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Citation for the original published paper (version of record):

Blomkvist, B., Dinér, P., Qasim, W., Josephson, P., Nykvist, V. (2019)
Student-Driven Development of Greener Chemistry in Undergraduate Teaching:
Synthesis of Lidocaine Revisited
Journal of Chemical Education

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Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:kth:diva-264909>

Student-Driven Development of Greener Chemistry in Undergraduate Teaching: Synthesis of Lidocaine Revisited

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S Supporting Information

ABSTRACT: Green chemistry and sustainable development have become increasingly important topics for the education of future chemists, but the implementation of green chemistry into the chemistry curriculum requires significant efforts from teachers, especially in laboratory education. A student-driven development of a greener synthesis of Lidocaine was performed by three first-cycle, third-year students as a part of their B. Sc. degree project with the goal to implement the procedure in an under-graduate organic chemistry course. The students were merely provided with the framework for the project and were given the opportunity to independently develop the project based on an analysis of the 12 principles of green chemistry. The “greenification” of the Lidocaine synthesis by the three students led to several green improvements of the standard procedure, for example, (1) decreased reaction temperature, (2) solvent replacement, (3) fewer equivalents of the starting material (diethylamine) by the use of an inorganic bulk base, (4) use of catalytic amounts of potassium iodide to promote the Finkelstein reaction, and (5) a two-step one-pot procedure. Furthermore, one of the developed procedures was successfully implemented in a full-scale organic chemistry laboratory course.

KEYWORDS: First-Year Undergraduate/General, Second-Year Undergraduate, Organic Chemistry, Green Chemistry, Reactions

INTRODUCTION

Recently, the United Nations have declared the 2030 Agenda for Sustainable Development to achieve a sustainable future for the planet.¹ In the same manner, academic universities such as KTH – Royal Institute of Technology have implemented policies to drive both education and research toward more sustainable development,² but the implementation into the educational system is often a slower and more tedious process. Different approaches have already been implemented to introduce the 12 principles of green chemistry³ into the curriculum including several “green” case studies,^{4,5} green chemistry laboratory exercises,^{6–8} courses in sustainability or green chemistry,^{9–12} and introduction of green chemistry undergraduate research into the curriculum.^{13,14}

The development of new laboratory courses with green chemistry content is often time-consuming and therefore also expensive, and often too little time and resources are allocated by the universities to drive this development forward. However, it would be more efficient and beneficial to let undergraduate students within the universities’ education

programs (B. Sc. and M. Sc.) develop green chemistry experiments as part of their degree projects, with a clear goal of implementing the procedures into the undergraduate education. In this way, students performing their undergraduate degree projects are trained in green chemistry development. Additionally, greener organic chemistry procedures can be implemented in future undergraduate teaching without overwhelming efforts from the faculty teachers. To exemplify this approach, three B. Sc. students developed three alternative, green protocols for the synthesis of Lidocaine, of which one was successfully implemented in a first-year undergraduate organic chemistry course.

PROJECT DESIGN

The B. Sc. degree projects are mandatory for all students within the educational programs (B.Sc. and M. Sc.) in

Received: August 17, 2018

Revised: April 15, 2019

Published: May 15, 2019

Chemical Engineering and Biotechnology at KTH – Royal Institute of Technology. The B. Sc. degree project extends over the whole semester (January–May) but runs at a 50% study pace, and thus, the project corresponds to half of a semester of studies (15 ECTS out of 30 ECTS). The synthesis procedure chosen for the project was the synthesis of Lidocaine, which is a popular procedure used in organic chemistry course laboratories around the world with about 50 000 hits on Google for a search on “synthesis of lidocaine”.

