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Regioselective Acylation of Secondary Hydroxyl Groups by Means BOP-Cl

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ABSTRACT

Methyl 2-O-acyl α-D-glucopyranosides are regioselectively formed with good yields by acylation of the correspondent 6-O-trityl pyranosides with carboxylic acids and (BOP-Cl). No acyl migration was observed in the deblocking of the primary hydroxyl group with p-toluensulfonic acid.

Key Words: BOP-Cl; Sugar; Methyl α-D-glucopyranoside; Secondary hydroxyl group.

Selective monoacylation of one of the many hydroxyl groups in monosaccharides is an important step in many synthetic procedures. Partially esterified

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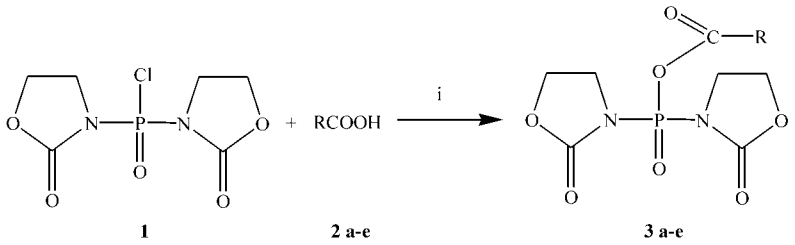
carbohydrates find applications in both scientific and technological research areas. They are widely used in food chemistry[1] and cosmetics[2] and are valuable intermediates in sugar chemistry.[3] They are important surfactants for biological studies[4] and unique tools for drug delivery processes across cellular membranes.[5] The higher reactivity of primary vs. secondary hydroxyl groups of carbohydrates has been exploited in the selective acylation[6–8] or phosphorylation.[9]

A regioselective formation of a number of 6-*O*- and 5′-*O* esters of methyl α,D-glucopyranosides and nucleosides, respectively, has been already achieved with a variety of carboxylic acids, aminoacids, and peptides[10–13] by means of bis (2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl, **1**, Scheme 1).[14] The regiochemistry of the process has been related to the reactivity of the intermediate mixed anhydride (**3a–e**) formed between BOP-Cl and the acid derivative (**2a–e**), and to steric constrains experienced by the approaching nucleophilic sites of the sugar substrates.

Here the effectiveness of BOP-Cl is exploited in the selective protection of the secondary hydroxyl groups of 6-*O*-tritylated glucopyranosides by means of commercially available carboxylic acids. The trityl group (Tr) was chosen for the transient protection of the 6-OH group of methyl α-D-glucopyranoside. This synthetic strategy was aimed at obtaining a clean removal of the temporary protection without interfering with the anomeric acetal linkage. Acid deblocking of the 6-OTr function could catalyze the thermodynamically controlled acyl migration within the secondary hydroxyl groups, but this risk is negligible for glucopyranosides if appropriate experimental conditions are chosen.[15] Tritylation of methyl α-D-glucopyranoside with trityl chloride in pyridine at 70°C, in the presence of dimethylamino pyridine (DMAP) afforded the correspondent 6-*O*-trityl derivative **4** in good yield.[16] It is interesting to note that the classical tritylation procedure[17] is



R = a: phenyl; b: 4-nitrophenyl; c: 2-nitrophenyl; d: 2-chlorophenyl; e: 1-naphthyl acetyl

i: pyridine, DMAP

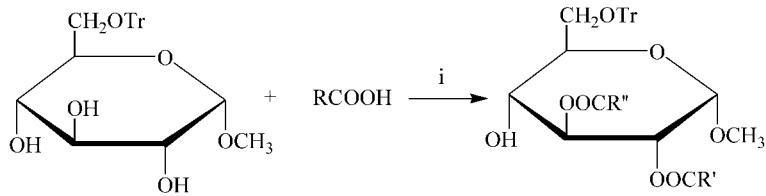
Scheme 1.

unsuitable for the protection of the gluco derivative; in fact, low yields (36%) were obtained when it was tritylated in pyridine at room temperature, whereas at 100°C a mixture of compounds was formed. The structure of **4** was easily assigned by ^{1}H-NMR spectroscopy and fast-atom bombardment mass spectrometry (FAB-MS).

