Synthesis of Peracetylated β -D-Glucopyranosyl Thioureas from Substituted 2-Aminobenzo-1', 3'-thiazoles

NGUYEN DINH THANH

Faculty of Chemistry
College of Science, Hanoi National University
19 Le Thanh Tong, Ha Noi 10000, Viet nam
nguyendinhthanh@hus.edu.vn

Received 6 April 2011; Accepted 7 June 2011

Abstract: Some peracetylated glucopyranosyl thioureas containing a heterocyclic ring system, benzo-1,3-thiazole have been prepared by the condensation reaction of tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate and corresponding substituted 2-amino-(6-substituted)benzo-1,3-thiazoles. Investigated heating conditions showed that the solventless microwave-assisted method gave higher yields of these thioureas.

Keywords: Glucopyranosyl isothiocyanate, Microwave-assisted, Monosaccharide, Thioureas

Introduction

Glycosyl isothiocyanates have been widely used as valuable intermediates in the synthesis of glycosyl derivatives¹. The isothiocyanates and glycosyl isothiocyanates have been the focus of synthetic attention during recent years because of their potential pharmacological properties². Thioureas and their derivatives show strong antibacterial activity and are versatile reagents in organic synthesis³. Benzo-1,3-thiazoles are bicyclic ring system with multiple applications. They have diverse chemical reactivity and broad spectrum of biological activity⁴, for examples, substituted 2-aminobenzo-1,3-thiazoles show antitumor⁵ and antimalarial activity⁶. Bis-substituted amidino benzo-1,3-thiazoles act as potential anti HIV agents⁷. Some peracetylated glucopyranosyl thioureas containing benzo-1,3-thiazole ring have been obtained in the previous time⁸ using conventional heating in solvent (dioxane, toluene or THF).

Experimental

All melting points were recorded on an electrothermal STUART SMP3 (BIBBY STERILIN-UK) apparatus and are uncorrected. The FTIR-spectra was recorded on Magna 760 FT-IR Spectrometer (Nicolet, USA) in form of KBr and using reflex-measure method.

^1H - and ^{13}C -NMR spectra was recorded on an Avance FT-NMR Spectrometer (Bruker, Germany) at 500.13 MHz and 125.76 MHz, respectively, using $\text{DMSO-}d_6$ as solvent and TMS as an internal standard. Mass spectra were recorded on Micromass AutoSpec Premier Instrument (WATERS, USA) using EI method and on 1100 LC-MSD Trap-SL (Agilent-Technologies, USA) and IONSPECK 910-MS (Varian, USA) using ESI method.

*General conventional heating method for synthesis of substituted N-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-N'-(benzo-1',3'-thiazol-2'-yl)thioureas (in cases of compounds **3a**, **3b** and **3m**) (Method A)*

A mixture of corresponding 2-aminobenzothiazoles **2** (2 mmol) and tetra-O-acetyl- β -D-glucopyranosyl isothiocyanate **1** (2 mmol) in dried dioxane (30 mL) and was heated in reflux for 20–25 h. Solvent was removed under reduced pressure to obtain the sticky residue that was triturated with ethanol and recrystallized from a mixture of ethanol and toluene (1:1 in volume) to afford solid compounds **3a**, **3b** or **3m**.

*General solvent-free microwave-assisted heating method for synthesis of substituted N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-N'-(benzo-1',3'-thiazol-2'-yl)thioureas (in cases of compounds **3a**, **3b** and **3m**)(Method B)*

A mixture of corresponding 2-aminobenzothiazoles **2** (2 mmol) and tetra-O-acetyl- β -D-glucopyranosyl isothiocyanate **1** (2 mmol) was grinded carefully and irradiated under reflux in microwave oven for 3-5 min. The mixture then had become dark-yellow pasty mass. The pasty mass was triturated with ethanol and recrystallized from a mixture of ethanol and toluene (1:1 in volume) to afford solid compounds **3a**, **3b** or **3m**.

