ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 6, pp. 890–893. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Author(s), 2019, published in Zhurnal Organicheskoi Khimii, 2019, Vol. 55, No. 6, pp. 967–971.

SHORT COMMUNICATIONS

Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 85th anniversary

Synthesis of 3-Aroyl-2-(polyfluoroalkyl)quinoxalines and 3-Aroyl-2-(polyfluoroalkyl)benzo[*g*]quinoxalines from Lithium 3-(Fluoroalkyl)-1,3-diketonates

V. I. Filyakova[a],* N. S. Boltacheva[a], and V. N. Charushin[a]

[a] *Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, Yekaterinburg, Russia*
**e-mail: filver@mail.ru*

Received April 11, 2019; revised April 23, 2019; accepted April 24, 2019

Abstract—A one-pot procedure has been developed for the synthesis of 3-aroyl-2-(polyfluoroalkyl)quinoxalines and 3-aroyl-2-(polyfluoroalkyl)benzo[*g*]quinoxalines by nitrosation of lithium 3-(polyfluoroalkyl)-1,3-diketonates and subsequent reaction with benzene-1,2-diamine or naphthalene-2,3-diamine, respectively.

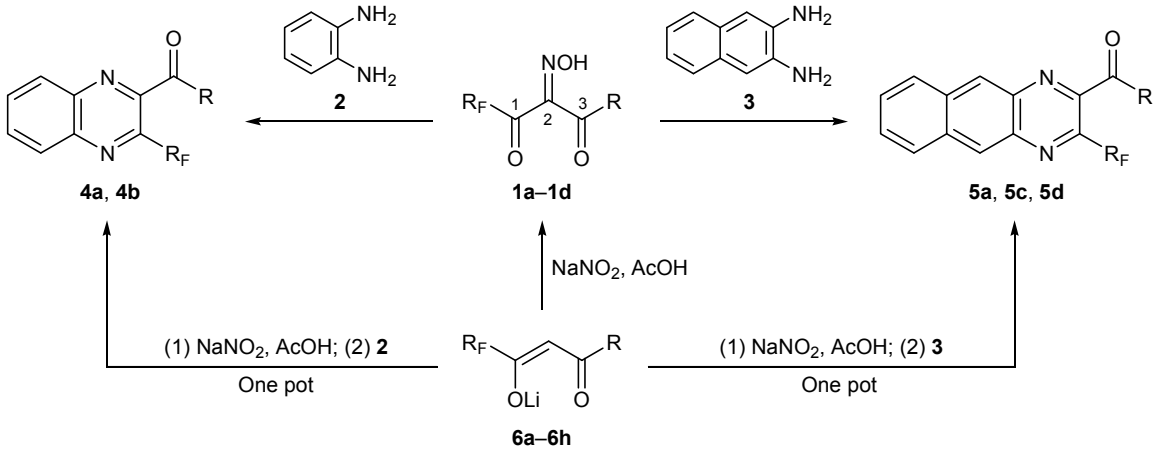
Keywords: fluorinated lithium 1,3-diketonates, benzene-1,2-diamine, naphthalene-2,3-diamine, 3-benzoyl-2-polyfluoroalkylquinoxalines, 3-aroyl-2-polyfluoroalkylbenzo[*g*]quinoxalines.

DOI: 10.1134/S107042801906023X

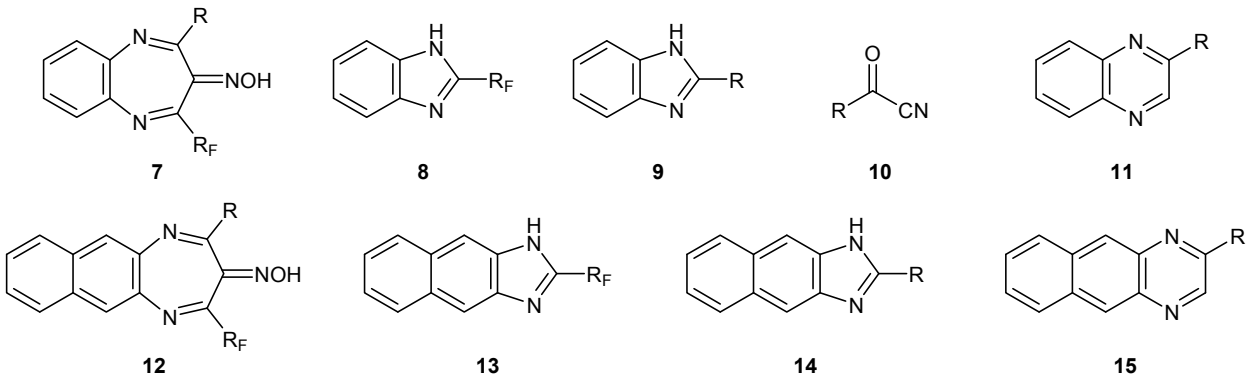
Fluorine-containing heterocycles occupy an important place among biologically active compounds, and their significance for medicine and technology continuously increases [1, 2].

