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**C<sup>2</sup>-ALKYLATION IN A THREE-COMPONENT REACTION OF FLUOROCARBONYL COMPOUNDS, PYRROLE DERIVATIVES AND MALONONITRILE IN COMPETITION WITH C<sup>2</sup>-OXYALKYLATION**

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**Abstract:** The C<sup>2</sup>-alkylation of pyrrole derivatives with 2-(2,2,2-trifluoroethylidene) malononitrile **1**, formed *in situ* from ethyl hemiacetal trifluoroacetaldehyde **2** and malononitrile in the presence of a base, has been carried out. As a result of this three-component reaction, nitriles were obtained - derivatives of 4,5,6,7-tetrahydroindole and pyrrole **4a**, **b**, **c**. A competing reaction is C<sup>2</sup>-oxyalkylation of the pyrrole ring with hemiacetal **2**. It has been shown that the side reaction can be completely suppressed by lowering the reaction temperature to -30°C. When the ethyl ester of trifluoropyruvic acid **3** reacts with pyrrole derivatives in the presence of malononitrile, the main reaction is the C<sup>2</sup>-oxyalkylation of the pyrrole ring, rather than its C<sup>2</sup>-alkylation formed *in situ* by alkene **10**. Nitriles **6** - **9** were obtained in high yields from pyrrole derivatives and alkene **10**. The structure of the compounds was confirmed by <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F NMR spectroscopy, mass spectrometry and high-resolution mass spectrometry.

**Keywords:** 2-(2,2,2-trifluoroethylidene)malononitrile, ethyl 3,3-dicyano-2-(trifluoromethyl) acrylate, substitution of 2-(2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)ethyl)malononitrile and ethyl 2-(dicyanomethyl)-3,3,3-trifluoro-2-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propanoate, three-component one-step synthesis, C<sup>2</sup>-alkylation, C<sup>2</sup>-oxyalkylation, trifluoroacetaldehyde ethyl hemiacetal, ethyl trifluoropyruvate, pyrrole and indole derivatives, malononitrile.

**Introduction**

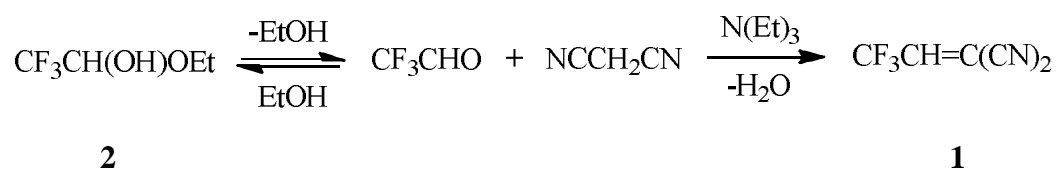
The synthesis of heterocyclic organofluorine compounds has attracted a lot of attention for many years. Their promise is especially noticeable in pharmaceutical chemistry; about 20% of all drugs contain at least one fluorine atom. However, the synthesis of these compounds often causes

unexpected difficulties [1-4]. Trifluoroacetaldehyde ethyl hemiacetal **2** and trifluoropyruvic acid ethyl ester **3** are some of the most important synthones with which heterocyclic compounds containing a trifluoromethyl group can be prepared. We previously reported on a three-component reaction of indole derivatives, **2** and malononitrile in the presence of a base, leading to 3-(1*H*-indol-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid nitriles in good yields [4]. Cyano pyrrole derivatives and THI are potentially biologically active substances, and can also be used as intermediates in further directed synthesis to search for new biologically active compounds or plant growth regulators [5]. Currently, multicomponent reactions have reached the level of advanced synthetic tools, the search and development of which is stimulated by the principles of waste-free chemical production, that is, "green chemistry". The use of the three-component synthesis procedure allows avoiding the stage of obtaining, purifying, and using fluorine-containing cyanoethylenes, which are known for their toxicity [6, 7].

In this work, we applied a three-component one-step synthesis to obtain fluorine-containing cyanide derivatives of pyrrole and indole, substituted at position 2, based on fluorocarbonyl compounds **2** and **3**.

