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Carbohydrate Research 337 (2002) 581–585

CARBOHYDRATE RESEARCH

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A substrate-unspecified glycosylation reaction promoted by copper(II) trifluoromethanesulfonate in benzotrifluoride

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Received 16 November 2001; accepted 20 January 2002

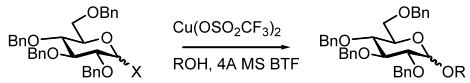
Abstract

A glycosylation reaction induced by copper(II) trifluoromethanesulfonate is described. Using benzotrifluoride as the reaction solvent, five kinds of glycosyl donors, a glucosyl chloride, a fluoride, a trichloroacetimidate, a 1-*O*-acetyl compound, and a lactol were activated to give the corresponding glucosides.

Keywords: Glycosylation; Copper(II) trifluoromethanesulfonate

1. Introduction

Glycosylation reactions that have been reported so far in the literature have been achieved by the appropriate combination of a leaving group on the anomeric carbon and suitable activating reagent(s). However, reagents that activate a variety of glycosyl donors are limited. Trimethylsilyl trifluoromethanesulfonate (triflate, hereafter) and boron trifluoride diethyl etherate have been reported as reagents that activate several kinds of glycosyl donors.[1–20] Recently, Mukaiyama and co-workers reported that $TrB(C_6F_5)_4$ activates thioglycosides, glycosyl fluorides, glycosyl phenylcarbonates, and lactols.[21] For a one-pot strategy of oligosaccharide synthesis, the search for reagents that activate several kinds of glycosyl donors is also important. Here we report a copper(II) triflate-mediated glycosylation reaction.[22] Using benzotrifluoride (BTF) as the reaction solvent,[23] copper(II) triflate was shown to activate five kinds of glycosyl donors, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**1a**), 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl fluoride (**1b**), 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl trichloroacetimidate (**1c**), 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**1d**), and 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**1e**) (Scheme 1).



1a: X = Cl (α/β > 99:1)
1b: X = F (α/β = 93:7)
1c: X = OC(=NH)CCl$_3$ (α/β = 88:12)
1d: X = OAc (α/β = 74:16)
1e: X = OH (α/β = 79:21)

Scheme 1.

2. Results and discussion

Glycosylation reactions of **1a**–**1e** are summarized in Table 1. Cyclohexylmethanol was used as a glycosyl acceptor. A stoichiometric amount of copper(II) triflate was used as a common activating reagent of the glycosyl donors, **1a**–**1e**. Diethyl ether, acetonitrile, 1,2-dichloroethane, and BTF were employed as the reaction solvents. BTF is a solvent with a relatively low toxicity that was introduced as an alternative of dichloromethane by Ogawa and Curran.[23] With the glucosyl chloride **1a**, the reaction took place at room temperature in each solvent (entries 1–4) to give **2**.[24] BTF gave the best yield among the solvents. The glucosyl fluoride **1b** showed similar reactivity in 1,2-dichloroethane or BTF (entries 5–8). No reaction took place in diethyl ether or acetonitrile. Trichloroacetimidate **1c** was activated easily in each solvent (entries

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3378-6215/02/$ - see front matter
PII: S0008-6215(02)00029-0

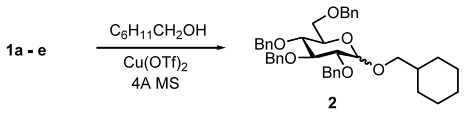
Table 1
Glycosylation reaction of **1a**–**1e** with cyclohexylmethanol using $Cu(OTf)_2$ [a]

