

# Highly Diastereoselective Thioglycosylation of Functionalized Peracetylated Glycosides Catalyzed by $\text{MoO}_2\text{Cl}_2$

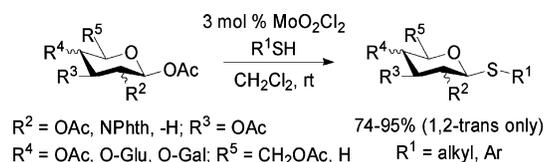
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## ABSTRACT



Among 18 oxometallic species,  $\text{MoO}_2\text{Cl}_2$  was found to be the most reactive in catalytic thioglycosylation of *O*-acetylated glycosides with functionalized thiols in  $\text{CH}_2\text{Cl}_2$ , leading cleanly to 1,2-*trans*-thioglycosides with exclusive diastereocontrol. The new catalytic protocol is applicable to a monoglycoside building block and  $\beta$ -(1 $\rightarrow$ 6)-*S*-linked-thiodisaccharide synthesis.

(Oligo)thioglycosides serve as key mediators for the recognition of cellular surface and receptor enzymes.<sup>1</sup> In addition, they are important *O*-glycan mimetics to study guest–host pairing events of glycoproteins in protein transport, cell-to-cell interaction, and signal transduction.<sup>2</sup> Surfactant-type thioglycosides have also been applied to tertiary structural re-constitution of deactivated membrane proteins bearing cysteine residues.<sup>3</sup> More importantly, monosaccharides possessing glycosidic sulfhydryl (SH) and arylthio (SAr) groups are versatile donors in carbohydrate synthesis and function as universal building blocks and key precursors in oligosaccharide synthesis.<sup>4</sup> By taking advantage of the differential reactivity of various thioglycosides, many desired sequences of oligosaccharides have been delicately constructed in one pot<sup>5</sup> in the presence of suitable glycosidic bond-forming promoters.<sup>6</sup>

Conventional methods of appending thioglycoside units to peracetylated sugars with thiols require the use of

stoichiometric, moisture-sensitive catalysts such as  $\text{ZnX}_2$ ,<sup>7</sup>  $\text{SnCl}_4$ ,<sup>8</sup>  $\text{FeCl}_3$ ,<sup>9</sup>  $\text{TiCl}_4$ - $\text{InCl}_3$ ,<sup>10</sup>  $\text{BF}_3$ - $\text{Et}_2\text{O}$ ,<sup>11</sup> and  $\text{TMSOTf}$ <sup>12a</sup> with moderate to good 1,2-*trans* selectivity. Notably, the catalytic application of  $\text{TMSOTf}$  mandates the use of air- and moisture-sensitive  $\text{Me}_3\text{SiSMe}$ <sup>12b</sup> or  $\text{Bu}_3\text{SnSEt}$ <sup>12c</sup> as the only thiol source. In addition, a one-pot iodination/thiogly-

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cosylation of peracetylated sugars catalyzed by I<sub>2</sub>/HMDS (60 mol % each) in the presence of MeSSMe or thiols has been demonstrated.<sup>13</sup> So far, only ZrCl<sub>4</sub> can mediate thioglycosylation of peracetylated glycosides with complete 1,2-*trans* selectivity at 0 °C in stoichiometric sense.<sup>14</sup> However, only a 1:1 mixture of  $\alpha/\beta$  anomers was obtained when the reaction was carried out at ambient temperature. Therefore, a new mild, water-tolerant, and stereoselective catalyst to fulfill such a transformation remains to be explored.

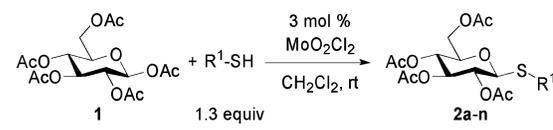
As part of our ongoing projects by using vanadyl and oxometallic species in catalyzing C–C and C–X bond formation,<sup>15</sup> asymmetric aerobic oxidative dehydrogenation<sup>16</sup> and coupling,<sup>17</sup> and photoinitiated DNA cleavage,<sup>18</sup> we evaluated the feasibility of catalyzing the thioglycosylation event by using amphoteric and water-tolerant oxometallic species. Herein we disclose our preliminary finding toward this end.

