Synthetic Application of Tris(methylthio)methyl Salts. An Efficient Route to Trithioorthocarboxylic Esters from Strongly Activated Aromatic and Heteroaromatic Systems[1]

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Nine trithioorthocarboxylic esters were synthesized by reaction of tris(methylthio)methyl methyl sulfate or tetrafluoroborate with electron-rich aromatic and heteroaromatic compounds, i.e. N,N-dialkylarylamines, pyrroles, and indoles. The new procedure is simple and offers the following advantages: easy preparation of reagents; mild reaction conditions; possibility to introduce two tris(methylthio)methyl groups into the same ring, good to excellent yields.

In connection with research on synthetic applications of heteroaromatic cation salts and related systems, in particular, on the use of 2-substituted 1,3-benzoxathiolium and 1,3-benzodithiolium salts as masked acylating agents for electron-rich aromatic and heteroaromatic compounds,[2,3] we investigated the possible use of tris(methylthio)methyl salts **2** for a similar synthetic purpose. On these salts, we have found only few substantial reports; in previous publications, synthetic procedures,[4,5,6] structural[7] and spectroscopic data,[5] and some significant chemical properties[4,5,6,8,9] of salts **2** have been briefly reported.

Of the reported procedures, the only practicable route involves the reaction of dimethyl trithiocarbonate with methylating agents.[10] Thus, the methylation of dimethyl trithiocarbonate **(1)** with dimethyl sulfate[4] or trimethyloxonium tetrafluoroborate[5,6] gives tris(methylthio)methyl methyl sulfate **(2a)** or tetrafluoroborate **(2b)**, respectively. However, in the original work, yields of the methyl sulfate were not reported (the salt **2a** was not

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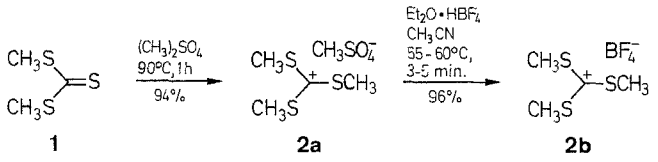
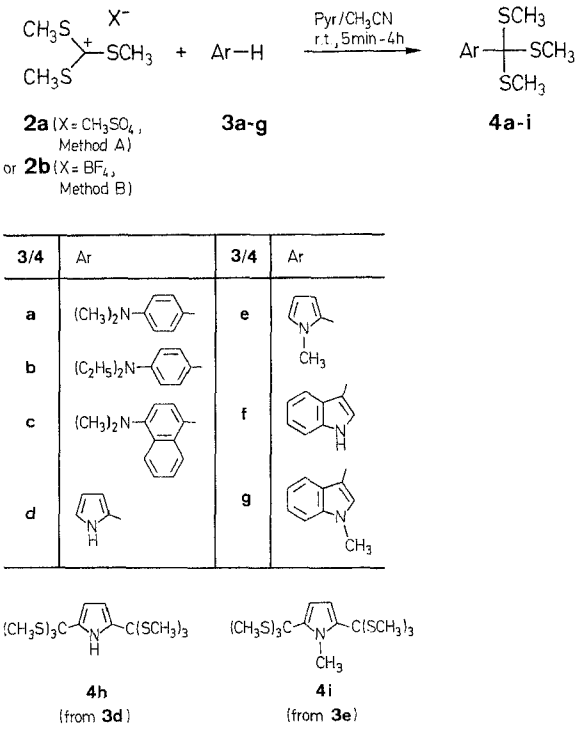
isolated) and the reported yields of tetrafluoroborate **2b** (62–79%) are unsatisfactory in our opinion. We therefore tried to elaborate a reliable procedure for the preparation of salts **2**. After a re-examination of the reaction of dimethyl trithiocarbonate with dimethyl sulfate, we found that methyl sulfate **2a** can be obtained in 94% yield by heating equimolecular amounts of the reaction components at 90°C for 1 hour with stirring (Scheme **A**, first step). The salt can be isolated as a white solid; however, it is highly hygroscopic and easily hydrolyzable and it should therefore be used at once for subsequent reactions. Further , we obtained the stable tetrafluoroborate **2b** in 96% yield by simply treating the crude salt **2a** with ether tetrafluoroboric acid-complex (Scheme **A**). Thus, the desired salts **2** have become easily available.



