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(Het)aryl difluoromethyl-substituted β-alkoxyenones: synthesis and heterocyclizations

Maksym Ya. Bugera,[a,b] Dr. Karen V. Tarasenko,[b,c] Dr. Ivan S. Kondratov,*[a,b] Dr. Igor I. Gerus,[b] Bohdan V. Vashchenko,[a,d] Viktor E. Ivasyshyn,[b]† Dr. Oleksandr O. Grygorenko*[a,d]

Dedicated to Professor Dr. Günter Haufe on the occasion of his 70th birthday

Abstract: An efficient approach to the preparation of β-alkoxyenones bearing (het)aryl difluoromethyl substituents is described. The method included acylation of acyclic or cyclic vinyl ethers with (het)aryl difluoroacetyl chlorides. The method worked well for most substrates, except aryl-substituted derivatives bearing electron-donating groups in *o*- or *p*-positions, and heteroaromatic compounds bearing sufficiently basic nitrogen atom. Synthetic utility of (het)aryl difluoromethyl-substituted β-alkoxyenones as *CCC* bis-electrophiles was demonstrated by heterocyclizations with common 1,2- and 1,3-bis-nucleophiles leading to compounds with (het)aryl–CF_2–(het)aryl motif, in particular (het)aryl difluoromethyl-substituted pyrazoles, isoxazoles, and pyrimidines – promising chemotypes for drug discovery.

Introduction

Introducing *gem*-difluoromethylene unit into organic compounds is an important design approach in medicinal,[1–5] agricultural,[6,7] and synthetic,[8–17] chemistry in view of improving physicochemical properties of derivatives.[18–22] The CF_2 moiety was considered as a bioisosteric replacement of methylene, carbonyl, or ether groups with improved metabolic stability.[23–25] Incorporation of the difluoromethylene linker between (hetero)aromatic rings improved activity and/or pharmacokinetic properties of the compounds as compared to their non-fluorinated counterparts.[26–29] In addition to that, the CF_2 fragment can be found in several marketed drugs including Gemcitabine, Ledipasvir, Lubiprostone, and Tafluprost (Figure 1).[3] Although synthesis of CF_2-substituted derivatives attracted considerable interest in recent years, methods for preparation of difluorodi(het)arylmethanes (i.e. compounds with CF_2-linker between two (het)aryl rings) are scarce in the literature. Most known approaches rely on *gem*-difluorination reactions, *i.e.* deoxofluorination of diarylketones (Scheme 1, **A**),[3,26–33] fluorodesulfurization of thioketones (**B**)[33–35] or thioketals (**C**).[36–42] Alternative strategy implies the use of building blocks already containing the (het)aryl difluoromethyl moiety; it is represented by [4+2] or [3+2] cycloadditions of 4,4-difluorobutynoates (**D**).[43]

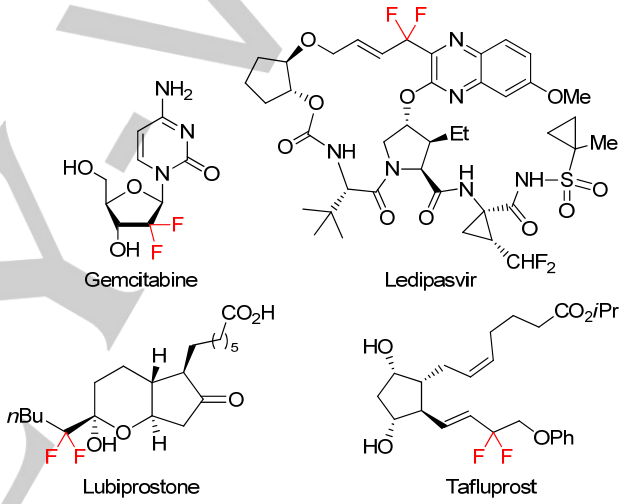
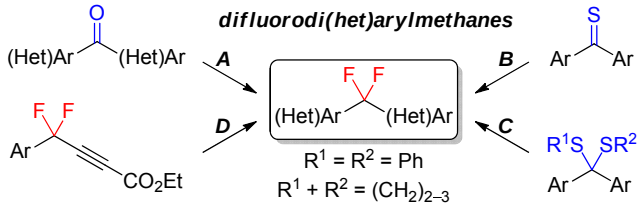
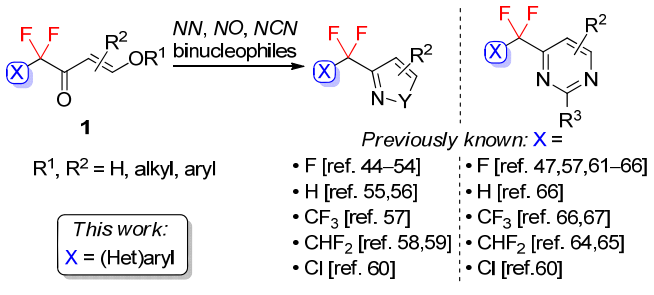


Figure 1. Marketed drugs bearing *gem*-difluoromethylene unit



Scheme 1. Known syntheses of difluorodi(het)arylmethanes



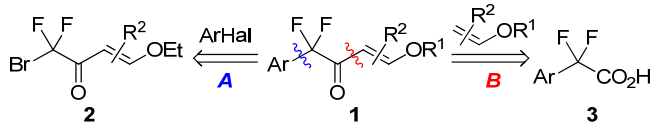
Scheme 2. β-Alkoxyenones **1** in the synthesis of fluorinated heterocycles

[a] M. Ya. Bugera, Dr. I. S. Kondratov, B. V. Vashchenko, Dr. O. O. Grygorenko
Enamine Ltd. (www.enamine.net),
Chervonotkatska Street 78, Kyiv 02094, Ukraine
E-mail: kondratov@mail.enamine.net (I.S.K.)
[b] M. Ya. Bugera, Dr. K. V. Tarasenko, Dr. I. S. Kondratov, Dr. I. I. Gerus, V. E. Ivasyshyn
V.P. Kukhar Institute of Bioorganic Chemistry & Petrochemistry, NAS of Ukraine, Murmanska Street 1, Kyiv 02660, Ukraine
[c] Dr. K. V. Tarasenko
Chemspace, Ilukstes iela 38-5, Riga, LV-1082, Latvia
[d] B. V. Vashchenko, Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua (O.O.G.)
† Current address: Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

In this work, we considered another approach to difluorodi(het)arylmethanes, which also relied on the use of (het)aryl difluoro methyl-substituted building blocks, namely, β-alkoxyenones of the type **1** (X = (het)aryl, Scheme 2). It should be noted that heterocyclizations of various fluorinated β-alkoxyenones **1** (X = H, F, Cl, CF_3, CHF_2) were reported in recent publications describing synthesis of fluoroalkyl-substituted pyrazoles,[44–60] isoxazoles,[54] and pyrimidines,[47,57,61–67] as well as other heterocycles.[31,68–73] However, no examples of (het)aryl difluoromethyl -substituted enones of the type **1** were reported to date.

