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Synthesis of *N*-Acetylglucosamine Aryl β-Glycosides Catalyzed by Crown Compounds

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Abstract—Glycosylation of various phenols with α-*D*-glucosaminyl chloride peracetate in a solid phase–liquid system catalyzed by crown compounds was studied. The highest yields of aryl β-glycosides were observed at room temperature in acetonitrile using anhydrous potassium carbonate as a base. The optimum phenol–glycosyl donor–base–crown ether ratio was 1 : 1 : 1 : 0.2.

Key words: glycosylation, aryl glycosides, N-acetylglucosamine glycosides, crown ether

INTRODUCTION

Carbohydrate aryl glycosides, including those of *N*-acetylglucosamine, have been extensively investigated as substrates in the studies on enzyme specificity (e.g. [1]), potential anti-infectious preparations [2, 3], and spacers [4].[2] MDP phenyl β-glycoside has displayed a high protective activity against *Salmonella typhi* [5]. At present, the phase-transfer catalysis with quaternary ammonium salts as catalysts [7, 8] is widely used for obtaining *N*-acetylglucosamine aryl glycosides along with such classic methods as oxazoline synthesis [6] and interaction of phenolates or phenols with 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-*D*-glucosaminyl chloride (**I**) in the presence of various bases in polar aprotic solvents [2, 9, 10].

RESULTS AND DISCUSSION

When attempting to simplify the scheme for obtaining MDP aryl glycosides, we established the synthesis of phenolic glycosides of *N*-acetylglucosamine in the solid phase–liquid system catalyzed by crown ethers to be rather convenient. Glycosylation of phenols with an equimolar amount of chloride (**I**) was performed in acetonitrile at room temperature in the presence of an equimolar amount of finely powdered anhydrous potassium carbonate and 20 mol % of 15-crown-5 ether. The method suggested does not need excess phenolic compound, is methodically facile, and requires mild, nondestructive conditions.

The reaction time did not usually exceed 24 h. Unsubstituted phenol, β-naphthol, and their derivatives were subjected to glycosylation. The glycosylation products were isolated by crystallization. The yields of glycosides (**IIa**)–(**IIq**) were 43–86%. In all cases only β-glycosides of *N*-acetylglucosamine formed as was demonstrated by the presence in their ^{1}H NMR spectra of the doublets of anomeric protons with the chemical shift in a range of 5.15–5.47 ppm and a coupling constant of 8–9 Hz (Table 1). The chemical shifts and the splitting of the proton signals of phenolic aglycons correlated with their structures. The signals of the backbone protons of the carbohydrate residues in all the products are characterized by similar values of chemical shifts and coupling constants.

A decrease in the proportion of 15-crown-5 to 1 mol % diminished the reaction rate and, consequently, the yield of the target glycosides. The enhancement of the amount of the catalyst, base, or phenol had practically no influence on the results of the synthesis. The substitution of dibenzo-18-crown-6 for 15-crown-5 also had no effect on the reaction time and the glycoside yield.

The best results for the glycosylation of phenol with chloride (**I**) were observed with acetonitrile as a solvent and potassium carbonate as a base (Table 2). The rise of the temperature of the reaction mixture up to 50–52°C resulted in a drop of the reaction time but simultaneously diminished the yield of glycoside (**IIa**). At a higher temperature, the products of the chloride (**I**) destruction prevailed along with a small amount of oxazoline (**III**).

As a rule, the glycosylation of phenols harboring electron acceptor substituents proceeded more slowly than the formation of aryl glycosides from phenols with electron donor groups, but with higher yields (Table 3).

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[2] Abbreviations: MDP, muramyl dipeptide, *N*-acetylmuramyl-*L*-alanyl-*D*-isoglutamine.

