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Preliminary communication

Synthesis of 2-deoxy-2-iodo-α-D-linked disaccharides: novel glycosidation reagents

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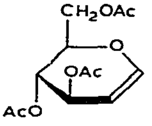
2-Deoxy-2-iodo sugars are useful intermediates in the synthesis of the corresponding 2-deoxy sugars[1]. The reductive cleavage of the carbon–iodine bond can be achieved in almost quantitative yields by catalytic hydrogenation in the presence of triethylamine, photolytic cleavage[2], and reduction by tributyltin hydride[3,4] or by the nickel boride method[5].

Protected glycals can be iodoalkoxylated by using iodonium bis(2,4,6-trimethylpyridine) perchlorate; thus, in the presence of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose, tri-*O*-acetyl-D-glucal reacted to yield 33% of the corresponding 2-deoxy-2-iodo-α-linked disaccharide[6]. Glycals react with *N*-bromosuccinimide in the presence of alcohols[3], and, in this way, disaccharides containing 2-bromo-2-deoxy-α-D-glycopyranosyl groups linked to the primary position on the next sugar residue were obtained in good yields. Thiem and coworkers[7] have used *N*-iodosuccinimide in the synthesis of disaccharides (yields, 50–82%) containing 2-deoxy-2-iodo-α-D-mannopyranosyl groups linked to primary as well as secondary positions.

We now report that silver imidazolate[8]–zinc chloride or silver imidazolate–mercury(II) chloride promote glycosylation and may be used, *inter alia*, in improved syntheses of 2-deoxy-2-iodo-α-D-mannopyranosides. For purposes of comparison, we report on the glycosylation of the alcohols previously used[7].

Silver imidazolate and either zinc chloride or mercury(II) chloride, in acetonitrile, were allowed to react with 3,4,6-tri-*O*-acetyl-D-glucal (**1**) and iodine. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranosyl chloride [**2**, δ ^{1}H (100 MHz, $CDCl_3$) 6.51 ($J_{1,2}$ ~0 Hz, H-1); δ ^{13}C (25 MHz, $CDCl_3$) 20.6, 20.6, 20.8 (3 CH_3CO), 23.1 (C-2), 61.5, 66.5, 68.6, 71.7 (4 C), and 100.8 (C-1)] and 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranosyl chloride [**3**, δ ^{1}H (100 MHz, $CDCl_3$) 5.93 (d, $J_{1,2}$ 9.5 Hz, H-1)] were formed in essentially quantitative yield in a ratio of ~5 : 1. Addition of the alcohols **4**, **5**, or **6** then gave the corresponding α-linked disaccharides **7**, **8**, and **9**. β-Linked glycosides arising from **3** were only obtained, as by-products, in reactions with such simple nucleophiles as methanol or azide, but hardly any such products were observed using the complex alcohols **4**, **5**, or **6**. The results are shown in Table I.



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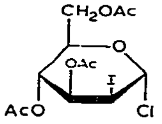

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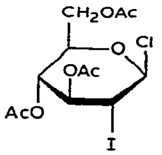

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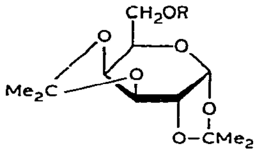

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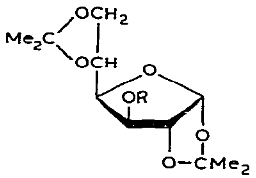

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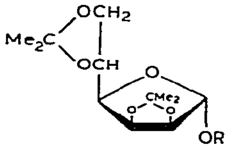

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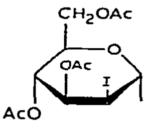

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TABLE I

SYNTHESIS OF 2-DEOXY-2-IODO-α-D-LINKED DISACCHARIDES

Alcohol	*Promoter*[a]	*Reaction time* (h)	*Product*[b]	*Yield (%)*	$[\alpha]_D^{20}$ (c 1, *chloroform*) (*degrees*)	
					Found	*Lit.*[7]
4	A	8	7[e]	80	−16	−16
	B	8		82		
	C	7 days		70		
5	A	8	8[d]	65	+20	+18
	B	8		71		
	C	7 days		37		
6	A	8	9[c]	70	+75	+80
	B	8		65		

