Carbohydrate Research, 40 (1975) 391–395

Note

Preparation of cyclic carbonates of sugar derivatives with some carbonylating agents*

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(Received September 10th, 1974; accepted in revised form, November 18th, 1974)

Cyclic carbonate groups have been used widely as protecting groups for vicinal hydroxyl groups, especially in the field of carbohydrate chemistry. Such groups are base-labile and comparatively acid-stable[1]. No general preparative procedure has been described for the cyclic 1,2-carbonates of sugars, although a number of such carbonates have been effectively prepared by the use of carbonylating agents other as phosgene–pyridine and haloformates–bases[1]. Low-yielding syntheses of α-D-glucofuranose 1,2;5,6-dicarbonate by the reaction of phosgene with D-glucose in pyridine[2] and 3,5-*O*-methylene-α-D-xylofuranose 1,2-carbonate by selective oxidation of 1,2:3,5-di-*O*-methylene-α-D-xylofuranose with permanganate[3], have been reported.

We therefore attempted the preparation of such cyclic carbonates in view of the reactivity of 1-*O*-phenoxycarbonyl sugar derivatives in glycosylation reactions[4]. For the present investigation, 1,1′-carbonyldiimidazole and ethyl or methyl chloroformate were used to effect carbonylation of 4,6-*O*-benzylidene-D-glucopyranose (**1**) and 4,6-*O*-ethylidene-D-glucopyranose (**2**). N.m.r. data for each product thus obtained are shown in Table I.

The reaction of **1** with 1,1′-carbonyldiimidazole was accomplished in anhydrous tetrahydrofuran, and subsequent treatment with acetic anhydride afforded 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranose 1,2-carbonate (**3**) in 90% yield. Similar treatment of **2** with 1,1′-carbonyldiimidazole, followed by acetylation, also afforded 3-*O*-acetyl-4,6-*O*-ethylidene-α-D-glucopyranose 1,2-carbonate (**4**), in 40% yield. The n.m.r. spectra of **3** and **4** demonstrated that they are not in the typical $^4C_1$(D) conformation but adopt a considerably flattened $^4C_1$(D) conformation, probably because of to the cyclic carbonate structure. These conformational aspects appear closely related to those of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose derivatives[6].

Subsequently, carbonylation was conducted by the use of ethyl and methyl chloroformates in the presence of triethylamine. The reaction of **2** with methyl

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*Part VIII of a series: Synthetic Studies by theUse of Carbonates. For Part VII: See H. Komura, T. Yoshino, and Y. Ishido, *Carbohyd. Res.*, 31 (1973) 154–156.

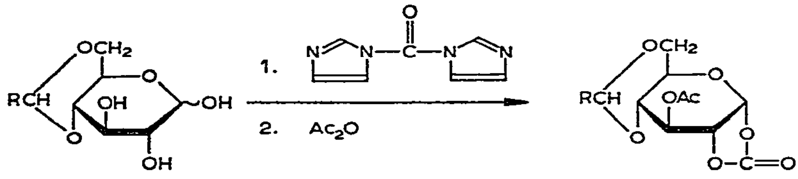
TABLE I

N.M.R. DATA OF COMPOUNDS 3–9

Compound	*Anomeric configuration*	*Solvent*	*Coupling constants (Hz)*			*Chemical shifts (δ)*			*Other specific signals*	
			$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	*H-1*	*H-2*	*H-3*		
3	α	Me_2SO-d_6	6.8	5.0	9.4	6.37	5.08	5.43	OAc	2.14
4	α	Me_2SO-d_6	6.5	5.0	9.0	6.31	5.01	5.28	OAc	2.14
5	α	$CDCl_3$	3.8	10.0	10.0	6.20	4.92	5.35		
7	α	$CDCl_3$	3.0	11.5	9.0	6.30	4.22	4.79		
8	α	$CDCl_3$	3.0	11.0	9.3	5.12	—[a]	4.86		
9	β	$CDCl_3$	8.0	9.5	9.5	5.48	3.70	4.94	2-OH	2.87
									$J_{2,OH}$	5.0 Hz

