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The synthesis of α,α-difluoroacetamides *via* electrophilic fluorination in the mixed-solvent of water and PEG-400

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ABSTRACT

Under mild conditions, a series of α,α-difluoro-β-ketoamides were synthesized with Selectfluor® as the F^+ source in the presence of K_2CO_3 in the mixed-solvent of water and PEG-400 ($V_{H_2O} : V_{PEG\text{-}400} = 3 : 1$), without additional phase-transfer catalyst. By using this approach, most cases examined in this study proceeded in nearly quantitative conversions regardless of the electronic nature of the substituent pattern.

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1. Introduction

A "CF_2 center" adds significant value to some pharmaceuticals [1] (examples including anaesthetics [2], enzyme inhibitors [3], sugar analogues [4], pesticides [5], herbicides [6], etc.) and materials [7] because it can bring unique features to the compounds [8]. Besides, "CF_2 center"-containing compounds are also very useful intermediates in organic synthesis [9], especially in asymmetric synthesis [10], labelling chemistry [11], radical chemistry [12], and for the preparation of fluorine-containing heterocyclic compounds [13]. Currently, many methods are available in the literature for the construction of a "CF_2 center". Firstly, it can be transformed from a variety of fluorine-containing small organic molecules (Eq. (1)). Among these examples, a variety of reactions using trifluoromethyl [12d,14] and *gem*-difluoromethylene [15] compounds have been reported. It should be also noted that nucleophilic substitution reactions of difluoromethylphenylsulfone with primary alkyl halides [16], the derivatization reaction of the difluoroimine synthons or the α-halo-α,α-difluoroketones [17], the addition reaction of difluoropropargyl bromide with imines [18], and the addition of $PhSeCF_2TMS$ to aldehydes or imines [19] are recent achievements for functionalized difluoromethylene compounds. The advantage of this strategy is that two C–F bonds can be introduced simultaneously without undergoing the process of monofluorination. However, the "CF_2 center" often cannot be freely introduced at any step especially in a multi-step process, which limited its development to some extent. In contrast, the most widely used method is the direct electrophilic fluorination reaction of parent carbonyl compounds or their enolates (Eq. (2)) [10d,20]. At present, elemental fluorine [21] or all kinds of electrophilic fluorination agents [22], such as $FClO_3$ [23], NF_3O [24], XeF_2 [25], $CsSO_4F$ [26], fluoroxy compounds R_FOF [27] including CF_3OF, CF_3CO_2F or AcOF (some of them are generated in situ) [22,28], organofluorine reagents involving iodine and/or iodo-compounds [29], have been developed as the reagents for electrophilic fluorination reactions. More recently much attention has been given to the fluoronitrogen compounds, such as NFSI and Selectfluor® (stable and readily available) [30]. In the process of the fluorination of carbonyl compounds, the substrates are firstly converted into the α-monofluorinated derivatives, and thence to the α,α-difluorinated derivatives, and the second step is the rate determining step [31]. Currently, in the most conversions, an excess of harmful, unstable or expensive F^+ source and various strong bases (such as NaH, KHMDS, LDA etc.) or metal catalyst, organic solvents, low temperatures or anhydrous conditions were used reluctantly in order to avoid the generation of monofluorinated compounds, shorten the reaction times and increase the yield of the difluorinated compounds. Additionally, these harsh conditions may limit the conversion in large-scale preparation for

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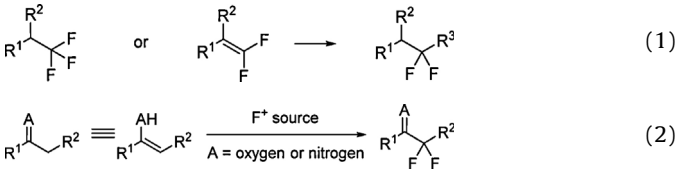
industrial applications.



