A Simple and High Yield General Route to Methyl α-Oxo Thiolcarboxylates

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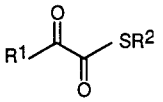
Methyl α-oxo thiolcarboxylates (aliphatic, aromatic and heteroaromatic) are obtained in good to excellent yields by hydrolysis of the corresponding trimethyl α-oxo trithioorthoesters with *N*-bromosuccinimide in aqueous THF or with HgO/35% aqueous HBF_4 in THF.

α-Oxo thiolcarboxylates **1** are an important class of synthetic intermediates, very frequently used in the field of antibiotics for the synthesis of cephalosporin derivatives.[1]



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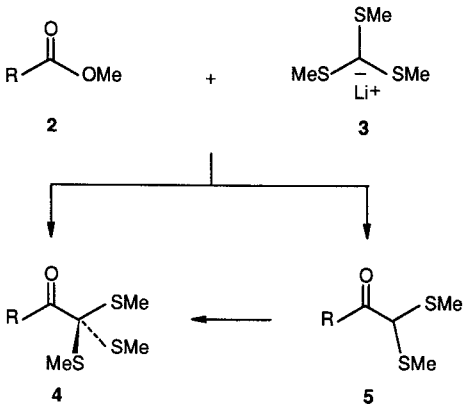
The procedures most commonly applied for their preparation, and often reported in patent literature, are based on the following reactions: i) the reaction of *S,S*-dialkyl dithiooxalates with Grignard reagents;[2] ii) the reaction of nitriles with the carbanion of methyl (methylthio)methyl sulfoxide, followed or by direct oxidation with copper(II) chloride or by acetylation and then oxidation with hydrogen peroxide or *m*-chloroperbenzoic acid;[3] iii) the reaction of esters with the carbanion of methyl (methylthio)methyl sulfoxide, followed by oxidation with sodium periodate;[4,5] and iv) the reaction of esters with the carbanion of (methylthio)methyl *p*-tolyl sulfone, followed by oxidation with hydrogen peroxide.[6,7] Starting with *S,S*-dialkyl dithiooxalates, nitriles or esters, the overall yields of these procedures varies usually between 30 and 70%.

Here we propose a route for the preparation of methyl α-oxo thiolcarboxylates **6** starting from the carboxylic esters **2** (Scheme). We reported[8] recently that esters **2** condense with tris(methylthio)methyllithium **(3)** in a one-pot reaction to give, either directly or via dimethyl α-oxo dithioacetals **5**, the trimethyl α-oxo trithioorthoesters **4** in almost quantitative yield. Meanwhile we found that compounds **4** can be further converted to methyl α-oxo thiolcarboxylates **6** (R = H, alkyl, aryl, heteroaryl) as shown in the Scheme. This route is simple, of general validity and results in high yields.

The literature reports only two examples for the conversion of **4** to **6**: i) the preparation of *S*-methyl phenylthioglyoxylate by treatment of 2,2,2-tris(methylthio)-1-phenylethanone with iodine and sodium hydrogen carbonate in diethyl ether/water under reflux for 7 h (94.5% yield);[9] and ii) the conversion of 1-[2-(6-formamido)pyridyl-2,2,2-tris(methylthio)ethanone to the corresponding thiol ester through oxidative hydrolysis with sodium periodate in acetic acid at 70°C for 30 minutes (74.8% yield).[5]

Our attempts to apply these procedures to various α-oxo trithioorthoesters either failed or resulted in not quite satisfactory yields of the corresponding methyl α-oxo



1	R				
a	Ph	e	2-Thienyl	i	H
b	4-ClC_6H_4	f	2-Pyrrolyl	j	*n*-C_9H_{19}
c	4-$MeOC_6H_4$	g	N-$PhSO_2$-2-Pyrrolyl	k	FCH_2
d	2-Furyl	h	3-Pyridyl	l	$MeOCH_2$

Scheme

thiolcarboxylates. In fact, according to the first procedure,[9] compounds **6a, b, h, j** were obtained in yields varying between 69 and 78%. Hydrolysis of **4i, l** failed. According to the second procedure,[5] compounds **6a, j** were obtained in about 70% yields. Hydrolysis of **4i** failed. On the other hand we found that the partial hydrolysis of **4** to **6** can be easily realized with *N*-bromosuccinimide (NBS) in aqueous THF at room temperature for 30 minutes (Procedure A) or with HgO/35% aqueous

