CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201104007

Organotin-Catalyzed Highly Regioselective Thiocarbonylation of Nonprotected Carbohydrates and Synthesis of Deoxy Carbohydrates in a Minimum Number of Steps

Wataru Muramatsu,* Satoko Tanigawa, Yuki Takemoto, Hirofumi Yoshimatsu, and Osamu Onomura[a]

The selective functionalization of polyols remains one of the most fundamental challenges for achieving the efficient synthesis of building blocks for natural product synthesis or new drug development.[1] The direct regioselective functionalization of the secondary hydroxy group in carbohydrates with nonenzymatic catalysts is of particular interest due to the difficulty in functionalizing one specific hydroxy group of the multiple present in carbohydrates. Over the last several decades, progress has been made in the catalytic regioselective acylation,[2] alkylation,[3] sulfonylation,[4] and glycosylation[5] of monosaccharides in the presence of an organometal catalyst or organocatalyst. Additionally, our group recently reported the regioselective acylation of monosaccharides by using an organotin catalyst.[2g] These catalytic methods are useful techniques for the protection or functionalization of a hydroxy group in carbohydrates in a minimum number of steps. However, some of these methods are not applicable to the monosaccharides with a nonprotected primary hydroxy group,[2j–k,3–5] and the resulting monofunctionalized carbohydrates are usually not the ideal precursors for further functionalization.[2–3] To resolve such problems, we began an investigation of the catalytic regioselective thiocarbonylation of nonprotected monosaccharides. This reaction would afford monothiocarbonates suitable for use as electrophiles in the synthesis of biologically interesting deoxy monosaccharides through the venerable Barton–McCombie deoxygenation[6] and new drug candidates by C–C bond formation or halogenation under radical reaction conditions.[7]

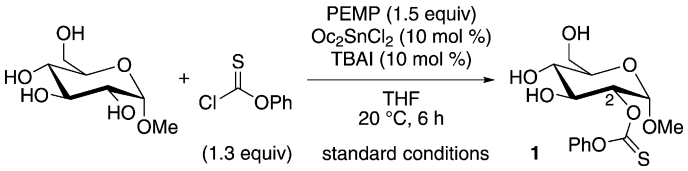
Tsuda, a pioneer in the field of regioselective thiocarbonylation of carbohydrates, and co-workers developed a useful approach for the selective introduction of a phenoxythiocarbonyl group at a secondary hydroxy group of methyl α-D-glucopyranoside by the use of Bu_2SnO, which gave 2-*O*-phenoxythiocarbonate in 83% yield with 94% regioselectivity.[8] However, this method is limited to the transformation of a select few monosaccharides (α-D-Glc, β-D-Glc, α-D-Xyl, and β-D-Xyl), and requires a stoichiometric amount of Bu_2SnO (1.5 equiv) under harsh conditions for the preparation of the tin acetal intermediate. In addition, the deoxygenation of nonprotected monothiocarbonates for the synthesis of deoxy saccharides has never been reported even by Tsuda.[9] Miller and co-workers also reported impressive organocatalytic thiocarbonylation of carbohydrates with good selectivity. However, this method requires a protecting group on primary hydroxy groups of carbohydrates for the selectivity.[10] Herein, we report the first catalytic regioselective thiocarbonylation of nonprotected monosaccharides by using organotin dichloride under mild conditions, and the synthesis of representative deoxy monosaccharides in a minimum number of steps through the Barton–McCombie deoxygenation.

