Synthesis of glycosyl cyanamides from azides: Application for the synthesis of N-hydroxyguanidinoglycosides

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A simple, concise and straightforward synthesis of a novel class of cyanamides and N-hydroxyguanidines in carbohydrate scaffolds starting from the corresponding azides in moderate to good yields has been described. The protocol is simple and mild with broad substrate scope involving primary and secondary azides of a range of monosaccharides and disaccharides.

Keywords: Azide, cyanamide, N-hydroxyguanidine, carbohydrate

Cyanamides are vital class of compounds which have unique structural features and wide reactivity. They are used as building blocks in synthesis of various biologically active molecules and can be efficiently converted into other functionalities through viable chemical routes. They are found in natural products and are important precursors in the synthesis of herbicides and pharmaceutically active heterocycles such as tumor inhibitors and vasodilators. They have also been used considerably in the fields of inorganic and materials chemistry. Literature reports for cyanamide preparation involve reaction of cyanogen bromide/chloride with amines or with imide salts, reaction of amines with other electrophilic cyanating agents. Other methods for cyanamide synthesis include Tiemann rearrangement of amidoximes, coupling reactions involving Pd isocyanides, allyl carbonates and trimethylsilyl azide, sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agent, desulfurization of dithiocarbamates using I2, diacetoxyiodobenzene (DIB). Among the known cyanating agents, usage of CNBr is the general and widespread method for the direct synthesis of cyanamide from corresponding amine. However this methodology has not been explored in carbohydrate chemistry for the synthesis of glycosyl cyanamides.

Besides the significant importance of cyanamide, the guanidine functionality is widely found in a number of natural products and synthetic compounds such as drugs and catalysts. They show large spectrum of biological activities ranging from antiviral, antifungal to neurotoxic and are attractive targets of drug design and discovery. Guanidinoglycosides have attracted tremendous research efforts in recent years because of their biochemical properties such as inhibition of HIV, inhibition of enzymes including thrombin, glycosidases, neuraminidases and nitric oxide synthases, antibacterial activity, antihypertensive activity, etc.

Some of the important guanidine containing aryls as well as aminoglycosidic antibiotics are illustrated in Figure 1. New synthetic methods, novel guanidinylating reagents have been developed for the synthesis of guanidine containing compounds. However, most of these reagents are not favourable for the synthesis of glycosylated guanidines with disadvantages such as incompatibility of sensitive functionalities and inconvenient preparatory procedures of the reagents.

Despite the tremendous research in guanidine containing sugars, a search of literature shows no example for N-hydroxyguanidine containing sugars. N-Hydroxyguanidines are the metabolic intermediates of NO releasing substrates catalysed by the action of heme containing enzymes such as Nitric Oxide synthases (NOSs) and peroxidases. Also a few non physiological N-hydroxyguanidines have been demonstrated to produce NO by catalysis of NOS or other enzyme such as cytochrome P450 (Ref. 18). Thus such enzymatic controlled NO generating
compounds could have potential biomedical applications and are attractive targets of drug discovery. Some substituted hydroxyguanidines have been shown to exhibit cytotoxicity and antitumour activity, used in treatment of pulmonary and cardiovascular disorders, hypoxia, memory loss, etc.\textsuperscript{19}

Reported methods for preparation of these \(N\)-hydroxyguanidines involve reaction of electrophilic nitrogen rich functional groups with hydroxyl amine\textsuperscript{17,20}, Jirgensons’ thiourea reagent based method\textsuperscript{21}, Martin’s method using Cbz-NCS and \(\text{NH}_2\text{-OTHP (Ref. 22). However the more general and convenient method for the synthesis of monosubstituted \(N\)-hydroxyguanidines is from primary amines through the intermediate cyanamide.\textsuperscript{20}}

In the quest to synthesize terminal \(N\)-hydroxyguanidinylated compounds, no references were found in literature for the synthesis of glycosyl cyanamides, and \(N\)-hydroxyguanidinoglycosides. However, glycosyl cyanamide was obtained as a side product in the synthesis of \(N,N\)-bis(glycosyl)cyanamides from reaction of peracetylated glycopyranoses with bis(trimethylsilyl)carbodiimide in the presence of Lewis acid\textsuperscript{23}. So, we took up this synthesis to achieve both targets in a simple and straightforward procedure. We herein describe a simple, mild and viable protocol as shown in the Scheme I.