Entry	Glycosyl donor	Solvent	Temperature (°C)	Time (h)	Yield [b] (%)	α/β [c] ratio
1	**1a**	Et_2O	rt	1.0	85	55/45
2	**1a**	CH_3CN	rt	2.5	31	26/74
3	**1a**	$(CH_2Cl)_2$	rt	3.0	81	40/60
4	**1a**	BTF	rt	4.5	93	31/69
5	**1b**	Et_2O	reflux	1.0	0	
6	**1b**	CH_3CN	reflux	1.0	0	
7	**1b**	$(CH_2Cl)_2$	reflux	1.0	82	59/41
8	**1b**	BTF	reflux	1.0	88	80/20
9	**1c**	Et_2O	rt	2.0	78	56/44
10	**1c**	CH_3CN	rt	1.5	69	48/52
11	**1c**	$(CH_2Cl)_2$	rt	2.0	60	45/55
12	**1c**	BTF	rt	4.5	81	42/58
13	**1d**	Et_2O	reflux	0.5	5	59/41
14	**1d**	CH_3CN	60	0.5	4	42/58
15	**1d**	$(CH_2Cl)_2$	60	0.5	88	59/41
16	**1d**	BTF	60	0.5	88	56/44
17	**1e**	Et_2O	reflux	0.7	0	
18	**1e**	CH_3CN	reflux	0.7	40	57/43
19	**1e**	$(CH_2Cl)_2$	reflux	0.7	8	31/69
20	**1e**	BTF	reflux	0.7	84	59/41

[a] The product is **2**.
[b] Isolated yield based on each glucosyl donor.
[c] Ratio was determined by HPLC using a YMC R-SIL-5 column (4.6 × 250 mm) with 15:1 *n*-hexane–EtOAc. Detection was by a differential refractive index detector.

9–12), but BTF showed the best yield as well. Copper(II) triflate activated the acetate **1d** in either 1,2-dichloroethane or BTF at 60 °C. In diethyl ether or acetonitrile the reaction was very slow (entries 13–16), and prolonging the reaction time for 24 h did not significantly increase the yield. The lactol **1e** was also activated by copper(II) triflate (entries 17–20). In BTF, the yield was the best among the solvents. In acetonitrile the reaction was slower than in BTF. In diethyl ether the reaction did not take place even when the reaction time was extended to 24 h. The slow reaction was observed in refluxing 1,2-dichloroethane. A combination of thioglucoside, phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-1-deoxy-α-D-glucopyranoside, and copper(II) triflate afforded a complex mixture (Scheme 2).

The reaction could be applied to more hindered alcohols as well as a sugar alcohol. With the secondary alcohol, cholesterol, the glucosyl chloride **1a**, and the trichloroacetimidate **1c** were activated at room temperature to give **3** (Table 2).[25] Activation of the fluoride **1b** and the acetate **1d** required 60 °C, and the lactol **1e** was activated under BTF reflux temperature (102 °C). A tertiary alcohol, 2-methyl-2-propanol, was also coupled with the glycosyl donors in BTF (Table 3). Thus, **1a**, **1b**, and **1d** were activated at 50–60 °C to give **4** in moderate yield.[26] The trichloroacetimidate **1c** was reacted at room temperature giving 91% yield of the product. Even the lactol was coupled at the BTF reflux temperature, but the yield was only 30%. When a sugar alcohol, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, was applied as a glycosyl acceptor, the fluoride **1b** and trichloroacetimidate **1c** afforded a disaccharide **5** in more than 80% yield (Table 4).[27] The other three glycosyl donors (**1a**, **1d**, and **1e**) gave the disaccharide in 50–70% yield.



Scheme 2.

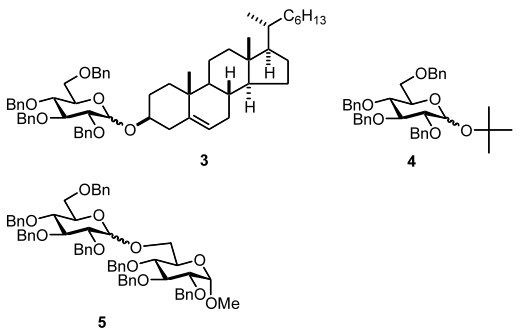


Table 2
Glycosylation reaction of **1a**–**1e** with cholesterol using $Cu(OTf)_2$ in BTF [a]

