Rapid Amide Coupling in Water for Undergraduate Laboratories

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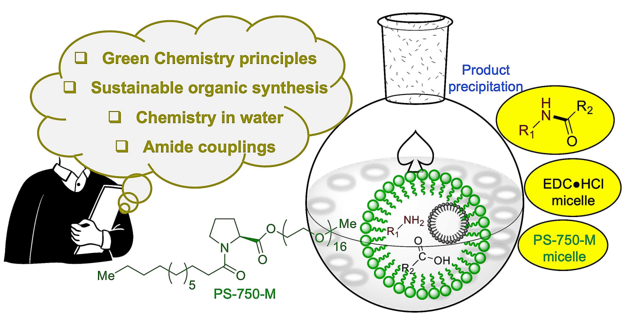
ABSTRACT

Chemistry in water is an emerging field that fulfills the fifth principle of Green Chemistry—replacing toxic organic solvents with their benign counterparts. Although some pharmaceutical industries have developed and adopted chemistry in water, its implementation in teaching laboratories is still limited. Therefore, we have designed an experiment dedicated to the undergraduate curriculum, covering sustainable, completely organic solvent-free amide coupling—it is one of the most heavily used reactions in the pharmaceutical industry. The designed experiment aims to acquaint students with the 12 principles of Green Chemistry, inform them of the shortcomings of the traditional synthetic procedures of amide coupling, make them aware of waste generation from toxic organic solvents, and show them the effectiveness of water as a benign reaction medium. With the training throughout the lab sessions, students were taught micellar catalysis, NMR (nuclear magnetic resonance) spectroscopy, IR (Infrared radiation) spectroscopy, separation techniques, and safety data.

GRAPHICAL ABSTRACT



KEYWORDS
Green chemistry, amide couplings, micellar catalysis, organic solvent-free chemistry.

Introduction

The Green Chemistry principles coined by Anastas and Warner have revolutionized the field of sustainability.[1–6] The American Chemical Society (ACS) Green Chemistry Institute launched various academic programs, including the summer school in Green Chemistry & Sustainable Energy, webinars, and videos, highlighting the sustainability challenges. These resources cover broader topics to promote Green Chemistry in higher education.[7–12] Likewise, the Beyond Benign organization also provides resources to educators and students to equip them with tools to practice sustainability.[13–16] These tools are helpful in fostering the environmental impacts of chemistry among students. Despite the availability of these resources and tools, the implementation of greener synthetic protocols in the teaching labs is still limited.[13,17–22] Predominantly, teaching labs still rely on the old curriculum, which includes traditional organic synthesis accompanied by longer reaction time, followed by reaction work-up, isolation, purification, and analysis of the desired compounds.[17,23,24] Often, the entire process consumes more than one lab session, i.e., > 4 h. Moreover, it often involves water- or air-sensitive reagents and toxic-organic solvents as a reaction medium and for product extraction and purification. Also, the assessment of waste generation from the synthetic pathway is not often used as a learning tool for students.[13,20,21]

The role of organic chemistry instructors is crucial for incorporating newer concepts of Sustainable Chemistry while designing an effective curriculum. Ideally, interactive discussions among the students, and careful textbook selection can give students a broader picture of the importance of the topic.[20,25] However, while covering sustainable chemistry topics, the curriculum should not be restricted only to the textbook—the labs and lectures must be synchronized.[13,18,19,26,27] During the execution of such new experiments, students get the opportunity to learn the harmful impacts of traditional organic synthesis, while understanding the need to replace outdated experiments. Other advantages of promoting sustainable chemistry practices include the minimization of potential chemical accidents and release of toxic volatiles while ensuring student safety.

