Synthesis of Glycosyl Cyanides by the Reaction of 1-S-Phosphorothioates of Carbohydrates with Trimethylsilyl Cyanide

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A new procedure is described for the synthesis of α,β-glycosyl cyanides by the reaction of per-O-benzylated S-α-D-glycopyranosyl phosphorothioates with trimethylsilyl cyanide in the presence of Lewis acid. Starting S-glycosyl phosphorothioates are prepared, directly, from O-benzyl protected reducing D-hexopyranoses (gluco-, galacto-, manno-) and alkylammonium salt of phosphorothioic acid under Lewis acid catalysis.

Introduction

Glycosyl cyanides are versatile, synthetic intermediates for the preparation of compounds of biological and chemical interest, irreversible enzyme-inhibitors and are of interest as chiral synths for many natural products.

Per-O-acetylated glycosyl cyanides have been prepared by the reaction of furanosyl and pyranosyl halides [1 - 4] with metal cyanides, most frequently mercuric cyanide, the reaction of 1-O-acetyl sugars with trimethylsilyl cyanide in the presence of Lewis acids [5, 6], by dehydration of amides of anhydroaldonic acids [7] and reductive dehydration of glycosyl nitromethanes [8]. O-Benzyl protected glycosyl cyanides have been obtained from glycosyl fluorides [9], glycosyl iodides generated in situ from 1-O-acetates [10], and from 1-O-acetyl sugars with trimethylsilyl cyanide [11].

Previously, S-glycosyl phosphorodithioates, having glycosylating properties, have been used in the stereoselective synthesis of O-glycosides [12], N-glycosides [13], oligosaccharides [14, 15] and glycosyl 1-O-esters [16].

We report here new application of 1-S-glycosyl phosphorothioates 5 – 7, stable, odorless and nontoxic reagents, in the synthesis of glycosyl cyanides 8 - 12 under mild conditions and in high yields in the reaction with trimethylsilyl cyanide and Lewis acid catalysis.

Results and Discussion

Recently we have described [17] that, catalysed by boron trifluoride etherate, the reaction of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (2) with the triethylammonium salt of 2-hydroxy-5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane (1) [18] affords per-O-benzylated S-α-glycopyranosyl phosphorothioate 5, stereoselectively. The catalysed phosphorylation of 1-O-unprotected sugars was now extended to 2,3,4,6-tetra-O-benzyl-D-galactopyranose (3) [19, 20] and 2,3,4,6-tetra-O-benzyl-D-mannopyranose (4) [20]. The reaction of 3 with 1 (according to 31P NMR) was accomplished after 24 h, to yield a mixture of three phosphorus containing products [8 31P NMR (ppm): 20.5, 19.25, 17.7 (integration) 1:6.6:0.9] from which product 6 was isolated in 51% yield (δ 31P NMR (ppm): 19.25). Similarly, when 4 was allowed to react with 1 after 24 h, 31P NMR analysis indicated that the crude reaction mixture also consisted of three P-products [8 31P NMR (ppm): 20.5, 19.8, 17.7 (integration) 1:1.7:6.5] from which product 7 is isolated in 38% yield (δ 31P NMR (ppm): 17.7). The α-configuration at the anomeric carbon atom of products 6 and 7 was assigned on the basis of 1H and 13C NMR spectra and of optical rotation values (see experimental).

S-α-Glycopyranosyl phosphorothioates 5 – 7 were reacted with trimethylsilyl cyanide in acetonitrile in the presence of boron trifluoride etherate. The reaction of S-glycosyl phosphorothioate 5 gave a mixture of β- and α-β-glycopyranosyl cyanide 8 [9, 11, 21] in 72% yield. Product 8 was analysed as

