Synthesis of Trimethyl α-Keto Trithioorthoesters and Dimethyl α-Keto Dithioacetals by Reaction of Acyl Chlorides, Anhydrides, Thiol Esters, and *N,N*-Dimethylamides with [Tris(methylthio)methyl]lithium

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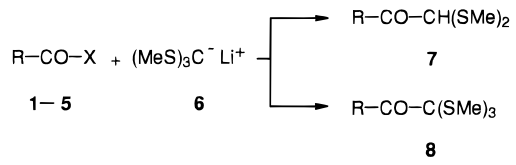
Trimethyl α-keto trithioorthoesters **8** and dimethyl α-keto dithioacetals **7** belong to two interesting classes of compounds able to be used as intermediates in organic synthesis.[1−3] In particular, the aromatic trithioorthoesters **8** have recently been employed as key intermediates for the realization of a new procedure for the synthesis of α-arylpropionic acids,[4] several of which exhibit remarkable analgesic and antiinflammatory activities.[5] We have already made a mechanistic and applicative study[1] on the reactions of [tris(methylthio)-methyl]lithium (**6**) with esters **1** (Scheme 1), and we arrived at one-pot reactions able to realize, easily and in excellent yield, the trithioorthoesters **8** or, depending on the conditions used, the dithioacetals **7**.

In the present research we made a study of the reactions of [tris(methylthio)methyl]lithium (**6**) with representative aromatic and aliphatic acyl chlorides **2**, anhydrides **3**, thiol esters **4**, and *N,N*-dimethylamides **5** for use as starting compounds, alternative to esters **1**, for the preparation of trimethyl α-keto trithioortoesters **8** and dimethyl α-keto dithioacetals **7** (Scheme 1). The reactions investigated, on which useful information is lacking in the literature, were seen to be relatively more complex than the reactions with esters, even though formally analogous. However, our earlier investigations[1] gave us the necessary background to reach specific synthetic solutions and make a mechanistic interpretation of new results.

First, the reaction studied was that of **6** with acyl chlorides **2**. In light of earlier research[1] on methyl benzoate (**1a**) and **6** (Table 1, entries 1 and 2), we reacted benzoyl chloride (**2a**) with **6** in a 1:1.25 molar ratio at −95 °C for 5 min (procedure A; entry 3) and in a 1:2.2 molar ratio at −78 °C for 30 min (procedure B; entry 4). Whereas the results in entries 4 and 2 coincide obtaining, in both cases, quantitative or almost quantitative yields

Scheme 1



1 X = OMe; **2** X = Cl; **3** X = OCOR; **4** X = SMe; **5** X = NMe_2

a R = Ph; **b** R = 4-ClC$_6$H$_4$; **c** R = 4-MeOC$_6$H$_4$; **d** R = 4-*i*-BuC$_6$H$_4$; **e** R = H; **f** R = Me; **g** R = Pr; **h** R = *t*-Bu; **i** R = *n*-C$_9$H$_{19}$

of dithioacetal **7a**, the result of entry 3 (Table 1) was quite different from that of entry 1 (Table 1). In fact, for identical reaction conditions and reagent molar ratio the reaction of **6** with **1a** (Table 1, entry 1) gave the trithioortoester **8a**, this clearly prevailing over the corresponding dithioacetal **7a**. Instead, the reaction of **6** with **2a** (Table 1, entry 3) resulted in not **8a**, but in a mixture of **7a**, the corresponding *O*-benzoyl derivative **13a**, the thiol ester **4a**, and tetrakis(methylthio)methane (**12**). The fact that the reaction of **6** with the acyl chloride **2a** differed from that with the ester **1a** can be interpreted when one considers how strongly the relative rates of the two steps in the formation of the tetrahedral intermediates **9** (Scheme 2; step a) and their subsequent conversion to **8** (step b) depend on the leaving groups. In fact, it has already been demonstrated[1] that with methyl benzoate the formation of **9** (R = Ph, X = OMe) takes place faster than the elimination of the methoxide anion, thus practically precluding any subsequent reaction between **8a** and **6** to give **7a**. On the contrary, in the present work where **6** was reacted with benzoyl chloride, the chloride anion is eliminated faster than the tetrahedral intermediate **9** (R = Ph, X = Cl) is formed; thus, the formation of **8a** is immediately followed by two fast reactions that give rise to the enolate **11a** and the corresponding *O*-benzoyl derivative **13a**. Furthermore, the formation of the thiol ester **4a**, absent in the reaction with methyl benzoate,[1] could arise from a collateral reaction between benzoyl chloride and **6**, the most likely source of methanethiolate ions. Instead, the reactions of entries 2 and 4 (Table 1) led exclusively to the dithioacetal **7a**; this is due to the excess of **6** that reacts not only with the trithioorthoester **8a** (as previously shown[1]) but also with the O-benzoyl derivative **13a** (in a collateral test; see Experimental Section, entry 48) and, finally, with the thiol ester **4a** (shown later). The reaction of entry 5 (Table 1), carried out under the conditions of entry 4 except that *N*-(methylthio)phthalimide (**14**; procedure C) was added to the reaction mixture before the reaction was quenched in water, produced the trithioorthoester **8a** exclusively. Comparable results were also obtained starting from the 4-substituted benzoyl chlorides **2b**−**d** (Table 1, entries 6−14). With regard to aliphatic acyl chlorides, the reaction between acetyl chloride (**2f**) and **6** according to procedure B (Table 1, entry 15) resulted in a dithioacetal **7f** and thiol ester **4f** mixture and consistent amounts of the trithioorthoester **8f** and tris-(methylthio)methane (**16**). The presence of **8f**, despite the excess of **6** that should have led to the complete conversion of **8f** into **7f**, can be explained by accepting that the reaction between **2f** and **6** follows two routes. The first, like that of the aliphatic esters,[1] leads to **7f** through the intermediates **9** (R = Me, X = Cl), **8f**, and **11f** (Scheme 2). The formation of the intermediate **11f** was confirmed by trapping it with benzoyl chloride or

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(2) Degani, I.; Dughera, S.; Fochi, R.; Gatti, A. *Synthesis* **1996**, 467.

