Formation of isomeric iodohydrins from terminal alkenes upon oxidation by a $RuCl_3$—$NaIO_4$ system

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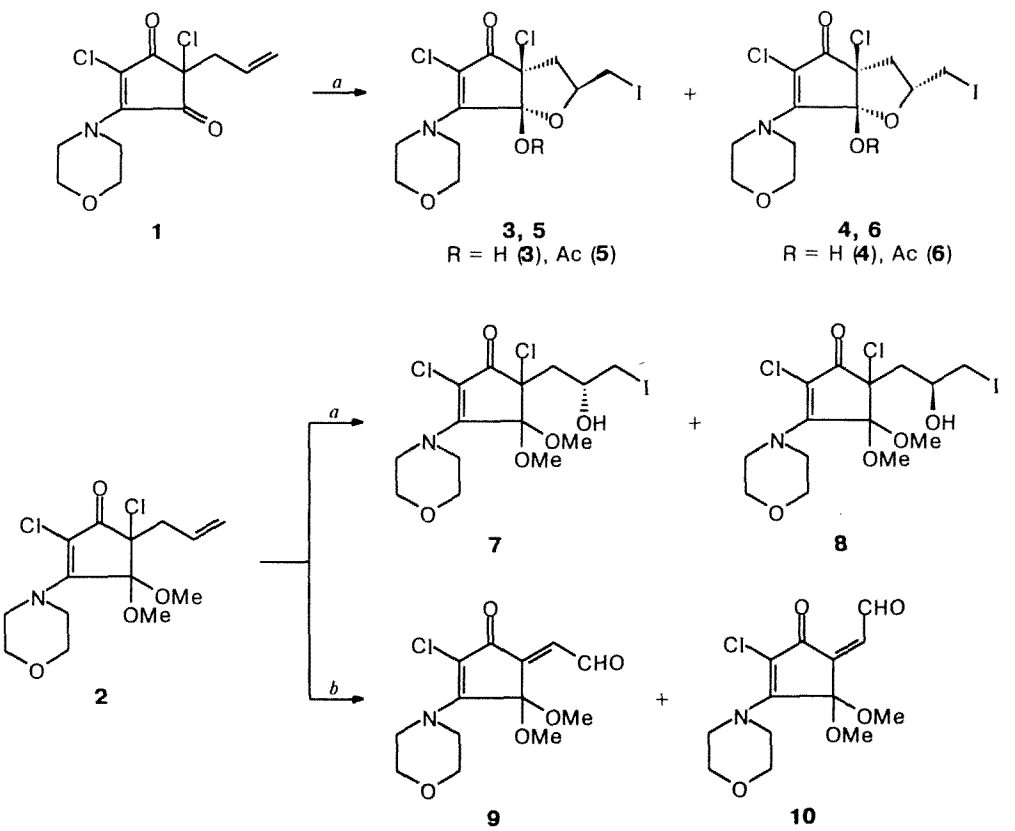
$RuCl_3$-catalyzed periodate oxidation of alkenes affords isomeric iodohydrins.

Key words: alkenes, catalysis, oxidation, iodohydrins.

The use of a $RuCl_3 \cdot nH_2O$ (catalyst)—$NaIO_4/CCl_4$—$MeCN—H_2O$ system makes it possible to oxidize alcohols, aldehydes, ethers, aromatic compounds, and olefins under mild conditions to form the corresponding acids, esters, and ketones in high yields.[1] It is believed[2—5] that $RuCl_3 \cdot nH_2O$ reacts with $NaIO_4$ to generate *in situ* a powerful oxidizing agent, RuO_4, which is generally responsible for the oxidation process. After oxidation of an organic molecule by this reagent, any low-valent ruthenium compounds that form undergo reoxidation by $NaIO_4$ to form RuO_4, which returns to the catalytic cycle.

We attempted to use this system for the oxidative cleavage of the terminal double bond in compound **1**, which was obtained by acid hydrolysis of dimethyl ketal (**2**) reported previously[6] (Scheme 1). However, the bicyclic hemiketal of iodohydrin (**3**) was isolated from the reaction mixture as a major product. This product con-

Scheme 1



1 **3, 5** R = H (**3**), Ac (**5**) **4, 6** R = H (**4**), Ac (**6**) **2** **7** **8** **9** **10**

Reagents and conditions: *a*. $RuCl_3 \cdot 3\ H_2O$—$NaIO_4$/MeCN—H_2O—CCl_4; *b*. OsO_4—$NaIO_4$/THF—H_2O.

