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CuI/PPh$_3$-catalyzed Sonogashira coupling reaction of aryl iodides with terminal alkynes in water in the absence of palladium

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The Sonogashira cross-coupling of aryl iodides with terminal alkynes catalyzed by a simple and inexpensive catalyst system of CuI/PPh$_3$ in water as the sole solvent has been reported. In the presence of CuI/PPh$_3$, with KOH used as a base, a number of aryl iodides were treated with alkynes to afford the corresponding products in moderate to excellent yields. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: water; copper(I) iodide; aryl iodide; terminal alkyne; Sonogashira coupling reaction

Introduction

The Sonogashira cross-coupling reaction of terminal acetylenes with aryl or vinyl halides has proved to be a powerful method for the creation of substituted alkynes,[1,2] which has been widely applied in the synthesis of natural products,[3,4] biologically active molecules[5,6] and materials science.[7] Typical procedures for the Sonogashira coupling utilize catalytic palladium and/or a copper cocatalyst and a base.[8–10] However, the palladium catalysts are expensive, which limits their application in industry. In recent years, copper-based catalysts have been proposed as an alternative to palladium-based catalysts for Sonogashira couplings, including CuI/PPh$_3$,[11] Cu(phen)(PPh$_3$)Br,[12,13] copper nanoparticles,[14,15] supported copper complexes,[16–18] CuBr/*rac*-BINOL,[19] Cu(I)/diamine,[20] CuI/dabco,[21] Cu(OAc)$_2$/DAB-Ph,[22] Cu[(phen)(PPh$_3$)$_2$]NO$_3$,[23] Cu(I)/amino acid[24] and other copper catalyst.[25–28] However, during most of these catalytic systems, organic solvents are usually employed as the reaction media, often creating safety, health and environmental issues owing to their flammability, toxicity and volatility. The use of water or aqueous solution represents one of the most economically and environmentally viable alternatives to organic solvents for metal-catalyzed reactions.[29–31] A number of Pd-catalyzed Sonogashira reactions have been successfully carried out in aqueous media.[32–38] However, few reports on Pd-free version of Sonogashira in aqueous media have been reported.[39–41] Recently, Chen and coworkers reported copper-catalyzed Sonogashira reaction in water under microwave irradiation or reflux conditions with longer reaction time; however, a stoichiometric amount of tetrabutylammonium bromide (TBAB) was necessary for satisfactory yields.[41] In this paper, we report the Sonogashira reaction of aryl iodides with terminal alkynes catalyzed by cheap and ready available CuI/PPh$_3$ in pure water using KOH as the base in the absence of additives.

Results and Discussion

Initially, we chose the coupling reaction of iodobenzene with phenylacetylene as a model reaction to determine the optimum conditions. We examined several bases for the Sonogashira reaction using CuI/PPh$_3$ at 120 °C for 2.5 h in water (Table 1). Among the bases, while KOH was found to be most effective, other inorganic bases were inferior, and the organic bases were less effective than KOH in this catalytic system. We then examined the effect of copper salts on the 1Sonogashira reaction of the model reaction (Table 2). Among the copper salts tested, CuI proved to be the best choice. Meanwhile, the reaction depends on the ratio of CuI with PPh$_3$. Only a trace of the desired product was obtained without PPh$_3$ (Table 3). The reaction temperature was also an important factor; performing the reaction at 90 °C afforded the product in 44% yield, and raising the temperature to 140 °C afforded the product in 95% yield (Table 3). Thus, the optimized conditions are CuI (5 mol%), PPh$_3$ (15 mol%), KOH (2 equiv), in water at 140 °C.

To examine the generality of the catalyst for the Sonogashira reaction, the reactions of a variety of aryl iodides with terminal acetylenes were investigated under the optimized conditions. As shown in Table 4, electron-rich, electron-neutral and electron-poor aryl iodides reacted with phenylacetylene to afford the corresponding products in excellent yields under the standard

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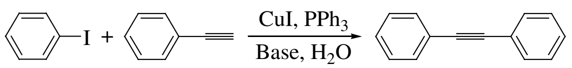
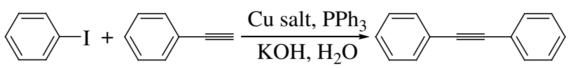
Table 1. Effect of base on the Sonogashira coupling reaction[a]



Entry	Base	Yield (%)[b]
1	Na_2CO_3	22
2	K_2CO_3	34
3	Cs_2CO_3	14
4	NaOH	28
5	KOH	84
6	K_3PO_4	56
7	NaOAc	4
8	Et_3N	16
9	(*i*-Pr)$_2$ NH	33
10	Piperidine	50
11	Pyrrolidine	46

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylacetylene (1.2 mmol), CuI (5 mol%), PPh_3 (15 mol%), and base (2.0 mmol) in degassed water (2.0 ml) at 120 °C for 2.5 h in a pressure tube.
[b] GC yield, using hexadecane as internal standard.

