JOC*Note*

A Facile One-Pot Synthesis of Alkyl Aryl Sulfides from Aryl Bromides

Jungyeob Ham, Inho Yang, and Heonjoong Kang*

Marine Biotechnology Laboratory and Research Institute of Oceanography, School of Earth and Environmental Sciences, Seoul National University, NS-80, Seoul 151-747, Korea

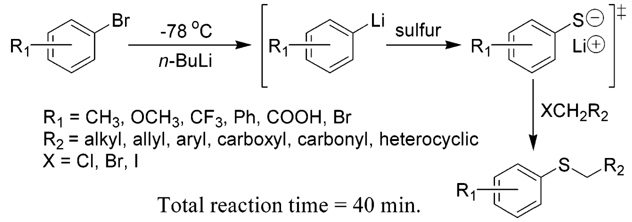
hjkang@snu.ac.kr

Received February 11, 2004

Abstract: A convenient one-pot synthetic method for the formation of alkyl aryl sulfides from various alkyl halides and lithium aryl thiolates that are prepared in situ by direct halogen−lithium exchange is reported. In particular, the method overcomes many of the problems encountered in previous reports; it is very quick, catalyst-free, and does not involve use of unstable aryl thiols.

The preparation of various alkyl aryl sulfides is one of the significant and widely used methods in organic[1,2] and medicinal chemistry.[3] Consequently, numerous synthetic methods for alkyl aryl sulfide formation have been developed. One general method is the condensation of activated alkyl halides with alkali metal aryl thiolate that is prepared from aryl thiol in the presence of strong bases.[4] However, the synthetic scope of this classical reaction is limited by its long reaction time, high reaction temperature, and low yield. Methods for the introduction of a carbon−sulfur bond with use of a transition metal catalyst (Pd, Cu) have also been developed.[5,6] Although these cross-coupling methods successfully yield versatile sulfides, they require a long reaction time and vigorous conditions to achieve acceptable yields. Furthermore, some aryl thiols are unstable to oxidation: their disulfide compounds are easily formed. Therefore, there are many inconvenient aspects in handling unstable thiols, including storage under an atmosphere of inert gas and keeping them away from oxidants or substances that give free radicals.

SCHEME 1. Preparation of Alkyl Aryl Sulfides from Various Aryl Bromides



Recently, the Glaxo-Smith-Kline research group has demonstrated a one-pot synthesis of alkyl aryl sulfide via a direct reduction and coupling of aromatic sulfonyl chlorides to activated alcohols.[7] However, this method is only applicable to the synthesis of alkyl *p*-substituted-aryl sulfides and the yields are moderately low.

During the course of our synthetic studies of bioactive compounds, we discovered a facile one-pot synthetic method for the formation of sulfide from aryl bromide. Although the preparation of sulfide from metal alkyl or aryl thiolate is a classical technique,[1,8] there has been no report of the synthesis of various alkyl aryl sulfides via lithium aryl thiolate that is prepared from aryl bromide and *n*-BuLi in the presence of sulfur. In this study, we report that easily prepared lithium thiolates couple directly with a variety of alkyl halides to give various alkyl aryl sulfides in good yields (Scheme 1).

In our reaction, a lithium thiolate intermediate was prepared in situ with use of the same equivalents (1 mmol) of aryl bromide and *n*-BuLi at −78 °C under nitrogen gas. Ten minutes after the start, sulfur powder (1 mmol) was added all at once. When the sulfur was

---

(1) (a) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: New York, 1996. (b) Jones. D. N. *Comprehensive Organic Chemistry*; Barton, D. H., Ollis, D. W., Eds.; Pergamon: New York, 1979; Vol. 3. (c) Patai, S. *The Chemistry of Functional Groups−The Chemistry of the Thiol Group*; Wiley: London, UK, 1974. (d) Wakefield, B. J. *Organolithium Methods*; Academic: London, 1988.

(2) (a) Field, L. *Synthesis* **1972**, 101. (b) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (c) Field, L. *Synthesis* **1978**, 713. (d) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973. (e) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641. (f) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 835.

