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RESEARCH ARTICLE

1,1-Difluoro-2-(bromo, azido)ethyl-substituted *β*-alkoxyenones: synthesis and heterocyclizations

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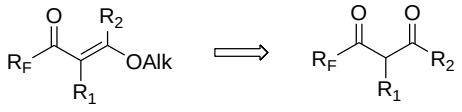
Abstract: New 5-bromo- and 5-azido-1-ethoxy-4,4-difluoropent-1-en-3-ones were synthesized and their reactivity was studied by nucleophilic substitution reactions and heterocyclizations with various binucleophiles.

Keywords: organic chemistry; fluorine; enones; nucleophilic substitution; heterocyclizations.

Introduction

Introducing fluorine atoms and fluorinated groups into organic molecules is a powerful and valuable instrument for purposefully adjusting of their chemical and physical properties purposefully especially in the search for new biologically active compounds. Though direct fluorination or polyfluoroalkylation methods are very attractive tools for constructing fluorinated compounds, fluorine-containing building blocks are often the more convenient starting reagents. One of such synthons is readily available *β*-alkoxyvinyl polyfluoroalkyl ketones **1** which may be considered as the chemical equivalent of 1,3-diketones (R_2 = Alk, Ar) or 1,3-ketoaldehydes (R_2 = H) (Figure 1) [1].



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R_1, R_2 = H, Alk, Ar

Figure 1. *β*-Alkoxyvinyl polyfluoroalkyl ketones **1** are the chemical equivalent of 1,3-dicarbonyl compounds.

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The enones **1** are easily afforded in a one-step reaction of alkyl vinyl ethers with polyfluoroacylating reagents [2] and widely used in organic synthesis as reactive and useful polyfluoroalkyl-containing building blocks for obtaining various fluorinated aliphatic and (hetero)aromatic compounds: enaminones [3], hydroxy [4] and amino acids [5-7], carbo- [8, 9] and heterocycles [10-15], etc. The variating R_1, R_2, and OAlk substituents at vinyl group allows to get a lot of different enones bearing various functional groups. One more way to get new perspective fluorinated building blocks is the modifying R_F group both the quantity of fluorine atoms and the structure of its skeleton. Previously we reported that the enones **1** with CF_2CO fragment can be synthesized by the reaction of alkyl vinyl ethers with acylating reagents bearing at last two fluorine atoms at *α*-position to carbonyl group, as example: XCF_2COCl (X = R_F, H, Cl, Br) [1], and $ArCF_2COCl$ [16]. It is worth to mention that the enones **1** bearing CH_2CF_2CO fragment are not synthesized till now although incorporation of the CH_2CF_2 linker instead of CH_2CH_2 between functional groups and (hetero)aromatic rings improved activity and/or pharmacokinetic properties of the compounds as compared to their non-fluorinated counterparts. In addition to that, the $NHCH_2CF_2$ fragment can be found in several experimental drugs (Figure 2) [17].

In this work, we explored a new approach to *gem*-difluoroethane bearing compounds, which also relied on the use of 1,1-difluoro-2-(bromo, azido) ethyl-substituted building blocks, namely, *β*-alkoxyenones **1** [R_F = $(Br,N_3)CH_2CF_2$, R_1 = R_2 = H, Figure 1], which were not.

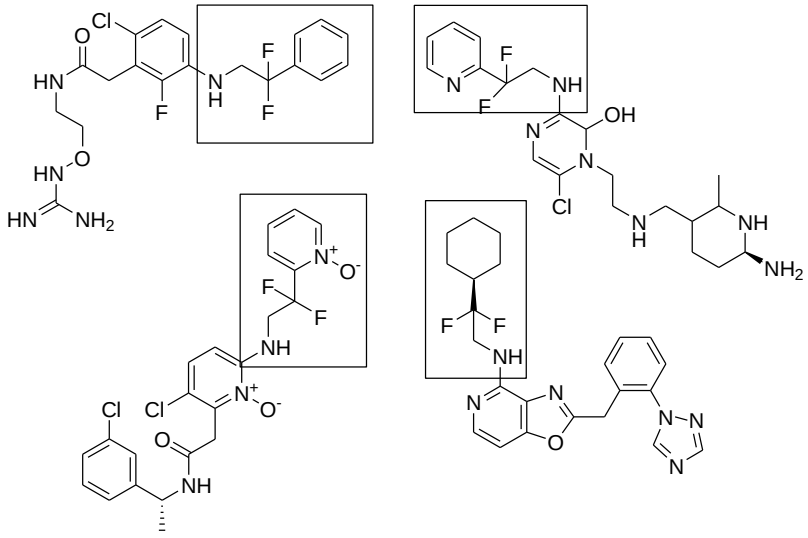


Figure 2. Examples of experimental drugs bearing 1-amino-2,2-difluoroethyl unit.

reported to date and can be good starting materials for the synthesis of various heterocyclic compounds containing 1-amino-2,2-difluoroethyl unit - $NH_2CH_2CF_2$.

