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The Synthesis of 1-Hydroxy-3-phenylsulphonylpiperidine-2-thione Derivatives Utilizing Methylthiothiocarbonylation as the Key Original Step.

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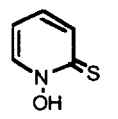
Abstract: Three 1-hydroxy-3-phenylsulphonylpiperidine-2-thione derivatives have been prepared from methylphenylsulphone in five steps. The key step was the preparation of a dithioester which was achieved in a very high yield using nBuLi, CS_2, and MeI.

Cyclic thiohydroxamic acids especially the 1-hydroxypyridine-2-thiones (**1**) have become very desirable compounds due to their many properties which range from anti-fungal agents[1] to derivatives which can selectively extract certain metal ions from aqueous media[2]. In continuing our search for novel thiohydroxamic acids for use in Barton ester chemistry we synthesised the three 1-hydroxypiperidine-2-thione derivatives **2**,**3** and **4**. Their synthesis involved an improved methylthiothiocarbonylation reaction.



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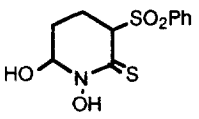

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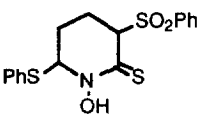

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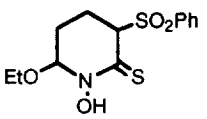

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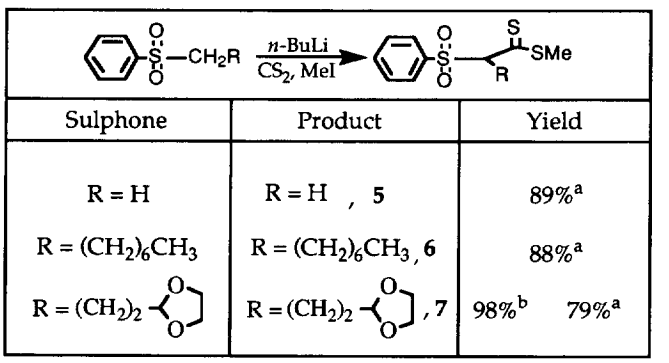
The key step to the preparation of these compounds was the synthesis of the known compound **5** from methylphenylsulphone. This has previously been prepared in a 20% yield by Ladurée *et al.*[3]. Veenstra and Zwanenberg have also reported the synthesis of this compound in a 53% yield[4]. In view of these yields it was decided to investigate the formation of the dithioacetate **5** from phenylmethylsulphone in an attempt to improve significantly the yield.

The literature shows that the preparation of alkyl dithioesters using carbon disulfide has always been difficult with yields usually well below 10%[5]. The major product was usually the corresponding dithioketene, and this has proved to be especially so when bases such as alkali-hydroxides, alcoholates, hydrides and amides were used[6]. In more recent years a few much higher yielding procedures have been presented. In two of the more notable publications, Konen *et al.* have shown that alkyl dithioesters can be produced in moderate to high yields from the corresponding carboxylic acid by treatment with *n*-butyllithium, carbon disulphide and methyl

iodide at -50°C to -78°C[7]. Baird and Bereman have prepared the corresponding methylthiothiocarbonyl derivative of a 1,3-dithiane in 85% yield using *n*-butyllithium, carbon disulphide and methyl iodide -28°C[8].

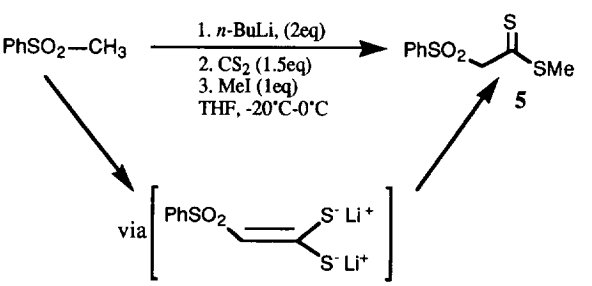
It was found that an excellent yield (Table 1) of **5** could be obtained by reacting the starting sulphone with *n*-butyllithium (2.0 equiv), carbon disulphide (1.5 equiv) and methyl iodide (1 equiv) (Scheme 1). Initially the reaction was performed at -40°C, but at this temperature we had problems with the precipitation of the di-lithium salt of the dithioketene (Scheme 1). It was later found that the reaction could be performed at 0°C with no decrease in the yield of the product. At this temperature the di-lithium salt did not precipitate. These conditions also gave high yields of the corresponding dithioesters (**6,7**) when attempted on two other sulphone derivatives (Table 1). Clearly the success of the synthesis depends on the carefully controlled addition of only one equivalent of methyl iodide.