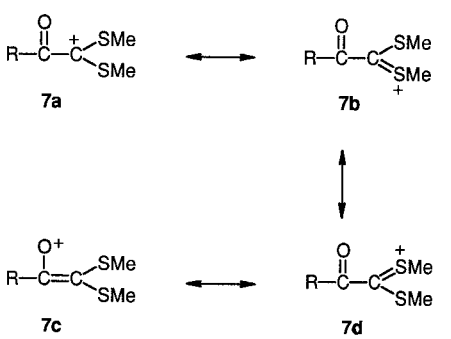


Table. Methyl α-Oxo Thiolcarboxylates **6a–l** Prepared

Product[a]	Procedure A		Procedure B		mp (°C) (solvent)[b] or bp (°C)/Torr	MS (70 eV) m/z (M^+)	IR (CCl_4) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ
	Ratio **4**: NBS	Yield (%)	Ratio **4**: HgO	Yield (%)				
6a	1 : 2.25	97	1 : 1.7	100	41[c] (CCl_4/P)	180	–[d]	–[d]
6b	1 : 2.25	100	1 : 1.7	98	46–47[e] (LP)	214	1685, 1730	–[d]
6c	1 : 2.25	90	1 : 1.7	90	65[e] (LP)	210	1680, 1730	–[d]
6d	1 : 3.50	94	1 : 1.7	100	82–83 (LP)	170	–[d]	–[d]
6e	1 : 2.25	100	1 : 1.7	95	44–45 (CCl_4/LP)	186	1680	2.05 (s, 3 H), 7.05–7.20 (m, 1 H), 7.60–7.80 (m, 1 H), 8.02–8.20 (m, 1 H)
6f[f]	1 : 2.25	94	1 : 1.7	91	70–71 (CCl_4/LP)	169	1688	2.42 (s, 3 H), 6.38–6.58 (m, 1 H), 7.25–7.40 (m, 1 H), 7.53–7.70 (m, 1 H)
6g	1 : 3.50	100	1 : 1.7	100	112–113 (CCl_4/LP)	309	1680	2.53 (s, 3 H), 6.35–6.50 (m, 1 H), 7.40–7.70 (m, 4 H), 7.80–8.10 (m, 3 H)
6h[g]	1 : 3.50	50	1 : 1.7	85	138–139/1.8	181	1685, 1735	2.53 (s, 3 H), 7.40–7.72 (m, 1 H), 8.45–8.73 (m, 1 H), 8.90–9.10 (m, 1 H), 9.45–9.60 (m, 1 H)
6i	–[h]	–	1 : 2.0	61[i]	–	104	–	–
6j	1 : 3.00	100	1 : 1.7	96	109–110/0.3	202 ($M^+ - CO$)	1680, 1728	0.70–1.00 (m, 3 H), 1.05–1.35 (m, 14 H), 2.30 (s, 3 H), 2.60–2.90 (m, 2 H)
6k	1 : 7.00	44	1 : 2.0	81	42–43/0.3	136	1672, 1740	2.45 (s, 3 H), 5.00 (s, 1 H), 5.75 (s, 1 H)
6l	1 : 7.00	57	1 : 2.0	83	58–59/0.4	148	1672, 1742	2.36 (s, 3 H), 3.43 (s, 3 H), 4.55 (s, 2 H)

[a] Satisfactory micronanalyses obtained for all new compounds (**6e–h, j–l**).
[b] P = Pentane.
[c] Lit.[15] mp 39.5–41 °C.
[d] Identical to those reportd in the literature: Ref. 15 for **6a**, Ref. 16 for **6b** and **6c**, and Ref. 17 for **6d**.
[e] Not reported in Ref. 16.
[f] Attempts to obtain **6f** by hydrolysis with KOH in EtOH of **6g**, failed.
[g] Reported in a patent[18] (inaccessible).
[h] For ratio varying from 1 : 2.25 to 1 : 7.00, **4i** disappeared and no trace of **6i** was found.
[i] Isolated as its 2,4-dinitrophenylhydrazone derivative (experimental).

HBF_4 in THF at room temperature for 30 minutes (Procedure B). As can be seen from the Table the yields from both the procedures, with only a few exceptions, are excellent.

The above mentioned reactions proceed likely by the S_N1 mechanism, in spite of the presence of a carbonyl group directly attached to the reaction center. Indeed, in the case of the substrates $R'COCR_2X$ (X being a leaving group), the reactions involving the cations as transient intermediates are essentially unaffected by a strong electron-withdrawing group, such as α-carbonyl, which only decreases S_N1 rates weakly. For an α-cyano group also, the rate-retarding effect is reduced. This indicates a resonance stabilization for the intermediate cations.[10] Therefore we suppose that the attack of Br^+ (from NBS), or Hg^{2+}, to a sulfur atom of a methylthio group increases the leaving group power thus favouring the hydrolysis of the α-oxo trithiorthoesters **4** by an S_N1 mechanism, through the formation of the intermediate carbocations **7**.[11] This explains the lower yields obtained in the hydrolysis of **4h, k, l**, where the presence of electron-withdrawing groups bonded to the carbonyl group disfavours to some extent the formation of the intermediate carbocations.

The qualifying characteristics of our route are: i) tris(methylthio)methane, the precursor of reagent **3** (Scheme), is more easily accessible[13] than precursors like methyl (methylthio)methyl sulfoxide[14] and (methylthio)-methyl *p*-tolyl sulfone[6] used in the known procedures; ii) the trimethyl α-oxo trithioorthoesters **4** can be converted to the corresponding methyl α-oxo thiolcarboxylates **6** by simple hydrolysis, instead of by oxidative hydrolysis as required by the other procedures; iii) the operating conditions are very simple; and iv) the overall yields are excellent.

