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Photolysis of glycopyranosyl azides C-1 substituted by cyano-, amido-, or tetrazolyl-groups

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Abstract

Photolysis of acetylated 1-cyano-D-glycopyranosyl azides led to the corresponding acetylated 4,5,6,7-tetrahydro-1,3-oxazepines, being isolated in moderate to good yields (34–58%). These ring-expanded compounds were formed by rearrangements involving migration of the endocyclic carbon atom attached to the anomeric centre. This seems to be the preferred reaction pathway, whatever the anomeric configuration (α/β) of the acetylated 1-cyano-D-glycopyranosyl azide used as the substrate. Rearrangement occurred without changing the stereochemistry of the migrating carbon. Photo-rearrangement of D-glycopyranosyl azides having either a carboxamido- or a tetrazolyl-anomeric group gave complex reaction mixtures.

1. Introduction

Glycomimetics,[1] being structurally similar to natural sugars, but generally with a quite different chemical behaviour, may exhibit significant biological properties, as far as sugar-processing enzymes are concerned.[2] This is why the synthesis of glycomimetics is a continuing challenge with possible applications in such important fields as medicine, food-industry, and pest-control. In connection with the well-known properties of azasugars,[1,2] and in continuation of earlier studies showing biological activities by nitrogen-containing, sugar-derived spirobicyclic structures,[3–5] we investigated the photo-, and thermolysis of a series of 1-substituted glycopyranosyl azides, as a route to completely unknown structures. Moreover, at the outset of this research, it was hoped that highly stereocontrolled transformations might be achieved. While photolysis of glycopyranosyl azides[6] has been shown to give products resulting from

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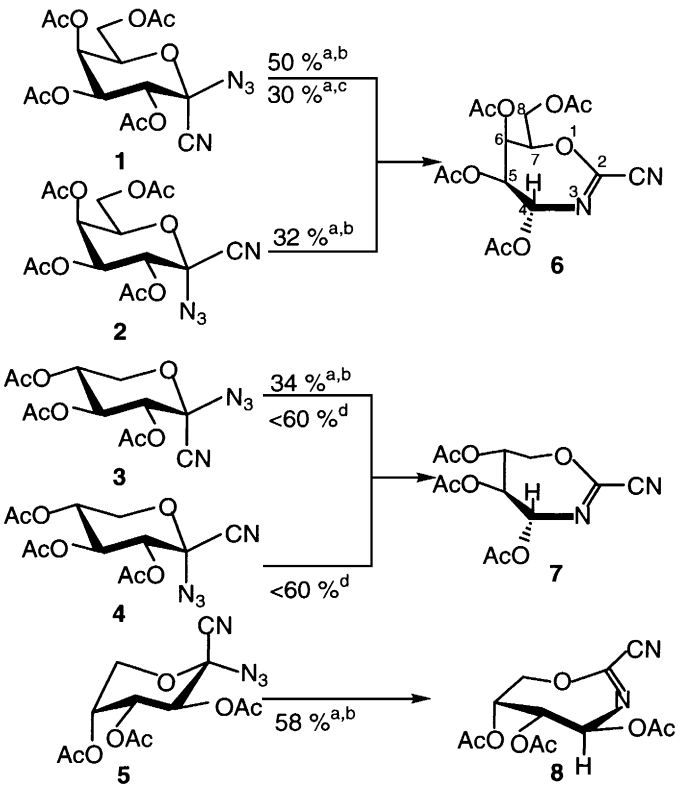
migration of the anomeric hydrogen atom to the intermediate nitrene (or nitrenoide), migration of other groups occurs for C-1 substituted glycosyl azides, having no hydrogen atom at the anomeric centre. In particular, oxygen migration was observed for the first time with 2,3,4,6-tetra-*O*-acetyl-1-methoxy-D-glucopyranosyl azides.[7] Moreover, migration of the endocyclic oxygen atom was predominant for the 1-methoxy-α-D-glucopyranosyl azide, while migration of the methoxy group and of the C-2 carbon atom were the preferred rearrangement pathways occurring in 1-methoxy-β-D-glucopyranosyl azide.[7] With the first substrate, the seven-membered ring-expanded structure obtained as the major product was shown to be stable, even after deacetylation. In contrast to the above-mentioned observations, we could demonstrate that neither photo-induced rearrangement of D-fructopyranosyl azides[8] nor thermolysis of 5-thio-D-xylopyranosyl azides[9] occurred in a stereocontrolled way. Interestingly these rearrangements differ markedly from each other, involving preferential migrations of the endocyclic alkyl-, and thiyl-residues, respectively. Glycopyranosylidene diazides were also found to rearrange upon photolysis to produce mainly ring-expanded products by migration of the endocyclic carbon atom.[10,11] Preliminary experiments with 1-cyano-glycopyranosyl azides[12] also showed that migration of the endocyclic carbon residue was the preferred rearrangement pathway. Since this called for a closer investigation, and since bioactivities have been reported for seven-membered polyhydroxylated structures,[13–15] other substrates were considered and our complete results are disclosed in the present paper.