Sulphone	Product	Yield
R = H	R = H , **5**	89%[a]
R = $(CH_2)_6CH_3$	R = $(CH_2)_6CH_3$, **6**	88%[a]
R = $(CH_2)_2$	R = $(CH_2)_2$, **7**	98%[b] 79%[a]

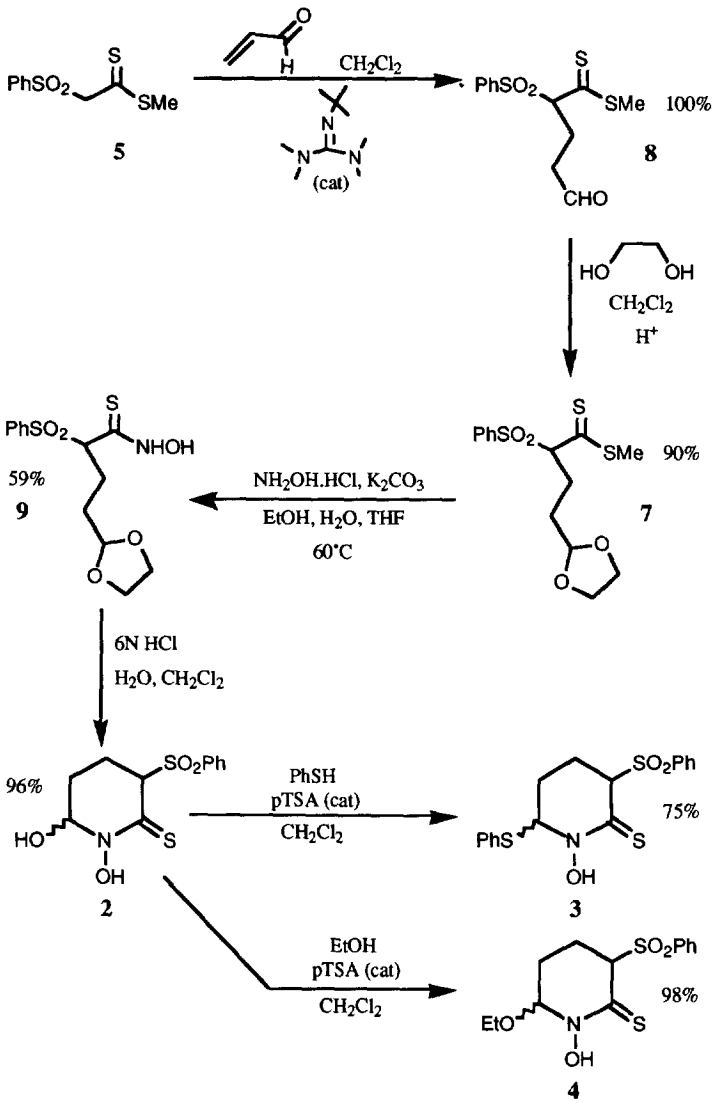
a. Isolated yield. b. Yield by NMR

Table 1



Scheme 1

Preparation of the cyclic thiohydroxamic acids **2, 3** and **4** was now easily achieved as shown in scheme 2. Compound **8** was prepared in a quantitative yield from a Michael addition between **5** and acrolein using *tert*-butyltetramethylguanidine as the base. This base was chosen because hindered guanidine bases have been shown to be potentially very useful in organic synthesis[9]. The aldehyde **8** was immediately protected almost quantitatively as the corresponding dioxolane **7** due to its instability at room temperature. The physical data for compound **7** were identical to those of the dioxolane **7** which had been directly prepared from the corresponding sulphone by reaction with nBuLi, CS_2 and MeI (Table 1).



Scheme 2

When **7** was treated with hydroxylamine (generated from aqueous hydroxylamine hydrochloride and potassium carbonate) at 60°C the thiohydroxamic acid **9** was obtained in a moderate yield. Cyclisation of **9** to give a high yield of cyclic hydroxamic acid **2** was easily achieved by rapidly stirring **9** in a mixture of 6N HCl and dichloromethane. When compound **2** was stirred with one equivalent of thiophenol in the presence of a catalytic amount of *p*-toluene sulphonic acid in dichloromethane at room temperature compound **3** was produced in a 75% yield after isolation. The hydroxamic acid **4** was obtained in a 98% yield as a very hydroscopic syrup if ethanol was employed instead of thiophenol.

