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Investigating thio-analogues of PSE acetals: a more complex reaction

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Abstract—The reaction of hydroxylated thiols with 1,2-bis-phenylsulfonylethylene was investigated: in contrast with diols, a more complex reaction was observed and application to carbohydrate-derived PSE oxathianes was envisaged.

We have recently developed a novel type of ethylidene acetals bearing a phenylsulfonyl appendage (PSE acetals), which can find use as effective protective groups in polyols and carbohydrate chemistry[1] or as handy precursors to ethenyl ethers.[2] Extension of our previous study to the elaboration of PSE thioacetals appeared profitable in several aspects:

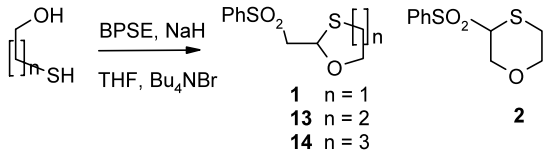
– compare with acid-stable PSE acetals in terms of behavior towards deprotection conditions
– acyl carbanion equivalence[3]
– introduce a stereogenic center—the newly-formed acetalic carbon—potentially exploitable in asymmetric synthesis[4]
– introduce a prochiral system, with a sulfur atom to be potentially tri-coordinated through oxidation

In connexion with our previous investigations,[2,5] the basic 1,3-oxathiolane model was first selected and our standard reaction conditions (NaH+nBu$_4$NBr in THF at rt) thus applied to a 1:1 mixture of 2-mercaptoethanol and (*Z*)-1,2-bis-phenylsulfonylethylene (BPSE). Besides the expected 2-phenylsulfonylmethyl-1,3-oxathiolane (**1**),[6] obtained in 50–75% yield according to trials, a side-product was formed (3–10% yield), to which the unusual structure of 3-phenylsulfonyl-1,4-oxathiane (**2**) [7] was attributed (Scheme 1).

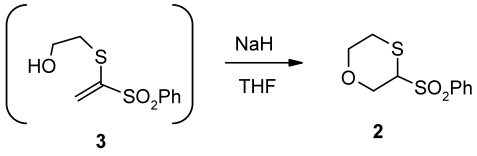
Ring-expanding rearrangements of 1,3-oxathiolanes are documented[8] but they normally require induction by strong electrophilic agents such as sulfuryl chloride;[9] it was therefore not likely that **1** could rearrange into **2** under basic conditions. Such flimsy hypothesis was finally ruled out by submitting again oxathiolane **1** to the basic conditions of its formation: no trace of oxathiane **2** could be detected after prolonged reaction time.

More realistic would be to envisage the formation of **2** through a base-induced ring-closing process involving the putative vinyl sulfone precursor 1-(2-hydroxyethylthio)-1-phenylsulfonylethylene **3**, whose intermediacy had in turn to be made clear (Scheme 2).

With a view to better putting into light the diverse steps of the process, the reaction conditions were modified (NEt_3 in THF at rt) so as to favor the chemoselective



Scheme 1.



Scheme 2.

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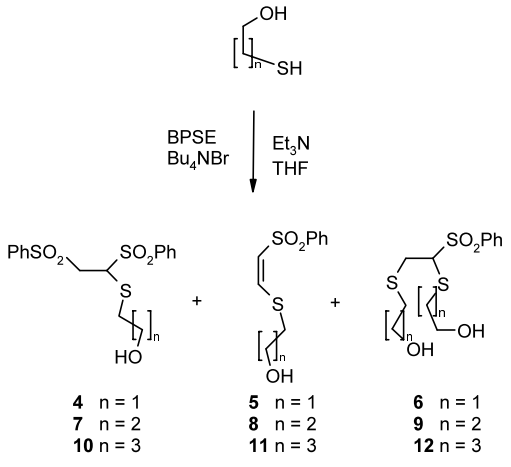
addition of the thiol group of 2-mercaptoethanol onto the electrophilic partner.

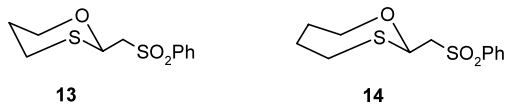
Applying the above conditions, three products could be isolated from the reaction in 4, 53 and 26% yield, respectively: first, the primary 1:1 adduct 1-(2-hydroxyethylthio)-1,2-bis-phenylsulfonylethane **4**,[10] then (*Z*)-vinyl sulfone **5Z**[11] resulting from base-induced phenylsulfinate elimination in **4**, and finally a more polar compound which was identified as a 2:1 adduct-1,2-bis-(2-hydroxyethylthio)-1-phenylsulfonylethane **6**,[12] derived from chimeric transient **3** (Scheme 3).

