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Note

A facile procedure for regioselective 1-*O*-deacylation of fully acylated sugars with sodium methoxide*

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In a series of studies on partial protection of carbohydrate derivatives, novel approaches to regioselective 1-*O*-deacetylation of fully acetylated sugars with bis(tributyltin) oxide, with potassium cyanide, and with potassium hydroxide have been reported from our laboratory[2]. We now report a new method for 1-*O*-deacetylation with an alkoxide which has been proved practical for a series of acetylated sugars.

RESULTS AND DISCUSSION

Prior to the procedures[2] mentioned, there had been that of Excoffier *et al.*[3], involving hydrazinolysis with hydrazine acetate in pyridine, which gave the corresponding hydrazone on application to furanose derivatives, that of Rowell and Feather[4], involving piperidinolysis, which afforded 3,4,6-tri-*O*-acetyl-D-glucopyranosylamine on application to 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose, and of Imagawa *et al.*[5], involving electrolytic methanolysis of the 1-*O*-acetyl group of 2-acetamido- as well as 2-benzamido-2-deoxy-D-glucopyranose derivatives, which is not applicable to ordinary sugar derivatives. Moreover, the procedure involving bis(tributyltin) oxide[2] is impractical as it entails troublesome removal of the resulting tributyltin acetate, *etc.* We thus set out to establish a further simplified and practical procedure for unmasking 1-*O*-acyl groups of fully acylated sugars, with the expectation of possibly being directed towards synthesis of the corresponding glycosyl fluorides and of many other useful glycosyl compounds**.

The complete unmasking of per-*O*-acylated sugar derivatives has generally

*Partial Protection of Carbohydrate Derivatives, Part 17. For Part 16, see ref. 1.
**See references cited in ref. 2.

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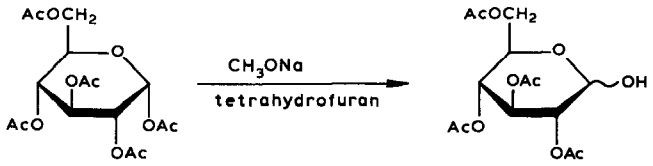
been performed in an alcohol in the presence of a catalytic amount of the corresponding alkoxide. On the other hand, a 1-*O*-acyl group is, due to the hemiacetal structure, accepted as being the most active ester function among the *O*-acyl groups involved in a per-*O*-acylated sugar. Therefore, we reasoned that we should be able to perform a highly regioselective 1-*O*-deacylation reaction by treating fully acylated sugars with an equimolar amount of an alkoxide in an aprotic solvent, without removing any other *O*-acyl groups.

Based on this assumption, the possibility of regioselective 1-*O*-deacetylation of fully acetylated sugars by the use of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (**1**) as a model compound, equimolar alkoxides, *i.e.*, sodium isopropoxide, and sodium, potassium, and lithium methoxide, and such solvents as dichloromethane, chloroform, benzene, dimethyl sulfoxide, *N,N*-dimethylformamide, 1,4-dioxane, and tetrahydrofuran was examined. On monitoring all of the attempted reactions, conducted on a small scale, it was found that the deacetylation reaction was likely to proceed moderately on using sodium or potassium methoxide in tetrahydrofuran at room temperature. Incidentally, the attempted reactions in such solvents as CH_2Cl_2, $CHCl_3$, and C_6H_6 were too slow to be useful, and those in dimethyl sulfoxide and *N,N*-dimethylformamide were accompanied by undesirable discoloration. Moreover, the reactions with sodium isopropoxide and lithium methoxide were inconvenient, as considerable proportions of **1** were left unchanged, and much further deacetylation was induced, according to t.l.c. It was therefore decided to perform the reaction with sodium (or potassium) methoxide in tetrahydrofuran.



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Treatment of **1** (200 mg, 512 μmol) with an equimolar amount of sodium or potassium methoxide at room temperature, followed by quenching with acetic acid, evaporation, and chromatographic separation on silica gel, gave 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**2**) (37 and 19% yield) and **1** (39 and 54% recovery yield), respectively. Both of these results led us to examine further the conditions using sodium methoxide with respect to its amount, the reaction temperature, and the reaction time. Thus, treatment with 2 mol. equiv. of the reagent for 20 min at the temperature of ice–salt proved the most appropriate for objective, regioselective 1-*O*-deacetylation of **1**.

