JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Radical Reactions of Alkyl 2-Bromo-2,2-difluoroacetates with Vinyl Ethers: "Omitted" Examples and Application for the Synthesis of 3,3-Difluoro-GABA

Ivan S. Kondratov,*[,†] Maksym Ya. Bugera,[†] Nataliya A. Tolmachova,[†,‡] Ganna G. Posternak,[‡] Constantin G. Daniliuc,[§] and Günter Haufe*[,§,∥]

[†]Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanska Str. 1, Kyiv, 02660, Ukraine

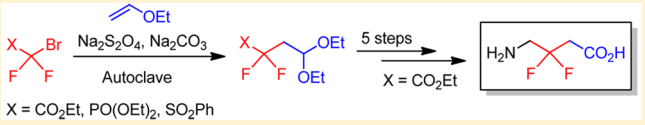
[‡]Enamine Ltd, Chervonotkatska Str. 78, Kyiv, 02094, Ukraine

[§]Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, 48149 Münster, Germany

[∥]Cells-in-Motion Cluster of Excellence, Universität Münster, Waldeyerstraße 15, 48149 Münster, Germany

Supporting Information

ABSTRACT: Addition reactions of perfluoroalkyl radicals to ordinary or polyfluorinated alkenes have been frequently used to synthesize perfluoroalkylated organic compounds. Here ethyl/methyl 2-bromo-2,2-difluoroacetate, diethyl (bromodifluoromethyl)phosphonate, [(bromodifluoromethyl)sulfonyl]benzene, and ethyl 2-bromo-2-fluoroacetate were involved in $Na_2S_2O_4$-mediated radical additions to vinyl ethers in the presence of alcohols to give difluoro or monofluoroacetyl-substituted acetals or corresponding difluoromethylphosphonate- and (difluoromethylphenyl)sulfonyl-substituted alkyl acetals. This methodology has also been applied as a key step in the synthesis of hitherto unknown 3,3-difluoro-GABA, completing the series of isomeric difluoro GABAs. Comparison of the pK_a values of 3-fluoro- and 3,3-difluoro-GABA with that of the fluorine free parent compound showed that introduction of each fluorine lead to acidification of both the amino and the carboxyl functions by approximately one unit.



INTRODUCTION

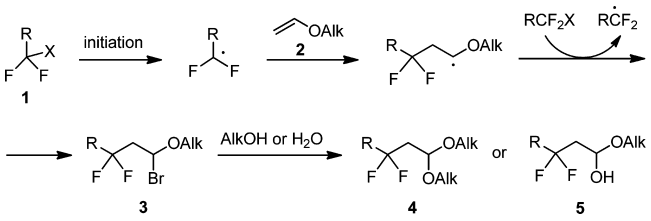
It is hard to overestimate the role of fluorine in modern pharmaceutical research, agrochemistry, and material science.[1] Due to versatile applications of organofluorine compounds, there is extensive development of new synthetic methods to introduce fluorine or fluorocontaining groups into organic molecules. Among other methods, generation of fluorocontaining radicals and their addition across C=C double bonds can be considered as an effective and promising method to obtain diverse fluoroorganic compounds.[2]

A typical example for addition reactions of fluorocontaining radicals to vinyl ethers leading to either acetals **4** or semiacetals **5** depending on the solvent used is depicted in Scheme 1.

Half a century ago, Tarrant and Stump first investigated such a reaction starting from various halofluoroalkanes (e.g., dibromodifluoromethane and bromochlorodifluoromethane) under UV initiation and characterized the corresponding products **3** and **4**.[3] Later Wakselman et al. applied the same conditions for the synthesis of ethyl 3,3,3-trifluoropropanoate[4a] and ethyl 3-bromo-3,3-difluoropropanoate[4b] via the corresponding fluorinated acetals. Later on Qing et al. optimized the synthesis of ethyl 3-bromo-3,3-difluoropropanoate[5] using Huang's mild conditions ($Na_2S_2O_4/Na_2CO_3$)[6] for radical initiation. These conditions were also applied in various other studies[7] including synthesis of new fluorocontaining sugar derivatives.[8] Furthermore, alternative other radical initiation conditions (e.g., BEt_3, UV etc.) and other polyfluorinated alkyl halides have also been applied.[9]

Most of the investigated examples included radical additions of various polyfluoroalkyl bromides/iodides (compound **1**, R = F, Cl, Br, R_f, etc.; X = Br, I) across different types of C=C double bond systems. In contrast, less attention has been paid to reactions using reagents bearing additional functional groups such as CO_2Alk, $PO(OAlk)_2$, SO_2R, etc. By way of example, 2-bromo-2,2-difluoroalkanoates of general structure **1** (R = CO_2Alk, X = Br) are readily accessible and belong to the most widely used reagents in organofluorine chemistry. Compounds **1** have been used for Reformatsky reactions,

Scheme 1. General Scheme of Fluorinated Radical Addition to Vinyl Ethers



Received: September 15, 2015
Published: November 9, 2015

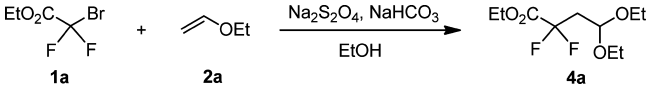
DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258−12264

diverse types of difluoroacetylation reactions of (hetero)-aromatic compounds and C=C double bond systems, and in other transformations leading to C−C bond formation.[10] Also 2-chloro-, 2-bromo-, 2-iodo- as well as 2-(phenyseleno)-2,2-difluoroacetates were involved in different radical additions to alkenes.[11] Surprisingly, there are no reports in the literature on the addition to readily available vinyl ethers.

RESULTS AND DISCUSSION

In this study we investigated reactions of ethyl and methyl bromodifluoroacetates, diethyl (bromodifluoromethyl)-phosphonate, [(bromodifluoromethyl)sulfonyl]benzene, and ethyl 2-bromo-2-fluoroacetate with vinyl ethers initiated by $Na_2S_2O_4$ and sodium bicarbonate in ethanol (Huang's conditions).[6] First we carried out the reaction of ethyl 2-bromo-2,2-difluoroacetate (**1a**) with ethyl vinyl ether (**2a**) (Table 1, entry 1) following a protocol described by Qing et al.[5] for the radical addition of dibromodifluoromethane to ethyl vinyl ether.

Table 1. Reaction of Ethyl 2-Bromo-2,2-difluoroacetate (1a) with Ethyl Vinyl Ether (2a) under Various Conditions



entry	temperature (°C)	time (h)	reagent ratio[a] **1a**:**2a**:$Na_2S_2O_4$:$NaHCO_3$	yield of **4a** (%)
1	60	2[b]	1.5:1:1.5:3	17
2	60	2[b]	1:2:1.5:3	29
3	60	2[c]	1:2:1.5:3	56
4	60	6[c]	1:2:1.5:3	65
5	60	10[c]	1:2:1.5:3	73
6	80	10[c]	1:2:1.5:3	66
7	60	24[c]	1:2:1.5:3	70

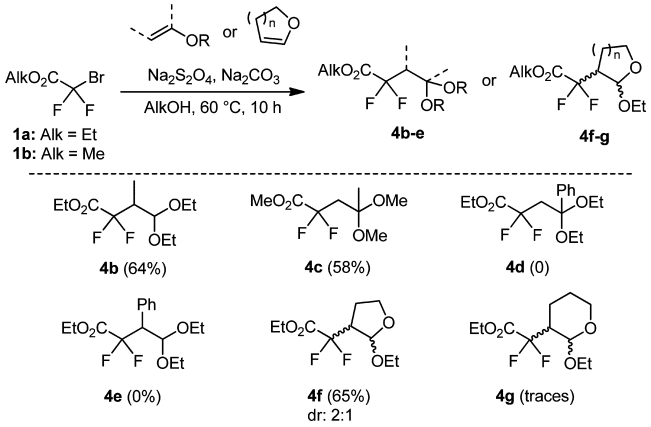
[a]In all the experiments the synthesis started from 10 mmol of ethyl 2-bromo-2,2-difluoroacetate (**1a**). [b]The reaction has been carried out using a dry ice-acetone condenser. [c]The reaction has been carried out in an autoclave.

