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Ph_2SO/Tf_2O: a Powerful Promotor System in Chemoselective Glycosylations Using Thioglycosides

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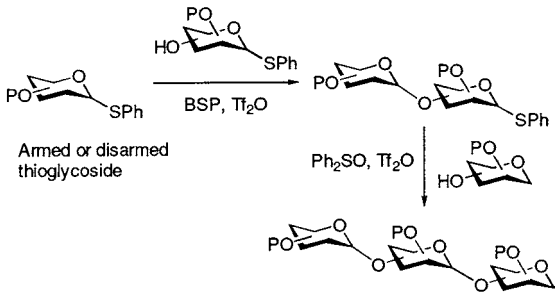
ABSTRACT



Diphenylsulfoxide in combination with triflic anhydride provides a very potent thiophilic glycosylation promotor system, capable of activating disarmed thioglycosides. The usefulness of this novel thiophilic activator is illustrated in a successful chemoselective glycosylation sequence in which the donor thioglycoside in the first condensation step may be either armed or disarmed.

Oligosaccharides and glycoconjugates, carbohydrate-based biomolecules with broad structural diversity, play a crucial role in a multitude of important biological processes.[1] Despite the recent advances in oligosaccharide synthesis,[2] there still is a demand for efficient and stereoselective glycosylation procedures. Thioglycosides have been shown to be attractive building blocks for the construction of oligosaccharides.[2d,e] Thus, the anomeric thiogroup may not only function as a protecting group but also as a leaving group in the formation of interglycosidic linkages. In addition, the glycosylating properties of thioglycosides can be tuned by varying the nucleophilicity of the anomeric sulfur atom[3] as well as the electron-withdrawing and -donating effects inherent to the protecting groups in the donor glycoside.[4] The difference in reactivity of thioglycosides can be exploited elegantly in a chemoselective glycosylation, in which a reactive ("armed")

[†] Both authors contributed equally to this work.

(1) *Carbohydrates in Chemistry and Biology*; Ernst B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vols. 1−4.

(2) (a) *Carbohydrates in Chemistry and Biology*; Ernst B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, Chapters 2−9. (b) Jung, K.-H.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423−4442. (c) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160. (d) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179−205. (e) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121. (f) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123. (g) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. (h) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

(3) (a) Sliedregt, L. A. J. M.; Zegelaar-Jaarsveld, K.; Van der Marel, G. A.; Van Boom, J. H. *Synlett* **1993**, 335−337. (b) Boons, G. J.; Geurtsen, R.; Holmes, D. *Tetrahedron Lett.* **1995**, 6325−6328.

(4) Reactivities of glycosyl donors can be tuned. For thioglycosides, see: (a) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65. (b) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (c) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1274−1277. (d) Mong, K.-K. T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4087−4090. Pentenyl glycosides: (e) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (f) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070. (g) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C. *Synlett* **1992**, 927−942. (h) Ley, S. V.; Priepke, H. W. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2292−2294. Fluorides: (i) Baeschlin, D. K.; Green, L. G.; Hahn, M. G.; Hinzen, B.; Ince, S. J.; Ley, S. V. *Tetrahedron: Asymmetry* **2000**, 173−197.

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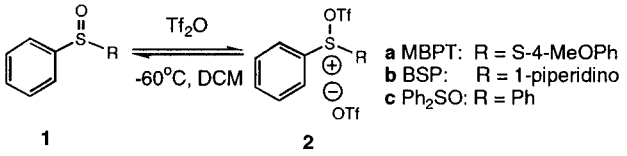
thiodonor is selectively activated with a mild thiophilic promotor and condensed with a relatively unreactive ("disarmed") thioglycoside.[5] The resulting thio disaccharide can then be activated by a more potent promotor in the next glycosidic coupling step, thus obviating the need for elaborate protecting group manipulations at the oligosaccharide stage. With the easy availability of a large variety of thioglycosidic building blocks, progress in oligosaccharide synthesis employing thioglycosides is highly dependent on the development of new thiophilic promotor systems. Thus far, relatively few efficient activation systems for disarmed thioglycosidic donors have been reported.[6]

Recently, a breakthrough in the development of novel thiophilic promotor systems was reported by Crich et al.,[6a] who showed that reaction of *S*-(4-methoxyphenyl)benzenethiosulfinate (MBPT, **1a**, Scheme 1) and trifluoromethanesulfonic anhydride (Tf_2O) results in sulfonium species **2a**, which was capable of promoting the notoriously difficult formation of a β-mannosidic linkage in excellent yield and stereoselectivity. The latter activation procedure could be improved by using the easily accessible 1-benzenesulfinyl piperidine (BSP, **1b**)/Tf_2O system, which, in contrast to **1a**/Tf_2O, can also be used for the activation of disarmed thioglycosides.[6b,7]