*General microwave-assisted heating method for synthesis of substituted N-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-N'-(benzo-1',3'-thiazol-2'-yl)thioureas (**3a-h**) (Method C)*

A mixture of corresponding 2-aminobenzothiazoles **2** (2 mmol) and tetra-O-acetyl- β -D-glucopyranosyl isothiocyanate **1** (2 mmol) was grinded carefully in dried dioxane (3-5 mL) and irradiated under reflux in microwave oven for 20–25 min. The mixture then had become yellow pasty. Solvent was removed under reduced pressure to obtain the sticky residue that was triturated with ethanol and recrystallized from a mixture of ethanol and toluene (1:1 in volume) to afford solid compounds **3**.

*N-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-N'-(6'-chlorobenzo-1',3'-thiazol-2'-yl)thiourea (**3a**)*

White solid; yield 65%; m.p. 210–212 °C; IR (KBr, cm^{-1}): 3175, 3032 (N–H), 1746 (C=O), 1223, 1042 (C–O–C), 1373 (C=S); ^1H NMR ($\text{DMSO-}d_6$): δ 13.22 & 12.19 (1H, *br*, NH), 9.65 & 9.13 (1H, *br*, NH), 5.89 (1H, *t*, $J=8.9$ Hz, H-1), 5.12 (1H, *t*, $J=9.0$ Hz, H-2), 5.45 (1H, *t*, $J=9.15$ Hz, H-3), 4.99 (1H, *t*, $J=9.35$ Hz, H-4), 4.11 (1H, *m*, H-5), 4.21 (1H, *dd*, $J=12.5$, 4.7 Hz, H-6a), 3.99 (1H, *dd*, $J=12.5$, 4.5 Hz, H-6b), 7.63 (1H, *br*, H-4'), 7.45 (1H, *d*, $J=8.0$ Hz, H-5'), 8.08 (1H, *br*, H-7'), 2.01–1.96 (12H, *s*, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR ($\text{DMSO-}d_6$): δ 81.3 (C-1), 72.3 (C-2), 72.6 (C-3), 70.4 (C-4), 67.9 (C-5), 61.6 (C-6), 121.6 (C-4'), 126.7 (C-5'), 127.6 (C-7'), 20.4–20.2 (4C, $4\times\text{CH}_3\text{CO}$), 169.9–169.2 (4C, $4\times\text{CH}_3\text{CO}$), signal of C=S is not appeared; EI-MS (m/z , (relative abundance, %)): 573 (4)/575 (1) (M^+/M^++2), 513 (1.2)/515 (0.8), 454 (2)/456 (1), 394 (1.4)/395 (0.6), 363 (1.4), 365 (1.2), 331 (5), 271 (3), 226 (100, BP)/228 (46), 288 (2), 184 (30), 186 (12), 191 (21), 133 (15), 109 (33); HRMS Calcd. for $\text{C}_{22}\text{H}_{24}^{35}\text{ClN}_3\text{O}_9\text{S}_2/\text{C}_{22}\text{H}_{24}^{37}\text{ClN}_3\text{O}_9\text{S}_2$: 573.0642 / 575.0613, found: 573.0637 / 575.0619.

N-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(6'-bromobenzo-1',3'-thiazol-2'-yl)thiourea (**3b**)

White solid; yield 62%; m.p. 200–202 °C; IR (KBr, cm^{-1}): 3168, 3024 (N–H), 1747 (C=O), 1224, 1044 (C–O–C), 1367 (C=S); ^1H NMR (DMSO- d_6): δ 13.21 & 12.22 (1H, *br*, NH), 9.65 & 9.13 (1H, *br*, NH), 5.88 (1H, *t*, $J=9.4$ Hz, H-1), 5.11 (1H, *t*, $J=9.2$ Hz, H-2), 5.45 (1H, *t*, $J=9.0$ Hz, H-3), 4.99 (1H, *t*, $J=9.75$ Hz, H-4), 4.11 (1H, *m*, H-5), 4.19 (1H, *dd*, $J=12.0$, 3.2 Hz, H-6a), 4.02 (1H, *dd*, $J=12.0$, 3.0 Hz, H-6b), 7.57 (1H, *br*, H-4'), 7.57 (1H, *dd*, $J=7.8$, 1.1 Hz, H-5'), 8.17 (1H, *br*, H-7'), 2.01–1.95 (12H, *s*, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 81.2 (C-1), 72.3 (C-2), 72.6 (C-3), 70.4 (C-4), 67.9 (C-5), 61.6 (C-6), 115.4 (C-4'), 124.4 (C-5'), 129.3 (C-7'), 20.4–20.2 (4C, $4\times\text{CH}_3\text{CO}$), 169.9–169.2 (4C, $4\times\text{CH}_3\text{CO}$), signal of C=S is not appeared; EI-MS (m/z , (relative abundance, %)): 617 (4)/619 (3) (M^+/M^++2), 502 (2)/500 (1.8), 438 (1)/440 (1.2), 398 (2.8)/400 (3), 350 (2), 270 (93)/272 (100) (BP), 228 (36), 230 (32), 191 (24), 133 (26), 109 (33); HRMS Calcd. for $\text{C}_{22}\text{H}_{24}^{79}\text{BrN}_3\text{O}_9\text{S}_2/\text{C}_{22}\text{H}_{24}^{81}\text{BrN}_3\text{O}_9\text{S}_2$: 617.0137 / 619.0117, found: 617.0129 / 619.0122.

