Polish J. Chem., **75**, 49–54 (2001) **ORGANIC CHEMISTRY**

Carbohydrates Dithiocarbonic Acid Esters and Their Application in Glycosylation Reactions

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(Received July 11th, 2000; revised manuscript July 27th, 2000)

Allyl dithiocarbonic acid esters are used as efficient glycosyl donors in the presence of soft activators. Different glycosides are obtained in good yields, isomer α being the main product.

Key words: dithiocarbonates, glycosides, glycosylation

Carbohydrates play a significant role in biological systems [1]. As a part of glycoproteins, glycolipids and various other glycoconjugates they are involved in such processes as cell-cell communication, molecular and cellular targeting, immunological response, bacterial and viral infection [1,2]. The elucidation of these regulatory functions demands model glycoconjugates, therefore, the chemical synthesis of glycosides is a challenging task. The well-established glycosylation methods, like the classical Koenigs-Knorr glycosylation, thioglycoside or trichloroacetimidate method, are common, yet there are no general synthetic procedures available for the construction of complex oligosaccharides [3–7].

In their recent work Fraser-Reid and his co-workers introduced a 4-pentenyl group as a new effective leaving group at the anomeric centre of the glycosyl donor [8]. The glycosylation reactions were promoted by an iodonium ion: iodonium dicollidine perchlorate (IDCP) [9], N-iodosuccinimide/trifluoromethanesulfonic acid (NIS-TfOH) [10] or N-iodosuccinimide/triethylsilyl trifluoromethane sulphate (NIS-Et_3SiOTf) [11]. The addition of iodonium ion to the double bond results in the formation of a cyclic ion that alkylates the oxygen and initiates intramolecular cyclization. The so formed tetrahydrofuran acts as an efficient leaving group and allows a substitution reaction at an anomeric carbon atom. Taking into account the mechanism of nucleophilic substitution, one can expect that a soft thiocarbonyl group should be more prone to alkylation than a carbonyl group. Considering these facts we pursued the possibility of using O-glycosyl-S-alkyl dithiocarbonates as glycosyl donors. Pougny *et al*. used O-glycosyl-S-methyl xanthates as glycosyl donors with boron trifluoride dibutyl etherate ($BF_3 \cdot Et_2O$) as an activating agent, but with low stereoselectivity [12].

RESULTS AND DISCUSSION

A phase-transfer catalyzed reaction was reported to be an effective method of synthesis of dithiocarbonates [13]. It allows obtaining the demanded product in one-step reaction in good yields. Our investigations show that K_2CO_3 can be used instead of aqueous base solution in this reaction, still enabling high yields of dithiocarbonates. Another way is to use strong basic reagents (alkali metal, sodium hydride or sodium amide) with imidazole as a catalyst in an anhydrous solvent in order to obtain the intermediate alcoholate, which then reacts with carbon disulphide. A xanthate can be further alkylated by different alkyl halides [13]. All methods described above were optimized for allylic dithiocarbonates. Obtained derivatives are stable and do not decompose for several months.

During the first stage of research all efforts were focused on optimization of glycosylation process. We have investigated several promoters to assess the influence they have on stereoselectivity and on the yield of glycosylation reaction. The main goal was to create a method of synthesis of 1,2-*cis* glucosides. For the purpose of research 2,3,4,6-tetra-O-benzyl-1-O-[(allylthio-thiocarbonyl]-α-D-glucopyranose was used as a donor. Methanol was chosen as the most suitable acceptor. Methoxy group protons are easy to identify and integrate, thus allow a quick and effective analysis of a xanthate structure and α:β ratio. Data presented in Table 1 show that activation can be achieved with "soft" electrophiles – NIS, I_2, and IDCP – at room temperature. Reactions are complete in a short time, isomer α being the main product. It is worthy to point out that IDCP promoted reaction leads only to the α isomer. However, long reaction time restricts its use with less reactive acceptors.

