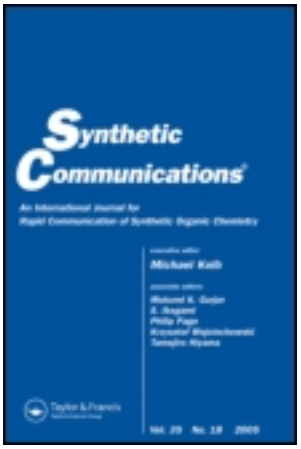

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Diaryl Disulfides via Mild Reduction of Arylsulfinates with Hydrazine Monohydrate in DMSO

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Accepted author version posted online: 07 Oct 2011.Version of record first published: 22 Dec 2011.

To cite this article: Rui-Heng Zhu & Xiao-Xin Shi (2012): Synthesis of Diaryl Disulfides via Mild Reduction of Arylsulfinates with Hydrazine Monohydrate in DMSO, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:8, 1108-1114

To link to this article: http://dx.doi.org/10.1080/00397911.2010.535947

Synthetic Communications®, 42: 1108–1114, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.535947

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SYNTHESIS OF DIARYL DISULFIDES VIA MILD REDUCTION OF ARYLSULFINATES WITH HYDRAZINE MONOHYDRATE IN DMSO

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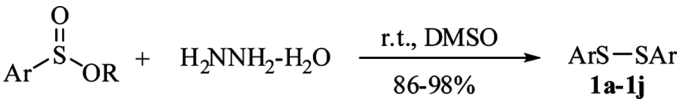
GRAPHICAL ABSTRACT



Abstract *Arylsulfinates were reduced with hydrazine monohydrate at room temperature in dimethylsulfoxide (DMSO) to afford diaryl disulfides in good yields. A dramatic solvent effect was observed, and DMSO was found to be the best solvent for the reaction.*

Keywords Arylsulfinate; disulfide; hydrazine monohydrate; reduction

INTRODUCTION

A disulfide bond (S-S bond) is an important functional group that occurs in natural products[1] and the three-dimensional structures of peptides and proteins.[2] Disulfides have exhibited many interesting biological activities[3] and have demonstrated wide applications in various aspects of material science.[4] Therefore, the synthesis of disulfides has been of considerable interest for chemists.[5]

Disulfides can usually be obtained via oxidation of mercaptans,[5b] but nobody would be glad to suffer from the notoriously unpleasant smell of mercaptans, especially in large-scale preparations. This prompted us to investigate other useful methods for large-scale preparation of disulfides. Herein, we report an efficient, mild, and general method for the synthesis of diaryl disulfides via the reduction of arylsulfinates with hydrazine monohydrate in dimethylsulfoxides (DMSO).

RESULTS AND DISCUSSION

We first attempted the reaction of methyl benzenesulfinate with hydrazine monohydrate under various conditions (Table 1). A dramatic solvent effect was

Received August 15, 2010.

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Table 1. Reaction of methyl benzenesulfinate with hydrazine monohydrate at room temperature in various solvents

Entry	Solvent	N_2H_4-H_2O (equiv.)	Time (h)	Product	Yield (%)[a]
1	DMSO	3	9	**1a**	98
2	DMSO	5	6	**1a**	98
3	DMSO	10	3	**1a**	97
4	DMF	5	15	**1a**	89
5	CH_3CN	5	15	**1a**	42[b]
6	THF	5	15	**1a**	19[b]
7	MeOH	5	15	**1a**	60[b]
8	EtOH	5	15	**1a**	53[b]
9	*i*-PrOH	5	15	**1a**	48[b]

[a]Isolated yield.
[b]35–70% of methyl benzenesulfinate was recovered.

