ortho-Lithiation of Benzene-1,2-dithiol: A Methodology for *ortho*-Functionalization of Benzene-1,2-dithiol

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Dedicated to Professor Albrecht Mewis on the occasion of his 60th birthday

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ortho-Functionalized Benzene-1,2-dithiols, Bis(benzene-1,2-dithiol), Ligand Synthesis

The *ortho*-lithiation of benzene-1,2-dithiol with three equivalents of *n*BuLi afforded mono- as well as di-*C*-lithiated intermediates. The surprising kinetically controlled formation of di-*C*-lithiated species offers the opportunity to obtain dimercaptobenzoic and -terephthalic acid derivatives in a onepot synthesis in reasonable yields. Both compounds are versatile building blocks for the synthesis of macrocycles containing arylenedithiol units. Focusing on novel terephthalic acid derivatives, two preparation routes, *via* amide and *via* alkyl linkage, respectively, have been elaborated. The reaction sequence (i) sulfur protection using either isopropyl or benzyl groups, (ii) transformation of the carboxylic function into an amide or an alkyl group and (iii) subsequent removal of the protection groups afforded the terephthaldiamidedithiol **6** and the 1,2-bis(2,3-dimercaptophenyl)ethane **11**.

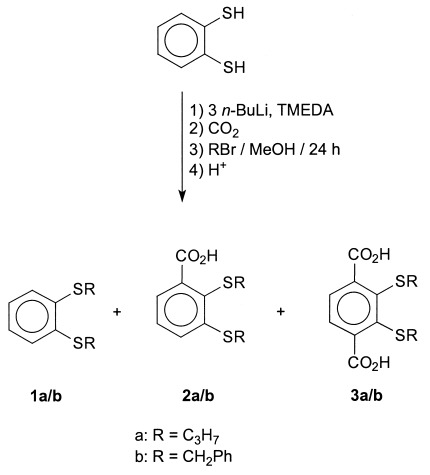
Introduction

The chemistry of benzene-1,2-dithiol is widely ranged. In organic synthesis it has been used as a precursor for 1,3-benzodithioles [1], organo-polysulfides [2] with antifungal activity [3], spirans [4] and macrocyclic sulfides [5]. The coordination chemistry of benzene-1,2-dithiolate ligands has also been studied intensively during the last decades [6]. The interest in benzene-1,2-dithiolate complexes was not only prompted by their remarkable electronic and magnetic properties in general, but also by their relevance as models for the active sites of metal containing enzymes [7]. However, ligands having two or more benzene-1,2-dithiolate donor sets were unknown until recently, when we reported the first amide- and alkyl-bridged tris- and bis(benzenedithiolate) ligands and their coordination chemistry [8]. In our attempt to synthesize *ortho*-functionalized benzenedithiols as building blocks for poly(benzenedithiolate) ligands we investigated the mechanism of the *ortho*-lithiation of benzene-1,2-dithiol based on the method described by Block *et al.* [9]. Herein, we report on the synthesis and molecular structures of several functionalized benzene-1,2-dithiol derivatives.

Results and Discussion

Generation and reactions of lithiated arenedithiols

For the preparation of diamide bridged poly(benzenedithiol) ligands we used the 2,3-di(alkylmercapto)benzoic acids **2a/b** as suitable precursors. These compounds can be prepared in moderate yields ($\sim$ 40 %) by direct *ortho*-lithiation of benzene-1,2-dithiol with at least three equivalents of *n*BuLi followed by treatment with dry CO_2 and subsequent alkylation of the thiol functions with alkylbromides as depicted in Scheme 1. In addition, this reaction sequence also afforded the 1,2-di(alkylmercapto)benzenes **1a/b** ($\sim$ 20 %) and surprisingly the 2,3-di(alkylmercapto)terephthalic acids **3a/b** ($\sim$ 30 %) as byproducts. These products can be isolated in analytically pure form by column chromatography (SiO_2, eluent: diethyl ether / petroleum ether / acetic acid 1 : 3 : 0.03). The addition of small amounts of acetic acid to the eluent turned out to



Scheme 1.

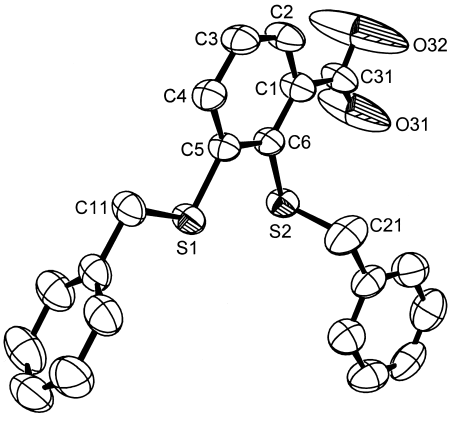


Fig. 1. Molecular structure of 2,3-di(benzylmercapto)-benzoic acid **2b**. Selected bond lengths [Å] and angles [°]: C1-C31 1.491(5), C5-S1 1.765(3), C6-S2 1.779(3), S1-C11 1.818(3), S2-C21 1.811(5), C31-O31 1.111(5), C31-O32 1.171(6); C2-C1-C31 117.5(3), C6-C1-C31 122.8(3), C4-C5-S1 123.0(3), C6-C5-S1 117.3(2), C1-C6-S2 123.0(2), C5-C6-S2 117.8(2), O31-C31-O32 115.7(4), O31-C31-C1 128.2(4), O32-C31-C1 116.1(4).

be essential to reduce the tailing phenomenon often observed for carboxylic acids on silicagel, which otherwise makes the separation of **2a/b** and **3a/b** very difficult.