1 **2a** **2b**

Scheme **A**

Salts **2** can be utilized to introduce the tris(methylthio)methyl group into electron-rich aromatic and heteroaromatic substrates to produce trithioorthocarboxylic esters **4** according to Scheme **B**.



Scheme **B**

Some reactions described in previous works appeared to be in contrast with our expectations. Thus, it was reported that tris(methylthio)methyl cation can be attacked by nucleophiles at three different sites: (a) at the central carbon atom, (b) at the methyl carbon atom, (c) at the sulfur atom,[5] this making the synthetic applicability of salts **2** problematic. In particular, heating of salt **2a** and *N,N*-dimethylaniline in acetic acid/pyridine did not give the trithioorthocarboxylic ester **4a**; instead, crystal violet was obtained in 5% yield.[4] Moreover, it was reported that 2-methylthio-1,3-dithiolan-2-ylium methyl sulfate, which is a carbenium salt analogous to salts **2**, reacted with *N,N*-dimethylaniline, indole, and phenols on heating in acetic acid/pyridine and, in some cases, with subsequent addition of perchloric acid, to give condensation products, but not the trithioorthocarboxylic esters **4**.[4]

We tried to improve these unsatisfactory results by using the same reaction conditions (except for mol ratio of reactants and reaction time) that had been successfully used in the above cited acylation reactions with 2-substituted 1,3-benzoxathiolium and 1,3-benzodithiolium salts.[2,3] Thus, the reactions of salts **2** with various electron-rich aromatic and heteroaromatic compounds, i.e., anisole, 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene, *N,N*-dialkylarylamines, pyrroles, and indoles, were carried out in acetonitrile as solvent in the presence of pyridine at

Table 1. Trithioorthocarboxylic Esters **4** Prepared

Product	Mol Ratio 2 : 3 (mmol)	Reaction Time (min)	Chromatography Solvent[a]	Method	Yield[b] (%)	mp (°C) (solvent) or bp (°C)/Torr	Molecular Formula[c]	MS[d] *m/z* (M^+)
4a	1.75 : 1	120	PE/acetone (9.8 : 0.2)	A B	50 60	65 (EtOH)	$C_{12}H_{19}NS_3$ (273.5)	273
4b	1.75 : 1	60	PE/acetone (9.8 : 0.2)	A B	70 72	18.5–20 (pentane)	$C_{14}H_{23}NS_3$ (301.5)	301
4c	1.75 : 1	60	PE/acetone (9.8 : 0.2)	A B	86 98	85 (EtOH)	$C_{16}H_{21}NS_3$ (323.5)	323
4d	1 : 3	5	PE/acetone (9.8 : 0.2)	A B	70 84	38.5 (pentane)	$C_8H_{13}NS_3$ (219.4)	219
4e	1 : 3	5	PE/acetone (9.8 : 0.2)	A B	81 87	125/0.4	$C_9H_{15}NS_3$ (233.4)	233
4f	1.75 : 1	5	PE/acetone (9 : 1)	A B	100 91	125 (MeOH)	$C_{12}H_{15}NS_3$ (269.4)	269
4g	1.75 : 1	5	PE/acetone (9.8 : 0.2)	A B	84 88	94 (EtOH)	$C_{13}H_{17}NS_3$ (283.5)	283
4h	3.5 : 1	30	PE/acetone (9.8 : 0.2)	A B	93 86	79 (EtOH)	$C_{12}H_{21}NS_6$ (371.7)	371
4i	3.5 : 1	4 h	PE/benzene (9.5 : 0.5)	A B	53[e] 65[e]	124 (EtOH)	$C_{13}H_{23}NS_6$ (385.7)	(338) (M^+-SCH_3)

[a] PE = Petroleum ether.
[b] Yield of isolated pure product.
[c] Satisfactory microanalyses obtained: C ±0.11, H ±0.10, N ±0.08, S ±0.12.
[d] Recorded on a double focusing Kratos MS80 (operating with direct inlet system at 70 eV).
[e] 2-Tris(methylthio)-1-methylpyrrole (**4e**) was also isolated in 26% (Method A) and (Method B) 21% yield, respectively.