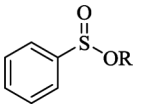
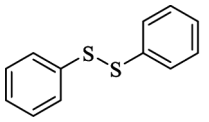
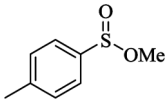
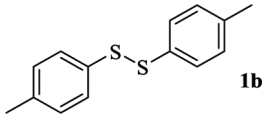
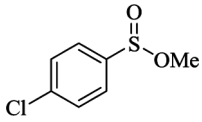
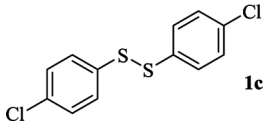
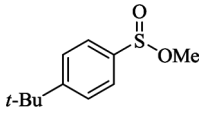
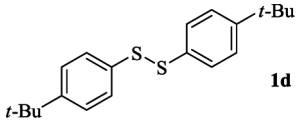
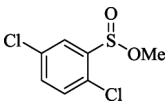
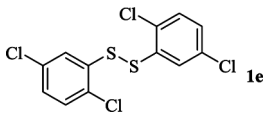
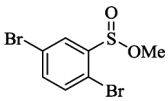
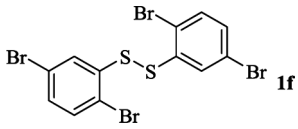
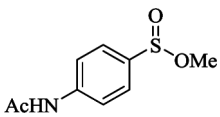
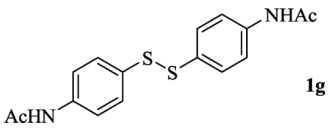
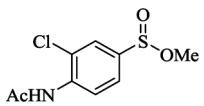
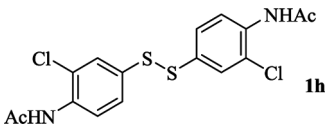
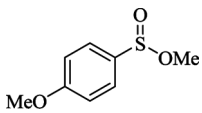
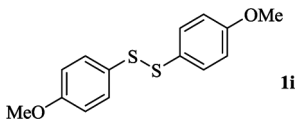
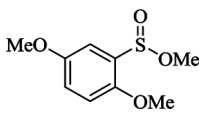
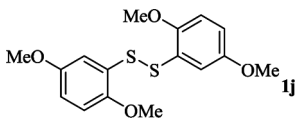
observed, although the reaction was very slow at room temperature in most solvents such as *N,N*-dimethylformamide (DMF), acetonitrile, tetrahydrofuran (THF), methanol, ethanol, and isopropanol (Table 1, entries 4–9), it was much faster in DMSO. The reduction of methyl benzenesulfinate with 3–10 molar equiv of hydrazine monohydrate in DMSO took place smoothly at room temperature to afford disulfide **1a** in nearly quantitative yields (Table 1, entries 1–3). Room temperature was crucial for good yield of the reaction, because the product disulfide **1a** would be overreduced when warmed to produce some amount of thiophenol as a by-product.[6]

The mild reduction in DMSO can be applied to various arylsulfinates. Twelve arylsulfinates as indicated in Table 2 were tested. All the tested arylsulfinates could be reduced with 1.5–10 molar equiv of hydrazine monohydrate at room temperature in DMSO to furnish diaryl disulfides **1a**–**1j** in good to excellent yields. Bulkiness of an alkyl group (R group) in a sulfinate obviously decreased the reaction rate (Table 2, entries 1–3). Electron-deficient arylsulfinates reacted fast and needed less molar equiv of hydrazine monohydrate (Table 2, entries 5, 7, and 8). In contrast, electron-rich arylsulfinates reacted much slower and needed more molar equiv of hydrazine monohydrate (Table 2, entries 6, 9, 11, and 12). Moreover, it was found that electron-withdrawing groups on the aryl ring favored the cleavage of disulfides,[6] and hence large excesses hydrazine monohydrate should be avoided (Table 2, entries 5, 7, and 8) to diminish the formation of thiophenols.

We have also tried reduction of aliphatic sulfinates under the same conditions. Unfortunately, the reaction of aliphatic sulfinates with hydrazine monohydrate in DMSO at room temperature was complicated, and the yields of corresponding dialkyl disulfides were less than 10%.

Kobayashi and Yamamoto[7] observed the reduction of sulfinates with anhydrous hydrazine to form disulfides during an attempt to prepare sulfinyl hydrazides. However, only a few examples were included in their report, so the scope and limitations were not clear yet. Moreover, reduction of sulfinates with anhydrous hydrazine were performed at 60–80 °C in their report, but the warming condition seems to be favorable for the cleavage of disulfides, especially for electron-deficient disulfides (Table 2, entries 5, 7, and 8).[6]

Table 2. Reduction of various arylsulfinates with hydrazine monohydrate at room temperature in dimethylsulfoxide

Entry	Sulfinate	N_2H_4-H_2O (equiv.)	Time (h)	Disulfide	Yield (%)[a]
				 **1a**	
1	R = Me	3	9	**1a**	98
2	R = Et	3	13	**1a**	95
3	R = *i*-Pr	8	15	**1a**	92
4		5	7	 **1b**	96
5		1.5	4	 **1c**	95
6		8	18	 **1d**	96
7		1.5	1	 **1e**	95
8		1.5	1	 **1f**	87
9		8	10	 **1g**	86
10		3	5	 **1h**	95
11		10	22	 **1i**	97
12		10	14	 **1j**	98

[a]Isolated yield.

