

Two routes to (11,12)-dihydrodibenzo[*c,g*][1,2]dithiocine

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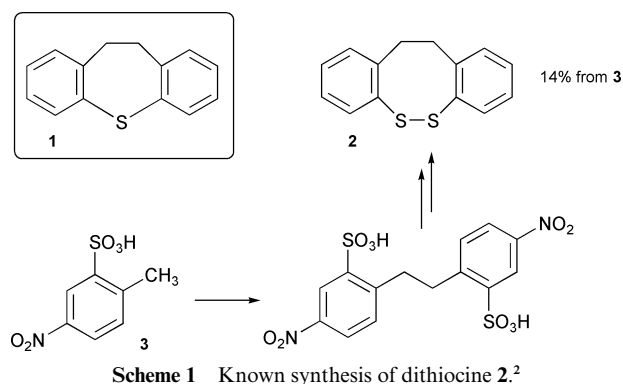
Received 1st December 2003, Accepted 12th March 2004

First published as an Advance Article on the web 26th April 2004

The title compound is made by two routes. One route features the separate introduction of two sulfur atoms and a double Pummerer reaction while the other route contains a direct introduction of both sulfur atoms using disulfur diimidazole.

Introduction

As part of a project concerned both with the use of chiral derivatives of thiepine **1**,¹ and with higher sulfides, we needed dithiocine **2**. This dithiocine **2** has been made before in an overall yield of 14% by a route involving five steps starting from sulfonic acid **3** (Scheme 1).² This acid is not readily available.



We needed to synthesise dithiocine **2** in a higher yield and by a route convenient for dithiocine itself and with a view to application to more complicated substrates. Dibromide **4** was available to us in gram quantities as it can readily be made by the method of Letsing and Skoog or associated modifications.^{3,4} It occurred to us that sulfur could be introduced to its bislithiated derivative.

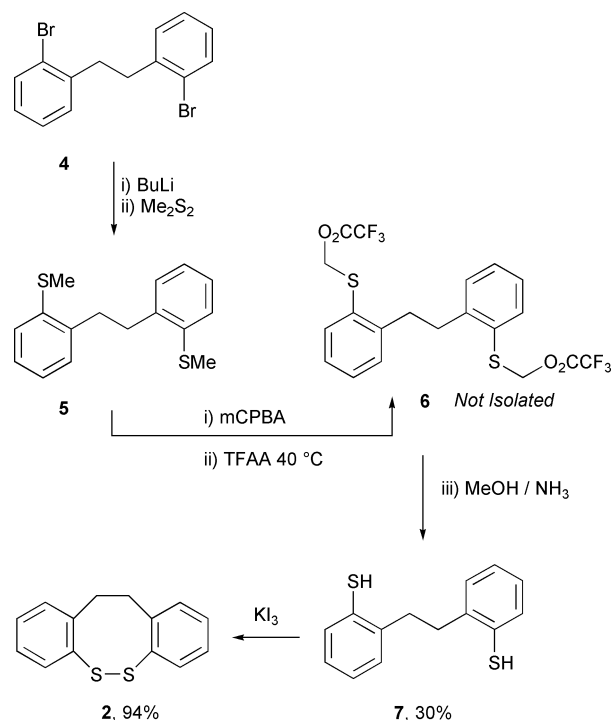
Results and discussion

Sulfur atoms can be introduced with electrophilic sulfur reagents but there are potential problems when this is done at two sites in a molecule simultaneously. With some reagents the two sites can work together and give alternative products. This problem is especially acute when the source is S_8 itself as there are numerous possibilities (like the sulfide or trisulfide). Installation of the two sulfur atoms independently is one strategy to avoid several possible products. Another is to use an electrophilic reagent that contains only two sulfur atoms. We present routes featuring each strategy in turn.

Route one: use of Me_2S_2

Syntheses of disulfides will often be approached by the oxidation of the appropriate dithiol⁵ and this strategy was used in the first route. Double lithiation of dibromide **4** followed by reaction with Me_2S_2 as the sulfur reagent gave the double sulfide product **5**. The reaction was very clean and the yield 92%. Demethylation of this compound was then needed. Because we had established that the method of Gingras *et al.*⁶ involving

sodium alkyl thiolates was too harsh for our more sensitive substrates, we used the milder method of Young *et al.*⁷ Thus a double Pummerer reaction followed by immediate treatment of the Pummerer product **6** with methanolic ammonia gave the dithiol **7** in 30% yield. Oxidation with KI_3 gave the dithiocine **2** in 94% yield (Scheme 2).

