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Friedel−Crafts alkylation of natural amino acid-derived pyrroles with CF_3-substituted cyclic imines

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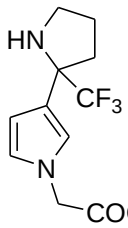
Experimental details

NMR (^{1}H, ^{19}F and ^{13}C) spectra were obtained on a Jeol ECX-400, Bruker VRX-400 or Bruker AM-300 spectrometer, chemical shifts for ^{1}H NMR data are referenced internally to tetramethylsilane (0.0); chemical shifts for ^{13}C NMR data are referenced to corresponding $CDCl_3$ (77.2); chemical shifts for ^{19}F NMR data are referenced to $CFCl_3$ (0.0) or $PhCF_3$ (-63.90). 2D HMBC NMR spectra were obtained on a Bruker AV 600 spectrometer. Electrospray ionization (ESI) mass spectra (MS) were obtained from methanol or acetonitrile solution. Melting points are uncorrected. TLC was carried out on precoated silica plates (Merck $60F_{254}$) with UV light visualization. Flash chromatography was performed using MP Silica 60 (320-630 mesh) with the indicated solvents. All reactions were conducted in oven dried glassware under nitrogen atmosphere. All reagents were purchased from Aldrich or unless otherwise stated. The starting trifluoromethyl imines **1a**−**c** were prepared by reaction of ethyl trifluoroacetate with *N*-vinylpyrrolidin-2-one, *N*-(diethoxymethyl)piperidin-2-one or *N*-vinylcaprolactam respectively according to the described procedure (see: N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler and V. G. Nenajdenko, *Synthesis*, 2010, 120).

Characterization data for the synthesized products



Ethyl {3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1H-pyrrol-1-yl}acetate **(7a)**, 71%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7.13 Hz, $CH_2\mathbf{CH_3}$), 1.81-1.99 (3H, m), 2.12-2.19 (1H, m), 2.32-2.39 (1H, m), 3.04-3.17 (2H, m, CH_2-N), 4.23 (2H, q, *J* = 7.13 Hz, COO$\mathbf{CH_2}CH_3$), 4.58 (2H, s, $\mathbf{CH_2}$-COOEt), 6.19-6.22 (1H, m, Ar-H), 6.62-6.63 (1H, t, *J* = 2.52 Hz, Ar-H), 6.68-6.69 (1H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 26.0, 34.0

(**C**H_2-C_q), 47.3 (CH_2-N), 50.8 (**C**$\mathbf{H_2}$-COOEt), 61.6 (COO**C**$\mathbf{H_2}$$CH_3$), 66.3 (q, J_{CF} = 27.3 Hz, **C**-CF_3), 107.8 (Ar), 119.7 (Ar), 122.1 (Ar), 124.4 (C_q, Ar), 127.5 (q, J_{CF} = 282.7 Hz, CF_3), 168.4 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -78.6 (CF_3). IR (KBr) 3367, 1753, 1155 cm^{-1}. Anal. calcd. for $C_{13}H_{17}F_3N_2O_2$: C, 53.79; H, 5.90; N, 9.65, Found: C, 53.85; H, 5.99; N, 9.58.

Preliminary structural assignments of compound **7a** were made using NMR data (^{1}H and ^{13}C). Indeed, the aromatic part of ^{1}H NMR spectrum of **7a** comprising two signals at 6.69 and 6.63 ppm which corresponds to hydrogen atoms located in α-position of pyrrole ring. These signals are downfield shifted (0.4-0.5 ppm) compared to signal of β-hydrogen atoms of pyrrole occurring at 6.21 ppm. In addition the gHMBC experiment for **7a** shown a three-bond proton-carbon correlation among two hydrogens of methylene group attached to pyrrole nitrogen and two α-carbons of the pyrrole ring (Figure S1). This correlation undoubtedly proves the structure of pyrrole **7a** having substituent at β-position.

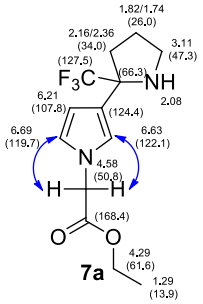
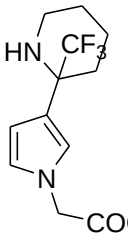
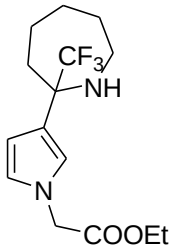


Figure S1 HMBC correlations, ^{1}H (top digits) and ^{13}C (in parentheses) chemical shifts of **7a**.