Under these conditions, the isolated yield was 17% presumably as a result of low conversion. The yield was higher using an excess of ethyl vinyl ether (Table 1, entry 2). In both experiments the reaction was carried out using ice-acetone condenser in order to avoid evaporation of ethyl vinyl ether. We supposed that even under effective cooling parts of **2a** escaped. Therefore, the reaction was carried out in an autoclave that significantly increased the yield (Table 1, entry 3).

Optimal conditions were 60 °C and 10 h (Table 1, entry 5), giving product **4a** in 73% yield. Even higher temperature or longer reaction time did not increase the yield. These validated conditions have been used for the synthesis of **4a** in 85 g scale.

Moreover, these conditions were also applied for the addition to several other vinyl ethers (Scheme 2). In case of the reaction with 1-ethoxypropene in ethanol and 2-methoxypropene in methanol,[12] the corresponding products **4b,c** were obtained. In the case of the reaction with 1-phenyl vinyl ether and 1-ethoxystyrene, the corresponding products **4d,e** were not identified in the respective crude product mixtures even after prolonged heating. The electron-withdrawing effect and/or steric hindrance of the phenyl group might be the reasons. In case of the reaction with 2,3-dihydrofuran, the corresponding product **4f** was obtained as mixture of diastereomers (dr, 1:2).

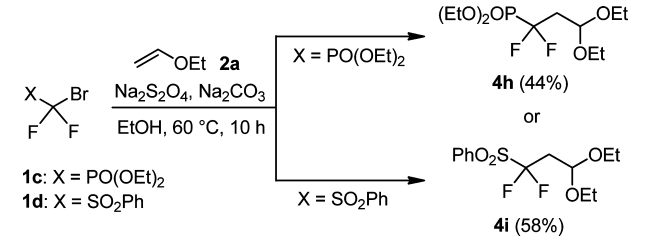
Scheme 2. Reactions of Ethyl 2-Bromo-2,2-difluoroacetate (1a) with Various Vinyl Ethers



Surprisingly, in the case of the reaction with 3,4-dihydropyran, we observed only traces of the expected product **4g** (identified in the NMR and mass spectra of the product mixture),[13] which could not be isolated. The major product formed was 2-ethoxytetrahydropyran. Thus, EtOH addition to 3,4-dihydropyran seems to occur faster than radical addition, although the conditions used are unusual compared to standard acid-catalyzed alcohol addition to vinyl ethers.

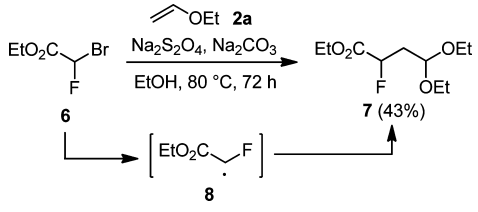
The optimized conditions have also been applied for reactions of diethyl (bromodifluoromethyl)phosphonate (**1c**)[14] and [(bromodifluoromethyl)sulfonyl]benzene (**1d**)[15] with ethyl vinyl ether (Scheme 3). Under these conditions the corresponding acetals **4h,i** have been isolated in moderate yield.

Scheme 3. Radical Additions of 1c,d Across Ethyl Vinyl Ether (2a) To Form Acetals 4h,i



Ethyl 2-bromo-2-fluoroacetate (**6**) has also been used for the radical reaction shown in Scheme 4. However, under the aforementioned conditions we observed only traces of the desired product **7**. Under forced conditions (80 °C, 72 h, autoclave, 3 equiv $Na_2S_2O_4$) the target compound was isolated in 43% yield, reflecting lower reactivity of radical **8** as compared to the difluoro species.

Scheme 4. Synthesis of Acetal 7 by Addition of Radical 8 to Ethyl Vinyl Ether (2a)



DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258−12264

Compounds **4a**–**i** and **7** can be considered as new potential building blocks for organofluorine chemistry having two functional groups, which can be involved independently in further transformations. In order to demonstrate the potential of these compounds, we applied **4a** for the synthesis of hitherto unknown difluoro analogue **9** of γ-aminobutyric acid (GABA) (Figure 1).

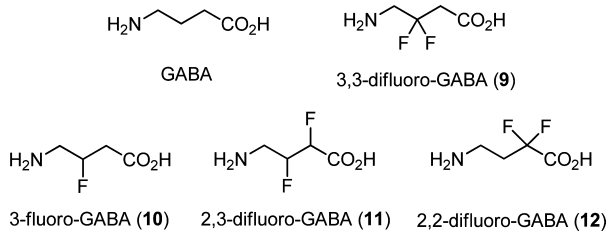


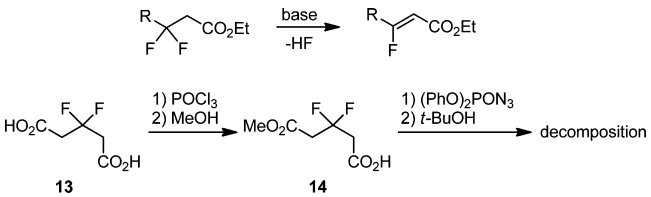
Figure 1. GABA and its fluorinated analogues **9**–**12**.

GABA is the major inhibitory neurotransmitter in the central nervous system, and its response is mediated by multiple receptors.[16] Various GABA analogues have been synthesized, and their binding affinity to different GABA receptors as well as to other targets has been shown. Successful commercialization of various GABA analogues (so-called GABAergic drugs) initiated further developments in the area.[17]

Racemic 3-fluoro-GABA (**10**) was first synthesized by Kolonitsch et al.[18] and studied as inactivator of γ-aminobutyric acid aminotransferase.[19] Both enantiomers of **10** were prepared by O'Hagan et al.[20a] and studied as GABA receptor as well as GABA aminotransferase ligands.[20a–c] Later Hunter et al. have synthesized all four stereoisomers of 2,3-difluoro-GABA (**11**) and investigated their properties as $GABA_C$ receptor agonists or antagonists.[21a,b] Moreover, compounds **11** have been used as starting materials for the synthesis of natural peptide analogues, and their properties have been studied.[21c,d] Another analogue, 2,2-difluoro-GABA (**12**), was also obtained previously.[22] In addition, **10** and **11** were also used as building blocks for the synthesis of potent S1P receptor agonists.[23] Several other fluorocontaining GABA analogues were synthesized and investigated.[24]

From the general interest point of view of fluorinated GABA analogues, it is surprising that 3,3-difluoro-GABA (**9**) has been omitted in the literature until today.

Scheme 5. General Scheme of HF Elimination from β,β-Difluorocarbonyl Compounds and Failed Attempt to Synthesize Compound 9 from 3,3-Difluoroglutaric Acid (13)



Analyzing possible pathways to obtain compound **9**, we suspected facile HF elimination under basic conditions as the main possible side process, which was found for a number of β,β-difluorocarbonyl compounds.[5,25] This assumption was confirmed by a failure to synthesize compound **9** from accessible 3,3-difluoroglutaric acid (**13**)[26] (Scheme 5). We observed decomposition of monoester **14** under typical conditions of Curtius rearrangement presumably as a result of HF elimination.

