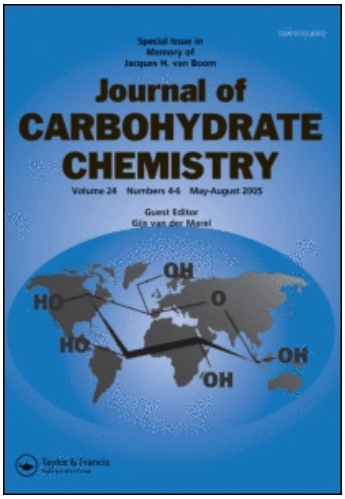

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SYNTHESIS OF *S*-GLYCOSYL XANTHATES BY PHASE TRANSFER CATALYZED SUBSTITUTION OF GLYCOSYL HALIDES

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ABSTRACT

Peracetylated glycosyl- and glycobiosyl bromides and chlorides **1-4** including acetochloroneuraminic acid **5** were stereoselectively transformed into their corresponding *S*-glycosyl xanthates **6-10** in high yield (91-98%) under phase transfer catalyzed conditions. The reactions occurred at room temperature using tetrabutylammonium hydrogen sulfate as the catalyst. The substitutions gave complete inversion of configuration and thus proceeded by an S_N2 type mechanism. Changing the organic solvent from methylene chloride to ethyl acetate had no detrimental effect on the outcome of the reactions but avoided an undesirable side reaction between the xanthate anion and methylene chloride.

INTRODUCTION

S-glycosyl xanthates[1-3] are versatile synthetic carbohydrate derivatives.[1-6] This family of compounds[6] and particularly the homologous *O*-ethyl *S*-sialyl dithiocarbonate[4,5] **10** have recently gained interest because of their use as efficient and stereoselective glycosyl donors in cases where the usual glycosyl halides and thioglycosides gave only modest results.[7] These *S*-glycosyl xanthates are also useful precursors to reducing sugars together with 1-deoxy and 1-thio- sugars as well as 1-thioglycosides.[1,6]

Previous syntheses of *S*-glycosyl xanthates have been relatively efficient. However, the finding that phase transfer catalysis (PTC) can be used as a general entry into a wide

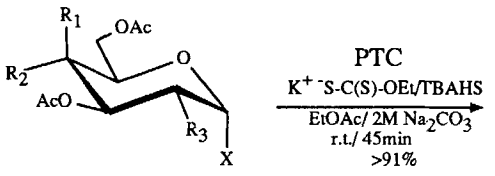
range of glycosyl derivatives, such as aryl *N*-acetylglucosaminides,[8] glycosyl phosphates[9] and azides[10] aryl 1-thiodisaccharides[11] and sialic acid derivatives[10,12,13] prompted us to apply PTC reaction conditions[8] for the synthesis of these derivatives.

RESULTS AND DISCUSSION

We have recently demonstrated[8-13] that phase transfer catalyzed nucleophilic displacements of a wide range of glycosyl halides could be best achieved at room temperature when tetrabutylammonium hydrogen sulfate (TBAHS) was used as the catalyst.[8] This catalyst, with its highly lipophilic cation and its non-nucleophilic (highly hydrophilic) counteranion, can be used in conjunction with various solvent combinations. Applying similar PTC conditions to the synthesis of *S*-glycosyl xanthates has now also proven to be effective. High yields of *S*-glycosyl xanthates were obtained under mild conditions using either methylene chloride or ethyl acetate and aqueous sodium carbonate or hydrogen carbonate. Moreover, the reactions were highly stereoselective since substitution occurred with inversion of configuration and no detectable products resulting from retention of the anomeric configurations were noticed in any of the crude reaction product mixtures (^{1}H, ^{13}C NMR). The PTC reactions were also found to be widely applicable to disaccharides,[11] to 2-acetamido-2-deoxy sugars,[8] and to the important family of sialic acid derivatives.[10,12,13]

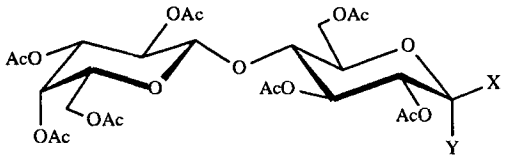
Thus, treatment of peracetylated glycosyl bromides or chlorides **1-5** having 1,2-*cis*-oriented participating groups (**1-4**) or a tertiary center (**5**) in either methylene chloride or ethyl acetate at room temperature with *O*-ethyl xanthic acid potassium salt (2 equiv), TBAHS as catalyst (1 equiv) and 2 M sodium carbonate as the aqueous phase gave almost quantitative yields of the corresponding 1,2-*trans* *S*-glycosyl xanthates. All the reactions were performed at room temperature and were completed within 45 min. The reactions occurred with complete anomeric inversion. Neither alternative anomers or glycosidic by-products were ever detected in the crude reaction mixtures by TLC, ^{1}H and ^{13}C NMR spectroscopy. The high yields obtained in the D-*gluco*-(**6**), D-*galacto*-(**7**) and D-*lacto*-(**9**) series are also noteworthy. Previous observations in our laboratories[12] have

