Isomerization of Trimethyl α-Keto Trithioorthocarboxylates into α,α-Bis(methylthio) Thiolcarboxylates. A New Rearrangement of Synthetic Interest

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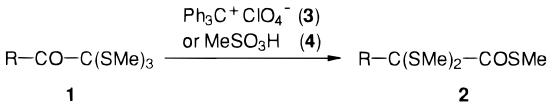
A study was made of the isomerization reaction of a great variety of trimethyl α-keto trithioorthocarboxylates to α,α-bis(methylthio) thiolcarboxylates, intermediates of high synthetic value for the synthesis of α-arylpropionic acids. The reaction was carried out in methylene chloride in the presence of catalytic amounts of trityl perchlorate or methanesulfonic acid and was complete in 2 h at rt. In most of the investigated cases the result was positive, the yields usually being greater than 90%. Also the reaction mechanism was subjected to an experimental study.

Since the accomplishment of effective procedures for the synthesis of trimethyl α-keto trithioorthocarboxylates **1** starting from the most common derivatives of carboxylic acids (*i.e.*, esters, acyl chlorides, anhydrides, thiol esters, and amides),[1,2] research has been directed toward the synthetic utilization of this class of essentially unexplored compounds. The most significant findings in this regard concern a new procedure of general validity for the preparation of α-arylpropionic acids:[3] it is well-known that some of them are important analgesics and antiinflammatory drugs.[4]

In the present work we report a study on the isomerization of trimethyl α-keto trithioorthocarboxylates **1** into methyl α,α-bis(methylthio) thiolcarboxylates **2** (Scheme 1), the fundamental, and more innovative, step of the procedure. As a rule isomerization is easily obtained in yields higher than 90% by stirring a solution of **1** in anhydrous methylene chloride for about 2 h under a nitrogen atmosphere, in the presence of catalytic amounts of trityl perchlorate (**3**; procedure A: molar ratio **1**:**3** = 1:0.15) or methanesulfonic acid (**4**; procedure B: molar ratio **1**:**4** = 1:0.5). A strictly anhydrous reaction environment was maintained since, as has been demonstrated in other research,[5] the same trimethyl α-keto trithioorthocarboxylates **1**, by treatment with soft or hard acids in aqueous medium, give, by partial hydrolysis, methyl α-keto thiolcarboxylates (R-CO-COSMe) in excellent yields. The investigated reactions, the reaction conditions, and the results are reported in Table 1.

From the synthetic point of view, it can be observed that the investigated reactions, carried out in the presence of both trityl perchlorate (**3**; procedure A) and methanesulfonic acid (**4**; procedure B), follow parallel courses. In fact with both catalysts the isomerization took place with all the trimethyl α-keto trithioorthocarboxylates **1**, where R is an aryl group (entries 1−8, 11, 12, 15−22, and 25−30), the only exceptions being the phenyl containing a chlorine or fluorine atom on the ortho positions (entries 9, 10, 13, 14, 23, and 24). Besides, simple aliphatic compounds gave positive results (entries 31−36), while those substituted with a chlorine or methoxy group in the α position remain unaltered, even on extending the reaction times and increasing the catalyst amounts (entries 37−40). For the reactions carried out in the presence of trityl perchlorate (**3**), the final mixtures were always found to contain not only the isomerization products but also methyl trityl sulfide (**6**) and triphenylmethanol (**9**). The results of such reactions (procedure A) can be rationalized by assuming that the **1** → **2** isomerization occurs through a multistep reaction where the trityl cation acts as a methanethiolate carrier (Scheme 2). In the first step the trityl cation would take a methanethiolate anion from **1**, giving rise to the intermediate cation **5** and trityl methyl sulfide (**6**); the methanethiolate anion would then transfer from **6** to the carbonyl carbon of cation **5**, giving rise to the oxyranic derivative **7** and the restoration of **3**. Further action of trityl perchlorate on **7** would lead to the intermediate cation **8**, together with methyl trityl sulfide (**6**). Finally these last intermediates could react, resulting in the isomerization product **2** and the restoration of catalyst **3**.

Scheme 1



a R = Ph; **b** R = 2-MeC_6H_4; **c** R = 4-MeC_6H_4; **d** R = 4-*i*-BuC_6H_4;
e R = 2-FC_6H_4; **f** R = 4-FC_6H_4; **g** R = 2-ClC_6H_4; **h** R = 4-ClC_6H_4;
i R = 4-BrC_6H_4; **j** R = 4-$MeOC_6H_4$; **k** R = 3-$PhCOC_6H_4$;
l R = 2,5-$Cl_2C_6H_3$; **m** R = 3,5-$Cl_2C_6H_3$; **n** R = 2-$C_{10}H_7$;
o R = 6-MeO-2-$C_{10}H_6$; **p** R = H; **q** R = Me; **r** R = *n*-C_9H_{19};
s R = FCH_2; **t** R = $MeOCH_2$

The proposed reaction scheme is supported by collateral experimental results: (i) the possibility of formation of the intermediate cation **5** was confirmed by the exchange reaction between methylthio and ethylthio groups that occurred when **1g**, that does not isomerize to **2g** (entry 13), was reacted with ethyl trityl sulfide in the presence of trityl perchlorate (**3**), giving at equilibrium the α-keto trithioorthocarboxylates **10**−**12** and methyl trityl sulfide (**6**) (Scheme 3); (ii) that the intermediate cation **8** can form was confirmed by the exchange reaction between methylthio and ethylthio groups: in fact

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(1) Barbero, M.; Cadamuro, I.; Degani, I.; Dughera, S.; Fochi, R. *J. Org. Chem.* **1995**, *60*, 6017.
(2) Degani, I.; Dughera, S.; Fochi, R.; Serra, E. *J. Org. Chem.* **1996**, *61*, 9572.
(3) Degani, I.; Dughera, S.; Fochi, R. (National Research Council of Italy) Italian Pat. MI96A 000500, 1996; PCT/EP 97/01258 (12.03.1997).
(4) For example, see: Hamor, G. H. In *Principles of Medicinal Chemistry;* Foye, W. O., Ed.; Lea & Febiger: Philadelphia, 1989; Chapter 23 and references cited therein.
(5) Degani, I.; Dughera, S.; Fochi, R.; Gatti, A. *Synthesis* **1996**, 467.

