

A Green Enantioselective Aldol Condensation for the Undergraduate Organic Laboratory

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The aldol condensation reaction typically appears in the second semester of the organic chemistry curriculum. Although the mixed condensation reaction between an aldehyde and the enolate of a ketone is more properly named the Claisen–Schmidt modification, it and related reactions often receive the designation of aldol condensation. The frequent appearance of the reaction in laboratory manuals (1), in lecture textbooks (2), on standardized organic chemistry examinations, and in biochemistry textbooks (3) underscores its importance. The examples of aldol condensations that appear in laboratory manuals and this *Journal* (4) frequently involve the use of aromatic aldehydes that readily undergo dehydration to give crystalline α,β -unsaturated products. These experiments offer the advantages of relatively fast reaction times, high yields, and easily purified products. However, immediate dehydration renders the stereochemical aspects of the addition irrelevant. More recently, attention in this *Journal* has turned to more environmentally benign condensation procedures, including solventless aldol (5), Claisen (6), and Cannizzaro (7) condensations.

Students at this university who take the second semester of the organic chemistry lecture typically co-enroll in our organic–inorganic synthesis laboratory course. Lab sections, with a maximum of 16 students per section, meet once a week for three hours. The aldol condensation the students perform in this course involves the proline-catalyzed condensation between acetone and isobutyraldehyde (Scheme I), which is based on the research literature (8).

The project requires two lab periods. During the first period, students listen to a pre-laboratory lecture about the background and procedural details of the project, complete the necessary calculations, and begin the initial condensation experiment. (The remainder of the period is available for completing work from the previous week or planning for the remainder of the aldol project.) During the second period, the students work up the reaction mixture and analyze the product using IR, ^1H NMR, ^{13}C NMR, and polarimetry. We have found that the crude product is sufficiently clean for analysis. A typical student yield of isolated product is about 50–65%. The 60 MHz ^1H NMR spectrum of the product in deuterated chloroform shows no evidence of unreacted aldehyde, dehydrated adduct, or proline. Polarimetry with a Rudolph Instruments DigiPol 781 automatic polarimeter

confirms that the major enantiomer exhibits a positive specific rotation, which corresponds with the literature value of $+61.7^\circ$ for a 96% excess of the (*R*)-enantiomer (8). Relatively dilute solutions (< 2 g of analyte/100 mL of chloroform) give optimal polarimetry data. Students typically obtain an ee of approximately 70% by this method (a detailed discussion is included in the Supplemental Material^W).

Hazards

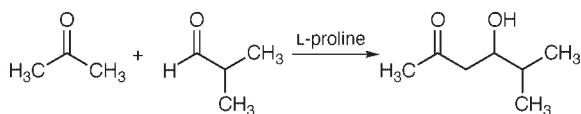
Acetone is flammable. Isobutyraldehyde is flammable and an irritant. Diethyl ether is flammable. Chloroform and deuterated chloroform are cancer suspect agents and mutagens.

Discussion

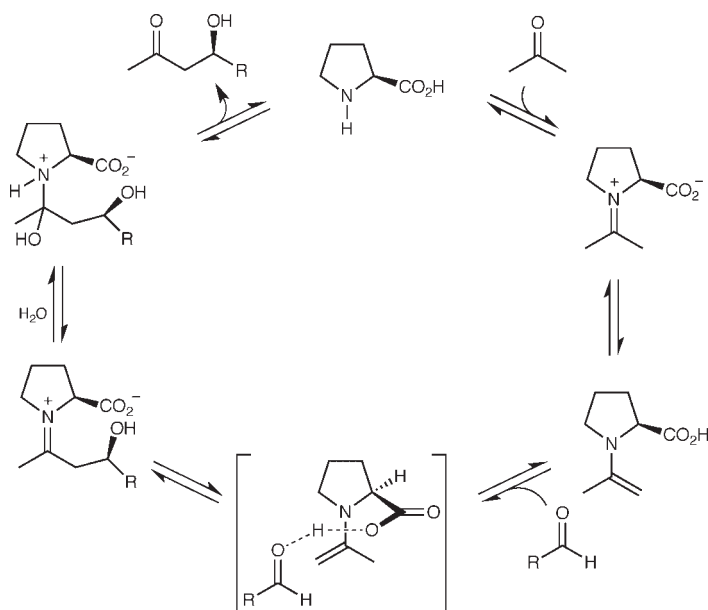
The pursuit of enantioselectivity has been a cornerstone of organic synthesis for several decades, especially in the pharmaceutical industry. A number of laboratory exercises that emphasize enantioselective synthesis have appeared in this *Journal* (9). This experiment lets students explore this important facet of chemical research while also permitting them to study one of the “classic” organic reactions. This particular procedure also exposes students to the innovation of amine-based asymmetric small molecule mimics of enzymes, which was first reported in 1974 (10) but has garnered appreciable interest only recently (11, 12). In this particular methodology, L-proline is thought to mimic a class I aldolase enzyme (8). Class I aldolase enzymes use an enamine-based mechanism to catalyze the direct addition of two unmodified carbonyl compounds whereas class II aldolases use a zinc cofactor.

