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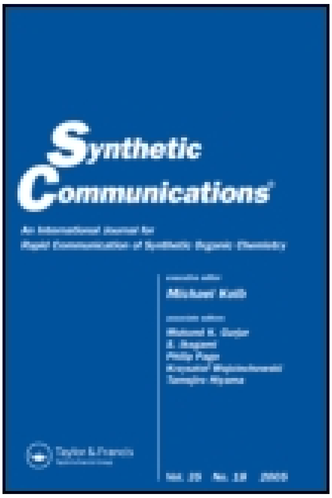

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CuI/PPh$_3$/PEG-Water: An Efficient Catalytic System for Cross-Coupling Reaction of Aryl Iodides and Alkynes

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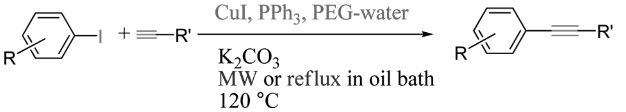
CuI/PPh$_3$/PEG–WATER: AN EFFICIENT CATALYTIC SYSTEM FOR CROSS-COUPLING REACTION OF ARYL IODIDES AND ALKYNES

Gong Chen, Jianwei Xie, Jiang Weng, Xinhai Zhu, Zhanchao Zheng, Jiwen Cai, and Yiqian Wan
School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou, China

GRAPHICAL ABSTRACT



Abstract *An efficient protocol for the copper-catalyzed Sonogashira coupling of aryl iodides with terminal acetylenes in water–polyethylene glycol has been established. Both electron-rich and electron-deficient aryl iodides were arylalkynated under microwave heating or reflux in oil bath to afford good to excellent yields.*

Keywords Alkynation; aqueous chemistry; copper; coupling; microwave-assisted chemistry

INTRODUCTION

Because of the presence of the aryl alkynes motifs in naturally occurring compounds and synthetic materials, as well as the extensive application of aryl alkynes both in industry and academic laboratories, pursuing an efficient and versatile strategy for construction of molecules containing aryl alkynes is of great interest. During past decades, the Sonogashira-type reaction has proved to be one of the most efficient and straightforward methods for the construction of carbon (sp2)–carbon (sp) bonds.[1] Typical procedures for the Sonogashira coupling utilize a catalytic palladium catalyst combined with CuI as a cocatalyst and a large amount of amine as base or cosolvent[2] Dramatic modifications have been made to achieve economic and environmentally friendly reactions, including the use of other cheaper metals such as copper[3] and nickel[4] in place of palladium catalyst, a copper-free version,[5] microwave irradiation technology,[3g–i,6] ionic liquid,[7] aqueous solvent,[8] and so on.

In recent years, significant efforts have been dedicated to develop economical and mild coupling reactions carried out in aqueous media or pure water, because

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these efforts would conquer one of the complications of the Sonogashira coupling: the reaction needs degassed solvents and has to be carried out under an inert atmosphere. Moreover, water is the most safe (water is nontoxic and nonflammable) and economical solvent.[9] The use of water as solvent in transition-metal-catalyzed coupling reactions makes the workup procedure easy. Compared to the extensive investigation of the palladium-catalyzed Sonogashira reaction in water,[8] the copper-catalyzed cross-coupling reaction between aryl halides and terminal alkynes remains less well studied.[3i]

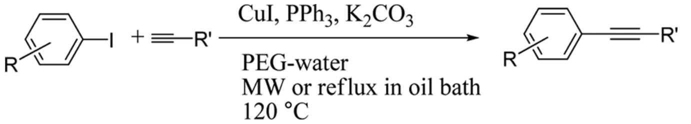
Our previous experiment has demonstrated that the copper-catalyzed coupling reaction of aryl iodides and terminal acetylenes can be conducted in water with excellent yields in the presence of 1 equivalent of tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst.[3i] Compared to TBAB or other toxic phase-transfer catalyst, polyethylene glycol (PEG) is known to be a nontoxic, recyclable, thermally stable, and inexpensive medium for phase-transfer catalyst.[10] Recently, Lamaty and coworkers described microwave-assisted copper-catalyzed alkynation of aryl iodides in various pure PEGs solvent. It was performed at relatively hash condition (at 150–220 °C for 1–2.5 h under microwave irradiation) with moderate yields, and the addition of PPh_3 gave no significant improvement in yield.[3h] Another microwave-assisted procedure using water–PEG as solvent also was conducted at high reaction temperature (175 °C) with limited substrate scope.[6a] The harsh reaction conditions make these methods difficult to apply in industry. Therefore, the development of a highly efficient procedure for the copper-catalyzed Sonogashira reaction is still an important topic in organic synthesis both in laboratories and in industry.

