

Green Chemistry Decision-Making in an Upper-Level Undergraduate Organic Laboratory

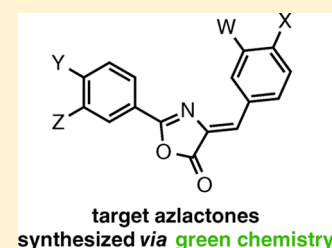
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S Supporting Information

ABSTRACT: A self-directed independent synthesis experiment was developed for a third-year undergraduate organic laboratory. Students were provided with the CAS numbers of starting and target compounds and devised a synthetic plan to be executed over two 4.5 h laboratory periods. They consulted the primary literature in order to develop and carry out an azlactone synthesis incorporating green chemistry principles and techniques without detailed guidance from course instructors. Final products were analyzed via proton NMR spectroscopy, IR spectroscopy, and melting point analysis to determine if students were successful in forming their assigned material. Extremely positive feedback about the experiment was collected and is presented.

KEYWORDS: Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Problem Solving/Decision Making, Catalysis, Green Chemistry, Heterocycles, Synthesis



Green chemistry instruction has become significant in the pedagogical literature during the past decade, with educators introducing sustainability to undergraduates in multiple ways.¹ Despite this, students are rarely required to apply their knowledge and understanding of green chemistry to appraise synthetic protocols from the primary literature critically.² Since 2008, 30–40 students have annually participated in an intensive laboratory that has an underlying theme of sustainability within a third-year undergraduate organic chemistry course.³ Green chemistry concepts are taught in lecture during the first few weeks and reinforced during practicals throughout the semester.^{4–8} For the final experiment present as the course capstone experience, students are required to develop independently a (typically) three- to four-step strategy for preparation of a personalized azlactone derivative. The synthesis is based on a defined starting material, with greener approaches receiving up to 20% bonus credit. Experimental plans are reviewed by teaching staff for cost and safety considerations; however, detailed feedback regarding proposal feasibility is not provided. Over four years, more than 130 students have been tasked with the synthesis of one of 35 different azlactones, with each derivative having been successfully synthesized at least once.

Although there are documented examples of multistep laboratory protocols and synthetic pathways developed by students, they are generally planned with substantial instructor guidance.⁹ Many organic laboratory procedures showcasing green principles have now been published;¹⁰ however, the experiment described herein is original in requiring student planning and independent decision-making within the context of sustainability. Azlactones were chosen as the target class of compound as they are readily accessible from commercially available reagents, amenable to combinatorial-style derivatization, and possess interesting (and educational) spectral

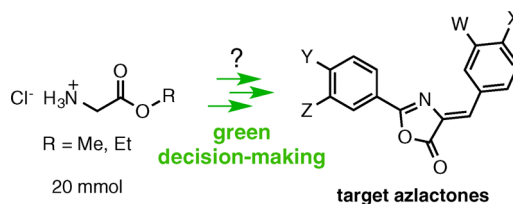
properties.^{11–13} Azlactones additionally have medicinal significance as important intermediates in the preparation of amino acids, peptides, and certain biosensors.¹⁴ The biological relevance of azlactones helps students understand how green chemistry principles might be employed to minimize the environmental impact of accessing important molecules.

EXPERIMENTAL OVERVIEW

Information Provided to Students

In keeping with fostering an upper-level, student-driven decision-making process as a primary learning objective, no concrete practical details are provided at any point before the experiment. Students are informed they have two laboratory periods to complete their synthesis (9 h total). They are provided with a preweighed sample of either the methyl or ethyl ester of glycine hydrochloride as a mandatory starting material (20 mmol, Scheme 1). Additionally, students are notified they must fully characterize their target azlactone and at least one intermediate compound. This information is distributed during week 6 of the 12-week semester. At the end of week 8, students submit a thoroughly researched proposal,

Scheme 1. Structures of Glycine Methyl and Ethyl Ester Hydrochlorides and the Target Azlactones



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including which reactions they intend to perform, the required reagents and solvents, and any hazards associated with each substance. Two weeks prove to be ample time for students to prepare their synthetic plan and make any revisions as necessary (if, for example, an unavailable or very expensive compound needs to be replaced).

Experimental Plans

Students are required to include several key features in their experimental plans that include the following:

- a retrosynthetic analysis
- schemes for all proposed reactions, with appropriate mechanisms
- a list of required chemicals, including CAS numbers, quantities required, physical properties, and hazards
- a list of intended glassware
- detailed experimental procedures for each synthetic step
- melting points and spectral data for the assigned azlactone product and intermediates (where available)
- complete literature references for intended reactions
- a discussion of the green chemistry features of their synthesis

Upon submission of the plans, the course instructor specifically examines protocols for safety and reagent cost; however, the perceived feasibility of the protocol is not directly commented on.

