Synthesis of heterocyclic compounds in acid-catalysed reactions of citral epoxides

Olga I. Yarovaya,*[a] Dina V. Korchagina,[a] Oksana V. Salomatina,[b] Marina P. Polovinka[a] and Vladimir A. Barkhash[a]

[a] *N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 3832 34 4752; e-mail: ooo@nioch.nsc.ru*
[b] *Department of Natural Sciences, Novosibirsk State University, 630090 Novosibirsk, Russian Federation*

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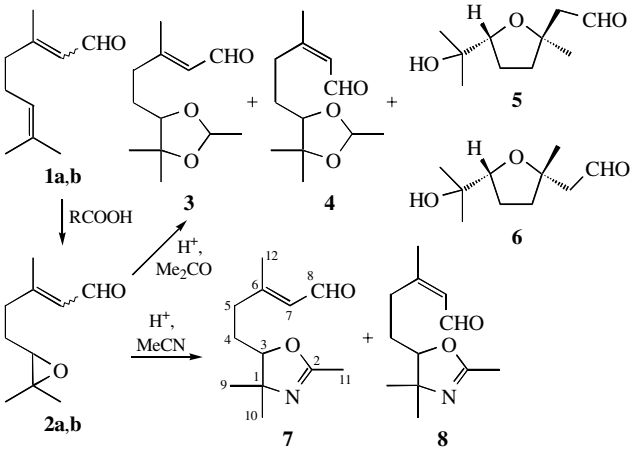
The interaction of citral 6,7-epoxides with acetonitrile catalysed by sulfuric acid results in the formation of substituted 2-oxazolines without affecting the aldehyde group of citral, whereas the interaction of citral 2,3-epoxides with acetone and acetonitrile results in the formation of bicyclic and tricyclic compounds.

Chemical reactions of terpene compounds are of considerable interest because various products can be prepared on this basis.[1] In this context, acid-catalysed reactions of terpenes and their oxygen-containing derivatives are of particular interest.[2] We studied the reactions of 6,7- and 2,3-epoxy derivatives of citral, which resulted in the formation of heterocyclic compounds. Previously,[3] we found that the dissolution of citral 6,7-epoxides **2a**,**b** in the acetone–water–sulfuric acid system resulted in the formation of substituted 1,3-dioxalanes **3** and **4** and substituted tetrahydrofurans **5** and **6** (Scheme 1). The ratio between the products depended on the duration of reaction in an acidic medium. We also found that the reaction of *E*-**2a** and citral *Z*-6,7-epoxides **2b** in a ratio of 2:1 (which were prepared by the action of peracetic acid on citral **1a**,**b**[3]) with acetonitrile under conditions of the Ritter reaction (MeCN, H_2SO_4, 0 °C) resulted in substituted 2-oxazolines **7** and **8**.† The ratio between the resulting heterocyclic compounds corresponds to the ratio between starting epoxides. The formation of 2-oxazolines from epoxides and nitriles is known;[4] however, we failed to find publications on the use of terpene epoxides as reagents for preparing compounds containing oxazoline rings.

The dissolution of an equimolar mixture of citral 2,3-epoxides **9a**,**b** (which were prepared by the action of hydrogen peroxide on citral in an alklaine medium[5]) in the acetone–water–sulfuric acid system resulted in bicyclic diol **11**‡ as the only product. Scheme 2 illustrates a conceivable mechanism of formation of this product, which includes acid-catalysed epoxide ring opening, interaction with the acetone molecule to form an acetal and intramolecular cyclization resulting in ion **10**. The dissolution of epoxides **9a**,**b** in the acetonitrile–sulfuric acid system (Ritter reaction conditions) did not result in product formation. In the case when the reaction was performed in the acetonitrile–acetone–sulfuric acid system, tricyclic compound **13**§ was the main product. Scheme 2 illustrates the mechanism proposed for the formation of compound **13** through the intermediate formation of ion **10** and the reaction of the latter with the acetonitrile molecule. The step of 5,6-dihydro-4*H*-1,3-oxazine ring formation in compound **13** can be classified as the Tilmans–Ritter reaction.[6] The proposed mechanism was supported by the fact that the dissolution of compound **11** in the acetonitrile–sulfuric acid system resulted in a mixture with product **13** as the main constituent.



Scheme 1 The numbering of carbon atoms shown in Schemes 1 and 2 does not coincide with the numbering of the system according to IUPAC and is given for only NMR interpretation purpose.

