

Objective 9. Understand nucleophilic addition reactions of O and C nucleophiles to C=O compounds.

to form diols, acetals, alcohols, cyanohydrins (acetals are common in bio)

**Skills:** Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu<sup>-</sup> and E<sup>+</sup>, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.

**Key ideas:** C=O bond has pi bond but bond is polarized. See resonance. Carbonyl C = E<sup>+</sup>. Reacts with Nu<sup>-</sup> to form Td intermediate. ID O and C Nu<sup>-</sup>.

Practice problems solutions:

1. The reactive site of aldehydes and ketones is the carbonyl carbon.

a. Explain why the carbonyl carbon is an electrophile.

b. Is the carbonyl carbon a strong or weak electrophile?

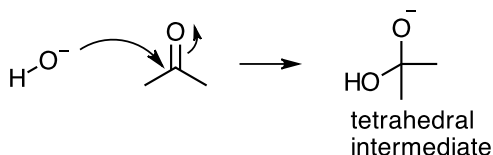
c. Use curved arrows to show how OH<sup>-</sup> reacts at the carbonyl carbon in acetone to form a tetrahedral intermediate.

d. Use curved arrows to show how H<sup>+</sup> reacts at the carbonyl oxygen in acetone. Draw a resonance structure of this product. Explain how this is a way to make the carbonyl carbon a better electrophile.

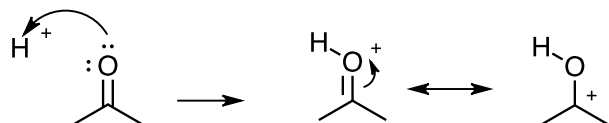
**Answer: a. C is less electronegative than O**

**b. Carbonyl C is a weak electrophile**

c.



d.



2. Grignard reaction to form C-C bond. Grignard reagent is prepared by reacting R-X with Mg to form RMgX.

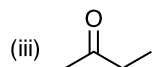
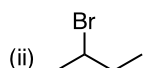
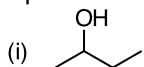
a. The R-Mg bond is polar because R is \_\_\_ electronegative than Mg. This makes R a \_\_\_\_\_.

**Answer: more, nucleophile**

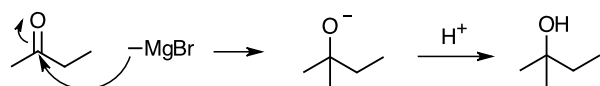
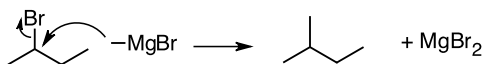
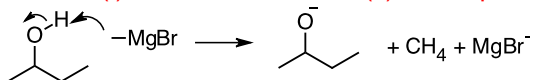
b. Name three electrophiles that react with RMgX.

**Answer: R<sup>+</sup>, OH<sup>-</sup>, NH<sub>2</sub><sup>-</sup>**

c. Use curved arrows to show how each compound below reacts with CH<sub>3</sub>MgBr. Identify the new C-C bond that forms in the product.



**Answer: (i) acid-base reaction, (ii) nucleophilic substitution reaction, (iii) nucleophilic addition reaction**



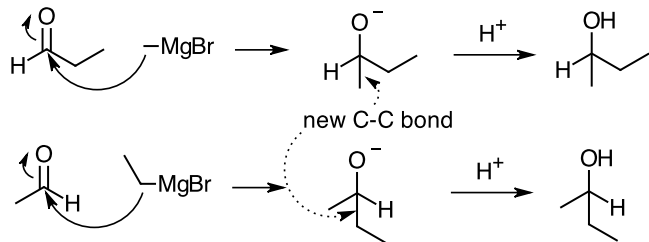
d. Synthesis using a Grignard reagent. You know a C-C bond forms to carbonyl C and the carbonyl C becomes the C bonded to the -OH group.

There are two ways to make Compound (i) from part c using a Grignard reaction.

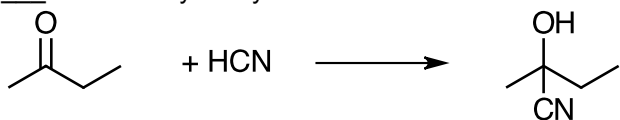
(i) Identify a Grignard reagent and carbonyl compound to make Compound (i) from part c.

