Tetrahedron Letters, Vol. 34, No. 13, pp. 2187-2190, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Novel Method for Activation of Thioglycosides, Combination of *N*-Bromosuccinimide and Triflic Acid Salts

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Key Words: glycosidation, thioglycoside, *N*-bromosuccinimide, tetrabutylammonium triflate, diphenyliodonium triflate.

Abstract: A combination of *N*-bromosuccinimide (NBS) with tetrabutylammonium triflate (Bu_4NOTf) or diphenyliodonium triflate (Ph_2IOTf) effectively activates thioglycosides to promote facile glycosidation with various glycosyl acceptors in good yields.

Thioglycosides are frequently used in the synthesis of complex carbohydrates since they are stable under wide range of reaction conditions but can be used as efficient glycosyl donors through activation with appropriate thiophilic reagents.[1] Recently, we described application of a hypervalent iodine reagent prepared from iodosobenzene (PhIO) and triflic anhydride (Tf_2O) to the activation of thioglycosides.[2]

In the present study, we describe another novel activation method for thioglycosides using a combination of *N*-bromosuccinimide (NBS) and triflic acid salts, i.e., tetrabutylammonium triflate (Bu_4NOTf) or diphenyliodonium triflate (Ph_2IOTf). NBS can be used to activate so-called "armed" thioglycoside.[3] However, the rate of glycosidation is not sufficiently high so that this reagent has not been used frequently in practical synthesis. Recently, van Boom et al. recommended use of *N*-iodosuccinimide (NIS) together with triflic acid (TfOH). This combination can effectively activate not only "armed" but also less reactive "disarmed" thioglycosides possessing esterified hydroxyl functions, whereas NIS alone was not effective for "disarmed" thioglycosides.[4,5] This acceleration effect seems to be attributed to the formation of a glycosyl triflate intermediate which reacts rapidly with glycosyl acceptor. However, the acidic reaction conditions with NIS-TfOH cause problems in using acid-labile compounds. We anticipated the use of a soluble triflic acid salt as a source of triflate anion in place of TfOH solves this problem. After completion of the glycosidation triflates are regenerated, the reaction medium being kept neutral throughout the process (Fig. 1). We thus used less expensive NBS as an activator and commercially available, crystalline Bu_4NOTf and Ph_2IOTf as catalysts.[6]

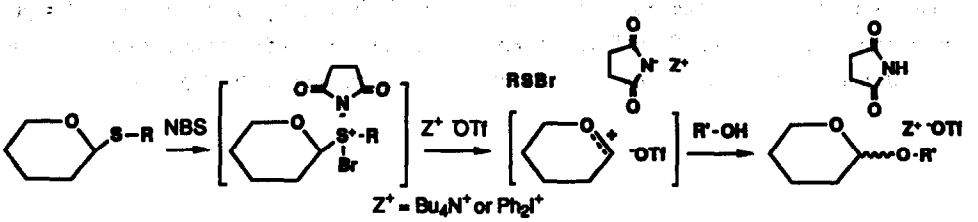


Fig. 1. Plausible reaction mechanism of the glycosidation with thioglycoside using NBS and a triflic acid salt.

The glycosidation reactions were carried out by use of 1 equivalent of NBS and 0.5 equivalent of triflates under N_2 atmosphere at -18°C in either dichloroethane or ether.[7] In case where acetonitrile was used as a solvent, NBS and triflic acid salts were added to a mixture of a donor and an acceptor at -78°C, and the temperature of the mixture was then raised to -18°C. The results are summarized in Table 1.

