Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2018, **28**, 126–127

Mendeleev Communications

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

Nadezhda V. Palysaeva,[a] Nadezhda S. Boltacheva,[b] Pavel A. Slepukhin,[b] Marina G. Pervova,[b] Vera I. Filyakova,*[b] Aleksei B. Sheremetev[a] and Valery N. Charushin[b,c]

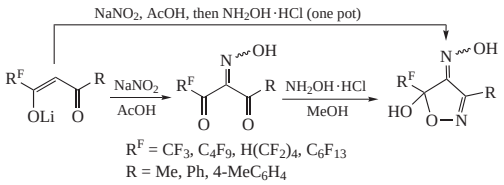
[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: sab@ioc.ac.ru*

[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russian Federation. E-mail: vif@ios.uran.ru*

[c] *Institute of Chemical Engineering, Ural Federal University, 620002 Ekaterinburg, Russian Federation. Fax: +7 343 374 3905; e-mail: charushin@ios.uran.ru*

DOI: 10.1016/j.mencom.2018.03.003

5-Hydroxy-5-(polyfluoroalkyl)isoxazol-4(5*H*)-one oximes have been obtained by nitrosation of lithium 3-polyfluoroalkyl-1,3-diketonates followed by treatment of intermediate 3-(polyfluoroalkyl)propane-1,2,3-trione 2-oximes with hydroxylamine hydrochloride. The one-pot protocol comprising both stages has been elaborated.



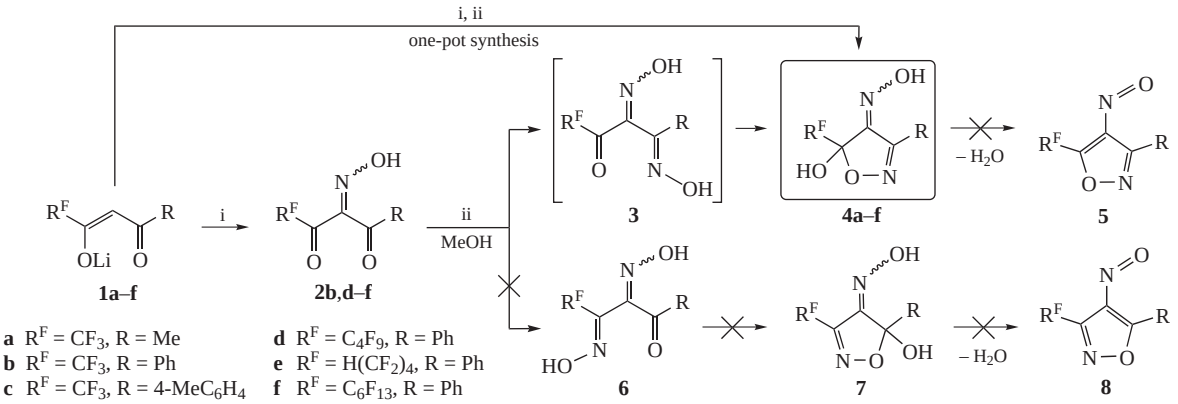
Isoxazoles are widely used in target synthesis of natural compounds and their analogues, for building and/or elongating carbon chains, constructing polycyclic molecules, as well as functionalization of olefin moieties in molecules.[1–3] Isoxazole ring being a pharmacophore is a common building block for the design of biologically active compounds[4,5] with antimicrobial,[6] antioxidant,[7] antifungal,[8] cyclooxygenase-inhibitive,[9] anticancer[10] and antitumor[11] properties.