2. Results and discussion

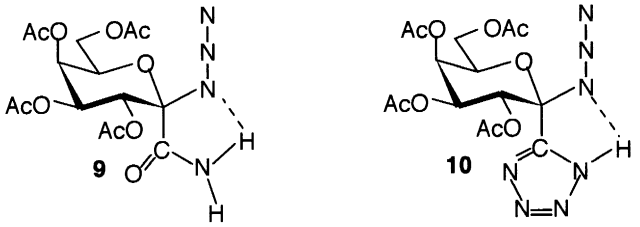
Our preliminary report[12] described the isolation of ring-expanded structures of the tetrahydrooxazepine type (**6**, **8**), produced in 50–58% yield by UV-light irradiation of 2,3,4,6-tetra-*O*-acetyl-1-cyano-β-D-galactopyranosyl azide **1** and 2,3,4-tri-*O*-acetyl-1-cyano-α-D-arabinopyranosyl azide **5**. The structure of **8** was unambiguously established by X-ray crystal structure analysis, which conclusively showed that migration of the endocyclic carbon atom occurred without changing its stereochemistry, as already noted.[8–10] When these investigations were extended to other 1-cyano-glycopyranosyl azides,[12,16] the same stable products could be isolated from either of the precursors, showing that their anomeric configuration had no decisive influence on the structure of the products, although changing yields (Scheme 1) were observed (**6**: 50 and 32% yield by photolysis of **1** and **2**, respectively; 30% yield by thermolysis of **1**). The ring expanded product **7** was isolated in a 34% yield from **3**. Its formation as a major photoproduct from the poorly accessible[16] 1-cyano-α-D-xylopyranosyl azide **4** was proved by NMR analysis of a crude reaction mixture. In related studies, we observed that products formed by migration of the endocyclic oxygen were stable either in the protected or deprotected form.[7,10] None of the expected similar products could be detected in the present study. It is hypothesized that the minor and more polar products visible under UV light on TLC plates could be produced by migration of the cyano group. The so produced *N*-cyano-glycono-iminolactones should be UV active due to the conjugated unsaturated system present. Their instability is expected, taking into consideration the lability observed earlier for related *N*-substituted glyconoimines.[8,17]

The photolyses of carboxamido- and tetrazolyl-azido[16] sugars **9** and **10** led to complex reaction mixtures from which no well-defined product could be isolated in spite of repeated attempts. For the tetrazolyl derivative, the known photosensivity of the tetrazolyl ring[18] may explain the unselective transformations observed. This also might be due to a possible hydrogen bond[19] between the azido group and the tetrazolyl ring in **10**. The existence of a similar hydrogen bond between the azido group and the NH in the carboxamide moiety in **9** was demonstrated both in solution[19] and in the solid state.[20] Such a hydrogen bond may influence the photodecomposition pathways.



[a] isolated yield; [b] photolysis; [c] thermolysis; [d] determined by ^{1}H NMR.