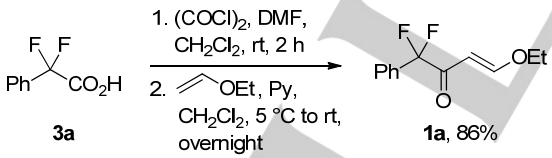
Results and Discussion

Two synthetic approaches to the title compounds were evaluated in this work, namely, sp^2–sp^3 coupling of (het)aryl halides with bromodifluoromethyl-substituted enones (*e.g.* **2**), as well as acylation of vinyl ethers with activated derivatives of difluoro(het)arylacetic acids **3** (Scheme 3).



Scheme 3. Retrosynthetic analysis of enones **1**

First of all, reaction of compound **2** with phenyl iodide was performed under conditions described previously for ethyl bromodifluoroacetate (Cu, DMSO, 60 °C, 12 h).[74–76] Unfortunately, complete decomposition of the starting enone was observed, and no traces of target product **1a** were detected in the reaction mixture. Meanwhile, acylation of ethoxyethene with acyl chloride obtained *in situ* from phenyl difluoroacetic acid **3a** proceeded smoothly in the presence of pyridine in CH_2Cl_2[45] and resulted in in 86% yield of **1a** (Scheme 4).

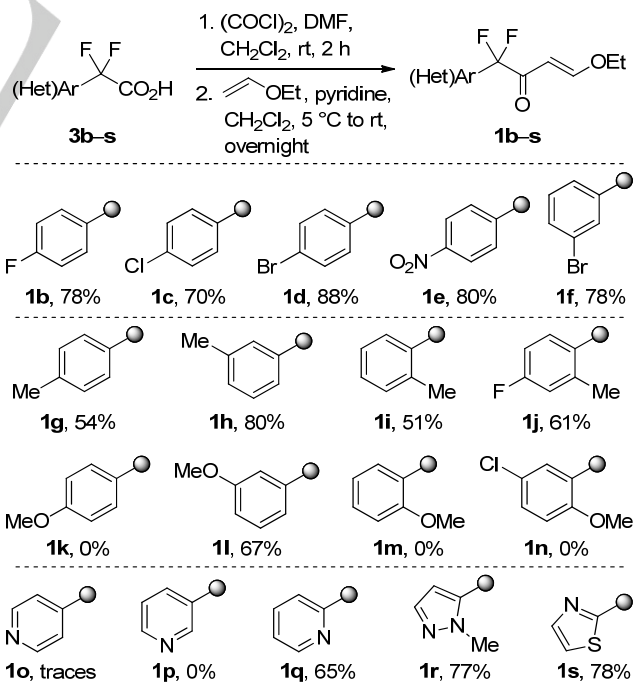


Scheme 4. Synthesis of enone **1a**

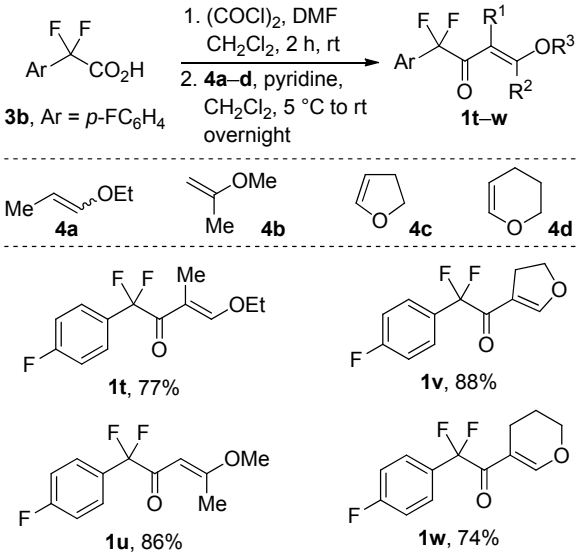
In order to study the scope and limitation of the method we extended the aforementioned approach to a series of aryldifluoroacetic acids bearing electron-withdrawing (**3b–f**) and electron-donating substituents (**3g–n**), as well as heteroaromatic counterparts, *i.e.* derivatives of pyridine (**1o–q**), pyrazole (**1r**), and thiazole (**1s**) (Scheme 5). In the case of electron-poor aryl-substituted compounds, the procedure worked well, and the corresponding enones **1b–f** were obtained in good yields (70–88%). On the contrary, deactivating effect was apparent for the substrates with electron-donating substituents in *o*- and *p*-positions of the aryl group. Thus, in the case of substrates **3g** and **3i** bearing *p*- and *o*-tolyl substituents, the yield of enones **1g** and **1i** was moderate (54% and 51%, respectively), whereas with *m*-tolyl-substituted derivative **3h**, the reaction has significantly better outcome (80% yield). This effect could be somewhat countervailed by incorporation of the fluorine atom: reaction with **3j** gave the target product **1j** in 61% yield. In the case of stronger electron-donating groups (*i.e.* methoxyl), the reaction did not take place in the case of *o*- and *p*-isomers (substrates **3k** and **3m**, respectively); even introducing the halogen atom (substrate **3n**) did not overcome this effect. Meanwhile, *m*-methoxy-substituted carboxylic acid **3l** gave corresponding enone **1l** in 67% yield. The observed deactivating effect of electron-donating groups is presumably related to diminished electrophilicity of the intermediate acyl chlorides.

The method was also suitable for heterocylic derivatives, *i.e.* 2-pyridyl-, 1-methylpyrazol-5-yl- and thiazol-2-yldifluoroacetic acids (**3q–s**). The corresponding hetaryl-substituted β-ethoxyenones **1q–s** were obtained in 63–78% yield. Unexpectedly, the reaction was not successful for the case of 3- and 4-pyridyl counterparts **3o** and **3p**. We address this to limited stability of the corresponding acyl halides, which is probably defined by the nitrogen atom basicity.

The method was successfully extended to other vinyl ethers, e.g. 1-ethoxyprop-1-ene (**4a**), 2-methoxypropene (**4b**), 2,3-dihydrofuran (**4c**), and 3,4-dihydro-*2H*-pyran (**4d**). Likewise to the case of ethoxyethene, the reaction with model *p*-fluorophenyl difluoroacetic acid **3b** led to the target enones **1t–w** in 74–88% yield (Scheme 6).



Scheme 5. Synthesis of enones **1b–s**



Scheme 6. Synthesis of enones **1t–w**

Stereochemistry of the products **1** was confirmed by $^{1}H - {}^{1}H$ NOE and $^{1}H - {}^{19}F$ HOESY experiments (Figure 2). In particular, considerable nuclear Overhouser effect was observed for the CH_2 unit protons upon irradiation of H-3 or Me-3 moieties of the compounds **1b**, **1t**, and **1u.** In addition to that, significant heteronuclear NOE correlations between the H-4 and fluorine atoms of the CF_2 group were found for all these products. Finally, values of vicinal coupling constants for the protons attached to the double bond were characteristic for the *trans* configuration (^{3}J = 12.3 Hz for all derivatives **1a–s**).