N-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(6'-methylbenzo-1',3'-thiazol-2'-yl)thiourea (**3c**)

White solid; yield 54%; m.p. 201–203 °C; IR (KBr, cm^{-1}): 3175, 3032 (N–H), 1748 (C=O), 1231, 1039 (C–O–C), 1370 (C=S); ^1H NMR (DMSO- d_6): δ 13.12 & 12.23 (1H, *br*, NH), 10.01 & 8.90 (1H, *br*, NH), 5.91 (1H, *t*, $J=9.0$ Hz, H-1), 5.12 (1H, *t*, $J=9.15$ Hz, H-2), 5.46 (1H, *t*, $J=9.35$ Hz, H-3), 5.00 (1H, *t*, $J=9.55$ Hz, H-4), 4.12 (1H, *m*, H-5), 4.23 (1H, *dd*, $J=12.4$, 4.7 Hz, H-6a), 4.03 (1H, *dd*, $J=12.4$, 1.9 Hz, H-6b), 7.52 (1H, *br*, H-4'), 7.24 (1H, *d*, $J=7.8$ Hz, H-5'), 7.69 (1H, *br*, H-7'), 2.02–1.95 (12H, *s*, $4\times\text{CH}_3\text{CO}$), 2.40 (3H, *s*, 6- CH_3); ^{13}C NMR (DMSO- d_6): δ 81.3 (C-1), 72.3 (C-2), 72.7 (C-3), 70.5 (C-4), 68.1 (C-5), 61.7 (C-6), 121.6 (C-4'), 127.6 (C-5'), 133.3 (C-7'), 20.5–20.2 (4C, $4\times\text{CH}_3\text{CO}$), 169.9–169.2 (4C, $4\times\text{CH}_3\text{CO}$), 20.8 (6- CH_3), signal of C=S is not appeared; ESI-MS (m/z , (relative abundance, %)): 553 (M^+ , 2), 494 (2), 434 (6), 374 (6), 314 (2), 271 (4), 206 (100, BP), 288 (2), 164 (36), 191 (4), 109 (22); HRMS Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_9\text{S}_2$: 553.1189, found 553.1197.

N-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(4',6'-dimethylbenzo-1',3'-thiazol-2'-yl)thiourea (**3d**)

