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Iodosobenzene-Triflic Anhydride as an Efficient Promoter for Glycosidation Reaction Using Thioglycosides as Donors

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Key Words: glycosidation, thioglycoside, promoter, iodosobenzene, trifluoromethanesulfonic anhydride.

Abstract: A reagent prepared *in situ* from iodosobenzene (PhIO) and trifluoromethanesulfonic anhydride (Tf_2O) was successfully applied to the activation of thioglycosides. Glycosidation with benzyl-protected methyl thioglycosides as glycosyl donors proceeded smoothly under mild reaction conditions. The same reagent also promoted glycosidation with less reactive acylated methyl thioglycosides in the presence of silica gel to form 1, 2-trans glycosides.

Thioglycosides, which are stable under wide range of reaction conditions but effectively activated for glycosidation by various thiophilic reagents, have been widely used as glycosyl donors in recent synthetic works on complex carbohydrates.[1] In the present study, we describe a novel activating reagent for thioglycosides, i.e., a combination of iodosobenzene (PhIO) and trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O).

Recently, a variety of hypervalent iodine (III) reagents have become available for organic synthesis.[2] For example, reagents prepared from PhIO and several acids such as BF_3•OEt_2, triflic acid (TfOH), or Tf_2O have been applied to various electrophilic reactions via hypervalent iodine oxidation.[2,3] Taniguchi et al. described that PhIO activated by 1 equivalent of Tf_2O reacted with alkynes, alkynylsilanes, and aromatic compounds to give vinyl-, alkynyl-, and aryl- (phenyl)(*p*-phenylene)bisiodonium triflate.[4] We anticipated that this reagent [PhIO-Tf_2O] can be used for selective activation of thioglycosides, since the reagent has strong electrophilicity with possible high chemoselectivity of hypervalent iodine to the sulfur atom. We also expected rapid glycosidation reaction via a glycosyl triflate intermediate formed as shown in Fig. 1.

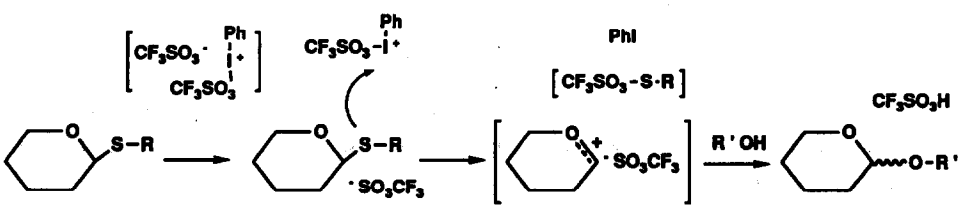


Fig. 1. Plausible reaction mechanism of the glycosidation using [PhIO-Tf_2O] as an activating reagent for thioglycosides.

