Conversion of Thionoesters and Thionolactones to Ethers; a General and Efficient Radical Desulfurisation

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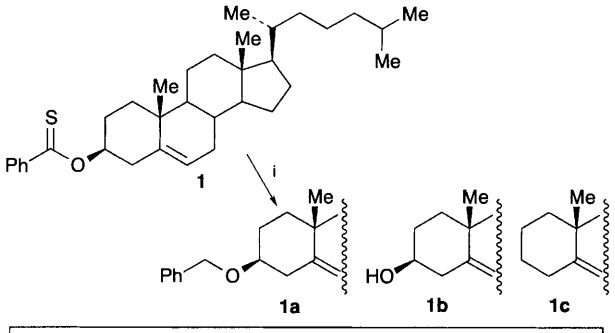
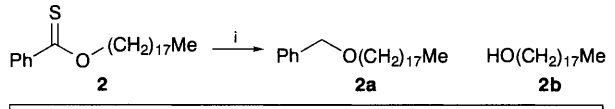
Triphenyltin hydride reduces thionoesters and thionolactones to their corresponding ethers in high yield.

The past few years have witnessed a dramatic growth in the development and application of free radical reactions in organic synthesis.[1] This advent is mainly a consequence of the availability of different sources of carbon-centred radicals, and the selectivity and mildness of radical based transformations. An important group of radical reactions with widespread synthetic usage relies upon the intriguing propensity of the thiocarbonyl functionality to undergo attack by tin-centred radicals.[2] As part of our program directed towards the construction of medium- and large-ring molecular frameworks we have developed several reactions involving the thiocarbonyl functionality and demonstrated its synthetic potential.[3] Here, we report the one-step conversion of thionoesters and thionolactones to the corresponding ethers using triphenyltin hydride, and describe the collected experimental evidence in support of a radical mechanism for this transformation.[4]

As shown in Scheme 1 treatment of the cholesterol-derived secondary thionobenzoate **1**[5] with 1.5 equiv. of Bu^n_3SnH and catalytic quantities of AIBN in refluxing toluene (*ca.* 110 °C) afforded a mixture of cholesterol **1b** and the deoxygenated derivative **1c** in 42 and 46% yield respectively, and in accordance with earlier observations.[6,7] When the reaction was repeated in the presence of 5.0 equiv. of Bu^n_3SnH, we obtained a mixture of the benzyl ether derivative **1a** and **1b** in 49 and 38% yields respectively. Gratifyingly, utilization of Ph_3SnH instead of Bu^n_3SnH, under otherwise identical conditions, provided exclusively the benzyl ether **1a** in 97% isolated yield (Scheme 1, entry 3). In an attempt to curtail the formation of deoxygenated products, we subjected the primary alcohol-derived thionobenzoate **2** to the above reaction (Scheme 1), since it is well known that primary alkyl radicals cannot be generated under such conditions. Indeed, in all these experiments benzyl ether **2a** and alcohol **2b** were the only products formed. Furthermore, and in consistence with the above results, reaction of **2** with Ph_3SnH produced almost exclusively **2a** (91% yield).†



Entry	R	equiv. of R_3SnH	Yield(%)	Yield(%)	Yield(%)
1	Bu^n	1.5	0	42	46
2	Bu^n	5.0	49	38	trace
3	Ph	5.0	97	trace	trace

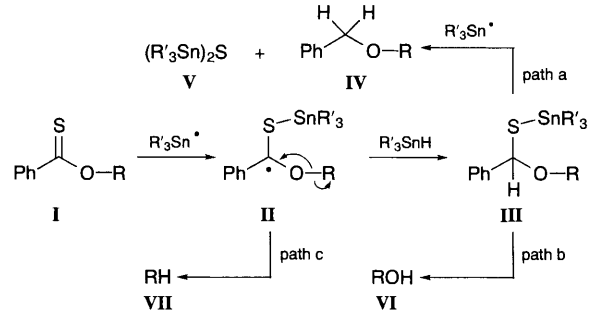


Entry	R	equiv. of R_3SnH	Yield(%)	Yield(%)
1	Bu^n	1.5	21	58
2	Bu^n	5.0	0	77
3	Ph	5.0	91	trace

