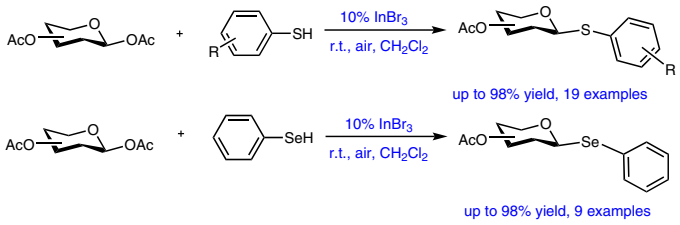
Synlett T. Ma et al. Letter

$InBr_3$-Catalyzed Synthesis of Aryl 1,2-*trans*-Thio(seleno)glycosides

Teng Ma
Changwei Li
Haijing Liang
Zhaoyan Wang
Lan Yu*
Weihua Xue*

School of Pharmacy, Lanzhou University, Lanzhou, 730000, P. R. of China
xuewh@lzu.edu.cn



Received: 25.05.2017
Accepted after revision: 23.06.2017
Published online: 20.07.2017
DOI: 10.1055/s-0036-1588507; Art ID: st-2017-w0399-l

Abstract $InBr_3$ is demonstrated to be an efficient catalyst for reactions of fully acetated aldoses with aryl mercaptans or selenophenol at room temperature, rapidly furnishing the corresponding thioglycosides or selenoglycosides with exclusively 1,2-*trans*-stereoselectivity. This bromide is an air- and moisture-stable Lewis acid and therefore the reactions can be performed in air atmosphere making the procedure simple to perform.

Key words $InBr_3$, thioglycosides, selenoglycosides, stereoselectivity, aldose acetates

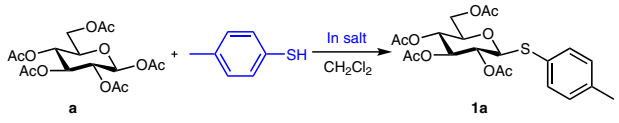
The synthesis and application of carbohydrate derivatives remains a subject of great interest because of the remarkable biological relevance of carbohydrate motifs. Among them, thioglycosides represent a valuable class of functional compounds, in which a sulfur atom has replaced the glycosidic oxygen atom. These glycomimetics exhibit apparent advantages over their parent molecules because they increase the metabolic stability and might lead to the rational design of new generations of therapeutic agents.[1] Additionally, a large number of naturally occurring antibiotics[2] and antitumor compounds possess thioglycoses as crucial structural moieties.[3] As thioglycosides are usually stable under many protecting group transformations, multifunctional derivatives can be produced relatively easily. Moreover, thioglycosides are readily converted into other glycosyl donors that are commonly used in oligosaccharide synthesis, including halides,[4] fluorides, and sulfoxides.[5] In particular, thioglycosides, featuring tunable reactivity dependent on different protecting groups, have been established to be attractive building blocks for the one-pot sequential assembly of complex oligosaccharides. Thus, synthesis of these organosulfur compounds with high efficiency is of great value.

Considerable effort has been directed toward the development of general and selective methods for preparing thioglycosides. Preparation of thioglycosides is accomplished by metal-catalyzed coupling reaction of aryl halides with nucleophilic thioglycosylating reagents,[6–8] although these nucleophiles are relatively inaccessible and their preparation requires tedious synthetic procedures and laborious chromatographic processes. The most commonly used strategy for the construction of *S*-glycosidic bonds involves treatment of peracetated aldoses with commercially available aryl mercaptans in the presence of Lewis acids. Diverse Lewis acids such as $FeCl_3$,[9] $ZiCl_4$,[10] $Et_2O{\cdot}BF_3$,[11] and $Cu(OTf)_2$[12] have been reported to enable the conversion; nevertheless, in most instances, high loading — often a stoichiometric amount — is required to achieve satisfactory yields. Especially, these Lewis acid catalyzed reactions usually give a mixture of α,β-anomers. To date, examples of glycosylating aryl mercaptans under the catalysis of transition metals remain scarce. MoO_2Cl_2 was first found to be an effective catalyst for reaction of fully acetated aldoses with thiols.[13] FeI_3 was then reported to be an alternative promoter.[14] Unfortunately, the strong sensitivity of these halides to moisture and air rendered the preparation and handling of them fairly difficult. Phenyl selenoglycosides constitute another category of useful glycosyl donors. They can be selectively activated in the presence of thioglycosides, which make them attractive in oligosaccharide synthesis.[15] Analogous to thioglycosides, they are mostly prepared from acid-activated reaction of peracetylated aldoses with phenylselenol. A potentially promising alternative protocol relies on the phenylselenolate anion generated in situ from the reduction of phenyldiselenide with reducing agents[16] and its subsequent nucleophilic attack toward glycosyl bromides.

