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Peracetylated *N*-Lactosyl-1,2,4-Thiadiazolidin-3-one Hydrochlorides: 합성과 항균 연구

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Novel Peracetylated *N*-Lactosyl-1,2,4-Thiadiazolidin-3-one Hydrochlorides: Synthesis and Antimicrobial Studies

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요약. Peracetylated lactosyl carbamides와 *N*-phenyl-*S*-chloro isothiocarbamoyl chloride를 고리화 반응을 시켜서 peracetylated *N*-Lactosyl-1,2,4-thiadiazolidin-3-one hydrochlorides를 합성하였으며, 얻어진 화합물을 이용하여 bacteria *S. aureus*, *E. coli*, *P. Vulgaris*, *P. Aeruginosa* and fungi *A. Niger*, *Penicillium* 항균 활성을 연구하였다.

주제어: Peracetylated lactosyl carbamides, Isothiocarbamoyl chloride, 고리화, Peracetylated lactosyl thiadiazolidin-3-one, 합성, 항균활성

ABSTRACT. In the present work we described oxidative cyclisation of peracetylated lactosyl carbamides with *N*-phenyl-*S*-chloro isothiocarbamoyl chloride and structural elucidation of novel peracetylated *N*-Lactosyl-1,2,4-Thiadiazolidin-3-one hydrochlorides. Antimicrobial activities of the title compounds were determined against bacteria *S. aureus*, *E. coli*, *P. Vulgaris*, *P. Aeruginosa* and fungi *A. Niger*, *Penicillium*.

Keywords: Peracetylated lactosyl carbamides, Isothiocarbamoyl chloride, Cyclisation, Peracetylated lactosyl thiadiazolidin-3-one, Synthesis, Antimicrobial activity

INTRODUCTION

Ureides are compounds, which essentially incorporate urea as a substructural component either in open or cyclic form. Some of the important pharmacological[1] activities ascribed to ureides are antiinfectives, antitumor, anticancer and for various metabolic disorders including diabetes and hyperlipidemia. In this view we recently reported the synthesis of peracetylated lactosyl *N*-carbamides, *N*-benzothiazolyl carbamides[2] by reaction of hepta acetyl lactosyl isocyanate[3] with aryl amines and benzothiazolyl carbamides respectively. Ureides and their heterocyclic derivatives[4] also possess antibacterial, antifungal and antitumor activity. *N*-lactosylated compounds and their derivatives are reported to show various applications in medicinal chemistry.[5-7]

In this work, we described the application of peracetylated lactosyl isocyanate in the synthesis of 1,2,4-thiadiazolidin-3-one containing lactosyl substituent by the cyclisation of 1-hepta-*O*-acetyl-α-lactosyl-3-aryl carbamides (**2a-g**) with *N*-phenyl-*S*-chloro isothiocarbamoyl chloride (**1**).

EXPERIMENTAL

Melting points were recorded on electro thermal melting point apparatus and are uncorrected. Specific rotations $[\alpha]_D$ were measured on a Equip-Tronics digital polarimeter model no EQ 800 at 31 ^oC in $CHCl_3$. IR spectra were recorded on a Perkin – Elmer spectrum RXI (4000 - 450 cm^{-1}) FTIR spectrometer. ^{1}HNMR spectrum were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as an internal reference. The mass spectra were recorded on a Jeol SX-102 mass spectrometer. 1-hepta-

***Table* 1.** Physical characterization and analytical data of compounds **3a-3g**

Entry	M.P. (°C)	Yield (%)	$[\alpha]_D^{31}$ (c, 1.0 in $CHCl_3$)	R_f ($CHCl_3$:EtOAc, 3:1)	Found (Calculated)	
					N	S
3a	126 - 128	73	+339.15°	0.72	4.23 (4.37)	3.20 (3.33)
3b	131 - 132	74	− 50.70°	0.81	4.12 (4.22)	3.17 (3.21)
3c	140 - 142	57	− 41.10°	0.68	4.03 (4.22)	3.13 (3.21)
3d	129 - 131	60	+30.42°	0.70	4.09 (4.22)	3.10 (3.21)
3e	120 - 122	65	−107.84°	0.86	4.20 (4.31)	3.20 (3.28)
3f	136 - 139	61	−30.00°	0.75	4.19 (4.31)	3.17 (3.28)
3g	123 - 124	68	+ 223.12°	0.73	4.17 (4.31)	3.21 (3.28)

