Learning Green Chemistry Principles by Comparing Three Synthetic Routes to a Copper-NHC (NHC = N-heterocyclic carbene) Complex

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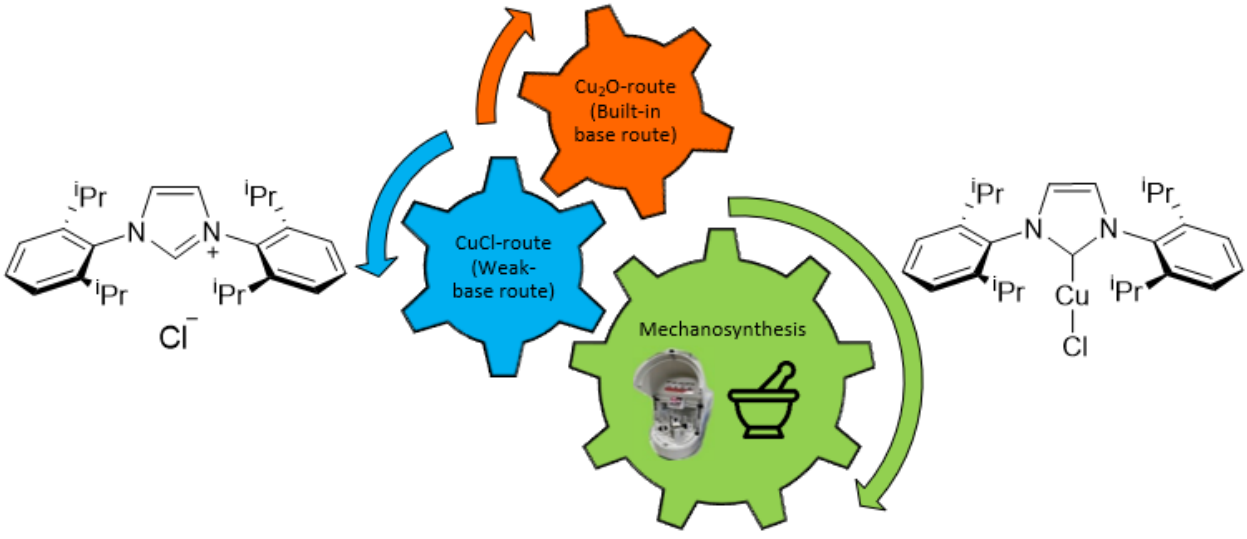
ABSTRACT

The implementation of a laboratory exercise in an undergraduate chemistry course, where students perform a comparison of three different synthetic methods towards [Cu(Cl)(IPr)]-complexes (IPr = *N*,*N*'-bis(2,6-diisopropylphenyl)imidazole-2-ylidene), is described. The students are introduced to the continuous improvement of reactions in terms of green chemistry and are provided a taste of mechanochemistry as a synthetic methodology. The direct comparison of three methods leading to the copper complexes provides an opportunity to teach green chemistry metrics including atom economy, environmental factor, mass intensity, reaction mass efficiency, optimum efficiency, as well as Green Star; and challenges them to question the use of solvents in chemical synthesis.

GRAPHICAL ABSTRACT



KEYWORDS

Second-Year Undergraduate, Upper-Division Undergraduate, Graduate Education/Research, Organometallic Chemistry, Hands-on Learning/Manipulations, Green Chemistry, Synthesis, Catalysis.

INTRODUCTION

During the past decade, the need for more sustainable and greener industries has been voiced by the international community.[1–3] The development of the sustainable development goals (SDGs) and the twelve principles of green chemistry have helped chemists in adapting their decision-making processes and have helped researchers to change to a "benign-by-design" way of thinking for their synthetic methods.[4,5] Scientists are now trained in achieving an increased awareness for environmental impact when designing new products and processes.[5] Additionally, working towards these green chemical goals can result in economic benefits due to the reduction of waste streams, the use of cheaper and renewable feedstocks, and the prevention of work-related injuries.[6]

