Efficient Multicomponent Synthesis of α-Trifluoromethyl Proline, Homoproline, and Azepan Carboxylic Acid Dipeptides

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Abstract: Cyclic imines bearing CF_3 and C_2F_5 group were successfully used for the first Ugi multicomponent synthesis of polyfluoroalkyl-substituted proline, homoproline, and azepan carboxylic acid derivatives. Based on the suggested reaction the first synthesis of dipeptides containing α-CF_3 cyclic amino acids residue was described. The scope and limitations of the approach are discussed.

Key words: amino acids, peptides, fluorine, multicomponent reactions, imines

Fluorinated analogues of proline were found to be very effective to control the *cis-trans* isomerisation of the prolyl bonds[1] and for the design of enzyme inhibitors.[2] Pipecolinic acid (homoproline) is abundant in many drugs and natural products such as immunosuppresants or cyclic peptides with antifungal activity.[3] Recently, the synthesis of α-trifluoromethyl (α-CF_3) proline [4] and C_2F_5-proline [5] have been described. CF_3-Imino acids derivatives (with five-, six-, or seven-membered cycle) have been also obtained by ring-closing metathesis.[6]

Modification of peptides and proteins by incorporation of α-CF_3 amino acids is a modern strategy in drug discovery[7] due to the unique stereoelectronic properties of the trifluormethyl group.[8] However, peptides containing α-CF_3 proline and its homologues are, to the best of our knowledge, still unexplored.

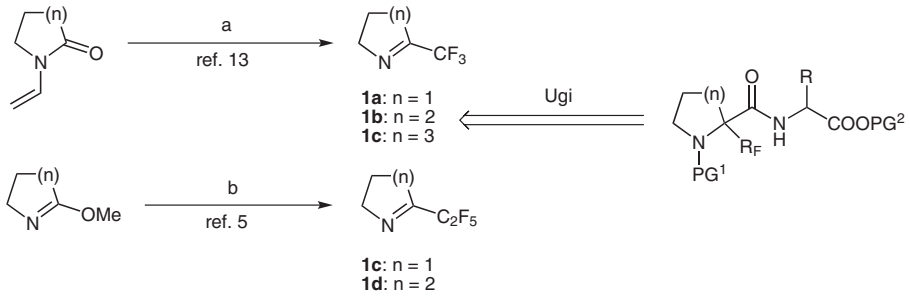
A conventional protocol for the peptide synthesis is based on condensation of protected amino acids.[9] However, the same approach can be ineffective in case of CF_3-amino acids due to low nucleophilicity of the amino group[10] and sterical hindrance of carboxy group by CF_3.[11] Therefore, the development of noncondensation approaches to dipeptides of α-CF_3 amino acids is a significant problem.

Substituted cyclic imines have been used for the Ugi synthesis of substituted proline and homoproline and their dipeptides.[12] Recently, we have developed the Ugi reaction with CF_3-carbonyl compounds and their imines.[13] We propose that the Ugi reaction can be used as an effective alternative of the condensative method for the synthesis of the target structures.

In this paper we report the first synthesis of α-CF_3 cyclic amino acids derivatives and dipeptides by Ugi reaction with polyfluoroalkylated cyclic imines (Scheme 1).

Polyfluoroalkyl-substituted cyclic imines **1a–e** can be easily prepared from commercially available compounds and very cheap fluorinated starting materials (CF_3COOEt or C_2F_5Li, prepared from C_2F_5H) in good yields (Scheme 1).[5,14] We decided to explore the synthetic potential of the Ugi multicomponent reaction with imines **1a–e**.

Using a model experiment for the Ugi reaction (entry 1, Table 1), we found the following optimal conditions: CH_2Cl_2, 0.1 M, –20 °C to r.t., 12 h (Scheme 2). The CF_3-substituted cyclic imines **1a–e** react only with strong acids, such as CCl_3COOH or CF_3COOH, and trifluoroacetic acid was the reagent of choice. It is important that



Scheme 1 MCR approach to dipeptides of α-CF_3 cyclic amino acids. *Reagents and conditions*: (a) CF_3COOEt, NaH then HCl (concd), reflux; (b) C_2F_5Li, $BF_3{\cdot}OEt_2$.

