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An Improved Reaction of tris(Methylthio) methane with Epoxides: Application to the Efficient Synthesis of β-Hydroxy Esters

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AN IMPROVED REACTION OF TRIS(METHYLTHIO)METHANE WITH EPOXIDES: APPLICATION TO THE EFFICIENT SYNTHESIS OF β-HYDROXY ESTERS.

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ABSTRACT: Tris(methylthio)methyllithium reacts efficiently with epoxides in THF:HMPA (5:1) at low temperature to give β-hydroxy orthotrithiocarboxylates which are converted to β-hydroxy esters in high yield.

Carboxy anion equivalents such as lithio orthothioformates (**1**) are known to undergo alkylation with a variety of electrophiles[1,2] including Michael acceptors[3] (Scheme 1).

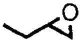
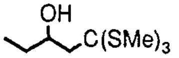
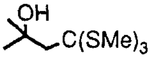
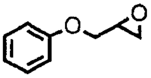
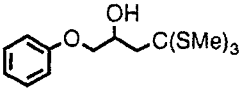
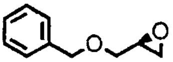
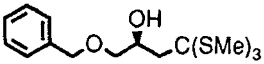
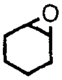
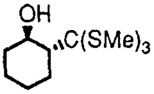
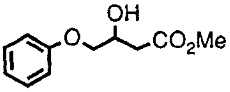
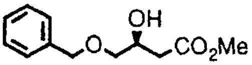
$$\mathrm{HC(SR)_3} \xrightarrow[\text{2) } E^+]{\text{1) nBuLi}} \mathrm{E\text{-}C(SR)_3} \longrightarrow \mathrm{E\text{-}CO_2Me}$$

1a, R=Me
1b, $R=C_6H_5$

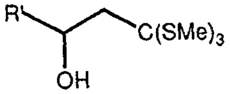
Scheme 1

Terminal epoxides however generally react with **1b** to give β-hydroxy orthothiocarboxylates (**2**) in only 25-30% yield[2,4], making the reaction impractical for preparative use. Further, this reaction is limited to temperatures below -45°C owing to the thermal instability of the orthothioformate anion[2]. This report describes a simple modification of the usual procedure which allows for the efficient alkylation of **1a** with epoxides at low temperature affording good to excellent yields of **2**, which are easily converted to β-hydroxy esters (**3**).

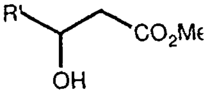
Table 1.

Entry	Reactant	Conditions[a]	Product		Yield (%)
1		A		2 a	88%
2		A		2 b	86%
3		A		2 c	91%
4		A		2 d	92%
5		A		2 e	44%
6	2 c	B		3 c	95%
7	2 d	C		3 d	88%

[a] conditions: A, $HC(Me)_3$ (1 eq.)/ nBuLi (1 eq.) then epoxide (1 eq.)/ THF/HMPA (5:1)/ -70 to -45°C; B, $HgCl_2$(4 eq.)/ HgO (1.7 eq.)/ $MeOH/H_2O$ (12:1); C, NBS (7 eq.)/ $NaHCO_3$ (12 eq.)/ MeOH/ H_2O (12:1).



2



3

When the anion of **1a** is generated in the presence of HMPA (17% by volume) in THF followed by the addition of an epoxide at -70°C and warmed to -45°C, the reaction is complete within 30 minutes. Isolated yields range from 86-92% for a representative group of terminal epoxides (Table 1, entry 1-4) and is lower for an internal epoxide (entry 5). The addition of HMPA possibly enhances the rate and hence yield of this reaction by 1) solvating the lithium cation causing an increase in the reactivity of the carbon nucleophile and 2) creating a more polar environment in which to stabilize the transition state.

Finally, the orthothiocarboxylate was unmasked with either $HgCl_2$/ HgO[5] (entry 6) in the case of **2c** or NBS[6] (entry 7) in the case of **2d**. Compound **3d** can be considered to be a selectively protected chiral malate derivative, synthesized in 2 steps from a commercially available chiral epoxide, and is an important intermediate in the synthesis of some natural products[7].

EXPERIMENTAL:

^1H-NMR spectra (300 MHz) were recorded in $CDCl_3$ solution with tetramethylsilane as internal standard. Flash chromatography was performed using Kieselgel 60 (230-400 mesh). Anhydrous THF was freshly distilled from sodium/benzophenone. All other reagents were used as received without further purification.