Table 2. Effect of copper salt on the Sonogashira coupling reaction[a]



Entry	Base	Yield (%)[b]
1	CuI	84
2	CuBr	44
3	CuCl	29
4	$Cu(NO_3)_2$	18
5	$CuSO_4$	27
6	$CuCl_2$	38
7	$Cu(OAc)_2$	23

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylacetylene (1.2 mmol), Cu salt (5 mol%), PPh_3 (15 mol%) and KOH (2.0 mmol) in degassed water (2.0 ml) at 120 °C for 2.5 h in a pressure tube.
[b] GC yield, using hexadecane as internal standard.

reaction conditions for 4 or 6 h (entries 1–9, Table 4). For *ortho*-substituted aryl iodides, 1-iodo-2-nitrobenzene reacted with phenylacetylene afforded the desired product in 91% yield (entry 10, Table 4); 2-iodotoluene only afforded product in 47% yield (entry 11, Table 4). Heteroatomatic compounds can also react with phenylacetylene in excellent yields, e.g. 2-iodothiophene reacted with phenylacetylene afforded the desired product in 89% yield (entry 12, Table 4), and 3-iodopyridine also gave the desired product in 91% yield (entry 13, Table 4). Good yields were obtained when aliphatic acetylene 1-octyne was used, e.g. iodobenzene reacted with 1-octyne gave the product in 75% yield (entry 14, Table 4) and 94% yield was obtained for 1-iodo-4-nitrobenzene (entry 15, Table 4).

Conclusion

In conclusion, we have demonstrated a simple, practical and economical CuI/PPh_3-catalyzed palladium-free Sonogashira reaction of aryl iodides with terminal alkynes in water in the presence of KOH. The advantages of this catalytic system include the palladium-free condition, low cost of catalyst, highly catalytic activity for both electron-rich and electron-poor aryl iodides and water as the sole solvent in the absence of additives.

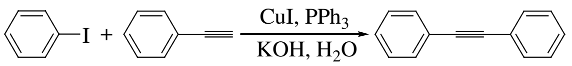
Experimental

All reactions were carried out under a nitrogen atmosphere. All halides and alkynes were purchased from Aldrich and Alfa. Copper(I) iodide (98%) was purchased from Alfa. NMR spectra were measured in $CDCl_3$ on a Varian Inova-400 NMR spectrometer with TMS as an internal reference.

Typical experimental procedure for cross-coupling of iodobenzene with phenylacetylene to afford diphenylacetylene (Table 4, entry 1)

A mixture of CuI (0.05 mmol), PPh_3 (0.15 mmol), KOH (2.0 mmol) and degassed water (2 ml) was stirred for 5 min in a pressure tube under nitrogen, then iodobenzene (1.0 mmol) and phenylacetylene (1.2 mmol) were added and the tube was sealed. The mixture was stirred at 140 °C for 4 h. Then it was cooled and extracted with diethyl ether (4 × 5 ml), then dried over Na_2SO_4. After evap-

Table 3. Effect of catalyst on the Sonogashira coupling reation[a]



Entry	Catalyst	Temperature (°C)	Time (*h*)	Yield (%)[b]
1	CuI (5 mol%), PPh_3 (15 mol%)	120 °C	2.5	84
2	CuI (5 mol%), PPh_3 (10 mol%)	120 °C	2.5	44
3	CuI (5 mol%), PPh_3 (5 mol%)	120 °C	2.5	39
4	CuI (5 mol%)	120 °C	2.5	Trace
5	CuI (5 mol%), PPh_3 (15 mol%)	140 °C	2.5	95
6	CuI (5 mol%), PPh_3 (15 mol%)	90 °C	2.5	44

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylacetylene (1.2 mmol), KOH (2.0 mmol), degassed water (2.0 ml), pressure tube.
[b] GC yield, using hexadecane as internal standard.

Table 4. CuI-catalyzed Sonogashira coupling reaction of aryl iodides with terminal alkynes[a]

$$\text{Ar-I} + \equiv\!\!-\text{R} \xrightarrow[\text{KOH, H}_2\text{O}]{\text{CuI, PPh}_3} \text{Ar}-\!\!\equiv\!\!-\text{R}$$

Entry	Aryl iodide	Terminal alkyne	Time (*h*)	Yield (%)[b]
1	C_6H_5I	PhC≡CH	4	91
2	*p*-$NO_2C_6H_4I$	PhC≡CH	4	95
3	*p*-$MeCOC_6H_4I$	PhC≡CH	4	93
4	*p*-MeC_6H_4I	PhC≡CH	6	90
5	*p*-$MeOC_6H_4I$	PhC≡CH	6	90
6	*p*-$CF_3C_6H_4I$	PhC≡CH	4	89
7	*m*-$NO_2C_6H_4I$	PhC≡CH	4	95
8	*m*-$MeOC_6H_4I$	PhC≡CH	6	92
9	*m*-ClC_6H_4I	PhC≡CH	4	84
10	*o*-$NO_2C_6H_4I$	PhC≡CH	6	91
11	*o*-MeC_6H_4I	PhC≡CH	6	47
12	2-Iodothiophene	PhC≡CH	4	89
13	3-Iodopyridine	PhC≡CH	6	91
14	C_6H_5I	*n*-$C_6H_{13}C{\equiv}CH$	6	75
15	*p*-$NO_2C_6H_4I$	*n*-$C_6H_{13}C{\equiv}CH$	6	94

[a] Reaction conditions: aryl iodide (1.0 mmol), terminal acetylene (1.2 mmol), CuI (5 mol%), PPh$_3$ (15 mol%) and base (2.0 mmol), degassed water (2.0 ml), at 140 °C in a pressure tube.

[b] Isolated yield.

oration under reduced pressure, the residue was purified by flash chromatography to give the product.

Supporting information

Supporting information may be found in the online version of this article.

Acknowledgments

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