Although these methods sometimes provide satisfactory yields, they suffer from laborious workup and high consumption of excess reagents. To our knowledge, examples of catalytic reactions that can be used to access selenoglycosides under mild conditions remain unknown. Therefore, there remains a need to develop an efficient catalyst that overcomes the above drawbacks.

Indium species are widely applied to mediate various reactions, producing diverse synthetic intermediates as well as many natural bioactive products. Another distinctive advantage of using indium compounds is that both indium metal and its derivatives are less toxic or even nontoxic.[17] Among a legion of readily accessible indium reagents, $InBr_3$ is a remarkably air- and water-stable crystalline solid. Moreover, it has been found to be an effective catalyst for the synthesis of important functional molecules.[18] Based on our previous work, herein we report $InBr_3$-promoted condensation of peracetylated aldoses with some simple arylthiols or selenophenol. In most cases, the reactions proceed smoothly to furnish thio(seleno)glycosides.

Table 1 Catalyst Optimization for the Thioglycoside Synthesis[a]



Entry	In salt (mol%)	Time (h)	Yield (%)[b]
1	$In(OTf)_3$ (10)	24	52
2	$In(NTf)_3$ (10)	24	39
3	$InCl_3$ (10)	24	26
4	$InBr_3$ (10)	2	97
5	InI_3 (10)	2	98
6	$InBr_3$ (5)	2	92

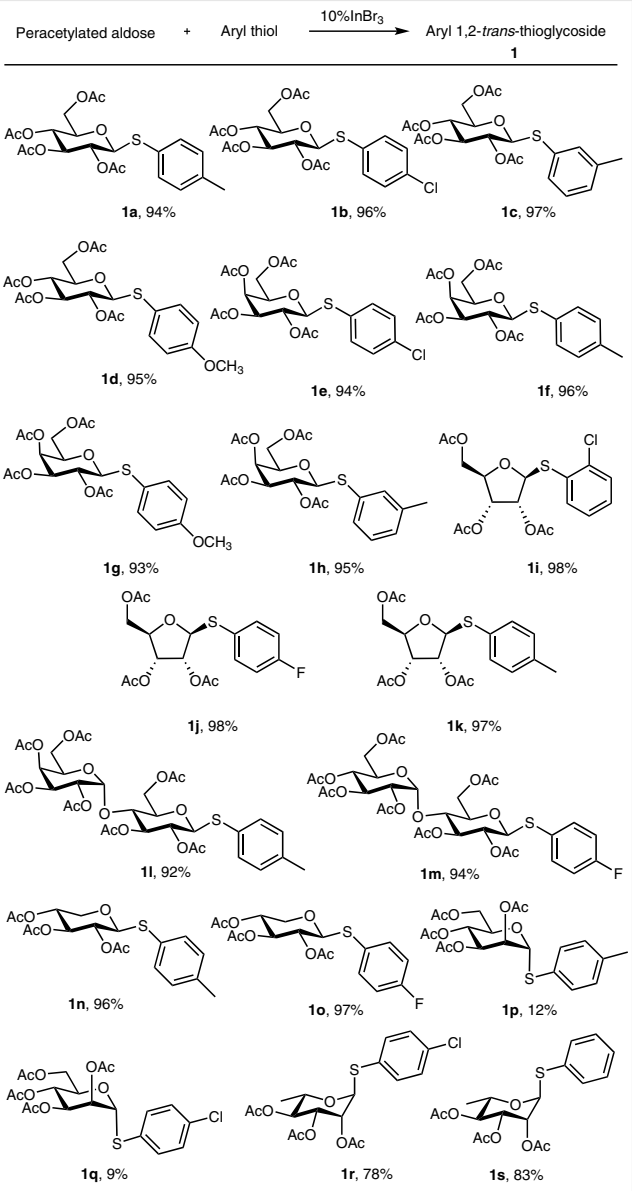
[a] The reactions were performed using **a** (0.1 mmol), *p*-thiocresol (0.12 mmol) and catalyst in CH_2Cl_2 (2 mL) at r.t. under air.
[b] Isolated yield.

