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Preliminary communication

Chemistry of the glycosidic linkage. An efficient synthesis of 1,2-*trans*-. '-saccharides*

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A large number of procedures reported in the literature[1] for the synthesis of 1,2-*trans*, di- and oligo-saccharides[2] are based, for the most part, on the original Koenigs–Knorr[3] and orthoester[4] methods. Although many modifications have been introduced over the years, the combined features of *generality* and *efficacy* can rarely be attributed to any one method. In a continuation of our studies on novel methods of glycosylation[5–7], we now report an efficient and apparently general method for the synthesis of 1,2-*trans*-linked disaccharide derivatives. The reaction consists in the treatment of acetylated glycosyl halides with a sugar derivative in the presence of silver trifluoromethanesulfonate (triflate) as the catalyst, and 1,1,3,3-tetramethylurea as the proton acceptor. Using this novel procedure, we have conducted systematic glycosylations with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**), among other related compounds, at the hydroxyl group situated individually on C-2, C-3, C-4, and C-6 of suitably protected sugar derivatives. The resulting (1→2)-, (1→3)-, (1→4)-, and (1→6)-β-linked disaccharide derivatives were respectively formed in a high state of anomeric purity, in preparatively significant yields, and with much manipulative simplification compared to previously reported methods.

In a typical procedure, a solution of **1** (0.41 g, 1 mmole) in dry dichloromethane (10 ml) was successively treated at 0° with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[8] (**2**; 0.564 g, 2 mmoles), 1,1,3,3-tetramethylurea (0.33 ml, 3 mmoles), and silver triflate (0.567 g, 2.2 mmoles) under rigorously anhydrous conditions. The suspension was stirred in the dark for 4 h at 0°, and filtered through a bed of Celite; the filtrate was washed with aqueous sodium hydrogencarbonate, and processed as usual, to give a syrup that contained **2**, traces of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose, and a major product, **3**. The latter could be crystallized directly from the mixture by trituration with methanol. For more-consistent recoveries, however, the syrup was chromatographed on silica (1:9 EtOAc–benzene), to give **3** as a clear syrup (0.29 g, 47%). Crystallization from methanol gave the

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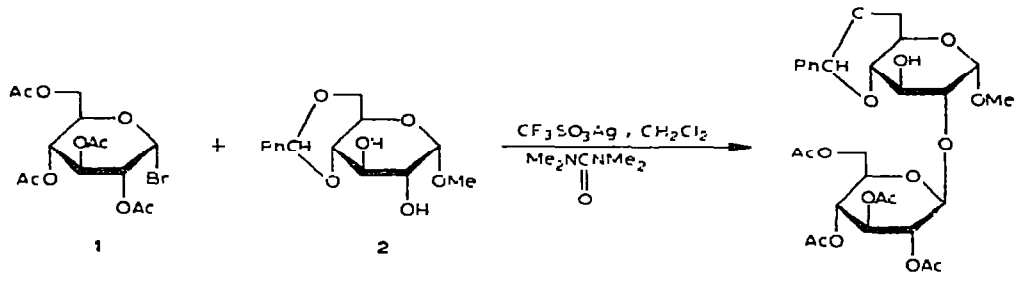
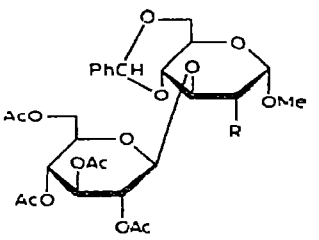


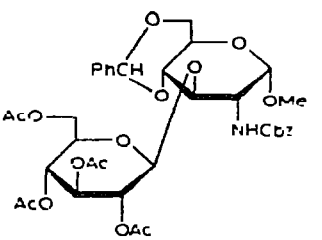
known disaccharide derivative* in two crops (41%), m.p. 226–227°, $[\alpha]_D^{25}$ +40.1° (*c* 0.72, $CHCl_3$); reported[9] (40%), m.p. 227–228°, $[\alpha]_D^{25}$ +42.4° ($CHCl_3$), and[10] (21%), m.p. 221–224°, $[\alpha]_D^{25}$ +45° ($CHCl_3$). Methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside was similarly prepared (4 h at 25°) in 15% yield**, m.p. 197–198°, $[\alpha]_D^{25}$ +50.1° (*c* 0.55, $CHCl_3$); reported[11] (15%), m.p. 197–198°, $[\alpha]_D$ +54.3° ($CHCl_3$).

