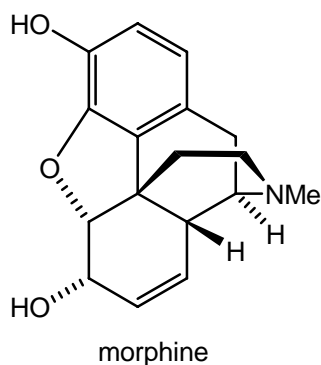

Carboxylic acids and derivatives: nucleophilic acyl substitution and α -substitution reactions

Answers to worked examples

WE 24.1 Esters from acyl chlorides (on p. 1104 in *Chemistry*³)

Reaction of morphine with two equivalents of ethanoyl chloride and excess pyridine produces heroin. Give the structure of heroin.

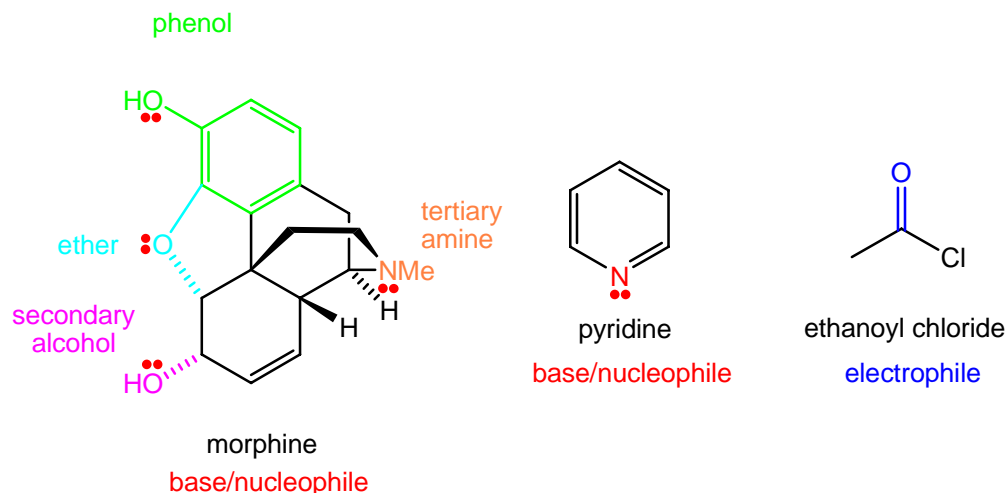


Strategy

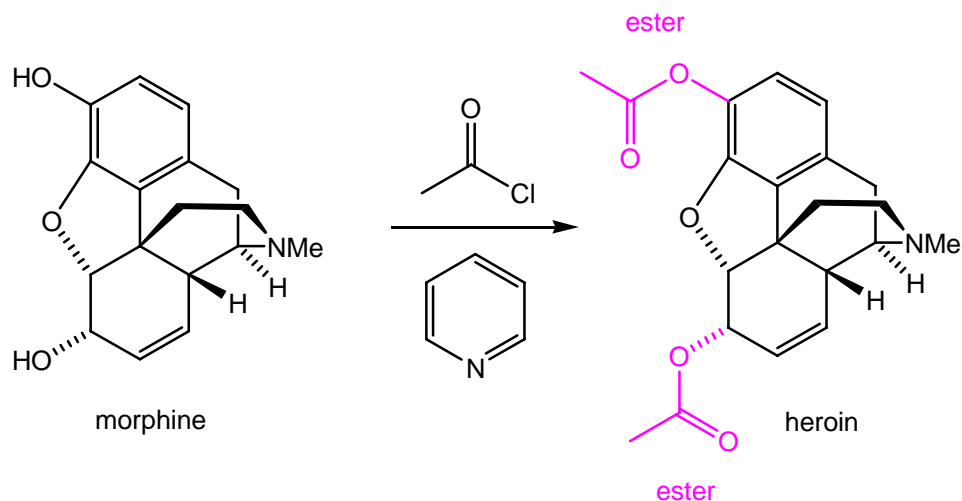
Draw out the structure of morphine and the reagents, ethanoyl chloride and pyridine, and name the functional groups present. Examine the reagents, deduce their relative reactivity, and draw out the resulting product.

Solution

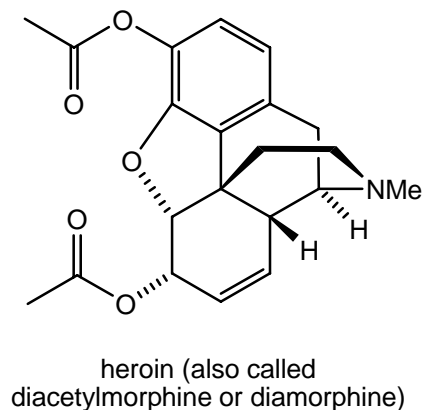
Morphine contains four heteroatom-based functional groups; the tertiary amine, phenol, secondary alcohol and ether. In all cases, these functional groups can act as a nucleophile or a base. The phenol and secondary alcohol can be easily functionalised as they both contain acidic O-H groups. Pyridine is a mild base/nucleophile, whereas, ethanoyl chloride is a potent electrophile.



Treatment of morphine with two equivalents of ethanoyl chloride (in the presence of an excess of pyridine) results in esterification of the two OH groups (of the phenol and secondary alcohol) to give the diester product, heroin, as shown below. Ethanoyl chloride acts as an electrophile, whereas, pyridine acts as a base and a nucleophile catalyst. These reactions involve nucleophilic addition to the carbonyl (C=O) group of ethanoyl chloride, followed by elimination of chloride; these processes are more commonly classed as acyl substitution reactions.



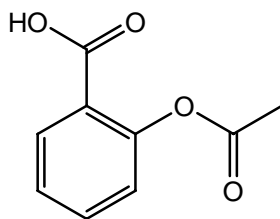
Answer



WE 24.3 Transesterification and aspirin (on p. 1114 in *Chemistry*³)

In our bodies, compounds called prostaglandins induce inflammation, pain, and fever. To provide relief from pain, aspirin acts by inhibiting an enzyme that catalyses the formation of prostaglandins. Aspirin reacts with an OH group within the active site of the enzyme to convert it into an ester (in a transesterification reaction), which inhibits the production of prostaglandins.

Representing the structure of the enzyme by Enzyme-OH, draw the structures of the products formed in the transesterification reaction.



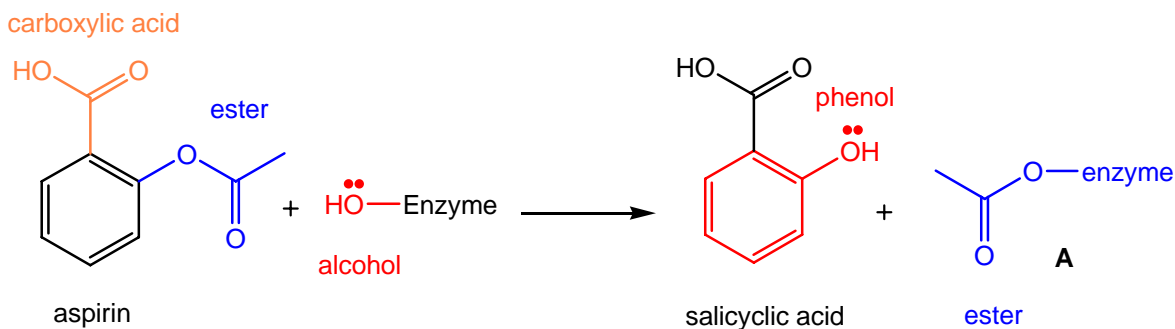
aspirin

Strategy

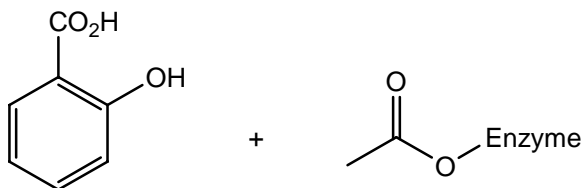
Draw out the structure of aspirin and the enzyme's active site, Enzyme-OH, and name the functional groups present. Locate the ester group in aspirin, and transfer it onto the enzyme's active site. Draw out the resulting products.

Solution

The enzyme's active site contains a nucleophilic hydroxyl group (HO-Enzyme). Aspirin contains a carboxylic acid group and an ester group; the carbonyl (C=O) group of the ester is more electrophilic than that of the carboxylic acid. Transesterification of ester group from the aspirin to the enzyme's active site, HO-Enzyme, gives the products, salicylic acid and the enzyme-ester **A**.

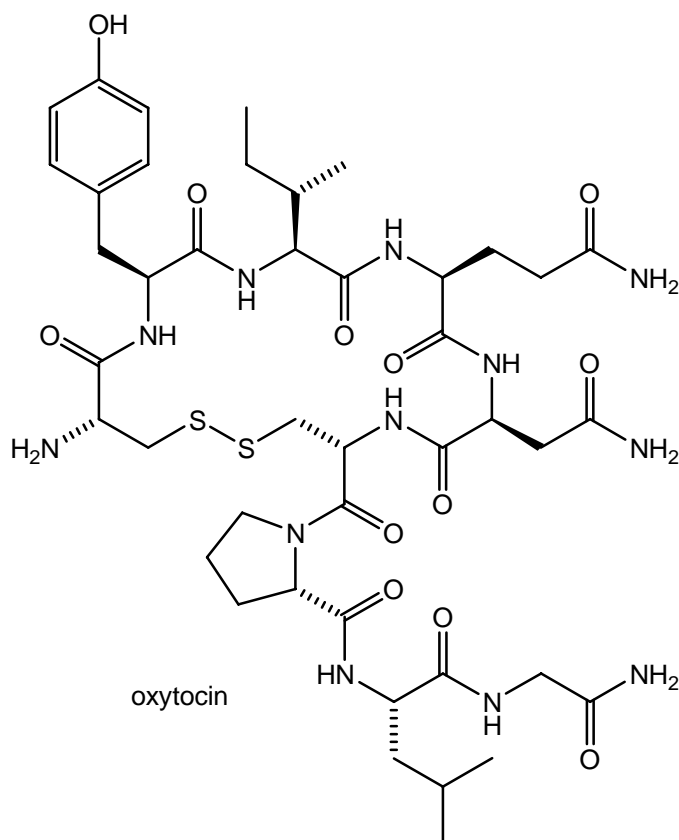


Answer



Answers to boxes**Box 24.1 Oxytocin, the hormone of love (on p. 1092 in *Chemistry*³)**

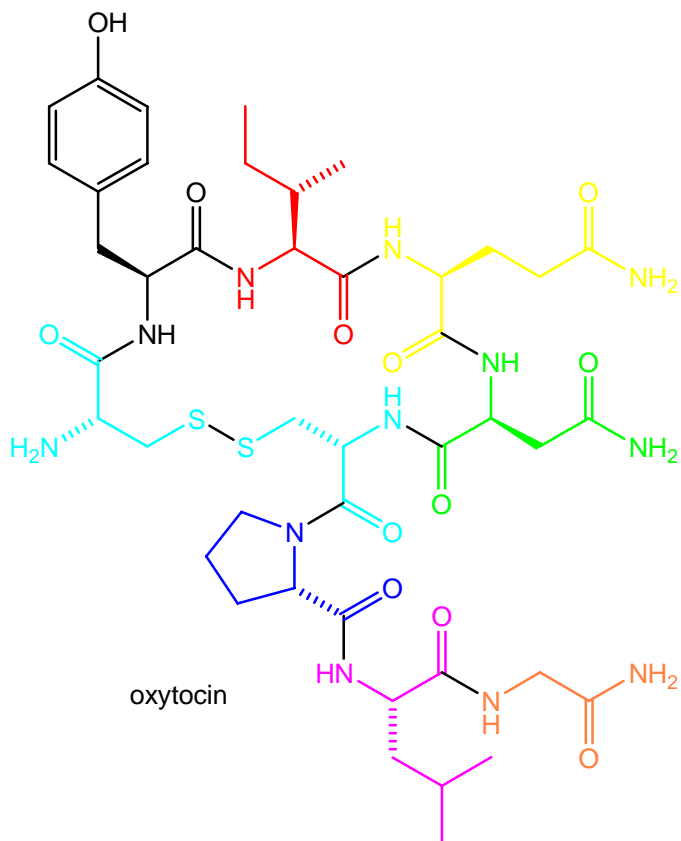
Amino acids link together to form peptides (see box 24.1 in p. 702 in *Chemistry*³). Draw the structures of the eight amino acids that, when linked together with $\text{H}_2\text{NCH}_2\text{CONH}_2$, form oxytocin. (Assume the S–S bond is not formed at this stage).

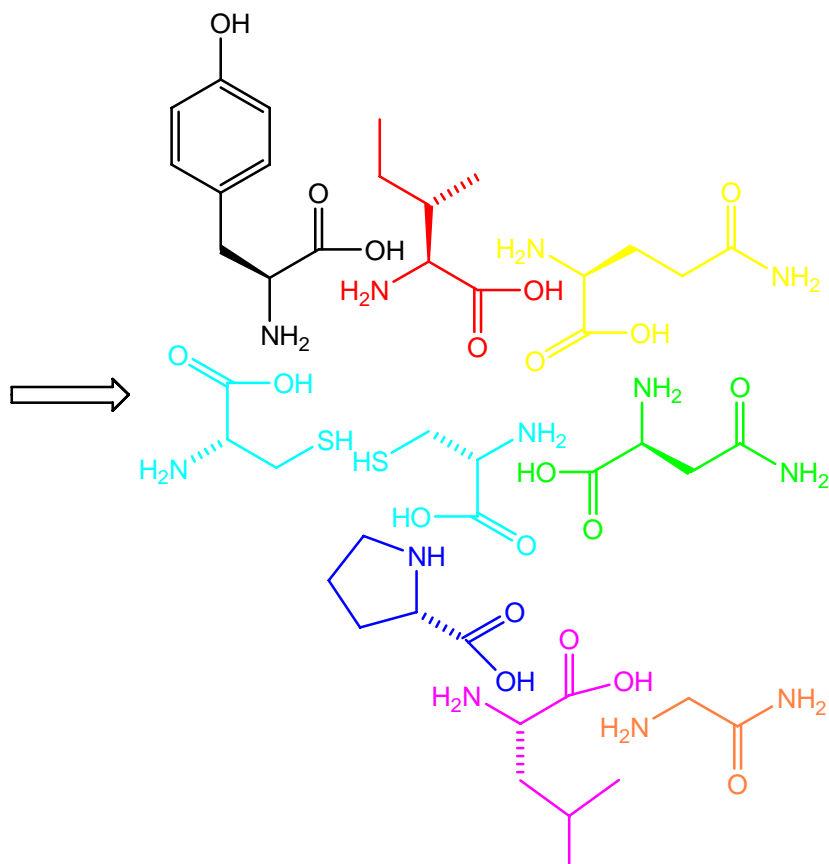
**Strategy**

Locate and highlight the eight amino acid derived peptides, $-\text{NH}-\text{CHR}-\text{C}=\text{O}-$, embedded in the structure of oxytocin. Remember these are peptides and not amino acids. To convert them back into their parent amino acid; the amide bond, $-\text{NH}-\text{C}=\text{O}-$, needs to be broken and hydrated to give the corresponding amino group, $-\text{NH}_2$, and the carboxylic acid, $-\text{CO}_2\text{H}$. In addition, the disulfide bond, $-\text{S}-\text{S}-$, has to be reduced to give the two corresponding thiol bonds, $-\text{SH}$ and $-\text{SH}$.

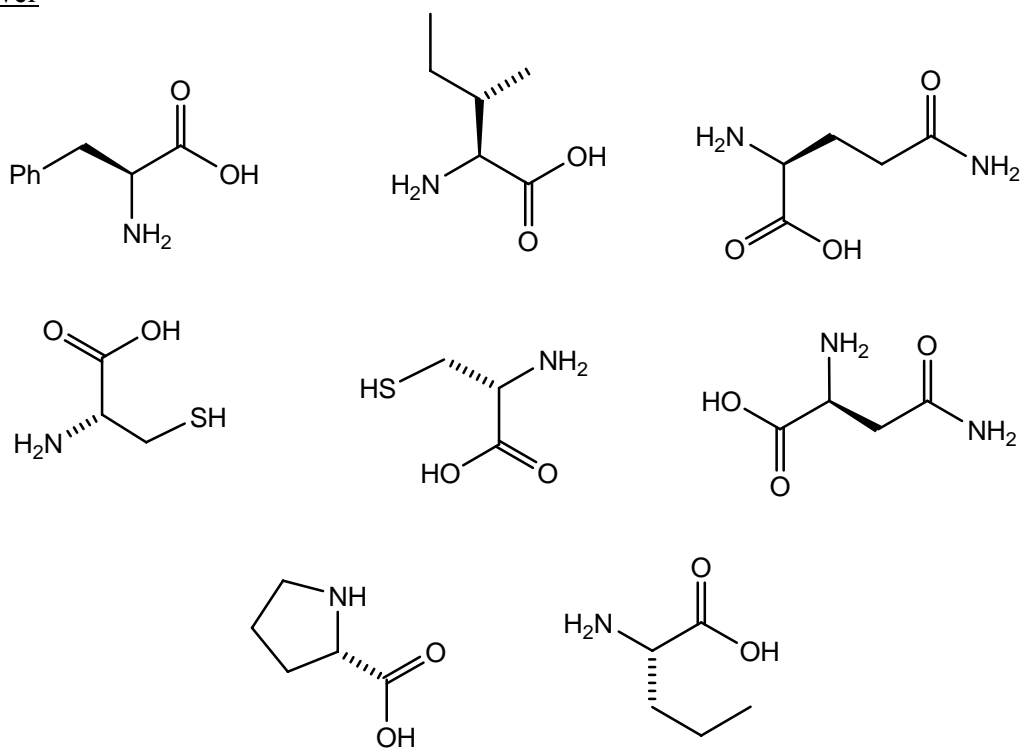
Solution

There are NINE amino acid peptides in oxytocin. Fragmentation and hydration of the amide bonds, reveals eight different amino acids; all are chiral with the exception of glycine, $\text{NH}_2\text{CH}_2\text{CO}_2\text{H}$. The only amino acid which appears twice in oxytocin is cysteine, $\text{NH}_2\text{CH}(\text{CH}_2\text{SH})\text{CO}_2\text{H}$. The structures of all these amino acids, which make up the structure of oxytocin, are shown below.





