Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 342 (2007) 753–756
Carbohydrate RESEARCH

Note

Synthesis of *N*- and *S*-bis-protected lactosyl isothiobiurets

Anvita S. Dandale,[a] Dattatraya V. Mangte[b] and Shirish P. Deshmukh[a,*]

[a]*P.G. Department of Chemistry, Shri Shivaji College, Akola 444 001, MS, India*
[b]*Research Support International Ltd, DIL Complex, Majiwada, Thane 400 610, India*

Received 3 September 2006; received in revised form 20 November 2006; accepted 27 November 2006
Available online 3 December 2006

Abstract—Several *N*,*S*-bis(hepta-*O*-acetyllactosyl)-1-aryl-2-isothiobiuret compounds have been synthesised for the first time by the reaction of *S*-(hepta-*O*-acetyl-β-lactosyl)-1-arylisothiocarbamides and hepta-*O*-acetyl-β-lactosyl isocyanate. The identities of these newly synthesised compounds were established on the basis of elemental analysis and IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: *S*-Lactosyl arylisothiocarbamides; Lactosyl isocyanate; Isothiobiurets; Synthesis

Urea, thiourea and their derivatives not only show strong antibacterial activity but are also versatile reagents in organic synthesis.[1] Glycosyl thioureides are important metabolic intermediates and can help to maintain metabolic balance and improve physical stamina, etc.[2] In view of this, we recently reported the synthesis of *S*-(hepta-*O*-acetyl-β-lactosyl)-1-arylisothiocarbamides[3] by the interaction of hepta-*O*-acetyl-α-lactosyl bromide[4] and aryl thiocarbamides.

Sugar isocyanates are important intermediates in the synthesis of various ureido-linked derivatives.[5] Protected sugar isocyanates have been prepared by reaction of protected glycosylamines with phosgene[6] or its safer synthetic surrogates[7] or haloformates[8] through sugar phosphanimines[9] or by oxidation of glycosyl isocyanides with pyridine-*N*-oxide[10,11] or by reaction of glycosyl halides with silver cyanate.[12] We report here for the first time the synthesis of protected lactosyl isocyanate by reaction of lactosyl bromide[4] with lead cyanate.

The aryl isothiocarbamides, because of their basic nature, are known to react with alkyl/aryl isocyanates to produce the corresponding 2-isothiobiurets. Several N- and S-glucosylated and S-lactosylated isothiobiurets have been reported and tested for their biological activity,[13–15] but there is no report on *N*- and *S*-bislactosyl isothiobiurets. In view of the applications of S- and N-lactosylated compounds in medicinal chemistry and in many other ways,[16–19] we herein report the synthesis of N- and S-bislactosylated isothiobiurets by the reaction of *S*-(hepta-*O*-acetyl-β-lactosyl)-1-arylisothiocarbamides and hepta-*O*-acetyl-β-lactosyl isocyanate.

N,*S*-Bis(hepta-*O*-acetyllactosyl)-1-aryl-2-isothiobiurets (**3a**–**g**) (Scheme 1) were prepared by the condensation of *S*-(hepta-*O*-acetyl-β-lactosyl)-1-arylisothiocarbamides (**2a**–**g**) and hepta–*O*-acetyl-β-lactosyl isocyanate (**1**) in benzene for 4 h. The solvent was distilled off, and the resultant sticky residue was triturated with petroleum ether to afford title compounds (**3a**–**g**) that were recrystallised with EtOH–water. IR spectra of the products show the characteristic absorption of lactose[20–22] in the range of 900–910 and 1000–1100 cm^{-1}. ^{1}H NMR spectra of the products show the characteristic of lactosyl protons[22–25] at δ 5.6–3.7. The ^{13}C NMR spectra show lactosyl carbons[25–27] at δ 78–61. Mass spectra show peaks of the lactose[28,29] unit at *m*/*z* 619, 559, 331, 169 and 109.

