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[3+2] Cycloaddition reactions of 1-substituted 3,3,3-trifluoropropenes with isonitriles – synthesis of pyrroles and pyrrolines

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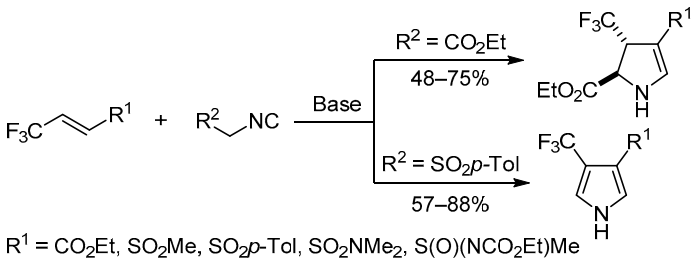


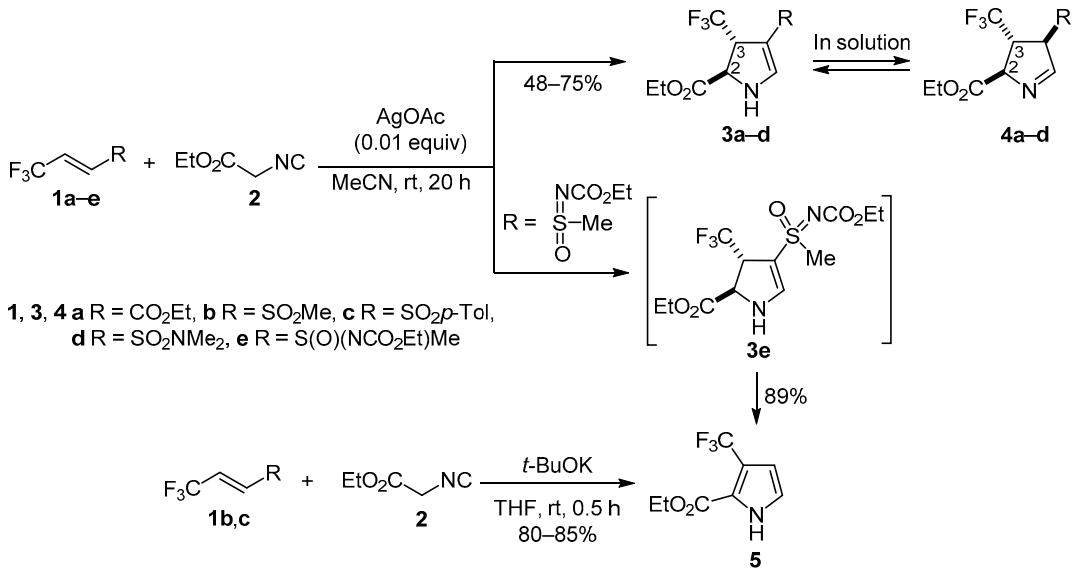
Cycloaddition reactions of 3,3,3-trifluoropropene derivatives containing an alkoxycarbonyl, sulfonyl, sulfoximine, or sulfamide substituent in position 1 with ethyl isocyanoacetate proceed with the formation of 3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrroles, whereas their reactions with tosylmethyl isocyanide lead to the formation of 4-(trifluoromethyl)-1*H*-pyrroles.

Keywords: ethyl isocyanoacetate, pyrrole, pyrrolidine, pyrroline, sulfamide, sulfone, sulfoximine, tosylmethyl isocyanide, trifluoromethyl group, cycloaddition.

The heterocyclic ring of pyrrole,[1] as well as of its hydrogenated derivatives pyrroline[2] and pyrrolidine,[3] is part of a large number of compounds of both synthetic and natural origin with a wide spectrum of biological activity. As a result, new structures based on these heterocycles are promising for biological research. The introduction of the trifluoromethyl group into the molecule of a heterocycle can have a significant effect on its chemical and biological properties[4] and, as a consequence, a significant number of pharmaceuticals and agrochemicals are of similar structure. The combination of the trifluoromethyl substituent with sulfur-containing pharmacophore groups, such as sulfamide or sulfoximine, in the molecule of a heterocycle can lead to a change or enhancement of the already existing biological activity. Therefore, the synthesis of new representatives of such functionalized compounds is an urgent task in heterocyclic chemistry. The literature describes many examples of clinically promising trifluoromethyl derivatives of pyrroline,[5] pyrrole,[6] and pyrrolidine.[7] At the same time, analogous compounds with a sulfur-containing substituent have been much less studied.[8]

[3+2] Cycloaddition reactions are one of the most versatile methods for constructing a five-membered ring. We have previously shown that the readily available electron-withdrawing olefins **1** with trifluoromethyl and sulfur-containing substituents can serve as convenient substrates for such reactions.[9] Continuing our studies on the synthesis of new heterocyclic compounds using the [3+2] cycloaddition method,[9] in this study we report on the preparation of five-membered substituted azaheterocycles by cycloaddition reactions of (*E*)-3,3,3-trifluoropropene derivatives **1a–e** containing an alkoxycarbonyl, sulfonyl, iminosulfonyl, or sulfamoyl group with isocyanomethylides formed from ethyl isocyanoacetate (**2**) or *p*-toluenesulfonylmethyl isocyanide (TOSMIC) (**6**). It is known that the reactions of substituted olefins with alkyl isocyanocetates lead to the formation of pyrrolines,[10] while in the reactions with tosylmethyl isocyanides, the intermediate α-tosylpyrrolines undergo *in situ* elimination of toluenesulfonate with the formation of pyrroles (the Van Leusen reaction).[11] However, data on the cyclization of compounds **1** with a sulfur-containing functional group is not found in the literature. A systematic study of them

Scheme 1



made it possible to synthesize novel substituted nitrogen-containing heterocycles, as well as to study the stereochemistry of reactions and the effect of the nature of substituents in the starting reagents on the structure of the final products.