Table 1. Glycosylation of 2,3,4,6-tetra-O-benzyl-O-[(allylthio)-thiocarbonyl]-α-D-glucopyranose.

Product	Reaction time	Activation	Yield	Selected NMR data		α:β
2a	0.5 h	NIS	70%	3.38 ($OCH_3\alpha$)	3.59 ($OCH_3\beta$)	2:1[a]
2a	1 h	I_2/TBABr	43%	3.30 ($OCH_3\alpha$)	3.51 ($OCH_3\beta$)	4:1[a]
2a	0.5 h	NIS/TfOH	85%	3.38 ($OCH_3\alpha$	3.58 ($OCH_3\beta$)	1:1[a]
2a	24 h	IDCP	50%	3.30 ($OCH_3\alpha$)		only α[a]
2b	0.5 h	NIS/TfOH	85%	H-1 signal buried		1:1[b]
2d	0.5 h	NIS/TfOH	20%	4.82 (3.66 Hz, H-1)		only α[c]
2c	1 h	NIS/TfOH	33%	4.7 (3.41 Hz, H-1)		only α[c]
2e	3 h	NIS/TfOH	49%	5.13 (3.75 Hz, H-1)		only α[c]
2f	24 h	NIS/TfOH	62%	5.52 (5.57 Hz, H-1) 4.81 (4.64 Hz, H-1′)		only α[c]

[a]Determined by ^{1}H NMR (methoxy protons); [b]determined by ^{1}H NMR (anomeric proton); [c]determined by ^{1}H NMR (anomeric protons).

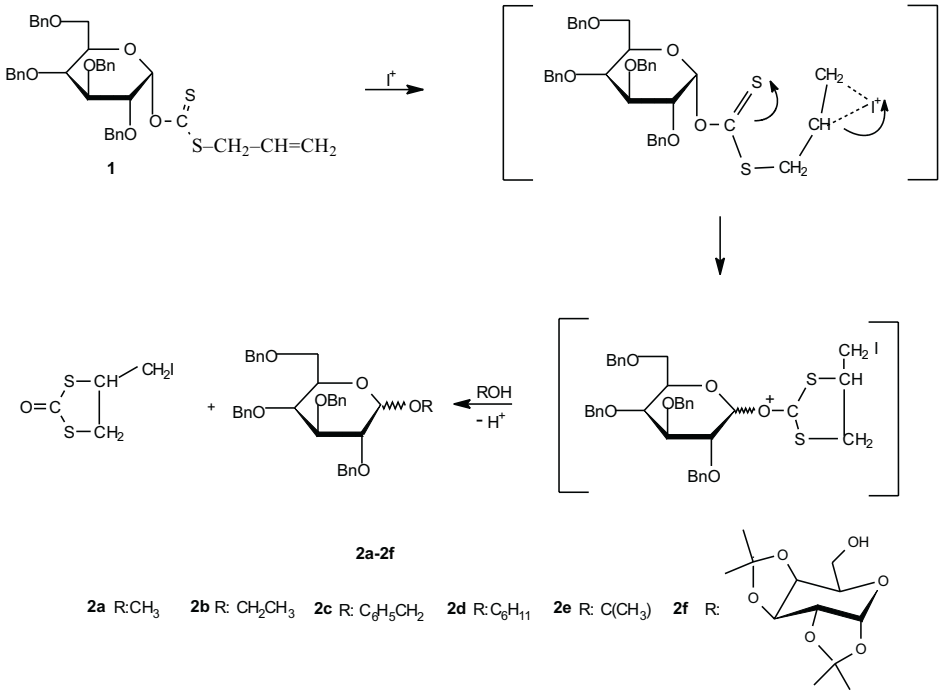
NIS in the presence of a catalytic amount of triflic acid was found to be the most effective for allylic dithiocarbonates activation. Average reaction time is 30 minutes,

whereby a mixture of glycosides was formed. We assumed that when methanol is exchanged for a bulk glycosyl acceptor, stereoselectivity would improve. This issue was examined on a series of different primary, secondary and tertiary alcohols (ethanol, benzyl alcohol, cyclohexanol and tert-butyl alcohol). The results show that bulk glycosyl acceptors cause an increase in stereoselectivity in favour of isomer α.