### Results and discussion

Developing systematic studies of the synthesis of fluorine-containing heterocyclic compounds, starting from fluorine-containing cyanoethylenes, we showed that the C<sup>2</sup>-alkylation of indoles with such a reactive alkene as 2-(2,2,2-trifluoroethylidene)malononitrile **1** can be carried out as a result of the three-component reaction of indoles, hemiacetal **2** and malononitrile in the presence of a base, i.e. without isolation of alkene formed *in situ* [4] (Scheme 1).

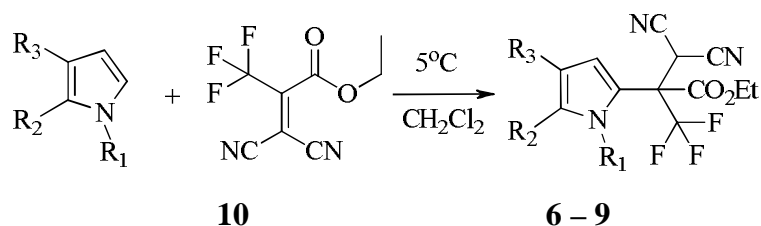


**Scheme 1.** Synthesis of 2-(2,2,2-trifluoroethylidene)malononitrile **1**.

This approach creates the prospect of widespread use of fluorinated cyanoethylenes without their preliminary isolation from the reaction mass. In this paper, we tried to expand a number of used heterocyclic substrates to 4,5,6,7-tetrahydroindole (THI), pyrrole and their N-methyl derivatives. In addition, we also used ethyl ether of trifluoropyruvic acid **3** as a polyfluorocarbonyl precursor of cyanoethylenes. The use of THI instead of indole in reactions with polyfluorocarbonyl compounds makes it possible to ultimately obtain not 3-, but 2-substituted indoles [8]. Unlike



(6 - 9%). Relative success was achieved only in the cases of unsubstituted THI and pyrrole at -30°C. Nitriles **7** and **9** were obtained by this method in 32 and 24% yields, respectively.



**Scheme 3.** Synthesis of nitriles **6 - 9** using alkene **10**,  
**6)**  $R_1=Me$ ,  $R_2+R_3=(CH_2)_4$ ; **7)**  $R_1=H$ ,  $R_2+R_3=(CH_2)_4$ ;  
**8)**  $R_1=Me$ ,  $R_2=R_3=H$ ; **9)**  $R_1=H$ ,  $R_2=R_3=H$ .

Unlike synthon **1**, alkene **10** is available and has been widely studied earlier using other examples [9]. It turned out that the interaction of THI, pyrrole and their N-Me-derivatives with alkene **10** leads to the products of regioselective C<sup>2</sup>-alkylation, nitriles **6 - 9**, in 77-85% yields (Scheme 3).

### Conclusions

Thus, the strategy developed by us for the synthesis of nitriles of hetaryl-2-cyano-4,4,4-trifluorobutanoic acid, based on the use of 2-(2,2,2-trifluoroethylidene)malononitrile, formed *in situ* from commercially available precursors [4], successfully extended to the synthesis of 2-substituted pyrroles and indoles - nitriles **4a - c** and **6 - 9**. It has been shown that the presence of hemiacetal **2** in the reaction mass leads to a competing reaction of C<sup>2</sup>-oxyalkylation of the pyrrole ring, which can be completely suppressed by lowering the reaction temperature to -30°C. In the case of ketoester **3**, when interacting with pyrrole, its derivatives and malononitrile, the main reaction is the C<sup>2</sup>-oxyalkylation of the pyrrole nucleus, rather than its C<sup>2</sup>-alkylation, formed *in situ* by alkene **10**. Nitriles **6 - 9** were obtained also in high yields from derivatives of pyrrole, THI and alkene **10**, previously synthesized from ketoester **3** and malononitrile in 61% yield.

### Experimental part

All starting compounds were purchased from Merck, Sigma-Aldrich and used without purification. All eluents and solvents: petroleum ether  $T_{bp} = 40-70^\circ\text{C}$  (PE), EtOAc (EA), DCM and triethylamine were purified by distillation before use. Merck Kieselgel 60 F254 TLC plates were used to monitor the reaction and detect substances. The products were purified by column chromatography using Merck Kieselgel 60 silica gel (0.06-0.20 mm).