We found that *E*-olefins **1a**–**d** regioselectively react with ethyl isocyanoacetate (**2**) at room temperature in MeCN to form 2,3-dihydro-1*H*-pyrroles **3a**–**d** in good and moderate yields (Scheme 1). To initiate the reaction, we used a catalytic amount (0.01 equiv) of AgOAc which, along with copper compounds, is often used in reactions involving alkyl isocyanoacetates and activated olefins.[10]

The structure of pyrrolines **3a**–**d** in the solid state was proved by X-ray structural analysis using the representative methylsulfonyl derivative **3b** (Fig. 1). In solution, however, compounds **3a**–**d** exist in the form of prototropic isomers Δ^2-pyrrolines **3a**–**d** and Δ^1-pyrrolines **4a**–**d**, the ratio of which in the NMR spectra changes depending on the solvent in which the spectra are recorded. Thus, in $CDCl_3$ solution, a ratio of 1:1.4 is observed for the mixture of pyrrolines **3b** and **4b**; in DMSO-d_6 solution, this ratio changes to 2.4:1, whereas in CF_3CO_2D solution, we observed signals of only a single isomer. The reactions of alkenes **1a**–**d** with isonitrile **2** were monitored using ^{19}F NMR spectroscopy of the reaction mixtures. The conversion of olefins **1a**–**c** was 83–91% according to the ^{19}F NMR spectra. In the case of compound **1d**, the reaction did not proceed as smoothly: along with a lower conversion (54%), side reactions occurred. Compound **3d** was isolated in 48% yield. However, in $CDCl_3$ solution, it was almost completely in the form of isomer **4d**, and we were unable to unambiguously characterize isomer **3d**. In the case of cycloaddition of alkene **1e** with a chiral iminosulfonyl substituent, the intermediate pyrroline **3e** undergoes ring aromatization by elimination of methane(*N*-carbethoxy)-imidosulfinic acid (Scheme 1). When the cycloaddition reaction of olefins **1b**,**c** and isonitrile **2** is carried out in THF in the presence of a base (*t*-BuOK), the sulfur-containing fragment is immediately eliminated from compounds **3b**,**c** with the formation of pyrrole **5**.

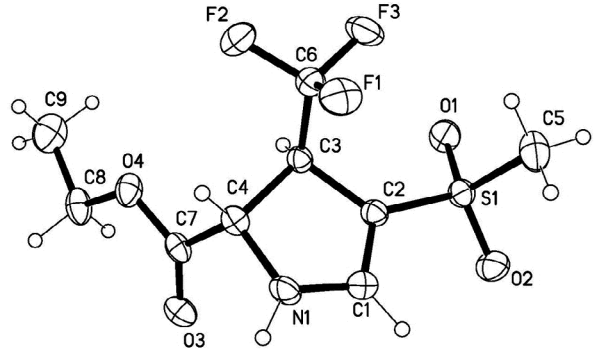


Figure 1. Molecular structure of compound **3b** with atoms represented as thermal vibration ellipsoids of 50% probability.

The assignment of the signals of Δ^2-pyrrolines **3a**–**d** and Δ^1-pyrrolines **4a**–**d** in the ^1H and ^{13}C NMR spectra in $CDCl_3$ solutions was carried out on the basis of the data of the ^1H–^{13}C HSQC spectrum of isomers **3b** and **4b**. The relative configuration of the substituents in the ring of pyrrolines **3** and **4 a**–**d** was determined based on the values of the coupling constants of the ring protons. Thus, the values of the coupling constant between the ring protons 2-CH and 3-CH of compounds **3** and **4 a**–**d** were $^3J_{HH}$ = 4.2–4.9 Hz, whereas these values were $^3J_{HH}$ = 4.5–4.6 Hz between the protons 3-CH and 4-CH of isomers **4a**–**d**, which indicates that the substituents at positions 2 and 3, as well as 3 and 4 have the *trans* arrangement in relation to each other. Similar values of the $^3J_{HH}$ constants were reported for similar substituted pyrroline structures with the *trans* arrangement of substituents.[10b] In the ^{13}C NMR spectra of isomers **3** and **4 a**–**d**, the signals of the C-3 carbon appeared in the form of quartets ($^2J_{CF}$ = 29.1–31.6 Hz) in the range of 45.0–49.3 ppm. The characteristic signals of the C-4 carbon of Δ^1-pyrrolines **4a**–**d** were observed at 75.9–77.3 ppm, whereas for Δ^2-pyrrolines **3a**–**d**, these signals could be observed in the 98.6–106.2 ppm range. The spectral data of ethyl 2-pyrrolecarboxylate **5** agree with the NMR data of the described 3-(trifluoromethyl)pyrrole-2-carboxylic acid methyl ester.[12]

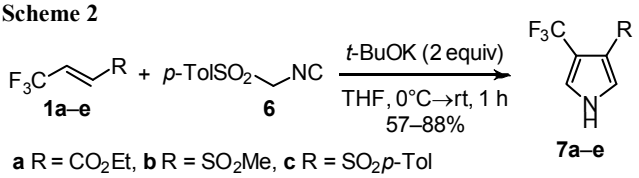
Next, we studied the cycloaddition reactions of 3,3,3-trifluoropropene derivatives **1a–e** with TOSMIC (**6**) (Scheme 2). It should be noted that this cyclization has been described only for β-perfluoroalkyl α,β-unsaturated carbonyl compounds with tosylmethyl isocyanides,[11e,f,13] while olefins with a sulfur-containing substituent have not been investigated in such reactions. In search of the optimal conditions for the generation of the isocyanomethylide anion and the reaction with alkene **1b** as a model substrate, we tested various bases, such as DBU, NaH, KOH, and *t*-BuOK, as well as solvents DMSO–Et_2O, DMF, THF. The best results were achieved when *t*-BuOK was used as the base and the reaction was carried out in THF. It was found that olefins **1a–e** react with TOSMIC (**6**) in the presence of a twofold amount of *t*-BuOK in THF upon cooling to form 1*H*-pyrroles **7a–e** in 57–88% yields (Scheme 2). The reactions proceed smoothly with full conversion of olefins **1** and are completed within 1 h, which made it possible to scale this process to obtain multigram amounts of 3,4-disubstituted pyrroles **7**.

Pyrroles **7a–e** are stable crystalline solids, the structure of which is consistent with the data of NMR spectroscopy, and the composition is confirmed by mass spectrometry and elemental analysis data. Compound **7a** was previously described in a patent,[13c] but no spectral characteristics were supplied. The signals of the ring carbon nuclei of compounds **7b–e** were unambiguously assigned using the ^{13}C APT NMR spectra. In the ^{13}C NMR spectra of compounds **7b–e**, the characteristic signals of the C-4 carbon atom appear as a quartet ($^2J_{CF}$ = 37.1–38.1 Hz) in the 110.4–112.7 ppm range, and the signals of the C-3 carbon atom are represented by a quartet at 116.2–121.2 ppm with the SSCC $^3J_{CF}$ = 1.2–2.1 Hz.

