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A Three-Step Synthesis of Benzoyl Peroxide

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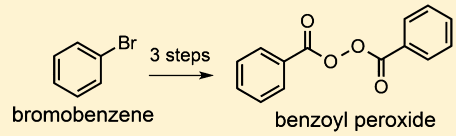
Supporting Information

ABSTRACT: Benzoyl peroxide is used as a bleaching agent for flour and whey processing, a polymerization initiator in the synthesis of plastics, and the active component of acne medication. Because of its simplicity and wide application, benzoyl peroxide is a target molecule of interest. It can be affordably synthesized in three steps from bromobenzene using procedures that can be performed in four, 4 h laboratory periods. This process includes a Grignard reaction to turn bromobenzene into benzoic acid, nucleophilic acyl substitution to transform the resulting carboxylic acid into an acid chloride, and the addition of H_2O_2/NaOH to the acid chloride to yield benzoyl peroxide. Most organic chemistry students are familiar with these traditional reaction mechanisms because they are covered in introductory organic chemistry courses. The starting materials for each reaction are commercially available, and the products can be readily characterized using NMR spectroscopy, IR spectroscopy, and melting point.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Grignard Reagents, Hands-On Learning/Manipulatives, Aromatic Compounds, Drugs/Pharmaceuticals, IR Spectroscopy, NMR Spectroscopy, Synthesis*

Since most useful synthesis targets require more than one synthetic step, it is imperative that undergraduate chemistry students be exposed to laboratories that require multistep transformations. To this aim nearly all of our second-semester organic chemistry laboratories are devoted to multistep synthesis projects. Here, the three-step synthesis of benzoyl peroxide (Figure 1) is described. The goal of this experiment is to give students experience completing a multistep transformation in order to prepare them for a capstone project where they are required to propose and execute a multistep synthesis of their choosing. In addition students learn how to scale literature procedures in order to use them with the amount of reagent synthesized from a previous step.

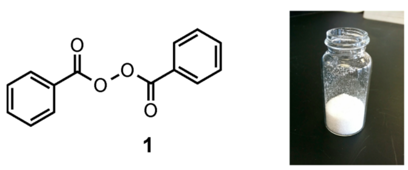


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Figure 1. Structure of benzoyl peroxide and a picture of student synthesized benzoyl peroxide.

Organic chemistry classes and their associated laboratories are usually filled with preprofessional students or students pursuing majors in chemistry, biology, nutrition, or dietetics. Benzoyl peroxide is a particularly interesting target because its applications are as wide and varied as the interests of students. Benzoyl peroxide is the most effective and most common ingredient in acne medications.[1,2] Its anti-inflammatory and antibacterial activities are effectively potent against the acne-causing bacteria *Propionibacterium acnes* (*P. acnes*).[3] This antibiotic is superior to other acne drugs because *P. acnes* does not commonly develop benzoyl peroxide resistance. Even though skin dryness and irritation can be common side effects with benzoyl peroxide medications, they can be avoided by strategies that allow a slow, controlled drug release.[4] In addition to showing effectiveness against *P. acnes*, benzoyl peroxide also has broad spectrum activity against Gram-positive and Gram-negative bacteria, as well as yeasts and fungi.[5]

Benzoyl peroxide also has applicability in industrial, food science, and dental applications. Chemically, it is used as a polymerization initiator for the synthesis of polystyrene and acrylate polymers and copolymers.[6] These polymers are crucial components to Super Glue, plexiglass, and many types of plastics. Benzoyl peroxide's bleaching properties make it a common additive in many foods, including flour, cheese, and whey. Exposing these foods to benzoyl peroxide whitens and brightens their color and serves as a sterilization agent.[7] Dental applications include using benzoyl peroxide as a polymerization agent for tooth cements and restoratives, or as a bleaching agent for whitening of teeth.[8]

■ EXPERIMENTAL OVERVIEW

Three different reaction types are required in the synthesis of benzoyl peroxide (Scheme 1). The first reaction type is the classical Grignard reaction between phenylmagnesium bromide and CO_2 to yield benzoic acid, **2**. This reaction has universal coverage in all organic texts and is an important carbon−carbon bond forming reaction used to synthesize carboxylic acids through one-carbon homologation of halides. Since Grignard reagents react with water, it also affords the opportunity for

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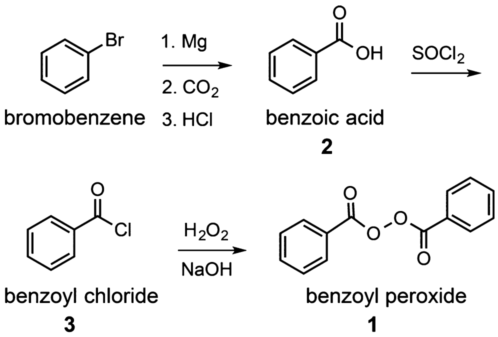
Scheme 1. Three-Step Synthesis of Benzoyl Peroxide



students to practice flame drying and moisture-exclusion techniques.

