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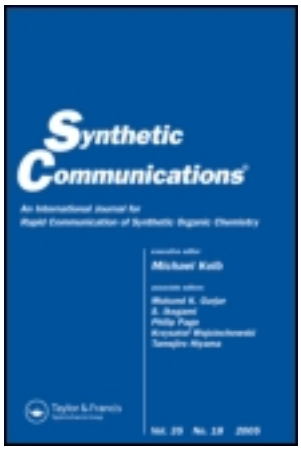

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Sonogashira Coupling Reaction with Palladium Powder, Potassium Fluoride in Aqueous Media

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Sonogashira Coupling Reaction with Palladium Powder, Potassium Fluoride in Aqueous Media

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ABSTRACT

A Sonogashira coupling reaction of aromatic iodides and bromides with terminal alkynes in the presence of palladium powder, potassium fluoride, cuprous iodide, and triphenylphosphine in aqueous media was developed. The reaction generates the corresponding coupling products aryl alkynes in good to excellent yields.

The palladium catalyzed carbon-carbon cross-coupling of organometallics with organoelectrophiles is an important synthetic reaction in

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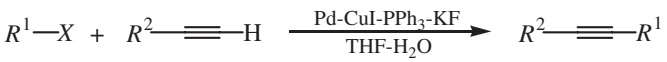
organic synthesis.[1] Most organometallic compounds are sensitive to air, moisture, or are toxic and often will not tolerate functional groups which may be important in complex syntheses. The Sonogashira coupling reaction of terminal alkynes and aryl or alkenyl halides is an efficient route to aryl alkynes.[2–7] Numerous applications to natural product syntheses have been reported by using Sonogashira coupling reaction, including the construction of complex enediyne antibiotics.[8–13] The classic Sonogashira reaction is generally carried out in organic solvent such as amines, benzene, and DMF along with complex palladium catalysts which are soluble in these solvents. These soluble palladium reagents tend to be expensive and sometimes difficult to manipulate and recover. The solvents also pose recyclability (waste handling) problems of their own. In addition, amine such as piperidine, diethylamine, and triethylamine are required in most Sonogashira reaction and they have a bad smell and add to the environmental burden. We recently reported that an energy efficient modification of the Sonogashira reaction by using palladium powder doped on the mixture of potassium fluoride and alumina under solventless reaction conditions, but the reaction is limited to aromatic iodides.[14]

Here, we wish to report a Sonogashira coupling reaction of aromatic or alkenyl iodides and bromides with terminal alkynes in the presence of palladium powder, potassium fluoride, cuprous iodide, and triphenylphosphine in aqueous media, which produces the corresponding coupling products aryl alkynes in good to excellent yields.



X = I, Br

Our initial attempt explored the reaction conditions for Sonogashira coupling reaction of terminal alkynes with aromatic halides. The results shown that the coupling reaction requires a base for the Sonogashira coupling reaction in aqueous media. Among the inorganic bases we tested, potassium fluoride was most effective. The palladium powder, triphenylphosphine and cuprous iodide were found to be essential in this reaction. The best reaction conditions for the Sonogashira coupling were found to be Pd (10 mg, 0.094 mmol, 99.9+% as a submicron powder), CuI (10 mg, 0.053 mmol), PPh_3 (100 mg, 0.379 mmol), KF (236 mg, 4.00 mmol), terminal alkyne (1.00 mmol), aryl halide (1.00 mmol), THF-H_2O (3/1, v/v, 6 mL), reaction temperature (60°C), and reaction time (8 h).