The carboxylic acids **2a/b** and **3a/b** are soluble in most organic solvents except for hexane. The molecular structures of **2b** and **3b** which have been determined by single crystal X-ray diffraction methods are depicted in Figures 1 and 2. Due to the hydrogen bonds between two carboxylic acid groups leading to an intermolecular oxygen-oxygen-distance

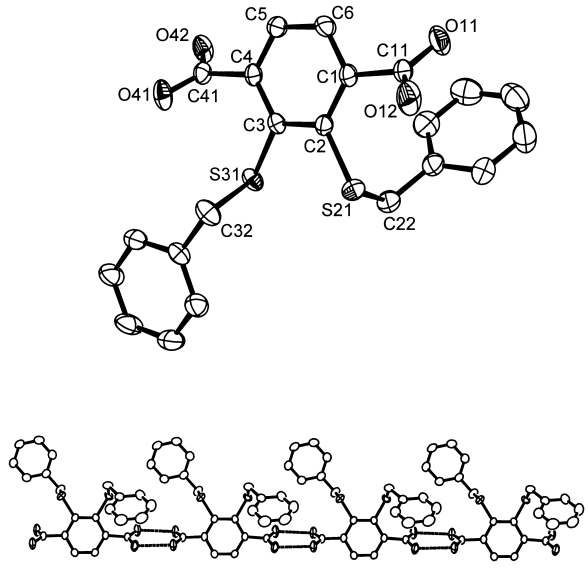


Fig. 2. Molecular structure of 2,3-di(benzylmercapto)-terephthalic acid **3b** (upper plot) and the two-dimensional endless chain (lower plot) of **3b** formed by hydrogen bonds. Selected bond lengths [Å] and angles [°]: C1-C11 1.503(3), C11-O11 1.250(3), C11-O12 1.266(3), C2-S21 1.778(2), S21-C22 1.824(3), C3-S31 1.778(2), S31-C32 1.830(2), C4-C41 1.504(3), C41-O41 1.254(3), C41-O42 1.267(3); C6-C1-C11 116.2(2), C2-C1-C11 123.2(2), O11-C11-O12 124.5(2), O11-C11-C1 117.6(2), O12-C11-C1 117.8(2), C1-C2-S21 121.5(2), C3-C2-S21 119.7(2), C4-C3-S31 118.3(2), C2-C3-S31 122.0(2), C5-C4-C41 118.5(2), C3-C4-C41 120.5(2), O41-C41-O42 124.7(2), O41-C41-C4 118.6(2), O42-C41-C4 116.6(2).

of 2.65 Å **2b** crystallizes as a dimer and the terephthalic acid derivative **3b** on the other hand forms a two-dimensional endless chain. As expected the S-C(sp^2) distances are slightly shorter (0.05 Å) than the S-C(sp^3) distances. However, the change of the frontier orbital energies of the aromatic system by the linkage of an additional carboxylic group does not affect the S-C(sp^2) bond length. In contrast to **2b**, the benzyl protecting groups in **3b** point to different sides of the aromatic ring formed by C1 - C6.

We were particularly interested in **3a/b** because terephthalic acid derivatives are versatile building blocks for the synthesis of poly(benzenedithiol) macrocycles. In general, two reaction pathways **A** and **B** leading to the formation of the di-*C*-lithiated species as an intermediate for the terephthalic acid derivatives **3** are feasible (Scheme 2).

To shed light onto the mechanism involved, we carried out lithiation experiments with benzene-

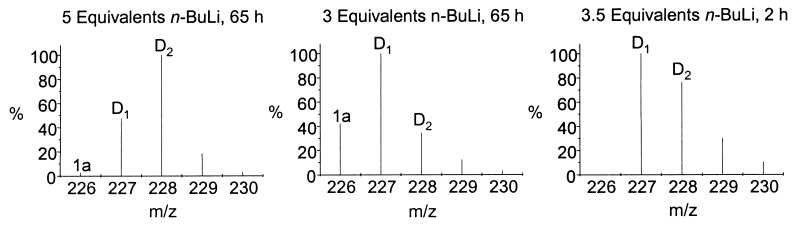
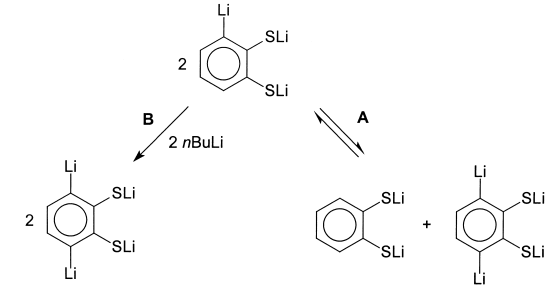
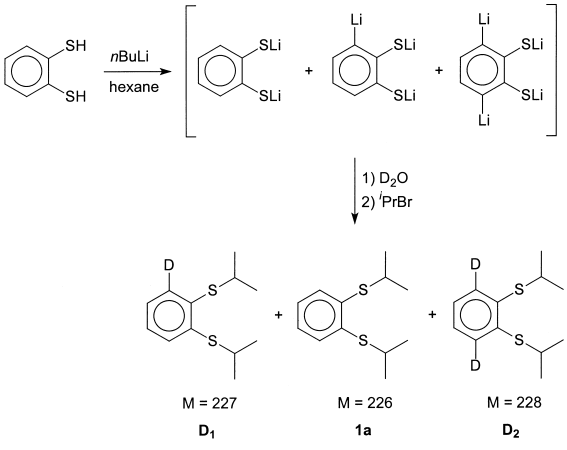


