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Synthesis of N-Alkyl Thiocarbamates, Derivatives of Monosaccharides

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Thiocarbamates, derivatives of monosaccharides are conveniently prepared by treatment of sugars with allyl or methyl isothiocyanates in the presence of DBU.

Key words: isothiocyanates, thiocarbamates, sugar thiocarbamates

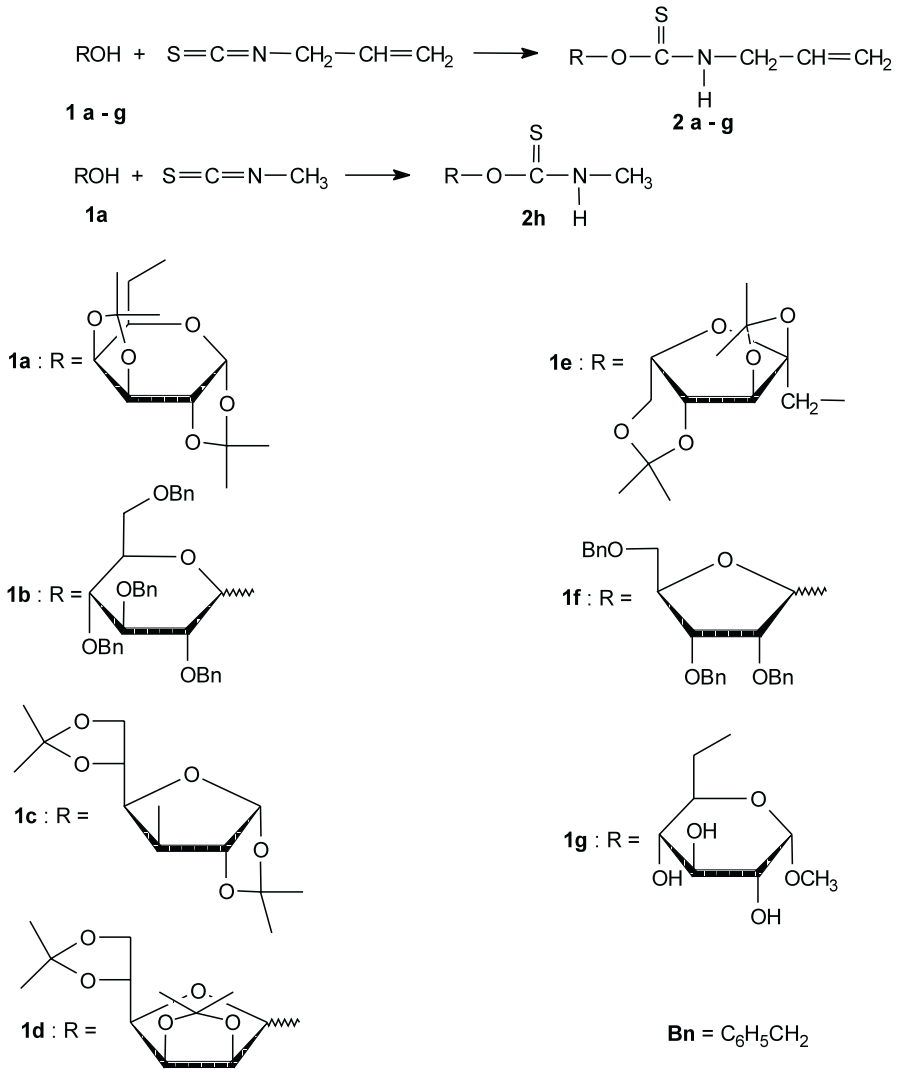
O-Alkyl thiocarbamates are valuable substrates in the synthesis of 1,3-thiazine derivatives [1,2]. A large number of thiazole, thiazoline, thiazolidine derivatives exhibit pharmacological and antifungal activity [2]. The family of thiocarbamates also gained interest because of their use as enzyme inhibitors in cancer treatment [3], bacterial infection [4] and as immunostimulants in Alzheimer or Parkinson deseases [5]. Many drug candidates, due to the low solubility in water, suffer from poor bioavailability and unfavourable distribution. It is well documented that derivatives of carbohydrates often constitute a biologically active form of natural, biologically active compounds [6]. Likewise there are numerous examples of synthetic drugs for which favourable tune up efficiency have been achieved by glycosidation [6].