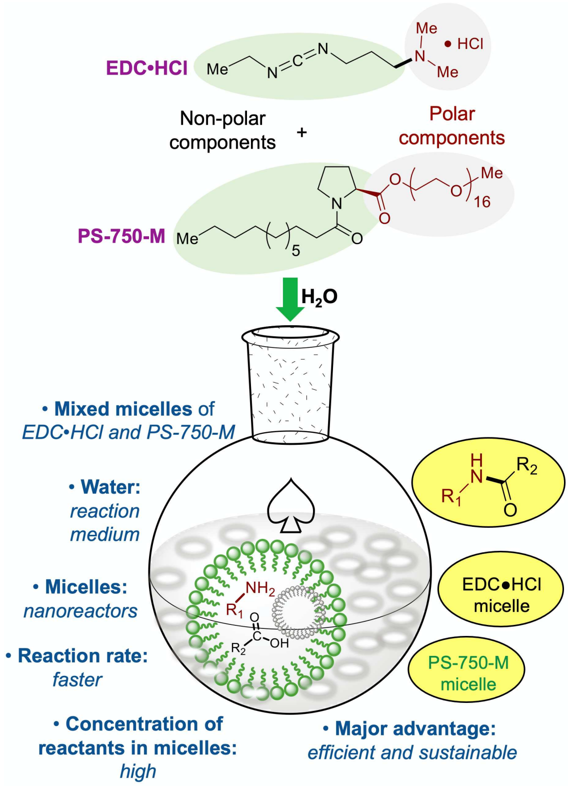


Figure 1. Organic solvent-free rapid amide coupling in water: Formation of mixed micelles of PS-750-M and EDC•HCl.

SPECIFIC AIMS

As our research group is dedicated to sustainable organic synthesis and catalysis, we decided to incorporate a new experiment into the present curriculum of the teaching lab at the University of Louisville, covering the various aspects of sustainable chemistry. The main aim of designing an experiment was to acquaint students to the sustainability and harmful impacts of solvents— this aim is aligned with the fifth principle of Green Chemistry, which promotes the use of benign solvents and auxiliaries.[1,28] Towards this goal, our group has developed a proline-based environmentally benign amphiphile, PS-750-M, that enables organic transformations in water.[29,30] Here, the word amphiphile means a molecule possessing both hydrophilic and hydrophobic components in a balanced ratio. This amphiphile has an optimal balance between the hydrophilic mPEG chain and the hydrophobic hydrocarbon region. Upon dissolving in water, amphiphile molecules self-aggregate to form nanomicelles.[29,30] It is anticipated that during the reaction, there is a very high local concentration of substrates inside these nanomicelles, which assists accomplishing faster reaction rates under these mild conditions.[30–34] Moreover, structurally mimicking toxic dipolar-aprotic organic solvents, such as DMF (*N*,*N*-dimethylformamide), DMAc (*N*,*N*-dimethylacetamide), and NMP (*N*-methyl pyrrolidone) with PS-750-M, may provide a sustainable and greener alternative that has proven effective for number of organic transformations, including monofluorinations of indoles,[32] amidations,[31,33] metal-catalyzed cross-couplings,[30,35–41] SNAr, etc.[42] Notably, there are only a few undergraduate curriculum activities that target educating students to eliminate the organic solvents by using water as a reaction medium.[18,43] Including the micellar catalysis concept in the lab will also provide an opportunity to students to study toxicity of organic solvents and waste generation.

Another objective was to update the curriculum with more industrially relevant chemical reactions which align laboratory experiences with real-world problems. The amide coupling is one of the most used reactions in pharmaceutical industries, due to its usage in synthesis of several active pharmaceutical ingredients (API).[44–46] Notably, ca. 16% reactions performed in medicinal chemistry laboratories are amide couplings.[47] Due to the high importance, our group has recently developed a sustainable protocol for organic-solvent-free amide couplings using water as a medium. The formation of mixed micelles of PS-750-M and EDC•HCl (acts as an ionic surfactant in water) enabled amidation in short reaction times and higher isolated yields (Figure 1).[31,33,34] We aimed to implement this methodology in the teaching lab with a special focus on introducing students to sustainable practices for waste reduction. The key feature of the protocol includes: 1) eliminated the need for any organic solvents in the reaction pathway, 2) the product precipitates out from the reaction mixture and can be isolated via simple filtration followed by water washings, eliminating toxic organic waste generation from product purifications; 3) the reaction completes within a few minutes.

Through the experiment, the students will learn the basic mechanism of the amide couplings and micellar catalysis (reaction in water). The isolation procedure, i.e., simple filtration, eliminates the reliance on toxic organic solvents, otherwise needed in product extraction and purification. The shorter reaction and processing time allows students to use characterization techniques in the same lab session. It includes thin-layer chromatography (TLC), nuclear magnetic resonance (^{1}H NMR), and infrared (IR) spectroscopy. All the experimental steps and pre-lab, as well as characterization can be done in a 4-

hour time, without extending the lab to multiple lab sessions. Simultaneously, we also wanted to teach the students about cautiously handling reagents, such as pyridine and EDC.

