Note

Sonogashira Coupling Reaction with Palladium Powder and Potassium Fluoride in Methanol

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A Sonogashira coupling reaction of aromatic halides with terminal alkynes in the presence of palladium powder, potassium fluoride, cuprous iodide and triphenylphosphine in methanol, giving the corresponding coupling products aryl alkynes in good to excellent yields, was investigated.

Keywords Sonogashira reaction, palladium powder, potassium fluoride, terminal alkyne, aryl alkyne

Introduction

The palladium catalyzed carbon-carbon cross-coupling of organometallics with organoelectrophiles is an important synthetic reaction in 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 Sonogashira reaction is generally carried out in expensive organic solvent such as amines, benzene, dioxane, and DMF along with the complex palladium catalysts which are soluble in these solvents. These soluble palladium reagents tend to be expensive and sometimes difficult to manipulate and recover. In addition, amines 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, a Sonogashira coupling reaction of aromatic or alkenyl iodides or bromides with terminal alkynes in the presence of palladium powder, potassium fluoride, cuprous iodide and triphenylphosphine in methanol, giving the corresponding coupling products aryl alkynes in good to excellent yields is reported.

$$R^1\text{—X} + R^2\text{—}\equiv\text{—H} \xrightarrow[CH_3OH]{\text{Pd-CuI-PPh}_3\text{-KF}} R^2\text{—}\equiv\text{—}R^1$$

X = I, Br

Results and discussion

The reaction conditions for Sonogashira coupling reaction of terminal alkynes with aromatic iodides are studied. The results are summarized in Table 1. Iodobenzene and 1-decyne were chosen as the model compounds for the optimization process.

Table 1 The optimization of Sonogashira coupling reaction conditions[a]

Run	Base	Pd (mg)	PPh_3 (mg)	CuI (mg)	Yield[b] (%)
1	K_2CO_3	10	100	10	42
2	KF	10	100	10	95
3	NaF	10	100	10	25
4	K_3PO_4	10	100	10	31
5	KOH	10	100	10	72
6	KF	0	100	10	0
7	KF	10	0	10	13
8	KF	10	100	0	24

[a] Reaction scale: iodobenzene (1.00 mmol), 1-decyne (1.00 mmol), base (4.00 mmol), methanol (5 mL), at 70 ℃ for 6 h. [b] Isolated yields.

From Table 1, it is evident that the yield of the coupling reaction lies on a base for the Sonogashira coupling reaction in methanol. Among the inorganic bases we tested, potassium fluoride was most effective. The palladium powder, triphenylphosphine and cuprous iodide were found to be essential

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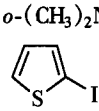
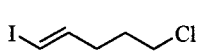
in this reaction. The best reaction conditions for the Sonogashira coupling were found to be Pd (10 mg, 0.094 mmol, 99.9 + % submicron powder), CuI (10 mg, 0.053 mmol), PPh_3 (100 mg, 0.379 mmol), KF (236 mg, 4.00 mmol), terminal alkyne (1.00 mmol) and aryl iodide (1.00 mmol) in methanol (5 mL) at 70 ℃ for 6 h.

The experimental results are summarized in Table 2. A variety of aromatic iodides were successfully coupled with aromatic terminal alkynes, as well as aliphatic terminal alkynes in excellent yields. But, non-terminal alkynes did not work. Meanwhile, heteroaromatic iodide and vinyl iodide went smoothly to couple with terminal alkynes to generate the corresponding coupling products. Aryl bromide also reacted with terminal alkyne to produce the coupling product in 76% yield. However, aryl chloride and aryl fluoride do not react and the starting materials are recovered unchanged. Substituent effects were also examined. The results indicated that a general electron-donating group or electron withdrawing group on the aromatic ring goes smoothly to react and lead to the desired product in excellent yield. Very strong electron-withdrawing group, also leads to a good yield. It is interesting to note that a bulky group on the *ortho*-position of the aromatic ring did not inhibit the reaction (Run 11, Table 2).

