

Bio-based Green Solvent Mediated Disulfide Synthesis via Thiol Couplings Free of Catalyst and Additive

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General information

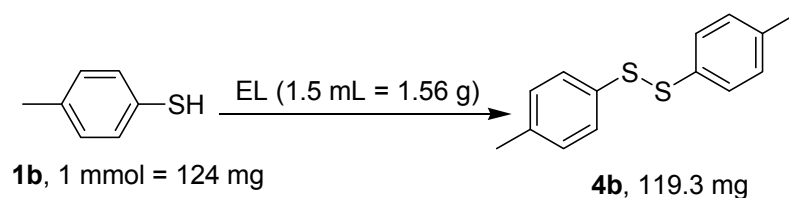
All chemicals and solvents used in our experiments were obtained from commercial sources and used directly without further treatment. All reactions were performed at open air atmosphere and monitored with TLC. ¹H and ¹³C NMR were recorded in 400 MHz apparatus using CDCl₃ as solvent. The frequency used for ¹H and ¹³C NMR measurement were 400 MHz and 100 MHz, respectively. The chemical shifts were recorded in ppm using TMS as internal standard.

General procedure for the synthesis of disulfides 4. In a 25 mL round bottom flask, 1.0 mmol thiol was located followed by 1.5 mL EL. The mixture was stirred with stirring bar for 12 h (TLC) at 60 °C and open air condition. Upon completion, 10 mL water was added to the reaction, and the resulting mixture was extracted with ethyl acetate (10 mL × 3). The organic phase was combined and dried with anhydrous Na₂SO₄. After filtering, the filtrate was collected and the solvent was removed at reduced pressure, the residue was subjected to silica gel column chromatography to give pure products.

Procedure for the synthesis of 6. To a 25 mL round bottom flask located **4a** (2 mmol), benzothiazole **5** (0.3 mmol) were added CuI (0.06 mmol), ligand **L** (0.06 mmol), Cs₂CO₃ (0.6 mmol) and DMSO (2 mL). The resulting mixture was heated at 120 °C for 16 h. After cooling down to room temperature, 10 mL water was added to the flask and the suspension was extracted with ethyl acetate (10 mL × 3). The organic layers were combined and dried with anhydrous Na₂SO₄. After filtering the solid away, the solvent was removed in vacuum. The residue was

subjected to column chromatography to give pure product.

Calculation of *E*-factor for representative reaction (entry 2, Table 2)



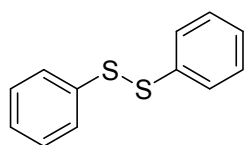
Amount of materials used in the synthesis: 124.0 mg + 1.56 g = 1684.0 mg

Amount of Product: 119.3 mg

Amount of wastes produced from the reaction: 1684.0-119.3 = 1564.7 mg

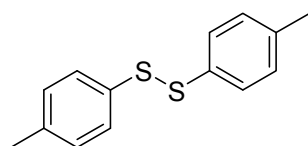
E-factor = 1564.7/119.3 = 13.1 kg·kg⁻¹

Characterization data



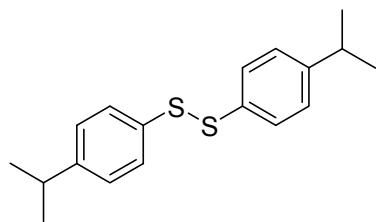
Diphenyl disulfide (4a)¹

White solid; mp 58-60 °C [lit. 59-61 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.49 (d, 4 H, *J* = 8.0 Hz), 7.30 (t, 4 H, *J* = 8.0 Hz), 7.25-7.20 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 137.04, 129.11, 127.51, 127.19.



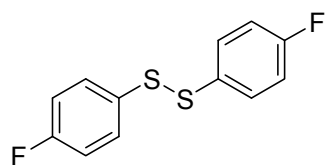
Dip-tolyl disulfide (4b)²

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 7.37 (d, 4 H, *J* = 8.0 Hz), 7.08 (d, 4 H, *J* = 8.0 Hz), 2.30 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 137.49, 133.97, 129.86, 128.59, 21.13.



