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Perbenzoylated *N*-Lactopyranosyl-3-Aryl Carbamides: Synthesis and Antimicrobial Studies

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ABSTRACT: Several 1-Hepta-*O*-benzoyl-â-D-lactopyranosyl-3-aryl carbamides have been synthesized by the condensation of Hepta-*O*-benzoyl-â-D-lactopyranosyl isocyanate with several aryl amines. The identities of these newly synthesised *N*-lactopyranosylcarbamides have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies. These compounds were assayed for their antibacterial activity and antifungal activity against some selected pathogenic organisms to get potent bioactive molecule.

Keywords: *N*-lactopyranosyl isocyanate, aryl amines, *N*-lactopyranosylcarbamides, antimicrobial studies.

INTRODUCTION

Urea and thiourea are important functional groups in numerous natural productsand drug intermediates, and are used as neutral receptor for various anions (anion complexation) [1] and building blocks for various heterocycles. Urea andthiourea derivatives possess many promising biological activities, such as herbicidal [2],antimicrobial [3],antioxidant [4] antiviral [5], anti-HIV [6] and antitumor [7] activity,while urea derivatives exhibit anti-inflammatory [8], antimalarial [9] and antidiabetic activities [10]. It was envisaged that the compounds containing these moieties in their molecular frame work might show enhanced biological activity. As a results of these factors and applications in various fields, synthesis of perbenzoylation of sugars and derivatives of such protected sugars become valuable in common transformations and in carbohydrate synthesis [11].

Keeping this in view and in continuation of our research for synthesis of sugar derivatives having pharmacological importance, we have reported novel *N*-lactopyranosylcarbamides.

EXPERIMENTAL

All the chemicals and solvents were obtained from commercial and purified using standard procedure wherever required. Melting points were taken by the open capillary method and were uncorrected. The reactions were monitored by thin layer chromatography on silica gel G plates (Merck silica- 60 F_{258}). Optical rotations $[\alpha]_D^{31}$ were measured on the Equip-Tronics EQ-800 Digital Polarimeter at 31°C in $CHCl_3$. The structures of all the newly synthesized compounds were confirmed by IR Spectra which recorded on Perkin-Elmer spectrum RXI FTIR Spectrometer (Range: 4000-450 cm^{-1}). ^{1}H NMRwas obtained on Bruker DRX-300 NMR spectrometer operating at 300 MHz Samples were prepared in $CDCl_3$ with TMS as an internal reference. Mass spectrawere obtained on Thermo Finnegan LCQ Advantage max ion trap mass spectrometer.

GENERAL PROCEDURE

Synthesis of Hepta-O-benzoyl-β-D-lactopyranosyl isocyanate (1)

To the suspension of hepta-*O*-benzoyl-α-D-lactopyranosyl bromide (0.015 M, 18 g) in sodium dried xylene (70 mL) was added lead cyanate (0.015 M, 4.62 g). The mixture was refluxed gently for 3 hr. with frequent shaking. The xylene filtrate was then treated with petroleum ether (60-80°C) with stirring a pale yellow solid obtained. This solid was expected hepta-*O*-benzoyl-β-D-lactopyranosyl isocyanate **(1)**. It was purified by dissolving it in minimum quantity of

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chloroform and precipitated with petroleum ether. (Scheme 1)

Synthesis of 1-hepta-*O*-benzoyl-β-D-lactopyranosyl-3-phenyl carbamide (3a)

Amixture of hepta-*O*-benzoyl-β-D-lactopyranosyl isocyanate (0.001 M, 1.1g) and aniline (0.001 M, 0.09 mL) in benzene solvent (25 mL) was allowed to reflux for 3 hr. on heating mental. After completion of reaction, benzene was distilled off and the product was isolated from the resultant sticky residue, on repeated trituration with petroleum ether, to afford a solid. It was crystallized from ethanol-water.