Therefore, according to retrosynthesis (Scheme 6), we considered an acetal group as a precursor of a carboxylic acid. According to a method used by Wakselman[4] and Qing,[5] an acetal can be oxidized to an ester, which on saponification leads to an acid. This leads logically to consideration of compound **4a** as a convenient starting material for the synthesis of **9**.

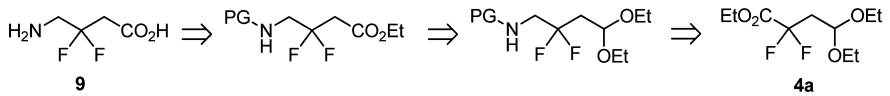
Initially, amide **15** was synthesized from the aforementioned ester **4a** (Scheme 7). Amide reduction with $LiAlH_4$ led to aminoacetal **16**, which was protected as phthalimide **17**. Subsequent MCPBA oxidation led to ester **18**, isolated in 44% yield. Deprotection with 6 N HCl under reflux and neutralization by ion-exchange chromatography gave the target **9**. Optimizing the protocol for large scale preparation of **9**, we found that formation of ester **18** was accompanied by partial hydrolysis of ester function. Therefore, we developed a one-pot variation for oxidation-deprotection steps without the isolation of **18** that delivered **9** in 86% yield (based on **17**, 2 steps). The method has been used to synthesize **9** in 10 g scale in 26% overall yield (based on **1a**, 6 steps).

The structure of product **9** was confirmed by X-ray analysis of its hydrochloride salt (Figure 2, see also SI). The packing diagram shows several close intermolecular N–H···Cl, N–H···O, and O–H···Cl contacts (Figure 2a) and also the *gauche*-orientation of the amino group with respect to both fluorine atoms (Figure 2b,c).[27] According to the X-ray data, the distance C–F···H_3N^+–C is 2.62(2) Å, which is slightly less than the sum of the van der Waals radii (2.67 Å).[28] This conformation is supposed to be stabilized as a result of *gauche*-C–F···H_3N^+–C interaction.[29]

According to a conclusion of O'Hagan et al.[20] GABA binds $GABA_A$ receptor in "zig-zag" mode around C3–C4, which corresponds to the observed conformation of **9** (Figure 2). Therefore, we anticipate that compound **9** might be a selective agonist of the $GABA_A$-receptor.

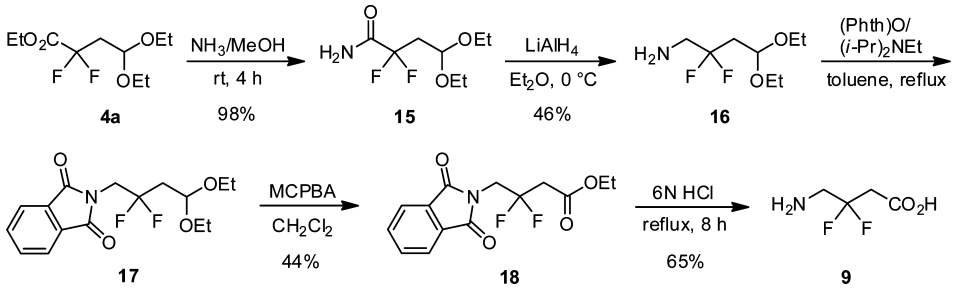
On the other hand as O'Hagan et al. have shown that both enantiomers of **10** are weaker agonists than GABA itself, which is probably due to the lower pK_a value of the amino group (see Figure 3), and as a result weaker electrostatic and H-bonding interactions to the surface of the receptors. Therefore, we have also measured pK_a values of synthesized **9** and compared it with the data of GABA and **10** (Figure 3).[20a,30] As expected, introduction of one more fluorine atom led to rise of acidity of carboxylic group and decrease of amino-group basicity.[31] Introduction of each fluorine lead to acidification of both the amino and the carboxyl functions by approximately one unit. Because of this, much weaker agonist activity in comparison with both GABA and **10** can be expected for compound **9**.

Scheme 6. Retrosynthesis of 3,3-Difluoro-GABA (9)



DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258–12264

Scheme 7. Synthesis of 9 starting from 4a



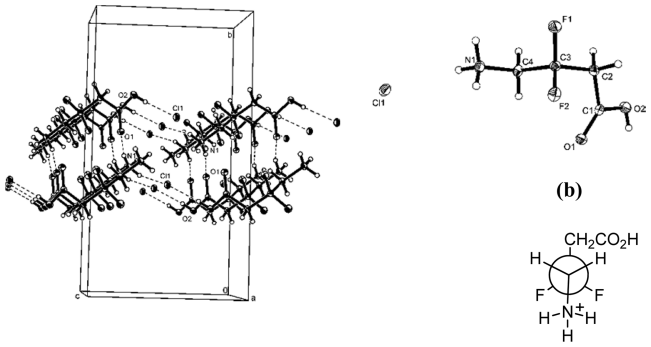


Figure 2. (a) Packing diagram of **9**·HCl showing N−H···Cl, N−H···O, and O−H···Cl contacts (thermals ellipsoids are shown with 30% probability). (b) Crystal structure of compound **9**·HCl. (c) Newman projection of the observed conformation.

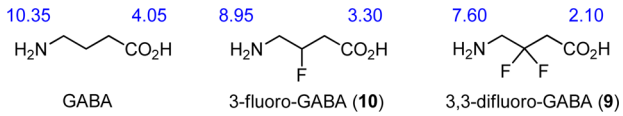


Figure 3. Comparison of measured pK_a values of compound **9** with earlier reported data for GABA and **10**.[20a,30]

CONCLUSION

We found that Huang's radical initiation conditions ($Na_2S_2O_4$) can be applied for the addition of a series of bromodifluoroacetamides containing reagents **1a−d** and even of ethyl 2-bromo-2-fluoroacetate (**6**) across vinyl ethers. The obtained products—acetals **4**—can be considered as promising building blocks for organofluorine chemistry that was demonstrated by application of ethyl 4,4-diethoxy-2,2-difluorobutanoate (**4a**) for the multigram synthesis of 3,3-difluoro-GABA (**9**).

EXPERIMENTAL SECTION

General Experimental Methods. Melting points are uncorrected. NMR spectra were recorded at 300, 400, 500, and 600 MHz (^{1}H) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. IR spectra were recorded as KBr pallets or by ATR technique. HRMS data (ESI-MS) were obtained using a ToF mass spectrometer. The progress of reactions was monitored by TLC plates (Merck, silica gel 60 F_{254}). For column chromatography, silica gel 60 (particle size 0.040−0.063 mm) was used. Ion-exchange chromatography was performed by standard technique.[32] Elemental analyses are correct within the limits of ±0.3% for C, H, N.

Synthesis of Acetals 4a−i. *General Procedure.* A mixture of the corresponding bromodifluoromethyl reagent **1a−d** (10 mmol), the corresponding vinyl ether **2** (20 mmol), sodium bicarbonate (2.52 g, 30 mmol), sodium dithionite (2.37 g, 15 mmol), and ethanol (50 mL) or methanol (for **4c**) was put into a stainless autoclave (250 mL). The autoclave was sealed, and the mixture was vigorously stirred at 60 °C for 10 h. Then the autoclave was cooled to room temperature, carefully opened (liberation of gases CO_2/SO_2), and treated with water (100 mL). The mixture was extracted with MTBE (3 × 50 mL). The combined organic layers were washed with water (3 × 100 mL), brine (50 mL), and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by distillation under reduced pressure using a Claisen condenser setup or by column chromatography giving pure products **4a−g**.