The reaction was repeated using (*E*)-BPSE instead of the above *Z*-stereomer,[13] to similarly afford a 50% yield of the (*E*)-vinyl sulfone **5E**,[14,15] together with 36% of **6**. When submitting either **5Z** or **5E** vinyl sulfone to harsher basic conditions (NaH in THF) in order to induce internal Michael addition, only moderate yields (ca. 60%) of 1,3-oxathiolane **1** were attained.

Extension to the case of 3-mercaptopropanol and 4-mercaptobutanol revealed a similar behavior in the NEt_3-catalyzed reaction with (*Z*)-BPSE: primary 1:1 adducts **7** and **10** (11 and 8% yield, respectively), (*Z*)-vinyl sulfones **8Z** and **11Z** (53 and 59% yield, respectively) and 2:1 adducts **9** and **12** (20 and 17% yield, respectively) were formed. Applying the above cyclization conditions to **8Z** resulted in a 68% yield of 1,3-oxathiane **13**,[16] whereas **11Z** was not converted into 1,3-oxathiepane **14** (Scheme 4). A similar behavior was observed when using the NaH-catalyzed one step procedure which furnished **13** in 90% yield while **14** was produced in ca. only 10% yield.

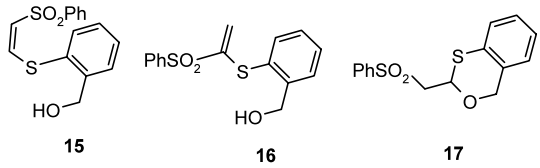


Scheme 3.



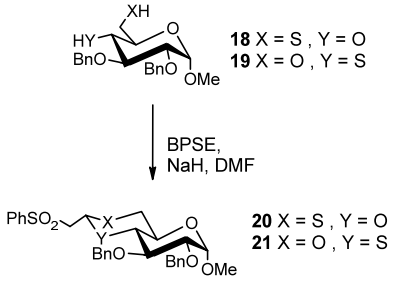
Scheme 4.

Finally, *o*-hydroxymethyl thiophenol—a conformationally more rigid system—was reacted with (*Z*)-BPSE under NEt_3 catalysis to produce (61% yield)[17] the major (*Z*)-vinyl sulfone **15Z**[18] together with its minor (10% yield) regioisomer **16**[19]—which is structurally closely related to the transient sulfone **3** hypothesized above. When applied to *o*-hydroxymethyl thiophenol in contrast, the NaH-catalyzed cycloacetalation only afforded 33% yield of 2-phenylsulfonylmethyl-4*H*-3,1-benzoxathiin **17**[20] (Scheme 5).



Scheme 5.

The above results reveal that extending our BPSE methodology to the elaboration of diverse thioacetal analogues can involve a more complex reaction sequence: from a synthetic viewpoint, the 1,3-oxathiane case unambiguously proved to be the most favorable. As inspired by De Lucchi's pioneering work in the isobornane series[21]—and besides developing in the lab the chiral precursor **13** as a matrix for stereoselection tools—we also considered to investigate the elaboration of enantiopure substrates by implanting of PSE 1,3-oxathianes on chiral templates such as saccharidic compounds. With this aim in view, the regioisomeric D-glucopyranosidic thiols **18** and **19** were synthesized (Scheme 6).



Scheme 6.

Applying the NaH-catalyzed one step procedure previously used for 3-mercaptopropanol, both the expected isomeric PSE 1,3-oxathianes **20** and **21** could be obtained in 72 and 83% yield, respectively. The synthesis and evaluation of carbohydrate-derived PSE thioacetals in stereocontrolled reactions is under current development in our group.

