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Reaction of 1,2-*trans*-glycosyl acetates with thiourea: a new entry to 1-thiosugars

Farid M. Ibatullin,[a,*] Konstantin A. Shabalin,[a] Janne V. Jänis[b] and Alexander G. Shavva[c]

[a]*Molecular and Radiation Biophysics Division, Petersburg Nuclear Physics Institute, Gatchina 188300, Russia*
[b]*Department of Chemistry, University of Joensuu, Joensuu, Finland*
[c]*Chemical Department of Petersburg State University, St.-Petersburg, Russia*

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Abstract—The reaction of 1,2-*trans*-glycosyl acetates with thiourea under boron trifluoride etherate catalysis affording acetylated *S*-glycosyl isothiourea derivatives is described. The isothiourea derivatives obtained can be readily transformed into the desired 1-thiosugar derivative by reaction with triethylamine and subsequent alkylation or acylation of the in situ formed 1-thioaldose.

1-Thiosugars have attracted considerable attention over the last decades. Due to their close structural similarity to the natural *O*-glycosides they have been widely used in biochemical[1] and structural[2] investigations of glycosidases. Owing to the stability of a thioglycosidic bond to enzymatic cleavage, thioglycosides have been considered as very promising candidates for the preparation of carbohydrate-based therapeutics.[3] Thioglycosides have found wide applications in carbohydrate chemistry as very convenient glycosyl donors. The current progress in the synthesis of complex oligosaccharides has been greatly related to the development of new versatile glycosylation methods utilizing thioglycosides as glycosyl donors.[4]

The Lewis acid catalyzed reaction of per-*O*-acetylated sugars with alkyl or aryl thiols[5] is one of the most often employed approaches for the synthesis of 1-thioglycosides. The method allows synthesizing target compounds in one step directly from readily available peracetylated sugars, although it often suffers from a number of drawbacks, including the necessity of working with malodorous and toxic mercaptans. This method often leads to the formation of anomerized products.

Alternatively, the conversion can be performed using alkyl- or arylthiotrimethylsilanes,[6] although they are less available than thiols and, therefore, require special preparation.

One of the most convenient and simple approaches for the stereoselective synthesis of 1,2-*trans*-thioglycosides is based upon utilization of *S*-glycosyl isothiourea derivatives as starting compounds.[7] Recently, we have shown that isothiourea derivatives of sugars can also be successfully applied for the synthesis of thiodisaccharides[8] and thiooligosaccharides.[9]

Up to now, the only method for the preparation of *S*-glycosyl isothiourea derivatives is the reaction of thiourea with glycosyl halides,[7] that are generally prepared from sugar peracetates.

However, sugar peracetates can also be used as very convenient glycosyl-donors, that have been widely utilized for glycosylation of various compounds,[10] including thiols[5] and thioacetic acid.[11] Nevertheless, no attempt has been made to investigate such reactions with thiourea, which might be a convenient approach to *S*-glycosyl isothiourea derivatives, and consequently to thioglycosides, avoiding the use of mercaptans and the halogenose preparation step.

Therefore, in the course of our current research[12] and interest in thioglycoside synthesis, we decided to investigate the reactivity of per-*O*-acetylated sugars with thiourea.

Thiourea readily reacts with various electrophiles, including carbenium ions, affording *S*-alkyl isothiouronium salts. So, reactions of thiourea with alkyl alcohols,[13] oxetanes,[14] or with benzoquinones[15] under strongly acidic conditions seem to proceed through a

* Corresponding author.

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formation of carbocation intermediate. Very recently a similar mechanism was postulated for the reaction of di- and trimethoxybenzyl alcohols with thiourea in acidic media, leading to the corresponding isothiourea derivatives.[16] It is known that most Lewis acid catalyzed reactions of 1,2-*trans*-glycosyl esters proceed through the formation of a 1,2-acyloxonium cation, as the key intermediate.[17] Therefore, we assumed that in the presence of Lewis acids, sugar peracetates would also be able to react with thiourea, due to the strong electrophilic character of the 1,2-acyloxonium ion.

Indeed, treatment of 1,2-*trans*-glycosyl acetates with thiourea in the presence of boron trifluoride etherate in acetonitrile at room temperature causes a slow disappearance of the staring sugar derivatives leading, according to TLC analysis, to formation of a more polar compound. At this temperature the conversion requires more than 48 hours for completion. At reflux, the reaction proceeds much faster and is generally over in 20 min with the full disappearance of the starting peracetates.

In several cases the resulting substances were isolated as solids by crystallization from an appropriate alcohol and characterized by mass and NMR spectrometry.[18] Electrospray ionization mass spectra of the resulting solids showed intensive signals of the ions corresponding to the adduct cations $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ and $[2M+H]^+$ as well as the signals of the fragment ions, including [M+H−76], that corresponds to the loss of thiourea.

