Regioselective Conversion of Anhydro Sugars into Halohydrins and X-Ray Study

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A rapid, easy, regio- and stereoselective synthesis of 3-halo-3-deoxy sugars using titanium tetrahalides is described. To fully confirm the stereochemistry of the synthetic products, the X-ray structure of benzyl 3-chloro-3-deoxy-β-L-xylopyranoside was determined.

Key words: Anhydro, Bromodeoxy, Chlorodeoxy and Iododeoxy Sugars, Titanium Tetrahalides

Introduction

The synthesis of halodeoxy sugars has received continuous interest in recent years because of their key role in the access to deoxy, aminodeoxy and unsaturated sugars [1]. Moreover, anhydro sugars are stable intermediates with unique properties of the oxirane ring to serve, both, as a protective group and readily accessible reaction sites which have led to their extensive exploitation in carbohydrate synthesis. Besides, they have the advantage of convenient removal of protection after the desired synthetic strategy has been accomplished [2 – 6]. Furthermore, regioselective conversion of epoxides to halohydrins is a useful tool for stereospecific syntheses of various synthons, since optically active epoxides are readily available [7]. A variety of reagents are known to convert epoxides to halohydrins. In particular, metal halides such as $FeCl_3$ [8], $SnCl_2$, $SnBr_2$, SnI_2 [9] or $CoCl_2$ in the presence of chlorotrimethylsilane [10] catalyse the cleavage of oxiranes. Several other methods are also known for the formation of halohydrins on carbohydrate templates, including Raney nickel [1], sulfuryl chloride [11], dibromomethyl methyl ether [12], dichloromethylene-(dimethyl)ammonium chloride, iron(III) chloride tribenzylamine and lithium bromide [13], and carbon tetrachloride in the presence of triphenylphosphine [14]. A reaction yielding high regioselectivity is the trans-diaxial opening of oxirane rings of 2,3-anhydro sugars with a titanium(IV) halide. The complex has recently been used by Shimizu *et al.* to achieve epoxide cleavages in a group of halohydrins [15]. Chloro- and iododeoxy sugars were already prepared in high yield in our own laboratory using a dichlorobis(benzonitrile) palladium (II) [16] and a titanium isopropoxide reagent in the presence of iodine and samarium iodide [17].

Thus, in continuation of our efforts to synthesize halodeoxy sugars in high yields and regioselectively, we wish to report herewith a rapid, easy and regioselective route for the synthesis of halodeoxy sugars in high yields using titanium(IV) halides.

Results and Discussions

The anhydro sugars **1 – 3** exist almost entirely in the favored half-chair conformations $H^0{}_5$ and $H_0{}^5$ [17 – 23]. Trans-diaxial opening by the titanium(IV) halide complex leads to benzyl 3-halo-3-deoxy-β-L-xylopyranosides **4 – 6**, benzyl 3-halo-3-deoxy-α-D-xylopyranosides **7 – 9** and benzyl 3-halo-3-deoxy-α-D-arabinopyranosides **10, 11**, respectively. The nucleophilic halide attack at position 3 is also favored by steric considerations, as position 2 is comparatively blocked by the bulky substituent at C-1. The anhydro sugars benzyl 2,3-anhydro-β-L-ribopyranoside

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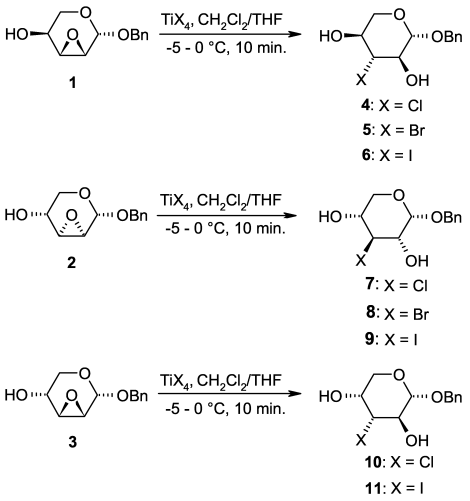

Scheme 1. Syntheses of halodeoxy sugars *via* 2,3-anhydropyranosides.

