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Preliminary communication

Chemistry of the glycosidic linkage. A rapid and efficient synthesis of carbohydrate 1,2-orthoesters*†

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Of the numerous methods reported in the literature for the synthesis of glycosides[1], few are as versatile and reproducible as that based on the 1,2-orthoester approach[2]. Indeed, many glycosides have been prepared by this method, including some having complex aglycons[1–3]. In spite of the minor side-reactions recently reported[4,5], glycosidations *via* orthoesters are generally characterized by a high degree of stereocontrol, leading to 1,2-*trans*-glycosides as the principal products in the majority of cases studied[4,5]. In addition to the now well-established methods[6–9] of preparation of carbohydrate 1,2-orthoesters, several modifications have been recently introduced[10,12] that lead to orthoesters containing a variety of alkoxyl groups. Although these methods are certainly meritorious in many respects, they share the common disadvantage that they are time consuming, and, in some cases, they are laborious.

We report herein the facile formation of 1,2-orthoesters by the treatment of reactive per-*O*-acylaldopentofuranosyl halides with *N*,*N*-dimethylformamide dialkyl acetals[13] as the source*** of the alkoxyl group. With per-*O*-acylaldohexopyranosyl halides, orthoester formation was accomplished in the same way, but in the presence of silver trifluoromethanesulfonate. Examples in the D-ribofuranose and D-glucopyranose series are described.

In a typical experiment, a solution of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl chloride[14] (1 mmole) in dry dichloromethane (10 ml) was treated with the appropriate acetal (1 mmole) at 0°. After being stirred for 1–2 h at** 25°, the solution was evaporated to dryness, traces of the reagent were removed by evaporation under vacuum (~0.1 torr), and the syrupy residue, containing the desired orthoester, was isolated by chromatography on silica gel. The orthoesters and their optical rotations are listed in Table I (see Scheme 1).

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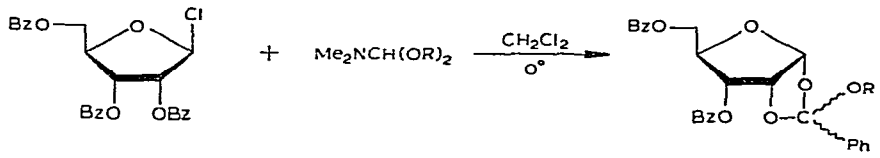
**Reaction invariably took place at 0° or lower.

***A number of *N*,*N*-dimethylformamide dialkyl acetals are commercially available.



Scheme 1

TABLE I

FORMATION OF D-RIBOFURANOSE 1,2-ORTHOESTERS[a–d]

Alkoxyl group (OR)	*Yield (%)*	$[\alpha]_D^{23}$ *(degrees) ($CHCl_3$)*	*Ref.*
Methoxyl	96	+104	15
Isopropoxyl	83	+75.8	–
Cyclohexyloxy	80	+98.3	–

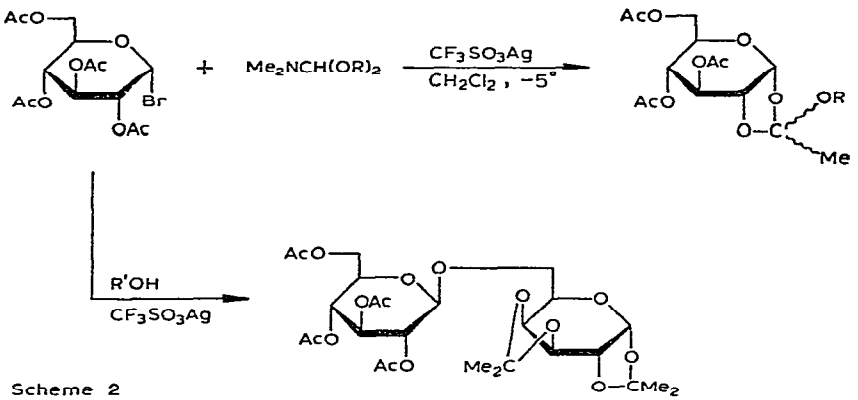
[a]The syrupy products showed the expected p.m.r. parameters (60 and 100 MHz), with evidence of the presence of *endo/exo* mixtures. [b]Methanolysis of the orthoesters (NaOMe–MeOH) gave the corresponding debenzoylated orthoesters as chromatographically homogeneous syrups. [c]Treatment of the products with aq. HCl–1,4-dioxane gave 2,3,5-tri-*O*-benzoyl-D-ribose, which, upon acetylation, gave 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, m.p. 130–131°, identical with an authentic sample. [d]Purification of the products from traces of tri-*O*-benzoyl-D-ribose was done by chromatography on silica gel (1:19 EtOAc–benzene).