^{1}H NMR spectra, in addition to all proton signals of the acetylated sugar moiety, contained characteristic signals at 9–9.5 ppm corresponding to four amide protons, belonging to the isothiouronium fragment of the molecule. ^{13}C NMR spectra contained a signal at 171.5–171.9, corresponding to the isothiouronium carbon. All NMR spectra have close similarity to those measured for *S*-glycosyl isothiouronium bromides, prepared using the common procedure.[19]

The substances obtained have shown the chemical behaviour typical for *S*-glycosyl isothiouronium halides, including a conversion into the corresponding acetylated thioglycoses in basic media and subsequent transformation into thioglycosides using known procedures. These observations allowed us to conclude that the substances obtained are *S*-glycosyl isothiourea derivatives.

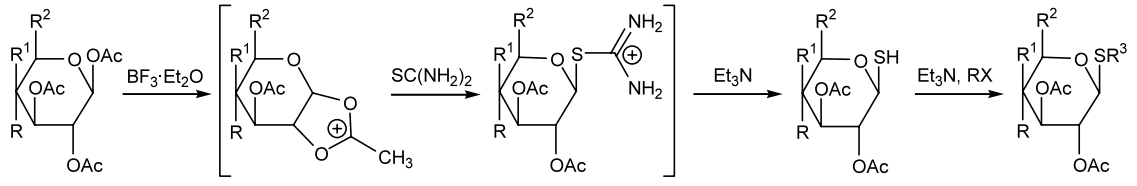
The strong 1,2-*trans*-stereoselectivity of the reaction may be explained by a BF_3 induced formation of the 1,2-acyloxonium ion as the reaction intermediate, which reacts with nucleophiles in only one possible way, leading exclusively to 1,2-*trans* substitution products (Scheme 1). The initially formed isothiourea derivatives do not undergo anomerization, unlike alkyl or aryl thioglycosides, which can often be obtained only in the anomerized form, even under mild reaction conditions.

The isothiourea intermediates obtained without isolation can be directly converted into thioglycosides by alkylation under basic conditions. This was performed according to a recently described literature method using the triethylamine promoted reaction in acetonitrile.[8]

Typical procedures are described as follows. To a solution of peracetylated mono- or disaccharide (10 mmol) in anhydrous acetonitrile (20 mL), thiourea (11.0 mmol) and BF_3–etherate (21.0 mmol) were added. The resulting mixture was refluxed until the full disappearance of the starting material, according to TLC, had occurred (20 min).[20] After cooling to room temperature, triethylamine (31 mmol) and alkyl halide (11 mmol) were added with stirring and the reaction mixture was kept at ambient temperature until the conversion was completed. The solvent was evaporated and the resulting syrup was diluted with toluene (30 mL) and washed with water. After drying ($MgSO_4$) and evaporation the residue was crystallized from an appropriate alcohol to give a pure product (Table 1).

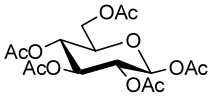
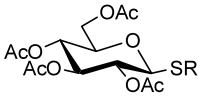
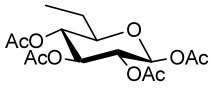
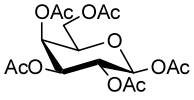
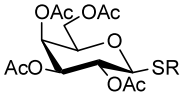
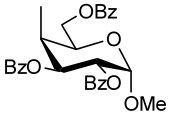
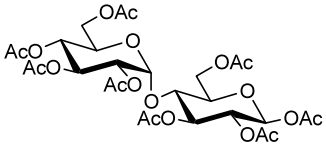
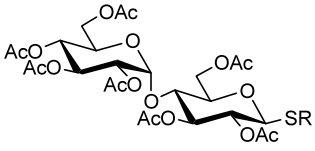
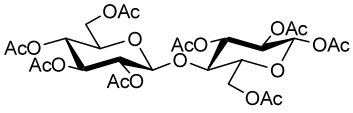
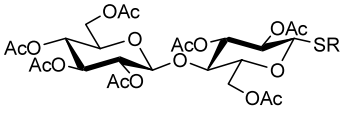
The interglycosidic bonds of oligosaccharides are stable under the described reaction conditions. Therefore, the method can also be successfully applied for the introduction of a thioglycosidic bond into oligosaccharides. This has been confirmed by syntheses of several thioglycosides of maltose and cellobiose.

Due to the anhydrous reaction conditions, the procedure may also be used for the conversion of sugar peracetates into glycosyl thioesters according to a recently described approach.[8] Using appropriate activated sugar derivatives for the coupling reaction, the procedure can be utilized for the synthesis of the corresponding thio-oligosaccharides, that has been shown to be successful for the syntheses of several thiodisaccharides, including acylated methyl glycoside of 4-thiogalactobiose (β-D-Galp-(1→4)-α-D-Galp-OMe) and octa-*O*-acetyl-4-thiogentiobiose (β-D-Glcp-(1→6)-α-D-Glcp).



