# Transition-Metal-Free Sonogashira-Type Coupling Reactions in Water

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**Keywords:** Cross-coupling / Microwaves / Transition metals / Water chemistry

Microwave-assisted transition-metal-free Sonogashira-type coupling reactions are described. The reactions are run in water as the sole solvent, without the need for copper(I) or any transition-metal–phosphane complex. The scope of the methodology was tested by reaction of a wide variety of aryl halides and heteroaryl halides. The reaction was also investigated under conventional heating conditions.

## Introduction

The Sonogashira cross-coupling reaction[1] of terminal acetylenes with aryl or vinyl halides has proved to be a powerful method for the creation of carbon−carbon bonds. In the past decade it has found many applications in the synthesis of scaffolds leading to molecular-scale electronic devices,[2] dendrimers,[3] estradiol[4] and entadiyne antibiotics[5] and carbohydrate sensors.[6] Classically mediated by a dual catalytic system of a palladium−phosphane complex and copper(I) iodide, it has been shown to be a mild and high-yielding reaction, tolerant to a wide variety of functional groups. However, a long reaction time and contamination of the product with the catalyst are the main drawbacks of the reaction. Therefore, there has recently been a lot of interest in improving the conditions for the Sonogashira reaction. Much effort has been put into the design of suitable catalyst systems i.e. for the coupling of less reactive aryl chlorides,[7] for diminishing alkyne dimerization[8] and for the avoidance of expensive phosphane ligands.[9] Resin-supported palladium−phosphane complexes, which allow the easy removal of the catalyst by filtration, have also recently been described.[10] Considerable effort has been made to avoid the requirement for copper, by the use of palladacycles[11] or specifically designed phosphane ligands.[12a−12g] Microwave heating has been successfully applied to speed up this generally slow cross-coupling reaction,[13] but the utilization of water as a cheap, readily available, nontoxic and nonflammable solvent for the Sonogashira reaction has been scarcely investigated so far.[12a,14] Recently, it has been demonstrated that tetrabutylammonium bromide (TBAB) greatly facilitates this reaction when performed in water at reflux,[12a] which can probably be ascribed to an enhancement of the solvation of the organic compounds. The necessity of the addition of TBAB in microwave-enhanced transition-metal-free Suzuki-type coupling reactions in water has been extensively commented on by Leadbeater et al.[15] During our studies on microwave-assisted transition-metal-catalyzed reactions,[16] we discovered that, in some cases, it was possible to perform the Sonogashira-type cross-coupling reaction without a transition-metal catalyst. These studies are reported below.

## Results and Discussion

As the starting point for our optimization studies, we decided to investigate the microwave-enhanced transition-metal-free cross-coupling reaction of 2-bromonaphthalene in water with phenylacetylene as the coupling partner. The reaction mixture was irradiated in a single-mode microwave cavity in a sealed vial using a preselected maximum temperature of 175 °C (150 W power).[17] The parameters were varied as presented in Table 1. The use of one equivalent of TBAB seems to be critical, as employing other phase-transfer catalysts or smaller amounts of TBAB resulted in decreased yields (Entries 5 and 14−18). The optimum ratio of 2-bromonaphthalene and phenylacetylene was found to be 1:2. Smaller amounts of phenylacetylene resulted in an inferior yield (Entry 1), owing to unchanged bromonaphthalene and also homocoupling and polymerization of the acetylene. The bases $Na_2CO_3$, $Cs_2CO_3$ and $K_3PO_4$ gave comparable results in the cross-coupling reactions (Entries 2, 7 and 9). In contrast, the inorganic bases $NaHCO_3$, $Ba(OH)_2$ and NaOAc (Entries 8, 10 and 11) as well as the organic bases triethylamine and Hünig's base (Entries 12 and 13) all gave inferior yields. An excess of base (4.0 equiv.) was found to be critical; the use of smaller amounts reduced the yields considerably (Entries 3 and 4). In addition, lower temperatures or shorter reaction times resulted in incomplete conversions and inferior yields (Entries 19−23). The cross-coupling of 2-bromonaphthalene with

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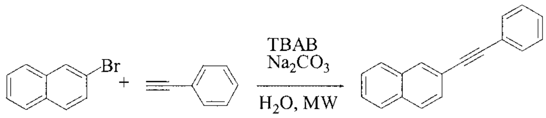
Table 1. Microwave-promoted Sonogashira-type coupling of 2-bromonaphthalene and phenylacetylene in water



