Full experimental and spectral details

ULTRASOUND-PROMOTED ENVIRONMENT-FRIENDLY SYNTHESIS OF 5-(3,3,3-TRIFLUORO-2-OXOPROPYLIDENE)PYRROLIDIN-2-ONES

[authors information deleted to maintain the integrity of the review process]

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General Experimental Methods

Methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate was prepared by us following reported procedure.^[1] TEA was distilled prior to use. All amines and ethanol were used as obtained commercially.

All reactions were carried out with a microtip probe connected to a 500 W Sonics Vibracell ultrasonic processor operating at 20 kHz at 20% of the maximum power output. The progress of reactions was monitored by TLC.

Melting points were recorded in open capillary on an Instrutherm DF-3600 II apparatus and are uncorrected.

Low-resolution mass spectra were obtained on a Varian 210 MS connected to a Varian 431 GC. The GC was equipped with a split-splitless injector, cross-linked to a Varian Factor Four™ capillary column (30 m × 0.25 mm), and helium was used as the carrier gas.

¹H NMR and ¹³C NMR spectra were acquired on a Bruker DPX400 spectrometer (400.13 MHz for ¹H and 100.62 MHz for ¹³C) in 5 mm sample tubes at 298 K in CDCl₃ or DMSO-*d*₆. For ¹H NMR spectra acquired in CDCl₃, chemical shifts are reported as δ values in ppm and are calibrated according to internal TMS. For ¹H NMR spectra acquired in DMSO-*d*₆, chemical shifts are reported as δ values in ppm and are calibrated according to internal DMSO. For ¹³C NMR spectra, chemical shifts are reported as δ values in ppm relative to chloroform or DMSO.

For the high resolution mass analyses, compounds were dissolved in a solution of 50% (v/v) chromatographic grade acetonitrile, 50% (v/v) deionized water and 0.1% formic acid. The solutions were infused directly individually into the ESI source by means of a syringe pump (Harvard Apparatus) at a flow rate of 10 μ L.min⁻¹. ESI(+)-MS were acquired using a hybrid high-resolution and high accuracy (5 μ L/L) microTof (Q-TOF) mass spectrometer

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(Bruker Scientific) under the following conditions: capillary and cone voltages were set to +3500 V and +40 V, respectively, with a de-solvation temperature of 100°C. The data were collected in the m/z range of 70–700 at the speed of two scans per second, providing the resolution of 50,000 (FWHM) at m/z 200.

The X-ray data were collected using a Bruker APEX II CCD area-detector diffractometer with graphite-monochromatised Mo K α radiation. The crystal structures of the complexes were solved using the SHELX package.^[2] All non-hydrogen atoms were refined with anisotropic displacement parameters, and the hydrogen atoms were included at their theoretical ideal positions. More detailed information about the structure determinations is given on pages S13-S16.

Experimental Procedures

Triethylamine (101 mg, 1.0 mmol) was added to a solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxohept-4-enoate **1** (240 mg, 1.0 mmol) and appropriated amine (1.0 mmol) in ethanol (15 mL). The mixture was sonicated for the time indicated in Table 1. Ethyl acetate (20 mL) was added and the organic layer was washed with H₂O (3 × 15 mL), dried with anhydrous MgSO₄ and concentrated under reduced pressure to afford the desired products. Products **3a**, **3b** and **4f** were obtained in acceptable purity grades without further purification. Products **4k** and **4q** were purified by recrystalization in hexane. Other products were purified by silica gel column chromatography using ethyl acetate and hexane as eluents (15:7 AcOEt/hexane for **4e**, 7:1 AcOEt/hexane for **4g** and **4i**, 4:1 AcOEt/hexane for **4h**, **4j**, **4m**, **4n**, **4p**, **4s** and **4t**, 5:1 AcOEt/hexane for **4l**, 7:3 AcOEt/hexane for **4o**, 20:1-20:7 AcOEt/hexane for **4r**).

²Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

Characterization data for compounds 3a,b and 4e-t

Methyl 7,7,7-trifluoro-4-((1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (3a):

Yield: 0.288 g (85%); yellowish oil; ^1H NMR (400 MHz, CDCl_3): δ ppm 11.39 (s, 1H), 5.36 (s, 1H), 4.23-4.19 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.60 (m, 4H), 2.33 (oct, 1H, $J = 6.3$ Hz), 1.05 (t, 6H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 177.0 (q, $J_{\text{CF}} = 33.0$ Hz), 171.6, 170.7, 170.3, 117.5 (q, $J_{\text{CF}} = 288.6$ Hz), 88.3, 62.0, 52.6, 52.1, 31.6, 26.8, 19.0, 17.6; MS-EI: m/z (%) 340 (M+1, 18), 339 (M, 5), 280 (100), 270 (19), 248 (32), 69 (8), 59 (23); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{14}\text{H}_{20}\text{F}_3\text{NO}_5$: 340.1372, found 340.1388.

Methyl 7,7,7-trifluoro-4-((1-methoxy-4-(methylthio)-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (3b):

Yield: 0.318 g (86%); yellowish oil; ^1H NMR (400 MHz, CDCl_3): δ ppm 11.26 (s, 1H), 5.38 (s, 1H), 4.69-4.64 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.72-2.53 (m, 8H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 177.0 (q, $J_{\text{CF}} = 33.2$ Hz), 171.6, 171.0, 170.6, 117.3 (q, $J_{\text{CF}} = 288.4$ Hz), 88.4 (q, $J_{\text{CF}} = 1.5$ Hz), 54.5, 53.0, 52.1, 31.6, 31.5, 29.7, 26.8, 15.1; MS-EI: m/z (%) 372 (M+1, 15), 371 (M, 7), 324 (13), 228 (80), 196 (88), 178 (33), 134 (30), 69 (27), 61 (100); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{14}\text{H}_{20}\text{F}_3\text{NO}_5\text{S}$: 372.1092, found 372.1106.

Methyl 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetate (4e):

Yield: 0.220 g (83%); yellowish solid; mp 111-112°C; ^1H NMR (400 MHz, CDCl_3): δ ppm 5.69 (s, 1H), 4.37 (s, 2H), 3.80 (s, 3H), 3.44-3.40 (m, 2H), 2.73-2.70 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 178.8 (q, $J_{\text{CF}} = 34.4$ Hz), 176.4, 167.4, 166.2, 116.2 (q, $J_{\text{CF}} = 293.4$ Hz), 91.4, 52.9, 41.8, 27.1, 26.8; MS-EI: m/z (%) 265 (M, <5), 245 (23), 206 (24), 196 (100), 168 (85), 138 (37), 108 (65), 69 (15); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{10}\text{H}_{10}\text{F}_3\text{NO}_4$: 266.0640, found 266.0635.

2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetamide (4f):

Yield: 0.202 g (81%); whitish solid; mp 192-195°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 7.57 (s, 1H), 7.25 (s, 1H), 5.86 (s, 1H), 4.24 (s, 2H), 3.25 (s, 2H), 2.66-2.64 (m, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 177.2, 177.0 (q, $J_{\text{CF}} = 32.5$ Hz), 171.0, 166.6, 116.2 (q, $J_{\text{CF}} = 292.5$ Hz), 89.9, 42.9, 27.1, 26.8; MS-EI: m/z (%) 250 (M, <5), 230 (65), 205 (30), 181 (100), 163 (54), 136 (32), 124 (58), 108 (83), 69 (55), 43 (60); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}_3$: 251.0644, found 251.0631.

1-propyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4g):

Yield: 0.221 g (94%); yellowish oil; ^1H NMR (400 MHz, CDCl_3): δ ppm 5.85 (s, 1H), 3.58 (t, 2H, $J = 7.5$ Hz), 3.37-3.33 (m, 2H), 2.65-2.62 (m, 2H), 1.64 (sext, 2H, $J = 7.5$ Hz), 0.96 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 178.8 (q, $J_{\text{CF}} = 33.9$ Hz), 177.2, 168.6, 116.5 (q, $J_{\text{CF}} = 291.5$ Hz), 91.0, 42.6, 27.3, 26.8, 19.9, 11.2; MS-EI: m/z (%) 235 (M, 10), 236 (M+1, 22), 166 (100), 138 (15), 124 (30), 68 (37); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{10}\text{H}_{12}\text{F}_3\text{NO}_2$: 236.0898, found 236.0887.

