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Synthesis of *N*-Lactosylated Thiourea and Benzothiazolyl Thiourea

Prashant V. Tale and Shirish P. Deshmukh

P.G. Department of Chemistry, Shri Shivaji College, Akola 444 001, Maharashtra, India

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ABSTRACT: *Several N-lactosylated aryl thioureas and benzothiazolyl thioureas have been prepared by the condensation of hepta-O-acetyl-β-D-lactosyl isothiocyanate with aryl amines and 2-aminobenzothiazole/substituted benzothiazoles. Hepta-O-acetyl-β-D-lactosyl isothiocyanate was prepared by the interaction of hepta-O-acetyl-α-D-lactosyl bromide and lead thiocyanate. The structures of these new N-lactosides have been established on the basis of IR, NMR, and mass spectral studies.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:306–309, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20207

INTRODUCTION

Glycosyl thioureas, glycosyl guanidine, and glycosyl derivatives of β-cyclodextrines have potential pharmacological properties [1–4] (such as treatment of AIDS, vectorized transport of drugs). The lactosyl isothiocyanate has been studied as hexose transporter inhibitor [5]. *N*-Lactosylated compounds and their derivatives are reported to show various applications in medicinal chemistry [6,7] and 2-amino-substituted benzothiazoles shows antitumor [8] and antimalarial [9] activity. Looking at the importance of these compounds, we plan to synthesize thioureas and benzothiazolyl thiourea containing β-D-lactosyl substituent on the nitrogen bond. For the synthesis of thiourea, conventional method was reported which is essentially based on the reaction of isothiocyanate and amines [10].

Here, we report the synthesis of several 1-hepta-*O*-acetyl-β-D-lactosyl-3-*N*-aryl thioureas **4a–g** and 1-hepta-*O*-acetyl-β-D-lactosyl-3-[2-*N*-substituted benzothiazolyl] thioureas **6a–g** by the condensation of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate **2** with aryl amines (**3a–g**) and 2-aminobenzothiazoles/substituted benzothiazoles **5a–g**. Required lactosyl isothiocyanate was prepared by the reaction of hepta-*O*-acetyl-α-D-lactosyl bromide **1** [11] with lead thiocyanate [12] (Fig. 1). Required 2-aminobenzothiazoles/substituted benzothiazoles were prepared by the oxidative cyclization of 1-aryl thiourea with the help of molecular bromine [13] and 1-aryl thiourea was prepared by reaction of aryl amine hydrochlorides with ammonium thiocyanate [14].

RESULT AND DISCUSSION

1-Hepta-*O*-acetyl-β-D-lactosyl-3-*N*-aryl thioureas **4a–g** (Fig. 2) and 1-hepta-*O*-acetyl-β-D-lactosyl-3-[2-*N*-substituted benzothiazolyl] thioureas **6a–g** (Fig. 3) are prepared by the condensation of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate **2** with aryl amines (**3a–g**) and 2-aminobenzothiazole/substituted benzothiazoles **5a–g** in benzene for 3 and 4 h, respectively. Then, the solvent was distilled off and sticky residue obtained was triturated with petroleum ether (60–80°C) to afford a white solid (**4a–g**) and (**6a–g**), respectively. The products were found to be desulfurized when boiled with alkaline lead acetate solution. IR spectrum of the products show characteristics absorption of lactose unit in the range of 900–910 and 1000–1100 cm^{-1} [15]. The coupling constants

Correspondence to: Shirish P. Deshmukh; e-mail: prashanttale@rediffmail.com.

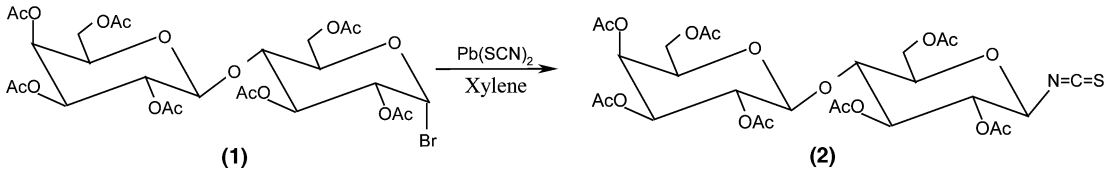


FIGURE 1

of the anomeric proton of lactosyl thioureas and benzothiazolyl thiourea ranged from 8 to 10 Hz, which indicated that the linkage between lactose unit and thioureas had the β-configuration [16,17]. Mass spectra of acetolactose unit [18] show peak at *m/z*, 619, 331, 169, and 109.