White solid; yield 78%; m.p. 206–208 °C; IR (KBr, cm^{-1}): 3174, 3024 (N–H), 1750 (C=O), 1226, 1036 (C–O–C), 1370 (C=S); ^1H NMR (DMSO- d_6): δ 12.76 & 12.10 (1H, *br*, NH), 10.10 & 8.91 (1H, *br*, NH), 5.95 (1H, *t*, $J=9.0$ Hz, H-1), 5.10 (1H, *t*, $J=9.05$ Hz, H-2), 5.45 (1H, *t*, $J=9.15$ Hz, H-3), 5.00 (1H, *t*, $J=9.3$ Hz, H-4), 4.12 (1H, *m*, H-5), 4.22 (1H, *dd*, $J=12.5$, 4.4 Hz, H-6a), 4.05 (1H, *dd*, $J=12.3$, 1.9 Hz, H-6b), 7.07 (1H, *s*, H-5'), 7.57 (1H, *br*, H-7'), 2.02–1.97 (12H, *s*, $4\times\text{CH}_3\text{CO}$), 2.52 (6H, *s*, 4- CH_3 & 6- CH_3); ^{13}C NMR (DMSO- d_6): δ 81.2 (C-1), 72.3 (C-2), 72.5 (C-3), 70.5 (C-4), 68.1 (C-5), 61.6 (C-6), 118.6 (C-4'), 128.2 (C-5'), 118.6 (C-6'), 133.3 (C-7'), 20.3–20.0 (4C, $4\times\text{CH}_3\text{CO}$), 169.8–169.1 (4C, $4\times\text{CH}_3\text{CO}$), 20.8 (6- CH_3), 17.4 (4- CH_3), signal of C=S is not appeared; ESI-MS (m/z , (relative abundance, %)): 568 ($[\text{M}+\text{H}]^+$, 90), 552 (10), 536 (45), 508 (8), 469 (15), 464 (7), 419 (5), 411 (8), 386 (10), 366 (15), 348 (14), 331 (35), 293 (35), 279 (55), 271 (20), 251 (8), 236 (14), 221 (100, BP), 205 (13), 179 (25), 171 (40), 165 (15), 113 (27), 109 (47), 102 (18); HRMS Calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_9\text{S}_2$: 567.13, found 567.17.

N-(2,3,4,6-Tetra-*O*-acetyl- β -*D*-glucopyranosyl)-*N'*-(6'-ethoxybenzo-1',3'-thiazol-2'-yl)thiourea (**3e**)

Light violet solid; yield 76%; ; m.p. 202–204 °C; IR (KBr, cm⁻¹): 3196, 3039 (N–H), 1747 (C=O), 1221, 1042 (C–O–C), 1368 (C=S); ¹H NMR (DMSO-*d*₆): δ 13.11 & 11.97 (1H, *br*, NH), 11.12 & 8.84 (1H, *br*, NH), 5.91 (1H, *t*, *J*=9.0 Hz, H-1), 5.12 (1H, *t*, *J*=9.15 Hz, H-2), 5.46 (1H, *t*, *J*=9.35 Hz, H-3), 4.93 (1H, *t*, *J*=9.5 Hz, H-4), 4.10 (1H, *m*, H-5), 4.22 (1H, *dd*, *J*=12.4, 4.7 Hz, H-6a), 4.00 (1H, *dd*, *J*=12.4, 4.7 Hz, H-6b), 7.34 (1H, *br*, H-4'), 7.02 (1H, *d*, *J*=7.1 Hz, H-5'), 7.62 (1H, *br*, H-7'), 2.01–1.95 (12H, *s*, 4×CH₃CO), 4.06 (2H, *q*, –OCH₂CH₃), 1.35 (3H, *t*, –OCH₂CH₃); ¹³C NMR (DMSO-*d*₆): δ 81.3 (C-1), 72.3 (C-2), 72.6 (C-3), 70.4 (C-4), 68.0 (C-5), 61.7 (C-6), 115.2 (C-4'), 115.2 (C-5'), 155.5 (C-6'), 106.0 (C-7'), 20.4–18.5 (4C, 4×CH₃CO), 170.0–169.3 (4C, 4×CH₃CO), 56.0 (–OCH₂CH₃), 14.6 (–OCH₂CH₃), signal of C=S is not appeared; ESI-MS (*m/z*, (relative abundance, %)): 584 ([M+H]⁺, 50), 550 (48), 525 (20), 347 (20), 331 (30), 271 (30), 237 (35), 210 (5), 195 (100, BP), 167 (30), 126 (5), 109 (35).

N-(2,3,4,6-Tetra-*O*-acetyl- β -*D*-glucopyranosyl)-*N'*-(6'-methoxycarbonyl-benzo-1',3'-thiazol-2'-yl)thiourea (**3f**)

