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S-(4-Methoxyphenyl) Benzenethiosulfinate (MPBT)/Trifluoromethanesulfonic Anhydride: A Convenient System for the Generation of Glycosyl Triflates from Thioglycosides

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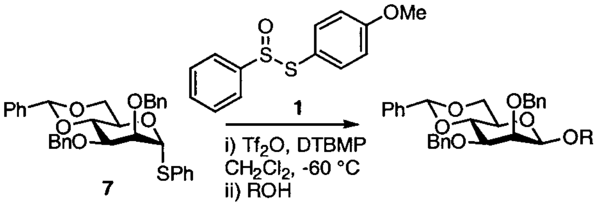
ABSTRACT



The combination of *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT, 1) and trifluoromethanesulfonic anhydride forms a powerful, metal-free, thiophile which readily activates thioglycosides, via glycosyl triflates, at −60 °C in dichloromethane, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine. The glycosyl triflates are rapidly and cleanly converted to glycosides, upon treatment with alcohols, in good yield and selectivity.

Benzenesulfenyl triflate (PhOTf) is a superior reagent for the activation of thioglycosides, converting them to highly reactive glycosyl triflates in a matter of minutes at −78 °C.[1,2] It has also proven to be the reagent of choice in the activation of glycosyl xanthates in coupling reactions, activating them rapidly at −40 °C.[3] In terms of reactivity, therefore, benzenesulfenyl triflate is clearly preferable to other common metal-free systems for the activation of thioglycosides such as dimethyl(methylthio)sulfonium triflate (DMTST),[4] methylsulfenyl triflate (MeSOTf),[5] benzeneselenyl triflate (PhSeOTf),[6] and iodonium dicollidine perchlorate (IDCP)[7] which are typically used at significantly higher temperatures and require much longer reaction times. Nevertheless, this potent electrophile has not been widely adopted in glycosylation chemistry. Most likely, the need to prepare benzenesulfenyl triflate in situ from benzenesulfenyl chloride and silver triflate, neither of which are ideal reagents, is in large part responsible for its lack of appreciation in all but a few laboratories. Indeed, benzenesulfenyl chloride itself is not commercially available owing to its limited shelf life and obnoxious odor, whereas silver triflate is light- and water-sensitive as well as expensive. Consequently we have been searching for a more convenient preparation of benzenesulfenyl triflate (or its equivalent) with a view to making this reagent more readily available and to facilitating ongoing projects in our own laboratory.

We report here that the combination of *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT, **1**) and trifluoromethane-

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[1] Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436.
[2] Crich, D.; Sun, S. *Tetrahedron.* **1998**, *54*, 8321−8348.
[3] Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706.
[4] Fugedi, P.; Garegg, P. J. *Carbohydrate Res.* **1986**, *149*, C9−C12.
[5] Dasgupta, F.; Garegg, P. J. *Carbohydrate Res.* **1988**, *177*, C13−C17.
[6] Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061−1064.
[7] Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275−278.

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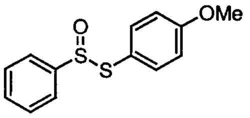
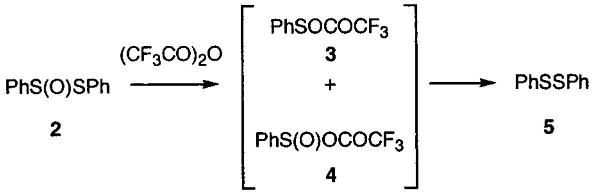
sulfonic anhydride fulfills most of our criteria. MPBT (**1**) is readily prepared, crystalline, and stable, while trifluoromethanesulfonic anhydride is a common commercial reagent. The system is metal-free and converts thioglycosides to glycosyl triflates very conveniently in a matter of minutes at −60 °C.



