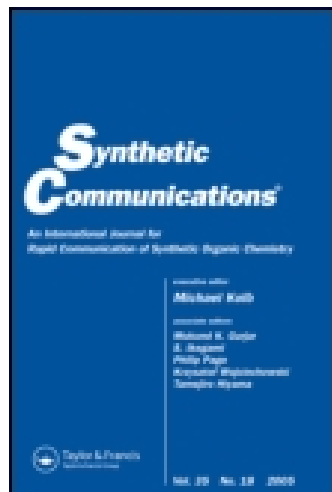


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Indium(III) Triflate-Mediated One-Step Preparation of Glycosyl Halides from Free Sugars

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INDIUM(III) TRIFLATE-MEDIATED ONE-STEP PREPARATION OF GLYCOSYL HALIDES FROM FREE SUGARS

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In(OTf)₃ has been found to be an efficient catalyst for the direct conversion of reducing sugars to their respective acylated glycosyl halides in good yields under mild conditions. The glycosyl halides so obtained can be converted to alkyl glycosides in the same pot by reacting them with the respective alcohols in good yield.

Keywords: Glycoside synthesis; indium(III) triflate; Lewis acid; one-step glycosyl halide synthesis

INTRODUCTION

Glycosyl halides are important glycosyl donors for the preparation of *O*- and *S*-glycosides. Traditionally acetochloro-, benzochloro-, and benzobromoglycoses are prepared from the corresponding reducing sugars via their respective per-*O*-esters in two steps.^[1] Preparation of glycosyl esters is generally achieved by treating the sugar with either the desired acid anhydride under catalysis by acids such as HClO₄/H₂SO₄^[2] or a Lewis acid^[3] or the desired acid halide/acid anhydride in pyridine.^[4] The glycosyl esters so obtained are subsequently treated with the desired halide donor reagent to obtain the desired glycosyl halide.^[1] We reasoned that if the sugar is treated with an acid halide in the presence of a Lewis acid, the hydrogen halide formed as by-product in the reaction must be available for reaction with the glycosyl ester obtained as an intermediate, thus leading to the formation of the respective glycosyl halide in one step (Fig. 1).

Based on our recent observations that In(OTf)₃ is a very efficient Lewis acid for the conversion of sugars to their per-*O*-acylated derivatives by reaction with stoichiometric quantities of the respective neat acid anhydrides^[5] we decided to investigate this reaction utilizing this novel Lewis acid^[6] for the purpose. The results are reported here.