We have concentrated on the synthesis of monosaccharide N-alkyl thiocarbamates that is a first step of a project devoted to the prodrug strategy. Conventional synthesis of N-alkyl thiocarbamate (addition of hydroxy derivatives) is restricted rather to primary alcohols [7], secondary ones are not reactive enough [8]. O-Alkyl thiocarbamates were also obtained by reaction of ammonium isocyanate, alcohols and alkyl halides albeit in low yield [9]. The main synthetic utility of O-sugar thiocarbamates consists of a radical deoxygenation of a secondary hydroxy group, by reduction of the imidazoyl thiocarbonyl derivatives, which are conveniently prepared by thiocarbamoylation of free hydroxy group with 1,1'-thiocarbonyl diimidazole [9]. Reaction of hydroxy groups of monosaccharides with benzyl isothiocyanate was studied by Austin and Balàz [10], but because of reversibility of this process, the method was not synthetically useful. Thus, an attempt was made to elaborate the synthetic procedure that would allow to obtain N-alkyl thiocarbamates, sugar derivatives.

RESULTS AND DISCUSSION

For the present study, the readily available, 1,2:3,4-di-O-isopropylidene-α-
-D-galactopyranose (**1a**) containing a reactive, primary hyd[illegible] was chosen as
a substrate. Treatment of **1a** with an excess of N-allyl iso[illegible]
toluene did not give, however, the expected product. The [illegible]
covered unchanged after several hours. The rate of a[illegible]
isocyanates and probably isothiocyanates can be increas[illegible]
with more powerful nucleophile+alcoholate [11, 12]. Nuc[illegible]
further increased in dipolar aprotic solvents, since they are s[illegible]
extent, and they exist in these solvents as more or less "naked
activations [13]. Taking this into account in a next series of ex[illegible]
with N-allyl isothiocyanate was performed in N,N-dimeth[illegible]
hexamethylphosphoroamide (HMPA) in presence of sodium
ganic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Go[illegible]
were obtained using DBU in DMF. In a series of optimization
position of solvents and the concentration of the base were eva[illegible]
were obtained in reaction of **1a** with allyl isothiocyanate
ene:HMPA (10:1 v/v), in the presence of potassium carbonate *a*

Scheme 1



It is noteworthy that good yields of N-alkyl thiocarbamate have also been obtained starting from unprotected glycoside such as methyl α-D-glucopyranoside. Addition of methyl α-D-glucopyranoside **(1g)** to allyl isothiocyanate, followed by acylation, results in formation of monosubstituted per-O-acetyl derivative **(2g)**. Under the proposed conditions, good regioselectivity was observed. The least sterically hindered primary hydroxy group underwent reaction and 6-O-thiocarbamate was obtained as the main product. Concluding, we have established simple and efficient method of synthesis of N-alkyl thiocarbamates, derivatives of carbohydrates. Study concerning biological activity and synthetic applications of these compounds is in progress.

EXPERIMENTAL

General methods. Optical rotations were measured with a Perkin Elmer 141 polarimeter using sodium lamp (589 nm) at room temperature. Elementar analyses were performed with a Perkin-Elmer 2400 analyzer. ^{1}H NMR spectra were recorded with a Varian 300 MHz spectrometer for solutions in $CDCl_3$ (internal TMS). TLC was performed on percoated plates of silica gel $60F_{254}$ (Merck), using toluene/ethyl acetate (2:1 v/v, system A) or hexane/ethyl acetate (3:1 v/v, system B) and the spots were visualized by spraying with sulphuric acid and palladium(II) chloride. Chromatographic purification was performed on silica gel 60 (Merck) 0.063–0.2 mm. All solutions were concentrated under diminished pressure at 40°C. Organic solutions were dried over anh. $MgSO_4$.

Starting materials. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (**1a**), 2,3,4,6-tetra-O--benzyl-D-glucopyranose (**1b**), 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**1c**), 2,3:5,6-di-O-isopropylidene-D-mannofuranose (**1d**), 2,3:4,6-di-O-isopropylidene-α-L-sorbofuranose (**1e**), 2,3,5-tri-O-benzyl-D-ribofuranose (**1f**) were prepared according to published procedures [15–17]. Methyl α-D-glucopyranoside (**1g**), N-allyl isothiocyanate, N-methyl isothiocyanate, DBU, K_2CO_3, solvents and molecular sieves 4 Å are commercially available (Aldrich, Merck, POCh) and were used without purification.