Ethyl 4,4-Diethoxy-2,2-difluorobutanoate (4a). Compound **4a** was obtained from ethyl 2-bromo-2,2-difluoroacetate (**1a**) (2.03 g, 10 mmol) and ethyl vinyl ether (**2a**) (1.44 g, 20 mmol). The product was purified by distillation under reduced pressure (bp 65−66 °C, 0.55−0.58 mbar) to give a colorless liquid. Yield: 1.75 g (73%).

The reaction was also carried out in large scale by the same procedure starting from ethyl 2-bromo-2,2-difluoroacetate (101 g, 0.5 mol), ethyl vinyl ether (**2a**) (72 g, 1.0 mol), sodium bicarbonate (126 g, 1.5 mol), sodium dithionite (130.5 g, 0.75 mol), and ethanol (1.0 L) in a 2 L autoclave. Yield: 85 g (71%). IR (ATR): ν = 1012, 1053, 1091, 1334, 1376, 1770, 2885, 2981 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.65 (t, 1H, J = 5.8 Hz), 4.24 (q, 2H, J = 7.1 Hz), 3.59 (dq, 2H, J_1 = 9.6, J_2 = 7.0 Hz), 3.44 (dq, J_1 = 9.6, 2H, J_2 = 7.0 Hz, 2H), 2.42 (td, 2H, J_1 = 14.6, J_2 = 5.9 Hz), 1.29 (t, 3H, J = 7.2 Hz), 1.12 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.1 (t, J = 32.4 Hz), 114.3 (t, J = 249.2 Hz), 97.4 (t, J = 7.6 Hz), 62.0, 61.9, 39.1 (t, J = 22.8 Hz), 14.5, 13.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −105.09 (t, J = 14.5 Hz) ppm. ESI-MS (m/z): calcd for $C_{10}H_{18}F_2NaO_4^+$ (263.1066). Found: 263.1065. Anal. calcd for $C_{10}H_{18}F_2O_4$: C, 49.99; H, 7.55. Found: C, 49.76; H, 7.69.

Ethyl 4,4-Diethoxy-2,2-difluoro-3-methylbutanoate (4b). Compound **4b** was obtained from ethyl 2-bromo-2,2-difluoroacetate (**1a**) (2.03 g, 10 mmol) and (*Z*/*E*)-1-ethoxyprop-1-ene (**2b**) (1.72 g, 20 mmol). The product was purified by distillation under reduced pressure (bp 67−70 °C, 0.55−0.58 mbar) to give a colorless liquid. Yield: 1.62 g (64%). IR (KBr): ν = 1010, 1048, 1129, 1213, 1296, 1345, 1772, 2890, 2981 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (d, 1H, J = 7.8 Hz), 4.24 (q, 2H, J = 7.2 Hz), 3.73−3.28 (m, 4H), 2.76−2.59 (m, 1H), 1.31 (t, 3H, J = 7.2 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.11 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.6 (dd, J_1= 34.3, J_2 = 31.8 Hz), 115.4 (dd, J_1 = 255.9, J_2 = 248.9 Hz), 101.6 (dd, J_1 = 8.3, J_2 = 3.4 Hz), 63.6, 61.7, 60.9, 41.4 (t, J = 21.6 Hz), 14.7, 14.2, 13.4, 7.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −105.64 (d, J = 264.6 Hz), − 121.46 (dd, J_1 = 264.6, J_2 = 24.8 Hz) ppm. ESI-MS (m/z): calcd for $C_{11}H_{20}F_2NaO_4^+$ (277.1222). Found: 277.1226. Anal. calcd for: $C_{11}H_{20}F_2O_4$: C, 51.96; H, 7.93. Found: C, 52.09; H, 7.84.

Methyl 2,2-Difluoro-4,4-dimethoxypentanoate (4c). Compound **4c** was obtained from methyl 2-bromo-2,2-difluoroacetate (**1b**) (1.89 g, 10 mmol) and 2-methoxyprop-1-ene (**2c**) (1.44 g, 20 mmol) in methanol. The product was purified by distillation under reduced pressure (bp 67−70 °C, 0.55−0.58 mbar) to give a colorless liquid. Yield: 1.23 g (58%). IR (ATR): ν = 1047, 1127, 1185, 1238, 1350, 1769, 2836, 2958 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3H), 3.12 (s, 6H), 2.45 (t, 2H, J = 15.3 Hz), 1.38 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.3 (t, J = 32.9 Hz), 116.3 (t, J = 249.3 Hz), 98.4 (t, J = 5.7 Hz), 52.9, 48.2, 41.6 (t, J = 23.1 Hz), 21.7 (t, J = 2.5 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −101.65 (t, J =

DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258−12264

15.3 Hz) ppm. ESI-MS (m/z): calcd for $C_8H_{14}F_2NaO_4^+$ (235.0752). Found: 235.0756. Anal. calcd for: $C_8H_{14}F_2O_4$: C, 45.28; H, 6.65. Found: C, 45.41; H, 6.49.

*Ethyl 2-(2-Ethoxytetrahydrofuran-3-yl)-2,2-difluoroacetate (**4f**).* Compound **4f** was obtained from ethyl 2-bromo-2,2-difluoroacetate (**1a**) (2.03 g, 10 mmol) and 2,3-dihydrofuran (**2f**) (1.40 g, 20 mmol). The product was purified by destillation under reduced pressure (bp 65−68 °C, 0.55−0.58 mbar) to give a colorless oil. Yield: 1.55 g (65%). The product was obtained as a 2:1 mixture of diastereomers, which were not separated. IR (ATR): ν = 1043, 1111, 1214, 1308, 1375, 1763, 2894, 2981 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.19 (d, 0.66H, J = 1.4 Hz), 5.11 (d, 0.33H, J = 5.3 Hz), 4.23−4.36 (m, 2H), 3.80−4.01 (m, 2H,), 3.61−3.74 (m, 1H), 3.30−3.49 (m, 1H), 2.77−3.04 (m, 1H), 2.32−2.46 (m, 0.33H). (m, 1.66H), 1.32 (t, 3H, J = 7.4 Hz), 1.15 (t, 2H, J = 6.8 Hz), 1.09 (t, 1H, J = 7.4 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.2 (t, J = 32.0 Hz, minor), 163.0 (t, J = 32.4 Hz, major), 114.8 (t, J = 252.5 Hz, major), 114.3 (dd, J_1 = 255.3, J_2 = 245.3, minor), 102.2 (t, J = 5.3 Hz, major), 101.1 (dd, J_1 = 7.3 Hz, J_2 = 3.2 Hz, minor), 65.9 (both), 63.1 (minor), 62.8 (major), 62.6 (major), 61.9 (minor), 50.6 (t, J = 21.5 Hz, major), 47.9 (t, J = 23.5 Hz, minor), 24.2 (major), 23.1 (minor), 14.6 (major), 14.2 (minor), 13.4 (both). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −98.70 (dd, 0.33F, J_1 = 272.0 Hz, J_2 = 11.5 Hz), − 108.36 (dd, 0.33F, J_1 = 272.0 Hz, J_2 = 17.5 Hz), − 110.48 (dd, 0.66F, J_1 = 258.5 Hz, J_2 = 15.5 Hz), − 111.46 (dd, J_1 = 258.5 Hz, J_2 = 15.5 Hz) ppm. ESI-MS (m/z): calcd for $C_{10}H_{16}F_2NaO_4^+$ (261.0909). Found: 261.0914. Anal. calcd for: $C_{10}H_{16}F_2O_4$: C, 50.42; H, 6.77. Found: C, 50.18; H, 6.65.