Similar glycosylation of methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[12] (1.7 mmoles) with **1** (2 mmoles) in the presence of silver triflate (2 mmoles) and 1,1,3,3-tetramethylurea (5 mmoles) for 6 h at 25°, followed by column chromatography, gave the disaccharide derivative **4** as a colorless, analytically pure foam in 86% yield (based on reacted aglycon); $[\alpha]_D^{25}$ +9.2° (*c* 1.63, $CHCl_3$). Treatment of **4** with sodium amalgam in 90% methanol for 3 h at 25°, and acetylation, gave the known, crystalline **5** (80%), m.p. 162–164°, $[\alpha]_D^{25}$ +21° (*c* 1, $CHCl_3$); reported[13] m.p. 164.5–166.5°, $[\alpha]_D$ +22 ($CHCl_3$).

The suitability of the method in the case of amino sugar derivatives was shown by the preparation of the disaccharide derivative **6**, isolated as a colorless, chromatographically homogeneous foam (82%), $[\alpha]_D^{25}$ +18.5° (*c* 3.02, $CHCl_3$), essentially as just described.



4 R = OTs
5 R = OAc

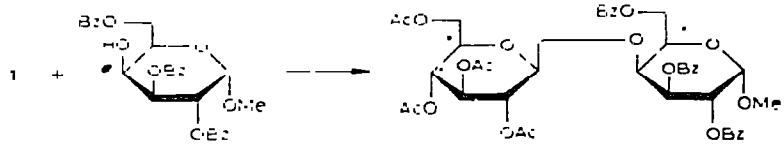


6
Cbz = $PhCH_2OCO$

*All new compounds gave correct microanalyses. All compounds exhibited n.m.r.-spectral characteristics that were in accord with their structures. Yields were not optimized.

**Obtained by direct crystallization. Chromatographic purification of a crude reaction-mixture gave a syrup (40%) that had chromatographic properties identical to those of the crystalline product.

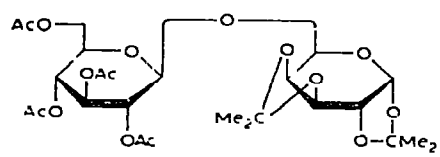
Methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[14] (7) was chosen as a model for glycosylation at the 4-hydroxyl group of a hexopyranoside derivative, particularly as, in this case, the steric requirements of the axial hydroxyl group would be expected to be a critical factor. Treatment of **1** (2 mmoles) with **7** (1 mmole), essentially as already described*, gave, after column chromatography, methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**8**) as an analytically pure foam (72%).



7 **8**

$[\alpha]_D^{25}$ +56.6° (*c* 0.5, $CHCl_3$). Under simulated reaction-conditions, but in the absence of **1**, the aglycon was recovered unchanged (4 h at 25°), demonstrating its stability, and precluding any possibility of ester migration during the glycosylation. Treatment of **8** with 1:12 (v/v) M H_2SO_4 in 1,4-dioxane during 18 h under reflux gave crystalline **7**. The (1→4)-linkage was also shown by mass-spectral data[15] on the permethylated analog of **8**; $[\alpha]_D^{25}$ +72.3° (*c* 0.54, $CHCl_3$). De-esterification of **8** (NaOMe, MeOH) gave the corresponding disaccharide derivative as a syrup [methyl α-D-lycobioside[16], $[\alpha]_D^{25}$ +94.9° (*c* 1.36, H_2O)] which, upon acid hydrolysis, gave D-glucose and D-galactose, identified chromatographically[17].

Finally, glycosylation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[18] (1.1 mmoles) with **1** (1.3 mmoles), in the presence of silver triflate (1.4 mmoles) and 1,1,3,3-tetramethylurea (3 mmoles) for 6–8 h at 0° gave, after chromatographic purification (72%), the known crystalline disaccharide derivative **9**, m.p. 140–141°, $[\alpha]_D^{25}$ −50° (*c* 1, $CHCl_3$); reported[10,19] (51–60%), m.p. 141° $[\alpha]_D$ −54.5° ($CHCl_3$).



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The new catalyst–acid acceptor combination reported herein should prove useful in the synthesis of a variety of 1,2-*trans*-linked oligosaccharides by utilizing glycosyl halide derivatives containing a participating ester function at C-2. The method is also suitable for the preparation of α-glycosides in the absence of a participating group, particularly when stereoelectronic conditions are favorable, as exemplified by the synthesis of novel glycoside analogs of the antitumor substance adriamycin[20]. The inclusion of 1,1,3,3-tetramethylurea

*An acid acceptor was not necessary in this case, provided that the conditions were anhydrous.

in the reaction mixture is particularly advantageous with aglycons that contain acid-sensitive groups (*e.g.*, 2, 3, 4, and 6), as, despite its very weak basicity, it is still capable of considerably diminishing the acidity of the triflic acid produced during the reaction. In addition, it does not interfere in the glycosylation reaction, and it is freely water-soluble, thus facilitating the isolation of the glycoside.

ACKNOWLEDGMENT

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