In the context of tackling the SDGs and implementing the twelve principles in the field of chemistry, great interest has focused on catalysis and mechanochemistry to increase the sustainability and safety of chemical reaction.[7] Combining both catalysis and mechanochemistry makes it possible to design cleaner and safer chemical synthesis by simultaneously addressing principles such as atom economy, and less hazardous synthesis, among others. Mechanochemistry has grown into one of the most interesting and important techniques for changing standard solvent-based synthesis into safer and more sustainable methods[8] and has recently been listed in the *'Ten chemical innovations that will change our world'* by IUPAC.[9] Mechanosynthesis allows to conduct chemical reactions with exclusion (total or partial) of solvents from the reaction environment, relegating solvent usage almost exclusively to the work-up phase,[8] making it possible to reduce the enormous amounts of solvents used in the modern chemical industry (*i.e.* solvents typically account for 80-90% of the mass used in fine-chemical or pharmaceutical processes).[10] In addition, the advantages of these techniques are not limited to the reduction of the environmental impact of chemistry alone, they also permit higher reaction rates, an increase in purity of the end-products, increased yields, and even permit new reaction pathways.[11–13] Therefore, mechanochemical techniques have found their way into all areas of chemistry, from organic and peptide syntheses, supra molecular chemistry to transition-metal catalyzed reactions.[14–22]

In the area of catalysis, a significant amount of research is dedicated to enhancing the reactivity and, in turn, lowering the catalyst loading, to reduce metal residues in the end-product and avoid extensive and expensive recycling strategies.[23,24] In this regard, through the work of Arduengo and co-workers, N-heterocyclic carbenes (NHCs) have quickly developed from a lab curiosity to state-of-the-art ligands in organometallic catalysis for their great electron-donating capabilities and increased stability, compared to generally used phosphine ligands.[25,26] The development of copper complexes and the use of catalysts based on copper in organic synthesis is an exciting opportunity for chemists in trying to broaden the use of abundant metals (such as Cu, Ni, Fe, etc.) and avoid rarer precious-group metals (such as Pt, Pd, Ru, etc.), increasing the sustainability of organic synthetic methods and lowering the manufacturing cost of catalysts.[27–29] The combination of NHCs and copper for transition metal-mediated catalysis began in 1993 when Arduengo and co-workers reported the first example of a copper-NHC complex, a cationic dicarbene complex,[30] followed by the first synthesis of monocarbene [Cu(Cl)(NHC)] complexes by Raubenheimer and co-workers,[31] and the first use of a NHC-ligated copper complex as a catalyst by Woodward and Fraser.[32] Finally, the first use of a well-defined Cu-NHC complex in catalysis, along with the herein used *N,N'*-bis(2,6-diisopropylphenyl)imidazole-2-ylidene ligand (IPr), was initially reported by Buchwald and co-workers in 2003.[33] These advances resulted in an expansion in the use of copper for numerous organic reactions, ranging from the Nobel prize winning Click reactions, hydrosilylations, Sonogashira coupling, and allylic substitutions, among many more possiblites.[34]

Recently, many new applications of mechanochemistry in the field of NHC organometallics and catalysis have been described, showing that every step of the way towards fine chemicals can be reshaped into a solvent-less operation. These manufacturing steps range from the synthesis of ligands,[35–37] the assembly of the metal complexes[35,38–45] and their use in catalytic reactions.[46–51] Specifically, the Lamaty group has described two mechanochemical methods showing the assembly of [Cu(NHC)Cl] complexes using a Ag-transmetalating agent[52] or by reaction of imidazolium salts with copper powder.[53]

