Synthesis of 2-Deoxyglycopyranosyl Thioureas from Glycals

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Abstract: The reaction of glycals with phenylselenenyl chloride followed by treatment with KNCS lead to 2-deoxy-2-phenylselenoglycopyranosyl isotiocyanates which were further transformed into 2-deoxyglycopyranosyl thioureas.

Key words: glycals, 2-deoxysugars, thioureas, isothiocyanates, phenylselenenyl chloride

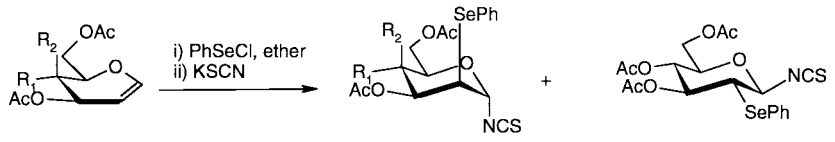
Sugar isothiocyanates are versatile synthetic intermediates in carbohydrate chemistry. By exploiting the strong electrophilic character of the NCS group, a wide variety of other functional groups can be accessed which, in turn, may be subjected to other transformations. The synthesis, chemistry and preparative applications of sugar isothiocyanates have been previously reviewed.[1,2] Glycals are also very versatile intermediates, especially in the synthesis of 2-deoxyglycosides, and different reports have exhaustively covered their synthetic applications.[3-8] In particular, the reactions of glycals with electrophilic sulfur and selenium reagents have been studied[9-17] and the factors controlling the stereoselectivity course of the reactions elucidated.[14] By application of these reactions, the introduction of nitrogen in the anomeric position was achieved using phenylselenenyl azide[18] or phenylselenenyl chloride followed by *N*-glycosidation with bis(trimethylsilyl)uracil[19] allowing the synthesis of 2-deoxyglycosyl azides and 2'-deoxypyranosyl nucleosides, respectively.

In this domain we have described[20] the application of glycals as glycosyl isothiocyanate precursors and reported a very convenient route for the simultaneous introduction of the iodo and isothiocyanate functionalities in a sugar molecule. Electrophilic addition of iodine(I) thiocyanate, generated in situ from silica supported KSCN and iodine, to the double bond leads exclusively to *trans*-2-deoxy-2-iodoglycopyranosyl isothiocyanates. The methodology is relevant for its efficiency, good stereoselectivity and simplicity.

We now report the synthesis of 2-deoxy-2-phenylselenoglycopyranosyl isothiocyanates and their transformation into 2-deoxyglycopyranosyl thioureas from glycals. Tri-*O*-acetyl-D-glucal (**1**) and -galactal (**2**) were chosen as starting materials. Reaction of **1** with phenylselenenyl chloride was followed by in situ addition of silica supported KSCN using ether as solvent. The *trans* addition compounds **3** (α-D-*manno*) and **4** (β-D-*gluco*) were isolated in 29 and 33% yield, respectively. However, when **2** was used only the stereoisomer with α-D-*talo* configuration **5** was obtained in 40% yield. The assignment of the product stereochemistry was based on vicinal proton $^3J_{H,H}$ and geminal heteronuclear $^1J_{C1,H1}$ coupling constants (see Table 2 and 3). Typically, H-1 for the β-gluco product **4** appeared at δ = 4.67 as a doublet ($J_{1,2}$ = 10.0 Hz), with H-2 appearing at δ = 3.15 as a triplet ($J_{1,2} \approx J_{2,3}$). In the case of the α-manno (**3**) and α-talo (**5**) isothiocyanates H-1 appeared at δ = 5.82 and 5.88 as a doublet ($J_{1,2}$ = 1.7 and 1.3 Hz), respectively, and H-2 appeared at δ = 3.98 and 3.60 as a doublet of doublets ($J_{2,3}$ = 4.4 Hz).