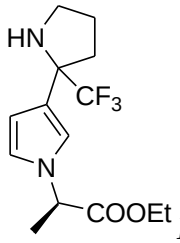


Ethyl {3-[2-(trifluoromethyl)piperidin-2-yl]-1H-pyrrol-1-yl}acetate **(7g)**, 62 %, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (3H, t, J = 7.13 Hz, CH_2**C**$\mathbf{H_3}$), 1.41-1.57 (3H, m), 1.65-1.72 (1H, m), 1.85-1.92 (1H, m), 1.96 (1H, bs, NH), 2.08-2.13 (1H, m), 2.77-2.84 (1H, m, CH_2-N), 2.87-2.92 (1H, m, **C**$\mathbf{H_2}$-N), 4.21 (2H, q, J = 7.13 Hz, COO**C**$\mathbf{H_2}$$CH_3$), 4.59 (2H, s, **C**$\mathbf{H_2}$-COOEt), 6.13-6.15 (1H, m, Ar-H), 6.63-6.66 (2H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 19.9, 25.6, 28.5 (bs, **C**H_2-C_q), 41.2 (CH_2-N), 50.9 (**CH$_2$**-COOEt), 59.4 (q, J_{CF} = 26.4 Hz, **C**-CF_3), 61.5 (COO**CH$_2$**CH_3), 108.9 (Ar), 120.0 (C_q, Ar), 121.9 (Ar), 122.0 (Ar), 126.5 (q, J_{CF} = 282.9 Hz, CF_3), 168.4 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -81.9 (CF_3). IR

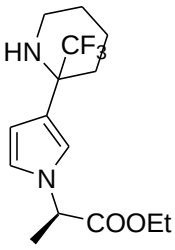
(Nujol) 3345, 1755, 1160 cm^{-1}. Anal. calcd. for $C_{14}H_{19}F_3N_2O_2$: C, 55.26; H, 6.29; N, 9.21, Found: C, 55.26; H, 6.35; N, 9.10.



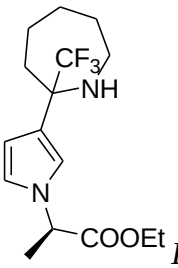
Ethyl {3-[2-(trifluoromethyl)azepan-2-yl]-1H-pyrrol-1-yl}acetate **(7i)**, 65 %, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (3H, t, *J* = 7.13 Hz, $CH_2\mathbf{CH_3}$), 1.31-1.52 (3H, m), 1.67-1.80 (4H, m), 2.04-2.12 (1H, m), 2.20-2.26 (1H, m), 2.93-2.95 (2H, m, CH_2-N), 4.21 (2H, q, *J* = 7.13 Hz, COO$\mathbf{CH_2}CH_3$), 4.56 (2H, s, $\mathbf{CH_2}$-COOEt), 6.19-6.21 (1H, t, *J* = 2.52 Hz, Ar-H), 6.60-6.62 (1H, t, *J* = 1.97 Hz, Ar-H), 6.68-6.70 (1H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.7, 29.9, 33.2, 33.9, ($\mathbf{C}H_2$-C_q), 43.6 (CH_2-N), 50.8 ($\mathbf{CH_2}$-COOEt), 61.5 (COO$\mathbf{CH_2}CH_3$), 62.4 (q, J_{CF} = 25.3 Hz, **C**-CF_3), 108.1 (Ar), 120.8 (Ar), 121.8 (Ar), 124.6 (C_q, Ar), 127.9 (q, J_{CF} = 286.5 Hz, CF_3), 168.4 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -78.7 (CF_3). IR (Nujol) 3390, 1755, 1145, 1149 cm^{-1}. Anal. calcd. for $C_{15}H_{21}F_3N_2O_2$: C, 56.59; H, 6.65; N, 8.80, Found: C, 56.30; H, 6.50; N, 8.83.