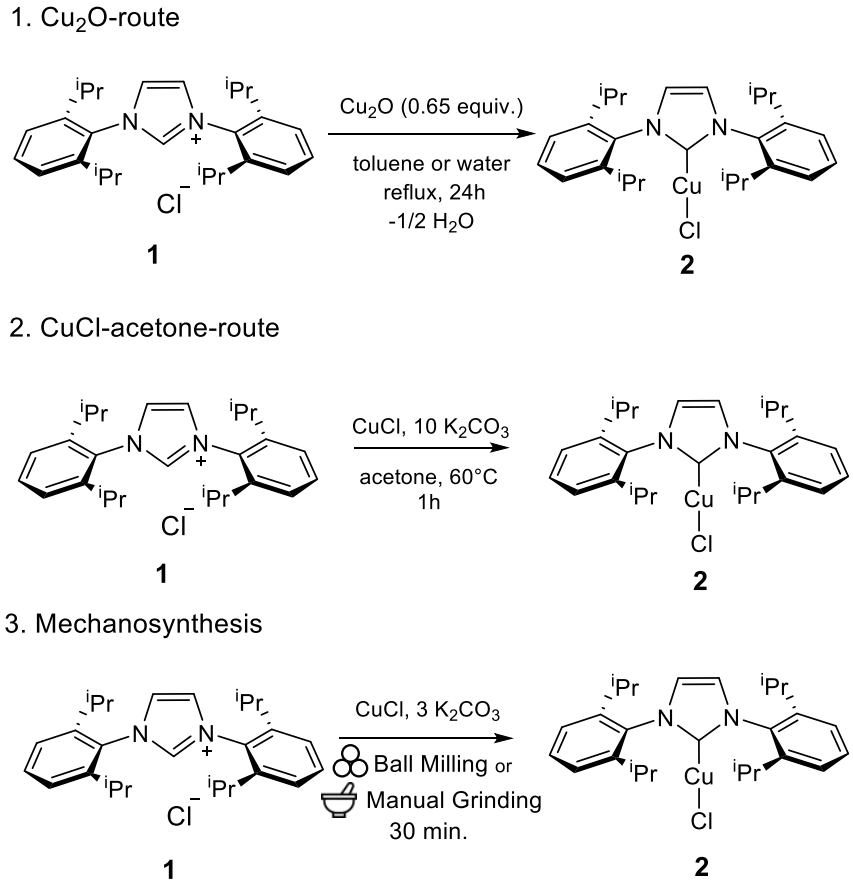
A few of the major challenges (apart from research related ones) in creating newer and safer methods for the chemical industry, are educational challenges, where students are assisted in understanding the importance of green chemistry. This goals is one of the core responsibilities of the educational system.[5,54]

Educational institutes have changed major sections of their curriculum to train future chemists in a system thinking approach towards sustainability and students of all levels are now taught the philosophy and practice of green chemistry.[55-57] However, educators can still benefit from new ideas for their "toolbox" in integrating green chemistry in their teaching and research, especially when practical laboratory experiments are concerned.[58,59]

It is therefore important to include catalysis and mechanochemistry in the curriculum of chemical education as early as possible in the educational process to make students aware of the future challenges they will face and how they can use these two methodologies to design sustainable methods. Recent work in chemical educational has shown that students display great interest and enthusiasm in learning sustainable methods and laboratory exercises, showing how chemists can implement changes in future chemical processes. Multiple laboratory exercises address the aspects of transition-metal catalysis[60–64] and mechanochemistry[65-69] for undergraduate students, but combining both techniques and showing students how chemical processes are adapted over time to achieve increased sustainability has been, to the best of our knowledge, overlooked. The recent development of a new synthetic methodology for [Cu(Cl)(NHC)] complexes[70] provides an excellent opportunity to create a new laboratory experiment for undergraduate students in which green chemistry, mechanochemistry and catalysis aspects are introduced, simultaneously. In this laboratory exercise, students are asked to synthesize the [Cu(Cl)(IPr)] complex using three different routes.[70-72] All three reaction pathways have been designed by the Cazin & Nolan research groups, showing that researchers keep adapting their synthetic methods to improve overall sustainability. The reactions used in this experiment were adapted from previously reported procedures for synthesizing catalysts, one of them using a solvent-free method with a planetary ball mill and is an approach that can be more simply and economically carried out using a mortar and a pestle.