1-(2-chloroethyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4h):

Yield: 0.224 g (88%); reddish oil; ^1H NMR (400 MHz, CDCl_3): δ ppm 5.95 (s, 1H), 3.97 (t, 2H, $J = 6.4$ Hz), 3.70 (t, 2H, $J = 6.4$ Hz), 3.40-3.37 (m, 2H), 2.68-2.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 178.9 (q, $J_{\text{CF}} = 34.3$ Hz), 176.9, 167.8, 116.4 (q, $J_{\text{CF}} = 291.4$ Hz), 91.6, 42.5, 39.2, 27.2, 26.9; MS-EI: m/z (%) 255 (M, <5), 256 (M+1, <5), 220 (33), 186 (100), 130 (45), 69 (12); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_9\text{H}_9\text{ClF}_3\text{NO}_2$: 256.0352, found 256.0343.

1-butyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4i):

Yield: 0.162 g (65%); yellowish oil; ^1H NMR (400 MHz, CDCl_3): δ ppm 5.85 (s, 1H), 3.60 (t, 2H, $J = 7.5$ Hz), 3.36-3.33 (m, 2H), 2.65-2.61 (m, 2H), 1.58 (quint, 2H, $J = 7.5$ Hz), 1.37 (sext, 2H, $J = 7.3$ Hz), 0.97 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 178.8 (q, $J_{\text{CF}} = 33.8$), 177.1, 168.5, 116.5 (q, $J_{\text{CF}} = 291.5$ Hz), 90.9, 40.8, 28.5, 27.3, 26.8, 20.1, 13.5;

MS-EI: m/z (%) 250 (M, 5), 193 (25), 180 (75), 152 (100), 138 (45), 110 (65), 69 (65);

HRMS-ESI: m/z $[MH]^+$ calcd. for $C_{11}H_{14}F_3NO_2$: 250.1055, found 250.1044.

1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4j):

Yield: 0.235 g (83%); brownish solid; mp 98-100°C (lit. 96-98°C)^[1]; 1H NMR (400 MHz, $CDCl_3$): δ ppm 7.37-7.28 (m, 3H), 7.24-7.22 (m, 2H), 5.89 (s, 1H), 4.79 (s, 2H), 3.37-3.33 (m, 2H), 2.72-2.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 178.6 (q, J_{CF} = 34.1 Hz), 177.2, 167.7, 133.9, 129.0, 128.3, 127.4, 116.3 (q, J_{CF} = 292.0 Hz), 92.2, 44.7, 27.3, 26.7; MS-EI: m/z (%) 283 (M, 18), 214 (100), 186 (25), 91 (80), 69 (7); HRMS-ESI: m/z $[MH]^+$ calcd. for $C_{14}H_{12}F_3NO_2$: 284.0898, found 284.0890.

1-phenyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4k):

Yield: 0.255 (95%); whitish solid; mp 146-149°C (lit. 146-149°C)^[1]; 1H NMR (400 MHz, $CDCl_3$): δ ppm 7.58-7.48 (m, 3H), 7.21-7.18 (m, 2H), 5.66 (s, 1H), 3.54-3.50 (m, 2H), 2.83-2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 179.2 (q, J_{CF} = 34.1 Hz), 176.5, 169.2, 133.2, 130.2, 129.8, 127.2, 116.4 (q, J_{CF} = 291.4 Hz), 92.7, 27.8, 27.0; MS-EI: m/z (%) 269 (M, 6), 200 (100), 172 (44), 144 (15), 77 (18), 51 (18); HRMS-ESI: m/z $[MH]^+$ calcd. for $C_{13}H_{10}F_3NO_2$: 270.0742, found 270.0731.

