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Efficient synthesis of carbohydrate thionolactones

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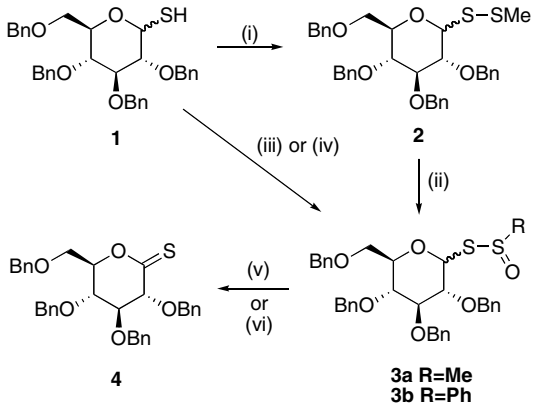
Abstract—Carbohydrate thionolactones may be efficiently synthesized from the corresponding 1-thio sugars via a two-step procedure involving formation of a glycosyl phenylthiosulfinate by treatment with either phenylsulfinyl chloride or 1-(phenylsulfinyl)piperidine (BSP), and subsequent thermal elimination in toluene.

Thiocarbonyl compounds are most commonly accessed by treatment of the corresponding carbonyl compound with Lawesson's reagent.[1] Although there are a few reports of the conversion of carbohydrate lactones to the corresponding carbohydrate thionolactones under these[2] or similar reaction conditions,[3] Vasella[4] concluded some time ago that the process was generally unreliable, and gave unsatisfactorily low yields. The findings of Vasella have been subsequently corroborated by other research groups.[5]

As part of an ongoing synthetic program, access was required to several carbohydrate thionolactones for a variety of purposes. Initial attempts at thionation of a variety of carbohydrate lactones with either Lawesson's or Belleau's reagents met with frustration, in line with the experiences of Vasella, and others (yields typically ~20%). Attention therefore turned to an approach developed by Vasella[4] and co-workers as a solution to this synthetic problem. Herein, formation of a glycosyl disulfide is achieved by treatment of a 1-thio sugar[6] with dimethyl(methylthio)sulfonium tetrafluoroborate. Regioselective oxidation of this glycosyl disulfide mediated by MCPBA produces a methyl glycosyl thiosulfinate, which then undergoes thermal elimination[7] to produce the corresponding thionolactone. This basic approach was tested with the *gluco* 1-thio sugar **1** using dimethyl(methylthio)sulfonium triflate (DMTST)[8] to access disulfide **2** (Scheme 1). The reaction sequence



Scheme 1. Reagents and conditions: (i) DMTST, pyridine, CH_2Cl_2, rt, 90%; (ii) MCPBA, CH_2Cl_2, 0 °C, 82%; (iii) MeSOCl, pyridine, Et_2O, 0 °C, 91%; (iv) PhSOCl, pyridine, Et_2O, 0 °C, 82%; (v) 120 °C, ~8 mbar, 49% from **3a**, 67% from **3b**; (vi) 4 Å molecular sieves, toluene, 120 °C, 63% from **3a**, 85% from **3b**.

did indeed yield the desired thionolactone with a much-improved yield and in higher purity as compared to the Lawesson's reagent approach. However, it was found in particular that the selective oxidation reaction of disulfide **2** could be somewhat troublesome and some methyl thiosulfonate product was inevitably produced[9] (typically at least ~15%) in addition to the desired methyl thiosulfinates such as **3a**.

