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# Iodine Monochloride/Silver Trifluoromethanesulfonate (ICl/AgOTf) as a Convenient Promoter System for *O*-Glycoside Synthesis

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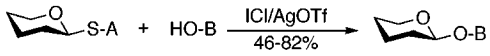
## ABSTRACT




A = Me, Et, Ph, C(S)OEt
B = saccharide moiety

**The novel promoter system iodine monochloride/silver trifluoromethanesulfonate (ICl/AgOTf) was evaluated with various thioglycoside donors and saccharide acceptors, and *O*-glycosides were obtained in 46–82% yield. Several practical advantages of the ICl/AgOTf system over known promoter systems were observed, such as convenient handling of the reagents and absence of byproducts related to *N*-succinimide.**

*O*-Glycosides, such as glycosphingolipids, are biologically significant inter alia as tumor-associated antigens and receptors for various bacterial and viral pathogens.[1] Consequently, numerous methods of *O*-glycosylation have been developed, of which thioglycoside methodology is one of the most versatile and widespread.[2] In short, such methodology employs a thioglycoside donor (e.g., having an alkylthio aglycon) which is *O*-glycosidically condensed with a carbohydrate acceptor in the presence of a thiophilic agent, where the latter is generated by a promoter system and transforms the aglycon into a good leaving group. There are numerous promoter systems for thioglycoside activation,[2,3] of which sulfenylhalides/silver trifluoromethanesulfonate, such as PhSCl/AgOTf[4] and MeSBr/AgOTf,[5] or *N*-iodosuc-

† Deceased in June 2000.

(1) (a) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, *14*, 2137−2160. (b) DeNinno, M. P. *Synthesis* **1991**, 583−593.

(2) *Carbohydrate Chemistry*, 1st ed.; Boons, G.-J., Ed.; Blackie Academic & Professional: London, 1998; and references therein.

(3) (a) *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: Amsterdam, 1996. (b) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997.

(4) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706.

(5) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13−C17.

(6) (a) Veeneman, G. H.; Van Leeuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331−1334. (b) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 270−272.

(7) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313−4316.

(8) (a) Turek, D. Ph.D. Thesis, Stockholm University, Stockholm, Sweden, 2000. (b) Andersson, M.; Konradsson, P.; Oscarsson, S.; Öhberg, L. *J. Carbohydr. Chem.*, in press.

(9) (a) Ravindranathan Kartha, K. P.; Cura, P.; Aloui, M.; Readman, S. K.; Rutherford, T. J.; Field, R. A. *Tetrahedron: Asymmetry.* **2000**, *11*, 581−593. (b) Ravindranathan Kartha, K. P.; Field, R. A. *Tetrahedron Lett.* **1997**, *38*, 8233−8236.

(10) Iodine monochloride is commercially available as a dry 1.0 M solution in dichloromethane. Silver trifluoromethanesulfonate is soluble in acetonitrile and easily dried in vacuo. The entire procedure is substantially free from offensive odors.

(11) **Representative Experimental Procedure.** A stirred solution of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (**1**; 76 mg, 0.15 mmol) and 2-(trimethylsilyl)ethyl 6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**; 50 mg, 0.10 mmol) in dichloromethane (0.75 mL) was cooled to −45 °C under an argon atmosphere. A solution of silver trifluoromethanesulfonate (77 mg, 0.30 mmol) in acetonitrile (0.50 mL) was added followed by dropwise addition of a 1.0 M solution of iodine monochloride in dichloromethane (0.25 mL, 0.25 mmol) during 10 min. After 2 h, diisopropylamine (0.20 mL, 1.4 mmol) was added and stirring was continued for 20 min. The reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed (heptane/ethyl acetate, 3:1 → 1:1) on silica gel to give 2-(trimethylsilyl)ethyl 6-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-β-D-glucopyranoside (**3**; 78.2 mg, 82%) as a syrup.

