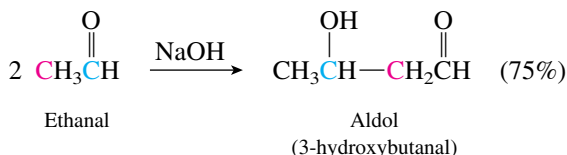


20.5 THE ALDOL CONDENSATION

You may have noticed that aldehydes were conspicuously absent from the examples of alkylation reactions presented in Sections 20.3 and 20.4. This is due to the high reactivity of the carbonyl carbon of an aldehyde as an electrophile. When an enolate anion nucleophile is generated from an aldehyde, under most circumstances it rapidly reacts with the electrophilic carbonyl carbon of an un-ionized aldehyde molecule. Although this reaction, known as the **aldol condensation**, interferes with the alkylation of aldehydes, it is a very useful synthetic reaction in its own right. The aldol condensation of ethanal is shown in the following equation:

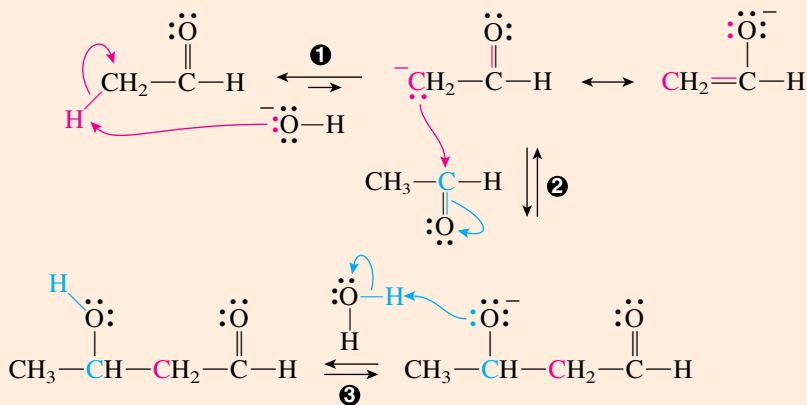


The product, 3-hydroxybutanal, is also known as aldol and gives rise to the name for the whole class of reactions.

The mechanism for this reaction is shown in Figure 20.3. For this mechanism to occur, both the enolate anion derived from the aldehyde and the un-ionized aldehyde must be present. To ensure that this is the case, hydroxide ion is most commonly used as the base. Because hydroxide ion is a weaker base than the aldehyde enolate anion, only a small amount of the enolate anion is produced. Most of the aldehyde remains

- ❶ The base, hydroxide ion, removes an acidic hydrogen from the α -carbon of the aldehyde. The conjugate base of the aldehyde is a stronger base than hydroxide, so the equilibrium for this first step favors the reactants.

However, enough enolate ion nucleophile is present to react with the electrophilic carbonyl carbon of a second aldehyde molecule.



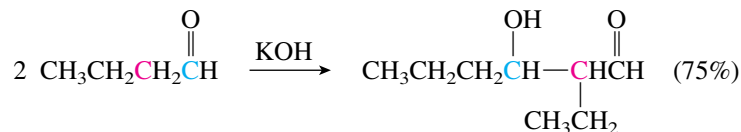
This part of the mechanism is just like the mechanism for the addition reactions of Chapter 18. ❷ The enolate nucleophile adds to the carbonyl carbon of a second aldehyde molecule, and ❸ the negative oxygen removes a proton from water. This step regenerates hydroxide ion, so the reaction is base catalyzed.