(3) (a) Emond, P.; Vercouillie, J.; Innis, R.; Chalon, S.; Mavel, S.; Frangin, Y.; Halldin, C.; Besnard, J.-C.; Guilloteau, D. *J. Med. Chem.* **2002**, *45*, 1253. (b) Winn, M.; Reilly, E. B.; Liu, G.; Huth, J. R.; Jae, H. S.; Freeman, J.; Pei, Z.; Xin, Z.; Lynch, J.; Kester, J.; von Geldern, T. W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G. F *J. Med. Chem.* **2001**, *44*, 4393. (c) Brown, P. J.; Winegar, D. A.; Plunket, K. D.; Moore, L. B.; Lewis, M. C.; Wilson, J. G.; Sundseth, S. S.; Koble, C. S.; Wu, Z.; Chapman, J. M.; Lehmann, J. M.; Kliewer, S. A.; Willson, T. M. *J. Med. Chem.* **1999**, *42*, 3785. (d) Liu, K. G.; Lambert, M. H.; Leesnitzer, L. M.; Oliver, W. R., Jr.; Ott, R. J.; Plunket, K. D.; Stuart, L. W.; Brown, P. J.; Willson, T. M.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2959. (e) Oliver, W. R.; Shenk, J. L., Jr.; Snaith, M. R.; Russell, C. S.; Plunket, K. D.; Bodkin, N. L.; Lewis, M. C.; Winegar, D. A.; Sznaidman, M. L.; Lambert, M. H.; Xu, H. E.; Sternbach, D. D.; Kliewer, S. A.; Hansen, B. C.; Willson, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5306.

(4) (a) Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357. (b) Hundscheld, F. J. A.; Tandon, V. K.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073. (c) Ouertani, M.; Collin, J.; Kagan, H. *Tetrahedron* **1985**, *41*, 3689. (d) Tsay, S.; Lin, L.; Furth, P.; Shum, C.; King, D.; Yu, S.; Chen, B.; Hwu, J. *Synthesis* **1993**, *3*, 329. (e) Cao, X.; Chen, T.; Chow, H.; Tu, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1297. (f) Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synth. Commun.* **1981**, 892. (g) Bradshaw, J. S.; South, J. A.; Hales, R. H. *J. Org. Chem.* **1972**, *37*, 2381. (h) Herriott, A. W. *Synth. Commun.* **1975**, 447.

(5) (a) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D., III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606. (b) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598. (c) Martínez, A. G.; Barcina, J. O.; Cerezo, A. F.; Subramanian, L. R. *Synlett* **1994**, 561. (d) Migita, T.; Shimizu, T.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (e) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (f) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133. (g) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13. (h) Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2048.

(6) (a) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (b) Hickman, R. J. S.; Christie, B. J.; Guy, R. W.; White, T. J. *Aust. J. Chem.* **1985**, *38*, 899. (c) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309.

(7) Martin, M. T.; Thomas, A. M.; York, D. G. *Tetrahedron Lett.* **2002**, *43*, 2145.

(8) (a) Boscato, J. F.; Catala, J. M.; Franta, E.; Brossas, J. *Tetrahedron Lett.* **1980**, *21*, 1519. (b) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. A. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073. (c) Malmström, J.; Gupta, V.; Engman, L. *J. Org. Chem.* **1998**, *63*, 3318. (d) Blanchard, P.; Jousselme, B.; Frère, P.; Roncali, J. *J. Org. Chem.* **2002**, *67*, 3961.

10.1021/jo049758h CCC: $27.50

completely dissolved at the same temperature, alkyl halide (1 mmol) was added to the reaction mixture. Subsequently, the cold bath was removed from the reactor and then the reaction mixture was stirred for another 15−20 min at room temperature. However, when the reaction temperature was higher than −30 °C in the halogen−lithium exchange step or maintained at −78 °C during the entire reaction, we could not obtain a high yield of the desired product as a result of byproduct formation. The desired product was isolated by flash column chromatography. Similar results were observed with both *n*-BuLi and *t*-BuLi. Aryl bromides and alkyl halides that are usable with our method are readily available from various chemical companies at reasonable prices. The available aryl bromides are generally more diverse and cheaper than aryl thiols. The major advantages of this reaction are speed and ease of use. The experimental results are summarized in Table 1.