The effectiveness of BOP-Cl as activating agent of carboxylic acids in the regioselective esterification of secondary hydroxyl groups in 6-*O*-protected monosaccharides was studied with the partially protected monosaccharide **4**. Although the reactions of carboxylic acids (**2a–e**) in the presence of BOP-Cl (**1**)/DMAP in pyridine are based on a preliminary activation of the acyl group through the formation of the mixed anhydrides **3a–e**[14] (Scheme 1), the subsequent formation of reactive symmetrical carboxylic anhydrides and acyl pyridinium derivatives cannot be excluded.

The reaction of **4** with BOP-Cl and benzoic acid **2a** affords mainly methyl 6-*O*-trityl-2-*O*-benzoyl α-D-glucopyranoside (**5a**), and **6a** and **7a** as side products (Scheme 2).

The data reported in Table 1 show that product yield is little affected by the ratios of substrate, reagents, and acylating agent used. Therefore, the experimental conditions reported in row 1 represent a useful compromise because a smaller excess of BOP-Cl and acid are required. The 2-*O*-benzoyl derivative **5a** (Scheme 2) was obtained after workup and short column chromatography. Structural assignment has been performed by ^{1}H-NMR spectroscopy, by means of extensive decoupling experiments. In particular, the H-2 proton of **5a** showed a low field signal with respect to the unprotected derivative **4**, and it was easily identified from the correlation with H-1 and H-3 protons. The structures of **6a** and **7a** were assigned similarly. FAB-MS provided the appropriate $(M-H)^-$ and fragment ions. When the



4 **2 a-e** **5 a-e**: R'=R; R"=H;
6 a-e: R'=H; R"=R;
7 a-e: R'=R"=R;

R = a: phenyl; b: 4-nitrophenyl; c: 2-nitrophenyl; d: 2-chlorophenyl; e: 1-naphthyl acetyl
i: pyridine, BOP-Cl, DMAP

Scheme 2.

Table 1. Benzoylation of methyl 6-*O*-trityl α-D-glucopyranoside **4** with BOP-Cl in different experimental conditions.

Reagent rel. ratio				Time	Yield %		
4	**2a**	**DMAP**	**BOP-Cl**	(hr)	**5a**	**6a**	**7a**
1.0	1.2	1.2	2.4	15	72.6	2.5	13.8
1.0	1.5	1.5	3.0	24	67.1	3.4	11.9
1.0	2.5	2.5	3.7	2	76.7	4.2	12.7
1.0	3.0	3.0	4.5	1	71.7	4.5	12.3

acylation process was carried out with benzoyl chloride in pyridine using the same ratio of acylating agent as for the BOP-Cl-mediated process, a mixture of the same compounds was obtained with lower regioselectivity. The reactivity order experienced in the above reported reaction is in agreement with earlier findings[18] (i.e., the equatorial 2-OH is the more reactive secondary group). The regioselective acylation of the secondary hydroxyl groups of a glucopyranoside can be achieved, therefore, directly from carboxylic acids by chemical methods with relative yields similar to those reported for the analogous enzymatic processes.[19]

Insights into the acylation mechanism of the BOP-Cl-mediated process have been achieved by carrying out the same esterification with substituted benzoic (**2b–d**) and 1-naphthyl acetyl (**2e**) acids. A lower regioselectivity was experienced when p-nitrobenzoic acid **2b** was used (Table 2). The electronic effect of the p-nitro group presumably increases the reactivity of the activated carboxylic group lowering the selectivity of the acylating process. It has been observed that the reactivity of the mixed anhydrides **3** (Scheme 1) is also lightly controlled by the bulkiness of the acyl moiety.[11] The acylation reaction with 2-nitrobenzoic acid **2c** (Table 2) was slower

Table 2. Acylation of methyl 6-*O*-trityl-α-D-glucopyranoside(**4**) with BOP-Cl.