(1)

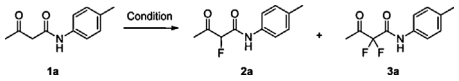
(2)

In fact, the α,α-difluoroacylacetamide moiety is a key structure of the human heart chymase inhibitors [32] and renin inhibitors [33]. The difluoromethylene ketone moiety, by interacting with the S′ subsite of the enzyme, increases the affinity and selectivity of human chymase [32]. So far a few cases have focused on the preparation of α,α-difluoro-β-ketoamides, in which acetoacetamides are in general as a special case of 1,3-dicarbonyl compounds [34]. And among them, preparation of 2,2-difluoro-3-oxo-*N*,3-diphenylpropanamide in water or solvent-free conditions was reported only in one case [34c]. To the best of our knowledge, there is no detailed investigation of the synthesis of α,α-difluoro-β-ketoamides to date, especially the consideration of a greener method such as avoiding the use of rigorous conditions, organic solvent and minimizing fluoride reagents, etc. Herein, we wish to report a greener approach on the synthesis of the α,α-difluoro-β-ketoamides by using acetoacetamides under mild conditions.

2. Results and discussion

Very recently, combined with our research on acetoacetamides in recent years [35], we developed a catalyst-free and highly selective method for the synthesis of α-monofluorinated acetoacetamides *via* electrophilic fluorination reaction of acetoacetamides **1** in PEG-400 [36]. During that research, we found that 2,2-difluoro-3-oxo-*N*-(*p*-tolyl)butanamide **3a** could be isolated in good yield (97%) by using commercially available Selectfluor® as the F^+ source at 60 °C (Table 1, entry 1), but our further investigation using various substrates revealed that this procedure employing the single use of PEG-400 was not suitable to obtain the difluoride **3** in high yield [37]. We are still interested in the high-yield synthesis of **3** under the widely applicable conditions. Davis et al. demonstrated that the higher temperatures or the more reactive potassium enolates enhanced the difluorination [34d]. We thereby deduced that increase in both solubility of the acetoacetamides in hot water and the their interaction with the base would result in the smooth production of the products **3**. Based on this idea, we examined water as well as mixed-solvent of water and PEG-400 for the difluorination of acetoacetamides. After many attempts (Table 1), we found that the yield of **3a** could be significantly improved from 19% to 97% by increasing the amount of K_2CO_3 from 0 to 1.0 equiv. along with a noticeably shorter reaction times (entries 2–4). The yield of **3a** was slightly lower (88%) by further increase of K_2CO_3 (2.2 equiv.), although it took a shorter time, at 25 °C (entry 5 vs. 4). As shown in entry 4, compared with PEG-400 (entry 1), water would be also one of the best solvents for this reaction. However, it was found that the reaction time could be greatly shortened without any affect on the product yield when the mixed-solvent of water in the ratio of 5 to 1 was used (entry 6 vs. 4). Finally, **3a** could be obtained in 99% yield when we treated 3-oxo-*N*-(*p*-tolyl)butanamide **1a** with Selectfluor® (2.2 equiv.), K_2CO_3 (1.0 equiv.) in water and PEG-400 (3.0 mL, 3:1 ratio) for 6.0 h at 25 °C (entry 7). Increase in the amount of K_2CO_3 could resulted in the higher yield of the di-substituted product (entries 8, 9 vs. 7, and 10 vs. 11). Similarly, the yield of **3a** could also be improved by increasing the proportion of PEG-400 in the mixed-solvent (entry 6 vs. 7 and 10). The reaction performed much better in hydrophilic ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) than in hydrophobic ionic liquids 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF_6) (entries 12–15), and the base was necessary for the conversion from **1a** to **3a** in ionic liquids. And among them, the best yield of **3a** (91%) was isolated from the [BMIM]BF_4 along with 8% **2a** at 25 °C after 20 h (entry 13).