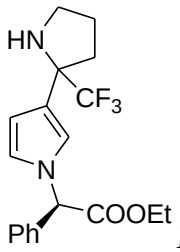
Ethyl 2-{3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1H-pyrrol-1-yl}propanoate **(7b)** mixture of diastereomers, ratio 1:1, 69 %, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, *J* = 7.12 Hz, $CH_2\mathbf{CH_3}$), 1.71 (3H, d, *J* = 7.23 Hz, CH$\mathbf{CH_3}$), 1.82-1.89 (2H, m), 1.93-2.01 (1H, m), 2.12-2.18 (1H, m), 2.32-2.39 (1H, m), 3.04-3.10 (1H, m, CH_2-N), 3.13-3.19 (1H, m, $\mathbf{CH_2}$-N), 4.18 (2H, q, *J* = 7.12 Hz, COO$\mathbf{CH_2}CH_3$), 4.69 (1H, q, *J* = 7.23 Hz, **CH**-COOEt), 6.18-6.20 (1H, m, Ar-H), 6.70-6.72 (1H, m, Ar-H), 6.75-6.77 (1H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_2-$\mathbf{C}H_3$), 18.1 (CH-$\mathbf{C}H_3$), 25.6, 33.9 and 34.0 ($\mathbf{C}H_2$-C_q), 42.3 (CH_2-N), 57.1 (**CH**-COOEt), 61.5 (COO$\mathbf{CH_2}CH_3$), 66.4 (q, J_{CF} = 27.3 Hz, **C**-CF_3), 107.3 (Ar), 117.7 (Ar), 119.9 and 120.0 (Ar), 123.9 (C_q, Ar), 127.5 (q, J_{CF} = 283.1 Hz, CF_3), 170.9 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -77.8 (CF_3). IR (KBr) 3373, 1741, 1190, 1151 cm^{-1}. Anal. calcd. for $C_{14}H_{19}F_3N_2O_2$: C, 55.26; H, 6.29; N, 9.21, Found: C, 55.36; H, 6.33; N, 9.17. [α]=+13.2º (c=1g/100ml in CH_2Cl_2).



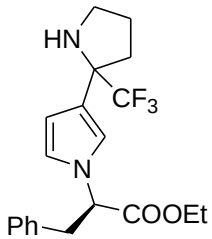
Ethyl 2-{3-[2-(trifluoromethyl)piperidin-2-yl]-1H-pyrrol-1-yl}propanoate **(7h)** mixture of diastereomers, ratio 1:1, 75 %, yellow solid, mp 46-48 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, *J* = 7.13 Hz, $CH_2\mathbf{CH_3}$), 1.44-1.56 (3H, m), 1.67-1.74 (4H, m incl. 1.73 (3H, d, *J* = 7.23 Hz, CH-$\mathbf{CH_3}$)), 1.84-1.98 (2H, m), 2.09-2.14 (1H, m), 2.78-2.85 (1H, m, CH_2-N), 2.89-2.94 (1H, m, $\mathbf{CH_2}$-N), 4.17 (2H, q, *J* = 7.13 Hz, COO$\mathbf{CH_2}CH_3$), 4.71 (1H, q, *J* = 7.23 Hz, **CH**-COOEt), 6.11-6.15 (1H, m, Ar-H), 6.72-6.76 (2H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_2-$\mathbf{C}H_3$), 17.9 and 18.0 (CH-$\mathbf{C}H_3$), 19.9, 25.6, 28.4 and 28.5 (bs, $\mathbf{C}H_2$-C_q), 41.2 (CH_2-N), 57.1 (**CH**-COOEt), 59.4 (q, J_{CF} = 26.4 Hz, **C**-CF_3), 61.4 (COO$\mathbf{CH_2}CH_3$), 108.4 (Ar), 119.4 and 119.5 (C_q, Ar), 119.7 and 119.8 (Ar), 119.9 and 120.0 (Ar), 126.5 (q, J_{CF} = 282.9 Hz, CF_3), 171.0 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -81.1 (CF_3). IR (KBr) 3338, 1728, 1167, 1149 cm^{-1}. Anal. calcd. for $C_{15}H_{21}F_3N_2O_2$: C, 56.59; H, 6.65; N, 8.80, Found: C, 56.60; H, 6.55; N, 8.89.