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Table 1. α,α-Bis(methylthio) Thiolcarboxylates 2

entry	R	procedure	molar ratio **1**:**3** or **1**:**4**	reaction time (h)	chromatographic solvent[a]	yield[b] (%) **2**	**6**	**9**
1	C_6H_5	A	1:0.15	2	PE−MeCOMe (9.5:0.5)	92	72	23
2		B	1:0.5	2		92		
3	2-$CH_3C_6H_4$	A	1:0.15	4	PE−Et_2O (9.8:0.2)	89	77	23
4		B	1:0.5	5		93		
5	4-$CH_3C_6H_4$	A	1:0.15	2	PE−Et_2O (9.8:0.2)	93	78	22
6		B	1:0.5	2		93		
7	4-*i*-$C_4H_9C_6H_4$	A	1:0.15	2	PE−CH_2Cl_2 (7:3)	94	73	23
8		B	1:0.5	2		93		
9	2-FC_6H_4	A	1:0.5	9	PE−Et_2O (9.8:0.2)	c	d	81
10		B	1:1.5	9		c		
11	4-FC_6H_4	A	1.0.15	2	PE−Et_2O (9.8:0.2)	91	78	12
12		B	1:0.5	2		93		
13	2-ClC_6H_4	A	1:0.5	9	PE−CH_2Cl_2 (7:3)	e	d	86
14		B	1:1.5	9		e		
15	4-ClC_6H_4	A	1:0.15	2	PE−Et_2O (9.8:0.2)	93	69	25
16		B	1:0.5	2		94		
17	4-BrC_6H_4	A	1:0.15	2	PE−Et_2O (9.8:0.2)	89	65	33
18		B	1:0.5	2		94		
19	4-$CH_3OC_6H_4$	A	1:0.15	2	PE−Et_2O (4:1)	93	77	17
20		B	1:0.5	2		93		
21	3-C_6H_5 COC_6H_4	A	1:0.15	2	PE−Et_2O (4:1)	91	83	d
22		B	1:1.5	8		94		
23	2,5-$Cl_2C_6H_3$	A	1:0.5	9	PE−CH_2Cl_2 (7:3)	f	d	86
24		B	1:1.5	9		f		
25	3,5-$Cl_2C_6H_3$	A	1:0.3	7	PE−CH_2Cl_2 (7:3)	61	71	20
26		B	1:5	6		64		
27	2-$C_{10}H_7$	A	1:0.15	2	PE−CH_2Cl_2 (7:3)	92	75	17
28		B	1:0.5	2		91		
29	6-CH_3O-2-$C_{10}H_6$	A	1:0.15	2	PE−Et_2O (4:1)	93	89	d
30		B	1:0.5	2		94		
31	H	A	1:0.2	2	PE−CH_2Cl_2 (7:3)	93	35	62
32		B	1:0.5	2		89		
33	CH_3	A	1:0.2	2	PE−CH_2Cl_2 (1:1)	85	75	20
34		B	1:1	2		83		
35	*n*-C_9H_{19}	A	1:0.2	2	PE−CH_2Cl_2 (9:1)	81	67	20
36		B	1:1	2		77		
37	FCH2	A	1:0.5	9	PE−MeCOMe (9.5:0.5)	g	d	85
38		B	1:1.5	9		g		
39	CH_3OCH_2	A	1:0.5	9	PE−MeCOMe (9.5:0.5)	h	d	83
40		B	1:1.5	9		h		

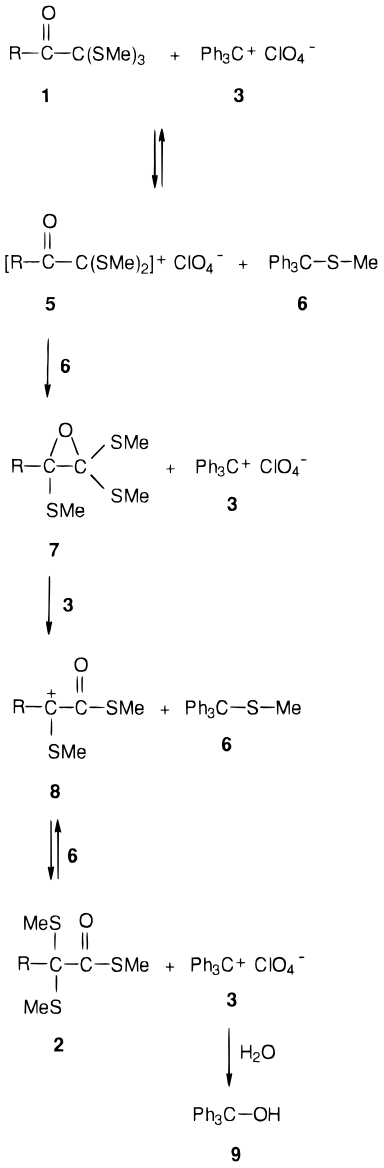
[a] PE = petroleum ether (40−70 °C). [b] Yields of pure isolated products. [c] The starting compounds **1e** was recovered in 87% yield. [d] Traces. [e] The starting compound **1g** was recovered in 86% yield. [f] The starting compound **1l** was recovered in 82 and 98% yield, respectively, in entries 23 and 24. [g] The starting compound **1s** was recovered in 95% yield. [h] The starting compound **1t** decomposed in entry 39; in entry 40 it was recovered in 86% yield.