Results and Discussion

First, we synthesized bromodifluoroethyl bearing enone **5** in good yield under the usual reaction conditions [1] by the reaction of ethyl vinyl ether with 3-bromo-2,2-difluoropropanoyl chloride **4**, which was obtained in 3 steps from readily available ethyl bromopyruvate by slightly modified method [18] – we used oxalyl chloride instead of phthaloyl chloride (Scheme 1).

Enone **5** is relatively stable; it can be distilled in vacuum and stored at +4 °C for months without changes. The structure of the enone **5** was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Thus, in the ^{19}F NMR spectra, the CF_2 group appeared as a triplet at -107.13 ppm ($^3J_{HF}$ 13.8 Hz). In the ^{1}H NMR spectra of **5**, the CH_2 group appeared at 3.72 ppm as triplet ($^3J_{HF}$ 13.8 Hz) and *trans*-vinyl protons as two doublets at 6.01 and 7.86 ppm ($^3J_{HH}$ 12.5 Hz). These chemical shifts of the signals were similar to that reported for previously synthesized enones with –CH=CH–CO– fragment [1, 16].

There are three electrophilic carbon atoms in the structure of the enone **5**: *β*-position of vinyl group, carbonyl group, and bromomethyl group (Figure 3).

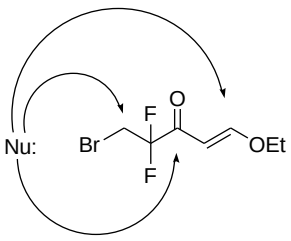
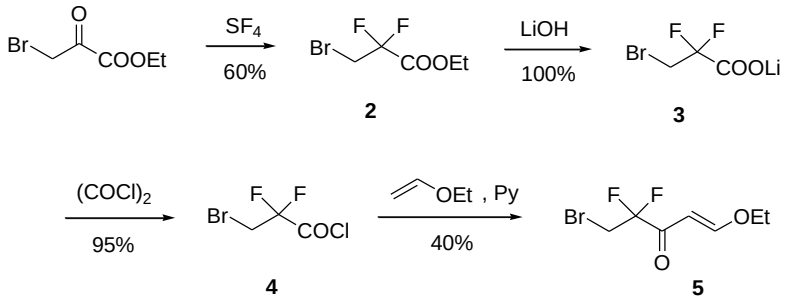


Figure 3. The possible pathways of nucleophilic attack on the enone **5**.

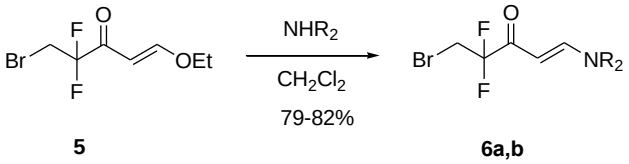
We found that enone **5** easily reacts with ammonia and morpholine afforded corresponding enaminones **6a,b** in high yield and no products of the bromine substitution were observed even at large excess of amines and elevated temperature (Scheme 2).

Also, no products of the bromine substitution were observed in the reaction of enone **5** with 1,2- and 1,3-bi-nucleophiles such as hydrazines, hydroxylamine, urea, and thiourea (Scheme 3). In particular, the reaction of enone **5** with hydrazine hydrate in AcOH proceeded smoothly at r.t. and led to corresponding pyrazole **7**, whereas methyl-hydrazine provided a mixture of isomeric pyrazoles **8a** and **8b** in 9 : 2 ratio (the designation of isomers was approved by its NMR data as in reference [19]). The reaction of enone **5** with hydroxylamine led to dihydroisoxazoline **9** which was dehydrated to isoxazole **10**. Unfortunately the reaction of enone **5** with urea and thiourea afforded very complex reaction mixtures and pyrimidines **11a** and **11b** were not isolated in pure form. However the formation of pyrimidine **11b** was firmly detected by ^{1}H and ^{19}F NMR spectroscopy: the signals of CF_2 group as two triplets ($^3J_{HF}$ ~14 Hz) are downfield shifted to -100.6 ppm and two pairs of doublets of CH protons of pyrimidine ring are observed at 9.11, 7.84 and 8.98, 7.71 ppm ($^3J_{HH}$ ~4.8 Hz). The signal doubling can be explained by thione-thiol tautomerism.

