Mild but Efficient Methods for Stereoselective Glycosylation with Thioglycosides: Activation by [*N*-Phenylselenophthalimide–$Mg(ClO_4)_2$] and [PhIO–$Mg(ClO_4)_2$]

Koichi Fukase,* Yoshihiko Nakai, Takeshi Kanoh, and Shoichi Kusumoto*

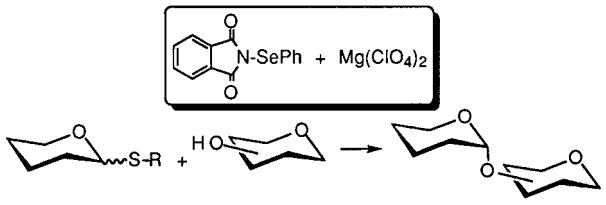
Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560, Japan

Fax: +81 6 850 5419; E-mail: koichi@chem.sci.osaka-u.ac.jp

Received 19 September 1997

Abstract: Combinations of *N*-phenylselenophthalimide (N-PSP) or iodosobenzene (PhIO) with $Mg(ClO_4)_2$ effectively promote glycosylation with thioglycosides under mild conditions. A 2,2,2-trichloroethoxycarbonyl group or trityl protecting group at the 6-position increased α-selectivity on glycosylation with 2-*O*-benzylated donors.

Thioglycosides have been used as versatile glycosyl donors since they are stable under various reaction conditions but can be selectively activated by appropriate thiophilic reagents. We have focused on a search for practically useful methods for mild but efficient activation of thioglycosides, thereby attempting to avoid the use of strongly acidic conditions. Until now we have described two methods for this purpose and furnished stereoselective glycosylation. One was the reaction with a combination of *N*-bromosuccinimide (NBS) and a catalytic amount of various salts of strong acids.[1,2] The other utilized hypervalent iodine reagents prepared from iodosobenzene (PhIO) and various acids.[3,4] By both methods glycosylation reactions proceed rapidly at low temperature (usually around -20 °C) in high yields. But in certain cases, particularly in the NBS-based reaction, the yields of α-glucosides were not satisfactory because a side reaction to form glycosyl bromides from the starting thioglycosides could not be avoided.[5] To overcome such disadvantage, we examined the use of other mild oxidants in combination with metal perchlorates and found the following two pairs to be very effective: combinations of either *N*-phenylselenophthalimide (N-PSP) or PhIO with a weakly Lewis acidic salt, $Mg(ClO_4)_2$, where highly α-selective glycosylation was achieved particularly when an appropriate protecting group was introduced at the 6-position of the donor molecule. These reagents are expected to be advantageous for application to solid-phase synthesis of oligosaccharides, since the selective glycosylation is effected at or even above room temperature.

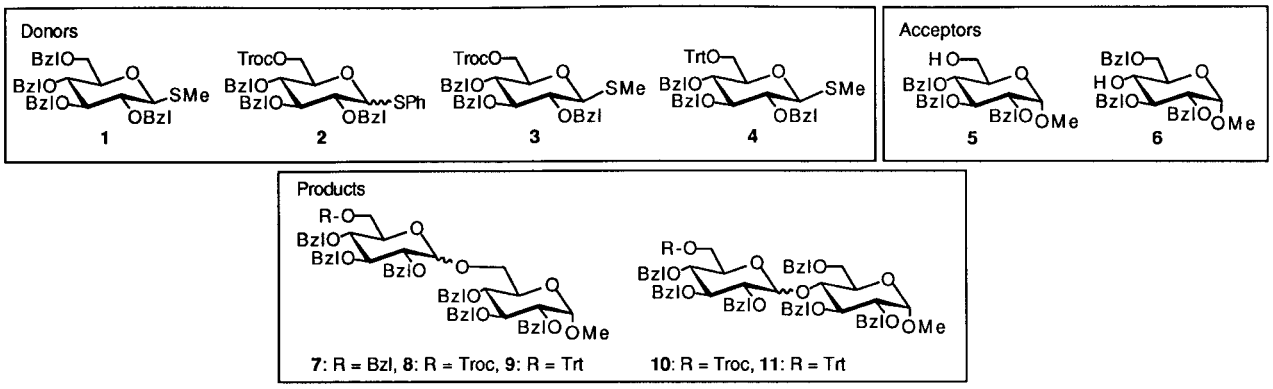


Shimizu et al. recently reported that N-PSP promotes glycosylation with thioglycosides when used in combination with TMSOTf but no stereoselectivity was observed under their reaction conditions.[6] In view of the results of our NBS–strong acid salts system,[2] we expected a similar stereoselective reaction with the N-PSP reagent by the combined use with a suitable salt.

Among many strong acid salts tested, only $Mg(ClO_4)_2$ can promote glycosylation in combination with N-PSP. This was in strong contrast to the reaction with NBS where addition of most strong acid salts dramatically enhanced the glycosylation. $Mg(ClO_4)_2$ works probably as a mild Lewis acid catalyst which matches the reactivity of N-PSP.

