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Laboratory Experiment

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Assessing Process Mass Intensity and Waste via an *aza*-Baylis–Hillman Reaction

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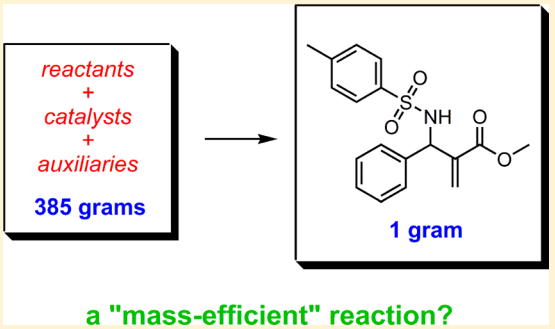
Supporting Information

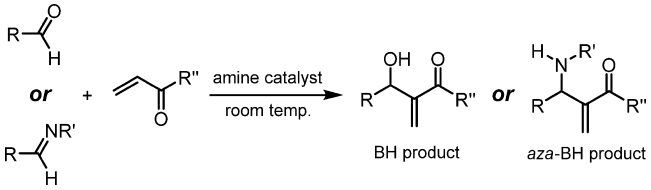
ABSTRACT: A synthetic procedure is outlined where upper-level undergraduate organic chemistry students perform a two-week, semimicroscale *aza*-Baylis–Hillman reaction to generate an allylic sulfonamide product. Students evaluate several green chemistry reaction metrics of industrial importance (process mass intensity (PMI), E factor, and reaction mass efficiency) and specifically learn the pivotal role that PMI plays in improving operational sustainability. Advantages and disadvantages of the various metrics are highlighted within the context of a multicomponent transformation eliciting current research activity.



KEYWORDS: *Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Addition Reactions, Aldehydes/Ketones, Catalysis, Esters, Green Chemistry, Synthesis*

The Baylis–Hillman (BH) and *aza*-Baylis–Hillman (*aza*-BH) reactions are currently of great interest as atom-efficient transformations under mild conditions that form multifunctional products.[1−4] In general terms, an α,β-unsaturated carbonyl compound is usually reacted with an aldehyde (BH) or an aldimine (*aza*-BH) under catalytic conditions to yield an allylic alcohol or amine (Scheme 1). The

Scheme 1. Generalized Baylis–Hillman and *aza*-Baylis–Hillman Reactions



industrial relevance of a BH reaction is exemplified within the Pfizer synthesis of sampatrilat, a vasopeptidase inhibitor prescribed as an antihypertensive.[5] In addition, the BH reaction between methyl acrylate and 4-pyridinecarboxaldehyde utilizing 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst has been described from a pedagogical perspective.[6] The *aza*-BH reaction can be undertaken as a multicomponent process if the aldimine is catalytically generated in situ (rather than being preformed),[7,8] adding a further environmentally friendly aspect. As such, these conversions showcase several fundamental green chemistry principles[9] of pertinence to college and university organic curricula.

There has recently been movement to incorporate the computation of various "green" metrics into undergraduate synthetic experiments.[10] Several procedures involve highlighting exceptional atom economy (AE) eq 1 as a guiding principle of green chemistry.[9,11,12] However, this specific metric is not viewed as being useful from a stand-alone perspective by the pharmaceutical industry.[13]

$$\text{AE: } \frac{M\text{ of desired product}}{\sum (M\text{ of reactants})} \times 100 \quad (1)$$

Of more significance are the notions of reaction mass efficiency (RME;[14] eq 2) and reaction E factor[15] (eq 3). It has been stated that "reaction mass efficiency combines key elements of chemistry and process and represents a simple, objective, easily derived and understood metric for use by chemists, process chemists or chemical engineers".[13] A reaction E factor provides a gauge of how much waste is formed by a process compared to the amount of isolated product.

$$\text{RME: } \frac{\text{actual mass of product}}{\sum (\text{mass of reactants utilized})} \times 100 \quad (2)$$

$$\text{E factor: } \frac{\text{mass of waste}}{\text{actual mass of product}} \quad (3)$$

Despite the usefulness of these two metrics, the one most highly regarded by many companies is that of *process mass intensity* (PMI) in eq 4. PMI has been chosen by the pharmaceutical industry (through the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable) as the mass-based green chemistry metric of choice.[16,17]

