Electronic supplementary materials *Mendeleev Commun.*, 2018, **28**, 126–127

Step by step and one-pot syntheses of 5-hydroxy-5-(polyfluoroalkyl)isoxazol-4(5*H*)-one oximes

Nadezhda V. Palysaeva, Nadezhda S. Boltacheva, Pavel A. Slepukhin, Marina G. Pervova, Vera I. Filyakova, Aleksei B. Sheremetev and Valery N. Charushin

Lithium enolates **1a-f** were obtained by condensation of polyfluorocarboxylic acid esters with methylketones by the procedure reported previously.[1,2] Oximes **2b,d-f** were obtained by the techniques reported previously.[3] The purity of the resulting compounds was checked by TLC on Sorbfil plates (UV-254) using $CHCl_3$ as the eluent. The plates were visualized using UV light and an aqueous solution of $Cu(OAc)_2$.

5-Hydroxy-3-phenyl-5-trifluoromethyl-4(5*H*)-isoxazolone oxime 4b, which is a very strong allergen, was obtained and analyzed separately from the other compounds at N.D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. Natural abundance ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300, 282 and 75 MHz, respectively). The chemical shifts in the NMR spectra were determined relative to the chemical shifts of DMSO-d_6 (for ^{1}H and ^{13}C) or to an external standard ($CClF_3$ for ^{19}F). The mass spectrum was recorded on a Finnigan MATINCOS 50 spectrometer (direct injection, electron impact, ionization energy = 70 eV). Elemental analysis was carried out with a PerkinElmerSeriesII 2400 instrument. The melting point was determined in a Gallenkamp melting unit and was not corrected.

Analytical studies were carried out using equipment of the Center for Joint Use “Spectroscopy and Analysis of Organic Compounds” at the I.Ya. Postovsky Institute of Organic Synthesis of the Russian Academy of Sciences (Ural Branch).

IR spectra were recorded with a Spectrum One B spectrometer (Perkin Elmer) using a diffuse reflectance unit.

Identification of the reaction products was carried out using a Trace GC Ultra DSQ II gas chromatography/mass spectrometer (USA), with a Thermo TR-5ms quartz capillary column, 30

min length and 0.25 mm in diameter, film thickness 0.25 μm (polymethylsiloxane, 5% of phenyl groups), and a quadrupole mass spectrometric detector (GC-MS). Scanning was performed in electron ionization mode (70 eV), at full ionic current, in the 20-1000 Da mass range. The initial column temperature was 40°C (exposure for 3 min), then heating was performed at a rate of 10°C/min. The final column temperature was 280°C. The inlet temperature was 250°C, the detector temperature was 200°C, and the transfer line temperature was 200°C. Helium was used as the carrier gas, flow division 1:50, flow through the column 1.0 ml/min.

^{1}H, ^{13}C and ^{19}F NMR spectra were obtained with a Bruker AVANCE-500 spectrometer using TMS (^{1}H) and C_6F_6 (^{19}F) as the internal standards. The chemical shifts in the ^{19}F NMR spectra are given with respect to $CFCl_3$ and are considered positive for increasing field. The melting points of compounds were determined using Boetius and Stuart SMP3 instruments. Elementary analyses were carried out on a CHN PE 2400 ser. II automatic analyzer (Perkin Elmer).

*General procedure for the synthesis of compounds **4** from oximes **2***

Hydroxylamine hydrochloride was added to a solution of oxime **2** in methanol (molar ratio of oxime **2** and hydroxylamine hydrochloride = 1:1.2). The reaction mixture was refluxed until the starting compounds disappeared (TLC monitoring). Methanol was evaporated and the residue was recrystallized from chloroform.

Caution! Isoxazoline oximes **4** are allergens. Therefore, safety precautions must be taken when handling these compounds. A good exhaust system, protective glasses and gloves are required. Of the compounds studied, compound **4b** was found to have the strongest allergic properties (it causes strong skin itch and facial oedema).

5-Hydroxy-3-phenyl-5-trifluoromethyl-4(5*H*)-isoxazolone oxime 4b

The reaction of oxime **2b** (0.13 g, 0.00051 mol) and hydroxylamine hydrochloride (0.042 g, 0.00061 mol) gave 0.12 g (92%) isoxazolone oxime (**4b**), mp 164–165ºC. Found, %: C, 46.25; H, 2.74; N, 10.72. $C_{10}H_7F_3N_2O_3$ (260.17), Calculated, %: C, 46.17; H, 2.71; N, 10.77. ^{1}H NMR 300 MHz, DMSO-d_6) δ: 7.48 (m, 3H, Ph), 7.61 (m, 2H, Ph), 9.56 (s, 1H, OH), 13.35 (s, 1H, NOH). ^{19}F NMR (282 MHz, DMSO-d_6) δ: -83.2. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 121.4 (q, C^5, J_{CF} = 34 Hz), 114.9 (q, CF_3, J_{CF} = 285 Hz), 128.0, 129.0, 130.0, 130.3 (Ph), 146.8 (<u>*C*</u>=NOH), 151.9 (<u>*C*</u>=N).

