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Preparation of 6,12-Imino-6H,12H-dibenzo[b,f]-1,5-dithiocins.

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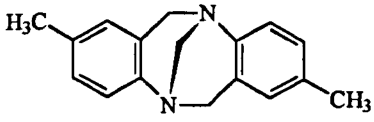
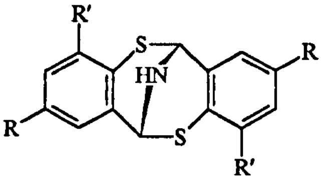
Abstract: Reaction of thiosalicylaldehydes **4a-c** with ammonium acetate affords 6,12-imino-6H,12H-dibenzo[b,f]-1,5-dithiocins **2a-c** in good to excellent yields. The V-shape of these molecules was confirmed by an X-ray structure determination.

Recently, molecules possessing a structurally well defined, V-shaped molecular cleft have attracted considerable attention due to their application toward problems in the areas of molecular recognition, self-assembly and supramolecular chemistry.[1,2] Molecules possessing molecular chirality in addition are of interest as potential chiral ligands and solvating agents.[3] Chiral molecules which lock two aromatic rings in almost perpendicular planes, such as Tröger's base **1**, are of special interest as DNA probes owing to their different possible modes of interaction with DNA and to their chiral properties. It would be advantageous to prepare this type of compound containing a readily functionalized group (such as a secondary amine) for which a variety of derivatives could be produced. We report here the facile preparation of a series of racemic 6,12-imino-6H,12H-dibenzo[b,f]-1,5-dithiocins **2a-c**,[4] which are molecules with potential application for these purposes.



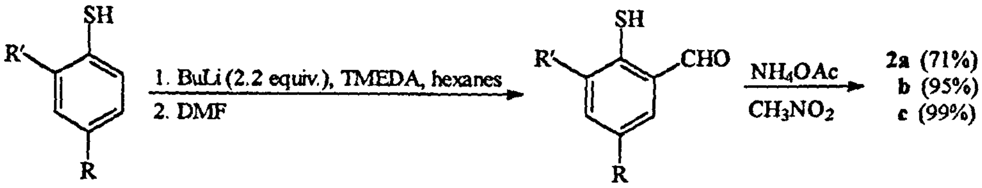
1



2a $R=R'=H$
b $R=CH_3$, $R'=H$
c $R=CH_3$, $R'=S^tBu$

Treatment of the thiosalicylaldehydes **4a-c**[5] with ammonium acetate (1.1 equiv.) in refluxing nitromethane for five hours resulted in the preparation of the bicyclic compounds **2a-c**[6] in good to excellent yields (Scheme 1). The 1,5-dithiocin derivative **2b** had been previously postulated as one of the possible products of the reaction of 2-(methylsulfanyl)-5-methylbenzaldehyde or the corresponding diethyl acetal with sodium in liquid ammonia.[7] Gol'dfarb *et al.*[7a] were unable to confirm **2b** as the correct structure as insufficient spectral evidence was available. Even earlier, Thiel *et al.*[8] had prepared the fully saturated, parent ring system, 1,5-dithia-2,6-iminocyclooctane, by treatment of 4-mercapto-3-methyl-2-butanone with ammonia. Our preparation of **2b** by a different route and X-ray crystallographic analysis (see below) of the closely analogous **2a** now confirms that the structure for **2b** originally postulated by Gol'dfarb was correct.

Scheme 1

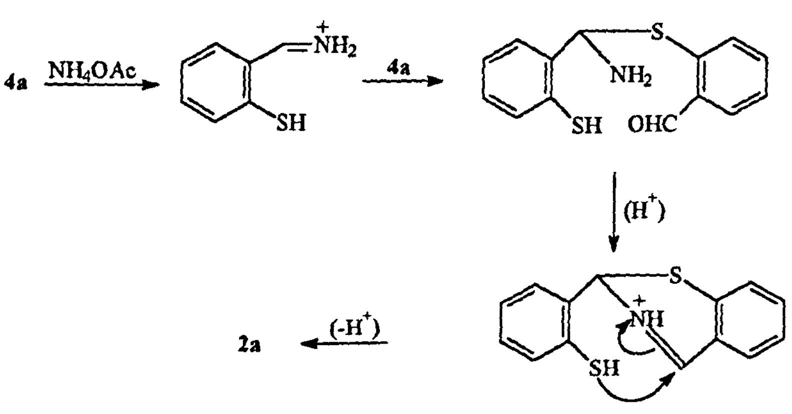


3a R=R'=H
(Ref. 9) **b** $R=CH_3$, R'=H
c $R=CH_3$, $R'=S^tBu$

4a R=R'=H (43%)
b $R=CH_3$, R'=H (37%)
c $R=CH_3$, $R'=S^tBu$ (41%)

The requisite aldehydes **4a-c** were prepared in the yields indicated (Scheme 1) by trapping the organolithium intermediates, formed by directed *ortho*-lithiation[9,10] of the precursor thiols **3a-c**, with N,N-dimethylformamide. Subsequent preparation of compounds **2a-c** shows the versatility of this reaction sequence for the preparation of even highly functionalized derivatives. Two sequential *ortho*-lithiation steps were used to convert 4-methylbenzenethiol **3b** into **4c**. The initial lithiation and trapping with *t*-butyl disulfide[9] introduces the *t*-butyl sulfide moiety, followed by introduction of the required aldehyde functionality as before. A possible mechanism for the transformation of thiosalicylaldehydes into the imino-1,5-dithiocins **2** is detailed in Scheme 2 for the conversion of **4a** into **2a**.