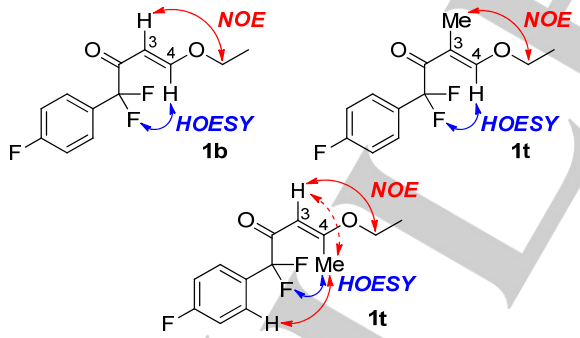
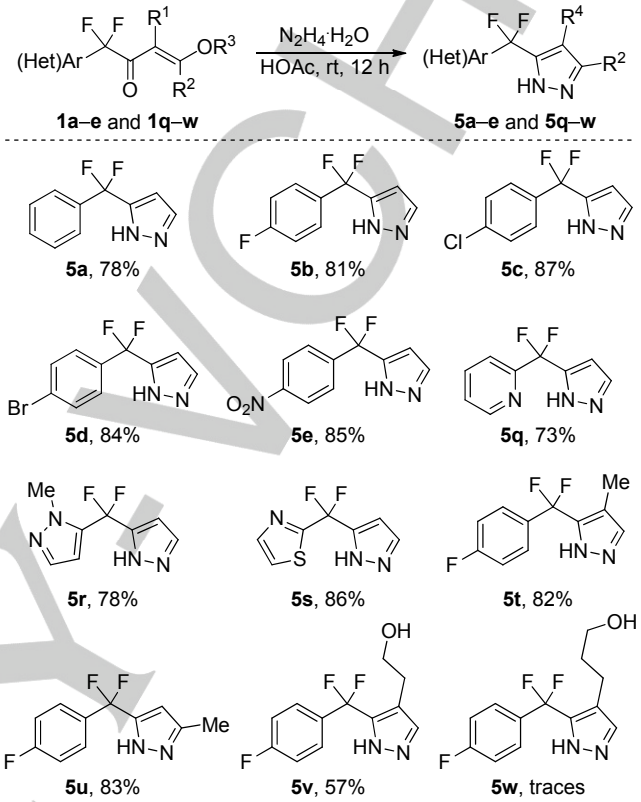
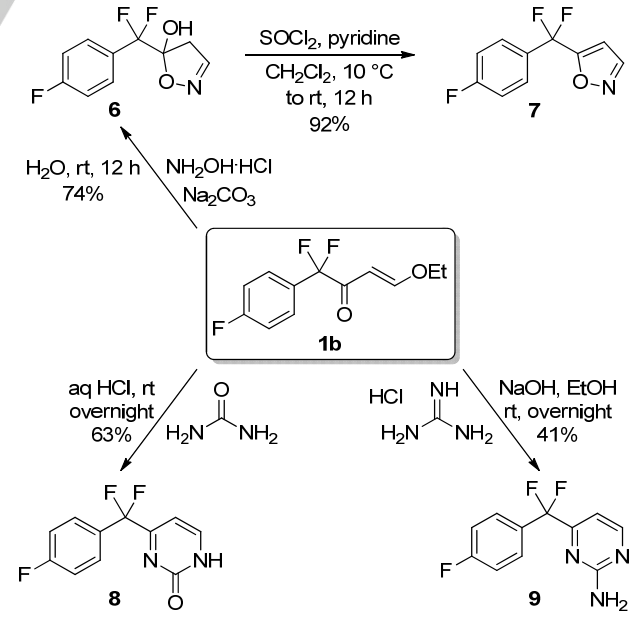


Figure 2. NOE experiments with compounds **1b**, **1t**, and **1u**

Synthetic utility of enones **1** as the *CCC* bis-electrophiles was demonstrated by condensation with common 1,2- and 1,3-binucleophiles. In particular, reaction of enones **1a–e** and **1q–w** with hydrazine hydrate in AcOH proceeded smoothly at rt and led to corresponding pyrazoles **5a–e** and **5q–u** in 73–87% yield (Scheme 7). Under these conditions, reaction of **1v** was accompanied by the dihydrofuran ring opening leading to pyrazole **5v** (57% yield). Notably, analogous transformation of **1w** proceeded slowly at rt, so that only traces of the product **5w** were detected after 96 h, while a complex mixture was formed when the reaction was performed at 60 °C.



Scheme 7. Synthesis of pyrazoles **5a–e** and **5q–w**



Scheme 8. Synthesis of heterocycles **7–9**

Heterocyclization of enone **1b** with another 1,2-bis-nucleophile, $NH_2OH,\cdot$in H_2O at rt led to isoxazolinol **6** in 74% yield, which did not underwent spontaneous dehydration (Scheme 8). Treatment of **6** with $SOCl_2$ and pyridine in CH_2Cl_2 resulted in the target isoxazole **7** in excellent yield (92%).

Finally, *NCN* bis-nucleophiles were studied in reaction with enone **1b** (Scheme 8). In particular, condensation of **1b** with urea in aq HCl gave pyrimidin-2(1*H*)-one **8** (63% yield), whereas reaction with guanidine hydrochloride afforded the corresponding 2-aminopyrimidine **9** in 41% yield.

Conclusions

Acylation of vinyl ethers with acyl chlorides generated in situ from difluoro(het)arylacetic acids was found to be an efficient method for the preparation of (het)aryl difluoromethyl-substituted β-alkoxyenones. In the case of ethoxyethene, the method worked well for the parent difluorophenylacetic acid, as well as its derivatives bearing electron-withdrawing groups at the aromatic ring. Substrates with donor substituents (*e.g.* methyl or methoxy) at the aryl moiety were less efficient; for the *o*- and *p*-methoxyphenyl-substituted derivatives, the method did not work at all. This effect might be addressed to diminished reactivity of the corresponding acyl chloride intermediates towards electrophilic attack at the vinyl ether.

Further extension of the substrate scope included difluoro-hetarylacetic acids, namely, 2-pyridyl-, 2-thiazolyl-, and 1-methyl-5-pyrazolyl-substituted derivatives. The method did not work for the 3- and 4-pyridyl counterparts having a slightly more basic nitrogen atom, possibly due to low stability of the corresponding acyl chlorides. Moreover, methyl-substituted and cyclic vinyl ethers could be introduced into the reaction successfully.

The target (het)aryl difluoromethyl-substituted β-alkoxyenones were obtained in 51–88% yield. They appeared to have sufficient reactivity as *CCC* bis-electrophiles towards hydrazine, hydroxylamine, urea, and guanidine (except dihydropyrane derivative), providing the corresponding fluorinated pyrazoles, isoxazoles, and pyrimidines in 41–92% yield. Thus, the title (het)aryl difluoromethyl-substituted β-alkoxyenones are convenient building blocks for the construction of various frameworks with (het)aryl-CF_2-(het)aryl motif – promising chemotypes for drug discovery.

