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A practical one-pot synthesis of *O*-unprotected glycosyl thioureas

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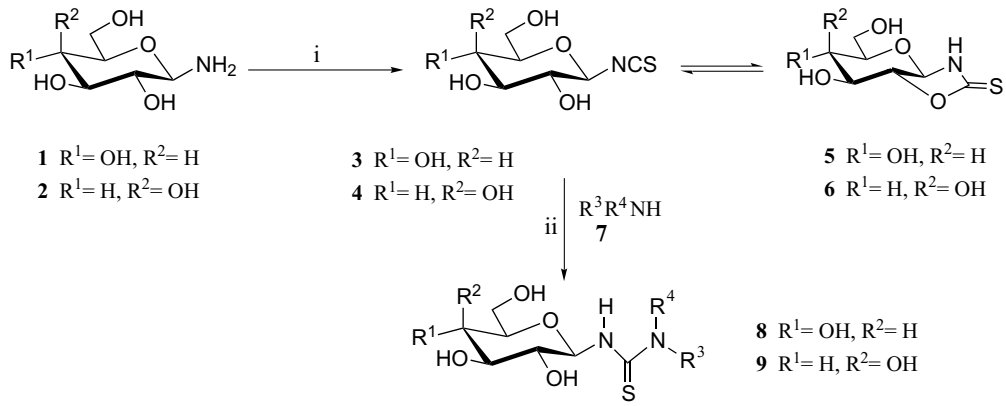
Abstract—An expeditious and high-yielding one-pot procedure to prepare different types of *O*-unprotected *N*-β-D-glycopyranosyl, *N*′-substituted thioureas and di-β-D-glucopyranosyl thioureido bolaamphiphiles from β-D-glycopyranosylamines via *O*-unprotected glycopyranosyl isothiocyanates has been developed. © 2001 Elsevier Science Ltd. All rights reserved.

Isothiocyanates are attractive synthons in organic chemistry due to their availability and their tendency to undergo nucleophilic additions and cycloadditions.[1,2] Particularly, sugar isothiocyanates have been used for the synthesis of a wide spectrum of carbohydrate derivatives, mostly having thiourea structure, of synthetic, biological and pharmaceutical interest.[3–5] Antiviral, antibacterial and antitumor agents have been prepared by reaction of glycosyl isothiocyanates with biologically active amines.[3,6] Recently, glycosyl isothiocyanates are being used to prepare glycodendrimers and glycoclusters, as mimetics of natural oligo- and polysaccharides that interact with the carbohydrate recognition domains of cell surface lectins.[7–9] Bridged thiourea calix-sugars have been prepared for molecular recognition studies.[10]

The facility of reaction between the NCS group and the hydroxyl groups of a sugar radical means that the availability of glycosyl isothiocyanates is practically limited to *O*-protected derivatives,[3] which have been prepared by reaction of acylated glycosyl halides with silver thiocyanate following the classical Fischer's method,[11] and variants including the use of potassium thiocyanate under phase-transfer catalysis[12] or melting the acylated glycosyl bromide with potassium thiocyanate.[13] Other methods involve the use of trimethylsilyl isothiocyanate and tin tetrachloride on peracetylated aldopyranoses[2] or the reaction of glycals with silica-supported KSCN in the presence of iodine.[14] Isothiocyanation of glycosylamines has been performed via *N*-protection as enamines, *O*-protection, removal of the enamine group and treatment with thiophosgene.[15]



Scheme 1. *Reagents and conditions*: (i) 1.2 equiv. $CSCl_2$, pH 8 ($NaHCO_3/CO_2$), −10°C, 30 min, 1:1 dioxane–water; (ii) 1.2 equiv. of **7a–h** (0.6 equiv. of **7i,j**), pH 9 ($NaHCO_3/CO_2$), rt, 2–5 h.

Keywords: isothiocyanates; thiocarbamates; thioureas; thiophosgene; bolaamphiphiles.

