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Selective desulfonylation in D-xylofuranose 3,5-disulfonates

PAVLE A. HADŽIĆ*# and NADA S.VUKOJEVIĆ

Institute of Chemistry, Faculty of Science, University of Novi Sad, trg Dositeja Obradovića 3, 21000 Novi Sad, Yugoslavia

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A method for the preparation of D-xylofuranose derivatives with a free terminal (C5) alcohol function was developed, starting from monocyclohexylidene-3,5-disulfonyl- or 5-*O*-sulfonyl-3-*O*-methyl ester. The regioselective displacement of the C5 sulfonyl ester function with acetate ion in dimethylsulfoxide afforded the corresponding 5-*O*-acetyl-1,2-*O*-cyclohexylidene-3-*O*-sulfonyl or 5-*O*-acetyl-3-*O*-methyl- -D-xylofuranose. These esters could be readily hydrolysed into the desired 1,2,3-trisubstituted xylofuranose.

Keywords: D-xylofuranose, sulfonyl ester, nucleophilic substitution, desulfonylation.

INTRODUCTION

For the preparation of D-xylofuranuronic acid, xylofuranose derivatives with free terminal (C5) hydroxyl function were needed for oxidation. The easily accessible 1,2-*O*-cyclohexylidene-3,5-di-*O*-sulfonyl- -D-xylofuranose was seen as a convenient starting material.

Examples of the selective sulfonylation of hydroxyl groups in carbohydrates are numerous. The selective regeneration of the alcohol function from disulfonates (polysulfonates) seems to be a more complicated task.

In this paper, we report on the two step, high yield preparation of 1,2,3-trisubstituted -D-xylofuranose. The method consists in the regioselective displacement of the 5-sulfonylester group in 3,5-di-*O*-sulfonyl esters of 1,2-*O*-cyclohexylidene- -D-xylofuranose with the acetate ion in dimethylsulfoxide. Subsequent hydrolysis of the 5-*O*-acetyl group is readily achieved with sodium hydroxide in methanol, giving high yields of the desired products, Scheme 1.

RESULTS AND DISCUSSION

Sulfonates are labile and undergo substitution or elimination reactions very easily. Direct methods for the conversion of sulfonates to alcohols (regeniration of the

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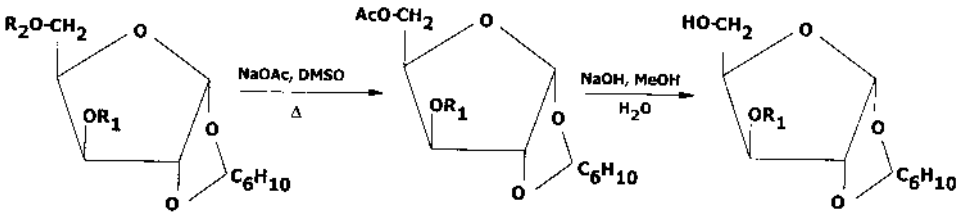

1 a,b,c 2 a,b,c 3 a,b,c

1	R_2	R_1
a	$PhSO_2$-	Me
b	$PhSO_2$-	$PhSO_2$-
c	Ts-	Ts-

2,3	R_1
a	Me
b	$PhSO_2$-
c	Ts-

Scheme 1. Formation of 1,2,3-trisubstituted derivatives of xylofuranose.

hydroxyl group), including reduction with sodium amalgam,[1] hydrogenolysis on nickel,[2] reduction with sodium in ammonia,[3] or the action of metal magnesium in methanol[4] are either too complicated for preparative work or are not appropriate for selective desulfonylation. Direct action of hydroxide ions on 3,5-disulfonyl esters of 1,2-alkylidene- -D-xylofuranose, particulary, is known to effect 3,5-anhydro ring closure[5] by an intramolecular nucleophilic C3 C5 attack.

On the other hand, highly regioselective substitution of primary 5-*O*-sulfonyl group in 3,5-disulfonyl esters of 1,2-*O*-cyclohexylidene- -D-xylofuranose with anionic nucleophiles (halogenes) was proven earlier in our laboratory,[6] pointing to the considerable difference in reactivity between a primary and a secondary sulfonyl ester group.