Figure 20.3

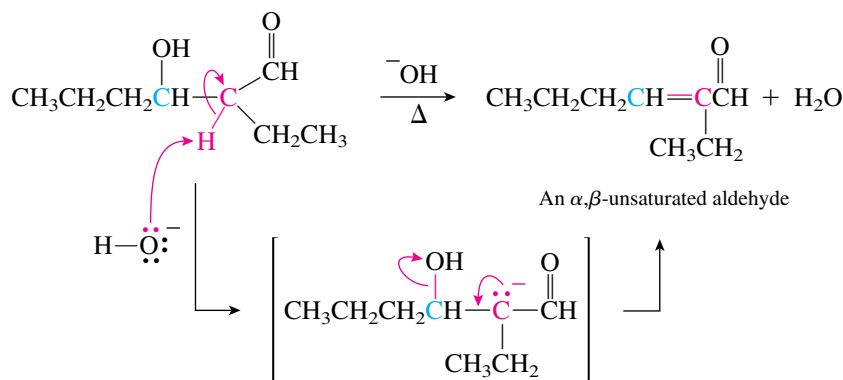
MECHANISM OF THE ALDOL CONDENSATION.

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Motion to view the
Mechanism of the
Aldol Condensation.

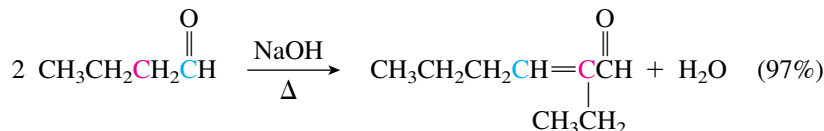
un-ionized and is available for reaction as the electrophile. Note that the strong bases described in Section 20.3, which would tend to convert most of the aldehyde molecules to enolate ions, are not used in aldol condensations. The addition of the enolate nucleophile to the aldehyde follows the same mechanism as the addition of other nucleophiles that were described in Chapter 18. Remember that the α -carbon of one aldehyde molecule bonds to the carbonyl carbon of a second aldehyde molecule, as illustrated in the following example:



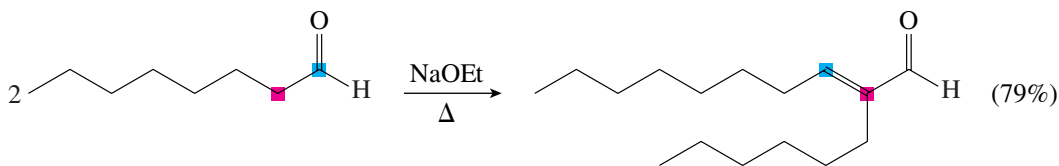
If the aldol condensation is conducted under more vigorous conditions (higher temperature, longer reaction time, and/or stronger base), elimination of water to form an α,β -unsaturated aldehyde usually occurs. This elimination is illustrated in the following example. Note that the α -carbon of one molecule is now doubly bonded to the carbonyl carbon of the other. (This text uses the symbol for heat, Δ , to indicate the vigorous conditions that cause eliminations to occur in these aldol condensations, even though other conditions might have been used.)



This elimination occurs by a somewhat different mechanism than those described in Chapter 9. Because the hydrogen on the α -carbon is relatively acidic, it is removed by the base in the first step to produce an enolate anion. Then hydroxide ion is lost from the enolate ion in the second step. Because this step is intramolecular and the product is stabilized by conjugation of its CC double bond with the CO double bond of the carbonyl group, even a poor leaving group such as hydroxide ion can leave. (This is an example of the E1cb mechanism described in the Focus On box on page 333 in Chapter 9.) Most aldol condensations are run under conditions that favor dehydration because the stability of the product helps drive the equilibrium in the desired direction, resulting in a higher yield. For example, the reaction of butanal shown previously results in a 75% yield of the aldol product. If the reaction is conducted so that dehydration occurs, the yield of the conjugated product is 97%.

