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Laboratory Experiment

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Comparing Amide-Forming Reactions Using Green Chemistry Metrics in an Undergraduate Organic Laboratory

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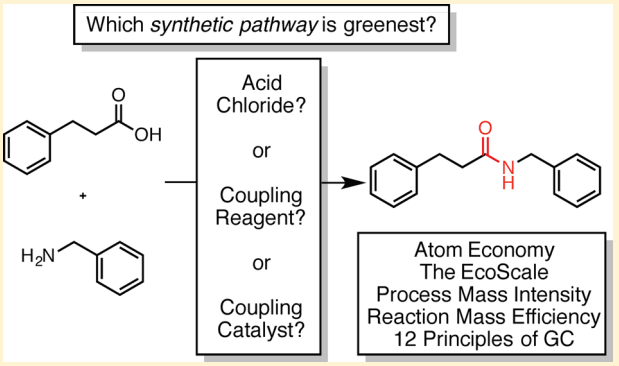
Supporting Information

ABSTRACT: In this laboratory experiment, upper-division undergraduate chemistry and biochemistry majors investigate amide-bond-forming reactions from a green chemistry perspective. Using hydrocinnamic acid and benzylamine as reactants, students perform three types of amide-forming reactions: an acid chloride derivative route; a coupling reagent promoted method; and a boric acid catalyzed condensation. After isolation of the common product, students assess the reactions using the 12 Principles of Green Chemistry and several green chemistry metrics: atom economy; reaction mass efficiency; process mass intensity; and the EcoScale. In addition to assessing what route is the greenest, students also compare the metrics to discern what aspects of green chemistry each metric captures. In order to extend sustainability to economic considerations, the projected "front-end" cost of synthesizing a kilogram of the amide is calculated based on data from each reaction. The experimental work is conducted over two 3 h laboratory periods.



KEYWORDS: *Upper-Division Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Amides, Catalysis, Green Chemistry*

Amides are ubiquitous functional groups found in synthetic polymers, small-molecule pharmaceuticals, proteins, and other biomolecules. In 2007, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable listed "amide formation avoiding poor atom economy reagents" as the top research priority for reactions currently used by the pharmaceutical industry.[1] Many introductory organic chemistry texts[2−5] discuss two approaches for the synthesis of amide bonds: the reaction of an amine with a reactive acid derivative (acid halide, acid anhydride, or ester) and the reaction of an amine with a carboxylic acid mediated by a coupling reagent such as dicyclohexylcarbodiimide (DCC). Reactions of acid halides with amines are effective in many instances, but they generally have poor functional group compatibility, safety concerns associated with the acid halide, and poor atom economy. Coupling reagents often mitigate problems associated with functional group compatibility and safety concerns, though poor atom economy remains a major disadvantage for such reagents. Considering this problem, recent research has explored new techniques for amide-bond synthesis, especially in the context of complex molecule and biomolecule synthesis.[6] Catalytic methods for amide-bond formation, generating only water as a byproduct, comprise an area of particular interest.[7,8] While recent undergraduate experiments involving amides expose students to modern stoichiometric coupling reagents,[9−11] this experiment places three amide-bond-forming reactions in the context of green chemistry, which aims to reduce or eliminate the use of hazardous materials and the production of waste.[12]

In this experiment, students must propose the greenest method for synthesizing *N*-benzyl-3-phenylpropanamide based on data obtained in the laboratory. Students synthesize this amide from benzylamine and hydrocinnamic acid using three methods: (1) an acid chloride route, (2) a coupling reagent route, and (3) a boric acid catalyzed route. After isolation and characterization of the amide product, the students compile their data and assess each reaction using the 12 Principles of Green Chemistry[12] and the following green chemistry metrics:[13−15] (a) atom economy,[16,17] (b) reaction mass efficiency (Curzons),[18] (c) process mass intensity,[19] and (d) the EcoScale.[20] The metrics are also compared to ascertain what aspects of green chemistry each metric evaluates. In lab reports, students analyze the three routes, compare the metrics, and propose the most sustainable amide-forming reaction based on the data. Finally, in order to relate a method's greenness to economic considerations, a cost projection of each reaction run on a scale to produce a kilogram of amide is performed, and that data set is compared to the outcomes of the metrics.[21]

