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One-pot synthesis of carbohydrate thionolactones from 1-thiosugars

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ABSTRACT

A general and efficient one-pot method for the synthesis of carbohydrate thionolactones from the corresponding 1-thiosugar is described involving the formation of an intermediate glycosyl *S*-*tert*-butyl thiosulfinate in situ by treatment of a thiol with commercially available *tert*-butylsulfinyl chloride in toluene at room temperature, followed by thermolysis. The method can also be used to generate reactive thioaldehydes and thioketones directly from thiols, which can be trapped in situ with a suitable diene.

Non-stabilized thiocarbonyl compounds have been shown to be useful intermediates in total synthesis[1] and also serve as efficient dienophiles in Diels–Alder [4+2] cycloaddition reactions.[2] To date, synthetic access to thiocarbonyls has relied mainly on the treatment of the corresponding carbonyl compound with a thionation reagent, such as Lawesson's or Belleau's reagents.[3] Whilst these methods have shown broad utility for the preparation of simple thiocarbonyl compounds, the direct thionation of carbohydrate *O*-lactones gives unsatisfactorily low yields of carbohydrate thionolactones, a finding corroborated by Vasella[4] and others.[5]

As part of an ongoing synthetic programme, access was required to several carbohydrate thionolactones for a variety of purposes. Previous efforts at preparation of carbohydrate thionolactones by direct thionation had met with frustration, and attention had subsequently turned towards more practical methods, such as the thermolysis of *S*-methyl thiosulfinates which were made by oxidation of glycosyl methyl disulfides, as developed by Vasella and co-workers.[4a] This synthetic approach did indeed yield the desired thionolactone with a much-improved yield and in higher purity as compared with direct thionation of the *O*-lactone using Lawesson's reagent, but was hampered by the undesired formation of glycosyl *S*-methyl thiosulfonates, either by over-oxidation of the disulfide starting materials or by disproportionation of methyl thiosulfinates under the prevailing reaction conditions (typically at least ~15%).[6]

In order to circumvent these problems, the synthesis of thionolactones via the corresponding glycosyl *S*-phenyl thiosulfinates, which are relatively more stable, was developed.[7] The two-step procedure involved treatment of a 1-thiosugar,[8] for example, *manno* thiol **1**, with a sulfinylating reagent, such as phenylsulfinyl chloride or benzenesulfinyl piperidine (BSP).[9] Subsequent thermolysis of the isolated *S*-phenyl thiosulfinate **2** in refluxing anhydrous toluene (110 °C) gave the desired thionolactone **3** in generally good yield following filtration through Celite® and purification by flash chromatography (typically 50–75% over the two steps, Scheme 1).

Although this procedure worked well for most 1-thiosugar substrates, and represented an improvement on previous methods, problems associated with synthesis of the intermediate *S*-phenyl thiosulfinates became apparent. In particular, the formation of stable mixed phenyl and symmetrical glycosyl disulfides, presumably initiated by reaction of unreacted glycosyl thiols with the phenyl thiosulfinate products, necessitated additional and often tedious purification steps, thus lowering the overall yield of thionolactone. Lowering the temperature used for thiosulfinate formation did suppress disulfide formation, but meant that considerably longer reaction times were required (up to 8 h).

A more direct and efficient route to thionolactones was sought, the ultimate aim being the development of an efficient one-pot method for the direct conversion of 1-thio sugars to the corresponding thionolactone, which could perhaps also be more generally applied to access other thiocarbonyl compounds directly from thiols. Although it is well known that thiocarbonyl compounds can be generated by the *syn* elimination of thiosulfinates,[10] there are, to the best of our knowledge, no examples in the literature that describe the generation of thiocarbonyl compounds *directly* from thiols.