Answer



Box 24.3 Fragrant esters (on p. 1101 in *Chemistry*³)

All six esters (A–F) shown above are prepared by reaction of an alcohol with a carboxylic acid in an esterification reaction. For each ester, draw the structures of the precursor alcohol and carboxylic acid.

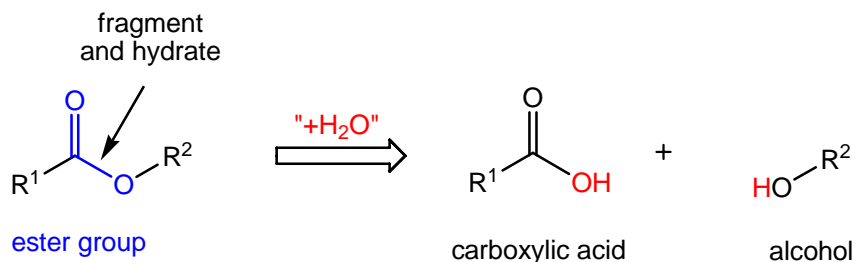
Strategy

Locate and highlight the ester group, $R^1(C=O)-O-R^2$. To convert them back into their parent carboxylic acid and alcohol; the ester bond, $-O=C-O-$, needs to be broken and hydrated to give the corresponding alcohol $HO-R^2$, and the carboxylic acid $R^1(C=O)-OH$.

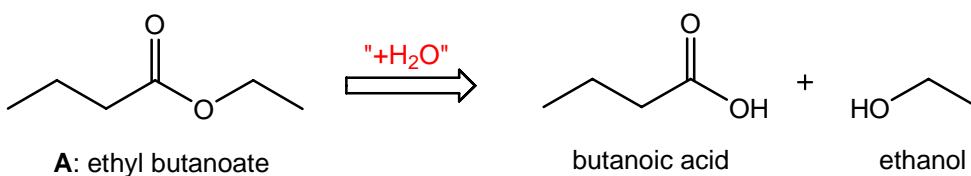
Draw out the parent carboxylic acid and alcohol components that make up each ester.

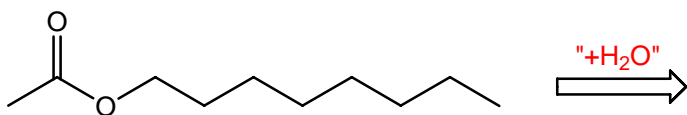
Solution

Each ester can be fragmented and hydrated to give the corresponding alcohol and carboxylic acid, as shown below.

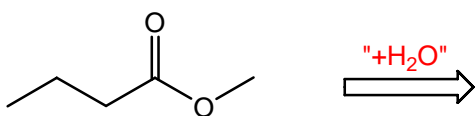
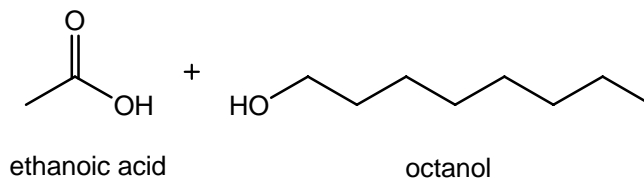


For the six esters, the parent carboxylic acids and alcohols are shown below.

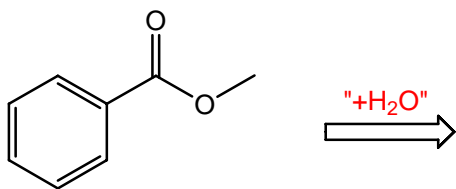
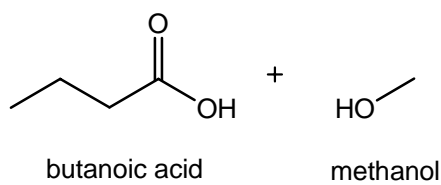




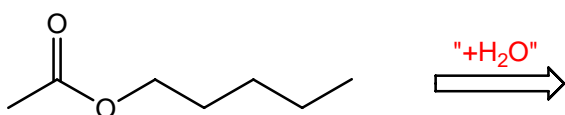
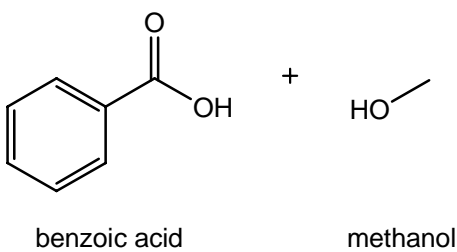
B: octyl ethanoate



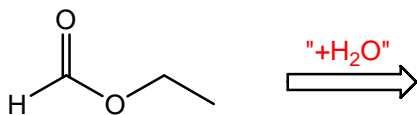
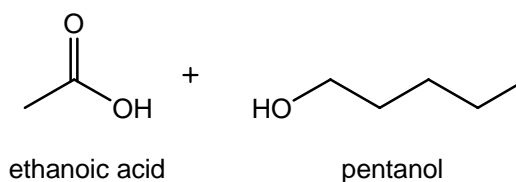
C: methyl butanoate



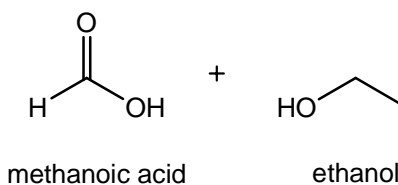
D: methyl benzoate



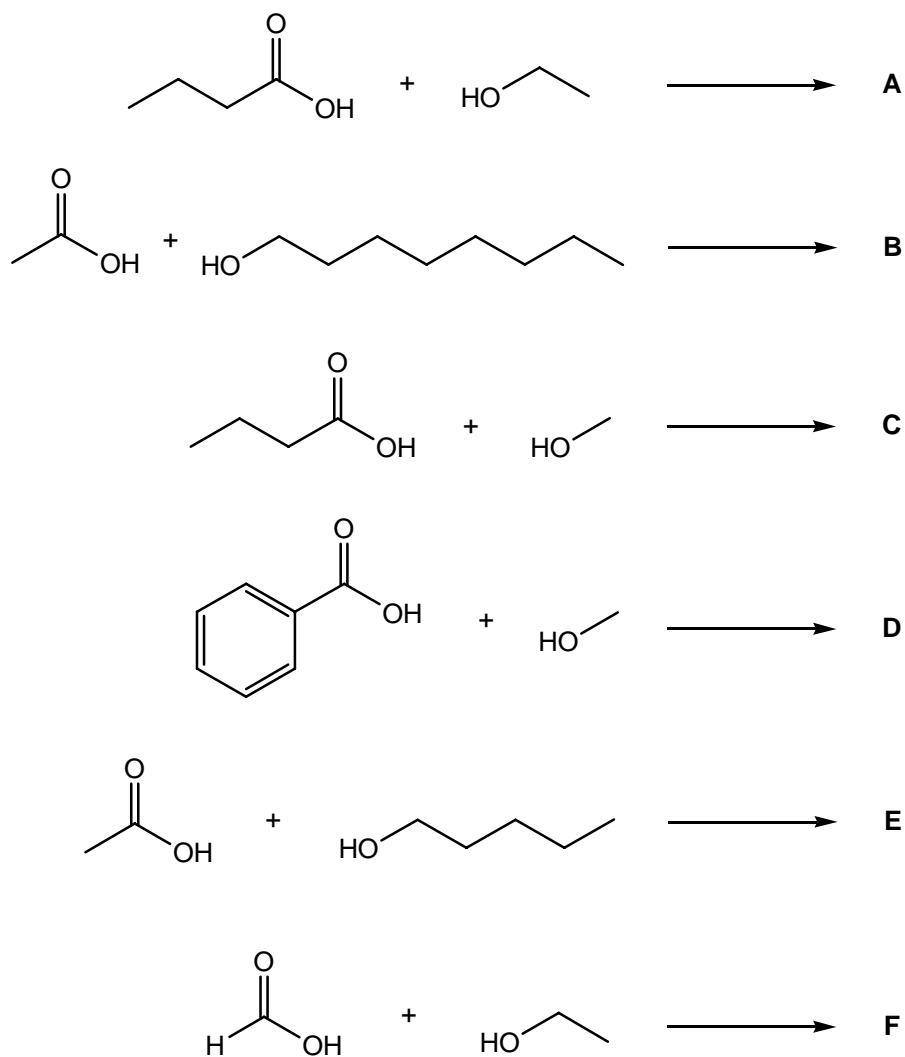
E: pentyl ethanoate



F: ethyl methanoate



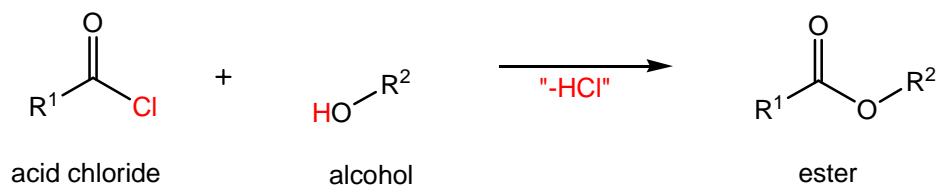
Answer

**Box 24.5 Combinatorial chemistry (on p. 1107 in *Chemistry*³)**

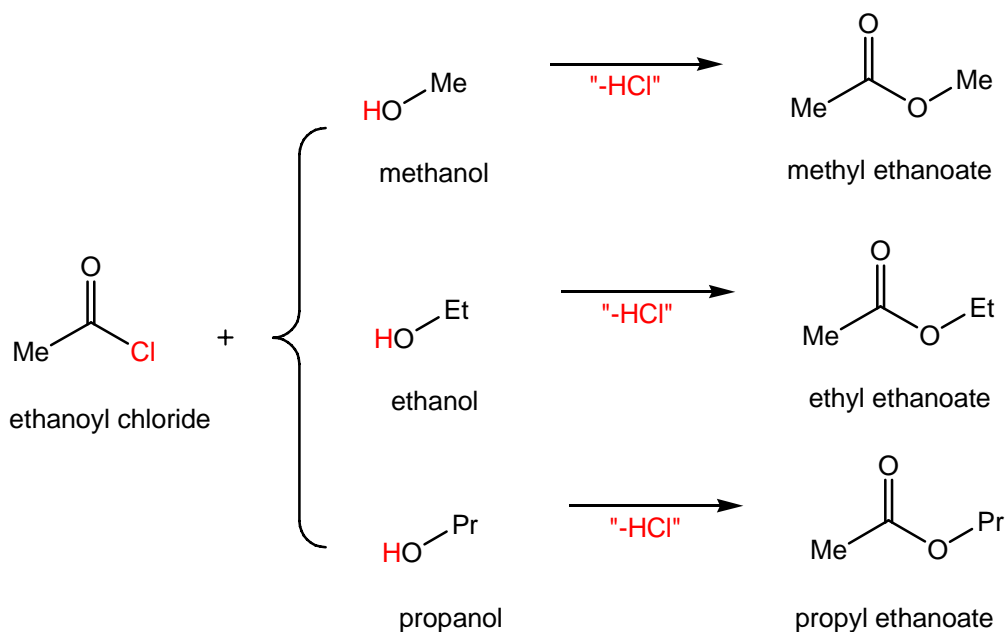
Show how libraries of esters are constructed by reacting methanol, ethanol, and propanol with ethanoyl chloride, propanoyl chloride, and butanoyl chloride.

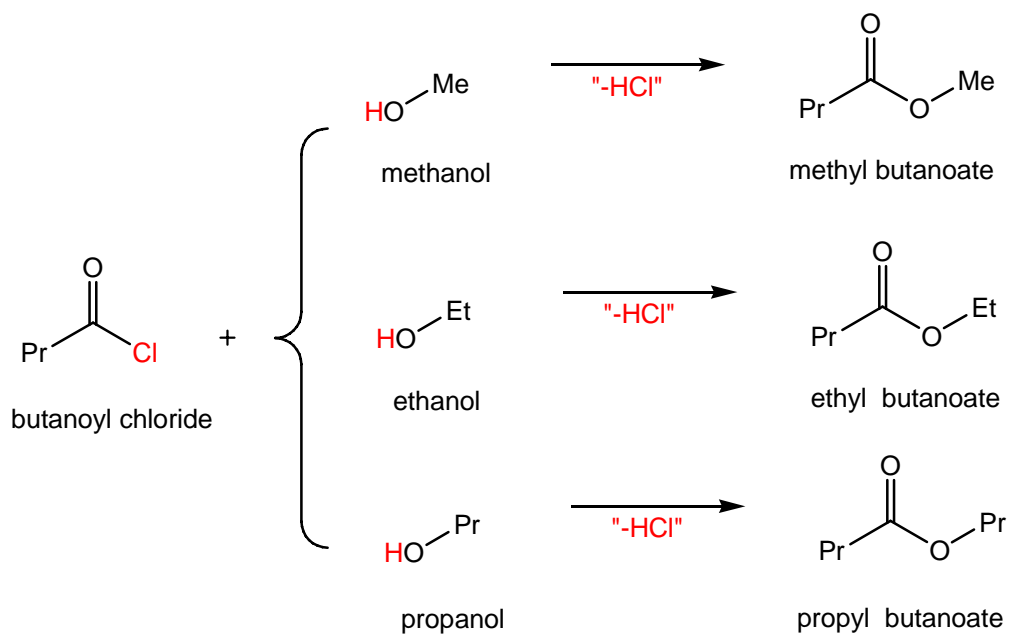
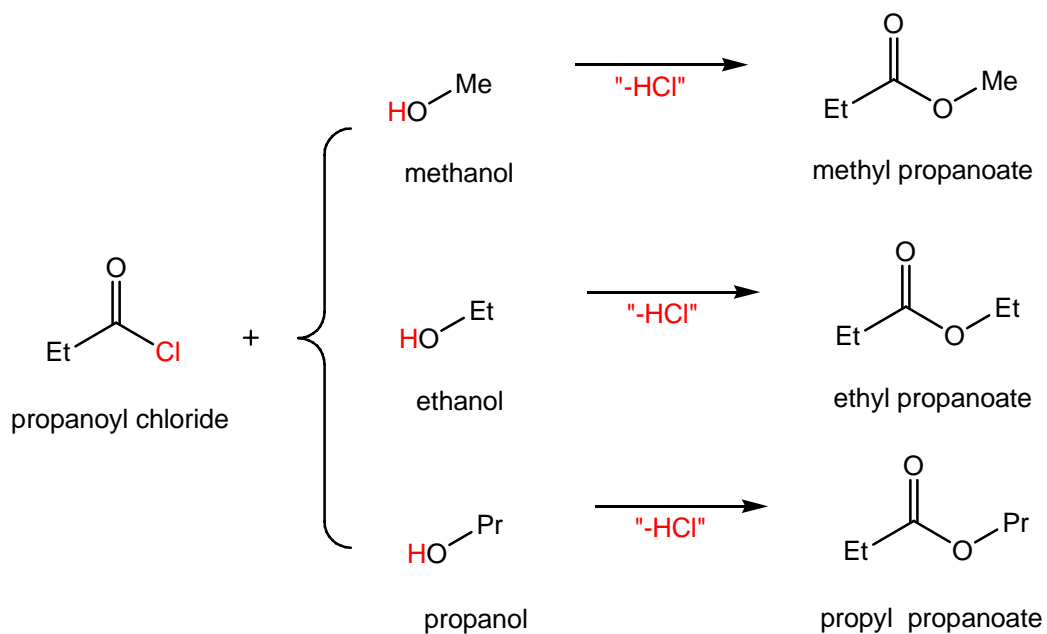
Strategy

Esters, like $R^1(C=O)O-R^2$, can be synthesised by addition of an alcohol, such as R^2OH , to an acid chloride, $R^1(C=O)Cl$, in the presence of a suitable base. Draw out the structures of the above acid chlorides and alcohols. For each acid chloride, use the THREE alcohols, MeOH, EtOH and PrOH, to make THREE esters. As there are THREE acid chlorides, there will be NINE ester products. Draw out the structure of these NINE ester products.

