Facile Synthesis of 1,2-*trans*-Nitrophenyl-1-Thioglycopyranosides

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1,2-*trans*-2-Nitro-, 4-nitro- and 2,4-dinitrophenyl-1-thioglycopyranosides were synthesized in high yield by condensation of per-*O*-acetyl-1-thioglucose with the appropriate nitro- or dinitrofluorobenzene in the presence of potassium carbonate. The pseudothiourea precursor was also used under these coupling conditions. 1,2-*trans*-4-Nitrophenyl-1-thioglycosides derived from β-D-galactose, β-D-xylose, α-L-arabinose and maltose were also obtained in good yield.

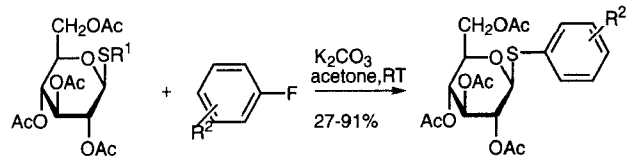
1-Thioglycosides are an important class of sugar derivatives. They are potent tools in studies on glycosylhydrolases in which they may either serve as inducers, competitive inhibitors, or as ligands for affinity chromatography.[1-5] Furthermore, during recent years, thioglycosides have been increasingly used in the synthesis of oligosaccharides because they are stable glycosyl donors[6-8] and may act as disarmed or armed synthons.[9]

Over the years, two main general methods for thioglycosylation have been reported. The first one involved the condensation of acetyl glycosyl halides with thiophenol in the presence of bases in different solvents.[5,8-12] The alternative method involved the coupling of per-*O*-acetylated compounds with thiols under acidic conditions.[13,14] De-*O*-acetylation,[10] the formation of anomeric mixtures[14] and the use of noxious and toxic thiophenol and solvent are the main drawbacks of these two methods. Two other methods which suppressed these drawbacks have also been reported. The first one is the free-radical addition of 1-thiosugars to alkenes;[15] the second is the reaction of glycosyl thiocyanates with Grignard reagents.[16]

In this paper we report a new, simple and effective method for the syntheses of peracetylated 1,2-*trans*-nitrophenyl-1-thioglycosides, involving an aromatic nucleophilic substitution of nitrofluorobenzene by acetylated pseudothiourea derivatives or 1-thioglycoses.

The general procedure for the preparation of acetylated pseudothioureas like **1** involves refluxing a solution of glycosyl halides, prepared from their corresponding per-*O*-acetylated precursors, with thiourea in acetone. During the reflux, the pseudothiourea derivatives may crystallize and a reductive cleavage as described by Černý et al[17] affords the expected 1-thiocompound **2** by direct crystallization (30–70% overall yield from the per-*O*-acetylated precursor). In some instances, acetylated 1-thio-β-D-glycoses may also be obtained by treatment of pseudothiourea derivatives with sodium or potassium carbonate.[18]

In the present investigation it has been found (Scheme 1) that 1-thio-β-D-glucose tetraacetate **(2)** on reaction with 2-nitro-, 4-nitro- and 2,4-dinitrofluorobenzenes **3a–c** in the presence of potassium carbonate, afforded the expected compounds **4a–c** in high yield (Table). The in situ cleavage of the isothiouronium salt **1** was also achieved but required extensive time at room temperature (24 h) to drive the reaction to completion.



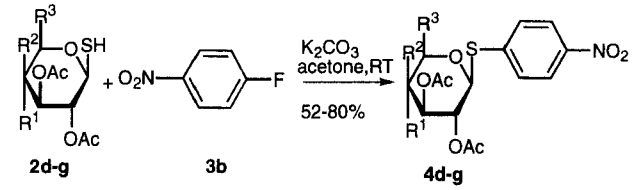
1 R^1 =C(NH_2)NH•HBr **3a-c** **4a-c**

2a R^1 =H

3, 4	R^2
a	2-NO_2
b	4-NO_2
c	2,4-NO_2

Scheme 1

4-Nitrophenyl-1-thio-β-D-galactopyranoside **4d**, β-D-xylopyranoside **4e**, α-L-arabinopyranoside **4f** and β-maltoside **4g** were also prepared from thiols **2d–g** by reacting with 4-fluoronitrobenzene **(3b)** (Scheme 2, Table).



2d-g **3b** **4d-g**

2, 4	R^1	R^2	R^3
d	H	OAc	CH_2OAc
e	OAc	H	H
f	H	OAc	H
g	α-Glc(OAc)4	H	CH_2OAc

Scheme 2

The simplicity and versatility of the proposed procedure for the synthesis of 1,2-*trans*-nitrophenyl-1-thioglycosides may encourage the use of these compounds in future.

Per-*O*-acetyl sugars[19] and 1-thioglycoses[17,18] were prepared according to well known procedures. A Büchi 535 melting point apparatus was used for measuring melting points. Optical rotations were determined at r.t. in $CHCl_3$ with a Perkin-Elmer 241 polarimeter.