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a mixture of anomers because attempts to separate \(\alpha\) from \(\beta\) by PLC failed. The \(\alpha:\beta\) ratio was 3:3.5, as determined by \(^{13}\)C NMR. Similarly, \(S\)-galactosyl phosphorothioate 6 afforded a mixture \(\alpha\)- (9) and \(\beta\)-D-galactopyranosyl cyanide (10) \([11]\) in 28% and 35% yields, respectively. In the case \(S\)-mannosyl phosphorothioate 7 also a mixture of \(\alpha\)- and \(\beta\)-D-mannopyranosyl cyanide 11 and 12, in 54% and 24% yields, was obtained. Both anomic mixtures (\(\alpha\), \(\beta\)-galacto and \(\alpha\), \(\beta\)-manno) were isolated and separated by preparative layer chromatography, and all glycosyl cyanides were characterized by spectroscopic analyses (see experimental). Of the three \(S\)-glycosyl phosphorothioates 5 - 7 examined, galacto derivative 6 proved to be the most reactive towards the silyl reagent and the manno derivative 7 was the least reactive.

Attempts to synthesise of glycosyl cyanides from sugar thiophosphates and cyanide polymer supported (Fluka) catalysed by Lewis acid were unsuccessful.

In conclusion, the acid-catalysed formation of 1-\(S\)-\(\alpha\)-glycosylphosphorothiolate from 1-OH unprotected sugars and alkylammonium salt of \(O\)-\(O\)-dialkylphosphorothioic acid and the subsequent acid catalysed C-glycosidation is reported. This method is applied to the new synthesis of anomic pairs of per-\(O\)-benzylated \(D\)-hexopyranosyl cyanides (2,6-anhydroheptononitriles).

**Experimental**

Melting points were determined with Boetius PHMK 05 apparatus and are uncorrected. Optical rotations were determined with the Polamat A polarimeter. IR spectra were obtained by using the Infinity MI-60 FT-IR spectrometer. \(^1\)H, \(^{13}\)C and \(^{31}\)P NMR were measured in CDCl\(_3\) solutions on a Bruker DPX spectrometer operating at 250.13 MHz, 62.9 MHz and 101.25 MHz, respectively. Elemental analyses were performed by Microanalytical Laboratory of this Institute on a Perkin Elmer PE 2400 CHNS analyzer. Preparative layer chromatography was performed on \(20 \times 20\) cm glass plates coated with 1 mm or 2 mm of silica gel 60 F\(_{254}\) (Merck). Detection was effected by exposure to iodine vapours and UV lamp. Solvents were dried and distilled prior to use. Trimethylsilyl cyanide was purchased from Aldrich.

**Preparation of \(S\)-glycosyl phosphorothioates 6 and 7**

Boron trifluoride etherate (3 mmol) was added to the solution of glycosyl substrates 3 or 4 (1 mmol) and organophosphorous reagent 1 (1 mmol) in 1,2-dichloroethane (25 ml). The course of reaction was monitored by \(^{31}\)P and \(^1\)H NMR spectroscopy. The mixture was kept at ambient temperature for 24 h, washed with satd. NaHCO\(_3\) (3 x 15 ml) and water (15 ml), dried (MgSO\(_4\)), concentrated in vacuo and the products were purified by crystallisation.

2-\(S\)-(2,3,4,6-Tetra-\(O\)-benzyl-\(\alpha\)-D-galactopyranosyl)-2-oxo-5,5-dimethyl-1,3-dioxaphosphorinane (6)

