Unusual transformation of trimethylsilyloxyisoxazolidines initiated by the fluoride ion

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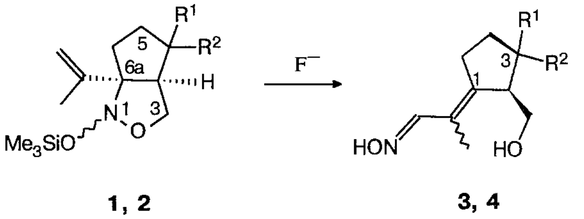
It was found that opening of the isoxazolidine ring of 6aα-isopropenyl-1α/β-trimethylsilyloxy-3,3aα,4,5,6,6a-hexahydro-(1*H*)-cyclopent[*c*]isoxazoles by the F^- ion initially gives an intermediate, a tertiary nitrosocompound detected by UV and NMR spectroscopy. Its transformation, finally, into α,β-unsaturated aldoximes probably involves an unprecedented allylic migration of the nitroso group.

Key words: trimethylsilyloxyisoxazolidine; nitroso compound; silylnitronate; 1,3-dipolar cycloaddition; aldoxime.

Previously[1] we reported an unusual transformation of isoxazolidines (**1**) under F^--initiated desilylation conditions into a mixture of isomeric oximes (**3**) (Scheme 1).

Scheme 1

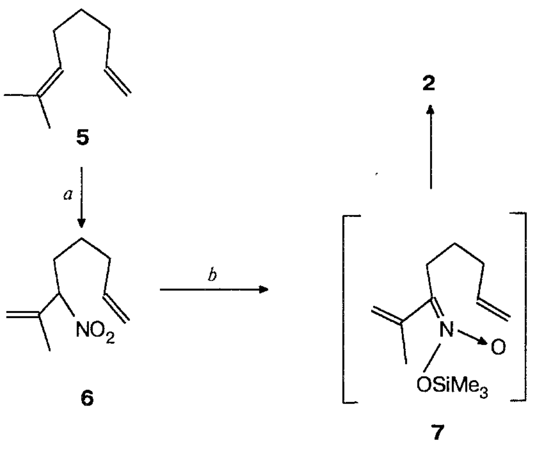


1,3: R^1 = Me, R^2 = OAc; **2,4**: $R^1 = R^2$ = H

A more detailed study of this process for silyloxy derivatives **2** related to **1** is the subject of this work.

A mixture (~2 : 1, ^{1}H NMR data, *cf.* Ref. 1) of invertomers **2** at the N atoms (including those labeled by ^{15}N) can be obtained from nitroolefin **6** under conditions similar to those reported[1] for acetates **1**. This mixture results from the highly regioselective (as in the case of **1**) intramolecular [3+2]-reaction of silylnitronate (**7**) generated *in situ* from **6** by the action of *N,N'*-bis(trimethylsilyl)acetamide (BSA). In turn, the previously unknown nitro derivative **6** was synthesized by a reported procedure[1,2] by treatment of diene **5** [3] with $NaNO_2$ in AcOH. A sample of compound **6** labeled by ^{15}N was obtained using the nitrite enriched with this isotope (~50 %) (Scheme 2).

Scheme 2



Reagents and conditions: *a*, $NaNO_2$/AcOH, 14→25 °C; *b*, BSA/NEt_3/PhMe/MeCN, boiling.

The silyloxyisoxazolidines **2** thus obtained were then subjected to mild desilylation with $KF \cdot 2H_2O$ (*cf.* Ref. 1) which in this case resulted in a chromatographically separable mixture of isomeric oximes *E*-**4**/*Z*-**4** ≈ 3 : 1 accompanied by an admixture (< 10 %) of diene **11** in a high overall yield.

According to the probable mechanism suggested previously, the **1**→**3** transformation is assumed to occur through three consecutive steps.[1] In the case of **2**, the first step probably involves the opening of the isoxazolid-