Students performed three synthetic methods for the preparation the [Cu(Cl)(IPr)] **2** complex (Scheme 1). All three reaction routes use the imidazolium salt IPr·HCl **1** as starting compound but employ different strategies for coordinating the N-heterocyclic carbene (NHC) to the metal. The first route employs Cu_2O as copper source, which can be thought of as containing an internal base and which can react with the imidazolium salt, creating the Cu-NHC bond. Toluene or water is used as solvent, to allow

for higher reaction temperatures (100-110 °C) and to avoid chlorinated solvents which are deleterious to both the environment and to the reaction outcome. The second route uses CuCl as a more stable, user-friendly, and cheaper copper source compared to Cu_2O. However, a base in the form of K_2CO_3 is needed to facilitate the liberation of the H^2 proton (proton located between the two *N* atoms) of the imidazolium salt. This route was developed for its milder and environmentally friendlier conditions by using acetone as a solvent (instead of toluene for some of the NHC ligands that were unreactive in water) and lowering the reaction temperature to 60 °C. The third and last reaction route is based on mechanochemical grinding as an energy source. Again, CuCl is used as a copper source and K_2CO_3 as an operating base. This route does not require the use of any solvents and is therefore performed with solids only in a planetary ball mill, or even better and cheaper, using a conventional pestle and mortar. All three routes conclude with the same work-up and permit students to compare all three reactions.



Scheme 1: Schematic representation of the three synthetic methods leading to [Cu(IPr)(Cl)] (**2**)

This experiment is designed for two 3 h laboratory periods, for undergraduate students in their second or third year of undergraduate studies. A first session includes the reaction set-up for the Cu_2O-route and the complete CuCl-acetone-route. The second session includes the work-up of the Cu_2O-route and the complete mechanosynthetic route. These sessions were one week apart, therefore, instructors stopped the synthesis through the Cu_2O-route after 24 hours of reaction by storing in the fridge the reaction mixture until the next session. For this first route, we opted to use water as a solvent due to safety concerns, however instructors who want to show a larger difference in terms of green chemistry between the three methods can use toluene in this route. This laboratory course was a part of a series of inorganic exercises and was preceded by a general course on inorganic chemistry. Knowledge of general laboratory techniques (i.e. a passing grade for the previous year's laboratory exercises) and a basic understanding of catalysis are pre-requisites. This exercise provides students an opportunity to think about how chemical reactions are constantly improved; to calculate and interpret green chemistry metrics; and to demonstrate the possibilities of mechanochemistry and solvent-free synthesis methods. The isolated copper complexes are saved for further use in a different laboratory exercise where students perform a Click reaction with benzyl azide and phenylacetylene ([3+2] cycloaddition), based on the article published by Ison and Ison.[60]

PEDAGOGICAL GOALS

The pedagogical goals (PGs) of this experiment are:

- To make students aware of the green chemistry principles and their use in the challenges of chemical development *(PG 1)*;
- To challenge the mainstream type of thinking: "Can you question the use of solvents *a priori*?" *(PG 2)*;
- To introduce students to mechanochemical principles and how this can help in developing solvent-free or solventless synthetic methodologies *(PG 3)*;
- To show students that avoiding or minimizing the use of solvents can result in comparable or even better reactivity, purity and yield *(PG 4*);
- To teach students green metrics, *i.e.* atom economy (AE), environmental factor (E-factor), mass intensity (MI), reaction mass efficiency (RME), optimum efficiency (OE), and Green

Star: what are they? How can they be calculated? how to interpret them and develop greener methods? *(PG 5)*

