JOC*Note*

Facile Introduction of SH Group on Aromatic Substrates via Electrophilic Substitution Reactions

Jean-Michel Becht, Alain Wagner,* and Charles Mioskowski*

Laboratoire de Synthèse Bioorganique, UMR 7514 associée au CNRS, Université Louis Pasteur de Strasbourg, Faculté de Pharmacie, 74 Route du Rhin, 67400 Illkirch, France

mioskowski@bioorga.u-strasbg.fr

Received January 6, 2003

Abstract: Herein, we describe a mild and efficient two-step procedure to introduce a thiol group on aromatic substrates. First, reaction with an activated sulfoxide leads to an arylsulfonium salt intermediate. Then, two successive β-elimination-based dealkylation reactions afford the desired arylthiols in good to excellent yields.

Sulfur-containing molecules and especially arylthiols possess potent radical scavenger properties and give strong interactions with metal atoms. As such they play a key role for the regulation of redox mechanisms in biological systems.[1−4] Also, arylthiols are found in anti-HIV and anti-cancer agents.[5]

It is noteworthy that, despite these broad utility, only a few methods to introduce a thiol group on an aromatic substrate are described in the literature. However, the common strategy relies on a two-reaction scheme in which the first reaction introduces an alkylsulfanyl group via either nucleophilic or electrophilic aromatic substitution and the second, a dealkylation reaction, uncovers the free thiol.

Although aromatic nucleophilic substitution is quite easy for haloarenes bearing an electron-withdrawing group, it requires harsh conditions for nonactivated haloarenes. For instance, the substitution of halobenzenes by various thiolates is carried out by heating the reaction mixture for several hours in DMF at 100 °C (Scheme 1, path a).[6] To overcome this drawback, palladium-catalyzed versions of aryl halides[7] or aryl alcohols[8] and thiolate anions couplings were developed. Alternatively, nucleophilic processes involving reaction of thiolate with an in situ formed benzyne intermediate[9] or an aryl radical[10] are also described.

Alkylsulfanyl groups can be introduced on electron-rich aromatic compounds through an electrophilic substitution pathway. In the first step the aromatic substrate reacts with a highly electrophilic sulfonium salt, and in a second step monodealkylation is performed using sodium iodide in refluxing methanol.[11] Typically electrophilic sulfonium moieties are generated by reaction of sulfoxides with hydrochloric acid,[12] triflic acid,[13,14] triflic anhydride,[15−17] or a mixture of phosphorus pentoxide and methanesulfonic acid[18] (Scheme 1, path b).

However, although nucleophilic and electrophilic pathways allow efficient introduction of alkylsulfanyl residues on aromatic compounds, there is to our knowledge no mild procedure to convert arylsulfanyls into arylthiols. Indeed, dealkylation reactions require harsh conditions such as, for example, treatment with thiolates[10,19−22] or sodium amide[23] in DMF/HMPT at 140 °C. Other procedures involve an oxidative process followed by Pummerer rearrangement[24] or a reductive cleavage achieved with sodium metal in HMPA.[25]

We therefore focused our attention to develop a novel reagent that would allow efficient dealkylation of the alkylsulfanyl intermediate under mild conditions. In our procedure the sulfur is introduced via an electrophilic sulfonium moiety. The removal of the two alkyl residues is advantageously achieved by β-elimination reactions. 3-(2-Methoxycarbonyl-ethanesulfinyl)-propionic acid methyl ester **1b** is synthesized and used to generate various bis(2-methoxycarbonyl-ethyl)-arylsulfonium salts **2** under reaction conditions inspired from literature reports (Scheme 2).[15]

This highly reactive sulfonium salt **1c** undergoes substitution reaction with aromatic substrates to afford the corresponding arylsulfonium salts **2**. Eventually, the desired arylthiols are unmasked by two consecutive β-elimination reactions.