Experimental Section

General. The solvents were purified according to the standard procedures.[77] Compounds **3a–t** were provided by Enamine Ltd. All other starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a 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. Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

General procedure for the preparation of enones 1a–x.

To a stirred solution of the corresponding difluoro(hetero)aryl acetic acid **3a–t** (5.00 mmol) in CH_2Cl_2 (10 mL), oxalyl chloride (1.26 g, 0.858 mL, 10.0 mmol) and DMF (1 drop) were added at rt. The solution was stirred at rt for 2 h until gas evolution ceased. Then the solvent was evaporated in *vacuo* to give crude acyl chloride, which was dissolved in CH_2Cl_2 (10 mL) and added dropwise to a solution of ethoxyethene (541 mg, 0.713 mL, 7.50 mmol) or the corresponding enol ether **4a–d** (7.50 mmol) and pyridine (791 mg, 0.805 mL, 10.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The solution was stirred at rt overnight and then diluted with H_2O (30 mL). The organic layer was separated, washed with H_2O (2×20 mL), saturated aq $NaHCO_3$ (2×20 mL), and brine (20 mL), dried over Na_2SO_4 and evaporated in *vacuo*. If necessary, the product was purified by flash chromatography on silica gel using hexanes as eluent.

(*E*)-4-Ethoxy-1,1-difluoro-1-phenylbut-3-en-2-one (1a).[68] Yield 973 mg (86%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 12.3 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.49 – 7.40 (m, 3H), 5.96 (d, *J* = 12.3 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.6 (t, *J* = 31.1 Hz), 166.4, 133.2 (t, *J* = 25.8 Hz), 130.7, 128.7, 125.6 (t, *J* = 6.2 Hz), 116.1 (t, *J* = 253 Hz), 98.9, 68.5, 14.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ –106.7. GC/MS (EI): *m/z* = 127 $[C_6H_5CF_2]^+$, 207 $[M–F]^+$. Anal. Calcd. for $C_{12}H_{12}F_2O_2$: C 63.71; H 5.35. Found: C 64.07; H 5.11.

(*E*)-4-Ethoxy-1,1-difluoro-1-(4-fluorophenyl)but-3-en-2-one (1b). Yield 952 mg (78%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 12.3 Hz, 1H), 7.55 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.11 (t, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 12.3 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.5 (t, *J* = 31.4 Hz), 166.7, 164.2 (d, *J* = 250 Hz), 129.2 (t, *J* = 25.1 Hz), 128.0 (dt, *J* = 8.7, 6.3 Hz), 115.9 (d, *J* = 22.2 Hz), 115.8 (t, *J* = 254 Hz), 98.6, 68.7, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.6, –110.2 (t, *J* = 2.5 Hz). GC/MS (EI): *m/z* = 145 $[p\text{-}FC_6H_4CF_2]^+$, 225 $[M–F]^+$. Anal. Calcd. for $C_{12}H_{11}F_3O_2$: C 59.02; H 4.54. Found: C 58.83; H 4.33.

(*E*)-1-(4-Chlorophenyl)-4-ethoxy-1,1-difluorobut-3-en-2-one (1c). Yield 912 mg (70%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 12.3 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 5.95 (d, *J* = 12.3 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.2 (t, *J* = 31.0 Hz), 166.8, 137.1, 131.7 (t, *J* = 26.3 Hz), 129.0, 127.2 (t, *J* = 6.1 Hz), 115.7 (t, *J* = 254 Hz), 98.6, 68.7, 14.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ –106.4. GC/MS (EI): *m/z* = 161/163 $[p\text{-}ClC_6H_4CF_2]^+$, 241/243 $[M–F]^+$. Anal. Calcd. for $C_{12}H_{11}ClF_2O_2$: C 55.30; H 4.25; Cl 13.60. Found: C 54.93; H 4.42; Cl 13.55.

(*E*)-1-(4-Bromophenyl)-4-ethoxy-1,1-difluorobut-3-en-2-one (1d). Yield 1.34 g (88%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 12.3 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 5.95 (d, *J* = 12.3 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.2 (t, *J* = 31.0 Hz), 166.8, 132.3 (t, *J* = 26.4

Hz), 132.0, 127.4 (t, *J* = 6.1 Hz), 125.4, 115.7 (t, *J* = 254 Hz), 98.6, 68.7, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.6. GC/MS (EI): *m/z* = 205/207 [*p*-$BrC_6H_4CF_2]^+$, 285/287 $[M–F]^+$. Anal. Calcd. for $C_{12}H_{11}BrF_2O_2$: C 47.24; H 3.63; Br 26.19. Found: C 47.61; H 3.68; Br 25.84.

(*E*)-4-Ethoxy-1,1-difluoro-1-(4-nitrophenyl)but-3-en-2-one (1e). Yield 1.08 g (80%). Brownish solid; mp 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.80 (d, *J* = 12.3 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 6.00 (d, *J* = 12.3 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.5 (t, *J* = 30.5 Hz), 167.5, 149.4, 139.4 (t, *J* = 26.1 Hz), 127.2 (t, *J* = 6.1 Hz), 123.8, 115.1 (t, *J* = 255 Hz), 98.3, 69.0, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.6. GC/MS (EI): *m/z* = 172 [*p*-$O_2NC_6H_4CF_2]^+$. Anal. Calcd. for $C_{12}H_{11}F_2NO_4$: C 53.14; H 4.09; N 5.16. Found: C 53.12; H 4.29; N 4.78.

(*E*)-1-(3-Bromophenyl)-4-ethoxy-1,1-difluorobut-3-en-2-one (1f). Yield 1.19 g (78%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 12.3 Hz, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 5.96 (d, *J* = 12.3 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.0 (t, *J* = 30.8 Hz), 166.9, 135.3 (t, *J* = 26.2 Hz), 133.9, 130.3, 128.9 (t, *J* = 6.5 Hz), 124.5 (t, *J* = 6.1 Hz), 122.8, 115.2 (t, *J* = 255 Hz), 98.6, 68.8, 14.4 (d, *J* = 40.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.6. GC/MS (EI): *m/z* = 205/207 [*m*-$BrC_6H_4CF_2]^+$. Anal. Calcd. for $C_{12}H_{11}BrF_2O_2$: C 47.24; H 3.63; Br 26.19. Found: C 47.24; H 3.31; Br 26.15.

(*E*)-4-Ethoxy-1,1-difluoro-1-(*p*-tolyl)but-3-en-2-one (1g). Yield 649 mg (54%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 12.3 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 5.93 (d, *J* = 12.3 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.8 (t, *J* = 31.3 Hz), 166.2, 141.0, 130.3 (t, *J* = 26.0 Hz), 129.4, 125.6 (t, *J* = 6.1 Hz), 116.3 (t, *J* = 253 Hz), 99.0, 68.5, 21.4, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.4. GC/MS (EI): *m/z* = 141 [*p*-$MeC_6H_4CF_2]^+$, 221 $[M–F]^+$, 240 $[M]^+$. Anal. Calcd. for $C_{13}H_{14}F_2O_2$: C 64.99; H 5.87. Found: C 64.78; H 5.55.

