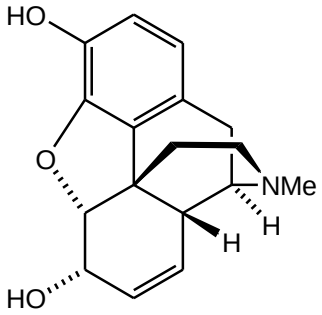
24

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

Answers to worked examples

WE 24.1 Esters from acyl chlorides (on p. 1112 in *Chemistry*^{3})

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



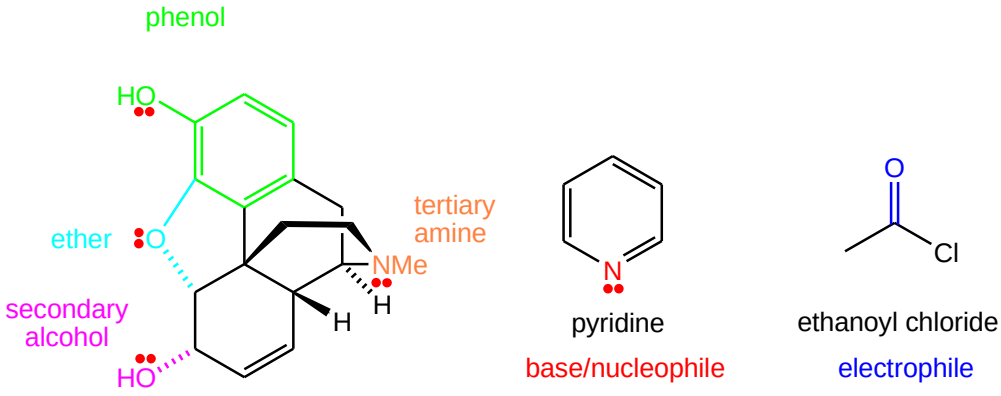
morphine

Strategy

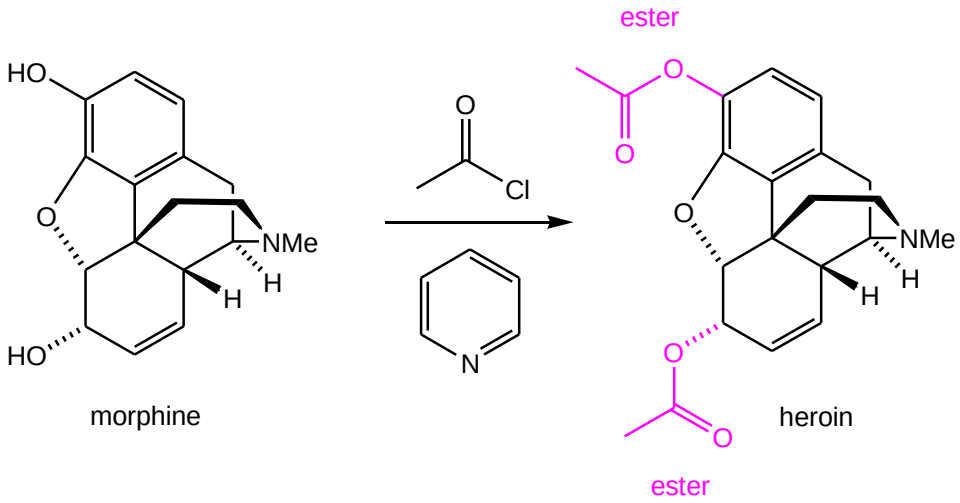
Draw out the structure of morphine and the reagents, ethanoyl chloride and pyridine, and name the functional groups present. Examine the reagents, deduce their relative reactivity, and draw out the resulting product.

Solution

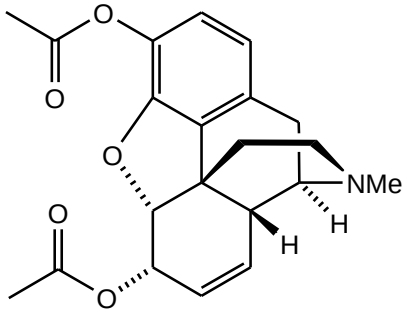
Morphine contains four heteroatom-based functional groups; the tertiary amine, phenol, secondary alcohol and ether. In all cases, these functional groups can act as a nucleophile or a base. The phenol and secondary alcohol can be easily functionalised as they both contain acidic O-H groups. Pyridine 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 an electrophile, whereas, pyridine acts a base and a nucleophile catalyst. These reactions involves 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.



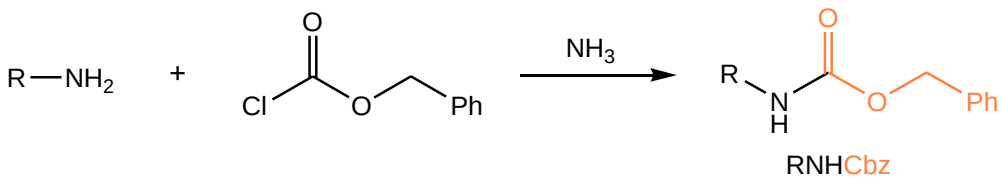
Answer



heroin (also called diacetylmorphine or diamorphine)

WE 24.2 Using an anhydride to protect amine groups (on p. 1117 in *Chemistry*[3])

Another common carbamate protecting group for amines is the carboxybenzyl (Cbz) group. The Cbz group is introduced by reaction of an amine with benzyl chloroformate ($PhCH_2OCOCl$) in the presence of a base (for example, Et_3N) as shown below. Propose a mechanism for this reaction.

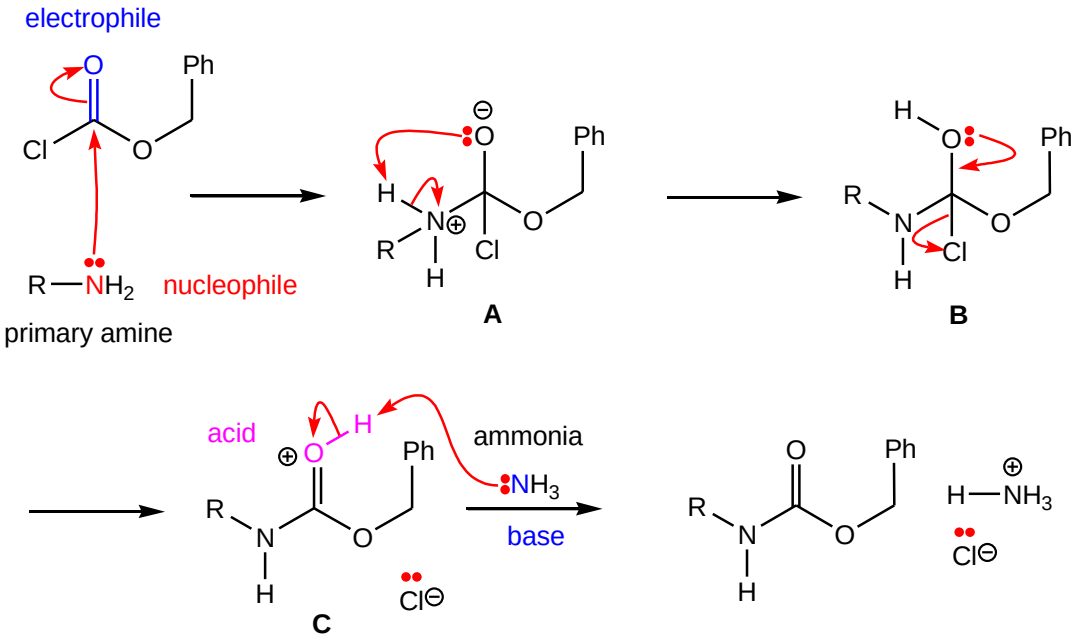


Strategy

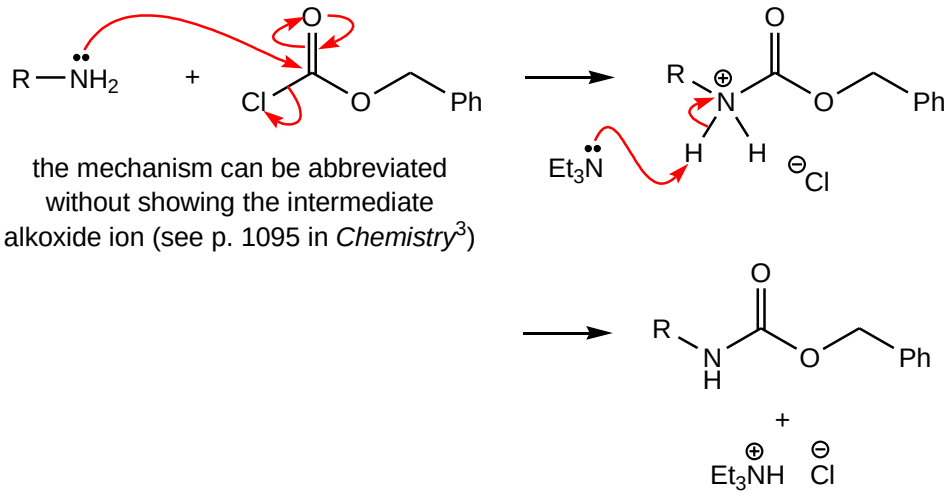
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

Nucleophilic addition of the primary amine, RNH_2, to the electrophilic carbonyl (C=O) group of benzyl chloroformate ($PhCH_2OCOCl$) leads to the tetrahedral zwitterion intermediate **A**. Internal proton exchange between the basic alkoxide and the acidic ammonium salt, in **A**, leads to the more stable hemi-aminal intermediate **B**. Lone-pair assisted elimination of chloride, Cl^-, using the non-bonded pair of electrons on the nitrogen atom of the aminal, in **B**, gives the intermediate oxonium ion **C**. Intermolecular proton exchange between this oxonium ion **C** and ammonia, NH_3, gives the required carbamate product.



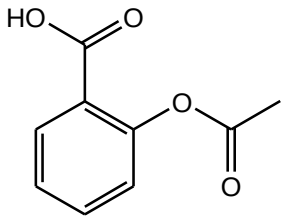
Answer



WE 24.3 Transesterification and aspirin (on p. 1122 in *Chemistry*^{3})

In your body, 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

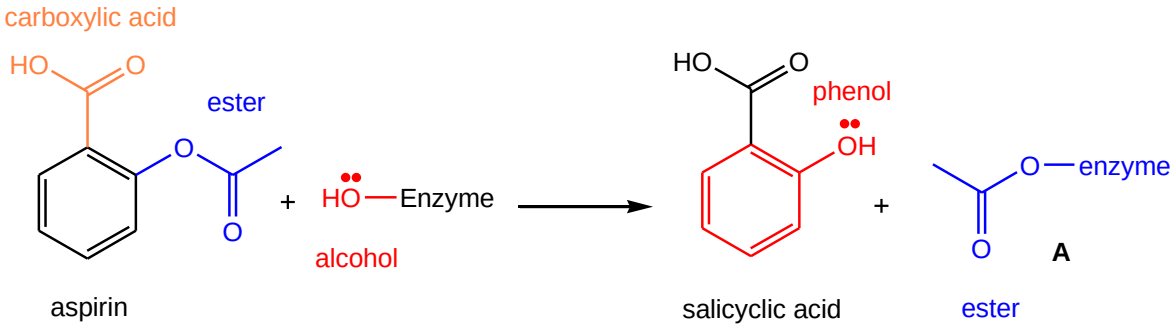
Strategy

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.

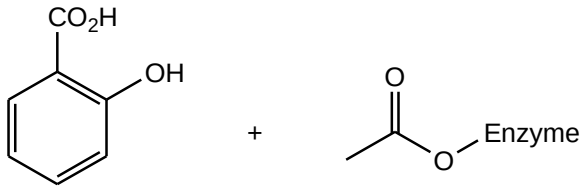
Solution

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, salicyclic acid and the enzyme-ester **A**.

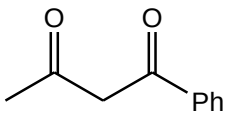


Answer



WE 24.4 Condensation reactions between an ester and a ketone (on p. 1131 in *Chemistry*[3])

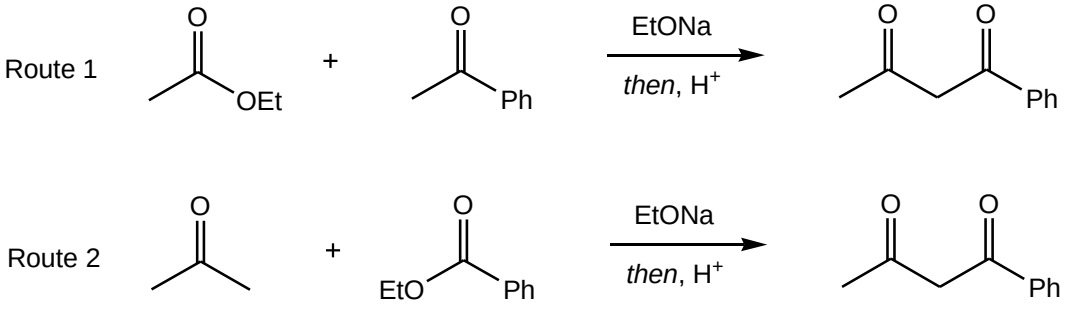
For both synthetic approaches shown in part (a) on p. 1125 in *Chemistry*[3]; describe the experimental conditions that would maximize the yield of 1-phenylbutane-1,3-dione.



1-phenylbutane-1,3-dione

Strategy

There are two synthetic routes described in part (a).



For route 1 - it is important that the enolate of $PhCOCH_3$ reacts with the less electrophilic carbonyl (C=O) group of ethyl actetate (CH_3CO_2Et).
For route 2 – acetone (CH_3COCH_3) is only one enolisable carbonyl component. However, it is also important that the enolate of CH_3COCH_3 reacts with the less electrophilic carbonyl (C=O) group of ethyl benzoate ($PhCO_2Et$).

As sodium ethoxide is a mild base (pK_a of EtOH = 16), the amount of enolate present is small; <1% for ketones; pK_a (ketone) = 20.

Solution

For route 1. To ensure the enolate ion ($PhCOCH_2^-$) reacts with the less electrophilic carbonyl (C=O) group of the ester, CH_3CO_2Et. Slow addition of a mixture of sodium ethoxide and $PhCOCH_3$ in ethanol, to a solution of ethyl acetate (CH_3CO_2Et) in ethanol is required. This is to maximise the Claisen condensation and minimise the aldol condensation.
For route 2. To ensure the enolate ion ($CH_3COCH_2^-$) reacts with the less electrophilic carbonyl (C=O) group of the ester, $PhCO_2Et$. Slow addition of a mixture of sodium ethoxide and CH_3COCH_3 in ethanol, to a solution of ethyl benzoate ($PhCO_2Et$) in ethanol is required. This is to maximise the Claisen condensation and minimise the aldol condensation.

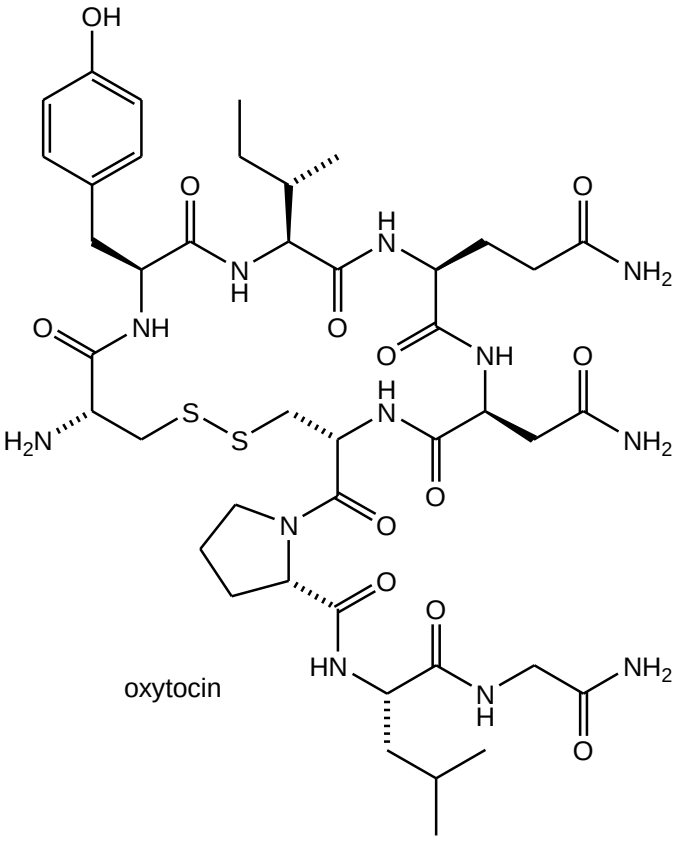
Answer

Using route 1: Slow addition of a mixture of ethoxide ion and $PhCOCH_3$ ensures that $PhCOCH_3$ is selectively deprotonated, to give an enolate ion ($PhCOCH_2^-$) which reacts with $MeCO_2Et$.
Using route 2: Slow addition of a mixture of ethoxide ion and CH_3COCH_3 ensures that CH_3COCH_3 is selectively deprotonated, to give an enolate ion ($CH_3COCH_2^-$) which reacts with $PhCO_2Et$.

Answers to boxes

Box 24.1 Oxytocin, the hormone of love (on p. 1100 in *Chemistry*^{3})

Amino acids links together to form peptides (see box 2.9 in p. 104 in *Chemistry*^{3}). Draw the structures of the eight amino acids that, when linked together with $H_2NCH_2CONH_2$, form oxytocin. (Assume the S–S bond is not formed at this stage).



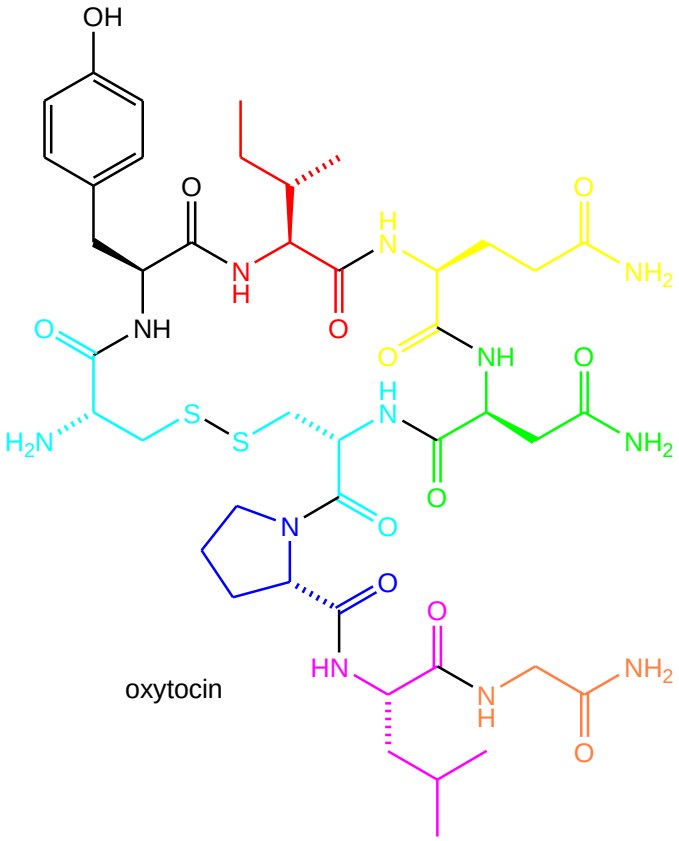
oxytocin

Strategy

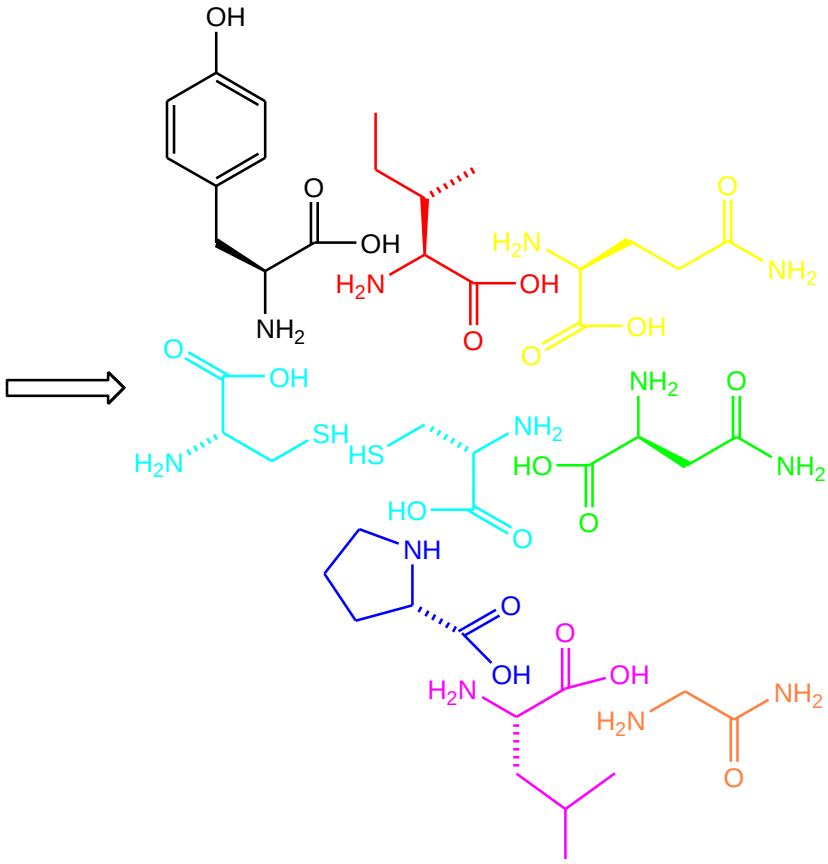
Locate and highlight the eight amino acid derived peptides, -NH-CHR-C=O-, embedded in the structure of oxytocin. Remember these are peptides and not amino acids. To convert them back into their parent amino acid; the amide bond, –NH-C=O-, needs to be broken and hydrated to give the corresponding amino group, $-NH_2$, and the carboxylic acid, $-CO_2H$. In addition, the disulfide bond, -S-S-, has to be reduced to give the two corresponding thiol bonds, -SH and –SH.