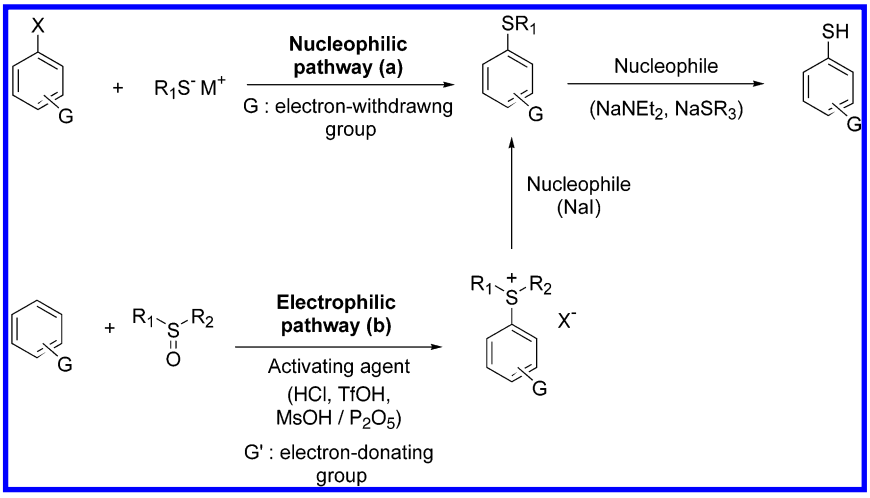
Compound **1b** was generated according to procedures described in the literature, from methyl acrylate and

* To whom correspondence should be addressed. Tel: 33-3-90-24-42-95. Fax: 33-3-90-24-43-06.

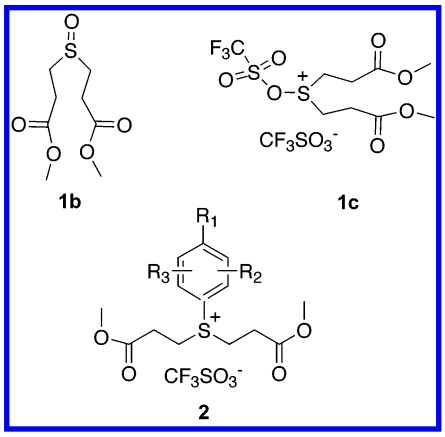
(1) Devasagayam, T. P.; Sundquist, A. R.; Di Mascio, P.; Kaiser, S.; Sies, H. *J. Photochem. Photobiol.* **1991**, 105.
(2) Motohashi, N.; Mori, I. *J. Inorg. Biochem.* **1986**, *26*, 205.
(3) Lindstad, R. I.; McKinley-McKee, J. S. *Eur. J. Biochem.* **1996**, *241*, 142.
(4) Karyakin, A. A.; Presnova, G. V.; Rubtsova, M. Y.; Egorov, A. M. *Anal. Chem.* **2000**, *72*, 3805.
(5) Mahmood, N.; Jhaumeer-Lauloo, S.; Sampson, J.; Houghton, P. J. *J. Pharm. Pharmacol.* **1998**, *50*, 1339.
(6) Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751.
(7) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-I.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.
(8) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606.
(9) Bates, R. B.; Janda, K. D. *J. Org. Chem.* **1982**, *47*, 4374.
(10) Beugelmans, R.; Bois-Choussy, M.; Boudet, B. *Tetrahedron* **1983**, *39*, 4153.
(11) Goethals, E.; Radzitzky, P. *Bull. Soc. Chim. Belg.* **1964**, *73*, 546.
(12) Hocker, J.; Ley, K.; Merten, R. *Synthesis* **1975**, 334.
(13) Olah, G. A.; Marinez, E. R.; Surya Prakash, G. K. *Synlett* **1999**, 1397.
(14) Yamamoto, K.; Miyatake, K.; Nishimura, Y.; Tsuchida, E. *Chem. Commun.* **1996**, 2099.
(15) Nenajdenko, V. G.; Vertelezkij, P. V.; Balenkova, E. S. *Sulfur Lett.* **1996**, *20*, 75.
(16) Nenajdenko, V. G.; Vertelezkij, P. V.; Gridnev, I. D.; Shevchenko, N. E.; Balenkova, E. S. *Tetrahedron Lett.* **1997**, 8173.
(17) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961.
(18) Akhtar, S. R.; Crivello, J. V.; Lee, J. L. *J. Org. Chem.* **1990**, *55*, 4222.
(19) Pinchart, A.; Dallaire, C.; Van Bierbeek, A.; Gingras, M. *Tetrahedron Lett.* **1999**, *40*, 5479.
(20) Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 543.
(21) Van Bierbeek, A.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 6283.
(22) Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1980**, *45*, 4376.
(23) Cabiddu, S.; Melis, S.; Piras, P. P.; Sotgiu, F. *Synthesis* **1982**, 583.
(24) Young, R. N.; Gauthier, J. Y.; Coombs, W. *Tetrahedron Lett.* **1984**, *25*, 1753.
(25) Testaferri, L.; Tiecco, M.; Tingoli, D.; Chianelli, D.; Montanucci, M. *Tetrahedron* **1982**, *38*, 3687.

