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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF *S*-HEPTA-*O*-BENZOYL LACTOSYL-1-ARYL-5-PHENYL-2,4-ISODITHIOBIURETS

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ABSTRACT

Condensation of *S*-hepta-*O*-benzoyl lactosyl-1-arylisothiocarbamides and phenyl isothiocyanate resulted in the formation of *S*-hepta-*O*-benzoyl lactosyl-1-aryl-5-phenyl-2,4-isodithiobiurets. The required lactosyl arylisothiocarbamides were prepared by the interaction of *S*-hepta-*O*-benzoyl lactosyl bromide with aryl thiocarbamides. These newly synthesized compounds were characterized on the basis of chemical transformation, elemental analysis and IR, ^{1}H NMR and Mass spectral studies. The polarimetric study of the titled compounds has been carried out. These compounds were screened for their antibacterial and antifungal activities against various pathogenic bacteria and fungi. The products showed good to moderate activity against above microorganisms.

Key words: Lactosyl arylisothiocarbamides, Phenyl isothiocyanate.

INTRODUCTION

Isodithiobiurets have been recognized as an important family of carbohydrate derivatives. They are widely used as precursors of various heterocyclic compounds[1,2]. Isodithiobiurets were reported to have hypnotic and anticonvulsant[3] properties. Glucosyl[4] and lactosyl[5,6] isodithiobiurets and their derivatives were studied for their antimicrobial and antifungal activities. These can be directly prepared by the reaction of alkyl/aryl isothiocyanate in common with thioureas. Synthetic method for lactosyl arylisothiocarbamides[7] is also known. These compounds were basic in nature and therefore, easily react with phenyl isothiocyanate and gave corresponding-2,4-isodithiobiurets. Looking towards the biological importance of *S*-lactosides, an attempt of synthesis of isodithiobiurets was made.

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EXPERIMENTAL

General procedure

Optical rotations $[\alpha]_D^{31}$ were measured on the Equip-Tronics EQ-800 Digital Polarimeter at 31°C in $CHCl_3$. IR Spectra were recorded on Perkin-Elmer spectrum RXI FTIR Spectrometer. ^1H NMR was obtained on Bruker DRX-300 MHz NMR Spectrometer. Samples were prepared in $CDCl_3$ with TMS as an internal reference. The mass spectra were obtained on Thermo Fennigan LCQ Advantage max ion trap mass spectrometer.

S-Hepta-O-benzoyl lactosyl-1,5-diphenyl-2,4-isodithiobiurets (3a-g)

A mixture of *S*-hepta-*O*-benzoyl lactosyl-1-phenyl isothiocarbamide (0.01M, 2 g) with phenyl isothiocyanate (0.01 M, 0.03 g) in dry benzene. The reaction mixture was refluxed for 9 hrs. The benzene was distilled off. The sticky mass obtained was triturated with petroleum ether (60-80°C) to furnish a crystalline solid **(3a)** (2 g). It was purified with ethanol-water, 145-147°C **(Scheme 1).** The physical characterization results are summarized in Table 1 **(3a-g)**. Compounds **(3b-g)** were also prepared by similar method.

Table 1: Characterization data of *S*-hepta-*O*-benzoyl lactosyl-1-aryl-5-phenyl-2,4-isodithiobiurets

