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An alternative route to 2-deoxysugar and 2,3-unsaturated sugar derivatives via the corresponding 1-nitro-1-alkenes

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Abstract

An efficient method for the preparation of suitably *O*-protected 2-deoxysugar oximes starting from corresponding sugar 1-nitro-1-alkenes and using tin(II) chloride as a reducing agent is described. The prepared oximes were further transformed into either free 2-deoxysugars or 2-deoxysugar nitriles and acids. 2,3-Unsaturated sugar oximes were also prepared starting from *O*-acetylated sugar 1-nitroalkenes. The preparation of 2-deoxy-D-glucose is representative.

2-Deoxysugars represent a very important group of organic compounds. They have been widely used in the study of various aspects of carbohydrate transport and metabolism and as one of the building blocks of certain nucleosides, nucleotides, and nucleic acids. Among them, 2-deoxy-D-glucose is also effective versus some viral infections.[1] Although a number of synthetic methods for the preparation of 2-deoxysugars have been published,[2–5] most of these represent a multistep synthesis and the overall yields are often too low.

Conversion of nitroalkenes into oximes has already been described[6] for the preparation of some methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-oximino-β-D-hexopyranosides using zinc and acetic acid as a reducing agent. Recently, we have found[7] that this method, when applied to *O*-acetylated sugar 1-nitroalkenes, afforded the corresponding 2,3-unsaturated sugar oximes exclusively. We now wish to report an alternative procedure based on the reduction of sugar 1-nitroalkenes with tin(II) chloride, which provides an efficient and simple method for the synthesis of 2-deoxysugar oximes[8] from which either free 2-deoxysugars or corresponding nitriles and acids can be prepared. Moreover, this approach enables us to prepare these compounds preferentially *O*-protected while protective groups can be base or acid sensitive. In contrast to zinc and acetic acid, in the case of starting per-*O*-acetylated sugar 1-nitroalkenes the use of tin(II) chloride resulted in the formation of a mixture of desirable 2-deoxysugar oximes and 2,3-unsaturated sugar oximes in the ratio of ca. 2:1. On the other hand, the formation of 2,3-unsaturated sugar

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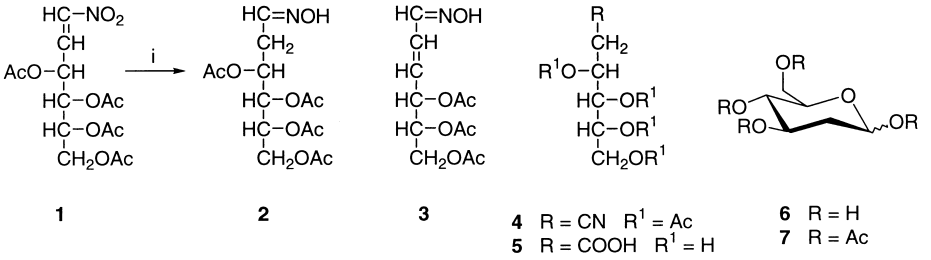
oximes was not observed when the hydroxyl group at the C-3 position of the starting 1-nitroalkene was blocked with an ether linked protective group. Tetraacetoxy-D-*arabino*-1-nitro-1-hexene (**1**, synthesized in three steps from D-arabinose)[9,10] and methyl 5,6-dideoxy-2,3-*O*-isopropylidene-6-nitro-α-D-*lyxo*-hex-5-enofuranoside (**8**, prepared in four steps from D-mannose)[11,12] are representative of those starting compounds having base and acid sensitive protective groups.

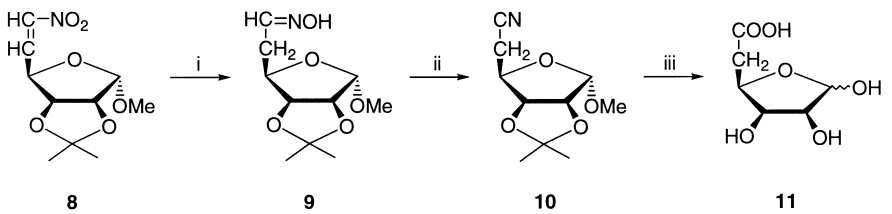
Treatment of **1** in ethyl acetate with tin(II) chloride dihydrate at room temperature gave a mixture of 2-deoxy-3,4,5,6-tetra-*O*-acetyl-D-*arabino*-hexose oxime **2** and 2,3-dideoxy-4,5,6-tri-*O*-acetyl-D-*erythro*-hex-2-enose oxime **3** which were separated by column chromatography (Scheme 1). The NMR spectra revealed that oxime **2** exists as a mixture of *E*- and *Z*-isomers. Although the proportion of the minor component is small, its formation is rather unusual for aliphatic aldoximes. Based on the fact that an appreciable amount of 2-deoxy-3,4,5,6-tetra-*O*-acetyl-D-*arabino*-hexononitrile **4** and only a small amount of acetylated oxime was isolated from the reaction of **2** with acetic anhydride, it can be concluded that the major isomer must be the *anti*-oxime because this type of reaction is known to be a *trans*-elimination.[13] On the other hand, compound **3** represented the 2,3-*trans*-unsaturated *anti*-oxime as a single isomer ($J_{2,3} = 15.8$ Hz) and no *syn*-oxime was observed contrary to the reduction of **1** with zinc and acetic acid where both *anti*- and *syn*-oximes were isolated and fully characterized.[7] All spectral and physical data of **3** were identical with those described for *anti*-oxime.[7]



