A novel Cu(II)-catalysed Sonogashira reaction

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In the presence of triphenylphosphine, a novel Cu(II)-catalysed Sonogashira reaction of aryl iodides and bromides with terminal alkynes has been developed, which generates the corresponding cross-coupling products in good yields.

Keywords: Sonogashira reaction, Cu(II) catalyst, aryl iodides, aryl bromides, terminal alkynes

The palladium complex catalysed coupling of terminal alkynes with aryl and alkenyl halides in the presence of a catalytic amount of CuI and an amine (the Sonogashira reaction) is one of the most powerful and straightforward methods for the formation of carbon–carbon bonds in organic synthesis.[1] This method has been widely used for the synthesis of natural products,[2] biologically active molecules,[3] nonlinear optical materials and molecular electronics,[4] dendrimeric and polymeric materials,[5] macrocycles with acetylene links[6] and polyalkynylated molecules.[7] In general, the traditional palladium-catalysed reaction conditions are mild and many reactions can be accomplished at ambient temperature. However, the Sonogashira reaction often generates homo-coupling products of terminal alkynes[8] along with the main reaction in considerable yields owing to the addition of CuI. These undesirable by-products are generally not easy to separate from the desired products due to very similar chromatographic mobility.[9] Furthermore, the reaction often proceeds in the presence of a more expensive homogeneous palladium complex catalyst, which makes the recovery of the metal tedious if not impossible, and might result in high palladium contamination of the products. In addition, amines, such as triethylamine and piperidine, required in most Sonogashira reactions, have a bad smell and add to the environmental burden.

A number of modifications, such as copper-free catalyst systems,[10] amine- and copper-free systems,[11] ligand-free systems,[12] palladium powder systems,[13] nickel systems,[14] environmental-friendly reaction media (including aqueous,[10n,15] solventless,[13] and ionic liquid[10m,16] systems), phase-transfer reaction conditions and hydrogen atmosphere conditions,[17] transition-metal free catalyst systems,[18] ligand-, copper- and amine-free system[19] and a CuI/*N,N*-dimethylglycine catalyst system[20] have been used to solve one or two of the above problems, but none of them solves all of the problems. Therefore, the development of simpler, more practical, economic and efficient catalyst systems is still an important objective in this area.

Here we report a novel Cu(II) catalysed Sonogashira reaction of aryl iodides and bromides with terminal alkynes. The reaction generates the corresponding cross-coupling products in good yields (Scheme 1).

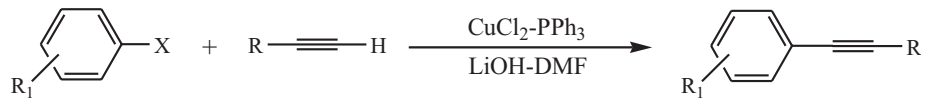
Results and discussion

In our initial screening experiments, when we searched for a cross-coupling protocol for the reaction of 4-iodoanisole and phenylacetylene, we observed that 4-iodoanisole could react with phenylacetylene in the presence of 10 mol% of $CuSO_4$ and 2 equivalents of K_2CO_3 in DMF at 100°C for 6 h to afford the desired cross-coupling product in 42% yield. Encouraged by this result, we continued to improve the yield by using the most efficient copper source and base. We were delighted that the desired product was obtained in 93% yield by using $CuCl_2$ as catalyst and LiOH as base (entry 1, Table 1). 91%, 88%, 70%, and 50% yields of the desired products were generated when the reactions were catalysed by CuI, CuCl, $CuSO_4$ and $Cu(OAc)_2$, respectively. However, no desired cross-coupling product was isolated when the reaction was carried out in the absence of any copper salt. In the next investigation, $CuCl_2$ was chosen as an effective catalyst in the Sonogashira coupling reaction for its high efficiency, commercial availability and stability in air.

During the course of our examination of the effect of base on the Sonogashira coupling reaction, LiOH was found to be the most effective (entry 1, Table 2). Other bases such as K_2CO_3, Na_3PO_4, KF and Cs_2CO_3, were substantially less effective, and piperidine and triethylamine were no longer the effective bases in this catalyst system (entries 2–7, Table 2).

The solvent also plays an important role in this reaction. The reaction conducted in DMF was most effective (entry 1, Table 3) and the use of DMSO and H_2O as solvents led to slower reactions (entries 5 and 7, Table 3). Poor yields of the cross-coupling products were observed while reactions were performed in dioxane and ethanol, respectively (entries 2 and 4, Table 3) and only trace amounts of desired products were isolated when the reactions were carried out in dichloromethane and acetonitrile (entries 3 and 6, Table 3).