The low reactivity of bromine atom in $BrCH_2CF_2$ fragment towards substitution reaction with *N*-nucleophiles is explained by electron withdrawing effect of neighboring difluoromethylene group. The azide anion is an excellent nucleophile and S_N2 displacement of primary bromide with sodium azide gives the corresponding alkyl azide which can be reduced into a primary alkyl amine by a wide variety of reagents or reaction systems [20]. Unfortunately, the reactions of enone **5** and heterocycles **9** and **10** with sodium azide in DMSO at 110 °C did not afford to the corresponding azides, we observed only a destruction of starting compounds. However azide **12** was obtained in good yield from pyrazole **7** after heating for 48 h in DMSO (Scheme 4).

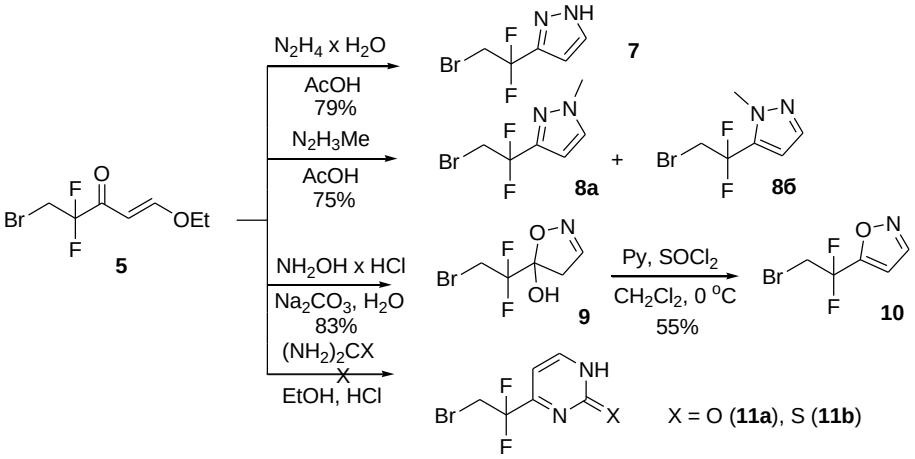


Scheme 1. Synthesis of 5-bromo-1-ethoxy-4,4-difluoropent-1-en-3-one **5**.

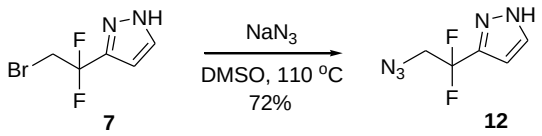


NR_2 = NH_2 (**a**), $N(CH_2CH_2)_2O$ (**b**)

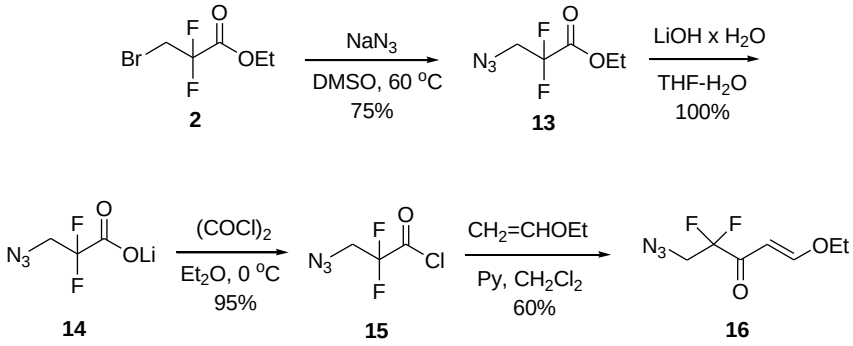
Scheme 2. Synthesis of 5-bromo-1-amino-4,4-difluoropent-1-en-3-ones **6a,b**.



