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Laboratory Experiment

Facile Amide Bond Formation with TCFH−NMI in an Organic Laboratory Course

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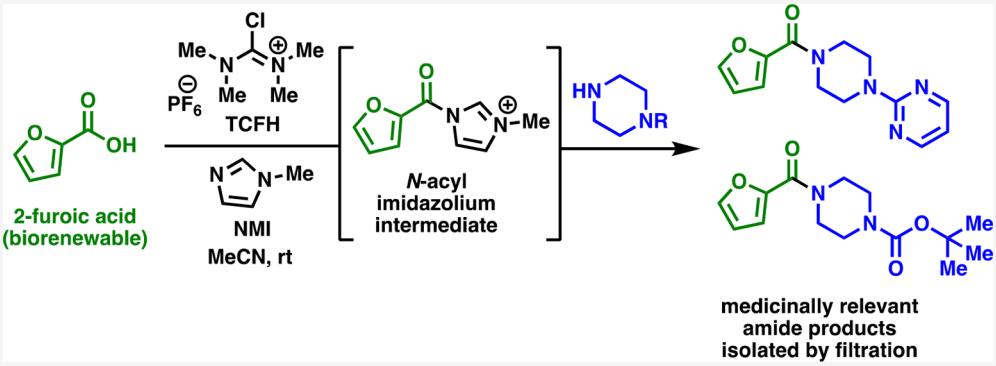

ABSTRACT: A new undergraduate organic laboratory experiment has been developed for amide bond formation between biorenewable 2-furoic acid and either of two substituted piperazines to prepare medicinally relevant amide products using a procedure with industrial significance. The reactions proceeded smoothly under ambient conditions using the combination of *N,N,N′,N′*-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI) in a minimal volume of acetonitrile with a direct crystallization upon addition of water. Students successfully collected their product by filtration and then characterized it by NMR (^{1}H, ^{13}C, COSY, DEPT-135, HSQC), IR, MS, and melting point. Students also explored the reaction mechanism and compared green chemistry aspects of their procedure with literature routes. A virtual version of the experiment was adapted for remote instruction.

KEYWORDS: *Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Collaborative/Cooperative Learning, Green Chemistry, Mechanisms of Reactions, NMR Spectroscopy*

INTRODUCTION

Amide bond formation is a fundamental transformation in many areas of chemistry due to the importance of amides for influencing molecular structure as well as interactions.[1] Therefore, introducing amides and amide bond formation into undergraduate curricula can provide students with practical knowledge and experience.[2] Indeed, many experiments found in this *Journal* have featured the synthesis of amides.[3] When planning the preparation of an amide, one is confronted with a myriad of choices for reagents and conditions since research in this area is extensive and ongoing. Unfortunately, many of the most popular conditions involve corrosive reagents (e.g., acid chlorides), elevated temperatures, multistep protocols, expensive chemicals, and/or skin sensitizers. Some require complex isolation procedures due to the reaction byproducts or impurities.[2] One way to find guidance in designing an experiment for undergraduate laboratories is to recognize an unexpected synergy between industrial processes and undergraduate laboratory experiments.[4] Chemistry which can be executed at large scales is intended to be safe, environmentally friendly, and reproducible. All of these are also criteria for successful undergraduate laboratory experiments. In the context of amide bond formation, the recently described combination of *N,N,N′,N′*-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI) is a versatile method for the mild and rapid synthesis of amides[5] that has seen applications at large scales.[6] The procedure benefits from a broad scope, high yields, and purity. The rapid reaction rates observed with TCFH−NMI are attributed to the highly reactive *N*-acyl imidazolium intermediates;[7] see Scheme 1 for an example. In addition, these conditions benefit from simple product isolation due to the water solubility of the reaction byproducts.[5] Notably, TCFH is not a skin sensitizer, in contrast to many commonly used, modern amide bond-forming reagents

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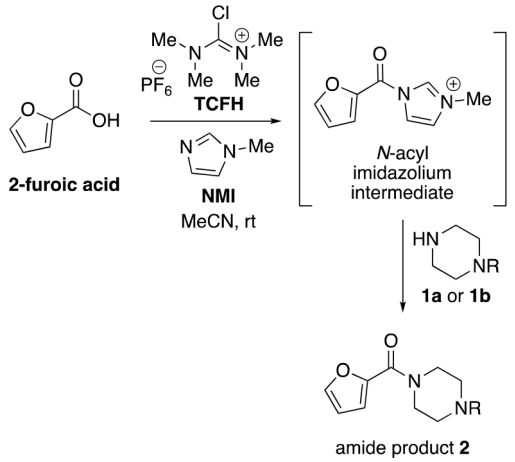
Scheme 1. Mild Synthesis of Amides Using TCFH−NMI



such as 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDAC) or 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU).[8]