when **2a** was reacted with ethyl trityl sulfide in the presence of trityl perchlorate (**3**), the products **13** and **14** formed at equilibrium, together with the acylic substitution products **15** and **16** and methyl trityl sulfide (**6**) (Scheme 4); (iii) after the formation of the intermediate **5**, the reaction proceeds to the final products, through the rearrangement of the oxygen atom not through the anionotropic rearrangement of the R group. In fact starting with **1a**, labeled at the carbonyl with ^{13}C, the R group in the isomerization product was found still bonded to the labeled carbon atom (Scheme 5). The hypothesized mechanism could also explain the lack of isomerization of the trimethyl α-keto trithioorthocarboxylates **1e**,**g**,**l**,**s**,**t**. In fact an accepted opinion[6a−c] is that the electron-withdrawing polar effects (inductive effects, especially field effects) of halogens are stronger from the ortho positions of the aryl groups than from the para and meta. Therefore only in trithioorthocarboxylates **1e**,**g**,**l** where ortho halogens are present (entries 9, 13, and 23) are the polar effects sufficiently intense to impede the formation of the corresponding cationic intermediates **8e,g,l**. In the same way the missing rearrangement of entries 37 and 39 can be attributed to the electron-withdrawing polar effects of chloro and methoxy substituents on the α-position of the alkyl groups. On the other hand the impossibility of forming the **8** type intermediates, where electronegative atoms or groups are near the cationic center, is indirectly confirmed by the following: reacting ethanethiol, under acid catalysis, with ethyl α-keto thiolcarboxylate **17** results in the corresponding α,α-bis(ethylthio) thiolcarboxylate **19** through the formation of the cationic intermediate **18**, as is generally accepted for thioketal formation; instead with ethyl α-keto thiolcarboxylate **20** there is no change (Scheme 6), the formation of the intermediate **21** not being able to take place.

In the cases reported in Table 1 where isomerization is promoted by methanesulfonic acid (**4**; procedure B), the result being similar to when trityl perchlorate (**3**) is used as catalyst, the hypothesizable reaction mechanism appears uncertain as no methanethiolate anion carrier can be identified.[7] However, even in the isomerization reaction of **1a** to **2a**, catalyzed by **4** in the presence of carbonyl labeled with ^{13}C, the result is identical to that using **3** (Scheme 5). This demonstrates that even in reactions

(6) For example, see: (a) *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1972; Chapter 2, and references cited therein. (b) Buckley, A.; Chapman, N. B.; Shorter, J. *J. Chem. Soc. B* ***1969****, 195. (c) Chapman, N. B.; Shorter, J.; Utley, J. H. P. J. Chem. Soc.* ***1962****, 1824.*

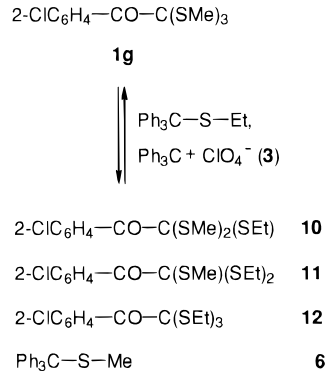
Scheme 2



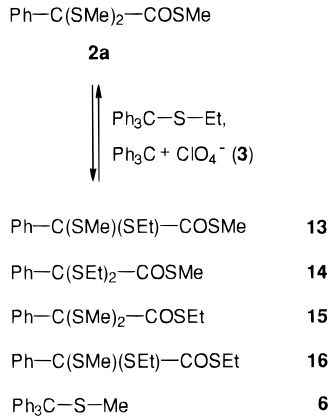
catalyzed by methanesulfonic acid no anionotropic rearrangement of the R group occurs; thus the mechanism must involve intramolecular and, perhaps, intermolecular rearrangements of methanethiolate anions.

In conclusion, this study details the field of applicability of the **1** → **2** isomerization that, as already stated, leads easily, and in excellent yields, to intermediates of high synthetic value.[3] Furthermore, the large amount of experimental information collected has, in the case of when the catalyst is trityl perchlorate (**3**), allowed us to make a reasonable interpretation of the isomerization mechanism; instead greater uncertainty still prevails in the interpretation of the innermost mechanism of isomerization reactions catalyzed by methanesulfonic acid (**4**).

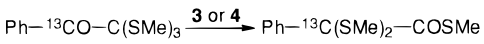
Scheme 3



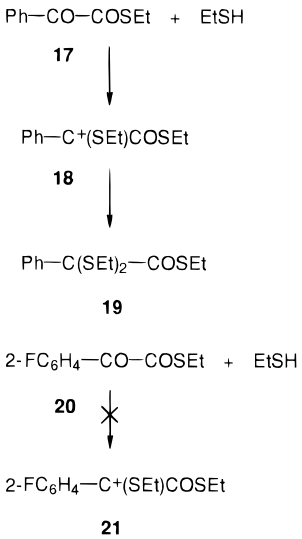
Scheme 4



Scheme 5



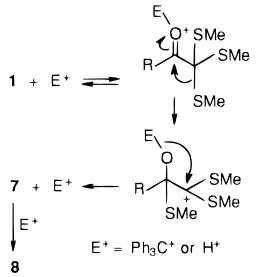
Scheme 6



Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$, unless otherwise noted. IR spectra were recorded

(7) One reviewer has suggested the following Scheme to formally interpret the reactions carried out in the presence of trityl perchlorate (**3**) or methanesulfonic acid (**4**).



However in the case of $E^+ = H^+$ where, according to the scheme, there should be a protonation at the carbonyl group, ab initio calculations, carried out at the MP2/6-31G(d) level and aimed to check this hypothesis, did not provide any conclusive information.

for solutions in CCl_4. Column chromatography and TLC were performed on Merck silica gel 60 (70−230 mesh ASTM) and GF 254, respectively. Petroleum ether refers to the fraction boiling in the range 40−70 °C and is abbreviated as PE. All of the reactions were performed in oven-dried glassware under an atmosphere of nitrogen. Details for reactions 1−40, chromatographic solvents, and yields of the products are listed in Table 1. Satisfactory microanalyses were obtained for all the new compounds.

Methyl 6-methoxy-2-naphthoate,[8] trityl perchlorate,[9] tris(methylthio)methane[10] and tris(ethylthio)methane[11] were prepared following literature procedures. All other compounds were purchased from the Aldrich Chemical Co.