On an initial meeting, three students were given the task to “greenify” the synthesis of Lidocaine with respect to the 12 principles of Green Chemistry, as shown below:³

1. Prevention.
2. Atom Economy.
3. Less Hazardous Chemical Syntheses.
4. Designing Safer Chemicals.
5. Safer Solvents and Auxiliaries.
6. Design for Energy Efficiency.
7. Use of Renewable Feedstocks.
8. Reduce Derivatives.
9. Catalysis.
10. Design for Degradation.
11. Real-time analysis for Pollution Prevention.
12. Inherently Safer Chemistry for Accident Prevention.

The starting point for the project originated from the procedure by Reilly in this *Journal*,¹⁵ which is a modified procedure based on the original patent.¹⁶ One week later, the students presented their ideas regarding the modifications of the literature procedure. Previously, positive results have been obtained by requiring students to apply acquired knowledge, for example, by critically assessing literature procedures.^{17–20} During the second meeting, several different green aspects of the synthesis were discussed between the students and the supervisor, and the following modifications were proposed to be tested, as shown below:

- “Greener” solvents including solvents from biosourced feedstocks (principle 7).
- Decreased reaction temperature (principle 6).
- Use of catalytic amounts of potassium iodide to promote a Finkelstein reaction (principle 9).
- Different inorganic bases instead of large excess of diethylamine (principle 2).
- Two-step one-pot procedure (principles 2 and 9).

All of these modifications were performed by the three B. Sc. students to achieve greener and overall more efficient procedures that can be implemented in a 5 h laboratory session in a first- or second-year undergraduate course. Our green developments differ clearly from previous greenifications of the synthesis of Lidocaine by Goodwin and co-workers²¹ and by Jeffrey and co-workers,^{22,23} which mostly focused on using neat conditions, that is, only diethylamine as solvent, and microwave irradiation for heating, which is less suitable for the course laboratory.

RESULTS AND DISCUSSION

Student-Based Optimization of Reaction Conditions in Synthesis of 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide

Screening of “Greener” Solvents. The starting material used in the S_N2 -reaction, *N*-(2,6-dimethylphenyl)-chloroacetamide was either synthesized according to the

procedure of Reilly and used without further purification, or was purchased from commercial sources.¹⁵ The full strategy for the B. Sc. project is outlined in the [Supporting Information \(p S2, Scheme S1\)](#). The initial screening of reaction conditions investigated alternative solvents to replace the fossil fuel-derived solvent toluene utilized in the original procedure. Ten different solvents were tested including more or less green, polar protic, and polar aprotic solvents, which are also known to efficiently promote the S_N2 -reaction according to the Finkelstein reaction ([Scheme 1](#)).

Scheme 1. Reaction Conditions: *N*-(2,6-Dimethylphenyl)chloroacetamide (0.1 mmol), Diethylamine (3 equiv), KI (0 or 10 mol %), Solvent (0.1 mL), 1 h, Oil Bath Temperature^a

^aEtOAc = ethyl acetate; CPME = cyclopentyl methyl ether; TBME = *tert*-butyl methyl ether; PEG-300 = polyethylene glycol ether; 2-methyl-THF = 2-methyl-tetrahydrofuran; MeOH = methanol; *t*-BuOH = *tert*-butanol; THF = tetrahydrofuran; MeCN = acetonitrile.

The reactions were initially performed in closed microwave vials (0.1 mmol scale) using three equivalents of diethylamine heating to the indicated temperature in an oil bath without addition of potassium iodide ([Scheme 1](#)). Of the ten tested solvents, only PEG-300 (93%) and glycerol (95%) gave high conversions similar to toluene (95%) under the chosen reaction conditions ([Supporting Information, p S4, Table S2, entries 1, 10–11](#)). The reaction proceeded well in acetonitrile (83%) and *tert*-butanol (79%) ([p S4, Table S2, entries 2 and 6](#)), while the other solvents gave less than 50% conversion ([Supporting Information, p S4, Table S2](#)). From the screening in microscale, glycerol gave almost full conversion of the starting material to Lidocaine, and therefore, it was chosen as a solvent to develop a larger scale procedure (5 mmol) without any addition of potassium iodide. In this procedure, the amide and diethylamine (3 equiv) were heated to 85 °C ([Supporting Information, Procedure A, S10](#)). After 1 h of reaction, water was added to the reaction mixture, and the product was collected via a simple filtration, which gave the isolated product in excellent to quantitative yield. The product was recrystallized from hot hexane or heptane to yield the product as needles (70–85% yield).