In this laboratory experiment, we sought to develop a modern, robust, and reproducible amide bond formation experiment for an undergraduate laboratory course using TCFH/NMI. We selected biorenewable 2-furoic acid[9] as the carboxylic acid component and two substituted piperazines (**1a** and **1b**) as the amine components (Figure 1). The resulting amide products **2a**

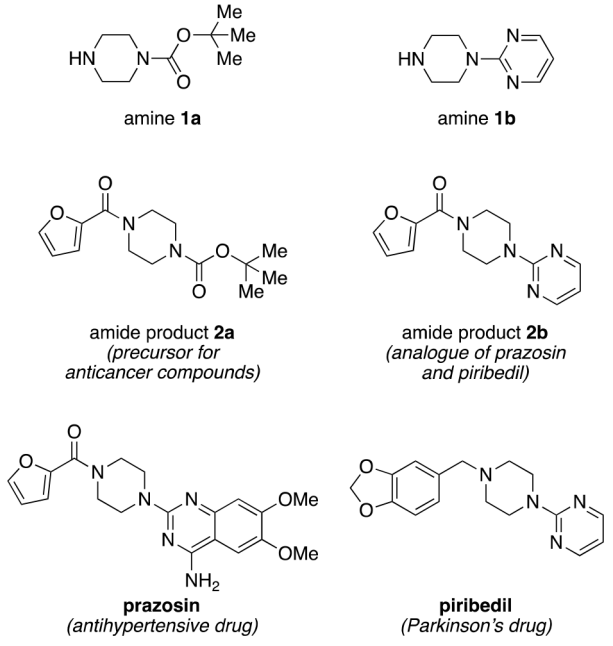


Figure 1. Amine reactants and amide products in this experiment, with the drugs prazosin and piribedil for structural comparison.

and **2b** are medicinally relevant and crystalline, allowing for a simple, streamlined isolation. Boc-protected amide **2a** is a precursor to human lactate dehydrogenase A inhibitors for applications in cancer treatment.[10] Pyrimidyl amide **2b**[11] is a structural analogue of the antihypertensive drug prazosin and the Parkinson's drug piribedil, demonstrating the applicability of the knowledge and experience students gain while executing the experiment.

PEDAGOGICAL SIGNIFICANCE

This experiment provides an opportunity for organic chemistry students to improve and demonstrate their skills in setting up a reaction, isolating pure product, analyzing spectral data, drawing reaction mechanisms, and evaluating green chemistry concepts of laboratory procedures. The experimental techniques are simple, and green chemistry aspects include a room-temperature reaction, few hazards, modest scale, and minimal waste.

The pedagogical goals of this experiment are for each student to

- perform an acylation reaction and isolate the amide product in good yield
- characterize their product using MS, IR, and several NMR techniques
- deduce a curved-arrow mechanism for the formation of the *N*-acyl imidazolium intermediate and its conversion into the amide product
- explain why *N*-acyl imidazoliums are more reactive electrophiles than *N*-acyl imidazoles
- compare the greenness of their procedure to a literature synthesis of the same product

EXPERIMENTAL OVERVIEW

The experiment described here was implemented in a single 3 h lab period in a second-semester organic laboratory course. In a 3 dram vial, students combined 2-furoic acid (0.100 g, 0.892 mmol), amine **1a** or **1b** (0.892 mmol), acetonitrile (1.0 mL), and *N*-methylimidazole (0.15 mL, 1.9 mmol). Then, TCFH (0.275 g, 0.981 mmol) was added in a single portion, and the reaction was stirred at room temperature. After 30 or 60 min,[12] water (3 mL) was added, and the reaction mixture was cooled in an ice bath for an additional 10 min. White crystals were isolated by suction filtration and air-dried. Students recorded the mass and melting point of their product and collected an IR spectrum, a mass spectrum, and a ^{1}H NMR spectrum. Student volunteers collected IR spectra for 2-furoic acid and amines **1a** and **1b** for comparison with the products. The instructor provided additional NMR spectra: COSY, ^{13}C, DEPT-135, and HSQC. This experiment was also adapted for remote instruction with details provided in the Supporting Information.