10.1021/jo034013h CCC: $25.00
Published on Web 06/06/2003

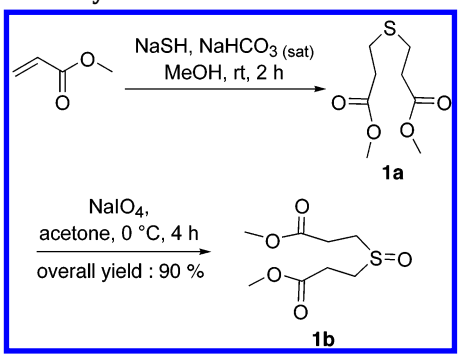
SCHEME 1. Synthesis of Arylthiols via Nucleophilic or Electrophilic Aromatic Substitution Pathways



SCHEME 2. Reagent and Intermediates Involved in the Electrophilic Substitution Process



SCHEME 3. Synthesis of 1b

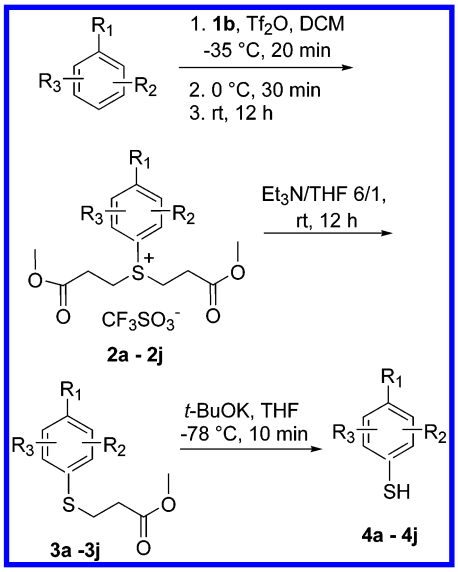


sodium thiolate[26] followed by sodium periodate oxidation of the sulfanyl **1a**, in 90% overall yield (Scheme 3).

The intermediate **1c** is generated by addition of triflic anhydride to a solution of **1b** in DCM, at −35 °C. Noteworthy, **1c** proved to be quite unstable at room temperature. It is thus better to generate **1c** in situ just before engaging it into the electrophilic aromatic substitution. In a first study, anisole was used as model substrate to optimize condensation and dealkylation reaction conditions.

(26) Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. *J. Org. Chem.* **1995**, *60*, 1665.