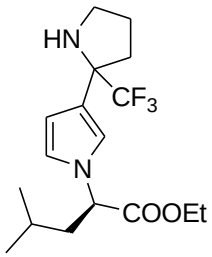
Ethyl 2-{3-[2-(trifluoromethyl)azepan-2-yl]-1H-pyrrol-1-yl}propanoate **(7j)** mixture of diastereomers, ratio 1:1, 60 %, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, *J* = 7.13 Hz, $CH_2\mathbf{CH_3}$), 1.29-1.48 (3H, m), 1.64-1.78 (7H, m incl. 1.68 (3H, d, *J* = 7.34 Hz, CH-$\mathbf{CH_3}$)), 2.04-2.10 (1H, m), 2.18-2.24 (1H, m), 2.91-2.93 (2H, m, CH_2-N), 4.14 (2H, q, *J* = 7.13 Hz, COO$\mathbf{CH_2}CH_3$), 4.66 (1H, q, *J* = 7.34 Hz, **CH**-COOEt), 6.14-6.16 (1H, m, Ar-H), 6.66-6.68 (1H, m, Ar-H), 6.74-6.76 (1H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_2-$\mathbf{C}H_3$), 18.0 and 18.1 (CH-$\mathbf{C}H_3$), 22.8 and 22.9, 30.0, 33.2 and 33.3, 34.0 ($\mathbf{C}H_2$-C_q), 43.7 (CH_2-N), 57.1 and 57.2 (**CH**-COOEt), 61.5 (COO$\mathbf{CH_2}CH_3$), 62.5 (q, J_{CF} = 24.9 Hz, **C**-CF_3), 107.7 (Ar), 118.9 (Ar), 119.7 and 119.8 (Ar), 123.8 (C_q, Ar), 128.0 (q, J_{CF} = 286.5 Hz, CF_3), 171.1 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -78.75 and 78.76 (CF_3). IR (Nujol) 3395, 1745, 1205, 1165, 1145 cm^{-1}. Anal. calcd. for $C_{16}H_{23}F_3N_2O_2$: C, 57.82; H, 6.98; N, 8.43, Found: C, 57.94; H, 7.00; N, 8.30. [α]=+10.8º (c=1g/100ml in CH_2Cl_2).



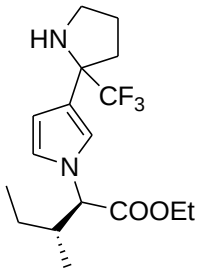
Ethyl phenyl{3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1H-pyrrol-1-yl}acetate **(7c)**, 81%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 7.06 Hz, CH_2**CH_3**), 1.81-1.87 (1H, m), 1.94-2.17 (3H, m incl. 2.06 (1H, bs, NH)), 2.32-2.37 (1H, m), 3.05-3.09 (1H, m, CH_2-N), 3.13-3.17 (1H, m, CH_2-N), 4.26-4.30 (2H, m, COO**CH_2**CH_3), 5.78 (1H, s, **CH**-COOEt), 6.21 (1H, bs, Ar-H), 6.70-6.71 (1H, m, Ar-H), 6.80 (1H, bs, Ar-H), 7.28-7.31 (2H, m. Ph), 7.38-7.41 (3H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 26.0, 34.0 (**C**H_2-C_q), 47.3 (CH_2-N), 61.9 (COO**CH_2**CH_3), 65.4 (**CH**-COOEt), 66.3 (q, J_{CF} = 27.6 Hz, **C**-CF_3), 107.5 (Ar), 118.8 (Ar), 121.2 (Ar), 124.2 (C_q, Ar), 127.5 (q, J_{CF} = 282.7 Hz, CF_3), 127.6 (Ph), 128.8 (Ph), 128.9 (Ph), 135.0 (C_q, Ph), 169.2 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -77.7 (CF_3). IR (KBr) 3369, 1747, 1153 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{21}F_3N_2O_2$ (M+H) 367.1628, found 367.1628.



