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Andrew, Oliver B, Sherwood, James and Hurst, Glenn A (2022) A greener synthesis of the antidepressant bupropion hydrochloride. JOURNAL OF CHEMICAL EDUCATION. pp. 3277-3282. ISSN: 0021-9584

https://doi.org/10.1021/acs.jchemed.2c00581

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Laboratory Experiment

A Greener Synthesis of the Antidepressant Bupropion Hydrochloride

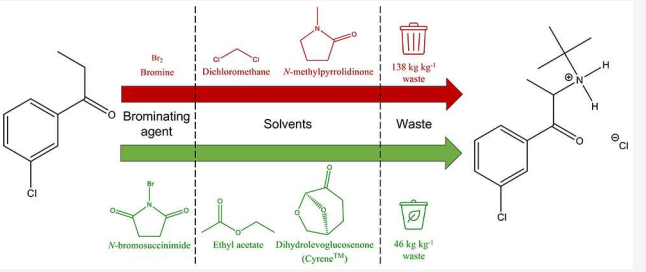
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Cite This: https://doi.org/10.1021/acs.jchemed.2c00581

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ABSTRACT: A laboratory experiment was developed to introduce systems thinking and green chemistry concepts through the synthesis of the antidepressant and smoking cessation aid, bupropion hydrochloride. The traditional synthesis has several issues from a green chemistry perspective: it uses the toxic solvents *N*-methylpyrrolidinone (NMP) and dichloromethane (DCM) and other hazardous chemicals including bromine and 12 M hydrochloric acid resulting in 138 kg of waste per kg of product. A greener synthesis has been developed with suitable improvements to the traditional procedure. The reprotoxic NMP and potentially carcinogenic DCM solvents have been substituted with the green biobased solvent Cyrene and ethyl acetate, respectively, and bromine has been substituted with *N*-bromosuccinimide. An alternate extraction method has also been developed using 1 M hydrochloric acid and ethyl acetate rather than 12 M hydrochloric acid and diethyl ether. These changes have also reduced waste by 92 kg kg^{-1}, and the resultant experiment is much safer to perform. As part of this laboratory experiment, students synthesize bupropion hydrochloride, and the adaptations to the traditional process are discussed and evaluated. Students are also introduced to the green metrics of atom economy, process mass intensity, and *E*-factor, which they use to quantify the greenness of the original and adapted procedures.



KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Hands-On Learning/Manipulatives, Green Chemistry, Synthesis*

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INTRODUCTION

There is an increasing pressure to develop sustainable manufacturing methods in the chemical industry to ease adverse effects on both human health and the environment.[1] A significant cause of this impetus for change is the United Nations Sustainable Development Goals (UN SDGs),[2] which were established to provide a framework of goals to tackle major global issues such as poverty, inequality, and sustainability. To best achieve the UN SDGs, it is vital to introduce concepts of sustainability early within chemistry education so that future chemists have the tools and mindset required to support sustainable practices. Using a systems thinking approach is particularly useful, making students think more holistically about processes and how they link to sustainability. Various approaches to incorporating systems thinking into green chemistry education have been reported,[3] including the development of a program of interactive workshops,[4] a competitive strategy card game,[5] and a new green chemistry curriculum to be used in an organic teaching laboratory.[6] A laboratory setting is useful for teaching green chemistry as it provides the opportunity to adapt existing content to introduce green chemistry concepts while allowing students to continue to develop their laboratory skills, without the need to add material to an already substantial core curriculum. Numerous laboratory experiments have been developed with this in mind, including an experiment focused on the valorization of waste orange peel,[7] an experiment showing the green reductive regioselective opening of epoxides,[8] and a demonstration on the valorization of sour milk to form a bioplastic.[9]

