Carbohydrate Research, 133 (1984) 147–151
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Regioselective alkylation, benzoylation, and *p*-toluenesulfonylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside

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(Received March 27th, 1984; accepted for publication, April 24th, 1984)

The secondary hydroxyl groups in methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**1**) show[1], towards various reagents, little selectivity in partial etherification and esterification reactions, compared to those in the corresponding α-D-glucopyranoside derivative. Most of the selective benzylation[2], methylation[2,3], benzoylation[4–6], and sulfonylation[5,7] reactions of **1** attempted give the 2- and 3-monosubstituted derivatives in poor to moderate yields, because of (*a*) simultaneous formation of the 2,3-disubstituted derivatives in substantial proportions and (*b*) rather high recovery of unchanged starting-material **1**. Regioselective benzylation[8] and *p*-toluenesulfonylation[9] of **1**, using phase-transfer catalysis, were reported to give good yields of the 2-benzyl ether **3** and 2-sulfonate **13**, respectively.

Recently, David *et al.*[10,11] developed mild and efficient procedures for the regioselective benzoylation[10] and alkylation[11] of several derivatives of D-gluco- and D-galacto-pyranosides *via* the dibutylstannylene derivatives, and these methods[10,11] were extended to the selective alkylation[12,13] and benzoylation[13] of the diol derivatives of glycosides of L-fucose[12] and 6-deoxy-L-talose[13]. The application of these procedures[10,11] to the regioselective benzylation, allylation, methylation, benzoylation, and *p*-toluenesulfonylation of **1** is now described.

The results obtained with the regioselective reactions of **1** *via* the 2,3-*O*-dibutylstannylene derivative **2**, prepared by azeotropic removal[10,11,13] of water from a mixture of **1** and dibutyltin oxide in benzene, are shown in Table I. Alkylation of **2** with benzyl bromide or allyl bromide in boiling benzene, in the presence of tetrabutylammonium bromide[11], afforded high yields (~90%) of the 2- (**3**) and 3-benzyl (**4**) ethers and of the 2- (**5**) and 3-allyl (**6**) ethers, respectively; no 2,3-diethers were formed and no starting material **1** remained. Under conditions similar to those used for the benzylation and allylation of **2**, there was no reaction of **2** with methyl iodide, whereas treatment[10] of **2** with methyl iodide in *N,N*-dimethylformamide led

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0008-6215/84/$ 03.00

TABLE I

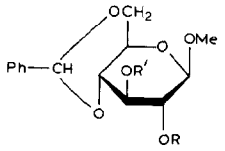
REGIOSELECTIVE BENZYLATION, ALLYLATION, METHYLATION, BENZOYLATION, AND *p*-TOLUENESULFONYLATION OF METHYL 4,6-*O*-BENZYLIDENE-β-D-GLUCOPYRANOSIDE *via* THE DIBUTYLSTANNYLENE DERIVATIVE

Reagent (mol. equiv.)	*Solvent*	*Temperature (°C)*	*Time (h)*	*Product*	*Yield*[a] *(%)*	*Solvent system*[b]	*M.p.*[c] *(degrees)*	$[\alpha]_D$[d] *(degrees)*	*References*
Benzyl bromide[e]	benzene	[f]	18	**3**	29	*2*	124–125	−27.6	2, 8
(2.5)				**4**	61	*3*	189–190	−47.2	2, 8
Allyl bromide[e]	benzene	[f]	18	**5**	33	*2*	146–147	−60.4	
(10)				**6**	60	*3*	165–166	−43.1	
Methyl iodide	*N,N*-dimethyl-	45	10	**7**	22	*2*	177–178	−70.1	2, 3
(22)	formamide			**8**	66	*3*	173–174	−59.3	2, 3
Benzoyl chloride[g]	benzene	room	2	**9**	4	*1*	185–186	+17.2	4, 5
(1.1)		temperature		**10**	49	*2*	202–203	−38.0	4, 5
				11	39	*3*	183–184	−110.0	4, 5
p-Toluenesulfonyl	benzene	room	20	**12**	5	*1*	160–161	−60.8	5, 7, 9
chloride[e]		temperature		**13**	21	*2*	123–124	−55.6	5, 7, 9
(1.1)				**14**	63	*3*	162–163	−81.1	5, 7, 9

[a]After column chromatography. [b]For elution of the product by column chromatography: (*1*) 9:1, (*2*) 4:1, and (*3*) 2:1 (v/v) benzene–ethyl acetate. [c]Not corrected. [d]In chloroform. [e]Plus tetrabutylammonium bromide (1.1 mol. equiv.). [f]Boiled gently under reflux. [g]Plus molecular sieve 4A.

to exclusive formation of the 2- (**7**) and 3-methyl (**8**) ethers with a negligible amount of unreacted, starting sugar **1**, in agreement with the previous observation[10].

Benzoylation of **2** with benzoyl chloride in benzene, in the presence of molecular sieve[10], gave the 2- (**10**) and 3-benzoate **11** in a total yield of 88%, together with the 2,3-dibenzoate **9** in 4% yield. An analogous benzoylation of **2** with benzoyl chloride in 1,4-dioxane, in the presence of triethylamine, was reported[6] to give a 50% yield of the monobenzoates (**10** and **11**), with recovery of a considerable proportion of **1**. Compound **2** reacted completely with *p*-toluenesulfonyl chloride in benzene, in the presence of tetrabutylammonium bromide, to give the 2- (**13**) and 3-sulfonate **14** in a total yield of 84%, in addition to a small proportion of the 2,3-disulfonate **12**, whereas no reaction of **2** with *p*-toluenesulfonyl chloride occurred in the absence of the catalyst.