(3) For a recent review on α-keto dithioacetals, see: Dondoni, A.; Colombo, L. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI Press, Ltd.: London, 1993; Vol. 1, Chapter 1 and references cited therein. For recent examples, see: Ozaki, Y.; Kubo, A.; Kim, S.-W. *Chem. Pharm. Bull.* **1993**, *41*, 481 and references cited therein. Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 946. da Silva, G. V. J.; Pelisson, M. M. M.; Constantino, M. G. *Tetrahedron Lett.* **1994**, *35*, 7327. Ando, R.; Morinaka, Y.; Takahashi, C.; Tamao, Y. (Mitsubishi Chem Ind) JP Pat. 06 345 722, 1994; *Chem. Abstr.* **1995**, *122*, 290337. Solladié, G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1996**, *52*, 2065 and references cited therein.

(4) Degani, I.; Dughera, S.; Fochi, R. (National Research Council of Italy) Italian Pat. MI96A 000500, 1996.

(5) 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.

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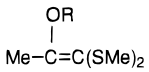
Table 1. Reactions of Acyl Chlorides 2, Anhydrides 3, Thiol Esters 4, and *N*,*N*-Dimethylamides 5 with [Tris(methylthio)methyl]lithium (6)

entry	R	X	procedure	chromatographic solvent[a]	yield[b] (%) 7	8	4	13	16	21
1	Ph	OMe	A[c]		13	85			*d*	
2		OMe	B[c]		100				*d*	
3		Cl	A	PE−CH_2Cl_2 (7:3)	36		20	38	*d*	
4			B		98				*d*	
5			C			94			*d*	
6	4-ClC_6H_4	Cl	A	PE−CH_2Cl_2 (7:3)	28		23	36	*d*	
7			B		94				*d*	
8			C			92			*d*	
9	4-$MeOC_6H_4$	Cl	A	PE−Et_2O (9:1)	22		15	55	*d*	
10			B		94				*d*	
11			C			95			*d*	
12	4-*i*-BuC_6H_4	Cl	A	PE−CH_2Cl_2 (7:3)	28		17	41	*d*	
13			B		95				*d*	
14			C			90			*d*	
15	Me	Cl	B	PE−CH_2Cl_2 (1:1)	33	36	*e*		49	
16			C			67	*e*		48	
17	*n*-C_9H_{19}	Cl	A	PE−CH_2Cl_2 (7:3)	8	17	9		42	
18			B		42	14	12		29	
19			C			56	11		30	
20	*t*-Bu	Cl	A	PE−CH_2Cl_2 (7:3)	47		*f*		*d*	
21			B		80[g]		*f*		9	
22	Ph	OCOPh	A	PE−CH_2Cl_2 (7:3)	48		4		7	
23			B		92				*d*	
24			C			93			*d*	
25	Pr	OCOPr	A	PE−CH_2Cl_2 (7:3)	47		*h*		3	
26			B		95				8	
27			C			90			3	
28	Ph	SMe	A	PE−CH_2Cl_2 (7:3)	50		37		10	*i*
29			B		95		4		9	*i*
30			C			92	4		4	*i*
31	4-ClC_6H_4	SMe	B	PE−CH_2Cl_2 (7:3)	95		5		9	*i*
32			C			94	4		4	*i*
33	4-$MeOC_6H_4$	SMe	B	PE−Et_2O (9:1)	96		4		4	*i*
34			C			94	4		8	*i*
35	4-*i*-BuC_6H_4	SMe	B	PE−CH_2Cl_2 (7:3)	95		4		4	*i*
36			C			94	6		5	*i*
37	Me	SMe	B	PE−CH_2Cl_2 (1:1)	64		*e*		34	*j*
38			C			61	*e*		30	*j*
39	*n*-C_9H_{19}	SMe	A	PE−CH_2Cl_2 (7:3)	24		60		31	*j*
40			B		61		23		32	*j*
41			C			61	7		30	*j*
42	C_6H_5	NMe_2	A			*k*				
43			B				*k*			
44	H	NMe_2	A	PE−CH_2Cl_2 (7:3)		89			*d*	
45			B			88			45	
46	*n*-C_9H_{19}	NMe_2	A			*k*				
47			B				*k*			

[a] PE = petroleum ether (40−70 °C). [b] Yields of pure isolated products. [c] Reported in ref 1. [d] Traces. [e] Determined by GC−MS analysis: MS *m*/*z* 90 (M^+). [f] Determined by GC−MS analysis: MS *m*/*z* 132 (M^+). [g] As previously reported,[1] **8h** cannot be obtained from **7h**. [h] Determined by GC−MS analysis: MS *m*/*z* 118 (M^+). [i] Dimethyl disulfide (**21**) was determined in the reaction mixtures by GC−MS analysis: MS *m*/*z* 94 (M^+). [j] No traces of dimethyl disulfide (**21**) were present in the reaction mixtures (GC−MS analysis). [k] The reaction failed.

trimethylsilyl chloride; the reactions gave **15a** and **15b** (Experimental Section, entries 49 and 50). The second

