Regioselective Synthesis of Polyfluoroalkyl Substituted 6,7-Dihydrobenzisoxazolones

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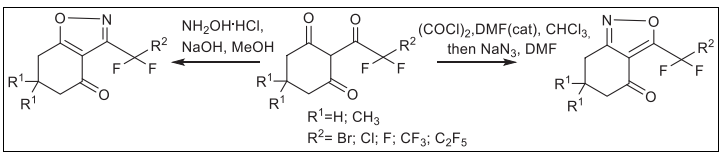
Received February 21, 2018

DOI 10.1002/jhet.3218

Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



Regioselective methods for synthesis of hitherto unreported both 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones with perfluoroalkyl or halogenodifluoromethyl substituents have been developed. 3-Polyfluoroalkyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones were prepared by the cyclocondensation of 2-polyfluoroalkanoylcyclohexane-1,3-diones with hydroxylamine. The regioisomeric 3-polyfluoroalkyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones were synthesized by the transformation of 2-polyfluoroalkanoylcyclohexane-1,3-diones into their vinylogous chlorides, followed by the interaction of obtained crude 3-chloro-2-polyfluoroalkanoyl-2-cyclohexen-1-ones with sodium azide in dimethylformamide.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

Heterocyclic compounds are an exceedingly important class of compounds, and they have attracted much attention for diverse biological studies. Heterocyclic moiety plays important functions in medicinal chemistry and serves as key template for development of therapeutic agents with unique properties [1]. Nitrogen containing heterocyclic rings with an oxygen atom are considered as one of the best combination in medicinal chemistry due to a broad spectrum of pharmacological activities [2,3]. Numerous heterocyclic compounds possessing an isoxazole ring (both isolated and fused to other mono or polycyclic systems) have been used as a base structure for the design of many pharmaceutical [4] and agrochemical agents [5]. Isoxazole, a five-membered heterocyclic azole ring, can be found in naturally occurring ibotenic acid along some of the marketed drugs as valdecoxib, flucloxacillin, cloxacillin, and dicloxacillin. It is also significant for showing antipsychotic activity in risperidone and anticonvulsant activity in zonisamide. The benzisoxazole scaffold and its analogues are important pharmacophores that can be found in biologically active compounds across a number of different therapeutic areas as anti-HIV, antimicrobial, antipsychotic, anti-inflammatory, analgesic, anticancer, and so on [6,7]. A large number of fluorine containing heterocyclic compounds are well known as important marketed drugs [8,9] and agrochemicals [10]. The selective introduction of fluorine atoms or polyfluoroalkyl groups into aromatic or heterocyclic moiety to modify the bioactivity of biomolecules is a well-established practice [11,12]. Previously synthesized 2-perfluoroalkanoylcyclohexane-1,3-diones [13] are very reactive compounds because of the presence of three electrophilic centers (one exocyclic and two endocyclic carbonyl groups) and can be used as building blocks in the synthesis of a large series of perfluoroalkyl-containing heterocyclic compounds. 2-Perfluoroalkanoylcyclohexane-1,3-diones and their enol derivatives are known to react with *N*,*N*-dinucleophiles such as phenylhydrazines or o-phenylenediamine to give corresponding fluorinated indazolones [14] and benzodiazepinones [15].

Therefore, in view of these observations and in conjunction with our previous interest in synthesis of heterocyclic compounds [16,17], we report herein a facile synthesis of novel regioisomeric 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones with perfluoroalkyl or halogenodifluoromethyl substituents.

RESULTS AND DISCUSSION

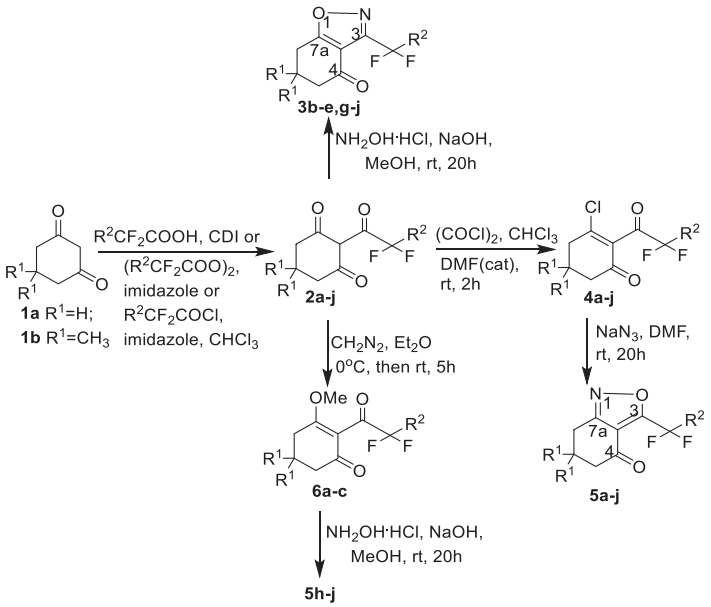
The most common synthetic approaches used to construct the fluorinated as well as nonfluorinated

isoxazoles up to the date include the condensation of β-diketones with hydroxylamine and the condensation of α,β-unsaturated compounds with hydroxylamine and 1,3-dipolar cycloaddition reactions [18,19]. The reaction of nitrile oxides with nonfluorinated cyclic β-diketones provides a regiospecific synthesis of isoxazoles with a wide variety of substituents [20,21]. However, reaction of nitrile oxides, generated *in situ* from trifluoroacetohydroximoyl bromide etherate, with cyclohexane-1,3-dione gave desired 3-(trifluoromethyl)-6,7-dihydrobenzo-1,2-isoxazol-4(5*H*)-one in a poor 29% yield [22]. The result of the reaction between fluorine-containing 1,3-diketones and hydroxylamine depended on such factors as the nature of constituents, the structure of β-diketone, and the reaction conditions [19,23]. For the synthesis of the target regioisomeric 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones, the strategy depicted in Scheme 1 was chosen.