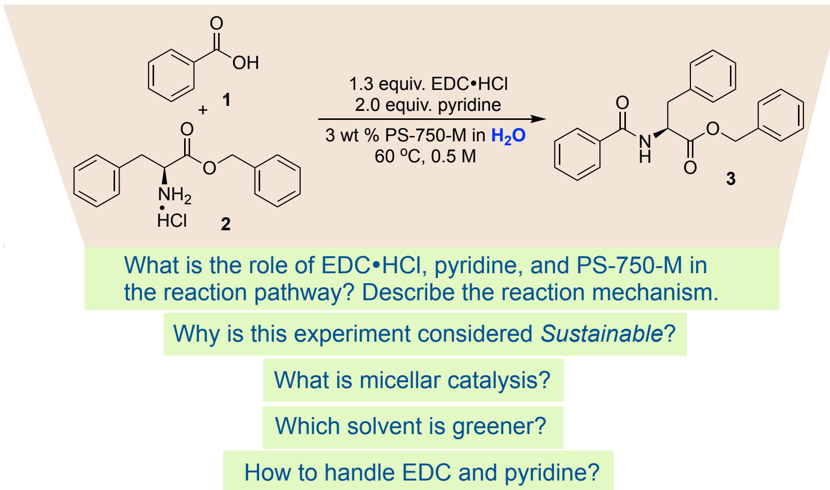
Table 1. The learning objectives for the designed experiment

	Activities and learning objectives
1	Performing the amide coupling reaction in water as a reaction medium – Why is water a greener medium?
2	Acquainting students to the 12 Principles of Green Chemistry and Sustainability.
3	Learning micellar catalysis with a special focus on theory and the design of surfactant and the micellization.
4	Aligning the theoretical concepts learned in the lecture with the experimental knowledge.
5	Gaining expertise in analytical techniques—TLC, NMR, and IR for the reaction progress and product characterization.

DESIGN OF THE EXPERIMENT

We focused on designing the experiment for Organic Chemistry Laboratory II (also called CHEM-344 at the University of Louisville) students starting from Spring 2021 to Spring 2023. First, the outline of experimental details was discussed, and the learning objectives were finalized. Some of the learning objectives are highlighted in Table 1. After defining these objectives, a lab handout was designed, which included the detailed reaction procedure and instructions for handling various reagents. It also highlighted the important observations for successfully conducting the experiments, the isolation procedure for the final product, and the required analysis—TLC, melting point, NMR, and IR analysis. The handouts were prepared in accordance with the experimental results and observations recorded by teaching assistants prior to the lab sessions.

To develop a basic understanding of amide couplings, the theory behind the reaction was first taught in the lecture under the topic of nucleophilic acyl substitution reactions. After the lecture course, prelab discussions were conducted highlighting the Green Chemistry principles, micellar catalysis, reaction details, and its mechanism. It also included pre- and post-lab assignments designed to further strengthen their knowledge. Some of the questions asked in these assignments and discussions are shown in Scheme 1. These questions were intended to examine the student's understanding of the basic concepts. These assignments were graded later, and the points were included in the final scores.

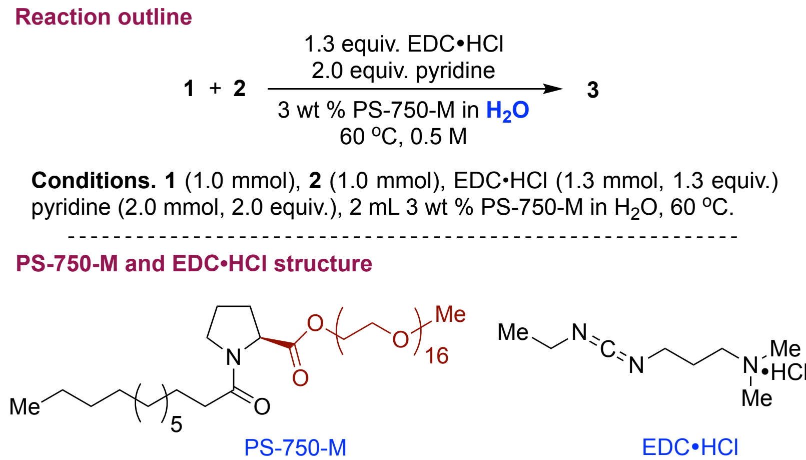


Scheme 1. Questions asked during the Lab assignments and discussions.