White solid; yield 57%; m.p. 202 – 203 °C; IR (KBr, cm⁻¹): 3182, 3024 (N–H), 1750 (C=O), 1223, 1038 (C–O–C), 1373 (C=S); ¹H NMR (DMSO-*d*₆): δ 13.22 & 12.33 (1H, *br*, NH), 9.85 & 9.23 (1H, *br*, N'H), 5.90 (1H, *t*, *J*=8.9 Hz, H-1), 5.12 (1H, *t*, *J*=9.15 Hz, H-2), 5.46 (1H, *t*, *J*=9.3 Hz, H-3), 5.00 (1H, *t*, *J*=9.35 Hz, H-4), 4.12 (1H, *m*, H-5), 4.21 (1H, *dd*, *J*=12.3, 4.6 Hz, H-6a), 4.01 (1H, *dd*, *J*=12.3, 4.5 Hz, H-6b), 7.68 (1H, *br*, H-4'), 8.00 (1H, *d*, *J*=8.4 Hz, H-5'), 8.54 (1H, *br*, H-7'), 2.02–1.95 (12H, *s*, 4×CH₃CO), 3.91 (3H, *s*, –OCH₃); ¹³C NMR (DMSO-*d*₆): δ 81.2 (C-1), 73.2 (C-2), 73.5 (C-3), 71.4 (C-4), 68.8 (C-5), 62.5 (C-6), 124.8 (C-4'), 125.6 (C-5'), 128.4 (C-7'), 20.5–20.2 (4C, 4×CH₃CO), 170.8–170.2 (4C, 4×CH₃CO), 166.7 (Ar–COOR), 53.0 (ArCOOCH₃), signal of C=S is not appeared; EI-MS (*m/z*, (relative abundance, %)): 597 (2), 537 (1), 478 (2), 418 (2), 358 (2), 331 (4), 288 (4), 250 (100, BP), 271 (6), 208 (46), 109 (40), 219 (52), 191 (31), 191 (39), 191 (31), 177 (56), 133 (21); HRMS Calcd. for C₂₄H₂₇N₃O₁₁S₂: 597.1087, found 597.1094.

N-(2,3,4,6-Tetra-*O*-acetyl- β -*D*-glucopyranosyl)-*N'*-(6'-ethoxycarbonylbenzo-1',3'-thiazol-2'-yl)thiourea (**3g**)

White solid; yield 48%; m.p. 203–205 °C; IR (KBr, cm⁻¹): 3170, 3030 (N–H), 1751 (C=O), 1228, 1040 (C–O–C), 1372 (C=S); ¹H NMR (DMSO-*d*₆): δ 12.28 (1H, *br*, NH), 9.23 (1H, *br*, NH), 5.90 (1H, *t*, *J*=8.9 Hz, H-1), 5.12 (1H, *t*, *J*=9.15 Hz, H-2), 5.46 (1H, *t*, *J*=9.3 Hz, H-3), 5.00 (1H, *t*, *J*=9.35 Hz, H-4), 4.12 (1H, *m*, H-5), 4.21 (1H, *dd*, *J*=12.3, 4.6 Hz, H-6a), 4.01 (1H, *dd*, *J*=12.3, 4.5 Hz, H-6b), 7.68 (1H, *br*, H-4'), 8.00 (1H, *d*, *J*=8.5 Hz, H-5'), 8.54 (1H, *br*, H-7'), 2.02–1.95 (12H, *s*, 4×CH₃CO), 4.35 (2H, *q*, –OCH₂CH₃), 2.40 (3H, *t*, –OCH₂CH₃); ¹³C NMR (DMSO-*d*₆): δ 81.3 (C-1), 72.3 (C-2), 72.6 (C-3), 71.4 (C-4), 67.9 (C-5), 61.6 (C-6), 123.7 (C-4'), 125.0 (C-5'), 127.4 (C-7'), 20.4–20.1 (4C, 4×CH₃CO), 169.8–169.2 (4C, 4×CH₃CO), 165.2 (Ar–COOR), 60.6 (–OCH₂CH₃), 14.1 (–OCH₂CH₃), signal of C=S is not appeared; ESI-MS (*m/z*, (relative abundance, %)): 612 ([M+H]⁺, 100, BP), 580 (5), 551 (20), 522 (25), 492 (14), 464 (24), 425 (15), 419 (40), 391 (5), 352 (5), 331 (3), 306 (8), 210 (4); HRMS Calcd. for C₂₅H₂₉N₃O₁₁S₂: 611.1243, M+H: 612.1316, found 612.1322.