Entry	Carboxylic acids	Time (hr)	m.p. (°C)	Yield (%) 5(a–e)	6(a–e)	7(a–e)
1	**2a**	15	85–86	72.6	2.5	13.8
2	**2b**	1	86–87	65.5	6.3	28.0
3	**2c**	7	65–66	56.2	19.6	14.2
4	**2d**	2	78–79	70.3	20.3	9.3
5	**2e**	16	82–83	72.5	16.2	11.2

than the corresponding esterification with the 4-nitro isomer showing that this effect is particularly important when the target is a secondary sugar hydroxyl group.

The 2-chlorobenzoic acid (**2d**) behaves as expected on the basis of the results so far reported, whereas the 2,6-dichloro derivative did not react with the same substrate even after prolonging the reaction time. It is known that the 2,6-dichlorobenzoic acid/BOP-Cl system is effective in the regioselective protection of the primary hydroxyl sugar moieties of gluco and mannopyranosides.[10] The lower reactivity observed with secondary hydroxyl groups has, therefore, to be ascribed to the steric hindrance of the sugar secondary hydroxyl groups. Accordingly, no reaction was obtained when **4** was treated with 2,6-dichlorobenzoyl chloride in pyridine in a classical acylating procedure. The comparison of entries 3 and 5 (Table 2) allows the discrimination between steric and electronic effects. Both **2c** and **2e** activated in situ by BOP-Cl undergo esterification with similar total conversion, after considerably different reaction times. On the basis of the experimental data, it can be suggested that the observed different regioselectivity is directly related to the bulkiness of the nucleophile and inversely proportional to the electrophilicity of the activated carboxyl group. Apart from the effect that a bulky 6-*O* trityl group may exert on the selective acylation of the secondary hydroxyl groups of pyranosides, the inversion of configuration of one of the ring carbon atoms affects at a greater extent the relative nucleophilicity of the linked hydroxyl groups. Among the number of procedures available for the detritylation process,[20] the best results were obtained when an excess of p-toluenesulfonic acid in dichloromethane was used at room temperature. The methyl 2-*O*-acyl-α-D-glucopyranosides **8a–e** were obtained with satisfactory isolated yields in only 15 min. No concomitant acyl migration or hydrolysis of the glycosidic linkage were observed. The data reported above clearly show that conventional chemistry can be successfully used for the selective acylation of methyl α-D-glucopyranoside at the C-2 through the transient protection of the primary hydroxyl group with the trityl group.

EXPERIMENTAL

Bis (2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl) was prepared as previously reported.[14] Methyl α-D-glucopyranoside and carboxylic acids (**2a–e**) were purchased from Fluka or Aldrich and were used without further purification. Pyridine was distilled from calcium hydride and stored under nitrogen. Dimethylformamide was distilled from phosphorus pentoxide and stored over Type 3A activated molecular sieves. Silica gel-precoated

plates were used for TLC, and Kieselgel 60 H without gypsum was used for short-column chromatography. NMR spectra were obtained from WM-300 Bruker spectrometer with Me_4Si as internal standard and $CDCl_3$ or DMSO-d_6 as solvents. Decoupling experiments allowed the measurement of the coupling constants in the case of multiplet signals; J values are given in Hz. FAB-Mass spectra were obtained on a Micromass (VG) ZAB 2F mass spectrometer, from 2 mm^3 of glycerol solution of sample by the standard gun operated with a neutral Xenon beam of 8 KeV and a neutral current of 10 μA. Melting points have been determined by a Kofler hot stage and are uncorrected.