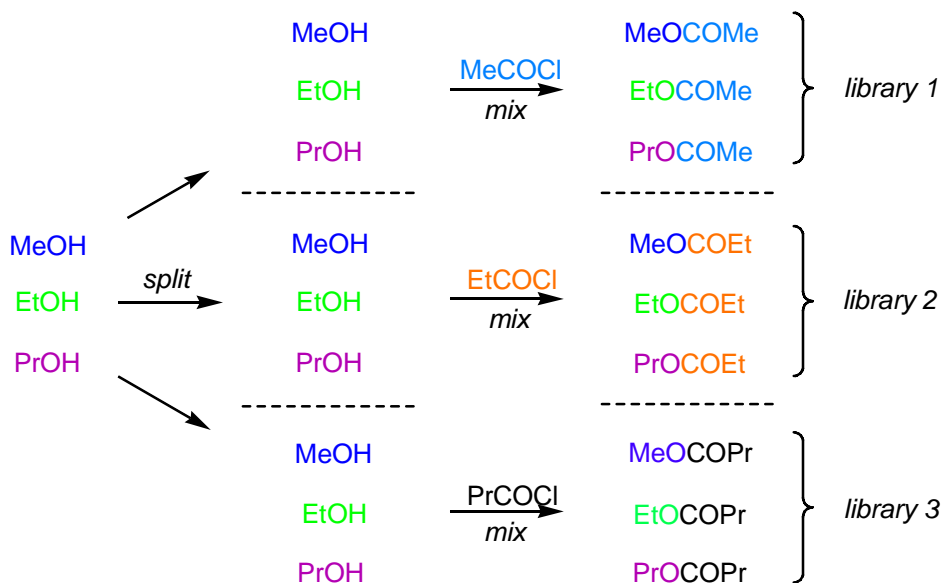
Solution

Combining three acid chlorides with three alcohols will make nine esters, as shown below. It is important to note, the total number comes from 3 multiplied by 3 (= 9), and NOT 3 plus 3 (= 6). For example, mixing a series of 5 acid chlorides and 5 alcohols would give a library of 25 (5×5) esters, and a series of 10 acid chlorides and 5 alcohols would give 50 (10×5) esters, and so on.

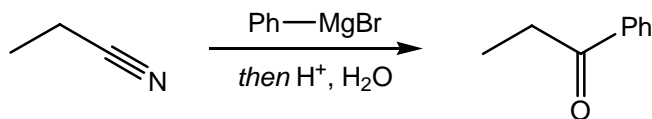




Answer

**Box 24.7 Hydrolysis of nitriles to form carboxylic acids (on p. 1117 in *Chemistry*³)**

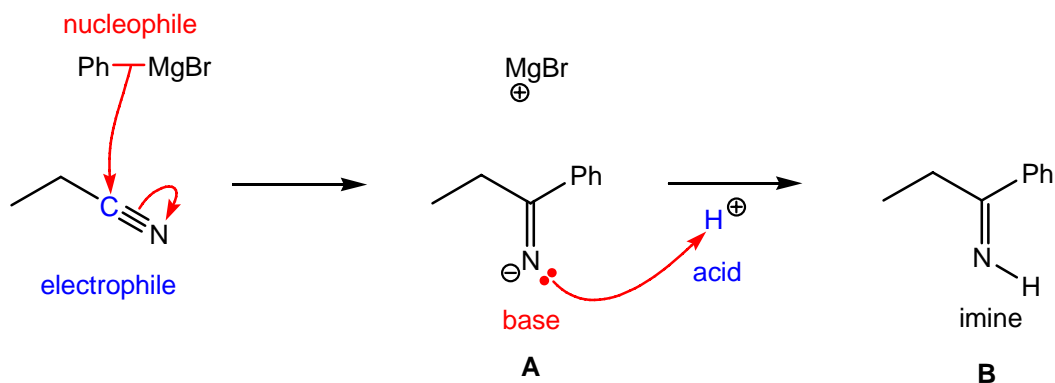
Propose a mechanism for the following reaction, which involves an intermediate imine (see section 9.7 on p.436 in *Chemistry*³ for the structure of imines).

Strategy

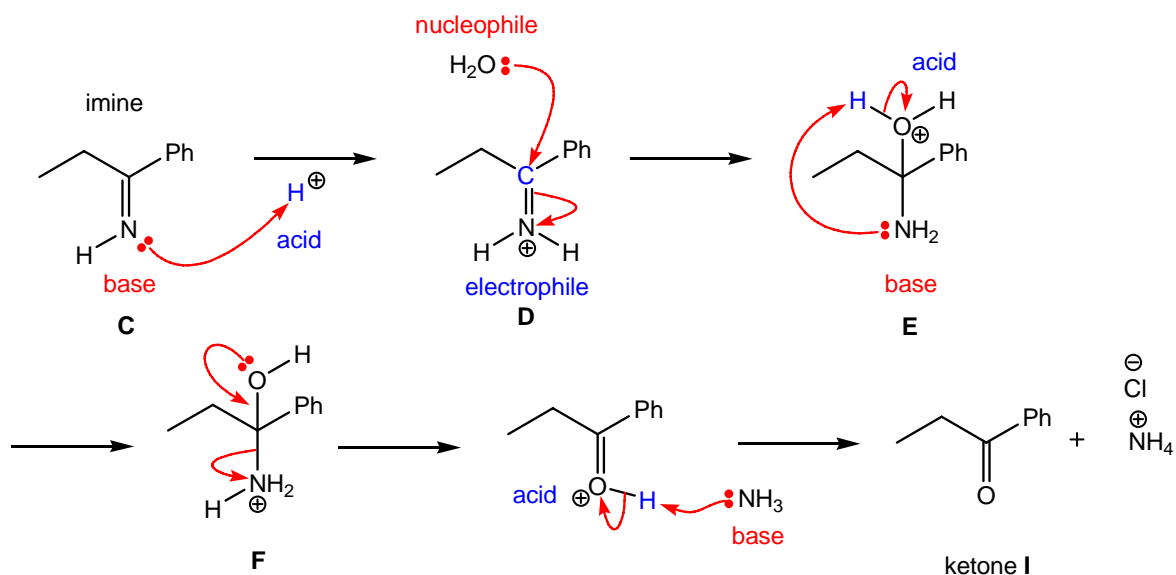
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

Solution

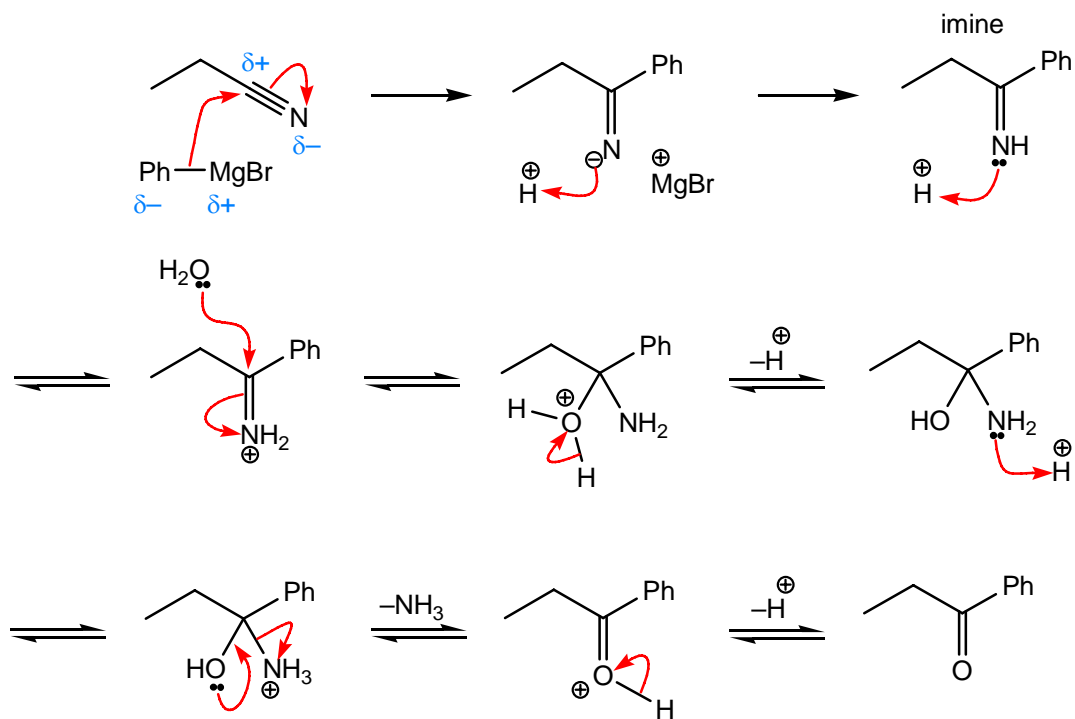
The Grignard reagent, Ph-MgBr is the nucleophile and ethyl cyanide, EtC \equiv N, is the electrophile in this reaction. Nucleophilic addition of the phenyl carbanion, Ph⁻, (from the nucleophilic Ph-MgBr bond) to the electrophilic nitrile group of ethyl cyanide leads to the trigonal intermediate **A**. Protonation of this basic iminium ion, in **A**, using aqueous mineral acid (dilute HCl in H₂O), gives the imine **B**.



Under prolonged acidic conditions, this imine, **B**, hydrolyses to give the ketone **I** and ammonium chloride. Protonation of the imine, in **C**, followed by nucleophilic addition of water to the electrophilic iminium ion **D** gives the hemi-aminal intermediate **E**. **Intramolecular** proton exchange, in **E**, followed by elimination of ammonia gives the oxonium ion **F**. **Intermolecular** proton exchange between the acidic oxonium ion **F** and basic ammonia gives the required ketone **I** and ammonium chloride. The mechanism of this process is shown below.



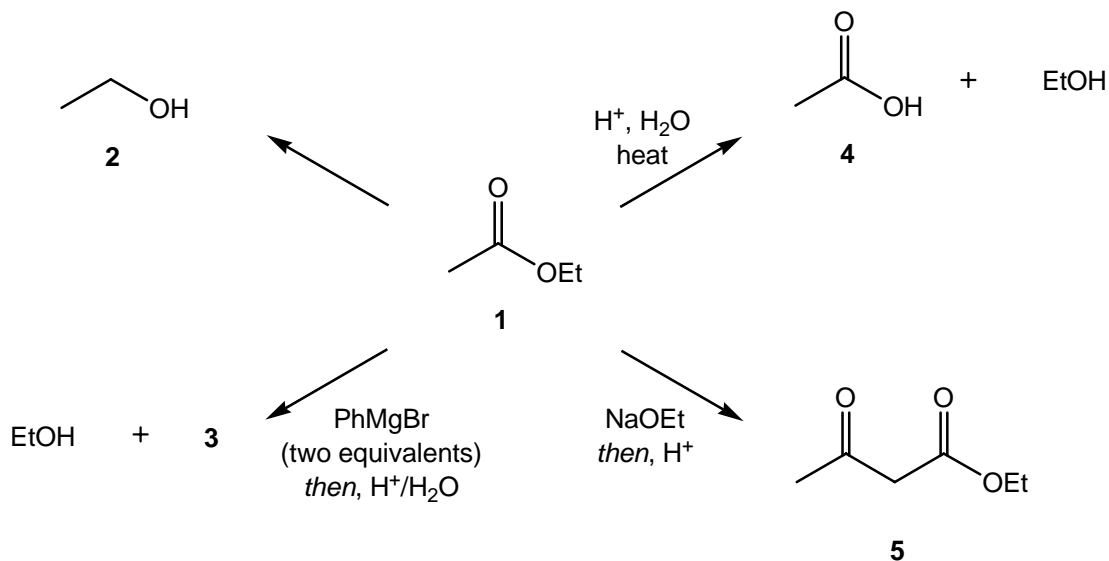
Answer



[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

Answers to end of chapter questions (on p. 1127 in *Chemistry*³)

1. The following queries are based on the reactions of ethyl ethanoate (**1**) shown below.



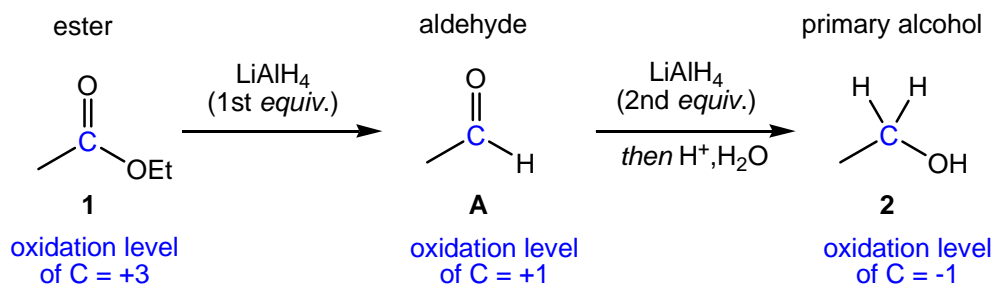
- (a) Give appropriate reagents for converting **1** into **2**. Is this an example of an oxidation or a reduction reaction?

Strategy

Draw out the starting material and product, assign their oxidation levels, and work out if an oxidation or reduction has occurred. Deduce which functional group has changed during this proposed reaction, and suggest reagents for this transformation.

Solution

The starting material **1** and product **2** contains ester and primary alcohol functionality, respectively. This process involves reduction, as there is a decrease in the oxidation level of the **carbon atom** of the ester group, in **1**, from +3 to -1 (in the primary alcohol **2**).



Reduction of the polar carbonyl group, of ester **1**, will require a polar reducing agent. The most suitable reagent for this reduction is lithium aluminium hydride (LiAlH_4); the use of a less reactive hydride source, like NaBH_4 , is NOT acceptable. Two equivalents of LiAlH_4 are required; the first equivalent reduces the ester to give the intermediate aldehyde **A**; the second equivalent reduced this aldehyde to the required primary alcohol **2**. Under these conditions, the reaction needs to be “worked-up” under acidic conditions (H^+ , H_2O) in order to protonate the intermediate alkoxide. For a detailed account of these mechanisms, see p. 1055 in *Chemistry*³.

Answer

This process involves reduction; a suitable reagent is LiAlH_4 , then H^+ .

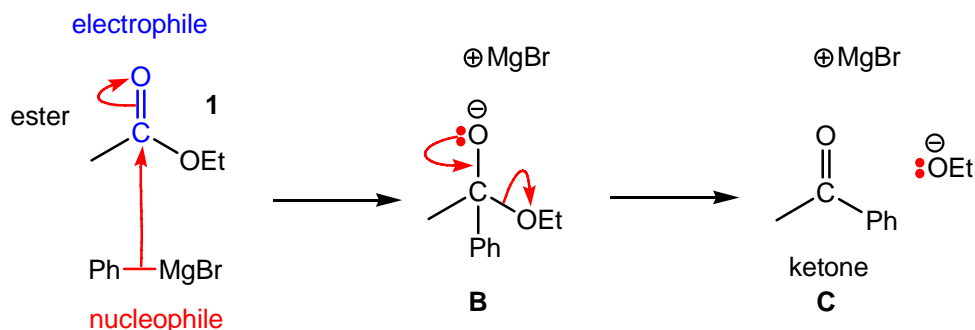
(b) Give the structure of organic compound **3**.

Strategy

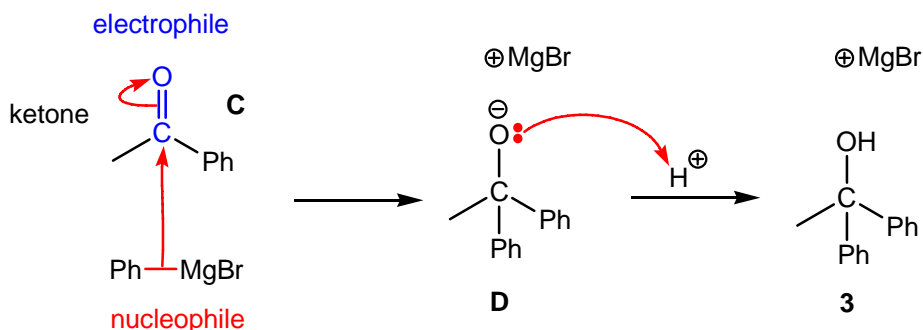
Draw out the reagents, ethyl ethanoate **1** and phenyl magnesium bromide (PhMgBr), and name the functional groups present. Examine the reagents, deduce their relative reactivity, and draw out the resulting product.

Solution

Ethyl ethanoate **1** is an ester, and acts as an electrophile in this reaction. The Grignard, phenyl magnesium bromide (PhMgBr) is a nucleophilic equivalent of a phenyl carbanion, Ph^- .



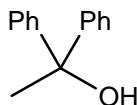
Nucleophilic addition of the first equivalent of phenyl magnesium bromide, using its nucleophilic Ph-MgBr bond, to the electrophilic carbonyl group of ethyl ethanoate **1** leads to the tetrahedral intermediate **B**. Elimination of ethoxide, EtO^- , gives the intermediate ketone **C**.



Nucleophilic addition of a second equivalent of phenyl magnesium bromide to the electrophilic carbonyl group of the intermediate ketone **C** leads to the tetrahedral intermediate **D**. Protonation of its basic alkoxide, in **D**, using aqueous mineral acid (dilute HCl in H_2O), gives the tertiary alcohol **3**. The mechanisms of these Grignard reactions are given on p. 1061 in *Chemistry*³.

Treatment of esters, like $\text{R}^1\text{CO}_2\text{R}^2$, with two equivalents of Grignard reagent, such as R^3MgBr , leads to the corresponding tertiary alcohol, $\text{R}^1\text{C}(\text{OH})\text{R}^3\text{R}^3$.

Answer



- (c) Oxygen-18 labelling is often used to establish the mechanism of a reaction. An ^{16}O oxygen in a starting material is replaced by an ^{18}O atom and the position of the ^{18}O

atom at the end of the reaction recorded using mass spectrometry (see section 13.1 on p.606 in *Chemistry*³).