RESULTS AND DISCUSSION

As a result of our ongoing investigation on microwave-assisted coupling reactions in aqueous media, [3i,11] we describe our results of using a copper-catalyzed Sonogashira reaction in aqueous PEGs. It is notable that the reactions performed well both under microwave irradiation (120 °C, 20–50 min) or with conventional thermal heating (reflux in 120 °C oil bath, 24 h), producing good to excellent yields (Scheme 1).

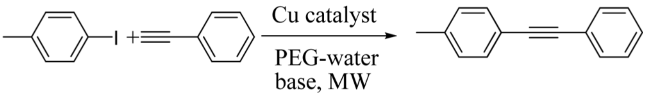
Initially, the coupling reaction between 4-iodotoluene and phenyl acetylene under microwave irradiation was employed as a model reaction to optimize the reaction in water with PEG600 and a series of organic cosolvents. As summarized in Table 1, dimethylformamide (DMF) and acetone showed beneficial effects on the reaction, while ethanol retarded the reaction. The best result was obtained using PEG600 as a cosolvent, resulting in 91% yield. When the ratio of water/PEG was 3:1, the yield increased to 96% (Table 1, entry 11).

Encouraged by these results, we explored further the effect of the chain length of PEGs on the reaction efficiency under the same reaction conditions. PEG1000 and



Scheme 1. Cross-coupling reaction of aryl iodides with alkynes in PEG-water.

Table 1. Optimization of the reaction conditions



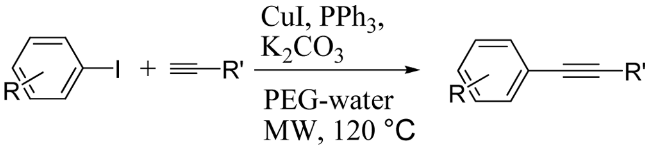
Entry	Catalyst[a]	Base[b]	Solvent[c]	Yield[d] (%)
1	CuI	K_2CO_3	H_2O	52
2	CuI	K_2CO_3	EtOH/H_2O (1:1)	42
3	CuI	K_2CO_3	DMF/H_2O (1:1)	86
4	CuI	K_2CO_3	Acetone/H_2O (1:1)	64
5	CuI	K_2CO_3	PEG600/H_2O (1:1)	91
6	$Cu(OAc)_2$	K_2CO_3	PEG600/H_2O (1:1)	83
7	CuO	K_2CO_3	PEG600/H_2O (1:1)	74
8	$Cu(NO_3)_2$	K_2CO_3	PEG600/H_2O (1:1)	41
9	Cu_2O	K_2CO_3	PEG600/H_2O (1:1)	47
10	CuI	K_2CO_3	PEG600/H_2O (1:3)	96
11	CuI	K_2CO_3	PEG300/H_2O(1:3)	77
12	CuI	K_2CO_3	PEG1000/H_2O (1:3)	92
13	CuI	K_2CO_3	PEG2000/H_2O (1:3)	91
14	CuI	K_2CO_3	PEG4000/H_2O (1:3)	45
15	CuI	KOH	PEG600/H_2O (1:3)	78
16	CuI	K_3PO_4	PEG600/H_2O (1:3)	76
17	CuI	Cs_2CO_3	PEG600/H_2O (1:3)	79
18	CuI	CsF	PEG600/H_2O (1:3)	24
19	CuI	Et_3N	PEG600/H_2O (1:3)	29
20	CuI	–	PEG600/H_2O (1:3)	0