**Results and Discussion**

The direct synthesis of hitherto unreported glycosyl cyanamides, was started from 2,3,4,6-tetra-\(O\)-acetyl-\(\beta\)-D-glucopyranosyl azide \(1a\) readily prepared from D-glucose according to the literature procedure\textsuperscript{24}. The azide was then reduced with \(\text{H}_2\) over 10\% Pd-C and subsequently reacted, without further purification than filtration, with cyanogen bromide and triethylamine (TEA), in THF. This circumvents the solvent evaporation and work up as the filtrate was taken for the next step directly. The formation of cyanamide was confirmed by IR where it showed strong absorption at 2137 cm\(^{-1}\) characteristic for \(\text{NH-CN}\) stretch. The desired glycosyl cyanamide was isolated after column chromatography in good yield (80\%) as a single \(\beta\)-isomer. The method wherein, \(\text{CNBr}\) and TEA were added to the reaction mass containing 10\% Pd-C after the complete reduction of glycosyl azide as monitored by TLC was also tried, but this procedure resulted in low yields (25\%) of glycosyl cyanamide.

The generality of this protocol was demonstrated with other sugar moieties possessing primary azides \(1g, 1h\) with different protections \textit{i.e.}, esters and ethers which were found to be stable under the reaction conditions employed. The present methodology was then successfully extended to secondary azides \(1b-d,\),...
### Table I — Preparation of glycosyl cyanamides and N-hydroxyguanidinoglycosides from glycosyl azides

<table>
<thead>
<tr>
<th>Azide</th>
<th>Glycosyl cyanamide</th>
<th>Yield(^{a}) (%)</th>
<th>(N)-hydroxyguanidinoglycoside</th>
<th>Yield(^{a}) (%)</th>
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— Contd
1e-f and disaccharides maltose, lactose 1i, 1j. All these compounds gave satisfactory yields of products as single isomers with high purity. These results are summarized in Table I. All the synthesized compounds were characterized by mass, $^1$H and $^{13}$C NMR spectral analysis.

Further, a series of N-hydroxyguanidinoglycosides hitherto unreported were synthesized employing glycosyl cyanamides (Schemes I and II). Initially, 2,3,4,6-tetra-O-acetyl-$\beta$-D-glucopyranosyl cyanamide (2a) in THF was treated with hydroxylamine hydrochloride in the presence of mild base i.e., anhydrous K$_2$CO$_3$ at RT. The reaction was completed after 3.5 hr as evidenced by disappearance of NH-CN stretch (2137 cm$^{-1}$) in IR spectra. Simple filtration and evaporation of the solvent yielded the crude product. The desired product was isolated after column chromatography in 65% yield, with $\beta$-configuration as evidenced by NMR. The $^{13}$C NMR showed a distinct peak at around $\delta$ 160 characteristic of guanidine quaternary carbon. Following similar conditions, a series of $\beta$-D-glycosyl cyanamides 2b-j with various protecting groups i.e., esters and ethers were converted to N-hydroxyguanidinoglycosides with yields as presented in Table I. Similarly, due to the diverse role of N-acetyl-D-glucosamine in the physiological activities, the above reaction conditions were applied to the commercially available D-glucosamine hydrochloride and the desired cyanamide and N-hydroxy derivatives were obtained in good yields (Scheme III). All the products were well characterized by NMR and mass spectral analysis. Due to the wide applications of guanidino glycosides, the synthesis of 2,3,4,6-tetra-O-acetyl-$\beta$-D-glucopyranosyl guanidine employing NH$_4$Cl in refluxing acetonitrile was undertaken. However the reaction of 2,3,4,6-tetra-O-acetyl-$\beta$-D-glucopyranosyl cyanamide with NH$_4$Cl in refluxing acetonitrile for 24 hr afforded low yield of only 22%.
Experimental Section

All acetyl and benzyl protected mono and disaccharide azides were prepared according to literature reports\textsuperscript{34}. All the solvents were dried and purified using recommended procedures in the literature whenever necessary. ESMS spectra were recorded at SID, IISc, Bangalore, \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Bruker AMX 300 MHz and 100 MHz spectrometer, respectively, at the Indian Institute of Science, Bangalore. IR spectra were recorded on a Shimadzu model FT-IR-8400S spectrophotometer at Bangalore University, Bangalore. TLC experiments were done using Merck TLC aluminum sheets (silica gel 60 F254) plate. Column chromatography was performed on silica gel (100-200 mesh) using ethyl acetate and hexane mixtures as eluent.