We investigated some transformations of the pyrroline ring such as oxidative dehydrogenation, reduction of the ring imine, as well as hydrolysis reactions using compound **3b** as a model (Scheme 3). The hydrolysis of α-pyrrolinecarboxylate **3b** by heating with dilute HCl gave α-pyrrolinecarboxylic acid **8** in 93% yield. In the ^1H NMR spectrum of the acid recorded in DMSO-d_6, the same ratio of Δ^2- and Δ^1-pyrrolines **8a**,**b** is observed as for the starting ester **3b**. For the oxidative dehydrogenation of pyrroline **3b** to pyrrole, we used the α-halogenation procedure followed by dehydrohalogenation by the action of a base.[2e,14] Thus, when compound **3b** is halogenated with an equimolar amount of NBS as a halogenating agent in CH_2Cl_2, an intermediate bromo derivative is formed at room temperature which is easily dehydrobrominated without isolation by the action of Et_3N to 2-pyrrolecarboxylate **9** isolated in 88% yield. Subsequent acidic hydrolysis of ester **9** under the conditions of prolonged heating with dilute HCl yielded 2-pyrrolecarboxylic acid **10** in high yield (Scheme 3).

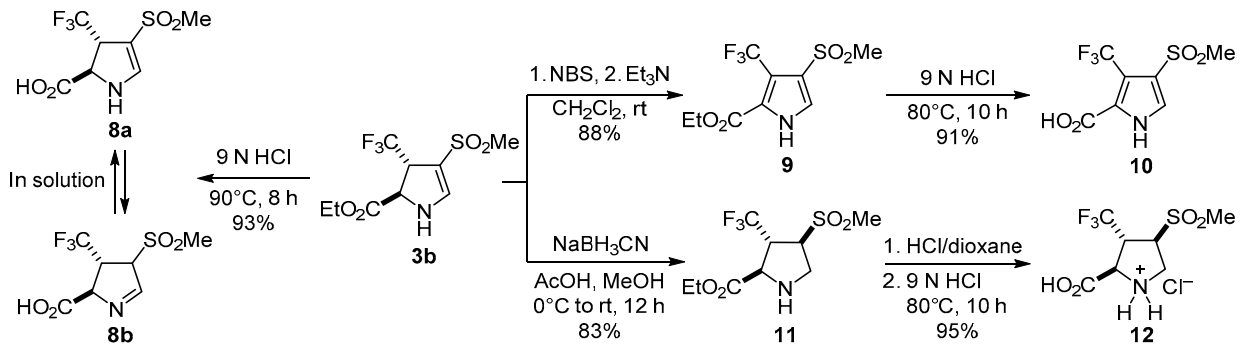
Reduction of the pyrroline ring of compounds **3** to the corresponding pyrrolidines followed by hydrolysis of the ester function constitutes a convenient synthetic route to β-trifluoromethyl-α-pyrrolidinecarboxylic acids with an exocyclic sulfur-containing substituent. It should be noted that of the few derivatives of α-pyrrolidinecarboxylates substituted at positions 3 and 4 of the ring by both a polyfluoroalkyl group and a sulfur-containing substituent, only 2,3,4,5-tetrasubstituted derivatives containing an aryl group at position 5[8h,i] and 2-pyridones[15] have been described. At the same time, of the 2,3,4-trisubstituted pyrrolecarboxylates containing in the molecule both the CF_3 group and a sulfonyl substituent, only ethyl 3-(trifluoromethyl)-2-(4-toluenesulfonyl)-1*H*-pyrrole-4-carboxylate[8a,b] as well as ethyl 3-(trifluoromethyl)-4-hexanesulfonyl-1*H*-pyrrole-2-carboxylate isolated in low yield from a binary mixture of products[16] are described. For the selective reduction of the double bond in pyrroline **3b**, the reduction procedure with sodium cyanoborohydride in the presence of an equimolar amount of AcOH turned out to be optimal. The reaction has a diastereoselective character, as evidenced by the NMR spectra of both the reaction mixture and ethyl pyrrolidine-2-carboxylate **11** isolated in 83% yield, characterized by a single set of signals. The relative position of the substituents in the ring of pyrrolidine **11** was established based on the values of the coupling constants of the protons 2-CH and 3-CH, as well as protons 3-CH and 4-CH which were 5.1 and 3.7 Hz, respectively, which is typical for *trans*-oriented substituents in substituted pyrrolidine rings.[9a] As a result of acid hydrolysis of ester **11** by heating with dilute HCl for 10 h, pyrrolidine-2-carboxylic acid **12** was obtained in the form

Scheme 2



a R = CO_2Et, **b** R = SO_2Me, **c** R = SO_2p-Tol
d R = SO_2NMe_2, **e** R = S(O)(NCO_2Et)Me

Scheme 3



of its hydrochloride salt in 95% yield (Scheme 3). Compound **12** can be considered as a proline analog substituted in the pyrrolidine ring by both the CF_3 group and a sulfur-containing functional group.

Since fluorinated analogs of amino acids, including proline, are widely used in medicinal and protein chemistry,[17] the approach we found has undoubted advantages over other multistep syntheses of structurally related compounds.

To conclude, we have studied the approach to the synthesis of novel 3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrroles as well as 4-(trifluoromethyl)-1*H*-pyrroles containing sulfonyl, sulfoximine, or sulfonamide groups by preparative cycloaddition reaction of the available (*E*)-β-fluoroalkyl vinyl sulfones, sulfoximines, and sulfonamides with isocyanomethylides. The obtained compounds proved to be convenient substrates for the synthesis of derivatives of 3-(trifluoromethyl)pyrrole-2-carboxylic acids and 3-(trifluoromethyl)pyrrolidine-2-carboxylic acids containing an exocyclic functionality.

