A Practical Amine-Free Synthesis of Symmetric Ureas and Thioureas by Self-Condensation of Iso(thio)cyanates

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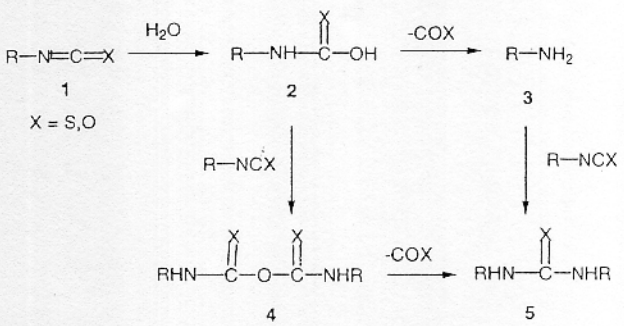
Abstract: Isocyanates and isothiocyanates are readily transformed into the corresponding symmetric *N,N'*-disubstituted ureas and thioureas upon treatment with pyridine-water with no formation of side products. Evidence is shown for an amine-free mechanistic pathway, probably involving (thio)carbamic anhydrides as reaction intermediates. The methodology is compatible with in situ generation of the isocyanate precursor from an acyl azide via Curtius rearrangement and with the presence of ester and amide functional groups in the molecule. Examples given include alkyl, aryl and carbohydrate substrates. This procedure allows the high yielding preparation of (thio)ureas in those cases where the related amine is not accessible.

Key words: ureas, thioureas, isocyanates, isothiocyanates, carbohydrates, condensation, addition reactions, dimerizations

The conventional methods reported for (thio)urea synthesis are essentially based on the reaction of a starting or transient amine with an iso(thio)cyanate or a (thio)carbonylating agent.[2] However, the presence of a free amino group in a complex polyfunctional substrate may lead to undesired side reactions that can seriously handicap the coupling yield. In our own effort to develop novel mixed thiourea-carbohydrate receptors,[3] we required an amine-free synthetic methodology to prepare *N,N'*-disubstituted symmetric thioureas that should overcome the problems of intra- and intermolecular acyl migration encountered when selectively *O*-acylated amino sugars are used as precursors.[4]

Symmetric *N,N'*-disubstituted (thio)ureas **5** are frequently found as side products in reactions involving (iso)thiocyanates **1**, their formation being associated to moisture. Actually, nucleophilic addition of water to the central heterocumulene carbon atom is a main decomposition route of (iso)thiocyanates.[5] The resulting adduct **2** is unstable and undergoes elimination of CO_2 (or COS) to give the corresponding amine **3** which, eventually, is trapped by a second (iso)thiocyanate molecule (Scheme 1). Upon further investigation, we discovered that the proportion of symmetric (thio)urea significantly increased during the attempted coupling of (iso)thiocyanates and low reactive nucleophiles in humid pyridine.[6] Interestingly, no products arising from O → N acyl migration were detected in the reaction mixtures when carbohydrate substrates were employed, suggesting a different mechanistic pathway. We reasoned that, in the presence of base, the (thio)carbamate species might be stabilised and act directly as the nucleophile, with no generation of a free amino group. The (thio)carbamic anhydride **4** thus formed would lead to the (thio)urea after elimination of CO_2 (or COS), probably through a four-membered ring intermediate, analogously to the accepted mechanism for the reaction of iso(thio)cyanates and carboxylic acids to give amides.[7] We have now investigated the self-condensation reaction of iso(thio)cyanates under the above reaction conditions and report on the high yielding preparation of the corresponding symmetric (thio)ureas (Table). The methodology is compatible with the presence of ester functionalities and allows the preparation of selectively *O*-acylated symmetric sugar thioureas from readily available carbohydrate isothiocyanates[8] regardless of the secondary or primary position location of the NCS group.



Scheme 1

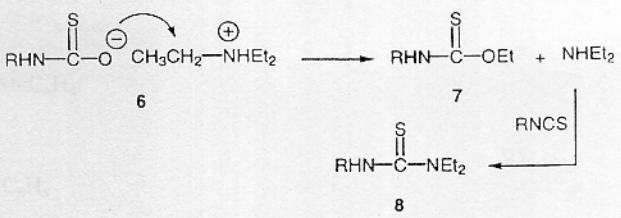
In optimizing the reaction conditions for dimerization of iso(thio)cyanates, the effect of a number of factors upon the products formed were investigated, including the nature of the base catalyst, solvent, substrate concentration, temperature and reaction time. The best yields were obtained by using pyridine/water, although no definitive correlations were observed for different relative proportions. Eventually, we chose to standardize the conditions used

for self-condensation of iso(thio)cyanates by employing 0.2 M solutions in 10:1 pyridine/water at room temperature or 60 °C. Although these conditions gave consistent and reproducible yields of (thio)ureas, with no formation of side products, we have also generated *N,N'*-disubstituted (thio)ureas using different concentrations, pyridine-water ratios and temperatures with only minor variations in results.

Aromatic isocyanates **1a–c** readily dimerized in 10:1 pyridine/water at room temperature (Table, Entries 1–3). Alternatively, the isocyanate precursor can be generated in situ from an acyl azide via a Curtius rearrangement by heating at 60 °C. Under identical reaction conditions, self-condensation of isothiocyanates **1d,e** proceeded at a much lower rate, needing 48 hours at 60 °C to be completed (Table, Entries 4, 5). In all cases the symmetric (thio)ureas were formed as the sole reaction products.