Hoping to optimize the process it was reasoned that intermediate thiosulfinates such as **3a** could in fact be accessed directly from 1-thio sugars, such as **1**, by treatment with a sulfinyl chloride. Sulfinyl chlorides can be prepared in situ by treatment of the corresponding disulfide

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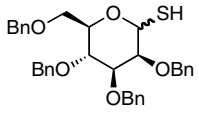
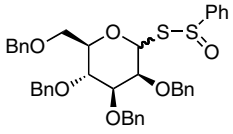
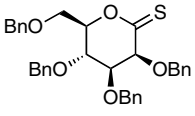
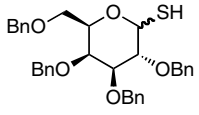
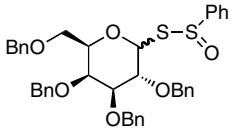
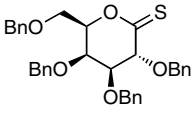
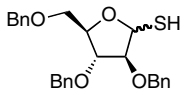
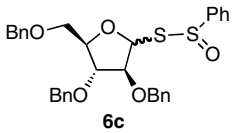
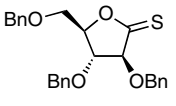
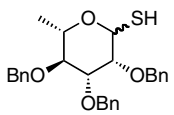
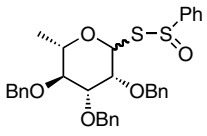
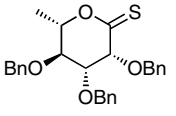
with sulfuryl chloride and acetic anhydride.[10] Indeed treatment of **1** with methyl sulfinyl chloride, prepared in situ from dimethyl disulfide, did produce the required methylthiosulfinate **3a** smoothly in an excellent 91% yield. In his original letter, Vasella[4] reported that thermal elimination of methyl glycosyl thiosulfinates was achieved most efficiently by heating under reduced pressure in the absence of solvent. In our hands, this solvent-free procedure always resulted in appreciable amounts of decomposition, and a correspondingly reduced product yield (e.g., 49% yield of **4** from **3a**). An alternative procedure consisting of heating the thiosulfinate in toluene in the presence of 4 Å molecular sieves was investigated. This procedure proved to be the method of choice; heating methylthiosulfinate **3a** to 120 °C in toluene in the presence of 4 Å molecular sieves for 15 min resulted in transformation to the corresponding thionolactone **4** in an improved, although still modest, 63% yield.

Previous experiences of the chemistry of the corresponding thiosulfonate[11] derivatives had pointed out the advantages of using aryl rather than alkyl substituted intermediates, both in terms of product yield and intermediate stability. Attention was therefore turned to the synthesis and use of the corresponding glycosyl phenylthiosulfinates in order to develop an improved synthetic procedure. Treatment of 1-thio sugar **1** with phenyl sulfinyl chloride, prepared in situ by reaction of diphenyldisulfide with sulfuryl chloride and acetic anhydride, smoothly produced the required phenyl thiosulfinate **3b** (82% yield).[12] Thermal elimination of **3b** was then performed by again heating in toluene at 120 °C in the presence of 4 Å molecular sieves for 15 min, and resulted in the formation of the thionolactone **4** in a substantially improved 85% yield, with little or no decomposition (Scheme 1).

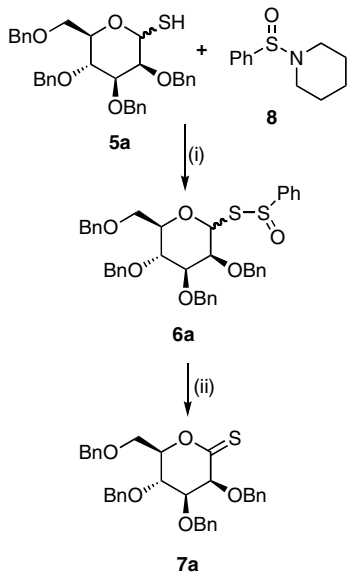
With seemingly optimal conditions in hand, the two-step procedure of formation of the glycosyl phenylthiosulfinate and thermal elimination was applied to a variety of 1-thio sugars (Table 1). In all cases, the starting thiols **5a**–**d** were smoothly converted into the desired phenyl thiosulfinates **6a**–**d**.[13] Thermal elimination[14] to produce thionolactones **7a**–**d**[15] also occurred smoothly and generally in high yields, though in the *rhamno* case some lactone side product was formed alongside the desired thionolactone **7d**, resulting in a somewhat reduced yield.