(ii) Identify a second way to make Compound (i) from part c using a different Grignard reagent and carbonyl compound.

Answer: new C-C bond forms at carbonyl C.

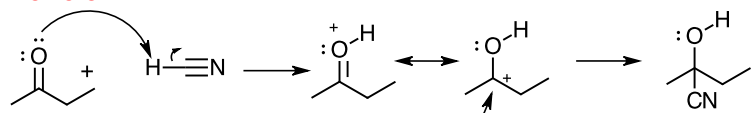


3. Cyanohydrins are found in natural products. A cyanohydrin has alcohol and nitrile groups bonded to the same carbon.  
a. (i) Use curved arrows to show how 2-butanone reacts with HCN to form a tetrahedral intermediate which reacts with \_\_\_ to form a cyanohydrin.

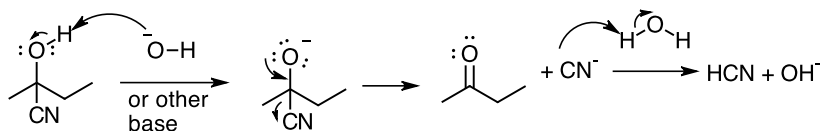
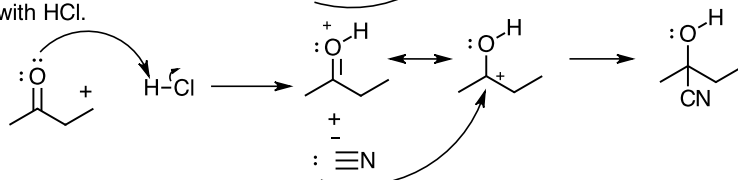


(ii) Use curved arrows to show how the cyanohydrin undergoes hydrolysis to form 2-butanone and HCN.

Answers:



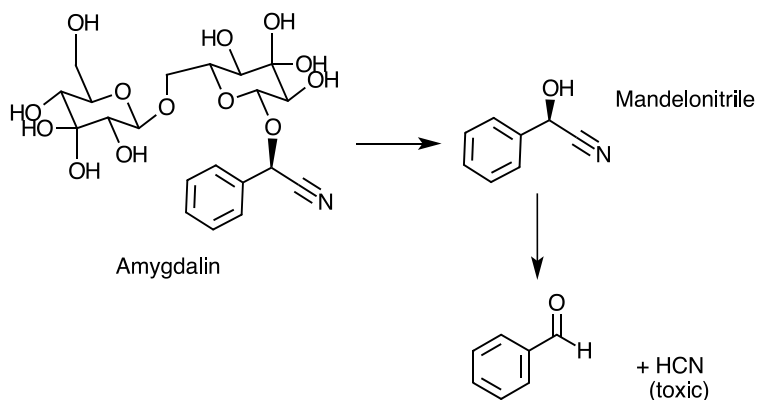
But HCN is a weak acid.  
Works better with NaCN  
with HCl.



b. Cyanohydrins are found in some natural products, e.g., mandelonitrile in the pits of cherries, apricots, and peaches. A cyanohydrin can form a carbonyl compound and hydrogen cyanide (HCN), a toxic gas (Reference: Klein, "Organic Chemistry", p. 948).

Which compound is the cyanonitrile cyanohydrin?

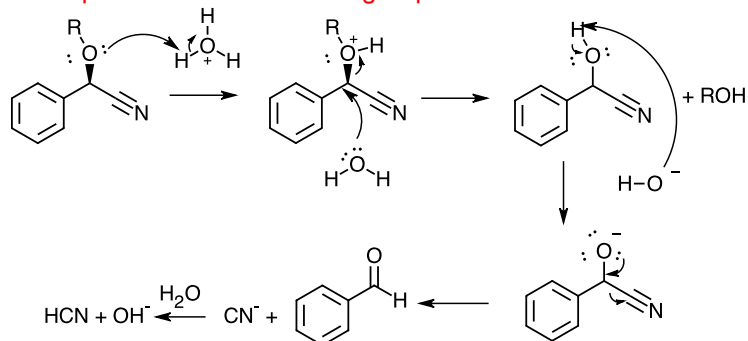
Use curved arrows to show how amygdalin forms mandelonitrile which forms benzaldehyde and HCN. Identify reaction conditions for each step.



Answers: mandelonitrile is the cyanohydrin.