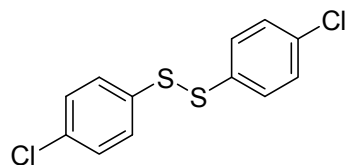
Di(4-isopropylphenyl) disulfide (4c)³

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 7.33 (t, 4 H, *J* = 8.0 Hz), 7.05 (t, 4 H, *J* = 8.0 Hz), 2.79-2.72 (m, 1 H), 1.12 (t, 12 H, *J* = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ = 148.32, 134.39, 128.27, 127.32, 33.84, 24.02;



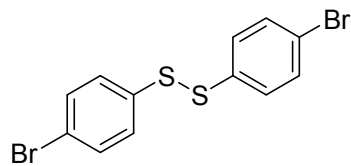
Di(4-fluorophenyl) disulfide (4d)^{3,4}

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 7.35 (dd, 4 H, *J*₁ = 8.0 Hz, *J*₂ = 4.2 Hz), 6.91 (t, 4 H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ = 162.76, 160.29, 131.08, 130.18 (d, *J*_{C-F} = 8.0 Hz), 115.23 (d, *J*_{C-F} = 22.0 Hz).



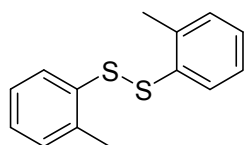
Di(4-chlorophenyl) disulfide (4e)²

Yellow solid; mp 62-63 °C [lit. 65-66 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.39 (d, 4 H, *J* = 8.0 Hz), 7.26 (d, 4 H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ = 135.13, 133.64, 129.33;



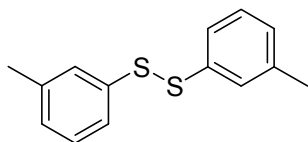
Di(4-bromophenyl) disulfide (4f)^{3,4}

Yellow solid; mp 94-96 °C [lit. 89-90 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.40 (d, 4 H, *J* = 8.0 Hz), 7.31 (d, 4 H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ = 135.78, 132.26, 129.44, 121.59;



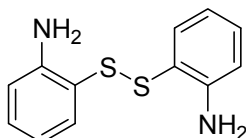
Dio-tolyl disulfide (4g)^{3,5}

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 7.50 (d, 2 H, *J* = 8.0 Hz), 7.11 (d, 6 H, *J* = 8.0 Hz), 2.41 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 137.34, 135.44, 130.41, 128.51, 127.36, 126.80, 20.12;



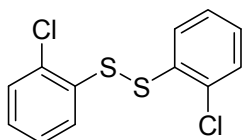
Dim-tolyl disulfide (4h)^{3,6}

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 7.29 (s, 4 H), 7.16 (t, 2 H, *J* = 7.6 Hz), 7.00 (d, 2 H, *J* = 7.2 Hz), 2.30 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 138.98, 136.91, 128.96, 128.04, 127.97, 124.52, 21.46;



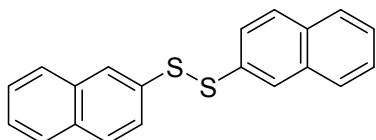
Di(2-aminophenyl) disulfide (4i)⁷

Yellow solid; mp 85-86 °C [lit. 93-94 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.16-7.12 (m, 4 H), 6.69-6.66 (m, 2 H), 6.58-6.54 (m, 2 H), 4.32 (brs, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 148.70, 136.89, 131.72, 118.71, 118.29, 115.34;



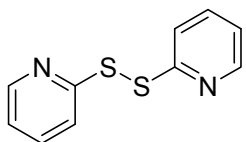
Di(2-chlorophenyl) disulfide (4j)⁸

Yellow solid; mp 85-87 °C [lit. 82-83 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.54 (dd, 2 H, *J*₁ = 8.0 Hz, *J*₂ = 1.2 Hz), 7.36 (d, 2 H, *J* = 8.0 Hz), 7.24-7.13 (m, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 134.34, 131.80, 129.75, 127.83, 127.63, 127.12;