Acknowledgements

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4. Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189–8190.
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6. Fully satisfactory spectroscopic data (MS, 250 MHz ^{1}H NMR and 62.5 MHz ^{13}C NMR) were obtained for all new compounds; selected NMR ($CDCl_3$) data for 1,3-oxathiolane **1**: δ 7.91 (bd, 2H, *ortho*-H-Ar), 7.52–7.72 (m, 3H, H-Ar), 5.48 (dd, 1H, $J_{vic}=5.6$ and 3.9 Hz, H-2), 4.18 (m, 1H, H-5a), 3.80 (m, 1H, H-5b), 3.68 (dd, 1H, $J_{gem}=14.4$ Hz, H-6a), 3.47 (dd, 1H, H-6b), 2.99 (m, 2H, H-4); 139.8 (C_{IV}-Ar), 134.4 (*para*-CH-Ar), 129.6 (*meta*-CH-Ar), 128.6 (*ortho*-CH-Ar), 79.6 (C-2), 72.0 (C-5), 62.4 (C-6), 33.3 (C-4); MS (Ionspray®): $[M+H]^+=245.0$.
7. Selected NMR data for 1,4-oxathiane **2**: δ 7.99 (bd, 2H, *ortho*-H-Ar), 7.52–7.73 (m, 3H, H-Ar), 4.78 (dd, 1H, $J_{gem}=13.1$, $J_{2a,3}=1.8$ Hz, H-2a), 4.11 (ddd, 1H, $J_{gem}=12.0$ Hz, $J_{vic}=2.9$ Hz, H-6a), 3.99 (dd, 1H, $J_{gem}=13.1$, $J_{2b,3}=3.3$ Hz, H-2b), 3.71 (ddd, 1H, $J_{gem}=12.0$ Hz, $J_{vic}=2.4$ Hz and 10.0 Hz, H-6b), 3.61 (bs, 1H, H-3), 3.09 (ddd, 1H, $J_{gem}=13.5$ Hz, $J_{vic}=3.6$ Hz and 10.0 Hz, H-5a), 2.15 (bd, 1H, $J_{gem}=13.5$ Hz, H-5b); 137.5 (C_{IV}-Ar), 134.4 (*para*-CH-Ar), 129.9 (*meta*-CH-Ar), 129.1 (*ortho*-CH-Ar), 67.9 (C-6), 66.2 (C-2), 59.0 (C-3), 23.6 (C-5); MS (Ionspray®): $[M+Na]^+=267.0$.
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10. Selected NMR data for 1:1 adduct **4**: δ 7.85–7.95 (m, 4H, *ortho*-H-Ar), 7.50–7.75 (m, 6H, H-Ar), 4.60 (dd, 1H, $J_{vic}=11.2$ and 2.0 Hz, H-1), 3.88 (dd, 1H, $J_{gem}=14.4$ Hz, $J_{vic}=11.2$ Hz, H-2a), 3.80 (bs, 2H, CH_2O), 3.40 (dd, 1H, $J_{gem}=14.4$, $J_{vic}=2.0$ Hz, H-2b), 3.07 (bs, 1H, OH), 2.77 (dd, 2H, CH_2S); 139.1 (C_{IV}-Ar), 134.9, 134.6 (*para*-CH-Ar), 130.0, 129.7 (*meta*-CH-Ar), 128.1 (*ortho*-CH-Ar), 62.4 (C-1), 60.9 (CH_2O), 55.1 (C-2), 36.9 (CH_2S); MS (Ionspray®): $[M+Na]^+=409.0$.
11. Selected NMR data for vinyl sulfone **5Z**: δ 7.99 (bd, 2H, *ortho*-H-Ar), 7.50–7.65 (m, 3H, H-Ar), 7.16 (d, 1H, $J_{vic}=10.5$ Hz, H-2), 6.25 (d, 1H, $J_{vic}=10.5$ Hz, H-1), 3.84 (bt, 2H, $J_{vic}=5.9$ Hz, CH_2O), 2.95 (bt, 2H, $J_{vic}=5.9$ Hz, CH_2S); 147.1 (C-2), 141.3 (C_{IV}-Ar), 133.6 (*para*-CH-Ar), 129.3 (*meta*-CH-Ar), 127.3 (*ortho*-CH-Ar), 123.2 (C-1), 62.1 (CH_2O), 38.9 (CH_2S); MS (Ionspray®): $[M+Na]^+=267.0$.
12. Selected NMR data for 2:1 adduct **6**: δ 7.96 (bd, 2H, *ortho*-H-Ar), 7.70 (m, 1H, *para*-H-Ar), 7.59 (m, 2H, *meta*-H-Ar), 4.34 (dd, 1H, $J_{vic}=11.5$ and 2.9 Hz, H-1), 3.76 (bd, 4H, CH_2O), 3.54 (bs, OH), 3.30 (bdd, 2H, $J_{gem}=13.9$ Hz, $J_{vic}=2.9$ Hz, H-2a, OH), 2.77 (m, 4H, CH_2S), 2.60 (dd, 1H, $J_{gem}=13.9$ Hz, $J_{vic}=11.5$ Hz, H-2b); 135.8 (C_{IV}-Ar), 134.5 (*para*-CH-Ar), 129.9 (*meta*-CH-Ar), 129.2 (*ortho*-CH-Ar), 70.2 (C-1), 61.4 and 61.0 (CH_2O), 36.6 and 36.4 (CH_2S), 32.6 (C-2); MS (Ionspray®): $[M+Na]^+=345.0$.