Glycosyl isothiocyanates exhibited a much higher tendency to dimerize as compared to aliphatic and aromatic derivatives. In a typical reaction procedure, a 0.2 M solution of the isothiocyanate in 10:1 pyridine/water is stirred at room temperature while monitoring by TLC. Although formation of the bis(glycosyl)thiourea is almost finished after 5–6 hours, the reaction mixture was stored for 24 hours to ensure completion. In some cases, heating at 60°C was found advantageous. Using these conditions, we have prepared a variety of peracetylated *N,N'*-bis(glycosyl)thioureas. Cases studied include monosaccharide and disaccharide derivatives as well as substrates bearing acetamido groups. The outcome of the reaction was, however, strongly dependent on the nature of the sugar template. Thus, whereas the β-D-hexopyranosyl derivatives **1f–j** yielded the respective dimerization products with total retention of the anomeric configuration (Table, Entries 6–10), the α-configurated D-mannopyranosyl isothiocyanate **1k** afforded an inseparable mixture of the α,α-, α,β- and β,β-epimers (Table, Entry 11). Their structure was confirmed by $J_{C\text{-}1,H\text{-}1}$ measurements[9] (α, 167 Hz; β, 155 Hz) and stereocontrolled synthesis (see below). Under the same reaction conditions, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiocyanate (**1l**) yielded a binary mixture of the symmetric β,β and unsymmetric α,β thioureas (Table, Entry 12). The relative proportions of anomers in the last two cases was dependent on reaction conditions. Nevertheless, thermodynamic equilibria were achieved after prolonged reaction times (Table, Entries 13, 14).

When the reaction was conducted in humid chloroform with triethylamine as the base catalyst, the dimerization process became slower and small amounts of byproducts were formed. Moreover, transient intermediates could be detected by TLC. Attempts to isolate these reaction species failed, however, although in some cases the decomposition products, i.e. the ethyl thiocarbamate **7** (isolated for R = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) and the trisubstituted thiourea **8** (isolated for R = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl), could be purified. Their formation can be explained assuming that the triethylammonium cation can undergo nucleophilic displacement of diethylamine by the postulated thiocarbamate anion **6**. The diethylamine liberated can then react with an isothiocyanate molecule to give the corresponding thiourea (Scheme 2).



Scheme 2

At present, it is not clear why the peracetylated α-D-mannopyranosyl and β-D-xylopyranosyl isothiocyanates **1k** and **1l** afforded mixtures of anomers under self-condensation reaction conditions. Since base-catalysed epimerization at C-1 of per-*O*-acetylated glycosylamines has been reported,[10] their formation through the hydrolytic pathway shown in Scheme 1 was suspected. To investigate this possibility, the anomerically pure thioureas were obtained. While in the case of **5l** (β,β) and **5l** (α,β) purification could be achieved by column chromatography, in the case of the mannose thioureas **5k** specific syntheses for the three isomers had to be devised. The symmetric α,α-derivative was isolated in pure form by the self-condensation reaction of **1k** in humid chloroform-triethylamine using short reaction times (Table, Entry 15). The α,β- and β,β-anomers were obtained by the coupling reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylamine hydrochloride (**9**) with the per-*O*-acetylated α- (**1k**) and β-D-mannopyranosyl isothiocyanate (**10**), respectively (Scheme 3). When the anomerically pure thioureas were subjected to the reaction conditions used for dimerization of the isothiocyanates, an identical thermodynamic equilibrium was achieved, indicating that anomerization occurred in the thioureas after dimerization of the isothiocyanates. Moreover, when the above experiment was effected in the presence of an iso(thio)cyanate, no crossed thiourea products were formed, discarding the formation of transient amines during the anomerization process.

The high reactivity of glycosyl isothiocyanates towards pyridine-promoted self-condensation contrasted with the stability of the 6-deoxy-6-isothiocyanato glycopyranosides **1m** and **1n**. No reaction was observed at temperatures lower than 50°C after 3 days. Nevertheless, a clean transformation into the corresponding (6→6)-thiourea linked pseudodisaccharides occurred at 60°C, the reaction being completed in 48 hours (Table, Entries 16, 17). Higher temperatures resulted in slight formation of deacetylation products with the corresponding loss of product purity.

The high yields obtained in the self-condensation of the methyl α-D-glycopyranoside derivatives **1m** and **1n**, bear-