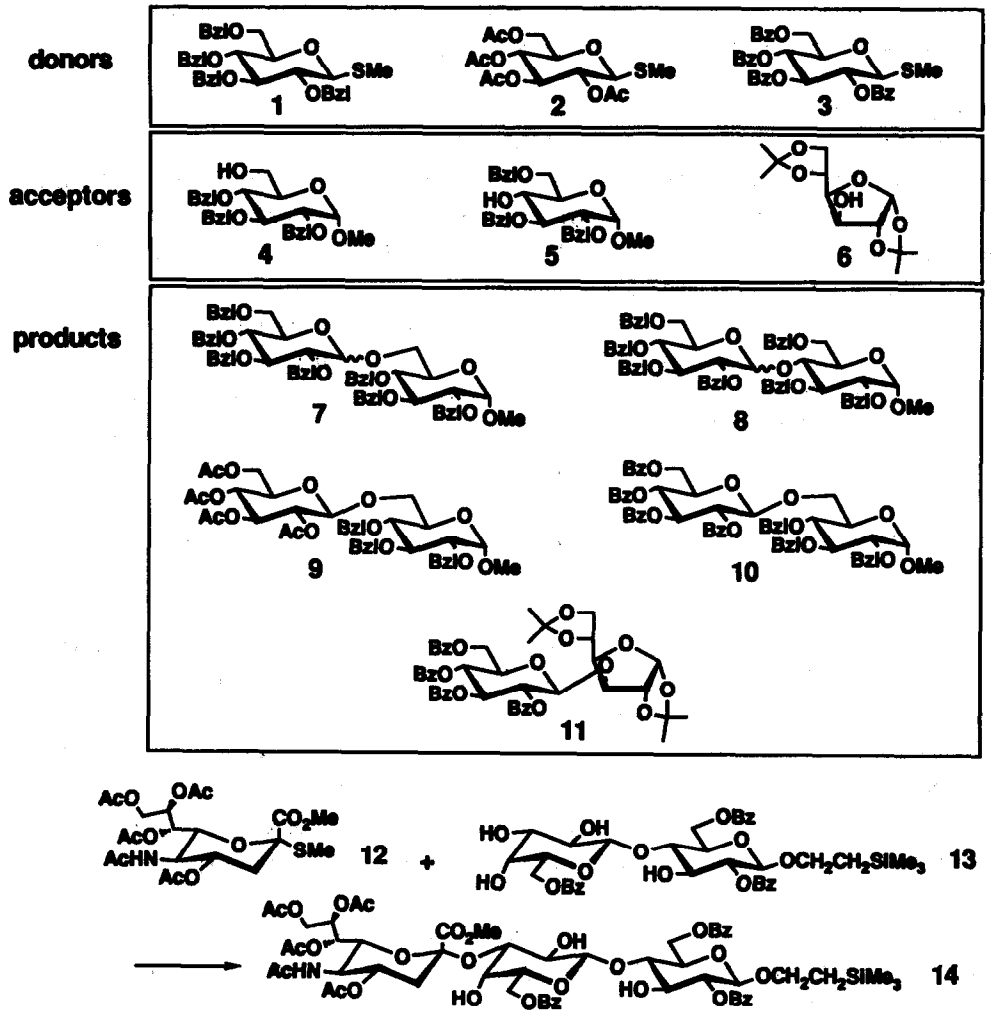
In fact, the reaction was remarkably accelerated by addition of triflic acid salts. Whereas the glycosidation of glycosyl acceptor **4** with methyl thioglucoside **1**, which is protected as the benzyl ether, did not complete even after 2 h at room temperature by use of NBS alone, the same reaction proceeded instantaneously by addition of Bu_4NOTf or Ph_2IOTf both in dichloroethane and in acetonitrile. The acceleration was also observed for a less reactive acceptor **5** (Table 1, entry 1-8). β-Glycosides were obtained preferentially in acetonitrile via the known α-nitrilium kinetic intermediates[8] by use of both triflates (entry 1 - 4). The β-orienting solvent effect of the nitrile was reduced in the case of acceptor **5** with a more hindered 4-hydroxyl group (entry 3, 4). In dichloroethane, essentially no stereoselectivities were observed (entry 5 - 8). In ether, an α-glycoside was obtained preferentially as expected (entry 9), though the reaction was much slower than in other solvents.[9]

By use of the present combination of NBS and triflic acid salt, the reaction of "disarmed" donors **2** and **3** proceeded slightly slower but also quite smoothly under mild reaction conditions to give 1,2-*trans* glycosides with complete selectivity in good yields (entry 10 - 12). The isopropylidene group was proved to be stable under this neutral glycosidation conditions (entry 12). Therefore, other acid-labile protecting groups can be used without problems.