Recently, it was reasoned that perhaps the intermediate glycosyl thiosulfinates may in fact be more conveniently synthesized directly from the corresponding thiols by treatment with 1-(phenylsulfinyl)piperidine **8**, commonly referred to as BSP (benzenesulfinyl piperidine), a commercially available and shelf-stable reagent introduced recently by Crich[16] and co-workers for the activation of thioglycosides. Pleasingly treatment of the *manno* thiol **5a** with BSP **8** produced the corresponding phenyl thiosulfinate **6a** smoothly in an excellent 89% yield; thio-

Table 1.

Entry	Thiol	Phenyl thiosulfinate	Thionolactone
a	 **5a**	 **6a** 80%	 **7a** 69%
b	 **5b**	 **6b** 87%	 **7b** 86%
c	 **5c**	 **6c** 78%	 **7c** 84%
d	 **5d**	 **6d** 76%	 **7d** 61%[a]

[a] Lactone was also produced (~20% yield) in addition to the desired thionolactone.



Scheme 2. Reagents and conditions: (i) CF_3CO_2H, CH_2Cl_2, rt, 89%; (ii) 4 Å molecular sieves, toluene, 120 °C, 69%.

sulfinate **6a** once again underwent thermal elimination to give the desired thiolactone **7a** (Scheme 2).

It can be concluded that treatment of 1-thio sugars with either phenylsulfinyl chloride, or BSP, and subsequent thermal elimination of the so-formed glycosyl phenyl thiosulfinates by heating in toluene in the presence of molecular sieves provides efficient and generally high yielding access to carbohydrate thionolactones. It is noteworthy that this two-step procedure effectively equates to the oxidation of a thiol to a thioketone, a synthetic transformation which it is not particularly straightforward to achieve. Investigations into the oxidation of thiols to thioketones in this manner, together with the use of carbohydrate thionolactones for the synthesis of a range of oligosaccharides and spiro-*C*/*O*-glycoside-containing natural products are currently under investigation, and the results will be reported in due course.