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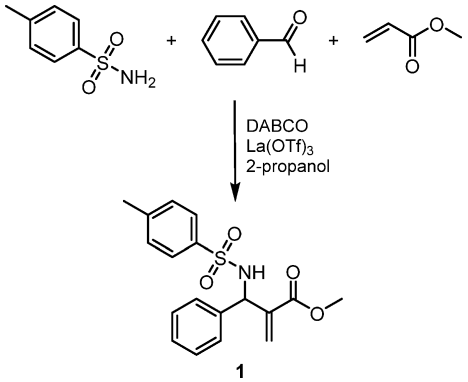
$$\text{PMI:}\ \frac{\text{mass of all input materials}}{\text{actual mass of product}} \quad (4)$$

When calculating PMI, all substances used in the reaction, workup and isolation including reactants, reagents, catalysts, solvents, drying agents, and workup and purification solvents are considered. The ideal PMI value is, therefore, unity (i.e., all utilized materials are combined into the final product or, alternatively, those that are not are recycled for further use). Although several undergraduate teaching experiments have included RME and E factor calculations as part of their studies,[18] the key PMI metric has rarely been integrated into an organic reaction analysis from a practical perspective.[10]

A two-week, semimicroscale synthetic experiment was designed and introduced into "Organic Synthesis Techniques," a third-year undergraduate course with a foundational theme of green chemistry.[19] The overarching objective was for students to evaluate an organic procedure critically in terms of various mass metrics of priority to the pharmaceutical industry, with an emphasis on PMI. In doing this, an *aza*-BH reaction modeled on one reported in the primary literature[8] was used as a teaching tool, particularly in the context of material inputs and waste. The specific methodology was chosen to highlight a "typical" research protocol, with a multicomponent reaction taking place between methyl acrylate, benzaldehyde, and *p*-toluenesulfonamide to form (methyl 2-methylene-3-[(*p*-toluenesulfonyl)amino]-3-phenylpropanoate (**1**, Scheme 2).

Scheme 2. Student Synthesis of Methyl 2-Methylene-3-[(*p*-toluenesulfonyl)amino]-3-phenylpropanoate via an *aza*-Baylis–Hillman Reaction



This was followed by dichloromethane extraction and aqueous washing/drying of the organic layer as part of product isolation. The *aza*-BH reaction undertaken had an intrinsic atom economy of 95% and featured dual catalysis by DABCO and lanthanum(III) triflate, a green Lewis acid.[20] Despite these qualities, students were charged with proposing experimental changes to improve the environmental profile of their work, bearing in mind results of the green metric calculations.

EXPERIMENTAL OVERVIEW

Students work individually. In addition to the reactants and catalysts, quantities of auxiliary materials used (reaction and extraction solvents, water, aqueous wash solutions and drying agents) are carefully measured throughout the experiment. During the first 2 h practical session, *p*-toluenesulfonamide, DABCO, $La(OTf)_3 \cdot H_2O$, molecular sieves and 2-propanol are combined in an Erlenmeyer flask. Benzaldehyde and methyl acrylate are added and the reaction mixture stirred at room temperature for 90 min. The flask is placed in an equipment locker until the second 4 h laboratory session (either one or 2 weeks later) when molecular sieves are removed by gravity filtration. Any unreacted imine is hydrolyzed under acidic conditions and the *aza*-BH product **1** is extracted with dichloromethane. The combined organic layers are washed with saturated aqueous $NaHCO_3$, aqueous NaOH, saturated aqueous NaCl, and dried with $MgSO_4$. The extraction solvent is evaporated under vacuum to generate **1** as a colorless oil in typical yields of 20–80% (0.35–1.38 g, average student yield 59%, literature yield 80%).[8] An IR spectrum (neat) and ^{1}H NMR spectrum are obtained.

