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Highly Diastereoselective Thioglycosylation of Functionalized Peracetylated Glycosides Catalyzed by MoO_2Cl_2

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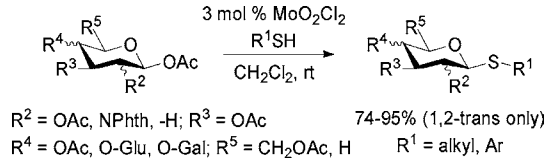
ABSTRACT



Among 18 oxometallic species, MoO_2Cl_2 was found to be the most reactive in catalytic thioglycosylation of *O*-acetylated glycosides with functionalized thiols in CH_2Cl_2, leading cleanly to 1,2-*trans*-thioglycosides with exclusive diastereocontrol. The new catalytic protocol is applicable to a monoglycoside building block and *β*-(1→6)-*S*-linked-thiodisaccharide synthesis.

(Oligo)thioglycosides serve as key mediators for the recognition of cellular surface and receptor enzymes.[1] 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.[2] Surfactant-type thioglycosides have also been applied to tertiary structural re-constitution of deactivated membrane proteins bearing cysteine residues.[3] 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.[4] By taking advantage of the differential reactivity of various thioglycosides, many desired sequences of oligosaccharides have been delicately constructed in one pot[5] in the presence of suitable glycosidic bond-forming promoters.[6]

Conventional methods of appending thioglycoside units to peracetylated sugars with thiols require the use of stoichiometric, moisture-sensitive catalysts such as ZnX_2,[7] $SnCl_4$,[8] $FeCl_3$,[9] $TiCl_4$-$InCl_3$,[10] BF_3-Et_2O,[11] and TMSOTf[12a] with moderate to good 1,2-*trans* selectivity. Notably, the catalytic application of TMSOTf mandates the use of air- and moisture-sensitive Me_3SiSMe[12b] or Bu_3SnSEt[12c] as the only thiol source. In addition, a one-pot iodination/thiogly-

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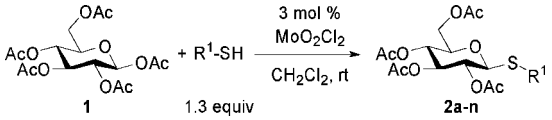
cosylation of peracetylated sugars catalyzed by I_2/HMDS (60 mol % each) in the presence of MeSSMe or thiols has been demonstrated.[13] So far, only $ZrCl_4$ can mediate thioglycosylation of peracetylated glycosides with complete 1,2-*trans* selectivity at 0 °C in stoichiometric sense.[14] However, only a 1:1 mixture of α/β 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,[15] asymmetric aerobic oxidative dehydrogenation[16] and coupling,[17] and photoinitiated DNA cleavage,[18] 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-β-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_2Cl_2 at ambient temperature. Among 18 different oxometallic species examined,[19] MoO_2Cl_2 (1 mol %) was found to be the most reactive and efficient catalyst, leading only to the β-anomer **2a** in 88% yield along with the recovery of the starting α-anomer **1** (7−8%). Some of the β-anomer **1** is isomerized into α-anomer **1** during the catalytic conditions, suggesting the involvement of an oxocarbenium ion intermediate. Notably, no desired product was obtained when $MoCl_5$ was employed as the catalyst, indicating the participating role of the oxometallic unit(s) in MoO_2Cl_2. 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).[20a,b] Notably, nonoxidative thiol group transfer of the current study has never been documented.[20c,d]

With the optimal thioglycosylation catalyst MoO_2Cl_2 in hand, we started to look at the substrate scope with aromatic and aliphatic thiols of varying steric and electronic demands. For the given β-anomer **1**, the current catalytic protocol is applicable to three different 4- and 2-substituted-benzenethiols (Table 1). In general, the sterically encumbered 2-substituted-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_3 and OCH_3) 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., α-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**.

Table 1. Effects of Thiol Substrates on the α-Thioglycosylation of β-Anomer **1** Catalyzed by MoO_2Cl_2



R^1SH	time, h	product	yield,[a] %
PhSH	14	**2a**	94
4-MeC_6H_4SH	16	**2b**	90
4-ClC_6H_4SH	10	**2c**	95
4-$MeOC_6H_4SH$	16	**2d**	86
2-NpSH	10	**2e**	94
2-$MeOC_6H_4SH$	20	**2f**	47
2-MeC_6H_4SH	20	**2g**	64
CH_3CH_2SH	8	**2h**	88[b]
$PhCH_2SH$	10	**2i**	81[b]
c-$C_6H_{11}SH$	12	**2j**	76[b]
t-BuSH[c]	64	**2k**	71[b]
$HS(CH_2)_3SH$	8	**2l**	68[b]
$HS(CH_2)_{10}CO_2Me$	8	**2m**	71[b]
$HS(CH_2)_2OTBS$	12	**2n**	64[b]

[a] Isolated yields after chromatographic purification. [b] 5 mol % of catalyst was used. [c] 3 equiv of *tert*-butylmercaptan was used.