Entry	Glycosyl donor	Temperature (°C)	Time (h)	Yield [b] (%)	α/β [c] ratio
1	**1a**	rt	16.6	41	70/30
2	**1b**	65	0.6	84	59/41
3	**1c**	rt	4.5	72	55/45
4	**1d**	60	0.5	65	60/40
5	**1e**	reflux	1.0	53	75/25

[a] The product is **3**.
[b] See Table 1.
[c] Ratio was determined by HPLC using a Crestpack C18S column (4.6 × 150 mm) with 10:1 MeOH–THF. Detection was by a differential refractive index detector.

Table 3
Glycosylation reaction of **1a**–**1e** with 2-methyl-2-propanol using $Cu(OTf)_2$ in BTF [a]

Entry	Glycosyl donor	Temperature (°C)	Time (h)	Yield [b] (%)	α/β [c] ratio
1	**1a**	50	2.0	38	65/35
2	**1b**	60	1.0	58	60/40
3	**1c**	rt	4.5	91	29/71
4	**1d**	60	5.0	54	68/32
5	**1e**	reflux	0.5	30	33/67

[a] The product is **4**.
[b] See Table 1.
[c] Ratio was determined by HPLC using a Crestpack C18S column (4.6 × 150 mm) with 5:1 MeOH–water. Detection was by a differential refractive index detector.

Table 4
Glycosylation reaction of **1a**–**1e** with methyl 2,3,4-tri-*O*-benzyl-α-D-glycopyranoside using $Cu(OTf)_2$ in BTF [a]

Entry	Glycosyl donor	Temperature (°C)	Time (h)	Yield [b] (%)	α/β [c] ratio
1	**1a**	50	3.0	65	83/17
2	**1b**	reflux	0.5	80	74/26
3	**1c**	rt	4.0	83	62/38
4	**1d**	60	1.2	50	86/14
5	**1e**	reflux	0.8	69	75/25

[a] The product is **5**.
[b] See Table 1.
[c] Ratio was determined by the ^1H NMR spectrum of the anomeric mixture.

In conclusion, copper(II) triflate activated the glucosyl chloride, the fluoride, the trichloroacetimidate, the acetate, and the lactol in good yield in BTF. Under these conditions, the glucosyl trichloroacetimidate was the most reactive, followed by the glucosyl chloride, the acetate, the fluoride, and then the lactol in that order. The reactivity of the two former reactive glycosyl donors and the two latter ones were clearly controlled by the reaction temperature. Each glycosyl donor was coupled with a primary, a secondary and even a tertiary alcohol under the reaction conditions.

3. Experimental

General procedure for the glycosylations.—The reactions were run under a positive pressure of argon. Acetonitrile and 1,2-dichloroethane used for the solvent of the reactions were distilled from calcium hydride. Diethyl ether was distilled from sodium benzophenone ketyl before use. Benzotrifluoride was distilled from phosphorus pentoxide.

Copper(II) triflate was dried before use by heating to 180–200 °C with a heat gun under reduced pressure

(ca. 1 mmHg). A benzene solution of each glycosyl donor (1.0 equiv) and an acceptor alcohol (1.1 equiv) was evaporated to azeotropically remove traces of water, and dissolved into the solvent (40 mL/mmol based on the amount of a glycosyl donor) listed in Tables 1–4. The solution was added to a mixture of dried copper(II) triflate (1.1 equiv) and powdered 4 Å molecular sieves (0.6 g/mmol). The mixture was stirred under the conditions listed in the tables. When the reaction was completed, the mixture was filtered through a cotton-Celite pad. Satd aq sodium hydrogen carbonate was added to the filtrate, and it was extracted with dichloromethane. The organic layer was washed with brine, dried over anhyd magnesium sulfate, filtered, and concentrated. Silica-gel column chromatography of the crude product, eluting with a mixture of *n*-hexane and EtOAc, gave an anomeric mixture of the glycosides. The α/β ratios of the mixtures were detected by HPLC (compounds **2**, **3**, and **4**) or by the ^{1}H NMR spectrum (**5**). Conditions of HPLC are provided in each table.