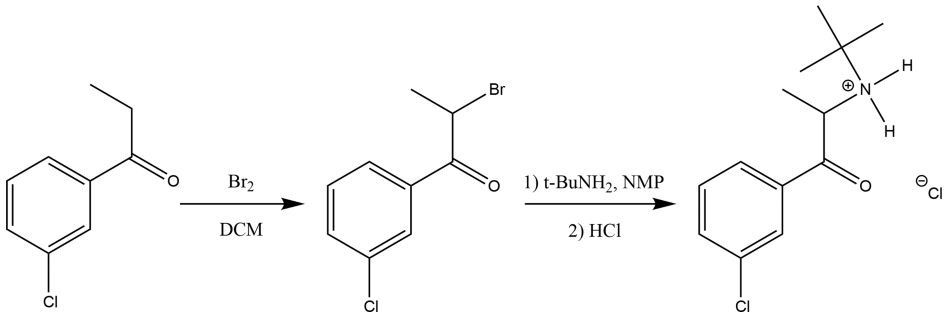
To introduce sustainable chemistry to undergraduate students, here we describe an experiment based on the synthesis of the common antidepressant and smoking cessation aid bupropion hydrochloride ((±)-2-(t-butyl-amino)-3′-chloropropiophenone). Marketed under the name Wellbutrin,[10] bupropion has been shown to be an effective antidepressant acting as a dopamine-norepinephrine reuptake inhibitor.[11,12] Chemically unrelated to typical antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors), bupropion manages to avoid the common adverse side effects of sexual dysfunction, weight gain, and somnolence.[13,14] Sold under the name Zyban,[15] bupropion is also applicable as a smoking cessation aid.[16] In 2019, bupropion was the 22nd

Received: June 14, 2022
Revised: August 10, 2022

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Scheme 1. A Previously Reported Synthesis of Bupropion Hydrochloride[20]



most prescribed drug in the US[17] and has since been added to the World Health Organization Model List of Essential Medicines.[18] An unfortunate reality is that many students suffer from mental health illnesses and many also smoke. This does however provide the opportunity to connect what is being taught to everyday life and could provide motivation for students who may find the experiment more interesting as a result. Context-based learning has been shown to raise the motivation of students, who engage with the content more.[19]

Bupropion hydrochloride is synthesized in a two-step process by brominating *m*-chloropropiophenone followed by amination with *tert*-butylamine and precipitating as its hydrochloride salt (as shown in Scheme 1), and it has already been reported as a suitable organic laboratory experiment.[20] However, from a green chemistry perspective, there are several issues with the synthesis of bupropion hydrochloride. The reprotoxic solvent *N*-methylpyrrolidinone (NMP) is used, which is now restricted by the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation.[21] Dichloromethane (DCM) is also used, despite being a suspected carcinogen. Other hazardous substances are also required, including elemental bromine (fatal if inhaled), 12 M hydrochloric acid (corrosive), and diethyl ether (extremely flammable and forms explosive peroxides). The quantity of waste produced by the reaction was determined using the green metric, *E*-factor, which includes all reaction masses except water to calculate the waste produced and is shown in eq 1. It was found that 138 kg of waste is produced per kg of product following the traditional synthesis route, whereas 25−100 kg kg^{-1} is typically produced on average in pharmaceutical industry processes.[22]

$$E\text{-factor} = \frac{\text{total waste (kg)}}{\text{mass of product (kg)}} \quad (1)$$

The laboratory experiment reported herein is suitable for implementation in an undergraduate teaching lab and can be used to introduce aspects of green chemistry while providing additional experience with synthetic techniques such as reflux and recrystallization. This can be applied for students studying chemistry modules and is designed for second year students, although it can be adapted for different levels of understanding. In this work, the laboratory experiment was implemented with 16 natural sciences students specializing in chemistry as part of a transitionary summer activity between year 1 and year 2.

INSTRUMENTATION

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Jeol ECS-400 NMR spectrometer (400 MHz ^{1}H, 101 MHz ^{13}C) at ambient temperature in D_2O. ^{1}H NMR spectra were referenced to the solvent signal at 4.79 ppm. Infrared (IR) spectra were obtained using a PerkinElmer FTIR/FTNIR Spectrum 400 between 600 and 4000 cm^{-1}.