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 > $PhCH_2$ > c-C_6H_{11} > *t*-Bu). In addition, the chemical yields dropped from 88% to 71%. Functionalized alkanethiols like 11-mercaptoundecanoate and 2-*tert*-butyldimethylsiloxyethanethiol (TBSO-$(CH_2)_2SH$) are also suitable substrates for the β-thioglycosylation, leading to **2m** and **2n** in satisfactory yields (64−71%). Notably, monothioglycosylation can be achieved for dithiols like 1,3-propanedithiol. The expected **2***l* can be isolated in 68% yield, thus allowing for subsequent functional group manipulation at the remaining thiol unit in **2***l*. Since all the recovered starting α-anomer **1** may be readily converted back to the original β-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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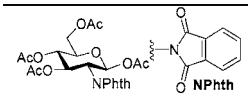
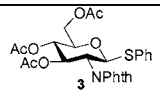
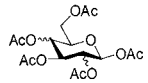
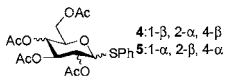
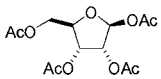
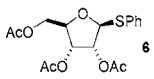
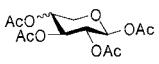
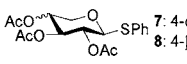
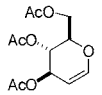
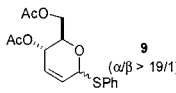
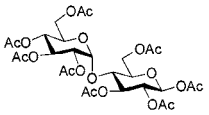
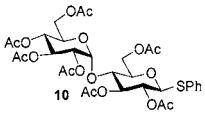
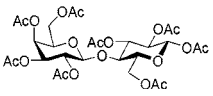
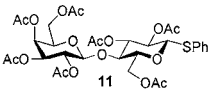
To gain insights into the origin of 1,2-*trans* diastereocontrol, 2-deoxy-2-phthalimido-β-D-glucose was also examined. It was found that exclusive β-thioglycosylation by benzenethiol under the optimal catalytic conditions was also observed, Table 2. This result suggests that anchimeric assistance by the neighboring C2-acyl groups is essential for the exclusive 1,2-*trans* selectivity in the thioglycosylation.

Table 2. Thioglycosylation of Peracetylated Sugars to the Corresponding 1-Phenylthioglycosides Catalyzed by MoO_2Cl_2

glycosides	time, h	product	yield, % [a]
	20	 **3**	90
	14 20	 **4**:1-β, 2-α, 4-β **5**:1-α, 2-β, 4-α	91 74
	14	 **6**	86
	12 12	 **7**: 4-α **8**: 4-β	92 89
	1/4 [b]	 **9** (α/β > 19/1)	93
	14	 **10**	94
	14	 **11**	95

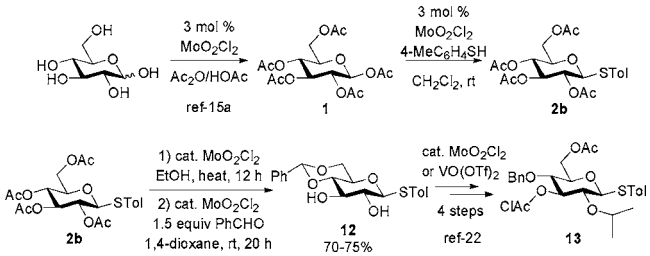
[a] Isolated yields after chromatographic purification. [b] Performed at 0 °C.

Several peracetylated β-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 β-1-phenylthiosugars **4** and **6**−**8** in 86−92% yields. In the mannose case, the corresponding α-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 α-selectivity (α/β > 19/1) presumably due to the preferred axial attack to avoid $A^{1,2}$-strain.[21]

Peracetylated dissaccharides derived from maltose and lactose were also suitable substrates for the highly diastereoselective thioglycosylation protocol. Exclusive formation of the corresponding β-thioglycosides **10** and **11** (94−95% yields) with intact 1→4′ glycosidic stereochemistry were achieved in 14 h.

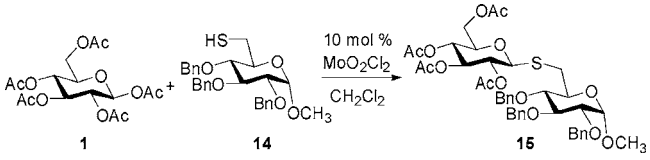
Thioglycosides protected with 4,6-benzylidene acetals are important precursors to highly functionalized saccharides.[22] Their conventional synthesis requires the initial preparation of 2,3,4,6-*O*-tetraacetylated monosaccharides followed by complete deacetylation under basic conditions (e.g., NaOMe/MeOH). We can now access a representative target **12** from D-glucose by using MoO_2Cl_2 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-benzylidene acetal **12** constitutes a precursor leading to a universal, fully functionalized, glycoside building block **13** for oligosaccharide synthesis.[22]

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



As a final demonstration for its practical application in β-(1→6)-*S*-linked-thiodisaccharide synthesis, we treated D-1,2,3,4,6-penta-*O*-acetyl-β-glucose **1** with methyl 2,3,4-tri-*O*-benzyl-6-thio-α-glucose **14** under the optimal reaction conditions. The desired β-(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 β-(1→6)-*S*-Linked-Thiodisaccharide Functional Synthesis



In conclusion, we have achieved the first successful catalytic use of neutral MoO_2Cl_2 for thioglycosylation of *O*-acetylated saccharides with exclusive 1,2-*trans*-diastereocontrols. The integration of various catalytic pathways mediated by MoO_2Cl_2 and $VO(OTf)_2$ allows for access of a functional glycoside building block **13**. A representative β-(1→6)-*S*-linked-thiodisaccharide **15** can also be provided

(21) The α/β selectivity reported with Lewis acids like BF_3-OEt_2, $SnCl_4$, and $Yb(OTf)_3$ 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.

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

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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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