(*E*)-4-Ethoxy-1,1-difluoro-1-(*m*-tolyl)but-3-en-2-one (1h). Yield 961 mg (80%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 12.3 Hz, 1H), 7.35 (d, *J* = 6.4 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.21 (m, 1H), 5.94 (d, *J* = 12.3 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.7 (t, *J* = 31.1 Hz), 166.3, 138.7, 133.1 (t, *J* = 25.6 Hz), 131.5, 128.6, 126.2 (t, *J* = 6.0 Hz), 122.7 (t, *J* = 6.2 Hz), 116.2 (t, *J* = 253 Hz), 98.9, 68.5, 21.5, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.7. GC/MS (EI): *m/z* = 141 [*m*-$MeC_6H_4CF_2]^+$, 221 $[M–F]^+$, 240 $[M]^+$. Anal. Calcd. for $C_{13}H_{14}F_2O_2$: C 64.99; H 5.87. Found: C 65.34; H 6.18.

(*E*)-4-Ethoxy-1,1-difluoro-1-(*o*-tolyl)but-3-en-2-one (1i). Yield 613 mg (51%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 12.3 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 1H), 5.89 (d, *J* = 12.3 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.2 (t, *J* = 31.2 Hz), 166.2, 136.9 (t, *J* = 3.2 Hz), 132.0, 131.4 (t, *J* = 23.5 Hz), 130.7, 126.3 (t, *J* = 9.0 Hz), 126.0, 116.8 (t, *J* = 253 Hz), 99.3, 68.5, 20.1, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –104.4. GC/MS (EI): *m/z* = 141 [*o*-$MeC_6H_4CF_2]^+$, 221 $[M–F]^+$, 240 $[M]^+$. Anal. Calcd. for $C_{13}H_{14}F_2O_2$: C 64.99; H 5.87. Found: C 65.09; H 5.54.

(*E*)-4-Ethoxy-1,1-difluoro-1-(4-fluoro-2-methylphenyl)but-3-en-2-one (1j). Yield 788 mg (61%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 12.3 Hz, 1H), 7.55 (dd, *J* = 8.4, 5.8 Hz, 1H), 7.02 – 6.80 (m, 2H), 5.91 (d, *J* = 12.3 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.9 (t, *J* = 31.5 Hz), 166.4, 163.8 (d, *J* = 250 Hz), 140.0 (dt, *J* = 8.4, 3.1 Hz), 128.5 (q, *J* = 9.2 Hz), 127.6 (td, *J* = 24.0, 3.0 Hz), 118.8 (d, *J* = 21.7 Hz), 116.5 (t, *J* = 254 Hz), 112.8 (d, *J* = 21.5 Hz), 99.01, 68.6, 20.1, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.4, –111.5. GC/MS (EI): *m/z* = 159 [4-fluoro-2-methylphenyl$CF_2]^+$, 221 $[M–F]^+$, 239 $[M]^+$. Anal. Calcd. for $C_{13}H_{13}F_3O_2$: C 60.46; H 5.07. Found: C 60.30; H 5.32.

(*E*)-4-Ethoxy-1,1-difluoro-1-(3-methoxyphenyl)but-3-en-2-one (1l). Yield 858 mg (67%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 12.3 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6 7.02 – 6.94 (m, 1H), 5.94 (d, *J* = 12.3 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4 (t, *J* = 31.0 Hz), 166.4, 159.8, 134.5 (t, *J* = 25.9 Hz), 129.9, 117.8 (t, *J* = 6.2 Hz), 116.6, 115.9 (t, *J* = 254 Hz), 111.0 (t, *J* = 6.3 Hz), 98.8, 68.5, 55.4, 14.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ –106.8. GC/MS (EI): *m/z* = 157 [*m*-$MeOC_6H_4CF_2]^+$, 237 $[M–F]^+$, 256 $[M]^+$. Anal. Calcd. for $C_{13}H_{14}F_2O_3$: C 60.93; H 5.51. Found: C 60.92; H 5.67.

(*E*)-4-Ethoxy-1,1-difluoro-1-(pyridin-2-yl)but-3-en-2-one (1q). Yield 738 mg (65%). Brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.5 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.06 (d, *J* = 12.3 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4 (t, *J* = 29.3 Hz), 166.2, 152.4 (t, *J* = 27.9 Hz), 149.6, 137.3, 125.3, 121.1 (t, *J* = 4.0 Hz), 114.0 (t, *J* = 254 Hz), 99.6, 68.3, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –108.9. GC/MS (EI): *m/z* = 128 [pyridin-2-yl$CF_2]^+$, 227 $[M]^+$. Anal. Calcd. for $C_{11}H_{11}F_2NO_2$: C 58.15; H 4.88; N 6.16. Found: C 58.48; H 4.65; N 6.19.

(*E*)-4-Ethoxy-1,1-difluoro-1-(1-methyl-1*H*-pyrazol-5-yl)but-3-en-2-one (1r). Yield 886 mg (77%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 12.3 Hz, 1H), 7.42 (s, 1H), 6.43 (s, 1H), 5.92 (d, *J* = 12.3 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.5 (t, *J* = 30.0 Hz), 167.1, 138.2, 134.1 (t, *J* = 31.2 Hz), 112.3 (t, *J* = 251 Hz), 107.8 (t, *J* = 3.8 Hz), 98.6, 68.8, 38.6, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.4. GC/MS (EI): *m/z* = 131 [1-methyl-1*H*-pyrazol-5-yl$CF_2]^+$, 211 $[M–F]^+$, 230 $[M]^+$. Anal. Calcd. for $C_{10}H_{12}F_2N_2O_2$: C 52.17; H 5.25; N 12.17. Found: C 52.06; H 4.89; N 12.20

(*E*)-4-Ethoxy-1,1-difluoro-1-(thiazol-2-yl)but-3-en-2-one (1s). Yield 910 mg (78%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 1H), 7.86 (d, *J* = 12.3 Hz, 1H), 7.54 (d, *J* = 3.1 Hz, 1H), 6.08 (d, *J* = 12.3 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.1 (t, *J* = 28.8 Hz), 167.0, 160.8 (t, *J* = 33.0 Hz), 144.0, 122.4, 112.42 (t, *J* = 253 Hz), 99.0, 68.6, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –99.9. GC/MS (EI): *m/z* = 134 [thiazol-2-yl$CF_2]^+$, 214 $[M–F]^+$, 233 $[M]^+$. Anal. Calcd. for $C_9H_9F_2NO_2S$: C 46.35; H 3.89; N 6.01; S 13.75. Found: C 46.36; H 4.21; N 5.97; S 14.10.