MS (EI), *m/z*: 260 $[M]^+$ (33), 242 $[M\text{-}H_2O]$ (3), 213 (6), 191 (6), 163 (5), 144 $[M\text{-}CF_3\text{-}H_2O\text{-}HCO]^+$ (21), 129 $[M\text{-}CF_3\text{-}2OH\text{-}CO]^+$ (32), 103 $[PhCN]^+$ (37), 77 $[Ph]^+$ (100), 69 $[CF_3]^+$ (45), 51 $[Ph\text{-}C_2H_2]^+$ (68).

5-Hydroxy-5-perfluorobutyl-3-phenyl-4(5*H*)-isoxazolone oxime 4d

The reaction of oxime **2d** (0.2 g, 0.00051 mol) and hydroxylamine hydrochloride (0.042 g, 0.00061 mol) gave isoxazolone oxime **4d** (0.19 g, 91%), mp 171.9–172.0 °C. Found, %: C, 37.80;

H, 1.72; N, 6.79, F 41.77. $C_{13}H_7F_9N_2O_3$. Calculated, %: C, 38.07; H, 1.76; N, 6.83, F 41.68. ^{1}H NMR 500 MHz, DMSO-d_6) δ: [7.43- 7.54 (m, 3H); 7.56 – 7.61 (m, 2H) Ph], 9.60 (d, 1H, *J* 2.04 Hz OH), 13.36 (s, 1H, NOH). ^{19}F NMR (470.5 MHz, DMSO-d_6) δ: -126.6 (d.m, 1F, C^1F_A, J_{AB} 287.2 Hz), -125.6 (d.m, 1F, C^1F_B, J_{AB} 287.2 Hz); -123.1 (d.m, 1F, C^2F_A, J_{AB} 287.3 Hz), -121.9 (d.m, 1F, C^2F_B, J_{AB} 287.3 Hz); -120.7 (d.m, 1F, C^3F_A, J_{AB} 295.1 Hz), -120.3 (d.m, 1F, C^3F_B, J_{AB} 295.1 Hz); -80.5 (t.m, 3F, *J* 9.9 Hz, CF_3). IR, cm^{-1}: 3453, 3176, 3067, 2897,1543, 1482, 1365, 1354, 1299, 1273, 1235, 1219, 1200, 1137, 1097, 1044, 966, 900, 773, 736, 694, 599.

5-Hydroxy-5-(1,1,2,2,3,3,4,4-octafluorobutyl)-3-phenyl-4(5*H*)-isoxazolone oxime 4e

The reaction of oxime **2e** (0.37 g, 0.00098 mol) and hydroxylamine hydrochloride (0.082 g, 0.0012 mol) gave isoxazolone oxime **4e** (0.38 g, 87%), mp 159.5–160 °C. Found, %: C, 39.45; H, 2.15; N, 7.10, F 38.65. $C_{13}H_8F_8N_2O_3$. Calculated, %: C, 39.81; H, 2.06; N, 7.14, F 38.75. ^{1}H NMR 500 MHz, DMSO-d_6) δ: 7.09 (t.t., 1H, $H(CF_2)_4$, ^2J 50.51 Hz, ^3J 5.78 Hz), [7.43- 7.53 (m, 3H); 7.58 – 7.60 (m, 2H) Ph], 9.50-9.53 (m, 1H, OH), 13.30 (s, 1H, NOH). ^{19}F NMR (470.5 MHz, DMSO-d_6) δ: -138.48 (m, 2F, HCF_2), -130.37 (d.m, 1F, C^3F_A, J_{AB} 286.8 Hz), -129.76 (d.m, 1F, C^3F_B, J_{AB} 286.8 Hz); -123.2 (d.m, 1F, C^2F_A, J_{AB} 283.9 Hz), -122.0 (d.m, 1F, C^2F_B, J_{AB} 283.9 Hz); -122.2 (d.m, 1F, C^1F_A, J_{AB} 295.35 Hz), -121.1 (d.m, 1F, C^1F_B, J_{AB} 295.35 Hz).