HAZARDS

Appropriate gloves, safety goggles, and a laboratory coat must be worn at all times throughout this experiment. For every substance requested by students and each proposed intermediate, the appropriate Sigma-Aldrich MSDS hazard and safety information had to be included in their experimental plans. During the proposal vetting process, any chemicals identified by the course instructor as unsafe are not permitted for use, and the student is asked to prepare an alternative plan that includes more appropriate compounds. Examples of substances selected for use and their associated hazards are included in the Supporting Information.

DISCUSSION

Greener Student Methodologies

The classical approach for preparing a simple azlactone derivative from an ester of glycine hydrochloride is relatively efficient, although it has features that are somewhat environmentally unfriendly. An amide intermediate is typically generated followed by chemoselective ester hydrolysis to form a derivative of hippuric acid. Heterocyclic ring formation is achieved by an Erlenmeyer-Plöchl reaction with an aromatic aldehyde (or ketone) in the presence of a stoichiometric amount of sodium acetate (Scheme 2).^{15–17}

As some of the assigned azlactone derivatives were absent from the literature, students often independently found and modified this methodology to suit their needs. Many students

appreciated that inclusion of a halogenated solvent, an amine base, and extended high temperatures in the classical protocol were all areas that could potentially be improved in the context of green chemistry. Representative examples of experimental plans indicated that students understood how to implement methods to decrease the environmental impact of their synthesis (Scheme 3). Substitution of triethylamine and chloroform with 2-methyltetrahydrofuran (an organic solvent indirectly derived from corn cobs) in the initial amine acylation step was undertaken by Student 1.¹⁸ This student also exploited aqueous reaction conditions and a nontoxic base (NaHCO_3) to access the amide intermediate in good yield.¹⁴ Finally, the student utilized a catalytic quantity of sodium acetate in the Erlenmeyer-Plöchl reaction between hippuric acid and *m*-methoxybenzaldehyde, rather than a stoichiometric amount.¹⁹

Inspection of the synthesis executed by Student 2 reveals a less green methodology for accessing the amide; however, catalysis was employed in the final ring-forming reaction via addition of an environmentally benign Lewis acid ($\text{Bi}(\text{OAc})_3$).²⁰ Although heating was still required in this step, the reaction was complete in less time (45 min) and, as such, less energy was consumed overall. In general, each student typically incorporated at least two fundamental green features into their strategy. They discussed “what was green, what was not green and what could have been greener” in formal reports based upon an American Chemical Society journal-style template.²¹ Although there were many potential literature methods that could be considered, this experiment sought, in part, to evaluate students on the basis of their ability to select a viable synthetic method that maximized incorporation of green chemistry approaches.

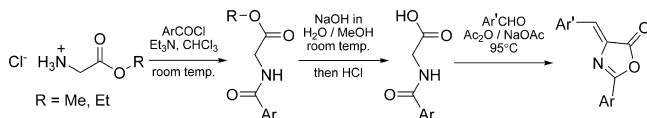
Student Success and Evaluation

On the basis of proton NMR and IR analysis, approximately 60–75% of students over four years synthesized their azlactone derivative to some extent. Experiment grading plans for situations where a student was unable to synthesize the target are included in the Supporting Information. Use of a combinatorial chemistry-type approach allowed instructors to compare synthetic outlines and experimental results easily between students, as all azlactones were structurally related and could be obtained through broadly similar methods. It could be argued that it was not possible to evaluate students fairly based solely on isolated yield, so emphasis was also placed on final product purity and successful preparation of intermediate compounds. The melting points of some azlactones were unavailable, so spectroscopic techniques were the primary methods used to determine if a compound had been successfully synthesized. Every azlactone product displayed a very characteristic $\text{C}=\text{O}$ infrared absorption ($\sim 1790\text{ cm}^{-1}$) and a clear singlet peak was apparent due to the vinylic proton in each ^1H NMR spectrum ($\delta 7.3\text{--}7.4$). Thus, students without a literature melting point value for their assigned compound were not at a significant disadvantage.

Student Feedback and Pedagogical Value

Despite the observation that around 25–40% of the class did not synthesize their assigned compound each year, feedback regarding the experiment was very positive. Students in the 2012 and 2013 cohorts were asked to respond to several questions with Likert-style scales after completing the experimental work and associated report.²² The responses to two statements are shown in Figure 1.

Scheme 2. Classical Procedure for Conversion of a Glycine Hydrochloride Ester into an Azlactone Derivative



Scheme 3. Representative Examples of Student Reactions Where Green Chemistry Features Were Incorporated