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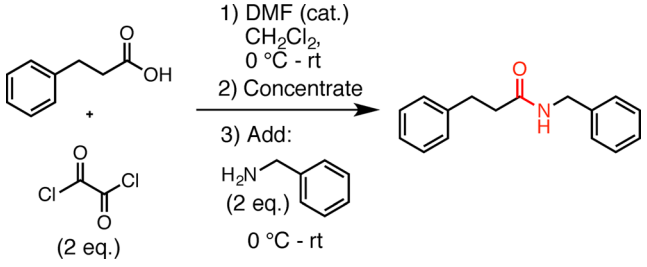
EXPERIMENTAL OVERVIEW

Students work either individually or in groups of two over two 3 h lab periods. The reactions and metrics are introduced in a prelab meeting. Students are assigned one of the three methods, and the reactions are started in the first lab period. In the second lab period, the reactions are worked up and the product is isolated, dried, weighed, and analyzed for identity and purity by ^{1}H NMR spectroscopy and melting point. The students share yield information, and the average is calculated for each method. This lab has been successfully implemented with over 20 upper-division undergraduates over the past two years. See the Supporting Information for full experimental details.

Acid Chloride Route

An overview of the acid chloride route is shown in Scheme 1.

Scheme 1. Acid Chloride Route



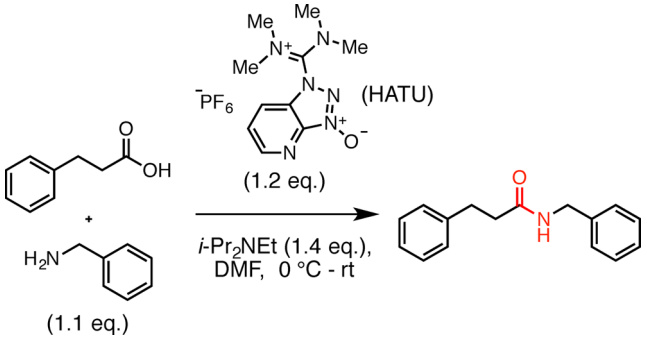
Students are generally familiar with formation of acid chlorides from carboxylic acids, but not necessarily using oxalyl chloride as the reactant. In regard to reaction stoichiometry, reactants hydrocinnamic acid and oxalyl chloride, as well as the amide product, all have coefficients of 1. The benzylamine reactant, however, has a reaction stoichiometry coefficient of 2 so that the HCl generated in the reaction is scavenged (see the Supporting Information). The mechanism is presented in a prelab period, highlighting the generation of the Vilsmeier reagent[22] *in situ* from a catalytic amount of dimethylformamide (DMF), and how formation of the acid chloride can be monitored using a bubbler (CO_2 and CO evolution stops upon reaction completion). Multiple concentration/dilution repetitions ensure that excess oxalyl chloride is removed from the reaction mixture before the addition of benzylamine. Students are cautioned about the proper handling of oxalyl chloride and the disposal of the rotary evaporator condensate.

HATU Coupling Route

An overview of the coupling reagent route is shown in Scheme 2.

HATU (*N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]-pyridin-1-ylmethylene]-*N*-methyl methanaminium hexafluorophosphate *N*-oxide) is a commercially available reagent for amide couplings that is commonly used in the discovery phase of pharmaceutical research.[23,24] In regard to reaction stoichiometry, the hydrocinnamic acid, benzylamine, HATU, and diisopropylethylamine reagents, as well as the amide product, all have coefficients of 1. In practice, reactants are used in slight excess relative to hydrocinnamic acid (see the Supporting Information). Unlike textbook DCC-mediated amide couplings, the byproducts of HATU couplings are water-soluble, thus facilitating purification of the amide product. The prelab discussion emphasizes mechanistic themes common to most coupling reagents.[11]

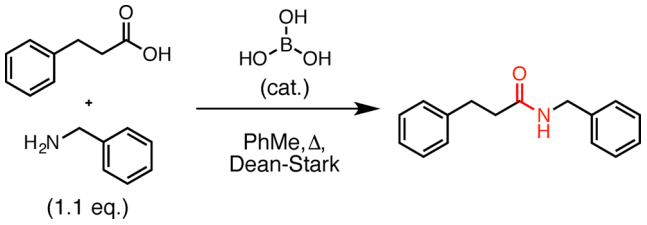
Scheme 2. Coupling Reagent Route



Boric Acid Route

An overview of the boric acid catalyzed route is shown in Scheme 3.

Scheme 3. Boric Acid Catalyzed Route



Boric acid catalyzes amide-bond formation between carboxylic acids and amines at elevated temperatures.[25] The hydrocinnamic acid, benzylamine, and amide product all have reaction stoichiometry coefficients of 1, though in practice the amine is used in slight excess (see the Supporting Information). The prelab discussion addresses the catalytic mechanism, and describes the proper use of a Dean−Stark trap since water must be removed from the mixture over the course of the reaction.