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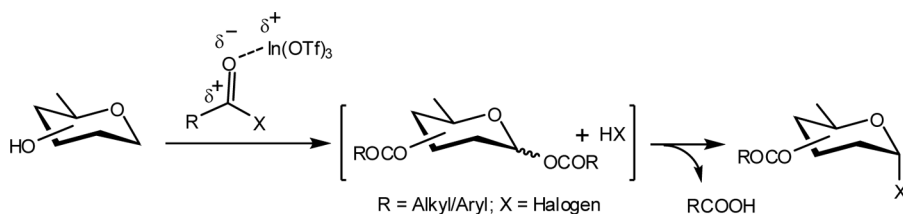
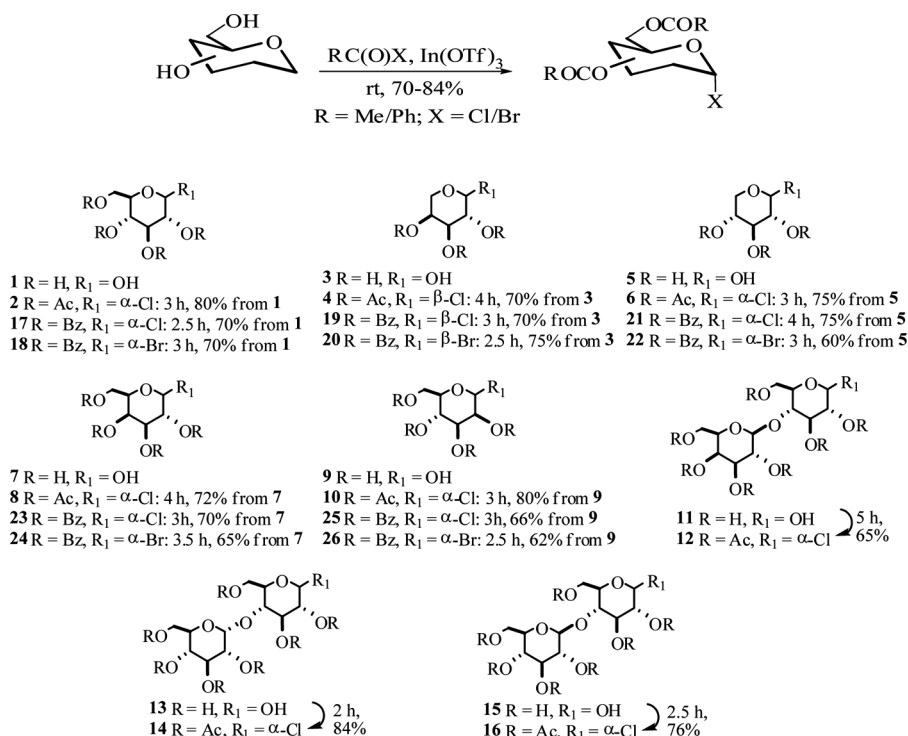


Figure 1. In(OTf)₃-mediated conversion of sugars to their acylated glycosyl halides.

RESULTS AND DISCUSSION

When D-glucose (**1**) was treated with acetyl chloride in the presence of In(OTf)₃, the sugar went into solution in about 25 min. After allowing the reaction to continue for an additional 2.5 h at rt, the expected acetochloro- α -D-glucopyranose (**2**) was obtained, following a simple aqueous workup, as a crystalline product in 80% yield (Scheme 1).

No reaction was observed in the absence of the metal triflate. Other sugars [pentoses: L-arabinose (**3**) and D-xylose (**5**); hexoses: D-galactose (**7**) and D-mannose

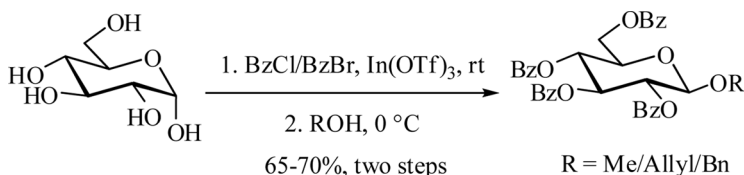


Scheme 1. In(OTf)₃-catalyzed one-step preparation of glycosyl halides from sugars.

(9); disaccharides: D-lactose (11), D-maltose (13), and D-cellobiose (15)] also reacted with ease, giving the respective acetochloro derivatives (4, 6, 8, 10, 12, 14, and 16 respectively) in good yields (Scheme 1). Other common Lewis acids such as AlCl_3 , ZnCl_2 , and InCl_3 were also investigated as possible alternatives for $\text{In}(\text{OTf})_3$. The results of the experiments conducted using 1 as the model substrate showed AlCl_3 to be ineffective for the reaction. In the case of ZnCl_2 , comparable efficiency [as for $\text{In}(\text{OTf})_3$ under the conditions reported (0.8 mol% of $\text{In}(\text{OTf})_3$)] required use of stoichiometric proportions of the catalyst and InCl_3 gave comparable results when it was used at about the 3.2 mol% level.

