# Synthetic Application of Lithiated Tris(methylthio)methane: Preparation of Aliphatic Methyl Thiolcarboxylates from the Corresponding Halides. Convenient Synthesis of Tris(methylthio)methane†

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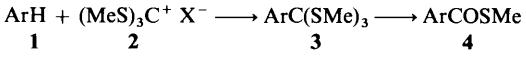
A thorough study directed towards the synthesis of methyl thiolcarboxylates was made on the basis of the following steps: (i) conversion of alkyl halides into the corresponding trimethyl trithioorthocarboxylates by using tris(methylthio)methyllithium in THF at −78 °C; (ii) selective hydrolysis of the intermediates to methyl thiolcarboxylates by using 35% aq. $HBF_4$ in DMSO or, in some cases, in THF. The overall yields of the two stages are, usually, between 70 and 88%. By this procedure it is also possible to incorporate $^{18}O$ in the carbonyl group of thiol esters (~98% isotopic purity). Furthermore, a new, convenient method for the preparation of tris(methylthio)methane as the precursor of tris(methylthio)methyllithium was developed.

Over the years many methods have been developed for the preparation of thiolcarboxylate esters (thiocarboxylic *S*-esters or thiol esters) in connection with their increasing synthetic utility.[1,2] Among the above, in our previous research[3,4] an efficient method for the preparation of electron-rich aromatic and heteroaromatic methyl thiolcarboxylates **4** has been achieved. It consists of a two-step sequence starting from an aromatic or heteroaromatic substrate **1** as reported in Scheme 1.




**Scheme 1**

In this work, which finds its origin in Seebach's research on the umpolung of the reactivity of carbonyl compounds through sulfur-containing reagents,[5] a thorough study on the applicability of the synthetic sequence reported in Scheme 2 to prepare aliphatic methyl thiolcarboxylates **8** is presented.

This work also comprises the development of a new, convenient method for the preparation of tris(methylthio)methane **9** as the precursor of lithium compound **6** (Scheme 3). With regard to the last objective it should be noted that although compound **9** is commercially available, it is quite expensive. Methods of preparation are reported in the literature, the most commonly used being based on the reaction of trimethyl orthoformate with methyl mercaptan.[6] However, this involves disagreeable problems in handling. In the course of this research we found that the tris(methylthio)methyl cation of salts **2** quickly and easily converts, in almost quantitative yield, into tris(methylthio)methane **9** by simple reduction with sodium borohydride in anhydrous acetonitrile (Scheme 3). As salts **2** are readily available[4] the new method will have the advantage of simply and economically providing notable amounts of compound **9**.

**Scheme 3** *Reagents and conditions:* i, $NaBH_4$, MeCN, 5–10 °C.

Apart from this useful objective, with regard to the synthesis of thiolcarboxylates **8** on the basis of Scheme 2, not much information is available in the literature on the conversion of the alkyl halides **5** into the corresponding trimethyl trithioorthocarboxylates **7** and it certainly cannot be used as a general method.[7–11] This conversion was evaluated by studying the reactions of numerous halides and dihalides with tris(methylthio)methyl lithium **6** under nitrogen in anhydrous tetrahydrofuran (THF) at −78 °C. An examination of the results reported in Table 1 leads to the following conclusions. The reactions of the lithium compound **6** with various alkyl and cycloalkyl halides (entries 1–21) likely take place *via* the $S_N2$ mechanism. At a temperature of −78 °C, at which there is no decomposition of the tris(methylthio)methyl anion, the reactions are highly selective and their success clearly depends both

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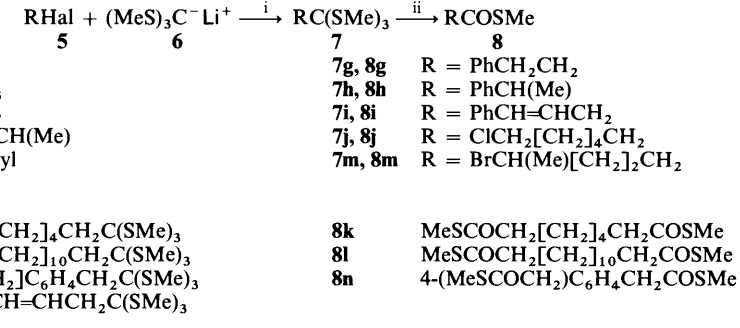



**Scheme 2** *Reagents and conditions:* i, THF, −78 °C; ii, Procedure A: DMSO, 35% aq. $HBF_4$ (19.5:0.5), 130 °C; Procedure B: THF, 35% aq. $HBF_4$ (19.5–19.0:0.5–1), ~70 °C.

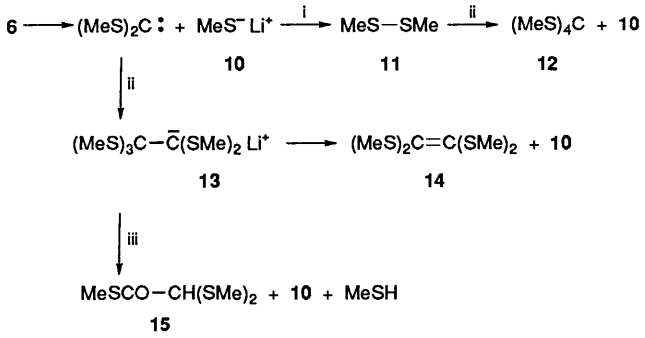
**Table 1** Trimethyl trithioorthocarboxylates **7a–o** and methyl thiolcarboxylates **8a–n**: reaction conditions and yields.

