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Bromodimethylsulfonium Bromide-Silver Triflate: A New Powerful Promoter System for the Activation of Thioglycosides

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Dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Bromodimethylsulfonium bromide (BDMS) in combination with silver triflate provides a very efficient thiophilic promoter system, capable of activating both "disarmed" and "armed" thioglycosides for glycosidic bond formation. The usefulness of this new promoter is illustrated by a successful reactivity-based one-pot oligosaccharide assembly.

Keywords: bromodimethylsulfonium bromide (BDMS); glycosylation; oligosaccharides; promoter; thioglycosides

Understanding the role of carbohydrates in biology is highly dependent on the development of new chemical glycosylation techniques to provide rapid, straightforward access to synthetic glycoconjugates.[1] Although methodology for glycosidic coupling continues to pose challenges for synthetic chemists and the synthesis of defined oligosaccharide sequences remains a problem requiring great skill and experimental versatility, major advances have been achieved by introducing a variety of different types of glycosyl donors and promoter systems for their activation.[2] Among the various glycosyl donors, thioglycosides are one of the most enduring and widely used donors due to their stability, accessibility, and compatibility.[3] The sulfur atom in a thioglycoside is a soft nucleophile, and is therefore able to react selectively with soft electrophiles.[4]

In the past years, many types of thiophilic promoters for the activation of thioglycosides have been developed, such as heavy metal cations [e.g., mercury(II) sulfate[5]], alkylating reagents [e.g., methyl trifluoromethanesulfonate (MeOTf)[6]], organosulfur compounds [e.g., dimethyl(thiomethyl)sulfonium trifluoromethanesulfonate (DMTST),[7] methylsulfenyl triflate (MeSOTf),[8] phenylsulfenyl triflate (PhSOTf),[9] diphenyl sulfoxide-triflic anhydride (Ph_2SO/Tf_2O),[10] benzenesulfinylpiperidine-triflic anhydride (BSP/Tf_2O),[11] *N*-(phenylthio)-ε-caprolactam-triflic anhydride,[12] benzenesulfinylmorpholine-triflic anhydride (BSM/Tf_2O),[13] dimethyl disulfide-triflic anhydride (Me_2S_2/Tf_2O)[14]], organoselenium compounds [e.g., benzeneselenyl triflate (PhSeOTf)],[15] and halogens [e.g., *N*-iodosuccinimide-triflic acid (NIS/TfOH),[16] *N*-bromosuccinimide (NBS),[17] iodonium dicollidine perchlorate (IDCP),[18] Ipy_2BF_4[19]]. Although these promoters are convenient for the assembly of oligosaccharides, some drawbacks and limitations have been encountered during glycosylation processes including accessibility,[13] stability, solubility, by-products,[11] purification,[20] and reagent handling issues. New, more convenient and powerful promoters for the activation of thioglycosides, especially for the low-reactivity thioglycoside donors, are still in great demand.

Bromodimethylsulfonium bromide (BDMS) (Figure 1),[21] a light orange solid compound, is a convenient "soft" electrophilic brominating reagent and readily binds to the "soft" sulfur atom. Since Meerwein's discovery of BDMS,[22] it has gained considerable interest in the field of organic chemistry, due to its easy handling and low cost, as well as its easy access and varied applications both as a catalyst[23] and as an effective reagent. However, BDMS has never been applied to glycosylation reactions. Herein we report

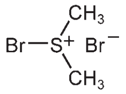


Figure 1. Bromodimethylsulfonium bromide (BDMS).

BDMS as a new promoter for the activation of thioglycosides.

A preliminary screening of reaction conditions showed that BDMS alone did not activate thioglycosides at all except in conjunction with silver triflate (AgOTf). Using the BDMS/AgOTf system, a series of glycosylation reactions was investigated by varying both the thioglycosides and the acceptors (Table 1).

Initially, the low-reactive, "disarmed" thioglycoside donors were chosen and evaluated. Glycosylations of

Table 1. Glycosylations promoted by BDMS/AgOTf.