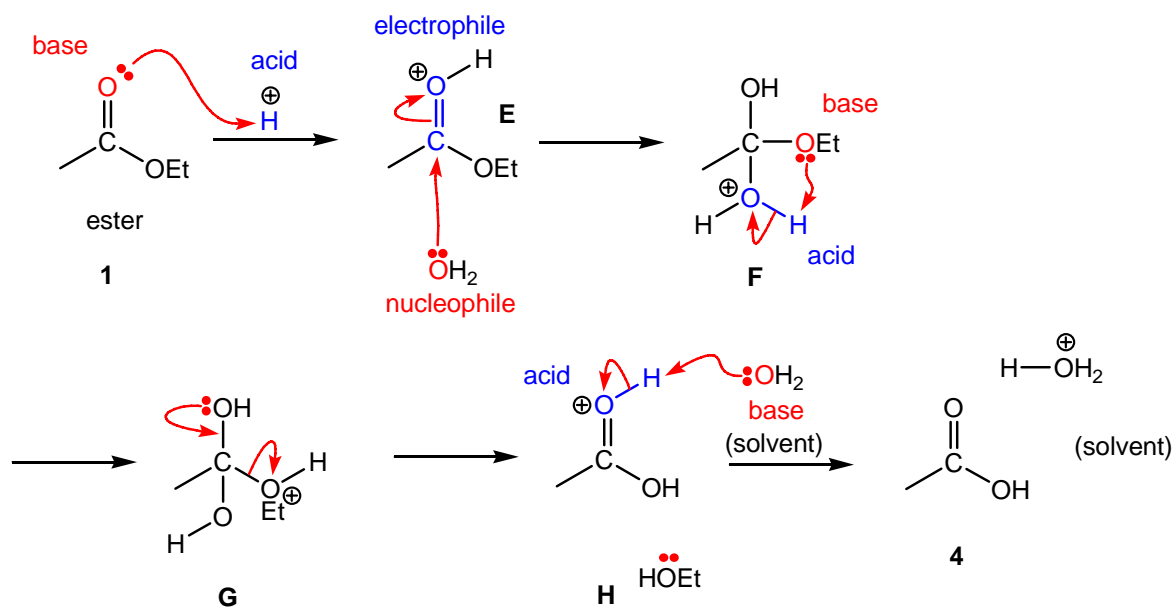
- (i) Draw a reaction mechanism to show how **1** is converted into **4** and EtOH.

Strategy

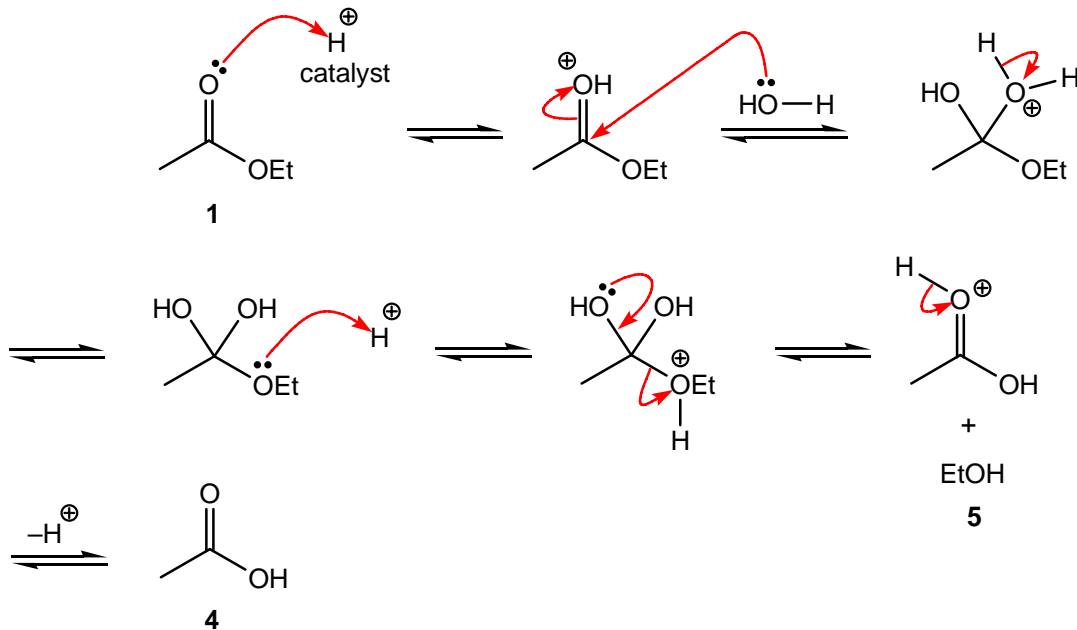
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

Solution

The ester **1** is the base, and H^+ is the acid. Protonation of the oxygen atom of the carbonyl (C=O) group of this ester **1** with H^+ gives the intermediate oxonium ion **E**. Nucleophilic addition of water (H_2O) to this oxonium ion, in **E**, leads to the protonated intermediate hydrate **F**. Intramolecular proton exchange between the basic ethoxy group and the acidic oxonium ion, in **F**, gives the intermediate **G**. Elimination of ethanol (EtOH), assisted by the non-bonded pair of electrons on the neighbouring hydroxyl (OH) group, gives the protonated ester **H**. Intermolecular acid-base exchange of **H** with another molecule of water (from the solvent) gives the required carboxylic acid **4** and ethanol. This mechanism involves the acid-catalysed hydrolysis of ester **1**, using an $A_{Ac}2$ mechanism, to give the corresponding carboxyl acid and alcohol components by cleavage of its acyl (Ac) group.



Answer



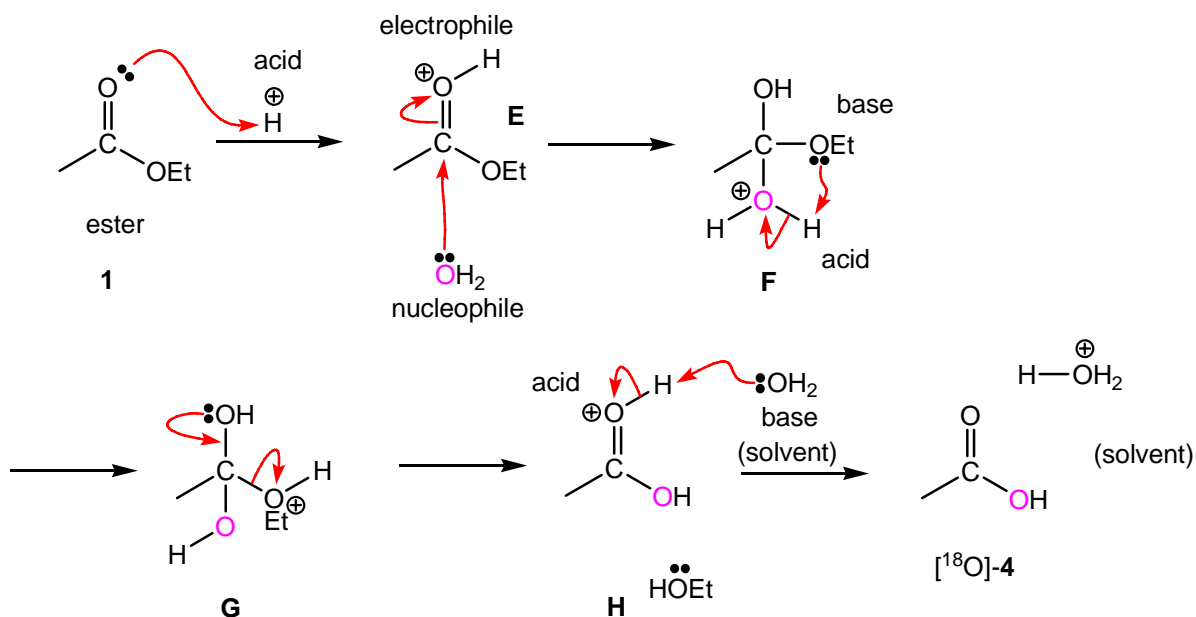
- (c) (ii) If **1** is heated with H_2^{18}O and H^+ , where does the ^{18}O atom appear at the end of the reaction?

Strategy

Non-isotopically labelled water is H_2O^{16} . Redraw the hydrolysis mechanism given in part (c)-(i) as given above, and replace “ H_2O ” with isotopically labelled water “ H_2O^{18} ” (or H_2O). In each step of this mechanism, carefully label the resulting position of this ^{18}O -labelled oxygen atom. Draw out the final products, and clearly label the ^{18}O -atom(s).

Solution

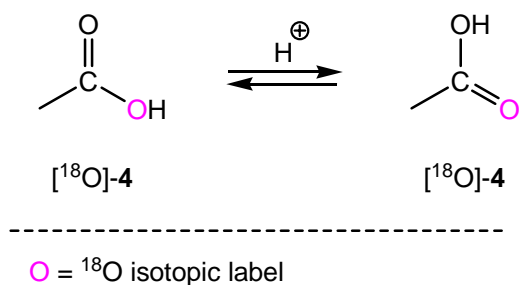
By simply replacing “ H_2O ” with labelled “ H_2O^{18} ” (as shown by H_2O in the mechanism below) and following the position of this ^{18}O -labelled oxygen atom throughout this mechanism - the initial product of this hydrolysis is a single ^{18}O -labelled carboxylic acid [^{18}O]-4.



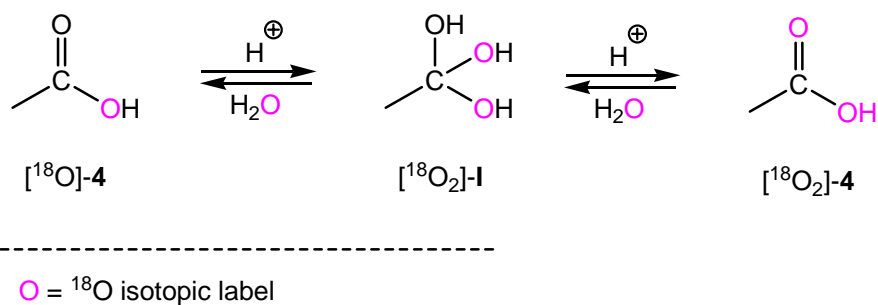
O = ^{18}O isotopic label

Under acidic conditions, this ^{18}O -labelled oxygen atom (on the OH group in [^{18}O]-4) can tautomerise into the $\text{C}=\text{O}^{18}$ group, and *vice versa*, as shown below. In essence, the two

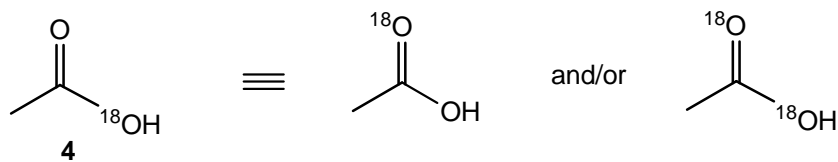
oxygen atoms of this carboxylic acid [¹⁸O]-4 are indistinguishable under this dynamic equilibrium; both isotopically labelled products are equally preferred.



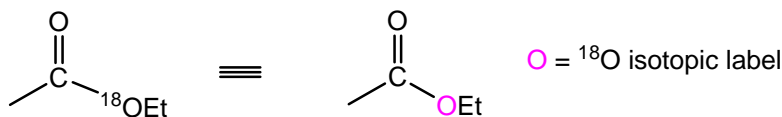
However, in the presence of an excess of ¹⁸O-labelled water (H₂¹⁸O), the fully ¹⁸O-labelled carboxylic acid [¹⁸O₂]-4 is preferred. This reaction proceeds *via* the intermediate hydrate [¹⁸O₂]-I. For further information about the mechanism of hydrate formation, see p. 1064 in *Chemistry*³.



Answer



- (c) (iii) If ethyl ethanoate, labelled with ¹⁸O as shown below, is heated with H₂O/H⁺, where does the ¹⁸O atom appear at the end of the reaction?

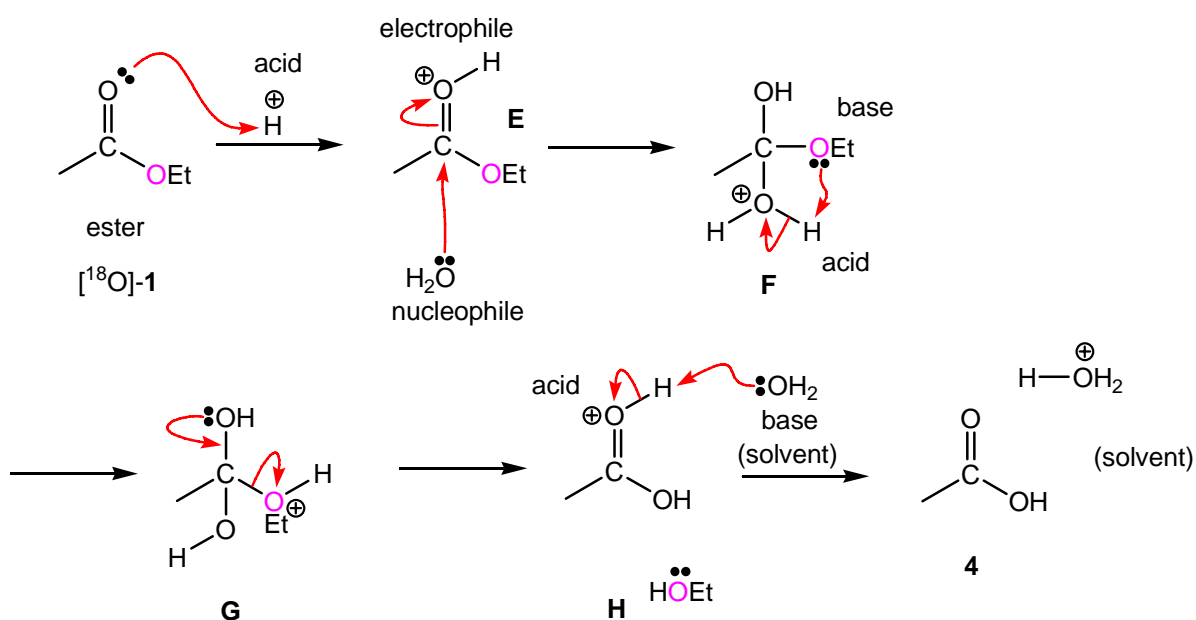


Strategy

Redraw the hydrolysis mechanism given in part (c)-(i) as given above, and replace ester **1** with isotopically labelled ester [¹⁸O]-**1**. In each step of this mechanism, carefully label the position of this ¹⁸O labelled oxygen atom. Draw out the final products, and clearly label the ¹⁸O atom.

Solution

By simply replacing the ester **1** with the labelled ester [¹⁸O]-**1** (as shown by the mechanism below), and following the position of this ¹⁸O-labelled oxygen atom throughout this mechanism; the product of this hydrolysis is the **unlabelled** carboxylic acid **4** and ¹⁸O-labelled ethanol (Et¹⁸OH). This reaction proceeds by an A_{Ac}2 mechanism where cleavage occurs at its acyl (Ac) group.



○ = ¹⁸O isotopic label

Answer

EtO¹⁸H

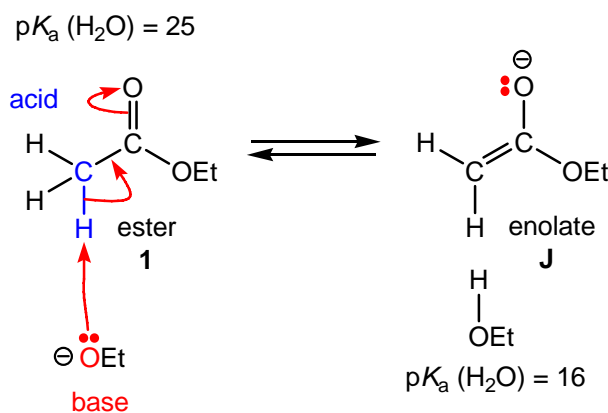
(d) Draw a reaction mechanism to show how **1** is converted into **5**.

Strategy

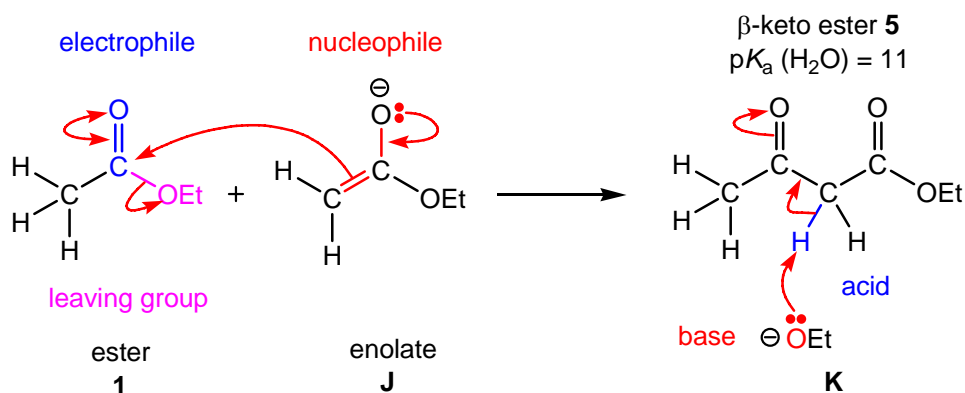
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

Solution

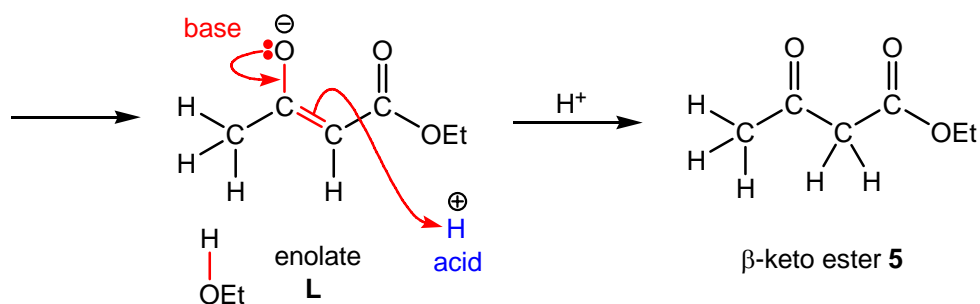
Deprotonation of ethyl ethanoate **1** [$pK_a(\text{H}_2\text{O}) = 25$] using ethoxide, EtO^- , as the Brønsted base, gives the thermodynamically less stable enolate **J** and its conjugate acid, ethanol [$pK_a(\text{H}_2\text{O}) = 16$].