The starting 2-perfluoroalkanoylcyclohexane-1,3-diones **2c–e,h–j** were prepared from commercially available cyclohexane-1,3-diones **1a,b** *via* a one-pot procedure, developed in our group [13]. The method involved C-acylation cyclohexane-1,3-diones **1a,b** with N-perfluoroacylimidazoles generated *in situ* from perfluorocarboxylic acid or perfluorocarboxylic acid anhydrides. That contrary to expectations, no formation of the desired products **2a,b,f,g** (unlike their perfluoroalkyl-substituted analogs) was observed when we used 1,1′-carbonyldiimidazole and 2-halogeno-2,2-difluoroacetic acid for the generation of N-acylimidazoles. Nevertheless, the previously unknown 2-(2-halogeno-2,2-difluoroacetyl)cyclohexane-1,3-diones **2a,b,f,g** were successfully prepared *via* C-acylation cyclohexane-1,3-diones **1a,b** with N-(2-halogeno-2,2-difluoroacetyl)imidazoles generated *in situ* from corresponding 2-halogeno-2,2-difluoroacetyl chlorides and imidazole in 63–71% yields.

Next, the reaction of hydroxylamine hydrochloride with 2-alkanoylcyclohexane-1,3-diones **2a–j** containing perfluoroalkyl or halogenodifluoromethyl substituents was investigated by us. The treatment of fluorinated cyclic β-triketones **2b–e,g–j** with an equimolar mixture of $NH_2OH{\cdot}HCl$ and NaOH in methanol at room temperature for 20 h led to the formation of 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones **3b–e,g–j** in 42–63% yield. Unfortunately, β-triketones **2a,f** containing bromodifluoromethyl group were unstable at the reaction conditions, and only the formation of complex mixture of unidentified products was observed. In fact, in the reactions of β-triketones **2b–e,g–j** with hydroxylamine, the nucleophilic attack of hydroxylamine amino group takes place on the electrophilic exocyclic carbonyl carbon attached to the polyfluoroalkyl group, followed by cyclocondensation,

Scheme 1. Synthesis of 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones **3b–e,g–j** and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones **5a–j**



which was in conformity with the reaction of nonfluorinated β-triketones and hydroxylamine hydrochloride [24].

To obtain polyfluoroalkyl 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones **5a–j** (regioisomers of isoxazolones **3a–j**), it is essential that a nucleophilic attack would be directed at the trigonal C3 center of 2-polyfluoroalkanoylcyclohexane-1,3-diones **2a–j**. It could be achieved *via* an initial transformation of β-triketones **2a–j** into their enol derivatives (vinylogous chlorides or methyl ethers). We synthesized diketovinyl chlorides **4a–j** and investigated their interaction with hydroxylamine hydrochloride. On the treatment of diketovinyl chlorides **4a–j** with an equimolar mixture of $NH_2OH{\cdot}HCl$ and NaOH in methanol at room temperature, we observed a formation of the complex mixture of products that contained trace amounts of 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones **3a–j** and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones **5a–j** (according to ^{1}H and ^{19}F NMR data). Then we investigated the interaction of chlorides **4a–j** with sodium azide; such type of transformation for 3-chloro-2-acetyl-2-cyclohexen-1-ones has been reported [25]. As a result, we developed a facile synthesis of 3-polyfluoroalkyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones **5a–j**. The method included a conversion of 2-polyfluoroalkanoylcyclohexane-1,3-diones **2a–j** into chlorides **4a–j** under an action of oxalyl chloride in the presence of DMF (as catalyst) in chloroform, followed by the treatment of obtained crude 3-chloro-2-polyfluoroalkanoyl-2-cyclohexen-1-ones **4a–j** with sodium azide in dimethylformamide (method 1). Target isoxazolones **5a–j** were prepared in good yields (72–76%) as a result of the initial vinylogous substitution of the trigonal C3 atom in the molecule of chlorides **4a–j** and the transformation of the unstable azides into the isoxazolones **5a–j**.

As known in the case of 2-acylcyclohexane-1,3-diones, the direction of N-nucleophilic attack by hydroxylamine could be altered by converting of the β-triketones into methyl enol ethers, followed by a reaction of the latter with hydroxylamine [24,26]. We synthesized 2-perfluoroalkanoyl-5,5-dimethyl-3-methoxy-2-cyclohexen-1-ones **4a–c** *via* O-methylation of compounds **2h–j** with diazomethane in 52–71% yields according to a published procedure [27]. The treatment of methyl ethers **4a–c** with an equimolar mixture of hydroxylamine hydrochloride and NaOH in methanol at room temperature for 8 h afforded 3-perfluoroalkyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones **5h–j** in 67–70% yields (method 2). The reaction proceeded *via* a vinylogous substitution mechanism with subsequent intramolecular cyclization. It is worthy to mention that our attempts to synthesize the methyl ethers of 2-perfluoroalkanoylcyclohexane-1,3-diones **2c–e** and 2-(2-halogeno-2,2-difluoroacetyl)cyclohexane-1,3-diones **2a, b,f,g** were unsuccessful because of their decomposition during a separation from the reaction mixture by column chromatography.