HAZARDS

Appropriate gloves, safety goggles, and a laboratory coat should be worn at all times throughout this experiment. *p*-Toluenesulfonamide causes severe eye irritation. DABCO is a flammable solid that is harmful if ingested and is a skin/respiratory tract irritant. Lanthanum(III) trifluoromethanesulfonate hydrate is irritating to the eyes, respiratory system, and skin. Benzaldehyde causes skin, eye, and respiratory tract irritation and is acutely toxic if swallowed. Methyl acrylate is highly flammable and toxic if swallowed, exposed to skin contact, or inhaled. 2-Propanol and methanol are highly flammable and irritating to the eyes and respiratory system. Dichloromethane causes skin, eye, and respiratory tract irritation and may be harmful if inhaled, swallowed, or absorbed through the skin. Aqueous sulfuric acid, aqueous sodium hydroxide, and $CDCl_3$ may cause chemical burns. $CDCl_3$ also causes irritation of the skin/respiratory system and is a possible carcinogen. Methyl 2-methylene-3-[(*p*-toluenesulfonyl) amino]-3-phenylpropanoate is an eye and skin irritant.

DISCUSSION

Process Mass Intensity Calculations

The experiment described herein was successfully performed by over 100 upper-level organic chemistry students during a three-year period. Formal reports included detailed PMI calculations for the *aza*-BH reaction that produced a typical value of 385 (assuming a product mass of 1.0 g), and an appraisal regarding the benefits of PMI as a metric. This number can be interpreted as 385 g of input substances needed to form 1.0 g of **1**. A breakdown indicating the relative nature of this material is shown in Figure 1. As PMI is defined as the total mass of input material divided by the mass of the obtained product, calculated student values were dependent on individual reaction yields, and varied between 279 and 1100 (taking into account the range of product yields from 20 to 80%). Although not specifically used by the undergraduates in this experiment, a

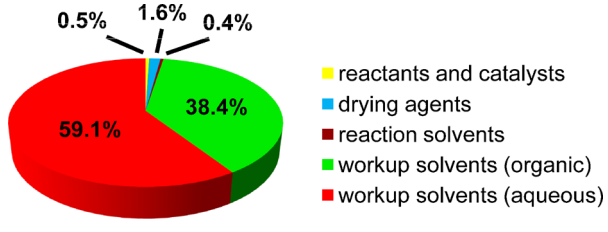


Figure 1. Summary of input material required to synthesize 1.0 g of **1**.

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useful online PMI calculation spreadsheet has been highlighted.[21]

It is dramatically clear from Figure 1 how much the reaction workup contributes to the input mass (over 97% when combining organic and aqueous solvents). In comparison, solvents (56%) and water (32%) are the major mass contributors to the types of materials used to synthesize active pharmaceutical ingredients.[16] A lack of workup consideration within the realm of "green" assertions has recently been reported.[22] The PMI metric is advantageous in this regard because neither AE nor RME include auxiliary materials necessary for the reaction and product isolation and purification. Calculation of PMI is also seen as a "front-end" approach, and that "to truly integrate green chemistry and engineering into chemical processes, one has to look at the inputs instead of the outputs".[16] It is inherently straightforward for a chemist to quantify accurately what is added during a laboratory procedure (assuming effective notebook documentation), and mass/energy inputs are primary metrics for designing new pharmaceuticals. Leahy et al. have stated chemical industry median PMI values of 433 for preclinical candidates and 68 for commercial products, and that GlaxoSmithKline have a manufacturing PMI target of 20 for the year 2015.[23] In a separate publication, the average solvent usage was 55 kg per kg product (range of 10−170) for 21 pharmaceutical products.[24]

Reaction Waste

Students were also able to assess the amount of waste generated by the *aza*-BH transformation by computation of the reaction E factor, where the ideal value is zero (i.e., no waste is formed). In contrast to PMI, water has historically not been included in E factor calculations, as doing so led to exceptionally high values that were problematic to compare for different processes.[15] Student E factor values varied between 130 and 516 (excluding the amount of water used). When 1.0 g of **1** was obtained as a representative mass, the calculated E factor was 180. A "waste inventory" summary of the performed *aza*-BH reaction is shown in Figure 2.

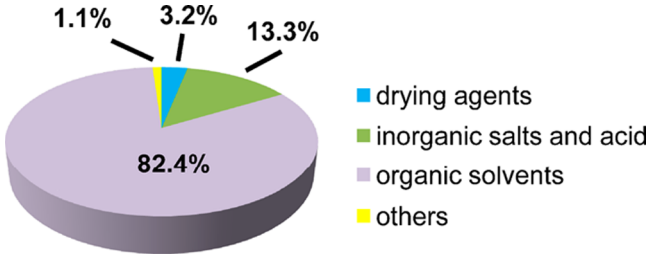

Figure 2. Summary of waste produced during student synthesis of **1** (1.0 g, water excluded, E factor = 180). "Others" includes unreacted starting materials and catalysts.

