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Note

New α-selective thermal glycosylation of acetyl-protected 2-acetamido-2-deoxy-β-D-glucopyranosyl diphenylphosphinate

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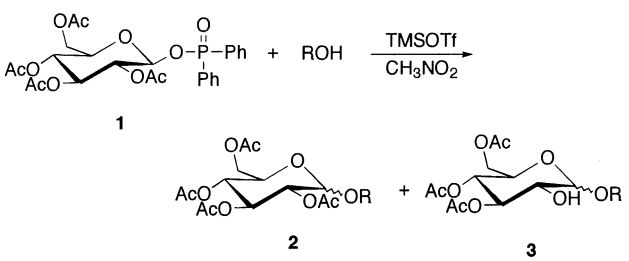
Abstract

This paper describes new α-selective thermal glycosylation using acetyl-protected 2-acetamido-2-deoxy-β-D-glucopyranosyl diphenylphosphinate (**4**) as a glycosyl donor. When the glycosylation of **4** with 1-hexanol was carried out under various conditions, the conditions using trimethylsilyl trifluoromethanesulfonate as a promoter in nitromethane at reflux temperature were most suitable for the formation of the α anomer. The glycosylation of **4** with the other common alcohols gave corresponding α-glycosides in relatively high yields under the conditions. When cholesterol, a very steric hindered alcohol, was used as a glycosyl acceptor, α-glycoside was also produced predominantly.

Keywords: Glycosylation; *N*-Acetyl-D-glucosamine; Diphenylphosphinate; α-Glycoside; Anomerization

Glycosides of 2-acetamido-2-deoxy-D-glucopyranose (*N*-acetyl-D-glucosamine) derivatives play an important role in organic and bioorganic chemistry. Among a variety of previously reported glycosylation procedures of *N*-acetyl-D-glucosamine derivatives, the stereoselectivity has been controlled mainly by the acetamido group at C-2, in which the reaction has proceeded through oxazoline-ring formation and β-glycosides were obtained almost exclusively [1]. Although α anomers have been formed by the anomerization of β anomers, which were initially formed by the glycosylation of acetylated 2-acetamido-2-deoxy-α-D-glucopyranosyl chloride with alcohols, as long a reaction time as 1.5–2 days is necessary for anomerization [2]. The other way to obtain α anomers is by the thermal glycosylation of the above glycosyl chloride in the presence of an acid scavenger [3]. To produce α anomers predominantly in the ther-



Scheme 1.

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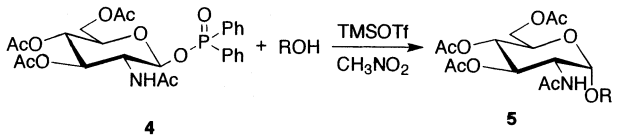

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Scheme 2.

Table 1
Glycosylation of **4** with 1-hexanol under various conditions [a]

Entry	Reaction temperature and time	Yield (%) [b]
		α/β anomers
1	40 °C, 2 h	1.4/30.7
2	40 °C, 2 h → reflux, 5 min	12.1/23.6
3	40 °C, 2 h → reflux, 2 h	33.9/trace
4	reflux, 2 h	57.8/trace

[a] Promoter; Me_3SiOTf, solvent; nitromethane, [**4**]:[glycosyl acceptor]:[Me_3SiOTf] = 1.0:2.0:1.0.

[b] Determined by ^1H NMR spectra using trimethylhydroquinone as an internal standard.

mal glycosylation, a high reaction temperature, such as 160 °C, was required and the acetylation of glycosyl acceptors proceeded as a side-reaction at that temperature.

The leaving group of glycosyl donors is one of the most fundamental parameters responsible for the selectivity and yield of glycosylation reactions. One of the current developments in the variation of leaving groups is glycosylation using glycosyl donors with phosphorus-containing leaving groups, such as phosphates [4], phosphinimidates [5,6], phosphoramidates [7–9], and phosphites [10–19]. Recently, we have reported the glycosylation of acetylated β-D-glucopyranosyl diphenylphosphinate (**1**) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in nitromethane (Scheme 1) [20]. The reaction proceeded through an orthoester intermediate to produce the corresponding glucosides **2** and the glucosides **3**, which were deacetylated at C-2. In the reaction, diphenylphosphinate was employed as a new leaving group of the glycosyl donor.

When this leaving group was applied to glycosylation using a *N*-acetyl-D-glucosamine derivative, we found the predominant formation of the corresponding α-glycosides under the selected conditions. We now report this new stereoselective thermal glycosylation using acetyl-protected 2-acetamido-2-deoxy-β-D-glucopyranosyl diphenylphosphinate (2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl diphenylphosphinate (**4**)), as a glycosyl donor (Scheme 2), which yields α-glycosides predominantly.