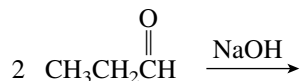


Another example is shown in the following equation:



PRACTICE PROBLEM 20.3

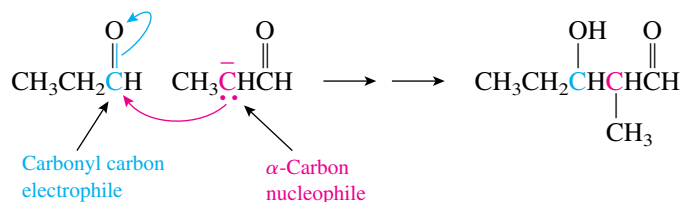
Show the product of this reaction:



Strategy

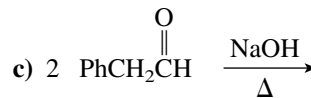
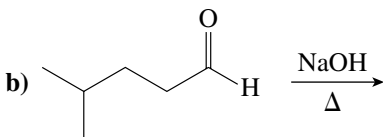
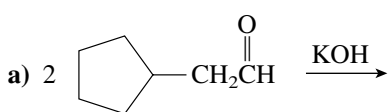
The key to determining the products of an aldol condensation is to remember that the nucleophile is an enolate anion, which is formed at the α -carbon of the aldehyde, and the electrophile is the carbonyl carbon of another aldehyde molecule. Therefore the product has the α -carbon of one aldehyde molecule bonded to the carbonyl carbon of another aldehyde molecule. Under milder conditions an OH group remains on the carbonyl carbon of the electrophile, whereas under vigorous conditions the α -carbon and the carbonyl carbon are connected by a double bond.

Solution



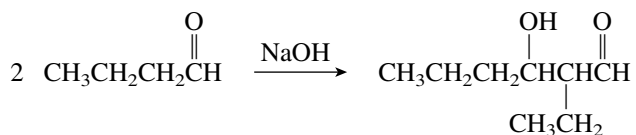
PROBLEM 20.9

Show the products of these reactions:

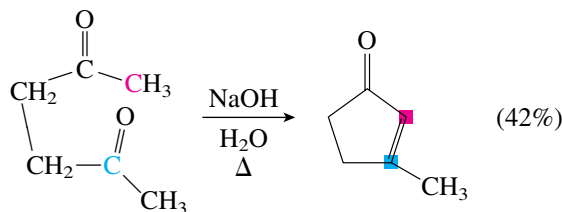


PROBLEM 20.10

Show all of the steps in the mechanism for this reaction:

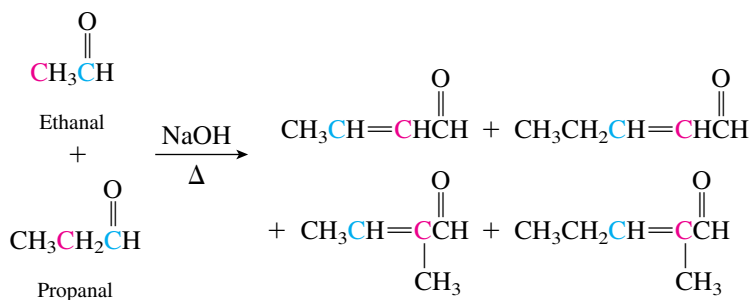


Ketones are less reactive electrophiles than aldehydes. Therefore, the aldol condensation of ketones is not often used because the equilibrium is unfavorable. However, the intramolecular condensation of diketones is useful if the size of the resulting ring is favorable (formation of five- and six-membered rings).

