

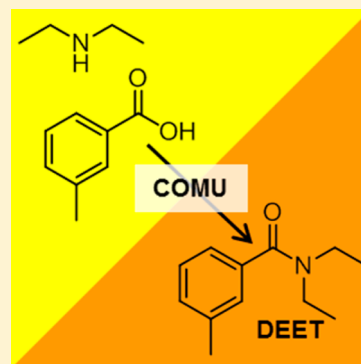
Operationally Simple Synthesis of *N,N*-Diethyl-3-methylbenzamide (DEET) Using COMU as a Coupling Reagent

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S Supporting Information

ABSTRACT: A novel procedure is described where students use COMU [(1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate], as a nonhazardous partner, in the one-pot coupling of a carboxylic acid and amine producing *N,N*-diethyl-3-methylbenzamide (DEET). Fundamental principles of carbonyl reactivity are understood, with potential for expansion to new methods of amide bond formation. The reaction can be monitored visually by virtue of the color change associated with the conversion, and all byproducts are conveniently water-soluble. This modern, microscale reaction is appropriate for a second-semester introductory undergraduate organic chemistry course: it can be performed during a 3 h laboratory period and is operationally straightforward. Curricular flexibility allows for this protocol to serve as a meaningful discussion of mechanistic organic chemistry and spectroscopy.



KEYWORDS: Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Amides, NMR Spectroscopy

The laboratory synthesis of *N,N*-diethyl-3-methylbenzamide (DEET) remains a popular experiment in both second-year and upper-division undergraduate chemistry courses.¹ As the most widely used active ingredient in insect repellants, students are familiar with the use of DEET as the best way to avoid the bites of mosquitoes, ticks, and other disease-carrying insects. Coupled with an increase in the prevalence of the West Nile Virus across much of North America,² the synthesis of DEET is particularly effective for connecting instruction in organic chemistry with topical issues outside the classroom. The conventional method of DEET synthesis in the undergraduate teaching laboratory is based on conversion of *m*-toluic acid to the corresponding acid chloride, followed by condensation with excess diethylamine. Typically, thionyl chloride is the reagent most commonly used for formation of the intermediate *m*-toluoyl chloride,³ with alternate methods using oxalyl chloride or triphosgene also reported.⁴ Such approaches invariably require isolation of the intermediate acid chloride. A one-pot method for the amidation of aryl nitriles, which can be applied to the synthesis of DEET, has also been described, but requires generation of an aminomagnesium bromide reagent.⁵

With a desire to create modern experiments that effectively frame and focus students' awareness of organic chemistry, and its place in society, this commonly used experiment was revisited. Of particular importance was a desire for operational simplicity, notably the avoidance of standard chlorinating reagents such as thionyl chloride or oxalyl chloride. Such reagents require rigorous exclusion of water from glassware and solvents, use of drying tubes, and isolation of the intermediate *m*-toluoyl chloride, often using a rotary evaporator necessarily

situated in a fumehood. An experiment and accompanying procedure that advanced students' skills in core laboratory techniques, in predicting and understanding reaction mechanisms, and in the utility of NMR spectroscopy was also sought. Methods that describe direct conversion of carboxylic acids to amides were considered worthy of investigation. Such approaches generally involve the in situ formation of an active ester, followed by attack of the corresponding amine.

The goal was to take a relatively standard protocol and increase its utility and pedagogical value in the laboratory by introducing students to modern amide coupling reactions from a synthetic and mechanistic perspective. Despite inclusion in most introductory organic chemistry texts, the use of coupling reagents in peptide bond formation is often not covered in great detail, and experiments which serve to increase the depth of coverage are beneficial. A variety of suitable reagents have been described for this purpose, with the most popular based on carbodiimide coupling mediated by benzotriazole additives, such as HOBt or HOAt.⁶ Owing to concerns about the safety of these reagents, particularly their potential explosive nature, attention was focused on the use of an alternative coupling reagent, (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)-dimethylamino-morpholino-carbenium hexafluorophosphate, known far more commonly by its acronym: COMU (Figure 1).