Table Conversion of Iso(thio)cyanates into *N,N'*-Disubstituted (Thio)ureas

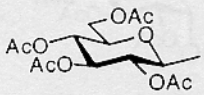
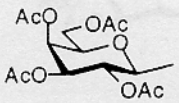
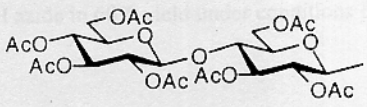
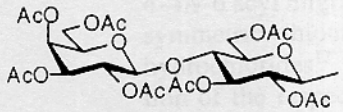
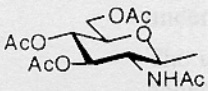
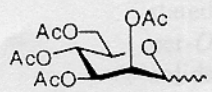
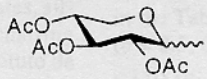
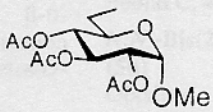
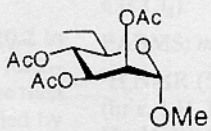
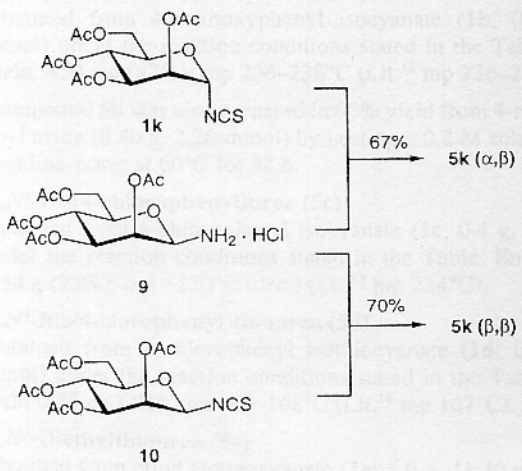
Entry	Reactant	Reaction Conditions[a]	Products RNHC(=X)NHR'	Yield (%)
1	phenyl isocyanate **1a**	A	**5a**: X = O, R = R' = Ph	85
2	*p*-methoxyphenyl isocyanate **1b**	A	**5b**[b]: X = O, R = R' = 4-OMeC$_6$H$_4$	87
3	*p*-chlorophenyl isocyanate **1c**	A	**5c**: X = O, R = R' = 4-ClC$_6$H$_4$	95
4	*p*-chlorophenyl isothiocyanate **1d**	B	**5d**: X = S, R = R' = 4-ClC$_6$H$_4$	77
5	ethyl isothiocyanate **1e**	B	**5e**: X = S, R = R' = Et	74
6	2,3,4,6-tetra-*O*-acetyl β-D-glucopyranosyl isothiocyanate **1f**	C	**5f**: X = S, R = R' = 	90
7	2,3,4,6-tetra-*O*-acetyl β-D-galactopyranosyl isothiocyanate **1g**	C	**5g**: X = S, R = R' = 	93
8	2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-cellobiosyl isothiocyanate **1h**	C	**5h**: X = S, R = R' = 	87
9	2,3,6,2',3',4',6'-hepta *O*-acetyl-β-lactosyl isothiocyanate **1i**	D	**5i**: X = S, R = R' = 	90
10	2-acetamido-2-deoxy 3,4,6-tri-*O*-acetyl-β-D glucopyranosyl isothiocyanate **1j**	C	**5j**: X = S, R = R' = 	72
11	2,3,4,6-tetra-*O*-acetyl α-D-mannopyranosyl isothiocyanate **1k**	C	**5k** (α,α), (α,β) and (β,β) X = S, R = R' = 	84 (18:78:4)

Table (continued)

Entry	Reactant	Reaction Conditions[a]	Products RNHC(=X)NHR'	Yield (%)
12	2,3,4-tri-*O*-acetyl-β-D xylopyranosyl isothiocyanate **1l**	C	**5l** (β,β) and (α,β) X = S; R = R'= 	74 (2:1)
13	**1k**	E	**5k** (α,α), (α,β) and (β,β)	83 (15:80:5)
14	**1l**	E	**5l** (β,β) and (α,β)	90 (1:1)
15	**1k**	F	**5k** (α,α)	25[c]
16	methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-glucopyranoside **1m**	B	**5m**: X =S, R = R'= 	95
17	methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-mannopyranoside **1n**	B	**5n**: X = S, R = R'= 	84

[a] Reaction conditions: reactant concentration was 0.2 M in 10:1 pyridine/water in all experiments excepting entry 15 (F) where the solvent was 20:2:1 $CH_2Cl_2/Et_3N/H_2O$; A, r.t., 2 h; B, 60 °C, 48 h; C, r.t., 24 h; D, 60 °C, 12 h; E, r.t., 48 h; F, r.t., 45 min.
[b] Compound **5b** was also prepared from *p*-methoxybenzoyl azide in 60% yield under conditions B.
[c] 60% of unreacted **1k** was recovered.



Scheme 3

ing the NCS functionality at the primary C-6 position, is particularly noteworthy. The related per-*O*-acetylated 6-amino-6-deoxy compounds are unknown due to fast *O*-4→*N*-6 acyl migration and previous attempts to obtain the symmetric thioureas using the corresponding amine hydrochlorides[12] resulted, likewise, in extensive formation of the respective amides. The present methodology afforded exclusively the thiourea adducts **5m** and **5n**, even under diluted reaction conditions, which strongly supports an amine-free mechanistic pathway (Scheme 1) under the reaction conditions described in this paper.[13]

The ureas and thioureas produced by this procedure are generally formed in near quantitative mass recovery and in ca. 80–100% purity after evaporation of the solvents, as indicated by ^{1}H NMR spectroscopic analysis. Thus, the yields reported in the Table under the optimal conditions stated are the isolated yields on purified products. The per-*O*-acetylated sugar thioureas are indefinitely stable as solids or in neutral solutions if protected from moisture. Nevertheless, an unprecedented epimerization at the anomeric position occurred in the presence of base in the cases of the mannopyranosyl and xylopyranosyl derivatives, which would need further investigation.

Optical rotations were measured at room temperature in 1 cm or 1 dm tubes. IR spectra were recorded on a FT-IR instrument. ^1H (and ^{13}C) NMR spectra were recorded at 500 (125.7) and 300 (75.5) MHz. In the FABMS spectra, the primary beam consisted on Xe atoms with a maximum energy of 8 keV. The samples were dissolved in *m*-nitrobenzyl alcohol and the positive ions were separated and accelerated over a potential of 7 keV. NaI was added as cationizing agent. TLC was performed with E. Merck precoated TLC plates, silica gel 30F-245, with visualization by UV light and by charring with 10% H_2SO_4. Microanalyses were performed by the Instituto de Investigaciones Químicas (Sevilla, Spain).

