ORGANIC LETTERS

2003
Vol. 5, No. 19
3483−3486

Palladium-Catalyzed Silylation of Aryl Bromides Leading to Functionalized Aryldimethylsilanols

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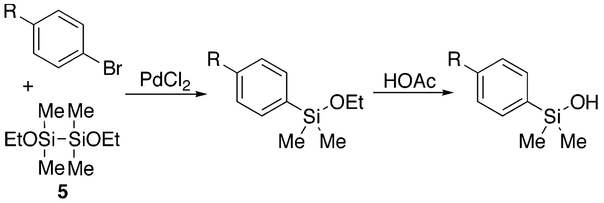
Received July 11, 2003

ABSTRACT



A mild and general palladium-catalyzed insertion of 1,2-diethoxy-1,1,2,2-tetramethyldisilane into a variety of aryl bromides affords the aryldimethylsilyl ethers in high yields. Hydrolysis of the ethers under pH-optimized conditions results in the exclusive formation of the desired aryldimethylsilanols.

Transition-metal-catalyzed cross-coupling has become a powerful and general method for the selective construction of carbon−carbon bonds due in large measure to the pioneering work of Stille and Suzuki on organotin- and organoboron-based reagents, respectively.[1] To avoid the toxicity and relatively low stability of the organotin and boron reagents, organosilicon reagents have proved to be a viable alternative in the cross-coupling reaction.[2] Recent reports from these laboratories have identified the specific advantages of aryl- and alkenyldimethylsilanols as substrates for palladium-catalyzed cross-coupling reactions.[3,4] Whereas hydrosilylation is often used to prepare alkenyldimethylsilanols, the preparation of aryl dimethylsilanols is limited to lithium−halogen exchange followed by trapping with a silicon electrophile.[5] Several transition-metal-catalyzed silylation reactions between aryl halides and triethoxysilane or hexamethyldisilane give arylsilanes; however, a general method for producing monooxygenated arylsilyl ethers or silanols has not been described. In general, silylations with triethoxysilane[6] proceed well with electron-rich and -neutral aryl iodides; however, electron-deficient aryl iodides suffer from significant amounts of reduction.[7] The scope of the silylation can be extended to include electron-rich and -neutral aryl bromides with the use of bulky phosphine ligands.[8] Recently, it has been shown that a limited number of electron-deficient aryl bromides and iodides also react with triethoxysilane in the presence of $[Rh(cod)(MeCN)_2]BF_4$.[9] Alternatively, palladium-catalyzed silylation with hexamethyldisilane gives a wide variety of both electron-rich and -deficient aryltrimethylsilanes; however, activation of the disilane by fluoride or hydroxide is required for efficient transfer.[10] It would be desirable to introduce dimethylsilanol units onto aryl groups by a direct method that would tolerate

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[1] *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

[2] (a) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (b) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531.

[3] Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357.

[4] Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

[5] (a) Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409. (b) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147.

[6] Triethoxysilane is highly toxic and may cause blindness.

[7] Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569.

[8] Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449.

[9] Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843.

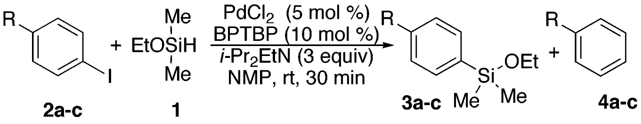
10.1021/ol035288m CCC: $25.00

a wide range of functional groups which are incompatible with lithium reagents.

To obtain the desired aryldimethylsilanols, a two-step process was envisioned that comprised an initial silylation of an aryl bromide to afford an aryldimethylsilyl ether, which could then be hydrolyzed to the aryldimethylsilanol under appropriate conditions. Herein we report a general, mild, one-pot palladium-catalyzed silylation and hydrolysis procedure that provides functionally diverse aryldimethylsilanols from the corresponding aryl bromides.

Initially, silylation with ethoxydimethylsilane (**1**) was investigated using 4-iodoanisole (**2a**). The predominant competing pathway in the formation of the desired aryldimethylsilyl ether (**3a**) was reduction to afford anisole (**4a**). After a brief optimization, the preferred reaction conditions involved stirring $PdCl_2$, 2-(di-*tert*-butylphosphino)biphenyl (BPTBP), and *i*-Pr_2EtN with 4-iodoanisole for 30 min to allow a homogeneous solution to form prior to addition of **1**. With this protocol, the reaction was complete in under 30 min at room temperature and only a small amount of anisole was formed. (Table 1, entry 1). However, with 4-iodoacetophenone (**2b**) or 4-iodonitrobenzene (**2c**), reduction became the predominant pathway (entries 2 and 3).