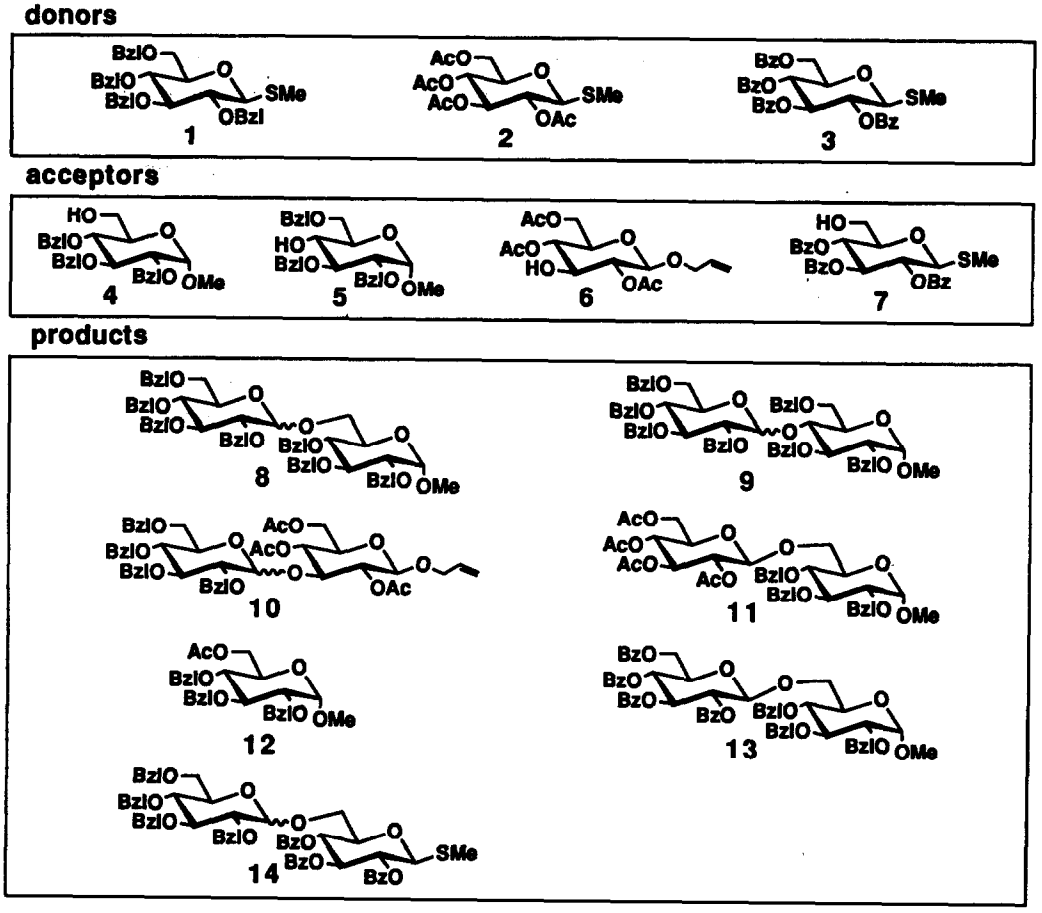
Glycosidation reactions were carried out by use of 1.2 equivalent of the activating reagent [PhIO-Tf_2O] under N_2 atmosphere at -18°C,[5, 6] and the results are summarized in Table 1. The glycosidation proceeded smoothly by use of so-called "armed" donor, methyl thioglucoside **1** whose 2-hydroxyl group was protected as benzyl ether.[7] No oxidative side-reaction was observed with the reagent at alcoholic hydroxyl groups. β-Glycosides were obtained preferentially by use of acetonitrile as a solvent via α-nitrilium kinetic intermediate (entry 1, 2).[1d, 8] The solvent effect of the nitrile was reduced in the case of a less reactive acceptor **5** with a free 4-hydroxyl group (entry 2). In dichloroethane very poor stereoselectivities were observed (entry 3, 4). No α-selectivity by solvent effect of ether was observed either (entry 5).

More reliable β-selective glycosidations can be effected by use of 2-*O*-acylated thioglucosides **2** and **3** with [PhIO-Tf_2O]. These 2-*O*-acylated donors are so-called "disarmed" donors since they are considerably less reactive than "armed" donors whose 2-OH groups are protected as ethers. In fact, the reaction rate of methyl 2,3,4,6-tetra-*O*-acetylthioglucoside **2** with acceptor **4** was slow, and the yield of the desired product **11** was low because of the undesirable formation of 6-*O*-acetylated acceptor **12** (24%) (entry 7). Quite interestingly, however, this glycosidation was dramatically enhanced with silica gel. The undesirable migration of an acetyl group was also significantly suppressed by silica gel (entry 8). The same enhancement was also observed in the case of benzoylated donor, 2,3,4,6-tetra-*O*-benzoylthioglucoside **3** (entry 9). The glycosidation proceeded immediately by either dropping the cold reaction mixture on silica gel or addition of silica gel to the reaction mixture to give the desired disaccharides **11** and **13** in good yields, respectively.

