

An Operationally Simple Sonogashira Reaction for an Undergraduate Organic Chemistry Laboratory Class

Philippa B. Cranwell,* Alexander M. Peterson, Benjamin T. R. Littlefield, and Andrew T. Russell

Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, U.K.

S Supporting Information

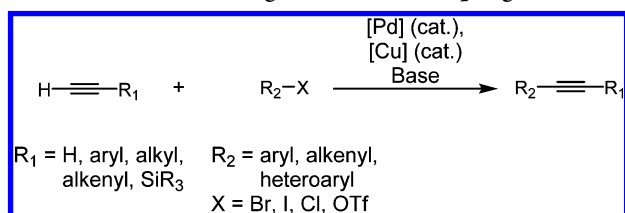
ABSTRACT: An operationally simple, reliable, and cheap Sonogashira reaction suitable for an undergraduate laboratory class that can be completed within a day-long (8 h) laboratory session has been developed. Cross-coupling is carried out between 2-methyl-3-butyne-2-ol and various aryl iodides using catalytic amounts of bis-(triphenylphosphine)palladium(II) dichloride, with copper(I) iodide as a cocatalyst, in triethylamine at room temperature, so a range of products can be prepared within a single group and results compared. The coupling itself is usually complete within 1.5 h and is easily monitored by TLC, leaving up to 6 h for purification and characterization. Purification is by “mini flash column chromatography” through a plug of silica encased in the barrel of a plastic syringe, so the procedure is amenable to large class sizes.

KEYWORDS: Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Alkynes, Aromatic Compounds, Catalysis, IR Spectroscopy, NMR Spectroscopy, Transition Elements



The Sonogashira reaction is used for coupling terminal alkynes to an sp^2 hybridized carbon, for example, an aryl or vinyl halide, in the presence of an amine base, a copper(I) species, and a palladium catalyst.¹ Since its disclosure in 1975, it has found widespread application in the fields of drug discovery, natural product and pharmaceutical synthesis, and polymer synthesis.² A representative Sonogashira cross-coupling reaction is shown in Scheme 1.

Scheme 1. General Sonogashira Cross-Coupling Reaction



One of the main advantages of the Sonogashira reaction is that it is possible to couple two different components together in a selective fashion under mild reaction conditions. There are alternative copper-mediated alkyne coupling reactions, for example the Castro–Stevens reaction³ and the Glaser–Hay coupling,⁴ but these can result in a multitude of byproducts, and functional group incompatibility is a problem due to the harsh conditions required.^{2b,5}

There are examples of preparative palladium-catalyzed cross-couplings reported in the literature that are suitable for use in an undergraduate laboratory; these include Suzuki,⁶ Heck,⁷ Negishi,⁸ and Sonogashira couplings.⁹ Of these, the Suzuki

reaction is most prevalent, presumably due to the reliability and robustness of this reaction. Usually, but not always, the undergraduate cross-coupling experiments are designed such that the isolated products are solids, which can be recrystallized and collected by suction filtration. The Sonogashira couplings reported are performed on the microscale and, therefore, are not necessarily suitable for students early in their university studies. Purification of products is by silica gel chromatography; however, they either require expensive chromatography columns for purification, and so are not necessarily suitable for larger class sizes, or use a pipet column, and so are suitable only for more advanced students. In addition, the reported Sonogashira coupling experiments do not allow for problem-solving by students, for example, the determination of the starting material and product structures using spectroscopic techniques and knowledge gleaned earlier in their chemical careers.

In this regard, the experiments reported here are important as they provide instructors with a laboratory class that is run on the gram-scale, incorporates a problem-based learning element, and can easily, and cheaply, be adapted as required depending on the number of students. The coupling step is usually complete within 1.5 h and can be easily monitored by TLC analysis. Purification of the final product can be achieved by filtration through a pad of silica encased in a syringe body, acting as a cheap, disposable surrogate for a glass column.