Amygdalin is an ether. The -OR group is a poor leaving group but is made into a better leaving group by protonating the O by treating with acid. Then, water can react at alpha C in a substitution reaction to form mandelonitrile.

Mandelonitrile is a cyanohydrin. Convert mandelonitrile to benzaldehyde like in Problem 3a. Use a base to remove the acidic proton from the alcohol group.



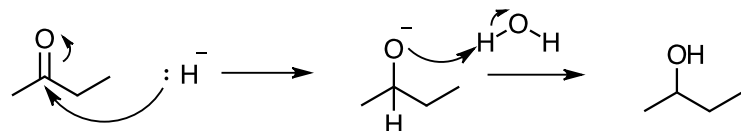
4. Reduction of aldehyde/ketone to alcohol. Hydride reducing agents, like  $\text{LiAlH}_4$  and  $\text{NaBH}_4$ , contain the hydride ion,  $\text{H}^-$ .

a. The hydride ion behaves like a \_\_\_\_\_.

b. Use curved arrows to show how 2-butanone reacts with  $\text{H}^-$  to form a tetrahedral intermediate which reacts with \_\_\_\_\_ to form an alcohol.

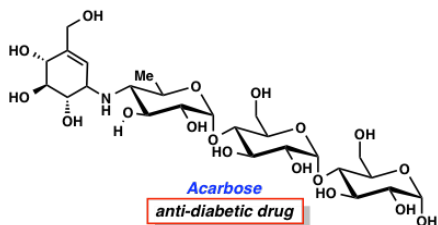
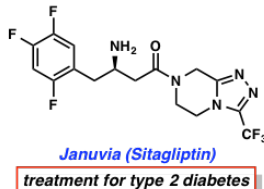
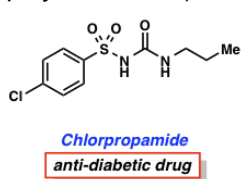
Answers: a. The hydride ion behaves like a nucleophile.

b. tetrahedral intermediate reacts with water.



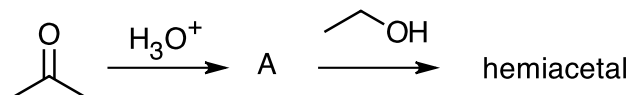
5. A hemiacetal has  $-\text{OH}$  and  $-\text{OR}$  groups bonded to the same carbon. An acetal has 2  $-\text{OR}$  groups bonded to the same carbon. Biology: polysaccharides are chains of monosaccharides connected by a glycosidic bond – an acetal linkage.

a. From LearnBacon.com: Common anti-diabetic drugs are Chlorpropamide, Metformin, Januvia, and Acarbose (a polysaccharide). How many acetals are present in Acarbose?



Answer: 2. See far right C on 2<sup>nd</sup> and 3<sup>rd</sup> rings.

b. Hemiacetal formation:

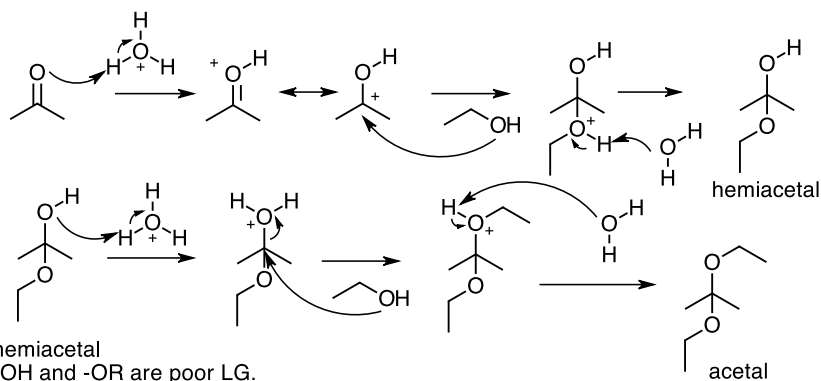


(i) Use curved arrows to show how Intermediate A and the hemiacetal is formed.

(ii) Circle the leaving group (LG) in the hemiacetal. Is this a good LG? If not, how can you make it a better LG?

