A Novel Silver Iodide Catalyzed Sonogashira Coupling Reaction

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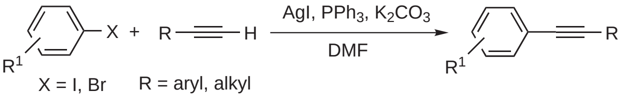
Abstract: A novel and efficient Ag-catalyzed Sonogashira coupling reaction has been developed. Terminal alkynes couple with aryl iodides and aryl bromides in the presence of silver iodide, triphenylphosphine and potassium carbonate to afford the corresponding cross-coupling products in high yields.

Key words: silver iodide, Sonogashira coupling reactions, terminal alkynes, aryl iodides, aryl bromides

In 1963, Stephens and Castro first discovered that diarylacetylenes were prepared by treating aryl iodides with cuprous acetylides in refluxing pyridine under a nitrogen atmosphere.[1] Later, Cassar observed that acetylene or monosubstituted acetylenes were converted into aryl- and vinyl-substituted acetylene derivatives by reaction with aryl and vinyl halides in the presence of a nickel or palladium triarylphosphine complex along with a base in 1975. With the palladium triphenylphosphine complexes, the conversion could be carried out catalytically under mild conditions.[2] Subsequently, Sonogashira et al. combined these two procedures into a cross-coupling reaction of terminal alkynes with aryl and alkenyl halides catalyzed by the palladium complexes in the presence of a catalytic amount of CuI and an amine (as solvent or in large excess) bearing his name in 1978.[3] Since then, the Sonogashira reactions have become one of the most powerful and straightforward methods for the formation of sp^2–sp carbon–carbon bonds in organic synthesis.[4] They have been widely used for the syntheses of natural products,[5] biologically active molecules,[6] non-linear optical materials and molecular electronics,[7] dendrimeric and polymeric materials,[8] macrocycles with acetylene links,[9] and polyalkynylated molecules.[10] However, a number of modifications for palladium catalyst systems, including copper-free,[11] amine- and copper-free,[12] ligand-free,[13] ligand-, copper- and amine-free,[14] have been used to solve the problems (homocoupling products of terminal alkynes along with the cross-coupling reaction owing to the addition of CuI, more expensive palladium complex catalyst, and a bad smell of amine used in the reaction) encountered in the traditional Sonogashira reaction conditions. Most recently, new catalytic systems without palladium, such as nickel system,[15] CuI system,[16] and transition-metal-free/microwave irradiation system[17] were demonstrated. Nevertheless, the development of new, practical, economic and efficient catalyst systems is still an important topic in this area. Recently, He developed a Ag-catalyzed intramolecular amidation of saturated C–H bonds and Li explored a silver-catalyzed three-component coupling of aldehyde, alkyne and amine.[18] The latter showed that the exclusive aldehyde–alkyne–amine coupling product was observed in the absence of phosphine, whereas in the presence of a phosphine ligand, exclusive aldehyde–alkyne coupling product was obtained. Although Pale et al. investigated extensively the Sonogashira coupling reactions of terminal alkynes or 1-trimethylsilyl acetylenes with vinyl triflates or aryl iodides in the presence of a catalytic amount of $Pd(PPh_3)_4$ and AgI or AgCl, and Mori developed a Pd/Ag-assisted Sonogashira reaction,[11q–t,12f–i,19] to the best of our knowledge, there is no report on the Sonogashira reaction catalyzed by silver alone. Some similar properties of silver with palladium and its cheap availability, it prompted us to try a silver-catalyzed Sonogashira reaction.

In this paper, we report a Sonogashira protocol in the presence of silver iodide (10 mol%), triphenylphosphine and potassium carbonate, which generates the corresponding cross-coupling products in good to excellent yields (Scheme 1).



Scheme 1

Our initial investigation was directed towards exploring the reaction conditions for the cross-coupling of *p*-iodotoluene with phenylacetylene catalyzed by silver.

We examined several different bases for the Sonogashira coupling reactions catalyzed by silver iodide. Potassium carbonate was found to be the most effective base. Other bases, such as potassium hydroxide, sodium hydroxide, caesium carbonate, potassium fluoride, sodium carbonate and potassium phosphate were substantially less effective, and triethylamine, diethylamine and piperidine were no longer the effective bases in this catalytic system, due to the strong coordination of organic bases containing nitrogen with silver(I) (Table 1, entries 1–10).

