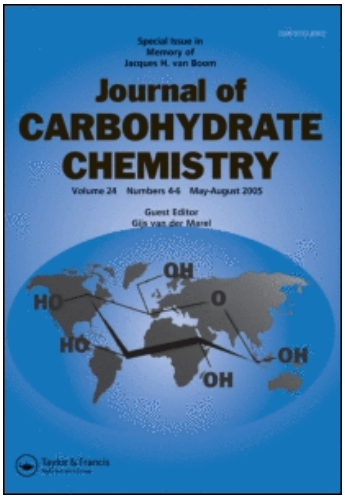

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SYNTHESIS OF A CHIRAL HEXANE-1,6-DINITRILE FROM D-GLUCOSE

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ABSTRACT

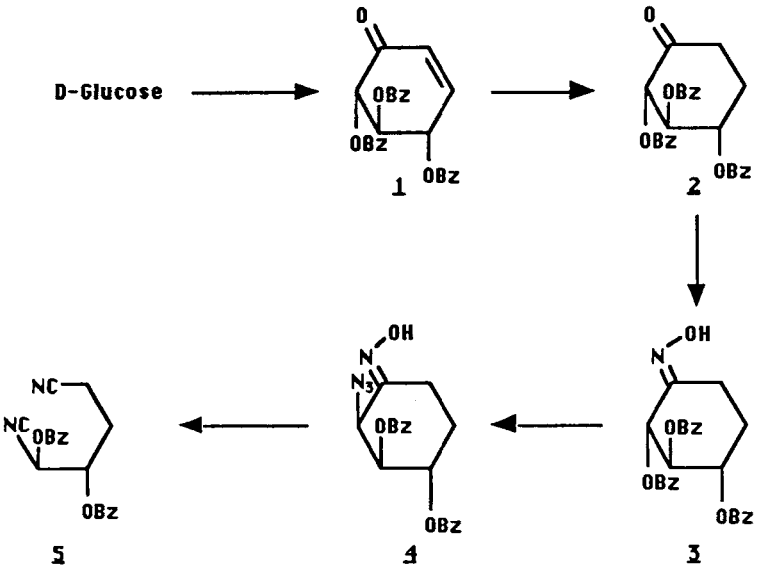
Using well-established methodology, D-glucose was transformed into a tribenzoyloxy cyclohexanone oxime derivative. Sodium azide treatment permitted the regiospecific exchange of the benzoyloxy group at a α-position relative to ketone oxime. Under standard Beckmann conditions the α-azido was oxime cleaved to provide an ω-dicyano compound.

INTRODUCTION

The easy access from carbohydrate derivatives to optically active cyclohexanones, via the Ferrier reaction,[1] has greatly extended the scope of sugars as starting materials in the synthesis of natural products.[2] We were interested in preparing chiral open-chain compounds and report here a method allowing the ready preparation of a disubstituted hexane 1,6-dinitrile from D-glucose. The key step of our scheme involves carbon-carbon bond cleavage of an α-azido cyclohexanone-oxime under standard Beckmann rearrangement conditions. To our knowledge only one such example has been reported in the literature in the steroid series.[3]

RESULTS AND DISCUSSION

In a recent paper Takahashi, Nomura and Satoh have described the C-C bond cleavage of α-azido steroidal ketoximes[3] in the presence of various reagents used to carry out Beckmann rearrangements. A mechanism for this interesting fragmentation reaction was also proposed.[3] In an attempt to synthesize open-chain optically active compounds for another project, we prepared the α-azido oxime 4 and investigated its behavior in the presence of phosphorus trichloride oxide. Compound 4 was available in three steps (Scheme 1) via the known 2L-(2,4/3)-2,3,4-tribenzoyloxycyclohex-5-enone 1. The latter was prepared from D-glucose according to well-established methodology.[4] Catalytic hydrogenation of 1 with 10% Pd/C furnished the cyclohexanone derivative 2 from which the E-oxime 3 was obtained. Lemieux et al. have shown that in the presence of sodium azide, an acetoxy group at an α-position relative to an oxime underwent exchange with the azide group via a nitroalkene intermediate.[5] When a dichloromethane solution of tribenzoyloxycyclohexanone E-oxime 3



SCHEME 1

was treated with n-tetrabutylammonium azide and a catalytic amount of triethylamine the α-azido oxime 4 (50.6%) was stereospecifically formed.[6] The epimeric azide could not be detected in the crude reaction mixture. In the presence of phosphorus trichloride oxide the α-azido oxime 4 furnished with carbon-carbon bond cleavage the disubstituted hexane 1,6-dinitrile 5 (54.5%).

The method presented in this paper shows the great potential of the Ferrier reaction to prepare open-chain chiral compounds from carbohydrates.

EXPERIMENTAL

General Procedures. The melting points were determined with a Buchi apparatus and are uncorrected. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. ^1H NMR spectra were recorded in chloroform-d solution at 400 MHz. The ^{13}C NMR spectrum was measured in chloroform-d solution at 50.31 MHz with a Bruker WP-200 spectrometer. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard (δ 0.000). Carbon-13 chemical shifts for aromatic carbons are not given. Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica get 60 PF_{254} (Merck) activated at 120 °C was the support for TLC and for column chromatography. The term "standard workup" means that the organic layer was washed with water, dried over Na_2SO_4, and filtered and the solvent was removed at reduced pressure.