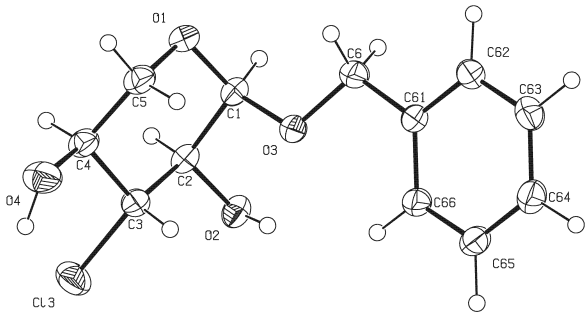

Fig. 1. ORTEP diagram of benzyl 3-chloro-3-deoxy-β-L-xylopyranoside (**4**).

(**1**), benzyl 2,3-anhydro-α-D-ribopyranoside (**2**) and benzyl 2,3-anhydro-α-D-lyxopyranoside (**3**) were synthesized according to the literature [24 – 26]. In the present work we found that epoxide ring opening in this group of 2,3-anhydrosugars with titanium(IV) halide results in the transformation to the corresponding 3-halo-3-deoxy sugars (Scheme 1).

It may be concluded from these results that epoxide-opening by titanium(IV) halide competes with other available methods in terms of yields and short preparation time of halodeoxy sugars. The reagent, however, imparts a greater degree of regioselectivity and effective control on epoxide migration [27]. NMR spectroscopy established $^1C_4$ conformations for the halodeoxy sugars **4** – **6**, **10** and **11** and $^4C_1$ conformations for **7** – **9**.

Fig. 1 shows the ORTEP diagram of benzyl 3-chloro-3-deoxy-β-L-xylopyranoside (**4**). Details of X-ray collection and refinement, bond distances and angles for compound **4** are collected in Tables 1 and 2.

Table 1. Details of X-ray data collection and refinement for compound **4.**

Moleculas formula	$C_{12}H_{15}ClO_4$
Formula weight	258.69
Temperature	213(2) K
Wavelength	1.54056 Å (Cu-K$_\alpha$)
Crystal system / space group	orthorhombic/ $P2_12_12_1$
Unit cell dimensions	$a = 5.7958(4)$ Å alpha = 90 deg. $b = 9.147(2)$ Å beta = 90 deg. $c = 22.148(3)$ Å gamma = 90 deg.
Volume	1174.1(3) Å^3
Z	4
Density (calculated)	1.463 g/cm^3
Absorption coefficient	2.911 mm^{-1}
$F(000)$	544
Crystal size / colour	$0.60 \times 0.20 \times 0.05$ mm / colourless
Theta range for data collection	5.23 to 64.94 deg.
Index ranges	$-6 \le h \le 1$, $-10 \le k \le 10$, $0 \le l \le 26$
Reflections collected	2690
Independent reflections	1997 [R(int) = 0.0559]
Reflections observed	1964
Criterion for observation	$I > 2\sigma(I)$
Absorption correction	Psi scans
Max. and min. transmission	0.9428 and 0.6766
Refinement method	Full matrix least squares on F^2
Data / restraints / parameters	1997 / 0 / 215
Goodness-of-fit on F^2	1.115
Final R indices (all)	$R_1 = 0.0484$, $wR_2 = 0.1348$
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0478$, $wR_2 = 0.1342$
Absolute structure parameter	0.01(3)
Extinction coefficient	0.027(2)
Largest diff. peak and hole	0.253 and -0.375 e·Å^{-3}