In agreement with these assignations is the observed $^1J_{C1,H1}$ values that for the α-glycosylpyranosyl isothiocyanates **3** and **5** (with an equatorial H-1) are higher (≈177 Hz) that in the case of the β-isothiocyanate **4** (with an axial H-1) (163.4 Hz). This is in accordance with the known rule that correlates the values of the heteronuclear coupling constant $^1J_{C1,H1}$ and the anomeric configuration[21] that is of special value in the case of the *manno* series. A literature survey regarding the value of this constant for glycosyl isothiocyanates indicates that this data is only available in two cases, namely, compounds **12** and **13** having an α-anomeric configuration.[22] In order to have more data, the $^1J_{C1,H1}$ coupling constant of other glycopyranosyl isothiocyanates were measured. An analysis of the results obtained (see Scheme 3) corroborate the tendency of the α-anomers to have higher values (>170 Hz) for this constant than the β-anomers (<170 Hz).

2-Deoxy-2-phenylselenoglycopyranosyl thioureas **6-8** were now prepared in high yield by reaction of com-



1 R_1= OAc; R_2= H
2 R_1= H; R_2= OAc

3 R_1= OAc; R_2= H; 29%
5 R_1= H; R_2= OAc; 40%

4; 33%

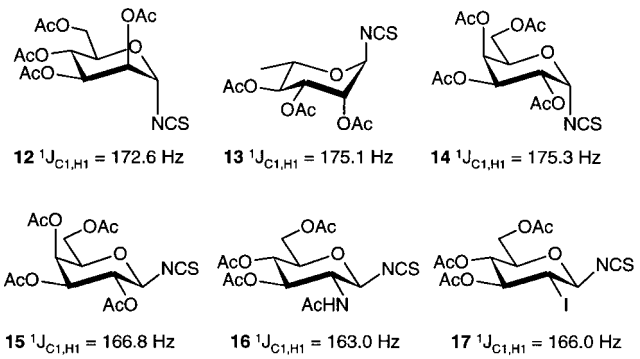
Scheme 1

Table 1 Experimental Yields and Physical Data for Compounds **3–8** and **11**

Product	Yield (%)	mp (ºC)	$[\alpha]_D$ (*c*, $CHCl_3$)[a]	IR ν (cm^{-1})	MS *m/z*
3	29	119–120	+130 (0.9)	2036, 2109, 1741	_b
4	33	96–97	– 37 (0.6)	2037, 1747	_b
5	40	syrup	+238 (1.2)	2007, 1749	CI: 429 $[M - NCS]^+$
6	100	77–78	+ 67 (0.3)	3551, 3414, 1746, 1618, 1233	_b
7	93	92	+ 14 (0.4)	3418, 3332, 1749, 1619, 1231	_b
8	100	syrup	+ 59 (2)	3320, 3204, 1746, 1244	FAB+: $C_{19}H_{24}N_2O_7SeS$ Calcd for $[M + Na]^+$ 527.0367. Found 527.0365
9[13]	80				
10[13]	73				
11	100	162–164	– 32 (1)	3427, 3358, 1740, 1714, 1556	_b

[a] Recorded at 23°C.
[b] Satisfactory microanalyses obtained: C, ±0.45; H, ±0.31; N, ±0.27; S, ±0.42. Exception, **7**: C +0.51.

pounds **3-5** with an excess of ammonia at 0 ºC. 2-Deoxyglycopyranosyl thioureas **9-11** were then accessed in good