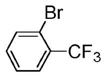
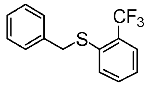
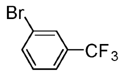
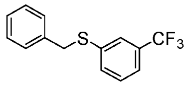
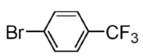
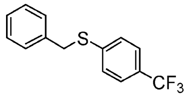
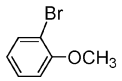
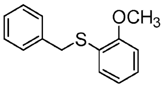
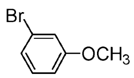
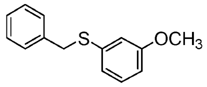
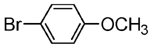
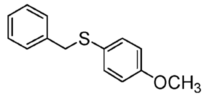
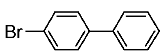
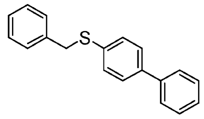
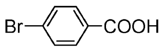
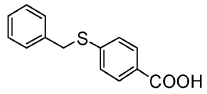
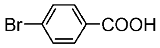
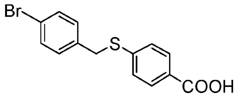
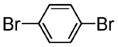
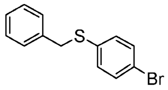
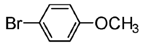
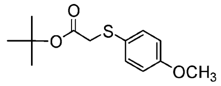
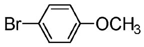
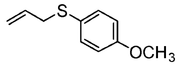
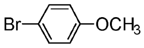
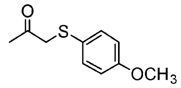
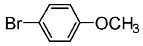
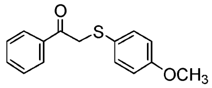
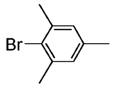
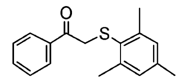
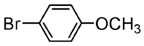
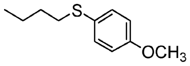
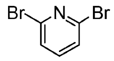
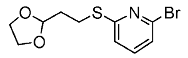
Interestingly, 4-bromobenzoic acid (entries 8 and 9), a starting material with an electron-withdrawing group (COOH), gave the desired sulfide in 91% and 89% yield, respectively, which could not be prepared by a direct reduction and coupling of 4-chlorosulfonylbenzoic acid to activated alcohols.[7]

It was found that unsaturated alkyl halides gave slightly better yields than did saturated alkyl halides. Indeed, when benzyl, allyl, carbonyl, or carboxyl halides (entries 7−15) were used as reactants, good yields were achieved (88−96%). By contrast, a saturated alkyl halide, such as 1-bromobutane (entry 16) or 2-(2-bromoethyl)-1,3-dioxolane (entry 17), gave a lower yield under the same conditions (75% and 79%, respectively). From the results, it was concluded that the major determinant of sulfide formation is not the electronic effect of aryl bromide, but the electrophilic affinity of alkyl halide to react with preformed lithium aryl thiolate.

Phenacyl bromide and chloroacetone were transformed into β-keto aryl sulfides (entries 13, 14, and 15), which are used as the starting materials for β-hydroxy sulfides, useful intermediates in organic synthesis[9] (91%, 94%, and 92%, respectively). Of particular note, we successfully obtained (i) a sterically hindered sulfide (entry 15) through the reaction of lithium mesityl thiolate with alkyl halide and (ii) a *n*-butyl aryl sulfide (entry 16) by reacting lithium anisole thiolate with 1-bromobutane that was produced as a byproduct of the halogen−lithium exchange step. Attempts to obtain monosubstituted aryl sulfides from dibrominated compounds such as 1,6-dibromopyridine and 1,4-dibromobenzene (entries 10 and 17) were also successful (88% and 79%, respectively).

In summary, we have developed a convenient one-pot synthetic protocol for the formation of alkyl aryl sulfides from various aryl bromides that have an electron-donating or -withdrawing group. Moreover, our method is very quick (less than 40 min) and catalyst-free, and can avoid the use of unstable arylthiols.

TABLE 1. Quick One-Pot Synthesis of Alkyl Aryl Sulfides

entry	aryl bromide	product	yield[a] (%)
1			82
2			71
3			96
4			76
5			72
6			92
7			93
8[b]			91
9[b]			89
10			88
11			96
12			91
13			91
14			94
15			92
16			75
17			79

[a] Yields are given for isolated products. [b] The reaction was performed in the presence of 2 equiv of *n*-BuLi.

