23

Aldehydes and ketones: nucleophilic addition and α-substitution reactions

Answers to worked examples

WE 23.1 Reduction of an aldehyde (on p. 1067 in *Chemistry*^{3})

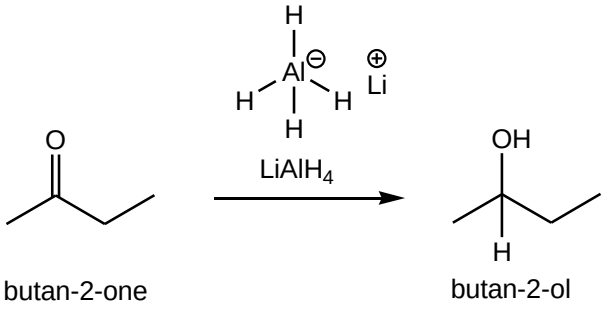
The organic product of the reaction of butan-2-one with $LiAlH_4$ followed by aqueous acid is butan-2-ol. Give a mechanism for this reaction.

Strategy

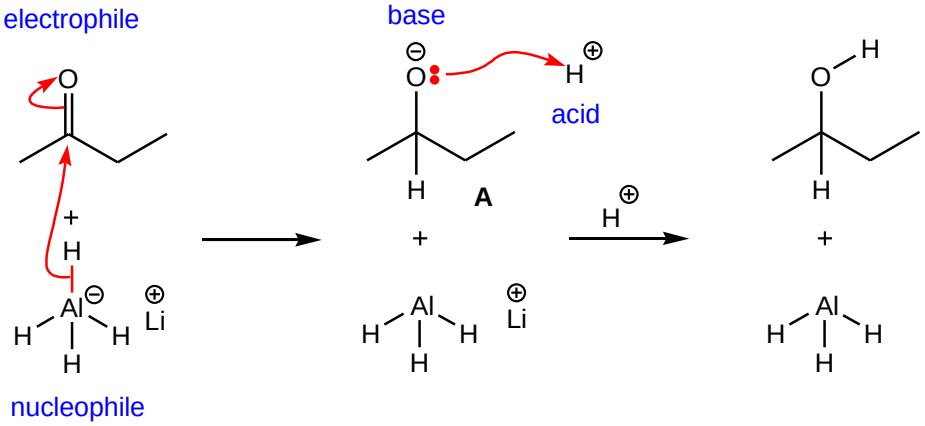
Draw out the starting materials, butan-2-one and $LiAlH_4$, and product, butan-2-ol. For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (→).

Solution

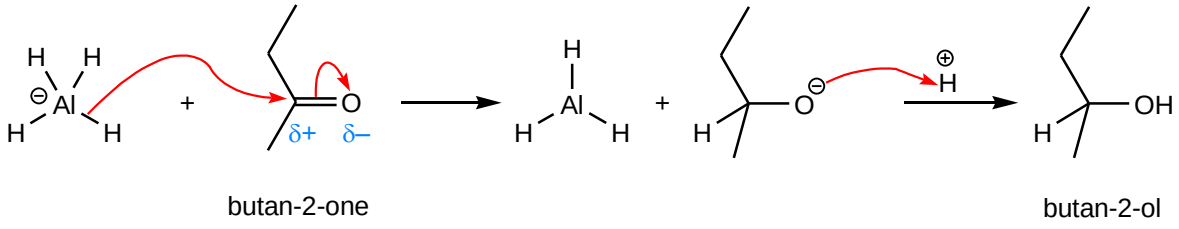
The structures of the starting materials and product are shown below.



$LiAlH_4$ is a nucleophilic source of hydride, and the ketone, butan-2-one, is the electrophile. Nucleophilic addition of hydride, from the high energy Al-H bonds, to the electrophilic carbonyl (C=O) group of butan-2-one gives the intermediate lithium alkoxide **A** and alane (AlH_3). [These intermediates can add together to form the corresponding –ate complex if you wish]. Protonation of this intermediate base, lithium alkoxide **A**, with aqueous mineral acid (HCl/H_2O) gives the required product, butan-2-ol. Butan-2-ol is a secondary alcohol, and the overall reaction is a reduction. The mechanism is shown below, and is discussed on p. 1057 in *Chemistry*[3].



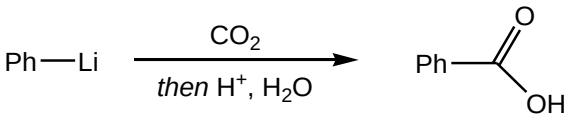
Answer



[This protonation step can also be depicted using a negative charge instead of a non-bonded pair of electrons.]

WE 23.2 Reaction with organometallics (on p. 1070 in *Chemistry*^{3})

Propose a mechanism to explain the following reaction.

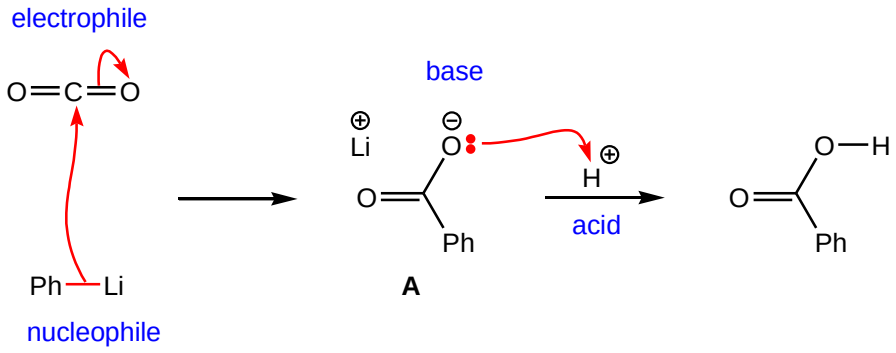


Strategy

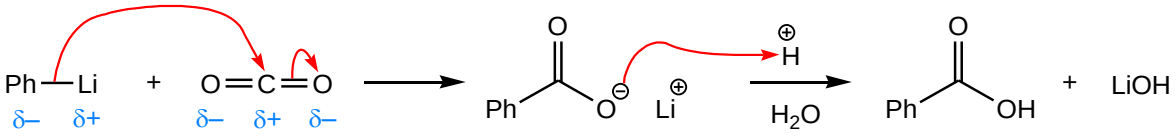
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

Nucleophilic addition of the phenyl carbanion, from the high-energy organolithium reagent, PhLi, to the electrophilic carbonyl (C=O) group of carbon dioxide (CO_2) gives the intermediate lithium carboxylate **A**. Protonation of this intermediate base, lithium carboxylate **A**, with aqueous mineral acid (HCl/H_2O) gives the required product, benzoic acid. Benzoic acid is a carboxylic acid, and this overall reaction is an informal reduction. The mechanism of this reaction is shown below; a related example is discussed on p. 1063 in *Chemistry*^{3}.



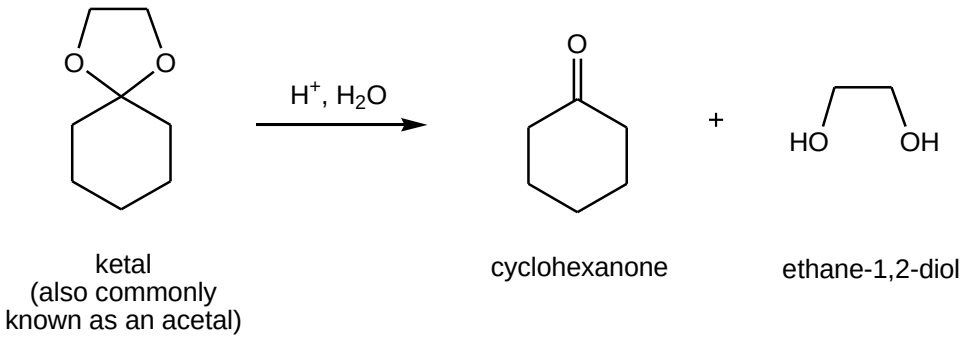
Answer



[This protonation step can also be depicted using a negative charge instead of a non-bonded pair of electrons.]

WE 23.3 Acetal formation (on p. 1076 in *Chemistry*^{3})

Give a mechanism to show how the acetal is converted back into cyclohexanone and ethane-1,2-diol using H^+/H_2O.

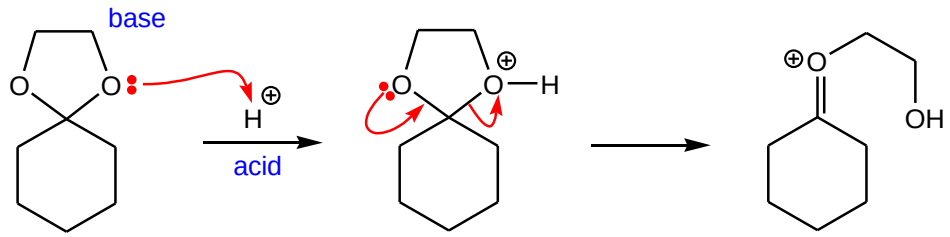


Strategy

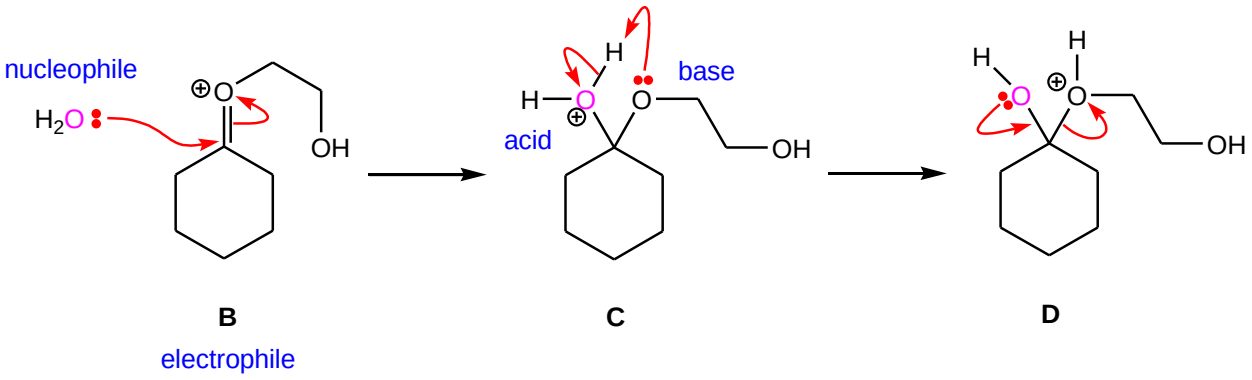
This reaction and its associated mechanism are simply the reverse of that outlined in the worked example 23.3. Remember the oxygen atom of the carbonyl group of cyclohexanone is derived from water (H_2O). For each step, within your proposed mechanism, you will need to decide whether the reaction involves 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 (→).

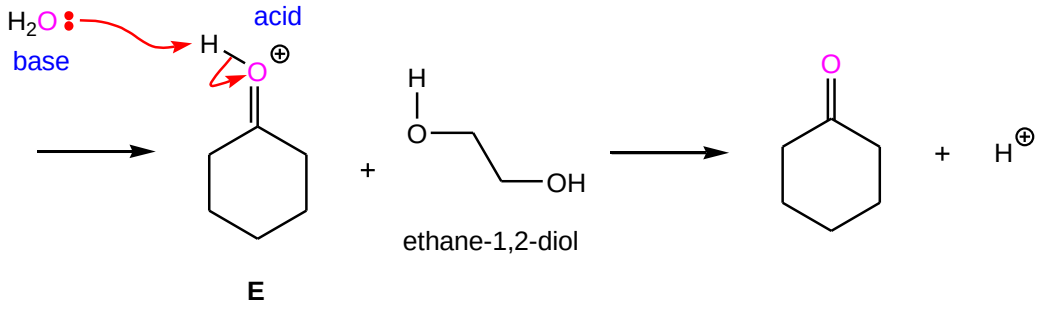
Solution

Protonation of the basic oxygen atom of the ketal with acid, H^+, leads to the intermediate protonated ketal **A**. This intermediate fragments through lone pair assisted cleavage of its C-O^+ bond using a non-bonded pair of electrons from the other oxygen atom of the ketal, in **A**, to give the intermediate oxonium ion **B**.

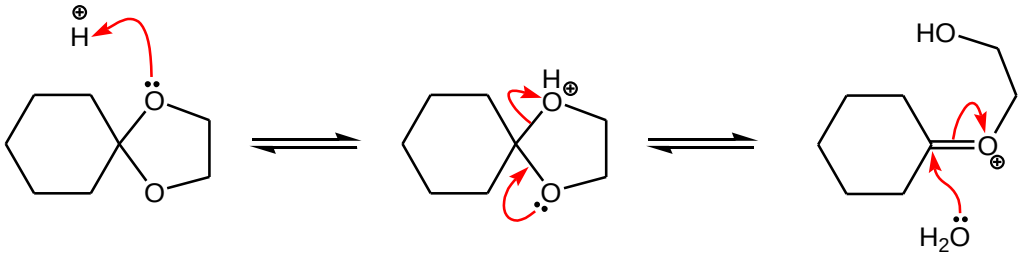


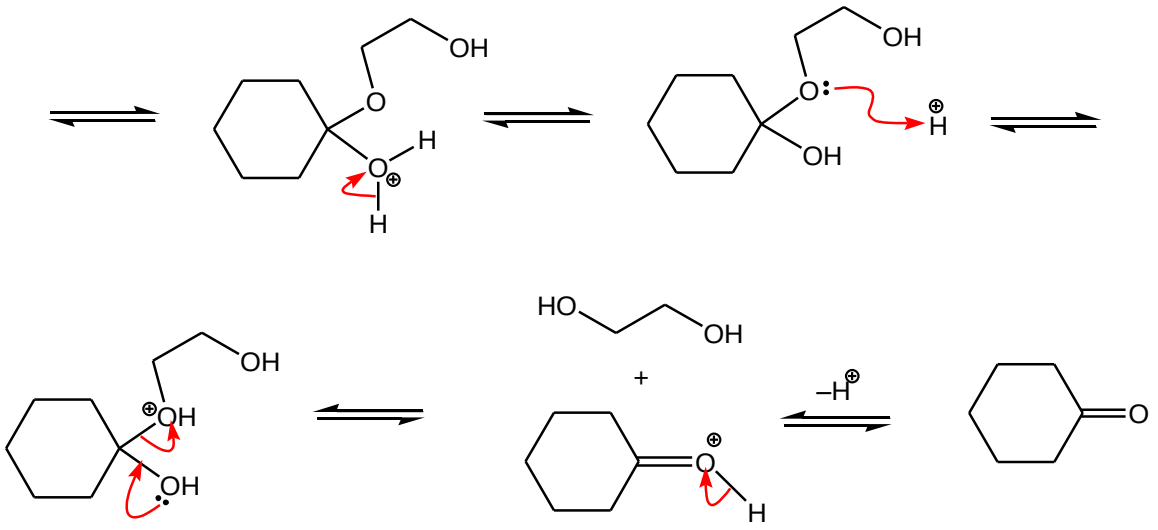
Nucleophilic addition of water to the electrophilic oxonium ion **B** leads to the protonated hemiketal **C**, followed by simple acid-base internal proton exchange gives the protonated hemiketal **D**. Reformation of the thermodynamically more stable carbonyl C=O group occurs by elimination of ethane-1,2-diol, in **D**, to give the intermediate protonated cyclohexanone **E**. Simple deprotonation of **E** with another molecule of water (H_2O) gives the required cyclohexanone.





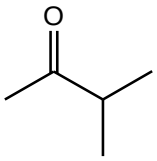
Answer

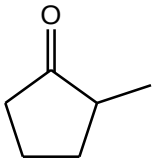




WE 23.4 Bromination of an unsymmetrical ketone (on p. 1085 in *Chemistry*[3])

Draw the different enol forms of the following unsymmetrical ketones and, for each compound, predict which is the more stable enol form.

(a) 

(b) 

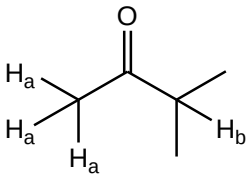
Strategy

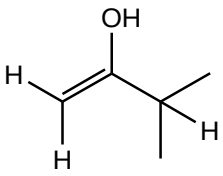
Enols are unstable tautomers of carbonyl-containing molecules; their enol content is usually less than 1% due to the strength of their carbonyl (C=O) double bond in their keto-form (a ketone or an aldehyde). In order to form an enol, the carbonyl-containing molecule must have an alpha C(sp^3)-H bond.

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 - only consider mono-enol formation.

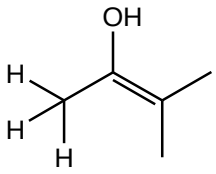
Solution

(a)





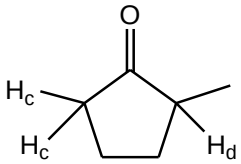
A

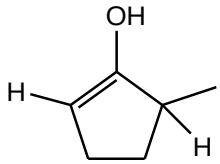


B

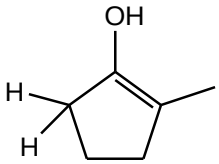
There are two chemically different alpha C(sp^3)-H bonds, namely, H_a and H_b, which can lead to two potential enols **A** and **B**, respectively. The more substituted enol **B** is more thermodynamically stable than enol **A** due to increased hyperconjugation from its neighbouring CH_3 groups; the relative amount of this enol (in a sample of this ketone) is <1%. For additional information on hyperconjugation; see p. 866 in *Chemistry*^{3}.