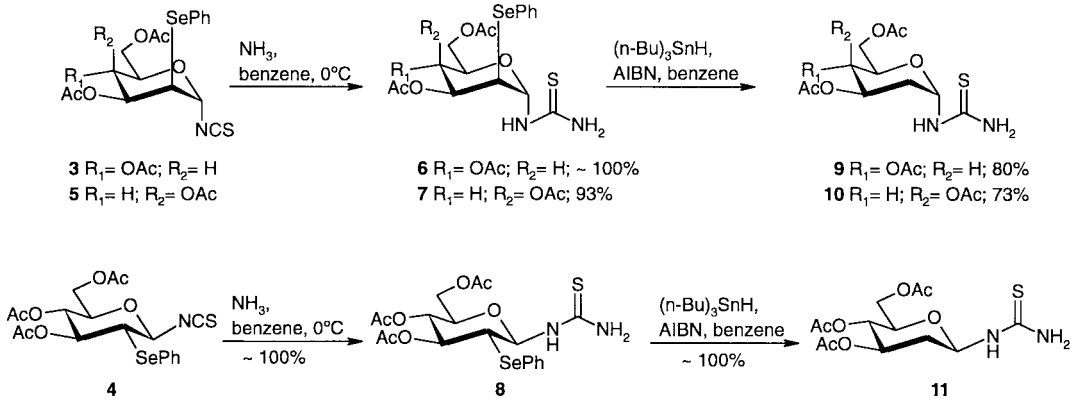
Scheme 3

to high yields by treatment of **6-8** with tributyltin hydride in the presence of a catalytic amount of AIBN. An alternative route starting from 2-deoxy-2-iodoglycopyranosyl isothiocyanates was previously described for the synthesis of compounds **9** and **10.**[20]

Mps were determined with a Reichert hotplate microscope and are uncorrected. Solutions were dried (Na_2SO_4) before concentration under diminished pressure. NMR spectra were obtained with a Bruker AM-300 spectrometer. Elemental analyses were performed with a Perkin-Elmer analyzer 240C. MS data (*m/z*) were obtained by the chemical ionization mode using methane as the ionizing gas with a Fisons VG Platform II instrument and molecular weights were obtained with a Fisons VG Autospec-Q instrument. Specific optical rotations were measured with a Perkin-Elmer Polarimeter 141. TLC and column chromatography were performed on precoated silica gel plates (Merck 60 F_{245}) and on Kieselgel 60 (Merck 230–400 mesh), respectively. All the evaporations were carried out under diminished pressure at 40 ºC.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phenylselenoglycopyranosyl Isothiocyanates 3-5. General Procedure

A mixture of the corresponding peracetylated glycal **1** or **2** (1 mmol) and phenylselenyl chloride (2 mmol) in anhyd Et_2O (6 mL) was stirred at r.t. under Ar and light protected. After 45 min KSCN (8 mmol) supported on silica [prepared by rotatory evaporation of an aqueous solution of KSCN (1.5 mmol) with silica gel (Merck 60) (3 $mmol.g^{-1}$) followed by drying] was added and the reaction was stirred for an additional 12 h. Et_2O was then removed in vacuo to



Scheme 2

Table 2 ^{1}H NMR Chemical Shifts (δ), Multiplicity and Coupling Constants (*J*, Hz) for Compounds **3–8** and **11**