5-(3,3,3-trifluoro-2-oxopropylidene)-1-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (**4l**):

Yield: 0.199 g (59%); whitish solid; mp 84-86°C; ^1H NMR (400 MHz, CDCl_3): δ ppm 7.79 (d, 1H, $J = 8.0$ Hz), 7.72 (t, 1H, $J = 7.9$ Hz), 7.51 (s, 1H), 7.43 (d, 1H, $J = 7.9$ Hz), 5.64 (s, 1H), 3.57-3.53 (m, 2H), 2.87-2.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 179.2 (q, $J_{\text{CF}} = 34.6$ Hz), 176.1, 168.2, 133.8, 132.9 (q, $J_{\text{CF}} = 33.5$ Hz), 130.9, 130.8 (q, $J_{\text{CF}} = 1.0$ Hz), 126.7 (q, $J_{\text{CF}} = 3.7$ Hz), 124.6 (q, $J_{\text{CF}} = 3.8$ Hz), 123.2 (q, $J_{\text{CF}} = 272.6$ Hz), 116.2 (q, $J_{\text{CF}} = 291.2$ Hz), 92.9, 27.8, 27.0; MS-EI: m/z (%) 337 (M, <5), 268 (100), 240 (50), 145 (9), 192 (4), 69 (12); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{14}\text{H}_9\text{F}_6\text{NO}_2$: 338.0616, found 338.0616.

1-(3-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4m**):

Yield: 0.182 g (61%); yellowish solid; mp 105-106°C; ^1H NMR (400 MHz, CDCl_3): δ ppm 7.46 (t, 1H, $J = 8.1$ Hz), 7.04 (dd, 1H, $J = 2.2$ Hz, $J = 8.4$ Hz), 6.77 (d, 1H, $J = 7.8$ Hz), 6.71 (t, 1H, $J = 2.1$ Hz), 5.69 (s, 1H), 3.84 (s, 3H), 3.53-3.49 (m, 2H), 2.83-2.79 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 179.2 (q, $J_{\text{CF}} = 34.2$ Hz), 176.4, 169.1, 160.9, 134.2, 130.9, 119.1, 116.3 (q, $J_{\text{CF}} = 291.4$ Hz), 115.5, 113.0, 92.9, 55.5, 27.8, 27.0; MS-EI: m/z (%) 299 (M, <5), 230 (100), 202 (>5), 69 (8); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{NO}_3$: 300.0848, found 300.0823.

1-(p-tolyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4n):

Yield: 0.155 g (55%); whitish solid; mp 139-140°C (lit. 129-131°C)^[1]; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.34 (d, 2H, *J* = 8.1 Hz), 7.06 (d, 2H, *J* = 8.1 Hz), 5.66 (s, 1H), 3.51-3.48 (m, 2H), 2.81-2.77 (m, 2H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 179.1 (q, *J*_{CF} = 34.1 Hz), 176.7, 169.5, 139.9, 130.7, 130.4, 126.8, 116.3 (q, *J*_{CF} = 291.4 Hz), 92.6, 27.7, 26.9, 21.1; MS-EI: *m/z* (%) 283 (M, 58), 214 (100), 186 (30), 158 (10), 91 (12); HRMS-ESI: *m/z* [MH]⁺ calcd. for C₁₄H₁₂F₃NO₂: 284.0898, found 284.0893.

1-(4-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4o):

Yield: 0.191 g (64%); whitish solid; mp 88-90°C (lit. 88-90°C)^[1]; ¹H NMR (200 MHz, CDCl₃): δ ppm 7.09 (s, 2H), 7.07 (s, 2H), 5.66 (s, 1H), 3.86 (s, 3H), 3.54-3.46 (m, 2H), 2.84-2.77 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ ppm 179.1 (q, *J*_{CF} = 34.2 Hz), 177.1, 169.8, 160.2, 128.2, 125.3, 115.3, 116.3 (q, *J*_{CF} = 291.2 Hz), 92.7, 55.5, 27.7, 26.9; MS-EI: *m/z* (%) 299 (M, 100), 230 (88), 202 (18), 188 (18), 159 (10); HRMS-ESI: *m/z* [MH]⁺ calcd. for C₁₄H₁₂F₃NO₃: 300.0848, found 300.0836.

