Phase Transfer Catalysis as a General and Stereoselective Entry into Glycosyl Azides from Glycosyl Halides

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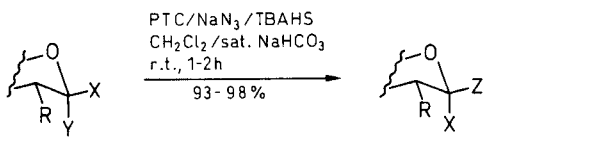
Peracetylated glycosyl- and glycobiosyl bromides and chlorides **1–5** including acetochloroneuraminic acid **6** were converted to their corresponding glycosyl azides **7–12** in 93–98% yields under phase transfer catalyzed conditions. The stereoselective reactions occurred with complete inversion at the anomeric centers to provide a general, high-yielding entry into 1,2-*trans*-glycosyl azides together with α-sialic acid azide.

Glycosyl azides have been recognized for some time as an important family of carbohydrate derivatives.[1,2] They have been widely used as precursors of glycopeptides[3] and heterocyclic *N*-glycosides.[4] The corresponding glycosyl amines, obtainable by reduction of the azide group or by direct aminolysis of reducing sugars, can be used as monomeric precursors of *N*-glycopolymers after suitable *N*-acryloylations.[5] Recent applications of the solid-phase peptide synthesis methodologies to glycopeptide preparations[6] have reactuated the interest in glycosyl azides.[7] This is particularly true in light of their uses as protected glycosyl acceptors.[8]

Previous syntheses of glycosyl azides from glycosyl halides were accomplished under homogeneous one-phase conditions with silver or sodium azides in chloroform or formamide, respectively.[1,2] More recently, trimethylsilyl azide in combination with a Lewis acid catalyst has also been conveniently used on glycosyl esters.[9]

Reports by Kunz et al.,[10] then by Thiem and Wiemann,[11] on the use of phase transfer catalysis (PTC) for the efficient synthesis of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl azide (**9**)[11] or its corresponding chitobiosyl analogue[10] with Aliquat 336[10] or tetrabutylammonium hydrogen sulfate (TBAHS)[11] in chloroform prompted us to apply our PTC conditions[12] to the synthesis of a wide range of glycosyl azides. Under the modified conditions reported here, the glycosyl azides **7–9** including disaccharides **10, 11**, and sialic acid **12** were prepared in excellent yields (93–98%, Table 1). Direct use of tetrabutylammonium azide in refluxing toluene has also been described for the preparation of **9** (70% yield).[13]



1-5 X = H, Y = Cl, Br, R = OAc, NHAc **7-11** X = H, Z = N_3, R = OAc, NHAc
6 X = Cl, Y = CO_2Me, R = H **12** X = N_3, Z = CO_2Me, R = H

Thus, treatment of 1,2-*cis*-peracetylated glycosyl- and glycobiosyl chlorides and bromides **1–5** and the β-acetochloroneuraminic acid derivative **6** with TBAHS (1 equivalent) and sodium azide (3–5 equivalent) in liquid two-phase system (CH_2Cl_2 saturated $NaHCO_3$) for 1–2 hours at room temperature afforded almost quantitative yields of their corresponding 1,2-*trans*-glycosyl azide derivatives **7–12** (Table 1). All the reactions occurred with complete anomeric inversions. No mixture of anomers or byproducts could be detected from the crude reaction mixtures by ^1H and ^{13}C NMR spectroscopy. Therefore, as previously observed,[12] the reactions were completely stereoselective. It is noteworthy to mention that the high yields obtained in the D-gluco- and D-galacto-series **1, 2** and **4, 5** in the nucleophilic substitutions with azide anions are in marked contrast to those previously observed when phenoxide anions were used as nucleophiles.[14] In those cases, competitive dehydrohalogenation accounted for almost 40% of the side products isolated. In the actual case, no elimination reactions occurred.

It is also worthy to mention that even in the case of the β-chloride **6**, the reaction proceeded stereoselectively and with inversion of configuration to provide the α-azide **12**.[15] No adverse solvent effects were noticed in all the

Table 1. PTC Synthesis of Glycosyl Azides from Glycosyl Halides

Sugar Derivatives	Yield (%)[a–c]	mp (°C) (solvent)	$[\alpha]_D^{23}$ ($c = 1$, $CHCl_3$)	Molecular Formula or Lit. mp (°C)[d]	Lit. $[\alpha]_D^{23}$[d]
glucose, **7**	93	138–139 (EtOH)	−31.0°	129 (dec)	−33.0°
galactose, **8**	96	103–104 (MeOH)	−14.0°	96	−16.2°
N-acglucosamine, **9**	98	166–167 (dec) (Et_2O/hexane)	−47.7°	160–161 (dec)	−43.0°
lactose, **10**	98	amorph.	−20.4°	$C_{26}H_{35}N_3O_{17}$ (661.6)	–
maltose, **11**	97	106–107 (EtOH)	+51.8°	91	+53°
sialic acid, **12**	>94[e]	84 ($CHCl_3$/hexane)	−26.5°	$C_{20}H_{28}N_4O_{12}$ (516.4)	–

