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Direct azidation of unprotected carbohydrates with $PPh_3/CBr_4/NaN_3$. Modulation of the degree of substitution

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Abstract—We describe herein a modified procedure for the direct and regioselective synthesis of polyazido-sugars, that currently requires multistep syntheses. This protocol allows to modulate the degree of azidation obtained when the reagents to substrate ratio is changed.

Azides are particularly useful in the field of carbohydrate chemistry. They are valuable precursors of amines because of their relatively high stability and chemical inertness. An important number of reagents such as borohydrides, triphenylphosphine, samarium(II) iodide and Pd/C under H_2 have been employed for the reduction of azides to amines. Azides can also be used as masking groups for amines. A mild conversion of amines into azides can be achieved by a transition metal-catalysed diazo-transfer reaction introduced by Wong and co-workers.[1]

The versatility of azides makes this class of compounds particularly helpful in the synthesis of oligosaccharides, glycosaminoglycans such as heparin,[2] aminoglycoside antibiotics,[3] azidonucleosides,[4] and carbopeptoids.[5] The recent development of the click chemistry reaction has dramatically increased the potential of sugars possessing an azido function for the synthesis of glycoconjugates,[6,7] by grafting them onto a saccharide,[8] a peptide[9] or a polymeric chain.[10,11]

The introduction of an azide onto a sugar is usually achieved by displacement of a leaving group such as bromide, tosyloxy or triflate with an azide ion. Hanessian et al.[12] introduced a $PPh_3/NCS/LiN_3$ mixture to achieve azidation at the primary position of glycosides. More recently, Demailly and co-workers[13] regioselectively synthesized anomeric glycosyl azides with the same system. A similar procedure using $PPh_3/CBr_4/LiN_3$ for the 6-azidation of pullulan and amylose has been reported by Kaplan and co-workers[14] Glycofuranosyl azides have been prepared from thiocarbonates.[15]

We are currently involved in a research programme dealing with the synthesis of new probes for studying multivalency. In order to obtain polyazido-saccharides as scaffolds for grafting different ligands by click chemistry, we have developed a procedure for the direct azidation of unprotected saccharides with $PPh_3/CBr_4/NaN_3$.

First experiments were performed on D-mannose to study the effect of increasing the number of equivalents of reagents. During this investigation, the PPh_3/CBr_4 and NaN_3/PPh_3 ratios were kept constant (1/1 and 5/1, respectively).

Results showed that total disappearance of the starting material requires at least 2 equiv of PPh_3/CBr_4. In order to simplify the purification and characterization of the products, crude azidosugars were acetylated in Pyr/Ac_2O. 2,3,4,6-Tetra-*O*-acetyl-D-mannopyranosyl azide **1** was isolated in 41% yield (Scheme 1).

These experimental conditions have been evaluated on different monosaccharides and the results obtained using

Keywords: Unprotected carbohydrates; Azidation; Polysubstitution; One pot synthesis.
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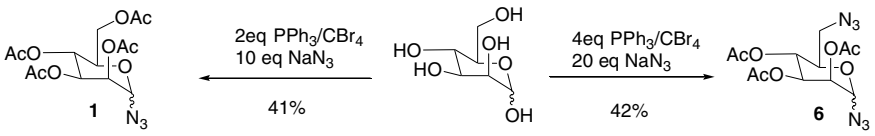
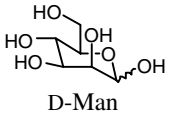
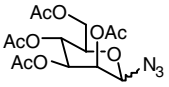
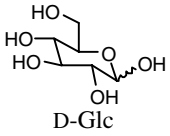
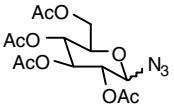
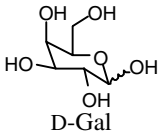
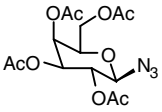
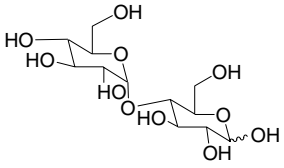
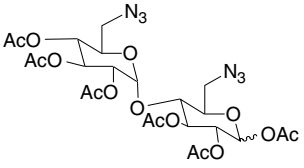
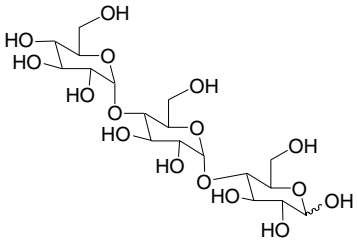
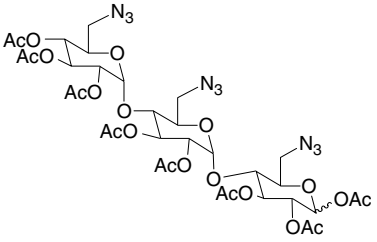


Scheme 1. Effect of the quantity of reagents on the azidation of mannose.