Fig. 3. Product distribution examined by EI-MS.



Scheme 2.



Scheme 3.

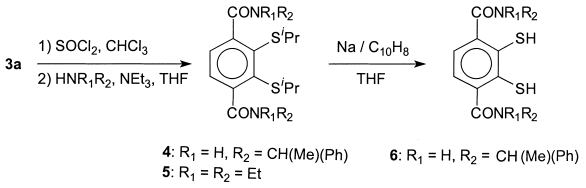
1,2-dithiol applying different amounts of lithiating reagent and various reaction times. In order to separate the deprotonation from the carbonylation step the generated lithium intermediates were trapped with excess D_2O and subsequently isopropylbromide (Scheme 3). The product ratios were examined by mass spectrometry (Fig. 3). Table 1 summarizes the resulting ratios of the three products **1a**, $\mathbf{D}_1$ and $\mathbf{D}_2$ relative to each other under consideration of their natural isotope distribution. The application of a five-fold excess of *n*BuLi leads after 65 h reaction time to a product distribution in which $\mathbf{D}_2$ is the main product with 65 %. However, even for the use of such an excess of *n*BuLi **1a** and $\mathbf{D}_1$ still contribute to the product mixture with 2 % and 33 %, respectively. These products must be formed by protonolysis during the relatively long reaction time. If three equivalents of *n*BuLi are employed, as expected, $\mathbf{D}_1$ is the main product with 62 %. However, $\mathbf{D}_2$ is still found in the mixture. On the other hand, the contributions of **1a** and $\mathbf{D}_2$ differ by 18 %, which does not support the equilibrium proposed for pathway **A**. The variation of reaction time and the use of 3.5 equivalents of *n*BuLi finally disclosed, that the lithiation process is already completed within two hours. The observation that no di(thioether) **1a** could be detected anymore provided further evidence to reject the equilibrium proposed in pathway **A**. Obviously, the formation of the di-*C*-lithiated species follows pathway **B** which includes a fast, kinetically controlled and irreversible second *C*-lithiation in the *para*-position to the first lithium atom by (local) excess of *n*BuLi. In addition, longer reaction times are unfavorable, but drive the protonolysis of the lithium intermediates. These results clearly demonstrate that the reaction conditions used in the third procedure are optimal for the preparation of both mono- as well as di-*C*-lithiated species.

Table 1. Relative ratios of **1a** and the deuterated species $\mathbf{D}_1$ and $\mathbf{D}_2$ under various reaction conditions with consideration of their natural isotope distributions.

Equivalents of *n*-BuLi	Reaction time [h]	Ratio **1a** [%]	Ratio D_1 [%]	Ratio D_2 [%]
5	65	2	33	65
3	65	28	62	10
3.5	2	–	64	36

Synthesis of amide derivatives

Macrocycles containing two (or more) benzene-1,2-dithiol units are accessible by bridging two (or more) molecules of **3a/b** twice. The reaction of the acid chlorides of **3a/b** with suitable diamines under dilute conditions is one possible route to



Scheme 4.

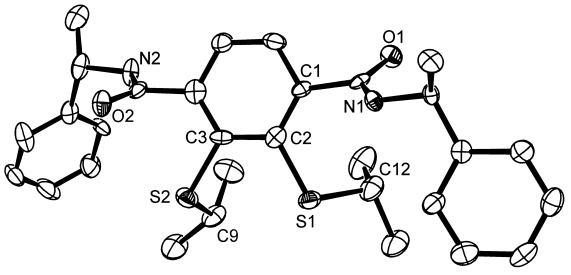


Fig. 4. Molecular structure of the chiral diamide **4**. Hydrogen atoms have been omitted. Selected bond lengths [Å] and angles [°]: S1-C2 1.789(7), S1-C12 1.838(8), S2-C3 1.799(7), S2-C9 1.836(7), N1-C7 1.348(8), N2-C8 1.318(8), O1-C7 1.233(8), O2-C8 1.219(8), C1-C2 1.363(9), C1-C6 1.405(10), C1-C7 1.509(9), C2-C3 1.400(9), C3-C4 1.354(10), C4-C5 1.407(10), C4-C8 1.525(9), C5-C6 1.364(10); C2-S1-C12 105.3(3), C3-S2-C9 103.2(3), C1-C2-S1 122.6(5), C3-C2- S1 118.0(5), C4-C3-S2 117.4(5), C2-C3-S2 121.3(5), C3-C4-C8 123.3(6), C5-C4-C8 116.9(6), O1-C7-N1 123.1(6), O1-C7-C1 120.9(5), N1-C7-C1 116.0(5), O2-C8-N2 124.3(6), O2-C8-C4 120.7(6), N2-C8-C4 115.0(6).