Trimethyl α-oxo trithioorthoesters **4** were prepared as previously reported by us.[8] *N*-Bromosuccinimide (NBS) was purchased from Aldrich. Light petroleum refers to the fraction boiling in the range 40–70 °C and is abbreviated as LP. Mass spectra were recorded on an HP 5970 B mass selective detector connected to an HP 5890 GC, cross-linked methyl silicone capillary column. α-Oxo thiolcarboxylates **6** are yellow compounds. Satisfactory microanalyses were obtained for all new compounds: C ± 0.07, H ± 0.06, S ± 0.08.

Methyl α-Oxo Thiolcarboxylates 6a–l; General Procedures:
Procedure A: A solution of trimethyl α-oxo trithioorthoester **4a–h, j** (10 mmol) in THF (2 mL) was added in one portion and with stirring to a solution of NBS (4.00–6.23 g, 22.5–35 mmol) in THF/H_2O (15:1, 8 mL). A mildly exothermic reaction occurred and the solution became at once deep yellow. Stirring at r.t. was maintained for 30 min. TLC (silica gel, LP/acetone, 9.5:0.5) and GC analyses showed the disappearance of the starting compound **4** and the presence of the title compound **6** and succinimide as only products. The reaction mixture was neutralized with 5% aq $NaHCO_3$ solution (50 mL), and extracted with Et_2O (2 × 50 mL).

The combined organic extracts were washed with H_2O (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford the virtually pure (TLC, GC, NMR) methyl α-oxo thiolcarboxylates **6a–h, j**. For the hydrolysis of **4k, l**, NBS (70 mmol, 12.46 g) in THF/H_2O (19 : 1, 20 mL) was used. Because of the high solubility of the thiol esters **6k, l** in H_2O, the neutralization was made with solid $NaHCO_3$ (6 g) and the washings were done with ice-cold sat. aq NaCl solution (50 mL). The crude residue obtained after evaporation of the solvent was purified by chromatography on a short silica gel column, using CH_2Cl_2/MeOH (9.8 : 0.2) as eluent. Hydrolysis of **4i** failed.

Procedure B: A solution of HgO (3.68 g, 17 mmol) in 35% aq HBF_4 (8.5 mL) was diluted with THF (8 mL). A solution of trimethyl α-oxo trithioorthoester **4a–h, j** (10 mmol) in THF (2 mL) was added in one portion with stirring. The reaction mixture became at once deep yellow. Stirring at r.t. was maintained for 30 min. TLC (silica gel, LP/acetone, 9.5 : 0.5) and GC analyses showed the disappearance of the starting compound **4** and the presence of the title compound **6** as the only product. KI (8.47 g, 51 mmol) was added. After stirring for a few min, the mixture was diluted with hot LP (50 mL) and the organic layer was decanted. Then the mixture was exhaustively extracted, with stirring and heating, with the same solvent (6 × 30 mL). The combined extracts were washed successively with a 5% aq $NaHCO_3$ solution (2 × 50 mL) and H_2O (2 × 50 mL), dried and evaporated under reduced pressure to afford the virtually pure (TLC, GC, NMR) methyl α-oxo thiolcarboxylates **6a–h, j**.

For the hydrolysis of **4i, k, l**, HgO (20 mmol, 4.33 g) in 35% aq HBF_4 (10 mL) and KI (60 mmol, 9.96 g) were needed. After the workup described above, the pure thiol esters **6k, l** were isolated. Owing to its solubility, *S*-methyl thioglyoxylate **(6i)** was instead isolated as its 2,4-dinitrophenylhydrazone. In this case, after completion of the hydrolysis (30 min), GC/MS analysis of the reaction mixture showed the presence of **6i**: $m/z = 104$ (M^+). A solution of 2,4-dinitrophenylhydrazine (1.98 g, 10 mmol) and concd HCl (1.04 g, 10 mmol) in EtOH (30 mL) was added. After heating for a few min, the mixture was worked up as described above, using $CHCl_3$ as solvent for the extractions (4 × 50 mL). The crude residue was purified by chromatography on silica gel with the same solvent as eluent, to afford the 2,4-dinitrophenylhydrazone of **6i** in 61% yield (1.73 g); mp 204–205 °C ($CHCl_3$/LP).

2,4-Dinitrophenylhydrazone of **6i**:

IR ($CHCl_3$): $\nu = 1660$ (C=O), 3300 cm^{-1} (N–H).

^1H NMR (CD_3COCD_3): $\delta = 2.00$ (s, 3H), 7.76 (s, 1H), 7.78 (d, 1H, $J = 9.00$ Hz), 8.22 (dd, 1H, $J = 9.00$, 3.00 Hz), 8.66 (d, 1H, $J = 3.00$ Hz).

MS: $m/z = 284$ (M^+).

$C_9H_8N_4O_5S$	calc.	C 38.03	H 2.84	S 11.28
(284.3)	found	38.08	2.87	11.30

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