Methyl 6-*O*-trityl-α-D-glucopyranoside (4)

A literature method[19] was followed with some modifications. A solution of α-D-glucopyranoside (5.049 g, 0.026 mol), trityl chloride (8.085 g, 0.029 mol), triethylamine (TEA) dry (6.25 mL), and dimethylaminopyridine DMAP (0.159 g, 0.0013 mol) in dry pyridine (120 mL) was stirred at 70°C for 12 hr, until a nearly complete conversion of substrate was achieved [TLC, $CHCl_3$-MeOH (90 : 10 v/v)]. The organic solution was washed with saturated aq. NH_4Cl and then with water. The dried organic layers afforded, after solvent evaporation to dryness, a yellowish oily residue which after recrystallization from ethanol gave **4**.

m.p. 153–154°C (lit[17] 154–155°C), 70% yield. ^{1}H-NMR (DMSO) δ (ppm): 7.49–7.18 (15 H, m, Ar), 4.92–4.75 (2H, m, 3-OH, 4-OH), 4.68 (1H, d, H_1; $J_{1,2} = 3.62$), 4.42–4.23 (1H, m, 2-OH), 3.68–3.59 (1H, m, H_{6a}), 3.47 (1H, m, H_3; $J_{3,4} = 9.41$), 3.42 (3H, s, OCH_3) 3.42–3.25 (2H, m, H_2, H_4), 3.15–3.03 (2H, m, H_5, H_{6b}, $J_{5,6b} = 9.63$). FABMS (-) m/z 435 (42.2%, M-H)$^-$, 193 (100).

Synthesis of Derivatives 5a–e

General procedure. A mixture of **4** (1.0 mmol), of appropriate carboxylic acid **2a–e** (1.2 mmol), BOP-Cl (2.4 mmol), and DMAP (1.2 mmol) in dry pyridine (25 mL) was allowed to react at room temperature. The progress of the reaction was followed by TLC [TLC, $CHCl_3$-MeOH (95 : 5 v/v)] (Table 2). Saturated aq. $NaHCO_3$ was then added, and the mixture was extracted with CH_2Cl_2. The organic layers were washed with saturated aq. NH_4Cl and water and evaporated to dryness, which gave yellowish oily residues that were purified by short-column chromatography [$CHCl_3$-MeOH (97.5 : 2.5 v/v)] to give **5a–e** (Table 2).

Methyl 2-*O*-benzoyl-6-*O*-trityl-α-D-glucopyranoside (5a)

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.15–7.21 (20H, m, Ar), 5.05 (1H, d, H-1; $J_{1,2} = 3.65$), 4.95 (1 H, dd, H-2; $J_{2,3} = 9.97$), 4.10 (1H, dd, H-3; $J_{3,4} = 8.65$), 3.85–3.71 (1H, m, H-5; $J_{5,6} = 4.90$), 3.65 (1H, dd, H-4; $J_{4,5} = 9.65$), 3.62–3.41 (2H, m, H-6; $J_{gem} = 9.22$), 3.38 (3H, s, CH_3). Anal. calcd. for $C_{33}H_{32}O_7$: C 73.32; H 5.97. Found C 73.20; H 6.00.

Methyl 2-*O*-4-nitrobenzoyl-6-*O*-trityl-α-D-glucopyranoside (5b)

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.20–7.10 (19H, m, Ar), 5.05 (1H, d, H-1; $J_{1,2} = 3.16$), 4.95 (1H, dd, H-2; $J_{2,3} = 9.90$), 4.09 (1H, dd, H-3; $J_{3,4} = 8.90$), 3.75–3.64 (1H, m, H-5; $J_{5,6} = 5.00$), 3.61 (1H, dd, H-4; $J_{4,5} = 9.53$), 3.59–3.40 (2H, m, H-6; $J_{gem} = 9.18$), 3.38 (3H, s, CH_3). Anal. calcd. for $C_{33}H_{31}NO_9$: C 67.68; H 5.33; N 2.39. Found C 67.80; H 5.30; N 2.40.

Methyl 2-*O*-2-nitrobenzoyl-6-*O*-trityl-α-D-glucopyranoside (5c)

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.92–7.24 (19 H, m, Ar), 5.05 (1 H, d, H-1; $J_{1,2} = 3.64$), 4.98 (1H, dd, H-2; $J_{2,3} = 9.83$), 3.99 (1H, dd, H-3; $J_{3,4} = 9.21$), 3.73–3.65 (1H, m, H-5; $J_{5,6} = 4.86$), 3.62 (1H, dd, H-4; $J_{4,5} = 9.67$), 3.59–3.42 (2H, m, H-6; $J_{gem} = 9.41$), 3.40 (3 H, s, CH_3). Anal. calcd. for $C_{33}H_{31}NO_9$: C 67.68; H 5.33; N 2.39. Found C 67.70; H 5.35; N 2.40.

