Unexpected cycloreversion of a tosylated sugar oxetane under E2 conditions. The facile formation of 2-(2-furanyl)-1,3-dioxolane from a novel 2,5:4,6-dianhydro-L-idose derivative

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Abstract: 2,5:4,6-Dianhydro-3-O-p-toluenesulfonyl-L-idose ethylene acetal (4) was synthesized with the aim of studying its chemical behavior in the presence of several basic agents (Bu₄NF/MeCN, NaOMe/MeOH, KOBut/ButOH/THF, and NaH/DMSO). Treatment of 4 with sodium hydride in dimethyl sulphoxide at room temperature unexpectedly gave the 2-(2-furanyl)-1,3-dioxolane. The mechanism of the process presumably involved the initial conversion of 4 to the corresponding 2,3-unsaturated derivative 5, followed by a facile oxetane ring cycloreversion by the elimination of formaldehyde.

Keywords: 2,5-anhydro-L-idose; 2,5:4,6-dianhydro-L-idose; sugar oxetanes; cycloreversion.

In a previous paper,¹ the conversion of D-glucose to 2,5-anhydro-L-threo-hex-2-enose ethylene acetal derivatives of type 1 (Scheme 1) was described. Stereospecific hydrogenation of 1, followed by several functional groups manipulations furnished the 3,6-dideoxy derivative 3, a convenient intermediate for the synthesis of both (+)-muscarine and (+)-epi-muscarine.¹² In the search for an alternative and presumably a more efficient route towards the divergent intermediate 3, a new multistep sequence was planned which involves the conversion of D-glucose to 3 via the 2,3-unsaturated derivative 5. It was further assumed that the postulated intermediate 5 might be available through an E2 process performed on the 3-O-tosyl ester 4. Therefore the preparation of the 2,5:4,6-dianhydro-L-idose derivative 4 was first attempted starting from the known³ tritosylate 6 (Scheme 2).

The synthesis started with a regioselective nucleophilic displacement of the primary tosyoxy function in 6 with a bromide anion. The resulting 6-bromo derivative 7 was isolated by flash column chromatography (94 %) and characterized by NMR and mass spectral data.⁴ Treatment of 7 with ethylene glycol and toluene-4-sulfonic acid in refluxing benzene with azeotropic removal of water⁵ afforded the corresponding 2,5-anhydro-L-idose
derivative 8 (68 %), the structure of which was assigned unambiguously by NMR and mass spectral data. The desired product 8 was thus obtained in 64 % overall yield with respect to the tri-\(O\)-tosyl derivative 6. However, when the last two-step sequence was carried out without purification of the 6-bromo derivative 7, product 8 was obtained in an overall yield of 70 % with respect to the starting compound 6. Reaction of 8 with silver oxide and silver triflate in refluxing tetrahydrofuran gave a good yield of the corresponding oxetane 4 (83 %), which was fully characterized by the corresponding spectral and analytical data.

The next step of the work was directed to the conversion of the tosyloxy-oxetane 4 into the corresponding unsaturated derivative 5. In the original synthesis of (+)-muscarine, 1 the desired unsaturated intermediate 1 was readily obtained by treatment of the corresponding 3-\(O\)-tosyl ester with tetrabutylammonium fluoride in boiling acetonitrile. An attempted conversion of 4 to 5 under similar reaction conditions 1 was unsuccessful. According to TLC, after 24 h the reaction mixture still contained a significant amount of the starting compound 4 along with several additional components of higher polarity. No
traces of the desired olefin 5 could be detected in the reaction mixture, neither could any of
the polar by-products be obtained in pure form due to their similar chromatographic prop-
ties. Treatment of 4 under more basic reaction conditions, with sodium methoxide in
refluxing methanol, resulted in the cleavage of the methanesulphonate ester group to afford
the corresponding alcohol 9, isolated in 41% yield along with a similar amount of the
starting compound 4. Conversely, when 4 was treated with non-nucleophilic bases, such as
potassium tert-butoxide in tetrahydrofuran, or sodium hydride in dimethyl sulphoxide at
room temperature, an unexpected reaction occurred resulting in the formation of 2-(2-fu-
ranyl)-1,3-dioxolane (10). In the case of the NaH/DMSO reagent system, the furfural de-
rrivative 10 was isolated by flash column chromatography in 45% yield. The 1H and 13C
NMR spectral data of the thus obtained product 10 were in reasonable agreement with
those already reported. 