Green Chemistry Metrics

With the infusion of green chemistry into lecture and laboratory curricula over the past few years,[26−29] many undergraduate experiments have incorporated the Twelve Principles of Green Chemistry[30−32] and green metrics such as atom economy,[21,30,33] process mass intensity,[34] reaction mass efficiency,[18,21] and the *E* factor[27,35] to evaluate syntheses. Established by Anastas and Warner in 1998,[12] the Twelve Principles of Green Chemistry are guidelines to help design and implement chemical processes in an environmentally benign manner. In assessing the Twelve Principles, the accomplishment of principle index (API) reported by Ribeiro and Machado was used (eq 1):[31]

$$\text{API} = \frac{\text{number of principles completed}}{\text{number of principles that apply}} \times 100 \quad (1)$$

The ideal value will be 100. Not all principles will apply to every process, thus, the denominator in eq 1 does not necessarily need to be 12 (see the Supporting Information).

Atom economy (AE)[16] is a percentage of how many atoms from reactants are incorporated into the desired product. Atom economy was calculated using eq 2:

$$\text{AE} = \frac{\text{MW of product}}{\sum(\text{MW of reactants})} \times 100\% \quad (2)$$

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Table 1. Typical Reaction Yield and Metric Data

Reaction	Isolated Yield, %	API (12 Principles)[a]	Atom Economy, %	Reaction Mass Efficiency,[b] %	Process Mass Intensity[c]	EcoScale[d]
Acid chloride	54	30	49	21 (43)	292	48
HATU	85	30	31	22 (72)	178	41
Boric acid	83	50	93	74 (79)	89	54

[a]This value ranges from 0 to 100. [b]Maximum value of RME is AE. Value in parentheses is the ratio of RME to AE (%). [c]The ideal process would have a PMI value of 1. [d]The ideal reaction would have a value of 100; the value could range from 0−100 (see ref 20).

The ideal value will be 100%. This metric accounts for all reactants used and for reaction stoichiometry, but it does not take solvents or other auxiliary materials (catalysts, desiccants, chromatography materials, etc.) into consideration, nor does it account for the isolated yield of the product or an excess of reactants used.

The reaction mass efficiency (RME, Curzons definition)[18] calculation takes into account the mass of the product obtained relative to the mass of the reactants used, as shown by eq 3:

$$\mathrm{RME}_{\mathrm{Curzons}} = \frac{\text{mass of product}}{\sum(\text{mass of reactants})} \times 100\% \quad (3)$$

The ideal process will have a value of 100%. Reaction mass efficiency accounts for both the isolated yield and any excess of reactants, but it does not account for solvents and other auxiliary materials used in a synthesis.

The process mass intensity (PMI)[19] assessment takes into account the masses of all reactants, solvents, and auxiliary materials in a process, as shown by eq 4:

$$\mathrm{PMI} = \frac{\sum(\text{mass of all materials used})}{\text{mass of product}} \quad (4)$$

The ideal process will have a PMI value of 1.

The reaction *E* factor[35] assessment is the ratio of the mass of waste generated to the mass of the product obtained, as shown by eq 5:

$$E\ \text{factor} = \frac{\text{mass of waste}}{\text{mass of product}} \quad (5)$$

The ideal process will have a value of 0. The *E* factor can be calculated from the PMI through the relationship *E* factor = PMI − 1.[14]

The EcoScale is a Web-based green metric that accounts for the yield, cost, safety, conditions, and the ease of workup/purification of a reaction by assigning penalty points to these parameters.[20] For example, reactions are penalized for hazardous reagents, extended reaction times at high temperatures, the use of specialized apparatuses, and so forth. The ideal reaction will have a value of 100. Reaction information is entered on the Web site,[20] and the EcoScale value is calculated (see the Supporting Information).

HAZARDS

Chemicals required are hydrocinnamic acid, benzylamine, oxalyl chloride, *N*,*N*-dimethylformamide, dichloromethane, saturated sodium bicarbonate solution, 1 M hydrochloric acid, sodium sulfate, HATU, Hünig's base (*N*,*N*-diisopropylethylamine (DIPEA)), ethyl acetate, boric acid, toluene, hexanes, and chloroform-*d*. See the Supporting Information for CAS numbers, supplier information, and a complete listing of all hazard statements. The product, *N*-benzyl-3-phenylpropionamide, has no known hazards, but students should handle it and all other reagents wearing standard personal protective equipment and using standard laboratory safety precautions in a fume hood. All manipulations of solvents, reagents, products, and waste are done in a fume hood.

