HETEROCYCLES, Vol. 103, No. , 2021, pp. -. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 21st November, 2020, Accepted, 14th December, 2020, Published online, 19th January, 2021
DOI: 10.3987/COM-20-S(K)47

N-GLYCOSYLATION OF *THIO*-GLYCOSIDE DERIVED FROM ODORLESS THIOLS USING HYPERVALENT IODINE(III) REAGENT

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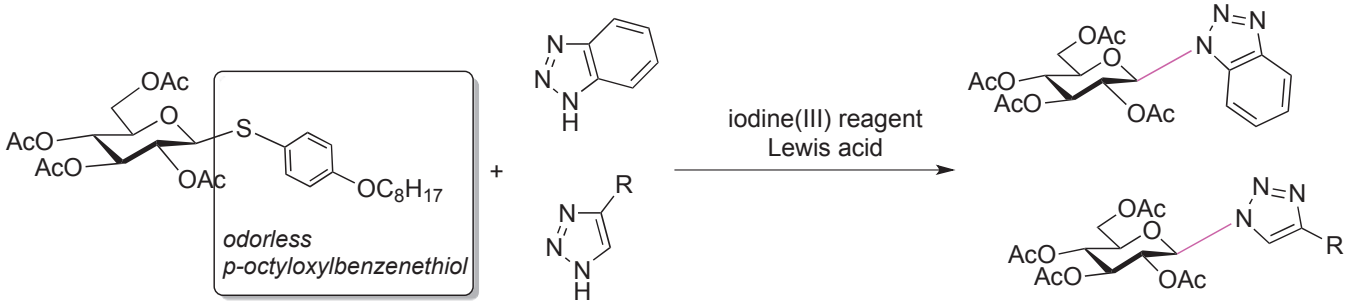
In Celebration of Professor Yasuyuki Kita on His 77th Birthday

Abstract – A general and efficient protocol for direct *N*-glycosylation using inexpensive and readily available thioglycosides prepared from an odorless sulfur source was established. The use of easily available reactants and the mild reaction conditions make this protocol feasible for practical applications.

INTRODUCTION

Glycosylation is the most important reaction in the fields of materials, agrochemicals, and pharmaceuticals. Various types of new glycosyl donors have been synthesized and used for glycosylation reactions.[1–5] Among them, thioglycosides are important glycosyl donors in oligosaccharide synthesis.[6–10] The anomeric *thio* functionality is stable to diverse chemical manipulation of various protecting groups and inert under several glycosylation conditions. They are easy to prepare and can be activated under very mild conditions as a glycosyl donor.[7] Although the use of thioglycoside has led to significant progress in the field of glycosylation reactions, their synthesis involves the use of volatile and foul-smelling thiols as substrates.[11–14] In our previous studies, we found that *p*-octyloxybenzenethiol was an odorless organic sulfur reagent, and the preparation of thioglycoside from this reagent and the subsequent glycosylation proceeded with high efficiency.[12,13] Furthermore, it has been found that thioglycoside prepared from odorless benzenethiol is activated by the combination of phenyliodine(III) bis(trifluoroacetate) (PIFA)

and TfOH, and the *O*-glycosylation reaction proceeds with relatively high efficiency.[15–17] As a part of our ongoing research on glycosylation, we recently developed an efficient *N*-glycosylation with azoles, which proceeded via the activation of thioglycoside donors using hypervalent iodine(III) reagents[18–23] as activators.[24] However, the thioglycosides were synthesized from odorous thiols, rendering them unsuitable for large-scale synthesis. In this paper, we report a practical *N*-glycosylation of thioglycosides that are derived from odorless thiols (Scheme 1).

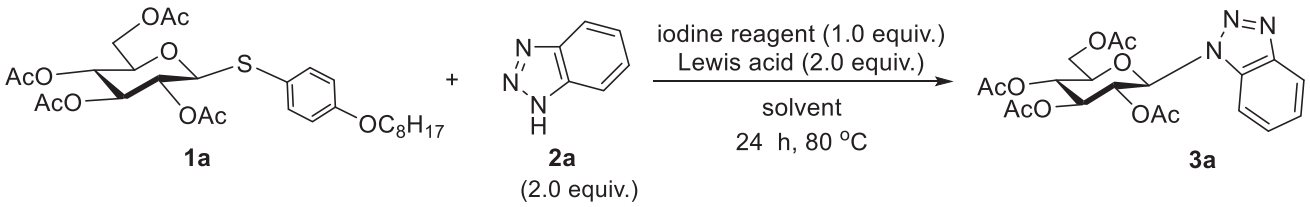


Scheme 1. The hypervalent iodine(III)-induced metal-free glycosylation using thioglycosides prepared with an odorless thiol