General procedure. Sugar **1a**–**g** (1 mmol) was dissolved in a mixture of toluene/HMPA (10:1 v/v, 3 ml/0.3 ml) containing micronised molecular sieves 4 Å (50 mg) and vigorously stirred at room temperature for 10 minutes. K_2CO_3 (1 mmol) and DBU (0.1 mmol for **1a** and **1b** or 1 mmol for **1c**, **1d**, **1e**, **1f** and **1g**) were added and after 10 minutes N-allyl isothiocyanate or N-methyl isothiocyanate (2 mmol) was added dropwise. The reaction was complete (TLC, for **1a** and **1b** system B; for **1c**, **1d**, **1e**, **1f** and **1g** system A) in four hours. The mixture was filtered, washed with 10% aqueous NaCl, dried, filtered, concentrated and the crude product was purified by column chromatography (hexane/ethyl acetate 8:1, 5:1 and 3:1 v/v).

1,2:3,4-Di-O-isopropylidene-6-O-[N-allyl thiocarbamoylo]-α-D-galactopyranose (2a). 72.4%, syrup, $[\alpha]_D^{20}$ –55.6^0 (c 0.55, $CHCl_3$), ^{1}H NMR δ: 1.30–1.52 (4s, 2x($\underline{CH_3}$)$_2$C=, 12H), 3.95 (d, 2H, J_{gem} = 7.0 Hz, -$^{1'}\underline{CH_2}^{2'}$CH=$^{3'}CH_2$), 4.18 (dq, 1H, $J_{5,6}$ = 3.9 Hz, $J_{5,6'}$ = 1.8 Hz, H-5), 4.28 (dd, 1H, $J_{4,5}$ = 8.1 Hz, H-4), 4.33 (dd, 1H, $J_{2,3}$ = 2.7 Hz, H-2), 4.43 (dd, 1H, $J_{5,6}$ = 3.6 Hz, H-6), 4.63 (dd, 1H, $J_{3,4}$ = 2.4 Hz, H-3), 4.80 (dd, 1H, J_{gem} = 11.7 Hz, H-6'), 5.12–5.16 (dq, 1H, J_{cis} = 10.2 Hz, $J_{3',1'}$ = 1.2 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.16–5.26 (dq, 1H, J_{gem} = 2.8 Hz, $J_{3',1'}$ = 1.5 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.53 (d, 1H, $J_{1,2}$ = 4.8 Hz, H-1), 5.74–5.92 (2dt, 1H, J_{cis} = 10.2 Hz, J_{trans} = 17.0 Hz, $J_{2',1'}$ = 6.5 Hz, -$^{1'}$CH$_2{}^{2'}\underline{CH}$=$^{3'}$CH$_2$), 6.47–6.54 (br.s, 1H, NH). Anal. Calcd. for $C_{16}H_{25}NO_6S$: C, 53.47; H, 7.01; N, 3.90; S, 8.92. Found: C, 53.45; H, 7.03; N, 3.92; S, 8.91.

2,3,4,6-Tetra-O-benzyl-1-O-[N-allyl thiocarbamoylo]-D-glucopyranose (2b). 72%, syrup, α:β = 1:3 (δ: 6.29 H-1α, δ: 4.42 H-1β), ^{1}H NMR δ: 3.62–4.00 (m, 6H, H-3, H-4, H-5, H-6', and -$^{1'}\underline{CH_2}^{2'}$CH=$^{3'}CH_2$), 4.10–4.30 (m, 2H, H-2, H-6), 4.42 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1β), 4.44; 4.58 (AB, 2H, J = 12.2 Hz, Ph$\underline{CH_2}$), 4.60; 4.80 (AB, 2H, J = 11.0 Hz, Ph$\underline{CH_2}$), 4.67; 4.74 (AB, 2H, J = 10.2 Hz, Ph$\underline{CH_2}$), 4.84; 4.98 (AB, 2H, J = 10.6 Hz, Ph$\underline{CH_2}$), 5.24–5.30 (dq, 1H, J_{cis} = 10.2 Hz, $J_{3',1'}$ = 1.2 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.24–5.38 (dq, 1H, J_{gem} = 2.8 Hz, $J_{3',1'}$ = 1.5 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.72–5.96 (2dt, 1H, J_{cis} = 10.2 Hz, J_{trans} = 17.1 Hz, $J_{2',1'}$ = 6.5 Hz, -$^{1'}$CH$_2{}^{2'}\underline{CH}$=$^{3'}$CH$_2$), 6.29 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1α), 6.42 – 6.48 (br. s, 1H, NH), 7.10–7.40 (m, 20H, Ph). Anal. Calcd. for $C_{38}H_{41}NO_6S$: C, 71.34; H, 6.46; N, 2.19; S, 5.01. Found: C, 71.31; H, 6.49; N, 2.17; S, 5.02.