After a series of optimization studies, we found that the selective thiocarbonylation at C(2)–OH of methyl α-D-glucopyranoside proceeded efficiently in the presence of 10 mol% of Oc_2SnCl_2, 10 mol% of tetrabutylammonium iodide (TBAI), 1.3 equiv of phenyl chlorothionoformate, and 1.5 equiv of 1,2,2,6,6-pentamethylpiperidine (PEMP)[10] as a less nucleophilic base in THF at 20 °C (Table 1, entry 1; 98% yield, no regioisomers or other derivatives). Table 1 provides information about the effect of a number of reaction parameters on the efficiencies of thiocarbonylation at C(2)–OH of methyl α-D-glucopyranoside. In the absence of Oc_2SnCl_2 or PEMP, essentially no reaction was observed (Table 1, entries 2 and 3). In the absence of TBAI, the yield was slightly lower due to failure to activate the phenyl chlorothionoformate as an electrophile (Table 1, entry 4; 93% yield). The use of other alkyl or aryl tin dichlorides instead of Oc_2SnCl_2 gave the desired product **1** in lower yield (Table 1, entries 5–7), as did the use of an alkyl tin oxide as a catalyst or a smaller amount of catalyst (Table 1, entries 8 and 9). Nucleophilic catalysts, such as *N,N*-dimethylaminopyridine (DMAP) and *N*-methylimidazole (NMI), deactivated the electrophile (Table 1, entries 10 and 11). The addition of $FeCl_3$[10] as a co-catalyst had no significant effect under the present reaction conditions (Table 1, entry 12; 40% yield). Dimethoxyethane (DME) can be used instead of

[a] Prof. Dr. W. Muramatsu, S. Tanigawa, Y. Takemoto, H. Yoshimatsu, Prof. Dr. O. Onomura
Graduate School of Biomedical Sciences
Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852-8521 (Japan)
E-mail: muramatu@nagasaki-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201104007.

Table 1. Regioselective thiocarbonylation of methyl α-D-glucopyranoside.



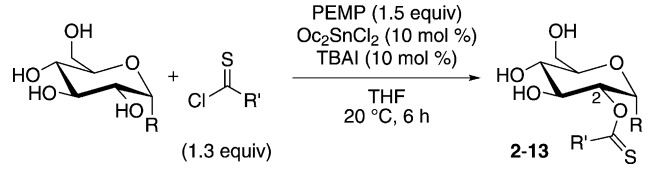
Entry	Variation from the standard conditions	Yield [%]
1	none	98
2	no Oc_2SnCl_2	<1
3	no PEMP[a]	<1
4	no TBAI	93
5	Me_2SnCl_2 instead of Oc_2SnCl_2	67
6	Bu_2SnCl_2 instead of Oc_2SnCl_2	89
7	Ph_2SnCl_2 instead of Oc_2SnCl_2	<1
8	Oc_2SnO instead of Oc_2SnCl_2	18
9	1 mol% of Oc_2SnCl_2	27
10	DMAP instead of TBAI	30
11	NMI instead of TBAI	24
12	$FeCl_3$ instead of TBAI	40
13	DME instead of THF	90

[a] 1,2,2,6,6-Pentamethylpiperidine.

THF as the solvent, at the expense of a slight decrease in chemical yield (Table 1, entry 13; 90% yield).

Furthermore, we examined the scope of this catalytic regioselective thiocarbonylation with respect to both the anomeric substituents of the α-D-glucopyranoside and the electrophile under the best suitable conditions (Table 2). In

Table 2. Scope of α-D-glucopyranoside and chlorothionoformate.