SCHEME 4. Two-Step Synthesis of Arylthiols via an Electrophilic Aromatic Substitution Reaction Followed by *β*-Elimination Reactions



Arylsulfonium salt **2a** is cleanly and quantitatively formed by adding dropwise a slight excess of triflic anhydride to a solution of **1b** and anisole in DCM at −35 °C over 20 min. The reaction mixture is then stirred at 0 °C for 30 min and at room temperature for 12 h (Scheme 4). According to ^{1}H NMR analysis, the crude reaction mixture contains >90% **2a**. Despite several attempts, we did not succeed in crystallizing **2a**. We thus decided to treat directly the crude reaction mixture under basic conditions in order to achieve the dealkylation reaction. Treatment of the crude **2a** with a THF/Et_3N mixture (1/6 v/v), at room temperature overnight, yielded **3a** quantitatively (Scheme 4).

Interestingly, none of the mild basic conditions tested allowed direct bis-dealkylation leading to **4a**. For instance, heating **2a** in the presence of various bases or acids, i.e., 1/6 THF/Et_3N, DIEA, BF_3·OEt_2, TFA/DCM, HCl_{aq}, did not yield any arylthiol. Only **3a** or the starting material were recovered.

The conversion of **3a** to the corresponding arylthiol **4a** required stronger basic conditions. It was found that the

TABLE 1. Synthesis of Arylthiols via Electrophilic Aromatic Substitution Reaction Followed by *β*-Elimination Reactions

entry	R_1	R_2	R_3	**3**[a]	**4**[a]	*ortho*/*para*[b]
1	-OMe	H	H	**3a** (95%)	**4a** (97%)	50/50
2	-Me	H	H	**3b** (91%)	**4b** (90%)	45/55
3	-OPh	H	H	**3c** (70%)	**4c** (96%)	18/82
4	NMe_2	H	H	**3d** (53%)	**4d** (94%)	0/100
5	1-OMe	3-OMe	H	**3e** (91%)	**4e** (95%)	0/100
6	1-OMe	2-OMe	H	**3f** (93%)	**4f** (97%)	0/100
7	1-Me	4-Me	H	**3g** (91%)	**4g** (96%)	
8	1-Me	3-Me	5-Me	**3h** (65%)	**4h** (71%)	
9[c]	H	H	H	**3i** (80%)	**4i** (90%)	
10	1-OMe	4-Br	H	**3j** (87%)	**4j** (93%)	
11	Br	H	H	no reaction		

[a] Yields given after purification of the crude reaction mixture by silica gel chromatography. [b] Relative proportion of the isomers as determined by ^{1}H NMR analysis of the crude mixture. [c] Benzene is used in large excess.

second *β*-elimination reaction proceeds very smoothly when using a 1 M solution of *t*-BuOK in THF at −78 °C (Scheme 4). After 10 min reaction, **4a** was isolated in an excellent 97% yield. For experimental convenience, we tested non-anhydrous conditions. For this purpose, **3a** was reacted at room temperature with several inorganic bases, using non-anhydrous ether as solvent. Under these conditions, solid *t*-BuOK afforded the desired thiol in more than 80% yield. Other bases such as $NaNH_2$ or $CaCO_3$ gave no reaction and only the starting material was recovered. Noteworthy, the direct conversion of **2a** to **4a** using a 1 M solution of *t*-BuOK in THF gave a lower yield (<60%).

Under the optimized reaction conditions, several aromatic substrates were reacted with **1b**. The resulting arylsulfonium salts **2** were transformed to the corresponding arylsulfanyls **3**, which were in turn converted to the corresponding arylthiols **4**. Obtained results are summarized in Table 1.