HAZARDS

2-Furoic acid and *N*-Boc-piperazine can cause skin and respiratory irritation. 2-Furoic acid can cause eye damage. *N*-Boc-piperazine and 1-(2-pyrimidyl)piperazine can cause skin and eye irritation. Tetramethylchloroformadinium hexafluorophosphate (TCFH) can cause skin, eye, and respiratory irritation.[8] Acetonitrile is flammable and an eye irritant. *N*-Methylimidazole (NMI) can cause serious skin burns and eye damage. Acetonitrile and chloroform-*d* are toxic if swallowed, in contact with skin, or inhaled. *N*-Methylimidazole and chloroform-*d* are suspected of causing cancer as well as damage to fertility or organs. Gloves, lab coats, and protective eyewear should be worn for this experiment. A chemical fume hood is recommended for handling TCFH, NMI, acetonitrile, and chloroform-*d*.

RESULTS AND DISCUSSION

This experiment was first implemented in a remote, online format during the COVID-19 pandemic with 21 second-semester organic students. The students were given a procedure,

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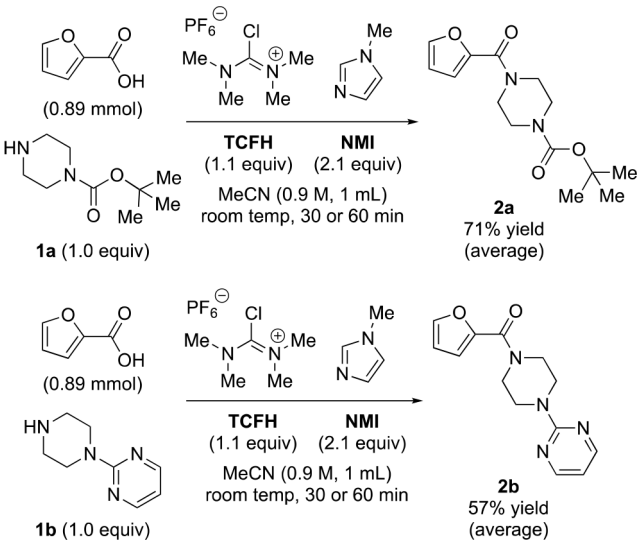
experimental data obtained by the authors, and a worksheet on product characterization, green chemistry, and reaction mechanisms. Each student completed this worksheet during a synchronous Zoom session in groups of 2−4 students per breakout room. The next year, this experiment was performed in-person by 16 second-semester organic students. In all cases, the students had previously demonstrated proficiency with a variety of NMR experiments, as well as with mass spectrometry and infrared spectroscopy.

Every student performing the coupling reaction produced their amide product successfully, with yields of 7−82% (average yield = 64% overall, 71% for **2a** and 57% for **2b**; see Scheme 2).

Scheme 2. Student Reaction Results



Fifteen of the 16 students had yields of 45% or greater, and the lone exception was attributed to a spill as well as not cooling the sample before filtering. Fortunately, this student was still able to obtain NMR, MS, IR, and melting point data for their product.

IR spectra were obtained using attenuated total reflectance (see Supporting Information pages S55−S59). 2-Furoic acid showed a very broad carboxylic acid O−H stretch at 2000−3300 cm^{-1} and a C═O stretch at 1680 cm^{-1}. The spectrum for *N*-Boc-piperazine (**1a**) had an amine N−H stretch at 3323 cm^{-1} and a C═O stretch at 1685 cm^{-1}, while pyrimidylpiperazine **1b** had no C═O stretch but an amine N−H stretch at 3288 cm^{-1}. The O−H and N−H stretches did not appear in the spectra for amide products **2a** and **2b**. Amide **2a** gave C═O stretches at 1688 and 1626 cm^{-1}, while amide **2b** had a single C═O stretch at 1621 cm^{-1}. Low-resolution mass spectra were obtained by atmospheric-pressure chemical ionization (APCI) in positive ion mode, resulting in peaks at m/z = 281 for $[\mathbf{2a} + H]^+$ and 259 for $[\mathbf{2b} + H]^+$ that students readily identified. Additional high-resolution data confirmed the target masses within 5 ppm accuracy (see Supporting Information pages S60−S62).

Students obtained clean ^{1}H NMR spectra for their products and were able to assign most of the signals correctly with the aid of the COSY, ^{13}C, DEPT-135, and HSQC spectra (see Supporting Information pages S21−S54). The three hydrogens on the furoyl group as well as the three pyrimidyl hydrogens on **2b** were identified by chemical shift, integration of peak area, COSY cross-peaks, magnitude of *J*-values, and by comparison of the spectra for **2a** and **2b**. The nine equivalent *tert*-butyl hydrogens of **2a** were readily distinguishable by integration and chemical shift. The piperazine methylene groups appeared as two distinct signals at δ = 3.8 and δ = 3.5 ppm (four hydrogens each, coupling in the COSY spectrum) for **2a**, while for **2b** all eight hydrogens were overlapping at δ = 3.9 ppm. The piperazine methylene groups could be resolved by heating the sample in DMSO-d_6 to 80 °C (see Supporting Information pages S25, S28, S41, and S44).