(b)





C

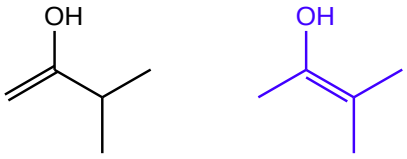


D

There are two chemically different alpha C(sp^3)-H bonds, namely, H_c and H_d, which can lead to two potential enols **C** and **D**, respectively. The more substituted enol **D** is more thermodynamically stable than enol **C** due to increased hyperconjugation from its neighbouring CH_3 group; the relative amount of this enol (in a sample of this ketone) is <1%.

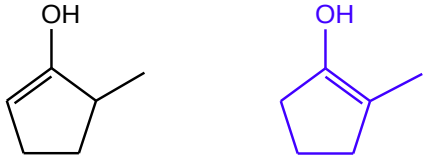
Answer

(a)



more stable
(more substituted
C=C bond)

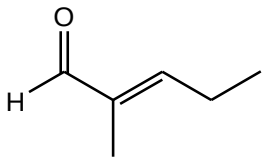
(b)

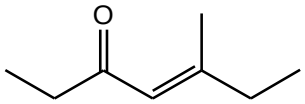


more stable
(more substituted
C=C bond)

WE 23.5 An aldol condensation reaction (on p. 1091 in *Chemistry*^{3})

Give the structure of the precursor aldehyde or ketone that would form the following compounds by aldol condensations.

(a) 

(b) 

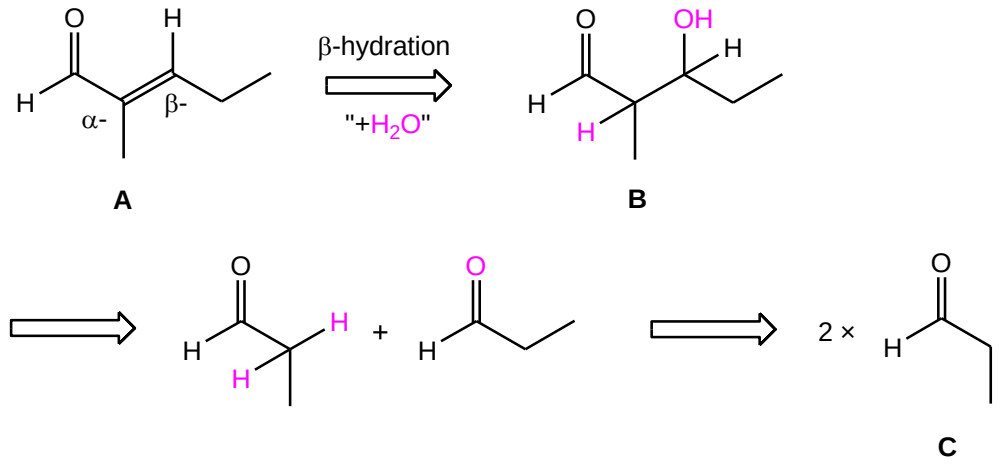
Strategy

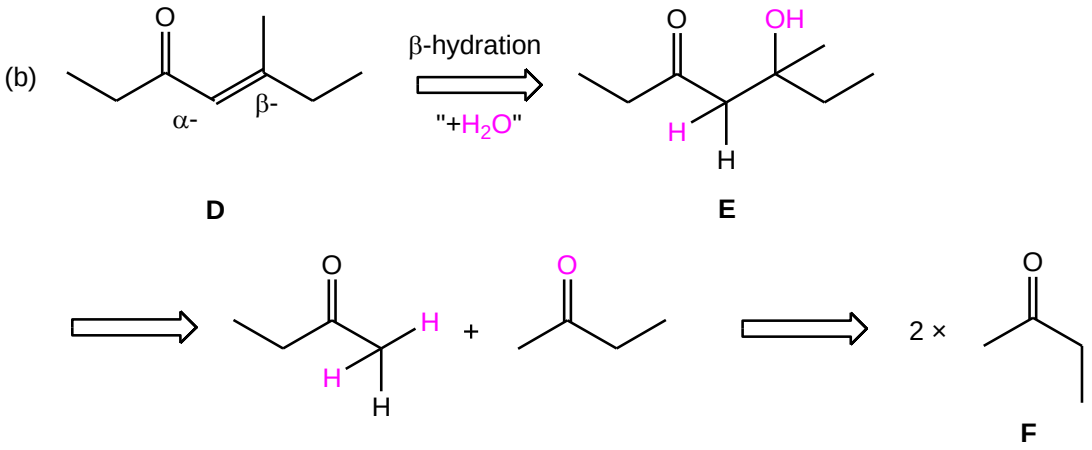
These products are derived from the condensation of two identical carbonyl-containing molecules. Both these products can be formed under acidic and basic conditions.

The required carbonyl-containing precursors can be revealed through β-hydration.

Solution

By working backwards, simple β-addition of water (H_2O) across the carbon-carbon double bond of enone **A** gives the intermediate β-hydroxy aldehyde **B**. Fragmentation of this intermediate (through enol formation, followed by tautomerisation) leads to two molecules of aldehyde, propanal **C**. Therefore, aldehyde **C** is the precursor for the product (a).

(a) 



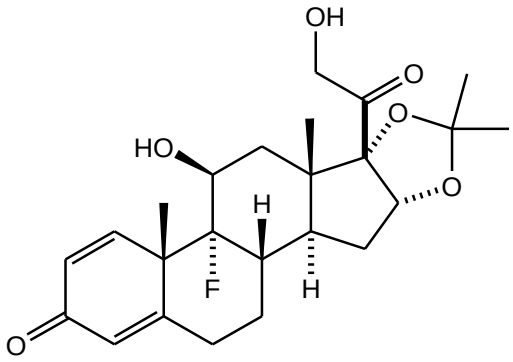
Once again, by working backwards, simple β-addition of water (H_2O) across the carbon-carbon double bond of enone **D** gives the intermediate β-hydroxy ketone **E**. Fragmentation of this intermediate (through enol formation, followed by tautomerisation) leads to two molecules of ketone, butan-2-one **F**. Therefore, ketone **F** is the precursor for the product (b).

Answer

Answers to boxes

Box 23.1 Cortisone and cortisol (on p. 1060 in *Chemistry*^{3})

Triamcinolone acetonide is a synthetic steroid, used to help treat inflammation in patients suffering from asthma and arthritis.



triamcinolone acetonide

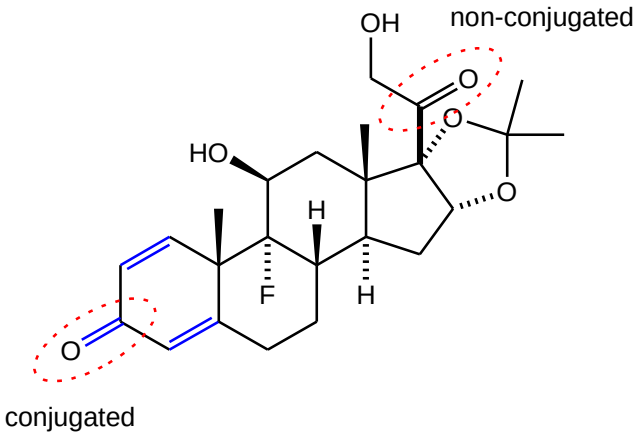
(a) Which of the two C=O bonds in triamcinolone acetonide is not conjugated?

Strategy

Highlight both carbonyl (C=O) groups in this molecule (by ringing them). A carbonyl group, which is conjugated, must be resonance stabilised using π- (from double or triple bonds) or non-bonded electrons (from a heteroatom) attached to its alpha-carbon atom.

Solution

There are two carbonyl (C=O) groups; the bottom one is conjugated due to the conjugation/resonance stabilisation from the two adjacent carbon-carbon (C=C) double bonds. The top carbonyl group is non-conjugated as there is neither a pi- bond nor a pair of non-bonded electrons attached to its alpha-carbon atom.



(b) For the C=O bond that is not conjugated, indicate the α-positions and determine the number of α-hydrogen atoms.

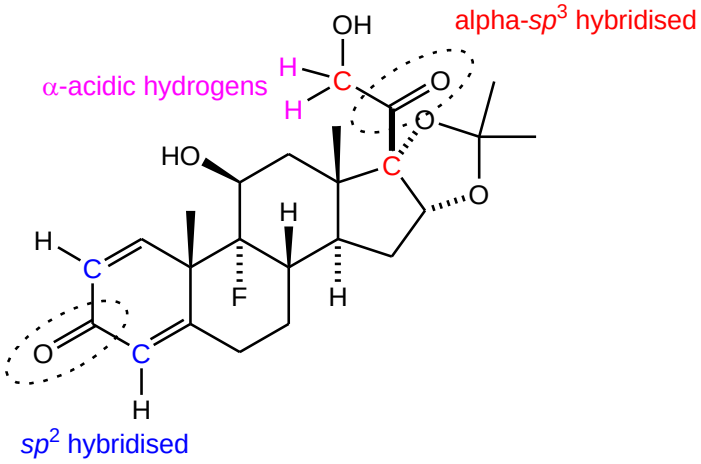
Strategy

Draw out this molecule, and include all alpha C(sp^3)-H bonds. Note: sp^3 NOT sp^2!

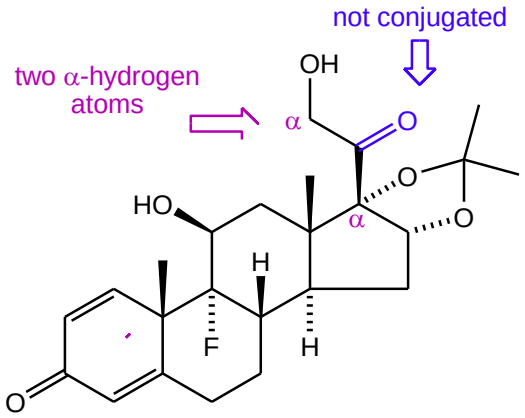
Solution

The non-conjugated carbonyl (C=O) group has TWO alpha-carbon atoms. The left-hand side alpha-carbon atom has TWO alpha-hydrogen atoms. In comparison, the right-hand side alpha-carbon atom has no acidic hydrogen atoms.

The conjugated carbonyl group has TWO alpha-carbon atoms; however, these are sp^2-hybridised and therefore the corresponding hydrogen atoms are non-acidic as they are orthogonal (90^o) to the carbonyl (C=O) group.



Answer



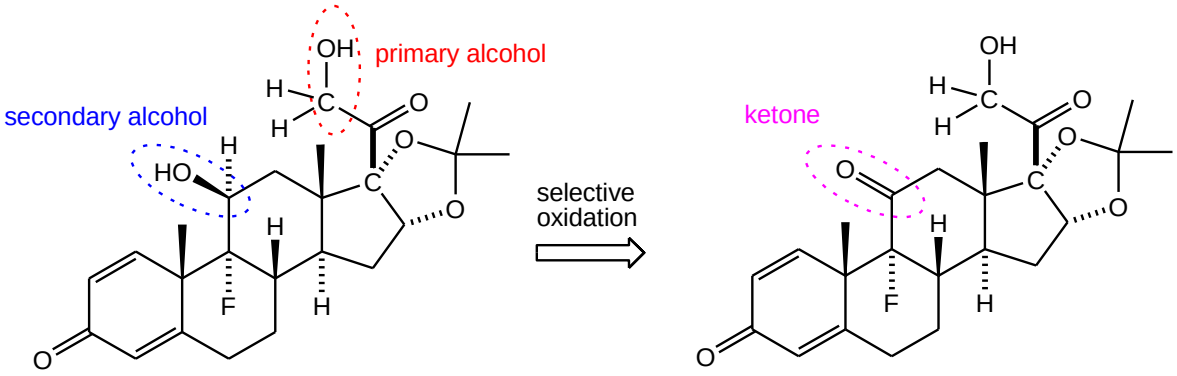
(c) Draw the structure of the product formed on oxidation of the secondary alcohol in triamcinolone acetonide.

Strategy

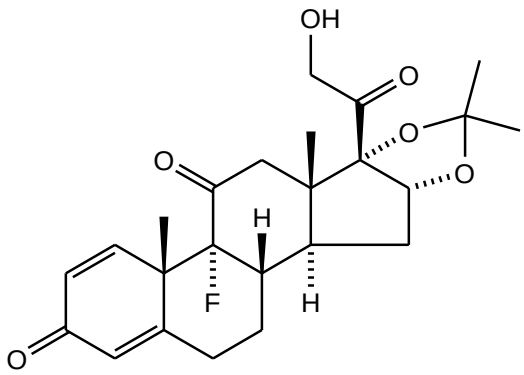
Highlight the secondary alcohol (CHOH) group in this molecule (by ringing it). Oxidation of a secondary alcohol, such as R_2CHOH, leads to a ketone, $R_2C{=}O$. The product can be drawn easily by replacing the CH-OH group with a C=O group.

Solution

There are two alcohols in this molecule, namely the primary alcohol (RCH_2OH) and secondary alcohol (R_1R_2CHOH). Selective oxidation of this secondary alcohol leads to the ketone as shown below.



Answer



Box 23.2 Oxidizing alcohols to carbonyls (on p. 1064 in *Chemistry*^{3})

The following questions relate to the mechanism of oxidation of the secondary alcohol shown in Figure 2 on page 1058 in *Chemistry*^{3}.

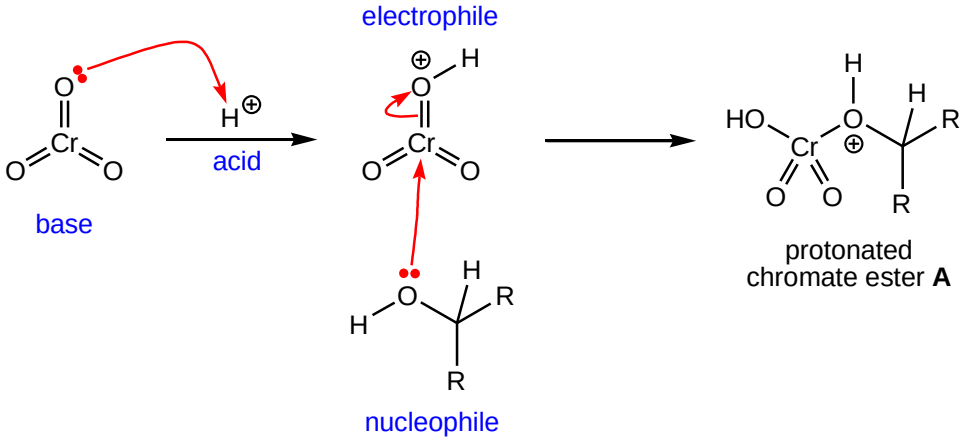
(a) What is the role of H^+ in the reaction?

Strategy

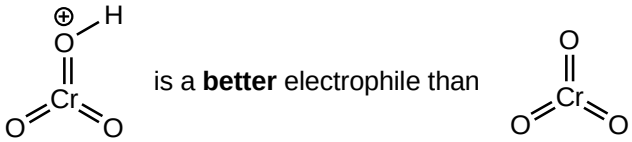
H^+ is as an acid. It promotes this oxidation and is regenerated at the end of this reaction (see Figure 2).

Solution

H^+ is as an acid catalyst. Protonation of chromium trioxide, CrO_3, with acid, H^+, leads to protonated chromium trioxide, CrO_3H^+. Nucleophilic addition of the secondary alcohol, R_2CHOH, to this protonated chromium trioxide, CrO_3H^+ is significantly faster than addition to the parent chromium trioxide, CrO_3, due to its increased electrophilicity.



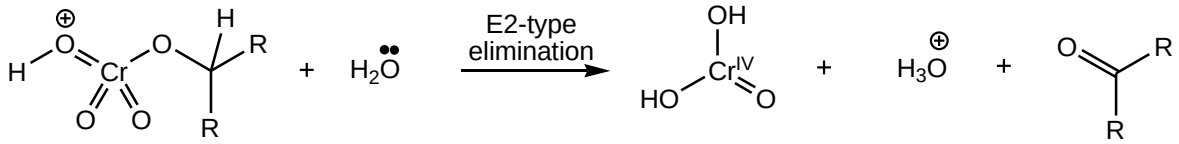
This is because of the developing negatively charged transition state (for the addition of R_2CHOH to CrO_3) is better stabilised by the positive charge on the oxygen atom of CrO_3H^+.



Answer

H^+ adds to CrO_3 and this converts it into a stronger electrophile.

