

Supporting Information for:

**Azo Group-assisted Nucleophilic Aromatic Substitutions in Haloarene  
Derivatives: Preparation of Substituted 1-Iodo-2,6-bispropylthiobenzenes**

Jason, T. Manka,<sup>§</sup> Virginia C. McKenzie, and Piotr Kaszynski\*

*Organic Materials Research Group*

Chemistry Department, Vanderbilt University

Nashville, TN 37235

## Experimental Section

Melting points were determined in open capillaries and are uncorrected.  $^1\text{H}$  NMR spectra were measured at either 300 or 400 MHz, and  $^{13}\text{C}$  NMR were measured at 75 MHz in  $\text{CDCl}_3$  and referenced to solvent.  $^{19}\text{F}$  NMR were obtained at 282 MHz in  $\text{CDCl}_3$  and referenced to  $\text{CFCl}_3$ . IR spectra of neat liquid or microcrystalline samples were recorded on AgCl plates, unless otherwise noted. Mass spectrometry data were acquired using a GC/MS instrument in EI mode. All reagents were used as received except as noted. DMSO was distilled from  $\text{CaH}_2$  and stored over molecular sieves.

**1,5-Dichloro-3-iodo-2,4-bis(propylthio)benzene (1c).** It was obtained in 62% yield as a colorless oil from amine **2c** (1.22 g, 3.9 mmol) in an analogous way to the procedure used to prepare iodide **1d**. In the diazotization step, propionic acid was substituted for AcOH.  $^1\text{H}$  NMR  $\delta$  1.02 (t,  $J = 7.4$  Hz, 6H), 1.62 (sextet,  $J = 7.2$  Hz, 4H), 2.89, (t,  $J = 7.2$  Hz, 4H), 7.61 (s, 1H);  $^{13}\text{C}$  NMR  $\delta$  13.5, 22.7, 38.7, 128.5, 130.4, 139.0, 139.6; EI-MS,  $m/z$  424, 422, 420 (M, 16:73:100); HRMS (FAB+) calcd for  $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{IS}_2$ : 419.9037. Found: 419.9016. Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{IS}_2$ : C, 34.22; H, 3.59. Found: C, 34.96; H, 3.59.

**3,5-Dichloro-2,6-bis(propylthio)aniline (2c).** Crude azo compound **13c** (7.5 g, 18.8 mmol) was reduced and purified as described for the preparation of compound **2d** to give 5.39 g (89% yield from **12c**) of an off-white solid: mp 36-37 °C;  $^1\text{H}$  NMR  $\delta$  0.98 (t,  $J = 7.3$  Hz, 6H), 1.57 (sextet,  $J = 7.3$  Hz, 4H), 2.72 (t,  $J = 7.3$  Hz, 4H), 5.74 (br. s, 2H), 6.92 (s, 1H);  $^{13}\text{C}$  NMR  $\delta$  13.5, 23.1, 36.6, 114.4, 118.5, 141.6, 154.2; IR (KBr) 3452 and 3343 (N-H)  $\text{cm}^{-1}$ ; EI-MS  $m/z$  313, 311, 309 (M, 8:11:36), 225 (100). Anal. Calcd for  $\text{C}_{12}\text{H}_{17}\text{Cl}_2\text{NS}_2$ : C, 46.45; H, 5.52; N, 4.51. Found: C, 46.65; H, 5.55; N, 4.64.

**3,5-Dichloro-4-nitrobenzoic Acid<sup>1</sup> (3, R = COOH).** A mixture of 4-amino-3,5-dichlorobenzoic acid (10.0 g, 48.5 mmol), AcOH (200 mL), 30%  $\text{H}_2\text{O}_2$  (85 mL) and conc.  $\text{H}_2\text{SO}_4$  (4 mL) was heated at 100 °C for 5 h with stirring. The mixture was

allowed to cool and ice water (0.5 L) was added. The yellow precipitate was filtered and dried to give crude acid **3**, R = COOH (7.14 g, 62% yield): mp 197-198 °C (lit.<sup>1</sup> mp 210-211 °C). This product was used without further purification.

**4-(2,3,5,6-Tetrachlorophenyldiazo)-*N,N*-dimethylaniline (8).** A solution of 2,3,5,6-tetrachloroaniline (5.00 g, 21.6 mmol) in AcOH was added dropwise to nitrosylsulfuric acid (23.8 mmol of NaNO<sub>2</sub>; see **1b**) at 5 °C. After stirring for 1.5 h, *N,N*-dimethylaniline (3.69 g, 3.50 mL, 30.3 mmol) was added and the solution was brought to a pH of ~5 with the addition of a conc. solution of NaOH. The reaction was allowed to stir overnight, the resulting precipitate was filtered, washed with brine, hot EtOH, and dried to give **8** (5.56 g, 71% yield) as a red-orange solid: mp 231-235 °C (dec.); <sup>1</sup>H NMR δ 3.13 (s, 6H), 6.75 (d, *J* = 9.2 Hz, 2H), 7.50 (s, 1H), 7.91 (d, *J* = 9.1 Hz, 2H); <sup>13</sup>C NMR δ 40.3, 111.3, 124.1, 125.8, 127.7, 132.2, 143.0, 153.7 (one signal, presumably C-N= was not found); IR (KBr) 1601 (C=C), 1144 (C-N) cm<sup>-1</sup>. Anal. Calcd for C<sub>14</sub>H<sub>11</sub>Cl<sub>4</sub>N<sub>3</sub>: C, 46.31; H, 3.05; N, 11.57. Found: C, 46.19; H, 2.99; N, 11.47.