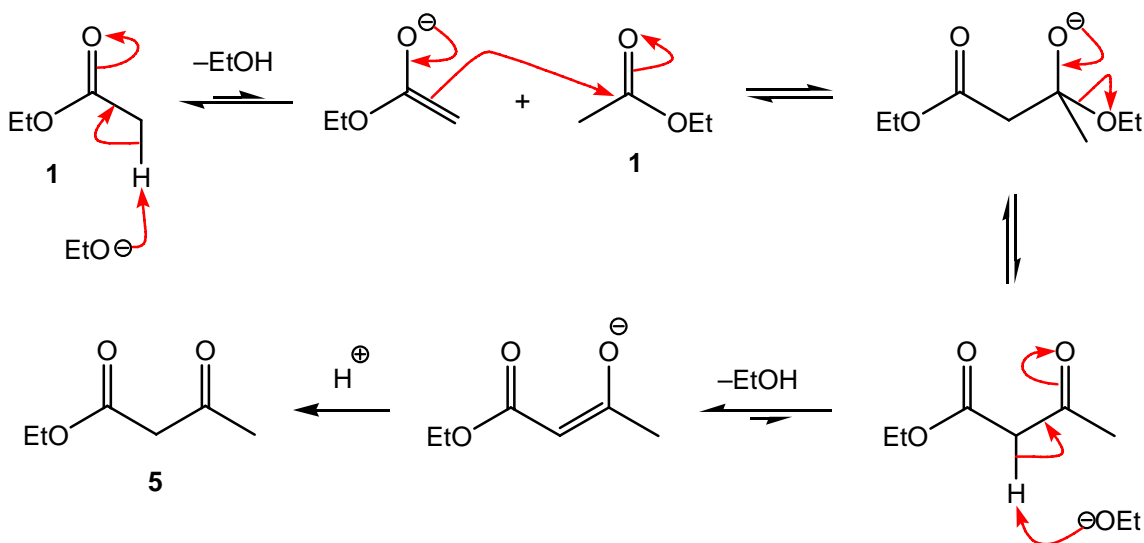
The product, β -keto ester **5**, is derived from **two** equivalents of ethyl ethanoate **1**. Nucleophilic addition of the enolate **J** (derived from the first equivalent of ester **1**) to the electrophilic carbonyl ($\text{C}=\text{O}$) group of the second equivalent of ester **1**, followed by elimination of ethoxide, EtO^- , leads to the required β -keto ester **5**. {This addition-elimination has been depicted using a double-headed curly arrow. If you are unsure about using this type of curly arrow, see p. 1095 in *Chemistry*³.}



However, as this β -keto ester **5** [pK_a (H_2O) = 11] is more acidic than both ethanol [pK_a (H_2O) = 16] and ethyl ethanoate **1** [pK_a (H_2O) = 25]; deprotonation of β -keto ester **5** (in **L**) using ethoxide, EtO^- , as the Brønsted base, gives the more thermodynamically stable enolate **K**. External protonation of enolate **K**, using an acid work-up gives the required β -keto ester **5** (in the absence of base).



Answer



[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

(e) Draw the major enol form of compound **5**.

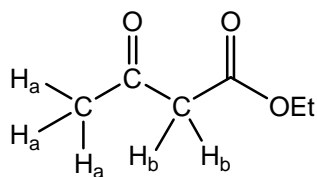
Strategy

Enols are unstable tautomers of carbonyl-containing molecules; their enol content is usually less than 1% due to the strength of their carbonyl (C=O) double bond in their keto-form (a ketone or an aldehyde). In order to form an enol, the carbonyl-containing molecule must have an alpha C(sp³)-H bond.

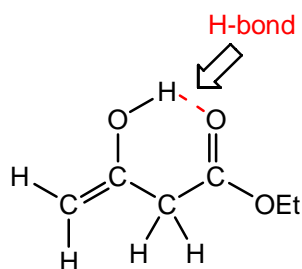
Draw out both molecules and include all alpha C(sp³)-H bonds. As enols are constitutional isomers of carbonyl-containing molecules, they can be easily drawn by replacing each H-C(sp³)-C=O unit for a C=C-OH unit. If there are two or more alpha C(sp³)-H bonds, draw out each enol separately and consider their stability. As enol formation is thermodynamically unfavoured, molecules that have two or more carbonyl groups you will only need to consider mono-enol formation.

Solution

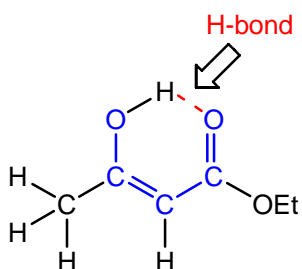
There are two chemically different alpha C(sp³)-H bonds, namely, H_a and H_b, which can lead to three potential enols **M** (derived from H_a) and, **N** and **O** (derived from H_b). The more substituted enols **N** and **O** are **more thermodynamically stable** than enol **M** due to conjugation (between their C=C and C=O bonds) and increased hyperconjugation from their neighbouring CH₃ groups. In all cases, intramolecular hydrogen bonding between the enolic OH group and the neighbouring carbonyl (C=O) bond helps to stabilise these enols. Enol **N** is slightly more stable than enol **O** as its remaining ester group is more stable; a carbonyl group of an ester is more stable than that of a ketone due to resonance stabilisation. The relative amount of these enols **N** and **O** (in a sample of this β-keto ester **5**) is *approximately* 50%. For further information about hyperconjugation; see p. 870 in *Chemistry*³.



β -keto ester **5**

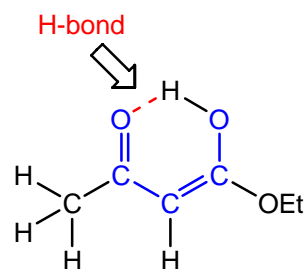


enol **M**



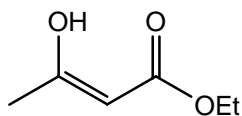
enol **N**

conjugation

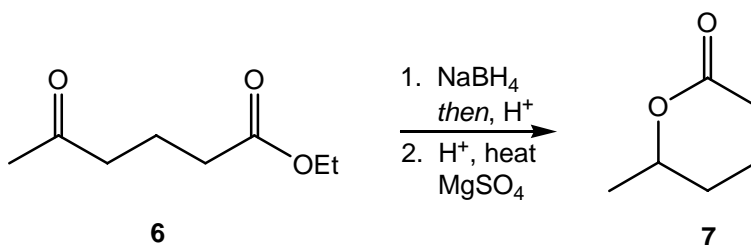


enol **O**

Answer



3. (a) The following queries relate to the formation of lactone **7** from keto-ester **6**.



- (i) Suggest a mechanism to explain the formation of **7**.

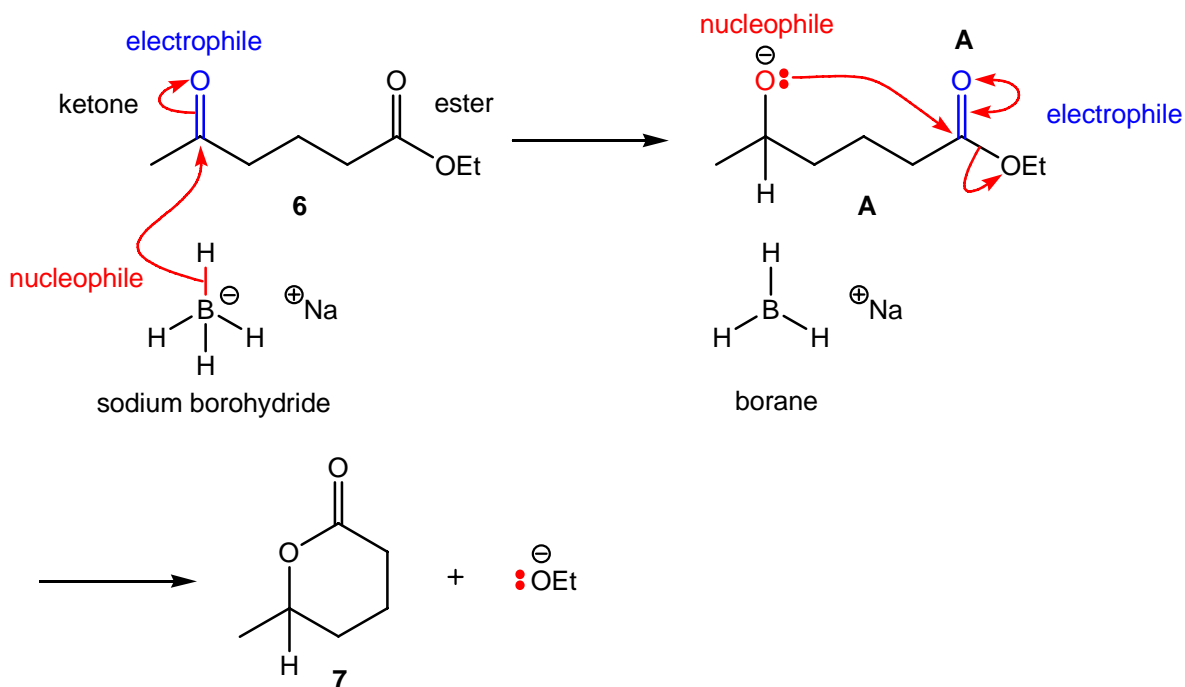
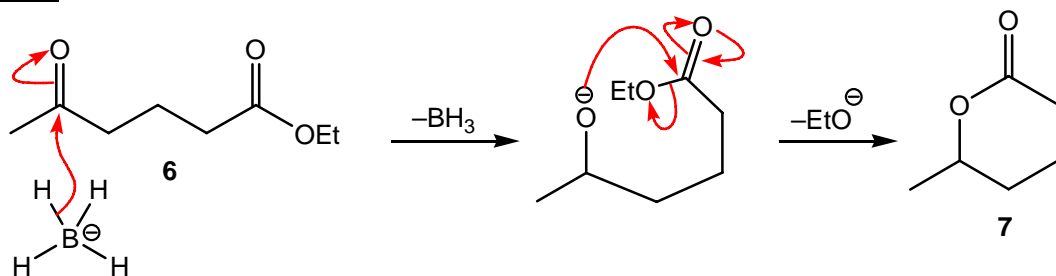
Strategy

For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

Solution

Sodium borohydride, NaBH_4 , is a nucleophilic hydride, H^- , equivalent. The α,ϵ -ketoester **6** is the electrophile in this reaction; the carbonyl ($\text{C}=\text{O}$) group of the ketone component is more electrophilic than its ester component.

Nucleophilic addition of hydride, H^- , from sodium borohydride (NaBH_4), using its nucleophilic H-B bond to the electrophilic carbonyl group of the ketone component of α,ϵ -ketoester **6**, followed by elimination of ethoxide (EtO^-) gives the required lactone **7**. Magnesium sulphate (MgSO_4) is used to remove traces of ethanol (EtOH) and water (H_2O) to promote the thermodynamic lactonisation. {This addition-elimination has been depicted using a double-headed curly arrow. If you are unsure about using this type of curly arrow, see p. 1095 in *Chemistry*³.}

Answer

- (a) (ii) Explain why the reaction of **1** with NaBH₄ is chemoselective.

Strategy

For this reaction to be chemoselective (or chemical selective), the reagent must be able to distinguish between different chemicals or functional groups through reactivity, and it must be selective; *i.e.*, **chemoselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

Solution

This carbonyl reduction is chemoselective as it occurs **ONLY** on the carbonyl (C=O) group of the ketone component of α,ϵ -ketoester **6** and **NOT** its ester component. This difference in reactivity is due to the relative stability of these carbonyl (C=O) containing functional

groups; a ketone is more reactive (less stable) and more electrophilic than an ester as it is NOT resonance stabilised. {For additional information on resonance stabilisation of esters, see p. 1096 in *Chemistry*³.}

Answer

NaBH₄ selectively reduces the C=O bond of the ketone because the carbonyl carbon atom of the ketone is a better electrophile than the carbonyl carbon atom of the ester. In the ester group, the positive mesomeric effect (+M) of the EtO group reduces the electrophilicity of the carbonyl carbon atom.

- (a) (iii) Give the structure of the organic product from reaction of **1** with LiAlH₄ then H⁺.

Strategy

Lithium aluminium hydride, LiAlH₄, is a nucleophilic hydride, H⁻, equivalent. The α,ϵ -ketoester **6** is the electrophile in this reaction; the carbonyl (C=O) group of the ketone component is more electrophilic than the ester component.

LiAlH₄ has higher ground-state energy than NaBH₄, and is therefore more reactive and nucleophilic. It is primarily used to reduce less electrophilic carbonyl (C=O) groups, such as esters and amides, in which NaBH₄ fails.

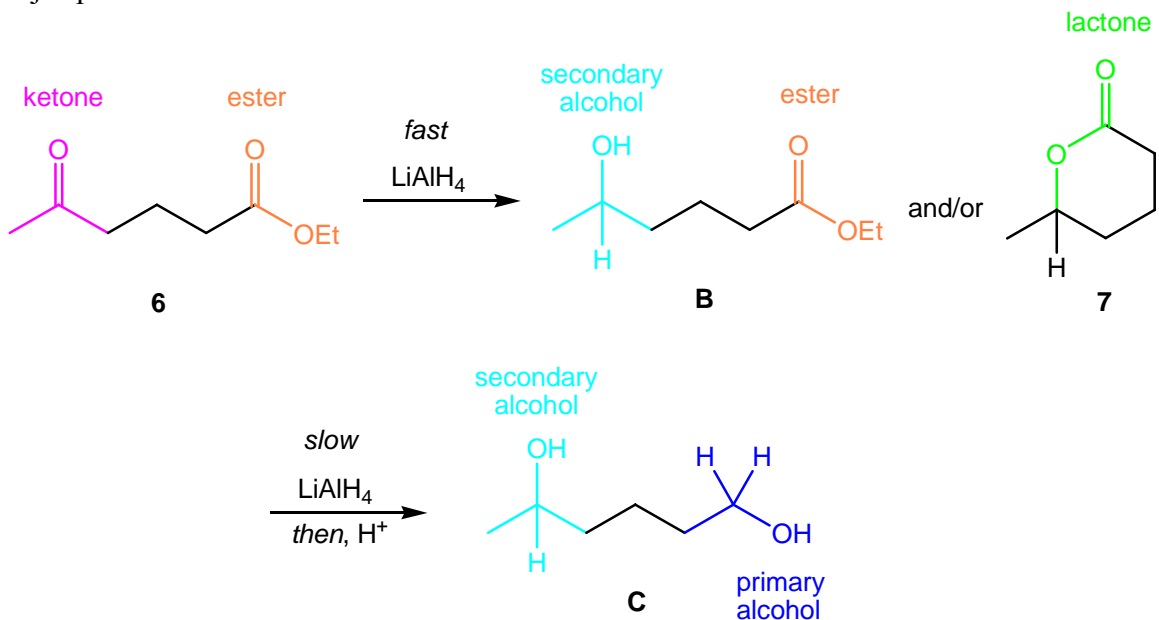
Draw the structure of the product derived from the reduction of both carbonyl (C=O) group of α,ϵ -ketoester **6**.

Solution

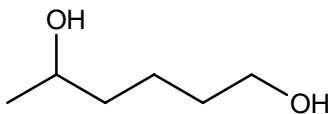
Reduction of the more electrophilic ketone component of the α,ϵ -ketoester **6**, using LiAlH₄, leads to the secondary alcohol **B**. This chemoselective reduction is faster than the corresponding reduction of the ester component. However, this intermediate secondary alcohol, in **B**, has the potential to cyclise to form the corresponding lactone **7**.

Using an excess of LiAlH₄, the carbonyl (C=O) groups of the ester (in **B**) and/or the lactone **7** are reduced to give the corresponding primary alcohol (in **C**).

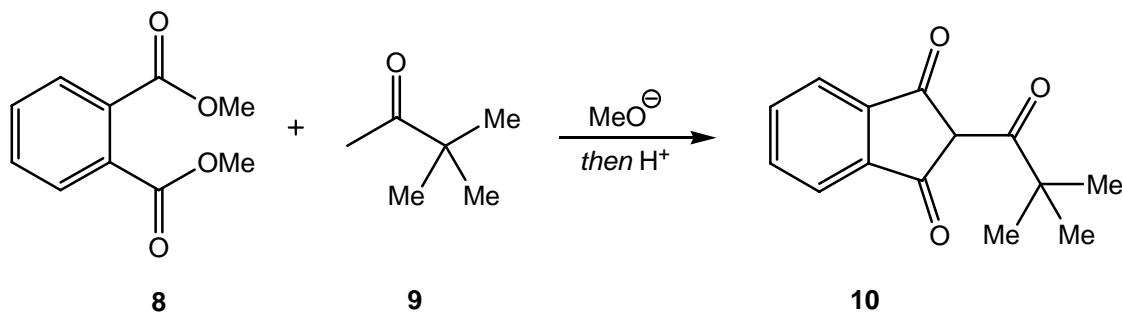
Reduction of the α,ϵ -ketoester **6**, using an excess of LiAlH_4 , gives the 1,5-diol **C** as the major product.



