ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 3, pp. 384–387. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Author(s), 2019, published in Zhurnal Organicheskoi Khimii, 2019, Vol. 55, No. 3, pp. 446–450.

SHORT COMMUNICATIONS

Synthesis of Fluorine-Containing 2-Pyrrolyl- and 2-Indolyl-Substituted 1,3-Benzothiazin-4-ones

E. V. Nosova[a, b],* A. D. Poteeva[b], G. N. Lipunova[a], P. A. Slepukhin[a, b], and V. N. Charushin[a, b]

[a] *Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, ul. S. Kovalevskoi/Akademicheskaya 22/20, Yekaterinburg, 620990 Russia*
**e-mail: emily74@rambler.ru*

[b] *Ural Federal University, ul. Mira 19, Yekaterinburg, 620002 Russia*

Received June 20, 2018; revised July 16, 2018; accepted September 8, 2018

Abstract—New 2-(1-methyl-1*H*-pyrrol-2-yl)- and 2-(1-methyl-1*H*-indol-3-yl)-5-fluoro- and -6,7,8-trifluoro-1,3-benzothiazin-4-ones have been synthesized in high yields by reaction of *o*-fluorobenzoyl isothiocyanates with C-nucleophilic 1-methyl-1*H*-pyrrole and 1-methyl-1*H*-indole, followed by base-catalyzed cyclization. The products were characterized by ^{1}H, ^{13}C, and ^{19}F NMR and mass spectra and X-ray diffraction data.

Keywords: *o*-fluorobenzoyl chlorides, aroyl isothiocyanates, 1-methylpyrrole, 1-methylindole, 1,3-benzothiazin-4-one, intramolecular cyclization.