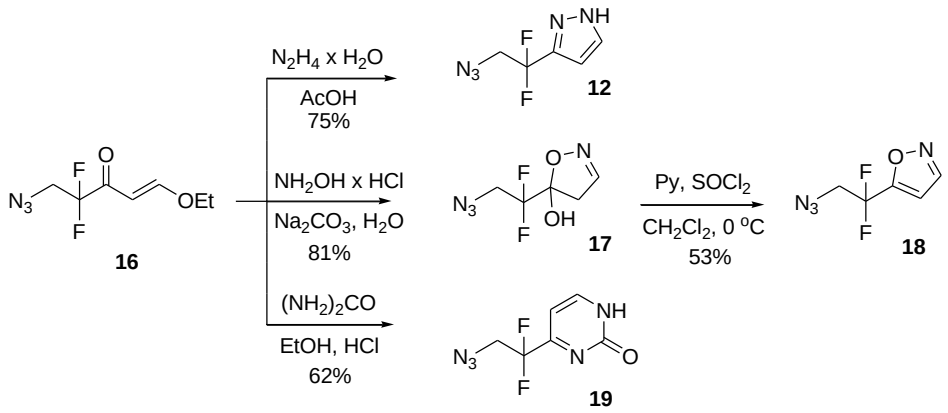
Scheme 3. Synthesis of 2-bromo-1,1-difluoroethyl substituted heterocycles **7**-**11**.



Scheme 4. Synthesis of 2-azido-1,1-difluoroethyl substituted pyrazole **12**.



Scheme 5. Synthesis of 2-azido-1,1-difluoroethyl substituted enone **16**.



Scheme 6. Synthesis of 2-azido-1,1-difluoroethyl substituted heterocycles **12**, **17**-**19**.

Next another way to obtain 2-amino-1,1-difluoroethyl substituted heterocycles was investigated. The most effective approach was the use of 1,1-difluoro-2-azidoethyl-substituted *β*-ethoxyenone **1** (R_F = $N_3CH_2CF_2$, R_1 = R_2 = H, Figure 1) as promising building block in the synthesis of aimed heterocycles after the reducing azido group into amino one. The most challenging was validation of the synthesis of 3-azido-2,2-difluoropropanoyl chloride **15**. Finally, after the substitution of bromine atom on azido group in ethyl 3-bromo-2,2-difluoropropanoat **2** by sodium azide at the heating in DMSO and the sequence of reactions we obtained enone **16** in good yield (Scheme 5).

Enone **16** is yellowish liquid with low stability even if it was stored at +4 °C and the best to use immediately after isolation. The structure of the enone **16** was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and the data are very similar to ones for enone **5**. Synthetic utility of enone **16** as the CCC bis-electrophiles was demonstrated by condensation with common 1,2- and 1,3-binucleophiles such as hydrazine, hydroxylamine, urea, and thiourea (Scheme 6). Pyrazole **12** and isoxazole **18** were obtained in good yields at the same reaction conditions as for enone **5**. The reaction of enone **16** with thiourea was unsuccessful in the contrast with urea that afforded pyrimidinone **19** after column chromatography.

Next we used the reduction of azido-bearing compounds to synthesize some heterocyclic compounds with 1-amino-2,2-difluoroethyl unit – $NH_2CH_2CF_2$. Thus the catalytic hydrogenation or the reduction under Staudinger reaction of enone **16** can afforded enone **20** which is interesting polyfuntionalized fluorocontaining building block (Scheme 7). Unfortunately, in both cases we obtained only very complex mixture of unidentified products with, possible, polymeric nature.

Surprisingly, we obtained a complex mixture of products under the catalytic hydrogenation of pyrazole **12** (Scheme 8).

The catalytic hydrogenation of pyrimidinone **19** afforded the compound **22** – the product of the reduction both azido group and pyrimidine ring in good yield and selective reduction of azido group in pyrimidinone **19** was successful under Staudinger reaction (Scheme 9). The structure of the compounds **22** and **23** was confirmed by ^{1}H and ^{19}F NMR spectroscopy.

Conclusions

We demonstrated several approaches to the synthesis of heterocyclic compounds with 1-(bromo,azido,amino)-2,2-difluoroethyl unit – $(Br,N_3,NH_2)CH_2CF_2$ based on new promising fluorocontaining building blocks – enones **5** and **16** for further applications in drug discovery, material science and agrochemistry.

Notes

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The authors declare no conflict of interest. The authors declare that there is no conflict of interest regarding the publication of this paper.

Experimental section

The solvents were purified according to the standard procedures. Column chromatography was performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6; fluorine signals from $CFCl_3$ as an internal standard. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Analytical Chemistry

Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine.