Products.—*Cyclohexylmethyl 2,3,4,6-tetra*-O-*benzyl-α*-D-*glucopyranside (α*-**2**)[24].—The product was purified by column chromatography on silica gel with 4:1 *n*-hexane–EtOAc to give an anomeric mixture of **2** that was separated by HPLC. HPLC retention time: 7.48 min (flow rate: 2.00 mL/min, pressure: 92 kg/cm^2); ^{13}C NMR (100 MHz in $CDCl_3$) δ 25.8 (CH_2), 25.9 (CH_2), 26.6 (CH_2), 30.0 (CH_2), 30.3 (CH_2), 37.7 (CH), 68.6 (CH_2), 70.1 (CH), 73.1 (CH_2), 73.5 (CH_2), 74.0 (CH_2), 75.2 (CH_2), 75.7 (CH_2), 77.9 (CH), 80.4 (CH), 82.2 (CH), 97.2 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.0 (CH), 128.1 (CH), 128.1 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 138.2 (C), 138.5 (C), 138.6 (C), 139.1 (C). The ^{1}H NMR spectral data were identical to the literature data.[24a]

Cyclohexylmethyl 2,3,4,6-tetra-O-*benzyl-β*-D-*glucopyranside (β*-**2**)[24]. HPLC retention time: 6.21 min; ^{13}C NMR (100 MHz in $CDCl_3$) δ 25.7 (CH_2), 25.7 (CH_2), 26.4 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 38.0 (CH), 68.9 (CH_2), 73.2 (CH_2), 74.6 (CH_2), 74.6 (CH), 74.7 (CH_2), 75.4 (CH_2), 75.5 (CH_2), 77.8 (CH), 82.1 (CH), 84.5 (CH), 103.6 (CH), 127.3 (CH), 127.4 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 138.1 (C), 138.2 (C), 138.5 (C), 138.6 (C). The ^{1}H NMR spectral data were identical to the literature data.[24a]

Cholesterol-3-yl 2,3,4,6-tetra-O-*benzyl-α*-D-*glucopyranside (α*-**3**)[25]. The product was purified by column chromatography on silica gel with 10:1 *n*-hexane–EtOAc to give an anomeric mixture of **3** that was separated by HPLC. HPLC retention time: 10.63 min (flow rate: 2.50 mL/min, pressure: 166 kg/cm^2). The NMR spectral data were identical to the literature data.

Cholesterol-3-yl 2,3,4,6-tetra-O-*benzyl-β*-D-*glucopyranside (β*-**3**)[25]. HPLC retention time: 13.02 min. The NMR spectral data were identical to the literature data.

tert-*Butyl 2,3,4,6-tetra*-O-*benzyl-α*-D-*glucopyranside (α*-**4**)[26]. The product was purified by column chromatography on silica gel with 40:1 *n*-hexane–EtOAc to give an anomeric mixture of **4**. HPLC retention time: 26.12 min (flow rate: 1.95 mL/min, pressure: 189 kg/cm^2). The NMR spectral data were identical to the literature data.

tert-*Butyl 2,3,4,6-tetra*-O-*benzyl-β*-D-*glucopyranside (β*-**4**)[26]. HPLC retention time: 32.83 min. The NMR spectral data were identical to the literature data.

Methyl 2,3,4-tri-O-*benzyl-6*-O-*(2,3,4,6-tetra*-O-*benzyl-α/β*-D-*glucopyranosyl)-α*-D-*glucopyranoside* (**5**)[26,27]. The product was purified by column chromatography on silica gel with 4:1 *n*-hexane–EtOAc to give an anomeric mixture of **5**. The NMR spectral data were identical to the literature data.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research (Grant no. 13874078) from the Japan Society for the Promotion of Science, The Naito Foundation, and by a Sunbor Grant from Suntory Institute for Bioorganic Research.

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