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Laboratory Experiment

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Microwave-Assisted Synthesis of 5-Phenyl-2-hydroxyacetophenone Derivatives by a Green Suzuki Coupling Reaction

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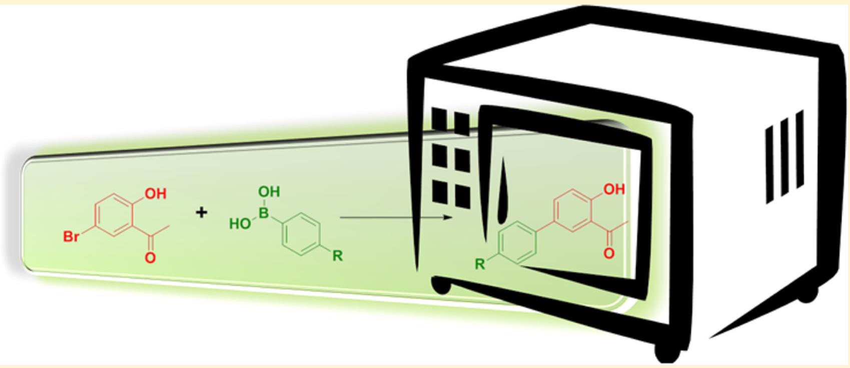
Ⓢ *Supporting Information*



ABSTRACT: In recent years, the use of boron-containing reagents in palladium-assisted C−C coupling reactions (the Suzuki reaction) has gained prominence due to the vast array of reagents commercially available. Consequently, the generation of carbon−carbon bonds, namely of functionalized biphenyl systems, is at present considered the backbone of organic synthesis. In this context, the design of eco-friendly protocols for the Suzuki reaction employing water as a solvent and the use of microwave-assisted procedures are imperative from an industrial point of view. The series of laboratory experiences described highlight the skillfulness of microwave-assisted synthesis to promote environmentally friendly Suzuki reactions. In the first laboratory class, 1-(4-hydroxy-4′-methoxy-[1,1′-biphenyl]-3-yl)ethanone and 1-(4′-chloro-4-hydroxy-[1,1′-biphenyl]-3-yl)ethanone are synthesized, and the crude products are obtained and purified. Students become acquainted with microwave equipment and several laboratory techniques, such as extraction, purification by filtration with celite, column chromatography, and thin-layer chromatography. In the second laboratory class, students check the purity of the compounds and acquire ^{1}H and ^{13}C NMR spectral data. The synthesized phenylacetophenone derivatives are key intermediates for the synthesis of many biological active molecules, namely, flavonoids, chromones, or coumarins, which are privileged structures for drug discovery. The experiments can be also performed with diverse arylboronic acids containing different electron donating and withdrawing groups, allowing the synthesis of a small library of benzopyran precursors. The experiments have been tested for three years by 75 graduate students in applied organic chemistry or medicinal chemistry curriculum units.

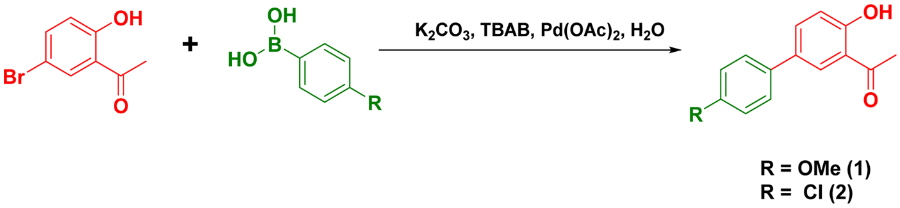
KEYWORDS: *Graduate Education/Research, Organic Chemistry, Hands-On Learning/Manipulatives, Problem Solving/Decision Making, Green Chemistry, Medicinal Chemistry, NMR Spectroscopy*