such diamide-bridged compounds. To investigate the chemical properties of such amides in general and to seek for the best thiol protection group we synthesized the secondary and chiral diamide **4** as well as the tertiary diamide **5**. Both compounds can be obtained in good yields by reaction of the acid chloride, generated by chlorination of **3a** with $SOCl_2$, with two equivalents of (*S*)-1-phenylethylamine or diethylamine, respectively, in the presence of triethylamine as a base (Scheme 4). Both compounds are soluble in halocarbon solvents, THF, methanol, and DMF and insoluble in hexane, pentane or water. In contrast to **4**, the tertiary diamide **5** is even soluble in diethyl ether. The decrease in solubility going from tertiary to secondary diamide is obviously due to the ability of the latter to form hydrogen bonds.

The subsequent reductive cleavage of the sulfur protecting isopropyl groups in **4** can be accomplished by treatment with metallic sodium / naphthalene in THF. Because of the convenience and the mild conditions of this reaction sequence, we found this method superior with respect to the standard procedure using sodium in liquid ammonia. Subsequent acidification with hydrochloric acid (37 %) lead to the formation of the dithiol **6**. However, we found that the isopropyl groups in **5** could not be removed using either $Na/C_{10}H_8$/THF nor Na/NH_3. Apparently the presence of two tertiary amides instead of secondary amides prevents the S-$CH(CH_3)_2$ bond cleavage. If tertiary terephthalamides are employed, the S-protecting group cannot be isopropyl but must be benzyl instead. The S-CH_2Ph bonds in the benzyl S-protected analogue of **5** are cleaved easily leading to the corresponding dithiol [8b]. In quest for an explanation of the difference in the reactivity between **4** and **5** we performed single crystal X-ray structure determinations of both. The molecular structures and the numbering schemes are depicted in Figures 4 and 5. Structural parameters for both compounds are unexceptional and no essential differences could be detected. In contrast to the *trans* position of the isopropyl groups in **5**, the isopropyl groups in **4** are found on the same side of the aromatic ring formed by the carbon atoms C1-C6 revealing a reduced steric crowding. However, the amide substituents of both **4** and **5** point in opposite directions and are strongly twisted out of the aromatic plane, which is expected for the tertiary amide **5** but rather unusual for the secondary

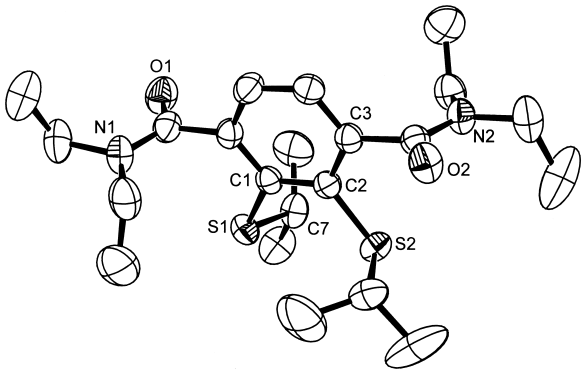
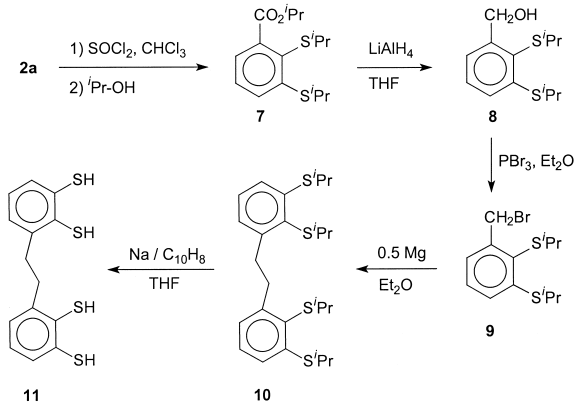


Fig. 5. Molecular structure of the tertiary diamide **5**. Hydrogen atoms have been omitted. Selected bond lengths [Å] and angles [°]: C1-S1 1.7768(19), S1-C7 1.830(2), C2-S2 1.776(2), C1-C2 1.402(3), C2-C3 1.400(3), C13-O1 1.227(3), C13-N1 1.339(3), S1-C1-C2 122.03(14), C1-C2-S2 122.07(15), C1-C2-C3 119.52(17), N1-C13-O1 123.7(2), C6-C13-O 119.57(19), C6-C13-N1 116.57(18), C1-S1-C7 101.17(9).