The structures of all new obtained compounds were confirmed by their IR, ^{1}H, ^{13}C, and ^{19}F NMR spectra and data of elemental analysis. From the spectral data, 2-(2-halogeno-2,2-difluoroacetyl)cyclohexane-1,3-diones **2a,b,f,g** were completely enolized in solution similar to 2-perfluoroacylcyclohexane-1,3-diones **2c–e,h–j** [14]. ^{1}H NMR spectra of the triacylmethanes **2a,b,f,g** showed a single enol proton signal as a broad singlet in the range of δ 15.02–15.27 ppm. Because of an influence of electronegative halogenopolyfluoroalkyl group, the strength of an intramolecular hydrogen bonding was obviously weakened and the resonance of enolic protons occurred at higher field than its usual position for 2-acylcyclohexane-1,3-diones (δ 17–18 ppm) [28]. The ^{13}C NMR spectra of β-triketones **2a,b,f,g** revealed a signal of the carbon atom of a carbonyl group of a halogeno-2,2-difluoroacetyl side chain at δ 185.3–186.1 ppm and broad signals of carbon atoms of cyclic carbonyl groups at δ 190.5–191.8 ppm and at δ 194.1–197.6 ppm. Such broadening was obviously connected with a fast exchange of the enolic proton between carbonyl groups of the cyclohexane-1,3-diones. In the ^{19}F NMR spectra of compounds **2a,f** and **2b,g**, singlets at δ −61.1 ppm or δ −63.7 ppm, respectively, were assigned to the fluorine atoms of a halogeno-2,2-difluoroacetyl group. The ^{13}C NMR spectra of isoxazolones **3b–e,g–j** revealed a signal of carbonyl carbon atoms (C4) and the signals of C–O (C7a) and C=N (C3) at δ 188.1–189.4, 182.4–183.3, and 150.5–155.4 ppm, respectively, while the signals of C4 (C=O), C3 (C–O), and C7a (C=N) carbon atoms in ^{13}C NMR spectra of isomeric isoxazolones **5a–j** were observed at δ 188.7–190.0, 156.7–162.6, and 164.2–165.1 ppm, respectively. The presence of fluorine atoms in structures of compounds **3**–**5** was confirmed by the observation of fluorine signals in the appropriate ranges of their ^{19}F NMR spectra.

CONCLUSIONS

In conclusion, we have described convenient syntheses of hitherto unreported both 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones with perfluoroalkyl or halogenodifluoromethyl substituents in a high regioselectivity. 3-Polyfluoroalkyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones were effectively prepared by the cyclocondensation of 2-polyfluoroalkanoylcyclohexane-

1,3-diones with hydroxylamine that proceeded at the most electrophilic exocyclic carbonyl group. The regioisomeric 3-polyfluoroalkyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones were synthesized by the transformation of 2-polyfluoroalkanoylcyclohexane-1,3-diones into their vinylogous chlorides, followed by the vinylogous substitution with sodium azide in dimethylformamide and the transformation of unstable azides to the isoxazolones.

EXPERIMENTAL

Materials and methods. All chemicals were commercially available and used as purchased without further purification. Solvents were dried and freshly distilled according to common practice. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500, 470, and 125 MHz, respectively) in $CDCl_3$ solutions. Residual solvent signals were used as internal standards for ^{1}H and ^{13}C NMR spectra (7.26 ppm for ^{1}H nuclei and 77.16 ppm for ^{13}C nuclei). External standard was used for ^{19}F NMR (α,α,α-trifluorotoluene signal at −63 ppm for ^{19}F NMR). IR spectra were recorded on an FTIR PerkinElmer Spectrum 100. The elemental analyses were performed on a Eurovector EA3000 CHNS-O analyzer. Melting points were determined on a Boetius hot stage. Column chromatography was performed on 70–230 mesh silica gel (eluent ethyl acetate:petroleum ether 1:10–1:5). The reaction progress and purity of the obtained compounds were controlled by thin-layer chromatography on pre-coated silica gel F_{254} plates. 2-Perfluoroalkanoylcyclohexane-1,3-diones **2c–e,h–j** [13], 3-chloro-2-perfluoroalkanoyl-2-cyclohexen-1-ones **4c–e, h–j** [29], 2-perfluoroalkanoyl-5,5-dimethyl-3-methoxy-2-cyclohexen-1-ones **6a–c** [15,27], and 3-(trifluoromethyl)-6,7-dihydrobenzo-1,2-isoxazol-4(5*H*)-one (**3c**) [22] have been described in literature.

General procedure for preparation of 2-(2-halogeno-2,2-difluoroacetyl)cyclohexane-1,3-diones (2a,b,f,g). To a stirred solution of respective 2-halogeno-2,2-difluoroacetic acid, namely, 2-bromo-2,2-difluoroacetic acid or 2-chloro-2,2-difluoroacetic acid (5 mmol), in dry chloroform (20 mL), oxalyl chloride (0.635 g, 5 mmol) and one drop of dimethylformamide were added at 0°C. After stirring at 0°C for 2 h, the obtained reaction mixture was added dropwise to a solution of imidazole (0.680 g, 10 mmol) in chloroform (30 mL) at 0°C. To the resultant suspension, a solution of cyclohexane-1,3-diones **1a,b** (3.75 mmol) and imidazole (0.255 g, 3.75 mmol) in dry chloroform (30 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 h, then the solution was washed with 5% solution of hydrochloric acid (3 × 25 mL) and water (1 × 25 mL) and dried (Na_2SO_4). The solution was evaporated in vacuo to give the title compounds **2a,b,f,g** in 63–71% yield.