Benzoic acid, **2**, produced from the first step is turned into a more electrophilic carboxylic acid derivative using $SOCl_2$. The second reaction type is the traditional method for synthesizing acid chlorides, but the hazards of thionyl chloride and the production of SO_2 gas as a reaction byproduct make it even more crucial that this reaction be performed in a fume hood. It is important to note that $SOCl_2$ has been used in other undergraduate multistep synthetic procedures, including the synthesis of the bug repellent DEET and the synthesis of novel flavones.[9,10]

The final reaction type is a nucleophilic addition elimination reaction between sodium hydroperoxide and two equivalents of benzoyl chloride. Sodium hydroperoxide is synthesized by adding NaOH to H_2O_2. This solution is slowly added to a cooled solution of benzoyl chloride to generate benzoyl peroxide. Benzoyl peroxide has been synthesized using this final step on an industrial scale.[11] The procedure reported here has been optimized for smaller amounts of reagents.

■ EXPERIMENT

In the first week, students generate phenylmagnesium bromide Grignard reagent in situ and react it with solid CO_2 to produce benzoic acid, **2**. Magnesium salts and unreacted bromobenzene are removed by two rounds of extraction. During the second week, crude benzoic acid is purified by recrystallization and the product is characterized by IR spectroscopy, ^{13}C NMR and ^{1}H NMR spectroscopy, and melting point. During the third lab period, **2** is converted to benzoyl chloride, **3**, by addition of thionyl chloride. Excess thionyl chloride is distilled and the crude product is characterized by IR spectroscopy and ^{13}C NMR and ^{1}H NMR spectroscopy. In the final laboratory period, students generate sodium hydroperoxide and add it to **3** to synthesize benzoyl peroxide, **1**, which is purified by recrystallization and characterized by IR spectroscopy, ^{13}C NMR and ^{1}H NMR spectroscopy, and melting point. Detailed procedures are given in the Supporting Information.

■ HAZARDS

All three steps of this experiment should be carried out in a fume hood. Magnesium is flammable and an irritant. Bromobenzene is an irritant and permeator in cases of eye and skin contact and is flammable. Diethyl ether is flammable and an irritant and permeator and can form explosive peroxides after long-term storage. Hydrochloric acid is corrosive and an irritant, permeator, and lung sensitizer. CO_2 is an asphyxiant and can cause burns to unprotected skin. Benzoic acid is an irritant to skin and eyes and a permeator in cases of skin contact. Thionyl chloride is an irritant and permeator, is water reactive, and can cause burns. It is also corrosive and harmful if inhaled. Benzoyl chloride is an irritant, permeator, and sensitizer. It may produce burns upon skin contact and is harmful if inhaled. Chloroform-*d* is a carcinogen, irritant, and permeator. Sodium hydroxide is corrosive and can cause burns upon skin contact. Ethyl acetate is an irritant and is flammable. Hexanes is an irritant and neurotoxin and is flammable. UV light can cause cancer upon long-term exposure and can cause retinal burns. Hydrogen peroxide is an irritant, permeator, and lung sensitizer. Methanol is flammable, an irritant in cases of skin and eye contact, and a permeator. Benzoyl peroxide is an irritant and may be combustible at high temperatures. Do not grind benzoyl peroxide or store it in large quantities. Melting point analysis is required to be done in unsealed melting point tubes. If benzoyl peroxide is heated in a closed environment, it has explosive properties. Wear goggles, gloves, and protective clothing throughout all procedures.