EXPERIMENTAL

IR spectra were recorded in Nujol, KBr on a FT-IR Perkin-Elmer RXI (4000–450 cm^{-1}) spectrophotometer. ^1H NMR spectra were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR Spectrometer in $CDCl_3$ solution with TMS as internal reference. The mass spectra FAB were recorded on a Jeol SX-102 mass spectrometer. Optical rotation $[\alpha]_D$ measured on a Equip-Tronics digital polarimeter EQ-800 for sample in $CHCl_3$.

Procedure: 1-Hepta-O-acetyl-β-D-lactosyl-3-N-aryl Thioureas **4a–g** *(Fig. 2)*

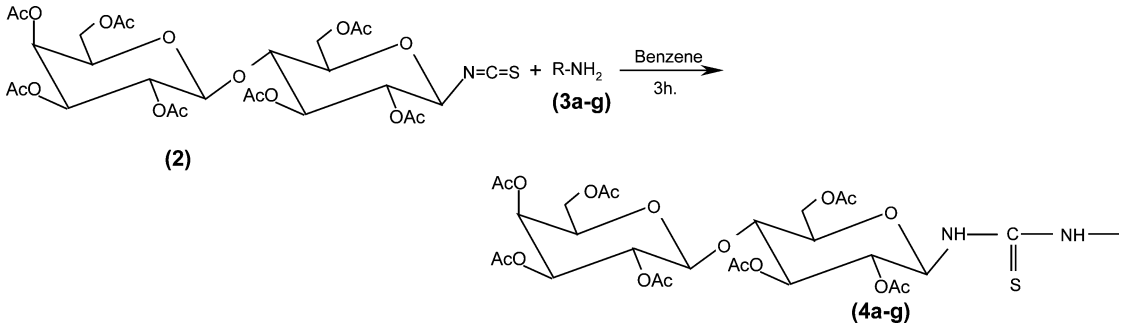
A mixture of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate **2** 0.005 and 0.005 mol of aryl amines (**3a–g**) in 20 mL of benzene was refluxed at 90°C for 3 h while monitoring by TLC. After completion of the reaction, the solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60–80°C) to afford a white solid (**4a–g**). The products were recrystallized from ethanol–water.

4a. mp 169°C; yield 83%, $[\alpha]_D^{28}$ +75.18° (*c*, 1.104); R_f 0.82 (CCl_4:EtOAc, 3:1); IR (KBr): 3342 (NH), 3024 (Ar-H), 2942 (ali C—H), 1760 (C=O), 1538 (C=N), 1372 (C—N), 1230 (C—O), 1048 (C=S), 1048, 912 (characteristic of lactose), 698 (monosubstituted benzene); ^1H NMR (ppm): δ 8.05 (1H, s, NH), 7.47–7.15 (5H, m, Ar-H), 6.57 (1H, d, NH, $J = 8.4$ Hz), 5.77 (1H, t, H-1, $J = 9.0$ Hz), 5.34 (2H, m, H-3,4′), 5.13 (1H, t, H-2′, $J = 9.6$ Hz), 4.95 (1H, d, H-1′, $J = 10.5$ Hz), 4.85 (1H, m, H-2), 4.70 (2H, m, H-3′, 4), 4.17 (3H, m, H-6,6′,6′), 3.87 (1H, m, H-6), 3.76 (2H, m, H-5,5′), 2.15–1.96 (21H, m, 7$COCH_3$); FABMS (*m/z*): 771 $(M + 1)^+$ (base peak), 711 (M−CH_3COOH), 669 (M − CH_3COOH, CH_2CO), 619 (M − $C_7H_7N_2S$), 559, 331, 169, 109. Anal. Calcd for $C_{33}H_{42}O_{17}N_2S$: C, 51.42; H, 5.45; N, 3.63; S, 4.15; Found: C, 51.35; H, 5.41; N, 3.55; S, 4.03%.

4b. mp 149°C; yield 62%; $[\alpha]_D^{28}$ +46.87° (*c*, 1.280); R_f 0.55 (CCl_4:EtOAc, 3:1.5); Anal. Calcd for $C_{33}H_{41}O_{17}N_2SCl$: C, 49.25; H, 5.09; N, 3.48; S, 3.97; Found: C, 49.20; H, 5.01; N, 3.39, S, 3.78%.