Scheme 5.

amide **4**. Steric rather than electronic effects must be made responsible for this observation [10].

The more striking difference in the solubility of these compounds demonstrates the strong influence of hydrogen bonds formed by amide protons. The dithiol **6** with secondary amide groups is solely soluble in dimethylformamide or dimethylacetamide. The decrease in solubility of **6** compared to its precursor **4** is caused by additional NH···S hydrogen bonds also indicated by a downfield shift of the amide proton resonances in the ^{1}H NMR spectra from 7.55 ppm in **4** to 9.04 ppm in **6**. The corresponding dithiol derived from **5** with tertiary amide groups on the other hand dissolves even in diethyl ether [8b] showing no significant difference in solubility to its sulfur protected analogue **5**. Therefore the reactivity difference can probably be attributed to the importance of an amide proton in the cleavage reaction of **4** rather than to steric or electronic effects in the aromatic system.

Synthesis of carbon linked derivatives

Recently we reported the use of the benzoic acid derivative **2a** as a precursor for diamide bridged bis(aryldithiol) compounds [8d]. However, the benzoic acid **2a** can also be applied as starting material for an alkyl linkage. For that purpose, **2a** has to be converted into the isopropyl ester **7** (yield 86 %) by reaction of the corresponding acid chloride with isopropanol (Scheme 5). The reduction of **7** with $LiAlH_4$ and subsequent acidification afforded the benzyl alcohol **8** (yield 80 %), which can quantitatively be brominated to the corresponding benzyl bromide **9** with PBr_3. Compound **9** can

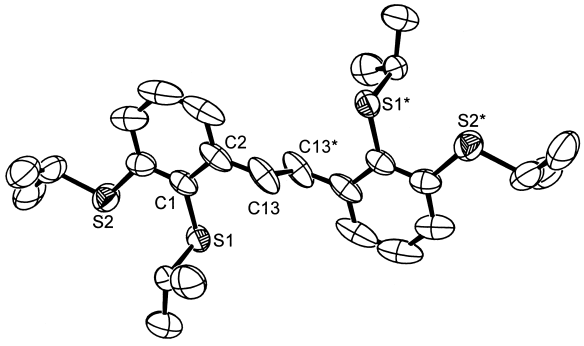


Fig. 6. Molecular structure of 1,2-bis[2,3-di(isopropylmercapto)phenyl]ethane **10**. Hydrogen atoms have been omitted. Selected bond lengths [Å] and angles [°]: C1-S1 1.776(2), C2-C13 1.497(4), C6-S2 1.771(3), C7-S2 1.817(3), C10-S1 1.836(3); C6-C1-S1 119.2(2), C2-C1-S1 120.0(2), C3-C2-C13 119.9(3), C1-C2-C13 122.5(3), C5-C6-S2 123.4(2), C1-C6-S2 117.2(2), C1-S1-C10 102.1(2), C6-S2-C7 106.2(1).

than undergo a Wurtz-type coupling reaction giving the sulfur protected bis(benzenedithiol) derivative **10** (yield 87 %). The reductive cleavage of the isopropyl groups analogous to **4** yielded **11** in acceptable purity after several washing steps. Further purification of **11** by recrystallization turned out to be difficult. Therefore we verified at least the identity of the sulfur protected compound **10** which can be crystallized from dichloromethane / hexane solution by single crystal X-ray structure determination. The molecular structure depicted in Fig. 6 unequivocally proves that two aryldithiol units are linked by a C_2 backbone.

Conclusion

Dimercaptoterephthalic acid derivatives found first as surprising byproducts in the synthesis of dimercaptobenzoic acid can be obtained in reasonable yields by certain control measures in the *ortho*-lithiation of dilithium-benz-1,2-dithiolate. Efforts to develop an alternative and more exclusive synthesis for dimercaptoterephthalic acid were unsuccessful so far. The appropriateness of certain thiol protection groups in the synthesis of amide linked poly(aryldithiol) macrocycles is restricted to the particular type of the amide function. In addition, dimercaptobenzoic acid derivatives are useful in the synthesis of solely alkyl-linked poly(aryldithiol) compounds. All the dithiols descibed here are new and promising ligands for coordination chemistry experiments.

Experimental Section

If not noted otherwise, all manipulations were performed in an atmosphere of dry argon by using standard Schlenk techniques. Solvents were dried by standard methods and freshly distilled prior to use. *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was purified by vacuum distillation from Na / benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 NMR spectrometer. Elemental analyses were performed at the Westfälische Wilhelms-Universität Münster on Vario EL III CHNS and Foss Heraeus CHN-O-Rapid elemental analyzers. Mass spectra were obtained using Varian MAT 212 (EI), and DANI 8521/Finnigan MAT IDT 800 (GCMS) spectrometers, respectively. IR spectra were recorded on a Bruker Vektor 22 with KBr wafers, those of liquids neat between KBr windows. Benzene-1,2-dithiol was prepared following a literature method [11]. The benzoic acid derivatives **2a** and **3a** were prepared as published [8a]. Compound **1a** was isolated as a byproduct during the preparation of **2a**. The terephthalic acid derivative **3b** was isolated as a byproduct during the preparation of **2b** [8b]. The preparation of diamide **5** [8b], bromide **9**, bis(dithiol) **11** and its precursor **10** has recently been reported [8d].

