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Copper(I)-Catalyzed Cross-Coupling Reaction of Alkynylsilanes with 1-Chloroalkynes

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Abstract: A variety of unsymmetrical 1,4-biaryl-1,3-butadiyne derivatives are synthesized by a copper(I)-catalyzed cross-coupling reaction of alkynylsilanes with 1-chloroalkynes in moderate to good yields. These reactions are derived from the transmetalation of an alkynyl group from silicon to copper in a polar solvent. © 1998 Elsevier Science Ltd. All rights reserved.

During our study on the transformation of organosilicon compounds directed toward new carbon-carbon bond-forming reactions, we discovered that, in the presence of copper(I) salts, transmetalation of silicon to copper occurred in aprotic polar solvents such as *N,N*-dimethyformamide (DMF).[1] Independently, Ito and Hosomi reported that alkynylsilanes cross-coupled with acid chlorides in the presence of a catalytic amount of copper(I) chloride.[2] These findings prompted us to investigate a novel *sp-sp* carbon bond-forming reaction with alkynyl silanes, since the structure of conjugated diynes is common in natural products,[3] particularly in antifungal agents.[4] Due to the versatility of conjugated diynes, a variety of synthetic methods are available via a homo- or cross-coupling reaction.[5] We alternatively report herein a convenient procedure for the formation of unsymmetrical conjugated diynes from the copper(I)-catalyzed cross-coupling reaction using alkynylsilanes and 1-chloroalkynes *under neutral conditions* (eq 1).

$$\underset{\mathbf{1}}{R^1\!-\!\equiv\!-\!SiMe_3} + \underset{\mathbf{2}}{R^2\!-\!\equiv\!-\!Cl} \xrightarrow[\text{DMF, 80°C}]{\text{CuCl (10 mol\%)}} \underset{\mathbf{3}}{R^1\!-\!\equiv\!-\!\equiv\!-\!R^2} \qquad (1)$$

First, we examined the cross-coupling reaction of trimethyl(4-methoxyphenylethynyl)silane (**1a**) with 1-chloro-2-phenylacetylene (**2a**) under some different reaction conditions and the results are listed in Table 1. In the presence of a catalytic amount of CuCl (10 mol%) and $Pd(PPh_3)_2Cl_2$ (10 mol%), the desired cross-coupled product **3a** was obtained in only 35% yield along with a homo-coupled product, 1,4-diphenyl-1,3-butadiyne (**4**), in 21% yield as shown in entry 1. To our surprise, the use of 10 mol% of CuCl, without addition of a palladium catalyst, allowed us to obtain higher yield of **3a** (80%, entry 2). The reactions carried out at lower

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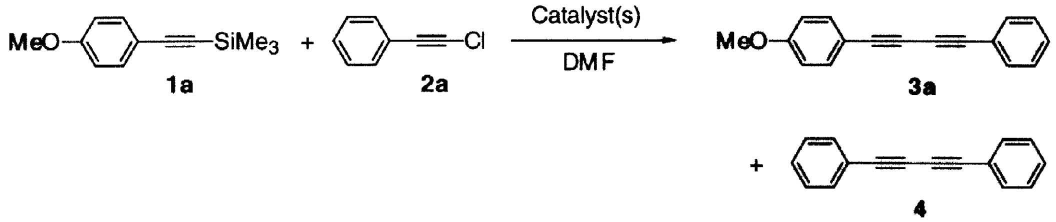
temperatures gave none (25 °C, entry 3) or <5% (60 °C, entry 4) yield of the product. When 1.5 mol of **1a** was added to **2a**, highest yield (90%) of **3a** was achieved (entries 2 *vs* 5). In place of CuCl, other copper(I) salts such as CuI were investigated and neither a catalytic nor a stoichometric amount was found to be effective for the present coupling reactions to proceed (entries 7 and 8). When CuOTf was used as a catalyst, a large amount of homo-coupled product **5** from **1a** was unexpectedly produced in 13% yield (entry 9). An addition of a copper catalyst is essential for the present reaction (entries 10 and 11).

Table 1. Optimization of the cross-coupling reaction of **1a** with **2a**[a]



Entry	**2a**/mol	Catalyst(s)	Temp/°C	Time/h	Yield/%	Yield/%
					3a[b]	**4**[c]
1	1.1	CuCl (10 mol%)-PdCl$_2$(PPh$_3$)$_2$ (10 mol%)	80	24	35	21
2		CuCl (10 mol%)		48	80	35
3			25	24	0	0
4			60		<5	<5
5	1.5		80	48	90	29
6[d]	1.0				29[e]	14
7	1.5	CuI (10 mol%)			54	11
8		CuI (1 mol)			58	39
9		CuOTf (10 mol%)			43[f]	70
10		PdCl$_2$(PPh$_3$)$_2$ (10 mol%)			0	0
11		none			0	0

[a] **1a** (1.0 mol) was used in DMF (5 mL). [b] GC yield based on **1a**. [c] GC yield based on **2a**. [d] The order of substrates was changed. [e] Symmetrical conjugated diyne **5** from **1a** was formed (42%). [f] Symmetrical conjugated diyne **5** from **1a** was formed (13%).