We initially ran the reaction of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**a**) with *p*-thiocresol. The desired transformation was examined using a variety of indium species (10% mol) in CH_2Cl_2 at room temperature for 2 h (Table 1). Treatment of the reaction with In $(OTf)_3$ gave the desired product **1a** in 52% yield (entry 1), but the reaction did not proceed to completion even after 24 h. This observation prompted us to screen other indium salts to promote glycosylation. The switch of the counterion to NTf^- decreased the yield to 39% (entry 2). Activation of the glycosylation with $InCl_3$ was less effective in the reaction for 24 h, giving a yield of 26% (entry 3). Further optimization of the reaction conditions with $InBr_3$ and InI_3 revealed that this reaction performed much better within 2 h, and compound **1a** was isolated in an excellent yield (entries 4 and 5). Although InI_3 is tolerant of water, its highly hygroscopic nature is inconvenient. In contrast, $InBr_3$ has high stability to air and moisture and is comparatively inexpensive, so this reagent was selected as the optimal catalyst in the protocol. A reduction of its loading to 5 mol% led to a slightly lower yield (entry 6). We also noted that the α-isomer of **a** was unreactive and that the substitution of alkylthiols for *p*-thiocreso did not lead to the formation of **1a**.

The thioglycosylation reaction could be performed on a gram scale. Treating a solution of **a** (3.90 g, 10.0 mmol) and *p*-thiocresol (1.49 g, 12.0 mmol) in CH_2Cl_2 (50 mL) with catalytic $InBr_3$ (354 mg, 1.0 mmol) for approximately 4 h, furnished **1a** in 93% yield.

With the optimal conditions in hand, the use of a range of commercially available arylthiols bearing substituents and various readily accessible aldosyl donors in the reactions was explored. As shown in Scheme 1, all of the expected thioglycosides were obtained within 2 h. Among them, 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose led to exclusive formation of the corresponding β-thioglycoside **2a–d**. Similar results were observed in the case of β-D-galactopyranosyl peracetates, and the expected β-configured product **2e–h** were isolated in almost quantitative yield. β-Ribofuranose tetraacetates also reacted in excellent yields (**1i–k**) with retention of β-configuration. Again, the procedures could be also applied to β-disaccharides (**1l–m**), with no detectable amounts of byproducts formed from cleavage of *O*-glycosidic bonds being observed and no unexpected α-thioglycosides were generated. Furthermore, peracetated β-pyranosides derived from pentoses such as a xylose were subjected to highly efficient thioglycosylation under the same conditions, giving the pure β-thioglycosides **1n–o**. Thus, these 1,2-*trans*-aldosyl acetates showed high reactivity, and the yields of the corresponding products were apparently not affected by substituents including electron-drawing or electron-donating groups on the arylthiols.

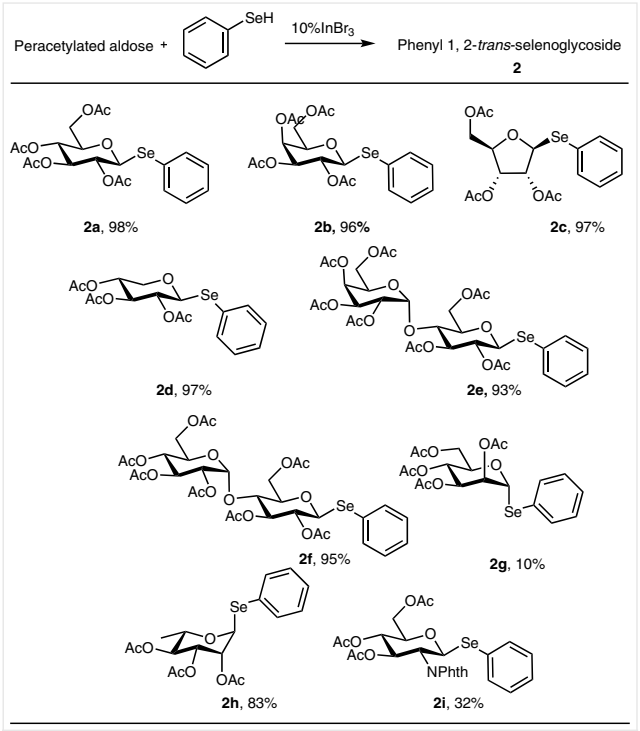
Attention was also paid to the anomeric selectivity and the isolated yields resulting from peracetated 1,2-*trans*-mannose under the same conditions. Disappointingly, it was found to be an unreactive donor. Its 1,2-*cis*-isomer was inseparable from an anomeric mixture, so a mixture of isomer (α/β ratio of 4:1) was used for further examination. Equally, only α-thioglycosides were formed, albeit in low yields (**1p–q**). The results from mannose are similar to observations reported by Weng.[14] Besides the above D-aldoses, common L-rhamnose was investigated in our study; curiously, protocols reported by Chen[13] and Weng did not provide experimental details on this. Alike to mannose, its derivatives from the entire acetylation exist anomerically as α-form. α-L-Rhamnopyranosyl tetraacetates underwent thioglycosylation to produced moderate yields of the α-glycoside **1r–s** as the only product, respectively.