Scheme 2



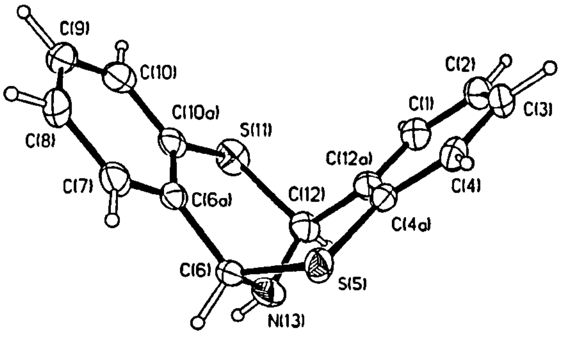


Figure 1. View of molecule **2a**[11] showing labelling scheme. Ellipsoids are shown at the 50% probability level.

Of particular interest here is the molecular chirality possessed by these molecules due to the 6,12-imino bridge locking the two aromatic rings into roughly perpendicular planes (*cf.* Tröger's base). We are currently developing ways to separate the enantiomers produced by this reaction. We have also initiated synthetic efforts towards the modification and further functionalization of the bridging secondary amine. The considerable potential of these molecules in molecular recognition and also as complexing ligands for heavy metals is currently being explored and will be reported in due course.

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4. *Typical procedure:* Benzenethiol (**3a**) was lithiated according to the procedure of Block *et al.*,[10b] by the slow addition of butyllithium (42.9 mmol) to a solution of **3a** (19.5 mmol) in dry TMEDA (43.0 mmol) and hexanes (60 mL) at 0 °C. The resulting turbid reaction mixture was stirred for 16h at 25 °C, then treated with

dry DMF (48.0 mmol). After an additional 16h, the resulting thick white slurry was diluted with diethyl ether (30 mL) and washed with 1M HCl (3 x 30 mL). The ethereal layer was then dried (Na_2SO_4) and concentrated to afford an orange oil. Flash chromatography eluting with CH_2Cl_2 ($R_f = 0.30$) afforded **4a**[5] in 43% yield. The thiosalicylaldehyde **4a** (8.4 mmol) was dissolved in dry nitromethane (40 mL) and treated with NH_4OAc (9.2 mmol), and the resulting tan solution refluxed for 5h. After cooling to room temperature, the reaction mixture was diluted with satd. NaCl (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried (Na_2SO_4) and concentrated to afford a brown solid, which was recrystallized from CH_2Cl_2-hexanes to afford **2a**[6] in 71% yield as a slightly yellow solid.

5. ^{1}H-NMR ($CDCl_3$) data for **4a-c**: (**4a**) δ 10.22 (s, 1H), 7.87 (dd, J=7.7, 1.6 Hz, 1H), 7.78 (dd, J=7.9, 1.6 Hz, 1H), 7.49 (td, J=7.9, 1.7 Hz, 1H), 7.38 (td, J=7.7, 1.6 Hz, 1H), 5.32 (s, 1H). (**4b**) δ 9.98 (s, 1H), 7.53 (d, J=8.5 Hz, 1H), 7.17 (m, 2H), 5.28 (s, 1H), 2.35 (s, 3H). (**4c**) δ 10.07 (s, 1H), 7.65 (d, J=1.7 Hz, 1H), 7.58 (d, J=1.7 Hz, 1H), 6.99 (s, 1H), 2.17 (s, 3H), 1.35 (s, 9H).

6. ^{1}H- and ^{13}C-NMR for compounds **2a-c**: (**2a**) mp 130-132°C; δ 7.27 (m, 2H), 7.06 (m, 6H), 5.74 (s, 2H), 2.89 (br s, 1H); δ 133.9 s, 130.0 s, 128.7 d, 128.0 d, 127.9 d, 124.8 d, 56.1 d. (**2b**) mp 206-207°C (lit.[6a] mp 206-206.5°C); δ 7.08 (s, 2H), 6.90 (s, 4H), 5.66 (s, 2H), 2.81 (br s, 1H), 2.27 (s, 6H); δ 134.5 s, 129.2 d, 129.0 d, 127.9 d, 127.6 s, 126 2 s, 56.1 d, 20.9 q. (**2c**) mp 44-46°C; δ 7.13 (s, 4H), 5.65 (s, 2H), 4.31 (s,1H) 2.25 (s, 6H), 1.22 (s, 18H); δ 138.8 d, 135.3 s, 135.2 s, 133.3 s, 130.7 d, 130.0 s, 57.5 d, 48.3 s, 31.0 q, 20.6 q.

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11. Crystals of **2a** ($C_{14}H_{11}NS_2$) are orthorhombic, space group *Pbca*, $a = 7.734(1)$, $b = 17.090(2)$, $c = 17.398(1)$ Å, $V = 2299.6(4)$ Å^3, $D_c = 1.487$ Mg·m^{-3}, $Z = 8$, Mo-Kα radiation, $\lambda = 0.71073$ Å, μ(Mo-Kα) = 0.435 mm^{-1}, $T = 173(2)$ K. Siemens P4 diffractometer, 2778 reflections (all unique) collected $6 < 2\theta < 60°$, the structure was solved by direct methods[12] and refined by full-matrix least-squares[13] based on F^2. All non-hydrogen atoms refined with anisotropic displacement parameters. H atoms were refined with isotropic thermal parameters. $R_1 = 0.0412$, w$R_2 = 0.0909$ for 2064 reflections with $F > 4\sigma(F)$ and $R_1 = 0.0647$, w$R_2 = 0.1033$ (all data). Minimum and maximum peaks in the final ΔF map -0.349 and 0.275 e·Å^{-3}. Details of molecular dimensions, atomic coordinates, thermal parameters and listings of observed and calculated structure factors have been deposited with the Cambridge Crystallographic Data Centre.

12. Sheldrick, G.M.; SHELXTL/PC, Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, U.S.A.

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