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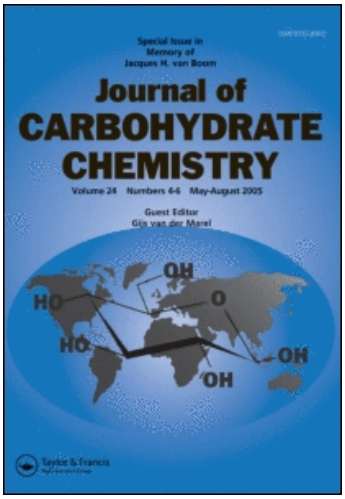

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
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To cite this Article Mugunthan, G. and Ravindranathan Kartha, K.P.(2008) 'Application of Ball Milling Technology to Carbohydrate Reactions-II. Solvent-Free Mechanochemical Synthesis of Glycosyl Azides', Journal of Carbohydrate Chemistry, 27: 5, 294 — 299
To link to this Article: DOI: 10.1080/07328300802161897
URL: http://dx.doi.org/10.1080/07328300802161897

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Journal of Carbohydrate Chemistry, 27:294–299, 2008
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ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300802161897

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Application of Ball Milling Technology to Carbohydrate Reactions-II. Solvent-Free Mechanochemical Synthesis of Glycosyl Azides‡

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Glycosyl azides have been prepared from a range of readily available glycosyl halides by a solvent-free mechanochemical procedure employing a planetary ball mill in good to excellent yields.

Keywords Glycosyl azides, Ball mill, Solvent-free synthesis

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INTRODUCTION

Synthetic carbohydrate chemistry relies heavily on the use of expensive protecting group manipulations, which is largely unavoidable, for carrying out selective reactions on polyfunctional molecules such as sugars. While on the

Received March 3, 2008; accepted April 24, 2008.
‡We have performed several (at least 25 including four 5-g scale reactions) preparative grinding experiments employing NaN_3 during this work and no untoward incidents of any kind were observed. Even though sodium azide is considered safe to handle, see reference [13], due caution must be exercised during all experiments involving NaN_3. For Part I see Ref. [8].
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one hand the high expenditure of chemicals, time, and work involved tends to greatly restrict the broad industrial use of carbohydrate derivatives, the advent of glycobiology and better understanding of the role of glyconjugates in various diseases have, on the other, led to greater demand for synthetic carbohydrates and their derivatives.[1] Hence, there is an increased need for more efficient and environment friendly ways of making carbohydrate derivatives. Glycosyl azides, for example, are highly useful in synthesizing various neoglycoconguates, which serve as mimics for glycoconjugates, by click chemistry.[2,3] Further, azides are good starting materials for preparing other nitrogen-containing functionalities such as amines, amides, ureas, carbodiimides, and others.

Different methods for the preparation of glycosyl azides have recently been reviewed by Györgydeák.[4] One of the early methods of synthesis, which is still in use, involves the reaction of a glycosyl halide with an inorganic azide, like sodium/silver azide, often using DMF as the solvent.[3] Variations of this method include the use of a phase transfer catalyst in a two-phase system.[5] Glysosyl azides can also be prepared by treating the corresponding per-*O*-acetylated sugars with $TMSN_3$ in the presence of a Lewis acid such as $SnCl_4$.[6,7] Also, treatment of the protected cyclic 1,2-sulfites of monosaccharides with NaN_3 in DMF has resulted in the formation of the corresponding 1,2-*trans*-linked glycosyl azides with a free 2-OH group.[4] However, to date no solvent free, greener synthesis of glycosyl azides has been reported.

We have recently observed that a commercially available planetary ball mill is very convenient for carrying out solvent-free reactions under standardized and reproducible conditions;[8] and the regioselective protection of the primary -OH group of various hexosides and a nucleoside was successfully carried out with high efficiency.[8] Further to this, we now report our findings on the displacement of different glycosyl halides by sodium azide under dry milling conditions.

RESULTS AND DISCUSSION

Initial studies for the optimization of the reaction conditions were carried out using acetobromoglucose (**1**) as the substrate. It was found that on treatment with 10 mol equiv of NaN_3 the reaction was complete in 8 h at 500 rpm giving the corresponding glycosyl azide **2** in virtually quantitative yield (entry 1, Table 1). Without the need for purification by column chromatography, neat product was obtained directly by crystallization after the aqueous workup. Use of less than 10 mol equiv of the inorganic azide required significantly longer reaction time (results not shown). The reaction was subsequently extended to other halide substrates (**3**, **5**, **7**, and **9**) derived, respectively, from D-galactose (another common hexose), *N*-acetyl-D-glucosamine (an aminosugar derivative), D-lactose (a disaccharide), and L-arabinose (a pentose sugar), and

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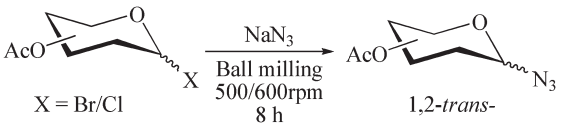
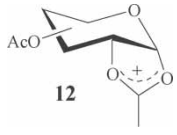
Table 1: Preparation of glycosyl azides from glycosyl bromides by dry ball milling.



