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HOW DOES ONE EXPERIMENT?

''Green'' Suzuki-Miyaura cross-coupling: An exciting mini-project for chemistry undergraduate students

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Abstract A three-week mini-project is described for an experimental Physical Chemistry or Organic Chemistry course. The activities include synthesis of a biphenyl (4-methoxybiphenyl) via the Suzuki-Miyaura cross-coupling reaction using an adapted domestic microwave oven. The technical skills and concepts that are typically presented in practical chemistry courses are covered, including microwave heating, separation of mixtures, TLC techniques, melting range determination, stoichiometric calculations, and GC–MS techniques.

PALABRAS CLAVE
Acoplamiento cruzado de Suzuki-Miyaura;
Síntesis sostenible;
Calentamiento por microondas;
Enseñanza de la química

Acoplamiento cruzado «verde» de Suzuki-Miyaura: un mini-proyecto emocionante para estudiantes de pregrado en química

Resumen Un mini-proyecto de 3 semanas se describe en un curso experimental de Fisicoquímica o Química Orgánica. Las actividades incluyen la síntesis de un bifenilo (4-metoxibifenil) a través de la reacción de acoplamiento cruzado de Suzuki-Miyaura usando un horno de microondas doméstico adaptado. Las habilidades técnicas y conceptos que normalmente se presentan en los cursos de química prácticos están cubiertos, incluyendo el calentamiento por microondas, la separación de mezclas, técnicas de TLC, la determinación del intervalo de fusión, cálculos estequiométricos, y las técnicas de GC-MS.

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Introduction

Recent advances in chemistry and specifically the emergence of green chemistry require that students be trained in catalytic organic reactions (Lenardão, Freitag, Dabdoub, Batista, & Silveira, 2003). Microwave heat, a global trend in eco-friendly synthesis, that can be applied in chemistry classes is very efficient and produces excellent results with a short reaction time (Dalmás et al., 2013; Konrath, Piedade, & Eifler-Lima, 2012; Teixeira et al., 2010). Thus, teaching mini-projects that involve more complex organic syntheses (e.g., C—C cross-coupling reactions) that are prepared using microwave heat presents a good method for a thorough training in organic chemistry (Aktoudianakis et al., 2008; Soares, Fernandes, Chavarria, & Borges, 2015). Therefore, the use of microwave heat technology in organic synthesis must be included in the training of future professionals.

To provide students with this experience, a three-week experiment (lab period = 3 h/week) is described based on the Suzuki-Miyaura cross-coupling reaction of phenylboronic acid (**1**) with 4-iodoanisole (**2**), which is catalyzed by Pd/C, to synthesize 4-methoxybiphenyl (**3**) via refluxing under air in an adapted domestic microwave oven (Scheme 1; Dalmás et al., 2013).

The primary goal of this experiment is to introduce students to a research environment by familiarizing them with the scientific literature and detailed laboratory procedures. At the conclusion of the three-week mini-project, students should be more comfortable with synthesizing organic compounds via C—C cross-coupling reactions, and they should also be able to identify reaction products using current chromatographic techniques (TLC and GC—MS). They also learn to report their results in a journal-ready format.

Experiment

The students work in groups of three. Prior to the initial laboratory period, students read journal articles related to the experiment (Aktoudianakis et al., 2008; Oliveira et al., 2015; Soares et al., 2015). During week one, a quick introduction to the microwave synthesis technique is provided. Students synthesize compound **3** via the Suzuki-Miyaura cross-coupling reaction that is catalyzed by Pd/C. Phenylboronic acid (1.5 mmol), 4-iodoanisole (1.0 mmol), Pd/C 10 wt.% loading (15 mg, 1.4 mol% of Pd), K_2CO_3 (2.0 mmol), and 8 mL of dimethylformamide (DMF) are refluxed under air in an adapted domestic microwave oven for an assigned time (30, 45, 50, 60, or 90 min). After the reaction time is complete, the mixture is stored under air at room temperature until the next class.

During week two, the retention factors (Rf) of compounds **1**, **2** and **3** (provided by professor) and the reaction mixture are determined using thin layer chromatography (TLC). To determine if the cross-coupling product forms, the students perform the experiment to isolate the 4-methoxybiphenyl from initial reaction mixture.

Week three focuses on the characterization of compound **3**. The students collect 4-methoxybiphenyl as white crystals and determine its melting range and mass chromatogram using GC—MS. The detailed procedures are in the Supporting Information.

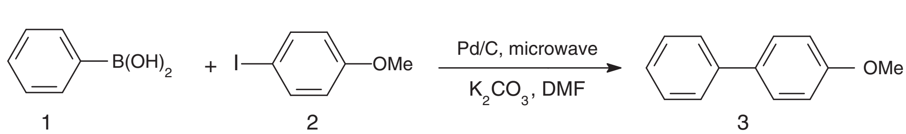
Results and discussion

The mini-project was implemented with 18 students in 2014 in an upper-division undergraduate course, Physical Chemistry II, Course Agroindustrial Engineering with an emphasis on agrochemistry. The course covered the basic techniques of catalysis that are applied in organic synthesis of bioactive compounds. Additionally, the mini-project was tested with 15 students in 2014 of Technical Course in Chemistry, discipline of Organic Chemistry III, in the Dom Feliciano School (Gravataí – RS, Brazil).

The students found it interesting to use an adapted domestic microwave oven to heat the Suzuki-Miyaura reaction mixture. This apparatus has already been used successfully in N—C cross-coupling reactions by our group (Dalmás et al., 2013). The yield ranged from 41% to 92% (Table 1), according to the heating time used. The low yields of compound **3** were associated with variables related to purification and the short reaction time. However, even with unsatisfactory results from the reaction, a fruitful discussion concerning the technical errors can occur. The reported melting range of the pure 4-methoxybiphenyl is 81–83.5 °C (Rosa, Rosa, Rominger, Dupont, & Monteiro, 2006). Each student group reported melting points that were within this range (Table 1). Moreover, the students analyzed the mass chromatogram obtained for compound **3** using the GC—MS technique. Representative data from a student group is provided in the Instructor's Notes in Supporting Information.

The longer reaction times resulted in higher yields. Approximately 90 min was necessary to fully convert the reagents to the cross-coupling product (previously tested). Group 1 obtained a higher than expected yield after 30 min. For this time, the conversion is low (~45%), and we believe the product contains traces of compound **2** (mp 50–53 °C) with **3**. There were no major differences in the yield obtained by the students in the technical course (Dom Feliciano) as opposed to those in the undergraduate (FURG) course for the reaction times of 45–60 min. However, the data from the undergraduates were more consistent (see Fig. 1). This shows the flexibility of the mini-project, which can be applied to both levels of education. For 90 min, group 10 likely lost the mass of the isolated product during the procedure.

These results were explained using the classic catalytic cycle for the Suzuki-Miyaura cross-coupling reaction (only



Scheme 1 Suzuki-Miyaura cross-coupling performed by students.