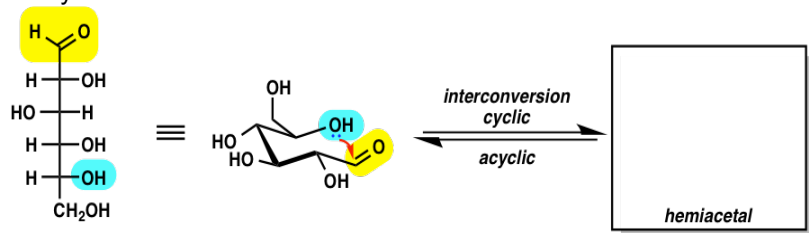
(iii) The hemiacetal reacts with  $\text{C}_2\text{H}_5\text{OH}$  to form an acetal. Use curved arrows to show how this reaction occurs.

Answers:



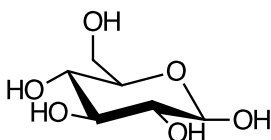
hemiacetal  
 -OH and -OR are poor LG.  
 Protonate to make into  
 better LG.

c. From LearnBacon.com: Sugar monomers interconvert between cyclic and acyclic forms (intramolecular process). Draw the cyclic structures that form.

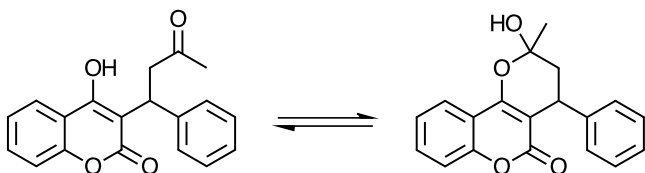


D-glucose

Answer:

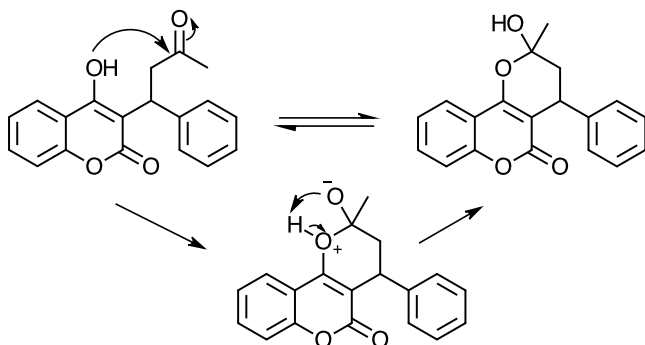


d. Warfarin (coumadin) is a blood thinning drug. It is also used in rat poison. Use curved arrows to show how the product is formed.



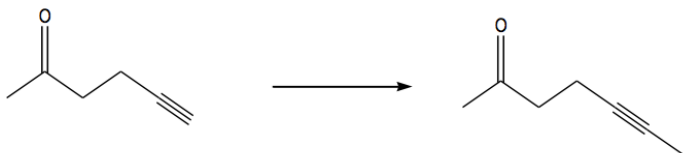
4-hydroxy coumarin  
 Active form

Answer:

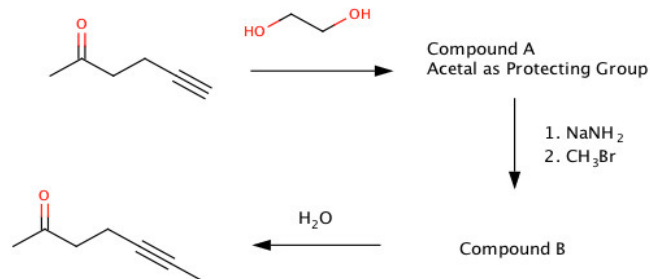


e. Acetals as protecting groups. Since acetals are ethers, which are unreactive, they can be used to “protect” a functional group from reacting when two reactive groups are in the same compound.