Entry	Halide substrate (1 mmol)	Product	Yield (%)	Melting point (°C)		Optical rotation (α)D	
				Observed	Reported	Observed	Reported
1	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**)	2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (**2**)	99	133–136[a]	131.8–135[10]	−37.5 (C = 1) MeOH	−37.4(10) (C = 1) MeOH
2	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**3**)	2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide (**4**)	98	90–91	90.9[10]	−8.0 (C = 1) MeOH	−13.8(10) (C = 1) MeOH
3	2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl chloride (**5**)	2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl azide (**6**)	98	168–170[a]	170–171[11]	−44.1 (C = 1.1) CHCl3	−46.3(11) (C = 1.1) CHCl3
4	Hepta-*O*-acetyl-α-Dlactosyl bromide (**7**)	Hepta-*O*-acetyl-β-D-lactosyl azide (**8**)	75	72–75[a]	74–76[12]	−16.6 (C = 0.6) CHCl3	−18(12) (C = 0.64) CHCl3
5	2,3,4-Tri-*O*-acetyl-β-L-arabinopyranosyl bromide (**9**)	2,3,4-Tri-*O*-acetyl-β-L-arabinopyranosyl azide (**10**)	87	68–70	—	−19.0 (C = 1) CHCl3)	—
6	2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**11**)	Glycosyl azide (**2**)	95	See entry 1			
7	Bromide **1** (5 g, 12.2 mmol approximately)	Glycosyl azide (**2**)	>99	See entry 1			

[a]Recrystallized from EtOAc/Petroleum ether (60–80°C).

the corresponding 1,2-*trans*-linked glycosyl azides (**4**, **6**, **8**, and **10**) were obtained in very good yields (see Table 1). Although 1,2-*trans*-linked products **4**, **6**, and **8** were obtained from the respective 1,2-*cis*-linked glycosyl bromides **3**, **5**, and **7**, this cannot prove whether the reaction proceeds by a direct displacement mechanism or via neighboring group participation by the C-2 substituent on the respective sugar ring. However, the exclusive formation of the β-L-arabinoside **10** from bromide **9** clearly indicated a reaction involving the cyclic oxocarbonium ion intermediate (the latter course) of general structure **12**. In order to further investigate the involvement of anchimeric assistance by the C-2-acyl group in the reaction, acetochloro- β-D-glucose (**11**)[9] was allowed to mix in the ball mill in the presence of NaN_3 (entry 6, Table 1) as described above. The product obtained was indentical with **2** in all respects, thus confirming the involvement of the cyclic oxocarbonium ion intermediate **12** formed from **11** via the C-2-acetoxy group participation. Further evidence for this mechanism was obtained from the reaction of acetobromomannose with NaN_3 wherein, again, the 1,2-*trans*-linked α-azide was the sole product obtained. No by-products were ever detected by TLC/NMR spectroscopy in any of these reactions. The reaction of bromide **1** was scaled up to the 5-g level without affecting the yield or quality of the product (entry 7, Table 1). In all the experiments described above the products obtained were sufficiently pure the for next chemical transformation.



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Solvent-free reactions of glycosyl halides with other nucleophilic reagents such as KSCN and KSAc, phenols, and mercaptans are currently under way, with the results showing a wide scope for making a range of sugar derivatives employing the greener, solvent-free ball milling technique.

CONCLUSION

We have developed a solvent-free highly efficient method for the synthesis of 1,2-*trans*-linked glycosyl azides that can be applied on multigram quantities.

EXPERIMENTAL

All reagent chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). TLC was performed on 0.2-mm Merck precoated silica gel 60 F254 aluminum sheets. Melting points were recorded on a capillary melting point apparatus and are uncorrected. Specific rotations were obtained on

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AUTOPOL IV polarimeter at 20°C. IR spectra were recorded on a Nicolet FT-IR Impact 410 instrument either as neat or KBr pellets. Mass spectra were obtained on ultraflex TOF/TOF MALDI mass spectrometer, which is equipped with a reflector and controlled by Flexcontrol 1.4 software package. NMR spectra were recorded on 300-MHz Bruker FT-NMR (Avance DPX300) spectrometer at 300 MHz for 1H and at 75.47 MHz for the ^{13}C nucleus. Chemical shifts are reported in ppm from TMS as the internal standard.

General Procedure for the Glycosyl Azide Synthesis using a Planetary Ball Mill

The appropriate glycosyl halide (1 mmol) and NaN_3 (10 mmol) were allowed to mix in a stainless steel (SS) jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d) for 8 h in a planetary ball mill (Retsch PM-100; Retsch GmbH & Co. KG, Germany) at 500/600 rpm. The mixture was then taken up in dichloromethane and was washed in a separatory funnel with cold water. The organic layer was dried (Na_2SO_4) and concentrated to syrup under reduced pressure; addition of ether resulted in the rapid crystallization, giving glycosyl azides suitable for subsequent synthetic reactions. Preparation of **2** in multigram (5 g and above) quantities from acetobromoglucose (**1**) resulted in the direct crystallization of **2** upon removal of solvent after the aqueous workup. All the compounds reported here have been reported previously. Their spectral data were in accordance with the expected structures and in agreement with literature values. The physical constants obtained are shown in Table 1.

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ACKNOWLEDGMENTS

G. Mugunthan likes to thank NIPER for the award of a research fellowship.

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