Gas chromatography (GC) was performed using an Agilent Technologies Hewlett-Packard 6890 GC, with a flame ionization detector (GC-FID) fitted with a Rxi-5HT capillary column (30 m × 250 mm × 0.25 mm nominal, max temperature 400 °C). Samples were dissolved in ethanol and filtered through a nylon filter. Helium was used as the carrier gas at a flow rate of 2 mL/min with a split ratio of 30:1 and a 5 μL injection. The initial oven temperature was 50 °C and was increased at a rate of 30 °C/min to 300 °C and held at this temperature for 5 min, with a total run time of 13.3 min. Injection temperature was 250 °C, and the detector temperature was 250 °C.

MATERIALS

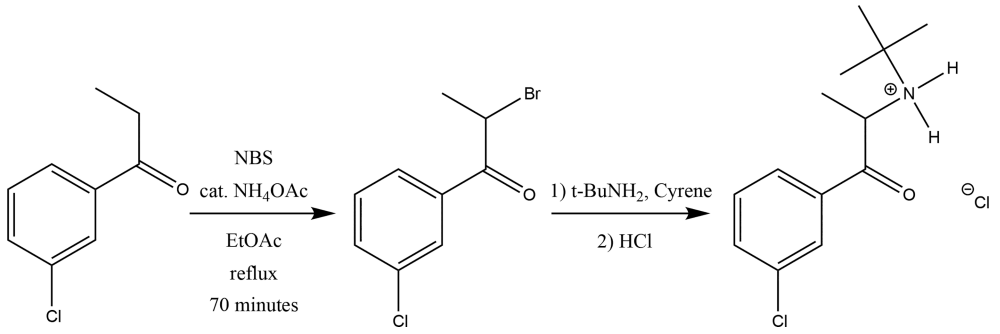
m-Chloropropiophenone (CAS 34841-35-5) was purchased from Acros Organics. *N*-Bromosuccinimide (CAS 128-08-5) and *tert*-butylamine (CAS 75-64-9) were purchased from Aldrich. Ammonium acetate (CAS 631-61-8) was purchased from Alfa Aesar. Ethyl acetate (CAS 141-78-6) and hydrochloric acid (CAS 7647-01-0) were purchased from Fischer Scientific. Cyrene (CAS 53716-82-8) was purchased from Circa. Propan-2-ol (CAS 67-63-0) was purchased from Sigma-Aldrich. All chemicals were used as received, except hydrochloric acid which was diluted to 1 M.

EXPERIMENTAL SECTION

m-Chloropropiophenone (0.5 g, 2.95 mmol) and *N*-bromosuccinimide (1.23 g, 6.93 mmol) were dissolved in EtOAc (5 mL). Ammonium acetate (0.024 g, 0.295 mmol) was added, and the solution was heated to reflux until the red bromine color disappeared after approximately 70 min. The solution was cooled to room temperature, filtered, and washed with water (10 mL). The EtOAc solvent was removed under reduced pressure affording an orange-brown oil. The conversion of step 1 was obtained by analyzing a sample of the intermediate using GC, dissolving the sample in ethanol. Cyrene (2.5 mL) and *tert*-butylamine (2.5 mL) were added, and the solution was stirred at 55−60 °C for 20 min. The solution was dissolved in EtOAc (15 mL) and washed with water (15 mL × 3). Hydrochloric acid, 1 M (12 mL), was added to the organic layer, which was separated after stirring. The aqueous layer was concentrated under reduced pressure affording an orange-brown paste. The residue was then crystallized from propan-2-ol (approximately 1 mL), before the crystals were collected via vacuum filtration, obtaining an

https://doi.org/10.1021/acs.jchemed.2c00581
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Scheme 2. A Greener Synthesis of Bupropion Hydrochloride



average yield of 68%. The product was then characterized by ^{1}H and ^{13}C NMR and IR spectroscopic analysis.

