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Synthesis of 1-tetra-*o*-acetyl-β-D-galactopyranosyl-3-aryl carbamides as microbial growth inhibitors

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ABSTRACT

Several 1-Tetra-O-acetyl-β-D-galactopyranosyl-3-aryl carbamides have been synthesized by the condensation of per-acetylated isocyanates of galactose with several amines. The identities of these newly synthesised N-galactosyl carbamides have been established on the basis of usual chemical transformations and IR, ^1H 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*-galactosyl isocyanate, aryl amines, *N*-galactosyl carbamides, antimicrobial screening.

INTRODUCTION

Some per-acetylated of sugars are important class of organic compounds in field of carbohydrate chemistry. Isocyanates of sugars are the versatile reagents in the field of synthetic carbohydrate chemistry. Glycosyl carbamides have great pharmacological aspects [1]. Many of these derivatives have been found to possess wide applications in industry as carbohydrate base detergent [2] and in medicine as anticancer [3] and antifungal agents [4,5].

The *N*-galactosylated [6,7] compounds also have been known for their great biological importance. They have been found use as diuretic agents, analgesics, antidiabetic compounds, bacteriostatic agents and some remarkable significant activities [8].

Hence, in present work, different aryl amines focused to fuse with *N*-galactosylated compound.

MATERIALS AND METHODS

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^oC 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}). ^1H NMR was obtained on Bruker DRX-300 NMR spectrometer operating at 300 MHz Samples were prepared in $CDCl_3$ with TMS as an internal reference. Mass spectra were obtained on Thermo Finnegan LCQ Advantage max ion trap mass spectrometer.

General Procedure

Synthesis of Tetra-*O*-acetyl-β-D-galactosyl isocyanate (I)

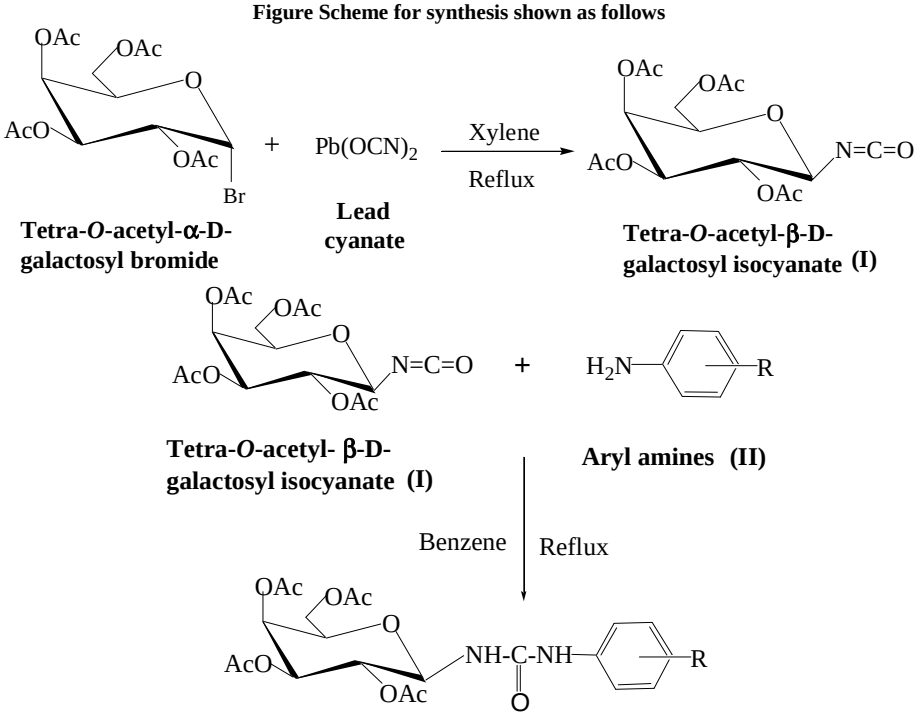
To the suspension of Tetra-*O*-acetyl-α-D-galactosyl bromide (0.039 M, 16 g) in sodium dried xylene (70 mL) was added lead cyanate (0.039 M, 11.3 g). The mixture was refluxed gently for 3 hr. with frequent shaking. The xylene filtrate was then treated with petroleum ether (60-80^{o}C) with stirring, a solid was obtained. This solid was expected Tetra-*O*-acetyl-β-D-galactosyl isocyanate **(I)**. It was purified by dissolving it in minimum quantity of chloroform and reprecipitating with petroleum ether. **(Scheme-1)**

Synthesis of 1-Tetra-*O*-acetyl-β-D-galactosyl-3-phenyl carbamide (3a)

To a benzene solution of Tetra-*O*-acetyl-β-D-galactosyl isocyanate (0.005 M, 1.86 g) in benzene (15 mL) was added aniline (0.005 M, 0.46 g) in benzene (5 mL) and the mixture was refluxed for 3 hr. on boiling water bath. Then, benzene was distilled off and the resultant sticky residue was triturated with petroleum ether (60-80^{o}C) to afford a solid. It was crystallized from ethanol-water.