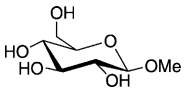
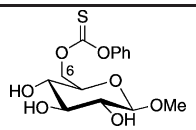
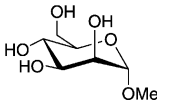
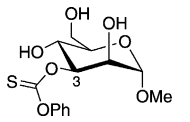
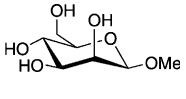
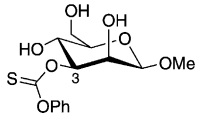
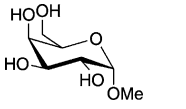
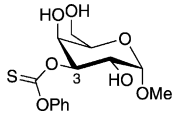
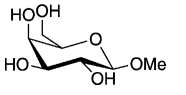
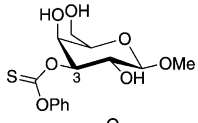
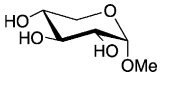
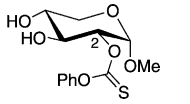
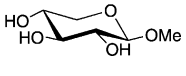
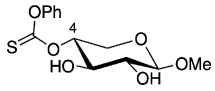
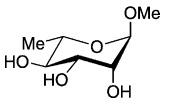
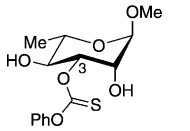
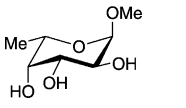
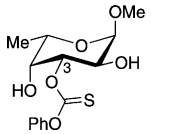
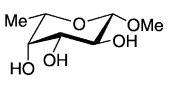
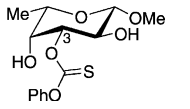
Entry	R	R′	Product	Yield [%]
1[a]	OOc	OPh	**2**	81
2	OPh	OPh	**3**	74
3[a]	OPNP[b]	OPh	**4**	75
4	SEt	OPh	**5**	87
5	F or Br	OPh	**6** or **7**	<1
6[a]	OMe	O(4-tolyl)	**8**	98
7	OMe	O(2-naphthyl)	**9**	>99
8[a]	OMe	O(4-Cl-Ph)	**10**	94
9[a]	OMe	O(4-F-Ph)	**11**	91
10	OMe	SPh or NMe_2	**12** or **13**	<1

[a] Dithiocarbonates were observed in <1–3% yield. [b] *p*-Nitrophenyl.

the case of the R substituents, for *O*-alkyl or *O*-aryl, thiocarbonylation proceeded with 74–81% yield and no regioisomers (Table 2, entries 1–3). Ethyl α-D-thioglucopyranoside,[11] a useful glycosyl donor, was converted by the same reaction to the corresponding thiocarbonate **5** in 87% yield with no regioisomers (Table 2, entry 4). In contrast, catalysis with α-D-glucopyranosyl fluoride and bromide,[12] which are widely used partners for *O*- and *C*-glycosylation, did not afford any of the desired products (Table 2, entry 5).[13] The use of chlorothionoformates with an electron-donating or electron-withdrawing group as an electrophile resulted in strong reactivity at the C(2)−OH, whereas neither phenyl chlorodithioformate nor dimethylthiocarbamoyl chloride showed reactivity for this reaction (Table 2, entry 10).

Based on these results, this catalytic system was used in the differentiation of primary or secondary hydroxy groups for a wide range of monosaccharides (Table 3). Monothiocarbonylation was selectively observed only at *cis*-1,2-diol moieties, with an equatorial OH group in derivatives of commercially available D-mannopyranoside (Table 3, entries 2 and 3), D-galactopyranoside (entries 4 and 5), α-D-xy-

Table 3. Regioselective thiocarbonylation of various monosaccharides.[a]

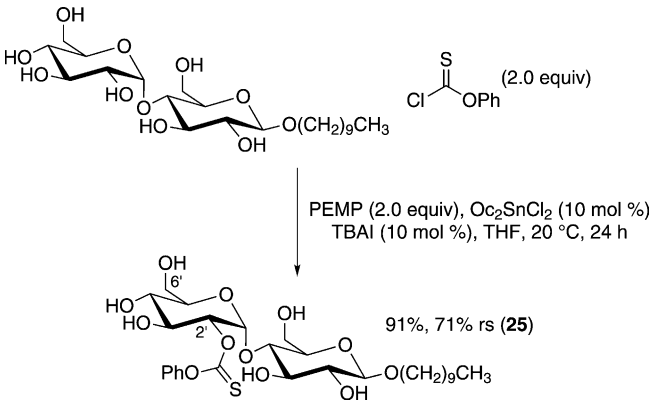
Entry	Substrate	Product		Yield [%]
1[b]			**14**	>99
2[c,d]			**15**	92
3[c–f]			**16**	80
4[d,e]			**17**	68
5[d,e]			**18**	53
6[g]			**19**	99[i]
7			**21**	94
8[c–d,h]			**22**	95
9[c,e,h]			**23**	90
10[c,d]			**24**	97

[a] For the reaction conditions, see Table 2. [b] Me_2SnCl_2 was used instead of Oc_2SnCl_2. [c] In acetone. [d] Cyclic thiocarbonates were observed in 2–17% yield. [e] TBAI (30 mol%) was used. [f] −20°C. [g] Without TBAI. [h] 0°C. [i] 76% regioselectivity (**19**/**20** = 76:24).

lopyranoside (entry 6), α-L-rhamnopyranoside (entry 8), and L-fucopyranoside (entries 9 and 10).

