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Functionalization of 2-trifluoromethyl-1*H*-pyrrole: a convenient entry into advanced fluorinated building blocks including all isomeric 2-(trifluoromethyl)prolines

Vasyl Yu. Hys,[a,b] Oleksandr I. Shevchuk,[a] Bohdan V. Vashchenko,[a,b] Dr. Oleksandr V. Karpenko,[a] Dr. Alina O. Gorlova,[a,c] Dr. Oleksandr O. Grygorenko*[a,b]

[a] V. Yu. Hys, O. I. Shevchuk, B. V. Vashchenko, Dr. O. V. Karpenko, Dr. A. O. Gorlova, Dr. O. O. Grygorenko
Enamine Ltd. (www.enamine.net),
Chervonotkatska Street 78, Kyiv 02094, Ukraine
[b] V. Yu. Hys, B. V. Vashchenko, Dr. O. O. Grygorenko
Taras Shevchenko National University of Kyiv
Volodymyrska Street 60, Kyiv 01601, Ukraine
E-mail: gregor@univ.kiev.ua
[c] Dr. A. O. Gorlova
Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02094, Ukraine

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Abstract: The synthetic utility of 2-trifluoromethyl-1*H*-pyrrole as a pharmaceutically relevant platform was demonstrated by the preparation of mono- and bifunctional C-2(5)- or C-3-substituted derivatives, i.e. regioisomeric sulfonyl halides, carboxylic acids, aldehydes, and nitriles. A series of modifications relied on lithiation or electrophilic substitution, which proceeded regioselectively on multigram scale, mostly in protecting-group-free mode.Subsequent catalytic hydrogenation of the pyrrole ring was also performed for synthesis of all isomeric 2-trifluoromethyl α- and β-prolines. These derivatives were considered as promising low-molecular-weight building blocks for synthesis, drug discovery, and agrochemistry.

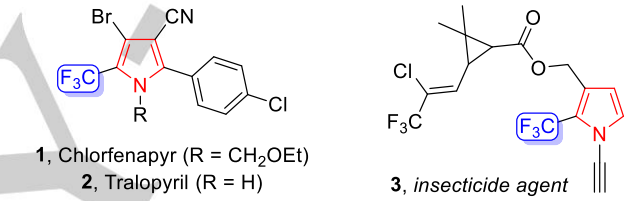
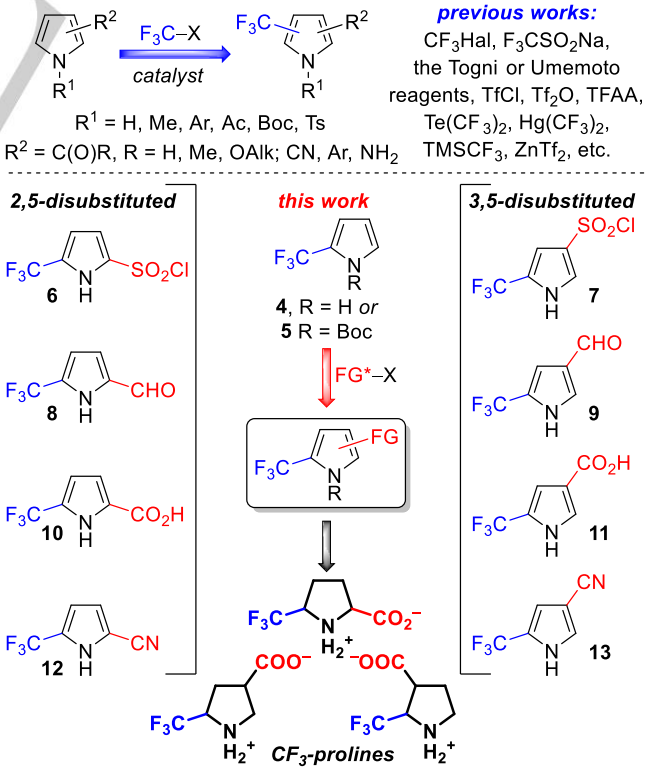


Figure 1. Some important 2-trifluoromethyl-1*H*-pyrroles **1**–**3**

Introduction

Pyrrole and pyrrolidine fragments are extensively represented in drug discovery with a wide range of natural derivatives and FDA-approved drugs.[1–4] In turn, significant number of fluorinated pharmaceuticals have been introduced to market over past decades, scaling from 2% of market in 1970s to 20% in recent years.[4–8] Introduction of the CF_3 substituent into α position of the pyrrole ring provided efficient insecticides, *i.e.* Chlorfenapyr (**1**), Tralopyril (**2**), and potent biocide **3** (Figure 1). It is not surprising therefore that approaches to fluoroalkyl-substituted heterocycles have become of significant importance in organic synthesis,[9–17] drug discovery,[18–21] and agricultural chemistry.[22–27] In many cases, trifluoromethyl-substituted pyrrole derivatives were obtained by the construction of the aromatic ring starting from the corresponding fluorinated precursors.[28–36] In recent years, numerous protocols for the one-step *C*-trifluoromethylation of pyrroles were developed, which relied on using CF_3I,[37–50] CF_3Br,[51–54] CF_3SO_2Na,[55–59] the Togni[60–63] or the Umemoto reagents,[64,65] TfCl,[66,67] Tf_2O,[68] trifluoroacetic anhydride,[69] $TMSCF_3$[70] etc (Scheme 1).[71–76] In general, (fluoro)alkylations of pyrroles proceed exclusively at the non-substituted α-position.[77–82] On the other hand, functionalization of the readily available CF_3-pyrroles has been underrepresented in the literature to date, being limited with monobromination of trisubstituted pyrroles (*e.g.* for the preparation of **2**[83] and its analogs[83,84]), dibromination,[85] and formylation[83] of disubstituted derivatives.

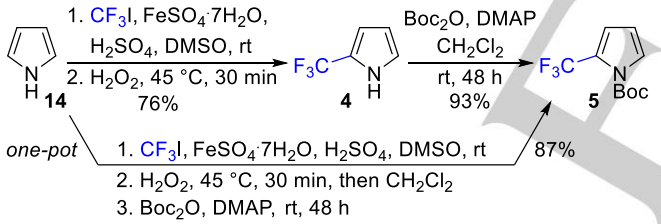


Scheme 1. Approaches to CF_3-substituted pyrroles

In this work, we have aimed at the incorporation of functional groups into the parent 2-trifluoromethyl-1*H*-pyrrole (**4**) or its *N*-Boc protected derivative **5** for the preparation of 2,5- and 3,5-disubstituted building blocks **6**–**13** (Scheme 1). In addition to that, we have envisaged the application of isomeric 2-(trifluoromethyl)pyrrolecarboxylates thus obtained for the synthesis of the correspondding α- and β-isomeric CF_3-prolines.

Results and Discussions

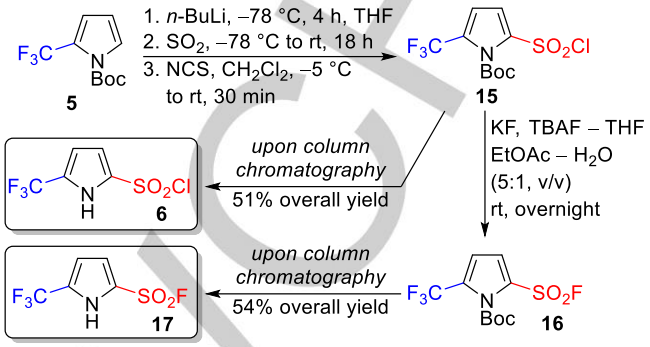
Synthesis of 2-trifluoromethyl-1*H*-pyrrole (**4**) was performed by an optimized literature method including trifluoromethylation of unsubstituted pyrrole (**14**).[41] It was found that small excess of CF_3I led to the significant formation of tar as well as the corresponding bis-trifluoromethylated pyrroles, which could not be separated from the target 2-trifluoromethyl-1*H*-pyrrole **4** by distillation in *vacuo* due to insignificant difference in their boiling points. Instead, product **4** was obtained in 76% yield on up to 80 g scale when an equimolar amount CF_3I was used as a solution in DMSO (Scheme 2). It should be noted that the evaporation of the reaction mixture during the work-up should be performed at rt due to the high volatility of **4** (bp 33–34 °C / 10 mmHg). The subsequent DMAP-mediated *N*-protection of **4** using Boc_2O in CH_2Cl_2 gave Boc-protected derivative **5** in excellent yield (93%) on up to 170 g scale after distillation in *vacuo*. Despite these satisfactory results, the synthesis of **5** was further optimized to be performed in a one-pot manner. Avoiding isolation of **4** gave **5** in better yield on the same scale (87% vs 71% for the two-step reaction sequence).