RESULTS AND DISCUSSION

We initially synthesized the donor glycoside prepared from *p*-octyloxyphenyl 2,3,4,6-tetra-*O*-acetyl-1-*thio*-β-D-glucopyranoside **1a** using our previously reported method.[12] The *N*-glycosylation was conducted using thioglycoside **1a** and 1,2,3-benzotriazole **2a** as the model substrates (Table 1). The combination of PIFA and TMSOTf in dichloroethane [$(CH_2)_2Cl_2$] was found to promote the glycosylation reaction at 80 °C, affording the *N*1 coupling product **3a** in 46% yield (entry 1). The yield did not improve remarkably in other solvents such as acetonitrile and $(CF_3)_2CHOH$ (HFIP) (entries 2 and 3). Treatment of thioglycoside **1a** in 10 mg/mL of molecular sieves 4A resulted in the formation of *N*-glycosylated product **3a** in a 75% yield (entry 4). No remarkable improvement in the yield was observed when other iodine(III) reagents such as phenyliodine(III) diacetate (PIDA) and PhI(OH)OTs were used (entries 5 and 6). When $BF_3 \cdot Et_2O$ was used, the reaction did not proceed and the desired product was not obtained (entry 7). For all the cases, a trace amount of the *N*2 coupling product was detected. *N*1 and *N*2 coupling products can be separated by column chromatography.

Table 1. Optimization of Reaction Conditions

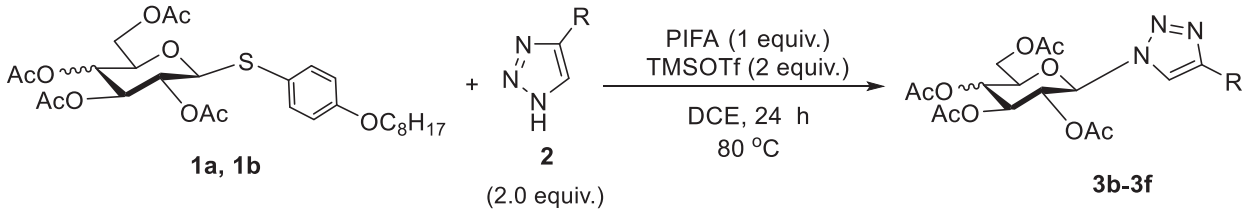


Entry	Iodine(III) reagent	Acid	Molecular sieves 4A	Solvent (0.1 M)	Yield (%)[a,b]
1	PIFA	TMSOTf	none	$(CH_2)_2Cl_2$ (DCE)	46
2	//	//	//	MeCN	n.d.
3	//	//	//	$(CF_3)_2CHOH$ (HFIP)	n.d.
4	//	//	10 mg/mL	$(CH_2)_2Cl_2$ (DCE)	75
5	PIDA	//	//	//	31
6	PhI(OH)OTs	//	//	//	n.d.
7	PIFA	$BF_3 \cdot Et_2O$	//	//	n.d.

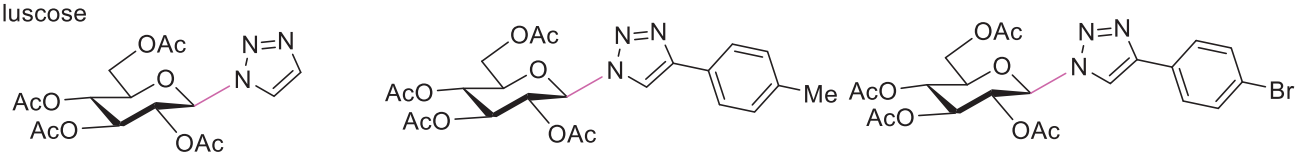
[a]Reaction conditions: nitrogen atmosphere, *thio*-glycoside **1a** (0.1 mmol), 1,2,3-benzotriazole **2a** (0.2 mmol), iodine(III) reagent (0.1 mmol), acid (0.2 mmol). [b] Isolated yield.