1a: ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 7.33 (dd, 2 H, Ar-H), 7.14 (dd, 2 H, Ar-H), 3.48 (m, ^3J = 6.4 Hz, 2 H, SCH), 1.33 (d, ^3J = 6.4 Hz, 12 H, CH_3). – ^{13}C{^{1}H} NMR (50.32 MHz, $CDCl_3$): δ = 137.5, 130.6, 126.3 (Ar-C), 36.8 (SCH), 22.8 (CH_3). – MS (EI): *m/z* (%) = 226 (60) $[M]^+$, 184 (25) $[M\text{-}C_3H_6]^+$, 142 (100) $[M\text{-}2C_3H_7]^+$, 108 (10) $[M\text{-}2C_3H_7\text{-}H_2S]^+$, 97 (16) $[C_5H_5S]^+$, 78 (46) $[C_6H_6]^+$, 41 (81) $[C_3H_5]^+$. – $C_{12}H_{18}S_2$ (226.39): calcd. C 63.66, H 8.01, S 28.32; found C 63.92, H 7.91, S 28.26. **2b:** ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 11.30 (s, br, 1 H, CO_2H), 7.52 - 6.93 (m, 13 H, Ar-H), 4.07 (s, 2 H, SCH_2), 4.03 (s, 2 H, SCH_2). – ^{13}C{^{1}H} NMR (50.32 MHz, $CDCl_3$): δ = 171.2 (CO_2H), 146.9, 137.6, 136.4, 135.8, 129.4, 129.2, 128.9, 128.7, 128.4, 128.3, 127.5, 127.4, 126.4 (Ar-C), 40.8 (SCH_2), 37.4 (SCH_2). – MS (EI): *m/z* (%) = 366 (6) $[M]^+$, 275 (3) $[M\text{-}CH_2Ph]^+$, 244 (10) $[M\text{-}SCH_2Ph]^+$, 91 (100) $[CH_2Ph]^+$. – $C_{21}H_{18}O_2S_2$ (366.49): calcd. C 68.82, H 4.95; found C 68.79, H 5.54.

3b: ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 9.21 (s, br, 1 H, CO_2H), 7.10 - 7.30 (m, 10 H, CH_2-Ar-*H*), 7.74 (s, 2 H, Ar-H), 4.13 (s, 4 H, SCH_2). ^{13}C{^{1}H} NMR (50.32 MHz, $CDCl_3$): δ = 170.0 (CO_2H), 140.6, 139.8, 136.0 (Ar-C), 130.0, 129.2, 128.6, 127.7 (CH_2-Ar-*C*), 42.8 (SCH_2). – MS (EI): *m/z* (%) = 410 (4) $[M]^+$, 320 (2) $[M\text{-}CH_2Ph]^+$, 91 (100) $[CH_2Ph]^+$. – $C_{22}H_{18}O_4S_2$ (410.50): calcd. C 64.37, H 4.42; found C 64.06, H 4.86.

Procedure 3 is described as an example for the mechanistic studies: To a mixture of 405 mg (2.85 mmol) of benzene-1,2-dithiol and 430 μl (2.87 mmol) of TMEDA in 20 ml of *n*hexane was added 4 ml of 2.5 M *n*BuLi in hexane (10 mmol) at -78 °C. The suspension was stirred at ambient temperature for 2 h and carefully quenched by adding 250 μl of D_2O. After stirring for another 1 h the solvent was removed *in vacuo*. The residue was dissolved in 40 ml of methanol and 806 μl (8.6 mmol) of isopropyl bromide was added to the solution. The resulting mixture was refluxed for 24 h and the solvent was evaporated *in vacuo* again. The residue was dissolved in 20 ml of diethyl ether and washed with water (2 × 20 ml). The organic phase was dried over $MgSO_4$. After removal of the solvent *in vacuo* a product mixture was obtained as a slightly yellow oil. MS (EI): *m/z* (%) = 228 (76.39) $[\mathbf{D}_2]^+$, 227 (100.00) $[\mathbf{D}_1]^+$.