Isoxazoles with polyfluoroalkyl substituents at 3- and/or 5-positions differ considerably from non-fluorinated analogues in terms of reactivity, physical properties and biological activity due to the strong electron-withdrawing effects of polyfluoroalkyl substituents.[12,13] Incorporation of fluorinated substituents makes molecules lipophilic thus favoring their migration through biomembranes.[12,13]

The treatment of substituted 1,3-diketones with hydroxylamine is a traditional method for the construction of the isoxazole ring.[5] We believed that for functionalized isoxazole synthesis, the use of 2-hydroxyimino-3-polyfluoroalkyl-1,3-diketones **2** as dicarbonyl precursors should be promising. Recently,[14] we reported an efficient conversion of lithium 3-(polyfluoroalkyl)-1,3-diketonates **1a–f** into 1,2,3-trione 2-oximes **2** (Scheme 1). The oxime function of compounds **2** can be easily transformed to C=O, NH_2, NO_2 and CN groups, or it can serve as a protective group.[15]

To the best of our knowledge, a reaction of oximes of fluorinated 1,3-diketones **2** with hydroxylamine has not been reported to date. Furthermore, information about similar reactions of non-fluorinated analogues is limited. For example, the reaction of acetyl(hydroxyimino)acetone (3-hydroxyiminopentane-2,4-dione) with an equimolar amount of hydroxylamine gave a mixture of *syn*- and *anti*-isomers of 3,5-dimethyl-5-hydroxy-4-hydroxyimino-2-isoxazoline.[16] On the other hand, monooximation of 2-hydroxyimino-1-(2-thienyl)butane-1,3-dione or 1-(2-hydroxybenzoyl)propane-1,2-dione 1-oxime did not lead to isoxazole derivatives but afforded bis-oximes.[17,18]

Herein we present results on the oximation of 2-hydroxyimino-3-polyfluoroalkyl-1,3-diketones **2b**,**d–f** (see Scheme 1). Theoretically, both carbonyl groups of compounds **2** can react with hydroxylamine and undergo subsequent intramolecular ring closure in the intermediate dioximes leading to regioisomeric dioximes **3** and/or **6**, isoxazolone oximes **4** and/or **7**, and the corresponding isoxazoles **5** and/or **8** (Scheme 1).



Scheme 1 *Reagents and conditions*: i, $NaNO_2$, AcOH; ii, $NH_2OH \cdot HCl$.

In fact, monooximation of compounds **2b**,**d**–**f** occurs with high chemoselectivity to give isoxazolone oximes **4b**,**d**–**f** (Scheme 1) in 84–91% yields (56.5–83.3% with respect to lithium diketonates). This result agrees with the well-known stabilization of adducts bearing geminal polyfluoroalkyl and hydroxy groups in various fluoroalkyl compounds, in particular, for reaction products of asymmetric fluoroalkyl-containing 1,3-diketones with hydroxylamine.[19]

Furthermore, we have found that compounds **4** can be obtained *via* a straightforward one-pot protocol from the corresponding lithium 1,3-diketonates **1** without isolation of the intermediate oximes **2**. The nitrosation of diketonates **1** with sodium nitrite in aqueous AcOH followed by treatment of the reaction mixture with an equimolar amount of hydroxylamine hydrochloride provides the target products **4** in up to 85% yields. Note that previous attempts to obtain oxime **2a** gave decomposition products,[20,21] hence a step-by-step synthesis of isoxazolone oxime **4a** is impossible. Meanwhile, the one-pot protocol allowed us to obtain compound **4a** in 55% yield.

Isoxazolone oximes **4a**–**f** appear as white powders soluble in diethyl ether and ethanol, and moderately soluble in dichloromethane and chloroform. Their IR spectra contain four broad intense bands of the =NO–H and O–H groups at 3453, 3176, 3067 and 2897 cm^{-1}, medium- or low-intensity bands at 1550 and 1480 cm^{-1} (C=N), and intense bands at 1230, 1170, 1160, 1130, 1090 and 980 cm^{-1} (C–F).[22] The mass spectra of compounds **4a**,**c**,**f** show low-intensity molecular ion peaks M^+ (0.7–3.0%) and diagnostic peaks corresponding to the loss of water $[M-H_2O]^+$ and nitrogen monooxide $[M-H_2O-NO]$.