Crystallisation from CCl\(_4\)-hexane gave 6 (0.223 g, 31.7%) m. p. 94-6 °C. Evaporation of mother liquors gave syrup, which crystallised from CCl\(_4\)-hexane gave an additional amount of 6 (0.136 g, 19.3%) m. p. 81-90 °C. Second crystallisation CCl\(_4\)-hexane gave 6 m. p. 100-2 °C; \([\alpha\]\(_{589}\) + 105.6° (c 1.25, CHCl\(_3\)); IR (KBr) \(\nu\) 1285 cm\(^{-1}\) (P=O). \(^{31}\)P NMR (CDCl\(_3\)) \(\delta\): 19.25 ppm; \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 0.77, 1.23 (2s, 6 H, 5,5-diMe), 3.57 - 3.91 (m, 3 H, H-5,6,6), 4.02 (m, 1 H, H-4), 4.12 (dd, 1 H, J\(_{2,3}\) = 10.5 Hz, J\(_{3,4}\) = 5.5 Hz, H-3), 4.34 (dd, 1 H, J\(_{1,2}\) = 5.5 Hz, H-2), 6.24 (dd, 1 H, J\(_{1,3}\) = 8.5 Hz, H-1), 4.0 - 5.0 (m, H-10), 7.28 - 7.35 (m, 2 H, H-2,3).
12 H, 4 × benzyl, 2 × OCH2); 7.26 - 7.4 (m, 20 H, Ph); 13C NMR (CDCl3) δ: 20.3 (d, 4JCp = 1.05 Hz, Meαα), 21.9 (Meαα), 32.2 (d, 3JCp = 6.7 HZ, C(Me2)), 75.7 (d, 3JCp = 6.2 Hz, C-2), 86.1 (d, 2JCp = 2.5 Hz, C-1), 77.4 (d, 2JCp = 7.2 Hz, OCH2), 78.0 (d, 2JCp = 7.2 Hz, OCH2), 68.2 (C-6), 72.2, 72.5, 73.2, 73.5, 74.4, 78.8, 79.1 (C-3, C-4, C-5, C-6, 4 × CH2 (benzyl)), 127.3 - 128.4 (20C, Ph), 137.7, 137.9, 138.4, 138.4 (4C, ipso Ph).

C30H44O5PS (704.75)
Calcd C 66.46 H 6.43 %,
Found C 66.31 H 6.76 %.

2-S-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinan (7)

Crystallisation by trituration with diethyl ether. The solution of 5 (0.354 g, 0.5 mmol), trimethylsilyl cyanide (0.5 ml, 3.74 mmol), boron trifluoride etherate (5 drops) and molecular sieves 4A in acetone (5 ml) was stirred at ambient temperature for 5 h under argon. The reaction mixture was concentrated in vacuo and the residue chromatographed by preparative layer chromatography using hexane-ethyl acetate (3:1) as the eluent. The faster running band (RF = 0.52, lit. [11] RF = 0.52) afforded a solid, which crystallized from ethyl acetate-hexane (3:1) to give 9 (0.095 g, 28.1%) m.p. 85-9 °C (lit. [11] m.p. 85-6 °C); \[\beta\] anomer δ: 3.45 - 3.56 (m, 2 H, H-6',6''), 3.80 (dd, 1 H, J3,4 = 9.75 Hz, H-3, H-4), 3.95 - 4.00 (m, 2 H, H-4, H-5), 4.10 (dd, 1 H, J1,2 = 6.25 Hz, H-2), 4.36 - 4.93 (m, 9 H, H-1, 4 × CH2Ph), 7.25 - 7.35 (m, 20 H, Ph) [lit. [11] \[\beta\] anomer δ: 3.50 (m, 2 H, H-6,6''), 3.81 (dd, 1 H, J3,4 = 9.8 Hz, H-3), 3.95 - 4.16 (m, 2 H, H-4, H-5), 4.10 (dd, 1 H, J1,2 = 6.0 Hz, H-2), 4.68 (d, 1 H, H-1)].

The slower running band (RF = 0.36, lit. [11] RF = 0.36) afforded 10 (0.118 g, 35%) m.p. 85-7 °C (lit. [11] m.p. 84-5 °C); [α]D +13.48° (c 1, CHCl3) [lit. [11] +29.6° (c 1, CDCl3)]; \[\beta\] NMR (CDCl3) δ: 3.45 - 3.56 (m, 2 H, H-6',6''), 3.80 (dd, 1 H, J3,4 = 9.75 Hz, H-3, H-4), 3.95 - 4.00 (m, 2 H, H-4, H-5), 4.10 (dd, 1 H, J1,2 = 6.25 Hz, H-2), 4.36 - 4.93 (m, 9 H, H-1, 4 × CH2Ph), 7.25 - 7.35 (m, 20 H, Ph) [lit. [11] \[\beta\] NMR (CDCl3, 300 MHz) δ: 3.50 (m, 2 H, H-6,6''), 3.81 (dd, 1 H, J3,4 = 9.8 Hz, H-3), 3.95 - 4.16 (m, 2 H, H-4, H-5), 4.10 (dd, 1 H, J1,2 = 6.0 Hz, H-2), 4.68 (d, 1 H, H-1)].

