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A very simple method for the preparation of symmetrical disulfides

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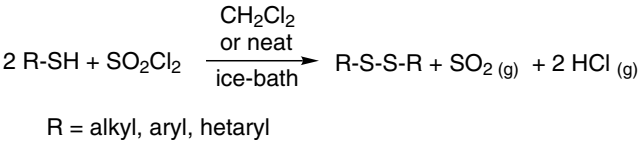
Abstract—A serendipitiously discovered, extremely simple, fast and previously unreported method for the preparation of symmetrical aliphatic, aromatic and heteroaromatic disulfides is reported. Addition of sulfuryl chloride to an alkyl- or arylthiol in a 1:2 ratio under solvent free conditions or in dichloromethane solution produces the corresponding disulfides in nearly quantitative yields with the concomitant elimination of gaseous SO_2 and 2 equiv of HCl. Thus, optimally the reaction needs no work-up at all leaving the disulfide as the sole product in excellent yield. In dichloromethane solution, the reaction is conveniently carried out in a rotary evaporator by mixing the solvent, thiol and SO_2Cl_2 in a round-bottomed flask followed by evaporation of the volatiles.

1. Introduction

Disulfides play significant roles in biological and chemical processes and serve as versatile reagents in organic synthesis.[1] Being readily available from commercial suppliers and easily synthesized, thiols serve as the most frequently employed precursors to disulfides. Consequently, the most exploited and well documented methods for disulfide preparation involve the controlled oxidation of thiols under a range of experimental conditions using a broad range of reagents and oxidants.[2–25] Nevertheless, most if not all of the previously reported methods produce the desired disulfide with concomitant formation of solid waste by-products requiring time and solvent consuming purification procedures prior to isolation of the pure product. Additional disadvantages include the use of often expensive, rare or toxic reagents and metal oxidants, low yields, long reaction times and high reaction temperatures, or the risk of overoxidation of the product disulfides to sulfoxides. Thus, there still exists a need for simple, clean and efficient oxidative methods that would produce the target disulfides in high yields without complicated work-up steps. Here we report a facile, cheap and extremely simple high yielding procedure for the preparation of some symmetrical disulfides based on the addition of sulfuryl chloride to the corresponding thiol in dichloromethane or, in the case of volatile thiols, under solvent free conditions



Scheme 1. Synthesis of symmetrical disulfides.

(Scheme 1). The only by-products produced in this reaction are gaseous SO_2 and HCl, which are both spontaneously eliminated from the reaction mixture leaving the disulfide as the sole product, in most cases in nearly quantitative yield. To our knowledge, this method has not been described previously in the literature and provides a high yield access to a range of symmetrical aliphatic, aromatic and heteroaromatic disulfides (Table 1).

Table 1. Synthesis of symmetrical disulfides

Substrate	Method[a]	Product	Yield (%)
n-$C_7H_{15}SH$	2	$C_7H_{15}SSC_7H_{15}$	96
n-$C_{12}H_{25}SH$	2	$C_{12}H_{25}SSC_{12}H_{25}$	98
Cyclohexylthiol	2	Dicyclohexyl disulfide	95
Benzylthiol	2	Dibenzyl disulfide	98
Fluorene-9-thiol	2	Difluoren-9-yl disulfide	98
Benzenethiol	2	Diphenyl disulfide	98
Benzenethiol	3	Diphenyl disulfide	99
2-Pyridinethiol	1	2,2′-Dipyridyl disulfide	96
2-Pyrimidinethiol	1	2,2′-Dipyrimidyl disulfide	69

[a] Method 1: CH_2Cl_2 solution. Method 2: Neat. Method 3: Reaction in CH_2Cl_2 solution on a rotary evaporator.

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Thus, in summary, we have developed a new useful, efficient and economically attractive method providing simple access to several useful symmetrical disulfides in excellent yields. Unless otherwise specified, all solvents and reagents were purchased from commercial suppliers and used without further purification. Fluorene-9-thiol was prepared from 9-bromofluorene according to a literature procedure.[26]

2. General procedures for the preparation of symmetrical disulfides

Method 1: To a solution of the thiol (2 equiv) in 20 mL of CH_2Cl_2 was added dropwise a solution of SO_2Cl_2 (1.1 equiv) in 20–30 mL of CH_2Cl_2. The reaction mixture was stirred for 30 min and evaporated to dryness to leave the desired disulfide.