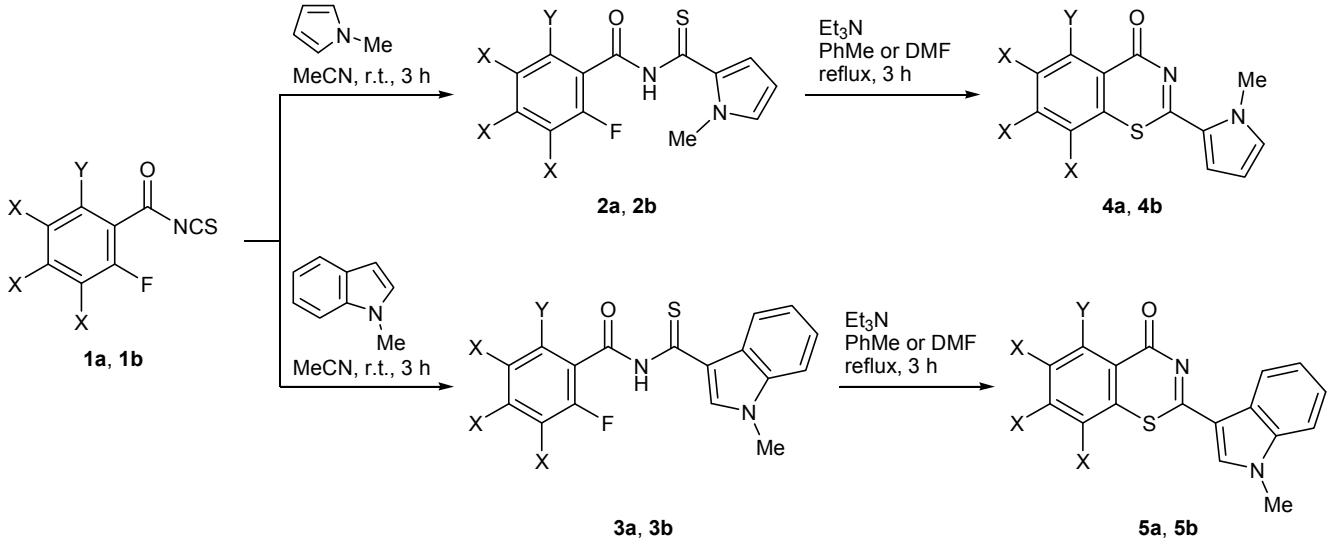
DOI: 10.1134/S1070428019030205

Increased interest in 2-substituted 1,3-benzothiazin-4-ones over the last decade is determined by the fact that 8-nitro-6-trifluoromethyl-1,3-benzothiazin-4-ones BTZ043 and PBTZ containing a piperidine or piperazine fragment in the 2-position showed high antimycobacterial activity against multidrug-resistant *M. Tuberculosis* strains [1, 2]. We previously synthesized a series of 2-substituted fluorine-containing 1,3-benzothiazin-4-ones which exhibited a high antimycobacterial activity at a MIC level of 0.3–1.0 nM [3]. There are data on another type of biological activity of 2-substituted benzothiazinones: 2-azinyl-1,3-benzothiazin-4-ones were found to inhibit oxidative stress-induced cardiomyocyte apoptosis [4].

Fluorine-free 2-hetaryl-1,3-benzothiazin-4-ones, including 2-pyrrolyl- and 2-indolyl-substituted derivatives, were synthesized by reaction of methyl 2-sulfanylbenzoate with the corresponding hetarenecarbonitriles [5]. However, fluorinated 2-sulfanylbenzoic acids are difficultly accessible compounds; therefore, in the present work fluorinated 1,3-benzothiazinones were obtained from 2-halobenzoyl isothiocyanates as starting compounds. Analogous approach was successfully utilized by us previously in the reaction of 2,6-difluorobenzoyl isothiocyanate (**1a**) with CH-acidic benzimidazoles and pyridines [6]. It was also shown that 2,3,4,5-tetrafluorobenzoyl isothiocyanate (**1b**) smoothly reacts with 2-aminopyridines to give the corresponding ureas capable of undergoing intramolecular cyclization to 2-(pyridin-2-ylamino)-1,3-benzothiazinones [7–10].

The addition of 1-methyl-1*H*-pyrrole and 1-methyl-1*H*-indole as C-nucleophiles to the N=C bond of isothiocyanates **1a** and **1b** smoothly occurred in acetonitrile at room temperature to give mixtures of primary addition products **2**, **3** and 1,3-benzothiazin-4-ones **4**, **5** (according to ^{1}H and ^{19}F NMR data). It should be noted that a 1 : 1 mixture of the corresponding addition product and 1,3-benzothiazin-4-one was also formed in the reaction of tetrafluorobenzoyl isothiocyanate (**1b**) with 2-(cyanomethyl)benzimidazole under analogous conditions [11]. Pure addition product **2a** was isolated by recrystallization of mixture **2a**/**4a** and characterized. The cyclization of **2** and **3** to targeted 2-substituted 1,3-benzothiazin-4-ones **4** and **5** was completed by heating in boiling toluene or dimethylformamide in the presence of triethylamine; the yields of **4** and **5** were 64–86%.

The structure of 1,3-benzothiazin-4-ones **4** and **5** was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR and mass spectra. The ^{1}H NMR spectra of **4** and **5** contained signals due to protons in the pyrrole (indole) fragment,



1a, **1b** **2a**, **2b** **4a**, **4b** **3a**, **3b** **5a**, **5b**

1–**5**: X = H, Y = F (**a**); X = F, Y = H (**b**).

whereas no NH signal was present. The 5-H proton in the spectra of 6,7,8-trifluoro derivatives **4b** and **5b** resonated as a doublet of doublets at δ 7.96–8.08 ppm. 5-Fluoro derivatives **4a** and **5a** displayed three signals of protons in the benzene ring at δ, ppm: 7.28–7.31 (6-H), 7.43–7.44 (8-H), and 7.66–7.69 m (7-H). In the ^{19}F NMR spectra of **4b** and **5b** we observed multiplet signals of three fluorine atoms. The fluorine atom in 5-fluoro derivatives **4a** and **5a** resonated at δ_F –109.0 and –109.5 ppm, respectively. The ^{1}H–^{13}C HMBC spectrum of **5a** showed a cross-peak between C^2 and protons of the NMe group, indicating that the 2-position is occupied by indol-3-yl rather than indol-2-yl substituent.