*Diethyl (3,3-Diethoxy-1,1-difluoropropyl)phosphonate (**4h**).* Compound **4h** was obtained from diethyl (bromodifluoromethyl)-phosphonate (**1c**) (2.67 g, 10 mmol) and ethyl vinyl ether (**2a**) (1.44 g, 20 mmol). The product was purified by column chromatography (cyclohexane/EtOAc, 4:1, R_f = 0.34) to give a colorless oil. Yield: 1.33 g (44%). IR (ATR): ν = 975, 1015, 1163, 1269, 1377, 2981 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (t, 1H, J = 5.2 Hz), 4.19 (m, 4H, J = 7.4 Hz), 3.58 (dq, 2H, J_1 = 9.3 Hz, J_2 = 7.1 Hz), 3.46 (dq, 2H, J_1 = 9.3 Hz, J_2 = 7.0 Hz), 2.34 (tt, 2H, J_1 = 19.9 Hz, J_2 = 5.3 Hz), 1.30 (t, 6H, J = 14.1 Hz), 1.12 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 118.9 (td, J_1 = 260.6 Hz, J_2 = 217.3 Hz), 96.7 (dd, J_1 = 8.0 Hz, J_2 = 5.0 Hz), 64.0 (d, J = 6.8 Hz), 61.2, 38.1 (td, J_1 = 19.7 Hz, J_2 = 14.1 Hz), 15.9 (d, J = 5.4 Hz), 14.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −111.91 (dt, J_1 = 107.0 Hz, J_2 = 19.9 Hz) ppm. ^{31}P NMR (201 MHz, $CDCl_3$): δ = 6.73 (t, J = 107.0 Hz) ppm. ESI-MS (m/z): calcd for $C_{11}H_{23}F_2NaO_5P^+$ (327.1143). Found: 327.1149. Anal. calcd for: $C_{11}H_{23}F_2O_5P$: C, 43.42; H, 7.62. Found: 43.54; H, 7.90.

*[(3,3-Diethoxy-1,1-difluoropropyl)sulfonyl]benzene (**4i**).* Compound **4i** was obtained from diethyl [(bromodifluoromethyl)sulfonyl]-benzene (**1d**) (2.71 g, 10 mmol) and ethyl vinyl ether (**2a**) (1.44 g, 20 mmol). The product was purified by column chromatography (cyclohexane/EtOAc, 20:1, R_f = 0.11) to give a colorless oil. Yield: 1.79 g (58%). IR (ATR): ν = 1064, 1096, 1160, 1340, 1378, 2886, 2979, 3005 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 2H, J = 7.8 Hz), 7.72 (t, 1H, J = 7.4 Hz), 7.57 (t, 2H, J = 7.7 Hz), 4.93 (t, 1H, J = 5.3 Hz), 3.72−3.40 (m, 4H), 2.67 (td, 2H, J_1 = 18.3 Hz, J_2 = 5.4 Hz), 1.16 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.0, 131.6, 130.4, 128.9, 122.6 (t, J = 283.5 Hz), 96.66 (t, J = 3.8 Hz), 61.47, 33.37 (t, J = 18.6 Hz), 14.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −103.32 (t, J = 18.7 Hz) ppm. ESI-MS (m/z): calcd for $C_{13}H_{18}F_2NaO_4S^+$ (331.0786). Found: 331.0795. Anal. calcd for $C_{13}H_{18}F_2O_4S$: C, 50.64; H, 5.88. Found: C, 50.33; H, 5.69.

*Ethyl 4,4-Diethoxy-2-fluorobutanoate (**7**).* Compound **7** was obtained from ethyl 2-bromo-2-fluoroacetate (**6**) (1.85 g, 10 mmol) and ethyl vinyl ether (**2a**) (1.44 g, 20 mmol) by the procedure similar to described above for compounds **4a−i** but under forced conditions (80 °C, 72 h, autoclave, 3 equiv $Na_2S_2O_4$). The product was purified by destillation under reduced pressure (bp 63−64 °C, 0.55−0.58 mbar) to give a colorless oil. Yield: 0.95 g (43%). IR (KBr): ν = 1073, 1102, 1144, 1334, 1387, 1399, 2895, 2990, 3024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.98 (ddd, 1H, J_1 = 48.8 Hz, J_2 = 7.9 Hz, J_3 = 4.1 Hz), 4.69 (dd, 1H, J_1 = 6.6 Hz, J_2 = 5.1 Hz), 4.21 (q, 2H, J = 7.0 Hz), 3.71−3.59 (m, 2H), 3.55−3.46 (m, 2H), 2.28−2.08 (m, 2H), 1.27 (t, 3H, J = 7.0 Hz), 1.19 (t, 3H, J = 6.8 Hz), 1.16 (t, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.5 (d, J = 23.6 Hz), 98.9 (d, J = 3.9 Hz), 86.2 (d, J = 182.5 Hz), 62.10, 62.08, 61.4, 36.9 (d, J = 20.2 Hz), 15.2, 15.1, 14.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 193.72 (ddd, J_1 = 48.8 Hz, J_2 = 28.2 Hz, J_3 = 22.0 Hz) ppm. ESI-MS (m/z): calcd for $C_{10}H_{19}FNaO_4^+$ (245.1160). Found: 245.1163. Anal. calcd for: $C_{10}H_{19}FO_4$: C 54.04; H 8.62. Found: C, 53.90; H, 8.86.

Synthesis of 4-Amino-3,3-difluorobutanoic Acid. *4-Diethoxy-2,2-difluorobutanamide (**15**).* Acetal **1a** (50.0 g, 0.21 mol) was dissolved in EtOH (200 mL), and a saturated solution of ammonia in MeOH (200 mL) was added dropwise at 5−10 °C under stirring. The mixture was stirred overnight at room temperature and then was concentrated under reduced pressure giving product **15**, which was used for the next step without purification. Yield: 43.4 g (98%), colorless solid, mp 72−75 °C. IR (KBr): ν = 1026, 1053, 1127, 1196, 1443, 1484, 1631, 1713, 2819, 2939, 2987, 3187, 3398 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.86 (s, 1H), 6.48 (s, 1H), 4.76 (t, 1H, J = 7.8 Hz), 3.73−3.54 (m, 2H,), 3.55−3.40 (m, 2H), 2.63−2.33 (m, 2H), 1.16 (t, 3H, J = 7.1 Hz), 1.15 (t, 3H, J = 7.1 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ= 166.3 (t, J = 29.6 Hz), 115.8 (t, J = 252.2 Hz), 97.0 (t, J = 6.6 Hz), 61.2, 37.7 (t, J = 22.7 Hz), 14.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −104.38 (t, J = 16.2 Hz) ppm. ESI-MS (m/z): calcd for $C_8H_{15}F_2NNaO_3^+$ (234.0912). Found: 234.0913. Anal. calcd for: $C_8H_{15}F_2NO_3$: C, 45.49; H, 7.16; N, 6.63. Found: C, 45.68; H, 6.88; N, 6.98.