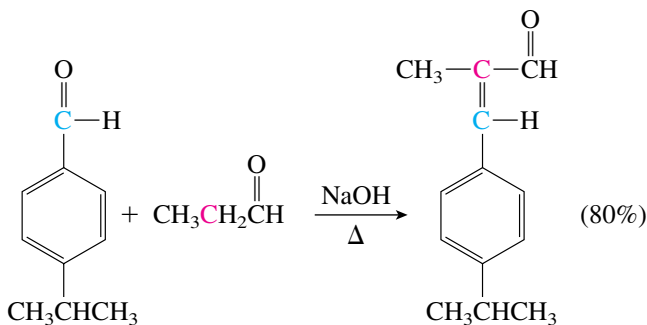


A diketone

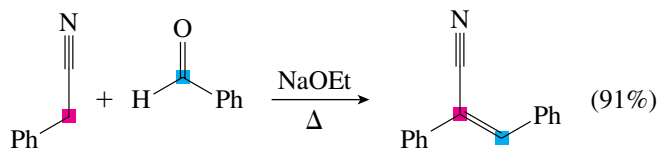
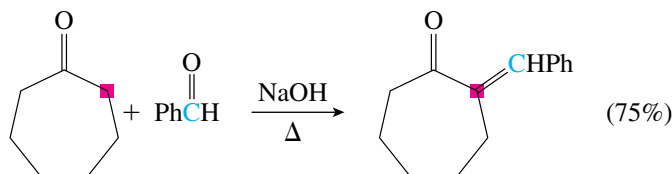
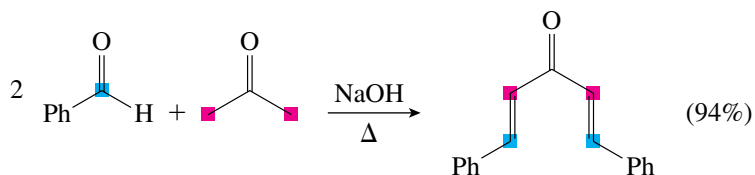
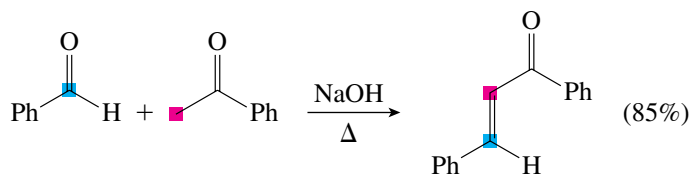
Often, it is desirable to conduct an aldol condensation in which the nucleophile and the electrophile are derived from different compounds. In general, such **mixed aldol condensations**, involving two different aldehydes, result in the formation of several products and for this reason are not useful. For example, the reaction of ethanal and propanal results in the formation of four products because there are two possible enolate nucleophiles and two carbonyl electrophiles:



Mixed aldol condensations can be employed if one of the aldehydes has no hydrogens on the α -carbon, so it cannot form an enolate ion and can only act as the electrophilic partner in the reaction. Aromatic aldehydes are especially useful in this role because the dehydration product has additional stabilization from the conjugation of the newly formed CC double bond with the aromatic ring. This stabilization makes the equilibrium for the formation of this product more favorable.

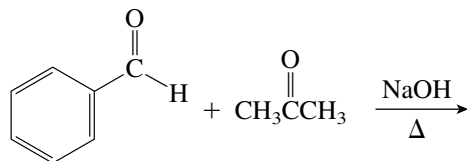


With an aromatic aldehyde as the electrophilic partner, the nucleophilic enolate ion can also be derived from a ketone or a nitrile. As illustrated in the following examples, this enables the aldol condensation to be used to form a wide variety of compounds:



PRACTICE PROBLEM 20.4

Show the product of this reaction:

