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Unexpected spontaneous ring-contraction rearrangement of trifluoromethylated 1,2-oxazine *N*-oxides to 1-pyrroline *N*-oxides

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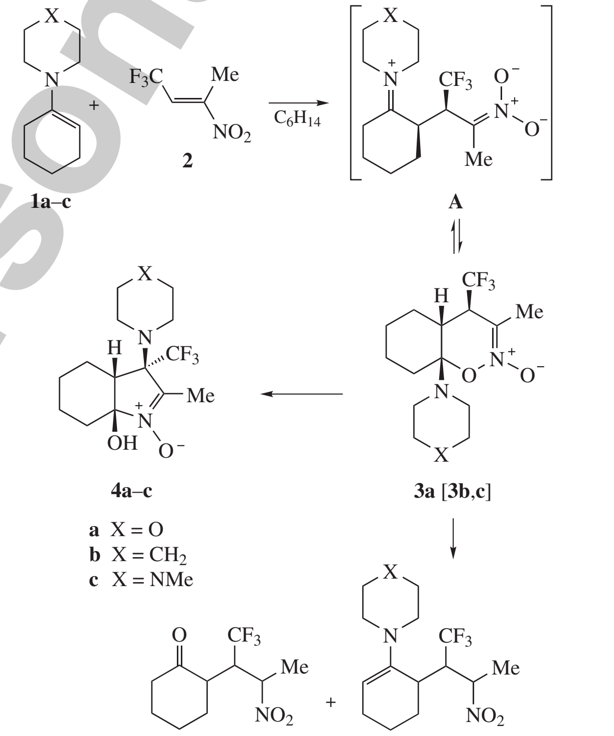
DOI: 10.1016/j.mencom.2011.09.016

6-Amino-4-trifluoromethyl-5,6-dihydro-4*H*-1,2-oxazine 2-oxides undergo spontaneous rearrangement into 4-amino-2-hydroxy-4-trifluoromethyl-3,4-dihydro-2*H*-pyrrole 1-oxides.

Conjugated nitroolefins are versatile intermediates in organic synthesis.[1,2] Their reactions with enamines initially lead to diastereoselective formation of a new C–C bond in the resulting dipolar intermediate, the further transformation of which depends on the nature of the reactants and affords 1,2-oxazine *N*-oxides (cyclic nitronates), cyclobutanes, or multisubstituted nitroalkylated enamines.[3] Generally nitroolefins and enamines undergo [4+2] cycloaddition to give cyclic nitronates. Such heterocycles are highly reactive towards 1,3-dipolar cycloaddition[4] and reactions with some nucleophiles[5] as well as can be transformed into γ-nitro ketones and γ-diketones.[3] In the reaction with α-keto enamines, the products of kinetic control are the 1,2-oxazine *N*-oxide derivatives, which are prone to undergo ring-contraction rearrangement into polysubstituted cyclopentanones[6] or cyclopentenes.[7]

Trihalomethylated nitroolefins can be of interest for biomedicinal chemistry and materials science. Owing to the electron-withdrawing power of both trihalomethyl and nitro groups, CX_3-nitroalkenes (X = F, Cl) serve as good dienophiles in the Diels–Alder reaction[8] and dipolarophiles in the 1,3-dipolar cycloaddition,[9] as well as heterodienes in an inverse electron-demand Diels–Alder reaction[10] and reactive acceptors in the Michael addition.[11] However, data on reactions of trihalomethylated conjugated nitroalkenes with enamines are very scarce. It has been only reported that (*E*)-1-nitro-3,3,3-trifluoropropene reacts with ethyl 3-morpholinocrotonate to give a cyclobutane derivative as a result of [2+2] cycloaddition,[12] whereas polyfluoroalkylated nitroalkenes react with cycloalkanone or acetophenone enamines to yield β-polyfluoroalkyl-γ-nitro ketones.[13] Recently, we reported a [4+2] cycloaddition of enamines derived from morpholine and methylketones to (*E*)-1,1,1-trichloro(trifluoro)-3-nitrobut-2-enes which gave a 1,2-oxazine *N*-oxides in a kinetically controlled process.[14]