■ INTRODUCTION

Green chemistry, also known as sustainable chemistry, is a rapidly growing research area that advocates the (re)design of chemical products and processes, involving the reducing or elimination of hazardous substances.[1] Recently, there has been great interest in developing green chemical reactions that make carbon−carbon bonds using water as a solvent and applying these reactions in academic and industrial lab settings. Consequently, deletion or replacement of organic solvents from reaction medium has been a major emphasis of green chemistry.[2] The use of water as a green solvent and microwave-assisted reactions as an alternative to conventional energy sources can be the best choice to perform chemical reactions.[2,3]

Palladium-catalyzed coupling reactions are one of the most described reactions in organic chemistry. Therefore, it is not surprising that a significant number of articles have been reported focused on the use of microwave irradiation to enhance palladium-catalyzed coupling reactions, such as Suzuki cross-coupling reactions.[2−4] In this context, the synthesis of biaryl compounds using metal-catalyzed cross-coupling reactions (e.g., Suzuki or Heck reactions) is a widely used route, namely for the synthesis of agrochemicals and of many natural complex compounds and/or biologically active compounds.[5−7] Biaryl systems are also in increasing demand for the development of new organic materials with novel properties (electronic, optical, etc.), playing an important role in blossoming areas such as nanotechnology.[3]

Scheme 1. Synthesis of Phenylacetophenone Derivatives via Suzuki Reaction



Although there are several lab proposals on the Suzuki reaction in this *Journal*,[8] the lab experiment described herein is focused on the synthesis of hydroxybenzophenone derivatives attained by cross-coupling reactions of two aryl synthons that are key building blocks for important benzopyran frameworks used in drug discovery and development projects.[9−11] The experiment complements, owing to the type of chemical structure and applications, those previously published in this *Journal* related to biaryl systems and the Suzuki reaction.[8] There are several advantages to the experiment described: a short time reaction (15 min), the use of an environmentally benign solvent (water) and of palladium(II) acetate, without the need for a phosphine ligand, an inert atmosphere is not required, and the ease of workup and purification steps. In addition, a small library of functionalized biaryl systems can be synthesized in a class through the use of structurally dissimilar boronic acids. The chemical versatility of the system allows generating a dynamic laboratory class, including a combinatorial process using isosteric and bioisosteric replacements appropriate for structure−activity−relationship studies.

2-Hydroxyacetophenones are considered to be key intermediates in the synthesis of many biological active molecules, namely in synthesis of benzopyrans, such as flavonoids, chromones, or coumarins derivatives, which are privileged structures for drug discovery.[10,12−14] Phenylacetophenone derivatives are synthesized by the Suzuki reaction (Scheme 1) using bromoacetophenones as starting materials, phenylboronic acid derivatives as reagents, palladium(II) acetate ($Pd(OAc)_2$) as a catalyst, and water as solvent. Tetrabutylammonium bromide (TBAB) is used as an additive.[15] The addition of TBAB has been shown to enhance the rate of the palladium-catalyzed Suzuki cross-coupling reaction in aqueous solvents, facilitating, for instance, the solvation of the organic substrates and stabilization of palladium nanoparticles.[16] Cross-coupling reactions of organoboron compounds involving transmetalation to aryl-palladium(II) halides proceeds smoothly when activated with suitable bases, such as K_2CO_3.[6,7] The reaction is assisted by microwave radiation and is optimized in relation to stoichiometry, temperature and reaction time. The reaction products are purified by celite filtration, liquid−liquid extraction, and column chromatography, and identified by nuclear magnetic resonance (NMR) spectroscopy.

The lab experiment has been planned to highlight the skillfulness of microwave-assisted synthesis to promote environmentally friendly Suzuki reactions, allowing the synthesis of key intermediates useful in organic or medicinal chemistry. Students become acquainted with microwave equipment, several organic laboratory operations such as extraction, purification by filtration with celite, column chromatography and thin-layer chromatography (TLC), and spectroscopic techniques. Students should be familiar with other basic techniques used in organic chemistry, namely, the use of ground glass chemical apparatus, melting point determination, recrystallization, vacuum filtration, drying and evaporation.