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Table 2. ^{1}H-NMR and ^{13}C-NMR of Trithioorthocarboxylic Esters **4**

Product	^{1}H-NMR ($CDCl_3$/TMS)[a] δ, J(Hz)		^{13}C-NMR ($CDCl_3$/TMS)[a] δ		
	$(SCH_3)_3$ (s)	Others	$S-CH_3$ (q)	$\underline{C}(SCH_3)_3$ (s)	Others
4a	2.02 (9H)	2.96 [s, 6H, $N(CH_3)_2$]; 6.60–6.72, 7.57–7.72 (2m, 1:1, $4H_{arom}$)	14.06	73.74	40.21 (q, NCH_3); 111.45, 128.92 (d, C_{arom}); 127.37, 149.68 (s, C_{arom})
4b	2.02 (9H)	1.16 (t, 6H, $2CH_2-C\underline{H}_3$, $J = 7$); 3.35 (q, 4H, $2C\underline{H}_2-CH_3$, $J = 7$); 6.53–6.69, 7.54–7.71 (2m, 1:1, $4H_{arom}$)	14.08	73.75	12.59 (q, $CH_2-\underline{C}H_3$); 44.15 (t, CH_2); 110.73, 129.06 (d, C_{arom}); 126.09, 147.09 (s, C_{arom})
4c	2.02 (9H)	2.88 [s, 6H, $N(CH_3)_2$]; 6.89–7.01, 7.39–7.61, 7.82–7.96, 8.17–8.38, 9.43–9.63 (5m, 1:2:1:1:1, $6H_{arom}$)	14.60	73.75	44.93 (q, NCH_3); 111.52, 124.04, 124.51, 124.75, 127.93, 128.61 (d, C_{arom}); 126.85, 129.75, 131.50, 151.89 (s, C_{arom})
4d	2.01 (9H)	6.00–6.13, 6.30–6.40 (2m, 1:1, H-3, H-4); 6.73–6.85 (m, 1H, H-5)	13.68	69.22	107.69, 110.24, 118.58 (d, C_{arom}); 129.18 (s, C_{arom})
4e	1.98 (9H)	3.96 (s, 3H, NCH_3); 5.90–6.00, 6.38–6.48 (2m, 1:1, H-3, H-4); 6.60–6.69 (m, 1H, H-5)	13.61	69.30	36.63 (q, NCH_3); 105.36, 113.69, 125.78 (d, C_{arom}); 127.10 (s, C_{arom})
4f	1.99 (9H)	7.10–7.39 (m, $4H_{arom}$); 8.32–8.48 (m, 1H, H-2)	13.78	69.42	111.04, 119.57, 122.48, 122.58, 124.99 (d, C_{arom}); 115.55, 124.67, 136.92 (s, C_{arom})
4g	2.00 (9H)	3.74 (s, 3H, NCH_3); 7.20–7.33 (m, $4H_{arom}$); 8.30–8.46 (m, 1H, H-2)	13.81	69.45	32.79 (q, NCH_3); 109.05, 119.14, 122.12, 122.52, 129.47 (d, C_{arom}); 113.73, 125.26, 137.71 (s, C_{arom})
4h	2.02 (18H)	6.19 (d, 2H, H-3, H-4, $J = 2.75$)	13.68	68.94	109.53 (d, C_{arom}); 130.12 (s, C_{arom})
4i	1.98 (18H)	4.34 (s, 3H, NCH_3); 6.37 (s, 2H, H-3, H-4)	13.76	69.67	35.55 (q, NCH_3); 111.78 (d, C_{arom}); 129.90 (s, C_{arom})