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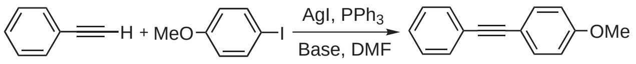
A significant effect of solvent was found in the coupling reaction. When the reactions were conducted in ethanol, isopropanol, *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide, good yields (88%, 89%, 92% and 91%, respectively) of products were obtained. Use of dioxane, methanol, acetonitrile, and tetrahydrofuran as solvents led to slower reactions, and no desired cross-coupling product was observed while reaction was performed in ethylene glycol (Table 2, entries 1–9). This solvent effect may result from the difference of the solubility of silver iodide, triphenylphosphine, potassium carbonate and starting materials in the above-mentioned solvents at the reaction temperature indicated in Table 2.

Table 1 Effect of Base on the Sonogashira Coupling Reaction[a]



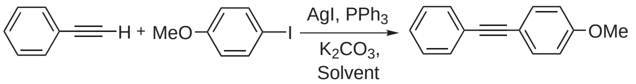
Entry	Base	Yield (%)[b]
1	K_2CO_3	92
2	Cs_2CO_3	86
3	Na_2CO_3	56
4	K_3PO_4	34
5	KOH	88
6	NaOH	87
7	KF	82
8	Et_3N	<5
9	Et_2NH	<5
10	Piperidine	<5

[a] Reagents and conditions: Phenylacetylene (102 mg, 1.00 mmol), *p*-iodotoluene (218 mg, 1.00 mmol), AgI (Aldrich, 99.999%, 23.5 mg, 0.10 mmol), PPh_3 (78.6 mg, 0.30 mmol), and base (2.00 mmol) in DMF (4.00 mL) at 100 °C for 8 h.
[b] Isolated yield.

We then turned our attention to ligand and silver salt effects. The silver salt and ligand are all essential to the reaction. No reaction occurs in the absence of silver salt or ligand. Among the ligands tested, triphenylphosphine proved to be the best choice (high yields of products and easy availability), while dppf and $P(OMe)_3$ were inferior. When other ligand, such as *N*,*N*-dimethylglycine, L-proline, α,α-bipyridine or 1,10-phenanthroline, was employed instead of triphenylphosphine for the above-mentioned reaction, no cross-coupling product was detected (Table 3, entries 1–7).

Meanwhile, the catalytic reactivity of silver salts decreases in order for the Sonogashira reaction: AgI ≈ AgOTf > AgBr > AgCl ≈ Ag_2O ≈ $AgNO_3$ (Table 4, entries 1–6). AgI was chosen as catalyst in the following investigation for its high efficiency, and easy commercial availability (Aldrich, AgI, 99.999%, \$24.10/1 g; $AgCF_3SO_3$, 99.95%, \$38.30/1 g).

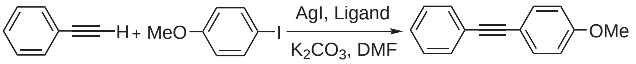
Table 2 Effect of Solvent on the Sonogashira Coupling Reaction[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]
1	MeOH	68	70
2	*i*-PrOH	80	89
3	THF	70	55
4	Dioxane	80	73
5	MeCN	70	67
6	EtOH	80	88
7	DMF	100	92
8	DMA	100	91
9	$(CH_2OH)_2$	100	0

[a] Reagents and conditions: Phenylacetylene (102 mg, 1.00 mmol), *p*-iodotoluene (218 mg, 1.00 mmol), AgI (Aldrich, 99.999%, 23.5 mg, 0.10 mmol), PPh_3 (78.6 mg, 0.30 mmol), and K_2CO_3 (276 mg, 2.00 mmol) in solvent (4.00 mL) at the temperature indicated in Table 2 for 8 h.
[b] Isolated yield.

