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Tetramethylguanidinium Azide as A New Reagent for the Stereoselective Synthesis of Glycosyl Azides

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Abstract Tetramethylguanidinium azide was used in the quantitative conversion of glycosyl halides **1 - 6** to the corresponding glycosyl azides **7 - 12**. The stereoselective reactions occurred with complete inversion at the anomeric centers.

Glycosyl azides are an important class of carbohydrate derivatives.[1] The corresponding glycosyl amines have been used as synthetic precursors of glycopeptides.[2] Recently, glycosyl amines have been used as chiral templates for the stereoselective syntheses of amino acids, amino nitriles, and aminophosphonic acid derivatives.[3]

The existing methods for the preparation of glycosyl azides can be divided into three categories. (1) Prepared from glycosyl halides, the most classical method calls for the use of metal azides (lithium, sodium, or silver azides) under homogeneous conditions.[1a,2c,4] This method generally affords moderate yields. High boiling solvents (eg. HMPA or DMF) and heating were sometimes required. (2) Prepared from glycosyl esters, this newer method utilizes trimethylsilyl azide and a Lewis acid catalyst (eg. BF_3, $SnCl_4$). The reported yields for compounds **7**, **9**, **10**, and **12** were 74-80%.[1b,4c,5] (3) Most recently, phase transfer reactions have been used for the efficient syntheses of a wide range of glycosyl azides. This two-phase system required a full equivalent of phase transfer reagent (tetrabutylammonium hydrogen sulfate or Aliquat 336) and 3-5 equivalents of sodium azide.[2d,2f,6]

We wish to report a convenient and high-yielding synthesis of glycosyl azides from glycosyl halides and 1,1,3,3-tetramethylguanidinium azide (TMGA; $[(Me_2N)_2CNH_2]N_3$),[7] a reagent which has rarely been used.[8] It is worth noting that TMGA has recently been used in the stereoselective synthesis of α-azido carboximides[9] and α-azido ketones.[10] To our knowledge, TMGA has not been previously employed for the synthesis of azidocarbohydrates.

Treatment of peracetylated or perbenzoylated glycosyl halides with TMGA (1-1.5 equiv.) in

dichloromethane led to *homogeneous* solutions which were stirred at room temperature for one or more hours. In most cases, the reactions were 80-100% complete after 2 hours, with the exception of 5-thioglycosyl bromide **5**, which required nearly 40 hours to complete the conversion at room temperature.[11] More TMGA may be added after 2 hours to accelerate the reactions. Up to 2 equivalents of TMGA has been used, the excess reagent showing no adverse effect on the reactions. The products, isolated as white solids in essentially *quantitative* yield after simple workup, were homogeneous by TLC and ^{1}H NMR spectroscopy. No by-products were detected from the ^{1}H NMR of the crude material. However, all crude products were passed through a short pad of silica gel to afford analytically pure samples for rotation measurements, MS, and/or combustion analyses. The purified yields are reported in Table 1.

Table 1. Synthesis of Glycosyl Azides from Glycosyl Halides and TMGA

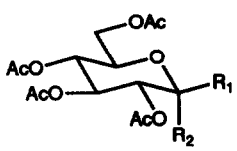
Substrate	Product	Ref.	Yield (%)	mp (°C) (solvent)	lit. mp (°C)	$[\alpha]_D$* (c; °C)	lit. $[\alpha]_D$* (°C)
1	**7**	1	99	130-131 (EtOH)	129 (dec)	-32.0° (0.07; 22)	-33.0° (19)
2	**8**	15	98	113-114 (EtOH)	113-114	-0.70° (0.2; 22)	-0.54° (22)
3	**9**	1	97	96 (MeOH)	96	-14.8° (0.08; 24)	-16.2° (20)
4	**10**	1	98	160.5 (dec) (EtOAc/Hexanes)	160-161 (dec)	-42.1° (0.14; 22)	-43.0° (20)
5	**11**	---	90-94	92-93 (EtOAc/Hexanes)	---	-11.6° (0.08; 20)	---
6	**12**	1	99	181 (dec) (EtOAc/Hexanes)	182-182.5	-26.5° (0.13; 21)	-30.9° (16)

* In $CHCl_3$.

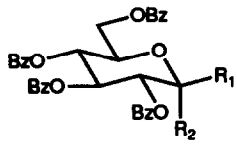
To test the compatibility of TMGA with acid labile protecting groups, compound **13**[12] was treated with 1.5 equivalent of TMGA in dichloromethane at reflux for 6 hours. The triflate was cleanly converted to azide **14**[13] in 97% yield after purification. No by-products were detected from the ^{1}H NMR of the crude material. This observation also demonstrated the potential usefulness of TMGA for the introduction of azido group at positions other than the anomeric center.

