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Complexation-Induced Activation of Sugar OH Groups. Regioselective Alkylation of Methyl Fucopyranoside via Cyclic Phenylboronate in the Presence of Amine

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Abstract: Methyl fucopyranoside undergoes highly regioselective 3-*O*-alkylation via complexation with phenylboronic acid, followed by treatment of the resulting 3,4-boronate with iodobutane in the presence of a tertiary amine and Ag_2O. The essential step is suggested to be regioselective activation of the 3-O nucleophilic center upon amine coordination with the O-bonded boron atom. © 1997 Elsevier Science Ltd.

Sugars have many OH groups which are usually not readily distinguishable. Functionalization of sugars including glycosidation has so far almost exclusively involved multistep and hence tedious protection/deprotection procedures, whose essence lies in *deactivation* of all but one OH group via protection or complexation. Little attention, on the other hand, has been paid to an alternative approach based on complexation-induced *activation* of a particular OH group. The regioselective functionalization using tin reagents is a notable exception in this respect.[1]

Arylboronic acids are well known to form cyclic boronates with sugars at the sites of vicinal 1,2-diols and 1,3-diols involving an exocyclic CH_2OH moiety.[2] These complexations have been elegantly applied to the separation,[3] transport,[4] and detection[5] of sugars. The present work is concerned with their synthetic applications. We report here that methyl fucopyranoside can be alkylated in a highly regioselective manner when its 3,4-phenylboronate is treated with a tertiary amine under the alkylation conditions.

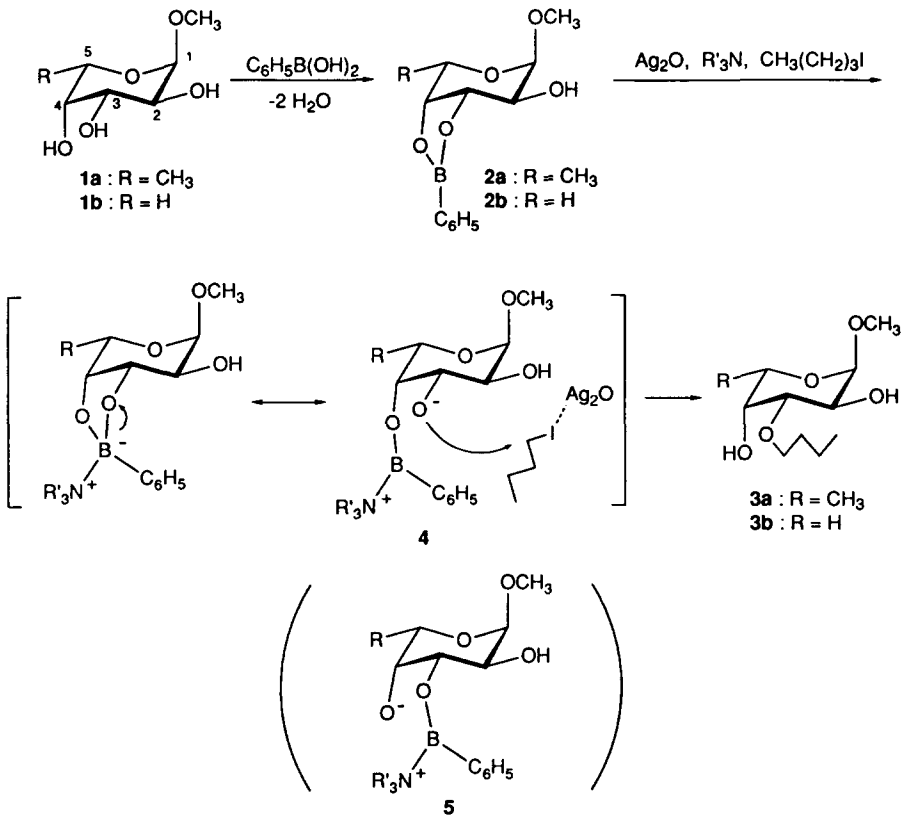
Methyl α-L-fucopyranoside (1a in the Scheme) has three OH groups, where 2-OH and 3-OH are trans and 3-OH and 4-OH are cis. It affords cyclic 3,4-boronate 2a exclusively and quantitatively upon occasional swirling of an equimolar mixture of fucoside 1a and phenylboronic acid ($C_6H_5B(OH)_2$) in CH_2Cl_2 containing Drierite or upon azeotropic water removal[2a] from the same mixture in benzene. Treatment of boronate 2a (0.40 mmol) in benzene (6 mL) with Ag_2O (2 mmol), triethylamine (0.40 mmol), and iodobutane (0.40 mmol) under reflux for 22 h affords 3-*O*-butylated product 3a (50%)[6] as the sole sugar derivative other than starting material 1a, together with butyltriethylammonium iodide (10%). The yield of

3a can be enhanced up to ~80% upon addition of another 1 equivalent of triethylamine and iodobutane in small portions in the period of 24 h.[7] The alkylation product 3a can be readily isolated by means of chromatography of prefiltered reaction mixture on silica gel. More simply, it is obtained in a practically pure form but with some loss when a CH_2Cl_2 solution of the filtrate is washed successively with aqueous 1N HCl, 5% NaOH, and saturated NaCl solutions.