On the basis of this result, in the present study we anticipated that the similar reaction of cyclohexanone-derived enamines **1** with (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **2**[15] should furnish the corresponding cyclic nitronates **3**. Instead, isomeric cyclic nitrones **4** resulting from an unexpected rearrangement of **3** through the unusual migration of the amino moiety and ring-contraction reaction were obtained (Scheme 1). Under optimal conditions, treatment of neat enamines **1b**,**c** with nitrobutene **2** for 7–12 days at room temperature open to atmospheric moisture gave nitrones **4b**,**c** in 38 and 41% yields, respectively. In the case of *N*-cyclohexenylmorpholine **1a** and when the reaction was performed in hexane, the expected 1,2-oxazine *N*-oxide **3a**, stereochemistry of



Scheme 1

which has been proved earlier,[14] was obtained in 71% yield. This could be due to the fact that compound **3a** is solid and during the course of reaction precipitated from hexane solution. While the solid compound **3a** was rather stable and could be stored at –10 °C for long period, in wet chloroform solution (7 days, ~20 °C) it rearranged to the corresponding 1-pyrroline *N*-oxide **4a** in 42% yield.[†] This yield was improved to 59% when the reaction

[†] NMR spectra were recorded at 400 or 500 MHz for ^1H, 376 or 471 MHz for ^{19}F and 100 or 126 MHz for ^{13}C.

(3S,3aR*,7aS*)-7a-Hydroxy-2-methyl-3-morpholino-3-trifluoromethyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole-1-oxide* **4a**. A solution of nitronate **3a** (0.32 g, 1.0 mmol) in wet chloroform (3 ml) was kept for 7 days at ~20 °C. After evaporation of the solvent the product was washed with chloroform. Yield 0.14 g (42%), mp 219–220 °C, colourless crystals; the yield was improved to 59% in the presence of a catalytic amount of

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was performed in the presence of a catalytic amount of morpholine. In wet benzene the yield was lower (31%), whereas in dry benzene the reaction did not occur. These data indicate that the base strength of secondary amines was not essential for the rearrangement since 1,2-oxazine *N*-oxide **3a**, the compound with a less basic amine due to the electron withdrawing oxygen atom,[16] undergoes a similar reaction in a solvent. The moderate yield of the rearrangement product is presumably due to a side reaction, where the base is abstracting the H-6 of the cyclohexane ring of the betaine **A** to give **5**. Indeed, in mother liquors trisubstituted nitroalkylated enamines **5** and γ-nitroketones **6** (hydrolysis products) were detected by ^{1}H and ^{19}F NMR spectroscopy, and no effort was made to isolate them in pure form (see Scheme 1).

Notably, nitrones **4** contained three contiguous stereogenic centres, but only one diastereomer was observed by ^{1}H NMR spectroscopy of the crude products. The structure and stereochemistry of compounds **4a–c** were established by IR, ^{1}H, ^{19}F and ^{13}C NMR spectroscopy using 2D ^{1}H–^{13}C HSQC and HMBC experiments and by single crystal X-ray diffraction analysis for **4a** (Figure 1).‡ The *cis*-fusion between the rings of **4** is not unexpected, because strong internuclear strains make the *trans*-fusion less favorable.

We can assume that isomerization of **3** to **4** was possible due to high C–H acidity of the proton in α-position to the trifluoromethyl group in dipolar intermediate **A**, which could be easily abstracted by the base to form **B** (nitrone–*N*-hydroxyenamine prototropic tautomerism through a 1,4-H shift[17]), followed by hydration and dehydration (intermediates **B** and **C**) to the corresponding α-nitrosoalkene **D**. In the latter, the amino fragment undergoes a migration to the carbon atom connected to the CF_3 group to give the intermediate *E*-oxime **E**. This reasoning is consistent with the presence of water in the reaction medium. The formation of the five-membered cyclic nitrones **4** seems to be largely preferred over that of the six-membered 1,2-oxazines **4′**. We believe that the structure of the cyclization products (**4** or **4′**) depends on the geometry of the intermediate **E**, the oxime group of which can act either as a nitrogen or as an oxygen nucleophile in the intramolecular addition at the carbonyl carbon atom[18] (Scheme 2).