The approach developed for the one-pot conversion of 1-thiosugars to thionolactones involved the generation of *S*-*tert*-butyl

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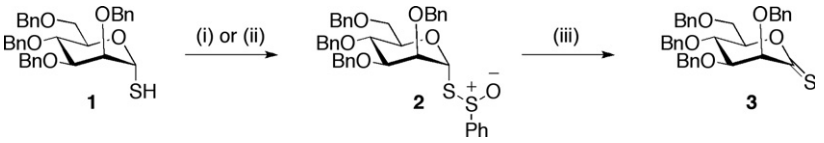


Scheme 1. Reagents and conditions: (i) PhS(O)Cl, pyridine, Et_2O, 0 °C, 80%; (ii) BSP, CF_3CO_2H, CH_2Cl_2, rt, 89%; (iii) 4 Å molecular sieves, toluene, 110 °C, 69%.

thiosulfinates[11] in situ using the commercially available *tert*-butylsulfinyl chloride, and then immediate thermolysis (Scheme 2). It was envisaged that these more sterically encumbered *S*-*tert*-butyl thiosulfinates would be less prone to the competing processes that had been observed in the phenyl series.

Initial screening of reaction conditions focussed on variation of the identity and stoichiometry of the added base, and the use of different heat sources for the thermolysis. Reaction of the D-*manno* 1-thiosugar **1** with excess *N*,*N*-diisopropyl diethylamine (DIPEA, 1.5 equiv) and *tert*-butylsulfinyl chloride (1.0 equiv) followed by conventional heating produced a somewhat complex mixture by t.l.c; the desired thionolactone **3** was isolated in only modest yield (42%), and in addition the unexpected D-*gluco* configured thionolactone **5** (10%) was also produced. Interestingly, a similar reaction that used microwave heating (300 W, 110 °C, 5 min) produced only the *gluco* product **5**, although in a modest yield (48%). The formation of the D-*gluco* configured thionolactone **5** from the α-D-mannosyl thiol **1**, which was the exclusive product in the case of microwave heating, undoubtedly occurs by base catalyzed epimerization of the thionolactone at the position α to the thiocarbonyl, to form the more thermodynamically stable equatorial *gluco* configured product.

However, the use of triethylamine (1.0 equiv) as the added base, together with a slight excess of *tert*-butylsulfinyl chloride (1.2 equiv), followed by conventional heating was found to produce the desired D-*manno* thionolactone **3** in an excellent 87% yield following purification by filtration and flash chromatography. With seemingly optimized reaction conditions in hand (Scheme 2),[12] attention was focused on the preparation of a panel of carbohydrate thionolactones,[13] as summarized in Table 1.

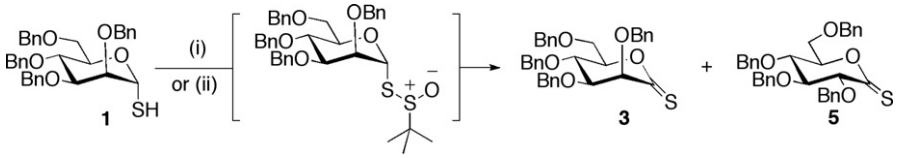
In the majority of cases examined, treatment of the 1-thiosugar with *tert*-butylsulfinyl chloride in the presence of triethylamine resulted in highly efficient conversion to the thiosulfinate intermediate after 10 min at room temperature, as observed by t.l.c and ESI-MS, with little or no disulfide formation detected. An exception was the D-galactosyl thiol **6** in which significant amounts of the symmetrical glycosyl disulfide were also detected by t.l.c. In this case the desired D-*galacto* thionolactone **7** was ultimately isolated in a more modest yield (55%). The reaction time required for complete thermolysis, which was usually in the order of 10 min, did vary slightly depending on the relative stabilities of the intermediate thiosulfinates. Thermolysis of D-glucosyl and D-galactosyl *S*-*tert*-butylthiosulfinates (Table, entries b and c, respectively) required longer reaction times (~20 min). Encouragingly, the previously described somewhat unstable D-*arabino* thionolactone **9**[3] and L-*rhamno* thionolactone **11**[7] were both isolated in excellent yields (62% and 84%, respectively), an illustration of the synthetic advantage of the one-pot method. The reaction of protected 1-thiosugars with different protecting group patterns was also investigated,[14] such as the 3-*O*-allyl protected D-glucosyl thiol **12** and the 4,6-*O*-benzylidine protected D-glucosyl **14** (Table, entries f and g). The corresponding thionolactones **13** and **15**, respectively, were readily prepared using the one-pot method, and were both isolated in good yields (82% and 74%,[15] respectively).