The molecular ions in the mass spectra of 1,3-benzothiazin-4-ones **4** and **5** had a relative intensity of 12–30%. The ion peak $[M - HetCN]^+$ (*m*/*z* 154) was the base one (I_{rel} 100%) only in the mass spectrum of 5-fluorobenzothiazinone **4a**, whereas the $[HetCN]^+$ ion was the most abundant for the other compounds (*m*/*z* 106 for **4b**; *m*/*z* 156 for **5a** and **5b**). It should be emphasized that elimination of RCN from the molecular ion is the main fragmentation pathway of 2-R-substituted 1,3-benzothiazin-4-ones [7] and pyrido[3,2-*e*]-[1,3]thiazin-4-ones [12].

According to the X-ray diffraction data, the thiazine ring in **4a** is not planar (Fig. 1), and the sulfur atom is disordered by two positions with a population ratio of 9 : 1. The disordered components deviate from the $C^6C^5N^3C^2$ plane by 0.165 and 0.346 Å, respectively. The C^4 atom deviates from that plane by 0.195 Å, and the O^1 atom, by 0.538 Å. The deviation of the oxygen atom is likely to be caused by the short intramolecular contact F···O. The pyrrole ring lies approximately in the mean-square plane of the benzothiazine system. In addition, short $C^8H\cdots O^1$ contact [1.5 – *x*, *y* – 0.5, 0.5 – *z*] is observed in crystal, presumably due to acidity of the 8-H proton located in the *ortho* position with respect to the 7-fluorine atom exerting a considerable –*I* effect.

Thus, we have synthesized in good yields 2-hetaryl-substituted fluorine-containing 1,3-benzothiazin-4-ones from readily accessible fluorobenzoyl isothiocyanates and C-nucleophilic heterocycles.

General procedure for the synthesis of 1,3-benzothiazin-4-ones 4a, 4b, 5a, and 5b. A solution of 0.456 g (6 mmol) of ammonium thiocyanate in 10 mL of anhydrous acetonitrile was added to a solution of 6 mmol of 2,6-difluorobenzoyl chloride or 2,3,4,5-tet-

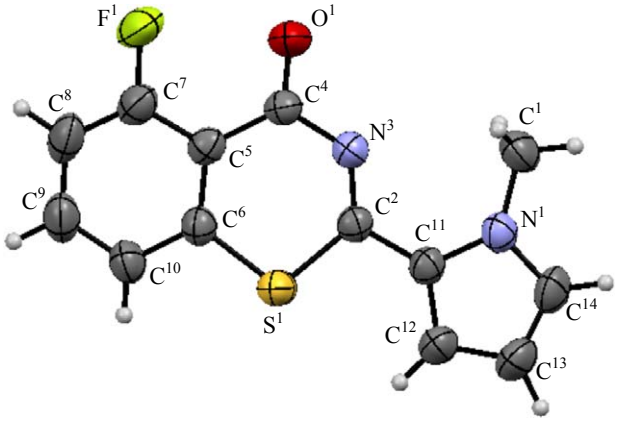


Fig. 1. Structure of the molecule of 5-fluoro-2-(1-methyl-1*H*-pyrrol-2-yl)-1,3-benzothiazin-4-one (**4a**) with atom numbering.

rafluorobenzoyl chloride in 3 mL of anhydrous acetonitrile. The mixture was heated for 5 min at 40°C, the precipitate of ammonium chloride was filtered off, and a solution of 6 mmol of 1-methyl-1*H*-pyrrole or 1-methyl-1*H*-indole in 5 mL of acetonitrile was added to the filtrate containing isothiocyanate **1a** or **1b**. The mixture was stirred for 3 h at room temperature, and the precipitate (mixture **2**/**4** or **3**/**5**) was filtered off and washed with hexane. The product was dissolved in 10 mL of anhydrous toluene (**2a**/**4a**, **2b**/**4b**, **3a**/**5a**, **3b**/**5b**) or 3 mL of anhydrous DMF (**2a**/**4a**, **3a**/**5a**), 0.18 mL (1.2 mmol) of triethylamine was added, and the mixture was refluxed for 3 h. After cooling, the precipitate was filtered off, washed with water, and recrystallized from DMSO.