2-(2-Bromo-2,2-difluoroacetyl)cyclohexane-1,3-dione (2a). This compound was obtained as colorless crystals, yield 63%, mp 80–82°C. IR (KBr): 1680 (C=O conjug. nonchelat), 1615 (C=O chelat.), 1545 (C=C) cm^{-1}. ^{1}H NMR: δ 2.06 (2H, qui, J = 6.6 Hz, CH_2), 2.57–2.77 (4H, m, $2CH_2$), 15.26 (1H, brs, OH). ^{13}C NMR: δ 19.0, 32.3 (br), 38.2 (br), 110.2, 113.3 (t, J = 313 Hz), 186.1 (t, J = 30 Hz), 191.8(br), 197.6 (br). ^{19}F NMR: δ −61.19 (s, CF_2). *Anal*. Calcd for $C_8H_7BrF_2O_3$: C, 35.71; H, 2.62. Found: C, 35.75; H, 2.64.

2-(2-Chloro-2,2-difluoroacetyl)cyclohexane-1,3-dione (2b). This compound was obtained as colorless crystals, yield 65%, mp 57–58°C. IR (KBr): 1680 (C=O conjug. Nonchelat.), 1620 (C=O chelat.), 1550 (C=C) cm^{-1}. ^{1}H NMR: δ 2.05 (2H, qui, J = 6.6 Hz, CH_2), 2.46–2.87 (4H, m, $2CH_2$), 15.16 (1H, brs, OH). ^{13}C NMR: δ 19.0, 32.2 (br), 38.1 (br), 110.6, 119.4 (t, J = 300 Hz), 185.8 (t, J = 32 Hz), 191.9 (br), 197.3 (br). ^{19}F NMR: δ −63.73 (s, CF_2). *Anal*. Calcd for $C_8H_7ClF_2O_3$: C, 42.78; H, 3.14. Found: C, 42.82; H, 3.17.

2-(2-Bromo-2,2-difluoroacetyl)-5,5-dimethylcyclohexane-1,3-dione (2f). This compound was obtained as colorless crystals, yield 71%, mp 75–78°C. IR (KBr): 1685 (C=O conjug. nonchelat), 1625 (C=O chelat.), 1560 (C=C) cm^{-1}. ^{1}H NMR: δ 1.12 (6H, s, $2CH_3$), 2.40–2.63 (4H, m, $2CH_2$), 15.27 (1H, brs, OH). ^{13}C NMR: δ 28.2, 31.2, 46.1 (br), 52.3 (br), 109.3, 112.1 (t, J = 313 Hz), 185.7 (t, J = 29.0 Hz), 193.1 (br,). ^{19}F NMR: δ −61.09 (s, CF_2). *Anal*. Calcd for $C_{10}H_{11}BrF_2O_3$: C, 40.43; H, 3.73. Found: C, 40.48; H, 3.75.

2-(2-Chloro-2,2-difluoroacetyl)-5,5-dimethylcyclohexane-1,3-dione (2g). This compound was obtained as colorless crystals, yield 69%, mp 76–78°C. IR (KBr): 1685 (C=O conjug. nonchelat), 1620 (C=O chelat.), 1565 (C=C) cm^{-1}. ^{1}H NMR: δ 1.11 (6H, s, $2CH_3$), 2.46–2.62 (4H, m, $2CH_2$), 15.04 (1H, brs, OH). ^{13}C NMR: δ 28.2, 31.1, 48.8 (br), 109.6, 119.3 (t, J = 300 Hz), 185.3 (t, J = 32 Hz), 190.5 (br), 194.1 (br).^{19}F NMR: δ −63.67 (s, CF_2).). *Anal*. Calcd for $C_{10}H_{11}ClF_2O_3$: C, 47.54; H, 4.39. Found: C, 47.50; H, 4.36.

General procedure for preparation of 3-polyfluoroalkyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones (3b–e,g–j). To a stirred solution of 2-polyfluoroalkanoylcyclohexane-1,3-diones **2a–j** (1.0 mmol) in methanol (25 mL), hydroxylamine hydrochloride (0.070 g, 1.0 mmol) and NaOH (0.040 g, 1.0 mmol) were added. After stirring at room temperature for 20 h, methanol was evaporated in vacuo. The obtained residue was dissolved in chloroform (40 mL), and the solution

was washed with water (1 × 25 mL) and then dried (Na_2SO_4). The solution was evaporated in vacuo and the crude residue was purified by silica gel column chromatography to give the title compounds (**3b–e,g–j**) in 42–63% yield.

3-(Chlorodifluoromethyl)-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3b). This compound was obtained as colorless crystals, yield 44%, mp 32–33°C. IR (KBr): 1700 (C=O), 1595, 1475 cm^{-1}. ^1H NMR: δ 2.29 (2H, qui, J = 6.4 Hz, CH_2), 2.60 (2H, t, J = 6.4 Hz, CH_2), 3.09 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR: 21.9, 23.2, 38.1, 112.9, 120.3 (t, J = 289 Hz), 155.5 (t, J = 33 Hz, C3), 183.3 (C7a), 189.2 (C4). ^{19}F NMR: δ −52.79 (s, CF_2). *Anal*. Calcd for $C_8H_6ClF_2NO_2$: C, 43.36; H, 2.73; N, 6.32. Found: C, 43.41; H, 2.76; N, 6.36.