In conclusion this work presents a new method for the preparation of dithioesters from CS_2 in high yields and also of high purity. One of the main attributes of this synthesis is that no purification is necessary until the thiohydroxamic acid **9**. This work also describes the synthesis of a new class of thiohydroxamic acids of potential use in radical chemistry.

Experimental

Melting points were taken on a Kofler hot stage melting point apparatus and are not corrected. IR spectra were recorded on a Perkin Ellmer 881 spectrophotometer. ^1H and ^{13}C NMR spectra were measured with a Varian Gemini 200 or a Varian XL-200E in $CDCl_3$ or D_6DMSO. Chemical Shifts are in p.p.m. downfield from tetramethylsilane used as an internal standard (δ values). Microanalyses were performed by Atlantic Microlab Inc., Norcross, GA. Solvents were used either as purchased or dried and purified by standard methods. All the reactions where necessary were effected under an inert atmosphere of argon. Flash column chromatography was performed using Kiessegel 60 (230-400 mesh, E. Merck).

Dithioacetate 5

Typical procedure: To a solution of methyl phenyl sulfone (7.0 g, 44.9 mmol) in THF (200 ml) was added slowly nBuLi (1.6M, 28 ml) at 0°C. After 30 min the solution was cooled to -20°C and CS_2 (1.4 ml, 22.4 mmol) was added and the temperature slowly raised to 0°C. After 30 min another equivalent of nBuLi (28 ml) was added to the reaction mixture at 0°C and the reaction stirred for 30 min. The mixture was cooled to -20°C and CS_2 (44.9 mmol, 2.8 ml) was added. At this point the mixture becomes red and the dilithium salt usually precipitates. Allowing the mixture to warm to 0°C makes the solution become homogeneous again. After 30 min MeI (2.8 ml, 44.9 mmol) was added and the reaction was stirred for 30 min at 0°C, and then poured into a cold solution of HCl (1M) followed by extraction with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the pure compound **5** (10.8 g, 89%) as determined by ^1H NMR. (orange needles) **m.p.** 46-48°C (CH_2Cl_2/hexanes) {lit[3]. **m.p.** 49°C}; **IR** (KBr):1300-1135-990 cm^{-1}; **^1H NMR** (200 MHz, $CDCl_3$) 2.55 (3H, s); 4.75 (2H, s); 7.5 (2H, m); 7.6 (1H, m); 7.8 (2H, m). **^{13}C NMR** (50 MHz, $CDCl_3$) 21.1 (CH_3); 74.5 (CH_2); 128.9 (CH); 134.2 (CH); 136.1 (Cq); 217.1 (C=S).

Dithioacetate 6

This compound was prepared in a manner analogous to that of **5** starting from the n-octyl phenyl sulphone[10] (2.0 g, 7.3 mmol). Chromatography of the residue on silica gel (ethyl acetate/hexane, 2/8) gave **6** as an orange oil (2.4 g, 88 %). **IR** (KBr): 1320-1308-1148 cm^{-1}; **^1H NMR** (200 MHz, $CDCl_3$) 0.85 (3H, m); 1.22 (10H, m); 2.2-2.4 (2H, m); 2.57 (3H, s); 4.7 (1H, m); 7.52 (2H, m); 7.62 (1H, m); 7.8 (2H, m). **^{13}C NMR** (50 MHz, $CDCl_3$) 13.7 (CH_3); 20.1 (CH_3); 22.2 (CH_2); 20.6 (CH_2); 28.5 (CH_2); 29.1 (CH_2); 31.4 (CH_2); 82.4 (CH); 128.9 (CH); 129.9 (CH); 134.1 (CH); 136.4 (Cq); 225.0 (C=S). **Anal.** Calcd for $C_{16}H_{24}O_2S_3$: C, 55.78; H, 7.02; S, 27.92 Found: C, 55.72; H, 7.07; S, 28.02.