Scheme 1 Reactions of peracetylated aldoses with aryl thiols. *Reagent and conditions*: peracetylated aldose (0.1 mmol), aryl thiol (0.12 mmol), $InBr_3$ (3 mg), CH_2Cl_2 (2 mL), r.t. under air for 2 h. Isolated yields based on aldose.

Phenylselenol is much more nucleophilic than thiophenol, so we envisaged that phenylselenol could be glycosylated. The reactions with phenylselenol are shown in Scheme 2. The best results were observed when pure β-aldosyl acetate was used as donor. Selenoglycosidation of these donors required a slightly shorter time to provide selenoglycosides (**2a–f**) with the anticipated complete β-stereoselectivity in excellent yields. No reaction was observed with α-mannose pentacetate donor. Re-examination of its anomeric mixture only afforded a low yield of selenomannoside with a single α-configuration (**2g**). With fully acetylated α-L-rhamnopyranoside used in reaction, 80% yield of pure α-selenoglycoside (**2h**) was obtained. In our protocol 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside is an inactive donor for thioglycosylation, but its phenyl β-D-selenoglycopyranoside could be obtained in low yield of 32% (**2i**) after stirring for 24 h.

^{1}H NMR spectroscopic data of these sulfur and selenium compounds showed that, in all the reactions, 1,2-*trans*-glycosides are exclusively generated without observable contamination of 1,2-*cis*-isomers during our study, which made the chromatographic purification straightforward. The sole formation of the 1,2-*trans* isomer of these glycosides in the can be explained by neighboring-group participation.



Scheme 2 Reactions of peracetylated aldoses with phenylselenol. *Reagents and conditions*: peracetylated aldose (0.1 mmol), selenoglycoside (0.12 mmol), $InBr_3$ (3 mg) and CH_2Cl_2 (2 mL), r.t. under air, >2 h. Isolated yields based on aldoses.

In conclusion, we have developed an efficient method for the formation of S- and Se-glycosidic bonds catalyzed by $InBr_3$. This method provides rapid access to thioglycosides[19] and selenoglycoside[20] with 1,2-*trans*-diastereoselectivity. Moreover, the $InBr_3$ catalyst is affordable and air- and moisture-stable, thus facilitating operation on the bench top. Given these advantages, we believe the method presented herein should find broad application in glycochemistry. Further exploration of the protocol for In-mediated glycosidation is being pursued in our laboratory.

Funding Information

We gratefully acknowledge financial support from the National Science Foundation of China (21402075, 51501080 and 21675070) and the Fundamental Research Funds for the Central Universities, Lanzhou University (lzujbky-2015-307, lzujbky-2016-146, and lzujbky-2017-62)

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588507.