The formation of the cyclic compounds described above is an interesting example of the nucleophilic addition of acetone and (or) acetonitrile molecules to cations, which includes rearrangements and intramolecular cyclizations. These compounds were not described previously. The structures of the compounds were determined by ^{1}H and ^{13}H NMR spectroscopy (COSY, $^1J_{C–H}$ 135 Hz;

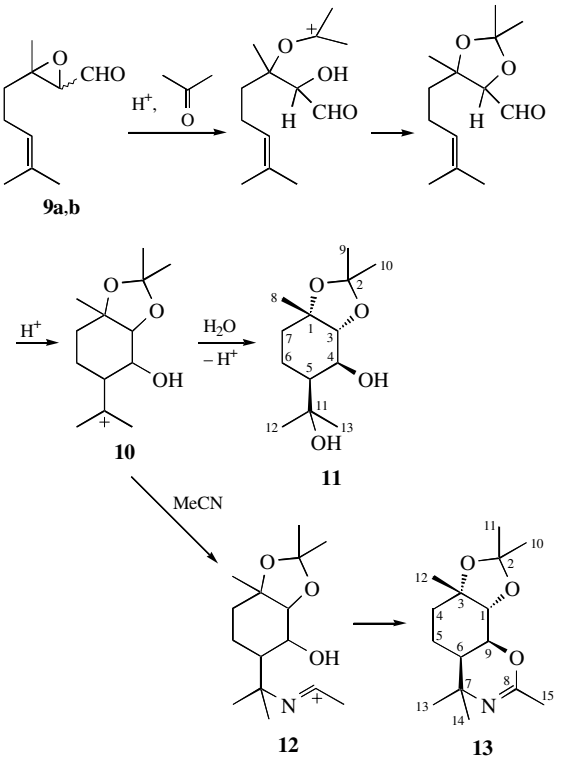
† Concentrated sulfuric acid (0.1 ml) was added to a solution of 6,7-epoxycitral **2a**,**b** (0.3 g, 1.8 mmol) and acetonitrile (3.0 ml), and the reaction mixture was stirred for 10 min at 0 °C. The reaction mixture was neutralised with a saturated Na_2CO_3 solution, and products were extracted with diethyl ether. The combined organic extracts were washed with water, dried ($MgSO_4$) and concentrated at a reduced pressure to give the crude product, which was then chromatographed (Al_2O_3 with activity II, a hexane/hexane–5% diethyl ether eluent was used) to give 0.2 g (53%) of a mixture of compounds **7** and **8** in a 2:1 ratio between isomers.

*(*E*)-3-Methyl-5-(2,4,4-trimethyl-4,5-dihydrooxazol-5-yl)pent-2-enal* **7**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 0.99 and 1.14 (s, 3H^9, 3H^{10}), 1.51–1.72 (m, 2H^4), 1.81 (s, 3H^{11}), 2.11 (d, 3H^{12}, $J_{12,7}$ 1.5 Hz), 2.17 (dddd, H^5, $J_{5,5'}$ 15 Hz, $J_{5,4}$ 10 Hz, $J_{5,4'}$ 6 Hz, $J_{5,7}$ 1 Hz), 2.35 (dddd, H$^{5'}$, J 15 Hz, $J_{5',4'}$ 10 Hz, $J_{5',4}$ 5 Hz, $J_{5',7}$ 1 Hz), 3.82 (dd, H^3, $J_{3,4}$ 10 Hz, $J_{3,4'}$ 3 Hz), 5.77 (dm, H^7, $J_{7,8}$ 8 Hz, J 1.5 and 1 Hz), 9.88 (d, H^8, J 8 Hz). ^{13}C NMR, δ: 67.93 (s, C-1), 161.64 (s, C-2), 87.36 (d, C-3), 27.78 (t, C-4), 37.64 (t, C-5), 160.84 (s, C-6), 127.37 (d, C-7), 189.69 (d, C-8), 22.74 and 29.16 (q, C-9, C-10), 14.01 (q, C-11), 17.46 (q, C-12).

(Z)-3-Methyl-5-(2,4,4-trimethyl-4,5-dihydrooxazol-5-yl)pent-2-enal **8**: ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$) δ: 0.98 and 1.14 (s, 3H^9, 3H^{10}), 1.51–1.72 (m, 2H^4), 1.82 (s, 3H^{11}), 1.90 (d, 3H^{12}, $J_{12,7}$ 1.5 Hz), 2.58 (ddd, H^5, $J_{5,5'}$ 13 Hz, $J_{5,4}$ 9 Hz, $J_{5,4'}$ 5 Hz), 2.67 (ddd, H$^{5'}$, J 13 Hz, $J_{5',4'}$ 9 Hz, $J_{5',4}$ 7 Hz), 3.84 (dd, H^3, $J_{3,4}$ 10 Hz, $J_{3,4'}$ 3 Hz), 5.78 (dm, H^7, $J_{7,8}$ 8 Hz, J 1.5 Hz), 9.84 (d, H^8, J 8 Hz). ^{13}C NMR, δ: 67.90 (s, C-1), 160.82 (s, C-2), 87.14 (d, C-3), 29.06 (t, C-4), 29.84 (t, C-5), 160.84 (s, C-6), 128.79 (d, C-7), 189.36 (d, C-8), 22.74 and 29.16 (q, C-9, C-10), 14.01 (q, C-11), 24.64 (q, C-12).

