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Synthesis of Flufenamic Acid: An Organic Chemistry Lab Sequence Using Boronic Acids and Nitrosoarenes under Transition-Metal-Free Conditions

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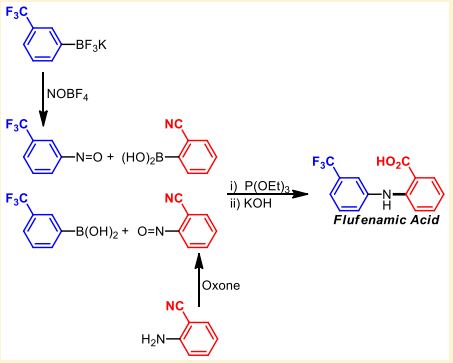
Supporting Information

ABSTRACT: A method for the synthesis of flufenamic acid, a nonstereoidal anti-inflammatory drug (NSAID) of the anthranilate family (fenams), is described as an experiment for the upper-division undergraduate organic chemistry laboratory. The key step is the formation of the diarylamine moiety of flufenamic acid by a novel reaction consisting of the coupling of nitrosobenzenes with boronic acids under transition-metal-free conditions. On the one hand, students can compare the performance of two different methods for the preparation of nitrosobenzenes (oxidation of amines and *ipso*-S_EAr reaction on potassium organotrifluoroborates). On the other hand, they compare the yields of two complementary examples for the coupling of nitrosobenzenes with boronic acids. The reactions are followed by thin layer chromatography, and the products are purified by percolation or by column chromatography. Students are also tasked with the confirmation of the structure of the products based on melting point, infrared, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy, and MS spectrometry.



KEYWORDS: *Upper-Division Undergraduate, Organic Chemistry, Collaborative/Cooperative Learning, Aromatic Compounds, Drugs/Pharmaceuticals, Nonmetals*

INTRODUCTION

The synthesis of best-selling pharmaceutical compounds is one of the most attractive laboratory experiments for organic chemistry students. In addition to serving as good targets for the acquisition of good manipulation skills, they constitute a link between organic chemistry and pharmacology. This is particularly appealing to upper-division organic chemistry students in pharmaceutical science courses.

In this experiment, students synthesize (in three, 3-h lab sessions) flufenamic acid (2-[[3-(trifluoromethyl)phenyl]-amino]benzoic acid, **1**),[1] a representative example of the fenamate family of nonstereoidal anti-inflammatory drugs (NSAIDs). NSAIDs (Figure 1) are among the best-selling drugs worldwide (there is an estimate of more than 100 million prescriptions per year in the USA alone). Their importance relies on their anti-inflammatory, analgesic (pain-reducing), and antifever actions, without the undesirable side effects of opioid analgesics (respiratory depression and addiction) or glucocorticoids (immunosuppression, hyperglycemia, osteoporosis, adrenal insufficiency, etc.). Aspirin, a derivative of salicylic acid (salicylates), is the best-known example of an NSAID. Furthermore, most relevant commercial NSAIDs approved for use in humans belong to the families of fenamic acid derivatives (fenamates), propionic acid derivatives (profens), acetic acid derivatives, and enolic acid derivatives (oxicams).

Fenamates are bioisosters of salicylates by replacement of an oxygen atom with an NH group. Besides flufenamic acid, other representatives of the fenam family of NSAIDs are mefenamic acid, mechlofenamic acid, tolfenamic acid, and etofenamate. They have higher anti-inflammatory activity than salicylates. In particular, flufenamic acid is effective in treating rheumatism, arthritis, and other musculoskeletal inflammatory disorders very effectively. Multiple laboratory experiments have been reported for the preparation of aspirin,[2] and some laboratory experiments are also available for the preparation of other NSAIDs such as acetaminophen or ibuprofen.[3] However, no synthesis of fenamates has been reported at a student level.

Flufenamic acid has a diarylamine structure. The diarylamines are an important class of organic compounds, frequently found among drugs, agrochemicals, dyes, radical-trapping antioxidants, electroluminescent materials, and ligands for transition-metal catalysis.[4] The most frequent syntheses for these types of compounds (Scheme 1) are based on transition-metal-catalyzed coupling reactions between anilines and halobenzenes such as the Ullmann−Goldberg[5] (Cu-catalyzed) and the Buchwald-Hartwig[6] reactions (Pd-catalyzed). The Cu-catalyzed coupling between anilines and

