

Laboratory Experiment: Synthesis and Characterization of 4-Methyl-N-(phenylacetyl)benzenesulfonamide through Cu(I)-Catalysis

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ABSTRACT. A three-component coupling reaction of phenylacetylene, *p*-toluenesulfonyl azide, and water through copper catalysis is described to provide knowledge of spectroscopy and catalytic reactions and to introduce current research topics in organic chemistry for second-year undergraduate students. In the presence of stoichiometric amounts of phenylacetylene, *p*-toluenesulfonyl azide, and triethylamine, the reaction was performed with 4 mol% CuCl in water as the sole solvent and was completed in 1.5 h. A practical purification method and recrystallization of the crude reaction mixture resulted in the rapid isolation of the desired product with yields of 42~65%. Students characterized 4-methyl-N-(phenylacetyl)benzenesulfonamide by using melting-point determination, infrared spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. This experimental procedure and spectroscopic data analysis will serve as a platform for students to apply classroom knowledge in practical state-of-the-art research.

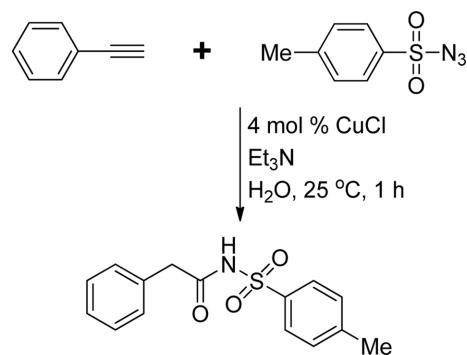
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INTRODUCTION

The field of transition-metal catalysis has yielded nine Nobel laureates since 2000,¹ which highlights the importance of organometallic chemistry in the field of synthetic chemistry. The importance of educating junior-level undergraduate students about transition-metal catalysis has been emphasized in several books, papers and review articles.^{2~6} However, the intrinsic limitation of transition-metals such as Pd, Rh, and Ir, i.e., *their scarcity in the Earth's crust*, has become a serious problem. The Chinese government, which is responsible for the production of over 97% of all rare-earth elements, is steadily decreasing the annual production of these elements.⁷ Thus, the use of Cu, a relatively abundant transition-metal in the Earth's crust, as a promising replacement for traditional Pd or Rh metals is attractive to organic chemists.⁸

Despite the importance of Cu chemistry, few undergraduate-laboratory experiments dealing with Cu catalysis are conducted.⁹ Moreover, organic chemistry laboratory experiments in Korea mostly consist of reactions developed a long time ago, such as the Grignard reaction of benzophenone with phenylmagnesium bromide, the hydroboration of 1-hexene with a BH₃-THF complex, and the Diels-Alder reaction of cyclopentadiene with maleic anhydride.¹⁰ These experiments help students understand what they learned in a textbook but do not represent the state-of-the-art studies currently conducted in organic laboratories.

In this paper, I describe the synthesis of 4-methyl-N-(phenylacetyl)benzenesulfonamide *via* a Cu(I)-catalyzed three-component coupling reaction of phenylacetylene, *p*-toluenesulfonyl azide, and water (*Scheme 1*).¹¹ This protocol provides an alternative synthetic pathway of preparing the amides for second-year students. The mechanism of a three-component coupling reaction should be more complicated than those of bi- or uni-molecular reactions, so it is very challenging for students to propose their plausible reaction mechanism.¹² This experiment includes the concept of Cu-assisted C–H activation, the synthetic application of alkynes, and the in-depth analysis of spectroscopic data. The related references of this experiment introduce students to state-of-the-art research topics, especially *C–H activation*.¹³



Scheme 1. Synthesis of 4-methyl-N-(phenylacetyl)benzenesulfonamide.

PEDAGOGICAL GOALS

This experiment was designed to accomplish two pedagogical goals. First, the experiment aims to help students apply what they learn in undergraduate organic chemistry courses in experiments, especially spectroscopic analysis and transition-metal catalysis, through hands-on experience. Furthermore, the synthesis of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide from phenylacetylene highlights the synthetic utility of alkynes. Second, this experiment serves as a preview of cutting-edge chemistry studies. Cu catalysis is a hot research subject, and this experiment allows students to explore a state-of-the-art research topic in the field of organic chemistry.

EXPERIMENTAL

The experiment was carried out in two 2-h laboratory sessions for second-year undergraduate students. The prelab materials were provided to students the week before the laboratory class along with a pedagogy document outlining the learning objectives, experimental procedures, and assessment (see the Supporting Information, page S1). Students worked in groups of two or three, and each lab class contained less than 12 groups.