***Table* 2.** Antibacterial and antifungal activities of compounds **3a-3g**

Entry	inhibition zone					
	Bacteria				Fungi	
	E. coli	*P. Vulgaris*	*S. aurues*	*P. Aeruginosa*	*A. niger*	*Penicillium*
3a	++++	++++	+++	+++	+++	----
3b	++	----	+++	+++	----	+++
3c	+++	+++	+++	----	++	+++
3d	----	+++	++	++++	----	++
3e	+++	++++	++++	++	+++	+++
3f	++++	+++	+++	+++	+++	----
3g	++++	++	++++	+++	+++	+++
Amikacin	+++	+++	++++	++++	-	-
Fluconazole	-	-	-	-	++++	++++

++++ Strongly active (Above 20 mm), +++ moderately active (15 mm to 20 mm), ++ weakly active (8 mm - 14 mm), ---- inactive (below 8 mm).

O-acetyl-*β*-lactosyl-3-aryl carbamides[2] (**2a-g**) were prepared by nuleophilic addition of hepta-*O*-acetyl lactosyl isocyanate with amines. *N*-phenyl-*S*-chloro isothiocarbamoyl chloride[8] was prepared by chlorination of phenyl isothiocyanate in chloroform.

The antimicrobial activity of synthesized compounds were tested *in vitro* against bacteria *S. aureus*, *E. coli*, *P. Vulgaris*, *P. Aeruginosa* and fungi *A. niger*, *Penicillium* by cup plate agar diffusion method. The compounds were taken at a concentration of 1 mg/mL and compared with Amikacin and Fluconazole as a positive control for different strains of bacteria and fungi for antibacterial and antifungal activity respectively (*Table* 2).

General procedure for synthesis of compound (3a-g).

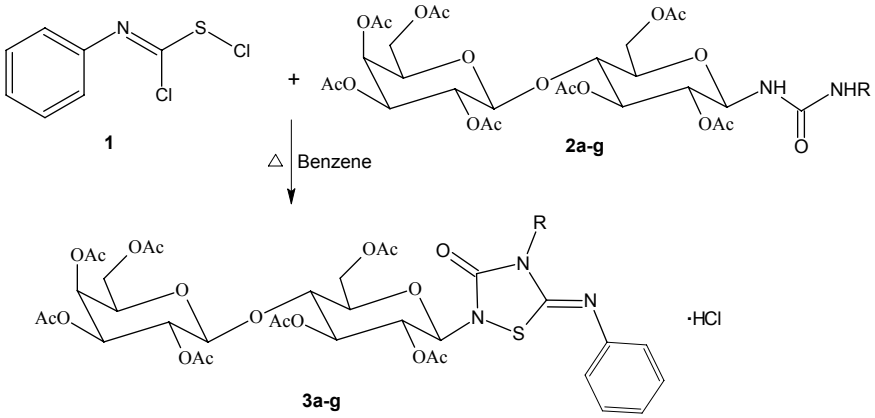
2-*N*-hepta-*O*-acetyl-β-lactosyl-4-*N*-aryl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochlorides (3a-g) (*Fig*. 1): *N*-phenyl-*S*-chloro isothiocarbamoyl chloride (**1**) (5 mmol) in benzene was added to 1-hepta-*O*-acetyl-*β*-lactosyl-3-aryl carbamide (**2a-g**) (5 mmol) in benzene and refluxed for 3 h. Reaction was monitored by TLC. The solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60 - 80°) to afford a white solid (**3a-g**). The product was crystalized from ethanol-water.

RESULTS AND DISCUSSION

The synthesis of title compounds (**3a-g**) *Fig.* 1 was achieved by the oxidative cyclization of 1-hepta-*O*-acetyl-β-lactosyl-3-aryl carbamide (**2a-g**) with *N*-phenyl-*S*-chloro isothiocarbamoyl chloride (**1**). The synthesized compounds were soluble in common organic solvents and insoluble in water. The structures of the title compounds 3a-g were confirmed by elemental analysis and IR, HNMR, Mass spectra.

The IR spectra[9-11] of the compounds showed strong characteristic absorption of lactose unit in the range of 900 - 910, 1000 - 1100 cm^{-1} for stretching vibration of C-H bond. The stretching band for acetyl C=O has appeared in the region 1749-1750 cm^{-1}. The absorption band for C=N and C-N has appeared in the region 1515 - 1597 cm^{-1} and 750 - 755 cm^{-1} respectively.

^{1}HNMR spectrum[10-15] of the products shows characteristic of lactosyl protons at δ 5.6-3.7 ppm and resonance signals for aromatic protons at δ 7.01-7.42 ppm. Acetyl protons are



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

***Fig.* 1**

appeared at δ 1.96-2.24 ppm.