The solution of 6 (0.434 g, 0.61 mmol), trimethylsilyl cyanide (1.2 ml, 0.892 g, 9 mmol), boron trifluoride etherate (5 drops) and molecular sieves 4MS in acetonitrile (6 ml) was stirred at ambient temperature for 0.5 h under argon. The reaction mixture was concentrated in vacuo and the residue chromatographed by preparative layer chromatography using hexane-ethyl acetate (3:1) as the eluent. The faster running band (RF = 0.52, lit. [11] RF = 0.52) afforded a solid, which crystallized from ethyl acetate-hexane (3:1) to give 9 (0.095 g, 28.1%) m.p. 85-9 °C (lit. [11] m.p. 85-6 °C); \[\beta\] anomer δ: 3.45 - 3.56 (m, 2 H, H-6',6''), 3.80 (dd, 1 H, J3,4 = 9.75 Hz, H-3, H-4), 3.95 - 4.00 (m, 2 H, H-4, H-5), 4.10 (dd, 1 H, J1,2 = 6.25 Hz, H-2), 4.36 - 4.93 (m, 9 H, H-1, 4 × CH2Ph), 7.25 - 7.35 (m, 20 H, Ph) [lit. [11] \[\beta\] NMR (CDCl3, 300 MHz) δ: 3.50 (m, 2 H, H-6,6''), 3.81 (dd, 1 H, J3,4 = 9.8 Hz, H-3), 3.95 - 4.16 (m, 2 H, H-4, H-5), 4.10 (dd, 1 H, J1,2 = 6.0 Hz, H-2), 4.68 (d, 1 H, H-1)].

1-Deoxy-2,3,4,6-tetra-O-benzyl-α-L-galactopyranosyl cyanide (11) and 1-deoxy-2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl cyanide (12)
gon. The reaction mixture was concentrated in vacuo and the residue chromatographed by preparative layer chromatography using hexane-ethyl acetate (3:1) as the eluent. The faster running band (RF = 0.48) gave 11 as a syrup (0.07 g, 53.8%); [α]D 78 +36.7° (c 1.0, CHCl3); 1H NMR (CDCl3) δ: 3.68 - 4.16 (m, H-1, H-2, H-3, H-4, H-5, H-6), 4.48 - 4.87 (m, 4xC H2Ph), 7.17 - 7.33 (m, 20 H, 4xCPh). 13C NMR (CDCl3) δ: 65.3, 68.4, 72.7, 72.8, 73.4, 74.7, 75.2, 77.0, 79.8 (C-1), 115.4 (CN), 127.7 - 128.6 (4xCPh), 137.0, 137.7, 137.9, 138.0 (4C, ipso, Ph).

The slower running band (RF = 0.31) gave 12 [10] as syrup (0.31 g, 24%); 1H NMR (CDCl3) δ: 3.41 - 3.48 (m, 1 H), 3.54 (dd, 1 H, J2,3 = 3 Hz, J5,4 = 9.25 Hz, H-3), 3.70 - 3.72 (m, 2 H), 3.92 (t, J = 9.25 Hz, H-4), 4.02 (d, 1 H, J1,2 = 1.75 Hz, H-2), 4.22 (s, 1 H, H-1), 4.52 - 4.65 (m, 6 H), 4.84 (d, 1 H, J = 10.7 Hz), 4.95 (d, 1 H, J = 6.25 Hz), 7.15 - 7.45 (m, 20 H) [lit. [10] 1H NMR (CDCl3, 250 MHz) δ: 3.31 - 3.37 (m, 1 H), 3.45 (dd, 1 H, J2,3 = 9.3 Hz, J3,4 = 2.3 Hz, H-3), 3.61 - 3.63 (m, 2 H), 3.83 (t, 1 H, J = 9.3 Hz, H-4), 3.92 (d, 1 H, J = 2.3 Hz, H-2), 4.12 (s, 1 H, H-1), 4.43 - 4.60 (m, 6 H), 4.76 (d, 1 H, J = 10.8 Hz), 4.83 (d, 1 H, J = 11.5 Hz), 4.90 (d, J = 11.5 Hz), 7.13 - 7.48 (m, 20 H, Ph)].

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