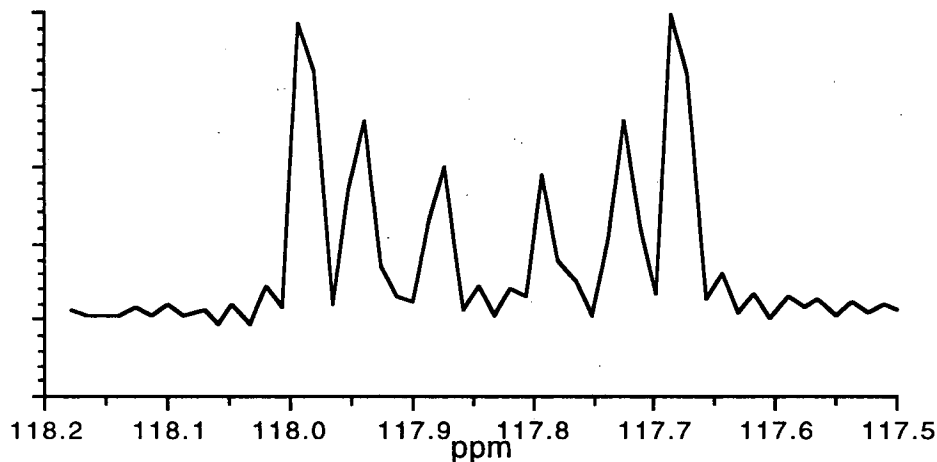
**4-(2,5-Dichloro-3,6-bis(propythio)phenyldiazo)-*N,N*-dimethylaniline (9).** A solution of azo compound **8** (300 mg, 0.83 mmol) in DMSO (15 mL) was added to a solution of 1-propanethiol (138 mg, 1.82 mmol) and NaH (73 mg, 1.82 mmol) in DMSO (5 mL), and the reaction mixture was stirred at 120 °C for 48 h. Most of the solvent was removed under reduced pressure. A fraction of the resulting crude material (60 mg) was separated by prep. TLC (benzene/CH<sub>2</sub>Cl<sub>2</sub>/hexanes, 1:2:7) and **9** was isolated as a fraction containing the dithiolated compound: mp 120-121 °C; <sup>1</sup>H NMR δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H), 1.46 (sextet, *J* = 7.3 Hz, 2H), 1.77 (sextet, *J* = 7.3 Hz, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 3.11 (s, 6H), 6.77 (d, *J* = 9.2 Hz, 2H), 7.18 (s, 1H), 7.91 (d, *J* = 9.2 Hz, 2H); <sup>13</sup>C NMR δ 13.3, 13.6, 21.7, 22.8, 34.2, 38.1, 40.3, 111.3, 121.7, 122.9, 123.8, 125.4, 138.8, 140.1, 143.0, 153.3, 156.6; IR (KBr) 1603 (C=C), 1144 (C-N) cm<sup>-1</sup>; HRMS (FAB<sup>+</sup>) *m/z* calcd for C<sub>20</sub>H<sub>26</sub>N<sub>3</sub>Cl<sub>2</sub>S<sub>2</sub>: 442.0945. Found: 442.0939.

**1,5-Dichloro-2,4-difluorobenzene<sup>2</sup> (11c).** Fresh NCS (33.38 g, 0.25 mol) was added in portions to a stirred solution of 1-chloro-2,4-difluorobenzene (29.7 g, 0.2 mol) in a mixture of trifluoroacetic acid (110 mL) and H<sub>2</sub>SO<sub>4</sub> (15 mL) at 55 °C. The mixture was allowed to stir overnight, poured into water (1.25 L), and the product extracted with hexanes. The solvent was removed and the crude product was purified by distillation (bp 166 °C, lit.<sup>2</sup> 167-168 °C) to give **11c** (28.9 g, 79% yield) as a clear colorless liquid: <sup>1</sup>H NMR δ 7.01 (t, *J* = 8.5 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H); <sup>13</sup>C NMR δ 106.0 (t, <sup>2</sup>*J*<sub>CF</sub> = 26 Hz), 117.0-117.3 (m), 131.1, 156.7 (dd, <sup>1</sup>*J*<sub>CF</sub> = 251 Hz, <sup>3</sup>*J*<sub>CF</sub> = 11 Hz); EI-MS *m/z* 186, 184, 182 (M, 13, 77, 100). Anal. Calcd for C<sub>6</sub>H<sub>2</sub>Cl<sub>2</sub>F<sub>2</sub>: C, 39.38; H, 1.10. Found: C, 39.29; H, 1.16.

