Solvent-Free Preparation of Glycosyl Isothiocyanates

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Received 20 April 1995; revised 31 May 1995

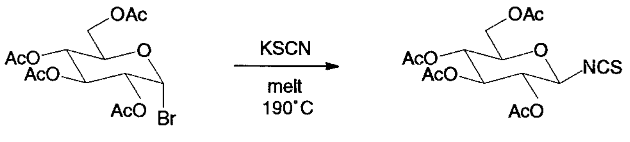
Dedicated to Professor R.R. Schmidt on occasion of his 60th birthday

By a novel solvent-free procedure, peracetylated glycosyl bromides are reacted with potassium thiocyanate in the melt to give the corresponding glycosyl isothiocyanates. The method is applicable to several glycosyl bromides tested, including classical hexoses and pentoses, deoxy sugars and even disaccharides. No glycosyl thiocyanates are obtained. In general, the glycosyl isothiocyanates are formed stereoselectively having 1,2-*trans* configuration in yields between 41–74%.

Isothiocyanates are versatile reagents in organic chemistry, since they easily undergo many important reactions, such as cycloadditions and nucleophilic additions.[1] Glycosyl isothiocyanates[2] have been used for the preparation of a variety of carbohydrate derivatives of synthetic, biological and pharmaceutical interest.[3] They have served as glycosidase inhibitors[4] and for the syntheses of glycosyl thiourea derivatives,[5] glycosylamino heterocycles,[6] nucleoside analogues,[7,8] or *N*-glycopeptides.[9]

The classical Fischer synthesis of glycosyl isothiocyanates[10] involves treatment of the acylated glycosyl bromide with silver thiocyanate in an apolar solvent such as anhydrous xylene. Problems with this synthesis arise from the ambident character of the thiocyanate anion. Depending on the conditions, the reaction can lead to the thiocyanate or the isothiocyanate derivative[11] which are difficult to separate. Therefore, several modifications for the preparation of glycosyl isothiocyanates have been introduced including the treatment of glycosylamines with thiophosgene,[12] the reaction of glycals with isothiocyanate derivatives,[13] or the reaction of glycosyl halides with less expensive thiocyanate salts such as lead thiocyanate[8] or potassium thiocyanate under phase-transfer catalysis.[14]

For the synthesis of thiourea coupled saccharide aggregates, an easy and cheap method for the large scale preparation of glycosyl isothiocyanates was required. We have investigated various approaches for the synthesis of 2,3,4,6-tetra-*O*-acetylglucosyl isothiocyanate (**2**) and obtained the most convenient results by reacting 2,3,4,6-tetra-*O*-acetylglucosyl bromide (**1**) with potassium thiocyanate in the melt. Melting glycosyl bromides has so far been a hardly ever used approach in carbohydrate synthesis.[15]



1 **2**

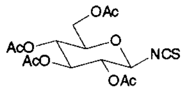
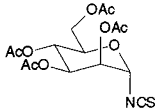
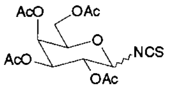
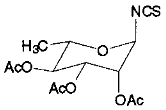
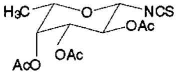
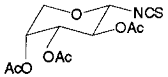
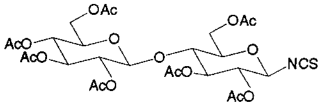
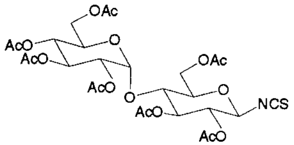
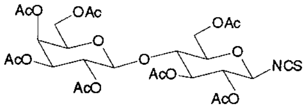
The reaction is over in less than 10 minutes and the product is easily obtained after a standard workup and purification procedure. Ten various glycosyl bromides were studied and this lead to the corresponding isothiocyanates listed in the table. The method was effective with all glycosyl bromides tested, including hexose and pentose derivatives, deoxy sugars and even disaccharides. It is especially noteworthy that no significant cleavage of the interglycosidic bond was observed. The yields of pure product range between 41 and 74%. The best yields of more than 70% were obtained with peracetylated arabinosyl bromide and maltosyl bromide leading to **7** and **9**, respectively. The glucosyl derivative **2** and the cellobiosyl derivative **8** were easily obtained in crystalline form whereas the other isothiocyanates were more difficult to crystallize or did not crystallize at all.

The reaction occurred highly stereoselectively in most cases. Only with the protected galactosyl bromide the two anomeric α- and β-glycosyl isothiocyanates were obtained in a ratio of about 1:9. In all cases, the reaction exclusively lead to the 1,2-*trans*-configurated glycosyl isothiocyanates. A 1,2-*trans* diequatorial orientation of the anomeric isothiocyanate function and the 2-*O*-acetyl group were obtained for the *gluco*-configurated product **2**, the *galacto*-configurated **4**, the L-fucose derivative **6**, and the α-configurated D-arabinose derivative **7**, as well as for the disaccharides **8**, **9**, and **10**. As expected the *manno*-configurated isothiocyanates **3** and **5** showed a 1,2-*trans* diaxial orientation. This was determined by gated decoupling experiments which showed heterocoupling constants $J_{C\text{-}1,H\text{-}1}$ of 172.6 and 175.1 Hz, respectively, and thus confirmed the anomeric α-configurations.[16]

The products were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and the physical data were compared with the available literature data. All NMR spectra could be completely assigned, however, only the most significant spectral data are given in the table. Except for products **3** and **5** the anomeric configuration could be easily determined by measuring the anomeric coupling constant $J_{1,2}$. Resulting from the anomeric NCS-functionality the chemical shifts of the anomeric protons ranged between 4.97 to 5.64 ppm. As expected the thermodynamically favoured isothiocyanates were obtained in all cases and no traces of the isomeric thiocyanates could be detected. Both isomers can be unequivocally distinguished by IR and NMR spectroscopy, the chemical shifts of H-1 and the NCS carbon being the most characteristic data.