Table 1. Silylation of Aryl Iodides with Dimethylethoxysilane



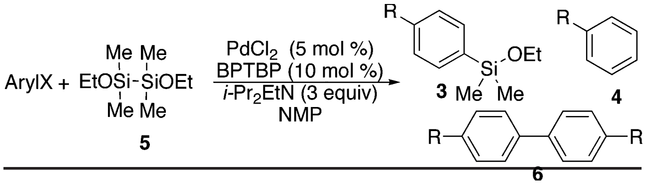
entry	aryl iodide	R	**3**, %[a]	**4**, %[a]
1	**2a**	−OMe	93	7
2	**2b**	−COMe	35	64
3	**2c**	$-NO_2$	5	90

[a] Reported as area % by GC analysis.

To overcome competitive reduction of the aryl halide, 1,2-diethoxy-1,1,2,2-tetramethyldisilane (**5**) was employed as the silylation reagent. Reaction of 4-iodoanisole (**2a**) with **5a** at ambient temperature or at 60 °C gave, in addition to **3**, large amounts of the homocoupling product (**6**) (Table 2, entries 1 and 2). The formation of **6** could be substantially suppressed by the use of 4-bromoanisole (**7a**) in place of **4a** (entry 3). Even an electron-deficient aryl bromide, ethyl 4-bromobenzoate (**7d**) (entry 4), gave almost exclusive formation of the silyl ether.

The next stage in the optimization involved changing both the ligand and the palladium source in the silylation of **7d**. In the ligand screen, only BPTBP yielded the desired product, whereas dppb and PPh_3 were ineffective (Table 3, entries 1−3). Changing the palladium source showed only a moderate effect (entries 1, 4, and 5), suggesting that the active catalytic species is a BPTBP-ligated palladium(0) species that is formed during the course of the reaction.

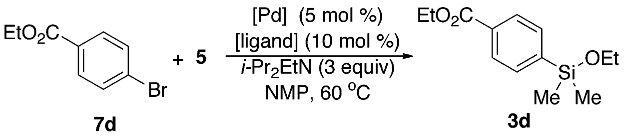
Table 2. Silylation of Aryl Halides with **5**



entry	ArylX	temp, °C	time, h	**3**, %[a]	**4**, %[a]	**6**, %[a]
1	**2a**	rt	48	66	17	16
2	**2a**	60	2	54	4	41
3	**7a**	60	10	94	3	1
4	**7d**	60	6	93	2	5

[a] Reported as area % by GC analysis.

Table 3. Effect of Palladium Source and Ligands on Silylation

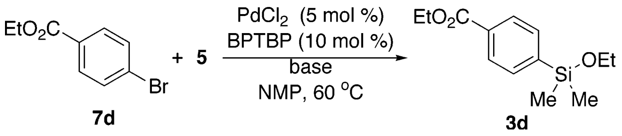


entry	catalyst	ligand	**3d**, %[a]
1	$PdCl_2$	BPTBP	90
2	$PdCl_2$	dppb	4
3	$Pd(PPh_3)_2Cl_2$		0
4	$Pd(dba)_2$	BPTBP	65
5	$[allylPdCl]_2$	BPTPB	87

[a] Determined at 2 h by GC analysis using an internal standard.

Decreasing the amount of the base from 3.0 to 1.1 equiv resulted in reaction stalling before silylation was complete (Table 4, entries 1 and 2). The use of a tertiary amine base allowed the reaction to reach completion, but *i*-Pr_2EtN was

Table 4. Effect of Base on Silylation



entry	base	equiv	**3d**, %[a]
1	*i*-Pr_2EtN	3.0	90
2	*i*-Pr_2EtN	1.1	55
3	Et_3N	3.0	45
4	pyridine	3.0	0.0
5	2,6-lutidine	3.0	0.0
6	*i*-Pr_2NH	3.0	0.3
7	KH_2PO_4	3.0	1 (31)[b]

[a] Determined at 2 h by GC analysis using an internal standard. [b] Amount of **8d** formed.

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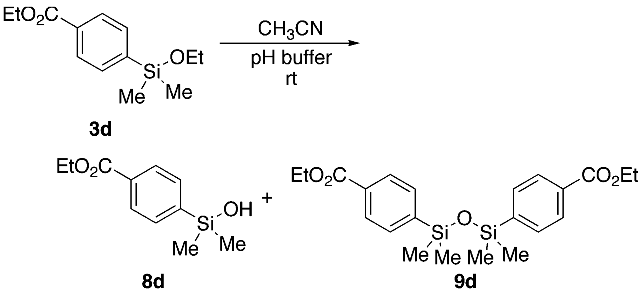
(10) (a) Shirakawa, E.; Kurahashi, T.; Yoshida, H.; Hiyama, T. *Chem. Commun.* **2000**, 1895. (b) Gooβen, L. J.; Ferwanah, A. S. *Synlett* **2000**, 1801.

superior to Et_3N (entry 3). Changing the base to pyridine, 2,6-lutidine, or *i*-Pr_2NH inhibited the reaction, and no conversion to the silyl ether was observed (entries 4−6). Interestingly, when KH_2PO_4 was used, silylation proceeded to 32% conversion with predominant in situ conversion to the silanol before the reaction stalled (entry 7).