Ethyl (2S)-3-phenyl-2-{3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1H-pyrrol-1-yl}propanoate **(7d)**, 74%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, *J* = 7.1 Hz, CH_2**CH_3**), 1.79-1.82 (1H, m), 1.92-1.96 (1H, m), 1.98 (1H, bs, NH), 2.09-2.12 (1H, m), 2.28-2.36 (1H, m), 3.03-3.11 (2H, m, CH_2-N), 3.19-3.38 (2H, AB part of ABX system), 4.18 (2H, q, *J* = 7.1 Hz, O**CH_2**CH_3), 4.64-4.67 (1H, m, X part of ABX system), 6.15 (1H, bs, Ar-H), 6.68-6.69 (2H, m, Ar-H), 6.96-6.98 (2H, m, Ph-H), 7.20-7.24 (3H, m. Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 26.1, 34.1, 39.9, 47.4 (CH_2-N), 61.8 (O**CH_2**CH_3), 64.0 (**CH**-CO_2Et), 66.4 (q, J_{CF} = 27.4 Hz, **C**-CF_3), 107.7 (Ar), 118.5 (Ar), 120.5 (Ar), 124.1 (C_q, Ar), 127.4 (q, J_{CF} = 282.4 Hz, CF_3), 128.6 (2C, Ph), 128.9 (2C, Ph), 129.0 (C_q, Ar), 136.1 (Ph), 169.9 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -77.65 and 77.62 (~1:1, CF_3 of both diastereomers). Anal. calcd. for $C_{20}H_{23}F_3N_2O_2$: C, 63.15; H, 6.09; N, 14.98, Found: C, 63.11; H, 6.09.

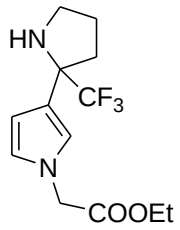


(R)-ethyl 2-(3-(2-(trifluoromethyl)pyrrolidin-2-yl)-1H-pyrrol-1-yl)-4-methylpentanoate **(7e)**, 87 %, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, J = 6.4 Hz, 3H,), -1.91 (1H, m), 2.05-2.08 (1H, m), 2.38 (1H, bs, NH), 2.38-2.47 (2H, m), 3.17-3.21 (2H, m), 3.77 (3H, s, CH_3-N), 7.11 (1H, s, Ar-H), 7.18 (1H, t, *J* = 7.1 Hz, Ar-H), 7.27 (1H, t, *J* = 7.5 Hz, Ar-H) 7.33 (1H, d, *J* = 7.1 Hz, Ar-H), 7.83 (1H, d, *J* = 7.5 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 32.7 (s, CH_3-N), 37.7 (bs, **C**H_2-C_q), 47.4 (CH_2-N), 67.3 (q, J_{CF} = 27.8 Hz, **C**-CF_3), 109.6 (Ar), 113.9 (C_q, Ar), 119.6 (Ar), 120.9 (Ar), 121.8 (Ar), 125.9 (C_q, Ar), 127.5 (Ar), 127.9 (q, J_{CF} = 284.6 Hz, CF_3), 137.5 (C_q, Ar). ^{19}F NMR (280 MHz, $CDCl_3$): δ -77.0 (CF_3). HRMS (ESI): calcd. for $C_{14}H_{16}F_3N_2$ (M+H) 269.1260, found 269.1270.