The alkyl and aryl iso(thio)cyanates used in this study were commercial grade. Per-*O*-acetylated glycopyranosyl isothiocyanates **1f–l**[8b] were prepared from the corresponding glycopyranosyl bromides[14] by treatment with KSCN and Bu_4NHSO_4 in MeCN, following the methodology of Camarasa et al.[15] Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-glucopyranoside (**1m**) and its D-*manno* epimer (**1n**) were prepared from the respective 6-amino-6-deoxy derivatives using thiophosgene as reported.[16] 2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosyl isothiocyanate[11] (**10**) was obtained in five steps from D-mannose via β-D-mannopyranosylamine[17] by using the known enamine protection strategy.[4a,8b] The same synthetic route provided 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylamine hydrochloride[11] (**9**).

Symmetric Ureas and Thioureas 5a–n from Iso(thio)cyanates 1a–n; General Procedure

A 0.2 M solution of the corresponding (iso)thiocyanate **1** (0.2 to 11.4 mmol) in 10:1 pyridine/H_2O (1 to 110 mL) was stirred for 2–48 h at 25–60°C while monitoring by TLC. The solvents were then removed under reduced pressure and the residue was purified by column chromatography using 1:1 EtOAc/hexanes as eluent. Specific reaction times and temperatures as well as isolated yields of symmetrical disubstituted (thio)ureas prepared by the foregoing procedure have been compiled in the Table. The known products **5a–f** were unequivocally identified by spectroscopic comparison (IR, NMR) with authentic specimens.

***N,N'*-Diphenylurea (5a)**

Obtained from phenyl isocyanate (**1a**; 1.0 g, 8.40 mmol) under the reaction conditions stated in the Table, Entry 1; yield: 760 mg (85%); mp 238–240°C (Lit.[18] mp 239°C).

***N,N'*-Bis(4-methoxyphenyl)urea (5b)**

Obtained from 4-methoxyphenyl isocyanate (**1b**; 0.57 g, 3.82 mmol) under the reaction conditions stated in the Table, Entry 2; yield: 450 mg (87%); mp 236–238°C (Lit.[18] mp 236–238°C).

Compound **5b** was also prepared in 65% yield from 4-methoxybenzoyl azide (0.40 g, 2.26 mmol) by heating a 0.2 M solution in 10:1 pyridine-water at 60°C for 48 h.

***N,N'*-Bis(4-chlorophenyl)urea (5c)**

Obtained from 4-chlorophenyl isocyanate (**1c**; 0.4 g, 2.57 mmol) under the reaction conditions stated in the Table, Entry 3; yield: 0.34 g (95%); mp >230°C (dec.) (Lit.[18] mp 284°C).

***N,N'*-Bis(4-clorophenyl)thiourea (5d)**

Obtained from 4-chlorophenyl isothiocyanate (**1d**; 0.56 g, 3.30 mmol) under the reaction conditions stated in the Table, Entry 4; yield 0.38 g (77%); mp 166–168°C (Lit.[19] mp 167°C).

***N,N'*-Diethylthiourea (5e)**

Obtained from ethyl isothiocyanate (**1e**; 1.0 g, 11.40 mmol) under the reaction conditions stated in the Table, Entry 5; yield: 0.56 g (74%); mp 76–78°C (Lit.[20] mp 78°C).

***N,N'*-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (5f)**

Obtained from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**1f**; 0.2 g, 0.51 mmol) under the reaction conditions stated in the Table, Entry 6; yield: 0.17 g (90%); mp 215–216°C; $[\alpha]_D$ +4 (c = 0.6, $CHCl_3$); (Lit.[5a] mp 205–206°C; $[\alpha]_D$ +5. Lit.[21] mp 220–221°C; $[\alpha]_D$ +8).

***N,N'*-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiourea (5g)**

Obtained from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl isothiocyanate (**1g**; 0.31 g, 0.79 mmol) under the reaction conditions stated in the Table, Entry 7; yield: 0.27 g (93%); mp 210–212°C; $[\alpha]_D$ +29 (c = 0.5, $CHCl_3$).

FABMS: m/z = 759 ($[M + Na]^+$).

^1H NMR (300 MHz, DMSO-d_6): δ = 8.34 (d, 1 H, J = 8.10 Hz, NH), 5.79 (dd, 1 H, J = 9.1, 8.1 Hz, H-1), 5.32–5.25 (m, 2 H, H-3, 4), 5.00 (t, 1 H, J = 9.1 Hz, H-2), 4.26 (t, 1 H, J = 6.3 Hz, H-5), 3.98 (m, 2 H, H-6a, 6b), 1.98, 1 97, 1.95, 1.93 (4 s, each 3 H, 4 $COCH_3$).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 189.0 (CS), 169.8, 169.6, 169.3 (CO), 81.6 (C-1), 71.4 (C-5), 70.6 (C-3), 68.2 (C-2), 67.6 (C-4), 61.3 (C-6), 20.5, 20.4, 20.3, 20.2 ($COCH_3$).

Anal. Calcd for $C_{29}H_{40}N_2O_{18}S$: C, 47.27; H, 5.48; N, 3.80; S, 4.34. Found C, 47.29; H, 5.62; N, 3.90; S, 4.28.

***N,N'*-Bis(2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-cellobiosyl)thiourea (5h)**

Obtained from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-cellobiosyl isothiocyanate (**1h**; 0.14 g, 0.2 mmol) under the reaction conditions stated in the Table, Entry 8; yield: 0.1 g (87%); $[\alpha]_D$ –28.7 (c = 1.0, CH_2Cl_2).

FABMS: m/z = 1335 ($[M + Na]^+$).