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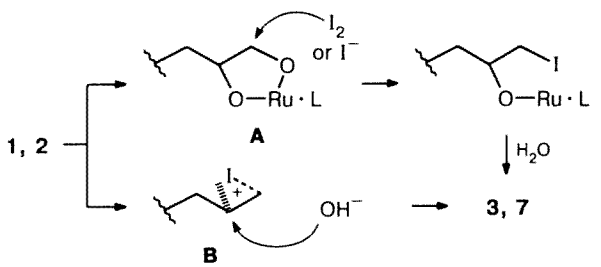
tained 5—10% of the 3α-epimer (**4**), which was difficult to separate. A mixture of epimers **3** and **4** was transformed to acetates (**5** and **6**) under the action of Ac_2O in Py. Under analogous conditions, a mixture of iodohydrins (**7** and **8**) was obtained from dimethyl ketal **2** in a ratio of 8 : 1, whereas OsO_4-catalyzed periodate cleavage[7] of dimethyl ketal **2** under conditions reported for analogous compounds[8] gave a mixture of the expected *Z*- and *E*-enals (**9** and **10**) in a ratio of 3 : 1 (^{1}H NMR) in a total yield of 70% (^{1}H NMR).

The structures of ketols **3** and **4** were based on the spectral data. Thus, the ^{1}H NMR spectrum of the predominant isomer **3** shows a high-field signal of diastereotopic protons at the C(4) atom, which was assigned to H_β because of the directed steric and electronic effects of the *cis*-oriented Cl atom at C(5). The coupling constant ($^3J_{4\beta,3}$ = 10.4 Hz) is indicative of the β orientation of the iodomethyl group at the C(3) atom.

The oxidation of dimethyl ketal **2** affords predominantly one diastereoisomer (**7**). The *R* configuration of the C(2′) chiral center, which is shown in Scheme 2, was assumed based on the similarity in the parameters of the ^{1}H NMR spectra for the diastereotopic protons at the C(1′) atom and those at the C(4) atom in the related compounds **3** and **5**.

Scheme 2



The formation of unusual products **3** and **7** can be rationalized as follows. OsO_4-catalyzed periodate oxidation of compound **2** was accompanied by liberation of insoluble $NaIO_3$ and decoloration of the reaction mixture, whereas when the oxidation was carried out in the presence of $RuCl_3$, the reaction mixture remained homogeneous. The appearance of the dark-red color typical of I_2 solutions is, apparently, associated with the fact that both the initial compound $RuCl_3$ and the low-valent Ru compounds that form after oxidation of the double bond reduce $NaIO_4$ to I_2 and, possibly, further to I^-. It can be suggested that the oxidative addition of RuO_4 to the terminal double bond of compounds **1** and **2** gives intermediate ruthenates of type **A**, which are opened regioselectively with I_2 or I^-. It was determined by TLC that several low-polar intermediates form at the initial stage. These compounds transform gradually to **3** and **7**, which is indicative of a competitive alternative reaction of the formation of iodohydrins initiated by I_2.

It was demonstrated by special experiments that the transformation **2**→**7** in an I_2/CCl_4—MeCN—H_2O system in the absence of $RuCl_3$ proceeds readily *via* the iodonium cation **B**. However, it is also evident that the catalytic amounts of $RuCl_3$ used in the experiments are insufficient to generate I_2 in the amount that is necessary for the stoichiometric reaction to proceed through path **B**. Therefore, iodohydrins **3** and **7** are obtained, apparently, through both pathways, *i.e.*, *via* intermediates **A** and **B**.

Therefore, in the design of a synthesis, the possible formation of iodohydrins from olefins through the action of a $RuCl_3$—$NaIO_4$ system should be taken into account.

Experimental

The IR spectra were recorded on an UR-20 or Specord M-80 spectrometer (as thin films or as Nujol mulls). The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively); Me_4Si was used as the internal standard; $CDCl_3$ was used as the solvent. The mass spectra were measured on an MKh-1320 instrument, the ionizing voltage was 70 eV, the temperature of an ionization chamber was 50—70 °C.

2-Allyl-2,5-dichloro-4-morpholinocyclopent-4-ene-1,3-dione (1). A 1 : 1 H_2SO_4—H_2O mixture (15 mL) was added to a solution of ketone **2** (1.4 g, 4.18 mmol) in MeOH (20 mL). The mixture was stirred at 50 °C for 6—8 h. After completion of the reaction (TLC), the methanol was evaporated, and the residue was extracted with $CHCl_3$. The combined organic extracts were dried with $MgSO_4$ and evaporated. Crystalline diketone **1** was obtained in a yield of 1.1 g (91%), m.p. 115 °C (ethyl acetate—hexane, 1 : 1). IR, ν/cm^{-1}: 1588, 1690, 1750. ^{1}H NMR ($CDCl_3$), δ: 2.76 (m, 2 H, CH_2); 3.75 (t, 4 H, 2 CH_2N, J = 4.8 Hz); 3.98 (m, 4 H, 2 CH_2O); 5.00—5.10 (m, 2 H, $=CH_2$); 5.10—5.40 (m, 1 H, CH=). ^{13}C NMR ($CDCl_3$), δ: 39.38 (CH_2); 48.59 (CH_2N); 62.55 (C(2)); 66.91 (CH_2O); 119.01 (C(5)); 121.64 and 129.09 (CH_2=CH); 150.44 (C(4)); 184.60 (C(1)); 191.05 (C(3)). Found (%): C, 49.00; H, 4.35; Cl, 24.27. $C_{12}H_{13}Cl_2NO_3$. Calculated (%): C, 49.65; H, 4.48; Cl, 24.13.