*4,4-Diethoxy-2,2-difluorobutanamide (**16**).* To a suspension of compound **15** (42.2 g, 0.20 mol) in Et_2O (600 mL), $LiAlH_4$ (9.49 g, 250 mmol) was added in portions under vigorous stirring at 0 °C during 1 h. Stirring was continued at 0 °C for 3 h. Then water was carefully added dropwise, and the precipitate formed was filtered off. The filtrate was dried by Na_2SO_4 and concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (64−63 °C, 0.55−0.58 mbar) or used for the next step without purification. Yield: 18.1 g (46%), colorless oil. IR (ATR): ν = 845, 1051, 1130, 1379, 2881, 2978 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.64 (t, 1H, J = 5.4 Hz), 3.61−3.68 (m, 2H), 3.46 (m, 2H), 2.91 (t, 2H, J = 16.0 Hz), 2.20 (td, 2H, J = 16.0 Hz, J_2 = 5.4), 1.39−1.23 (br. s, 2H), 1.15 (t, 6H, J = 7.1) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 122.9 (t, J = 240.0 Hz), 98.3 (t, J = 7.6 Hz), 61.7, 46.7 (t, J = 27.7 Hz), 38.9 (t, J = 24.6 Hz), 15.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −103.19 (t, J = 16.0 Hz) ppm. ESI-MS (m/z): calcd for $C_8H_{17}F_2NNaO_2^+$ (220.1120). Found: 220.1128.

*2-(4,4-Diethoxy-2,2-difluorobutyl)isoindoline-1,3-dione (**17**).* A mixture of 4,4-diethoxy-2,2-difluorobutyl-1-amine (**16**) (18 g, 91 mmol), *N*-ethyl-*N*,*N*-di(isopropyl)amine (13.7 g, 106 mmol), and phthalic anhydride (15.13 g, 102 mmol) was refluxed in toluene (500 mL) with Dean−Stark apparatus for ∼3 h until complete water release. Then the solution was concentrated under reduced pressure, and the corresponding product **17** was purified by crystallization or by column chromatography (hexane/EtOAc, 2:1, R_f = 0.60). Yield: 27.4 g (92%). Colorless solid, mp 85−87 °C. IR (KBr): ν = 1041, 1074, 1106, 1128, 1192, 1335, 1383, 1723, 1778, 2921, 2980, 3022, 3485 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.85−7.80 (m, 2H), 7.72−7.66 (m, 2H), 4.80 (t, 1H, J = 5.5 Hz), 4.12 (t, 2H, J = 15.4 Hz), 3.74−3.45 (m, 4H), 2.30 (td, 2H, J = 15.4, 5.5 Hz), 1.19 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.1, 133.8, 131.4, 123.1, 119.2 (t, J = 245.2 Hz), 97.7 (t, J = 6.8 Hz), 61.7, 41.6 (t, J = 26.5 Hz), 39.8 (t, J = 26.5 Hz), 14.7 ppm. ^{19}F NMR (367 MHz, $CDCl_3$): δ = −99.98 (qwint, J = 15.4 Hz) ppm. ESI-MS (m/z): calcd for $C_{16}H_{19}F_2NNaO_4^+$ (350.1174). Found: 350.1179. Anal. calcd for: $C_{16}H_{19}F_2NO_4$: C, 58.71; H, 5.85; N, 4.28. Found: C, 58.90; H, 5.73; N, 4.51.

*Ethyl 4-(1,3-Dioxoisoindolin-2-yl)-3,3-difluorobutanoate (**18**).* A stirred mixture of compound **17** (2.7 g, 8.3 mmol), MCPBA (tech. 80%, 1.9 g, 11 mmol), and conc. H_2SO_4 (4−5 drops) in CH_2Cl_2 (20 mL) was refluxed overnight. After cooling the precipitate formed was filtered and washed with cold CH_2Cl_2 (3 × 20 mL). The filtrate was washed with 20% $NaHSO_3$ (10 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (10 mL). The solvent was removed, and the residue was purified by column chromatography (hexane/EtOAc, 3:1, R_f = 0.45). Yield: 0.99 g (44%). Colorless solid, mp 91−93 °C. ^1H NMR (500

DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258−12264

MHz, $CDCl_3$): δ = 7.88 (m, 2H), 7.75 (m, 2H), 4.32 (t, 2H, J = 13.6 Hz), 4.23 (q, 2H, J = 7.1 Hz), 3.02 (t, 2H, J = 14.7 Hz), 1.30 (d, 3H, J = 7.2 Hz) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.5, 166.3 (t, J = 7.5 Hz), 134.3, 131.7, 123.7, 118.9 (t, J = 246.7 Hz), 61.4, 41.3 (t, J = 29.7 Hz), 40.6 (t, J = 26.8 Hz), 14.0 ppm. ^{19}F NMR (564 MHz, $CDCl_3$): δ = −98.17 to −98.29 (tt, J_1 = 14.7, J_2 = 13.6 Hz) ppm. ESI-MS (m/z): calcd for $C_{14}H_{13}F_2NNaO_4^+$ (320.0705): Found: 320.0700. Anal. calcd for: $C_{14}H_{13}F_2NO_4$: C, 56.57; H, 4.41; N, 4.71. Found: C, 56.39; H, 4.59; N, 4.90.

*4-Amino-3,3-difluorobutanoic acid (**9**).* (A) By hydrolysis of compound **18**: Compound **18** (0.90 g, 3 mmol) in 6 N HCl (10 mL) was stirred under reflux for 8 h. The mixture was cooled and extracted with EtOAc (3 × 30 mL) to remove phthalic acid formed. The aqueous solution was concentrated under reduced pressure. The residue was dissolved in water, and the amino acid was isolated by ion-exchange chromatography. The obtained ammonia solutions were concentrated, dissolved in water, and concentrated in vacuo again in order to remove traces of ammonia. Yield: 0.34 g (81%). (B) "One-pot" synthesis starting from compound **17**. A stirred mixture of **17** (27 g, 83 mmol), MCPBA (tech. 80%, 19 g, 110 mmol), and conc. H_2SO_4 (4−5 drops) in CH_2Cl_2 (200 mL) was refluxed overnight. The residue was concentrated under reduced pressure, mixed with 6 N HCl (100 mL), and stirred under reflux for 8 h. The mixture was cooled and extracted with EtOAc (3 × 200 mL) to remove phthalic acid and *meta*-chlorobenzoic acid. The water solution was concentrated under reduced pressure. The residue was dissolved in water, and the corresponding amino acid was isolated by ion-exchange chromatography. The obtained ammonia solutions were concentrated, dissolved in water, and concentrated under reduced pressure again in order to remove traces of ammonia. Yield: 9.92 g (86%). Colorless solid, mp 160 °C (with decomp.). IR (KBr): ν = 1031, 1121, 1186, 1219, 1289, 1392, 1426, 1603, 1658, 3027, 2964 cm^{-1}. ^{1}H NMR (500 MHz, D_2O): δ = 3.52 (t, 2H, J = 15.1 Hz), 2.86 (t, 2H, J = 16.6 Hz) ppm. ^{13}C NMR (126 MHz, D_2O): δ = 173.4 (t, J = 6.5 Hz), 119.0 (t, J = 243.0 Hz), 43.3 (t, J = 23.2 Hz), 42.1 (t, J = 26.0 Hz) ppm. ^{19}F NMR (376 MHz, D_2O): δ = −101.92 (tt, J_1 = 16.6 Hz, J_2 = 15.1 Hz) ppm. ESI-MS (m/z): calcd for $C_4H_7F_2NNaO_2^+$ (162.0337). Found: 162.0334. Anal. calcd for: $C_4H_7F_2NO_2$: C, 34.54; H, 5.07; N, 10.07. Found: C, 34.67; H, 4.93; N, 10.26.

