Tetrahedron Letters,Vol.30,No.48,pp 6641-6644,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

SYNTHESIS AND PROPERTIES OF METHYL 5,6,7,8-TETRA-O-ACETYL-3-DEOXY-3-DIAZO-D-ARABINO-OCT-2,4-DIULOSONATE

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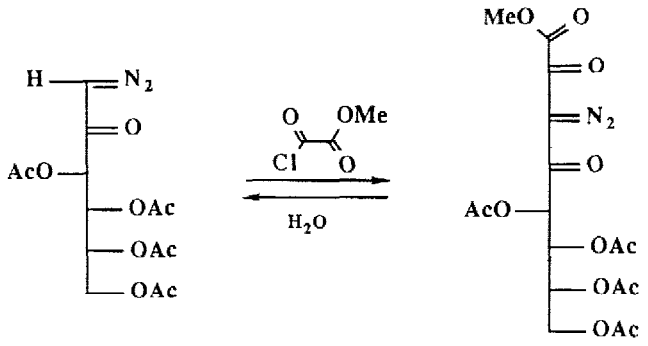
The diazo-α,α'-diketo-aldonic acid 3 is prepared from the 1-deoxy-1-diazo-fructose 1 by condensation with methyl oxalyl chloride in 61 % yield. The title compound 3 is very labile towards base but is moderately stable towards acid. These properties are contrary to those observed for normal diazoalkanes.

Although a number of synthetic procedures have been developed to elongate the carbon chain of carbohydrates [1,2,3,4], there are often problems if two highly functional fragments are to be connected [5]. Carbohydrates which carry terminal diazo groups can easily be prepared from the corresponding aldonyl chlorides and diazomethane [6]. These molecules should be able to undergo further carbon chain elongation. In addition, the diazo group can easily be converted to other functional groups [7]. We found that 1-diazo-2-keto-sugars undergo further chain elongation if reacted with a highly activated carboxylic acid chloride. The reaction scheme described here gives easy access to carbohydrates having a 2-keto-3-deoxy aldonic acid structure. The same functionality is found in biologically important aldonic acids like 2-keto-3-deoxy-D-manno-octulosonic acid (KDO) [8] or neuraminic acids [9].

3,4,5,6-Tetra-O-acetyl-1-deoxy-1-diazo-*keto*-D-fructose (**1**) is prepared by reaction of 2,3,4,5-tetra-O-acetyl-D-arabonyl chloride with diazomethane [10]. Reaction of **1** with methyl oxalyl chloride **2** in the presence of N,N-diisopropylethylamine results in the formation of the expected condensation product **3**. Methyl 5,6,7,8-tetra-O-acetyl-3-deoxy-3-diazo-D-arabino-oct-2,4-diulosonate (**3**) is obtained in 61% yield after column chromatography. The base is necessary to neutralize HCl formed during the reaction. Produced as a by-product from the reaction of **1** with HCl is 1-chloro-1-deoxy-3,4,5,6-tetra-O-acetyl-keto-D-fructose. If inadequately dried solvents or reagents are used, the 1-chloro-1-deoxy-fructose can become the sole product in the reaction. Attempts to use other simple acid chlorides like acetyl chloride or benzoyl chloride as electrophilic components for the chain elongation of **1** were not successful.



1 3

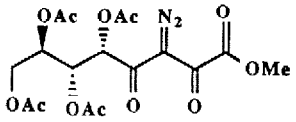
The $J_{H,H}$ coupling constants of 3 suggest that the carbon chain adopts an extended *zigzag* conformation from C5 to C8. The fragment from C1 to C4 has most likely a planar all-*s*-trans conformation due to repulsions of the functional groups (cf. figure 1). The UV-absorption of 3 and the IR-spectrum of 3 show very good agreement with data from other diazo-α,α'-dicarbonyl compounds [11]. The diazo-α,α'-diketo compound 3 shows very unusual reactivity. Contrary to all observations made earlier for other carbohydrate diazoketones [12] 3 readily reacts with traces of water. In a slow cleavage reaction water reacts with 3 to form the educt **1**. The reaction is probably initiated by a selective nucleophilic attack of the water molecule on the carbonyl atom C2 of 3. Other products which would result from an alternative nucleophilic attack of the water molecule at carbonyl atom C4 are not observed. No traces of compounds resulting from an electrophilic attack of the protons on the diazo group were identified. When using methanol-d_4 as a solvent, 3 reacts within 24h in quantitative yield to form the educt **1a** that carries a deuterium atom at C1. Catalytic amounts of base like triethylamine accelerate the retro-reaction strongly. In the presence of triethylamine the reaction of 3 with water is complete within 1.5h.