Solution

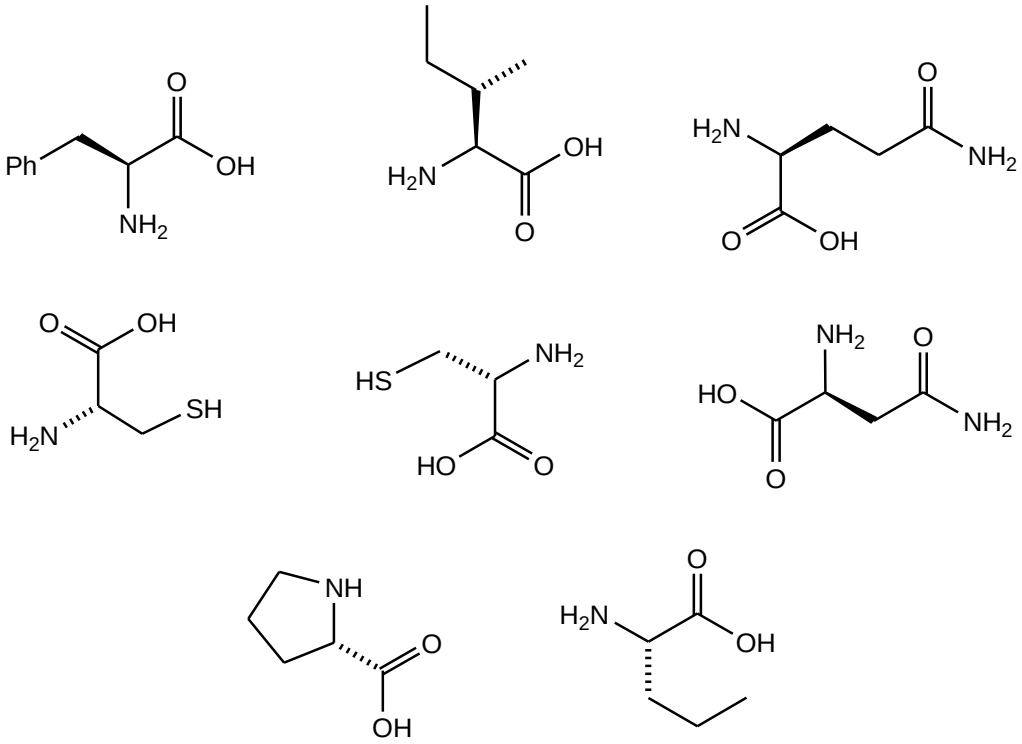
There are NINE amino acid peptides in oxytocin. Fragmentation and hydration of the amide bonds, reveals eight different amino acids; all are chiral with the exception of glycine, $NH_2CH_2CO_2H$. The only amino acid which appears twice in oxytocin is cysteine, $NH_2CH(CH_2SH)CO_2H$. The structures of all theses amino acids, which make up the structure of oxytocin, are shown below.



oxytocin

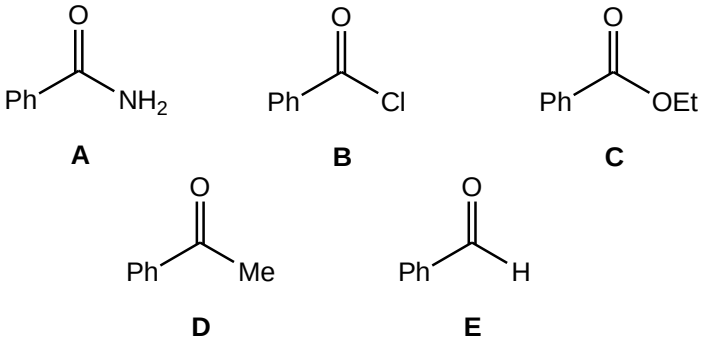


Answer



Box 24.2 Relative reactivity of carboxylic acid derivatives (on p. 1103 in *Chemistry*^{3})

Place the five carbonyl compounds **A**–**E** in decreasing order of reactivity towards nucleophilic attack.



Strategy

In this process, the carbonyl (C=O) groups of compounds **A**-**E** are the electrophiles. The more electrophilic they are, the more susceptible they will be to nucleophilic addition.

As all these compounds, **A**-**E**, contain a Ph-C=O group; their relative electrophilicity will be controlled by the $-NH_2$ group (in **A**), -Cl group (in **B**), -OEt group (in **C**), -Me group (in **D**) and the H atom (in **E**).

The most electrophilic compound will contain the most electron-withdrawing substituent; work out the strength of these electron-withdrawing (or donating) substituents.

Solution

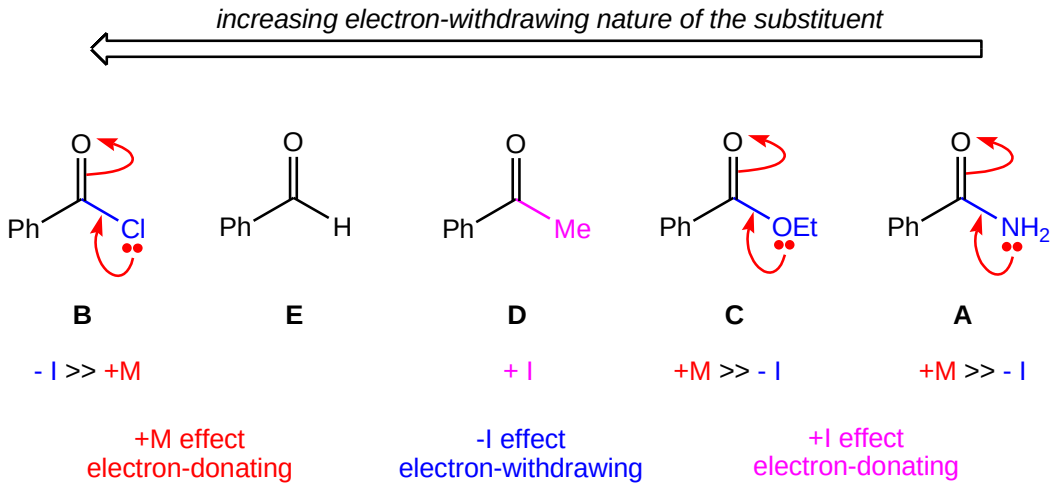
Let's first consider the amino-, ester and chloro substituents, in **A**-**C**, which contain non-bonded electrons.

Compound **A** is an amide; this will be the least electrophilic compound as its amino- ($-NH_2$) group is strongly electron-donating (+M effect > -I effect). The non-bonded pair of electrons on the nitrogen atom of this amino group ($-NH_2$) is significantly more electron-donating [into the carbonyl (C=O) group of the amide **A**], than the electron-withdrawing nature of its nitrogen atom due to its electronegativity.

Compound **B** is an acid chloride; this will be the most electrophilic compound as the 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 the acid chloride **A**] due to poor 3*p*(Cl)-2*p*(C) orbital overlap.

The electronegativity of this chlorine atom is responsible for the overall electron-withdrawing nature of this atom.

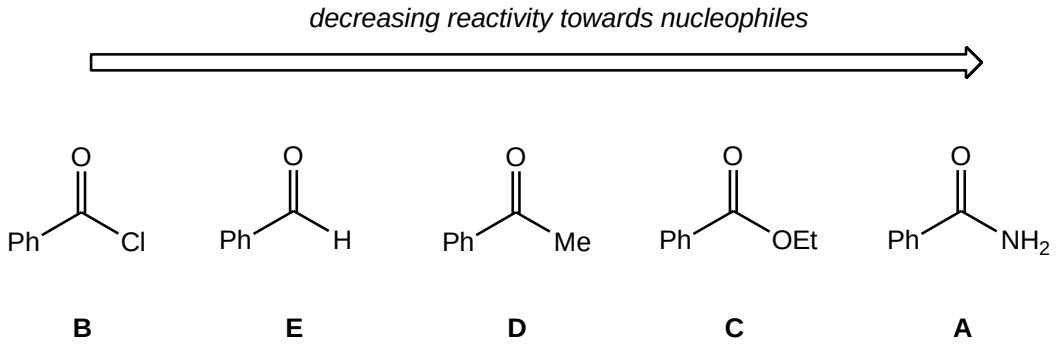
Compound **C** is an ester; its electrophilicity is in between that of an acid chloride **B** and an amide **A**. The ethoxyl group (-OEt) in **C** is more electron-withdrawing than the amino group (-NH_2) in **A** due to increased electronegativity. Even though the oxygen atom in **C** is more electronegative than the chlorine atom in **A**, the ester **C** is **less electrophilic** than the acid chloride **A**. This is due to better orbital overlap of a non-bonded pair of electrons on the oxygen atom, with its neighbouring carbonyl (C=O) group; 2*p*(O)-2*p*(C) orbital overlap in **C** is better quality than 3*p*(Cl)-2*p*(C) orbital overlap in **A**.



Let's now consider the remaining compounds **D** and **E**, which do not contain non-bonded pairs of electrons on their substituents.

Compound **D** is a ketone; it is more electrophilic than an ester **A**, as the methyl group is slightly electron-donating (+I effect). This inductive effect is weaker than the +M effect of the ester **C**.

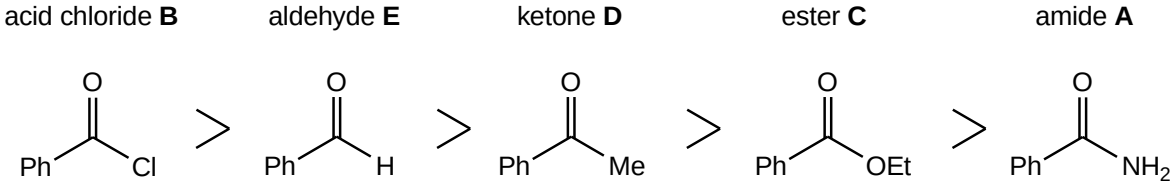
Compound **E** is an aldehyde; this compound is the benchmark as its H atom is neither electron-donating nor withdrawing.



The overall electrophilicity of these carbonyl-containing molecules are:

acid chloride **A** > aldehyde **E** > ketone **D** > ester **C** > amide **A**

Answer



Box 24.3 Fragrant esters (on p. 1109 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.

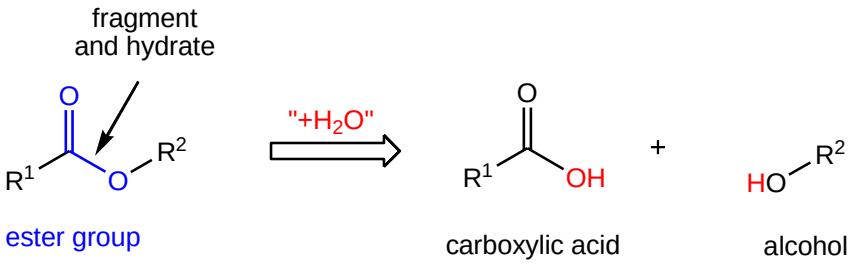
Strategy

Locate and highlight the ester group, $R^1(C{=}O)\text{-}O\text{-}R^2$. 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 $HO\text{-}R^2$, and the carboxylic acid $R^1(C{=}O)\text{-}OH$.

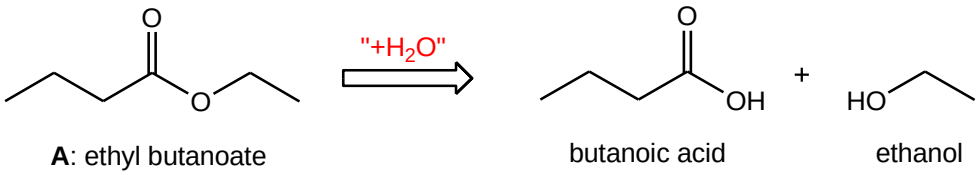
Draw out the parent carboxylic acid and alcohol components that make up each ester.

Solution

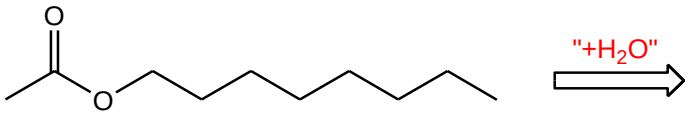
Each ester can be fragmented and hydrated to give the corresponding alcohol and carboxylic acid, as shown below.



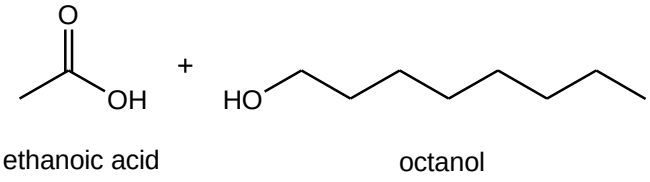
For the six esters, the parent carboxylic acids and alcohols are shown below.

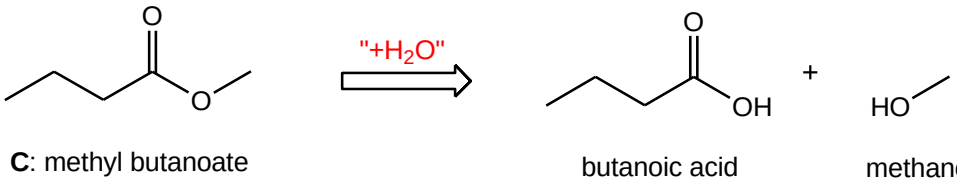


A: ethyl butanoate

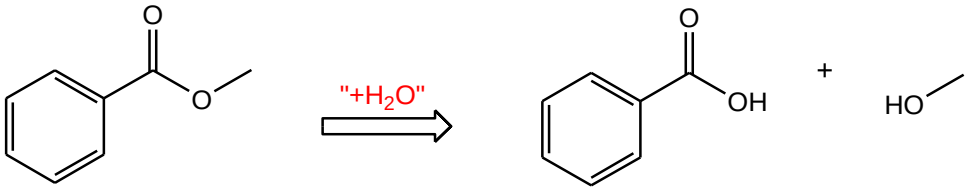


B: octyl ethanoate

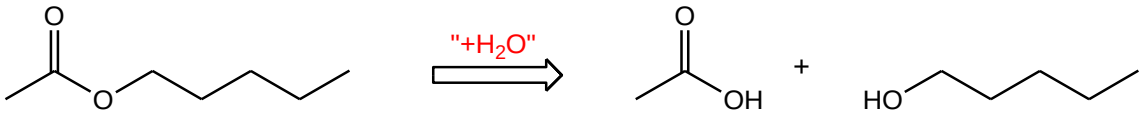




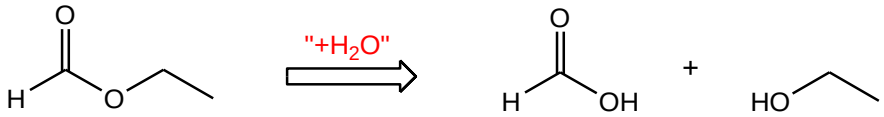
C: methyl butanoate



D: methyl benzoate benzoic acid methanol

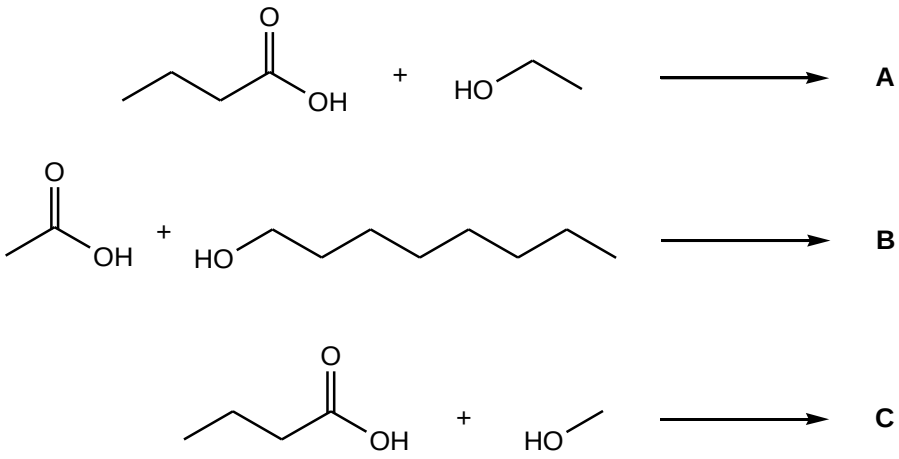


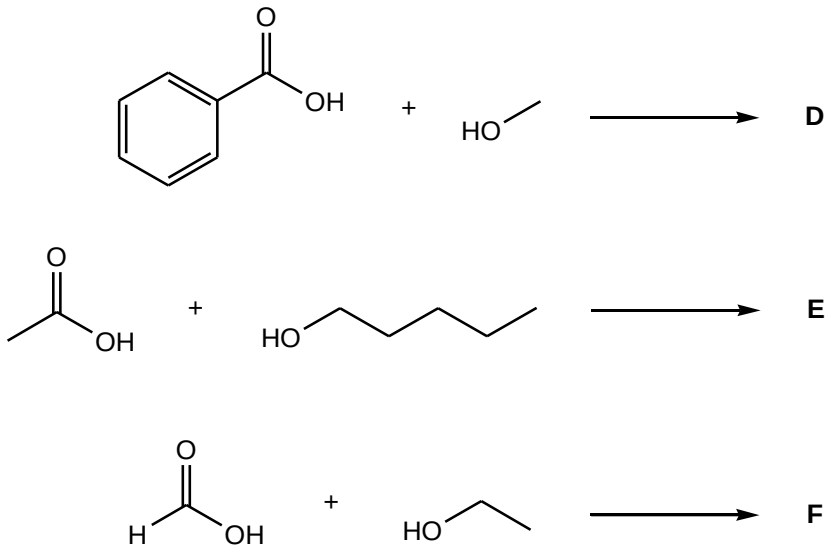
E: pentyl ethanoate ethanoic acid pentanol



F: ethyl methanoate methanoic acid ethanol

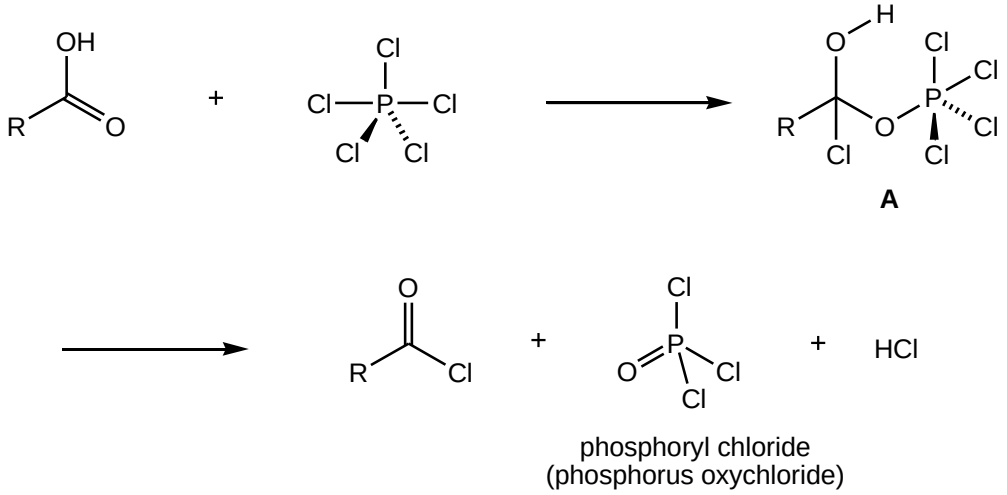
Answer





Box 24.4 Halogenation of carboxylic acids (on p. 1110 in *Chemistry*^{3})

The mechanisms of the reactions of carboxylic acids with PCl_5 and $SOCl_2$ are similar. As shown here, PCl_5 reacts with a carboxylic acid to form an intermediate phosphorus(V) compound (**A**), which breaks down to form the acyl chloride, $POCl_3$, and HCl.



Propose a mechanism to show how **A** is formed, and then how it is converted into the acyl chloride.