If water is eliminated from the waste analysis, an "average" student E factor of 180 can be checked against literature values for different industry sectors. The fine chemicals industry segment has an E factor range of 5−50 kg waste/kg product, whereas the range for the pharmaceutical segment is 25−100 kg waste/kg product.[15] Students appreciated that this placed their synthesis outside these dimensions in terms of waste production and that water was not accounted for. The point was also underscored that the majority of nonaqueous waste came from organic solvents, and primarily from the workup rather than reaction itself. If water was considered, calculations showed it contributed over 53% of the total waste mass. Measurements based on water consumption are seen as increasingly important,[25] as evidenced by a 2012 survey of 18 chemical manufacturers indicating that "water usage" was a widely implemented green chemistry-related metric.[26]

Every class was required to critique each metric in terms of its apparent disadvantage(s). One student criticism made of the E factor is that it focuses on what is left at the end of a process in terms of desired material and waste and is, therefore, a "lagging" rather than a "leading" concept. The point has been made that a proactive metric, such as PMI, holds superiority over a waste metric by increasing efficiency, rather than managing costs.[25] An extension is that the nature of the waste is generally not considered by the E factor: 1 kg of NaCl is viewed in exactly the same way as 1 kg of NaCN. An "environmental quotient" (EQ) was introduced by Sheldon to manage this aspect where an "unfriendliness" Q value was assigned to each waste compound and then multiplied by a process E factor.[15] In the same way, the PMI metric treats all input materials as being equivalent in terms of their environmental impact and toxicological effects.

Student Improvements

Having determined and interpreted several industrially relevant green metrics, students were expected to propose ways in which the *aza*-BH reaction might be enhanced in terms of sustainability. Responses to this question largely indicated that students realized the reaction workup should be targeted. Many suggestions focused on reducing the PMI (and E factor) by different means. These included ideas such as lowering the quantity of aqueous wash solutions/recycling them for future students (or sharing solutions between the class on a given laboratory day), reducing the amount of dichloromethane used during product extraction, or replacing this solvent with a greener alternative (e.g., 2-methyltetrahydrofuran) that could potentially be recycled.[27] It should be noted that complete recycling of the aqueous wash solutions would still not lower the reaction E factor to that typically observed in the pharmaceutical industry.[15] Crucially, very few students gave attention to the reaction itself in terms of mass metrics. Calculation of a characteristic RME (55%, based on a product mass of 1.0 g and an atom economy of 95%) indicated inefficiency due to the moderate reaction yield. However, improving the yield to 100% (or adopting other strategies such as attempting to recycle the catalyst/reaction solvent) would have little to no effect on the PMI or E factor. Some students made the meaningful point that mass-based metrics should ideally be used as part of a more-encompassing life-cycle assessment, which permits estimation of the cumulative environmental impacts associated with a given process or product across its entire life cycle.[28,29]

■ CONCLUSION

A standard organic research literature procedure was adapted for the teaching laboratory in order to demonstrate principles of process mass and waste review.[8] Notably, the authors of this paper did not make any "green" claims about the reported chemistry, so students were faced with the experimental investigation and discussion without any preconceptions. The actions of (i) accurately measuring quantities of all input materials and (ii) calculation of personal metrics based on the isolated product yield had a positive impact regarding

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appreciation of how much mass was utilized. Students acknowledged that although a reaction itself may appear intrinsically green (high atom economy, use of catalysis, etc.), the metrics of greatest industrial impact include a recognition of all matter used and that a routine workup can enormously contribute to waste. Consequently, chemistry program undergraduates became better-prepared to take an up-front approach to material handling when designing synthetic pathways of their own. Written reports indicated understanding of the pros and cons of different green metrics and the position of process mass intensity as the highest-regarded global mass metric by pharmaceutical companies. Although PMI is not a perfect concept, recognizing that industry now places a major focus on inputs rather than outputs represents an important paradigm shift in green chemistry training.

■ ASSOCIATED CONTENT

Supporting Information

Laboratory instructions and report requirements for undergraduates; notes for the instructor, detailed green chemistry metric calculations, *aza*-BH mechanistic considerations and representative student product spectra. 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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