General procedure for glycosyl cyanamide, 2a-j:
To the stirred solution of the azide (1 mmol) in THF (5 mL), 10\% Pd/C (10\% w/w) was added and stirred under hydrogen atmosphere (balloon) for 3 hr. The reaction mixture was then filtered over celite pad into RB, washed twice with THF (5 mL each). To the combined filtrate cyanogen bromide (1.5 mmol), TEA (1.2 mmol) were added and the reaction mixture stirred for 3 hr. After completion of reaction as judged by TLC, solvent was evaporated in \textit{vacuo} and the residue was taken in EtOAc, washed with citric acid (10 mL), followed by 5\% Na\textsubscript{2}CO\textsubscript{3} (10 mL). Finally, the EtOAc extract was washed with brine (10 mL) and the organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. Column chromatography of the crude product (hexane/EtOAc mixtures) afforded the cyanamide.

Spectral data for glycosyl cyanamides

\textit{N-(2,3,4,6-Tetra-O-acetyl-\beta-D-glucopyranosyl)cyanamide}, 2a. Gummy; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 5.42–5.36 (t, \(J = 9.4\) Hz each, 1H, H-3), 5.24 (br s, 1H, NH), 5.20 (t, \(J = 9.4\) Hz each, 1H, H-2), 5.18–4.95 (m, 1H, H-4), 4.76 (d, \(J = 8.5\) Hz each, 1H, H-1), 4.25–4.03 (m, 2H, H-6a,b), 3.74–3.68 (m, 1H, H-5), 3.84 (dd, \(J = 9.5\) Hz, 2H, PhCH\textsubscript{2}), 3.83 and 3.80 (2 s, 12H, COCH\textsubscript{3}). ESI-MS: Calcd for C\textsubscript{35}H\textsubscript{30}N\textsubscript{2}O\textsubscript{5}: m/z 572.22. Found: 573.19 [M+H]\textsuperscript{+}.

\textit{N-(2,3,4,6-Tetra-O-benzyl-\beta-D-glucopyranosyl)cyanamide}, 2b. Gummy; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 7.42–7.23 (m, 20H, Ph), 5.31 (br s, 1H, NH), 4.96 and 4.60 (2 d, \(J = 11.0\) Hz, 2H, PhCH\textsubscript{2}), 4.95 and 4.63 (2 d, \(J = 11.5\) Hz, 2H, PhCH\textsubscript{2}), 4.77 and 4.65 (2 d, \(J = 11.8\) Hz, 2H, PhCH\textsubscript{2}), 4.50 and 4.43 (2 d, \(J = 12.0\) Hz, 2H, PhCH\textsubscript{2}), 4.04 (dd, \(J_{3,4} = 3.5\) Hz, \(J_{4,5} = 0.5\) Hz, 1H, H-4), 3.85 (dd, \(J_{1,2} = 9.5\) Hz, \(J_{3,2} = 9.5\) Hz, 1H, H-2), 3.67–3.59 (m, 4H, H-3, H-5 and H-6a,b), 4.74 (d, \(J = 8.3\) Hz each, 1H, H-1); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 138.7, 138.1, 137.6, 137.4, 128.8–127.5 (20C), 116.0, 84.6, 77.5, 77.2, 75.6, 75.1, 74.7, 73.8, 73.3, 72.1, 68.7; IR (Neat): 2239 cm\textsuperscript{-1}; ESI-MS: Calcd for C\textsubscript{35}H\textsubscript{30}N\textsubscript{2}O\textsubscript{5}: m/z 564.26. Found: 565.27 [M+H]\textsuperscript{+}.