The reason for the formation of β-glycoside with methyl alcohol remains obscure. Partly it may be related to the very high reactivity of this glycosyl acceptor and its reaction, according to synchronic reaction at the anomeric carbon atom in the stage of cyclization. Steric hindrance of the hydroxyl group of the reacting alcohol was found to decrease the rate of glycosylation. One can expect that in these cases the reaction takes place according to the ion-pair mechanism with preferential formation of α-glycoside [14].

The most effective procedure – NIS/TfOH as promoter – was then applied in a disaccharide synthesis. ^{1}H-NMR spectra confirmed the formation of the α-glycosidic linkage and the structure of the product was established as 1,2:3,4-di-O-isopropylidene-6-O-[2,3,4,6–tert-O-benzyl-α-D-glucopyranose]-α-D-galactopyranose. Initially we considered an electrophilic process to the allylic bond that involves a cyclization reaction (Scheme 1).

Scheme 1



During the course of our study we were able to obtain a heterocyclic compound and establish its structure 4-(iodomethyl)-1,3-dithiolan-2-one (**3**) and thus prove the assumed mechanism of the glycosidation reaction.

Summing up, we have found that glycosyl allyl dithiocarbonates constitute interesting, reactive glycosyl donors, that can be activated under mild conditions, giving 1,2-*cis*-glycosides with high stereoselectivity. Further investigations on that class of compounds will be conducted in our laboratory.

EXPERIMENTAL

General methods. ^{1}H NMR spectra were recorded at 300 MHz with aVarian spectrophotometer for solutions in $CDCl_3$ (internal tetramethylsilane). All evaporations were performed under diminished pressure at 80°C. Column chromatography was performed on silica gel 60, Merck (70–230 mesh), eluted with toluene and toluene–ethyl acetate solvent systems: A 100:1, B 70:1, C 50:1 (v/v). All reactions were monitored by TLC on precoated plates of silica gel G (Merck); components were detected by spraying plates with palladium chloride in water (sulphur compounds) and 10% sulphuric acid in ethanol followed by heating.

Starting materials. 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose was prepared according to published procedures. Methanol, ethanol, cyclohexanol, benzyl alcohol, NIS, TfOH, TBABr, I_2, K_2CO_3, NaH, imidazole, carbon disulphide, allyl bromide and solvents are commercially available and were used without purification. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose and IDCP were prepared according to published procedures.

General procedures: Synthesis of 2,3,4,6-tetra-O-benzyl-1-O-[(allylthio)-thiocarbonyl]-α-D-glucopyranose (**1**). **Procedure A. Sodium hydride**. To a solution of tetra-O-benzyl-α-D-glucopyranose (0.26 mmol) in dry THF (3 ml), sodium hydride (0.26 mmol) and imidazole (catalytic amount) were added and the mixture was vigorously stirred at room temperature. Carbon disulphide (0.26 mmol) and then allyl bromide (0.26 mmol) were added, reaction was monitored by TLC (toluene/ethyl acetate, 8/1, v/v). Usually the reaction was complete after1 hour. The reaction mixture was filtered, toluene (5 ml) was added, the filtrate was washed with water (4×5 ml), dried over anhydrous $MgSO_4$ and concentrated. The remaining syrup was chromatographed on a silica gel column to give pure **1**; yield 80%.