| Starting RHal **5** | Entry No | $RC(SMe)_3$ **7** | Chromatographic solvent[a] | Yield[b] (%) | Entry No | RCOSMe **8** | Procedure | Reaction time (*t*/h) | Yield (%)[b,c] from **7** | Overall yield (%)[b,c] from **5** without isolation of **7** |
|---|---|---|---|---|---|---|---|---|---|---|
| $n\text{-}C_4H_9Br$ | 1 | **7a** | LP–B (9.5:0.5) | 91 | 22 | **8a** | A | 0.25 | 76 | 70 |
| | | | | | 23 | **8a** | B | 2.5 | 84 | 78 |
| $n\text{-}C_{12}H_{25}Cl$ | 2 | **7b** | LP–B (9.5:0.5) | tr[d] | | | | | | |
| $n\text{-}C_{12}H_{25}Br$ | 3 | **7b** | LP–B (9.5:0.5) | 89 | 24 | **8b** | A | 0.25 | 95 | 84 |
| | | | | | 25 | **8b** | B | 5 | 97 | 86 |
| $n\text{-}C_{12}H_{25}I$ | 4 | **7b** | LP–B (9.5:0.5) | 81 | | | | | | |
| $n\text{-}C_{18}H_{37}Br$ | 5 | **7c** | LP–B (9:1) | 86 | 26 | **8c** | A | 0.5 | 94 | 82 |
| $C_6H_{13}CH(Me)Br$ | 6 | **7d** | | tr[d,e] | | | | | | |
| $C_6H_{13}CH(Me)I$ | 7 | **7d** | LP–B (9.8:0.2) | 51[f] | 27 | **8d** | A | 0.25 | | ≤8 |
| | | | | | 28 | **8d** | B | 1 | 96 | 68 |
| $c\text{-}C_5H_9Br$ | 8 | **7e** | LP–B (9.5:0.5) | 12[g] | 29 | **8e** | A | 0.1 | | ≤8 |
| | | | | | 30 | **8e** | B | 1 | | 35 |
| $c\text{-}C_6H_{11}Br$ | 9 | *h* | | | | | | | | |
| $PhCH_2Cl$ | 10 | **7f** | LP–B (8:2) | 72[i] | 31 | **8f** | A | 1.5 | 95 | 80 |
| $PhCH_2Br$ | 11 | **7f** | LP–B (8:2) | 81[i] | 32 | **8f** | A | 1.5 | 95 | 80 |
| | | | | | 33 | **8f** | B | 5 | | 80 |
| $PhCH_2CH_2Br$ | 12 | **7g** | LP–B (7:3) | 82 | 34 | **8g** | A | 1 | 91 | 73 |
| | | | | | 35 | **8g** | B | 5 | 92 | 74 |
| PhCH(Me)Br | 13 | **7h** | LP–B (8:2) | 35[j] | 36 | **8h** | A | 4 | | *k* |
| | | | | | 37 | **8h** | B | 8 | | 73 |
| $PhCH{=}CHCH_2Cl$ | 14 | **7i** | LP–EE (8.5:1.5) | 86 | 38 | **8i** | A | 12 | | *l* |
| | | | | | 39 | **8i** | B | 48 | 46 | 40 |
| $ClCH_2[CH_2]_4CH_2Br$ | 15 | **7j** | LP–EE (9.8:0.2) | 86[m] | 40 | **8j** | A | 0.25 | 97 | 83 |
| $BrCH_2[CH_2]_4CH_2Br$ | 16 | **7k** | LP–EE (9.8:0.2) | 87 | 41 | **8k** | A | 0.25 | 93 | 82 |
| $BrCH_2[CH_2]_{10}CH_2Br$ | 17 | **7l** | LP–EE (9.5:0.5) | 91 | 42 | **8l** | A | 0.25 | 96 | 87 |
| $BrCH(Me)[CH_2]_2CH_2Br$ | 18 | **7m** | LP–EE (9:1) | *m,n* | 43 | **8m** | A | 0.25 | | ≤8 |
| | | | | | 44 | **8m** | B | 0.75 | | 88 |
| $Me[CH_2]_9CH(Br)CH_2Br$ | 19 | *o* | | | | | | | | |
| $4\text{-}ClCH_2C_6H_4CH_2Cl$ | 20 | **7n** | LP–B (7:3) | 74[p] | 45 | **8n** | A | 1.25 | 90 | 74 |
| $ClCH_2CH{=}CHCH_2Cl$ | 21 | **7o** | LP–EE (9.9:0.1) | 80 | 46 | **8o** | A | *l* | | |
| | | | | | 47 | **8o** | B | *l* | | |