This reaction of Hepta-*O*-benzoyl-β-D-lactopyranosyl isocyanate was also extended to several other aryl amines and the corresponding 1-Hepta-*O*-benzoyl-β-D-lactopyranosyl-3-aryl carbamides **(3b-g)** have been isolated. **(Scheme 2)**

Spectral Data

1]IR (KBr, cm^{-1}): υ, 3010 (Ar C-H), 2970 (Ali C-H), 2105 (N=C=O), 1730 (C=O), 1453(C-N), 1100 (C-O), 1025& 906 (Characteristic of lactose);

^{1}H NMR (CDCl$_3$, ppm): δ 7.35-6.68 (m, 35H, Ar-H), 5.69-3.45 (m, 14H, lactosyl protons); **Mass (m/z):** 1095(M$^+$), 1053, 932, 579, 135. (Anal. Calcd. for $C_{62}H_{49}O_{18}N$, Require: C, 67.94; H, 4.47; N, 1.27, Found: C, 67.83; H, 4.38; N, 1.23%.)

3a]IR (KBr, cm^{-1}): υ, 3452 (-NH), 3011 (Ar C-H), 2967 (Ali C-H), 1729 (C=O), 1269(C-N), 1174 (C-O), 1026 & 903(Characteristic of lactose), 708 (Mono substituted benzene);

^{1}H NMR (CDCl$_3$, ppm): δ 7.61-6.80 (m, 40H, Ar-H), 5.73 (s, 1H, NH), 5.49 (s, 1H, NH), 5.31-3.71 (m, 14H, lactosyl protons);

Mass (m/z):1188(M$^+$), 1145, 976, 932, 579, 135. (Anal. Calcd. for $C_{68}H_{56}O_{18}N_2$, Requires: C, 68.68; H, 4.71; N, 2.35, Found: C, 68.52; H, 4.69; N, 2.31%.)

3d]IR (KBr, cm^{-1}): υ, 3423 (-NH), 3016 (Ar C-H), 2962 (Ali C-H), 1729 (C=O), 1270 (C-N), 1170 (C-O), 1028 & 908(Characteristic of lactose), 808 (disubstituted benzene);

^{1}H NMR (CDCl$_3$, ppm): δ 7.62-6.12 (m, 39H, Ar-H), 5.74 (s, 1H, NH), 5.63 (s, 1H, NH), 5.61-4.55 (m, 14H, lactosyl protons), 1.14 (s, 3H, CH_3);

Mass (m/z):1202(M$^+$), 1159, 976, 932, 579, 135. (Anal. Calcd. for $C_{69}H_{58}O_{18}N_2$, Requires: C, 68.88; H, 4.82; N, 2.32, Found: C, 68.71; H, 4.65; N, 2.26%.)

3g]IR (KBr, cm^{-1}): υ, 3387 (-NH), 3015 (Ar C-H), 2966 (Ali C-H), 1729 (C=O), 1269 (C-N), 1170 (C-O), 1025& 910(Characteristic of lactose), 806 (disubstituted benzene);

^{1}H NMR (CDCl$_3$, ppm): δ 7.35-6.68 (m, 39H, Ar-H), 5.74 (s, 1H, NH), 5.69 (s, 1H, NH), 5.31-3.71 (m, 14H, lactosyl protons);

Mass (m/z):1222(M$^+$), 1179, 976, 948, 579, 135. (Anal. Calcd. for $C_{68}H_{55}O_{18}N_2Cl$, Requires: C, 66.74; H, 4.49; N, 2.29, Found: C, 66.62; H, 4.40; N, 2.23%.)

Antimicrobial Studies

All the compounds have been screened for both antibacterial and antifungal activities using cup plate agar diffusion method [12-14] by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1 mg/ml using dimethyl sulphoxide as solvent. Amikacin (100µg/ml) was used as a standard for antibacterial and antifungal activity and Fluconazole (100µg/ml) as a standard for antifungal activity. The compounds were screened for antibacterial activity against *Escherichiacoli*, *Staphylococcusaureus*, *Proteusvulgaris*, *Salmonellatyphi*, *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. 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 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.