(b) Formation of the ketone from the chromate ester, may take place by a different elimination mechanism. If the chromate ester is protonated, it can react with water in an E2-type elimination to form the ketone (see below). Suggest a mechanism for this reaction. (E2 reactions are discussed in section 20.4 on p. 937 in *Chemistry*^{3}).



protonated
chromate ester

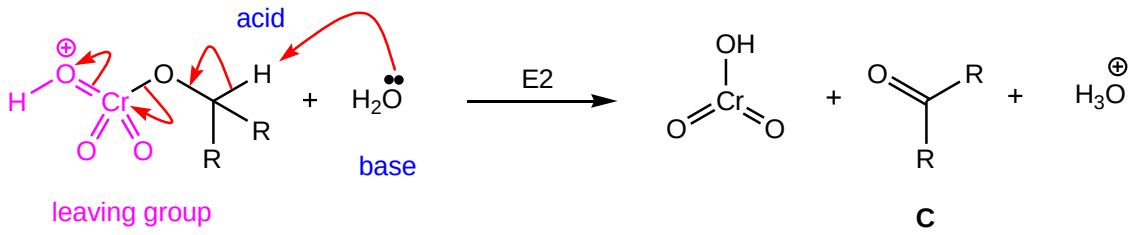
Strategy

For 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 (→).

E2 elimination is a concerted elimination involving an acid-base combination.

Solution

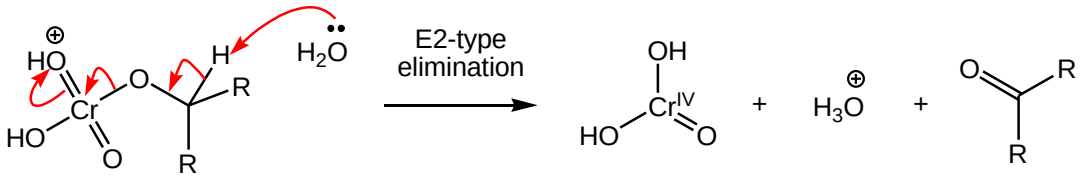
For this E2 elimination, the protonated chromate ester **B** is the acid, and water (H_2O) is the base. Anti-periplanar E2 elimination of the leaving group, $O{=}Cr(OH)_2$, from the protonated chromate ester **B**, using water (H_2O) as the base, gives the required ketone **C**. The mechanism of this process is shown below.



protonated
chromate ester **B**

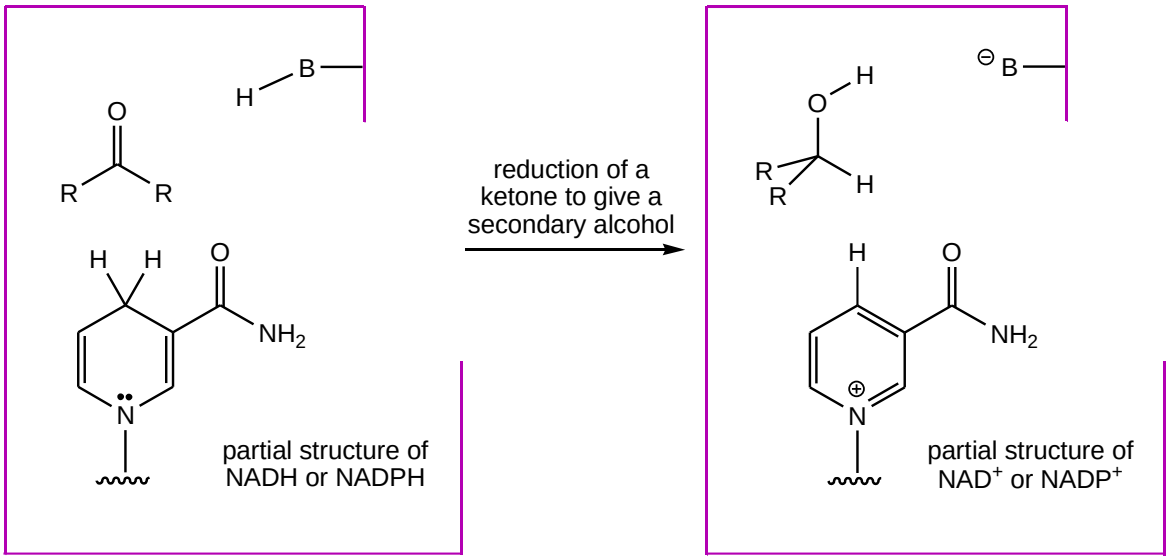
C

Answer



Box 23.3 Hydride transfer in nature (on p. 1066 in *Chemistry*^{3})

In the reaction shown below; use curly arrows to show the movement of electrons when either NADH or NADPH reduces the ketone.



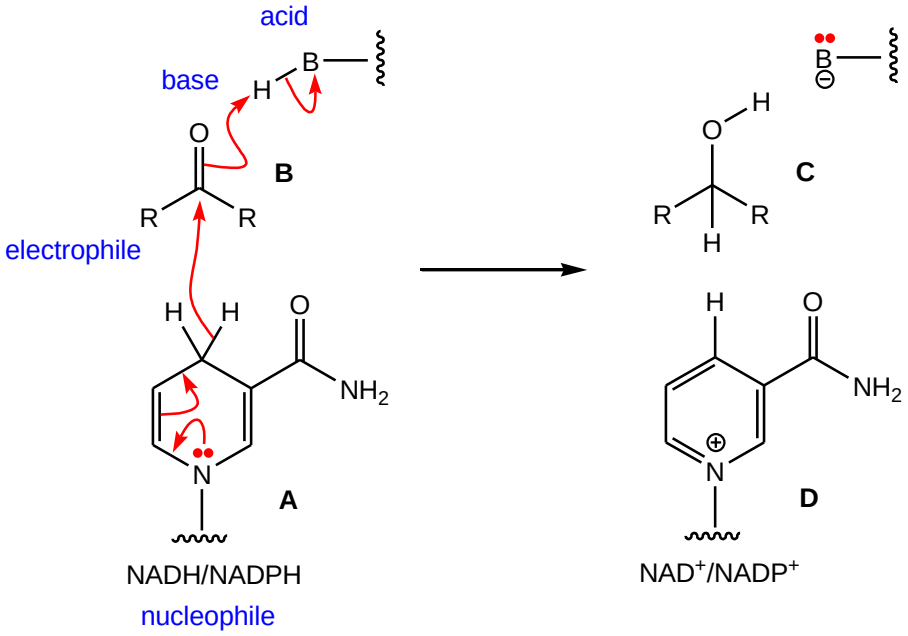
Strategy

For 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 (→).

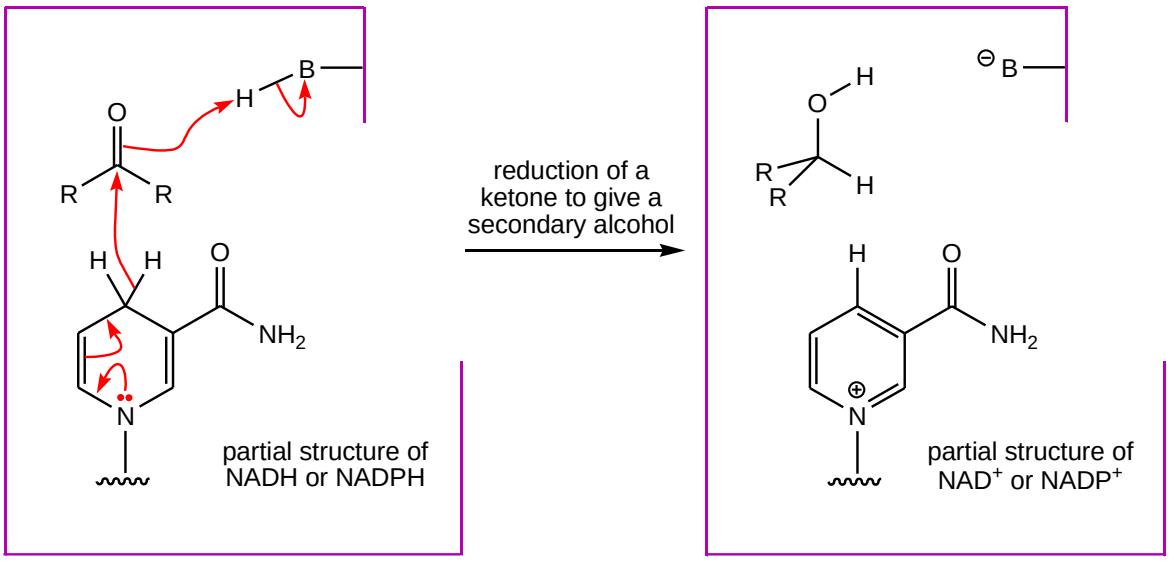
This reduction is reversible, and therefore could be considered as a retro-E2 elimination.

Solution

NADH and NADPH are nucleophilic sources of hydride, and the ketone, $R_2C=O$, is the electrophile. Nucleophilic addition of hydride, from the dihydropyridine ring of either NADH or NADPH (**A**), to the electrophilic carbonyl (C=O) group of ketone **B**, followed by concerted deprotonation of the neighbouring acid, -BH, leads to the secondary alcohol **C** and the pyridinium salt $NAD^+/NADP^+$ (**D**). These reactions are subtly different to classical $NaBH_4/LiAlH_4$ reductions as they occur in a concerted single-step, and are general acid catalysed. The mechanism of this reaction type is shown below.



Answer



Box 23.4 A short history of organometallics (on p. 1069 in *Chemistry*[3])

In poly(propene), the methyl groups on the carbon chain can have different relative orientations. In *isotactic* poly(propene), all of the methyl groups are on the same side of the carbon chain; in *syndiotactic* poly(propene), the positions of the methyl groups alternate; whereas, in *atactic* poly(propene), the positions of the methyl groups are random. Given the partial structure of atactic poly(propene) shown here, draw partial structures of both isotactic and syndiotactic poly(propene).

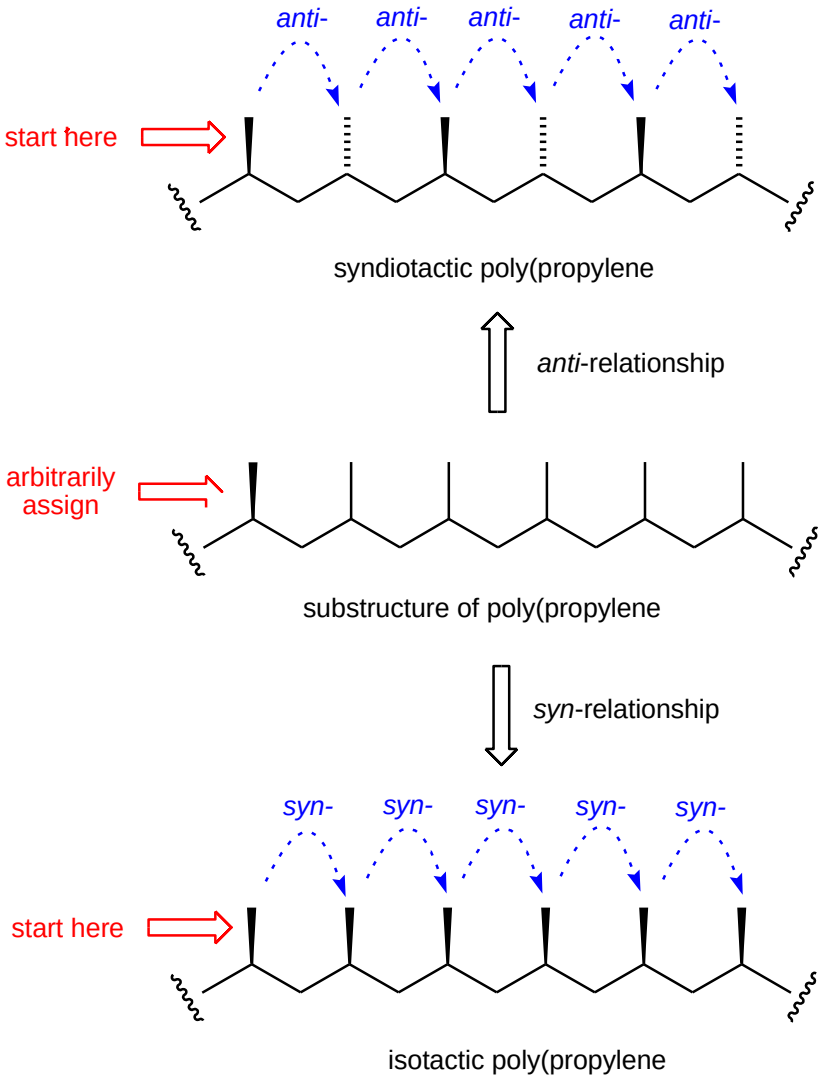
Strategy

Draw out the substructure of poly(propylene). For the isotactic isomer, all methyl groups are on the same face of the molecule; they have a *syn*-relationship. Whereas, for the syndiotactic isomer, all these methyl groups are sequentially on opposite faces of the molecule; they have an *anti*-alternating relationship to each other.

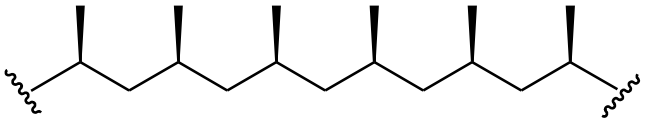
Solution

The substructure of poly(propylene) is shown below. The furthest left-hand configuration has been arbitrarily assigned as coming forward using a bold wedge. For the syndiotactic

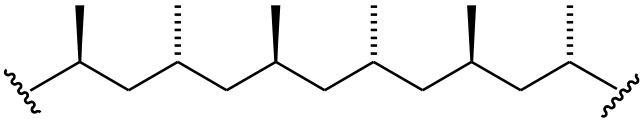
isomer, the remaining methyl groups (and relative chiral centres) have a sequential *anti*-relationship. Whereas, for the isotactic isomer, the remaining methyl groups (and relative chiral centres) are on the same face of this molecule and they all have a sequential *syn*-relationship.



Answer



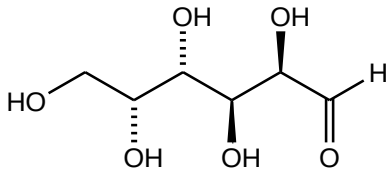
isotactic poly(propylene)



syndiotactic poly(propylene)

Box 23.5 The structure of glucose (on p. 1073 in *Chemistry*^{3})

The structure of the open-chain form of the sugar D-galactose is shown here. Draw the structures of the two galactopyranoses.



D-galactose

Strategy

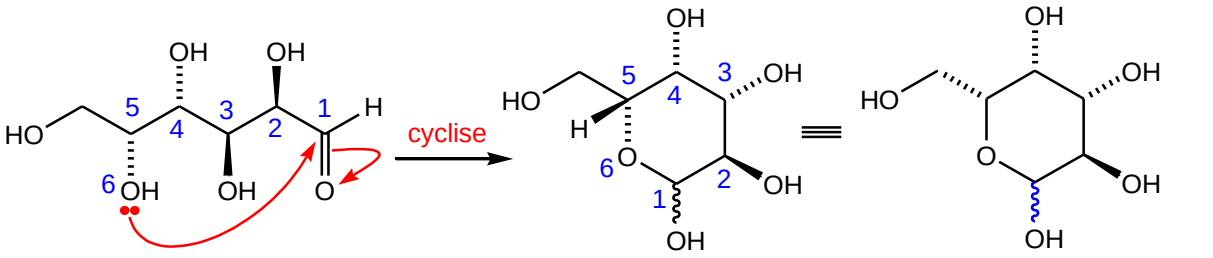
D-Galactose contains four chiral centres. Galactopyranose is a closed chain form of galactose that contains a six-membered pyranose ring. On formation of the hemiacetal (pyranose) ring, a new chiral centre is formed.

Work out which hydroxyl (OH) group is needed to form the required six-membered acetal, and cyclise it onto the aldehyde group to form two diastereoisomeric (epimeric) galactopyranoses.