EXPERIMENTAL PROCEDURE

The experimental procedure adopted by students during the teaching lab is as follows: Benzyl *L*-phenylalaninate•HCl (**1**) (1.0 mmol, 1 equiv.), benzoic acid (**2**) (1.0 mmol, 1 equiv.) and EDC•HCl (0.32 mmol, 1.3 equiv.) were placed in a 10 mL reaction vial equipped with a PTFE-coated magnetic stir bar. 2 mL 3 wt % aqueous PS-750-M was added to the reaction mixture. Pyridine (0.5 mmol, 2.0 equiv.) was taken using a syringe and added to the reaction mixture. The weighing/collection and addition of EDC and pyridine were carefully performed inside the fume hood (special instructions were given to use these reagents inside the hood without any possible exposure). The reaction vial was closed with a screw cap. The reaction mixture was allowed to stir at 60 °C on a pre-heated hotplate (heating block). The observations were recorded after 10, 20, 30, and 40 minutes. Initially, the solution became cloudy. A solid formation was observed in the reaction mixture after 15 to 20 minutes. After the reaction completion, as monitored by TLC, stirring was stopped and the reaction mixture was allowed to cool to rt. Cold deionized water was added (1 mL) to get the maximum precipitation. Solid was filtered using a pre-weighed Whatman filter paper. The collected solid material was washed with deionized water (3 x 1mL) and dried under reduced pressure to obtain the pure product, which was further analyzed using melting point, IR, and ^{1}H NMR analysis.

Note: The reaction work-up and TLC analyses were performed inside the fume hood.



Scheme 2. Reaction of 1 and 2 under mild aqueous micellar conditions to form amide product 3.

OBSERVATIONS AND RESULTS

The experiment was conducted in Spring 2021 (32 students), Spring 2022 (30 students), and Spring 2023 (9 students) semesters under the supervision of teaching assistants. Before setting up the reaction, special instructions were given to students highlighting the toxicity of reagents and their careful use inside the fume hood with the proper use of gloves. Each student was asked to observe the reaction every 10 minutes and note down the starting point of the product's precipitation. On average, students reported the first precipitation after 17 minutes of setting up the reaction. The precipitation gradually increased over time. TLC was performed after 30 and 40 minutes to determine the reaction completion. Traces of unreacted starting material were observed in a few cases. In such cases, the reaction was run for an additional 10 to 20 minutes. However, the average time for reaction completion and full precipitation of final product **3** was 41 minutes (Figure 2). Cold water was added in some cases for the maximum precipitation of the final product. After filtration, the product obtained was dried under a vacuum for an average of 15 to 20 minutes. The yield of the final product was recorded.

Time	0 min	10 min.	20 min	30 min	40 min
Precipitation	No	Yes (slight)	Yes (slight)	Yes (moderate)	Yes (high)
Observations	The solution was cloudy. The solid material started clumping at the bottom of the flask	The precipitates started appearing in the solution	More precipitates accumulated	More product precipitation	A slight increase in product precipitation
Pictures					

Figure 2. The reaction progress observed by students.

In spring 2021, the average yield of **3** for 32 students was 38%. However, in spring 2022, the average isolated yield reported by 30 students was increased to 77% (8 students reported a yield greater than 100%, which was not considered in the average yield calculations). The unusually high yields of more than 100% were mostly due to the product not being properly dried. In the ongoing Spring 2023 semester, an excellent average yield of 92% was observed by 9 students. The increase in the average yield of **3** in spring 2022 and 2023 compared to spring 2021 can be attributed to several factors. One of the major factors was the addition of cold water into the reaction mixture maximized the product precipitation resulted in a higher yield of the final product. In addition, the amine source was changed to a more stable HCl salt of amine **2.** Notably, pyridine was used to facilitate precipitation of water-insoluble product. Lesser water-solubility of 2,6-lutidine helps solubilizing the product in micelles, hampering product precipitation. Also, one week prior to the final labs, teaching assistants were asked to perform the reactions, where all the possibilities for yield losses were discussed, and the steps to avoid partial precipitation of **3** were highlighted. The effectiveness of the prior discussions led to higher average yields in Spring 2022 and

2023. The findings and the possible solutions for yield losses were also included in the handouts for Spring 2022 and 2023 semesters.

Figure 3 shows the TLC of the final reaction mixture, which was analyzed after 40 minutes to confirm the reaction completion. Starting material (benzoic acid) was spotted with the reaction mixture on a TLC plate and then eluted with 30 % EtOAc in hexane. The spot for the product **3** was observed just below that of acid (**1**) at R*f* ≈ 0.50 on TLC. The TLC of the isolated product was also checked, which showed the purity of the final product after the extraction with no unwanted side products.