By reacting 4-aryl-1,1,1-trifluorobutane-2,3,4-trione 3-oximes **1** with benzene-1,2-diamine (**2**) and naphthalene-2,3-diamine (**3**) we previously synthesized new quinoxaline derivatives: 3-aroyl-2-(trifluoromethyl)quinoxalines **4** and 3-aroyl-2-(trifluoromethyl)benzo[*g*]quinoxalines **5**. However, analogous reactions of oximes **1** containing a longer polyfluoroalkyl group (R_F = C_3F_7, $H(CF_2)_4$, C_4F_9, C_6F_{13}) led to the formation of complex mixtures of condensation and fragmentation products at different ratios [3]. In this communication, we report the results of one-pot synthesis of compounds **4** and **5** directly from the corresponding lithium 3-(polyfluoroalkyl)-1,3-diketonates **6** without preliminary isolation of oximes **1**. This approach was successfully utilized by us in the synthesis of 5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine [4] and 5-hydroxy-5-(polyfluoroalkyl)-1,2-oxazol-4(5*H*)-one oximes [5]. In particular, the one-pot procedure allowed us to obtain 5-hydroxy-3-methyl-5-(trifluoromethyl)-1,2-oxazol-4(5*H*)-one oxime whose stepwise synthesis is impossible because of instability of the corresponding oxime [5].

In fact, by successive treatment of diketonates **6a**–**6d** with sodium nitrite and diamine **2** or **3** without isolation of intermediate oximes **1**, we obtained compounds **4a**, **4b**, **5a**, **5c**, and **5d** in 60 to 75% yield. It should be noted that only one-pot protocol made it possible to isolate and characterize previously unknown compound **5d**. Our attempts to synthesize oxime **1d** by nitrosation of lithium diketonate **6d** resulted in the formation of decomposition product, 3-(4-methoxyphenyl)-2-oxopropanenitrile. However, neither compounds **4** and **5** nor benzo(naphtho)diazepine derivatives **7** and **12** were formed as the major products from lithium diketonates **6e**–**6h** containing a longer fluoroalkyl substituent [R_F = C_3F_7, $H(CF_2)_4$, C_4F_9, C_6F_{13}]. According to the GC/MS data, the qualitative composition of the product mixtures was the same as in the reactions of oximes **1** with diamines **2** and **3** (compounds **7**–**15**) [3], but the major components were benzo- or naphthoimidazoles **8** and **13** which could be synthesized by simpler methods [6]. Presumably, imidazoles **8** and **9** are products of transformations of 1,5-diazepines **7** in acid medium [6, 7]. Correspondingly, naphthoimidazoles **13** and **14**



i: $NaNO_2$, AcOH; R_F = CF_3 (**a**–**c**), HCF_2 (**d**), C_3F_7 (**e**), $H(CF_2)_4$ (**f**), C_4F_9 (**g**), C_6F_{13} (**h**); R = Ph (**a**, **e**–**h**), 4-MeC_6H_4 (**b**), 2,4-$Me_2C_6H_3$ (**c**), 4-$MeOC_6H_4$ (**d**).



are formed from naphthodiazepines **12**. Quinoxalines **11** and benzo[*g*]quinoxalines **15** are products of the reaction of ketonitriles **10** with diamines **2** and **3**, respectively.

Despite limitations related to the length of the polyfluoroalkyl substituent, the described procedure can be regarded as a convenient method for the synthesis of 2-(difluoromethyl)- and 2-(trifluoromethyl)-substituted quinoxaline derivatives **4** and **5** whose range could be extended via variation of the R substituent in **6** and of the 1,2-diamine component. In particular, using the one-pot procedure, we synthesized new compounds **5c** and **5d**. It should be emphasized that introduction of a di- or trifluoromethyl group into molecules of biologically active heterocycles, undoubtedly including quinoxaline derivatives, offers a great potential for drug design [8–12].