Table 1

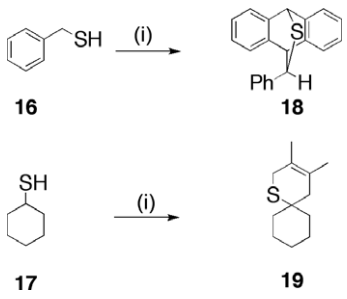
Entry	Thiol	Thionolactone	Yield (%)
a	**1**	**3**	87
b	**4** (α:β, 1:6)	**5**	85
c	**6**	**7**	55
d	**8** (α:β, 1:1)	**9**	62
e	**10**	**11**	84
f	**12** (α:β, 1:5)	**13**	82
g	**14**	**15**	74[a]

[a] Contaminated with ca. 20% di-*tert*-butylthiosulfinate by-product by ^1H NMR.

The final aspect of the study was to investigate the compatibility of the one-pot method towards non-carbohydrate thiols, in



Scheme 2. Reagents and conditions: (i) *tert*-butylsulfinyl chloride (1.0 equiv), DIPEA (1.5 equiv), 3 Å molecular sieves, toluene, rt; then heat to 110 °C, 3, 42%, 5, 10%; (ii) *tert*-butylsulfinyl chloride (1.2 equiv), Et_3N (1.0 equiv), 3 Å molecular sieves, toluene, rt; then heat to 110 °C, 3, 87%.



Scheme 3. Reagents and conditions: (i) *tert*-butylsulfinyl chloride (1.2 equiv), Et_3N (1.0 equiv), 3 Å molecular sieves, toluene, rt; then anthracene (10 equiv), heat to 110 °C, 65%; (ii) *tert*-butylsulfinyl chloride (1.2 equiv), Et_3N (1.0 equiv), 3 Å molecular sieves, toluene, rt; then 2,3-dimethyl-1,3-butadiene (10 equiv), heat to 110 °C, 43%.

order to expand its scope and synthetic utility. Treatment of benzyl mercaptan **16** and cyclohexyl mercaptan **17** with *tert*-butylsulfinyl chloride and triethylamine in toluene smoothly produced the respective *S*-*tert*-butyl thiosulfinates as monitored by t.l.c. Thermal elimination of thiosulfinates gave the respective thiocarbonyl compounds, which were trapped in situ with an added diene (10 equiv), to produce the isolated cycloadducts **18**[10] and **19**,[16] respectively (Scheme 3).

In conclusion, an efficient method for the synthesis of carbohydrate thionolactones has been developed, in which they may be accessed directly from the corresponding 1-thiosugars. This one-pot method represents an improvement on existing methods in terms of efficiency, product purity and overall yield. Furthermore, this chemistry has been demonstrated to allow access to thioketones and thioaldehydes directly from thiols, a transformation that, unlike the oxidation of alcohols to aldehydes and ketones, is far from trivial. The direct conversion of thiols to thiocarbonyl compounds may thus serve as a useful entry into the routine preparation of these synthetically useful compounds.