Table 3 Effect of Ligand on the Sonogashira Coupling Reaction[a]

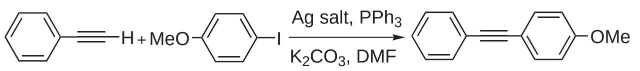


Entry	Ligand	Yield (%)[b]
1	PPh_3	92
2	Dppf	81
3	$P(OMe)_3$	70
4	*N*,*N*-Dimethylglycine	0
5	L-Proline	0
6	α,α-Bipyridine	0
7	1,10-Phenanthroline	0

[a] Reagents and conditions: Phenylacetylene (102 mg, 1.00 mmol), *p*-iodotoluene (218 mg, 1.00 mmol), AgI (Aldrich, 99.999%, 23.5 mg, 0.10 mmol), ligand (0.30 mmol), and K_2CO_3 (276 mg, 2.00 mmol) in DMF (4.00 mL) at 100 °C for 8 h.
[b] Isolated yield.

During the course of our further optimization of the reaction conditions, when using a 10 mol% loading of silver iodide, the reactions were generally complete in a matter of hours, but the time, as expected, was inversely proportional to the temperature. A reaction temperature of 100 °C was found to be optimal. Thus, the optimized reaction conditions for this Sonogashira reaction are silver iodide (10 mol%), triphenylphosphine (30 mol%), potassium carbonate (2 equiv) in *N*,*N*-dimethylformamide at 100 °C for eight hours.

Table 4 Effect of Silver Salt on the Sonogashira Coupling Reaction[a]



Entry	Silver Salt	Yield (%)[b]
1	AgI	92
2	$AgNO_3$	75
3	AgCl	78
4	AgBr	89
5	Ag_2O	77
6	AgOTf	91

[a] Reagents and conditions: Phenylacetylene (102 mg, 1.00 mmol), *p*-iodotoluene (218 mg, 1.00 mmol), Ag salt (0.10 mmol), PPh_3 (78.6 mg, 0.30 mmol), and K_2CO_3 (276 mg, 2.00 mmol) in DMF (4.00 mL) at 100 °C for 8 h.

[b] Isolated yield.

To survey the generality of this Sonogashira-type reaction, we investigated the reactions using a variety of aryl iodides and bromides, and a wide range of terminal alkynes as the substrates under the present reaction conditions. The results are shown in Table 5. As can be seen from Table 5, electron-neutral, electron-rich and electron-poor aryl iodides reacted with phenylacetylene very well to generate the corresponding cross-coupling products in good to excellent yields under the standard reaction conditions (Table 5, entries 1–9). For an *ortho*-substituted aryl iodide, a relatively lower yield was isolated under the present reaction conditions (Table 5, entry 8). Regardless of their electronic characters, both of the aromatic terminal alkynes and aliphatic terminal alkynes component coupled smoothly with iodobenzene to produce the desired products in good to excellent yields (Table 5, entries 3 and 10–15). Activated aryl bromides also reacted with phenylacetylene to provide the products in excellent yields (Table 5, entries 16–19). However, for an electron-rich aryl bromide, only a moderate yield (62%) was obtained even if the reaction was performed for 12 hours (Table 5, entry 20). It is worth noting that the regioselective Sonogashira cross-coupling products were formed for substituted aryl halides, such as *p*-$CH_3COC_6H_4I$, *p*-$CH_3COC_6H_4Br$, *m*-CNC_6H_4I, and *p*-CNC_6H_4Br (Table 5, entries 5, 9, 17, 19).[20]

Table 5 AgI-Catalyzed Sonogashira Coupling Reaction[a]

Entry	Terminal alkyne	Organic halide	Yield (%)[b]
1	PhC≡CH	*p*-$MeOC_6H_4I$	92
2	PhC≡CH	*p*-MeC_6H_4I	93
3	PhC≡CH	PhI	95
4	PhC≡CH	*p*-$O_2NC_6H_4I$	99
5	PhC≡CH	*p*-$MeCOC_6H_4I$	94
6	PhC≡CH	*p*-$CF_3C_6H_4I$	99
7	PhC≡CH	*m*-$O_2NC_6H_4I$	80
8	PhC≡CH	*o*-$CF_3C_6H_4I$	73
9	PhC≡CH	*m*-CNC_6H_4I	91
10	*p*-$CH_3C_6H_4C{\equiv}CH$	PhI	96
11	*p*-$C_6H_5C_6H_4C{\equiv}CH$	PhI	94
12	*p*-$FC_6H_4C{\equiv}CH$	PhI	98
13	*p*-$BrC_6H_4C{\equiv}CH$	PhI	95
14	*n*-$C_8H_{17}C{\equiv}CH$	PhI	80
15	*n*-$C_6H_{13}C{\equiv}CH$	PhI	83
16	PhC≡CH	2-Bromopyridine	99
17	PhC≡CH	*p*-CNC_6H_4Br	92
18	PhC≡CH	*p*-$O_2NC_6H_4Br$	95
19	PhC≡CH	*p*-$MeCOC_6H_4Br$	85
20	PhC≡CH	*p*-MeC_6H_4Br	62[c]