\textit{N-(2,3,4,6-Tetra-O-acetyl-\beta-D-galactopyranosyl)cyanamide}, 2c. Gummy; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 5.42–5.36 (t, \(J = 9.4\) Hz each, 1H, H-3), 5.24 (br s, 1H, NH), 5.20 (t, \(J = 9.4\) Hz each, 1H, H-2), 5.18–4.95 (m, 1H, H-4), 4.76 (d, \(J = 8.5\) Hz each, 1H, H-1), 4.25–4.03 (m, 2H, H-6a,b), 3.74–3.68 (m, 1H, H-5), 2.09, 2.06, 2.03, 2.01 (4 s, 12H, COCH\textsubscript{3}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 170.8, 170.2, 169.5, 169.3, 114.1, 82.1, 73.6, 72.0, 68.5, 70.1, 61.7, 20.9 (2C), 20.3 (2C); IR (Neat): 2235 cm\textsuperscript{-1}; ESI-MS: Calcd for C\textsubscript{35}H\textsubscript{30}N\textsubscript{2}O\textsubscript{5}: m/z 572.11. Found: 573.19 [M+H]\textsuperscript{+}.

\textit{N-(2,3,4,6-Tetra-O-benzyl-\beta-D-galactopyranosyl)cyanamide}, 2d. Gummy; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 7.42–7.23 (m, 20H, Ph), 5.29 (br s, 1H, NH), 4.98 and 4.62 (2 d, \(J = 11.0\) Hz, 2H, PhCH\textsubscript{2}), 4.97 and 4.61 (2 d, \(J = 11.5\) Hz, 2H, PhCH\textsubscript{2}), 4.78 and 4.68 (2 d, \(J = 11.8\) Hz, 2H, PhCH\textsubscript{2}), 4.51 and 4.44 (2 d, \(J = 12.0\) Hz, 2H, PhCH\textsubscript{2}), 4.02 (dd, \(J_{3,4} = 3.5\) Hz, \(J_{4,5} = 0.5\) Hz, 1H, H-4), 3.84 (dd, \(J_{3,2} = 9.5\) Hz, \(J_{2,3} = 9.5\) Hz, 1H, H-2), 3.66–3.58 (m, 4H, H-3, H-5 and H-6a,b), 4.73 (d, \(J = 8.4\) Hz each, 1H, H-1); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 138.5, 137.9, 137.7, 137.6, 128.5–127.4
1,3,4,6-Tetra-O-acetyl-2-deoxy-2-(cyanamido)-β-D-glucopyranose, 2e. Gummy; 1H NMR (CDCl3, 300 MHz): δ 5.47 (d, J = 8.4 Hz, 1H, H-1), 5.04 (m, 2H, H-3 and H-4), 4.34 (dd, J6,6b = 12.4 Hz, J5,6b = 2.0 Hz, 1H, H-6b), 3.82 (m, 1H, H-5), 3.04 (t, J = 8.4 Hz each, 1H, H-2), 2.19, 2.11, 2.09, 2.04 (4s, 12H, COCH3); 13C NMR (CDCl3, 100 MHz): δ 170.6, 169.6, 169.9, 169.2, 121.6, 95.2, 75.1, 72.7, 68.2, 61.7, 55.5, 20.9, 20.7, 20.6, 20.2; IR (Neat): 2223 cm⁻¹; ESI-MS: Calcd for C36H38N2O9: m/z 564.26. Found: 565.32 [M+H]+.