Ethyl Trityl Sulfide. Ethanethiol (3.72 g, 60 mmol) was added dropwise to a suspension of sodium hydride (1.44 g, 60 mmol) in anhydrous THF (75 mL), previously cooled with an ice bath to 0−5 °C. After the addition was complete, the cooling bath was removed and trityl perchlorate (**3**; 17.13 g, 50 mmol) was added in one portion, under stirring. After being stirred at rt for about 30 min, GC and TLC (PE) analyses showed that the reaction was complete. Usual workup afforded a crude product that was purified by chromatography on a short column, eluting with PE. The yield of the pure title compound was 89% (13.55 g): mp 129−130 °C (PE) (lit.[12] mp 132 °C); MS *m*/*z* 243 (M^+ − SEt); ^{1}H NMR δ 1.13 (t, J = 7.0 Hz, 3H), 2.27 (q, J = 7.0 Hz, 2H), 7.70−7.80 (m, 15H).

Methyl 4-Isobutylbenzoate. Prepared by reaction of 4-isobutylbenzoyl chloride[13] (9.83 g, 50 mmol) with anhydrous methanol (100 mL). After the usual workup, the crude product was purified by column chromatography, eluting with PE−CH_2Cl_2 (7:3, v/v). The yield was quantitative (9.60 g): bp 80−81 °C/0.3 mmHg; MS *m*/*z* 192 (M^+); ^{1}H NMR δ 0.88 (d, J = 6.0 Hz, 6H), 1.10−2.12 (m, 1H), 2.48 (d, J = 7.0 Hz, 2H), 3.80 (s, 3H), 7.05 and 7.80 (2 d, 1:1, J = 8.4 Hz, 4H); IR 1732 cm^{-1} (CO). The title compound is mentioned in the literature,[14] but yield and physical, analytical, and spectroscopic data are not reported.

Methyl 3-[Dimethoxy(phenyl)methyl]benzoate. Methanesulfonic acid (**4**; 0.96 g, 10 mmol) was added to a solution of 3-benzoylbenzoic acid (11.30 g, 50 mmol) in anhydrous methanol (75 mL), and the mixture was heated under a gentle reflux until disappearance of the starting compound (5 h; TLC: PE−Et_2O, 4:1, v/v). The only product formed was methyl 3-benzoylbenzoate. The reaction mixture was cooled, and trimethyl orthoformate (75 mL, 77 mmol) was added. After 24 h of stirring at rt, TLC analysis (PE−Et_2O, 4:1, v/v) showed the presence of the title compound as the only product. This was isolated virtually pure (TLC, NMR) in 89% yield (12.74 g), after usual workup: mp 89−90 °C (CCl_4−pentane); MS *m*/*z* 286 (M^+); ^{1}H NMR δ 3.02 (s, 6H), 3.78 (s, 3H), 7.05−7.90 and 8.00−8.12 (2 m, 8:1, 9H); IR 1732 cm^{-1} (CO).

Trimethyl α-Keto Trithioorthocarboxylates 1. Trimethyl α-keto trithioorthocarboxylates **1a,h,j,l,p,r**−**t** were prepared following the procedures previously reported by us.[1] According to the same procedures, compounds **1b,c**−**g,i,k,m**−**o,q** were also prepared. Starting compounds and chromatographic solvents used for the new preparations are listed below, together with yields and physical and spectroscopic data for compounds **1**.

1b: methyl 2-methylbenzoate; PE−CH_2Cl_2 (7:3, v/v); 98%; bp 160−161 °C/0.4 mmHg; MS *m*/*z* 225 (M^+ − SMe); ^{1}H NMR δ 2.11 (s, 9H), 2.36 (s, 3H), 7.05−7.40 and 8.05−8.35 (2 m, 3:1, 4H); IR 1680 cm^{-1} (CO).

1c: methyl 4-methylbenzoate; PE−CH_2Cl_2 (7:3, v/v); 93%; bp 143−144 °C/0.3 mmHg; MS *m*/*z* 225 (M^+ − SMe); IR 1670 cm^{-1} (CO); ^{1}H NMR data identical to those reported.[15]

1d: methyl 4-isobutylbenzoate; PE−CH_2Cl_2 (7:3, v/v); 95%; bp 130−131 °C/0.4 mmHg (lit.[2] bp 130−131 °C/0.4 mmHg); MS *m*/*z* 267 (M^+ − SMe); spectral data identical to those reported.

1e: methyl 2-fluorobenzoate; PE−Et_2O (9.8:0.2, v/v); 93%; bp 159−160 °C/0.8 mmHg; MS *m*/*z* 229 (M^+ − SMe); ^{1}H NMR δ 2.18 (s, 9H), 6.90−7.55 and 7.90−8.30 (2 m, 3:1, 4H); IR 1692 cm^{-1} (CO).

1f: methyl 4-fluorobenzoate; PE−Et_2O (9.8:0.2, v/v); 92%; mp 68−69 °C (PE); MS *m*/*z* 229 (M^+ − SMe); ^{1}H NMR δ 2.07 (s, 9H), 6.90−7.35 and 8.40−8.75 (2 m, 1:1, 4H); IR 1672 cm^{-1} (CO).

1g: methyl 2-chlorobenzoate; PE−CH_2Cl_2 (7:3, v/v); 98%; mp 83−84 °C (CCl_4); MS *m*/*z* 245 (M^+ − SMe); ^{1}H NMR δ 2.22 (s, 9H), 7.25−7.63 and 8.05−8.35 (2 m, 3:1, 4H); IR 1700 cm^{-1} (CO).

1i: methyl 4-bromobenzoate; PE−CH_2Cl_2 (7:3, v/v); 92%; mp 59−60 °C (PE); MS *m*/*z* 289, 291 (M^+ − SMe); ^{1}H NMR δ 2.12 (s, 9H), 7.66 and 8.48 (2 d, 1:1, J = 9.0, 4H); IR 1675 cm^{-1} (CO).