General Procedure for the Conversion of Epoxides to β-Hydroxy orthothiocarboxylates: 3-Hydroxytris(methylthio)-pentane (2a). To a solution of tris(methylthio)methane (770 mg, 5 mmol) in 12 mL of THF/HMPA (5:1), cooled to -70°C under an atmosphere of nitrogen, was added a 1.6 M solution of nBuLi (3.1 mL, 5 mmol) in hexane. The yellow solution was stirred for 15 minutes. Neat 1,2-epoxybutane (Aldrich) (430 uL, 5 mmol) was added via syringe and the reaction flask was transferred to a dry ice/acetonitrile bath (-45°C). After 30 minutes the reaction was poured into H_2O and extracted with ethyl acetate. The organic phase was washed (2X) with H_2O, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Silica gel chromatography (15% EtOAc/hexane) afforded 1.00 g (88%) of product as a colorless oil. 1H-NMR: δ 0.97 (t, J=7 Hz, 3H), 1.4-1.6 (m, 2H), 1.95 (dd, J=15 Hz, J=2Hz, 1H), 2.08 (dd, J=15 Hz, J=9 Hz, 1H), 2.15 (s, 9H), 4.13 (m, 1H); IR (neat) 3470 (m), 1460 (w), 1430 (m), 1410 (m) cm^{-1}. Anal. calc'd. for $C_8H_{18}S_3O$: C, 42.44; H, 8.01; S, 42.48. Found: C, 42.56; H, 8.02; S, 42.30.

3-Hydroxy-3-methyltris(methylthio)butane (2b). Isobutylene oxide (Lancaster) (409 uL, 5 mmol) was converted to 3-hydroxy-3-methyl-tris(methylthio)butane and purified by silica gel chromatography using 10% EtOAc/hexane as the eluent to give 970 mg (4.29 mmol, 86%) of colorless oil. ^1H-NMR: δ 1.40 (s, 6H), 2.17 (s, 9H), 2.21 (s, 2H); IR (neat) 3470 (m), 1460 (w), 1450 (w), 1430 (m), 1410 (m), 1160 (s) 1160 (s) cm^{-1}. Anal. calc'd. for $C_8H_{18}S_3O$: C, 42.44; H, 8.01. Found: C, 42.75; H, 7.78.

3-Hydroxy-4-phenoxytris(methylthio)butane (2c). 1,2-Epoxy-3-phenoxypropane (Aldrich) (680 uL, 5 mmol) was converted to 3-hydroxy-4-phenoxytris(methylthio)butane and purified by silica gel chromatography using 70% CH_2Cl_2/ hexane as the eluant to give 1.39 g (4.57 mmol, 91%) of colorless oil. ^1H-NMR: δ 2.16 (s, 9H), 2.21 (dd, J=15 Hz, J=8 Hz, 1H), 2.29 (dd, J=15 Hz, J=3Hz, 1H), 3.55 (d, J=4 Hz, 1H), 3.91

(dd, J=10 Hz, J=8 Hz, 1H), 4.03 (dd, J=10 Hz, J=5 Hz, 1H), 4.62 (m, 1H), 6.9-7.0 (m, 5H), 7.28 (t, J=8 Hz, 2H); IR (neat) 3450 (m), 1600 (s), 1585 (s), 1490 (s), 1465 (w), 1450 (w), 1430 (m), 1410 (m), 1240 (s) cm^{-1}. Anal. calc'd. for $C_{13}H_{20}S_3O_2$: C, 51.28; H, 6.62; S, 31.59. Found: C, 51.19; H, 6.58; S, 31.58.