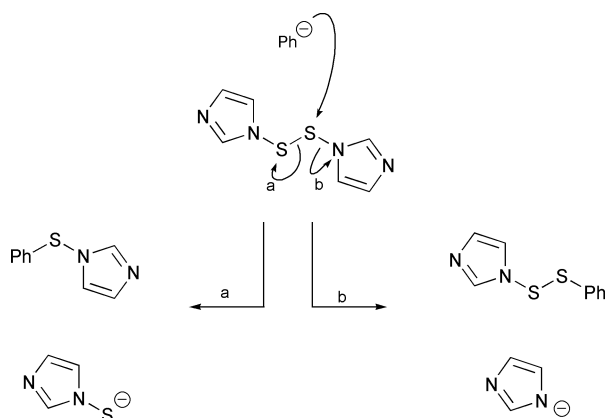


Scheme 2 Route one to dithiocine **2**—a double Pummerer rearrangement.

The overall yield from dibromide **3** was thus 28%. Although this doubled the best yield known to date it was not really good enough for our purposes and we moved on to our second strategy for the dithiocine.

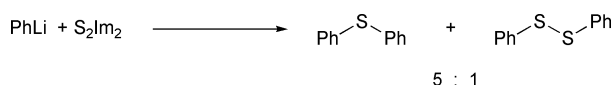
Route two: disulfur diimidazole

Unlike Me_2S_2 where every molecule of reagent donates only *one* of its sulfur atoms to the product, the idea with S_2Im_2 is that both are used. We have previously shown that sulfur diimidazole⁸ can be used as a doubly electrophilic source of sulfur in reactions with organolithium species.¹ The analogous S_2Im_2 can be prepared in a similar way.⁸ Potentially, more things can go wrong with S_2Im_2 as a reagent because it has more than one variety of leaving group—both an imidazole anion (arrow b) and a sulfurimidazole anion (arrow a)(Scheme 3).

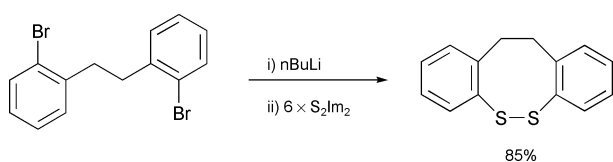


Scheme 3 S_2Im_2 has two types of leaving group.

Thus as well as a disulfide, reaction with nucleophiles may well give sulfides. Indeed, reaction of S_2Im_2 with $PhLi$ gave *mostly* the sulfide (Scheme 4). It should be remembered that $PhSSPh$ reacts with $PhLi$ to give $PhSPh$ so that even if the disulfide *is* made, it may undergo further reaction. Despite all these pitfalls, reaction of lithiated **3** with S_2Im_2 did indeed give the disulfide with an impressive 85% yield (Scheme 5).



Scheme 4 Reaction of $PhLi$ with S_2Im_2 .



Scheme 5 Route two—using S_2Im_2 .

Conclusions

Although the above two routes start with the same dibromide, with the first strategy the two sulfur atoms are introduced independently and the sulfur sulfur bond is made later. With the second strategy the sulfur sulfur bond is already in place. Both routes gave compounds with identical characterisation data but these did *not* agree with the data of Zheltov *et al.* most notably their compound melts at a temperature 150 °C greater than ours.²

Experimental

Flash chromatography was performed using Merck 9385 Kieselgel 60 according to Still.⁹ Thin layer chromatography (TLC) was performed using commercially available glass plates coated with Merck silica Kieselgel 60F₂₅₄. The compounds were visualised by a Mineralight UV lamp or by dipping into a potassium permanganate solution in aqueous sodium hydroxide and heating with a hot air gun.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infra red spectra were recorded on a Perkin Elmer 141 spectrophotometer as liquid films or as solutions in dichloromethane on sodium chloride plates. All nuclear magnetic resonance (NMR) spectra were recorded as solutions using tetramethylsilane as the internal reference on a Jeol GX270 MHz, GX400 MHz or λ 300 MHz spectrometer. All mass spectra were recorded on a Fisons Autospec mass spectrometer and were determined by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) techniques.