Scheme 2. Synthesis of 2-trifluoromethyl-1*H*-pyrroles **4** and **5**

In general, metalation reaction occur by α-position;[86–88] therefore, the synthesis of α-isomeric sulfonyl chloride **6** from **5** relied on lithiation, trapping of the resulting organolithium intermediate with SO_2, and subsequent oxidative chlorination. Lithiation of **5** with LDA or LiTMP at –78 °C or 0 °C was unfruitful due to the low conversion of the starting material. Instead, complete metalation was achieved in the case of using *n*-BuLi at –78 °C after 4 h (Scheme 3). It should be outlined that this step had moderate scalability: increasing the loading of the starting material over 35 g led to diminished yield of the product.

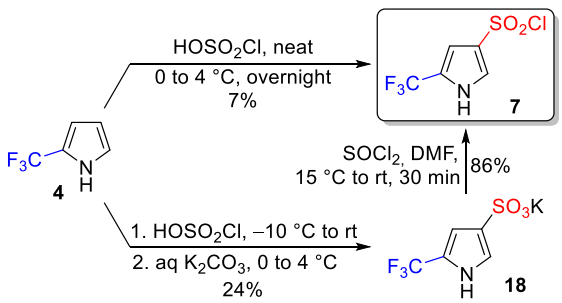
Dropwise addition of SO_2 in THF to the resulting lithiated derivative gave the corresponding sulfinate, which was then suspended in CH_2Cl_2 and subjected to the reaction with NCS. Sulfonyl chloride **15** had limited stability which resulted in significant tar formation upon the chlorination and the product isolation. Attempted chromatographic purification of crude **15** on silica gel resulted in its complete transformation into the target *N*-deprotected sulfonyl chloride **6** (51% overall yield). Taking into account higher stability of sulfonyl fluorides as compared to chlorides, we aimed at preparation of SO_2F derivative **16**. Crude sulfonyl chloride **15** was involved in the reaction with 1 M TBAF in THF and KF in EtOAc – H_2O (5:1, v/v) at rt. Nevertheless, an attempted chromatographic purification of crude **16** also gave the target *N*-deprotected derivative **17** in 54% yield.



Scheme 3. Preparation of α-isomeric sulfonyl chloride **6** and fluoride **17**

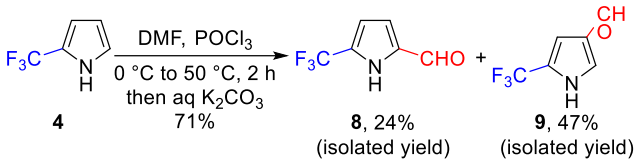
Further transformations relied on various electrophilic substitution reactions of **4** or **5**. In general, the S_EAr reactions proceed at α- or β-positions of electron-rich pyrrole ring, while the regioselectivity could be tuned by presence of strong electron-withdrawing groups at C-2 atom, which favours substitution by C-4 and C-5 positions.[87–90] We have studied two protection-group-free protocols for the synthesis of β-isomeric sulfonyl chloride **7**. The direct one-step sulfonylation of **4** with 10-fold excess of chlorosulfonic acid at 0 °C gave unfruitful results: due to predominant tar formation, target compound **7** was obtained in only 7% yield after work-up and chromatographic purification (Scheme 4). An alternative three-step process, which included synthesis of potassium sulfonate **18** followed by chlorination with $SOCl_2$ was more fruitful. In order to increase the method efficiency, the reaction sequence commenced from pyrrole (**14**), so that isolation of **4** was omitted. Instead, HSO_3Cl was added to its CH_2Cl_2 solution at –10 °C. The subsequent quenching with aq K_2CO_3 at 0 °C gave potassium salt **18** (24% yield) having limited solubility in non-polar solvents, which simplified its separation from the tar formed. Finally, the reaction of **18** with $SOCl_2$ in DMF resulted in the target derivative **7** in 86% yield on up to 40 g scale after recrystallization from hexanes – EtOAc (4:1, v/v).

Next, isomeric aldehydes **8** and **9** were obtained through the Vilsmeier – Haack formylation of **4** (Scheme 5).



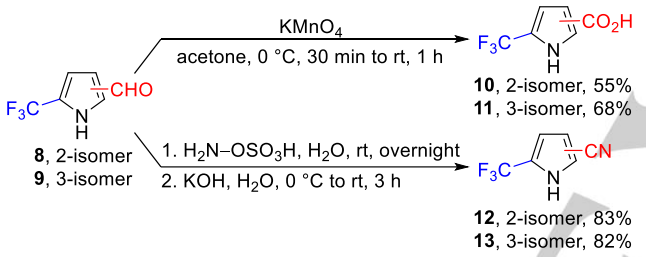
Scheme 4. Approaches to β-sulfonyl chloride **7**

To our delight, despite a mixture of α- and β-regioisomers was formed in *ca.* 1:2 ratio, building blocks **8** and **9** were easily separable by column
chromatography and could be isolated in 24% and 47% yields, respectively, on up to 50 g scale (of **9**).



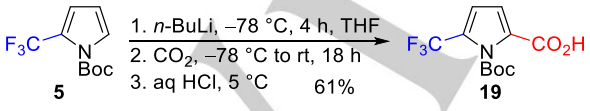
Scheme 5. Synthesis of regioisomeric aldehydes **8** and **9**

α-Isomeric carbaldehyde **8** was then subjected to oxidation with $KMnO_4$ in acetone for the preparation of corresponding carboxylic acid **10** (55% yield). In turn, the reaction of **8** with hydroxylamine-*O*-sulfonic acid followed by treatment with KOH provided the target nitrile **12** in 83% yield (Scheme 6). Isomeric β-carboxylic acid **11** and β-nitrile **13** were obtained in the same manner from aldehyde **9** in 68% and 82% yield, respectively.



Scheme 6. Approaches to 2,5-disubstituted building blocks **10**–**13**

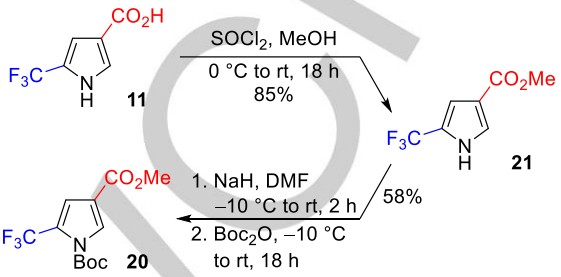
An alternative approach to α-isomeric carboxylic acid relied on lithiation of **5** followed by reaction with dry CO_2 and acidification with aq HCl to pH = 3. Unlike analogous SO_2X derivatives **15** and **16**, carboxylic acid **19** was stable under the reaction conditions, and no tar formation or *N*-deprotection was observed (Scheme 7). Thus, pyrrole **19** was obtained in 61% yield after simple trituration of the crude product with hexanes, and no chromatographic purification was necessary.



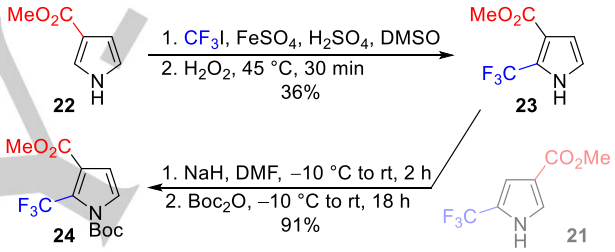
Scheme 7. Synthesis of 2,5-disubstituted carboxylic acid **19**

The synthesis of β-isomeric *N*-Boc protected carboxylate **20** relied on the esterification of **11** with $SOCl_2$ – MeOH, which gave ester **21** in 85% yield. The subsequent NaH-mediated deprotonation of **21** followed by the reaction with Boc_2O gave the target ester **20** in 58% yield (Scheme 8). Interestingly, the direct *N*-Boc protection of aldehyde **9** or carboxylic acid **11** failed in all attempts.

An attempted synthesis of compound **21** by trifluoromethylation of methyl 1*H*-pyrrole-3-carboxylate (**22**) resulted in 2,3-disubstituted regioisomer **23**, and no 3,5-disubstituted counterpart **21** was observed (Scheme 9). Notably, such transformation was not described in the literature previously. The subsequent *N*-protection of **22** was performed by treatment with NaH and Boc_2O and gave β-regioisomeric *N*-Boc carboxylate **24** obtained on 40 g scale in one run (91% yield).