N-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(6'-propoxycarbonyl-benzo-1',3'-thiazol-2'-yl)thiourea (**3h**)

White solid; yield 60%; m.p. 205–206 °C; IR (KBr, cm^{-1}): 3172, 3036 (N–H), 1748 (C=O), 1227, 1042 (C–O–C), 1370 (C=S); ^1H NMR ($\text{DMSO}-d_6$): δ 13.35 & 12.26 (1H, *br*, NH) 9.86 & 9.23 (1H, *br*, NH), 5.91 (1H, *t*, $J=8.7$ Hz, H-1), 5.13 (1H, *t*, $J=8.8$ Hz, H-2), 5.46 (1H, *t*, $J=8.8$ Hz, H-3), 4.99 (1H, *t*, $J=8.6$ Hz, H-4), 4.12 (1H, *m*, H-5), 4.22 (1H, *dd*, $J=12.3$, 4.6 Hz, H-6a), 4.03 (1H, *dd*, $J=12.3$, 4.5 Hz, H-6b), 7.80 (1H, *br*, H-4'), 8.02 (1H, *d*, $J=8.4$ Hz, H-5'), 8.56 (1H, *br*, H-7'), 2.01–1.96 (12H, *s*, $4\times\text{CH}_3\text{CO}$), 4.03 (2H, *t*, $-\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.77 (2H, *m*, $-\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.10 (3H, *t*, $-\text{OCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR ($\text{DMSO}-d_6$): δ 81.3 (C-1), 72.3 (C-2), 72.6 (C-3), 70.4 (C-4), 67.9 (C-5), 61.6 (C-6), 123.8 (C-4'), 124.9 (C-5'), 127.5 (C-7'), 20.4–20.2 (4C, $4\times\text{CH}_3\text{CO}$), 169.9–169.3 (4C, $4\times\text{CH}_3\text{CO}$), 165.3 (Ar–COOR), 66.1 ($-\text{OCH}_2\text{CH}_2\text{CH}_3$), 21.6 ($-\text{OCH}_2\text{CH}_2\text{CH}_3$), 10.3 ($-\text{OCH}_2\text{CH}_2\text{CH}_3$), signal of C=S is not appeared; EI-MS (m/z , (relative abundance, %)): 625 (M^+ , 4), 565 (4), 506 (6), 446 (5), 385 (3), 331 (12), 288 (9), 277 (31), 271 (1), 109 (26), 219 (72), 191 (21), 220 (12), 177 (36), 236 (100, BP), 219 (75), 194 (30), 178 (40), 169 (18), 133 (19); HRMS Calcd. for $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_{11}\text{S}_2$: 625.1399, found 625.1406.

Results and Discussion

We have previously reported on the synthesis of some *N*-(tetra-*O*-acetyl- β -D-glucopyranosyl) thioureas containing 4,6-diarylpyrimidine components using microwave-assisted method⁹. Hence it is quite interesting to synthesize thioureas having benzothiazole component and glucose moiety. In view of the interest in synthesis of these thioureas, a synthetic method has been involved for use of the microwave-assisted heating instead the conventional one. This method is becoming an increasingly popular method of heating which replaces the classical method because it proves to be a clean, cheap, and convenient method¹⁰.

The required 2-aminobenzo-1',3'-thiazole/6-substituted 2-aminobenzo-1',3'-thiazoles **2** were prepared by previous procedures^{11–13}. Tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate **1** was prepared from *D*-glucose by method described in reference^{1,14}. Thioureas **3a–h** were synthesized by condensation reaction of isothiocyanate **1** and corresponding amonibenzothiazoles **2a–h** (Scheme 1).

Scheme 1. Synthesis of *N*-(tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(benzo-1',3'-thiazol-2'-yl)thioureas **3a–h**

We have investigated the reaction of tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate **1** with 2-amino-6-substituted-benzo-1',3'-thiazoles **2** in different reaction conditions: conventional, solvent-free microwave-assisted and microwave-assisted in solvent (dioxane) heating (Scheme 1). 2-Aminobenzo-1,3-thiadiazoles **2a** (R=6-Cl) and **2b** (R=6-Br) were used in these investigations. The obtained results, which are represented in Table 1, are shown that the appropriate condition for this reaction is microwave-assisted heating in dried dioxane. As shown in Table 1, the solvent-free microwave-assisted heating method (method B) took place in shorter reaction time than the microwave-assisted heating method in dried

dioxane (method C) (3–5 min *versus* 20–30 min). However, the lower yield was in method B because the reaction product was decomposed in part in solventless conditions, then reaction carried out in higher temperature.