The method for the selective desulfonylation in xylofuranose-3,5-disulfonates was based on experimental observations in the preparation of the 5-*O*-acetyl-3-*O*-methyl derivative **1a**. Namely, it was found that when acetate ions are present in nonstoichiometric large amounts in dimethylsulfoxide, they quantitatively displace the primary sulfonyl ester group in **1a** in a short time on boiling the reaction mixture (Scheme 1). Simple workup of the reaction mixture gave 5-*O*-acetyl derivative **2a** in a high isolated yield.

On applying the same rigorous experimental conditions to 3,5-disulfonyl esters **1 b,c**, an unexpected outcome of the reaction was registered: the 3,5-disulfonyl esters **1 b,c** gave exclusively the 5-*O*-acetyl-3-*O*-sulfonates **2 b,c**. Analysis of the reaction mixture by TLC revealed that no 3,5-diacetate, 5-sulfonyl-3-*O*-acetate, nor 3,5-anhydro ring was formed, pointing to the high selectivity of the action of the acetate ion. It seems that key to the high reaction rate of the nucleophilic substitution, and the unespectedly short reaction times, lies in the ability of dimethylsulfoxide to solvate cationic species, which leads to the more nucleophilic acetate anion.[7]

On the other side, the high regioselectivity in the displacement of the primary sulfonyl group in the xylofuranose disulfonyl derivatives **1 b,c** could be understood in

line with the well known evidence relating to the inability of an anionic nucleophile to effect the displacement of certain secondary leaving groups attached to a furanose ring.[8]

The resulting acetyl derivatives **2a,b,c** are easily and selectively hydrolyzed in sodium hydroxide-methanol system at room temperature. On hydrolysis, they gave the 3-*O*-methyl derivative **3a**, or the 3-*O*-sulfonyl ester derivatives **3 b,c**, suitable for oxidation at their terminal C5 position.

The starting 5-*O*-sulfonyl-3-*O*-methyl derivative **1a** was prepared by selective C5 sulfonylation, followed by C3 methylation with MeI/silver(I) oxide, while the sulfonyl esters **1b,c** are prepared from 1,2-*O*-cyclohexylidene- -D-xylofuranose under the standard sulfonylation procedure (sulfonyl halide in pyridine).

EXPERIMENTAL

General methods

Melting points were determined on a Büchi SMP 50 apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer model 577 spectrometer. NMR spectra were taken on a Bruker AC250E apparatus in $CDCl_3$, using Me_4Si as an internal standard. The chemical shifts ( ) are expressed in ppm (*s*, *d*, *t* and *m* denote, respectively, singlet, dublet, triplet and multiplet form of the signal). The assignmats of the signals in the ^{1}H-NMR spectra are given after the description of the synthesis, while the assignments of the signals in the ^{13}C-NMR spectra are given in Table I. Mass spectra were recorded with a Finingen MAT311A spectrometer, the first number in the referring spectra denotes the *m*/*z* value, while the numbers in parenthesis correspond to the abundance of the mass peaks. Optical rotations were measured on an automatic polarimeter Polamat A (Karl Zeiss, Jena). TLC was performed on Silica gel alufolien (Merck 5333), with benzene–ethyl acetate 4:1 as mobile phase. Visualisation of the spots was achieved by spraying with 50 % sulphuric acid and subsequent heating to 150 ºC. All organic extracts were dried with anhydrous sodium sulphate.

5-O-*Benzenesulfonyl-1,2-cyclohexylidene-3*-O-*methyl*-α-*D-xylofuranose (**1a**)*

5-*O*-Benzenesulfonyl-1,2-cyclohexylidene-3- -D-xylofuranose (10.0 g, 27.7 mmol) and silver(I) oxide (30 g, 129.3 mmol) were refluxed in iodomethane (100 mL) for 20 h. After cooling to room temperature, chloroform (200 mL) was added to the reaction mixture upon which an insoluble material separated. Evaporation of the solvent under vacuo left a crude product, which on crystallysation from methanol gave crystalline **1a**, m.p. 111 ºC (10.34 g, 97 %), $_D^{20} = -24.42$ (*c* 1.0, $CHCl_3$).

For $C_{18}H_{24}O_7S$, found: C 56.48, H 6.52, calculated: C 56.24, H 6.29.

Mass spectra: 384(M^+, 11), 341(14), 267(7), 233(40), 150(31), 55(31)

^{1}H-NMR: 1.32–1.73, *m*, 10H, from cyclohexylidene; 3.31, *s*, 3H, methyl; 3.73, *d*, 1H, H-3, $J_{3,4} = 3.1$; 4.13, *dd*, 1H, H-5a, $J_{5a,4} = 5.8$, $J_{5a,5b} = 9.4$; 4.30, *dd*, 1H, H-5b, $J_{5b,4} = 5.9$; 4.36, *m*, 1H, H-4; 4.53, *d*, 1H, H-2, $J_{1,2} = 3.7$; 5.83, *d*, 1H, H-1; 7.52–7.98, group of signals, 5H, aromatic.