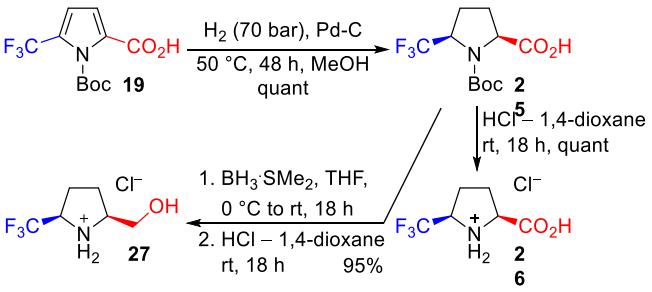


Scheme 8. Preparation of 3,5-disubstituted carboxylate **20**



Scheme 9. Preparation of 2,3-disubstituted carboxylate **24**

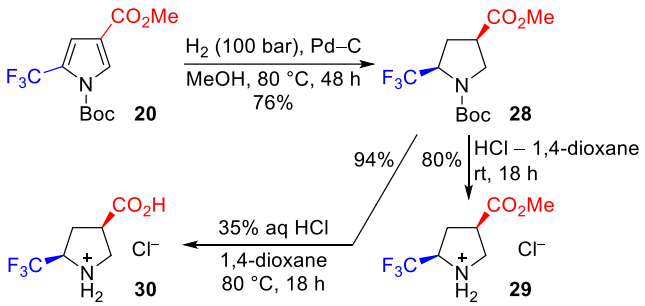
The synthetic utility of regioisomeric *N*-Boc-protected pyrrole-carboxylates **19**, **20**, and **24** was demonstrated by their catalytic hydrogenation into the corresponding proline derivatives. Thus, hydrogenation of **19** in an autoclave (H_2, 70 bar) in the presence of 10% Pd-C at 50 °C was completed within 48 h, and *cis*-diastereomer **25** was formed as the sole product in quantitative yield (Scheme 10). The subsequent deprotection of **25** with HCl – 1,4-dioxane gave 5-(trifluoromethyl)proline **26** as hydrochloride in quantitative yield. Also, reduction of **25** with $BH_3{\cdot}SMe_2$ in THF followed by treatment with HCl – 1,4-dioxane proceeded smoothly and resulted in amino alcohol **27** as hydrochloride in 95% yield.



Scheme 10. Synthesis of 2,5-disubstituted pyrrolidines **26** and **27** (relative configurations are shown)

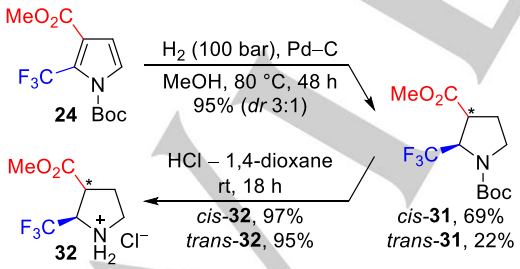
Although the synthesis of *cis*-5-trilfuoromethylproline via similar hydrogenation of ethyl ester of **10** was described by Kondratov and co-workers,[91] the overall synthetic sequence proposed in this work (4 steps from pyrrole, 53% overall yield) is much more convenient for the multigram preparation of this amino acid (which was validated on up to 20 g scale).

The catalytic hydrogenation of β-isomeric carboxylate **20** also proceeded in a diastereoselective manner, and corresponding pyrrolidine derivative **28** was obtained as a single *cis* diastereomer in 76% yield (Scheme 11). The Boc group cleavage in **28** with HCl – 1,4-dioxane at rt led to aminoester **29** (80% yield), while the reaction of **28** with 35% aq HCl in 1,4-dioxane at 80 °C was applied for the preparation of amino acid **30** (94% yield, hydrochloride).



Scheme 11. Preparation of 5-trifluoromethyl-β-proline **30** (relative configurations are shown)

Finally, the catalytic hydrogenation of carboxylate **24** proceeded under harsher conditions, *i.e.* H_2 (100 bar), Pd-C, 80 °C; this transformation was less diastereoselective as compared to the case of **19** and **20**. Corresponding pyrrolidine **31** was obtained as a *ca.* 3:1 mixture of *cis* and *trans* diastereomers in excellent total yield (95%), which could be separated by HPLC (Scheme 12). The pure *cis*-**31** and *trans*-**31** were isolated in 69% and 22% yield, respectively. Deprotection of *cis*- and *trans*-**31** was carried out with HCl – 1,4-dioxane and provided α-trifluoromethyl-β-proline methyl esters *cis*- and *trans*-**32** in 97% and 95% yield, respectively.



Scheme 12. Preparation of 2-trifluoromethyl-β-proline derivatives **32** (relative configurations are shown)

It should be noted that several syntheses of 2-[92–94] and 5-trifluorometyl-β-prolines[94,95] were described in the literature, all of them relying not on the hydrogenation of the pyrrole derivatives but on the construction of the pyrrolidine ring. The known approaches to 2-trifluorometyl-β-proline, i.e. an elegant annulation of β-chloroethylsulfinamide[92] or *tert*-butyl (2-chloroethyl)carbamate[93] to β-trifluoromethylacrylates developed by Marcoux and co-workers from Bristol Myers Squibb, although proceeded with good *trans* diastereoselectivity, were documented only for the milligram scale. The cycloaddition of a CF_3-substituted azomethine ylide was not regioselective and provided both 2- and 5-trifluorometyl-β-prolines.[94] In turn, the literature synthesis of 5-trifluorometyl-β-proline via the cyclization of homoallyl sulfinamide proceeded with low diastereoselectivity.[95]

The relative configuration of the synthesized pyrrolidine derivatives was confirmed by NOE experiments, which were performed with derivatives **25**, **28**, *cis*- and *trans*-**31** (Figure 2).

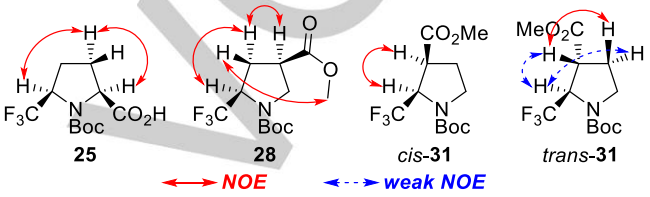


Figure 2. NOE experiments with pyrrolidines **25**, **28**, and **31**

Conclusion

While trifluoromethylation of pyrroles has been studied widely over the recent years, decoration of the readily accessible CF_3-pyrroles with functional groups was underrepresented in the literature to date. This work reveals the synthetic potential of parent 2-trifluoromethyl-1*H*-pyrrole through a series of very robust and reliable regioselective chemical modifications based on either electrophilic substitution or lithiation. After the preparation of the title compound (or its *N*-Boc derivative) was optimized on the *ca*. 100-g scale, these modifications provided a convenient entry to multigram quantities of CF_3-substituted pyrrole building blocks (i.e. sulfonyl halides, aldehydes, carboxylic acids, or nitriles). Their synthetic potential was demonstrated by the preparation of all isomeric 2-trifluoromethyl α- and β-prolines, which can be considered as pyroglutamic acid isosteres. The developed reaction sequences were typically shorter and more amendable for the scale-up than the known literature approaches to these amino acids; moreover, they showed moderate to excellent *cis* diastereoselectivity. The regioisomeric pyrrole and pyrrolidine derivatives obtained in this work are promising low-molecular-weight building blocks for organic synthesis, drug discovery, and agrochemistry, which are now readily available to the scientific community.