| Entry | PhCCH (equiv.)[a] | Base/equiv. | PTC/equiv. | Time (min) | Temp. (°C) | Power (W) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1.0**[c] | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 46 |
| 2 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 83 |
| 3 | 2.0 | **$Na_2CO_3$/3.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 61 |
| 4 | 2.0 | **$Na_2CO_3$/2.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 31 |
| 5 | 2.0 | $Na_2CO_3$/4.0 | **($n$Bu)$_4$NBr/0.5** | 15 | 175 | 150 | 44 |
| 6 | 2.0 | $Na_2CO_3$/4.0 | **($n$Bu)$_4$NBr/1.5** | 15 | 175 | 150 | 83 |
| 7 | 2.0 | **$Cs_2CO_3$/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 81 |
| 8 | 2.0 | **$NaHCO_3$/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 62 |
| 9 | 2.0 | **$K_3PO_4$/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 81 |
| 10 | 2.0 | **$Ba(OH)_2$/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 18 |
| 11 | 2.0 | **Na(OAc)/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 14 |
| 12 | 2.0 | **$Et_3N$/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 0 |
| 13 | 2.0 | **($i$Pr)$_2$EtN/4.0** | ($n$Bu)$_4$NBr/1.0 | 15 | 175 | 150 | 0 |
| 14 | 2.0 | $Na_2CO_3$/4.0 | **($n$Bu)$_4$NCl/1.0** | 15 | 175 | 150 | 14 |
| 15 | 2.0 | $Na_2CO_3$/4.0 | **($i$Pr)$_4$NI/1.0** | 15 | 175 | 150 | 39 |
| 16 | 2.0 | $Na_2CO_3$/4.0 | **($n$Bu)$_4$N(OAc)/1.0** | 15 | 175 | 150 | 59 |
| 17 | 2.0 | $Na_2CO_3$/4.0 | **($n$Bu)$_4$N($HSO_4$)/1.0** | 15 | 175 | 150 | 0 |
| 18 | 2.0 | $Na_2CO_3$/4.0 | **PEG/1.0** | 15 | 175 | 150 | 0 |
| 19 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | **5** | 175 | 150 | 34 |
| 20 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | **10** | 175 | 150 | 61 |
| 21 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | 15 | **100** | 150 | 0 |
| 22 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | 15 | **125** | 150 | 11 |
| 23 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | 15 | **150** | 150 | 51 |
| 24 | 2.0 | $Na_2CO_3$/4.0 | ($n$Bu)$_4$NBr/1.0 | **720** | 175 | **oil bath** | 0[d] |

[a] Aryl halide (1 mmol). [b] Isolated yields. [c] Conditions different from those in Entry 2 are in bold. [d] Increasing the oil bath temperature to 210 °C did not result in any detectable reaction.

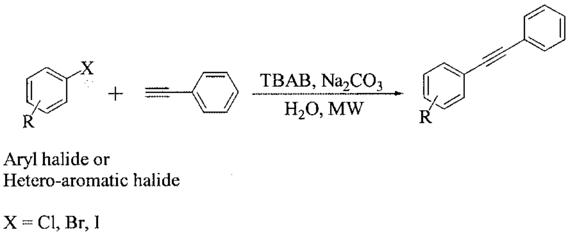
phenylacetylene was also investigated under conventional heating conditions. However, no reaction occurred at 175 °C, even after 12 hours (Entry 24) and increasing the oil bath temperature to 210 °C did not result in any detectable reaction. This could point to the fact that a specific microwave effect plays a role in the transition-metal-free Sonogashira-type coupling.

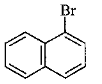
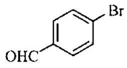
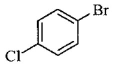
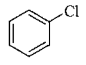
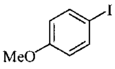
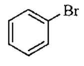
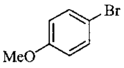
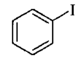
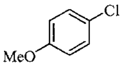
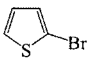
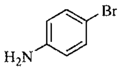
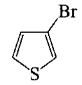
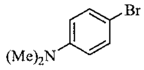
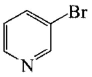
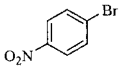
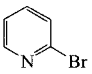
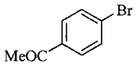
In order to prove that the reactions were indeed run under transition-metal-free conditions, the crude reaction mixtures were subjected to AAS-MS in order to determine the palladium and copper content.[18] No metals were detected above the limit of 1 ppm. Furthermore, levels of other catalytically active metals (Ni, Fe, Zn, Co, Pt, Rh and Ir) were found not to exceed 1 ppm. Together with the use of new materials (glassware, magnetic stirring bars, reagents and solvents) in the reactions and the reproducibility of the results, this makes it clear that no catalytic contaminants are involved.