^1H NMR (500 MHz, $CDCl_3$, 313 K): δ = 7.0 (br s, 1 H, NH), 5.35 (br s, 1 H, H-1), 5.25 (t, 1 H, J = 8.6 Hz, H-3), 5.10 (t, 1 H, J = 9.3 Hz, H-3'), 5.03 (t, 1 H, J = 8.6 Hz, H-4'), 4.89 (dd, 1 H, J = 9.3, 8.0 Hz, H-2'), 4.81 (t, 1 H, J = 8.6 Hz, H-2), 4.48 (m, 1 H, H-6a), 4.46 (d, 1 H, J = 8.0 Hz, H-1'), 4.33 (dd, 1 H, J = 12.5, 4.4 Hz, H-6'a), 4.09 (dd, 1 H, J = 12.5, 4.1 Hz, H-6b), 4.01 (dd, 1 H, J = 12.5, 2.1 Hz, H-6'b), 3.75 (m, 1 H, H-5), 3.73 (t, 1 H, J = 8.6 Hz, H-4), 3.62 (ddd, 1 H, J = 9.3, 4.4, 4.1 Hz, H-5'), 2.09, 2.05, 2.04, 2.01, 2.00, 1.97, 1.84 (7 s, each 3 H, 7 $COCH_3$).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 183.2 (CS), 171.9, 170.5, 170.3, 169.4, 169.3, 169.0 (CO), 100.7 (C-1'), 82.5 (C-1), 76.3 (C-4), 74.1 (C-5), 72.9 (C-3'), 72.0 (C-5), 71.5 (C-2'), 71.1 (C-2), 67.8 (C-4'), 61.8 (C-6), 61.6 (C-6'), 20.9, 20.8, 20.7 ($COCH_3$).

Anal. Calcd for $C_{53}H_{72}N_2O_{34}S$: C, 48.47; H, 5.52; N, 2.13. Found C, 48.35; H, 5.43; N, 2.11.

***N,N'*-Bis(2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-lactosyl)thiourea (5i)**

Obtained from 2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-lactosyl isothiocyanate (**1i**, 0.30 g, 0.44 mmol) under the reaction conditions stated in Table 1, entry 9. Yield 0.26 g (90%); mp 143–145° C; $[\alpha]_D$ = –11.2 (c 0.6, $CHCl_3$)

FABMS: m/z 1335 ($[M+Na]^+$).

^1H NMR (300 MHz, DMSO-d_6): δ = 8.22 (d, 1 H, J = 9.0 Hz, NH), 5.48 (t, 1 H, J = 9.0 Hz, H-1), 5.20 (m, 2 H, H-3, 4'), 5.13 (dd, 1 H, J = 10.5, 3.0 Hz, H-3'), 4.87 (m, 2 H, H-2, 2'), 4.80 (d, 1 H, J = 8.2 Hz, H-1'), 4.29 (m, 1 H, H-5), 4.21 (m, 1 H, H-6a), 3.97 (m, 3 H, H-6b, 6'a, 6'b), 3.81 (m, 2 H, H-4, 5'), 2.09, 2.02, 2.00, 1.98, 1.96, 1.93, 1.88 (7 s, each 3 H, 7 $COCH_3$).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 186.5 (CS), 170.4, 170.3, 170.2, 169.8, 169.7, 169.3 (CO), 101.1 (C-1'), 82.5 (C-1), 76.8 (C-4), 74.8 (C-5), 73.3 (C-2), 71.6, 71.5, 71.1, 69.6 (C-3, 2', 3', 5'), 67.7 (C-4'), 62.7 (C-6), 61.5 (C-6'), 20.6, 20.5, 20.3, 20.2, 20.1 ($COCH_3$).

Anal. Calcd for $C_{53}H_{72}N_2O_{34}S$: C, 48.47; H, 5.52; N, 2.13; S, 2.44. Found C, 48.47; H, 5.73; N, 2.19; S, 2.17.

***N,N'*-Bis-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)thiourea (5j)**

Obtained from 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl isothiocyanate (**1j**; 0.26 g, 0.66 mmol) under the reaction conditions stated in the Table, Entry 10; yield: 0.17 g (72%); mp 250°C (dec.); $[\alpha]_D$ –17 (*c* = 0.5, $CHCl_3$).

FABMS: m/z 757 ($[M+Na]^+$).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (d, 1 H, *J* = 8.9 Hz, NHCS), 8.05 (d, 1 H, *J* = 9.6 Hz, NHCO), 5.48 (t, 1 H, *J* = 8.9 Hz, H-1), 5.04 (t, 1 H, *J* = 8.9 Hz, H-3), 4.82 (t, 1 H, *J* = 8.9 Hz, H-4), 4.18 (dd, 1 H, *J* = 12.0, 4.2 Hz, H-6a), 3.96 (q, 1 H, *J* = 8.9 Hz, H-2), 3.90 (br d, 1 H, *J* = 12.0 Hz, H-6b), 3.72 (m, 1 H, H-5), 1.97, 1.95, 1.89, 1.76 (4 s, each 3 H, 4 $COCH_3$).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 185.5 (CS), 169.9, 169.4, 169.2 (CO), 82.1 (C-1), 73.5 (C-5), 72.0 (C-3), 68.4 (C-4), 61.6 (C-6), 51.5 (C-2), 22.6, 20.5, 20.4, 20.3 ($COCH_3$).

Anal. Calcd for $C_{29}H_{42}N_4O_{16}S$: C, 47.41; H, 5.76; N, 7.63; S, 4.36. Found C, 47.42; H, 6.22; N, 7.28; S, 4.06.