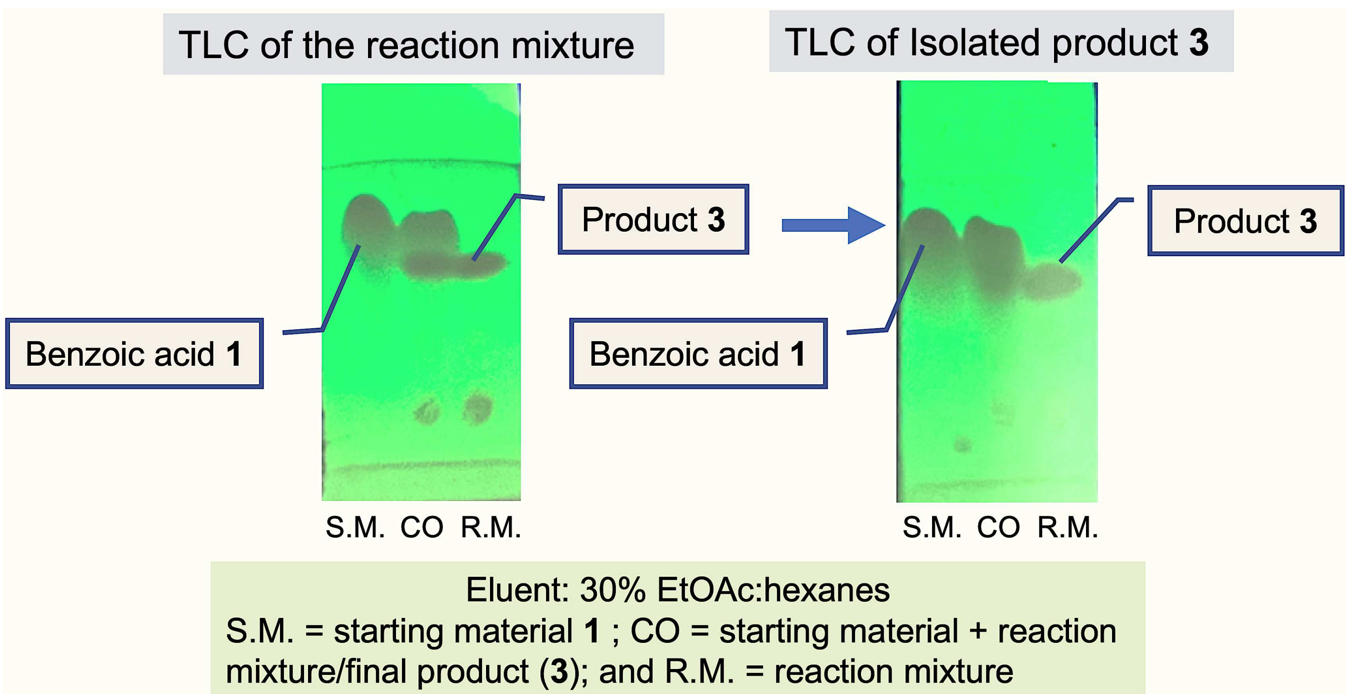


Figure 3. TLC analysis of reaction mixture and isolated final product after filtration.

Next, the final products were characterized using the melting point that was further compared to the literature value. The average results for the melting point ranged from 97-100 ^{o}C, which is within the range of literature value (98-99 ^{o}C).[31] After confirming the purity of the final product with TLC and melting point, the final product was characterized by ^{1}H NMR analysis. All students were able to perform the ^{1}H NMR analysis. The students were asked to assign signals for each proton in the ^{1}H NMR spectrum of the final product. The proton signals highlighted in Figure 4 were emphasized. Students were asked to identify the signals corresponding to NH, the proton at the chiral center (H_3), diastereotopic protons (H_1 and H_1'), and benzylic protons (H_2 and H_2') with their splitting patterns. Six points were assigned in the discussion part of lab reports to explain the splitting patterns and chemical shifts in the ^{1}H NMR spectra for various characteristic protons. Most students successfully identified all these protons in the recorded NMR data.

Next, the IR analysis was performed for the amide product to identify the IR signals for the amidic NH and the two carbonyls in the final product **3** (Figure 5). All the students were asked to perform the IR analysis. The students were able to identify NH stretch with a small doublet at 3294 and 3272 cm^{-1}. The bend for the NH appeared at 1535 cm^{-1}. The two carbonyl signals were identified at 1736 and 1640 cm^{-1}. Students were also asked to compile all the data and write a lab report based on their observations and findings with a detailed discussion section. The points were allocated for the mechanism, an explanation of the role of different reagents and PS-750-M, the importance of organic solvent-free methodology, and detailed characterization data for the final product.