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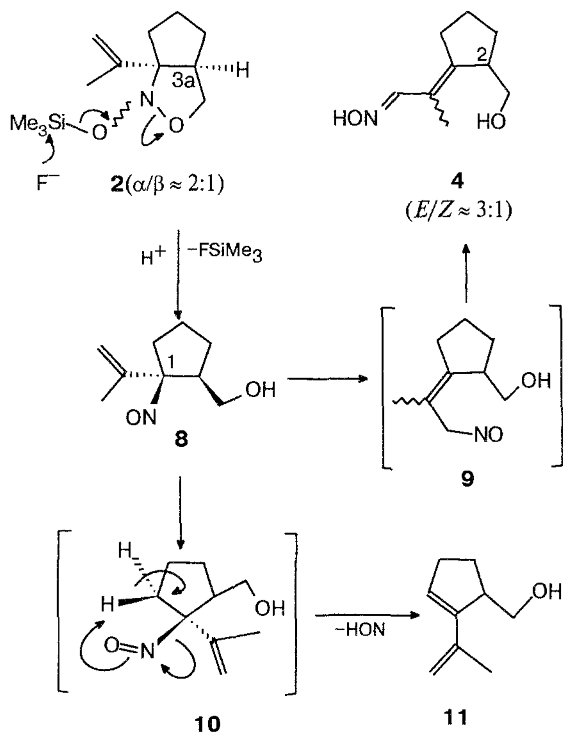
†Deceased.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 461—464, March, 1994.

ine ring by F$^-$ to give a tertiary nitroso compound (**8**). The latter then rearranges to a primary compound (**9**), which rapidly isomerizes into oximes **4**, or undergoes β-elimination into diene **11** *via* probable transition state **10** (*cf.* Ref. 4) (Scheme 3).

Scheme 3



In fact, only one intermediate product, the highly reactive compound **8**, can be detected definitely when the reaction is performed in the detectors of UV or NMR spectrometers. In particular, the presence of this product in the reaction mixture is indicated by the fact that an UV absorption band at $\lambda_{max} \approx 700$ nm typical of nitroso compounds appears at $-15\div0$ °C.[5] The intensity of this band reaches a maximum at -10 °C and then decreases as the temperature rises to 0 °C; simultaneously, the intensity of the absorption band of aldoximes **4** at $\lambda_{max} \approx 251$ nm increases (*cf.* Ref. 5).

Furthermore, we could detect ^{1}H, ^{13}C, and ^{15}N NMR spectra of nitroso compound **8** in low-temperature experiments when silyloxy derivative **2** was treated with potassium fluoride in CD$_3$OD/CD$_3$CN solution in the tube of a NMR spectrometer at $-30\div-17$ °C. When a sample of ^{15}N-**2** is used, the ^{15}N NMR spectrum of the reaction mixture displays an intense signal at δ 598.57 for the nitroso group;[6] the doublet signal of the C-6a atom in the ^{13}C NMR spectrum (δ 118.32) has a coupling constant $J_{^{15}N-^{13}C} \approx 17$ Hz.

The structure of isoxazolidines **2** never reported previously and those of compounds **4** and **11** isolated in the pure state by flash-chromatography on SiO$_2$ were confirmed by spectral and elemental analyses. In particular, the geometry of the exocyclic double bond of the aldoximes, the major *E*-**4** and minor *Z*-**4** isomers, was established by 2D-NOESY experiments which revealed that the CH$_3$ and CH$_2$O groups are drawn together in the former isomer, while the HCN protons are drawn together with those of CH$_2$O in the latter isomer. It is noteworthy that additional signals are present in the ^{1}H NMR spectra of freshly prepared samples of **4**, including a signal at δ 7.1; the relative integral intensities of these signals rapidly decrease when the solutions in CDCl$_3$ are stored at 20 °C. These facts indicate that aldoximes **4** initially exist as mixtures of the *syn* and *anti* forms; the former readily isomerize into the thermodynamically more stable *anti*-isomers (*cf.* Ref. 4). In particular, these isomers are characterized by small (≤3 Hz) $J_{^{15}N-^{13}C}$ coupling constant (*cf.* Ref. 7).

As noted above, isoxazolidines **2** were isolated as a mixture of two N-invertomers, the ratio of which (**2a**/**2b** ≈ 2 : 1) was established by comparing the relative integral intensities of the ^{1}H NMR signals for the protons of the Me$_3$SiO groups belonging to these compounds with δ = 0.17 and 0.20, respectively. The 2D-NOESY spectrum of the major epimer **2a** recorded for the Me$_3$SiO group displays distinct cross-peaks with protons from CH$_3$, α-HC-3, and α-HC-3a, which makes it possible to conclude that this group has an α-orientation relative to the isoxazolidine ring. The above Overhauser effects are not observed for the minor component of the mixture (**2b**) attributed to the β-series.

Thus, it has been found that opening of the ring in silyloxyisoxazolidines **2** by the action of F$^-$ occurs *via* tertiary nitroso compound **8**. The nature of its allylic isomerization, which is evidently unprecedented, and β-elimination of the nitroso group resulting in oximes **4** and diene **11** require further investigations.