For electron-rich aromatic compounds such as anisole (entry 1) or toluene (entry 2), the adducts **3** are obtained in excellent yields as equimolar mixtures of *ortho* and *para* isomers. The sterically more hindered diphenyloxide (entry 3) yields the expected product as a 82:18 mixture of the *para* and *ortho* isomers. Interestingly, in the cases of *N*,*N*-dimethylaniline (entry 4), 1,3-dimethoxybenzene (entry 5), and 1,2-dimethoxybenzene (entry 6) only one isomer is isolated in good to excellent yields. 1,4-Dimethylbenzene (entry 7) and 1,3,5-trimethylbenzene (entry 8) give the expected **3** in good yields. For less activated aromatic compounds such as benzene (entry 9), the desired **3** is isolated in a 80% yield if benzene is used in large excess. 4-Bromoanisole (entry 10) yields the corresponding **3**, in 87% yield. On the other hand, bromobenzene gives no reaction and only the starting material is recovered. Eventually, the reaction leading to the corresponding arylthiols **4** worked very well in every case. It is to be noted that in each case some traces (<5%) of the corresponding disulfides are obtained as byproduct.

Interestingly, the methylpropionate chain appears as a valuable thiol protecting group that is stable in acidic and basic media and cleanly removed upon treatment with strong bases. It supplements the arsenal of existing thiol protecting groups developed for amino acid[27] and alkanethiol[28] chemistry.

In this paper, we have developed a facile high-yielding mild procedure to introduce a thiol function on an aromatic derivative. In a first step, an arylsulfanyl intermediate is prepared via electrophilic substitution using 3-(2-methoxycarbonyl-ethanesulfinyl)-propionic acid methyl ester and triflic anhydride. As with other electrophilic aromatic substitutions the regioselectivity of the reaction is governed by classical stereoelectronic effect. In a second step the thiol function is unmasked by simple treatment with *t*-BuOK in THF.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded using a 200 MHz or a 300 MHz instrument in $CDCl_3$. Chemical shifts are reported in parts per million (*δ*) downfield from TMS. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), and m (multiplet). IR absorbances are reported in reciprocal centimeters (cm^{-1}). The mass spectra were recorded on a Finnigan-Mat 4600 mass spectrometer by the ionization technique using ammonia gas. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Dichloromethane (DCM) was distilled with $CaCl_2$. All syntheses using our methodology were performed in dry glassware and under an atmosphere of argon. Compounds **4a**, **4b**, **4f**, **4g**, and **4i** are commercially available.

3-(2-Methoxycarbonyl-ethanesulfinyl)-propionic Acid Methyl Ester 1b. A solution containing **1a**[22] (9.90 g, 47.8 mmol) and $NaIO_4$ (11.12 g, 47.8 mmol) in a mixture of acetone (75 mL) and water (75 mL) is stirred at 0 °C for 2 h and then warmed to room temperature during 3 h. Acetone is evaporated under vacuum. The aqueous phase is extracted with DCM (3 × 100 mL). The organic phases are collected, dried over $MgSO_4$, and concentrated under vacuum to yield **1b** as a white solid in 90% yield (9.56 g, 43.0 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 2.96 (m, 8H), 3.74 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 26.8, 47.1, 52.2, 171.6. IR ($CHCl_3$): 2998, 2951, 1739, 1439, 1362, 1238, 1171, 1024 cm^{-1}. MS: $[M + NH_4]^+$ 240. Anal. Calcd for $C_8H_{14}O_5S$: C, 43.23; H, 6.35; O, 35.99. Found: C, 43.09; H, 6.37; O, 36.04.

Typical Procedure for Synthesis of Aryl-Sulfanyl-Propionic Acid Methyl Esters 3a−3h and 3j. To a solution of the aromatic compound (1.0 mmol) and **1b** (290 mg, 1.3 mmol) in DCM (5.5 mL) is added dropwise at −40 °C triflic anhydride (0.25 mL, 1.5 mmol). The reaction mixture is stirred at −35 °C for 20 min and warmed to 0 °C for 30 min and eventually to room temperature for 12 h. The solvent is removed under reduced pressure, and the crude **2** is dried under vacuum for 1 h. Compound **2** is reacted in a mixture of Et_3N (6 mL) and THF (1 mL) at room temperature for 12 h. The solvents are concentrated under reduced pressure. The crude reaction mixture is dried under vacuum and filtered on silica gel to yield the corresponding **3**.

