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Laboratory Experiment

A Greener Synthesis of the Nonsteroidal Anti-inflammatory Drug Celecoxib

Francis Ho, James Sherwood,* and Glenn A. Hurst*

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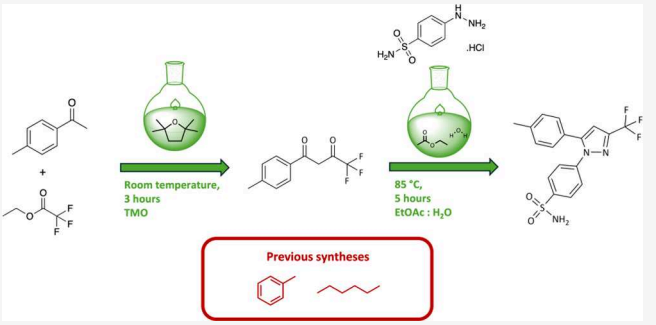
ABSTRACT: A laboratory experiment was developed to introduce green chemistry concepts through the synthesis of the nonsteroidal, anti-inflammatory drug, celecoxib. There are a range of issues based on the traditional synthesis of celecoxib including the use of a toxic solvent such as toluene, which is becoming severely restricted in its use, and other issues such as high energy consumption due to long reaction times together with wasteful extractions. A greener synthesis has been developed by making use of 2,2,5,5-tetramethyloxolane (TMO), a hindered ether, as a solvent that can be potentially biobased together with reducing reaction times and optimizing extraction procedures. These changes reduced waste by over 100 kg per kilogram of product. When implemented with students, they synthesized celecoxib, and the adaptations to the traditional process were discussed and evaluated using green chemistry metrics in conjunction with the DOZN tool together with the underlying reaction mechanisms.



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

INTRODUCTION

The United Nations Sustainable Development Goals (UN SDGs)[1] have provided significant impetus to the development of sustainable chemical manufacturing methods to reduce adverse effects on human health and the environment. Quality education (Goal 4) is essential to equip future chemists with the knowledge and skills to deliver sustainable change. A systems thinking-based pedagogic framework is well suited to sustainability instruction where green chemistry serves as a vital component to transform the chemical industry sector.[2] There is an expanding portfolio of resources demonstrating the incorporation of systems thinking into green chemistry education in a range of environments and levels.[3] This has included laboratory instruction, enabling the introduction and advancement of green chemistry concepts, while facilitating the development of laboratory skills. A range of resources from valorization experiments to greener syntheses have been developed.[4−11]

To introduce green chemistry to undergraduate students, a laboratory experiment is described based on the synthesis of the nonsteroidal anti-inflammatory drug (NSAID), celecoxib. Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide) was one of the first selective cyclooxygenase-2 (COX-2) inhibitors to reach the market and is used in the treatment of acute pain and arthritis.[12] The mechanism of action involves inhibition of the cyclooxygenase (COX) enzymes, where celecoxib selectively inhibits COX-2. This is in contrast to traditional NSAIDs that exhibit greater action toward COX-1.[13] The market size for celecoxib is projected to grow significantly over the coming years to meet demand for therapeutics for age-related conditions.[14] Celecoxib (**1**) was initially synthesized and identified as a candidate by Penning and colleagues.[15] The synthesis involves a Claisen condensation of 4′-methylacetophenone (**2**) and ethyl trifluoroacetate (**3**) to produce diketone 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione (TFBD, **4**), subsequently undergoing a pyrazole cyclo-condensation with 4-sulfonamidophenylhydrazine hydrochloride (4-SAPH, **5**) to produce celecoxib (**1**) (Scheme 1).

