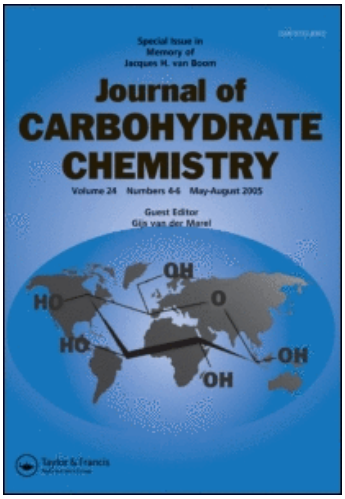

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Lithium Triflate as a New Promoter of Glycosylation Under Neutral Conditions

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LITHIUM TRIFLATE AS A NEW PROMOTER OF GLYCOSYLATION UNDER NEUTRAL CONDITIONS[1]

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ABSTRACT

The glycosyl donors 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate and 3,4,6-tri-*O*-benzyl-α-D-fucopyranosyl trichloroacetimidate were activated under neutral conditions with a catalytic amount (0.05 equiv) of lithium triflate and reacted with a series of alcohols including an acid sensitive sugar to give the corresponding glycosides in high yields. The stereoselectivity of the glycosylation was improved by introducing a participating group next to the anomeric position.

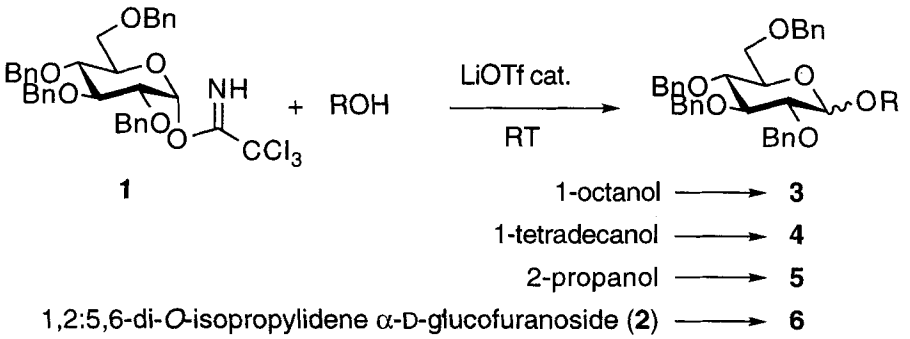
INTRODUCTION

Anomeric trichloroacetimidates are among the most effective glycosyl donors used in the chemical synthesis of oligosaccharides. The glycoside donor is usually activated by strong Lewis acids such as trimethylsilyl trifluoromethanesulfonate,[2] boron trifluoride etherate[3] or zinc bromide.[4] These catalysts require special attention (e.g. low temperature or molecular sieves), especially if acid labile protective groups or glycosidic bonds are present. It is therefore worthwhile to eliminate these constraints by developing

new catalysts for the activation of anomeric trichloroacetimidates. Two appreciable improvements using neutral salts as promoters have been reported recently. The first method, described by Krepinsky,[5] uses silver triflate in a stoichiometric amount with the imidate to afford excellent yields of glycosides at room temperature. The second method, reported by Waldmann,[6] uses a 1 M solution of lithium perchlorate in organic solvents and proceeds equally well for *O*-glycoside synthesis under mild conditions. But, an expensive and toxic metal salt such as silver triflate or potentially dangerous salt such as lithium perchlorate[7] can limit their uses. The concept of this work was to increase the electropositivity of the lithium cation by using the triflate anion which is more electroattractive than the perchlorate anion.[8] In this way, we demonstrate that lithium triflate which can be used in catalytic amounts (0.05 equiv), can promote glycosylation in good yield from perbenzylated anomeric trichloroacetimidate glycosides. Furthermore, this catalyst is not toxic and can be easily prepared at low cost.[9] Subsequent to our findings, lithium triflate was shown to be an effective catalyst for aminolysis of oxiranes[10] and useful as a cocatalyst together with trityl tetrakis(pentafluorophenyl) borate in the preparation of α-D-ribofuranosides. [11]

RESULTS AND DISCUSSIONS

First, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (**1**) was used as glycosyl donor model. A series of alcohols (1-octanol, 1-tetradecanol and 2-propanol) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**2**), sensitive to acid conditions, were used as acceptors.[12]



The experimental results are listed in Table 1. Yields are given after purification by chromatography on silica gel. Anomeric ratios were determined by ^{13}C NMR.