Methyl 2-*O*-o-chlorobenzoyl-6-*O*-trityl-α-D-glucopyranoside (5d)

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.00–7.15 (19H, m, Ar), 5.09 (1H, d, H-1; $J_{1,2} = 3.58$), 4.91 (1H, dd, H-2; $J_{2,3} = 8.52$), 4.05 (1H, dd, H-3; $J_{3,4} = 9.58$), 3.83–3.71 (1H, m, H-5; $J_{5,6} = 5.00$), 3.65 (1H, dd, H-4; $J_{4,5} = 9.78$), 3.62–3.40 (2H, m, H-6; $J_{gem} = 9.21$), 3.39 (3H, s, CH_3). Anal. calcd. for $C_{33}H_{31}ClO_7$: C 69.93; H 5.43; Cl 6.16. Found C 70.00; H 5.45; Cl 6.15.

Methyl 2-*O*-1-naphthyl acetyl-6-*O*-trityl-α-D-glucopyranoside (5e)

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.00–7.12 (22 H, m, Ar), 4.89 (1H, d, H-1; $J_{1,2} = 3.62$), 4.68 (1H, dd, H-2; $J_{2,3} = 9.80$), 3.90 (1H, dd, H-3;

$J_{3,4} = 9.04$), 3.77–3.61 (1H, m, H-5; $J_{5,6} = 4.79$), 3.51 (1H, dd, H-4; $J_{4,5} = 9.77$), 3.49–3.32 (2H, m, H-6; $J_{gem} = 9.56$), 3.30 (3H, s, CH_3). Anal. calcd. for $C_{38}H_{36}O_7$: C 78.48; H 6.00. Found C 78.60; H 5.90. Synthesis of **8a–e**. General procedure. A solution of **5a–e** (0.5 mmol) and p-toluensulfonic acid (1.5 mmol) in CH_2Cl_2 (10 cm^3) was stirred for 15–25 min. The oily residues obtained, after solvent evaporation, were purified by short-column chromatography [$CHCl_3$-MeOH (95 : 5 v/v)] to give **8a–e**.

Methyl 2-*O*-benzoyl-α-D-glucopyranoside (8a)

m.p. 125–127°C, 68% yield. ^{1}H-NMR (DMSO) δ (ppm): 8.50–7.50 (5 H, m, Ar), 5.30 (1H, d, OH, J = 5.76), 5.20 (1H, d, OH, J = 5.76), 4.87 (1H, d, H-1; $J_{1,2} = 3.49$), 4.67 (1H, dd, H-2; $J_{2,3} = 9.80$), 4.60 (1H, t, OH, J = 5.80), 3.76 (1H, ddd, H-3; $J_{3,4} = 9.57$), 3.68 (1H, ddd, H-4; $J_{4,5} = 9.20$), 3.61–3.48 (1H, m, H-5; $J_{5,6} = 5.85$), 3.46–3.33 (2H, m, H-6; $J_{gem} = 14.01$), 3.35 (3H, s, CH_3). Anal. calcd. for $C_{14}H_{18}O_7$: C 56.37; H 6.08. Found C 56.50; H 6.05. FABMS (-) m/z 297 (100%, M-H)$^-$, 193 (22.8).

Methyl 4-*O*-p-nitrobenzoyl-α-D-glucopyranoside (8b)

m.p. 110–112°C, 77% yield. ^{1}H-NMR (DMSO) δ (ppm): 8.42–7.10 (4H, m, Ar), 5.43 (1H, d, OH, J = 5.32), 5.24 (1H, d, OH, J = 5.05), 5.01 (1H, t, OH, J = 4.95), 4.90 (1H, d, H-1; $J_{1,2} = 3.27$), 4.71 (1H, dd, H-2; $J_{2,3} = 10.00$), 3.79 (1H, ddd, H-3; $J_{3,4} = 9.17$), 3.73–3.61 (1H, m, H-5; $J_{5,6} = 4.91$), 3.54 (1H, ddd, H-4; $J_{4,5} = 9.28$), 3.52–3.36 (2H, m, H-6; $J_{gem} = 11.21$), 3.25 (3H, s, CH_3). Anal. calcd. for $C_{14}H_{17}NO_9$: C 48.98; H 4.99; N 4.08. Found C 49.00; H 4.95; N 4.10. FABMS (-) m/z 343 (100%, M$^-$), 193 (54).