Product	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	Others
3[a]	5.82 d (1.7)	3.98 dd (4.4, 1.8)	5.34 dd (9.6, 4.4)	5.43 t (9.6)	4.11 m	4.21 m		7.56, 7.32 (2 m, C_6H_5) 2.14 ,2.08, 1.81 (3 s, $OCOCH_3$)
4[a]	4.67 d (10.0)	3.15 dd (10.9, 10.2)	5.12 dd (11.1, 9.1)	4.99 t (9.5)	3.54 ddd (10.0, 4.8, 2.2)	4.22 dd (12.4, 4.8)	4.06 dd (12.4, 2.2)	7.70, 7.40 (2 m, C_6H_5)
5[a]	5.88 d (1.3)	3.60 dd (4.3, 1.6)	5.40 m		4.38 m	4.22 dd (11.4, 5.9)	4.15 dd (11.4, 7.0)	7.54, 7.33 (2 m, C_6H_5) 2.22 , 2.13, 2.08 (3 s, $OCOCH_3$)
6[a]	5.50 br s	3.91 dd (4.3, 2.7)	5.23 dd (8.6, 4.3)	5.33 t (8.6)	4.08 ddd (8.6, 6.3, 2.5)	4.26 dd (12.3, 6.3)	4.17 dd (12.3, 2.5)	7.60, 7.32 (2 m, C_6H_5) 7.04, 6.65 (2 br s, NH, NH_2), 2.10 , 2.07, 1.82 (3 s, $OCOCH_3$)
6[b]	6.20 br s	3.88 m	5.35 dd (8.7,4.2)	5.21 t (8.9)	3.88 m			8.86 (d, *J* = 8.8 Hz, NH) 7.57, 7.30 (2 m, C_6H_5), 2.02 , 2.01, 1.66 (3 s, $OCOCH_3$)
7[a]	5.50 m	3.44 t (4.4)	5.31 m	5.39 m	4.30 m	4.41 dd (11.4, 8.2)	4.17 dd (11.4, 3.8)	7.70 (br s, NH), 7.59, 7.35 (2 m, C_6H_5), 6.49 (br s, NH_2), 2.18, 2.15, 2.07 (3 s, $OCOCH_3$)
7	6.05 m	3.59 t (4.3)	5.20 br s	5.44 br s	4.20–4.03 m			8.58 (d, *J* = 8.1 Hz, NH), 7.58, 7.30 (2 m, C_6H_5), 6.49 (br s, NH_2), 2.08, 1.98 (3 s, $OCOCH_3$)
8[a]		3.11 br t (10.5)	5.16 dd (10.9, 9.0)	4.96 t (9.5)	3.61 m	4.22 dd (12.5, 5.2)	4.06 br d (11.9)	7.69, 7.38 (2 m, C_6H_5), 7.13 (br s, NH), 6.50 (br s, NH_2), 2.11 , 2.04, 2.03 (3 s, $OCOCH_3$)
8[b]	5.28 br s	3.43 t (10.5)	4.76 t (9.6)	5.08 dd (10.9, 9.1)	3.71 ddd (10.0, 4.6, 2.6)	4.15 dd (12.3, 4.6)	3.95 dd (12.3, 3.6)	8.19 (d, *J* = 9.8 Hz, NH), 7.58, 7.30 (2 m, C_6H_5), 7.25 (br s, NH_2), 2.11 , 2.04, 2.03 (3 s, $OCOCH_3$)
11[b]	4.28 dd (11.2, 5.2)	3.76 ddd (9.7, 4.6, 2.2) 2.40 m	5.07 ddd (11.2, 9.6, 5.2)	4.93 t (9.7)	3.76 ddd (9.7, 4.6, 2.2)	4.08 m		7.65 (br s, NH), 6.68 (br s, NH), 1.95, 1.90, 1.81 (3 s, $OCOCH_3$)

[a] $CDCI_3$ as solvent
[b] DMSO-d_6 as solvent

give a crude product that was purified by column chromatography (Et_2O-hexane 1:1)

***N*-(3',4',6'-Tri-*O*-acetyl-2'-deoxy-2'-phenylselenoglycopyranosyl) Thioureas 6-8. General Procedure**

Anhydrous NH_3 was bubbled through a solution of the corresponding glycosyl isothiocyanate **3-5** (1 mmol) in anhyd benzene (25 mL) cooled with an ice-water bath. After 10 min. the mixture was warmed at r.t. and the solvent removed in vacuo to give a crude product that was purified by column chromatography (Et_2O followed by EtOAc).

***N*-(3',4',6'-Tri-*O*-acetyl-2'-deoxyglycopyranosyl) Thioureas 9-11. General Procedure**

A solution of the corresponding 2-deoxy-2-phenylselenenylglycosyl thiourea (**6-8**) (1 mmol), Bu_3SnH (2.2 eq.) and α,α'-azobis(isobutyronitrile) (10-15 mg) in anhyd benzene (25 mL) was boiled until reaction was complete as judged by TLC. After cooling the reaction was concentrated and purified by column chromatography. (EtOAc:Hexane, 2:1)