pointed out the ease with which competitive dehydrohalogenation reactions occur in these series with nucleophiles of high basicities. In those cases, the above side reactions could sometimes account for almost 40% of the by-products encountered. In the present case, no such elimination reaction occur. The reactions were slightly faster in ethyl acetate than in methylene chloride. Control experiments have revealed that the *O*-ethyl *S*-potassium dithiocarbonate was consumed by reacting with methylene chloride when used as a solvent. Indeed, when the reaction was conducted in the absence of the glycosyl halides, methylene bis-(*O*-ethyl xanthate) [$(EtO\text{-}C(S)S)_2CH_2$] was obtained (CI-MS, ^1H and ^{13}C NMR) in good yields. Therefore, the reactions could be most efficiently performed in ethyl acetate without the use of a large excess of the nucleophilic reagent and thus avoiding an undesirable side reaction.

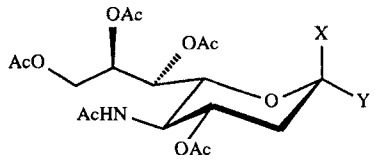


1 R_1=H, R_2=R_3=OAc, X=Br
2 R_1=R_3=OAc, R_2=H, X=Br
3 R_1=H, R_2=OAc, R_3=NHAc, X=Cl

6 R_1=H, R_2=R_3=OAc
7 R_1=R_3=OAc, R_2=H
8 R_1=H, R_2=OAc, R_3=NHAc



4 X=H, Y=Br
9 X=SC(S)OEt, Y=H



5 X=Cl, Y=CO_2Me
10 X=SC(S)OEt, Y=CO_2Me

The case of the sialic acid *S*-glycosyl xanthate **10** is also worthy of mention. The yield of chromatographically purified product (91%) compared well with the most recent synthesis (71%).[4] The β-chloride **5** was thus substituted with complete inversion to provide the α-xanthate **10**. The usual ease[7] with which derivative **5** forms the dehydrochlorination by-product is a clear indication that the reaction conditions used in the present study are quite mild. The importance of compound **10** is fully revealed with the recent finding that it can act as a powerful glycosyl donor in complex

sialyloligosaccharide syntheses.[4-5] Thus, access to this stable crystalline compound by the high yielding phase transfer catalyzed conditions described herein should provide further incentive for its use.

As previously mentioned, glycosyl xanthates can provide the corresponding 1-thioglycosides in high yield upon heating with sodium iodide in acetone.[1] Thus, treatment of **10** with sodium iodide in refluxing acetone (results not shown) provided sialic acid ethyl 2-thio-α-glycoside in almost quantitative yield (TLC). However, the above ethyl 2-thio-α-sialoside can also be synthesized directly from **5** and ethanethiol under the above PTC conditions (62% yield).[13]

Most of the above *S*-glycosyl xanthates were previously known compounds[6] and their physical data (mp, $[\alpha]_D$) are in good agreement with reported values. The fully assigned (HETCOR, COSY) ^1H and ^{13}C NMR spectroscopic data of **6-10** confirmed their anomeric configurations (Tables 1, 2). Although the sialic acid α-*S*-glycosyl xanthate **10** does not contain an anomeric proton, the anomeric configuration was inferred on the basis of the characteristic downfield shift of its H-3e signal relative to that of the β-anomer (Table 1). The H-3e signals in α-anomers of sialic acid are usually observed ~0.5 ppm downfield of those of the β-anomers.[14] This assignment was also confirmed by the chemical shift of H-4 (4.87 ppm, $CDCl_3$), a value typical of α-anomers.[4] There was no major effect on the chemical shift of this proton when the spectrum was taken in C_6D_6 (4.82 ppm, lit.,[4] 4.81 ppm).