5-Fluoro-2-(1-methyl-1*H*-pyrrol-2-yl)-1,3-benzothiazin-4-one (4a). Yield 86% (in DMF), 82% (in toluene), mp 148–150°C. ^{1}H NMR spectrum, δ, ppm: 4.10 s (3H, CH_3), 6.26 d.d (1H, 4′-H, J = 4.1, 2.5 Hz), 7.17 d.d (1H, 3′-H, J = 4.1, 1.6 Hz), 7.28 m (1H, 5′-H), 7.31 d.d (1H, 6-H, J = 10.1, 8.4Hz), 7.44 d (1H, 8-H, J = 8.0 Hz), 7.69 t.d (1H, 7-H, J = 8.1, 5.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 37.7 (CH_3), 99.5 ($C^{4'}$), 110.0 ($C^{3'}$), 112.2 (C^{4a}, J = 10 Hz), 116.5 (C^6, J = 22 Hz), 119.6 ($C^{5'}$), 122.2 (C^8, J = 4 Hz), 126.6 ($C^{2'}$), 134.2 (C^7, J = 8 Hz), 137.0 (C^{8a}, J = 1 Hz), 160.3 (C^2), 161.8 (C^5, J = 260 Hz), 165.7 (C=O, J = 4 Hz). ^{19}F–{^{1}H} NMR spectrum: δ_F –109.50 ppm. Mass spectrum, m/z (I_{rel}, %): 260 (30) $[M]^+$, 154 (100), 126 (29), 110 (21), 106 (26), 105 (13), 69 (11). Found, %: C 60.07; H 3.56; N 10.11. $C_{13}H_9FN_2OS$. Calculated, %: C 59.99; H 3.49; N 10.77. M 260.29.

6,7,8-Trifluoro-2-(1-methyl-1*H*-pyrrol-2-yl)-1,3-benzothiazin-4-one (4b). Yield 71% mp 199–201°C. ^{1}H NMR spectrum, δ, ppm: 4.06 s (3H, CH_3), 6.32 d.d (1H, 4′-H, J = 4.2, 2.5 Hz), 7.31 d.d (1H, 3′-H, J = 4.2, 1.6 Hz), 7.40 m (1H, 5′-H), 7.96 d.d.d (1H, 5-H, J = 10.5, 7.5, 2.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 37.7 (CH_3), 110.1 ($C^{4'}$), 112.2 ($C^{3'}$), 115.1 ($C^{2'}$), 118.4 (C^5, J = 18, 4 Hz), 120.8 ($C^{5'}$), 124.4 (C^{4a}), 137.0 (C^{8a}, J = 11 Hz), 145.3 (C^8, J = 258, 17, 4 Hz), 151.6 (C^7, J = 263, 16, 13 Hz), 158.3 (C^6, J = 252, 18, 5 Hz), 161.9 (C^2), 164.5 (C=O). ^{19}F–{^{1}H} NMR spectrum, δ_F, ppm: –136.87 d.d (1F, 6-F, J = 21.1, 5.9 Hz), –139.38 d.d (1F, 8-F, J = 20.7, 4.5 Hz), –155.25 d.d (1F, 7-F, J = 20.7, 21.1 Hz). Mass spectrum, m/z (I_{rel}, %): 296 (25) $[M]^+$, 194 (35), 190 (34), 177 (47), 162 (27), 149 (37), 106 (100), 105 (26), 99 (39), 93 (12), 85 (75), 80 (13), 69 (10), 57 (11), 45 (12), 44 (39), 43 (18), 41 (11). Found, %: C 52.67; H 2.26; N 9.51. $C_{13}H_7F_3N_2OS$. Calculated, %: C 52.70; H 2.38; N 9.46. M 296.27.

5-Fluoro-2-(1-methyl-1*H*-indol-3-yl)-1,3-benzothiazin-4-one (5a). Yield 81% (in DMF), 69% (in toluene), mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 3.92 s (3H, CH_3), 7.33–7.37 m (3H, 5′-H, 6-H, 6′-H), 7.50 m (1H, 8-H), 7.58 m (1H, 7′-H), 7.70 m (1H, 7-H), 8.44 m (1H, 4′-H), 8.53 s (1H, 2′-H). ^{13}C NMR spectrum, δ_C, ppm: 33.5 (CH_3), 99.5 ($C^{3'}$), 111.2 ($C^{7'}$), 112.3, 112.6 (C^{4a}, J = 11 Hz), 116.4 (C^6, J = 22 Hz), 121.8 ($C^{4'}$), 122.1 (C^8, J = 5 Hz), 122.8, 123.6, 124.7, 134.0 (C^7, J = 10 Hz), 136.8 ($C^{2'}$), 137.9 ($C^{7'a}$), 161.7 (C^5, J = 267 Hz), 164.2 (C^2), 166.0 (C=O, J = 4 Hz). ^{19}F–{^{1}H} NMR spectrum: δ_F –109.02 ppm. Mass spectrum, m/z (I_{rel}, %): 310 (15) $[M]^+$, 157 (11), 156 (100), 155 (24), 154 (15), 126 (12). Found, %: C 65.87; H 3.66; N 9.21. $C_{17}H_{11}FN_2OS$. Calculated, %: C 65.79; H 3.57; N 9.03. M 310.35.

