

23.6: INTRAMOLECULAR ALDOL REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate an intramolecular aldol reaction.
2. identify the product formed when a given dicarbonyl compound undergoes an intramolecular aldol condensation.
3. identify the dicarbonyl compound which, when treated with a suitable base, could be used to prepare a given cyclic enone by an intramolecular aldol condensation.

STUDY NOTES

“Intramolecular ” means “within the same molecule.” You have already seen some examples of intramolecular reactions in previous chapters. Another term for intramolecular aldol reaction is “internal aldol reaction.”

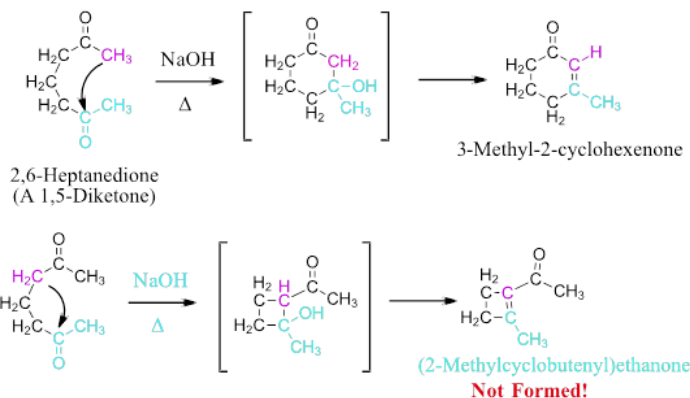
INTRAMOLECULAR ALDOL REACTION

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. The term “Intramolecular” means “within the same molecule.” In this case, it means that the enolate donor and the electrophilic acceptor of an aldol reaction are contained in the same molecule such as dialdehydes, keto aldehydes, or diketones. In these cases, the small distance between the donor and acceptor leads to faster reaction rates for intramolecular condensations making intermolecular condensations (which require two molecules to collide in solution) less favorable.

In most cases multiple sets of α -hydrogens need to be considered when determining the donor/acceptor roles for the reaction, which might lead to a mixture of products. The intramolecular aldol reaction of a 1,5-diketone, 2,6-heptanedione, could possibly yield either the six-membered ring product, 3-methyl-2-cyclohexenone, or the four-membered ring product, (2-methylcyclobutenyl)ethanone. However, the cyclohexanone product is exclusively formed.

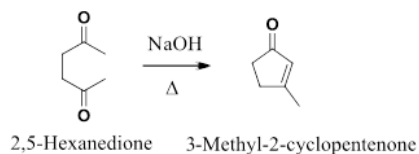
This product selectivity is possible due to all of the steps of the mechanism being reversibly, which tends to produce the most stable product. As with most ring forming reactions, five and six membered rings are preferred due to their relative lack of ring strain compared to other sized rings (See Sections 4.4 & 4.5). Once equilibrium is reached, the relatively strain free and therefore more thermodynamically stable, cyclohexanone product will be preferably formed.

Example



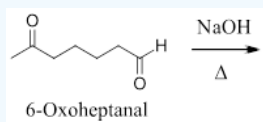
Similar analysis can be used to predict the products of other intramolecular aldol reactions. In a similar reaction, 1,4-diketones, such as 2,5-hexanedione, only form the five-membered ring product, ex. 3-methyl-2-cyclopentenone, without any of the possible cyclopropane product forming.

Example



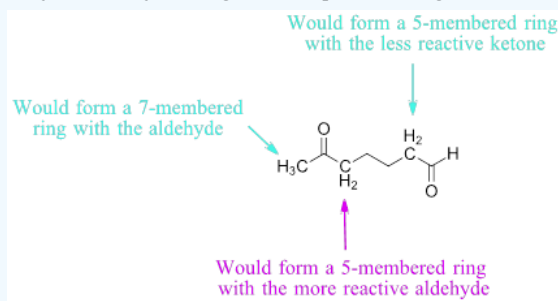
? WORKED EXAMPLE

Please draw the expected product of an intramolecular aldol condensation with the following molecule:

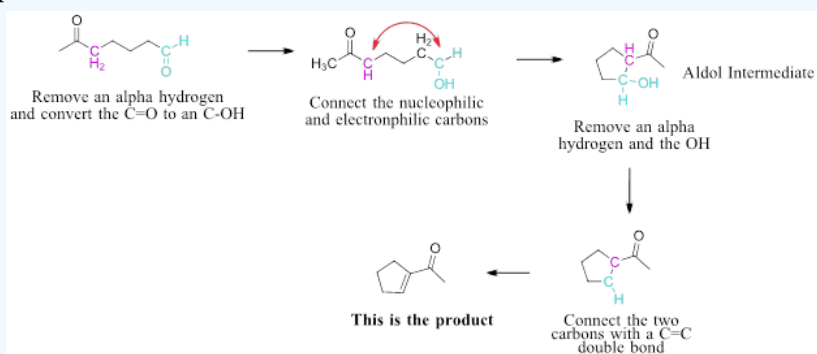


Answer

Analysis: 6-Oxoheptanal has three unique sets of alpha-hydrogens which could be deprotonated to form an enolate. Selecting the correct set involves analyzing the carbonyl reactivity's along with the possible ring sizes of the products.

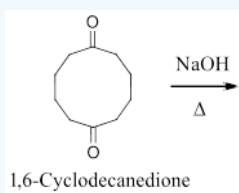


Solution: Once the preferred alpha-hydrogens are determined go through the steps discussed in the previous sections to determine the aldol condensation product. Remember to form the aldol intermediate first.



? EXERCISES 23.6.1

- Briefly explain why the molecule, 2,4-pentanedione, when reacted with a base would mostly likely not produce an intramolecular aldol condensation product.
- Draw the product of the following aldol condensation:

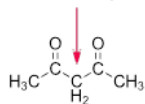


Answers

- 2,4-Pentanedione like other 1,3-Diketones have particularly acidic alpha-hydrogens between the two carbonyl. When base is applied these will be the first to deprotonate and form an enolate. For an intramolecular aldol condensation to occur an alpha-hydrogen one of the methyl groups would have to be removed which would be difficult.

2)

Most Acidic α -Hydrogens



2,4-Pentanedione



Bicyclo[5.3.0]dec-1(7)-en-2-one

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