These pedagogical goals were assessed by the students' ability to perform the reactions e.g. the attained product purity and yield, questions asked during and after the laboratory exercises and the evaluation of their reports of the practical. In this report, students make a comparison between the three synthetic routes, describing the main advantages and drawbacks of each strategy. In this comparison, the students are asked to calculate 6 green metrics (AE, E-factor, MI, RME, OE, and Green Star) and discuss their meaning. These metrics were selected because they are easily calculated, encompass a large and holistic range of criteria, and address as many of the 12 principles as possible.[73-77] The latter metric, Green Star, is determined by filling in an excel sheet provided by instructors, in which students give a score, ranging from 1 to 3, on 10 of the green chemistry principles. Depending on these scores, a graphical representation of the Green Star metric can be generated and the Green Star Area Index (GSAI) is calculated. This results in the generation of a graphic which allows at a glance to determine which method is the greener, and on which area recommendation could be made to further improve the method. Only 10 out of the 12 principles are assessed in this metric due to the 4th (designing safer chemicals) and 11th (real time analysis for pollution prevention) principles not being applicable in this laboratory exercise.[78] The excel sheet is based on the Green Star paper by Ribeiro and co-workers,[78] adapted for student use in a teaching environment. This excel document, along with the correct calculation of the other green metrics, is provided in the Supporting Information. Work-up procedures are not included in the calculation of the green metrics because the same work-up is used for all three reaction procedures. In this manner, students only focus on the differences between the synthetic reactions. Additionally, because of the large excess of solvents used in the work-up, including them in the calculation can mask major differences in the reactions.[73]

EXPERIMENTAL SECTION

The CuCl-acetone-route was performed using 10 equivalents of K_2CO_3 to achieve a faster reaction time of 1 hour, compared to the 2 equivalents and 24 hours reaction time found in literature.[70] This was done to address time constraints. Again, instructors who want to show a larger difference in the first and second reaction routes can decrease the amount of base used, resulting in lower values for the MI

and E-factor of reaction 2. The mechanosynthesis route was performed in two different ways: in the first year this exercise was performed, students used a planetary ball mill, and in a second year, the students did the reaction manually using a mortar and pestle.

For the experiments using the ball mill, students were asked to prepare the reaction vessel and notify an instructor when ready, to accompany them to the ball mill. For this, a Fritsch Pulverisette 5 planetary ball mill was used and operated by the instructor. As such equipment might not be available, this laboratory exercise was also implemented using a simple mortar and pestle. The reaction can be performed by grinding the solid reactants in a mortar and pestle for 30 minutes to 1 hour, however, this can be quite tedious, and results may differ from one operator to another due to human error associated with inconsistent grinding. Using a mortar and pestle, instructors achieved an average isolated yield of 64% after 30 minutes of grinding. Intermediate NMR samples can be taken to assess the conversion of the reaction and appropriate action (i.e. more grinding) can be taken to reach completion.

The work-up for the Cu_2O-route consists of addition of dichloromethane, phase separation followed by drying of the organic phase using Na_2SO_4. The solvent-based reaction routes proceed with filtering the reaction solution and collecting the filtrate, from which volatiles are evaporated using a rotary evaporator. Then, for all three reaction routes, the solids are dissolved in dichloromethane (1mL), to which pentane (3 mL) is added to induce product precipitation. The product is then collected by filtration, and dried *in vacuo*. After drying, a sample is collected for NMR analysis using deuterated chloroform as solvent.

Final product identity was determined using ^1H Nuclear Magnetic Resonance (NMR) spectroscopy, recorded on a Bruker ADVANCE 400 MHz spectrometer, using the residual solvent peak (δ_H = 7.26 ppm for $CDCl_3$) as reference. Detailed protocols given to students, as well as a correction key for the green metrics and an example of the expected NMR data are provided in the Supplementary Information.

HAZARDS

The laboratory exercises must be conducted in accordance with good hygiene and safety practices. Students must wear lab coats, protective gloves, and safety goggles at all times during the experiments and all reactions must be carried out in a fume hood. Acetone, pentane, and toluene are flammable

solvents whose vapors are toxic and may cause drowsiness or dizziness. Toluene may cause damage to organs through prolonged or repeated exposure. Dichloromethane is a toxic liquid and should be handled with care. Copper(I)-oxide and copper(I)-chloride are harmful when swallowed or when in contact with skin. Potassium carbonate and IPr·HCl may cause irritation to skin, eyes, and the respiratory system. To the best of our knowledge, the properties of [Cu(Cl)(IPr)] have not been thoroughly investigated. This should be handled with appropriate caution. Waste should be collected and separated into the appropriate waste streams as they are toxic for aquatic life and the environment. A more detailed analysis of the hazards associated with this laboratory exercise can be found in the Supplementary Information.

