

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF S-HEPTA-O-BENZOYL LACTOSYL-1-ARYLISOTHIOCARBAMIDES

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ABSTRACT

Several *S*-hepta-*O*-benzoyl lactosyl-1-aryl isothiocarbamides have been synthesized by the interaction of hepta-*O*-benzoyl lactosyl bromide and arylthiocarbamides. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations, IR, ¹H NMR and Mass spectral analysis.

Keywords: Lactosyl bromide, aryl thiocarbamides, arylisothiocarbamides.

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INTRODUCTION

Thiolactosides constitute an important family of carbohydrate derivatives. These carbohydrate derivatives bearing *S*-linked functionalities at anomeric position are biologically and pharmacologically important¹. Urea, thiourea and their derivatives are versatile reagent in organic synthesis and show strong antibacterial activity². Various reports on glucosyl thioureides^{3,4}, galactosyl thioureides⁵ and analogs are found. Thiolactosides also show contribution in medicinal chemistry and show antidiabetic and antituberculosis⁶ significance. Lactosyl bromide⁷ is an important intermediate in the synthesis of *N*- and *S*-lactosylated compounds. In present communication seven *S*-hepta-*O*-benzoyl lactosyl-1-aryl isothiocarbamides (3) have been reported. They were prepared by the interaction of hepta-*O*-benzoyl lactosyl bromide (1) and aryl thiocarbamides⁸ (2a-g).

EXPERIMENTAL

All the melting points recorded are found uncorrected. IR spectra were recorded on Perkin-Elmer spectrum RXI FTIR spectrometer. ¹H NMR was obtained on Bruker DRX-300 NMR Spectrometer at 300 MHz. Samples were prepared in CDCl₃ with TMS as an internal reference. The mass spectra were obtained on Thermo Fennigan LCQ Advantage max ion trap mass spectrometer. Optical rotations [α]_D³¹ were measured on the Equip-Tronics EQ-800 Digital Polarimeter at 31°C in CHCl₃.

RESULTS AND DISCUSSION

Isopropanolic (40 ml) suspension of hepta-*O*-benzoyl lactosyl bromide (1) (0.01M, 11.32 gm) and phenyl thiourea (2a) (0.01M, 1.52 gm) was heated on water bath at about 70°C until the suspension gets cleared. The clear solution was kept at room temperature for 20 hours. It was mixed with 100 ml distilled water. This aqueous solution was acidic and non-desulphurisable when boiled with alkaline plumbite solution. The aqueous solution was basified with ammonium hydroxide afforded a sticky mass which was not solidified on standing for several hours. It was purified by ethanol and water. It gave charring test and was found to be non-desulphurisable. Its specific rotation was found [α]_D³¹ -30° (c, 0.980 in CHCl₃).

The IR, ¹H NMR and mass spectral analysis⁹⁻¹³ and elemental analysis (Table 1) clearly indicated the product and was assigned the structure as *S*-hepta-*O*-benzoyl lactosyl-1-phenyl isothiocarbamide (3a).

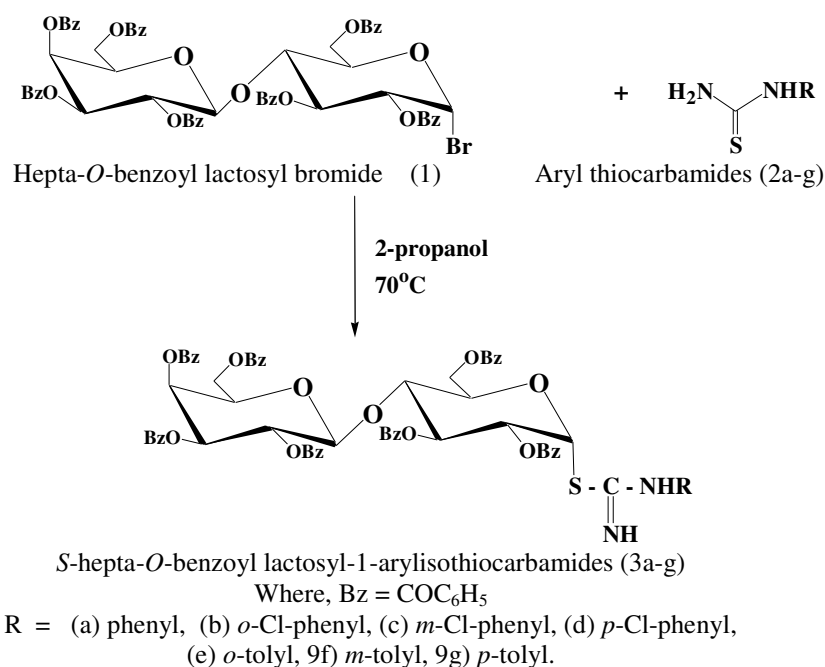
When the interaction of hepta-*O*-benzoyl lactosyl bromide (1) was extended to other aryl thiocarbamides (2b-g) the related *S*-hepta-*O*-benzoyl lactosyl-1-aryl isothiocarbamides (3b-g) were isolated.