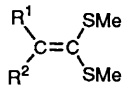
[a] LP = light petroleum; B = benzene; EE = diethyl ether. [b] Yields of pure isolated products. [c] Chromatographic solvent was LP–EE (9.8:0.2). [d] tr = traces. [e] The reaction was protracted for 10 h. GC-MS analysis of the crude reaction mixture showed the following compounds: the starting 2-bromooctane and **14** as major products and traces of compounds **9**, **12** and **7d**. [f] On $SiO_2$ **7d** tends to hydrolyse to **8d**. By chromatography of the crude reaction mixture, the following compounds were also isolated: the starting 2-iodooctane (24%), **8d** (19%), **14** (19%) and **9** and **12** (traces). [g] The reaction was protracted for 10 h. On $SiO_2$, **7e** tends to decompose. By chromatography of the crude reaction mixture, **7e** was isolated in only 10–12% yield. The following compounds were also isolated: **9** (16%), **14** (36–43%) and **12** (traces). [h] The reaction was carried out for 10 h. No trace of [tris(methylthio)methyl]cyclohexane was formed. [i] By-products **16a** and **8f** were also isolated in 4 and 5% yield in entry 10, and 2 and 3% yield in entry 11. [j] On $SiO_2$, **7h** tends to change into **16b** and **8h**. By chromatography of the crude reaction mixture, compounds **16b** and **8h** were also isolated in 10 and 38% yield, respectively. [k] See Experimental section. [l] Only polymeric material was obtained. Attempts to carry out the hydrolysis at a lower temperature failed. [m] Compounds **7j** and **7m** were the only products obtained even when 12 mmol of BuLi and 20 mmol of compound **9** were used for 10 mmol of dihalide. [n] Attempts to isolate compound **7m** by chromatography on $SiO_2$ failed. The following hydrolysis compounds were obtained: **8m** (56%) and $MeSCH(Me)[CH_2]_2CH_2COSMe$ (11%), b.p. 106 °C at 1 mmHg (Found: C, 49.9; H, 8.3; S, 33.25. $C_8H_{16}OS_2$ requires C, 49.96; H, 8.39; S, 33.34%); $\nu_{max}(CCl_4)/cm^{-1}$ 1690 (CO); $\delta_H(CCl_4)$ 1.30 (3 H, d, *J* 6.00, Me), 1.50–1.80 (4 H, m, 2 $CH_2$), 2.05 (3 H, s, MeS), 2.30 (3 H, s, MeSCO) and 2.40–2.75 (3 H, m, CH and $CH_2CO$); $\delta_C(CDCl_3)$ 11.27 (q, Me), 12.74 (q, SMe), 20.53, 22.97 (t, $CH_2$), 35.31 (q, MeSCO), 40.62 (d, CH), 43.38 (t, $CH_2CO$) and 199.04 (s, CO); $M^+$, 192. [o] The reagents' molar proportions were the following: dihalide: **9**: BuLi = 1:1:1.1. Dodec-1-ene was obtained as the only product, in quantitative yield. [p] Compound **8n** was also isolated in 6% yield.

on the substrate's structure and on the nature of the halogen, according to known rules,[12] even though not specifically detailed for the anion **6**. This provides sure suggestions for various synthetic projects. However, for a correct execution of the reactions the following observations appear useful. In the first place the by-products, sometimes present only in trace and at other times in significant amounts, should be given due consideration. In the cases where the halides do not, or only partially react, with substrate **6**, and if the reaction is carried out in such a way as to avoid any contact of the reagents with air while the temperature is raised from −78 °C to ambient, tetrakis(methylthio)ethylene **14** [that is, the result of the decomposition of tris(methylthio)methyl anion],[7,8] is formed in considerable amounts. However, if, during the raising of the temperature, the reaction mixture comes into contact with air, tetrakis(methylthio)methane **12** and *S*-methyl bis(methylthio)-thioacetate **15** will also be found, sometimes in significant amounts. A collateral investigation was carried out on tris-(methylthio)methyl lithium; after its formation, the nitrogen stream was interrupted, letting the reaction mixture come into contact with air during the temperature increase from −78 °C to room temperature. This resulted in the formation of compound **14**, and consistent amounts of compounds **12** and **15** as well. Therefore it is clear that in the case of air-contaminated reactions, compound **12** can originate by oxygen oxidation of the methanethiolate anion of salt **10** (derived from the decomposition of salt **6**) to dimethyl disulfide **11**, followed by the known reaction of the last with any still undecomposed salt **6**.[8] Furthermore, thiol ester **15** could form as a consequence of the reaction of water with the salt **13** (Scheme 4).

A last observation concerns the isolation and purification of trithioorthoesters **7**. In general these compounds are thermally unstable and, through the loss of methyl mercaptan, often give rise to the corresponding elimination products **16** or, in particularly hydrolysing conditions, they tend partly to convert into the corresponding thiol esters **8**. In several cases such a




**Scheme 4** *Reagents:* i, $O_2$; ii, **6**; iii, water



**16**

**16a** $R^1$ = H, $R^2$ = Ph
**16b** $R^1$ = Me, $R^2$ = Ph
**16c** $R^1$ = H, $R^2$ = PhCH=CH

lability can be an impediment to their isolation and purification, but not, as will be shown, to obtaining thiol esters **8**.

The last step in reaching the final target of this work is the production of thiol esters **8** through selective hydrolysis of trithioorthoesters **7**. The simplest procedure reported in the literature concerning this conversion refers to the hydrolysis of trithioorthoesters **3** into thiol esters **4**; this was easily realized by heating compounds **3** in aq. dimethyl sulfoxide (DMSO) or in DMSO–aq. $HBF_4$.[4] However, these conditions were not suitable for the conversion **7**→**8**. In fact, none of the cases examined resulted in the desired conversion by simply heating compound **7** in aq. DMSO, conditions which, in some cases, led to elimination products. Furthermore, in the presence of $HBF_4$ at the previously adopted concentrations (DMSO–35% aq. $HBF_4$ 4:1),[4] thiol esters **8** underwent a pronounced subsequent hydrolysis to carboxylic acids. Therefore the previous hydrolysis conditions were suitably adapted and the results are reported in Table 1. In numerous cases (entries 22, 24, 26, 31, 32, 34, 40, 41, 42, 45; Procedure A) the hydrolysis of thioorthoesters **7** to thiol esters **8** gave excellent yields in DMSO, with drastically diminished concentrations of $HBF_4$ (DMSO–35% aq. $HBF_4$ 39:1). In other cases (entries 28, 30, 37, 39, 44; Procedure B) it was necessary to substitute DMSO with THF; in this latter solvent the reaction times needed to be increased, but the hydrolyses were fully selective. The only case in which the hydrolysis failed concerned compound **7o** (entries 46, 47).

