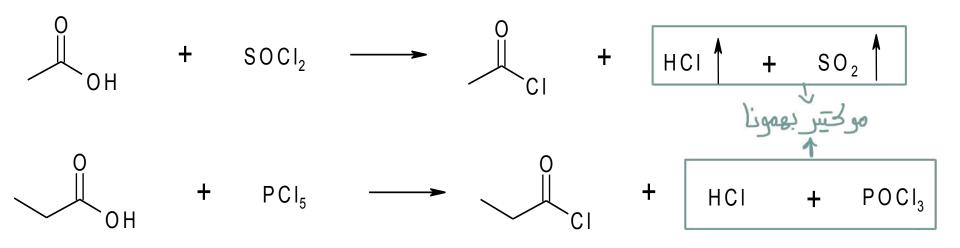
- The functional group of an acid halide is an acyl group bonded to a halogen.
  - The most widely used are the acid chlorides.
  - To name, change the suffix -ic acid to -yl chloride.



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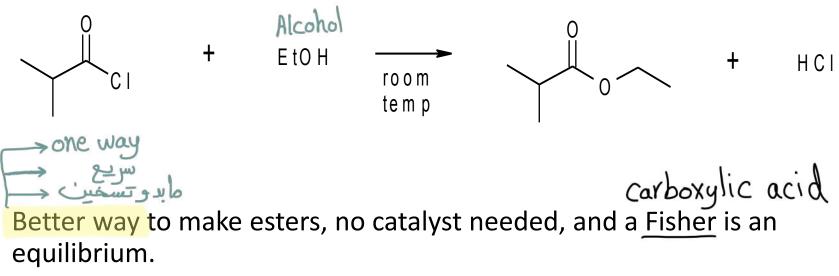
# تحضيرهم معب Acyl Halides: Preparation بتفيرهم معب لأنهم اقل استقرار

Socl<sub>2</sub> Prepared from acids using thionyl chloride or phosphorus pentachloride, i.e.

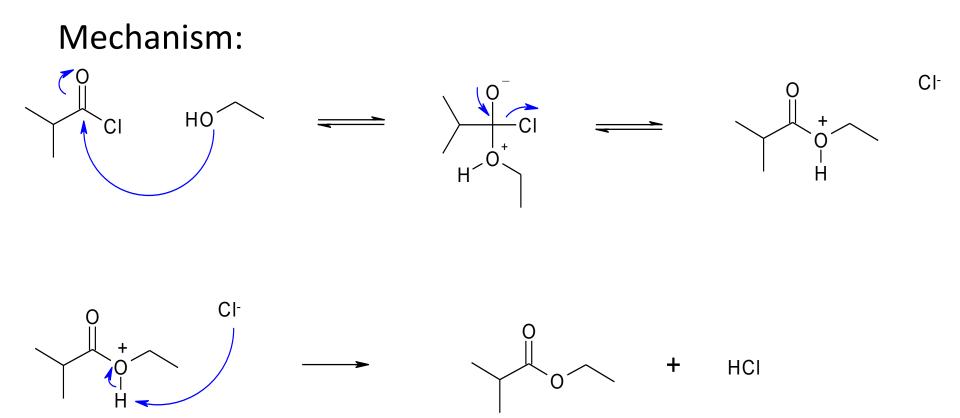


### Acyl Halides ---> Ester

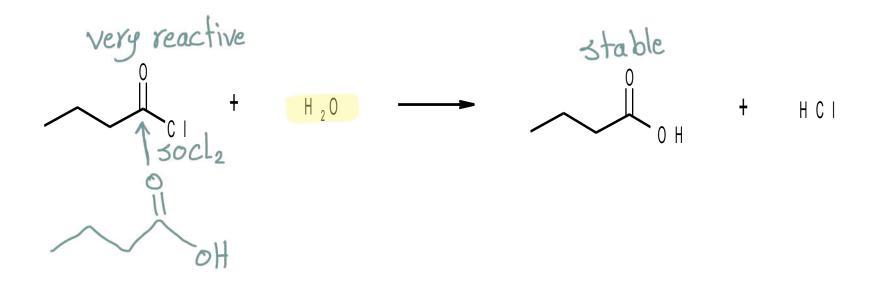
Acyl halides are much more reactive than acids or esters, therefore reactions occur in milder conditions, don't normally need to heat or use acid catalysts.



Note: the HCl normally fumes and is an irritant.



*Hydrolysis* will produce the acid, i.e.



Ammonolysis will produce the amide, i.e.