Spectral data

(3a) IR (KBr) : ν 3460 cm^{-1} (N-H), 1728 cm^{-1} (C=O), 1655 cm^{-1} (C=N), 1454 cm^{-1} (C-N), 1271 cm^{-1} (C-O), 1026, 858 (characteristic of lactose unit) and 709 cm^{-1} (C-S); $^1\text{HNMR}$ (CDCl_3): δ 8.14- 7.16 (40 H, m, Ar-H); δ 5.76 -5.39 (14 H, m, lactose ring protons); δ 5.75 (2H, s, 2N-H). MS (m/z): 1204 (M^+), 1083, 1053, 976, 948, 932, 918, 579. Anal. Found : C, 67.70; H, 4.70; N, 2.30 S, 2.26 Calcd. For $\text{C}_{68}\text{H}_{56}\text{O}_{17}\text{N}_2\text{S}$: C, 67.77; H, 4.65; N, 2.32; S, 2.74 %

(3b) IR (KBr) : ν 3469 cm^{-1} (N-H), 1728 cm^{-1} (C=O), 1632 cm^{-1} (C=N), 1453 cm^{-1} (C-N), 1271 cm^{-1} (C-O), 1028 (characteristic of lactose unit) and 710 cm^{-1} (C-S); $^1\text{HNMR}$ (CDCl_3): δ 8.07- 7.18 (39 H, m, Ar-H); δ 5.74 -5.43 (14 H, m, lactose ring protons); δ 5.73 (1H, s, 2N-H), δ 6.1 (1H, s, N-H). MS (m/z): 1238 (M^+), 1203, 1133, 1103, 1053, 976, 932, 579. Anal. Found : C, 63.70; H, 4.25; N, 2.18 S, 2.77 Calcd. for $\text{C}_{68}\text{H}_{55}\text{O}_{17}\text{N}_2\text{SCl}$: C, 65.85; H, 4.43; N, 2.3; S, 2.88 %

(3c) IR (KBr) : ν 3458 cm^{-1} (N-H), 1718 cm^{-1} (C=O), 1627 cm^{-1} (C=N), 1403 cm^{-1} (C-N), 1265 cm^{-1} (C-O), 1026 (characteristic of lactose unit) and 710 cm^{-1} (C-S); $^1\text{HNMR}$ (CDCl_3): δ 8.09- 7.15 (39 H, m, Ar-H); δ 5.64 -5.33 (14 H, m, lactose ring protons); δ 5.81 (1H, s, 2N-H), δ 6.0 (1H, s, N-H). MS (m/z): 1238 (M^+), 1203, 1133, 1103, 1053, 976, 932, 579. Anal. Found : C, 63.84; H, 4.25; N, 2.13 S, 2.65 Calcd. for $\text{C}_{68}\text{H}_{55}\text{O}_{17}\text{N}_2\text{SCl}$: C, 65.85; H, 4.43; N, 2.3; S, 2.88 %



Scheme-1

(3d) IR (KBr) : ν 3449 cm^{-1} (N-H), 1714 cm^{-1} (C=O), 1622 cm^{-1} (C=N), 1433 cm^{-1} (C-N), 1260 cm^{-1} (C-O), 1025 (characteristic of lactose unit) and 708 cm^{-1} (C-S); $^1\text{HNMR}$ (CDCl_3): δ 8.19- 7.15 (39 H, m, Ar-H); δ 5.44 -5.33 (14 H, m, lactose ring protons); δ 5.41 (1H, s, 2N-H), δ 5.8 (1H, s, N-H). MS (m/z): 1238 (M^+), 1203, 1133, 1103, 1053, 976, 932, 579. Anal. Found : C, 63.81; H, 4.25; N, 2.11 S, 2.66 Calcd. for $\text{C}_{68}\text{H}_{55}\text{O}_{17}\text{N}_2\text{SCl}$: C, 65.85; H, 4.43; N, 2.3; S, 2.88 %

