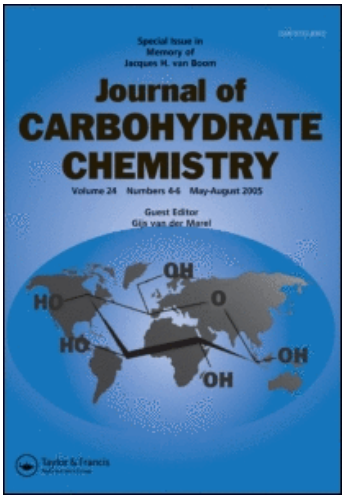

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Lennart Blomberg[ab]; Thomas Norberg[ab]
[a] Organic Synthesis Department, BioCarb Technology AB, Lund, Sweden [b] Organic Chemistry II, The Lund Institute of Technology, Lund, Sweden

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EFFICIENT CONVERSION OF THIOGLYCOSIDES INTO GLYCOSYL FLUORIDES USING DIMETHYL(METHYLTHIO)SULFONIUM TETRAFLUOROBORATE

Lennart Blomberg* and Thomas Norberg

Organic Synthesis Department,
BioCarb Technology AB, S-223 70 Lund, Sweden
(address for communication: Organic Chemistry II, The Lund Institute of Technology, P.O. Box 124, S-221 00 Lund, Sweden)

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ABSTRACT

Alkyl and aryl thioglycosides were converted in high yield into the corresponding α-glycosyl fluorides by treatment with dimethyl(methylthio)-sulfonium tetrafluoroborate. Glycosidic linkages and most protective groups are not affected by the reaction conditions. Glycosyl fluorides are proposed to be intermediates in glycosylations promoted by dimethyl(methylthio)-sulfonium tetrafluoroborate.

INTRODUCTION

Thioalkyl or thioaryl groups are useful temporary protective groups for the anomeric position in oligosaccharide synthesis. Their versatility is based

on the fact that a thioglycoside is relatively stable to most reaction conditions used for protective group manipulation, but is reactive enough towards thiophilic reagents to be activated into glycosylation agents.[1]

Activation can be effected either in one step with reagents such as methyl triflate,[2] dimethyl(methylthio)sulfonium triflate,[3] dimethyl-(methylthio)sulfonium tetrafluoroborate,[3,4] nitrosyl tetrafluoroborate,[5] iodonium di(collidine)perchlorate,[6] phenylmercury triflate,[7] benzene-selenyl triflate,[8] sulfuryl chloride,[9] or in two steps, the first usually being conversion of the thioglycoside into a glycosyl halide in the absence of acceptor. Two-step activation is most useful in cases where the glycosyl acceptor is itself a thioglycoside, and therefore would react rapidly with the direct-activating reagents, e. g., methyl triflate. In this way, complex oligosaccharide structures can be assembled stepwise using thioglycoside blocks.

Glycosyl bromides have been used most frequently as intermediates in two-step activation of thioglycosides, since they are easily obtained by treating the thioglycoside with bromine.[10,11] Glycosyl chlorides or the even more stable glycosyl fluorides can, however, also be used. Fluorides can be activated for glycosidation by reagents such as stannous chloride/silver perchlorate,[12] boron trifluoride etherate,[13] triflic anhydride,[14] tris(4-bromophenyl)ammonium hexachloroantimonate,[15] silicon-based catalyst,[16] or other Lewis acids.[17] The glycosyl fluorides themselves can be obtained from thioglycosides by treatment with reagent such as 4-methyl-(difluoroiodo)benzene,[18] or by other methods such as hydrogen fluoride,[19] silver fluoride,[20] DAST,[21,22] DAST/NBS,[23] 2-fluoro-1-methyl-pyridinium tosylate,[24] pyridinium poly(hydrogen)fluoride,[25,26] *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine.[27] The field has been recently reviewed.[28,29,30,31,32,33,34]

We now report a simple, alternative way to generate glycosyl fluorides from thioglycosides at room temperature, using the mild reagent dimethyl-(methylthio)sulfonium tetrafluoroborate, which is a non-hygroscopic, crystalline solid, commercially available or easily prepared from simple reagents.[35] The reaction conditions did not affect glycosidic linkages or sensitive protecting groups such as benzylidene acetals. Even free hydroxyl groups could in some instances be tolerated.

