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EXPERIMENT 1

SOLVENTLESS REACTIONS: THE ALDOL REACTION

Chemical Concepts

Carbonyl chemistry; the aldol reaction; melting points of solids and mixtures; recrystallization.

Green Lessons

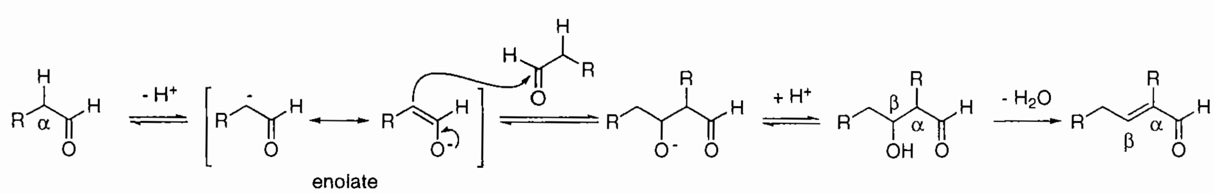
Solventless reactions between solids; atom economy.

Estimated Lab Time

1 – 2 hours

Introduction

The aldol condensation represents a powerful general method for the construction of carbon-carbon bonds, one of the central themes of synthetic organic chemistry. In the base-catalyzed aldol condensation reaction, deprotonation alpha (adjacent) to a carbonyl group affords a resonance-stabilized anion called an enolate, which then carries out nucleophilic attack at the carbonyl group of another molecule of the reactant. (Analogous acid-catalyzed reactions are also well-known.) The product, a beta-hydroxy carbonyl compound, often undergoes facile elimination of water (dehydration), affording an alpha, beta-unsaturated carbonyl compound as the final product.



Mechanism of the base-catalyzed aldol condensation

Aldol condensation reactions between two different carbonyl compounds can lead to complex product mixtures, due to the possibility of enolate formation from either reactant and to the possibility of competing "homo" coupling rather than the desired "cross" coupling.

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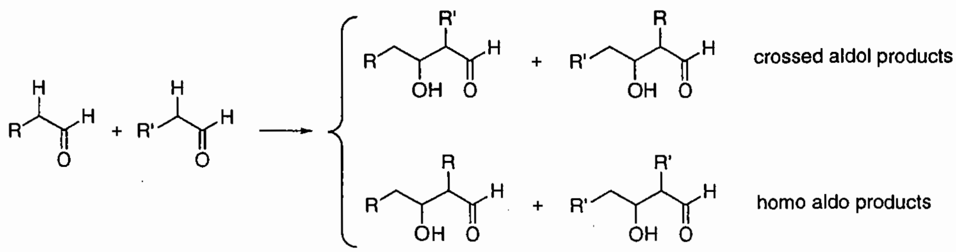
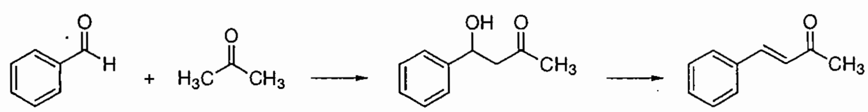


"Crossed" aldol condensation can afford complex mixtures

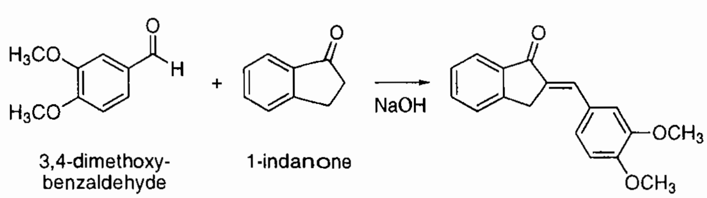
If, however, only one of the carbonyl compounds has alpha hydrogens available for deprotonation and enolate formation, the "crossed" aldol reaction can provide synthetically useful yields of products. Thus, for example, benzaldehyde cannot be converted to an enolate, yet reacts readily with enolates of other carbonyl compounds, including acetone.