Mass spectra[16-17] exhibited molecular ion peak along with characteristic fragments of lactose unit at *m*/*z*, 619, 559, 331, 169 and 109.

Antimicrobial Activity.

The results of the title compounds for preliminary antibacterial testing are shown in *Table* 2. The results revealed that the majority of the synthesized compounds showed varying degree of inhibition against the tested microorganisms. The phenyl and tolyl derivatives have the best overall antibacterial profile than chloro phenyl derivatives. Compounds 3a, 3f and 3g were found to be more active than standard while 3b and 3d were almost inactive against *E. coli*. All the tested compounds except 3d exhibited moderate to good activity against *S. Aurues*. Compound 3d showed comparable activity against *P. Aeruginosa* to standard while others were less to moderartely active. Compounds 3a and 3e were found more active than standard against *P. Vulgaris* while others were less to moderate acitve. Again in antifungal activity compounds 3a, 3b, 3d and 3f showed no activity than the other derivatives of the same series. Although the rest of the compounds showed varying degree of inhibition, none were as effective as Fluconazole. In general, the inhibitory activity against the bacteria was higher than that of the fungi.

2-*N*-hepta-*O*-acetyl-*β*-lactosyl-4-*N*-phenyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3a): IR (ν/cm^{-1}): 1749 (C=O), 1597 (C=N), 1372 (C-N), 1229 (C-O), 905 and 1050 (lactose), 754 (C-S); ^{1}HNMR ($CDCl_3$) (δ/ppm): 7.45-7.15 (m, 5H, Ar-H), 5.36-3.77 (m, 14H, lactose unit), 2.18-1.97 (m, 21H, 7$COCH_3$); Mass (*m*/*z*): (M^+) 960, 887, 883, 869, 619, 331, 211, 169, 109.

2-*N*-hepta-*O*-acetyl-*β*-lactosyl-4-*N*-*o*-Cl-phenyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3b): IR (ν/cm^{-1}): 1752 (C=O), 1590 (C=N), 1373 (C-N), 1230 (C-O), 905 and 1051 (lactose), 755 (C-S); ^{1}HNMR ($CDCl_3$) (δ/ppm): δ 7.30-7.04 (m, 4H, Ar-H), 5.35-3.77 (m, 14H, lactose unit), 2.21 - 1.96 (m, 21H, 7$COCH_3$); Mass (*m*/*z*): (M^+) 994, 922, 859, 796, 619, 331, 211, 169, 109.

2-*N*-hepta-*O*-acetyl-*β*-lactosyl-4-*N*-*m*-Cl-phenyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3c): ^{1}HNMR ($CDCl_3$) (δ/ppm): δ 7.46-7.14 (m, 4H, Ar-H), 5.18-3.74 (m, 14H, lactose unit), 2.10-1.88 (m, 21H, 7$COCH_3$).

2-*N*-hepta-*O*-acetyl-*β*-lactosyl-4-*N*-*p*-Cl-phenyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3d): ^{1}HNMR ($CDCl_3$) (δ/ppm): δ 7.39-7.11 (m, 4H, Ar-H), 5.21-3.72 (m, 14H, lactose unit), 2.25-1.92 (m, 21H, 7$COCH_3$).

2-*N*-hepta-*O*-acetyl-*β*-lactosyl-4-*N*-*o*-tolyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3e): ^{1}H NMR ($CDCl_3$) (δ/ppm): δ 7.46-7.20 (m, 4H, Ar-H), 5.36-3.75 (m, 14H, lactose unit), 2.24-1.97 (m, 21H, 7$COCH_3$).

2-*N*-hepta-*O*-acetyl-*β*-lactosyl-4-*N*-*m*-tolyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3f): ^{1}H NMR ($CDCl_3$) (δ/ppm): δ 7.39-7.08 (m, 4H, Ar-H), 5.64-3.70 (m, 14H, lactose unit), 2.20 - 1.92 (m, 21H, 7$COCH_3$).

2-*N*-hepta-*O*-acetyl-*β*--lactosyl-4-*N*-*p*-tolyl-5-phenylimino-1,2,4-Thiadiazolidin-3-one hydrochloride (3g): IR (ν/cm^{-1}): 1750 (C=O), 1515 (C=N), 1372 (C-N), 1230 (C-O), 906 and 1051 (lactose), 750 (C-S); ^{1}HNMR ($CDCl_3$) (δ/ppm): δ 7.42-7.01 (m, 4H, Ar-H), 5.52-3.77 (m, 14H, lactose unit), 2.24-1.96 (m, 21H, 7$COCH_3$); Mass (*m*/*z*): (M^+) 974, 901, 883, 619, 559, 331, 211, 169, 109.

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