The ^{1}H NMR spectra (in DMSO-d_6) of isoxazolone oximes **4a**–**f** contain singlets of C–OH protons at δ 9.45–9.62 and N–OH protons at δ 13.26–13.36. Spectrum of compound **4e** contains a triplet of triplets of the $H(CF_2)_4$ group at δ_H 6.10 (^1J 52 Hz, ^3J 5.3 Hz). The ^{19}F NMR spectra of CF_3-containing compounds **4a**–**c** show singlets at δ –83.31, –83.20 and –82.11, respectively (*cf.* ref. 23). The ^{19}F NMR spectra of compounds **4d**,**e** contain four AB systems for diastereotopic fluorine atoms of the CF_2 groups, which evidences that the $H(CF_2)_4$ and C_4F_9 groups are located at the asymmetric center. The presence of the C^5 atom quartet with J_{CF} 33.98 Hz at δ 98.57 in the ^{13}C NMR spectrum of compound **4a** indicates that the CF_3 and OH groups are arranged geminally.

The structure of isoxazolone oxime **4f** was unambiguously confirmed by single-crystal X-ray diffraction (Figure 1).†

In conclusion, we developed an efficient synthesis of 5-hydroxy-5-(polyfluoroalkyl)isoxazol-4(5*H*)-one oximes **4a**–**f** prospective for using in syntheses of practically valuable materials.

† *Crystal data for* **4f**. Crystal of **4f** ($C_{15}H_7F_{13}N_2O_3$, recrystallized from $CHCl_3$) is triclinic, space group $P\bar{1}$, a = 6.754(5), b = 10.546(12) and c = 13.318(5) Å, α = 85.63(6)°, β = 83.28(4)°, γ = 83.07(7)°, V = = 933.4(13) Å^3, Z = 2, μ(CuKα) = 1.946 mm^{-1}; 20609 reflections were measured (6.7° ⩽ 2θ ⩽ 132.12°), 3216 unique (R_{int} = 0.0404, R_σ = 0.0247) were used in all calculations. The final values were wR_2 = 0.1937 (all data) and R_1 = 0.0636 [$I > 2\sigma(I)$]. GooF = 1.026. Largest diff. peak/hole is 0.48/–0.40 e Å^{-3}.

XRD analysis was accomplished on an Xcalibur 3 automated four-circle diffractometer with a CCD-detector using the standard procedure [295(2) K, CuKα irradiation, graphite monochromator, ω-scans with 1° steps]; empirical absorption correction was applied. Using Olex2,[24] the structure was solved with the ShelXS[25] program using direct methods and refined with the olex2.refine[26] package using Gauss–Newton minimisation. All non-hydrogen atoms were refined in anisotropic approximation, the H-atoms were placed in the calculated positions and refined in the riding model with dependent isotropic displacement parameters. Due to strong librations, the fluorine atoms of the disordered fragments in the perfluoroalkyl moiety were refined with restrained displacement parameters using the ISOR command.

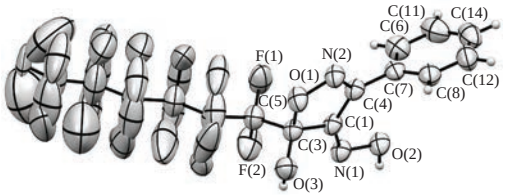


Figure 1 Molecular structure of compound **4f**.

This study was supported by the program of the Ural Branch of the Russian Academy of Sciences (project no. 18-3-3-12 for N.S.B., V.I.F. and V.N.Ch.).

Online Supplementary Materials

Supplementary data associated with this article (synthetic procedures and characterization of products) can be found in the online version at doi: 10.1016/j.mencom.2018.03.003.