■ RESULTS AND DISCUSSION

A multistep synthesis is used as a capstone project in our second-semester organic chemistry laboratory course. Students are required to propose a three- to four-step synthesis of their choosing using an experimental planning model published by Graham and co-workers.[12] Students often choose targets for these projects from multistep procedures previously published in this *Journal*. This has included the synthesis of chrysanthemic acid, a Prozac precursor, a Japanese beetle pheromone, and piperine (the component in black pepper that makes people sneeze).[13−16] While these targets are interesting and require procedures of appropriate complexity for a second-semester organic chemistry student, they often require expensive reagents and have intermediates that are not commercially available. This makes them unattractive for completion by larger lab sections and leaves students frustrated when they have an unsuccessful step since they cannot move forward with their synthesis. The synthesis of benzoyl peroxide circumvents both of these problems since reagents and synthetic intermediates are relatively inexpensive and are commercially available. In addition, all three mechanisms required for this synthesis are typically taught in second-semester organic chemistry lectures and the benzoyl peroxide product has multiple uses that are of interest to students of a variety of majors.

Pedagogically, the synthesis of benzoyl peroxide aimed to do the following: (1) Illustrate a multistep synthesis and the concept of scaling modifications. (2) Provide opportunities for students to increase their proficiency in the purification techniques of distillation, recrystallization, and extraction. (3) Use multiple validation methods to confirm a product's identity (IR spectroscopy, ^{13}C NMR and ^{1}H NMR spectroscopy, and melting point). (4) Demonstrate the procedures needed to complete a water sensitive reaction.

The experiment was designed for completion in four, 4 h lab periods using standard organic glassware. Four, 3 h lab periods would also work, but students would have less in-lab time for data analysis. For in-class testing, experiments were completed by three lab sections, each consisting of 5 to 10 student pairs. Each time the project was executed during weeks 3−6 of a 14 week second semester. It is important to note that the synthetic intermediates **2** and **3** are relatively inexpensive and commercially available. Thus, students who were unsuccessful completing a step still progressed forward with their synthesis the following week. Over half of the lab groups were able to complete the three-step synthesis without being given commercially available intermediates. Overall, the average success rate for any reaction in this sequence was 86% with 72 out of 84 attempted reactions yielding enough product to analyze and to move forward to another step.

The synthesis of benzoic acid from bromobenzene allowed students to practice techniques needed for moisture sensitive reactions through the use of drying tubes and flame drying. The reaction was heated at reflux and purified by extraction and recrystallization. Student yields for successful reactions ranged from 30 to 65%. An IR spectrum showed a carboxylic acid OH stretch, a carbonyl stretch at 1685 cm^{-1}, and a C−O stretch at 1287 cm^{-1}. A ^{1}H NMR spectrum clearly showed three distinct signals in the aromatic region with 2:1:2 ratios that can be deciphered by their apparent first-order splitting pattern. A ^{13}C NMR spectrum showed evidence of the introduction of a carbonyl by the presence of a signal at 172.7 ppm. Representative student spectra for all products are in the Supporting Information. Melting points were also reliable methods for characterization as they were usually within a couple of degrees of literature reports. Note: If NMR spectroscopy is not available, students will be able to interpret their data using changes in IR frequencies and melting points of reaction products in this step and subsequent steps.

The synthesis of benzoyl chloride required reflux, TLC analysis, and purification by distillation. Student yields varied from 50% to quantitative. An IR spectrum showed the disappearance of an OH stretch and a change in the carbonyl stretch from 1685 to 1775 cm^{-1}. Again, a ^{1}H NMR spectrum showed three distinct peaks in the aromatic region with 2:1:2 ratios that can be deciphered by their apparent first-order splitting patterns. These peaks had slightly different chemical shifts than the starting material. A key difference in the ^{13}C NMR spectrum of starting material and the product was a shift of the carbonyl carbon signal from 172.7 to 168.4 ppm.

The synthesis of benzoyl peroxide required the addition of in situ generated sodium hydrogen peroxide to benzoyl chloride and subsequent purification by recrystallization. Student yields for successful conversions ranged from 30 to 50%. Melting point analysis using slightly damp samples of benzoyl peroxide in unsealed melting point tubes produced melting point ranges within 1−2 degrees of literature reports.[17] It is important to note that the tubes must be unsealed as benzoyl peroxide has explosive properties when heated in a closed environment. Instructor tests using overloaded samples in sealed melting point tubes resulted in the tube cracking when heated. An IR spectrum showed the appearance of an absorbance at 1203 cm^{-1} to confirm the presence of the C−O functionality in the product. Again, students were able to show that a reaction had occurred by frequency changes in both the ^{13}C NMR and ^{1}H NMR spectra. The overall yield for the complete three-step synthesis ranged between 10 and 20%.