Since its development in 2009, COMU has become an important synthetic tool in the chemistry of peptide bond formation, and it is considered a third generation of uronium-type coupling reagent.⁷ The morpholine moiety in COMU has

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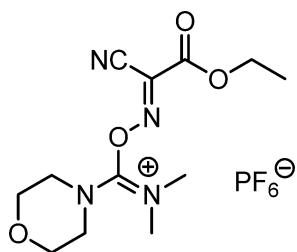
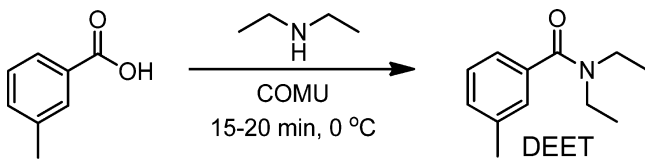


Figure 1. Structure of the coupling reagent COMU.

a remarkable effect on the stability (crystalline and shelf-stable) and reactivity of the reagent. A new synthetic experiment was developed for the introductory undergraduate organic chemistry laboratory that utilizes COMU as a nonhazardous coupling partner in a one-pot synthesis of DEET. This operationally simple reaction occurs in *N,N*-dimethylformamide (DMF) using *m*-toluic acid, COMU, and diethylamine in a 1:1:2.2 ratio (Scheme 1).

Scheme 1. Student Preparation of DEET Using the Coupling Agent COMU



The experiment is easily completed in a 3 h laboratory period with a short reaction time (15–20 min), allowing the experiment to serve also as a convenient introduction to (or a reacquaintance with) liquid–liquid extraction and use of a rotary evaporator. While students have a reasonable understanding of the use of thionyl chloride and oxalyl chloride in the activation of carboxylic acids for reaction with nucleophiles, in the current experiment they are required to problem-solve in small groups during the laboratory to determine how COMU functions in an analogous manner. Physical characterization of the DEET product using proton and carbon NMR spectroscopy provides interesting points for discussion, particularly through the use of variable temperature NMR spectroscopy. The experiment described herein was performed in the introductory organic chemistry laboratory and was designed to reinforce and expand upon material discussed as part of the second-semester curriculum. To the best of our knowledge, this represents the first example of the use of the coupling reagent COMU in the teaching laboratory.⁸

EXPERIMENTAL OVERVIEW

Students work individually. The experiment requires one 3 h laboratory period to complete. *m*-Toluic acid (1 equiv) and COMU (1 equiv) are added sequentially to a stirred solution of diethylamine (2.2 equiv) in DMF at 0 °C. The solution turns bright yellow immediately upon the addition of COMU and is stirred for another 15–20 min, at which point it turns orange, indicating reaction completion. Following an aqueous workup, DEET is obtained as an essentially pure product. Analysis is done by NMR spectroscopy, including variable temperature NMR spectroscopy. Full details are available in the Supporting Information.

HAZARDS

Appropriate personal protection (safety goggles, gloves, lab coat) should be worn at all times. COMU causes skin and eye irritation and may cause respiratory irritation. DMF is flammable, causes eye and skin irritation, and may be harmful if swallowed. Diethylamine is a highly flammable liquid that is harmful in contact with skin and harmful if swallowed or inhaled. *m*-Toluic acid and DEET are irritants that may be harmful if swallowed or inhaled. Diethyl ether is an extremely flammable liquid that causes serious eye irritation and is harmful if swallowed or inhaled. Chloroform-*d*₃ is irritating to the skin and respiratory system and is a possible carcinogen.

DISCUSSION

Students enrolled in a second-semester introductory organic chemistry course have familiarity with basic laboratory techniques, including liquid–liquid extraction and distillation. This laboratory provides an illustration of the use of liquid–liquid extraction as a workup procedure in an organic chemical reaction. NMR spectroscopy is typically introduced in the second-semester course, and this laboratory provides the first practical exposure to instrument operation and spectrum acquisition. Approximately 50 students completed the experiment easily in a 3 h laboratory period, with spectra typically provided during the next laboratory session, or available via Dropbox. Students found the one-pot synthesis of DEET to be operationally straightforward, and, with all byproducts easily removed in an aqueous workup, the vast majority obtained the DEET product with exceptional purity. Yields in this experiment were typically in the range of 70–80% (average student yield 76%), with students more than capable of managing reagents at the microscale, with the reaction conducted using 1 mmol of *m*-toluic acid. This is particularly significant given the moderately high cost of the COMU reagent.