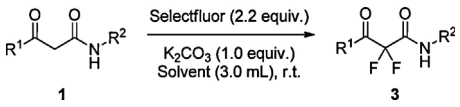
Table 1
Survey of reaction conditions.[a]



Entry	Solvent	Base (equiv.)	T (°C)[c]	Time	Yield (%)[b] **1a**:**2a**:**3a**
1	PEG-400	K_2CO_3 (0)	60	20 h	0:0:97
2	H_2O	K_2CO_3 (0)	25	6 d	49:31:19
3	H_2O	K_2CO_3 (0.5)	25	8 d	0:6:93
4	H_2O	K_2CO_3 (1.0)	25	15 h	0:0:97
5	H_2O	K_2CO_3 (2.2)	25	2.5 h	0:0:88
6	H_2O:PEG-400 (5:1)	K_2CO_3 (1.0)	25	6 h	0:6:93
7	H_2O:PEG-400 (3:1)	K_2CO_3 (1.0)	25	6 h	0:0:99
8	H_2O:PEG-400 (3:1)	K_2CO_3 (0.5)	25	6 h	0:18:81
9	H_2O:PEG-400 (3:1)	K_2CO_3 (0.3)	25	6 h	0:28:71
10	H_2O:PEG-400 (1:1)	K_2CO_3 (1.0)	25	2 h	0:0:99
11	H_2O:PEG-400 (1:1)	K_2CO_3 (0)	25	2 h	10:53:37
12	[BMIM]BF_4	K_2CO_3 (0)	25	20 h	37:63:0
13	[BMIM]BF_4	K_2CO_3 (1.0)	25	20 h	0:8:91
14	[BMIM]PF_6	K_2CO_3 (0)	60	20 h	61:38:0
15	[BMIM]PF_6	K_2CO_3 (1.0)	60	24 h	0:71:29

[a] All reactions were carried out with acetoacetamide **1a** (0.5 mmol), Selectfluor® (2.2 equiv.) as the F^+ source, unless otherwise indicated.
[b] Isolated yield.
[c] Oil bath temperature.

Table 2
The preparation of α,α-difluoro-β-ketoamides.[a]



Entry	Substrate **1**	Time (**A**/**B**)[b]	Product **3**	Yield/%[c] (**A**/**B**)[b]
1	R^1 = Me, R^2 = 4-Me-Ph	15 h/6 h	**3a**	97/99
2	R^1 = Me, R^2 = 2-Me-Ph	17 h/8 h	**3b**	99/99
3	R^1 = Me, R^2 = 2,4-diMe-Ph	29 h/10 h	**3c**	99/98
4	R^1 = Me, R^2 = 2-MeO-Ph	8 h/4 h	**3d**	97/98
5	R^1 = Me, R^2 = 4-MeO-Ph	3 d/16 h	**3e**	92/99
6	R^1 = Me, R^2 = 4-EtO-Ph	10 d/11 h	**3f**	97[d]/97
7	R^1 = Me, R^2 = Ph	12 h/5 h	**3g**	99/99
8	R^1 = Me, R^2 = 2-Cl-Ph	10 h/5 h	**3h**	99/98
9	R^1 = Me, R^2 = 4-Cl-Ph	6 d/8 h	**3i**	97[d]/99
10	R^1 = Me, R^2 = 5-Cl-2-MeOPh	6 d/10 h	**3j**	98[d]/98
11	R^1 = Me, R^2 = 4-COOEt-Ph	22 h/7 h	**3k**	98/98
12	R^1 = Me, R^2 = 4-MeO-Benzyl	3 d/16 h	**3l**	90[e]/92
13	R^1 = Me, R^2 = Benzyl	2 d/10 h	**3m**	92[d]/90
14	R^1 = Me, R^2 = 4-Cl-Benzyl	5 d/10 h	**3n**	97[d]/96
15	R^1 = $(CH_3)_2CH$, R^2 = Ph	7 d/15 h	**3o**	40[d,f]/94
16	R^1 = Ph, R^2 = 4-Me-Ph	4 d/2 d	**3p**	19[d,g]/93[d]