CONCLUSION

In conclusion, a very mild reduction of arylsulfinates with hydrazine monohydrate at room temperature has been fully studied. The reaction conditions were optimized (Table 1), a dramatic solvent effect was observed, and DMSO was found to be the most appropriate solvent for the reaction. Diaryl disulfides could be obtained in good yields from the reduction of various arylsulfinates in DMSO (Table 2).

EXPERIMENTAL

All chemicals were analytically pure and were used as received from commercial suppliers. ^{1}H NMR spectra were acquired on a Bruker AM-500 instruments. Chemical shifts were given on the δ scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on Nicolet Magna IR-550 instrument. Mass spectra were recorded on a HP5989A device. Column chromatography was performed on silica gel (Qingdao Ocean Chemical Corp.).

Typical Procedure for the Reaction of Arylsulfinates with Hydrazine Monohydrate in Dimethylsulfoxide

Hydrazine monohydrate (6.02 g, 0.12 mol) was added to a solution of methyl benzenesulfinate (6.25 g, 40.01 mmol) in DMSO (40 mL). The resulting solution was then stirred at room temperature for 9 h. After the reaction was complete, water (150 mL) was added, and the aqueous solution was extracted twice with benzene (2×80 mL). Extracts were combined and dried over anhydrous $MgSO_4$. Removal of solvent under vacuum gave the crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:9) through a short silica column to afford diphenyl disulfide **1a** (4.28 g, 19.60 mmol) in 98% yield. Compounds **1b**–**1j** were obtained from the same procedure in the yields as indicated in Table 2. High-resolution ^{1}H NMR spectra showed that the purities of all compounds **1a**–**1j** were greater than 99%.

Characterization Data of Compounds 1a–1j

Compound 1a. Mp 59–60 °C, white crystals. IR (KBr film) 2925, 1947, 1864, 1575, 1475, 1436, 1296, 1072, 1022, 738, 687, 464 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.21 (t, $J = 7.5$ Hz, 2H), 7.29 (dd, $J_1 = 7.5$ Hz, $J_2 = 7.8$ Hz, 4H), 7.49 (d, $J = 7.8$ Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 127.8, 128.1, 129.7, 137.6. MS (EI) m/z (%) 218 (M^+, 100), 185 (15), 154 (14), 140 (3), 109 (36), 77 (2), 65 (7). Anal. calcd. for $C_{12}H_{10}S_2$: C, 66.01; H, 4.62. Found: C, 66.14; H, 4.55.

Compound 1b. Mp 45–46 °C, white crystals. IR (KBr film) 3020, 2915, 1894, 1633, 1488, 1398, 1377, 1182, 1117, 1077, 1014, 802, 480 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 7.10 (d, $J = 8.0$ Hz, 4H), 7.38 (d, $J = 8.0$ Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 21.7, 129.2, 130.4, 134.6, 138.0. MS (EI) m/z (%) 246 (M^+, 100), 213 (4), 182 (7), 123 (48), 91 (3), 77 (5). Anal. calcd. for $C_{14}H_{14}S_2$: C, 68.25; H, 5.73. Found: C, 68.60; H, 5.65.

Compound 1c. Mp 70–71 °C, white crystals. IR (KBr film) 3078, 1896, 1645, 1568, 1471, 1429, 1386, 1112, 1093, 1010, 816, 741, 491 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27 (d, $J = 8.5$ Hz, 4H), 7.40 (d, $J = 8.5$ Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 129.9, 130.2, 134.3, 135.8. MS (EI) m/z (%) 290 ($M^+ + 4$, 15), 288 ($M^+ + 2$, 68), 286 (M^+, 100), 222 (7), 145 (29), 143 (82), 108 (29). Anal. calcd. for $C_{12}H_8Cl_2S_2$: C, 50.18; H, 2.81. Found: C, 49.87; H, 2.60.

Compound 1d. Mp 88–89 °C, white crystals. IR (KBr film) 2964, 2902, 1905, 1590, 1486, 1397, 1266, 1114, 1010, 828, 556 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.29 (s, 18H), 7.32 (d, $J = 8.4$ Hz, 4H), 7.44 (d, $J = 8.4$ Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 31.9, 35.2, 126.8, 128.4, 134.7, 151.1. MS (EI) m/z (%) 332 ($M^+ + 2$, 6), 331 ($M^+ + 1$, 13), 330 (M^+, 62), 315 (100), 286 (6), 165 (4), 150 (18), 122 (6), 91 (3). Anal. calcd. for $C_{20}H_{26}S_2$: C, 72.67; H, 7.93. Found: C, 72.71; H, 7.84.