***N,N'*-Bis(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thiourea, *N*-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)-*N'*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)thiourea, and *N,N'*-Bis-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)thiourea [5k (α,α), (α,β), and (β,β)]:**

Obtained as an inseparable mixture by treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl isothiocyanate (**1k**; 0.2 g, 0.51 mmol) with pyridine-water under the reaction conditions stated in the Table, Entry 13; yield: 0.17 g (90%); α,α:α,β:β,β ratio = 15:80:5 (^{1}H integration).

Compound 5k (α,α)

This compound was isolated in pure anomeric form from the reaction of **1k** (0.2 g, 0.51 mmol) with $CHCl_3/Et_3N/H_2O$ under the reaction conditions stated in the Table, Entry 15; yield: 0.075 g, 40%; amorphous; $[\alpha]_D$ +47.6 (*c* = 0.8, CH_2Cl_2).

UV(CH_2Cl_2): λ = 258 nm (ε_{mM} = 12.8).

FABMS: *m/z* = 759 ($[M + Na]^+$).

IR (KBr): ν = 3567, 3337, 2967, 1744, 1539, 1206, 1036 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (br d, 1 H, NH), 5.72 (br s, 1 H, H-1), 5.33–5.27 (m, 2 H, H-2, 3), 5.17 (t, 1 H, *J* = 9.0 Hz, H-4), 4.38 (dd, 1 H, *J* = 12.2, 6.2 Hz, H-6a), 4.20 (dd, 1 H, *J* = 12.2, 2.7 Hz, H-6b), 4.06 (ddd, 1 H, *J* = 9.0, 6.2 Hz, 2.7 H-5), 2.10, 2,06, 2.04, 2.03 (4 s, each 3 H, 4 $COCH_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 185.1 (CS), 170.6, 170.0, 169.8, 169.4 (CO), 79.5 (C-1), 71.7 (C-5), 68.9 (C-4), 68.7 (C-2), 68.2 (C-3), 61.8 (C-6), 20.6 ($COCH_3$).

Anal. Calcd for $C_{29}H_{40}N_2O_{18}S$: C, 47.28; H, 5.47; N, 3.80. Found C, 47.27; H, 5.23; N, 3.71.

Compound 5k (α,β)

This compound was prepared stereoselectively by the coupling reaction of **1k** (194 mg, 0.43 mmol) with 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylamine hydrochloride (**9**; 0.191 g, 0.5 mmol) in pyridine (5 mL); yield: 0.196 g (67%); amorphous, $[\alpha]_D$ +36.5 (*c* = 0.9, $CHCl_3$); UV(CH_2Cl_2)

λ = 258 nm (ε_{mM} 14.9).

FABMS: *m/z* = 759 ($[M+Na]^+$).

IR (film): ν = 3392, 2963, 1753, 1539, 1370, 1223, 1053 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, 1 H, *J* = 2.6 Hz, NHα), 7.26 (d, 1 H, *J* = 8.3, NHβ), 5.97 (dd, 1 H, *J* = 8.3, 1.0 Hz, H-1β), 5.50 (d, 1 H, *J* = 2.6 Hz, H-1α), 5.48 (dd, 1 H, *J* = 3.2, 1.0 Hz, H-2β), 5.31 (t, 1 H, *J* = 2.6 Hz, H-2α), 5.24 (t, 1 H, *J* = 8.4 Hz, H-4α), 5.22 (dd, 1 H, *J* = 8.4, 2.6 Hz, H-3α), 5.19 (t, 1 H, *J* = 10.0 Hz, H-4β), 5.12 (dd, 1 H, *J* = 10.0, 3.2 Hz, H-3β), 4.28 (dd, 1 H, *J* = 12.9, 5.0 Hz, H-6aα), 4.27 (dd, 1 H, *J* = 12.4, 5.3 Hz, H-6aβ), 4.07 (dd, 1 H, *J* = 12.4, 2.2 Hz, H-6bβ), 4.00 (m, 1 H, H-5α), 3.98 (dd, 1 H, *J* = 12.9, 1.7 Hz, H-6bα), 3.78 (ddd, 1 H, *J* = 10.0, 5.3, 2.2 Hz, H-5β), 2.18, 2.14, 2.06, 2.05, 2.02, 2.01, 2.00, 1.94 (8 s, each 3 H, 8 $COCH_3$).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 184.1 (CS), 170.7, 170.6, 170.4, 170.2, 169.8, 169.7, 169.6, 169.4 (CO), 80.9 (C-1β), 80.6 (C-1α), 74.2 (C-5β), 71.5 (C-3β), 70.3 (C-5α), 69.8 (C-2β), 69.3 (C-4β), 68.1 (C-2α), 65.8 (C-3α), 65.4 (C-4α), 61.8 (C-6α), 61.6 (C-6β), 20.8, 20.7, 20.6, 20.4 ($COCH_3$).

Anal. Calcd for $C_{29}H_{40}N_2O_{18}S$: C, 47.28; H, 5.47; N, 3.80; S, 4.35. Found C, 47.41; H, 5.39; N, 3.82; S, 4.31.

Compound 5k (β,β)

This compound was stereoselectively prepared by the coupling reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl isothiocyanate (**10**; 0.1 g, 0.26 mmol) with 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylamine hydrochloride (**9**; 0.098 g, 0.26 mmol) in pyridine (5 mL); yield: 0.135 g (70%); amorphous; $[\alpha]_D$ –9.7 (*c* = 0.8, $CHCl_3$);

UV(CH_2Cl_2): λ = 255 nm (ε_{mM} 13.2).