We started out by using penta-*O*-acetyl- $\beta$ -D-glucose **1** and thiophenol (1.3 equiv) as a test thioglycosylation system with a diverse array of oxometallic species (1–5 mol %) in optimal solvent CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature. Among 18 different oxometallic species examined,<sup>19</sup> MoO<sub>2</sub>Cl<sub>2</sub> (1 mol %) was found to be the most reactive and efficient catalyst, leading only to the  $\beta$ -anomer **2a** in 88% yield along with the recovery of the starting  $\alpha$ -anomer **1** (7–8%). Some of the  $\beta$ -anomer **1** is isomerized into  $\alpha$ -anomer **1** during the catalytic conditions, suggesting the involvement of an oxocarbenium ion intermediate. Notably, no desired product was obtained when MoCl<sub>5</sub> was employed as the catalyst, indicating the participating role of the oxometallic unit(s) in MoO<sub>2</sub>Cl<sub>2</sub>. Molybdenum species have been recognized as competent oxidative sulfur-transfer catalysts in episulfide formation of strained cyclic alkenes and transsulfidation of isonitriles (RN≡C) to isothiocyanates (RN=C=S).<sup>20a,b</sup> Notably, nonoxidative thiol group transfer of the current study has never been documented.<sup>20c,d</sup>

With the optimal thioglycosylation catalyst MoO<sub>2</sub>Cl<sub>2</sub> in hand, we started to look at the substrate scope with aromatic and aliphatic thiols of varying steric and electronic demands. For the given  $\beta$ -anomer **1**, the current catalytic protocol is

applicable to three different 4- and 2-substituted-benzenethiols (Table 1). In general, the sterically encumbered 2-sub-

**Table 1.** Effects of Thiol Substrates on the  $\alpha$ -Thioglycosylation of  $\beta$ -Anomer **1** Catalyzed by MoO<sub>2</sub>Cl<sub>2</sub>



R <sup>1</sup> SH	time, h	product	yield, <sup>a</sup> %
PhSH	14	<b>2a</b>	94
4-MeC <sub>6</sub> H <sub>4</sub> SH	16	<b>2b</b>	90
4-ClC <sub>6</sub> H <sub>4</sub> SH	10	<b>2c</b>	95
4-MeOC <sub>6</sub> H <sub>4</sub> SH	16	<b>2d</b>	86
2-NpSH	10	<b>2e</b>	94
2-MeOC <sub>6</sub> H <sub>4</sub> SH	20	<b>2f</b>	47
2-MeC <sub>6</sub> H <sub>4</sub> SH	20	<b>2g</b>	64
CH <sub>3</sub> CH <sub>2</sub> SH	8	<b>2h</b>	88 <sup>b</sup>
PhCH <sub>2</sub> SH	10	<b>2i</b>	81 <sup>b</sup>
c-C <sub>6</sub> H <sub>11</sub> SH	12	<b>2j</b>	76 <sup>b</sup>
<i>t</i> -BuSH <sup>c</sup>	64	<b>2k</b>	71 <sup>b</sup>
HS(CH <sub>2</sub> ) <sub>3</sub> SH	8	<b>2l</b>	68 <sup>b</sup>
HS(CH <sub>2</sub> ) <sub>10</sub> CO <sub>2</sub> Me	8	<b>2m</b>	71 <sup>b</sup>
HS(CH <sub>2</sub> ) <sub>2</sub> OTBS	12	<b>2n</b>	64 <sup>b</sup>

<sup>a</sup> Isolated yields after chromatographic purification. <sup>b</sup> 5 mol % of catalyst was used. <sup>c</sup> 3 equiv of *tert*-butylmercaptan was used.

stituted-benzenethiols are less reactive (20 h) and lower yielding (47–64% yields) than the corresponding 4-substituted ones (16 h; 86–90% yields). In addition, thiols bearing electron-donating substituents (e.g., CH<sub>3</sub> and OCH<sub>3</sub>) are less reactive (16 h) and lower yielding (86–90% yields) than those (10 h and 94–95% yields) bearing electron-withdrawing substituents (e.g., Cl and benzo-fused 2-Np). Notably, about 44% and 32% of the isomerized substrate (i.e.,  $\alpha$ -anomer **1**) was recovered respectively in the cases of slower reacting 2-methyl- and 2-methoxybenzenethiols which are responsible for the lower isolated yields in the products **2f** and **2g**.

