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Copper-Catalyzed Coupling Reaction of Terminal Alkynes with Aryl- and Alkenyliodonium Salts

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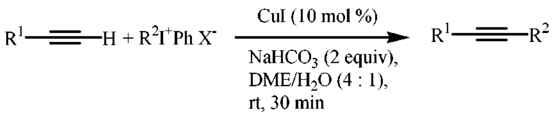
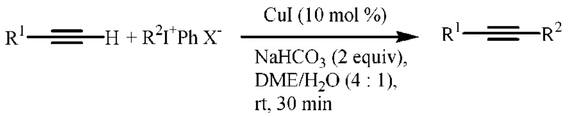
ABSTRACT



The copper iodide-catalyzed cross-coupling of terminal alkynes with hypervalent iodonium salts was accomplished with CuI (10 mol %) and $NaHCO_3$ (2 equiv) in DME/H_2O (4:1) at room temperature for 30 min to afford arylalkynes or enynes under mild conditions.

The palladium(0)/CuI-catalyzed cross-coupling of aryl or vinyl halides and triflates in the presence of amine base to form arylalkynes and conjugated enynes is known as the Sonogashira coupling reaction[1−3] and is widely utilized in the synthesis of natural products and chemical materials. Alternatively, the coupling reaction of aryl halide with copper(I) acetylides in boiling pyridine, which is known as the Castro−Stephens reaction,[4] and the coupling of terminal alkynes with vinyl halide in the presence of a stoichiometric amount of copper species are also known.[5] Recently Miura et al.[6] reported the CuI-2PPh_3-catalyzed coupling of aryl or vinyl iodide with terminal alkynes at elevated temperature (120 °C) in DMF. The copper-catalyzed coupling of alkynes under mild conditions is needed. In connection with our programs to utilize iodonium salts in copper-catalyzed cross-coupling,[7] herein we wish to report CuI-catalyzed coupling of terminal alkynes with hypervalent iodonium salts to form arylalkynes and enynes (Scheme 1).[8]

Scheme 1



A series of experiments were performed to find an optimum condition for the coupling of phenylacetylene (**1a**) with diphenyliodonium tetrafluoroborate (**2a**). This cross-

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[1] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, 4467−4470.

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[8] The palladium-catalyzed carbonylative cross-coupling of terminal alkynes with hypervalent iodonium salts was reported by us. (a) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S. *Chem. Commun*. **1996**, 835−836. (b) Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* **1997**, 874−876.

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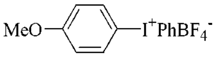
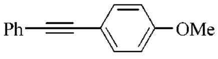
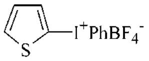
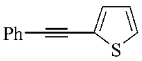
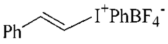
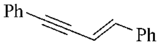
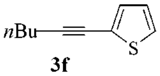
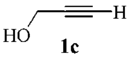
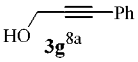
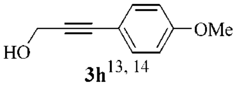
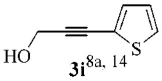
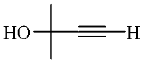
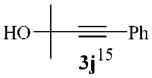
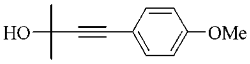
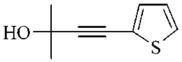
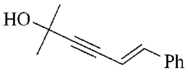
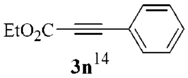
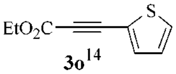
Table 1. Cu-Catalyzed Cross-Coupling of Terminal Alkynes with Hypervalent Iodonium Salts

Entry	Substrate	Iodonium Salts	Products	Yield (%)
1	Ph—≡—H **1a**	$Ph_2I^+BF_4^-$ **2a**	Ph—≡—Ph **3a**	85
2	**1a**	 **2b**	 **3b**	75
3	**1a**	 **2c**	 **3c**	72
4	**1a**	 **2d**	 **3d**	70
5	*n*Bu—≡—H **1b**	**2a**	*n*Bu—≡—Ph **3e**	63
6	**1b**	**2c**	 **3f**	62
7	 **1c**	**2a**	 **3g**[8a]	68
8	**1c**	**2b**	 **3h**[13, 14]	68
9	**1c**	**2c**	 **3i**[8a, 14]	66
10	 **1d**	**2a**	 **3j**[15]	56
11	**1d**	**2b**	 **3k**[14,15]	58
12	**1d**	**2c**	 **3l**[14, 16]	57
13	**1d**	**2d**	 **3m**[14, 17]	57
14	EtO_2C—≡ **1e**	**2a**	 **3n**[14]	68
15	**1e**	**2c**	 **3o**[14]	62

coupling was very sensitive to the catalysts. Of the catalysts tested, CuI, CuCl, CuBr, CuCN, CuOAc, and $CuCl_2$, CuI was the best of choice. With CuCl, CuCN, CuOAc, and $CuCl_2$, almost no reaction occurred. As a suitable base, $NaHCO_3$ was the most preferred; K_2CO_3 and Na_2CO_3 gave rather low yields. The bases Et_3N, Et_2NH, and NaOH were almost ineffective. As solvent, DME/H_2O (4:1) was most suitable.