<table>
<thead>
<tr>
<th>TABLE I. NMR Spectral data for 10 (in CDCl3)</th>
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<td>Chemical shift δ (ppm) and J (Hz)</td>
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Thermal decomposition of simple oxetanes has already been described in the litera-
ture. Such a transformation has been reported for the oxetane itself and for some
3,3-diaklooxetanes, but in the temperature range 395–484 ºC and 407–448 ºC, respec-
tively. Cycloreversions of several non-carbohydrate oxetanes under laser flash photolysis
conditions were also recently described. However, the room temperature decomposi-
tion of sugar oxetanes under basic conditions has not been reported in the chemical litera-
ture so far.

Presumably, the conversion of 4 to 10 occurred via two successive reactions. The
first one is the expected E2 elimination of 4 to the corresponding 2,3-unsaturated de-
rrivative 5. The subsequent process presumably involved a facile cycloreversion of the
oxetane ring in 5 whereby the furfural derivative 10 was formed after elimination of
formaldehyde. It appears that the presence of a double bond in the five-member ring of
5 activates the oxetane ring towards the cycloreversion process. This assumption was
verified by molecular modelling (HyperChem Molecular Modelling Package, release
were performed *in vacuo* to identify the most stable conformation of the intermediate. This was done by using the conformational search module in HyperChem with a conjugate gradient limit of 0.01 kcal/mol Å. Endocyclic torsional variations were treated by applying the usage directed scheme with restricted ranges for ring torsion flexing in conjunction with a non-Metropolis criterion. High energy structures were defined as those possessing energies of 6 kcal/mol greater than the lowest accepted conformation, also those with relative energy differences within 0.05 kcal/mol were discarded in the post-optimisation runs. All low energy conformers that fell within the specified acceptance criteria were further refined by second series optimisations in which only the acyclic torsional parameters were varied by applying a lower gradient limit (0.001 kcal/mol Å). This procedure identified the conformer 5a as the most stable structure (Fig. 1). The same procedure was applied to the saturated oxetane 9 whereby the lowest energy conformation 9a was obtained. Moreover, structures 5a and 9a were finally optimised by using the semiempirical PM3 method. Preliminary results of these calculations showed that the oxetane ring of 5a has a unique distribution of positive and negative charge arranged in an alternating order that is favourable for the elimination of a mol of formaldehyde from 5 leading to the formation of 10. Conversely, PM3 calculations performed on the saturated oxetane 9a showed that both positive and negative charges are distributed over neighbouring atoms of the oxetane ring, with the negative charge located at the C-6 and O-6, while the positive charge was distributed over the C-4 and C-5. We believe that such a different charge distribution in 5a and 9a is responsible for the thermal stability of 9a, as well as for the high reactivity of the unsaturated derivative 5.

In conclusion, an unexpected base catalysed cycloreversion reaction of the newly synthesized sugar oxetane 4 has been described in this work. The mechanism of the process has been reasonably explained on the basis of preliminary semi-empirical PM3 calculations performed on the postulated intermediate 5.