Table 1. Saccharides obtained with 2 equiv PPh_3/CBr_4 and 10 equiv NaN_3 per monosaccharide unit

Entry	Substrates	Products		Ratio α/β	Yield (%)
1	 D-Man		**1**[19]	1/1	41
2	 D-Glc		**2**[16,20]	1/4	39
3	 D-Gal		**3**[16,17]	Pure β	40
4	 Maltose		**4**		49
5	 Maltotriose		**5**[21]		41

2 equiv PPh_3/CBr_4 unit are summarized in Table 1. Yields are given after acetylation and purification of the products over silica gel.

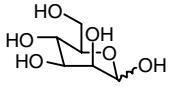
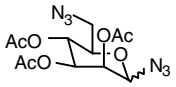
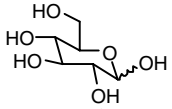
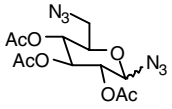
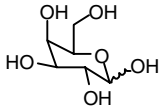
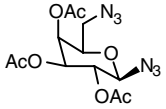
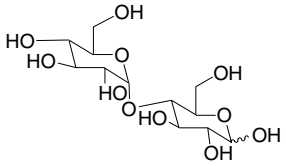
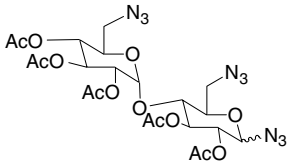
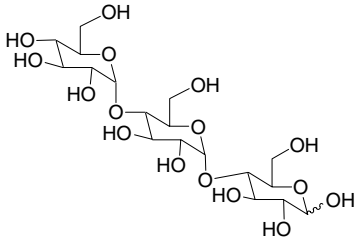
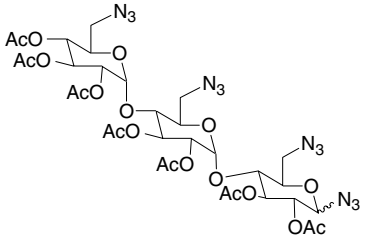
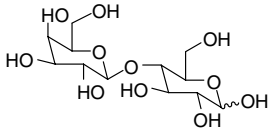
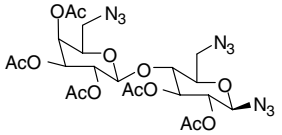
Monosaccharides (mannose, glucose and galactose, Table 1, entries 1–3) gave the glycosylazide derivatives. No stereoselectivity was observed for D-Man, while the β-azide was the major (D-Glc) or the unique (D-Gal) product of the reaction.

We have also extended this methodology to di- and trisaccharides: maltose, lactose and maltotriose using 2 equiv PPh_3/CBr_4 per monosaccharide unit. We were very pleased to see that compounds **4** and **5**, containing, respectively, two and three azides, could be isolated with this protocol. Surprisingly, first azidation occurs in the C-6 position of maltose and maltotriose. The possibility of hydrolysis of initially formed bromosugars, although not observed for monosaccharides, cannot be completely ruled out. Experiments conducted on lactose were disappointing, and the expected compound could not be isolated from a complex mixture of side-products.

Increasing the reagent to substrate ratio led to further substitution. We were pleased to observe the formation of 1,6-disubstituted mannose derivative **6** (Scheme 1) when more than 2 equiv of PPh_3/CBr_4 was used. Compound **6** could be obtained in a maximum of 42% yield when the quantity of PPh_3/CBr_4 was increased to 4 equiv.

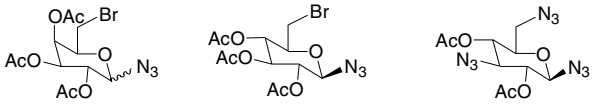
These conditions (4 equiv PPh_3/CBr_4 per monosaccharide unit) were applied to our substrates, and the results are summarized in Table 2.