[a] All compounds gave ≥ 81% crystalline yields, except **10** (amorphous).
[b] Combustion analyses: C, N ±0.3; H ±0.2.
[c] IR ($CHCl_3$): $\nu_{N\equiv C} = 2120 \pm 1\ cm^{-1}$.
[d] Reviewed in Ref. 2.
[e] The crude chloride **6** was used (> 95% pure).

above transformations[12] since using ethyl acetate gave identical results. Changing the aqueous phase from saturated $NaHCO_3$ to 2 M Na_2CO_3 had no adverse effect except, perhaps, for a slight increase in reaction rate.

Most of the above glycosyl azides were known compounds[2] and the physical data (mp, $[\alpha]_D$) are in good agreement with reported values. The fully assigned (HETCOR, COSY) ^1H and ^{13}C NMR spectroscopic data of **7–12**, confirms the anomeric configuration ($J_{1,2} \sim 8.7 \pm 0.2$ Hz; C-1, δ = 87.4–88.3) of all the compounds (Table 2 and 3). Although there is no anomeric proton, in the case of the α-sialic acid azide **12** the anomeric configuration was inferred on the basis of the characteristic downfield shift of H-3e signal of the α-anomer relative to that of the β-anomer which usually differ by ~0.5 ppm.[15] This is also confirmed by the typical chemical shifts[16] of H-4 and H-7 which appeared at δ = 5.03 and ~5.32, respectively ($CDCl_3$). There was no major effect for these two protons when the spectrum was taken in benzene-d_6 (δ = 4.98 and 5.48, respectively).

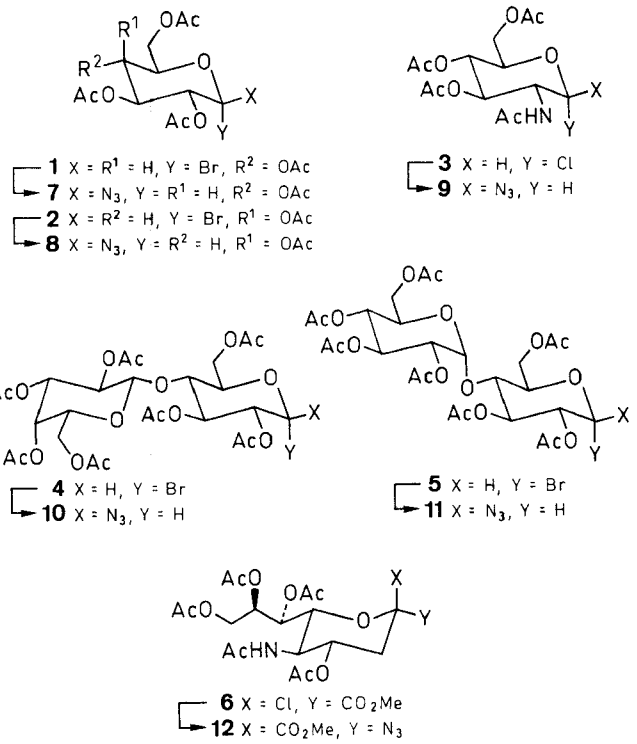


Table 2. ^1H NMR Data of Compounds **7–12** ($CDCl_3$, 300 MHz)[a], δ, J (Hz)

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{6,6'}$)	H-6′ ($J_{5,6'}$)	
7	4.65 (8.9)	4.96 (9.3)	5.22 (9.5)	5.11 (9.9)	3.79 (4.7)	4.28 (12.5)	4.17 (2.4)	
8	4.58 (8.5)	5.15 (10.4)	5.01 (3.3)	5.40 (1.1)	3.99 (5.9)	4.13–4.17 (ABX) (–, 7.1)		
9	4.75 (9.3)	3.89 (10.3)	5.23 (9.5)	5.07 (9.7)	3.77 (4.7)	4.25 (12.5)	4.13 (2.4)	5.79 (NH) (9.2)
10 Glc	4.61 (8.8)	4.85 (9.5)	5.19 (9.0)	3.79 (10.0)	3.68 (4.9)	4.49 (12.5)	4.02–4.14 (2.1)	
Gal	4.46 (7.9)	5.09 (10.4)	4.93 (3.4)	5.33 (1.1)	3.85 (7.2)	4.02–4.14 (–)		
11 Glc	4.69 (8.7)	4.77 (9.0)	5.24 (8.9)	4.00 (9.6)	3.76 (4.5)	4.49 (12.3)	4.02 (2.6)	
Glc′	5.39 (4.1)	4.84 (10.5)	5.33 (9.5)	5.03 (10.2)	3.92 (3.6)	4.19–4.26 (ABX) (–, 2.2)		
12[b,e]	–	–	1.70 (H-3a)[c] 2.55 (H-3e) ($J_{3a,3e}$ 13.0) ($J_{3a,4}$ 11.8) ($J_{3e,4}$ 4.9)	4.98 (10.4)	4.36 (10.6) (10.3, NH)	3.78 ($J_{6,7}$ 2.2)	5.48 (H-7)[d] ($J_{7,8}$ 6.4)	

