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Electrophilic Reactions of 7-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine: a Way Towards New Building Blocks

Abstract

Aim. To synthesize new fluoro-containing building blocks for medicinal chemistry purposes using electrophilic reactions of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine.

Results and discussion. Synthetic approaches to 5-halogeno- and 5-acyl-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizines have been developed. The obtained new trifluoromethyl-containing pyrrolyzines are promising building blocks for medicinal chemistry.

Experimental part. The synthesis of the target compounds began with known 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine and included halogenation and acylation reactions using *N*-halogen succinimides and acylating reagents.

Conclusions. New synthetic approaches to a number of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizines with various substituents, such as halogen atoms or acyl groups, at the position 5 of the pyrrole ring have been developed. This opens the door to the use of such promising trifluoromethyl-containing building blocks for medicinal chemistry needs.

***Keywords*:** trifluoromethyl; heterocycles; electrophilic reactions; halogenation; acylation; organic synthesis

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Електрофільні реакції 7-(трифлуорометил)-2,3-дигідро-1*H*-піролізину – шлях до нових будівельних блоків

Анотація

Мета. Синтезувати нові флуоровмісні будівельні блоки для потреб медичної хімії за допомогою електрофільних реакцій 7-(трифлуорометил)-2,3-дигідро-1*H*-піролізину.

Результати та їх обговорення. Було розроблено синтетичні підходи до 5-галогено- та 5-ацил-7-(трифлуорометил)-2,3-дигідро-1*H*-піролізинів. Отримані нові трифлуорометил-вмісні піролізини є перспективними будівельними блоками для медичної хімії.

Експериментальна частина. Синтез цільових сполук було здійснено на основі відомого 7-(трифлуорометил)-2,3-дигідро-1*H*-піролізину з використанням реакцій галогенування та ацилювання дією *N*-галогеносукцинімідів і ацилювальних реагентів.

Висновки. Розроблено нові синтетичні підходи до одержання ряду 7-(трифлуорометил)-2,3-дигідро-1*H*-піролізинів з різноманітними замісниками: атомами галогенів або ацильними групами в положенні 5 пірольного циклу. Це дозволяє використовувати синтезовані речовини як перспективні трифлуорометилвмісні будівельні блоки в дослідженнях у царині медичної хімії.

***Ключові слова*:** трифлуорометил; гетероцикли; електрофільні реакції; галогенування; ацилювання; органічний синтез

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Introduction

Naturally occurring pyrrolizidine alkaloids have been reported to possess extensive biological activities, and significant attention has been paid to the development of general methods for the syntheses of this fluorine-containing azabicyclic system [1]. One of the promising ways to the synthesis of fluorinated pyrrolizidines is the use of trifluoromethyl bearing pyrroles as the starting compounds [2]. Furthermore, the trifluoromethylated pyrrole ring is a pivotal structural unit of many pharmacologically active natural products, bioactive molecules, and building blocks in organic synthesis [3, 4].

Recently, we reported a convenient synthesis of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**1**) starting from readily available proline and *β*-ethoxyvinyl trifluoromethyl ketone in a good yield in two stages (Scheme 1) [5, 6]. And we found that simply adding trifluoroacetic anhydride (TFAA) to the solution of pyrrolizine **1** in dichloromethane at room temperature led to trifluoroacetylation of the pyrrole ring at the α-position (Scheme 1) [5]. Based on the reported data, we have assumed that the electrophilic reactions of pyrrolizine **1** are of interest to obtain the diversity of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizines bearing various substituents at the position 5 of the pyrrole ring, which are promising building blocks for medicinal chemistry. In this work, we focused on the development of electrophilic reactions of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**1**) with *N*-halogen succinimides and acylation reagents.

Results and discussion

The synthetic part of our work began with 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**1**) prepared on a 30 gram scale starting from *L*-proline and *β*-ethoxyvinyl trifluoromethyl ketone and using the previously method reported [5]. To obtain the halogeno-substituted series, compound **1** was reacted with *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimides in DMF solution (Scheme 2).