FABMS: *m/z* = 759 ($[M+Na]^+$), 737 (20, $[M + H]^+$).

IR (film): ν = 3308, 2963, 2924, 1750, 1539, 1373, 1242, 1090, 1055 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 318 K): δ = 6.09 (d, 1 H, *J* = 8.4 Hz, NH), 5.87 (br d, 1 H, H-1), 5.40 (dd, 1 H, *J* = 10.0, 3.2 Hz, H-3), 5.18 (t, 1 H, *J* = 10.0 Hz, H-4), 5.12 (dd, 1 H, *J* = 3.2, 1.1 Hz, H-2), 4.26 (dd, 1 H, *J* = 12.3, 5.6 Hz, H-6a), 4.04 (dd, 1 H, *J* = 12.3, 2.3 Hz, H-6a), 3.78 (ddd, 1 H, *J* = 10.0, 5.6, 2.3 Hz, H-5), 2.18, 2.07, 2.01, 1.95 (4 s, each 3 H, 4 $COCH_3$).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 183.1 (CS), 170.9, 170.3, 169.7, 169.6 (CO), 80.5 (C-1), 73.7 (C-5), 71.3 (C-3), 69.7 (C-2), 65.1 (C-4), 62.1 (C-6), 20.7 ($COCH_3$).

Anal. Calcd for $C_{29}H_{40}N_2O_{18}S$: C, 47.28; H, 5.47; N, 3.80; S, 4.35. Found C, 47.31; H, 5.34; N, 3.82; S, 4.36.

***N,N*-Bis(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiourea and *N*-(2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl)-*N'*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiourea [5l (β,β) and (α,β)]**

Obtained as a mixture by treatment of 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl isothiocyanate (**11**; 0.3 g, 0.9 mmol) with pyridine/water under the reaction conditions stated in the Table, Entry 14; yield: 0.21 g (74%); β,β:α,β ratio = 1:1 (^{1}H integration). Pure samples of both isomers were obtained after column chromatography of the crude product using 1:1 EtOAc/hexanes as eluent.

Compound 5l (β,β)

Amorphous solid (0.1g, 36%); R_f 0.27 (1:1, EtOAc/hexanes); $[\alpha]_D$ +9.1 (*c* = 0.6, $CHCl_3$).

UV($CHCl_3$): λ = 270 nm (ε_{mM} 12.8).

FABMS: *m/z* = 615 ($[M + Na]^+$), 593 ($[M + H]^+$).

IR (film): ν = 3342, 2924, 2854, 1747, 1539, 1226, 1066, 1038 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, 1 H, *J* = 7.8 Hz, NH), 5.42 (br s, 1 H, H-1), 5.34 (t, 1 H, *J* = 9.3 Hz, H-3), 4.99 (ddd, 1 H, *J* = 11.5, 9.3, 5.7 Hz, H-4), 4.90 (t, 1 H, *J* = 9.3 Hz, H-2), 4.11 (dd, 1 H, *J* = 11.5, 5,7 Hz, H-5a), 3.51 (t, 1 H, *J* = 11.5 Hz, H-5b), 2.08, 2.05, 2.04 (3 s, each 3 H, 3 $COCH_3$).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 185.2 (CS), 171.3, 169.6, 169.5 (CO), 82.9 (C-1), 72.0 (C-3), 70.9 (C-2), 68.9 (C-4), 64.1 (C-5), 20.5 ($COCH_3$).

Anal. Calcd for $C_{23}H_{32}N_2O_{14}S$: C, 46.62; H, 5.44; N, 4.72. Found C, 46.60; H, 5.65; N, 4.73.

Compound 5l (α,β)

Amorphous solid (0.11 g, 38%); R_f 0.15 (1:1, EtOAc/hexanes); $[\alpha]_D$ = +38.3 (*c* = 0.6, $CHCl_3$).

UV($CHCl_3$): λ = 272 nm (ε_{mM} 12.8).

FABMS: *m/z* = 615 ([M + Na])$^+$, 593 ([M + H])$^+$.

IR (film): ν = 3357, 2922, 2852, 1751, 1543, 1223, 1042 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7. 30 (br s, 1 H, NHα), 6.75 (br s, 1 H, NHβ), 5.67 (br s, 1 H, H-1α), 5.48 (br s, 1 H, H-1β), 5.34 (t, 1 H, *J* = 7.9 Hz, H-3α), 5.26 (t, 1 H, *J* = 9.3 Hz, H-3β), 5.00 (m, 1 H, H-2α), 4.99 (ddd, 1 H, *J* = 10.5, 9.3, 5.7 Hz, H-4β), 4.94 (t, 1 H, *J* = 9.3 Hz, H-2β), 4.90 (ddd, 1 H, *J* = 8.1, 7.9, 4.7 Hz, H-4α), 4.09 (dd, 1 H, *J* = 10.5, 5.7 Hz, H-5aβ), 3.93 (dd, 1 H, *J* = 12.0, 4.7 Hz, H-5aα), 3.67 (dd, 1 H, *J* = 12.0, 8.1 Hz, H-5bα), 3.47 (t, 1 H, *J* = 10.5 Hz, H-5bβ), 2.12, 2.08, 2.07, 2.06, 2.05, 2.04 (6 s, each 3 H, 6 $COCH_3$).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 185.6 (CS), 169.6, 169.5, 169.4, 169.0 (CO), 83.3 (C-1β), 78.7 (C-1α), 71.9 (C-3β), 70.6 (C-2β), 68.9 (C-4β), 68.3(C-2α), 68.1 (C-3α), 67.6 (C-4α), 64.3 (C-5β), 61.4 (C-5α), 20.5 ($COCH_3$).