[a] Assignments based on HETCOR and COSY experiments. Chemical shifts referenced to internal $CHCl_3$ at δ = 7.24; OAc: δ = 1.95–2.14.
[b] Benzene-d_6 solution, many overlapping signals in $CDCl_3$ (200 MHz).
[c] Approximate value, signals obscured by acetyl group.
[d] H-8, 5.72 ($J_{8,9a}$ 2.5, $J_{8,9b}$ 6.0); H-9a, 4.73 ($J_{9a,9b}$ 12.4); H-9b, 4.39; NH, 4.14, MeO, 3.33, Ac, 1.58–1.96.
[e] In $CDCl_3$: 5.34–5.30 (AB system, H-7, H-8); 5.16 (NH): 5.03 (H-4); 4.33 (H-9a); 4.11 (H-9b); 4.04 (H-5); 3.87 (H-6, OMe); 2.55 (H-3e); 1.81 (H-3a); 1.87–2.13 (5s, 15H, Ac). Coupling constants are the same as in benzene -d_6.

Table 3. ^{13}C NMR Data of Compounds **7–12** ($CDCl_3$, 75.4 MHz)[a], δ

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C=O	Ac(Me)
7	87.9	70.6	72.6	67.8	74.0	61.6	169.2–170.6 (4s)	20.5, 20.7 (3s)
8	88.2	68.0	70.7	66.8	72.8	61.2	169.3–170.3 (4s)	20.5, 20.6, 20.7 (2s)
9	88.3	53.9	72.0	68.1	73.8	61.8	169.5–170.3 (4s)	20.3, 20.4, 20.5, 23.0 (NHAc)
10 Glc	87.7	70.9	72.5	75.8	74.8	61.7	169.0–170.3 (7s)	20.5, 20.6 (3s), 20.7 (2s), 20.8
Gal	101.1	69.0	71.0	66.5	70.7	60.8		
11 Glc	87.4	71.5	75.1	72.3	74.2	62.5	169.4–170.5 (7s)	20.5, 20.6 (3s), 20.7 (2s), 20.8
Glc′	95.7	69.9	69.2	67.9	68.6	61.4		
12	166.8	88.6	36.1	[b]	48.3	[b]	169.5–170.3	20.3–20.6 (OAc), 22.6 (NAc)

[a] Assignments based on HETCOR and COSY experiments. Chemical shifts referenced to internal $CDCl_3$ at δ = 77.0.
[b] C-4, C-6, C-7, C-8: 67.0, 68.7, 69.1, 73.5 unassigned; C-9, 61.8; OMe, 53.0

In conclusion, a mild, completely stereoselective and high yielding entry into useful glycosyl azides has been achieved under PTC conditions. The procedure is compatible with acid- and base-labile protecting groups. Readily available reagents were used without the requirements of heavy metals, high boiling solvents or Lewis acids. The reaction occurred with complete inversion of configuration at the anomeric centers and is also effective with a tertiary center as exemplified with the sialic acid derivative **12**.

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter for 0.5–1.0% solutions in $CHCl_3$ at r.t. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 Spectrometer at 300 MHz in $CDCl_3$ with references at 7.24 ppm ($CHCl_3$) and at 77.0 ppm ($CDCl_3$), respectively. Assignments were based on COSY and HETCOR experiments. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ) or Guelph Chemical Laboratories Ltd. (Ont.). FT-IR spectra were recorded with a Bomen MB-100 spectrophotometer using solutions in $CHCl_3$. All the per-*O*-acetylated glycosyl bromides **1, 2, 4, 5** and chlorides **3, 6** were prepared by the standard HBr/AcOH (35% w/w) **(1, 2, 4, 5)** or AcCl **(3, 6)** procedures. The glycosyl halides were purified by silica gel column chromatography before use except for **6** (> 95% pure by ^1H NMR). TLC was performed on silica gel 60-F254 plates using hexane, EtOAc (1:1, v/v) containing 0.5% *i*-PrOH as eluant; detection was made under UV light and by charring with the $CeSO_4/(NH_4)_6Mo_7O_{24}/H_2SO_4$reagent. Column chromatography was performed on silica gel 60 (230–400 mesh, Merck No. 9385).