Four straight alkanethiols of varying steric attributes were also examined. The rates of catalytic thioglycosylation were significantly decreased up to a factor of 8 with increasing steric demands of the thiols (i.e., Et > PhCH<sub>2</sub> > c-C<sub>6</sub>H<sub>11</sub> > *t*-Bu). In addition, the chemical yields dropped from 88% to 71%. Functionalized alkanethiols like 11-mercaptoundecanoate and 2-*tert*-butyldimethylsilyloxyethanethiol (TBSO-(CH<sub>2</sub>)<sub>2</sub>SH) are also suitable substrates for the  $\beta$ -thioglycosylation, leading to **2m** and **2n** in satisfactory yields (64–71%). Notably, monothioglycosylation can be achieved for dithiols like 1,3-propanedithiol. The expected **2l** can be isolated in 68% yield, thus allowing for subsequent functional group manipulation at the remaining thiol unit in **2l**. Since all the recovered starting  $\alpha$ -anomer **1** may be readily converted back to the original  $\beta$ -anomer **1** and the catalyst can be recovered from the aqueous layer, the current catalytic protocol is unprecedented and meets the standard of green chemistry.

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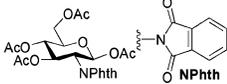
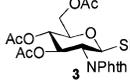
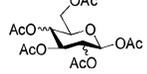
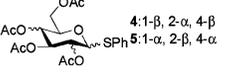
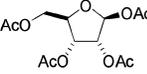
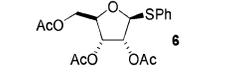
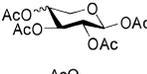
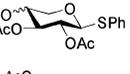
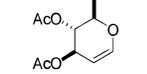
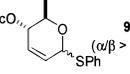
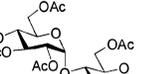
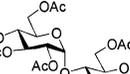
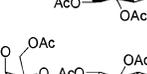
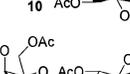
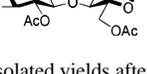
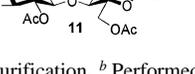
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To gain insights into the origin of 1,2-*trans* diastereocontrol, 2-deoxy-2-phthalimido- $\beta$ -D-glucose was also examined. It was found that exclusive  $\beta$ -thioglycosylation by benzenethiol under the optimal catalytic conditions was also observed, Table 2. This result suggests that anchimeric

**Table 2.** Thioglycosylation of Peracetylated Sugars to the Corresponding 1-Phenylthioglycosides Catalyzed by MoO<sub>2</sub>Cl<sub>2</sub>

glycosides	time, h	product	yield, % <sup>a</sup>
	20		90
	14		91
	20		74
	14		86
	12		92
	12		89
	1/4 <sup>b</sup>		93
	14		94
	14		95

<sup>a</sup> Isolated yields after chromatographic purification. <sup>b</sup> Performed at 0 °C.

assistance by the neighboring C2-acyl groups is essential for the exclusive 1,2-*trans* selectivity in the thioglycosylation.

Several peracetylated  $\beta$ -D-monosaccharides derived from galactose, mannose, ribose, xylose, and arabinose were further investigated. In all cases except the mannose derivative, the thioglycosylations by benzenethiol were complete in 12–14 h leading to the corresponding  $\beta$ -1-phenylthio-sugars **4** and **6–8** in 86–92% yields. In the mannose case, the corresponding  $\alpha$ -1-phenylthiomannose **5** was obtained in 74% yield within 20 h. Remarkably, the thioglycosylation of 3,4,6-tri-*O*-acetyl-D-glycal by PhSH was complete in 15 min at 0 °C and led to Ferrier-type product **9** with high  $\alpha$ -selectivity ( $\alpha/\beta > 19/1$ ) presumably due to the preferred axial attack to avoid A<sup>1,2</sup>-strain.<sup>21</sup>

