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Copper-Free Sonogashira Coupling Reaction with $PdCl_2$ in Water under Aerobic Conditions

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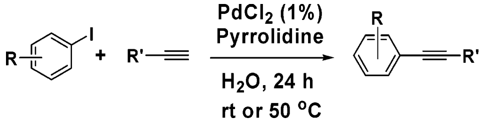

A mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal acetylenes in water under aerobic conditions has been developed. The use of 1 mol % $PdCl_2$ in the presence of pyrrolidine allows the coupling reaction to proceed at room temperature or 50 °C with good to excellent yields.

The Sonogashira reaction of terminal acetylenes with aryl or vinyl halides provides a powerful tool for C−C bond formation, which has been widely applied to diverse areas such as natural product synthesis and material science.[1] Typical procedures for the Sonogashira coupling utilize catalytic palladium with a metal cocatalyst and a base.[2] The most widely employed cocatalysts are copper salts, which mediates homocoupling of terminal alkynes when the copper acetylide is exposed to oxidative agents or air.[3] This side reaction is problematic when the terminal acetylenes are difficult to obtain. The use of other cocatalysts such as zinc, tin, boron, aluminum, Ag_2O, and AgOTf have been developed to address this issue,[4] but additional steps are needed to make these agents.

Recently, a palladium system modified by a bulky, electron-rich phosphine ligand (such as P^tBu_3) has been reported to display unusually high activity in the Sonogashira reaction of aryl bromides.[5] In the meantime, significant progress has been made in the Sonogashira reaction to give diminished homocoupling.[6] Many of the reactions were carried out without copper salts,[7] which provides the opportunity to develop the Sonogashira reaction under aerobic conditions, because the copper-mediated oxidative homocoupling of acetylene is prevented.[3]

In this paper, we present our contribution to the field by developing a mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal acetylenes in water under aerobic conditions.

In connection with our development of a chemical genetic approach to analyzing biological systems by using interfacing small molecule libraries,[8] we needed to synthesize a variety of phenyl acetylenes using the Sonogashira reaction. One of the complications with the Sonogashira couplings is that the reaction need degassed solvents, and have to be carried out under an inert atmosphere.[5] This is particularly inconvenient when the reactions are carried out in multiple vessels for library generation. Therefore, the development of a convenient method is an important objective in this effort.

To realize this goal, we screened a variety of coupling conditions and were pleased to find that the coupling

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(1) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, 1998; Chapter 10. (c) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prepr. Proced. Int.* **1995**, *27*, 127. (d) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.4.

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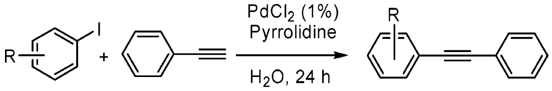
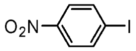
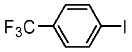
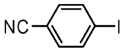
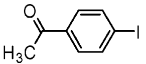
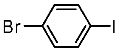
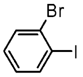
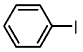
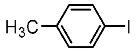
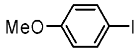
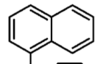
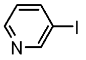
10.1021/jo048599z CCC: $30.25

TABLE 1. Sonogashira Reactions of Phenylacetylene with Phenyl Iodides

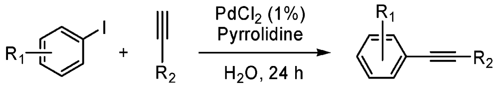


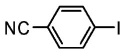
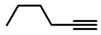
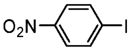
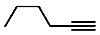
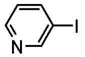
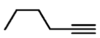
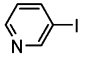
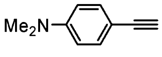
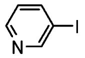
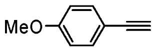
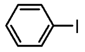
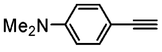
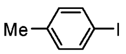
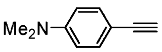
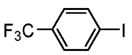
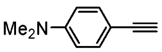
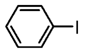
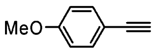
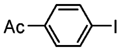
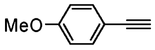
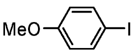
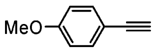
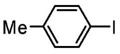
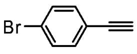
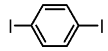
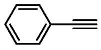
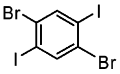
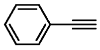
entry	Iodide	temp.	product	yield[a]
1		25 °C	**1a**	97%
2		25 °C	**1b**	90%
3		25 °C	**1c**	95%
4		25 °C	1**d**	89%
5		50 °C	1**e**	82%
6		50 °C	**1f**	88%
7		50 °C	1**g**	94%
8		50 °C	1**h**	90%
9		50 °C	**1i**	85%
10		50 °C	1k	85%
11		50 °C	1l	95%

