# A Simple Method for the Preparation of Glycosyl Isothiocyanates

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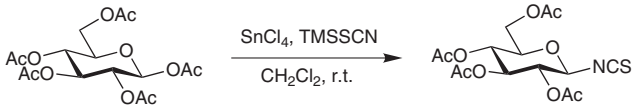
**Abstract:** Glycosyl isothiocyanates became accessible from the corresponding peracetylated sugars in one step, by application of trimethylsilyl isothiocyanate and a Lewis acid in dichloromethane at room temperature.

**Key words:** carbohydrates, isothiocyanates, disaccharides, anomeric purity, glycomimetics

Isothiocyanates are versatile reagents in organic chemistry since they easily undergo many important reactions, such as cycloaddition and nucleophilic addition reactions.[1] Glycosyl isothiocyanates[2] are used for the preparation of a variety of carbohydrate derivatives of synthetic, biological and pharmaceutical interest.[3] For example, they serve as glycosidase inhibitors[4] and for the synthesis of glycosyl thiourea derivatives,[5] glycosylamino heterocycles,[6] nucleoside analogues,[7,8] *N*-glycopeptides,[9] or glycodendrimers.[10]

Almost a century ago, E. Fischer reported the synthesis of O-acetylated glycosyl isothiocyanates from the corresponding glycosyl bromides using silver thiocyanate.[11] However, due to the ambident character of the thiocyanate anion, the isomeric glycosyl thiocyanates are often obtained as side products of the reaction,[12] causing a severe purification problem. Therefore, a variety of alternative methods for the preparation of glycosyl isothiocyanates has been published over the years, such as treatment of glycosylamines with thiophosgene,[13] the reaction of glycals with isothiocyanate derivatives,[14] and the reaction of glycosyl halides with less expensive thiocyanate salts such as lead thiocyanate[8] or potassium thiocyanate under phase-transfer catalysis,[15] or melting KSCN with the peracetylated glycosyl bromides.[16]

In the course of our studies on the synthesis of oligosaccharide mimetics, we developed a simple method for the preparation of O-protected lactosyl isothiocyanate, starting from the corresponding peracetylated sugar.[17] Herein we describe the broad applicability of this short synthesis, which delivers various glycosyl isothiocyanates from the acetylated precursors by application of trimethylsilyl isothiocyanate (TMSSCN) under Lewis acid catalysis in dichloromethane (Scheme 1). From all Lewis acids investigated for this reaction, tin tetrachloride proved to be the best promotor. The reaction is carried out at room temperature and the product is obtained after an easy standard workup. The scope of this method was tested with eight different peracetylated sugars (Table 1).




**Scheme 1**

The procedure was applicable to standard hexoses, deoxy sugars, pentoses as well as disaccharides, showing that the interglycosidic bond is not sensitive to the applied reaction conditions. In Table 1, the results obtained with this new method starting from the peracetylated sugars, are compared to those obtained with the melting method, which starts with the acetyl-protected glycosyl bromides.[16] Using the TMSSCN method, yields for the most part higher than those reported earlier[16] were obtained, ranging from 41% to 86%, while one step less is required for the new synthetic pathway. Significant NMR data (H-1, C-1, NCS) are compared to those reported. The stereochemical outcome of the $SnCl_4$-promoted reaction is mostly in agreement with the results obtained under melting conditions, which clearly provide thermodynamic control of the reaction. However, in the case of D-arabinose (entry 6) a 2:3-anomeric α,β-mixture was obtained with TMSSCN, whereas melting the respective arabinosyl bromide surprisingly led to the α-isothiocyanate as the only product.[16] Moreover, in the case of L-fucose (entry 4) mainly the α-configured product was obtained, starting from fucose peracetate, while the melting reaction gave the β-fucosyl isthiocyanate. The two fucosyl anomers can be distinguished without any problems by their anomeric coupling constants $J_{1,2}$. It can be assumed that the two reactions, which are compared in Table 1, proceed via different mechanisms, which remain to be investigated. Nevertheless, it may be considered as advantageous to use either one or the other approach for the stereoselective preparation of either α- or β-fucosyl isothiocyanates, respectively.

In conclusion, a mild one-step procedure for the synthesis of a variety of glycosyl isothiocyanates is reported, which might be also sufficient for oligosaccharides and sugar derivatives with a sophisticated protecting-group pattern, thus facilitating the synthesis of spacer-modified glycomimetics.