Acknowledgements

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References and notes

1. See, for example: Scheibye, S.; Shabana, R.; Lawesson, S.-O.; Romming, C. *Tetrahedron* **1982**, *38*, 993–1001, and references cited therein.
2. Kahne, D.; Yang, D.; Jin Lim, J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716–8717.
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. Hürzeler, M.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 995–1012.
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. For a summary of some 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.
7. (a) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3939–3944; (b) Baldwin, J. E.; Lopez, R. C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1029–1030; (c) Baldwin, J. E.; Lopez, R. C. G. *Tetrahedron* **1983**, *39*, 1487–1498.
8. Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9–C12.
9. Thiosulfonate side product 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.
10. Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067–4069.
11. For a demonstration of the greater merits of glycosyl phenylthiosulfonate reagents (PTS) over the corresponding methylthiosulfonate (MTS) derivatives see: Davis, B. G.; Fairbanks, A. J.; Gamblin, D. P.; Garnier, P.; Oldham, N. J.; Ward, S. J. *Org. Biomol. Chem.* **2003**, *1*, 3642–3644.
12. Some glycosyl phenyl disulfide (~12%) was also isolated from this reaction.
13. Typical experimental procedure: a solution of benzenesulfinyl chloride (2 equiv) in dry diethyl ether (10 ml) was added slowly to a stirred solution of the 1-thioglycopyranose (1 equiv, ~100 mg) and pyridine (1.5 equiv) in dry diethyl ether (5 ml) under an atmosphere of argon at room temperature. After 30 min, the mixture was diluted with diethyl ether, quenched by the addition of dilute 1 M aqueous H_2SO_4, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (typically petrol/ethyl acetate; 5:1 to 2:1) to give the glycosyl phenyl thiosulfinate, as a mixture of diastereomers.
14. Typical experimental procedure: a solution of glycosyl phenyl thiosulfinate (~100 mg) and 4 Å molecular sieves (~100 mg) were suspended in anhydrous toluene (1 ml), and the mixture was heated at 120 °C under an atmosphere of argon. After 15 min, TLC (typically petrol/ethyl acetate; 5:1) indicated complete reaction. The mixture was cooled to room temperature, filtered through Celite® and concentrated in vacuo. The residue was purified by flash column chromatography (typically petrol/ethyl acetate, 7:1) to yield the thiolactone.
15. All new compounds exhibited spectral data consistent with their structures. Selected data: **7b** a yellow oil: $[\alpha]_D^{20}$ +76 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, C_6D_6) 3.50 (1H, dd, $J_{3,4} = 2.5$ Hz, $J_{2,3} = 7.8$ Hz, H-3), 3.57–3.65 (2H, m, H-6, 6′), 3.87 (1H, dd, $J_{4,5} = 1.7$ Hz, $J_{3,4} = 2.5$ Hz, H-4), 4.08 (1H, td, $J_{4,5} = 1.7$ Hz, $J_{5,6} = 5.5$ Hz, H-5), 4.12 (1H, d, $J = 11.8$ Hz, C*H*′HPh), 4.20 (1H, d, $J = 11.8$ Hz, C*H*H′Ph), 4.25 (1H, d, $J = 12.0$ Hz, CH*H*′Ph), 4.41 (1H, d, $J = 11.8$ Hz, C*H*H′Ph), 4.47 (1H, d, $J = 11.3$ Hz, CH*H*′Ph), 4.61 (1H, d, $J = 8.1$ Hz, C*H*H′Ph), 4.62 (1H, d, $J = 10.8$ Hz, CH*H*′Ph), 4.81 (1H, d, $J = 11.6$ Hz, C*H*H′Ph), 5.24 (1H, d, $J = 10.8$ Hz, CH*H*′Ph), 7.06–7.22 (20H, m, Ar-H); δ_C (100.6 MHz, C_6D_6) 67.9 (C-6), 72.9 (C-4), 72.5, 73.5, 74.7, 75.0 (4 × *C*H_2Ph), 80.3 (C-3), 81.7 (C-5), 84.3 (C-2), 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 128.8, 138.2, 138.4, 138.5 (Ar-C), 217.9 (C=S); *m*/*z* (ES^+) 613 ($M + NH_4^+ + MeCN$, 100%); HRMS calcd for $C_{34}H_{34}O_5NaS$ (MNa^+) 577.2025, found 577.2020. **7d** a yellow oil; δ_H (400 MHz, C_6D_6)

1.27 (3H, d, $J_{5,6} = 6.3$ Hz Hz, CH_3), 3.57 (1H, dd, $J_{2,3} = 2.5$ Hz, $J_{3,4} = 8.0$ Hz, H-3), 3.92–4.02 (2H, m, H-4, 5), 4.13 (1H, d, $J = 11.6$ Hz, CHH'Ph), 4.26 (1H, d, $J_{2,3} = 3.0$ Hz, H-2), 4.35, 4.46 (2H, ABq, $J = 11.6$ Hz, CH_2Ph), 4.62 (1H, d, $J = 11.8$ Hz, CHH$'$Ph), 4.96 (1H, d, $J = 11.8$ Hz, CHH'Ph), 5.25 (1H, d, $J = 11.3$ Hz, CHH$'$Ph), 7.15–7.32 (15H, m, Ar-H); δ_C (62.9 MHz, C_6D_6) 19.0 (C-6), 72.0 (C-5), 73.0, 73.3, 78.2 ($3 \times CH_2$Ph), 78.3 (C-4), 82.4 (C-3), 83.4, (C-2), 128.2, 128.4, 128.5, 128.6, 137.7, 138.2, 138.5 (Ar-C), 216.3 (C=S); HRMS calcd for $C_{27}H_{28}O_4NaS$ (MNa^+) 471.1601, found 471.1600.

16. Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.