^{1}H NMR: (400 MHz, D_2O) δ ppm 8.04 (d, J = 1.83 Hz, 1 H, Ar−H), 7.96 (dd, J = 7.79, 0.92 Hz, 1 H, Ar−H), 7.70 (d, J = 7.79 Hz, 1 H, Ar−H), 7.52 (td, J = 7.79, 1.23 Hz, 1 H, Ar−H), 5.14 (q, J = 7.19 Hz, 1 H, CH), 1.56 (d, J = 6.87 Hz, 3 H, CH_3), 1.31 (s, 9 H, $-C(CH_3)_3$).

^{13}C NMR: (101 MHz, D_2O) δ ppm 196.20 (C═O), 135.42 (Ar−C), 135.03 (Ar−C), 133.22 (Ar−C), 130.90 (Ar−C), 128.90 (Ar−C), 127.48 (Ar−C), 58.99 ($-\underline{C}(CH_3)_3$), 53.68 (CH), 25.38 ($-C(\underline{C}H_3)_3$), 17.65 (CH_3).

IR: ν_{max} (cm^{-1}) 1689 (−C═O), 1559 (−N−H).

HAZARDS

All steps should be carried out in a fume hood. *N*-Bromosuccinimide is suspected of causing genetic defects, is very toxic to aquatic life, and may cause an allergic skin reaction. *tert*-Butylamine is toxic if inhaled, and 1 M HCl causes severe skin burns and eye damage and may be corrosive to metals. Ethyl acetate and propan-2-ol are both highly flammable, cause eye irritation, and may cause drowsiness. Cyrene causes serious eye irritation. *m*-Chloropropiophenone and ammonium acetate are both not hazardous substances. The product bupropion hydrochloride is harmful if swallowed.

DEVELOPING A GREENER SYNTHESIS

While independent from the UN SDGs, the 12 Principles of Green Chemistry have similar aims, providing a holistic set of tenets designed to aid chemists in achieving sustainability within chemistry through careful design.[23,24] Following these Principles of Green Chemistry, the previously reported synthesis has been adapted,[20] with the aim of utilizing safer, green alternatives to the toxic solvents and chemicals, while also reducing the volume of waste produced by the reaction.

Substituting Bromine

N-Bromosuccinimide (NBS) was selected as an alternative brominating agent to bromine, following a reported method of α-bromination which used ammonium acetate as a catalyst.[23] While NBS is still a hazardous substance, it is a solid at room temperature whereas bromine vaporizes readily, meaning the significant risk from fugitive emissions is avoided by using NBS rather than bromine, especially when measuring the reagent mass prior to use. The reported procedure used carbon tetrachloride as the solvent despite having severe adverse effects on human health and the environment.[25] DCM was instead trialed as it is a common alternative to CCl_4. The reaction was incomplete after 3 h however, and only 53% conversion had been achieved, determined by GC analysis. Instead, ethyl acetate was tested as the solvent as it had already been determined to be a suitable alternative to DCM when using bromine. It was found to be an effective alternative, achieving >97% conversion of *m*-chloropropiophenone into the intermediate 2-bromo-*m*-chloropropiophenone after refluxing for approximately 70 min. For comparison, >99% conversion is achieved while following the traditional method using bromine. A longer reaction time is required for the reflux, extending the length of the experiment, although it is still possible to complete within approximately 4 h. A larger equivalent of NBS was required than that reported, finding 2.35 equiv moles to be the most effective. As NBS decomposes over time, the most effective equivalent will be affected by the purity of the NBS. The purity of the NBS used was determined to be 94% using the integration values from ^{1}H NMR analysis.