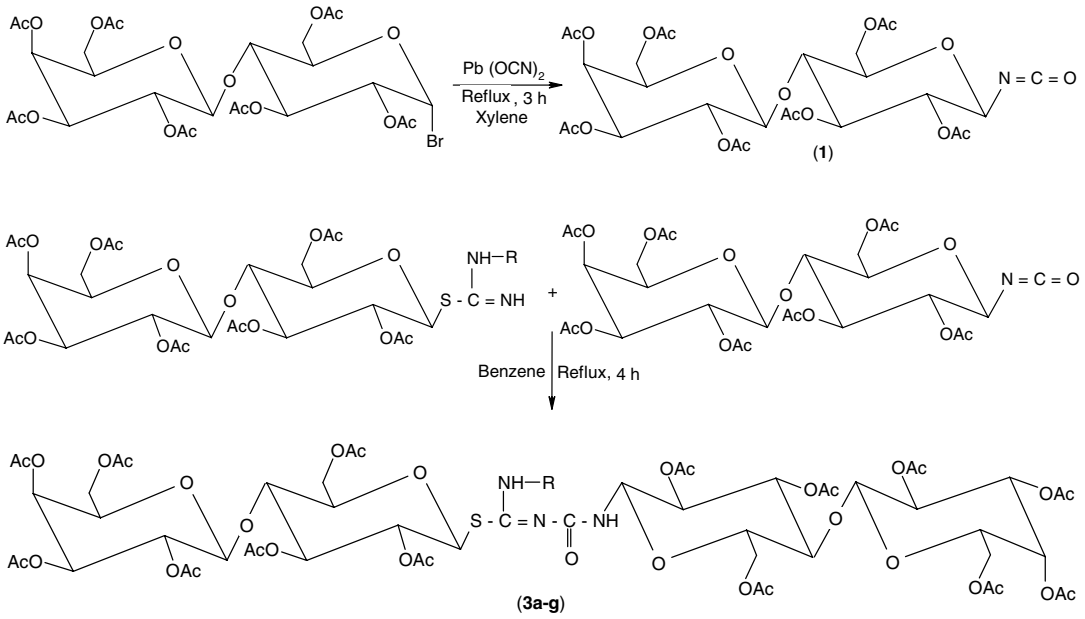
1. Experimental

1.1. General

Specific rotations $[\alpha]_D$ were measured on a Equip-Tronics digital polarimeter model no. EQ 800 at 31 °C in

* Corresponding author. E-mail: spd_dattatraya@rediffmail.com

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.11.025



Scheme 1. R = (a) phenyl, (b) *o*-chlorophenyl, (c) *m*-chlorophenyl, (d) *p*-chlorophenyl, (e) *o*-tolyl, (f) *m*-tolyl, (g) *p*-tolyl. Ac = $COCH_3$.

$CHCl_3$. IR spectra were recorded on a Perkin–Elmer RXI FTIR spectrometer (4000–450 cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-300 spectrometer operating at 300 and 75 MHz, respectively, in $CDCl_3$ solution with TMS as the internal reference. The mass spectra were recorded on a Jeol SX-102 mass spectrometer.

1.2. Hepta-*O*-acetyl-β-lactosyl isocyanate (1)

Hepta-*O*-acetyl-β-lactosyl isocyanate (**1**) was prepared by the condensation of hepta-*O*-acetyl-α-lactosyl bromide (5 mmol, 349 mg) and lead cyanate (5 mmol, 145 mg) in boiling sodium-dried xylene (25 mL) for 3 h. Lead bromide that formed was filtered, and the filtrate was concentrated. The sticky mass obtained was triturated with petroleum ether, and hepta-*O*-acetyl-β-lactosyl isocyanate precipitated out. It was purified in a minimum quantity of $CHCl_3$ and petroleum ether (237 mg). The purity of the product was checked by TLC. Yield 71.8%; mp 112–114 °C; $[\alpha]_D^{31}$ −280 (*c* 0.983, $CHCl_3$); R_f 0.88 (3:2 $CHCl_3$–EtOAc); IR (KBr): 2968, 2121, 1751, 1435, 1233, 1053 and 905 (lactose); ^1H NMR ($CDCl_3$): δ 5.36–3.77 (m, 14H, lactose unit), 2.16–1.97 (m, 21H, $7COCH_3$); FABMS: *m*/*z* 661 (M^+). Anal. Calcd for $C_{27}H_{33}NO_{18}$: C, 49.0; H, 5.29; N, 2.11; Found: C, 48.61; H, 5.26; N, 1.98.