Scheme 1. Activated Sulfonium Species **2a**−**c**, Generated by Reaction of **1a**−**c** with Triflic Anhydride



As part of a program aimed at the development of efficient synthetic strategies toward biologically important oligosaccharides,[8] we investigated the applicability of **1a**/**b** in combination with Tf_2O as promotors in the stereoselective construction of β-mannosamine linkages. We observed that activating agent **2a** failed to effectuate the condensation of *S*-phenyl-2-azido-3-*O*-benzyl-4,6-di-*O*-benzylidene thiomannoside (**3a**, Figure 1) with a variety of acceptors.[9] We could circumvent this limitation by replacing the thiophenyl function in **3a** by the more nucleophilic thio(*p*-methoxyphenyl) group in **3b**. MBPT/Tf_2O (**2a**)-mediated condensations of thiomannoside **3b** led to the isolation of a variety of disaccharides in high yield and stereoselectivity.[9] In the course of these studies, we also explored the application of the more potent thiophilic promotor system BSP/Tf_2O (**2b**) in the condensation reactions of phenylthioglycosides. To our surprise, this promotor system also proved to be unable to activate mannosazide **3a**.[10] Even more intriguing, the use of other disarmed donors such as glucosazide **4** and rhamnosides **5a**/**b** also did not result in productive BSP/Tf_2O (**2b**)-mediated glycosylations.

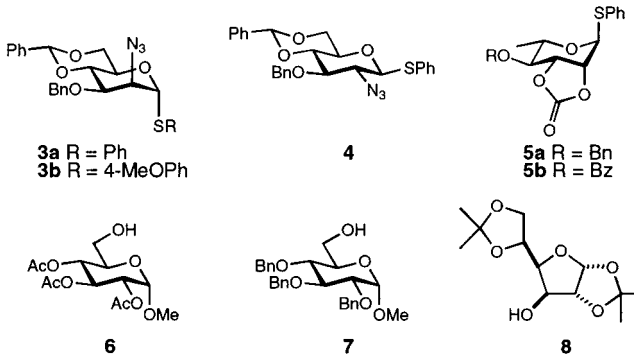


Figure 1. Glycosyl donors (**3**−**5**) and acceptors (**6**−**8**) employed in the Ph_2SO/Tf_2O mediated couplings.

Gin et al. recently reported an innovative dehydrative glycosylation strategy,[11] based on the powerful electrophile diphenylsulfide bis(trifluoromethanesulfonate) (**2c**), generated in situ from diphenyl sulfoxide (**1c**) and Tf_2O. It occurred to us that **2c**, which lacks the nitrogen lone pair stabilization of **2b**, would be a stronger electrophile capable of activating not only anomeric hydroxyl groups but also the weakly nucleophilic thiofunction present in disarmed thioglycosides.

The Ph_2SO/Tf_2O (**2c**) promotor system was evaluated using the above-mentioned disarmed donor phenyl thioglycosides **3a**, **4**, and **5a**/**b** and acceptors **6**−**8** (Figure 1). Indeed phenyl thiomannoside **3a** was readily activated with diphenylsulfide bis(triflate) at low temperatures (−60 °C) and condensed with acceptors **6**−**8** to give disaccharides **9**−**11**, respectively, in excellent yields (Table 1, entries 1−3). Condensations of **3a** with the relatively unreactive acetylated glucoside **6** as well as its more reactive benzylated congener **7** both occurred with comparable β-selectivity. The more stereocongested acceptor **8** was condensed with **3a** in equal efficiency, but with a lower stereoselectivity, as compared to **6** and **7**. Interestingly, smooth activation and glycosidation

(5) (a) Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455−458. (b) Zhu, T.; Boons, G.-J. *Org. Lett.* **2001**, *3*, 4201−4203. (c) Fridman, M.; Solomon, D.; Yogev, S.; Baasov, T. *Org. Lett.* **2002**, *4*, 281−283. (d) Veeneman, G. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275−278. See also ref 4b−d.

(6) (a) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067−4069. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020. (c) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 5175−5178. (d) Ercegovic, T.; Meijer, A.; Magnusson, G.; Ellervik, U. *Org. Lett.* **2001**, *3*, 913−915.

(7) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867−8869.