1,2:5,6-Di-O-isopropylidene-3-O-[N-allyl thiocarbamoylo]-α-D-glucofuranose (2c). 72.3%, syrup, $[\alpha]_D^{20}$ –39.4^0 (c 1.98, $CHCl_3$), ^{1}H NMR δ: 1.25–1.58 (4s, 2×($\underline{CH_3}$)$_2$C=, 12H), 3.90 (d, 2H, J_{gem} = 7.0 Hz, -$^{1'}\underline{CH_2}^{2'}$CH=$^{3'}CH_2$), 4.00–4.28 (br. m, 5H, H-3, H-4, H-5, H-6 and H-6'), 4.68–4.75 (dd, 1H, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 3.7 Hz, H-2), 5.17–5.24 (dq, 1H, J_{cis} = 10.3 Hz, $J_{3',1'}$ = 1.2 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.24–5.28 (dq, 1H, J_{gem} = 2.8 Hz, $J_{3',1'}$ = 1.5 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.68–5.96 (2dt, 1H, J_{cis} = 10.3 Hz, J_{trans} = 17.1 Hz, $J_{2',1'}$ = 6.5 Hz, -$^{1'}$CH$_2{}^{2'}\underline{CH}$=$^{3'}$CH$_2$), 5.86 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 6.37 (br. s, 1H, NH). Anal. Calcd. for $C_{16}H_{25}NO_6S$: C, 54.67; H, 7.29; N, 3.75; S, 8.59. Found: C, 54.65; H, 7.31; N, 3.73; S, 8.60.

2,3:5,6-Di-O-isopropylidene-1-O-[N-allyl thiocarbamoylo]-D-mannofuranose (2d). 70.5%, syrup, α:β = 1:1 (δ: 5.38 H-1α, δ: 4.63 H-1β), ^{1}H NMR δ: 1.25–1.52 (4s, 2×($\underline{CH_3}$)$_2$C=, 12H), 3.86 (d, 2H, J_{gem} = 7.0 Hz, -$^{1'}\underline{CH_2}^{2'}$CH=$^{3'}CH_2$), 4.00–4.14 (m, 3H, H-3, H-4, H-6 and H-6'), 4.14–4.23 (m, 1H, H-5), 4.36–4.46 (m, 1H, H-3), 4.63 (d, 1H, $J_{1,2}$ = 5.7 Hz, H-1β), 4.80–4.88 (m, 1H, H-2), 5.16–5.28 (dq, 1H, J_{cis} = 10.3 Hz, $J_{3',1'}$ = 1.2 Hz, -$^{1'}$CH$_2{}^{2'}$CH=$^{3'}\underline{CH_2}$), 5.22–5.30 (dq, 1H, J_{gem} = 2.8 Hz, $J_{3',1'}$ = 1.5 Hz,

-$^{1'}CH_2{}^{2'}CH=^{3'}\underline{CH_2}$), 5.38 (d, 1H, $J_{1,2}$ = 2.1 Hz, H-1α), 5.76–5.96 (2dt, 1H, J_{cis} = 10.3 Hz, J_{trans} = 17.1 Hz, $J_{2',1'}$ = 6.6 Hz, -$^{1'}CH_2{}^{2'}\underline{CH}=^{3'}CH_2$), 6.37 (br. s, 1H, NH). Anal. Calcd. for $C_{16}H_{25}NO_6S$: C, 53.47; H, 7.01; N, 3.90; S, 8.92. Found: C, 53.55; H, 7.23; N, 3.83; S, 9.02.