RESULTS AND DISCUSSION

The amide product is a white crystalline solid.[36] In most instances, material of suitable purity (by ^{1}H NMR spectroscopy, Supporting Information) was isolated using the supplied protocols. Students evaluated the ^{1}H NMR spectra to confirm the structure of the product, and to determine if organic solvent or reagents remained in the samples. Groups compiled data for each reaction and reported average isolated yields. Both the boric acid route and the HATU route consistently afforded good isolated yields, while the acid chloride route generally provided a fair yield of the product (see instructor notes). Students then assessed each reaction using the accomplishment of principle index, atom economy, reaction mass efficiency (Curzons), process mass intensity, and the EcoScale. This laboratory experiment has been conducted using these metrics, but other metrics such as generalized reaction mass efficiency,[37] effective mass yield,[38] or EATOS[39] can be included or substituted at the discretion of the instructor. Typical results from a representative lab period are shown in Table 1.

For the calculation of the accomplishment of principle index for the Twelve Principles of Green Chemistry, students first decided which of the Twelve Principles applied, and then assessed whether each reaction met the criteria for accomplishment of that principle (see the Supporting Information).[31] This takes into account waste production, reagent excess, chemical hazards, and energy use, among others, but does not factor in yield. In this project, students selected 10 of the 12 principles as being relevant (principles 4 and 11 concern product design and analytical techniques). By this metric, students reported that the boric acid catalyzed route was superior to the other two methods, accomplishing 5 of the 10 relevant principles. Using the atom economy metric, the boric acid route was by far the best method with an atom economy of 93%. The acid chloride route had an atom economy of 49%, and the HATU route had an atom economy of 31%. The mechanism for each transformation informs these atom economy numbers, as the boric acid catalyzed reaction incorporates nearly all of the starting material atoms into the product, while the other two reactions produce several byproducts (see the Supporting Information). For reaction mass efficiency, typical results show that the boric acid route had the highest RME value, and the HATU route and acid chloride routes had much lower values. In this analysis, the excess of reagents used for the latter two reactions was the major contributor to these lower assessments. In order to compare the three routes, however, the ratio of RME to AE must be considered because AE is the maximum value of RME for a given route.[40] As such, despite a low RME value for the HATU route, its RME is 72% of AE on account of the high yield for the reaction. This value is closer to the RME to AE ratio found in the high-yielding boric acid route (79%).

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Conversely, the lower yield of the oxalyl chloride route affords an RME that is only 43% of the route's AE. Using process mass intensity, the boric acid route was assessed as the greenest with a typical PMI of 89, followed by the HATU route and then the oxalyl chloride route. In this assessment, auxiliary materials, especially the workup, contributed to higher scores. Using the EcoScale calculation, the boric acid route and the acid chloride route were comparable with typical values of 48 and 54, respectively, while the HATU route was slightly less ideal with a value of 41. Yield is the major factor contributing to the EcoScale score, however, chemical hazards and energy consumption also contribute (see the Supporting Information for penalties assessed).

Having the best results in each metric, students exclusively identified the boric acid route as the greenest method. The major factors cited in lab reports contributing to this were the use of a catalyst to form the amide bond, the generation of water as the only byproduct of the reaction, and that precipitation of the product from the reaction mixture facilitated the workup. However, many students drew attention to its prolonged reflux time as a major disadvantage. The HATU route was described as high yielding, but the metrics suggest that it is not a green process (students attributed its adoption at the bench scale to its ease-of-execution). The high molecular weight coupling reagent was identified as a disadvantage, as was the workup. Students identified the acid chloride route as the least green. No advantages for this method were listed in lab reports. The acid chloride route's major disadvantages were the hazards and number of manipulations associated with forming the acid chloride, as well as the use of excess organic solvent and reagents.

Table 2 shows which metrics capture these observations. While RME and PMI are quantitative mass-based metrics, the API and the EcoScale broadly account for other concerns such as material hazards and energy input.