5-O-*acetyl-1,2*-O-*cyclohexylidene-3*-O-*methyl*-α-*D-xylofuranose (**2a**)*

5-*O*-Benzenesulfonyl-1,2-*O*-cyclohexylidene-3-*O*-methyl- -D-xylofuranose (1.15 g, 3 mmol), anhydrous sodium acetate (2.4 g, 29 mmol) and dimethylsulfoxide were mixed together in a 50 mL round-bottom, long neck reaction flask, and heated with an open flame and boiled for 10–15 s. After cooling to room temperature, the semi-solid reaction mixture was extracted with benzene–petroleum ether 1:1 (5 20 mL). The combined extracts were washed with concentrated aqueous sodium chloride (2 10 mL), dried, and decolourised with active carbon. Evaporation of solvent in vacuo and distillation at 150 ºC/0.02 mm Hg gave pure **2a** as an oil (800 mg, 92.7 %).

TABLE I. ˙C-NMR spectral parameters of compounds 1-3 (in ppm)

No.	C1	C2	C3	C4	C5	3', 4', 5'	2', 6'	C1'	Aromatic	C=O	Me
1a	104.51	80.53	83.37	77.11	67.14	23.30, 23.61, 24.57	35.47, 36.21	112.44	127.70, 129.07, 133.71, 135.45 Cq		57.54
2a	104.75	80.94	84.34	77.97	62.42	23.51, 23.81, 24.81	35.65, 36.36	112.41		170.84	20.86 57.86
2b	104.24	82.52	81.66	76.21	60.61	23.24, 23.58, 24.55	35.44, 36.01	113.51	127.70, 129.35, 134.22, 135.56 Cq	170.04	20.45
2c	104.22	82.51	81.43	76.21	60.70	23.21, 23.56, 24.53	35.43, 36.00	113.07	127.72, 129.90, 132.49 Cq, 145.38 Cq	170.00	20.61 21.67
3a	104.42	81.13	85.28	79.90	60.59	23.43, 23.73, 24.73	35.65, 36.30	112.27			57.67
3b	104.16	82.82	81.93	79.25	59.50	23.39, 23.7, 24.68	35.67, 36.15	113.31	127.82, 129.51, 134.44, 135.54 Cq		
3c	104.06	82.73	81.62	79.18	59.42	23.28, 23.61, 24.58	35.58, 36.05	113.0	127.75, 130.01, 132.3 Cq, 145.58 Cq		21.56

For $C_{14}H_{22}O_6$, found: C 58.97, H 7.64, calculated: C 58.73, H 7.75.

Mass spectra: 286(M^+, 79), 255(12.5), 244(100), 170(36), 151(49).

^{1}H-NMR: 1.3–1.7, *m*, 10H, from cyclohexylidene; 2.08, *s*, 3H, acetyl methyl group; 3.39, *s*, 3H, methoxy methyl group; 3.74, *d*, 1H, H-3, $J_{3,4}$ = 3.1; 4.19, *dd*, 1H, H-5a, $J_{5a,5b}$ =12.6, $J_{4,5a}$=8.5; 4.32–4.40, *m*, 2H, H-5b and H-4; 4.56, *d*, 1H, H-2, $J_{1,2}$ = 3.8; 5.92, *d*, 1H, H-1.

5-O-*Acetyl-3*-O-*benzenesulfonyl-1,2*-O-*cyclohexylidene*-α-*D-xylofuranose* ***(2b)***

3,5-di-*O*-Benzenesulfonyl-1,2-*O*-cyclohexylidene- -D-xylofuranose (2.0 g, 3.92 mmol), anhydrous sodium acetate (4.0 g, 48.8 mmol) and dimethylsulfoxide (10 mL) were mixed together in a 50 mL round-bottom, long neck reaction flask and heated with an open flame and boiled for 10–15 s. On cooling, the reaction mixture formed a semi-solid mass, which was extracted with benzene–petroleum ether 1:1 (5 20 mL). The combined extracts were washed with concentrated aqueous sodium chloride (3 10 mL), dried, and the solvent evaporated. The remaining oil solidified on standing, and after crystallisation from methanol–ethyl acetate gave **2b**, m.p. 111–112 ºC (1.52 g, 94 %). $_D^{20}$ = –27.31 (*c* 0.997, $CHCl_3$).