5β,7-Dichloro-1β-hydroxy-3β-iodomethyl-8-morpholino-2-oxabicyclo[3.3.0]oct-7-en-6-one (3) and its 3α-epimer (4). $RuCl_3 \cdot 3\ H_2O$ (8 mg, 0.03 mmol) was added to a stirred suspension of compound **1** (0.4 g, 1.38 mmol) and $NaIO_4$ (0.56 g, 5.0 mmol) in a MeCN—CCl_4—H_2O mixture (2 : 2 : 3 v/v, 14 mL). The mixture was stirred at ~20 °C for 12 h and then extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on SiO_2 (a 10 : 1 MeOH—$CHCl_3$ mixture was used as the eluent). The initial diketone **1** was isolated in a yield of 0.1 g, and a mixture of isomeric iodohydrins **3** and **4** was obtained in a yield of 0.3 g (62% with respect to the consumed **1**) in a ratio of 10 : 1 (^{1}H NMR). **Compound 3.** IR, ν/cm^{-1}: 1572, 1576, 1584, 1688, 3256. ^{1}H NMR ($CDCl_3$), δ: 2.17 (dd, 1 H, 4-H_β, J = 10.4 and 13.6 Hz); 2.96 (dd, 1 H, 4-H_α, J = 5.2 and 13.6 Hz); 3.20—3.40 (m, 2 H, CH_2I); 3.50 (s, 1 H, OH); 3.68—3.75 (m, 1 H, 3-H); 3.75—4.20 (m, 8 H, 2 CH_2O,

2 CH_2N). ^{13}C NMR ($CDCl_3$), δ: 5.38 (CH_2I); 44.37 (C(4)); 49.86 (CH_2N); 67.19 (CH_2O); 74.44 (C(5)); 75.37 (C(3)); 100.93 (C(1)); 105.80 (C(7)); 158.81 (C(8)); 185.49 (C(6)).

Compound 4. ^{13}C NMR ($CDCl_3$), δ: 7.45 (CH_2I); 45.90 (C(4)); 49.86 (CH_2N); 67.18 (CH_2O); 76.84 (C(5)); 78.88 (C(3)); 98.50 (C(1)); 107.26 (C(7)); 160.10 (C(8)); 185.00 (C(6)).

1β-Acetoxy-5β,7-dichloro-3β-iodomethyl-8-morpholino-2-oxabicyclo[3.3.0]oct-7-en-6-one (5) and its 3α-epimer (6) were obtained in a yield of 86% by acylating a mixture of **3** and **4** with Ac_2O—Py (1 : 3) at 20 °C. **Compound 5.** IR, ν/cm^{-1}: 1480, 1600, 1710, 1760. ^1H NMR ($CDCl_3$), δ: 2.21 (s, 3 H, Me); 2.46 (dd, 1 H, 4-H_β, J = 10.6 and 12.9 Hz); 3.05 (dd, 1 H, 4-H_α, J = 5.8 and 12.9 Hz); 3.30—3.40 (m, 2 H, CH_2I); 3.84—4.20 (m, 9 H, 3-H, 2 CH_2O, 2 CH_2N). ^{13}C NMR ($CDCl_3$), δ: 3.56 (CH_2I); 22.03 (Me); 42.30 (C(4)); 49.83 (CH_2N); 66.89 (CH_2O); 72.02 (C(5)); 80.05 (C(3)); 101.56 (C(1)); 109.16 (C(7)); 157.94 (C(8)); 167.16 (CO); 185.53 (C(6)). Mass spectrum, m/z: 475 $[M]^+$ (83), 432 $[M-MeCO]^+$ (5), 415 $[M-MeCO_2H]^+$ (4), 398 $[M-Cl-CH_2=C=O]^+$ (44), 306 $[M-I-CH_2=C=O]^+$ (14), 290 $[M-MeI-MeCO]^+$ (67), 288 $[M-I-MeCO_2H]^+$ (100), 61 $[AcOH_2]^+$ (17), 43 $[MeCO]^+$ (59).