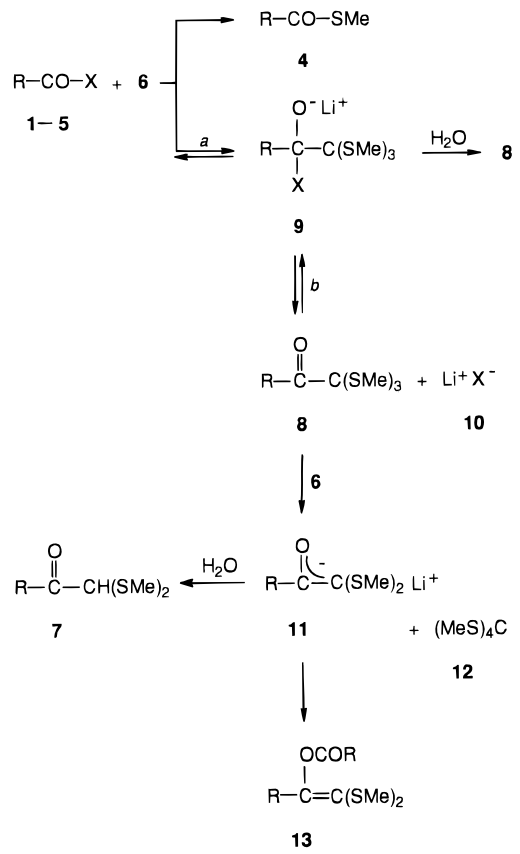


15a R = COPh
15b R = $SiMe_3$

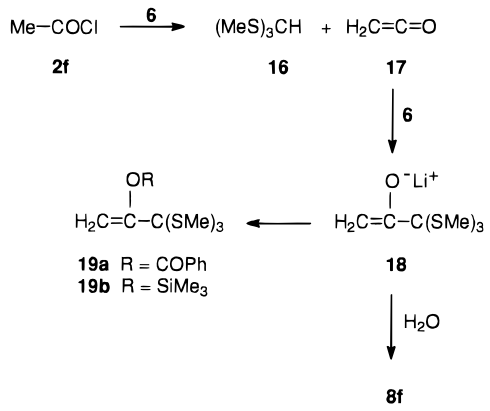
route, accessible only with aliphatic acyl chlorides where at least one α hydrogen is present, proceeds (Scheme 3) in two steps: dehydrochlorination due to the action of **6** results in the formation of tris(methylthio)methane (**16**) and ketene **17**, this latter then adds to **6** to form the enolate **18**, which remains unaltered in the reaction mixture and, after the quenching with water, supplies **8f**. This second route was demonstrated by isolating consistent amounts of **16**, present only in trace amounts in the reactions conducted with aromatic acyl chlorides, and also by trapping the intermediate **18** through reaction with benzoyl chloride or trimethylsilyl chloride to obtain the derivatives **19a** and **19b** (Experimental Section, entries 49 and 50). The results with decanoyl chloride (**2i**; Table 1, entries 17 and 18) can be interpreted in the same way. Instead, pivaloyl chloride (**2h**), which cannot give rise to the ketene, results in the dithioacetal **7h** exclusively (Table 1, entries 20 and 21). Like the aromatic dithioacetals, the aliphatic dithioacetals **7** can also be converted into the corresponding trithioorthoesters **8** by treatment with *N*-(methylthio)phthalimide (**14**), though in lower yields (Table 1, entries 16 and 19).

With regard to the anhydrides, benzoic anhydride (**3a**) and butyric anhydride (**3g**) were reacted with **6**. With procedure A both anhydrides gave the corresponding dithioacetals **7a** and **7g** in close to 50% yield (Table 1,

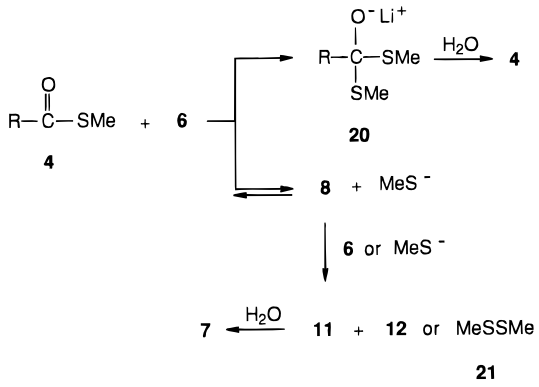
Scheme 2



Scheme 3



Scheme 4



entries 22 and 25), together with an approximately equal molar amount of tetrakis(methylthio)methane (**12**) and a rather small amount of the corresponding thiol esters **4a** and **4g** and tris(methylthio)methane (**16**). No trithioorthoesters **8a** and **8g** were obtained, not even in traces. Evidently, the tetrahedral intermediate **9a** (R = Ph, X = OCOPh), rapidly gives rise to the enolate **11a**, with the total consumption of **6**; on quenching the reaction mixture with water **7a** formed. From the point of view of only synthetic objectives, procedures B and C lead, respectively, to excellent yields of the dithioacetals **7a** and **7g** (Table 1, entries 23 and 26) and the trithioorthoesters **8a** and **8g** (Table 1, entries 24 and 27).

Procedures A and B were also applied to the thiol esters **4**: in procedure A (Table 1, entry 28), *S*-methyl thiobenzoate (**4a**) reacted with **6** to give the dithioacetal **7a** in 50% yield and dimethyl disulfide (**21**); furthermore, consistent amounts of **4a** and a moderate amount of tris(methylthio)methane (**16**) were recovered. Following procedure B, it was found that **4a** reacted completely with **6** until the almost quantitative formation of **7a**, and again **21** was identified (Table 1, entry 29). In procedure A, *S*-methyl decanethioate (**4i**) reacted with **6** (Table 1, entry 39) to give **7i** in low yield but no dimethyl disulfide (**21**); in procedure B, even with a reaction time of up to 3 h, **7i** was obtained with a maximum yield of 61%; **16** was also recovered in a fairly large amount (compared with the reaction conducted with **4a**), and no disulfide **21** was present (Table 1, entry 40). The different behavior of the aliphatic thiol ester **4i**, compared with the aromatic thiol ester **4a**, can be attributed to the different rate of formation of the tetrahedral adducts **20i** and **20a** (Scheme 4) in irreversible reactions, competitive with those leading to the enolates **11i** and **11a**. After the quenching of the reaction mixture with water, both **20i** and **20a** can restore the starting thiol esters. It can be assumed that in the case of **4i** the rate of the reaction resulting in the aliphatic adduct **20i** is comparable with that of the reaction that, in the slow stage, gives first **8i** and then, irreversibly, **11i**. Therefore, the reaction between **4i** and **6** is incomplete, giving **7i** and consistent amounts of **4i** and tris(methylthio)methane (**16**). On the contrary, in the case of **4a** the reaction giving rise to the aromatic adduct **20a** is much slower than that giving **8a** and then **11a**. Therefore, the reaction between **4a** and **6** gives **7a** exclusively. The results of some collateral tests (see Experimental Section, entries 51−57) confirm these hypotheses.