The scope of our methodology was investigated by treating phenylacetylene with various aromatic halides under the optimized reaction conditions; a wide variety of functional groups are tolerated (Table 2). As expected, the chlorobenzene derivatives proved to be inert under these coupling conditions (Entries 2, 5 and 11), and complete regioselectivity was found for the reaction of 4-bromo-1-chlorobenzene (Entry 2). However, to our surprise, no reaction was observed with either bromobenzene or iodobenzene (Entries 12 and 13), even at 210 °C. Application of our strategy to other aryl halides bearing electron-donating (Entries 3, 4, 6 and 7) or electron-withdrawing (Entries 8 and 9) substituents was successful, but 4-bromobenzaldehyde exclusively underwent a Cannizaro reaction (Entry 10). Heterocyclic halides (Entries 14−16) also seem to be suitable substrates for this reaction, although the reaction of 2-bromopyridine met with failure (Entry 17).

In conclusion, we have demonstrated that the cross-coupling reaction of a variety of aryl halides with phenylacetylene in water, under controlled microwave irradiations, can be performed without the application of palladium or copper or any other transition-metal catalyst. In this manner, problems of intrinsic toxicity and air sensitivity of transition-metal complexes can be avoided, as well as the use of expensive phosphane ligands or special resins. Moreover, because these reactions can be run with water as the sole solvent, these Sonogashira-type coupling reactions are an exquisite example of real "Green Chemistry". The mechanistic aspects of this remarkable coupling reaction are currently under investigation.

Table 2. Microwave-promoted Sonogashira-type coupling of aryl halides and phenylacetylene in water



| Entry | Aryl halide[a] | Time (min) | Yield (%)[b] | Entry | Aryl halide[a] | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| **1** |  | 10 | 76[c] | **10** |  | 15 | 0[h] |
| **2** |  | 20 | 76[c,d] | **11** |  | 25 | 0[i] |
| **3** |  | 15 | 78[c] | **12** |  | 25 | 0[i] |
| **4** |  | 20 | 70[c] | **13** |  | 25 | 0[i] |
| **5** |  | 20 | 0[e] | **14** |  | 15 | 86 |
| **6** |  | 25 | 66[f] | **15** |  | 15 | 84 |
| **7** |  | 25 | 59[f] | **16** |  | 20 | 83[c] |
| **8** |  | 15 | 52[g] | **17** |  | 20 | 0[i] |
| **9** |  | 15 | 85[c] | | | | |

[a] A mixture of the aryl halide (1 mmol), phenylacetylene (2.0 mmol), $Na_2CO_3$ (4.0 mmol), TBAB (1.0 mmol) and water (3.0 mL) was irradiated at a preselected temperature of 175 °C at 150 W maximum power for the time indicated. [b] Isolated yield. [c] Some traces of starting aryl halide were detected with EI-MS. [d] Reaction occurs exclusively at the bromo functionality. [e] At 210 °C a trace of the desired compound was detected with EI-MS. [f] The reaction is slow and does not run to completion. [g] Partial decomposition was observed. [h] Gives exclusively the Cannizzaro reaction products 4-bromobenzyl alcohol and 4-bromobenzoic acid in 86 % combined yield. [i] No reaction was observed, even at 210 °C.

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[17] The mono-mode Discover microwave reactor (CEM Corporation P. O. Box 200 Matthews, NC 28106) was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in sealed (aluminum-Teflon® crimp-top) large (10 mL) microwave process vials.

[18] The AAS-MS was performed with a Shimadzu AA-220 Atomic Absorption − Flame Emission Spectrophotometer.

[19] **Typical Experimental Procedure:** 2-Bromonaphthalene (1 mmol, 207 mg), phenylacetylene (2 mmol, 202 mg), tetra(*n*-butyl)ammonium bromide (1 mmol, 322 mg) and sodium carbonate (4 mmol, 424 mg) were suspended in water (3 mL) in a 10 mL glass vial equipped with a small stirring magnet. The vial was tightly sealed using an aluminum-Teflon crimp-top and irradiated in the cavity of a monomode Discover apparatus (CEM corporation) for 15 minutes at a temperature of 175 °C, using an irradiation power of 150 W. After the reaction time, the vial was cooled to 60 °C by gas-jet cooling. The resultant mixture was partitioned between diethyl ether and water, and the aqueous-phase was extracted with diethyl ether (×3). The combined organic layers were dried on magnesium sulfate and the solvents were removed in vacuo to furnish the crude product. This was purified by column chromatography (silica gel, hexane) to furnish 2-phenylethynylnaphthalene as colorless solid. M.p. 112 °C (A. R. Katritzky, A. A. A. Abdel-Fattah, M. Wang, *J. Org. Chem.* **2002**, *67*, 7526: 111 °C). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.34-7.36$ (m, 3 H), $7.46-7.49$ (m, 2 H), $7.56-7.59$ (m, 3 H), $7.78-7.81$ (m, 3 H), 8.05 (s, 1 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 89.7$, 89.8, 120.6, 123.3, 126.5, 126.6, 127.8, 128.0, 128.3, 1128.4, 131.4, 131.7, 132.8, 133.0 ppm. EI-MS $[M^+]$ (%): 229 (100).

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