Scheme 1. Photo- and thermo-induced decomposition of 1-cyano-glycosyl azides **1**–**5**



From all the gathered observations gained from the photo- and thermolysis of 1-cyano glycopyranosyl azides investigated, it can be concluded that they undergo photo-induced rearrangements with preferred migration of the endocyclic carbon atom as observed for related cyclic (D-fructopyranosyl azides[8] and D-glucopyranosylidene diazides[10,11]) and acyclic azidoethers.[21] Similar rearrangements of glycosyl azides in the presence of tin(IV) chloride have been reported.[22] For 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl azides,[9] in spite of the presence of an anomeric hydrogen atom, thermally induced rearrangement of the intermediate species involves migration of the ring sulfur atom, in analogy with the thermal reactivity of acyclic azidothioethers.[23] We could not find any evidence suggesting that rearrangements of 1-substituted glycosyl azides of the cyclic azido ether and azidothioether categories depend upon the anomeric configuration of the substrates whose behaviour paralleled that of acyclic models. Only 1-methoxy-D-glycopyranosyl azides,[7] which are cyclic azidoacetals, undergo stereocontrolled rearrangements as a consequence of stereoelectronic effects controlled by the configuration of the anomeric centre.

3. Experimental

3.1. Photolysis: typical procedure

A solution of 2,3,4,6-tetra-*O*-acetyl-1-cyano-β-D-galactopyranosyl azide **1** (109 mg, 0.274 mmol) in dry benzene (7 mL) was introduced in a quartz tube (external diameter 13 mm), placed at a close distance (~1 cm) from a medium pressure mercury lamp (Hanovia, 450 W), used without any filter. Monitoring by TLC showed that **1** (R_f 0.65 in ethyl acetate:*n*-hexane 4:6) was converted into two products (R_f 0.54 and 0.32), the more polar one being well visible on the TLC plates under UV light. Irradiation was applied for ~5 h (temperature of the reaction mixture ~35°C). After evaporation of benzene under reduced pressure, the residue was applied to a column of silica gel irrigated with ethyl acetate:*n*-hexane 4:6, to yield **6** (50.9 mg, 0.137 mmol, 50%). The other compound could not be recovered from the column.

Photolyses of **2**, **3**, **5**, **9**, and **10** were carried out following the above-mentioned typical procedure, with, in the case of **3** and **5**, a slight modification. When the photo-induced rearrangement of these substrates (65 mg, 0.2 mmol) in benzene (2 mL) was completed (~2.5 h), the reaction mixture was diluted with diethyl ether (10 mL), and the organic phase was washed with aq $NaHCO_3$ (3 mL), water (3×4 mL), then dried (Na_2SO_4), before purification by chromatography. Compounds **3** and **5** (R_f 0.67 in ethyl acetate:*n*-hexane 1:1) were converted into two products (R_f 0.46, 0.28 and 0.53, 0.28, respectively, in ethyl acetate:*n*-hexane 1:1). Besides the major, more mobile products **7** (20 mg, 34% yield) and **8** (34.6 mg, 58% yield), small amounts (~4 mg) of the minor products visible under UV light were obtained in an impure state, as shown by ^{1}H NMR. Photolysis of the difficult to prepare compound **4** was carried out on a small scale (26.6 mg) while a parallel experiment was made with **3**. ^{1}H NMR analysis of the crude reaction mixtures led to very similar spectra, showing in both cases the presence of **7** as the major product (60% in each case, based on comparison of the intensity of the acetyl signals).