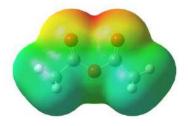


Need 2 equivalents of  $NH_3$ , 1 makes the amide, the other neutralizes the HCl.  $NH_3 + Hcl \rightarrow i$  بنستفر $P_3$  بنستفر $P_3$ 

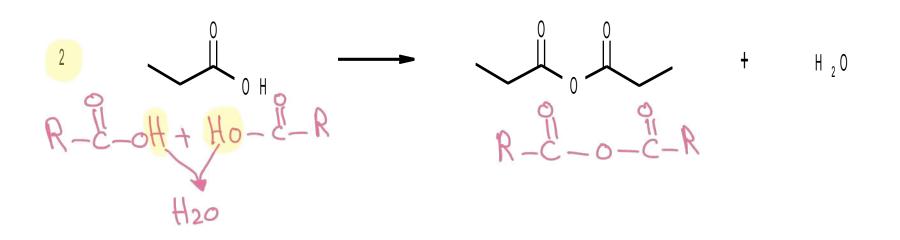
Acyl halides are also used in Friedel-Crafts acylation reactions.

# Acid Anhydrides

Another more reactive form is the *anhydride*.

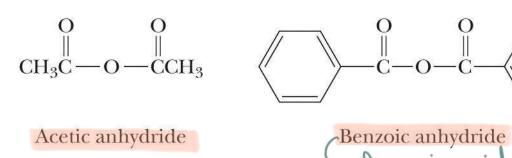


Made by reacting two acid molecules together with the loss of a water molecule, i.e.



### Acid Anhydrides

- The functional group of an acid anhydride is two acyl groups bonded to an oxygen atom.
  - Anhydrides may be symmetrical (two identical acyl groups) or mixed (two different acyl groups).
  - To name, replace acid of the parent acid by anhydride.

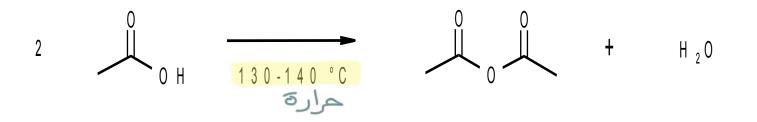


Acetic benzoic anhydride (a mixed anhydride)

CH<sub>2</sub>C

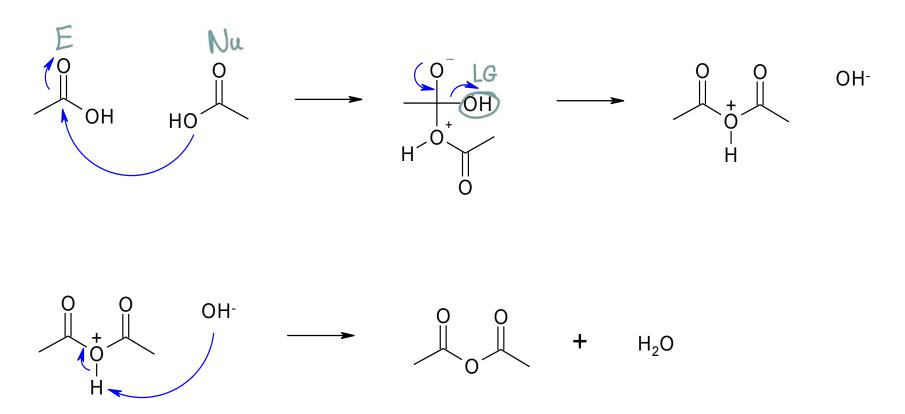
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Anhydrides can be made by heating an acid, i.e.

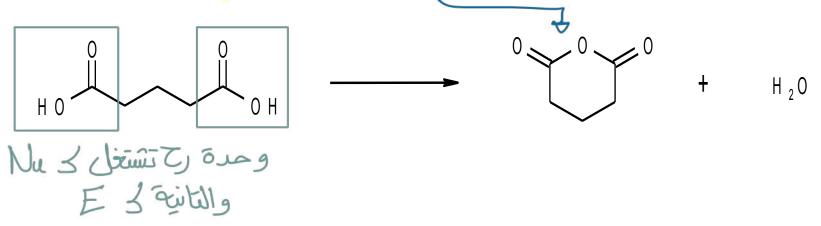


The high temperature drives off the water and drives the reaction forward.

