

# Green Carbonyl Condensation Reactions Demonstrating Solvent and Organocatalyst Recyclability

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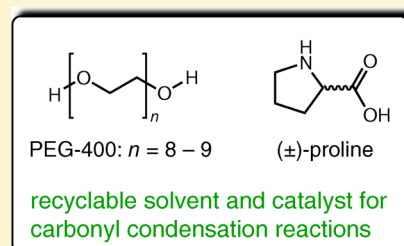
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**S** Supporting Information

**ABSTRACT:** A procedure is described where students undertake consecutive Knoevenagel and Michael reactions in one pot under green conditions to obtain a condensation product. Fundamental lecture principles of carbonyl group reactivity and catalysis are underscored. The recyclable nature of both an environmentally benign solvent (polyethylene glycol) and organocatalyst (proline) is demonstrated, in conjunction with other sustainability features. This semimicroscale reaction is conveniently performed during a 3.5 h period either toward the end of an introductory organic course or within an upper-level mechanistic laboratory.

**KEYWORDS:** Second-Year Undergraduate, Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Catalysis, Green Chemistry, Mechanisms of Reactions, Microscale Lab, NMR Spectroscopy, Solutions/Solvents

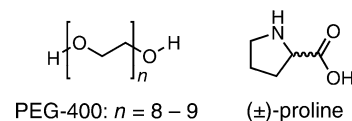


The concept of recycling as a waste management strategy is a fundamental principle of green chemistry.<sup>1,2</sup> From a pedagogical perspective, effort has been made to recycle consumer products, including newspapers and soda bottles.<sup>2</sup> The recycling of organic solvents used for cleaning glassware and in thin-layer chromatography has also been reported.<sup>3-5</sup> However, comparatively little attention has been paid to concurrent recycling of a reaction solvent and catalyst in student teaching laboratories.<sup>6</sup> Mak et al. described synthesis of an ionic liquid followed by use and reuse as a Mannich reaction medium,<sup>7</sup> and a similar research approach was applied to the preparation of fenpropimorph, an agricultural fungicide.<sup>8</sup> Certain solid-phase superacids and transition-metal catalysts have also been effectively collected and recycled for further undergraduate use.<sup>9</sup> In 2000, Reed and Hutchison outlined the generation of adipic acid from cyclohexene under conditions of solvent (water) and catalyst ( $\text{Na}_2\text{WO}_4$  and Aliquat 336) co-recycling.<sup>10</sup> A new procedure showcasing facile reclamation of an environmentally friendly reaction solvent and organocatalyst would, therefore, be a welcome addition to the introductory organic laboratory curriculum.

There is currently much interest in utilizing polyethers as greener solvents for organic transformations.<sup>11</sup> Multicomponent reactions in polymeric ethylene glycol (polyethylene glycol or PEG) and other green solvents have recently been reviewed.<sup>12</sup> PEG solvents exhibit low toxicity, are nonvolatile and readily recyclable, and, as polyethers, are stable toward a variety of reaction conditions, including elevated temperatures. Use of PEG with a molecular weight of 200 (PEG-200) as a greener solvent for undergraduate Diels–Alder reactivity was published,<sup>13</sup> although heating was required and recycling did not take place. The heavier PEG-400 was additionally exploited

as the solvent in a microwave-irradiated manufacture of nitrophen, a herbicide.<sup>14</sup>

A 3.5 h synthetic experiment was developed for the introductory organic curriculum, which has two overarching goals. The first goal is for students to learn about some fundamental concepts of green chemistry in terms of atom economy, catalysis, energy efficiency, solvent and catalyst recycling, and waste management. A second goal is for students to construct a reasonable mechanism for the observed reaction, based on theoretical knowledge of carbonyl condensation chemistry. The overall transformation features consecutive Knoevenagel and Michael condensations while showcasing the recyclability of both PEG-400 as the solvent and racemic proline as an organocatalyst (Figure 1). The specific reactions



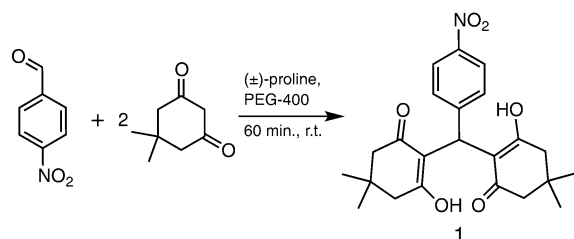
**Figure 1.** Structures of PEG-400 and (±)-proline.

occur between 4-nitrobenzaldehyde and 2 equiv of 5,5-dimethylcyclohexane-1,3-dione (dimedone) at room temperature to form 2,2'-[(4-nitrophenyl)methylene]bis[3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one], **1** (Scheme 1).