Answer



(b) The following queries relate to the formation of compound **10**.



(i) Suggest a mechanism to explain the formation of **10**.

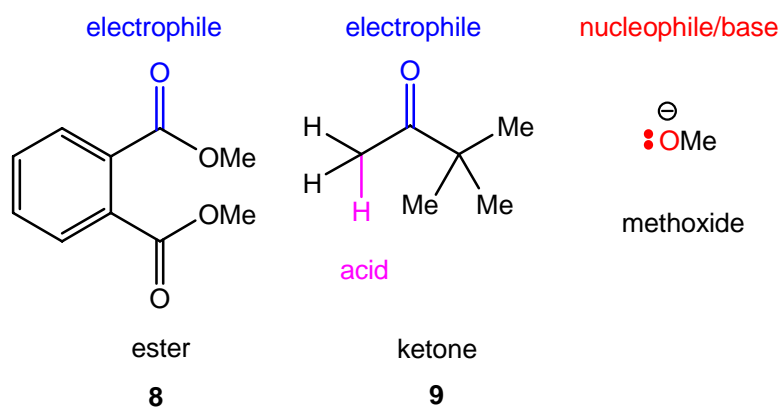
Strategy

For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base

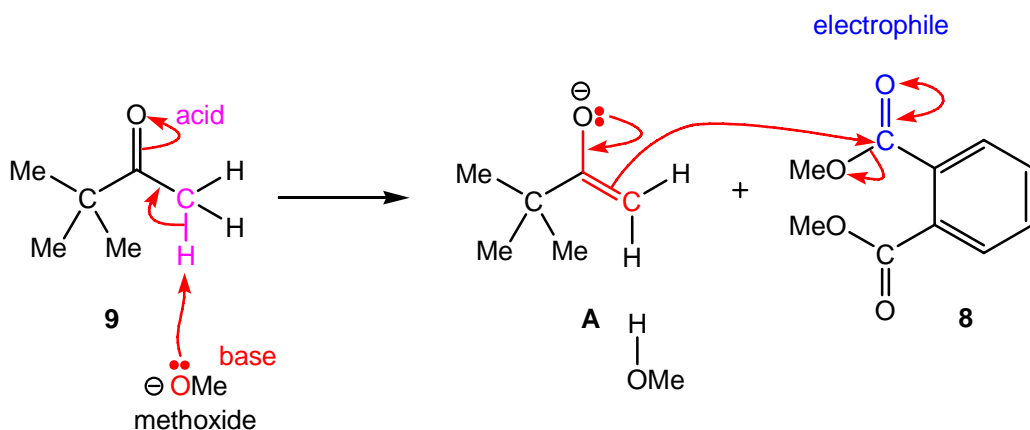
processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

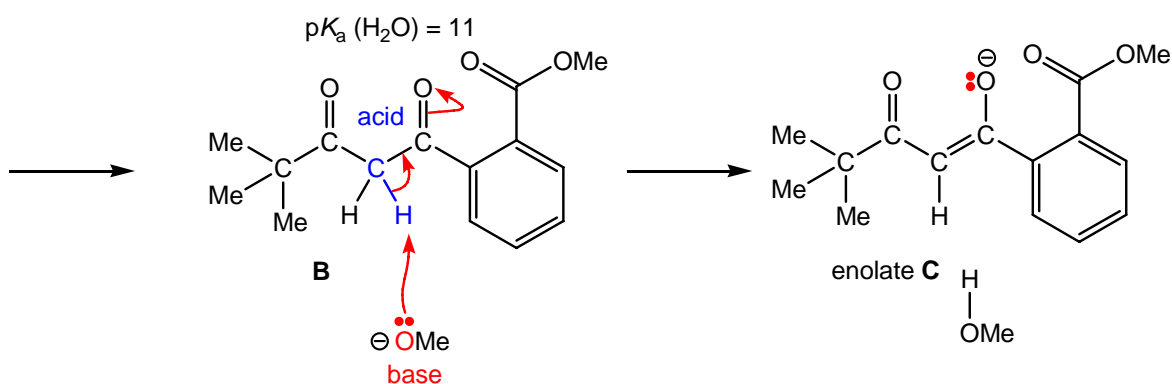
Solution

By examining the reagents, the ester **8** is an electrophile, ketone **9** is either an electrophile or an acid, and methoxide, MeO^- , is either a nucleophile or a base. However, methoxide, MeO^- , must be the active component of this mixture, and it has to initially act as a base (as nucleophilic additions to either **8** or **9** are not product determining steps).

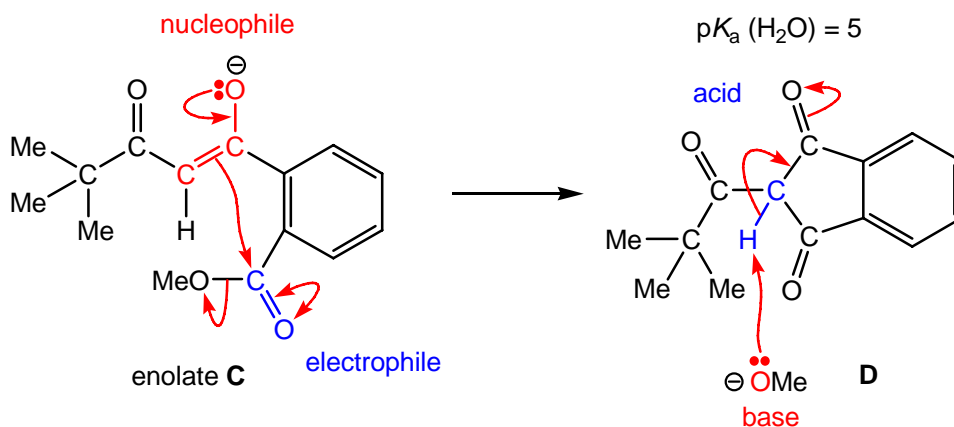


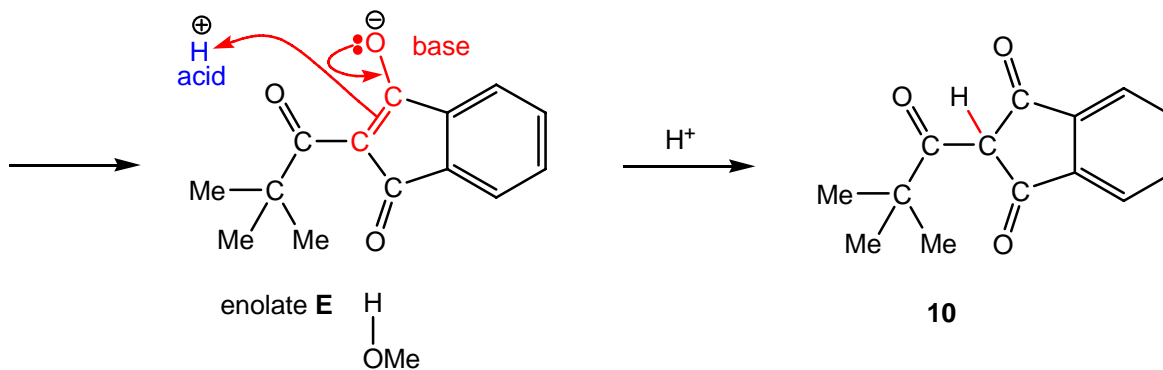
Deprotonation of ketone **9** [$\text{p}K_{\text{a}}(\text{H}_2\text{O}) = 20$] with methoxide, MeO^- , as the Brønsted base, gives the thermodynamically less stable enolate **A** and methanol [$\text{p}K_{\text{a}}(\text{H}_2\text{O}) = 16$].



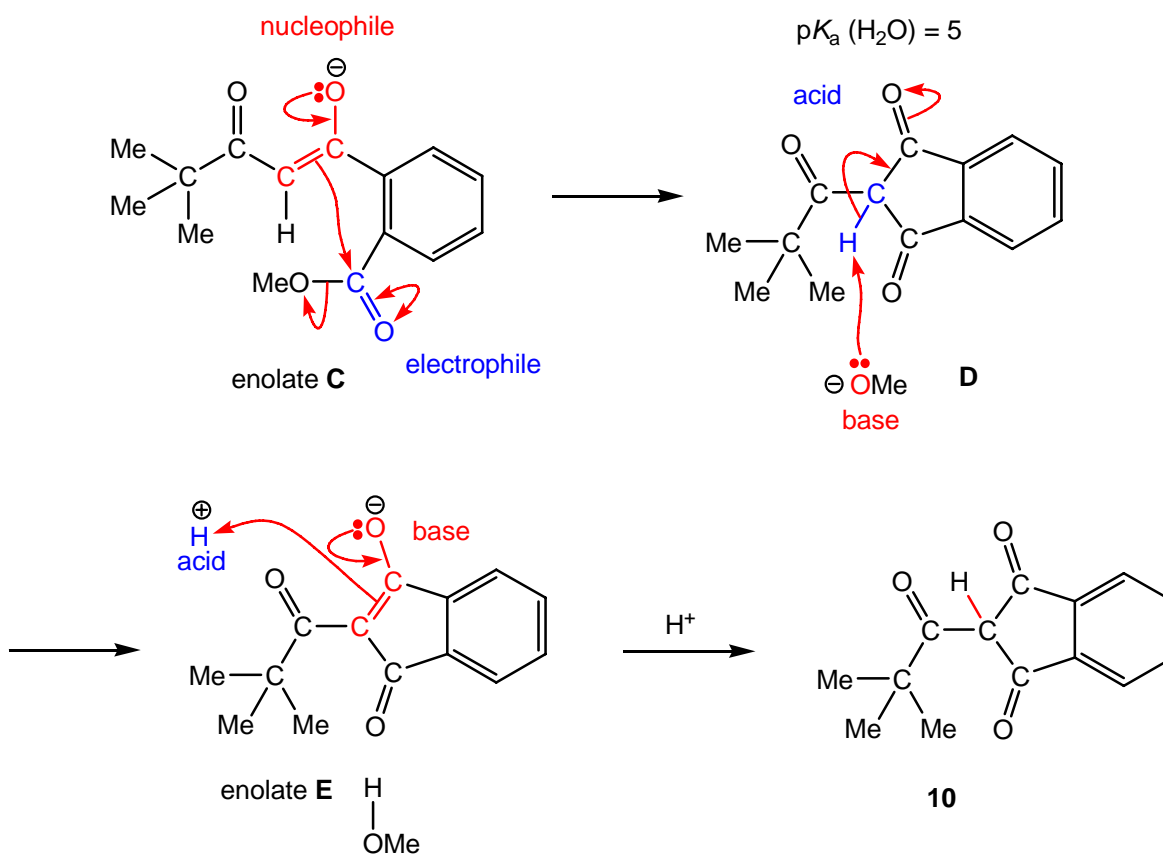


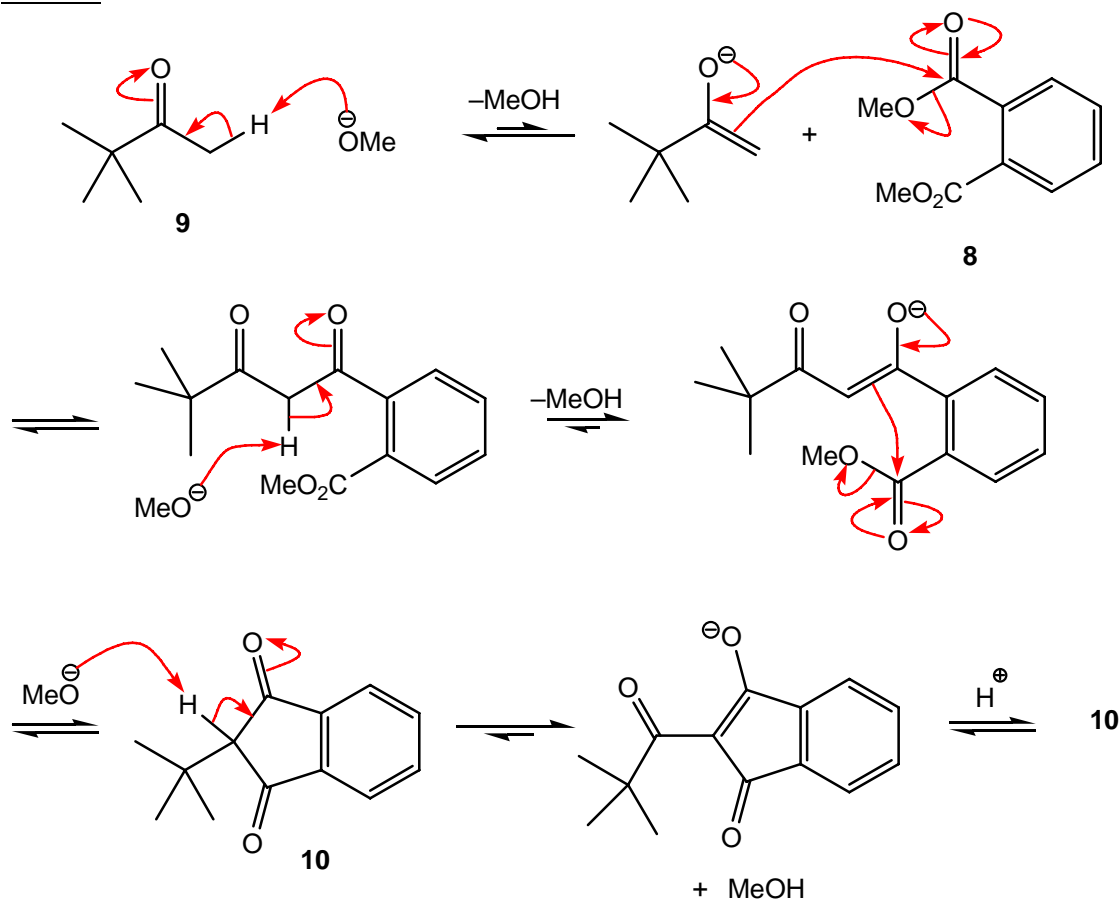
The product triketone, **10**, is derived from the addition of this enolate **A** to the diester **8**. Nucleophilic addition of this enolate **A** to one of the two electrophilic carbonyl ($\text{C}=\text{O}$) groups of the diester **8**, followed by elimination of methoxide, MeO^- , leads to the intermediate β -ketoester **B**. {This addition-elimination has been depicted using a double-headed curly arrow. If you are unsure about using this type of curly arrow, see p. 1095 in *Chemistry*³.} **However**, this intermediate **B** [$pK_a(\text{H}_2\text{O}) = 11$] is more acidic than both methanol [$pK_a(\text{H}_2\text{O}) = 16$] and the original ketone **9** [$pK_a(\text{H}_2\text{O}) = 20$]; deprotonation of intermediate **B** using methoxide, MeO^- , as the Brønsted base leads to **more** thermodynamically stable enolate **C**.





Intramolecular nucleophilic addition of this enolate, in **C**, to the electrophilic ester, followed by elimination of methoxide, MeO^- , leads to the intermediate triketone **D**. **However**, this intermediate **D** [$\text{p}K_{\text{a}}(\text{H}_2\text{O}) = 5$] is acidic and subsequent deprotonation with methoxide, MeO^- , as the Brønsted base leads to the **most** thermodynamically stable enolate **E**. External protonation of this enolate, **E**, using an acid work-up gives the required triester **10** (in the absence of base).



Answer

[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

(b) (ii) Draw two different enol forms of compound **5**.

Strategy

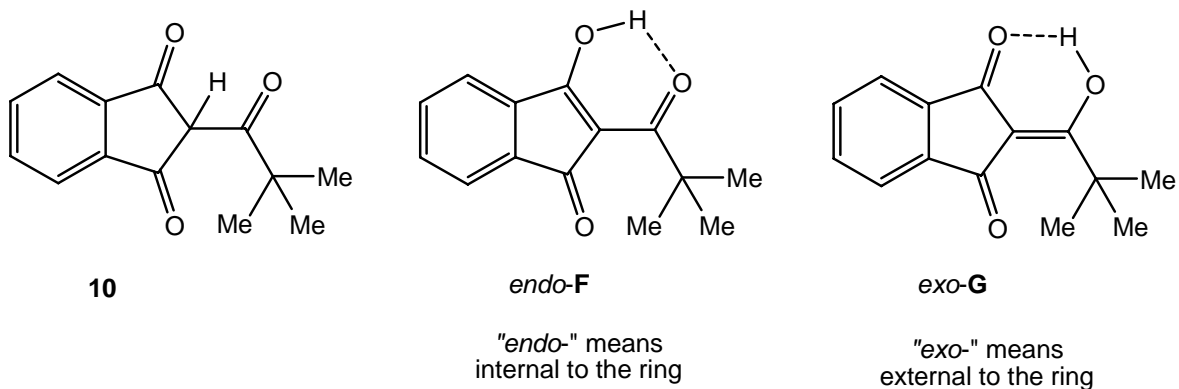
Enols are unstable tautomers of carbonyl-containing molecules; their enol content is usually less than 1% due to the strength of their carbonyl ($\text{C}=\text{O}$) double bond in their keto-form (a ketone or an aldehyde). In order to form an enol, the carbonyl-containing molecule must have an α $\text{C}(\text{sp}^3)\text{-H}$ bond.