Other *N*-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(6-substituted benzo-1',3'-thiazol-2'-yl)thioureas **3** were synthesized using method C by the condensation of tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate **1** and corresponding 2-aminobenzo-1',3'-thiazoles **2** (Scheme 1). This reaction was executed by microwave irradiation for 25–30 min (Table 2).

Table 1. Some investigations of preparation of thioureas **3a** and **3b**

Entry	Yield		
	Method A	Method B	Method C
3a	45% (20 h)	45% (3 min)	62% (20 min)
3b	52% (20 h)	56% (3 min)	65% (25 min)

*Method A: Conventional heating (t_{reaction}); Method B: Solvent-free microwave-assisted heating (t_{reaction}); Method C: Microwave-assisted heating in 3 mL of anhydrous dioxane (t_{reaction}).

Table 2. Reaction Time for synthesis of thioureas **3a-h**

Entry	R	MW Irradiation Time, min	Entry	R	MW Irradiation Time, min
3a	6-Cl	20	3e	6-OEt	25
3b	6-Br	25	3f	6-CO ₂ Me	30
3c	6-Me	25	3g	6-CO ₂ Et	30
3d	4,6-(Me) ₂	30	3h	6-CO ₂ Pr	30

In the almost cases, 2-aminobenzo-1',3'-thiazole and peracetylated glucopyranosyl isothiocyanate were dissolved in dioxane for some first minutes of microwave irradiation (MWI), and then the reaction mixture became pasty. The solvent was distilled off, and resultant sticky residue was triturated with ethanol to afford title compound **3a-h** that were recrystallized with ethanol: toluene (1:1). The nucleophilic addition of 2-aminobenzo-1',3'-thiazole to tetra-*O*-acetyl- β -D-glucopyranosyl isothiocyanate has taken place fairly easily. All of these thioureas could be dissolved in a mixture of ethanol and toluene (1:1 in volume) solvent and could not be dissolved in ethanol and water. Their structures have been confirmed by spectroscopic data (such as IR, NMR and mass spectra).

IR spectra of thioureas **3a-h** show the some characteristic absorption bands in the range of 3469–3490, 3168–3196 (ν_{NH}), 1746–1754 ($\nu_{\text{C=O acetyl}}$), 1692–1715 ($\nu_{\text{C=O aromatic esters}}$), 1367–1373 ($\nu_{\text{C=S}}$) cm^{-1} . Spectral (¹H and ¹³C NMR) data of thioureas **3a-h** show that their resonance signals in NMR spectra could be divided into some parts, as follows: region of pyranose ring, one of aromatic ring and one of acetyl functions. Protons in pyranose ring had chemical shifts from δ =4.00 ppm to δ =5.90 ppm. The coupling constants between proton H-1 and H-2 were ³*J*=8.9–9.3 Hz, it's indicated that C-1'-N was lying on *equatorial* position, *i.e.* these substituted *N*-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(benzo-1',3'-thiazol-2'-yl)-thioureas were β -anomers. Protons H-1, H-2, H-3 and H-4 had resonance signals as triplet, because each proton interacted with two other neighbor ones. Proton H-5 had doublet of doublet signal since its interactions with proton H-6a and proton H-6b, the coupling constants were ³*J*_{5,6a}=4.5–4.8 Hz, ³*J*_{5,6b}=1.5–1.8 Hz and ³*J*_{5,4}=9.5–9.7 Hz^{9,15-17}. In COSY spectra of compounds **3f**, it's shown that there are the interaction of proton H-5 with protons H-6a and H-6, since proton H-6a was closer proton H-5 in space than proton H-6b, hence,

the coupling constant $^3J_{5,6a}$ was larger than $^3J_{5,6b}$ ones. Protons in benzo-1',3'-thiazole ring had chemical shifts in region $\delta=7.5$ –8.1 ppm. Each magnetic signal of protons in NH-thiourea groups appeared two peaks, one peak was downfield at $\delta=13.35$ –12.10 ppm and $\delta=11.12$ –9.66 ppm, which belonged to the structure **3a-h**, and another one was upfield at 12.31–11.97 ppm and $\delta=9.23$ –8.90 ppm, which belonged to the structure **3'''a-h**, because the existence of two geometric isomers of thioureas **3a-h** due to the tautomerism of thiourea group that make benzothiazolylamino component rotated around C–N bond (Figure 1).