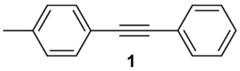
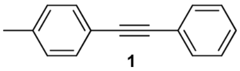
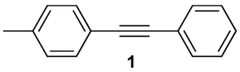
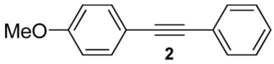
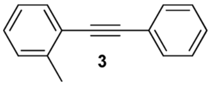
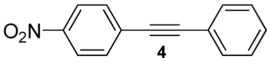
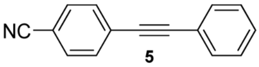
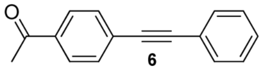
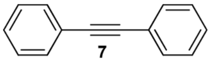
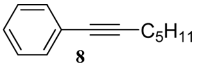
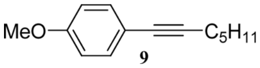
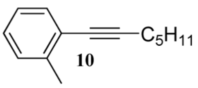
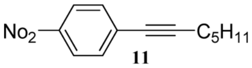
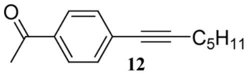
[a] 2 Equiv. PPh_3 was used as ligand based on copper source.
[b] 2 Equiv. base was used based on 4-iodotoluene.
[c] 2 g in total, weight ratio.
[d] Isolated yields.

PEG2000 showed slightly less efficiency than PEG600. Substituting PEG600 with PEG4000 led to dramatic decrease of yield from 96% to 45%. PEG300 was also less efficient than PEG600. PEGs not only acted as cosolvent but also as a phase-transfer catalyst (PTC), similar to crown ethers at the same reaction conditions, and the phase catalytic activity was influenced by the PEG molecular weight, chain end effects, and so on.[10f] Hence, we further investigated the conditions to optimize the base and copper catalyst sources (Table 1). CuI, as expected, was remarkably effective in the test conditions, whereas $Cu(OAc)_2$ and CuO give moderate yields (83% and 74%, respectively). It should be noted that K_2CO_3, a readily available weak base, gave the best result among the tested bases, including KOH, K_2CO_3, K_3PO_4, Cs_2CO_3, CsF, and Et_3N.

The coupling reactions of various aryl iodides and alkynes were performed under microwave irradiation to investigate the scope and limitation of the optimum conditions. As summarized in Table 2, both electron-rich and electron-deficient aryl iodides can be coupled with aryl alkynes smoothly at 120 °C in a short reaction time. Even the hindered *o*-iodotoluene could provide good yield (90%) with only a bit longer reaction time of 30 min. The reaction between aryl iodides and hept-1-yne

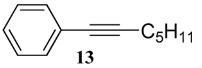
Table 2. Cross-coupling reaction of aryl iodides with alkynes under microwave irradiation[a]



Entry	Product	Time (min)	Yield[b] (%)
1	 **1**	20	96
2	 **1**	30	88
3	 **1**	30	69
4	 **2**	20	92
5	 **3**	30	90
6	 **4**	20	97
7	 **5**	20	94
8	 **6**	20	93
9	 **7**	20	88
10	 **8**	50	87
11	 **9**	50	91
12	 **10**	50	86
13	 **11**	50	73
14	 **12**	50	81

(*Continued*)

Table 2. Continued

Entry	Product	Time (min)	Yield[b] (%)
15	 **13**	50	82

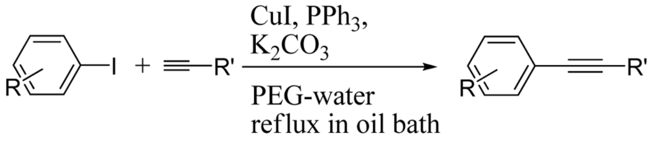
[a]Reaction conditions: 0.5 mmol aryl iodide, 1.2 mmol phenyl acetylene, or 1.5 mmol hept-1-yne, 0.05 mmol CuI, 0.1 mmol PPh_3, 0.5 g PEG600, 1 mmol K_2CO_3 in 1.5 g water, 120 °C, under microwave irradiation.

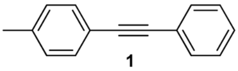
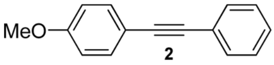
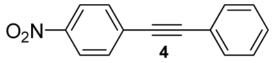
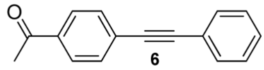
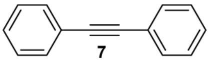
[b]Isolated yield.

need more time (50 min) to consume the starting materials completely, and the amount of hept-1-yne should be increased to 1.5 equivalents compared with aryl iodides (Table 2, entries 10–15).