Table 1. Reaction conditions and products in the glycosidation using [PhIO-Tf_2O] as an activating reagent for thioglycosides.

entry	D[a]	A[a]	D / A	solvent	time	P[a]	yield(%)	α : β
1	**1**	**4**	1 / 0.8	CH_3CN	1 min <	**8**	81	1: 12
2	**1**	**5**	1 / 1.1	CH_3CN	1 min <	**9**	85	1: 5.8
3	**1**	**4**	1 / 1	$(CH_2Cl)_2$	1 min <	**8**	78	1: 1.5
4	**1**	**5**	1 / 1.1	$(CH_2Cl)_2$	1 min <	**9**	85	1: 1.1
5	**1**	**4**	1 / 1	ether	15 h	**8**	79	1: 1.3
6	**1**	**6**	1 / 1	$(CH_2Cl)_2$	1 min <	**10**	78	1: 0.7
7	**2**	**4**	1 / 0.7	$(CH_2Cl)_2$	1 h	**11**	42	0 : 1
8[b]	**2**	**4**	1 / 0.8	$(CH_2Cl)_2$	–	**11**	77	0 : 1
9[c]	**3**	**4**	1 / 0.9	$(CH_2Cl)_2$	–	**13**	94	0 : 1
10[d]	**1**	**7**	1.5 / 1	CH_3CN	1 min <	**14**	99	1 : 6

a) D = donor, A = acceptor, P = product. b) The reaction proceeded instantaneously by dropping the reaction mixture to silica gel. c) The reaction proceeded instantaneously by addition of dried silica gel on the reaction mixture. d) The reaction was carried out at - 30°C.



The mechanism of the acceleration by silica gel is still to be investigated but is of great practical importance as demonstrated for example in the following chemospecific glycosidation. The reaction of perbenzylated thioglucoside **1** ("armed" donor) with partially-benzoylated thioglucoside **7** ("disarmed" acceptor) in acetonitrile gave the desired disaccharide **14** [9, 10] to be used directly for the subsequent glycosidation in the presence of silica gel.

Another particular advantage of the present reagent is that the C-C double bond was stable under the glycosidation conditions (entry 6), although many of the strong thiophilic regents used for the activation of thioglycosides attack the allyl protecting groups and other C-C double bonds.

Because of its high reactivity and chemoselectivity described in this paper, [PhIO-Tf_2O] will be versatile for the synthesis of complex oligosaccharides. High chemoselectivity of this reagent to thioglycosides suggests that other hypervalent iodine reagents may also be applicable for the activation of thioglycosides.

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4. Furuki, R.; Kitamura, T.; Taniguchi, H. *63rd National Meeting of the Chemical Society of Japan*, Higashi-Osaka, March 1992, Abstr. No. 3E439.
5. A typical reaction procedure is as follows. 1) Preparation of the activating reagent: To a mixture of PhIO (71.0 mg, 323 μmol) and Molecular Sieves 4A (500 mg) in dry dichloroethane (2.0 ml) was added Tf_2O (54 μl, 320 μmol), and the mixture was stirred at room temperature for 70 min to give a reddish-brown solution of the activating reagent. 2) Glycosidation reaction: 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 was added the above solution of the activating reagent at -18°C, and the mixture was stirred at the same temperature for 5 min. Ethyl acetate and saturated aqueous $NaHCO_3$ solution was 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 an oily product as a mixture of α- and β-anomers: Yield 206 mg (78%).
6. In acetonitrile, the solution of [PhIO-Tf_2O] was added to a mixture of a donor and an acceptor at -78°C. The temperature of the mixture was then raised to -18°C. Acetonitrile used for the glycosidation must be purified by refluxing for 3 h with P_2O_5 followed by careful distillation under N_2 atmosphere.
7. The reaction was completed within 1 min at -18°C both in dichloroethane and in acetonitrile.
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9. The terminologies, "armed" and "disarmed", were introduced by Fraser-Reid et al. to differentiate the reactivities of n-pentenyl glycosides. The more reactive n-pentenyl glycosides whose 2-OH group are protected with ether-type protecting groups are called "armed", and the less reactive 2-*O*-acylated n-pentenyl glycosides are called "disarmed", respectively: Mootoo, D. R.; Konradsson, P.; Udodong, U; Fraser-Reid, B. *J. Am. Chem. Soc.* **1990**, *110*, 5583.
10. The chemospecific glycosidation of "armed" donor and "disarmed" acceptor were also effected by use of either thioglycosides[1a)] or n-pentenyl glycosides[9)] using iodonium dicollidine perchlorate as a promoter.

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