The preparation of benzochloro- as well as benzobromosugars promoted by $\text{In}(\text{OTf})_3$ was also tried. Thus, treatment of monosaccharides such as 1, 3, 5, 7, and 9 with BzCl/BzBr in the presence of the metal triflate resulted in the desired smooth reaction, and the respective halides 17/18, 19/20, 21/22, 23/24, and 25/26 were obtained in good yields (Scheme 1). However, similar reactions with the disaccharides 11/13/15 led to the cleavage of the interglycosidic linkage, giving the corresponding 2,3,4,6-tetra-*O*-benzoylated glycosyl halides of the monosaccharides expected of them.

The applicability of the present method for the preparation of simple alkyl/substituted alkyl glycosides such as the methyl, allyl, and benzyl glycosides of hexoses such as 1 and 7 often used as starting materials in many synthetic carbohydrate transformations was also verified by conducting model one-pot, two-step reactions in which the initially formed glycosyl halide was treated with the desired alcohol in a subsequent step in the same pot. Methyl/allyl/benzyl 2,3,4,6-tetra-*O*-acetyl-/benzoyl- β -D-glucopyranosides were thus also synthesized successfully (Scheme 2). Although obvious, it is important to note that while the latter may serve as a convenient method for the preparation of simple alkyl glycosides such as those described (wherein the aglycon residues are derived from cheap and commercially available alcohol acceptors, excess use of which therefore may be acceptable), it may not be suitable for building sugar–sugar linkages as required in oligosaccharide synthesis (considering the cost involved; detailed optimization studies will be necessary for assessing the actual sugar acceptor requirement in the second step). Because an acyl halide (the halide donor reagent) is used in excess of the stoichiometric requirement during the initial glycosyl halide preparation, a corresponding proportion of the glycosyl donor reagent (needed for the desired glycoside synthesis in the second step) should be expected to be consumed in its possible side reaction with the acyl halide, as a result of which an increase in the glycosyl acceptor requirement is experienced.



Scheme 2. $\text{In}(\text{OTf})_3$ -catalyzed one-pot preparation of alkyl glycosides.

CONCLUSIONS

In(OTf)₃ has been found to be effective in the conversion of free sugars to their respective glycosyl halides in one step. The glycosyl halides so prepared can be converted to alkyl glycosides in the same pot in a sequential manner if desired. We hope that the method will find wide acceptance in the area of synthetic carbohydrate chemistry.

EXPERIMENTAL

General Procedure for the Preparation of the Glycosyl Halide

The free sugar was suspended in an excess amount of acetyl chloride or benzoyl chloride/bromide and was stirred at room temperature. In(OTf)₃ (25 to 40 mg/g sugar or its derivative, see Scheme 1) was added, and stirring was continued until thin-layer chromatography (TLC) showed the reaction to be complete. In small-scale reactions, the reaction mixture was diluted with CH₂Cl₂ and washed successively with aqueous Na₂CO₃ and brine. The organic layer was then dried (Na₂SO₄) and concentrated to give the product. In large-scale preparations, the reaction mixture was poured into ice-cold dilute Na₂CO₃ solution with stirring (pH, approximately 7.5), and the product was allowed to crystallize in the refrigerator and was separated by filtration. The products were recrystallized from diethyl ether and petroleum ether. The products thus obtained were pure enough in most of the cases for use elsewhere directly or else were purified by column chromatography. The following compounds were prepared: **2**,^[7] **4**,^[8] **6**,^[9] **8**, **10**,^[7] **12**,^[10] **14**,^[7] **16**,^[11] **17**, **18**,^[12] **19**,^[13] **20**,^[14] **21**,^[13] **22**,^[14] **23**,^[15] **24**,^[16] **25**, and **26**.^[12]

Typical Procedure for the Preparation of **2**

In(OTf)₃ (25 mg, 4.4×10^{-2} mmol, 0.79 mol%) was added at room temperature, to a suspension of D-glucose (**1**, 1.0 g, 5.55 mmol) in acetyl chloride (7 ml), and stirring was continued until TLC (EtOAc-*n*-hex, 1:1, v/v) showed complete consumption of the starting sugar. No undissolved sugar was visible at this stage. Aqueous workup and crystallization of the halide formed yielded crystalline 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl chloride (**2**, 1.62 g, 80%).^[7]