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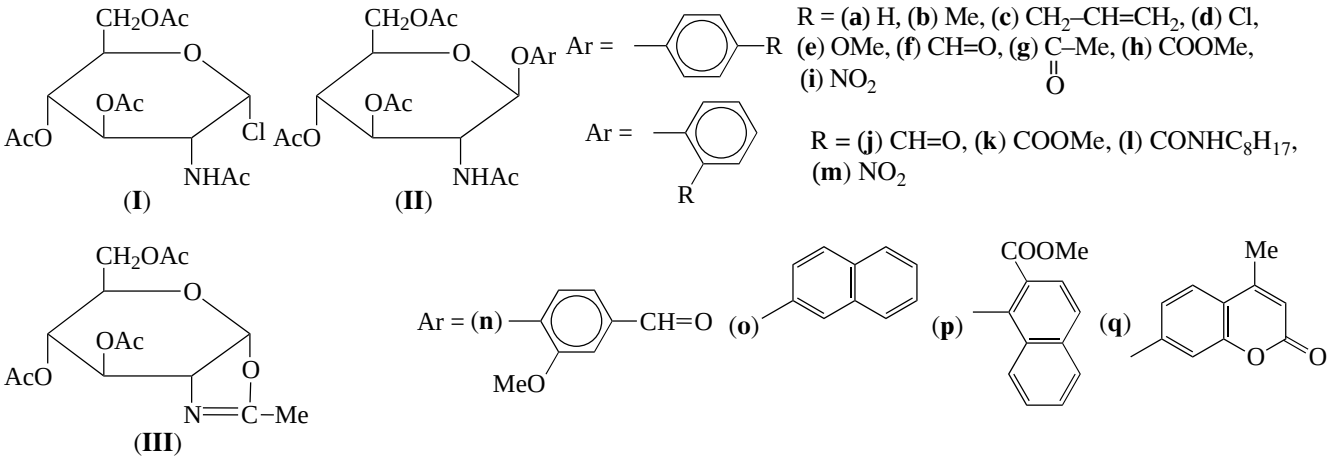
Table 1. ^{1}H NMR spectra of β-glycosides (**IIa**)–(**IIq**)*

Proton	Chemical shifts, ppm (*J*, Hz)								
	(**IIa**)	(**IIb**)	(**IIc**)	(**IId**)	(**IIe**)	(**IIf**)	(**IIg**)	(**IIh**)	(**IIi**)
H1 ($J_{1,2}$)	5.28 d (8)	5.20 d (8)	5.18 d (8)	5.27 d (8)	5.15 d (9)	5.46 d (8)	5.44 d (8)	5.40 d (8)	5.47 d (8)
H2	4.14 ddd	4.12 ddd	4.25 ddd	4.09 ddd	4.09 ddd	4.14 ddd	4.15 ddd	4.14 ddd	4.12 ddd
($J_{2,3}$)	(10)	(11)	(10.5)	(10.5)	(10)	(10)	(10)	(10)	(10)
H3	5.42 dd	5.40 dd	5.37 dd	5.43 dd	5.40 dd	5.47 dd	5.45 dd	5.42 dd	5.46 dd
($J_{3,4}$)	(9.5)	(9.5)	(9.5)	(9.5)	(10)	(9)	(9)	(9.5)	(9.5)
H4	5.15 dd	5.14 dd	5.15 dd	5.13 dd	5.14 dd	5.15 dd	5.15 dd	5.14 dd	5.15 dd
($J_{4,5}$)	(9.5)	(9.5)	(9.5)	(9.5)	(10)	(9)	(9)	(9.5)	(9.5)
H5	3.88 ddd	3.85 ddd	3.87 ddd	3.88 ddd	3.81 ddd	3.96 ddd	3.94 ddd	3.95 ddd	3.95 ddd
($J_{5,6a}$; $J_{5,6b}$)	(2.5; 5.0)	(2.5; 5.0)	(2.5; 5.5)	(2.5; 5.5)	(2.5; 5.5)	(2.5; 5.5)	(2.5; 5.5)	(2.5; 5.5)	(2.5; 5)
H6a, b	4.16 dd, 4.29 dd	4.15 dd, 4.28 dd	4.18 dd, 4.28 dd	4.15 dd, 4.29 dd	4.15 dd, 4.30 dd	4.17 dd, 4.30 dd	4.17 dd, 4.29 dd	4.16 dd, 4.28 dd	4.17 dd, 4.29 dd
($J_{6a,6b}$)	(12)	(12)	(12)	(12.5)	(12)	(12)	(12)	(12)	(12.5)
NAc, OAc	1.95 s, 2.05 s, 2.06 s, 2.08 s	1.95 s, 2.04 s, 2.06 s, 2.08 s	1.94 s, 2.05 s, 2.06 s, 2.08 s	1.95 s, 2.05 s, 2.06 s, 2.07 s	1.97 s, 2.04 s, 2.06 s, 2.08 s	1.95 s, 2.07 s, 2.08 s (6H)	1.95 s, 2.07 s, 2.08 s (6H)	1.94 s, 2.06 s, 2.08 s (6H)	1.97 s, 2.07 s, 2.09 s (6H)
NH	5.75 d	5.75 d	5.69 d	5.87 d	5.79 d	5.82 d	5.88 d	5.81 d	5.70 d
($J_{2,NH}$)	(9)	(8)	(9)	(8.5)	(9)	(9)	(9)	(8.5)	(8.5)
CH_{arom}	7.01 m, 7.28 m	6.89 d, 7.07 d	7.02 d, 7.14 d	6.93 d, 7.24 d	6.81 d, 6.23 d	7.10 d, 7.83 d	7.03 d, 7.91 d	7.01 d, 7.97 d	7.10 d, 8.19 d
R		2.29 s	3.34 dd, 3.36 dd, 4.98 dd, 5.02 dd, 5.93 m		3.77 s	9.91 s	2.53 s	3.89 s	