Compound 1e. Mp 81–82 °C, white crystals. IR (KBr film) 3050, 2975, 1565, 1446, 1417, 1375, 1241, 1140, 1091, 1031, 855, 808, 578 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.16 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.3$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 2.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 127.5, 128.9, 130.8, 131.4, 134.6, 136.5. MS (EI) m/z (%) 360 ($M^+ + 4$, 11), 358 ($M^+ + 2$, 45), 356 (M^+, 100), 354 ($M^+ - 2$, 70), 288 (19), 286 (29), 179 (36), 177 (56), 144 (20), 142 (56), 107 (8). Anal. calcd. for $C_{12}H_6Cl_4S_2$: C, 40.47; H, 1.70. Found: C, 40.42; H, 1.73.

Compound 1f. Mp 111–112 °C, white crystals. IR (KBr film) 2923, 1635, 1557, 1436, 1401, 1365, 1239, 1084, 1011, 798, 762 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.23 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 2.1$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 120.6, 123.1, 130.5, 132.1, 134.9, 138.8. MS (EI) m/z (%) 538 ($M^+ + 4$, 20), 536 ($M^+ + 2$, 68), 534 (M^+, 100), 532 ($M^+ - 2$, 65), 530 ($M^+ - 4$, 16), 376 (21), 374 (40), 372 (19), 295 (12), 267 (19), 188 (37), 186 (35), 107 (12). Anal. calcd. for $C_{12}H_6Br_4S_2$: C, 26.99; H, 1.13. Found: C, 27.35; H, 1.18.

Compound 1g. Mp 181–182 °C, white crystals. IR (KBr film) 3304, 2950, 1651, 1597, 1539, 1493, 1397, 1321, 1267, 1022, 970, 816, 742, 503 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.04 (s, 6H), 7.43 (d, $J = 8.5$ Hz, 4H), 7.59 (d, $J = 8.5$ Hz, 4H), 10.08 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 24.0, 119.7, 129.4, 130.1, 139.5, 168.5. MS (EI) m/z (%) 332 (M^+, 100), 290 (3), 167 (14), 166 (13), 125 (18), 124 (61), 80 (4). Anal. calcd. for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.96; H, 4.62; N, 8.12.

Compound 1h. Mp 189–190 °C, white crystals. IR (KBr film) 3284, 2935, 1664, 1575, 1518, 1378, 1300, 1050, 805 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.08 (s, 6H), 7.47 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.0$ Hz, 2H), 7.62 (d, $J = 2.0$ Hz, 2H), 7.77 (d, $J = 8.6$ Hz, 2H), 9.57 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 23.3, 126.5, 126.7, 127.1, 128.5, 132.5, 134.9, 168.7. MS (EI) m/z (%) 402 ($M^+ + 1$, 34), 400 ($M^+ - 1$, 47), 365 (4), 360 (8), 358 (10), 201 (9), 200 (8), 160 (33), 158 (100), 124 (11), 43 (8). Anal. calcd. for $C_{16}H_{14}Cl_2N_2O_2S_2$: C, 47.88; H, 3.52; N, 6.98. Found: C, 48.24; H, 3.31; N, 6.64.

Compound 1i. Mp 43–44 °C, white crystals. IR (KBr film) 2937, 2835, 2044, 1878, 1590, 1491, 1289, 1247, 1172, 1031, 825, 636, 625 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79 (s, 6H), 6.83 (d, $J = 8.8$ Hz, 4H), 7.40 (d, $J = 8.8$ Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 56.0, 115.2, 129.1, 133.3, 160.5. HRMS m/z calcd. for $C_{14}H_{14}O_2S_2$ (M^+) 278.0435. Found: 278.0434.

Compound 1j. Mp 69–70 °C, white crystals. IR (KBr film) 2999, 2938, 2832, 2045, 1596, 1582, 1483, 1463, 1434, 1269, 1215, 1180, 1052, 1019, 866, 798 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.69 (s, 6H), 3.84 (s, 6H), 6.69 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.9$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 2.9$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 56.3, 57.1, 112.3, 113.0, 114.1, 126.2, 151.4, 154.9. HRMS m/z calcd. for $C_{16}H_{18}O_4S_2$ (M^+) 338.0647. Found 338.0649.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (No. 20972048) and the Shanghai Educational Development Foundation (Dawn Program No. 03SG27) for financial support of this work.

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