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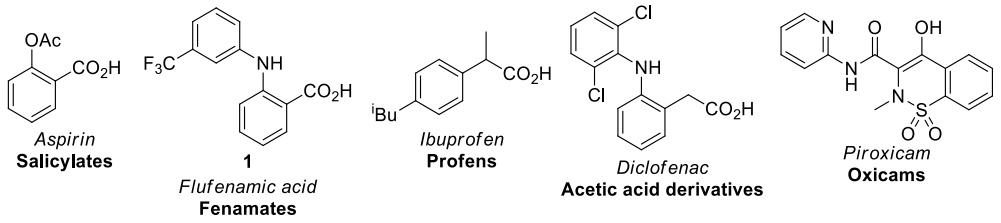
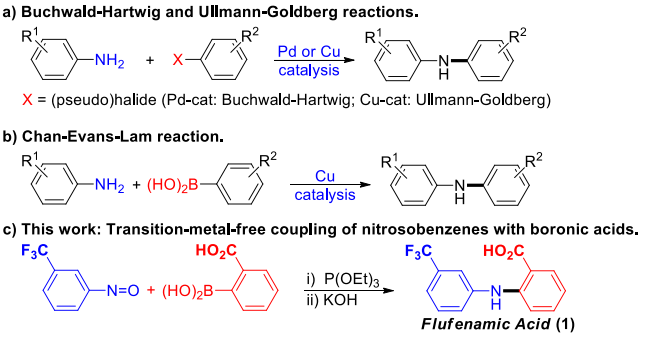


Figure 1. Structures of flufenamic acid and other representative NSAIDs.

Scheme 1. Syntheses of Diarylamines



boronic acids (Chan-Evans-Lam reaction)[7,8] is also popular.[9] These reactions require the use of expensive metal catalysts, the presence of ligands, and extensive individual optimization of reaction conditions. Many transition-metal catalysts are highly toxic and sensitive to air or moisture. Residual traces of heavy metals in the final product can be difficult to remove. Because of their potential toxicity, this is not acceptable in pharmaceutical applications.

In particular, flufenamic acid and other N-arylanthranilic acids have been synthesized by the Ullmann−Goldberg condensation between *o*-halobenzoic acids and anilines.[1,10,11] The reaction usually requires harsh conditions, long reaction times, and yields are low. In this experiment, we have chosen as a key step a new approach that uses boronic acids and nitrosobenzenes as reaction partners in a C−N bond-forming reaction that is carried out under transition-metal-free conditions.[12,13] This step simultaneously exploits the electrophilicity of the nitroso group and the nucleophilicity of a boronic acid that has been activated as an ate complex by coordination to nitrogen. The reaction is promoted by $P(OEt)_3$, which serves as an oxygen scavenger because of the formation of a strong P=O bond (see Discussion Section). The subproduct of the reaction, triethyl phosphate, is much less toxic than transition-metal wastes. Boric acid, another subproduct of the reaction, is of low toxicity. Therefore, the experiment minimizes the generation of hazardous substances. In the experiment, students compare the performance of two complementary examples to this coupling. In addition, they compare two different methods for the preparation of nitrosobenzenes (oxidation of amines and *ipso*-S_EAr reaction on potassium organotrifluoroborates).

PEDAGOGICAL SIGNIFICANCE

In the introductory undergraduate organic chemistry laboratory, students' attention is focused on learning basic laboratory skills for setting up reactions and purification of organic compounds. In advanced undergraduate courses, the experiments are generally designed to review the abilities acquired in the introductory lab in connection with the aspects of reactivity covered in lectures. From a pedagogical point of view, this approach allows students to acquire a better understanding of the theoretical aspects of organic chemistry. However, the advanced undergraduate organic chemistry laboratory is a very good place to introduce new concepts and reactions that are not generally addressed in theoretical courses.

With the final goal of synthesizing flufenamic acid (in three, 3-h lab sessions), the aim of this experiment is two-fold. First, it acquaints students with the chemistry of nitroso compounds, an almost overlooked case among the nitrogen-containing functional groups covered in second-year undergraduate organic chemistry courses.[14] In recent years, nitroso compounds have become of great importance in organic synthesis as a viable alternative to other nitrogen-containing reagents. Second, it allows them to expand their knowledge of the chemistry of boronic acids.[15] These compounds are widely known currently for their participation as reagents in the transition-metal-catalyzed Suzuki[16] or Chan-Evans-Lam reactions.[7] However, they can also participate in other types of transformations as well, even without the need for metal catalysis.[17] This aspect of the reactivity of boronic acids is less well-known to students and is currently an active area of research. Theoretical background for a better understanding of these reactions is provided in the Handout for Students (see Supporting Information, S82).