Experimental

IR spectra (ν/cm^{-1}) of solutions in CHCl$_3$ were recorded on a Specord M-80 spectrophotometer; UV spectra were obtained on a Specord UV-VIS instrument. ^{1}H NMR spectra (δ) were recorded on Bruker WM-250 (250.13 MHz) and AMX-400 (400.13 MHz) spectrometers, while ^{13}C NMR (50.32 MHz) and ^{15}N NMR spectra (20.29 MHz) were recorded on a Bruker AC-200 instrument. ^{1}H and ^{13}C NMR chemical shifts were measured in the δ scale relative to the solvent (7.27 for ^{1}H and 77.0 for ^{13}C), and those for ^{15}N were measured relative to CH$_3$NO$_2$ as the external standard (negative shifts correspond to higher field strengths). EI mass spectra were obtained on Varian MAT CH-6 and Varian MAT 311A instruments at 70 eV. R_f values are given for a fixed layer of Silufol-grade SiO$_2$.

2-Methyl-3-nitro-1,7-octadiene (6). NaNO$_2$ (11.0 g, 0.16 mol) was added portionwise over 40 min at 14 °C to a vigorously stirred solution of compound **5** (1.08 g, 8.69 mmol) (*cf.* Ref. 3) in AcOH (33 mL). The reaction mixture was heated to 25 °C over 1 h, kept for 15 h at this temperature, and then treated with pentane and water. The aqueous layer was separated and extracted with pentane. The combined organic layer was washed with water, dried with Na_2SO_4, filtered through a layer of SiO_2 (30 mm), and concentrated *in vacuo*. The residue (1 g) was distilled to give 0.63 g (43 %) of nitrodiene **6**: b.p. 69—70 °C (4 Topp), n_D^{20} 1.4598, IR: 725, 920, 995, 1205, 1380, 1440, 1550, 1640, 2925, 2975—3010. ^1H NMR: 1.41 (quint, 2 H, HC-5, J = 7.7 Hz); 1.8—2.3 (m, 4 H, CH_2); 1.81 (br.s, 3 H, CH_3); 4.92 (dd, 1 H, HCN, J = 9 Hz and 6.7 Hz); 5.0 (m, 2 H, $H_2C=C$); 5.16 and 5.19 (br.s, 2 H, HC-1); 5.8 (m, 1 H, HC=C). ^{13}C NMR: 18.04 (CH_3); 24.91 (C-4); 30.30 and 32.84 (C-5, C-6); 92.70 (C-3, for ^{15}N-**6** d, $J_{^{13}C-^{15}N}$ = 5.8 Hz); 115.37 (C-8); 118.32 (C-1); 137.35 (C-7); 138.64 (C-2). ^{15}N NMR ($CDCl_3$) for ^{15}N-**6**: 11.99. MS, *m/z*: 123 $[M-46]^+$. Found (%): N, 8.15. $C_9H_{15}NO_2$. Calculated (%): N, 8.28.

6aα-Isopropenyl-1α-trimethylsilyloxy-3,3aα,4,5,6,6a-hexahydro-(1*H*)-cyclopent[*c*]isoxazole (2a) and 6aα-isopropenyl-1β-trimethylsilyloxy-3,3aα,4,5,6,6a-hexahydro-(1*H*)-cyclopent[*c*]isoxazole (2b). A solution of compound **6** (1.0 g, 5.91 mmol), BSA (2.41 g, 11.9 mmol), and Et_3N (0.29 g, 2.87 mmol) in toluene (4 mL) and MeCN (0.4 mL) was boiled (Ar) for 4 h and then treated with pentane and water. The aqueous layer was separated and extracted with pentane. The usual workup of the combined organic layer gave 1.2 g of a product. Distillation of the latter *in vacuo* gave 1.08 g (76 %) of the mixture **2a**/**2b** ≈ 2 : 1 (^1H NMR data), b.p. 55—57 °C (1 Torr), n_D^{20} 1.4674. IR: 670, 725, 850, 845, 900, 920, 940, 1205, 1250, 1375, 1450, 1645, 2880—2960. ^1H NMR: 0.17 (**2a**) and 0.20 (**2b**) (s, 9 H, CH_3); 1.4—2.2 (m, 6 H, CH_2); 1.83 (br.s, 3 H, CH_3); 3.1 (m, 1 H, HC-3a); 3.61 (**2a**) (dd, 1 H, β-HC-3, J = 7.9 Hz and 2.9 Hz); 3.96 (**2b**) (dd, 1 H, β-HC-3, $J_1 = J_2$ = 7.9 Hz); 4.19 (**2b**) (dd, 1 H, α-HC-3, J = 9.1 Hz and 7.9 Hz); 4.49 (**2a**) (dd, 1 H, α-HC-3, J = 8.7 Hz and 7.9 Hz); 4.74 and 4.83 (**2a**) (br.s, 2 H, $H_2C=C$); 4.80 and 5.02 (**2b**) (br.s, 2 H, $H_2C=C$). ^{13}C NMR: −0.42 (**2b**) and −0.22 (**2a**) (CH_3Si); 20.32 (**2a**) and 20.59 (**2b**) (CH_3); 23.58, 27.58; 30.65, 32.93, 34.87, 38.01 (CH_2); 45.02 (**2a**) and 48.96 (**2b**) (C-3a); 73.82 (**2b**) and 75.20 (**2a**) (C-3); 91.85 (**2b**) and 92.38 (**2a**) (C-6a); 109.69 (**2a**) and 110.18 (**2b**) ($H_2\underline{C}=C$); 145.62 (**2a**) and 147.02 (**2b**) ($H_2C=\underline{C}$). ^{15}N NMR* for ^{15}N-**2** ($CDCl_3$): −117.48 (**2a**); −122.06 (**2b**). MS, *m/z*: 241 $[M]^+$. Found (%): N, 5.70. $C_{12}H_{23}NO_2Si$. Calculated (%): N, 5.80. Mol. weight 241.4.