■ EXPERIMENTAL DETAILS

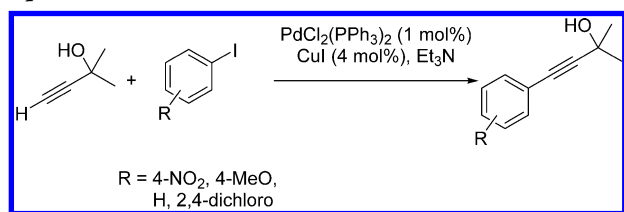
This experiment is designed for students who have already experienced a year of undergraduate practical chemistry, and, in our department, sits at the end of a 5-week organic chemistry laboratory course. The aim of the course is to develop students such that they start to independently think for themselves about the glassware and timing that they need to use during an experiment. Additionally, students are expected to determine the structures of their starting material and products from both the data provided and the data they collect. From an instructor's viewpoint, assessing the suitability of a video for showing how to perform a new chemical technique was a goal.

For the duration of the course, students work in pairs in a day-long laboratory class (8 h). In week 1, students are split into four groups and allocated an aryl iodide substrate: iodobenzene (A), 1-iodo-4-nitrobenzene (B), 4-iodoanisole (C), or 2,4-dichloriodobenzene (D) corresponding to the experiment they would undertake in week 5. Students are given the procedure for their allocated week 5 experiment in week 1 so they can read it during the previous weeks. To add a problem-solving element to the experiment, students are not given the structure of the aryl iodide or product, only the molecular weight and hypothetical elemental analysis data.

Students complete risk assessments prior to each weekly session and complete an informal online test related to the experiments they are allocated. In addition to this, in week 5, students watch a short video that details how to perform mini flash column chromatography, a technique they have not previously encountered.

Students degas triethylamine for 10 min by bubbling with nitrogen and add 2-methyl-3-buten-2-ol, the aryl iodide, and copper(I) iodide, followed by the palladium catalyst (Scheme 2). Each experiment is designed such that students have 1 g of

Scheme 2. Sonogashira Cross-Coupling Used in this Experiment



the starting aryl iodide. As the reaction progresses, the product can be observed as a precipitate in the flask. The reaction is monitored by TLC using 10% ethyl acetate/hexane or petroleum ether (40–60) as the eluent, and, upon completion, the reaction is diluted by addition of ethyl acetate and quenched with 2 M HCl. The organic phase is separated and dried and the solvent removed. At this point (usually after 3 h) there is a natural break in the procedure. It is possible to leave the crude material at this stage and undertake the purification in a subsequent laboratory class (allow approximately 3 h for purification).

Purification is achieved by passing the crude product through a short plug of silica encased in a plastic syringe body, which replaces the need for an expensive, and more easily broken, glass column. The crude material is loaded in toluene (1 mL) and the silica plug washed with petroleum ether (60 mL), to remove any unreacted starting material, and then with 1:1 Et₂O/petroleum ether (60 mL) to elute the product.

The products are isolated as solids or oils, and students characterize their product by melting point (if applicable) and IR and ¹H NMR spectroscopy. Students are also provided with ¹³C NMR, DEPT135, hypothetical elemental analysis, and HRMS data to aid with characterization and identification, as well as a ¹H NMR spectrum of pure material so that they can comment on the purity of their product.

■ HAZARDS

Safety glasses, nitrile gloves, and a laboratory coat should be worn at all times in the laboratory. All hazardous materials should be used and disposed of in accordance with local health and safety rules. 2-Methyl-3-buten-2-ol is highly flammable, is harmful if swallowed, has shown limited evidence of carcinogenic effect, and can cause serious damage to eyes. Iodobenzene is harmful if swallowed and can irritate eyes. 4-Iodobenzene and bis(triphenylphosphine)palladium(II) dichloride have no notified hazards but should be treated as toxic. 4-Iodoanisole and 2,4-dichloriodobenzene are irritants. 1-Iodo-4-nitrobenzene is an irritant and harmful. Copper(I) iodide is harmful if swallowed, an irritant, and toxic to aquatic organisms. Triethylamine is highly flammable, is harmful, and can cause severe burns. Solutions of 2 M HCl should be prepared in a fume cupboard. Ethyl acetate is highly flammable, is irritating to eyes, and may cause drowsiness and skin dryness. *n*-Hexane is a neurotoxin. Petroleum ether (40–60) is highly flammable, irritating to skin, harmful by prolonged exposure and if swallowed, toxic to aquatic organisms; there is a risk of impaired fertility, and the vapors may cause drowsiness. Silica gel is harmful if inhaled and so should only be used in a fume cupboard. Sodium thiosulfate and magnesium sulfate have no notified hazards but should be treated as toxic. Deuterated chloroform is harmful if swallowed, causes skin and eye irritation, is toxic if inhaled, is a suspected carcinogen, is a teratogen, and can cause damage to organs through prolonged or repeated exposure. The products have no reported hazards and therefore should be treated as toxic.