Experimental

^{1}H, ^{13}C (APT ^{13}C), ^{19}F NMR (400, 100, 376 MHz, respectively), COSY, and ^{1}H–^{13}C HSQC spectra were acquired on a Bruker Avance-400 spectrometer in $CDCl_3$ or DMSO-d_6, using the residual solvent signals as internal standards ($CDCl_3$: 7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei), C_6F_6: –162.9 ppm relative to $CFCl_3$ for ^{19}F nuclei. GC/MS spectra were recorded on a Hewlett-Packard 5890/5972 system with 70 eV in the EI ionization mode. LC/MS spectra were registered on an Agilent 1100 Series system equipped with an Agilent LC/MSD SL Diode Array Mass Selective Detector, atmospheric pressure chemical ionization. Elemental analysis was performed in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Elemental analysis data was obtained by the express gravimetric method (C, H), Schöniger ignition method (S), and Pregl–Dumas method (N). Melting points were determined on a Boetius heating bench.

All solvents were dried and distilled before use according to standard routines. Monitoring of the reactions was done by ^{19}F NMR spectroscopic examination of the reaction mixtures. Merck 60 (70–230 μm) silica gel was used for column chromatography, SUPELCO® Analytical UV 254 plates were used for thin-layer chromatography.

Compounds **1b–e** were obtained from the corresponding hydrates of trifluoromethyl ketones.[9a]

Synthesis of 3-(trifluoromethyl)-2-pyrrolines 3a–d and 3-(trifluoromethyl)-1-pyrrolines 4a–d (General method). AgOAc (5 mg, 0.02 mmol) was added to a solution of 3,3,3-trifluoropropene derivative **1a–d** (2.00 mmol) and ethyl isocyanoacetate (**2**) (0.41 g, 2.10 mmol) in anhydrous MeCN (7 ml). The reaction mixture was stirred at room temperature for 20 h. The solvent was then evaporated to dryness under reduced pressure. For compounds **3a–c**, the residue after evaporation was treated with a 4:1 PhH–Et_2O mixture (5 ml), the formed precipitate was filtered off, washed with PhH (2 ml), and dried. Products **3a–c** do not require additional purification; analytical samples were obtained by crystallization. For compound **3d**, the oily residue after evaporation of the reaction mixture was purified by column chromatography on silica gel (EtOAc–hexane, 2:1).

Diethyl 3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-2,4-dicarboxylate (3a) and diethyl 3-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole-2,4-dicarboxylate (4a), a mixture of two isomers **3a**:**4a** in 8:1 ratio. Yield 0.40 g (72%), light-brown solid, mp 69–70°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.23* (3H, t, ^3J = 7.2, $OCH_2C\underline{H}_3$); 1.28–1.30 (3H, m, $OCH_2C\underline{H}_3$); 1.29** (3H, t, ^3J = 7.2, $OCH_2C\underline{H}_3$); 3.78–3.82 (1H, m, 3-CH); 4.04* (1H, qd, $^3J_{HF}$ = 7.8, ^3J = 3.2, 3-CH); 4.11–4.16** (2H, m, $OC\underline{H}_2CH_3$); 4.21–4.24 (1H, m, 4-CH); 4.22–4.25** (2H, m, $OC\underline{H}_2CH_3$); 4.44* (1H, d, ^3J = 2.8, 2-CH); 4.92 (1H, d, ^3J = 4.6, 2-CH); 5.16* (1H, br. s, NH); 7.42* (1H, d, ^3J = 2.4, 5-CH); 7.62–7.64 (1H, m, 5-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.1** ($OCH_2\underline{C}H_3$); 14.4** ($OCH_2\underline{C}H_3$); 45.4 (q, $^2J_{CF}$ = 29.1, C-3); 48.5* (q, $^2J_{CF}$ = 30.5, C-3); 57.5 (q, $^3J_{CF}$ = 1.7, C-2); 59.7** ($O\underline{C}H_2CH_3$); 62.4 ($O\underline{C}H_2CH_3$); 61.8* (q, $^3J_{CF}$ = 2.8, C-2); 62.7* ($O\underline{C}H_2CH_3$); 75.9 (q, $^3J_{CF}$ = 1.6, C-4); 98.6* (C-4); 126.1* (q, J_{CF} = 281.7, CF_3); 126.3 (q, J_{CF} = 275.9, CF_3); 151.5* (C-5); 163.5 (C-5); 164.5* (C=O); 166.9 (C=O); 169.1 (C=O); 170.8* (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –71.5 (3F, d, $^2J_{FH}$ = 9.2, CF_3); –73.8* (3F, d, $^2J_{FH}$ = 7.8, CF_3). Mass spectrum** (LC/MS), *m*/*z*: 282 $[M+H]^+$. Mass spectrum* (GC/MS), *m*/*z* (I_{rel}, %): 281 [M] (23), 236 (40), 208 (38), 188 (23), 162 (51), 164 (26), 140 (66). Mass spectrum (GC/MS), *m*/*z* (%): 281 [M] (12), 236 (21), 208 (23), 164 (35), 162 (33), 140 (28), 136 (100), 116 (65). Found, %: C 46.99; H 5.06; N 4.99. $C_{11}H_{14}F_3NO_4$. Calculated, %: C 46.98; H 5.02; N 4.98.

Ethyl 4-methanesulfonyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (3b) and ethyl 4-methanesulfonyl-3-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate (4b), a mixture of isomers **3b**:**4b** in a ratio of 1:1.4. Yield 0.43 g (75%), colorless crystals, mp 100–101°C (MTBE). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.33 (3H, t, ^3J = 7.2, $OCH_2C\underline{H}_3$); 1.35* (3H, t, ^3J = 7.2, $OCH_2C\underline{H}_3$); 2.99* (3H, s, SO_2CH_3); 3.04 (3H, s, SO_2CH_3); 3.85* (1H, qdd, $^3J_{HF}$ = 8.1, ^3J = 4.9, ^3J = 4.6, 3-CH); 4.28* (2H, q, ^3J = 7.2, $OC\underline{H}_2CH_3$); 4.28–4.36 (3H, m, $OC\underline{H}_2CH_3$, 3-CH); 4.51* (1H, d, ^3J = 4.9, 2-CH); 4.54 (1H, d, ^3J = 4.2, 2-CH); 5.13* (1H, dd, ^3J = 4.6, ^3J = 2.9, 4-CH); 5.25 (1H, br. s, NH); 7.38 (1H, d, ^3J = 2.9, 5-CH); 7.73–7.75* (1H, m, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.1** ($OCH_2\underline{C}H_3$); 40.1* (SO_2CH_3); 44.9 (SO_2CH_3); 45.1* (q, $^2J_{CF}$ = 29.7, C-3); 49.3 (q, $^2J_{CF}$ = 30.6, C-3); 62.6 (q, $^3J_{CF}$ = 2.8, C-2); 63.0** ($O\underline{C}H_2CH_3$); 74.3* (C-2); 77.3* (C-4); 104.5 (C-4); 125.4 (q, J_{CF} = 281.0, CF_3); 125.5* (q, J_{CF} = 281.2, CF_3); 153.4 (C-5); 159.0* (C-5); 168.3* (C=O): 169.5 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –71.3* (3F, d, $^2J_{FH}$ = 8.1, CF_3); –72.9 (3F, d,

* Hereinafter in the Experimental, the signals of the major isomer are indicated with an asterisk (*), signals of both isomers are indicated with two asterisks (**).