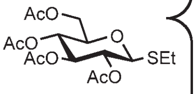
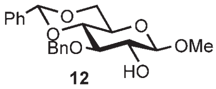
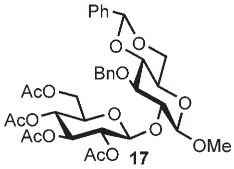
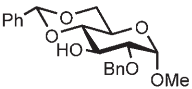
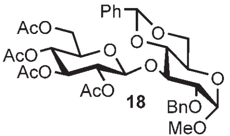
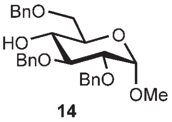
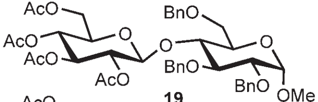
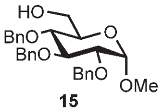
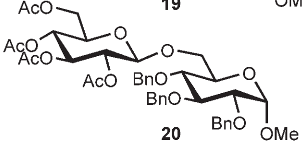
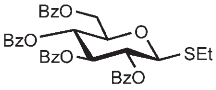
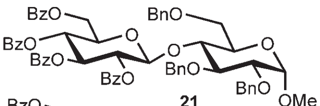
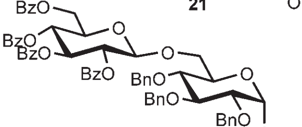
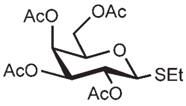
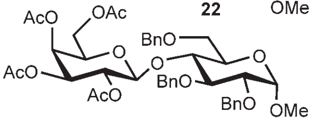
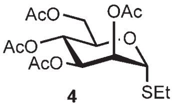
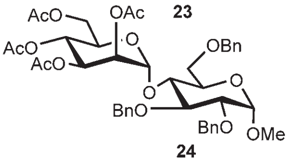
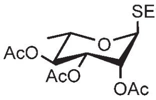
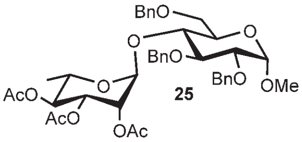
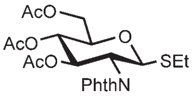
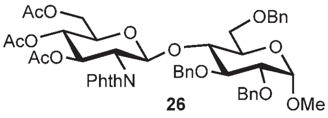
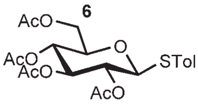
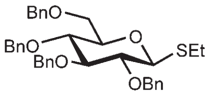
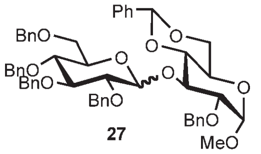
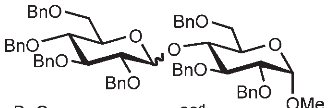
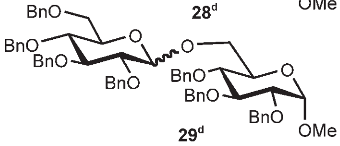
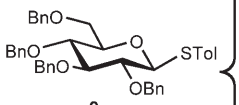
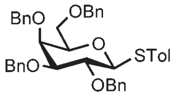
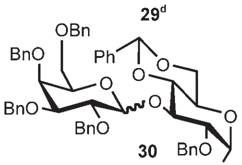
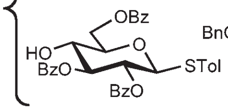
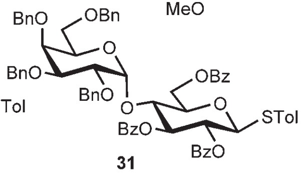
Entry	Glycosyl donor	Glycosyl acceptor	Disaccharide	Yield[a] (α/β)
1	 **1**	 **12**	 **17**	96% (β)
2		 **13**	 **18**	87% (β)
3		 **14**	 **19**	97% (β)
4		 **15**	 **20**	46% (β)
5	 **2**	**14**	 **21**	89% (β)
6		**15**	 **22**	78% (β)
7	 **3**	**14**	 **23**	91% (β)
8	 **4**	**14**	 **24**	95% (α)
9	 **5**	**14**	 **25**	98% (α)
10	 **6**	**14**	 **26**	82% (β)
11	 **7**	**12**	**17**	79% (β)

Table 1. (Continued)

Entry	Glycosyl donor	Glycosyl acceptor	Disaccharide	Yield[a] (α/β)
12	 **8**	**13**	 **27**	92% (1.2/1)[d]
13		**14**	 **28**[d]	78% (1/1)[d]
14		**15**	 **29**[d]	79% (1/2)[d]
15	 **9**	**13**	**27**	97% (2.1/1) 96% (3.6/1)[b] 98% (1/1.4)[c]
16		**14**	**28**[d]	94% (1.4/1) 89% (2.1/1)[b] 90% (1/2.1)[c]
17		**15**	**29**[d]	94% (1/1.2) 93% (1.1/1)[b] 89% (1/4)[c]
18	 **10**	**13**	 **30**	97% (3.2/1)[d]
19		 **16**	 **31**	90% (>20/1)[d,e] 92%(α)[b,e]

[a] *General conditions:* acceptor (1.0 equiv.), donor (1.2 equiv.), BDMS (1.4 equiv.), AgOTf (3.2 equiv.), dichloromethane (DCM), –35 °C for 30 min, then to ambient temperature if necessary.