For $C_{19}H_{24}O_8S$, found: C 55.22, H 5.58, calculated: C 55.32, H 5.86.

Mass spectra: 412(M^+, 65.1), 328(15.4), 371(85.9), 240(21.6), 150(81.7).

^{1}H-NMR: 1.33–1.72, *m*, 10H, from cyclohexylidene; 1.96, *s*, 3H, methyl; 4.03, *dd*, 1H, H-5a, $J_{5a,5b}$ = 11.65, $J_{5a,4}$ = 5.8; 4.15, *dd*, 1H, H-5b, $J_{5b,4}$ = 6.7; 4.41, *m*, 1H, $J_{3,4}$ = 2.9; 4.70, *d*, 1H, H-2, $J_{1,2}$ = 3.7; 4.91, *d*, 1H, H-3; 5.94, *d*, 1H, H-1; 7.54–7.98, 5H, aromatic.

5-O-*Acetyl-1,2*-O-*cyclohexylidene-3*-O-*tosyl*-α-*D-xylofuranose*[9] ***(2c)***

1,2-*O*-cyclohexylidene-3,5-di-*O*-tosyl- -D-xylofuranose[10] (2.0 g, 3.71 mmol), anhydrous sodium acetate (4.0 g, 48.8 mmol) and dimethyl sulfoxide (10 mL) were mixed together in a 50 mL round-bottom, long neck reaction flask and heated with an open flame and boiled for 10–15 s. On cooling, the reaction mixture formaed a semisolid mass, which after the described workup and crystallisation from methanol–ethyl acetate 9:1, gave **2c**, m.p. 136–138 ºC (1.37 g, 87 %), $_D^{20}$ = –27.17 (*c* 0.91, $CHCl_3$).

Mass spectra: 426(M^+, 65.1), 397(21.5), 382(71.2), 254(35.8), 169(54.8), 139(74.4).

^{1}H-NMR: 1.31–1.72, *m*, 10H, from cyclohexylidene; 1.96, *s*, 3H, acetyl methyl group; 2 methyl group; 4.04, *dd*, 1H, H-5a, $J_{5a,5b}$ = 11.6, $J_{5a,4}$ = 5.7; 4.15, *dd*, 1H, H-5b, $J_{5b,4}$ = 6.7; 4.41, *m*, 1H, H-4, $J_{3,4}$ = 2.9; 4.70, *d*, 1H, H-2, $J_{1,2}$ = 3.7; 4.88, *d*, 1H, H-3; 5.94, *d*, 1H, H-1; 7.37 and 7.81, 2*d*, 4H, aromatic.

1,2-O-*Cyclohexylidene-3*-O-*methyl*-α-*D-xylofuranose* ***(3a)***

The 5-*O*-acetyl-1,2-*O*-cyclohexylidene-3-*O*-methyl derivative **2a** (750 mg, 2.6 mmol) was added to sodium hydroxide (0.5 g) dissolved in methanol (5 mL), and left at room temperature. The end of reaction was established after 30 min (vide TLC). The reaction mixture was concentrated in an evaporator and chloroform (50 mL) added. The chloroform solution was washed with concentrated sodium chloride, dried and decolourised with active carbon. Evaporation of chloroform left **3a** as an oil (560 mg, 88 %). Analysis vide TLC revealed a single spot.

Mass spectra: 244(M^+, 30.12), 202(52.3), 139(36.5), 100(15.07), 55(39.17).

^{1}H-NMR: 1.33–1.74, *m*, 10H, from cyclohexylidene; 2.38, *bs*, 1H, O*H*; 3.43, *s*, 3H, methyl; 3.82, *d*, 1H, H-3, $J_{3,4}$ = 3.0; 3.85–3.96, *m*, 2H, 5-CH_2, $J_{5a,5b}$ = 11.9, $J_{5a,4}$ = 7.3, $J_{5b,4}$ = 5.2; 4.27, *m*, 1H, H-4; 4.58, *d*, 1H, H-2, $J_{1,2}$ = 3.7; 5.95, *d*, 1H, H-1.