1,3,4,6-Tetra-O-benzyl-2-deoxy-2-(cyanamido)-β-D-glucopyranose, 2f. Gummy; 1H NMR (CDCl3, 300 MHz): δ 7.46–7.23 (m, 20H, Ph), 5.54 (1H, br s, NH), 4.92 and 4.60 (2 d, J = 11.0 Hz, 2H, PhCH2), 4.96 and 4.58 (2 d, J = 11.0 Hz, 2H, PhCH2), 4.76 and 4.68 (2 d, J = 11.0 Hz, 2H, PhCH2), 4.50 and 4.45 (2 d, J = 11.5 Hz, 2H, PhCH2), 5.48 (d, J = 8.0 Hz, 1H, H-1), 5.01 (m, 2H, H-3 and H-4), 4.30 (dd, 1H, J6a,6b = 12.0 Hz, J6a = 4.5 Hz, 6-6a), 4.02 (dd, 1H, J6a,6b = 12.0 Hz, J5,6b = 2.0 Hz, H-6b), 3.80 (m, 1H, H-5), 3.01 (t, 1H, J2,2 = 8.0 Hz each, H-2); 13C NMR (CDCl3, 100 MHz) δ 138.5, 138.3, 137.4, 137.2, 128.5–127.2 (20C), 118.1, 95.6, 75.2, 72.4, 68.1, 61.8, 55.7, 77.0, 76.1, 75.2, 75.0; IR (Neat): 2226 cm⁻¹; ESI-MS: Calcd for C36H38N2O9: m/z 564.26. Found: 565.32 [M+H]+.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-(cyanamido)-β-D-glucopyranoside, 2g. Gummy; 1H NMR (CDCl3, 300 MHz): δ 5.42 (t, J = 9.6 Hz each, 1H, H-3), 5.21 (br s, 1H, NH), 4.71–4.84 (m, 2H, H-2 and H-1), 4.70–4.61 (m, 1H, H-4), 4.61–4.47 (m, 2H, H-6b and H-6), 3.95–3.81 (m, 1H, H-6a), 3.23 (s, 3H, OMe), 2.09, 2.05, 2.00 (3s, 9H, COCH3); 13C NMR (CDCl3, 100 MHz): δ 173.5, 170.7, 170.5, 118.5, 96.4, 72.6, 70.7, 69.8, 69.0, 55.4, 41.5, 20.9, 20.8, 20.7; IR (Neat): 2228 cm⁻¹; ESI-MS: Calcd for C40H39N2O10: m/z 596.45. Found: 597.65 [M+H]+.

General procedure for N-hydroxyguanidinoglucoside, 3a-j: To a solution of glycosyl cyanamid (1.0 mmol) in THF (5 mL), NH2OH.HCl and anhydrous K2CO3 (2.0 mmol) were added successively. The reaction mixture was stirred for 3–3.5 hr until completion (as monitored by TLC). Solvent was evaporated in vacuo and residue was taken in EtOAc, washed with citric acid (10 mL), followed by 5% Na2CO3 (10 mL). Finally washed with brine (10 mL) and organic layer was dried over Na2SO4. Column chromatography of the crude product (hexane/EtOAc mixtures) afforded the N-hydroxyguanidinylated compound.

Spectral data for N-hydroxyguanidinoglucosides

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-N-hydroxyguanidine, 3a. Gummy; 1H NMR (CDCl3, 300 MHz): δ 5.84 (br s, 1H, NH), 5.44–5.30 (t, J = 9.6 Hz each, 1H, H-3), 5.01 (m, 2H, H-3 and H-4), 4.34 (dd, J5,6b = 12.4 Hz, J6a,6b = 12.4 Hz, 1H, H-6a), 4.18 (1H, br s, NH), 4.09 (dd, J6a,6b = 12.4 Hz, J5,6b = 2.0 Hz, 1H, H-6b), 3.82 (m, 1H, H-5), 3.04 (t, J = 8.4 Hz each, 1H, H-2), 2.19, 2.11, 2.09, 2.04 (4s, 12H, COCH3); 13C NMR (CDCl3, 100 MHz): δ 138.7, 138.1, 137.6, 128.8–127.5 (15C), 118.5, 96.4, 77.5, 77.2, 75.6, 75.1, 72.6, 70.7, 69.8, 69.0, 41.5; IR (Neat): 2231 cm⁻¹; ESI-MS: Calcd for C36H38N2O9: m/z 488.23. Found: 489.31 [M+H]+.
Hz each, 1H, H-3), 5.21 (t, J = 9.4 Hz each, 1H, H-2), 5.16–4.96 (m, 1H, H-4), 4.71 (d, J = 8.3 Hz each, 1H, H-1), 4.22–4.00 (2 d, J = 11.0 Hz, 2H, PhCH₂), 3.69–3.67 (m, 1H, H-5), 2.12, 2.08, 2.07, 2.04 (4 s, 12H, 4 COCH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 170.5, 170.1, 169.9, 169.0, 157.9, 82.5, 73.6, 71.6, 68.1, 66.4, 61.5, 20.3 (2C), 20.1(2C); IR (Neat): 3374, 1601 cm⁻¹; ESI-MS: Calcd for C₁₅H₁₂N₅O₁₀: m/z 405.13. Found: 406.24 [M+H]⁺.

