ELSEVIER

Carbohydrate Research 303 (1997) 367–372

CARBOHYDRATE RESEARCH

Note

# A mild one-step selective conversion of primary hydroxyl groups into azides in mono- and oligo-saccharides

José Luis Jiménez Blanco [a], José Manuel García Fernández [a,*], Andrée Gadelle [b], Jacques Defaye [b,*]

[a] *CSIC and Universidad de Sevilla, Instituto de Investigaciones Químicas, Américo Vespucio s / n, Isla de la Cartuja, E-41092 Sevilla, Spain*

[b] *CNRS and Université Joseph Fourier-Grenoble I, Département de Pharmacochimie Moléculaire / Glucides, BP 138, F-38243 Meylan, France*

Received 27 March 1997; accepted 3 June 1997

**Abstract**

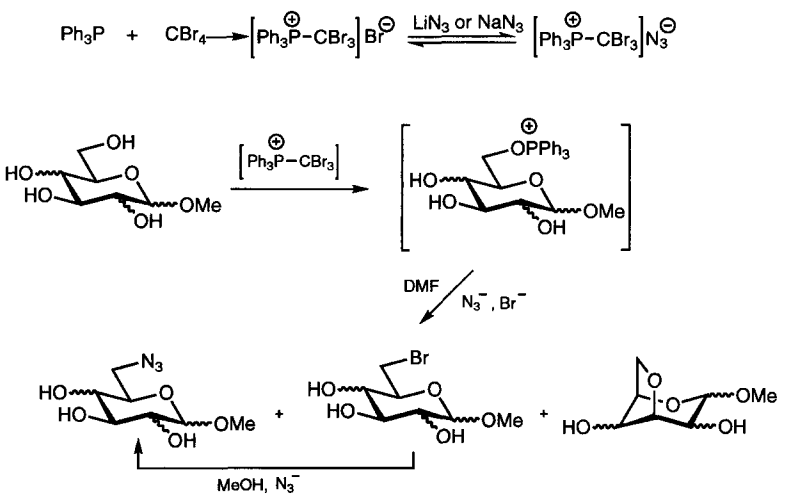
The direct azidation reaction of several monosaccharide methyl glycopyranosides, sucrose, $\alpha,\alpha$-trehalose, cyclomaltohexaose and cyclomaltoheptaose with sodium azide in the presence of triphenylphosphine–carbon tetrabromide is reported. The optimal reaction conditions require pre-formation of the reactive species before addition of the sugar substrate. Formation of the primary azidodeoxy compound is accompanied by simultaneous formation of the corresponding primary bromodeoxy and 3,6-anhydro derivatives in the glycopyranoside series, the former being transformed in situ into the azide by quenching of the reaction mixture with methanol before increasing the temperature. Interestingly, good selectivity towards the primary C-6 position of the glucopyranosyl moiety as compared to the fructofuranosyl one was observed in the case of sucrose, advantage of which has been taken in an improved preparation of 2,3,4,1′,3′,4′,6′-hepta-*O*-acetyl-6-azido-6-deoxysucrose (45% yield from sucrose). Sodium or lithium azide reagents were found equally effective. The azide functionality could be reduced without previous purification and the resulting amino sugar isolated by cation-exchange column chromatography, as illustrated for the preparation of $6^{I}$-amino-$6^{I}$-deoxycyclomaltoheptaose. © 1997 Elsevier Science Ltd.

*Keywords:* Sugar azides; Sucrose; $\alpha,\alpha$-Trehalose; Cyclodextrins; Amino sugars

Direct selective replacement of primary hydroxyl groups by azide in unprotected non-reducing carbohydrates derivatives was first reported by Hata et al. [1] in the nucleoside series by using the carbon tetrabromide–triphenylphosphine–lithium azide reagent system in dry *N*,*N*-dimethylformamide. The methodology has been further extended to the total as well as partial functionalization of the primary hydroxyl rim in cyclodextrins [2,3], and quite recently

* Corresponding authors.


*PII* S0008-6215(97)00176-6



Scheme 1.