5-Halogeno-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizines **3a-c** were obtained in high yields. The structure confirmation for pyrrolizines **3a–c** was based on ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. Thus, in the ^{19}F NMR spectra, the CF_3 group appeared as a singlet at *ca.* –57.4 ppm. These chemical shifts of the CF_3 group signals were similar to that reported for the CF_3 group in 3-trifluoromethylpyrroles [5–7]. In the ^{13}C NMR spectra of **3a–c**, the carbon of the pyrrole ring substituted by a CF_3 group appeared at 105–108 ppm as quartets ($^{2}J_{CF}$ ~ 38 Hz). Finally, the structure of product **3b** was proved by NOE experiments (Figure).

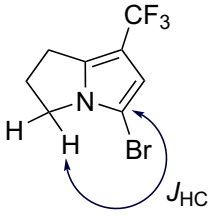
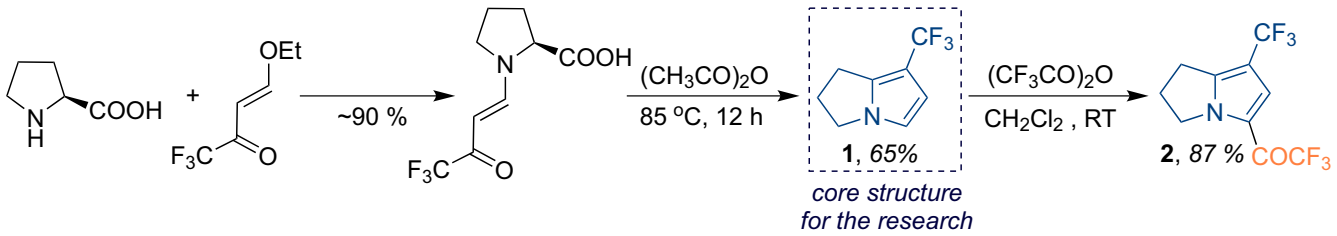
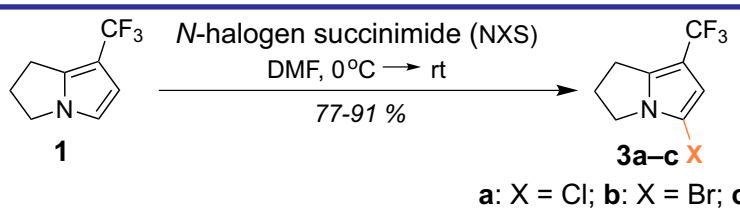


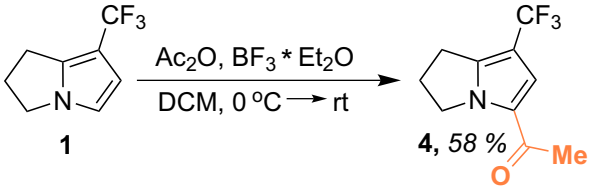
Figure. ^{1}H{^{13}C}-NOE of 5-bromo-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine **3b**



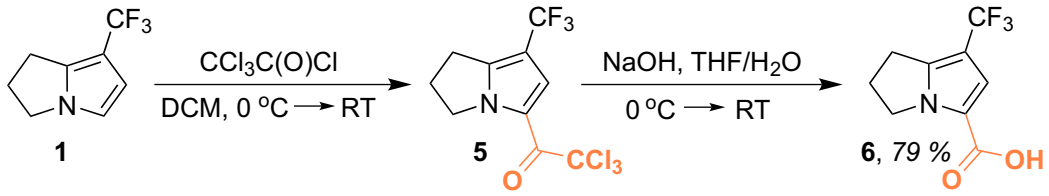
Scheme 1. Synthetic approach to 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**1**) and 2,2,2-trifluoro-1-[7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizin-5-yl]ethanone (**2**)



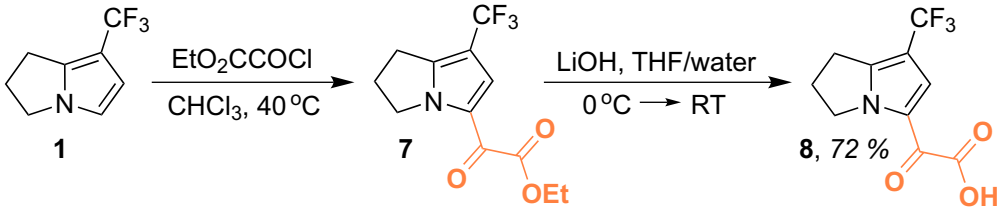
Scheme 2. Synthesis of 5-halogeno-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizines **3a–c**