With the optimal conditions in hand, we further investigated the substrate scope and generality of this *N*-glycosylation. Table 2 shows that the reaction of thioglycoside **1** with various triazoles **2** gave the desired coupling products **3b-3f** in good yields. For 1,2,3-triazole **2b**, *N*-glycosylation proceeded smoothly, producing the *N*-glycosylation product **3b** in satisfactory yield. Furthermore, 4-aryl-1*H*-1,2,3-triazoles **2c** and **2d** afforded the corresponding products **3c** and **3d** in moderate yields. Next, thiogalactoside **1b**, derived from *p*-octyloxybenzenethiol, was reacted with triazoles **2c** and **2d**. Acetyl-protected thiogalactose **1b** reacted smoothly with 4-aryl-1*H*-1,2,3-triazole **2c**, producing **3e** in 46% yield. Bromo-substituted 4-aryl-1*H*-1,2,3-triazole **2d** afforded the corresponding *N*-glycosylated product **3f** in 43% yield.

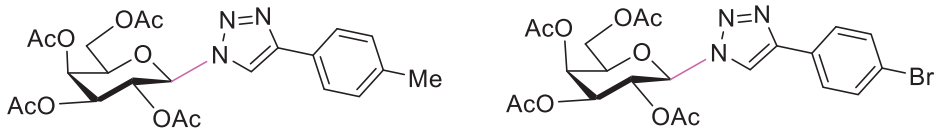
Table 2. Substrate scope of the *N*-glycosylation[a,b]



Gluscose

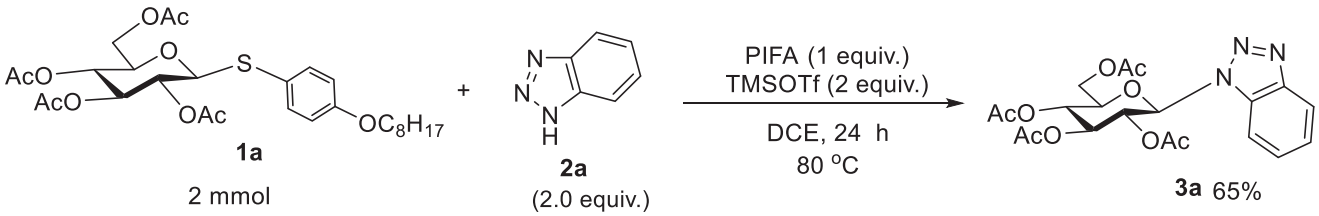


Galactose



[a]Reaction conditions: under a nitrogen atmosphere, thioglycoside **1** (0.1 mmol), triazole **2** (0.2 mmol), PIFA (0.1 mmol), TMSOTf (0.2 mmol). [b] Isolated yield.

To further demonstrate the practicality and efficiency of the developed method, a scale-up reaction was performed. It is noteworthy that the *N*-glycosylated product **3a** could be synthesized on a gram-scale (1 mol) from the reaction of thioglycoside **1a**, derived from an odorless thiol, and benzotriazole **2a** (Scheme 2).



Scheme 2. Large scale synthesis

In summary, a transition metal-free, hypervalent iodine(III) mediated oxidative *N*-glycosylation was developed using thioglycosides that were derived from odorless thiol. The reaction proceeded under mild conditions, affording the corresponding *N*-glycosylated products in good yields. These carbohydrate units can readily couple with various triazoles. The new synthetic route developed in this study did not require any specific technique or sensitive reagents, and the gram-scale synthesis of the desired product could be successfully achieved. This method is expected to be more eco-friendly, as the use of unpleasant smelling

thiols can be avoided. The synthesis requires readily available starting materials, is operationally simple, has good scalability, and is expected to be useful in organic syntheses.

EXPERIMENTAL

Instrumentation: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C on a JEOL JMN-400 spectrometer operating at 400 MHz, using tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). Column chromatography and TLC were conducted on Merck silica gel 60 (230-400 mesh) and Merck silica gel F254 plates (0.25 mm), respectively. The spots and bands were detected by UV irradiation (254 and 365 nm).