1-(4-fluorophenyl)-5-(3,3,3-trifluor-2-oxopropylideno)-2-pyrrolidinona (4p):

Yield: 0.129 g (45%); yellowish solid; mp 141-144°C; ^1H NMR (400 MHz, CDCl_3): δ ppm 7.27-7.17 (m, 4H), 5.63 (s, 1H), 3.53-3.50 (m, 2H), 2.83-2.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 179.1 (q, $J_{\text{CF}} = 34.4$ Hz), 176.5, 169.0, 162.9 (d, $J_{\text{CF}} = 250.8$ Hz), 129.2 (d, $J_{\text{CF}} = 9.0$ Hz), 129.0 (d, $J_{\text{CF}} = 3.3$ Hz), 117.3 (d, $J_{\text{CF}} = 23.2$ Hz), 116.2 (q, $J_{\text{CF}} = 291.3$ Hz), 92.7, 27.7, 26.9; MS-EI: m/z (%) 287 (M, 10), 288 (M+1, <5), 218 (100), 190 (50), 69 (9); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{13}\text{H}_9\text{F}_4\text{NO}_2$: 288.0648, found 288.0644.

1-(4-chlorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4q):

Yield: 0.182 g (60%); whitish solid; mp 163-165°C (lit. 163-165°C)^[1]; ^1H NMR (400 MHz, CDCl_3): δ ppm 7.53 (d, 2H, $J = 8.6$ Hz), 7.15 (d, 2H, $J = 8.6$ Hz), 5.65 (s, 1H), 3.52-3.48 (m, 2H), 2.82-2.78 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ ppm 179.1 (q, $J_{\text{CF}} = 34.4$ Hz), 176.3, 168.7, 135.8, 131.5, 130.4, 128.5, 116.2 (q, $J_{\text{CF}} = 291.3$ Hz), 92.7, 27.7, 26.9; MS-EI: m/z (%) 303 (M, 47), 305 (M+2, 13), 234 (100), 206 (27), 178 (8), 143 (7), 111 (7), 75 (15); HRMS-ESI: m/z $[\text{MH}]^+$ calcd. for $\text{C}_{13}\text{H}_9\text{ClF}_3\text{NO}_2$: 304.0352, found 304.0351.

1-(4-bromophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4r):

Yield: 0.205 g (59%); brownish solid; mp 156-160°C (lit. 151-153°C)^[1]; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.70 (d, 2H, *J* = 8.6 Hz) 7.09 (d, 2H, *J* = 8.6 Hz), 5.66 (s, 1H), 3.53-3.49 (m, 2H), 2.83-2.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 179.1 (q, *J*_{CF} = 34.4 Hz), 176.3, 168.6, 133.5, 132.0, 128.8, 123.9, 116.2 (q, *J*_{CF} = 291.4 Hz), 92.8, 27.8, 26.9; MS-EI: *m/z* (%) 347 (M, 22), 349 (M+2, 15), 278 (100), 252 (22), 171 (17), 69 (17); HRMS-ESI: *m/z* [MH]⁺ calcd. for C₁₃H₉BrF₃NO₂: 347.9847, found 347.9848.

1-(2,4-dimethylphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4s):

Yield: 0.151 g (51%); whitish solid; mp 141-143°C; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.20 (s, 1H), 7.15 (d, 1H, *J* = 7.9 Hz), 6.94 (d, 1H, *J* = 7.9 Hz), 5.44 (s, 1H), 3.54-3.50 (m, 2H), 2.82-2.78 (m, 2H), 2.38 (s, 3H), 2.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 179.1 (q, *J*_{CF} = 34.3 Hz), 176.5, 169.0, 140.3, 134.9, 132.4, 129.2, 128.4, 127.2, 116.2 (q, *J*_{CF} = 291.34 Hz), 92.5, 27.7, 27.0, 21.1, 17.0; MS-EI: *m/z* (%) 297 (M, 100), 298 (M+1, 8), 228 (100), 200 (52), 187 (20); HRMS-ESI: *m/z* [MH]⁺ calcd. for C₁₅H₁₄F₃NO₂: 298.1055, found 298.1036.