$^2J_{FH}$ = 7.8, CF_3). Mass spectrum** (LC/MS), *m*/*z*: 288 $[M+H]^+$. Mass spectrum* (GC/MS), *m*/*z* (I_{rel}, %): 194 (22), 161 (20), 136 (100), 135 (23), 116 (31), 80 (21). Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 207 (51), 179 (34), 162 (46), 161 (100), 142 (48), 133 (23), 40 (23). Found, %: C 37.61; H 4.26; N 4.82; S 11.10. $C_9H_{12}F_3NO_4S$. Calculated, %: C 37.63; H 4.21; N 4.88; S 11.16.

Ethyl 4-(toluene-4-sulfonyl)-3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate (3c) and ethyl 4-(toluene-4-sulfonyl)-3-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate (4c), a mixture of isomers **3c**:**4c** in a ratio of 1:7. Yield 0.49 g (67%), beige crystals, mp 101–102°C (PhH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.26 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 1.27* (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 2.41 (3H, s, SO_2CH_3); 2.47* (3H, s, SO_2CH_3); 3.75* (1H, qdd, $^3J_{HF}$ = 9.0, ^3J = 4.5, ^3J = 4.5, 3-CH); 4.17–4.23** (2H, m, $OC\underline{H}_2CH_3$); 4.24–4.27 (1H, m, 3-CH); 4.48 (1H, d, ^3J = 4.4, 2-CH); 4.53* (1H, d, ^3J = 4.5, 2-CH); 5.01* (1H, dd, ^3J = 4.5, ^3J = 2.5, 4-CH); 5.19 (1H, br. s, NH); 7.27 (2H, AA'XX' system, $^3J_{AX}$ = 7.9, H Ar); 7.72 (2H, AA'XX' system, $^3J_{AX}$ = 7.9, H Ar); 7.41* (2H, AA'XX' system, $^3J_{AX}$ = 7.9, H Ar); 7.78* (2H, AA'XX' system, $^3J_{AX}$ = 7.9, H Ar); 7.51–7.53 (1H, m, 5-CH); 7.62–7.64* (1H, m, 5-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.0 ($OCH_2\underline{C}H_3$); 14.1* ($OCH_2\underline{C}H_3$); 21.6 ($C_6H_4\underline{C}H_3$); 21.8* ($C_6H_4\underline{C}H_3$); 44.9* (q, $^2J_{CF}$ = 30.4, C-3); 49.1 (q, $^2J_{CF}$ = 31.3, C-3); 62.7 (C-2); 62.8* ($O\underline{C}H_2CH_3$); 63.0 ($O\underline{C}H_2CH_3$); 75.1* (C-2); 76.9* (C-4); 106.2 (C-4); 124.9 (q, J_{CF} = 281.8, CF_3); 125.4* (q, J_{CF} = 279.2, CF_3); 127.2 (CH Ar); 129.2* (CH Ar); 129.4 (CH Ar); 130.5* (CH Ar); 133.2* (C Ar); 139.2 (C Ar); 143.3 (C Ar); 146.5* (C Ar); 152.9 (C-5); 159.1* (C-5); 167.7* (C=O); 169.7 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –72.0* (3F, d, $^2J_{FH}$ = 9.0, CF_3); –72.5 (3F, d, $^2J_{FH}$ = 8.2, CF_3). Mass spectrum** (LC/MS), *m*/*z*: 364 $[M+H]^+$. Mass spectrum* (GC/MS), *m*/*z* (I_{rel}, %): 207 (64), 179 (32), 162 (60), 161 (100), 142 (51), 133 (24). Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 253 (24), 208 (24), 207 (61), 162 (41), 161 (59), 154 (26), 153 (56), 136 (48), 133 (27), 116 (21), 92 (23), 91 (97), 44 (51), 40 (100). Found, %: C 49.61; H 4.46; N 3.87; S 8.77. $C_{15}H_{16}F_3NO_4S$. Calculated, %: C 49.58; H 4.44; N 3.85; S 8.82.

Ethyl 4-(dimethylsulfamoyl)-3-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate (4d). Yield 0.30 g (48%), yellowish oil, R_f 0.7 (EtOAc–hexane, 2:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.35 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 2.98 (6H, s, $N(CH_3)_2$); 3.75 (1H, qdd, $^3J_{HF}$ = 9.1, ^3J = 4.6, ^3J = 4.6, 3-CH); 4.27–4.35 (2H, m, $OC\underline{H}_2CH_3$); 4.52 (1H, d, ^3J = 4.6, 2-CH); 5.08 (1H, dd, ^3J = 4.6, ^3J = 3.0, 4-CH); 7.68–7.69 (1H, m, 5-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.3 ($OCH_2\underline{C}H_3$); 38.0 ($N(CH_3)_2$); 45.0 (q, $^2J_{CF}$ = 31.6, C-3); 62.9 ($O\underline{C}H_2CH_3$); 71.3 (C-2); 77.30 (C-4); 125.9 (q, J_{CF} = 277.9, CF_3); 160.3 (C-5); 168.4 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –71.7 (3F, d, $^3J_{FH}$ = 9.1, CF_3). Mass spectrum (LC/MS), *m*/*z*: 317 $[M+H]^+$. Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 243 (25), 209 (27), 189 (45), 161 (28), 136 (100), 116 (48), 108 (81). Found, %: C 37.99; H 4.76; N 8.82; S 10.10. $C_{10}H_{15}F_3N_2O_4S$. Calculated, %: C 37.97; H 4.78; N 8.86; S 10.14.