To a cooled solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1 mmole) in dry dichloromethane (10 ml) were successively added the appropriate *N,N*-dimethylformamide dialkyl acetal (1 mmole) and silver trifluoromethanesulfonate (1 mmole), and the solution was stirred for 15 min at −5°. The suspension was filtered through a bed of Celite and charcoal, and the filtrate was washed with aqueous sodium hydrogen carbonate, and processed as usual, to give a syrupy residue that contained the orthoester and traces of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose. Purification was achieved by chromatography on silica gel with 1:19 EtOAc–benzene. Pertinent data are listed in Table II (see Scheme 2).

When applied to the D-*galacto* series, the same procedure afforded 3,4,6-tri-*O*-acetyl-α-D-galactopyranose 1,2-(2-methyl orthoacetate) as a syrup (70%)*; $[\alpha]_D^{23}$ +72.3° (*c* 1.72, chloroform).

In connection with these studies, we also report the facile, Lewis acid-catalyzed transformation of several of the orthoesters here described into the corresponding β-D-glycosides. Thus, individual treatment of the orthoesters belonging to the D-ribofuranose series with stannic chloride (0.1 mmole or less per mmole of orthoester) in dichloromethane during 2 h at 25° led to the corresponding β-D-glycosides in over 85% yield. Similarly, methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, m.p. 104–105° (EtOH),

*A small proportion of the corresponding glycoside was also formed.



Scheme 2

TABLE II

FORMATION OF D-GLUCOPYRANOSE 1,2-ORTHOESTERS[a,b]

Alkoxyl group (OR)	*M.p.*[c] *(degrees)*	*Yield (%)*[d]	$[\alpha]_D$ *(degrees)*[e] *($CHCl_3$)*	*Ref.*
Methoxyl	syrup	87	+27	6
Isopropoxyl	118–119	79	+30[f]	7
Propoxyl	syrup	76	+38.1	7
Butoxyl	syrup	74	+33.8	–
Neopentyloxy	97–98	75	+25[f]	–

[a]The products showed the expected p.m.r. parameters, with evidence of the presence of *endo/exo* mixtures. Their ratios were generally in agreement with those reported in the literature. [b]All of the orthoesters were chemically characterized by being subjected to methanolysis (NaOMe–MeOH) and solvolysis (aq. HCl–1,4-dioxane), and the respective products were isolated and further characterized. [c]Crystalline orthoesters were obtained by repeated recrystallization of the initially obtained, chromatographically homogeneous, solid residues or syrups. [d]Yields pertain to chromatographically homogeneous products in each case, but not necessarily to pure diastereoisomeric compounds. [e]Optical rotation values are in agreement with those reported in the literature within ±5°. [f]Rotation of the crystalline orthoester.

$[\alpha]_D^{23}$ −13° (*c* 0.18, chloroform)[16], was prepared in ~60% yield (not optimized) from the corresponding orthoester. Previously, such rearrangements were effected by using acid catalysts, such as *p*-toluenesulfonic acid[5,17] and 2,6-dimethylpyridinium perchlorate[12] among others[2,3]. The merits of Lewis acid catalysts are therefore worthy of further exploration in view of the present results and other data concerning related glycosidations[18].

Finally, we point out a preparatively interesting observation in connection with the use of silver trifluoromethanesulfonate in the formation of orthoesters. Treatment of a suspension containing 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1 mmole) and the silver salt (1 mmole) in dichloromethane (10 ml) with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose during 15 min at 0° gave the known[19], crystalline, disaccharide derivative

1,2:3,4-di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (60%), m.p. 141°, $[\alpha]_D$ −50° (*c* 1.0, chloroform). The corresponding neopentyl β-D-glucoside, m.p. 134–135°, was similarly prepared. This observation extends the utility of silver trifluoromethanesulfonate as a useful catalyst in glycosidation reactions[19], and demonstrates the fundamental difference in the nature of the attacking species (when an alcohol and the corresponding *N,N*-dimethylformamide dialkyl acetal are respectively used) with regard to the formation of a glycoside or an orthoester, respectively (see Scheme 2).

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