Solvent Substitution

Following the fifth Green Chemistry Principle of Safer Solvents and Auxiliaries which advises using safer green solvents where possible, the reprotoxic solvent NMP was substituted with the much less hazardous Cyrene (dihydrolevoglucosenone), a green biobased solvent.[26] Derived in a simple two-step process from cellulose,[27,28] Cyrene is a renewable alternative to toxic dipolar aprotic solvents such as NMP and DMF (which are petrochemically sourced). Cyrene has an additional benefit over NMP from a green chemistry perspective as it does not contain any nitrogen or sulfur heteroatoms, unlike NMP which contains nitrogen, thus avoiding NO_x and SO_x emissions upon incineration which would lead to atmospheric pollution.[29] Cyrene was found to be an effective solvent during the amination step, although a longer heating time of 20 min was required for the reaction to complete, whereas 10 min of heating was required for the reaction to complete when using NMP as the solvent. An educational video about Cyrene and Green Chemistry was developed by the University of York and the Universidad de Zaragoza and is available on YouTube at Green Yorgoza.[30] One potential problem with using Cyrene for teaching purposes however is that it may be more difficult to source, and it may be more expensive than NMP. However, there is currently an ongoing project to develop a 1000 T/Year Cyrene plant in France that is due to open in 2023 which will hopefully help alleviate this issue. To the authors' knowledge, this is the first reported use of Cyrene in a laboratory experiment.

Waste Minimization

Optimization of the amination was undertaken, in which reduced volumes of both Cyrene and *tert*-butylamine were tested. A high excess of *tert*-butylamine is traditionally used to reduce the reaction duration, as its steric bulk hinders the rate

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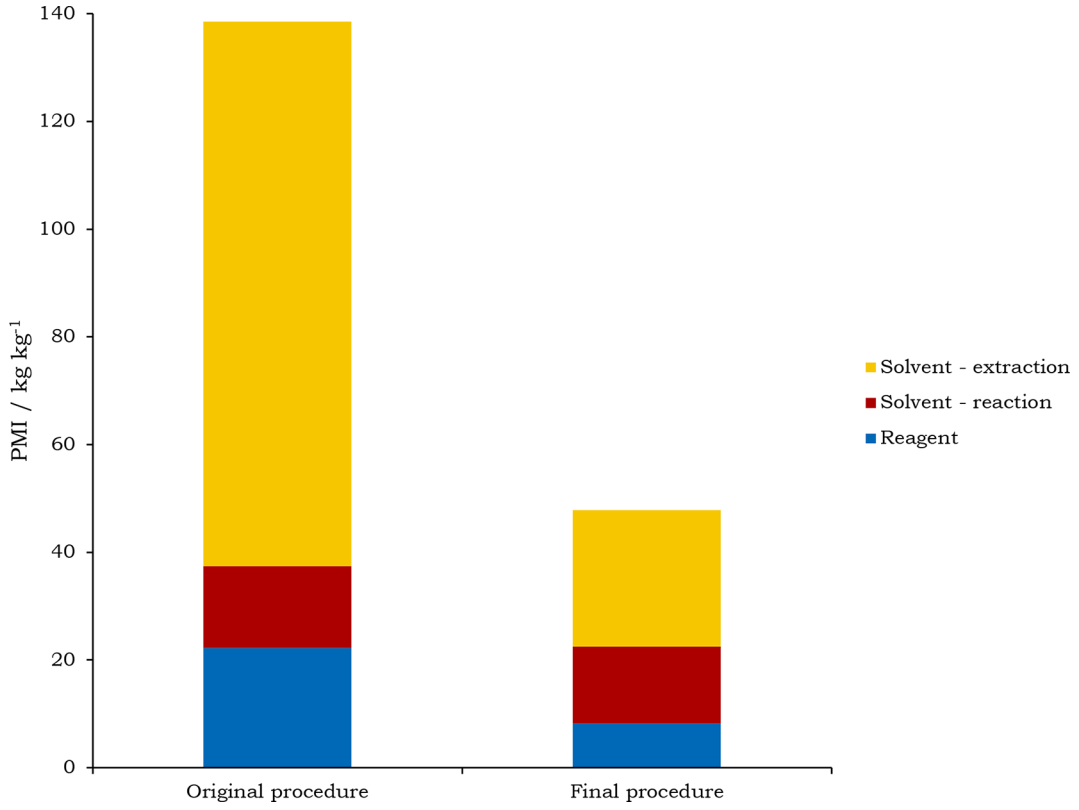