Experimental Section

All starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR

and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

2-(Trifluoromethyl)-1*H*-pyrrole (4).[41,49,66] The compound was obtained *via* the optimized literature protocol described previously for the 1.0 mmol scale.[41] H_2SO_4 (96%, 41.5 mL, 73.1 g, 0.745 mol) and $FeSO_4{\cdot}7H_2O$ (61.9 g, 0.224 mol) were added to DMSO (750 mL) at rt. Then, CF_3I (146 g, 0.745 mol) was blown into the reaction mixture, and pyrrole (**14**, 51.7 mL, 50.0 g, 0.745 mol) was added at rt. Next, 9 M aq H_2O_2 (149 mL, 1.36 mol) was slowly added dropwise at 45 °C. The resulting mixture was stirred at 45 °C for 30 min, then cooled to rt and poured into H_2O – ice (1500 g; 1:1, v/m). Aqueous mixture was extracted with CH_2Cl_2 (3×250 mL), combined organic layers were washed with H_2O (2×250 mL), saturated aq K_2CO_3 (250 mL) and brine (250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (100 mL) and evaporated in *vacuo* at 20 °C (NOTE: significant losses of the product were observed if the temperature exceeded 40 °C). The compound was purified by distillation in *vacuo*. Yield 76.5 g (76%); colorless liquid; bp 33–34 °C / 10 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (br s, 1H), 7.02 (q, *J* = 2.4 Hz, 1H), 6.62 – 6.48 (m, 1H), 6.20 – 6.09 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 122.4, 122.2 (q, *J* = 266 Hz), 119.1 (q, *J* = 38.5 Hz), 110.0 (q, *J* = 3.0 Hz), 108.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ –57.6. GC/MS (EI): *m/z* = 135 $[M]^+$. Anal. Calcd. for $C_5H_4F_3N$: C 44.46; H 2.98; N 10.37. Found: C 44.16; H 3.12; N 10.61.

***tert*-Butyl-2-(trifluoromethyl)-1*H*-pyrrole-1-carboxylate (5).**[49,70] 2-(Trifluoromethyl)-1*H*-pyrrole (**4**) (101 g, 0.745 mol) was dissolved in CH_2Cl_2 (1000 mL), and DMAP (9.11 g, 74.5 mmol) was added. Boc_2O (188 mL, 179 g, 0.820 mol) was added dropwise to the mixture at rt. The reaction mixture was stirred at rt until gas evolution ceased (*ca.* 48 h), then washed with H_2O (2×250 mL), 10% aq citric acid (100 mL), saturated aq K_2CO_3 (250 mL), and brine (250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (250 mL) and evaporated in *vacuo* at 40 °C. The crude product was purified by distillation in *vacuo*. Yield 163 g (93%); colorless liquid; bp 37–39 °C / 1 mmHg. Also, the compound was obtained in an one-pot manner from pyrrole **14** *via* the same protocol using the crude 2-(trifluoromethyl)-1*H*-pyrrole (**4**) solution in CH_2Cl_2 obtained after extraction without its evaporation. Yield 152 g (87% in two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.19 (t, *J* = 3.3 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 125.8 (q, *J* = 1.9 Hz), 121.7 (q, *J* = 41.1 Hz), 120.5 (q, *J* = 266 Hz), 117.8 (q, *J* = 4.5 Hz), 109.6, 85.6, 27.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –58.8. GC/MS (EI): *m/z* = 235 $[M]^+$. Anal. Calcd. for $C_{10}H_{12}F_3NO_2$: C 51.07; H 5.14; N 5.96. Found: C 51.07; H 4.75; N 5.93.

5-(Trifluoromethyl)-1*H*-pyrrole-2-sulfonyl chloride (6) A solution of **5** (35.0 g, 0.149 mol) in THF (1000 mL) was cooled to –78 °C under argon atmosphere. Then, 2.5 M *n*-BuLi in hexanes (71.4 mL, 0.178 mol) was added dropwise at –78 °C, and the resulting solution was stirred at –78 °C for 4 h. Then, 2.95 M SO_2 in THF (150 mL, 0.411 mol) was added dropwise at –78 °C, the reaction mixture was slowly warmed up to rt and stirred for 18 h. Most of the solvent was evaporated in *vacuo*, and the residue was dissolved in CH_2Cl_2 (1000 mL). The solution was cooled to –5 °C, and NCS (30.1 g, 0.222 mol) was added in portions at –5 °C. The resulting mixture was warmed up to rt, stirred for 30 min, then washed with ice-cooled H_2O (2×500 mL), 10% aq HCl (250 mL), saturated aq K_2CO_3, and brine. The organic phase was dried over Na_2SO_4, filtered through a pad of silica gel (250 mL) and evaporated in *vacuo* to give the crude *tert*-butyl 2-(chlorosulfonyl)-5-(trifluoromethyl)-1*H*-pyrrole-1-carboxylate (**15**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 4.1 Hz, 1H), 6.77 (d, *J* = 4.1 Hz, 1H), 1.67 (s, 9H).

The subsequent purification of *N*-Boc sulfonyl chloride **15** by column chromatography using gradient hexanes – $CHCl_3$ as eluent was accompanied by the Boc group cleavage and gave pure **6**. Yield 17.6 g (51%); brownish powder; mp 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (br s, 1H), 7.08 (s, 1H), 6.72 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.5, 126.7 (q, *J* = 41.2 Hz), 119.4 (q, *J* = 269 Hz), 116.7, 111.4 (q, *J* = 2.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.3. LC/MS (CI): *m/z* = 232/234 $[M–H]^–$. Anal. Calcd. for $C_5H_3ClF_3NO_2S$: C 25.71; H 1.29; N 6.00; S 13.72; Cl 15.18. Found: C 25.59; H 1.14; N 5.69; S 13.35; Cl 14.91.

5-(Trifluoromethyl)-1*H*-pyrrole-3-sulfonyl chloride (7). Method A: 2-(Trifluoromethyl)-1*H*-pyrrole (**4**) (40.8 g, 0.302 mol) was added dropwise to HSO_3Cl (200 mL, 352 g, 3.02 mol) at 0 °C. The resulting solution turned black; then it was left at 4 °C overnight and poured onto ice (1500 mL). The resulting solution was extracted with cold to 5 °C EtOAc (3×500 mL), the combined organic extracts were washed with cold H_2O (3×500 mL), saturated aq K_2CO_3 (*ca.* 250 mL) to pH ~ 7, brine (300 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The compound was purified by column chromatography on silica gel using hexanes – EtOAc (7:3) as eluent. R_F = 0.70. Yield 4.94 g (7%). **Method B:** A suspension of potassium sulfonate **18** (see below) (46.0 g, 0.182 mol) in DMF (500 mL) was cooled to 15 °C. Then, $SOCl_2$ (21.1 mL, 0.291 mol) was added dropwise at 15 °C, the reaction mixture was warmed up to rt and stirred for 30 min. The resulting solution was poured onto ice – H_2O (1500 g, 1:1, m/v) and extracted with cold (5 °C) EtOAc (3×500 mL). The combined organic extracts were washed with cold H_2O (3×500 mL), saturated aq K_2CO_3 (*ca.* 250 mL) to pH = 7, brine (300 mL), dried over Na_2SO_4, filtered through a pad of silica gel (250 mL) and evaporated in *vacuo*. The compound was purified by recrystallization from hexanes – EtOAc (250 mL, 4:1, v/v). Yield 36.6 g (86%); colorless solid; mp 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (br s, 1H), 7.65 (s, 1H), 7.11 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 129.1, 124.9, 123.2 (q, *J* = 41.4 Hz), 119.5 (q, *J* = 268 Hz), 109.3 (q, *J* = 2.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.1. LC/MS (CI): *m/z* = 232/234 $[M–H]^–$. Anal. Calcd. for $C_5H_3ClF_3NO_2S$: C 25.71; H 1.29; N 6.00; S 13.72; Cl 15.18. Found: C 26.08; H 1.49; N 5.79; S 13.71; Cl 14.95.

5-(Trifluoromethyl)-1*H*-pyrrole-2-carbaldehyde (8).[44,45,60] $POCl_3$ (123 mL, 202 g, 1.32 mol) was added dropwise to DMF (900 mL) at 0 °C. The solution was allowed to warmed up to rt, and 2-(trifluoromethyl)-1*H*-pyrrole (**4**, 89.4 g, 0.662 mol) was added dropwise. The resulting mixture was stirred at 50 °C for 2 h, then cooled and poured onto ice – saturated aq K_2CO_3 (1000 mL). Aqueous mixture was extracted with EtOAc (3×250 mL), combined organic extracts were washed with H_2O (2×250 mL) and brine (2×250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (250 mL) and evaporated in *vacuo*. A mixture of regioisomers **8** and **9** thus obtained was separated by column chromatography on silica gel using hexanes – EtOAc (7:3, v/v) as eluent. R_f = 0.71. Yield 25.9 g (24%); colorless solid; mp 92–94 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (br s, 1H), 9.66 (s, 1H), 6.98 (s, 1H), 6.69 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.6, 133.8, 127.4 (q, *J* = 40.3 Hz), 120.2 (q, *J* = 268 Hz), 120.1, 111.3 (q, *J* = 2.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.5. GC/MS (EI): *m/z* = 163 $[M]^+$. Anal. Calcd. for $C_6H_4F_3NO$: C 44.19; H 2.47; N 8.59. Found: C 44.42; H 2.42; N 8.20.