Scheme 1. Proposed mechanism for boron trifluoride etherate catalyzed reaction of sugar acetates with thiourea.

Table 1. Synthesis of 1,2-*trans*-thioglycosides

Entry	Starting sugar peracetate	Product	R	Yield(%)
1			Me	57
2			Bn	68
3			Ac	71[a]
4				83[b]
5			All	55
6			Et	66
7			4-NO_2Bn	78
8			2,4-di-NO_2Ph	69
9				85[b]
10			Et	80
11			4-NO_2Bn	74
12			Bz	74[a]
13			Et	70

[a] 4.5 mmol of triethylamine and 2.5 mmol Ac_2O (entry 3) or BzCl (entry 11) were used per 1.0 mmol of starting sugar peracetate;

[b] 1.3 mmol of starting sugar peracetate was used per 1.0 mmol of 6-iodo- (entry 4) or 4-triflyl- (entry 8) glucose derivatives.

Conclusion

The reactions described here of 1,2-*trans*-glycosyl acetates with thiourea represent a novel simple route to 1,2-*trans*-glycosyl isothiourea derivatives. The reactions provide a very convenient tool for the synthesis of various 1-thiosugar derivatives, including thioglycosides, thiooligosaccharides and glycosyl thioesters.

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18. Selected data[21] for several isolated *S*-glycosyl isothiourea derivatives:

    2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl isothiourea derivative. ^{1}H NMR (DMSO-d_6): δ 9.17, 9.01 (2s, each 2H, 2×NH_2), 5.62 (d, 1H, $J_{1,2}$=9.9 Hz, H-1), 5.31 (dd, 1H, $J_{3,4}$=9.6 Hz, H-3), 5.11 (dd, 1H, $J_{2,3}$=9.6 Hz, H-2), 5.10 (dd, 1H, $J_{4,5}$=9.6 Hz, H-4), 4.20 (dd, 1H, $J_{6a,6b}$=12.1 Hz, $J_{5,6a}$=4.9 Hz, H-6a), 4.14 (m, 1H, H-5), 4.09 (dd, 1H, H-6b), 2.05, 2.02, 1.99, 1.97 (each s, 4×3H, 4×Ac). ^{13}C NMR (DMSO-d_6): δ 175.2, 174.7, 174.5, 174.42 (4×CO-Ac), 171.5 ($SC(NH_2)_2$), 85.05 (C-1), 80.6, 77.6, 73.9, 72.6 (C-5, C-3, C-2, C-4), 66.8 (C-6), 25.6, 25.5, 25.4, 25.3 (CH_3-Ac). HRMS (m/z): 407.1096 (407.1124 calcd for $C_{15}H_{22}N_2O_9S$ [M+H]$^+$).

    2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl isothiourea derivative. ^{1}H NMR (DMSO-d_6): δ 9.27, 9.04 (2s, 2×2H, 2×NH_2), 5.61 (d, 1H, $J_{1,2}$=9.9 Hz, H-1), 5.39 (dd, 1H, $J_{4,5}$=1.0 Hz, H-4), 5.24 (dd, 1H, $J_{3,4}$=3.4 Hz, H-3), 5.12 (dd, 1H, $J_{2,3}$=10.0 Hz, H-2), 4.39 (td, 1H, $J_{5,6a}$=7.0 Hz, $J_{5,6b}$=5.4 Hz, H-5), 4.11 (dd, 1H, $J_{6a,6b}$=11.5 Hz, H-6a), 4.07 (dd, 1H, H-6b), 2.14, 2.08, 2.01, 1.95 (4s, 4×3H, 4×Ac). ^{13}C NMR (DMSO-d_6): δ 175.1, 175.0, 174.8, 174.5 (4×CO-Ac), 171.6 ($SC(NH_2)_2$), 85.5 (C-1), 79.7, 75.6, 72.3, 71.5 (C-5, C-3, C-2, C-4), 66.5 (C-6), 25.63, 25.6, 25.5, 25.4 (4×CH_3-Ac). HRMS (m/z): 407.1113 (407.1124 calcd for $C_{15}H_{22}N_2O_9S$ [M+H]$^+$).

