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STANNOUS TRIFLATE MEDIATED GLYCOSIDATIONS. A STEREOSELECTIVE SYNTHESIS OF 2-AMINO 2-DEOXY-β-D-GLUCOPYRANOSIDES DIRECTLY WITH THE NATURAL N-ACETYL PROTECTING GROUP.

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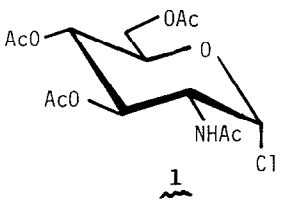
Abstract : Various 2-acetamido 2-deoxy β-D-glucopyranosides have been prepared in good yield from the crystalline 2-acetamido 3,4,6-tri-O-acetyl 2-deoxy α-D-glucopyranosyl chloride using stannous triflate as promoter.

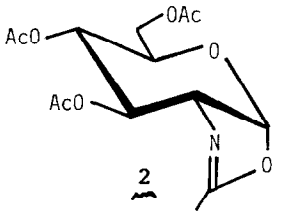
The presence on cell-membrane of oligosaccharides which play a variety of important roles[1] associated with intercellullar recognition and interaction and are receptors for enzymes, hormones, proteins and viruses, have stimulated interest in oligosaccharide synthesis.

However, glycosidation is still a major problem in organic synthesis as no universal method has been devised for the construction of the glycosidic linkage and each individual oligosaccharide poses a new challenge for the organic chemist. Among all the different coupling reactions which are necessary to achieve the synthesis of natural oligosaccharides, the preparation of the 1,2-trans 2-acetamido 2-deoxy β-D-glucopyranoside bond is especially of importance, considering the widespread occurence of aminosugars in glycoconjugates of biological significance. These aminosugars are usually found as acetamido derivatives, so the direct synthesis using the N-acetyl protecting group on the sugar donor would avoid additional blocking-deblocking reactions on elaborated derivatives and would give improved overall yields.

Starting with the easily available 2-acetamido 3,4,6-tri-O-acetyl 2-deoxy α-D-glucopyranoside chloride **1**[2], usual promoters for the Koenigs-Knorr reactions such as silver triflate give poor results in glycosidation because the oxazoline derivative **2** is preferentially formed under the conditions of the reaction. To overcome this difficulty, other amino protecting groups have been used with success such as phtalimido[3] or allyloxycarbonyl groups.[4] Alternatively, 2-acetamido 3,4,6-tri-O-acetyl 2-deoxy β-D-glucopyranosides may be obtained under acidic catalysis from the preformed oxazoline derivative **2**[5] but the main disadvantage is the moderate yield of the coupling reaction.



1



2

Two of us have already shown[6] that stannous triflate[7] might be used as promoter in Koenigs-Knorr type reaction between acetobromoglucose and various alcohols including sugar derivatives.

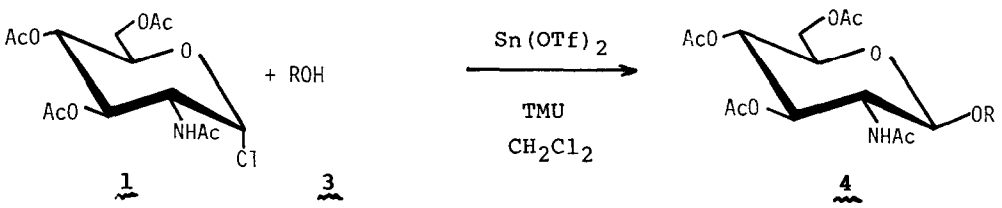
We now want to report that stannous triflate can promote the coupling reaction between compound **1** and several alcohols to give β-glycosidation directly with the natural N-acetyl protecting group. The reaction is completely stereoselective, and no evidence for the formation of α-anomers was found either by tlc or analytical hplc.

Among several bases (diisopropylamine, triethylamine, collidine and 1,1,3,3-tetramethylurea) and several solvents (DMF, THF, CH_2Cl_2 and toluene) we found that the combination of 1,1,3,3-tetramethylurea in CH_2Cl_2 as indicated in the typical procedure gave the best results.

