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Syntheses and Antimicrobial Activities of 4-Aryl-5-phenylimino-3-*S*-(hepta-*O*-acetyl Lactosyl)-1,2,4-thiadiazolines

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ABSTRACT: *A series of 4-aryl-5-phenylimino-3-S-(hepta-O-acetyl lactosyl)-1,2,4-thiadiazolines have been synthesized by the interaction of S-(hepta-O-acetyl lactosyl)-1-arylisothiocarbamides and S-chloro-N-phenyl isothiocarbamoyl chloride. The title compounds were characterized on the basis of elemental analysis and IR, NMR, mass spectral studies. The title compounds exhibited comparable antimicrobial activities against pathogens such as E. coli, S. aureus, P. vulgaris, S. typhi, A. niger, and Candida guilliermondii.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:390–392, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20310

INTRODUCTION

Recently, in our laboratory, we reported the synthesis of lactosyl thioureides [1] and their analog [2] in view of their pharmacological activity [3–6]. Literature survey revealed that the heterocyclic derivatives of sugars possess antibacterial and antitumor activities [7]. With this point of view, we wish to report the syntheses of few 4-aryl-5-phenylimino-3-*S*-(hepta-*O*-acetyl lactosyl)-1,2,4-thiadiazolines (**3**) by the interaction of *S*-(hepta-*O*-acetyl lactosyl)-1-arylisothiocarbamides (**1**) [1] and *S*-chloro-*N*-phenyl isothiocarbamoyl chloride (**2**) [8,9].

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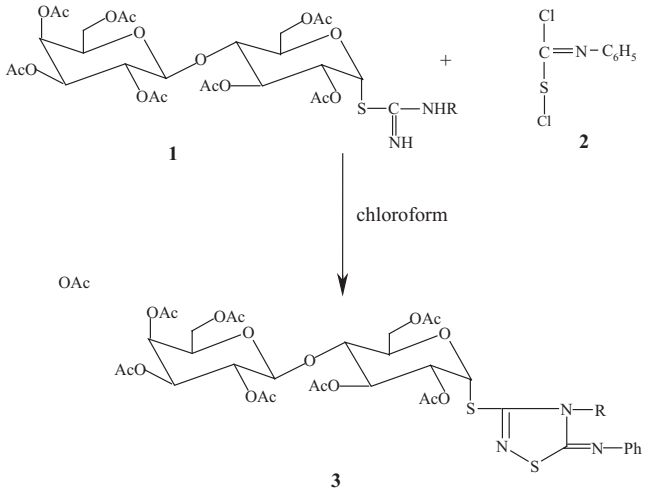
RESULTS AND DISCUSSION

S-chloro-*N*-phenyl isothiocarbamoyl chloride (0.0025 mol, 0.5 g) in chloroform (10 mL) was added gradually to a well-cooled solution of *S*-(hepta-*O*-acetyl lactosyl)-1-phenylisothiocarbamide (**1a**) (0.0025 mol, 1.9 g) in chloroform (20 mL) (Scheme 1). The reaction was quite brisk and exothermic with the evolution of hydrogen chloride. The resultant solution was allowed to stand for several hours until no solid was separated out. The chloroform was distilled off. The sticky mass obtained was triturated with petroleum ether (60–80°), and granular solid was obtained (**3a**). It gave charring test and nondesulphurisable when boiled with an alkaline plumbite solution.

The IR spectrum [11,12] of the product shows characteristics absorption of the lactose unit in the ranges of 900–910 and 1000–1100 cm^{-1}. The mass spectra [19] of the acetolactose unit show the peak at *m/z* 619, 331, 229, 169, 127, and 109.

On the basis of elemental analysis and IR [10–13], NMR [11–16], and mass spectral studies [17–19] (experimental), the product with mp 125–127°C was assigned the structure 4-phenyl-5-phenylimino-3-*S*-(hepta-*O*-acetyl lactosyl)-1,2,4-thiadiazoline (**3a**).

When the interaction of *S*-chloro-*N*-phenyl isothiocarbamoyl chloride was extended to other *S*-(hepta-*O*-acetyl lactosyl)-1-arylisothiocarbamides, the respective 4-aryl-5-phenylimino-3-*S*-(hepta-*O*-acetyl lactosyl)-1,2,4-thiadiazolines (**3b–g**) were isolated.



SCHEME 1 Where R: (a) phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d) *p*-Cl-phenyl, (e) *o*-tolyl, (f) *m*-tolyl, and (g) *p*-tolyl; and Ac: $COCH_3$ (acetyl) Ph: C_6H_5 (phenyl).

EXPERIMENTAL

General Methods

Melting points were determined with an electrothermal melting point apparatus and were uncorrected. IR spectra were recorded on KBr on an FT IR Perkin Elmer (4000–450 cm^{-1}) spectrophotometer. ^1H NMR spectra are run on a Bruker DRX-300 instrument operating at 300 MHz using a $CDCl_3$ solution with TMS as internal standard and mass spectra on a Jeol SX-102 FAB instrument. Specific rotations were recorded on a digital polarimeter.