From a synthetic point of view, it is important to note that instead of first isolating trimethyl trithioorthocarboxylates **7** the hydrolysis can be carried out advantageously on the raw reaction materials since overall yields of thiol esters **8** increase (Table 1) and their separation from the other reaction products can be realized quickly and without complications through chromatography.

On completing this study it was also ascertained (taking into consideration only one example, although there appears no foreseeable impediment to us making a generalization) that the possibility exists of incorporating $^{18}O$ into the carbonyl group of thiol esters. Thus, the hydrolysis of 1,1,1-tris(methylthio)tridecane **7b** carried out in anhydrous DMSO in the presence of $HBF_4$-diethyl ether complex (54% in $Et_2O$) and $H_2{}^{18}O$ (98% $^{18}O$) under nitrogen, and by carefully avoiding moisture, resulting in the incorporation of $^{18}O$ into the carbonyl group (~98% isotopic purity).

## Experimental

*General Details*—$^1H$ NMR spectra were recorded on a Hitachi-Perkin-Elmer R-24B spectrometer (60 MHz) for solutions in tetrachloromethane. The chemical shifts are expressed in ppm ($\delta$) relative to internal tetramethylsilane and *J*-values are in Hz. Mass spectra were recorded on an HP 5970 B mass-selective detector connected to an HP 5890 GC; cross-linked methyl silicone capillary column (70 eV). IR spectra were recorded on a Perkin-Elmer 599B spectrophotometer for solutions in tetrachloromethane.

Satisfactory elemental analyses were obtained for all the new compounds.

All the reactions involving organometallic compounds were performed under nitrogen in oven-dried glassware. 2.5 Mol $dm^{-3}$ butyllithium in hexane and anhydrous THF and acetonitrile were purchased from Aldrich. Light petroleum refers to the fraction boiling in the range 40–70 °C. Extracts were dried over $Na_2SO_4$.

Tris(methylthio)methyl tetrafluoroborate **2** (X = $BF_4$) and tris(methylthio)methyl methyl sulfate **2** (X = $MeSO_4$) were prepared as previously reported.[4]

*Tris(methylthio)methane* **9**.—Powdered $NaBH_4$ (3.78 g, 0.1 mol) was added to anhydrous MeCN (250–280 $cm^3$) previously cooled at 5–10 °C in an ice-bath, under $N_2$. After this mixture had been stirred for 15 min, tris(methylthio)methyl tetrafluoroborate **2** (X = $BF_4$) (24.01 g, 0.1 mol) was added in one portion. The mixture was vigorously stirred for 1 h longer. During the reaction, moisture must be carefully avoided to prevent the formation of variable amounts of the by-product tetrakis(methylthio)methane **12**. Then the mixture was poured into water and extracted with $Et_2O$ (3 × 150 $cm^3$). The collected extracts were washed repeatedly with water (5 × 80 $cm^3$), dried, and evaporated under reduced pressure. Virtually pure (TLC, GC-MS) title compound **9** was obtained in quantitative yield (15.40 g), b.p. 116 °C at 18 mmHg (lit.,[8] b.p. 96–98 °C at 10 mmHg); $\delta_H(CCl_4)$ 2.20 (9 H, s, 3 × SMe) and 4.60 (1 H, s, CH), identical with data reported;[8] $M^+$, 154.

Identical results were obtained by reduction of methyl tris(methylthio)methyl sulfate **2** (X = $MeSO_4$).

*Trimethyl Trithioorthocarboxylates* **7**. *Typical Procedures.*—1,1,1-*Tris(methylthio)tridecane* **7b**. (a) In entry 3, a solution of tris(methylthio)methane **9** (1.54 g, 10 mmol) in anhydrous THF (10 $cm^3$) was cooled to −78 °C under $N_2$. A 2.5 mol $dm^{-3}$ solution of BuLi in hexane (4.4 $cm^3$, 11 mmol) was added dropwise during 10 min and the mixture was stirred for 2 h. A solution of 1-bromododecane (2.49 g, 10 mmol) in anhydrous THF (20 $cm^3$) was gradually added in the course of 20 min and the mixture was stirred at −78 °C for a further 3 h. The cooling bath was removed and the reaction mixture was allowed to warm gradually to room temperature (*ca.* 1 h), then was treated with saturated aq. $NH_4Cl$ (100 $cm^3$) and extracted with $Et_2O$ (2 × 100 $cm^3$). The collected extracts were washed successively with 5% aq. NaOH (50 $cm^3$) and water (2 × 50 $cm^3$), dried, and evaporated under reduced pressure. The crude residue was chromatographed on a silica gel column with light petroleum–benzene (9.5:0.5) as eluent. The first eluted product was the *title compound* **7b** (2.87 g, 89%), m.p. 12 °C (from pentane). The second eluted product was the starting compound **9** (0.08 g, 5% recovery).

(b) Starting from 1-iodododecane (entry 4), *title compound* **7b** was obtained in 81% yield (2.61 g). By-products were: 1-methylthiododecane (0.11 g, 5%), b.p. 156 °C at 16 mmHg (lit.,[13] 156 °C at 16 mmHg), $M^+$, 216; and traces (determined by GC–MS) of compound **12**, hexadecane and tetracosane.

(c) Starting from 1-chlorododecane (entry 2), compound **7b** was obtained only in trace amounts, even for a protracted

reaction time of 10 h. In this reaction the starting compound was recovered (90% yield) and by-products were: compound **12** (traces, determined by GC-MS) and tetrakis(methylthio)-ethylene **14** (0.81 g, 76%), m.p. 62 °C (from light petroleum) (lit.,[8] 60–61 °C); $M^+$, 212.