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ЊОЧЕКИВАНА ЦИКЛРОВЕРЗИЈА ТОЗИЛОВАНОГ ШЕЋЕРНОГ ОКСЕТАНА У УСЛОВИМА Е2 ЕЛИМИНАЦИЈЕ. ЛАКО ФОРМИРАЊЕ
2-(2-ФУРАНИЛ)-1,3-ДИОКСОЛАНА ИЗ НОВОГ ДЕРИВАТА
2,5:4-ДИАНХИДРО-1-ИДОЗЕ

ВЕЛИМИΡ ПОПСАВИН, ЉУБИЦА РАДИЋ, МИРИЈАНА ПОПСАВИН И ВЕРА ТИРИН-НОВТА

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Нови дериват 2,5:4-дийнхидро-1-идозе 4 добијен је вишефазним трансформацијама d-глюзозе, а затим је испитано његово хемијско понаšање у присуству неколико базних агенаса (Bu4N+/MeCN, NaOMe/MeOH, KOBu/BrOH/TIH, NaH/DMSO). Реакцијом је дошло 4 са натројум-хидридом у диметилсулфоксиду, неочекивано је добијен 2-(2-фуранил)-1,3-диксоколан (10). Предложен је механизам ове необичне трансформације, који највероватније обухвата инхибицију Е2 елиминациони процес, праћен накладним фрагментацијама отварањем оксетанског престена уз издијање формалдегида.