1.3. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-aryl-2-isothiobiurets (3a–g)

Condensation of *S*-(hepta-*O*-acetyl-β-lactosyl)-1-aryl-isothiocarbamides (**2a**–**g**, 5 mmol) and hepta-*O*-acetyl-β-lactosyl isocyanate (**1**, 5 mmol, 330 mg) in benzene (20 mL) was carried out on boiling water bath for 4 h. The solvent was evaporated, and the sticky residue obtained was triturated with petroleum ether to afford the title compounds (**3a**–**g**). The products were recrystallised from EtOH–water (Table 1).

1.3.1. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-phenyl-2-isothiobiuret (3a). IR (KBr): 3455, 2974, 1752, 1598, 1373, 1230, 1052 and 906 (lactose), 762; ^1H NMR ($CDCl_3$): δ 7.45–7.28 (m, 5H, Ar–H), 5.36 (s, 2H, N–H), 5.21–

Table 1. Physical data of *N*,*S*-bis(hepta-*O*-acetyllactosyl)-1-aryl-2-isothiobiurets (**3a**–**3g**)

Reactant (mg)	Product	Mp (°C)	Yield, mg (%)	$[\alpha]_D^{31}$ (*c*, $CHCl_3$)	R_f (3:2 $CHCl_3$–EtOAc)
1a (385)	**3a**	148–150	540 (75.6)	−109 (1.01)	0.95
1b (402)	**3b**	100–102	581 (79.4)	−59.8 (1.17)	0.92
1c (402)	**3c**	106–108	561 (76.7)	−79.9 (1.17)	0.88
1d (402)	**3d**	102–105	461 (63.0)	−78.2 (1.15)	0.89
1e (392)	**3e**	144–146	621 (86.1)	−26.3 (1.14)	0.92
1f (392)	**3f**	105–107	441 (61.1)	−102 (1.17)	0.94
1g (392)	**3g**	169–170	641 (88.8)	−52.6 (1.14)	0.93

3.77 (m, 28H, lactose unit), 2.2–1.96 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.73–20.34 (14CH_3CO), 77.42–60.73 (lactose unit), 136.5–128.93 (aromatic); 170.45–169.02 (14CO); FABMS: *m*/*z* 1431. Anal. Calcd for $C_{60}H_{77}N_3O_{35}S$: C, 50.31; H, 5.38; N, 2.93; S, 2.23. Found: C, 50.52; H, 5.24; N, 2.75; S, 2.03.

1.3.2. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-*o*-chlorophenyl-2-isothiobiuret (3b). IR (KBr): 3435, 2941, 1750, 1600, 1373, 1234, 904 and 1050 (lactose), 752; ^{1}H NMR ($CDCl_3$): δ 7.46–7.33 (m, 4H, Ar–H), 6.60 (s, 2H, NH), 5.50–3.70 (m, 28H, lactose unit), 2.15–1.96 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.70–20.32 (14CH_3CO), 77.43–60.72 (lactose unit), 135.4–127.4 (aromatic); 170.5–169.1 (14CO); FABMS: *m*/*z* 1465. Anal. Calcd for $C_{60}H_{76}ClN_3O_{35}S$: C, 49.41; H, 5.18; N, 2.86; S, 2.18. Found: C, 49.59; H, 4.86; N, 2.57; S, 2.00.