Experimental Part

General

All chemicals and reagents were obtained from commercial suppliers and used as such without further purification. Solvents were dried and distilled according to standard procedures. The reactions were monitored by thin-layer chromatography, carried out on 0.25 mm silica gel plates (60 F-254, Merck, Darmstadt, Germany). Plates were visualized under UV light (where appropriate), sprayed with an orcinol/H_2SO_4/$FeCl_3$ solution and heated to develop. Column chromatography was performed on silica gel 60 (0.063 – 0.200 mm, Merck, Darmstadt, Germany) using the indicated solvent system. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker AC 250 (^{1}H NMR: 250 MHz, ^{13}C NMR:

Table 2. Bond distances [Å] and angles [deg] for compound **4**.

Cl(3)-C(3)	1.795(3)	O(1)-C(1)	1.426(4)
O(1)-C(5)	1.432(4)	O(2)-C(2)	1.428(4)
O(3)-C(1)	1.409(4)	O(3)-C(6)	1.429(4)
O(4)-C(4)	1.414(4)	C(1)-C(2)	1.521(5)
C(2)-C(3)	1.528(4)	C(3)-C(4)	1.516(4)
C(4)-C(5)	1.514(5)	C(6)-C(61)	1.501(5)
C61)-C(66)	1.388(5)	C(61)-C(62)	1.392(5)
C(62)-C(63)	1.391(5)	C(63)-C(64)	1.384(5)
C(64)-C(65)	1.379(5)	C(65)-C(66)	1.395(5)
C(1)-O(1)-C(5)	112.4(2)	C(1)-O(3)-C(6)	113.3(2)
O(3)-C(1)-O(1)	111.5(3)	O(3)-C(1)-C(2)	107.2(2)
O(1)-C(1)-C(2)	111.1(3)	O(2)-C(2)-C(1)	110.6(3)
O(2)-C(2)-C(3)	112.9(3)	C(1)-C(2)-C(3)	110.0(3)
C(4)-C(3)-C(2)	110.0(3)	C(4)-C(3)-Cl(3)	110.6(2)
C(2)-C(3)-Cl(3)	109.9(2)	O(4)-C(4)-C(5)	105.9(3)
O(4)-C(4)-C(3)	113.7(3)	C(5)-C(4)-C(3)	107.7(3)
O(1)-C(5)-C(4)	111.6(3)	O(3)-C(6)-C(61)	110.0(3)
C(66)-C(61)-C(62)	119.3(3)	C(66)-C(61)-C(6)	121.7(3)
C(62)-C(61)-C(6)	119.0(3)	C(63)-C(62)-C(61)	120.3(3)
C(64)-C(63)-C(62)	120.1(3)	C(65)-C(64)-C(63)	119.8(3)
C(64)-C(65)-C(66)	120.4(3)	C(61)-C(66)-C(65)	120.0(3)

63 MHz) or a Bruker WM 400 spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz). The chemical shifts are reported in parts per million (ppm) on a δ scale with TMS as internal standard. The EI, FAB and FD mass spectra were recorded on a Finnigan MAT 312 mass spectrometer connected to a PDO 11/34 (DEC) computer system. Optical rotations were obtained with an LEP AZ polarimeter (Zeiss, Jena) at 546 nm. All melting points are uncorrected.

General procedure for the preparation of halodeoxy sugars

To a stirred solution of the 2,3-anhydro sugars **1 – 3** (354 mg, 1 mmol) in 20 ml dry THF, 2 equivalents of the corresponding titanium(IV) halide was added dropwise to the stirred mixture at 0 °C under argon. Stirring was continued at 0 °C for 5 – 20 min, until TLC showed no starting 2,3-anhydro sugar. The reaction mixture was then quenched with ice-cold water and extracted with ethyl acetate (3×20 ml). The organic layer was then collected, washed with water (30 ml), brine (30 ml), finally with water and the solvent evaporated in *vacuo*. The resulting crude solid was then collected and purified on a column of silica gel (20% ethyl acetate/dichloromethane).