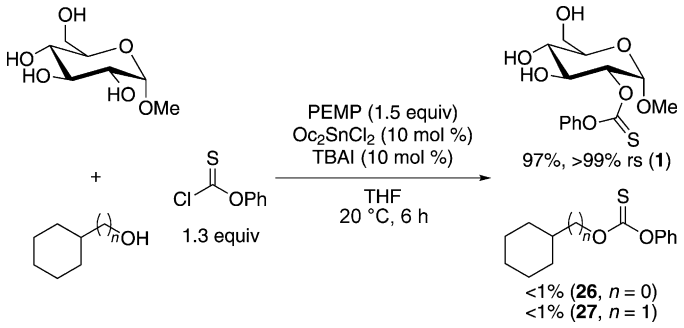
In the case of α-D-xylopyranoside, however, reduced regioselectivity in thiocarbonylation was observed, to give 2- and 4-*O*-phenoxythiocarbonates (**19** and **20**) in a ratio of 76:24 (Table 3, entry 6).[4,8b] In the absence of *cis*-1,2-diol moieties in monosaccharides, less hindered hydroxy groups in monosaccharides, β-D-glucopyranoside and β-D-xylopyranoside, were selectively activated by the organotin catalyst and then thiocarbonated in >99 and 94% yield with no regioisomers (Table 3, entries 1 and 7).

The protocol was applied to the regioselective thiocarbonylation of dissacharide with two highly reactive primary hydroxy groups and five secondary hydroxy groups. Treatment of decyl β-D-maltoside with 2.0 equivalents of phenyl chlorothionoformate and 2.0 equivalents of PEMP in the presence of 10 mol% of Oc_2SnCl_2 and 10 mol% of TBAI at 20°C for 24 h gave **25** in 91% yield with 71% regioselectivity (rs; 2′-*O*/6′-*O* = 71:29). Thus, the catalytic regioselective thiocarbonylation of decyl β-D-maltoside was sluggish in the presence of Oc_2SnCl_2 and TBAI probably due to the sterically crowded environment around C(2′)–OH in the decyl β-D-maltoside (Scheme 1).



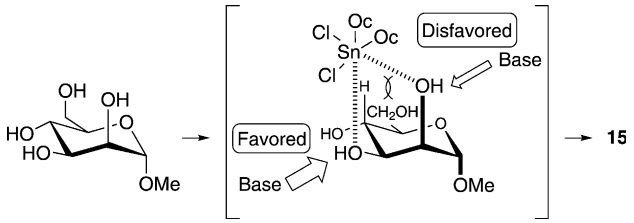
Scheme 1. Regioselective thiocarbonylation of a disaccharide.

In addition, competitive thiocarbonylation between methyl α-D-glucopyranoside and monoalcohols afforded **1** selectively in 97% yield with >99% regioselectivity (Scheme 2).



Scheme 2. Competitive thiocarbonylation between methyl α-D-glucopyranoside and monoalcohols.