$^1\text{H}$ ,  $^{13}\text{C}$  JMODECHO and  $^{19}\text{F}$  NMR spectra were recorded on a Bruker Avance<sup>TM</sup>400 spectrometer at 400, 100, and 376 MHz, respectively. The chemical shifts of protons were determined relative to the residual  $\text{CDCl}_3$  signals (7.26 ppm) and recalculated to the  $\text{SiMe}_4$  signal. The  $^{19}\text{F}$  NMR spectra were recorded with the suppression of the H-F spin-spin interaction. The chemical shifts of  $^{19}\text{F}$  nuclei were determined relative to  $\text{CFCl}_3$  as an external standard.

Mass spectra were recorded on a Finnigan Polaris Q instrument (ion trap, EI, ionizing electron energy 70 eV) by direct sample injection. High resolution mass spectra were recorded on a Bruker micrOTOF II instrument (electrospray ionization (ESI)). The measurements were performed on positive (capillary voltage 4500 V) or negative (capillary voltage 3200 V) ions. Mass scanning range  $m/z$  50-3000 Da, external or internal calibration (Electrospray Calibrant Solution, Fluka). We used a syringe injection of the substance for solutions in acetonitrile, methanol, or water, the flow rate was  $3\mu\text{L}/\text{min}$ . Spray gas nitrogen ( $4\text{l}/\text{min}$ ), interface temperature  $180^\circ\text{C}$  [10].

***General procedure for the preparation of nitriles 4a - d and 6 - 9  
by three-component one-stage synthesis***

Freshly distilled DCM (2ml), malonitrile (0.1g, 1.5mmol), trifluoro-acetaldehyde ethyl hemiacetal **2** or ethyl trifluoropyruvate **3** (0.216g or 0.255g, respectively, 1.5mmol), triethylamine (0.1g) and 5-7 granules of dried molecular sieves with a pore size of 4A are loaded into a round-bottom flask equipped with a magnetic stir bar. The flask is closed with a septa, vacuumed and filled with argon, cooled to the planned temperature ( $+5^\circ\text{C}$  or  $-30^\circ\text{C}$ ) and a pyrrole derivative or THI (1.5mmol) dissolved in 1 ml of DCM is injected with a syringe. The reaction mass is kept at the planned temperature ( $+5^\circ\text{C}$  or  $-30^\circ\text{C}$ ) overnight. Then the reaction mixture was diluted with a mixture of DCM and PE (10ml, 1/1) and transferred to a chromatographic column containing 100ml of silica gel. The reaction mass is eluted with a mixture of DCM and PE (1/1), gradually increasing the solvent gradient by adding EA to 3-5%. Alcohols **5** are the first to leave the column, their  $R_f$  is 0.6-0.9, then nitriles **4** with  $R_f$  equal to 0.3-0.6 (PE/EA = 8/2). Solutions of purified products **4** and **5** are evaporated at reduced pressure and re-evaporated with 20 ml of DCM.

***General method of synthesis of nitriles 6 - 9 via alkene 10.***

Freshly distilled DCM (2ml) and a pyrrole or THI derivative (1.5mmol) are loaded into a round-bottom flask equipped with a magnetic stir bar. The flask is closed with a septa, vacuumed three times consecutively and filled with argon, cooled to  $+5^\circ\text{C}$  and with using a syringe, alkene **10** (0.327g, 1.5mmol) dissolved in 1ml of DCM is injected. The reaction mass is kept at  $+5^\circ\text{C}$  for 2-3 hours. Then the reaction mixture was diluted with a mixture of DCM and PE (10ml, 1/1) and

transferred on a glass filter containing 10 ml of silica gel. Nitriles **6 - 9** are eluted with a mixture of DCM and PE (1/1), a nitrile solution is collected and evaporated at reduced pressure, then re-evaporated with DCM (20 ml).