Table 2. Reaction Characteristics with Associated Metrics

Reaction Attribute	Associated Metrics
High MW reagents	AE, RME, PMI
Excess reagents	API, RME, PMI
High yield	RME, PMI, EcoScale
Use of a catalyst	API, PMI, EcoScale
Excess solvent	API, PMI
Minimal workup	API, PMI, EcoScale
Excess auxiliary materials	API, PMI, EcoScale
Prolonged reflux	API, EcoScale
Hazardous reagents	API, EcoScale
Minimal byproduct	API, AE

Students were asked to consider the usefulness of the metrics without any prior discussion indicating that process mass intensity is used often by the pharmaceutical industry.[41] All students, however, identified process mass intensity as the most comprehensive mass metric. The general reasoning for this consensus was the "quantitative accounting for all of the materials" used in a reaction from setup to workup. Both atom economy and reaction mass efficiency do not factor solvents and auxiliary materials into the calculations. Reaction features not captured by PMI included "elevated reaction temperatures or water used in the reflux condenser." The API and the EcoScale, however, capture such aspects and, when used in conjunction with PMI, offer a more complete assessment of a reaction's greenness. The API and the EcoScale by themselves do not offer a complete assessment, moreover, because they are largely qualitative. For example, using the API, a reaction is penalized the same regardless of whether it uses a reactant in 11% excess or 100% excess. Likewise, using the EcoScale, students noted that the point distribution was arbitrary. For example, a reaction heated to reflux for 2 h is penalized the same as a reaction heated to reflux for 24 h.

Cost projections for the syntheses of a kilogram of the amide product were conducted by scaling the isolated yield data for each route (see the Supporting Information). The best possible prices from the Sigma-Aldrich Web site[42] were used, but students were also encouraged to look for alternative suppliers in their own lab reports. Table 3 shows representative data for a cost projection.

Table 3. Costs for Reagents for the Synthesis of a Kilogram of the Amide Product

Reagent[a]	Acid Chloride Method[b]	HATU Method[c]	Boric Acid Method[d]
Benzylamine	$220.91	$75.42	$77.13
Hydrocinnamic acid	$488.84	$317.90	$310.33
DMF	$7.32	$951.55	[e]
CH_2Cl_2	$2259.13	[e]	[e]
Oxalyl chloride	$209.53	[e]	[e]
HATU	[e]	$35759.26[f]	[e]
i-Pr_2NEt	[e]	$302.76	[e]
Boric acid	[e]	[e]	$0.45
Toluene	[e]	[e]	$401.16
Workup[g]	$1723.01	$1739.22	$1633.67
Total	$4908.72	$39146.12	$2422.74

[a]Best prices (in U.S. dollars) from Sigma-Aldrich Web site used: see ref 41. [b]Projected using 7.75 mol of hydrocinnamic acid. [c]Projected using 5.04 mol of hydrocinnamic acid. [d]Projected using 4.91 mol of hydrocinnamic acid. [e]Not used in this method. [f]Available at lower cost elsewhere. [g]See the Supporting Information.

The boric acid route was one-half as expensive as the acid chloride route and 16 times less expensive than the HATU route. Students often noted the high cost of the coupling reagent. Students were able to find alternative suppliers for HATU ($1.40/g at Oakwood Products, Inc.), but the rank order of cost for the methods did not vary with this substitution (see the Supporting Information). Separating out the workup in these calculations lets students see how large of an impact such procedures have.[43] For example, the workup cost for the boric acid route is over twice as great as the cost of materials required for the reaction itself!

In formal lab reports, many students reported a predisposition that assumed that a greener process would necessitate higher costs. While this estimation is by no means all-inclusive of costs associated with an industrial process, this exercise was able to show that the economic interests of chemical industry are not necessarily at odds with the aims of green chemistry, and that research into greener methods could be beneficial to both financial and environmental concerns. In a postlab question asking students to suggest research aims that could further improve amide-bond formation, many proposed the discovery of a low-cost catalyst capable of promoting amide-bond formation at room temperature.[8] Such an endeavor is influenced by mass-based metrics and qualitative metrics alike.

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CONCLUSIONS

Amides have importance across a number of chemical fields, and the search for greener synthetic methods is an active area of research. Upper-division students performed three types of amide-bond-forming reactions and evaluated each using green chemistry metrics. Students identified the boric acid catalyzed route as the greenest and least expensive. The HATU route was high yielding, but ultimately not sustainable considering both the metrics and costs. The acid chloride route's major detractions were the hazards associated with forming the acid chloride and the excessive use of organic solvents. Process mass intensity was seen as a comprehensive mass metric, but more qualitative metrics such as the API or the EcoScale were necessary to capture chemical hazards or energy input. The open-ended discovery nature of the experiment allowed students to make data-based conclusions regarding green chemistry and exposed them to the cost considerations of the methods investigated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00090.

Instructions for students, student questions, instructor notes, CAS registry numbers, and ^{1}H NMR spectra (PDF, DOCX)

Instructions for students and student questions (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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