When using alkyl lithium reagents, best results were obtained using Hamilton 1700 series gas-tight teflon tipped microsyringes (<1000 μ l) which did not require lubrication, and Hamilton 1700 series gas-tight teflon tipped syringes (>1 ml) lubricated with poly(dimethylsiloxane) 200® fluid with a viscosity of 100 centistokes. All solvents were distilled before use; dry solvents were purchased from Fluka. Distilled 40–60 °C petroleum ether was used for flash chromatography and distilled 60–80 °C petroleum ether for recrystallisations.

S,S' -Dimethylbibenzyl-2,2'-dithiol **5**

Bibenzyl **4** (2.00 g, 5.88 mmol) was dissolved in dry THF (20 ml) under an argon atmosphere and cooled to –78 °C. Then *n*-BuLi (5.18 ml of a 2.5 M solution, 13.0 mmol) was added dropwise to the stirred solution. After the addition was complete the reaction solution is stirred for a further 0.5 h at –78 °C. Dimethyl disulfide (3.18 ml, 35.3 mmol) was then added and the reaction was stirred for a further 1 h at this temperature before being allowed to warm to room temperature overnight. Water (10 ml) was added and the reaction stirred for 0.5 h. The layers were separated and the aqueous layer extracted with dichloromethane (3 \times 10 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate yielded the *methylsulfane* as platelets (1.49 g, 92.4%); mp. 83–84.5 °C (from dichloromethane)(lit.² 89–90 °C); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1588 (Ar), 745 (S–CH₃) and 704 (S–CH₃); δ_H (300 MHz; $CDCl_3$) 7.24–7.06 (8 H, m, ArH), 3.02 (4 H, s, ArCH₂) and 2.48 (6 H, s, SMe); δ_C (75.5 MHz; $CDCl_3$) 139.8 (1 or 2-ArC), 137.3 (1 or 2-ArC), 129.2 (ArC), 126.8 (ArC), 125.7 (ArC), 125.0 (ArC), 34.1 (ArCH₂) and 15.9 (SMe); m/z (EI) 274 (M⁺, 9%), 259.0619 (M⁺ Me. $C_{16}H_{18}S_2$ requires 259.0615), 227 (M⁺ SMe, 4) and 137 (ArCH₂, 100).

Bibenzyl-2,2'-dithiol **7**

Methylsulfane **5** (1.00 g, 3.65 mmol) was dissolved in dichloromethane (20 ml). Then 57–86% *m*-CPBA (396 mg) was added and the solution stirred at room temperature for 0.1 h. Sodium sulfite (1.00 g) was added and the reaction mixture stirred for 0.1 h. The suspension was filtered and the filtrate concentrated under reduced pressure. The product was dissolved in trifluoroacetic anhydride (30 ml), heated to reflux and stirred at this temperature for 0.5 h. The solution was allowed to cool to room temperature and concentrated under reduced pressure. The residue was dissolved in a mixture of methanol (20 ml) and triethylamine (20 ml) and once again concentrated under reduced pressure. The crude product was dissolved in chloroform (20 ml), washed with a saturated ammonium chloride solution (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate yielded the *dithiol* as a powder (270 mg, 30.1%); mp 62–63 °C (from dichloromethane); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2560 (SH), 1589 (Ar) and 1569 (Ar); δ_H (300 MHz; $CDCl_3$) 7.30–7.04 (8 H, m, ArH), 3.37 (2 H, s, ArSH) and 2.97 (4 H, s, ArCH₂); δ_C (75.5 MHz; $CDCl_3$) 139.6 (2-ArC), 131.0 (1-ArC), 130.3 (ArC), 129.8 (ArC), 126.9 (ArC), 126.2 (ArC) and 34.8 (ArCH₂); m/z (CI) 247.0614 ([MH]⁺. $C_{14}H_{15}S_2$ requires 247.0615), 246 ([MH] + H, 62%), 213 ([MH] + H₂S, 51) and 137 (100).

