A New Procedure for the Synthesis of Glycosyl Isothiocyanates

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Sugar isothiocyanates are versatile synthetic intermediates which have been used as precursors of different sugar derivatives, such as glycosylthioureas[1], glycosylamino acids[2], and nucleosides[3,4,5]. Besides, several glycosyl isothiocyanates are specific enzyme inhibitors[6,7].

The most general and widely used method for the preparation of sugar isothiocyanates consists of the reaction of a glycosyl halide with silver isothiocyanate[8,9]. Other methods, less used and giving poor yields, are the reaction of glycosylamines with thiophosgene[6] and the reaction of glycals with thiocyanate and isothiocyanate derivatives[10,11].

We describe a new, cheap, and experimentally simple procedure for the synthesis of sugar isothiocyanates by the reaction of sugar halides with potassium thiocyanate in a polar aprotic solvent in the presence of a tetraalkylammonium salt as catalyst. We first carried out the preparation of the known isothiocyanates **1**[12] and **2**[13] by treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide and 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride with potassium thiocyanate in acetonitrile and in the presence of tetrabutylammonium hydrogen sulfate. Glucosamine isothiocyanate **2** contained traces of the isomeric thiocyanate, **2a**, detected by an I.R. band at 2285 cm^{-1} assigned to the SCN-group.

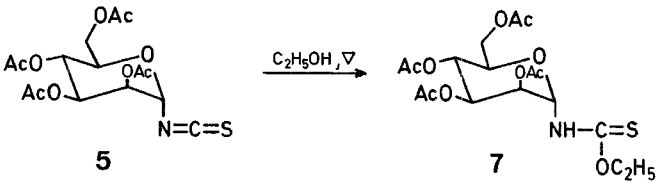
Then, we extended the procedure to the preparation of the unknown glycosyl isothiocyanates **3**, **4**, **5**, and **6** (Table). The β-ribofuranosyl and α-arabinopyranosyl isothiocyanates **3** and **4** were obtained from 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride and 2,3,4-tri-*O*-benzoyl-β-D-arabinopyranosyl bromide following the same procedure. Using tetrabutylammonium iodide as catalyst, 2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl chloride led to the α-mannopyranosyl isothiocyanate **5**. In the case of the reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl chloride with potassium thiocyanate in the presence of tetrabutylammonium hydrogen sulfate, a 3:1 mixture of the anomeric glucosyl isothiocyanates **6a** and **6b** was obtained, which was separated chromatographically. When this latter reaction was achieved with tetrabutylammonium bromide as catalyst, a 6:1 ratio of **6a** to **6b** was obtained. The higher yield of the α-anomer **6a**, in relation to the β-anomer **6b**, could be explained on the basis of the halide ion-catalytic effect produced by the tetrabutylammonium bromide[14].

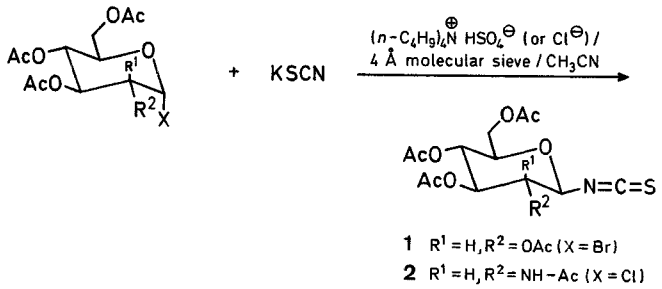
As expected, the fact of obtaining only one anomeric glycosyl isothiocyanate, having 1,2-*trans* configuration, or an anomeric mixture depended on the presence of the participating 2-*O*-acyl group or the non-participating benzyl group in the glycosyl halide used as starting material.

The detection of the glucosamine thiocyanate derivative **2a** demonstrates that these reactions occur via the previous formation of the glycosyl thiocyanate which, in the presence of the catalyst, isomerizes into the corresponding isothiocyanate[15].

It should be noted that although these reactions require a classical phase-transfer catalyst, that is a tetraalkylammonium salt, they cannot be considered as phase-transfer reactions, since they take place in only one phase.

Structural assignments of all these compounds were made on the basis of their microanalyses, I.R. and ^{1}H-N.M.R. spectral data. The structure of the α-mannopyranosyl isothiocyanate **5** was further supported by transformation into the corresponding ethoxythiocarbonylamino derivative **7**.