Procedure B. Phase Transfer Catalysis (liquid/liquid system). A solution of tetra-O-benzyl--α-D-glucopyranose (0.29 mmol) in toluene (20 ml), tetrabutylammonium bromide (0.29 mmol) and 50% aqueous sodium or potassium hydroxide solution (10 ml) was vigorously stirred at room temperature. Carbon disulphide (0.29 mmol) and allyl bromide (0.29 mmol) were added and the reaction was monitored by TLC (toluene/ethyl acetate, 8/1, v/v); yield 92%.

Procedure C. Phase Transfer Catalysis (liquid/solid system). A solution of tetra-O-benzyl--α-D-glucopyranose (0.5 mmol) in dry acetone/toluene (10 ml), tetrabutylammonium bromide (0.5 mmol) and potassium carbonate (0.35 mmol) was stirred at room temperature. Carbon disulphide (0.5 mmol) and allyl bromide (0.5 mmol) were added and the heterogeneous mixture was stirred for 24 hours; yield 69%.

Procedure D. A solution of tetra-O-benzyl-α-D-glucopyranose (0.3 mmol) in dry toluene, sodium hydride (0.6 mmol) and imidazole (catalytic amount) was vigorously stirred at room temperature. Carbon disulphide (0.3 mmol) and allyl bromide (0.3 mmol) were added and the mixture was stirred for 24 hours; yield 51%.

2,3,4,6-Tetra-O-benzyl-O-[(allylthio)-thiocarbonyl]-α-D-glucopyranose (1). ^{1}H NMR δ: 3.50–3.83 (m, 6H), 4.05 (d, 2H, J_{gem} = 7.1 Hz), 4.40–5.04 (4AB, 8H, 4Ph$\underline{CH_2}$), 4.87 (d, 1H, J = 3.7 Hz, H-1), 5.16 (2dt, 1H, J_{cis} = 10.0 Hz, $J_{3',1'}$ = 1.2 Hz), 5.23 (2dt, 1H,J_{gem} = 2.7 Hz,$J_{3',1'}$ = 1.5 Hz), 5.85 (2dt, 1H, J_{trans} = 16.8 Hz, J_{cis} = 10.0 Hz,$J_{2',1'}$ = 6.8 Hz,), 7.2–7.4 (m, 20 H, Ph).

General procedures of glycosylation: Procedure 1. NIS, IDCP, I_2/TBABr. A solution of donor **1** (0.09 mmol) and acceptor **a** (0.18 mmol) in dry toluene (2 ml) was stirred in the presence of Drierite for 30 minutes at room temperature. After that time activator was added (0.12 mmol). The reaction was followed by TLC (toluene: ethyl acetate, 8/1, v/v). It was complete after 80 min. The reaction mixture was filtered and the filtrate was washed with 10% aqueous $Na_2S_2O_3$ solution (once), then with water (3×5 ml), dried over anhydrous $MgSO_4$ and concentrated. The remaining syrup was chromatographed through a silica gel column to give pure products.

Procedure 2. NIS/TfOH. A solution of donor **1** (0.06 mmol) and the acceptor **b–f** (0.12 mmol) in dry toluene (2 ml) was stirred in the presence of Drierite at room temperature. After 30 minutes NIS (0.06 mmol) and saturated solution of TfOH in toluene (0.006 mmol, *ca*. 0.15 M) were added (dropwise). The reaction was followed by TLC (toluene:ethyl acetate, 8/1, v/v). Work-up with triethylamine, 10% sodium thiosulphate and water (3×5 ml) followed by column chromatography afforded the products.