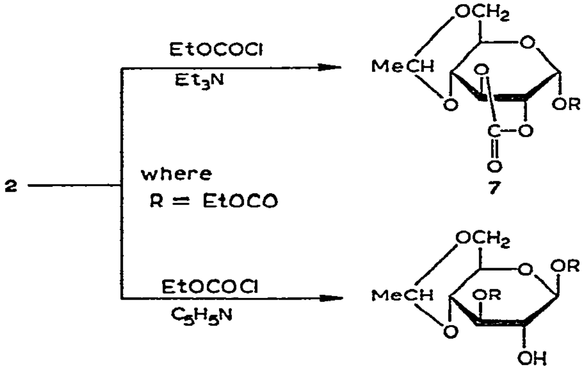
[a] This signal overlapped with another signal.

chloroformate unexpectedly afforded 4,6-*O*-benzylidene-1,2,3-tri-*O*-methoxycarbonyl-α-D-glucopyranose (**5**) and 4,6-*O*-ethylidene-1-*O*-methoxycarbonyl-D-glucopyranose 2,3-carbonate (as an anomeric mixture, **6**), in 31 and 18% yields, respectively. In contrast, similar reaction of **2** with ethyl chloroformate afforded 1-*O*-ethoxycarbonyl-4,6-*O*-ethylidene-α-D-glucopyranose 2,3-carbonate (**7**) in 47% yield as single, crystalline product. As may be seen from Table I, the *J* values of ring protons in **7** correspond well to those of methyl 4,6-*O*-benzylidene-α-D-glucopyranose 2,3-



1 R = Ph
2 Me

3 R = Ph
4 Me



7

9

carbonate (**8**), which was prepared according to the method of Doane *et al.*[7]. Incidentally, the foregoing crude product-mixtures were shown (t.l.c.) to be composed of four or five products, and such combinations of ethyl or methyl chloroformate with triethylamine were thus concluded to be unsuitable as a preparative procedure for the cyclic carbonate.

On the other hand, the use of pyridine in place of triethylamine in the reaction of **2** with ethyl chloroformate led mainly to 1,3-di-*O*-ethoxycarbonyl-4,6-*O*-ethylidene-β-D-glucopyranose (**9**), isolated in 70% yield; such a sugar derivative having a free hydroxyl group at C-2 in the pyranose ring may constitute a useful synthetic intermediate.

EXPERIMENTAL

General. — Melting points are uncorrected. I.r. spectra were taken with Hitachi EPI-2S or 215 spectrophotometers. N.m.r. spectra were determined with Varian XL-100, NV-14, or T-60 spectrometers in chloroform-*d* or Me_2SO-d_6 with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-1-sulfonate as the internal standard.

Reaction of 4,6-O-benzylidene-D-glucopyranose (**1**) *with 1,1′-carbonyldiimidazole.* — To a suspension of 4,6-*O*-benzylidene-D-glucopyranose[8] (**1**) (2.7 g, 10 mmol) in anhydrous tetrahydrofuran (40 ml), was added dropwise a solution of 1,1′-carbonyldiimidazole[5] (1.7 g, 11 mmol) in anhydrous tetrahydrofuran (20 ml) at room temperature, and the resulting mixture was then stirred for 3 h, after which time acetic anhydride (10 ml) was added, keeping the temperature at 0° in an ice-bath. The mixture was kept overnight at room temperature and then poured into ice–water (20 volumes). Crystals thus precipitated were recrystallized from ethanol to give 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranose 1,2-carbonate (**3**); yield 3.2 g, (90%), m.p. >220° (dec), $[\alpha]_D^{22}$ +35° (*c* 1.0, acetone); $\nu_{C=O}$ 1815 (five-membered cyclic carbonate) and 1735 cm^{-1} (acetate).

Anal. Calc. for $C_{16}H_{16}O_8$: C, 57.14; H, 4.80. Found: C, 57.09; H, 5.07.

Reaction of 4,6-O-ethylidene-D-glucopyranose (**2**) *with 1,1′-carbonyldiimidazole* — The carbonylation and subsequent acetylation of 4,6-*O*-ethylidene-D-glucopyranose[9] (**2**) (9.7 g, 50 mmol) was conducted as before by the use of 1,1′-carbonyldiimidazole (15.3 g, 100 mmol) and acetic anhydride (50 ml), and the crystals thereby obtained were recrystallized from ethanol to give 3-*O*-acetyl-4,6-*O*-ethylidene-α-D-glucopyranose 1,2-carbonate (**4**); yield 4.8 g (40%), m.p. 189–190°, $[\alpha]_D^{22}$ +65° (*c* 1.0, acetone); $\nu_{C=O}$ 1820 (five-membered cyclic carbonate) and 1740 cm^{-1} (acetate).

Anal. Calc. for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15. Found: C, 48.28; H, 5.29.