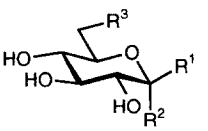
Table 1
Products formed by the action of the triphenylphosphine–carbon tetrabromide–metal azide system (1.1:1.1:5 mol/equiv ratio) [a] on non-reducing carbohydrates

| Entry | Substrate | Reaction conditions [b] | Reaction products (%) [c] | | | Residual starting material |
|---|---|---|---|---|---|---|
| | | | 6-azido-6-deoxy | 6-bromo-6-deoxy | 3,6-anhydro | |
| 1 | **1** | A ($NaN_3$) | **2** (51) [7–9] | **3** (44) [10,11] | | **1** (5) |
| 2 | **1** | A ($LiN_3$) | **2** (53) | **3** (45) | | **1** (2) |
| 3 | **4** | A ($NaN_3$) | **5** (18) [7] | **6** (27) [11] | | **4** (55) |
| 4 | **4** | A ($LiN_3$) | **5** (16) | **6** (29) | | **4** (55) |
| 5 | **7** | A ($NaN_3$) | **8** (38) [7,8,12] | **9** (44) [11] | **10** (13) [13] | **7** (5) |
| 6 | **7** | A ($LiN_3$) | **8** (23) | **9** (48) | **10** (12) | **7** (18) |
| 7 | **11** | A ($NaN_3$) | **12** (4) [7,8,12] | | **13** (21) [13] | **11** (75) |
| 8 | **11** | A ($LiN_3$) | **12** (8) | | **13** (8) | **11** (86) |
| 9 | **14** | A ($NaN_3$) | | | **15** (8) [13] | **14** (92) |
| 10 | **14** | A ($LiN_3$) | | | **15** (8) | **14** (92) |
| 11 | **1** | C ($NaN_3$) | **2** (96) (93) [e] | | | **1** (4) |
| 12 | **4** | C ($NaN_3$) | **5** (39) (33) [e] | | | **4** (61) |
| 13 | **7** | C ($NaN_3$) | **8** (85) (83) [e] | | **10** (11) (9) [e] | **7** (9) |
| 14 | **11** | C ($NaN_3$) | **12** (6) [e] | | **13** (16) (14) [e] | **11** (74) |
| 15 | **14** | C ($NaN_3$) | | | **15** (17) (14) [e] | **14** (83) |
| 16 | **16** | C ($NaN_3$) [d] | **17** (51) (45) [e] [14]<br>**19** (10) (6) [e] [6,15] | | | **16** (39) |
| 17 | **16** | C ($NaN_3$) | **17** (40) (36) [e]<br>**19** (35) (30) [e] | | | **16** (25) |
| 18 | **20** | C ($NaN_3$) | **21** (13) [e] [6,8,16] | | | |
| 19 | **22** | B ($NaN_3$) | **23** (22) [e] [2,6] | | | |
| 20 | **24** | B ($NaN_3$) | **25** (53) [e] [2,6,14] | | | |
| 21 | **22** | B ($NaN_3$) [d] | **26** (17) [e] [3,17,18] | | | |
| 22 | **24** | B ($NaN_3$) [d] | **27** (15) [e] [3,17,18] | | | |

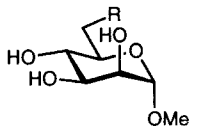
[a] Except when otherwise stated, the mol/equiv ratio for di- and oligo-saccharide substrates refers to primary hydroxyl groups.
[b] See Experimental, procedures A, B, and C.
[c] Assessed by $^{13}C$ NMR spectroscopy, using the intensities of the signals for C-6 atoms.
[d] A 1:1.1:1.1:5 sugar substrate–triphenylphosphine–carbon tetrabromide–sodium azide molar ratio was used.
[e] Isolated yields.

to polysaccharides [4]. Excellent primary versus secondary hydroxyl group selectivities were obtained in every case. However, the reaction seems to be highly sensitive to structural changes in the substrate. Thus, the yields in the synthesis of 5′-azido-5′-deoxy-β-D-ribonucleosides ranged from 92% using uridine as substrate to complete absence of reaction with $N^2$-benzoylguanosine [1], whereas hexakis(6-azido-6-deoxy)cyclomaltohexaose and heptakis(6-azido-6-deoxy)cyclomaltoheptaose were obtained in 25 and 56% yields, respectively [2]. In order to gain a deeper insight into the scope and limitations of this approach, and in connection with our continuing interest in primary aminodeoxy sugars as synthetic intermediates [5,6], we have re-examined the foregoing transformation for a variety of non-reducing saccharide substrates.