Screening of KI and Bulk Bases as Additives. Next, the students performed the S_N2 -substitution reaction using the same conditions, but now in the presence of potassium iodide (10 mol %) to investigate if iodide could accelerate the substitution reaction according to the Finkelstein mechanism ([Supporting Information, p S2](#)). Most of the solvents showed an improvement of the conversion compared to the conditions

without potassium iodide, and the largest increase was observed in tetrahydrofuran (from 33% to 94% conv.), acetonitrile (from 83% to 99% conv.), and *tert*-butanol (from 79% to 98% conv.) (Supporting Information, p S4, Table S2). Both glycerol and PEG-300 gave almost complete conversion, which also was the case without added iodide, while the other solvents gave lower conversions (Supporting Information, p S4, Table 2). Tetrahydrofuran, acetonitrile, *tert*-butanol, and PEG-300 were chosen as the best solvents to investigate if the excess diethylamine could be replaced by a simple inorganic bulk base. In these reactions, 1.5 equiv of diethylamine was replaced with an inorganic bulk base (1.5 equiv), either potassium carbonate or potassium phosphate, and the reaction was run for 30 min at the indicated temperature (Scheme 2).

Scheme 2. Reaction Conditions: *N*-(2,6-Dimethylphenyl)chloroacetamide (0.1 mmol), Diethylamine (3 equiv), KI (10 mol %), Solvent (0.1 mL), 30 min, Oil Bath Temperature

The highest conversions were obtained in acetonitrile using K₂CO₃ (91%) and K₃PO₄ (86%), which were even higher than the conversion obtained with three equivalents of diethylamine (79%) (Supporting Information, p S5, Table S3). This confirmed that acetonitrile was a good choice of solvent both to promote a Finkelstein reaction and to replace the excess diethylamine. On the other hand, both PEG-300 and *tert*-butanol gave lower conversions with the inorganic bases (less than 50%) compared to using three equivalents of diethylamine. By extending the reaction time to 1 h in acetonitrile, the amounts of both potassium carbonate and diethylamine could be further decreased to 1.1 equiv with no significant drop of the conversion of the reaction (97% conversion, Supporting Information, p S6, Table S4).

Evaluation of Synthesis by Three Testpilot Students.

After the initial optimization, the B. Sc. students designed a laboratory procedure (Supporting Information, pp S6–7) that was evaluated by three first-year “testpilot students” in the organic chemistry course laboratory with the B. Sc. students as instructors. The testpilot students executed the procedure within 5 h and obtained Lidocaine in moderate to excellent

yields (65%, 66%, and 94%) (Supporting Information, p S6, Table S6). The main problem with the developed laboratory procedure was the time aspect of the experiment. In the procedure, ethyl acetate was used in the extraction of the basic water phase (NaOH, 1 M). This led to long evaporation times that are problematic in a standard course laboratory with larger groups of students. Ethyl acetate could be replaced with other solvents with lower boiling points, such as diethyl ether or dichloromethane, but at the expense of lower mass recovery and the use of less green solvents (Supporting Information, p S6, Table S5). In addition, the extraction step generates large amounts of organic waste, and therefore, an alternative workup procedure was developed. In the modified procedure, the reaction mixture solvent (acetonitrile) was first evaporated under vacuum, after which ethanol was added to the solid crude reaction mixture, followed by water. The resulting solution was cooled in a NaCl-ice bath (1:3), and the product precipitated and was collected via vacuum filtration.²⁴ The modified procedure (Supporting Information, Procedure B, S11) gave the isolated product as a solid in 77% to 85% yield,²⁵ but with a much better product-to-organic-waste ratio compared to the workup procedure involving extraction.