The reagents' molar ratio reported above in entry 4 was also used in entries 1–15, 18.

1,1,8,8-*Hexatris(methylthio)octane* **7k**. In entry 16, the reaction was carried out for 3 h as described above, starting from compound **9** (3.08 g, 20 mmol) in anhydrous THF (20 $cm^3$), 2.5 mol $dm^{-3}$ BuLi in hexane (8.8 $cm^3$, 22 mmol) and 1,6-dibromohexane (2.44 g, 10 mmol) in anhydrous THF (40 $cm^3$). The crude residue obtained after the usual work-up was chromatographed on a silica gel column with light petroleum–$Et_2O$ (9.8:0.2) as eluent to afford the *title compound* **7k** in 87% yield (3.39 g), m.p. 79 °C (from $CCl_4$–light petroleum).

The same reagents' molar ratio was used in entries 17, 20, 21.

Physical properties and spectral data of compounds **7** are reported in Table 2.

*Thermal Decomposition of Tris(methylthio)methyllithium* **6**.—(*a*) A dispersion of lithium salt **6** in THF was prepared as described above by the reaction of compound **9** (1.54 g, 10 mmol) in anhydrous THF (10 $cm^3$) with 2.5 mol $dm^{-3}$ BuLi in hexane (4.4 $cm^3$, 11 mmol) at −78 °C under $N_2$ for 2 h. Then the nitrogen stream was maintained until the temperature of the reaction mixture increased from −78 °C to ambient (*ca.* 2 h). According to the literature,[8] the usual work-up afforded compound **14** in quantitative yield (1.06 g), m.p. 62 °C (from light petroleum).

(*b*) After the formation of lithium salt **6** as above, the nitrogen stream was interrupted, letting the reaction mixture come into contact with air during the temperature increase from −78 °C to ambient. The residue obtained after the usual work-up was chromatographed on a silica gel column, with light petroleum–benzene (9.5:0.5) as eluent, to afford three products. The first eluted product was tetrakis(methylthio)methane **12** (0.60 g, 60%), m.p. 64–65 °C (from light petroleum) (lit.,[8] 65–66 °C); $M^+ - SCH_3$, *m/z* 153. The second eluted product was starting compound **9** (0.12 g, 8% recovery) and the third was S-*methyl bis(methylthio)thioacetate* **15** (0.40 g, 44%), b.p. 104 °C at 1 mmHg (Found: C, 32.9; H, 5.5; S, 52.7. $C_5H_{10}OS_3$ requires C, 32.94; H, 5.53; S, 52.75%); $M^+$, 182. Compound **15** had been prepared before in very low yield, but it was not adequately purified.[14] $^1H$ NMR and IR data were identical with those reported;[14] $\delta_C(CDCl_3)$ 11.56 (q, *J* 142, *Me*SCO), 13.05 [q, *J* 140, $(MeS)_2CH$], 60.18 (d, *J* 150, CH) and 193.59 (s, CO).

*Hydrolysis of Trimethyl Trithioorthocarboxylates* **7** *to* S-*Methyl Thiolcarboxylates* **8**; *Typical Procedures*.—S-*Methyl tridecanethioate* **8b**. (a) *Procedure A*: in entry 24, a mixture of compound **7b** (3.22 g, 10 mmol), DMSO (19.5 $cm^3$) and 35% aq. $HBF_4$ (0.5 $cm^3$) was heated at 130 °C in an oil-bath for 15 min, until a TLC test on $SiO_2$ with light petroleum–$Et_2O$ (9.5:0.5) as developer showed the disappearance of the starting material **7b** and the presence of only compound **8b**. The reaction mixture was poured into water (100 $cm^3$) and extracted with $Et_2O$ (2 × 80 $cm^3$). The collected extracts were washed repeatedly with water (4 × 50 $cm^3$), dried, and evaporated under reduced pressure. Virtually pure (TLC, GC-MS, NMR) *title compound* **8b** was obtained in 95% yield (2.32 g), m.p. 18 °C (from pentane).

The hydrolysis was carried out in the same way on the crude reaction mixture from entry 3. After the usual work-up, the crude residue was chromatographed on a short silica gel column with light petroleum–$Et_2O$ (9.8:0.2) as eluent, to afford pure compound **8b** (2.05 g). The overall yield, calculated on the amount of starting 1-bromododecane, was 84%.

The same reagents' ratio was used in entries 22, 26, 27, 29, 34, 38, 40, 43.

(*b*) *Procedure B:* in entry 25, a mixture of compound **7b** (3.22 g, 10 mmol), THF (19.5 $cm^3$) and 35% aq. $HBF_4$ (0.5 $cm^3$) was heated at gentle reflux (~70 °C) in an oil-bath until completion of the hydrolysis (*ca.* 5 h). Work-up as described above afforded virtually pure compound **8b** in 97% yield (2.37 g).

As described in Procedure A, the hydrolysis was also carried out directly on the crude reaction mixture from entry 3. Pure compound **8b** was obtained in 86% overall yield (2.10 g).

The same reagents' ratio was used in entries 23, 28, 30, 35, 44.

S-*Methyl 2-phenylpropanethioate* **8h**. (*a*) *Procedure A*: in entry 36, the crude reaction mixture from entry 13 was directly treated with DMSO–35% aq. $HBF_4$ (19:1; 20 $cm^3$ for 10 mmol of compound **7h**) and heated very slowly (*ca.* 30 min) to 130 °C. A TLC test [$SiO_2$; light petroleum–$Et_2O$, (9.8:0.2)] of the reaction mixture at 80 °C showed the change of the starting material **7h** into alkene **16b**, which hydrolysed very slowly in these conditions (4 h). After the usual work-up, a mixture of two products was obtained: title compound **8h** and *S*-methyl 2-phenylpropenethioate (4:1; ~65–70% yield). The two products could not be separated. The structure of the by-product was confirmed by GC-MS ($M^+$, 178) and NMR spectroscopy: $\delta_H(CDCl_3)$ 2.29 (3 H, s, SMe), 5.69 (1 H, s, CH), 6.08 (1 H, s, CH) and 7.28 (5 H, m, Ph), identical with that reported.[15]

The same reagents' ratio was used in entries 31, 32.