1.3.3. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-*m*-chlorophenyl-2-isothiobiuret (3c). ^{1}H NMR ($CDCl_3$): δ 7.36–7.24 (m, 4H, Ar–H), 6.59 (s, 2H, NH), 5.51–3.78 (m, 28H, lactose unit), 2.18–1.18 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.71–20.32 (14CH_3CO), 77.43–60.73 (lactose unit), 131.1–123.1 (aromatic); 170.45–169.03 (14CO). Anal. Calcd for $C_{60}H_{76}ClN_3O_{35}S$: C, 49.14; H, 5.18; N, 2.86; S, 2.18. Found: C, 49.62; H, 5.02; N, 2.66; S, 2.11.

1.3.4. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-*p*-chlorophenyl-2-isothiobiuret (3d). ^{1}H NMR ($CDCl_3$): δ 7.37–7.29 (m, 4H, Ar–H), 5.35 (s, 2H, NH), 5.11–3.77 (m, 28H, lactose unit), 2.20–1.90 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.29–20.41 (14CH_3CO), 77.42–60.77 (lactose unit), 130.1–126.1 (aromatic); 170.68–169.07 (14CO). Anal. Calcd for $C_{60}H_{76}ClN_3O_{35}S$: C, 49.14; H, 5.18; N, 2.86; S, 2.18. Found: C, 49.02; H, 5.12; N, 2.59; S, 2.07.

1.3.5. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-*o*-tolyl-2-isothiobiuret (3e). IR (KBr): 3421, 2969, 1751, 1596, 1372, 1052 and 906 (lactose), 763; ^{1}H NMR ($CDCl_3$): δ 7.61–7.29 (m, 4H, Ar–H), 5.48 (s, 2H, NH), 5.35–3.78 (m, 28H, lactose unit), 2.2–1.96 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.73–20.30 (14CH_3CO), 77.43–60.73 (lactose unit), 131.69–127.52 (aromatic); 170.50–169.06 (14CO); FABMS: *m*/*z* 1445. Anal. Calcd for $C_{61}H_{79}N_3O_{35}S$: C, 50.65; H, 5.46; N, 2.90; S, 2.21. Found: C, 50.53; H, 5.29; N, 2.58; S, 1.96.

1.3.6. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-*m*-tolyl-2-isothiobiuret (3f). ^{1}H NMR ($CDCl_3$): δ 7.49–7.07 (m, 4H, Ar–H), 6.61 (s, 2H, NH), 5.66–3.74 (m, 28H, lactose unit), 2.2–1.96 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.70–20.31 (14CH_3CO), 77.42–60.71 (lactose unit), 129.61–128.02 (aromatic), 170.44–169.01 (14CO). Anal. Calcd for $C_{61}H_{79}N_3O_{35}S$: C, 50.65; H, 5.46; N, 2.90; S, 2.21. Found: C, 50.60; H, 5.41; N, 2.66; S, 2.16.

1.3.7. *N*,*S*-Bis(hepta-*O*-acetyllactosyl)-1-*p*-tolyl-2-isothiobiuret (3g). ^{1}H NMR ($CDCl_3$): δ 7.43–7.12 (m, 4H, Ar–H), 6.25 (s, 2H, NH), 5.52–3.74 (m, 28H, lactose unit), 2.18–1.96 (m, 42H, 14$COCH_3$); ^{13}C NMR ($CDCl_3$): δ 20.80–20.42 (14CH_3CO), 77.43–60.78 (lactose unit), 130.61–129.73 (aromatic), 170.70–169.04 (14CO). Anal. Calcd for $C_{61}H_{79}N_3O_{35}S$: C, 50.65; H, 5.46; N, 2.90; S, 2.21. Found: C, 50.58; H, 5.33; N, 2.63; S, 1.85.

Acknowledgements

The authors are thankful to RSIC, CDRI, Lucknow, for providing spectral data. The authors also thank Principal Dr. S. G. Bhadange for providing necessary facilities.