Scheme 3. The synthesis of 5-acetyl-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**4**)



Scheme 4. The synthesis of 5-trichloroacetyl-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**5**) and 7-(trifluoromethyl)-2,3-dihydro-1*H*-c-5-carboxylic acid (**6**)



Scheme 5. The synthesis of ethyl 2-oxo-2-(7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizin-5-yl)acetate (**7**) and 2-oxo-2-(7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizin-5-yl)acetic acid (**8**)

Next, we developed acylation reactions of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (**1**). Previously, we demonstrated easy trifluoroacetylation of pyrrolizine **1** by TFAA at the position 5 of the pyrrole ring at room temperature and no reaction of pyrrolizine **1** with acetic anhydride at 110 °C [5, 6]. We found that pyrrolizine **1** reacted with acetic anhydride under catalysis by boron trifluoride–ether complex, and 5-acetyl derivative **4** was obtained in a moderate yield (Scheme 3).

Similarly, to the reaction with TFAA, pyrrolizine **1** smoothly reacted with trichloroacetyl chloride without any catalysts, and 5-trichloroacetyl derivative **5** was obtained in a high yield. Compound **5** was not isolated in its pure form, but was subjected to the next stage, namely the haloform decomposition under the alkaline hydrolysis, to obtain carboxylic acid **6** (79% yield from **1**) (Scheme 4).

In addition, pyrrolizine **1** smoothly reacted with ethyl oxalyl chloride without any catalysts, and ester **7** was obtained in a high yield. Compound **7** was not isolated in its pure form, but was subjected to the alkaline hydrolysis to obtain carboxylic acid **8** (72% yield from **1**) (Scheme 5).

The structural assignment of pyrrolizines **4**–**8** was based on ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy.

■ Conclusions

New synthetic approaches to a number of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizines with various substituents, such as halogen atoms or acyl groups, at the position 5 of the pyrrole ring have been developed. It allows using the compounds obtained as promising trifluoromethyl-containing building blocks for medicinal chemistry purposes.

■ Experimental part

The solvents were purified according to the standard procedures. Melting points were measured in open capillary tubes and were given uncorrected. ^{1}H, ^{13}C{H}, and ^{19}F{H} NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer and a Varian Unity Plus 400 spectrometer. NMR chemical shifts were reported in ppm (δ scale) using TMS and CCl_3F as internal standards, respectively. The elemental analysis was performed in the Analytical Chemistry Laboratory of the V. P. Kukhar Institute of Bioorganic Chemistry

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and Petrochemistry of the National Academy of Sciences of Ukraine.

The general procedure for the halogenation of 7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine (1)

To a stirred solution of **1** (3.5 g, 20 mmol) in DMF (40 mL), the corresponding *N*-halogen succinimide (20 mmol) was added portion-wise at 0–5 °C. After 5 h of stirring at RT, the reaction mixture was diluted with water (120 mL) and extracted with MTBE. The organic layer was washed twice with water, dried over Na_2SO_4, and evaporated under reduced pressure to give corresponding 5-halogeno-7-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolizine.

5-Chloro-7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizine (**3a**)

A white solid at 0 °C. Yield – 83%. Low-melting. Anal. Calcd for $C_8H_7ClF_3N$, %: C 45.84; H 3.37; N 6.68. Found, %: C 45.89; H 3.41; N 6.58. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.56 (2H, quint, $^3J_{HH}$ = 7.3 Hz); 2.97–3.04 (2H, m); 3.94 (2H, t, $^3J_{HH}$ = 7.2 Hz); 6.21 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –57.38 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 24.52; 26.82; 45.01; 105.25 (q, $^2J_{CF}$ = 38.1 Hz); 106.29 (q, $^3J_{CF}$ = 3.0 Hz); 110.86; 123.21 (q, $^1J_{CF}$ = 265.6 Hz); 135.28 (q, $^3J_{CF}$ = 4.4 Hz).

5-Bromo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizine (**3b**)

A yellow solid at 0 °C. Yield – 91%. Low-melting. Anal. Calcd for $C_8H_7BrF_3N$, %: C 37.82; H 2.78; N 5.51. Found, %: C 37.75; H 2.79; N 5.57. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.54 (2H, quint, $^3J_{HH}$ = 7.3 Hz); 2.98–3.03 (2H, m); 3.91 (2H, t, $^3J_{HH}$ = 7.2 Hz); 6.30 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –57.41 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 25.37; 26.63; 46.53; 95.56; 106.99 (q, $^2J_{CF}$ = 38.0 Hz); 110.77 (q, $^3J_{CF}$ = 3.0 Hz); 123.65 (q, $^1J_{CF}$ = 265.9 Hz); 137.39 (q, $^3J_{CF}$ = 4.4 Hz).