1k: methyl 3-[dimethoxy(phenyl)methyl]benzoate; PE−Et_2O (9:1, v/v). The product obtained was 1-{3-[dimethoxy(phenyl)methyl]phenyl}-2,2,2-tris(methylthio)ethanone. Its structure was confirmed by its ^{1}H NMR spectrum: δ 1.98 (s, 9H), 3.08 (s, 6H), 6.90−7.70 and 8.02−8.40 (2 m, 7:2, 9H). This acetal was treated with concd HCl (5 mL), and the reaction mixture was stirred at rt until completion of the hydrolysis (1 h). After usual workup, virtually pure (TLC, NMR) 1-(3-benzoylphenyl)-2,2,2-tris(methylthio)ethanone (**1k**) was obtained in 93% yield: mp 119−120 °C (CCl_4−PE); MS *m*/*z* 315 (M^+ − SMe); ^{1}H NMR δ 2.05 (s, 9H), 7.10−8.00 and 8.38−8.78 (2 m, 7:2, 9H); IR 1675 cm^{-1} (CO).

1m: methyl 3,5-dichlorobenzoate; PE−CH_2Cl_2 (7:3, v/v); 95%; mp 129−130 °C (PE); MS *m*/*z* 280 (M^+ − SMe); ^{1}H NMR δ 2.24 (s, 9H), 7.03−7.70 and 8.32−8.50 (2 m, 1:2, 3H); IR 1680 cm^{-1} (CO).

1n: methyl 2-naphthoate; PE−CH_2Cl_2 (7:3, v/v); 97%; mp 77−78 °C (PE); MS *m*/*z* 261 (M^+ − SMe); ^{1}H NMR δ 2.03 (s, 9H), 7.20−7.90, 8.15−8.40, and 8.85−8.98 (3 m, 5:1:1, 7H); IR 1670 cm^{-1} (CO).

1o: methyl 6-methoxy-2-naphthoate;[8] PE−Et_2O (4:1, v/v); 94%; mp 112−113 °C (PE−CCl_4); MS *m*/*z* 291 (M^+ − SMe); ^{1}H NMR δ 2.02 (s, 9H), 3.83 (s, 3H), 6.93−7.15, 7.43−7.80, 8.18−8.45, and 8.85−8.98 (4 m, 2:2:1:1, 6H); IR 1670 cm^{-1} (CO).

1q: methyl acetate; PE−CH_2Cl_2 (1:1, v/v); 82%; mp 105−106 °C (PE) (lit.[2] mp 105−106 °C) ; MS *m*/*z* 149 (M^+ − SMe); spectral data identical to those reported.

Methyl α,α-Bis(methylthio) Thiolcarboxylates 2. Representative Procedures. *S*-Methyl Bis(methylthio)phenylthioacetate (2a). Procedure A. In entry 1 (Table 1) 2,2,2-tris(methylthio)-1-phenylethanone (**1a**; 2.58 g, 10 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL). The colorless solution was maintained at rt (20−25 °C), under stirring and under an atmosphere of nitrogen. Trityl perchlorate (**3**; 0.51 g, 1.5 mmol) was added in one portion: a red solution was at once obtained. Progress of the reaction was monitored by GC and TLC (PE−MeCOMe, 9.5:0.5, v/v) analyses, and stirring was continued for 2 h, until disappearance of the starting compound **1a**. The deep red solution was diluted with CH_2Cl_2 (100 mL) and then poured into 5% $NaHCO_3$ (150 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (100 mL). The combined organic extracts were washed with water (2 × 100 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was column chromatographed, eluting with PE−MeCOMe (9.5:0.5, v/v), to afford three products. The first eluted product was methyl trityl sulfide (**6**; 0.31 g, 72% with regard to **3**): mp 106−107 °C (PE)

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(lit.[16] mp 106 °C); MS *m*/*z* 243 (M^+ − SMe); ^{1}H NMR δ 1.82 (s, 3H), 7.05−7.45 (m, 15H). The second eluted product was the title compound **2a** (2.37 g, 92%). The third eluted product was triphenylmethanol (**9**; 0.09 g, 23% with regard to **3**), mp 161−162 °C ($CHCl_3$−PE), identical to that of an authentic sample of commercial origin (Aldrich).

Procedure B. In entry 2 (Table 1) a solution of methanesulfonic acid (**4**; 0.48 g, 5 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise at rt (20−25 °C), during 10 min, to a stirred solution of trithioorthocarboxylate **1a** (2.58 g, 10 mmol) in the same solvent (18 mL), maintained under an atmosphere of nitrogen. The solution changed from colorless to yellow. After 2 h of stirring, GC and TLC (PE−MeCOMe, 9.5:0.5, v/v) analyses showed the disappearance of the starting compound **1a** and the presence of one only product. The crude residue, obtained after a workup identical to that described above, was the virtually pure (TLC, GC, NMR) title compound **2a** (2.37 g, 92%).

Physical properties of α,α-bis(methylthio) thiolcarboxylates **2** are as follows:

2a: bp 155−156 °C/0.3 mmHg; MS *m*/*z* 258 (M^+); ^{1}H NMR δ 1.97 (s, 6H), 2.24 (s, 3H), 7.05−7.32 and 7.32−7.62 (2 m, 3:2, 5H); IR 1680 cm^{-1} (CO).

2b: mp 57−58 °C (PE); MS *m*/*z* 272 (M^+); ^{1}H NMR δ 1.93 (s, 6H), 2.40 and 2.42 (2 s, 1:1, 6H), 7.00−7.40 and 7.62−7.90 (2 m, 3:1, 4H); IR 1680 cm^{-1} (CO).

2c: mp 66−67 °C (PE); MS *m*/*z* 272 (M^+); ^{1}H NMR δ 2.02 (s, 6H), 2.30 and 2.40 (2 s, 1:1, 6H), 7.15−7.45 and 7.50−7.85 (2 d, 1:1, J = 8.0 Hz, 4H); IR 1680 cm^{-1} (CO).

2d: bp 180−181 °C/0.3 mmHg; MS *m*/*z* 314 (M^+); ^{1}H NMR δ 0.96 (d, J = 6.96 Hz, 6H), 1.25−2.10 (m, 1H), 2.00 (s, 6H), 2.28 (s, 3H), 2.50 (d, J = 6.40 Hz, 2H), 7.04 and 7.45 (2 d, 1:1, J = 8.2 Hz, 4H); IR 1680 cm^{-1} (CO).