Examples of organocatalysis in teaching laboratories have become more prevalent in recent years.<sup>15-18</sup> Notably, chiral L-proline was employed as the organocatalyst in an enantioselective aldol condensation<sup>17</sup> and a Robinson annulation.<sup>18</sup> Sequential aldol and Michael reactions were reported both in a

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**Scheme 1. Student Preparation of 2,2'-[(4-Nitrophenyl)methylene]bis[3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one], 1**



solvent-free sustainable context<sup>19</sup> and without a specific focus on green chemistry.<sup>20</sup> The experiment described herein was performed over 90 times by introductory organic students over a two-year period. It was based on separate previous accounts of Knoevenagel and Michael reactions in PEG-400<sup>21,22</sup> and designed to reinforce content discussed toward the end of a second-year undergraduate organic course.

The protocol was additionally modified at one institution and operated as a “discovery-based” experiment in an upper-level organic reaction mechanisms course. The reaction was undertaken by 30 undergraduate students with adapted learning objectives. Students were not informed of the isolated product in this instance and were required to problem-solve in small groups during the laboratory to predict its composition. They deduced the correct product structure by physical characterization (melting point, proton NMR, and IR spectroscopy) and proposed an appropriate mechanism. Finally, students discussed the main sustainability concepts apparent in the experiment in a more open-ended context, having been previously exposed to green chemistry principles in earlier courses.

## EXPERIMENTAL OVERVIEW

In an introductory organic course, 4-nitrobenzaldehyde and dimeredone (1:2 molar ratio) were added to (±)-proline in PEG-400 and vigorously stirred for 60–75 min. After reaction completion was determined by thin-layer chromatography, ice-cold water was added and stirring continued for 10 min, causing a white precipitate to form. The crude product was collected by vacuum filtration and recrystallized from absolute ethanol to generate purified **1** in typical yields of 30–80% (average student yield 55%, lit.<sup>23</sup> yield 97%), mp 188–190 °C (lit.<sup>23</sup> mp 190–191 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm): 11.80 (enol OH, s), 8.13 (2H, d, *J* = 7 Hz), 7.26 (2H, d, *J* = 7 Hz), 5.54 (1H, s), 2.52–2.31 (8H, m), 1.24 (6H, s), 1.12 (6H, s). The mixture of PEG-400 and (±)-proline was recycled by either each student or the laboratory instructor via evaporation of water under vacuum. Similar results were obtained in an upper-level mechanistic course (yields of 40–80%, average 60%).

## HAZARDS

Appropriate gloves, safety goggles, and a laboratory coat should be worn at all times throughout this experiment. PEG-400, 4-nitrobenzaldehyde, (±)-proline, and dimeredone may be harmful if absorbed through the skin and possibly cause respiratory tract irritation. Ethanol and ethyl acetate are highly flammable and toxic by ingestion. Hexane is highly flammable and hazardous by ingestion and may be toxic to the peripheral nervous system, skin, and central nervous system. Chloroform-*d*<sub>3</sub> causes

irritation of the skin and respiratory system, may cause chemical burns, and is a possible carcinogen. 2,2'-[(4-Nitrophenyl)methylene]bis[3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one] is irritating to the eyes, respiratory system, and skin.