Finally, an investigation was made into the reactions of *N*,*N*-dimethylamides **5** with **6**. The only positive result was with **5e** that, following both procedures A and B, gave the trithioorthoester **8e** in high yield (Table 1, entries 44 and 45). The amides **5a**,**i** remained unaltered (Table 1, entries 42, 43, 46, and 47). With **5e**, it appears that in the absence of adverse steric and electronic effects it is possible to form the tetrahedral intermediate **9e** (R = H, X = NMe_2), its stability being sufficiently high to impede further conversions to **8e** and then to **7e**.

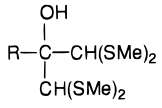
With the aim of obtaining both the dithioacetals **7** and the trithioorthoesters **8**, the amides **5** were reacted with [bis(methylthio)methyl]lithium (**22**), more reactive than **6** in that it is less stabilized and less bulky; the corresponding dithioacetals **7** were obtained. Thus, the amides **5a**,**d**,**e**,**f**,**i** were reacted with **22** in a molar ratio of 1:1 at −78 °C for 30 min (procedure D), resulting in the corresponding dithioacetals **7a**,**d**,**e**,**f**,**i** in excellent yields (Table 2, entries 58, 60, 62, 64, and 66). Finally, the trithioorthoesters **8a**,**d**,**e**,**f**,**i** were obtained by eliminating the *N*,*N*-dimethylamine from the tetrahedral intermediates by treatment with anhydrous methanol and evapo-

Table 2. Reactions of Acyl Chlorides 2, Anhydrides 3, Thiol Esters 4, and *N*,*N*-Dimethylamides 5 with [Bis(methylthio)methyl]lithium (22)

entry	R	X	procedure	chromatographic solvent[a]	yield[b] (%) 7	8	23
58	Ph	NMe_2	D	PE−CH_2Cl_2 (7:3)	100		
59			E			92	
60	4-*i*-BuC_6H_4	NMe_2	D	PE−CH_2Cl_2 (7:3)	95		
61			E			91	
62	H	NMe_2	D	PE−CH_2Cl_2 (4:1)	78		
63			E			83	
64	Me	NMe_2	D	PE−CH_2Cl_2 (1:1)	89		
65			E			91	
66	*n*-C_9H_{19}	NMe_2	D	PE−CH_2Cl_2 (7:3)	100		
67			E			93	
68	Ph	Cl	F	PE−CH_2Cl_2 (3:2)	78		13
69	Ph	OCOPh	F	PE−CH_2Cl_2 (3:2)	80		12
70	Ph	SMe	F	PE−CH_2Cl_2 (3:2)	83[c]		9
71	Pr	OCOPr	F	PE−CH_2Cl_2 (7:3)	46		45
72	*n*-C_9H_{19}	Cl	F	PE−CH_2Cl_2 (7:3)	42		48
73	*n*-C_9H_{19}	SMe	F	PE−CH_2Cl_2 (7:3)	54[d]		14

[a] PE = petroleum ether (40−70 °C). [b] Yields of pure isolated products. [c] **4a** was also isolated in 3% yield. [d] **4i** was also isolated in 20% yield.

ration under nitrogen stream and subsequently adding sodium hydride and then *N*-(methylthio)phthalimide (**14**) to the reaction mixtures (procedure E; Table 2, entries 59, 61, 63, 65, and 67). Following this last route, the preparation of both the dithioacetals **7** and the trithioorthoesters **8**, starting from the amides **5**, is particularly advantageous in that the reactions need only half the amount of the reagent [bis(methylthio)methyl]lithium (**22**) compared to the reagent [tris(methylthio)methyl]-lithium (**6**) used in the reactions with esters **1**, acyl chlorides **2**, anhydrides **3**, and thiol esters **4**. Instead, the use of **22** for compounds **1**−**4** introduces a synthetic complication due to a more or less consistent amount of tertiary alcohols **23** (procedure F; Table 2, entries 68−73).



23a R = Ph
23b R = Pr
23c R = *n*-C_9H_{19}

At the end of this work the following conclusions were drawn: (i) acyl chlorides **2**, anhydrides **3**, thiol esters **4**, and *N*,*N*-dimethylamides **5**, like esters **1**,[1] can be advantageously used as starting compounds for the synthesis of trimethyl α-keto trithioorthoesters **8** and dimethyl α-keto dithioacetals **7**; (ii) for compounds **1**−**4** the most appropriate reagent to reach this synthetic goal is, in all cases, [tris(methylthio)methyl]lithium (**6**); (iii) for the *N*,*N*-dimethylamides **5**, with the sole exception of *N*,*N*-dimethylformamide that gives a positive reaction also with **6**, the products **7** and **8** can be obtained using, as the reagent, [bis(methylthio)methyl]lithium (**22**) instead of **6**; (iv) using aromatic derivatives **2**−**5** as the starting compounds, these, like aromatic esters **1**,[1] give excellent yields (usually >95%) of the corresponding products **7** and **8**; (v) aliphatic compounds **2**−**4** give products **7** and **8** in a decidedly lower yield than those given by aliphatic esters **1**;[1] (vi) *N*,*N*-dimethylamides **5**, when available, are very good starting compounds for the synthesis of products **7** and **8**, both for the excellent yield and because the amount of reagent required for the reactions is half that of the amount of reagent required by the other compounds **1**−**4**; and (vii) the mechanistic study that was done is a reliable guide for the choice of conditions to adopt, depending on the class to which the starting compounds to be used belong.

Experimental Section

^{1}H NMR and IR spectra were recorded for solutions in $CDCl_3$ and CCl_4, respectively. Column chromatography was performed on Merck silica gel 60 (70−230 mesh ASTM). 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. Chromatographic solvents and yields of the products are listed in Tables 1 and 2.

Acyl chlorides **2a**−**c**,**f**,**h**,**i**, anhydrides **3a**,**g**, *N*,*N*-dimethylamides **5a**,**e**,**f**, butyllithium (2.5 M solution in hexane), trimethylsilyl chloride, sodium thiomethoxide, sodium hydride, bis(methylthio)methane, and anhydrous THF were purchased from Aldrich. Tris(methylthio)methane (**16**),[6] *N*-(methylthio)phthalimide (**14**),[7] 4-isobutylbenzoyl chloride (**2d**),[8] thiol esters **4a**−**c**,[9] **4f**,[10] and **4i**,[11] *S*-ethyl thiobenzoate and *S*-ethyl decanethioate,[12] and *N*,*N*-dimethyldecanamide (**5i**)[13] were prepared following literature procedures.