6,7,8-Trifluoro-2-(1-methyl-1*H*-indol-3-yl)-1,3-benzothiazin-4-one (5b). Yield 64%, mp 307–309°C. ^{1}H NMR spectrum, δ, ppm: 3.98 s (3H, CH_3), 7.34 m (2H, 5′-H, 6′-H), 7.57 m (1H, 7′-H), 8.08 d.d.d (1H, 5-H, J = 9.6, 8.0, 1.7), 8.50 m (1H, 4′-H), 8.70 s (1H, 2′-H). ^{13}C NMR spectrum, δ_C, ppm: 34.6 (CH_3), 110.9, 113.5, 118.6 (C^5, J = 18, 5 Hz), 120.2, 121.4, 121.9, 122.3, 122.8, 136.9, 137.1, 137.9 (C^{8a}, J = 11 Hz), 145.4 (C^8, J = 259, 18, 5 Hz), 152.2 (C^7, J = 258, 17, 12 Hz), 157.9 (C^6, J = 254, 17, 6 Hz), 162.8 (C^2), 164.8 (C=O). ^{19}F–{^{1}H} NMR spectrum, δ_F, ppm: –134.01 d.d (1F, 6-F, J = 21.4, 5.0 Hz), –135.42 d.d (1F, 8-F, J = 20.6, 5.0 Hz), –152.90 d.d (1F, 7-F, J = 20.8, 21.4 Hz). Mass spectrum, m/z (I_{rel}, %): 346 (12) $[M]^+$, 190 (3.6), 157 (12), 156 (100), 155 (23). Found, %: C 59.05; H 2.70; N 8.03. $C_{17}H_9F_3N_2OS$. Calculated, %: C 58.96; H 2.62; N 8.09. M 346.33.

2,6-Difluoro-*N*-(1-methyl-1*H*-pyrrole-2-carbothioyl)benzamide (2a) was isolated by recrystallization of mixture **2a**/**4a** from ethanol, mp 117–119°C. ^{1}H NMR spectrum, δ, ppm: 3.94 s (3H, CH_3), 6.11 m (1H, 4′-H), 6.88 m (1H, 3′-H), 7.05 m (2H, 3-H, 5-H), 7.19 m (1H, 5′-H), 7.49 m (1H, 4-H), 11.9 br.s (1H, NH). ^{19}F–{^{1}H} NMR spectrum: δ_F –112.78 ppm. Mass spectrum, m/z (I_{rel}, %): 280 (43) $[M]^+$, 141 (100) $[C_6H_3F_2C(O)]^+$, 123 (29), 113 (39), 112 (11), 107 (69), 106 (23), 105 (13), 80 (19), 63 (20), 39 (11). Found, %: C 55.77; H 3.65; N 9.92. $C_{13}H_{10}F_2N_2OS$. Calculated, %: C 55.71; H 3.60; N 9.99. M 280.30.

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded from solutions in DMSO-d_6 on a Bruker Avance-400 spectrometer; the chemical shifts were measured relative to tetramethylsilane (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standard. The mass spectra (electron impact)

were recorded on a Shimadzu GCMS-QP2010 Ultra instrument. The elemental compositions were determined using a Perkin Elmer 2400 Series II CHN analyzer. The melting points were measured with a Boetius melting point apparatus.