Proton	Chemical shifts, ppm (*J*, Hz)							
	(**IIj**)	(**IIk**)	(**III**)	(**IIm**)	(**IIn**)	(**IIo**)	(**IIp**)	(**IIq**)
H1 ($J_{1,2}$)	5.37 d (8.5)	5.20 d (8.5)	5.24 d (8.5)	5.53 d (8)	5.41 d (8)	5.40 d (8)	5.32 d (8.5)	5.41 d (8)
H2	4.24 ddd	4.18 ddd	4.44 ddd	3.93 ddd	4.07 ddd	4.20 ddd	4.59 ddd	4.19 m
($J_{2,3}$)	(10)	(10)	(10.5)	(10)	(10.5)	(10)	(10)	(10)
H3	5.43 dd	5.39 dd	5.31 dd	5.61 dd	5.51 dd	5.45 dd	5.23 dd	5.45 dd
($J_{3,4}$)	(9.5)	(9.5)	(9.5)	(9.5)	(9.5)	(9)	(9.5)	(9.5)
H4	5.17 dd	5.17 dd	5.17 dd	5.14 dd	5.14 dd	5.16 dd	5.20 dd	5.15 dd
($J_{4,5}$)	(9.5)	(9.5)	(9.5)	(9.5)	(9.5)	(9)	(9.5)	(9.5)
H5	3.92 ddd	3.76 ddd	3.88 ddd	3.91 ddd	3.87 ddd	3.94 ddd	3.49 ddd	3.97 ddd
($J_{5,6a}$; $J_{5,6b}$)	(2; 5)	(2.5; 5)	(2; 5.5)	(2; 5)	(2.5; 5.5)	(2.5; 5.5)	(2; 5)	(2.5; 5.5)
H6a, b	4.18 dd, 4.30 dd	4.14 dd, 4.28 dd	4.13 dd, 4.31 dd	4.21 dd, 4.29 dd	4.16 dd, 4.28 dd	4.19 dd, 4.30 dd	3.76 dd, 4.14 dd	4.19 m, 4.29 dd
($J_{6a,6b}$)	(12.5)	(12)	(12.5)	(12.5)	(12)	(12)	(12.5)	(12.5)
NAc, OAc	1.95 s, 2.06 s, 2.08 s (6H)	1.97 s, 2.04 s, 2.06 s, 2.07 s	1.92 s, 2.05 s, 2.06 s, 2.07 s	1.98 s, 2.05 s, 2.07 s, 2.09 s	1.97 s, 2.05 s, 2.07 s (6H)	1.95 s, 2.06 s, 2.08 s (6H)	1.74 s, 2.00 s, 2.05 s, 2.09 s	1.97 s, 2.07 s, 2.09 s, 2.10 s
NH	5.98 d	6.42 d	6.30 d	5.94 d	5.81 d	5.82 d	7.06 d	6.06 d
($J_{2,NH}$)	(7.5)	(7.5)	(9)	(7.5)	(8)	(8.5)	(8)	(8.5)
CH_{arom}	7.13–7.84 m	7.15–7.80 m	6.99–8.07 m	7.17–7.80 m	7.21–7.43 m	7.18 m, 7.41 m, 7.77 m	7.51–8.43 m	6.15 s, 6.94 m, 7.48 m
R	10.37 s	3.88 s	0.87 t, 1.28 m, 1.61 m, 3.30 ddt, 3.55 ddt, 7.43 t		3.90 s 9.89 s		3.96 s	2.40 s

