Regioselective Synthesis of Stable 2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ols and Derived Fluorinated Heterocycles

Orazio A. Attanasi, Paolino Filippone,* Barbara Guidi, Fabio Mantellini, Stefania Santeusanio*

Organic Chemistry Institute, University of Urbino, Piazza della Repubblica 13, 61029 Urbino, Italy
Fax +39(0722)2907; E-mail: attanasi@uniurb.it

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Abstract: 1,2-Diaza-1,3-butadienes react regioselectively with trifluoromethylated β-dicarbonyl compounds to give stable 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivatives, which upon treatment with trifluoromethanesulphonic anhydride or with heterogeneous catalysts give rise to fluorinated 1-aminopyrrole derivatives in good to excellent yields. The reaction of 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivative with 2-haloketone affords fluorinated furo[2,3-*b*]pyrroline derivative, while that of diethyl 1-[(anilinocarbonyl)amino]-2-methyl-5-(trifluoromethyl)-1*H*-pyrrole-3,4-dicarboxylate with hydrazine hydrate affords fluorinated pyrrolo[3,4-*d*]pyridazindione derivative.

Key words: 1,2-diaza-1,3-butadienes, Michael additions, regioselectivity, 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ols, heterocycles

1,2-Diaza-1,3-butadienes[1–12] have been demonstrated as powerful building blocks in heterocycle ring assembly.[13–23] Pyrrole ring systems are important in organic chemistry,[24–26] because they constitute the skeleton of natural products, antibiotics and polymers. As a part of our research program directed towards the synthesis of five-membered heterocycles, we have developed a very efficient protocol for the preparation of 1-aminopyrrole derivatives.[13,14] The nucleophilic attack of the methylene group of 1,3-dicarbonyl compounds at the heterodiene system of conjugated azoalkenes resulted in a hydrazone intermediate via Michael-type addition. The subsequent ring closure by the hydrazone nitrogen on the keto group of β-dicarbonyl compounds provided 2,3-dihydro-1*H*-pyrrol-2-ol derivatives, rarely isolable or even detectable as stable compounds because of the prompt dehydration process producing pyrrole heterocycles.[27] Indeed, 2,3-dihydro-1*H*-pyrrol-2-ol derivatives as stable compounds were achieved only in the reaction of conjugated azoalkenes with β-dicarbonyl compounds having an activated methinic group where the lack of a hydrogen atom in α-position with respect to hydroxyl function can not initiate the dehydration process.[28–30] Since the introduction of a fluorine atom into organic molecules often results in considerable modification of their physical, chemical and biological activity,[31–33] it is not surprising that the investigation of methods for the preparation of fluorine-containing compounds has been an area of intensive activity in the past few decades. Due to its powerful electron-withdrawing ability, the trifluoromethyl group lead to significant changes in the regiochemistry when compared with non-fluorinated analogues.[34] Therefore, we decided to study in detail the reaction between 1,2-diaza-1,3-butadienes and trifluoromethylated 1,3-dicarbonyl compounds.

In the presence of catalytic amounts of CH_3ONa in THF at room temperature, 1,2-diaza-1,3-butadienes (**1a**–**c**) reacted with 1,1,1-trifluoro-2,4-pentanedione (**2a**) to give **3**. The reaction pathway showed regioselective spontaneous heteroring closure at the -*C*O-CF_3 group giving stable 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivatives (**4a**–**c**) (80–83%). In fact, pyrrole derivatives (**5a**–**c**) deriving from the ring closure of the -*C*O-CH_3 group and subsequent loss of trifluoroacetic acid molecule were present only in smaller amount (4–6%) (Scheme 1, Table 1). Under the same reaction conditions, 1,2-diaza-1,3-butadienes (**1a**–**f**) reacted regiospecifically with hexafluoroacetylacetone (**2b**), and trifluoromethyl-substituted 1,3-dicarbonyl compounds (**2c**–**e**) affording stable 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivatives (**4d**–**o**) (61–93%) (Scheme 1, Table 1).

It is worthy of emphasizing that 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivatives **4a**,**c**,**d**,**f**,**h**,**i** (Table 1) were also advantageously obtained also in solvent-free conditions by using a molar ratio 1:7 between 1,2-diaza-1,3-butadienes **1a**–**d** and trifluoromethylated β-dicarbonyl compounds **2a**–**c**, respectively. In particular, compounds **4a**,**d**,**f** precipitate spontaneously from the reaction medium and were easily isolated by filtration. In all cases derivatives **4a**–**o** were obtained as diastereomeric mixtures (diastereomeric ratio ranging from 50:50 to 69:31).