Note that 6-hydroxy-5,6-dihydro-4*H*-1,2-oxazines of type **4′**, which are the ring tautomers of the mono oximes of saturated

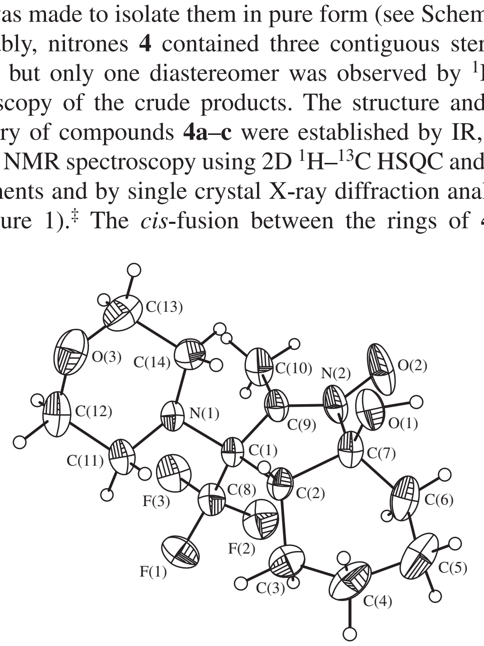
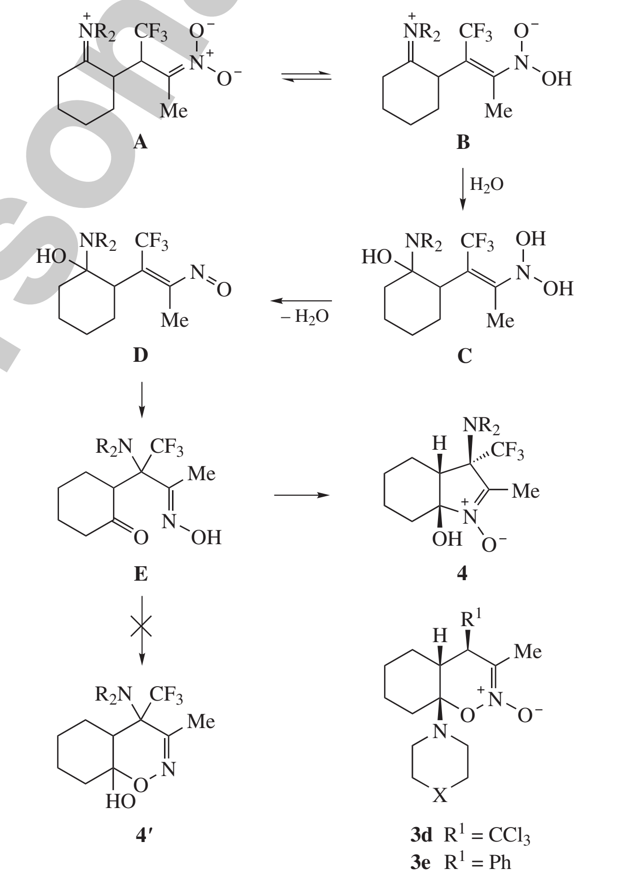


Figure 1 Molecular structure of nitrone **4a** (thermal ellipsoids at 50% probability level).



Scheme 2

morpholine. ^{1}H NMR ($CDCl_3$) δ: 1.1–2.6 (m, 9H, 4CH$_2$, H-3a), 2.17 (s, 3H, Me), 2.76 [dt, 2H, N(C*H*H)$_2$, *J* 11.6, 4.5 Hz], 2.96 [dt, 2H, N(CH*H*)$_2$, *J* 11.6, 4.5 Hz], 3.66–3.74 [m, 4H, O(CH$_2$)$_2$], 6.88 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: 100.8 (br. s, CF_3). ^{1}H NMR (DMSO-d_6/$CDCl_3$) δ: 1.4–2.1 (m, 8H, 4CH$_2$), 2.04 (s, 3H, Me), 2.55 (dd, 1H, H-3a, *J* 9.2, 7.5 Hz), 2.58 [dt, 2H, N(C*H*H)$_2$, *J* 11.4, 4.5 Hz], 2.73 [dt, 2H, N(CH*H*)$_2$, *J* 11.4, 4.5 Hz], 3.69 [t, 4H, O(CH$_2$)$_2$, *J* 4.5 Hz], 7.06 (s, 1H, OH). ^{19}F NMR (DMSO-d_6/$CDCl_3$) δ: 100.0 (s, CF_3). ^{13}C NMR (DMSO-d_6/$CDCl_3$) δ: 12.0 (Me), 18.8 (C-6/5), 20.5 (C-5/6), 23.5 (C-4), 29.4 (C-7), 41.8 (C-3a), 47.9 (NCH$_2$), 66.9 (OCH$_2$), 75.1 (q, C-3, $^2J_{C,F}$ 25.6 Hz), 98.9 (C-7a), 125.3 (q, CF_3, $^1J_{C,F}$ 290.2 Hz), 136.6 (C-2). IR (KBr, ν/cm^{-1}): 3169, 1613. Found (%): C, 51.98; H, 6.66; N, 8.68. Calc. for $C_{14}H_{21}F_3N_2O_3$ (%): C, 52.17; H, 6.57; N, 8.69.