It was well documented that most of the palladium catalyst system in PEG could be readily recycled. To check the reusability of this $CuI/PPh_3/PEG–H_2O$ system, the coupling reaction of 4-iodotoluene and phenyl acetylene was carried out as a model reaction. After the initial experiment, the reaction mixture was extracted with diethyl ether. The resulting mixture was used in the next run. The second run of this reaction gave a little decrease in isolated yield (88%) with

Table 3. Cross-coupling reaction of aryl iodides with phenyl acetylene under conventional thermal heating conditions[a]



Entry	Product	Yield (%)[b]
1	 **1**	89 91[c]
2	 **2**	83
3	 **4**	87
4	 **6**	89
5	 **7**	84

[a]Reaction conditions: 0.5 mmol aryl iodide, 1.2 mmol phenyl acetylene, 0.05 mmol CuI, 0.1 mmol PPh_3, 0.5 g PEG600, 1 mmol K_2CO_3 in 1.5 g water, reflux in oil bath under balloon nitrogen gas protection for 24 h.

[b]Isolated yield.

[c]Large-scale reaction condition: 20 mmol 4-iodotoluene, 24 mmol phenyl acetylene, 2 mmol CuI, 4 mmol PPh_3, 20 g PEG600, 10 mmol K_2CO_3 in 60 g water, reflux in oil bath under balloon nitrogen gas protection for 24 h.

prolongation of the reaction time to 30 min (Table 2, entry 2). The isolated yield decreased dramatically to 69% in the third run (Table 2, entry 3).

Although a shorter reaction time is beneficial for library generation, and was easily accomplished under microwave irradiation, the conventional thermal heating is still a favorable option in large-scale synthesis both in industry and in academic laboratories. Moreover, the conventional thermal heating devices are much less expensive than a professional microwave synthesizer. Hence, we conducted the reactions in an oil bath and also carried out the model reaction on a relative large scale by taking 20 mmol of 4-iodotoluene and 24 mmol of phenylacetylene. As summarized in Table 3, the coupling reactions proceeded equally successfully under reflux in the CuI/PPh_3/PEG–H_2O system with the reaction time increasing from minutes to hours, and the large-scale reaction proceeded without any difficulty to give excellent yields of the corresponding product under the present conditions.

CONCLUSIONS

In summary, an efficient CuI/PPh_3/PEG–H_2O system has been developed for the coupling reaction of aryl iodides and alkynes. It works well either under microwave irradiation or conventional thermal heating. This offers a practical alternative to the more general Sonogashira-type reaction procedure for both high-throughput pharmaceutical research in laboratories and large scale synthesis in industry.

EXPERIMENTAL

Microwave-assisted coupling reactions were carried out in the CEM Discover microwave in glass vessels (capacity 10 mL) sealed with a septum with a stirring option. Column chromatography was performed with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography (TLC) was carried out with Merck silica- gel GF254 plates. All products were characterized by electron impact–mess spectrometry (EI-MS) and ^1H NMR data, which were compared to the literature. ^1H NMR spectra were recorded at room temperature on a Varian Mercury-Plus 300 instrument with solvent as reference. Mass spectra were recorded on a Thermo Trace DSQ EI-mass spectrometer.

General Procedure for the Coupling Reaction of Aryl Iodides and Terminal Acetylenes Under Microwave Irradiation

A 10 mL glass tube was charged with CuI (10 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol), and H_2O (1.5 g). The mixture was stirred for 15 min at room temperature. PEG600 (0.5 g), aryl iodide (0.5 mmol), phenylacetylene (62 mg, 1.2 mmol), and K_2CO_3 (138 mg, 1 mmol) were added to this solution. The vessel was sealed with a septum and placed into the microwave cavity. The temperature of the mixture was ramped from r t to 120 °C under microwave irradiation, and it took 40–60 s. Once 120 °C was reached, the reaction mixture was held at this temperature for 20 min. After allowing the mixture to cool to room temperature, the reaction mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel to give the target product.

General Procedure for the Coupling Reaction of Aryl Iodides and Phenyl Acetylenes Under Reflux Conditions

CuI (10 mg, 0.05 mmol), PPh$_3$ (26 mg, 0.1 mmol), and H$_2$O (1.5 g) were added to a 10 mL flask. The mixture was stirred for 15 min at room temperature. PEG600 (0.5 g), aryl iodide (0.5 mmol), phenylacetylene (62 mg, 1.2 mmol) and K$_2$CO$_3$ (138 mg, 1 mmol), were added to this solution. The resulting mixture was stirred in oil bath preheated to 120 °C (0.5 g PEG600 in 1.5 g water, bp: 101 °C) under balloon nitrogen gas protection for 24 hr. The reaction mixture was then extracted with EtOAc (3×15 mL), and the combined organic layer was dried over Na$_2$SO$_4$. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel to give the target product.