Reaction of **2** *with methyl chloroformate in the presence of triethylamine.* — To a suspension of **2** (1.1 g, 5 mmol) in anhydrous 1,4-dioxane (10 ml) containing triethylamine (4.0 g, 40 mmol), was added a solution of methyl chloroformate (4.7 g, 50 mmol) in 1,4-dioxane (10 ml) dropwise with stirring at 0° (cooling in an ice-bath). After stirring the resultant mixture for 2 or 3 h at room temperature, ethyl acetate

(50 ml) was added, and the organic layer was washed sucessively with water (30 ml), aqueous 0.5M sodium hydroxide (30 ml), aqueous M hydrochloric acid (30 ml), and then water (30 ml) saturated with sodium chloride. After drying the organic layer over anhydrous calcium chloride, it was evaporated *in vacuo* to a thick syrup, which was then crystallized and recrystallized from methanol to give 4,6-*O*-ethylidene-1,2,3-tri-*O*-methoxycarbonyl-α-D-glucopyranose (**5**); yield 0.58 g (31%) as colorless crystals, m.p. 136–138°, $[\alpha]_D^{22}$ +110° (*c* 1.0, chloroform); $\nu_{C=O}$ 1730 and 1740 cm^{-1} (acyclic carbonate).

Anal. Calc. for $C_{14}H_{20}O_{12}$: C, 44.21; H, 5.30. Found: C, 44.37; H, 5.25.

Colorless crystals obtained by concentration of the filtrate *in vacuo* were recrystallized from methanol to give 4,6-*O*-ethylidene-1-*O*-methoxycarbonyl-D-glucopyranose 2,3-carbonate (**6**) as an anomeric mixture; yield 0.26 g (18%); $\nu_{C=O}$ 1760 (acyclic carbonate), 1810, 1830, and 1840 cm^{-1} (five-membered cyclic carbonate); n.m.r. data ($CDCl_3$): δ 6.34 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1 of the α-anomer) and 5.88 (1-proton doublet, $J_{1,2}$ 7.5 Hz, H-1 of the β-anomer).

Anal. Calc. for $C_{11}H_{14}O_9$: C, 45.52; H, 4.86. Found: C, 45.30; H, 4.84.

Reaction of **2** *with ethyl chloroformate in the presence of triethylamine.* — As described in the previous experiment, the carbonylation of **2** was conducted by use of **2** (1.1 g, 5 mmol), ethyl chloroformate (16.2 g, 150 mmol), and triethylamine (9.0 g, 90 mmol), and subsequent recrystallization from ethanol afforded 1-*O*-ethoxycarbonyl-4,6-*O*-ethylidene-α-D-glucopyranose 2,3-carbonate (**7**); yield 0.71 g (47%), m.p. 211–212°, $[\alpha]_D^{22}$ +30° (*c* 1.0, chloroform); $\nu_{C=O}$ 1760 (acyclic carbonate), 1815, 1830, and 1840 cm^{-1} (five-membered cyclic carbonate).

Anal. Calc. for $C_{12}H_{16}O_9$: C, 47.37; H, 5.30. Found: C, 47.60; H, 5.26.

Reaction of **2** *with ethyl chloroformate in the presence of pyridine.* — To a suspension of **2** (1.1 g, 5 mmol) in anhydrous 1,4-dioxane (40 ml) containing pyridine (1.6 g, 20 mmol), was added ethyl chloroformate (3.3 g, 30 mmol) dropwise in the solvent as already described. Crystallization and recrystallization of the resulting product from ethanol afforded 1,3-di-*O*-ethoxycarbonyl-4,6-*O*-ethylidene-β-D-glucopyranose (**9**); yield 1.47 g (70%), m.p. 188.5–190°, $[\alpha]_D^{22}$ −160° (*c* 0.6, chloroform); $\nu_{C=O}$ 1745, 1765 (acyclic carbonate), and ν_{OH} 3400 cm^{-1}.

Anal. Calc. for $C_{14}H_{22}O_{10}$: C, 48.00; H, 6.33. Found: C, 48.40; H, 6.38.

ACKNOWLEDGMENTS

The authors are grateful to the members of Laboratory of Organic Analysis, Tokyo Institute of Technology, for the elementary analyses, and to Dr. Masatsune Kainosho, Ajinomoto Inc., and Mr. Katsuhiko Kushida, Nippon Electric Varian, for recording the n.m.r. spectra. They also thank the Ministry of Education, Japanese Government, for a Scientific Research Grant-in-aid.

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