Anal. Calcd for $C_{23}H_{32}N_2O_{14}S$: C, 46.62; H, 5.44; N, 4.72. Found C, 46.59; H, 5.27; N, 4.72.

***N,N'*-Bis(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosid-6-yl)thiourea (5m)**

Obtained from methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-glucopyranoside (**1m**; 0.2 g, 0.55 mmol) under the reaction conditions stated in the Table, Entry 16; yield: 0.18 g (95%); amorphous; R_f 0.22 (1:1 EtOAc/hexanes); $[\alpha]_D$ +136.0 (*c* = 0.9, CH_2Cl_2).

UV(CH_2Cl_2): λ = 252 nm (ε_{mM} 12.8).

FABMS: *m/z* = 703 ([M + Na]$^+$), 681 ([M + H]$^+$).

IR (film): ν = 3476, 3380, 1753, 1547, 1227 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 323 K): δ = 6.76 (t, 1 H, *J* = 5.8 Hz, NH), 5.47 (d, 1 H, *J* = 9.7 Hz, H-3), 4.94 (d, 1 H, *J* = 3.6 Hz, H-1), 4.84 (t, 1 H, *J* = 9.7 Hz, H-4), 4.79 (dd, 1 H, *J* = 9.7, 3.6 Hz, H-2), 4.00 (ddd, 1 H, *J* = 9.7, 5.8, 2.7 Hz, H-5), 3.78 (ddd, 1 H, *J* = 14.8, 5.8, 2.7 Hz, H-6a), 3.50 (dt, 1 H, *J* = 14.8, 5.8 Hz, H-6b), 3.43 (s, 3 H, OCH_3), 2.04, 2.03, 1.97 (3 s, each 3 H, 3 $COCH_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$, 313 K): δ = 184.5 (CS), 170.0, 169.7, 169.6 (CO), 96.6 (C-1), 70.8 (C-2), 69.7 (C-4), 69.4 (C-3), 68.0 (C-5), 55.4 (OMe), 44.7 (C-6), 20.4, 20.3 ($COCH_3$).

Anal. Calcd for $C_{27}H_{40}N_2O_{16}S$: C, 47.64; H, 5.92; N, 4.11; S, 4.71. Found C, 47.58; H, 6.00; N, 4.30; S, 4.78.

***N,N'*-Bis(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-mannopyranosid-6-yl)thiourea (5n)**

Obtained from methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-mannopyranoside (**1n**; 0.2 g, 0.55 mmol) under the reaction conditions stated in the Table, Entry 17; yield: 0.16 g (84%); amorphous; R_f 0.11 (1:1 EtOAc/hexanes); $[\alpha]_D$ +58.7 (*c* = 1.0, CH_2Cl_2).

FABMS: *m/z* = 702 ([M + Na]$^+$).

IR (film) 3436, 1760, 1640, 1236 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 313 K): δ = 6.56 (br s, 1 H, NH), 5.29 (dd, 1 H, *J* = 10.0, 3.5 Hz, H-3), 5.20 (dd, 1 H, *J* = 3.5, 1.4 Hz, H-3), 5.09 (t, 1 H, *J* = 10.0 HZ, H-4), 4.64 (d, 1 H, *J* = 1.4 Hz, H-1), 3.91 (ddd, 1 H, *J* = 10.0, 7.6, 2.2 Hz, H-5), 3.87 (m, 1 H, H-6a), 3.42 (m, 1 H, H-6b), 3.36 (s, 3 H, OCH_3), 2.10, 2.04, 1.95 (3 s, each 3 H, 3 $COCH_3$).

^{13}C NMR (125.7 MHz, $CDCl_3$, 313 K): δ = 184.1 (CS), 171.0, 170.1, 169.7, (CO), 98.5 (C-1), 69.4 (C-2, 5), 68.7 (C-3), 67.1 (C-4), 55.3 (OCH_3), 45.2 (C-6), 20.9, 20.7, 20.6 ($COCH_3$).

Anal. Calcd for $C_{28}H_{40}N_2O_{16}S$: C, 47.64; H, 5.82; N, 4.04. Found C, 47.82; H, 5.82; N, 4.09.

Reactions of Glucopyranosyl and Xylopyranosyl Isothiocyanates (1f and 1l, respectively) in $CHCl_3/Et_3N/H_2O$

A solution of the corresponding isothiocyanate (0.1 mmol) in 20:2:1 $CHCl_3/Et_3N/H_2O$ (2.3 mL) was stirred for 24 h at r.t. TLC monitoring (1:1 EtOAc/hexanes) of the mixture showed the presence of residual starting material, the expected symmetric thiourea (**5f** or **5l**) and a faint new spot having an intermediate retention time. Evaporation of the solvent under reduced pressure resulted in transformation of this unidentified product, to a great extent, into two main compounds having very close retention times. Attemps to purify the transient intermediate by preparative thin layer chromatography likewise resulted in decomposition. Instead, small amounts of ethyl *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamate (**7**, R = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; from **1f**) and *N,N*-diethyl-N'-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiourea (**8**, R = 2,3,4,6-tetra-*O*-acetyl-α-D-xylopyranosyl; from **1l**) were isolated using 1:1 EtOAc/hexanes as eluent. The identity of these compounds was stablished by comparison of their spectroscopic data with those of authentic specimes obteined by reaction of **1f** and **1l** with ethanol and diethylamine, respectively.[22]

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