The pedagogic goals of this experiment are for students to (1) become familiarized with nitrosobenzenes and compare the performance of two different methods for their synthesis; (2) become familiarized with new reactions of boronic acids, and compare the yields of two complementary examples for the coupling of nitrosobenzenes with boronic acids under transition-metal-free conditions; and (3) review the synthesis of carboxylic acids by the hydrolysis of nitriles. As learning outcomes, they will be able to (1) monitor reactions by TLC; (2) purify organic compounds by column chromatography; (3) identify products by melting point, infrared, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy, and MS spectrometry; and (4) search for reactions in databases (answer prelab and postlab questions). Collaborative working is also exercised because students will have to compare their results in a discussion session.

Assessment of the achievement of these learning goals was conducted using a prelab questionnaire, grading oral discussions between students and instructors throughout the experiment and the discussion sessions, and from the answers to a postlab questionnaire. All students have achieved the learning outcomes, increased their knowledge of the reactivity of nitroso compounds and boronic acids, and were more comfortable carrying out multistep reaction sequences, reading contemporary literature, understanding new reaction mechanisms and interpreting spectral data, in particular, NMR spectra of fluorine-containing molecules.

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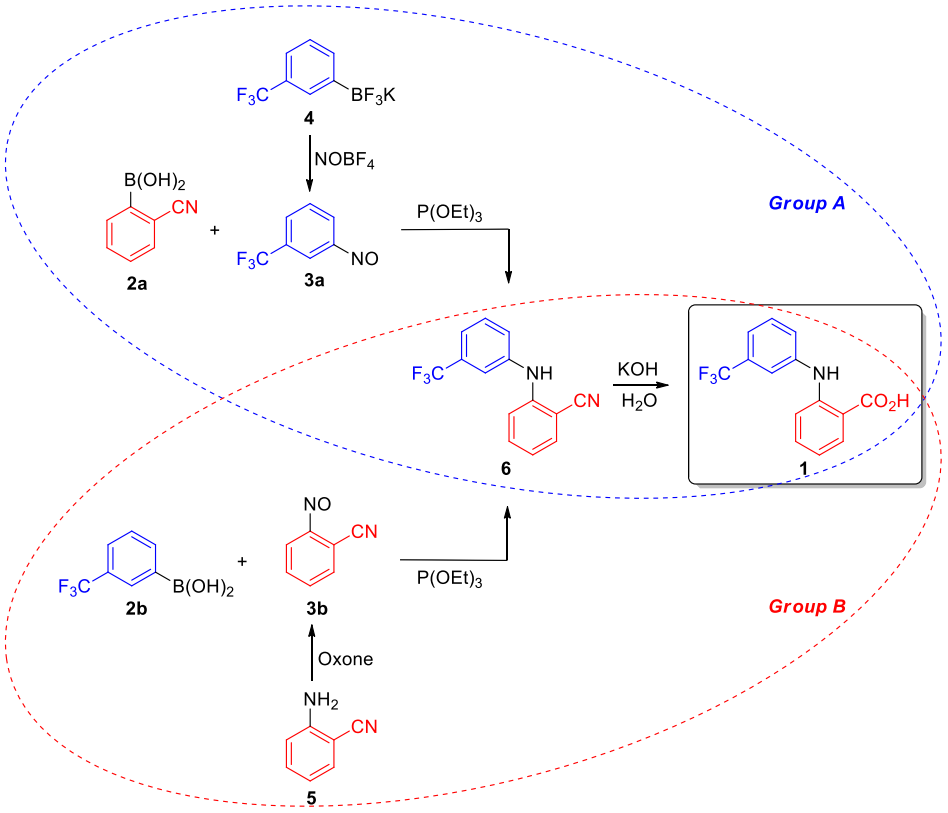
Scheme 2. Transition-Metal-Free Sequence To Synthesize Flufenamic Acid Using Boronic Acids and Nitrosoarenes



EXPERIMENTAL OVERWIEW

The overall synthetic strategy is presented in Scheme 2. The experiment is carried out by two groups of students (Group A and Group B) that follow two complementary approaches to converge on key intermediate 2-[[3-(trifluoromethyl)phenyl]-amino]benzonitrile (**6**). The difference between both approaches relies on the substitution patterns of the reaction partners: Students in Group A prepare **6** by reacting 2-(cyanophenyl)boronic acid (**2a**) with 1-nitroso-3-(trifluoromethyl)benzene (**3a**), while students in Group B prepare **6** by reacting [3-(trifluoromethyl)phenyl]boronic acid (**2b**) with 2-nitrosobenzonitrile (**3b**). Last, the nitrile group in **6** is hydrolyzed to afford the target **1** (both groups). Each member of the group works individually. Students are tasked with the comparison of both approaches for the synthesis of **6** and for the preparation of nitrosobenzenes **3a** and **3b**.