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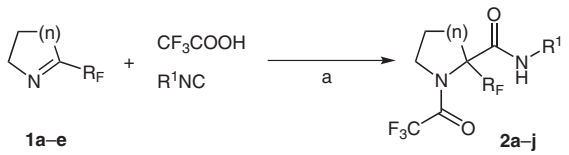


Scheme 2 *Reagents and conditions*: (a) CH_2Cl_2, –20 °C to r.t., 12 h.

Table 1 The Ugi Reaction with Polyfluorosubstituted Cyclic Imines[15,16]

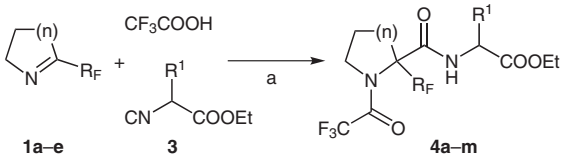
Entry	n	R_F	R^1	Product	Yield (%)
1	1	CF_3	*t*-Bu	**2a**	80
2	1	CF_3	Bn	**2b**	81
3	1	C_2F_5	*t*-Bu	**2c**	61
4	2	CF_3	*t*-Bu	**2d**	63
5	2	CF_3	Et	**2e**	75
6	2	CF_3	4-MeOBn	**2f**	89
7	2	C_2F_5	Bn	**2g**	70
8	2	C_2F_5	4-EtOBn	**2h**	71
9	3	CF_3	*t*-Bu	**2i**	59
10	3	CF_3	4-MeOBn	**2j**	70

the trifluoroacetyl group can be easily removed subsequently from products in mild conditions.[12]

The CF_3-substituted five- and six-membered cyclic imines **1a**,**c** react smoothly, and the corresponding proline and homoproline derivatives were isolated in high yields (Table 1). Imines **1b**,**d** containing the C_2F_5 group also react similarly and give fluorinated products **2c**,**g** in good yields. Previously, we have observed the formation of exocyclic double-bond product **A** in the Ugi reaction with seven-membered Me-imine (Scheme 3). In the case of **1e** it is not possible, and target products **2i**,**j** are formed in good yields.

In general, polyfluorosubstituted cyclic imines react smoothly and appear to be cheap and very effective starting materials for one-step, multicomponent preparation of 2-polyfluorosubstituted proline, homoproline, and azepan carboxylic acid derivatives.

Several times, isocyanoacetic acid derivatives were used for the multicomponent synthesis of substituted amino acid dipeptides. The combination of polyfluoroalkylated imines **1** and isocyanoacetic acid derivatives **3** opens a new effective one-step approach to earlier unknown dipeptides **4a**–**k** (Scheme 4) containing CF_3- and C_2F_5-substituted proline and its homologues and natural amino acid residues (Table 2). All compounds were isolated in good yields as a mixture of diastereomers (ca. 1:1, according to GC–MS of reaction mixtures), that is usual for the Ugi reaction.[12]

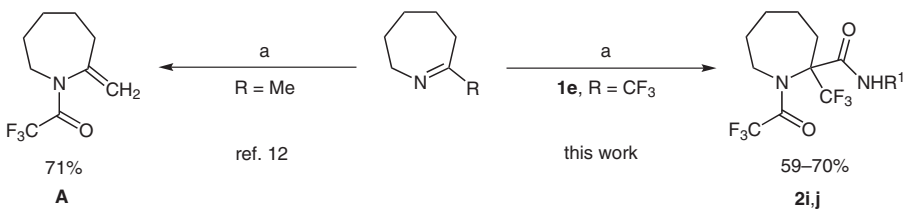


Scheme 4 *Reagents and conditions*: (a) CH_2Cl_2, 0.1 M, –20 °C to r.t., 12 h.