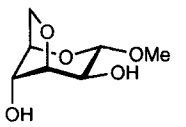
The mechanism for the primary hydroxyl group → azide exchange is believed to involve a phosphonium salt intermediate which further undergoes nucleophilic displacement by the azide anion [1]. However, the presence of other nucleophiles in the reaction medium, such as the bromide anion and secondary hydroxyl groups from the carbohydrate substrate, may result in competitive side reactions, as shown in the methyl aldohexopyranoside series (Scheme 1). Thus, a 1:1.1:1.1 substrate–carbon tetrabromide–triphenylphosphine molar equivalent ratio and a large excess of lithium azide resulted in a mixture of starting material, 6-azido-6-deoxy, 6-bromo-6-deoxy, and 3,6-anhydro derivatives, their relative proportions being dependent upon the sugar substrate. Moreover, some dispersion of results was observed within a series of repeated experiments. Better reproducibility was achieved by pre-formation of the phosphonium salt species at 0 °C before addition of the glycoside. Interestingly, using this protocol, the cheaper sodium azide reagent was just as effective as lithium azide (Table 1, entries 1–10).



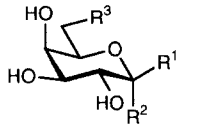
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 1 | H | OMe | OH |
| 2 | H | OMe | $N_3$ |
| 3 | H | OMe | Br |
| 4 | OMe | H | OH |
| 5 | OMe | H | $N_3$ |
| 6 | OMe | H | Br |



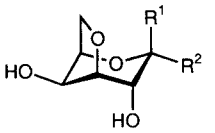
**7** R = OH
**8** R = $N_3$
**9** R = Br



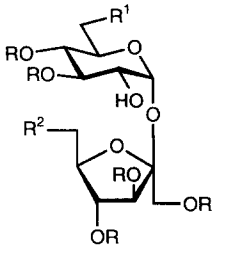
**10**



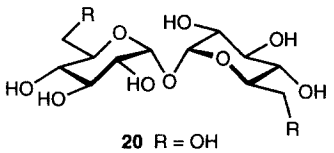
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **11** | H | OMe | OH |
| **12** | H | OMe | $N_3$ |
| **14** | OMe | H | OH |



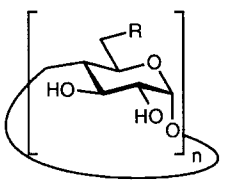
| | $R^1$ | $R^2$ |
|---|---|---|
| **13** | H | OMe |
| **15** | OMe | H |



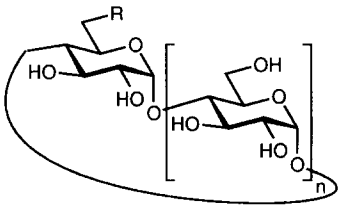
| | R | $R^1$ | $R^2$ |
|---|---|---|---|
| **16** | H | OH | OH |
| **17** | H | $N_3$ | OH |
| **18** | Ac | $N_3$ | OAc |
| **19** | H | $N_3$ | $N_3$ |



**20** R = OH
**21** R = $N_3$



| | n | R |
|---|---|---|
| **22** | 6 | OH |
| **23** | 6 | $N_3$ |
| **24** | 7 | OH |
| **25** | 7 | $N_3$ |



| | n | R |
|---|---|---|
| **26** | 5 | $N_3$ |
| **27** | 6 | $N_3$ |
| **28** | 6 | $NH_2$ |

Attempts at improving the yield in the azidodeoxy derivative by changes in the reagents ratio were unsuccessful, whereas longer reaction times or higher temperatures resulted in the formation of several by-products, including dibromo derivatives, as seen from the FAB mass spectra of the crude reaction mixture. Nevertheless, the 6-bromo-6-deoxy glycoside could be converted in situ into the corresponding azide by quenching the reaction mixture with an

excess of methanol before increasing the temperature (Scheme 1). By using this procedure, almost quantitative yields of the 6-azido-6-deoxy aldohexopyranosides **2** and **8** were obtained from the corresponding α-D-*gluco* and α-D-*manno* glycopyranosides **1** and **7**, respectively. In contrast, methyl β-D-glucopyranoside reacted to only a limited extent under the same conditions, affording **5** in low yield, and methyl α- and β-D-galactopyranosides were almost unreactive, the main reaction products being the 3,6-anhydro compounds **13** and **15**, respectively (Table 1, entries 11–15).