2L-(2,4/3)-2,3,4-Tribenzoyloxycyclohexanone (2). To a solution of 1 (0.3 g, 0.66 mmol) in ethyl acetate (10 mL) was added 10% Pd/C and the mixture was hydrogenated at normal pressure. After the reaction was complete, the mixture was filtered through kieselguhr. Evaporation of the solvent gave 2 (0.25 g, 82%) as fine needles: mp 142-145°C; $[\alpha]_D^{22}$ = -2.9° (c = 0.85, chloroform); mass spectrum (chemical ionization) (M^+ + H) 459; ^1H NMR δ 8.17-7.33 (m, 15H, 3Ph), 6.03 (t, 1H, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3), 5.83 (d, 1H, $J_{2,3}$ = 10 Hz, H-2), 5.76 (m, 1H, H-4),2.93 and 2.60 (m, 3H, H-5e, H-6e and H-6a), 1.98 (m, 1H, H-5a).

Anal. Calcd for $C_{27}H_{22}O_7$: C, 70.74; H, 4,80. Found: C, 70.42; H, 4.91.

2L-(2,4/3-2,3,4-Tribenzoyloxycyclohexanone E-oxime (3). To a solution of 2 (0.2 g, 0.44 mmol) in a 1:1 mixture (6 mL) of dry methanol and dry pyridine was added hydroxylamine hydrochloride (0.114 g, 1.65 mmol) and the mixture was stirred at room temperature for 8 h. Evaporation of the solvent was followed by chromatography of the crude residue (hexane/ethyl acetate, 8:2) affording the E-oxime 3 (0.198 g, 96%) as a syrup: $[\alpha]_D^{22}$ = -21° (c = 1.13, chloroform); mass spectrum (chemical ionization) (M^+ + H) 474; ^{1}NMR δ 8.00-7.30 (m, 15H, 3Ph), 5.88 (m, 2H, H-2 and H-3), 5.47 (m, 1H, H-4), 3.34 (m, 1H, H-6e),2.39 (m, 2H, H-5e and H-6a), 1.93 (m, 1H, H-5a); ^{13}C NMR δ: 153.1 (C-1), 73.4 and 71.7 (C-2 and C-3), 71.5 (C-4), 25.7 (C-6), 18.2 (C-5).

Anal. Calcd for $C_{27}H_{23}NO_7$: C, 68.50; H, 4.86; N, 2.96. Found: C, 69.02; H, 4.72; N, 3.01.

2L-(2,3,4)-2-Azido-3,4-dibenzoyloxycyclohexanone E-oxime (4). To a solution of n-tetrabutylammonium azide (o.293 g, 1.03 mmol) and a catalytic amount of triethylamine in dry dichloromethane (5 mL) was added 3 (0.147 g, 0.31 mmol) in dry dichloromethane (5 mL). The mixture was heated to 50 °C for 24 h, extracted with dichloromethane and the residue chromatographed (hexane/ethyl acetate, 8:2) affording 4 (52 mg, 50.6%) as a syrup: $[\alpha]_D^{22}$ = -10° (c = 0.5, chloroform) and also the starting oxime 3 (26 mg): mass spectrum (chemical ionization) (M^+ + H) 395; ^{1}H NMR δ 8.03-7.30 (m, 10H, 2Ph), 5.68 (td, 1H, $J_{3,4} = J_{4,5a}$ = 9 Hz, $J_{4,5e}$ = 4 Hz, H-4), 5.50 (dd, 1H, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), 4.72 (d, 1H, $J_{2,3}$ = 4Hz, H-2), 3.24 (m, 1H, H-6e), 2.40 (m, 2H, H-5e and H-6a), 1.75 (m, 1H, H-5a).

Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.57; N, 14,21. Found; C, 70.07; dH, 4.50; N, 14.28.

2S,3S-Dibenzoyloxyhexane-1,6-dinitrile (5). To a solution of 4 (25 mg, 0.063 mmol) in dry pyridine (1.5 mL) was added phosphorus trichloride oxide (0.08 mL) and the mixture was heated to 110 °C for 1 h. After dilution with water and extraction with dichloromethane, the residue was chromatographed (hexane/ethyl acetate, 7:3) giving pure 5 (12 mg, 54.5%) as fine needles: mp 137-140 °C; $[\alpha]_D^{22}$ = -5.1° (c = 0.8, chloroform); mass spectrum (chemical ionization) (M^+ + H) 348; ^{1}H NMR δ 8.10-7.45 (m, 10H, 2Ph), 5.90 (d, 1H, $J_{2,3}$ = 6 Hz, H-2), 5.62 (m, 1H, H-3), 2.63 (m, 2H, H-5, H-5'), 2.48 (m, 2H, H-4 and H-4'); ^{13}C NMR δ: 118.1 (C-1), 114.2 (C-6), 69.3 (C-3), 62.1 (C-2), 26.6 (C-4), 13.9 (C-5).

Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.60; N, 8.05. Found: C, 68.72; H, 4.70; N, 8.17.

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