Table 2 Synthesis of Polyfluoroalkylated Dipeptides

Entry	n	R_F	R^1	Product	Yield (%)
1	1	CF_3	Me	**4a**	61
2	1	CF_3	Bn	**4b**	60
3	1	CF_3	$MeSCH_2CH_2$	**4c**	67
4	1	CF_3	$EtOOCCH_2CH_2$	**4d**	51
5	1	CF_3	3-indolylCH_2	**4e**	59
6	1	C_2F_5	Me	**4f**	53
7	2	CF_3	H	**4g**	79
8	2	CF_3	Me	**4h**	56
9	2	CF_3	$MeSCH_2CH_2$	**4i**	44
10	2	CF_3	$EtOOCCH_2CH_2$	**4j**	50
11	2	C_2F_5	Me	**4k**	50
12	3	CF_3	H	**4l**	54
13	3	CF_3	*i*-Pr	**4m**	59

In conclusion the first example of the Ugi reaction with 2-polyfluoroalkyl-substituted pyrroline, piperideine, and tetrahydroazepine was described. The reaction opens a new straightforward route to polyfluorosubstituted proline, homoproline, and azepan carboxylic acid derivatives. The reaction represents a general one-step approach to construct a broad variety of earlier unknown orthogo-



Scheme 3 Seven-membered imines in the Ugi reaction. *Reagents and conditions*: (a) Ugi conditions: TFA, R^1NC, CH_2Cl_2, 0.1 M, –20 °C to r.t.

nally protected dipeptides, containing polyfluorosubstituted cyclic amino acid residues from very cheap fluorinated starting materials.

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References and Notes

(1) (a) Renner, C.; Alefelder, S.; Bae, J. H.; Budisa, N.; Huber, R.; Moroder, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 923. (b) Improta, R.; Benzi, C.; Barone, V. *J. Am. Chem. Soc.* **2001**, *123*, 12568. (c) Golbik, R.; Yu, C.; Weyher-Stingl, E.; Huber, R.; Moroder, L.; Budisa, N.; Schiene-Fischer, C. *Biochemistry* **2005**, *44*, 16026.

(2) Chen, L.; Kim, Y. M.; Kucera, D. J.; Harrison, K. E.; Bahmanyar, S.; Scott, J. M.; Yazbeck, D. *J. Org. Chem.* **2006**, *71*, 5368.

(3) Wu, W.-J.; Raleigh, D. P. *J. Org. Chem.* **1998**, *63*, 6689; and references therein.

(4) Chaume, G.; Van Severen, M.-C.; Marinkovic, S.; Brigaud, T. *Org. Lett.* **2006**, *8*, 6123.

(5) Shevchenko, N. E.; Nenajdenko, V. G.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2008**, *129*, 390.

(6) (a) Osipov, S. N.; Bruneau, C.; Picquet, M.; Kolomiets, A. F.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2053. (b) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Picquet, M.; Dixneuf, P. H. *Eur. J. Org. Chem.* **2001**, 3891. (c) Eckert, M.; Monnier, F.; Thchetnikov, G. T.; Titanyuk, I. D.; Osipov, S. N.; Toupet, L.; Dérien, S.; Dixneuf, P. H. *Org. Lett.* **2005**, *7*, 3741.

(7) (a) Moldeni, M.; Pesenti, C.; Sani, M.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2004**, *125*, 1735. (b) Koksch, B.; Sewald, N.; Hofmann, H.-J.; Burger, K.; Jakubke, H.-J. *J. Pept. Sci.* **1997**, *3*, 157.

(8) (a) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753. (b) Zanda, M. *New J. Chem.* **2004**, *28*, 1401. (c) Jäckel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483.

(9) (a) Hodgson, D. R. W.; Sanderson, J. M. *Chem. Soc. Rev.* **2004**, *33*, 422. (b) Thust, S.; Koksch, B. *Tetrahedron Lett.* **2004**, *45*, 1163.

(10) Kobsev, S. P.; Soloshonok, V. A.; Yagupol'skii, Y. u. L.; Kukhar', V. P. *J. Gen. Chem. USSR* **1989**, *59*, 801.

(11) Nagai, T.; Nishioka, G.; Koyama, M.; Ando, A.; Mild, T.; Kumadaki, I. *J. Fluorine Chem.* **1992**, *57*, 229.