Table. Compounds **4a–g** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)		$[\alpha]_D$		^{13}C NMR ($CDCl_3$/TMS), δ (sugar ring carbons)
			found	reported	found (c, $CHCl_3$)	reported	
4a	0.5	82	147–148	140[21]	−85 (0.5)	−67[21]	84.2 (C-1), 76.0, 73.8, 68.4, 68.2, 62.3
4b	0.3 (24)[b]	81 (27)[c]	183–184	177–183[1]	−34 (0.8)	−33[1]	84.1 (C-1), 75.9, 73.4, 69.5, 67.9, 61.9
4c	0.3	91	203–204	200–201[22]	−96 (0.5)	−104[22]	83.2 (C-1), 76.4, 73.5, 69.2, 68.0, 62.2
4d	4	54[d,e]	157	158–159[9]	−12 (0.7)	−7[9]	84.4 (C-1), 74.6, 71.4, 67.4, 66.5, 61.5
4e[f]	3	52[d]	155		−80 (0.6)		84.7 (C-1), 70.8, 69.4,. 67.9, 64.6
4f[f]	2	55[d]	145		−30 (0.7)		84.8 (C-1), 69.8, 69.3, 67.0, 64.7
4g[f]	2	80	166		−40 (0.9)		95.5 (C-1'), 83.7 (C-1), 76.2, 75.9, 72.3, 70.2, 69.8, 69.0, 68.5, 67.4, 62.6, 61.3

[a] Yield of pure compound isolated after one crystallization.
[b] From isothiouronium salt.
[c] From per-*O*-acetylated β-D-glucose.
[d] From isothiouranium salts.
[e] In this case an anomeric mixture was obtained (α/β = 1 : 3).
[f] Satisfactory microanalyses obtained: C ± 0.08, H ± 0.10, N ± 0.01, S ± 0.20.

The NMR spectra were recorded with a Bruker AC 300 at 303°C in $CDCl_3$ with TMS as external standard. All reactions were performed in dried solvent and monitored by TLC (Merck F 254) using petroleum ether (bp 40–65°C/EtOAc 2:1) as developing eluent. Detection was effected by observation under UV light, then dipping into H_2SO_4/MeOH/H_2O mixture and charring.

1,2-*trans*-Nitrophenyl-1-thioglycosides; General Procedures:
From Pseudothiourea Derivative **1**: The crude bromide obtained from penta-*O*-acetyl β-D-glucopyranose (1 mmol) by the described procedure[20] was dissolved in acetone (10 mL) and thiourea was added (0.08 g, 1.1 mmol). After refluxing for 30 min under stirring and cooling, TLC revealed the absence of the bromide. To this solution were added sequentially 4-nitrofluorobenzene (**3b**; 0.14 g, 1 mmol), K_2CO_3 (0.2 g) and H_2O (0.4 mL). The resulting mixture was stirred 1 d at r.t., then diluted with CH_2Cl_2 (20 mL), filtered and evaporated. The expected thioglycoside **4b** was isolated by crystallization from EtOH.

From 1-Thioglycoses **2a, 2d–2g:** To a well-stirred suspension of K_2CO_3 (0.2 g) in acetone (20 mL) were added sequentially 1-thioglycose (1 mmol), 4-nitrofluorobenzene (**3b**; 1.1 mmol) and H_2O (0.1 mL). The resulting mixture was stirred at r.t. for 0.3–4 h (Table), diluted with CH_2Cl_2 (20 mL), filtered and the solution was evaporated. The expected compound was isolated by crystallization from EtOH.

4e: ^1H NMR ($CDCl_3$): δ = 2.05, 2.08 (s, 9H, CH_3), 3.53 (dd, J = 7.7, 12.1 Hz, 1H, H-5a), 4.32 (dd, J = 4.5, 12.1 Hz, 1H, H-5b), 4.92 (ddd, J = 4.5, 7.4, 7.7 Hz, 1H, H-4), 4.97 (t, J = 7.4 Hz, 1H, H-2), 5.04 (d, J = 7.4 Hz, 1H, H-1), 5.18 (t, J = 7.4 Hz, 1H, H-3), 7.51, 8.03 (m, 4H_{arom}).

4f: ^1H NMR ($CDCl_3$): δ = 2.02, 2.04, 2.06 (s, 9H, CH_3), 3.75 (dd, J = 2.4, 12.6 Hz, 1H, H-5a), 4.17 (dd, J = 4.9, 12.6 Hz, 1H, H-5b), 5.01 (d, J = 7.0 Hz, 1H, H-1), 5.15 (dd, J = 3.3, 7.9 Hz, 1H, H-3), 5.25 (dd, J = 7.0, 7.9 Hz, 1H, H-2), 5.31 (m, 1H, H-4), 7.52, 8.05 (m, 4H_{arom}).

4g: ^1H NMR ($CDCl_3$): δ = 1.98, 2.00, 2.02, 2.04, 2.06 (s, 21H, CH_3), 3.76 (m, 1H, H-5), 3.95 (m, 2H, H-4, H'-5), 4.05 (dd, J = 2.3, 12.4 Hz, 1H, H-6a), 4.21 (dd, J = 4.5, 12.4 Hz, 2H, H-6a, H'-6b), 4.51 (dd, J = 2.6, 12.4 Hz, 1H, H-6b), 4.82 (dd, J = 4.0, 7.5 Hz, 1H, H'-2), 4.83 (t, J = 9.0 Hz, 1H, H-2), 4.84 (d, J = 9.0 Hz, 1H, H-1), 5.01 (t, J = 10.0 Hz, 1H, H'-4), 5.29 (m, 2H, H-3, H'-3), 5.36 (d, J = 4.0 Hz, 1H, H'-1), 7.51, 8.10 (m, 4H_{arom}).

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