Method 2: To the thiol (2 equiv) was added SO_2Cl_2 (1.1 equiv) during a period of 5–10 min. The reaction mixture was stirred for 30 min and the excess reagents evaporated using a rotary evaporator to leave the desired disulfide.

Method 3: A solution of the thiol (2 equiv) dissolved in 20–30 mL of CH_2Cl_2 was combined with a solution of SO_2Cl_2 in 20 mL of CH_2Cl_2 in a round-bottomed flask. The flask was placed on a rotary evaporator and concentrated to dryness to leave the desired disulfide.

2.1. Synthesis of diheptyl disulfide

From *n*-heptanethiol (6.60 g, 50 mmol) using method 2 in an ice bath, diheptyl disulfide (6.32 g, 96%) was obtained as a pale yellow liquid. IR (KBr disk): 2956, 2855, 1465, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, $J = 7.1$ Hz, 6H), 1.20–1.39 (m, 16H), 1.65 (quin, 4H, $J = 7.4$ Hz), 2.65 (t, 4H, $J = 7.4$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.04, 22.58, 28.47, 28.88, 29.21, 31.70, 39.18. EIMS *m*/*z* (RA): 262 (M^+, 14), 164 (14), 131 (12), 101 (3), 87 (5), 58 (5), 57 (100), 55 (23). HRMS calcd 262.1789 for $C_{14}H_{30}S_2$. Found 262.1785.

2.2. Synthesis of didodecyl disulfide

From *n*-dodecanethiol (10.10 g, 50 mmol) using method 2 in an ice bath, didodecyl disulfide (9.89 g, 98%) was obtained as white crystals. IR (KBr disk): 2923, 2851, 1470, 718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, $J = 7.0$ Hz, 6H), 1.24–1.37 (m, 36H), 1.65 (quin, $J = 7.3$ Hz, 4H), 2.66 (t, $J = 7.3$ Hz, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.11, 22.67, 28.53, 29.22, 29.23, 29.34, 29.51, 29.59, 29.63, 29.64, 31.90, 39.21. EIMS *m*/*z* (RA): 402 (M^+, 58), 201 (21), 87 (22), 85 (31), 71 (55), 69 (29), 57 (100), 55 (48). HRMS calcd 402.3354 for $C_{24}H_{50}S_2$. Found 402.3355. Mp 29–31 °C.

2.3. Synthesis of dicyclohexyl disulfide

From cyclohexylthiol (5.80 g, 50 mmol) using method 2 in an ice bath, dicyclohexyl disulfide (5.46 g, 95%) was obtained as a transparent liquid. IR (KBr disk): 2928, 2852, 1447, 1260, 996 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.34 (m, 10H), 1.55–1.63 (m, 2H), 1.72–1.80 (m, 4H), 1.97–2.03 (m, 4H), 2.61–2.69 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 25.66, 26.05, 32.81, 49.91. EIMS *m*/*z* (RA): 230 (M^+, 15), 148 (38), 84 (8), 83 (100), 82 (4), 81 (6), 55 (56), 53 (4). HRMS calcd 230.1163 for $C_{12}H_{22}S_2$. Found 230.1165.

2.4. Synthesis of dibenzyl disulfide

From benzylthiol (1.24 g, 10 mmol) using method 2, dibenzyl disulfide (1.20 g, 98%) was obtained as white crystals. IR (KBr disk): 3053, 3031, 1494, 1453, 758, 696 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.72 (s, 4H), 7.25–7.29 (m, 4H), 7.31–7.37 (m, 6H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 41.60, 127.28, 128.37, 129.35, 137.28. EIMS *m*/*z* (RA): 246 (M^+, 44), 182 (4), 181 (24), 153 (2), 123 (7), 121 (8), 92 (43), 91 (100). HRMS calcd 246.0537 for $C_{14}H_{14}S_2$. Found 246.0535. Mp 66–68 °C.