The proposed mechanism of catalysis for the proline-catalyzed aldol condensation involves an iminium ion precursor of the reactive enamine intermediate (Scheme II). During the addition of the enamine to the aldehyde, the rigid pyrrolidine ring of the enamine and an intermolecular hydrogen bond between the carboxylate group of the enamine and the aldehyde oxygen both contribute to the enantioselection.

This experiment illustrates several of the principles of green chemistry. The reaction proceeds at ambient temperature and pressure and requires neither an inert atmosphere nor purification and drying of the reagents. The reagents require no modification. The promoter is used in a catalytic rather than stoichiometric amount. Moreover, the catalyst is theoretically obtainable from renewable sources, biodegradable, and readily available in both enantiomeric forms. The water-solubility of the catalyst allows for its easy removal from the reaction mixture. Furthermore, when only one enantiomeric product is desired, an enantioselective process gener-



Scheme I. Proline-catalyzed aldol condensation between acetone and isobutyraldehyde.



Scheme II. Proposed catalytic cycle of the direct aldol condensation of acetone and isobutyraldehyde with L-proline; R is $-\text{CH}(\text{CH}_3)\text{CH}_3$.

ally offers a higher atom economy. Condensation reactions, by following an addition mechanism, also have an inherently higher atom economy.

However, this experiment also illustrates some of the trade-offs involved in green chemistry. The most glaring example is that the acetone is used in large excess so as to function as both reagent and solvent and to suppress side reactions, such as dehydration of the adduct or self-condensation of the isobutyraldehyde. This large excess leads to poor overall atom economy and effective mass yield. In addition, the acetone is volatile and flammable. Another volatile and flammable organic solvent, ether, is used to extract the product from the reaction mixture. The separated aqueous layer contains not only the proline catalyst but also NaCl and possibly some unreacted acetone and isobutyraldehyde. Finally, the reaction proceeds slowly. Product does not begin to appear for about 24 hours, and at least 48 hours are necessary to obtain an appreciable yield. For a process to be recognized as green, it ultimately needs to be viable in an industrial setting. The time limitation alone calls into question the viability of this process. However, as Thomas Goodwin has written, "an asymptotic approach to green chemistry" is the only realistic option because room for improvement always exists (13). This experiment represents a step in the green direction.

Acknowledgments

The Rudolph Instruments DigiPol 781 automatic polarimeter was purchased with grant funding from NSF-DUE 9952602, Camille & Henry Dreyfus Special Grant in the Chemical Sciences SG-00-055, and Millikin University. The Anasazi FT-NMR upgrade was purchased with grant funding from NSF-DUE 9751301 and Millikin University. Jessica Sjoken, a Millikin University undergraduate student, optimized the experimental procedure, which the author developed during a junior academic leave sponsored by Millikin University. The author is also grateful for a Dorothy & Moses

Passer Chemical Education Grant that enabled him to attend the 2001 Green Chemistry in Education Workshop at the University of Oregon.

Supplemental Material

Instructions for the students and notes for the instructor are available in this issue of *JCE Online*.

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