Development of Two-Step, One-Pot Procedure.

Because the Finkelstein conditions (above) efficiently promoted the S_N2 substitution in acetonitrile, acetonitrile was also tested as a solvent in the acylation step in order enable a two-step, one-pot procedure (Scheme 3).

Chloroacetyl chloride (1.1 equiv) was first added dropwise to a solution of 2,6-dimethylaniline in acetonitrile and was heated for 30 min at 40 °C to achieve full acylation of the aniline. Potassium carbonate (2.2 equiv) was added, and the solution was stirred for an additional 30 min at 40 °C. Potassium iodide (10 mol %) and diethylamine (1.1 equiv) were subsequently added, and the reaction mixture was refluxed for 1 h and subjected to the same workup conditions as in procedure B. In this two-step, one-pot reaction (Supporting Information, Procedure C, S12), Lidocaine was obtained as a white solid in 85% yield.²⁵

Evaluation of Green Chemistry Project

Evaluation of B. Sc. Project by B. Sc. Students. After the project, the three B. Sc. degree project students were subjected to a short survey (Table 1) that asked for their opinions about the B. Sc. degree project (Supporting Information, S16–18). The six questions (Q1–Q6) in the survey were mostly concerned with the green chemistry aspects of the project.

The overall impression by the B. Sc. students of the green chemistry project was excellent (Table 1, Q1:5.0). The group members stated that they had a good collaboration with each other (Table 1, Q4:4.33), which was of utmost importance for a positive outcome of the project. Another positive result from the survey was that the students perceived that their

Scheme 3. Reaction Conditions: (i) 2,6-Dimethylaniline (5.0 mmol), Chloroacetyl chloride (1.1 equiv), MeCN (10 mL), 40 °C, 30 min.; (ii) K₂CO₃ (2.2 equiv), Room Temperature, 30 min; (iii) Diethylamine (1.1 equiv), KI (10 mol %), Reflux, 1 h

Table 1. Scale for Survey Questions Provided to B. Sc. Students after B. Sc. Project

Questions	Scale for Responses		Mean Score (N = 3)
	1 Indicates	5 Indicates	
Q1 What is your overall impression of the B. Sc. Project?	Bad	Good	5.00
Q2 Did the B. Sc. project increase your understanding of the concept green chemistry?	Not at all	Much	4.33
Q3 Did the green chemistry project influence your interest in organic chemistry?	Less interested	More interested	4.67
Q4 How was the collaboration in the group?	Bad	Good	4.33
Q5 To what degree did you have to independently think about green chemistry in the B. Sc. project?	Not much	Much	4.67
Q6 After the B. Sc. project, I better understand the connections between green chemistry and sustainable development.	No better understanding	Much better understanding	3.67

understanding of the concept green chemistry increased (Table 1, Q2:4.33) and at the same time influenced their interest for organic chemistry in a positive manner (Table 1, Q3:4.67). This suggests that the integration of green chemistry into organic chemistry could lead to an increased interest for synthetic organic chemistry. The most important result of the survey is that the students had to think independently about green chemistry (Table 1, Q5:4.67) during the project. This suggests that the students acquired skills at higher-level skills in the Blooms' taxonomy,²⁶ which means that the students learned how to design and develop their own experiments and were able to evaluate and summarize their results in a report. The result also shows that the most difficult part was to connect the green chemistry project with sustainable development, in general (Table 1, Q6:3.67). The reason for this could be related to the strong focus the project had on modifying the synthesis of Lidocaine, and an additional literature assignment regarding sustainable development could potentially have shifted the focus to a more general connection to sustainable development.

