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BORON TRIFLUORIDE ETHERATE AS AN EFFECTIVE REAGENT FOR THE STEREOSELECTIVE ONE-POT CONVERSION OF ACETYLATED 2-TRIMETHYLSILYLETHYL GLYCOSIDES INTO SUGAR 1,2-TRANS-ACETATES.

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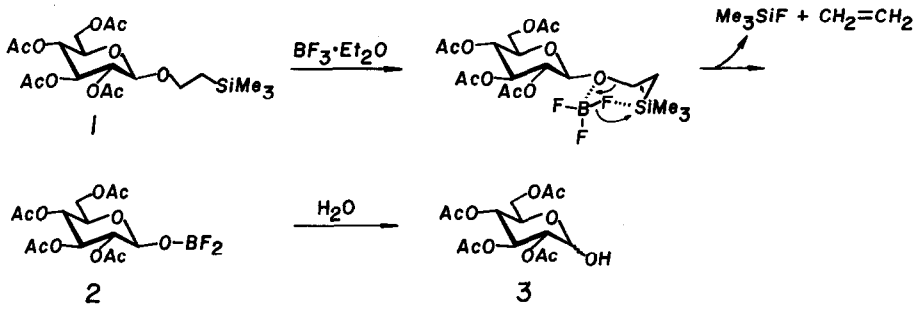
SUMMARY: Treatment of 2-trimethylsilylethyl glycosides with boron trifluoride etherate in the presence of acetic anhydride gave the corresponding sugar acetate in >90% isolated yield and with a 1,2-trans:cis ratio of >20:1. The sugar with a free anomeric hydroxyl group was obtained when acetic anhydride was omitted.

Sugar 1,2-trans- acetates are suitable glycosyl donors for Lewis acid-promoted glycoside synthesis[1]. Stereoselective methods for the preparation of these compounds are however scarce, especially for oligosaccharide glycosides. The usual methods consist of removal of temporary anomeric protecting groups (e.g. methyl, benzyl and allyl) followed by acetylation of the anomeric hydroxyl group. This technique normally gives mixtures of 1,2-trans and -cis acetates with a low trans/cis ratio. Recently, Lipshutz et al.[2] reported the preparation of 2-trimethylsilylethyl glycosides and their subsequent cleavage into the corresponding free sugar by $LiBF_4$ or a 1:1 mixture of $LiF/BF_3 \cdot Et_2O$. It occurred to us that the cleavage product (or some intermediate) could have conserved its anomeric stereostructure and that the presence, in the reaction mixture, of a suitable acylating agent would yield an acylated sugar with the same anomeric configuration as the starting 2-trimethylsilylethyl glycoside.

We found that when $BF_3 \cdot Et_2O$ was added to a stirred mixture of 2-trimethylsilylethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (1) and LiF in CH_3CN, the cleavage reaction was much slower than when no LiF was present (cf. Table 1). This clearly indicates that the formation of $LiBF_4$ rather retards than promotes the reaction and that $BF_3 \cdot Et_2O$ itself is the reactive species acting in a six-membered complex with the glycoside. This is in contrast to the mechanistic

interpretation put forward by Lipshutz et al.[2], in which fluoride ion is considered to be the reactive species. In fact, 0.8-1 equivalent of $BF_3 \cdot Et_2O$ effects the cleavage much faster than an excess of $LiBF_4$ or any of the fluoride salt/$BF_3 \cdot Et_2O$ complexes that we have tested (LiF, NaF, KF, CsF).

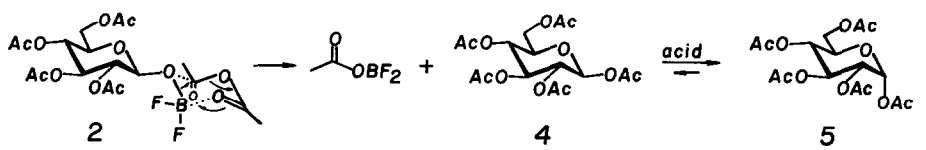


1 2 3

The formation of the difluoroborate 2 (probably a trimeric complex[3]) was indicated by the following observations: i) ethylene was formed in the reaction; the effluent gases decolourised Br_2 in CCl_4; ii) evaporation of all volatile material from the crude reaction mixture gave a hygroscopic glass; iii) the glass in CD_3CN showed ^{11}B-nmr signals at 20.8 and 18.1 ppm downfield from the $BF_3 \cdot Et_2O$ signal[3]. This is consistent with a compound of formula 2 but also with a borate that could presumably be formed by disproportionation of 2, thus liberating BF_3 to continue the cleavage reaction. The stoichiometry of the reaction thus permits complete cleavage of the glycosides by the use of 1/3 equivalent of $BF_3 \cdot Et_2O$, although the reaction was impractically slow (>4 days).