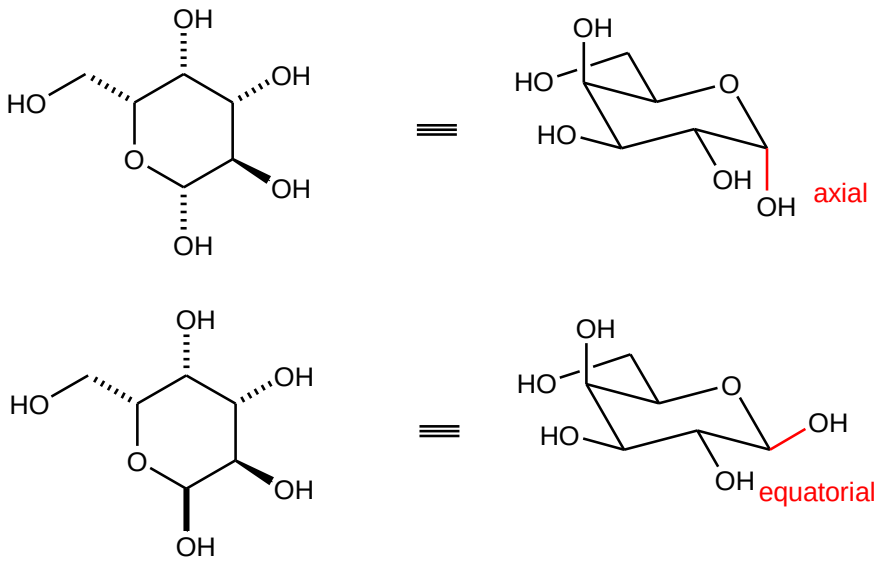
Solution

By drawing out the structure of D-galactose, and pre-numbering the pyranose ring from the aldehyde group (position 1) to the required hydroxyl (OH) group (at position 6) reveals the connectivity of the required pyranose ring. Formation of the pyranose (hemiacetal) ring is

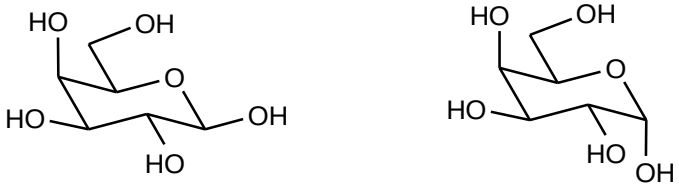
reversible and under thermodynamic control. Nucleophilic addition of the hydroxyl group (at position 6) to the aldehyde, generates an unequal mixture of diastereoisomeric cyclic hemiacetals. The remaining chiral centres are unchanged; however their conformation has changed.



These two diastereoisomeric pyranoses can be drawn in their more conventional chair arrangement, as shown below. The OH group of the hemiacetal can adopt either an axial or equatorial position. Usually, the axial position is favoured due to the anomeric effect.

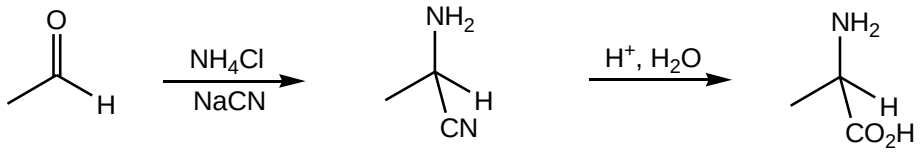


Answer



Box 23.6 Imines and hydrazones in organic synthesis (on p. 1079 in *Chemistry*^{3})

The amino acid alanine is prepared from ethanal by the Strecker synthesis shown below. Suggest a mechanism to explain how ethanal is converted into 2-aminopropanenitrile.



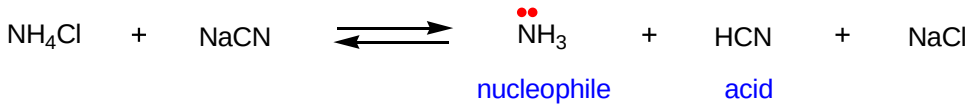
ethanal 2-aminopropanenitrile alanine

Strategy

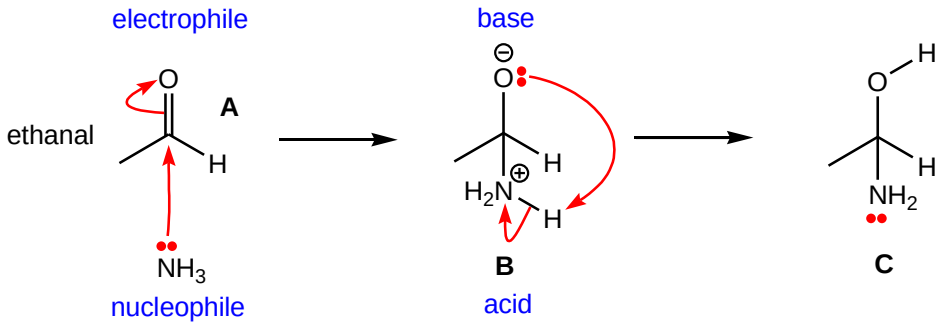
For your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the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

Solution

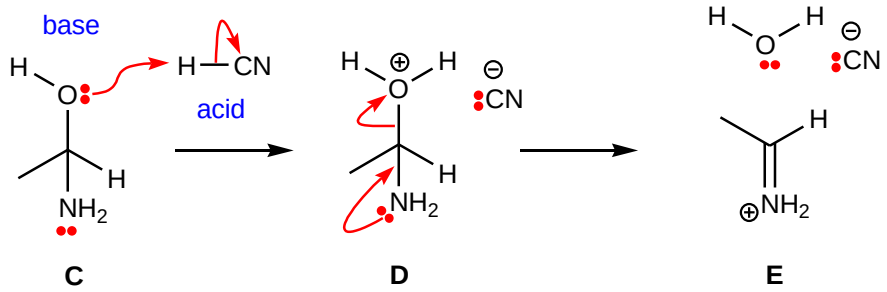
Under acid-base equilibrating conditions, small quantities of ammonia (NH_3) and hydrogen cyanide (HCN; pK_a = 7) are formed from ammonium chloride (NH_4Cl; pK_a = 9) and sodium cyanide (NaCN). It is important to note, in this reaction, ammonia is the active nucleophile and not cyanide (^-CN).



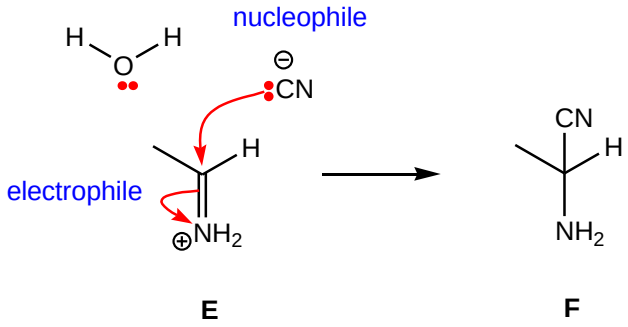
Nucleophilic addition of ammonia (NH_3) to the electrophilic carbonyl group of acetaldehyde **A**, gives the corresponding tetrahedral intermediate **B**. Simple proton exchange using an internal acid and base combination leads to the aminal intermediate **C**.



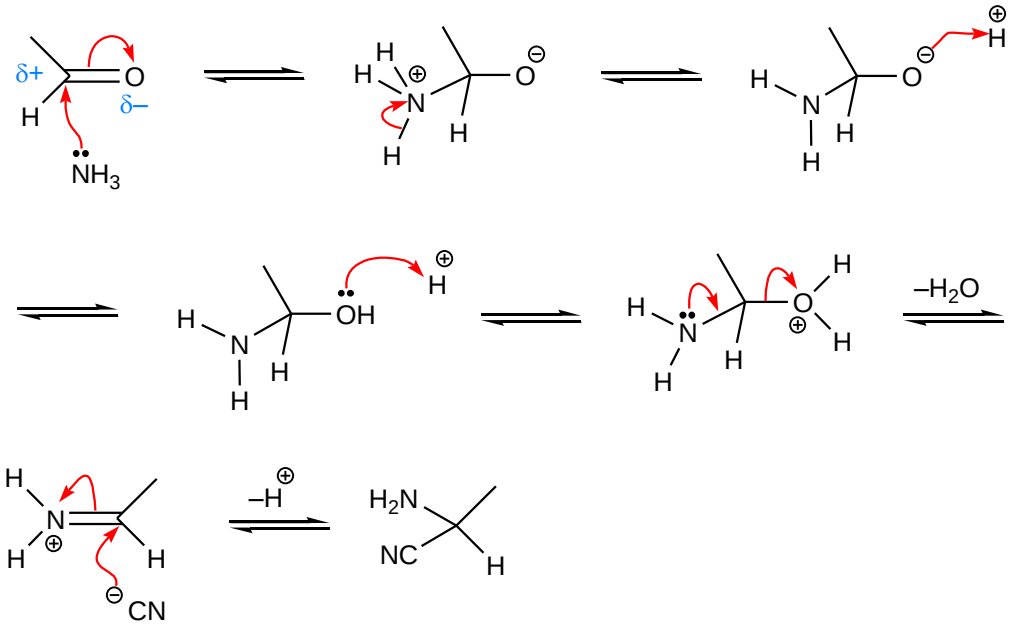
Protonation of this aminal intermediate **C** using HCN (p*K*a = 7) gives the oxonium ion **D**; subsequent elimination of water (H_2O) leads to the intermediate iminium ion **E**.



Nucleophilic addition of cyanide ($^-$CN) to the electrophilic iminium ion **E** gives the required product **F**.



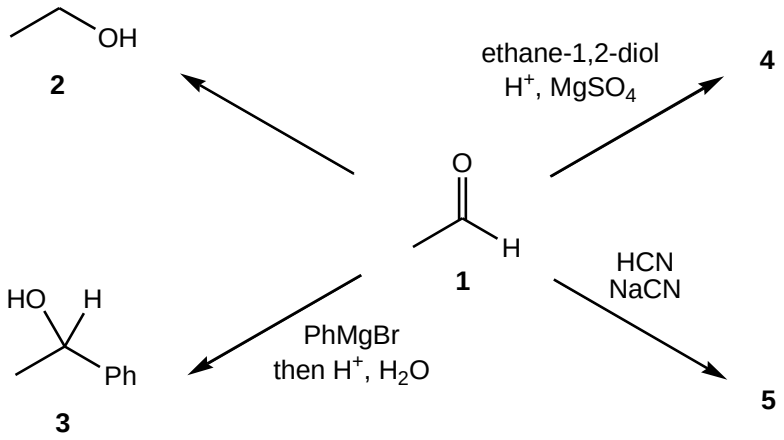
Answer



[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. 1095 in *Chemistry*^{3})

1. The following questions are based on the reactions of ethanal (**1**) shown below.



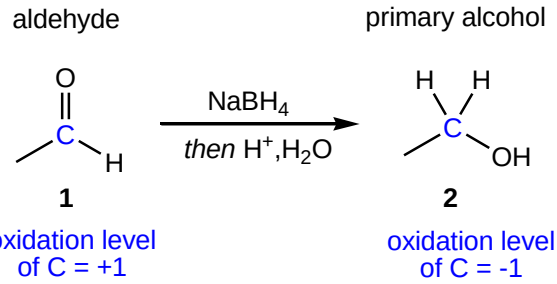
(a) Give appropriate reagents for converting **1** into **2**. Is this an example of an oxidation or a reduction reaction?

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

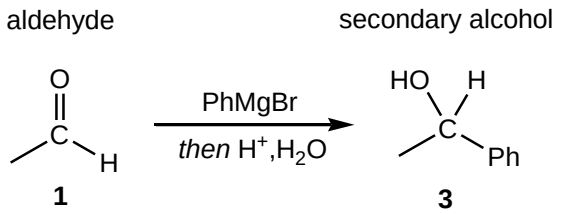


Reduction of the polar carbonyl group, of aldehyde **1**, requires a polar reducing agent. The most suitable reagent for this reduction is sodium borohydride ($NaBH_4$); the use of a more reactive hydride source, like $LiAlH_4$, is acceptable. Under both conditions, the reaction needs to be "worked-up" under acidic conditions (H^+, H_2O) in order to protonate the intermediate alkoxide. For a detailed account of these mechanisms, see p. 1061 in *Chemistry*^{3}.

Answer

$NaBH_4$ or $LiAlH_4$ then H^+. This process is a reduction.

(b) Draw a reaction mechanism to show how **1** is converted into **3**.

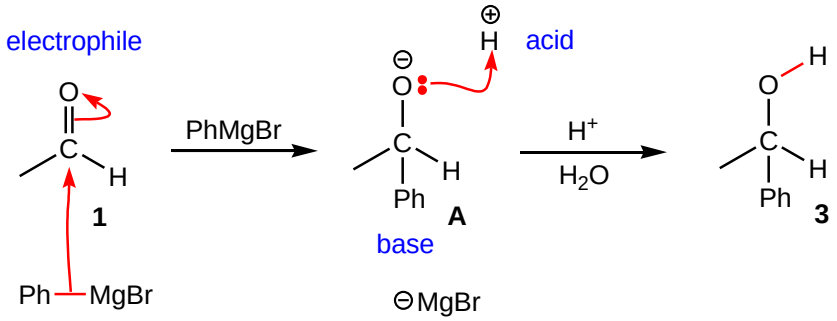


Strategy

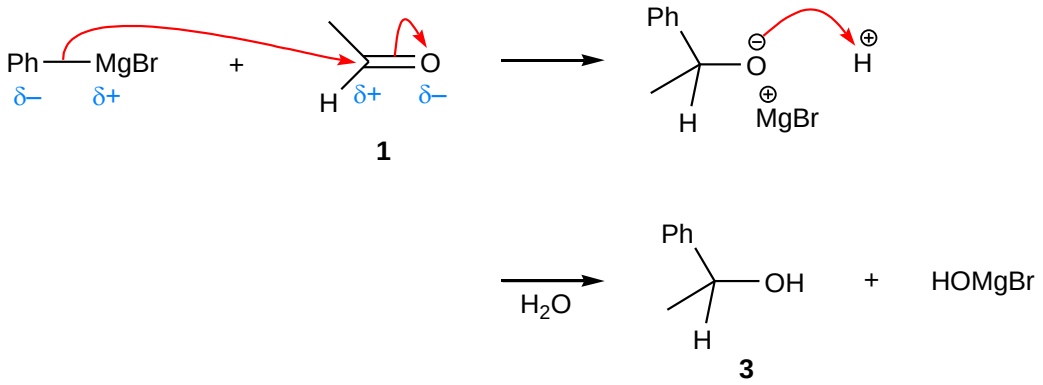
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

Nucleophilic addition of the phenyl carbanion, Ph^-, (from the nucleophilic Ph-MgBr bond) to the electrophilic carbonyl group of acetaldehyde **1** leads to the tetrahedral intermediate **A**. Protonation of this basic alkoxide, in **A**, using aqueous mineral acid (dilute HCl in H_2O), gives the required secondary alcohol **3**.



Answer



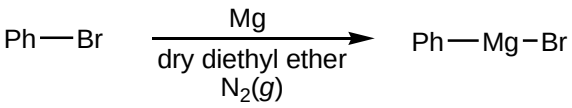
[Movement of electrons can also be depicted using a negative charge or a non-bonded pair of electrons.]

(c) Suggest a method for preparing PhMgBr.

Strategy

Grignard reagents, like RMgBr, are generally prepared from the corresponding aliphatic and aryl bromide (RBr) and magnesium.

Solution



Phenyl magnesium bromide, PhMgBr, is a common Grignard reagent. It is prepared by the slow addition of magnesium (ribbon) to a solution of bromobenzene (PhBr) in **dry** diethyl ether (solvent) under an **inert** atmosphere (*e.g.*, N_2 or Ar).

In the presence of water (as in wet diethyl ether), this Grignard reagent would simply deprotonated it, to form benzene (Ph-H) as a byproduct. Whereas, in the presence of air [in particular $O_2(g)$], phenol (Ph-OH) is formed as a further byproduct; for additional information, see p. 1062 in *Chemistry*^{3}.

Answer

PhBr and Mg in dry diethyl ether.

(d) Give structures for organic compounds **4** and **5**.

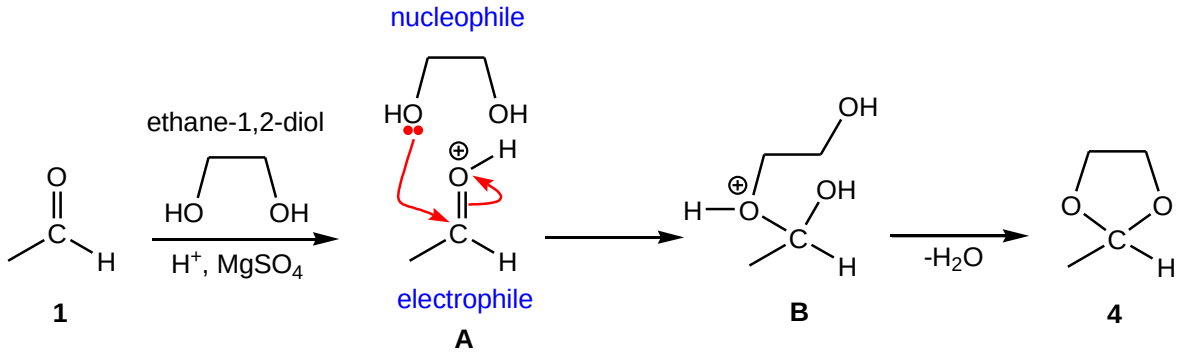
Strategy

Acetaldehyde **1** is an electrophilic aldehyde. In both reactions draw out the reagents, and work out which is the complementary nucleophile. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile and electrophile combination. Suggest structures for the products **4** and **5**.