    2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl isothiourea derivative: ^{1}H NMR (DMSO-d_6): δ 9.10 (s, 4H, 2×NH_2), 5.70 (d, 1H, $J_{1,2}$=7.8 Hz, H-1), 5.16 (dd, 1H, $J_{3,4}$=7.8 Hz, H-3), 5.03 (dd, 1H, $J_{2,3}$=7.8 Hz, H-2), 4.98 (td, 1H, $J_{4,5a}$=4.3 Hz, $J_{4,5b}$=7.8 Hz, H-4), 4.15 (dd, 1H, $J_{5a,5b}$=12.1 Hz, H-5a), 3.68 (dd, 1H, H-5b), 2.06, 2.03, 2.01 (3s, 3×3H, 3×Ac). ^{13}C NMR (DMSO-d_6): δ 174.6, 174.4, 174.3 (3×CO-Ac), 171.9 ($SC(NH_2)_2$), 85.88 (C-1), 75.1, 73.4, 72.3 (C-3, C-2, C-4), 69.5 (C-5), 25.6, 25.5, 25.4 (3×CH_3-Ac). HRMS (m/z): 335.0900 (335.0913 calcd for $C_{12}H_{19}N_2O_7S$ [M+H]$^+$).

    2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl isothiourea derivative. ^{1}H NMR (DMSO-d_6): δ 9.20, 8.96 (2s, 2×2H, 2×NH_2), 5.58 (d, 1H, $J_{1,2}$=10.1 Hz, H-1), 5.28 (dd, 1H, $J_{3',4'}$=9.6 Hz, H-3′), 5.18 (dd, 1H, $J_{3,4}$=9.1 Hz, H-3), 4.98 (dd, 1H, $J_{4,5}$=9.8 Hz, H-4′), 4.88 (dd, 1H, $J_{2,3}$=9.5 Hz, H-2), 4.82 (d, 1H, $J_{1',2'}$=8.0 Hz, H-1′), 4.65 (dd, 1H, $J_{2',3'}$=9.6 Hz, H-2′), 4.39 (dd, 1H, $J_{6a,6b}$=12.0 Hz, H-6a), 4.24 (dd, 1H, $J_{6'a,6'b}$=12.5 Hz, 6′a), 4.08 (dd, 1H, H-6b), 4.02 (m, 1H, $J_{5',6'a}$=4.2 Hz, $J_{5',6'b}$=2.2 Hz, H-5′), 3.99 (m, 1H, H-5), 3.94 (dd, 1H, $J_{4,5}$=8.7 Hz, H-4), 9.93 (dd, 1H, H-6′b), 2.08, 2.04, 2.00, 1.98, 1.97, 1.96, 1.91(7s, 7×3H, 7×Ac). ^{13}C NMR (DMSO-d_6): δ 175.4, 175.2, 174.8, 174.6, 174.5, 174.4, 174.2 (7×CO-Ac), 171.6 ($SC(NH_2)_2$), 104.78 (C-1′), 84.78 (C-1), 81.7, 80.7, 77.6, 77.3, 76.4, 75.7, 74.1, 72.9, (C-4, C-5, C-3′, C-2, C-5′, C-2′, C-3, C-4′), 67.0, 66.7 (C-6′, C-6), 25.7, 25.6, 25.5, 25.4, 25.36, 25.3, 25.25 (7×CH_3-Ac). HRMS (m/z): 695.2025 (695.1969 calcd for $C_{27}H_{39}N_2O_{17}S$ [M+H]$^+$).
19. See for example data for 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl isothiouronium bromide: ^{1}H NMR (DMSO-d_6): δ 9.39, 9.17 (2s, 2×2H, 2×NH_2), 5.85 (d, 1H, $J_{1,2}$=10.1 Hz, H-1), 5.37 (dd, 1H, $J_{4,5}$=1.1 Hz, H-4), 5.21 (dd, 1H, $J_{3,4}$=3.4 Hz, H-3), 5.09 (dd, 1H, $J_{2,3}$=9.9 Hz, H-2), 4.51 (td, 1H, $J_{5,6a}$=6.4 Hz, $J_{5,6b}$=5.9 Hz, H-5), 4.08 (dd, 1H, $J_{6a,6b}$=11.5 Hz, H-6a), 4.05 (dd, 1H, H-6b), 2.12, 2.07, 2.00, 1.93 (4s, 4×3H, 4×Ac). ^{13}C NMR (DMSO-d_6): δ 169.94, 169.92, 169.7, 169.4 (4×CO-Ac), 166.5 ($SC(NH_2)_2$, 80.06 (C-1), 74.4, 70.5, 67.2, 66.4 (C-5, C-3, C-2, C-4), 61.3 (C-6), 20.6, 20.5, 20.46, 20.4 (4×CH_3-Ac).
20. The *S*-glycosyl isothiourea derivatives can be isolated on this step by an addition of pyridine (21.0 mmol) and concentration of resulting mixture under the reduced pressure. A dilution of the obtained syrups with 2-propanol (5–10 mL) resulted in precipitation of pyridine–boron trifluoride complex, which was removed by filtration. The resulting filtrates were diluted with 2-propanol (20–30 mL) to give crystalline products, which were recrystallised from 2-propanol or from ethanol to give the target products.[18]
21. The NMR data is presented using the convention followed in *Carbohydrate Research* (see Instructions to Authors).