Ethyl 3-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (5) was obtained by the same way as compounds **3a–d**. After evaporation of MeCN, the residue was treated with EtOAc (10 ml) and extracted with H_2O (2×5 ml). The organic extract was dried over Na_2SO_4, the solvent was evaporated to dryness, the oily residue was purified by flash chromatography (eluent hexane–Et_2O, 4: 1). Yield 0.37 g (89%), yellowish clear oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 4.35 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 6.51 (1H, t, ^3J = 2.5, H-4); 6.90 (1H, t, ^3J = 2.5, H-5); 10.09 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.1 ($OCH_2\underline{C}H_3$); 61.4 ($O\underline{C}H_2CH_3$); 110.5 (q, $^3J_{CF}$ = 4.0, C-4); 119.0 (q, $^2J_{CF}$ = 37.8, C-3); 120.7 (q, $^3J_{CF}$ = 3.2, C-2); 121.3 (q, $^4J_{CF}$ = 1.6, C-5); 122.9 (q, J_{CF} = 267.1, CF_3); 160.0 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –58.3 (3F, s, CF_3). Mass spectrum, *m*/*z*: 206 $[M–H]^-$. Found, %: C 46.46; H 3.82; N 6.84. $C_8H_8F_3NO_2$. Calculated, %: C 46.38; H 3.89; N 6.76.

Synthesis of ethyl 3-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (5) from compounds 1b,c (General method). 3,3,3-Trifluoropropene derivative **1b**,**c** (1.00 mmol) and ethyl isocyanoacetate (**2**) (0.20 g, 1.05 mmol) were added to a solution of *t*-BuOK (0.11 g, 1.00 mmol) in dry THF (8 ml). The reaction mixture was stirred at room temperature for 0.5 h, then poured into saturated aqueous NaCl (7 ml), and the resulting mixture was extracted with EtOAc (2×7 ml). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated to dryness, and the oily residue was purified by flash chromatography (eluent hexane–Et_2O, 4:1). Yield 0.36 g (85%) from olefin **1b**, 0.33 g (80%) from olefin **1c**, yellowish clear oil.

Synthesis of 4-(trifluoromethyl)-1*H*-pyrrole derivatives 7a–e (General method). A solution of 3,3,3-trifluoropropene derivative **1a–e** (2.00 mmol) and TOSMIC (**6**) (0.41 g 2.10 mmol) in anhydrous THF (5 ml) was added with vigorous stirring at 0°C to a solution of *t*-BuOK (0.47 g, 4.20 mmol) in dry THF (5 ml) at such a rate as to not let the temperature of the reaction mixture rise above 5°C. The mixture was kept at 0–5°C for 10 min and stirred for another 1 h at room temperature. Saturated aqueous NaCl (5 ml) was added, and the resulting mixture was extracted with EtOAc (3×7 ml). The combined organic extracts were washed with H_2O (10 ml), dried over Na_2SO_4. The solvent was evaporated to dryness, and the solid residue was purified by crystallization.

Ethyl 4-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (7a). Yield 0.35 g (80%), mp 161–163°C ($C_2H_4Cl_2$) (mp 163–164°C[14]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.36 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 4.32 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 7.24–7.26 (1H, m, CH); 7.49–7.51 (1H, m, CH); 9.10 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.0 ($OCH_2\underline{C}H_3$); 61.2 ($O\underline{C}H_2CH_3$); 114.5 (q, $^2J_{CF}$ = 37.1, C-4); 115.5 (q, $^3J_{CF}$ = 1.8, C-3); 120.8 (q, J_{CF} = 6.3, C-5); 122.9 (q, J_{CF} = 266.0, CF_3); 126.3 (C-2). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –58.2 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 206 $[M–H]^-$. Found, %: C 46.49; H 3.86; N 6.80. $C_8H_8F_3NO_2$. Calculated, %: C 46.38; H 3.89; N 6.76.

3-Methanesulfonyl-4-(trifluoromethyl)-1*H*-pyrrole (7b). Yield 0.35 g (83%), white crystals, mp 117–118°C (PhMe). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.12 (3H, s, CH_3); 7.58 (1H, t, ^3J = 1.5, CH); 7.59 (1H, t, ^3J = 1.5, CH); 12.37 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 45.3 (CH_3); 110.4 (q, $^2J_{CF}$ = 37.1, C-4); 121.2 (q, $^3J_{CF}$ = 1.4, C-3); 123.1 (q, $^3J_{CF}$ = 6.1, C-5); 122.8 (q, J_{CF} = 265.6, CF_3); 127.1 (C-2). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –54.4 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 212 $[M–H]^-$. Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 213 [M] (77), 198 (100), 150 (79), 131 (37), 115 (21), 107 (22). Found, %: C 33.85; H 2.86; N 6.60; S 15.00. $C_6H_6F_3NO_2S$. Calculated, %: C 33.80; H 2.84; N 6.57; S 15.04.

3-(Toluene-4-sulfonyl)-4-(trifluoromethyl)-1*H*-pyrrole (7c). Yield 0.35 g (57%), white crystals, mp 175–176°C ($PhCH_3$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.36 (3H, s, CH_3); 7.11 (1H, t, ^3J = 1.5, CH); 7.45 (1H, t, ^3J = 1.5, CH); 7.38 (2H, AA'XX' system, $^3J_{AX}$ = 7.2, H Ar); 7.72 (2H, AA'XX' system, $^3J_{AX}$ = 7.2, H Ar); 12.25 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 21.0 (CH_3); 110.4 (q, $^2J_{CF}$ = 38.1, C-4); 121.2 (q, $^3J_{CF}$ =1.8, C-3); 123.5 (q, $^3J_{CF}$ = 6.1, C-5); 122.6 (q, J_{CF} = 267.0, CF_3); 126. 9 (CH Ar); 127.9 (C-2, CH Ar); 139.9 (C Ar); 143.5 (C Ar). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –54.5 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 288 $[M–H]^-$. Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 289 [M] (100), 182 (75), 108 (50), 107 (20), 91 (20). Found, %: C 49.92; H 3.52; N 4.84; S 11.04. $C_{12}H_{10}F_3NO_2S$. Calculated, %: C 49.82; H 3.48; N 4.84; S 11.08.