(12) Jacob, L. A.; Chen, B. L.; Stec, D. *Synthesis* **1993**, *6*, 611−614.

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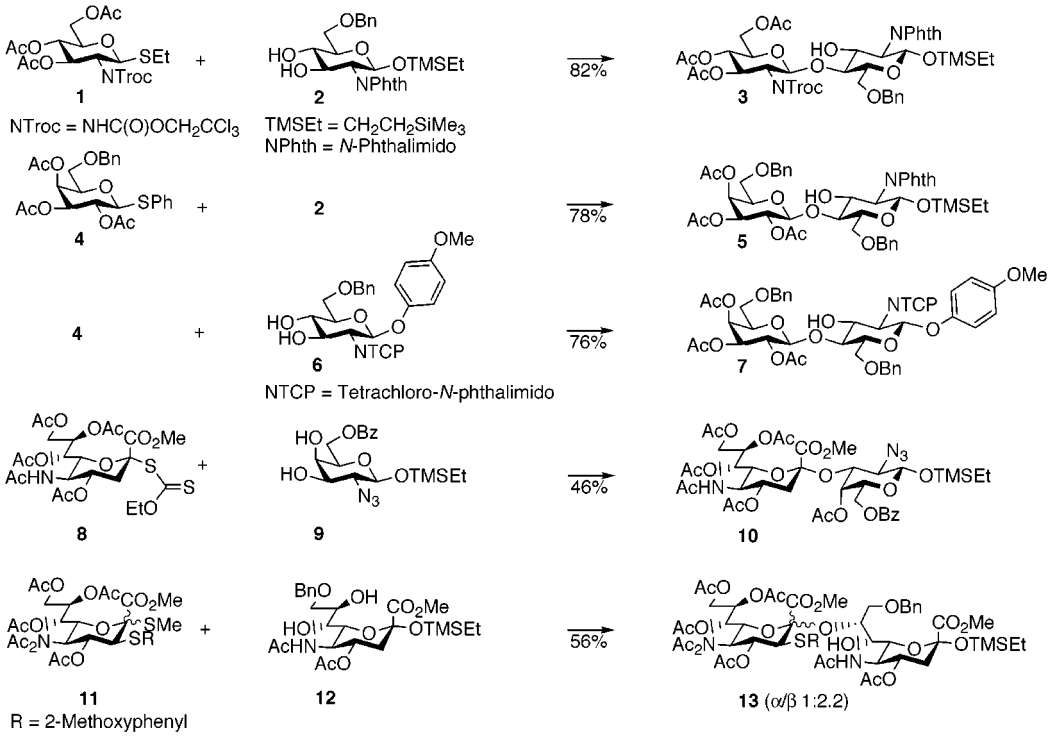
**Scheme 1.** Evaluation of ICl/AgOTf as Promoter System for Various *O*-Glycosylations with Thioglycoside Donors




cinimide (NIS) combined with either trifluoromethanesulfonic acid (TfOH)[6] or silver trifluoromethanesulfonate[7] appear to be the most commonly used. These systems are substantially comparable as regards yield of the desired *O*-glycosylated product. Hence, practical aspects such as preparation time, reagent handling and ease of reagent/product purification play an important role in the choice of promoter system. This is especially true for nonspecialists entering the present field. Since sulfenyl halides are toxic, malodorous and unstable, thus also requiring preparation by the practitioner immediately before the reaction at hand, they are seldom a first choice. As a consequence, the *N*-iodosuccinimide systems are often preferred. However, those systems generate *N*-succinimide, which can be troublesome to separate from the desired *O*-glycoside product by conventional silica gel chromatography. Furthermore, it has recently been reported that *N*-succinimidyl glycosides are potential byproducts, especially with reactive donors and unreactive acceptors.[8]

Iodine and its interhalogen compounds have been used for thioglycoside activation, e.g., in the preparation of glycosyl halides.[9] We now report the novel promoter system iodine monochloride/silver trifluoromethanesulfonate (ICl/AgOTf). This combination was found to have none of the aforementioned drawbacks and provides both efficient and practical[10] means of performing *O*-glycoside synthesis with thioglycoside donors.