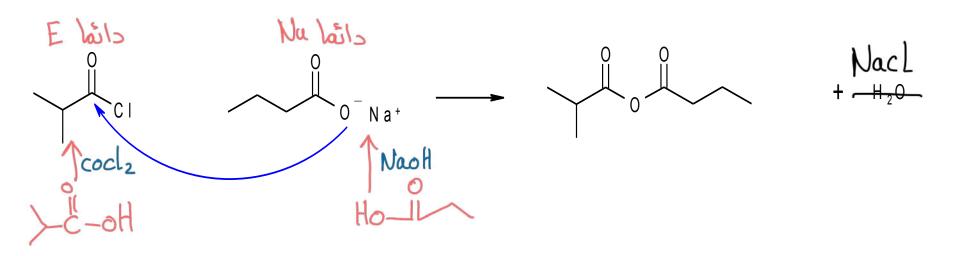
#### Mechanism:



Diacids form cyclic anhydrides, i.e.

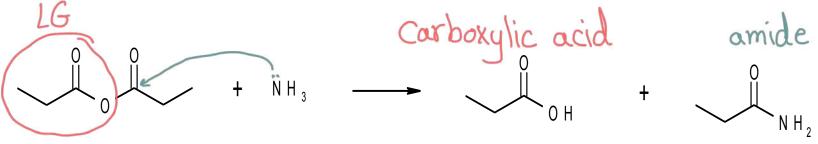


Mixed anhydrides can be made, but you need to use an acyl halide and an acid (or salt) other wise you get a mixture of products, this way only the acid (or salt) can act as the nucleophile, i.e.



# Acid Anhydrides

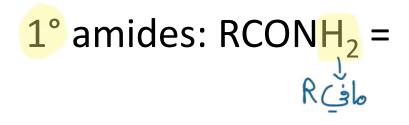
Anhydrides undergo nucleophilic acyl substitution and are more reactive than acids or esters, but not acyl halides, i.e.

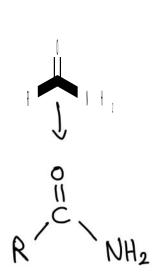


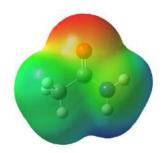
Alcohol and water react the same way as ammonia. The "leaving group" is a carboxylate ion which will get protonated to form the acid.

### Amides $OH \rightarrow R$

# *Amides* are the least reactive of the acid derivatives.

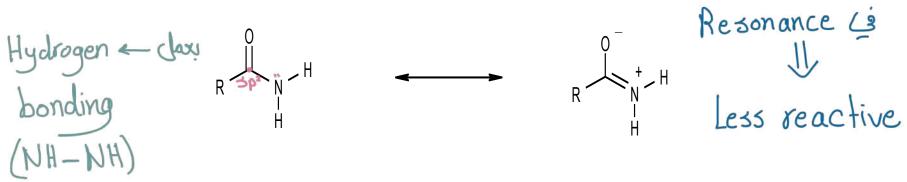






# Amides

The N atom in an amide is  $sp^2$  hybridized (and planar). This allows the lone pair electrons on the amide N to interact with the carbonyl  $\pi$  system, i.e.



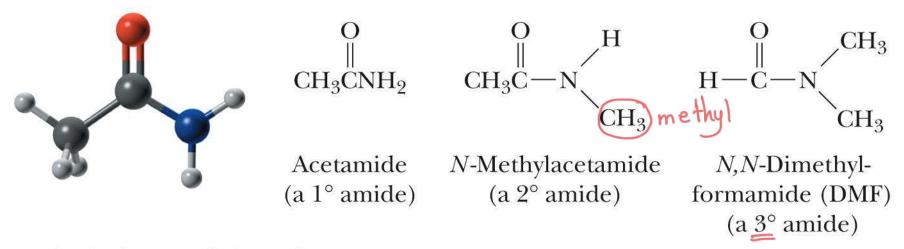
This means the amide bond is rigid to rotation the same as a C=C  $\pi$  bond.

# Amides

The amide group possess both a hydrogen bond donor and acceptors so form strongly H-bonded complexes similar to alcohols and acids. This means they are soluble in water and have high MP & BP for their size.

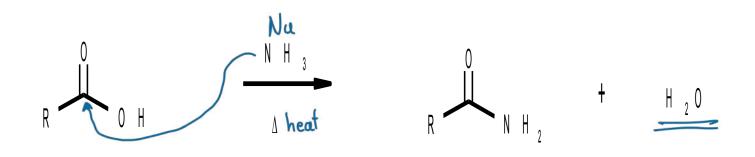
### Amides

- The functional group of an amide is an acyl group bonded to a trivalent nitrogen.
  - IUPAC: drop -ic acid from the name of the parent acid and add -amide.
  - If the amide nitrogen is bonded to an alkyl or aryl group, name the group and show its location on nitrogen by N-.