1-(2-chloro-4-nitrophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4t):

Yield: 0.087 g (25%); yellowish solid; mp 198-199°C; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.84 (d, 1H, *J* = 2.4 Hz), 7.78 (d, 1H, *J* = 8.6 Hz), 7.43 (dd, 1H, *J* = 2.4 Hz, *J* = 8.6 Hz), 5.70 (s, 1H), 3.57-3.53 (m, 2H), 2.88-2.84 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 178.1 (q, *J*_{CF} = 34.8 Hz), 175.3, 167.3, 148.6, 133.8, 132.4, 132.0, 128.8, 125.1, 116.1 (q, *J*_{CF} = 291.2 Hz), 93.1, 27.7, 26.9; MS-EI: *m/z* (%) 348 (M, <5), 349 (M+1, <5), 279 (100), 233 (55), 205 (10), 69 (11); HRMS-ESI: *m/z* [MH]⁺ calcd. for C₁₃H₈ClF₃N₂O₄: 349.0203, found 349.0212.

Crystallographic data to compound 4e

Table 1. Crystal data and structure refinement for **4e**.

Empirical formula	C ₁₀ H ₁₀ F ₃ NO ₄	
Formula weight	265.19	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 8.5257(9) Å	a = 90°.
	b = 4.9691(6) Å	b = 94.063(7)°.
	c = 27.362(3) Å	g = 90°.
Volume	1156.3(2) Å ³	
Z	4	
Density (calculated)	1.523 Mg/m ³	
Absorption coefficient	0.147 mm ⁻¹	
F(000)	544	
Crystal size	0.353 x 0.206 x 0.174 mm ³	
Theta range for data collection	2.395 to 27.201°.	
Index ranges	-10 ≤ h ≤ 10, -4 ≤ k ≤ 6, -34 ≤ l ≤ 35	
Reflections collected	15890	
Independent reflections	2552 [R(int) = 0.0368]	
Completeness to theta = 25.242°	98.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.99946 and 0.99891	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2552 / 0 / 163
Goodness-of-fit on F^2	1.037
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0641$, $wR_2 = 0.1804$
R indices (all data)	$R_1 = 0.1037$, $wR_2 = 0.2101$
Extinction coefficient	n/a
Largest diff. peak and hole	0.504 and -0.339 e. $\text{\AA}^{-3}$

Table 2. Bond lengths [Å] and angles [°] for **4e**.

O(4)-C(9)	1.329(3)
O(4)-C(10)	1.451(4)
O(3)-C(9)	1.188(3)
N(1)-C(4)	1.370(3)
N(1)-C(1)	1.397(4)
N(1)-C(8)	1.449(3)
F(2)-C(7)	1.328(4)
F(3)-C(7)	1.303(4)
O(1)-C(1)	1.205(3)
O(2)-C(6)	1.208(4)
C(4)-C(5)	1.358(4)
C(4)-C(3)	1.505(4)
C(5)-C(6)	1.434(4)
C(5)-H(3)	0.9300
C(9)-C(8)	1.506(4)
C(2)-C(1)	1.486(4)
C(2)-C(3)	1.511(4)
C(2)-H(6A)	0.9700
C(2)-H(6B)	0.9700
F(1)-C(7)	1.278(4)
C(6)-C(7)	1.517(5)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(3)-H(7A)	0.9700

C(3)-H(7B)	0.9700
C(10)-H(10A)	0.9600
C(10)-H(10B)	0.9600
C(10)-H(10C)	0.9600
C(9)-O(4)-C(10)	115.8(3)
C(4)-N(1)-C(1)	112.9(2)
C(4)-N(1)-C(8)	125.6(2)
C(1)-N(1)-C(8)	121.3(2)
C(5)-C(4)-N(1)	124.1(2)
C(5)-C(4)-C(3)	128.0(2)
N(1)-C(4)-C(3)	107.9(2)
C(4)-C(5)-C(6)	121.3(2)
C(4)-C(5)-H(3)	119.3
C(6)-C(5)-H(3)	119.3
O(3)-C(9)-O(4)	124.9(3)
O(3)-C(9)-C(8)	126.1(2)
O(4)-C(9)-C(8)	109.0(2)
C(1)-C(2)-C(3)	105.4(2)
C(1)-C(2)-H(6A)	110.7
C(3)-C(2)-H(6A)	110.7
C(1)-C(2)-H(6B)	110.7
C(3)-C(2)-H(6B)	110.7
H(6A)-C(2)-H(6B)	108.8
O(2)-C(6)-C(5)	127.3(3)
O(2)-C(6)-C(7)	116.2(3)
C(5)-C(6)-C(7)	116.5(3)