Students assigned the ^{13}C NMR signals to the structures using the HSQC spectrum to correlate carbons with attached hydrogens and the DEPT-135 spectrum to distinguish CH and CH_3 groups (positive signals) from C (absent) and CH_2 groups (negative signals). Carbons with no attached hydrogens also tend to appear as low-intensity signals, while signals representing multiple equivalent carbons (as in the *tert*-butyl methyl groups and two of the pyrimidine carbons) tend to result in higher-intensity signals in the ^{13}C NMR spectra. Chemical shift values were also informative for these assignments. Interestingly, the piperazine carbons appeared as a very broad signal at δ = 44 ppm for **2a**. For **2b**, these carbons gave rise to a moderately sharp peak at δ = 44 ppm overlapping an extremely broad and low signal centered around δ = 46 ppm. Sample student spectra are provided in the Supporting Information. As in the case of the ^{1}H NMR, the ^{13}C NMR signals for the piperazine methylenes could be resolved by heating the sample in DMSO-d_6 to 80 °C (see Supporting Information pages S34, S36, S50, and S52).

Student performance on key learning objectives for this experiment is provided in Table 1. For each task, 84% or more of the students demonstrated proficiency across both the remote and in-person offerings of this experiment. Students in remote instruction performed slightly worse on the objectives relating to NMR and IR spectroscopy assignments than in-person students but better on reaction mechanisms (objectives 3 and 4). For a more detailed comparison of the two cohorts, see Supporting Information page S20. A minor difference between the two groups was the change in green metrics from the *E* factor[13] during remote instruction to process mass intensity (PMI) during in-person instruction. We made this change because PMI is a less subjective mass-based metric that removes the ambiguity about whether waste should be considered benign or not.[14]

Table 1. Student Learning Outcomes

Learning Objective	Students Should Be Able to	Students[a] Successfully Performing Task, %
1	Obtain desired product in ≥50% yield	88[b]
2	Explain the reactivity difference of *N*-acyl imidazoliums and *N*-acyl imidazoles	86
3	Correctly complete the TCFH−NMI mechanism	89
4	Correctly assign ^{1}H NMR signals	89
5	Correctly assign IR signals	92
6	Correctly assign MS signal	100
7	Compare the greenness of procedures	94
8	Correctly calculate *E* factor or PMI[c]	86

[a]N = 37, including both remote and in-person instruction. [b]N = 16 for in-person instruction only. [c]*E* factor was used for remote instruction and updated to process mass intensity for in-person instruction.

The average PMI values for students preparing amide products **2a** and **2b** were 32 and 43, respectively, which are superior to the calculated values from literature preparations of

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these compounds: 4000 for **2a**[10] and 49 for **2b**.[11] Neither literature procedure was optimized with a teaching laboratory in mind, and both employ hazardous dichloromethane as a solvent. Other less-than-ideal aspects of the literature methods include a solvent-intensive extraction step, column chromatography, and a sensitizing reagent (HBTU) in the synthesis of **2a**. The literature synthesis of **2b** involves a corrosive acid chloride and expensive solid-supported reagents.

CONCLUSIONS

This experiment generates medicinally relevant amide products by coupling biorenewable 2-furoic acid with either of two amines using a modern, industrially inspired reagent combination of TCFH–NMI[5] at room temperature. In comparison to other *JCE* methods to prepare amides, this experiment proceeds smoothly at room temperature, allows rapid product isolation by filtration, uses minimal (and relatively green) solvents,[15] and avoids sensitizing reagents.[8] Neither an inert atmosphere nor anhydrous solvents are required. Undergraduate students were guided through the reaction mechanism; isolated pure products; characterized their products by NMR, IR, and MS; and compared the greenness of their procedure to a literature method. Students successfully met the expected learning objectives in both virtual and in-person formats. This project arose from a collaboration between a pharmaceutical process chemist and an undergraduate academic laboratory instructor. We hope that it inspires future academic–industrial partnerships to further chemical education and help promote the principles of green chemistry in the laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.2c00760.

Student handout, instructor notes with list of chemicals, and representative student spectra (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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