Table 1. Summary of the glycosylation reactions

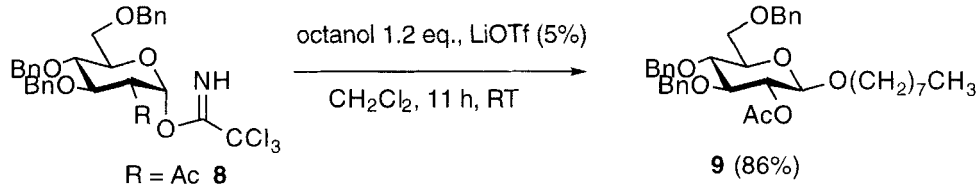
Compound	ROH	Solvent	LiOTf	Reaction time (h)	Yield (%)	Anomeric ratio (α:β)
3	1.4 eq.	CH_2Cl_2	0.05 eq.	16	84	30:70
3	1.2 eq.	CH_3CN	1 eq.	20	84	25:75
4	1.2 eq.	CH_2Cl_2	0.05 eq.	22	67	18:82
4	1.2 eq.	CH_3CN	1 eq.	12	79	15:85
5	1.4 eq.	CH_2Cl_2	0.05 eq.	24	78	38:62
5	1.2 eq.	CH_3CN	1 eq.	20	77	27:73
6	1.4 eq.	CH_2Cl_2	0.05 eq.	96	60	55:45
6	0.75 eq.	CH_3CN	0.5 eq.	86	77	55:45

Primary and secondary alcohols afforded the glycosides **3**, **4** and **5** in good yields. Despite the long reaction time, **2** survived until the reaction was finished and **6** was obtained in satisfactory yields. In dichloromethane, only 0.05 equivalent of lithium triflate was required to promote the glycosylation of **1**. In order to obtain the same results in acetonitrile in a tolerable reaction time, a 1:1 molar ratio of lithium triflate to **1** was necessary. The high affinity of the lithium cation for nitrogen could explain simultaneously the activation of the trichloroacetimidate and its deactivation in acetonitrile. For each solvent, the formation of anomeric mixtures was observed because of the presence of the non-participating benzyl protective groups.

To improve the selectivity, we tried to prepare a glycoside from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (**7**) and 1-octanol in 1,2-dichloroethane using lithium triflate as a promoter. At room temperature, no reaction took place. Even after increasing the temperature to 50 °C and with a large excess of lithium triflate (5 equiv), we only observed a trace amount of glycosylation product, with decomposition compounds as the main products. We then tried to prepare **3** from **1** with 0.05 equivalent of lithium triflate in the presence of 1 equivalent of α-peracetylated glucoside. In this case, **3** was formed as previously in high yield. This competition experiment proved that lithium was not complexed to the acetate groups of **7**. Lithium cation does not seem to be able to promote the glycosylation of peracetylated trichloroacetimidates which are less reactive than the perbenzylated sugars.

Finally, the stereoselectivity of the glycosylation was improved by introducing a participating group next to the anomeric position. Thus, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-