reaction proceeded well using $PdCl_2$ in water[9] in the presence of pyrrolidine under aerobic conditions. We then studied the effect of various reaction parameters (palladium catalyst, base, temperature) on the outcome of the coupling reaction with phenyl acetylene and phenyl iodide as the substrates. It was found that among the catalysts tested [$PdCl_2$, PdI_2, $Pd(OAc)_2$, and $PdCl_2(PPh_3)_2$], $PdCl_2$ proved to be the most efficient. Among the bases used [triethylamine, pyridine, pyrrolidine, K_2CO_3, Na_2CO_3, $NaHCO_3$, $CsCO_3$, and CsOAc], pyrrolidine was the best choice. For the temperatures evaluated [25, 50, and 80 °C], 50 °C gave the best result. Taken together, good to excellent results were obtained when the reactions were carried out with 1 mol % of $PdCl_2$ in water[9] at 50 °C in the presence of pyrrolidine as base under aerobic conditions. As shown in Table 1, the optimized catalyst system is quite general and tolerant of a range of functionalities. For the electron-deficient phenyl iodides, the coupling reactions were carried out at 25 °C, and the others needed a higher temperature.

To examine the scope for this coupling reaction, a variety of terminal acetylenes were coupled with different phenyl iodides, and good results were obtained (Table 2). The coupling reaction of 2, 5-diiodo-1,4-dibromobenzene with phenyl acetylene (entry 14 in Table 2) gave 2,5-diphenylacetylene-1,4-dibromobenzene in 65% yield. It is noteworthy that the same coupling reaction was tried using other Sonogashira reaction conditions (such as $PdCl_2(PPH_3)_2$/CuI/Et_3N or $Pd(PPH_3)_4$/CuI/Et_3N), and only trace amounts of the desired product were obtained.

TABLE 2. Sonogashira Reactions of Acetylenes with Phenyl Iodides



entry	Iodide	acetylene	temp.	product	yield[a]
1			25 °C	**2a**	70%
2			25 °C	**2b**	85%
3			25 °C	**2c**	71%
4			50 °C	**2d**	85%
5			50 °C	**2e**	81%
6			50 °C	**2f**	76%
7			50 °C	**2g**	70%
8			25 °C	**2h**	82%
9			25 °C	**1i**	84%
10			25 °C	**2i**	80%
11			50 °C	**2j**	75%
12			50 °C	**2k**	68%
13			50 °C	**2l**	80%
14			50 °C	**2m**	65%

Although a number of Sonogashira reactions that were carried out in aqueous media were reported previously with CuI as a cocatalyst,[10] the advantages of this copper-free Sonogashira reaction are its insensitivity to air and its production of only trace amounts of homocoupling products of terminal acetylenes.

To evaluate the concentration effect of $PdCl_2$ in the Sonogashira reaction, we have tried the lifetime of palladium catalyst with 0.1 mol % of Pd loading and used phenyl iodide and phenyl acetylene as substrates to do the coupling reaction. As a result, 93% coupling product was obtained, and no Pd precipitation was observed after 24 h, which may indicate an effect of palladium concentration on the rate of Pd cluster formation.[11]

In conclusion, we have developed a mild copper-free Sonogashira coupling of aryl iodides and terminal acetylenes in water using pyrrolidine as base[12] under aerobic conditions. Current work in our laboratories is focused

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(9) To run the chemical reaction in water, see: Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. Application of ligand-free palladium for the Heck and Suzuki reactions in water, see: (a) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 5, p 153. (b) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.

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on extending the synthetic scope and carrying out the kinetic study of this reaction.

Experimental Section

Typical Procedure for the Sonogashira Coupling Reaction. $PdCl_2$ (0.02 mmol), iodide (2.0 mmol), H_2O (2.5 mL), and pyrrolidine (0.83 mL, 10 mmol) were added to a flask under aerobic conditions, and the resulting mixture was stirred at 50 °C for 5 min. To this solution was added acetylene (2.4 mmol), and the reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic layer was dried with anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by flash chromatography to give the desired product.

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Supporting Information Available: Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Th use of pyrrolidine as base in the Sonogashira reaction was reported during the time our manuscript was being reviewed. See: Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* **2004**, *2*, 2161.