(12) Nenajdenko, V. G.; Gulevich, A. V.; Balenkova, E. S. *Tetrahedron* **2006**, *62*, 5922.

(13) Gulevich, A. V.; Shevchenko, N. E.; Balenkova, E. S.; Röschenthaler, G.-V.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 11706.

(14) The CF_3-imines **1a**,**c**,**e** were prepared using a standard Claisen condensation and subsequent decarboxylation, details will be published in due course.
Synthesis of 2-CF_3 Pyrroline (1a)
The stirred suspension of 60% NaH (26.7 g 0.665 mol) in anhyd THF (250 mL) was heated at reflux while a mixture of freshly distilled *N*-vinylpyrrolidin-2-one (55.0 g, 0.50 mol) and ethyl trifluoroacetate (78.0 g, 0.55 mol) was slowly added. After refluxing for an additional hour the reaction mixture was cooled to r.t. and carefully diluted with solution of AcOH (40 g) in H_2O (100 mL). The organic layer was separated and the solution of crude keto lactam product was slowly added to 6 N HCl (0.5 L) under stirring and heating at reflux. THF was removed during the addition by use of the distilling head. After heating at reflux for 60 h the reaction mixture was cooled to 0 °C, made basic to pH 12 by using 50% KOH aq and extracted with Et_2O (4 × 100 mL). The combined organic layers were dried over K_2CO_3 and concentrated under atmospheric pressure to give 73 g of crude cyclic hemi-aminal product as an oil that solidified under cooling. To remove H_2O the cyclic hemi-aminal was distilled at atmospheric pressure to the receiving flask charged with anhyd Na_2SO_4 (20 g). The drying agent was removed by filtration to afford 54.0 g (79% yield) of product as a clear, colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.97–2.12 (m, 2 H), 2.70–2.78 (m, 2 H), 3.98–4.08 (m, 2 H). ^{19}F NMR (188 MHz, $CDCl_3$): δ = –71.4 (s, 3 F). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.9 (q, *J* = 285.4 Hz, CF_3), 115.9 (q, *J* = 35.4 Hz), 62.2, 33.7, 22.6. HRMS (EI): *m/z* calcd for $C_5H_6F_3N$: 137.0452; found: 137.0462.

(15) **General Procedure for the Ugi Reaction**
The imine (1 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (1 mmol), then isocyanide was added at –20 °C. The mixture was stirred for 12 h and treated with a mixture of EtOH–HCl aq (10:1, 0.5 mL) to remove any remaining isocyanide. The solvent was evaporated, and the residue was purified by column chromatography (hexane–EtOAc,4:1).