To evaluate the full potential of the present promoter system, we decided to perform the glycosylations with some representative substrates. A considerable variety of protective groups was thereby also subjected to the reaction conditions (Scheme 1 and Table 1).[11]

The results set forth demonstrate the general applicability of the present method, and the yields obtained are all comparable to those obtained by other methods. Moreover, since it has been reported that iodine monochloride/silver tetrafluoroborate in methanol can iodinate even deactivated aromatic rings,[12] we find it noteworthy that no aromatic

**Table 1.** Reaction Data for Scheme 1

| donor | acceptor | mole ratio[a] | reaction conditions[b] | product[c] | yield[d,e] (%) |
|---|---|---|---|---|---|
| **1**[14] | **2**[14] | 1.5:1.0:2.5:3.0 | MeCN/$CH_2Cl_2$ 1:2, −45 °C, 2 h | **3**[14] | 82 |
| **4**[15] | **2** | 1.3:1.0:2.5:3.0 | MeCN/$CH_2Cl_2$ 5:12, −78 °C, 1 h | **5**[15] | 78 |
| **4** | **6**[15] | 1.4:1.0:2.5:3.0 | MeCN/$CH_2Cl_2$ 1:2, −78 °C, 3 h | **7**[15] | 76 |
| **8**[16] | **9**[17] | 1.5:1.0:1.5:1.5 | MeCN/$CH_2Cl_2$ 4:3, MS 3 Å, −78 °C, 2.5 h | **10**[17] | 46 |
| **11**[18] | **12**[18] | 1.0:1.6:1.4:1.4 | MeCN, MS 3 Å, −40 °C, 2 h | **13**[18] | 56 |

[a] Donor/acceptor/ICl/AgOTf. [b] Solvents and molecular sieves were dried and activated, respectively, using conventional methods. [c] NMR data were in agreement with those reported in the literature. [d] Based on the substrate (donor or acceptor) present in the smallest amount. [e] Unoptimized yields.

addition of iodine was observed in the glycosylations (see **7** and **13** in particular). All of the reactions appeared to be very rapid, also for the least reactive donor **4**, albeit they were allowed to progress at least 1 h for practical reasons. Also note that the iodonium species generated by this method selectively reacts with an anomeric methylthio group in the presence of a 2-methoxyphenylthio ring substituent (donor **11**).[13]

(13) Using MeSBr/AgOTf as alternative promoter system gave the same diastereomeric ratio, and the mixture was inseparable by conventional silica gel chromatography.

(14) Ellervik, U.; Magnusson, G. *Carbohydr. Res.* **1996**, *280*, 251−260.
(15) Ellervik, U.; Magnusson, G. *J. Org. Chem.* **1998**, *63*, 9314−9322.
(16) Marra, A.; Sinay, P. *Carbohydr. Res.* **1990**, *195*, 303−308.
(17) Wilstermann, M.; Kononov, L. O.; Nilsson, U.; Ray, A. K.; Magnusson, G. *J. Am. Chem. Soc.* **1995**, *117*, 4742−4754. The crude product was acetylated to facilitate purification.
(18) Ercegovic, T. Ph.D. Thesis, The Lund Institute of Technology, University of Lund, Lund, Sweden, 2001, in press. Available at http://www.lub.lu.se/dissdb/ in pdf format as of February 27, 2001.

In summary, we believe that the efficiency and convenient handling of the ICl/AgOTf promoter system can provide an attractive alternative in *O*-glycoside synthesis with thioglycoside donors.

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**Supporting Information Available:** Complete experimental details and $^1$H NMR spectra for compounds **11**−**13** as well as HR FAB-MS spectra for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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