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Preliminary communication

Synthesis of glycosides: reactions of the anomeric hydroxyl group with nitrogen–phosphorus betaines*

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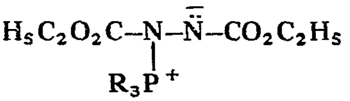
The need for mild, efficient, and stereospecific methods for the synthesis of glycosides has evoked much research into developing new procedures[1]. Recently, new glycoside-forming reactions have been reported which utilize appropriately protected sugar derivatives having a free anomeric hydroxyl group[2–5]. Two of these procedures[2,5] involve the intermediacy of glycosyl sulfonates and are, therefore, related to the method reported by Eby and Schuerch[6]. We now describe the use of betaines (**1**) formed from trivalent organophosphorus compounds and diethyl azodicarboxylate in the synthesis of glycosides.


$$\mathrm{H_5C_2O_2C{-}\underset{\underset{R_3P^{+}}{|}}{N}{-}\bar{\ddot{N}}{-}CO_2C_2H_5}$$

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In the carbohydrate field, the betaines (**1**) have been employed for the preparation of nucleosides[7] and monosaccharide carbonates[8], for the amination[9] and acylation[10] of sugar derivatives, and for the synthesis of *O*-phthalimido derivatives[11] and carbohydrate–saccharin conjugates[12]. Alkyl aryl ethers have been prepared[13] in good yields by the method. However, when 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**2**) was treated with triphenylphosphine, diethyl azodicarboxylate, and cyclohexanol in dry tetrahydrofuran, only traces of the cyclohexyl glycosides could be detected by t.l.c. Consequently, mercuric halides were introduced into the reaction, with the expectation that they might facilitate the formation of the presumed glycosyloxyphosphonium salt and also possibly decrease the competing formation of *N*-glycosyl-1,2-diethoxycarbonylhydrazine[9].

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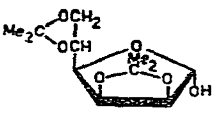
*Dedicated to the memory of Sir Edmund Hirst, C.B.E., F.R.S.



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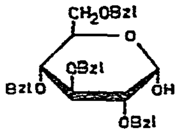

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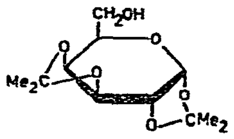

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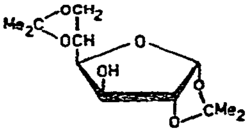

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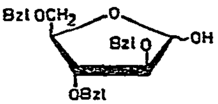

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The experimental procedure for the preparation of the glycosides was as follows. To a stirred solution of the phosphine (1.2 equiv.) in dry tetrahydrofuran (10 ml) were added diethyl azodicarboxylate (1.2 equiv.) and mercuric halide (1.2 equiv.), and the mixture was stirred for 5 min. The reducing sugar derivative was added and then, after 10 min, the alcohol (1 equiv.), and the mixture was stirred at the designated temperature. The progress of each reaction was monitored by t.l.c., and the products were isolated when the occurrence of essentially no further reaction was indicated. The reaction mixture was concentrated to dryness; a solution of the residue was passed through a short column of basic alumina, and the glycoside(s) isolated by column chromatography on silica gel.

The results with three reducing sugar derivatives are given in Table I. All of the product glycosides gave elemental analyses and n.m.r. data consistent with the assigned structures, or had physical constants in agreement with those published. The distribution of anomers for the reactions with **2** is noteworthy, as the preparation of the 6-chloropurinyl[7] and phthaloyl[9] derivatives from **2** afforded the β anomer as the major product. Furthermore, when 2,3,4,6-tetra-*O*-methyl-D-glucopyranose was treated with 6-chloropurine, diethyl azodicarboxylate, and methyldiphenylphosphine, only the β nucleoside was isolated, whereas 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**3**) gave glycosides having α:β ratios of 3–4.6. A possible explanation is that the reaction, with a mercuric halide present, involves the intermediacy of glycosyl halides, in which case the reaction may be amenable to halide-ion catalysis[14] and the effects of temporary blocking groups[6] at C-6. The method suffers from the possibility of such competing side-reactions as glycosyl carbonate or hydrazine formation; these side-reactions might become significant in cases involving sterically hindered alcohols.

The present approach to glycoside synthesis is a mild and viable procedure which circumvents the need for glycosyl halides and is compatible with acid-labile protecting groups.

ACKNOWLEDGMENT

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TABLE I

DATA FOR GLYCOSIDE SYNTHESIS

Glycosyl moiety	*Alcohol*	*Reaction conditions*[a]		*Mercuric halide*	*Phosphine*	*Product glycoside*	
		Reaction time (h)	*Temperature*			*Total yield (%)*	*α:β Ratio*
2	Cyclohexanol	24	Ambient	$HgCl_2$	Ph_3P	54.6	6.8
		24	Reflux	$HgCl_2$	Ph_3P	54.1	1.5
		24	Ambient	$HgBr_2$	Ph_3P	67.6	2.3
		3	Reflux	$HgBr_2$	Ph_3P	71.7	2.6
		24	0°	HgI_2	Ph_3P	57.5	2.5
		12	Ambient	HgI_2	Ph_3P	72	2.8
2	2	12	Ambient	HgI_2	Ph_3P	21	*d*
		24	Ambient	HgI_2	$MePh_2P$	20	*d*
3	Cyclohexanol	~24	Ambient	$HgCl_2$	Ph_3P	77	2[b]
		12	Ambient	$HgBr_2$	Ph_3P	80	3–4.6[b]
		12	Ambient	HgI_2	Ph_3P	54.6	0.8[b]
		24	Ambient	HgI_2	$MePh_2P$	65.5	1
3	4	24	Ambient	$HgBr_2$	Ph_3P	80.5	2[c]
3	5	24	Ambient	$HgBr_2$	Ph_3P	38.3	*d*
		48	Ambient	$HgBr_2$	$MePh_2P$	31	*d*
3	3	48	Ambient	$HgBr_2$	$MePh_2P$	28.3	*d*
		24	Ambient	HgI_2	$MePh_2P$	40.6	*d*
6	Cyclohexanol	24	Ambient	$HgCl_2$	Ph_3P	61.7	0.5
		24	Ambient	$HgBr_2$	Ph_3P	55.5	0.9

[a] All of the reactions were performed in tetrahydrofuran. [b] The anomeric composition of the product mixture was determined by ^{13}C-n.m.r. spectroscopy. [c] The anomeric composition of the product mixture was determined by ^{13}C-n.m.r. spectroscopy and analytical high-performance liquid chromatography. [d] Only the presence of the α anomer was detected.

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