Conducting the reaction

In the first 2-h laboratory session, students first reviewed the reaction procedure and safety precautions with an instructor. Students sequentially added *p*-toluenesulfonyl azide (1.1 equiv), copper iodide (4 mol%), and phenylacetylene (1.0 equiv) to a 25-mL round-bottom flask equipped with a stir bar and dissolved the reagents in distilled water (2 mL) under air. The reaction was initiated by the dropwise addition of triethylamine (1.1 equiv), and the reaction mixture was stirred for 1 h at ambient temperature. The reaction was quenched with an aqueous acidic solution and extracted with CH₂Cl₂. After combining the organic layers, students performed thin-layer chromatography on SiO₂ plates by eluting the combined layers with 1:5 EtOAc/*n*-hexanes to check the presence of remaining phenylacetylene and the formation of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide. Each group was asked to qualitatively report the spot size of the remaining phenylacetylene in the postlab report (no starting material, trace, or significant amount).

Product purification and characterization

The combined organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Recrystallization with

hot CH₂Cl₂ and *n*-hexane yielded a solid product. Students collected the solid *via* filtration and dried the product under air for 40 min. Students recorded the weight of the obtained product and conducted an experiment to determine the melting point. Due to instrument availability, only two groups in each class obtained Fourier-transform infrared (FT-IR) spectra. Other groups were provided with copies of two groups' spectra. The ¹H and ¹³C nuclear magnetic resonance (NMR) spectra of the representative sample collected from students were obtained by an instructor, and copies were given to students to analyze the structure.

Hazards

p-Toluenesulfonyl azide must be prepared inside a fume hood by a skilled instructor before the laboratory class due to the explosive danger of *p*-toluenesulfonyl azide and the toxicity of the reagents required to prepare the chemical. Students handling *p*-toluenesulfonyl azide should stay away from a heat source.¹⁴ Sodium azide is highly toxic and very dangerous for the environment. *p*-Toluenesulfonyl chloride is a corrosive substance, and acetone is a harmful volatile liquid. This experiment should be performed in a fume hood, mostly due to Et₃N, which is a volatile and harmful liquid with a pungent smell. Students must be equipped with protective gear, including a laboratory coat, safety glasses, and gloves, during the laboratory class. Phenylacetylene is harmful and flammable. CuI is a skin irritant. Methylene chloride is a suspected toxic carcinogen and an irritant to the skin, eyes, and lungs. *n*-Hexanes is flammable and neurotoxic. The 1 M aqueous hydrochloric acid solution and saturated aqueous ammonium chloride solution are corrosive. Anhydrous sodium sulfate is nonhazardous. The detailed hazard information of 4-methyl-*N*-(phenylacetyl)benzenesulfonamide has not been reported yet but should be regarded as a skin and eye irritating toxin.

RESULTS AND DISCUSSION

A total of 105 students conducted this experiment over two semesters working in groups of two or three in a laboratory class with less than 25 students. Each class had an instructor, and students performed the reactions under the guidance of an instructor.

All groups made the desired product without any difficulties. Students found the spots of the remaining phenylacetylene and the desired product on thin-layer chromatography (TLC) plates with a 254-nm UV lamp. The analysis indicated that the product was more polar than the starting material. One or two groups in a class reported trace amounts of

phenylacetylene by TLC analysis, while the other groups reported no remaining starting material. This deviation might be caused by an error during the measurement of phenylacetylene, as these students obtained % yields of 4-methyl-N-(phenylacetyl)benzenesulfonamide that were similar to those of the other groups.

Students obtained the desired product with yields of 42~65%. All groups observed the formation of the desired product. The literature reported that the product was a white solid, but most groups obtained 4-methyl-N-(phenylacetyl)benzenesulfonamide as an ivory solid. However, the ^1H NMR spectra indicated that few impurities existed in the product (see the Supporting Information, page S5). Students suggested that the recrystallization step was responsible for the moderated % yield. For example, students commented that they used too much hot CH_2Cl_2 to dissolve the crude product, resulting in less than 50% yield. Most students obtained a melting point in the range of 148–150 °C, consistent with the melting point reported in the literature (146–148 °C).

Due to limited instrument availability and laboratory-class time, the instructor selected two groups in each class to obtain FT-IR spectra. Students were provided copies of the FT-IR spectra and the NMR spectra. Students assigned the peak at 1681 cm^{-1} to a carbonyl stretch, indicating a carbonyl group exists in the product. Some students also commented in their report that the peak at approximately 3200 cm^{-1} corresponded to an N–H stretching vibration from an amide moiety (see the Supporting Information, page S6).

Analyses of the NMR spectra were more challenging to students. Most students did not have any difficulties assigning the N–H and two alkyl C–H protons. However, the assignments of the aryl C–H protons were not trivial, and students provided various answers based on the numbers of each proton. In the ^{13}C NMR spectra, all students noted that the peak at δ 169.59 indicated the presence of a carbonyl moiety. Students also easily determined that the two peaks at δ 43.77 and δ 21.82 each corresponded to an sp^3 carbon in the product.