***S*-Methyl 4-Isobutylthiobenzoate (4d).** According to the procedure previously reported[9] for the synthesis of **4a**, the title compound **4d** was obtained in 98% yield, starting from 4-isobutylbenzoyl chloride[8] (**2d**): bp 100−101 °C/0.03 mmHg; MS *m*/*z* 208 (M^+); ^{1}H NMR δ 0.92 (d, *J* = 6.40 Hz, 6H), 1.65−2.20 (m, 1H), 2.50 (s, 3H), 2.58 (d, *J* = 6.40 Hz, 2H), 7.23 and 7.92 (2 d, 1:1, *J* = 8.50 Hz, 4H); IR 1675 cm^{-1} (CO).

***N*,*N*-Dimethyl-4-Isobutylbenzamide (5d).** According to the procedure previously reported[13] for the preparation of **5i**, the title compound **5d** was obtained in 98% yield, starting from 4-isobutylbenzoyl chloride[8] (**2d**): bp 126−127 °C/0.3 mmHg; MS *m*/*z* 205 (M^+); ^{1}H NMR δ 0.92 (d, *J* = 6.40 Hz, 6H), 1.70−2.10 (m, 1H), 2.55 (d, *J* = 6.40, 2H), 3.12 (s, 6H), 7.28 and 7.52 (2 d, 1:1, *J* = 8.50 Hz, 4H); IR 1648 cm^{-1} (CO).

Reactions of Acyl Chlorides 2, Anhydrides 3, Thiol Esters 4, and *N*,*N*-Dimethylamides 5 with [Tris(methylthio)methyl]lithium (6): Representative Procedures. Procedure A. According to the procedure previously reported[1] for the reaction of esters **1** with **6**, in entry 3 (Table 1) a solution of benzoyl chloride (**2a**; 1.41 g, 10 mmol) in anhydrous THF (5 mL) was added dropwise during 5 min to a suspension of [tris(methylthio)methyl]lithium (**6**), obtained from tris(methylthio)-methane[6] (**16**; 1.93 g, 12.5 mmol) and BuLi (2.5 M solution in hexane; 5.5 mL, 13.75 mmol) in THF (10 mL) at −95 °C under N_2. After being stirred at −95 °C for a further 5 min, the resulting clear solution was directly quenched with diethyl ether−water (200 mL, 1:1). The aqueous layer was separated and extracted again with diethyl ether (80 mL). The combined organic extracts were washed with water (3 × 50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was column chromatographed with PE−CH_2Cl_2 (7:3, v/v) as eluent. The following five products were obtained: tetrakis(methylthio)methane (**12**; 1.03 g, 51%) [mp 64−65 °C (PE) (lit.[1] mp 64−65 °C)]; tris(methylthio)methane (**16**) [GC−MS *m*/*z* 154 (M^+); traces]; *S*-methyl thiobenzoate (**4a**; 0.30 g, 20%); 2,2-bis(methylthio)-1-phenylethenyl benzoate (**13a**; 0.60 g, 38%); and 2,2-bis(methylthio)-1-phenylethanone (**7a**; 0.76 g, 36%).

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Entries 6, 9, 12, 17, 20, 22, 25, 28, 39, and 44 were also performed according to procedure A; entries 42 and 46 failed (Table 1). GC−MS analysis of the crude reaction mixture from entry 28 showed the presence of dimethyl disulfide (**21**), MS *m*/*z* 94 (M^+); the same compound was not present in entry 39. Entry 20 afforded **7h**; no traces of **8h** were present. Entry 44 afforded **8e**; no traces of **7e** were present.

Procedure B. Entry 4 (Table 1) was performed as described above, varying the reagents' molar ratio and temperature and time. A solution of **2a** (1.41 g, 10 mmol) in anhydrous THF (5 mL) was added dropwise during 5 min to a suspension of **6** prepared at −78 °C under N_2 starting from **16** (3.39 g, 22 mmol) and BuLi (9.7 mL, 24.2 mmol) in anhydrous THF (20 mL). Stirring at −78 °C was continued until disappearance of the reaction intermediates, *i.e.*, **4a**, and **13a** (about 30 min; GC−MS analysis). After workup identical to that described above, the crude residue was chromatographed on a short column with PE−CH_2Cl_2 (7:3, v/v) as eluent to afford **12** (1.90 g, 95%), **16** (traces; identified by GC−MS), and α-keto dithioacetal **7a** (2.08 g, 98%).

Entries 7, 10, 13, 15, 18, 21, 23, 26, 29, 31, 33, 35, 37, 40, and 45 were also performed according to procedure B; entries 43 and 47 failed (Table 1). GC−MS analysis of the crude reaction mixtures from entries 29, 31, 33, and 35 showed the presence of dimethyl disulfide (**21**), MS *m*/*z* 94 (M^+); no traces of the same compound were present in entries 37 and 40. Entry 45 afforded **8e**; no traces of **7e** were present.

Procedure C. According to the procedure previously reported,[1] in entry 5 (Table 1) a solution of *N*-(methylthio)-phthalimide (**14**; 2.90 g, 15 mmol) in anhydrous THF (10 mL) was added to the reaction mixture prepared as described above in entry 4 (Table 1) for procedure B. After the addition was complete, the cooling bath was removed, and the reaction mixture was allowed to warm to rt. Stirring was continued for a further 1 h until disappearance of dithioacetal **7a** (GC analysis). After the above workup, the crude residue was chromatographed on a short column with PE−CH_2Cl_2 (7:3, v/v) as eluent to afford **12** (1.92 g, 96%), **16** (traces; identified by GC−MS), and 2,2,2-tris(methylthio)-1-phenylethanone (**8a**; 2.42 g, 94%).

Entries 8, 11, 14, 16, 19, 24, 27, 30, 32, 34, 36, 38, and 41 were also performed according to procedure C (Table 1). GC−MS analysis of the crude reaction mixtures from entries 30, 32, 34, and 36 showed the presence of dimethyl disulfide (**21**), MS *m*/*z* 94 (M^+); no traces of the same compound were present in entries 38 and 41.