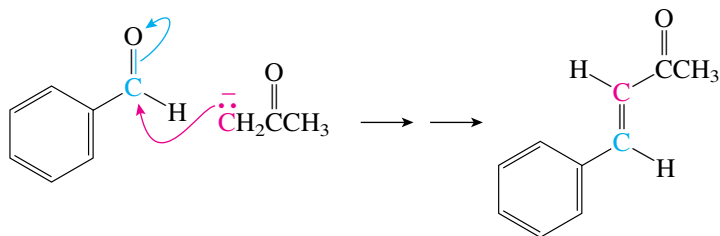


Strategy

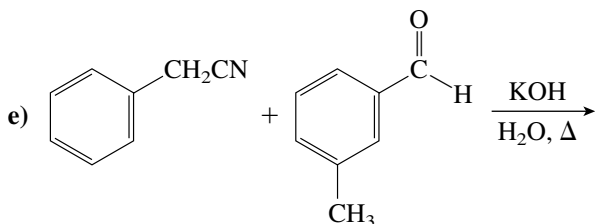
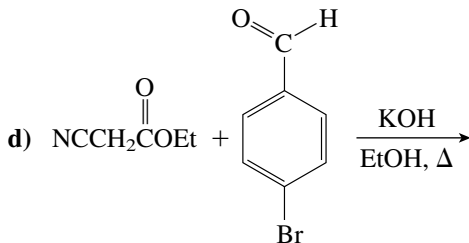
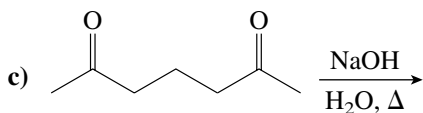
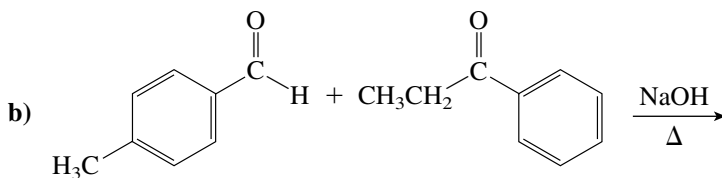
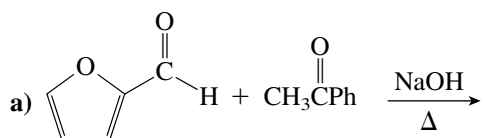
Again, the key is to identify the nucleophile (the enolate anion) and the electrophile (the carbonyl carbon).

Solution

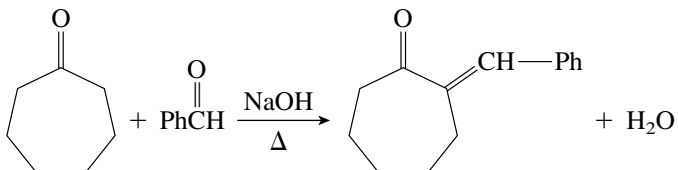
In this example the enolate anion can be derived only from acetone. The electrophile is the more reactive carbonyl carbon, that of benzaldehyde.

**PROBLEM 20.11**

Show the products of these reactions:

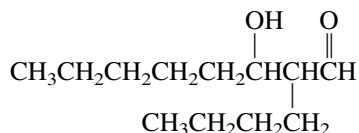
**PROBLEM 20.12**

Show all of the steps in the mechanism for this reaction:



PRACTICE PROBLEM 20.5

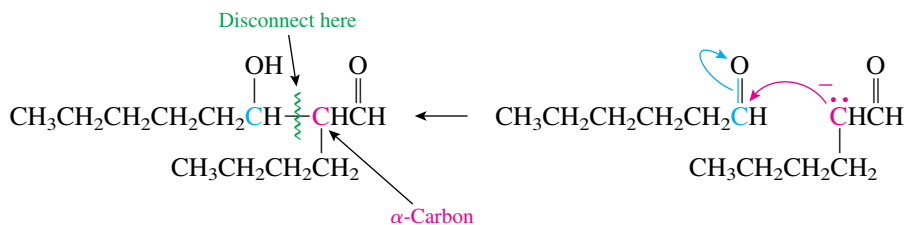
Show how the aldol condensation could be used to synthesize this compound:



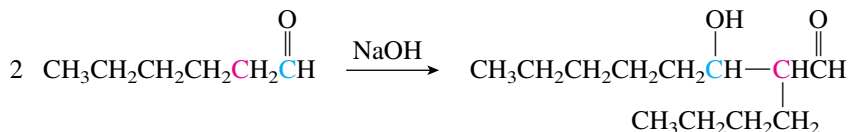
Strategy

First identify the carbon–carbon bond that could be formed in an aldol condensation. This is the bond between the α -carbon of the carbonyl group of the product and the carbon that is either doubly bonded to it or has a hydroxy substituent. Disconnection of this bond gives the fragments needed for the aldol condensation. Remember, the α -carbon of the product is the nucleophilic carbon of the enolate anion and the carbon to which it is bonded is the electrophilic carbonyl carbon.