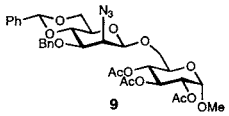
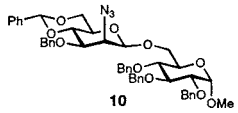
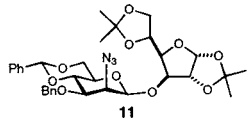
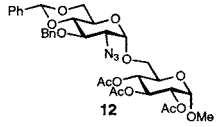
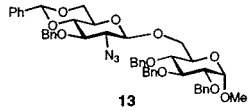
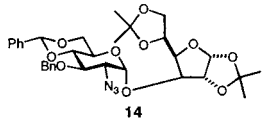
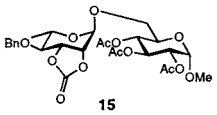
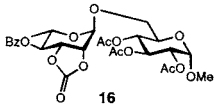
(8) (a) Codée, J. D. C.; Van der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. H. *Eur. J. Org. Chem.* **2002**, 3954−3965. (b) Kamst, E.; Zegelaar-Jaarsveld, K.; Van der Marel, G. A.; Van Boom, J. H.; Lugtenberg, B. J. J.; Spaink, H. P. *Carbohydr. Res.* **1999**, *321*, 176−189. (c) Duynstee, H.; De Koning, M. C.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 4129−4132. (d) Timmers, C. M.; Wighert, S. C. M.; Leeuwenburgh, M. A.; Van der Marel, G. A.; Van boom, J. H. *Eur. J. Org. Chem.* **1998**, *1*, 91−97.

(9) Litjens, R. E. J. N.; Leeuwenburgh, M. A.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8693−8696.

(10) BSP/Tf_2O-mediated glycosylations of the more nucleophilic **3b** proceeded uneventfully and with yields and α/β ratios comparable to those of the MBPT/Tf_2O system.

(11) (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279. (c) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414−417.

Table 1. Results of Ph_2SO/Tf_2O-Mediated Glycosylations

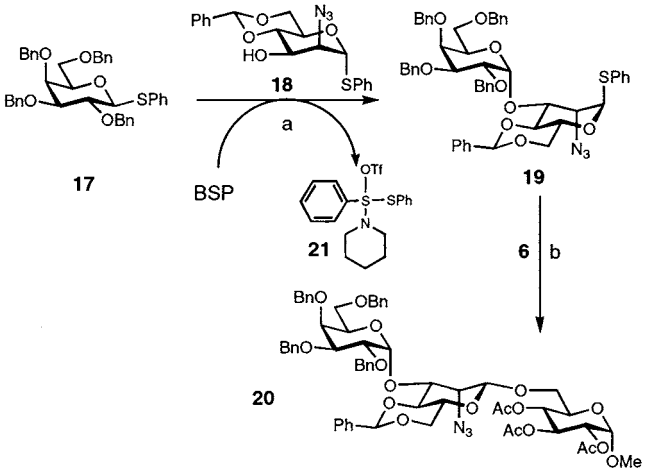
entry	donor+ acceptor	product	yield (%) (α:β)
1	**3a + 6**	 **9**	93 (1:4)
2	**3a + 7**	 **10**	88 (1:4)[a]
3	**3a + 8**	 **11**	91 (1:2)
4	**4 + 6**	 **12**	85 (4:1)
5	**4 + 7**	 **13**	91 (1:5)[a]
6	**4 + 8**	 **14**	80 (3:1)
7	**5a + 6**	 **15**	92 (8:1)
8	**5b + 6**	 **16**	85 (4:1)

[a] Anomeric ratio determined from an anomeric mixture by ^1H NMR analysis.

also occurred readily in the glucosazide series (entries 4−6). However, a striking difference in stereochemistry of the newly introduced glycosidic bond in disaccharides **12**/**14** and **13** was observed. Thus, condensation of glucosazide **4** and glucoside **6** or **8** gave the α-linked disaccharides (i.e., **12** and **14** in entry 4 and 6, respectively) predominantly, while condensation of donor **4** and acceptor **7** proceeded with a high degree of *β*-selectivity (**13**, entry 5).[12] These results agree with the finding that the nature of the protecting groups in the acceptor can have a profound effect on the stereochemical outcome of a glycosylation.[13] The Ph_2SO/Tf_2O-promoted coupling of rhamnosides **5a** and **5b** with **6** (entries 7, 8) proceeded in high yield and expected α-selectivity.[14]

As the next research objective, we employed the thus established difference in reactivity between the BSP/Tf_2O and Ph_2SO/Tf_2O reagents in the development of a novel chemoselective oligosaccharide synthesis strategy. As a first example, the construction of trisaccharide **20** was undertaken (Scheme 2). The armed thiogalactose donor **17** was activated

Scheme 2. Chemoselective Glycosylation[a]