* Working frequency is 200 MHz in the case of glycosides (**IId**) and (**IIj**) and 300 MHz in the case of other derivatives.



A paradoxical situation was observed at the glycosylation of vanillin containing substituents of both types. In this case, the reaction time was the shortest (4.5 h) and the yield the highest (86%).

EXPERIMENTAL

Melting points were determined on a PTP instrument (Russia). Optical rotation (λ 546) was measured on a Polamat-A polarimeter at 20–22°C. ^{1}H NMR spectra were registered on a Varian Gemini-200 instrument (200 MHz) or on a Varian VXR-300 spectrometer (300 MHz) using Me_4Si as the internal standard. Chemical shifts (δ, ppm) and coupling constants (*J*, Hz) are given. TLC were performed on precoated Silufol UV-254 plates (Kavalier). The spots were visualized by thermal carbonization or exposure to the iodine vapor.

Table 2. Glycosylation of phenol with chloride (**I**) in the presence of various bases

Reaction conditions		Reaction time, h*	Yield (**IIa**), %
base	solvent		
20–25°C			
K_2CO_3	MeCN	7	43
K_2CO_3	$C_2H_4Cl_2$	28	36
Na_2CO_3	MeCN	17.5	23
KOH	MeCN	9	22
NaOH	MeCN	8.5	24
PhOK	MeCN	4	25
PhONa	MeCN	11.5	21
50–52°C			
K_2CO_3	MeCN	0.67	30
"	$C_2H_4Cl_2$	2.5	31
"	C_6H_6	3	16

* Until chloride (**I**) disappeared (according to TLC).

The developing systems used were (A) 15 : 1 chloroform–ethanol and (B) 10 : 1 benzene–ethanol. The elemental analysis data for compounds synthesized matched the calculated values.

Dichloroethane was washed with concentrated sulfuric acid and sodium bicarbonate solution, dried, and distilled over P_2O_5. Acetonitrile was dried and distilled over P_2O_5. The crown compounds used contained no less than 98% of the main substance.

For studying the effect of temperature, solvent, and phenol or base nature on the glycosylation, the reactions were performed using 500 mg (1.37 mmol) of chloride (**I**). Glycosides were isolated on a Silica gel 70–230 mesh (Aldrich; 1.0 × 15 cm) column eluted with benzene ⟶ benzene–isopropanol (50 : 1).

General glycosylation procedure. To a solution of chloride (**I**) (1.0 g, 2.74 mmol) [11] in acetonitrile (25 ml) were added an equimolar amount of phenol, powdered anhydrous sodium bicarbonate (380 mg, 2.74 mmol), and 15-crown-5 (120 mg, 0.55 mmol), and the mixture was stirred at room temperature up until the glycosyl donor disappeared (TLC control in systems A and B). The precipitate was filtered off, and the filtrate was evaporated. The residue was dissolved in chloro-

Table 3. Glycosylation of substituted phenols with chloride (**I**) at room temperature in acetonitrile in the presence of potassium carbonate

Phenol	Reaction time, h*	Yield, %
p-Chlorophenol	7.5	48
p-Methoxyphenol	9	37
p-Cresol	11.5	41
p-Hydroxybenzaldehyde	15.5	84
Methyl *p*-hydroxybenzoate	17.5	61
Vanillin	4.5	86

* Until chloride (**I**) disappeared (according to TLC).