First, we examined the glycosylation reaction using **4** with 1-hexanol under various conditions ([**4**]:[1-hexanol]:[promoter] = 1:2:1) to establish appropriate conditions for the formation of the α anomer. Table 1 shows the results of the glycosylation in the presence of TMSOTf in nitromethane solvent; TMSOTf and nitromethane were more effective for the production of the α anomer than the other promoters and solvents such as $SnCl_4$ and acetonitrile, respectively. The yields of α and β anomers were directly determined by ^1H NMR spectra of the reaction mixtures. The reaction proceeded smoothly for 2 h at the reflux temperature in nitromethane solvent to give the α anomer predominantly (entry 4, Table 1), whereas only the β anomer was obtained at lower temperature, e.g., 40 °C (entry 1). When the reaction mixture of entry 1 was heated at reflux temperature, initially formed β anomer was gradually anomerized to the α anomer (entries 2 and 3). Thus, there are two possibilities for the reaction route to form α anomer in the glycosylation of **4**; one is the direct route via the free oxonium cationic intermediate, and the other one is the anomerization of the β anomer initially formed.

The thermal glycosylation of **4** with various alcohols as glycosyl acceptors was carried out under the conditions of entry 4 in Table 1 (Table 2). In the reaction of **4** with common alcohols, α glycosides were obtained predominantly (entries 1–4). Furthermore, cholesterol, a very steric hindered alcohol, also gave a corresponding α-glycoside as a predominant product, although the yield was lower than that using other alcohols (entry 5).

In conclusion, we examined the thermal glycosylation of **4** having diphenylphosphinate as a leaving group in the presence of TMSOTf in nitromethane. The reaction of **4** with various alcohols proceeded at reflux temperature to give the α-glycosides predominantly.

1. Experimental

General.—TMSOTf, nitromethane, and liquid alcohols as glycosyl acceptors were purified by distillation under reduced pressure prior to use. The other reagents were used without further purification. NMR spectra were recorded on a Varian Mercury 200 spectrometer. Melting points were determined on a Yanako micro melting point apparatus. Optical rotations were measured with a Jasco DIP-370 digital polarimeter.

*2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl diphenylphosphinate* (**4**) *[12].*—Diphenyl *N*,*N*-diethylphosphoramidite [21–23] (25.7 g, 99.8 mmol) in CH_2Cl_2 (100 mL) was added to a solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose [12] (13.7 g, 39.4 mmol) and 1,2,4-triazole (10.9 g, 157 mmol) in CH_2Cl_2 (500 mL), and stirred for 12 h at room temperature (rt). The solution was evaporated, diluted with diethyl ether, washed with ice-cold satd aq $NaHCO_3$, and water, dried over Na_2SO_4, filtered, and dried in vacuo. Then the residue was dissolved in CH_2Cl_2 (100 mL) and H_2O_2 (30 wt%, 50 mL) was added to the solution. After the mixture was stirred for 1 h at rt, the solution was washed with satd aq $NaHCO_3$, dried over Na_2SO_4, filtered, and dried in vacuo. The crude product was purified by silica gel column chromatography (1:3 hexane–EtOAc), and the resulting material was washed with diethyl ether to give **4** as a white powder (9.18 g, 16.8 mmol, 42.5% yield); mp 158–160 °C; $[\alpha]_D$ +59.7° (*c* 0.66, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.97–2.10 (4 s, 12 H, $CH_3C{=}O$), 3.96–4.23 (m, 3 H, H-5, 6), 4.40 (m, 1 H, H-2), 5.21 (t, 1 H, *J* 9.2 Hz, H-4), 5.33 (t, 1 H, *J* 9.2 Hz, H-3), 5.60 (q, 1 H, J_{HCCH} 7.6, J_{HCOP} 3.2 Hz, H-1), 6.41 (d, 1 H, *J* 8.8 Hz, NH), 7.58 (m, 10 H, C_6H_5). Anal. Calcd for $C_{26}H_{30}NO_{10}P$: C, 57.04; H, 5.52; N, 2.56. Found: C, 56.91; H, 5.50; N, 2.51.

General procedure for the glycosylation reactions.—Under argon, **4** (0.100 g, 0.180 mmol) and alcohol (0.360 mmol) were mixed in nitromethane (2.00 mL) at rt. Then, Me_3SiOTf (0.180 mmol, 0.0353 mL) was added to the solution and the mixture was heated under reflux temperature for 2 h. The mixture was diluted with $CHCl_3$, washed with satd aq $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated. The yields of respective isomers were determined by the integrated ratio of the anomeric peaks with an aromatic peak of trimethyl hydroquinone as an internal standard in the ^{1}H NMR spectra of the reaction mixtures ($CDCl_3$). The obtained crude products were isolated by silica gel column chromatography. The analytical data of the isolated α-glycosides are shown as follows.

*Hexyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-glucopyranoside.*—$[\alpha]_D$ +81.9° (*c* 1.5, chloroform); ^{1}H NMR ($CDCl_3$): δ 0.88–0.94 (t, 3 H, *J* 6.4 Hz, CH_2CH_3), 1.25–1.42 (m, 6 H, $(CH_2)_3CH_3$), 1.58–1.71 (m, 2 H, OCH_2CH_2), 1.96–2.10 (4 s, 12 H, $CH_3C{=}O$), 3.56 (m, 2 H, OCH_2CH_2), 3.94 (m, 1 H, H-5), 4.17 (m, 2 H, H-6), 4.34 (m, 1 H, H-2), 4.83 (d, 1 H, *J* 3.8 Hz, H-1), 5.11 (t, 1 H, *J* 9.0 Hz, H-4), 5.21 (t, 1 H, *J* 9.0 Hz, H-3), 5.67 (d, 1 H, *J* 9.6 Hz, NH). Anal. Calcd for $C_{20}H_{33}NO_9$: C, 55.67; H, 7.71; N, 3.25. Found: C, 56.19; H, 8.23; N, 3.28.

*Cyclohexyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-glucopyranoside.*—$[\alpha]_D$ +89.8° (*c* 0.76, chloroform); ^{1}H NMR ($CDCl_3$): δ 0.83–1.86 (m, 10 H, $-(CH_2)_5-$), 2.09–1.95 (4 s, 12 H, CH_3), 3.54 (m, 1 H, $OCH(CH_2)CH_2$), 4.00–4.21 (m, 3 H, H-5, 6), 4.31 (m, 1 H, H-2), 4.98 (d, 1 H, *J* 3.8 Hz, H-1), 5.10 (t, 1 H, *J* 9.6 Hz, H-4), 5.22 (t, 1 H, *J* 9.6 Hz, H-3), 5.65 (d, 1 H, *J* 9.4 Hz, NH). Anal. Calcd for $C_{20}H_{31}NO_9$: C, 55.93; H, 7.28; N, 3.26. Found: C, 55.90; H, 7.59; N, 3.31.

Table 2
Glycosylation of **4** with various alcohols [a]

Entry	Glycosyl acceptor	Yield (%) [b]
		α/β anomers
1	1-Hexanol	57.8 (54.4)/trace
2	Methanol	35.2/7.9
3	Cyclohexanol	77.6 (63.6)/14.0
4	Allyl alcohol	40.0 (22.3)/6.8
5	Cholesterol	(28.0)/nd

[a] Promoter; Me_3SiOTf, solvent; nitromethane, temperature; reflux, reaction time; 2 h, [**4**]:[glycosyl acceptor]:[Me_3SiOTf] = 1.0:2.0:1.0.

[b] Determined by ^{1}H NMR spectra using trimethylhydroquinone as an internal standard. Values in parentheses are isolated yields by silica gel column chromatography.

2-Propenyl 2-acetamido-3,4,6-tri-O-*acetyl-2-deoxy*-α-D-*glucopyranoside*.—$[\alpha]_D$ +79.8° (*c* 1.4, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.96–2.10 (4 s, 12 H, CH_3), 3.94–4.42 (m, 6 H, CH_2=CH and H-2,5,6), 4.90 (d, 1 H, *J* 3.6 Hz, H1), 5.13–5.36 (m, 4 H, CH_2=CHCH_2O and H-3, 4), 5.69 (d, 1 H, *J* 9.6 Hz, NH), 5.90 (m, 1 H, CH_2=C*H*). Anal. Calcd for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.50; N, 3.62. Found: C, 52.65; H, 6.81; N, 3.56.

Cholesteryl 2-acetamido-3,4,6-tri-O-*acetyl-2-deoxy*-α-D-*glucopyranoside*.—Mp 202–204 °C; $[\alpha]_D$ +62.6° (*c* 1.2, chloroform); ^{1}H NMR ($CDCl_3$): δ 0.85–2.35 (m, 43 H, C–CH_3, C–CH_2–C, and C–CCH(C)C of cholesteryl group), 1.96–2.09 (4 s, 12 H, CH_3), 3.46 (m, 1 H, OCH of cholesteryl group), 4.05–4.25 (m, 3 H, H-5, 6), 4.97 (d, 1 H, *J* 3.8 Hz, H1), 5.10 (t, 1 H, *J* 9.8 Hz, H-4), 5.22 (t, 1 H, *J* 9.8 Hz, H-3), 5.36 (d, 1 H, *J* 4.8 Hz, CH=C), 5.64 (d, 1 H, *J* 9.2 Hz, NH). Anal. Calcd for $C_{40}H_{63}NO_9$: C, 68.44; H, 9.05; N, 2.00. Found: C, 68.25; H, 8.93; N, 1.97.

Methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside could not be separated by column chromatography from the reaction mixture.

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