**2-(2,2,2-Trifluoro-1-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)ethyl)malononitrile (4a)**

In 3CR procedure at +5°C: yield 57% (0.24g); at -30°C: yield 69% (0.29g). Transparent light yellow slowly solidifying oil,  $R_f = 0.4$  (PE+EA, 0.8+0.2).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ, ppm., *J*/Hz): 1.77-1.89 (4H, m, 2CH<sub>2</sub>); 2.53-2.59 (4H, m, 2CH<sub>2</sub>); 3.48 (3H, s, Me); 4.21-4.28 (1H, m, CHCF<sub>3</sub>); 4.38 (1H, d, 6.2 Hz, CH(CN)<sub>2</sub>); 6.35 (1H, s, 3(C)H THI).

**<sup>13</sup>C NMR JMODECHO** (CDCl<sub>3</sub>, δ, ppm., *J*/Hz): 22.02 (CH<sub>2</sub>); 22.75 (CH<sub>2</sub>); 22.95 (CH<sub>2</sub>); 23.28 (CH<sub>2</sub>); 25.07 (CH(CN)<sub>2</sub>); 29.58 (NMe); 41.86 (q, 30.3 Hz, CHCF<sub>3</sub>); 108.66 (3(C) THI); 110.50 (CN); 110.71 (CN); 116.19; 118.04; 123.69 (q, 281.1 Hz, CF<sub>3</sub>); 131.20.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, δ, ppm.): -68.31 (CF<sub>3</sub>).

**MS** (EI, 70 eV), *m/z* (*I*<sub>rel</sub> (%)): 281 [M]<sup>+</sup> (2.45); 216 [M - CH(CN)<sub>2</sub>]<sup>+</sup> (100).

**HRMS** (ESI, neg. ions), C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>, found *m/z*: 280.1076 [M - H]<sup>-</sup>. Calculated: 280.1067.

**2-(2,2,2-Trifluoro-1-(4,5,6,7-tetrahydro-1H-indol-2-yl)ethyl)malononitrile (4b)**

In 3CR procedure at +5°C: yield 39% (0.155g); at -30°C: yield 75% (0.3g). Transparent light yellow slowly solidifying oil,  $R_f = 0.4$  (PE+EA, 0.8+0.2).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ, ppm., *J*/Hz): 1.74-1.84 (4H, m, 2CH<sub>2</sub>); 2.48-2.58 (4H, m, 2CH<sub>2</sub>); 4.00-4.07 (1H, m, CHCF<sub>3</sub>); 4.34 (1H, d, 4.8 Hz, CH(CN)<sub>2</sub>); 6.20 (1H, d, 2.4 Hz, 3(C)H THI); 8.08 (1H, br. s., NH).

**<sup>13</sup>C NMR JMODECHO** (CDCl<sub>3</sub>, δ, ppm., *J*/Hz): 22.56 (CH<sub>2</sub>); 22.60 (CH<sub>2</sub>); 23.05 (CH<sub>2</sub>); 23.44 (CH<sub>2</sub>); 25.22 (CH(CN)<sub>2</sub>); 44.79 (q, 30.3Hz, CHCF<sub>3</sub>); 110.46 (CN); 110.60 (CN); 111.17 (3(C) THI); 114.15; 118.38; 123.77 (q, 281.4 Hz, CF<sub>3</sub>); 130.64.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, δ, ppm.): -67.88 (CF<sub>3</sub>).

**MS** (EI, 70 eV), *m/z* (*I*<sub>rel</sub> (%)): 267 [M]<sup>+</sup> (2.1); 202 [M - CH(CN)<sub>2</sub>]<sup>+</sup> (100).

**HRMS** (ESI, neg. ions), C<sub>13</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>, found *m/z*: 266.0921 [M - H]<sup>-</sup>. Calculated: 266.0911.

**2-(2,2,2-Trifluoro-1-(1-methyl-1H-pyrrol-2-yl)ethyl)malononitrile (4c)**

In 3CR procedure at +5°C: yield 54% (0.185g); at -30°C: yield 71% (0.24g). Transparent light yellow slowly solidifying oil,  $R_f = 0.2$  (PE+EA, 0.8+0.2).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ, ppm., *J*/Hz): 3.65 (3H, s, NMe); 4.12-4.19 (1H, m, CHCF<sub>3</sub>); 4.33 (1H, d, 6.6 Hz, CH(CN)<sub>2</sub>); 6.23 (1H, m, Ar); 6.54 (1H, m, Ar); 6.74 (1H, m, Ar).