Benzyl 3-chloro-3-deoxy-β-L-xylopyranoside (**4**)

Colourless needles; yield 97%. – M.p. 152 °C (lit. 152 °C [17]); – $[\alpha]_D = +6.85°$ $c = 0.13$, $CHCl_3$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.6 – 128.2$ (Ar-*C*), 97.11 (C-1), 69.7 (C-2), 72.3 (C-4), 70.6 (O*C*H$_2$Ph), 66.2 (C-5), 62.3 (C-3). – MS (FD): $m/z = 258$. – $C_{12}H_{15}ClO_4$ (258.69): calcd. C 55.71, H 5.84; found C 55.73, H 5.76.

Benzyl 3-bromo-3-deoxy-β-L-xylopyranoside (**5**)

Colourless needles; yield 82%. – M.p. 128 – 129 °C; – $[\alpha]_D = +85.10°$ ($c = 0.04$, $CHCl_3$). – ^{1}H NMR (250 MHz, CD_3OD): $\delta = 7.31 – 7.25$ (m, 5H, Ar-*H*), 4.86 (d, $J =$ 11.1 Hz, 1H, OC*H*HPh), 4.56 (d, $J = 11.1$ Hz, 1H, OC*H*HPh), 4.28 (d, $J = 7.0$ Hz, 1H, 1-H), 4.01 (dd, $J = 4.8$, 11.2 Hz, 1H, 5'-H), 3.68 – 3.92 (m, 2H, 3-H, 4-H), 3.57 (dd, $J = 9.7$, 7.0 Hz, 1H, 2-H), 3.18 (dd, $J = 11.3$, 9.1 Hz, 1H, 5-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 –$ 128.6 (Ar-*C*), 102.5 (C-1), 73.8 (C-2), 71.7 (C-4), 71.2 (O*C*H$_2$Ph), 66.85 (C-5), 59.69 (C-3). – MS (FD): $m/z =$ 303. – $C_{12}H_{15}BrO_4$ (303.15): calcd. C 47.54 H 4.99; found C 47.59, H 5.02.

Benzyl 3-iodo-3-deoxy-β-L-xylopyranoside (**6**)

Colourless needles; yield 91%. – M. p. 144 – 145 °C (lit. 145 °C [16]); – $[\alpha]_D = +156.45°$ ($c = 0.14$, $CHCl_3$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 – 128.6$ (Ar-*C*), 102.5 (C-1), 74.2 (C-2), 71.89 (C-4), 71.5 (O*C*H$_2$Ph), 67.4 (C-5), 40.4 (C-3). – MS (FD): $m/z = 350$. – $C_{12}H_{15}IO_4$ (350.16): calcd. C 41.16; H 4.32; found C 41.14, H 4.34.

Benzyl 3-chloro-3-deoxy-α-D-xylopyranoside (**7**)

Colourless needles; yield 92%. – M.p. 158 – 160 °C (lit. 159 – 160 °C [17]); – $[\alpha]_D = +18.45°$ ($c = 0.20$, $CHCl_3$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 – 128.6$ (Ar-*C*), 97.2 (C-1), 72.4 (C-2), 71.5 (C-4), 69.8 (O*C*H$_2$Ph), 66.4 (C-5), 62.4 (C-3). – MS (FD): $m/z = 258$. – $C_{12}H_{15}ClO_4$ (258.69): calcd. C 55.71, H 5.84; found C 55.61, H 5.75.

