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Tetrahedron Letters 47 (2006) 267–271
Tetrahedron Letters

Catalytic and stereoselective glycosylation with glycosyl *N*-trichloroacetylcarbamate

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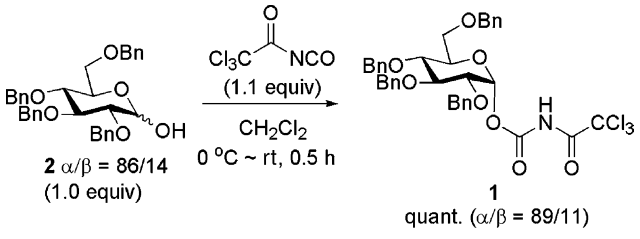
Received 9 August 2005; revised 3 November 2005; accepted 7 November 2005
Available online 22 November 2005

Abstract—Catalytic and stereoselective glycosylation efficiently proceeded by activating a glycosyl *N*-trichloroacetylcarbamate with a catalytic amount of Lewis acids in the presence of a glycosyl acceptor and molecular sieves 5 Å. Catalytic and one-pot dehydrative glycosylation of a 1-hydroxy carbohydrate was also performed stereoselectively by the reaction with trichloroacetyl isocyanate followed by activation with a catalytic amount of activators.

For an efficient *O*-glycosyl bond formation,[1] it is desirable that glycosyl donors should be prepared conveniently, and thus-prepared glycosyl donors should be activated under mild conditions to realize stereoselective glycosylation. From these viewpoints, we were interested in the high reactivity of trichloroacetyl isocyanate, which usually reacts with alcohols under neutral conditions to give the corresponding *N*-trichloroacetyl carbamates, and we were also interested in the possibility that the *N*-trichloroacetyl carbamate group would work as a good leaving group. Although some glycosylation reactions of glycosyl carbamates have been reported to date, glycosyl carbamates were activated with a stoichiometric amount of activators in these cases. For example, Kunz and Zimmer reported a glycosylation of glycosyl *N*-allylcarbamates by activation of the allylic double bond with soft electrophiles,[2] and Lacombe and co-workers reported a glycosylation by activating glycosyl *N*-phenylcarbamates with 1.5 equiv of BF_3–Et_2O.[3] Various combinations of glycosyl carbamates and a stoichiometric amount of Lewis acids were investigated by Redlich and co-workers.[4] The only exception was that glycosyl *N*-alkyl-*N*-*p*-toluenesulfonylcarbamates were activated with a catalytic amount of Me_3SiOTf,[5] but, in that case, *N*-unalkylated sulfonylcarbamates were not activated with a catalytic amount of Me_3SiOTf, and *N*-methylation or *N*-cyanomethylation was needed for the catalytic activation. In this letter, we describe catalytic and stereoselective glycosylation with a glycosyl *N*-trichloroacetylcarbamate, and catalytic one-pot dehydrative glycosylation of 1-hydroxy carbohydrate.

N-Trichloroacetylcarbamate donor **1** was prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **2** ($\alpha/\beta = 86/14$, determined by ^1H NMR in C_6D_6) by the reaction of 1.1 equiv of trichloroacetyl isocyanate in dry CH_2Cl_2 at room temperature (Scheme 1).[4] The reaction completed within 30 min, and evaporation of CH_2Cl_2 in vacuo gave **1** quantitatively as a mixture of anomers ($\alpha/\beta = 89/11$, determined by ^1H NMR). Thus-prepared donor **1** could be employed in the next glycosylation reaction without any further purification, and was stored in a refrigerator. If necessary, **1** was purified by column chromatography on silica gel, and the α-anomer of **1** was isolated in 72% yield.[6]



Scheme 1. Preparation of a glycosyl donor **1**.