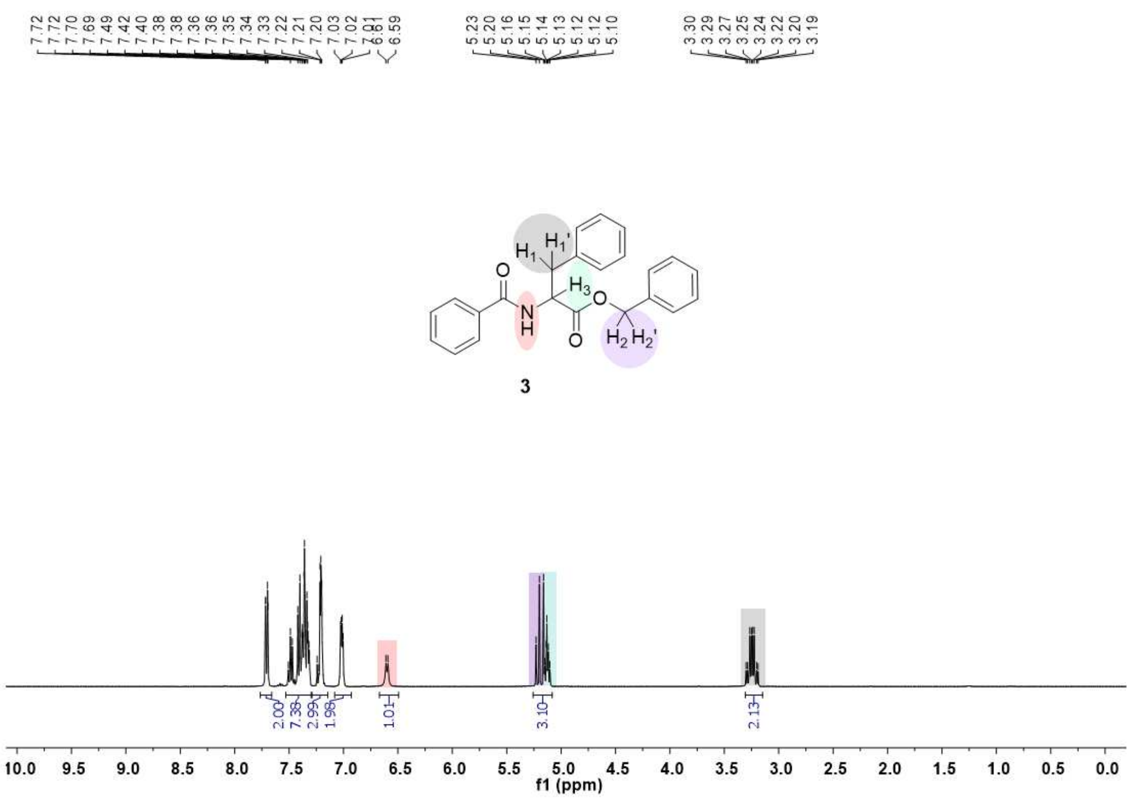


Figure 4. ^{1}H NMR analysis of isolated product 3 (400 MHz, solvent $CDCl_3$).

Later, the Lab reports were graded to get insights into the extent to which the students could understand the content of the course. Most students explained the reaction mechanism and the role of EDC•HCl in acid activation. Also, students successfully answered the questions based on Sustainable Chemistry and identified the hazards of organic solvents to the environment with inherent benefits related to chemistry in water. The experiment also helped students learn how to operate NMR and IR instruments and interpret data. The success of this course can be seen in the final grades of the students. The average grade for the Spring 2021 session was 94% for 29 students. The trend was similar in Spring 2022, with an average grade of 89% (31 students). The initial data for the Spring 2023 session showed again a higher grade point percentage of 95% (9 students). The following outlined learning objectives and the outcome, students' performance during the course, and feedback indicated the success of our initiatives toward sustainable chemistry lab practices (also see Supporting Information, page XX).

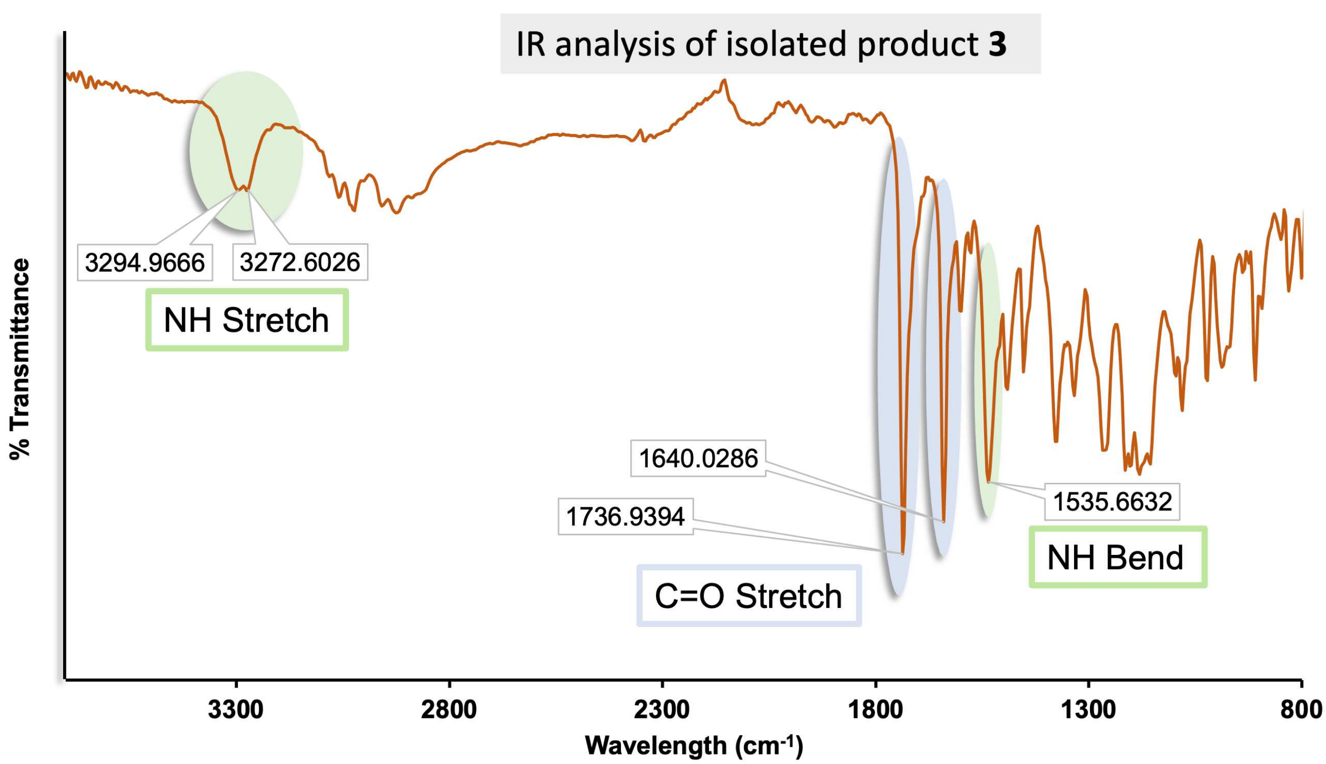


Figure 5. IR analysis of isolated product 3.

Pedagogical Goals, Learning Outcomes, and Assessment.

• **Introducing students to solvent waste from organic reactions – performing reaction in water as a medium.** The purpose of introducing an experiment on solvents waste from organic reactions to undergraduate laboratories was to educate students about the organic waste generated from such reactions. Lab reports showed that 97% of students discussed the waste produced during reaction workup, isolation, and column chromatography. Students also calculated their reaction's E Factor, which addresses organic waste, and learned about the importance of organic-solvent-free transformations. Overall, the lab reports indicate that students gained knowledge about the origin of organic waste, the significance of organic-solvent-free transformations, and the E factor.

• **Introducing sustainability concept – principles of green chemistry.** In addition to conducting experiments, the lab aimed to educate students about sustainability, recycling, and cost-effectiveness. The lab reports submitted by students indicated that they became familiar with recycling and sustainability, which in turn can reduce the cost of a product. During discussions, students mentioned the recycling of PS-750-M and pyridine used in the reactions. They also pointed out that water and urea derived from EDC are byproducts of the reaction. Additionally, 50% of the students raised the question of whether the urea-type byproduct could be dehydrated to generate EDC again or not.

• **Learning micellar catalysis.** In this class, students learned about micellar catalysis, critical micellar concentration, amphiphile design, and the dynamic nature of micelles. In their lab reports, they discussed the use of PS-750-M in the reaction, the structural components of PS-750-M, the hydrophilic and hydrophobic parts of the molecule, and how its structural features and dynamic nature allowed for an organic solvent-free reaction and product isolation in water. Students also compared the structure of DMF and the proline core of PS-750-M, which have similar structural features, such as the presence of 3° amide. Almost 90% of the students included these components in their lab reports. The formation of micelles of PS-750-M was addressed in post-lab questions, and over 90% of the students answered this correctly.

