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Laboratory Experiment

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# Aza-Michael Reaction for an Undergraduate Organic Chemistry Laboratory

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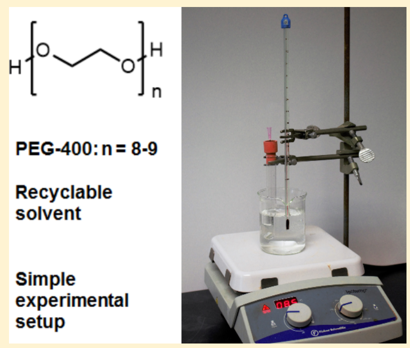
*Supporting Information*

**ABSTRACT:** A green, aza-Michael reaction is described that can be used to teach undergraduate students conjugate addition of nitrogen nucleophile to an *α,β*-unsaturated ester. Students analyze spectral data of the product obtained from the assigned reaction to determine product structure and propose the mechanism of its formation. The experiment requires simple glassware and can be performed during a 3 to 4 h laboratory period in the second semester of introductory organic chemistry after acyl substitution and conjugate addition have been covered in a lecture class.




**KEYWORDS:** *Second-Year Undergraduate, Laboratory Instruction, Problem Solving/Decision Making, Inquiry-Based/Discovery Learning, Organic Chemistry, Synthesis, NMR Spectroscopy*

## ■ INTRODUCTION

Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.[1−5] There has been an increased emphasis on introducing microscale and green labs in the undergraduate chemistry curriculum because these are complementary pedagogies that encourage cost cutting, waste minimization, and hazard-exposure minimization.[6] Implementing this curricular approach is challenging, but many schools are pursuing it because it generates increased student interest.

A few undergraduate experiments involving the Michael reaction have been reported,[7−10] but they do not have a green chemistry emphasis. The aza-Michael reaction results in C−N bond formation[11] and has many uses in organic synthesis.[12] A green, aza-Michael reaction that uses PEG-400 as the solvent[13] and involves the addition of an amine to the *β* position of an *α,β*-unsaturated carbonyl compound to give a *β*-amino carbonyl compound as the product is described herein for an introductory organic chemistry laboratory course.

In any chemical transformation, solvents account for the largest volume and are the main contributors to generated waste. PEG-400 is a green solvent because it is nonvolatile and nonflammable, exhibits low toxicity, is stable over a variety of reaction conditions, and is recyclable.[14] Other attributes of PEG-400 include ease of workup, good solvating capability, and low cost.

Conjugate addition and acyl substitution reactions are often covered toward the end of a second semester of an introductory organic chemistry lecture course. At this stage, students typically are overwhelmed with the amount of information they have received, and may often find it hard to comprehend new material. Most students, when asked to write a reaction for an *α,β*-unsaturated ester with an amine, quickly write an amide product resulting from acyl substitution as they think about the reactivity series of carboxylic acid derivatives. In the discovery-based lab described herein, students determine the product and hence the mechanism, and must rely on their ability to interpret NMR data. This approach makes it easier for students to comprehend the reaction. Additional advantages are

(1) The experimental setup is very simple and requires basic glassware,
(2) Yield is quantitative if the experiment is performed skillfully,
(3) Starting materials are inexpensive,
(4) Students are introduced to various green chemistry principles, and
(5) Technical skills acquired during the semester are reinforced.

## ■ SYNTHETIC OVERVIEW

The experiment was modified to run with no specialized glassware and to give high yields in one, 3 to 4 h laboratory period. The *α,β*-unsaturated ester chosen was methyl acrylate (**1**) and the amine chosen was diethyl amine (**2**). The experiment gives students an opportunity to integrate and apply

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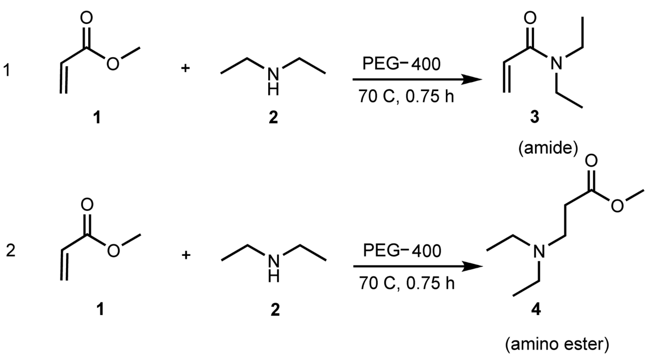
their knowledge of spectroscopy—specifically, IR, $^1$H NMR and $^{13}$C NMR—to identify the product (Scheme 1). Lab skills of students are challenged because the experiment was microscale. Since the primary pedagogic objective of this experiment is to teach students 1,4-conjugate addition using aza-Michael reaction, interpreting the results based on spectral data and proposing a mechanism explaining the formation of the product adds pedagogical value to the experiment.