Solution

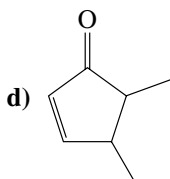
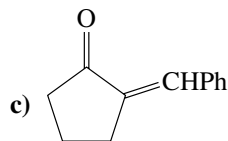
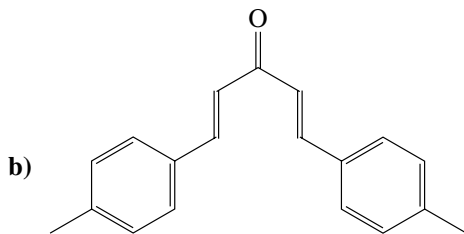
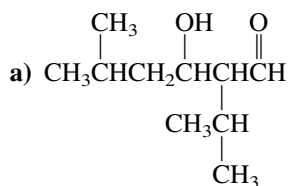


So the synthesis is



PROBLEM 20.13

Show how the aldol condensation could be used to synthesize these compounds.



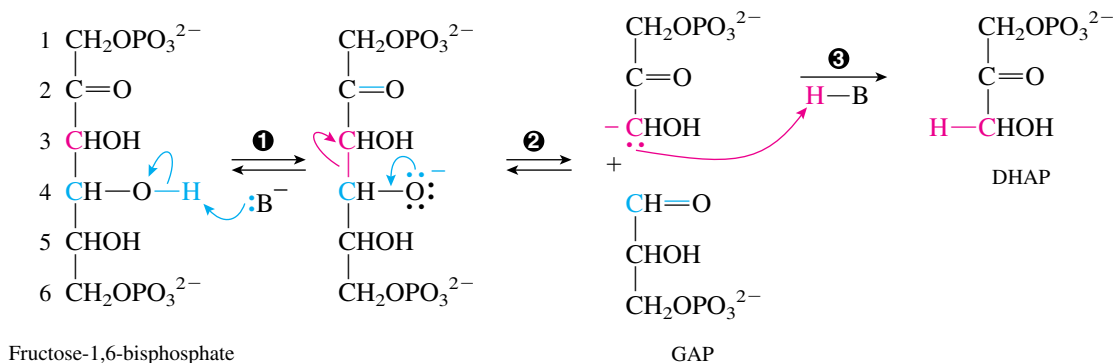
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Focus On Biological Chemistry

The Reverse Aldol Reaction in Metabolism

The initial product of an aldol condensation has a hydroxy group on the β -carbon to a carbonyl group. Sugars also have hydroxy groups on the β -carbon to their carbonyl groups, so they can be viewed as products of aldol condensations. In fact, a reverse aldol condensation is used in the metabolism of glucose (glycolysis) to cleave this six-carbon sugar into two three-carbon sugars.

To cleave a six-carbon sugar into two three-carbon fragments by a reverse aldol condensation, there must be a carbonyl group at C-2 and a hydroxy group at C-4. Therefore, glucose is first isomerized to fructose during its metabolism. The substrate for the cleavage reaction is the diphosphate ester, fructose-1,6-bisphosphate. In step ①, a proton is removed from the hydroxy group on C-4. The bond between C-3 and C-4 is then broken in step ②, which is the reverse of the aldol condensation, producing glyceraldehyde-3-phosphate (GAP) and the enolate ion of dihydroxyacetone phosphate (DHAP). This enolate ion is protonated in step ③. GAP and DHAP can be interconverted by the same process that interconverts glucose and fructose and thus provide a common intermediate for further metabolism.



20.6 ESTER CONDENSATIONS

So far, we have seen that an enolate anion is able to act as a nucleophile in an $\text{S}_{\text{N}}2$ reaction (Sections 20.3 and 20.4) and also in an addition reaction to the carbonyl group of an aldehyde in the aldol condensation (Section 20.5). It also can act as a nucleophile in a substitution reaction with the carbonyl group of an ester as the electrophile. When an ester is treated with a base such as sodium ethoxide, the enolate ion that is produced can react with another molecule of the same ester. The product has the α -carbon of one ester molecule bonded to the carbonyl carbon of a second ester molecule, replacing the alkoxy group. Examples of this reaction, called the **Claisen ester condensation**, are provided by the following equations: