Oxidations of Cyclic Hemiacetals with Selenium Dioxide

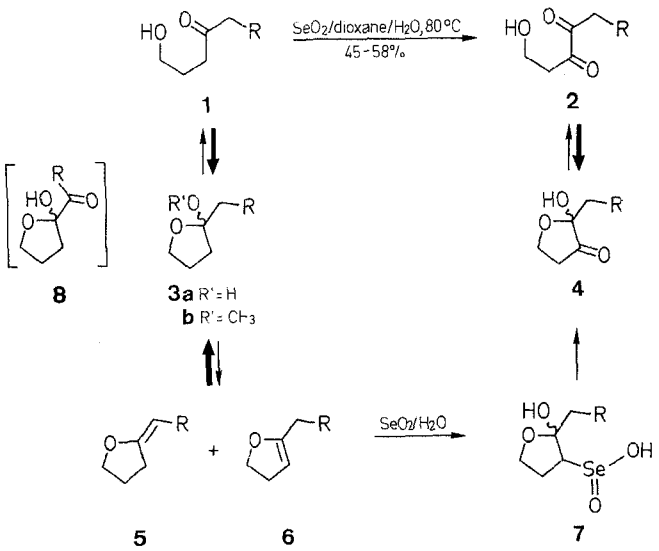
Károly Kánai,*[a] István Tömösközi[b]

[a] CHINOIN Research Centre, H-1325 Budapest, Hungary
[b] Central Research Institute for Chemistry, H-1025 Budapest, Hungary

A convenient one-step regioselective synthesis of cyclic α-oxo-hemiacetals **10**, **12**, and **14** by the selenium dioxide oxidation of hemiacetals **9**, **11**, and **13**, respectively, is reported.

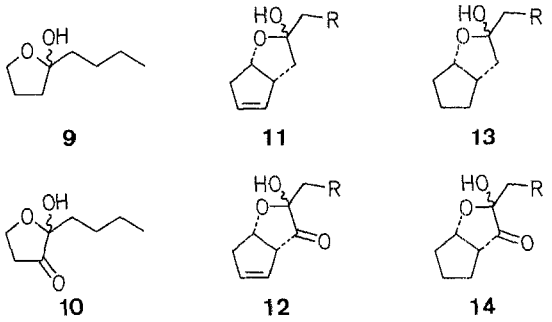
The oxidation of α-methylene carbonyl compounds with selenium dioxide is a well known procedure.[1,2] We have used this reagent to oxidize γ-hydroxy ketones **1** and have found that this provides a simple and regioselective method for synthesizing 2-hydroxy-3-oxotetrahydrofurans with general structure **4**.

Such compounds have been previously accessible only by multistep routes[3] from the dihydrofurans **6**, the preparation of which is complicated by formation of the *exo*-methylene isomer **5** as a contaminant. In contrast, reaction of the tautomeric mixture **1** ⇄ **3a** with 1.2 equivalents of selenium dioxide in moist dioxane at 80 °C proceeds almost exclusively through oxidation of the ring methylene group in the 3-position of **3** (Table). Only traces of **8**, the product of oxidation of an *exo*-methylene group, were observed. All our attempts to isolate **8** have failed.

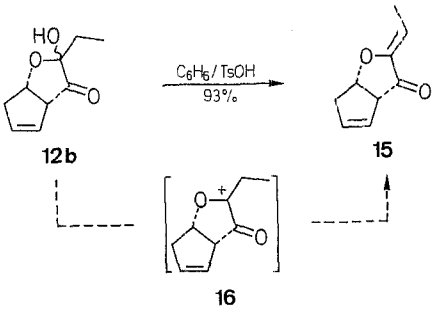


Scheme **A**

For convenience, either the hemiacetal **3a** or the acetal **3b** can be used in this reaction since, in the presence of water, **3b** is rapidly converted into **3a** by cleavage under catalytic action of the strongly acidic selenium oxide hydrate. By this means, compounds **9**, **11**, and **13** were converted to **10**, **12**, and **14**, respectively.



The structure of the products was elucidated by ^{1}H-NMR spectroscopy. In the cases of **10**, **12d**, and **14b**, the identification of the exocyclic methylene group was hampered by the presence of overlapping multiplets, hence in these cases the structure was further confirmed by comparison with authentic samples.[4] The structure of **12b** was also confirmed by its ready dehydration in benzene, with *p*-toluenesulfonic acid as catalyst, to the fully characterized **15**.



Scheme **B**

Compound **15** appears to form selectively. The configuration of **15** was tentatively assigned as Z-isomer on the basis of comparative ^{1}H-NMR data in two solvents.[5] The Z-geometry of the double bond can be explained by mechanistic considerations as well. The presumed carbocation **16** could be stabilized by loss of proton from the adjacent methylene group to give a sterically less hindered Z-isomer.

To explain the regioselectivity we assume that **6**, formed by consecutive equilibria from **1** in low concentration, although in higher concentration[6] than **5**, constitutes the actual species attacked by the selenium dioxide. This view is born out by the fact that under identical conditions oxidation of **6** gave the same products. Further support was gained from the observation that blocking the hydroxy group of **1** by acetylation leads to a striking decrease of reactivity, probably because formation of highly reactive enolic species[7] is a relatively unfavorable process. Under the reaction conditions used γ-acetoxyketones were recovered unchanged, apart from negligible decomposition.