**Scheme 1. Two Possible Outcomes for Reaction of an α,β-Unsaturated Ester with a Secondary Amine**




## ■ EXPERIMENT

Students add **1** (1 mmol) and **2** (1 mmol) to PEG-400 (2.0 mL) in a 5−10 mL test tube, and cap the test tube with a rubber septum with a needle inserted for venting. The solution is heated in a water bath at 70 °C for 45 min and cooled to room temperature. The reaction mixture is extracted two times with diethyl ether (2.0 mL), the ether extracts are dried, and the ether is evaporated to give crude product. The product is purified on a silica gel column. Students characterize the product by IR, $^1$H NMR, and $^{13}$C NMR spectroscopy and identify the product based on spectral analyses. Details of the procedure and spectral information are provided in the Supporting Information.

## ■ HAZARDS

General lab safety procedures should be followed, which include wearing gloves, protective eye gear, and performing the reaction in a well-ventilated area. All organic chemicals used are hazardous and direct contact with them should be avoided. Diethyl ether is highly flammable and direct flames should be avoided. Silica gel is a skin and eye irritant. Needle used for venting the reaction is sharp and poses a potential hazard. Care should be taken while handling the needle. The needles should be disposed of in an appropriate sharps container. PEG-400 and the product β-alanine *N*,*N*-diethyl methyl ester are eye irritants and mild skin permeators. Methyl acrylate, diethylamine, and $CDCl_3$ are serious eye and skin permeators and can cause inflammation of affected area. In case of contact, immediately remove contaminated clothing and flush area with plenty of water. If inhaled, move to fresh air.

## ■ RESULTS AND DISCUSSION

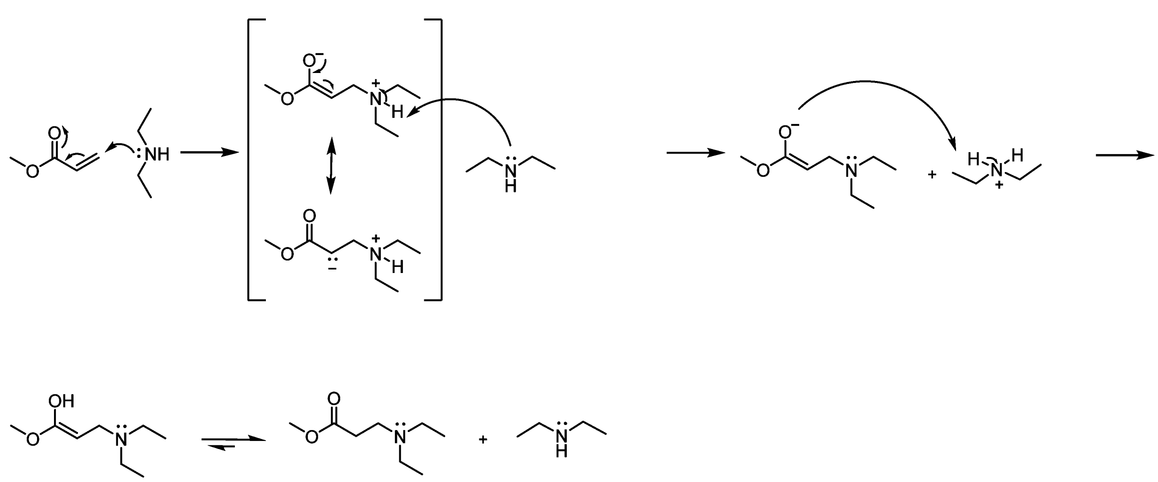
Reaction of an α,β-unsaturated ester with an amine using traditional organic solvents, such as tetrahydrofuran or cyclohexane, is slow and does not go to completion even after 48 h;[11] hence, the reaction using traditional solvents is unsuitable for inclusion in a 3 to 4 h undergraduate laboratory. In an effort to incorporate green chemistry principles in an introductory organic chemistry laboratory course, the use of PEG-400 as a "green" alternative to traditional organic solvents drastically reduced reaction times (to 1.5 h) and increased product yields (47−60%). The reaction time was reduced further (0.75 h) and the yield was maximized (50−100%) by performing the reaction at 70 °C.