Experimental Section

General Procedure for the Formation of Alkyl Aryl Sulfides from Aryl Bromides. To a solution of aryl bromide (2 mmol) in anhydrous THF (15 mL) was added slowly a solution

---

[9] (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363. (b) Ishibashi, H.; Takamuro, I.; Mizukami, Y.; Irie, M.; Ikeda, M. *Synth. Commun.* **1989**, *19*, 443. (c) Goergens, U.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1064. (d) Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tamao, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3465. (e) Nunno, L. D.; Franchini, C.; Nacci, A.; Scilimati, A.; Sinicropi, M. S. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1913. (f) Iriuchijima, S.; Maniwa, K.; Tauchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 4280.

of *n*-BuLi (1.6 N in hexane, 2 mmol) at −78 °C and the solution was stirred for 15 min under N$_2$ atmosphere. Sulfur powder (2 mmol) was then added. After the reaction mixture changed to a clean yellow solution, alkyl halide (2 mmol) was slowly added and then the reaction mixture warmed to room temperature for 20 min. The reaction was monitored by thin-layer chromatography. After the reaction was completed, it was quenched with aqueous NH$_4$Cl (15 mL). The organic layer was separated and then the aqueous layer (entries 8 and 9 were acidified to approximately pH 2.0 with aqueous 1 N HCl) was extracted with ethyl acetate (2 × 10 mL). The combined extract was washed with water, dried over MgSO$_4$, filtered, and evaporated under reduced pressure to give the crude product. The crude compound was purified by chromatography on silica gel to obtain the desired compound.

Benzyl 2-Trifluoromethylphenyl Sulfide (entry 1). The title compound was prepared from 2-bromobenzotrifluoride and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a pink solid (440 mg, 82% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.63 (d, 1H, $J = 7.6$ Hz), 7.38 (d, 2H, $J = 3.4$ Hz), 7.32∼7.23 (m, 6H), 4.15 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 136.8, 136.2, 132.3, 132.2, 129.9, 129.4, 128.9, 127.2 (q, $J = 5.7$ Hz), 126.5, 126.0, 39.7. MS (EI) *m/z* 268 (M$^+$, 45), 246 (10), 92 (24), 91 (100), 65 (28).

Benzyl 3-Trifluoromethylphenyl Sulfide (entry 2). The title compound was prepared from 3-bromobenzotrifluoride and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a clear oil (381 mg, 71% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.51 (br s, 1H), 7.39 (t, 2H), 7.33 (d, 1H), 7.28 (m, 5H), 4.13 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 138.3, 137.0, 133.0, 131.6 (q, $J = 32$ Hz), 129.5, 129.2, 129.0, 128.9, 127.9, 126.5 (q, $J = 3.7$ Hz), 123.3, 39.1. MS (EI) *m/z* 268 (M$^+$, 33), 91 (100), 65 (10).

Benzyl 4-Trifluoromethylphenyl Sulfide (entry 3). The title compound was prepared from 4-bromobenzotrifluoride and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a white solid (515 mg, 96% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.48 (d, 2H, $J = 8.2$ Hz), 7.36−7.25 (m, 7H), 4.19 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 142.5, 136.7, 129.1, 129.0, 128.3, 127.9, 126.0 (q, $J = 3.9$ Hz), 38.1. MS (EI) *m/z* 268 (M$^+$, 49), 92 (12), 91 (100), 65 (14).

Benzyl 2-Methoxyphenyl Sulfide (entry 4). The title compound was prepared from 2-bromoanisole and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a white solid (350 mg, 76% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30−7.18 (m, 7H), 6.84 (m, 2H, $J = 7.8$ Hz), 4.09 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 157.9, 137.9, 130.8, 129.3, 128.8, 128.0, 127.4, 124.8, 121.4, 110.9, 56.2, 37.7. MS (EI) *m/z* 230 (M$^+$, 76), 92 (15), 91 (100), 65 (18).

Benzyl 3-Methoxyphenyl Sulfide (entry 5). The title compound was prepared from 3-bromoanisole and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a clear oil (332 mg, 72% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.32−7.24 (m, 5H), 7.16 (t, 1H), 6.86 (d, 1H), 6.82 (t, 1H), 6.65 (dd, 1H), 4.11 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 160.1, 138.1, 137.8, 130.0, 129.2, 128.9, 127.6, 122.1, 115.2, 112.6, 55.6, 39.2. MS (EI) *m/z* 230 (M$^+$, 100), 197 (12), 139 (14), 92 (38), 91 (50), 65 (34).

Benzyl 4-Methoxyphenyl Sulfide (entry 6). The title compound was prepared from 4-bromoanisole and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a white solid (424 mg, 92% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28−7.16 (m, 7H), 6.77 (d, 2H, $J = 8.6$ Hz), 3.97 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 159.6, 138.5, 134.5, 129.8, 129.3, 128.8, 127.3, 114.8, 55.7, 41.6. MS (EI) *m/z* 230 (M$^+$, 100), 196 (31), 140 (34), 139 (26), 125 (10), 92 (13), 91 (80), 65 (12).