With optimized conditions in hand for the synthesis of the silyl ether, its hydrolysis to the silanol was investigated next. A well-known complication in the hydrolysis of silyl ethers (under either acidic or basic conditions) to the silanols **8** is the competitive dimerization of **8** to the disiloxanes **9**.[11] Although the pH dependence of hydrolysis of alkyltriethoxysilyl ethers[12a] and the dimerization of alkylsilanols[12b] have been studied, no reports describe the relative amounts of **8** and **9** formed during the hydrolysis of silyl ethers. Thus, a study on the effect of pH on the hydrolysis and dimerization was undertaken. The optimization of the hydrolysis was performed with unpurified silylation product mixtures with the consequence that the reaction medium is intrinsically basic because of the residual *i*-Pr_2EtN from the silylation reaction. Addition of either acidic or basic buffers to this mixture resulted in a variety of in situ-formed ammonium buffers of different pH. To create a homogeneous solution, acetonitrile was added along with either an acetate or phosphate buffer. GC analysis allowed for monitoring the conversion of **3d** to both **8d** and **9d**. Analysis of the reactions with acetate buffers showed that the conversion to **8d** is high when the pH is held below 7 (Table 5, entries 1−6). Increasing the pH above 7 resulted in a slower hydrolysis reaction (entry 7). The ratio of **8d**:**9d** appears to be ideal in the pH 5−7 range, with increased amounts of **9d** formed either above or below this pH range (entries 1−7). The phosphate buffers gave disappointingly slow hydrolysis except at pH > 9, where the ratio of **8**:**9** is unacceptably high (entries 8−12). These trends become clear when conversions are plotted against reaction pH (Figure 1). The results are in agreement with earlier studies that show that mildly acidic conditions (near pH 4) maximize hydrolysis of the silyl ether and minimize dimerization.[13] The simplest buffer system that falls into the ideal pH 5−7 range is a 1.0 M acetic acid/ammonium acetate buffer at pH 5.6. Using this protocol, the hydrolysis of the silyl ether is complete within 2 h and the amount of **9d** formed is kept below 1%.

Table 5. pH Dependence on the Hydrolysis and Dimerization of **3d**



entry	concn, M	buffer	pH of buffer	pH of reaction	**8d**, %[a]	ratio of **8d**:**9d**
1	10.0	HOAc	1.07	4.20	75	97.1:2.9
2	2.0	HOAc	2.02	5.16	83	99.2:0.8
3	1.0	HOAc	2.23	5.63	77	98.9:1.1
4	1.0	HOAc/NaOAc	2.89	6.17	80	99.4:0.6
5	1.0	HOAc/NaOAc	3.79	6.31	82	98.8:1.2
6	1.0	HOAc/NaOAc	4.92	6.97	80	99.2:0.8
7	1.0	HOAc/NaOAc	5.98	8.98	62	86.5:13.5
8	1.0	KH_2PO_4/K_2HPO_4	4.46	6.98	25	98.7:1.3
9	1.0	KH_2PO_4/K2HPO	5.44	7.25	17	98.0:2.0
10	1.0	KH_2PO_4/K_2HPO_4	6.70	8.62	18	95.4:4.6
11	1.0	KH_2PO_4/K_2HPO_4	7.96	9.06	63	85.5:14.5
12	1.0	KH_2PO_4/K_2HPO_4	8.72	9.00	63	83.1:16.9

[a] Determined by GC analysis vs internal standard.

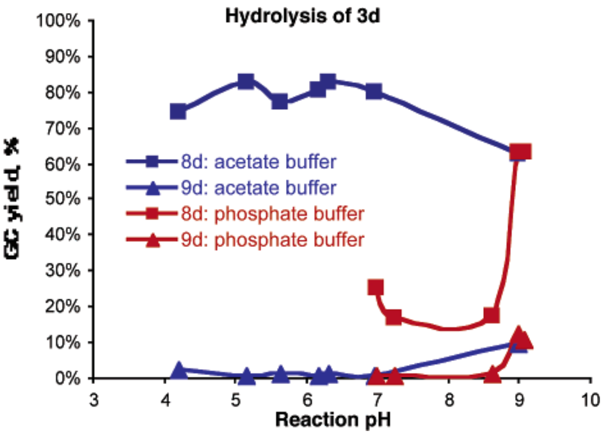


Figure 1. pH Dependence of formation of **8d** and **9d**.