The route in Scheme 1 has been optimized, resulting in various processes that have been used for commercialization.[16−18] Notably, a patent derived from this process development describes the synthesis of celecoxib with toluene as a solvent for Claisen condensation (step 1) and as the extraction solvent in the resultant acid workup. Toluene is also the recrystallization solvent for the purification of celecoxib following the second cyclo-condensation step.[19] Toluene is a candidate for substitution given its presence on the Registration, Evaluation, Authorisation and Restriction of

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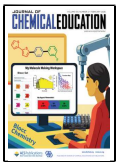

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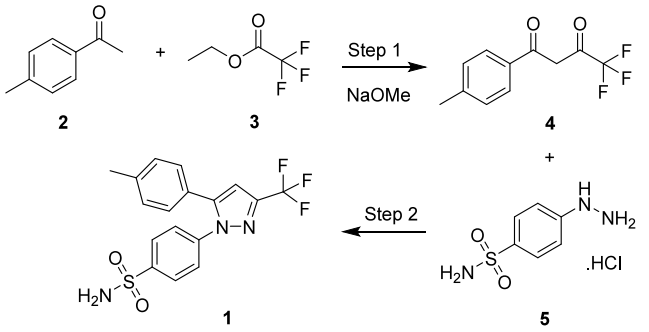
Scheme 1. Synthesis of Celecoxib (1)



Chemicals (REACH) restricted substances list.[20] Specifically, toluene is suspected to be toxic to reproduction alongside being recognized as a hazardous air pollutant by the EPA.[21]

2,2,5,5-Tetramethyloxolane (TMO), a recently proposed 'hindered-ether'[22] solvent, has previously been shown to exhibit similar properties to toluene, exemplified by their Hansen solubility parameters and boiling points.[23] TMO is not expected to have the same chronic toxicity issues as aromatic solvents including toluene (Figure 1).[24] TMO has demonstrated competitive performance to toluene across a diverse range of reactions from Buchwald-Hartwig aminations, Suzuki-Miyaura and Sonogashira cross-couplings to esterifications and biologically catalyzed polyester syntheses.[22,23,25,26] TMO can be straightforwardly prepared from 2,5-dimethylhexane-2,5-diol with high yield and selectivity.[27] Furthermore, a biobased route to TMO from methyl levulinate has been performed.[28]

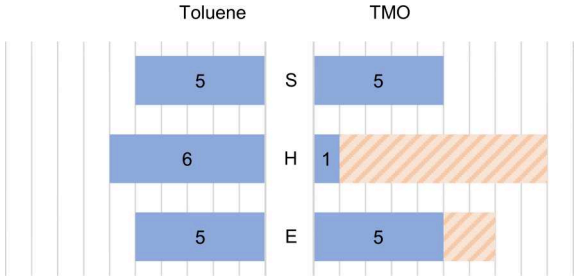


Figure 1. CHEM21 solvent greenness scores describing safety (S), health (H), and environment (E) for toluene (left) and TMO (right). Uncertainty due to lack of testing is shown by striped bars.

The laboratory experiment reported in this work serves as a greener alternative to the standard protocol, making use of TMO as an alternative solvent to toluene. It is suitable for implementation in an undergraduate teaching lab and can be used to introduce aspects of green chemistry while providing further experience of synthetic preparatory and characterization techniques. The learning objectives associated with this laboratory experiment are to

1. Demonstrate organic synthetic and characterization techniques in the synthesis of celecoxib
2. Identify the need to substitute solvents with 'green' alternatives
3. Use a systems thinking approach to critically evaluate the greenness of the synthetic route of celecoxib using green metrics and tools

This experiment can be applied for students studying chemistry modules and is designed for upper division/third year students over 1 or 2 days, although it can be adapted for different levels of understanding. In this work, the laboratory experiment was implemented with groups of upper division chemistry students. The success of the reaction was evaluated using the freely available green chemistry metric Process Mass Intensity (PMI) and the 'Quantitative Green Chemistry Evaluator' (DOZN 2.1) tool.[29] The former measures the mass of substances required to produce the intended product (kg per kilogram), and the DOZN tool evaluates a synthesis against the 12 principles of green chemistry to produce a numerical score (low scores are preferential).