O(1)-C(1)-N(1)	122.2(3)
O(1)-C(1)-C(2)	129.6(3)
N(1)-C(1)-C(2)	108.2(2)
N(1)-C(8)-C(9)	110.8(2)
N(1)-C(8)-H(8A)	109.5
C(9)-C(8)-H(8A)	109.5
N(1)-C(8)-H(8B)	109.5
C(9)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	108.1
C(4)-C(3)-C(2)	105.4(2)
C(4)-C(3)-H(7A)	110.7
C(2)-C(3)-H(7A)	110.7
C(4)-C(3)-H(7B)	110.7
C(2)-C(3)-H(7B)	110.7
H(7A)-C(3)-H(7B)	108.8
F(1)-C(7)-C(6)	113.5(3)
F(3)-C(7)-C(6)	114.6(3)
F(2)-C(7)-C(6)	110.6(3)
O(4)-C(10)-H(10A)	109.5
O(4)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
O(4)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5

Table 3. Torsion angles [°] for **4e**.

C(1)-N(1)-C(4)-C(5)	-175.7(2)
C(8)-N(1)-C(4)-C(5)	-0.6(4)
C(1)-N(1)-C(4)-C(3)	3.8(3)
C(8)-N(1)-C(4)-C(3)	178.9(2)
N(1)-C(4)-C(5)-C(6)	177.5(3)
C(3)-C(4)-C(5)-C(6)	-1.9(5)
C(10)-O(4)-C(9)-O(3)	-2.9(4)
C(10)-O(4)-C(9)-C(8)	175.1(3)
C(4)-C(5)-C(6)-O(2)	6.5(5)
C(4)-C(5)-C(6)-C(7)	-174.2(3)
C(4)-N(1)-C(1)-O(1)	177.9(3)
C(8)-N(1)-C(1)-O(1)	2.5(4)
C(4)-N(1)-C(1)-C(2)	-1.7(3)
C(8)-N(1)-C(1)-C(2)	-177.0(2)
C(3)-C(2)-C(1)-O(1)	179.3(3)
C(3)-C(2)-C(1)-N(1)	-1.2(3)
C(4)-N(1)-C(8)-C(9)	-84.4(3)
C(1)-N(1)-C(8)-C(9)	90.3(3)
O(3)-C(9)-C(8)-N(1)	-8.9(4)
O(4)-C(9)-C(8)-N(1)	173.1(2)
C(5)-C(4)-C(3)-C(2)	175.2(3)
N(1)-C(4)-C(3)-C(2)	-4.3(3)
C(1)-C(2)-C(3)-C(4)	3.3(3)
O(2)-C(6)-C(7)-F(1)	16.3(5)

C(5)-C(6)-C(7)-F(1)	-163.1(4)
O(2)-C(6)-C(7)-F(3)	144.4(4)
C(5)-C(6)-C(7)-F(3)	-35.0(5)
O(2)-C(6)-C(7)-F(2)	-101.6(4)
C(5)-C(6)-C(7)-F(2)	79.0(4)

^1H NMR and ^{13}C NMR spectra for compounds 3a,b and 4e-t

Figure 1: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of methyl 7,7,7-trifluoro-4-((1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (**3a**).

Figure 2: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of methyl 7,7,7-trifluoro-4-((1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (**3a**).

Figure 3: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of methyl 7,7,7-trifluoro-4-((1-methoxy-4-(methylthio)-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (**3b**).