A successful "crossed" aldol condensation

Homo coupling of acetone (or other ketones) is generally not a problem in such reactions, as the aldol condensation of ketones is generally not a very efficient reaction. (More specifically, each step of the aldol condensation is reversible under the reaction conditions – at least until the dehydration step – and thus equilibrium is established. With aldehydes, equilibrium favors the aldol product, but with ketones, primarily for steric reasons, very little aldol condensation product is present at equilibrium.)

In this experiment, you will explore the aldol condensation reaction of 3,4-dimethoxybenzaldehyde and 1-indanone.



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In contrast to typical experimental procedures for aldol condensation reactions, this reaction will be carried out without solvent. Ongoing research is revealing a number of reactions that proceed nicely in the absence of solvent, representing the best possible solution to choice of a benign solvent. Although these reactions are frequently referred to as "solid-state" reactions, it has been noted [41] that in many cases, mixture of the solid reactants results in melting, so that the reactions actually occur in the liquid, albeit solvent-free state. This melting phenomenon is interesting and actually represents one of the key points of this experiment. You have learned that impurities lead to lower melting points. Here, you will experience this in a vivid way – as you mix the two solid reactants, they will melt. In addition to providing a memorable demonstration of the impact of impurities on melting points and illustrating the possibility of carrying out organic reactions in the absence of solvents, this experiment highlights another key green concept – the design of efficient, atom-economical reactions. The aldol condensation, if effected without dehydration, has an atom economy of 100% and requires only a catalytic amount of acid or base, and even with dehydration, the atom economy remains quite high.

Pre-Lab Preparation

1. Study the technique sections in your lab manual regarding melting points and recrystallization.
2. Carry out pre-lab preparations as described in Chapter 11, section 11.6A, or as called for by your instructor.

Experimental Procedure

SAFETY PRECAUTIONS: Use care to avoid contact with solid sodium hydroxide or the reaction mixture.

41. G. Rothenberg, A. P. Downie, C. L. Raston, and J. L. Scott, "Understanding Solid/Solid Organic Reactions," *J. Am. Chem. Soc.* **2001**, *123*, 8701-8708.

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Reaction

1. Place 0.25 g of 3,4-dimethoxybenzaldehyde and 0.20 g of 1-indanone in a test tube. Using a metal spatula, scrape and crush the two solids together until they become a brown oil. Use care to avoid breaking the test tube.
2. Add 0.05 g of finely ground (using a mortar and pestle) solid NaOH to the reaction mixture and continue scraping until the mixture becomes solid.

Workup and purification

3. Allow the mixture to stand for 15 minutes, then add about 2 mL of 10% aqueous HCl solution. Scrape well in order to dislodge the product from the walls of the test tube. Check the pH of the solution to make sure it is acidic.
4. Isolate the solid product by vacuum filtration, continuing to pull air through the solid to facilitate drying. Determine the mass of the crude product.
5. Recrystallize the product from 90% ethanol/10% water, using the hot solvent first to rinse any remaining product from the test tube. You should not require more than 20 mL of solvent to effect this recrystallization.

Characterization

6. Determine the mass and melting point of the recrystallized product. (A typical melting point range is 178 – 181 °C.)

Post-Lab Questions and Exercises

1. Describe the physical properties (color and state) of your crude product. Report the mass and percent of theoretical yield of the crude product.
2. Report the color and melting point range of your recrystallized product. Report the mass and percent of theoretical yield of the recrystallized product.

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3. Calculate the atom economy for the reaction.
4. Perform an economic analysis for the preparation of your product.

Experiment Development Notes

This experiment was adapted from the primary literature. Any number of solventless aldol reactions are possible [41], and it may be attractive to allow students some latitude in choosing their reactants, taking care to avoid unexpectedly hazardous reagents or products. The reactants reported here were chosen deliberately to highlight the melting point depression phenomenon; other pairs of reagents may or may not visibly melt upon mixing.