EXPERIMENTAL SECTION

Instrumentation

^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were obtained using a Jeol ECS-400 NMR spectrometer (400 MHz ^{1}H, 101 MHz ^{13}C, and 376 MHz ^{19}F) at ambient temperature in DMSO-d_6 or chloroform-d. ^{1}H NMR spectra were referenced to the solvent signal at 2.50 ppm (DMSO-d_6) and 7.26 ppm (chloroform-d). ^{13}C NMR spectra were referenced to the solvent at 77.0 ppm (chloroform-d) and 39.52 ppm (DMSO-d_6). Infrared (IR) spectra were obtained using a PerkinElmer FTIR/FTNIR Spectrum 400 between 600 cm^{-1} 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 x 250 mm × 0.25 mm nominal, max temperature 400 °C). Samples were dissolved in ethanol and filtered through a nylon filter or cotton wool. Hydrogen was used as the carrier gas at a flow rate of 2 mL/min with a split ratio of 30:1 and a 1 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 290 °C and the detector temperature was 320 °C.

Materials

All chemicals were used as received unless otherwise stated. 2,5-Dimethylhexane-2,5-diol (CAS: 110−03−2) was purchased from Alfa Aesar and Fluorochem. HCZB-150E Zeolite was obtained from Clariant. 4′-Methylacetophenone (CAS: 122−00−9) was purchased from Sigma-Aldrich. Isopropyl trifluoroacetate (CAS: 400−38−4) was purchased from Apollo Scientific. Ethyl trifluoroacetate (CAS: 383−63−1) was purchased from TCI and Fluorochem. Sodium methoxide was purchased from Sigma-Aldrich. Hydrochloric acid (37%) was purchased from Fisher Scientific and diluted to create aqueous solutions of 20% and 32% HCl. 4-sulfonamidophenylhydrazine hydrochloride (**5**) (CAS: 17852−52−7) was purchased from Apollo and Fluorochem.

Sodium methoxide (0.197 g, 3.64 mmol, 1.4 equiv) was added to a 50 mL round-bottom flask followed by the addition of TMO (1.5 mL). Stirring was initiated and ethyl trifluoroacetate (**3**) (0.340 mL, 2.86 mmol, 1.1 equiv) 4′-methylacetophenone (**2**) (0.344 mL, 2.58 mmol, 1.0 equiv) was added. The reaction mixture was stirred at room temperature (22 °C) for 1 h. The reaction mixture was directly filtered under vacuum to isolate the product and kept under vacuum for 40 min to remove further solvent to yield 4,4,4-trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (**4**) as a cream-white solid (typical student yield of 0.43 g, 1.9 mmol, 73%, range of yields was 40%−89%).

IR ν_{max} (cm^{-1}) 1667, 1621, 1603, 1568, 1530, 1505, 1478, 1373, 1313, 1275, 1246, 1209, 1181, 1164, 1131, 1115, 940, 843, 808, 777, 750, 724, 688;

^{1}H NMR (400 MHz, d_6-DMSO) δ ppm: 7.71 (d, 2H, J = 8.2 Hz, Ar−H), 7.19 (d, 2H, J = 8.2 Hz, Ar−H), 5.96 (s, 1H, $COCH_2CO$), 2.32 (s, 3H, CH_3);

^{13}C NMR (101 MHz d_6-DMSO) δ ppm: 185.83, 169.01 (q, J = 27.9 Hz), 140.05, 139.01, 128.81, 126.77, 119.52 (q, J = 291.9 Hz), 87.01, 20.97;

^{19}F NMR (376 MHz, d_6-DMSO) δ ppm: −74.39;

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HRMS (ESI) m/z calc. for $C_{11}H_8F_3O_2$: 229.0482 $[M\text{-}H]^-$; found 229.0483.

4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (**4**) (0.2414 g, 1.049 mmol, 1.0 equiv)was added to a 25 mL round-bottom flask. Ethyl acetate (2 mL), deionized water (2 mL) and hydrochloric acid (0.4 mL, 32%, 10.17 M) were added, and the reaction stirred for 5 min. 4-sulfonamidophenylhydrazine hydrochloride (**5**) (0.258 g, 1.14 mmol, 1.1 equiv) was added, and the reaction heated to 55 °C for 2 h. The reaction mixture was cooled to room temperature; the ethyl acetate removed under vacuum and filtered. The product was washed with deionized water (10 mL) to yield celecoxib (**1**) (typical student yield of 0.29 g, 0.78 mmol, 73%, range of yields was 48%−100%).