3-(Trifluoromethyl)-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3c). This compound was obtained as colorless crystals, yield 57%, mp 43–44°C. IR (KBr): 1702 (C=O), 1599, 1495 cm^{-1}. ^1H NMR: δ 2.29 (2H, qui, J = 6.4 Hz, CH_2), 2.61 (2H, t, J = 6.4 Hz, CH_2), 3.10 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR: δ 22.0, 23.1, 38.0, 113.5, 119.2 (q, $J_{C\text{-}F}$ = 272 Hz), 151.3 (q, $J_{C\text{-}F}$ = 40 Hz, C3), 183.1 (C7a), 189.4 (C4). ^{19}F NMR: δ −63.79 (s, CF_3). *Anal*. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.80; H, 2.91; N, 6.79.

3-(Perfluoroethyl)-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3d). This compound was obtained as colorless crystals, yield 46%, mp 51–53°C. IR (KBr): 1702 (C=O), 1594, 1479 cm^{-1}. ^1H NMR: δ 2.28 (2H, q, J = 6.4 Hz, CH_2), 2.60 (2H, t, J = 6.5 Hz, CH_2), 3.11 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR: δ 21.8, 23.2, 38.3, 109.6 (tq, $J_{C\text{-}F}$ = 256 Hz, 41 Hz), 114.5, 117.2 (qt, $J_{C\text{-}F}$ = 287 Hz, 35 Hz), 150.8 (t, J = 31 Hz, C3), 183.0 (C7a), 188.8 (C4). ^{19}F NMR: δ −82.92 (3F, m, CF_3), −112.49 (2F, m, CF_2). *Anal*. Calcd for $C_9H_6F_5NO_2$: C, 42.37; H, 2.37; N, 5.49. Found: C, 42.43; H, 2.40; N, 5.53.

3-(Perfluoropropyl)-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3e). This compound was obtained as colorless crystals, yield 45%, mp 29–31°C. IR (KBr): 1707 (C=O), 1592, 1470 cm^{-1}. ^1H NMR: δ 2.28 (2H, q, J = 6.4 Hz, CH_2), 2.59 (2H, t, J = 6.4 Hz, CH_2), 3.11 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR: δ 21.8, 23.2, 38.3, 108.5 (tm, $J_{C\text{-}F}$ = 268 Hz), 111.7 (tt, $J_{C\text{-}F}$ = 258, 33 Hz), 114.7, 117.8 (qt, $J_{C\text{-}F}$ = 258, 33 Hz), 151.0 (t, $J_{C\text{-}F}$ = 30 Hz, C3), 183.1 (C7a), 188.6 (C4). ^{19}F NMR: δ −80.10 (3F, m, CF_3), −110.21 (2F, m, CF_2), −125.45 (2F, m, CF_2). *Anal*. Calcd for $C_{10}H_6F_7NO_2$: C, 39.36; H, 1.98; N, 4.59. Found: C, 39.32; H, 1.95; N, 4.55.

3-(Chlorodifluoromethyl)-6,6-dimethyl-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3g). This compound was obtained as colorless crystals, yield 42%, mp 65–66°C. IR (KBr): 1695 (C=O), 1590, 1475 cm^{-1}. ^1H NMR: δ 1.19 (6H, s, $2CH_3$), 2.48 (2H, s, CH_2), 2.94 (2H, s, CH_2). ^{13}C NMR: δ 28.4, 35.5, 36.9, 52.5, 111.9, 120.2 (t, J = 289 Hz), 155.4 (t, J = 33 Hz, C3), 182.8 (C7a), 188.7 (C4). ^{19}F NMR: δ −52.64 (s, CF_2). *Anal*. Calcd for $C_{10}H_{10}ClF_2NO_2$: C, 48.11; H, 4.04; N, 5.61. Found: C, 48.17; H, 4.07; N, 5.66.

3-(Trifluoromethyl)-6,6-dimethyl-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3h). This compound was obtained as colorless crystals, yield 55%, mp 40–41°C. IR (KBr): 1705 (C=O), 1600, 1480 cm^{-1}. ^1H NMR: δ 1.18 (6H, s, $2CH_3$), 2.47 (2H, s, CH_2), 2.94 (2H, s, CH_2). ^{13}C NMR: δ 28.4, 35.5, 36.8, 52.4, 112.5, 119.2 (q, $J_{C\text{-}F}$ = 272 Hz), 151.2 (q, $J_{C\text{-}F}$ = 40 Hz, C3), 182.6 (C7a), 188.8 (C4). ^{19}F NMR: δ −63.67 (s, CF_3). *Anal*. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.47; H, 4.30; N, 5.95.

3-(Perfluoroethyl)-6,6-dimethyl-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3i). This compound was obtained as colorless crystals, yield 63%, mp 27–29°C. IR (KBr): 1710 (C=O), 1595, 1470 cm^{-1}. ^1H NMR: δ 1.17 (6H, s, $2CH_3$), 2.47 (2H, s, CH_2), 2.95 (2H, s, CH_2). ^{13}C NMR: δ 28.1, 35.5, 36.6, 52.5, 109.4 (tq, $J_{C\text{-}F}$ = 256, 41 Hz), 113.4, 118.2 (qt, $J_{C\text{-}F}$ = 287, 35 Hz), 150.5 (t, $J_{C\text{-}F}$ = 31 Hz, C3), 182.4 (C7a), 188.1 (C4). ^{19}F NMR: δ −83.04 (3F, m, CF_3), −112.50 (2F, m, CF_2). *Anal*. Calcd for $C_{11}H_{10}F_5NO_2$: C, 46.65; H, 3.56; N, 4.95. Found: C, 46.60; H, 3.52; N, 4.91.