IR, cm^{-1}: 3453, 3176, 3067, 2897, 1541, 1495, 1392, 1366, 1282, 1229, 1170, 1158, 1127, 1082, 1048, 980, 953, 901, 920, 853, 806, 776, 714, 697.

5-Hydroxy-5-perfluorohexyl-3-phenyl-4(5*H*)-isoxazolone oxime 4f

The reaction of oxime **2f** (0.3 g, 0.00061 mol) and hydroxylamine hydrochloride (0.051 g, 0.00073 mol) gave isoxazolone oxime **4f** (0.26 g, 84%), mp 168–168.7 °C. Found, %: C, 35.24; H, 1.39; N, 5.47, F 48.50. $C_{15}H_7F_{13}N_2O_3$. Calculated, %: C, 35.31; H, 1.38; N, 5.49, F 48.41. ^{1}H NMR 500 MHz, DMSO-d_6) δ: [7.43- 7.54 (m, 3H); 7.55 – 7.60 (m, 2H) Ph], 9.59-9.62 (m, 1H, OH), 13.36 (s, 1H, NOH). IR, cm^{-1}: 3418, 3154, 3062, 2872, 1552, 1472, 1366, 1317, 1201, 1145, 1128, 1092, 1031, 993, 959, 920, 896, 723, 694, 647.

GC-MS (EI, in acetone, TIC): t_R 22.32 min. MS, *m/z* ($I_{rel.}$, %): 510 $[M]^{+\cdot}$ (9.0), 492 $[M\text{-}H_2O]^{+\cdot}$ (9.4), 462 $[M\text{-}H_2O\text{-}NO]^{+\cdot}$ (2.0), 434 $[M\text{-}C_6H_4]^+$ (6.7), 319 $[C_6F_{13}]^+$ (2.6), 231 $[C_5F_9]^+$ (6.1), 209 (7.2), 191 $[M\text{-}C_6F_{13}]^+$ (5.4), 181 $[C_4F_7]^+$ (8.7), 169 $[C_3F_7]^+$ (13.2), 143 $[C_4F_5]^+$ (52.3), 131 $[C_3F_5]^+$ (50.8), 119 $[C_2F_5]^+$ (34.1), 103 $[C_6H_5CN]^+$ (100), 100 $[C_2F_4]^+$ (15.6), 77 $[C_6H_5]^+$ (61.1), 69 $[CF_3]^+$ (54.2), 51 $[HCF_2]^+$ (26.6), 45 $[CH_3NO]^+$ (16.8), 39 $[HF_2]^+$ (5.1), 27 $[HCN]^+$ (5.1).

X-ray structural analysis of isoxazolone oxime **4f** (Figure S1) indicates that at room temperature the perfluoroalkyl is characterized by strongest librations of the fluorine atoms relative to the carbon-carbon bonds. Moreover, the carbon atoms are also characterized by high thermal parameters and strong anisotropism of the latter. As a result, only the coordinates of atoms in the CF_2 group at the isoxazoline moiety can be localized with some certainty. The

positions of the remaining atoms in the perfluoroalkyl moiety were determined rather tentatively. This results in rather a strong difference between the structural model and the observed diffusion pattern (R_1= 6.36 %) and gives a number of anomalous C-F bond lengths and bond angles.[†]

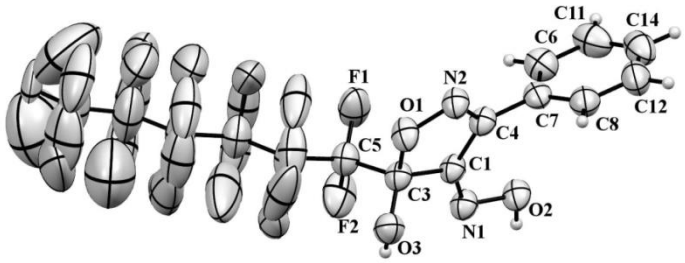

Figure S1 Compound **4f** in thermal ellipsoids at 50% probability.

The main specific feature of the crystal packing of the compound **4f** is that it contains a system of intermolecular hydrogen bonds (IMHB) that allow reliable localization of the positions of non-hydrogen atoms in the heterocyclic moiety. In fact, the OH groups of oxime moieties form IMHB with nitrogen in the isoxazoline moiety (O2-H2…N2 [x+1, y, z]), which results in the formation of polymer chains. These polymer chains are linked with each other by OH…O contacts between the hydroxyl of the isoxazoline ring and the oxygen atom of the oxime group (O3-H3A…O2 [-x+1, -y+1, -z+1]) (Figure S2).[‡]

[†] Probably, the structural model can be improved using a laborious procedure for introducing a multiple disordering of the atom positions in the perfluoroalkyl chain, but it appears inexpedient at this stage of the study due to the small importance of this moiety for proving the structure of the reaction product.