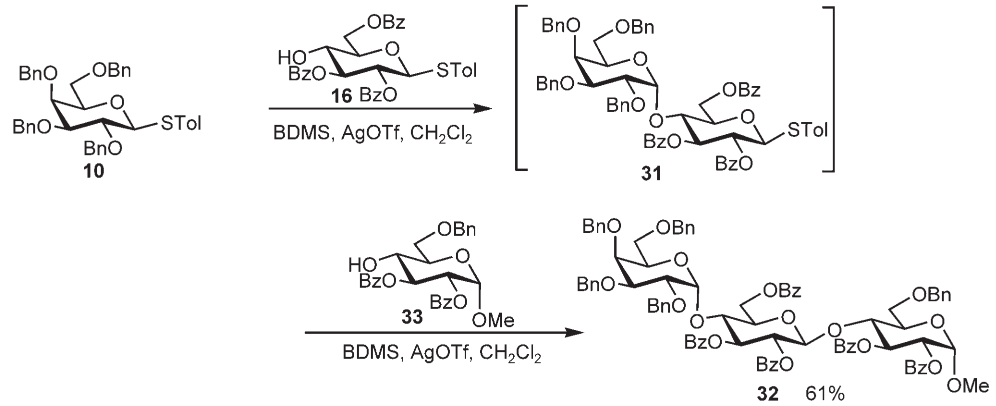
[b] DCM/Et_2O = 1/1.

[c] DCM/CH_3CN = 3/1.

[d] α/β ratio determined by ^{1}H NMR spectroscopy.

[e] Acceptor (1 equiv.), donor (1.2 equiv.), BDMS (0.7 equiv.), AgOTf (3.0 equiv.).

the "disarmed" ethyl thioglucoside donor **1** with the D-glucose acceptors **12**, **13**,[24] and **14** (entries 1–3) having a free hydroxy group at the C-2, C-3, and C-4 positions proceeded smoothly within 30 min. Interestingly, the glycosyl coupling between donor **1** and the acceptor **15** with the C-6 hydroxy exposed resulted in low yield (entry 4), as the 6-*O*-acetylated acceptor was isolated in 32% yield arising from an acetyl transfer[25] from the donor **1**. This undesired process was avoided when the benzoylated glucosyl donor **2** was employed instead of **1** (entry 6). The glycosylation reaction of donor **2** with the hindered acceptor **14** yielded disaccharide **21** as a single anomeric isomer as well (entry 5). The other "disarmed" ethyl thioglycoside donors such as galactose (entry 7), mannose (entry 8), rhamnose (entry 9), and glucosamine (entry 10) moieties were also checked. As shown, a number of 4-*O*-linked disaccharides, which suffered from either side products when promoted by NIS-TfOH using "armed" thioglycoside donors or poor yields when promoted by DMTST using "disarmed" thioglycoside donors in the preparation procedures,[26] were prepared in high yields when the relatively low reactive acceptor **14** was used. However, the coupling of D-glu-



Scheme 1. Reactivity-based one-pot glycosylation of **32**.

cose acceptor **12** and "disarmed" *p*-tolyl thioglycoside donor **7** in which the ethyl group of donor **1** was replaced by a *p*-tolyl group afforded disaccharide **17** in lower yield (79%, entry 11) when compared with that of the coupling between **12** and **1** (96%, entry 1), presumedly due to the donor's lower reactivity. It seems that ethyl thioglycosides are better than *p*-tolyl thioglycosides for "disarmed" donors. In all cases, glycosylation reactions provided the expected 1,2-*trans*-linked disaccharides by virtue of neighboring group participation, no orthoesters were detected.

Subsequently, the activation of "armed" thioglycosides was examined. The glycosylation of perbenzylated ethyl thioglucoside **8**, devoid of a participating group at the *O*-2 position, proceeded in excellent yield but with no anomeric selectivity with acceptor **13** (entry 12). Similarly, the coupling of donor **8** with acceptor **14** also gave poor stereoselectivity (entry 13). Interestingly, glycosylation of the highly reactive acceptor **15** with **8** provided a slight β-linked selectivity (entry 14). Compared with donor **8**, the glycosylations of the "armed" perbenzylated *p*-tolyl thioglucoside **9** smoothly afforded disaccharides **27**–**29** in further improved yields and with poor to modest α/β stereoselectivity (entries 15–17). The selectivity was shifted significantly toward the α isomer by the use of ether or toward the β isomer by the use of acetonitrile as cosolvents, this may be explained by the participation of the solvent.[27] However, the glycosylation of the perbenzylated *p*-tolyl thiogalactoside **10** with the acceptor **13** having a free hydroxy group at the C-3 position, proceeded in excellent yield and with good α-selectivity (entry 18). Disaccharide **31**, which suffered from by-products when using NIS-TfOH as promoter in its preparation,[26] was obtained in high yield. It turns out that *p*-tolyl thioglycosides work more efficiently than ethyl thioglycosides in the case of "armed" glycosyl donors.