Evaluation of B. Sc. Project Procedure in Laboratory Course Setting. To evaluate the feasibility of the newly developed procedures, procedure B was tested in a first-year organic chemistry course with about 130 students participating in the laboratory course. Of the 130 students, 59 students performed the synthesis of Lidocaine according to procedure B, while the other students performed a S_N1 substitution reaction. The students were able to perform the procedure within the allocated time (5 h), and the yields obtained by the students were, in general, good to excellent (see Figure 1)

Figure 1. Distribution of yields obtained from students (59) performing the synthesis of Lidocaine (procedure B) in a laboratory setting.

considering that it was their first organic synthesis in the lab course. An analysis of the yields shows that 78% of the students were able to obtain a yield above 50%, and the average and median yields were 63% and 67%, respectively. The reason for the lower average yield relates to a few "mistakes" in the workup procedure that led to a loss of product material and, hence, low yields (4–8% yield). The melting points were generally slightly lower than the literature values due to insufficient time to dry the material after the aqueous filtration.

After the synthesis was performed, a short survey (Q1–Q4, Table 2) was carried out to gain insight into the students attitudes toward green/sustainable chemistry. Before performing the laboratory procedure, the students were given a short introductory lecture (about 15 min) about the basic concept of green chemistry, and some questions regarding green chemistry were introduced in the questions to be handed-in before performing the experiment (Supporting Information, p S14).

The survey showed that the students' previous knowledge regarding green/sustainable chemistry was quite low (Table 2, Q1:2.31), which is not surprising since it was the first time that the students were introduced to the subject. However, after the experimentation, the students felt that their perception of green chemistry had increased (Table 2, Q2:3.45), and this indicates that the experiments designed with green chemistry in mind can have an impact on the students' attitudes toward green/sustainable chemistry. The importance of these concepts from a student perspective is also reflected in the fact that they agreed with that it is important that green/sustainable chemistry is an integral part of their chemical engineering education and that it will impact their future careers (Table 2, Q3:4.66 and Q4:4.39). In the student's lab reports, they were asked to reflect on the green aspects of the performed synthesis of Lidocaine and how these aspects would work in an industrial scale. In the lab reports, it is clear that the students were able to analyze and reflect on different green aspect of the synthesis they had performed (Supporting Information, S19–25). For example, the reflections included discussion about the hazards, toxicity, and availability of the reactants and solvents, but comments were also made about the impact of Lidocaine in the environment. Several students discussed the energy consumption of the reaction (prolonged heating, cooling, evaporation) and how this would be handled on an industrial scale. The students also commented on the fact that they used a catalyst (KI) to lower the activation barrier of the reaction, which leads to lower energy consumption compared to the original procedure. From the lab reports, one noted that some differences in what the students included in their calculation of the atom economy (catalysts, bulk base) led to different conclusions regarding whether the performed synthesis was

Table 2. Student Green Chemistry Knowledge and Attitude Survey Results after Performing the Synthesis of Lidocaine

Questions	Scale for Responses		Mean Score (N = 55)
	1 Indicates	5 Indicates	
Q1 How was your previous knowledge of green/sustainable chemistry prior to this course experiment?	Very low	Very high	2.31
Q2 Did the preparation and experimentation help you to improve your perception of green/sustainable chemistry?	Not at all	Very much	3.45
Q3 Do you think it is important that green/sustainable chemistry is an integral part of your chemical engineering education?	Not at all	Very important	4.66
Q4 Do you think that green chemistry and sustainability will be important in your future career?	Not at all	Very important	4.39

Table 3. Green Chemistry Questions and Discussion Points Related to Alternative Lidocaine Procedures

Procedure	Modification	Green Chemistry Discussion Points
A	Solvent replacement	What is a green solvent? What are the benefits and drawbacks of different solvents? Discuss solvents from renewable sources vs fossil sources.
B	Finkelstein conditions	Analyze the synthesis with respect to the reagents used (calculate reaction mass efficiency). How environmentally friendly are these reagents? What is the role of iodide? Is the reaction catalytic? Energy consumption?
C	Two-step, one-pot reaction	Calculate the approximate E-factor for the synthesis and compare to the original procedure. What are the benefits of one-pot-two-step procedures? Any drawbacks? What is the role of iodide? Is the reaction catalytic?

green. However, the reports clearly showed that even first-year undergraduate students were able to analyze their synthesis with regard to the 12 principles of Green Chemistry.