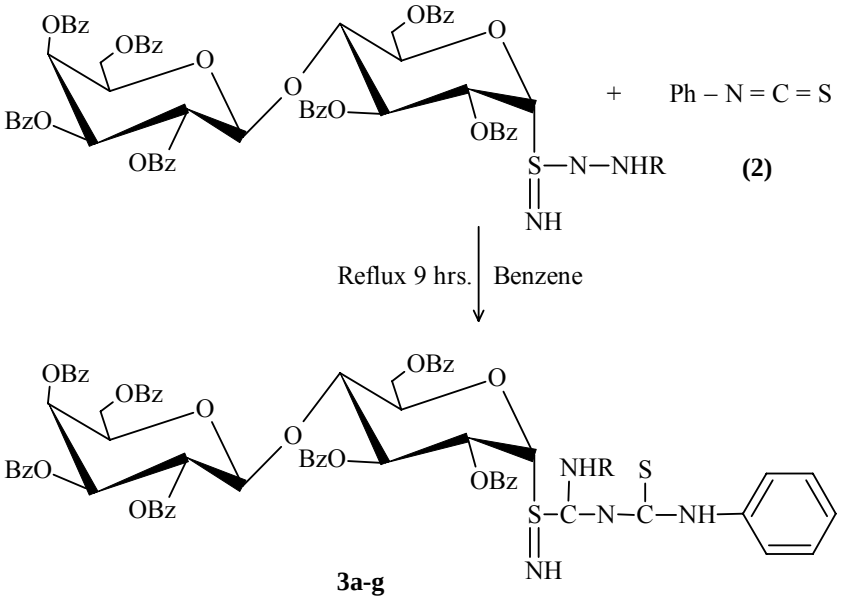
Reactants: - i) Hepta-*O*-benzoyl lactosyl -1-arylisothiocarbamides **(0.01M)**

ii) Phenyl isothiocyanate **(0.01M)**

Compd.	% Yield	m. p. (°C)	$[\alpha]_D^{31}$ ($CHCl_3$)	Found (Calcd.)	
				N (%)	S (%)
3a	74	145-147	-216.28° (c,o.980)	3.13 (3.12)	4.77 (4.76)
3b	82	158	-226^0 (c, 0.693)	3.05 (3.04)	4.65 (4.64)
3c	78	165	-210^0 (c, 0.986)	3.05 (3.04)	4.65 (4.64)
3d	80	176-178	-202^0 (c, 0.786)	3.05 (3.04)	4.65 (4.64)

Cont…

Compd.	% Yield	m. p. (^oC)	$[\alpha]_D^{31}$ ($CHCl_3$)	Found (Calcd.)	
				N (%)	S (%)
3e	62	132	-310^0 (c, 0.966)	3.10 (3.09)	4.72 (4.73)
3f	69	194	-148^0 (c, 1.006)	3.10 (3.09)	4.72 (4.73)
3g	72	118	-169^0 (c, 1.040)	3.10 (3.09)	4.72 (4.73)



Scheme 1

Where, Bz = $-COC_6H_5$ and

R = (a) Phenyl, (b) *o*-Tolyl, (c) *m*-Tolyl, (d) *p*-Tolyl, (e) *o*-Cl-Phenyl, (f) *m*-Cl-Phenyl and (g) *p*-Cl-Phenyl.

Spectral data

(3a) IR (KBr) : ν 3483 cm^{-1} (N-H), 2973 cm^{-1} (C-H), 1728 cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1453 cm^{-1} (C-N), 1271 cm^{-1} (C-O), 1027,858 (characteristic of lactose unit) and 710 cm^{-1} (C-S); **^{1}H NMR** ($CDCl_3$): δ 8.06-7.09 (45 H, m, Ar-H); δ 5.71-3.61(14 H, m, lactose

ring protons); δ 5.35 (2H, s, 2N-H). **MS (*m/z*):** 1339 (M^+), 1218, 1053, 976, 948, 932, 918, 579. Anal. Found : C, 67.10; H, 4.70; N, 3.02 S, 4.34 Calcd. For $C_{75}H_{61}O_{17}N_3S_2$: C, 67.21; H, 4.56; N, 3.12; S, 4.76 % z.