(3e) IR (KBr) : ν 3472 cm^{-1} (N-H), 1721 cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1454 cm^{-1} (C-N), 1453 cm^{-1} (C-O), 1027, 855, (characteristic of lactose unit) and 710 cm^{-1} (C-S); $^1\text{HNMR}$ (CDCl_3): δ 8.05- 7.18 (39 H, m, Ar-H); δ 5.79 -5.39 (14 H, m, lactose ring protons); δ 2.9 (3H, s, Ar- CH_3), δ 6.8-6.7 (2H, s, N-H). MS (m/z): 1218 (M^+), 1133, 1097, 1053, 932, 918, 579. Anal. Found : C, 60.78; H, 4.56; N, 2.30, S, 2.41 Calcd. For $\text{C}_{69}\text{H}_{58}\text{O}_{17}\text{N}_2\text{S}$: C, 67.98; H, 4.76; N, 2.31; S, 2.56 %

(3f) IR (KBr) : ν 3469 cm^{-1} (N-H), 1728 cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1454 cm^{-1} (C-N), 1453 cm^{-1} (C-O), 1027, 855, (characteristic of lactose unit) and 710 cm^{-1} (C-S); $^1\text{H NMR}$ (CDCl_3): δ 8.05- 7.18 (39 H, m, Ar-H); δ 5.79 -5.39;(14 H, m, lactose ring protons); δ 2.03 (3H, s, Ar- CH_3), δ 6.5-6.7(2H, s, N-H). MS (m/z): 1218 (M^+), 1133, 1097, 1053, 932, 918, 579. Anal. Found : C, 58.78; H, 4.16; N, 2.0; S, 2.48 Calcd. For $\text{C}_{69}\text{H}_{58}\text{O}_{17}\text{N}_2\text{S}$: C, 67.98; H, 4.76; N, 2.31; S, 2.56 %

(3g) IR (KBr) : ν 3469 cm^{-1} (N-H), 1728 cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1454 cm^{-1} (C-N), 1453 cm^{-1} (C-O), 1027, 855, (characteristic of lactose unit) and 710 cm^{-1} (C-S); $^1\text{H NMR}$ (CDCl_3): δ 8.05- 7.18 (39 H, m, Ar-H); δ 5.79 -5.39;(14 H, m, lactose ring protons); δ 2.04 (3H, s, Ar- CH_3), δ 6.2-6.7(2H, s, N-H). MS (m/z): 1218 (M^+), 1133, 1097, 1053, 932, 918, 579. Anal. Found : C, 65.78; H, 4.36; N, 2.2 S, 2.49 Calcd. For $\text{C}_{69}\text{H}_{58}\text{O}_{17}\text{N}_2\text{S}$: C, 67.98; H, 4.76; N, 2.31; S, 2.56 %

Table-1: Characterization data of *S*-hepta-*O*-benzoyl lactosyl-1-arylisothiocarbamides (3a-g)

S. No.	Product	Yield (%)	m. p. ($^{\circ}\text{C}$)	$[\alpha]_{\text{D}}^{31}$ (c, in CHCl_3)	Analysis (%): Found(Required)	
					N	S
1.	3a	70	94	-30 $^{\circ}$ (c, 0.980)	2.30(2.32)	2.26(2.74)
2.	3b	54	102	-70 $^{\circ}$ (c, 0.693)	2.18(2.3)	2.77(2.88)
3.	3c	49	126	-90 $^{\circ}$ (c, 0.986)	2.13(2.3)	2.65(2.88)
4.	3d	58	98	-10 $^{\circ}$ (c, 0.786)	2.11(2.3)	2.66(2.88)
5.	3e	60	108	-130 $^{\circ}$ (c, 0.966)	2.30(2.31)	2.41(2.56)
6.	3f	69	138	-148 $^{\circ}$ (c, 1.006)	2.02(31)	2.48(2.56)
7.	3g	74	118	-169 $^{\circ}$ (c, 1.040)	2.2 (2.31)	2.49(2.56)

Antimicrobial activities

All the compounds have been screened for both antibacterial and antifungal activities using cup plate agar diffusion method by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1mg/mL using dimethyl sulphoxide as solvent. Amikacin (100 $\mu\text{g/ml}$) was used as a standard for antibacterial and antifungal activity and fluconazole (100 $\mu\text{g/ml}$) as a standard for antifungal activity. The compounds were screened for antibacterial activity against *Escherichia Coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Salmonella typhi*, *Klebsiella Pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis* in nutrient agar medium and for antifungal activity against *Candida albicans* and *Aspergillus niger* in potato dextrose agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify on the surface of the media, microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore the cavities. 0.1mL portions of the test compounds in solvent were added into these wells. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37 $^{\circ}\text{C}$ for 24h and 30 $^{\circ}\text{C}$ for 48h for antibacterial and antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured.