Figure 4: ^{13}C NMR spectrum, in CDCl_3 at 100 MHz, of methyl 7,7,7-trifluoro-4-((1-methoxy-4-(methylthio)-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (**3b**).

Figure 5: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of methyl 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetate (**4e**).

Figure 6: ^{13}C NMR spectrum, in CDCl_3 at 100 MHz, of methyl 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetate (**4e**).

Figure 7: ¹H NMR spectrum, in DMSO-d₆ at 400 MHz, of 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetamide (**4f**).

Figure 8: ¹³C NMR spectrum, in DMSO-*d*₆ at 100 MHz, of 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetamide (**4f**).

Figure 9: DEPT 135 spectrum, in DMSO- d_6 at 100 MHz, of 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetamide (**4f**).

Figure 10: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of 1-propyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4g**).

Figure 11: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-propyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4g**).

Figure 12: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of 1-(2-chloroethyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4h**).

Figure 13: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(2-chloroethyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4h**).

Figure 14: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 1-butyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4i**).

Figure 15: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-butyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4i**).

Figure 16: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4j**).

Figure 17: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4j**).

Figure 18: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 1-phenyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4k**).

Figure 19: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-phenyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4k**).

Figure 20: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 5-(3,3,3-trifluoro-2-oxopropylidene)-1-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (**41**).

Figure 21: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 5-(3,3,3-trifluoro-2-oxopropylidene)-1-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (**4l**).

Figure 22: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of 1-(3-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4m**).

Figure 23: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(3-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4m**).

Figure 24: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 1-(p-tolyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4n**).

Figure 25: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(p-tolyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4n**).

Figure 26: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of 1-(4-fluorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4p**).

Figure 27: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(4-fluorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4p**).

Figure 28: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 1-(4-chlorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4q**).

Figure 29: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(4-chlorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4q**).

Figure 30: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 1-(4-bromophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4r**).

Figure 31: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(4-bromophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4r**).

Figure 32: ^1H NMR spectrum, in CDCl_3 at 400 MHz, of 1-(2,4-dimethylphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4s**).

Figure 33: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(2,4-dimethylphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4s**).

Figure 34: ¹H NMR spectrum, in CDCl₃ at 400 MHz, of 1-(2-chloro-4-nitrophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4t**).

Figure 35: ¹³C NMR spectrum, in CDCl₃ at 100 MHz, of 1-(2-chloro-4-nitrophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4t**).

MS-EI spectra for compounds 3a,b and 4e-t

Figure 36: Mass spectrum of methyl 7,7,7-trifluoro-4-((1-methoxy-3-methyl-1-oxobutan-2-yl)amino)-6-oxohept-4-enoate (**3a**).

Figure 37: Mass spectrum of methyl 7,7,7-trifluoro-4-((1-methoxy-3-(methylthio)-1-oxopropan-2-yl)amino)-6-oxohept-4-enoate (**3b**).

Figure 38: Mass spectrum of methyl 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetate (**4e**).

Figure 39: Mass spectrum of 2-(2-oxo-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-1-yl)acetamide (**4f**).

Figure 40: Mass spectrum of 1-propyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4g**).

Figure 41: Mass spectrum of 1-(2-chloroethyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4h**).

Figure 42: Mass spectrum of 1-butyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4i**).

Figure 43: Mass spectrum of 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4j**).

Figure 44: Mass spectrum of 1-phenyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4k**).

Figure 45: Mass spectrum of 5-(3,3,3-trifluoro-2-oxopropylidene)-1-(3-(trifluoromethyl)phenyl)pyrrolidin-2-one (**4l**).

Figure 46: Mass spectrum of 1-(3-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4m**).

Figure 47: Mass spectrum of 1-(p-tolyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4n**).

Figure 48: Mass spectrum of 1-(4-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4o**).

Figure 49: Mass spectrum of 1-(4-fluorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4p**).

Figure 50: Mass spectrum of 1-(4-chlorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4q**).

Figure 51: Mass spectrum of 1-(4-bromophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4r**).

Figure 52: Mass spectrum of 1-(2,4-dimethylphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**4s**).

Figure 53: Mass spectrum of 1-(2-chloro-4-nitrophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (4t).