In addition to **1** (see Entry 1, Table I), the β anomer of **1** (Entries 2–4), 1,2,3,4,6-penta-*O*-acetyl-α- (Entry 5), and -β-D-galactopyranose (Entries 6–8), -α- (Entry 9), and -β-D-mannopyranose (Entry 10), 1,2,3,4-tetra-*O*-acetyl-α- (Entry

TABLE I

REGIOSELECTIVE 1-*O*-DEACETYLATION OF FULLY ACETYLATED SUGAR DERIVATIVES WITH SODIUM METHOXIDE[a]

Entry	*Per-O-acetyl derivative of*	*Reaction time (min)*	*Yield of HO-1 derivative (%)*	*Recovery of starting material (%)*
1	α-D-Glucopyranose	20	82	12
2	β-D-Glucopyranose	20	62	19
3		60	80	10
4		70	82	9
5	α-D-Galactopyranose	45	90	2
6	β-D-Galactopyranose	30	76	12
7		45	76	3
8		70	73	—
9	α-D-Mannopyranose	8	86	9
10[b]	β-D-Mannopyranose	25	65	19
11	α-D-Xylopyranose	25	80	5
12	β-D-Xylopyranose	35	70	14
13	β-D-Ribopyranose	30	72	15
14	β-D-Ribofuranose	5	56	29
15		10	73	18
16		30	73	8
17	*N*-Ac-α-D-Glucosamine	25	63	2
18	*N,N*-Phth-α-D-Glucosamine	35	58	25
19	*N,N*-Phth-α-D-Glucosamine	20	82	8
20[c]	β-Maltose	25	67	30
21	α-Cellobiose	30	72	10

[a]All of the reactions were performed by using each sugar acetate (512 μmol) and sodium methoxide (2 mol. equiv.; 2.5 and 1.5 mol. equiv. for Entries 4 and 18, respectively) in tetrahydrofuran (5 mL) at the temperature of an ice–salt bath. [b]This reaction was performed on half the scale. [c]Only this reaction was performed at room temperature, due to the low solubility of β-maltose octaacetate.

11), and -β-D-xylopyranose (Entry 12), -β-D-ribopyranose (Entry 13), and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (Entries 14–16) were subjected to 1-*O*-deacetylation; the results thus obtained and the conditions used are summarized in Table I.

As may be seen from the Table, their corresponding HO-1 sugar derivatives were obtained in 65–90% isolated yields. Moreover, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (Entry 17) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranose (Entries 18 and 19) also gave the corresponding HO-1 derivatives, in 63 and 82% yields, respectively, under similar conditions; these products should be useful as the starting materials for synthetic studies of cell-surface oligosaccharides. Furthermore, similar treatment was applied to such disaccharide acetates as 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose [β-maltose octaacetate] and 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranose [α-cellobiose octaacetate], which gave the corresponding HO-1 derivatives in 67 and 72% yield, respectively.

Next, the procedure was extended to benzoates, *i.e.*, 1,2,3,4,6-penta-*O*-

TABLE II

REGIOSELECTIVE 1-*O*-DEACYLATION OF ACYLATED SUGARS BY THE USE OF SODIUM METHOXIDE[a]

Entry	*Acyl derivative of*	*Acyl substituent(s)*		*Reaction time (min)*	*Yield of the HO-1 deriv. (%)*	*Recovery yield of starting material (%)*
		Position 1	*Other positions*			
1	α-D-Glucopyranose	Bz	Bz	10	67	16
2	α-D-Glucopyranose	Bz	Bz	13	90	5
3	β-D-Ribofuranose	Ac	Bz	100	64	11
4	β-D-Ribofuranose	Ac	Bz	75	72	9
5	β-D-Ribofuranose	Ac	Bz	50	77	7
6	β-D-Ribofuranose	Bz	Bz	150	46	20

[a]All of the reactions were performed by using each of the acylated sugars (0.5 mmol) and sodium methoxide (2 mol. equiv.; 2.5 and 3.0 mol. equiv. for Entries 4 and 5, respectively) in tetrahydrofuran (5 mL), with cooling in an ice–salt bath.

benzoyl-α-D-glucopyranose, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, and 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose, although it is generally accepted that the *O*-benzoyl group is more stable than the *O*-acetyl group toward a nucleophile[5]; the results thus obtained are summarized in Table II. Entries 1–6 demonstrate the utility of the present method for the 1-*O*-deacylation of these derivatives. The *O*-debenzoylation of the perbenzoate of α-D-glucopyranose is quite superior to that involving its treatment with bis(tributyltin) oxide in toluene at reflux[2], which gave 1,2,3,6-tetra-*O*-benzoyl-α-D-glucopyranose in 10% yield, in addition to 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose in 60% yield (see Entries 1 and 2); the milder reaction conditions of the current procedure must bring about such a difference. The 1-*O*-debenzoylation reaction of the perbenzoate of β-D-ribofuranose was rather slower than that of the perbenzoate of α-D-glucopyranose and was followed by undesired, further debenzoylation to give products more polar than the HO-1 product (46% isolated yield) in t.l.c.; consequently, the reaction should be quenched within 2.5 h.

It is thus concluded that the present procedure is the simplest and most practical for performing regioselective 1-*O*-deacylation of fully acylated sugar derivatives, as compared with any of the preceding procedures, owing to its simplicity, *i.e.*, treatment with 2–3 molar equivalents of an alkoxide for a short time at the temperature of an ice-salt bath, followed by quenching with acetic acid, evaporation of the resulting solution, extraction, and flash column-chromatography on silica gel.