Figure 1. Comparison of the contributions to the PMI from the original and final procedures.

of reaction. Unfortunately, it was determined that the volume of neither the Cyrene nor *tert*-butylamine could be reduced significantly without resulting in a longer reaction time which would be unsuitable for an undergraduate teaching lab. However, this provides the opportunity to highlight to students that green chemistry is often rather ambiguous, seeking an acceptable compromise between unfavorable factors.

As most of the waste produced from the reaction originated from the workup procedure, an alternate method was also used. A method reported in an abandoned patent for the synthesis of bupropion hydrochloride[31] was adapted for this synthesis procedure. The method makes use of ethyl acetate and 1 M HCl, avoiding the extremely flammable diethyl ether and the hazardous 12 M HCl, making the process much safer. Additionally, a reduced number of chemical washes is required using a smaller volume of solvent compared to the original procedure, helping reduce the volume of waste produced by the reaction. To further reduce the absolute volume of waste produced as well as reduce the cost of the experiment, the scale of the reaction was reduced by 50%.

Greener Synthesis

These adaptations were collated to develop a final greener procedure as shown in Scheme 2, from which bupropion hydrochloride is synthesized with an average yield of 68% in approximately 4 h. The NMR and IR data matched that previously reported[20,32] with no impurities present and are available in the Supporting Information.

The *E*-factor was calculated and showed the waste produced by the reaction decreased by 92 kg kg^{-1}, now totaling 46 kg kg^{-1} (a reduction of 66%). The atom economy of the reaction was also calculated using eq 2, which evaluates the theoretical efficiency of a reaction by the incorporation of atoms from the reactants into the product(s) (by mass). The atom economy of the greener process was determined to be 61%, which is slightly lower than the 63% for the traditional process. This reduction is a result of substituting the bromine for NBS, which has a slightly larger molecular mass. Students can discuss whether this loss of efficiency is acceptable given the reduced hazards of NBS versus bromine. The reaction mass efficiency (RME) of the reaction was also calculated using eq 3, which makes use of the atom economy, yield, and stoichiometry to evaluate the efficiency of a reaction. The RME of the traditional process was determined to be 4%, improving to 12% for the greener method. These values are very poor and are due to the average atom economy and the high excess of *tert*-butylamine required. The different contributions to the process mass intensity (PMI) were also calculated using eq 4 and compared to those from the original process in Figure 1. PMI is similar to the *E*-factor except it analyzes the mass used by a reaction rather than the waste produced. The solvent used during the extraction has been reduced considerably by 76 kg kg^{-1} although the reagents have increased by 5.5 kg kg^{-1}. This is because an increased volume of HCl is required as it is more dilute. Additionally, all the toxic chemicals have been substituted with greener alternatives where possible, and the hazards have been further minimized by using the more benign ethyl acetate and more dilute 1 M HCl rather than the extremely flammable diethyl ether and concentrated 12 M HCl. A tabulated overview of all the changes made to the traditional synthesis procedure is shown in Table 1.

$$\text{atom economy} = \frac{\text{product molecular weight}}{\sum \text{reactant molecular weight}} \times 100 \quad (2)$$

https://doi.org/10.1021/acs.jchemed.2c00581
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$$\text{RME} = \frac{\text{mass of product}}{\text{mass of all reactants}} \times 100 \quad (3)$$

$$\text{PMI} = \frac{\text{total mass in a process or process step (kg)}}{\text{mass of product (kg)}} \quad (4)$$