Benzyl 4-Biphenyl Sulfide (entry 7). The title compound was prepared from 4-bromobiphenyl and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a white solid (514 mg, 93% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70−7.20 (m, 14H), 4.15 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 140.8, 139.6, 137.8, 135.9, 131.8, 130.4, 129.3, 129.2, 128.9, 128.3, 127.9, 127.7, 127.6, 127.4, 127.3, 39.5. MS (EI) *m/z* 276 (M$^+$, 84), 91 (100).

4-Benzylsulfanylbenzoic Acid (entry 8). The title compound was prepared from 4-bromobenzoic acid, *n*-BuLi (2 equiv), and benzyl bromide. Flash chromatography (eluent: 5% MeOH in CH$_2$Cl$_2$) gave the pure product as a white solid (445 mg, 91% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.5 (br s, 1H), 7.82 (d, 2H, $J = 8.4$ Hz), 7.43−7.25 (m, 7H), 4.35 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.8, 143.7, 137.6, 130.5, 129.7, 129.3, 128.6, 128.1, 127.3, 36.2. MS (EI) *m/z* 244 (M$^+$, 54), 92 (13), 91 (100), 65 (15).

4-(4-Bromobenzylsulfanyl)benzoic Acid (entry 9). The title compound was prepared from 4-bromobenzoic acid, *n*-BuLi (2 equiv), and 4-bromobenzyl bromide. Flash chromatography (eluent: 5% MeOH in CH$_2$Cl$_2$) gave the pure product as a white solid (575 mg, 89% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.9 (br s, 1H), 7.82 (d, 2H, $J = 8.4$ Hz), 7.50 (d, 2H, $J = 8.4$ Hz), 7.40 (d, 2H, $J = 11.8$ Hz), 7.37 (d, 2H, $J = 11.8$ Hz), 4.33 (s, 2H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.7, 143.3, 137.4, 132.2, 131.8, 130.5, 128.4, 127.5, 121.1, 35.4. MS (EI) *m/z* 324 (M$^+$ − ^{81}Br, 25), 322 (M$^+$ − ^{79}Br, 24), 171 (99), 169 (100), 90 (22), 89 (14).

Benzyl 4-Bromophenyl Sulfide (entry 10). The title compound was prepared from 1,4-dibromobenzene and benzyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a pink solid (491 mg, 88% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, 2H, $J = 8.6$ Hz), 7.28 (m, 5H), 7.14 (d, 2H, $J = 8.6$ Hz), 4.08 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 137.4, 135.8, 132.2, 131.9, 129.1, 128.9, 127.7, 120.7, 39.5. MS (EI) *m/z* 280 (M$^+$ − ^{81}Br, 17), 278 (M$^+$ − ^{79}Br, 17), 92 (10), 91 (100), 65 (10).

(4-Methoxyphenylsulfanyl)acetic Acid *tert*-Butyl Ester (entry 11). The title compound was prepared from 4-bromoanisole and *tert*-butyl bromoacetate. Flash chromatography (eluent: hexane) gave the pure product as a clear oil (488 mg, 96% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42 (d, 2H, $J = 8.8$ Hz), 6.83 (d, 2H, $J = 8.8$ Hz), 3.79 (s, 3H), 3.43 (s, 2H), 1.39 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 169.4, 159.9, 134.3, 125.7, 114.9, 81.9, 55.7, 40.0, 28.3. MS (EI) *m/z* 254 (M$^+$, 49), 199 (13), 198 (100), 153 (52), 139 (43), 57 (33).

1-Allyl 4-Methoxyphenyl Sulfide (entry 12). The title compound was prepared from 4-bromoanisole and allyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a clear oil (328 mg, 91% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33 (d, 2H, $J = 9.8$ Hz), 6.82 (d, 2H, $J = 9.8$ Hz), 5.82 (m, 1H), 5.01 (s, 1H), 4.97 (dd, 1H, $J = 8.0$ and 1.3 Hz), 3.78 (s, 3H), 3.42 (d, 2H, $J = 7$ Hz). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 159.5, 134.4, 134.3, 126.2, 117.6, 114.8, 55.7, 39.7, 30.7. MS (EI) *m/z* 180 (M$^+$, 63), 140 (14), 139 (100).