Figure 1. Possible tautomeric forms of *N*-(tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(benzo-1',3'-thiazol-2'-yl)thioureas **3a-h**.

The ^{13}C NMR spectrum of *N*-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-(benzo-1',3'-thiazol-2'-yl)thioureas **3a-h** had some characters, as follows^{9,15-17}: the carbon atoms had resonance signals in region $\delta=61.5$ –82.5 ppm; the carbon atoms in benzo-1',3'-thiazole ring had chemical shifts in region of $\delta=96.0$ –158.5 ppm. The carbon atom in C=S bond was not appeared. The carbon atoms in acetyl function had chemical shifts in region $\delta=20.2$ –20.5 ppm (methyl groups) and $\delta=169.0$ –171.0 ppm (C=O bonds).

Conclusion

In summary, the easy availability of peracetylated glucopyranosyl isothiocyanate allowed the preparation of *N*-(tetra-*O*-acetyl- β -D-glucopyranosyl)-*N'*-substituted thioureas having benzo-1,3-thiazole ring in high yield. These thioureas were synthesized in microwave-assisted and solventless conditions.

Acknowledgment

Financial support for this work (Project code: 104.01-2010.50) was provided by Vietnam's National Foundation for Science and Technology Development (NAFOSTED).

References

1. Witczak Z J, Adv Carbohydr Chem Biochem., Tipson R S, Ed., Academic Press: New York, 1986; Vol. 44, p. 91.
2. Yasuo G and Isao S, *Synthetic Commun.*, 1999, **29**, 1493.
3. Cao L H, Zhou C I, Gao H Y and Liu Y T, *J Chin Chem Soc.*, 2001, **48**, 207.
4. Lacova M, Chovaneova J, Hyblova O and Varkonda S, *Chem Pap.*, 1991, **45**, 411.
5. Bradsaw T D, Chua M S, Browne H L, Trapan V, Sausville E A and Stevens M F G, *Br J Cancer*, 2002, **86**, 1348.

6. Hout S, Azas N, Darque A, Robin M, Di Giorgio C, Gasquet M, Galy J and Timon-David P, *Parasitology*, 2004, **129**, 525.
7. Racane L, Tralic-Kulenovic V, Fiseo-Jakic L, Boykin D W and Karmiski-Zamola G, *Heterocycles*, 2001, **55**, 2085.
8. (a) Bama K G and Rajani K B, *Indian J Chem.*, 1988, **27**, 1157; (b) Liu Y-H and Cao L-H, *Carbohydr Res.*, 2008, **343**, 615.
9. Thanh N D and Mai N T T, *Carbohydr Res.*, 2009, **344**, 2399.
10. Loupy A, *Microwave in organic synthesis*, 2nd Edition, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006, **1**, 579.
11. Wood J L, *Organic Reactions*, Adams R, Bachmann W E, Johnson J R, Fieser L F, Snyder H R, Eds., Academic Press: New York, 1947, **3**, 240.
12. (a) Smith T D, *Anal Chem Acta*, 1960, **22**, 249; (b) Pattan S R, Suresh C, Pujar V D, Reddy, V V K, Rasal V P and Koti B C, *Indian J Chem.*, 2005, **44B**, 2404.
13. Naim S S, Sing S K and Sharma S, *Indian J Chem.*, 1991, **30B**, 494.
14. Bama K G and Rajanik K B, *Indian J Chem.*, 1988, **27B**, 1157.
15. Somsák L, Felföldi N, Kónya B, Hüse C, Telepó K, Bokor E and Czifrák K, *Carbohydr Res.*, 2008, **343**, 2083.
16. Caballero R B, Mota J F and Perez J A G, *Carbohydr Res.*, 1986, **154**, 280.
17. Fernández J M G, Ortiz-Mellet C, Blanco J L J, Fuentes J, Dínez M J, Estrada M D, López-Castro A and Pérez-Garrido S, *Carbohydr Res.*, 1996, **286**, 55.