(16) **Selected Analytical Data**
Compound **2a**: yield 80%; colorless oil; R_f = 0.8 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 1.97–2.63 (m, 2 H), 2.25–2.60 (m, 2 H), 3.67–3.85 (m, 1 H), 3.90–4.07 (m, 1 H), 6.00 (br s, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.7 (s, 3 F), –69.1 (s, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 156.1 (m), 124.9 (q, *J* = 285.4 Hz, CF_3), 115.9 (q, *J* = 288.4 Hz, CF_3), 52.4, 49.6 (m), 33.8, 28.3, 23.8 ppm. HRMS (EI): *m/z* calcd for $C_{12}H_{16}F_6N_2O_2$: 334.1116; found: 334.1112.
Compound **2c**: yield 61%; white solid, mp 55–57 °C; R_f = 0.8 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 2.00–2.19 (m, 2 H), 2.38–2.55 (m, 2 H), 3.50–3.75 (m, 1 H), 3.90–4.20 (m, 1 H), 6.1 (br s, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.8 (s, 3 F), –80.5 (s, 3 F), –106.2, –107.7, –109.0, –110.5 (AB system, δ_A = –109.3 ppm, δ_B = –107.4 ppm, $^2J_{AB}$ = 275.9 Hz, 2 F) ppm. HRMS (EI): *m/z* calcd for $C_{13}H_{16}F_8N_2O_2$: 384.1084; found: 384.1080.
Compound **2g**: yield 70%; white solid; mp 121–123 °C; R_f = 0.8 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.68–1.87 (m, 3 H), 1.94–2.17 (m, 2 H), 2.31–2.55 (m, 1 H), 3.38 (t, *J* = 14.7 Hz, 1 H), 3.82–4.11 (m, 1 H), 4.40–4.68 (m, 2 H), 6.0 (br s, 1 H), 6.86 (d, *J* = 8.6 Hz), 7.19–7.43 (m, 5 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –71.2 (s, 3 F), –80.6 (s, 3 F), –106.2, –107.7, –109.6, –111.1 (AB system, δ_A = –110.0 ppm, δ_B = –107.4 ppm, $^2J_{AB}$ = 281.1 Hz, 2 F) ppm. HRMS (EI): *m/z* calcd for $C_{17}H_{16}F_8N_2O_2$: 432.1084; found: 432.1102.
Compound **2i**: yield 59%; colorless oil; R_f = 0.8 (hexanes–EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.30 (m, 1 H), 1.36 (s, 9 H), 1.66–1.90 (m, 3 H), 1.90–2.00 (m, 1 H), 2.05–2.17 (m, 2 H), 2.23–2.33 (m, 1 H), 3.20–3.30 (m, 1 H), 3.90–4.00 (m, 1 H), 5.40 (br s)ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –69.8 (s, 3 F), –70.1 (s, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 157.4 (q, *J* = 35.9 Hz), 125.9 (q, *J* = 289.8 Hz), 116.3 (q, *J* = 288.3 Hz), 70.2 (q, *J* = 24.9 Hz), 52.0, 46.2, 33.0, 30.5, 28.6, 22.3, 28.3 ppm. HRMS (EI): *m/z* calcd for $C_{14}H_{20}F_6N_2O_2$: 362.1429; found: 362.1433.

Compound **4b** (mixture of diastereomers, ca. 1:1): yield 60%; yellow oil; R_f = 0.6 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24, 1.25 (dt, *J* = 6.9 Hz, 3 H), 1.90–2.15 (m, 2 H), 2.26–2.50 (m, 2 H), 3.10–3.22 (m, 2 H), 3.65–3.85 (m, 1 H), 3.89–4.04 (m, 1 H), 4.09–4.30 (m, 2 H), 4.80–4.95 (m, 1 H) 6.6 (br s, 1 H), 7.00–7.35 (m, 5 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –69.2 (s, 3 F), –73.6, –73.7 (ds, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.5, 164.1, 163.9, 155.4 (q, *J* = 34.4 Hz), 135.3, 135.2, 129.3, 129.2, 128.4, 127.1, 121.7, 121.6 (dq, *J* = 286.6 Hz), 118.8 (q, *J* = 277.6 Hz), 72.7 (m), 61.7, 61.6, 53.7, 53.5, 49.5, 37.5, 37.3, 33.8, 33.7, 23.6, 13.8 ppm. HRMS (EI): *m/z* calcd for $C_{19}H_{20}F_6N_2O_4$: 454.1327; found: 454.1333.

Compound **4f** (mixture of diastereomers, ca. 1:1): yield 53%; yellow oil; R_f = 0.6 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.3 Hz, 3 H), 1.40–1.55 (m, 3 H), 1.97–2.25 (m, 2 H), 2.45–2.70 (m, 2 H), 3.60–3.81 (m, 1 H), 4.00–4.40 (m, 3 H), 4.45–4.70 (m, 1 H), 6.00, 7.50 (br ds, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.2, –73.3 (ds, 3 F), –79.8, –80.0 (ds, 3 F), –105.5, –107.0, –107.6, –108.7 (AB system, δ_A = –108.3 ppm, δ_B = –106.3 ppm, $^2J_{AB}$ = 277.6 Hz), –106.0, –107.4, –109.0, –110.2 (AB system, δ_A = –109.2 ppm, δ_B = –107.2 ppm, $^2J_{AB}$ = 277.6 Hz)ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 172.1, 163.9, 163.8, 156.8, 115.9 (q, *J* = 286.9 Hz), 108.0–126.0 (unresolved signals, C_2F_5 group), 72.7 (m), 61.8, 61.7, 49.7 (m), 49.1, 34.1, 23.1, 17.8, 17.7, 14.0 ppm. HRMS (EI): *m/z* calcd for $C_{14}H_{16}F_8N_2O_4$: 428.0982; found: 428.0978.

