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

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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 arylsulfoxonium 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 thiols 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 halides7 or aryl alcohols8 and thiolate anions couplings were developed. Alternatively, nucleophilic processes involving reaction of thiolate with an in situ formed benzene intermediate9 or an aryl radical10 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 sulfonyl halide salt, and in a second step monodealkylation is performed using sodium iodide in refluxing methanol.11 Typically electrophilic sulfonyl moieties are generated by reaction of sulfones with hydrochloric acid,12 triflic acid,13,14 triflic anhydride,15–17 or a mixture of phosphorus pentoxide and methanesulfonic acid18 (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 arylsulfonils into arylthiols. Indeed, dealkylation reactions require harsh conditions such as, for example, treatment with thiolates10,19–22 or sodium amide23 in DMF/HMPA at 140 °C. Other procedures involve an oxidative process followed by Pummerer rearrangement24 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 sulfonylum moiety. The removal of the two alkyl residues is advantageously achieved by β-elimination reactions. 3-(2-Methoxycarbonyl-ethanesulfinyl)-proionic acid methy ester 1b is synthesized and used to generate various bis(2-methoxycarbonyl-ethyl)-aryl sulfonium 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

sodium thiolate\textsuperscript{26} followed by sodium periodate oxidation of the sulfanyl \textit{1a}, in 90\% overall yield (Scheme 3).

The intermediate \textit{1c} is generated by addition of triflic anhydride to a solution of \textit{1b} in DCM, at $-35^\circ$C. Noteworthy, \textit{1c} proved to be quite unstable at room temperature. It is thus better to generate \textit{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.

\[ \text{Arylsulfonium salt } 2a \text{ is cleanly and quantitatively formed by adding dropwise a slight excess of triflic anhydride to a solution of } 1b \text{ and anisole in DCM at } -35^\circ \text{C over 20 min. The reaction mixture is then stirred at } 0^\circ \text{C for 30 min and at room temperature for 12 h (Scheme 4). According to } ^1\text{H NMR analysis, the crude reaction mixture contains } \geq 90\% \text{ } 2a. \text{ Despite several attempts, we did not succeed in crystallizing } 2a. \text{ 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 \text{ with a THF/Et}_3\text{N mixture (1/6 v/v), at room temperature overnight, yielded } 3a \text{ quantitatively (Scheme 4).}

Interestingly, none of the mild basic conditions tested allowed direct bis-dealkylation leading to \textit{4a}. For instance, heating \textit{2a} in the presence of various bases or acids, i.e., 1/6 THF/Et$_3$N, DIPEA, BF$_3$â€‘OEt$_2$, TFA/DCM, HCl$_{aq}$, did not yield any arylthiol. Only \textit{3a} or the starting material were recovered.

The conversion of \textit{3a} to the corresponding arylthiol \textit{4a} required stronger basic conditions. It was found that the

The optimized reaction conditions, several aromatic substrates were reacted with 1b. The resulting arylsulfonium salts 2 were transformed to the corresponding arylsulfanyl 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 diphenyl ether (entry 3) yields the expected product as a 5:1 mixture of the para and ortho isomers. Interestingly, in the cases of N,N-dimethylaniline (entry 4), 1,3-dimethoxybenzene (entry 5), and 2,4-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 83% yield if benzene is used in large excess. 4-Bromoanisole (entry 10) yields the corresponding disulfides are obtained as byproduct.

**Experimental Section**

**General Methods.** \(^1H\) and \(^13C\) NMR spectra were recorded using a 200 MHz or a 300 MHz instrument in \(CDCl_3\). Chemical shifts are reported in parts per million (ppm) 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.

**Typical Procedure for Synthesis of Aryl-Sulfanyl-Proionic Acid Methyl Ester 3a-3h and 3j.** To a solution of the aromatic compound (1.0 mmol) and NaOtBu (11.12 g, 47.8 mmol) in a mixture of 5% (75 mL) and water (75 mL) is stirred at 0 °C for 2 h and then warmed to room temperature for 3 h. Acetone is evaporated under vacuum. The aqueous phase is extracted with DCM (3 x 100 mL). The organic phases are collected, dried over MgSO\(_4\), and concentrated under vacuum to yield 4a using our methodology were performed in dry glassware and under an atmosphere of argon. Compounds 4a, 4b, 4f, 4g, and 4i are commercially available.
1H NMR (300 MHz, CDCl 3): δ 2.67 (t, 2H, J = 7.3 Hz), 3.21 (t, 2H, J = 7.3 Hz), 3.72 (s, 3H). 13C 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, 1421, 1266, 741 cm⁻¹. MS: [M + NH₄]⁺ 214. Anal. Calcld for C₂₃H₂₅O₅S: C, 61.20; H, 6.16; O, 16.30. Found: C, 61.01; H, 6.18; O, 16.34.

Typical Procedure for Synthesis of Aryliothiones 4a--4d and 4g--4j. 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 under vacuum. The crude mixture is then washed with 1 N HCl (2 mL), and the aqueous phase is extracted with AcOEt and concentrated under reduced pressure, and dried under vacuum.

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). 13C NMR (75 MHz, CDCl 3): δ 40.3, 112.5, 123.3, 134.1, 135.0, 150.6. IR (CHCl 3): 3070, 2920, 1594, 1544, 1359, 1225, 1194, 1096, 949, 907, 814, 734 cm⁻¹. MS: [M + NH₄]⁺ 171. Anal. Calcld for C₂₀H₁₈NS: C, 62.70; H, 7.23. Found: C, 62.63; 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). 13C 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, 1349, 1375, 1292, 1248, 1080, 913, 729 cm⁻¹. MS: [M + NH₄]⁺ 237. Anal. Calcld for C₁₂H₁₄BrO: 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 under vacuum. The crude 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 MgSO₄, concentrated under reduced pressure, and dried under vacuum. The crude 4 is purified through filtration on silica gel.

2,4-Dimethoxy-thiophenol 4e. Colorless oil. 1H NMR (200 MHz, CDCl 3): δ 3.55 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 6.46 (m, 2H), 7.19 (d, 1H, J = 8.3 Hz). 13C 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): 3062.92; H, 1597, 1579, 1498, 1463, 1435, 1308, 1210, 1166, 1031, 907, 734 cm⁻¹. MS: [M + NH₄]⁺ 188. Anal. Calcld for C₁₀H₁₀O₂S: 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, 2H, J = 19.2 Hz), 6.91 (dd, 1H, J = 17.9 Hz, 1.9 Hz). 13C 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): 2988, 2930, 1582, 1501, 1463, 1442, 1398, 1323, 1254, 1225, 1181, 1137, 1024, 874, 799, 763 cm⁻¹. MS: [M + NH₄]⁺ 188. Anal. Calcld for C₁₀H₁₀O₂S: 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). 13C 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 + NH₄]⁺ 156. Anal. Calcld for C₁₀H₁₁S: 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, 3H), 3.13 (s, 1H), 6.90 (s, 2H). 13C 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 + NH₄]⁺ 170. Anal. Calcld for C₁₀H₁₂S: C, 70.99; H, 7.94. Found: C, 71.17; H, 7.97.

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