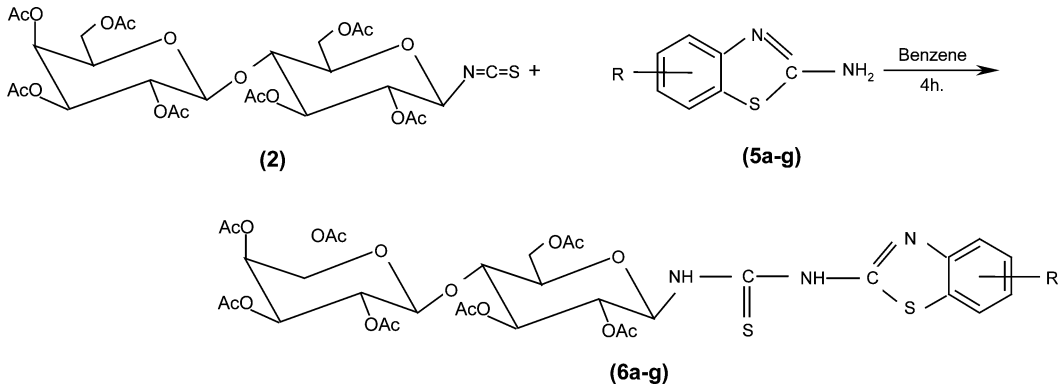
4c. mp 153°C; yield 48%; $[\alpha]_D^{28}$ −111.11° (*c*, 1.080); R_f 0.56 (CCl_4:EtOAc, 3:1.5); Anal. Calcd for $C_{33}H_{41}O_{17}N_2SCl$: C, 49.25; H, 5.09; N, 3.48; S, 3.97; Found: C, 49.17; H, 5.05; N, 3.47; S, 3.79%.

4d. mp 139°C; yield 86%; $[\alpha]_D^{28}$ +130.66° (*c*, 1.148); R_f 0.82 (CCl_4:EtOAc, 3:0.6); IR (KBr): 3340 (NH), 3024 (Ar-H), 2980 (ali C—H), 1754 (C=O), 1530



R = phenyl, b) o-Cl-phenyl, c) m-Cl-phenyl, d) p-Cl-phenyl, e) o-tolyl, f) m-tolyl, g) p-tolyl

FIGURE 2



R = a)H, b) 4-Cl, c) 5-Cl, d) 6-Cl, e) 4-Me, f) 5-Me, g) 6-Me.

FIGURE 3

(C=N), 1370 (C—N), 1232 (C—O), 1048 (C—S), 1048, 912 (characteristic of lactose), 832 (1,4-disubstituted benzene), 602 (C–Cl); ^{1}H NMR (ppm): δ 7.78 (1H, s, NH), 7.12–7.39 (4H, m, Ar-H), 6.52 (1H, d, NH, J = 7.8 Hz), 5.73 (1H, t, H-1, J = 9.0 Hz), 5.34 (2H, m, H-3,4′), 5.14 (1H, t, H-2′), 4.95 (1H, d, H-1′, J = 10.5 Hz), 4.85 (1H, m, H-2), 4.76 (2H, m, H-3′,4), 4.18 (3H, m, H-6,6′,6′), 3.87 (3H, m, H-5,5′,6), 2.16–1.96 (21H, m, 7$COCH_3$); FABMS (*m*/*z*): 805 $(M+1)^+$ (base peak), 769 (M − Cl), 709 (M − CH_3COOH, Cl), 619 (M − $C_7H_6N_2SCl$), 559, 331, 169, 109. Anal. Calcd for $C_{33}H_{41}O_{17}N_2SCl$: C, 49.25; H, 5.09; N, 3.48; S, 3.97; Found: C, 49.20; H, 5.00; N, 3.29; S, 3.72%.

4e. mp 148°C; yield 79%; $[\alpha]_D^{28}$ +61.61° (*c*, 1.136); R_f 0.58 (CCl_4:EtOAc, 3:1); Anal. Calcd for $C_{34}H_{44}O_{17}N_2S$: C, 52.04; H, 5.61; N, 3.57; S, 4.08; Found: C, 52.00; H, 5.53; N, 3.56; S, 3.75%.