Preparation of diamide **4***:* Two drops of *N,N*-dimethylformamide and thionyl chloride (1 ml) were added to a solution of **3a** (1.04 g, 3.31 mmol) in chloroform (10 ml). The reaction mixture was heated under reflux conditions for 3 h and allowed to cool to ambient temperature. Volatiles were removed *in vacuo* and the residue redissolved in THF. The yellowish solution was then added dropwise to a solution of (*S*)-1-phenylethylamine (900 μl, 6.98 mmol) and triethylamine (1 ml, 7.17 mmol) in THF (40 ml). The mixture was filtered after stirring for 12 h and the solvent was evaporated *in vacuo*. The residue was washed with diethyl ether (2 × 20 ml), redissolved in dichloromethane and washed with saturated brine. The organic phase was dried over $MgSO_4$. Removal of the solvent *in vacuo* gave **4** (1.435 g, 2.76 mmol, 83 %) as an off-white powder. IR (KBr): $\tilde{\nu}$ = 3287 (st, N-H), 3060 (s, Ar-H), 2972, 2927, 2865 (m, SC-H), 1642 (st, C=O), 1531 (st, C=O), 700 (s, Ar-H) cm^{-1}. – ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 7.55 (s, 2 H, Ar-H), 7.49 - 7.21 (m, 10 H, Ar-H), 7.15 (d, ^3J = 8.0 Hz, 2 H, CONH), 5.32 (m, 2 H, NCH), 3.38 (sept, 2 H, SCH), 1.60 (d, ^3J = 6.8 Hz, 6 H, CH(CH_3)), 1.12 (d, ^3J = 6.8 Hz, 6 H, SCH(CH_3)$_2$), 1.04 (d, ^3J = 6.4 Hz, 6 H, SCH(CH_3)$_2$). – ^{13}C{^{1}H} NMR (50.32 MHz, $CDCl_3$): δ = 166.7 (CONH), 143.4, 142.6, 137.9, 129.0, 128.6, 127.4, 126.4 (Ar-C), 49.5 (NCH), 41.2 (SCH), 22.7 (CH_3), 21.5 (CH_3). – MS (EI): *m/z* (%) = 520 (100) $[M]^+$, 373 (21), 105 (28) $[C_7H_5O]^+$. – $C_{30}H_{36}N_2O_2S_2$ (520.74): calcd. C 69.19, H 6.97, N 5.38, S 12.31; found C 68.84, H 6.99, N 5.28, S 12.51.

Preparation of dithiol **6***:* A sample of **4** (1.35 g, 2.6 mmol) and naphthalene (1 g, 7.8 mmol) were dissolved in THF (50 ml) and pieces of sodium (300 mg, 13 mmol) were added. The reaction mixture was stirred for 12 h at ambient temperature and methanol (5 ml) was added dropwise. The stirring was continued for 30 min. and the solvent was evaporated *in vacuo*. The residue was dissolved in degassed water (50 ml) and washed with diethyl ether (3 × 20 ml). The aqueous phase was then acidified with hydrochloric acid (37 %) to pH = 2 upon which

Table 2. Selected crystal and data collection details for **2b**, **3b**, **4**, **5** and **10**.

	2b	**3b** ∗ $CHCl_3$	**4**	**5**	**10**
Formula	$C_{21}H_{18}O_2S_2$	$C_{23}H_{19}Cl_3O_4S$	$C_{30}H_{36}N_2O_2S_2$	$C_{22}H_{36}N_2O_sS_2$	$C_{26}H_{38}S_4$
fw [amu]	366.47	529.85	520.73	424.65	478.80
a [Å]	40.7590(10)	9.5770(10)	10.1020(10)	10.434(2)	9.0676(6)
b [Å]	12.7660(10)	11.3410(10)	8.5394(9)	17.614(2)	10.3173(7)
c [Å]	7.6430(10)	11.5650(10)	32.535(3)	13.648(2)	15.3445(11)
α [deg]	90	05.560(10)	90	90	90
β [deg]	92.040(10)	99.280(10)	93.329	103.33(2)	106.891(2)
γ [deg]	90	1.130(10)	90	90	90
V [Å^3]	3974.4(6)	1191.6(2)	2801.9(5)	2440.7(7)	1373.6(2)
λ [Å]	0.71073	1.54178	0.71073	0.71073	0.71073
Instrument	Kappa CCD	Kappa CCD	D8 APEX	CAD 4	D8 APEX
Temp [K]	198(2)	223(2)	153(2)	293(2)	233(2)
d_{calc} [g cm^{-1}]	1.225	1.477	1.234	1.156	1.158
Space group	$C2/c$	$P\bar{1}$	$P2_1$	$P2_1/n$	$P2_1/c$
Z	8	2	4	4	2
μ [mm^{-1}]	0.278	5.364	0.219	0.237	0.357
Abs. correct.	SORTAV	SORTAV	SADABS	none	SADABS
Unique data	4531	4860	7256	3170	1790
Obs. data [$I > 2(I)$]	3180	4521	6663	2609	1524
$R1$ (obs.) [%]	7.92, $wR1$ = 25.70	4.74, $wR1$ = 13.06	7.24, $wR1$ = 18.94	3.76, $wR1$ = 9.37	3.79, $wR1$ = 9.69
$R2$ (all) [%]	10.75, $wR2$ = 28.67	5.07, $wR2$ = 13.28	7.76, $wR2$ = 19.34	5.11, $wR2$ = 10.10	4.46, $wR2$ = 10.27
GOF	1.043	1.041	1.077	1.061	1.032
No. of variables	227	292	658	262	136
Res. elec. dens. [e/Å^3]	0.961 / –0.927	0.759 / –0.946	1.110 / –0.341	0.194 / –0.203	0.247 / –0.167