IR ν_{max} (cm^{-1}) 3333, 3231, 3099, 2927, 1596, 1563, 1498, 1473, 1446, 1404, 1374, 1346, 1274, 1229, 1134, 1102, 1093, 1016, 981, 970, 952, 906, 845, 819, 801, 791, 761, 742, 720, 682;

^{1}H NMR (400 MHz, d_6-DMSO) δ ppm: 7.89 (d, 2H, J = 8.70 Hz, Ar−H), 7.55 (d 2H, J = 8.70 Hz, Ar−H), 7.54, (s, 2H, NH_2), 7.24−7.19 (m, 4H, Ar−H), 7.18 (s, 1H, CH), 2.31 (s, 3H, CH_3);

^{13}C NMR (101 MHz d_6-DMSO) 145.32, 144.04, 142.25 (q, J = 37.8 Hz), 141.18, 139.16, 129.48, 128.83, 126.87, 126.04, 125.42, 121.35 (d, J = 268.8 Hz), 106.19, 20.84;

^{19}F NMR (376 MHz, d_6-DMSO) δ ppm: −60.57;

HRMS (ESI) m/z calc. for $C_{17}H_{13}F_3N_3O_2S$: 380.0686 $[M\text{-}H]^-$; found 380.0679.

An alternative 2 day protocol is provided in the Supporting Information.

HAZARDS

All steps should be carried out in a fume hood. There are several chemicals with associated hazards that are highlighted in the risk assessment as part of the student lab script and technician guide in the Supporting Information. Particular care and attention need to be taken when handling sodium methoxide (given its flammability), 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione and 4-sulfonamidophenyl hydrazine hydrochloride (given their toxicity to aquatic life), and celecoxib (due to teratogenic properties). Given the above, approval from the school safety officer should be sought when conducting this experiment with upper division undergraduate students.

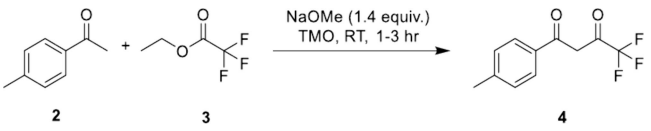
DEVELOPING A GREENER SYNTHESIS

The introduction of TMO as a replacement for toluene, as used in the patented procedure of Anumula et al.,[19] was compared to an alternative greener synthesis using ethanol as a solvent by Scholtz and Riley.[18] The 12 Principles of Green Chemistry were implemented to evaluate and guide the utilization of safer, green alternatives to the toxic solvents and chemicals, while also reducing the volume of waste produced.

Step 1: Synthesis of 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione

TMO was prepared via a procedure adapted from a screen of conditions and scale up by Byrne et al. from 2,5-dimethyl-2,5-hexanediol using a H-BEA zeolite.[23] The TMO collected was dried with magnesium sulfate. The TMO was subsequently dried using 3Å molecular sieves, where the water content was determined to be 0.18%. A student-led optimization of the synthesis of TFBD (**4**) in TMO was undertaken on a 0.2 g scale. An amount of 1.1 equiv ethyl trifluoroacetate (**3**) was initially added, and the reaction was stirred for 5 min. 4′-Methylacetophenone (**2**) was then added and 98% conversion to the step 1 product (**4**) was achieved (by ^{1}H NMR, see Scheme 1). Isolation by trituration with hexane limited the yield to 70%. It was observed that the cream-white product precipitated out of the reaction solution as it formed. To circumvent the inefficient extraction step that is responsible for a significant amount of hazardous organic solvent waste, we directly isolated the insoluble product from solution by vacuum filtration. When scaled up to 0.59 g/1.1 equiv of **3**, 1.0 equiv of **2** and 1.4 equiv of sodium methoxide (Scheme 2),

Scheme 2. Synthesis of 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (4) with 2,2,5,5-Tetramethyloxolane (TMO)



an average yield of 75% was obtained, with a range of 48%−94% obtained by the students (Figure 2). Further optimization