Solution

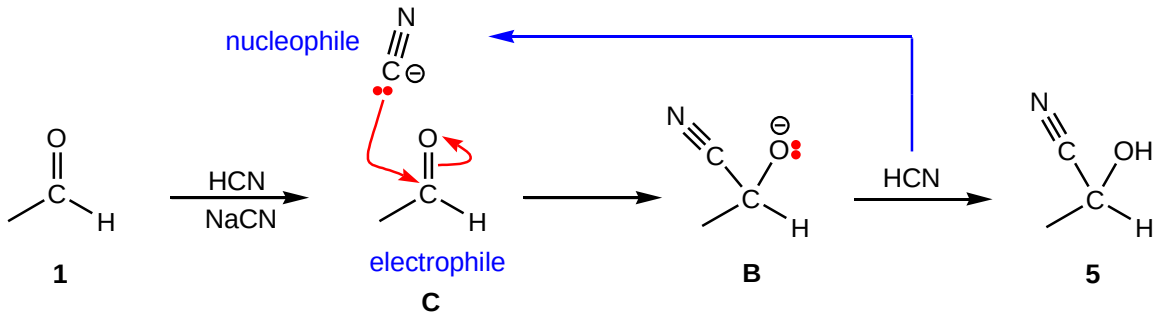
*Formation of product **4***

Ethane-1,2-diol is a nucleophile and acetaldehyde **1** is an electrophile in this reaction. Increasing the electrophilicity of acetaldehyde through protonation, as in **A**, followed by nucelophilic addition of ethane-1,2-diol gives the intermediate hemiacetal **B**. Under acid conditions, water can be eliminated, followed by intramolecular cyclisation of the remaining primary alcohol gives the cyclic acetal **4** as the product. Anhydrous magnesium sulfate ($MgSO_4$) is needed to drive the equilibrium over to the product **4** by removing water from the reaction mixture. The mechanism of this reaction is given on p. 1070 in *Chemistry*^{3}.



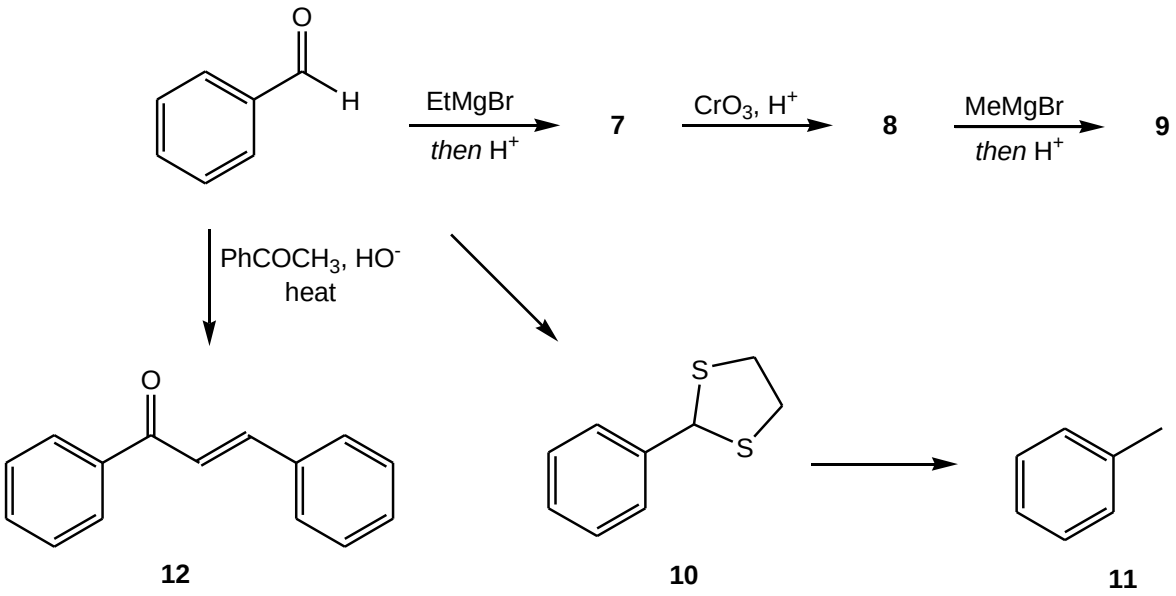
Formation of product ***5***

Cyanide ($^-$CN) is a nucleophile and acetaldehyde **1** is an electrophile in this reaction. Nucleophilic addition of cyanide to the electrophilic carbonyl group of acetaldehyde **1**, as in **C**, followed by protonation of the basic alkoxide using hydrogen cyanide (HCN; pK_a = 7) gives cyanohydrin **5** as the product. Under these conditions, cyanide ($^-$CN) is regenerated. The mechanism of this reaction is given on p. 1062 in *Chemistry*[3].



Solution

2. The following questions are based on the reactions of benzaldehyde (**1**) shown here.



(a) Draw the structures of organic compounds **7**–**9**.

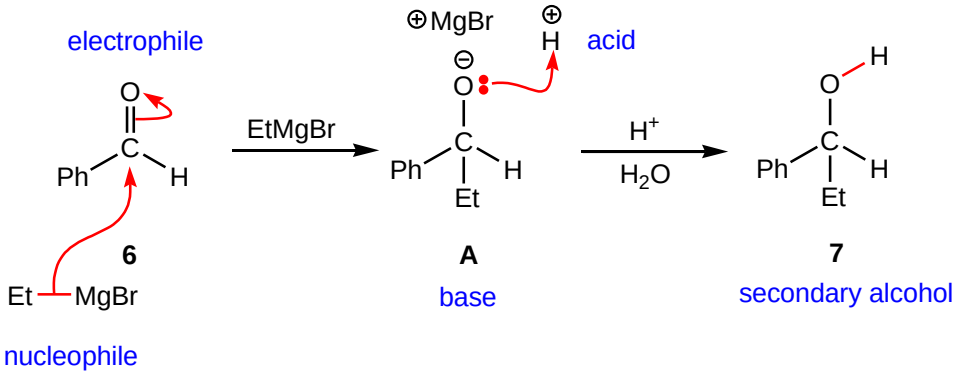
Strategy

Benzaldehyde **1** is an electrophilic aldehyde. In the first reaction, draw out the reagents, and work out which is the complementary nucleophile. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile and electrophile combination. Suggest a structure for product **7**. As this synthesis is sequential, there is no additional information about the structures of **8** and **9**; you will need to examine the reagents and deduce what reaction types might be occurring.

Solution

Formation of product 7

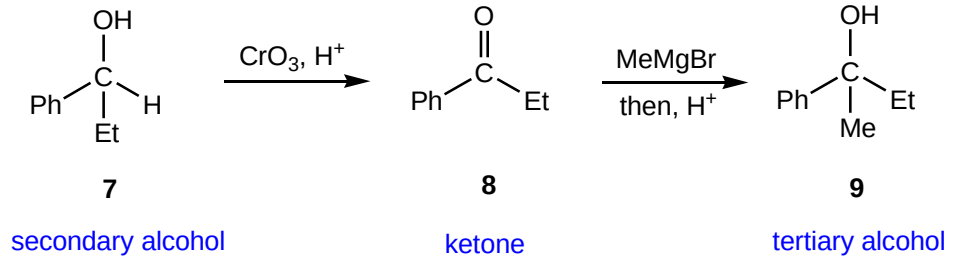
The Grignard reagent, Et-MgBr is a nucleophile and benzaldehyde **6** is an electrophile in this reaction. Nucleophilic addition of the ethyl carbanion, Et^-, (from the nucleophilic Et-MgBr bond) to the electrophilic carbonyl group of benzaldehyde **6** leads to the tetrahedral intermediate **A**. Protonation of the basic alkoxide, in **A**, using aqueous mineral acid (dilute HCl in H_2O), gives the unknown product **7**.



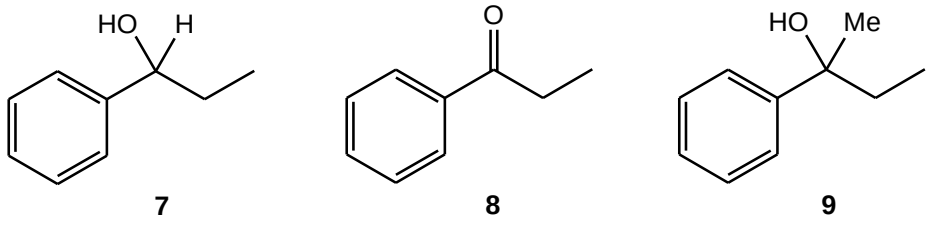
*Formation of products **8** and **9***

The reagents for step **7**→**8** are chromium trioxide (CrO_3) and H^+; these are classical oxidation conditions (see p. 1058 in *Chemistry*^{3}). Oxidation of the secondary alcohol **7** under these conditions would give the ketone **8** as the unknown product.

The reagents for step **8**→**9** are methyl magnesium bromide (MeMgBr), followed by an acidic work-up (*then*, H^+); these are traditional Grignard addition conditions (see p. 1063 in *Chemistry*^{3}). Addition of the Grignard reagent, MeMgBr, to the ketone **8** would give the tertiary alcohol **9** as the unknown product.



Answer



(b) Suggest reagents that will convert **6** into **10**, and **10** into **11**.

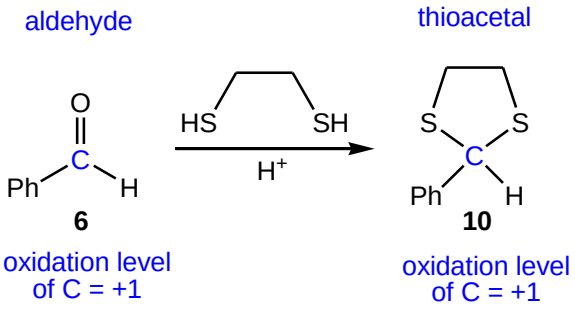
Strategy

For each step, draw out the starting material and product, assign their oxidation levels, and work out if an oxidation or reduction has occurred. Deduce which functional groups have changed during these reactions, and suggest reagents for these transformations.

Solution

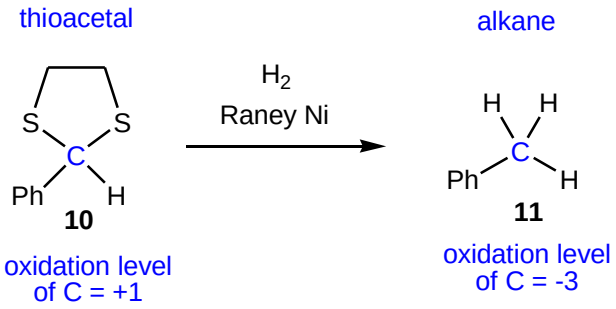
*For conversion of **6→10***

The starting material **6** and product **10** contains aldehyde and thioacetal functionality, respectively. This process is neither an oxidation nor a reduction, as there is no change in the oxidation level of the carbon of the aldehyde group, in benzaldehyde **6**. Therefore, this reaction must involve an exchange process, where both the C-O bonds of the carbonyl (C=O) group are replaced with two individual C-S bonds. Suitable reagents for this transformation are ethane-1,2-dithiol ($HSCH_2CH_2SH$) and H^+. As this reaction involves dehydration (loss of water) - addition of anhydrous $MgSO_4$ will promote this process.



*For conversion of **10→11***

The starting material **10** and product **11** contains thioacetal and alkane functionality, respectively. This process involves reduction, as there is a decrease in the oxidation level of the carbon of the thioacetal group, in **10**, from +1 to -3 (in the toluene **11**). Reduction of the non-polar covalent C-S bonds can be achieved using Raney Nickel (Raney-Ni) and molecular hydrogen (H_2).



Answer

Conversion of **6** into **10**: reagents are ethane-1,2-dithiol ($HSCH_2CH_2SH$), H^+ and anhydrous $MgSO_4$

Conversion of **10** into **11**: reagents are Raney Ni and H_2.

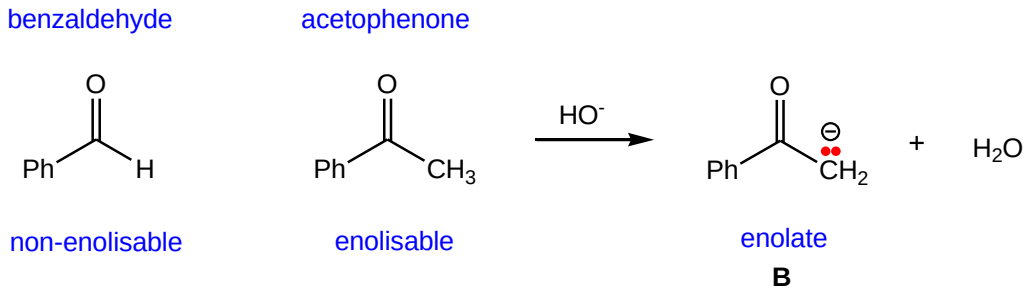
(c) Give a mechanism that explains how **6** is converted into **12**.

Strategy

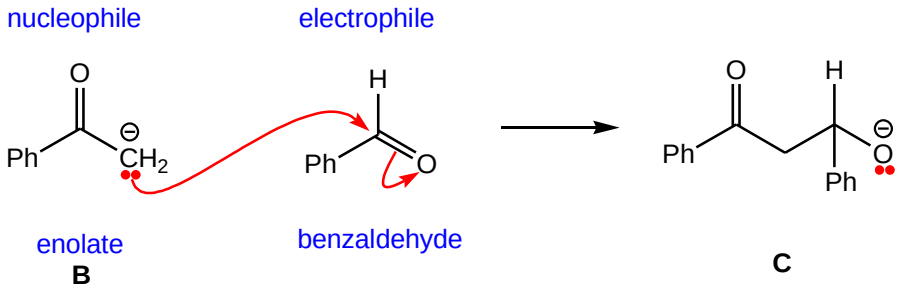
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

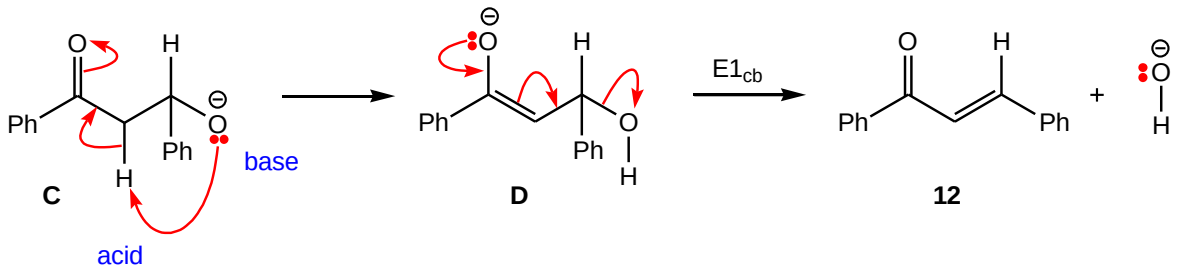
Enone **12** is derived from the crossed-aldol condensation between a non-enolisable aldehyde, benzaldehyde, and a less electrophilic enolisable ketone, acetophenone. The active nucleophile in this reaction is the enolate **B**, derived from the deprotonation of acetophenone using hydroxide as the base.



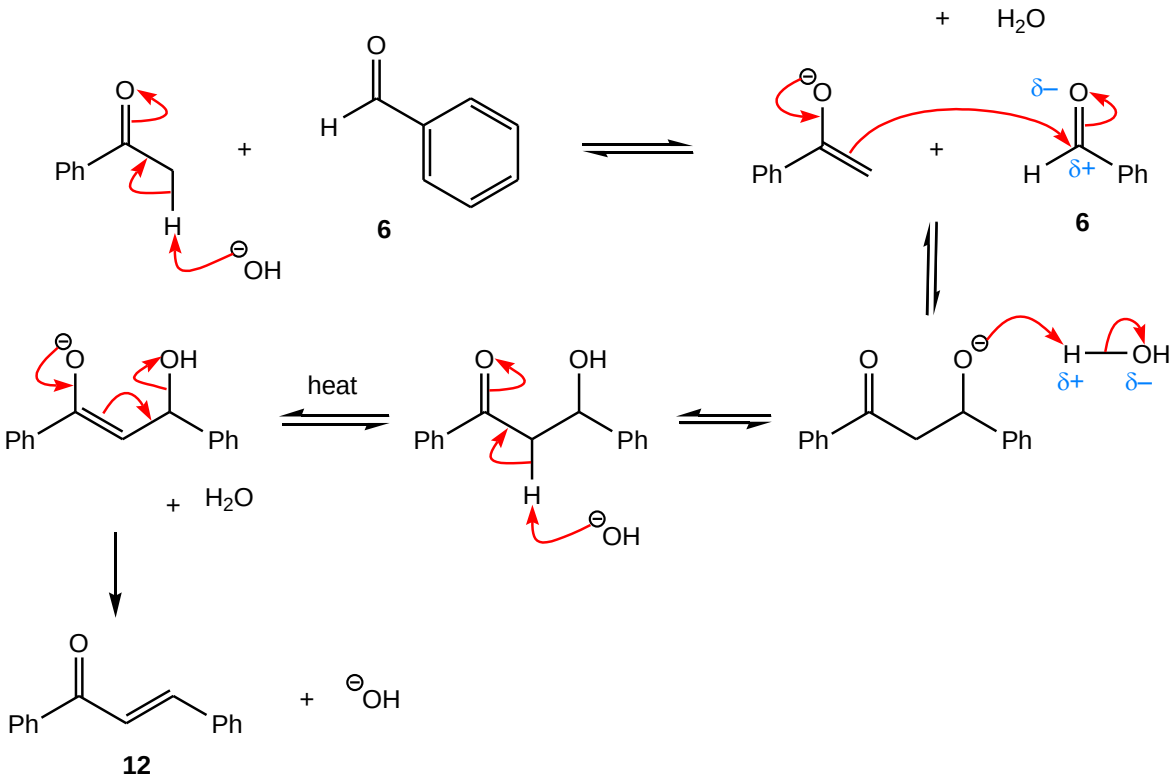
Nucleophilic addition of this enolate, **B**, to the more electrophilic carbonyl group of the non-enolisable aldehyde, benzaldehyde, gives the intermediate aldolate **C**.