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References

(1) Witczak, Z. J. *Adv. Carbohydr. Chem. Biochem*. **1986**, *44*, 91.
(2) García-Fernández, J. M.; Ortiz-Mellet, C. *Sulfur Reports*. **1996**, *19*, 61.
(3) Toshima, K. and Tatsuta, K. *Chem.Rev*. **1993**, 93, 1503.
(4) Danishefsky, S. J. and Bilodeau, M. T. *Angew.Chem.Int.Ed.Engl*. **1996**, *35*, 1380.
(5) Bilodeau M.T.; Danishefsky S.J. In *Modern Methods in Carbohydrate Synthesis*; Khan, S.H.; O'Neill, R.A., Eds.; Harwood Academic: Amsterdan, 1996; p 171.
(6) Michalska, M.; Borowiecka, J. *J. Carbohydr. Chem*. **1983**, *2*, 99.

Table 3 ^{13}C NMR ($CDCl_3$) Data (δ and $^1J_{C\text{-}1,H\text{-}1}$) for Compounds **3–8** and **10**

Product	C-1	C-3,4,5	C-6	C-2	Others
3	85.3 (176.4)	72.1, 70.6, 66.4	61.9	48.4	135.1, 129.6, 128.7 (C_6H_5), 20.8, 20.7, 20.5 (3 *C*H_3CO)
4	85.6 (163.4)	73.2, 71.9, 69.0	61.7	48.6	142.1 (NCS), 137.1, 129.6, 129.5, 124.2 (C_6H_5), 20.8, 20.7, 20.6 (3 *C*H_3CO)
5	86.8 (177.3)	70.2, 66.6, 65.8	61.6	47.3	134.5, 129.7, 128.6 (C_6H_5), 20.9, 20.7 (3 *C*H_3CO)
6	82.8	70.5, 70.3, 66.8	61.9	45.3	184.1 (CS), 134.8, 129.5, 128.5 (C_6H_5), 20.8, 20.7, 20.3 (3 *C*H_3CO)
7	83.6	69.3, 67.4, 66.4	61.7	44.7	184.2 (CS), 134.7, 129.7, 129.2, 128.6 (C_6H_5), 20.9, 20.8 (3 *C*H_3CO)
8	84.1	73.2, 72.8, 69.5	61.9	46.2	184.3 (CS), 137.2, 129.6, 129.5 (C_6H_5), 20.9, 20.8, 20.7 (3 *C*H_3CO)
11	80.6	73.6, 70.7, 68.7	62.2	35.2	183.9 (CS), 21.0, 20.9, 20.7 (3 *C*H_3CO)

(7) Boroviecka, J.; Lipka, P.; Michalska, M. *Tetrahedron* **1988**, *44*, 2067.
(8) Michalska, M.; Borowiecka, J.; Lipka, P.; Rokita-Trygubowicz,T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1619.
(9) Jaurand, G.; Beau, J.-M.; Sinaÿ, P. J. *Chem. Soc., Chem. Commun.* **1981**, 572.
(10) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723.
(11) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75.
(12) Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem*. **1990**, *55*, 5.
(13) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem*. **1992**, *57*, 2084.
(14) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825
(15) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837.
(16) Kim, C. U.; Luh, B. Y.; Martin, J. C. *J. Org. Chem*. **1991**, *56*, 2642.
(17) Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett*. **1988**, *29*, 2711.
(18) Giuliano, R. M.; Davis, R. S.; Boyko, W. J. *J. Carbohydr. Chem*. **1994**, *13*, 1135.
(19) El-Laghdach, A.; Matheu, M. I.; Castillón, S. *Tetrahedron* **1994,** *50*, 12219.
(20) Santoyo-González, F.; García-Calvo-Flores, F.; Isac-García, J.; Hernández-Mateo, F.; García-Mendoza, P.; Robles-Díaz, R. *Tetrahedron* **1994**, *50*, 2877.
(21) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
(22) Lindhorst, T. K.; Kieburg, C. *Synthesis* **1995**, 1228.

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