1 MPBT

Our investigation of the thiosulfinates was based on earlier work from the Oae group in which it was established that thiosulfinate **2** reacts with trifluoroacetic anhydride at −20 °C to give a complex mixture of products. The mixture was thought to contain the sulfenyl carboxylate **3** and sulfinyl carboxylate **4** and resulted, ultimately, in the formation of diphenyl disulfide **5** (Scheme 1).[8]

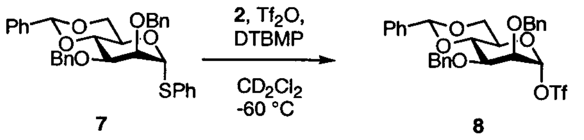
Scheme 1



We reasoned that the more reactive Tf_2O would react rapidly with **2** at lower temperatures and provide two molecules of benzenesulfenyl triflate cleanly. To investigate this proposal, we prepared the thiosulfinates **1**, **2**, and **6** according to a standard literature procedure involving reaction of the sulfinyl chloride with the appropriate thiol, followed by recrystallization.[9,10] It is noteworthy that **1**, **2**, and **6** are all crystalline, odorless, and stable on the laboratory bench at room temperature when stored in standard amber bottles.

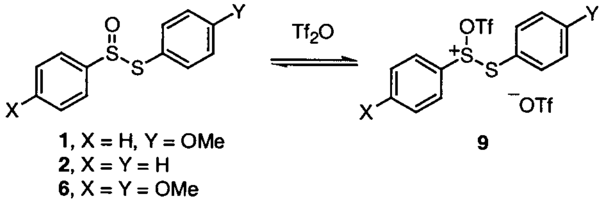
In an exploratory NMR tube experiment, a solution of the thiosulfinate **2** in CD_2Cl_2, cooled to −78 °C, was treated with Tf_2O. The tube was rapidly inserted into the precooled (−78 °C) probe of the spectrometer and the ^1H and ^{19}F NMR spectra were recorded. To our surprise, the ^{19}F spectrum displayed only two peaks, corresponding to Tf_2O and the formation of a species indistinguishable from TfO^- (at δ 4.26 and δ −3.07, respectively). The low-temperature ^1H NMR spectrum of the same reaction mixture showed that not all the thiosulfinate **2** had been consumed. Nevertheless, in a further low-temperature NMR experiment, the thioglycoside **7** was shown to be converted to the corresponding glycosyl triflate **8** (Scheme 2).[11]

Scheme 2



This series of observations led us to the conclusion that the reaction of the thiosulfinate **2** with Tf_2O at low temperature is an equilibrium (Scheme 3) and perhaps stops after the initial sulfonylation. This equilibrium may then be displaced in the forward direction by the addition of a trap for the thiophile, i.e., a thioglycoside.

Scheme 3



Attempts to shift this equilibrium by substituting this reagent led to the realization that optimum results were obtained with **1**, with **6** having comparable reactivity. At the present time it is not clear whether the actual electrophile generated is benzenesulfenyl triflate or a species such as **9**. What is clear, however, is that a readily available, metal-free, preparation of a potent thiophile from two stable reagents is at hand.

To demonstrate the synthetic potential of these systems, a series of couplings were carried out with the most reactive system, namely, **1** and Tf_2O. The results of these experiments are presented in Table 1. As can be seen the β:α ratio observed was comparable to those obtained by both the sulfoxide and the thioglycoside methods.[1,2,12] The greater reactivity of MPBT (**1**) over the thiosulfinate **2** can clearly be seen from the reaction of the thiomannoside **7** with the acceptor **14**, whereby only 30% of the starting thiomannoside **7** was converted to the desired β-mannoside when the

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[8] Morishita, T.; Furukawa, N.; Oae, S. *Tetrahedron*. **1981**, *37*, 3115−3120.

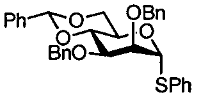
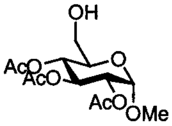
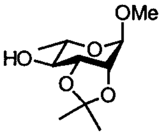
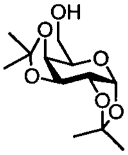
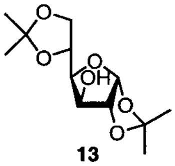
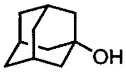
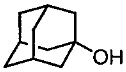
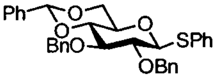
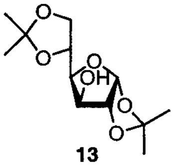
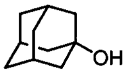
[9] Backer, H. J.; Kloosterziel, H. *Recl. Trav. Chim. Pays Bas*. **1954**, *73*, 129−139.