Compound **4i** (mixture of diastereomers, ca. 1:1): yield 44%; colorless oil; R_f = 0.6 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.3 Hz, 3 H), 1.70–1.95 (m, 4 H), 2.05–2.40 (m, 6 H), 2.40–2.55 (m, 2 H), 3.35–3.60 (m, 1 H), 3.85–4.10 (m, 1 H), 4.21 (q, *J* = 7.3 Hz, 2 H), 4.53–4.70 (m, 1 H), 6.55–6.80 (m, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.05, –68.41 (ds, 3 F), –70.0, –70.1 (ds, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 171.3, 164.5, 164.0, 157.0 (m), 125.3, 125.1 (dq, *J* = 289.8 Hz), 115.9 (q, *J* = 287.6 Hz), 66.3 (m), 61.8, 52.2, 42.0, 41.7, 30.9, 30.6, 29.7, 29.5, 28.2, 27.7, 21.5, 21.3, 15.2, 15.2, 15.1, 15.0, 13.9 ppm. HRMS (EI): *m/z* calcd for $C_{16}H_{22}F_6N_2O_4S$: 452.1205; found: 452.1220.

Compound **4k** (mixture of diastereomers, ca. 1:1): yield 50%; colorless oil; R_f = 0.6 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.20–1.35 9m, 3 H), 1.44 (t, *J* = 7.3 Hz, 3 H), 1.70–1.87 (m, 3 H), 1.90–1.25 (m, 2 H), 2.30–2.50 (m, 1 H), 3.20–3.50 (m, 1 H), 3.80–4.00 (m, 1 H), 4.10–4.30 (m, 2 H), 4.45–4.68 (m, 1 H), 6.6, 6.2 (br ds, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –70.6, –70.5 (ds, 3 F), –79.9, –79.8 (ds, 3 F), –106.2, –107.7, –109.7, –111.2 (AB system, δ_A = –110.0 ppm, δ_B = –107.4 ppm, $^2J_{AB}$ = 277.6 Hz), –106.3, –107.8, –109.5, –111.0 (AB system, δ_A = –109.8 ppm, δ_B = –107.5 ppm, $^2J_{AB}$ = 277.6 Hz)ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 172.3, 162.7, 162.6, 157.5 (q, *J* = 36.6 Hz), 116.0 (q, *J* = 287.6 Hz), 111.0–124.0 (unresolved signals, C_2F_5 group), 67.9 (m), 61.8, 61.7, 49.0, 48.9, 48.8 (m), 26.8, 26.3, 20.3, 30.2, 18.0, 17.7, 14.3, 14.2, 13.9, 13.8 ppm. HRMS (EI): *m/z* calcd for $C_{15}H_{18}F_8N_2O_4$: 442.1139; found: 442.1133.

Compound **4l**·H_2O: yield 54%; colorless oil; R_f = 0.6 (hexanes–EtOAc, 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz), 1.55–1.65 (m, 1 H), 1.80–2.05 (m, 4 H), 2.50–2.70 (m, 1 H), 3.00–3.15 (m, 1 H), 3.60–3.70 (m, 1 H), 4.02 (d, *J* = 18.0 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.54 (q, *J* = 18.0 Hz, 1 H), 4.9 (br s, 1 H) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.3 (q, *J* = 9.7 Hz, 3 F), –80.4 (q, *J* = 9.7 Hz, 3 F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 169.6, 169.1, 124.6 (q, *J* = 288.4 Hz), 122.4 (q, *J* = 291.3 Hz), 96.5 (q, *J* = 34.4 Hz), 70.2 (m), 60.3, 44.0, 42.7 (m), 32.6, 30.0, 29.9, 22.5, 13.9 ppm. HRMS (EI): *m/z* calcd for $C_{13}H_{16}F_6N_2O_4$: 378.1014; found: 378.1000.