The X-ray diffraction data for compound **4a** were obtained from a 0.45×0.37×0.28-mm single crystal (brown prism) at 295(2) K on an Xcalibur E diffractometer with a CCD detector (Cu K_α radiation, λ 154.184 pm, graphite monochromator). An empirical correction for absorption (μ = 2.520 mm^{-1}) was applied. Monoclinic crystal system, space group *C*2/*c*; $C_{13}H_9FN_2OS$; unit cell parameters: *a* = 12.318(11), *b* = 8.659(2), *c* = 22.544(14) Å; β = 105.685(2)°; *V* = 2315(3) $Å^3$; *Z* = 8. Total of 10733 reflection intensities were measured in the range 4.07 < θ < 65.34, including 1831 independent reflections (R_{int} = 0.0556), and 1705 reflections with $I > 2\sigma(I)$; completeness 96.4% for θ = 65.34°. The structure was solved by the direct method and was refined against F^2 by the least-squares method using SHELXTL package [13]. All hydrogen atoms were placed in directly calculated positions which were refined according to the riding model in isotropic approximation. Goodness of fit *S* = 1.006; final divergence factors: R_1 = 0.0437, wR_2 = 0.1272 for reflections with $I > 2\sigma(I)$; R_1 = 0.0478, wR_2 = 0.1309 for all independent reflections. Maximum and minimum residual electron density peaks 0.258 and –226 $\bar{e}$ $Å^{-3}$, respectively. The X-ray diffraction data for compound **4a** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1529104) and are available at *http://www.ccdc.cam.ac.uk*.

FUNDING

This study was performed under financial support by the Russian Science Foundation (project no. 15-13-00077P) and by the Ministry of Science and Higher Education of the Russian Federation (state contract no. 4.6351.2017/8.9).

CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

REFERENCES

1. Chetty, S., Ramesh, M., Singh-Pillay, A., and Soliman, M.E.S., *Bioorg. Med. Chem. Lett*., 2017, vol. 27, p. 370. doi 1016/j.bmcl.2016.11.084
2. Pasca, M.R., Degiacomi, G., Ribeiro, A.L., Zara, F., DeMori, P., Heym, B., Mirrione, M., Brerra, R., Pagani, L., Pucillo, L., Troupioti, P., Makarov, V., Cole, S.T., and Riccardi, G., *Antimicrob. Agents Chemother*., 2010, vol. 54, p. 1616. doi 1128/AAC.01676-09
3. Nosova, E.V., Lipunova, G.N., Kravchenko, M.A., Laeva, A.A., and Charushin, V.N., *Pharm. Chem. J*., 2008, vol. 42, p. 169. doi 1007/s11094-008-0083-0
4. Kimura, H., Sato, Y., Tajima, Y., Suzuki, H., Yukitake, H., Imaeda, T., Kajino, M., Oki, H., Takizawa, M., and Tanida, S., *Chem. Biol*., 2010, vol. 17, p. 1282. doi 1016/j.chembiol.2010.10.011
5. Kajino, M., Kawada, A., Nakayama, Y., Kimura, H., and Twaraishi, T., EP Patent Appl. no. 1424336, 2004.
6. Nosova, E.V., Laeva, A.A., Trashakhova, T.V., Golovchenko, A.V., Lipunova, G.N., Slepukhin, P.A., and Charushin, V.N., *Russ. J. Org. Chem*., 2009, vol. 45, p. 904. doi 1134/S1070428009060189
7. Nosova, E.V., Lipunova, G.N., Laeva, A.A., and Charushin, V.N., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1544. doi 1134/S1070428006100253
8. Yu, L. and Wei, Y., US Patent Appl. Pub. no. 2014/0303152, 2014.
9. Yu, L. and Wei, Y., EP Patent Appl. no. 2719691, 2014.
10. Yu, L. and Wei, Y., CN Patent no. 103508980, 2016.
11. Nosova, E.V., Lipunova, G.N., Laeva, A.A., and Charushin, V.N., *Russ. Chem. Bull., Int. Ed*., 2005, vol. 54, p. 733. doi 10.1007/s11172-005-0312-6
12. Koscik, D., Kristian, P., Gonda, J., and Dandarova, E., *Collect. Czech. Chem. Commun*., 1983, vol. 48, p. 3320. doi 10.1135/cccc19833315
13. Sheldrick, G.M., *Acta Crystallogr., Sect. A*, 2008, vol. 64, p. 112. doi 10.1107/S0108767307043930