N-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)-N-hydroxyguanidine, 3b. Gummy; ¹H NMR (CDCl₃, 300 MHz): δ 7.39–7.26 (m, 20H, Ph), 5.91 (br s, 1H, NH), 4.87 and 4.56 (2 d, J = 11.0 Hz, 2H, PhCH₂), 4.94 and 4.51 (2 d, J = 11.5 Hz, 2H, PhCH₂), 4.77 and 4.69 (2 d, J = 11.8 Hz, 2H, PhCH₂), 4.53 and 4.45 (2 d, J = 12.0 Hz, 2H, PhCH₂), 4.72 (d, J = 8.2 Hz each, 1H, H-1), 4.09 (dd, J = 3.5 Hz, J = 0.5 Hz, 1H, H-4), 3.83 (dd, J = 9.5 Hz, J = 9.5 Hz, 1H, H-2), 3.63–3.59 (m, 4H, H-3, H-5, H-6a,b); ¹³C NMR (CDCl₃, 100 MHz): δ 138.7, 138.1, 137.5, 137.4, 128.6–127.5 (20C), 160.5, 84.6, 77.5, 77.3, 75.7, 75.6, 74.7, 73.9, 73.3, 72.1, 68.9; IR (Neat): 3375, 1603 cm⁻¹; ESI-MS: Calcd for C₃₅H₃₉N₃O₁₀: m/z 597.28. Found: 598.34 [M+H]⁺.

N-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-N-hydroxyguanidine, 3c. Gummy; ¹H NMR (CDCl₃, 300 MHz): δ 5.86 (br s, 1H, NH), 5.47–5.32 (t, J = 9.2 Hz each, 1H, H-3), 5.24 (t, J = 9.4 Hz each, 1H, H-2), 5.18–4.98 (m, 4H, H-4), 4.72 (d, J = 8.7 Hz each, 1H, H-1), 4.21–4.04 (m, 2H, H-6a,b), 3.69–3.66 (m, 1H, H-5), 2.14, 2.09, 2.06, 2.03 (4 s, 12H, 4 COCH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 170.8, 170.3, 169.8, 169.1, 157.9, 82.6, 73.8, 71.9, 68.1, 66.8, 61.9, 20.5 (2C), 20.1(2C); IR (Neat): 3372, 1604 cm⁻¹; ESI-MS: Calcd for C₃₅H₃₉N₃O₁₀: m/z 405.13. Found: 406.16 [M+H]⁺.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-(N-hydroxyguanidino)-β-D-glucopyranoside, 3g. Gummy; ¹H NMR (CDCl₃, 300 MHz): δ 5.92 (br s, 1H, NH), 5.40 (t, J = 9.6 Hz each, 1H, H-3), 4.84–4.70 (m, 2H, H-2, H-1), 4.70–4.63 (m, 1H, H-4), 4.61–4.45 (m, 2H, H-6b, H-5), 3.95–3.83 (m, 1H, H-6a), 3.22 (s, 3H, OMe), 2.90, 2.04, and 2.01 (3s, 9H, COCH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 173.6, 170.5, 170.1, 162.5, 96.4, 72.6, 70.8, 69.6, 69.0, 55.6, 41.5, 21.2, 20.8, 20.4; IR (Neat): 3364, 1605 cm⁻¹; ESI-MS: Calcd for C₅₁H₄₁N₃O₁₂: m/z 777.14. Found: 738.26 [M+H]⁺.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-(N-hydroxyguanidino)-β-D-glucopyranoside, 3h. Gummy; ¹H NMR (CDCl₃, 300 MHz): δ 7.46–7.22 (m, 15H, Ph), 5.97 (br s, 1H, NH), 5.48 (t, J = 9.6 Hz each, 1H, H-3), 4.90 and 4.65 (2 d, J = 11.0 Hz, 2H, PhCH₂), 4.87 and 4.63 (2 d, J = 11.5 Hz, 2H, PhCH₂), 4.77 and 4.60 (2 d, J = 11.5 Hz, 2H, PhCH₂), 4.83–4.74 (m, 2H, H-2 and H-1), 4.68–4.67 (m, 1H, H-4), 4.61–4.55 (m, 2H, H-6b and H-5), 3.95–3.83 (m, 1H, H-6a), 3.27 (s, 3H, OMe); ¹³C NMR (CDCl₃, 100 MHz): δ 138.9, 138.5, 137.7, 128.8–127.5 (20C), 158.2, 96.4, 77.6, 77.4,
75.7, 75.3, 72.7, 70.9, 69.9, 69.3, 41.8; IR (Neat): 3338, 1621 cm⁻¹; ESI-MS: Calcd for C₂₉H₄₃N₄O₆; m/z 521.25. Found: 522.33 [M+H]⁺.