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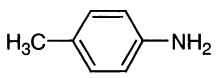
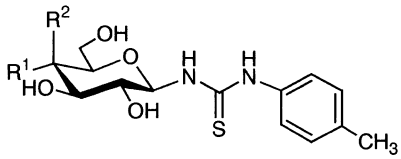
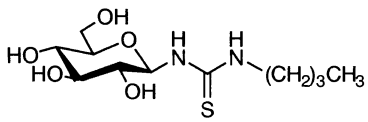
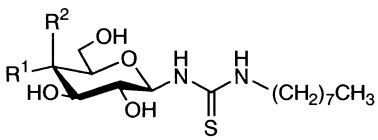
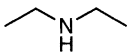
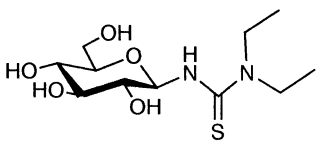
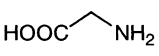
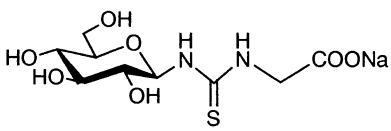
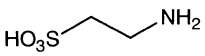
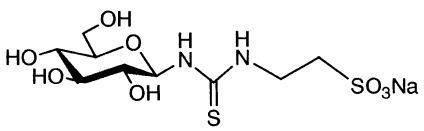
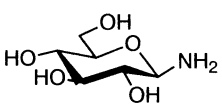
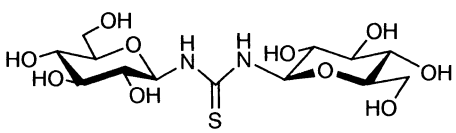
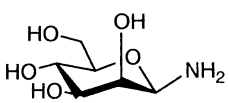
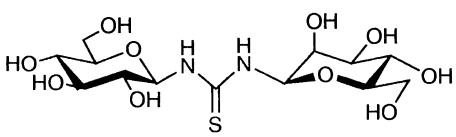
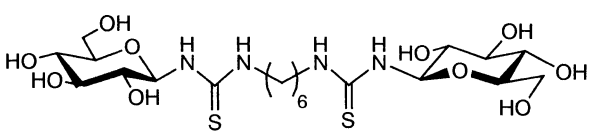
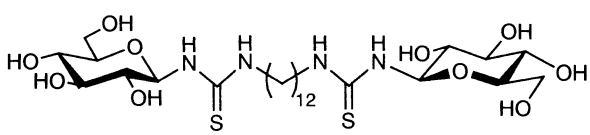
The transformation of *O*-unprotected glucosyl (maltosyl, lactosyl)amines into glycosyl isothiocyanates by reaction with thiophosgene has been reported[16–19] and they have been used as potent irreversible glycosidase inhibitors and as affinity labels of proteins involved in the transport of carbohydrates across cell membranes.

Table 1. Conversion of β-D-glycosylamines (**1**, **2**) into thioureas **8** (D-*gluco*) and **9** (D-*galacto*)

Entry	R^3R^4NH	7	Products	8, 9	Yield (%)[a]
1		**7a**		**8a** **9a**	66 58
2	$CH_3(CH_2)_3NH_2$	**7b**		**8b**	63
3	$CH_3(CH_2)_7NH_2$	**7c**		**8c** **9c**	72 61
4		**7d**		**8d**	62
5		**7e**		**8e**	74
6		**7f**		**8f**	72
7		**7g**		**8g**	55
8		**7h**		**8h**	73
9	$H_2N(CH_2)_6NH_2$	**7i**		**8i**	84
10	$H_2N(CH_2)_{12}NH_2$	**7j**		**8j**	78

[a] Isolated yields

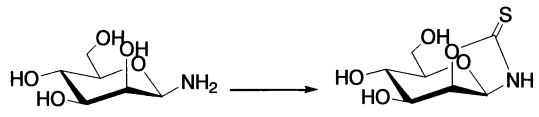
However, these compounds were later shown to undergo fast decomposition under physiological conditions[20] and no further chemistry has been described. β-D-Glucopyranosyl isothiocyanate (**3**) was prepared in low yield (22%) and this compound was spectroscopically characterised only by an IR absorption, and no reactions of the NCS group were described.[17]