• **Aligning theory with practical knowledge.** The lab was designed to complement the lecture by teaching organic solvent-free reactions and micellar catalysis. In the lecture, students did not learn about the use of organic solvents and micellar catalysis, but in the lab, they learned how the selection of the reaction medium can reduce reaction time and organic waste. In their lab report, over 95% of the students mentioned a fast reaction rate and product appearance within the first 50 minutes. Also, our aim was to help students understand the reaction mechanism and the role of coupling agents when using carboxylic acid and amine as coupling partners. They accurately illustrated the reaction mechanism and explained how the amide bond was formed by EDC activation of the carboxylic acid and how the micelles of PS-750-M accelerated the reaction rate. These questions helped bridge the gap between what they learned in the lecture and what they experienced in the lab. More than 90% of the students correctly identified the role of each of the reagents in the reaction in their prelab questions. Additionally, more than 90% of the students answered correctly how to synthesize an amide using other strategies and why it is difficult to form an amide by reacting a carboxylic acid with an amine in the absence of any coupling agent.

• **Analytical techniques.** The lab course was designed to teach students about different laboratory techniques in one session, while linking it to the lecture course and introducing micellar catalysis. The lab aimed to teach analytical techniques such as the correct use of TLC, visual observation of the reaction progress, melting point determination to gauge product purity, and NMR and IR spectroscopy analysis to prove product identity and purity. During the lab session, more than 90% of students observed a precipitate of the product formed within 50 minutes of reaction time. They included pictures of their reaction progress in their lab reports.

Additionally, 95% of students reported TLC (R_f value) and melting point data (in °C) close to the reference, confirming pure product formation. However, 5% of students reported a deviation of melting point from the reference due to low product purity caused by incomplete reaction. They found that disturbing the reaction by removing it from the heating plate caused incomplete reaction. They also supported their product purity with ^1H NMR. Moreover, more than 85% of students were able to identify critical signals in the ^1H NMR of the product in their lab reports. Although students were aided with

NMR interpretation, most could predict where the different signals would occur using NMR tables (which was also a pre-lab question). However, they needed assistance with determining splitting patterns. This was an excellent lesson for them to deepen their understanding of NMR spectroscopy further. All students correctly identified NH and C(O) stretches and NH bend for the amide functional group in the IR spectrum of their product.

Safety and Hazard Statement

It's crucial to carry out all experiments inside a fume hood. While handling the chemicals, students must wear lab coats, gloves, and protective glasses to avoid any contact with their skin and eyes. The goal of using EDC is to introduce students to micellar catalysis, water-based chemistry, and solvent-free transformations in one experiment and a single lab session. Otherwise, many other better coupling agents are available which doesn't serve all the above-mentioned purposes together. EDC•HCl and benzoic acid are dangerous to the skin, can cause severe eye damage, and are harmful if swallowed. It's essential to handle and weigh EDC•HCl inside the fume hood because of its high sensitization potency.[48] Moreover, students must wear two layers of gloves, protective clothing, and safety glasses to avoid any skin or eye contact. Pyridine can cause nausea, vomiting, diarrhea, and abdominal pain if swallowed or comes in contact with the skin. Therefore, it's necessary to use pyridine inside the fume hood and wear two layers of gloves and protective clothing. If gloves become contaminated, change them immediately. Finally, to avoid exposure, weighing of all these chemicals should be performed inside the fume hood.

Conclusion

A comprehensive course (lab and lecture parts separately) on sustainable chemistry was offered to the students, where the students were taught about the importance of sustainable chemistry to organic synthesis. Awareness and knowledge of sustainable chemistry was acquired among the students. Simultaneously, students learned the shortcomings of reactions in traditional toxic organic solvents. Students were taught about amide couplings in water with an emphasis on learning analytical tools, such as NMR and IR spectroscopy. The course made students aware of sustainable practices and safe handling of chemicals while building a fundamental understanding of micellar catalysis. More than one sustainable chemistry experiments are required to change the old curriculum, which will potentially help update the students with the latest research topics.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.XXXXXXX. [ACS will fill this in.] Example brief descriptions with file formats indicated are shown below; customize for your material.

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NOTE

PI's lab may provide PS-750-M free of cost upon request (only for teaching labs).

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