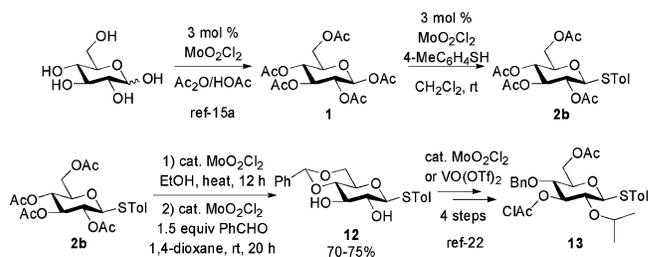
Peracetylated disaccharides derived from maltose and lactose were also suitable substrates for the highly diastereoselective thioglycosylation protocol. Exclusive formation

(21) The  $\alpha/\beta$  selectivity reported with Lewis acids like BF<sub>3</sub>·OEt<sub>2</sub>, SnCl<sub>4</sub>, and Yb(OTf)<sub>3</sub> ranged from 5/1 to 9/1, see: (a) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J.; Golik, J.; Vyas, D. *J. Org. Chem.* **1990**, *55*, 1979. (b) Halcomb, R. L.; Wittman, M. D.; Olson, S. H.; Danishefsky, S. J.; Golik, J. *J. Am. Chem. Soc.* **1991**, *113*, 5080. (c) Takhi, M.; Abdel-Rahman, A. A.-H.; Schmidt, R. R. *Synlett* **2001**, *3*, 427.

of the corresponding  $\beta$ -thioglycosides **10** and **11** (94–95% yields) with intact 1→4' glycosidic stereochemistry were achieved in 14 h.

Thioglycosides protected with 4,6-benzylidene acetals are important precursors to highly functionalized saccharides.<sup>22</sup> Their conventional synthesis requires the initial preparation of 2,3,4,6-*O*-tetraacetylated monosaccharides followed by complete deacetylation under basic conditions (e.g., NaOMe/MeOH). We can now access a representative target **12** from D-glucose by using MoO<sub>2</sub>Cl<sub>2</sub> as the sole catalyst for a four-step, peracetylation–thioglycosylation–deacetylation acetal formation sequence in 70–75% overall yield without purification of any intermediates, Scheme 1. Notably, the 4,6-

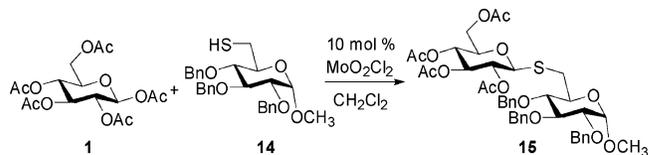
**Scheme 1.** Synthesis of a Universal Glycoside Building Block **13**



benzylidene acetal **12** constitutes a precursor leading to a universal, fully functionalized, glycoside building block **13** for oligosaccharide synthesis.<sup>22</sup>

As a final demonstration for its practical application in  $\beta$ -(1→6)-*S*-linked-thiodisaccharide synthesis, we treated D-1,2,3,4,6-penta-*O*-acetyl- $\beta$ -glucose **1** with methyl 2,3,4-tri-*O*-benzyl-6-thio- $\alpha$ -glucose **14** under the optimal reaction conditions. The desired  $\beta$ -(1→6)-*S*-linked-thiodisaccharide **15** was furnished in 74% isolated yield with complete retention at both glycosidic centers, Scheme 2.

**Scheme 2.** A Representative  $\beta$ -(1→6)-*S*-Linked-Thiodisaccharide Functional Synthesis



In conclusion, we have achieved the first successful catalytic use of neutral MoO<sub>2</sub>Cl<sub>2</sub> for thioglycosylation of *O*-acetylated saccharides with exclusive 1,2-*trans*-diastereocontrols. The integration of various catalytic pathways mediated by MoO<sub>2</sub>Cl<sub>2</sub> and VO(OTf)<sub>2</sub> allows for access of a functional glycoside building block **13**. A representative  $\beta$ -(1→6)-*S*-linked-thiodisaccharide **15** can also be provided

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smoothly by the newly developed catalytic thioglycosylation process, which augurs well for its extensive use in delicate carbohydrate syntheses.

**Acknowledgment.** We thank the National Science Council of Taiwan for generous financial support of this research.

**Supporting Information Available:** Spectral data and characterization for products **2a–n**, **3–12**, **14**, and **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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