RESULTS AND DISCUSSION

This study gave students a first taste of mechanochemistry. The experiments were performed twice; the first group, which included 18 students, performed the mechanochemical experiments using a ball mill. The second group, which included 16 students, performed the mechanochemical experiments using a mortar and pestle. The students were divided into groups of two to perform the experiments in two 3-hour laboratory periods. We observed that the set-up of the Cu_2O-route took around 1 hour and the set-up of the CuCl-acetone and mechanosynthesis route each took around 30 minutes. The work-up procedures took around 1 hour. Each group of students obtained an amount of the desired complex through each of the synthetic methods, which they used to calculate the yield of their reactions and the green metrics. Students were found to have trouble working on a small 100 mg-scale, therefore the reactions were scaled up to 200-300 mg scale. All reactions reached completion, however, students lost significant amounts of product due to a lack of experience with silica gel, often washing them insufficiently during the filtration step. Yields were therefore often considerably lower (25 – 70 %) compared to those obtained by instructors or those reported in the literature. Instructors also noticed some minor impurities in the isolated compounds resulting in greyish or yellowish powders instead of the desired white complexes. However, some of the mortar and pestle experiments did not proceed to completion because of insufficient grinding by the students. This resulted in the presence of cuprate

species or even unreacted NHC salt in the final product. These unreacted species are easily detected in the NMR spectra, showing three different sets of peaks (ESI, figure S4). This allowed to detect the incomplete conversion of the reaction, after which these students grinded for an extra 15 minutes the reaction mixture to reach full completion. In their experimental report, the majority of the students successfully calculated all green metrics (Table 1) and unanimously concluded that the mechanosynthesis route is the greener synthetic method. Only the calculation of the E-factor was problematic for some students as they forgot to take the mass of the solvent into account. The main advantages reported for the mechanochemical route are the lack of solvent, the shorter reaction time, and room temperature condition. The disadvantage that is often considered is the cost of the ball mill, or the tediousness and the human error when grinding manually (Figure 1). The construction of the green star led to some difficulties, out of the 30 scores that had to be given, on average 18 were correct. Especially when assessing principle 12, most students made mistakes (6 out of 36 were correct). Students seem to forget the dangers (e.g. flammability) of commonly used solvents. This highlights the need to keep students aware of the dangers they face when working with chemicals throughout their education as chemists, as they often underestimate the risks found in a laboratory setting.[79]

Table 1. Successful calculations of the green metrics.