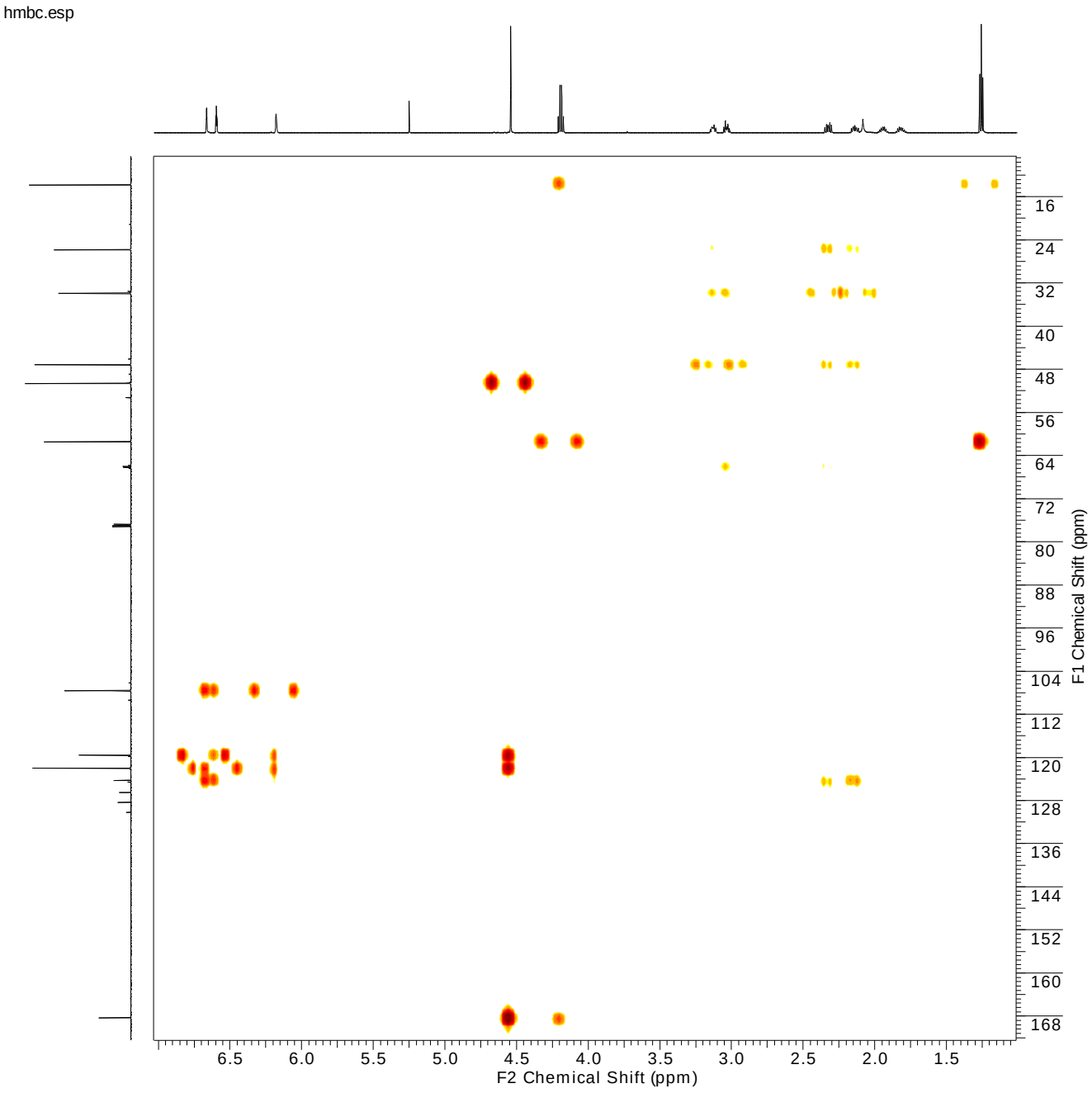


Ethyl 3-methyl-2-{3-[2-(trifluoromethyl)pyrrolidin-2-yl]-1H-pyrrol-1-yl}pentanoate **(7f)**, 68%, yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, *J* = 7.43 Hz, $CHCH_2$**CH_3**), 0.91-1.00 (4H, m incl. 0.96 (3H, d, *J* = 6.60 Hz, CH**CH_3**)), 1.12-1.18 (1H, m, CH**CH_2**CH_3), 1.27 (3H, t, *J* = 7.15 Hz, $COOCH_2$**CH_3**), 1.80-1.86 (1H, m), 1.94-2.00 (1H, m), 2.04 (1H, bs, NH), 2.12-2.20 (2H, m), 2.32-2.37 (1H, m), 3.05-3.09 (1H, m, CH_2-N), 3.13-3.17 (1H, m, CH_2-N), 4.14-4.25 (3H, m, COO**CH_2**CH_3 and **C**H-COOEt), 6.16 (1H, bs, Ar-H), 6.73-6.74 (1H, m, Ar-H), 6.79-6.80 (1H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (CH_3), 14.0 (CH_3), 15.5 (CH_3), 24.7, 26.0, 34.0 (**C**H_2-C_q), 38.0 (CH), 47.3 (CH_2-N), 61.3 (COO**CH_2**CH_3), 67.6 (**CH**-COOEt), 66.3 (q, J_{CF} = 27.3 Hz, **C**-CF_3), 107.2 (Ar), 118.3 (Ar), 120.7 (Ar), 123.8 (C_q, Ar), 127.4 (q, J_{CF} = 282.5 Hz, CF_3), 170.2 (CO). ^{19}F NMR (280 MHz, $CDCl_3$): δ -77.8 (CF_3). IR (KBr) 1741, 1151 cm^{-1}.HRMS (ESI): calcd. for $C_{17}H_{25}F_3N_2O_2$ (M+H) 347.1941, found 347.1942.