Acknowledgements

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References and notes

1. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263–6276.
2. For a comprehensive review concerning the preparation and reactivity of thiocarbonyl compounds, see: Molina, M. T.; Yáñez, M.; Mó, O.; Notario, R.; Abboud, J.-L. M. In *The Chemistry of Double-bonded functional groupsFunctional Groups*; Patai, S., Ed.; John Wiley and Sons Ltd, 1997; pp 1355–1496.
3. For a report on the use of Belleau's reagent see: Barrett, A. G. M.; Lee, A. C. *J. Org. Chem.* **1992**, *57*, 2818–2824.
4. (a) Hürzeler, M.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 995–1012; (b) Hürzeler, M.; Bernet, B.; Mäder, T.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 1779–1801; (c) Bernet, B.; Mäder, T.; Vasella, A. *Helv. Chim. Acta* **1997**, *80*, 1260–1278.
5. (a) Belhadj, T.; Goekjian, P. G. *Tetrahedron Lett.* **2005**, *46*, 8117–8120; (b) Hagan, J. P. *J. Org. Chem.* **1993**, *58*, 506–508.
6. Thiosulfonate side-products may be produced either by direct over-oxidation of the thiosulfinate or more probably by thiosulfinate disproportionation under the reaction conditions. See: Kice, J. L.; Cleveland, J. P. *J. Am. Chem. Soc.* **1974**, *95*, 109–112.
7. Chayajarus, K.; Fairbanks, A. J. *Tetrahedron Lett.* **2006**, *47*, 3517–3520.
8. Thiols were made by treatment of the corresponding glycosyl xanthate with sodium methoxide. Xanthates were themselves made directly from the hemiacetal, following the method of Vasella (see Ref. 4a). For a summary of alternative synthetic routes to 1-thio sugars see: Horton, D.; Wander, J. D. In *The Carbohydrates*; Pigman, W. W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. IB, pp 799–842.
9. Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.
10. (a) Baldwin, J. E.; Lopez, R. C. G. *Tetrahedron* **1982**, *39*, 1487–1493; (b) Aslam, M.; Block, E. *Tetrahedron Lett.* **1985**, *26*, 2259–2262.
11. The use of commercially available trichloromethanesulfinyl chloride in order to form trichloromethanethiosulfinates in situ was also investigated, but significant amounts of by-products were detected by t.l.c and ESI-MS and the resulting thiosulfinates proved surprisingly stable towards thermolysis.
12. *Typical experimental procedure:* to a stirring suspension of thiol (0.05 M) and activated 3 Å molecular sieves (~100 mg) in dry toluene were added triethylamine (1.0 equiv) and *tert*-butylsulfinyl chloride (1.2 equiv) at room temperature. The mixture was stirred at room temperature for 10 min, at which time t.l.c (typically petroleum spirit 40–60 °C-ethyl acetate; 5:1) indicated reaction completion. For Table entries a–g, the mixture was then heated to gentle reflux (110 °C) for 10 min. The mixture was then cooled to room temperature and filtered through Celite®, eluting with toluene. The filtrate was then concentrated in vacuo at 20 °C and the resulting crude oil purified immediately by flash silica chromatography to afford the thionolactone. For thiosulfinates derived from thiols **16** and **17**, excess diene (10 equiv) was added to the mixture prior to heating, and the reaction mixture was stirred at reflux (110 °C) for 1 h. After this time t.l.c. indicated reaction completion. The filtrate was evaporated in vacuo and the resulting oil purified by flash silica chromatography to afford the cycloadducts.