Table. Oxidation of Cyclic Hemiacetals with Selenium Dioxide

Starting Material	Product	R	Yield (%)[a]	Molecular Formula[b]	IR (neat)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ
9	**10**		50	$C_8H_{14}O_3$ (158.2)	1720 (CO); 3320 (OH)	0.92 (t, 3H); 1.15–2.50 (m, 9H); 3.85 (m, 2H)
11a	**12a**	H	48	$C_8H_{10}O_3$ (154.1)	1725 (CO); 3320 (OH)	1.35 (s, 3H); 2.40 (m, 3H); 2.95 (m, 1H); 4.65 (m, 1H); 5.50, 5.90 (2 m, 1H each)[e]
11b	**12b**	CH_3	45	$C_9H_{12}O_3$ (166.2)	1720 (CO); 3320 (OH)	0.94 (t, 3H); 1.75–2.65 (m, 5H); 3.05 (m, 1H); 4.85 (m, 1H); 5.55, 5.85 (2 m, 1H each)[e]
11c	**12c**	C_6H_5	42	$C_{14}H_{14}O_3$ (230.3)	1725 (CO); 3325 (OH)	2.60–3.15 (m, 5H, with singlet at 2.90 for CH_2–Ph); 3.75 (m, 1H); 5.55 (m, 2H); 5.95 (m, 1H); 7.20–7.95 (m, 5H)[f]
11d	**12d**	$(CH_2)_3CO_2CH_3$	58	$C_{13}H_{18}O_5$ (254.3)	1720 (CO); 3325 (OH)	1.15–2.60 (m, 11H); 2.85 (m, 1H); 3.65 (s, 3H); 4.75 (m, 1H); 5.50, 5.85 (2 m, 1H each)[e]
13a	**14a**	H	46	$C_8H_{12}O_3$ (156.2)	1725 (CO); 3320 (OH)	1.30 (s, 3H); 1.5–2.15 (m, 7H); 2.85 (m, 1H); 4.50 (m, 1H)[e]
13b	**14b**	n-C_3H_7	55	$C_{11}H_{18}O_3$ (198.2)	1720 (CO); 3320 (OH)	0.95 (t, 3H); 1.15–2.35 (m, 13H); 2.85 (m, 1H); 4.55 (m, 1H)[e]

[a] Yield of pure, isolated product.
[b] The microanalyses are in satisfactory agreement with the calculated values: C ±0.27, H ±0.29.
[c] Recorded on a Pye-Unicam SP-1000 infrared spectrophotometer.
[d] Obtained on a Bruker WP-80 DS spectrometer.
[e] Measured in $CDCl_3$.
[f] Measured in Acetone-d_6.

Selenium Dioxide Oxidation of Cyclic Hemiacetals; General Procedure: Selenium dioxide (12 mmol) is added to a stirred solution of cyclic hemiacetal (10 mmol) in moist dioxane (dioxane/water, 20:1) at 80 °C. Stirring is continued for 1 h and the reaction mixture is then cooled and filtered. The filtrate is evaporated and the residue is dissolved in ethyl acetate (50 mL) washed with 10% aq. $NaHCO_3$ solution (10 mL) and dried (Na_2SO_4). After evaporation of the solvent, the oily residue is purified by flash chromatography on silica gel (eluent: 30% ethyl acetate in hexane).

3-Ethylidene-4-oxo-1-oxa-*cis*-bicyclo[3.3.0]oct-6-ene (15):
A solution of **12b** (168 mg, 1 mmol) and *p*-toluenesulfonic acid (10 mg) in dry benzene (10 mL) is stirred for 2 h at 80 °C. The reaction is quenched by the addition of sat. $NaHCO_3$ solution (1 mL). The organic layer is washed with brine (3 mL) and dried (Na_2SO_4). Removal of the solvent gives **15** as an oil which is purified by flash chromatography on silica gel (20% ethyl acetate in hexane: $R_f = 0.25$).

$C_9H_{10}O_2$ (150.2) calc. C 72.0 H 6.71
found 71.76 6.28

IR (neat): ν = 1720 (C=O); 1650, 1620 cm^{-1} (C=C).

MS: *m/z* (rel. int. %) = 150 (M^+, 85).

UV (CH_3OH): λ_{max} = 285 nm (ε = 7900).

^{13}C-NMR ($CDCl_3$/TMS): δ = 10,65, 41.66, 58.26, 80.62, 102.10, 126.32, 132.90, 148.89, 197.23.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.55 (d, 3H, J = 7.3 Hz); 2.25 (m, 2H); 3.1 (m, 1H); 4.5 (m, 1H); 5.35 (m, 2H); 5.55 (q, 1H, J = 7.3, 7.5 Hz).

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(4) Authentic samples of **10, 12d** and **14b** were prepared from the corresponding dihydrofurans (cf **6**) by the following known[3] sequence of reactions: 1. OsO_4/*N*-methylmorpholine-*N*-oxide in THF; 2. methanol/pyridinium tosylate; 3. Oxidation with PDC.[8] Samples obtained in the selenium dioxide oxidation processes were also converted into methyl acetals (methanol/$Et_2O \cdot BF_3$) prior to comparison by TLC, IR, ^{1}H-NMR and MS.
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