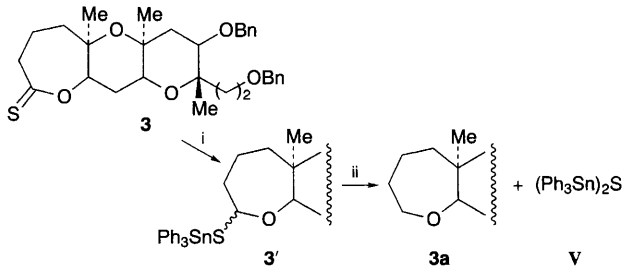
Scheme 1 *Reagents and conditions*: i, R_3SnH, 0.05 equiv. of AIBN, toluene (0.01 mol dm^{-3} based on substrate), 110 °C, 20 min

The formation of the deoxygenated derivative **1c** can be explained *via* the known Barton–McCombie radical deoxygenation mechanism (Scheme 2, path c, **I** → **II** → **VII**).[7] In accordance with this scheme the relatively stable carbon radical intermediate **II** can be further reduced to **III**. Subsequent radical desulfurisation of **III** should then provide benzyl ether **IV** (Scheme 2, path a), while, alternatively, cleavage of the mixed thioketal functionality within **III** could account for the formation of the alcohol **VI** (Scheme 2, path b).

In order to provide support for this mechanism we treated thionolactone **3** with 1.5 equiv. of Ph_3SnH and were able to isolate the stable mixed thioketal **3'** in 86% yield (Scheme 3).‡ Furthermore upon treatment of **3'** with additional 3.0 equiv. of Ph_3SnH under radical conditions (catalytic AIBN, toluene, 110 °C), a smooth reaction took place affording benzyl ether **3a** and the bis(triphenyltin) sulfide **V** in 88 and 78% isolated yields



Scheme 2 Proposed mechanism of reductive desulfurisation

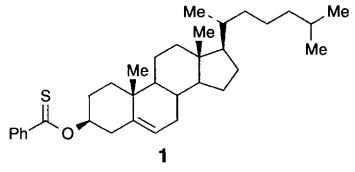
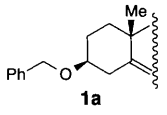
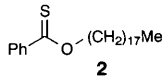
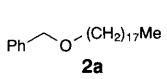
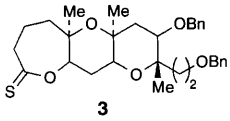
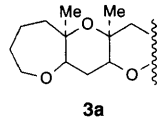
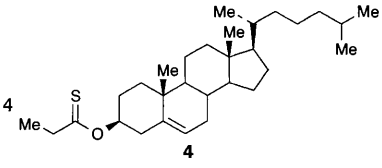
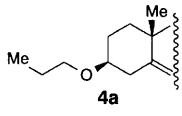
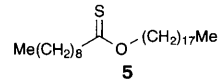
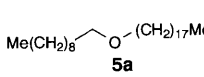
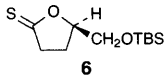
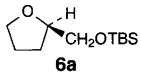
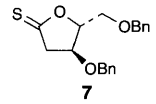
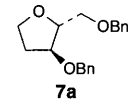
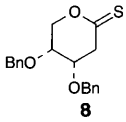
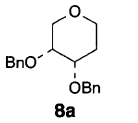
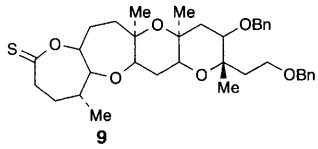
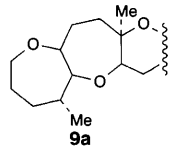
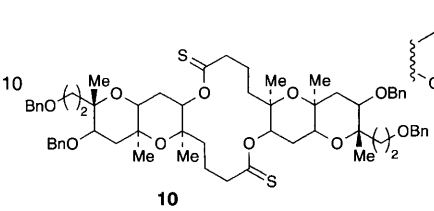
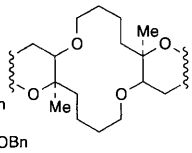