The first day is dedicated to the preparation of nitrosobenzenes **3a** and **3b**. The students compare the performance of two methods for the preparation of two different nitrosobenzenes: *ipso*-S_EAr reaction on potassium organotrifluoroborates using $NOBF_4$ (synthesis of **3a**, acetonitrile, room temperature, 30 min) (Group A) and oxidation of amines using oxone (synthesis of **3b**, dichloromethane/H_2O, room temperature, 1.5 h) (Group B). The progress of these reactions is followed by TLC. The products are isolated by extraction (dichloromethane) and purified by a simple percolation through silica gel. Also on the first day, the students carry out a discussion session of the prelab questions.

The second day, students compare the yields of two different examples for the transition-metal-free C−N coupling reaction between two commercial boronic acids and nitrosobenzenes that lead to **6**, using $P(OEt)_3$ as a promoter (tetrahydrofuran, room temperature, 20 min): reaction of boronic acid **2a** with nitroso compound **3a** (Group A) and reaction of boronic acid **2b** with nitroso compound **3b** (Group B). The progress of the reactions is followed by TLC. Compound **6** is purified by column chromatography. Also on day 2, both groups of students set up the hydrolysis reaction that transforms the nitrile group in **6** into the carboxylic acid in **1** (KOH, methanol/H_2O, 100 °C, overnight). The progress of the hydrolysis reaction is followed by TLC.

The last day is devoted to the isolation and purification of **1** by acidification, followed by extraction and column chromatography.

None of the transformations in the sequence involves the use of transition metals, and the transformations are carried out without the need for an inert gas atmosphere or, especially, dried solvents. See the Supporting Information (S16) for full experimental details.

The students determine the structures of the products based on their melting points, infrared, ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopy, and MS spectrometry. The presence of the trifluoromethyl group in the target molecule and in some of the intermediates is noteworthy. In particular, the C−F couplings found in the ^{13}C NMR spectra are highly instructive because these are topics that are not often discussed at the introductory levels. Also, the MS fragmentation pattern of flufenamic acid serves to review the so-called *ortho*-effect.

The discussion is completed in a postlab seminary session. In this discussion session, the students compare the performance of the syntheses of nitrosobenzenes carried out by Group A (synthesis of **3a** by *ipso*-S_EAr on potassium [3-(trifluoromethyl)phenyl]borate **4**) and Group B (synthesis of **3b** by oxidation of the amino group in 2-aminobenzonitrile **5**) in terms of yields of the products, purity, hazards, and

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simplicity of the experimental procedures. In addition, they compare the yields and purity of the two approaches for the synthesis of **6** and discuss the literature, reaction mechanisms, and spectroscopic and spectrometric data.

HAZARDS

Goggles and gloves should be worn throughout the lab sessions, and the experiments should be performed in a properly ventilated hood. Standard precautions should be taken when handling all chemicals, which are toxic if swallowed. Potassium [3-(trifluoromethyl)phenyl]-trifluoroborate causes skin irritation and serious eye irritation and may cause respiratory irritation. 3-Trifluoromethyl-phenylboronic acid, 2-cyanophenylboronic acid, and 2-amino-benzonitrile can cause skin, eye, and respiratory irritation. 2-Aminobenzonitrile may also cause an allergic skin reaction. The hazards of 1-nitroso-3-(trifluoromethyl)benzene, 2-nitro-sobenzonitrile, and 2-[[3-(trifluoromethyl)phenyl]amino]-benzonitrile are not known; therefore, they must be treated as toxic. Flufenamic acid is toxic if swallowed and causes skin irritation and serious eye irritation. Triethyl phosphite is a flammable liquid and vapor, harmful if swallowed, and may cause an allergic skin reaction. Triethyl phosphate, subproduct of the reaction, is harmful if swallowed and causes serious eye irritation. Ingestion or absorption of boric acid, a subproduct of the reaction, may cause erythematous lesions on the skin and mucous membranes. Nitrosonium tetrafluoroborate causes serious eye damage and severe skin burns. Oxone causes severe skin burns and eye damage and may produce an allergic reaction. Potassium hydroxide causes severe skin burns and eye damage and may be corrosive to metals. Hydrogen chloride causes skin irritation and serious eye damage and may cause drowsiness or dizziness. Repeated exposure may cause skin dryness or cracking. Solvents and their vapors (tetrahydrofuran, methanol, acetone, acetonitrile, methylene chloride, hexane, and ethyl acetate) are highly flammable substances that cause serious eye, respiratory, and skin irritation. They may cause respiratory irritation and drowsiness or dizziness. *n*-Hexane is neurotoxic. Tetrahydrofuran may form explosive peroxides. Chloroform-d_1 is carcinogenic in cases of chronic exposure. Dimethyl sulfoxide-d_6 is a flammable liquid. Silica gel is carcinogenic. All manipulations involving silica gel should be carried out in a fume hood, and it should be discarded in appropriately labeled containers. Solid and liquid waste should be disposed of in properly labeled containers as halogenated or nonhalogenated waste.