The reactions were stereoselective with complete inversion at the anomeric centers. Both base-sensitive and acid labile protecting groups survived. The physical data of all known compounds were in excellent agreement with literature values. All compounds were fully

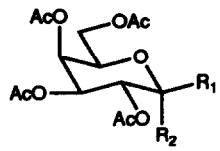
characterized by ^{1}H, ^{13}C (APT), COSY, and HETCOR.[14] The physical and spectral data of **8**[15] and previously unknown azide **11** are represented in the reference section.[16]



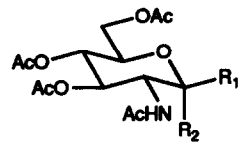
1 R_1=H, R_2=Br
7 R_1=N_3, R_2=H



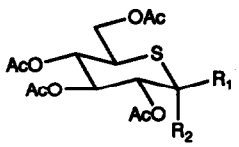
2 R_1=H, R_2=Br
8 R_1=N_3, R_2=H



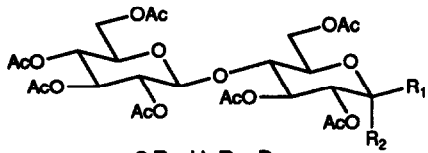
3 R_1=H, R_2=Br
9 R_1=N_3, R_2=H



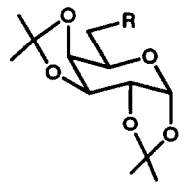
4 R_1=H, R_2=Cl
10 R_1=N_3, R_2=H



5 R_1=H, R_2=Br
11 R_1=N_3, R_2=H



6 R_1=H, R_2=Br
12 R_1=N_3, R_2=H



13 R=OSO_2CF_3
14 R=N_3

In conclusion, TMGA is an excellent reagent for the quantitative conversion of glycosyl halides to glycosyl azides. The one-phase reactions proceed with complete stereoselectivity. High boiling solvents, Lewis acids, and heating are not required.

General Procedure. To glycosyl halides in CH_2Cl_2 (0.24 to 0.33 M) was added TMGA (1-1.5 equiv.) in one batch. The homogeneous solutions were stirred at room temperature until TLC indicated total consumption of the halides. Solvent was removed *in vacuo*. Et_2O was then added and stirred for a few minutes to produce a white precipitate, which was filtered and washed with Et_2O. The filtrate was washed once with H_2O and dried (anhyd. Na_2SO_4). Concentration *in vacuo* afforded pure glycosyl azides in quantitative yields. The products were chromatographed or crystallized for melting point, rotation measurements, and combustion analyses.

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7 a) Shortly after our initial study of TMGA in the synthesis of glycosyl azides, both Lancaster and Alfa terminated the production of this reagent (ca. end of 1990) partially due to slow sales. However, TMGA can be readily prepared (Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426). b) The NMR data of TMGA: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (2H, bs), 3.05 (12H, s); ^{13}C NMR (75MHz, $CDCl_3$) δ 161.31 (e), 39.13 (o). c) TMGA is soluble in halogenated solvents, partially soluble in EtOAc, and insoluble in Et_2O or THF.

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13 a) Gibson, A. R.; Melton, L. D.; Slessor, K. N. *Can. J. Chem.* **1974**, *52*, 3905; b) Bundle, D. R. *J. Chem. Soc. Perkin Trans.I*, **1979**, 2751; c) $[\alpha]_D^{22}$ -97.0° (c 0.1, $CHCl_3$) (lit. $[\alpha]_D^{22}$ -99° in $CHCl_3$).

14 The spectra are available from the authors upon request.

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16 **2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl azide (8):** Mp 113-114°C (EtOH); $[\alpha]_D^{21}$ -0.70° (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.09-7.84 (12H, m, ArH), 7.58-7.24 (8H, m, ArH), 6.01 (1H, dd, $J_{3,4}$=9.6 Hz, H-3), 5.79 (1H, dd, $J_{4,5}$=9.9 Hz, H-4), 5.57 (1H, dd, $J_{2,3}$=9.3 Hz, H-2), 5.04 (1H, d, $J_{1,2}$=8.7 Hz, H-1), 4.72 (1H, dd, $J_{5,6'}$=3 Hz, $J_{6,6'}$=12.3 Hz, H-6'), 4.56 (1H, dd, $J_{5,6}$=5.1 Hz, $J_{6,6'}$=12.3 Hz, H-6), 4.32 (1H, m, H-5); ^{13}C NMR ($CDCl_3$) δ 166.16, 165.77, 165.15, 165.11, 88.37 (C-1), 74.50 (C-5), 72.81 (C-3), 71.31 (C-2), 69.18 (C-4), 62.84 (C-6). Anal. Calcd for $C_{34}H_{27}N_3O_9$: C, 65.70; H, 4.38; N, 6.76. Found: C, 65.32; H, 4.12; N, 6.58.

2,3,4,6-Tetra-O-acetyl-5-thio-β-D-glucopyranosyl azide (11): Colorless needles, mp 92-93°C (EtOAc/Hexanes), $[\alpha]_D^{20}$ -11.6° (c 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.20 (1H, dd, $J_{4,5}$=10.5 Hz, H-4), 5.12 (1H, dd, $J_{2,3}$=9.5 Hz, H-2), 5.01 (1H, dd, $J_{3,4}$=9.6 Hz, H-3), 4.53 (1H, d, $J_{1,2}$=9.3 Hz, H-1), 4.23 (1H, dd, $J_{5,6}$=5.7 Hz, $J_{6,6'}$=12.0 Hz, H-6), 4.09 (1H, dd, $J_{5,6'}$=3.3 Hz, $J_{6,6'}$=12.0 Hz, H-6'), 3.27 (1H, m, H-5); ^{13}C NMR ($CDCl_3$) δ 170.44, 169.60, 169.26, 169.19, 73.85 (C-2), 73.02 (C-3), 71.34 (C-4), 62.53 (C-1), 61.16 (C-6), 42.33 (C-5), 20.61, 20.55, 20.49, 20.41. Anal. Calcd for $C_{14}H_{19}N_3O_8S$: C, 43.18; H, 4.92; N, 10.79; S, 8.23. Found: C, 43.02; H, 4.89; N, 10.67; S, 8.59.

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