Table 2. Saccharides obtained with 4 equiv PPh_3/CBr_4 and 20 equiv NaN_3 per monosaccharide unit

Entry	Substrates	Products		Ratio α/β	Yield (%)
1	 D-Man		**6**[15]	1/1	42
2	 D-Glc		**7**[22]	1/3	39
3	 D-Gal		**8**	Pure β	20
4	 Maltose		**9**	1/3	49
5	 Maltotriose		**10**	1/3	26
6	 Lactose		**11**	Pure β	13

All substrates gave substituted derivatives containing azides at both anomeric and primary positions. With the exception of mannose, the β anomers of glycosyl azides are preferentially or exclusively formed. In the case of lactose, increasing the molar ratio of PPh_3/CBr_4 allowed us to isolate compound **11** as a single isomer in a low yield of 13% (Table 2, entry 6). On the other hand, the corresponding derivative from maltose (compound **9**) was obtained in 49% yield. The differences observed on the reactivity and selectivity between lactose and maltose indicate the importance of the spatial presentation of the hydroxyl groups.

Isolation and characterization of side-products gave some indications on the reaction mechanism. From the reaction mixtures with glucose and galactose, 6-bromoglycosyl azides **12** and **13**, respectively, were identified (Scheme 2). A stepwise control of the reaction by mass spectrometry confirmed that initial bromation occurred, according to the standard mechanism when using PPh_3/CBr_4[16] and other known methods of sugar halogenation.[17]



12 19% from Gal alpha/beta ratio (1/9) **13** 12% from Glc **14** 11% from Glc

Scheme 2. The isolation of side-products.

Interestingly, the mass spectrum of the isolated minor compound **14** (Scheme 2) indicated the presence of three azides. In addition, the ^1H NMR spectrum showed an

important upfield shift for H-3 in compound **14** (ca. 1.6 ppm) compared to H-3 of **7**, confirming the presence of an azide at this position. This compound is as far as we know the first glycopyranose derivative described bearing such a number of azides.

^{13}C NMR and DEPT experiments were particularly helpful to determine the nature of the substituents at the primary position. For any hexopyranose, the C-6 bearing a bromide, an azide or an acetate has a particular chemical shift of 28, 51 and 62 ppm, respectively (Table 3).

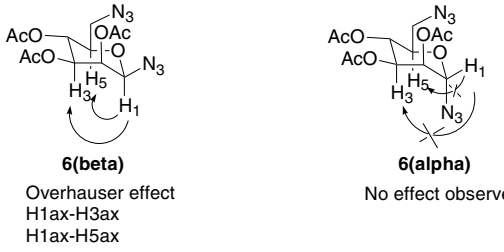
Concerning the anomeric position, compounds containing an azide instead of an acetate show upfield shifts of at least 0.5 ppm for H-1α and 1 ppm for H-1β (e.g., compounds **4** and **9**, Table 3). Anomeric configuration of glycosyl azides was undoubtedly assigned from $^{3}J_{1,2}$ values, except for mannosides **6α** and **6β**. To resolve this problem, we performed a NOE experiment and we observed two Overhauser effects between H1ax–H3ax and H1ax–H5ax for one of the compounds, which was assigned as the β anomer (Scheme 3).[18]

In summary, we have developed a procedure to obtain diverse azidosaccharides from unprotected sugars. We demonstrated the possibility to modulate the number and the position of azido groups on saccharides by varying the number of equivalents of reagents. Despite the moderate yields obtained, this reaction is particularly valuable for the direct and regioselective synthesis of polyazido-sugars, previously obtained in multi-step synthesis. Azidosugars described herein could also represent interesting substrates for the synthesis of new aminoglycosides and glycoconjugates. We have already employed this methodology with success for the synthesis of multivalent ligands and this will be reported in due course.