■ RESULTS

Of the 62 students (31 pairs) who undertook the experiments, all managed to prepare enough of their allocated product to collect the data required. All pairs were able to select suitable glassware for each step with minimal intervention from instructors, and all successfully completed the silica gel column without having seen that particular technique before. Yields were generally good and comparable with instructor yields (Table 1).

As the reaction progressed, a suspension formed, providing a valuable visual cue for the success of the reaction and when to carry out TLC analysis (Figure 1). If this suspension was not formed within 1 h of starting the reaction, students were advised to restart the experiment. The reaction failed in only 3 cases out of the 31 pairs performing the experiment. When restarted, under the guidance of an instructor, the reaction worked well, and all students completed the practical in the allocated time. All reactions went to completion within 1.5 h in a laboratory at 24 °C. The reaction with 1-iodo-4-nitrobenzene went to completion most rapidly in approximately 30 min, so these students were able to work up the reaction and perform the purification ahead of the others. 4-Iodoanisole was the slowest to reach completion, taking approximately 90 min.

Table 1. Yields of Each Sonogashira Coupling Reaction

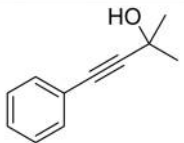
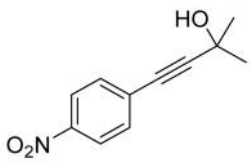
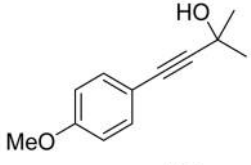
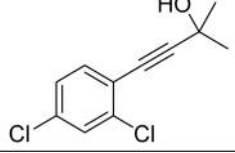
Product	Instructor Yield	Student Yield Average, % (Range); N = 31
	89%	70% (41–100%)
	quant.	60% (31–85%)
	90%	72% (63–93%)
	77%	55% (14–81%)



Figure 1. Photograph of the reaction at $t = 0$ (left) and when complete (right). Substrate in this case is 1-iodo-4-nitro-benzene.

Purification was by short flash column chromatography through a short plug of silica encased in a syringe. Fortunately, a B19 adaptor fitted tightly inside a 20 mL syringe barrel so the solvent was pushed through the silica plug using bellows (Figure 2). This provided a cheap, efficient, and reliable method of purification that did not require expensive equipment or specialized glassware. Upon initial loading of the sample in toluene, an orange band was seen at the base of the column. When the sample was eluted with petroleum ether, the band moved a little, but typically stopped around halfway down, presumably as the toluene was also eluted. Only when 50% diethyl ether/petroleum ether was used did the product elute from the column, as evidenced by the eluent turning yellow/orange. A short video was prepared, which is available in the Supporting Information, that students were encouraged to watch before the session, and an information sheet was also provided for reference.



Figure 2. Photograph of silica gel column the students used to purify their product.

Although samples A–C all become solids upon standing, sample B was the only sample that solidified during the time allocated in the laboratory session. The melting point students obtained was in agreement with ours (instructor 70–73 °C, student 67–71 °C). This is in agreement with observations where samples A and C were slow to solidify and usually required at least a few hours or overnight. In these cases students did not collect melting point data, but did collect ^1H NMR and IR spectra (see Supporting Information for representative student spectra).

The ^1H NMR spectra obtained showed that all products were prepared in acceptable purity; impurities observed were residual solvent from the silica gel column. Occasionally, students used ethyl acetate instead of diethyl ether during the chromatography. This was not an issue in terms of separation, but did lead to residual ethyl acetate peaks in the ^1H NMR spectrum. Where students achieved a low yield, it was attributed to either not washing the magnesium sulfate after drying/filtration thoroughly or not transferring all crude product to the silica gel column.