[a] Reactions were carried out with acetoacetamides **1** (0.5 mmol), Selectfluor® (1.1 mmol), K_2CO_3 (0.5 mmol), solvent (3.0 mL) at room temperature, unless otherwise indicated.
[b] **A**: reactions were performed in H_2O, **B**: reactions were performed in mixed-solvent (V_{H_2O} : $V_{PEG-400}$ = 3 : 1).
[c] Isolated yield.
[d] 60 °C was used.
[e] 10% **2l** was isolated and difluorinated product **3l** could not be promoted by prolonging reaction time.
[f] 22% **2o** and 26% **1o** were isolated and difluorinated product **3o** could not be promoted by prolonging reaction time.
[g] The yield of monofluorinated **2p** was 22% and 57% substrate **1p** was recovered.

With the optimized conditions in hand, the effect of various β-keto amides were then further evaluated in water and the mixed-solvent, respectively (Table 1, entries 4 and 7). As shown in Table 2, in the reactions of *N*-aryl substituted acetoacetamides in water, the experiments showed that the electronic effect of the substituents on the aromatic ring, either electron-donating groups (EDG) (Me, OMe, OEt; entries 1–6, **A**) or electron-withdrawing groups (EWG) (Cl, COOEt; entries 8–11, **A**) coupled with aryl-unsubstituted substrate (entry 7, **A**), did not exert any significant effect on the difluorination reaction. The desired difluorinated products **3a**-**k** were isolated in the yields of 92–99%. For benzyl substituted amides **1l-n**, these compounds could also produce the corresponding products **3l-n** in excellent yields albeit the reaction periods are longer (entries 12–14, **A**). On the other hand, substrates with isobutyroyl or benzoyl moiety in place of acetyl group (**1o**, **1p**) afforded the difluorinated products **3o** and **3p** in much lower yields in water (entries 15–16, **A**). This is mainly due to the low enol content of their molecule at equilibrium in water [34d,38].

Compared with the reactions carried out in water, it should be emphasized herein that by using a mixed-solvent (V_{H_2O} : $V_{PEG\text{-}400} = 3:1$) as the reaction media, the reaction for all substrates including **1o** and **1p** could complete in a dramatically shorter time period to provide the corresponding products **2** in excellent yields at room temperature (entries 1–16, **B**). It is deduced that the improved solubility of acetoacetamides in the mixed-solvent possibly made the difluorination easier to proceed in the absence of any additional phase-transfer catalyst.

3. Conclusions

In conclusion, the electrophilic fluorination of acetoacetamides for the facile synthesis of α,α-difluoro-β-ketoamides has been developed by using Selectfluor® as the F^+ source in the presence of K_2CO_3 in the mixed-solvent of water and PEG-400 in the ratio of 3 to 1. As the increase in the efficiency, the present method does not involve the requirement of the use of additional phase-transfer catalyst and problematic work-up. The electrophilic fluorination of other 1,3-dicarbonyl derivatives to form 2,2-difluoro-l,3-dicarbonyl analogues under green conditions are in progress in our lab.

4. Experimental

All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. ^{1}H NMR, ^{13}C NMR and ^{19}F spectra were recorded on a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz, ^{19}F: 376.5 MHz at 25 °C). Chemical shifts are reported in ppm units relative to TMS as internal standard for ^{1}H and ^{13}C resonances, and CCl_3F for the ^{19}F resonance. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a Bruker MicroTOF mass spectrometer Bruker micrOTOF (ESI-oa-TOF). Melting points were measured on a YuHua X-5 apparatus. IR spectra were recorded on a Bio-Rad FTS-40 FT-IR spectrophotometer as KBr pellets. All reactions were monitored by TLC with GF 254 silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