Dithioacetate 7

This compound was prepared in a manner analogous to that of **5** starting from 2-((3-phenylsulphonyl)propyl)-1,3-dioxolane[11] (8.5 g, 33.2 mmol). Chromatography of the residue on silica gel (ethyl acetate/hexane, 2/8) gave **7** (8.1 g, 70 %) (orange needles). **m.p.** 75°C (CH_2Cl_2/hexanes); **IR** (KBr): 131-1279-1136-1001-926-898 cm^{-1}; **^1H NMR** (200 MHz, $CDCl_3$)1.7 (2H, m); 2.5 (2H, m) 2.58 (3H, s); 3.85 (4H, m); 4.84 (2H, m); 7.52 (2H, m); 7.65 (1H, m); 7.82 (2H, m). **^{13}C NMR** (50 MHz, $CDCl_3$) 20.2 (CH_3); 24.5 (CH_2) 29.6

(CH_2) 64.8 (CH_2); 64.9 (CH2O); 81.6 (CH); 103.4 (CH); 128.7 (CH); 129.9 (CH); 134.1 (CH); 136.3 (Cq); 224.6 (C=S). **Anal.** Calcd for $C_{14}H_{18}O_4S_3$: C, 48.52; H, 5.23; S, 27.76 Found: C, 48.52; H, 5.27; S, 27.66.

Aldehyde 8

From Michael addition of **5** to acrolein

To a solution of **5** in dicholromethane (15 ml) was added at room temperature a solution of acrolein in dichloromethane and one drop of the *t*-butyl tetramethylguanidine. The solution was stirred for 30 min and washed successively with dilute cold aqueous HCl, water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The aldehyde **8** (3.0 g, 100%) was obtained pure as determined by NMR. This was an unstable orange oil. **IR** (film): 1718-1306-1144-1081 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) 2.58 (7H, SCH_3, 1s, 4H, m); 4.8 (1H, m); 7.54 (2H, m); 7.65 (1H, m); 7.8 (2H, m); 9.7 (CHO). **^{13}C NMR** (50 MHz, $CDCl_3$) 20.5 (SCH_3); 23.2 (CH_2); 39.7 (CH_2); 80.4 (CH); 128.8 (CH); 129.9 (CH); 134.4 (CH); 136 (Cq); 200.2 (CHO); 223.8 (C=S).

From **7**

A solution of **7** in a mixture of CH_3COOH/H_20 (40 ml, 1/1) was stirred at 90°C for 1 h. The mixture was then diluted with dichloromethane and washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography of the residue on silica gel (EtOAc/Hexanes, 2/8) afforded the aldehyde **8** (1.21 g, 51%) identical to the product obtained by the Michael addition reaction.

Dioxolane 7 (from the aldehyde 8)

To a solution of the aldehyde **8** (1.0 g, 3.3 mmol) in dichloromethane (2 ml) was added at room temperature ethylene glycol (184 µl, 3.3 mmol) and pTSA (60 mg, 0.3 mmol). The reaction mixture was stirred for 2h and then washed with cold water, dried over $MgSO_4$, filtered and evaporated to give the pure dioxolane **7** (1.0 g, 90%) as determined by NMR. This compound was identical to the dithioacetate previously obtained from 2-((3-phenylsulphonyl)propyl)-1,3-dioxolane.

Thiohydroxamic acid 9

An aqueous solution of NH_2OH was obtained by reacting $NH_2OH.HCl$ (7.3 g, 104.8 mmol) with K_2CO_3 (7.3 g, 52.4 mmol) in water (55 ml).This solution was then added dropwise at room temperature to the dithioacetate **7** (12.1 g, 34.9 mmol) (prepared from the aldehyde **6**) dissolved in a mixture of THF (50 ml) and EtOH (10ml). The reaction mixture was stirred for 24h then extracted first with ether and then with ethyl acetate. The aqueous layer was then acidified with HCl (6M) and extracted with ethyl acetate. The ethyl acetate layers were combined and dried over $MgSO_4$, filtered and evaporated. Upon addition of ether to the residue the white thiohydroxamic acid **9** precipitated. Yield after filtration (6.8 g, 59%). **m.p.** 134°C (CH_2Cl_2/hexanes) **IR** (KBr): 3190-1433-1356-1298-1129 cm^{-1}; **^{1}H NMR** (200 MHz, d_6-DMSO) 1.3-1.6 (2H, m); 1.8-2.3 (2H, m); 3.76 (4H, m); 4.3 (1H, dd, J_1= 3.4 Hz, J_2= 11.33 Hz); 4.76 (1H, t, J= 4.43 Hz); 7.6-7.9 (6H, m); 10.5 (1H, br). **^{13}C NMR** (50 MHz, d_6-DMSO) 22.4 (CH_2); 29.6 (CH_2); 64.3 (CH_2); 64.4 (CH_2); 70.6 (CH); 102.5 (CH); 128.9 (CH); 129.4 (CH); 134.3 (CH); 136.6 (Cq).

