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A New, Powerful Glycosylation Method: Activation of Thioglycosides with Dimethyl Disulfide–Triflic Anhydride

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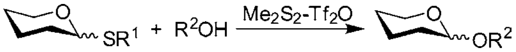
ABSTRACT



Dimethyl disulfide reacts with triflic anhydride to provide a highly reactive electrophile. Various thioglycosides, differing in their thio aglycons, carbohydrate units, and protecting group pattern, were activated with Me_2S_2–Tf_2O in the presence of different glycosyl acceptors. The reactions proceeded at low temperatures within a short time, affording oligosaccharides in high yields both on primary and secondary hydroxyls. Armed and disarmed glycosyl donors were activated equally efficiently.

The development of efficient glycosylation methods is crucial for the synthesis of oligosaccharides, glycoconjugates, and other carbohydrate-containing complex natural products, as well as for the improvement of solid-phase synthesis of oligosaccharides.[1] Major advances have been achieved by introducing a variety of different types of glycosyl donors and promoter systems for their activation.[1a] Among the various classes of glycosyl donors, thioglycosides proved to be particularly advantageous,[2] and today they are the most frequently used type of compounds in oligosaccharide syntheses.[3] Thioglycosides are mostly crystalline and have long shelf lives, and as they are stable under most protecting group transformations, highly functionalized derivatives are made relatively easily.[2,4] Importantly, as a result of the stability of the thioglycoside function, this class of compounds can serve not only as glycosyl donors but also as glycosyl acceptors. This feature, combined with the tunable reactivity of thioglycosides, could be taken advantage of in the development of various synthetic strategies for higher oligosaccharides.[5]

The very stability of thioglycosides, however, has presented problems for a long time in attempts to use them as glycosyl donors. Early methods to activate thioglycosides with heavy metal salts, by analogy with the Koenigs−Knorr reaction, proved to be of limited usefulness.[6] A different concept, activating thioglycosides by organosulfur compounds, has been developed by one of us, which resulted in the introduction of dimethyl(methylthio)sulfonium triflate (DMTST) as a promoter.[7] DMTST is a powerful alkylsulfenylating agent[7] that proved to be efficient in a wide range of glycosylation reactions. Following the introduction of DMTST, other reagents, based on the same principle, including methylsulfenyl triflate,[8] phenylsulfenyl triflate,[9] and the related seleno analog,[10] have been developed. Sulfena-

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[2] (a) Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97−108. (b) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179−205.

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[6] (a) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 55−61. (b) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. *Chem. Lett.* **1979**, 487−490. (c) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17−C22. (d) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215−3217. (e) Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162−165.

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mide-type activators in combination with Lewis acids such as the PhSNPhth−TMSOTf,[11] EtSNPhth−TrB(C_6F_5)$_4$,[12] and *N*-(phenylthio)-ϵ-caprolactam−Tf_2O[13] systems have also been proposed. More recently the list of organosulfur compounds activating thioglycosides was further expanded by using various sulfinates in admixture with triflic anhydride.[14] These sulfinates include *S*-(4-methoxyphenyl)benzenethiosulfinate,[15] benzenesulfinyl-piperidine (BSP),[16] diphenyl sulfoxide,[17] and benzenesulfinyl-morpholine.[18]

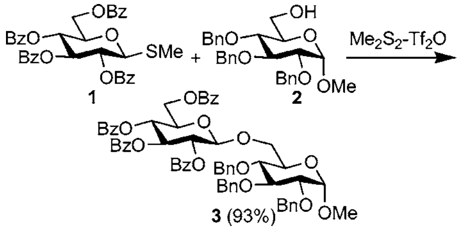
An attractive feature of some of these promoter systems containing sulfinyl derivatives lies in their power, glycosylation successfully being performed at low temperatures. Nevertheless, as most of these sulfinyl derivatives are not commercially available,[19] improvement of their synthetic accessibility, as well as their stability and solubility, is desired.[20]

We were interested in developing a powerful promoter system for the activation of thioglycosides that could be used at low temperatures and at the same time use commercially available inexpensive chemicals. We hypothesized that, by analogy with the preparation of DMTST, dimethyl disulfide might react not only with methyl triflate but also with triflic anhydride. The primary product of this reaction could be expected to be more reactive than DMTST as one of the methyl groups of DMTST would be replaced by the strongly electron-withdrawing trifluoromethanesulfonyl group. Although in the literature we found no data on the reaction of disulfides with sulfonic acid anhydrides, an NMR-tube experiment clearly showed that dimethyl disulfide reacts with triflic anhydride in a fast reaction.