The required *S*-hepta-*O*-acetyl lactosyl-1-arylisothiocarbamides [1] were prepared by the interaction of hepta-*O*-acetyl lactosyl bromide [20] and aryl thiocarbamides [21]. *S*-chloro-*N*-phenyl isothiocarbamoyl chloride [8,9] was prepared by the following known procedure:

3a: mp 125–127°C, yield 99.52%, $[\alpha]_D^{31}$ −302.43° (*c*, 1.025, $CHCl_3$). IR (KBr): 3024, 1748, 1630, 1596, 1444, 1226, 1057, 756 cm^{-1}; FABMS (*m/z*): $(M^+ + 1)$ 904, 619, 331, 229, 169, 127, 109; ^1H NMR (ppm): δ 7.5–7.2 (m, 10H, Ar), δ 5.5–4.1 (m, 14H, lactose unit), 2.1–1.9 (m, 21H, $7COCH_3$). Anal. Calcd for $C_{40}H_{45}O_{17}N_3S_2$; C, 53.16; H, 4.98; N, 4.65; S, 7.08. Found: C, 53.02; H, 4.85; N, 4.76; S, 7.16.

3b: mp 123–125°C, yield 94.42%, $[\alpha]_D^{31}$ −154.58° (*c*, 1.035, $CHCl_3$). IR (KBr): 2978, 1746, 1631, 1594, 1443, 1224, 1057, 759 cm^{-1}; FABMS (*m/z*): (M^+) 937, 619, 559, 331, 229, 169, 127, 109; ^1H NMR (ppm): δ 7.5–6.9 (m, 9H, Ar), δ 5.3–3.7 (m, 14H, lactose unit), 2.1–1.9 (m, 21H, $7COCH_3$). Anal. Calcd for $C_{40}H_{44}O_{17}N_3S_2Cl$; C, 51.23; H, 4.70; N, 4.48; S, 6.83. Found: C, 51.24; H, 4.59; N, 4.06; S, 6.19.

3c: mp 160–162°C, yield 77.42%, $[\alpha]_D^{31}$ −254.9° (*c*, 1.020, $CHCl_3$). Anal. Calcd for $C_{40}H_{44}O_{17}N_3S_2Cl$; C, 51.23; H, 4.70; N, 4.48; S, 6.83. Found: C, 51.13; H, 4.63; N, 4.57; S, 7.03.

3d: mp 147–150°C, yield 81.54%, $[\alpha]_D^{31}$ −238.56° (*c*, 1.006, $CHCl_3$). Anal. Calcd for $C_{40}H_{44}O_{17}N_3S_2Cl$; C, 51.23; H, 4.70; N, 4.48; S, 6.83. Found: C, 51.16; H, 4.61; N, 4.51; S, 6.99.

3e: mp 152–154°C, yield 94.59%, $[\alpha]_D^{31}$ −321.63° (*c*, 1.026, $CHCl_3$). IR (KBr): 2981, 1751, 1596, 1233, 1055, 759 cm^{-1}; FABMS (*m/z*): (M^+) 917, 784, 619, 559, 331, 229, 169, 127, 109; ^1H NMR (ppm): δ 7.4–7.1 (m, 9H, Ar), δ 5.3–3.7 (m, 14H, lactose unit), 2.1–1.8 (m, 21H, $7COCH_3$). Anal. Calcd for $C_{41}H_{47}O_{17}N_3S_2$; C, 53.65; H, 5.13; N, 4.58; S, 6.97. Found: C, 53.56; H, 5.03; N, 4.48; S, 7.17.

3f: mp 134–135°C, yield 90.09%, $[\alpha]_D^{31}$ −117.07° (*c*, 1.025, $CHCl_3$). Anal. Calcd for $C_{41}H_{47}O_{17}N_3S_2$; C, 53.65; H, 5.13; N, 4.58; S, 6.97. Found: C, 53.59; H, 5.07; N, 4.48; S, 7.19.

3g: mp 132–134°C, yield 90.09%, $[\alpha]_D^{31}$ −241.54° (*c*, 1.035, $CHCl_3$). Anal. Calcd for $C_{41}H_{47}O_{17}N_3S_2$; C, 53.65; H, 5.13; N, 4.58; S, 6.97. Found: C, 53.57; H, 5.06; N, 4.63; S, 7.17.

Antimicrobial Activity

Antibacterial Activity. The compounds (**3a–g**) were screened for their antibacterial activity against various pathogenic bacteria such as *E. coli*, *S. aureus*, *P. vulgaris*, *S. typhi*, *A. niger*, and *Candida guilliermondii* using the cup plate method [22] at a concentration of 100 μg cm^{-1} in DMF using co-trimazine (25 μg cm^{-1}) for bacteria. The compounds **3a** and **3e** exhibited higher activity against *S. aureus*, while other compounds were less to moderately active against other bacteria.

Antifungal Activity. The compounds (**3a–g**) were also screened for their antifungal activity against *A. niger* and *C. guilliermondii* using the cup plate method [22] at a concentration of 100 μg cm^{-1} in DMF using standard griseofulvine (10 μg cm^{-1}). The compounds **3a**, **3b**, and **3f** exhibited higher activity against *A. niger*, while **3b** and **3d–g** are sensitive toward *C. guilliermondii*. The other compounds were less to moderately active against used fungi.

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