Spectral Data for All Products

4-(Phenylethynyl)toluene (1)[8e]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.40$ (s, 3H), 7.17 (d, $J = 8.1$ Hz, 2H), 7.33–7.39 (m, 3H), 7.46 (d, $J = 8.1$ Hz, 2H), 7.52–7.56 (m, 2H). EI-MS (m/z) = 192 [M]$^+$.

4-(Phenylethynyl)anisole (2)[12]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 3.84$ (s, 3H), 6.87–6.90 (m, 2H), 7.26–7.35 (m, 3H), 7.47–7.54 (m, 4H). EI-MS (m/z) = 208 [M]$^+$.

2-(Phenylethynyl)toluene (3)[3j]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.42$ (s, 3H), 7.12–7.20 (m, 3H), 7.20–7.26 (m, 3H), 7.37–7.44 (m, 3H). EI-MS (m/z) = 192 [M]$^+$.

4-(Phenylethynyl)nitrobenzene (4)[8e]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.39$–7.41 (m, 3H), 7.55–7.57 (m, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 8.22 (d, $J = 8.4$ Hz, 3H). EI-MS (m/z) = 223 [M]$^+$.

4-(Phenylethynyl)benzonitrile (5)[8e]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta =$ 7.37–7.39 (m, 3H), 7.53–7.56 (m, 2H), 7.59–7.63 (m, 4H). EI-MS (m/z) = 203 [M]$^+$.

4-(Phenylethynyl)acetophenone (6)[8e]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 2.63$ (s, 3H), 7.36–7.38 (m, 3H), 7.54–7.57 (m, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.94 (d, $J = 8.1$ Hz, 2H). EI-MS (m/z) = 220 [M]$^+$.

Diphenylacetylene (7)[12]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.35$–7.40 (m, 6H), 7.54–7.57 (m, 4H). EI-MS (m/z) = 178 [M]$^+$.

1-(1-Heptynyl)-4-methylbenzene (8)[13]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.96$ (t, $J = 7.1$ Hz, 3H), 1.35–1.51 (m, 4H), 1.59–1.66 (m, 2H), 2.36 (s, 3H), 2.42 (t, $J = 7.1$ Hz, 2H), 7.10 (d, $J = 7.9$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H). EI-MS (m/z) = 186 [M]$^+$.

1-(1-Heptynyl)-4-methoxybenzene (9)[12]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.94$ (t, $J = 7.0$ Hz, 3H), 1.36–1.45 (m, 4H), 1.57–1.64 (m, 2H), 2.38 (t, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 6.80-6.83 (m, 2H), 7.32–7.35 (m, 2H). EI-MS (m/z) = 202 [M]$^+$.

1-(1-Heptynyl)-2-methylbenzene (10)[12]. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3H), 1.35–1.53 (m, 4H), 1.60–1.67 (m, 2H), 2.43 (s, 3H), 2.47 (t, $J = 6.9$ Hz, 2H), 7.08–7.14 (m, 1H), 7.16-7.18 (m, 2H), 7.35–7.38 (m, 1H). EI-MS (m/z) = 186 [M]$^+$.

1-(1-Heptynyl)-4-nitrobenzene (11)[13]. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, $J = 6.9$ Hz, 3H), 1.37–1.48 (m, 4H), 1.62–1.67 (m, 2H), 2.45 (t, $J = 7.2$ Hz, 2H), 7.49–7.52 (m, 2H), 8.13-8.16 (m, 2H). EI-MS (m/z) = 217 $[M]^+$.

1-(4-(Hept-1-ynyl)phenyl)ethanone (12)[3j]. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, $J = 7.2$ Hz, 3H), 1.36–1.48 (m, 4H), 1.59–1.68 (m, 2H), 2.44 (t, $J = 7.2$ Hz, 2H), 2.59 (s, 3H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.87 (d, $J = 8.1$ Hz, 2H). EI-MS (m/z) = 214 $[M]^+$.

1-Phenyl-1-heptyne (13)[12]. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, $J = 7.2$ Hz, 3H), 1.37–1.49 (m, 4H), 1.58–1.66 (m, 2H), 2.42 (t, $J = 7.1$ Hz, 2H), 7.26–7.30 (m, 3H), 7.38–7.42 (m, 2H). EI-MS (m/z) = 172 $[M]^+$.

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