Internal proton exchange from the alpha-carbon in **C** to the alkoxide, as shown below, followed by $E1_{cb}$ elimination of hydroxide leads to the most stable conjugated product, enone **12**.

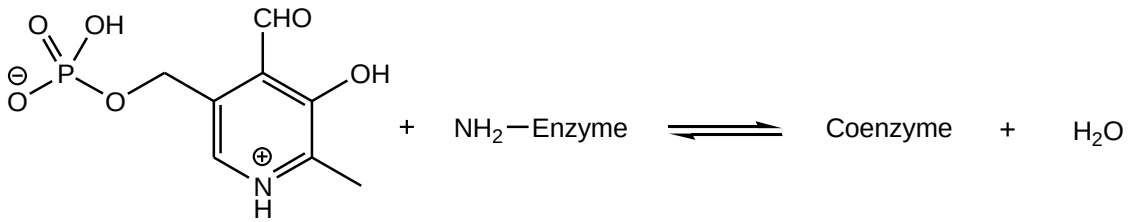


Answer



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

3. In nature, pyridoxal phosphate reacts with an enzyme (abbreviated as H_2N–Enzyme) to form a coenzyme that catalyses the conversion of α-amino acids into α-keto acids.



pyridoxal phosphate

(a) Draw the structure of the coenzyme and name the functional group that is formed.

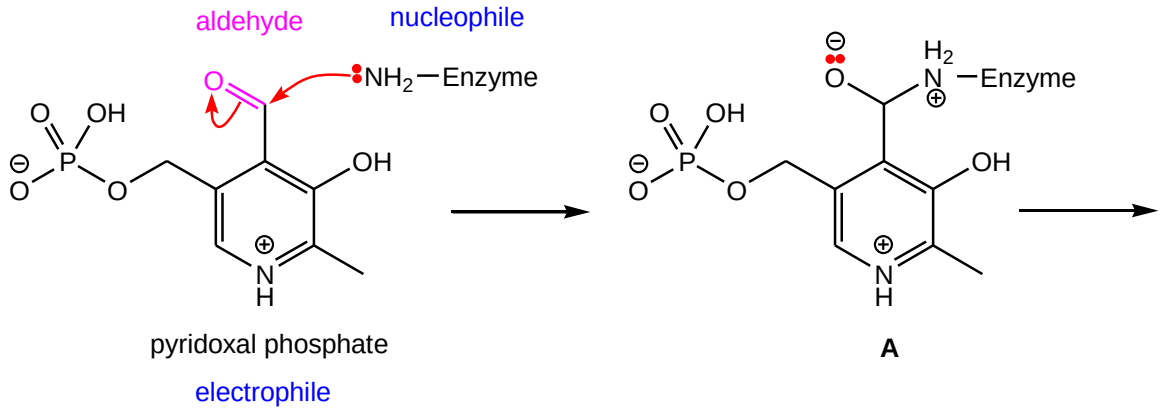
Strategy

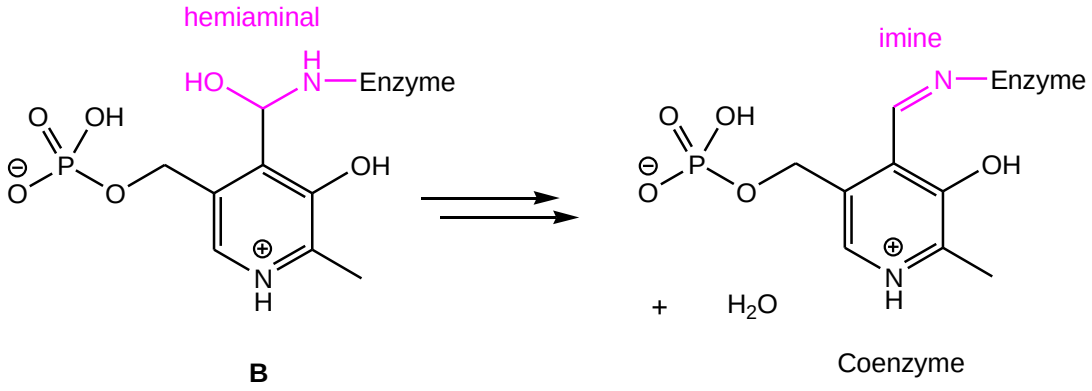
This process must involve an **addition-elimination reaction**, as there is ONLY one formal product, "the coenzyme". As the byproduct is water (H_2O), this reaction is neither a reduction nor an oxidation. Protonation of the amino-enzyme cannot be the product-determining step as only the co-enzyme product is formed. [Proton transfer would lead to two products]. Therefore, the amino-enzyme is the nucleophile in this process.

In this reaction, draw out the reagents and work out which functional group in pyridoxal phosphate is the complementary electrophile. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile and electrophile combination. Suggest a structure for the coenzyme and name the new functional group.

Solution

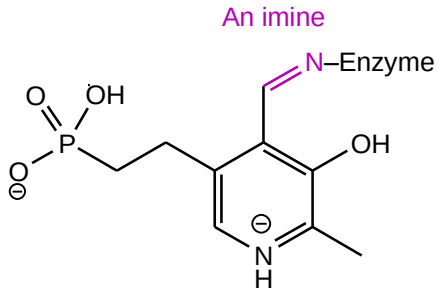
Nucleophilic **addition** of the amino-enzyme to the electrophilic carbonyl group of the aldehyde (in the pyridoxal phosphate) leads to the tetrahedral intermediate **A**. Internal proton exchange between the ammonium ion and the alkoxide leads to the hemiaminal **B** and subsequent **elimination** of water gives the co-enzyme as the product. In essence, this reaction involves the formation of a substituted imine (as part of the co-enzyme substructure) using an aldehyde (in pyridoxal phosphate) and a primary amine (in amino-enzyme). For the mechanism of imine formation, see p. 1073 in *Chemistry*[3].





B

Answer



(b) Is the coenzyme formed by an addition reaction, a substitution reaction, or an addition–elimination reaction? Explain your reasoning.

Strategy

For substitution and addition-elimination reactions, TWO or more reagents will lead to TWO or more products. For addition reactions, TWO or more reagents will give ONE product.

As there are two reagents (pyridoxal phosphate and amino-enzyme) and two products (co enzyme and water), this reaction cannot be an addition reaction. You will need to consider the other two options.

Solution

This reaction involves the nucleophilic addition of a primary amine (amino-enzyme) to the electrophilic carbonyl group of pyridoxal phosphate, followed by elimination of water from

the hemiaminal (see part a) to give the coenzyme. Overall, this reaction is an addition-elimination process.

Answer

This is an addition-elimination reaction. The amine group adds to the C=O bond to form a hemiaminal which loses water in an elimination reaction.

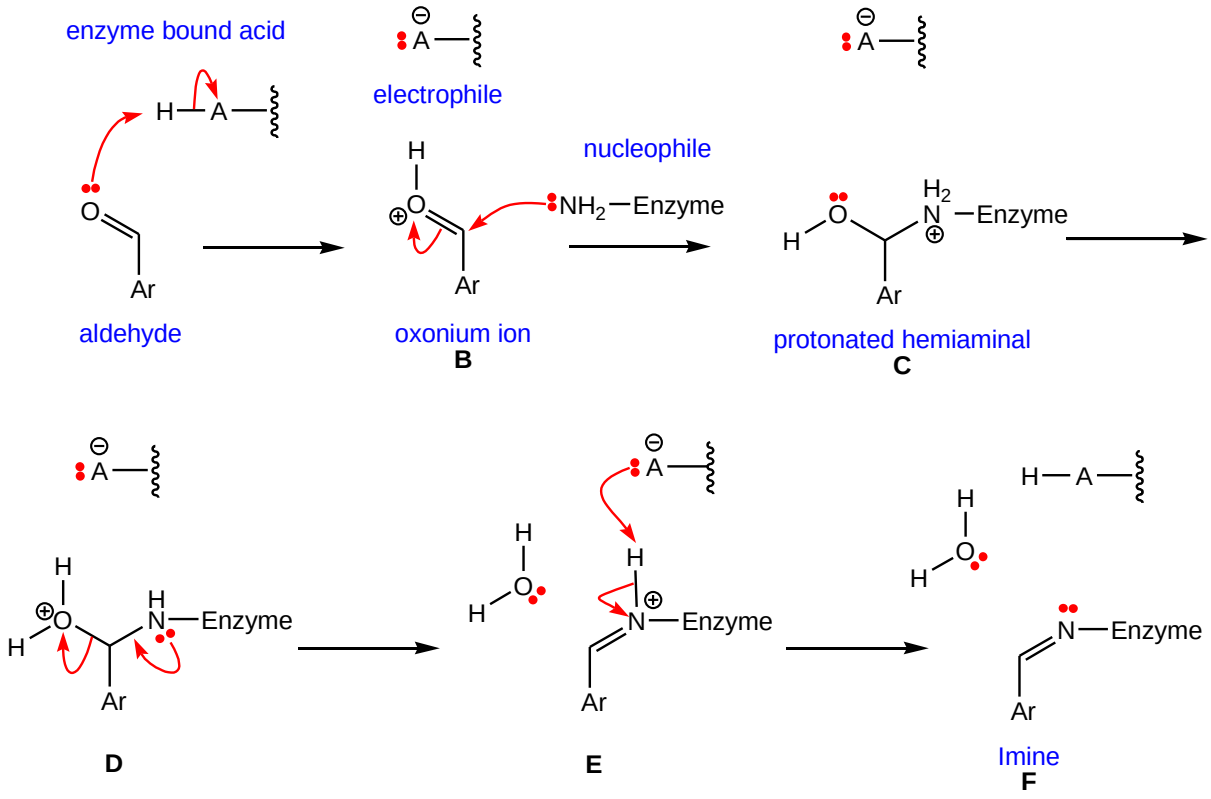
(c) An acid within the active site of the enzyme plays an important part in the mechanism of the reaction to produce the coenzyme. Explain the role of an acid in this type of transformation.

Strategy

From the above statement, imine formation (within the coenzyme) is acid-catalysed. Generally, protonation of a carbonyl group can increase its electrophilicity, and protonation of a hydroxyl (OH) group can increase its leaving ability. In order to examine the role of an acid, you must first draw out the mechanism of this reaction.

Solution

Protonation of the aromatic aldehyde using an enzyme bound acid, H-A, gives the oxonium ion **B**. Nucleophilic addition of the amino-enzyme to this activated electrophile (to give the protonated hemiaminal **C**) is significantly faster than that of the parent aromatic aldehyde. Protonation of the hydroxyl (OH) group, in **C**, by internal proton exchange with the ammonium ion leads to the oxonium ion **D**. Elimination of water (H_2O), from **D**, assisted by the non-bonded pair of electrons on the nitrogen atom, gives the protonated imine **E**. [This proton transfer step is paramount as it increases the leaving ability of the OH group; H_2O is a much better leaving group than HO^-.] Deprotonation of **E** using the conjugate base (A^-) of the enzyme bound acid gives the required imine and the parent enzyme bound acid, H-A. The mechanism of this reaction is discussed in detail on p. 1073 in *Chemistry*^{3}.



Answer

An acid catalyst is required to convert the hemiaminal into the imine. Protonation of the hemiaminal converts the OH group into a better leaving group, so that elimination of water takes place (rather than HO^-).

(d) Give the general structure of an α-amino acid, with one α-hydrogen atom.

Strategy

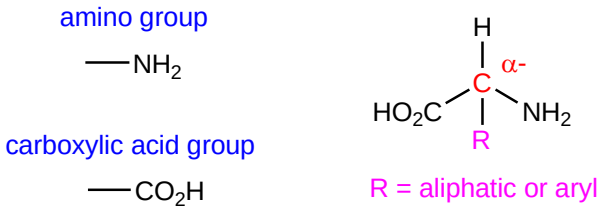
An α-amino acid is a molecule, which has both amino ($-NH_2$) and carboxylic acid ($-CO_2H$) groups attached to the same alpha-carbon atom. In addition, this alpha-carbon atom is attached to ONE hydrogen atom.

Solution

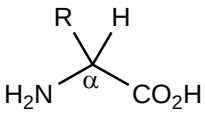
From this question, three of the four substituents on the alpha-carbon atom of this α-amino acid have already been defined; namely an amino (NH_2) group, a carboxylic acid (CO_2H)

group, and a hydrogen (H) atom. The remaining substituent must be either an aliphatic (Me, Et, etc) or an aryl group (Ph-, Ar etc).

The generic structure of this α-amino acid is shown below.



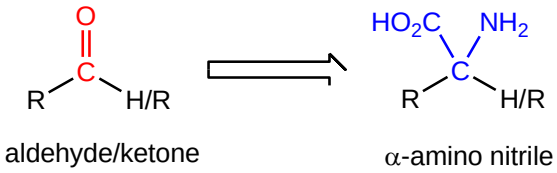
Answer



(e) Suggest a method for converting aldehydes and ketones into α-amino acids in the laboratory.

Strategy

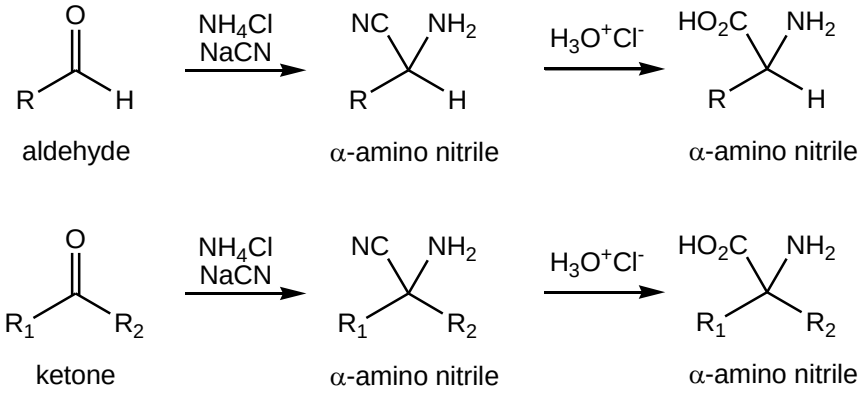
In order to achieve this transformation, the carbonyl (C=O) groups of the aldehyde/ketone must be replaced with an amino (NH_2) and a carboxylic acid (CO_2H) group.



aldehyde/ketone α-amino nitrile

Solution

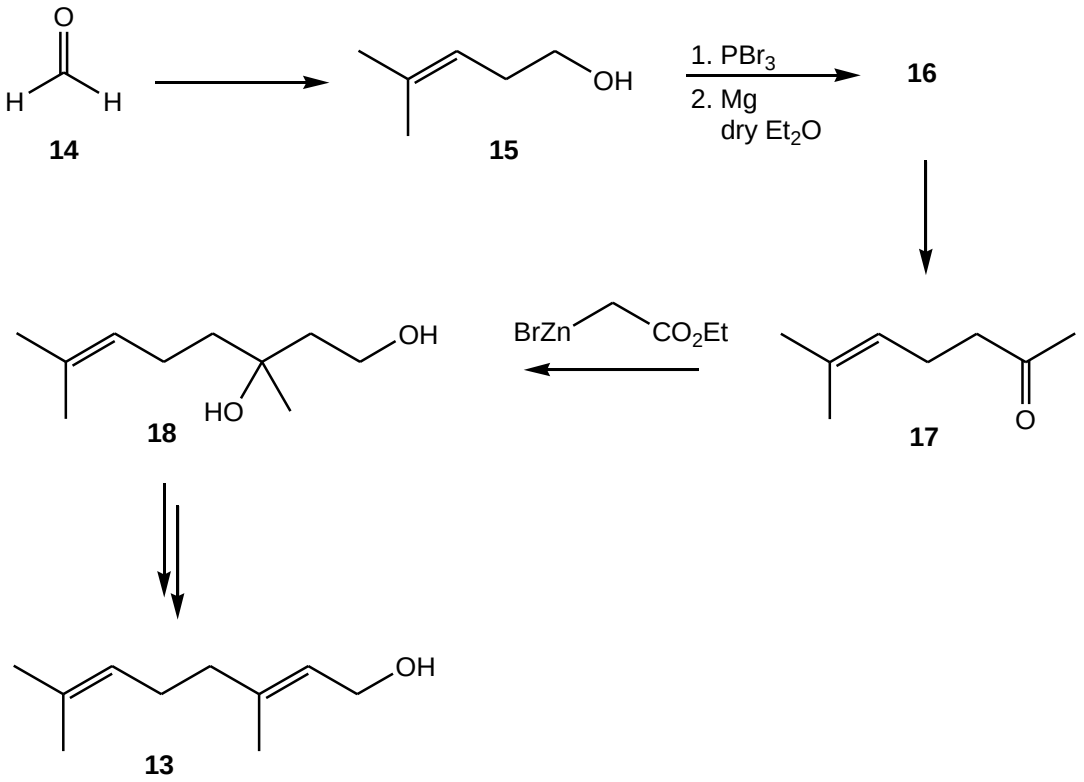
We have already seen in Box 23.6 (on p. 1073 in *Chemistry*^{3}) that an amino group and a masked carboxylic acid group (a nitrile) can be introduced in a single step using NH_4Cl and NaCN. Hydrolysis of this intermediate α-amino nitrile, under acidic or basic conditions will give the required α-amino acid. This is called a Strecker reaction.