3-(Perfluoropropyl)-6,6-dimethyl-6,7-dihydrobenzo-1,2-isoxazol-4(5H)-one (3j). This compound was obtained as colorless oil, yield 52%. IR (film): 1710 (C=O), 1595, 1470 cm^{-1}. ^1H NMR: δ 1.17 (6H, s, $2CH_3$), 2.46 (2H, s, CH_2), 2.95 (2H, s, CH_2). ^{13}C NMR: δ 28.0, 35.1, 36.6, 52.5, 108.4 (tm, $J_{C\text{-}F}$ = 268 Hz), 111.6 (tt, $J_{C\text{-}F}$ = 258, 33 Hz), 113.6, 117.6 (qt, $J_{C\text{-}F}$ = 288, 34 Hz), 150.7 (t, $J_{C\text{-}F}$ = 30 Hz, C3), 182.5 (C7a), 187.9 (C4). ^{19}F NMR: δ −80.18 (3F, m, CF_3), −110.32 (2F, m, CF_2), −125.63 (2F, m, CF_2). *Anal*. Calcd for $C_{12}H_{10}F_7NO_2$: C, 43.26; H, 3.03; N, 4.20. Found: C, 43.32; H, 3.06; N, 4.25.

General procedure for preparation of 3-chloro-2-(2-halogeno-2,2-difluoroacetyl)-2-cyclohexen-1-ones (4a,b,f,g). To a stirred solution of 2-(2-halogeno-2,2-difluoroacetyl) cyclohexane-1,3-diones (**2a,b,f,g**) (1.0 mmol) in dry chloroform (20 mL), oxalyl chloride (0.635 g, 3.0 mmol) and one drop of dimethylformamide were added. After stirring at room temperature for 2 h, chloroform and residual oxalyl chloride were evaporated in vacuo. The crude residue was purified by silica gel column chromatography to give the title compounds **4a,b,f,g** in 75–78% yield.

2-(2-Bromo-2,2-difluoroacetyl)-3-chlorocyclohex-2-en-1-one (4a). This compound was obtained as colorless oil, yield 78%. IR (film): 1755 (C=O), 1685 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR: δ 2.16 (2H, qui, J = 6.3 Hz, CH_2), 2.53 (2H, t, J = 6.2 Hz, CH_2), 2.86 (2H, t, J = 6.1 Hz, CH_2). ^{13}C NMR: δ 21.5, 34.7, 36.2, 113.5 (t, J = 319 Hz), 134.7, 159.0, 184.6 (t, J = 31 Hz), 193.0. ^{19}F NMR: δ

−61.19 (s, CF_2). *Anal*. Calcd for $C_8H_6BrClF_2O_2$: C, 33.42; H, 2.10. Found: C, 33.38; H, 2.07.

2-(2-Chloro-2,2-difluoroacetyl)-3-chlorocyclohex-2-en-1-one (4b). This compound was obtained as colorless oil, yield 77%. IR (film): 1755 (C=O), 1685 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR: δ 2.16 (2H, qui, J = 6.2 Hz, CH_2), 2.54 (2H, t, J = 6.2 Hz, CH_2), 2.85 (2H, t, J = 6.1 Hz, CH_2). ^{13}C NMR: δ 21.5, 34.6, 36.2, 119.4 (t, J = 305 Hz), 135.0, 158.7, 184.5 (t, J = 34 Hz), 193.1. ^{19}F NMR: δ −64.96 (s, CF_2). *Anal*. Calcd for $C_8H_6Cl_2F_2O_2$: C, 39.54; H, 2.49. Found: C, 39.49; H, 2.47.

2-(2-Bromo-2,2-difluoroacetyl)-3-chloro-5,5-dimethylcyclohex-2-en-1-one (4f). This compound was obtained as colorless oil, yield 75%. IR (film): 1755 (C=O), 1685 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR: δ 1.15 (6H, s, $2CH_3$), 2.39 (2H, s, CH_2), 2.72 (2H, s, CH_2). ^{13}C NMR: δ 27.9, 33.8, 48.4, 50.0, 113.5 (t, J = 319 Hz), 133.7, 157.0, 184.4 (t, J = 31 Hz), 193.1. ^{19}F NMR: δ −61.08 (s, CF_2). *Anal*. Calcd for $C_{10}H_{10}BrClF_2O_2$: C, 38.07; H, 3.19. Found: C, 38.01; H, 3.15.

2-(2-Chloro-2,2-difluoroacetyl)-3-chloro-5,5-dimethylcyclohex-2-en-1-one (4g). This compound was obtained as colorless oil, yield 76%. IR (film): 1755 (C=O), 1685 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR: δ 1.14 (6H, s, $2CH_3$), 2.39 (2H, s, CH_2), 2.72 (2H, s, CH_2). ^{13}C NMR: δ 27.9, 33.8, 48.3, 50.0, 119.4 (t, J = 305 Hz), 134.0, 156.8, 184.3 (t, J = 34 Hz), 193.2. ^{19}F NMR: δ −64.84 (s, CF_2). *Anal*. Calcd for $C_{10}H_{10}Cl_2F_2O_2$: C, 44.31; H, 3.72. Found: C, 44.36; H, 3.74.

General procedure for preparation of 3-polyfluoroalkyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones (5a–j). Method 1. To a stirred solution of 2-polyfluoroalkanoylcyclohexane-1,3-diones **2a–j** (1.0 mmol) in dry chloroform (20 mL), oxalyl chloride (0.635 g, 3 mmol) and one drop of dimethylformamide were added. After stirring at room temperature for 2 h, chloroform and residual oxalyl chloride were evaporated in vacuo to dryness. To a stirred solution of obtained crude 3-chloro-2-polyfluoroalkanoyl-2-cyclohexen-1-ones **4a–j** in dimethylformamide (15 mL), sodium azide (0.078 g, 1.2 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 20 h, and dimethylformamide was evaporated in vacuo. The obtained residue was dissolved in chloroform (40 mL), the solution was washed with water (1 × 10 mL) and dried (Na_2SO_4). The solution was evaporated in vacuo, and the crude residue was purified by silica gel column chromatography to give the title compounds **5a–j** in 72–76% yield.