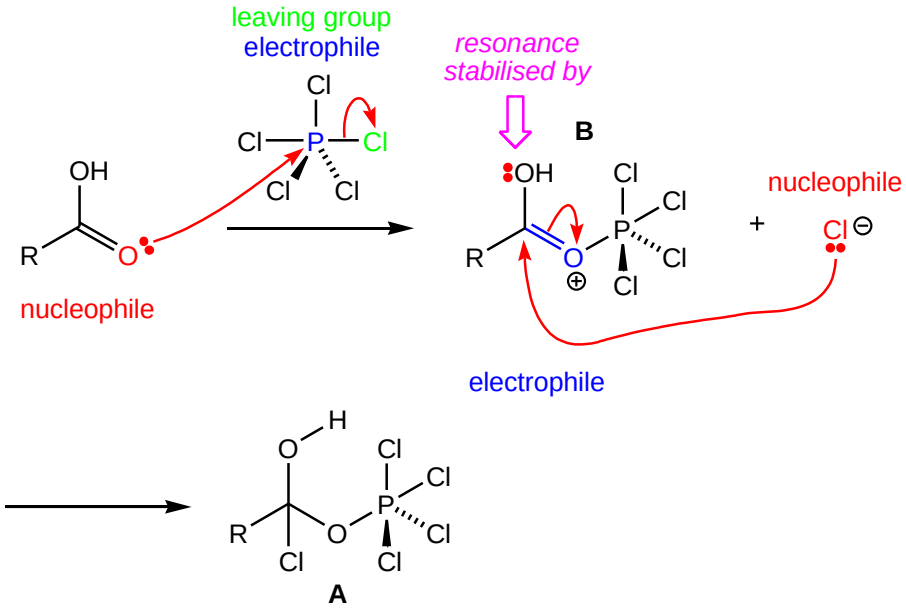
Strategy

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 (→).

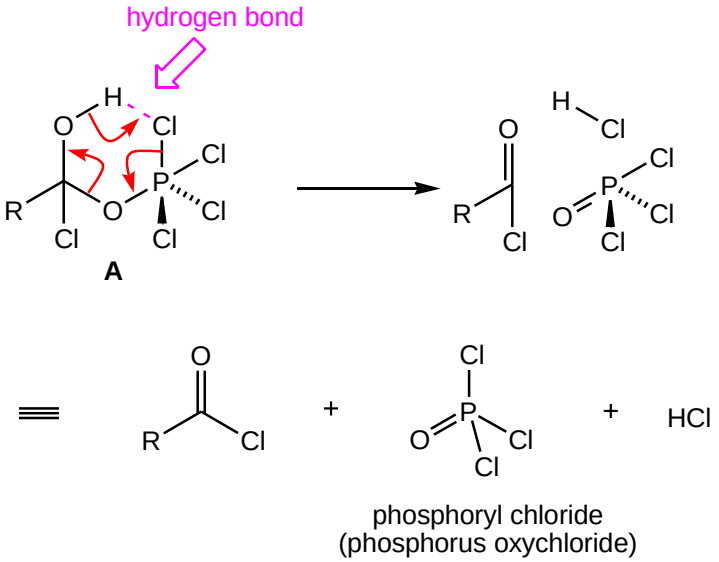
Solution

PCl_5 is a potent electrophile, and therefore the **carbonyl (C=O) group** of the carboxylic acid **is the nucleophile**.

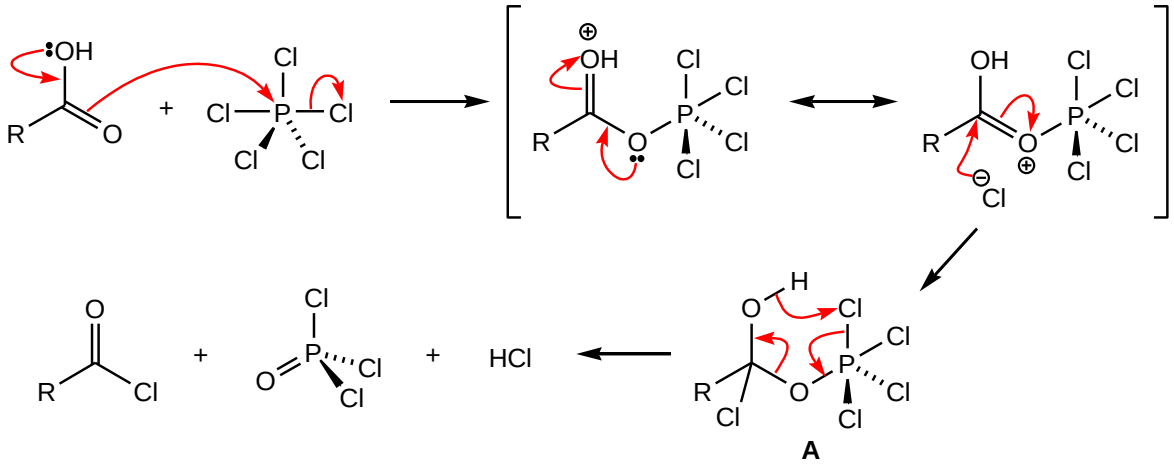
Formation of intermediate **A**: nucleophilic addition, involving the oxygen atom of the carbonyl (C=O) group of the carboxylic acid, RCO_2H, to the electrophilic phosphorus atom of PCl_5, followed by chloride (Cl^-) elimination gives the resonance stabilised intermediate oxonium ion **B**. Charge neutralisation, by chloride (Cl^-) addition to the high-energy positively charged oxonium ion, as shown in **B**, leads to the intermediate **A**.



Formation of acid chloride: fragmentation of intermediate **A** can occur by a concerted six-electron elimination (Ei) pathway. This is promoted by intramolecular hydrogen bonding between the OH group and the neighbouring Cl atom, as shown below.



Answer

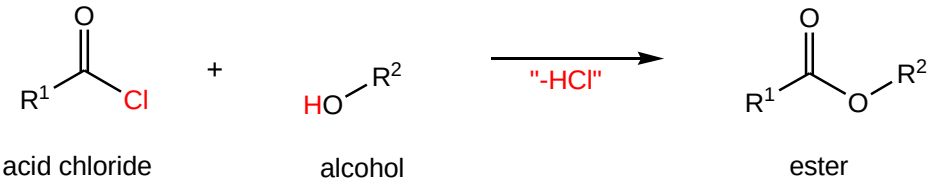


Box 24.5 Combinatorial chemistry (on p. 1115 in *Chemistry*[3])

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

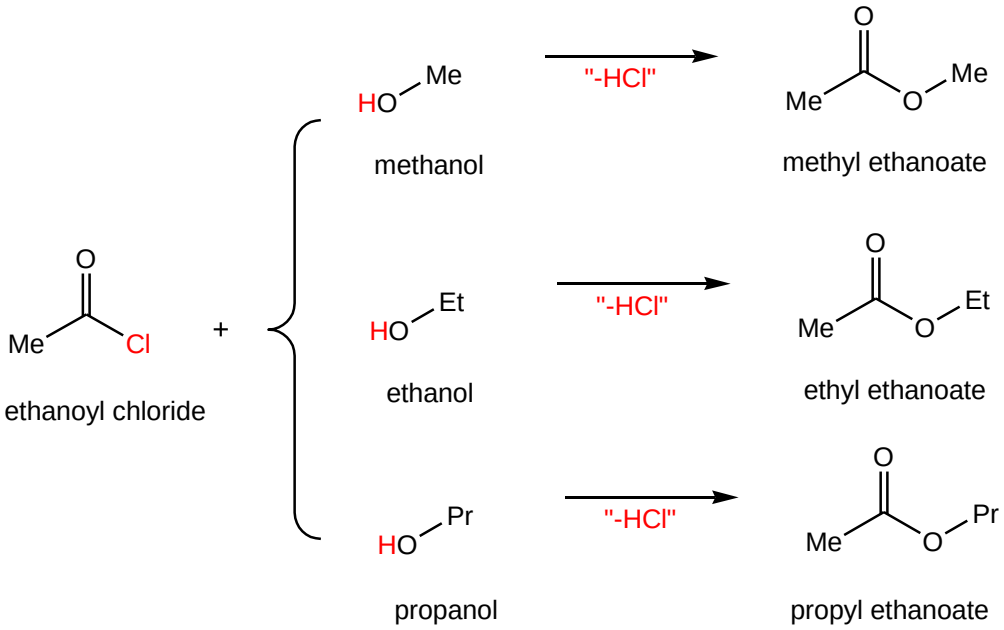
Strategy

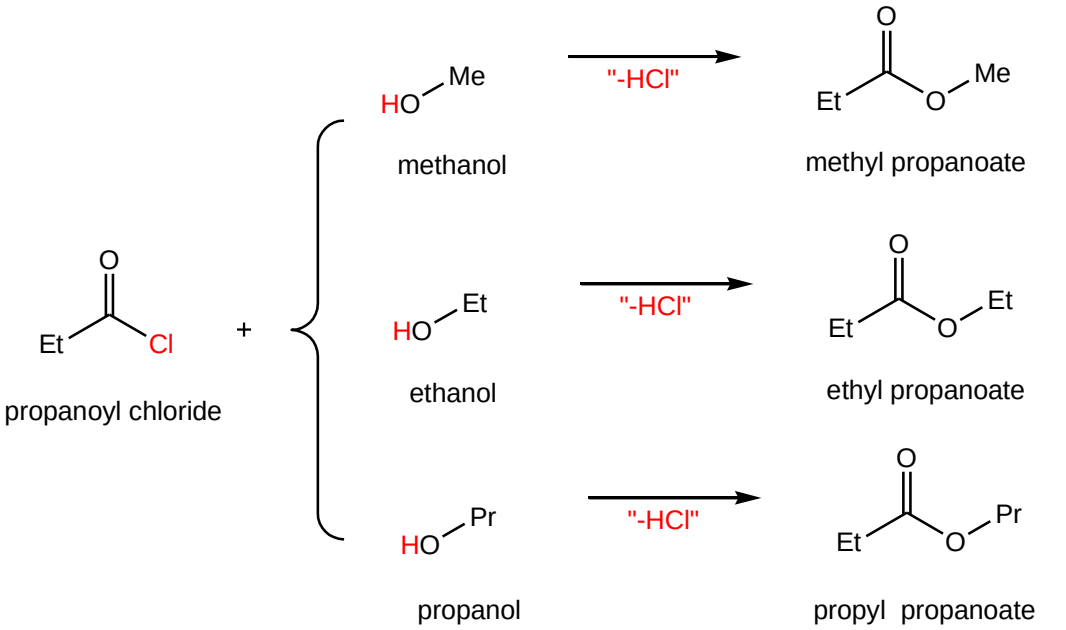
Esters, like $R^1(C{=}O)O\text{-}R^2$, can be synthesised by addition of an alcohol, such as R^2OH, to an acid chloride, $R^1(C{=}O)Cl$, in the presence of a suitable base. Draw out the structures of the above acid chlorides and alcohols. For each acid chloride, use the THREE alcohols, MeOH, EtOH and 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.

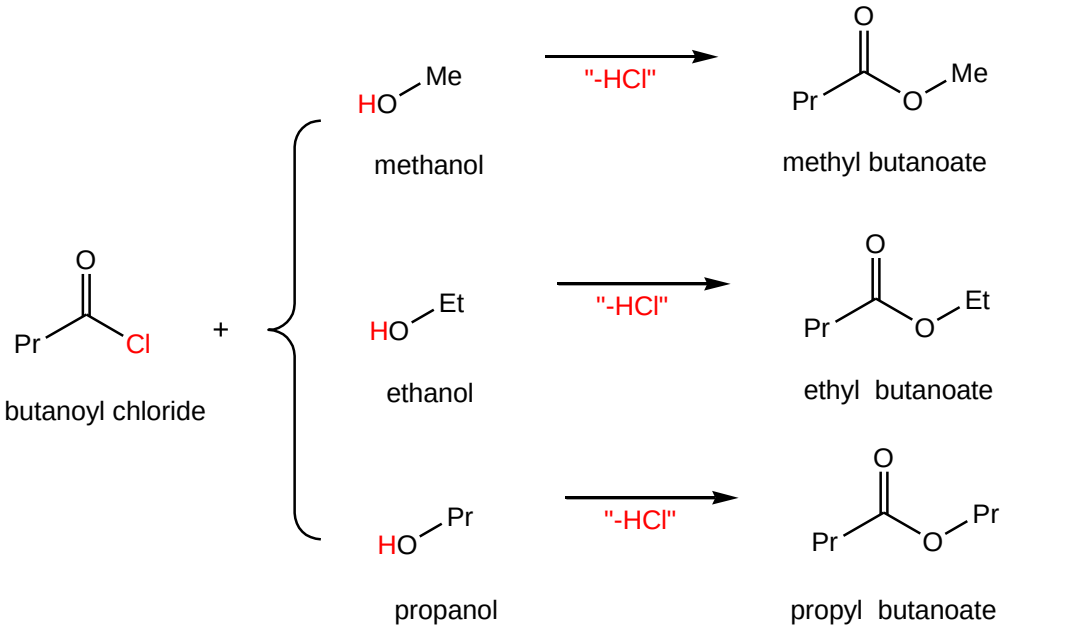


Solution

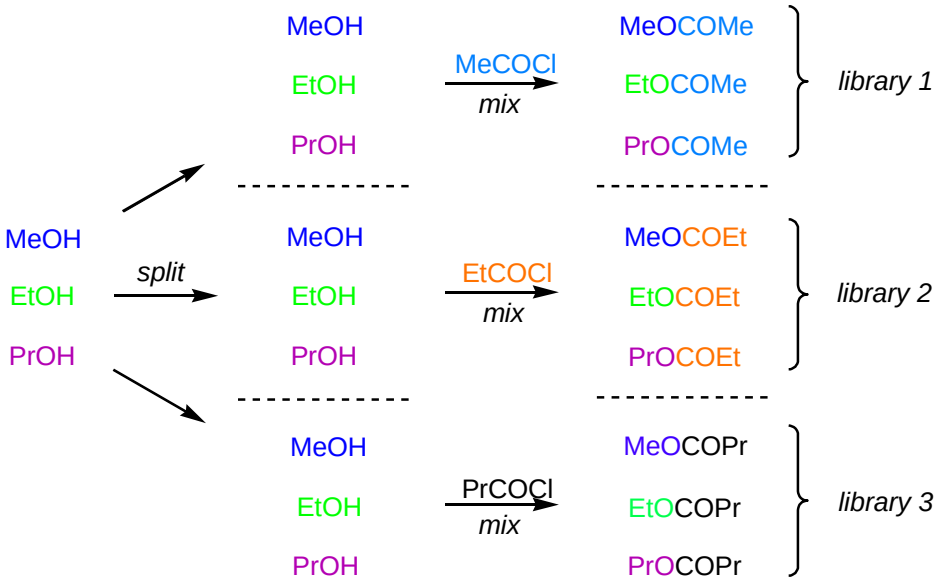
Combining three acid chlorides with three alcohols will make nine esters, as shown below. It is important to note, the total number comes from 3 multiplied by 3 (= 9), and NOT 3 plus 3 (= 6). For example, mixing a series of 5 acid chlorides and 5 alcohols would give a library of 25 (5 × 5) esters, and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







Answer



Box 24.6 Making soap (on p. 1120 in *Chemistry*[3])

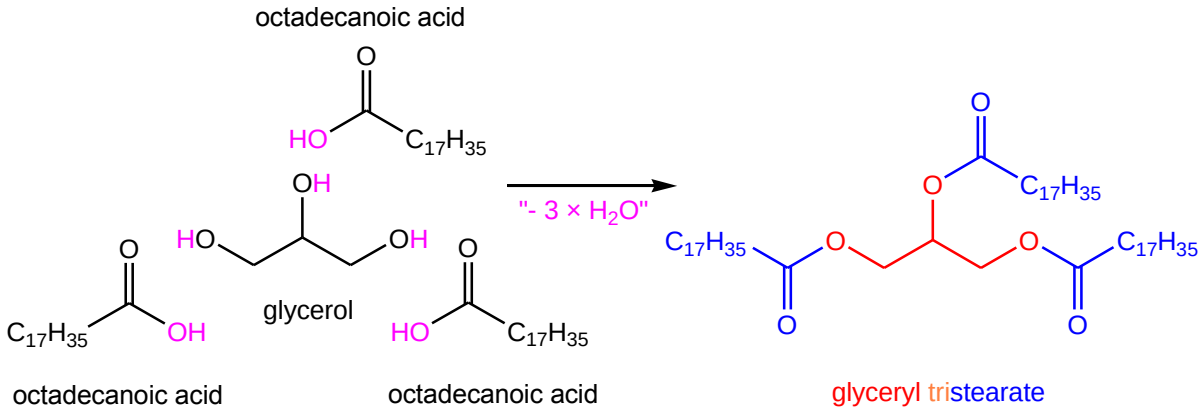
Glyceryl tristearate (tristearin) is the main saturated fat in beef. Saponification of a molecule of glyceryl tristearate using an excess of aqueous sodium hydroxide produces three molecules of sodium stearate. Draw the structure of glyceryl tristearate and explain why it is a saturated fat.

Strategy

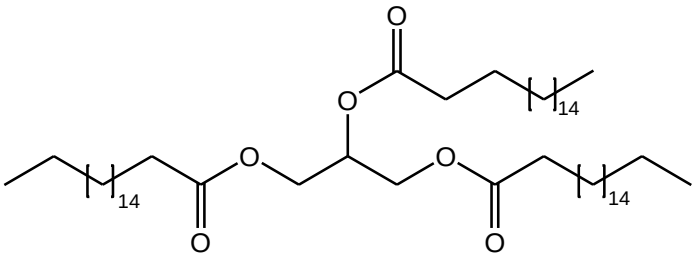
A typical ester, alkyl alkanoate, is derived from alkanol and alkanoic acid. Glyceryl tristearate (tristearin) is a triester of stearic acid and glycerol.

Solution

Stearic acid is simply octadecanoic acid, $C_{17}H_{35}CO_2H$, and glycerol is a triol, $HOCH_2CH(CH_2OH)CH_2OH$. The structures of these compounds are on p. 1114 in *Chemistry*[3]. Simply couple these four components together using ester bonds, and draw out the structure of glyceryl tristearate.



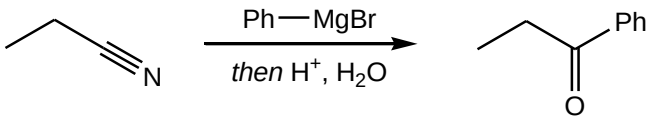
Answer



Sodium stearate is a saturated fat because the carbon chain does not contain any carbon-carbon double (C=C) bonds; it is fully saturated with hydrogen atoms.

Box 24.7 Hydrolysis of nitriles to form carboxylic acids (on p. 1125 in *Chemistry*[3])

Propose a mechanism for the following reaction, which involves an intermediate imine (see section 2.7 on p.100 in *Chemistry*[3] for the structure of imines).

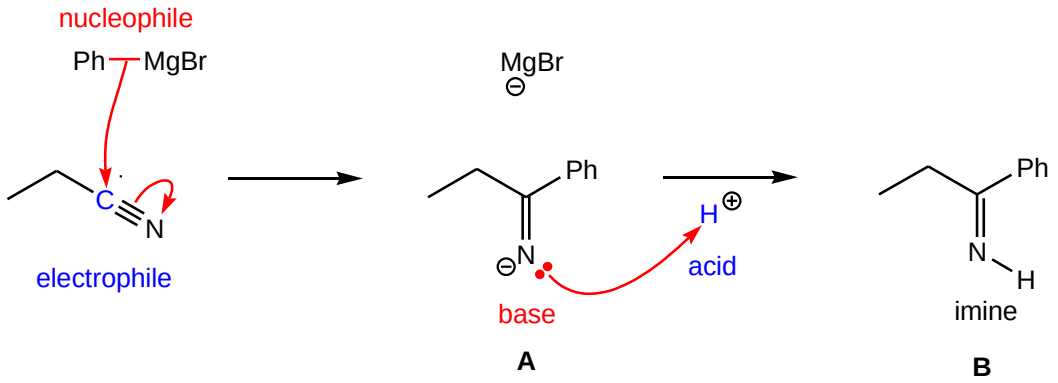


Strategy

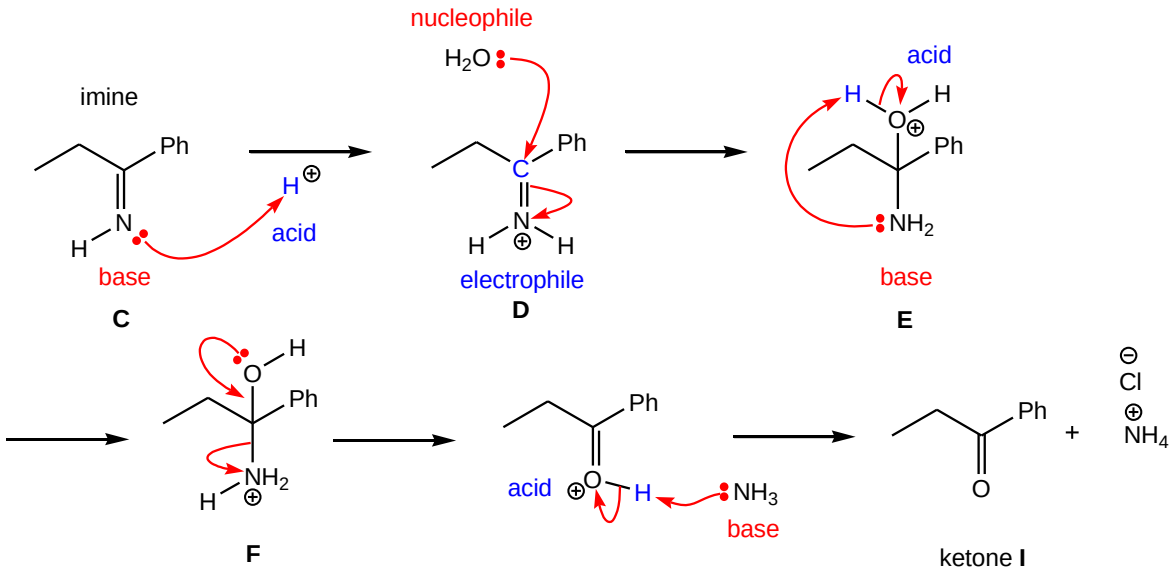
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