(*b*) *Procedure B:* in entry 37, the crude reaction mixture from entry 13 was treated directly with THF–35% aq. $HBF_4$ (19:1; 20 $cm^3$ for 10 mmol of compound **7h**) and heated at gentle reflux (~70 °C) until disappearance of the starting material **7h** and then of the dithioalkene **16b**. The crude residue obtained after the usual work-up was purified by rapid chromatography on a small silica gel column with light petroleum–$Et_2O$ (9.8:0.2) as eluent. Pure *compound* **8h** was obtained in 73% overall yield (1.31 g); b.p. 92 °C at 1 mmHg.

The intermediate, 1,1-bis(methylthio)-2-phenylpropene **16b**, was isolated in 10% yield in entry 13 (see footnote *j* of Table 1), b.p. 102 °C at 1 mmHg (lit.,[10] b.p. 96–98 °C at 0.3 mmHg); $M^+$, 210; NMR data were identical with those reported.[10]

The reagents' ratio used in entry 37 was also used in entry 33.

S-*Methyl 4-phenylbut-3-enethioate* **8i**. *Procedure B:* in entry 39, a mixture of compound **7i** (2.70 g, 10 mmol), THF (18.5 $cm^3$) and 35% aq. $HBF_4$ (1.5 $cm^3$) was heated at gentle reflux. The starting material **7i** changed immediately into the butadiene **16c** (determined by GC-MS and NMR spectroscopy), which hydrolysed very slowly in these conditions (48 h). The residue obtained after the usual work-up was chromatographed on $SiO_2$ with light petroleum–$Et_2O$ (9.8:0.2) as eluent to afford the pure *title compound* **8i** (0.88 g, 46%), b.p. 142 °C at 2.5 mmHg.

Identical results were obtained when carrying out the hydrolysis directly on the crude reaction mixture from entry 14.

In a collateral proof, compound **7i** (10 mmol) was treated with THF (19.5 $cm^3$) and 35% aq. $HBF_4$ (0.5 $cm^3$) and the reaction mixture was heated at gentle reflux until disappearance of the starting compound (18 h). The usual work-up afforded 1,1-*bis(methylthio)*-4-*phenylbuta*-1,3-*diene* **16c** (1.39 g, 63%) and compound **8i** (0.40 g, 21%). Compound **16c** had b.p. 152 °C at 12 mmHg (Found: C, 64.8; H, 6.3; S, 28.8. $C_{12}H_{14}S_2$ requires C, 64.82; H, 6.35; S, 28.84%); $\delta_H(CDCl_3)$ 2.40 (3 H, s, SMe), 2.42 (3 H, s, SMe), 6.37 [1 H, d, *J* 5.00, $CH{=}C(SMe)_2$], 6.52–6.62 (1 H, m, =CH) and 7.06–7.40 (6 H, m, =CH and Ph); $M^+$, 222.

S,S-*Dimethyl Octanebis(thioate)* **8k**. *Procedure A:* in entry 41, a mixture of compound **7k** (6.24 g, 10 mmol), DMSO (39 $cm^3$) and 35% aq. $HBF_4$ (1 $cm^3$) was heated at 130 °C until completion of the hydrolysis (15 min). The reaction mixture was worked up as described above to give the pure *title compound* **8k** (2.18 g, 93%), m.p. 50 °C (from pentane).