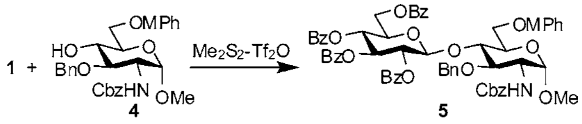
The thioglycoside activating capability of the dimethyl disulfide−triflic anhydride (Me_2S_2−Tf_2O) reagent was tested by the reaction of the benzoylated thioglycoside (**1**) with the D-glucose acceptor (**2**) having a primary hydroxyl group free (Scheme 1). The reaction was complete in 10 min at 0 °C and afforded the disaccharide (**3**) in 93% yield.

The amount of the reagent required for promoting glycosylations was studied on the coupling of **1** with the D-glucosamine derivative **4** (Scheme 2). Using 0.5, 1.0, 1.5, and 2.0 equiv of Me_2S_2−Tf_2O, the yields of **5** were 55%, 72%, 79%, and 79%, respectively. These results indicate that a stoichiometric amount of the promoter is needed, and in subsequent work a 1.5-fold excess of the reagent was used.

Scheme 1. Glycosylation of a Primary Hydroxyl Using Me_2S_2−Tf_2O



Scheme 2. Effect of the Amount of Promoter on Yield



	Me_2S_2-Tf_2O equiv	yield
	0.5	55%
MPh =	1.0	72%
4-methoxyphenyl	1.5	79%
	2.0	79%

Some of the essential reaction conditions having been established, the scope of this new glycosylation reaction was investigated by using a variety of different glycosyl donors and acceptors (Table 1).

Me_2S_2−Tf_2O-promoted glycosylations of thioglycosides on secondary hydroxyls proceeded easily. Reactions of **1** with the D-glucose derivatives **6**, **8**, and **10** (entries 1−3) having a free hydroxyl group at the C-4, C-3, and C-2 positions, respectively, were performed at −40 °C and afforded the disaccharides **7**, **9**, and **11** within a few minutes. As can be seen from Table 1, the promoter activates glycosyl donors not only from neutral monosaccharides of different configurations (D-*gluco*, D-*galacto*, L-*ido*, D-*manno*) but the aminosugar (**12**) and the uronic acid (**14**) thioglycosides as well. Several of the acceptors had the 4-OH group free, to which generally low reactivity is attributed. The yields obtained with these acceptors (entries 1, 5, 7−11) indicate that the low reactivity of the 4-OH group was readily overcome by the power of the activation method. The thioglycoside donors had the most frequently used aglycons (Me, Et, Ph); they all reacted equally well, irrespective of their aglycon. The reagent and the reaction conditions are compatible with most of the commonly used protecting groups. In the case of reactants containing the acid-sensitive acetal and *tert*-butyl groups (entries 2, 3, 5, 9, 10), the reaction mixture was buffered by 2,6-di-*tert*-butyl-4-methylpyridine. The disarmed thioglycosides in Table 1 invariably afforded *trans*-glycosides as a result of neighboring group participation.

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(19) Diphenyl sulfoxide is commercial. We thank one of the reviewers informing us that BSP also became commercially avialable recently.