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

Figure Scheme for synthesis shown as follows



Tetra-*O*-acetyl-α-D-galactosyl bromide — **Lead cyanate** — **Tetra-*O*-acetyl-β-D-galactosyl isocyanate (I)**

Tetra-*O*-acetyl- β-D-galactosyl isocyanate (I) + **Aryl amines (II)**

Benzene, Reflux

1-Tetra-*O*-acetyl-β-D-galactosyl-3-aryl carbamides (IIIa-g)

Scheme 2

Where, OAc = $OCOCH_3$

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

Spectral Data

3a] IR (KBr, cm^{-1}) : υ, 3479 (-NH), 3010 (Ar C-H), 2969 (Ali C-H), 1752 (C=O), 1430 (C-N), 1175 (C-O), 1011 & 894 cm^{-1} (Characteristic of galactose);

^{1}H NMR ($CDCl_3$, ppm): δ 7.26-7.12 (m, 5H, Ar-H), 6.36 (s, 1H, NH), 5.34 (s, 1H, NH), 5.81-4.06 (m, 7H, galactosyl protons), 2.26-1.61 (m, 12H, acetyl protons);

Mass (m/z): 466 (M^{+}), 387, 331, 169, 109. (Anal. Calcd. for $C_{21}H_{26}O_{10}N_2$, Requires: C, 54.40; H, 5.57; N, 6.00; Found C, 54.26; H, 5.42; N, 5.83%.)

3d] IR (KBr, cm^{-1}) : υ, 3361 (-NH), 3016 (Ar C-H), 2973 (Ali C-H), 1751 (C=O), 1431 (C-N), 1237 (C-O), 1053 & 908 cm^{-1} (Characteristic of galactose);

^{1}H NMR ($CDCl_3$, ppm): δ 7.18-6.95 (m, 4H, Ar-H), 6.38 (s, 1H, NH), 5.63 (s, 1H, NH), 5.81-4.0 (m, 7H, galactosyl protons), 2.34-2.00 (m, 12H, acetyl protons), 1.19 (s, 3H, CH_3);

Mass (m/z): 480 (M^+), 331, 211, 169, 109. (Anal. Calcd. for $C_{22}H_{28}O_{10}N_2$, Requires: C, 55.00; H, 5.83; N, 5.83, Found: C, 54.82; H, 5.74; N, 5.72%)

3e] IR (KBr, cm^{-1}) : υ, 3461 (-NH), 3011 (Ar C-H), 2960 (Ali C-H), 1751 (C=O), 1430 (C-N), 1238 (C-O), 1053 & 909 cm^{-1} (Characteristic of galactose);

^{1}H NMR ($CDCl_3$, ppm): δ 7.16-7.06 (m, 4H, Ar-H), 6.34 (s, 1H, NH), 5.69 (s, 1H, NH), 5.79-3.89 (m, 7H, galactosyl protons), 2.35-2.01 (m, 12H, acetyl protons);

Mass (m/z): 500 (M^+), 331, 211, 169, 109. (Anal. Calcd. for $C_{21}H_{25}O_{10}N_2Cl$, Requires: C, 50.04; H, 5.00; N, 5.60, Found: C, 49.82; H, 4.70; N, 5.53%.)

Antimicrobial Screening

All the compounds have been screened for both antibacterial and antifungal activities using cup plate agar diffusion method [9-11] 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 *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. 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 DISCUSSION

Herein, we report the synthesis of various 1-Tetra-*O*-acetyl-β-D-galactosyl-3-aryl carbamides **(3a-g)** by inteaction of Tetra-*O*-acetyl-β-D-galactosyl isocyanate (**1**) and various aryl amines **(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 [12-14] IR, ^{1}H NMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded.

Table 1: Physical characterization of 1-Tetra-*O*-acetyl-β-D-galactosyl-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	63.78	92-94	+ 133.9° (0.37)	5.83 (6.00)	0.78
2	3b	70.65	131-133	+ 117.6 ° (0.34)	5.74 (5.83)	0.70
3	3c	62.20	102-104	+ 91.8° (0.32)	5.79 (5.83)	0.80
4	3d	65.80	127-129	+ 155.0° (0.35)	5.72 (5.83)	0.82
5	3e	53.40	130-132	+ 205.8° (0.34)	5.52 (5.60)	0.85
6	3f	62.56	138-140	+ 242.4° (0.33)	5.51 (5.60)	0.72
7	3g	64.27	123-125	+ 187.5° (0.35)	5.53 (5.60)	0.74

Satisfactory C and H analysis were found in all cases.

Antibacterial studies of these compounds indicated that compounds 3a and 3f were found to be active against *E.coli* and rest of were found to be moderately active. Compound 3a exihibited most significant activity against *S.aureus.* Compounds 3a, 3b and 3d active towards *S. typhi.* All the other compounds exihibited low to moderate activity. The results of antifungal activities are also tabulated in Table 2. Compounds 3a, 3e, 3f and 3g are most effectively active against *C. albicance*, 3b, 3c, 3e and 3g actively inhibited *A. niger*. While other compounds inhibited moderate activity.

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. albicancs*	*A. niger*
3a	20	24	19	23	18	20	18	21	20
3b	17	16	15	22	17	19	16	19	22
3c	15	16	-	12	12	14	-	14	24
3d	19	12	16	21	20	19	21	20	19
3e	18	14	15	16	-	14	17	23	22
3f	21	16	16	17	15	16	22	19	20
3g	18	19	15	18	18	12	-	22	23
Amikacin	25	27	25	26	-	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).*

CONCLUSION

The synthesized *N*-galactosyl 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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