The results of the CuI-catalyzed cross-coupling reaction of terminal alkynes with aryl- and alkenyliodonium salts are summarized in Table 1. The phenylacetylene (**1a**) reacted with Ph_2I^+ BF_4^- in the presence of CuI (10 mol %) and $NaHCO_3$ (2 equiv) in DME/H_2O (4:1) at room temperature for 30 min to afford diphenylacetylene (**3a**)[8a,9] in 85% yield

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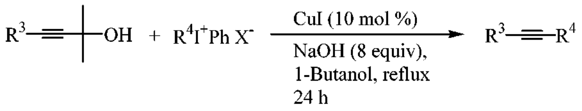
(9) A typical procedure is as follows. To a stirred solution of diphenyliodonium tetrafluoroborate (**2a**) (1.00 g, 2.70 mmol) in DME/H_2O (4:1, 10 mL) at room temperature was added $NaHCO_3$ (499 mg, 5.94 mmol) followed by phenylacetylene (**1a**) (303 mg, 2.97 mmol). The reaction mixture was stirred for 30 min and quenched with a saturated aqueous NH_4Cl solution (5 mL). The mixture was extracted with diethyl ether (20 mL × 3), and the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was separated by SiO_2 column chromatography (hexane, $R_f = 0.48$) to give diphenylacetylene (**3a**)[8a] (409 mg, 85%): ^1H NMR (500 MHz, $CDCl_3$) $\delta = 7.54$ (m, 6H), 7.54 (m, 4H); IR (KBr) $\nu = 3063, 1560, 1500, 1070, 918\ cm^{-1}$; MS ($m/e$) = 178 ($M^+$, base peak), 152, 89, 88, 76.

(entry 1 in Table 1). It is notable that no homo-coupling products were detected under these conditions. Under the same conditions, *p*-methoxyphenyl(phenyl)iodonium salt **2b** as electrophile, *p*-methoxyphenyl transferred product **3b**[10] was afforded as the sole product (entry 2). This method was applied to alkenyl-substituted iodonium salt **2d**, and the coupled enyne **3d**[8a] was obtained in 70% yield (entry 4). 1-Hexyne **1b** and propargyl alcohol **1c** were utilized in this coupling method. 1-Hexyne (**1b**) was treated with iodonium salts **2a** and **2c** to afford the coupling products **3e**[8a] and **3f**[8a] (entries 5 and 6). The substituted propargyl alcohols **1c** and **1d** were also used in the copper-catalyzed cross-coupling (entries 8−13). This copper-catalyzed cross-coupling method was extended to electron-deficient alkynes. Ethyl propiolate was reacted with iodonium salts **2a** and **2c** to afford the aryl-substituted propiolates **3n**[11] and **3o**[12] in 68 and 62% yields, respectively (entries 14 and 15).[11]

Next we investigated the one-pot and direct coupling of the acetylenic alcohols **3j**−**3m** with hypervalent iodonium salts in the presence of copper catalyst CuI under basic conditions. Indeed, acetylenic alcohols **3j**−**3m** can be transformed into arylethynes under these conditions (Scheme 2).[18,19]

Scheme 2



The results of the direct and one-pot cross-coupling of acetylenic alcohol **3** with hypervalent iodonium salts **2** under copper catalysis to form disubstituted acetylenes are summarized in Table 2. The acetylenic alcohol **3j** reacted with *p*-methoxyphenyl(phenyl)iodonium salt **2b** in the presence of CuI (10 mol %) with NaOH and 1-butanol at reflux for 24 h to afford the disubstituted acetylene **3b** in 70% yield (entry 1 in Table 2). Under the same conditions, the acetylenic alcohol **3j** was treated with iodonium salts **2c** and **2d** to provide **3c**[8a] and **3d** (entries 2 and 3). Alternatively, the acetylenic alcohols **3k**−**3m** were readily deprotected and coupled in a one-pot procedure under the same conditions to give **3b**, **3c**, and **3d** in moderate yields (entries 4−6).

Table 2. One-Pot Direct Cross-Coupling of Acetylenic Alcohol with Hypervalent Iodonium Salts in the Presence of CuI under Basic Conditions

entry	substrate	iodonium salt	product	yield (%)
1	**3j**	**2a**	**3a**	80
2	**3j**	**2b**	**2b**	70
3	**3j**	**2c**	**3c**	62
4	**3j**	**2d**	**3d**	63
5	**3k**	**2a**	**3b**	66
6	**3l**	**2a**	**3c**	60
7	**3m**	**2a**	**3d**	56

In summary, we have developed a new and mild protocol for Sonogashira coupling with CuI as catalyst utilizing hypervalent iodonium salts as the electrophilic coupling partners and multiple Sonogashira reactions for the synthesis of disubstituted acetylenes.

Acknowledgment. This work is supported by a National Research Laboratory Grant by the Korea Ministry of Science and Technology and KOSEF-CMDS (Center for Molecular Design and Synthesis).