2f: bp 159−160 °C/0.5 mmHg; MS *m*/*z* 276 (M^+); ^{1}H NMR δ 2.02 (s, 6H), 2.32 (s, 3H), 6.92−7.35 and 7.55−7.85 (2 m, 1:1, 4H); IR 1680 cm^{-1} (CO).

2h: mp 89−90 °C (PE); MS *m*/*z* 292 (M^+); ^{1}H NMR δ 1.97 (s, 6H), 2.25 (s, 3H), 7.05 and 7.55 (2 d, 1:1, J = 8.0 Hz, 4H); IR 1680 cm^{-1} (CO).

2i: mp 100−101 °C (PE); MS *m*/*z* 336, 338 (M^+); ^{1}H NMR δ 1.95 (s, 6H), 2.24 (s, 3H), 7.30−7.40 (m, 4H); IR 1680 cm^{-1} (CO).

2j: bp 189−190 °C/0.5 mmHg; MS *m*/*z* 288 (M^+); ^{1}H NMR δ 1.88 (s, 6H), 2.16 (s, 3H), 3.68 (s, 3H), 6.70 and 7.40 (2 d, 1:1, J = 8.7 Hz, 4H); IR 1680 cm^{-1} (CO).

2k: mp 93−94 °C (CCl_4−PE); MS *m*/*z* 362 (M^+); ^{1}H NMR δ 1.93 (s, 6H), 2.22 (s, 3H), 7.05−8.00 (m, 9H); IR 1672 cm^{-1} (CO).

2m: mp 110−111 °C (PE); MS *m*/*z* 327 (M^+); ^{1}H NMR δ 2.02 (s, 6H), 2.32 (s, 3H), 7.22−7.40 and 7.50−7.65 (2 m, 1:1, 4H); IR 1680 cm^{-1} (CO).

2n: bp 210−211 °C/0.4 mmHg; MS *m*/*z* 308 (M^+); ^{1}H NMR δ 2.06 (s, 6H), 2.32 (s, 3H), 7.10−7.88 and 7.88−8.05 (2 m, 6:1, 7H); IR 1680 cm^{-1} (CO).

2o: mp 118−119 °C (CCl_4−PE); MS *m*/*z* 338 (M^+); ^{1}H NMR δ 2.03 (s, 6H), 2.30 (s, 3H), 3.90 (s, 3H), 6.95−7.20, 7.50−7.75, and 7.83−7.92 (3 m, 2:3:1, 6H); IR 1678 cm^{-1} (CO).

2p: bp 104 °C/1 mmHg (lit.[10] bp 104 °C/1 mmHg); MS *m*/*z* 182 (M^+); spectral data identical to those reported.

2q: bp 100−101 °C/0.4 mmHg; MS *m*/*z* 196 (M^+); ^{1}H NMR δ 1.78 (s, 3H), 2.10 (s, 6H), 2.28 (s, 3H); IR 1680 cm^{-1} (CO).

2r: bp 163−164 °C/0.4 mmHg; MS *m*/*z* 308 (M^+); ^{1}H NMR δ 0.65−1.05 and 1.05−1.75 (2 m, 14:3, 17H), 1.75−2.15 (m, 2H), 2.10 (s, 6H), 2.36 (s, 3H); IR 1682 cm^{-1} (CO).

Reaction of 1-(2-Chlorophenyl)-2,2,2-tris(methylthio)-ethanone (1g) with Ethyl Trityl Sulfide in the Presence of Trityl Perchlorate (3). A mixture of trithioorthocarboxylate **1g** (0.58 g, 2 mmol) and ethyl trityl sulfide (0.61 g, 2 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) under an atmosphere of nitrogen. Trityl perchlorate (**3**; 0.20 g, 0.06 mmol) was added in one portion and under stirring: a brown solution was at once obtained. Stirring at rt was continued for 30 min. GC analysis of the reaction mixture showed the presence of several compounds; between them, methyl trityl sulfide (**6**) and ethyl trityl sulfide were the major products. The crude residue obtained after the workup described in procedure A was fractionated by column chromatography, eluting with PE−CH_2Cl_2 (7:3, v/v). Four fractions were collected. After evaporation of the solvent under reduced pressure, the first fraction gave a solid substance (0.72 g) which was a mixture of compound **6**, MS *m*/*z* 243 (M^+ − SMe), and the starting ethyl trityl sulfide, MS *m*/*z* 243 (M^+ − SEt), in a 3:1 ratio (determined by GC). The second fraction gave an oily substance (0.25 g) as a mixture of several products. By GC and GC−MS analyses, the following compounds were recognized: 1-(2-chlorophenyl)-2-(ethylthio)-2,2-bis(methylthio)ethanone (**10**), MS *m*/*z* 259 (M^+ − SMe) and 245 (M^+ − SEt), and 1-(2-chlorophenyl)-2,2-bis(ethylthio)-2-(methylthio)ethanone (**11**), MS *m*/*z* 273 (M^+ − SMe) and 259 (M^+ − SEt), as major products (ratio **10**:**11** = 1.7:1, determined by GC analysis), and traces of 1-(2-chlorophenyl)-2,2,2-tris(ethylthio)ethanone (**12**), MS *m*/*z* 273 (M^+ − SEt), and *S*-methyl 2-chlorophenyloxothioacetate, MS *m*/*z* 186 (M^+ − CO). The third fraction gave an oil substance (0.33 g) which was a mixture of **10** and the starting compound **1g**, in a 1.6:1 ratio. The four fraction afforded triphenylmethanol (**9**; 0.11 g).