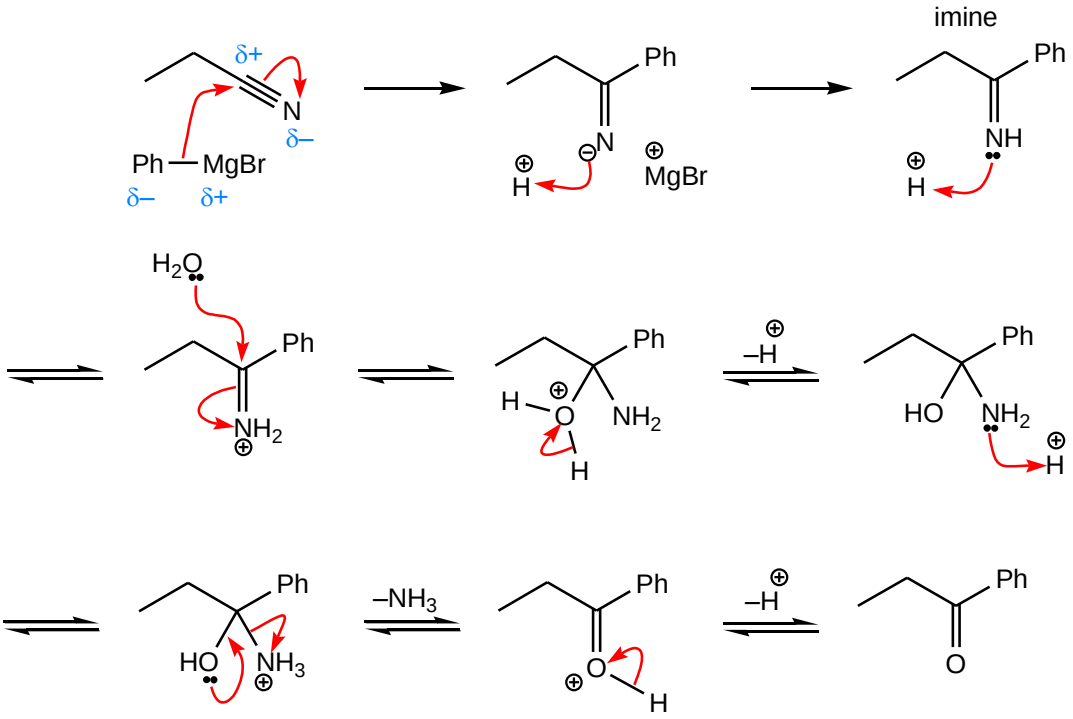
The Grignard reagent, Ph-MgBr is the nucleophile and ethyl cyanide, EtC≡N, is the electrophile in this reaction. Nucleophilic addition of the phenyl carbanion, Ph^-, (from the nucleophilic Ph-MgBr bond) to the electrophilic nitrile group of ethyl cyanide leads to the trigonal intermediate **A**. Protonation of this basic iminium ion, in **A**, using aqueous mineral acid (dilute HCl in H_2O), 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**. **Intra**molecular proton exchange, in **E**, followed by elimination of ammonia gives the oxonium ion **H**. **Inter**molecular proton exchange between the acidic oxonium ion **H** and basic ammonia gives the required ketone **I** and ammonium chloride. The mechanism of this process is shown below.



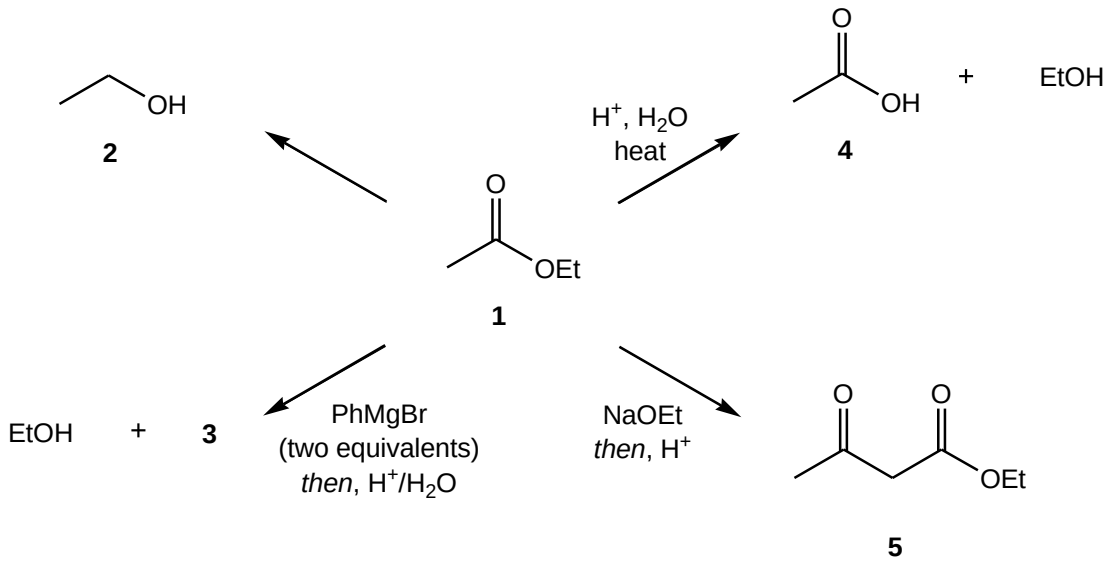
Answer



[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. 1134 in *Chemistry*^{3})

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



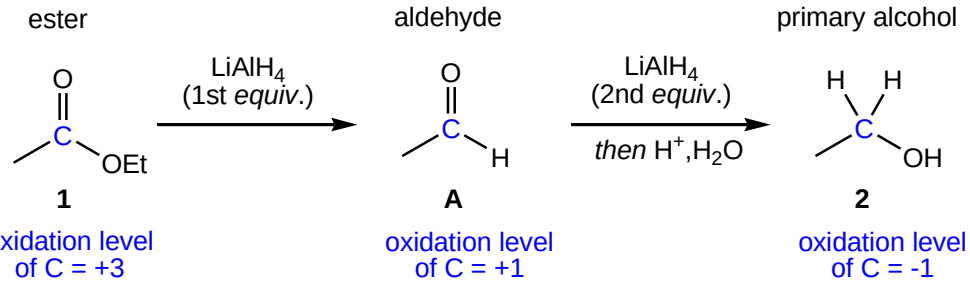
(a) Give appropriate reagents for converting **1** into **2**. Is this an example of an oxidation or a reduction reaction?

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. 1057 in *Chemistry*^{3}.

Answer

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

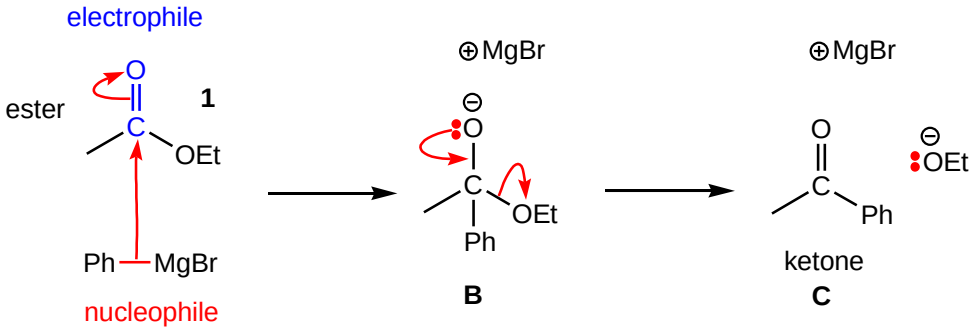
(b) Give the structure of organic compound **3**.

Strategy

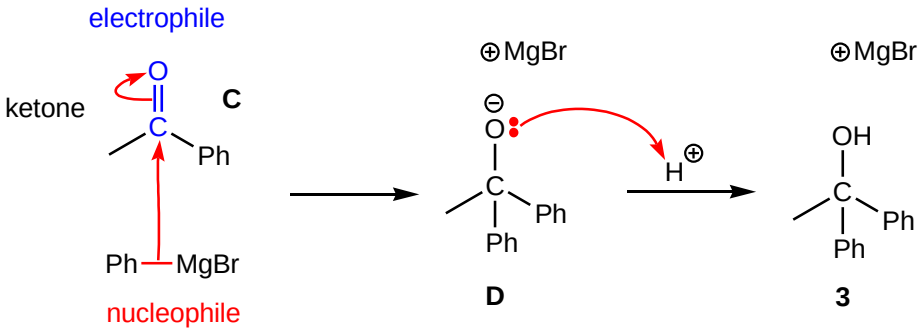
Draw out the reagents, ethyl ethanoate **1** and phenyl magnesium bromide (PhMgBr), and name the functional groups present. Examine the reagents, deduce their relative reactivity, and draw out the resulting product.

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^-.



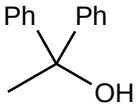
Nucleophilic addition of the first equivalent of phenyl magnesium bromide, using its nucleophilic Ph-MgBr bond, to the electrophilic carbonyl group of ethyl ethanoate **1** leads to the tetrahedral intermediate **B**. Elimination of ethoxide, EtO^-, gives the intermediate ketone **C**.



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. 1063 in *Chemistry*^{3}.

Treatment of esters, like $R^1CO_2R^2$, with two equivalents of Grignard reagent, such as R^3MgBr, leads to the corresponding tertiary alcohol, $R^1C(OH)R^3R^3$.

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 12.1 on p.556 in *Chemistry*^{3}).

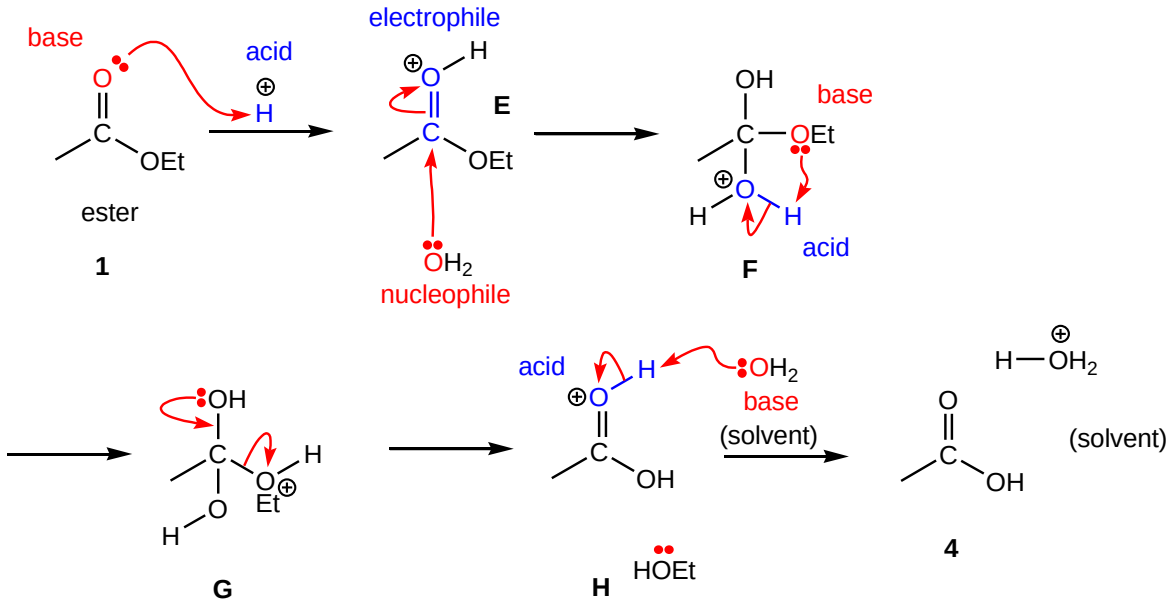
(i) Draw a reaction mechanism to show how **1** is converted into **4** and EtOH.

Strategy

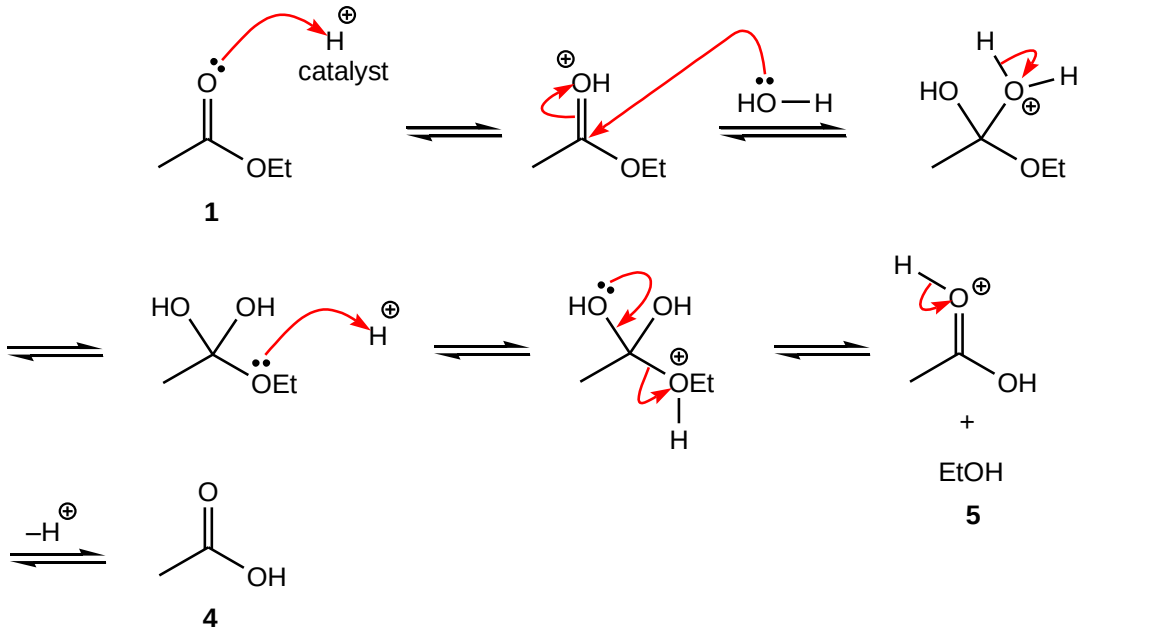
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

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



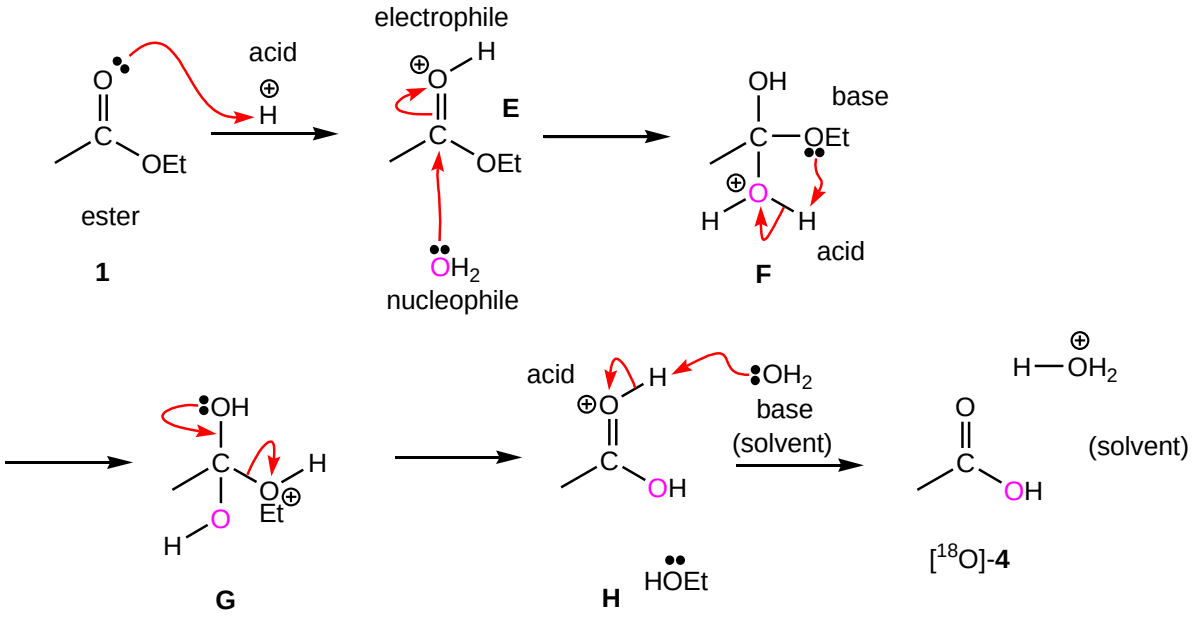
(c) (ii) If **1** is heated with $H_2{}^{18}O$ and H^+, where does the ^{18}O atom appear at the end of the reaction?

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).

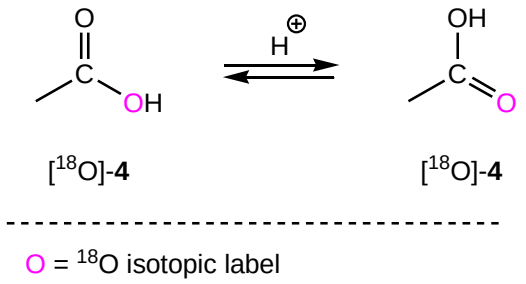
Solution

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**.

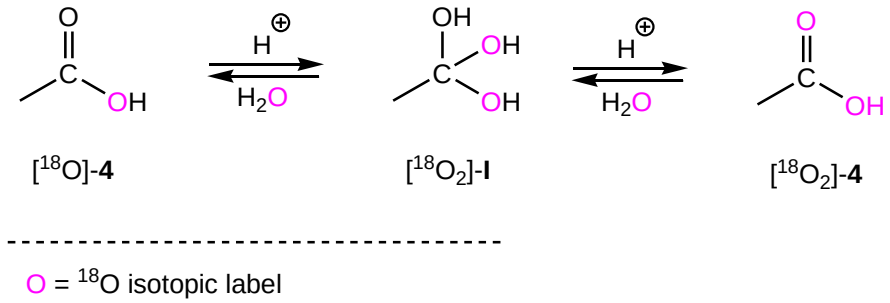


Under acidic conditions, this ^{18}O-labelled oxygen atom (on the OH group in [^{18}O]-**4**) can tautomerise into the C=O^{18} group, and *vice versa*, as shown below. In essence, the two

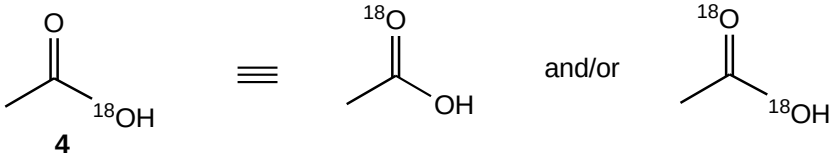
oxygen atoms of this carboxylic acid [^{18}O]-**4**] are indistinguishable under this dynamic equilibrium; both isotopically labelled products are equally preferred.



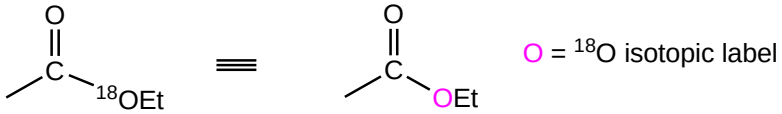
However, in the presence of an excess of ^{18}O-labelled water (H_2O^{18}), the fully ^{18}O-labelled carboxylic acid [$^{18}O_2$]-**4** is preferred. This reaction proceeds *via* the intermediate hydrate [$^{18}O_2$]-**I**. For further information about the mechanism of hydrate formation, see p. 1066 in *Chemistry*[3].



Answer



(c) (iii) If ethyl ethanoate, labelled with ^{18}O as shown below, is heated with H_2O/H^+, where does the ^{18}O atom appear at the end of the reaction?