Synthesis

*Ethyl 3-bromo-2,2-difluoropropanoate (**2**).*

The solution of ethyl bromopyruvate (120.0 g, 0.615 mol) in 100 mL of CH_2Cl_2 was placed in 1000 mL autoclave made of Hastelloy nickel alloy and water (5.55 mL, 0.307 mol) was added. The reaction vessel was cooled down by liquid nitrogen and SF4 (232.0 g, 2.15 mol) was condensed into a reaction vessel. Cooling bath was removed, and the mixture was allowed to warm up to a room temperature. It was then stirred for 18 h. The gaseous products were vented off into a trap with aqueous solution of NaOH (1M). To the residue 516.5 g (6.15 mol) of $NaHCO_3$ was added by portions. The organic faze was separated by filtration and concentrated under reduced pressure to afford the desired product. The final product was purified by distillation. Yield: 80.1 g, 60%, yellowish liquid, b.p. 85 °C, 60 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (q, J = 7.1 Hz, 2H), 3.59 (t, J = 14.6 Hz, 2H), 1,36 (t, J = 7.1 Hz, 3H) [18].

*Lithium 3-bromo-2,2-difluoropropanoate (**3**).*

The solution of propanoate **2** (45 g, 0.207 mol) and $LiOH \cdot H_2O$ (8.7 g, 0.207 mol) in the mixture of THF (400 mL) and water (50 mL) was stirred at rt overnigth. The reaction mixture was concentrated under reduced pressure to afford the desired product. Yield: 40.37 g, 100%, white crystals which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (t, J = 15.8 Hz); ^{19}F {H} NMR (376 MHz, DMSO-d_6) δ -103.44 (s).

*3-Bromo-2,2-difluoropropanoyl chloride (**4**).*

To a stirred suspension of Lithium salt **3** (40.37 g, 0.207 mol) in diethyl ether (400 mL) the solution of oxalyl chloride (78.87 g, 0.621 mol) was added dropwise at 0 °C. After stirring at rt overnight the reaction mixture was filtered, an inorganic precipitate was washed with diethyl ether (100 mL) and the ethereal solution was concentrated under reduced pressure without heating to afford the desired product. Yield: 40.88 g, 95%, colorless liquid which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (t, J = 12.6 Hz); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -101.27 (s).

*(E)-5-Bromo-1-ethoxy-4,4-difluoropent-1-en-3-one (**5**).*

To the solution of ethyl vinyl ether (28.4 g, 0.394 mol) and pyridine (31.2 g, 0.394 mol) in 200 mL of CH_2Cl_2 propanoyl chloride **4** (40.8 g, 0.197 mol) was added dropwise at 0 °C. After stirring at rt overnight the reaction mixture was quenched with water (200 mL). Organic phase was washed with water (2x100 mL), and 2% solution of citric acid (50 mL), was dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired product. The final product was purified by distillation. Yield: 19.15 g, 40%, yellowish liquid, b.p. 95 °C, 10 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 12.4 Hz, 1H), 6.01 (d, J = 12.4 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 13.9 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.15 (t, J = 29.1 Hz), 167.15, 114.30 (t, J = 255.7 Hz), 98.44, 68.61, 28.46 (t, J = 29.2 Hz), 14.37; ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -107.13 (s). Anal. Calcd for $C_7H_9BrF_2O_2$: C, 34.59; H, 3.73. Found: C, 34.81; H, 3.55.

*(Z)-1-Amino-5-bromo-4,4-difluoropent-1-en-3-one (**6a**).*

To the solution of enone **5** (0.5 g, 0.002 mol) in MeOH (3 mL) 20% solution of ammoniac in MeOH (0.17 g, 0.002 mol) was added at 0 °C. After stirring at rt overnight the reaction mixture and concentrated under reduced pressure to afford the desired product. Yield: 0.36 g, 82%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79-9.20 (br.s, 1H), 7.14 (m, 1H), 6.10-5.70 (br.s, 1H), 5.53 (dm, J = 7.5 Hz, 1H), 3,71 (t, J = 13.9 Hz, 2H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -107.42 (s). Anal. Calcd for $C_5H_6BrF_2NO$: C, 28.06; H, 2.83; N, 6.55. Found: C, 27.91; H, 2.98; N, 6.41.