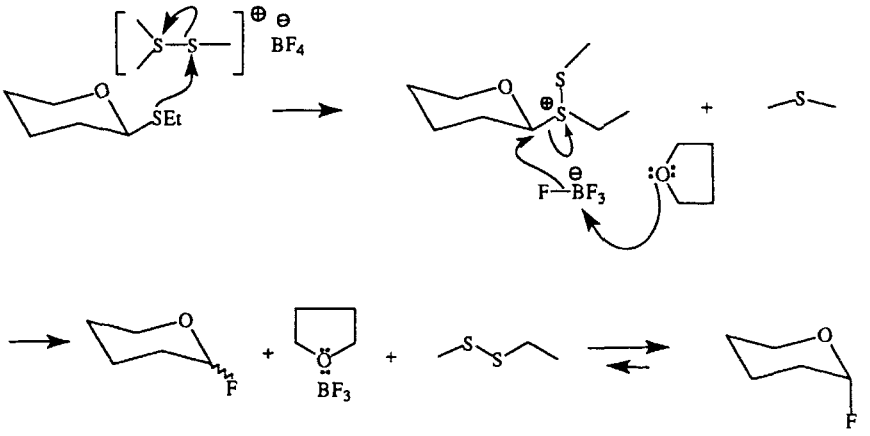


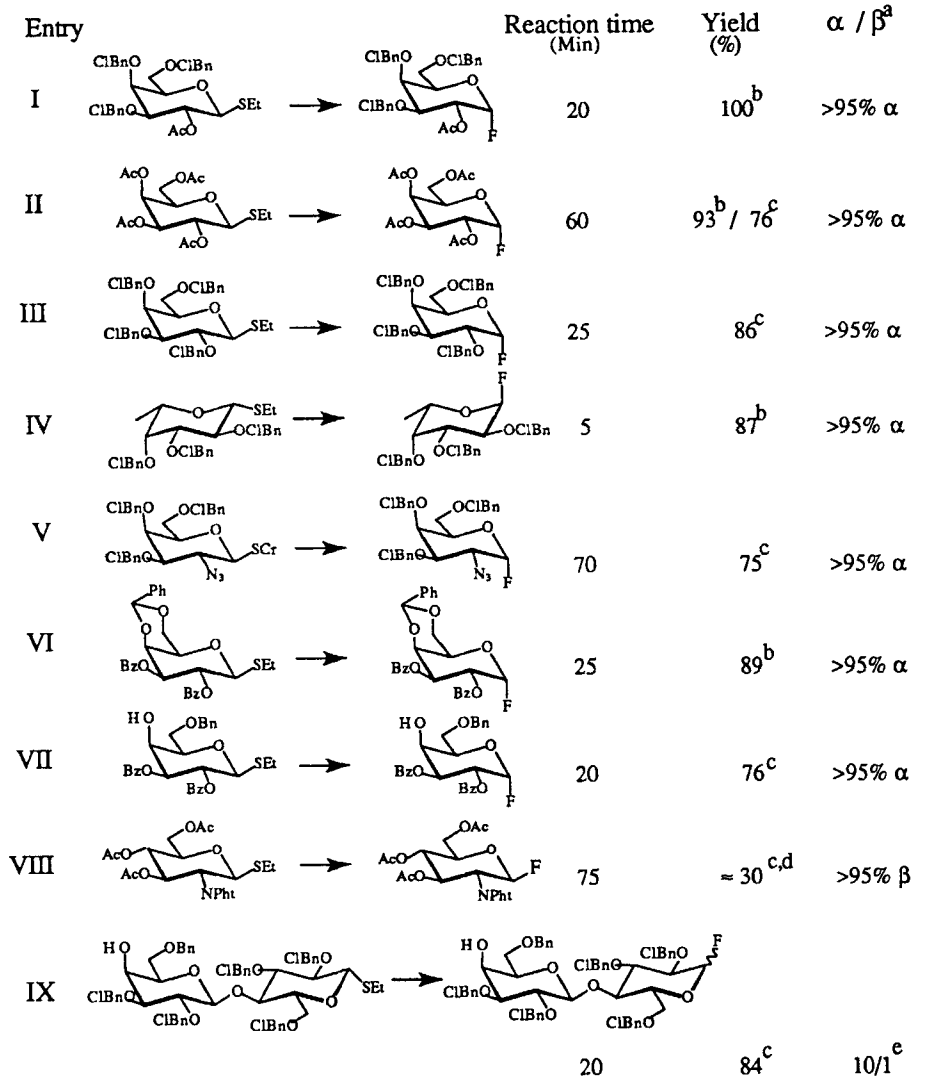
FIG. 1. Suggested mechanism for glycosyl fluoride formation.