13. BPSE is commercially available in both *Z*- and *E*-stereoforms.
14. Retention of configuration in Michael additions on BPSE was initially reported by Meek and Fowler. See: Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 985–991.
15. Selected NMR data for vinyl sulfone **5E**: δ 7.85 (bd, 2H, *ortho*-H-Ar), 7.50–7.65 (m, 3H, H-Ar), 7.76 (d, 1H, $J_{vic}=14.7$ Hz, H-2), 6.27 (d, 1H, $J_{vic}=14.7$ Hz, H-1), 3.82 (bt 2H, $J_{vic}=6.1$ Hz, CH_2O), 2.98 (bt, 2H, $J_{vic}=6.1$ Hz, CH_2S); 146.0 (C-2), 140.0 (C_{IV}-Ar), 133.3 (*para*-CH-Ar), 129.4 (*meta*-CH-Ar), 127.3 (*ortho*-CH-Ar), 122.0 (C-1), 60.5 (CH_2O), 35.2 (CH_2S); MS (Ionspray®): $[M+Na]^+=267.0$.
16. Selected NMR data for 1,3-oxathiane **13**: δ 7.90 (bd, 2H, *ortho*-H-Ar), 7.52–7.65 (m, 3H, H-Ar), 5.27 (dd, 1H, $J=9.1$ and 2.4 Hz, H-2), 3.96 (bd, 1H, $J_{gem}=12.5$ Hz, H-6a), 3.61 (dd, 1H, $J_{gem}=14.7$ Hz, $J_{vic}=9.3$ Hz, H-7a), 3.53 (ddd, 1H, $J_{gem}=12.5$ Hz, H-6b), 3.28 (dd, 1H, $J_{gem}=14.7$ Hz, $J_{vic}=2.4$ Hz, H-7b), 3.07 (ddd, 1H, $J_{gem}=13.5$ Hz, H-4a), 2.74 (bd, 1H, $J_{gem}=13.5$ Hz, H-4b), 1.82 (m, 1H, H-5a), 1.63 (bd, 1H, $J_{gem}=13.9$ Hz, H-5b); 140.0 (C_{IV}-Ar), 133.8 (*para*-CH-Ar), 129.0 (*meta*-CH-Ar), 128.0 (*ortho*-CH-Ar), 76.6 (C-2), 69.6 (C-6), 61.2 (C-7), 28.2 (C-4), 24.8 (C-5); MS (Ionspray®): $[M+Na]^+=281.0$.
17. (*E*)-BPSE analogously afforded a 54% yield of **15E**.
18. Selected NMR data for vinyl sulfone **15Z**: δ 7.99 (bd, 2H, *ortho*-H-Ar), 7.11 (d, 1H, $J_{vic}=10.3$ Hz, H-2), 6.26 (d, 1H, $J_{vic}=10.3$ Hz, H-1), 4.73 (s, 2H, CH_2O), 3.28 (bs, 1H, OH); 147.2 (C-2), 142.7, 141.1 (C_{IV}-Ar), 123.1 (C-1), 63.1 (CH_2O); MS (Ionspray®): $[M+Na]^+=329.0$.
19. Selected NMR data for vinyl sulfone **16**: δ 7.95 (bd, 2H, *ortho*-H-Ar), 6.58 (d, 1H, $J_{gem}=2.0$ Hz) and 5.54 (d, 1H, $J_{gem}=2.0$ Hz, C$=$CH_2), 4.53 (s, 2H, CH_2O), 2.25 (bs, 1H, OH); 148.8 (C-1), 143.8, 140.9, 138.7 (C_{IV}-Ar), 125.8 (C-2), 62.9 (CH_2O); MS (Ionspray®): $[M+Na]^+=329.0$.
20. Selected NMR data for 4*H*-3,1-benzoxathiin **17**: δ 7.95 (bd, 2H, *ortho*-PhSO$_2$), 7.50–7.70 (m, 3H, PhSO$_2$), 7.20–7.00 (m, 4H, H-Ar), 5.63 (dd, 1H, $J_{vic}=2.8$ Hz and 9.0 Hz, H-2), 4.73 (AB system, 2H, $J_{gem}=15.0$ Hz, CH_2O), 3.78 (dd, 1H, $J_{gem}=14.7$ Hz, $J_{vic}=8.8$ Hz, CH$_2$SO$_2$), 3.44 (dd, 1H, $J_{gem}=14.7$ Hz, $J_{vic}=2.8$ Hz, CH$_2$SO$_2$); 139.9 (C_{IV}-PhSO$_2$), 134.1 (*para*-CH-PhSO$_2$), 130.4, 129.3, 128.3, 127.7, 127.6, 126.0 and 125.4 (CH-Ar), 75.2 (C-2), 69.2 (C-4), 61.1 (CH_2SO_2); MS (Ionspray®): $[M+Na]^+=329.0$.
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