5-(Trifluoromethyl)-1*H*-pyrrole-3-carbaldehyde (9). The compound was obtained from 4 alongside with aldehyde **8**. A mixture of regioisomers **8** and **9** was separated by column chromatography on silica gel using hexanes – EtOAc (7:3, v/v) as eluent. R_f = 0.38. Yield 50.7 g (47%); yellowish crystals; mp 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 9.44 (br s, 1H), 7.55 (s, 1H), 7.06 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.5, 127.9, 126.7, 123.1 (q, *J* = 40.7 Hz), 120.8 (q, *J* = 267 Hz), 109.2 (q, *J* = 2.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.5. GC/MS (EI): *m/z* = 163 $[M]^+$. Anal. Calcd. for $C_6H_4F_3NO$: C 44.19; H 2.47; N 8.59. Found: C 43.94; H 2.29; N 8.87.

5-(Trifluoromethyl)-1*H*-pyrrole-2-carboxylic acid (10). $KMnO_4$ (60.7 g, 0.384 mmol) was added in portions at 0 °C for 30 min to a solution of aldehyde **8** (25.0 g, 153 mmol) in acetone (300 mL). The reaction mixture was warmed up to rt for 1 h, and $Na_2S_2O_4$ (2.66 g, 15.3 mmol) was added. The resulting mixture was stirred for 15 min and filtered through a pad of silica gel (100 mL), then washed with 1.7 M aq NaOH solution

(100 mL, 0.169 mol). The cqueous phase was separated and acidified with aq HCl at 0 °C to pH = 7. The resulting solution was then extracted with EtOAc (3×100 mL), washed with H_2O (2×100 mL) and brine (2×100 mL), dried over Na_2SO_4, filtered through a pad of silica gel (125 mL) and evaporated in *vacuo*. Yield 15.1 g (55%); beige solid; mp 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.63 (br s, 1H), 7.02 (s, 1H), 6.63 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.8, 127.5, 123.7 (q, *J* = 39.3 Hz), 121.2 (q, *J* = 267 Hz), 114.6, 110.9 (q, *J* = 3.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.1. LC/MS (CI): *m/z* = 178 $[M–H]^–$. Anal. Calcd. for $C_6H_4F_3NO_2$: C 40.24; H 2.25; N 7.82. Found: C 40.61; H 2.03; N 8.21.

5-(Trifluoromethyl)-1*H*-pyrrole-3-carboxylic acid (11). $KMnO_4$ (81.5 g, 0.516 mmol) was added in portions at 0 °C for 30 min to a solution of aldehyde **9** (33.6 g, 0.206 mmol) in acetone (350 mL). The reaction mixture was warmed up to rt for 1 h, and $Na_2S_2O_4$ (3.58 g, 20.6 mmol) was added. The resulting mixture was stirred for 15 min and filtered through a pad of silica gel (100 mL), then washed with 1.7 M aq NaOH solution (135 mL, 0.230 mmol). Aqueous phase was separated and acidified with aq HCl at 0 °C to pH = 7. The resulting solution was then extracted with EtOAc (3×125 mL), washed with H_2O (2×125 mL) and brine (2×125 mL), dried over Na_2SO_4, filtered through a pad of silica gel (150 mL) and evaporated in *vacuo*. Yield 25.1 g (68%); beige solid, mp 136–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 7.57 (q, *J* = 1.4 Hz, 1H), 7.06 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.0, 127.3, 121.3 (q, *J* = 266 Hz), 120.4 (q, *J* = 39.4 Hz), 117.2, 111.1 (q, *J* = 3.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –60.7. LC/MS (CI): *m/z* = 178 $[M–H]^–$. Anal. Calcd. for $C_6H_4F_3NO_2$: C 40.24; H 2.25; N 7.82. Found: C 40.26; H 2.18; N 8.19.

5-(Trifluoromethyl)-1*H*-pyrrole-2-carbonitrile (12).[96] Aldehyde **8** (20.0 g, 0.123 mol) was added to a solution of hydroxylamine *O*-sulfonic acid (48.5 g, 0.429 mmol) in H_2O (500 mL). The mixture was stirred at rt overnight, then cooled to 0 °C, and a solution of KOH (48.2, 0.859 mmol) in H_2O (200 mL) was added dropwise at 0 °C. The reaction mixture was warmed up to rt, stirred at rt for 3 h, then extracted with CH_2Cl_2 (3×250 mL). The combined organic layers were washed with H_2O (2×250 mL), brine (2×100 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Yield 16.3 g (83%); colorless crystals; mp 103–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 6.87 (s, 1H), 6.62 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 125.7 (q, *J* = 40.9 Hz), 120.3, 119.7 (q, *J* = 268 Hz), 112.7, 110.7 (q, *J* = 2.9 Hz), 103.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.1. LC/MS (CI): *m/z* = 159 $[M–H]^–$. Anal. Calcd. for $C_6H_3F_3N_2$: C 45.01; H 1.89; N 17.5. Found: C 45.39; H 1.60; N 17.61.

5-(Trifluoromethyl)-1*H*-pyrrole-3-carbonitrile (13). Aldehyde **9** (23.0 g, 0.141 mol) was added to a solution of hydroxylamine *O*-sulfonic acid (55.9 g, 0.494 mol) in H_2O (500 mL). The mixture was stirred at rt overnight, then cooled to 0 °C, and KOH (55.4 g, 0.987 mmol) in H_2O (200 mL) was added dropwise at 0 °C. The reaction mixture was warmed up to rt, stirred at rt for 3 h, then extracted with CH_2Cl_2 (3×250 mL). Combined organic layers were washed with H_2O (2×250 mL), brine (2×100 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Yield 18.5 g (82%); yellowish powder; mp 116–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 7.40 (q, *J* = 1.4 Hz, 1H), 6.87 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 127.9, 122.3 (q, *J* = 41.1 Hz), 119.8 (q, *J* = 267 Hz), 115.0, 112.9 (q, *J* = 3.1 Hz), 94.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –60.8. LC/MS (CI): *m/z* = 159 $[M–H]^–$. Anal. Calcd. for $C_6H_3F_3N_2$: C 45.01; H 1.89; N 17.5. Found: C 44.77; H 1.96; N 17.72.

5-(Trifluoromethyl)-1*H*-pyrrole-2-sulfonyl fluoride (17). The crude sulfonyl chloride **15** (*ca.* 48.7 g, 0.146 mol) was dissolved in EtOAc – H_2O (600 mL, 5:1, v/v) at rt. Then, 1 M TBAF in THF (29.2 mL, 29.2 mmol) and KF (25.4 g, 0.438 mol) were added. The reaction mixture was stirred overnight, organic phase was separated, washed with H_2O (2×100 mL) and brine (100 mL), dried over Na_2SO_4, filtered through a pad of silica gel (100 mL) and evaporated in *vacuo* to give the crude *tert*-butyl 2-(fluorosulfonyl)-5-(trifluoromethyl)-1*H*-pyrrole-1-carboxylate (**16**). The compound existed as a *ca.* 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 3.3 Hz, 0.5H) and 7.23 (d, *J* = 3.3 Hz, 0.5H), 6.82 (d, *J* = 3.7 Hz, 0.5H) and 6.81 (d, *J* = 3.7 Hz, 0.5H), 1.66 (s, 4.5H) and 1.66 (s, 4.5H). ^{19}F NMR (470 MHz, $CDCl_3$) δ 63.5, –59.0.

The subsequent purification of *N*-Boc sulfonyl fluoride **16** by column chromatography using gradient hexanes – *t*-BuOMe as eluent was accompanied by the Boc-group cleavage and gave pure **17**. Yield 17.1 g (54%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 6.74 (d, *J* = 3.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.6 (q, *J* = 40.7 Hz), 121.7 (q, *J* = 32.4 Hz), 119.4 (q, *J* = 269 Hz), 118.8, 111.7 (q, *J* = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ 69.5, –61.4. LC/MS (CI): *m/z* = 216 $[M–H]^–$. Anal. Calcd. for $C_{10}H_{11}F_4NO_4S$: C 37.86; H 3.50; N 4.42; S 10.11. Found: C 37.66; H 3.73; N 4.54; S 10.06.