We have investigated various approaches for the synthesis of **3** and obtained the most convenient results by reacting β-D-glucopyranosyl amine[21] (**1**) with thiophosgene (Scheme 1) in a buffered medium ($NaHCO_3/CO_2$, pH 8). After standard workup and purification procedure, a mixture of **3** and the corresponding 1,2-cyclic thiocarbamate **5** was obtained (64%);[22] the **3**:**5** ratio measured by integration of ^1H NMR signals was 1:5 in $(CD_3)_2SO$ and 3:2 in D_2O, showing that **3** and **5** are in a solvent dependent equilibrium. This mixture could be transformed into thioureas (Table 1) by adding alkyl or aryl amines **7a**–**c**, diethylamine **7d**,[23] the aminoacids glycine or taurine **7e**,**f**, or *O*-unprotected glycosylamines **7g**,**h** to the same flask where **3**/**5** were formed. Similarly, bolaamphiphiles[24] **8i** and **8j** were prepared using α,ω-polymethylenediamines **7i** and **7j**.

Thioureas **8a**–**d** were purified by silica gel column chromatography and more polar compounds **8e**–**j** were purified by gel filtration chromatography. Similarly, we have obtained **9a** and **9c** starting from β-D-galactopyranosylamine **2**.

The reaction of β-D-mannopyranosylamine **10** with thiophosgene in the conditions described above for the synthesis of **3** produced the *cis* bicyclic thiocarbamate **11** (46%), which did not react with amines as latent isothiocyanate. The ^1H NMR spectrum in D_2O of **11** showed no signals for mannopyranosyl isothiocyanate. The different behaviour of the *cis*- and *trans*-hydrindanes-type systems **11** and **5** (**6**) could be explained by the strain of the ring fusion in the *trans*-isomer, as a consequence of the unfavourable puckering of the six-membered ring.[25]

The widely used methodology for the synthesis of glycosyl thioureas involves the coupling of *O*-acylated glycosyl isothiocyanates with amines or aminosugars followed by Zemplen deacetylation.[3,26,27] However, this reaction has been found to be occasionally unsuccessful or low yielding.[3] In addition, an unexpected base-catalysed anomerisation reaction for α and β-D-mannopyranosyl thioureido derivatives has been described upon Zemplen deacetylation.[28,29] This result contrasts with the preparation of **8h**, which did not show anomerisation.



10 **11**

In conclusion, a rapid and practical two-step one-pot procedure for the synthesis of *O*-unprotected *N*-glycopyranosyl, *N*′-substituted thioureas from 1,2-*trans* arranged glycopyranosyl amines has been developed. This represents a better alternative to the currently used *O*/*N* protection–deprotection steps in the synthesis of glycosyl thioureas and thiourea-tethered pseudooligosaccarides[30] and bolaamphiphiles.[31]

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References

1. Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*, 1–24.
2. Al-Masoudi, N.; Hassan, N. A.; Al-Soud, Y. A.; Schmidt, P.; Gaafar, A. E.-D. M.; Weng, M.; Marino, S.; Schoch, A.; Amer, A.; Jochins, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 947–953.
3. García Fernández, J. M.; Ortiz Mellet, C. *Adv. Carbohydr. Chem. Biochem.* **2000**, *55*, 35–135.
4. Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267–1277.
5. Fernández-Bolaños, J. G.; Zafra, E.; López, O.; Robina, I.; Fuentes, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3011–3023 and references cited therein.
6. (a) Todoulou, O. G.; Papadaki-Valiraki, A. E.; Filippatos, E. C.; Ikeda, S.; De Clercq, E. *Eur. J. Med. Chem.* **1994**, *29*, 127–131; (b) Povarov, L. S.; Potapova, N. P.; Bakina, E. V.; Preobrazhenskaya, M. N.; Rozynov, B. V. *Bioorg. Khim.* **1992**, *18*, 1117–1126.
7. Roy, R. *Curr. Opin. Struct. Biol.* **1996**, *6*, 692–702.
8. Lindhorst, T. K.; Kieburg, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *108*, 2083–2086.
9. Walter, M.; Lindhorst, T. K. *20th International Carbohydrate Symposium*; Hamburg, Germany, 2000, abstr. B-134, p. 125.
10. Saitz-Barrie, C.; Torres-Pinedo, A.; Santoyo González, F. *Synlett* **1999**, 1891–1894.
11. Fischer, E. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1377–1393.
12. Camarasa, M. J.; Fernández-Resa, P.; García-López, M. T.; de la Heras, F. G.; Menéndez-Castrillón, P. P.; San Félix, A. *Synthesis* **1984**, 509–510.
13. Lindhorst, T. K.; Kieburg, C. *Synthesis* **1995**, 1228–1230.
14. Santoyo González, F.; García-Calvo-Flores, F.; Isac-García, J.; Hernández-Mateo, F.; García-Mendoza, P.; Robles-Díaz, R. *Tetrahedron* **1994**, *50*, 2877–2894.
15. Pradera, M. A.; Molina, J. L.; Fuentes Mota, J. *Tetrahedron* **1995**, *51*, 923–934.
16. Taverna, R. D.; Langdon, R. G. *Biochem. Biophys. Res. Commun.* **1973**, *54*, 593–599.
17. Khorlin, A. Ya.; Shiyan, S. D.; Lakhtima, O. E.; Shulman, M. L. *Bioorg. Khim.* **1975**, *1*, 393–395.