Thus, we have developed an efficient one-pot procedure for the synthesis of 3-aroyl-2-(difluoromethyl)- and 3-aroyl-2-(trifluoromethyl)quinoxalines and -benzo[*g*]quinoxalines **4** and **5** on the basis of accessible fluoroalkyl-containing building blocks, lithium 1,3-diketonates **6** [13–15]. The proposed procedure avoids a number of operations related to the isolation of oximes **1** and provides substantial economy of time and chemicals and reduction of wastes. Therefore, it conforms to the green chemistry and atom economy principles.

Lithium diketonates **6a**–**6h** were prepared according to the procedure described [13]; their characteristics were given in [15]. Compounds **6c** and **6d** were not reported previously.

Lithium (*Z*)-4-(2,4-dimethylphenyl)-1,1,1-trifluoro-4-oxobut-2-en-2-olate (6c). Yield 34 g (71%), white powder, mp 315–316°C. IR spectrum, ν, cm^{-1}: 582 m (O–Li), 691 m, 799 m, 1138 s (C–F), 1185 s (C–F), 1243 m (C–F), 1280 s (C–F), 1301 s (C–F), 1473 s, 1524 m (C=C_{arom}), 1621 (C=C–C=O), 2955 br (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.27 s (3H, CH_3), 2.33 s (3H, CH_3), 5.62 s (1H, =CH), 7.00 s (1H, H_{arom}), 7.03 d (1H, H_{arom}, ^3J = 7.60 Hz), 7.26 d (1H, H_{arom}, ^3J = 7.60 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F 87.85 ppm, s (CF_3).

Lithium (*Z*)-1,1-difluoro-4-(4-methoxyphenyl)-4-oxobut-2-en-2-olate (6d). Yield 3.7 g (79%), white

powder, mp 243–245°C. IR spectrum, ν, cm^{-1}: 543 m (O–Li), 786 m, 1028 m, 1054 m (C–F), 1113 m (C–F), 1173 s (C–F), 1255 s (C–F), 1351 s (C–F), 1455 s (C=C), 1504 s, 1533 m, 1568 m, 1597 s (C=C_{arom}), 1614 m (C=C–C=O), 2970 br (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.80 s (3H, OCH_3), 5.94 t (1H, HCF_2, ^3J = 55.60 Hz), 6.03 s (1H, =CH), 6.95 d (2H, H_{arom}, ^3J = 8.80 Hz), 7.82 d (2H, H_{arom}, ^3J = 8.80 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F 39.88 ppm, d (HCF_2, ^3J = 55.60 Hz).

Reaction of lithium diketonates 6 with arenediamines 2 and 3 (*general procedure*). A solution of 1.15 mol of sodium nitrite in 2–3 mL of water was added with stirring to a solution of 1 mol of diketonate **6** in 4–8 mL of acetic acid, maintaining the temperature at 10°C. The mixture was stirred for 1 h at room temperature, 1 mol of diamine **2** or **3** was added, and the mixture was kept until the initial compounds disappeared (TLC). The mixture was poured into water and extracted with methylene chloride, the extract was filtered through a layer of silica gel (in some cases, column chromatography was applied with methylene chloride as eluent), the filtrate was concentrated, and hexane was added until a solid precipitated. The precipitate was filtered off and dried in air.

Phenyl[3-(trifluoromethyl)quinoxalin-2-yl]methanone (4a). Yield 0.81 g (74%), white powder, mp 78–79°C [3].

(4-Methylphenyl)[3-(trifluoromethyl)quinoxalin-2-yl]methanone (4b). Yield 0.73 g (68%), white powder, mp 108–109°C [3].

(4-Phenyl)[3-(trifluoromethyl)benzo[*g*]quinoxalin-2-yl]methanone (5a). Yield 1 g (63%), white powder, mp 158–159°C [3].