Benzyl 3-bromo-3-deoxy-α-D-xylopyranoside (**8**)

Colourless needles; yield 75%. – M. p. 125 – 126 °C; – $[\alpha]_D = +139.13°$ ($c = 0.42$, $CHCl_3$). – ^{1}H NMR (250 MHz, CD_3OD): $\delta = 7.24 – 7.40$ (m, 5H, Ar-*H*), 4.71 (d, $J =$ 11.91 Hz, 1H, OC*H*HPh), 4.53 (d, $J = 11.90$ Hz, 1H, OC*H*HPh), 4.65 (d, $J = 7.4$ Hz, 1H, 1-H), 4.02 (dd, $J = 9.8$, 10.4 Hz, 1H, 5-H), 3.47 – 3.77 (m, 4H, 2-H, 3-H, 4-H, 5'-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 – 128.6$ (Ar-*C*), 99.0 (C-1), 74.0 (C-2), 72.2 (C-4), 72.3 (O*C*H$_2$Ph), 64.0 (C-5), 60.4 (C-3). – MS (FD): $m/z = 303$. – $C_{12}H_{15}BrO_4$ (303.15): calcd. C 47.54, H 4.99; found C 47.52, H 5.00.

Benzyl 3-iodo-3-deoxy-α-D-xylopyranoside (**9**)

Colourless needles; yield 81%. – M.p. 75 – 76 °C (lit. 75 °C [16]); – $[\alpha]_D = +56.55°$ ($c = 0.12$, $CHCl_3$). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 – 128.6$ (Ar-*C*), 96.7 (C-1), 73.8 (C-2), 71.5 (C-4), 69.8 (O*C*H$_2$Ph), 62.4 (C-5), 42.5 (C-3). – MS (FD): $m/z = 350$. – $C_{12}H_{15}IO_4$ (350.16): calcd. C 41.16, H 4.32; found C 41.20, H 4.28.

Benzyl 3-chloro-3-deoxy-α-D-arabinopyranoside (**10**)

Colourless needles; yield 94%. – M. p. 142 – 143 °C (lit. 142 °C [17]); – $[\alpha]_D = +95.12°$ ($c = 0.18$, $CHCl_3$). – ^{13}C

NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 - 128.6$ (Ar-*C*), 96.6 (C-1), 73.3 (C-2), 71.5 (C-4), 69.8 (O*C*H_2Ph), 62.4 (C-5), 59.4 (C-3). – MS (FD): $m/z = 258$. – $C_{12}H_{15}ClO_4$ (258.69): calcd. C 55.71, H 5.84; found C 55.62, H 5.90.

Benzyl 3-iodo-3-deoxy-α-D-arabinopyranoside (**11**)

Colourless needles; yield 87%. – M.p. 160 °C (lit. 160 °C [16]); – $[\alpha]_D = -48.92°$ ($c = 12$, MeOH). – ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 128.1 - 128.5$ (Ar-*C*), 102.5 (C-1), 72.5 (C-2), 70.8 (O*C*H_2Ph), 70.4 (C-4), 67.2 (C-5), 37.8 (C-3). – MS (FD): $m/z = 350$. – $C_{12}H_{15}IO_4$ (350.16): calcd. C 41.16; H 4.32; found C 41.10, H 4.37.

Crystal structure determination of benzyl 3-chloro-3-deoxy-β-L-xylopyranoside (**4**)

The crystal structure of compound **4** was determined by the single-crystal X-ray diffraction method. Preliminary examination and data collection were performed with Cu-K_α radiation ($\lambda = 1.54056$ Å) on an ENRAF-NONIUS CAD4 diffractometer operating in the omega scan mode. 1997 independent reflections were measured within the range of $\theta = 5.23 - 64.94°$. The initial positions for all non-hydrogen atoms were obtained by using direct methods of the SHELXS-97 program [28]. The structure was refined using of the SHELXL-97 program [29]. Positional and displacement parameters for non-hydrogen atoms were refined using a full-matrix least-squares refinement procedure. Atomic positions of hydrogen atoms were determined from a difference Fourier map and refined isotropically. Crystal data and crystallographic details are presented in Tables 1 and 2. Fig. 1 shows the ORTEP plot of **4**. Atomic parameters, isotropic displacement parameters, additional bond distances and angles and structure factors for compound **4** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 209834.

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