The strong dependence of the outcome of the reaction upon small structural changes in the sugar template suggest that this azidation system could be appropriate for the regioselective functionalization of non-reducing oligosaccharides containing various primary hydroxyl groups. Thus, conditions were found to prepare 6-azido-6-deoxysucrose (**17**) in 45% yield after purification as its known heptaacetate **18** (Table 1, entry 16). It may be noted that the previous synthesis of **18**, a starting material for the preparation of 6-amino derivatives of sucrose [14], requires five steps from sucrose. A synthesis of the heptabenzoate of **17** in four steps has also been reported [19].

No selectivity was, however, observed for symmetrical glucooligosaccharides using identical reaction conditions. Thus, α,α-trehalose (**20**) afforded 13% of the corresponding primary diazide **21**, the non-symmetrical monoazide being not isolated in pure form. Results concerning the direct preparation of hexakis(6-azido-6-deoxy)cyclomaltohexaose (**23**) and heptakis(6-azido-6-deoxy)cyclomaltoheptaose (**25**) as well as the corresponding $6^I$-azido-$6^I$-deoxy derivatives (**26** and **27**, respectively) from the corresponding fully unprotected cyclodextrins almost matched those previously reported using lithium azide (Table 1, entries 17–22). Nevertheless, it must be stressed that the more common two-step methodology involving the nucleophilic displacement of $6^I$-deoxyhalo or $6^I$-sulfonyloxy leaving groups is still more efficient for the preparation of the respective azidodeoxy cyclodextrins [6,20–22].

Purification of sugar azides was generally achieved after acetylation of the reaction mixture. Alternatively, the azido group could be reduced and the resulting amino sugar purified by cation-exchange column chromatography as illustrated by the preparation of $6^I$-amino-$6^I$-deoxycyclomaltoheptaose (**28**), which allows an easy separation from polysubstituted derivatives.

In conclusion, we have shown that sodium azide can replace the lithium salt in the direct substitution of primary hydroxyl groups of non-reducing carbohydrates by azide with triphenylphosphine–carbon tetrabromide–metal azide, without loss in yield and selectivity, by pre-formation of the phosphonium reactive species. Advantage may be taken of the observed structural dependence of the reaction for the selective functionalisation of substrates bearing several non-equivalent primary hydroxyl groups.

## 1. Experimental

*General methods.*—The composition of the reaction mixtures was assessed by $^{13}C$ NMR spectroscopy for solns in $D_2O$ using Bruker AC 200 and AMX 500 instruments (50.3 and 125.7 MHz, respectively) and an antigate pulse sequence. Flash and column chromatography were carried out on Silica Gel 60 (E. Merck, 230–400 mesh). LC of **28** was carried out with a Perkin–Elmer chromatograph, fitted with a LC 30 refractometric detector, a 10205 integrator, and a LiChrosorb $NH_2$ (7 mμ, 250 × 4.6 mm) column (3:22 MeOH–$H_2O$).

*General procedure for the preparation of sugar azides.*—Typically, a 1:1.1:1.1:5 sugar substrate–triphenylphosphine–$CBr_4$–$LiN_3$ or $NaN_3$ mol/equiv ratio was used. To the stirred mixture of triphenylphosphine and metal azide (see Table 1) in DMF (5 mL) at 0 °C, a soln of $CBr_4$ in DMF (5 mL) was dropwise added while avoiding initial heating. After 30 min, the sugar (0.5 g) was added portionwise and the resulting mixture was further stirred at room temperature for 24 h and processed using one of the following procedures A–C.