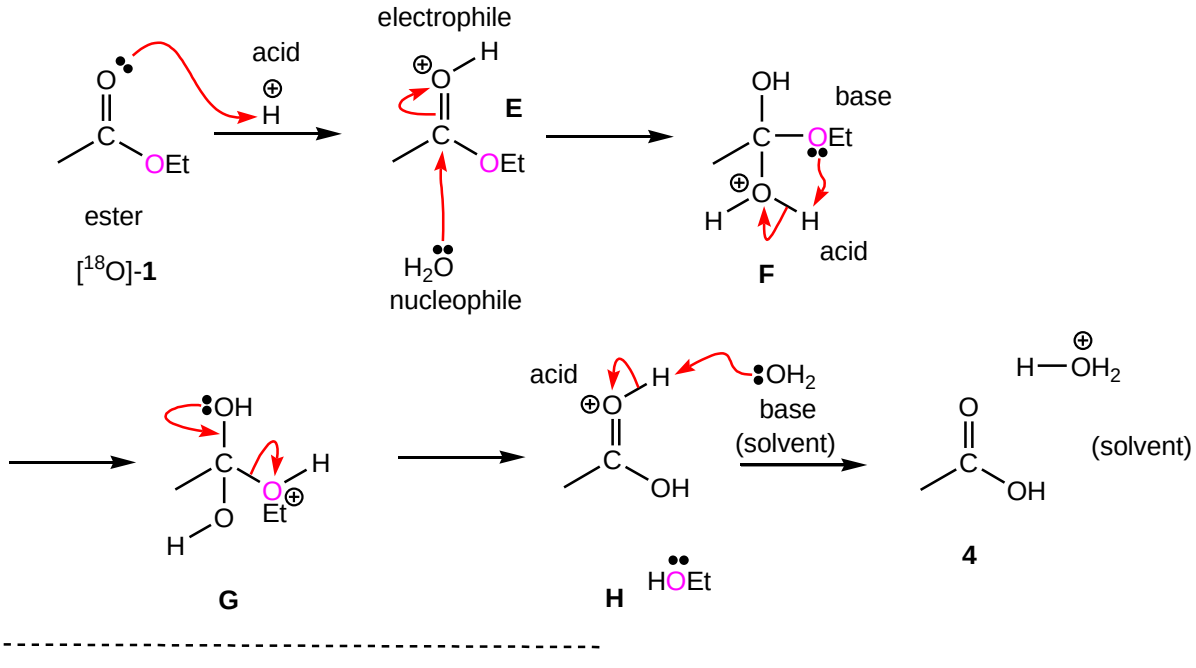


Strategy

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

Solution

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



Answer

EtO^{18}H

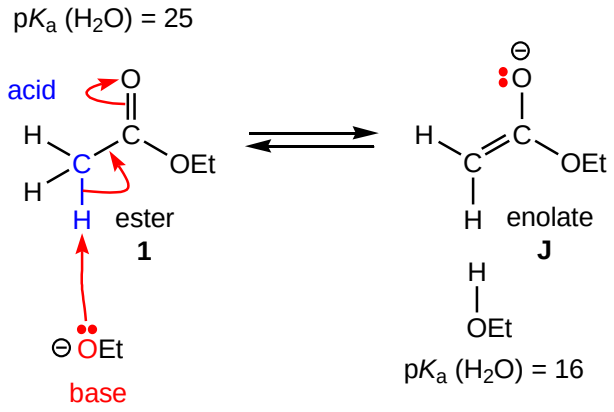
(d) Draw a reaction mechanism to show how **1** is converted into **5**.

Strategy

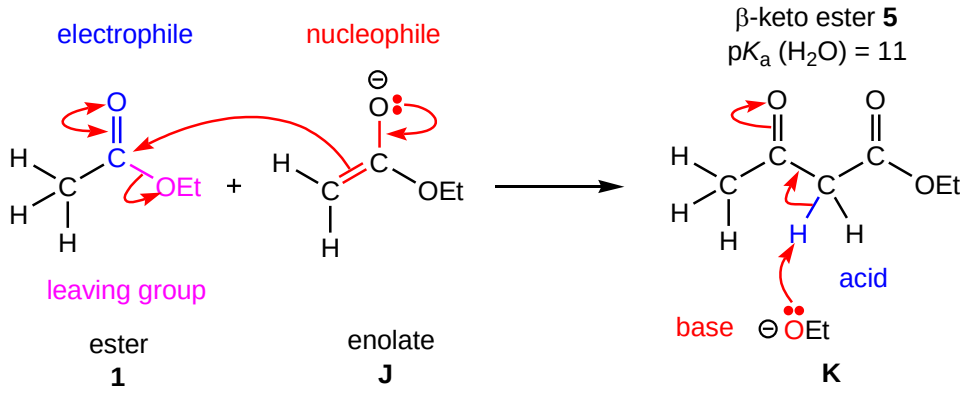
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

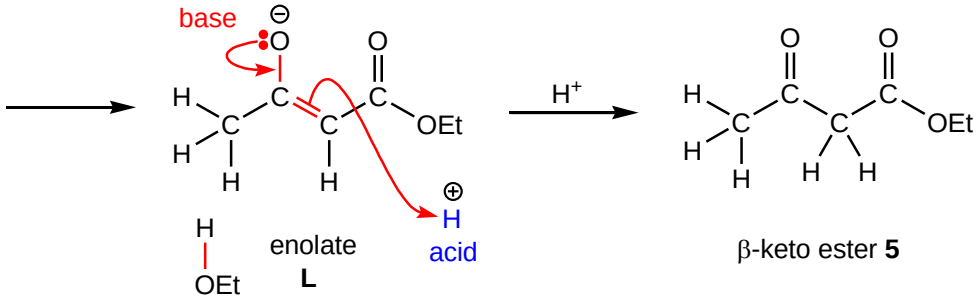
Deprotonation of ethyl ethanoate **1** [pK_a (H_2O) = 25] using ethoxide, EtO^-, as the Brønsted base, gives the thermodynamically less stable enolate **J** and its conjugate acid, ethanol [pK_a (H_2O) = 16].



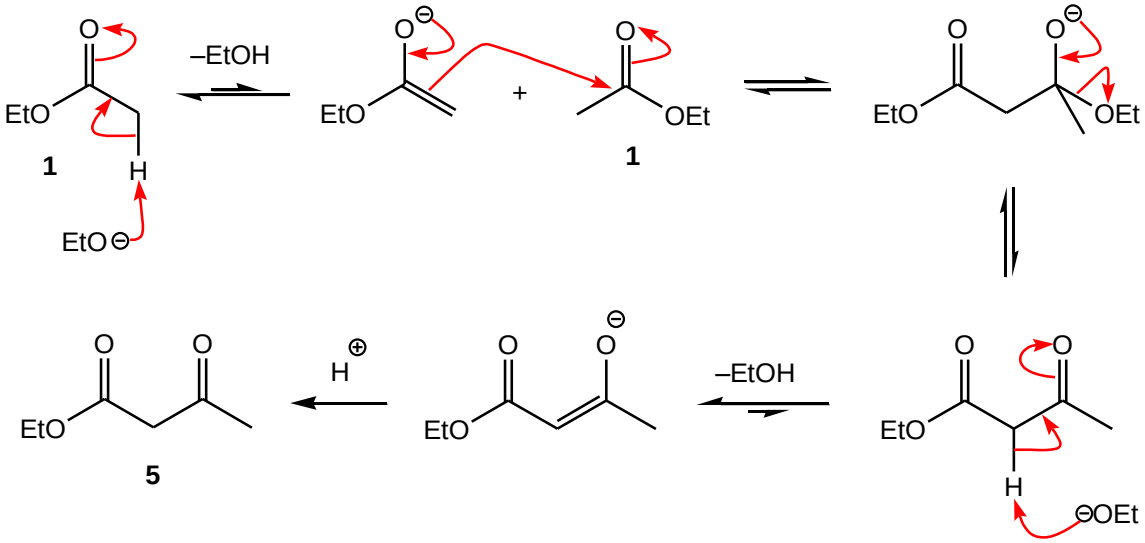
The product, β-keto ester **5**, is derived from **two** equivalents of ethyl ethanoate **1**. Nucleophilic addition of the enolate **J** (derived from the first equivalent of ester **1**) to the electrophilic carbonyl (C=O) group of the second equivalent of ester **1**, followed by elimination of ethoxide, 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. 1097 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**.

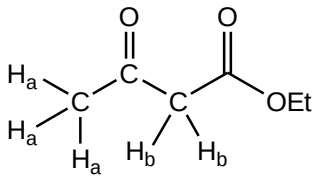
Strategy

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(sp^3)-H bond.

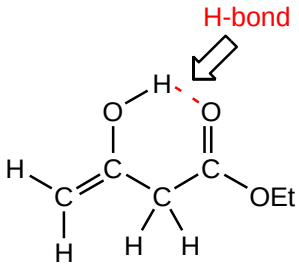
Draw out both molecules and include all alpha C(sp^3)-H bonds. As enols are constitutional isomers of carbonyl-containing molecules, they can be easily drawn by replacing each H-C(sp^3)-C=O unit for a C=C-OH unit. If there are two or more alpha C(sp^3)-H bonds, draw out each enol separately and consider 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

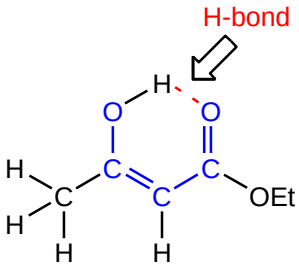
There are two chemically different alpha C(sp^3)-H bonds, namely, H_a and H_b, which can lead to three potential enols **M** (derived from H_a) and, **N** and **O** (derived from H_b). The more substituted enols **N** and **O** are **more thermodynamically stable** than enol **M** due to conjugation (between their C=C and C=O bonds) and increased hyperconjugation from their neighbouring CH_3 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. 866 in *Chemistry*^{3}.



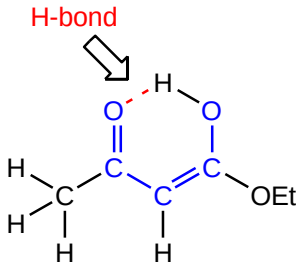
β-keto ester **5**



enol **M**



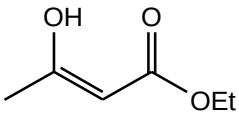
enol **N**



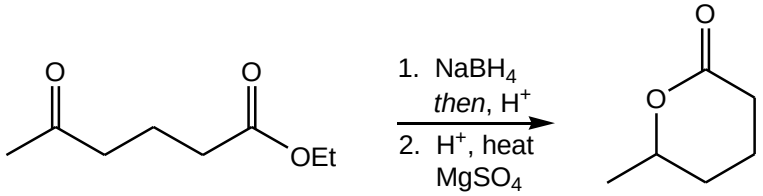
conjugation

enol **O**

Answer



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



6 **7**

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

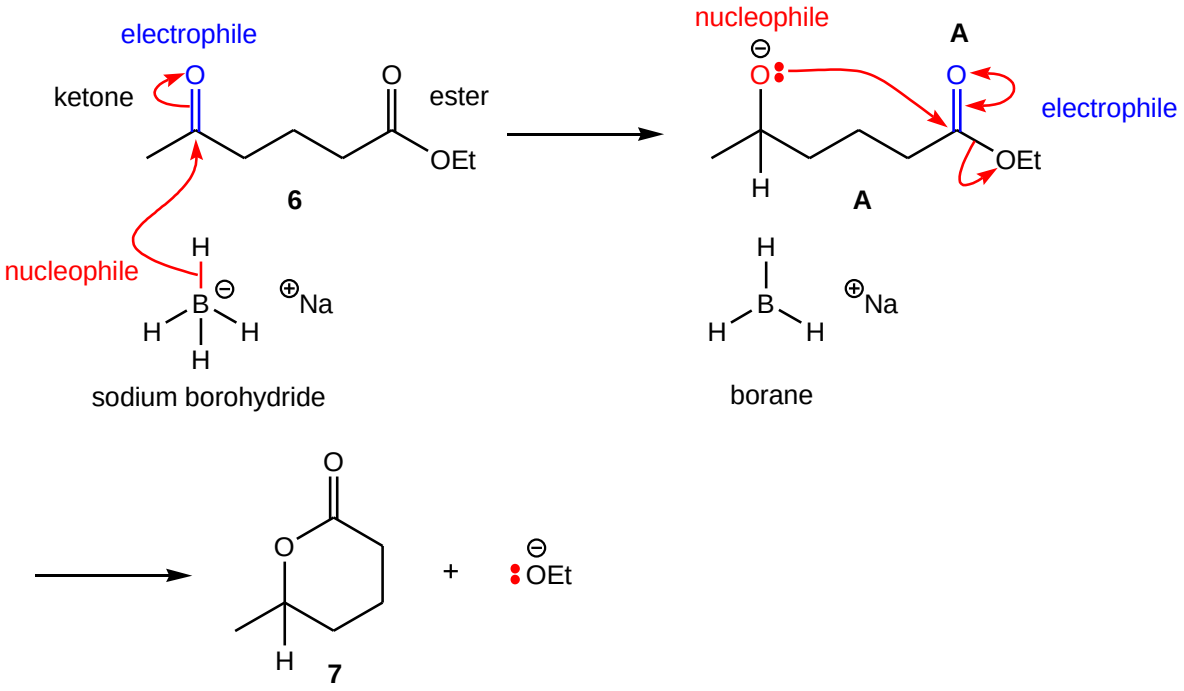
Strategy

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 (→).

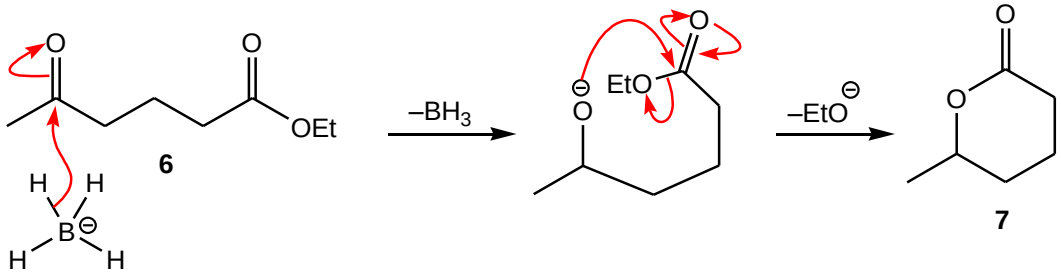
Solution

Sodium borohydride, $NaBH_4$, 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 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. 1097 in *Chemistry*^{3}.}



Answer



(a) (ii) Explain why the reaction of **1** with $NaBH_4$ 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. 1098 in *Chemistry*^{3}.}

Answer

$NaBH_4$ 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 $LiAlH_4$ then H^+.

Strategy

Lithium aluminium hydride, $LiAlH_4$, 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.

$LiAlH_4$ has higher ground-state energy than $NaBH_4$, 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 $NaBH_4$ fails.

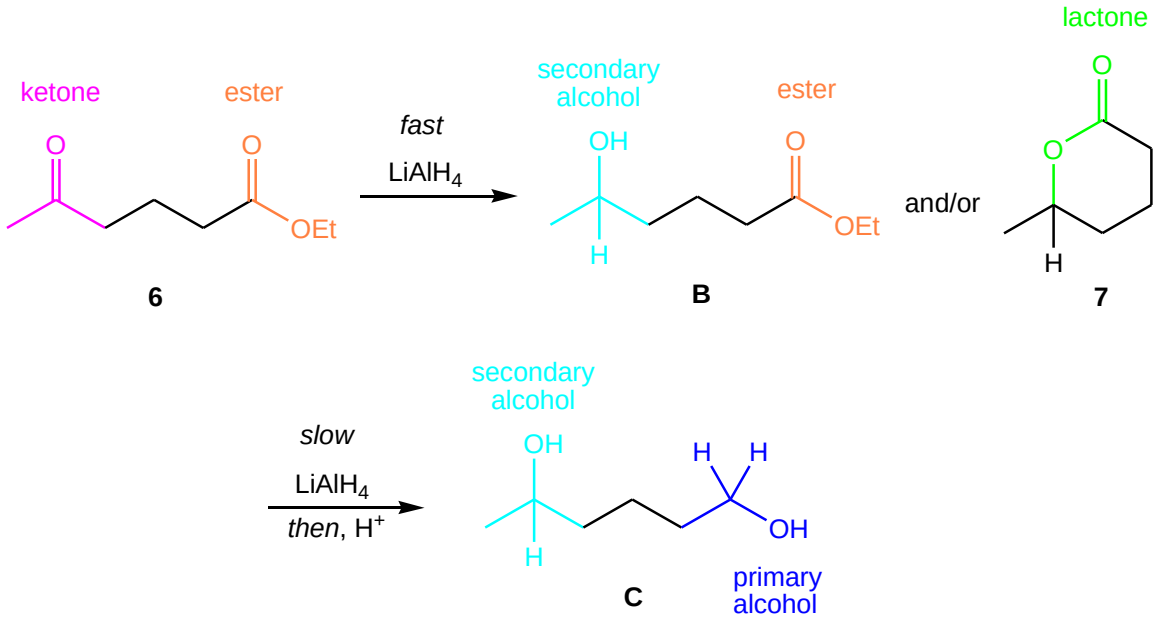
Draw the structure of the product derived from the reduction of both carbonyl (C=O) group of α,ε-ketoester **6**.

Solution

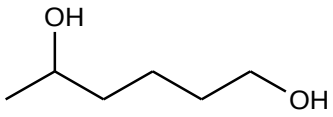
Reduction of the more electrophilic ketone component of the α,ε-ketoester **6**, using $LiAlH_4$, leads to the secondary alcohol **B**. This chemoselective reduction is faster than the corresponding reduction of the ester component. However, this intermediate secondary alcohol, in **B**, has the potential to cyclise to form the corresponding lactone **7**.

Using an excess of $LiAlH_4$, 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**).

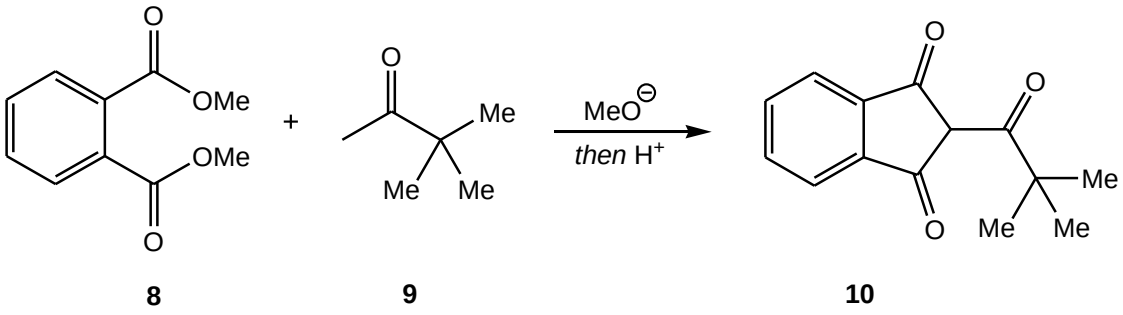
Reduction of the α,ε-ketoester **6**, using an excess of $LiAlH_4$, gives the 1,5-diol **C** as the major product.



Answer



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



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

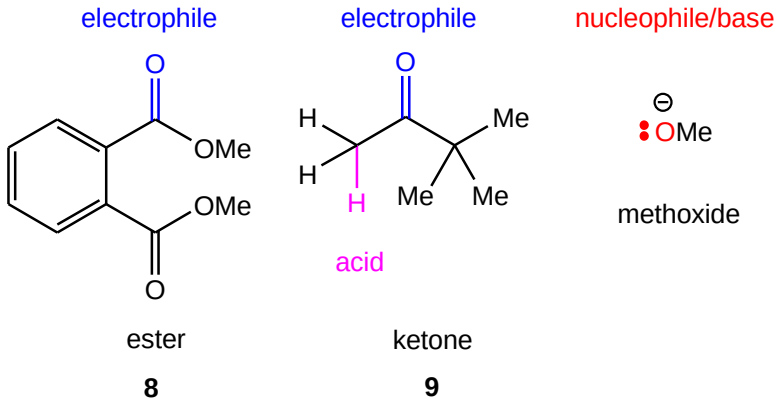
Strategy

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

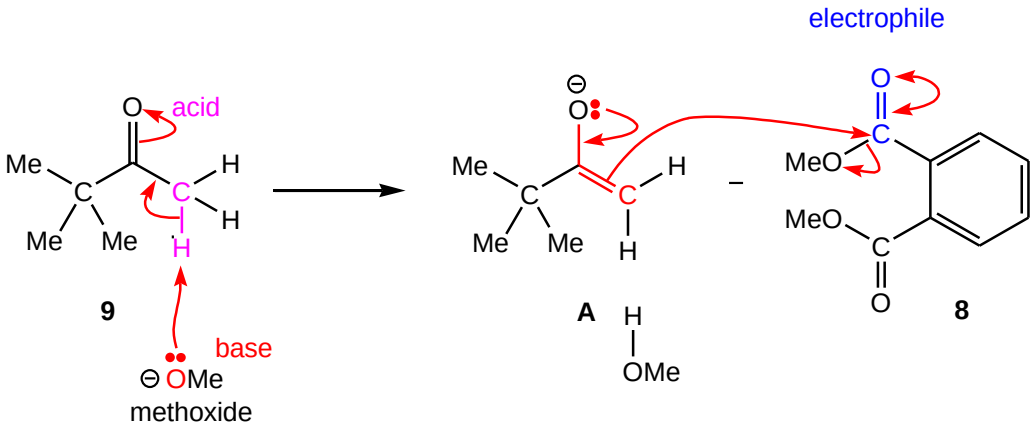
processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (→).

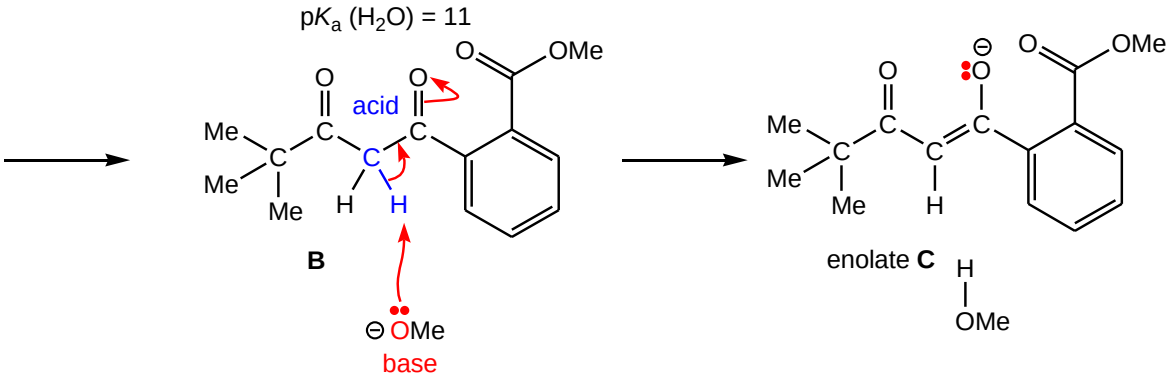
Solution

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).