Scheme 3 *Reagents and conditions*: i, 1.5 equiv. of Ph_3SnH, 0.05 equiv. of AIBN, toluene (0.01 mol dm^{-3} based on substrate), 110 °C, 10 min, 86%; ii, 3.0 equiv. of Ph_3SnH, 0.05 equiv. of AIBN, toluene (0.01 mol dm^{-3} based on substrate), 110 °C, 20 min, 88% of **3a** and 78% of bis-(triphenyltin)sulfide **V**

respectively. It is noteworthy that in the absence of AIBN no reaction was observed, excluding an ionic mechanism for path a.

We attribute the difference in the reaction pathway to the different behaviour and stability of the Sn-H bond.[1] The less reactive Bu^n_3SnH acts simultaneously as a hydrogen radical donor and as a Lewis acid (path a and b respectively) producing ultimately **IV** and **VI**. In contrast, the more reactive Ph_3SnH acts solely as a hydrogen radical donor giving rise exclusively to the benzyl ether **IV** (Scheme 2).

Table 1 Reduction of thionoesters and thionolactones[a]

Entry	Subtrate	Product	Yield (%)[b]
1	 **1**	 **1a**	97
2	 **2**	 **2a**	91
3	 **3**	 **3a**	95[c]
4	 **4**	 **4a**	93
5	 **5**	 **5a**	94
6	 **6**	 **6a**	79
7	 **7**	 **7a**	77
8	 **8**	 **8a**	90[d]
9	 **9**	 **9a**	99
10	 **10**	 **10a**	72

[a] *Reagents and conditions*: 5.0 equiv. of Ph_3SnH, 0.05 equiv. of AIBN, toluene (0.01 mol dm^{-3}; based on substrate), 110 °C, 20 min; TBS = Me_2SiBu^t. [b] Isolated yield after column chromatography. [c,d] Bis(triphenyltin)sulfide **V** was also isolated in 78 and 75% yield, respectively.

The results summarised in Table 1 demonstrate the versatility and generality of this new reaction. Primary or secondary alcohol-derived thionoesters (entries 1, 2, 4, 5) are smoothly converted to the corresponding ethers in high overall yields. In addition, thionolactones (entries 3, 6–10) can be easily reduced to the corresponding cyclic ethers with good yield and with no observed formaton of ring-opened by-products. The general applicability of this reaction is further exemplified by the smooth transformation of the 14-membered dithionolactone **10** (entry 10) to the corresponding cyclic ether **10a** in a single step and in 72% yield.

In summary, we describe herein a general method for the one-step conversion of thionoesters and thionolactones to their corresponding ethers, and propose a radical mechanism for this reduction. Since the thiocarbonyl functionality can be conveniently obtained by thionation of esters and lactones, this process allows ultimately for the conversion of esters to ethers.¶ It is anticipated that this method will find wide use as a mild and efficient procedure for the formation of linear and cyclic ethers.

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Footnotes

† All new compounds exhibited satisfactory spectral, analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

‡ *General procedure* (**3** → **3a**): To a solution of the thionolactone **3** (525 mg, 1 mmol) and Ph_3SnH (1.7 g, 5.0 mmol) in toluene (100 ml) at 110 °C was added 2,2′-azobis(*iso*-butyronitrile) (24 mg, 0.15 mmol) in small intervals and over a period of 1 hour. The progress of the reaction was followed by TLC and after complete disappearance of the starting material the reaction mixture was concentrated and subjected to flash chromatography [silica, 5 → 20% diethyl ether in hexane] to give ether **3a** (469 mg, 0.95 mmol, 95%).