[‡] Unfortunately, available data of the structural experiment do not allow us to reliably localize the positions of the hydrogen atoms in these IMHB.

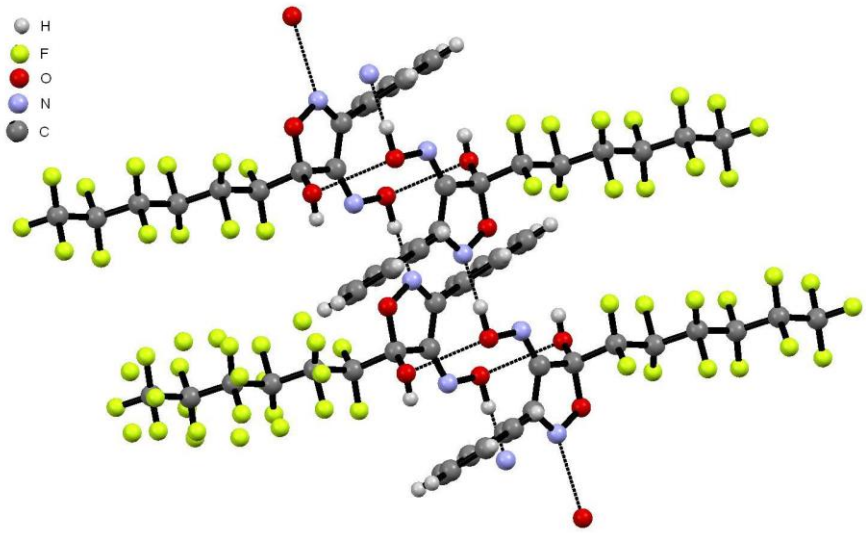

Figure S2 Hydrogen bonds in a crystal of compound **4f**.

*General procedure for synthesizing isoxazolone oximes **4** from lithium 1,3-diketonates **1** (one-pot synthesis)*

A flask with a solution of lithium diketonate **1** in acetic acid was placed in an ice bath and an aqueous solution of sodium nitrite was added dropwise with stirring while maintaining the temperature of the reaction mixture at about 10°C. After that, the ice bath was removed. The reaction mixture was warmed to room temperature, stirred for 1h, and hydroxylamine hydrochloride was added with stirring. The stirring was continued until the starting compounds disappeared and the new product formed (TLC monitoring). Water (100 ml) was added and the mixture was extracted with diethyl ether (3×20 ml). The ethereal extract was filtered through silica gel, ether was evaporated, and the residue was recrystallized from chloroform.

5-Hydroxy-3-methyl-5-trifluoromethyl-4(5*H*)-isoxazolone oxime 4a

The reaction of lithium diketonate **1a** (1.2 g, 0.0075 mol), acetic acid (18 ml), sodium nitrite (0.6 g, 0.0086 mol) in water (9 ml) and hydroxylamine hydrochloride (0.625 g, 0.009 mol) gave isoxazolone oxime **4a** (0.81 g, 55%), mp 145–145.4 °C.

Found, %: C, 30.42; H, 2.52; N, 14.13, F 28.73. $C_5H_5F_3N_2O_3$. Calculated, %: C, 30.32; H, 2.54; N, 14.14, F 28.77. ^{1}H NMR 500 MHz, DMSO-d_6) δ: 2,32 (s, 3H, CH_3), 9.18 (s, 1H, OH), 13.20 (s, 1H, NOH). ^{19}F NMR (470.5 MHz, DMSO-d_6) δ: -83.31 (s, CF_3). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 13.93 (s, CH_3), 98.57 (q, C^5, J_{CF} 33.98 Hz), 121.26 (q, CF_3, J_{CF} 285.15 Hz), 148.99, 149.53.

IR, cm^{-1}: 3303, 3157, 2905, 2736, 1665, 1455, 1438, 1394, 1281, 1254, 1194, 1101, 1056, 1037, 1021, 956, 933, 897, 731, 704, 677.