1-(*E*/*Z*)-2-Hydroxymethyl-(1-*anti*-oximinopropylidene-2)-cyclopentanes (4) and 5-hydroxymethyl-1-isopropenyl-1-cyclopentene (11). A solution of compound **2** (0.38 g, 1.57 mmol) in THF (2 mL) was added in one portion at −30 °C (Ar) to a vigorously stirred suspension of $KF\cdot 2H_2O$ (0.3 g, 3.19 mmol) in MeOH (2 mL) and THF (2 mL). The reaction mixture was heated to 25 °C in 30 min, kept for 1 h, diluted with ether, and filtered. The precipitate was washed with ether on a filter, and the combined filtrate was concentrated *in vacuo* to give 0.3 g of a substance which was chromatographed on SiO_2 (20 g). Gradient elution from hexane to ethyl acetate (up to 40 % of the latter) gave successively compounds **11** (15 mg, 7 %), *Z*-**4** (50 mg, 19 %), and *E*-**4** (0.15 g, 56 %).

Oxime *Z*-**4** has the form of colorless crystals, m.p. 122—123 °C (ether—hexane). IR: 670, 690, 730, 930, 960, 1020, 1060, 1245, 1275, 1310, 1325, 1335, 1380, 1425, 1460, 1680, 2880, 2960, 3000, 3280 (KBr). UV (EtOH), λ_{max}/nm: 251 (ε 26800). ^1H NMR: 1.4—2.0 (m, 6 H, HC-3, HC-4 and HC-5); 1.82 (br.s, 3 H, CH_3); 3.0 (m, 1 H, HC-2); 3.33 (dd, 1 H, HCO, J = 11.0 Hz and 9.7 Hz); 3.56 (dd, 1 H, HCO, J = 11.0 Hz and 5.5 Hz); 8.16 (s, 1 H, HC=N). ^{13}C NMR: 14.27 (CH_3); 22.42, 28.84, 31.17 (CH_2); 44.48 (C-2); 64.22 (CH_2O); 122.43 ($CH_3\underline{C}=C$); 150.76 (C-1); 151.21 (CN). ^{15}N NMR for ^{15}N-*Z*-**4** ($CDCl_3$): −32.19. MS, *m/z*: 169 $[M]^+$; calculated for $C_9H_{15}NO_2$: mol. weight 169.2.

Oxime *E*-**4** is a colorless oil, R_f 0.26 (hexane—ethyl acetate, 1 : 1). IR: 670, 690, 1020, 1060, 1300, 1330, 1380, 1435, 1445, 1680, 2880, 2960, 3350 (KBr). UV (EtOH), λ_{max}/nm: 251 (ε 10600). ^1H NMR: 1.6—1.9 (m, 4 H, CH_2); 1.89 (br.s, 3 H, CH_3); 2.45 (m, 2 H, HC-5); 3.05 (m, 1 H, HC-2); 3.46 (dd, 1 H, HCO, J = 10.8 Hz and 9.7 Hz); 3.63 (dd, 1 H, HCO, J = 10.8 Hz and 6.5 Hz); 8.09 (s, 1 H, HC=N). ^{13}C NMR: 14.35 (CH_3); 23.52, 28.40, 29.78 (CH_2); 45.96 (C-2); 63.37 (CH_2O); 122.42 ($CH_3\underline{C}=C$); 150.73 (C-1); 151.29 (CN). ^{15}N NMR for ^{15}N-*E*-**4** ($CDCl_3$): −31.32. MS, *m/z*: 169 $[M]^+$. Found (%): N, 8.29. $C_9H_{15}NO_2$. Calculated (%): N, 8.28.