4.1. General procedure for the synthesis of α,α-difluoro-β-ketoamides **3** in the mixed-solvent

The mixture of 3-oxo-*N*-*p*-tolylbutanamide **1a** (96 mg, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol) was well stirred for 1.0 h in the mixed-solvent of water and PEG-400 (V_{H_2O} : $V_{PEG\text{-}400} = 3$: 1, 3.0 mL) before Selectfluor® (390 mg, 2.2 mmol) was added. Then the reaction mixture was stirred at room temperature for 6.0 h (monitored by TLC), then to the mixture was added water (10.0 mL), extracted with diethyl ether (15.0 mL × 3). The solvent was removed under reduced pressure, and the residue was purified by a short flash silica gel column chromatography to give compound **3a** (112 mg, 99%) (Eluent: petroleum ether/ethyl acetate = 5/1).

4.1.1. 2,2-Difluoro-3-oxo-N-(p-tolyl)butanamide (**3a**)

Light yellow solid; mp: 67–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1 H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 2.48 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.33 (t, *J* = 28.0 Hz), 158.96 (t, *J* = 26.7 Hz), 135.95, 133.07, 129.79, 120.57, 109.13 (t, *J* = 264.8 Hz), 25.30, 20.98; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.5; IR (KBr, neat): ν 3349, 1670, 1602, 1544, 1110, 950, 814

4.1.2. 2,2-Difluoro-3-oxo-N-(o-tolyl)butanamide (**3b**)

White solid; mp: 45–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.21–7.13 (m, 3H), 2.47 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.26 (t, *J* = 28.2 Hz), 159.32 (t, *J* = 26.7 Hz), 133.11, 130.83, 130.77, 126.92, 126.78, 123.75, 109.13 (t, *J* = 264.8 Hz), 25.06, 17.19; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.4; HRMS (ESI): calcd for $C_{11}H_{11}F_2NO_2$ ([(M+1)]$^+$) 228.0836, found 228.0831; IR (KBr, neat): ν 3351, 1673,1540, 1463, 1128, 751

4.1.3. N-(2,4-dimethylphenyl)-2,2-difluoro-3-oxobutanamide (**3c**)

Light yellow solid; mp: 41–43 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.02 (d, *J* = 8 Hz, 2H), 2.49 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.34 (t, *J* = 28.0 Hz), 159.14 (t, *J* = 26.7 Hz), 136.71, 131.43, 130.47, 130.36, 127.42, 123.47, 109.17 (t, *J* = 264.4 Hz), 25.22, 20.88, 17.28; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.4; HRMS (ESI): calcd for $C_{12}H_{13}F_2NO_2$ ([(M + 1)]$^+$) 242.0993, found 242.0987; IR (KBr, neat): ν 3299, 1698, 1653, 1540, 1506, 1139, 1116, 875, 808

4.1.4. 2,2-Difluoro-N-(2-methoxyphenyl)-3-oxobutanamide (**3d**)

Yellow solid; mp: 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.28 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8 Hz, 1H), 3.89 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.94 (t, *J* = 28.1 Hz), 158.55 (t, *J* = 26.8 Hz), 148.38, 125.75, 125.36, 121.03, 119.99, 110.27, 107.09 (t, *J* = 192.7 Hz), 55.85, 25.24; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.4; HRMS (ESI): calcd for $C_{11}H_{11}F_2NO_3$ ([(M+1)]$^+$) 244.0785, found 244.0780; IR (KBr, neat): ν 3408, 1695, 1565, 1491, 1466, 1253, 1128, 756

4.1.5. 2,2-Difluoro-N-(4-methoxyphenyl)-3-oxobutanamide (**3e**)

Light yellow solid; mp: 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.37 (t, *J* = 28.1 Hz), 158.89 (t, *J* = 26.7 Hz), 157.62, 128.64, 122.29, 114.41, 109.19 (t, *J* = 263.8 Hz), 55.56, 25.36; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.5; HRMS (ESI): calcd for $C_{11}H_{11}F_2NO_3$ ([(M+H)]$^+$) 244.0785, found 244.0780; IR (KBr, neat): ν 3327, 1683, 1653, 1558, 1540, 1515, 1119, 819