Table 4. Characteristics of aryl 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-*D*-glucopyranosides (**IIa**)–(**IIq**)*

Aryl glycoside (**II**)	Aglycon	Yield, %	Mp, °C	$[\alpha]_{546}$ (*c* 1.0, chloroform), degree**	Ref.
a	Phenyl	45	205–206	–13	–
		73	203–204	–14.5	[6]
b	*p*-Tolyl	43	192–194	–16	–
		84	197.4–197.8	–10.9	[10]
c	*p*-Allylphenyl	45	190–191	–19	–
d	*p*-Chlorophenyl	47	211–212	–12	–
		66	212.6–213.5	–9.6	[10]
e	*p*-Methoxyphenyl	43	191–192	–12	–
		85	195.8–196.4	–11.9	[9]
f	*p*-Formylphenyl	86	225–227	–17	–
		67	226.8–227.6	–16.9	[10]
g	*p*-Acetophenyl	83	213	–25	–
		55	219–220	–14.6 (acetone)	[7]
h	*p*-Methoxycarbonylphenyl	59	204–207	–10	–
		–	–	–	–
i	*p*-Nitrophenyl	76	236–238	–49	–
		39	240	–46.2 (acetone)	[7]
		76–78	238–239		[8]
j	*o*-Formylphenyl	64	192–193	–37	–
		40	193–194	–	[2]
k	*o*-Methoxycarbonylphenyl	55	199–200	–17	–
		31.5	202–203	–	[2]
l	*o*-(*N*-octylcarbamoyl)phenyl	48	81–82	–48	–
		–	–	–	–
m	*o*-Nitrophenyl	61	194–196	+67	–
		42	196–197	+3.4 (acetone)	[7]
n	(2-Methoxy-4-formyl)phenyl	84	201–203	–4	–
		–	–	–	–
o	(Naphthyl-2)	44	217–218	–8	–
		70	220.1–220.5	–65.8	[9]
p	(2-Methoxycarbonylnaphthyl-1)	45	185–187	–10	–
		–	–	–	–
q	(4-Metylumbelliferyl)	63	247–248	–27	–
		32	253–254	–18.7	[12]

* The data of the present study and from literature are given in the upper and lower lines, respectively.

** The literature data (solutions in chloroform, unless otherwise specified).

form (50 ml) and washed with 1 N KOH (20 ml) and water (2 × 20 ml). The organic layer was separated, dried with anhydrous Na_2SO_4, and evaporated. The characteristics of aryl 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-*D*-glucopyranosides (**II**) synthesized are given in Table 4.

REFERENCES

1. Del Rio, L.A. and Berkeley, R.C.W., *Anal. Biochem.*, 1975, vol. 66, pp. 405–411.

2. Burker, S.A., Plevey, R.G., Simmonds, R.G., and Stacey, M., *Tetrahedron*, 1966, no. 8, pp. 611–619.

3. Arita, H., Sugita, K., Nomura, A., Sato, K., and Kawanami, J., *Carbohydr. Res.*, 1978, vol. 62, pp. 143–154.
4. Lefrancier, P., Derrien, M., Lederman, I., Nief, F., Choay, J., and Lederer, E., *Int. J. Peptide Protein Res.*, 1978, vol. 11, pp. 289–296.
5. Zemlyakov, A.E., Tsikalov, V.V., Kur'yanov, V.O., and Chirva, V.Ya., *Bioorg. Khim.*, 2001, vol. 27, pp. 390–394.
6. Zurabyan, S.E., Antonenko, T.S., and Khorlin, A.Ya., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1969, no. 9, pp. 2043–2044.
7. Leaback, D.H. and Walker, P.G., *J. Chem. Soc.*, 1957, no. 12, pp. 4754–4760.
8. Zurabyan, S.E., Volosyuk, T.P., and Khorlin, A.Ya., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, no. 7, pp. 1612–1614.
9. Roy, R. and Tropper, F., *Synth. Commun.*, 1990, vol. 20, pp. 2097–2102.
10. Roy, R. and Tropper, F.D., *Can. J. Chem.*, 1991, vol. 69, pp. 817–821.
11. Horton, D., *Methods in Carbohydrate Chemistry. Vol. 6*, Whistler, R.L. and Bemiller, J.N., Eds., New York: Academic, 1972. Translated under the title *Metody issledovaniya uglevodov*, Moscow: Mir, 1975, pp. 221–224.
12. Dunstan, D. and Hough, L., *Carbohydr. Res.*, 1972, vol. 23, pp. 425–426.