Compound 6. ^{13}C NMR ($CDCl_3$), δ: 8.11 (CH_2I); 42.52 (C(4)); 48.86 (CH_2N); 67.14 (CH_2O); 73.23 (C(5)); 82.46 (C(3)); 100.30 (C(1)); 110.36 (C(7)); 158.44 (C(8)); 167.16 (CO); 185.53 (C(6)).

2,5-Dichloro-5-(2α-hydroxy-3-iodopropyl)-4,4-dimethoxy-3-morpholinocyclohept-2-en-1-one (7) and its 2′β-epimer (8). A mixture of iodohydrins **7** and **8** (8 : 1, ^1H NMR) was obtained in a yield of 0.25 g (51% with respect to the consumed **1**) from a mixture of ketone **2** (0.45 g, 1.34 mmol), $NaIO_4$ (0.5 g, 2.34 mmol), and $RuCl_3 \cdot 3\ H_2O$ (8 mg, 0.03 mmol) analogously to compound **3**. **Compound 7.** IR, ν/cm^{-1}: 1640, 1736, 1784, 1824. ^1H NMR ($CDCl_3$), δ: 2.10 (dd, 1 H, 2′-H_β, J = 8.5 and 15.2 Hz); 2.33 (dd, 1 H, 2′-H_α, J = 1.4 and 15.2 Hz); 3.26 (d, 2 H, CH_2I, J = 8.5 Hz); 3.29 (s, 3 H, Me); 3.48 (s, 3 H, Me); 3.70—4.10 (m, 10 H, 4 CH_2, CH—O, OH). ^{13}C NMR ($CDCl_3$), δ: 14.25 (CH_2I); 45.67 (CH_2); 49.59 (CH_2O); 67.11 (CH_2N—); 66.98 (CH—O); 74.06 (C(5)); 102.89 (C(4)); 107.11 (C(2)); 159.04 (C(3)); 188.05 (C(1)). Mass spectrum, m/z: 479 $[M]^+$ (4), 448 $[M-MeO]^+$ (6.6), 338 $[M-CH_2I]^+$ (21), 320 $[M-CH_2I-H_2O]$ (63), 308 $[M-CH(OH)CH_2I]^+$ (100), 170 $[CH(OH)CH_2I]^+$ (53), 142 [MeI] (40), 127 $[I]^+$.

Compound 8. ^{13}C NMR ($CDCl_3$), δ: 14.25 (CH_2I); 45.84 (CH_2); 50.19 (CH_2N); 52.23 (MeO); 53.31 (MeO); 67.11 (CH—O); 73.46 (C(5)); 107.11 (C(4)); 107.90 (C(2)); 165.88 (C(3)); 191.44 (C(1)).

2-Chloro-5-(*E*,*Z*-formylmethylidene)-4,4-dimethoxy-3-morpholinocyclopent-2-en-1-ones (9 and 10). OsO_4 (18 mg, 0.07 mmol) was added to a stirred solution of compound **2** (0.32 g, 0.95 mmol) in a 3 : 1 THF—H_2O mixture (9 mL). After 20 min, a solution of $NaIO_4$ (0.88 g, 4.11 mmol) in H_2O (8 mL) was added dropwise to the black mixture that was obtained. After completion of the reaction (TLC), the precipitate of $NaIO_3$ that formed was filtered off, and the filtrate was diluted with H_2O (20 mL), extracted with $CHCl_3$ (3×15 mL), and dried with Na_2SO_4. The combined extracts were concentrated. The residue was purified by column chromatography on SiO_2 (a 1 : 1 ethyl acetate—hexane mixture was used as the eluent), and a mixture of aldehydes **9** and **10** (3 : 1) was obtained in a yield of 0.2 g (70%). **Compound 9.** ^1H NMR ($CDCl_3$), δ: 3.24 (s, 6 H, Me); 3.79—4.09 (m, 8 H, CH_2O, CH_2N); 6.03 (d, 1 H, =CH, J = 7.5 Hz); 10.93 (d, 1 H, CHO, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 49.08 (CH_2O); 52.28 (Me); 67.28 (CH_2N); 103.90 (C(4)); 111.24 (C(2)); 128.14 (=CH); 142.69 (C(5)); 157.48 (C(2)); 180.71 (C(1)); 191.31 (CHO).

Compound 10. ^1H NMR ($CDCl_3$), δ: 3.23 (s, 6 H, Me); 6.60 (d, 1 H, =CH, J = 8.3 Hz); 10.25 (d, 1 H, CHO, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 49.08 (CH_2O); 52.58 (MeO); 67.33 (CH_2N); 105.81 (C(4)); 111.24 (C(2)); 125.33 (=CH); 144.31 (C(5)); 156.53 (C(2)); 180.15 (C(1)); 192.14 (CHO).

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