Glycosylation reactions were carried out under a N_2 atmosphere in ether by the use of 1.5 equiv of N-PSP and 0.5 equiv of $Mg(ClO_4)_2$[7] against a donor.[8] An excess (1.2 equiv or 1.6 equiv) of a donor was used against the acceptor. As summarized in Table 1, the desired glycosides were obtained in good yields in all cases, though the reaction rates were much lower than those by NBS-strong acid salts. Glycosylation of the 6-OH group of acceptor **6** with 2,3,4,6-tetra-*O*-benzyl *S*-phenyl thioglycoside

Table 1. Glycosylation Reactions by Combination of N-PSP and $Mg(ClO_4)_2$



entry	Donor	Acceptor	Donor/Acceptor	Temp./°C	Time/day [a]	Product	Yield(%)	α : β [b]
1	**1**	**5**	1.2	25	2	**7**	93	88 : 12
2	**2**	**5**	1.2	25	1	**8**	83	95 : 5
3	**3**	**5**	1.2	25	2	**8**	84	97 : 3
4	**4**	**5**	1.2	25	2	**9**	91	98 : 2
5	**2**	**6**	1.6	30	3	**10**	73	91 : 9
6	**3**	**6**	1.6	30	2	**10**	76	93 : 7
7	**4**	**6**	1.6	35	1	**11**	76	97 : 3

[a]The reaction time was estimated by TLC analysis on silica gel. [b]The anomer ratios were determined by comparison of the intensities of the methyl signals of the disaccharides in ^1H NMR

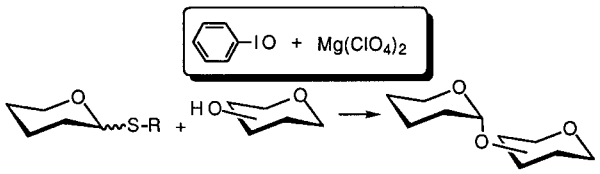
Table 2. Glycosylation Reactions by Combination of PhIO and $Mg(ClO_4)_2$

entry	Donor	Acceptor	Donor/Acceptor	Temp./°C	Time/min [a]	Product	Yield(%)	α : β [b]
1	**1**	**5**	1.2	25	15	**7**	73	88 : 12
2	**2**	**5**	1.2	25	30	**8**	73	95 : 5
3	**2**	**6**	1.5	25	15	**10**	85	91 : 9
4	**4**	**5**	1.2	25	5	**9**	64	96 : 4

[a]The reaction time was estimated by TLC analysis on silica gel. [b]The anomer ratios were determined by comparison of the intensities of the methyl signals of the disaccharides in ^1H NMR

1 gave disaccharide **7** in good yield with moderate α-selectivity (entry 1). α-Selectivity was improved by using 6-*O*-Troc thioglycosides **2** and **3** by virtue of the influence of the Troc function (entry 2, 3).[4,9,10] Since the present glycosylation reaction proceeds under neutral conditions, we attempted to employ an acid-sensitive trityl (Trt) group as a protecting group. Interestingly, the 6-*O*-Trt survived and showed a more potent α-directing effect than the 6-*O*-Troc group, probably owing to shielding of the β-face of the anomeric cationic transition-state by the bulky 6-*O*-Trt group (entry 4).

The reaction of a more hindered, 4-hydroxy group-free acceptor **6** was also effected by use of 1.6 equiv of 6-*O*-Troc thioglycosides **2**, **3** and 6-*O*-Trt thioglycoside **4** at slightly higher temperatures. The desired disaccharides **10** and **11** were also obtained in good yields with high α-selectivity (entry 5-7).



The above satisfactory results with $Mg(ClO_4)_2$ prompted us to attempt the combination of PhIO–$Mg(ClO_4)_2$. Fine tuning of the reactivity of the reagents was expected to be possible through correct choice of the added salts.[11] In fact, PhIO–$Mg(ClO_4)_2$ was capable of mild but efficient activation of thioglycosides to result in highly α-selective glycosylation. The reactions were carried out under conditions similar to those described above for N-PSP–$Mg(ClO_4)_2$; by the use of 1.5 equiv of PhIO and 0.5 equiv of $Mg(ClO_4)_2$ against a donor under a N_2 atmosphere in ether. As shown in Table 2, the 6-*O*-Troc group enhanced α-selective glycosylation (entry 2, 3). The glycosylation of the hindered 4-OH-free acceptor **6** also proceeded in good yield (entry 3). α-Selectivity was also enhanced by the 6-*O*-Trt group in this case, though the yield of the disaccharide did not exceed 70% because of the partial cleavage of Trt group (entry 4) during the reaction.[12]

As described, the combinations of N-PSP with $Mg(ClO_4)_2$ and PhIO with $Mg(ClO_4)_2$ effectively promote glycosylation with thioglycosides. α-Selective glycosidation was effected by virtue of 6-*O*-Troc or 6-*O*-Trt groups of a 2-*O*-benzylated donor. The simple experimental procedure and high stereoselectivity provide one of the most versatile method for glycosylation. The glycosylation reactions proceed cleanly at room temperature under mild and homogeneous conditions without serious side-reactions.