\[N-(2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl)glycoluril-N-hydroxyguanidine, 3i\]

Gummy: ¹H NMR (CDCl₃, 300 MHz): δ 5.88 (br s, 1H, NH), 5.23 (t, J = 9.0 Hz each, 1H, H-3), 5.02 (dd, J₁,₂ = 10.2 Hz, J₂,₃ = 7.8 Hz, 1H, H-2), 4.94–4.91 (m, 2H, H-2' and H-4'), 4.71 (d, J = 9.1 Hz each, 1H, H-1), 4.43 (d, J = 7.7 Hz, 1H, H-1'), 4.31 (dd, J₂,₃ = 10.3 Hz, J₃,₄ = 1.4 Hz, 1H, H-3'), 4.09–4.05 (m, 3H, H-4 and H-6a,b), 3.93–3.87 (m, 1H, H-5), 3.77–3.68 (m, 2H, H-6a,b), 3.66–3.64 (m, 1H, H-5'), 2.12, 2.10, 2.07, 2.06, 2.04, 2.01, 1.94 (7 s, 21H, COCH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 170.2 (2C), 170.1 (2C), 169.7 (2C), 169.5, 159.3, 101.4, 89.2, 82.2, 74.5, 73.2, 77.4, 71.3, 71.0, 69.2, 66.8, 62.7, 61.0, 21.1 (2C), 20.6 (3C), 20.5 (2C); IR (Neat): 3368, 1614 cm⁻¹; ESI-MS: Calcd for C₂₁H₂₃N₃O₁₅; m/z 693.22. Found: 694.41 [M+H]⁺.

\[N-(2,3,6-Tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranosyl)glycoluril-N-hydroxyguanidine, 3j\]

Gummy: ¹H NMR (CDCl₃, 300 MHz): δ 7.00–4.70 (m, 35H), 5.95 (br s, 1H, NH), 5.69 (d, 1H, J = 5.0 Hz, H-1'), 5.02–3.42 (m, 26H), 3.28 (d, J = 8.5 Hz each 1H, H-1); ¹³C NMR (CDCl₃, 100 MHz): δ 160.6, 138.8 (2C), 137.9 (2C), 137.4 (2C), 136.9, 129.0–126.6 (35C), 98.0, 86.2, 81.8, 75.6 (2C), 75.9 (2C), 75.7, 75.1, 74.6, 74.1, 73.6 (2C), 73.2 (2C), 73.1, 71.3, 68.8, 66.0; IR (Neat): 3376, 1609 cm⁻¹; ESI-MS: Calcd for C₅₂H₆₇N₃O₁₅; m/z 1029.47. Found: 1030.57 [M+H]⁺.

Conclusion
In summary, a simple and direct protocol allowing the synthesis of cyanamides and N-hydroxyguanidines in carbohydrate scaffolds starting from the corresponding azides in moderate to good yields is delineated. The protocol is simple and mild with broad substrate scope involving primary and secondary azides of a range of monosaccharides and disaccharides.

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