4.1.6. N-(4-ethoxyphenyl)-2,2-difluoro-3-oxobutanamide (**3f**)

Light yellow solid; mp: 91–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.42 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.99 (q, *J* = 6.8 Hz, 2H), 2.50 (s, 3H), 1.39 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.40 (t, *J* = 28.2 Hz), 158.87 (t, *J* = 26.6 Hz), 157.01, 128.41, 122.29, 114.96, 109.18 (t, *J* = 264.8 Hz), 63.81, 25.36, 14.82; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.5; HRMS (ESI):

calcd for $C_{12}H_{13}F_2NO_3$ ([(M+1)]$^+$) 258.0942, found 258.0936; IR (KBr, neat): ν 3342, 1716, 1684, 1558, 1516, 1252, 1118, 829

*4.1.7. 2,2-Difluoro-3-oxo-N-phenylbutanamide (**3g**)*

Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.54 (d, J = 8 Hz, 2H), 7.33 (t, J = 8 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.26 (t, J = 28.2 Hz), 159.13 (t, J = 27.1 Hz), 135.61, 129.25, 126.09, 120.60, 109.04 (t, J = 264.8 Hz), 25.19; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.4; HRMS (ESI): calcd for $C_{10}H_9F_2NO_2$ ([(M+1)]$^+$) 214.0680, found 214.0674; IR (KBr, neat): ν 3317, 1691, 1548, 1448, 1135, 1114, 753, 690

*4.1.8. N-(2-chlorophenyl)-2,2-difluoro-3-oxobutanamide (**3h**)*

Light yellow solid; mp: 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 1H), 7.144 (t, J = 7.6 Hz, 1H), 2.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.77 (t, J = 28.3 Hz), 158.96 (t, J = 27.2 Hz), 132.44, 129.42, 127.97, 126.58, 123.94, 121.89, 108.85 (t, J = 264.9 Hz), 25.21; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.2; HRMS (ESI): calcd for $C_{10}H_8ClF_2NO_2$ ([(M+1)]$^+$) 248.0290, found 248.0284; IR (KBr, neat): ν 3404, 1709, 1652, 1541, 1447, 1127, 755

*4.1.9. N-(4-chlorophenyl)-2,2-difluoro-3-oxobutanamide (**3i**)*

Light yellow solid; mp: 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.18 (t, J = 28.3 Hz), 159.36 (t, J = 27.4 Hz), 134.64, 130.94, 129.13, 122.04, 109.07 (t, J = 264.9 Hz), 25.20; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.3; HRMS (ESI): calcd for $C_{10}H_8ClF_2NO_2$ ([(M+1)]$^+$) 248.0290, found 248.0284; IR (KBr, neat): ν 3323, 1757, 1696, 1604, 1548, 1493, 1404, 1123, 830

*4.1.10. N-(5-chloro-2-methoxyphenyl)-2,2-difluoro-3-oxobutanamide (**3j**)*

Yellow solid; mp: 46–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 7.09 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.97 (t, J = 28.3 Hz), 158.76 (t, J = 27.2 Hz), 146.96, 126.22, 126.17, 125.32, 120.11, 111.15, 108.91 (t, J = 264.9 Hz), 56.28, 25.38; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.4; HRMS (ESI): calcd for $C_{11}H_{10}ClF_2NO_3$ ([(M+1)]$^+$) 278.0396, found 278.0390; IR (KBr, neat): ν 3396, 1751, 1706, 1539, 1484, 1125, 1024, 807, 644

*4.1.11. Ethyl 4-(2,2-difluoro-3-oxobutanamido)benzoate (**3k**)*

Yellow solid; mp: 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 2.46 (s, 3H), 1.36 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.16 (t, J = 26.9 Hz), 166.03, 159.42 (t, J = 27.2 Hz), 139.84, 130.86, 127.63, 119.86, 108.89 (t, J = 265.3 Hz), 61.25, 25.25, 14.32; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.2; HRMS (ESI): calcd for $C_{13}H_{13}F_2NO_4$ ([(M+1)]$^+$) 286.0891, found 286.0885.