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REFERENCES

1. (a) Lemieux, R. U. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 221–222, and the references cited therein; (b) Lemieux, R. U. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 223–224; (c) Lemieux, R. U. In *Methods in Carbohydrate Chemistry*; R. L. Whistler,

- M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 224–225; (d) Fletcher Jr., H. G. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 226–228; (e) Fletcher Jr., H. G. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 228–230; For other methods, see Wang, Q.; Fu, J.; Zhang, J. A facile preparation of peracetylated α -aldopyranosyl chlorides with thionyl chloride and tin tetrachloride. *Carbohydr. Res.* **2008**, *343*, 2989–2991, and the references cited therein; Ibatullin, F. M.; Selivanov, S. I. Reaction of 1,2-*trans*-glycosyl acetates with phosphorus pentachloride: New efficient approach to 1,2-*trans*-glycosyl chlorides. *Tetrahedron Lett.* **2002**, *43*, 9577–9580, and the references cited therein; see also Ref. 7.
2. Wolfrom, M. L.; Thompson, A. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 211–215, and the references cited therein.
 3. Kartha, K. P. R.; Field, R. A. Iodine: A versatile reagent in carbohydrate chemistry, IV: Per-*O*-acetylation, regioselective acylation, and acetolysis. *Tetrahedron* **1997**, *53*, 11753–11766, and references cited therein.
 4. (a) Fletcher Jr., H. G. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 234–237; (b) Van Cleve, J. W. In *Methods in Carbohydrate Chemistry*; R. L. Whistler, M. L. Wolfrom (Eds.); Academic Press Inc.: New York, 1963; vol. 2, pp. 237–238.
 5. Giri, S. K.; Verma, M.; Kartha, K. P. R. Indium(III) triflate: A highly efficient catalyst for reactions of sugars. *J. Carbohydr. Chem.* **2008**, *27*, 464–478.
 6. (a) Gregg, B. T.; Golden, K. C.; Quinn, J. F. Indium(III)trifluoromethanesulfonate as a mild, efficient catalyst for the formation of acetals and ketals in the presence of acid-sensitive functional groups. *Tetrahedron* **2008**, *64*, 3287–3295; (b) Tran, A. T.; Deydier, S.; Bonnaffe, D.; Narvor, C. L. Regioselective green anomeric deacetylation catalyzed by lanthanide triflates. *Tetrahedron Lett.* **2008**, *49*, 2163–2165; (c) Nakamura, M.; Endo, K.; Nakamura, E. Indium triflate-catalyzed vinylation of β -ketoesters with acetylene gas. *Org. Lett.* **2005**, *7*(15), 3279–3281; (d) Ghosh, R.; Maiti, S.; Chakraborty, A.; Halder, R. Indium triflate: A reusable catalyst for expeditious chemoselective conversion of aldehydes to acylals. *J. Mol. Catal. A: Chem.* **2004**, *215*, 49–53; (e) Mineno, T. A fast and practical approach to tetrahydropyranylation and depyranylation of alcohols using indium triflate. *Tetrahedron Lett.* **2002**, *43*, 7975–7978; (f) Yadav, J. S.; Reddy, B. V. S.; Sadashiv, K.; Harikishan, K. Indium triflate-catalyzed ring opening of aziridines with carboxylic acids. *Tetrahedron Lett.* **2002**, *43*, 2099–2101; (g) Frost, C. G.; Hartley, J. P.; Whittle, A. J. Indium-catalyzed aryl and alkyl sulfonylation of aromatics. *Synlett* **2001**, *6*, 830–832; (h) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. Efficient aromatic and heteroatom acylations using catalytic indium complexes with lithium perchlorate. *Tetrahedron Lett.* **2001**, *42*, 773–775; (i) Chauhan, K. K.; Frost, C. G. Advances in indium-catalyzed organic synthesis. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3015–3019; (j) Prajapati, D.; Laskar, D. D.; Sandhu, J. S. Indium trifluoromethanesulfonate [In(OTf)₃]: A novel reusable catalyst for intramolecular Diels–Alder reactions. *Tetrahedron Lett.* **2000**, *41*, 8639–8643; (k) Li, C.-J.; Chan, T.-H. Organic syntheses using indium-mediated and catalyzed reactions in aqueous media. *Tetrahedron* **1999**, *55*, 11149–11176; (l) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. Indium triflate: An efficient catalyst for acylation reactions. *Synlett* **1999**, *11*, 1743–1744; (m) Kobayashi, S.; Nagayama, S.; Busujima, T. Lewis acid catalysts stable in water: Correlation between catalytic activity in water and hydrolysis constants and exchange rate constants for substitution of inner-sphere water ligands. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288; (n) Cintas, P. Synthetic organoindium chemistry: What makes indium so appealing? *Synlett* **1995**, 1087–1096.

