

Comparing the Traditional with the Modern: A Greener, Solvent-Free Dihydropyrimidone Synthesis

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Currently there is much interest in performing organic reactions under solvent-free conditions (1). Eliminating a reaction medium directly addresses one of the twelve principles of green chemistry that implores “avoid using solvents, separation agents, or other auxiliary chemicals” (2, 3). Moreover, solvent-free processes often exhibit significant rate enhancements due to increased reactant concentrations. Several pedagogical experiments highlighting solventless reactivity have previously been published in this *Journal* and elsewhere (4, 5). We discuss herein a different approach to teaching green chemistry concepts where mid-level undergraduates concurrently complete “traditional” and “modern” (solvent-free) versions of a multi-component reaction, within the same three-hour laboratory period. This expedites a direct, instructive comparison between old and new synthetic methods in terms of energy usage, atom economies, and catalytic strategies.

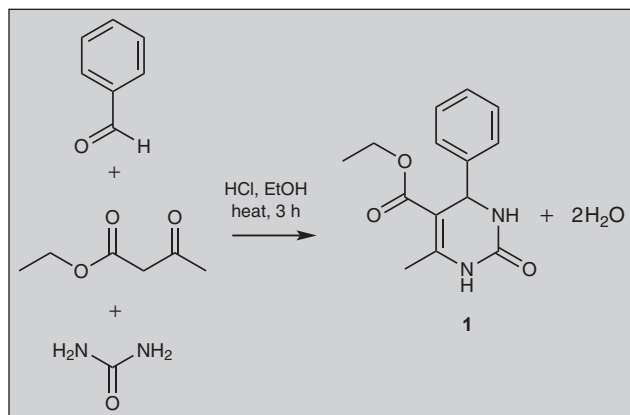
The Biginelli reaction dates from 1893 (6) and represents a classical approach for preparation of 3,4-dihydropyrimidin-2(1H)-ones. The reaction historically involves lengthy reflux of an aromatic aldehyde, a β -ketoester, and urea in the presence of a mineral acid catalyst and alcohol solvent (Scheme I; ref 7). 3,4-Dihydropyrimidin-2(1H)-ones are of medicinal interest as vasodilatory calcium-channel blockers (8) and anti-viral, anti-bacterial, and anti-inflammatory agents (9). In 2001, Holden and Crouch (10) described a microscale Biginelli reaction in this *Journal* as a modification of traditional macroscale experiments (7). This shortened the reaction time from three hours to 90 minutes, facilitating preparation of ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate **1** in a single laboratory session.

The last decade has seen many literature reports of solvent-free Biginelli syntheses that attempt to improve the environmental profile and reduce reaction time. Several procedures utilize Lewis acid catalysts rather than mineral acids (11). We chose to adapt the methodology of Sun et al. (12) featuring zinc(II) chloride as an inexpensive and readily available Lewis acid catalyst for 3,4-dihydropyrimidin-2(1H)-one synthesis (Scheme II). Use of ZnCl_2 furthermore permits solvent-free preparation of **1** in 15 minutes (conveniently undertaken by each student during the reflux portion of the traditional method). Compound **1** is synthesized by both approaches without need for recrystallization and is easily characterized by melting point, proton NMR spectroscopy, and IR spectroscopy. The experiment is performed soon after students learn about enolate ions and associated carbonyl addition reactions during lectures.

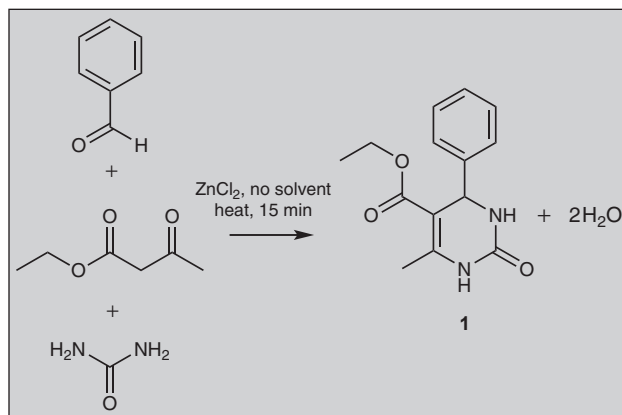
Experimental Overview

Traditional Synthesis of Ethyl 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**1**)

Traditional preparation of **1** involves scale-up of the previous educational experiment (10). Benzaldehyde (2.50 mmol, used without purification), ethyl acetoacetate (3.80 mmol), and urea (2.50 mmol) are combined in a 10 mL round-bottomed flask, followed by addition of 95% ethanol (1 mL). Two drops of concentrated HCl are added to the flask. The mixture is stirred and refluxed vigorously for 90 minutes (during which time the modern synthesis is accomplished). The reaction mixture is allowed to cool to room temperature and further in an ice bath. The solid Biginelli product is collected under vacuum,



Scheme I. A traditional Biginelli synthesis.