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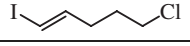
Table 1 summarizes the experimental results of Sonogashira coupling reaction. A variety of aromatic iodides were successfully coupled with aromatic terminal alkynes and aliphatic terminal alkynes to produce the corresponding aryl alkynes in excellent yields. Meanwhile, heteroaromatic iodide and vinyl iodide went smoothly to couple with terminal alkynes to generate the desired coupling products. Aryl bromides also reacted with terminal alkynes to form the coupling products in good yields. However, aryl chloride and aryl fluoride did not react with terminal alkynes under reaction conditions and the starting materials are recovered unchanged. Substituent effects were investigated. The results indicated that the electronic characteristics of a general electron-donating group (such as CH_3O, $(CH_3)_2N$, CH_3) or a general electron-withdrawing group (such as CH_3CO, F) on the aromatic ring were relatively insensitive to the coupling reaction. Very strong electron-withdrawing group (such as NO_2) on the aromatic ring also led to a good yield of coupling product. It is interesting

Table 1. Sonogashira coupling reaction of organic halides with terminal alkynes.

Entry	R^1X	R^2	Yield[a] (%)
a	C_6H_5I	*n*-C_8H_{17}	94
b	C_6H_5Br	*n*-C_8H_{17}	78
c	C_6H_5I	*n*-C_6H_{13}	91
d	C_6H_5I	C_6H_5	95
e	*p*-$CH_3C_6H_4I$	*n*-C_8H_{17}	93
f	*p*-$CH_3C_6H_4Br$	*n*-C_8H_{17}	81
g	*p*-$CH_3OC_6H_4I$	*n*-C_8H_{17}	90
h	*p*-$CH_3OC_6H_4Br$	*n*-C_8H_{17}	76
i	*o*-FC_6H_4I	*n*-C_8H_{17}	92
j	*p*-FC_6H_4I	C_6H_5	94
k	*p*-$CH_3COC_6H_4I$	C_6H_5	93
m	*p*-$CH_3COC_6H_4Br$	C_6H_5	84
n	*p*-$NO_2C_6H_4I$	C_6H_5	87
o	*o*-$(CH_3)_2NC_6H_4I$	C_6H_5	90
p		C_6H_5	86
q		C_6H_5	90

[a]Isolated yields.

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to note that a bulky group on the ortho-position of the aromatic ring did not inhibit the reaction (Entry o).

It is important to note that the palladium powder can be recovered and recycled by a simple decantation of the reaction solution. In one series of experiments, we carried out six consecutive preparation of 1-phenyl-1-decyne with no significant loss in product yields.

In conclusion, a reliable and practical procedure for the synthesis of arylacetylenes via a Sonogashira coupling reaction was developed which involves the use of potassium fluoride, palladium powder, cuprous iodide, and triphenylphosphine in aqueous media. The significant advantages of the procedure are operational simplicity, mild reaction conditions, excellent yields, and cleaner reaction media.

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EXPERIMENTAL

Melting points were recorded on a WRS-1A melting point apparatus and are uncorrected. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AZ 300 spectrometer. Chemical shift are given as δ value with reference to tetramethylsilane (TMS) as internal standard. GC/MS data were obtained by using a Hewlett-Packard 6890 series GC equipped with a 5983 mass selective detector. The reagents were received from commercial supply without purification prior to use. Products were purified by flash column chromatography.

General Procedure for Sonogashira Reaction of Aryl or Alkenyl Halides with Terminal Alkynes

Aryl or alkenyl iodide or bromide (1.00 mmol) and terminal alkyne (1.00 mmol) were added to a mixture of KF (236 mg, 4.00 mmol), palladium powder (10 mg, 0.094 mmol, 99.9+% as a submicron powder), cuprous iodide (10 mg, 0.053 mmol), and triphenylphosphine (100 mg, 0.376 mmol) contained in a clean round-bottomed flask with THF-H_2O (3/1, v/v, 6 mL) solution. The mixture solution was stirred at 60°C for 8 h on an oil bath. After cooling, ether (10 mL) was added to extract the products. After the organic layer was dried with anhydrous sodium sulfate, the solvents were evaporated under reduced pressure. The product was purified by flash chromatography to yield the desired aryl alkyne.