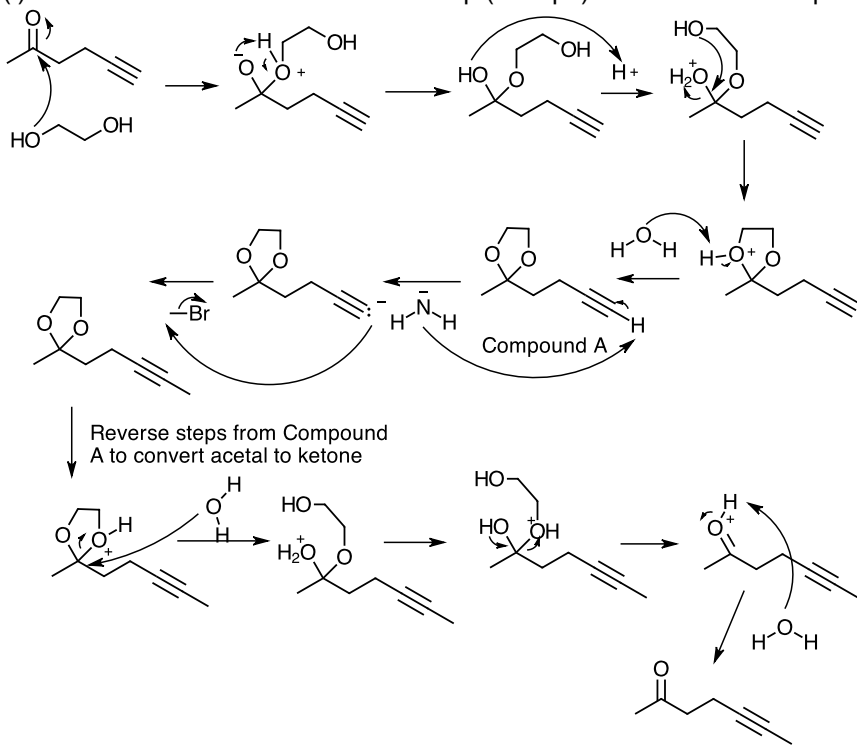
Example: You want to do the following reaction. You can use a strong base to make the remove the proton from the alkyne (to make the acetylide ion) but the strong base will also react at the carbonyl carbon (ketone).



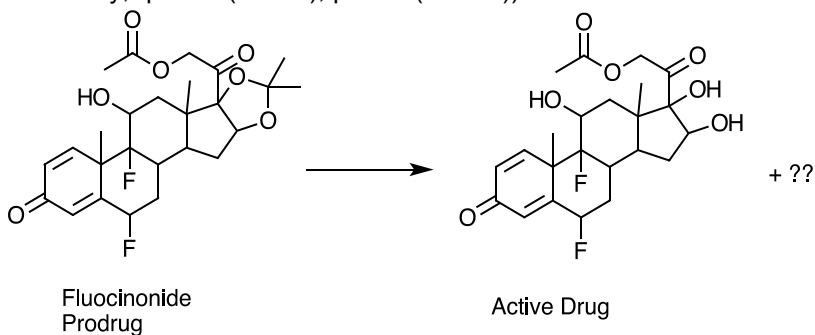
So you can protect the ketone group by converting it to an acetal. The acetal is unreactive so you now you can use a strong base to remove the proton from the alkyne to make the acetylide ion and then use \_\_\_\_\_ to form a C-C bond. To convert the acetal back to a ketone, do a hydrolysis reaction.



(i) Use curved arrows to show each step (3 steps) in this reaction sequence.



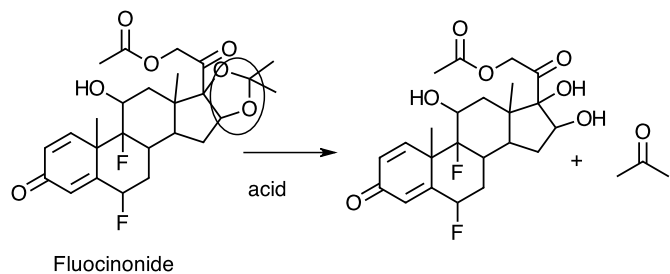
(ii) Flucinonide treats skin conditions, e.g., eczema. This compound is a prodrug and is an acetal. (See Klein, "Organic Chemistry," p. 930 (1<sup>st</sup> ed.), p. 946 (2<sup>nd</sup> ed.))



Circle the acetal group in flucinonide.

What conditions convert the prodrug to the active drug? (Hint: how can you convert the acetal back to the carbonyl compound and alcohol? See Step 3 in the reaction sequence from the previous problem.)

Answers:



6. Gem diol (from Gemini – twins. Twin –OH groups on the same C)

Use curved arrows to show how acetone reacts with  $\text{H}_3\text{O}^+$  to form a tetrahedral intermediate which reacts with \_\_\_ to form a gem diol.

Answers: acetone reacts with  $\text{H}_3\text{O}^+$  to form a tetrahedral intermediate which reacts with water to form a gem diol.