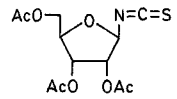
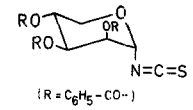
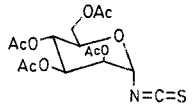
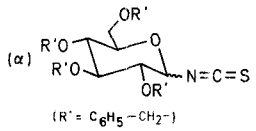




1 $R^1 = H, R^2 = OAc$ (X = Br)
2 $R^1 = H, R^2 = NH-Ac$ (X = Cl)

Glycosyl Isothiocyanates; General Procedure:
A mixture of potassium thiocyanate (0.2 g, 2 mmol), tetrabutylammonium salt (1 mmol), and molecular sieve (4 Å, 1.5 g) in anhydrous acetonitrile (50 ml) is stirred at room temperature for 2 to 3 h. Then, the sugar halide (1 mmol) is added and the mixture is refluxed until the reaction is complete as detected by T.L.C. Then the mixture is filtered and the filtrate evaporated to dryness under reduced pressure to afford a residue, which is chromatographed on preparative T.L.C. [silica gel; ethyl acetate/hexane (2:3) for **1**,**2**,**3** and **5**, and ethyl acetate/hexane (1:7) for **4** and **6**].

Table. Glycosyl Isocyanates **1–6** prepared

Product	Catalyst	Reaction time [h]	Yield [%][a]	m.p. [°C][b]	$[\alpha]_D$ (c 1, $CHCl_3$)	Molecular formula[c] or Lit. m.p.; $[\alpha]_D$	I.R. ν_{NCS} [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ_{H-1} [ppm]	$J_{1,2}$ [Hz]
1	$(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$	3	71 (80)	112°	+5°	m.p. 112–113°; 1.5–12°[12]	(KBr) 2110	5.62	8.5
2	$(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$	3	66 (80)	159°	+9°	m.p. 161°C; +9°[13]	(Nujol) 2100	5.35	9
3	 $(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$	1	55 (80)	syrup	−3°	$C_{12}H_{15}NO_7S$ (317.1)	(film) 2050	5.82	3.3
4	 $(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$	4	62 (70)	foam	−114°	$C_{27}H_{21}NO_7S$ (503.2)	(Nujol) 2040	5.38	5.5
5	 $(C_4H_9)_4N^{\oplus}I^{\ominus}$	2	72 (90)	92–94°	+132°	$C_{15}H_{19}NO_9S$ (389.1)	(Nujol) 2090	5.50[d]	2[d]
6 a (α)	 $(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$	2	62 (75)	syrup	+73°	$C_{35}H_{35}NO_5S$ (581.3)	(film) 2050	5.45	3.6
	$(C_4H_9)_4N^{\oplus}Br^{\ominus}$	2	73 (80)						
6 b (β)	$(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$	2	22 (25)	syrup	+12°	$C_{35}H_{35}NO_5S$ (581.3)	(film) 2050	–[e]	–[e]
	$(C_4H_9)_4N^{\oplus}Br^{\ominus}$	2	12 (20)						

[a] Yield of pure isolated product; values in parentheses are yields of crude products based on the glycosyl halide used. The markedly lower yields of isolated products in some cases are due to the high reactivity/instability of the isothiocyanate group.

[b] Not corrected.

[c] Satisfactory microanalyses obtained: C, ±0.38; H, ±0.34; N, ±0.33; S, ±0.35.

[d] In $CDCl_3$ solution.

[e] Included in a multiplet at δ = 4.47–5.00 ppm for the 4 benzylic CH_2 groups.

Ethyl *N*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-thiocarbamate (7):

A solution of the mannopyranosyl isothiocyanate **5** (0.20 g, 0.51 mmol) in ethanol (40 ml) is refluxed for 1 h. After this time, T.L.C. examination shows that the reaction is complete. Evaporation of the ethanol leaves a residue, which is chromatographed by preparative T.L.C. (ethyl acetate hexane, 2/3) to give analytically pure **7** as a foam; yield: 0.22 g.

$C_{17}H_{24}NO_{10}S$	calc.	C 47.00	H 5.52	N 3.22	S 7.37
(434.1)	found	47.19	5.86	2.89	7.36

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.33 (t, 3H, O—C—CH_3); 4.46 (q, 2H, O—CH_2); 5.30 (d, 1H, H—1); 7.43 ppm (br.s, 1H, NH).

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