‡ 2,3-Epoxycitral **9a**,**b** (0.35 g, 2.1 mmol) was added to a solution of acetone (2 ml), water (0.3 ml) and concentrated sulfuric acid (0.05 ml), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was neutralised with a saturated Na_2CO_3 solution, extracted with diethyl ether, washed with water and dried ($MgSO_4$). The crude product (0.24 g) was chromatographed (alkaline Al_2O_3, a hexane/hexane–5% diethyl ether eluent was used) to give 0.07 g of compound **11** (low yield may be explained by degradation of the product during purification).

*(3*aR*,4S*,5S*,7*aS*)-5-(1-Hydroxy-1-methylethyl)-2,2,7*a-trimethylhexahydrobenzo[1,3]dioxol-4-ol* **11**: ^{1}H NMR ($CDCl_3$ + CCl_4) δ: 1.24 (s, 3H^{12}), 1.36 (s, 3H^{13}), 1.29 (s, 3H^9), 1.40 (s, 3H^{10}), 1.33 (s, 3H^8), 1.47 (ddd, H^{5a}, $J_{5a,6a}$ 11 Hz, $J_{5a,6e}$ 5 Hz, $J_{5a,4e}$ 2.5 Hz), 1.50–1.65 (m, 2H^6), 1.68 (m, 2H^7), 2.76 (br. s, OH), 4.04 (br. s, OH), 3.67 (d, H^{3e}, $J_{3e,4e}$ 3 Hz), 4.47 (ddd, H^{4e}, J 3 and 2.5 Hz, $J_{4e,6e}$ 1.5 Hz). ^{13}C NMR, δ: 78.55 (s, C-1), 107.14 (s, C-2), 81.59 (d, C-3), 68.60 (d, C-4), 44.13 (d, C-5), 17.74 (t, C-6), 36.17 (t, C-7), 24.40 (q, C-8), 27.15 and 28.41 (q, C-9, C-10), 73.45 (s, C-11), 28.69 and 29.34 (q, C-12, C-13).



Scheme 2

§ 2,3-Epoxycitral (0.5 g, 2.9 mmol) was added to a solution of acetonitrile (5 ml), acetone (0.5 ml) and sulfuric acid (0.5 ml), and the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was neutralised with a saturated Na_2CO_3 solution, extracted with diethyl ether, washed with water and dried ($MgSO_4$). The crude product (0.43 g) was chromatographed (alkaline Al_2O_3, a hexane/hexane–5% diethyl ether eluent was used) to give 0.16 g (20%) of compound **13**.

*(3*aS*,5*aR*,9*aS*,9*bR*)-2,2,3*a*,6,6,8-Hexamethyl-4,5,5*a*,6,9*a*,9*b*-hexahydro-3*aH*-1,3,9-trioxa-7-azacyclopenta[*a*]naphthalene* **13**: ^{1}H NMR ($CDCl_3$ + CCl_4) δ: 1.02 (m, H^{5a}), 1.09 (s, 3H^{13}), 1.18 (s, 3H^{14}), 1.23 (s, 3H^{12}), 1.30 (s, 3H^{10}), 1.41 (s, 3H^{11}), 1.52 (ddtd, H^{5e}, $J_{5e,5a}$ 13.5 Hz, $J_{5e,6a}$ 4 Hz, $J_{5e,4}$ 4 Hz, $J_{5e,9e}$ 1.5 Hz), 1.63 (m, 2H^4), 1.65 (ddd, H^{6a}, $J_{6a,5a}$ 13 Hz, J 4 Hz, $J_{6a,9}$ 3 Hz), 1.82 (s, 3H^{15}), 3.78 (d, H^{1e}, $J_{1e,9e}$ 2.5 Hz), 4.59 (ddd, H^9, J 3, 2.5 and 1.5 Hz). ^{13}C NMR, δ: 79.13 (d, C-1), 107.46 (s, C-2), 78.22 (s, C-3), 35.27 (t, C-4), 19.41 (t, C-5), 37.13 (d, C-6), 51.24 (s, C-7), 154.03 (s, C-8), 70.81 (d, C-9), 27.04 and 28.28 (q, C-10, C-11), 23.53 (q, C-12), 28.12 and 31.24 (q, C-13, C-14), 21.13 (q, C-15). MS, *m/z*: 267.18372 [M]$^+$ (calc. for $C_{15}H_{25}NO_3$: 267.18343).

LRJMD, $J_{C–H}$ 10 Hz). Compound **11** exhibited an upfield shift of the signal of the C^4 atom in the ^{13}C NMR spectrum on the replacement of the OH group by the OD group because of an isotope effect.

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