Draw out both molecules and include all α $\text{C}(\text{sp}^3)\text{-H}$ bonds. As enols are constitutional isomers of carbonyl containing molecules, they can be easily drawn by replacing each

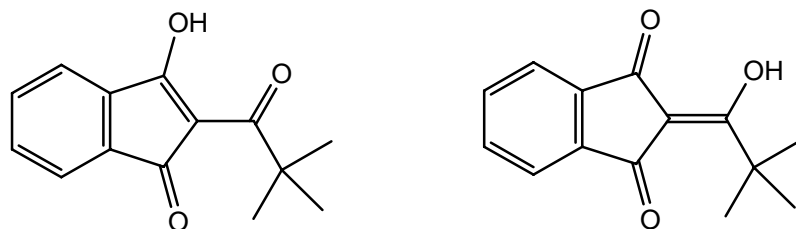
H-C(sp^3)-C=O unit for a C=C-OH unit. If there are two or more alpha C(sp^3)-H bonds, draw out each enol separately and consider their stability. As enol formation is thermodynamically unfavoured, molecules that have two or more carbonyl groups you will only need to consider mono-enol formation.

Solution

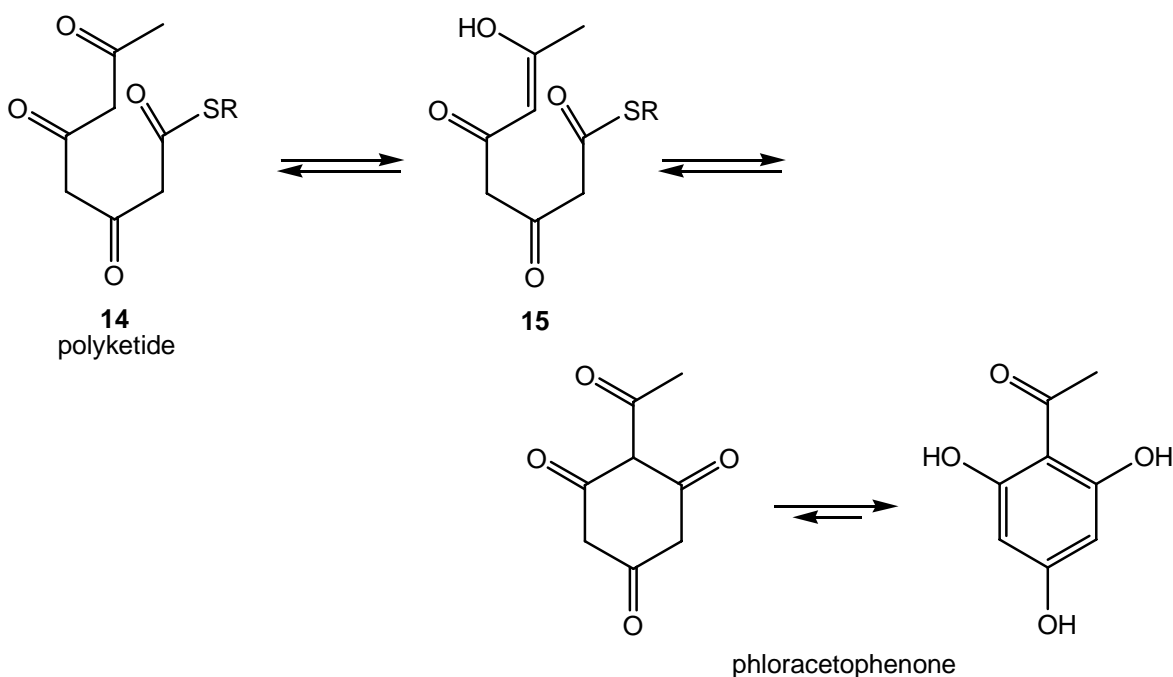
There is ONLY one alpha C(sp^3)-H bond within the triester **10**; however, this can lead to TWO different enols, *endo-F* and *exo-G*. Both are equally favoured.



Answer



5. In nature, aromatic compounds are formed by the cyclization of polyketide chains (containing alternating C=O and CH₂ groups) in the presence of enzymes. The polyketide chains have a thioester group (RCOSR) at the end of the chain, which, like esters, react in Claisen-type reactions. For example, thioester **1** is converted into phloracetophenone. Phloracetophenone, obtained from the plant *Curcuma comosa*, has been shown to lower cholesterol levels in animals.



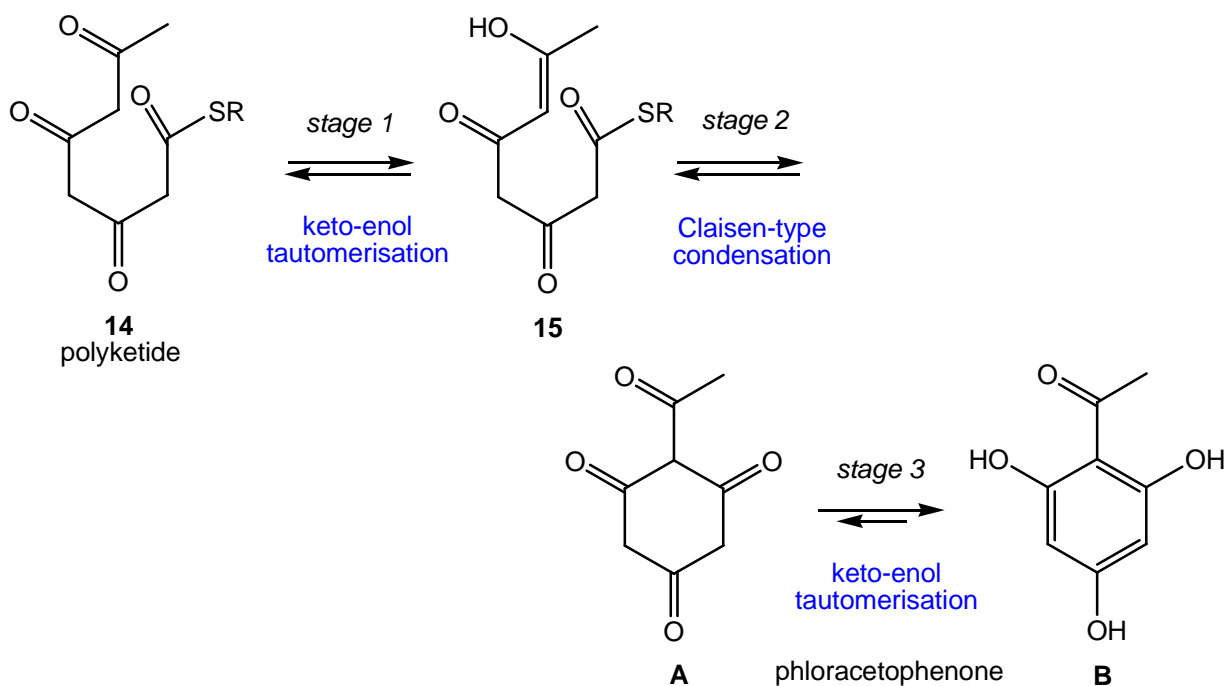
- (a) Propose a mechanism that explains how compound **2** is converted into phloracetophenone.

Strategy

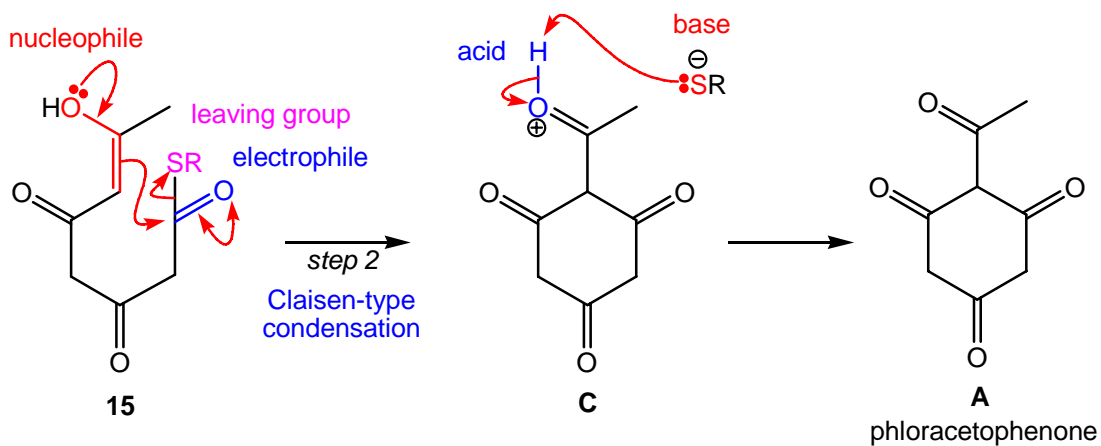
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

Solution

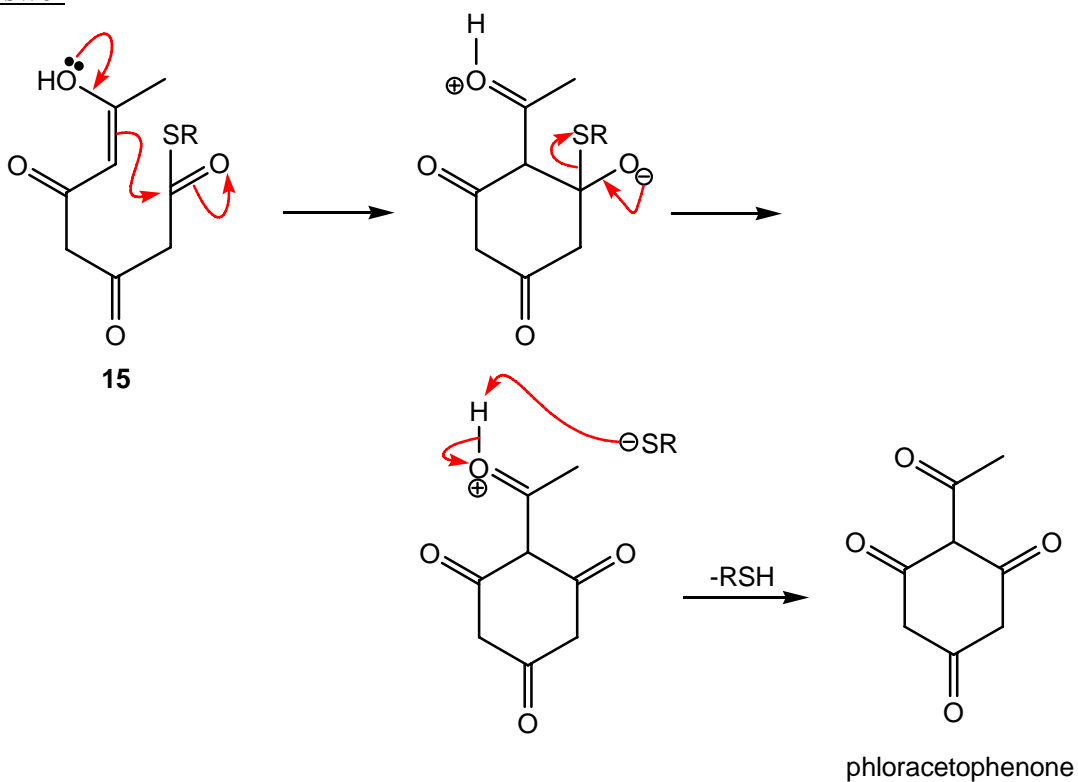
This sequence of reactions consists of three stages. Stage 1 (**14**→**15**) involves classical keto-enol tautomerisation; stage 2 (**15**→**A**) involves a Claisen-type condensation; and stage 3 (**A**→**B**) involves keto-enol tautomerisation. The enol tautomer of phloracetophenone **B** is more thermodynamically stable than its keto tautomer **A**.



Nucleophilic addition of the conjugated enol to the electrophilic carbonyl (C=O) group of the thioester, **15**, followed by elimination of thiolate, RS^- , leads to the intermediate oxonium ion, **C**. {This addition-elimination has been depicted using a double-headed curly arrow. If you are unsure about using this type of curly arrow, see p. 1095 in *Chemistry*³.} Deprotonation of oxonium ion **C** using the basic thiolate, RS^- , gives the keto-tautomer of phloracetophenone **A**. For further information about Claisen reactions, see p. 1121 in *Chemistry*³.

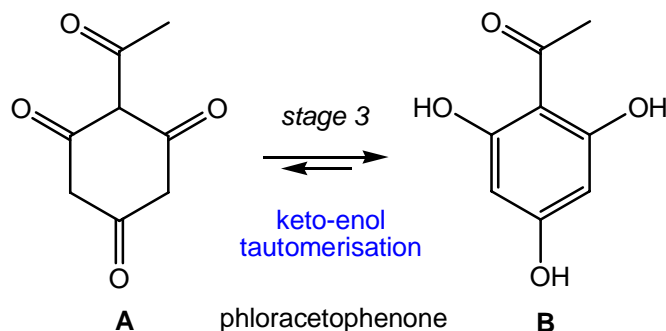


Answer



[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

- (b) For phloracetophenone, explain why the position of the equilibrium lies heavily to the right.



Strategy

Stage 3 (**A**→**B**) of this reaction sequence involves keto-enol tautomerisation. The enol tautomer of phloracetophenone **B** is **more thermodynamically stable** than its keto-tautomer **A**. Account for this stability.

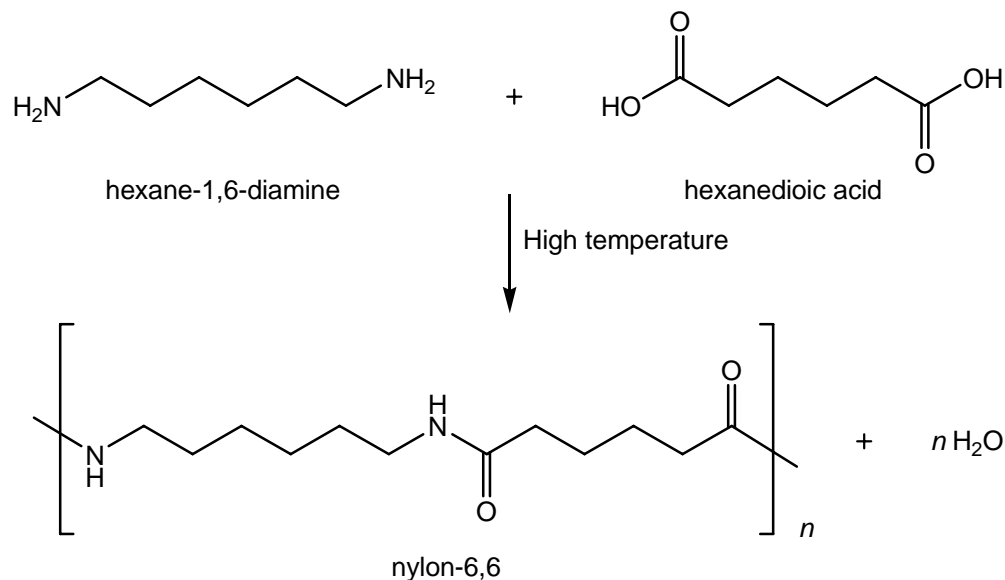
Solution

Enol-tautomer **B** is aromatic, and is more stable than its non-aromatic keto-tautomer **A**. This electronic stability is due to the cyclic and planar nature of the substituted benzene ring which contains 6- π electrons with non-interrupted (continuous) conjugation.

Answer

Enolisation of the three C=O bonds produces a stable aromatic ring.

2. Nylon-6,6 is a synthetic polyamide. It is formed by heating hexane-1,6-diamine with hexanedioic acid in a condensation polymerization reaction.



- (a) Why is the formation of nylon-6,6 called a *condensation* polymerization?

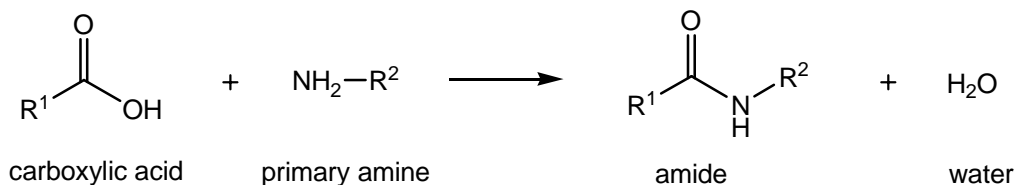
Strategy

A condensation reaction involves the addition of two or more molecules to give one or more products and **water** as the **byproduct**.

Examine the above reaction, and deduce if water (H_2O) is produced.

Solution

Nylon-6,6 involves sequential amide bond formation, by condensing a primary amine with a carboxylic acid. The byproduct of this process is water (H_2O). As both starting materials contain two identical functional groups [di-amines (in hexane-1,6-diamine) and di-carboxylic acids (in hexanedioic acid)], therefore polymerisation will occur.



Answer

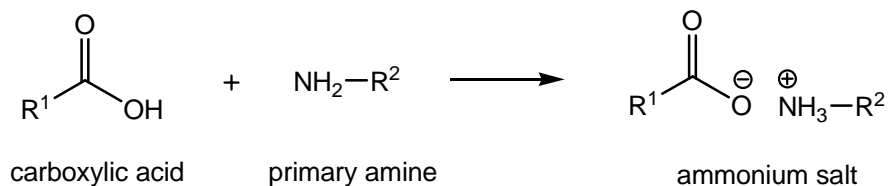
Two molecules of the monomer combine with the elimination of a molecule of water.

- (b) Why does the formation of nylon-6,6 from hexane-1,6-diamine and hexanedioic acid require heating?

Strategy

Condensation reactions require heat to remove the byproduct, water (H₂O), from the reaction vessel in order to drive the equilibrium over.