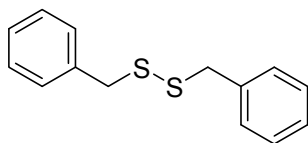
Dinaphth-2-yl disulfide (4k)⁷

Pale yellow solid; mp 135-137 °C [lit. 136-137 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.98 (s, 4 H), 7.78-7.71 (m, 6H), 7.61 (d, 2 H, *J* = 7.2 Hz), 7.44 (s, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 133.76, 132.98, 132.00, 128.52, 127.30, 127.00, 126.28, 126.01, 125.77, 125.15;



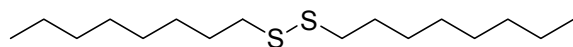
Dipyridin-2-yl disulfide (4l)²

Yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 8.40-8.38 (m, 2 H), 7.55-7.53 (m, 4H), 7.06-7.02 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 158.86, 149.58, 137.48, 121.17, 119.65;



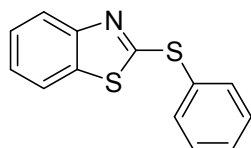
Dibenzyl disulfide (4m)²

Pale yellow solid; mp 63-65 °C [lit. 58-59 °C]; ¹H NMR (CDCl₃, 400 MHz) δ = 7.33-7.26 (m, 6 H), 7.23 (d, 4 H, *J* = 8.0 Hz), 3.58 (s, 4 H); ¹³C NMR (CDCl₃, 100 MHz) δ = 137.42, 129.52, 128.57, 127.52, 43.28;



1,2-Dioctyl disulfane (4n)⁹

Colorless liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 2.60 (t, 4 H, *J* = 7.2 Hz), 1.61 (q, 4 H, *J* = 7.2 Hz), 1.30-1.21 (m, 20 H), 0.81 (t, 6 H, *J* = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ = 39.19, 31.85, 29.75, 29.25, 29.23, 28.57, 22.69, 14.12.



2-(Phenylthio)benzo[d]thiazole (6)¹⁰

Pale yellow liquid; ¹H NMR (CDCl₃, 400 MHz) δ = 7.78 (d, 1 H, *J* = 8.0 Hz), 7.63 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 1 H, *J* = 8.0 Hz), 7.41-7.35 (m, 3 H), 7.30 (t, 1 H, *J* = 7.6 Hz), 7.15 (t, 1 H, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ = 169.79, 153.94, 135.54, 135.42, 130.54, 129.98, 129.91, 126.21, 124.37, 121.96, 120.84.

References

- (1) R. Leino, J.-E. Lönnqvist, *Tetrahedron Lett.* 2004, **45**, 8489-8491.
- (2) M. Oba, K. Tanaka, K. Nishiyama, W. Ando, *J. Org. Chem.* 2011, **76**, 4173-4177.
- (3) H. Xiao, J. Chen, M. Liu, H. Wu, J. Ding, *Phosphorus Sulfur Silicon* 2009, **184**, 2553-2559.
- (4) D. R. Dreyer, H.-P. Jia, A. D. Todd, J. Geng, C. W. Bielawski, *Org. Bio. Chem.* 2011, **9**, 7292-7295.
- (5) N. Taniguchi, *Tetrahedron* 2012, **68**, 10510-10515.
- (6) B. Zeynizadeh, *J. Chem. Res. (S)* 2002, **11**, 564-566.
- (7) J. L. G. Ruano, A. Parra, J. Alemán, *Green Chem.* 2008, **10**, 706-711.
- (8) G. L. Regina, V. Gatti, V. Famiglioni, F. Piscitelli, R. Silvestri, *ACS Comb. Sci.* 2012, **14**, 258-262.
- (9) N. Iranpoor, H. Firouzabadi, D. Khalili, *Tetrahedron Lett.* 2012, **53**, 6913-6915.
- (10) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K.-W. Huang and X. Liu, *J. Org. Chem.* 2011, **76**, 8999-9007.