*Procedure A*: The reaction was quenched by addition of MeOH (10 mL), concd, and the residue was suspended in water (50 mL). Residual triphenylphosphine and triphenylphosphine oxide were then filtered off and the filtrate was washed with toluene (2 × 20 mL), demineralised by treatment with Amberlite® MB-6113 mixed ($H^+$, $OH^-$) ion-exchange resin (20 mL) and freeze-dried.

*Procedure B*: After addition of MeOH (10 mL), the soln was demineralised as above and concd. The residue was suspended in acetone (50 mL) and the solid was separated by filtration, washed with acetone and dried.

*Procedure C*: The quenched reaction mixture (MeOH, 100 mL) was heated at 120 °C overnight before being processed as in A.

The reaction mixtures arising from the treatment of **1**, **4**, **7**, **11**, **14**, **16**, **20**, **22**, and **24** with triphenylphosphine–$CBr_4$–$NaN_3$ (Table 1, entries 1–20) were peracetylated (1:1 $Ac_2O$–pyridine, 10 mL for 1 g of sample) and subjected to column chromatography using hexanes–EtOAc in different relative proportions (Table 1, entries 11–18) or 16:1 benzene–EtOH (Table 1, entries 19 and 20) as eluents. Compounds **26** and **27** (Table 1, entries 21 and 22, respectively) were purified, without previous derivatization, by column chromatography (9:1 → 4:1 and 9:1 MeCN–$H_2O$, respectively) as reported previously [3].

*2, 3, 4, 1′, 3′, 4′, 6′ - Hepta - O - acetyl - 6 - azido - 6 - deoxysucrose* (**18**).—The reaction mixture arising from the treatment of sucrose (**16**, 0.5 g, 1.46 mmol) with the triphenylphosphine–$CBr_4$–$NaN_3$ system as just indicated (procedure C, Table 1, entry 16) was acetylated (1:1 $Ac_2O$–pyridine, 5 mL, overnight). The peracetylated product, which showed three spots on TLC (2:3 EtOAc–hexanes, two elutions) was subjected to flash chromatography with the same eluent to give, sequentially, 2,3,4,1′,3′,4′-hexa-*O*-acetyl-6.6′-diazido-6,6′-dideoxysucrose (**19**, 0.06 g, 6%) [15], **18** (0.42 g, 45%), and sucrose octaacetate (0.25 g, 26%). Compound **18** had $[\alpha]_D^{20}$ +74.0° (*c* 1, $CHCl_3$), lit. $[\alpha]_D^{25}$ +76.1° (*c* 1, $CHCl_3$) [14]; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): δ 170.1, 169.7, 169.6 (2 C), 169.5, 169.2, 169.1 (6 C=O), 103.9 (C-2′), 89.6 (C-1), 79.0.75.7, 74.4 (C-3′ to C-5′), 70.1, 69.4, 69.2, 69.0 (C-2 to C-5), 63.2, 62.5 (C-1′, C-6′), 50.5 (C-6), 20.6, 20.3 and 20.2 (6 Ac).

*6′-Amino-6′-deoxycyclomaltoheptaose hydrochloride* (**28**).—The reaction mixture arising from the treatment of dried cyclomaltoheptaose (**24**, 2.85 g, 2.51 mmol) in DMF (20 mL) with triphenylphosphine (1.5 g, 5.72 mmol), $NaN_3$ (0.43 g, 6.63 mmol) and $CBr_4$ (2.20 g, 6.63 mmol), as already indicated in procedure C, was dissolved in DMF (20 mL) and a soln of triphenylphosphine (2.61 g, 8.77 mmol) in DMF (20 mL) was dropwise added. The reaction mixture was kept at room temperature for 1 h, then cooled at 0 °C and $NH_4OH$ (30%, 3 mL) was added. The soln was stirred at room temperature overnight, concd, the residue was suspended in acetone (250 mL) and the resulting solid collected by filtration. Cation-exchange column chromatography (Bio-Rad® AG 50W-X8 resin, 50–100 mesh, $H^+$ form, eluent water to 0.25 M aq NaCl) afforded **27** (0.43 g, 15%): mp 201 °C dec, lit. 201 °C [23]; $[\alpha]_D$ +86° (*c*, 0.5), lit. $[\alpha]_D$ +86.4° [22]; $^1H$ and $^{13}C$ NMR in agreement with data in ref. [22]. Its purity was further confirmed by analytical RPLC ($t_R$ 30 min).