Keywords: Glycosylation; Lewis acids; Solvent effects; Synthetic methods.
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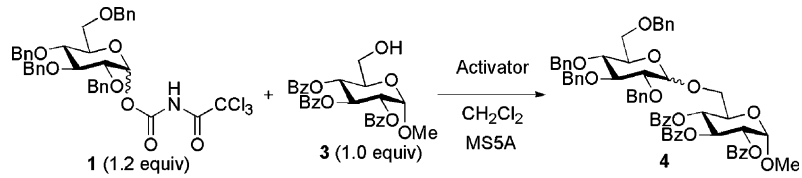
doi:10.1016/j.tetlet.2005.11.027

Table 1. Effect of Lewis acids in glycosylation with the donor **1**[a]



Entry	Activator (equiv)	Solvent	Reaction conditions	Isolated yield (%)	α/β[b]
1	$Zn(OTf)_2$ (1.2)	CH_2Cl_2	rt, 2 days	0	—
2	TfOH (1.2)	CH_2Cl_2	rt, 2 h	40	71/29
3	$Sc(OTf)_3$ (1.2)	CH_2Cl_2	rt, 1.5 h	49	40/60
4	$Mg(ClO_4)_2$ (1.2)	CH_2Cl_2	rt, 2.5 h	73	73/27
5	$Cu(OTf)_2$ (1.2)	CH_2Cl_2	rt, 1.5 h	84	74/26
6	Me_3SiOTf (1.2)	CH_2Cl_2	0 °C, 20 min	95	61/39
7	Me_3SiOTf (0.2)	CH_2Cl_2	0 °C, 1 h	92	70/30
8	$SnCl_4$ (1.2)	CH_2Cl_2	0 °C, 20 min	61	47/53
9	$SnCl_4$ (0.2)	CH_2Cl_2	0 °C, 2 h then rt, 2 h	84	44/56
10	Me_3SiOTf (1.2)	Et_2O	0 °C, 8 h	98	87/13
11	Me_3SiClO_4 (1.2)	Et_2O	0 °C, 1 h	99	93/7
12	Me_3SiClO_4 (0.2)	Et_2O	0 °C, 3 h	97	94/6
13[c]	Me_3SiClO_4 (0.1)	Et_2O	0 °C, 18 h	98	93/7
14	Me_3SiOTf (1.2)	MeCN	−40 °C, 40 min	93	6/94
15[c]	Me_3SiOTf (0.2)	EtCN	−40 °C, 40 min then −23 °C, 1 h	93	7/93

[a] The donor **1** (α/β = 89/11) was used unless otherwise noted.
[b] Determined by ^1H NMR (500 MHz) and HPLC.
[c] The α-isomer of **1** was employed.

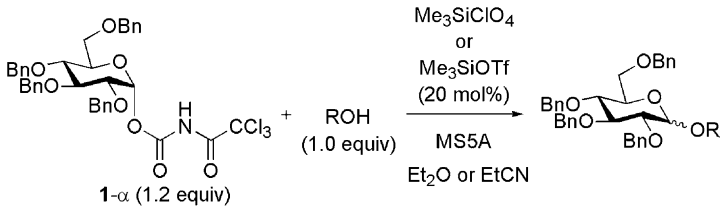
With the glycosyl donor **1** in hand, we next screened suitable activation conditions in the glycosylation of **1** with methyl 2,3,4-tri-*O*-benzoyl-D-glucoside **3** in the presence of molecular sieves 5 Å in CH_2Cl_2 (Table 1, entries 1–6, and 8). It was found that 1.2 equiv of Me_3SiOTf smoothly catalyzed the glycosylation at 0 °C to afford a disaccharide **4** in 95% yield as a mixture of anomers (α/β = 61/39). The same reaction proceeded slowly by using other Lewis acids such as $Mg(ClO_4)_2$ and $Cu(OTf)_2$ even at room temperature, and $Zn(OTf)_2$ did not activate the donor **1**.