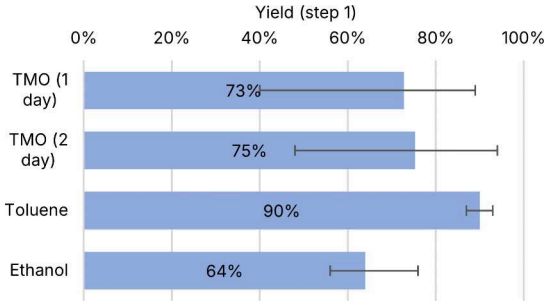


Figure 2. Yields obtained for Step 1 for a method suitable for a 1-day full experiment in TMO (1 h) or over 2 days (3 h and extended drying) in TMO, toluene, or ethanol. Error bars represent full range of student yields.

reduced the reaction time from 3 to 1 h (73% yield, range of 40%−89%). Despite the similar boiling point of TMO to toluene (112 vs 111 °C), it was noted that TMO proved to be more challenging to remove by rotary evaporation than toluene. Solvent removal by rotary evaporation can be extended, or **4** can be transferred to a watch glass to air-dry (up to 72 h). Alternatively, the product can be dried on a high vacuum line (for 40 min). The use of the shorter reaction time and vacuum line drying permitted a 1-day synthetic protocol of final product **1**, otherwise a 2-day class is required. If it is not possible to obtain or synthesize TMO then ethanol may be used, resulting in slightly lower yields (Figure 2).

Step 2: Synthesis of Celecoxib

The synthesis of celecoxib was first completed in ethanol by heating to reflux over 20 h.[16] The batch synthesis proposed by Scholtz and Riley requires a heating period of 17 h at 80 °C with 1.1 equiv of TFBD (**4**) and 1.0 equiv of 4-SAPH (**5**), followed by extraction with ethyl acetate then subsequent removal of the solvent to isolate celecoxib.[18] Replicating the Scholtz and Riley procedure on a 0.5 g scale yielded an oily dark yellow product that showed substantial impurities. A further attempt with the addition of 32% hydrochloric acid was performed. After the solvent was removed, the crude product was washed with water, yielding celecoxib with no appreciable impurities but in a poor 27% yield.

As previously described in the literature,[16,19] pyrazole ring synthesis (Step 2, Scheme 1) has also been accomplished in a 50:50 (v/v) biphasic mixture of ethyl acetate and water with a significantly shorter period of heating than described by

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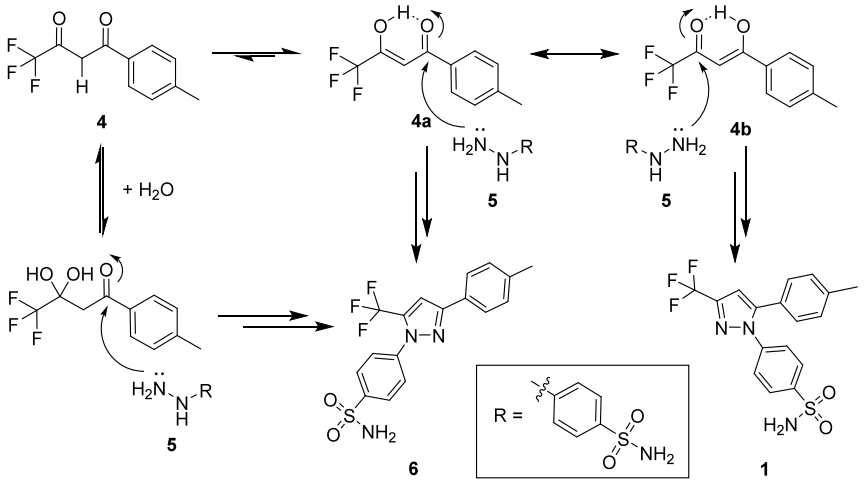
Scheme 3. Mechanism Showing the Formation of Celecoxib (1) and Its Regioisomer (6) *via* an Enol Intermediate or Geminal-Diol



Scholtz and Riley (2−5 h vs 17 h).[18] Reddy et al. also describe this step performed in water with comparable yield, which is appealing from a green chemistry perspective.[16] However, an impediment to using aqueous media is the greater formation of the regioisomeric impurity (**6**) of celecoxib (**1**). The regioselectivity of the reaction can be attributed to the formation of a diketone dihydrate at the carbonyl adjacent to the $-CF_3$ group,[16] Otherwise, an enol is formed (**4b**), preferentially with the aryl carbonyl so that some conjugation is gained and the relatively more electron deficient trifluoromethyl acyl carbonyl can receive the terminal nucleophilic nitrogen of the hydrazine (**5**), leading to the formation of the pyrazole with the $-CF_3$ group at the 3 position, which is celecoxib (**1**) (Scheme 3).