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REFERENCES

4. Compound 7 (супра) [α]D +56.88° (c, 0.9 in CHCl3); 1H-NMR (CDCl3): δ 1.28 and 1.45 (2×s, 3 H each, CMe2), 2.45 and 2.48 (2×s, 3 H each, 2×MeC6H4SO2), 3.52 (dd, 1 H, J5,6a = 4.2, J6a,6b = 12.3 Hz, H-6a), 3.57 (dd, 1 H, J5,6b = 3.2 Hz, H-6b), 4.50 (dd, 1 H, J3,4 = 2.7, J4,5 = 6.5 Hz, H-4), 7.49 (m, 1 H, H-5), 4.82 (d, 1 H, J1,2 = 3.5 Hz, H-2), 5.00 (d, 1 H, H-3), 5.84 (d, 1 H, H-1), 7.29–7.96 (m, 8 H, 2×MeC6H4SO2); 13C-NMR (CDCl3): δ 21.62 and 21.68 (2×MeC6H4SO2), 26.33 and 26.59 (CMe2), 31.46 (C-6), 74.97 (C-5), 77.99 (C-4), 80.39 (C-3), 82.28 (C-2), 104.42 (C-1), 113.04 (CMe2), 128.01, 128.28, 129.71, 130.08, 132.28, 133.49, 145.22 and 145.73 (2×CMe2), 145.18 (MeC6H4SO2), 13.52 (MeC6H4SO2), 3.52 (MeC6H4SO2), 4.47 (MeC6H4SO2), 4.96 (MeC6H4SO2), 7.31–7.83 (2×MeC6H4SO2).
6. Compound 8: m.p. 154 °C (from MeOH); [α]D +95.96° (c, 1.15 in CHCl3); 1H-NMR (CDCl3): δ 2.46 (s, 3 H, MeC6H4SO2), 3.40–3.60 (m, 2 H, J6a,6b = 10.9, J6b,6c = 6.1, J5,6b = 3.5 Hz, H-6), 3.59–3.98 (m, 4 H, 2×CH2-диксоколе), 4.09 (dd, 1 H, J1,2 = 6.5, J5,6a = 3.5 Hz, H-2), 4.47 (m, 1 H, J3,4 = 3.5 Hz, H-3), 4.61 (dd, 1 H, J1,2 = 1.2 Hz, H-4), 4.88 (d, 1 H, H-1), 4.96 (dd, 1 H, H-3), 7.35 and 7.82 (2×d, 2 H each, MeC6H4SO2); 13C-NMR (CDCl3): δ 21.53 (MeC6H4SO2), 27.30 (C-6), 64.92 and 65.04 (2×CH2-диксоколе), 74.28 (C-4), 79.77 (C-2), 80.88 (C-3), 84.09 (C-3), 101.18 (C-1), 127.97, 129.62, 132.66 and 145.18 (MeC6H4SO2). FAB MS: m/z 446 (M+Na), 424 (M+H).
7. Compound 4: m.p. 137–138 °C (from MeOH); [α]D +77.58° (c, 0.27 in CHCl3); 1H-NMR (CDCl3): δ 2.45 (s, 3 H, MeC6H4SO2), 3.67–4.05 (m, 4 H, 2×CH2-диксоколе), 4.32 (dd, 1 H, J1,2 = 6.5, J5,6a = 3.3 Hz, H-2), 4.42 (dd, 1 H, J5,6a = 2.5, J6a,6b = 8.4 Hz, H-6a), 4.81 (dd, 1 H, J5,6b = 4.7 Hz, H-6b), 5.01 (d, 1 H, H-3), 5.02 (d, 1 H, H-1), 5.07 (m, 1 H, J1,2 = 3.8 Hz, H-5), 5.28 (d, 1 H, H-4), 7.31–7.83 (2×d, 2 H each, MeC6H4SO2); 13C-NMR (CDCl3): δ 21.60 (MeC6H4SO2), 65.17 (2×CH2-диксоколе), 77.60 (C-5), 77.93 (C-6), 80.59 (C-2), 80.89 (C-3), 88.91 (C-4), 100.97 (C-1), 128.10, 129.64, 133.02 and 145.06 (MeC6H4SO2). EI MS: m/z 343 (M+H). Anal. Calcd. for C13H13O5S: C, 52.62; H, 5.30; S, 9.37. Found: C, 52.82; H, 5.32; S, 9.17.
8. 2,5:4,6-Dianhydro-6-йдозе етилене акетал (9): To a suspension of 4 (0.1712 g, 0.50 mmol) in dry MeOH (3 mL) was added 1 M NaOMe in MeOH (2 mL). The resulting mixture was refluxed for 3 h, then hea
tralized with 1 M AcOH in MeOH (2 mL) and evaporated. Flash column chromatography (9:1 tolu-ene–Me$_2$CO) of the residue gave pure 9 (0.0384 g, 41 %) as a colourless syrup, [α]$_D^2$ +9.26º (c, 1.1 in CHCl$_3$); $^1$H-NMR (CDCl$_3$): δ 3.07 (bs, 1 H, exchangeable with D$_2$O, OH), 3.89–4.14 (m, 4 H, 2×CH$_2$-dioxolane), 4.33 (d, 1 H, $J_{2,3}$ = 3.0 Hz, H-3), 4.42 (m, 2 H, H-2 and H-6a), 4.81 (dd, 1 H, $J_{5,6b}$ = 8.3 Hz, H-6b), 5.05 (m, 1 H, H-5), 5.14 (d, 1 H, $J_{4,5}$ = 3.8 Hz, H-4), 5.30 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1); $^{13}$C-NMR (CDCl$_3$): δ 65.10 and 65.41 (2×CH$_2$-dioxolane), 74.19 (C-3), 77.18 (C-5), 77.75 (C-6), 81.16 (C-2), 91.35 (C-4), 102.32 (C-1). FAB MS: m/z 189 (M$^+$+H), 187 (M$^+$–H), 171 (M$^+$–OH).

9. 2-(2-Furanyl)-1,3-dioxolane (10): To a solution of 4 (0.3424 g, 1.00 mmol) in dry DMSO (7 mL) was added NaH (80 % dispersion in mineral oil, 0.06 g, 1.00 mmol). The mixture was stirred for 16 h at room temperature, then poured into 5 % aq NH$_4$Cl and extracted with Et$_2$O (6×10 mL). The combined extracts were dried (Na$_2$SO$_4$) and evaporated to a yellow liquid (0.0913 g). Flash column chromatography of the residue gave pure 10 (0.0628 g, 45 %) as a colourless liquid. $^1$H and $^{13}$C-NMR data are presented in Table I. FAB MS: m/z 141 (M$^+$+H); HR MS (ES$^+$): m/z 163.0370 (M$^+$+Na). Calcd. for C$_7$H$_8$O$_3$Na: 163.0371.