RESULTS AND DISCUSSION

During oligosaccharide synthesis work,[4] using one-step activation of thioglycosides with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSB) in the presence of glycosyl acceptor, we observed that an intermediate was formed during the reaction. We therefore investigated the reaction of DMTSB with thioglycosides in the absence of glycosyl acceptor. The results with some representative thioglycosides are shown in FIG. 2 and TABLE 1.

In all cases but entry **VIII**, clean and rapid conversion into glycosyl fluorides was observed. They must have been formed by reaction of the activated thioglycoside with the fluoroborate ion. A suggested mechanism is shown in FIG. 1.

The reaction takes place with almost complete selectivity indicating that a pure inversion mechanism is involved or more likely, as suggested above, that an initially formed α/β fluoro mixture is anomerized to the more thermodynamically stable α-isomer by the simultaneously formed boron trifluoride etherate.[27] Only in entry **IX** minor amounts of the β-isomer were seen, and in entry **VIII**, where the β-anomer is the more stable anomer.



a. >95% α indicates that no visible traces of the β-isomer could be detected by NMR.
b. Not chromatographed.
c. Flash chromatographed.
d. The reaction did not go to completion. Prolonged reaction time (18 h) did not lead to completion and other products were formed as well. Flash chromatography gave a mixture of unreacted starting material and glycosyl fluoride. The yield is estimated from the integrals of the anomeric protons.
e. Flash chromatography yielded an α/β mixture. The ratio was estimated from the anomeric protons.

ClBn = p-chlorobenzyl, Cr = p-methylphenyl

FIG. 2. Thioglycoside conversion into glycosyl fluorides with DMTSB.

TABLE 1. Chemical shifts[d,e] and coupling constants for the glycosyl fluorides.

Nucleus	I	II[a]	III	IV	V
H-1 ($J_{1,2}$, $J_{1,F}$)	5.73 (2.7, 54.4)	5.78 (2.7, 53.4)	5.61 (2.6, 53.6)	5.60 (2.7, 54.0)	5.61 (2.6, 53.3)
H-2 ($J_{2,3}$, $J_{2,F}$)	5.31 (10.4, 24.0)	5.16 (10.9, 23.8)	3.97 (10.1, 24.8)	3.97 (10.1, 24.7)	3.93 (10.6, 24.4)
H-3 ($J_{3,4}$)	3.91 (2.8)	5.34 (3.2)	3.89 (2.7)	3.90 (2.7)	3.90 (2.5)
H-4 ($J_{4,5}$)	4.00 (<1.0)	5.50 (0.9)	3.98 (1.2)	3.68 (1.2)	4.04 (n.d.)
H-5 ($J_{5,6}$)	4.11 (6.6)	4.38 (6.8)	4.10 (6.6)	4.07 (6.5)	4.11 (5.9)
H-6 ($J_{6,6'}$)	3.54 (n.d.)	4.09 (11.3)	3.53 (n.d.)	----	3.55 (9.2)
H-6' ($J_{5,6'}$)	3.57 (n.d)	4.14 (6.3)	3.53 (n.d)	——	3.58 (9.2)
C-1 ($J_{C,F}$)	104.9 (225.3)	104.3 (228.6)	105.8 (227.0)	105.8 (224.1)	106.3 (226.0)