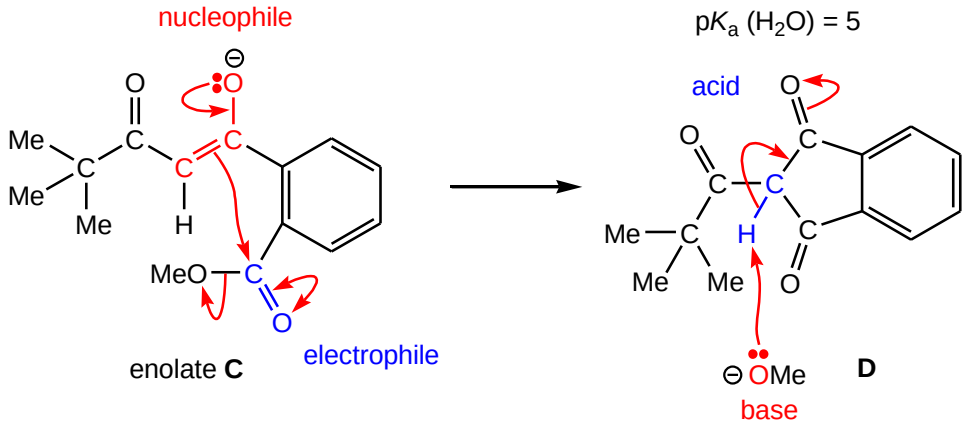


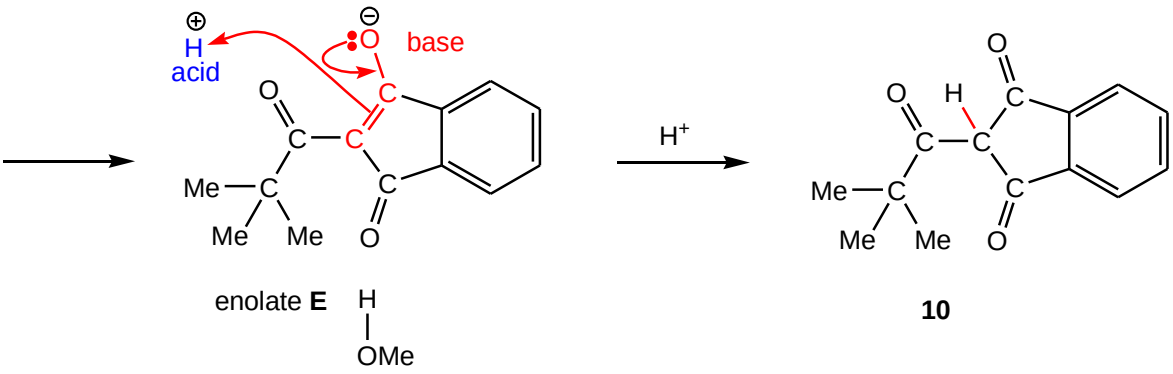
Deprotonation of ketone **9** [pK_a (H_2O) = 20] with methoxide, MeO-, as the Brønsted base, gives the thermodynamically less stable enolate **A** and methanol [pK_a (H_2O) = 16].



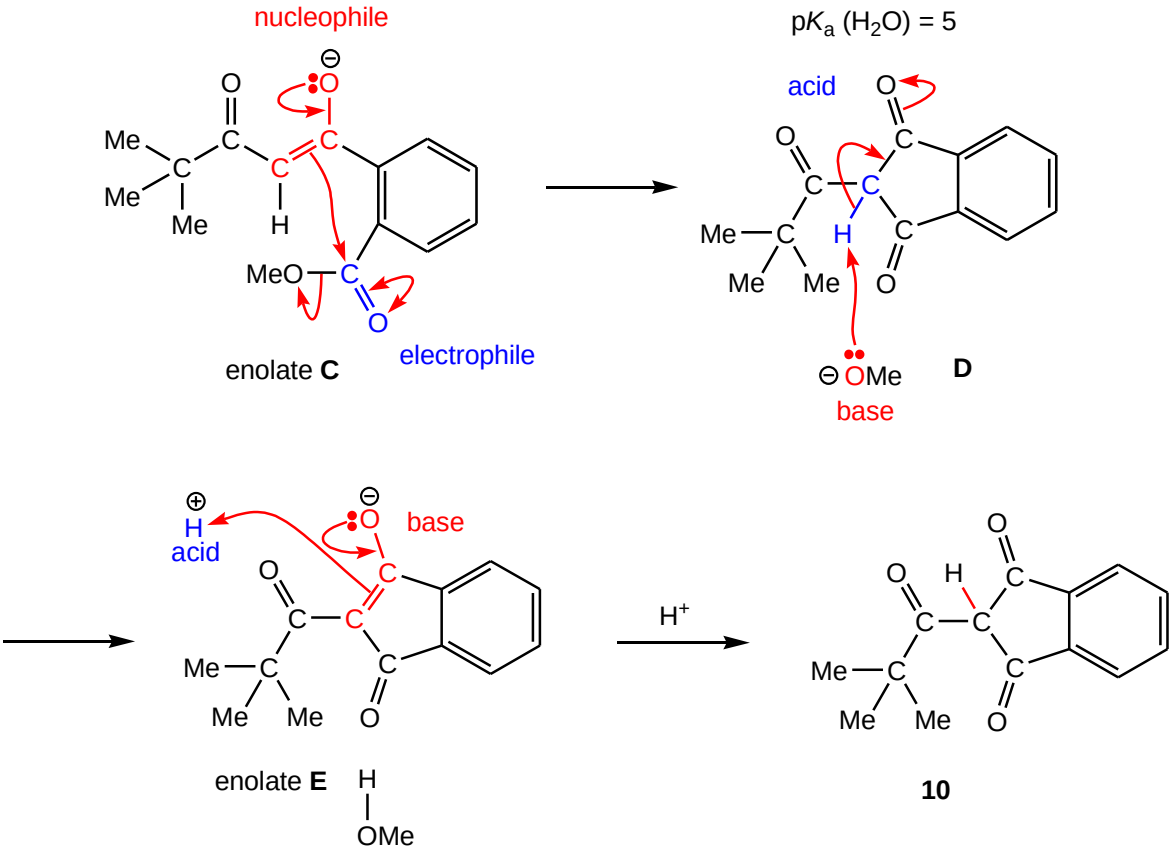


The product triketone, **10**, is derived from the addition of this enolate **A** to the diester **8**. Nucleophilic addition of this enolate **A** to one of the two electrophilic carbonyl (C=O) groups of the diester **8**, followed by elimination of methoxide, MeO^-, leads to the intermediate β-ketoester **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. 1097 in *Chemistry*[3].} **However**, this intermediate **B** [pK_a (H_2O) = 11] is more acidic than both methanol [pK_a (H_2O) = 16] and the original ketone **9** [pK_a (H_2O) = 20]; deprotonation of intermediate **B** using methoxide, MeO^-, as the Brønsted base leads to **more** thermodynamically stable enolate **C**.

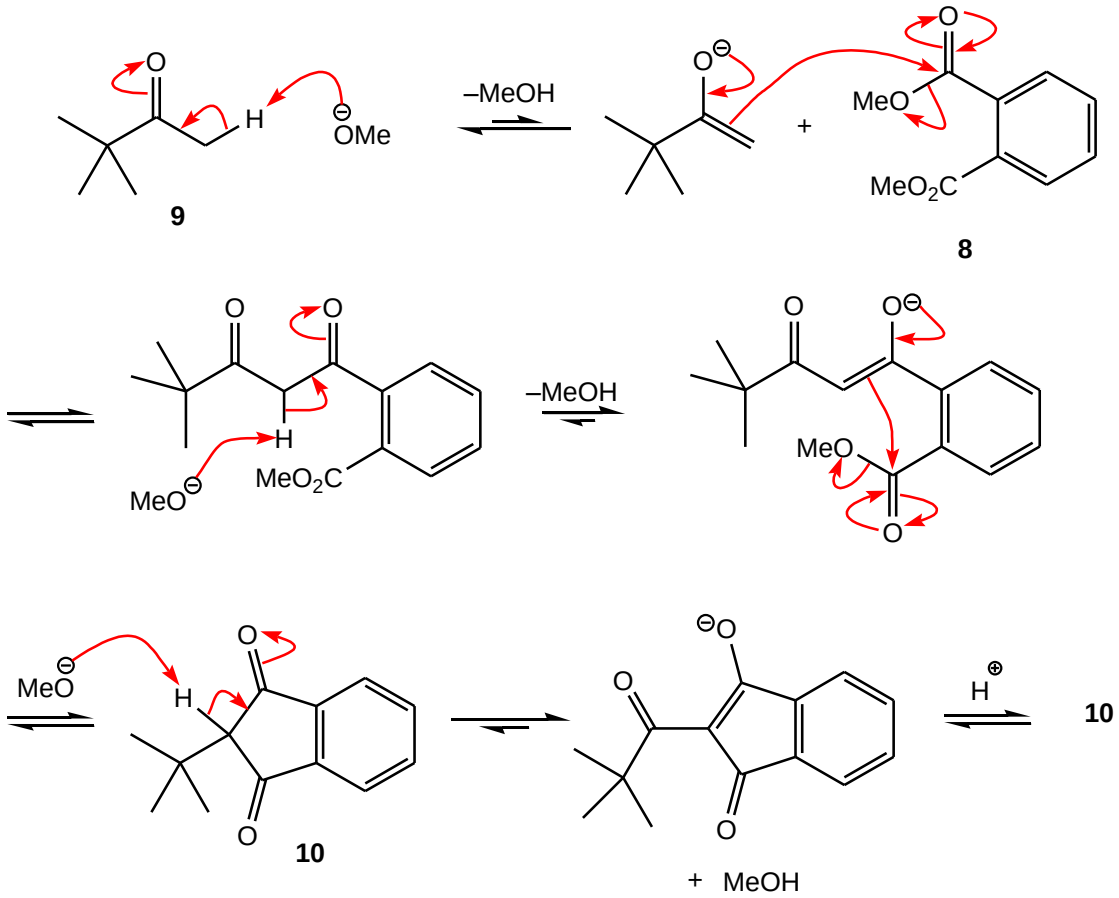




Intramolecular nucleophilic addition of this enolate, in **C**, to the electrophilic ester, followed by elimination of methoxide, MeO^-, leads to the intermediate triketone **D**. **However**, this intermediate **D** [pK_a (H_2O) = 5] is acidic and subsequent deprotonation with methoxide, MeO^-, as the 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 **10**.

Strategy

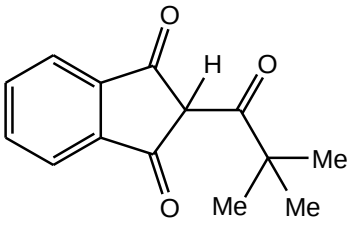
Enols are unstable tautomers of carbonyl-containing molecules; their enol content is usually less than 1% due to the strength of their carbonyl (C=O) double bond in their keto-form (a ketone or an aldehyde). In order to form an enol, the carbonyl-containing molecule must have an alpha C(sp^3)-H bond.

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

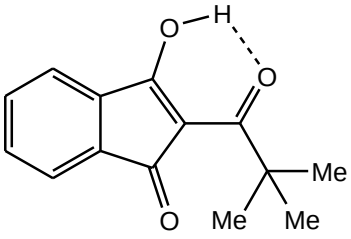
H-C(sp^3)-C=O unit for a C=C-OH unit. If there are two or more alpha C(sp^3)-H bonds, draw out each enol separately and consider their stability. As enol formation is thermodynamically unfavoured, molecules that have two or more carbonyl groups you will only need to consider mono-enol formation.

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.

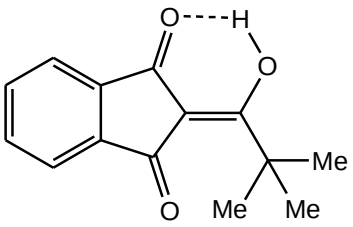


10



endo-**F**

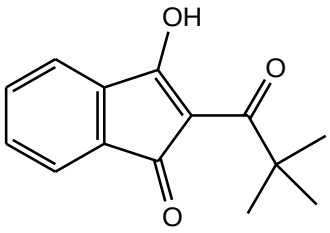
"endo-" means internal to the ring

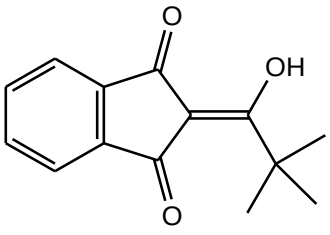


exo-**G**

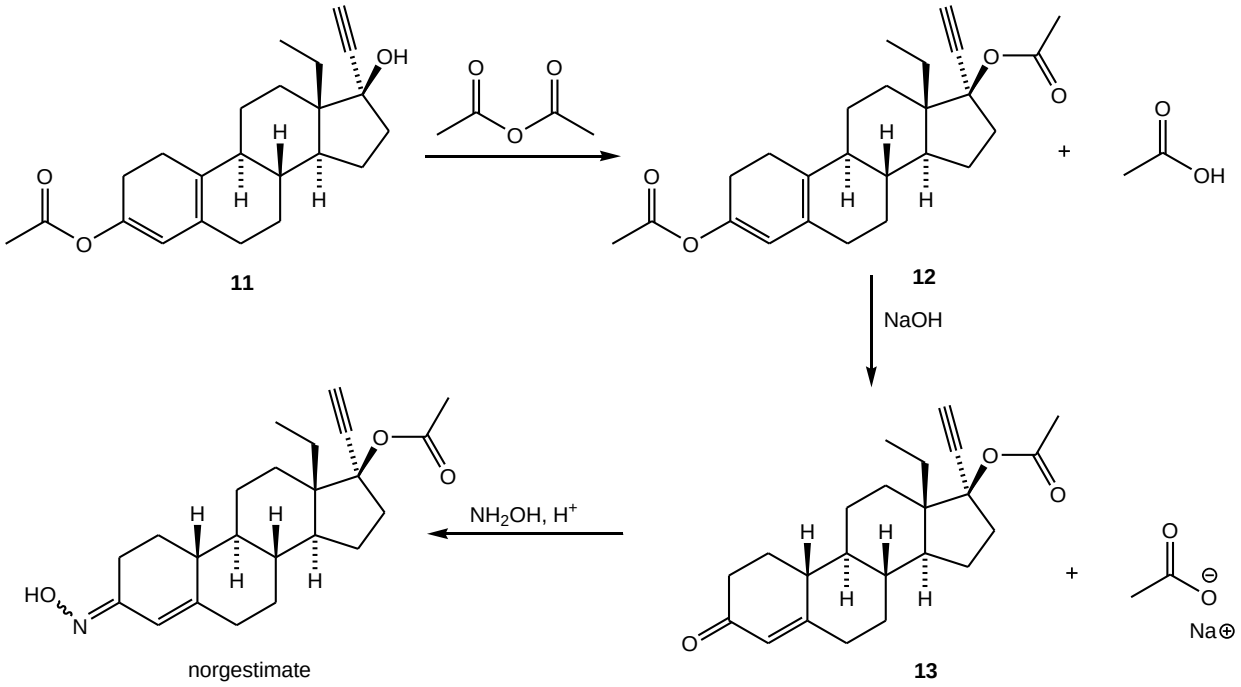
"exo-" means external to the ring

Answer





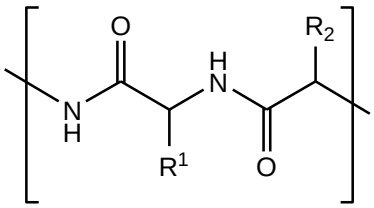
3. Part of a synthesis of the oral contraceptive norgestimate is shown below.



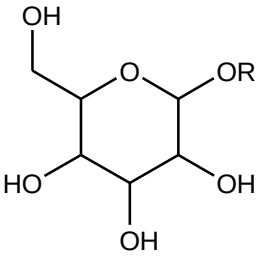
(a) To what class of compound does norgestimate belong—is it a peptide, a fatty acid, a steroid, or a carbohydrate?

Strategy

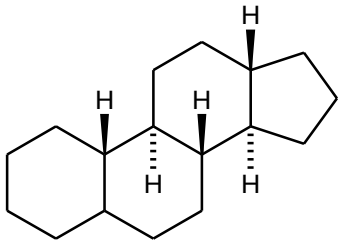
Carefully consider the carbon skeleton of this molecule. A peptide contains repeating -NHCHRCO- units; a fatty acid contains a long chain alkyl group, typically with ten or more carbon atoms; a steroid contains four-fused rings (three cyclohexane rings and one cyclopentane ring); and a carbohydrate contains either a five- or six-membered cyclic ether, typically with four or five hydroxyl groups, respectively.



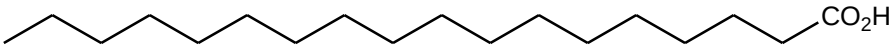
a peptide



a carbohydrate



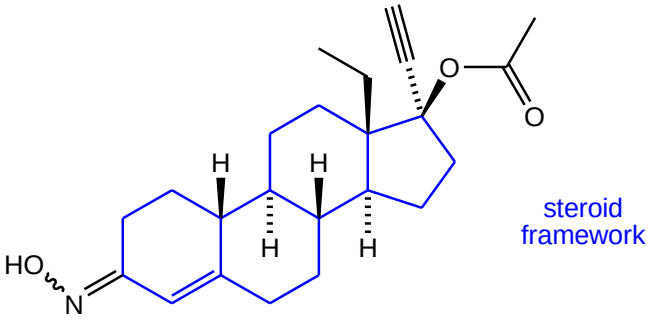
a steroid



a fatty acid

Solution

Norgestimate is a steroid, as it contains the all-important four-fused rings; this has been highlighted in blue, as shown below.



norgestimate

Answer

A steroid.

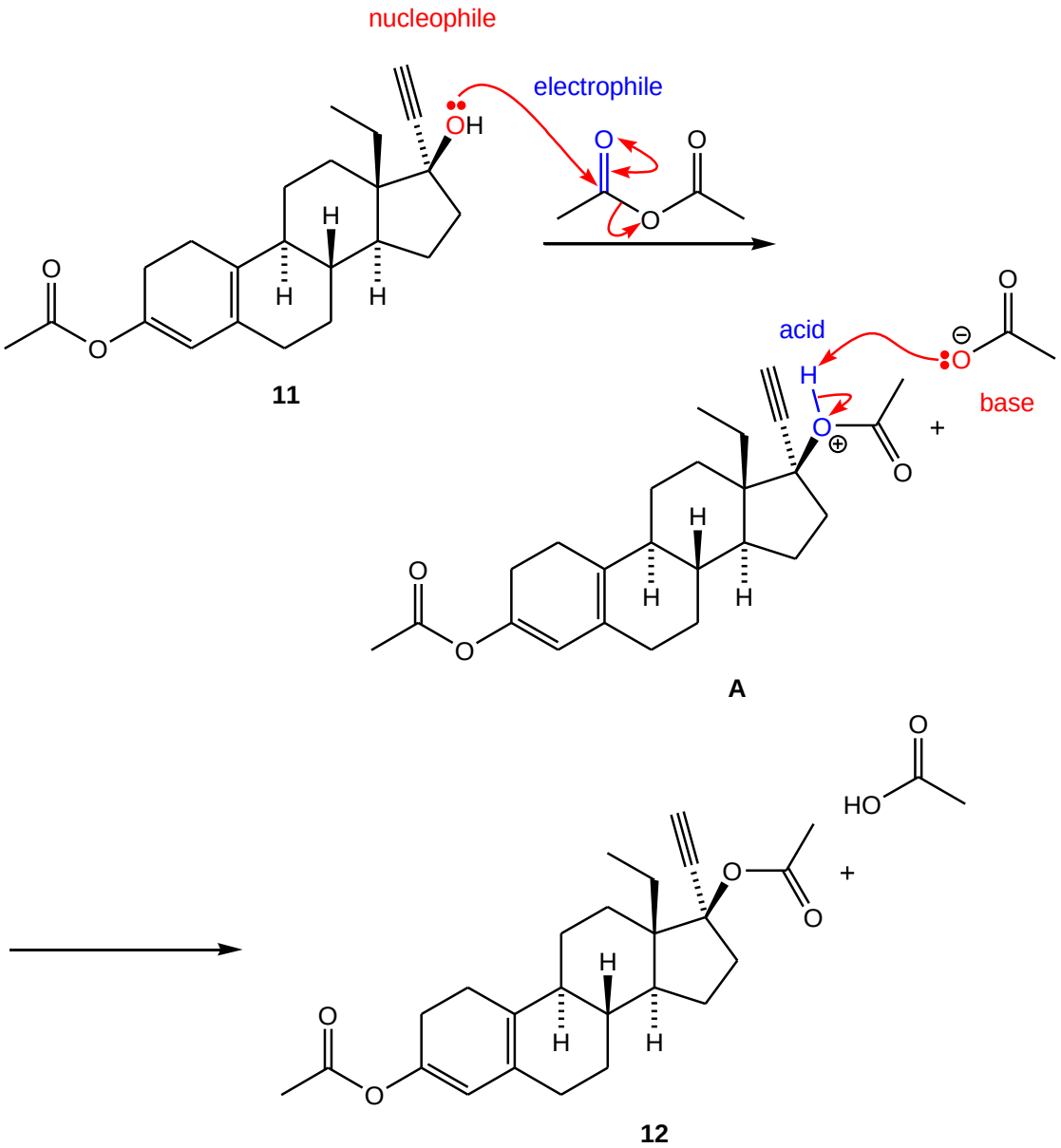
(b) Propose a mechanism to explain the conversion of alcohol **11** into ester **12**.