[a] Key: (a) BSP, Tf_2O, TTBP, DCM, $(EtO)_3P$ quench, 73%; (b) Ph_2SO, Tf_2O, TTBP, DCM, 64%.

by BSP/Tf_2O and condensed with disarmed thiomannosazide **18**. Unfortunately, although we initially observed the formation of the expected condensation product, deterioration of dimer **19** occurred. Apparently, the transiently formed *S*-thiophenyl species **21**[15] activates the dimer thioglycoside **19** resulting in hydrolysis during aqueous workup. On the basis of this assumption, we reasoned that the timely addition of a suitable reagent capable of quenching **21** would lead to more effective glycosylation. Indeed, addition of triethyl phosphite[16] prior to the aqueous workup led to the isolation of the desired α-linked disaccharide **19** in 74% yield. Activation of **19** by Ph_2SO/Tf_2O and condensation with glucose acceptor **6** proceeded uneventfully, and with excellent stereoselectivity, to provide trisaccharide **20** in 64% yield.

The potency of the Ph_2SO/Tf_2O activator system was next demonstrated in the assembly of trisaccharide **25** (Scheme 3). Activation of disarmed galactose **22** with BSP/Tf_2O

(12) This unprecedented *β*-selectivity can be explained by the rapid direct S_N2-like displacement of the intermediate α-triflate, which has also been observed when MeOH was used as acceptor: Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930.

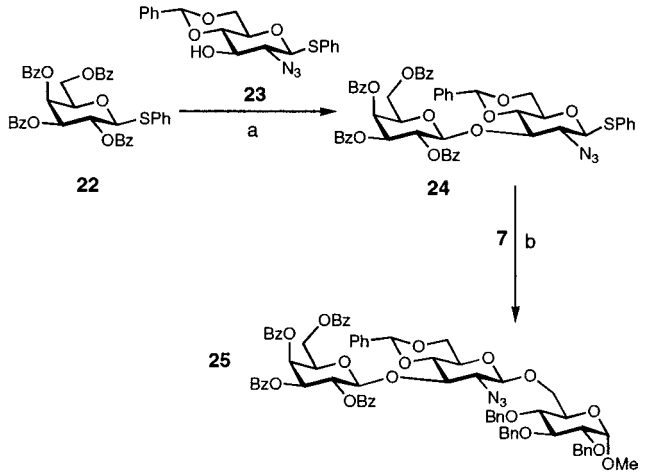
(13) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−224. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.

(14) In contrast to **5a**/**b**, phenyl 2,3-*O*-carbonyl-4-*O*-(*tert*-butyldimethylsilyl)-1-thio-α-L-rhamnopyranoside could be activated by the BSP/Tf_2O system, suggesting that the silyl protecting group has an arming effect on the thioglycoside: Crich, D.; Li, H. *J. Org. Chem.* **2001**, *67*, 4640−4646.

(15) Tentative triflate species **21** was independently generated by treatment of **1b** with 1.0 equiv of thiophenol. Addition of phenyl thioglycosides (e.g., mannosazide **3a**) to this reaction mixture led at higher temperatures (~0 °C) to decomposition of the donor glycosides.

(16) Sliedregt, L. A. J. M.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015−4018.

Scheme 3. Chemoselective Glycosylation[a]



[a] Key: (a) BSP, Tf_2O, TTBP, DCM, $(EtO)_3P$ quench, 64%; (b) Ph_2SO, Tf_2O, TTBP, DCM, 61%.

followed by treatment with thioglycoside **23** and quenching with $(EtO)_3P$ afforded dimer **24** in an efficient chemoselective glycosylation process. Subsequent Ph_2SO/Tf_2O-mediated activation of **24** and condensation with methylglucoside **7** furnished the β-linked trimer **23** (61%).

In conclusion, we have demonstrated Ph_2SO/Tf_2O to be a powerful thiophilic promotor system capable of activating disarmed thioglycosides. In exploiting the difference in reactivity of the BSP/Tf_2O and Ph_2SO/Tf_2O activating agents, we have developed a novel chemoselective condensation sequence in which both armed and disarmed thiodonors can be chemoselectively condensed in the first glycosylation step. Research is currently underway to evaluate the scope and limitations of both reagents in chemoselective condensations using different thiodonors (for instance, *p*-methoxyphenyl and phenyl thioglycosides) and 1-hydroxyl glycosyl donors.

Acknowledgment. We thank the Council for Chemical Sciences of the Netherlands Organization for Scientific Research (CW-NWO), the Netherlands Technology Foundation (STW), and Organon N.V. for financial support.

Supporting Information Available: General coupling procedures and characterizations of **9**−**16**, **19**, **20**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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