Scheme 1. Reagents and conditions: (i) $SnCl_2 \cdot 2H_2O$, EtOAc, rt

In addition to the spectral methods, identification of **2** was also confirmed indirectly—by its conversion (deacetylation and deoximation by the acid-catalyzed exchange method using levulinic acid[14]) to the known[3,4] 2-deoxy-D-*arabino*-hexose **6** characterized[5,15–17] as 1,3,4,6-tetra-*O*-acetate **7**. Moreover, deacetylation and hydrolysis of nitrile **4** under acidic conditions afforded known[18] 2-deoxy-D-*arabino*-hexonic acid (2-deoxy-D-gluconic acid) **5** (Scheme 1).

In the case of starting 1-nitroalkene **8** (Scheme 2), only methyl 5-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexodialdo-1,4-furanoside oxime **9** was obtained as an unseparable mixture of *anti*- (major product) and *syn*-isomers and no elimination product was observed. By the use of acetic



Scheme 2. Reagents and conditions: (ii) Ac_2O, reflux; (iii) 1N HCl, EtOH, H_2O, reflux

anhydride, the oxime **9** was converted into methyl 5-cyano-5-deoxy-2,3-*O*-isopropylidene-α-D-lyxofuranoside **10**. In addition, deoximation of **9** afforded methyl 5-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexodialdo-1,4-furanoside **11**. On the other hand, preferential acid hydrolysis of the glycoside bond and isopropylidene fragments in **9** followed by reduction with $NaBH_4$ and deoximation produced known 2-deoxy-D-glucose **6**.

In conclusion, this procedure provides an alternative method for the synthesis of 2-deoxysugar oximes.[2,4] Since the oxime group may be modified through a variety of reactions, this method may be of use for preparing further interesting and not so readily available sugar derivatives. The limiting factor is, of course, the availability of suitably *O*-protected starting sugar 1-nitroalkenes.

1. Experimental

Typical procedure for the preparation of **2** and **3**: A mixture of **1** (1.8 g, 5.0 mmol) and tin(II) chloride dihydrate (2.25 g, 10.0 mmol) in ethyl acetate (70 mL) was rapidly stirred for 6 h at room temperature. After filtration and washing the filtrate twice with $CHCl_3$ the solvents were evaporated. The residue was separated on a column of silica gel using hexane:ethyl acetate, 2:3 (eluent A) giving **2** (yield: 1.0 g, 58%) and oily **3** (yield: 0.4 g, 28%). In an analogous procedure starting from **8** and using hexane:ethyl acetate, 3:2 (eluent B) for column chromatography, oily oxime **9** (82%) was obtained as a mixture of *E*- and *Z*-isomers which were not separated (one spot on TLC).

Typical procedure for the preparation of **4**: A solution of **2** (1.04 g, 3.0 mmol) in acetic anhydride (10 mL) was heated under reflux for 1 h. The solvent was evaporated under reduced pressure, the residue was taken up in ether and washed with cold 5% $NaHCO_3$ solution. After drying over $MgSO_4$, the solvent was evaporated to yield the crude product. Recrystallization from ether afforded **4** (yield: 0.80 g, 81%). Dehydration of oxime **9** was carried out under the same conditions to give oily product **10** (74%) which was purified by column chromatography using eluent B.

Preparation of **5**: After usual deacetylation (MeONa, MeOH, rt) of **4** (1.65 g, 5.0 mmol), the crude product (0.82 g) was heated under reflux with hydrochloric acid (30%, 10 mL) for 12 h. Evaporation to dryness and recrystallization of the product from ethanol afforded **5** (0.79 g, 88%) having mp 145–146°C and $[\alpha]_D$ +5.6 (*c* 1, H_2O). Reported[2,3] data: mp 145°C, $[\alpha]_D$ +5.

Preparation of **6**: The crude product from deacetylation of **2** (1.74 g, 5.0 mmol) was heated with levulinic acid (5 g) in 1N HCl (25 mL) at 40°C for 8 h. Extraction with ether and evaporation of water under reduced pressure afforded crude **6**. Recrystallization from acetone yielded pure **6** (599 mg, 73%) having mp 141–143°C. Reported[3,4] mp 142–144°C and 140–143°C.