the off-white product precipitated. The precipitate was filtered off, washed with water and diethyl ether and dried *in vacuo* to give an off-white powder (1.03 g, 2.36 mmol, 91 %). IR (KBr): $\tilde{\nu}$ = 3297 (st, N-H), 3031 (w, Ar-H), 2978, 2932 (m, C-H), 2510 (m, S-H), 1618 (st, C=O), 1531 (st, C=O), 700 (s, Ar-H) cm^{-1}. ^{1}H- NMR (200.13 MHz, DMF-D_7): δ = 9.04 (d, ^3J = 7.8 Hz, 2 H, CONH), 7.54 - 7.23 (m, 12 H, Ar-H), 5.26 (m, 2 H, NCH), 1.56 (d, ^3J = 7.6 Hz, 6 H, CH_3). – $^{13}C\{^1H\}$ NMR (50.32 MHz, DMF-D_7): δ = 168.7 (CONH), 145.2, 136.8, 133.3, 129.0, 127.4, 126.8, 125.0 (Ar-C), 49.8 (NCH), 22.6 (CH_3). – MS (EI): *m/z* (%) = 436 (10) [M]$^+$, 335 (14), 106 (100). – $C_{24}H_{24}N_2O_2S_2$ (436.58): calcd. C 66.03, H 5.54, N 6.42, S 14.69; found C 66.29, H 5.21, N 6.35, S 14.82.

Preparation of ester **7***:* Two drops of *N,N*-dimethylformamide and thionyl chloride (0.5 ml) were added to a solution of **2a** (1.0 g, 3.7 mmol) in chloroform (5 ml). The reaction mixture was heated under reflux conditions for 3 h and allowed to cool to ambient temperature. Volatiles were removed *in vacuo*. The reaction product was redissolved in pyridine (5 ml) and isopropanol (10 ml) was added. After being stirred for 12 h, the mixture was poured into water (50 ml) and extracted with diethyl ether (3 × 20 ml). The organic phase was dried over $MgSO_4$. Removal of the solvent and column chromatography (SiO_2, eluent: diethyl ether / petroleum ether 2:1) yielded **7** (910 mg, 3.2 mmol, 86 %) as a yellowish oil. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 7.31 (m, 2 H, Ar-H), 7.20 (dd, 1 H, Ar-H), 5.30 (m, 1 H, OCH), 3.52 (m, 2 H, SCH), 1.39 (d, 12 H, SCH(CH_3)$_2$), 1.22 (d, 6 H, OCH(CH_3)$_2$). – $^{13}C\{^1H\}$ NMR (50.32 MHz, $CDCl_3$): δ = 168.1 (CO), 145.7, 141.7, 129.7, 128.6, 127.8, 123.6 (Ar-C), 69.1 (OCH), 39.4 (SCH), 35.9 (SCH), 23.0, 22.6, 21.8 (CH_3). – MS (EI): *m/z* (%) = 312 (100) [M]$^+$, 269 (12) [M-C_3H_7]$^+$, 253 (17) [M-OC_3H_7]$^+$, 209 (42), 195 (64), 41 (37). – $C_{16}H_{24}O_2S_2$ (312.48): calcd. C 61.50, H 7.74, S 20.52; found C 61.79, H 7.70 S 20.23.

Preparation of alcohol **8***:* A sample of **7** (500 mg, 1.76 mmol) was dissolved in diethyl ether (20 ml) and added dropwise to a suspension of $LiAlH_4$ (67 mg, 1.76 mmol) in diethyl ether (10 ml). The reaction mixture was stirred at ambient temperature for 12 h. Hydrolysis with water and sulfuric acid resulted in the formation of two phases. The organic phase was separated, washed with aqueous $NaHCO_3$ solution (20 ml) and water (20 ml), and dried over $MgSO_4$. Removal of the solvent and column chromatography (SiO_2, eluant: diethyl ether / petrol ether 1 : 3) afforded **8** as a colorless oil (360 mg, 1.40 mmol, 80 %). The analytical data were identical to those of the product prepared by reaction

of lithium 2,3-bis(isopropylmercapto)benzene and paraformaldehyd [8d].

X-ray crystallography: Data were collected on an Enraf-Nonius KappaCCD, on a Bruker AXS APEX or on an Enraf-Nonius CAD4 diffractometer. Both area detector systems are equipped with rotating anodes, the CAD4 system with a sealed tube. All data sets except for **3b**, where Cu-K_α radiation was applied, were measured with Mo-K_α radiation. Empirical absorption corrections were applied on the basis of multiple intensity measurements utilizing the programs SORTAV [12] and SADABS [13]. All structures were solved by direct methods with SHELXS [14] and were refined with anisotropic thermal parameters for non-hydrogen atoms using SHELXL [15]. Hydrogen atoms were added to the structure models in calculated positions and were allowed to refine as riding atoms. ORTEP [16] was used for all drawings. The correct enantiomer of **4** was determined based on a Flack parameter of –0.08(14). Additional data collection and refinement details are listed in Table 2. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 194105 - 194109. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: (+44) 1223-336033; e-mail: deposit@ccdc.ac.uk).

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