[a] A, Ag imidazolate–$ZnCl_2$; B, Ag imidazolate–$HgCl_2$; C, none; 2,4,6-trimethylpyridine was used as acid acceptor. [b] ^{1}H-N.m.r. spectra were in agreement with those published[7]. [c] δ ^{13}C-N.m.r. data (100 MHz, $CDCl_3$): δ 20.5, 20.6, 20.8, 169.1, 169.6, 170.3 (3 OAc); 24.5, 25.1, 25.8, 26.7 [2 $C(CH_3)_2$]; 28.7 (C-2); 61.9, 66.6, 67.3, 68.8, 69.8, 72.8, 79.4, 81.3, 84.9 (5 C′, 4 C); 96.8 (C-1′); 102.3 (C-1); and 109.1, 112.8 [2 *C*$(CH_3)_2$]. [d] M.p. 122° [from ether–light petroleum (b.p. 40–60°)]; lit.[7] m.p. 128.5°; δ (^{13}C): 20.5, 20.5, 20.8, 169.2, 169.5, 170.4 (3 OAc); 25.2, 26.2, 26.6, 26.8 [2 $C(CH_3)_2$]; 28.3 (C-2); 62.3, 67.5, 67.8, 68.7, 69.7, 72.3, 81.4, 81.6, 83.7 (5 C′, 4 C); 102.3 (C-1); 105.2 (C-1′); and 109.3, 112.0 [2 *C*$(CH_3)_2$]. [e] δ (^{13}C): 20.6, 20.7, 20.9, 169.4, 169.7, 170.6 (3 OAc); 24.5, 24.9, 26.0, 26.1 [2 *C*$(CH_3)_2$]; 29.5 (C-2); 62.1, 66.1, 67.0, 67.4, 69.1, 69.2, 70.5, 70.6, 70.9 (5 C′, 4 C); 96.2 (C-1′); 101.3 (C-1); and 108.6, 109.4 [2 *C*$(CH_3)_2$].

The chloride **2** may also be made by mixing the glycal **1** with iodine, silver nitrate, and zinc chloride in acetonitrile. This indirect method gives a higher yield of **2** than the direct addition to **1** of pre-made iodine monochloride[10]. Addition, *in situ*, of the alcohols **4** and **5** to **2**, using 2,4,6-trimethylpyridine as acid acceptor, gave the disaccharides **7** and **8**, but the yields were significantly lower than those obtained in the "imidazolate-promoted" reactions. Also, attempts to glycosidate **2** in the absence of silver imidazolate, by using as promoters either silver trifluoromethanesulfonate together with 2,4,6-trimethylpyridine as acid acceptor, or silver carbonate in various solvents, resulted in slow, inefficient reactions, presumably due to the higher affinity of the silver ions for I-2 rather than Cl-1.

A mixture of silver imidazolate[8] (0.350 g, 2 mmol) and zinc chloride [0.409 g, 3 mmol; prepared by melting hydrated zinc(II) chloride in a drying pistol at 350°, evacuating, and storing over phosphorus(V) oxide] or (preferably, because of ease of work-up) mercury(II) chloride (0.814 g, 3 mmol) in dry acetonitrile (12 ml) containing molecular sieves (3 Å) was stirred at room temperature for 1 h. 3,4,6-Tri-*O*-acetyl-D-glucal[9] (**1**; 0.408 g, 1.5 mmol) and iodine (0.508 g, 2 mmol) were added and the mixture was stirred at room temperature for 1 h. T.l.c. (toluene–ethyl acetate 1:1, in which the initial spots were not allowed to dry before running the chromatogram) revealed the formation of a u.v.-absorbing product **2** having an R_F value higher than that of **1**, which no longer was present. The appropriate alcohol (**4**, **5**, or **6**) (0.260 g, 1 mmol) was added, the mixture was stirred at room temperature for 4 h, more iodine (0.127 g, 0.5 mmol) and silver imidazolate (0.087 g, 0.5 mmol) were then added, and stirring was continued for another 4 h at room temperature.

Toluene and ethyl acetate (10 ml of each) were added and then triethylamine (3 ml). The mixture was transferred to the top of a short (~10 cm) column of silica gel and eluted with toluene–ethyl acetate (1:1). Care was taken to avoid prolonged elution after the emergence of the organic product, since this caused contamination with Lewis acids. In large-scale preparations, the product (after elution) may be washed first with aqueous potassium iodide in reactions using mercury(II) chloride and then with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$) in the presence of a few drops of triethylamine, and concentrated before final chromatographic purification, if necessary.

In the reactions performed in the absence of imidazolates, a mixture of silver nitrate (0.340 g, 2 mmol) and zinc chloride (0.204 g, 1.5 mmol) in dry acetonitrile (10 ml) containing molecular sieves (3 Å) was stirred at room temperature for 30 min. 3,4,6-Tri-*O*-acetyl-D-glucal (**1**; 0.272 g, 1 mmol) and iodine (0.457 g, 1.8 mmol) were added. After the mixture had been stirred at room temperature for 1 h, t.l.c. revealed the formation of a u.v.-absorbing product having an R_F value higher than that of **1**, which no longer was present. The appropriate alcohol (**4** or **5**) (0.260 g, 1 mmol) and 2,4,6-trimethylpyridine (0.144 g, 1.2 mmol) were then added, the reaction vessel was covered with aluminium foil, and the mixture was stirred for 7 days. The product was then worked-up and purified as described above.

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