Having students perform the multistep synthesis of benzoyl peroxide early in second-semester organic chemistry laboratories has improved student confidence when executing procedures later in the semester. This has had a great impact on students' ability to plan and execute a capstone multistep synthesis project like those described by Graham and coworkers.[12] When compared to previous semesters, a greater percentage of students were able to complete their capstone synthesis of a multistep target of their choosing. Students were also able to scale synthetic procedures for these projects without class time dedicated to reviewing this concept.

■ ASSOCIATED CONTENT

Supporting Information

Notes for the instructor; student handout; NMR and IR spectra of intermediates and product. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Eady, E.; Cove, J.; Joanes, D. Topical antibiotics for the treatment of acne vulgaris: a critical evaluation of the literature on thier clinical benefit and comparative efficacy. *J. Dermatol. Treat.* **1990**, *1* (4), 215−226.

(2) Tripathi, S. V.; Gustafson, C. J.; Huang, K. E.; Feldman, S. R. Side effects of common acne treatments. *Expert Opin. Drug Saf.* **2013**, *12* (1), 39−51.

(3) Dreno, B. Topical antibacterial therapy for acne vulgaris. *Drugs* **2004**, *64* (21), 2389−2397.

(4) Nokhodchi, A.; Jelvehgari, M.; Siahi, M. R.; Mozafari, M. R. Factors affecting the morphology of benzoyl peroxide microsponges. *Micron* **2007**, *38* (8), 834−840.

(5) Kligman, A. M.; Leyden, J. J.; Stewart, R. New uses for benzoyl peroxide: a broad-spectrum antimicrobial agent. *Int. J. Dermatol.* **1977**, *16* (5), 413−417.

(6) Mikheev, Y. A.; Zaikov, G. E. Functions of a molecular sponge in heterophase chain reactions of block polymers as illustrated by the arylation of polystyrene by dibenzoyl peroxide. *Plast. Massy* **1996**, *39* (6), 3−15.

(7) Abe-Onishi, Y.; Yomota, C.; Sugimoto, N.; Kubota, H.; Tanamoto, K. Determination of benzoyl peroxide and benzoic acid in wheat flour by high-performance liquid chromatography and its identification by high-performance liquid chromatography-mass spectrometry. *J. Chromatogr., A* **2004**, *1040* (2), 209−214.

(8) Kwon, T.-Y.; Bagheri, R.; Kim, Y. K.; Kim, K.-H.; Burrow, M. F. Cure mechanisms in materials for use in esthetic dentistry. *J. Invest. Clin. Dent.* **2012**, *3* (1), 3−16.

(9) Knoess, H. P.; Neeland, E. G. A modified synthesis of the insect repellent DEET. *J. Chem. Educ.* **1998**, *75* (10), 1267−1268.

(10) Letcher, R. M. An undergraduate organic laboratory project involving independent synthesis of novel flavones. *J. Chem. Educ.* **1980**, *57* (3), 220−221.

(11) La Berge, R. G.; Johnson, L. J. *Preparation of Benzoyl Peroxide.* U.S. Patent 3,674,858, 1972.

(12) Graham, K. J.; Schaller, C. P.; Johnson, B. J.; Klassen, J. B. Student-Designed Multistep Synthesis Projects in Organic Chemistry. *Chem. Educ.* **2002**, *7* (6), 376.

(13) Schatz, P. F. Synthesis of chrysanthemic acid. A multistep organic synthesis for undergraduate students. *J. Chem. Educ.* **1978**, *55* (7), 468−470.

(14) Perrine, D. M.; Sabanayagam, N. R.; Reynolds, K. J. Synthesis of NMP, a fluoxetine (Prozac) precursor, in the introductory organic laboratory. *J. Chem. Educ.* **1998**, *75* (10), 1266.
(15) Bartlett, P. A.; Marlowe, C. K.; Connolly, P. J.; Banks, K. M.; Chui, D. W. H.; Dahlberg, P. S.; Haberman, A. M.; Kim, J. S.; Klassen, K. J.; Lee, R. W.; Lum, R. T.; Mebane, E. W.; Ng, J. A.; Ong, J.-C.; Sagheb, N.; Smith, B.; Yu, P. Synthesis of frontalin, the aggregation pheromone of the southern pine beetle: a multistep organic synthesis for undergraduate students. *J. Chem. Educ.* **1984**, *61* (9), 816–817.
(16) Sloop, J. C. Microscale synthesis of the natural products carpanone and piperine. *J. Chem. Educ.* **1995**, *72* (2), A25–A27.
(17) Young, J. A. Benzoyl peroxide. *J. Chem. Educ.* **2006**, *83* (5), 696.