(2,4-Dimethylphenyl)[3-(trifluoromethyl)benzo-[*g*]quinoxalin-2-yl]methanone (5c). Yield 0.53 g (58%), white powder, mp 146.2–146.6°C. IR spectrum, ν, cm^{-1}: 1042 s (C–F), 1140 s (C–F), 1166 m (C–F), 1200 s (C–F), 1413 m (C=C), 1557 m (C=N), 1611 m (C=N), 1661 s (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.40 s (3H, CH_3), 2.70 s (3H, CH_3), 7.04 d (1H, H_{arom}, J = 7.95 Hz), 7.21 s (1H, H_{arom}), 7.44 d (1H, H_{arom}, J = 7.95 Hz); 7.64–7.70 m (2H), 8.09–8.10 m (1H), 8.15–8.19 m (1H), 8.73 (1H), and 8.87 m (1H) (H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.64, 21.96, 96.10, 119.65, 120.74 q (CF_3, $^1J_{CF}$ = 276.3 Hz), 121.84, 126.33, 128.11, 128.37, 128.44, 128.66, 128.82, 128.10, 131.18, 133.35, 133.73, 134.94, 135.53, 136.01, 139.88, 141.47 q (C^3, $^2J_{CF}$ = 36.19 Hz), 141.90, 144.37, 150.22, 192.82 (C=O). ^{19}F NMR spectrum ($CDCl_3$): δ_F 97.99 ppm, s (CF_3). Found, %: C 69.49; H 3.79; N 7.51 F 14.80. $C_{22}H_{15}F_3N_2O$. Calculated, %: C 69.47; H 3.97; N 7.36, F 14.98.

[3-(Difluoromethyl)benzo[*g*]quinoxalin-2-yl]-(4-methoxyphenyl)methanone (5d). Yield 0.5 g (65%), white powder, mp 172–173°C. IR spectrum, ν, cm^{-1}: 1042 s (C–F), 1079 s (C–F), 1119 s (C–F), 1150 m (C–F), 1170 m (C–F), 1274 s (C–F), 1441 m (C=C), 1512 m (C=N), 1592 s (C=N), 1649 s (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.91 s (3H, OCH_3), 7.01 d (2H, H_{arom}, J = 8.90 Hz), 7.23 t (1H, HCF_2, J = 54.90 Hz), 7.64–7.68 m (2H, H_{arom}), 8.08 d (2H, H_{arom}, J = 8.90 Hz); 8.10–8.18 m (2H), 8.76 s (1H), and 8.84 s (1H) (H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 55.61, 96.09, 111.78 t (HCF_2, J_{CF} = 243.08 Hz), 114.01, 114.58, 126. 77, 127.98, 128.64, 128.75, 128.77, 133.44, 134.96, 135.03, 135.56, 136.58, 146.57 t (C^3, J_{CF} = 23.77 Hz), 149.27, 164.66, 190.83, (C=O). ^{19}F NMR spectrum ($CDCl_3$): δ_F 43.36 ppm, d (HCF_2, J = 54.90 Hz). Found, %: C 69.22; H 3.73; N 7.71, F 10.44. $C_{21}H_{14}F_2N_2O_2$. Calculated, %: C 69.23; H 3.87; N 7.69, F 10.43.

The reactions of diketonates **6f**, **6g**, and **6h** with diamines **2** and **3** led to the formation of complex mixtures of products. According to the GC/MS data, the major components of these mixtures were benzimidazole **8f** and naphthoimidazoles **13g** and **13h**.

2-(1,1,2,2,3,3,4,4-Octafluorobutyl)-1*H*-benzimidazole (8f). Retention time 16.68 min; *m*/*z* 318 $[M]^+$.

2-(1,1,1,2,2,3,3,4,4-Nanofluorobutyl)-1*H*-naphtho[2,3-*d*]imidazole (13g). Retention time 21.81 min; *m*/*z* 386 $[M]^+$.

2-(1,1,2,2,3,3,4,4,5,5,6,6,6-Tridecafluorohexyl)-1*H*-naphtho[2,3-*d*]imidazole (13h). Retention time 22.30 min; *m*/*z* 486 $[M]^+$.

The fragmentation patterns of the molecular ions of **8f**, **13g**, and **13h** were consistent with their structures.

The products were identified by GC/MS on a Trace GC Ultra DSQ II instrument (USA); Thermo TR-5ms quartz capillary column, 30 m×0.25 mm, film thickness 0.25 μm; quadrupole mass detector; total ion monitoring, a.m.u range 20–1000; electron impact ionization (70 eV); oven temperature programming from 40°C (3 min) to 280°C at a rate of 10 deg/min; injector temperature 250°C, detector and interface temperature 200°C; carrier gas helium, split ratio 1:50, flow rate 1.0 mL/min.

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance-500 spectrometer relative to tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) as internal standard. The IR spectra (diffuse reflectance) of solid samples were recorded in the range 400–4000 cm^{-1} on a Perkin Elmer Spectrum One FT-IR instrument. The elemental analyses were obtained with a Perkin Elmer 2400 analyzer.