13. All new compounds exhibited spectral data consistent with their structures. *Selected data:* **13** a yellow oil: $[\alpha]_D^{20}$ +82 (*c* 1.0 $CHCl_3$); ν_{max} (KBr disc) 3087, 3063, 3030, 2907, 2867, 1094, 1496, 1454, 1367, 1177, 1094, 738, 698 cm^{-1}; δ_H (500 MHz, C_6D_6) 3.67–3.71 (2H, m, H-6, $OCHH'C{=}CH_2$), 3.75 (1H, dd, $J_{6'\text{-}6} = 11.4$ Hz, $J_{6'\text{-}5} = 1.9$ Hz, H-6′), 3.86 (1H, ddt, $J_{gem} = 12.9$ Hz, $J_{vic} = 5.4$ Hz, $J = 1.6$ Hz, $OCHH'C{=}CH_2$), 3.99 (1H, dd, $J_{3\text{-}4} = 4.4$ Hz, $J_{3\text{-}2} = 2.2$ Hz, H-3), 4.13 (1H, dd, $J_{4\text{-}5} = 10.1$ Hz, $J_{4\text{-}3} = 4.4$ Hz, H-4), 4.40, 4.49 (2H, ABq, $J_{AB} = 12.3$ Hz, CH_2Ph), 4.55, 4.72 (2H, ABq, $J_{AB} = 11.7$ Hz, CH_2Ph), 4.65, 4.84 (2H, ABq, $J_{AB} = 12.0$ Hz,) 4.77 (1H, d, $J_{2\text{-}3} = 2.2$ Hz, H-2), 5.03 (1H, dq, $J_Z = 10.4$ Hz, $J = 1.6$ Hz, $CH{=}CH_EH_Z$), 5.10–5.14 (2H, m, H-5, $CH{=}CH_EH_Z$), 5.73 (1H, ddt, $CH{=}CH_2$), 7.16–7.39 (15H, m, Ar-H); δ_C (125 MHz, C_6D_6) 68.1 (C-6), 70.7 ($OCH_2C{=}CH_2$), 71.7 (CH_2Ph), 73.1 (CH_2Ph), 73.6 (CH_2Ph), 77.4 (C-4), 80.8 (C-5), 81.9 (C-3), 83.6 (C-2), 117.3 ($CH{=}CH_2$), 127.5, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 128.6, 128.7, (Ar CH), 134.3, 137.5, 138.4, 138.5 (Ar C, $CH{=}CH$), 215.1 (C═S); *m/z* (ES^+) 522.2 ($M{+}NH_4^+$, 100%); HRMS calcd for $C_{30}H_{32}NaO_5S$ (MNa^+) 527.1863, found 527.1858. Compound **15** a yellow oil: $[\alpha]_D^{20}$ +42 (*c* 1.0 $CHCl_3$); ν_{max} (KBr disc) 3091, 3044, 2912, 2867, 1497, 1455, 1367, 1302, 1267, 1209, 1181, 1109, 1014, 750, 698, 642 cm^{-1}; δ_H (500 MHz, C_6D_6) 3.45(1H, t, $J_{4\text{-}3} = 10.4$ Hz, H-6), 3.85 (1H, dd, $J_{4\text{-}3} = 10.1$ Hz, $J_{4\text{-}5} = 6.6$ Hz, H-4), 4.13–4.15 (1H, m, H-3), 4.20 (1H, dd, $J_{6'\text{-}6} = 10.4$ Hz, $J_{6'\text{-}5} = 5.4$ Hz, H-6′), 4.43 (2H, s, CH_2Ph), 4.55, 4.75 (2H, AB q, $J_{AB} = 12.0$ Hz, CH_2Ph), 4.85 (1H, br s, H-2), 4.91–4.96 (1H, m, H-5), 5.20 (1H, s, PhC*H*), 7.17–7.59 (15H, m, Ar-H); δ_C (125 MHz, C_6D_6) 68.1 (C-6), 69.6 (C-5), 71.6 ($PhCH_2$), 71.9, ($PhCH_2$), 80.8 (C-3), 81.1 (C-4), 85.8 (C-2), 101.7 (PhCH), 126.5, 126.6, 126.7, 127.5, 127.9, 128.0, 128.1, 128.3, 128.3, 128.4, 128.5, 128.6, 128.7, 128.7, 129.3, (Ar CH), 137.1, 137.5, 137.8 (Ar C), 213.9 (C═S); *m/z* (ES^+) 480.2 ($M{+}NH_4^+$, 100%); HRMS calcd for $C_{27}H_{26}NaO_5S$ (MNa^+) 485.1393, found 485.1387.
14. Thionolactones bearing ester protection of the hydroxyl groups undergo ready β-elimination processes as demonstrated by Vasella. See Ref. 4a.
15. One caveat to the use of this method is that di-*tert*-butyl thiosulfinate is produced as the stable thermolysis by-product, and in this case it was found to contaminate the thionolactone product **15**.
16. Degl'Innocenti, A.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A.; Cerreta, F. *Tetrahedron Lett.* **1993**, *34*, 873–876.