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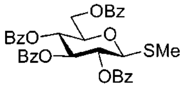
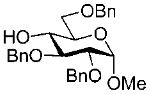
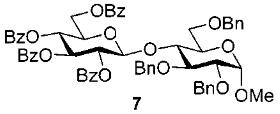
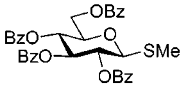
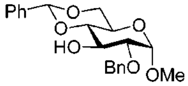
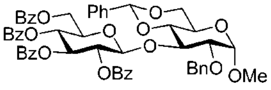
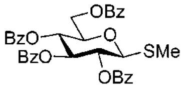
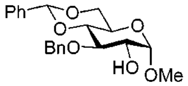
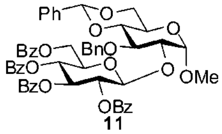
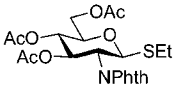
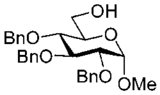
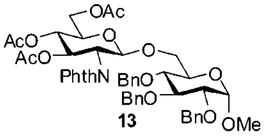
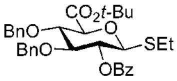
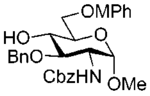
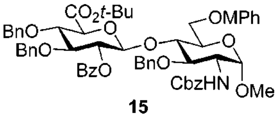
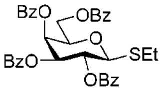
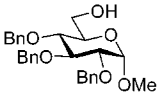
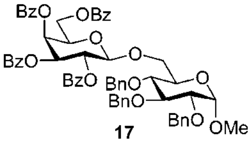
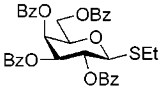
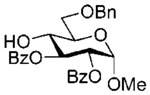
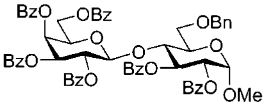
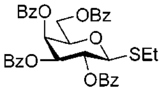
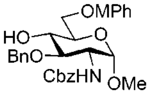
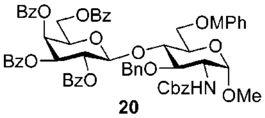
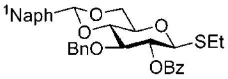
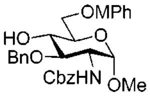
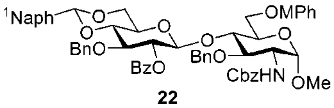
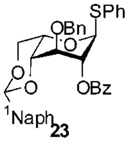
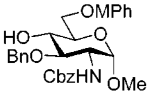
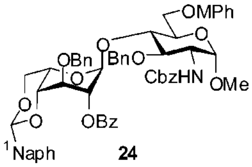
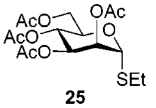
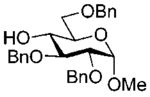
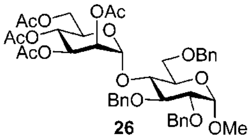
Table 1. Glycosylations Using $Me_2S_2-Tf_2O$

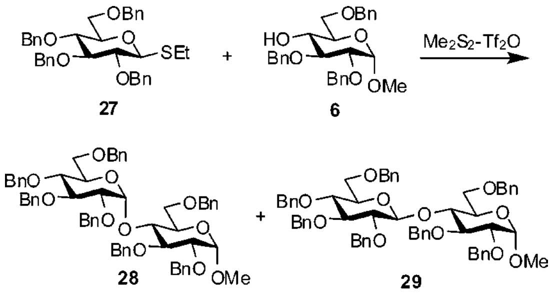
entry	donor	acceptor	product	yield
1	 **1**	 **6**	 **7**	67%
2	 **1**	 **8**	 **9**	76%
3	 **1**	 **10**	 **11**	93%
4	 **12**	 **2**	 **13**	85%
5	 **14**	 **4**	 **15**	83%
6	 **16**	 **2**	 **17**	87%
7	 **16**	 **18**	 **19**	85%
8	 **16**	 **4**	 **20**	79%
9	 **21**	 **4**	 **22**	88%
10	 **23**	 **4**	 **24**	90%
11	 **25**	 **6**	 **26**	79%

[1]Naph = naphth-1-yl

As expected, the promoter activates armed thioglycosides even more easily. Reaction of the benzylated thioglycoside **27** with **6** in dichloromethane afforded the disaccharides **28** and **29** in excellent combined yield but in low stereoselectivity (Scheme 3). The α/β ratio could be shifted significantly toward the α isomer by using ether or toward the β isomer by using acetonitrile as cosolvents. Similar solvent effects have been observed before in other glycosylation methods[1a,b,7b,21] and can be explained by the participation of the solvent.

In summary, using commercially available, inexpensive dimethyl disulfide we have developed a highly powerful

Scheme 3. Solvent Effects on the Stereoselectivity of Glycosylations



entry	solvent	yield **28**	yield **29**
1	CH_2Cl_2	44%	43%
2	Et_2O-CH_2Cl_2	70%	23%
3	MeCN-CH_2Cl_2	23%	63%

promoter for the activation of thioglycosides. The Me_2S_2–Tf_2O reagent activates thioglycosides at low temperatures, and glycosylations are complete within a short time.

Since our results were presented at different symposia,[22] successful applications of our glycosylation method have already been implemented.[23]

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Supporting Information Available: Experimental procedures and full characterization for all new disaccharides. This material is available free of charge via the Internet at http://pubs.acs.org.

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