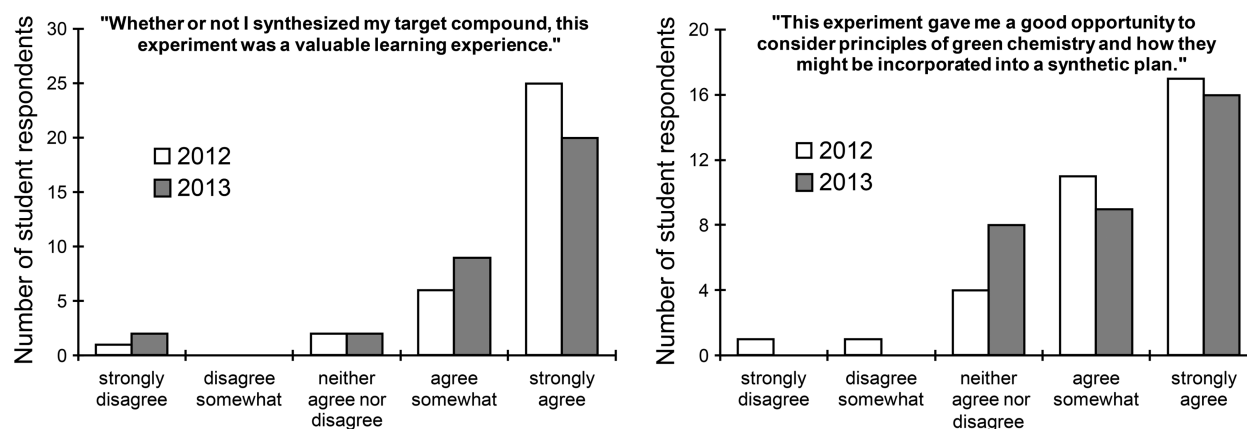
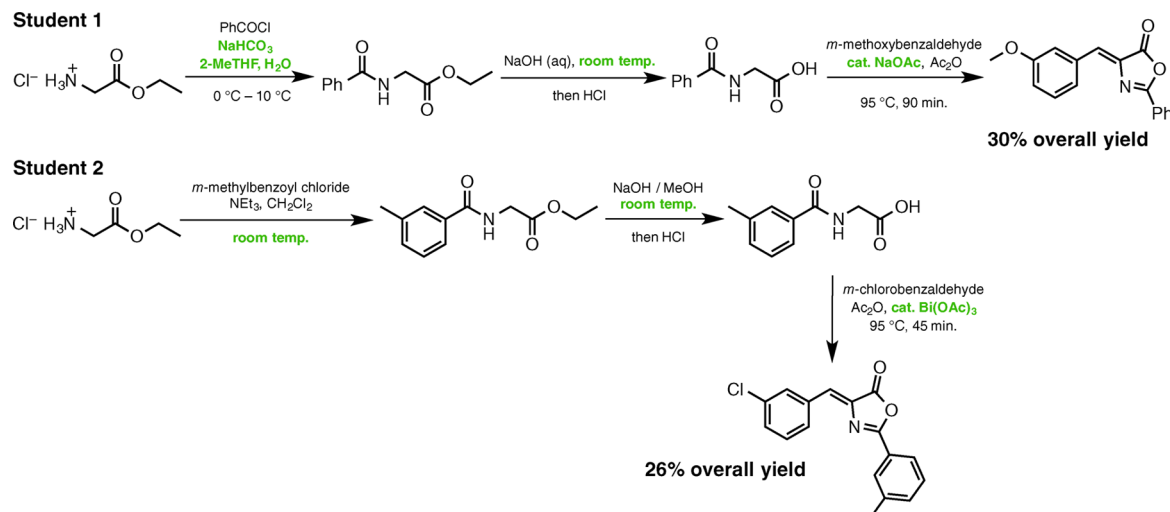


Figure 1. Results from a two-year student postlaboratory questionnaire: 34 students in 2012 and 33 students in 2013.

In addition to this, students from both the 2012 and 2013 classes were prompted to provide written comments regarding the experiment. Some representative responses are as follows:

- Good experience. Teaches you how to think on your feet when your laid-out synthesis has some oversight, or something did not go as planned.
- Two experiments should be like this experiment with the first one semi-independent.
- This experiment was a great experience and a lot of fun. However, not all experiments should be like this (only one) because it is very stressful and time-consuming.
- This experiment was a valuable learning experience. It helped to better my research skills and it was a good exercise in problem solving.
- I enjoyed this experiment as it was a great learning experience as to how real lab research is performed. However, I wish I had known that not all journals are "right" in their experimental procedure.
- This experiment was the only one where I was forced to figure things out by myself. It is a great way to learn - hitting unexpected roadblocks and conquering them.
- Awesome experiment. Harsh. But awesome.
- Overall I think the experiment was a great idea and is an essential part of preparing for graduate work.

- Please include a microwave in this experiment; not only is it "green" chemistry, but also saves a lot of time.

CONCLUSION

On the basis of their feedback, it was clear that students found this independent synthesis experiment to be an important academic experience. Even though many students initially felt overwhelmed by the task and some were not able to synthesize their target compound, they appreciated the value of self-motivated learning. Indeed, some students began to consider graduate studies in chemistry due to their level of interest and success with this experiment. Virtually every student showed an insight into the sustainability concepts taught earlier in the course by incorporating and explaining green chemistry aspects of their synthesis. Relatively few undergraduate procedures are able to provide an insight into the world of postgraduate research, so laboratories such as this are vital to a curriculum in order to expose students to the reality of self-directed experimentation.

ASSOCIATED CONTENT

Supporting Information

Background information for students, notes for the instructor, representative reports with azlactone product spectra, and

extensive experiment feedback. 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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