[a] Recorded on a Bruker WP 80 SY spectrometer.

room temperature for 5 min–4 hours. Under these conditions, insufficiently activated methoxybenzenes failed to react whereas strongly activated *N,N*-dialkylarylamines, pyrroles, and indoles gave the expected trithioorthocarboxylic esters **4** in good to excellent yields (Table 1). From most of the reactions, tetrakis(methylthio)methane **(5)** and *S,S*-dimethyl dithiocarbonate **(6)** were also isolated in varying amounts. These products were formed by hydrolysis of tris(methylthio)methyl salts **2** both during the reaction (owing to traces of moisture, as shown by ^{1}H-NMR analysis of the reaction mixtures) and during the aqueous work-up.

With salt **2b**, the yields of trithioorthocarboxylic esters **4** are generally better than with salt **2a**; however, this lower efficiency of salt **2a** is made up for by its faster preparation and its lower cost.

It is worthy of note that in the case of *N,N*-dialkylarylamines and indoles (indole and 1-methylindole), the electrophilic aromatic substitutions take place at the more activated positions 4 or 3, respectively, with exclusive formation of mono-trithioorthocarboxylic esters. In the case of pyrroles (pyrrole and 1-methylpyrrole), on the other hand, the reactions produce mono- or bis-trithioorthocarboxylic esters, depending on the mol ratio of the reactants, by attack at the activated positions 2 and 5.

The new method makes possible the synthesis of the novel tris(methylthio)methyl derivatives of *N,N*-dialkylarylamines, pyrroles, and indoles under mild conditions. These results are also attractive with respect to the synthetic potentiality of the trithioorthocarboxylic ester function.[11,12]

Dimethyl Trithiocarbonate (1) (cf. Ref. 13, 14):
A mixture of $Na_2S \cdot 9H_2O$ (24 g, 0.1 mol), CS_2 (7.6 g, 0.1 mol), and tricaprylmethylammonium chloride (Aliquat 336®; 0.2 g) in H_2O (30 mL) is vigorously stirred at room temperature for 90 min. To the resultant red solution of sodium trithiocarbonate, Me_2SO_4 (25.2 g, 0.2 mol) is added, dropwise and with stirring, over a period of 1 h. During this period the temperature of the mixture is maintained at ~ 10 °C by cooling with an ice bath. Stirring is then continued at room temperature for 1 h, until the aqueous solution becomes colorless. The organic phase is extracted with petroleum ether (2 × 150 mL) and the extract is washed with H_2O (2 × 80 mL) and filtered through a 10 cm layer of silica gel, using petroleum ether as eluent. After evaporation of the solvent *in vacuo*, the virtually pure (GLC and NMR analysis) product **1** is obtained; yield: 13.27 g (96%); bp 101–102 °C/12 Torr (Lit.[15] bp 118 °C/28 Torr).

^{1}H-NMR ($CDCl_3$): $\delta = 2.75$ (s), in agreement with Ref.15.

Tris(methylthio)methyl Methyl Sulfate (2a):
A mixture of dimethyl trithiocarbonate (**1**; 1.38 g, 10 mmol) and Me_2SO_4 (1.26 g, 10 mmol) is heated, with slow stirring, in an oil-bath at 90 °C for 1 h and then allowed to stand at room temperature until cool (15–20 min). The white precipitate formed is crushed in a small amount of dry Et_2O, filtered by suction, washed with dry Et_2O, and dried *in vacuo*; yield: 2.48 g (94%); mp 66–67 °C. Salt **2a** is very sensitive to moisture and its immediate use is advisable; it could not be analyzed satisfactorily.

^{1}H-NMR (CF_3CO_2D): $\delta = 3.17$ (s, 9H, $3SCH_3$); 3.96 (s, 3H, OSO_3CH_3).

^{13}C-NMR (CF_3CO_2D): $\delta = 21.59$ (q, SCH_3); 56.94 (q, OSO_3CH_3); 233.08 (s, C^+).