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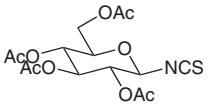
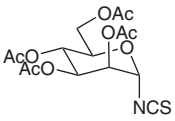
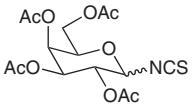
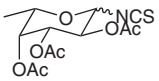
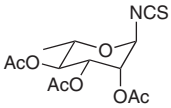
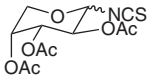
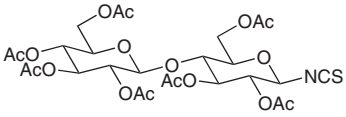
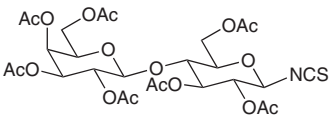
**Table 1** Glycosyl Isothiocyanates **1**–**8**[a]

| Entry | Glycosyl isothiocyanates | | Anomeric ratio[b] | Yield (%) | $^1$H NMR data $\delta_{H\text{-}1}$ [ppm] ($J_{1,2}$[Hz]) | $^{13}$C NMR data $\delta_{C\text{-}1}$, $\delta_{NCS}$ [ppm] |
|---|---|---|---|---|---|---|
| 1 |  | found: | only β | 51 | 5.03 (8.3) (β) | 83.43, 144.18 (β) |
| | | reported: | only β | 60 | 5.02 (8.2) (β) | 83.47, 144.22 (β) |
| 2 |  | found: | only α | 70 | 5.57 (2.0) (α) | 82.77, 144.20 (α) |
| | | reported: | only α | 57 | 5.55 (2.0) (α) | 82.81, 144.17 (α) ($J_{C\text{-}1,H\text{-}1}$ 172.6 Hz)[c] |
| 3 |  | found: | α/β (1:8) | 69 | 5.00 (8.8) (β)<br>5.91 (3.8) (α) | 83.93, 143.73 (β)<br>83.65, 144.27 (α) |
| | | reported: | α/β (1:9) | 57 | 4.98 (8.6) (β)<br>5.90 (4.0) (α) | 83.96, 143.70 (β)<br>82.72, 144.26 (α) |
| 4 |  | found: | α/β (8:1) | 65 | 5.85 (4.2) (α)<br>4.97 (8.8) (β) | 82.93, 143.21 (α)<br>83.98, 143.21 (β) |
| | | reported: | only β | 51 | 4.97 (8.6) (β) | 84.02, 143.21 (β) |
| 5 |  | found: | only α | 86 | 5.47 (1.2) (α) | 82.78, 143.11 (α) |
| | | reported: | only α | 41 | 5.47 (1.5) (α) | 82.96, 143.33 (α) ($J_{C\text{-}1,H\text{-}1}$ 175.1 Hz[b]) |
| 6 |  | found: | α/β (1:1.6) | 68 | 5.86 (1.5) (β)<br>5.01 (6.0) (α) | 82.95, 142.31 (β)<br>83.23, 143.71 (α) |
| | | reported: | only α | 74 | 5.01 (6.1) (α) | 82.90, 141.17 (α) |
| 7 |  | found: | only β | 41 | 4.97 (8.7) (β) | 83.33, 144.08 (β) |
| | | reported: | only β | 53 | 4.97 (8.7) (β) | 83.36, 144.08 (β) |
| 8 |  | found: | only β | 49 | 4.99 (8.4) (β) | 83.35, 144.15 (β) |
| | | reported: | only β | 41 | 4.98 (8.1) (β) | 83.29, 144.01 (β) |

[a] Reported values are from reference 16.
[b] Anomers could be separated by flash chromatography.
[c] Obtained from the gated decoupled NMR spectrum.

The $^1$H and $^{13}$C NMR data were recorded in $CDCl_3$ on a Bruker spectrometer ARX 300 or on a Bruker DRX 500. As internal standard TMS was used. TLC was performed on Merck silica gel plates GF 245 with detection under UV light. Flash column chromatography was performed on silica gel 60 (ICN, 0.032–0.063 mm).

**Glycosyl Isothiocyanates; General Procedure**

The fully acetylated sugar (0.5 mmol) and $SnCl_4$ (0.5 mL, 1 M soln in anhyd $CH_2Cl_2$) were dissolved in anhyd $CH_2Cl_2$ (3 mL). After 5 min TMSSCN (0.55 mmol) was added and the reaction mixture was stirred at r.t. for 2 d. Then, sat. aq $NaHCO_3$ soln was added and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic phases were washed with $H_2O$ (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with cyclohexane–EtOAc–$CH_2Cl_2$ (1:1:1) as the eluent in all the cases reported here.

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