In conclusion, a mild, highly stereoselective and high yielding entry into useful *S*-glycosyl xanthates has been performed under previously developed PTC conditions.[8-13] Readily available reagents were used. The reactions occurred with complete inversion of configuration at the anomeric centers and the method is also effective with a tertiary center as exemplified by the sialic acid derivative **10**. Application of this PTC methodology to other sialic acid derivatives has also proven to be very successful.[10,12,13]

EXPERIMENTAL

General Procedure. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter

TABLE 1. ^{1}H NMR Data of *S*-glycosyl xanthates **6-10** ($CDCl_3$, 300 MHz)[a]

Compound[b,c]		H-1 ($J_{1,2}$ Hz)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{6,6'}$)	H-6' ($J_{5,6'}$)	H-7 ($J_{6,7}$, $J_{7,8}$)	H-8 ($J_{8,9}$)	H-9 ($J_{9,9'}$)	H-9' ($J_{8,9'}$)
6		5.40 (10.4)	5.11 (9.0)	5.27 (9.3)	5.04 (9.9)	3.78 (4.9)	4.19 (12.5)	4.05 (2.2)	---	---	---	---
7		5.43 (9.7)	5.33 (9.2)	5.12 (3.4)	5.38 (3.3)		3.96 - 4.07 m		---	---	---	---
8		5.42 (10.9)	4.36 ---	5.06 - 5.22 (AB) (- - - , 9.4)		3.78 (4.9)	4.22 (12.5)	4.09 (2.3)	5.69(NH) ($J_{2,NH}$ 9.4)	---	---	---
9	Glc	5.41 (10.6)	5.07 (9.1)	5.28 (8.4)	3.80 (10.0)	3.72 (1.9)	4.43 (11.8)	4.03-4.14	---	---	---	---
	Gal	4.44 (7.9)	5.09 (10.4)	4.92 (3.5)	5.33 (1.2)	3.85 (6.8)	4.03 - 4.14 m (- - -, 6.8)					
10[d,e]		---	---	1.99(H-3a) ($J_{3a,3e}$ 12.9) ($J_{3a,4}$ 11.5)	4.87 (10.2)	4.00 (10.8)	4.55	---	5.27-5.32(AB) (1.7, -) (2.5)		4.31 (12.7)	4.17 (5.2)
				2.60(H-3e) ($J_{3e,4}$ 4.8)								

a. Assignments based on HETCOR and COSY experiments. Chemical shifts in ppm referenced to internal $CHCl_3$ at 7.24 ppm.

b. OAc, NAc: 1.85 - 2.13 ppm.

c. Ethyl: (CH_2): 4.57-4.62 (q, J 7.1 Hz) (**6-9**), 4.52 and 4.79 (dq, J 7.1, 10.6 Hz, **10**), (CH_3): 1.35-1.40 (t, **6-10**).

d. NH: 5.23 (J 9.8 Hz, **10**).

e. $CO_2\underline{Me}$: 3.78 ppm.

TABLE 2. ^{13}C NMR Data of compounds **6-10** ($CDCl_3$, 75.4 MHz)[a]

Compound[b]		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	CH_2	CH_3[c]
6		85.3	67.8	73.5	68.2	76.1	61.4	- - -	- - -	- - -	70.5	13.2
7		86.0	65.8	71.8	67.2	75.0	61.3	- - -	- - -	- - -	70.6	13.6
8		87.5	51.5	73.9	67.9	76.5	61.8	- - -	- - -	- - -	70.7	13.5
9	Glc	85.5	68.7	73.8	75.9	77.2	62.0	- - -	- - -	- - -	70.7	13.6
	Gal	101.0	69.0	70.9	66.6	70.7	60.8					
10[d,e]		168.7	86.5	37.1	68.9	48.9	75.2	67.8	70.4	62.1	70.5	13.3

a. Assignments based on HETCOR and COSY experiments. Chemical shifts in ppm referenced to internal $CDCl_3$ at 77.0 ppm.

b. Carbonyl (Ac): 169.1-170.3 ppm; CH_3 (OAc): 20.1-21.1 ppm; CH_3(NAc): 23.0-23.2 ppm (**8, 10**)

c. C = S: 209.8-210.5 ppm; 207.3 ppm (**10**)

d. $CO_2\underline{Me}$: 53.3 ppm

for 0.5-1.0% solutions in chloroform at room temperature unless stated otherwise. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 Spectrometer at 300 MHz in deuterochloroform solutions with references at 7.24 ppm ($CHCl_3$) and at 77.0 ppm ($CDCl_3$) respectively. Full spectral assignments were based on COSY and HETCOR experiments. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ) or Guelph Chemical Laboratories Ltd. (Ont.). All the per-*O*-acetylated glycosyl bromides **1,2,4** and chlorides **3,5** were prepared by the standard HBr-HOAc (35% w/w) (**1,2,4**)[15] or AcCl (**3**,[16] **5**[17]) procedures. The glycosyl halides were purified by silica gel column chromatography before use except for **5** (>95% pure by ^{1}H NMR). TLC was performed on silica gel 60-F254 plates using chloroform, ethyl acetate (5:1 - 1:1, v/v) containing (in some cases) 0.5% isopropyl alcohol as eluant; detection was made under UV light and by charring with the $CeSO_4/(NH_4)_6Mo_7O_{24}/H_2SO_4$ reagent. Column chromatography was performed on silica gel 60 (230-400 mesh, Merck No. 9385).