## DISCUSSION

### Green Features

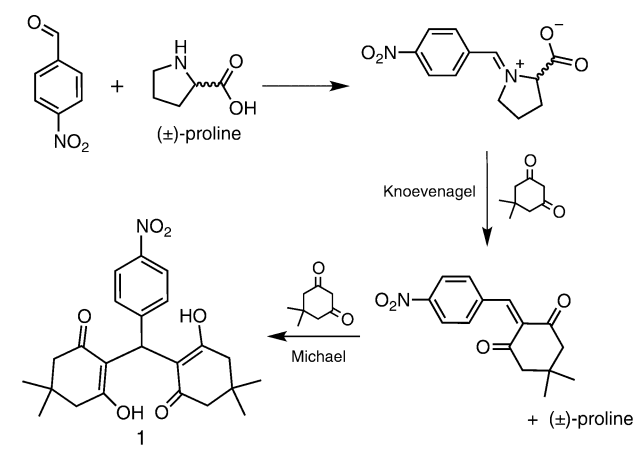
Reports written by introductory organic students demonstrated a thorough understanding of the green and sustainable aspects of their work. The students calculated the intrinsic atom economy (based on molecular weights of the reactants and product)<sup>24</sup> to be exceptionally high (96%) with 1 equiv of water formed as the only byproduct. Moreover, the experimental atom economy (obtained by taking into account actual reactant and product masses)<sup>24</sup> was also determined to be 96%, as no excess reagents were added. By consulting material safety data sheets for reactants and solvents, students recognized that PEG-400, dimeredone, and (±)-proline are environmentally benign compounds. They additionally noted the reaction was undertaken at room temperature, thus promoting energy efficiency. In comparison, upper-level students who had learned about sustainability in previous courses were able to identify the green features with less guidance.

As PEG-400 is completely miscible with polar solvents,<sup>12</sup> product isolation was facilitated by precipitation with cold water. This allowed each class to collect the crude solid via vacuum filtration, and recycle the PEG-400 and (±)-proline by rotary evaporation or distillation of H<sub>2</sub>O. In the latter instance, student reports indicated that it should be possible to recycle the water for another reaction workup. Racemic proline was evident in an NMR spectrum of the retrieved PEG-400, and the solvent and catalyst mixture could be recycled at least twice for other undergraduate students to use. Alternatively, the instructor pooled reaction filtrates from one student group and evaporated water in one batch between laboratory periods. Whoever performed the recycling, most introductory and upper-level students discussed there was in fact a cost to reclaiming the PEG-400 and (±)-proline and that the overall process was less energy efficient than first appeared.

### Mechanism and Curricular Flexibility

This laboratory highlighted several mechanistic considerations of carbonyl group reactivity at both the introductory and upper-year levels. (±)-Proline generates an electrophilic iminium ion from 4-nitrobenzaldehyde<sup>25</sup> that readily reacts with 1 equiv of dimeredone, forming a Knoevenagel adduct (Scheme 2). Similar organocatalysis was exploited using β-alanine during the undergraduate Verley–Doebner preparation of cinnamic acids.<sup>26,27</sup> A subsequent Michael addition of the second dimeredone equivalent furnished the isolated compound as a dienol rather than a tetraketone.<sup>23</sup> Introductory-level undergraduate students confirmed this observation in their reports after acquiring product <sup>1</sup>H NMR and IR spectra. They noted the appearance of two downfield enol protons (δ11.80) and characteristic IR stretching absorbances (2720 cm<sup>-1</sup> and 1586 cm<sup>-1</sup>) corresponding to O–H and C=C bonds, respectively. Subsequently, students were able to complete a template that represented each fundamental mechanistic step and intermediate for the overall transformation. Comprehension of operative carbonyl condensation chemistry was reflected in the

Scheme 2. Iminium Ion Organocatalysis during Formation of 1



ability to draw curved arrows on the template that correctly represented electron flow.

The nature of the product additionally made the experiment a worthy and challenging inclusion in an upper-level mechanistic course. In this case students were required to propose a likely structure during laboratory time by working collaboratively and confirm their prediction with spectroscopic evidence at hand. Student reports included mechanisms drawn “from scratch” based on understanding of reaction conditions and functional group interconversions, as a template was not provided. Similar condensation reactions utilizing Meldrum’s acid were incorporated as discovery-oriented puzzles.<sup>28,29</sup> One such tandem Knoevenagel–Michael reaction sequence formed a somewhat more predictable tetraester using DMF as a nonrecyclable solvent.<sup>28</sup>

## CONCLUSION

The reaction between 4-nitrobenzaldehyde and dimedone allowed undergraduate students the opportunity to observe recycling of both the solvent and an organocatalyst. Within this framework, students became aware of the following additional green chemistry principles: waste management, atom economy, energy efficiency, and benign reagents and catalysis. The procedural simplicity and reliability led to consistent results that reinforced theoretical concepts taught in lecture. Lastly, and of great appeal, students were exposed to a modern, unconventional solvent currently under investigation as a green alternative for many fundamental transformations.

## ASSOCIATED CONTENT

### Supporting Information

Instructions for second-year and third-year students; notes for the instructor and representative product spectra. This material is available via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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