Potassium 5-(trifluoromethyl)-1*H*-pyrrole-3-sulfonate (18). H_2SO_4 (96%, 41.6 mL, 76.1 g, 0.745 mol) and $FeSO_4·7H_2O$ (62.1 g, 0.224 mol). were added to DMSO (750 mL). Then, CF_3I (146 g, 0.745 mol) was blown into the reaction mixture, and pyrrole (**14**, 51.7 mL, 50.0 g, 0.745 mol) were added. Then, 9 M aq H_2O_2 (149 mL, 1.36 mol) was added dropwise at 45 °C, and the resulting mixture was stirred at 45 °C for 30 min. Then, the solution was cooled to rt and ice – H_2O (1500 g, 1:1, m/v) was added. Aqueous solution was extracted with CH_2Cl_2 (3×250 mL), combined organic extracts were washed with H_2O (2×250 mL), saturated aq K_2CO_3 (250 mL) and brine (250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (100 mL). Obtained solution was cooled to –10 °C and HSO_3Cl (48.9 mL, 86.6 g, 0.743 mol) was added dropwise. Then, the reaction mixture was warmed to rt, and the solvent was evaporated in *vacuo*. Saturated aq K_2CO_3 (250 mL) was added in portions to the residue at 0 °C, and the resulting solution was left at 4 °C overnight. The precipitate formed was filtered, washed with cold H_2O (3×50 mL) and *t*-BuOMe (3×250 mL), and dried over P_2O_5 in *vacuo*. Yield 45.3 g (24%); colorless crystals; decomposed upon heating to 203 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.03 (s, 1H), 6.55 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 132.8, 121.9 (q, *J* = 266 Hz), 121.1, 118.5 (q, *J* = 38.7 Hz), 108.5 (d, *J* = 3.5 Hz). ^{19}F NMR (470 MHz, DMSO-d_6) δ –57.6. LC/MS (CI): *m/z* = 214 $[M–K]^+$. Anal. Calcd. for $C_5H_3F_3KNO_3S$: C 23.71; H 1.19; N 5.53; S 12.66. Found: C 23.85; H 0.84; N 5.91; S 12.64.

1-(*tert*-Butoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylic acid (19). A solution of 2-(trifluoromethyl)-1*H*-pyrrole (35.0 g, 0.149 mol) in THF (1000 mL) was cooled to –78 °C under argon atmosphere. Then, 2.5 M *n*-BuLi in hexanes (71.4 mL, 0.178 mol) was added dropwise at –78 °C, the resulting solution was stirred at –78 °C for 4 h and then poured onto dry CO_2 (1000 g, 22.7 mol). The reaction mixture was warmed up to rt and stirred for 18 h. The solvent was evaporated in *vacuo*, and the residue was dissolved in H_2O (100 mL). The aqueous solution was washed with *t*-BuOMe (2×250 mL), cooled to 5 °C and acidified with 10% aq HCl until pH = 3. The resulting mixture was extracted with *t*-BuOMe (3×250 mL), combined organic layers were washed with H_2O (2×250 mL) and brine (2×250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (250 mL) and evaporated in *vacuo*. The crude product was purified by trituration from cold hexanes (250 mL). Yield 25.3 g (61%); pinkish solid; mp 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 3.9 Hz, 1H), 6.63 (d, *J* = 3.9 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 147.1, 126.9 (q, *J* = 40.2 Hz), 126.5, 119.7 (q, *J* = 269 Hz), 118.3, 112.8 (q, *J* = 4.1 Hz), 87.3, 27.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.4. LC/MS (CI): *m/z* = 278 $[M–H]^–$. Anal. Calcd. for $C_{11}H_{12}F_3NO_4$: C 47.32; H 4.33; N 5.02. Found: C 47.29; H 4.30; N 4.69.

1-(*tert*-Butyl) 3-methyl 5-(trifluoromethyl)-1*H*-pyrrole-1,3-dicarboxylate (20). A mixture of NaH (60%, 2.24 g, 55.9 mmol) in DMF (150 mL) was cooled to –10 °C under argon atmosphere. Then, a solutiom of pyrrole **21** (9.00 g, 46.6 mmol) in DMF (15 mL) was added dropwise. The resulting mixture was stirred at rt for 2 h, then cooled to –10 °C and Boc_2O (13.9 mL, 13.2 g, 60.4 mmol) was added dropwise. The solution was stirred for at –10 °C for 1 h, then warmed up to rt and stirred for another 18 h. The resulting mixture was poured into ice – H_2O (300 g, 1:1, m/v), aqueous mixture was extracted with *t*-BuOMe (3×150 mL). Combined organic extracts were washed with H_2O (150 mL), brine (2×800 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude product was purified by recrystallization from hexanes (25 mL). Yield 7.93 g (58%); yellowish crystals; mp 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.09 (s, 1H), 3.83 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2, 146.4, 129.7, 122.6 (q, *J* = 41.0 Hz), 119.8 (q,

J = 267 Hz), 117.3 (q, J = 4.5 Hz), 116.9, 87.06, 51.6, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.5. LC/MS (CI): m/z = 238 $[M–H_2C=C(CH_3)_2+H]^+$, 294 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}F_3NO_4$: C 49.15; H 4.81; N 4.78. Found: C 49.49; H 4.80; N 4.94.

Methyl 5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (21). A solution of carboxylic acid **11** (10.0 g, 55.8 mmol) in MeOH (100 mL) was cooled to 0 °C, and $SOCl_2$ (5.28 mL, 8.64 g, 72.6 mmol) was added dropwise at 0 °C. The resulting solution was warmed up to rt and stirred for 18 h. Then, the solvent was evaporated in *vacuo,* and H_2O (200 mL) was added to the residue. Aqueous mixture was extracted with *t*-BuOMe (3×200 mL), combined organic layers were washed with H_2O (2×200 mL), saturated aq K_2CO_3 (100 mL), brine (100 mL), dried over Na_2SO_4, filtered through a pad of silica gel (100 mL) and evaporated in *vacuo*. Yield 9.16 g (85%); colorless solid; mp 124–127 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.66 (s, 1H), 6.90 (s, 1H), 3.71 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.0, 127.4, 121.2 (q, J = 266 Hz), 120.7 (q, J = 39.6 Hz), 115.9, 110.9 (q, J = 3.2 Hz), 51.3. ^{19}F NMR (470 MHz, DMSO-d_6) δ –58.6. LC/MS (CI): m/z = 192 $[M–H]^–$. Anal. Calcd. for $C_7H_6F_3NO_2$: C 43.54; H 3.13; N 7.25. Found: C 43.75; H 2.81; N 6.94.

Methyl 1*H*-pyrrole-3-carboxylate (22).[97,98] A solution of 1*H*-pyrrole-3-carboxylic acid (75.0 g, 0.675 mmol) in MeOH (750 mL) was cooled to 0 °C, and $SOCl_2$ (58.9 mL, 96.5 g, 811 mmol) was added dropwise at 0 °C. The resulting solution was warmed up to rt and stirred for 18 h. Then, the solvent was evaporated in *vacuo,* and H_2O (1000 mL) was added to the residue. Aqueous mixture was extracted with *t*-BuOMe (3×500 mL), combined organic layers were washed with H_2O (2×500 mL), saturated aq K_2CO_3 (250 mL), brine (250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (250 mL) and evaporated in *vacuo*. Yield 69.2 g (82%); colorless solid; 87–90 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (br s, 1H), 7.46 – 7.31 (m, 1H), 6.80 (dd, J = 2.4, 2.1 Hz, 1H), 6.42 (dd, J = 2.4, 1.3 Hz, 1H), 3.68 (s, 3H). LC/MS (CI): m/z = 94 $[M–OMe]^+$, 126 $[M+H]^+$. Anal. Calcd. for $C_6H_7NO_2$: C 57.59; H 5.64; N 11.19. Found: C 57.99; H 5.44; N 11.21.