In conclusion, a method is presented which uses readily available and inexpensive reagents without the requirement of any additives such as heavy metals and solvents. The procedure was successfully tested with a wide range of different carbohydrates, monosaccharides as well as disaccharides. However, the method was not applicable to 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopy-

Table. Glycosyl Isothiocyanates **2**–**10** Prepared

Product	Yield (%)	mp (°C)		$[\alpha]_D$		IR (KBr/neat) ν_{NCS} (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ (H-1), $J_{1,2}$ (Hz)	^{13}C NMR ($CDCl_3$/TMS)	
		found	reported	found	reported			δ (C-1)	δ (NCS)
2β 	60	110	112–113[11]	−2.4	+1.9–5.0[11] (CHCl$_3$)	2102	5.64 (8.6)	83.47	144.22
3α 	57	syrup	92–94[14]	+114.5	+132[14] (CHCl$_3$)	2018	5.55 (2.0)	82.81 (d)[a]	144.17 ($J_{C-1,H-1}$ = 172.6 Hz)
4β **4α**[b] 	57[c]	94[c]	92–94[17]	+33.9[c]	–	2109[c]	4.98 (8.64) (β) 5.90 (4.07) (α)	83.96 82.72	143.70 (β) 144.26 (α)
5α 	41	102	–[d]	−173.6	–	2033	5.47 (1.5)	82.96 (d)[a]	143.33 ($J_{C-1,H-1}$ = 175.1 Hz)
6β 	51	97–98	–[d]	−8.6	–	2040	4.97 (8.6)	84.02	143.21
7α 	74	syrup	syrup[8]	+46.9	–	2039	5.01 (6.1)	82.90	141.17
8β 	53	209	208–209[11]	−7.6	−8.6[11] (CHCl$_3$)	2027	4.97 (8.7)	83.36	144.08
9β 	73	134–136	120–123[8]	+70.9	–	2029	5.05 (8.6)	83.07	144.30
10β 	41	syrup	170[18]	+5.5	+14.3[18] (MeOH)	2029	4.98 (8.1)	83.29	144.01

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[a] Gated decoupled spectrum.

[b] $\alpha/\beta = \sim 1:9$.

[c] β-Form.

[d] Satisfactory elementary analyses obtained: C ±0.03, H ±0.04, N ±0.07, S ±0.07.

ranosyl chloride. Despite this limitation one may expect that the list of positive examples can be further expanded.

Melting points were determined on an Leitz melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer polarimeter 243 at r.t. in CH_2Cl_2 ($c = 1.0$). IR spectra were taken on a FT-IR ATI Mattson Instruments (USA). The ^1H and ^{13}C NMR data were recorded in $CDCl_3$ on a Bruker spectrometer AMX-400 at 400 MHz (^1H) or on a Bruker AC-250 at 62.9 MHz (^{13}C). As internal standard TMS was used. Where necessary, assignments were based on COSY and GATED-DECOUPLING experiments. All peracetylated glycosyl bromides were prepared by the standard HBr/AcOH (Merck, 33%) procedures and aqueous workup. They were purified by crystallization or silica gel chromatography and characterized by NMR before use. TLC was performed on Merck silica gel plates GF 245 with detection under UV light and by charring with H_2SO_4 in MeOH (10% v/v). Formed product could be distinguished from the starting material by its characteristic UV absorption. Flash column chromatography was performed on silica gel 60 (Merck, 0.04–0.063 mm, 230–400 mesh).

Glycosyl Isothiocyanates; General Procedure:

The glycosyl bromide (1 equiv, typically 1 g) was mixed with KSCN (10 equiv). In the case of crystalline glycosyl bromides the mixture was homogenized in a mortar. Otherwise the glycosyl bromide was dissolved in a small amount of EtOAc, KSCN was added and the solution was then evaporated to dryness. The mixture was melted at 190°C in a round bottom flask under N_2 atmosphere and magnetic stirring using an oil bath. After a low viscosic melt had been obtained the reaction was carried on for 5 min, and the mixture was then cooled to r.t. Water and CH_2Cl_2 were added to dissolve the melt and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography with toluene/EtOAc as eluent (4:1 for **2**, **3**, and **4**; 7:1 for **5**, **6**, and **7**; 2:1 for **9** and **10**). Wherever possible the purified products were crystallized from hexane/Et_2O.

We wish to thank Professor St. G. Withers and Professor J. Thiem for providing the generous environment for this work and the Bundesministerium für Forschung und Technologie (BMFT) for financial support.

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