5-Iodo-7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizine (**3c**)

A yellow solid at 0 °C. Yield – 77%. Low-melting. Anal. Calcd for $C_8H_7IF_3N$, %: C 31.92; H 2.34; N 4.65. Found, %: C 31.99; H 2.31; N 4.59. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.54 (2H, quint, $^3J_{HH}$ = 7.2 Hz); 3.02–3.12 (2H, m); 3.87 (2H, t, $^3J_{HH}$ = 7.1 Hz); 6.48 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –57.34 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 25.38; 25.83; 47.72; 108.05; 108.19 (q, $^2J_{CF}$ = 37.8 Hz); 117.68 (q, $^3J_{CF}$ = 2.9 Hz); 123.01 (q, $^1J_{CF}$ = 266.0 Hz); 139.27 (q, $^3J_{CF}$ = 4.1 Hz).

1-[7-(Trifluoromethyl)-2,3-dihydro-1H-pyrrolizin-5-yl]ethanone (**4**)

To the solution of **1** (5.25 g, 30.0 mmol) in DCM (100 mL), a boron trifluoride–ether complex (45.0 mmol) was added. The resulting solution was cooled to 0 °C on an ice-water bath, and acetic anhydride (2.98 mL, 31.5 mmol) was added while keeping the internal temperature below 5 °C. After the addition, the reaction mixture was slowly heated to RT, and then stirred at the same temperature for 16 h. The resulting solution was washed with water (100 mL), saturated aq $NaHCO_3$ (2×100 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by distillation (b.p. 61–62 °C/1 mbar) to give a colorless liquid solidified upon standing to a white low-melting solid.

Yield – 58%. M. p. 42–44 °C. Anal. Calcd for $C_{10}H_{10}F_3NO$, %: C 55.30; H 4.64; N 6.45. Found, %: C 55.45; H 4.72; N 6.39. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.34 (3H, s); 2.52 (2H, quint, $^3J_{HH}$ = 7.5 Hz); 2.92 (2H, t, $^3J_{HH}$ = 7.6 Hz); 4.29 (2H, t, $^3J_{HH}$ = 7.3 Hz); 7.01 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –57.58 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 23.41; 25.32; 26.25; 48.16; 106.54 (q, $^2J_{CF}$ = 38.1 Hz); 117.78 (q, $^3J_{CF}$ = 3.2 Hz); 122.96 (q, $^1J_{CF}$ = 266.1 Hz); 127.04; 143.13 (q, $^3J_{CF}$ = 3.7 Hz); 187.14.

2,2,2-Trichloro-1-[7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizin-5-yl]ethanone (**5**)

To the solution of **1** (5.25 g, 30.0 mmol) in DCM (100 mL), trichloroacetyl chloride (3.65 mL, 33.0 mmol) was added at 0–5 °C. After the addition, the reaction mixture was slowly heated to RT and then stirred at the same temperature for 16 h. After completing the reaction, the solvent was evaporated under reduced pressure to obtain **5** as an orange solid. The crude material was used in the next step without further purification.

A crude yield – 97%. M. p. 116–118 °C. Anal. Calcd for $C_{10}H_7Cl_3F_3NO$, %: C 37.47; H 2.20; N 4.37. Found, %: C 37.38; H 2.18; N 4.32. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.63 (2H, quint, $^3J_{HH}$ = 7.7 Hz); 3.03 (2H, t, $^3J_{HH}$ = 7.7 Hz); 4.41 (2H, t, $^3J_{HH}$ = 7.3 Hz); 7.54 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –58.02 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 187.14; 143.13 (q, $^3J_{CF}$ = 3.7 Hz); 127.04; 122.96 (q, $^1J_{CF}$ = 266.1 Hz); 117.78 (q, $^3J_{CF}$ = 3.2 Hz); 106.54 (q, $^2J_{CF}$ = 38.1 Hz); 48.16; 26.25; 25.32; 23.41.