(S)-(+)-3-Hydroxy-4-(benzyloxy)tris(methylthio)butane (2d). (R)-(-)-2-(benzyloxymethyl)oxirane (Aldrich) (760 uL, 5 mmol) was converted to (S)-(+)-3-hydroxy-4-(benzyloxy)tris(methylthio)butane and purified by silica gel chromatography using CH_2Cl_2 as eluent to give 1.46 g (4.59 mmol, 92%) of colorless oil. ^{1}H-NMR: δ 2.07-2.19 (m, 11H), 3.49 (d, J=4 Hz, 1H), 3.41-3.53 (m, 2H), 3.43 (m, 1H), 4.57 (s, 2H), 7.27-7.38 (m, 5H); IR (neat) 3460 (m), 1490 (w), 1450 (m), 1430 (m), 1410 (m), 1115 (s), 1095 (s) cm^{-1}; $[\alpha]^{25}_D$ = +27.6° (c=11.24 mg/mL, $CHCl_3$). Anal. calc'd. for $C_{14}H_{22}S_3O_2$: C, 52.79; H, 6.96; S, 30.20. Found: C, 52.93; H, 6.82; S, 30 39.

(trans)-2-Tris(methylthio)methylcyclohexanol (2e). Cyclohexene oxide (Aldrich) (505 uL, 5 mmol) was converted to (trans)-2-tris(methylthio)methylcyclohexanol and purified by silica gel chromatography using 10% EtOAc/hexane as eluent to give 550 mg (2.18 mmol, 44%) of colorless oil. ^{1}H-NMR: δ 1.1-1.4 (m, 4H), 1.67-1.79 (m, 2H), 1.87-1.97 (m, 1H), 2.0-2.14 (m, 2H), 2.24 (s, 9H), 4.0 (m, 1H), 4.70 (s, 1H); IR (neat) 3430 (m), 1440 (m), 1430 (m), 1410 (m), 1110 (m), 1070 (m) cm^{-1}. Anal. calc'd. for $C_{10}H_{20}S_3O$: C, 47.57; H, 7.99; S, 38.10. Found: C, 47.61; H, 7.99; S, 37.82.

Methyl 3-hydroxy-4-phenoxybutanoate (3c). To a solution of **2c** (532 mg, 1.75 mmol) in 30 mL of MeOH/H_2O (12:1) was added HgO (636 mg, 2.94 mmol) and $HgCl_2$ (1.93 g, 7.11 mmol). The reaction mixture was stirred at room temperature for 1 hour, then filtered and washed with CH_2Cl_2 (50 mL). The filtrate was diluted with H_2O (50 mL) and extracted (2X 50 mL) with CH_2Cl_2. The organic layer was washed with 75% NH_4OAc (2X 50 mL) and sat'd. NH_4Cl (2X 50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Silica gel chromatography (35% EtOAc/hexane) afforded 350 mg (95%) of colorless oil. ^{1}H-NMR: δ 2.70 (m, 2H), 3.05 (d, J=5 Hz, 1H), 3.74 (s, 3H), 4.00 (d, J=6 Hz, 2H), 4.43 (m, 1H), 6.92 (d, J=8 Hz, 2H), 6.97 (t, J=8 Hz, 1H), 7.29 (t, J=8 Hz, 2H); IR (neat) 3450 (m), 1735 (s), 1450 (m), 1435 (s) cm^{-1}. Anal. calc'd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.50; H, 6.79.

Methyl 3-hydroxy-4-benzyloxybutanoate (3d). To a suspension of **2d** (500 mg, 1.57 mmol) and $NaHCO_3$ (1.58 g, 18.84 mmol) in 26 mL of MeOH/H_2O (12:1), cooled in an ice bath, was added N-bromosuccinimide (1.96 g, 11.00 mmol). The reaction mixture was stirred at 5°C for 5 minutes then at ambient temperature for 10 minutes. A solution of aq. 10% $Na_2S_2O_5$ (5 mL) was added then the mixture was concentrated under reduced pressure to remove most of the MeOH. The reaction mixture was patitioned between H_2O and Et_2O/hexane (1:1), then washed (2X) with H_2O, dried ($MgSO_4$), filtered and evaporated under reduced pressure. Silica gel chromatography (35% EtOAc/hexane) afforded 310 mg (88%) of colorless oil. ^{1}H-NMR: δ 2.56 (d, J=6 Hz, 2H), 3.50 (m, 2H), 3.70 (s, 3H), 4.25 (m, 1H), 4.57 (s, 2H), 7.35 (m, 5H); IR (neat) 3450 (m), 1730 (s), 1595 (m), 1585 (m), 1495 (m). $[\alpha]^{25}_D = +8.2°$ (c=8.5 mg/mL, $CHCl_3$). HRMS (exact mass): calc'd. for $C_{12}H_{16}O_4$: 224.1048. Found: 224.1068.

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