**<sup>13</sup>C NMR JMODECHO** (CDCl<sub>3</sub>, δ, ppm., J/Hz): 25.12 (CH(CN)<sub>2</sub>); 33.99 (NMe); 41.91 (q, 30.6 Hz, CF<sub>3</sub>CH); 108.58; 110.16 (CN); 110.46 (CN); 110.75; 118.33; 123.52 (q, 280.7 Hz, CF<sub>3</sub>); 125.41.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, δ, ppm.): -68.39 (CF<sub>3</sub>).

**MS** (EI, 70 eV), *m/z* (I<sub>rel</sub> (%)): 227 [M]<sup>+</sup> (4.9); 162 [M - CH(CN)<sub>2</sub>]<sup>+</sup> (100).

**HRMS** (ESI, neg. ions), C<sub>10</sub>H<sub>8</sub>F<sub>3</sub>N<sub>3</sub>, found *m/z*: 226.0591 [M - H]<sup>-</sup>. Calculated: 226.0598.

***Ethyl 2-(dicyanomethyl)-3,3,3-trifluoro-2-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)propanoate (6)***

In 3CR procedure at +5°C: yield 6% (0.03g); at -30°C: yield 9% (0.05g); *via* alkene **10**: yield 81% (0.43g). Transparent light yellow slowly solidifying oil, R<sub>f</sub>= 0.3 (PE+EA, 0.8+0.2).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ, ppm., J/Hz): 1.40 (3H, t, 7.1 Hz, Me); 1.70-1.83 (4H, m, 2CH<sub>2</sub>); 2.45-2.49 (4H, m, 2CH<sub>2</sub>); 3.34 (3H, s, NMe); 4.42-4.52 (2H, m, CH<sub>2</sub>); 4.57 (1H, s, CH(CN)<sub>2</sub>); 6.17 (1H, s, 3(C)H THI).

**<sup>13</sup>C NMR JMODECHO** (CDCl<sub>3</sub>, δ, ppm., J/Hz): 13.78 (CH<sub>3</sub>); 22.33 (CH<sub>2</sub>); 22.72 (CH<sub>2</sub>); 22.95 (CH<sub>2</sub>); 23.13 (CH<sub>2</sub>); 29.39 (CH(CN)<sub>2</sub>); 31.23 (NMe); 64.54 (q, 30.1 Hz, CF<sub>3</sub>C); 64.94 (CH<sub>2</sub>); 109.84 (CN); 110.03 (CN); 111.52 (3(C) THI); 115.94; 117.94; 123.20 (q, 280.2 Hz, CF<sub>3</sub>); 133.26; 164.67.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, δ, ppm.): -65.30 (CF<sub>3</sub>).

**MS** (EI, 70 eV), *m/z* (I<sub>rel</sub> (%)): 353 [M]<sup>+</sup> (3.3); 288 [M - CH(CN)<sub>2</sub>]<sup>+</sup> (100).

**HRMS** (ESI, neg. ions), C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>, found *m/z*: 352.1270 [M - H]<sup>-</sup>. Calculated: 352.1278.

***Ethyl 2-(dicyanomethyl)-3,3,3-trifluoro-2-(4,5,6,7-tetrahydro-1H-indol-2-yl)propanoate (7)***

In 3CR procedure at +5°C: yield 7% (0.035g); at -30°C: yield 32% (0.165g); *via* alkene **10**: yield 77% (0.39g). Transparent light yellow slowly solidifying oil, R<sub>f</sub>= 0.5 (PE+EA, 0.8+0.2).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ, ppm., J/Hz): 1.43 (3H, t, 7.1 Hz, Me); 1.73-1.81 (4H, m, 2CH<sub>2</sub>); 2.45-2.56 (4H, m, 2CH<sub>2</sub>); 4.46-4.56 (2H, m, CH<sub>2</sub>); 4.76 (1H, s, CH(CN)<sub>2</sub>); 6.11 (1H, s, 3(C)H THI); 8.45 (1H, br. s., NH).