4-(Trifluoromethyl)-1*H*-pyrrole-3-sulfonic acid dimethylamide (7d). Yield 0.43 g (88%), pale-brown crystals, mp 125–126°C (PhH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.77 (6H, s, $N(CH_3)_2$); 7.22 (1H, t, ^3J = 1.5, CH); 7.33 (1H, t, ^3J = 1.5, CH); 9.54 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 37.5 $N(CH_3)_2$); 112.7 (q, $^2J_{CF}$ = 37.2, C-4); 116.5 (q, $^3J_{CF}$ = 2.1, C-3); 122.3 (q, $^3J_{CF}$ = 6.1, C-5); 122.4 (q, J_{CF} = 267.4, CF_3); 126.6 (C-2). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –57.4 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 243 $[M+H]^+$. Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 242 [M] (100), 223 (26), 198 (76), 150 (59), 135 (34), 115 (40), 107 (27), 44 (45), 42 (60). Found, %: C 34.81; H, 3.77; N 11.58; S 13.20. $C_7H_9F_3N_2O_2S$. Calculated, %: C 34.71; H 3.75; N 11.57; S 13.24.

Ethyl {[4-(trifluoromethyl)-1*H*-pyrrol-3-yl](methyl)-oxido-λ^4-sulfanylidene}carbamate (7e). Yield 0.42 g (74%), pale-brown crystals, mp 116–117°C (PhH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.26 (3H, t, ^3J = 7.0, $OCH_2\underline{C}H_3$); 3.29 (3H, s, SCH_3); 4.10 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 7.12 (1H, t, ^3J = 1.5, CH); 7.16 (1H, t, ^3J = 1.5, CH); 10.83 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.3 ($OCH_2\underline{C}H_3$); 46.2 (SCH_3); 62.5 ($O\underline{C}H_2CH_3$); 111.7 (q, $^2J_{CF}$ = 37.5, C-4); 116.5 (q, $^3J_{CF}$ = 1.2, C-3); 122.3 (q, J_{CF} = 266.9, CF_3); 123.7 (q, $^3J_{CF}$ = 5.9, C-5); 127.1 (C-2); 159.9 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –57.3 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 285 $[M+H]^+$. Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 239 [M] (100), 193 (20), 182 (96), 181 (87), 166 (61), 150 (40), 139 (39), 115 (22), 44 (47). Found, %: C 38.06; H 3.95; N 9.89; S 11.24. $C_9H_{11}F_3N_2O_3S$. Calculated, %: C 38.03; H 3.90; N 9.86; S 11.28.

4-Methanesulfonyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylic acid (8a) and 4-methanesulfonyl-3-(trifluoromethyl)-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid (8b), a mixture of isomers **8a**:**8b** in a ratio of 2.4:1. A mixture of ester **3b** (172 mg, 0.60 mmol) and 9 M aqueous HCl (3 ml) was heated with stirring at 90°C for 8 h. Then, the reaction mixture was concentrated under reduced pressure until the formation of a solid residue which was dried in an oil pump vacuum (10^{-3} mmHg). Yield 0.14 g (93%), hygroscopic beige solid, mp >235°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.95* (3H, s, SO_2CH_3); 3.27 (3H, s, SO_2CH_3); 3.79 (1H, qd, $^3J_{HF}$ = 9.5, ^3J = 4.2, 3-CH); 4.05* (1H, qd, $^3J_{HF}$ = 9.5, ^3J = 4.2, 3-CH); 4.62* (1H, d, ^3J = 4.2, 2-CH); 5.16–5.18 (1H, m, 4-CH); 5.28 (1H, d, ^3J = 4.2, 2-CH); 5.90** (1H, br. s, CO_2H); 7.43–7.45* (1H, m, 5-CH); 7.84–7.85 (1H, m, 5-CH); 8.00* (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 38.8** (SO_2CH_3); 42.9 (q, $^2J_{CF}$ = 29.8, C-3); 48.5 (q, $^2J_{CF}$ = 29.8, C-3); 62.0* (C-2); 72.4 (C-2); 76.3 (C-4); 99.2* (C-4); 125.9** (q, J_{CF} = 279.2, CF_3); 154.1 (C-5)*; 159.7 (C-5); 169.6 (C=O); 171.2 (C=O). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): –71.3* (3F, d, $^2J_{FH}$ = 8.5, CF_3); –69.3 (3F, d, $^2J_{FH}$ = 9.5, CF_3). Mass spectrum (LC/MS), *m*/*z*: 260 $[M+H]^+$. Found, %: C 32.45; H 3.11; N 5.49; S 12.30. $C_7H_8F_3NO_4S$. Calculated, %: C 32.44; H 3.11; N 5.40; S 12.37.

Ethyl 3-(trifluoromethyl)-4-methanesulfonyl-1*H*-pyrrole-2-carboxylate (9). A solution of pyrroline **3b** (287 mg, 1.00 mmol) and NBS (187 mg, 1.05 mmol) in CH_2Cl_2 (5 ml) was stirred for 10 h. The reaction mixture was washed with H_2O (2×5 ml), the organic phase was dried over Na_2SO_4, filtered, and Et_3N (0.25 ml, 1.80 mmol) was added to the filtrate. The reaction mixture was stirred for 10 h and the solvent was evaporated under reduced pressure. The residue was treated with EtOAc (5 ml), the mixture was washed with H_2O (2×5 ml), and the organic extract was dried over Na_2SO_4. After evaporation of the solvent, the solid residue was treated with of Et_2O (5 ml), the separated precipitate was filtered off, dried, and crystallized. Yield 250 mg (88%), pale-yellow needles, mp 108–109°C (PhH–hexane, 2:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.38 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 3.21 (3H, s, SO_2CH_3); 4.40 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 7.62 (1H, s, CH); 9.25 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.0 ($OCH_2\underline{C}H_3$); 44.8 (SO_2CH_3); 62.6 ($O\underline{C}H_2CH_3$); 115.2 (q, $^2J_{CF}$ = 39.0, C-3); 121.5 (q, J_{CF} = 270.0, CF_3); 125.1 (q, $^3J_{CF}$ = 3.2); 125.7 (q, $^3J_{CF}$ = 1.8); 127.7 (C-2); 159.0 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –53.9 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 284 $[M–H]^-$. Mass spectrum (GC/MS), *m*/*z* (I_{rel}, %): 285 [M] (48), 257 (34), 222 (100), 202 (62), 220 (30). Found, %: C 37.92; H 3.52; N 4.84; S 11.34. $C_9H_{10}F_3NO_4S$. Calculated, %: C 37.90; H 3.53; N 4.91; S 11.24.