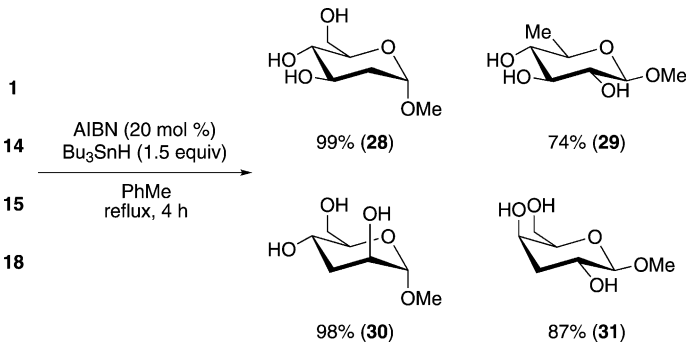
The regioselectivity of these monosaccharides in this catalytic monothiocarbonylation can be explained as follows. Coordination of the organotin catalyst with *cis*-diol moieties in these monosaccharides proceeds with relative stability after moving freely among diol moieties. Since the coordination of metal ions may increase the acidity of hydroxy groups, even a weak base, such as PEMP, is sufficient to induce deprotonation. In addition, since an axial hydrogen atom adjacent to the reacting axial OH group in the *cis*-1,2-diol moiety restricts the approach of PEMP (1,3-diaxial interaction), the most accessible hydroxy group, the equatorial OH group, may be attacked by PEMP and hence thiocarbonated (Scheme 3). However, it is still unclear why the



Scheme 3. Plausible explanation of the regioselective thiocarbonylation of monosaccharides (for example, methyl α-D-mannopyranoside).

C(3)–OH groups of α-D-galactopyranoside and α-L-fucopyranoside are more reactive than the C(2)–OH groups of the corresponding monosaccharides (Table 3, entries 4 and 9).

The monothiocarbonates **1**, **14**, **15**, and **18** synthesized by organotin-catalyzed regioselective thiocarbonylation were smoothly converted to the corresponding deoxy saccharides **28**–**31** in 74–99% yield under standard Barton–McCombie deoxygenation conditions (Scheme 4).



Scheme 4. Synthesis of deoxy monosaccharides in a minimum number of steps. AIBN = 2,2'-azobisisobutyronitrile.

In conclusion, a catalytic process for the thiocarbonylation of nonprotected monosaccharides and disaccharides with high yields and high regioselectivity under mild conditions was developed. The catalysis method is applicable to a wide range of nonprotected carbohydrates. The regioselectivity of the thiocarbonylation is found to be intrinsic to the carbohydrate based on the stereorelationship among hydroxy

groups. In addition, the monosaccharides were chemoselectively converted to the corresponding monothiocarbonates in the presence of monoalcohols. The resulting monothiocarbonates were readily converted to the corresponding deoxy carbohydrates in good yield and in a minimum number of steps. The proposed reaction forms the basis for the development of a method for the direct functionalization of nonprotected carbohydrates and also provides new insight into carbohydrate–metal ion interaction and its activation process.

Experimental Section

General procedure for the regioselective thiocarbonylation of nonprotected monosaccharide catalyzed by organotin dichloride: After stirring a mixture of methyl α-D-glucopyranoside (194.2 mg, 1.0 mmol) and dioctyl tin dichloride (41.6 mg, 0.10 mmol) in THF (10 mL) in a brown vial at RT for 10 min, tetrabutylammonium iodide (36.9 mg, 0.10 mmol), phenyl chlorothionoformate (0.175 mL, 1.3 mmol), and 1,2,2,6,6-pentamethylpiperidine (0.271 mL, 1.5 mmol) were added to the suspension at 20 °C. After stirring vigorously for 6 h at 20 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo (water bath temperature: <20 °C). The residue was purified by SiO_2 column chromatography (hexane/ethyl acetate = 3:1–0:1) to give methyl 2-*O*-phenoxythiocarbonyl-α-D-glucopyranoside **1** (322.3 mg, 98 %) as a white solid.

Acknowledgements

This research was funded by Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Keywords: alcohols · deoxygenation · organometallic catalysis · protecting groups · regioselectivity

[1] For examples, see: a) C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616; b) C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang, S.-C. Hung, *Nature* **2007**, *446*, 896; c) C. A. Lewis, J. Merkel, S. J. Miller, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6007; d) C. A. Lewis, K. E. Longcore, S. J. Miller, P. A. Wender, *J. Nat. Prod.* **2009**, *72*, 1864; e) K. Yoshida, T. Furuta, T. Kawabata, *Tetrahedron Lett.* **2010**, *51*, 4830.