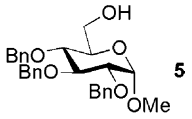
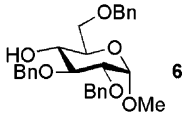
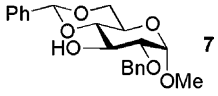
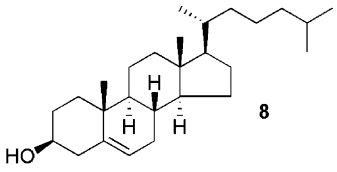
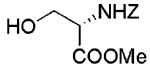
As in glycosylation with other glycosyl donors, such as glycosyl fluorides,[7] good α-selectivity (α/β = 87/13) was observed in the Me_3SiOTf-catalyzed glycosylation in Et_2O (entry 10). The α-selectivity was further improved to a ratio of α/β = 93/7 by changing the activator Me_3SiOTf to Me_3SiClO_4 (entry 11).[8] The high reactivity of **1** led us to consider that a catalytic amount of Me_3SiClO_4 might catalyze the present glycosylation. As expected, when a catalytic amount (20 mol %) of Me_3SiClO_4 was employed, the reaction proceeded smoothly to give **4** in 97% yield while maintaining the high α-selectivity (entry 12). Even 10 mol % of Me_3SiClO_4 catalyzed the glycosylation efficiently (entry 13). In this case, purified α-isomer of **1** was used for the glycosylation, and the α,β-selectivity did not change compared to the case of using an α,β-mixture of **1**, which suggested that Me_3SiClO_4 effectively activated a carbamate carbonyl group of **1**, and then an oxonium cation intermediate was formed in the present glycosylation. The catalytic glycosylation needed longer reaction time compared to the stoichiometric glycosylation, and nearly quantitative yields of disaccharides **4** were obtained in both stoichiometric and catalytic glycosylation. Interestingly, the present catalytic glycosylation had to be carried out in the presence of MS5A because Me_3SiClO_4-catalyzed glycosylation did not proceed in the presence of MS4A or MS3A. The reason for the outstanding effects of MS5A was not clear, but the similar effects of MS5A were observed in the catalytic glycosylation of glycosyl fluorides.[9]

β-Selective glycosylation (α/β = 6/94) was performed by using MeCN[10] as a solvent and a stoichiometric amount of Me_3SiOTf[11] (entry 14). In this case, the reaction proceeded at a lower temperature (−40 °C) than in the case of the α-selective reaction in Et_2O. Catalytic β-selective glycosylation was also realized by using 20 mol % of Me_3SiOTf in EtCN[12] to afford a disaccharide **4** in 93% yield with a ratio of α/β = 7/93, and the α,β-selectivity was not influenced by the α,β-ratio of the donor **1** (entry 15).

Next, the scope and limitations of the catalytic and stereoselective glycosylation with **1** were investigated by using various glycosyl acceptors under α- and β-selective glycosylation conditions (Table 2). Glycosyl acceptors having primary, secondary, and even tertiary hydroxy groups readily reacted with the glycosyl donor **1** in Et_2O to give α-glycosides in high yields and with high α-selectivity by using 20 mol % of Me_3SiClO_4. On the other hand, though high β-selectivity was observed in Me_3SiOTf-catalyzed glycosylation in EtCN with glycosyl acceptors having a primary hydroxy group, moderate β-selectivities were observed in the cases of acceptors having secondary and tertiary hydroxy groups because higher reaction temperature was required for the reaction of secondary and tertiary hydroxy groups than primary hydroxy groups. *t*-BuOH reacted with **1**

Table 2. Stereoselective and catalytic glycosylation of **1** with various acceptors