EXPERIMENTAL

General methods. — Melting points were determined on a micro-melting-point apparatus (Yanagimoto Co., Ltd., Japan), and are uncorrected. Specific rotations were determined with a JASCO DIP-4 apparatus. T.l.c. was conducted

on Merck silica gel $60F_{254}$, with monitoring of each spot of starting materials and products by use of a u.v. lamp (254 nm) or by heating (150°) after spraying with 5% aqueous sulfuric acid solution. Column chromatography was performed on Merck silica gel 60 (230–400 mesh) in the manner of flash chromatography[6]. ^{1}H-N.m.r. spectra were recorded with a Varian EM-360 apparatus for solutions in deuteriochloroform, with tetramethylsilane as the internal standard.

The peracetates of α- (**1**)[7] and β-D-glucopyranose[7], α-[7] and β-D-galactopyranose[8], α-[9] and β-D-mannopyranose[10], α-[11] and β-D-xylopyranose[11], β-D-ribopyranose[12], β-D-ribofuranose[13], 2-acetamido-2-deoxy- [14] and 2-deoxy-2-phthalimido-α-D-glucopyranose[15], and β-maltose[3], and the perbenzoates of α-D-glucopyranose[16] and β-D-ribofuranose[17] were prepared, from sugars commercially available, according to the methods reported. Cellobiose octaacetate and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, in addition to the sodium methoxide used, were purchased from Aldrich Chemical Co.

Regioselective 1-O-deacetylation of **1** *(representative procedure).* — To a suspension of 90% sodium methoxide (60.4 mg, equivalent to 1.07 mmol of pure sample), in tetrahydrofuran (5 mL) chilled in an ice–salt (3:1, w/w) bath with stirring, was added **1** (200 mg, 512 μmol) and the mixture was stirred for 20 min; the reaction was then quenched with acetic acid (100 μL) by stirring for 10 min. The mixture was evaporated, and a solution of the residue in chloroform was washed three times with water, dried (anhydrous sodium sulfate), and evaporated, and the residue was subjected to separation by flash column-chromatography using benzene–ethyl acetate. Compounds **1** (24 mg, 12% recovery yield) and **2** (145 mg, 82% yield) were obtained as the 1st and 2nd fraction, respectively. The latter was syrupy, and was identified with an authentic sample[2] through ^{1}H-n.m.r. spectrocopy: δ 4.5–5.8 (5 H, m, H-1,2,3,4, and O*H*), 3.5–4.5 (3 H, m, H-5,6,6′), 2.07, 2.03, and 2.07 (12 H, 3 s, 4 Ac).

The regioselective, 1-*O*-deacylations of the other acylated sugars were performed similarly, giving the results summarized in Tables I and II. All of the 1-OH sugar derivatives were identified with the corresponding, known compounds[2] by ^{1}H-n.m.r. spectroscopy, except for the following.

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-D-glucopyranose was isolated as white needles, m.p. 168–170° (from benzene), $[\alpha]_D^{22}$ +63.4° (*c* 1.01, $CHCl_3$) {lit.[15] β anomer, m.p. 166–167°, $[\alpha]_D^{21}$ +52.8° (*c* 1.25, chloroform)}; ^{1}H-n.m.r.: δ 7.98–7.55 (4 H, m, aromatic-ring protons), 5.80–4.80 (3 H, m, H-1,3,4), 4.40–3.70 (5 H, m, H-2,5,6,6′, and O*H*), 2.05, 1.98, and 1.82 (9 H, 3 s, 3 Ac).

Anal. Calc. for $C_{20}H_{21}NO_{10}$: C, 55.18; H, 4.86; N, 3.22. Found: C, 54.93; H, 4.84; N, 3.08.

2,3,5-Tri-O-benzoyl-D-ribofuranose was obtained as a white glass, $[\alpha]_D$ +71.8° (*c* 1.14, chloroform) {lit.[17] β anomer, m.p. 102–104°, $[\alpha]_D$ +69.0° (chloroform)}; ^{1}H-n.m.r.: δ 8.40–7.00 (15 H, m, 3 PhCO), 6.15–5.29 (3 H, m, H-1,2,3), 5.05–4.40 (3 H, m, H-4,5,5′), 4.25 (2/3 H, br d, $J_{1,OH}$ 4 Hz, 2/3 O*H*), and

3.85 (1/3 H, br d, $J_{1,OH}$ 8 Hz, 1/3 O*H*); the broad doublets at δ 4.25 and 3.85 disappeared on addition of deuterium oxide.

Anal. Calc. for $C_{26}H_{22}O_8$: C, 67.53; H, 4.80. Found: C, 67.68; H, 4.87.

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