3-(4-*N*,*N*-Dimethylaminophenyl)-sulfanyl-propionic Acid Methyl Ester 3d. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.57 (t, 2H, *J* = 7.2 Hz), 2.96 (s, 6H), 2.99 (t, 2H, *J* = 7.2 Hz), 3.67 (s, 3H), 6.66 (d, 2H, *J* = 8.7 Hz), 7.34 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 31.7, 34.4, 40.3, 51.6, 112.7, 119.2, 134.8, 150.2, 172.4. IR ($CHCl_3$): 3080, 2946, 1739, 1594, 1507, 1437, 1352, 1243, 1192, 1168, 817. MS: $[M + NH_4]^+$ 257. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; O, 13.37. Found: C, 59.98; H, 7.18; O, 13.40.

3-(2,4-Dimethoxyphenyl)-sulfanyl-propionic Acid Methyl Ester 3e. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.55 (t, 2H, *J* = 7.2 Hz), 3.03 (t, 2H, *J* = 7.2 Hz), 3.66 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 6.44 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 28.8, 34.3, 51.5, 55.2, 55.6, 98.9, 104.6, 112.7, 135.4, 160.1, 161.1,

(27) Sheehan, J. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1158.
(28) Zervas, L.; Photaki, I.; Ghelis, N. *J. Am. Chem. Soc.* **1963**, *85*, 1337.

172.2. IR ($CHCl_3$): 3002, 2946, 1734, 1493, 1594, 1486, 1210, 905, 734 cm^{-1}. MS: $[M + NH_4]^+$ 274. Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29; O, 24.96. Found: C, 56.41; H, 6.30; O, 24.91.

3-(3,4-Dimethoxyphenyl)-sulfanyl-propionic Acid Methyl Ester 3f. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.60 (t, 2H, $J = 7.2$ Hz), 3.08 (t, 2H, $J = 7.2$ Hz), 3.69 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.82 (d, 1H, $J = 8.4$ Hz), 7.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8, 34.2, 51.5, 55.8, 111.4, 115.5, 125.0, 125.3, 148.7, 148.9, 172.0. IR ($CHCl_3$): 3008, 2956, 1734, 1584, 1504, 1254, 910, 734 cm^{-1}. M.S: $[M + NH_4]^+$ 274. Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29; O, 24.96. Found: C, 56.14; H, 6.30; O, 24.99.

3-(2,5-Dimethylphenyl)-sulfanyl-propionic Acid Methyl Ester 3g. Colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.35 (s, 3H), 2.65 (t, 2H, $J = 7.3$ Hz), 3.14 (t, 2H, $J = 7.3$ Hz), 3.70 (s, 3H), 6.94 (d, 1H, $J = 7.6$ Hz), 7.07 (d, 1H, $J = 7.6$ Hz), 7.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 20.8, 28.2, 34.0, 51.6, 127.2, 129.9, 130.0, 133.9, 135.2, 135.9, 172.1. IR ($CHCl_3$): 3018, 2950, 1739, 1602, 1486, 1434, 1357, 1248, 1171, 812 cm^{-1}. MS: $[M + NH_4]^+$ 242. Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.25; H, 7.19; O, 14.26. Found: C, 64.44; H, 7.17; O, 14.30.

3-(2,4,6-Trimethylphenyl)-sulfanyl-propionic Acid Methyl Ester 3h. Colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.50 (s, 6H), 2.51 (t, 2H, $J = 7.1$ Hz), 2.90 (t, 2H, $J = 7.1$ Hz), 3.65 (s, 3H), 6.94 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 29.9, 34.4, 51.2, 128.8, 128.9, 138.1, 142.9, 172.2. IR ($CHCl_3$): 3016, 2951, 1739, 1602, 1437, 1357, 1243, 1173, 853 cm^{-1}. MS: $[M + NH_4]^+$ 256. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; O, 13.42. Found: C, 65.74; H, 7.59; O, 13.39.