(3d) IR (KBr) : ν 3483 cm^{-1} (N-H), 2972 cm^{-1} (C-H), 1728 cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1453 cm^{-1} (C-N), 1272 cm^{-1} (C-O), 1026 (characteristic of lactose unit) and 710 cm^{-1} (C-S); **^{1}H NMR** ($CDCl_3$): δ 7.42-7.18 (44 H, m, Ar-H); δ 5.92 -3.79 (14 H, m, lactose ring protons); δ 7.2 (2H, s, 2N-H). **MS (*m/z*):** 1373 (M^+), 1252, 1053, 976, 932, 579. Anal. Found : C, 63.85.; H, 4.55; N, 2.88 ; S, 3.77 Calcd. for $C_{75}H_{60}O_{17}N_3S_2Cl$: C, 65.55; H, 4.43; N, 3.09; S, 4.73 %

(3f) IR (KBr) : ν 3468 cm^{-1} (N-H), 2971 cm^{-1} (C-H), 1729 cm^{-1} (C=O), 1601 cm^{-1} (C=N), 1452 cm^{-1} (C-N), 1269 cm^{-1} (C-O), 1026, 855, (characteristic of lactose unit) and 710 cm^{-1} (C-S); **^{1}H NMR** ($CDCl_3$): δ 7.88- 7.18 (44 H, m, Ar-H); δ 5.87 – 3.67 (14 H, m, lactose ring protons); δ 2.3 (3H, s, Ar-CH_3), δ 7.2 (2H, s, N-H). **MS (*m/z*):** 1353 (M^+), 1232, 1053, 932, 918, 579. Anal. Found : C, 66.12; H, 4.56; N, 2.48; S, 3.50 Calcd. For $C_{76}H_{63}O_{17}N_3S_2$: C, 66.42; H, 4.58; N, 3.09; S, 4.76 %

RESULTS AND DISCUSSION

Condensation of *S*-hepta-*O*-benzoyl lactosyl-1-arylisothiocarbamides with phenyl isothiocyanate was carried out by refluxing in dry benzene for 9 hrs, it gave a clear solution. The benzene was distilled off. The sticky mass obtained was triturated with petroleum ether (60-80^{0}C) furnishing a crystalline solid. It was purified with ethanol-water. It was desulphurisable, when boiled with alkaline plumbite solution.

IR spectra of the products show characteristic absorption of lactose unit[8,9] in the bands 900-910 and 1000-1100 cm^{-1}. Mass spectra show characteristic fragmentation of lactose unit[10,11].

The IR, ^{1}H NMR and Mass spectral analysis and elemental analysis (Table 1) clearly indicated that the product the structure as *S*-hepta-*O*-benzoyl lactosyl-1,5-diphenyl-2,4-isodithiobiurets **(3a)**.

When the interaction of phenyl isothiocyanate was extended to other *S*-hepta-*O*-benzoyl lactosyl -1-arylisothiocarbamides, the related *S*-hepta-*O*-benzoyl lactosyl-1-aryl-5-phenyl-2,4-isodithiobiurets **(3b-g)** were obtained.

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 1 mg/mL using dimethyl sulphoxide as solvent. Amikacin (100 μg/mL) was used as a standard for antibacterial and antifungal activity and fluconazole (100 μg/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 albicancs* and *Aspergillus niger* in potato dextrose agar medium. Then sterilized agar media were poured into petri dishes; allowed to solidify on the surface of the media and microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8 mm diameter (pre-sterilized) was used to bore the cavities. 0.1 mL 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°C for 24 h and 30°C for 48 h for antibacterial and antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured. The results are presented in Table 2.

Table 2: Antimicrobial activities of *S*-hepta-*O*-benzoyl lactosyl-1-aryl-5-phenyl-2,4-isodithiobiurets

Compd.	Antibacterial*							Antifungal**	
	E. coli	***S. aureus***	***P. vulgaris***	***S. typhi***	***K. Pneumoniae***	***P. aeruginosa***	***B. subtilis***	***C. albicance***	***A. niger***
3a	18	14	20	16	19	15	12	07	09
3b	23	13	13	12	15	17	22	10	07
3c	19	20	-	10	17	-	13	08	11
3d	-	17	22	-	13	13	17	07	-
3e	13	19	12	-	20	-	15	07	09
3f	16	15	17	14	-	14	-	07	08
3g	12	19	17	11	14	-	13	09	08

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