2.5. Synthesis of difluoren-9-yl disulfide

From fluorene-9-thiol (1.98 g, 10 mmol) using method 2 in an ice bath, difluoren-9-yl disulfide (1.94 g, 98%) was obtained as white crystals. IR (KBr disk): 3037, 1443, 735, 426 cm^{-1}. ^1H NMR (400 MHz,): δ 4.68 (s, 2H), 7.19 (t, 4H, $J = 7.5$ Hz), 7.29 (t, 4H, $J = 7.5$ Hz), 7.55 (d, 4H, $J = 7.5$ Hz), 7.64 (d, 4H, $J = 7.5$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 53.54, 119.85, 125.38, 127.47, 128.41, 140.89, 144.06. EIMS *m*/*z* (RA): 394 (M^+, 2), 198 (6), 197 (10), 196 (30), 166 (20), 165 (100), 164 (9), 152 (10). HRMS calcd 394.0850 for $C_{26}H_{18}S_2$. Found 394.0853. Mp 156–158 °C.

2.6. Synthesis of diphenyl disulfide

From benzenethiol (11 g, 100 mmol) using method 2, diphenyl disulfide (10.70 g, 98%) was obtained as white crystals. Alternatively, on 10 mmol scale using method 3, diphenyl disulfide (1.08 g, 99%) was likewise obtained as white crystals. IR (KBr disk): 3069, 1578, 1474, 740, 686 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.26–7.30 (m, 2H), 7.35–7.40 (m, 4H), 7.50–7.53 (m, 4H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 127.17, 127.57, 129.46, 135.75. EIMS *m*/*z* (RA): 218 (M^+, 96), 185 (18), 154 (24), 109 (100), 77 (11), 69 (14), 65 (40), 51 (12). HRMS calcd 218.0224 for $C_{12}H_{10}S_2$. Found 218.0225. Mp 59–61 °C.

2.7. Synthesis of 2,2′-dipyridyl disulfide

From 2-pyridinethiol (0.56 g, 5 mmol) using method 1 in an ice bath, 2,2′-dipyridyl disulfide (0.53 g, 96%) was obtained as a yellow powder. IR (KBr disk): 3414, 3051, 3018, 2421, 1605, 1444, 770, 616 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.35 (ddd, $J = 7.5$ Hz, $J = 4.8$ Hz, $J = 0.9$ Hz, 2H), 7.69 (dt, $J = 8.1$ Hz, $J = 0.9$ Hz, 2H), 7.88 (ddd, $J = 8.1$ Hz, $J = 7.5$ Hz, $J = 1.8$ Hz, 2H), 8.55 (ddd, $J = 4.8$ Hz, $J = 1.8$ Hz, $J = 0.9$ Hz, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 119.64, 121.87, 138.25, 149.67, 157.27. EIMS *m*/*z* (RA): 220 (M^+, 100), 187 (16), 156 (56), 155 (26), 129

(8), 83 (8), 78 (42), 51 (15). HRMS calcd 220.0129 for $C_{10}H_8N_2S_2$. Found 220.0133. Mp 127–129 °C.

2.8. Synthesis of 2,2′-pyrimidyl disulfide

From 2-pyrimidinethiol (1.12 g, 10 mmol) using method 1 in an ice bath, di-2-pyrimidyl disulfide (0.77 g, 69% yield) was obtained as a yellow powder after filtration. IR (KBr disk): 3071, 3035, 1597, 1432, 744, 627 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.35 (dt, $J = 4.8$ Hz, $J = 0.5$ Hz, 2H), 8.69 (dd, $J = 4.8$ Hz, $J = 0.5$ Hz, 4H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 119.16, 158.58, 167.84. EIMS *m/z* (RA): 222 (M^+, 98), 158 (100), 112 (15), 80 (28), 79 (39), 57 (17), 53 (27), 52 (19). HRMS calcd 222.0034 for $C_8H_6N_4S_2$. Found 222.0026. Mp 139–141 °C.

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