Many students agreed that this experiment was helpful to understand spectroscopic analysis, which students learned in organic chemistry (see the Supporting Information for the postlab survey results, page S7-S8). Among 28 respondents, 15 students marked “Strongly Agree,” and 10 students marked “Agree”. The strong agreement proves that parallel learning of spectroscopy in a classroom and laboratory was effective. Therefore, this experiment is appropriate for second-year undergraduate students because spectroscopy in organic chemistry is generally taught during the second-

year in college. Delivering the concept of Cu catalysis was also satisfactory. Although the detailed reaction mechanism and catalytic cycle were not covered deeply in this experiment, 18 students among the 28 respondents agreed that they understood the importance and the essential concept of Cu catalysis, including Cu-mediated $sp\text{-C-H}$ activation, Cu-acetylidy formation, and the attack of Cu-acetylidy with *p*-toluenesulfonyl azide. One student commented that this experiment surprised him, as it involved a novel route to an amide from an alkyne and azide rather than a traditional coupling of an acid and amine.

CONCLUSION

A Cu-catalyzed amide synthesis was conducted by second-year undergraduate students. The reaction process was simple and straightforward. Students performed an extraction, a recrystallization, and the determination of the melting point of the product. FT-IR and NMR spectral analyses enhanced the students’ understanding of spectroscopy. Students had the chance to learn chemistry dealing with Cu catalysis. Feedback from students proved that the pedagogical goals of this experiment were achieved.

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Supporting Information. Additional supporting information is available in the online version of this article.

REFERENCES

1. Nobel Prizes and Laureates in Chemistry. https://www.nobelprize.org/nobel_prizes/chemistry/laureates/ (accessed April 2016).
2. (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 5th ed.; John Wiley & Sons: Hoboken, NJ, 2009; p 1. (b) Spessard, G O.; Miessler, G L. *Organometallic Chemistry*, 2nd ed.; Oxford University Press: UK, 2010; p 1. (c) Hegedus, L. S.; Söderberg, B. C. G. *Transition Metals in the Synthesis of Complex Organic Molecules*, 3rd ed.; University Science Books: Sausalito, CA, 2010; p 1.
3. (a) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003. (b) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (d) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.
4. American Association for the Advancement of Science (AAAS). *Benchmarks for Science Literacy*; Oxford University Press: New York, 1993.

5. Osborne, J.; Dillon, J. *Science Education in Europe*; The Nuffield Foundation: London, 2008.
6. Schwarz, C. V.; Reiser, B. J.; Davis, E. A.; Kenyon, L.; Acher, A.; Fortus, D.; Shwartz, Y.; Hug, B.; Krajcik, J. *J. Res. Sci. Teach.* **2009**, *46*, 632.
7. Nakamura, E.; Sato, K. *Nat. Mater.* **2011**, *10*, 158.
8. (a) Guo, X. X.; Gu, D. W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (b) McCann, S. D.; Stahl, S. S. *Acc. Chem. Res.* **2015**, *48*, 1756. (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.
9. For examples, reported in this journal, see (a) Gliński, M.; Ulkowska, U.; Iwanek, E. *J. Chem. Educ.* **2016**, *93*, 1623. (b) Lipschutz, B. H.; Boskovic, Z.; Crowe, C. S.; Davis, V. K.; Whittemore, H. C.; Vosburg, D. A.; Wenzel, A. G. *J. Chem. Educ.* **2013**, *90*, 1514. (c) Ison, E. A.; Ison, A. *J. Chem. Educ.* **2012**, *89*, 1575. (d) Mendes, D. E.; Schoffstall, A. M. *J. Chem. Educ.* **2011**, *88*, 1582. (e) Hansen, T. V.; Wu, P.; Sharpless, W. D.; Lindberg, J. G. *J. Chem. Educ.* **2005**, *82*, 1833.
10. Grignard reaction, see: (a) Williamson, K. L.; Masters, K. M. *Macroscale and Microscale Organic Experiments*, 6th ed.; Cengage Learning: Belmont, CA, 2011; p 490. Hydroboration/Oxidation, see: (b) Kono, H.; Hooz, J. *Org. Synth.* **1973**, *53*, 77. Markovnikov Hydration of 1-Hexene, see: (c) McKee, J. R.; Kauffman, J. M. *J. Chem. Educ.* **1982**, *59*, 695. Diels-Alder reaction, see: (d) Williamson, K. L.; Masters, K. M. *Macroscale and Microscale Organic Experiments*, 6th ed.; Cengage Learning: Belmont, CA, 2010; p 617.
11. (a) Cho, S. H.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1897. (b) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347. (c) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046.
12. For the detailed information on the reaction mechanism, see the page 8 and 9 in SI.
13. For the references as prelab materials, see: (a) Davies, H. M. L.; Bois, J. D.; Yu, J. Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
14. For the preparative methods and handling of *p*-toluenesulfonyl azide, see: (a) E-Eros Encyclopedia of Reagents for Organic Synthesis. <http://onlinelibrary.wiley.com/doi/10.1002/047084289X.rt141/abstract> (accessed April 2017).