Table 1. Tabulated Overview of the Changes Made to the Synthesis Procedure

	Traditional Method	Greener Method
Brominating agent	Bromine	NBS
Bromination solvent	DCM	EtOAc
Amination solvent	NMP	Cyrene
Washes	5 × water	3 × water
	3 × diethyl ether	1 × EtOAc
HCl concentration/M	12	1
Waste produced/kg kg^{-1}	138	46
Atom economy/%	63	61
Reaction mass efficiency/%	4	12

While the greenness of the reaction has improved by minimizing the waste and improving the safety of the reaction, there are some limitations of the final procedure from a green chemistry perspective. As previously mentioned, the high excess of *tert*-butylamine needed results in a loss in mass efficiency as well as an increased volume of waste produced. Additionally, the experiment requires approximately 4 h, whereas the original procedure was designed to be completed within 2 h, meaning there is a greater energy demand which conflicts with the sixth Green Chemistry Principle of designing for energy efficiency. An increased volume of process water is also needed, further worsening the environmental impact of the reaction. These limitations can be discussed with students to highlight how there is often a threshold regarding how much a process can be improved upon with some factors remaining inherently less desirable.

IMPLEMENTATION WITH STUDENTS

Once the final procedure had been developed, a series of questions were also developed for the students to complete after the experiment and are available in the student lab script. The questions aim to help students understand how the reaction works by asking the students to propose the reaction mechanism and discuss why a large excess of *tert*-butylamine is required. The students then evaluate the greenness of the reaction and the changes made using a systems thinking approach. To aid in this evaluation, students are introduced to three green metrics: atom economy, process mass intensity, and *E*-factor. Students also discuss the substitution of bromine with NBS, and which of the 12 Principles of Green Chemistry have been applied. Model answers are available in the instructor guide (Supporting Information).

As previously mentioned, the laboratory experiment was implemented with a group of first year natural sciences students specializing in chemistry. It was found that the reflux in step one was complete within 30−60 min, as opposed to the usual 70 min. This is likely due to the NBS used having a different purity compared to that used while designing the experiment, because of the degradation issue previously mentioned. There was a range of 30 min between reflux times, and this could be due to students being less accurate at the mass balance while measuring out the starting materials. From GC analysis, a high conversion was still obtained with an average of 95% conversion. Otherwise, the laboratory experiment went smoothly with the students stating that they enjoyed the experiment and the chance to learn about green chemistry. The students processed their characterization data, answered the questions relatively comprehensively, and were hence able to meet the learning objectives of the laboratory experiment.

CONCLUSION

Adaptations to the process used to synthesize bupropion hydrochloride have been made to improve the environmental impact of the reaction while reducing the hazards of the reaction such that it can safely be implemented in undergraduate teaching laboratories. This provides the opportunity to introduce systems thinking and green chemistry concepts to students while conducting an experiment already developed for an introductory organic laboratory class. The context-based learning approach of this laboratory experiment will hopefully provide motivation for the students. Students can be taught about the 12 Principles of Green Chemistry, showing how they can be implemented. The green solvent Cyrene can also be discussed, and students are introduced to and use the three green metrics: atom economy, process mass intensity, and *E*-factor. While there are still factors limiting the greenness of the reaction, e.g., 46 kg kg^{-1} of waste is still produced and an excess of *tert*-butylamine is required, these cannot be avoided to keep the protocol suitable for an undergraduate teaching laboratory. These limiting factors provide additional discussion points that can be raised with the students.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.2c00581.

Student lab script (PDF, DOCX)
Instructor guide (PDF, DOCX)
Technician guide (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acs.jchemed.2c00581
J. Chem. Educ. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

The authors wish to thank the technical team at Chemistry at York for their support, particularly Helen Burrell, Richard Gammons, and Phil Helliwell.

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https://doi.org/10.1021/acs.jchemed.2c00581
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