The next issue was to determine if BDMS/AgOTf could be used in a reactivity-based oligosaccharide synthesis.[26,28] Indeed, this promoter system worked well, by using the ratio of 0.55/1 (BDMS/donor) to minimize the formation of side products and changing the amount of AgOTf to improve the yield, as shown in Table 1 (entry 19). A substoichiometric amount of BDMS was used on the assumption that the reaction might provide *p*-TolSOTf which could, in turn, promote glycosylation. Finally, as examplified in Scheme 1, a one-pot synthesis of trisaccharide **32** was carried out in satisfactory yield and with good stereoselectivity, demonstrating that this novel promoter system can be applied in the one-pot assembly of oligosaccharides.

In conclusion, by the use of the easy-to-handle and low-cost BDMS, we have identified this reagent to be a new and highly powerful promoter for the activation of both "disarmed" and "armed" thioglycosides. This proceeds by the *in situ* combination of BDMS with AgOTf, which then serves to activate the thioglycoside for glycosidic bond formation. This overcomes some limitations of the current methods, and this efficient promoter can be employed in one-pot oligosaccharide assembly. We are currently attempting to find an alternative to the expensive co-promoter (AgOTf) and extend the scope of this new procedure.

Experimental Section

Preparation of Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (17)

A mixture of **1** (25.4 mg, 0.0645 mmol), **12** (20.0 mg, 0.0538 mmol), silver triflate (44.3 mg, 0.172 mmol), and activated AW-300 molecular sieves (0.30 g) in dichloromethane (4.0 mL) was cooled to −35 °C. After stirring for 5 min, bromodimethylsulfonium bromide (16.8 mg, 0.0753 mmol) was added to the mixture. The reaction mixture was stirred for 15 min at −35 °C, then allowed to warm to ambient temperature. The mixture was quenched with triethylamine (0.2 mL). The precipitate was filtered off through a pad of Celite and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc, 3:1) to afford **17** as a white foam; yield: 36.3 mg (96%).

Preparation of Methyl 6-*O*-benzyl-2,3-di-*O*-benzoyl-4-*O*-[2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-glucopyranosyl]-α-D-glucopyranoside (32)

A mixture of **10** (23.7 mg, 0.0367 mmol), **16** (20.0 mg, 0.0334 mmol), silver triflate (20.6 mg, 0.0802 mmol), and activated 4 Å molecular sieves (0.30 g) in anhydrous dichloromethane (2.0 mL) and diethyl ether (2.0 mL) was cooled to −35 °C. After stirring for 5 min, bromodimethylsulfonium bromide (4.5 mg, 0.0200 mmol) was added to the mixture. The reaction mixture was stirred for 45 min at −35 °C, then at −15 °C for 15 min. The formation of disaccharide **31** was monitored by TLC (petroleum ether : EtOAc 5:2). After the starting materials were consumed, the reaction mixture was cooled to −20 °C. Subsequently, **33** (19.7 mg, 0.0401 mmol) and silver triflate (30.9 mg, 0.120 mmol) were added. The reaction mixture was stirred for 5 min followed by addition of bromodimethylsulfonium bromide (5.2 mg, 0.0234 mmol). The mixture was stirred at −20 °C for 90 min, then allowed to warm to the ambient temperature. After stirred for another 30 min, the mixture was quenched with triethylamine (0.2 mL). The precipitate was filtered off through a pad of Celite and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (toluene: acetonitrile, 30:1) to afford **32** as a white foam; yield: 30.2 mg (61%).

Acknowledgements

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References

[1] a) P. J. Garegg, *Adv. Carbohydr. Chem. Biochem.* **2004**, *59*, 69; b) *Best Synthetic Methods*: *Carbohydrates*, (Ed.: H. M. I. Osborn), Academic Press, London, **2003**.

[2] P. Fügedi, in: *The Organic Chemistry of Sugars*, (Eds.: D. E. Levy, P. Fügedi), CRC Press, Boca Raton, FL, **2005**, p 89.