Method 2. To a stirred solution of 2-perfluoroalkanoyl-5,5-dimethyl-3-methoxy-2-cyclohexen-1-ones **6a–c** (1.0 mmol) in methanol (25 mL), hydroxylamine hydrochloride (0.070 g, 1.0 mmol) and NaOH (0.040 g, 1.0 mmol) were added. After stirring at room temperature for 20 h, methanol was evaporated in vacuo. The resultant residue was purified by silica gel column chromatography to give the title compounds **5h–j** in 67–70% yield.

3-(Bromodifluoromethyl)-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5a). This compound was obtained as colorless crystals, yield 76% (method 1), mp 31–33°C. IR (KBr): 1705 (C=O), 1615 cm^{-1}. ^1H NMR: δ 2.20 (2H, qui, J = 6.4 Hz, CH_2), 2.62 (2H, t, J = 6.4 Hz, CH_2), 3.00 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR: δ 21.5, 22.2, 39.7, 108.7 (t, $J_{C\text{-}F}$ = 304 Hz), 113.2, 162.6 (t, $J_{C\text{-}F}$ = 34 Hz, C3), 165.0 (C7a), 189.9 (C4). ^{19}F NMR: δ −49.83 (s, CF_2). *Anal*. Calcd for $C_8H_6BrF_2NO_2$: C, 36.12; H, 2.27; N, 5.26. Found: C, 36.16; H, 2.30; N, 5.31.

3-(Chlorodifluoromethyl)-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5b). This compound was obtained as colorless crystals, yield 74% (method 1), mp 42–43°C. IR (KBr): 1705 (C=O), 1615 cm^{-1}. ^1H NMR: δ 2.20 (2H, qui, J = 6.4 Hz, CH_2), 2.62 (2H, t, J = 6.3 Hz, CH_2), 3.01 (2H, t, J = 6.3 Hz, CH_2). ^{13}C NMR: δ 21.5, 22.2, 39.6, 113.9, 118.6 (t, J = 290 Hz), 161.5 (t, J = 38 Hz, C3), 165.1 (C7a), 189.8 (C4). ^{19}F NMR: δ −52.74 (s, CF_2). *Anal*. Calcd for $C_8H_6ClF_2NO_2$: C, 43.36; H, 2.73; N, 6.32. Found: C, 43.41; H, 2.77; N, 6.35.

3-(Trifluoromethyl)-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5c). This compound was obtained as colorless crystals, yield 73% (method 1), mp 57–59°C. IR (KBr): 1709 (C=O), 1626 cm^{-1}. ^1H NMR: δ 2.20 (2H, qui, J = 6.4 Hz, CH_2), 2.62 (2H, t, J = 6.3 Hz, CH_2), 3.01 (2H, t, J = 6.3 Hz, CH_2). ^{13}C NMR: δ 21.4, 22.1, 39.5, 115.9 (q, $J_{C\text{-}F}$ = 276 Hz), 118.6, 157.5 (q, $J_{C\text{-}F}$ = 45 Hz, C3), 164.9 (C7a), 190.0 (C4). ^{19}F NMR: δ −63.44 (s, CF_3). *Anal*. Calcd for $C_8H_6F_3NO_2$: C, 46.84; H, 2.95; N, 6.83. Found: C, 46.89; H, 2.97; N, 6.87.

3-(Perfluoroethyl)-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5d). This compound was obtained as colorless crystals, yield 72% (method 1), mp 55–57°C. IR (KBr): 1712 (C=O), 1622 cm^{-1}. ^1H NMR: δ 2.20 (2H, qui, J = 6.4 Hz, CH_2), 2.63 (2H, t, J = 6.3 Hz, CH_2), 3.03 (2H, t, J = 6.3 Hz, CH_2). ^{13}C NMR: δ 21.5, 22.0, 39.8, 108.5 (tq, $J_{C\text{-}F}$ = 259 Hz, 42 Hz), 117.8, 118.1 (qt, $J_{C\text{-}F}$ = 287 Hz, 36 Гц), 157.3 (t, $J_{C\text{-}F}$ = 34 Hz, C3), 165.1 (C7a), 189.3 (C4). ^{19}F NMR: δ −83.47 (3F, m, CF_3), −114.78 (2F, m, CF_2). *Anal*. Calcd for $C_9H_6F_5NO_2$: C, 42.37; H, 2.37; N, 5.49. Found: C, 42.43; H, 2.40; N, 5.53.

3-(Perfluoropropyl)-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5e). This compound was obtained as colorless crystals, yield 72% (method 1), mp 41–43°C. IR (KBr): 1712 (C=O), 1614 cm^{-1}. ^1H NMR: δ 2.20 (2H, qui, J = 6.4 Hz, CH_2), 2.61 (2H, t, J = 6.4 Hz, CH_2), 3.03 (2H, t, J = 6.2 Hz, CH_2). ^{13}C NMR: δ 21.5, 22.0, 39.8, 108.4 (tm, $J_{C\text{-}F}$ = 268 Hz), 111.5 (tt, $J_{C\text{-}F}$ = 261 Hz, 33 Hz), 117.0 (qt, $J_{C\text{-}F}$ = 288, 34 Hz), 118.0, 157.2 (t, $J_{C\text{-}F}$ = 34 Hz, C3), 165.1 (C7a), 189.1 (C4). ^{19}F NMR: δ

−80.32 (3F, m, CF_3), −112.42 (2F, m, CF_2), −125.29 (2F, m, CF_2). *Anal*. Calcd for $C_{10}H_6F_7NO_2$: C, 39.36; H, 1.98; N, 4.59. Found: C, 39.30; H, 1.95; N, 4.55.