Control runs indicate the following aspects of the present reaction. (1) Silver oxide is essential; no reaction takes place in its absence. (2) The presence of an appropriate tertiary amine such as triethylamine, pyridine, and 4-dimethylaminopyridine but not quinuclidine is also very important although strictly not essential; a small amount (~4%) of 3a still results in the absence of any amine. (3) The choice of solvent is also important. Acetone in place of benzene slightly lowers the yield of 3a. Ethanol fails to give even a trace amount of 3a. In general, use of a polar solvent or a strong amine (quinuclidine) promotes the direct amine-iodoalkane reaction to give the corresponding quaternary ammonium salt and hence inhibits the desired sugar alkylation. (4) Most importantly, the phenylboronate capping of the diol moiety is essential for the present reaction. Uncomplexed fucoside 1a is soluble in refluxing acetone. It is recovered unreacted under conditions (Ag_2O/$(CH_3CH_2)_3N$/$CH_3(CH_2)_3I$) where boronate 2a readily affords the alkylation product 3a. These results clearly indicate that complexation-induced *activation* of the otherwise unreactive sugar 3-OH group is in fact taking place.

Although the involvement of many species leaves mechanistic ambiguities, a plausible one is shown in the Scheme. This is based on the well-known interactions of the Lewis acid-base type between Ag^+ and halides and between trivalent boron species and amines.[4b,5c,8] An essential feature is the Ag^+- and amine-promoted activation respectively of the electrophilic center in iodobutane and the nucleophilic center in alkyl boronate. The question then is regioselectivity. Amine coordination may lead to the more effective 3-O^- nucleophile (4) than 4-O^- (5) (Scheme), since the 3-O^- moiety in the former is equatorially oriented and is less hindered than the 4-O^- moiety in the latter which occupies an axial position and may be further blocked by the nearby 5-CH_3 group. Arabinoside 1b lacks this methyl group. Boronate 2b derived therefrom gives rise to a 4:1 mixture of the 3-*O*- (3b) and 4-*O*-alkylation products. The 3-O^- anion (4) may be stabilized via hydrogen bonding with the adjacent 2-OH group (3-O^-···H-O-2). This is not essential, however. *Cis*-1,2-cyclohexanediol-derived boronate has no adjacent OH group and readily undergoes alkylation to give the corresponding monoalkylation product (*cis*-1,2-cyclohexanediol monobutyl ether) exclusively under the present reaction conditions.

This work demonstrates that the phenylboronate group in combination with a tertiary amine can be used to activate the sugar OH groups. A promising aspect of this approach is that the formation of sugar-boronates is highly regioselective.[2f] The scope and mechanism in more detail are now under investigation, using various sugar derivatives and various functionalizations including glycosidation.[9]



Scheme

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6. The assignment is based on the COSY (H-H and H-C) NMR spectra in reference to the deshielding effect of an introduced alkyl group which causes a downfield shift by ~10 ppm in the ^{13}C NMR resonance of the carbon atom carrying the alkoxy group. (a) Usui, T.; Yamaoka, N.; Matsuda, K.; Tuzimura, K.; Sugiyama, H,; Seto, S. *J. Chem. Soc., Perkin Trans. I* **1973**, 2425-2432. (b) Dorman, D.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 1355-1361. The ^{13}C chemical shifts for product 3a in DMSO-d_6 are δ (δ = 39.7 for DMSO-d_6) 100.47 (1-C), 67.10 (2-C), 78.31 (3-C), 68.45 (4-C), 65.89 (5-C), 16.69 (6-C), 54.66 (OCH_3), 68.38 ($OCH_2CH_2CH_2CH_3$), 31.87 ($OCH_2CH_2CH_2CH_3$), 18.96 ($OCH_2CH_2CH_2CH_3$), 14.04 ($OCH_2CH_2CH_2CH_3$).
7. The amine and iodobutane should be added slowly in small portions. Otherwise, 2,3-di-*O*-dibutylated product is obtained in a significant amount.
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9. Preliminary examinations indicate that the present method with or without suitable modifications is applicable to (1) glycosidation using, for example, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide instead of alkylation and (2) alkyl glucopyranoside and galactopyranoside in place of fucopyranoside as a substrate. Glucoside forms a 4,6-boronate, which affords a 6-substitution product. Galactoside, on the other hand, forms both 4,6-boronate and 3,4-boronate, which lead to 6- and 3-substitution products, respectively.

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