4-Methanesulfonyl-3-(trifluoromethyl)-1*H*-pyrrole-2-carboxylic acid (10). A mixture of ester **9** (114 mg, 0.40 mmol) and 9 M aqueous HCl (3 ml) was heated with

stirring at 80°C for 10 h. Then, the reaction mixture was concentrated under reduced pressure until the formation of a solid residue which was dried in an oil pump vacuum (10^{-3} mmHg). Yield 94 mg (91%), hygroscopic beige solid, mp >190°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.21 (3H, s, CH_3); 3.64 (1H, br. s, NH); 7.55–7.56 (1H, m, CH); 13.29 (1H, br. s, CO_2H). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 44.4 (CH_3); 112.6 (q, $^2J_{CF}$ = 38.1, C-3); 121.7 (q, J_{CF} = 267.8, CF_3); 124.6 (q, $^3J_{CF}$ = 1.6); 125.7 (q, $^3J_{CF}$ = 3.5); 127.2 (C-2); 159.5 (C=O). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –51.6 (3F, s, CF_3). Mass spectrum (LC/MS), *m*/*z*: 258 $[M+H]^+$. Found, %: C 49.92; H 3.52; N 4.84; S 11.04. $C_7H_6F_3NO_4S$. Calculated, %: C 49.82; H 3.48; N 4.84; S 11.08.

Ethyl 4-methanesulfonyl-3-(trifluoromethyl)-2-carboxylate (11). A solution of glacial AcOH (66 mg, 1.10 mmol) in MeOH (2 ml), followed by $NaBH_3CN$ (75.6 mg, 1.20 mmol) was added with stirring at 0°C to a solution of pyrroline **3b** (287 mg, 1.00 mmol) in anhydrous MeOH (8 ml). The reaction mixture was stirred at room temperature for 12 h. Then, the solvent was evaporated under reduced pressure and the residue was treated with EtOAc (10 ml). The insoluble precipitate was filtered off, the filtrate was washed with saturated aqueous $NaHCO_3$ (2×2 ml), dried over Na_2SO_4, and the solvent was evaporated to dryness to afford an analytically pure compound. Yield 0.24 g (83%), yellowish transparent viscous oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.30 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 2.63 (1H, br. s, NH); 2.97 (3H, s, SO_2CH_3); 3.35 (1H, qdd, $^3J_{HF}$ = 9.1, ^3J = 5.1, ^3J = 3.8, 3-CH); 3.34 (1H, dd, AB system, J = 12.5, ^3J = 7.4, 5-CH_2) and 3.72 (1H, dd, AB system, J = 12.5, ^3J = 3.8, 5-CH_2); 3.62 (1H, ddd, ^3J = 7.4, ^3J = 3.8, ^3J = 3.8, 4-CH); 3.97 (1H, d, ^3J = 5.1, 2-CH); 4.22–4.30 (2H, m, $OC\underline{H}_2CH_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.1 ($OCH_2\underline{C}H_3$); 39.8 (SO_2CH_3); 49.1 (q, $^2J_{CF}$ = 27.4, C-3); 49.4 (C-5); 62.3 (q, $^3J_{CF}$ = 1.7, CH); 62.5 ($O\underline{C}H_2CH_3$); 63.7 (CH); 126.0 (q, J_{CF} = 277.3, CF_3); 170.2 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –70.2 (3F, d, $^2J_{FH}$ = 9.1, CF_3). Mass spectrum, *m*/*z*: 290 $[M+H]^+$. Found, %: C 37.44; H 4.86; N 4.90; S 11.00. $C_9H_{14}F_3NO_4S$. Calculated, %: C 37.37; H 4.88; N 4.84; S 11.08.

4-Methanesulfonyl-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid hydrochloride (12). HCl, 20% solution in 1,4-dioxane (1 ml) was added with stirring to a solution of ester **11** (173 mg, 0.60 mmol) in 1,4-dioxane (2 ml). After some time, a white precipitate of hydrochloride of ester **11**·HCl precipitated. The suspension was stirred for 30 min, the precipitate was filtered off, dissolved in 9 M aqueous HCl (3 ml), and the resulting mixture was heated with stirring at 80°C for 10 h. The reaction mixture was concentrated under reduced pressure until the formation of a solid residue which was dried in an oil pump vacuum (10^{-3} mmHg). The dried residue was treated with Et_2O (5 ml), and the precipitate that separated was filtered off and dried. Yield 0.17 g (95%), beige solid, mp > 235°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.28 (3H, s, SO_2CH_3); 3.68 (1H, dd, AB system, J = 13.7, ^3J = 8.3, 5-CH_2) and 3.82 (1H, dd, AB system, J = 13.7, ^3J = 3.7, 5-CH_2); 3.80 (2H, br. s, NH_2^+); 4.03 (1H, qdd, $^3J_{HF}$ = 9.5, ^3J = 4.0, ^3J = 3.6, 3-CH); 4.59 (1H, ddd, ^3J = 8.3, ^3J = 4.0, ^3J = 3.7, 4-CH); 4.77 (1H, d, ^3J = 3.6, 2-CH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 38.8 (SO_2CH_3); 45.5 (C-5); 45.7 (q, $^2J_{CF}$ = 30.3, C-4); 58.9 (CH); 59.7 (CH); 125.2 (q, J_{CF} = 280.2, CF_3); 166.9 (C=O). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): –69.1 (3F, d, $^2J_{FH}$ = 9.5, CF_3). Mass spectrum (LC/MS), *m*/*z*: 262 $[M-HCl+H]^+$. Found, %: C 28.21; H 3.76; N 4.82; S 10.70. $C_7H_{11}ClF_3NO_4S$. Calculated, %: C 28.24; H 3.72; N 4.71; S 10.77.

X-ray structural analysis of compound 3b was performed on a Bruker SMART APEX II diffractometer. Crystals of compound **3b** were obtained from MTBE solution. The results were solved by the direct method and refined by the least-squares technique using the Bruker SHELXTL software package.[18] The full set of X-ray structural data was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2018284).

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