[10] **Preparation of *S*-(4-Methoxyphenyl) benzenethiosulfinate (MPBT, 1):** Sulfuryl chloride (2.75 mL, 34.35 mmol) was slowly added to a mixture of diphenyl disulfide (2.50 g, 11.45 mmol) and acetic anhydride (2.16 mL, 22.9 mmol) cooled to 0 °C. After 20 min of stirring, the orange solution was concentrated under reduced pressure. The residue (PhSOCl) was diluted with Et_2O (25 mL) and slowly added to a solution containing 4-methoxybenzenethiol (2.80 mL, 22.9 mmol) and pyridine (2.04 mL, 25.2 mmol) in Et_2O (25 mL) at room temperature under an argon atmosphere. After 20 min of stirring, the mixture was quenched by the addition of 1 M H_2SO_4 (40 mL). The organics were separated, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Crystallisation from ether−petroleum ether (bp 40−60 °C) gave the title product (4.36 g, 72%) as a pale yellow solid: mp 76−77 °C, lit.[9] mp 77−78 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (3 H, s, OMe), 6.87 (2 H, d, $J = 9$ Hz, 2 × ArH), 7.40 (2 H, d, $J = 9$ Hz, 2 × ArH), 7.45−7.48 (3 H, m, 3 × ArH), and 7.60−7.63 (2 H, m, 2 × ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 114.9, 119.6, 124.4, 129.0, 131.5 144.2, and 161.9.

[11] The α-mannosyl triflate **7** can be readily identified by the appearance of a broad singlet at δ 6.20 attributed to the anomeric proton in the ^1H NMR spectrum and from a signal at δ 0.01 in the ^{19}F NMR spectrum.[2]

[12] Crich, D.; Cai, W. *J. Org. Chem*. **1999**, *64*, 4926−4930.

Table 1. Coupling Reactions of Thioglycosides

entry	donor	acceptor	thiosulfinate	product (% yield)[a]	β:α ratio[b]
1	 **7**	 **10**	**1**	76	>10:1
2	**7**	 **11**	**1**	80	>10:1
3	**7**	 **12**	**1**	70	~5:1
4	**7**	 **13**	**1**	75	>10:1
5	**7**	 **14**	**1**	79	>10:1
6	**7**	 **14**	**2**	30% conversion[c]	>10:1
7	 **15**	 **13**	**1**	76	1:>10
8	**15**	 **14**	**1**	84	1:>10

[a] Isolated yield. [b] Ratio determined from the integrals in the crude ^{1}H NMR spectra. [c] Determined from the integrals in the crude ^{1}H NMR spectrum.

reaction was performed in the presence of the thiosulfinate **2** (entries 5 and 6).[13]

In summary, treatment of MPBT (**1**) with Tf_2O furnishes an electrophile comparable in activity to PhSOTf, though attempts to identify the electrophile have so far proved unsuccessful. The combination of MPBT (**1**) with Tf_2O is a new and powerful method for the in situ formation of glycosyl triflates from thioglycosides. Moreover, this method has allowed access to *β*-mannosides and α-glucosides in good yield and selectivity. MPBT (**1**) is crystalline and stable and can be readily prepared in good yield from inexpensive starting materials.

Acknowledgment. We thank NIGMS for support of this work (GM-57335).

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[13] **General experimental protocol for the preparation of glycosides:** To a stirred solution containing the thioglycoside (0.185 mmol), MPBT (**1**, 0.231 mmol), DTBMP (0.462 mmol), and activated 3 Å powdered sieves in dichloromethane (5 mL) at −60 °C under argon is added Tf_2O (0.370 mmol). After 5 min, a solution of the glycosyl acceptor (0.370 mmol) in dichloromethane (2 mL) is added. The reaction mixture is stirred for 2 min at −60 °C and then quenched with methanol, warmed to room temperature, filtered, washed with saturated aqueous $NaHCO_3$, followed by brine, dried ($MgSO_4$), and concentrated under reduced pressure. The glycosides are isolated by chromatography on silica gel.