3-(5-Bromo-2-methoxyphenyl)-sulfanyl-propionic Acid Methyl Ester 3j. White solid. ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (t, 2H, $J = 7.5$ Hz), 3.15 (t, 2H, $J = 7.5$ Hz), 3.70 (s, 3H), 3.88 (s, 3H), 6.73 (d, 1H, $J = 8.1$ Hz), 7.30 (dd, 1H, $J = 8.1$, 2.5 Hz), 7.38 (d, 1H, $J = 2.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.0, 33.8, 52.0, 56.0, 111.0, 112.9, 125.9, 130.1, 132.1, 157.1, 169.2. IR ($CHCl_3$): 3075, 2946, 1731, 1571, 1473, 1434, 1370, 1246, 1173, 1075, 1026, 814 cm^{-1}. MS: $[M + NH_4]^+$ 323. Anal. Calcd for $C_{11}H_{13}O_3BrS$: C, 43.29; H, 4.29; O, 15.72. Found: C, 43.13; H, 4.28; O, 15.68.

3-Phenyl-sulfanyl-propionic Acid Methyl Ester 3i. To a solution of **1b** (290 mg, 1.3 mmol) in DCM (5.5 mL) and benzene (1 mL) is added dropwise at −40 °C triflic anhydride (0.25 mL, 1.5 mmol). The reaction mixture is stirred at −35 °C for 30 min and warmed to 0 °C for 30 min and eventually to room temperature for 12 h. The solvent is removed under reduced pressure, and the crude **2i** is dried under vacuum for 1 h and is then reacted in a mixture of Et_3N (6 mL) and THF (1 mL) at room temperature for 12 h. The solvents are evaporated under vacuum. The crude reaction mixture is dried under reduced pressure and filtered on silica gel to yield the corresponding **3i** as a colorless oil in 80% yield (204 mg, 1.04 mmol). ^1H NMR (200 MHz, $CDCl_3$): δ 2.67 (t, 2H, $J = 7.3$ Hz), 3.21 (t, 2H, $J = 7.3$ Hz), 3.72 (s, 3H), 7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.0, 34.2, 51.2, 126.5, 129.0, 130.1, 135.2, 172.1. IR ($CHCl_3$): 3051, 2986, 1736, 1586, 1436, 1491, 1266, 741 cm^{-1}. MS: $[M + NH_4]^+$ 214. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; O, 16.30. Found: C, 61.01; H, 6.18; O, 16.34.

Typical Procedure for Synthesis of Arylthiols 4a−4d and 4g−4j. A 1 M solution of *t*-BuOK in THF (5.5 mL, 4.0 mmol) is added dropwise at −78 °C to a solution of **3** (1.0 mmol) in THF (4.5 mL). The reaction mixture is stirred at −78 °C for 10 min, quenched by addition of 1 N HCl (1 mL), and concentrated under vacuum. The crude reaction mixture is then washed with 1 N HCl (2 mL), and the aqueous phase is extracted with AcOEt (3 × 10 mL). The organic phases are dried under $MgSO_4$, filtered, concentrated under reduced pressure, and dried under vacuum. The crude **4** is purified by filtration on silica gel.

4-Thio-(*N*,*N*-dimethyl)-benzene 4d. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, 6H), 6.62 (d, 2H, $J = 8.7$ Hz), 7.35 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.3, 112.5, 123.3, 134.1, 150.6. IR ($CHCl_3$): 3070, 2920, 1589, 1504, 1445, 1359, 1225, 1194, 1096, 949, 907, 814, 734 cm^{-1}. MS: $[M + NH_4]^+$ 171. Anal. Calcd for $C_8H_{11}NS$: C, 62.70; H, 7.23. Found: C, 62.92; H, 7.21.

