1-Benzenesulfinyl Piperidine (BSP)/Triflic Anhydride: An Effective Combination for the Hydrolysis of Dithioacetals

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Dedicated with respect to the memory of Prof. R. A. Lemieux.

Abstract: The combination of 1-benzenesulfinyl piperidine and triflic anhydride, in conjunction with an aqueous workup, hydrolyses a broad range of dithioacetals to the corresponding carbonyl compounds under very mild, non-oxidative conditions.

Key words: acetals, aldehydes, hydrolyses, ketones, protecting groups

Dithioacetals are some of the most robust protecting groups for aldehydes and ketones, whether introduced directly onto the pre-existing function,[1] or indirectly as part of an umpolung[2] or linch-pin strategy[3,4] in a key step of a synthetic route.[5] The very robust nature of dithioacetals that renders them effective protecting groups, however, is a contributing factor in their being some of the more difficult ones to remove. As is to be expected under such circumstances, a considerable range of methods for the hydrolysis of dithioacetals is in common usage,[1,5] but there still exists ample scope for improved, and especially milder and metal-free reagents and conditions. We now describe how the combination of 1-benzenesulfinyl piperidine (**BSP**)[6] and triflic anhydride, developed in this laboratory for the rapid, low temperature activation of thioglycosides,[7] provides an effective means of dithioacetal activation and hydrolysis.

A brief survey of reaction conditions revealed that addition of triflic anhydride to a mixture of 2-(1-naphthyl)-1,3-dithiane and **BSP** (Figure 1) in dichloromethane at –60 °C, followed after 10 min by aqueous THF and then gradual warming to room temperature resulted in the clean hydrolysis to the corresponding aldehyde. A number of hydrolyses were conducted by this general protocol with the results illustrated in Table 1, from which it will be noted that the protocol is suitable for dithianes, dithiolanes, acyclic dithioacetals, and oxathiolanes derived from both aldehydes and ketones. The only variation in the standard protocol involves, in the case of acid sensitive substrates, the inclusion of the mild, hindered base 2,4,6-tri-*tert*-butylpyrimidine (**TTBP**, Figure 1)[6,8] to buffer the triflic acid released.

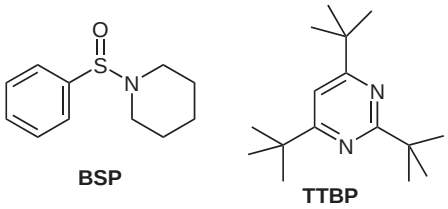

Figure 1

By way of reaction mechanism, we anticipate that the sulfonium ion formed on triflation of the sulfonamide oxygen in **BSP** is the active species responsible for initial electrophilic attack on the thioacetal function similar to the manner in which it activates thioglycosides.[7]

In conclusion an extremely mild, efficient protocol has been derived for the hydrolysis of dithioacetals. Given that the protocol is closely related to the BSP/Tf_2O method for the activation and coupling of thioglycosides,[7] wherein considerable functional group compatibility has already been demonstrated,[7,9–11] it is expected that the new method will be suitable for use in target molecule synthesis.

Experimental Protocol The substrate and **BSP** (1 equiv) were dissolved in CH_2Cl_2 to give a solution of approximately 0.03 M in substrate which was then cooled under Ar with stirring to –60 °C. Tf_2O (1.1 equiv) was then added dropwise over a period of 1 min. After stirring for 20 min at –60 °C, a 1:1 mixture of THF and water (10 equiv H_2O) was added and stirring continued for 20 min before the reaction mixture was allowed to warm to room temperature. Saturated aqueous $NaHCO_3$ was then added, followed by extraction with CH_2Cl_2. The combined extracts were washed with 1 M NaOH and brine, then dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the crude reaction mixture on silica gel then afforded the pure products. In the case of acid sensitive substrates and/or products the reaction mixture is buffered by the inclusion of **TTBP** (2 equiv) to the mixture of **BSP** and/or substrate.

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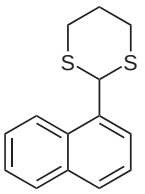
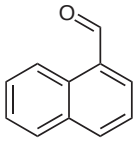
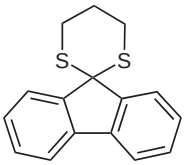
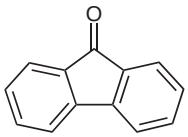
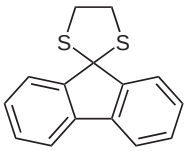
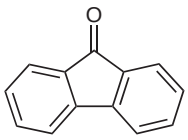
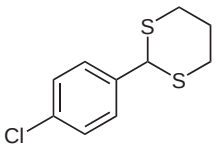
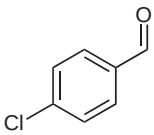
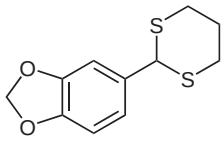
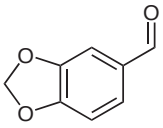
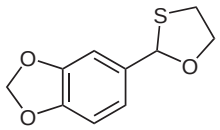
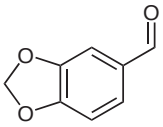
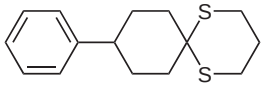
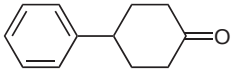
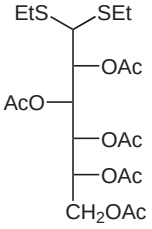
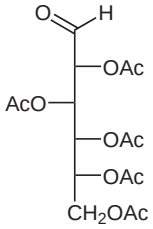
Table 1 Hydrolysis of Dithiols and Thioacetals by BSP/Tf_2O[a,b]

Substrate	Product	Yield (%)
		83
		91
		90
		88
		84
		76
		81
		78

[a] All substrates and products were known compounds whose physical and spectral data corresponded with the literature.
[b] TTBP was added to entries 5, 6 and 8.

References

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**.
(2) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 639.
(3) Smith, A. B.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925.
(4) Smith, A. B.; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001.
(5) Bulman Page, C.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643.
(6) Commercially available from www.Lakeviewsynthesis.com.
(7) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.
(8) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.
(9) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867.
(10) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640.
(11) Crich, D.; de la Mora, M. A.; Cruz, R. *Tetrahedron* **2002**, *58*, 35.