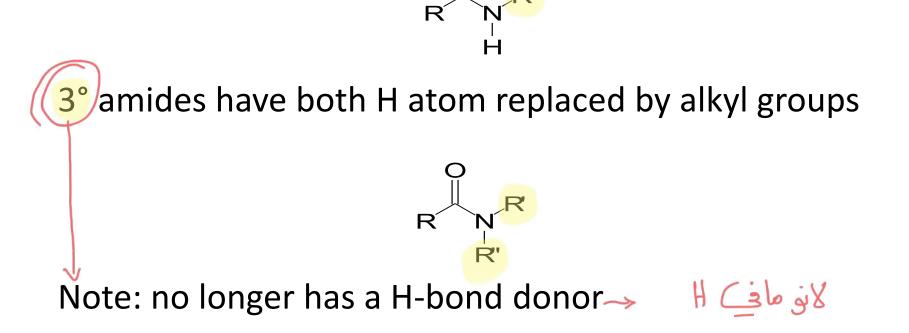
### **Amides: Preparation**

1° amides can be prepared by: reacting NH<sub>3</sub> with esters, acyl halides or anhydrides. They can also be prepared from acids but require heating, i.e.



### Amides:

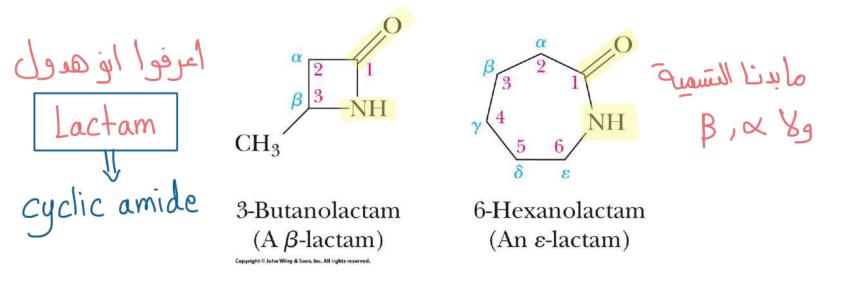
2° amides have one H atom replaced by an alkyl group



### Lactam

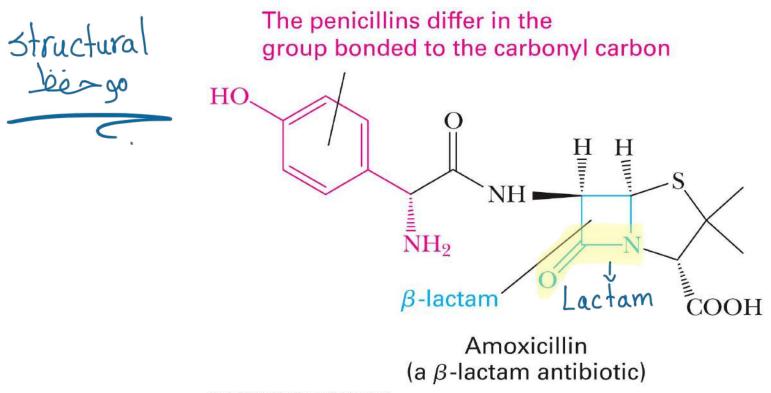
# Lactam: a cyclic amide.

- Name the parent carboxylic acid, drop the suffix -ic acid and add -lactam.
- The location of the nitrogen atom in the ring is commonly indicated by a Greek letter,  $\alpha$ ,  $\beta$ , etc.



### The Penicillins

- The penicillins are a family of  $\beta$ -lactam antibiotics.
  - The structural feature common to all penicillins is a β-lactam ring fused to a five-membered ring containing one S atom and one N atom.

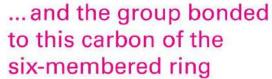


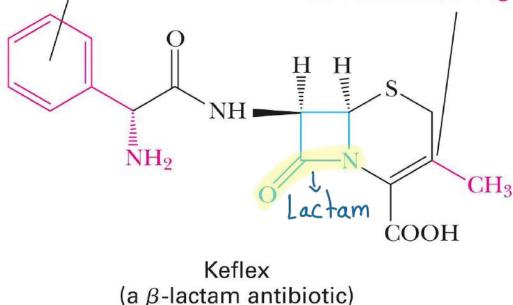
### Cephalosporins

The cephalosporins are also β-lactam antibiotics.

The cephalosporins differ in the group bonded to the carbonyl carbon...