To survey the generality of this Sonogashira-type reaction, we next investigated the reaction using a variety of aryl iodides and bromides, with a wide range of terminal alkynes as substrates under the standard reaction conditions. The results are shown in Table 4. Electron-neutral, electron-rich and electron-poor aryl iodides reacted with aromatic terminal alkynes very well to generate the corresponding cross-coupling products in excellent yields (entries 1–5, Table 4). An aliphatic terminal alkyne was also reacted with iodobenzene to form the cross-coupling product in good yield (entry 5, Table 4). Regardless of their electronic characters, the aromatic terminal alkynes component coupled smoothly with aryl iodides to produce the desired products in excellent yields. Activated aryl bromides reacted with phenylacetylene and 4-ethynyltoluene to generate the corresponding products in good to excellent yields (entries 6–10, Table 4). For an electron-



Scheme 1

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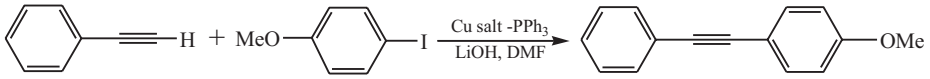
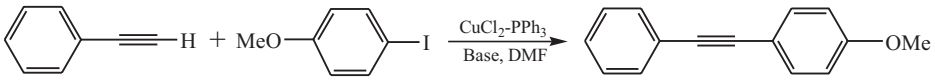
Table 1 Effect of copper source on the Sonogashira reaction[a]



Entry	Copper salt/amount	Yields/%[b]
1	$CuCl_2$ (10% mol)	93
2	CuCl (10% mol)	88
3	CuI (10% mol)	91
4	$Cu(OAc)_2$ (10% mol)	50
5	$CuSO_4$ (10% mol)	70

[a]Phenylacetylene (1.00 mmol), 4-iodoanisole (1.00 mmol), Cu salt (0.10 mmol), PPh_3 (0.30 mmol), LiOH (2.00 mmol) in DMF (4 ml) at 100°C for 6 h. [b]Isolated yields.

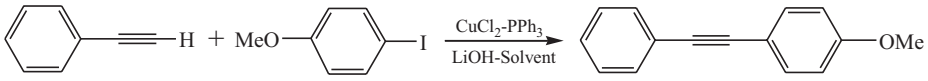
Table 2 Effect of base on the Sonogashira reaction[a]



Entry	Base	Yields/%[b]
1	LiOH	93
2	K_2CO_3	75
3	KF	60
4	Na_3PO_4	70
5	Cs_2CO_3	50
6	Et_3N	17
7	Piperidine	12

[a]Phenylacetylene (1.00 mmol), 4-iodoanisole (1.00 mmol), $CuCl_2$ (0.10 mmol), PPh_3 (0.30 mmol), base (2.00 mmol) in DMF (4 ml) at 100°C for 6 h. [b]Isolated yields.

Table 3 Effect of solvent on the Sonogashira reaction[a]



Entry	Solvent/Temp./°C	Yields/%[b]
1	DMF/100	93
2	Dioxane/75	10
3	CH_2Cl_2/40	trace
4	C_2H_5OH/80	12
5	H_2O/100	83
6	CH_3CN/80	trace
7	DMSO/100	87

[a]Phenylacetylene (1.00 mmol), 4-iodoanisole (1.00 mmol), $CuCl_2$ (0.10 mmol), PPh_3 (0.30 mmol), LiOH (2.00 mmol) in solvent (4 ml) at the temperature indicated in Table 3 for 6 h. [b]Isolated yields.

Table 4 Cu(II) Catalysed Sonogashira reaction[a]

Entry	Organic halide	Terminal alkyne	Yields/% [b]
1	*p*-$CH_3OC_6H_4I$	$C_6H_5C{\equiv}CH$	93
2	C_6H_5I	$C_6H_5C{\equiv}CH$	99
3	*p*-$O_2NC_6H_4I$	$C_6H_5C{\equiv}CH$	91
4	*p*-$CH_3COC_6H_4I$	*p*-$CH_3C_6H_4C{\equiv}CH$	90
5	C_6H_5I	*n*-$C_8H_{17}C{\equiv}CH$	78
6	2-Bromopyridine	$C_6H_5C{\equiv}CH$	75
7	*p*-$CH_3COC_6H_4Br$	$C_6H_5C{\equiv}CH$	92
8	*p*-$O_2NC_6H_4Br$	$C_6H_5C{\equiv}CH$	89
9	*p*-$CH_3COC_6H_4Br$	*p*-$CH_3C_6H_4C{\equiv}CH$	87
10	*p*-CNC_6H_4Br	$C_6H_5C{\equiv}CH$	86
11	*p*-$CH_3OC_6H_4Br$	$C_6H_5C{\equiv}CH$	33

[a]Terminal alkyne (1.00 mmol), organic halide (1.00 mmol), $CuCl_2$ (0.10 mmol), PPh_3 (0.30 mmol), LiOH (2.00 mmol) in DMF (4 ml) at 100°C for 6 h. [b]Isolated yields.

rich aryl bromide, a relatively lower yield was obtained under the present reaction conditions (entry 11, Table 4).