RESULTS AND DISCUSSION

This experiment was performed by four groups of four students each, divided into two subgroups (Group A and Group B, 2 students per group) in an upper-division undergraduate (fourth year, second semester) organic chemistry lab course.

Students in Group A started by transforming **4** into **3a**, while students in Group B began by transforming **5** into **3b**. After extraction and percolation, they checked the purity of their products by TLC. Nitrosobenzene **3a** was obtained almost pure, whereas nitrosobenzene **3b** was obtained with a small amount of the azoxybenzene resulting from dimerization, which was observed on TLC and ^{1}H NMR spectroscopy (approximately 10%, determined by integration of the ^{1}H NMR spectrum, see Supporting Information, S75). Yields ranged between 30−45% for compound **3a** and 68−71% for compound **3b**. With both nitrosobenzenes in hand, the students undertook the synthesis of **6** by coupling **2a** with **3a** (Group A) or **2b** with **3b** (Group B). The yields for the coupling of **2a** with **3a** (Group A) were rather low, ranging between 31 and 35% after chromatography. Although the yield was modest, the procedure was reliable. On the other hand, the yields for the coupling of **2b** with **3b** (Group B) were much higher, ranging between 65 and 68%. In both cases, the purification of **6** was carried out by column chromatography. The chromatography carried out by Group A was more difficult because two spots were observed on TLC. The product has the lowest R_f value. The highest R_f value corresponds to the azoxybenzene derived from nitroso compound **3a**, which was formed during the coupling reaction between **3a** and **2a**. The students could observe it in the column chromatography because it was a bright yellow color. The students checked the purity of their products by comparison of the experimental melting point with literature values. Finally, the basic hydrolysis of the nitrile group in **6** into the carboxylic acid group of **1** was carried out. No particular hazards were encountered in leaving these reactions unattended. A closed water circulation system (15 °C) was used to cool the refrigerants, and all tubing was secured with clamps under the instructor's supervision. The product was isolated by acidification followed by extraction and chromatography. Yields ranged between 58 and 70%. It is very important to adjust the pH correctly in the acidification step (pH = 3); otherwise, the yield may decrease. Note that pK_a of diarylamines is much lower than that of anilines, so there is little chance of amine protonation unless the pH is too low.[18]

In the discussion session, students compared the performance of both procedures for the synthesis of nitroso compounds.[19,20] Because the isolation procedure was similar, the reaction time tended to favor the method that used an organotrifluoroborate as starting material (synthesis of **3a**). However, yields of the oxidation procedure (synthesis of **3b**) were higher. Also, obtaining **3b** with the corresponding azoxybenzene (TLC spotting and ^{1}H NMR spectroscopy) was compared to obtaining **3a** free of the azoxybenzene. This may be attributed to the electronic effect of the *o*-CN group, which makes the nitroso group of **3b** more electron deficient, thus favoring dimerization. However, the students also noted that **3a** was slowly transformed into an azoxybenzene when reacting with **2a** (TLC following of the reaction). When comparing the yields of the synthesis of **6**, the approach followed by Group B (coupling of **2b** with **3b**) was clearly favored. This can be explained, again, by the higher electrophilicity of the nitroso group in **3b**, which may favor the step in which $P(OEt)_3$ bonds to nitrogen. In addition, the boron group of **2b** is less sterically hindered than that of **2a**, which may favor the step in which the N−B bond is formed. Overall, taking into account yields of the syntheses of the nitroso compounds **3**, yields in the synthesis of **6**, the balance of reaction times, simplicity of purification, toxicity of reagents, and waste disposal, the students concluded that the synthesis carried out by group B performed better.