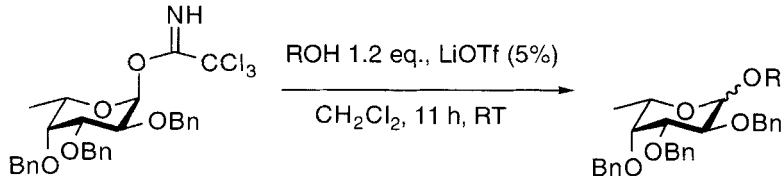
D-glucopyranosyl trichloroacetimidate (**8**) prepared from 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-gluco-pyranose,[13] reacted with 1-octanol in the presence of lithium triflate (0.05 equiv) to afford octyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**9**) in 86% yield (the α-anomer was present in only 5% yield). It is noteworthy that, starting from the peracetylated trichloroacetimidate **7** and using a variety of alcohols, concentrated solution of lithium perchlorate in organic solvents led to the formation of the orthoester in place of the expected β-glycoside. [6b]



R = Ac **8**
R = Bn **10**

9 (86%)

In the case of fucose, glycosylation using the corresponding trichloroacetimidate is sometimes hampered when the perbenzylated fucosyl donor which is highly reactive and sensitive to acid conditions[14] is used. However, Waldmann reported that 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl trichloroacetimidate (**10**)[15] can be activated under mild conditions with a 1 M solution of lithium perchlorate in dichloromethane.[16] We found that catalytic amounts of lithium triflate were sufficient to promote fucosylation by **10**. Thus, **10** was reacted with 1-octanol and 2-propanol in the presence of lithium triflate (0.05 equiv) to afford an anomeric mixture of the corresponding fucosides **11** and **12** in high yields. It is noteworthy that both alcohols gave rise to opposite diastereoselectivities, 2-propanol led to the α anomer whereas 1-octanol led to a 85/15 mixture in favor of the β anomer.



1-octanol ⟶ **11**, 89%, α/β 15/85, 3 h
2-propanol ⟶ **12**, 85%, α/β 70/30, 5 h 30

In fact, we prepared **11** for comparison with two different Lewis acid catalysts (0.05 equiv of trimethylsilyl trifluoromethanesulfonate or boron trifluoride etherate in

dichloromethane at room temperature). In each case, glycosylation was instantaneous with an α:β ratio of 15:85 as observed with lithium triflate. These experiments suggested that activation by lithium triflate follows the normal way of classical acidic activation of trichloroacetimidate.

EXPERIMENTAL

General methods. NMR spectra were recorded with Brüker AM250 and 400 and AC 200 and 250 spectrometers. Chemical shifts are given in ppm downfield from internal tetramethysilane; signal multiplicity is indicated as follow: s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet and br for broad. IR spectra were recorded using a Brüker FT instrument. Optical rotations were determined at 20 °C using a Jasco DIP-370 digital polarimeter. Flash chromatography was performed using 6-35 μ silica gel (60) purchased from S.D.S. company. TLC was run using Merck 60 F254 plates, and visualized first with UV light and second by heating after alcoholic sulfuric or phosphomolybdic acid treatment. Melting points were measured on a Reichert apparatus and are uncorrected. Elementary analyses were performed at the "Service Central de Microanaly e du C.N.R.S."

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl Trichloroacetimidate (8). To a solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose[13] (732 mg, 1.49 mmol) in dichloromethane (5 mL) was added trichloroacetonitrile (0.37 mL, 3.72 mmol) and sodium hydride (11 mg, 0.45 mmol). The reaction mixture was stirred for 4 h at room temperature and filtered. The solution was concentrated and the residue was purified by chromatography (90:10:1 hexane-ethyl acetate-triethylamine) to give **8** (600 mg, 65%): $[\alpha]_D^{20}$ + 80 (c 3.27, dichloromethane); IR (NaCl) 3338, 3031, 2925, 2867, 1748, 1673, 1497, 1454, 1366, 1294, 1231, 1052, 796, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$) 8.56 (1 H, s, NH), 7.45-7.06 (15 H, m, H-ar), 6.54 (1 H, d, 3.4 Hz, H-1), 5.08 (1 H, dd, 9.8, 3.4 Hz, H-2), 4.87, 4.83, 4.76, 4.63, 4.57, 4.49 (6 H, d, 12 Hz, 3 x Ph-CH_2), 4.09 (1 H, d, 9.5 Hz, H-3), 4.02 (1 H, ddd, 8.5, 3, 2 Hz, H-5), 3.88 (1 H, dd, 9.5, 8.5 Hz, H-4), 3.95 (1 H, dd, 11, 3 Hz, H-6), 3.68 (1 H, dd, 11, 2 Hz, H-6'), 1.90 (3 H, s, OAc). ^{13}C NMR ($CDCl_3$) 171.06 (CO), 161.98 (CNH), 139.29, 138.83 (OCH$_2$*Ph*), 129.45, 129.20, 128.96, 128.84, 128.80 (OCH$_2$*Ph*), 95.06 (C-1), 80.49, 78.71, 74.47, 73.40 (C-2, C-3, C-4, C-5), 76.45, 74.57 (O*C*H$_2$Ph), 68.88 (C-6), 21.65 (CO*C*H$_3$).