**Table 2** Physical properties of compounds **7a–o** and **8a–n**

| Compound 7 | M.p. (°C) (solvent)[a] or b.p. (°C)/mmHg | Lit. data or formula[b] | $M^+ - SCH_3$ ($M^+$ of **16**)[c] (*m/z*) | $\delta_H(CCl_4)$, *J*(Hz) $C(SMe)_3$ (9 H, s) | Others |
|---|---|---|---|---|---|
| **7a** | 100/1 | $C_8H_{18}S_3$ | 163 (162) | 2.10 | 0.95–1.15 (3 H, m, Me), 1.20–1.90 (6 H, m, 3 × $CH_2$) |
| **7b** | 12 (P) | $C_{16}H_{34}S_3$ | 275 (274) | 2.05 | 085–1.05 (3 H, m, Me), 1.20–1.85 (22 H, m, 11 × $CH_2$) |
| **7c** | 40–41 (P) | $C_{22}H_{46}S_3$ | (358) | 2.00 | 0.80–0.95 (3 H, m, Me), 1.20–1.35 and 1.55–1.80 (34 H, 2 m, 1:16, 17 × $CH_2$) |
| **7d** | 132/0.9 | $C_{12}H_{26}S_3$ | 219 (218) | 2.03 | 0.80–1.35 (17, m, $C_8H_{17}$) |
| **7e** | 110/1 | $C_9H_{18}S_3$ | 175 (174) | 2.10 | 1.50–1.80 (9 H, m, c-$C_5H_9$) |
| **7f** | 130/0.07 | 166/0.3 [10] | 197 (196) | *g* | |
| **7g** | 18 (P) | 195/0.1 [10] | 211 (210) | *g* | |
| **7h** | 44 (P)[j] | $C_{12}H_{18}S_3$ | 211 (210) | 1.90 | 1.52 (3 H, d, *J* 7.00, Me), 3.15 (1 H, q, *J* 7.00, CH), 7.00–7.40 (5 H, m, Ph) |
| **7i** | oil[k] | $C_{13}H_{18}S_3$ | 223 (222) | 1.93 | 2.55–2.68 (2 H, m, $CH_2$), 6.15–6.25 (2 H, m, 2 × CH), 6.95–7.15 (5 H, m, Ph) |
| **7j** | 152/0.1 | $C_{10}H_{21}ClS_3$ | (224) | 2.10 | 1.35–1.90 (10 H, m, 5 × $CH_2$), 3.49 (2 H, t, *J* 6.00, $CH_2Cl$) |
| **7k** | 79 (C–LP) | $C_{14}H_{30}S_6$ | (294)[l] | 2.04 (18 H) | 1.25–1.50 and 1.50–1.70 (12 H, 2 m, 1:2, 6 × $CH_2$) |
| **7l** | 16 (P) | $C_{20}H_{42}S_6$ | (378)[n] | 1.95 (18 H) | 1.10–1.35 and 1.50–1.70 (24 H, 2 m, 2.5:1, 12 × $CH_2$) |
| **7m** | *o* | $C_9H_{19}BrS_3$ | 255–257 (254–256) | 2.00 | 1.60–1.85 (9 H, m, 3 × $CH_2$ and Me), 4.01 (1 H, q, *J* 6.00, CH) |
| **7n** | 117–118 (C–LP) | $C_{16}H_{26}S_6$ | (314)[p] | 1.98 (18 H) | 3.14 (4 H, s, 2 × $CH_2$), 7.18 (4 H, br s, ArH) |
| **7o** | 24 (P) | $C_{12}H_{24}S_6$ | (264)[q] | 2.00 (18 H) | 2.55 (4 H, d, *J* 4.00, 2 × $CH_2$), 5.68 (2 H, t, *J* 4.00, 2 × CH) |

| Compound 8 | M.p. (°C) (solvent)[a] or b.p. (°C)/mmHg | Lit. data or formula[b] | $M^+$ (*m/z*) | IR ($CCl_4$) $\nu_{max}/cm^{-1}$ | $\delta_H(CCl_4)$, *J* (Hz) SMe (3 H, s) | Others |
|---|---|---|---|---|---|---|
| **8a** | 58/12 | 153.5–154/750[d] | 117[e] | *f* | *f* | |
| **8b** | 18 (P) | $C_{14}H_{28}OS$ | 229[e] | 1692 | 2.10 | 0.65–0.85 (3 H, m, Me), 1.10–1.25 (20 H, m, 10 × $CH_2$), 2.34 (2 H, t, *J* 7.00, $CH_2CO$) |
| **8c** | 44–45 (E) | $C_{20}H_{40}OS$ | 313[e] | 1680 | 2.11 | 0.70–0.90 (3 H, m, Me), 1.00–1.30 (32 H, m, 16 × $CH_2$), 2.36 (2 H, t, *J* 7.00, $CH_2CO$) |
| **8d** | 84/1.5 | $C_{10}H_{20}OS$ | 173[e] | 1690 | 2.18 | 0.75–0.95 (3 H, m, Me[$CH_2$]$_5$) 1.08 (3 H, d, *J* 7.00, CHMe), 1.15–1.35 (10 H, m, 5 × $CH_2$), 2.45 (1 H, m, CH) |
| **8e** | 44/1 | $C_7H_{12}OS$ | 144 | 1690 | 2.10 | 1.30–1.85 (8 H, m, $CH_2$), 2.60–2.90 (1 H, m, CH) |
| **8f** | 89/1 | 55–57/0.1 [16c] | 166 | *h* | *h* | |
| **8g** | 98/1[i] | $C_{10}H_{12}OS$ | 180 | 1692 | 2.20 | 2.70–2.90 (4 H, m, 2 × $CH_2$), 7.00–7.12 (5 H, m, Ph) |
| **8h** | 92/1 | 78–80/0.1 [16c] | 180 | *h* | *h* | |
| **8i** | 142/2.5 | $C_{11}H_{12}OS$ | 192 | 1692 | 2.20 | 3.28 (2 H, d, *J* 5.00, $CH_2$), 5.80–6.32 (2 H, m, 2 × CH), 7.05–7.25 (5 H, m, Ph) |
| **8j** | 104/1 | $C_8H_{15}ClOS$ | 179[e] | 1690 | 2.15 | 1.10–1.85 (8 H, m, 4 × $CH_2$), 2.40 (2 H, t, *J* 6.00, $CH_2CO$), 3.38 (2 H, t, *J* 6.00, $CH_2Cl$) |
| **8k** | 50 (P) | $C_{10}H_{18}O_2S_2$ | 187[m] | 1692 | 2.16 (6 H) | 1.15–1.62 (8 H, m, 4 × $CH_2$), 2.40 (4 H, t, *J* 6.00, 2 × $CH_2CO$) |
| **8l** | 56–57 (P) | $C_{16}H_{30}O_2S_2$ | 271[m] | 1692 | 2.12 (6 H) | 1.05–1.40 (20 H, m, 10 × $CH_2$), 2.37 (4 H, t, *J* 7.00, 2 × $CH_2CO$) |
| **8m** | 88/1 | $C_7H_{13}BrOS$ | 177–179[m] | 1692 | 2.20 | 1.55–1.85 (7 H, m, 2 × $CH_2$ and Me), 2.25–2.35 (2 H, m, $CH_2CO$), 3.80–4.15 (1 H, m, CH) |
| **8n** | 80–81 (C–LP) | $C_{12}H_{14}O_2S_2$ | 254 | 1690 | 2.10 (6 H) | 3.55 (4 H, s, 2 × $CH_2$), 7.00 (4 H, br s, ArH) |