4-Methoxy-3-thio-bromobenzene 4j. Colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 3.86 (s, 1H), 3.88 (s, 3H), 6.71 (d, 1H, $J = 8.8$ Hz), 7.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 111.8, 112.8, 123.1, 128.7, 131.1, 153.8. IR ($CHCl_3$): 3003, 2930, 1576, 1478, 1460, 1439, 1375, 1292, 1248, 1080, 913, 729 cm^{-1}. MS: $[M + NH_4]^+$ 237. Anal. Calcd for C_7H_7BrOS: C, 38.37; H, 3.22; O, 7.30. Found: C, 38.26; H, 3.21; O, 7.32.

Typical Procedure for Synthesis of 4e and 4f. A 1 M solution of *t*-BuOK in THF (1.65 mL, 1.2 mmol) is added dropwise at −78 °C to a solution of **4e** and **4f** (1.0 mmol) in THF (4.5 mL). The reaction mixture is stirred at −78 °C for 10 min, quenched by addition of 1 N HCl (1 mL), and concentrated under vacuum. The crude reaction mixture is then washed with 1 N HCl (2 mL), and the aqueous phase is extracted with AcOEt (3 × 10 mL). The organic phases are dried under $MgSO_4$, filtered, concentrated under reduced pressure, and dried under vacuum. The crude **4** is purified by filtration on silica gel.

2,4-Dimethoxy-thiophenol 4e. Colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ 3.55 (s, 1H), 3.80 (s, 3H), 3.88 (s, 3H), 6.46 (m, 2H), 7.19 (d, 1H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.8, 98.9, 104.9, 130.6, 133.4, 159.2, 161.4. IR ($CHCl_3$): 3008, 2930, 1597, 1579, 1489, 1463, 1435, 1308, 1210, 1166, 1031, 907, 734 cm^{-1}. MS: $[M + NH_4]^+$ 188. Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; O, 18.79. Found: C, 56.32; H, 5.94; O, 18.83.

3,4-Dimethoxy-thiophenol 4f. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 3.42 (s, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 6.76 (d, 1H, $J = 7,9$ Hz), 6,86 (d, 1H, $J = 1,9$ Hz), 6,91 (dd, 1H, $J = 7,9$ Hz, 1,9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7, 55.8, 111.2, 113.9, 123.3, 128.5, 149.0, 149.4. IR ($CHCl_3$): 2998, 2930, 1582, 1501, 1463, 1442, 1398, 1323, 1254, 1225, 1181, 1137, 1024, 874, 799, 763 cm^{-1}. MS: $[M + NH_4]^+$ 188. Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; O, 18.79. Found: C, 56.54; H, 5.90; O, 18.76.

2,5-Dimethyl-thiophenol 4g. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.30 (s, 3H), 3.24 (s, 1H), 7.08 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 20.5, 128.3, 129.9, 130.1, 130.9, 134.6, 136.2. IR ($CHCl_3$): 3018, 2921, 1600, 1562, 1468, 1435, 907, 732 cm^{-1}. MS: $[M + NH_4]^+$ 156. Anal. Calcd for $C_8H_{10}S$: C, 69.51; H, 7.29. Found: C, 69.73; H, 7.31.

2,4,6-Trimethyl-thiophenol 4h. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.36 (s, 6H), 3.13 (s, 1H), 6.90 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 22.0, 127.0, 128.8, 134.7, 136.2. IR ($CHCl_3$): 3023, 2920, 1600, 1561, 1468, 1439, 1372, 1062, 907, 732 cm^{-1}. MS: $[M + NH_4]^+$ 170. Anal. Calcd for $C_9H_{12}S$: C, 70.99; H, 7.94. Found: C, 71.17; H, 7.97.

Acknowledgment. We thank the Ministère de la Recherche et de l'Enseignement for financial support of this work through a MENRT grant to J.-M. Becht.

JO034013H