Table 1. Reaction conditions and products in the glycosidation using NBS and either Ph_2IOTf or Bu_4NOTf as activating reagents for thioglycosides.

entry	D[a]	A[b]	D / A	additive	solvent	time[c]	P[d]	yield(%)	α : β[e]
1	1	4	1 / 0.8	Ph_2IOTf	CH_3CN	<1 min	7	90	1: 12
2	1	4	1 / 0.8	Bu_4NOTf	CH_3CN	<1 min	7	98	1: 13
3	1	5	1 / 1.1	Ph_2IOTf	CH_3CN	<1 min	8	92	1: 3.3
4	1	5	1 / 1.1	Bu_4NOTf	CH_3CN	<1 min	8	86	1: 2.1
5	1	4	1 / 1	Ph_2IOTf	$(CH_2Cl)_2$	<1 min	7	88	1: 0.8
6	1	4	1 / 1	Bu_4NOTf	$(CH_2Cl)_2$	<1 min	7	73	1: 1
7	1	5	1 / 1.1	Ph_2IOTf	$(CH_2Cl)_2$	<1 min	8	85	1: 1.3
8	1	5	1 / 1.1	Bu_4NOTf	$(CH_2Cl)_2$	<1 min	8	87	1: 0.4
9	1	4	1 / 1	Ph_2IOTf	ether	15 h	7	84	1: 0.17
10	2	4	1 / 0.7	Bu_4NOTf	$(CH_2Cl)_2$	20 min	9	74	0 : 1
11	3	4	1 / 1.1	Bu_4NOTf	$(CH_2Cl)_2$	15 min	10	76	0 : 1
12	3	6	1 / 1	Bu_4NOTf	$(CH_2Cl)_2$	1.5 h	11	70	0 : 1

a) D = donor, b) A = acceptor, c) The reaction time was estimated by TLC analysis on silica-gel, d) P = product, e) The anomer ratios of compounds **7** and **8** were determined by comparison of the intensities of methyl signals in ^1H NMR, since their complete separation was difficult by silica-gel column chromatography.



This glycosidation method was then applied to the synthesis of a more complex sugar chain of ganglioside GM_3. 2-(Trimethylsilyl)ethyl *O*-(6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-β-D-glucopyranoside (**13**) was used as a glycosyl acceptor according to Hasegawa's procedure.[10] In order to introduce an α-sialosyl group, the glycosidation of a methyl thioglycoside of *N*-acetylneuraminic acid (**12**) and **13** was carried out in propionitrile at -50°C.[10] An excess (2.7 equivalents) of donor **12** and NBS and 0.5 equivalent of Bu_4NOTf were used against acceptor **13**. The desired α-glycoside **14** was obtained in 70% yield with 24% recovery of acceptor **13**.[11]

The present combination of NBS and triflic acid salts activates both "armed" and "disarmed" thioglycosides under mild and neutral reaction conditions to give high yields of glycosides, providing one of the most practically useful method for the glycosidation. The experimental procedure is quite simple and requires only commercially available crystalline, stable, and not hygroscopic reagents.

The present work was supported in part by the Grant-in-Aid for Scientific Research on Priority Areas No. 04220108 from the Ministry of Education, Science and Culture, Japan.

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5. A combination of NBS and TfOH was recently described for the β-selective glycosidation with 2-*O*-benzylated thioglycosides in propionitrile: Sasaki, M.; Tachibana, K.; Nakanishi, H. *Tetrahedron Lett.* **1991**, *32*, 6873.
6. We first expected that Ph_2IOTf alone might promote such a glycosidation reaction of a thioglycoside as observed in our previous work.[2] However, no glycoside was formed (from 1 and 4) with this reagent before NBS was added.
7. A typical procedure is as follows. To a solution of thioglycoside 1 (152 mg, 266 μmol) and acceptor 4 (123 mg, 266 μmol) in dry dichloroethane (4.0 ml) was added Molecular Sieves 4A (1.0 g) under N_2 atmosphere, and the mixture was stirred at room temperature for 100 min. To the mixture were added NBS (47.3 mg, 266 μmol) and Ph_2IOTf (53 mg, 120 μmol) at -18°C, and the mixture was stirred at the same temperature for 15 min. Ethyl acetate and a saturated aqueous $NaHCO_3$ solution were added and Molecular Sieves 4A was removed by filtration. The organic layer was washed with brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to give an oily product as a mixture of α- and β-anomers: Yield 230 mg (88%).
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(Received in Japan 2 December 1992)