■ EXPERIMENTAL PROCEDURE

Students work individually or in groups of two. Detailed procedures are described in the Supporting Information.

Synthesis and Purification of 5-Phenyl-2-hydroxyacetophenone Derivatives (First Laboratory Class)

5-Bromo-2-hydroxyacetophenone and either (4-methoxyphenyl)boronic acid or (4-chlorophenyl)boronic acid react in a microwave oven (400 W, 15 min, 150 °C) in the presence of potassium carbonate, TBAB, and $Pd(OAc)_2$ in water to give 1-(4-hydroxy-4′-methoxy-[1,1′-biphenyl]-3-yl)-ethanone (**1**) or 1-(4′-chloro-4-hydroxy-[1,1′-biphenyl]-3-yl)-ethanone (**2**), respectively (Scheme 1). The reaction is followed by TLC. Purification of the product includes celite filtration, liquid−liquid extraction, and silica gel column chromatography. Fractions from the column are analyzed by TLC; the fractions containing the product are combined, and the solvent is evaporated to obtain solid products.

Structural Characterization of 5-Phenyl-2-hydroxyacetophenone Derivatives (Second Laboratory Class)

The purity of each product is checked by TLC and/or melting-point. Students acquire ^1H NMR and ^{13}C NMR spectra using deuterated chloroform as a solvent. From the chemical shifts and coupling constants, the structure of the phenylacetophenone derivative is proposed. Students also acquire the spectra data of the acetophenone used as starting material and use it to complement the spectral analysis.

Each student (or group) submits a comprehensive lab report one or 2 weeks after completing the experiment.

■ HAZARDS

Use of protective clothing, goggles, gloves and protection mask for solid particles (when silica column is packed) are required. 5-Bromo-2-hydroxyacetophenone and its derivatives can cause skin and severe eye irritation and may cause respiratory irritation. Heptane and ethyl acetate are highly flammable, and if swallowed and inhaled can cause skin, eye, and respiratory tract irritation. Silica gel causes irritation of the respiratory tract; dust beads may cause skin and eye irritation. Deuterated chloroform is harmful and causes skin irritation. Further information on potential hazards in handling laboratory chemicals is available in the Supporting Information.

■ RESULTS AND DISCUSSION

Over a three-year period, a total of 75 graduate students have successfully completed the experiment. In the first laboratory class, students synthesized 1-(4-hydroxy-4′-methoxy-[1,1′-biphenyl]-3-yl)ethanone (**1**) or 1-(4′-chloro-4-hydroxy-[1,1′-

biphenyl]-3-yl)ethanone (**2**), and purified the desired compound; **1** was obtained in 75−80% yields and **2** was obtained in 50−65% yields. In this class, students became acquainted with microwave instrumentation and diverse laboratory purification techniques, such as filtration using celite (filter agent), extraction, silica gel column chromatography and TLC. In general, the coupling reactions were readily completed by students and the final compounds have been obtained in sufficient yield and purity for characterization. In the second laboratory class, students checked the purity of the compound by TLC and/or melting point. Students then acquired and analyzed ^{1}H NMR and ^{13}C NMR spectroscopic data. Students acquired their own spectra and reviewed the basic concepts of structural analysis.

The experiment was designed to validate the application of microwave-assisted synthesis in the Suzuki reaction by the synthesis of 5-phenyl-2-hydroxyacetophenone derivatives, important intermediates in medicinal chemistry, namely, benzopyran scaffolds. The experiment has several advantages, such as a short reaction time, mild reaction conditions, and satisfactory product yields. In fact, after optimization of the reaction conditions (400 W for 15 min at 150 °C), the waiting time to complete the reaction was reduced, allowing students to perform the purification step in the same laboratory class period. Due to a reduction in the formation of byproducts, the purification by column chromatography was trouble-free and students obtained the final products in high yields. In the follow-up lab class, students checked the purity of the compounds by TLC and/or melting-point and acquired ^{1}H and ^{13}C NMR spectroscopic data for the structural characterization of the product(s).