Answer

Use the Strecker synthesis. React aldehyde/ketone with NH_4Cl and NaCN (to give an intermediate α-amino nitrile), followed by H^+/H_2O (gives the required α-amino acid); for additional information; see p. 1073 in *Chemistry*^{3}.

4. A synthetic route to the naturally occurring terpene geraniol (**13**) is shown here.



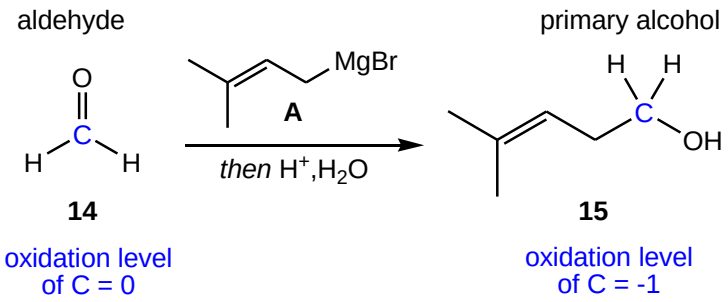
(a) Suggest reagents that will convert **14** into **15**.

Strategy

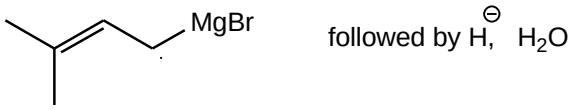
Draw out the starting material and product, assign their oxidation levels, and work out if an oxidation or reduction has occurred. Deduce which functional group has changed during this proposed reaction, and suggest reagents for this transformation.

Solution

The starting material **14** and product **15** contains aldehyde and primary alcohol functionality, respectively. This process involves an informal reduction, as there is a decrease in the oxidation level of the carbon atom of the aldehyde group, in **14**, from 0 to -1 (in the primary alcohol **15**). Interestingly, this change in oxidation levels can only occur by the addition of a carbon-based substituent. As the aldehyde **14** is a strong electrophile, a suitable reagent for this transformation would be a nucleophilic carbanion, such as Grignard reagent **A**. Treatment of formaldehyde **14** with the Grignard reagent **A**, followed by an acid work-up (H^+, H_2O) would lead to the required primary alcohol **15**, as shown below.



Answer



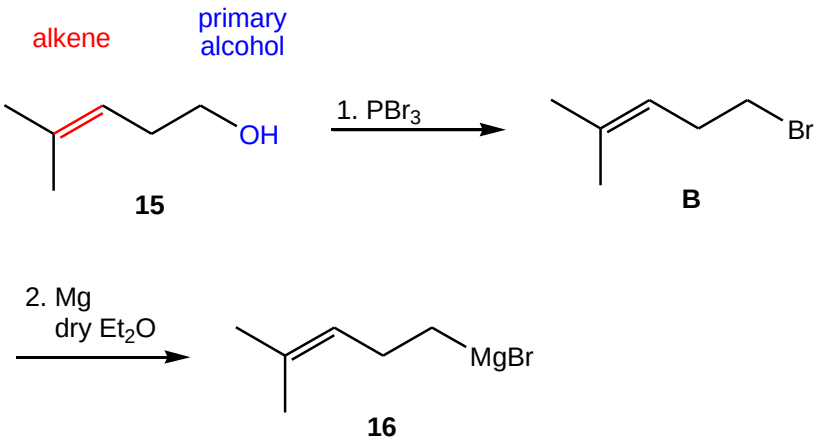
(b) Give the structure of organic compound **16.** Why is it important to use *dry* Et_2O?

Strategy

Draw out the starting material and name the functional groups present. Examine the reagents, deduce their relative reactivity, and draw out the resulting product.

Solution

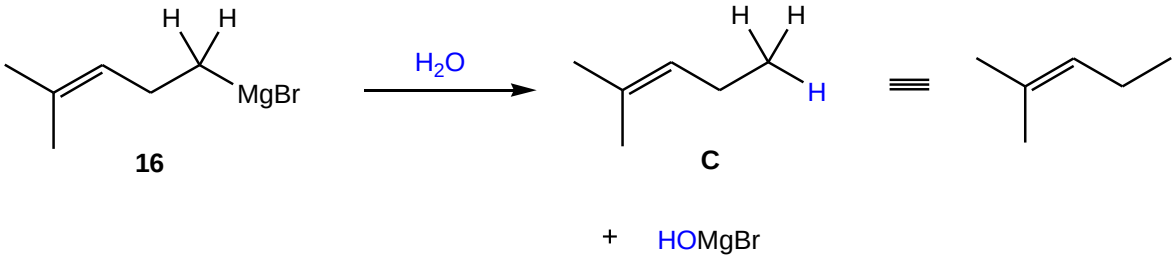
The starting material, **15**, contains two functional groups, namely an alkene and primary alcohol. However, the primary alcohol, in **15**, is more nucleophilic than the alkene.



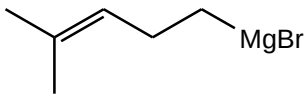
The first reagent, phosphorus tribromide (PBr_3) is an electrophile and acts as a bromide source. It is generally used to convert an aliphatic alcohol (ROH) into the corresponding

aliphatic bromide (RBr). The mechanism of this reaction can be found on p. 920 in *Chemistry*[3]. Treatment of the primary alcohol, in **15**, with PBr_3 would give the required bromide **B**.

The second reagent, magnesium (Mg), is an electron-transfer reagent; $Mg \rightarrow Mg^{2+} = 2\ e^-$. Addition of the magnesium to the bromide, **B**, would give the corresponding **Grignard** reagent **16**. The mechanism of this reaction can be found on p. 1062 in *Chemistry*[3]. The use of dry diethyl ether (Et_2O) as solvent is important, as in the presence of water (as in wet diethyl ether), this Grignard reagent would simply deprotonated it to form the corresponding alkane, in **C**, and BrMgOH. Usually, this reaction is performed under an **inert** atmosphere (*e.g.*, N_2 or Ar) and in the absence of air [in particular $O_2(g)$] as the corresponding alcohol **15** (and related peroxides) can also be formed.



Answer



Dry Et_2O must be used otherwise the Grignard reagent will react with water to form $Me_2C{=}CHCH_2CH_3$ and HOMgBr.

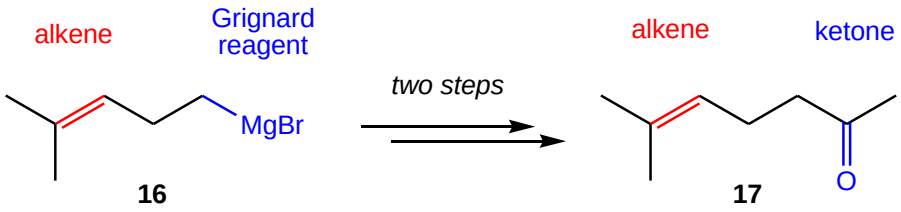
(c) Suggest reagents for a *two-step* synthesis of ketone **17** from **16**.

Strategy

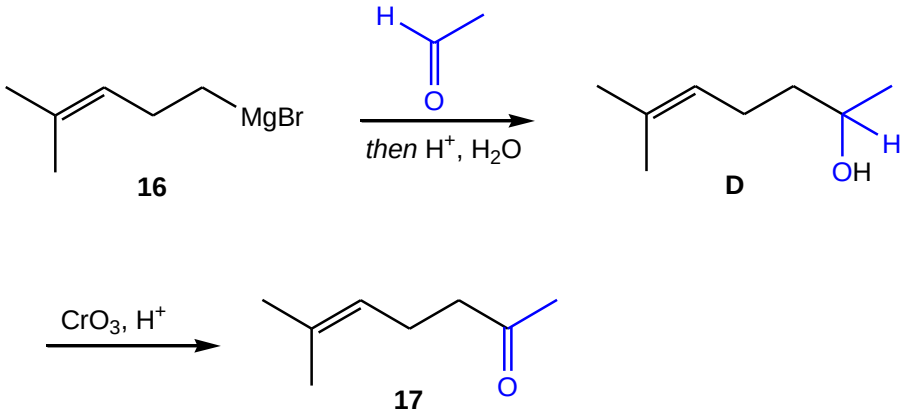
With the structure of the starting material **16** deduced. Draw of the structures of the starting material **16** and product **17**, name the functional groups present, and work out their relative reactivity. Suggest reagents for this two-step process.

Solution

Both the starting material, **16**, and the product, **17**, contains the same alkene group. The only change in functionality has been the interconversion of the Grignard reagent, in **16**, to the ketone, in **17**. The Grignard reagent (RMgBr), in **16**, is more nucleophilic than the alkene group.



As Grignard reagents, like **16**, are nucleophilic carbanion sources, these can add to aldehyde or ketones to give secondary or tertiary alcohols, respectively. Oxidation of secondary alcohols using CrO_3 can lead to ketones; this particular two-step transformation involving a Grignard reagent, followed by oxidation, converts a simple aldehyde into a ketone.



Working backwards, oxidation of the secondary alcohol **D** with CrO_3/H^+ would give the required ketone, in **17**. Formation of the intermediate secondary alcohol **D** can be achieved by addition of the Grignard reagent, **16**, to acetaldehyde (MeCHO), followed by an acid work-up (H^+, H_2O). The reagents which are required for this two-step transformation are; step 1 - MeCHO, followed by H^+/H_2O; and step 2 – CrO_3/H^+.

Answer

Step 1: CH_3CHO then H^+, H_2O; Step 2: CrO_3, H^+

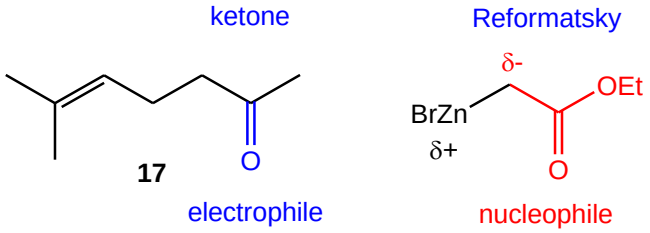
(d) Propose a mechanism for the reaction of **17** with $BrZnCH_2CO_2Et$ (Reformatsky reagent), then H^+ to give hydroxy-ester **18**.

Strategy

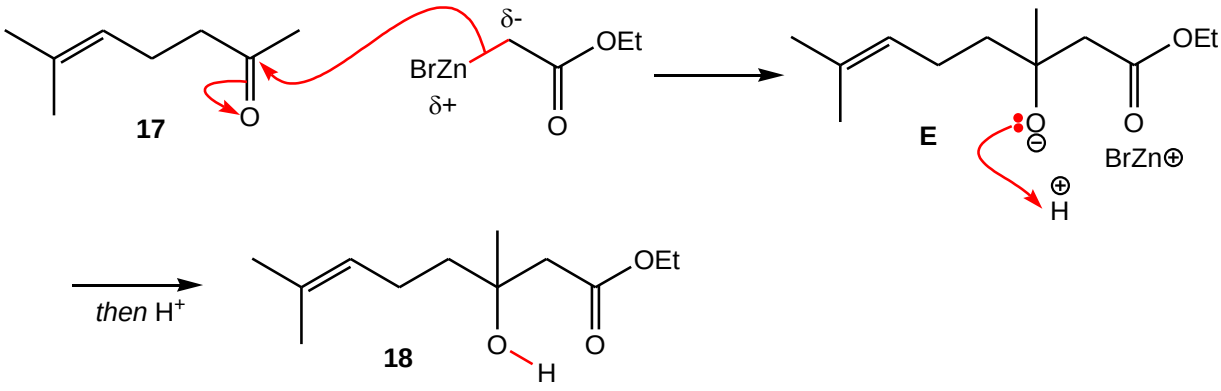
For each step within your proposed mechanism, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly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

Solution

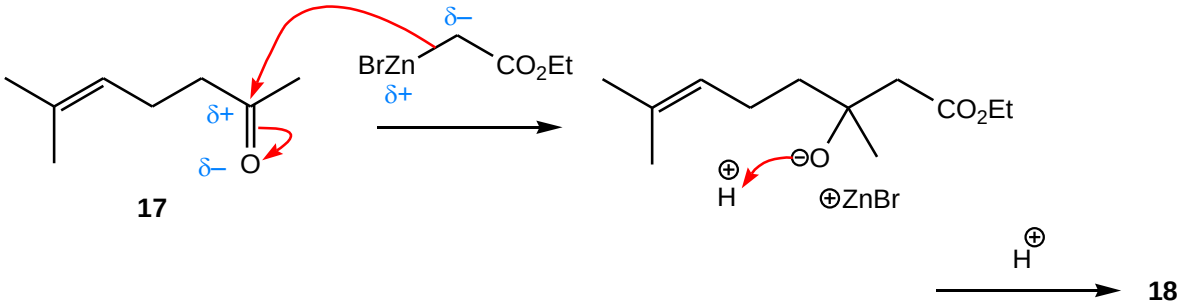
The electrophilic carbonyl group, in **17**, has been converted into a tertiary alcohol, in **18**, by addition of a nucleophilic Reformatsky reagent, $BrZnCH_2CO_2Et$. The alkene group, in **17**, remains unchanged in the product, **18**.



Nucleophilic addition of the Reformatsky reagent, $BrZnCH_2CO_2Et$ (using its reactive $^{\delta-}C\text{-}Zn^{\delta+}$ bond), to the electrophilic carbonyl group of the ketone, in **17**, gives the intermediate zinc alkoxide **E**. Protonation of this alkoxide, in **E**, using an acid work-up (H^+, H_2O) gives the required product, β-hydroxy ester **18**. This is a Reformatsky reaction; for additional information, see p. 1079 in *Chemistry*^{3}.



Answer



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

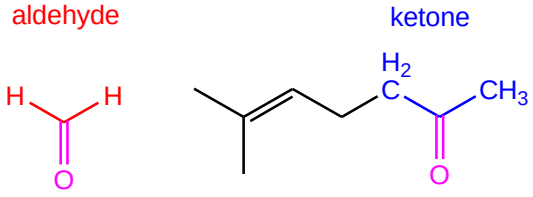
(e) Would you expect **14** or **17** to react more rapidly with $BrZnCH_2CO_2Et$? Explain your reasoning.

Strategy

As the Reformatsky reagent, $BrZnCH_2CO_2Et$, is the common nucleophile in these reactions; draw out the structures of **14** and **17**, and deduce which reagent has the more electrophilic carbonyl (C=O) group. {Hint: the more electrophilic carbonyl group in either **14** or **17** will react faster with this reagent}.

Solution

The carbonyl (C=O) group of formaldehyde **14** is more electrophilic than the carbonyl (C=O) group of ketone **17**. This is because of the reduced electrophilicity of ketone **17** due to its steric demanding and electron-donating alkyl substituents, CH_2R and CH_3. Formaldehyde **14** will react in preference to ketone **17**.

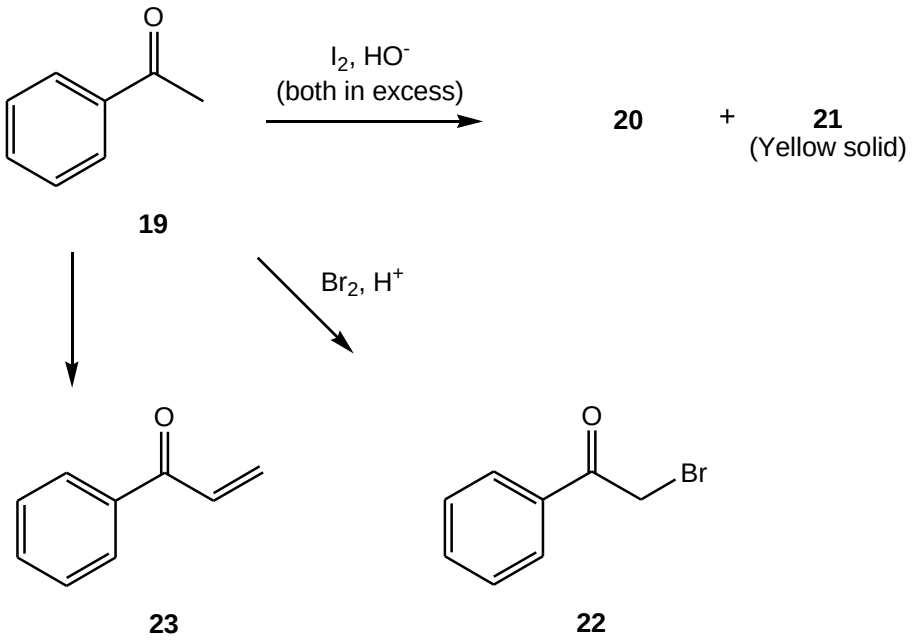


14 **17**

Answer

Aldehyde **14** would react more rapidly with $BrZnCH_2CO_2Et$ than ketone **17**. The C=O bond in **17** is less reactive to nucleophile addition for steric (the two alkyl groups hinder the approach of the nucleophile) and electronic (the two alkyl groups each exert a +I effect and this reduces the electrophilicity of the carbon atom in the C=O bond) reasons.