A variety of aryl bromides were then subjected to the one-pot silylation/hydrolysis procedure (Table 6). Good yields were obtained with a range of substrates within a reasonable reaction time. Increasing the amount of disilane **5** from 1.1 to 1.5 equiv effected a substantial increase in yield for a number of substrates (entries 1−3 and 6−7), although not for **8d** (entry 4). The excess of **5** appears to increase the rate of the silylation compared to reduction or homocoupling.

In the purification of the crude silanol products, a portion of the palladium leached through the silica gel column, affording colored products. Several palladium scavengers were screened and evaluated by visual inspection of the products and ease of removal. It was found that 2-(dimethylamimo)ethanethiol hydrochloride was the simplest and most cost-effective palladium scavenger.[14] This solid is added directly to the hydrolysis reaction mixture and is removed with the palladium in the aqueous extraction.

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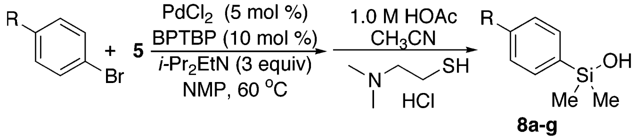
(11) (a) Akerman, E. *Acta Chem. Scand.* **1956**, *10*, 298. (b) Rutz, W.; Lange, D.; Popowski, E.; Kelling, H. *Z. Anorg. Allg. Chem.* **1986**, *536*, 197. (c) Shirai, N.; Moriya, K.; Kawazoe, Y. *Tetrahedron* **1986**, *42*, 2211.

(12) Pohl, E. R.; Osterholtz, F. D. *Polym. Sci. Technol.* **1985**, *27*, 157. (b) Pohl, E. R.; Osterholtz, F. D. In *Silanes, Surfaces and Interfaces*; Leyden, D. E., Ed.; Gordon and Breach: New York, 1986; Vol. 1, pp 481−500.

(13) Osterholtz, F. D.; Pohl, E. R. *J. Adhes. Sci. Technol.* **1992**, *6*, 127.

(14) Both trisodium thiocyanuracic acid (see: Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311) and mercapto-functionalized silica gel (Silicycle, Quebec City) were also investigated with lesser success.

Table 6. Silylation and Hydrolysis of 4-Substituted Aryl Bromides

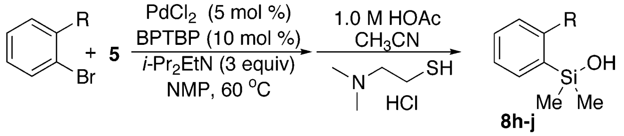


			1.1 equiv of **5**		1.5 equiv of **5**	
entry	R	product	time, h	yield, %[a]	time, h	yield, %[a]
1	OCH_3	**8a**	24	55	18	76
2	$COCH_3$	**8b**	4	64	4	70
3	NO_2	**8c**	4	54	4	72
4	CO_2Et	**8d**	4	79	4	81
5	CN	**8e**	4	79	4	80
6	CH_2OTHP	**8f**			4	69
7	CH_3	**8g**	18	60	12	71

[a] Yield of isolated, chromatographically pure material.

To probe the scope of this reaction, several 2-substituted aryl bromides were investigated. Silylation of 2-bromobenzonitrile occurred under the general reaction conditions (Table 7, entries 1 and 2); however, both ethyl 2-bromobenzoate and 2-bromoanisole showed no conversion to the product under these conditions. It is believed that the low reactivity of these substrates is not entirely a steric effect but that the Pd(II)-aryl species is coordinately stabilized by the neighboring substituent. To circumvent this problem, the silylation of ethyl 2-bromobenzoate and 2-bromoanisole were carried out at 80 °C. This minor modification proved to be effective for these substrates, although the yields were lower than for the corresponding 4-substituted aryl bromides (entries 3−4).

Table 7. Silylation and Hydrolysis of 2-Substituted Aryl Bromides



entry	R	product	temp, °C	equiv of **5**	time, h	yield, %[a]
1	CN	**8h**	60	1.1	24	57
2	CN	**8h**	60	1.5	12	82
3	CO_2Et	**8i**	80	1.5	24	56
4	OCH_3	**8j**	80	2.0	18	47[b]

[a] Yield of isolated, chromatographically pure material. [b] Starting material was recovered (10%).

In summary, we have developed a general procedure for the formation of aryldimethylsilanols from aryl bromides by a one-pot silylation/hydrolysis procedure. The hydrolysis conditions are sufficiently mild that formation of the disiloxane is minimized. Investigations are underway to utilize these silanols in cross-coupling reactions and to further expand this silylation method to include alkenyl halides.

Acknowledgment. We are grateful to the National Institutes of Health (RO1 GM63167) for generous financial support. J.M.K. thanks the University of Illinois for a graduate fellowship.

Supporting Information Available: Detailed procedures for the synthesis of **5**, all silylation reactions, and full characterization of **8a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035288M