(*E*)-4-Ethoxy-1,1-difluoro-1-(4-fluorophenyl)-3-methylbut-3-en-2-one (1t). Yield 994 mg (77%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.50 (dd, *J* = 8.3, 5.3 Hz, 2H), 7.11 (t, *J* = 8.3 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.75 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4 (t, *J* = 30.3 Hz), 164.0 (d, *J* = 250 Hz), 163.8 (t, *J* = 7.8 Hz), 130.4 (td, *J* = 25.8, 3.0 Hz), 127.9 (dt, *J* = 8.6, 6.1 Hz), 117.1 (t, *J* = 253 Hz), 115.8 (d, *J* = 22.0 Hz), 113.1, 71.1, 15.4, 8.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ –94.3, –110.2 – –110.7 (m). GC/MS (EI): *m/z* = 145 [*p*-$FC_6H_4CF_2]^+$, 258 $[M]^+$. Anal. Calcd. for $C_{13}H_{13}F_3O_2$: C 60.46; H 5.07. Found: C 60.81; H 4.85.

(*E*)-1,1-Difluoro-1-(4-fluorophenyl)-4-methoxypent-3-en-2-one (1u). Yield 1.05 g (86%). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd,

J = 8.4, 4.8 Hz, 2H), 7.11 (t, *J* = 8.4 Hz, 2H), 5.82 (s, 1H), 3.73 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.6 (t, *J* = 29.7 Hz), 179.6, 164.1 (d, *J* = 250 Hz), 129.8 (t, *J* = 26.3 Hz), 128.0 (dd, *J* = 14.7, 6.3 Hz), 116.1 (t, *J* = 255 Hz), 115.8 (d, *J* = 22.1 Hz), 92.5, 56.3, 20.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ –104.8, –110.3– –110.7 (m). GC/MS (EI): *m/z* = 145 [*p*-$FC_6H_4CF_2]^+$, 244 $[M]^+$. Anal. Calcd. for $C_{12}H_{11}F_3O_2$: C 59.02; H 4.54. Found: C 59.37; H 4.71.

1-(4,5-Dihydrofuran-3-yl)-2,2-difluoro-2-(4-fluorophenyl)ethanone (1v). Yield 1.06 g (88%). Colorless solid; mp 80–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.55 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.12 (t, *J* = 8.4 Hz, 2H), 4.56 (t, *J* = 9.8 Hz, 2H), 2.90 (t, *J* = 9.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9 (t, *J* = 32.6 Hz), 164.2 (d, *J* = 251 Hz), 162.5 (t, *J* = 9.7 Hz), 129.6 (td, *J* = 26.1, 3.1 Hz), 127.9 (dt, *J* = 8.7, 6.2 Hz), 116.4 (t, *J* = 253 Hz), 115.9 (d, *J* = 22.1 Hz), 115.2, 73.2, 27.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –99.4, –110.1 – –110.2 (m). GC/MS (EI): *m/z* = 145 [*p*-$FC_6H_4CF_2]^+$, 223 $[M–F]^+$, 242 $[M]^+$. Anal. Calcd. for $C_{12}H_9F_3O_2$: C 59.51; H 3.75. Found: C 59.35; H 4.09.

1-(3,4-Dihydro-2*H*-pyran-5-yl)-2,2-difluoro-2-(4-fluorophenyl)-ethanone (1w). Yield 948 mg (74%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.51 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.11 (t, *J* = 8.5 Hz, 2H), 4.10 (t, *J* = 4.9 Hz, 2H), 2.28 (t, *J* = 6.3 Hz, 2H), 1.89 (p, *J* = 6.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.5 (t, *J* = 30.6 Hz), 164.1 (d, *J* = 250 Hz), 161.8 (t, *J* = 9.1 Hz), 130.2 (td, *J* = 25.8, 3.0 Hz), 127.9 (dt, *J* = 8.6, 6.1 Hz), 116.9 (t, *J* = 253 Hz), 115.8 (d, *J* = 22.1 Hz), 112.4, 67.5, 21.0, 18.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ –95.2, –109.7 – –110.8 (m). GC/MS (EI): *m/z* = 145 [*p*-$FC_6H_4CF_2]^+$, 237 $[M–F]^+$, 256 $[M]^+$. Anal. Calcd. for $C_{13}H_{11}F_3O_2$: C 60.94; H 4.33. Found: C 60.86; H 4.22.

General procedure for the preparation of pyrazoles 5a–e and 5q–v. To a solution of enone **1a–e** or **1q–v** (1.00 mmol) in HOAc (10 mL), hydrazine hydrate (551 mg, 1.10 mmol) was added, and the mixture was stirred at rt for 12 h. Then the solvent was evaporated in *vacuo*, and the residue was dissolved in CH_2Cl_2 (10 mL). The organic layer was washed with H_2O (2×10 mL), saturated aq $NaHCO_3$ (2×10 mL), and brine (10 mL), dried over Na_2SO_4, and evaporated in *vacuo* to give the target product **5**.

5-(Difluoro(phenyl)methyl)-1*H*-pyrazole (5a). Yield 151 mg (78%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.58 (br s, 1H), 7.62 (d, *J* = 6.7 Hz, 2H), 7.50 – 7.41 (m, 4H), 6.41 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (t, *J* = 32.7 Hz), 136.9 (t, *J* = 27.4 Hz), 130.4, 130.1, 128.6, 125.9 (t, *J* = 5.5 Hz), 118.3 (t, *J* = 238 Hz), 104.2 (t, *J* = 2.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –87.4. LC/MS (CI): *m/z* = 175 $[M–F]^+$, 193 $[M–H]^–$. Anal. Calcd. for $C_{10}H_8F_2N_2$: C 61.85; H 4.15; N 14.43. Found: C 61.72; H 4.06; N 14.57.

5-(Difluoro(4-fluorophenyl)methyl)-1*H*-pyrazole (5b). Yield 172 mg (81%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (br s, 1H), 7.59 (dd, *J* = 8.3, 5.4 Hz, 2H), 7.51 – 7.46 (m, 1H), 7.11 (t, *J* = 8.3 Hz, 2H), 6.41 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9 (d, *J* = 250 Hz), 148.7 (t, *J* = 32.3 Hz), 132.9 (td, *J* = 28.0, 3.0 Hz), 130.1, 128.2 (dt, *J* = 8.8, 5.4 Hz), 117.9 (t, *J* = 238 Hz), 115.6 (d, *J* = 22.0 Hz), 104.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ –86.4, –110.5 – –111.4 (m). LC/MS (CI): *m/z* = 193 $[M–F]^+$, 211 $[M–H]^–$. Anal. Calcd. for $C_{10}H_7F_3N_2$: C 56.61; H 3.33; N 13.20. Found: C 56.41; H 2.99; N 13.39.

5-((4-Chlorophenyl)difluoromethyl)-1*H*-pyrazole (5c). Yield 199 mg (87%). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.41 (br s, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 6.42 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5 (t, *J* = 32.6 Hz), 136.6, 135.4 (t, *J* = 27.9 Hz), 130.1, 128.9, 127.4 (t, *J* = 5.3 Hz), 117.8 (t, *J* = 238 Hz), 104.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ –87.5. LC/MS (CI): *m/z* = 209/211 $[M–F]^+$, 229/231 $[M+H]^+$. Anal. Calcd. for $C_{10}H_7F_3N_2$: C 56.61; H 3.33; N 13.2. Found: C 56.85; H 3.15; N 12.99.