Tris(methylthio)methyl Tetrafluoroborate (2b):
The above mixture containing tris(methylthio)methyl methyl sulfate **(2a)** is diluted with dry MeCN (2.5 mL) and then treated with ether tetrafluoroboric acid complex (54% in Et_2O, 1.5 mL). The mixture is then heated in a water bath at 55–60 °C for a few minutes until a solution is obtained. This solution is poured into dry Et_2O (150 mL), previously cooled with an ice bath. Tris(methylthio)methyl tetrafluoroborate **(2b)** precipitates immediately as colorless crystals which are isolated by suction, washed several times with dry Et_2O, and dried in vacuo; yield: 2.30 g (96%); mp 168–170 °C, from dry MeCN/Et_2O (Lit.[5] mp 167.5–169 °C).

^{1}H-NMR (CF_3CO_2D): $\delta = 3.17$ (s), in agreement with Ref.[5].

^{13}C-NMR (CF_3CO_2D): $\delta = 21.41$ (q, SCH_3), 233.57 (s, C^+).

Tetrafluoroborate **2b** is more easily handled than the corresponding methyl sulfate **2a** for it is less sensitive to moisture and can be stored in well-closed bottles at low temperature.

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1-Dimethylamino-4-[tris(methylthio)methyl]naphtalene (4c); Typical Procedures:

Method A, using Salt **2a**: Tris(methylthio)methyl methyl sulfate (**2a**; 4.62 g, 17.5 mmol) is added, in one portion and with stirring, to a mixture of 1-dimethylaminonaphthalene (1.71 g, 10 mmol) and dry pyridine (1.38 g, 17.5 mmol) in dry MeCN (5 mL). The reaction is weakly exothermic and **2a** dissolves at once. The mixture is stirred at room temperature until the reaction is complete [TLC analysis on silica gel with petroleum ether/acetone (9.8:0.2) as eluent shows the disappearance of 1-dimethylaminonaphthalene after 1 h; at this point, if CD_3CN is used as solvent, the ^{1}H-NMR spectrum of the mixture shows signals corresponding to the unreacted salt **2a** and to by-products **5** and **6**, in addition to the signals corresponding to product **4c** and to pyridinium ions). The mixture is then treated with water (100 mL) and extracted with Et_2O (2 × 100 mL). The ether extracts ae washed with 5% NaOH solution (2 × 50 mL) and with H_2O (2 × 50 mL) and are dried (Na_2SO_4). Evaporation of the filtrate under reduced pressure yields a crude residue which is chromatographed on silica gel, using petroleum ether/acetone (9.8:0.2) as eluent. The first eluted product is *tetrakis(methylthio)methane* **(5)** [yield: 0.68 g (39%); mp 65°C, from ethanol (Lit.[9], mp 65°C)]. The second eluted product is *S,S-dimethyl dithiocarbonate* **(6)**; [bp 58–59°C/16 Torr (Lit.[16] bp 58–59°C/16 Torr); yields vary due to volatility]. (The ^{1}H-NMR spectra of **5** and **6** are identical to those reported[9,16]). The third collected product is *1-dimethylamino-4-[tris(methylthio)methyl]naphtalene* **(4c)**; yield: 2.78 g (86%); mp 85°C (from EtOH).

Method B, using Salt **2b**: A mixture of tris(methylthio)methyl tetrafluoroborate (**2b**; 4.20 g, 17.5 mmol), 1-dimethylaminonaphthalene (1.71 g, 10 mmol), dry pyridine (1.38 g, 17.5 mmol), and dry MeCN (5 mL) is worked-up as described above; yield of by-product **5**: 0.61 g (35%); yield of pure product **4c**: 3.17 g (98%).

This work was supported by the National Research Council of Italy (CNR), Progetto Finalizzato "I.P.R.A.", and by Ministero della Pubblica Istruzione (MPI).

Received: 21 April 1987; revised: 24 July 1987

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