X-ray Diffraction. Data sets were collected with a standard diffractometer. Programs used: data collection, COLLECT (R. W. W. Hooft, 2008, Delft, The Netherlands); data reduction Denzo-SMN;[33] absorption correction, Denzo;[34] structure solution SHELXS-97;[35] structure refinement SHELXL-97.[36] R-values are given for observed reflections, and wR^2 values are given for all reflections.

*X-ray Crystal Structure Analysis of 3,3-Difluoro-GABA (**9**) × HCl.* Formula $C_4H_8ClF_2NO_2$, M = 175.56, colorless crystal, 0.15 × 0.15 × 0.10 mm, a = 4.7744(1), b = 16.1844(4), c = 8.8835(2) Å, β = 96.455(1)°, V = 682.1(0) Å^3, ρ_{calc} = 1.710 g cm^{-3}, μ = 0.538 mm^{-1}, empirical absorption correction (0.923 ≤ T ≤ 0.948), Z = 4, monoclinic, space group $P2_1/c$ (no. 14), λ = 0.71073 Å, T = 223(2) K, ω and φ scans, 4152 reflections collected ($\pm h$, $\pm k$, $\pm l$), 1661 independent (R_{int} = 0.021) and 1552 observed reflections [$I > 2\sigma(I)$], 107 refined parameters, R = 0.028, wR^2 = 0.073, max. (min.) residual electron density 0.36 (−0.21) e·Å^{-3}. The hydrogen at N1 and O2 atoms were refined freely; others were calculated and refined as riding atoms.

pK_a Measurements. The p*K*a values of the compounds were determined by potentiometric titration, whereby the compounds were first dissolved at 4 mM in 10 mL of aqueous 0.15 M NaCl, acidified by addition of 1.5 mL 1 M HCl, and slowly titrated with 0.2 M sodium hydroxide while measuring the equilibrium pH of the solution. Titration and pH data collection were done automatically at the speed of 8.5 mL of 0.2 M NaOH/h using a syringe driver and Bluetooth-connected pH meter. The titration curves were analyzed in Microsoft Excel and Prism 5.01 (GraphPad) to calculate pK_a values. Ondansetrone, tris(hydroxymethyl)aminomethane, and glycine were used as reference pK_a compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02171.

X-ray crystallographic data of compound **9** (CIF)
Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: vanya.ko@mail.ru.
*E-mail: haufe@uni-muenster.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the Deutsche Forschungsgemeinschaft (Ha 2145/9-1; AOBJ: 560896). We also thank Enamine Ltd. (Kiev) for technical and financial support and especially Dr. S. Zozulya and R. Morev (Bienta, Enamine Biology Services) for measuring the pK_a values. We express our appreciation to Dr. S. I. Vdovenko and O. A. Fedorenko (Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences, Ukraine) for measuring the IR spectra.

■ REFERENCES

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.: Hoboken, NJ, 2008. (f) *Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Tressaud, A., Haufe, G., Eds.; Elsevier: Amsterdam, 2008; pp 553−778. (g) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, U.K., 2009; pp 3−198. (h) *Fluorine in Pharmaceutical and Medicinal Chemistry. From Biophysical Aspects to Clinical Application*; Gouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012; pp 139−331.

(2) (a) Dolbier, W. R., Jr. In *Organofluorine Chemistry. Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer-Verlag: Berlin, Germany, 1997; pp 97−163. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH Verlag GmbH & Co: Weinheim, Germany, 2013; pp 107−167. (c) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V. *Chem. Rev.* **2015**, *115*, 973.

(3) Tarrant, P.; Stump, E. C. *J. Org. Chem.* **1964**, *29*, 1198.

(4) (a) Molines, H.; Wakselman, C. *J. Fluorine Chem.* **1987**, *37*, 183. (b) Leroy, J.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1987**, *52*, 290.

(5) Peng, S.; Qing, F.-L.; Li, Y.-Q.; Hu, C.-M. *J. Org. Chem.* **2000**, *65*, 694.

(6) (a) Huang, W.-Y.; Xie, Y.; Lu, L. *Chin. J. Chem.* **1991**, *9*, 167. (b) Huang, W.-Y. *J. Fluorine Chem.* **1992**, *58*, 1. (c) Wu, F.-H.; Huang, B.-N.; Lu, L.; Huang, W.-Y. *J. Fluorine Chem.* **1996**, *80*, 91.

(7) (a) Guan, H.-P.; Luo, B.-H.; Wang, Q.-F.; Hu, C.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 279. (b) Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 4649. (c) Wang, Y.; Zhu, S. *Tetrahedron Lett.* **2001**, *42*, 5741. (d) Sène, A.; Diab, S.; Hienzsch, A.; Cahard, D.; Lequeux, T. *Synlett* **2009**, *2009*, 981.

(8) (a) Tews, S.; Miethchen, R.; Reinke, H. *Synthesis* **2003**, 707. (b) Linclau, B.; Vinader, V.; Boydell, A. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5677. (c) Miethchen, R.; Tews, S.; Shaw, A. K.; Röttger, S.; Reinke, H. *J. Carbohydr. Chem.* **2004**, *23*, 147. (d) Wegert, A.; Hein, M.;

DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258−12264

Reinke, H.; Hoffman, N.; Miethchen, R. *Carbohydr. Res.* **2006**, *341*, 2641. (e) Valdersnes, S.; Sydnes, L. K. *Eur. J. Org. Chem.* **2009**, *2009*, 5816.
(9) (a) Sasaoka, S.; Uno, M.; Joh, T.; Imazaki, H.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1991**, 86. (b) Uneyama, K.; Kanai, M. *Tetrahedron Lett.* **1991**, *32*, 7425. (c) Wakselman, C.; Molines, H.; Tordeux, M. *J. Fluorine Chem.* **2000**, *102*, 211. (d) Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. *J. Org. Chem.* **2007**, *72*, 5824. (e) Dudziński, P.; Matsnev, A. V.; Thrasher, J. S.; Haufe, G. *Org. Lett.* **2015**, *17*, 1078.
(10) For recent examples of addition reactions of methyl/ethyl difluoroacetate moieties across double bonds see: (a) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780. (b) Ohtsuka, Y.; Yamakawa, T. *Tetrahedron* **2011**, *67*, 2323. (c) Colombel, S.; Sanselme, M.; Leclerc, E.; Quirion, J. C.; Pannecoucke, X. *Chem. - Eur. J.* **2011**, *17*, 5238. (d) Wang, X.; Fang, X.; Xiao, H.; Yin, Y.; Xia, H.; Wu, F. *J. Fluorine Chem.* **2012**, *133*, 178. (e) Moens, M.; Verniest, G.; De Schrijver, M.; ten Holte, P.; Thuring, J.-W.; Deroose, F.; De Kimpe, N. *Tetrahedron* **2012**, *68*, 9284. (f) Lin, Q.; Chu, L.; Qing, F.-L. *Chin. J. Chem.* **2013**, *31*, 885. (g) Sun, X.; Yu, S. *Org. Lett.* **2014**, *16*, 2938. (h) Xiao, Y.-L; Guo, W.-H.; He, G.-Z.; Pan, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 9909 and references cited therein.. (i) Belhomme, M.-C.; Bayle, A.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2015**, *2015*, 1719 and references cited therein.. (j) Shao, C.; Shi, G.; Zhang, Y.; Pan, S.; Guan, X. *Org. Lett.* **2015**, *17*, 2652. (k) Thomson, C. S.; Dolbier, W. R., Jr. *J. Fluorine Chem.* **2015**, *178*, 327. (l) Yu, C.; Iqbal, N.; Park, S.; Cho, E. J. *Chem. Commun.* **2014**, *50*, 12884.
(11) (a) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 5125. (b) Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zagatti, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252. (c) Julià, L.; Bosch, M. P.; Rodriguez, S.; Guerrero, A. *J. Org. Chem.* **2000**, *65*, 5098. (d) Murakami, S.; Ishii, H.; Fuchigami, T. *J. Fluorine Chem.* **2004**, *125*, 609. (e) Xiao, F.; Wu, F.; Shen, Y.; Zhou, L. *J. Fluorine Chem.* **2005**, *126*, 63. (f) Ghattas, W.; Hess, C. R.; Iacazio, G.; Hardré, R.; Klinman, J. P.; Réglier, M. *J. Org. Chem.* **2006**, *71*, 8618. (g) Murakami, S.; Ishii, H.; Tajima, T.; Fuchigami, T. *Tetrahedron* **2006**, *62*, 3761. (h) Moreno, B.; Quehen, C.; Rose-Hélène, M.; Leclerc, E.; Quirion, J.-C. *Org. Lett.* **2007**, *9*, 2477. (i) Yang, X.; Yuan, W.; Gu, S.; Yang, X.; Xiao, F.; Shen, Q.; Wu, F. *J. Fluorine Chem.* **2007**, *128*, 540. (j) Leung, L.; Linclau, B. *J. Fluorine Chem.* **2008**, *129*, 986. (k) De Schutter, C.; Pfund, E.; Lequeux, T. *Tetrahedron* **2013**, *69*, 5920.
(12) In order to avoid peresterification the reaction with 2-methoxypropene was carried out with methyl 2-bromo-2,2-difluoroacetate in methanol.
(13) Compound **4g** is a mixture of two diastereomers (1:3, NMR). The most characteristic signals are in ^{19}F NMR: δ = −107.24 (dd, 1F, J_1 = 264.3 Hz, J_2 = 12.8 Hz, F_a of CF_2, diastereomer 1, 1F), −108.54 (dd, 1F, J_1 = 264.3 Hz, J_2 = 10.9 Hz, F_b of CF_2, diastereomer 1), −109.90 (dd, 1F, J_1 = 264.7 Hz, J_2 = 3.3 Hz, F_a of CF_2, diastereomer 2), −120.37 (dd, 1F, J_1 = 264.7 Hz, J_2 = 25.6 Hz, F_b of CF_2, diastereomer 2), and in mass-spectrometry (ESI-MS (m/z): calcd for $C_{10}H_{16}F_2NaO_4^+$: 261.0909. Found: 261.0907).
(14) Previously Lequeux et al. carried out the reaction under similar conditions but starting from diisopropyl (difluoroiodomethyl) phosphonate, see ref 7d.
(15) Previously a similar reaction was carried out by Hu et al. starting from [(difluoroiodomethyl)sulfonyl]benzene under different conditions, see ref 9d.
(16) Watanabe, M.; Maemura, K.; Kanbara, K.; Tamayama, T.; Hayasaki, H. *International Reviews of Cytology*; Jeon, K. W., Ed.; Academic Press: London, 2002; Vol. *213*, pp 1−47.
(17) Froestl, W. *Future Med. Chem.* **2011**, *3*, 163.
(18) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 772.
(19) Silverman, R. B.; Levy, M. A. *J. Biol. Chem.* **1981**, *256*, 11565.
(20) (a) Deniau, G.; Slawin, A. M. Z.; Lebl, T.; Chorki, F.; Issberner, J. P.; van Mourik, T.; Heygate, J. M.; Lambert, J. J.; Etherington, L.-A.; Sillar, K. T.; O'Hagan, D. *ChemBioChem* **2007**, *8*, 2265. (b) Yamamoto, I.; Deniau, G. P.; Gavande, N.; Chebib, M.; Johnston, G. A.R.; O'Hagan, D. *Chem. Commun.* **2011**, *47*, 7956. (c) O'Hagan, D. *Future Med. Chem.* **2011**, *3*, 189.
(21) (a) Wang, Z.; Hunter, L. *J. Fluorine Chem.* **2012**, *143*, 143. (b) Yamamoto, I.; Jordan, M. J. T.; Gavande, N.; Doddareddy, M. R.; Chebib, M.; Hunter, L. *Chem. Commun.* **2012**, *48*, 829. (c) Hu, X.-G.; Thomas, D. S.; Griffith, R.; Hunter, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6176. (d) Hunter, L.; Butler, S.; Ludbrook, S. B. *Org. Biomol. Chem.* **2012**, *10*, 8911.
(22) Okano, T.; Takakura, N.; Nakano, Y.; Okajima, A.; Eguchi, S. *Tetrahedron* **1995**, *51*, 1903.
(23) Hale, J. J.; Doherty, G.; Toth, L.; Li, Z.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M.; Milligan, J.; Shei, G.-J.; Chrebet, G.; Bergstrom, J.; Card, D.; Rosenb, H.; Mandala, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3495.
(24) (a) Yamazaki, T.; Ohnogi, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1990**, *1*, 215. (b) Shaitanova, E. N.; Gerus, I. I.; Belik, M. Y.; Kukhar, V. P. *Tetrahedron: Asymmetry* **2007**, *18*, 192. (c) Gerus, I. I.; Mironets, R. V.; Shaitanova, E. N.; Kukhar, V. P. *J. Fluorine Chem.* **2010**, *131*, 224. (d) Wen, L.; Yin, L.; Shen, Q.; Lu, L. *ACS Catal.* **2013**, *3*, 502. (e) Kwiatkowski, P.; Cholewiak, A.; Kasztelan, A. *Org. Lett.* **2014**, *16*, 5930.
(25) For recent similar examples of HF-elimination see: (a) Csuk, R.; Prell, E. *Tetrahedron* **2010**, *66*, 1313. (b) Hajduch, J.; Duda, Z.; Beran, J.; Kvíčala, J.; Paleta, O. *J. Fluorine Chem.* **2014**, *162*, 45. (c) Lecea, M.; Grassin, A.; Ferreiro-Mederos, L.; Choppin, S.; Urbano, A.; Carreño, M. C.; Colobert, F. *Eur. J. Org. Chem.* **2013**, *2013*, 4486. (d) Nihei, T.; Yokotani, S.; Ishihara, T.; Konno, T. *Chem. Commun.* **2014**, *50*, 1543.
(26) Cohen, O.; Rozen, S. *Tetrahedron* **2008**, *64*, 5362.
(27) CCDC-1411813 (compound **9** × HCl) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(28) (a) Bondi, A. *J. Phys. Chem.* **1961**, *68*, 441. (b) Batsanov, S. S. *Inorg. Mater.* **2001**, *37*, 871.
(29) (a) Lankin, D. C.; Chandrakumar, N. S.; Rao, N. S.; Spangler, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 3356. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 38. (d) Hu, X.-G.; Hunter, L. *Beilstein J. Org. Chem.* **2013**, *9*, 2696.
(30) Brandariz, I.; Fiol, S.; Herrero, R.; Vilarino, T.; de Vicente, M. S. *J. Chem. Eng. Data* **1993**, *38*, 531.
(31) Morgenthaler, M.; Schweizer, E.; Hoffmann-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Müller, K. *ChemMedChem* **2007**, *2*, 1100.
(32) Weiss, J.; Weiss, T. *Handbook of Ion Chromatography*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004.
(33) Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307.
(34) Otwinowski, Z.; Borek, D.; Majewski, W.; Minor, W. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2003**, *59*, 228.
(35) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1990**, *46*, 467.
(36) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.

DOI: 10.1021/acs.joc.5b02171
J. Org. Chem. 2015, 80, 12258−12264