Physical properties of compounds **7a**−**c**,**e**,**h**,**i** and **8a**−**c**,**e**,**i** were identical to those reported by us in ref 1; physical properties of the new α-keto dithioacetals **7**, α-keto trithioorthoesters **8**, and *O*-acyl derivatives **13** are as follows.

7d: mp 101−102 °C (PE); MS *m*/*z* 268 (M^+); ^{1}H NMR δ 0.92 (d, *J* = 6.40 Hz, 6H), 1.40−1.90 (m, 1H), 2.20 (s, 6H), 2.62 (d, *J* = 6.40 Hz, 2H), 5.42 (s, 1H), 7.40 and 8.15 (2 d, *J* = 8.00 Hz, 4H); IR 1682 cm^{-1} (CO).

7f: bp 68−69 °C/0.4 mmHg; MS *m*/*z* 150 (M^+); IR and ^{1}H NMR identical to those reported (bp and yield are not reported).[14]

7g: bp 84−85 °C/0.4 mmHg; MS *m*/*z* 178 (M^+); ^{1}H NMR δ 0.92 (t, *J* = 7.00 Hz, 3H), 1.40−1.90 (m, 2H), 2.10 (s, 6H), 2.72 (t, *J* = 7.00 Hz, 2H), 4.42 (s, 1H); IR 1718 cm^{-1} (CO).

8d: bp 130−131 °C/0.4 mmHg; MS *m*/*z* 267 (M^+ − SMe); ^{1}H NMR δ 0.90 (d, *J* = 6.00 Hz, 6H), 1.10−1.70 (m, 1H), 2.02 (s, 9H), 2.48 (d, *J* = 6.40 Hz, 2H), 7.00 and 8.20 (2 d, *J* = 8.00 Hz, 4H); IR 1668 cm^{-1} (CO).

8f: mp 105−106 °C (PE); MS *m*/*z* 149 (M^+ − SMe); ^{1}H NMR δ 2.10 (s, 9H), 2.60 (s, 3H); IR 1708 cm^{-1} (CO).

8g: bp 106−107 °C/0.4 mmHg; MS *m*/*z* 177 (M^+ − SMe); ^{1}H NMR δ 1.03 (t, *J* = 7.00 Hz, 3H), 1.50−1.97 (m, 2H), 2.08 (s, 9H), 3.05 (t, *J* = 7.00 Hz, 2H); IR 1705 cm^{-1} (CO).

13a: mp 75−76 °C (PE) (lit.[15] mp 75 °C); MS *m*/*z* 316 (M^+); ^{1}H NMR identical to that reported;[15] IR 1740 cm^{-1} (CO).

13b: mp 88−89 °C (PE); MS *m*/*z* 385 (M^+); ^{1}H NMR δ 2.30 (s, 3H), 2.38 (s, 3H), 7.30−7.85 and 8.00−8.35 (2 m, 3:1, 8H); IR 1745 cm^{-1} (CO).

13c: bp 168−170 °C/0.2 mmHg; MS *m*/*z* 376 (M^+);^{1}H NMR δ 2.32 (s, 3H), 2.38 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 6.80−7.30, 7.50−7.90 and 8.00−8.40 (3 m, 2:1:1, 8H); IR 1732 cm^{-1} (CO).

13d: bp 178−179 °C/0.2 mmHg; MS *m*/*z* 428 (M^+); ^{1}H NMR δ 0.92 (d, *J* = 6.00 Hz, 12H), 1.60−2.15 (m, 2H), 2.32 (s, 3H), 2.38 (s, 3H), 2.40−2.80 (m, 4H), 7.10−7.80 and 8.10−8.40 (2 m, 3:1, 8H); IR 1740 cm^{-1} (CO).

Reaction of [Tris(methylthio)methyl]lithium (6) with 2,2-Bis(methylthio)-1-phenylethenyl Benzoate (13a). In entry 48, a solution of **13a** (1.58 g, 5 mmol) in anhydrous THF (5 mL) was added to a suspension of **6**, prepared from tris-(methylthio)methane (**16**; 1.69 g, 11 mmol) and BuLi (4.84 mL, 12.1 mmol) in THF (10 mL) at −78 °C, cooling being maintained for 30 min. GC−MS analysis showed the disappearance of **13a** and the presence of **12** and **7a**, as major products, and **16**, as minor product. After usual workup of the reaction mixture, the crude residue was column chromatographed, eluting with PE−CH_2Cl_2 (7:3, v/v), to give **12** (0.95 g, 95%), **16** (traces), and 2,2-bis(methylthio)-1-phenylethanone (**7a**; 2.01 g, 95%).

O-Benzoylation of Enolates 11 (R = Me) and 18. In entry 49 the reaction mixture, obtained according to procedure B as described in entry 15, starting from acetyl chloride (**2f**: 0.79 g, 10 mmol), **16** (3.39 g, 22 mmol), and BuLi (9.7 mL, 24.2 mmol) in THF (20 mL), was stirred at −78 °C under N_2 for 30 min. GC−MS analysis of a sample of the resulting solution, directly quenched with water, showed the presence of four products: **7f**, **16**, **8f**, and **12**. A solution of benzoyl chloride (**2a**; 1.41 g, 10 mmol) in THF (5 mL) was added, maintaining the temperature at −78 °C. Then, the cooling bath was removed and the reaction mixture was allowed to warm to rt and maintained for 30 min. GC−MS analysis showed the disappearance of **7f** and **8f**. The crude residue obtained after the above workup, was column chromatographed, eluting with PE−CH_2Cl_2 (1:1, v/v) to give **12** (0.62 g, 31%), **16** (1.65 g, 48%), and an oily substance comprising a mixture of **15a** and **19a** in a 1:3 ratio (determined by ^{1}H NMR; 1.70 g). Some attempts to separate the last two compounds failed; their structures were, however, confirmed by GC−MS and ^{1}H NMR.