7-(Trifluoromethyl)-2,3-dihydro-1H-pyrrolizine-5-carboxylic acid (**6**)

To the solution of **5** (3.19 g, 10 mmol) in THF (20 mL), sodium hydroxide (1.4 g, 35 mmol) in water (30 mL) was added at 0–10 °C. The resulting solution was stirred for 16 h at RT, and most of the organic solvent was evaporated under reduced pressure. The residue was washed

with MTBE (2×20 mL) and acidified with 10 M HCl to pH 1. The product was isolated by filtration to obtain **6** as a gray solid.

Yield – 81%. M. p. 184–185 °C. Anal. Calcd for $C_9H_8F_3NO_2$, %: C 49.32; H 3.68; N 6.39. Found, %: C 49.48; H 3.40; N 6.32. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.41-2.48 (2H, m); 2.90 (2H, t, $^3J_{HH}$ = 7.6 Hz); 4.20 (2H, t, $^3J_{HH}$ = 7.3 Hz); 6.96 (1H, s); 12.63 (1H, br. s). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –55.75 (s, CF_3). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 23.77; 26.23; 48.15; 104.95 (q, $^2J_{CF}$ = 37.1 Hz); 115.92; 119.75; 123.76 (q, $^1J_{CF}$ = 265.6 Hz); 142.20 (q, $^3J_{CF}$ = 3.9 Hz); 160.95.

Ethyl 2-oxo-2-(7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizin-5-yl)acetate (**7**)

To the solution of **1** (5.25 g, 30.0 mmol) in $CHCl_3$ (100 mL), ethyl chlorooxoacetate (3.67 mL, 33.0 mmol) was added at 0–5 °C. After the addition, the reaction mixture was slowly heated to 40 °C and then stirred at the same temperature for 16 h. After completing the reaction, the reaction mixture was cooled to RT, and the solvent was evaporated under reduced pressure to obtain **7** as a light-yellow liquid. The crude material was used in the next step without further purification.

A crude yield – 99%. Light-yellow liquid. Anal. Calcd for $C_{12}H_{12}F_3NO_3$, %: C 52.37; H 4.39; N 5.09. Found, %: C 52.42; H 4.41; N 5.05. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.40 (3H, t, $^3J_{HH}$ = 7.3); 2.60 (2H, quint, $^3J_{HH}$ = 7.5 Hz); 2.99 (2H, t, $^3J_{HH}$ = 7.6 Hz); 4.43–4.30 (m, 4H); 7.53 (1H, s). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: –58.08 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 13.48; 23.70; 26.01; 48.49; 61.91; 108.63 (q, $^2J_{CF}$ = 38.6 Hz); 122.75 (q, $^1J_{CF}$ = 266.5 Hz); 123.50 (q, $^3J_{CF}$ = 3.4 Hz); 146.47 (q, $^3J_{CF}$ = 3.4 Hz); 161.40; 172.23.

2-Oxo-2-(7-(trifluoromethyl)-2,3-dihydro-1H-pyrrolizin-5-yl)acetic acid (**8**)

To the solution of **7** (2.75 g, 10 mmol) in THF (20 mL), lithium hydroxide (0.36 g, 15 mmol) in water (20 mL) was added at 0–10 °C. The resulting solution was stirred for 16 h at RT, and the organic solvent was evaporated under reduced pressure. The residue was washed with MTBE (2×20 mL) and acidified with 10 M HCl to pH 1. The product was isolated by filtration to obtain **8** as a brown solid.

Yield – 73%. M. p. 168–170 °C. Anal. Calcd for $C_{10}H_8F_3NO_3$, %: C 48.59; H 3.26; N 5.67. Found, %: C 48.51; H 3.31; N 5.72. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.54 (2H, quint, $^3J_{HH}$ = 7.5 Hz); 2.94 (2H, t, $^3J_{HH}$ = 7.6 Hz); 4.27 (2H, t, $^3J_{HH}$ = 7.2 Hz); 7.41 (1H, s); 11.85 (1H, br. s). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: –56.34 (s, CF_3). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 25.85; 28.37; 50.93; 108.93 (q, $^2J_{CF}$ = 37.6 Hz); 124.48; 125.45 (q, $^1J_{CF}$ = 266.0 Hz); 126.16; 149.00 (q, $^3J_{CF}$ = 3.6 Hz); 166.07; 177.20.

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