References

1. Cao, L. H.; Zhou, C. J.; Gao, H. Y.; Liu, Y. T. *J. Chin. Chem. Soc.* **2001**, *48*, 207–210.
2. Goodman, I. *Adv. Carbohydr. Chem. Biochem.* **1958**, *13*, 215–236.
3. Mangte, D. V.; Deshmukh, S. P. *J. Indian Chem. Soc.* **2005**, *82*, 1025–1026.
4. Mangte, D. V.; Deshmukh, S. P. *Int. J. Chem. Sci.* **2004**, *2*, 159–163.
5. Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jimenez, J. L.; Light, M. E.; Palacios, J. C.; Pérez, E. M. S. *Eur. J. Org. Chem.* **2006**, 657–671.
6. Ichikawa, Y.; Nishiyama, T.; Isobe, M. *J. Org. Chem.* **2001**, *66*, 4200–4205.
7. Bigi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140–148.
8. Ukita, C.; Hamada, A.; Yoshida, M. *Chem. Pharm. Bull.* **1964**, *12*, 454–459.
9. Pintér, I.; Kovács, J.; Tóth, G. *Carbohydr. Res.* **1995**, *273*, 99–108.
10. Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Synlett* **2000**, *9*, 1253–1256.
11. Prosperi, D.; Ronchi, S.; Lay, L.; Rencurosi, A.; Russo, G. *Eur. J. Org. Chem.* **2004**, 395–405.
12. Fischer, E. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1377–1381.
13. Korpe, G. V.; Deshmukh, S. P. *J. Indian Chem. Soc.* **2002**, *79*, 972–973.
14. Bhagat, S. K.; Deshmukh, S. P.; Mohammad, M. *J. Indian Chem. Soc.* **2003**, *80*, 916–917.
15. Mangte, D. V.; Deshmukh, S. P. *Indian J. Chem.* **2006**, *45B*, 1285–1287.
16. Clamp, J. R.; Haugh, L.; Hickson, J. L.; Whistler, R. L. *Adv. Carbohydr. Chem. Biochem.* **1961**, *16*, 159–206.
17. Baria, C. S.; Antinio, T. P.; Santoyo-Gonzalez, F. *Synlett* **1999**, *12*, 1891–1894.
18. Rollan, A. French Pat. 937,719, 1948.
19. Suami, T.; Machinami, T.; Hisamatsu, T. *J. Med. Chem.* **1979**, *22*, 247–250.

20. Segal, L.; O'Conner, R. T.; Eggerton, F. V. *J. Chem. Soc.* **1960**, *82*, 2807–2810.
21. Varma, R.; Kulkarni, S. Y.; Jose, C. I.; Pansare, V. S. *Carbohydr. Res.* **1984**, *133*, 25–32.
22. Zhiqun, D.; Fanqui, Q.; Chentai, W. *J. Chem. Res. (S)* **2001**, *3*, 106–107.
23. Bax, A.; Egan, W.; Kóvač, P. *J. Carbohydr. Chem.* **1984**, *3*, 593–611.
24. Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
25. Jimenez-Blanco, J. L.; Barria, C. S.; Benito, J. M.; Mellet, C. O.; Fuentes, J.; Santoyo-Gonzalez, F.; Garcia Fernandez, J. M. *Synthesis* **1999**, *11*, 1907–1914.
26. Goux, W. J. *Carbohydr. Res.* **1988**, *184*, 47–85.
27. Isac-Garcia, J.; Calvo-Flores, F. G.; Hernandez-Mateo, F.; Santoya-Gonzalez, F. *Eur. J. Org. Chem.* **2001**, 383–390.
28. Hassan, H. H. A. M.; Husseiny, H. F. E. *Pol. J. Chem.* **2001**, *75*, 803–811.
29. Lönngren, J.; Svensson, S. *Adv. Carbohydr. Chem. Biochem.* **1974**, *29*, 41–106.