The transformation can be understood (Scheme 3)[12,21] starting from the nucleophilic addition of $P(OEt)_3$ to the oxygen atom of the nitroso group in **3a** or **3b**. This will give rise to a tetravalent phosphorus intermediate (**I**), which can lead to a nitrene (**II**) by the elimination of $O{=}P(OEt)_3$. Either unsaturated species (**I** or **II**) can add to the vacant orbital on

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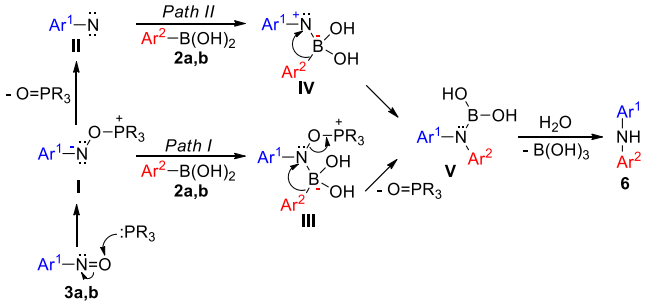
Scheme 3. Explanation of the Key C−N Bond-Forming Step



boron in **2a** or **2b**, giving rise to a boronate species (**III** or **IV**) able to transfer the nucleophilic aryl group from boron to the electrophilic nitrogen. Protonation of the final aminoboronate **V** upon workup affords **6**, together with boric acid as a byproduct.

With the aid of the explanations and literature cited in the Handout for Students (see Supporting Information, S82), the students did not have particular difficulties in understanding the mechanisms of the different transformations involved in the sequence.

Examples of spectra of products obtained by the students are given in the Supporting Information (S57). The IR spectra of compound **6** showed the NH absorption of the amine around 3345 cm^{-1} and of the CN at 2221 cm^{-1}. The IR spectra of compound **1** showed a broad and very strong absorption centered around 3020 cm^{-1} belonging to the O−H stretching. The NH (3335 cm^{-1}) and CO (1662 cm^{-1}) absorptions are also observed as well as the lack of a nitrile absorption at ∼2100 cm^{-1}. A comparison of both spectra showed the successful conversion of the cyano group to acid after hydrolysis. Therefore, students can use IR spectroscopy to determine if the synthesis of flufenamic acid was successful. The characterization of compounds **3a**, **3b**, **6**, and **1** by ^{1}H NMR spectroscopy was used in the discussion session to review the typical splitting patterns of different types of substituted aryl rings (*meta*-substitution in **3a**, *ortho*-substitution in **3b**). The ^{1}H NMR spectra of compounds **6** and **1** were complicated due to the presence of the two aromatic rings. The ^{19}F NMR spectra of compounds **3a**, **6**, and **1** had only slight differences, with a single signal around δ = −63 ppm in all cases (see Supporting Information, S57, for the actual values), thus showing the absence of fluorine-containing impurities. However, the splitting in the ^{13}C NMR spectra was highly instructive. Quartets for the CF_3 groups (^{1}J around 270 Hz), *ipso*-C (^{2}J around 30 Hz), and *ortho*-C (^{3}J around 4 Hz) were observed, while the rest of the carbons appear as singlets. This allowed the unambiguous assignment of these signals. The MS spectra of **1** showed the loss of 18 mass units characteristic of the *ortho*-effect present in *o*-substituted benzoic acids. The M-18 fragment was the base peak of the spectrum. The subsequent loss of 28 units (CO) was also noticeable.

CONCLUSION

A synthesis of flufenamic acid using nitrosobenzenes and boronic acids under transition-metal-free conditions was described to be used in the upper-division organic chemistry laboratory course. The key step was the coupling of nitrosobenzenes with boronic acids under transition-metal-free conditions. Students compared the performance of two different methods for the synthesis of nitrosobenzenes and two different examples to the key C−N bond-forming reaction. Grading of prelab and postlab questionnaires and discussion with instructors during the lab and postlab sessions put forward that the students that participated in this experiment consolidated their knowledge of the reactivity of nitroso compounds and boronic acids, their preparation skills in a multistep sequence, their ability to understand reaction mechanisms, and the interpretation of IR, ^{1}H, ^{13}C, ^{19}F NMR, and MS spectra.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.8b00824.

Required reagents, safety and waste disposal information, lists of chemicals and equipment, handouts, questionnaires, additional notes for instructors, copies of characterization data collected from student samples, guide for discussion sessions (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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