It has been observed that all of these synthesized compounds showed nearly the same inhibitory activity as that of the standard Amikacin and Fluconazole. Similarly it has also been observed that some of these compounds exhibited interesting microbial activities. **3a, 3b, 3d, 3f** exhibited most significant activity against *Salmonella* and *E.coli* while **3e** inhibited *S.aureus* and *P.vulgaris*. All other compounds exhibited low to moderate activity. The results are presented in (Table 2).

Table-2:Antimicrobial activities of S-Lactosides (3a-g).

Compd.	Antibacterial**							Antifungal**	
	<i>E. Coli</i>	<i>S. aureus</i>	<i>P. vulgaris</i>	<i>S. typhi</i>	<i>K. Pneumonia</i>	<i>P. aeruginosa</i>	<i>B. Subtilis</i>	<i>C. albicans</i>	<i>A. Niger</i>
3a	21	14	16	22	19	15	12	07	09
3b	23	13	13	19	15	17	22	10	07
3c	19	20	-	10	17	-	16	08	11
3d	19	17	22	24	13	13	17	07	-
3e	13	19	24	-	11	-	15	07	09
3f	18	15	17	23	-	14	-	07	08
3g	12	19	17	11	14	-	13	09	08
Amikacin	28	23	25	28	22	25	22	-	-
Fluconazole	-	-	-	-	-	-	-	18	24

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive.

Escherichia coli (*E. coli*), *Staphalococcus aureus* (*S. aureus*), *Proteus vulgaris* (*P. vulgaris*), *Salmonella typhi* (*S. typhi*), *Klebsiella Pneumoniae* (*K. Pneumoniae*), *Psudomonas auriginosa* (*P. auriginosa*), *Bacillus subtilis*, *Candida albicans* (*C. albicans*) and *Aspergillus niger* (*A. niger*).

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REFERENCES

- 1.M. Jose, Garcia Fernandez and Carmen Ortiz Mellet, *Adv. Carbohydr. Chem. Biochem.*, **55**, 97 (2000).
- 2.L. H. Cao, C. J. Zhou, H. Y. Gao, Y. T. Liu, *J. Chin. Chem. Soc.*, **48**, 207 (2000).
- 3.I. D. Bedekar and M. G. Paranjpe, *J.Indian Chem. Soc.*, **58**, 1014, (1981).
- 4.S. K. Bhagat and M. G. Paranjpe, *Asian J. Chem.*, **14**(1), 243, (2002).
- 5.B. S. Gabhe, G. V. Korpe and S. P. Deshmukh, *J.Indian Chem. Soc.*, **82**, 1042 (2007)
- 6.M.Tomoya, N.Shigery, K. Kazuo and S. Testsuo, *Bull. Chem. Soc.*, **48**, 3763, (1976).
7. P. C. Scheuzer and F. Smith, *J. Am. Chem. Soc.*, **76**, 3234 (1954).
- 8.H. Krall and R. D. Gupta, *J. Indian Chem. Soc.*, **12**,629 (1935).
- 9.(a)R. M. Silverstain and G. C. Bassler, "Spectrometric Identification of Organic Compounds", 5th ed., John Wiley & sons, Inc, New York, 1991; (b) D.H. Williams and Ian Fleming, "Spectrometric Methods of Organic Chemistry", 4th ed., Tata-McGraw Hill, 1991; (c) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", 8th ed., Prentice hall, 1991.
10. R. Verma, S. Y. Kulkarni, C. I. Jose and V. S. Pansave, *Carbohydr. Res.*, **25**, 133 (1984).
11. S. A. Barker, J. Homer, M. C. Keith and L. F. Thomas, *J. Chem. Soc.*, 1538(1963).
12. S. A. Barker, E.J. Bourne, R. Stephens and D.H.Whiffen, *J.Chem, Soc.*, 3468 (1954).
13. Carla Prata, Nathie Mora, J. Lacombe, Maurizis and B. Pucci, *Carbohydr. Res.*, **4**, 321, (1999).

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