(4*R*,5*S*,6*S*,7*R*)-4,5,6-Triacetoxy-7-acetoxymethyl-2-cyano-4,5,6,7-tetrahydro-1,3-oxazepine **6**. Mp 96–98°C (diethyl ether/petroleum ether); $[\alpha]_D^{20}$ +96 (c 1.28, chloroform); ^{1}H NMR ($CDCl_3$, 200 MHz) 6.52 (d, 1H, $J_{4,5}$ 9.6 Hz, H-4), 5.54 (d, 1H, $J_{6,7}$ ~0 Hz, H-6), 5.01 (dd, 1H, $J_{5,6}$ 2.3 Hz, H-5), 4.48 (t, 1H, $J_{7,8}$ 6.9 Hz, H-7), 4.22 (dd, 1H, $J_{7,8'}$ 6.1 Hz, H-8), 4.11 (dd, 1H, $J_{8,8'}$ 11.8 Hz, H-8′), 2.20, 2.13, 2.11, 2.03 (4s, 3H each, acetyl groups attached, respectively, to positions 6, 4, 8, and 5); ^{13}C NMR ($CDCl_3$, 50 MHz) 132.8 (C-2), 111.3 (CN), 79.0 (C-4), 78.2 (C-7), 69.8 (C-5), 66.5 (C-6), 61.4 (C-8), 170.2, 169.5, 169.3, 169.3 (C=O at position 8, 6, 5, and 4, respectively), 20.8, 20.6, 20.5, 20.4 (acetyl); unambiguous assignments of the ^{1}H and ^{13}C NMR spectra have been made by heteronuclear 2D correlations (HMBC gradients, HMQC gradients); MS (CI, NH_3) *m/z* 371 $[M+1]^+$. Anal. calcd for $C_{15}H_{18}O_9N_2$ (370): C, 48.65; H, 4.90; N, 7.56. Found: C, 48.42; H, 5.10; N, 7.60.

(4*R*,5*S*,6*R*)-4,5,6-Triacetoxy-2-cyano-4,5,6,7-tetrahydro-1,3-oxazepine **7**. Syrup; $[\alpha]_D^{20}$ −18 (c 0.375, chloroform); R_f 0.46 in ethyl acetate:*n*-hexane 1:1; ^{1}H NMR ($CDCl_3$, 200 MHz) 6.71 (d, 1H, $J_{4,5}$ 9.7 Hz, H-4), 5.30 (dd, 1H, $J_{5,6}$ 4.5 Hz, H-5), 5.23 (dq, 1H, $J_{6,7}$ 1.4 Hz, H-6), 4.75 (dd, 1H, $J_{6,7'}$ 3.0 Hz, H-7), 4.32 (dd, 1H, $J_{7,7'}$ 13.8 Hz, H-7′), 2.16, 2.12, 2.08 (3s, 3 H each, acetyl groups); ^{13}C NMR ($CDCl_3$, 75 MHz) 133.2 (C-2), 110.9 (CN), 78.7, 73.1, 72.3 (C-4, C-5, C-6), 69.0 (C-7), 169.5, 169.5, 168.8, 20.8, 20.7, 20.5 (acetyl); MS (CI, NH_3) *m/z* 299 $[M+1]^+$. Anal. calcd for $C_{12}H_{14}O_7N_2$ (298): H, 4.73. Found: H, 4.70.

(4*S*,5*R*,6*R*)-4,5,6-Triacetoxy-2-cyano-4,5,6,7-tetrahydro-1,3-oxazepine **8**. Mp 98–99°C (diethyl ether/petroleum ether); $[\alpha]_D^{20}$ −150 (c 0.35, chloroform); R_f 0.53 in ethyl acetate:*n*-hexane 1:1; ^{1}H NMR ($CDCl_3$, 200 MHz) 6.55 (d, 1H, $J_{4,5}$ 9.5 Hz, H-4), 5.42 (m, 1H, $J_{6,7}$ 4.5 Hz, H-6), 5.07 (dd, 1H, $J_{5,6}$ 2.5 Hz, H-5), 4.41 (dd, 1H, $J_{6,7'}$ 1.3 Hz, H-7), 4.18 (dd, 1H, $J_{7,7'}$ 13.5 Hz, H-7), 2.19, 2.14, 2.06 (3s, 3H each, acetyl groups); ^{13}C NMR ($CDCl_3$, 50 MHz) 133.3 (C-2), 111.5 (CN), 79.3, 69.9, 67.4 (C-4, C-5,

C-6), 69.9 (C-7), 169.6, 169.3, 169.3, 20.8, 20.7, 20.5 (acetyl); MS (CI, NH_3) *m/z* 299 $[M+1]^+$. Anal. calcd for $C_{12}H_{14}O_7N_2$ (298): C, 48.33; H, 4.73; N, 9.39. Found: C, 48.52; H, 4.78; N, 9.43.

3.2. Thermolysis

Compound **1** (0.5 g, 1.26 mmol) in boiling xylene (30 mL) was also subjected to thermolysis for 36 h, to afford **6** in a 30% yield.

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