Methyl 2,3,4,6-tetra-O-benzylo-α,β-D-glucopyranoside (2a): Reaction of **1** with methanol according to **procedure 1** and **2** afforded **2a** as syrup. Isomers were separated. Isomer α: $[\alpha]_D^{24}$14.8 (c 1.0) {lit.[15] $[\alpha]_D^{25}$ 20.9 (c 0.7, $CHCl_3$)}. ^{1}H NMR δ: 3.38 (s, 3H, OCH_3), 3.52–3.78 (m, 5H), 3.98 (dd~t, 1H, J = 9.3 Hz,), 4.46–4.82 (AB, 2H, J = 10.6 Hz, Ph$\underline{CH_2}$), 4.47–4.60 (AB, 2H, J = 12.1 Hz, Ph$\underline{CH_2}$), 4.66–4.79 (AB, 2H, J = 12.1 Hz, Ph$\underline{CH_2}$), 4.80 (d, 1H, H-1, J = 2.6 Hz,), 4.81–4.99 (AB, 3H, J = 10.1 Hz, Ph$\underline{CH_2}$), 7.2–7.4 (m, 20H, Ph). Isomer β: $[\alpha]_D^{24}$ 4 15.0 (c 0.5) {lit. [16] $[\alpha]_D^{20}$ 11.4 (c 1.0, $CHCl_3$)}. ^{1}H NMR δ: 3.36–3.50 (m, 3H), 3.60–3.80 (m, 5H), 3.58 (s, 3H, OCH_3), 4.31 (d, 1H, H-1, J = 7.8 Hz,), 7.21–7.42 (m, 20H, Ph).

Ethyl 2,3,4,6-tetra-O-benzyl-α,β-D-glucopyranoside (2b): Reaction of **1** with ethanol according to **procedure 2** (NIS/TfOH) afforded **2b** as syrup. Isomer β: ^{1}H NMR δ: 1.23 (q, $OCH_2\underline{CH_3}$), 3.48 (t, $O\underline{CH_2}CH_3$), 3.6–3.74 (m), 3.78 (dd, 1H, J = 11.0 Hz, J = 2.7 Hz, H-6), 3.86–4.04 (m), 4.13 (ddd, H-5), 4.37 (s,1 H, H-1), 4.52 and 4.81 (AB, 2H, J = 10.6 Hz, Ph$\underline{CH_2}$), 4.57 and 4.63 (AB, 2H, J = 12.3 Hz, Ph$\underline{CH_2}$), 4.74 and 5.00 (AB, 2H, J = 11.2 Hz, Ph$\underline{CH_2}$), 4.78 and 4.98 (AB, 2H, J = 12.8 Hz, Ph$\underline{CH_2}$),7.2–7.4 (m, 20H, Ph). Isomer α: ^{1}H NMR δ: 1.2–1.3 (q, $OCH_2\underline{CH_3}$), 3.4–3.8 (m, 6H), 4.00 (ddd, H-5, 1H), 4.38–5.02 (m, 4Ph$\underline{CH_2}$, H-1), 7.2–7.4 (m, 20H, Ph).

1,2,3,4,6–Penta-O-benzyl-α-D-glucopyranoside (2c): Reaction of **1** with benzyl alcohol according to **procedure 2** (NIS/TfOH) afforded **2c** as syrup. Product was purified on a column of silica gel, yield 32.9%. $[\alpha]_D^{24}$ 4 39.2 (c 1.18) {lit. [17] $[\alpha]_D^{25}$ 55.8 (c 1.63, $CHCl_3$)}. ^{1}H NMR δ: 3.4–4.9 (m, 5H, H-2,3,5,6,6′), 4.05 (dd, 1H, J = 9.3 Hz, H-4), 4.4–5.10 (5AB, 10H, 5Ph$\underline{CH_2}$), 4.81 (d, 1H, J = 3.4 Hz, H-1), 7.22–7.42 (m, 25H, Ph).