4f. mp 109°C; yield 76%; $[\alpha]_D^{28}$ +68.96° (*c*, 1.160); R_f 0.84 (CCl_4:EtOAc, 3:2); IR (KBr): 3353 (NH), 3020 (Ar-H), 2934 (ali C—H), 1747 (C=O), 1538 (C=N), 1377 (C—N), 1232 (C—O), 1055 (C=S), 1055, 904 (characteristics of lactose), 762 (1,3-disubstituted benzene); ^{1}H NMR (ppm): δ 7.86 (1H, s, NH), 7.35–6.93 (4H, m, Ar-H), 6.54 (1H, d, NH, J = 8.7 Hz), 5.77 (1H, t, H-1, J = 9 Hz), 5.34 (2H, d, H-3,4′), 5.13 (1H, t, H-2′, J = 9.3 Hz), 4.94 (1H, d, H-1′, J = 10.5 Hz), 4.86 (1H, m, H-2), 4.66 (2H, m, H-3′,4), 4.17 (3H, m, H-6,6′,6′), 3.87 (1H, m, H-6), 3.76 (2H, m, H5,5′), 2.38 (3H, s, Ar-CH_3), 2.15–1.16 (21H, m, 7$COCH_3$); FABMS (*m*/*z*): 784 $(M+1)^+$ (base peak), 768 (M − CH_3), 708 (M − CH_3COOH, CH_3), 619 (M − $C_8H_9N_2S$), 559, 331, 169, 109. Anal. Calcd for $C_{34}H_{44}O_{17}N_2S$: C, 52.04; H, 5.61; N, 3.57; S, 4.08; Found: C, 52.01; H, 5.59; N, 3.52; S, 3.81%.

4g. mp 124°C; yield 64%; $[\alpha]_D^{28}$ +248.01° (*c*, 1.008); R_f 0.64 (CCl_4:EtOAc, 3:0.9); Anal. Calcd for $C_{34}H_{44}O_{17}N_2S$: C, 52.04; H, 5.61; N, 3.57; S, 4.08; Found: C, 51.98; H, 5.50; N, 3.53; S, 4.01%.

1-Hepta-O-acetyl-β-D- lactosyl-3-[2-N-substituted benzothiazolyl] Thioureas **6a–g** *(Fig. 3)*

A mixture of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate **2** 0.005 and 0.005 mol 2-aminobenzothiazoles/substituted benzothiazoles **5a–g** in 20 mL of benzene was refluxed at 90°C for 4 h while monitoring by TLC. After completion of the reaction, the solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60–80°C) to afford white solid (**6a–g**). The products were recrystallized from ethanol–water.

6a. mp 127°C; yield 93%; $[\alpha]_D^{28}$ +15.97° (*c*, 1.252); R_f 0.61 (CCl_4:EtOAc, 3:2); IR (KBr): 3342 (NH), 3020 (Ar-H), 2945 (ali C—H), 1763 (C=O), 1532 (C=N), 1377 (C—N), 1236 (C=O), 1055 (C=S), 1055, 915 (characteristic of lactose), 743 (C—S); ^{1}H NMR (ppm): δ 7.82 (1H, s, NH), 7.71–7.26 (4H, m, Ar-H), 5.70 (1H, t, H-1, J = 8.7 Hz), 5.41 (3H, m, H-3,4′, NH), 5.20 (1H, m, H-2′), 4.87 (1H, d, H-1′, J = 8.7 Hz), 4.50 (2H, m, H-2,3′), 4.23 (4H, m, H-4,6,6′,6′), 3.89 (3H, m, H-5,5′,6), 2.17–1.65 (21H, m, 7$COCH_3$); FABMS (*m*/*z*): 828 $(M+1)^+$ (base peak), 768 (M + 1 − CH_3COOH), 708 (M + 1 − 2CH_3COOH), 619 (M − $C_8H_6N_3S_2$), 559, 331, 169, 109. Anal. Calcd for $C_{34}H_{41}O_{17}N_3S_2$: C, 49.33; H, 4.95; N, 5.07; S, 7.73; Found: C, 49.25; H, 4.88; N, 4.97; S, 7.68%.

6b. mp 165°C; yield 65%; $[\alpha]_D^{28}$ +112.45° (*c*, 1.156); R_f 0.86 (CCl_4:EtOAc, 3:2), Anal. Calcd for $C_{34}H_{40}O_{17}N_3S_2Cl$: C, 47.38; H, 4.64; N, 4.87; S, 7.42; Found: C, 47.31; H, 4.60; N, 4.75; S, 7.33%.