Methyl 2-*O*-2-nitrobenzoyl-α-D-glucopyranoside (8c)

m.p. 123–125°C, 70% yield. ^{1}H-NMR (DMSO) δ (ppm): 8.15–7.10 (4H, m, Ar), 5.41 (1H, d, OH, J = 5.28), 5.32 (1H, d, OH, J = 5.00), 5.06 (1H, t, OH, J = 5.12), 4.85 (1H, d, H-1; $J_{1,2} = 3.45$), 4.75 (1H, dd, H-2; $J_{2,3} = 9.90$), 3.70 (1H, ddd, H-3; $J_{3,4} = 9.80$), 3.50 (1H, ddd, H-4; $J_{4,5} = 9.25$), 3.48–3.37 (1H, m, H-5; $J_{5,6} = 5.25$), 3.34–3.23 (2H, m, H-6, $J_{gem} = 11.39$), 3.20 (3H, s, CH_3). Anal. calcd. for $C_{14}H_{17}NO_9$: C 48.98; H 4.99; N 4.08. Found C 48.80; H 5.00; N 4.10. FABMS (-) m/z 343 (100%, M$^-$), 193 (67).

Methyl 2-*O*-2-chlorobenzoyl-α-D-glucopyranoside (8d)

m.p. 154–155°C, 77% yield. ^{1}H-NMR (DMSO) δ (ppm): 7.88–7.12 (4H, m, Ar), 5.38 (1H, d, OH, J = 5.73), 5.26 (1H, d, OH, J = 5.86), 4.98 (1H, d, H-1; $J_{1,2} = 3.64$), 4.71 (1H, dd, H-2; $J_{2,3} = 9.95$), 4.47 (1H, t, OH, J = 5.80), 3.76 (1H, ddd, H-3; $J_{3,4} = 8.79$), 3.74–3.67 (1H, m, H-5; $J_{5,6} = 5.82$), 3.54 (1H, ddd, H-4; $J_{4,5} = 9.57$), 3.52–3.41 (2H, m, H-6, $J_{gem} = 11.75$), 3.38 (3 H, s, CH_3). Anal. calcd. for $C_{14}H_{17}ClO_7$: C 50.38; H 5.15; Cl 10.66. Found C 50.50; H 5.15; Cl 10.60. FABMS (-) m/z 331 (37%, M-H)$^-$, 193 (100).

Methyl 2-*O*-1-naphthyl acetyl-α-D-glucopyranoside (8e)

m.p. 120–121°C, 75% yield. ^{1}H-NMR (DMSO) δ (ppm): 8.00–7.40 (7H, m, Ar), 5.36 (1H, d, OH, J = 5.40), 5.25 (1H, d, OH, J = 5.32), 4.69 (1H, d, H-1; $J_{1,2} = 3.60$), 4.60 (1H, t, OH, J = 5.19), 4.48 (1H, dd, H-2; $J_{2,3} = 9.73$), 3.74 (1H, ddd, H-3; $J_{3,4} = 9.28$), 3.70 (1H, ddd, H-4; $J_{4,5} = 9.54$), 3.67–3.56 (1H, m, H-5; $J_{5,6} = 5.04$), 3.51–3.41 (2H, m, H-6, $J_{gem} = 11.14$), 3.36 (3H, s, CH_3). Anal. calcd. for $C_{19}H_{22}O_7$: C 62.97; H 6.12. Found C 63.00; H 6.10. FABMS (-) m/z 361 (23.5%, M-H)$^-$, 193 (100).

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