Students assigned spectra during the laboratory session so they could ask for help if required and instructors could explain the ^{13}C NMR and DEPT135 spectra, as they had only just met these techniques in lectures. During interpretation of the ^{13}C spectrum of sample A, confusion arose among students due to two of the carbon resonances overlapping at 128.4 ppm. In samples B and C, the protons are in an AA'BB' system so are chemically, but not magnetically, equivalent, giving rise to additional peaks. The issue was not addressed directly with these samples, but, if students asked, the phenomenon of magnetic equivalence within NMR spectroscopy was explained. With sample D, some students suggested an alternative structure, 4-(2,5-dichlorophenyl)-2-methylbut-3-yn-2-ol, which would have had a very similar NMR spectrum and the same HRMS data. In all cases, if students did not assign the protons/carbons correctly they were not penalized too harshly, but their reasoning was followed to ensure that it was logical.

DISCUSSION

This reaction was extremely successful, with all students reaching the end and collecting data on their products. Additionally, all were able to independently select glassware

required and could elucidate the starting materials and products from both the data provided and the data they collected. For instructors, the video proved to be an invaluable resource for explaining a technique with which the students had no previous experience. Students commented that the video was an effective way to provide information about performing the chromatography, and they were observed referring to it during the class using smartphones or tablets. They also commented that, because the video showed them what to do, they felt more confident trying new techniques without close guidance from an instructor. Additionally, the instructors observed that the session was less demanding on them as the students had a better idea of the procedure and were generally better informed and more engaged.

The different reactivity of the aryl iodide substrates ensured that the cohort workup period was spread out, so demands on each item of equipment were minimized; therefore, queues where students were waiting for equipment, rather than being productive, were avoided. An additional benefit was that each cohort reached the more technically challenging chromatography stage at different times, so instructors were able to concentrate on smaller groups of students that needed help. In the cases where the chromatography was less successful, it was due to students either using too much silica, so that elution was more difficult, or loading the sample in too much toluene, so that the product eluted from the column earlier than expected.

This laboratory class was designed to be more demanding than the previous classes due to students having to make their own decisions about the glassware needed; therefore, this experiment was more heavily weighted in the overall course mark. During the experimental writeup, greater emphasis was placed upon interpretation/reporting of data and identifying the starting materials and products. There were also questions in the writeup instructions, available in the Supporting Information, that were designed to encourage the students to read around the area and recall information that they were given earlier in their undergraduate studies.

CONCLUSION

An operationally simple Sonogashira cross-coupling has been developed which is cheap to run and does not require any expensive glassware. The coupling reaction itself was quick, reliable, and complete within 1.5 h. Purification using a cheap version of flash column chromatography allowed students to see an additional purification method to the recrystallization or filtration they usually see in an undergraduate laboratory. This experiment has provided a platform that allowed students to develop a hands-on appreciation of the equipment required for each procedure, as well as introducing them to the concept of transition metal catalysis in organic synthesis. The video resource explaining silica gel column chromatography was invaluable in helping to deliver information about how to perform this technique both before and during the laboratory class.

ASSOCIATED CONTENT

Supporting Information

Detailed reagent and supply list, protocols for laboratory instructors, student handouts and demonstration videos, and analytical data for products (including melting points, NMR data, and IR spectra). This material is available via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: p.b.cranwell@reading.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The University of Reading Department of Chemistry undergraduate teaching laboratories are acknowledged for their help when piloting this practical class. Laurence Harwood is acknowledged for his generous support with lab space and equipment. The Undergraduate Research Opportunities Placement (UROP) scheme is gratefully acknowledged for funding and support (A.M.P. and P.B.C.).