General procedure for the synthesis of azido compounds: The starting free carbohydrate (1.38 mmol of monosaccharide unit) and sodium azide (451 or 902 mg, 13.9 or 27.7 mmol) are dissolved in anhyd DMF (8 mL) at rt PPh_3 (0.728 or 1.455 g, 2.77 or 5.55 mmol) is added to the mixture and after 30 s of stirring, CBr_4 (0.920 or 1.84 g, 2.77 or 5.55 mmol) dissolved in anhyd DMF (2 or 4 mL) is added. The resulting mixture is stirred at rt for 60 h under nitrogen. Methanol (5 mL) is added and the solution is filtered. After evaporation under reduced pressure, H_2O (20 mL) and toluene (20 mL) are added. The mixture is vigorously stirred and ethyl acetate is added dropwise until it becomes clear. The organic layer is extracted with water (3×20 mL). Aqueous layers are combined and the solution is evaporated under vacuum. The dry residue is dissolved in pyridine/acetic anhydride (50 mL, 1/1). After 12 h at rt the solvent is removed under reduced pressure and the residue is dissolved in ethyl acetate (20 mL). The organic layer is washed with water (20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (cyclohexane/ethyl acetate or toluene/diethyl ether) leading to azido compounds.

Table 3. Significant ^{13}C NMR chemical shifts for compounds **4**–**14**

Compound	Anomeric *C*	*C*-6
4	88.9 (α), 91.4 (β)	50.7, 50.8, 51.0 (α, β)
5	88.8 (α), 91.2 (β)	50.8 (α, β)
6	87.5 (α), 85.1 (β)	50.9 (α), 51.1 (β)
7	86.2 (α) 88.0 (β)	51.1 (α), 51.3 (β)
8	88.7 (β)	50.8 (β)
9	86.2 (α), 87.5 (β)	50.8 (α), 50.9 (β)
10	86.4 (α), 87.5 (β)	51.1, 51.2 (α), 50.9, 51.0 (β)
11	87.7 (β)	50.1, 50.6
12	86.9 (α), 87.5 (β)	27.9 (α), 27.4 (β)
13	87.8 (β)	30.2 (β)
14	88.0 (β)	51.1 (β)



Scheme 3. NOE experiment for the determination of compound **6**.

Acknowledgements

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18. All new compounds were characterized by spectroscopical methods. Analytical data for compound **6**:
6-Azido-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-mannopyranosyl azide (**6α**): $[\alpha]_D^{23}$ −39 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.39$ (d, 1H, $J_{1,2}$ 1.9 Hz, *H*-1), 5.31–5.19 (m, 2H, *H*-3, *H*-4), 5.12 (dd, 1H, $J_{2,3}$ 2.9 Hz, *H*-2), 4.09 (ddd, 1H, *H*-5), 3.34 (m, 2H, 2*H*-6), 2.14, 2.04, 1.97 (three s, 9H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 169.9, 169.7 (3*C*O), 87.5 (*C*-1), 72.0 (*C*-5), 69.2 (*C*-2), 68.1 (*C*-3), 66.5 (*C*-4), 50.9 (*C*-6), 20.8, 20.7, 20.4 (3*C*H$_3$). HRMS (ES+): Found: 379.0979. $C_{12}H_{16}N_6O_7Na$ requires 379.0978 [M+Na$^+$].
6-Azido-6-deoxy-2,3,4-tri-*O*-acetyl-β-D-mannopyranosyl azide (**6β**): $[\alpha]_D^{23}$ −9 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.44$ (d, 1H, $J_{1,2}$ 1.1 Hz, $J_{2,3}$ 3.2 Hz, *H*-2), 5.21 (t, 1H, $J_{3,4}$ 9.4 Hz, *H*-4), 5.03 (dd, 1H, *H*-3), 4.75 (d, 1H, *H*-1), 3.74 (ddd, 1H, *H*-5), 3.44 (dd, 1H, $J_{5,6}$ 6.4 Hz, $J_{6,6'}$ 12.7 Hz, *H*-6), 3.40 (dd, 1H, $J_{5,6'}$2.9 Hz, *H*-6′), 2.21, 2.05, 1.98 (three s, 9H, 3CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 169.7 (3*C*O), 85.1 (*C*-1), 76.5 (*C*-5), 70.9 (*C*-3), 69.3 (*C*-2), 66.5 (*C*-4), 51.1 (*C*-6), 20.8, 20.6 (3*C*H$_3$); HRMS (ES+): Found: 379.0974. $C_{12}H_{16}N_6O_7Na$ requires 379.0978 [M+Na$^+$].
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