5. The following questions are based on the reactions of acetophenone (**19**) shown below.



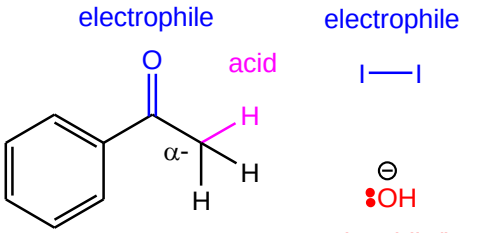
(a) Draw the structures of organic compounds **20** and **21**.

Strategy

Acetophenone **19** is an electrophilic ketone, which contains three acidic alpha-hydrogen atoms. In this reaction, draw out the reagents, and work out which other reagent could be either the complementary nucleophile or base. Work your way into this question by attempting to draw a mechanism using your chosen nucleophile/base and electrophile/acid combination. Suggest structures for the products **20** and **21**.

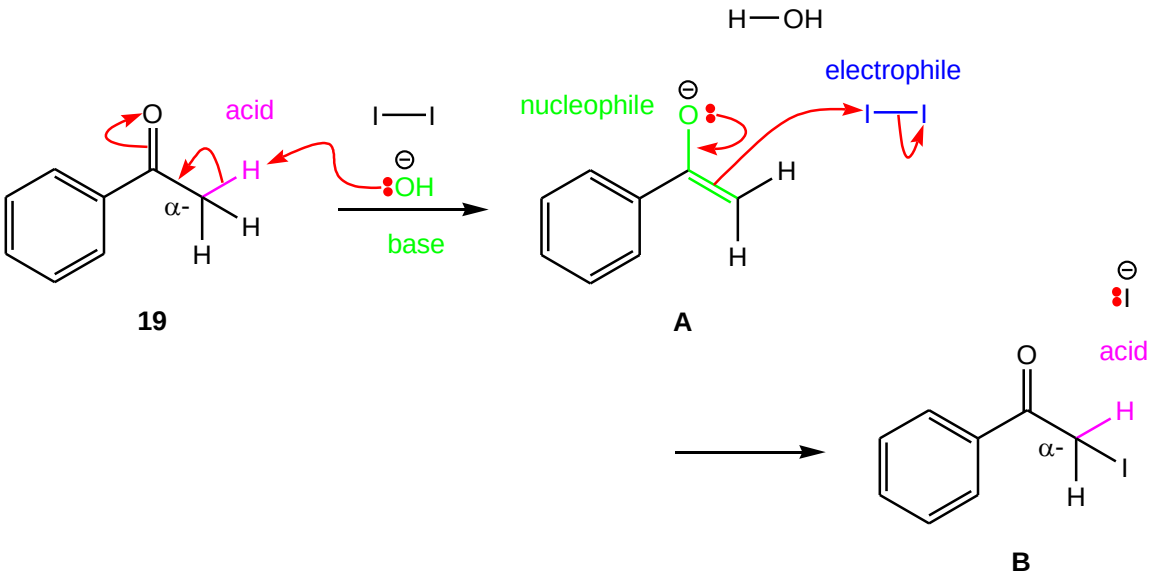
Solution

The first step in this reaction cannot involve iodine (I_2) as it is neither a base nor a nucleophile; iodine is an electrophile. Hydroxide (HO^-) does not act as a nucleophile in this step, as this is not a product-determining reaction; *c.f.* hydrate formation is generally unfavourable (see p. 1066 in *Chemistry*^{3}). Therefore, in the first step of this reaction, acetophenone **19** acts as an acid, and hydroxide acts as a base (HO^-).



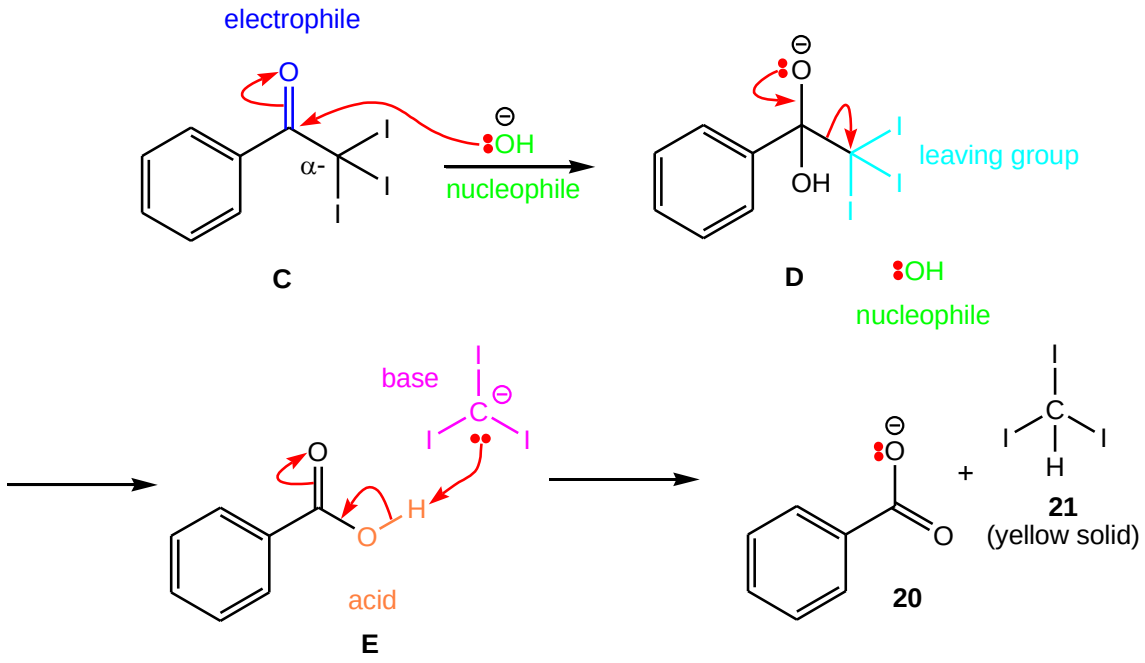
19

Deprotonation of acetophenone **19** using hydroxide, HO^-, (gives the corresponding enolate **A**), followed by electrophilic iodination (using I_2) leads to the intermediate α-iodo acetophenone **B**. Interestingly, this intermediate is more acidic than the original acetophenone **19**, and therefore successive iodinations can occur (using the excess reagents) to give the tri-iodo acetophenone **C**.

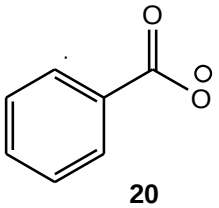


19 **A** **B**

As this tri-iodo acetophenone **C** can no longer act as an acid (as there are no more acidic alpha hydrogen atoms available); the electrophilicity of this carbonyl (C=O) bond is now important. Nucleophilic addition of hydroxide, HO^-, to this carbonyl (C=O) group (to give **D**), followed by elimination of $^-CI_3$ gives benzoic acid **E** as the product. Acid-base equilibration between these species leads to the more stable benzoate **20** and the yellow crystalline tri-iodoform **21**.



Answer



20

CHI_3

21

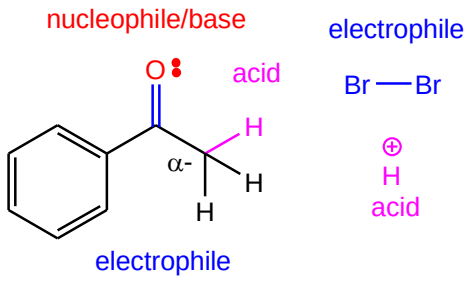
(b) Give a mechanism that explains how **19** is converted into **22**.

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 (→).

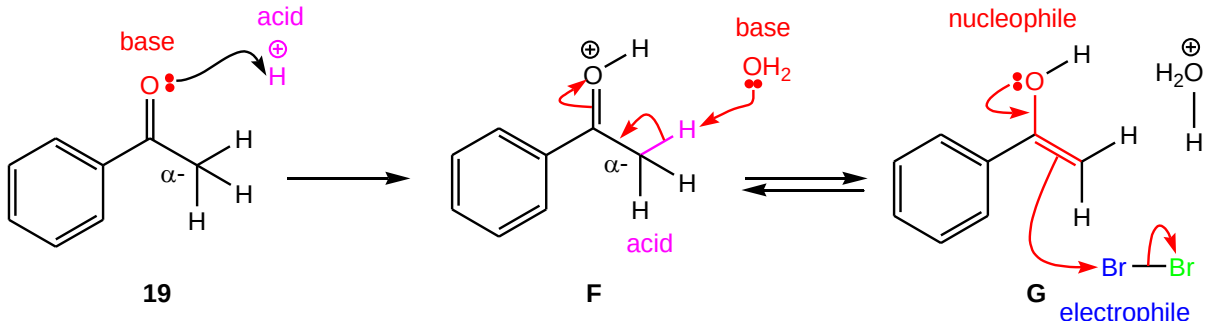
Solution

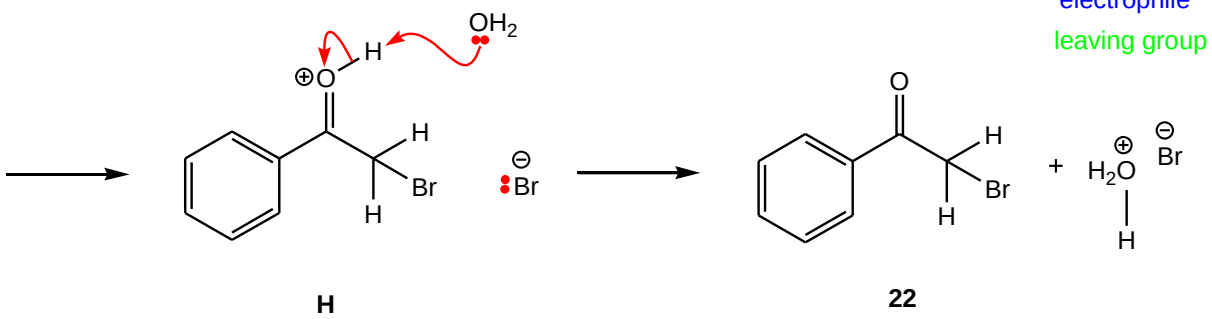
Looking at the reagents, Br_2 is an electrophile and H^+ is an acid. For acetophenone **19**, only the complementary nucleophilic and basic nature of the oxygen atom of its carbonyl (C=O) group is important, as it also has the same electrophilic/acidic nature as the other reagents.



19

Protonation of the oxygen atom of the carbonyl (C=O) group of acetophenone **19** with acid, H^+, leads to the intermediate oxonium ion **F**. Deprotonation of this oxonium ion **F**, using water (H_2O) as the base, gives the intermediate enol **G**. This tautomerisation process is reversible, and the amount of enol content is generally less than 1%.



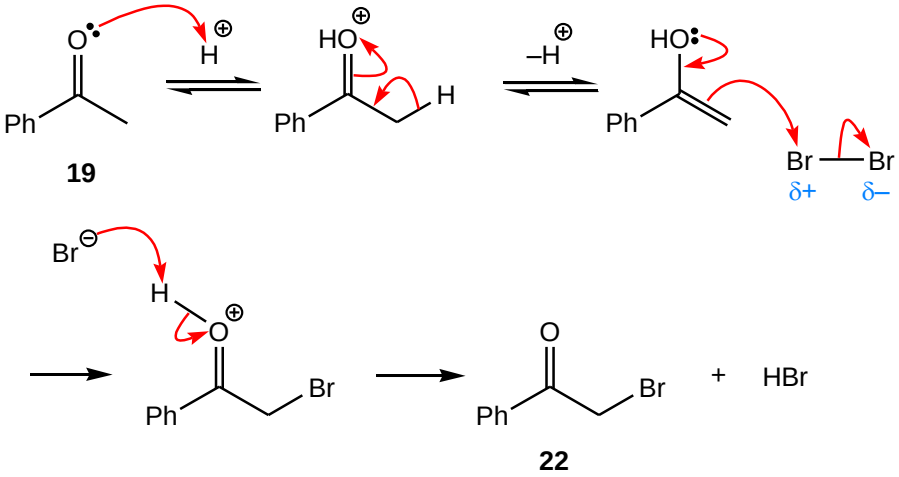


H

Electrophilic addition of bromide (Br_2) to this nucleophilic enol, as shown in **G**, leads to the protonated α-bromoacetophenone **H**. Acid-base equilibration between this acid, **H**, and water (H_2O) gives the required α-bromoacetophenone **22** as the product. It is interesting to note, bromination under acidic conditions leads to mono-bromination, whereas, under basic

conditions tri-bromination (and sequential cleavage to tribromoform) occurs. For further information about this reaction type, see p. 1081 in *Chemistry*[3].

Answer



19 **22**

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

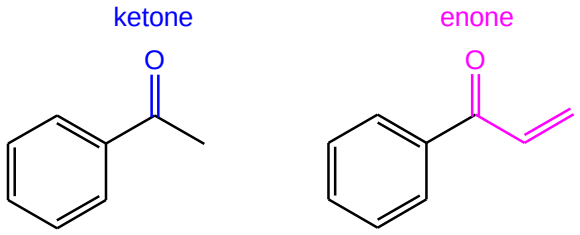
(c) Suggest reagents that will convert **19** into **23.**

Strategy

Draw of the structures of the starting material **19** and the product **23**, name the functional groups present, and work out their relative reactivity. Suggest reagents for this synthetic transformation.

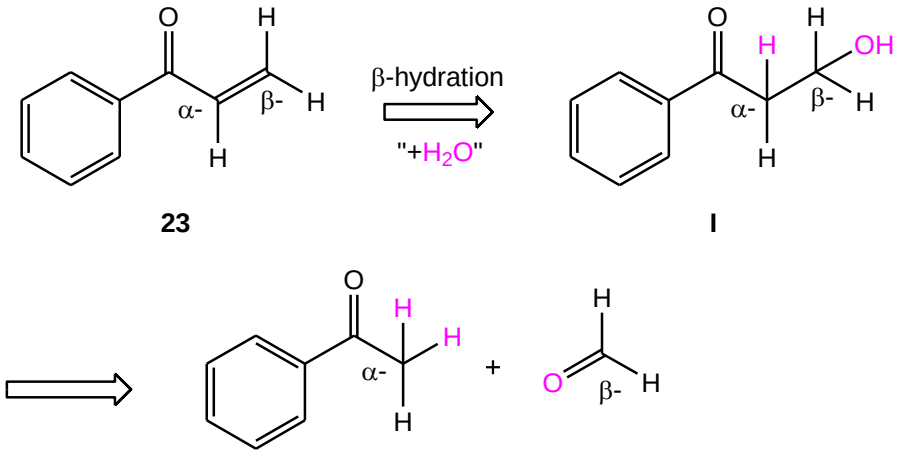
Solution

The starting material **19** is a ketone and the product **23** is an enone. Enones are traditionally made using aldol condensations (see p. 1083 in *Chemistry*[3]).



19 **23**

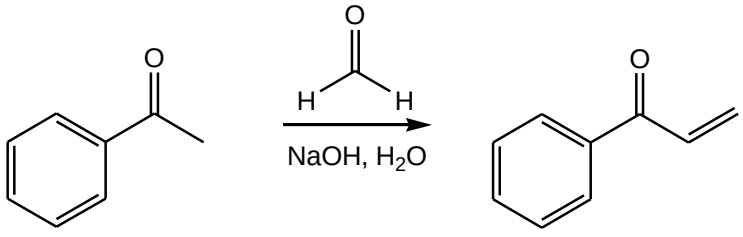
The required carbonyl-containing precursors for this aldol condensation can be revealed through β-hydration. By working backwards; simple β-addition of water (H_2O) across the carbon-carbon double bond of enone **23** gives the intermediate β-hydroxy aldehyde **I**. Fragmentation of this intermediate (through enol formation, followed by tautomerisation) leads to acetophenone **19** and formaldehyde ($O{=}CH_2$).



23 **I**

19

Treatment of acetophenone **19** and formaldehyde ($O{=}CH_2$) under basic conditions, such as aqueous sodium hydroxide (NaOH, H_2O), gives the required enone **23**. This is an example of a crossed aldol condensation involving non-enolisable and enolisable carbonyl components. For additional information, see p. 1084 in *Chemistry*[3].



19 **23**

Answer

HCHO, HO^-, heat

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