Methyl 2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (23). H_2SO_4 (96%, 30.2 mL, 55.5 g, 0.543 mol) and $FeSO_4·7H_2O$ (45.3 g, 0.163 mol) were added to DMSO (750 mL) at rt. Then, CF_3I (117 g, 0.598 mol) was blown into the reaction mixture, and methyl 1*H*-pyrrole-3-carboxylate (**22**, 67.9 g, 0.543 mol) was added at rt. Next, 9 M aq H_2O_2 (108 mL, 1.36 mol) was slowly added dropwise at 45 °C. The resulting mixture was stirred at 45 °C for 30 min, then cooled to rt and poured into H_2O – ice (1500 g; 1:1, v/m). Aqueous mixture was extracted with *t*-BuOMe (3×500 mL), combined organic layers were washed with H_2O (2×500 mL), saturated aq K_2CO_3 (2×250 mL) and brine (250 mL), dried over Na_2SO_4, filtered through a pad of silica gel (100 mL) and evaporated in *vacuo*. The crude compound was purified by recrystallization from hexanes – *t*-BuOMe (4:1, v/v). Yield 37.8 g (36%); colorless crystals; mp 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 122.6 (q, J = 40.3 Hz), 120.3 (q, J = 268.0 Hz), 119.0, 116.2 (q, J = 2.1 Hz), 113.0, 51.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.9. LC/MS (CI): m/z = 192 $[M–H]^–$. Anal. Calcd. for $C_7H_6F_3NO_2$: C 43.54; H 3.13; N 7.25. Found: C 43.31; H 3.42; N 7.14.

1-*tert*-Butyl 3-methyl 2-(trifluoromethyl)-1*H*-pyrrole-1,3-dicarboxylate (24). A mixture of NaH (60%, 6.96 g, 0.174 mol) in DMF (500 mL) was cooled to –10 °C under argon atmosphere. Then, a solutiom of pyrrole **23** (28.0 g, 0.145 mol) in DMF (50 mL) was added dropwise. The resulting mixture was stirred at rt for 2 h, then cooled to –10 °C and Boc_2O (43.2 mL, 41.0 g, 0.188 mol) was added dropwise. The solution was stirred for at –10 °C for 1 h, then warmed up to rt and stirred for another 18 h. The resulting mixture was poured into ice – H_2O (1000 g, 1:1, m/v), aqueous mixture was extracted with *t*-BuOMe (3×500 mL). Combined organic extracts were washed with H_2O (500 mL), brine (2×250 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Yield 38.7 (91%); yellowsih oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 3.3 Hz, 1H), 6.38 (d, J = 3.3 Hz, 1H), 3.76 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 147.0, 124.9 (q, J = 1.6 Hz), 124.1 (q, J = 2.6 Hz), 120.5 (q, J = 40.5 Hz), 119.7 (q, J = 269 Hz), 111.0, 86.8, 52.2, 27.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –56.1. LC/MS (CI): m/z = 238 $[M–H_2C=C(CH_3)_2+H]^+$, 294 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}F_3NO_4$: C 49.15; H 4.81; N 4.78. Found: C 49.09; H 4.96; N 4.68.

***cis*-1-(*tert*-Butoxycarbonyl)-5-(trifluoromethyl)pyrrolidine-2-carboxylic acid (25).** 10% Pd–C (5.0 g) was added to a solution of **24** (25.0 g, 89.5 mmol) and in MeOH (250 mL), which was then hydrogenated at 50 °C for 48 h under H_2 (70 bar) in an autoclave. The resulting mixture was filtered, and the filtrate was evaporated in *vacuo*. Yield 25.1 g (99%); colorless solid; mp 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 4.50 – 4.25 (m, 2H), 2.49 – 2.20 (m, 2H), 2.19 – 2.01 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.5, 154.0, 126.2 (q, J = 279 Hz), 80.5, 60.8, 58.6 (q, J = 34.0 Hz), 29.1, 28.2, 25.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –75.5. LC/MS (CI): m/z = 282 $[M–H]^–$. Anal. Calcd. for $C_{11}H_{16}F_3NO_4$: C 46.65; H 5.69; N 4.95. Found: C 46.86; H 6.09; N 4.67.

***cis*-5-(Trifluoromethyl)pyrrolidine-2-carboxylic acid hydrochloride (26).**[91,99,100] *N*-Boc F_3C-proline **25** (25.0 g, 88.3 mmol) was added to 4 M HCl –1,4-dioxane (250 mL). The reaction mixture was stirred at rt for 18 h, then evaporated in *vacuo* at 60 °C. Yield 19.4 g (100%); yellowish crystals; mp 131–132 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 3H), 4.39 – 4.28 (m, 1H), 4.26 (t, J = 7.3 Hz, 1H), 2.29 – 2.12 (m, 2H), 2.12 – 2.01 (m, 1H), 2.00 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.2, 125.0 (q, J = 280 Hz), 60.3, 58.5 (q, J = 31.9 Hz), 27.6, 24.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ –72.1. LC/MS (CI): m/z = 182 $[M–H–HCl]^–$. Anal. Calcd. for $C_6H_9ClF_3NO_2$: C 32.82; H 4.13; N 6.38; Cl 16.14. Found: C 32.92; H 3.79; N 6.62; Cl 15.92.

***cis*-(5-(Trifluoromethyl)pyrrolidin-2-yl)methanol hydrochloride (27).** A solution of *N*-Boc F_3C-proline **25** (18.4 g, 65.1 mmol) in THF (250 mL) was cooled to 0 °C under argon atmosphere. Then, 10 M $BH_3·SMe_2$ in THF (13.2 mL, 0.132 mol) was added dropwise, and the reaction mixture was warmed to rt and stirred for 18 h. Next, the mixture was cooled to 0 °C and MeOH (26.3 mL, 20.9 g, 0.651 mmol) was slowly added at 10 °C. Most of solvents was evaporated in *vacuo* and the residue was diluted with in H_2O (300 mL). Aqueous solution was the extracted with EtOAc (3×100 mL), combined organic phases were washed with H_2O (2×100 mL) and brine (2×100 mL), dried over Na_2SO_4, filtered through a pad of silica gel (100 mL) and evaporated in *vacuo*. Then, the residue was added to 4 M HCl –1,4-dioxane (250 mL) and the reaction mixture was stirred at rt for 18 h. The solvent was evaporated in *vacuo*, and crystals thus obtained were dried over P_2O_5 in *vacuo*. Yield 12.7 g (95%); yellowish powder; mp 71–72 °C. ^{1}H NMR (400 MHz, D_2O) δ 4.37 (h, J = 7.4 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.64 (dd, J = 12.9, 8.5 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.13 (tdd, J = 12.9, 7.4, 5.0 Hz, 2H), 1.85 – 1.72 (m, 1H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (br s, 2H), 4.47 (h, J = 8.1 Hz, 1H), 3.94 – 3.25 (m, 4H), 2.31 – 2.19 (m, 1H), 2.12 – 1.96 (m, 2H), 1.85 – 1.71 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 124.3 (q, J = 279 Hz), 63.2, 59.9, 58.3 (q, J = 32.4 Hz), 25.8, 24.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ –71.1. LC/MS (CI): m/z = 170 $[M–HCl+H]^+$. Anal. Calcd. for $C_6H_{11}ClF_3NO$: C 35.05; H 5.39; N 6.81; Cl 17.24. Found: C 34.93; H 5.65; N 6.85; Cl 16.93.

***cis*-1-(*tert*-Butyl) 3-methyl 5-(trifluoromethyl)pyrrolidine-1,3-dicarboxylate (28).** Pd-C (10%, 5.0 g) was added to a solution of pyrrole **20** (5.00. g, 17.0 mmol) in MeOH (100 mL), which was then hydrogenated at 80°C for 48 h under H_2 atmosphere (100 bar) in autoclave. Then, the resulting mixture was filtered, and the filtrate was evaporated in *vacuo*. The crude compound was purified by flash chromatography using gradient hexanes – *t*-BuOMe as eluent. The compound existed as a *ca.* 5:4 mixture of rotamers. Yield 3.84 g (76%); colorless crystals; mp 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 – 4.32 (m, 1H), 4.07 – 3.91 (m, 1H), 3.66 (s, 3H), 3.43 (t, J = 9.6 Hz, 1H), 2.99 (p, J = 8.5 Hz, 1H), 2.44 – 2.32 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.9, 153.9 and 153.5, 125.5 (q, J = 282 Hz), 81.0, 57.1 (q, J = 22.6 Hz), 52.2, 48.7 and 48.3, 42.0 and 41.4, 29.0, 28.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ –76.0. LC/MS (CI): m/z = 198 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 244 $[M–Ot\text{-}Bu]^+$, 242 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{12}H_{18}F_3NO_4$: C 48.48; H 6.10; N 4.71. Found: C 48.10; H 6.50; N 4.97.

