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CHEMISTRY OF THE GLYCOSIDIC LINKAGE. LEWIS ACID CATALYZED GLYCOSIDATIONS WITH AMIDE ACETALS AND LACTIM ETHERS.* †

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Over the years, a large number of synthetic methods leading to simple glycosides have been described in the literature.[1] Of these, the most widely used, have been the classical Fischer[2] alcoholysis, and the Koenigs-Knorr [3] glycosidation, and their respective, numerous modifications. [1] In the search of innovative synthetic routes to simple and complex glycosides, we were interested in devising methods that require the minimum number of reagents, and in no more than stoichiometric quantities, while maintaining such features as simplicity of operation, efficacy, and stereocontrol.

We communicate herein, a mild and highly efficient method for the synthesis of 1,2-trans alkyl glycosides, as exemplified by preparations in the D-ribofuranose and D-glucopyranose series, starting from the readily available respective peracyl derivatives. The reaction consists in the activation of the sugar derivative (1 equiv.), with a Lewis acid catalyst such as stannic chloride (1 equiv.) in dichloromethane, presumably leading to 1,2-acyloxonium intermediates, followed by treatment with an N,N-dimethylformamide dialkyl acetal (1 equiv.) [4,5] which is the source of the aglycone in the glycosides.

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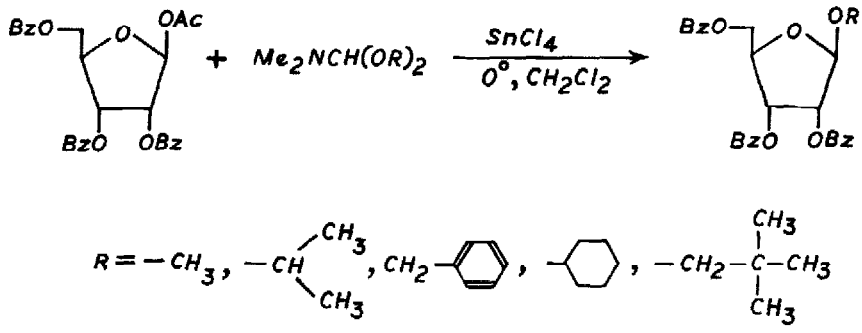


The solution is stirred at 0° for 2 h, then it is treated with aq. $NaHCO_3$ and worked up in the usual manner to give a syrup or a crystalline residue that consists essentially of the glycoside. Purification is achieved by direct crystallization or by chromatography over silica gel (5% EtOAc in benzene). Pertinent data are listed in Table 1.

TABLE 1

GLYCOSIDATION OF 1-O-ACETYL-2,3,5-TRI-O-BENZOYL-β-D-RIBOFURANOSE [a]

Alkoxy group (OR)	mp	%	$[\alpha]_D^{23}$ (degrees) ($CHCl_3$)	Ref.
O-methyl	syrup	95	55	6
O-isopropyl	syrup	96	45	-
O-benzyl	65°	90	20	7
O-cyclohexyl	syrup	90	23.7	-
O-neopentyl	syrup	93	35.5	-

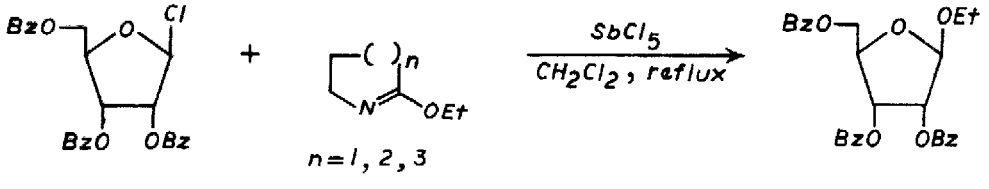
[a] The products exhibited the expected p.m.r. (60, 100 MHz) and mass spectral characteristics, and they were anomerically pure. The syrupy glycosides were further characterized by debenzoylation to the parent alkyl β-D-ribofuranosides; methyl, mp 76°, $[\alpha]_D$ -55 (H_2O); cyclohexyl, mp 139°, $[\alpha]_D$ -85.7° (MeOH); neopentyl, mp 110°; $[\alpha]_D$ -60° (MeOH).

Treatment of a cooled solution of β-D-glucose pentaacetate (1 mmole) in dichloromethane (10 ml), with stannic chloride (1-2 mmoles)

(0°, 10 min), followed by addition of N,N-dimethylformamide dimethylacetal (1-2 mmoles), and stirring for 2-3 h, gave crystalline methyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (83%); mp 104°; $[\alpha]_D^{23}$ -16° (c 1.0, $CHCl_3$) [8,9]. The corresponding β-benzyl glycoside was similarly prepared (47%); mp 97-98°; $[\alpha]_D^{23}$ -42° (c 1.0, MeOH). [10]

The presently described glycosidation using amide acetals as the source of the aglycone has the advantages of circumventing the use of the often unstable glycosyl halides, particularly in the pentofuranose series, and of requiring quasi-stoichiometric quantities of reagents. It is of interest that while the Lewis acids and the amide acetals are, individually, acidic and basic reagents respectively in protic media, the nature of the reactive species [11] formed in solution is such, that little, if any, degradation occurs. In essence, the method is a unique example of a glycosidation with an aprotic reagent, under mild, and essentially "neutral" conditions. Mechanistic studies suggest the intermediacy, at least in part, of orthoesters, resulting from the sustained attack of the 1,2-acyloxonium ions in the respective sugar derivatives, by the alcoholate species, followed by Lewis-acid mediated rearrangement [12] to the corresponding glycosides.

Lewis acid-catalyzed glycosidation in the D-ribofuranose series could also be achieved using lactim ethers as the source of the aglycone, but under conditions requiring heating at reflux in dichloromethane and an excess of reagent. Thus, treatment of 2,3,5,-tri-O-benzoyl-β-D-ribofuranosyl chloride with antimony pentachloride and an excess of O-ethyl caprolactim in dichloromethane (reflux, 4 h) gave ethyl 2,3,5-tri-O-benzoyl-β-D-ribofuranoside as a syrup (90%); $[\alpha]_D^{23}$ +50° (c 1.5, $CHCl_3$) [6].



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