3-O-*Benzenesulfonyl-1,2*-O-*cyclohexylidene*-α-*D-xylofuranose* ***(3b)***

The 5-*O*-acetyl-3-*O*-benzenesulfonyl derivative **2b** (4.12 g, 10 mmol) was added to a solution of sodium hydroxide (0.5 g) in mixture of methanol (80 mL) and water (20 mL) and left stirring at room temperature. After 10 min all the solid had dissolved and TLC revealed the end of reaction after 30 min. The reaction mixture was concentrated to approximately 15 mL, and chloroform (100 mL) added. Washing the chloroform layer with concentrated sodium chloride, drying and evaporation of the chloroform left **3b** as a colourless oil (3.40 g, 92 %), pure according to TLC.

Mass spectra: 370(M^+, 3.12), 327(2.8), 285(1.5), 139(4.19), 98(44.9), 69(39.2).

^{1}H-NMR: 1.2–1.9, *m*, 10H, from cyclohexylidene; 2.32, *t*, 1H, 5-OH, $J_{OH,5\text{-}CH_2}$ = 6.3; 3.60, *m*, 1H, H-5a, $J_{5a,5b}$ = 11.8, $J_{4,5a}$ = 6.1; 3.77, *m*, 1H, H-5b, $J_{4,5b}$ = 6.6; 4.33, *td*, 1H, H-4, $J_{3,4}$ = 2.5; 4.56, *d*, 1H, H-2, $J_{1,2}$ = 3.7; 4.92, *d*, 1H, H-3; 5.89, *d*, 1H, H-1; 7.53–7.99, *m*, 5H, aromatic.

1,2-O-*Cyclohexylidene-3*-O-*tosyl*-α-*D-xylofuranose*[11] ***(3c)***

5-*O*-Acetyl-1,2-*O*-cyclohexylidene-3-*O*-tosyl- -D-xylofuranose (**2c**) (4.26 g) was added to a solution of sodium hydroxide (0.5 g) in methanol (100 mL) and left stirring at room temperature. Thin-layer chromatography showed the complete disapearance of the starting material and the formation of a more polar product. The reaction mixture was then concentrated to about 20 mL and chloroform (100 mL) added. The chloroform solution was washed with concentrated sodium chloride (3 15 mL), decolourised with active carbon, dried and evaporated to leave an oil which crystallysed on standing. Recrystallisation from di-*iso*-propyl ehter– petrolether gave **3c**, m.p. 87 ºC (3.17 g, 83 %). $_D^{20}$ = –7.22 (*c* 0.97, $CHCl_3$).

For $C_{18}H_{24}O_7S$, found: C 56.40, H 6.13, S 8.23, calculated: C 56.23, H 6.29, S 8.33.

Mass spectra: 384(M^+, 100), 343(78.9), 267(14), 155(57), 139(84).

^{1}H-NMR: 1.27–1.8, *m*, 10H, from cyclohexylidene; 2.01, *t*, 1H, 5-O*H*, $J_{H5,OH}$ = 6.5; 2.48, *s*, 3H, CH_3; 3.65, *m*, 1H, H-5a, $J_{5a,5b}$ = 11.9, $J_{5a,4}$ = 6.4; 3.80, *m*, 1H, H-5b, $J_{5b,4}$ = 6.4; 4.36, *td*, 1H, H-4, $J_{3,4}$ = 2.8; 4.59, *d*, 1H, H-2, $J_{1,2}$ = 3.7; 4.92, *d*, 1H, H-3; 5.91, *d*, 1H, H-1.

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И З В О Д

СЕЛЕКТИВНО ДЕСУЛФОНОВАЊЕ 3,5-ДИСУЛФОНАТА D-КСИЛОФУРАНОЗЕ

ПАВЛЕ А. ХАЦИЋ* и НАДА С. ВУКОЈЕВИЋ

Институт за хемију, Природно-математички факултет, Универзитет у Новом Саду, Трг Д. Обрадовића 3, 21000 Нови Сад

Разрађена је метода за добијање деривата D-ксилофуранозе са слободном терминалном (C5) алкохолном групом. Поступак полази од лако доступних 3,5-дисулфонил естара моноциклохексилиден-D-ксилофуранозе и састоји се у селективној супституцији 5-сулфонилестарске групе ацетилном групом. Селективна супституција се врши ацетатним јоном из натријум-ацетата у диметилсулфоксиду, при чему настају одговарајући 5-ацетати. Ови се лако хидролизују натријум-хидроксидом у систему метанол–вода дајући високе приносе 1,2,3-трисупституисаних деривата D-ксилофуранозе.

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