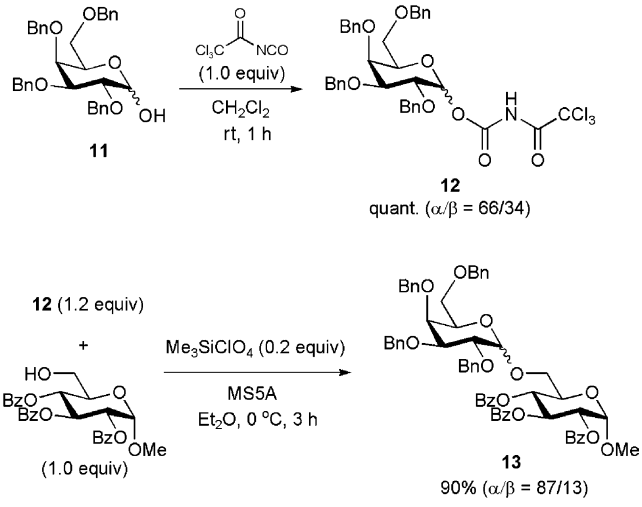


Acceptors (ROH)	α-Selective glycosylation[a]	β-Selective glycosylation[b]
 **5**	0 °C, 4 h 99% α/β = 94/6	−40 °C, 0.5 h then −23 °C, 3 h 97% α/β = 7/93
 **6**	0 °C, 5 h 93% α/β = 90/10	−40 °C, 1.5 h then −23 °C, 16 h 83% α/β = 15/85
 **7**	0 °C, 3 h 86% α/β = 96/4	−20 °C, 1 h 74% α/β = 17/83
 **8**	0 °C, 4 h 93% α/β = 94/6	0 °C, 2 h then rt, 1 h 88% α/β = 21/79
 **9**	0 °C, 3 h 90% α/β = 92/8	−40 °C, 0.5 h then −23 °C, 4.5 h 88% α/β = 20/80
 **10**	0 °C, 19 h 89% α/β = 86/14	rt, 4 days[c] 38% α/β = 39/61

[a] Me_3SiClO_4 (20 mol %) in Et_2O.
[b] Me_3SiOTf (20 mol %) in EtCN.
[c] The glycosyl donor **1** (1.0 equiv) and *t*-BuOH (2.0 equiv) were employed.

very slowly in EtCN, and the corresponding *t*-butyl glycoside was obtained in low yield (38%). Moreover, a glycosyl donor **12** which was prepared from 2,3,4,6-tetra-*O*-benzyl-D-galactose **11** (quant., α/β = 66/34) was smoothly activated with a catalytic amount of Me_3SiClO_4 to give a disaccharide **13** in 90% yield (α/β = 87/13, Scheme 2).

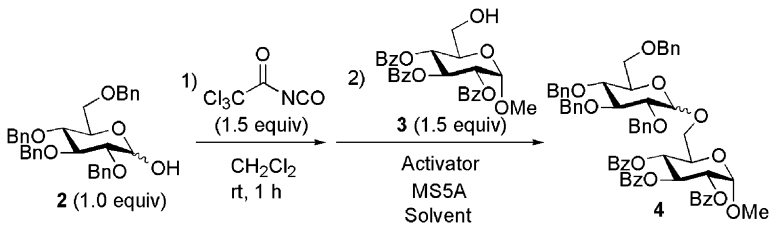
Most of the conventional glycosylation reactions have been conducted by two steps: that is (1) isolation of a glycosyl donor having a latent leaving group at the anomeric position and (2) activation of the leaving group in the presence of a glycosyl acceptor. When glycosyl donors are unstable to be isolated, it is desirable to perform the glycosylation by derivatizing a stable 1-hydroxy carbohydrate to a reactive glycosyl donor, followed by the successive activation in a one-pot manner. The one-pot glycosylation (i.e., dehydrative glycosylation)[13] was then investigated by the activation of in situ-formed **1** as a model reaction, though **1** was stable to be isolated (Table 3). In this dehydrative glycosylation starting from **2**, CH_2Cl_2 was used as co-solvent in the preparation of the carbamate donor **1** because of



Scheme 2. Catalytic glycosylation with a donor **12**.

the low solubility of **2** in Et_2O and EtCN. Stoichiometric one-pot glycosylation proceeded smoothly by using

Table 3. One-pot dehydrative glycosylation



Entry	Activator (equiv)	Solvent[a]	Reaction conditions	Isolated yield (%)	α/β[b]
1[c]	Me_3SiClO_4 (1.5)	Et_2O	0 °C, 0.5 h	99	93/7
2	Me_3SiClO_4 (0.2)	Et_2O	0 °C, 0.5 h	88	91/9
3[c]	Me_3SiOTf (1.5)	EtCN	−40 °C, 0.5 h then −23 °C, 0.5 h	88	8/92
4	Me_3SiOTf (0.2)	EtCN	−40 °C, 1 h then −23 °C, 1 h	85	12/88

[a] Solvent/CH_2Cl_2 = 5/1.
[b] Determined by ^1H NMR (500 MHz).
[c] MS5A was not used.

1.5 equiv of Me_3SiClO_4 in Et_2O or Me_3SiOTf in EtCN to afford α- or β-glycoside, respectively, in high yields (entries 1 and 3). Also, catalytic one-pot dehydrative glycosylation proceeded stereo- selectively in the presence of MS5A (entries 2 and 4). The one-pot stoichiometric glycosylation proceeded smoothly in the absence of MS5A, while the one-pot catalytic glycosylation needed MS5A.