Green Chemistry Reflections for Teachers and Students in Different Procedures for Synthesis of Lidocaine

The three developed procedures contain different levels of green chemistry that could be used as discussion points at various levels of undergraduate teaching (Table 3). From a pedagogical perspective, it is interesting to discuss the nucleophilicity and leaving group ability of iodide and how the addition of iodide can influence the yield and rate of the reaction. In these discussions, both pros and cons can be raised for the Finkelstein reaction.

For example, on the positive side, the fossil fuel-derived toluene was replaced with acetonitrile, less diethylamine was used due to the use of an innocuous and cheap inorganic base, and a lower reaction temperature saves energy compared to the original procedure. On the negative side, it could be argued that acetonitrile is not the greenest solvent, but at least acetonitrile is rated at the same level as toluene.²⁷ However, the use of acetonitrile as a solvent also opens the opportunity to develop a procedure in which both the acylation and the S_N2 reaction are performed in a two-step, one-pot reaction without additional workup procedures. The two-step, one-pot procedure (Procedure C) is more time-consuming, compared to the one-step procedure (Procedures A and B), and is best applied at a later stage of the student's organic chemistry education, where green metrics, such as atom economy and E-value, have been covered in the curriculum.

CONCLUSIONS

Three B. Sc. students were able to investigate and develop greener, alternative procedures for the synthesis of Lidocaine, which can be implemented in first- or second-year undergraduate teaching in organic chemistry. The procedures have increasing levels of complexity, starting from a simple solvent replacement (from fossil fuel-derived toluene to biosourced glycerol) and ending with a two-step, one-pot procedure involving the Finkelstein reaction. The procedure that best fits the curriculum and the students' level of knowledge can be chosen by the course responsible. The described student-

driven development of green chemistry procedures open opportunities for larger and more ambitious green chemistry developments in undergraduate teaching compared to faculty-driven developments. In addition to providing new, greener procedures in organic chemistry within the undergraduate teaching, the student-driven project also educates B. Sc. degree project students in green chemistry, providing them with knowledge that can be utilized in courses at higher levels and in their future careers as chemists. One of the procedures was evaluated in a full-scale laboratory course setting with 59 students performing the synthesis of Lidocaine. The experimental results were satisfying, and 78% of the students obtained more than 50% yield. A short survey of the impact of green chemistry on the students showed an increased interest in green/sustainable chemistry and that green/sustainable chemistry will be an important part of their future careers. In addition, it was clear from the lab reports that the first-year students were able to analyze and reflect on different green aspect of the synthesis they performed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: [10.1021/acs.jchemed.8b00567](https://doi.org/10.1021/acs.jchemed.8b00567).

Experimental work by students including outline for B. Sc. project, experimental work by bachelor students, procedures, notes for instructors, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the "test students" (C. H. Lee, L. Montarroyos, G. Persson) who were willing to evaluate the course lab procedure

outside their own curriculum and all students in KD1230 (spring 2019) who performed the Lidocaine synthesis in our lab course. P.D. and B.B. thank KTH – Royal Institute of Technology for financial support.

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- (24) If a fine white powder is observed at the bottom of the round-bottom flask, it is most likely potassium carbonate, and adding more water dissolves it and yields the product. Additionally, prolonged cooling might partially freeze the solution, but letting the ice melt by warming to room temperature makes isolation of product easier.
- (25) The product can be recrystallized from hot hexane or heptane (1 mL/g crude product) yielding white needle-like crystals (900–1000 mg, 75–85%).
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