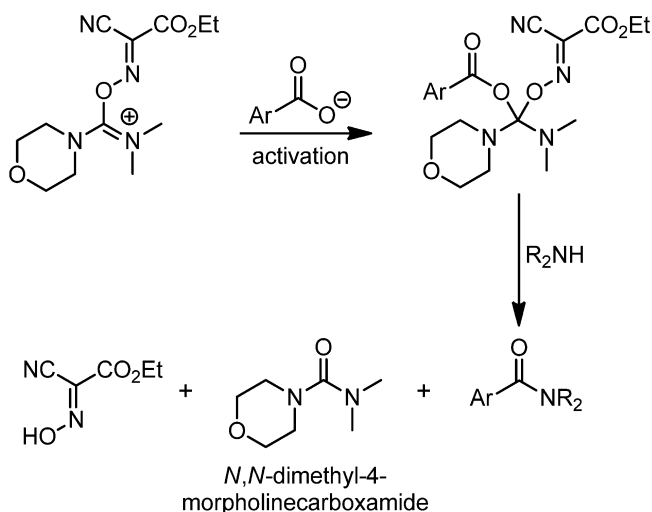
A very useful characteristic of COMU is that the course of the reaction can be followed due to a change in color, which depends on the type of base used.⁷ Thus, shortly after the addition of the coupling reagent, a solution of *m*-toluic acid and diethylamine in DMF has turned bright yellow, and, once the reaction is complete, the solution becomes orange. In a variation of this reaction, the reaction may also be performed using diethylamine (1.0 equiv) and 2,2,6,6-tetramethylpiperidine (TMP) as a non-nucleophilic base (1.2 equiv) in place of diethylamine alone, resulting in a functionally identical experimental procedure where the color change is now from pink to colorless. Students find these observations particularly interesting, with the color change allowing for easy visual or colorimetric monitoring. Occasionally, trace amounts of the reaction solvent, DMF, or the coupling byproduct, *N,N*-dimethyl-4-morpholinecarboxamide, are observed in NMR spectra, but the latter provides mechanistic clues and thus an interesting discussion point (see below).

Pedagogical Enhancements

Opportunities exist for pedagogical enhancement depending on time and resources. The laboratory can be used to highlight interesting mechanistic considerations associated with carbonyl group reactivity and, in particular, the COMU coupling reagent. With the overall reaction requiring attack of the amine at the carbonyl carbon of the acid, most students are able to identify the need for activation of the carboxylic acid through introduction of a nonacidic electron-withdrawing group.

Students are also typically aware of the acyl halide approach and can discuss the utility of reagents such as thionyl chloride and, less commonly, oxalyl chloride. However, it is not immediately obvious how the COMU reagent functions in an analogous way, and in a one-pot reaction with no isolated intermediate. An outline mechanism is shown in Scheme 2. In

Scheme 2. Outline of Mechanism for the Coupling Reagent COMU



seeking out the manner in which COMU activates the carboxylic acid, students are forced to analyze a complex and unusual reagent structure, to determine possible electrophilic sites within this structure, and to identify potential leaving groups. To provide guidance, indicating that *N,N*-dimethyl-4-morpholinecarboxamide is a reaction byproduct can be useful (as can its occasional appearance in a student's NMR spectrum).

The spectroscopic data acquired also allowed for pedagogical enhancement through discussion of the rotameric nature of the newly formed amide bond in DEET.⁹ Using standard acquisition parameters, this dynamic process causes the proton NMR signals for the ethyl groups to appear as two pairs of broad singlets for each of the methylene and methyl groups. An analogous effect is observed via the doubling of signals in the carbon NMR spectrum. A discussion of restricted rotation caused by the resonance interaction between the nitrogen lone pair and the carbonyl group is straightforwardly comprehended by students. This leads nicely to a discussion of temperature effects, and students are able to verify the anticipated change in appearance when provided with proton and carbon NMR spectra of DEET recorded at 373 K.¹⁰ In these spectra, the broad peaks in the proton NMR merge to give the anticipated and sharp quartet and triplet for the methylene and methyl groups, respectively. Coupling constants were easily determined. A similar effect is observed with respect to the doubling of signals previously seen in the carbon NMR, with the slightly broadened appearance of the methylene carbon signal presumably due to quadrupolar effects of nitrogen.¹¹ Such pedagogical enhancements might be beyond most students in a second-semester introductory organic chemistry course, but would certainly add value to the inclusion of this reaction in an upper-level organic chemistry laboratory.

The students' performance in the laboratory and the quality of their reports indicated that the pedagogical goals of the

experiment were met. Through concise and coherent laboratory reports that include a complete mechanism for the reaction, students demonstrated an understanding and appreciation for modern amide coupling reactions.

CONCLUSION

A one-pot, operationally simple synthesis of DEET was devised for students in a second-semester organic chemistry course. Utilizing COMU as a nonhazardous coupling partner, the experiment benefited from short reaction times and no necessary purification. Students were able to determine the progress of the reaction through simple color monitoring and were exposed to modern, unconventional reagents, requiring them to apply fundamental organic chemistry principles to determine the reagent's mode of function.

ASSOCIATED CONTENT

Supporting Information

Instructions for students; additional notes and images for the instructor; representative student NMR data recorded at 297 and 373 K. 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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