Thus, α- or β-selective glycosylation of using glycosyl *N*-trichloroacetylcarbamate **1** as a glycosyl donor proceeded efficiently by activating the donor with a catalytic amount of Me_3SiClO_4 in Et_2O or Me_3SiOTf in EtCN, respectively, in the presence of MS5A.[14] Preparation of **1** from a 1-hydroxy carbohydrate **2** and successive stereoselective and catalytic glycosylation were also realized in a one-pot manner, and the desired α- or β-glycoside was obtained directly from **2**. The easy operation of the present glycosylation, especially one-pot dehydrative glycosylation, would be useful in the synthesis of oligosaccharides or bioactive compounds having carbohydrate parts.

Acknowledgements

The authors thank for the financial support from Novartis Foundation, Japan, for the Promotion of Science, and this work was partially supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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6. The preparation of **1**: to the stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **2** (1.00 g, 1.85 mmol) in dry CH_2Cl_2 (freshly distilled from CaH_2, 5 mL) was added trichloroacetyl isocyanate (0.24 mL, 2.01 mmol) at 0 °C. After the reaction mixture was stirred for 0.5 h at room temperature (26 °C), the solvent was evaporated in vacuo to give **1** as a colorless syrup (quant., α/β = 89/11, determined by ^1H NMR). If necessary, the α-isomer (R_f = 0.40, hexane/AcOEt = 3/1) and the β-isomer (R_f = 0.34, hexane/AcOEt = 3/1) were separated, and the α-isomer was isolated in 72% yield by column chromatography on silica gel (hexane/AcOEt = 7/1). α-Isomer: ^1H NMR (500 MHz, $CDCl_3$): 8.37 (s, 1H), 7.36–7.13 (m, 20H), 6.39 (d, *J* = 3.7 Hz, 1H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.48 (d, *J* = 12.4 Hz, 1H), 3.97 (t, *J* = 9.6 Hz, 1H), 3.91 (m, 1H), 3.79–3.72 (m, 3H), 3.66 (dd, *J* = 10.5, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 157.4, 148.6, 138.3, 137.7, 137.5, 137.0, 128.4, 128.2, 128.0, 127.8, 127.6, 127.5, 93.7, 91.5, 81.2, 78.3, 76.5, 75.5, 75.1, 73.4, 73.4, 67.7. β-Isomer: ^1H NMR (500 MHz, $CDCl_3$): 8.20 (s, 1H), 7.33–7.12 (m, 20H), 5.62 (d, *J* = 8.2 Hz, 1H), 4.91–4.72 (m, 4H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 3.80–3.57 (m, 6H).
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10. Kreuzer, M.; Thiem, J. *Carbohydr. Res.* **1986**, *149*, 347–361.
11. Me_3SiClO_4 was not employed for β-selective glycosylation because it was reported that ClO_4^- was a suitable counter anion for α-selective glycosylation and less effective for β-selective glycosylation.[15]

12. EtCN gave better results for β-selective catalytic glycosylation with **1** than MeCN.
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14. Typical experimental procedure for the catalytic glycosylation is as follows (Table 1, entry 12): to a stirred suspension of MS5A (120 mg), the acceptor **3** (20.0 mg, 0.040 mmol), and the donor **1** (34.6 mg, 0.047 mmol) in dry Et_2O (3 mL) was added a solution of Me_3SiClO_4 in Et_2O (0.1 N, 0.08 mL, prepared from Me_3SiCl and $AgClO_4$) at 0 °C. After the reaction mixture was stirred at 0 °C for 3 h, the reaction was quenched by adding saturated $NaHCO_3$ solution and the mixture was filtered through Celite pad, extracted with AcOEt. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. A crude product was purified by preparative TLC (silica gel, benzene/AcOEt = 10:1) to afford **4** (a colorless oil, 39.5 mg, 0.038 mmol, 97%) as a mixture of anomers (α/β) = 94/6, determined by ^1H NMR (500 MHz) and by HPLC (Pegasil 60-5, hexane/AcOEt = 4:1, 1 mL/min, 254 nm).
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