18. Shulman, M. L.; Lakhtina, O. E.; Khorlin, A. Ya. *Biochem. Biophys. Res. Commun.* **1977**, *74*, 455–459.
19. Mullins, R. E.; Langdon, R. G. *Biochemistry* **1980**, *19*, 1199–1205.
20. Rees, W. D.; Gliemann, J.; Holman, G. D. *Biochem. J.* **1987**, *241*, 857–862.
21. Isbell, H. C.; Frush, H. L. *J. Org. Chem.* **1958**, *23*, 1309–1319.
22. Selected data for **3**: IR 2045 cm^{-1} (NCS); ^1H NMR (500 MHz, D_2O): δ 4.94 (d, 1H, $J_{1,2}=8.2$ Hz, H-1), 3.43 (t, 1H, $J_{2,3}=8.2$ Hz, H-2) ppm; ^{13}C NMR (125.7 MHz, D_2O): δ 143.2 (NCS), 86.9 (C-1); selected data for **5**: ^1H NMR (500 MHz, D_2O): δ 5.09 (d, 1H, $J_{1,2}=9.6$ Hz, H-1), 4.07–4.09 (m, 1H, H-2) ppm; ^{13}C NMR (125.7 MHz, D_2O): δ 193.7 (CS), 88.2 (C-1) ppm; HREIMS for **3** and **5** calcd for $C_7H_{11}NO_5S$ $[M]^+$ 221.0358, found 221.0356.
23. Selected data for **8d**: mp 104–106°C (from ethanol); $[\alpha]_D^{28}$ −8.5 (*c* 1.17 in water); ^1H NMR (500 MHz, D_2O): δ 5.67 (d, 1H, $J_{1,2}=8.8$, H-1) ppm; ^{13}C NMR (125.7 MHz, D_2O): δ 180.0 (C=S), 86.4 (C-1) ppm.
24. Fuhrhop, J.-H.; Helfrich, W. *Chem. Rev.* **1993**, *93*, 1565–1582.
25. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp. 771–787.
26. Broan, C. J.; Butler, A. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, 731–740.
27. Fuentes, J.; Molina, J. L.; Pradera, M. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2517–2532.
28. Benito, J. M.; Ortiz Mellet, C.; Sadalapure, K.; Lindhorst, T. K.; Defaye, J.; Fernández, J. M. *Carbohydr. Res.* **1999**, *320*, 37–48.
29. Blanco, J. L.; Barria, C. S.; Benito, J. M.; Ortiz Mellet, C.; Fuentes, J.; Santoyo-González, F.; Fernández, J. M. *Synthesis* **1999**, 1907–1914.
30. García Fernández, J. M.; Ortiz Mellet, C.; Maciejewski, S.; Defaye, J. *Chem. Commun. (Cambridge)* **1996**, 2741–2742.
31. Prata, C.; Mora, N.; Polidori, A.; Lacombe, J.-M.; Pucci, B. *Carbohydr. Res.* **1999**, *321*, 15–23.