3-(Bromodifluoromethyl)-6,6-dimethyl-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5f). This compound was obtained as colorless crystals, yield 71% (method 1), mp 46–48°C. IR (KBr): 1700 (C=O), 1615 cm^{-1}. ^1H NMR: δ 1.13 (6H, s, $2CH_3$), 2.48 (2H, s, CH_2), 2.85 (2H, s, CH_2). ^{13}C NMR: δ 28.2, 34.8, 34.9, 53.5, 108.6 (t, $J_{C\text{-}F}$ = 304 Hz), 112.3, 162.4 (t, $J_{C\text{-}F}$ = 35 Hz, C3), 164.5 (C7a), 189.6 (C4). ^{19}F NMR: δ −49.74 (s, CF_2). *Anal*. Calcd for $C_{10}H_{10}BrF_2NO_2$: C, 40.84; H, 3.43; N, 4.76. Found: C, 40.91; H, 3.47; N, 4.80.

3-(Chlorodifluoromethyl)-6,6-dimethyl-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5g). This compound was obtained as colorless crystals, yield 75% (method 1), mp 30–32°C. IR (KBr): 1710 (C=O), 1620 cm^{-1}. ^1H NMR: δ 1.13 (6H, s, $2CH_3$), 2.48 (2H, s, CH_2), 2.85 (2H, s, CH_2). ^{13}C NMR: δ 28.2, 34.9, 53.4, 113.1, 118.6 (t, $J_{C\text{-}F}$ = 290 Hz), 161.2 (t, $J_{C\text{-}F}$ = 38 Hz, C3), 164.6 (C7a), 189.5 (4). ^{19}F NMR: δ −52.61 (s, CF_2). *Anal*. Calcd for $C_{10}H_{10}ClF_2NO_2$: C, 48.11; H, 4.04; N, 5.61. Found: C, 48.06; H, 4.00; N, 5.56.

3-(Trifluoromethyl)-6,6-dimethyl-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5h). This compound was obtained as colorless oil, yield 75% (method 1), 67% (method 2). IR (film): 1714, 1635 cm^{-1}. ^1H NMR: δ 1.12 (6H, s, $2CH_3$), 2.47 (2H, s, CH_2), 2.85 (2H, s, CH_2). ^{13}C NMR: δ 28.0, 29.6, 34.6, 53.2, 114.8, 117.3 (q, $J_{C\text{-}F}$ = 273 Hz), 157.2 (q, $J_{C\text{-}F}$ = 45 Hz, C3), 164.2 (C7a), 189.4 (C4). ^{19}F NMR: δ −63.36 (s, CF_3). *Anal*. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.57; H, 4.36; N, 6.04.

3-(Perfluoroethyl)-6,6-dimethyl-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5i). This compound was obtained as colorless crystals, yield 73% (method 1), 67% (method 2), mp 26–27°C. IR (KBr): 1714, 1620 cm^{-1}. ^1H NMR: δ 1.11 (6H, s, $2CH_3$), 2.46 (2H, s, CH_2), 2.85 (2H, s, CH_2). ^{13}C NMR: δ 27.8, 34.4, 34.6, 53.3, 108.4 (tq, $J_{C\text{-}F}$ = 259 Hz, 41 Hz), 116.9, 117.9 (qt, $J_{C\text{-}F}$ = 288 Hz, 36 Hz), 156.7 (t, $^2J_{C\text{-}F}$ 34 Hz, C3), 164.4 (C7a), 188.8 (C4). ^{19}F NMR: δ −83.67 (3F, m, CF_3), −114.88 (2F, m, CF_2). *Anal*. Calcd for $C_{11}H_{10}F_5NO_2$: C, 46.65; H, 3.56; N, 4.95. Found: 46.60; H, 3.52; N, 4.91.

3-(Perfluoropropyl)-6,6-dimethyl-6,7-dihydrobenzo-2,1-isoxazol-4(5H)-one (5j). This compound was obtained as colorless oil, yield 75% (method 1), 70% (method 2). IR (film): 1717, 1620 cm^{-1}. ^1H NMR: δ 1.13 (6H, s, $2CH_3$), 2.48 (2H, s, CH_2), 2.88 (2H, s, CH_2). ^{13}C NMR: δ 27.9, 34.4, 34.7, 53.4, 108.3 (tm, $J_{C\text{-}F}$ = 269 Hz), 110.5 (tt, $J_{C\text{-}F}$ = 261 Hz, 33 Hz), 117.1, 117.4 (qt, $J_{C\text{-}F}$ = 288 Hz, 33 Hz), 156.7 (t, $J_{C\text{-}F}$ = 34 Hz, C3), 164.4 (C7a), 188.7 (C4). ^{19}F NMR: δ −80.40 (3F, m, CF_3), −112.52 (2F, m, CF_2), −126.45 (2F, m, CF_2). *Anal*. Calcd for $C_{12}H_{10}F_7NO_2$: C, 43.26; H, 3.03; N, 4.20. Found: C, 43.21; H, 3.98; N, 4.15.

Acknowledgments. This work was financially supported by the Belarusian Republican Foundation for Fundamental Research (grant Kh16K–037) and by State Fund for Fundamental Research of Ukraine (grant F73/18–2017).

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