1-(4-Methoxyphenylsulfanyl)propan-2-one (entry 13). The title compound was prepared from 4-bromoanisole and chloroacetone. Flash chromatography (eluent: hexane) gave the pure product as a clear oil (357 mg, 91% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35 (d, 2H, $J = 8.8$ Hz), 6.83 (d, 2H, $J = 8.8$ Hz), 3.79 (s, 3H), 3.54 (s, 2H), 2.26 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 204.0, 160.0, 134.0, 125.0, 115.2, 55.7, 46.9, 28.4. MS (EI) *m/z* 196 (M$^+$, 100), 154 (11), 153 (92), 139 (23), 138 (26).

2-(4-Methoxyphenylsulfanyl)-1-phenylethanone (entry 14). The title compound was prepared from 4-bromoanisole and phenacyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a yellow oil (486 mg, 94% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.90 (d, 2H, $J = 7.2$ Hz), 7.55 (t, 1H), 7.43 (t, 2H), 7.34 (d, 2H, $J = 8.8$ Hz), 6.80 (d, 2H, $J = 6.8$ Hz), 4.12 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 194.7, 160.1, 135.9, 135.0, 133.7, 129.1, 129.0, 125.0, 115.1, 55.7, 43.2. MS (EI) *m/z* 258 (M$^+$, 100), 153 (38), 139 (11), 105 (79), 77 (20).

1-Phenyl-2-(2,4,6-trimethylphenylsulfanyl)ethanone (entry 15). The title compound was prepared from mesityl bromide and phenacyl bromide. Flash chromatography (eluent: hexane) gave the pure product as a yellow oil (498 mg, 92% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87 (d, 2H, $J = 6.3$ Hz), 7.55 (t, 1H, $J = 7.4$ Hz), 7.42 (t, 2H, $J = 6.6$ Hz), 6.89 (s, 2H), 3.92 (s, 2H), 2.38 (s, 6H), 2.25 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 194.9, 143.5, 142.2, 139.2, 135.9, 133.6, 129.5, 129.1, 128.9, 41.2, 22.1, 21.4. MS (EI) *m*/*z* 270 (M^+, 60), 223 (11), 165 (43), 151 (13), 150 (15), 119 (15), 105 (100), 91 (19), 77 (26).

1-Butyl 4-Methoxyphenyl Sulfide (entry 16). The title compound was prepared from 4-bromoanisole and 1-bromobutane that is automatically generated as a byproduct during the lithium−halogen exchange reaction step. Flash chromatography (eluent: hexane) gave the pure product as a clear oil (295 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32(d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.7 Hz), 3.79 (s, 3H), 2.82 (t, 2H), 1.55 (m, 2H), 1.40 (m, 2H), 0.89 (t, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.1, 133.3, 127.3, 114.9, 55.7, 35.9, 31.8, 22.2, 14.0. MS (EI) *m*/*z* 196 (M^+, 95), 153 (180), 141 (11), 140 (100), 139 (44), 125 (31).

2-Bromo-6-(2-[1,3]dioxolan-2-ylethylsulfanyl)pyridine (entry 17). The title compound was prepared from 2,6-dibromopyridine and 2-(2-bromoethyl)-1,3-dioxolane. Flash chromatography (eluent: hexane/ethyl acetate [10:1]) gave the pure product as a yellow oil (459 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.11 (m, 3H), 5.05 (t, 1H), 4.02 (m, 2H), 3.91 (m, 2H), 3.27 (t, 2H), 2.11 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.7, 142.0, 138.3, 123.5, 121.0, 103.6, 65.3, 33.7, 25.3. MS (EI) *m*/*z* 291 ($M^+ - {}^{81}$Br, 25), 289 ($M^+ - {}^{79}$Br, 24), 218 (34), 216 (40), 205 (20), 203 (19), 192 (17), 191 (67), 190 (18), 189 (64), 158 (10), 156 (10), 110 (16), 109 (15), 101 (20), 100 (81), 99 (35), 73 (100), 57 (10).

Acknowledgment. J.H. was supported by the BK21 program, Ministry of Education and Human Resources, Korea. This work was supported by grant M1-0311-00-0145 from the Molecular and Cellular BioDiscovery Research Program, Ministry of Science and Technology, Korea.

Supporting Information Available: ^{1}H, ^{13}C NMR, and mass spectra of the purified products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049758H