[2] a) S. Nishino, Y. Ishido, *Carbohydr. Res.* **1986**, *155*, 161; b) T. Kurahashi, T. Mizutani, J. Yoshida, *J. Chem. Soc. Perkin Trans. 1* **1999**, 465; c) T. Kurahashi, T. Mizutani, J. Yoshida, *Tetrahedron* **2002**, *58*, 8669; d) K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869; e) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890; f) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, Y. Uruno, R Stragies, *Synthesis* **2008**, 747; g) Y. Demizu, Y. Kubo, H. Miyoshi, T. Maki, Y. Matsumura, N. Moriyama, O. Onomura, *Org. Lett.* **2008**, *10*, 5075; h) Y. Ueda, W. Muramatsu, K. Mishiro, T. Furuta, T. Kawabata, *J. Org. Chem.* **2009**, *74*, 8802; i) E. V. Evtushenko, *J. Carbohydr. Chem.* **2010**, *29*, 369; j) R. S. Dhiman, R. Kluger, *Org. Biomol. Chem.* **2010**, *8*, 2006; k) D. Lee, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 3724.

[3] L. Chan, M. S. Taylor, *Org. Lett.* **2011**, *13*, 3090.

[4] a) M. J. Martinelli, R. Vaidyanathan, V. V. Khan, *Tetrahedron Lett.* **2000**, *41*, 3773–3776; b) M. J. Martinelli, R. Vaidyanathan, J. M. Pawlak, N. K. Nayyar, U. P. Dhokte, C. W. Doecke, L. M. Zollars, E. D. Moher, V. V. Khau, B. Košmrlj, *J. Am. Chem. Soc.* **2002**, *124*, 3578.

[5] C. Gouliaras, D. Lee, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 13926.

[6] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574; b) D. H. R. Barton, P. Blundell, J. Dorchak, D. O. Jang, J. Cs. Jaszberenyi, *Tetrahedron* **1991**, *47*, 8969; c) D. H. R. Barton, J. Dorchak, J. Cs. Jaszberenyi, *Tetrahedron* **1992**, *48*, 7435.

[7] a) G. E. Keck, D. F. Kachensky, *J. Org. Chem.* **1986**, *51*, 2487; b) M. J. Kelly, R. F. Newton, S. M. Roberts, J. F. Whitehead, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2352; c) D. H. R. Barton, P. I. Dalko, S. D. Géro, *Tetrahedron Lett.* **1992**, *33*, 1883.

[8] a) M. E. Haque, T. Kikuchi, K. Kanemitsu, Y. Tsuda, *Chem. Pharm. Bull.* **1986**, *34*, 430; b) M. E. Haque, T. Kikuchi, K. Kanemitsu, Y. Tsuda, *Chem. Pharm. Bull.* **1987**, *35*, 1016.

[9] Tsuda reported the deoxygenation of acetylated monothiocarbonates, see Ref. [8].

[10] M. Sánchez-Roselló, A. L. A. Puchlopek, A. J. Morgan, S. J. Miller, *J. Org. Chem.* **2008**, *73*, 1774.

[11] G. Vic, J. J. Hastings, O. W. Howarth, D. H. G. Crout, *Tetrahedron: Asymmetry* **1996**, *7*, 709.

[12] These monosaccharides were synthesized from commercially available 2,3,4,6-tetraacetyl α-D-glucopyranosyl fluoride and bromide, see: S. M. Wilkinson, C. W. Liew, J. P. Mackay, H. M. Salleh, S. G. Withers, M. D. McLeod, *Org. Lett.* **2008**, *10*, 1585.

[13] α-D-Glucopyranosyl 2,2,2-trichloroacetimidate was not stable under these reaction conditions (11 % yield, >99 % regioselectivity, full conversion).

Received: December 21, 2011
Revised: February 3, 2012
Published online: March 13, 2012

Please note: minor changes have been made to this manuscript since its publication in "Chemistry—A European Journal" Early View.
The Editor.