References and Notes

(1) Lian, G.; Zhan, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 12.
(2) Hoeksema, H.; Bannister, B.; Birkenmeyer, R. D.; Kagan, F.; Magerlein, B. J.; Mackellar, F. A.; Schroeder, W.; Slomp, G.; Herr, R. R. *J. Am. Chem. Soc.* **1964**, *86*, 4223.
(3) Nicolau, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556.
(4) Sugiyama, S.; Diakur, J. M. *Org. Lett.* **2000**, *2*, 2713.
(5) Tsegay, S.; Williams, R. J.; Williams, S. J. *Carbohydr. Res.* **2012**, *357*, 16.
(6) For Pd-catalyzed thioglycosylation, see: (a) Brachet, E.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 477. (b) Brachet, E.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Adv. Synth. Catal.* **2013**, *355*, 2627. (c) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. Eur. J.* **2015**, *21*, 1.
(7) For Ni-catalyzed thioglycosylation, see: Brachet, E.; Brion, J.-D.; Messaoudi, S.; Alami, M. A. *Chem. Eur. J.* **2013**, *19*, 15276.
(8) For Cu-catalyzed thioglycosylation, see: Yuan, X.; Kou, Y.; Yu, L.; Zhang, Z.-X.; Xue, W. *Org. Chem. Front.* **2015**, *2*, 1604.
(9) Dasgupta, F.; Singh, P. P.; Srivastava, H. C. *Carbohydr. Res.* **1980**, *80*, 346.
(10) Contour, M.-O.; Defaye, J.; Little, M.; Wong, E. *Carbohydr. Res.* **1989**, *193*, 283.
(11) Das, S. K.; Roy, N. *Carbohydr. Res.* **1996**, *296*, 275.
(12) Tai, C.-A.; Kulkarni, S. S.; Hung, S.-C. *J. Org. Chem.* **2003**, *68*, 8719.
(13) Weng, S.-S.; Lin, Y.-D.; Chen, C.-T. *Org. Lett.* **2006**, *8*, 5633.
(14) Weng, S.-S. *Tetrahedron Lett.* **2009**, *50*, 6414.
(15) Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269.
(16) (a) Mukherjee, C.; Tiwari, P.; Misra, A. K. *Tetrahedron Lett.* **2006**, *47*, 441. (b) Crich, D.; Suk, D.-H.; Sun, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2861.
(17) For a review on the application and nature of indium reagents, see: Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271.
(18) For selected examples, see: (a) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. (b) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (c) Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, 948. (d) Wang, P.; Song, S.; Miao, Z.; Yang, G.; Zhang, A. *Org. Lett.* **2013**, *15*, 3852.
(19) **$InBr_3$-Catalyzed Reaction of Fully Acetylated Aldose with Aryl Thiol; Typical Procedure**: To a solution of β-ribofuranose tetraacetate (0.1 mmol) and 4-fluorobenzenethiol (0.12 mmol) in CH_2Cl_2 (2 mL) was added $InBr_3$ (0.01 mmol) and the reaction mixture was stirred for 2 h at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the resulting residue was subjected to flash chromatograph (petroleum ether–EtOAc, 4:1) to afford the desired product **1j**. Yield: 98%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 8.8, 5.2 Hz, 2 H), 7.04 (t, *J* = 8.7 Hz, 2 H), 5.18–5.24 (m, 3 H), 4.23–4.29 (m, 2 H), 4.10 (dd, *J* = 12.8, 5.4 Hz, 1 H), 2.11 (s, 3 H), 2.08 (s, 3 H), 2.05 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 169.5, 169.3, 164.4, 161.9, 136.3, 126.3, 116.1, 88.0, 80.1, 73.6, 71.3, 63.3, 20.7, 20.5. HRMS (ESI): *m*/*z* [M +H]$^+$ calcd for $C_{17}H_{20}FO_7S$: 387.0914; found: 387.0917.
(20) **$InBr_3$-Catalyzed Reaction of Fully Acetylated Aldose with Phenylselenol; Typical Procedure**: To a solution of β-ribofuranose tetraacetate (0.1 mmol) and phenylselenol (0.12 mmol) in CH_2Cl_2 (2 mL) was added $InBr_3$ (0.01 mmol) and the reaction mixture was stirred for 1.5 h at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the resultant residue was rapidly eluted through a short column of silica gel (ethyl acetate–petroleum ether, 30%) to give the desired product **2c**. Yield: 97%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 6.4 Hz, 2 H), 7.38–7.27 (m, 3 H), 5.55 (d, *J* = 4.0 Hz, 1 H), 5.43–5.38 (m, 1 H), 5.26 (t, *J* = 5.2 Hz, 1 H), 4.32–4.23 (m, 2 H), 4.12–4.05 (m, 1 H), 2.08 (s, 6 H), 2.07 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.6, 169.4, 135.6, 129.2, 128.6, 83.2, 80.0, 75.5, 71.2, 63.2, 20.8, 20.6, 20.5. HRMS (ESI): *m*/*z* [M +H]$^+$ calcd for $C_{17}H_{21}O_7Se$: 417.0452; found: 417.0454.