*4.1.12. 2,2-Difluoro-N-(4-methoxybenzyl)-3-oxobutanamide (**3l**)*

Light yellow solid; mp: 51–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 3H), 4.40 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.34 (t, J = 28.3 Hz), 161.07 (t, J = 27.0 Hz), 159.48, 129.33, 128.42, 114.36, 109.21 (t, J = 263.6 Hz), 55.36, 43.25, 25.25; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.9; HRMS (ESI): calcd for $C_{12}H_{13}F_2NO_3$ ([(M+Na)]$^+$) 280.0761, found 286.0756.

*4.1.13. N-benzyl-2,2-difluoro-3-oxobutanamide (**3m**)*

White solid; mp: 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H), 6.88 (br, 1H), 4.45 (d, J = 6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.38 (t, J = 28.2 Hz), 161.20 (t, J = 27.0 Hz), 136.33, 129.03, 128.18, 127.89, 109.22 (t, J = 264.0 Hz), 43.73, 25.29; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −114.9; IR (KBr, neat): ν 3306, 1667, 1575, 1424, 1147, 1102, 1064, 724

*4.1.14. N-(4-chlorobenzyl)-2,2-difluoro-3-oxobutanamide (**3n**)*

Light yellow solid; mp: 59–62 °C; ^{1}H NMR (400 MHz, DMSO): δ 9.75 (br, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.34 (d, J = 6.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO): δ 195.97 (t, J = 27.7 Hz), 160.82 (t, J = 27.1 Hz), 136.96, 131.80, 129.16, 128.95, 128.39, 128.15, 109.10 (t, J = 262.7 Hz), 41.71, 24.84; ^{19}F NMR (DMSO, 376.5 MHz): δ −119.2; HRMS (ESI): calcd for $C_{11}H_{10}ClF_2NO_2$ ([(M+Na)]$^+$) 284.0266, found 284.0260.

*4.1.15. 2,2-Difluoro-4-methyl-3-oxo-N-phenylpentanamide (**3o**)*

Light yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.55 (d, J = 8 Hz, 2H), 7.34 (t, J = 8 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 3.25 (h, J = 6.8 Hz, 1H), 1.21 (s, 1H), 1.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.92 (t, J = 26.5 Hz), 159.48 (t, J = 26.9 Hz), 135.73, 129.27, 126.01, 120.52, 109.45 (t, J = 265.7 Hz), 36.49, 17.89; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −113.3; HRMS (ESI): calcd for $C_{12}H_{13}F_2NO_2$ ([(M+H)]$^+$) 242.0993, found 242.0987; IR (KBr, neat): ν 3323, 1743, 1700, 1603, 1548, 1448, 1122, 754

*4.1.16. 2,2-Difluoro-3-oxo-3-phenyl-N-(p-tolyl)propanamide (**3p**)*

Light yellow solid; mp: 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.17 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.51–7.45 (m, 4H), 7.13 (d, J = 8.4 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.34 (t, J = 27.0 Hz), 159.28 (t, J = 27.0 Hz), 135.80, 135.10, 133.25, 131.60, 130.48, 129.74, 128.89, 120.50, 110.87 (t, J = 264.9 Hz), 20.98; ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −107.8; HRMS (ESI): calcd for $C_{16}H_{13}F_2NO_2$ ([(M+1)]$^+$) 290.0993, found 290.0987; IR (KBr, neat): ν 3260, 1715, 1673, 1538, 1514, 1157, 1122, 815

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.03.016.

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