To investigate the regioselectivity of the reaction, the preparation of celecoxib in water was implemented on a 0.18 g scale with 1.0 equiv of TFBD (**4**), 1.1 equiv of 4-SAPH (**5**), and heated at 85 °C for 2 h. The product was filtered and washed with water. Here, 48% yield was achieved with approximately 30% impurities. This reaction was repeated in water with 0.1 mL of 32% hydrochloric acid and a 56% yield was achieved with approximately 8% of the regioisomeric impurity, identified via the downfield shift of the $-CH_3$ and Ar−H doublet peaks of the regioisomer (**6**) in the ^{1}H NMR spectra as reported in a comprehensive characterization effort of celecoxib (**1**) and its impurities by Satyanarayana et al.[30]

The solvent system of 50:50 ethyl acetate-water (16 mL total) then was implemented at a 0.4 g scale with 1.0 equiv of TFBD (**4**, 0.066 mol.dm^{-3}), followed by addition of 0.4 mL of 32% hydrochloric acid then 1.1 equiv of 4-SAPH (**5**), with heating to 85 °C for two hours. A yield of 44% was achieved for celecoxib (**1**) with no appreciable impurities. An extended five-hour reaction time resulted in an improved 61% yield and equal purity. A further iteration to assess a more concentrated reaction mixture was then evaluated. A reactant concentration of 0.174 mol.dm^{-3} with respect to **4**, where 3 mL of ethyl acetate and 3 mL of water was used, and the reaction was heated for two hours. A yield of 64% was obtained. Interestingly, **1** was observed to partly precipitate out of the reaction mixture. The penultimate iteration at a yet higher reactant concentration of 0.262 mol.dm^{-3} with respect to **4**, using 2 mL of ethyl acetate and 2 mL of water resulted in an average yield of 75% (61%−86%, see Figure 3). This reaction

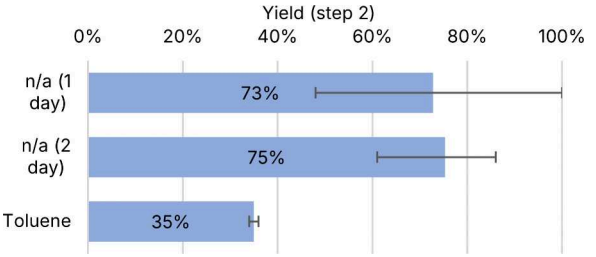


Figure 3. Yields obtained for the biphasic iteration of Step 2 suitable for a 1-day full experiment or over 2 days with and without toluene recrystallization. Error bars represent the full range of student yields.

is applicable for a 2-day practical class. Finally, the protocol was adapted to be suitable for a 1-day class. The reaction temperature was reduced to 55 °C and after 2 h to give an average yield of 73%, although the range of yields obtained by students was large, between 48%−100%. Nevertheless, because it can be completed in 1 day this final version was the preferred route to **1**, as shown in Scheme 4. Recrystallization from toluene was attempted but found to be unnecessary.[19]

Metrics Assessment

Alongside the synthesis (yield) optimization, the greenness of the procedure was monitored using the Process Mass Intensity (PMI) metric and the multiparameter DOZN tool.[29] The procedure patented by Anumula et al.[19] (labeled 'Industrial' in Figure 4) was compared to the Scholtz and Riley procedure ('Literature' in Figure 4).[18] The former uses toluene for the solvent in Step 1 (Scheme 2) and again for recrystallization in Step 2 (Scheme 4); the latter uses ethanol in both Step 1 and Step 2 as a solvent, and purification of intermediate **4** is performed by trituration with hexane. The metrics describing our procedures have been calculated with and without the synthesis of TMO included. The PMI values given in Figure 4 show that solvent use dominates the amount of waste generated in most procedures. When the synthesis of TMO is included in the PMI calculation, the waste generated is attributed to its 2,5-dimethylhexane-2,5-diol precursor. Otherwise, the inclusion of the TMO synthesis only has a minor effect on PMI, increasing from 46 to 52 for the 2-day protocol due to the water byproduct of TMO synthesis and the spent zeolite catalyst and some losses in the synthesis. The volume of