Metric	Successful calculations[a]
AE	92%
RME	85%
OE	85%
MI	77%
E-factor	62%

[a] Percentages based on a total of 13 groups, rounded to the nearest integer

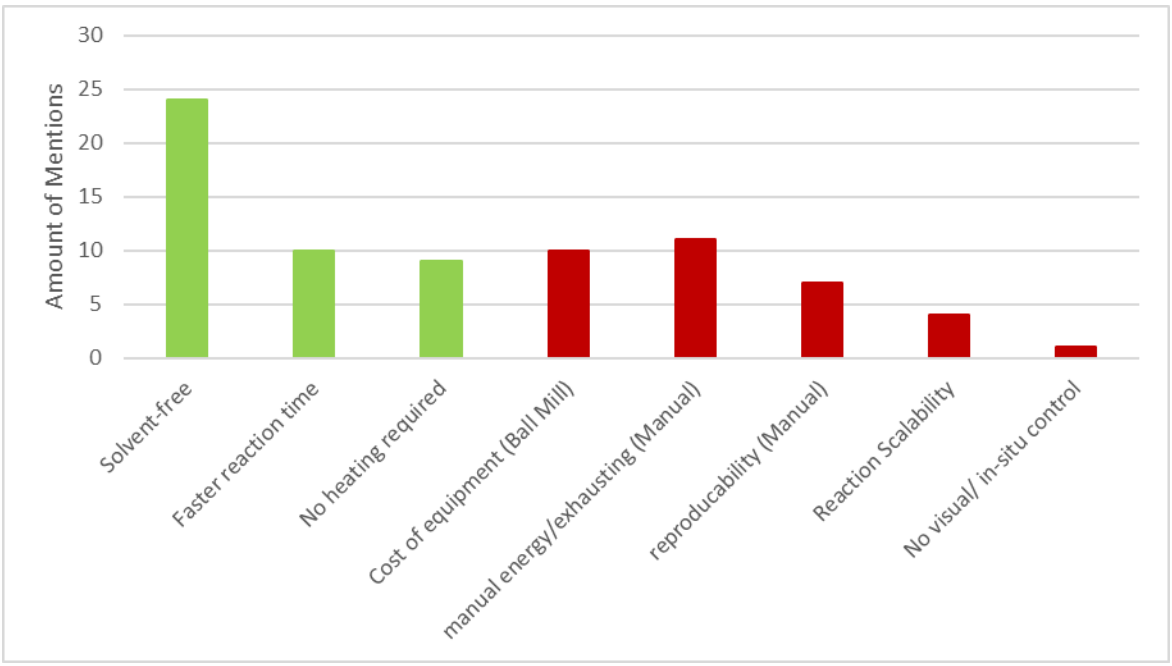


Figure 1: Students' responses when asked for the advantages (green) and the main disadvantage (red) of the mechanosynthesis strategy (N=28)

The report also included questions querying the students' experience during this exercise and their views of green and sustainable chemistry. While students still consider the use of solvents necessary in most chemical reactions many of them commented that the work-up procedure still uses dichloromethane and pentane, which can open discussions to further improvement of the method through the use of greener solvents (to replace CH_2Cl_2). In this context, the discussion with students can then be opened to select new solvents by teaching them about guides for solvent selection[80] such as Sanofi's Solvent Selection Guide[81] or the ACS GCI Pharmaceutical Roundtable Solvent Selection Guide.[82] In this case, acetone can be used for the extraction of the mechanochemistry vessels and as solvent for the recrystallisation, along with heptane or cyclohexane as greener alternatives for pentane. Instructors' results on these alternative solvents can be found in the supporting information. An additional laboratory session can be organized to implement these proposed changes of the students and further improve their thinking about green chemistry and solvent choice. In addition, discussions about how solvents are determined solvent selections guides can be prompted, using the comparative study reported by by Prat and co-workers,[83] which show that on a third of the investigated solvents, companies'

recommendations differ. Teachers can use this information to have a more in depth discussion on what it means for a solvent to be problematic, that classifications are affected by culture and policies, and that this is a perpetually moving field.[84] Additionally, instructors can use this practical experience to teach students in a theoretical class about the different roles that solvents have in chemical reactions, from dispersion and bringing into contact of the reagents, moderating heat flow in and out of the reaction, and even playing a non-innocent role for the reaction mechanism. Detailed results of this inquiry can be found in the supplementary information.

CONCLUSION

The students gave very positive feedback in their post laboratory reports. They realized that mechanochemistry is a potentially powerful tool to avoid/diminish solvent use in chemical synthesis, a tool they have not considered using before. They were made aware of the green chemistry principles (*PG1*) and how mechanochemistry can help reduce waste (*PG3*) and lead to good yields compared to the standard solvent methods (*PG4*). Students were also challenged to rethink the use of solvents in chemical synthesis (*PG2*). Lastly, the students were successful in calculating the green metrics and constructing a Green Star (*PG5*). The latter indicated that assessing the safety of chemicals and designing reactions for accident prevention is still a topic that is troublesome for students. Additionally, the experiment stimulated the students to think about green chemistry and they indicated that this topic should be included more in their education as chemists, even in non-specialized courses.

ASSOCIATED CONTENT

Supporting Information

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

Safety data, notes for instructors, student lab instructions, sample ^{1}H-NMR spectra, and detailed results of the students' inquiry (PDF)

Green Star template used by the students (EXCEL)

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