Thiohydroxamic 2

To a suspension of the thiohydroxamic acid **9** (1.4 g, 4.4 mmol) in dichloromethane (10 ml) was added HCl (6N, 10 ml). The reaction mixture was stirred until all the suspension has disappeared (approximately 2-3 hrs). The reaction mixture was then diluted with dichloromethane and successively washed with water and brine.

The organic layer was dried over $MgSO_4$, filtered and evaporated to give the pure thiohydroxamic acid **2** (1.2 g, 96%) as a mixture of two isomers (8/2). major product: **m.p** (dec) 121-131°C (CH_2Cl_2/EtOH) **IR** (KBr): 3433-1401-1295-1133-1080-976 cm^{-1}; **^{1}H NMR** (200 MHz, d_6-DMSO/$CDCl_3$) 2.05 (1H, m); 2.2-2.8 (3H, m); 4.58 (1H, d); 5.44 (1H, m); 7.35 (1H, md); 7.6 (2H, m); 7.7 (1H, m); 7.9 (2H, m); 10.6 (1H, s). **^{13}C NMR** (50 MHz, d_6-DMSO/$CDCl_3$) 15.8 (CH_2); 26.7 (CH_2); 69.4 (CH); 79.9 (CH); 128.2 (CH); 128.7 (CH); 133.5 (CH); 137.7 (Cq); 173.3 (C=S). **Anal.** Calcd for $C_{11}H_{13}NO_4S_2$: C,45.97; H, 4.56; N, 4.87. Found: C, 46.08; H, 4.51; N, 4.81.

Thiohydroxamic acid 3

To a solution of the thiohydroxamic acid **2** (3.3 g, 11.6 mmol) in dichloromethane (50 ml) was added thiophenol (1.2 ml, 11.6 mmol) and pTSA (500 mg). The solution was stirred for 5 h then diluted with dichloromethane and washed successively with an aqueous solution of K_2CO_3, water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give the pure thiohydroxamic acid **3** (3.3 g, 75%) which recrystallized in a mixture of dichloromethane/hexane. **m.p.** (dec) 122-124°C (CH_2Cl_2/hexanes) **IR** (KBr): 3448-1483-1428-1387-1285-1118 cm^{-1}; **^{1}H NMR** (200MHz, $CDCl_3$) 2.1-2.3(1H, m); 2.4 (1H, m); 2.85 (1H, m); 3.1-3.3 (1H, m); 4.42 (1H, dd, J_1= 4.6 Hz, J_2= 1.4 Hz); 5.32 (1H, d, J= 4.78 Hz); 7.35 (3H, m); 7.55 (4H, m); 7.65 (1H, m); 7.85 (1H, m). **^{13}C NMR** (50 MHz, $CDCl_3$) 17.8 (CH_2); 28.1 (CH_2); 68.7 (CH); 69.5 (CH); 128.7 (CH); 129.1 (CH); 129.5 (CH); 132.1 (Cq); 134.3 (CH); 137.6 (Cq); 173.1 (C=S). **Anal.** Calcd for $C_{17}H_{17}NO_3S_3$: C, 53.79; H, 4.51; N, 3.69; S, 25.34. Found: C, 53.66; H, 4.47; N, 3.67; S, 25.25.

Thiohydroxamic acid 4

To a solution of the thiohydroxamic acid **2** (107 mg, 0.37 mmol) in dichloromethane (5 ml) was added ethanol (2 ml) and pTSA (20 mg, 0.1 mmol). The solution was stirred for 6 h then diluted with dichloromethane and washed successively with water and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give the pure thiohydroxamic acid **4** as a hygroscopic syrup (120 mg, 100%). **IR** (film): 3350-1301-1141-1084 cm^{-1}; **^{1}H NMR** (200MHz, $CDCl_3$) 1.2 (3H, t); 2.1-2.4-2.8 (4H, m); 3.8-4 (2H, m); 4.4 (1H, m); 5.2 (1H, m); 7.5 (2H, m); 2.65 (1H, m); 2.85 (2H, m); 10.5 (1H, OH, s). **^{13}C NMR** (50 MHz, $CDCl_3$) 15.3 (CH_3); 17.1 (CH_2); 27.2 (CH_2); 68.3 (CH_2); 69.7 (CH); 86.7 (CH); 128.7 (CH); 129.5 (CH); 134.1 (CH); 137.9 (Cq); 173.5 (C=S).

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