Scheme II. A modern Biginelli synthesis.

rinsed with water and 95% ethanol, and dried to typically yield 35–90% of **1** [average 62%, lit. yield 58% (10); mp 204–206 °C, lit. mp 203–205 °C (13)].

Modern Synthesis of Ethyl 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**1**)

During the reflux time of the traditional synthesis, benzaldehyde (2.00 mmol, used without purification), ethyl acetoacetate (2.00 mmol), and urea (3.00 mmol) are combined in an unstoppered 10 mL Erlenmeyer flask, followed by addition of zinc(II) chloride (0.42 mmol). The mixture is stirred and heated in a water bath at 70–80 °C until solidification occurs (usually 15 minutes). The solid Biginelli product is ground to a fine powder, collected under vacuum, rinsed with water and 95% ethanol, and dried to typically yield 40–93% of **1** [average 65%, lit. yield 90% (12); mp 203–205 °C].

Hazards

Benzaldehyde is a cancer suspect agent and mutagen (14). Zinc(II) chloride is toxic by ingestion and inhalation and corrosive on contact with skin (15). Ethyl acetoacetate and urea (16) are irritating to the eyes, respiratory system, and skin. The Biginelli reaction product **1** displays no significant medicinal activity but causes eye irritation and is harmful if inhaled or swallowed. Ethanol is highly flammable and toxic if swallowed. Concentrated hydrochloric acid causes burns and is irritating to the respiratory system. Appropriate gloves, safety goggles, and a laboratory coat should be worn at all times.

Discussion

This experiment was designed to expose undergraduates to contemporary research in the context of green chemistry foundations. We felt it crucial that students execute both traditional and modern reactions to gain an appreciation of how synthetic chemistry is evolving, rather than simply being directed to literature regarding the traditional Biginelli synthesis. Although the procedure is described for each student to complete both reactions, a straightforward adjustment allows the class to work in pairs if equipment availability is a concern. In this instance, one student can undertake the traditional synthesis while his or her partner attempts the modern approach, with results being shared, encouraging collaborative learning.

Multiple green lessons are reinforced by comparison of the traditional and modern Biginelli synthetic methods. Eradication of any auxiliary substance is clearly a “step in the green direction” (17). Running the reaction solvent-free additionally leads to a six-fold rate acceleration with attendant improvement in energy efficiency (also highlighted as a green principle; refs 2 and 3). This is dramatically underscored as students usually complete the modern method product isolation and characterization before the traditional reflux time is over! The rate quickening does not come with a sacrifice in product purity, as evidenced by measured melting points and proton NMR spectra.

The class is prompted to consider concepts of atom economy within the Biginelli reaction framework. A simple calculation indicates this multi-component cyclocondensation is intrinsically nearly 88% atom-efficient as the only “waste” generated is two water molecules (18, 19).¹ However, computation of *experimental* atom economies reveals a distinction in greenness

of the two methods.² Taking into account reactant and product masses rather than molar masses (20), the traditional Biginelli synthesis is 72% atom-efficient whereas the solvent-free strategy is 80% atom-efficient. The difference arises from altering reactant stoichiometries when designing modern reaction conditions and is a corollary benefit of removing the solvent. It is noteworthy that average student chemical yields routinely obtained by each approach are almost identical. Pooling yields for each method promotes calculation of overall reaction efficiencies, providing a sense of how many reactant atoms are actually incorporated into the 3,4-dihydropyrimidin-2(1*H*)-one product.³

Students also recognize the traditional synthesis has a prominent green feature that is upheld in the modern approach. This relates to usage of environmentally benign solvents (water and ethanol) in product purification and the non-requirement of recrystallization. Importance of the green principle “use catalysts, not stoichiometric reagents” (2, 3) is further showcased by both procedures. This is tempered by acknowledgement that neither catalyst is recycled at the end of the experiment. We find this an excellent opportunity to reinforce the notion that improvements can always be made in designing green synthetic pathways.

Conclusion

Direct comparison between traditional and modern variations of a fundamental reaction within the same laboratory period is a valuable learning experience. Microscale solvent-free preparation of a medically high-profile 3,4-dihydropyrimidin-2(1*H*)-one is achieved on heating benzaldehyde, ethyl acetoacetate, and urea in the presence of ZnCl₂ for fifteen minutes. Significantly, students learn about green chemistry concepts in the milieu of present-day research with special focus on improvements in energy efficiency and atom economy.

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Notes

1. Percentage theoretical atom economy for a reaction is $[(M \text{ of desired product}) / \Sigma(M \text{ of reactants})] \times 100$ as designated by Trost (18).
2. Percentage experimental atom economy is defined (20) as $[(\text{“obtainable” mass of product}) / \Sigma(\text{mass of reactants utilized})] \times 100$.
3. Calculations of theoretical atom economy for the Biginelli reaction, experimental atom economies for the traditional and modern methods and overall reaction efficiencies are included in the online material.

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