**<sup>13</sup>C NMR JMODECHO** (CDCl<sub>3</sub>, δ, ppm., J/Hz): 13.59 (Me); 22.44 (CH<sub>2</sub>); 22.50 (CH<sub>2</sub>); 22.91 (CH<sub>2</sub>); 23.30 (CH<sub>2</sub>); 27.46 (CH(CN)<sub>2</sub>); 58.71 (q, 27.4 Hz, CF<sub>3</sub>C); 65.15; 109.93; 110.06 (CN); 110.15 (CN); 113.63; 118.38; 122.71 (q, 286.8 Hz, CF<sub>3</sub>); 131.19; 163.46.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, δ, ppm.): -67.37 (CF<sub>3</sub>).

**MS** (EI, 70 eV), *m/z* (I<sub>rel</sub> (%)): 339 [M]<sup>+</sup> (3.3); 274 [M - CH(CN)<sub>2</sub>]<sup>+</sup> (100).

**HRMS** (ESI, neg. ions), C<sub>16</sub>H<sub>16</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>, found *m/z*: 338.1121 [M - H]<sup>-</sup>. Calculated: 338.1122.

***Ethyl 2-(dicyanomethyl)-3,3,3-trifluoro-2-(1-methyl-1H-pyrrol-2-yl)propanoate (8)***

In 3CR procedure at +5°C: yield 0.0% (0.0g); at -30°C: yield 0.0% (0.0g); *via alkene 10*: yield 85% (0.38g). Transparent light yellow slowly solidifying oil,  $R_f = 0.4$  (PE+EA, 0.8+0.2).

**$^1\text{H NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ , ppm.,  $J/\text{Hz}$ ): 1.38 (3H, t, 7.1 Hz, Me); 3.62 (3H, s, NMe); 4.41-4.50 (2H, m,  $\text{CH}_2$ ); 4.70 (1H, s,  $\text{CH}(\text{CN})_2$ ); 6.13 (1H, m, Ar); 6.65 (1H, m, Ar); 6.75 (1H, m, Ar).

**$^{13}\text{C NMR JMODECHO}$**  ( $\text{CDCl}_3$ ,  $\delta$ , ppm.,  $J/\text{Hz}$ ): 13.42 (Me); 29.10 (NMe); 36.23 ( $\underline{\text{CH}}(\text{CN})_2$ ); 58.82 (q, 27.3 Hz,  $\text{CF}_3$ ); 64.17; 106.99; 110.39; 110.40 (CN); 110.61 (CN); 121.93; 123.27; 123.35 (q, 285.2 Hz,  $\text{CF}_3$ ); 164.37.

**$^{19}\text{F NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ , ppm.): -66.70 ( $\text{CF}_3$ ).

**MS** (EI, 70 eV),  $m/z$  ( $I_{\text{rel}}$  (%)): 299  $[\text{M}]^+$  (5.8); 234  $[\text{M} - \text{CH}(\text{CN})_2]^+$  (100).

**HRMS** (ESI, neg. ions),  $\text{C}_{13}\text{H}_{12}\text{F}_3\text{N}_3\text{O}_2$ , found  $m/z$ : 298.0801  $[\text{M} - \text{H}]^-$ . Calculated: 298.0809.

***Ethyl 2-(dicyanomethyl)-3,3,3-trifluoro-2-(1H-pyrrol-2-yl)propanoate (9)***

In 3CR procedure at +5°C: yield 6% (0.025g); at -30°C: yield 24% (0.103g); *via alkene 10*: yield 79% (0.337g). Transparent light yellow slowly solidifying oil,  $R_f = 0.4$  (PE+EA, 0.8+0.2).

**$^1\text{H NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ , ppm.,  $J/\text{Hz}$ ): 1.41 (3H, t, 7.1 Hz, Me); 4.49-4.51 (2H, m,  $\text{CH}_2$ ); 4.83 (1H, s,  $\text{CH}(\text{CN})_2$ ); 6.27 (1H, m, Ar); 6.41 (1H, m, Ar); 6.90 (1H, m, Ar); 9.07 (1H, br. s., NH).