(3S,3aR*,7aS*)-7a-Hydroxy-2-methyl-3-piperidino-3-trifluoromethyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole-1-oxide* **4b**. This compound was prepared from enamine **1b** and nitrobutene **2** (10 days, solvent-free conditions). Yield 38%, mp 187–188 °C, colourless crystals. ^{1}H NMR ($CDCl_3$) δ: 1.0–1.9 (m, 13H, 6CH$_2$, H-7a), 2.18 (s, 3H, Me), 2.57 (dd, 1H, H-3a, *J* 11.7, 5.8 Hz), 2.64–2.75 [m, 3H, N(C*H*H)$_2$, H-7b], 2.9–3.1 [br. s, 2H, N(CH*H*)$_2$], 7.53 (s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: 101.0 (br. s, CF_3). IR (KBr, ν/cm^{-1}): 3153, 1610. Found (%): C, 56.22; H, 7.24; N, 8.65. Calc. for $C_{15}H_{23}F_3N_2O_2$ (%): C, 56.24; H, 7.24; N, 8.74.

(3S,3aR*,7aS*)-7a-Hydroxy-2-methyl-3-(4-methylpiperazino)-3-trifluoromethyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole-1-oxide hydrate* **4c**. This compound was prepared from enamine **1c** and nitrobutene **2** (12 days, solvent-free conditions). Yield 41%, mp 116–117 °C, colourless crystals. ^{1}H NMR ($CDCl_3$) δ: 1.0–1.9 (m, 7H, 3CH$_2$, H-7a), 2.18 (s, 3H, Me), 2.26 (s, 3H, MeN), 2.43 [br. s, 4H, N(CH$_2$)$_2$], 2.57 (dd, 1H, H-3a, *J* 11.3, 5.8 Hz), 2.66 (dm, 1H, H-7b, *J* 14.8 Hz), 2.78 [m, 2H, N(C*H*H)$_2$], 3.05 [m, 2H, N(CH*H*)$_2$], 7.12 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: 100.7 (br. s, CF_3). IR (KBr, ν/cm^{-1}): 3196, 1614. Found (%): C, 50.98; H, 7.43; N, 11.86. Calc. for $C_{15}H_{24}F_3N_3O_2\cdot H_2O$ (%): C, 50.98; H, 7.42; N, 11.89.

‡ At 295 K crystals of **4a** ($C_{14}H_{21}F_3N_2O_3$) are triclinic, space group $P\bar{1}$, a = 7.5968(14), b = 8.6575(18) and c = 12.3628(8) Å, α = 89.216(14)°, β = 87.472(11)°, γ = 64.925(15)°, V = 735.7(2) Å^3, Z = 2, d_{calc} = 1.455 g cm^{-3}, μ = 0.126 mm^{-1}, F(000) = 340. Diffraction data were collected on an Xcalibur 3 automatic single-crystal diffractometer (graphite-monochromated MoKα radiation, ω-scans). The structures were solved by direct methods and refined by the full-matrix least-squares method using the SHELX-97 program package.[22] The H atoms were located geometrically using the riding model.

CCDC 805670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2011.

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γ-dicarbonyl compounds, have been reported.[19] They were obtained from phenacyl or *p*-bromophenacyl bromide oximes and certain enamines; the formation of isomeric cyclic nitrones was not observed in this case. All our attempts to carry out a similar ring-contraction reaction with CCl_3-analogue, namely (*E*)-1,1,1-trichloro-3-nitrobut-2-ene,[20] failed. In this case, rather stable 4-trichloromethyl-1,2-oxazine *N*-oxides **3d** were only obtained and no evidence was found for their rearrangement.[14] Apparently, the observed rearrangement inheres just in 4-trifluoromethyl-1,2-oxazine *N*-oxides. It is worthwhile to note that 4-phenyl-1,2-oxazine *N*-oxides **3e** (see Scheme 2) are prone to undergo ring-opening.[21]

In conclusion, we have discovered the first example of a cyclic nitrone formation *via* ring-contraction rearrangement, which can provide some impetus for the preparation of other related derivatives, which can serve as promising substrates for 1,3-dipolar cycloaddition reactions.

This work was supported by the Russian Foundation for Basic Research (grant no. 11-03-00126).

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Received: 28th March 2011; Com. 11/3705

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