A general procedure for the formation of unsymmetrical conjugated diyne (**3**) is as follows: To a solution of copper chloride (2.4 mg, 0.02 mmol, 10 mol%) in DMF (1.5 mL) was added 1-chloro-2-phenylacetylene (**2a**) (50 mg, 0.37 mmol) at room temperature. To the mixture was added trimethyl(4-methoxyphenylethynyl)silane (**1a**) (50 mg, 0.25 mmol). The reaction mixture was stirred for 48 h at 80 °C, quenched with 3 M HCl, and extracted with diethyl ether (25 mL x 2). The combined ethereal layer was washed with NaHCO$_3$ aq. solution, then with brine and dried over MgSO$_4$. Filtration and evaporation provided a brown oil. Column chromatography (SiO_2, hexane : dichloromethane = 10 : 1) gave 36 mg (65%) of **3a** as a colorless solid.

Results of the present coupling reaction using a variety of alkynylsilanes with 1-chloroalkynes are summarized in Table 2. This reaction is affected by the substituents in the *para*-position of an aromatic ring. Alkynylsilane **1a** bearing an electron-donating group produced the coupled products in higher yield (entries 1-3) than that bearing an electron-withdrawing group, e.g., **1b** (entries 4-6). Alkynylsilane (**1c**) reacted with 1-chloroalkynes (**2b** or **2c**) bearing an electron-withdrawing group to give **3d** and **3f** in 62 and 85% yield, respectively (entries 7 and 8). Although **3a** was furnished from the reaction of **1a** and **2a** in 90% yield as observed in entry 1, the opposite combination of **1c** with **2d** bearing an electron-donating group gave **3a** in only 43% yield (entry 9).

Table 2. Cu(I)-catalyzed cross-coupling reaction of alkynylsilanes (**1**) with 1-chloroalkynes (**2**)[a]

Entry	Alkynylsilane (**1**) (R^1 =)	1-Chloroalkyne (**2**) (R^2 =)	Time/h	Product	Yield/%[b]
1	4-MeO-C_6H_4- (**1a**)	C_6H_5- (**2a**)	48	**3a**	90 (65)
2		4-MeCO-C_6H_4- (**2b**)	48	**3b**	97 (52)
3		4-Cl-C_6H_4- (**2c**)	48	**3c**	95 (54)
4	4-MeCO-C_6H_4- (**1b**)	**2a**	96	**3d**	69
5		**2c**	48	**3e**	60 (42)
6		4-MeO-C_6H_4- (**2d**)	48	**3b**	60
7	C_6H_5- (**1c**)	**2b**	48	**3d**	62 (56)
8		**2c**	48	**3f**	85 (53)
9		**2d**	48	**3a**	43
10	4-NC-C_6H_4- (**1d**)	**2b**	48	**3g**	93 (61)
11	4-^{t}BuMe$_2$SiO-C_6H_4- (**1e**)	**2c**	48	**3h**	62 (32)

[a] Typical procedure: **1** (1.0 mol) and **2** (1.5 mol) were used in DMF (5 mL) at 80 °C. [b] GC yield based on **1a** and isolated yields are given in parentheses.

Although a protocol of the Cadiot-Chodkiewicz coupling[6] is established that involves a copper(I)-catalyzed reaction of terminal acetylenes ($R^1C{\equiv}CH$) with 1-haloacetylenes ($R^2C{\equiv}CX$) (X = Br, I) in the presence of a base such as diethylamine (Et_2NH),[7] the reaction of *1-chloroalkynes with terminal acetylenes* often furnishes unsymmetrical diynes in poor yields under the standard Cadiot-Chodkiewicz condition[8] or a copper(I)/palladium co-catalyst system.[9] The low reactivity is ascribed to the inertness of 1-chloroalkynes compared with 1-bromo- and 1-iodoalkynes. We also examined the reaction of 1-chloroalkynes with terminal acetylenes at 80 °C and observed that complex mixtures of unidentified products resulted.[10] For success in the clean formation of the desired cross-coupled products, an appropriate combination of alkynylsilanes ($R^1C{\equiv}CSiMe_3$) and 1-chloroalkynes ($R^2C{\equiv}CCl$) is essential, as we discussed above.

In summary, we have developed a convenient route to the formation of unsymmetrical conjugated diynes using 1-chloroalkynes and alkynyltrimethylsilanes in moderate to high yields via transmetalation of an alkynylsilane to a copper(I) catalyst. Since this method can be carried out under neutral conditions without any base, it will find further applications in the synthesis of polyynes and cyclic alkynes.

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