[a] Reagents and conditions: Terminal alkyne (1.00 mmol), organic halide (1.00 mmol), AgI (Aldrich, 99.999%, 23.5 mg, 0.10 mmol), PPh_3 (78.6 mg, 0.30 mmol), K_2CO_3 (276 mg, 2.00 mmol) in DMF (4.00 mL) at 100 °C for 8 h.

[b] Isolated yield.

[c] Reaction for 12 h.

In 2003, Leadbeater reported the transition-metal-free Suzuki coupling reaction[21] and Sonogashira-type coupling (under microwave irradiation conditions).[17] Two years later, after delicate analysis of the microamount palladium in the reaction mixtures, including ultrapure water and commercially available sodium carbonate by ICP–MS, Leadbeater found that, although the reaction can be run without the need for addition of a transition-metal catalyst, palladium contaminants down to a level of 50 ppb found in commercially available sodium carbonate are responsible for the generation of the biaryl rather than, as previously suggested, an alternative non-palladium-mediated pathway.[22] Inspired by their results, we therefore investigated how much palladium is present in potassium carbonate, *N*,*N*-dimethylformamide, triphenylphosphine and silver iodide in our Sonogashira reaction system in order to establish whether this process is only catalyzed by Ag and not by a microamount palladium or a Ag/Pd mixture. We analyzed the *N*,*N*-dimethylformamide, potassium carbonate, triphenylphosphine and silver iodide used in the reaction by ICP–MS and found that the palladium level is 0.32, 9.15, 5.32, and 2.64 ppb, respectively, which we believe to be too low to be catalytically active. The organic reagents used in the reactions were all purified prior to use and we believe them to be palladium free. Therefore, we expected that this reaction was catalyzed by Ag alone. Although the investigation of mechanism of Ag/Pd catalysis showed that the corresponding alkynyl silver was formed after mixing the alkyne and silver salt,[23] the Ag-catalyzed Sonogashira coupling reaction mechanism in the absence of any palladium is not fully clear and a further investigation is currently underway in our laboratory.

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(20) The unique Sonogashira coupling products were characterized by mp, ^{1}H NMR and ^{13}C NMR, and MS.
(4-Acetylphenyl)phenylacetylene: mp 95-96 °C (Lit.[24] 94–96 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.41 Hz, 2 H), 7.58 (d, J = 8.41 Hz, 2 H), 7.52-7.54 (m, 2 H), 7.33-7.36 (m, 3 H), 2.57 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 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. MS (relative intensity, %): m/z = 220 (60) [M^+], 205 (100), 176 (48), 151 (18), 102 (10), 88 (19).
(4-Cyanophenyl)phenylacetylene: mp 109–110 °C (Lit.[25] 108.5–109.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.66 (m, 4 H), 7.53–7.57 (m, 2 H), 7.36–7.40 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0 ($2 \times$ C), 131.8, 129.1, 128.5, 128.2, 122.2, 118.5, 111.4, 93.7, 87.7. MS: (relative intensity, %): m/z = 203 (100) [M^+], 176 (8), 151 (5), 75 (5).
(3-Cyanophenyl)phenylacetylene: mp 69–71 °C (Lit.[25] 70–71 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (t, J = 1.50 Hz, 1 H), 7.73 (dt, J = 1.50, 7.80 Hz, 1 H), 7.59 (dt, J = 1.50, 7.80 Hz, 1 H), 7.52–7.55 (m, 2 H), 7.45 (t, J = 7.80 Hz, 1 H), 7.35–7.39 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.6, 134.8, 131.7, 131.3, 129.2, 128.9, 128.4, 124.8, 122.2, 118.0, 112.8, 91.7, 86.8. MS (relative intensity, %): m/z = 203 (100) [M^+], 176 (7), 151 (5), 75 (5).

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