References

1 A. A. Akhrem, F. A. Lakhvich and V. A. Khripach, *Chem. Heterocycl. Compd.*, 1981, **17**, 853 (*Khim. Geterotsikl. Soedin.*, 1981, 1155).
2 F. A. Lakhvich, E. V. Koroleva and A. A. Akhrem, *Chem. Heterocycl. Compd.*, 1989, **25**, 359 (*Khim. Geterotsikl. Soedin.*, 1989, 435).
3 T. M. V. D. Pinho e Melo, *Curr. Org. Chem.*, 2005, **9**, 925.
4 W. Shi, J. Hu, N. Bao, D. Li, L. Chen and J. Sun, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 147.
5 V. Kumar and K. Kaur, *J. Fluorine Chem.*, 2015, **180**, 55.
6 A. Padmaja, T. Payani, G. D. Reddy and V. Padmavathi, *Eur J. Med. Chem.*, 2009, **44**, 4557.
7 A. Padmaja, C. Rajasekhar, A. Muralikrishna and V. Padmavathi, *Eur. J. Med. Chem.*, 2011, **46**, 5034.
8 M. M. M. Santos, N. Faria, J. Iley, S. J. Coles, M. B. Hursthouse, M. Luz Martins and R. Moreira, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 193.
9 J. J. Talley, D. L. Brown, J. S. Carter, M. J. Graneto, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, R. S. Rogers, A. F. Shaffer, Y. Y. Zhang, B. S. Zweifel and K. Seibert, *J. Med. Chem.*, 2000, **43**, 775.
10 A. Kamal, E. V. Bharathi, J. S. Reddy, M. J. Ramaiah, D. Dastagiri, M. K. Reddy, A. Viswanath, T. L. Reddy, T. B. Shaik, S. N. C. V. L. Pushpavalli and M. P. Bhadra, *Eur. J. Med. Chem.*, 2011, **46**, 691.
11 P. Diana, A. Carbone, P. Barraja, G. Kelter, H.-H. Fiebig and G. Cirrincione, *Bioorg. Med. Chem.*, 2010, **18**, 4524.
12 *Fluorine Compounds. Synthesis and Application*, ed. N. Ishikawa, Kodansha, Tokyo, 1986.
13 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd edn., Wiley-VCH, Weinheim, 2013.
14 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.
15 A. I. Mikhaleva, A. B. Zaitsev and B. A. Trofimov, *Russ. Chem. Rev.*, 2006, **75**, 797 (*Usp. Khim.*, 2006, **75**, 884).
16 R. Fruttero, R. Calvino, B. Ferrarotti, A. Gasco, S. Aime, R. Gobetto, G. Chiari and G. Calestani, *J. Chem. Soc., Perkin Trans. 2*, 1987, 523.
17 G. Rai, C. J. Thomas, W. Leister and D. J. Maloney, *Tetrahedron Lett.*, 2009, **50**, 1710.
18 S. S. Ibrahim, *Ind. Eng. Chem. Res.*, 2001, **40**, 37.
19 R. Aggarwal, A. Bansal and A. Mittal, *J. Fluorine Chem.*, 2013, **145**, 95.
20 M. J. Crookes, P. Roy and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1015.
21 V. I. Saloutin, Y. V. Burgart, Z. E. Skryabina and O. G. Kuzueva, *J. Fluorine Chem.*, 1997, **84**, 107.
22 D. Lin-Vien, N. B. Colthup, W. G. Faterley and J. G. Grasselli, *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*, Academic Press, New York, 1991, pp. 128, 202.
23 V. Kumar, R. Aggarwal and S. P. Singh, *J. Fluorine Chem.*, 2006, **127**, 880.
24 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.
25 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.
26 L. J. Bourhis, O. V. Dolomanov, R. J. Gildea, J. A. K. Howard and H. Puschmann, *Acta Crystallogr.*, 2015, **A71**, 59.

Received: 11th July 2017; Com. 17/5307

CCDC 1561921 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.