1 R = R' = H
2 R, R' = $SnBu_2$
3 R = Bzl, R' = H
4 R = H, R' = Bzl
5 R = All, R' = H
6 R = H, R' = All
7 R = Me, R' = H
8 R = H, R' = Me
9 R = R' = Bz
10 R = Bz, R' = H
11 R = H, R' = Bz
12 R = R' = Ts
13 R = Ts, R' = H
14 R = H, R' = Ts

Bzl = $PhCH_2$, All = $H_2C{=}CH{-}CH_2$

The preponderance of the 3-substituted derivatives **4, 8,** and **14** over the 2-substituted derivatives **3, 7,** and **13** in the selective benzylation, methylation, and *p*-toluenesulfonylation of **1**, respectively, accords with the results[2,3,5,7] obtained previously, but contrasts with the results of the regioselective benzylation[8] and *p*-toluenesulfonylation[9] of **1**, using phase-transfer catalysis, in which a higher reactivity at HO-2 than at HO-3 was indicated. Therefore, the stannylene procedure, described here, complements the phase-transfer techniques[8,9] for the preparation of the 3-benzyl ether **4** and 3-sulfonate **14** in good yields.

EXPERIMENTAL

The general experimental conditions were the same as those described previously[14].

General procedure for the regioselective reactions of **1**. — A suspension of **1** and dibutyltin oxide (1.1 mol. equiv.) in benzene (60 mL/g of **1**) was boiled under reflux, with azeotropic removal of water by a Dean–Stark condenser. After ~30

min, the mixture became homogeneous and clear, and heating was continued for a further 1.5 h; the solution was then concentrated to two-thirds of its original volume by continued evaporation.

For benzylation or allylation, the solution of **2** was cooled to ~50°, and tetrabutylammonium bromide and the respective alkyl bromide were added. The mixture was stirred and boiled gently under reflux, with exclusion of moisture, and evaporated to dryness. In the benzylation, water was evaporated repeatedly from the residue. A solution of the residue in chloroform was washed with water, dried, and evaporated, and the residue was fractionated on a column of silica gel with the solvent systems indicated in Table I.

For methylation, the solution of **2** was evaporated to dryness. The resulting solid was dried *in vacuo,* and dissolved in anhydrous *N,N*-dimethylformamide (15 mL/g of **1**). Methyl iodide was added, and the mixture was stirred, evaporated, processed, and chromatographed on a column of silica gel, as just described.

For benzoylation, the solution of **2** was cooled to room temperature, molecular sieve 4A (3 g/g of **1**) and benzoyl chloride were added, and the mixture was stirred. The solids were filtered off, and washed with chloroform. The filtrate and washings were combined, and evaporated to a syrup, which was dissolved in chloroform. The solution was washed successively with water, aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was fractionated on a column of silica gel.

For *p*-toluenesulfonylation, tetrabutylammonium bromide and *p*-toluenesulfonyl chloride were added to a cooled (to room temperature) solution of **2**, and the mixture was stirred, evaporated, processed, and chromatographed as before.

Characterization of the products. — The derivatives **3, 4,** and **7–14** that were obtained were known compounds[2–9], and they were identified by direct comparison with authentic samples. The product obtained by the regioselective allylation of **1** was shown by t.l.c. (4:1 benzene–ethyl acetate) to contain two monoallyl derivatives, having R_F values of 0.40 (**5**) and 0.22 (**6**).

To distinguish the two monoallyl ethers, methyl 3-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**6**) was synthesized separately, as follows. 2,4,6-Tri-*O*-acetyl-3-*O*-allyl-α-D-glucopyranosyl bromide[15] {5.12 g; m.p. 69–70° (from ether–petroleum ether), $[\alpha]_D^{26}$ +173.5° (*c* 1.7, chloroform)} was dissolved in a mixture of anhydrous methanol (5 mL) and dry dichloromethane (60 mL) containing mercuric cyanide (3.1 g) and molecular sieve 4A (5 g). The mixture was stirred for 6 h at room temperature, diluted with dichloromethane (100 mL), washed successively with water, aqueous potassium bromide, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. A solution of the syrupy product in dry methanol (60 mL) was treated with a catalytic amount of sodium methoxide. The solution was kept overnight at room temperature, made neutral with Amberlite IR-120 (H^+) ion-exchange resin, the suspension filtered, and the filtrate evaporated.

A mixture of the residue, α,α-dimethoxytoluene (2.9 g), and *p*-toluenesulfonic acid monohydrate (0.1 g) in acetonitrile (25 mL) was stirred for 2 h at room

temperature. The acid was neutralized with triethylamine, and the solution evaporated to a solid, which was dissolved in chloroform. The solution was washed with water, dried, and evaporated, to give a crystalline mass which, on recrystallization from ethanol, gave **6** (2.90 g, 72%); m.p. and mixed m.p. 165–166°, $[\alpha]_D^{26}$ −43.8° (*c* 1.2, chloroform); n.m.r. data (chloroform-*d*): δ 7.53–7.30 (m, 5 H, Ph), 5.52 (s, 1 H, benzylic H), 3.55 (s, 3 H, OMe), and 2.98 (d, 1 H, $J_{2,OH-2}$ 2 Hz, exchangeable with D_2O, HO-2).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.25; H, 6.80.

For compound **5**, n.m.r. data (chloroform-*d*): δ 7.52–7.28 (m, 5 H, Ph), 5.48 (s, 1 H, benzylic H), 3.53 (s, 3 H, OMe), and 2.78 (d, 1 H, $J_{3,OH-3}$ 2 Hz, disappeared on deuteration, HO-3).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.20; H, 6.97.

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