Conclusion

In conclusion, we have developed a novel Cu(II)-catalysed Sonogashira reaction in the presence of PPh_3. The method has the advantages of an efficient catalyst system, simple operation and high yields.

Experimental

Physical measurements and materials

Melting points were recorded on a WRS-2B melting point apparatus and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded at 300 or 250 MHz, and 75 or 62.5 MHz respectively by a Bruker NMR spectrometer using $CDCl_3$ as solvent. Chemical shifts are given as δ values with reference to tetramethylsilane (TMS) as internal standard. The reagents were received from a commercial supplier without purification prior to use. Products were purified by flash column chromatography.

General procedure for Sonogashira reaction

Under a nitrogen atmosphere, an oven-dried round-bottomed flask was charged with a terminal alkyne (1.0 mmol), aryl halide (1.00 mmol), LiOH (2.00 mmol), $CuCl_2$ (0.10 mmol), PPh_3 (0.30 mmol), and DMF (4 ml). The reaction mixture was placed in an oil bath at 100°C for 6 h. After cooling to the room temperature, Et_2O (25 ml) was added. The organic layer was successively washed with water (10 ml) and brine (10 ml) and dried over Na_2SO_4. The solution was filtered, concentrated, and the residue was purified by flash chromatography on silica gel to give the desired cross-coupling product.

(4-Methoxyphenyl)phenylacetylene: M.p. 59–60°C (lit.[21] 57–61°C); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.53–7.46 (m, 4H), 7.37–7.30 (m, 3H), 6.87 (dd, J = 8.7, 2.1 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.5, 133.0, 131.4, 128.3, 127.9, 123.5, 115.3, 113.9, 89.3, 88.0, 55.3.

Diphenylacetylene: M.p. 60–61°C (lit.[22] 60–62°C); ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.54–7.50 (m, 4H), 7.32–7.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 131.6, 128.3, 128.2, 123.3, 89.4.

1-Phenyl-1-decyne: Oil.[23] ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.40–7.36 (m, 2H), 7.28–7.22 (m, 3H), 2.38 (t, J = 7.0 Hz, 2H), 1.64–1.53 (m, 2H), 1.45–1.28 (m, 10 H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 131.5, 128.1, 127.3, 124.2, 90.3, 80.6, 31.9, 29.2, 29.1, 28.9, 28.8, 22.7, 19.4, 14.1.

(4-Nitrophenyl)phenylacetylene: M.p. 121–122°C (lit.[24] 120–121°C); ^1H NMR ($CDCl_3$, 250 MHz) δ: 8.19 (m, J* = 8.8 Hz, 2H), 7.64 (m, J* = 8.8 Hz, 2H), 7.56–7.52 (m, 2H), 7.39–7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 146.9, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 122.0, 94.7, 87.5.

(4-Acetylphenyl)phenylacetylene: M.p. 95–96°C (lit.[25] 94–96°C); ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.91 (m, J* = 8.4 Hz, 2H), 7.58 (m, J* = 8.4 Hz, 2H), 7.54–7.52 (m, 2H), 7.36–7.33 (m, 3H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 197.1, 136.1, 131.7, 131.6, 128.7, 128.4, 128.2, 128.1, 122.6, 92.6, 88.6, 26.5.

2-(2-Phenylethynyl)pyridine: Oil.[26] ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.60 (dd, J = 5.1 Hz, J = 0.9 Hz, 1H), 7.68–7.59 (m, 3H), 7.51 (dd, J = 8.1 Hz, J = 0.9 Hz, 1H), 7.37–7.33 (m, 3H), 7.23–7.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 149.9, 143.2, 136.0, 131.9, 128.8, 128.2, 127.0, 122.6, 122.0, 89.1, 88.4.

(4-Cyanophenyl)phenylacetylene: M.p. 109–110°C (lit.[27] 108.5–109.5°C); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.65–7.59 (m, 4H), 7.56–7.53 (m, 2H), 7.40–7.37 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 132.0 (2C), 131.8, 129.1, 128.5, 128.2, 122.2, 118.5, 111.4, 93.7, 87.7.

(4-Acetylphenyl)-p-tolylacetylene: M.p. 124–126°C (lit.[28] 124–126°C); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.99 (m, J* = 6.0 Hz, 2H), 7.68 (m, J* = 6.0 Hz, 2H), 7.49 (m, J* = 6.0 Hz, 2H), 7.27 (m, J* = 6.0 Hz, 2H), 2.35 (s, 3H); 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 197.2, 139.1, 135.9, 131.7, 131.6, 129.1, 128.4, 128.1, 119.5, 93.1, 88.1, 26.4, 21.5.

For the unresolved AA'XX' ^1H NMR systems above $J^* = J_{23} + J_{25}$

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