GC-MS (EI, in ethanol, TIC): t_R 14.76 min. MS, *m/z* ($I_{rel.}$, %): 198 $[M]^{+\cdot}$ (9.8), 180 $[M–H_2O]^+$ (0.2), 150 $[M–H_2O\text{-}NO]^+$ (1.8), 137 $[M–H_2O\text{-}H_2CN\text{-}CH_3]^+$ (6.7), 129 $[M–CF_3]^+$ (100), 111 $[M–CF_3\text{-}H_2O]^+$ (11.5), 88 $[M–CF_3\text{-}CH_3CN]^+$ (14.5), 85 $[M–CF_3\text{-}CH_2NO]^+$ (18.3), 69 $[CF_3]^+$ (100), 67 $[M–CF_3\text{-}CH_2NO\text{-}H_2O]^+$ (44.0), 45 $[CH_3NO]^+$ (14.9), 44 $[CH_2NO]^+$ (55.2), 42 $[CH_3CNH]^+$ (91.0), 30 $[NO]^+$ (12.1), 27 $[HCN]^+$ (14.7).

5-Hydroxy-3-(4-methylphenyl)-5-trifluoromethyl-4(5*H*)-isoxazolone oxime 4c

The reaction of lithium diketonate **1c** (0.59 g, 0.0025 mol), acetic acid (6 ml), sodium nitrite (0.2 g, 0.0029 mol) in water (3 ml) and hydroxylamine hydrochloride (0.21 g, 0.003 mol) gave isoxazolone oxime **4c** (0.58 g, 85%), mp 153.5–154.4ºC.

Found, %: C, 47.99; H, 3.60; N, 10.16, F 20.49. $C_{11}H_9F_3N_2O_3$. Calculated, %: C, 48.18; H, 3.31; N, 10.22, F 20.79. ^{1}H NMR 500 MHz, DMSO-d_6) δ: 2,35 (s, 3H, CH_3), [7.27 (d, 2H, *J* 8.03 Hz); 7.49 (d, 2H, *J* 8.03 Hz) C_6H_4], 9.45 (s, 1H, OH), 13.26 (s, 1H, NOH). ^{19}F NMR (470.5 MHz, DMSO-d_6) δ: -82.11 (s, CF_3).

IR, cm^{-1}: 3291, 3171, 2897, 2710, 1666, 1615, 1509, 1452, 1369, 1271, 1192, 1136, 1079, 997, 968, 905, 820, 734, 700.

GC-MS (EI, in $CHCl_3$, TIC): t_R 23.23 min. MS, *m/z* ($I_{rel.}$, %): 274 $[M]^{+\cdot}$ (49.1), 256 $[M–H_2O]^+$ (10.9), 226 $[M–H_2O\text{-}NO]^+$ (18.9), 157 $[M–H_2O\text{-}NO\text{-}CF_3]^+$ (34.7), 143 $[M–H_2O\text{-}CF_3\text{-}CH_2NO]^+$ (15.8), 116 $[CH_3C_6H_3CN]^+$ (28.2), 91 $[CH_3C_6H_4]^+$ (54.2), 69 $[CF_3]^+$ (100), 51 $[HCF_2]$ (11.5), 45 $[CH_3NO]^+$ (31.2), 30 $[NO]^+$ (22.3).

5-Hydroxy-5-(1,1,2,2,3,3,4,4-octafluorobutyl)-3-phenyl-4(5*H*)-isoxazolone oxime 4e

The reaction of lithium diketonate **1e** (0.66 g, 0.00186 mol), acetic acid (10 ml), sodium nitrite (0.15 g, 0.0022 mol) in water (3 ml) and hydroxylamine hydrochloride (0.13 g, 0.00186 mol) gave isoxazolone oxime **4e** (0.59 g, 78%), mp 159.5–160 ºC. The IR and ^{1}H NMR spectra of this sample were identical to the spectra of compound **4e** obtained by oximation of oxime **2e** (method 1).

References

1. V.I. Filyakova, N.S. Karpenko, O.A. Kuznetsova and K.I. Pashkevich, *Russ. J. Org. Chem.*,1998, **34**, 381 (*Zh. Org. Khim.*, 1998, **34**, 411).
2. N. S. Boltacheva, V. I. Filyakova, E. F. Khmara, O. V. Koryakova and V. N. Charushin. *Russ. J. Gen. Chem.*, 2010, **80**, 179 (*Ross. Khim. Zh.***,** 2010, **53** (1), 54).
3. V. I. Filyakova, N. S. Boltachova, M. G. Pervova, N. V. Palysaeva, P. A. Slepukhin, A. B. Sheremetev and V. N. Charushin, *Mendeleev Commun*., 2017, **27**, 464.