Cyclohexyl 2,3,4,6–tetra-O-benzyl-α-D-glucopyranoside (2d). Reaction of **1** with cyclohexyl alcohol according to **procedure 2** (NIS/TfOH) afforded **2d** as syrup. Product was purified on a column of silica gel, yield 20%. $[\alpha]_D^{24}$ 41.9 (c 0.94) {lit. [18] $[\alpha]_D^{25}$ 42.0 (c1.0, $CHCl_3$)}. ^{1}H NMR δ: 1.2–2.00 (m, 9 H), 3.4–4.1 (m, 7H, H-2,3,4,5,6,6′, C_6H_{11}), 4.45 and 4.74 (AB, 2H, J = 12.0 Hz, Ph$\underline{CH_2}$), 4.46 and 4.83 (AB, 2H, J = 10.7 Hz, Ph$\underline{CH_2}$), 4.61and 4.65 (AB, 2H, J = 12.0 Hz, Ph$\underline{CH_2}$), 4.81 and 5.01 (AB, 2H, J = 11.0 Hz, Ph$\underline{CH_2}$), 4.96 (d, 1H J = 3.7 Hz, H-1), 7.2–7.41 (m, 20H, Ph).

Tert-butyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (2e): Reaction of **1** with t-butyl alcohol according to **procedure 2** (NIS/TfOH) afforded **2e** as syrup. $[\alpha]_D^{24}$ 40.6 (c 0.52) {lit. [19] $[\alpha]_D^{25}$ 41.5 (c 0.61, $CHCl_3$)}. ^{1}H NMR δ: 1.22 (s, 9H), 4.44 and 4.64 (AB, 2H, J = 12.2 Hz, Ph$\underline{CH_2}$), 4.46 and 4.83 (AB, 2H, J = 10.8 Hz, Ph$\underline{CH_2}$), 4.54 and 4.98 (AB, 2H, J = 10.5 Hz, Ph$\underline{CH_2}$), 4.66 and 4.72 (AB, 2H, J = 11.7 Hz, Ph$\underline{CH_2}$), 5.14 (d, 1H, J = 3.8 Hz, H-1), 7.2–7.4 (m, 20H, Ph).

1,2:3,4-Di-O-isopropylidene-6-O-[2,3,4,6–tert-O-benzyl-α-D-glucopyranose]-α-D-galactopyranose (2f): Reaction of **1** with **2** according to **procedure 2** afforded **2f** as syrup. Product was purified on a column of silica gel, yield 62.1%. $[\alpha]_D^{24}$ 15.2 (c 1.0) {lit. [20] $[\alpha]_D^{20}$ 11.0 (c 0.87, $CHCl_3$)}. ^{1}H NMR δ: 1.2 and 1.4 (2s, 12H, CH_3), 3.54–3.86 (m, 8 H), 3.87–4.08 (m, 5H), 4.16 (dd, 1H, J = 8.1 Hz, H-6′), 4.31 (dd, 1H, $J_{2,3}$ = 4.6 Hz, J_{12} = 2.2 Hz, H-2), 4.36 (dd, 1H, J = 8.1 Hz, H-6), 4.42–5.04 (m, 8H), 5.52 (d, 1H, J = 5.4 Hz, H-1), 7.2–7.4 (m, 20 H, Ph).

4-(Iodomethyl)-1,3-dithiolan-2-one (3): Glycosylation of **1** was performed according to **procedure 2**.The remaining syrup was chromatographed through a silica gel column. The product showing the highest R_f was isolated. The data obtained are in accordance with literature [21]. ^{1}H NMR δ: 4.26 (sextet with finer splitting, 1H), 3.54 (dd, 1H, $J_{4,4'}$ = 10.3 Hz, $J_{4,3}$ = 4.2 Hz, H-4), 3.68 (dd~t, 1H, $J_{4',4}$ = 10.5 Hz, H-4′), 3.79 (dd, 1H, $J_{1,1'}$ = 12.2 Hz, $J_{1,3}$ = 4.2 Hz, H-1), 3.91 (dd, 1H, $J_{1',1}$ = 12.2 Hz, $J_{1',3}$ = 5.1 Hz, H-1′).

Acknowledgments

Financial support from the Polish State Committee for Scientific Research (Grant No. 3 T09A 031 17) is gratefully acknowledged.

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