2,3:4,6-Di-O-isopropylidene-1-O-[N-allyl thiocarbamoylo]-α-L-sorbofuranose (2e). 69.9 %, white sediment, m.p. = 140° C, $[\alpha]_D^{20}$–2.2^0 (c 0.5, $CHCl_3$), ^{1}H NMR δ: 1.25–1.51 (4s, 2x($\underline{CH_3}$)$_2$C=, 12H), 3.98 (d, 2H, J_{gem} = 7.0 Hz, -$^{1'}\underline{CH_2}{}^{2'}CH=^{3'}CH_2$), 4.03–4.85 (m, 2H, H-6 and H-6'), 4.16–4.24 (m, 1H, H-5), 4.32 (dd, 1H, $J_{4,3}$ = 10.9 Hz, $J_{4,5}$ = 2.2 Hz, H-4), 4.48 (br.s, 1H, H-3), 4.63 (d, 1H, $J_{1,1'}$ = 11.72 Hz, H-1), 4.93 (d, 1H, $J_{1',1}$ = 11.72 Hz, H-1'), 5.16–5.24 (dq, 1H, J_{cis} = 10.2 Hz, $J_{3',1'}$ = 1.2 Hz, -$^{1'}CH_2{}^{2'}CH=^{3'}\underline{CH_2}$), 5.20–5.30 (dq, 1H, J_{gem} = 2.8 Hz, $J_{3',1'}$ = 1.5 Hz, -$^{1'}CH_2{}^{2'}CH=^{3'}\underline{CH_2}$), 5.75–5.96 (2dt, 1H, J_{cis} = 10.2 Hz, J_{trans} = 17.3 Hz, $J_{2',1'}$ = 6.5 Hz, -$^{1'}CH_2{}^{2'}\underline{CH}=^{3'}CH_2$), 6.42 (br. s, 1H, NH). Anal. Calcd. for $C_{16}H_{25}NO_6S$: C, 53.47; H, 7.01; N, 3.90; S, 8.92. Found: C, 53.45; H, 7.03; N, 3.87; S, 8.94.

2,3,5-Tri-O-benzyl-1-O-[N-allyl thiocarbamoylo]-D-ribofuranose (2f). 75%, syrup, α:β = 1:2.5 (δ: 4.64 H-1α, δ: 3.64 H-1β), ^{1}H NMR δ: 3.54–3.62 (m, 2H, H-5 and H-5'), 3.64 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1β), 3.72–3.80 (m, 1H, H-2), 3.97 (d, 2H, J_{gem} = 7.0 Hz, -$^{1'}\underline{CH_2}{}^{2'}CH=^{3'}CH_2$), 4.04–4.09 (m, 1H, H-3), 4.16–4.22 (m, 1H, H-4), 4.32; 4.42 (AB, 2H, J = 11.2 Hz, Ph$\underline{CH_2}$), 4.64 (s, 1H, H-1α), 4.48; 4.56 (AB, 2H, J = 12.0 Hz, Ph$\underline{CH_2}$), 4.74; 4.88 (AB, 2H, J = 12.2 Hz, Ph$\underline{CH_2}$), 5.08–5.12 (dq, 1H, J_{cis} = 10.0 Hz, $J_{3',1'}$ = 1.2 Hz, -$^{1'}CH_2{}^{2'}CH=^{3'}\underline{CH_2}$), 5.14–5.18 (dq, 1H, J_{gem} = 2.8 Hz, $J_{3',1'}$ = 1.5 Hz, -$^{1'}CH_2{}^{2'}CH=^{3'}\underline{CH_2}$), 5.62–5.78 (2dt, 1H, J_{cis} = 10.0 Hz, J_{trans} = 17.6 Hz, $J_{2',1'}$ = 6.6 Hz, -$^{1'}CH_2{}^{2'}\underline{CH}=^{3'}CH_2$), 6.0 (br. s, 1H, NH), 7.1–7.4 (m, 20H, Ph). Anal. Calcd. for $C_{30}H_{33}NO_5S$: C, 69.34; H, 6.40; N, 2.70; S, 6.17. Found: C, 69.30; H, 6.42; N, 2.72; S, 6.20.

Methyl 2,3,4-tri-O-acetyl-6-[N-allyl thiocarbamoylo]-α-D-glucopyranoside (2g). Reaction of **1g** with allyl isothiocyanate according to the general procedure in 6 hours in acetic anhydride (4.4 mmol), and pyridine (4.62 mmol) and stirring was prolonged for 12 hours. The mixture was filtered, washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated and the crude product was purified by column chromatography (system B) to afford **2g** syrup in 69.5% yield, $[\alpha]_D^{20}$ 62.2^0 (c 1, $CHCl_3$), ^{1}H NMR δ: 2.00–2.20 (3s, 9H, 3×OAc), 3.41 (s, 3H, OCH_3), 4.00 (m, 1H, H-5), 4.08–4.22 (m, 3H, H-6', -$^{1'}\underline{CH_2}{}^{2'}CH=^{3'}CH_2$), 4.24–4.32 (dd, 1H, $J_{6,6'}$ = 12.3 Hz, $J_{6,5}$ = 4.6 Hz, H-6), 4.88–4.95 (dd, 1H, $J_{4,3}$ = 10.0 Hz, $J_{4,5}$ = 3.6 Hz, H-4),4.98 (

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