When the cleavage reaction was performed with 1 in the presence of acetic anhydride (Ac_2O), the corresponding acetates 4 and 5 were the sole products formed. With polar solvents such as CH_3NO_2, CH_3CN, and Ac_2O, and >1 equiv. of $BF_3 \cdot Et_2O$, the acetates were formed rapidly, but the β/α-ratio was low (~1:5). In contrast, apolar solvents such as $C_6H_5CH_3$ or CH_2Cl_2 and <1 equiv. of $BF_3 \cdot Et_2O$ permitted the isolation of β/α-acetates in the ratio >20:1 and >90% yield (Table 1).

The acetylation reaction presumably proceeds between the difluoroborate 2 (or some similar species) and Ac_2O in a six-membered complex as shown below. When succinic anhydride was used instead of Ac_2O, no acylation occurred. This corroborates the mechanistic interpretation because succinic anhydride is unable to adopt the necessary transition-state geometry. Anomerisation of the β-acetate to the more stable α-acetate can then take place with the help of Lewis acids that are present in the reaction mixture (cf. Table 1; 2 equiv. of $BF_3 \cdot Et_2O$).

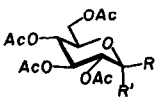


2 4 5

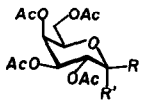
Preliminary experiments have shown that i) other Lewis acids (e.g. $FeCl_3$, $ZnCl_2$, $ZnBr_2$, $SnCl_4$) are also effective for the cleavage of 2-trimethylsilylethyl glycosides and for their transformation into 1,2-trans acetates and ii) acyclic anhydrides other than Ac_2O (such as $(p\text{-}NO_2C_6H_4CO)_2O$) can be used for anomeric O-acylation. The possibility of using these compounds in Lewis acid-mediated glycosylations is currently being investigated. A full account of this work will be reported in due course.

We realise the implications of this method and suggest its general use for temporary anomeric protection in connection with the synthesis of oligosaccharides and their glycosides.

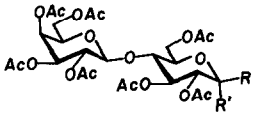
Table 1. Product distribution and yields in the reaction of 2-trimethylsilylethyl glycosides and boron trifluoride etherate.



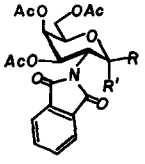
1, 3, 4, 5



6, 7, 8



9, 10, 11



12, 13, 14

1, 6, 9, 12: R=O⌒$SiMe_3$; R'=H

3: R,R'=H,OH

4, 7, 10, 13: R=OAc; R'=H

5, 8, 11, 14: R=H; R'=OAc

Starting Glycoside	Reaction conditions[a]	Product	Yield[b]	β/α-ratio[c]
1	0.8 equiv. $BF_3 \cdot Et_2O$, 15 equiv. Ac_2O, toluene, 2 h	4, 5	93%	99:1
6	"	7, 8	92%	96:4
9	"	10, 11	95%	98:2
12	"	13, 14	93%	97:3
1	2.0 equiv. $BF_3 \cdot Et_2O$, Ac_2O, 2 h	4, 5	85%	20:80
1	0.9 equiv. $BF_3 \cdot Et_2O$, CH_3CN, 50min	3	87%	d
1	0.9 equiv. $BF_3 \cdot Et_2O$ added to a stirred solution of 0.9 equiv. LiF in CH_3CN, 1 h	3	10%[e]	d

a) See experimental. b) Products isolated by chromatography on silica gel.
c) Determined by gc and nmr. d) Not determined. e) Reaction not complete.

Experimental: The glycosides 1, 6 and 9 were prepared from the corresponding 1-bromo sugars and 2-trimethylsilylethanol using $HgO/HgBr_2$, as described by Lipshutz[2], and 12 using silver triflate. All new compounds had satisfactory spectral data.

General method for the cleavage of 2-trimethylsilylethyl glycosides.

The glycoside 1 (0.11 mmol) was dissolved in dry CH_3CN (0.6 mL). $BF_3 \cdot Et_2O$ (0.09 mmol) was added and the mixture was stirred for 50 min at room temperature. Addition of water, extraction with CH_2Cl_2 and removal of the solvents gave 3 (purity >95% according to ^{1}H-nmr).

General method for the stereoselective preparation of sugar 1,2-trans acetates directly from the 2-trimethylsilylethyl glycosides.

The glycoside 1, 6, 9, or 12 (0.11 mmol) was dissolved in a dry $C_6H_5CH_3/Ac_2O$ mixture (0.6 mL), and $BF_3 \cdot Et_2O$ (0.09 mmol) was added. The mixture was stirred at room temperature for ca 2 h, CH_2Cl_2 (5 mL) was added and the solution was washed with 5% $NaHCO_3$-solution and water, dried and filtered through silica to give the pure acetates after removal of the solvent (Table 1). The β/α ratio was determined by gas chromatography or ^{1}H-nmr spectroscopy.

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