Table 2 Sonogashira coupling reaction of organic halides with terminal alkynes

Run	R^1X	R^2	Yield[a] (%)
1	C_6H_5I	*n*-C_8H_{17}	95
2	C_6H_5Br	*n*-C_8H_{17}	76
3	C_6H_5I	*n*-C_6H_{13}	92
4	C_6H_5I	C_6H_5	94
5	*p*-$CH_3C_6H_4I$	*n*-C_8H_{17}	91
6	*p*-$CH_3OC_6H_4I$	*n*-C_8H_{17}	91
7	*o*-FC_6H_4I	*n*-C_8H_{17}	90
8	*p*-FC_6H_4I	C_6H_5	90
9	*p*-$CH_3COC_6H_4I$	C_6H_5	91
10	*p*-$NO_2C_6H_4I$	C_6H_5	85
11	*o*-$(CH_3)_2NC_6H_4I$	C_6H_5	89
12		C_6H_5	82
13		C_6H_5	90

[a] Isolated yields.

The Sonogashira reaction of terminal alkynes with aryl halides is catalyzed by Pd(0) and assisted by Cu(I) in the presence of base. The developed coupling was carried out directly using zero valence palladium powder (submicron), cuprous iodide, triphenylphosphine and potassium fluoride (an inorganic base), which is soluble in methanol. It seems that the reactivity of palladium powder is lower than that of palladium complex or Pd(0) generated *in situ*. But, it is important to note that the palladium powder can be recovered and recycled by a simple decantation of the reaction solution. In a 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 aryl alkynes via a Sonogashira coupling reaction was developed which involves the use of potassium fluoride, palladium powder, cuprous iodide and triphenylphosphine in methanol. The operation is simple affording the desired products in good yields.

Experimental

Melting points were recorded on a WRS-1A melting point apparatus and were uncorrected. All ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AZ 300 spectrometer. Chemical shifts were 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 of Sonogashira reaction of aryl or alkenyl iodide with terminal alkynes

Aryl or alkenyl iodide (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 submicron powder), cuprous iodide (10 mg, 0.053 mmol) and triphenylphosphine (100 mg, 0.376 mmol) contained in a clean round-bottomed flask with methanol (5 mL). The mixture solution was stirred at 70 ℃ for 6 h on an oil bath. After cooling, ethyl 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 giving the desired aryl alkyne.

1-Phenyl-1-decyne Oil.[15] ^1H NMR ($CDCl_3$, 300 MHz) 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 ($CDCl_3$, 75 MHz) 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] ^1H NMR ($CDCl_3$, 300 MHz) 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 ($CDCl_3$, 75 MHz) 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 ℃ (lit.[17] 60—62 ℃); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.56—7.53 (m, 4H), 7.34—7.30 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz)

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 ($CDCl_3$, 300 MHz) 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, 10 H), 0.89 (t, J = 6.47 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 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 ($CDCl_3$, 300 MHz) 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, 10 H), 0.88 (t, J = 6.08 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 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 ($CDCl_3$, 300 MHz) 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, 10 H), 0.88 (t, J = 6.38 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 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—110 ℃;[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.54—7.48 (m, 4H), 7.38—7.35 (m, 3H), 7.09—7.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 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—96 ℃;[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.92 (d, J = 8.44 Hz, 2H), 7.60 (d, J = 8.41 Hz, 2H), 7.54—7.52 (m, 2H), 7.37—7.35 (m, 3H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 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—122 ℃;[17] ^{1}H NMR ($CDCl_3$, 300 MHz) 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); ^{13}C NMR ($CDCl_3$, 75 MHz) 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).

1-(2-*Dimethylaminophenyl*) *phenylacetylene* M.p. 46—47 ℃;[17] ^{1}H NMR ($CDCl_3$, 300 MHz) 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 ($CDCl_3$, 75 MHz) 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 ℃;[17] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.52—7.48 (m, 2H), 7.32—7.24 (m, 5H), 6.99—6.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 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 ($CDCl_3$, 300 MHz) 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 ($CDCl_3$, 75 MHz) 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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