RESULTS AND DISCUSSIONS

Herein, we report the synthesis of various 1-Hepta-*O*-benzoyl-β-D-lactopyranosyl-3-aryl carbamides **(3a-g)** by inteaction of Hepta-*O*-benzoyl-β-D-lactopyranosyl isocyanate (**1**) and

variousarylamines **(2)**. All products were crystallized from ethanol before recording the physical data (Table 1). The purity of compound was checked by TLC. The spectral analysis [15-17] IR, ^{1}HNMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded.

Antibacterial studies of these compounds indicated that compounds 3c and 3d were found to be active against *E.coli* and rest of were found to be moderately active. Compounds3d, 3e and 3fexhibited most significant activity against *S.aureus.*Compounds 3a and 3cwere foundactive against *P.vulgaris.*Compound3d was active towards *S. typhi*. All the other compounds exhibited low to moderate activity. The results of antifungal activities are also tabulated in Table2. Compounds 3a,3b and 3d were most effectively active against *C. albicance*3c, 3dand3f actively inhibited *A. niger*. While other compounds inhibited moderate activity.

CONCLUSION

The synthesized *N*-lactopyranosyl carbamides showed significant antimicrobial activities and lead for the development of new drugs due to the nature of presence of oxygen and nitrogen present in it. The method adopted in this investigation is simple efficient inexpensive and is useful in synthesizing pharmacologically important molecules.

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Table 1
Physical characterization of 1-Hepta-*O*-benzoyl-β-D-lactopyranosyl-3-aryl carbamides (3a-g)

Sr. No.	*Product (3a-g)*	*Yield (%)*	*m. p. (°C)*	*$[\alpha]_D^{31}$ (c, $CHCl_3$)*	*Elemental Analysis Found (Required) N*	*R_f (3:2, $CHCl_3$:EtOAc)*
1	3a	88.58	116-118	-30.23° (0.99)	2.31 (2.35)	0.81
2	3b	63.58	151-153	-42.05 ° (0.91)	2.27 (2.32)	0.82
3	3c	53.64	130-132	-36.20° (0.92)	2.28 (2.32)	0.87
4	3d	83.20	146-148	-49.12° (0.98)	2.26 (2.32)	0.85
5	3e	78.12	125-127	-60.38° (0.96)	2.21 (2.29)	0.79
6	3f	81.52	140-142	-90.60° (0.98)	2.25 (2.29)	0.73
7	3g	72.14	137-139	-20.43° (0.95)	2.23 (2.29)	0.75

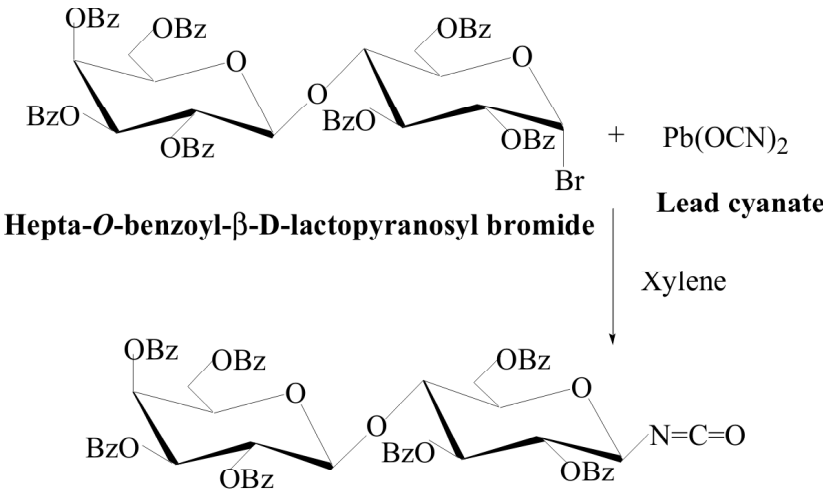
Satisfactory C and H analysis were found in all cases.