15a: MS *m*/*z* 254 (M^+); ^{1}H NMR δ 2.22, 2.28, and 2.33 (3 s, 1:1:1, 9H), 7.44−7.60 and 8.10−8.16 (2 m, 3:2, 5H); identical to that of an authentic sample prepared by treatment of **7f** (0.30 g, 2 mmol) with sodium hydride (0.05 g, 2.2 mmol) and then benzoyl chloride (0.28 g, 2 mmol) in anhydrous THF (10 mL) at rt for 30 min. The sample was purified by chromatography on a short column with PE−CH_2Cl_2 (1:1, v/v), as eluent; 0.49 g, 96%; bp 132−133 °C/0.3 mmHg; IR 1640 cm^{-1} (CO).

19a: MS *m*/*z* 300 (M^+); ^{1}H NMR δ 2.16 (s, 9H), 5.30 and 5.52 (2 d, 1:1, *J* = 2.56 Hz, 2H), 7.44−7.60 and 8.10−8.16 (2 m, 3:2, 5H).

O-Silylation of Enolates 11 (R = Me) and 18. In entry 50 the reaction was carried out as described above in entry 49, with addition of trimethylsilyl chloride (1.09 g, 10 mmol) to the reaction mixture instead of benzoyl chloride. GC−MS analysis of the reaction mixture showed the disappearance of the intermediates **7f** and **8f** and the presence of four major products: **16**, **15b**, MS *m*/*z* 222 (M^+), **12** and **19b**, MS *m*/*z* 268 (M^+). After quenching with water (50 mL), GC−MS analysis showed the presence of **16** and **12**, the almost complete disappearance of **15b** and **19b**, and the appearance of **7f** and **8f**, rising from hydrolysis of silyl derivatives. The crude residue, obtained after usual workup, was chromatographed, eluting with PE−CH_2Cl_2 (1:1, v/v), to afford four products: **12** (0.78 g, 39%), **16** (1.44 g, 42%), **8f** (0.39 g, 20%), and **7f** (0.27 g, 18%).

Reactions of [Tris(methylthio)methyl]lithium (6) with *S*-Ethyl Thiobenzoate and *S*-Ethyl Decanethioate. (1) In entry 51 the reaction mixture, obtained according to procedure B, starting from *S*-ethyl thiobenzoate (0.83 g, 5 mmol), tris-(methylthio)methane **16** (1.69 g, 11 mmol), and BuLi (4.84 mL, 12.1 mmol) in THF (10 mL), was stirred at −78 °C under N_2 for 30 min. GC and GC−MS analyses of a sample of the resulting solution, quenched directly with water, showed the presence of ethyl methyl disulfide, MS *m*/*z* 108, **7a**, and **12**, as major products, **16** as minor product, and a small amount of *S*-methyl thiobenzoate (**4a**) and *S*-ethyl thiobenzoate. After usual workup of the reaction mixture, the crude residue was column chromatographed with PE−CH_2Cl_2 (7:3, v/v) as eluent to afford **12** (0.81 g, 81%), **16** (0.10 g, 6%), an oily substance comprising a mixture of **4a**, MS *m*/*z* 152 (M^+), and the starting *S*-ethyl

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thiobenzoate, MS *m*/*z* 166 (M^+), in a 1:1.2 ratio (determined by GC; 0.05 g) and **7a** (0.99 g, 93%).

(2) In entry 52 the reaction was carried out according to the above procedure starting from *S*-ethyl decanethioate (1.08 g, 5 mmol) instead of *S*-ethyl thiobenzoate. The crude residue, obtained after usual workup, was column chromatographed with PE−*t*-BuOH (9:1, v/v) as eluent to afford **12** (0.56 g, 56%), **16** (0.51 g, 30%), an oily substance comprising a mixture of *S*-methyl decanethioate (**4i**), MS *m*/*z* 202 (M^+), and the starting *S*-ethyl decanethioate, MS *m*/*z* 216 (M^+), in a 1:1.2 ratio (determined by GC; 0.27 g) and **7i** (0.81 g, 62%).

Reaction of [Tris(methylthio)methyl]lithium (6) with *S*-Ethyl Decanethioate and Quenching with Deuterium Oxide. In entry 53 the reaction mixture, obtained according to entry 52, was directly quenched with D_2O. After usual workup, the crude residue was column chromatographed with PE−*t*-BuOH (9:1, v/v) as eluent to afford **12** (0.61 g, 61%); tris(methylthio)deuteriomethane (**16**, H = D; 0.44 g, 26%), MS *m*/*z* 155 (M^+), confirmed by ^{1}H NMR; an oily substance comprising a mixture of *S*-methyldecanethioate (**4i**) and the starting compound *S*-ethyl decanethioate, MS *m*/*z* 216 (M^+), in a 1:1.2 ratio (determined by GC; 0.27 g), and 1,1-bis(methylthio)-1-deuterio-2-undecanone (**7i**, H = D; 0.80 g, 61%), MS *m*/*z* 263 (M^+), confirmed by ^{1}H NMR.

Reactions of Sodium Thiomethoxide with *S*-Ethyl Thiobenzoate and *S*-Ethyl Decanethioate. (1) In entry 54, sodium thiomethoxide (0.39 g, 5.5 mmol) was added, under stirring, to a solution of *S*-ethyl thiobenzoate (0.83 g, 5 mmol) in anhydrous THF (5 mL), maintaining the temperature at −78 °C. Progress of the reaction was monitored by GC. After 30 min of stirring and cooling, GC analysis of a sample, directly quenched with water, showed the presence of two compounds: *S*-methyl thiobenzoate (**4a**) and the starting *S*-ethyl thiobenzoate, in a ratio of 1:30. The ratio became 1:1.2 after 8 h. In a collateral proof, the reaction was carried out at rt. Ratios of the two thiobenzoates were 1:15 after 30 min and 1:1.2 after 3 h.

(2) According to the above procedure, in entry 55, sodium methyl mercapture (0.39 g, 5.5 mmol) was added to a solution of *S*-ethyl decanethioate (1.08 g, 5 mmol) in anhydrous THF (5 mL) at −78 °C. After 30 min, GC analysis of a sample, directly quenched with water, showed the presence of two compounds: *S*-methyl decanethioate (**4i**) and the starting *S*-ethyl decanethioate, in a ratio of 1:1.15.