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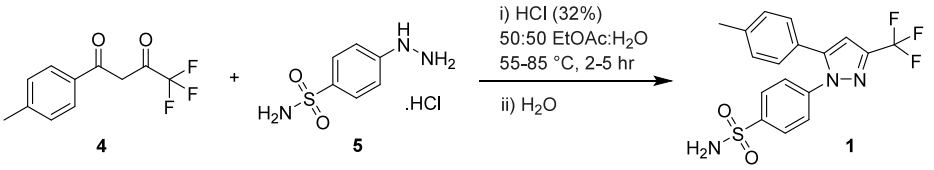
Scheme 4. Synthesis of Celecoxib (1) from 4,4,4-Trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione (4)



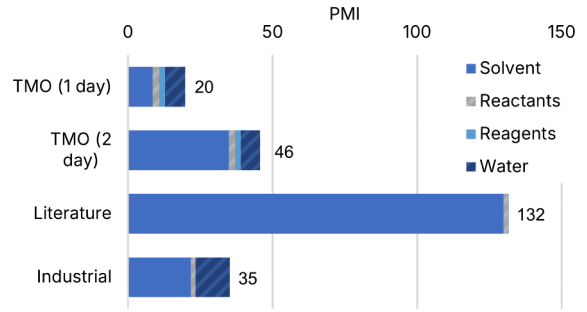


Figure 4. Comparison of the contributions to the Process Mass Intensity (PMI) from previous and adapted procedures to synthesize celecoxib (**1**) in 2 steps. TMO (where used) is designated as a solvent, and its synthesis is excluded. Equivalent charts including the synthesis of TMO are in the Supporting Information.

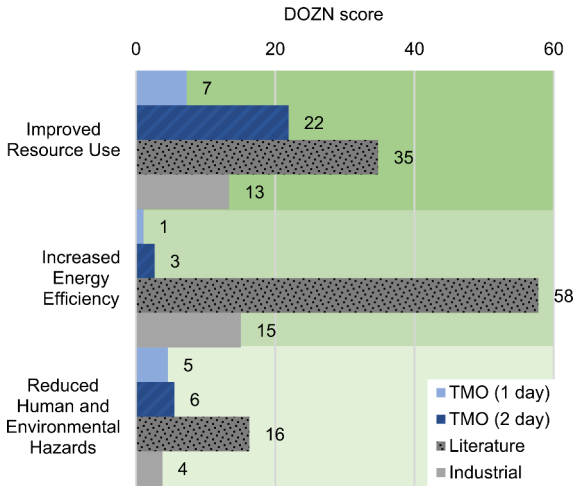


Figure 5. DOZN scores for waste, energy, and hazards (/100) from previous and adapted procedures to synthesize celecoxib (**1**) in 2 steps.

TMO needed in the 1-day protocol is small enough not to change the PMI when its synthesis is included. Our procedures are comparable in waste quantity to the patented toluene-based synthesis (PMI = 35).[19] The industrial process is less wasteful than the 2 day protocol using TMO because of the greater yields compared to our student cohort. Nevertheless, the PMI we achieved is superior to the Scholtz and Riley procedure due to the quantity of workup solvent used,[18] and further reduced to 20 with the 1-day procedure. A further advantage of our method is the lack of high hazard auxiliaries. By removal of toluene and hexane from the procedure, the waste is less hazardous.