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(10) Kang, S.-K.; Baik, T.-G.; Song, S.-Y. *Synlett* **1999**, 327−329.

(11) Recently Stang et al. reported the palladium-catalyzed arylation of electron-deficient alkynes using diaryliodonium salts. See: Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859−860.

(12) Brittain, J. M.; Jones, A.; Taheri, A. N. *Tetrahedron* **1980**, *36*, 7609−7618.

(13) Hurley, A. L.; Welker, M. E.; Day, C. S. *J. Organomet. Chem.* **2000**, 150−159.

(14) The spectral and physical data of **3h**, **3j**, **3k**, **3l**, **3m**, **3n** and **3o. 3h**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (t, 1H, $J = 6$ Hz), 3.81 (s, 3H), 4.49 (d, 2H, $J = 6$ Hz), 6.84 (dd, 2H, $J = 6.5$, 2 Hz), 7.38 (dd, 2H, $J = 6.5$, 2 Hz); IR (KBr) $\nu = 3250$, 2963, 2233, 1603, 1509, 1291, 1253 cm^{-1}; HRMS calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0682. **3j**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 6H), 7.28 (m, 3H), 7.41 (m, 2H); IR (KBr) $\nu = 3395$, 3058, 2983, 2232, 1953, 1881, 1598, 1490 cm^{-1}; HRMS calcd for $C_{11}H_{12}O$ 160.0888, found 160.0889. **3k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (s, 6H), 3.80 (s 3H), 6.82 (d, 2H $J = 9$ Hz), 7.35 (d, 2H $J = 9$ Hz); IR (KBr) $\nu = 3378$, 3043, 2981, 2839, 2228, 1607, 1510, 1463, 1249 cm^{-1}; HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0994. **3l**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (s, 6H), 6.94 (m, 1H), 7.17 (m, 1H), 7.22 (m, 1H); IR (KBr) $\nu = 3357$, 3108, 2983, 2222, 1518, 1452, 1261 cm^{-1}; HRMS calcd for $C_9H_{10}OS$ 166.0452, found 166.0453. **3m**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 6H), 6.16 (d, 1H, $J = 16.5$ Hz), 6.93 (d, 1H, $J = 16.5$ Hz), 7.35 (m, 5H); IR (KBr) $\nu = 3356$, 3029, 2981, 2213, 1491, 1448, 1366, 1164, 953 cm^{-1}; HRMS calcd for $C_{13}H_{14}O$ 186.1045, found 186.1048. **3n**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, 3H, $J = 7$ Hz), 4.30 (q, 2H, $J = 7$ Hz) 7.37 (m, 2H), 7.44 (m, 1H), 7.58 (m, 2h); IR (neat) $\nu = 3083$, 3038, 2985, 2210, 1715, 1491, 1368, 1240 cm^{-1}; HRMS calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0680. **3o**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, 3H, $J = 7$ Hz), 4.30 (q, 2H, $J = 7$ Hz) 7.05 (m, 1H), 7.47 (m, 2H); IR (neat) $\nu = 3091$, 2989, 2214, 2129, 1769, 1665, 1584, 1470, 1370, 1271 cm^{-1}; HRMS calcd for $C_9H_8O_2S$ 180.0245, found 180.0245.

(15) Berigbreite, D. E.; Liu, Y. S. *Tetrahedron Lett.* **1992**, *38*, 7843−7846.

(16) Mal'kina, A. G.; Brandsma, L.; Vasilevsky, B. A.; Trofima, B. A. *Synthesis* **1996**, 589−590.

(17) Ooi. T.; Miura, T.; Maruoka, K. *J. Am. Chem. Soc.* **1998**, *120*, 10790−10791.

(18) The direct cross-coupling between acetylenic alcohols and aryl halide under basic conditions with Pd(0)/CuI catalysts is known. See: Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910−1913.

(19) Typical procedure is as follows. To stirred solution of 2-methyl-4-phenyl-3-butyn-2-ol (**3j**) (1.00 g, 6.24 mmol), 4-methoxyphenyl(phenyl)-iodonium tetrafluoroborate (**2b**) (2.49 g, 6.24 mmol), and CuI (0.12 g, 0.63 mmol) in butanol (10 mL) was added NaOH (2.00 g, 49.92 mmol). The reaction mixture was heated at reflux for 24 h and then quenched with a saturated aqueous NH_4Cl solution (5 mL). The reaction mixture was extracted with diethyl ether (20 mL × 3), and the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was separated by SiO_2 column chromatography (EtOAc/hexane = 1:10, $R_f = 0.52$) to give 1-methoxy-4-(phenylethynyl)benzene (**3b**) (910 mg, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 3.83$ (s, 3H), 6.88 (d, 2H, $J = 8.5$ Hz), 7.29 (m, 3H), 7.49 (m, 4H); IR (KBr) $\nu = 3080$, 2958, 1617, 1405 cm^{-1}; MS (m/e) = 208 (M$^+$), 207 (base peak), 193, 165.