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1-Phenyl-1-decyne. Oil.[15] ^{1}H NMR ($CDCl_3$): δ 7.41–7.39 (m, 2H), 7.28–7.24 (m, 3H), 2.37 (t, $J = 6.99$ Hz, 2H), 1.64–1.55 (m, 2H), 1.45–1.32 (m, 10H), 0.88 (t, $J = 6.44$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 131.4, 128.1, 127.4, 124.2, 90.2, 80.5, 31.8, 29.2, 29.1, 28.9, 28.8, 22.8, 19.3, 14.0. MS m/z (%): 214 (M^+, 11), 171 (3), 157 (20), 143 (55), 129 (69), 115 (100), 91 (41).

1-Phenyl-1-octyne. Oil.[16] ^{1}H NMR ($CDCl_3$): δ 7.42–7.38 (m, 2H), 7.29–7.25 (m, 3H), 2.38 (t, $J = 6.95$ Hz, 2H), 1.68–1.59 (m, 2H), 1.51–1.36 (m, 6H), 0.89 (t, $J = 6.72$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 131.6, 128.0, 127.4, 124.1, 90.3, 80.6, 31.6, 28.8, 22.7, 19.4, 14.1. MS m/z (%): 186 (M^+, 23), 157 (18), 143 (59), 129 (60), 115 (100), 91 (35).

Diphenylacetylene. M.p.: 59–61°C (Lit.[17] 60–62°C). ^{1}H NMR ($CDCl_3$): δ 7.56–7.53 (m, 4H), 7.34–7.30 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 131.5, 128.2, 128.1, 123.2, 89.2. MS m/z (%): 178 (M^+, 100), 152 (20), 126 (9), 89 (15).

1-(4-Methylphenyl)-1-decyne. Oil.[17] ^{1}H NMR ($CDCl_3$): δ 7.30 (d, $J = 7.95$ Hz, 2H), 7.10 (d, $J = 7.55$ Hz, 2H), 2.36 (t, $J = 7.69$ Hz, 2H), 2.30 (s, 3H), 1.62–1.57 (m, 2H), 1.43–1.29 (m, 10H), 0.89 (t, $J = 6.47$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 137.1, 131.5, 128.7, 121.0, 89.4, 80.5, 31.9, 29.2, 29.1, 28.9, 28.8, 22.9, 21.3, 19.4, 14.1. MS m/z (%): 228 (M^+, 19), 185 (4), 171 (10), 157 (32), 143 (35), 131 (100), 115 (20), 91 (14).

1-(4-Methoxylphenyl)-1-decyne. Oil.[17] ^{1}H NMR ($CDCl_3$): δ 7.31 (d, $J = 8.74$ Hz, 2H), 6.90 (d, $J = 8.75$ Hz, 2H), 3.76 (s, 3H), 2.34 (t, $J = 7.05$ Hz, 2H), 1.65–1.57 (m, 2H), 1.45–1.27 (m, 10H), 0.88 (t, $J = 6.08$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.1, 132.9, 116.4, 113.9, 88.8, 80.2, 55.2, 31.8, 29.2, 29.1, 28.9, 22.2, 19.4, 14.1. MS m/z (%): 244 (M^+, 19), 201 (5), 188 (24), 173 (30), 159 (31), 147 (100), 121 (35), 115 (20), 91 (14).

1-(2-Fluorophenyl)-1-decyne. Oil.[17] ^{1}H NMR ($CDCl_3$): δ 7.41–7.36 (m, 1H), 7.28–7.19 (m, 1H), 7.04–6.98 (m, 2H), 2.45 (t, $J = 6.87$ Hz, 2H), 1.65–1.57 (m, 2H), 1.48–1.32 (m, 10H), 0.88 (t, $J = 6.38$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 162.5 (d, $J = 248.2$ Hz), 133.5, 129.0 (d, $J = 7.5$ Hz), 123.7 (d, $J = 3.5$ Hz), 115.3 (d, $J = 21.7$ Hz), 112.6 (d, $J = 15.5$ Hz), 95.9 (d, $J = 3.1$ Hz), 74.0, 31.9, 29.2, 29.1, 28.9, 28.6, 22.7, 19.5, 14.0. MS m/z (%): 232 (M^+, 50), 175 (34), 161 (75), 147 (66), 133 (100), 109 (58).