ACKNOWLEDGMENTS

This study was performed using the facilities of the "Spectroscopy and Analysis of Organic Compounds" joint center (Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences).

FUNDING

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 18-03-00112A).

CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

REFERENCES

1. *Fluorine in Heterocyclic Chemistry*, Nenajdenko, V., Ed., Cham: Springer, 2014, vols. 1, 2. doi 10.1007/978-3-319-04346-3; 10.1007/978-3-319-04435-4
2. Politanskaya, L.V., Selivanova, G.A., Panteleeva, E.V., Tretyakov, E.V., Platonov, V.E., Nikul'shin, P.V., Vinogradov, A.S., Zonov, Ya.V., Karpov, V.M., Mezhenkova, T.V., Vasilyev, A.V., Koldobskii, A.B., Shilova, O.S., Morozova, S.M., Burgart, Ya.V., Shchegolkov, E.V., Saloutin, V.I., Sokolov, V.B., Aksinenko, A.Yu., Nenajdenko, V.G., Moskalik, M.Yu., Astakhova, V.V., Shainyan, B.A., Tabolin, A.A., Ioffe, S.L., Muzalevskiy, V.M., Balenkova, E.S., Shastin, A.V., Tyutyunov, A.A., Boiko, V.E., Igumnov, S.M., Dilman, A.D., Adonin, N.Yu., Bardin, V.V., Masoud, S.M., Vorobyeva, D.V., Osipov, S.N., Nosova, E.V., Lipunova, G.N., Charushin, V.N., Prima, D.O., Makarov, A.G., Zibarev, A.V., Trofimov, B.A., Sobenina, L.N., Belyaeva, K.V., Sosnovskikh, V.Ya., Obydennov, D.L., and Usachev, S.A., *Russ. Chem. Rev*., 2019, vol. 88, p. 425. doi 10.1070/RCR4871
3. Boltacheva, N.S., Slepukhin, P.A., Pervova, M.G., Filyakova, V.I., and Charushin, V.N., *Russ. J. Gen. Chem*., 2019, vol. 89, p. 350. doi 10.1134/S1070363219030083
4. Boltacheva, N.S., Filyakova, V.I., and Charushin, V.N., RU Patent no. 2642924, 2018; *Byull. Izobret*., 2018, no. 4.
5. Palysaeva, N.V., Boltacheva, N.S., Slepukhin, P.A., Pervova, M.G., Filyakova, V.I., Sheremetev, A.B., and Charushin, V.N., *Mendeleev Commun*., 2018, vol. 28, p. 126. doi 10.1016/j.mencom.2018.03.003
6. *Comprehensive Organic Chemistry*, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1979, vol. 4.
7. Filyakova, V.I., Boltacheva, N.S., Sevenard, D.V., and Charushin, V.N., *Russ. Chem. Bull., Int. Ed*., 2010, vol. 59, no. 9, p. 1791. doi 10.1007/s11172-010-0314-x
8. Purser, S., Moore, P.R., Swallow, S., and Gouverneur, V., *Chem. Soc. Rev*., 2008, vol. 37, p. 320.
9. *Fluorine in Medicinal Chemistry and Chemical Biology*, Ojima, I., Ed., Chichester: Wiley, 2009.
10. Smart, B.E., *Chem. Rev*., 1996, vol. 96, p. 1555.
11. Filler, R., Kobayashi, Y., and Yagupolskii, L.M., *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Amsterdam: Elsevier, 1993.
12. Fujiwara, Y., Dixon, J.A., Rodriguez, R.A., Baxter, R.D., Dixon, D.D., Collins, M.R., Blackmond, D.G., and Baran, P.S., *J. Am. Chem. Soc*., 2012, vol. 134, p. 1494.
13. Filyakova, V.I., Karpenko, N.S., Kuznetsova, O.A., and Pashkevich, K.I., *Russ. J. Org. Chem*., 1998, vol. 34, p. 381.
14. Sevenard, D.V., Khomutov, O.G., Boltachova, N.S., Filyakova, V.I., Vogel, V., Lork, E., Sosnovskikh, V.Ya., Iaroshenko, V.O., and Roschenthaler, G.V., *Z. Naturforsch., Teil B*, 2009, vol. 64, p. 541.
15. Boltacheva, N.S., Filyakova, V.I., Khmara, E.F., Koryakova, O.V., and Charushin, V.N., *Russ. J. Gen. Chem.,* 2010, vol. 80, p. 179. doi 10.1134/S1070363210010305