(11,12)-Dihydrodibenzo[*c,g*][1,2]dithiocine **2** (by route one)

Dithiol **7** (200 mg, 0.813 mmol) was dissolved in chloroform (10 ml) to which an excess of potassium triiodide was added. The resulting solution was washed with a saturated solution of sodium sulfonate (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallisation from petroleum ether yielded the *disulfide* as a powder (187 mg, 94.3%).

(11,12)-Dihydrodibenzo[*c,g*][1,2]dithiocine 2 (by route two)

Bibenzyl **4** (3.00 g, 8.82 mmol) was dissolved in dry THF (30 ml) under an argon atmosphere and cooled to -78°C . Then *n*-BuLi (7.77 ml of a 2.5 M solution, 19.4 mmol) was added dropwise to the stirred solution. After the addition was complete the reaction solution is stirred for a further 0.5 h at 78°C . Disulfur diimidazole⁸ (10.5 g, 52.9 mmol) was then added and the reaction was stirred for a further 1 h at this temperature before being allowed to warm to room temperature overnight. Water (10 ml) was added and the reaction stirred for 0.5 h. The layers were separated and the aqueous layer extracted with dichloromethane (3×10 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography, eluting with petroleum ether–ethyl acetate yielded the disulfide as a yellow powder (1.82 g, 84.5%); mp $41\text{--}42.5^{\circ}\text{C}$ (from petroleum ether)(lit.,² $192\text{--}193^{\circ}\text{C}$); $\nu_{\text{max}}(\text{CH}_2\text{Cl}_2)/\text{cm}^{-1}$ 1589 (Ar), 1563 (Ar) and 683 (S–S); $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 7.44 (2 H, br d, *J* 7.9, 4-ArH), 7.17–7.04 (6 H, m, ArH) and 3.31 (4 H, s, ArCH); $\delta_{\text{C}}(75.5 \text{ MHz}; \text{CDCl}_3)$ 142.2 (4a-ArC), 134.5 (12a-ArC), 131.2 (4-ArC), 130.3 (ArC), 127.6 (ArC), 126.2 (ArC) and 33.4 (ArCH₂); *m/z* (EI) 244.0377 (M^+ $\text{C}_{14}\text{H}_{12}\text{S}_2$ requires 244.0380) and 212 (*M* + S, 100%).

Reaction of phenyl lithium with disulfur diimidazole

Phenyl lithium (0.96 ml of a 1.8 M solution, 1.73 mmol) was added to dry THF (50 ml) under an argon atmosphere and cooled to -78°C . Disulfur diimidazole⁸ (2.05 g, 10.4 mmol) was added and the reaction is stirred for a further 1 h at this temperature before being allowed to warm to room temperature overnight. Water (20 ml) was added and the reaction stirred for 0.5 h. The layers were separated and the aqueous layer extracted

with dichloromethane (3×10 ml). The combined organic extracts were washed with a saturated solution of ammonium chloride (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was dissolved in dichloromethane, filtered through a pad of silica and concentrated under reduced pressure. ^{13}C NMR indicated a mixture of diphenylsulfide;¹⁰ $\delta_{\text{C}}(75.5 \text{ MHz}; \text{CDCl}_3)$ 131.9 (ArC), 130.1 (ArC) and 127.1 (ArC), and diphenyldisulfide;¹¹ $\delta_{\text{C}}(75.5 \text{ MHz}; \text{CDCl}_3)$ 129.9 (ArC), 128.4 (ArC) and 128.1 (ArC). Addition of $\text{Cr}(\text{acac})_2$ (30 mg) to the NMR sample allowed for an accurate integration of the ^{13}C -NMR signals.¹² The ratio of diphenylsulfide to diphenyldisulfide was found to be 5 to 1.

Acknowledgements

Support of this work by the University of Bristol via a University Scholarship (to A.H.) and by the School of Chemistry is gratefully acknowledged.

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† Our data do not match those of Zheltov *et al.* (ref. 2). Not only is the melting point out but the chemical shift at 3.31 ppm is reported as 3.15 ppm. Given we have made the compound by two quite separate methods and obtained identical characterisation data we are confident we have made the correct material.