6c. mp 198°C; yield 70%; $[\alpha]_D^{28}$ +55.55° (*c*, 1.080); R_f 0.82 (CCl_4:EtOAc, 3:2), Anal. Calcd for

$C_{34}H_{40}O_{17}N_3S_2Cl$: C, 47.38; H, 4.64; N, 4.87; S, 7.42; Found: C, 47.28; H, 4.57; N, 4.72; S, 7.35%.

6d. mp 156°C, yield 80.89%; $[\alpha]_D^{28}$ +84.17° (*c*, 1.188); R_f 0.60 (CCl_4:EtOAc, 3:2); IR (KBr): 3342 (NH), 3020 (Ar-H), 2945 (ali C—H), 1753 (C=O), 1538 (C=N), 1377 (C—N), 1055 (C=S), 1055, 915 (characteristic of lactose), 738 (C—S), 604 (C–Cl); ^{1}H NMR (ppm): δ 7.73 (1H, s, NH), 7.41–7.08 (3H, m, Ar-H), 5.67 (1H, t, H-1, $J = 8.4$ Hz), 5.30 (3H, m, H-3,4′, NH), 5.14 (1H, t, H-2′, $J = 8.2$ Hz), 5.02 (1H, d, H-1′, $J = 9.9$ Hz), 4.87 (1H, m, H-2), 4.49 (2H, m, H-3′,4), 4.22 (3H, m, H-6,6′,6′), 3.89 (3H, m, H-5,5′,6), 2.16–1.63 (21H, m, $7COCH_3$); FABMS (*m*/*z*): 862 $(M + 1)^+$, 788 $(M - C_6H_3)$, 724 (M − Cl, CH_2CO, CH_3COOH), 678 $(M + 1 - C_7H_5N_2SCl)$, 619 $(M - C_8H_5N_3S_2Cl)$, 331 (base peak), 169, 109. Anal. Calcd for $C_{34}H_{40}O_{17}N_3S_2Cl$: C, 47.38; H, 4.64; N, 4.87; S, 7.42; Found: C, 47.30; H, 4.58; N, 4.80; S, 7.30%.

6e. mp 116°C; yield 82%; $[\alpha]_D^{28}$ +29.67° (*c*, 1.008), R_f 0.74 (CCl_4:EtOAc, 3:2), Anal. Calcd for $C_{35}H_{43}O_{17}N_3S_2$: C, 49.94; H, 5.11; N, 4.99; S, 7.60; Found: C, 49.88; H, 5.03; N, 4.84; S, 7.58%.

6f. mp 184°C; yield 64%; $[\alpha]_D^{28}$ +99.63° (*c*, 1.104); R_f 0.84 (CCl_4:EtOAc, 3:2); IR (KBr): 3331 (NH), 2966 (ali C—H), 1758 (C=O), 1527 (C=N), 1382 (C—N), 1237 (C—O), 1049 (C=S), 1049, 920 (characteristic of lactose); ^{1}H NMR (ppm): δ 7.58 (1H, s, NH), 7.26 (3H, m, Ar-H), 5.71 (1H, t, H-1, $J = 7.8$ Hz), 5.41 (3H, m, H-3,4′, NH), 5.14 (1H, m, H-2′), 4.97 (1H, d, H-1′, $J = 9$ Hz), 4.50 (2H, m, H-2,3′), 4.21 (4H, m, H-4,6,6′,6′), 3.89 (3H, m, H-5,5′,6), 2.50 (3H, s, Ar-CH_3), 2.17–1.66 (21H, m, $7COCH_3$); FABMS (*m*/*z*): 842 $(M + 1)^+$, 826 $(M - CH_3)$, 782 $(M + 1 - CH_3COOH)$, 766 $(M - C_6H_3)$, 695 (M − CS, CH_2CO, CH_3COOH), 619 $(M - C_9H_8N_3S_2)$, 559, 331 (base peak), 169, 109. Anal. Calcd for $C_{35}H_{43}O_{17}N_3S_2$: C, 49.94; H, 5.11; N, 4.99; S, 7.60; Found: C, 49.85; H, 5.03; N, 4.89; S, 7.51%.

6g. mp 169°C; yield 76%; $[\alpha]_D^{28}$ +75.18° (*c*, 1.064); R_f 0.73 (CCl_4:EtOAc, 3:2); Anal. Calcd for $C_{35}H_{43}O_{17}N_3S_2$: C, 49.94; H, 5.11; N, 4.99; S, 7.60; Found: C, 49.81; H, 5.00; N, 4.87; S, 7.48%.

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