Reaction of *S*-Methyl Bis(methylthio)phenylthioacetate (2a) with Ethyl Trityl Sulfide in the Presence of Trityl Perchlorate (3). Compound **3** (0.10 g, 0.3 mmol) was added in one portion and under stirring to a solution of compound **2a** (0.52 g, 2 mmol) and ethyl trityl sulfide (0.61 g, 2 mmol) in anhydrous CH_2Cl_2 (15 mL), maintained at rt and under an atmosphere of nitrogen: a red solution was at once obtained. Stirring at rt was continued for 1 h, and the reaction mixture was worked up as described in procedure A. Then the crude residue was fractionated by column chromatography, eluting with PE−CH_2Cl_2 (7:3, v/v). Four fractions were collected. After evaporation of the solvent under reduced pressure, the first fraction gave a solid substance (0.58 g) which was a mixture of methyl trityl sulfide (**6**), MS *m*/*z* 243 (M^+ − SMe), and the starting ethyl trityl sulfide, MS *m*/*z* 243 (M^+ − SEt), in a 1.5:1 ratio (determined by GC). The second fraction gave an oil substance (0.28 g) as a mixture of several products. By GC and GC−MS analyses, the following compounds were recognized: *S*-methyl (ethylthio)(methylthio)phenylthioacetate (**13**), MS *m*/*z* 272 (M^+), 225 and 197 (M^+ − SMe and − CO), *S*-methyl bis(ethylthio)phenylthioacetate (**14**), MS *m*/*z* 286 (M^+) and 211 (M^+ − COSMe), *S*-ethyl bis(methylthio)phenylthioacetate (**15**), MS *m*/*z* 272 (M^+), 211 and 183 (M^+ − SEt and − CO), and *S*-ethyl (ethylthio)(methylthio)phenylthioacetate (**16**), MS *m*/*z* 286 (M^+), 225 and 197 (M^+ − SEt and − CO). Third and fourth fractions afforded the starting compound **2a** (0.22 g, 42%) and triphenylmethanol (**9**; 0.10 g), respectively.

Methyl [1-^{13}C]benzoate. Methanesulfonic acid (0.19 g, 2 mmol) was added to a solution of [1-^{13}C]benzoic acid (1.23 g, 10 mmol) in anhydrous methanol (6 mL), and the reaction mixture was heated under gentle reflux until disappearance of the starting compound (about 5 h). Usual workup afforded virtually pure (GC and NMR) title compound in 90% yield (1.12 g): MS *m*/*z* 137 (M^+, 38), 106 (M^+ − OMe, 100); ^{13}C NMR δ 51.87 (q, J = 146 Hz, Me), 128.16, 129.40, and 132.70 (d, J = 161 Hz, CH), 130.02 (d, $J_{1-C,^{13}CO}$ = 74.80 Hz, 1-C), and 166.90 (s, ^{13}CO).

2,2,2-Tris(methylthio)-1-phenyl[1-^{13}C]ethanone. Prepared according to the procedure reported for the synthesis of 2,2,2-tris(methylthio)-1-phenylethanone,[1] starting from methyl [1-^{13}C]benzoate. The yield of the title compound was 91%: mp 35 °C (PE); MS *m*/*z* 212 (M^+ − SMe; 13), 153 [$C(SMe)_3$; 100], 106 (Ph − ^{13}CO, 57); ^{13}C NMR δ (CD_3COCD_3) 13.19 (q, J = 140 Hz, Me), 78.72 [d, $J_{C,^{13}CO}$ = 42.73 Hz, $C(SMe)_3$], 128.34, 130.40, and 133.33 (d, J = 160 Hz, CH), 135.08 (d, $J_{1-C,^{13}CO}$ = 57 Hz, 1-C), and 193.24 (s, ^{13}CO).

Isomerization of 2,2,2-Tris(methylthio)-1-phenyl[1-^{13}C]ethanone into *S*-Methyl Bis(methylthio)phenyl[2-^{13}C]thioacetate in the Presence of Trityl Perchlorate (3). The reaction was carried out according to procedure A, as described above for entry 1, starting from Ph-^{13}CO-$C(SMe)_3$ (0.52 g, 2 mmol) and **3** (0.10 g, 0.3 mmol) in anhydrous CH_2Cl_2

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(4 mL). The following three products were isolated: **6** and **9**, respectively in yields of 78% (0.07 g) and 25% (0.02 g) with regard to **3**, and the title compound Ph-^{13}C(SMe)$_2$-COSMe in 88% yield (0.46 g). The structure of the last product was confirmed by MS and ^{13}C NMR data: MS *m*/*z* 259 (M^+; 2), 184 (M^+ − COSMe, 100), 137 (M^+ − COSMe, and − SMe, 13), 122 (Ph − ^{13}CS, 82); ^{13}C NMR δ 12.77 (q, J = 140 Hz, Me), 76.46 (s, ^{13}C), 128.06 (d, J = 160 Hz, CH), 136.89 (d, $J_{1-C,^{13}C}$ = 44.08 Hz, 1-C), and 198.07 (d, $J_{CO,^{13}C}$ = 47.47 Hz, CO).

Isomerization of 2,2,2-Tris(methylthio)-1-phenyl[1-^{13}C]ethanone into *S*-Methyl Bis(methylthio)phenyl[2-^{13}C]thioacetate in the Presence of Methanesulfonic Acid (4). The reaction was carried out according to procedure B, as described above for entry 2, starting from Ph-^{13}CO-C(SMe)$_3$ (0.52 g, 2 mmol) and **4** (0.10 g, 1 mmol) in anhydrous CH_2Cl_2 (4 mL). The only reaction product was *S*-methyl bis(methylthio)phenyl[2-^{13}C]thioacetate (0.45 g, 87%).