Strategy

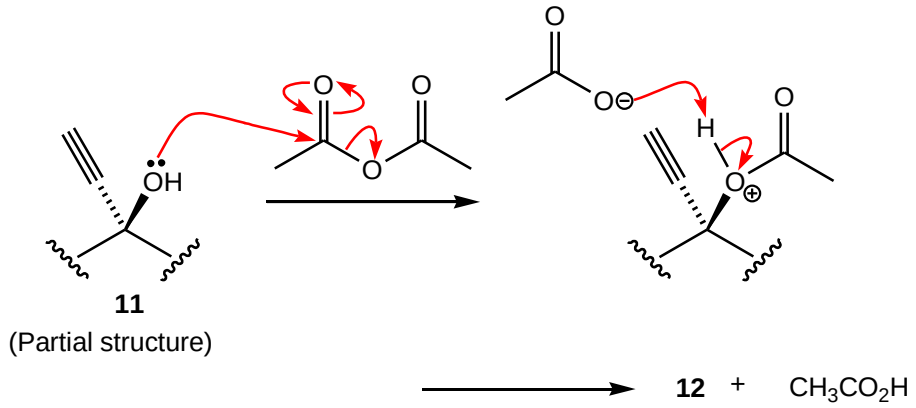
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

The alcohol, in **11**, is the nucleophile, and ethanoic anhydride (acetic anhydride, Ac_2O) is the electrophile. Nucleophilic addition of the alcohol (OH) group, in **11**, to the electrophilic carbonyl (C=O) group of ethanoic anhydride, followed by elimination of ethanoate, AcO^-, leads to the intermediate oxonium ion **A**. {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. 1097 in *Chemistry*[3].} Deprotonation of this oxonium ion **A** using ethanoate, AcO^-, as the base gives the required product **12**, and ethanoic acid, $MeCO_2H$, as the byproduct. The mechanisms for these steps are shown below.



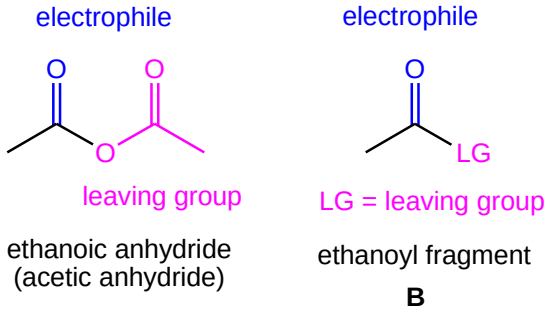
Answer



(c) Give the structure of a reagent, other than ethanoic anhydride, that will convert **11** into **12.**

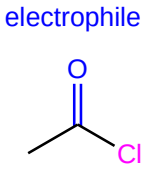
Strategy

Enthanoic anhydride is an electrophile in this reaction, where one of its carbonyl (C=O) groups is the electrophilic component, and ethanoate is the leaving group. A general reagent, such as **B**, would contain the all-important ethanoyl (MeCO) group bonded to a *pro*-leaving group.



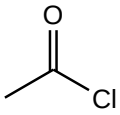
Solution

There are many potential reagents that can act as an electrophilic ethanoyl (MeC=O) source. One of the simplest is ethanoyl chloride, where the chlorine atom acts the *pro*-leaving group. The structure of ethanoyl chloride is shown below.



ethanoyl chloride

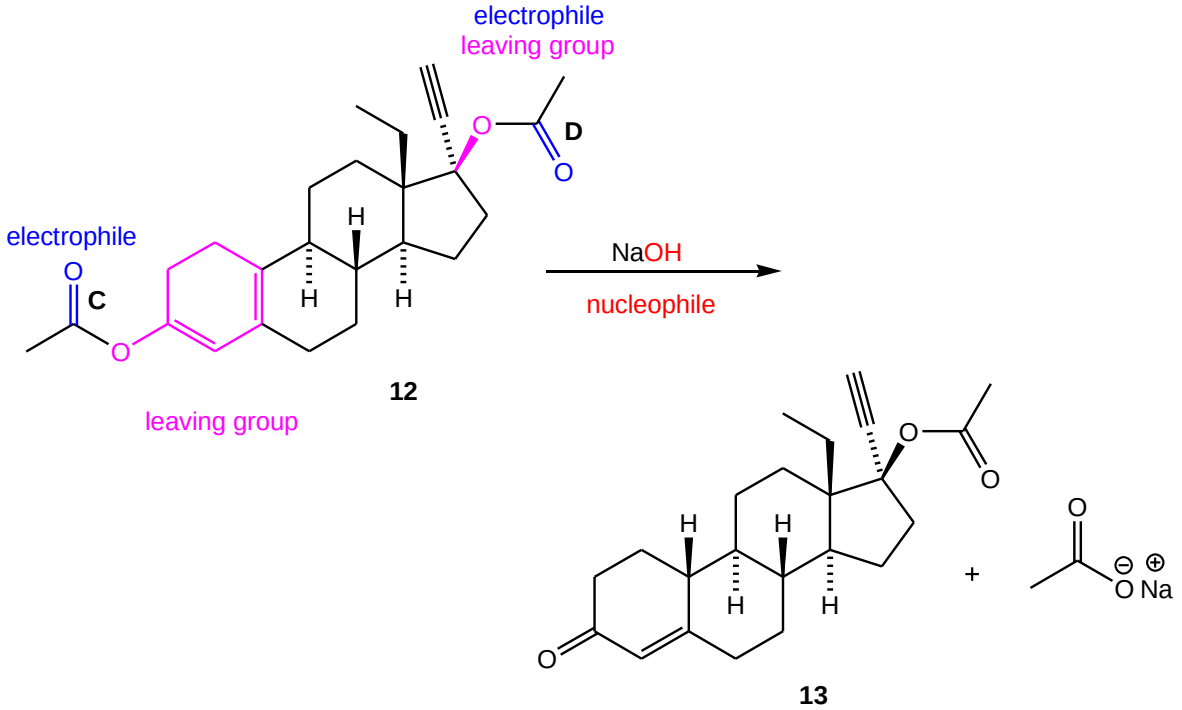
Answer



(d) Explain why NaOH reacts with only one of the ester groups in compound **12**. (*Hint*: consider the relative electrophilicity of the carbonyl carbons.)

Strategy

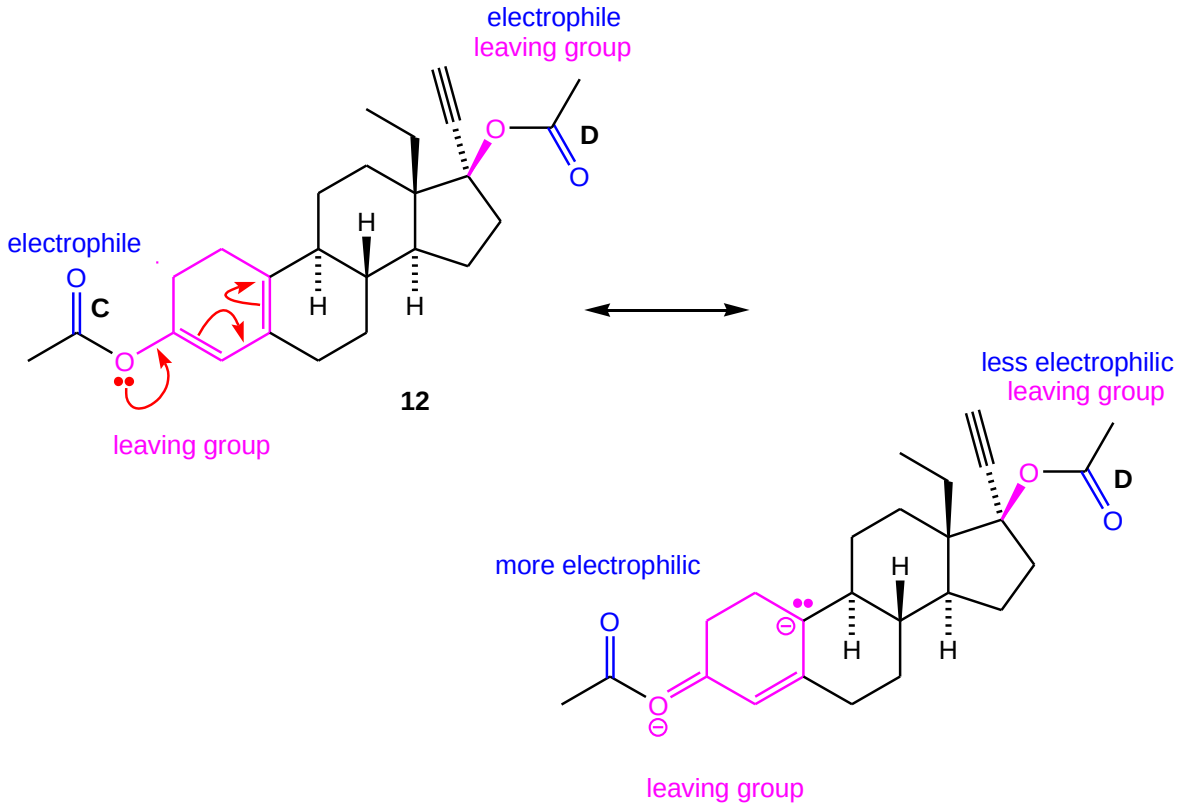
Hydroxide, HO^-, is the common nucleophile in both of these reactions. From the scheme below, nucleophilic addition preferentially occurs at the carbonyl (C=O) group of the enol ethanoate, **C**, to give the ketone **13**. This carbonyl (C=O) group, **C**, must be more electrophilic than the one in the ethanoate ester, **D**.



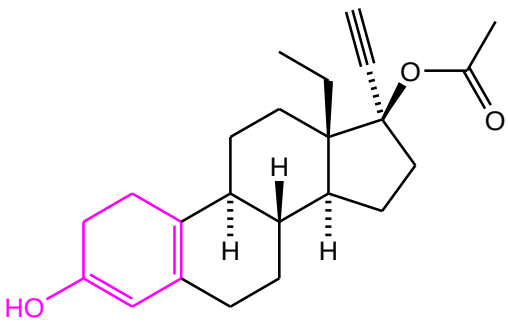
Rationalise this observation by considering their relative leaving groups.

Solution

The carbonyl group (C=O) of the enol ethanoate, **C**, is more electrophilic than that of the ethanoate ester, **D**, because of the conjugation present in the enol form, as shown below, which increasing its *pro*-leaving ability.

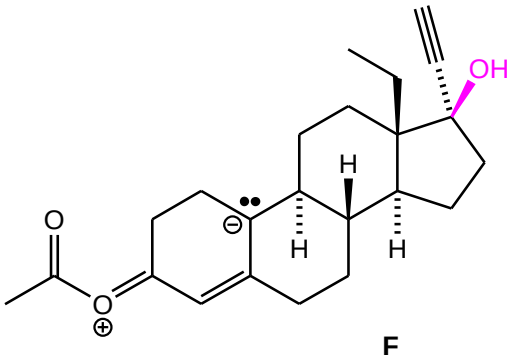


This stabilisation is also evident from the relative acidity of their conjugate acids. Enol, **E**, is more acidic [pK_a (H_2O)= 9] than the tertiary alcohol **D** [pK_a (H_2O)= 16] because its conjugate base is more stable through resonance.



E

leaving group
pK_a = 9

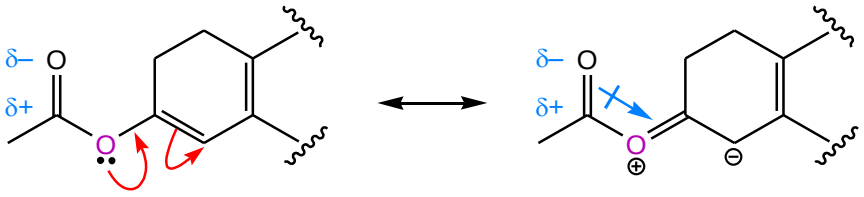


F

leaving group
pK_a = 16

Answer

Hydroxide ion selectively reacts with the most electrophilic carbonyl carbon. When the ester group is joined to a C=C bond, the lone pair of electrons on the singly bonded oxygen is shared between the C=O and C=C bonds. Delocalisation of the electrons onto the C=C bond makes the carbonyl carbon more electrophilic.



12
(partial structure)

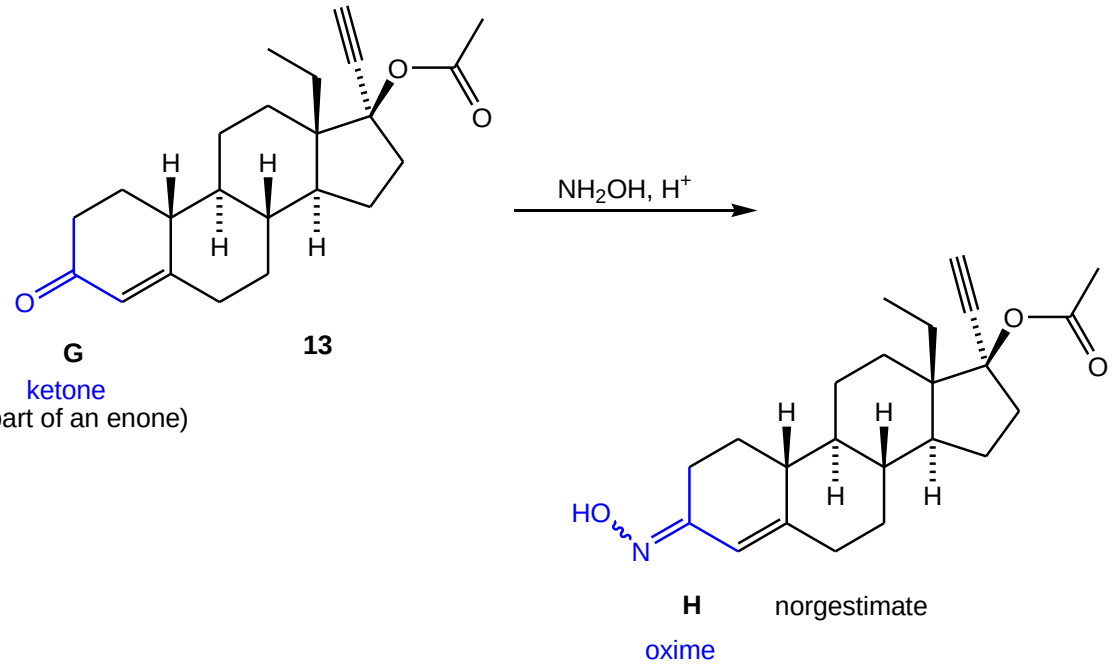
(e) What functional group is formed when compound **13** reacts with NH_2OH and H^+?

Strategy

Carefully consider the changes in functionality between the starting material, **13**, and the product, norgestimate. It is important to note that the alkane backbone of this molecule is not a functional group but its carbon skeleton.

Solution

For this reaction, there is only one change in functionality. The ketone group, **G**, in **13** has been replaced with an oxime group, **H**, in norgestimate.



G
ketone
(as part of an enone)

13

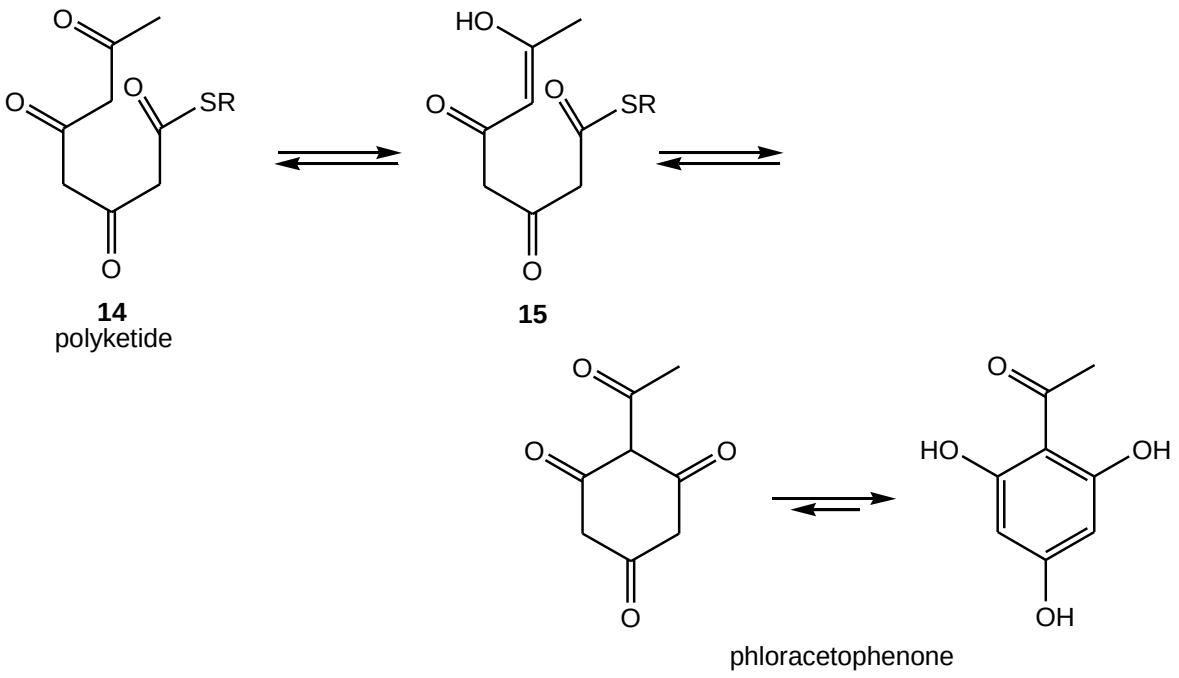
H
oxime

norgestimate

Answer

An oxime.

4. In nature, aromatic compounds are formed by the cyclization of polyketide chains (containing alternating C=O and CH_2 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 **14** is converted into phloracetophenone. Phloracetophenone, obtained from the plant *Curcuma comosa*, has been shown to lower cholesterol levels in animals.



14
polyketide

15

phloracetophenone

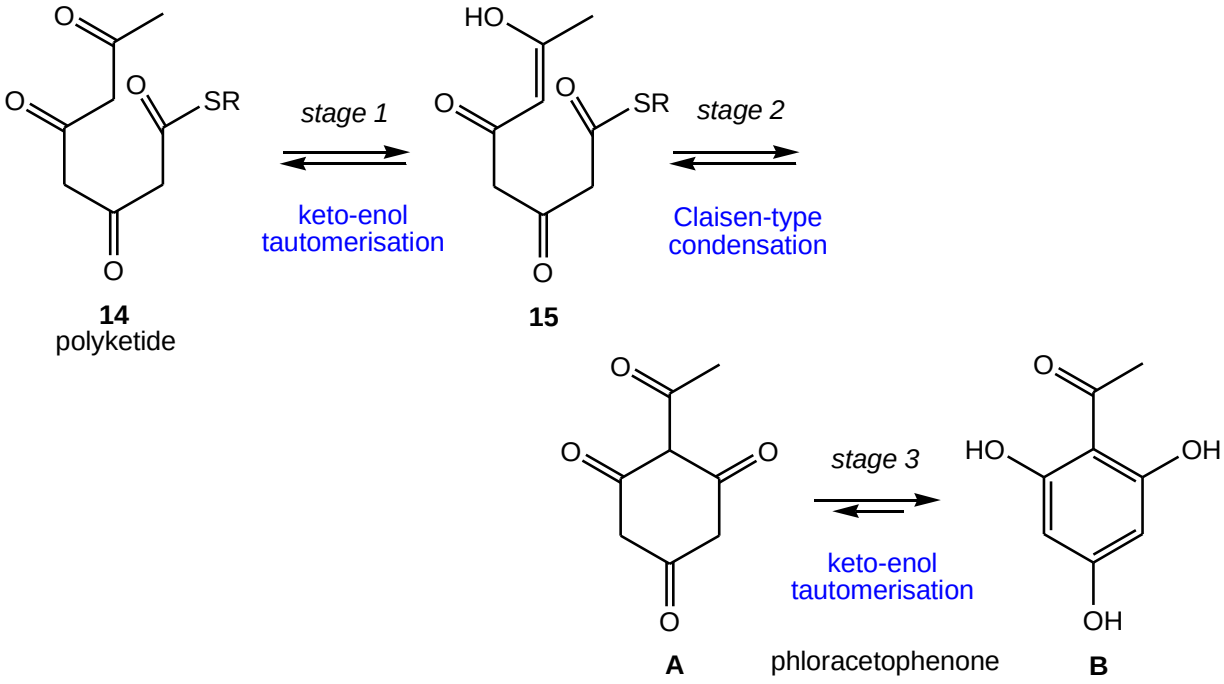
(a) Propose a mechanism that explains how compound **15** is converted into phloracetophenone.