The synthesis of β-alanine *N*,*N*-diethyl methyl ester (**4**) proceeded via one step (Scheme 1, reaction 2). The starting material, (**1**), reacted with (**2**) at 70 °C for 45 min to give (**4**) in 50−100% yield. Mechanistic overview of the reaction is provided in Scheme 2.

The experiment has been run three times in an organic chemistry II laboratory course at the University of Pittsburgh, Johnstown in Fall 2014 with 9 students and Spring 2015 with 23 students, and at SUNY New Paltz in Spring 2015 with 48 students. The experiment was performed by students in groups of two. Due to odd number of students in both semesters, one group had three students.

A green chemistry handout describing 12 green chemistry principles and post-lab questions are provided in the Supporting Information. Students demonstrated a thorough understanding of the green and sustainable aspects of this

**Scheme 2. Mechanistic Overview of the Synthesis of 4**

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reaction. Most students (90%) were able to correctly answer the two questions pertaining to green chemistry.

Prior to this particular experiment, most organic chemistry laboratory experiments involved reactions whose products and reaction mechanisms were well-known. Consequently, students were using spectroscopic data for verification purposes only. This experiment enabled students to use spectroscopic data to identify the product—in this case, whether the product was an amide formed via a nucleophilic acyl substitution mechanism (Scheme 1, reaction 1), or an amino ester formed via a 1,4-addition mechanism (Scheme 1, reaction 2).

A pre-lab exercise (Supporting Information) completed by students indicated that they had a thorough understanding of spectroscopy (83–100%). This exercise guided students through the $^{1}$H NMR interpretation, wherein they were asked to predict the number of $^{1}$H signals for (**3**) and (**4**), estimate the chemical shifts for each of these peaks (from chemical shift table), and predict the multiplicity of these peaks. For the $^{13}$C NMR, students were asked to predict the number of signals for each of the two possible products (**3**) and (**4**) and see if they had the right number of signals with appropriate chemical shifts (as determined by $^{13}$C chemical shift chart).

Students confirmed the formation of product (**4**) in their observations after acquiring $^{1}$H NMR and IR spectra. They recognized the characteristic IR absorbance for esters (~1740 cm$^{-1}$) confirming the formation of product (**4**). They ruled out the formation of the amide (**3**) as that would have resulted in a lower carbonyl stretch. Number of signals and their chemical shifts in $^{1}$H and $^{13}$C NMR spectra further confirmed the formation of the aza-Michael product (**4**). Students could also propose a viable mechanism for the product (97–99%). The pre-lab exercise helped students to answer questions that involved critical thinking concepts associated with this experiment.

While answering post-lab questions (Supporting Information), a majority of students could write a balanced chemical equation (97%), based on the limiting reagent (97%) and percentage yield (100%). Students calculated the intrinsic atom economy to be 100% with formation of no byproduct. By consulting material safety data sheets for reactants and solvents, students recognized PEG-400 as an environmentally benign solvent and could recognize the green and sustainable aspects of their work (90%). On the basis of the IR and NMR analyses, students correctly proposed the structure of the product formed (100%).

It is important to mention that the nongreen aspects of this reaction should be recognized and appropriate steps should be taken to make the experiment greener. These steps should include looking at the workup and purification procedures carefully.[15] As long as the students are very careful with the workup, column chromatography can be avoided or can be performed on a very small scale (e.g., 25 mg) to reduce the solvent consumption.

## ■ CURRICULAR FEASIBILITY

The experiment can be performed using inexpensive glassware such as test tubes, Pasteur pipets, and low-cost starting materials. This increases the potential for adoption of the reaction as a green undergraduate laboratory procedure.

## ■ CONCLUSION

PEG-400 is a nontoxic and inexpensive reaction medium used for an aza-Michael reaction of methyl acrylate and diethylamine. Recyclability of the solvent makes this reaction economically feasible. Simplicity of glassware and procedure led to consistent results that reinforced theoretical concepts taught in the lecture class (conjugate addition and acyl substitution). The take-home exercise gave students an opportunity to understand reaction mechanisms and use their spectroscopic skills to identify the product. Within the experimental framework, various green chemistry principles were discussed and students became aware of atom economy, waste management, and benign reagents.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00615.

Student handout that outlines the detailed experimental procedure, pre- and post-laboratory exercises, instructor's notes, CAS numbers for all chemicals used in the lab, green-chemistry handout, detailed spectral analysis, and answers to the pre- and post-lab exercises along with spectra of starting materials and product (PDF, DOCX)

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### Notes

The authors declare no competing financial interest.

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