The diazo-α,α'-diketo aldonic acid 3 shows a relatively high stability towards acids. No reaction products are observed after heating 3 in conc. acetic acid at 60°C for 7d. A solution of 3 in 5% trifluoroacetic acid in methanol is moderately stable, several days of heating at ca. 40°C result in the cleavage of acetate groups before the diazo functional group is lost. The stability of 3 towards acids is in contrast to the properties of normal diazo groups including all diazo group containing carbohydrates which readily react with acids. Only very little variation is possible in the reaction conditions as the educt **1** is very acid labile and the product 3 turns out to be very base labile. Over the whole reaction time the reaction mixture has to be kept well buffered because too much acid destroys the diazoketone **1** and too much base destroys the product 3.

In the ^{13}C-NMR spectrum of 3 the resonances of the carbonyl carbon atoms C2 and C4 , with δ_{C2} = 172.74 and δ_{C4} = 185.78 (cf. Tab I), are shifted to high field by about 17 or 4 ppm respectively compared to normal α-keto-diazoalkanes [13]. This is expected if the π-electron system from C1 to C4 is in conjugation. This supports a planar conformation of the fragment from C1 to C4. Additional

evidence for the conjugation of the head group C1 to C4 of **3** is present in the extreme downfield shift of the diazo carbon atom at δ = 84.51 compared to **1** which has a chemical shift of the diazo carbon atom of δ = 54.81. A transfer of electron density from C3 to the electron attracting carbonyl groups C2 and C4 is very likely responsible for the observed changes in the reactivity of **3** compared to that of normal diazoalkanes (cf. figure 1). However, neither a single carbonyl group in an α-position to a diazo group, as found in **1**, nor an α-methoxycarbonyl-α'-keto diazo group as found in methyl 4,5,6,7,8-tetra-O-acetyl-2-desoxy-2-diazo-D-gluco-oct-3-ulosonate are sufficient to cause a reaction with water at neutral pH [14]. Thus, more than the combined electron withdrawing effect of an α-keto and an α-carboxylester function is necessary to cause this change in reactivity. Currently, we are testing different ways to selectively modify the diazo functional group of **3**.

Figure 1: Conformation of **3**.



Tab I: Selected ^{13}C-NMR chemical shifts of **1** and **3**.

	$\underline{C}O_2Me$	C=O	$C=N_2$	C=O	CHOAc	CHOAc	CHOAc	CH_2OAc
1			54.8	189.8	75.1	69.8	69.1	62.5
3	160.7	172.7	84.5	185.8	74.2	68.6	67.8	62.0

Experimental: Methyl 5,6,7,8-Tetra-O-acetyl-3-deoxy-3-diazo-D-arabino-oct-2,4-diulosonate (**3**): 0.17 g (1.4 mmol) Methyl oxalyl chloride (**2**) is slowly added via a syringe to a solution of 0.5 g (1.4 mmol) **1** and 0.18 g (1.4 mmol) N,N-diisopropylethylamine in 10 ml abs. THF under inert gas atmosphere. After stirring the reaction mixture for 8h, further amounts of **2** are added until the educt **1** is no longer visible on TLC. After removal of the solvents under reduced pressure the residue is separated by flash-chromatography using diethyl ether - petroleum ether (3:1). Recrystallization from diethyl ether - petroleum ether yields 0.38 g **3** (61 %). Mp. 86-87°C, $[\alpha]_D^{20}$ = +83.33° (c = 3.4 in $CHCl_3$). Elemental analysis for $C_{17}H_{20}N_2O_{12}$ (444.35) Calc.: C 45.95 %, H 4.54 %, N 6.30 %; Found: C 45.86 %, H 4.38 %, N 6.22 %. UV spectrum (diethyl ether): λ_{max} = 246 nm (ϵ = 9150). IR spectrum (KBr): 2132 cm^{-1}: N=N; 1720 br, 1650 cm^{-1}: C=O. ^{1}H-NMR spectrum (CD_3COCD_3, 300 MHz): δ = 6.008 (d, H-5), 5.515 (dd, H-6), 5.376 (ddd, H-7), 4.333 (dd, H-8a), 4.228 (dd, H-8b), 3.939 (s, OCH_3), 2.109, 2.087, 2.014, 1.997 (s, OAc); $J_{5,6}$ = 1.6; $J_{6,7}$ = 8.9; $J_{7,8a}$ = 2.6; $J_{7,8b}$ = 4.8; $J_{8a,8b}$ = -12.6 Hz. ^{13}C-NMR spectrum (C_6D_6, 20.1 MHz): δ = 160.65 (C1); 172.74 (C2); 84.51 (C3); 185.78 (C4); 74.22, 68.59, 67.77 (C5, C6, C7); 62.03 (C8); 53.00 (OCH_3); 2x170.08; 2x169.73 ($CH_3\underline{C}OO$); 20.23; 2x20.00;

19.79 ($\underline{C}H_3COO$). CI mass spectrum (isobutane): $M+H^+$: m/e=445 (89%), $M+H^+-N_2$-CO-2xHOAc-CH_2CO: 227 (100%).

We would like to thank the Deutsche Forschungsgemeinschaft for financial support.

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(Received in USA 21 July 1989)