Acknowledgments. The present work was financially supported in part by Grants-in-Aid for Scientific Research No. 07680630 and on Priority Areas Nos. 06240105 and 08245229 from the Ministry of Education, Science and Culture, Japan.

References and Notes

(1) Fukase, K.; Hasuoka, A.; Kusumoto, S. *Tetrahedron Lett.* **1993**, *34*, 2187.

(2) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51*, 4923.

(3) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Kusumoto, S. *Tetrahedron Lett.* **1992**, *33*, 7165.

(4) Fukase, K.; Kinoshita, I.; Kanoh, T.; Hasuoka, A.; Kusumoto, S. *Tetrahedron* **1996**, *52*, 3897.

(5) Combinations of NBS-$LiClO_4$ and NBS-$LiNO_3$ were found to promote highly α-selective glucosylation with *O*-benzylated thioglucosides as donors in ether. When these reagents were applied to a donor possessing a 6-*O*-(2,2,2-trichloroethoxy-carbonyl) (Troc) group which is known to favor α-glycosylation,[9,10] the corresponding α-glucosides were obtained in sufficiently high stereoselectivity but the yields were low because of the formation of the corresponding glycosyl bromide.

(6) Shimizu, H.; Ito, Y.; Ogawa, T. *Synlett* **1994**, 535.

(7) When the amount of $Mg(ClO_4)_2$ was reduced to 0.25 equiv to the donor, the reaction took a longer period (ca. 1.5 times) for completion. But no such obvious difference in the reaction rate was observed when the amount of the perchlorate was increased from 0.5 to 1.0 equiv.

(8) General procedure: To a solution of a thioglycoside (180 μmol) and an acceptor (150 μmol) in dry ether (2.0 ml) was added molecular sieves 4A (200 mg) under a N_2 atmosphere. To the mixture were added N-PST (82 mg, 270 μmol) and $Mg(ClO_4)_2$ (20 mg, 90 μmol), and the mixture was stirred at 25 °C for 1 day. 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 $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to give a product.

(9) Fukase, K.; Yoshimura, T.; Kotani, S.; Kusumoto, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 473.

(10) Suda, Y.; Bird, K.; Shiyama, T.; Koshida, S.; Marques, D.; Fukase, K.; Sobel, M.; Kusumoto, S. *Tetrahedron Lett.* **1996**, *37*, 1053.

(11) In our previous study, α-selective glycosylation was effected in ether by use of $SnCl_2$-$AgClO_4$, $SnCl_4$-$AgClO_4$, $BiCl_3$-$AgClO_4$, and $SbCl_3$-$AgClO_4$ as catalysts.[4] Lately, we found the combination of PhIO with lanthanide perchlorates $[Ln(ClO_4)_3 \cdot nH_2O]$[13] also effectively promotes α-selective glycosylations with 2-*O*-benzylated donors. Part of the water of crystallization in $Ln(ClO_4)_3 \cdot nH_2O$ must be removed by stirring the mixture of a donor, an acceptor, and $Ln(ClO_4)_3 \cdot nH_2O$ in the presence of molecular sieves 4A for 3 h prior to the addition of PhIO. Perchlorates of Yb, Ho, Gd, Er are more effective than those of Pr, Ce, La, Eu. TMSCl-$AgClO_4$ is also a good catalyst for α-selective glycosylation.

(12) Previously, Houdier et al. reported that bulky 6-*O*-substituents such as Trt or *t*-butyldimethylsilyl groups increase significantly the proportion of α product in the iodonium dicollidine perchlorate-promoted glycosylation with pent-5-enyl and thioethyl glycosides: Houdier, S.; Vottero, P. J. A. *Carbohydr. Res.* **1992**, *232*, 349. Recently, Boons et al. also reported that the 6-*O*-Trt group in thioglycosides withstand glycosylation with *N*-iodosuccinimide (NIS) and a catalytic amount of triflic acid and favors the formation of α-glycosides. A combination of NIS–trimethylsilyl triflate was also shown to be effective. The α-selectivity, as far as given in their paper, is lower than that in our present work: Boons, G.-J.; Bowers, S; Coe, D. M. *Tetrahedron Lett.* **1997**, *38*, 3773. Probably because of the cleavage of the Trt group during the reaction, the yields of the glycosylation were generally moderate in these papers.

(13) Glycosylation with glycosyl fluorides catalyzed by lanthanide perchlorates: Kim, W.-S.; Hosono, S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 4443.