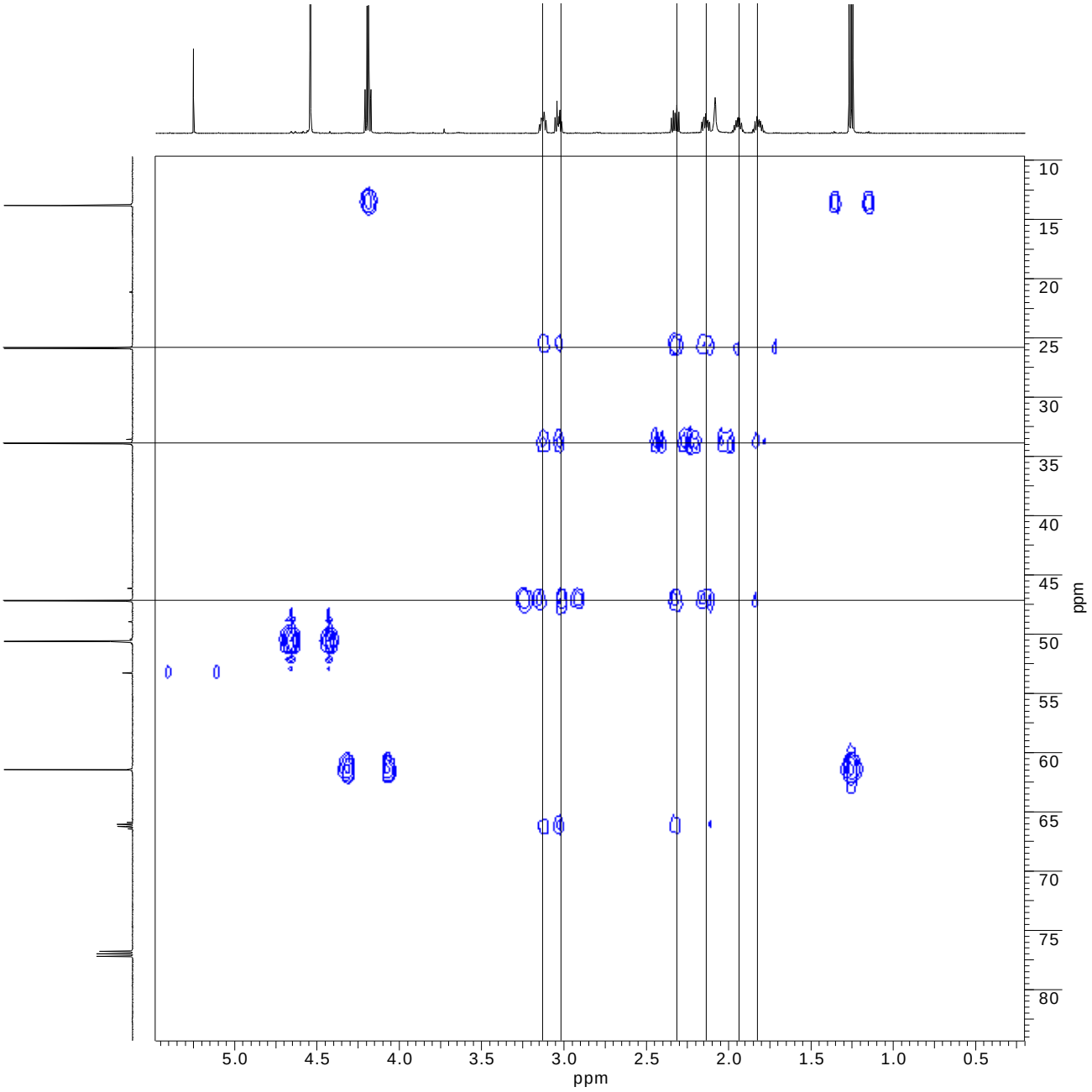
2D gHMBC spectrum of 7a



The overview



The "pyrrolidine" part



The "pyrrole" part