***O*-Ethyl *S*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl) dithiocarbonate (6).** The following represents a typical general procedure. To a solution of the appropriate glycosyl halide **1-5** (1 mmol), tetrabutylammonium hydrogen sulfate (TBAHS, 1 mmol) and *O*-ethyl xanthic acid potassium salt (Aldrich, MI, USA, 1.2 or 2 mmols) in methylene chloride (2 mmols KSC(S)OEt; 5 mL/mmol halide) or ethyl acetate (1.2 mmol KSC(S)OEt; 5 mL/mmol halide) was added 2 M sodium carbonate (5 mL/mmol halide) (or saturated sodium hydrogen carbonate). The two phase reaction mixture was vigorously stirred at room temperature until TLC showed disappearance of the starting halide (<45 min). Ethyl acetate (10 times the reaction volume) or methylene chloride was then added. The organic phase was separated and successively washed with saturated sodium hydrogen carbonate, water and brine. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford pure *S*-glycosyl xanthates **6-10**.

Compound **6** crystallized in the flask on standing at 4 °C and was obtained in 98% yield; mp 64.8-66.9 °C (prisms); $[\alpha]_D$ + 30.2° (*c* 1.0, chloroform); Lit.:[18] mp 88-89 °C (needles, dimorphic form); $[\alpha]_D$ + 30.8° (*c* 3.197, chloroform).

Anal. Calcd for $C_{17}H_{24}O_{10}S_2$: C, 45.13; H, 5.35; S, 14.17. Found: C, 45.16; H, 5.34; S, 14.29.

***O*-Ethyl *S*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl) dithiocarbonate (7).** The residue obtained after concentration of the organic extracts was chromatographed on a silica gel column using ethyl acetate-hexane (3:5, v/v) as eluant. The homogeneous fractions were concentrated to dryness to give pure **7** which crystallized on standing, 91% yield; mp 79.5-80.4 °C (CH_2Cl_2, ether, hexanes); $[\alpha]_D$ + 49.7° (*c* 0.95, chloroform); Lit.[1] 79-80 °C; $[\alpha]_D$ + 51.6° (*c* 1.0, chloroform).

Anal. Calcd for $C_{17}H_{24}O_{10}S_2$: C, 45.13; H, 5.35; S, 14.17. Found: C, 44.88; H, 5.12; S, 14.40.

***O*-Ethyl *S*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl) dithiocarbonate (8).** The oily residue obtained upon concentration of the organic extracts crystallized from ether-diisopropyl ether to give **8** in 91% yield; mp 139.0-140.2 °C; $[\alpha]_D$ + 33.3° (*c* 1.1, chloroform).

Anal. Calcd for $C_{17}H_{25}NO_9S_2$: C, 45.22; H, 5.58; N, 3.10; S, 14.20. Found: C, 45.02; H, 5.68; N, 3.04; S, 14.12.

***O*-Ethyl *S*-[2,3,6,-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl] dithiocarbonate (9).** The oily residue obtained upon concentration of the organic extracts was purified on a silica gel column eluted with methylene chloride-ethyl acetate (6:1, v/v) to provide pure **9** in 96% yield. Compound **9** was obtained as a foam and failed to crystallize; $[\alpha]_D$ + 2.3° (*c* 1.4, chloroform). Molecular weight for $C_{29}H_{40}O_{18}S_2$: 740, MS (CI-ether), 740.8 (1.1%, M + 1), 680.9 (4.4%, M-COS + 1), 619.1 (46.2%, M-EtOC(S)S).

***O*-Ethyl *S*-[Methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-α-D-*glycero*-D-*galacto*-2-nonulopyranosyl)onate] dithiocarbonate (10).** The oily residue obtained upon concentration of the organic extracts was purified by column chromatography over silica gel, using 1:2 toluene-ethyl acetate as eluant to provide pure **10** as a foam in 91% yield. Crystallization from benzene-pentane afforded **10** (72%); mp 98 °C; $[\alpha]_D$ + 84.7° (*c* 1.0, chloroform); Lit.[4] : mp 102-104 °C, $[\alpha]_D$ + 79° (*c* 1.0, chloroform). ^{1}H NMR spectra

were recorded for both $CDCl_3$ (Table 1) and C_6D_6 solutions for comparison with literature data.[4]

Anal. Calcd for $C_{23}H_{33}NO_{13}S_2$: C, 46.38; H, 5.58; N, 2.35; S, 10.77. Found: C, 46.45; H, 5.61; N, 2.41; S, 10.50.

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