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An efficient and stereoselective synthesis of 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-(exo-alkyl orthoacetates)

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Summary: The treatment of acetobromoglucose with N,N-dimethylformamide dialkyl acetals in the presence of tetra-n-butylammonium bromide affords the corresponding 1,2-exo-alkyl orthoacetates in a pure form and in almost quantitative yields.

Carbohydrate 1,2-orthoesters have been long known[1] and have been used for the synthesis of 1,2-trans-glycosides, including some having complex aglycons[2]. The synthesis of 1,2-trans-glycosides from 1,2-orthoesters by the "direct glycosylation" and the "two-stage glycosylation"[3,4] is based on an acid-catalyzed rearrangement reaction using catalytic amounts of mercuric bromide in nitromethane, hindered pyridinium perchlorate salts in solvent of low polarity and p-toluenesulphonic acid, among others[3-6]. The methodology has been considerably improved to allow the synthesis of di-, tri- and oligosaccharides. In spite of the occurence of minor side reactions[3,4], glycosylations by the orthoester method are generally characterized by a high degree of stereocontrol leading to 1,2-trans- glycosides as the principal products.

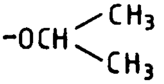
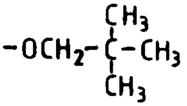
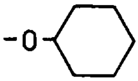
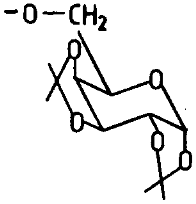
There are at present, several methods in the literature for the preparation of carbohydrate 1,2-orthoesters[5-11] containing a variety of alkoxyl groups including sugar derivatives. While preparatively usefull in many respects, many of these methods are, nevertheless, time consuming and laborious, requiring the use of heavy metal catalysts and/or hindered pyridines as proton acceptors, and conduct invariably to exo/endo mixtures of carbohydrate 1,2-orthoesters.

We report in this communication the efficient and stereoselective synthesis of 3,4,6-tri-O-acetyl- α-D-glucopyranose 1,2-(exo-alkyl orthoacetates), by the treatment of the easily accessible 1,2-cis-glycosyl halide (acetobromoglucose) in the presence of tetra-n-butylammonium bromide as the catalyst with N,N-dimethylformamide dialkyl acetals as the source of the alkoxyl groups[5,12,13] (Scheme 1).

In a typical experiment, a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **1** (1 mmole) and tetra-n-butylammonium bromide (1 mmole) in dry dichloromethane (10 ml) was treated with the corresponding amide acetal (1 mmole). After being stirred for 18 h at 40°C, the solution was cooled to room temperature and diluted with chloroform (20 ml). The organic solution was washed twice with water (2 x 10 ml), dried over anhydrous calcium chloride, filtered and evaporated to afford the desired, pure exo-orthoester in almost quantitative yields; this could be used for further chemical reactions without any need for further purification. The series of the exo-orthoesters prepared and their physical characteristics are listed in table I. The exo-orthoesters readily crystallized in the appropriate solvents.