The DOZN tool can be used to rank synthetic procedures according to each of the 12 Principles of Green Chemistry. These scores can be aggregated into 3 categories representing 'Improved Resource Use', 'Increased Energy Efficiency", and 'Reduced Human and Environmental Hazards', or a single overall average score can be made. Here, we show the 3 categories to give a fuller account of the greenness of each procedure (Figure 5). Each score has a maximum value of 100 and lower scores are preferable. 'Improved Resource Use' follows a trend similar to that calculated by PMI (Figure 4), and including TMO synthesis as part of the celecoxib (**1**) process is actually beneficial because its high atom economy improves the average material utilization of the whole procedure (see Supporting Information). 'Increased Energy Efficiency' is poor for the Scholtz and Riley 'Literature' procedure because of the long reaction time,[18] and by contrast the scores are very low for the optimized TMO procedures. The 'Reduced Human and Environmental Hazards' category also penalizes the 'Literature' procedure because of the use of hexane in particular, but overall, the scores are low in this category. It appears that human toxicity is not a strong factor in determining the DOZN 'Reduced Human and Environmental Hazards' category score once substance volumes are minimized.

IMPLEMENTATION WITH STUDENTS

Upon confirmation of the final procedure, postlaboratory questions for students to attempt were also developed and are available with model answers via the Supporting Information. The questions aim to assist students in determining how the reaction works by asking them to propose relevant reaction mechanisms. Students then consider advantages and disadvantages of toluene as a solvent, followed by evaluating the reaction holistically using various green chemistry metrics including atom economy, process mass intensity, and use of the DOZN tool. On the latter, following adoption of the DOZN tool for both research and instruction,[31,32] students are introduced to the tool via an online video tutorial.[33] Further to determining these metrics, students evaluate which process components contribute toward the process mass intensity, allowing them to appreciate problematic areas and opportunities to further enhance the process, considering possible green chemistry actions. Finally, students are asked to identify and explain how the process aligns with relevant Principles of Green Chemistry and, in doing so, develop an appreciation for the role that systems thinking has in conducting green chemistry. Student answers to these questions, in conjunction with the purity and yield of the product, were used as the assessment for this laboratory experiment.

The laboratory experiment was implemented with two groups of six (totaling 12) upper division undergraduate chemistry students. The synthesis was proved to be highly repeatable with good purity (Figures 2 and 3). Students initially completed the experiment over 2 days, with step 1 being completed in the first week and then dried in air until 7 days later when step 2 was undertaken to form the celecoxib product. The experiment was then safely amended such that

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step 2 is performed shortly after step 1 with more effective drying of intermediate **4** (via vacuum line or longer rotary evaporation). Students commented that they enjoyed the experiment and the chance to learn about green chemistry in the context of the synthesis of a pharmaceutical compound. They found the fact that they were making a recognizable commercial product via a greener route than the published standard particularly exciting. Indeed, this has also been found to the be the case for other laboratory experiments where a commercial product is synthesized.[9,34−37] The students fully characterized their products and answered the postlaboratory questions well, meeting the learning objectives of the activity.

There is also additional scope for instructors to implement this exercise as a more open-ended problem-based learning miniproject that is conducted over several sessions. Students could, for example, be provided with the literature standard and tasked to identify opportunities for making the process greener and enacting these designs within a laboratory setting. Through this, students could experiment with performing their own optimizations.

CONCLUSION

Adaptations to the process used to synthesize the nonsteroidal anti-inflammatory drug celecoxib have been made to improve the environmental impact of the reaction such that it can safely be implemented in undergraduate teaching laboratories. This provides the opportunity to introduce green chemistry concepts to students while conducting an experiment already developed for an introductory organic laboratory class that has significant appeal and relevance to students given the function of celecoxib as a drug for arthritis. Students can be taught about the 12 Principles of Green Chemistry, showing how they can be implemented in the context of the laboratory experiment, together with a potential comparison made to previously published routes. The green solvent TMO can also be discussed, and its utility as a potential alternative to toluene, and students use green chemistry metrics to justify their conclusions. While there are still factors limiting the greenness of the reaction, this offers the opportunity to discuss the fact that doing green chemistry is a journey and we can always work to attempt to make a process greener in cognizance of inherent limitations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.5c01453.

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

AUTHOR INFORMATION

Corresponding Authors

James Sherwood − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, England, United Kingdom*; Email: james.sherwood@york.ac.uk

Glenn A. Hurst − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, England, United Kingdom*; orcid.org/0000-0002-0786-312X; Email: glenn.hurst@york.ac.uk

Author

Francis Ho − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, England, United Kingdom*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jchemed.5c01453

Notes

The authors declare no competing financial interest.

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