[a] P = pentane; C = $CCl_4$; LP = light petroleum; E = EtOH. [b] Satisfactory microanalyses were obtained. Compounds **7**: C ± 0.08; H ± 0.05; S ± 0.06%. Compounds **8**: C ± 0.09; H ± 0.06; S ± 0.05%. [c] By heating, compounds **7** tended to lose methanethiol and consequently changed, fully or only partly, into ketene dithioacetals **16**. [d] Ref. 16*a* [e] $M^+ - CH_3$. [f] Identical with that reported: ref. 16*b*. [g] Identical with that reported in ref. 10. [h] Identical with that reported in ref. 16*c*. [i] Compound **8g**, but not its physical data, is reported in ref 16*d*. [j] In ref. 10 it is reported that compound **7h** cannot be purified, because attempts to distil it produced compound **16b**. [k] Attempts to distil compound **7i** produced some ketene dithioacetal **16c** together with polymeric material. [l] $M^+$ of $(MeS)_2C{=}CH[CH_2]_4CH{=}C(SMe)_2$ was obtained from **7k** by loss of 2 molecules of MeSH. [m] $M^+ - SCH_3$. [n] $M^+$ of $(MeS)_2C{=}CH[CH_2]_{10}CH{=}C(SMe)_2$ was obtained from **7l** by loss of 2 molecules of MeSH. [o] See footnote *n* of Table 1. MS and NMR spectra were recorded on the crude reaction mixture. [p] $M^+$ of 4-[$(MeS)_2C{=}CH]C_6H_4CH{=}C(SMe)_2$ obtained from **7n** by loss of 2 molecules of MeSH. [q] $M^+$ of $(MeS)_2C{=}CHCH{=}CHCH{=}C(SMe)_2$ obtained from **7o** by loss of 2 molecules of MeSH.

Direct hydrolysis of the crude reaction mixture from entry 16 afforded compound **8k** in 82% overall yield (1.92 g).

The same reagents' ratio was used in entries 42, 45, 46.

Physical properties and spectral data for compounds **8** are reported in Table 2.

*Collateral Proofs of Hydrolysis of Thioorthoesters* **7** *to Thiol Esters* **8**. *Typical Procedures*.—The mixtures used previously[3] for hydrolysis of aromatic and heteroaromatic trimethyl trithioorthocarboxylates **3** to the corresponding methyl thiolcarboxylates **4** were tested as follows:

(*a*) Compound **7b** (3.22 g, 10 mmol) was treated with DMSO–water (4:1; 20 $cm^3$) and the mixture was heated at 130 °C. After 10 h, substrate **7b** was unchanged.

(*b*) Compound **7f** (2.44 g, 10 mmol) was heated at 130 °C in DMSO–water (4:1; 20 $cm^3$) until disappearance of the starting compound (*ca.* 4 h). The crude residue obtained after the usual work-up was chromatographed on $SiO_2$ with light petroleum–benzene (9.5:0.5) as eluent, to afford two products. The first eluted product was compound **16a** (1.10 g, 56%), b.p. 132 °C at 1.5 mmHg (lit.,[17] b.p. 94–96 °C at 0.25 mmHg); $M^+$, 196; NMR data were identical with those

reported.[17] The second eluted product was thiol ester **8f** (0.22 g, 13%).

(*c*) Compound **7b** was treated with DMSO–aq. 35% $HBF_4$ (4:1; 20 $cm^3$) and the mixture was heated at 130 °C until disappearance of the starting compound [15 min; TLC: $SiO_2$; light petroleum–$Et_2O$ (9.8:0.2)] and was then poured into water (100 $cm^3$) and extracted with $Et_2O$ (2 × 80 $cm^3$). The collected extracts were washed with 5% aq. NaOH (2 × 50 $cm^3$). The solid product, which separated at the interface, was collected by filtration. This product, after acidification with $H_2SO_4$, afforded tridecanoic acid (0.49 g, 23%), m.p. 42–43 °C (from pentane) (lit.,[18] 41–42 °C). Then the $Et_2O$ extracts were washed with water (50 $cm^3$), dried, and evaporated. The residue was virtually pure compound **8b** (1.88 g, 77%).

When the hydrolysis was protracted for 4 h, the only product was tridecanoic acid (1.82 g, 85%).

Identical results were obtained with the other compounds **7**: in the above conditions the hydrolysis was not selective and the corresponding thiol esters **8** were obtained, but always in yields lower than 70%.

*Labelled* S-*Methyl Tridecanethioate* **8b** (n-$C_{12}H_{25}C$-$^{18}$OSMe).—The reaction required thoroughly anhydrous conditions and was carried out in oven-dried glassware under nitrogen; DMSO was dried with molecular sieves and then distilled on calcium hydride under reduced pressure (12 mmHg). Compound **7b** (1.25 g, 4 mmol) was treated with the above dried DMSO–$H_2{}^{18}O$ (98% $^{18}O$) (9.5:0.5; 7.36 and 0.39 $cm^3$) and $HBF_4{\cdot}Et_2O$ complex (54% in $Et_2O$; 0.07 g) and then the hydrolysis was carried out at 130 °C, with careful avoidance of moisture, until disappearance of the starting material (*ca.* 1 h). The usual work-up afforded the title compound (0.90 g, 95%), MS ($M^+ - CH_3$, 231) gave evidence that the labelled oxygen appears in the carbonyl group (~98% isotopic purity, determined by using a double-focusing Kratos MS 80 spectrometer).

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