Nucleus	VI	VII	VIII[b]	IX (Glc)[c]	IX (Gal)
H-1 ($J_{1,2}$, $J_{1,F}$)	6.08 (2.6, 53.7)	6.00 (2.8, 53.8)	6.11 (7.9, 52.2)	5.52 (2.6, 53.3)	4.25 (7.8 --)
H-2 ($J_{2,3}$, $J_{2,F}$)	5.86 (10.8, 23.2)	5.81(10.6, 24.2)	4,46 (10.6, 13.7)	3.44 (9.6, 25.4)	3.53 (9.3 --)
H-3 ($J_{3,4}$)	5.79 (3.3)	5.68 (2.9)	3.24 (9.4)	3.81 (9.1)	3.26 (3.3)
H-4 ($J_{4,5}$)	4.73 (0.9)	4.55 (n.d.)	5.24 (10.7)	4.00 (10.3)	4.03 (1.1)
H-5 ($J_{5,6}$)	4.16 (2.1)	4.33 (4.5)	4.01 (4.8)	3.82 (n.d.)	3.32 (7.7)
H-6 ($J_{6,6'}$)	4.40 (13.0)	3.84,(10.4)	4.36 (12.3)	3.53 (n.d.)	3.63 (9.8)
H-6' ($J_{5,6'}$)	4.15 (1.8)	3.88 (4.7)	4.24 (2.3)	3.53 (n.d.)	3.50 (5.4)
C-1 ($J_{C,F}$)	105.5 (227.0)	105.1 (227.4)	104.3 (216.7)	105.4 (227.1)	102.5 ---

a. II has previously been reported.[33]

b. The β configuration was confirmed by $J_{C,H}$ =179 Hz compared to $J_{C,H}$ ≈185 Hz for the α-anomers.

c. β-anomer H-1 (Glc) ($J_{1,2}$, $J_{1,F}$) = 5.21 (7, 53)

d. ^1H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ at 25 °C, 25mg/mL.

e. Chemical shifts of the ^1H NMR resonances are relative to Me_4Si (δ = 0) or $CHCl_3$ (δ = 7.24) and for ^{13}C NMR relative to $CDCl_3$ (δ = 77.0).

n.d., not determined

Since fluorides are formed easily from thioglycosides with DMTSB, the possibility exists that glycosidations with DMTSB are in essence two-step reactions, the first step being conversion of the thioglycoside into a glycosyl fluoride, which then reacts with the acceptor under promotion of boron trifluoride, formed in the first reaction. By first reacting the thioglycoside of entry IV with 1.0 eq. of DMTSB to yield the glycosyl fluoride as described, and then adding 1.0 eq. of ethyl 3-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside directly to the reaction mixture, the corresponding α1-2 disaccharide could be isolated in approximately 45% yield.[36]

This reaction was not further considered or optimized but the result shows nevertheless that the fluorides indeed can be intermediates in DMTSB promoted glycosylation as suggested above.

As seen in entry **VII** and **IX**, less reactive hydroxyl groups are not affected under the reaction condition used. However, in entry **VII**, prolonged reaction time (over the weekend) gave what appeared to be the 1,4-anhydro derivative in approximately 50% yield.[37] Attempts to react 2-hydroxy and 2,3-hydroxy thioglycosides under the given standard conditions gave several products besides the glycoside fluoride (which was rapidly destroyed) and was not further considered.

