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

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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. 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 thioacyralkyl functionality to undergo attack by tin-centred radicals. As part of our program directed towards the construction of medium- and large-ring molecular frameworks we have developed several reactions involving the thioacyralkyl functionality and demonstrated its synthetic potential. 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.

As shown in Scheme 1 treatment of the cholesterol-derived secondary thionobenzoate 1 with 1.5 equiv. of Bu₂SnH 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. When the reaction was repeated in the presence of 5.0 equiv. of Bu₂SnH, we obtained a mixture of the benzyl ether derivative 1a and 1b in 49 and 38% yields respectively. Gratifyingly, utilization of Ph₂SnH instead of Bu₂SnH, 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 consistency with the above results, reaction of 2 with Ph₂SnH produced almost exclusively 2a (91% yield).†

The formation of the deoxygenated derivative 1c can be explained via the known Barton–McCombie radical deoxygenation mechanism (Scheme 2, path c). In accordance with this scheme the relatively stable carbon radical intermediate II can be further reduced to III. Subsequent radical desulphurisation of III should then provide benzyl ether IV (Scheme 2, path a), while, alternatively, cleavage of the mixed thioether 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 Ph₂SnH and were able to isolate the stable mixed thioether 3' in 86% yield (Scheme 3). Furthermore upon treatment of 3' with additional 3.0 equiv. of Ph₂SnH 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 respectively.

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**Scheme 1** Proposed mechanism of reductive desulfurisation.

**Scheme 2** Proposed mechanism of reductive desulfurisation.

**Scheme 3** Reagents and conditions: i. 1.5 equiv. of Ph₂SnH, 0.05 equiv. of AIBN, toluene (0.01 mol dm⁻³ based on substrate), 110 °C, 10 min, 86%; ii. 3.0 equiv. of Ph₂SnH, 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.
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. The less reactive Bu₃SnH 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 Ph₃SnH acts solely as a hydrogen radical donor giving rise exclusively to the benzyl ether IV (Scheme 2).

The results summarised in Table 1 demonstrate the versatility and generality of this new reaction. Primary or secondary alcohol-derived thioesters (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 formation of ring-opened by-products. The general applicability of this reaction is further exemplified by the smooth transformation of the 14-membered dithiolactone 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 thioesters and thiolactones 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 Ph₃SnH (1.7 g, 5.0 mmol) in toluene (100 mL) at 110°C was added 2,2'-azobisiso-butynitrile (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 3â: Colourless oil; Rf = 0.46 (silica, 25% diethyl ether in hexane); IR (film) νmax/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, CDCl₃) (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, CH₂Ph), 4.50 (s, 2 H, CH₂Ph), 4.37 (d, J = 11.5 Hz, 1 H, CH₂Ph), 3.65–3.59 (m, 2 H, OCH₂), 3.53 (dd, J = 11.5, 5.0 Hz, 1 H, CHO), 3.37 (dd, J = 11.5, 5.0 Hz, 1 H, CHO), 3.13–1.90 (m, 6 H, CH₂), 1.38–1.16 (m, 6 H, CH₂), 1.20 (s, 3 H, CH₃), 1.11 (s, 3 H, CH₃) and 1.06 (s, 3 H, CH₃). 13C NMR (125 MHz, CDCl₃) δ 138.5, 138.4, 138.2, 136.9, 136.8, 136.7, 136.6, 136.5, 129.4, 129.8, 128.7, 128.6, 128.5, 128.3, 128.3, 128.2, 127.7, 127.5, 127.4, 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, calc'd for C₉₃H₇₀O₃S₅S₄N₆C₆ (M + C₄H₅) 2001.925, found 1999.698.
3a Colourless oil; Rf = 0.23 (silica, 25% diethyl ether in hexane); IR (film) νmax/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, CDCl₃) δ 7.31–7.08 (m, 10 H, ArH), 4.38 (d, J = 11.5 Hz, 1 H, CH₂Ph), 4.32 (s, 2 H, CH₂Ph), 4.21 (d, J = 11.5 Hz, 1 H, CH₂Ph), 3.80 (dt, J = 9.0, 0.7 Hz, 1 H, CH₃), 3.70 (dd, J = 11.5, 5.5 Hz, 1 H, CHO), 3.66–3.57 (m, 2 H, CH₂Ph), 3.47–3.39 (m, 2 H, CHO). 3.33 (dd, J = 9.0, 0.7 Hz, 1 H, CHO), 2.22 (dd, J = 11.5, 5.0 Hz, 1 H, CH), 2.17–2.12 (m, 2 H, CH₂), 1.97–1.93 (m, 2 H, CH₂), 1.90–1.87 (m, 1 H, CH), 1.42–1.31 (m, 6 H, CH₂), 1.38 (s, 3 H, CH₃), 1.37 (s, 3 H, CH₃) and 1.28 (s, 3 H, CH₃). 13C NMR (125 MHz, CDCl₃) δ 138.5, 138.4, 138.2, 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, 40.2, 29.4, 28.3, 21.8, 21.4, 19.7 and 17.4. HRMS, calc'd for C₇₃H₅₃O₇S₄N₅C₆ (M + C₄H₅) 627.2087, found 627.2066.

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Table 1 Reduction of thioesters and thionolactones

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* Reagents and conditions: 5.0 equiv. of Ph₃SnH, 0.05 equiv. of AIBN, toluene (0.01 mol dm⁻³); based on substrate, 110°C, 20 min; TBS = Me₃SiBu. † Isolated yield after column chromatography. ‡ Bistriphenylmethylsulfide V was also isolated in 78 and 75% yield, respectively.
The starting thioesters 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.

References