Reactions of Adducts 20a and 20i with [Tris(methylthio)methyl]lithium (6). (1) In entry 56, sodium thiomethoxide (0.39 g, 5.5 mmol) was added, under stirring, to a solution of *S*-methyl thiobenzoate (**4a**; 0.76 g, 5 mmol) in anhydrous THF (5 mL) at rt. After 3 h, the mixture containing the adduct **20a** was added, under stirring, to a suspension of **6**, prepared from tris(methylthio)methane (**16**; 1.69 g, 11 mmol) and BuLi (4.84 mL, 12.10 mmol) in THF (5 mL) at −78 °C and under N_2. Also, when the reaction time at −78 °C was extended to 2 h, the reaction could not take place. In fact, GC−MS analysis of a sample, directly quenched with water, showed the only presence of the starting compounds **16** and **4a**. These, after usual workup of the reaction mixture, were separated by chromatography, eluting with PE−CH_2Cl_2 (7:3, v/v): **16** (1.62 g, 96%); **4a** (0.71 g, 94%).

(2) According to the above procedure, in entry 57, sodium methyl mercapture (0.39 g, 5.5 mmol) was added to a solution of *S*-methyl decanethioate (**4i**; 1.01 g, 5 mmol) in anhydrous THF (5 mL) at −78 °C. After being stirred for 30 min, the mixture containing the adduct **20i** was added to a suspension of **6**, prepared from **16** (1.69 g, 11 mmol) and BuLi (4.84 mL, 12.10 mmol) in THF (5 mL) at −78 °C and under N_2. Also, when the reaction time at −78 °C was extended to 2 h, the reaction could not take place, as above. The crude residue, obtained after usual workup, was chromatographed, eluting with PE−*t*-BuOH (9:1, v/v), to afford **16** (1.54 g, 91%) and the starting compounds **4i** (0.97 g, 96%) as the only compounds.

Reactions of Acyl Chlorides 2, Anhydrides 3, Thiol Esters 4, and *N*,*N*-Dimethylamides 5 with [Bis(methylthio)methyl]lithium (22). Representative Procedures. Procedure D. According to the procedure previously reported[1] for the reaction of esters **1** with **22**, in entry 58 (Table 2), a solution of *N*,*N*-dimethylbenzamide (**5a**; 1.49 g, 10 mmol) in anhydrous THF (5 mL) was added dropwise during 5 min to a solution of **22**, obtained from bis(methylthio)methane (1.08 g, 10 mmol) and BuLi (2.5 M solution in hexane; 4.4 mL, 11 mmol) in THF (10 mL) at −78 °C under N_2. After being stirred at −78 °C for a further 30 min, the reaction mixture was directly quenched with diethyl ether−water (200 mL, 1:1). The crude residue, obtained after usual workup, was virtually pure (GC, TLC, NMR) 2,2-bis(methylthio)-1-phenylethanone (**7a**; 2.12 g, 100%).

Entries 60, 62, 64, and 66 (Table 2) were also performed according to procedure D.

Procedure E. In entry 59 (Table 2), the reaction mixture obtained according to procedure A in entry 58 was allowed to warm to rt (20−25 °C). Anhydrous MeOH (0.35 g, 11 mmol) was added, and the nitrogen stream was increased to remove *N*,*N*-dimethylamine that developed. Stirring was continued for 1 h. Then sodium hydride (0.26 g, 11 mmol) was added: an exothermic reaction with hydrogen evolution immediately occurred. After 10 min, a solution of *N*-(methylthio)phthalimide (**14**; 2.89 g, 15 mmol) in THF (10 mL) was added, and stirring was continued for a further 1 h, until GC analysis showed the disappearance of the intermediate **7a** and the presence of **8a** as the only product. The crude residue, obtained after usual workup, was chromatographed on a short column, eluting with PE−CH_2Cl_2 (7:3, v/v), to afford 2,2,2-tris(methylthio)-1-phenylethanone (**8a**) (2.37 g, 92%).

Entries 61, 63, 65, and 67 (Table 2) were also performed according to procedure E.

Procedure F. In entry 68 (Table 2), a solution of benzoyl chloride (**2a**; 1.41 g, 10 mmol) in anhydrous THF (5 mL) was added dropwise during 5 min to a solution of **22**, obtained from bis(methylthio)methane (2.16 g, 20 mmol) and BuLi (8.8 mL, 22 mmol) in THF (10 mL) at −95 °C under N_2. After being stirred at −95 °C for a further 5 min, the reaction mixture was usually worked up and the crude residue was chromatographed, eluting with PE−CH_2Cl_2 (3:2, v/v). The first eluted product was the starting bis(methylthio)methane (isolated in variable amounts as no particular device was adopted for trapping it). The second eluted product was **7a** (1.65 g, 78%). The third eluted product was 1,1,3,3-tetrakis(methylthio)-2-phenylpropan-2-ol (**23a**; 0.41 g, 13%): mp 53 °C (PE) (lit.[1] mp 53 °C); MS *m*/*z* 320 (M^+); IR and ^{1}H NMR identical to those reported. Yield of the last compound increased when the reaction was carried out at higher temperatures and protracting reaction times (*e.g.*, at −15 °C for 3 h: 48%).

Entries 69−73 (Table 2) were also performed according to procedure F.

Physical properties of compounds **23b**,**c** are as follows.

1,1-Bis(methylthio)-2-[bis(methylthio)methyl]pentan-2-ol (23b): bp 152−153 °C/0.4 mmHg; MS *m*/*z* 286 (M^+); ^{1}H NMR δ 0.82−1.15, 1.20−1.70 and 1.70−1.90 (3 m, 3:2:2, 7H), 2.28 (s, 12H), 2.80 (br s, 1H; it disappeared after addition of D_2O), 4.30 (s, 2H); IR 3500 cm^{-1} (OH).

1,1-Bis(methylthio)-2-[bis(methylthio)methyl]undecan-2-ol (23c): bp 192 °C/0.4 mmHg (lit.[1] bp 192 °C/0.4 mmHg); MS *m*/*z* 370 (M^+); IR and ^{1}H NMR identical to those reported.

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