PTC Synthesis of Glycosyl Azides 7–12; General Procedure:
To a solution of the appropriate glycosyl halides **1–6** (1 equiv), TBAHS (1 equiv) and NaN_3 (3–5 equiv) in CH_2Cl_2 (1 mL/100 mg of the halides) was added sat. aq. $NaHCO_3$ (1 mL/100 mg of the halides). The two phase mixture was vigorously stirred at r.t. for 1–2 h, after which time TLC indicated complete transformation of the halides. When the halides and the azides have the same R_f, conversions are confirmed by ^1H and ^{13}C NMR spectroscopy of the crude reaction mixture. EtOAc (10 times the volume of CH_2Cl_2) was then added, the organic phase separated and successively washed with sat. $NaHCO_3$, H_2O (2×) and brine. The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure to afford pure glycosyl azides **7–12**. The dried azides **7–12** were homogeneous by TLC, ^1H and ^{13}C NMR spectroscopy. They were however crystallized (Table 1 for solvents) for combustion analyses, mp and $[\alpha]_D$ measurements. The yields of **7–12** varied from 93–98% (Table 1).

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(1) Bertho, N.; Nüssel, H. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 836.
(2) Micheel, F.; Klemer, A. *Adv. Carbohydr. Chem. Biochem.* **1961**, *16*, 85.
(3) Garg, H.G.; Jeanloz, R.W. *Adv. Carbohydr. Chem. Biochem.* **1985**, *43*, 135.
(4) Micheel, F.; Baum, G. *Chem. Ber.* **1957**, *90*, 1595.
(5) Kallin, E.; Lönn, H.; Norberg, T.; Elofsson, M. *J. Carbohydr. Chem.* **1989**, *8*, 597.
Roy, R.; Laferriere, C.A. *J. Chem. Soc., Chem. Commun.* **1990**, 1709.
(6) Kunz, H.; Dombo, B. *Angew. Chem.* **1988**, *100*, 732; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 711.
Paulsen, H.; Adermann, K.; Merz, G.; Schultz, M.; Weichert, U. *Staerke* **1988**, *40*, 465.
Hollósi, M.; Kollát, E.; Laczkó, I.; Medzihradszky, K.F.; Thurin, J.; Otvös, L.Jr. *Tetrahedron Lett.* **1991**, *32*, 1531.
(7) Anisfeld, S.T.; Lansbury, P.T.Jr. *J. Org. Chem.* **1990**, *55*, 5560.
(8) Kunz, H. *Angew. Chem.* **1987**, *99*, 297; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 294.
(9) Paulsen, H.; Györgydeak, Z.; Friedmann, M. *Chem. Ber.* **1974**, *107*, 1568.
Kunz, H.; Sager, W.; Schanzenbach, D.; Decker, M. *Liebigs Ann. Chem.* **1991**, 649.
(10) Kunz, H.; Waldmann, H.; März, J. *Liebigs Ann. Chem.* **1989**, 45.
(11) Thiem, J.; Wiemann, T. *Angew. Chem.* **1990**, *102*, 78; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 80.
(12) Roy, R.; Tropper, F.D. *Can. J. Chem.* **1991**, *69*, 817.
Tropper, F.D.; Andersson, F.O.; Grand-Maître, C.; Roy, R. *Synthesis* **1991**, 734.
Roy, R.; Tropper, F.D.; Grand-Maître, C. *Can. J. Chem.* **1991**, *69*, 1462.
(13) Augé, C.; Gautheron, C.; Pora, H. *Carbohydr. Res.* **1989**, *193*, 288.
(14) Roy, R.; Tropper, F.D.; Romanowska, A.; Letellier, M.; Cousineau, L.; Meunier, S.J.; Boratynski, J. *Glycoconjugate J.* **1991**, *8*, 75.
(15) Compound **12** is known but has never been fully characterized.
Friebolin, H.; Baumann, W.; Brossmer, R.; Keilich, G.; Supp, M.; Ziegler, D.; Nicolai von, H. *Biochem. Int.* **1981**, *3*, 321.
Kessler, J.; Hech, J.; Tanenbaum, S.W.; Flashner, M. *J. Biol. Chem.* **1982**, *257*, 5056.
(16) Paulsen, H.; Deessen, H. von *Carbohydr. Res.* **1986**, *146*, 147.