Materials: $PhI(OCOCF_3)_2$ (PIFA), 1,2,3-triazole, and 1,2,3-benzotriazole are commercially available and were used as received. All other starting materials are commercially available and were used without further purification.

p-Octyloxyphenyl 2,3,4,6-tetra-*O*-acetyl-1-*thio*-β-D-glucopyranoside **1a** was synthesized by the method in the literature,[12] i.e., $BF_3{\cdot}Et_2O$ (3.5 mL, 27.6 mmol) was added to a solution of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose (4.95 g, 12.7 mmol), and *p*-octyloxybenzenethiol (6.61 g, 27.7 mmol) in CH_2Cl_2(50 mL) at 0 °C and the mixture was stirred for 20 h at room temperature (rt). After the reaction, the reaction mixture was poured into ice water and extracted with EtoAc. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane–EtoAc= 2 : 1) to afford *p*-Octyloxyphenyl 2,3,4,6-tetra-*O*-acetyl-1-*thio*-β-D-glucopyranoside **1a** (6.44 g, 89%) as a colorless syrup. H-NMR (C_5D_5N) : δ 0.83 (3H, t, *J* = 7.1 Hz), 1.22 (8H, m), 1.36 (2H, m), 1.71 (2H, quint., *J* = 6.6 Hz), 1.978, 1.982, 2.02, 2.13 (each 3H, s), 3.90 (2H, t, *J* = 6.6 Hz), 4.13 (1H, ddd, *J* = 10.1, 4.9, 2.4 Hz, H-5), 4.41 (1H, dd, *J* = 12.3, 2.4 Hz, H-6), 4.50 (1H, dd, *J* = 12.3, 4.9 Hz, H6), 5.18 (1H, d, *J* = 10.0 Hz, H-1), 5.40 (1H, dd, *J* = 10.0, 9.5 Hz, H-2), 5.43 (1H, t, *J* = 9.5 Hz, H-4), 5.77 (1H, t, *J* = 9.5 Hz, H-3), 7.04, 7.75 (each 2H, d, AB type, *J* = 8.8 Hz, Ar). *p*-Octyloxyphenyl 2, 3,4,6-tetra-*O*-acetyl1-thio-β-D-galactopyranoside **1b** was also prepared from 1,2,3,4,6-penta-*O*-acetyl-D-galactose tetraacetate and *p*-octyloxybenzenethiol with good yield (81%).[25]

General Procedure for Glycosylation Reaction

To a stirred solution of *p*-octyloxyphenyl 2,3,4,6-tetra-*O*-acetyl-1-*thio*-β-D-glucopyranoside **1a** and 1,2,3-benzotriazole **2a** (0.2 mmol, 2 equiv) in $(CH_2)_2Cl_2$ (2 mL, 0.05 M), TMSOTf (0.2 mmol, 2 equiv) was added at room temperature. PIFA (0.1 mmol, 1 equiv) was subsequently added to the reaction mixture with stirring, and then the mixture was further stirred for 24 h at 80 °C. The reaction was

monitored by TLC. A saturated aqueous solution of sodium hydrogen carbonate was added to the mixture upon completion of the reaction. The aqueous phase was extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The crude residue was purified by column chromatography on silica gel to obtain the pure glycosylation product **3a** in 85% yield.

Characterization of the *N*-glycosylation products 3

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-benzo[*d*][1,2,3]triazole 3a

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 4.10 (1H, ddd, *J* = 10.0, 4.8, 2.0 Hz, H5), 4.22 (1H, dd, *J* = 12.8, 2.4 Hz), 4.33 (1H, dd, *J* = 12.8, 4.8 Hz), 5.38 (1H, dd, *J* = 10.0, 9.4 Hz), 5.52 (1H, dd, *J* = 9.4, 9.4 Hz), 5.78 (1H, dd, *J* = 9.4, 9.4 Hz), 6.21 (1H, d, *J* = 9.6 Hz, H1), 7.43 (1H, dd, *J* = 8.0, 7.2 Hz), 7.57 (1H, dd, *J* = 8.0, 7.2 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 8.08 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 20.6, 20.6, 20.7, 61.6, 67.8, 69.2, 72.7, 75.0, 86.0, 101.6, 120.3, 124.8, 128.4, 131.7, 146.5, 168.6, 169.5, 170.15, 170.5 ppm.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-[1,2,3]-triazole 3b