Table 1

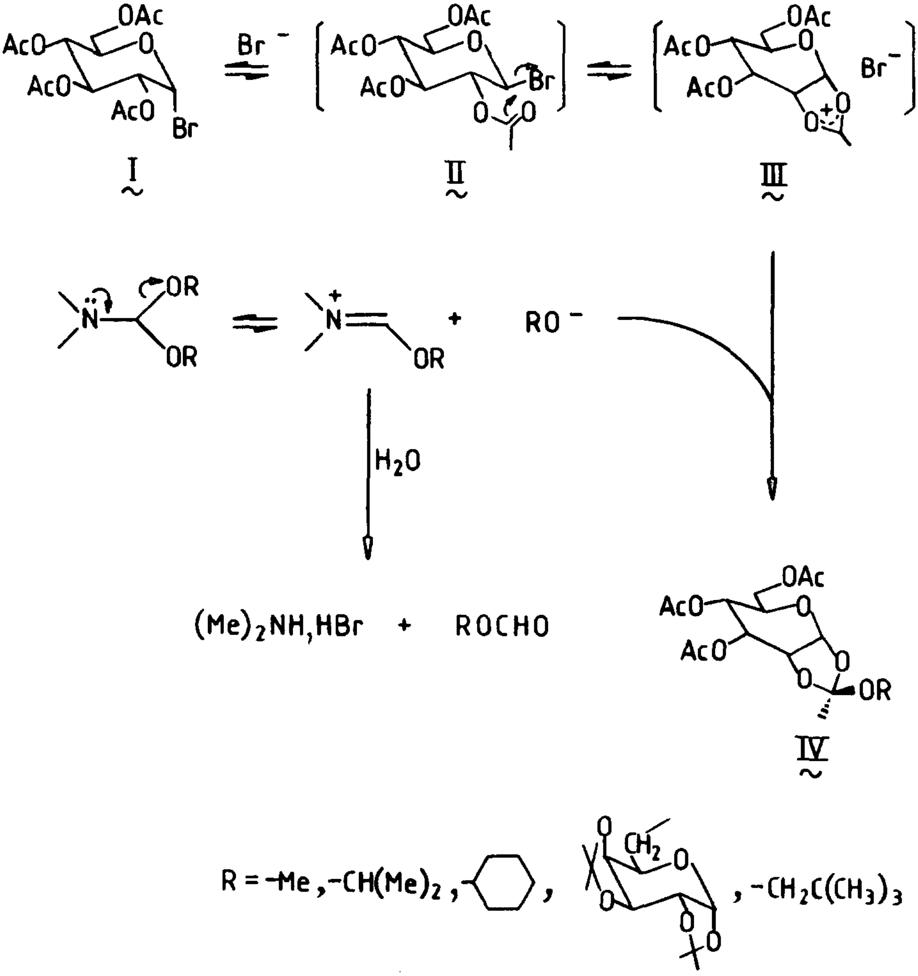
Formation of 3,4,6-tri-*O*-acetyl-α-*D*-glucopyranose 1,2-(*exo*-alkyl orthoacetates)[a] of general formula **IV**.

Alkoxyl group (OR)	**M.p. °C**	**$[\alpha]^{23}_{D}$ degree**	**Ref**
$-OCH_3$	Syrup	+ 27 (*c*.2.52, $CHCl_3$)	8
 $-OCH(CH_3)_2$	117-118	+ 28 (*c*.2.75, $CHCl_3$)	7
 $-OCH_2-C(CH_3)_3$	94-95	+ 29.6 (*c*.2.76, $CHCl_3$)	5
	74-75	+ 32.4 (*c*.3.71, $CHCl_3$)	-
	92-93[b]	- 5.4 (*c*.2.80, $CHCl_3$)	-

[a]: The 1,2-(*exo*)-orthoesters were obtained in near quantitative yields.

[b]: The disaccharide 1,2-orthoester was obtained by column chromatography, in order to separate it from the 6-*O*-formyl-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactopyranose formed during this reaction, and was then recrystallized.

The synthesis of the 1,2-*exo*-orthoesters of complex carbohydrates, can be accomplished, by using the same, aforementionned reactants and conditions, and the sugar derivatives of amide acetals. The sugar derivatives of the amide acetals are formed *in situ* by the *trans*-acetalisation (exchange) of the corresponding partially protected sugar derivatives (2 mmoles) with *N*,*N*-dimethylformamide dimethyl acetal (1 mmole)[12,14,15] in dry dichloromethane for 4 h at room temperature, followed by evaporation to dryness under vacuum.



Scheme 1

It is evident that the preparation of the 1,2-*exo*-orthoesters reported here, results from the quantitative trapping of the 1,2-acyloxonium intermediate III with the reactive alcoxide species provided by the amide acetal. The formation of the acyloxonium ion III is dependent on the epimerisation of the 1,2-*cis*-glycosyl bromide I into the 1,2-*trans*-isomer II which is promoted by the addition of the halide ion. It is suggested that this stereoselective synthesis results from the attack of the alcoxide species from the less sterically hindered side of the 1,2-acyloxonium ion III to yield quantitatively the 1,2-*exo*-orthoester **IV.**

The structure of the 1,2-exo-orthoesters is supported by the analytical data and the ^{1}H-n.m.r. spectroscopy analysis. The presence of only one H-1 doublet centered at δ 5.12 p.p.m. and singlet at 1.72 p.p.m. assigned to the endo-methyl group (C-CH_3) at C-2 of the dioxolane ring, indicates that the 1,2-orthoesters obtained are exo-isomers.

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