**1,5-Dibromo-2,4-difluorobenzene<sup>3</sup> (11d).** A solution of bromine (22.6 g, 141 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added dropwise to a mixture 1-bromo-2,4-difluorobenzene (24.8 g, 128 mmol), electrolytic grade iron powder (2 g) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 50 °C (oil bath) over a 1.5 h period. The mixture was stirred for additional 3 h at 50 °C and poured into a 10% solution of Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (150 mL). Organic products were extracted with CH<sub>2</sub>Cl<sub>2</sub>, extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent removed. The resulting crude product was short path distilled (100 °C/ 25 Torr; lit.<sup>4</sup> bp 35-38 °C/ 2 Torr) to give **11d** (30.1 g, 86% yield) as a low melting solid: <sup>1</sup>H and <sup>13</sup>C NMR and MS spectra virtually identical to those reported.<sup>4</sup>

**1,3-Dichloro-4,6-difluoro-5-phenyldiazobenzene (12c).** 1,5-Dichloro-2,4-difluorobenzene (**11c**, 9.14 g, 50 mmol) was converted to **13c** in an analogous way used to prepare compound **12d**. Two sequential crystallizations of the crude product from MeOH gave 4.4 g (combined two crops) of an orange crystalline mixture of *trans* and *cis* isomers **12c**. The product remaining in the mother liquor was separated on a silica gel column (CH<sub>2</sub>Cl<sub>2</sub>/hexanes, 1:7) to give the total of 4.93 g of the pure *trans* (first fraction) and small amounts of the *cis* (later fraction) isomers of **12c**. The total yield of isolated isomeric mixture of **12c** was 9.32 g or 65%. *Trans* isomer: mp 85-86 °C; <sup>1</sup>H NMR δ 7.42

(t,  $J = 7.1$  Hz, 1H), 7.45-7.49 (m, 3H), 7.85-7.88 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  117.7-118.0 (m), 123.2, 129.1, 129.7, 132.6 (t,  $^2J_{\text{CF}} = 11$  Hz), 132.7, 149.8 (dd,  $^1J_{\text{CF}} = 261$  Hz,  $^3J_{\text{CF}} = 3$  Hz), 152.8; EI-MS  $m/z$  290, 288, 286 (M,3:17:25), 77 (100). Anal Calcd for  $\text{C}_{12}\text{H}_6\text{Cl}_2\text{F}_2\text{N}_2$ : C, 50.20; H, 2.11; N, 9.76. Found: C, 50.25; H, 2.02; N, 9.74. *Cis* isomer:  $^1\text{H}$  NMR  $\delta$  6.84 (d,  $J = 7.3$  Hz, 2H), 7.16-7.28 (m, 4H).



A section of  $^{13}\text{C}$  NMR spectrum of *trans* **12c**.

**1,3-Dichloro-5-phenyldiazo-4,6-bis(propylthio)benzene (13c).** An isomeric mixture of azo derivative **12c** (5.6 g, 19.5 mmol) was dithiolated in an analogous way to the preparation of compound **13d**, to give 7.5 g of a red-orange oil that was used without purification for the next step. An analytical sample was obtained by column chromatography ( $\text{CH}_2\text{Cl}_2$ /hexanes, 1:3):  $^1\text{H}$  NMR  $\delta$  0.87 (t,  $J = 7.3$  Hz, 6H), 1.46 (sextet,  $J = 7.3$  Hz, 4H), 2.66 (t,  $J = 7.3$  Hz, 4H), 7.55-7.59 (m, 4H), 7.95-8.00 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  13.1, 22.6, 37.9, 123.0, 124.4, 128.4, 129.1, 131.9, 140.5, 151.8, 163.0. Anal Calcd. for  $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_2\text{S}_2$ : C, 54.13; H, 5.05; N, 7.01. Found: C, 54.31; H, 4.95; N, 6.99.

## References

- (1) Horrom, B. W.; Lynes, T. E. *J. Med. Chem.* **1963**, *6*, 528-532.
- (2) Vorozhtsov, N. N. Jr.; Yakobson, G. G.; Krizhechkovskaya, N. I. *Khim. Nauka i Prom.* **1958**, *3*, 404-405; *Chem Abstr.* **1958**, *52*, 19987h.
- (3) Wang, Z.-X.; Duan, W.; Wiebe, L. I.; Balzarini, J.; De Clercq, E.; Knaus, E. E. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 11-40.
- (4) Nazarpack-Kandlousy, N.; Nelen, M. I.; Goral, V.; Eliseev, A. V. *J. Org. Chem.* **2002**, *67*, 59-65.