5-((4-Bromophenyl)difluoromethyl)-1*H*-pyrazole (5d). Yield 229 mg (84%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.25 (br s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 – 7.43 (m, 3H), 6.42 (d, *J* = 1.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5 (t, *J* = 32.8 Hz), 135.9 (t, *J* = 27.9 Hz), 131.8, 130.1, 127.7 (t, *J* = 5.4 Hz), 124.9, 117.8 (t, *J* = 238 Hz), 104.3 (t, *J* = 2.7 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –87.8. LC/MS (CI): *m/z* = 253/255 $[M–F]^+$, 273/275 $[M+H]^+$. Anal. Calcd. for $C_{10}H_7BrF_2N_2$: C 43.98; H 2.58; N 10.26; Br 29.26. Found: C 44.25; H 2.76; N 10.48; Br 29.06.

5-(Difluoro(4-nitrophenyl)methyl)-1*H*-pyrazole (5e). Yield 203 mg (85%). Brownish solid; mp 83–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (br s, 1H), 8.28 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.63 – 7.57 (m, 1H), 6.49 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 148.2 (t, *J* = 32.7 Hz), 142.8 (t, *J* = 28.0 Hz), 130.3, 127.2 (t, *J* = 5.5 Hz), 123.8, 117.2 (t, *J* = 239 Hz), 104.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –89.3. LC/MS (CI): *m/z* = 240 $[M+H]^+$. Anal. Calcd. for $C_{10}H_7F_2N_3O_2$: C 50.22; H 2.95; N 17.57. Found: C 49.88; H 3.30; N 17.34.

2-(Difluoro(1*H*-pyrazol-5-yl)methyl)pyridine (5q). Yield 142 mg (73%). Brownish solid; mp 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.31 (br s, 1H), 8.64 (d, *J* = 4.5 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 1.0 Hz, 1H), 7.38 – 7.29 (m, 1H), 6.51 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (t, *J* = 29.5 Hz), 149.6, 147.5 (t, *J* = 31.7 Hz), 137.3, 130.4, 125.0, 120.5 (t, *J* = 4.2 Hz), 116.3 (t, *J* = 239 Hz), 104.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ –93.5. LC/MS (CI): *m/z* = 196 $[M+H]^+$. Anal. Calcd. for $C_9H_7F_2N_3$: C 55.39; H 3.62; N 21.53. Found: C 55.75; H 3.62; N 21.41.

5-(Difluoro(1*H*-pyrazol-5-yl)methyl)-1-methyl-1*H*-pyrazole (5r). Yield 154 mg (78%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.26 (br s, 1H), 7.52 (d, *J* = 1.4 Hz, 1H), 7.42 (s, 1H), 6.52 (d, *J* = 1.9 Hz, 1H), 6.35 (s, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (t, *J* = 32.0 Hz), 137.9, 137.5 (t, *J* = 32.1 Hz), 130.3, 114.1 (t, *J* = 234 Hz), 108.4 (t, *J* = 3.5 Hz), 104.3, 38.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –86.1. LC/MS (CI): *m/z* = 199 $[M+H]^+$. Anal. Calcd. for $C_8H_8F_2N_4$: C 48.49; H 4.07; N 28.27. Found: C 48.17; H 3.91; N 27.90

2-(Difluoro(1*H*-pyrazol-5-yl)methyl)thiazole (5s). Yield 173 mg (86%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.53 (br s, 1H), 8.04 – 7.75 (m, 1H), 7.63 (s, 1H), 7.50 (d, *J* = 3.1 Hz, 1H), 6.61 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9 (t, *J* = 35.4 Hz), 146.6 (t, *J* = 31.8 Hz), 143.8, 130.4, 121.8, 114.8 (t, *J* = 238 Hz), 104.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ –83.5. LC/MS (CI): *m/z* = 202 $[M+H]^+$. Anal. Calcd. for $C_7H_5F_2N_3S$: C 41.79; H 2.51; N 20.89; S 15.94. Found: C 41.85; H 2.57; N 21.06; S 15.63.

5-(Difluoro(4-fluorophenyl)methyl)-4-methyl-1*H*-pyrazole (5t). Yield 185 mg (82%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.12 (br s, 1H), 7.55 (dd, *J* = 8.0, 5.5 Hz, 2H), 7.26 (s, 1H), 7.11 (t, *J* = 8.5 Hz, 2H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7 (d, *J* = 250 Hz), 145.5 (t, *J* = 31.9 Hz), 132.8 (td, *J* = 28.3, 3.2 Hz), 130.0, 128.1 (dt, *J* = 8.8, 5.3 Hz), 118.7 (t, *J* = 238 Hz), 115.5 (d, *J* = 22.0 Hz), 114.34, 8.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –87.1, –110.6 – –111.4 (m). LC/MS (CI): *m/z* = 207 $[M–F]^+$, 227 $[M+H]^+$. Anal. Calcd. for $C_{11}H_9F_3N_2$: C 58.41; H 4.01; N 12.38. Found: C 58.28; H 4.16; N 12.19.

5-(Difluoro(4-fluorophenyl)methyl)-3-methyl-1*H*-pyrazole (5u). Yield 188 mg (83%). Yellowish solid; mp 50–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (br s, 1H), 7.52 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.04 (t, *J* = 8.5 Hz, 2H), 6.13 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7 (d, *J* = 249

Hz), 149.2 (t, *J* = 33.2 Hz), 140.9, 133.0 (td, *J* = 28.0, 3.1 Hz), 128.1 (dt, *J* = 8.7, 5.4 Hz), 117.7 (t, *J* = 237 Hz), 115.4 (d, *J* = 21.9 Hz), 103.2, 10.7. ^{19}F NMR (470 MHz, $CDCl_3$) δ –86.8, –110.7 – –112.2 (m). LC/MS (CI): *m/z* = 207 $[M–F]^+$, 227 $[M+H]^+$. Anal. Calcd. for $C_{11}H_9F_3N_2$: C 58.41; H 4.01; N 12.38. Found: C 58.74; H 3.82; N 12.29.

2-(5-(Difluoro(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)ethanol (5v). Yield 146 mg (57%). Yellowish solid; mp 101–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (br s, 1H), 7.68 (s, 1H), 7.56 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.30 (t, *J* = 8.3 Hz, 2H), 4.66 (t, *J* = 5.2 Hz, 1H), 3.54 (q, *J* = 6.9 Hz, 2H), 2.66 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.9 (d, *J* = 247 Hz), 144.9 (t, *J* = 33.4 Hz), 133.0 (td, *J* = 27.1, 2.2 Hz), 129.3, 128.2 (dd, *J* = 14.0, 5.3 Hz), 119.3 (t, *J* = 235 Hz), 115.5, 115.2 (d, *J* = 22.0 Hz), 61.3, 27.2. ^{19}F NMR (470 MHz, DMSO-d_6) δ –83.5, –110.5 – –111.3 (m). LC/MS (CI): *m/z* = 257 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{11}F_3N_2O$: C 56.25; H 4.33; N 10.93. Found: C 55.97; H 4.11; N 10.55.