Strategy

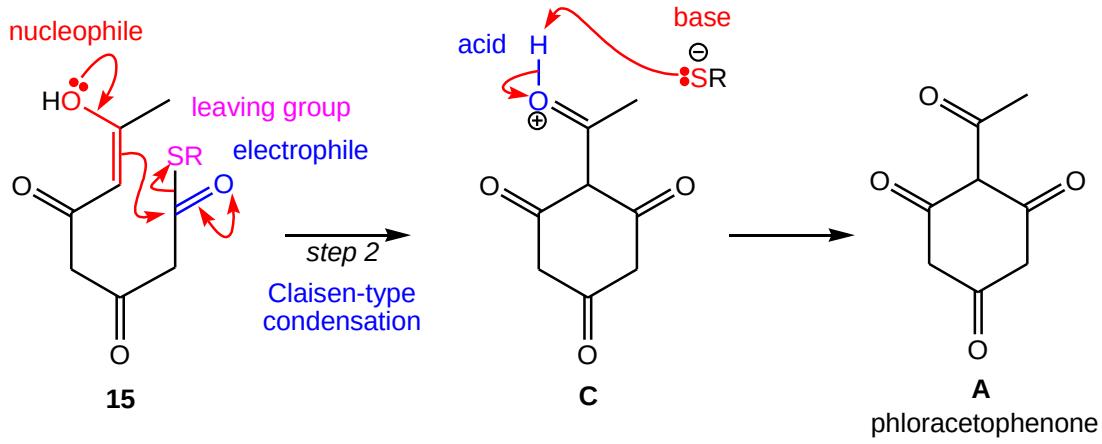
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

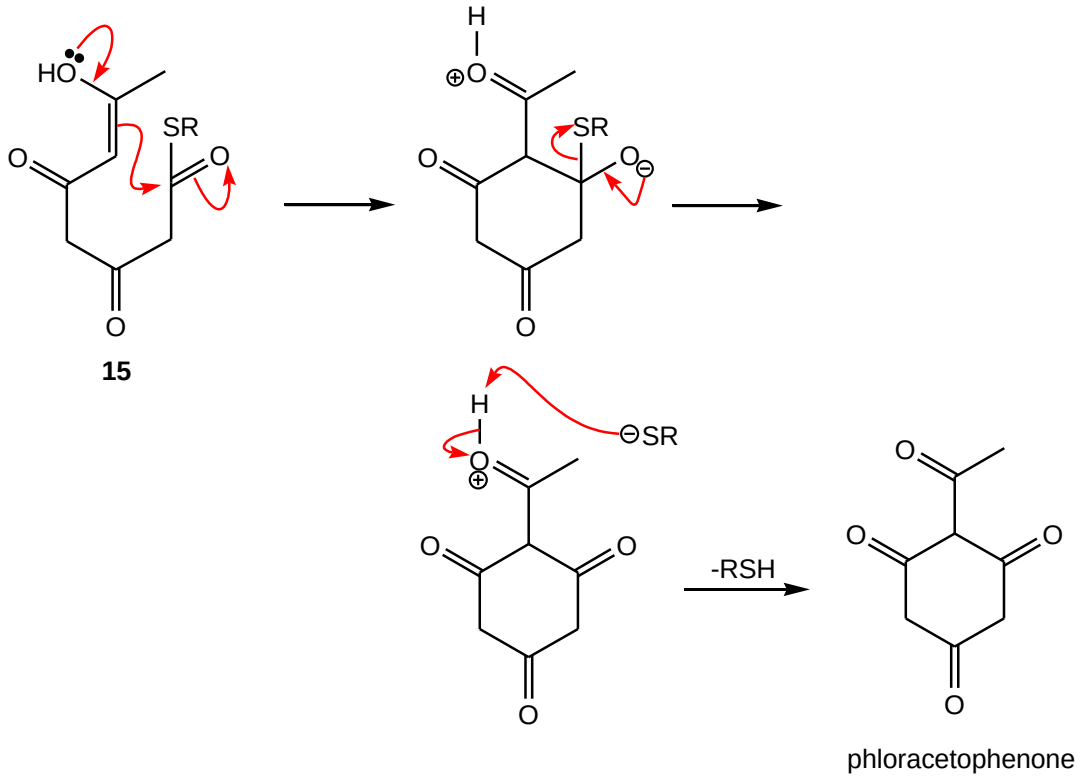
This sequence of reactions consists of three stages. Stage 1 (**14**→**15**) involves classical keto-enol tautomerisation; stage 2 (**15**→**A**) involves a Claisen-type condensation; and stage 3 (**A**→**B**) involves keto-enol tautomerisation. The enol tautomer of phloracetophenone **B** is more thermodynamically 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. 1097 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. 1123 in *Chemistry*^{3}.

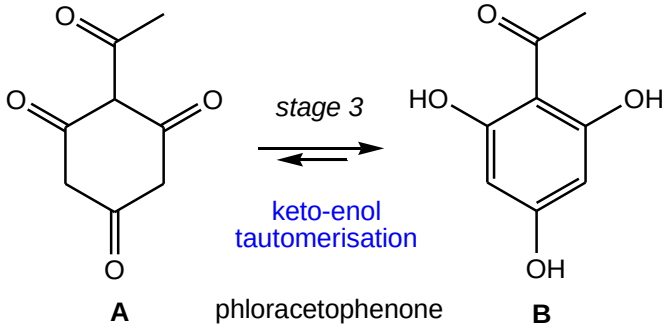


Answer



[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.

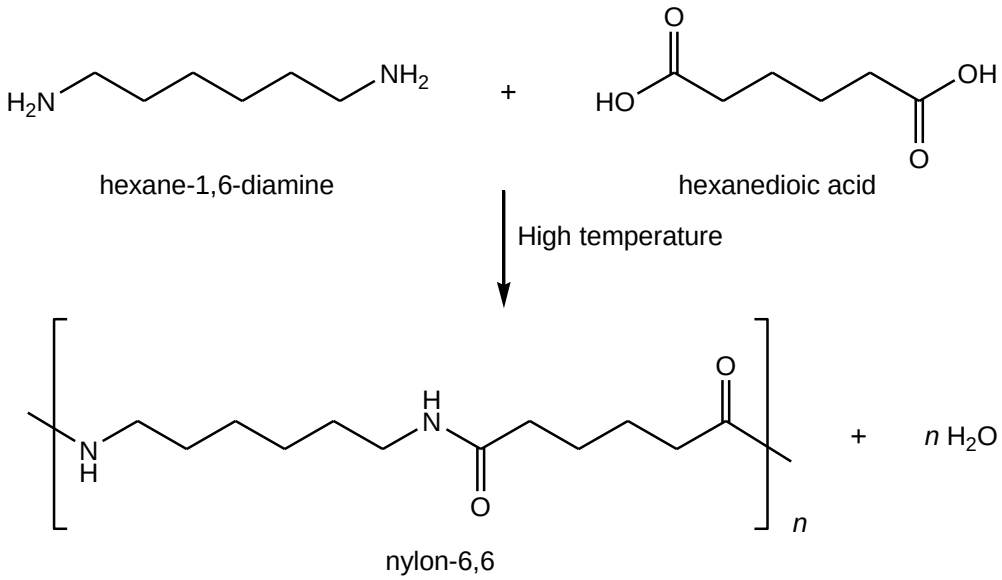
Solution

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-pi electrons with non-interrupted (continuous) conjugation.

Answer

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

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



nylon-6,6

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

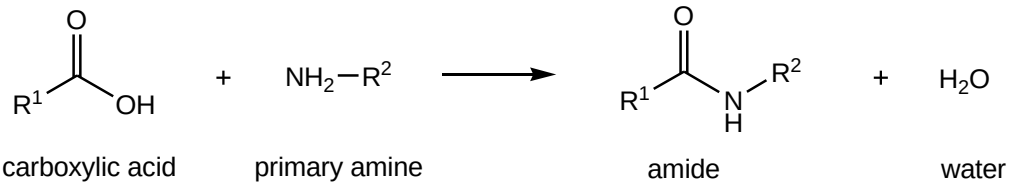
Strategy

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.



carboxylic acid primary amine amide water

Answer

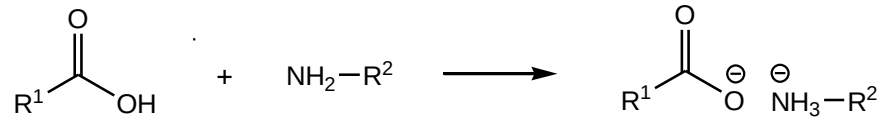
Two molecules of the monomer combine with the elimination of a molecule of water.

(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 (H_2O), 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.



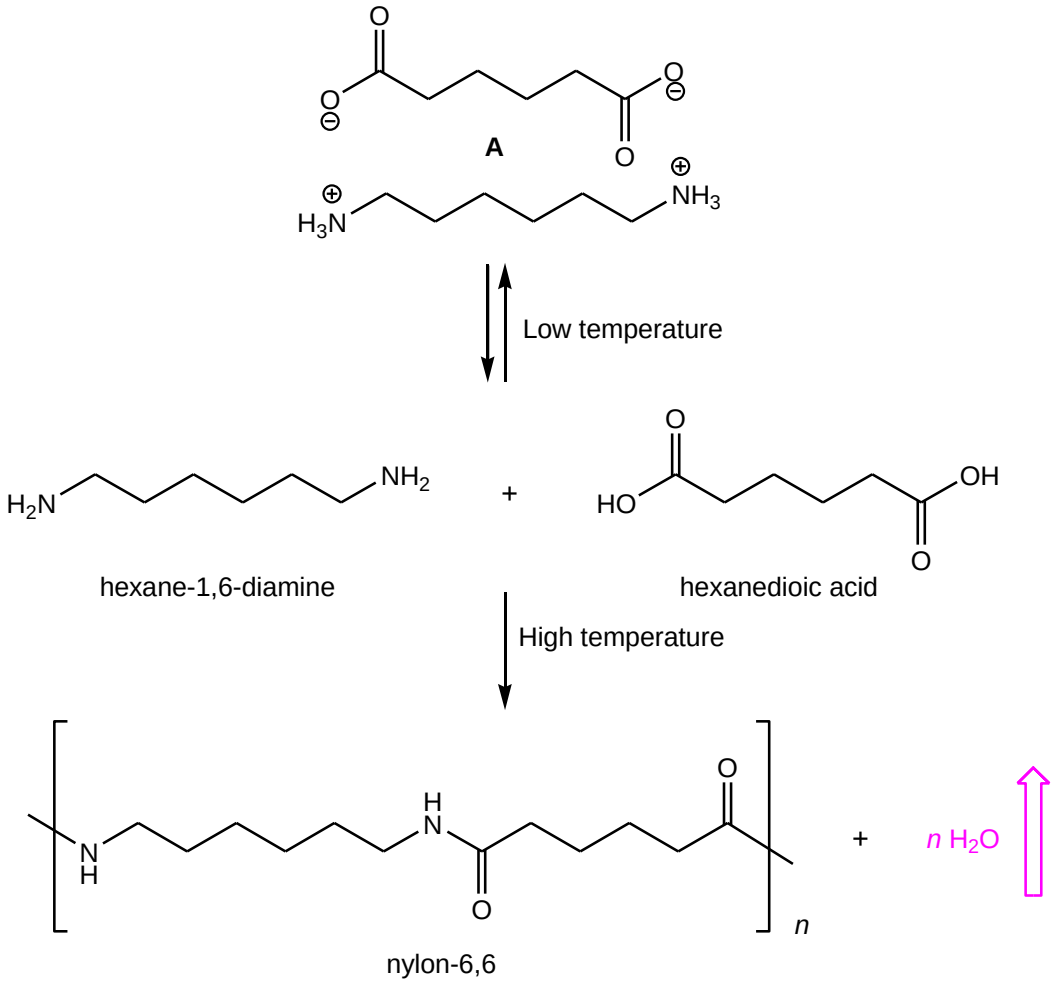
carboxylic acid primary amine ammonium salt

Solution

Addition of hexane-1,6-diamine to hexanedioic acid [pK_a (H_2O) = 5], gives the more stable diammonium salt **A** [pK_a (H_2O) = 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 (H_2O). This process is unfavourable. However, by continually removing the byproduct, water (H_2O), from this equilibrium, through heating to >100^{o}C forces this water to evaporate, and therefore drives the equilibrium towards the required product, nylon-6,6.



Answer

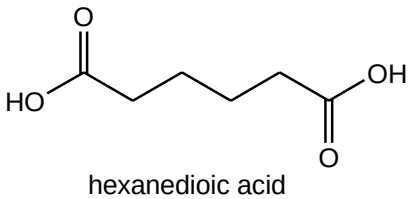
At room temperature, the amine and carboxylic acid react to form a salt, not an amide bond.

(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?

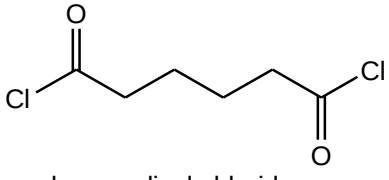
Strategy

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.



hexanedioic acid



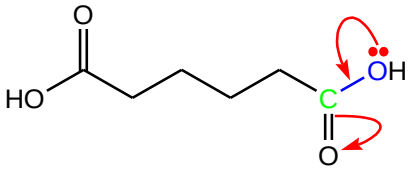
hexanedioyl chloride

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

Solution

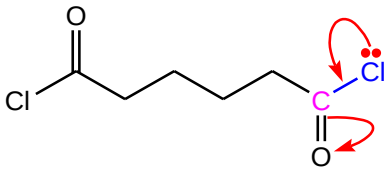
Hexanedioyl chloride is a better electrophile than hexanedioic acid for this condensation reaction as its chlorine (-Cl) atom is strongly electron-withdrawing (-I effect > + M effect). The non-bonded pairs of electrons on this chlorine atom are poorly electron-donating [into the carbonyl (C=O) group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



+M effect > -I effect
less electrophilic

hexanedioic acid



-I effect > +M effect
more electrophilic

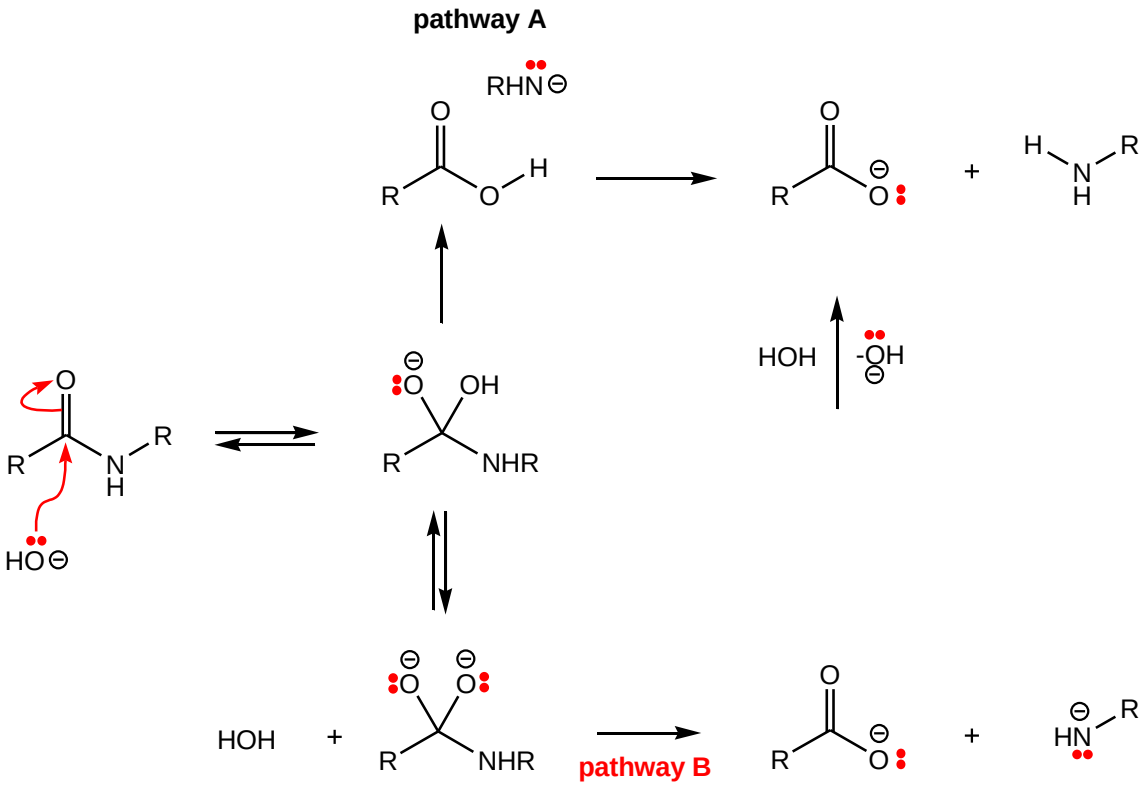
hexanedioyl chloride

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.

(d) 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.

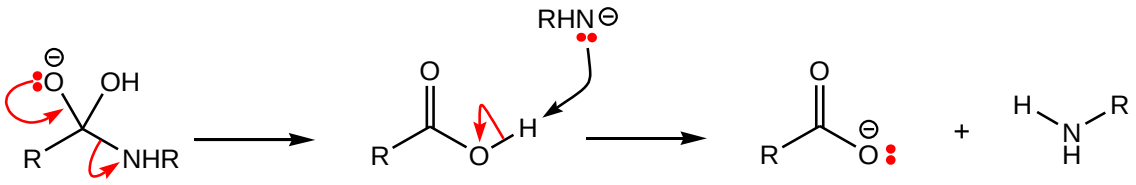
Strategy

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 (→).

Solution

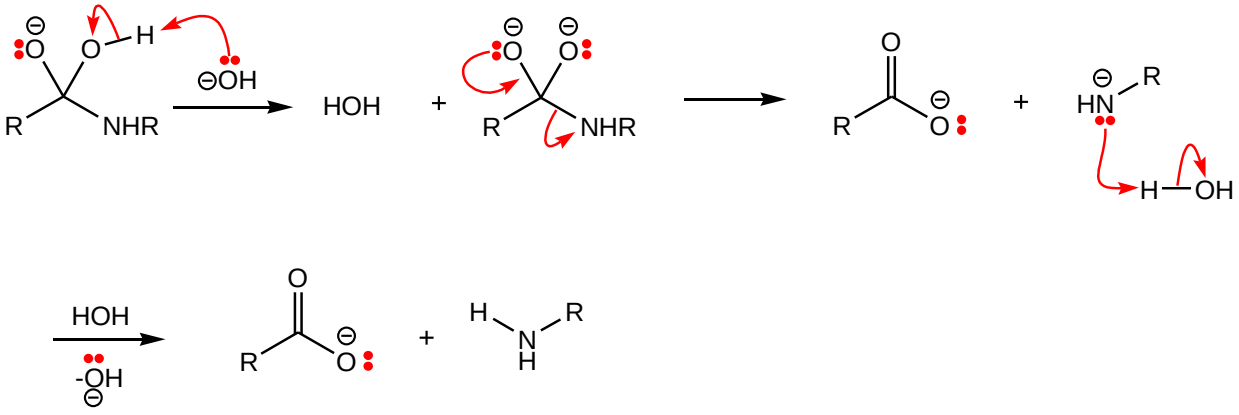
For pathway **A**: Lone-pair assisted elimination of the amide, RHN^-, using the non-bonded pair of electrons on the alkoxide, gives the intermediate carboxylic acid, RCO_2H. Deprotonation of this carboxylic acid, using the basic amide, RHN^-, gives the more stable carboxylate and primary amine, RNH_2.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

pathway A



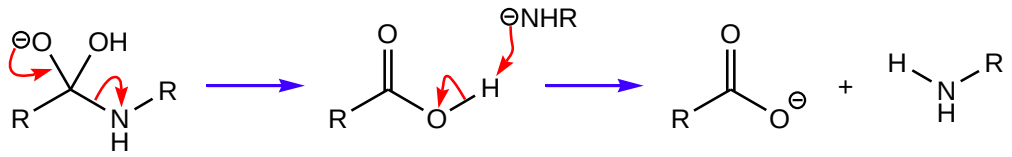
For pathway **B**: Deprotonation of the alcohol (OH) group using the non-bonded pair of electrons on the hydroxide (HO^-) leads to the intermediate di-anionic alkoxide. Lone-pair assisted elimination of the amide, RHN^-, using the non-bonded pair of electrons on the alkoxide, gives the intermediate carboxylate, 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 B

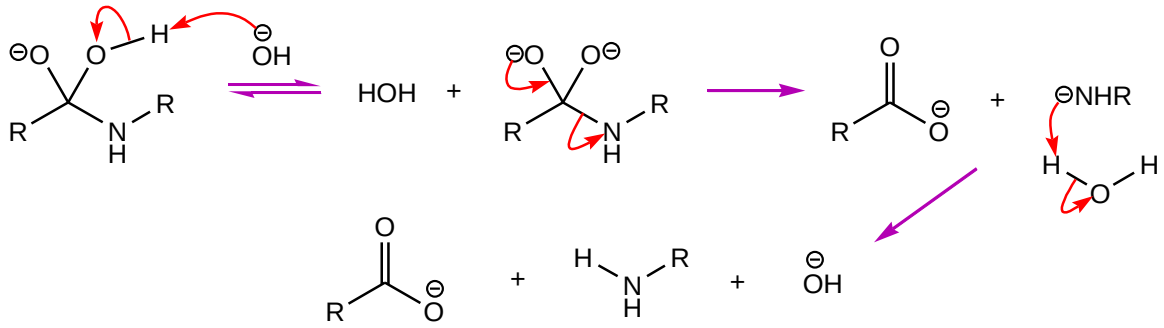


Answers

Path A



Path B



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

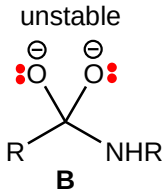
(d) (ii) Under what conditions would you expect path B be favoured over path A?

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.

Solutions provided by J. Eames (j.eames@hull.ac.uk)