§ *Selected physical and spectral data* for **3′**: Colourless oil; R_f = 0.46 (silica, 25% diethyl ether in hexane); IR (film) ν_{max}/cm^{-1} 2988 (m), 2934 (m), 1454 (m), 1379 (m), 1098 (s), 1062 (s), 1021 (m), 998 (m), 730 (m) and 697 (s); ^1H NMR (500 MHz, $CDCl_3$) (major isomer) δ 7.79–7.63 (m, 6 H, ArH), 7.43–7.25 (m, 19 H, ArH), 5.26 (dd, *J* = 11.5, 5.0 Hz, 1 H, SCH), 4.55 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 4.50 (s, 2 H, CH_2Ph), 4.37 (d, *J* = 11.5 Hz, 1 H, C*H*HPh), 3.65–3.59 (m, 2 H, OCH), 3.53 (dd, *J* = 11.5, 5.0 Hz, 1 H, CHO), 3.27 (dd, *J* = 11.5, 5.0 Hz, 1 H, CHO), 3.08 (dd, *J* = 12.0, 3.5 Hz, 1 H, CHO), 2.11–1.90 (m, 6 H, CH), 1.38–1.16 (m, 6 H, CH), 1.20 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3) and 1.7 (s, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.4, 138.2, 136.9, 136.8, 136.8, 136.7, 136.6, 129.4, 129.4, 128.8, 128.7, 128.6, 128.5, 128.3, 128.3, 128.2, 127.7, 127.5, 127.5, 79.9, 78.5, 77.9, 77.3, 76.8, 73.0, 72.6, 72.4, 70.8, 65.9, 44.1, 40.2, 40.1, 36.5, 28.8, 22.2, 19.5, 18.0 and 17.2; HRMS, calcd for $C_{49}H_{56}O_5SSnCs$ (M + Cs^+): 1009.1925, found 1009.1968.

3a Colourless oil; R_f = 0.23 (silica, 25% diethyl ether in hexane); IR (film) ν_{max}/cm^{-1} 2986 (m), 2933 (s), 2860 (s), 1454 (m), 1378 (m), 1274 (m), 1207 (m), 1097 (s), 1062 (s), 1027 (m), 734 (m), 697 (m), 666 (m) and 609 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.08 (m, 10 H, ArH), 4.38 (d, *J* = 11.5 Hz, 1 H, CH*H*Ph), 4.32 (s, 2 H, CH_2Ph), 4.21 (d, *J* = 11.5 Hz, 1 H, CH*H*Ph), 3.80 (dt, *J* = 9.0, 7.0 Hz, 1 H, CH), 3.70 (dd, *J* = 11.5, 5 Hz, 1 H, CHO), 3.66–3.57 (m, 2 H, CH_2Ph), 3.47–3.39 (m, 2 H, CHO), 3.33 (dd, *J* = 9.0, 7.0 Hz, 1 H, CHO), 2.22 (dd, *J* = 11.5, 5.0 Hz, 1 H, CH), 2.17–2.12 (m, 2 H, CH), 1.97–1.93 (m, 2 H, CH), 1.90–1.87 (m, 1 H, CH), 1.42–1.31 (m, 6 H, CH), 1.38 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3) and 1.28 (s, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 128.3, 128.3, 127.7, 127.6, 127.5, 127.4, 78.4, 78.0, 73.0, 72.6, 70.9, 68.1, 66.0, 44.6, 40.3, 40.3, 29.4, 28.3, 21.8, 21.4, 19.7 and 17.4; HRMS, calcd for $C_{31}H_{42}O_5Cs$ (M + Cs^+): 627.2087, found 627.2060.

¶ The starting thionoesters and thionolactones were prepared (68–89% yield) from the corresponding esters and lactones by thionation with Lawesson's reagent at 140 °C in toluene for 8–24 h.

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