Spectroscopic and analytical data: compound **2** (a mixture of *E*- and *Z*-isomers): $R_f = 0.26$ (eluent A); mp 61–62°C; $[\alpha]_D$ +28 (*c* 1, MeOH). ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 7.36$ (t, $J_{1,2} = 6.5$ Hz, 1H, H-1), 6.84 (t, $J_{1,2} = 5.3$ Hz, 1H, H-1), 5.40 (m, 1H, H-3), 5.33 (m, 1H, H-3), 5.30 (m, $J_{4,5} = 7.5$ Hz, 2H, 2H-4), 5.15 (m, $J_{5,6} = 2.8$ Hz, $J_{5,6'} = 4.8$ Hz, 2H, 2H-5), 4.25 (dd, $J_{6,6'} = 12.6$ Hz, 2H, 2H-6), 4.13 (dd, 2H, 2H-6′), 2.69 (m, 2H, H-2), 2.45 (m, 2H, H-2), 2.14 (CH_3), 2.07 ($2CH_3$), 2.06 ($2CH_3$), 2.05 ($3CH_3$). ^{13}C NMR ($CDCl_3$, 75.46 MHz): $\delta = 170.5$ (2C=O), 170.1 (2C=O), 169.8 (4C=O), 148.0 and 146.7 (C-1), 70.2 and 70.0 (C-4), 68.2 (2C-5), 67.7 and 67.3 (C-3), 61.7 (2C-6), 31.4 and 27.2 (C-2), 20.7 ($4CH_3$), 20.6 ($4CH_3$). Anal. calcd for $C_{14}H_{21}NO_9$: C, 48.43; H, 6.05; N, 4.04. Found: C, 48.52; H, 6.10; N, 4.01; compound **3** (*anti*-oxime): spectral and analytical data were essentially the same as described previously;[13] compound **4**: mp 159–160°C; $[\alpha]_D$ +24 (*c* 1, MeOH). ^1H NMR ($CDCl_3$): $\delta = 5.36$ (dd, $J_{3,4} = 2.3$ Hz, $J_{4,5} = 6.8$ Hz, 1H, H-4), 5.33 (ddd, $J_{2a,3} = 5.8$ Hz, $J_{2b,3} = 5.5$ Hz, 1H, H-3), 5.16 (ddd, $J_{5,6a} = 2.6$ Hz, $J_{5,6b} = 4.2$ Hz, 1H, H-5),

4.25 (dd, $J_{6a,6b}$ = 12.6 Hz, 1H, H_a-6), 4.17 (dd, 1H, H_b-6), 2.77 (dd, $J_{2a,2b}$ = 17.0 Hz, 1H, H_a-2), 2.59 (dd, 1H, H_b-2), 2.20, 2.14, 2.08 and 2.06 ($4CH_3$). ^{13}C NMR ($CDCl_3$): δ = 170.4, 170.1, 169.7 and 169.6 (4C=O), 115.4 (CN), 69.6 (C-4), 68.0 (C-5), 65.2 (C-3), 61.5 (C-6), 20.7 (C-2), 20.6, 20.5, 20.4 and 20.3 ($4CH_3$). MS (EI): m/z (%) = 256 (15), 217 (11), 167 (12), 154 (14), 145 (25), 115 (19), 103 (16), 43 (100). Anal. calcd for $C_{14}H_{19}NO_8$: C, 51.05; H, 5.83; N, 4.25. Found: C, 51.12; H, 5.87; N, 4.20; compound **9** (a mixture of *E*- and *Z*-isomers): R_f = 0.47 (eluent B); $[\alpha]_D$ +68 (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$): δ = 7.53 (t, $J_{5,6}$ = 5.8 Hz, 1H, H-6), 6.92 (t, $J_{5,6}$ = 5.3 Hz, 1H, H-6), 4.90 (s, 1H, H-1), 4.88 (s, 1H, H-1), 4.68 (dd, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.66 (dd, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.57 (d, 1H, H-2), 4.56 (d, 1H, H-2), 4.12 (m, 2H, 2H-4), 3.33 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 2.64 (dd, $J_{4,5}$ = 7.1 Hz, 2H, H-5), 2.63 (dd, $J_{4,5}$ = 7.0 Hz, 2H, H-5), 1.47 and 1.31 (2s, each 6H, $2CMe_2$). ^{13}C NMR ($CDCl_3$): δ = 148.5 (2C-6), 112.3 ($2CMe_2$), 106.7 and 106.6 (C-1), 84.8 and 84.7 (C-4), 79.9 and 77.7 (C-2), 77.0 and 76.3 (C-3), 54.3 ($2OCH_3$), 28.8 and 24.7 (C-5), 25.7 and 24.6 ($2CMe_2$). Anal. calcd for $C_{10}H_{17}NO_5$: C, 51.93; H, 7.42; N, 6.06. Found: C, 52.10; H, 7.48; N 6.02; compound **10**: $[\alpha]_D$ +81 (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$): δ = 4.91 (s, 1H, H-1), 4.70 (dd, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 4.59 (d, 1H, H-2), 4.21 (dt, $J_{4,5}$ = 6.8 Hz, 1H, H-4), 3.35 (s, 3H, OCH_3), 2.74 (d, 2H, H-5), 1.47 and 1.32 (2s, each 3H, CMe_2). ^{13}C NMR ($CDCl_3$): δ = 117.1 (CN), 113.1 (CMe_2), 107.1 (C-1), 84.9 (C-4), 79.2 (C-2), 75.1 (C-3), 54.8 (OCH_3), 25.8 and 24.7 (CMe_2), 17.6 (C-5).

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