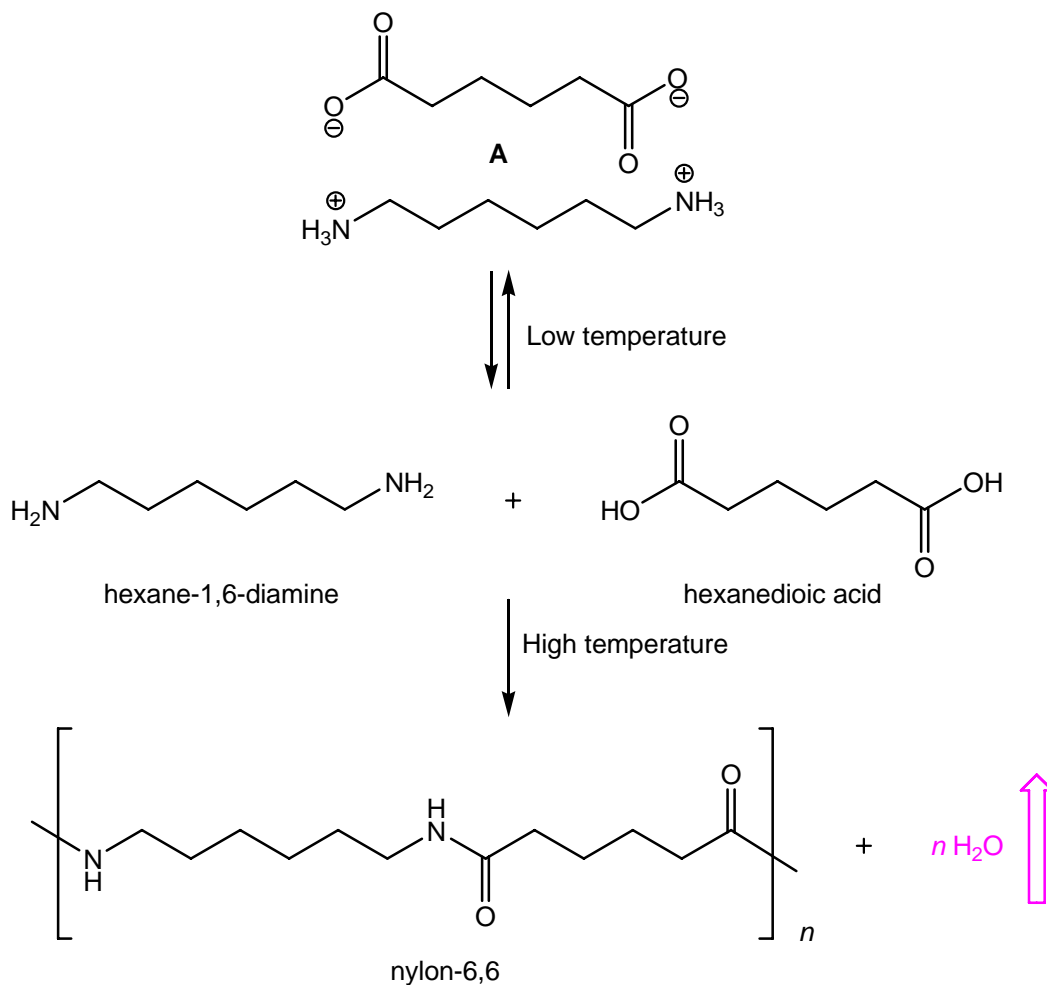
Addition of an amine (base) to a carboxylic acid (acid) will form a more stable ammonium salt.

Solution

Addition of hexane-1,6-diamine to hexanedioic acid [$\text{p}K_{\text{a}}(\text{H}_2\text{O}) = 5$], gives the more stable diammonium salt **A** [$\text{p}K_{\text{a}}(\text{H}_2\text{O}) = 9$].

At low temperature, the equilibrium favours formation of the ammonium salt **A**. However, at high temperature, this proton exchange is reversible.

Formation of nylon-6,6 occurs by nucleophilic addition of the diamine, hexane-1,6-diamine, to the electrophilic dicarboxylic acid, hexanedioic acid, followed by elimination of water (H₂O). This process is unfavourable. However, by continually removing the byproduct, water (H₂O), from this equilibrium, through heating to >100°C forces this water to evaporate, and therefore drives the equilibrium towards the required product, nylon-6,6.



Answer

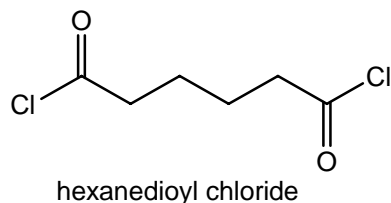
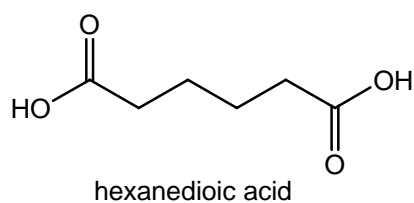
At room temperature, the amine and carboxylic acid react to form a salt, not an amide bond.

- (c) If hexanedioic acid is replaced by hexanedioyl dichloride, then reaction with hexane-1,6-diamine forms nylon-6,6 at room temperature. Why does the polymerization using hexanedioyl dichloride take place under milder reaction conditions?

Strategy

The rate-limiting step for amide formation is the nucleophilic addition of the amine to the electrophilic carboxylic acid derivative. For both reactions outlined above, the nucleophile,

hexane-1,6-diamine, is the same. This reaction appears to be faster for the more electrophilic hexanedioyl dichloride.

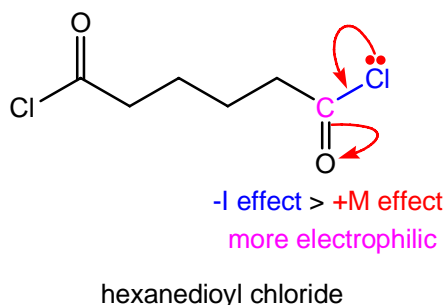
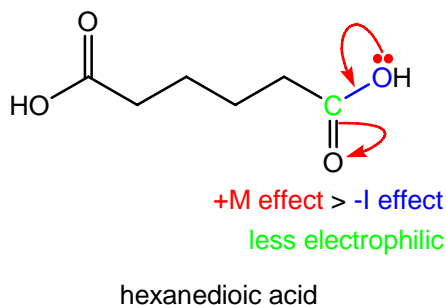


Draw out the reagents, hexanedioyl dichloride and hexanedioic acid, and account for their relative electrophilicity.

Solution

Hexanedioyl chloride is a better electrophile than hexanedioic acid for this condensation reaction as its chlorine (-Cl) atom is strongly electron-withdrawing (-I effect > +M effect). The non-bonded pairs of electrons on this chlorine atom are poorly electron-donating [into the carbonyl (C=O) group of hexanedioyl chloride] due to poor $3p(\text{Cl})-2p(\text{C})$ orbital overlap. The electronegativity of this chlorine atom is responsible for the overall electrophilicity of this acid chloride.

Even though the oxygen atom in hexanedioic acid is more electronegative than the chlorine atom in hexanedioyl chloride, hexanedioic acid is **less electrophilic** than hexanedioyl chloride. This is due to better quality orbital overlap of a non-bonded pair of electrons on the oxygen atom with its neighbouring carbonyl (C=O) group; $2p(\text{O})-2p(\text{C})$ orbital overlap in hexanedioic acid is better quality than $3p(\text{Cl})-2p(\text{C})$ orbital overlap in hexanedioyl chloride.

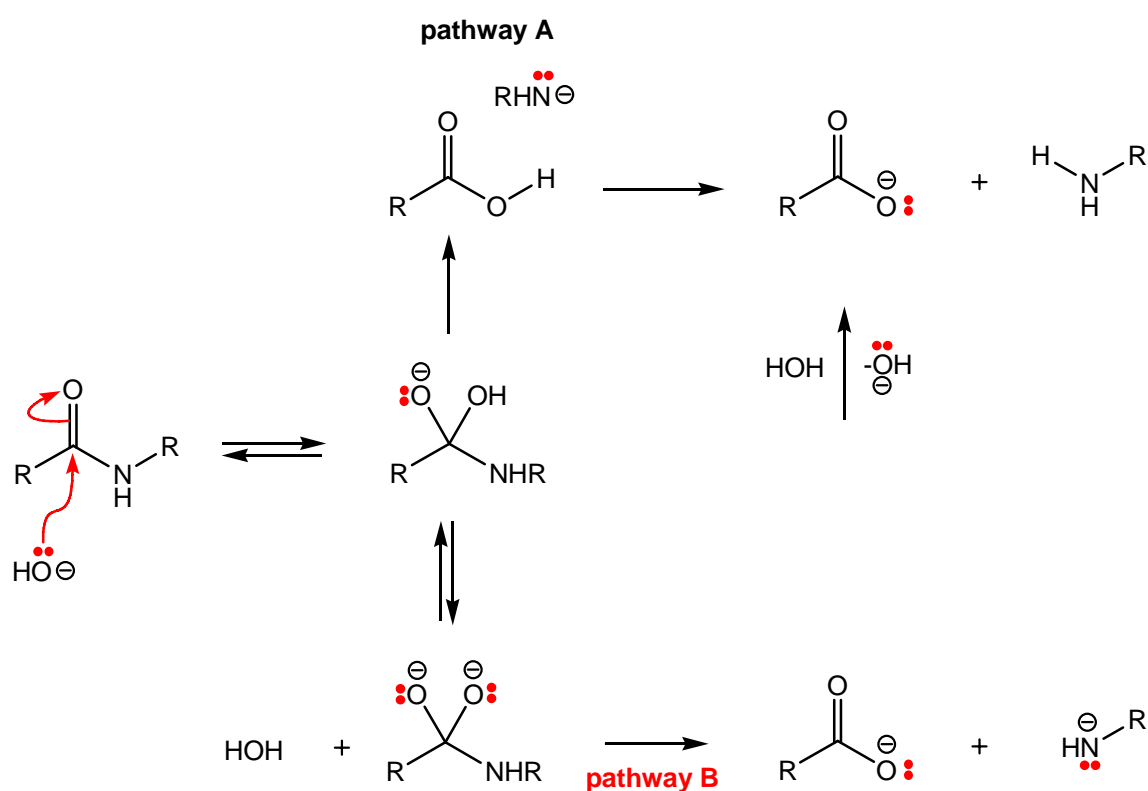


Nucleophilic addition of hexane-1,6-diamine, to the more electrophilic hexanedioyl chloride is preferred, and therefore this reaction will proceed faster at a lower temperature.

Answer

Acyl chlorides have a particularly electrophilic carbon atom and react rapidly with amines in nucleophilic acyl substitution reactions.

- (c) Nylon-6,6 is recycled by hydrolyzing all of the amide bonds to reform the monomers, and then re-polymerizing. Hydrolysis of amide bonds under basic conditions requires heating in a concentrated aqueous solution of hydroxide ion. As shown below, two reaction pathways are possible.



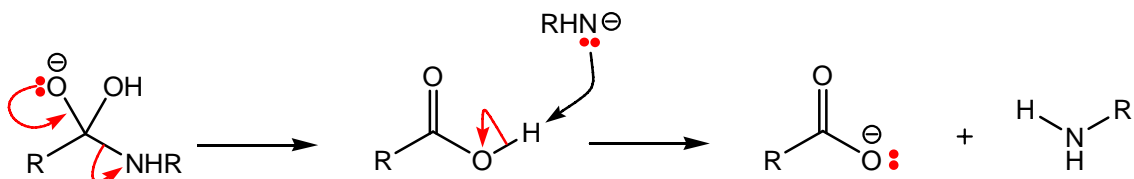
- (i) Use curly arrows to show the movement of electrons in paths **A** and **B**.

Strategy

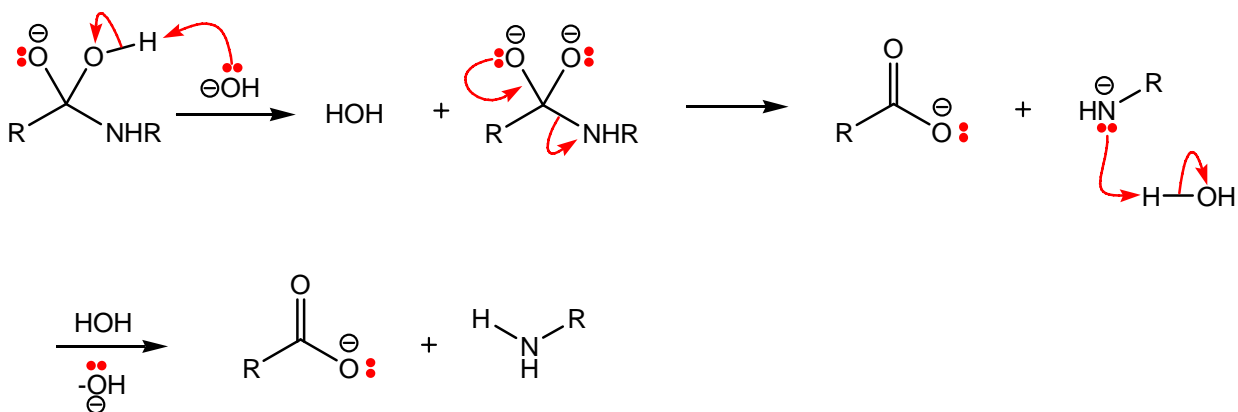
Copy out these pathways, and for each step within these mechanisms, you will need to draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow).

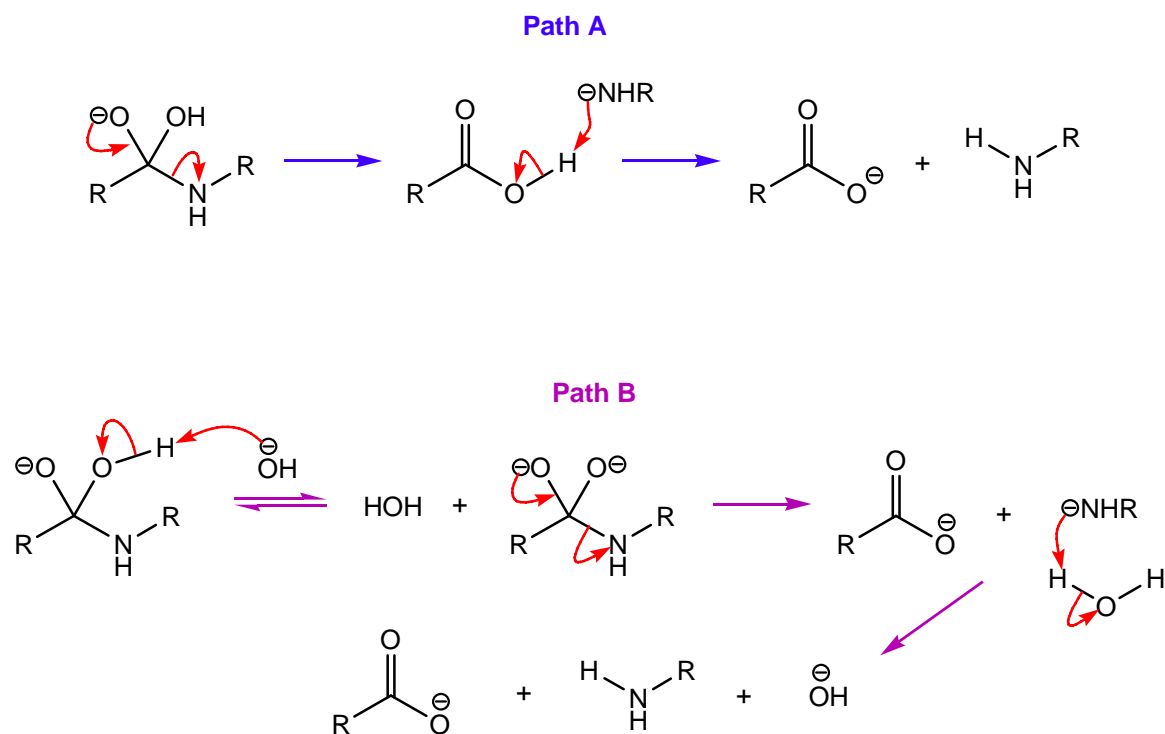
Solution

For pathway **A**: Lone-pair assisted elimination of the amide, RHN^- , using the non-bonded pair of electrons on the alkoxide, gives the intermediate carboxylic acid, RCO_2H . Deprotonation of this carboxylic acid, using the basic amide, RHN^- , gives the more stable carboxylate and primary amine, RNH_2 . The curly arrows for these processes are shown below.

pathway A

For pathway **B**: Deprotonation of the alcohol (OH) group using the non-bonded pair of electrons on the hydroxide (HO^-) leads to the intermediate di-anionic alkoxide. Lone-pair assisted elimination of the amide, RHN^- , using the non-bonded pair of electrons on the alkoxide, gives the intermediate carboxylate, RCO_2^- . Deprotonation of the byproduct, water (H_2O), using basic amide, RHN^- , gives the more stable hydroxide, HO^- , and primary amine, RNH_2 . The curly arrows for these processes are shown below.

pathway BAnswers



[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

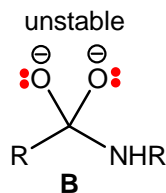
(d) (ii) Under what conditions would you expect **path B** be favoured over **path A**?

Strategy

For pathway **B** to occur, hydroxide, HO^- , is required (as shown in the original scheme).

Solution

Pathway **A** is the more favourable pathway, as it does not proceed *via* the unstable intermediate di-anionic alkoxide **B**. However, under very basic conditions (high pH), pathway **B** will become **more favoured**.



Answer

Path B will be favoured over path A when using a particularly high concentration of hydroxide ion.

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