Anal. Calcd for $C_{31}H_{22}NO_7Cl_3$: C, 58.46; H, 5.06; N, 2.20; O, 17.58; Cl, 16.70. Found: C, 58.26; H, 5.19; N, 2.26; O, 17.48; Cl, 16.74.

Octyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (9). To a solution of **8** (59 mg, 93 μmol) and lithium triflate (0.72 mg, 4.6 μmol) in dichloromethane (0.46 mL) was added 1-octanol (18 μL, 111 μmol). The reaction mixture was stirred for 11 h at room temperature, diluted with dichloromethane (5 mL), washed with water (5 mL), dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (95:5 hexane-ethyl acetate) to give **9** (49 mg, 91%): $[\alpha]_D^{20}$ + 9 (*c* 1.04, dichloromethane); IR (NaCl) 2918, 2853, 1740, 1499, 1451, 1378, 1361, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) 7.50-7.10 (15 H, m, H-ar), 5.00 (1 H, dd, 9, 8 Hz, H-2), 4.81, 4.79, 4.68, 4.64, 4.60, 4.55 (6 H, d, 11.5 Hz, 3 x Ph-CH_2), 4.34 (1 H, d, 8 Hz, H-1), 3.88 (1 H, dt, 9.5, 6.5 Hz, OCH_aH$_{a'}$CH$_2$), 3.70 (4 H, m,), 3.46 (2 H, m), 1.93 (3 H, s, OAc), 1.55 (2 H, m, OCH$_2$CH_2), 1.23 (10 H, m, (CH_2)$_5$CH$_3$), 0.87 (3 H, s, CH$_3$); ^{13}C NMR ($CDCl_3$) 169.33 (CO), 138.10, 137.82 (OCH$_2$*Ph*), 128.31, 127.93, 127.93, 127.75, 127.63 (OCH$_2$*Ph*), 100.90 (C-1), 82.90, 78.00, 75.09, 73.10 (C-2, C-3, C-4, C-5), 75.09, 73.40 (O*C*H$_2$Ph), 69.61, 68.71 (C-6, O*C*H$_2$CH$_2$), 31.72, 29.40, 29.21, 25.80, 22.56 (CH$_3$(*C*H$_2$)$_6$), 20.80 (CO*C*H$_3$), 14.02 (*C*H$_3$(CH$_2$)$_7$).

Anal. Calcd for $C_{37}H_{48}NO_7$: C, 73.48; H, 8.00; O, 18.52. Found: C, 73.23; H, 8.04; O, 18.66.

Octyl 2,3,4-tri-*O*-benzyl-β-L-fucopyranoside (11). To a solution of 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl trichloroacetimidate[15] (50 mg, 86 μmol) and lithium triflate (0.67 mg, 4 μmol) in dichloromethane (0.43 mL) was added 1-octanol (16 μL, 103 μmol). The reaction mixture was stirred for 3 h at room temperature, diluted with dichloromethane (10 mL), washed with water (5 mL), dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (90:10 hexane-ethyl acetate) to give **11**α (6 mg, 13%) followed by **11**β (36 mg, 66%).