## Acknowledgements

J.L.J.B. thanks the Junta de Andalucia (Sevilla, Spain) for a doctoral fellowship. J.M.G.F. thanks the Centre National de la Recherche Scientifique (Paris) for a research associate position. This work was supported by the European Commission DG12 under the FAIR programme contract no. FAIR-CT95-0300.

## References

[1] T. Hata, I. Yamamoto, and M. Sekine, *Chem. Lett.*, (1975) 977–980.
[2] J. Boger, R.J. Corcoran, and J.-M. Lehn, *Helv. Chim. Acta*, 61 (1978) 2190–2218.
[3] S. Hanessian, A. Benalil, and C. Laferrière, *J. Org. Chem.*, 60 (1995) 4786–4797.
[4] A.L. Cimecioglu, D.H. Ball, S.H. Huang, and D.L. Kaplan, *Macromolecules*, 30 (1997) 155–156.
[5] J.M. García Fernández, C. Ortiz Mellet, S. Maciejewski, and J. Defaye, *J. Chem. Soc., Chem. Commun.*, (1996) 2147–2148.
[6] J.M. García Fernández, C. Ortiz Mellet, J.L. Jiménez Blanco, J. Fuentes Mota, A. Gadelle, A. Coste-Sarguet, and J. Defaye, *Carbohydr. Res.*, 268 (1995) 57–71.
[7] J.M. García Fernández, C. Ortiz Mellet, and J. Fuentes, *J. Org. Chem.*, 58 (1993) 5192–5199.
[8] B. Castro, Y. Chapleur, and B. Gross, *Bull. Soc. Chim. Fr.*, (1973) 3034–3039.
[9] B. Castro, Y. Chapleur, and B. Gross, *Tetrahedron Lett.*, 49 (1972) 5001–5004.
[10] A.K.M. Anisuzzaman and R.L. Whistler, *Carbohydr. Res.*, 61 (1978) 511–518.
[11] J.E.G. Barnett, *Adv. Carbohydr. Chem.*, 22 (1967) 177–227.
[12] K. Tsujihara, H. Kurita, and M. Kawazu, *Bull. Chem. Soc. Jpn.*, 40 (1977) 1567–1571.
[13] E.S. Stevens, *Carbohydr. Res.*, 244 (1993) 191–195.
[14] T. Suami, T. Kato, K. Kanai, S. Ohki, and H. Yamashita, *J. Carbohydr. Chem.*, 3 (1984) 417–427.
[15] R. Khan, C.L. Bhardwaj, K.S. Mufti, and M.R. Jenner, *Carbohydr. Res.*, 78 (1980) 185–189.
[16] G. Birch and A.C. Richardson, *Carbohydr. Res.*, 8 (1968) 411–415.
[17] L.D. Melton and K.N. Slessor, *Carbohydr. Res.*, 18 (1971) 29–37.
[18] S.E. Brown, J.H. Coates, D.R. Coghlan, C.J. Easton, S.J. van Eyk, W. Janowski, A. Lepore, S.F. Linclon, Y. Luo, B.L. May, D.S. Schiesser, P. Wang, and M.L. Williams, *Aust. J. Chem.*, 46 (1993) 953–958.

[19] L. Hough and K.S. Mufti, *Carbohydr. Res.*, 25 (1972) 497–503.
[20] Z. Szurmai, A. Liptak, and J. Szejtli, *Stärke*, 42 (1990) 447–449.
[21] A. Kasselouri, M. Munoz, H. Parrot-Lopez, and W. Coleman, *Pol. J. Chem.*, 67 (1993) 1981–1985.
[22] R.C. Petter, C.T. Salek, G. Sikorski, G. Kumaravel, and F.-T. Lin, *J. Am. Chem. Soc.*, 112 (1990) 3860–3868.
[23] N. Hofman-Bang, *Acta Chem. Scand.*, 11 (1975) 581–582.