**$^{13}\text{C NMR JMODECHO}$**  ( $\text{CDCl}_3$ ,  $\delta$ , ppm.,  $J/\text{Hz}$ ): 13.49 (Me); 27.49 ( $\underline{\text{CH}}(\text{CN})_2$ ); 58.56 (q, 27.6 Hz,  $\text{CF}_3$ ); 65.40; 109.61; 109.95 (CN); 110.03 (CN); 110.81; 116.07; 121.70; 122.59 (q, 286.5 Hz,  $\text{CF}_3$ ); 163.26.

**$^{19}\text{F NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ , ppm.): -67.47 ( $\text{CF}_3$ ).

**MS** (EI, 70 eV),  $m/z$  ( $I_{\text{rel}}$  (%)): 285  $[\text{M}]^+$  (5.4); 220  $[\text{M} - \text{CH}(\text{CN})_2]^+$  (100).

**HRMS** (ESI, neg. ions),  $\text{C}_{12}\text{H}_{10}\text{F}_3\text{N}_3\text{O}_2$ , found  $m/z$ : 284.0657  $[\text{M} - \text{H}]^-$ . Calculated: 284.0652.

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## References

1. J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, The importance of fluorine in the life science industry, *Chem. Rev.*, **2013**, 114, 2432–2506. doi: 10.1021/cr4002879.
2. E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, Fluorine in Pharmaceuticals: Looking Beyond Intuition, *J. Med. Chem.*, **2015**, 58, 8315–8359. doi: 10.1021/acs.jmedchem.5b00258.
3. J.-P. Bégué, D. Bonnet-Delpon, Recent advances (1995–2005) in fluorinated pharmaceuticals based on natural products, *J. Fluorine Chem.*, **2006**, 127, 992–1012. doi.org/10.1016/j.jfluchem.2006.05.006.
4. O. Yu. Fedorovskii, N. D. Chkanikov, Three-component one-step synthesis of new nitriles – 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid, *Fluorine Notes*, **2021**, 134, 3-4. doi: 10.17677/fn20714807.2021.01.02.
5. O. Yu. Fedorovskii, A. Yu. Volkonskii, A. S. Golubev, Yu. Ya. Spiridonov, N. D. Chkanikov, Synthesis of ethyl  $\alpha$ -nitro- $\beta$ -trifluoromethyl acrylate and  $\beta$ -trifluoromethyl-substituted tryptophan analogs and their plant growth regulating activity, *Russian Chemical Bulletin*, **2017**, 66(6), 1116-1121. doi.org/10.1007/s11172-017-1863-z.
6. W. J. Middleton, 1,1-Dicyano-2,2-bis(trifluoromethyl)ethylene, *J. Org. Chem.*, **1965**, 30, 1402-1407. doi.org/10.1021/jo01016a013.
7. N. D. Chkanikov and A. S. Golubev, C-Oxyalkylation of Arylamines, Enamines, and Nitrogen-Containing Heterocycles with Polyfluorinated Carbonyl Compounds as a Synthetic Route to Biologically Active Compounds, *INEOS OPEN*, **2021**, 4(1), 1–19. doi: 10.32931/io2105r.
8. Sigan Andrei L., Gusev Dmitrii V., Chkanikov Nikolai D., Shmidt Elena Yu, Ivanov Andrei V., Mihaleva Al'bina I., Hydroxyalkylation of 4,5,6,7-tetrahydroindole with polyfluorocarbonyl compounds as a route to 2-substituted indoles, *Tetrahedron Letters*, Elsevier BV (Netherlands), **2011**, 52(39), 5025-5028. doi.org/10.1016/j.tetlet.2011.07.071.
9. V. Yu. Tyutin, N. D. Chkanikov, A. F. Kolomietz, A. V. Fokin, Synthesis of esters of 3,3-dicyano-2-(trifluoromethyl)acrylic acid and their reactions with arylamines, *J. Fluorine Chem.*, **1991**, 51, 323-334. doi.org/10.1016/S0022-1139(00)80188-8.
10. Tsedilin A. M., Fakhrutdinov A. N., Eremin D. B., Zalesskiy S. S., Chizhov A. O., Kolotyorkina N. G., Ananikov V. P., How sensitive and accurate are routine NMR and MS measurements?, *Mendeleev Comm.*, **2015**, 25, 454. doi.org/10.1016/j.mencom.2015.11.019.