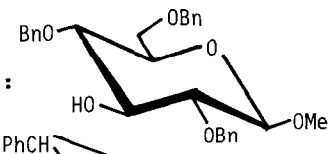
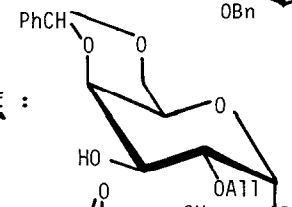
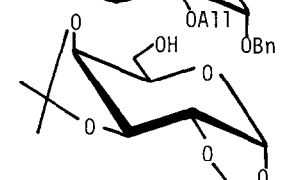
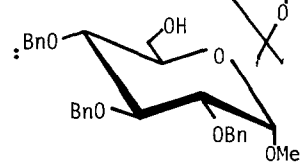
A minor amount of oxazoline **2** was formed as a by-product. We have verified that it was not an intermediate in the reaction since the rate and the yield of glycosidation were considerably lowered when the oxazoline was used as starting material (only 1.5 % yield of glycosidation after 16 h at room temperature).

The results are given in table I.

Table I



1 **3** **4**

entry	ROH	1:3 ratio	yields[a] of **4a-h**[8] (%)
1	**3a** : MeOH	1:5	86
2	**3b** : iPrOH	1:4	57
3	**3c** : $MeOCO(CH_2)_7CH_2OH$	1:2	81
4	**3d** : PhOH	1:5	87
5	**3e** : 	2:1	46 (83)[b]
6	**3f** : 	2:1	23 (40)[b]
7	**3g** : 	2:1	77 (94)[b]
8	**3h** : 	2:1	73 (87)[b]

[a] Yields for products which look pure on chromatographic and spectroscopic (90 or 250 MHz ^1H NMR) examination after isolation by crystallisation and/or preparative hplc.

[b] Yields in brackets based on starting material recovery.

Typical experimental procedure for disaccharide synthesis.[9]

A solution of alcohol **3** (1 mmol) and 1,1,3,3-tetramethylurea (1.5 mmol) in CH_2Cl_2 (5 ml) was added to a stirred suspension of 2-acetamido 3,4,6-tri-O-acetyl 2-deoxy α-D-glucopyranosyl chloride (1.5 mmol), stannous triflate (1.5 mmol) and 4 A molecular sieves in CH_2Cl_2 (5 ml). After two days at room temperature the reaction mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ solution. The organic phase was dried and concentrated in vacuo to give a residue from which the pure 2-acetamido 3,4,6-tri-O-acetyl 2-deoxy β-D-glucopyranoside was separated by preparative silica gel chromatography.

Acknowledgments.

We wish to thank Professor Serge DAVID for his interest, the CNRS and the University of Paris-Sud for their financial support.

Notes and references

1. Geoffrey M.W. Cook, J. Cell. Sci. Suppl. 4, 1986, 45.
2. Biochemical Preparations, 1971, 13, 9.
3. R.U. Lemieux, T. Takeda and B.Y. Chung, A.C.S. Symp. Ser. 1976, 39, 90.
4. P. Boullanger and G. Descotes, Tetrahedron Lett., 1986, 27 (23), 2599.
5. M. Kiso and L. Anderson, Carbohydrate Res., 1985, 136, 309.
6. A. Lubineau and A. Malleron, Tetrahedron Lett., 1985, 26 (14), 1713.
7. Commercially available from Fluka. For its preparation see : T. Mukaiyama, N. Iwasawa, R.W. Stevens and T. Haga, Tetrahedron, 1984, 40 (8), 1381.
8. All compounds gave correct analytical and spectroscopic data. The physical data for the new **4f**, **4h** are :
   4f : mp 221-222°C (methanol). $[\alpha]_D^{20}$ +97° (c 1.13 CH_2Cl_2). Anal. Calcd for $C_{37}H_{45}NO_{14}$: C, 61.06; H, 6.23; O, 30.78. Found : C, 60.82; H, 6.20; O, 30.54.
   4h : mp 187-188°C (ether). $[\alpha]_D^{20}$ +27° (c 1.13 CH_2Cl_2). Anal. Calcd for $C_{42}H_{51}NO_{14}$: C, 63.54; H, 6.48; O, 28.22. Found : C, 63.46; H, 6.47; O, 28.36.
9. In the case of alkyl or aryl β-D-glycosides, a 2 to 5-fold excess of the alcohols **3a-d** (see table I) is used to ensure complete transformation of compound **1**.

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