The reactions were performed in THF as solvent but proceed almost equally well in other ethers like diethyl ether or dioxane. Even diglyme is a suitable solvent. On the other hand solvents like DMF, dichloromethane, acetonitrile, or nitromethane gave mainly degradation products and/or unreacted starting material with no or only traces of the glycosyl fluoride. However, addition of only 5% THF to dichloromethane gave a major improvement of the yield (TLC results). This finding is consistent with the fact that the expected side product boron trifluoride reacts with ethers to form a complex whereby this strong Lewis acid is made less reactive. Boron trifluoride etherate has previously been reported as a promotor for glycosidation reactions.[13]

It has previously been reported that nitrosyl tetrafluoroborate can be used as a promotor in glycosidation reactions with thioglycosides.[5] We therefore investigated the formation of fluorides with this reagent and with some other electrophilic fluoroborate salts such as nitryl, tropylium, *p*-nitrophenyldiazonium, and trimethyloxonium tetrafluoroborate. We found (TLC results) that under the same conditions used with DMTSB the nitryl and

nitrosyl salts gave the expected product while the others did not react. Therefore it is possible that the reported promotion with nitrosyl tetrafluoroborate[5] can in fact also be glycosidation via the fluoride. However, the reaction did not proceed as cleanly as with DMTSB and the initially formed fluoride was rapidly converted to other products, while the DMTSB reaction product remained intact for a longer time. It is also possible that nitryl tetrafluoroborate could be used as promotor for glycosidation reactions which, to our knowledge, have not been tested.

In summary, we have shown that glycosyl fluorides can be obtained in a simple way from aryl or alkyl thioglycosides in high yield and under mild conditions. The simple workup procedure, washing and evaporation of the solvent (the by-products are water soluble or volatile except in the case of **V**) and eventually flash chromatography makes this reaction preparatively very useful. This further extends the usefulness of thioglycosides in oligosaccharide synthesis.

EXPERIMENTAL.

General Methods: The starting materials were synthesized according to: **I** and **IV**,[38] **II**,[39] **III** and **VII**,[40] **V**,[41] **VI**,[42] **VIII**,[43] **IX**.[44] All reactions were performed in anhydrous analytical grade solvents (Fluka). Powdered molecular sieves 4Å (Fluka) for reactions were activated at 300 °C under vacuum overnight. DMTSB was synthesized as described,[33] recrystallized from acetonitrile/ether, dried under vacuum and stored at room temperature. Reactions were performed in flame-dried vessels. HPTLC plates Si 60 (Merck) were used for TLC and developed by dipping in 5% H_2SO_4 and charring by warming. Flash chromatography was performed on Merck silica gel 60, 40-63μ with HPLC solvents for elution. NMR spectra were recorded with a Bruker AM 500 instrument.

Standard procedure for converting thioglycosides into glycosyl fluorides: To 1.0 g of the thioglycoside was added 20 mL THF and 2.0 g of 4Å molecular sieves. The suspension was stirred at room temperature for 5 minutes and then 1.2 eq. of DMTSB was added. The reaction was monitored by TLC with toluene/ethyl acetate 10:1 as mobile phase (except **IX**, 15:1 and **I**, toluene/ethyl

acetate/dichloromethane 4:2:1). When complete conversion was achieved, 0.5 mL of pyridine was added to quench the reaction. In all cases, except **VII**, almost no by-products could be observed besides a minor starting spot.

The reaction mixture was filtered directly into a separatory funnel and diluted with 50 mL ethyl acetate, washed twice with 0.5 M aqueous sulfuric acid, twice with saturated aqueous sodium bicarbonate and once with water. The organic phase was dried with magnesium sulfate and concentrated. Flash chromatography was performed by dissolving the residue in toluene and applying to a short column. Two column volumes of toluene were first passed through the column and thereafter the product was eluted with appropriate toluene/ethyl acetate mixtures. Appropriate fractions were collected and concentrated to dryness.

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