11α: $[\alpha]_D^{20}$ - 94 (*c* 1, dichloromethane); IR (NaCl) 2927, 2856, 1497, 1454, 1358, 1103, 1045, 1028, 734, 697 cm^{-1}; ^1H NMR ($CDCl_3$) 7.47-7.01 (15 H, m, H-ar), 4.98, 4.89, 4.82, 4.74, 4.67, 4.66 (6 H, d, 12, 11.7, 11.5 Hz, 3 x Ph-CH_2), 4.78 (1 H, d, 4 Hz, H-1), 4.02 (1 H, dd, 9.5, 4 Hz, H-2), 3.94 (1 H, dt, 9.5, 2.5 Hz, H-3), 3.87 (1 H, q, 6.5 Hz, H-5), 3.66 (1 H, d, 2.5 Hz, H-4), 3.58 (1H, dt, 9.5, 7 Hz, OCH_aH$_{a'}$CH$_2$), 3.43 (1 H, dt, 9.5, 6 Hz, OCH$_a$$H_{a'}CH_2$), 1.59 (2 H, m, OCH$_2CH_2$), 1.27 (10 H, m, CH$_3$(C$H_2$)$_5$), 1.09 (3 H, d, 6.5 Hz, CH$_3$-fuc), 0.88 (3 H, t, 6 Hz, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$) 139.05, 138.78, 138.66 (OCH$_2$*Ph*), 128.42, 128.25, 128.15, 127.92, 127.52, 127.43 (OCH$_2$*Ph*), 97.38 (C-1), 79.47, 77.64, 76.37, 66.07 (C-2, C-3, C-4, C-5), 74.76, 73.29, 73.14 (O*C*H$_2$Ph), 68.13 (O*C*H$_2$CH$_2$), 31.84, 29.43, 29.27, 26.17, 22.66 (CH$_3$(*C*H$_2$)$_6$), 16.63 (*C*H$_3$-fuc), 14.10 (*C*H$_3$(CH$_2$)$_7$).

Anal. Calcd for $C_{35}H_{46}O_5$: C, 76.89; H, 8.48; O, 14.63. Found: C, 76.64; H, 8.36; O, 14.55.

11β: $[\alpha]_D^{20}$ - 21 (*c* 1.33, dichloromethane); IR (2928, 2856, 1497, 1454, 1378, 1093, 1028, 733, 697 cm^{-1}); ^1H NMR ($CDCl_3$) 7.46-7.24 (15 H, m, H-ar), 4.98, 4.95, 4.79, 4.71, 4.69 (6 H, d, 12 Hz, 3 x Ph-C*H*2), 4.34 (1 H, d, 8 Hz, H-1), 3.97 (1H, dt, 9, 6.5 Hz, OC*H*$_a$H$_{a'}$CH2), 3.83 (1 H, dd, 10, 8 Hz, H-2), 3.60-3.49 (3 H, m, H-3, H-4, OCH$_a$*H*$_{a'}$CH2), 3.46 (1 H, q, 6.25 Hz, H-5), 1.66 (2 H, m, OCH2*CH*2), 1.28 (10 H, m, CH3(*C*H2)5), 1.19 (3 H, d, 6.25 Hz, CH3-fuc), 0.89 (3 H, t, 6 Hz, *C*H3CH2); ^{13}C NMR ($CDCl_3$) 138.91, 138.69, 138.63 (OCH2*Ph*), 128.53, 128.36, 128.25, 128.17, 128.11, 127.54 (*OCH2Ph*), 103.85 (C-1), 82.54, 79.50, 76.26, 70.22 (C-2, C-3, C-4, C-5), 75.11, 74.49, 73.17 (O*C*H2Ph), 69.88 (O*C*H2CH2), 31.85, 29.76, 29.48, 29. 28, 26.21 (CH3(*C*H2)6), 16.89 (*C*H3-fuc), 14.13 (*C*H3(CH2)7).

Anal. Calcd for $C_{35}H_{46}O_5$: C, 76.89; H, 8.48; O, 14.63. Found: C, 76.99; H, 8.58; O, 14.57.

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