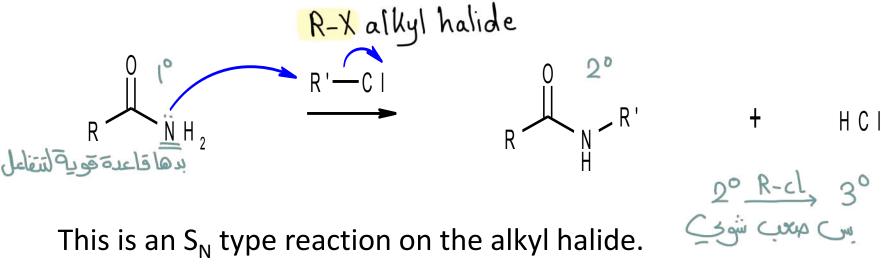




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### **Amides: Preparation**

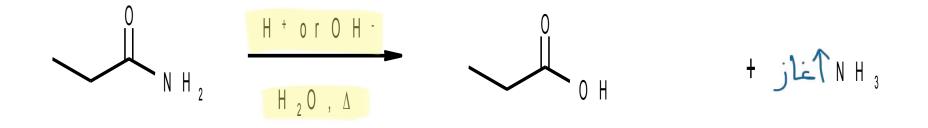
The N atom is weakly nucleophilic due to the lone pair electrons, but less than expected as they are conjugated to the carbonyl group. 2° amides can be prepared by reacting a 1° amide with an alkyl halide, i.e.

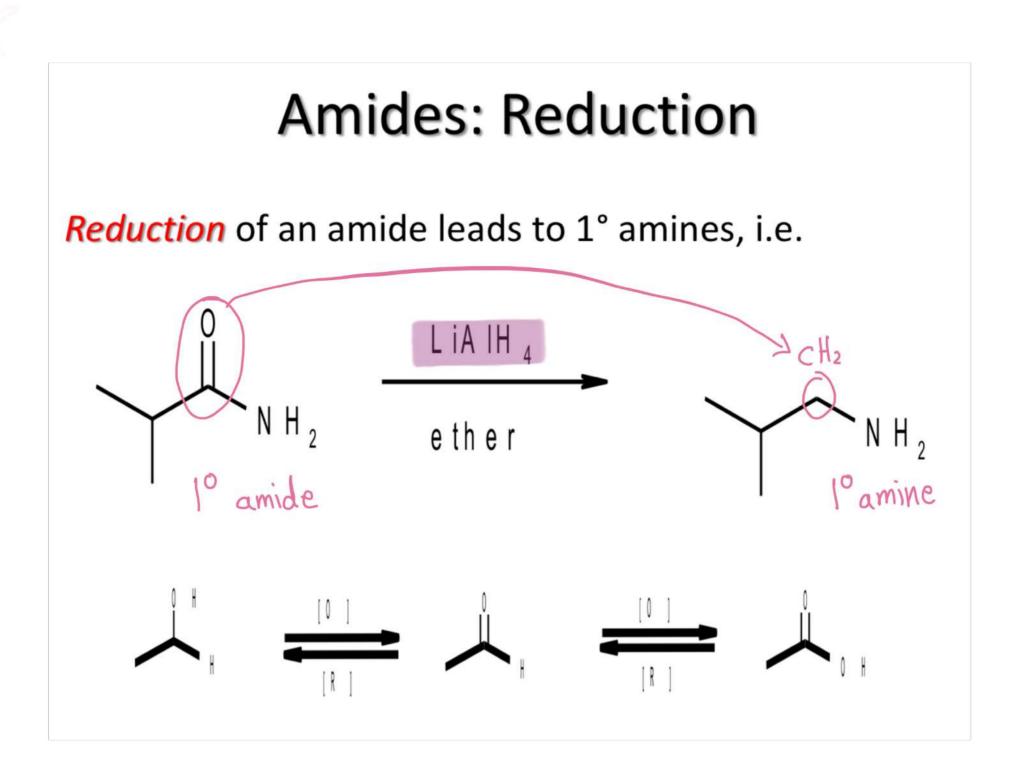


The initial product can react again to produce a 3° amide.

# Amides: Hydrolysis

*Hydrolysis* of an amide leads back to a carboxylic acid. Requires the use of an acid or base catalyst, i.e.





# تلخيص تفاعلات الامين والتحضير

النواتج	العوامل المساعدة	المتفاعلات	الطريقة
Primary amide	1) X 2) heat	<ol> <li>Derivatives</li> <li>carboxylic acid</li> </ol>	Primary amide prep. Ammonolysis
Secondary / Tertiary amide	Х	Primary amide	Secondary/ Tertiary amide prep.
Carboxylic acid + NH3	Acid or base catalyst in H2O with Heat	Amide	Hydrolysis
Primary amine	LiAlH4	Amide	Amide reduction

#### وبهيك بكون انتهى تفريغ chapter 10 🖤



#النادي-الطبي #معكم-خطوة-بخطوة