*(E)-5-Bromo-4,4-difluoro-1-morpholinopent-1-en-3-one (**6b**).*

To the solution of enone **5** (0.5 g, 0.002 mol) in CH_2Cl_2 (5 mL) morpholine (0.18 g, 0.002 mol) was added at 0 °C. After stirring at rt overnight the reaction mixture was concentrated under reduced pressure to afford the desired product. Yield: 0.46 g, 79%, yellow lowmelting solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 12.5 Hz, 1H), 5.55 (d, J = 12.5 Hz, 1H), 3.71-3.66 (m, 2H), 3.49 (m, 2H), 3.40 (m, 2H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -107.21 (s). Anal. Calcd for $C_9H_{12}BrF_2NO_2$: C, 38.05; H, 4.26; N, 4.93. Found: C, 37.78; H, 4.41; N, 4.82.

*3-(2-Bromo-1,1-difluoroethyl)-1H-pyrazole (**7**).*

To the solution of enone **5** (5.0 g, 0.02 mol) in acetic acid (100 mL) hydrazine hydrate (1.05 g, 0.021 mol) was added dropwise under stirring at rt. After stirring at rt overnight the reaction mixture was concentrated under reduced pressure. The rest was resolved in MTBE (50 mL), the organic phase was washed with 2% solution of $NaHCO_3$ (50 mL), was dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired product. Yield: 3.56 g, 82%, yellow lowmelting solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.85-12.89 (br.s, 1H), 7.69 (br.s, 1H), 6.54 (br.s, 1H), 3.88 (t, J = 13.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.97 (t, J = 30.8 Hz), 130.36, 116.33 (t, J = 240.2 Hz), 103.82 (t, J = 2.6 Hz), 32.67 (t, J = 33.4 Hz); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -95.47 (s). Anal. Calcd for $C_5H_5BrF_2N_2$: C, 28.46; H, 2.39; N, 13.28. Found: C 28.72; H 2.65; N, 13.02.

*3-(2-Bromo-1,1-difluoroethyl)-1-methyl-1H-pyrazole and 5-(2-bromo-1,1-difluoroethyl)-1H-pyrazole (**8a**) and (**8b**).*

Analogously as for pyrazole **7** from enone **5** (1.0 g, 0.004 mol) and methylhydrazine (0.19 g, 0.004 mol). Yield: 0.70 g, 75%, yellow oil. Major pyrazole **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (br.d, J = 1.2 Hz, 0.82H), 6.48 (br.d,

J = 1.2 Hz, 0.82H), 3.94 (t, *J* = 13.8 Hz, 1.64H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -94.52 (s, 2.46F).

Minor pyrazole **8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br.s, 0.18H), 6.49 (br.s, 0.18H), 4.02 (s, 0.54), 3.88 (t, *J* = 13.3 Hz, 0.36H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -92.77 (s, 0.36F). Anal. Calcd for $C_6H_7BrF_2N_2$: C, 32.02; H, 3.14; N, 12.45. Found: C 32.31; H 3.05; N, 12.62.

*5-(2-Bromo-1,1-difluoroethyl)-4,5-dihydroisoxazol-5-ol (**9**).*

To the solution of enone **5** (5.0 g, 0.02 mol) and $H_2NOH{\cdot}HCl$ (1.43 g, 0.02 mol) in water (50 mL) Na_2CO_3 (2.22 g, 0.021 mol) was added by portions. After stirring at rt overnight the reaction mixture was extracted with CH_2Cl_2 (2x50 mL). Organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired product. Yield: 3.93 g, 83%, yellow lowmelting solid which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 3.97-3.57 (m, 3H), 3.52 (d, *J* = 19.1 Hz, 1H), 3.08 (d, *J* = 19.1 Hz, 1H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -111.07 (d, *J* = 252.2 Hz, 1F), -112.14 (d, *J* = 252.2 Hz, 1F).

*5-(2-Bromo-1,1-difluoroethyl)isoxazole (**10**).*

To the solution of dihydroisoxazolol **9** (3.82 g, 0.017 mol) and pyridine (1.60 g, 0.02 mol) in CH_2Cl_2 (50 mL) $SOCl_2$ (2.41 g, 0.02 mol) was added dropwise at 0 °C. After stirring at rt overnight the reaction mixture was quenched with water (50 mL), organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired product. Yield: 1.95 g, 55%, yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 6.62 (s, 1H), 3.89 (t, *J* = 13.1 Hz, 2H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -97.09 (s). Anal. Calcd for $C_5H_4BrF_2NO$: C, 28.33; H, 1.90; N, 6.61. Found: C 28.01; H 1.75; N, 6.48.