***cis*-4-(Methoxycarbonyl)-2-(trifluoromethyl)pyrrolidin-1-ium chloride (29).** *N*-Boc pyrrolidine **28** (2.50 g, 8.41 mmol) was added to 4 M HCl – 1,4-dioxane (20 mL). The reaction mixture was stirred at rt for 18 h and

then evaporated in *vacuo*. The residue was diluted with *t*-BuOMe (20 mL), precipitate was filtered, washed with *t*-BuOMe (2×10 mL) and dried over P_2O_5 in *vacuo*. The crude compound was purified by flash chromatography using gradient hexanes – *t*-BuOMe as eluent. Yield 1.57 g (80%); fusible yellowish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 2H), 4.47 (s, 1H), 3.61 (s, 3H), 3.52 – 3.44 (m, 1H), 3.40 – 3.29 (m, 2H), 2.59 – 2.50 (m, 1H), 2.13 – 2.05 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6, APT) δ 171.4, 124.3 (q, *J* = 280 Hz), 57.9 (q, *J* = 32.6 Hz), 52.9, 47.7, 41.5, 28.4. ^{19}F NMR (470 MHz, DMSO-d_6) δ –71.3. LC/MS (CI): *m/z* = 198 $[M–HCl+H]^+$. Anal. Calcd. for $C_7H_{11}ClF_3NO_2$: C 35.99; H 4.75; N 6.00; Cl 15.17. Found: C 35.99; H 4.81; N 6.15; Cl 15.09.

***cis*-4-Carboxy-2-(trifluoromethyl)pyrrolidin-1-ium chloride (30).** *N*-Boc amino ester **28** (1.50 g, 5.05 mmol) was added to 35% aq HCl (10 mL) and 1,4-dioxane (10 mL), and the rextion mixture was stirred at 80 °C for 18 h. The resulting mixture was evaporated in *vacuo*, and the residue was dried over P_2O_5 in *vacuo*. Yield 1.04 g (94%); beige solid; mp 196–197 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 4.58 (h, *J* = 8.0 Hz, 1H), 3.53 (dd, *J* = 11.2, 8.6 Hz, 1H), 3.42 – 3.31 (m, 2H), 2.58 (dt, *J* = 13.1, 8.0 Hz, 1H), 2.13 (dt, *J* = 13.1, 9.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3, 124.2 (q, *J* = 279 Hz), 58.0 (q, *J* = 32.4 Hz), 47.6, 41.5, 28.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ –71.4. LC/MS (CI): *m/z* = 184 $[M–HCl+H]^+$. Anal. Calcd. for $C_6H_9ClF_3NO_2$: C 32.82; H 4.13; N 6.38; Cl 16.14. Found: C 32.75; H 3.83; N 6.73; Cl 15.94.

1-*tert*-Butyl 3-methyl 2-(trifluoromethyl)pyrrolidine-1,3-dicarboxylate (31). Pd-C (10%, 5.0 g) was added to a solution of pyrrole **20** (5.00. g, 16.8 mmol) in MeOH (100 mL), which was then hydrogenated at 80°C for 48 h under H_2 atmosphere (100 bar) in autoclave. Then, the resulting mixture was filtered, and the filtrate was evaporated in *vacuo*. The compound was obtained as a *ca.* 3:1 mixture of diastereomers. The crude product was purified by HPLC using gradient MeCN – H_2O as eluent.

***cis*-1-*tert*-Butyl 3-methyl 2-(trifluoromethyl)pyrrolidine-1,3-dicarboxylate (*cis*-31).** Yield 2.71 g (69%); colorless oil. The compound existed as a *ca*. 3:2 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 7.7 Hz, 1H), 4.56 (d, *J* = 7.7 Hz, 0.6H), 3.64 (s, 3H), 3.49 – 3.35 (m, 2H), 3.19 – 3.07 (m, 1H), 2.51 – 2.32 (m, 1H), 2.05 (dtd, *J* = 13.2, 7.4, 2.4 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 169.0 and 169.0, 154.2 and 153.5, 124.8 (q, *J* = 283 Hz) and 124.7 (q, *J* = 283 Hz), 81.0 and 80.8, 59.1 (q, *J* = 32.8 Hz) and 59.0 (q, *J* = 33.6 Hz), 52.1, 45.4 and 44.9, 44.7 and 43.9, 28.1, 25.4 and 24.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –72.0, –72.2. LC/MS (CI): *m/z* = 197 $[M–CO_2–H_2C=C(CH_3)_2]^+$, 244 $[M–Ot\text{-}Bu]^+$, 241 $[M–H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{12}H_{18}F_3NO_4$: C 48.48; H 6.10; N 4.71. Found: C 48.29; H 6.40; N 4.84.

***trans*-1-*tert*-Butyl 3-methyl 2-(trifluoromethyl)pyrrolidine-1,3-dicarboxylate (*trans*-31).** Yield 864 mg (22%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 1H), 3.66 (s, 3H), 3.64 – 3.47 (m, 1H), 3.36 – 3.23 (m, 1H), 3.16 – 3.07 (m, 1H), 2.28 – 2.08 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, APT) δ 172.1, 125.1 (q, *J* = 283 Hz), 80.8, 60.3 (q, *J* = 31.7 Hz), 52.4, 46.0, 28.0, 27.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –75.4. Anal. Calcd. for $C_{12}H_{18}F_3NO_4$: C 48.48; H 6.10; N 4.71. Found: C 48.84; H 5.98; N 4.74.

3-(Methoxycarbonyl)-2-(trifluoromethyl)pyrrolidin-1-ium chloride (32). The corresponding *N*-Boc pyrrolidine **31** (2.50 g, 8.41 mmol) was added to 4 M HCl – 1,4-dioxane (20 mL). The reaction mixture was stirred at rt for 18 h and then evaporated in *vacuo*. The residue was diluted with *t*-BuOMe (20 mL), precipitate was filtered, washed with *t*-BuOMe (2×10 mL) and dried over P_2O_5 in *vacuo*.

***cis*-3-(Methoxycarbonyl)-2-(trifluoromethyl)pyrrolidin-1-ium chloride (*cis*-32).** Yield 76.2 mg (97%); colorless crystals; mp 103–105 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 2H), 4.79 (pd, *J* = 8.4, 3.0 Hz, 1H), 3.64 (s, 3H), 3.56 – 3.51 (m, 1H), 3.46 (dtd, *J* = 11.2, 7.6, 3.0 Hz, 1H), 3.34 (tdd, *J* = 11.2, 7.6, 3.0 Hz, 1H), 2.27 – 2.16 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.1, 123.4 (q, *J* = 281 Hz), 59.6 (q, *J* = 32.0 Hz), 52.8, 45.0, 43.3, 27.1. ^{19}F NMR (470 MHz, DMSO-d_6) δ –67.5. Anal. Calcd. for $C_7H_{11}ClF_3NO_2$: C 35.99; H 4.75; N 6; Cl 15.17. Found: C 35.78; H 4.65; N 5.92; Cl 15.04.

***trans*-3-(Methoxycarbonyl)-2-(trifluoromethyl)pyrrolidin-1-ium chloride (*trans*-32).** Yield 76.2 mg (97%); colorless crystals; mp 96–97 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 2H), 4.63 (p, *J* = 7.7 Hz, 1H), 3.69 (s, 3H), 3.53 (q, *J* = 7.7 Hz, 1H), 3.36 – 3.22 (m, 2H), 2.33 (dq, *J* = 13.8, 6.7 Hz, 1H), 2.15 (dq, *J* = 14.9, 7.7 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.7, 124.0 (q, *J* = 2810 Hz), 59.6 (q, *J* = 32.3 Hz), 53.3, 46.5, 43.4, 28.6. ^{19}F NMR (470 MHz, DMSO-d_6) δ –70.5. Anal. Calcd. for $C_7H_{11}ClF_3NO_2$: C 35.99; H 4.75; N 6.00; Cl 15.17. Found: C 36.02; H 4.83; N 5.98; Cl 15.07.

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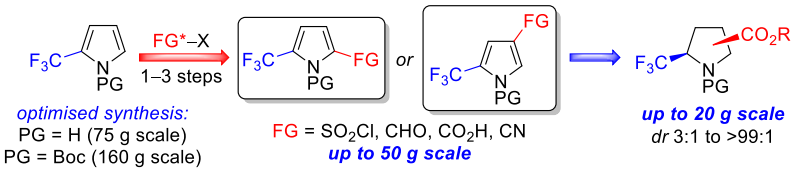
Trifluoromethylpyrroles



Efficient synthetic protocols for incorporation of functional groups into the simplest α-trifluoromethylpyrroles were developed as providing an entry into advanced low-molecular weight fluorinated building blocks, including all isomeric α-trifluoromethylprolines.

Institute and/or researcher Twitter usernames: @EnamineLtd @KyivUniversity @DrGregor2