Triethyl α-Keto Trithioorthocarboxylates: Representative Procedure. 2,2,2-Tris(ethylthio)-1-phenylethanone. [Tris(ethylthio)methyl]lithium was prepared according to the procedure previously reported for the synthesis of [tris(methylthio)methyl]lithium,[1] by reaction of tris(ethylthio)methane[11] (2.45 g, 12.5 mmol) and BuLi (2.5 M solution in hexane; 5.5 mL, 13.75 mmol) in anhydrous THF (15 mL), at −95 °C under N_2. After 2 h of stirring, a white suspension was obtained. Then a solution of methyl benzoate (1.36 g, 10 mmol) in the same solvent (5 mL) was added dropwise during 5 min. After being stirred at −95 °C for a further 5 min, the resulting solution was directly quenched with Et_2O−water (200 mL, 1:1). Usual workup afforded a crude reaction mixture that was chromatographed, eluting with PE−CH_2Cl_2 (7:3, v/v). The following three products were isolated. The first eluted product was tetrakis(ethylthio)methane (0.13 g, 0.51 mmol): mp 34−35 °C (pentane) (lit.[11] mp 33−34 °C); MS *m*/*z* 195 (M^+ − SEt). The second eluted product was the title compound (2.31 g, 77%): bp 179−180 °C/0.3 mmHg; MS *m*/*z* 239 (M^+ − SEt); ^{1}H NMR δ 1.22 (t, J = 7.0 Hz, 9H), 2.65 (q, J = 7.0 Hz, 6H), 7.10−7.45 and 8.15−8.38 (2 m, 3:2, 5H); IR 1672 cm^{-1} (CO). The third eluted product was 2,2-bis(ethylthio)-1-phenylethanone (0.26 g, 11%): bp 169−170 °C/0.4 mmHg; MS *m*/*z* 240 (M^+); ^{1}H NMR δ 1.36 (t, J = 7.0 Hz, 6H), 2.50−2.95 (m, 4H), 5.36 (s, 1H), 7.25−7.68 and 7.88−8.22 (2 m, 3:2, 5H); IR 1688 cm^{-1} (CO). The two last products are known,[17] but physical, spectroscopic, and analytical data are not reported.

2,2,2-Tris(ethylthio)-1-(2-fluorophenyl)ethanone. Prepared as described above, starting from tris(ethylthio)methane (2.45 g, 12.5 mmol), BuLi (2.5 M solution in hexane; 5.5 mL, 13.75 mmol), and methyl 2-fluorobenzoate (1.54 g, 10 mmol) in anhydrous THF (15 mL). In this case the by products, *i.e.* tetrakis(ethylthio)methane, MS *m*/*z* 239 (M^+ − SEt), and 2,2-bis(ethylthio)-1-(2-fluorophenyl)ethanone, MS *m*/*z* 258 (M^+), were formed only in traces. Chromatography of the crude reaction mixture, eluting with PE−CH_2Cl_2 (7:3), afforded the pure title compound in 89% yield (2.82 g): bp 142−143 °C/0.4 mmHg; MS *m*/*z* 257 (M^+ − SEt); ^{1}H NMR δ 1.28 (t, J = 7.0 Hz, 9H), 2.80 (q, J = 7.0 Hz, 6H), and 7.05−7.85 and 8.15−8.55 (2 m, 3:1, 4H); IR 1698 cm^{-1} (CO).

Ethyl α-Oxo Thiolcarboxylates 17 and 20. Representative Procedure. *S*-Ethyl Phenylthioglyoxylate (17). Prepared according to the procedure previously reported[5] for the hydrolysis of 2,2,2-tris(methylthio)-1-phenylethanone, starting from 2,2,2-tris(ethylthio)-1-phenylethanone (3.00 g, 10 mmol) and *N*-bromosuccinimide (4.00 g, 22.5 mmol) in THF/H_2O (15:1, 10 mL) at rt for 30 min. Usual workup afforded the virtually pure (TLC, GC) title compound in 92% yield (1.78 g): bp 130−131 °C/0.25 mmHg (lit.[18] bp 121−122 °C/5 mmHg); MS *m*/*z* 194 (M^+); ^{1}H NMR δ 1.38 (t, J = 7.0 Hz, 3H), 3.08 (q, J = 7.0 Hz, 2H), and 7.30−7.90 and 8.00−8.45 (2 m, 3:2, 5H); IR 1688 cm^{-1} (CO).

***S*-Ethyl (2-Fluorophenyl)oxothioacetate (20).** Prepared in the same way starting from 2,2,2-tris(ethylthio)-1-(2-fluorophenyl)ethanone (3.18 g, 10 mmol) and *N*-bromosuccinimide (6.23 g, 35 mmol) in THF/H_2O (15:1, 10 mL) at rt for 30 min. Usual workup afforded the virtually pure (TLC, GC) title compound in 81% yield (1.72 g): bp 119−120 °C/0.3 mmHg; MS *m*/*z* 212 (M^+); ^{1}H NMR δ 1.50 (t, J = 7.0 Hz, 3H), 3.21 (q, J = 7.0 Hz, 2H), and 7.15−8.25 (m, 4H); IR 1688 cm^{-1} (CO).

***S*-Ethyl Bis(ethylthio)phenylthioacetate (19).** A mixture of *S*-ethyl phenylthioglyoxylate (**17**; 1.94 g, 10 mmol), H_2SO_4 (0.20 g, 2 mmol), and ethanethiol (25 mL) was stirred at rt for 9 h, until GC and TLC (PE−CH_2Cl_2, 7:3) analyses showed the disappearance of the starting compound. Usual workup afforded a crude residue that was column chromatographed, eluting with PE−CH_2Cl_2 (7:3), to afford the pure title compound in 85% yield (2.55 g): bp 165−166 °C/0.3 mmHg; MS *m*/*z* 300 (M^+); ^{1}H NMR δ 1.18 (t, J = 7.0 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 2.38 (q, J = 7.0 Hz, 4H), 2.80 (q, J = 7.0 Hz, 2H), and 7.05−7.32 and 7.32−7.63 (2 m, 3:2, 5H); IR 1678 cm^{-1} (CO).

The reaction of *S*-ethyl (2-fluorophenyl)oxothioacetate (**20**) with ethanethiol and H_2SO_4 failed, also using a major amount of acid (molar ratio **20**:H_2SO_4 = 1:1) and carrying out the reaction at 30 °C for 24 h. After usual workup, 71% of the starting compound was recovered; no traces of S-ethyl bis(ethylthio)(2-fluorophenyl)thioacetate were present (GC−MS analysis).

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Supporting Information Available: Elemental analyses of all new compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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