*3-(2-Azido-1,1-difluoroethyl)-1H-pyrazole (**12**).*

A. The solution of pyrazole **7** (1.0 g, 0.0058 mol) and NaN_3 (0.92 g, 0.014 mol) in DMSO (5 mL) was stirred at 110 °C for 48 h. The reaction mixture was quenched with water (50 mL), extracted with MTBE (2x30 mL), organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired product. Yield: 0.72 g, 72%, braun oil.

B. Analogously as for pyrazole **7** from enone **16** (0.5 g, 0.0024 mol) and hydrazine hydrate (0.122 g, 0.0024 mol). Yield: 0.39 g, 75%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.3-11.3 (br.s, 1H), 7.67 (s, 1H), 6.60 (s, 1H), 3.89 (t, *J* = 13.4 Hz, 2H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -98.61 (s). Anal. Calcd for $C_5H_5F_2N_5$: C, 34.69; H, 2.91; N, 40.45. Found: C 34.91; H 2.65; N, 40.18.

*Ethyl 3-azido-2,2-difluoropropanoate (**13**).*

The solution of ester **2** (20.0 g, 0.092 mol) and NaN_3 (9.0 g, 0.138 mol) in DMSO (150 mL) was stirred overnight at 60 °C. The reaction mixture was quenched with water (500 mL), extracted with MTBE (2x80 mL), organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired product. Yield: 12.41 g, 75%, yellow liquid which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (q, *J* = 7.1 Hz, 2H), 3.73 (t, *J* = 12.7 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -110.81 (s).

*Lithium 3-azido-2,2-difluoropropanoate (**14**).*

Analogously as for Li salt **3** from propanoate **13** (12 g, 0.067 mol) and $LiOH{\cdot}H_2O$ (2.81 g, 0.067 mol). Yield: 10.5 g, 100%, yellowish crystals which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.66 (t, *J* = 14.9 Hz); ^{19}F {H} NMR (376 MHz, DMSO-d_6) δ -108.34 (s).

*3-Azido-2,2-difluoropropanoyl chloride (**15**).*

Analogously as for chloro anhydride **4** from Lithium salt **14** (10.0 g, 0.064 mol) and oxalyl chloride (22.0 g, 0.191 mol). Yield: 10.3 g, 95%, yellow liquid which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (t, *J* = 12.3 Hz); ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -110.70 (s).

*(E)-5-Azido-1-ethoxy-4,4-difluoropent-1-en-3-one (**16**).*

Analogously as for enone **5** from chloro anhydride **15** (1.0 g, 0.0059 mol), ethyl vinyl ether (0.85 g, 0.012 mol) and pyridine (0.94 g, 0.012 mol). Yield: 0.91 g, 75%, yellow oil which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 12.4 Hz, 1H), 5.99 (d, *J* = 12.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.72 (t, *J* = 13.5 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.55 (t, *J* = 28.5 Hz), 167.15, 115.39 (t, *J* = 256.9 Hz), 98.36, 68.59, 51.38 (t, *J* = 27.3 Hz), 14.29; ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -111.60 (s). Anal. Calcd for $C_7H_9F_2N_3O_2$: C, 40.98; H, 4.42; N, 20.48. Found: C, 41.21; H, 4. 25; N, 20.13.

*5-(2-Azido-1,1-difluoroethyl)-4,5-dihydroisoxazol-5-ol (**17**).*

Analogously as for dihydroisoxazolol **9** from enone **16** (1.0 g, 0.0049 mol), $H_2NOH{\cdot}HCl$ (0.37 g, 0.0054 mol), and Na_2CO_3 (0.57 g, 0.0054 mol). Yield: 0.76 g, 81%, yellow oil which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 5.00-4.50 (br.s, 1H), 3.95-3.69 (m, 2H), 3.48 (d, *J* = 19.0 Hz, 1H), 3.03 (dm, *J* = 19.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.16, 117.74 (t, *J* = 251.5 Hz), 104.01 (t, *J* = 30.0 Hz), 50.88 (t, *J* = 27.7 Hz), 43.15; ^{19}F {H} NMR (376 MHz, $CDCl_3$) δ -115.16 (s). Anal. Calcd for $C_5H_6F_2N_4O_2$: C, 31.26; H, 3.15; N, 29.16. Found: C, 31.52; H, 3.37; N, 28.88.