REFERENCES

- (1) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen With Bromoalkenes, Iodoarenes, and Bromopyridines. *Tetrahedron Lett.* **1975**, *16* (50), 4467–4470.
- (2) (a) Negishi, E.; Anastasia, L. Palladium Catalysed Alkynylation. *Chem. Rev.* **2003**, *103* (5), 1979–2017. (b) Chinchilla, R.; Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107* (3), 874–922.
- (3) (a) Castro, C. E.; Stevens, R. D. Substitutions by Ligands of Low Valent Transition Metals. A Preparation of Toluens and Heterocyclics from Aryl Iodides and Cuprous Acetylides. *J. Org. Chem.* **1963**, *28* (8), 2163. (b) Stevens, R. D.; Castro, C. E. The Substitution of Aryl Iodides with Cuprous Acetylides. A Synthesis of Toluens and Heterocyclics. *J. Org. Chem.* **1963**, *28* (12), 3313–3315.
- (4) Glaser, C. Contribution to the Chemistry of Phenylacetylenes. *Ber. Dtsch. Chem. Ges.* **1869**, *2* (1), 422–424.
- (5) Copper-free Sonogashira couplings are known: (a) Urgaonkar, S.; Verkade, J. G. Ligand-, Copper-, and Amine-Free Sonogashira Reaction of Aryl Iodides and Bromides with Terminal Alkynes. *J. Org. Chem.* **2004**, *69* (17), 5752–5755. (b) Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. Efficient and Copper-Free Sonogashira Cross-Coupling Reaction Catalyzed by Pd(OAc)₂/Pyrimidines Catalytic System. *Eur. J. Org. Chem.* **2005**, *20*, 4256–4259.
- (6) (a) Hamilton, A. E.; Buxton, A. M.; Peeples, C. J.; Chalker, J. M. An Operationally Simple Aqueous Suzuki–Miyaura Cross-Coupling Reaction for an Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2013**, *90* (11), 1509–1513. (b) Callam, C. S.; Lowary, T. L. Suzuki Cross-Coupling Reactions: Synthesis of Unsymmetrical Biaryls in the Organic Laboratory. *J. Chem. Educ.* **2001**, *78* (7), 947–948. (c) Hill, N. J.; Bowman, M. D.; Esselman, B. J.; Byron, S. D.; Kreitinger, J.; Leadbeater, N. E. Ligand-Free Suzuki–Miyaura Coupling Reactions Using an Inexpensive Aqueous Palladium Source: A Synthetic and Computational Exercise for the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2014**, *91* (7), 1054–1057. (d) Costa, N. E.; Pelotte, A. L.; Simard, J. M.; Syvinski, C. A.; Deveau, A. M. Discovering Green, Aqueous Suzuki Coupling Reactions: Synthesis of Ethyl (4-Phenylphenyl)acetate, a Biaryl with Anti-Arthritic Potential. *J. Chem. Educ.* **2012**, *89* (8), 1064–1067. (e) Harper, B. A.; Rainwater, J. C.; Birdwhistell, K.; Knight, D. A. Aqueous-Phase Palladium-Catalyzed Coupling. A Green Chemistry Laboratory Experiment. *J. Chem. Educ.* **2002**, *79* (6), 729–731. (f) Aktoudianakis, E.; Chan, E.; Edward, A. R.; Jarosz, I.; Lee, V.; Mui, L.; Thatipamala, S. S.; Dicks, A. P. “Greening Up” the Suzuki Reaction. *J. Chem. Educ.* **2008**, *85* (4), 555–557. (g) Soares, P.; Fernandes, C.; Chavarria, D.; Borges, F. Microwave-Assisted Synthesis of 5-Phenyl-2-hydroxyacetophenone Derivatives by a Green Suzuki Coupling Reaction. *J. Chem. Educ.* **2014**, DOI: 10.1021/ed400498w.
- (7) (a) Martin, W. B.; Kateley, L. J. The Heck Reaction: A Microscale Synthesis Using a Palladium Catalyst. *J. Chem. Educ.* **2000**, *77* (6), 757–759. (b) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P.

Introduction to Homogeneous Catalysis: Carbon–Carbon Bond Formation Catalyzed by a Defined Palladium Complex. *J. Chem. Educ.* **2000**, 77 (1), 92–95.

(8) Ball, D. B.; Wilson, R. Organometallic Mediated Organic Synthesis: A Reaction Sequence for an Advanced Integrated Laboratory Course. *J. Chem. Educ.* **2002**, 79 (1), 112–114.

(9) (a) Brisbois, R. G.; Batterman, W. G.; Kragerud, A. R. Synthesis of 4-Nitro-1-pentynylbenzene: An Example of Transitional Metal-Mediated Cross-Coupling. *J. Chem. Educ.* **1997**, 74 (7), 832–833.

(b) Goodwin, T. E.; Hurst, E. M.; Ross, A. S. A Multistep Synthesis of 4-Nitro-1-ethynylbenzene Involving Palladium Catalysis, Conformational Analysis, Acetal Hydrolysis, and Oxidative Decarbonylation. *J. Chem. Educ.* **1999**, 76 (1), 74–75.