The experiment was designed for chemistry-based curricula, namely, chemistry and chemical engineering or medicinal chemistry courses, and is best suited for students that have taken general, organic, and analytical chemistry. An instructor can take the advantage of the diversity of commercial boronic acids and can propose that each student (or group) synthesize different phenylacetophenone derivatives. Additional experiments, such as changing reaction parameters (stoichiometry, residence time and temperature), can also be designed. In this context, it is recommended to include a stage in the second lab class for data discussion. An instructor can also present the transformation of the hydroxyacetophenone derivatives into coumarins or chromones as an extra classroom experiment.[9,10] The complete data related with the experiment are available in Supporting Information.

The average success of students in realizing the integrated experience was 86%. In general, students obtained adequate amount of compounds to complete the hands-on experience of structural characterization.

The goals of the laboratory course in which this experiment is included are to introduce students to what goes on in real chemistry laboratories. To get maximum benefit from the laboratory, students needed to be free to learn by doing. Therefore, students were expected to be familiar with the procedure for the experiment before coming to the lab. In general, the experiment was easy to perform and produced clear and obvious results, and left a long-term impression on students. Student interest was heightened and it was demonstrated to students how the techniques that they learned in organic chemistry lab could help them in their future careers. Although good results were the ultimate goal, determining why an experiment did not work and understanding the experiment was equally or more valuable.

In Graduate Education/Research courses, students frequently have a positive attitude and willingness to learn and, in turn, recognize that lab classes play a very important role in their education. They are strongly motivated as they apply factual material and spend time in lab courses with “hands-on” experiments. These assumptions may explain that in the described experiment no significant shortcomings have been documented. Although TLC conditions to monitor the reaction and melting-points were not given in the protocol, in general and with very close supervision, students quickly attained the objectives. No difficulties in the purification step and acquisition of NMR spectra have been detected. However, in the interpretation of NMR data, some drawbacks have been noticed; students were advised to use molecular model kits to assist in the visualization process. Furthermore, a theoretical class for data discussion is strongly recommended.

A lab report was written according standard guidelines.[17] In general, students had difficulties with a written assessment and in reporting the laboratory work in a scientific way. Thus, it is strongly advised that, during the lab work, strategies should be implemented to foster students’ literacy, namely, posing questions to stimulate their critical and logical thinking.

As laboratory grading is partially subjective, students have been evaluated by their general preparedness and effort. Moreover, during the last laboratory session, a laboratory exam was given. The lab grade was determined as follows: instructor evaluation (25%), pre-laboratory assignment and evaluation of lab reports (50%), laboratory examination (25%).

■ CONCLUSION

A laboratory experiment was designed to motivate organic chemistry students. Students became acquainted with microwave reactors and with some laboratory techniques, such as filtration, extraction, evaporation, column chromatography and TLC. Students collected and interpreted their own ^{1}H and ^{13}C NMR spectroscopic data, and reviewed the basic concepts for structural identification of organic compounds. In addition, they inferred about the influence of activating and deactivating substituents (−Cl is an inductively electron-withdrawing group but an electron donor through resonance, and $-OCH_3$ is an electron-donating group through resonance) on the Suzuki microwave-assisted coupling reaction, and noticed in the ^{1}H NMR spectra their shielding/deshielding and spin−spin splitting electron effects.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Instructions for the students; notes for the instructor; NMR spectra of 1-(4-hydroxy-4′-methoxy-[1,1′-biphenyl]-3-yl)-ethanone (**1**) and 1-(4′-chloro-4-hydroxy-[1,1′-biphenyl]-3-yl)ethanone (**2**) and starting acetophenone for using in classroom, especially for those without direct access to an instrument. 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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