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (3H s), 2.01 (3H s), 2.05 (3H s), 2.06 (3H s), 4.01 (1H, ddd, *J* = 10.0 Hz, H5), 4.14 (1H, dd, *J* = 2.0 Hz), 4.29 (1H, dd, *J* = 12.4, 4.8 Hz), 5.26-5.21 (1H, m), 5.47-5.39, (2H, m), 5.93, (1H, d, *J* = 9.5 Hz, H1), 7.76 (1H, s), 7.83 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 20.5, 20.6, 20.7, 61.6, 67.9, 70.4, 72.8, 75.2, 85.9, 122.1, 134.6, 169.1, 169.5, 170.0, 170.5 ppm.

4-*p*-Tolyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole 3c

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (3H, s), 2.01 (3H, s), 2.06 (3H, s), 2.35 (3H, s), 3.99-4.03 (1H, m) 4.13 (1H, dd, *J* = 12.4, 1.6 Hz), 4.30 (1H, dd, *J* = 12.6, 5.0 Hz), 5.24 (1H, t, *J* = 9.6 Hz), 5.43 (1H, t, *J* = 9.6 Hz), 5.47 (1H, t, *J* = 9.6 Hz), 5.91 (1H, d, *J* = 8.0 Hz, H1) 7.21 (2H, d, *J* = 7.6 Hz,), 7.69 (2H, d, *J* = 8.0 Hz), 7.94 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 20.5, 20.6, 20.7, 21.3, 61.6, 67.8, 70.2, 72.8, 75.1, 85.7, 117.3, 125.8, 127.1, 129.5, 138.4, 148.5, 168.9, 169.3, 169.9, 170.4 ppm.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(4-bromophenyl)-[1,2,3]-triazole 3d

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (3H, s), 2.01 (3H, s), 2.06 (3H, s), 2.23 (3H, s), 4.03 (1H, ddd, *J* = 10.2, 4.8, 2.0 Hz), 4.16 (1H, dd, *J* = 12.8, 2.0 Hz), 4.33 (1H, dd, *J* = 12.7, 5.1 Hz), 5.26 (1H, dd, *J* = 10.0, 9.2 Hz), 5.44 (1H, dd, *J* = 9.6, 9.2 Hz), 5.50 (1H, dd, *J* = 9.6, 9.2 Hz), 5.92 (1H, d, *J* = 9.2 Hz, H1), 7.56 (2H, d, *J* = 8.4 Hz), 7.71 (2H, d, *J* = 8.4 Hz), 8.00 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 20.5, 20.6, 20.7, 61.6, 67.7, 70.2, 72.7, 75.3, 85.9, 117.8, 122.5, 127.4, 128.9, 132.0, 147.4, 169.0, 169.3, 169.9, 170.4 ppm.

4- *p*-Tolyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazole 3e

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.84 (3H, s), 1.97 (3H, s), 2.05 (3H, s), 2.24 (3H, s), 2.33 (3H, s), 4.17-4.25 (3H, m), 5.27 (1H, dd, *J* = 9.0, 3.2 Hz, 1H), 5.58 (1H, d, *J* = 2.8 Hz), 5.65 (1H, t, *J* = 7.2 Hz),

5.89 (1H, d, J = 9.6 Hz, H1), 7.19 (2H, d, J = 8.0 Hz), 7.86 (2H, d, J = 7.2 Hz), 8.01 (1H, s): ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 20.4, 20.5, 20.6, 21.1, 61.1, 66.8, 67.7, 70.7, 73.9, 86.2, 117.7, 125.8, 128.4, 128.7, 129.8, 148.3, 169.0, 169.7, 169.9, 170.2 ppm.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-4-(4-bromophenyl)-[1,2,3]-triazole 3f

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.25 (3H, s), 4.17-4.25 (3H, m), 5.27 (1H, dd, J = 9.2, 3.2 Hz), 5.58 (1H, d, J = 3.0 Hz), 5.65 (1H, t, J = 7.4 Hz), 5.92 (1H, d, J = 9.6 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.73 (2H, d, J = 8.8 Hz), 8.06 (s, 1H) ppm.

ACKNOWLEDGEMENTS

This work was supported by JSPS Grant-in-Aid for Scientific Research (C) Grant Number 20K05520 and Young Scientists Grant Number 19K16328.

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