1-(4-Fluorophenyl)phenylacetylene. M.p.: 108–109°C (Lit.[17] 108–110°C). ^{1}H NMR ($CDCl_3$): δ 7.54–7.48 (m, 4H), 7.38–7.35 (m, 3H), 7.09–7.01 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 162.4 (d, $J = 248.0$ Hz), 133.5 (d, $J = 8.8$ Hz), 131.5, 128.4, 123.1, 119.3 (d, $J = 5.8$ Hz), 115.7 (d, $J = 22.5$ Hz), 89.1, 88.3. MS m/z (%): 196 (M^+, 100), 175 (11), 144 (7), 98 (16).

1-(4-Acetylphenyl)phenylacetylene. M.p.: 95–97°C (Lit.[17] 95–96°C). ^{1}H NMR ($CDCl_3$): δ 7.92 (d, $J = 8.44$ Hz, 2H), 7.60 (d, $J = 8.41$ Hz, 2H),

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7.54–7.52 (m, 2H), 7.37–7.35 (m, 3H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 197.1, 136.0, 131.7, 131.6, 128.6, 128.4, 128.2, 128.1, 122.7, 92.6, 88.7, 26.5. MS m/z (%): 220 (M^+, 62), 205 (100), 176 (51), 151 (21), 102 (11), 88 (22).

1-(4-Nitrophenyl)phenylacetylene. M.p.: 120–121°C (Lit.[17] 120–122°C). ^{1}H NMR ($CDCl_3$): δ 8.22 (d, $J = 8.84$ Hz, 2H), 7.65 (d, $J = 8.71$ Hz, 2H), 7.56–7.52 (m, 2H), 7.38–7.36 (m, 3H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 146.8, 132.2, 131.7, 130.2, 129.2, 128.4, 123.6, 122.0, 94.7, 87.5. MS m/z (%): 223 (M^+, 100), 193 (42), 176 (80), 165 (31), 151 (44), 139 (10), 126 (15).

***N,N*-Dimethyl-2-(phenylethynyl)benzeneamine.** M.p.: 46–48°C (Lit.[17] 46–47°C). ^{1}H NMR ($CDCl_3$): δ 7.56–7.48 (m, 3H), 7.36–7.20 (m, 4H), 6.91–6.86 (m, 2H), 2.98 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 154.5, 134.2, 131.2, 129.1, 128.2, 127.9, 123.7, 120.2, 116.8, 114.8, 94.5, 89.0, 43.3. MS m/z (%): 220 (M^+, 100), 204 (23), 178 (20), 144 (70).

2-Phenylethynylthiophene. M.p.: 51–53°C (Lit.[17] 51–53°C). ^{1}H NMR ($CDCl_3$): δ 7.52–7.48 (m, 2H), 7.32–7.24 (m, 5H), 6.99–6.96 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 131.9, 131.5, 128.3, 127.1, 127.0, 123.4, 122.9, 93.1, 82.6. MS m/z (%): 184 (M^+, 100), 152 (20), 139 (20), 92 (10).

7-Chloro-1-phenyl-3-hepten-1-yne. Oil.[17] ^{1}H NMR ($CDCl_3$): δ 7.45–7.43 (m, 2H), 7.32–7.29 (m, 3H), 6.24–6.13 (m, 1H), 5.74 (d, $J = 16.92$ Hz, 1H), 3.51 (t, $J = 6.82$ Hz, 2H), 2.36–2.28 (m, 2H), 1.93–1.84 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 142.5, 131.5, 128.1, 128.0, 123.3, 111.0, 88.5, 87.8, 44.1, 31.5, 30.1. MS m/z (%): 206, 204 (M^+, 16, 50), 155 (60), 141 (100), 128 (24), 115 (76), 91 (20).

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