5-(Difluoro(4-fluorophenyl)methyl)-4,5-dihydroisoxazol-5-ol (6). Na_2CO_3 (607 mg, 5.73 mmol) was added to a mixture of enone **1b** (2.00 g, 8.19 mmol) and hydroxylamine hydrochloride (743 mg, 10.7 mmol) in H_2O (15 mL) at rt. The resulting mixture was stirred at rt for 12 h, and then *t*-BuOMe was added. The organic layer was separated, dried over Na_2SO_4, and evaporated in *vacuo*. The residue was recrystallized from $CHCl_3$. Yield 1.41 g (74%). Yellowish solid; mp 139–141 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.64 (dd, *J* = 8.7, 6.1 Hz, 2H), 7.54 (d, *J* = 1.3 Hz, 1H), 7.31 (t, *J* = 8.7 Hz, 2H), 3.43 (d, *J* = 19.0 Hz, 1H), 2.94 (d, *J* = 19.0 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.3 (d, *J* = 247 Hz), 147.9, 129.4 (dd, *J* = 15.1, 6.4 Hz), 129.1 (td, *J* = 26.4, 3.2 Hz), 118.6 (t, *J* = 249 Hz), 115.0 (d, *J* = 22.0 Hz), 104.3 (t, *J* = 33.1 Hz), 42.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ –105.1 (d, *J* = 14.7 Hz), –110.5. LC/MS (CI): *m/z* = 232 $[M+H]^+$. Anal. Calcd. for $C_{10}H_8F_3NO_2$: C 51.96; H 3.49; N 6.06. Found: C 52.23; H 3.74; N 6.42.

5-(Difluoro(4-fluorophenyl)methyl)isoxazole (7). $SOCl_2$ (400 mg, 0.244 mL, 3.37 mmol) was added dropwise to a solution of isoxazoline **6** (600 mg, 2.60 mmol) and pyridine (616 mg, 0.627 mL, 7.79 mmol) in CH_2Cl_2 (10 mL) at 10 °C. The mixture was stirred at rt for 12 h, then washed with H_2O (3×10 mL), dried over Na_2SO_4, and evaporated in *vacuo*. Yield 511 mg (92%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.0 Hz, 1H), 7.58 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.15 (t, *J* = 8.4 Hz, 2H), 6.51 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 (t, *J* = 38.4 Hz), 163.3, 150.1, 130.2 (td, *J* = 26.9, 3.2 Hz), 127.9 (dt, *J* = 8.9, 5.7 Hz), 116.1, 114.7 (t, *J* = 242 Hz), 103.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ –91.6, –108.8 – –109.7 (m). LC/MS (CI): *m/z* = 214 $[M+H]^+$. Anal. Calcd. for $C_{10}H_6F_3NO$: C 56.35; H 2.84; N 6.57. Found: C 55.97; H 2.84; N 6.71.

4-(Difluoro(4-fluorophenyl)methyl)pyrimidin-2(1*H*)-one (8). To a solution of **1b** (500 mg, 2.05 mmol) and urea (129 mg, 2.15 mmol) in H_2O (5 mL), saturated aq HCl (0.388 mL, 4.09 mmol) was added. The mixture was stirred at rt overnight, the precipitate formed was filtered, washed with pre-cooled EtOH (3 mL), and dried under air. Yield 310 mg (63%). Yellowish solid; mp 205–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (br s, 1H), 8.21 (d, *J* = 6.3 Hz, 1H), 7.65 (dd, *J* = 8.2, 5.4 Hz, 2H), 7.33 (t, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 6.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.8 (t, *J* = 30.9 Hz), 163.4 (d, *J* = 248 Hz), 156.3, 151.2, 130.7 (td, *J* = 27.2, 2.8 Hz), 128.2 (dt, *J* = 9.0, 5.9 Hz), 116.9 (t, *J* = 246 Hz), 115.9 (d, *J* = 22.2 Hz), 99.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ –96.7, –109.5. LC/MS (CI): *m/z* = 221 $[M–F]^+$, 241 $[M+H]^+$. Anal. Calcd. for $C_{11}H_7F_3N_2O$: C 55.01; H 2.94; N 11.66. Found: C 54.93; H 3.24; N 11.72.

4-(Difluoro(4-fluorophenyl)methyl)pyrimidin-2-amine (9). NaOH (123 mg, 3.07 mmol) was added to a solution of **1b** (500 mg, 2.05 mmol) and guanidine hydrochloride (293 mg, 3.07 mmol) in EtOH (20 mL). The resulting suspension was stirred at rt overnight, then evaporated in *vacuo*. The residue was diluted with H_2O (10 mL) and EtOAc (10 mL), the organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo. The residue was recrystallized from hexanes. Yield 201 mg (41%). Yellowish solid; mp 181–183 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, *J* = 4.0 Hz, 1H), 7.60 (t, *J* = 6.7 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.02 (s, 2H), 6.93 – 6.84 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.5, 163.1 (d, *J* = 248 Hz), 162.5 (t, *J* = 31.0 Hz), 160.5, 131.6 (t, *J* = 27.4 Hz), 128.1 (dt, *J* = 8.9, 5.8 Hz), 117.4 (t, *J* = 243 Hz), 115.8, 104.9. ^{19}F NMR (470 MHz, DMSO-d_6) δ –95.4, –109.9. LC/MS (CI): *m/z* = 240 $[M+H]^+$. Anal. Calcd. for $C_{11}H_8F_3N_3$: C 55.23; H 3.37; N 17.57. Found: C 55.61; H 3.49; N 17.55.

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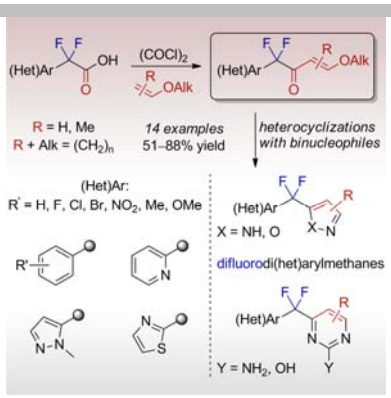
FULL PAPER

Synthesis of β-alkoxyenones decorated with (het)aryl difluoromethyl substituents, as well as utility of these substrates for heterocyclizations leading to fluorinated pyrazoles, oxazoles and pyrimidines is described.



Organofluorine compounds

Maksym Ya. Bugera,
Karen V. Tarasenko,
Ivan S. Kondratov, Igor I. Gerus,*
Bohdan V. Vashchenko,
Viktor E. Ivasyshyn,
*Oleksandr O. Grygorenko**

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(Het)aryl difluoromethyl -substituted β-alkoxyenones: synthesis and heterocyclizations