Diene **11** is a colorless oil, R_f 0.47 (hexane—ethyl acetate, 2 : 1). IR: 900, 975, 1020, 1070, 1380, 1440, 1460, 1550, 2950, 3020, 3420, 3620. UV (EtOH), λ_{max}/nm: 239 (ε 9600). ^1H NMR: 1.7—2.6 (m, 4 H, CH_2); 1.91 (br.s, 3 H, CH_3); 3.1 (m, 1 H, HC-5); 3.52 (dd, 1 H, HCO, J = 10.5 Hz and 6.4 Hz); 3.68 (dd, 1 H, HCO, J = 10.5 Hz and 4.2 Hz); 4.95 (m, 2 H, $H_2C=C$); 5.85 (m, 1 H, HC=C). ^{13}C NMR: 21.11 (CH_3); 27.98 and 31.48 (CH_2); 47.13 (C-5); 64.74 (CH_2O); 112.50 ($H_2\underline{C}=C$); 130.60 ($H\underline{C}=C$); 138.83 and 143.77 (—C=). High-resolution MS, *m/z*: 138 $[M]^+$. Found: mol. weight 138.10423; calculated for $C_9H_{14}O$: mol. weight 138.10445.

A solution of compound **2** (50 mg, 0.21 mmol) in CD_3CN (0.1 mL) was added at −40 °C (Ar) to a solution of KF (12 mg, 0.21 mmol) in CD_3OD (0.5 mL) placed in the ampule of an NMR spectrometer (d = 5 mm). The ampule was put in the detector of a Bruker AC-200 spectrometer cooled to −17 °C and kept for 2.5 h at this temperature, then a ^1H NMR spectrum of the reaction mixture was recorded. In addition to signals of the unreacted **2** (conversion ~40 % according to the ^1H NMR data), the spectrum contained signals of nitroso compound **8**: 1.4—2.3 (m, 6 H, CH_2); 1.65 (br.s, 3 H, CH_3); 2.93 (dddd, 1 H, HC-2, J = 10.8 Hz, 9.7 Hz, 7.2 Hz, and 3.7 Hz); 3.60 (dd, 1 H, HCO, J = 11.1 Hz and 9.7 Hz); 4.60 (dd, 1 H, HCO, J = 11.1 Hz and 3.7 Hz); 4.93 and 5.23 (br.s, 2 H, $H_2C=C$). Heating the reaction mixture to 0 °C in 30 min and keeping it for 1 h resulted in complete conversion of the original compound **2** and intermediate **8**; the ^1H NMR spectrum contained the sum of the resonance signals of oximes **4** and diene **11**. Their relative integral intensities were *E*-**4**/*Z*-**4**/**11** ≈ 3 : 1 : 1.

A solution of ^{15}N-**2** (0.1 g, 0.6 mL) in CD_3CN (0.6 mL) was added in one portion at −40 °C (Ar) to KF (60 mg, 1.03 mmol) in CD_3OD (1.5 mL) placed in the ampule of an NMR spectrometer (d = 10 mm). The ampule was put in the detector of a Bruker AC-200 spectrometer cooled to −30 °C and kept for 5 h (the conversion of **2** under these conditions is ~80 %, ^1H NMR data), then NMR spectra of the reaction mixture were recorded. ^{15}N NMR for ^{15}N-**8**: 598.57; ^{13}C NMR: 20.86 (CH_3); 22.93, 30.36; 30.79 (CH_2); 52.67 (C-2); 63.37 (CH_2O); 115.31 ($H_2\underline{C}=C$); 118.32 (d, C-1, $J_{^{13}C-^{15}N}$ = 17 Hz); 143.54 ($H_2C=\underline{C}$). After heating the reaction mixture to 0 °C in 30 min and keeping it for 1 h, the ^1H NMR spectrum contained the sum of the resonance signals of oximes **4** and diene **11**, the ratio of which was almost the same as in the previous experiment.

The authors are grateful to V. A. Petukhov for his assistance in conducting some of the experiments and in interpreting the UV spectral data.

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* The signal assignments are based on two-dimensional inverse correlation spectroscopy $^1H-^{15}N$ (HMQC).[8]

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Received June 30, 1993