[3] a) S. Oscarson, in: *Carbohydrates in Chemistry and Biology*, (Eds.: B. Ernst, G. W. Hart, P. Sinay), Wiley-VCH, Weinheim, **2000**, Vol 1, p 93; b) J. D. C. Codée, R. E. J. N. Litjens, L. J. van den Bos, H. S. Overkleeft, G. A. van der Marel, *Chem. Soc. Rev.* **2005**, *34*, 769.

[4] T. Norberg, in: *Modern Method in Carbohydrate Synthesis*, (Eds.: S. H. Khan, R. A. O'Neill), Harwood Academic, Netherlands, **1996**, p 82.

[5] R. J. Ferrier, N. Vethaviyasar, *Carbohydr. Res.* **1973**, *27*, 55.

[6] H. Lönn, *Chem. Commun. Univ. Stockholm* **1984**, *1*.

[7] P. Fügedi, P. J. Garegg, *Carbohydr. Res.* **1986**, *149*, C9.

[8] F. Dasgupta, P. J. Garegg, *Carbohydr. Res.* **1988**, *177*, C13.

[9] V. Martichonok, G. M. Whitesides, *J. Org. Chem.* **1996**, *61*, 1702.

[10] a) B. A. Garcia, J. L. Poole, D. Y. Gin, *J. Am. Chem. Soc.* **1997**, *119*, 7597; b) J. D. C. Codee, R. E. J. N. Litjens, R. den Heeten, H. S. Overkleeft, J. H. van Boom, G. A. van der Marel, *Org. Lett.* **2003**, *5*, 1519.

[11] D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015.

[12] S. G. Durón, T. Polat, C.-H. Wong, *Org. Lett.* **2004**, *6*, 839.

[13] C. Wang, H. Wang, X. Huang, L.-H. Zhang, X.-S. Ye, *Synlett* **2006**, 2846.

[14] J. Tatai, P. Fügedi, *Org. Lett.* **2007**, *9*, 4647.

[15] Y. Ito, T. Ogawa, *Tetrahedron Lett.* **1988**, *29*, 1061.

[16] a) P. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313; b) H. M. Zuurmond, S. C. Van der Laan, G. A. Van der Marel, J. H. Van Boom, *Carbohydr. Res.* **1991**, *215*, C1; c) B. Mukhopadhyay, B. Collet, R. A. Field, *Tetrahedron Lett.* **2005**, *46*, 5923.

[17] a) K. C. Nicolaou, S. P. Seitz, D. P. Papahatjis, *J. Am. Chem. Soc.* **1983**, *105*, 2430; b) S. Valerio, A. Iadonisi, M. Adinolfi, A. Ravidà, *J. Org. Chem.* **2007**, *72*, 6097.

[18] G. H. Veeneman, J. H. Van Boom, *Tetrahedron Lett.* **1990**, *31*, 275.

[19] K.-T. Huang, N. Winssinger, *Eur. J. Org. Chem.* **2007**, 1887.

[20] T. Ercegovic, A. Meijer, G. Magnusson, U. Ellervik, *Org. Lett.* **2001**, *3*, 913.

[21] G. A. Olah, Y. D. Vankar, M. Arvanaghi, G. K. Surya Prakash, *Synthesis* **1979**, 720.

[22] H. Meerwein, K. F. Zenner, R. Gipp, *Justus Liebigs Ann. Chem.* **1965**, *688*, 67.

[23] a) C. Md. Lokman Hakim, *Synlett* **2006**, 1619, and references cited therein; b) A. T. Khan, M. A. Ali, P. Goswami, L. H. Choudhury, *J. Org. Chem.* **2006**, *71*, 8961; c) A. T. Khan, T. Parvin, L. H. Choudhury, *Eur. J. Org. Chem.* **2008**, 834; d) B. Jiang, Y. Dou, X. Xu, M. Xu, *Org. Lett.* **2008**, *10*, 593.

[24] We attempted to buffer the reaction medium using TTBP, but no reaction occurred because TTBP might probably combine with the bromonium ion. Fortunately, the benzylidene group survived under general coupling conditions.

[25] T. Nukada, A. Berces, D. M. Whitfield, *J. Org. Chem.* **1999**, *64*, 9030.

[26] Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734.

[27] a) R. U. Lemieux, *Pure. Appl. Chem.* **1971**, *25*, 527; b) D. Vankar, P. S. Vankar, M. Behrendt, R. R. Schmidt, *Tetrahedron* **1991**, *47*, 9985.

[28] a) N. L. Douglas, S. V. Ley, U. Lucking, S. L. Warriner, *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 51; b) Y. Wang, X.-S. Ye, L.-H. Zhang, *Org. Biomol. Chem.* **2007**, *5*, 2189.