Table 2
Results of antimicrobial activity tests of the synthesized compounds (3a-g)

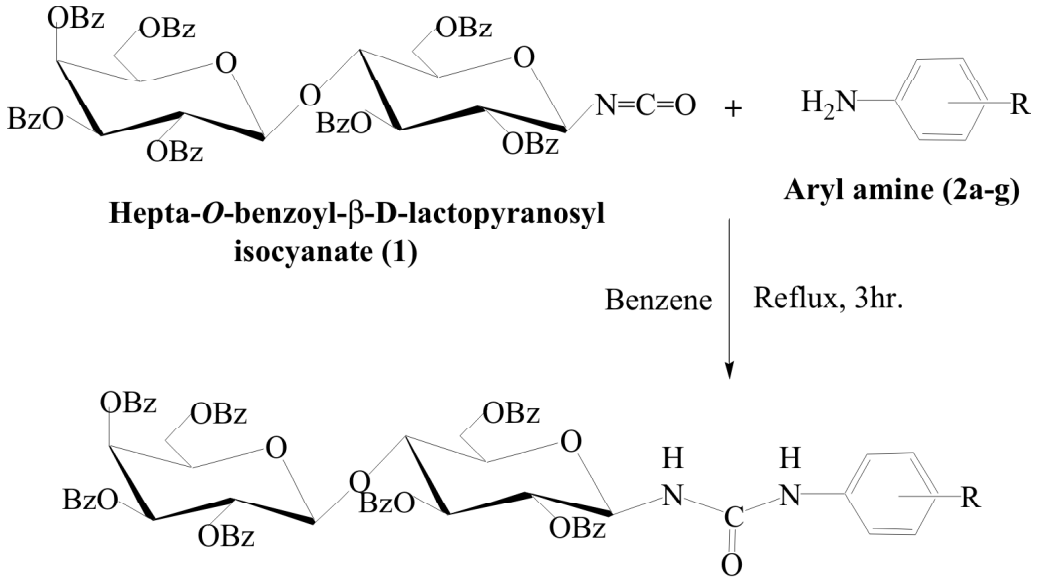
Compd.	*Antibacterial***							*Antifungal***	
	E. Coli	*S. aureus*	*P. vulgaris*	*S. typhi*	*K. Pneumoniae*	*P. aeruginosa*	*B. Subtilis*	*C. albicance*	*A. niger*
3a	17	15	22	16	-	15	-	21	17
3b	19	-	19	15	15	20	17	22	18
3c	21	15	20	19	16	18	18	19	21
3d	20	22	19	21	20	21	22	23	22
3e	-	20	15	18	19	15	-	17	20
3f	17	21	17	15	18	-	15	16	22
3g	11	15	18	13	13	19	17	19	17
Amikacin	25	27	25	26	25	26	24	-	-
Fluconazole	-	-	-	-	-	-	-	28	26

** zone of inhibition in mm (15 or less) resistance, (16-20 mm) moderate and (more than 20mm) sensitive. *Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), Proteus vulgaris (P. vulgaris), Salmonella typhi (S. typhi), Klebsialla Pneumoniae (K. Pneumoniae), Pseudomonas auriginosa (P. auriginosa), Bacillus subtilis (B. subtlis), Candida albicancs (C.albicancs) and Aspergillus niger (A. niger).*

Scheme for synthesis shown as follows



Scheme 1



Scheme 2

Where, OBz = $OCOC_6H_5$

R = a) -H, b) *o*-CH_3, c) *m*-CH_3, d) *p*-CH_3, e) *o*-Cl, f) *m*-Cl, g) *p*-Cl.

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