*5-(2-Azido-1,1-difluoroethyl)isoxazole (**18**).*

Analogously as for isoxazole **9** from dihydroisoxazolol **19** (0.74 g, 0.0038 mol), pyridine (0.31 g, 0.0039 mol), and $SOCl_2$ (0.46 g, 0.0039 mol). Yield: 0.30 g, 62%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 6.65 (s, 1H), 3.91 (t, *J* = 13.2 Hz, 2H); ^{19}F {H} NMR (376 MHz, $CDCl_3$)

δ -97.09 (s). Anal. Calcd for $C_5H_4F_2N_4O$: C, 34.49; H, 2.32; N, 32.18. Found: C, 34.27; H, 2.49; N, 31.79.

*4-(2-Azido-1,1-difluoroethyl)pyrimidin-2(1H)-one (**19**).*

To the solution of enone **16** (0.5 g, 2.4 mmol) and urea (0.146 g, 2.4 mmol) in ethanol (5 mL) conc. HCl (0.5 g, 5.9 mmol) was added and stirred for 48 h at rt. The reaction mixture was concentrated under reduced pressure and the desired product was purified by column chromatography with eluent $CHCl_3$: MeOH (50 : 1). Yield: 0.36 g, 53%, yellow lowmelting compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8-12.3 (br.s, 1H), 8.24 (d, J = 6.3 Hz, 1H), 6.68 (d, J = 6.3 Hz, 1H), 4.11 (t, J = 14.6 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.10 (t, J = 28.6 Hz), 156.53, 151.71, 118.13 (t, J = 246.5 Hz), 100.01, 52.34 (t, J = 26.8 Hz); ^{19}F {H} NMR (376 MHz, DMSO-d_6) δ -105.63 (s). Anal. Calcd for $C_6H_5F_2N_5O$: C, 35.83; H, 2.51; N, 34.82. Found: C, 35.97; H, 2.42; N, 35.11.

*4-(2-Amino-1,1-difluoroethyl)tetrahydropyrimidin-2(1H)-one (**22**).*

To the solution of pyrimidinone **19** (0.12 g, 0.6 mmol) in ethyl acetate (5 mL) 10% Pd/C (0.15 g) was added and the reaction mixture was stirred under hydrogen for 48 h at rt. The catalyst was filtered off and washed with ethyl acetate (5 mL). The solution was concentrated under reduced pressure to afford the desired product. Yield: 0.082 g, 77%, yellow lowmelting compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (br.s, 1H), 5.14 (br.s, 1H), 3.88 (m, 1H), 3.41 (m, 1H), 3,30 (m, 1H), 3.25-2.98 (m, 2H), 2.02 (m, 2H); ^{19}F {H} NMR (470 MHz, $CDCl_3$) δ -115.58 (dm, J = 250.6 Hz), -118.64 (dm, J = 250.6 Hz). Anal. Calcd for $C_6H_{11}F_2N_3O$: C, 40.22; H, 6.19; N, 23.45. Found: C, 40.01; H, 6.32; N, 23.19.

*4-(2-Amino-1,1-difluoroethyl)pyrimidin-2(1H)-one (**23**).*

To the solution of pyrimidinone **19** (0.33 g, 1.6 mmol) in THF (5 mL) triphenylphosphine (0.47 g, 1.8 mmol) and water (0.15 g, 8 mmol) were added and stirred overnight at rt. The reaction mixture was concentrated under reduced pressure and the desired product was purified by crystallization from benzene. Yield: 0.232 g, 81%, yellowish crystals, mp 86-88 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 6.2 Hz, 1H), 6.60 (d, J = 6.2 Hz, 1H), 3.45-3.15 (br.s, 2H), 3.17 (t, J = 14.7 Hz, 2H); ^{19}F {H} NMR (376 MHz, DMSO-d_6) δ -107.74 (s). Anal. Calcd for $C_6H_7F_2N_3O$: C, 41.15; H, 4.03; N, 23.99. Found: C, 41.38; H, 3.81; N, 23.87.

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1,1-Дифлуоро-2-(бромо, азидо)етилзаміщені β-алкоксиенони: синтез та реакції гетероциклізації

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Резюме: Синтезовано нові 5-бромо- та 5-азидо-1-етокси-4,4-дифлуоропент-1-ен-3-они та досліджено їх реакційну здатність за допомогою реакцій нуклеофільного заміщення та гетероциклізації з різними бінуклеофілами.

Ключові слова: органічна хімія; флуор; енони; нуклеофільне заміщення; реакції гетероциклізації.