7. Montero, J.-L.; Winum, J.-Y.; Leydet, A.; Kamal, M.; Pavia, A. A.; Roque, J.-P. A convenient synthesis of peracetylated glycosyl halides using bismuth(III) halides as catalysts. *Carbohydr. Res.* **1997**, *297*, 175–180.
8. Brauns, D. H. Fluoro-acetyl derivatives of sugars. III. Optical rotation and atomic dimension (continued). *J. Am. Chem. Soc.* **1924**, *46*, 1484–1488.
9. Kovács, G.; Micskei, K.; Somsák, L. Preparation of acetylated pyranoid glycols from glycosyl halides by chromium(II) complexes under aqueous biphasic conditions. *Carbohydr. Res.* **2001**, *336*, 225–228.
10. Xue, W.; Cheng, X.; Fan, J.; Diao, H.; Wang, C.; Dong, L.; Luo, Y.; Chen, J.; Zhang, J. A novel stereoselective synthesis of 1,2-*trans*-thioaldoses. *Tetrahedron Lett.* **2007**, *48*, 6092–6095.
11. Dick, W. E.; Wesleder, D. Facile synthesis of 1,2-*trans*-O-acetylglycosyl chloride derivatives of cellobiose, lactose, and D-glucose. *Carbohydr. Res.* **1976**, *46*(2), 173–182.
12. Ness, R. K.; Fletcher Jr., H. G.; Hudson, C. S. The reaction of 2,3,4,6-tetrabenzoyl- α -D-glucopyranosyl bromide and 2,3,4,6-tetrabenzoyl- α -D-mannopyranosyl bromide with methanol: Certain benzoylated derivatives of D-glucose and D-Mannose. *J. Am. Chem. Soc.* **1950**, *72*, 2200–2205.
13. Durette, P. L.; Horton, D. Conformational studies on pyranoid sugar derivatives by NMR spectroscopy: Conformational equilibria of some peracetylated aldopentopyranosyl halides in solution. *Carbohydr. Res.* **1971**, *18*, 57–80.
14. Fletcher Jr., H. G.; Hudson, C. S. The reactions of tribenzoyl- β -D-arabinopyranosyl bromide and tribenzoyl- α -D-xylopyranosyl bromide with methanol. *J. Am. Chem. Soc.* **1950**, *72*, 4173–4177.
15. Yoon, S.; Kim, D.; Shin, J. E. N. A facile synthesis of p-nitrophenyl glycosides. *Bull. Korean Chem. Soc.* **1994**, *15*, 559–563.
16. Polat, T.; Linhardt, R. J. Zinc triflate-benzoyl bromide: A versatile reagent for the conversion of ether into benzoate protecting groups and ether glycosides into glycosyl bromides. *Carbohydr. Res.* **2003**, *338*, 447–449.