Spectroscopical data exclude intramolecular ring closure of **3** into 3-(trifluoroacetyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivatives as shown by the absence of -*C*O-CF_3 group in the ^{13}C NMR spectra of compounds **4a**–**c**,**g**–**o**, while the presence of -*C*O-CF_3 carbon in the ^{13}C NMR spectra of **4d**–**f** is clearly detectable (δ = 186–187 ppm, $^2J_{CF}$ = 35 Hz).

Even in the presence of $CuCl_2 \cdot 2H_2O$ as catalyst, the reaction between **1** and **2** produced **4** within several weeks and any attempt of dehydration at room temperature according to the methodology used with success in our previous investigation[27] did not result in the aromatization confirming the stability of **4a**–**o**.

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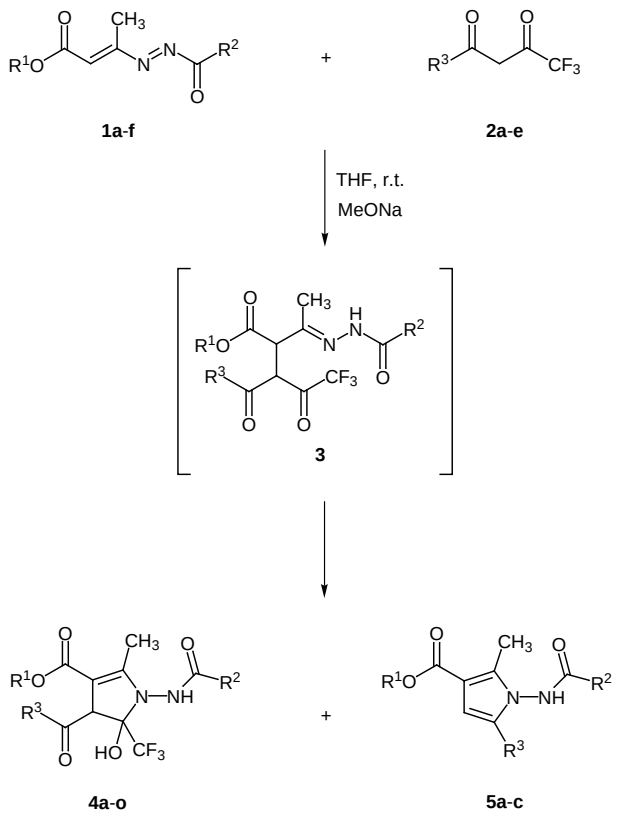
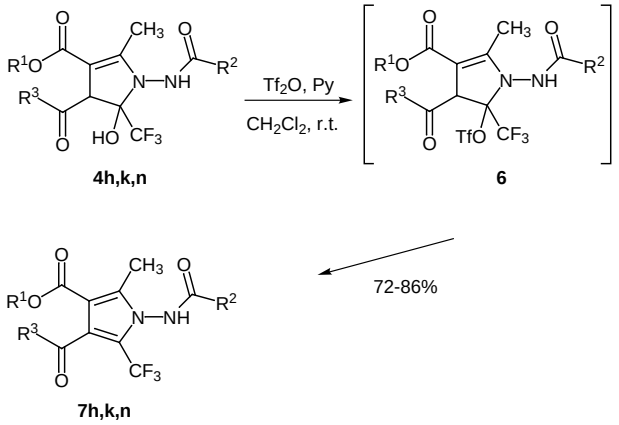


Scheme 1

Since trifluoromethylated nitrogen-containing aromatic heterocycles are of great interest in biological[32,33,35,36] and agrochemical[37] fields, we made efforts to find an efficient route for the aromatization process of the title compounds **4a**–**o**. Among the methods available in the literature for this purpose, we selected the transformation of hydroxyl function to a better leaving group. The treatment of **4h**,**k**,**n** with Tf_2O (trifluoromethanesulphonic anhydride) in the presence of an excess of anhydrous pyridine (anhydrous CH_2Cl_2, r.t.), showed to successfully provided 1-aminopyrrole derivatives **7h**,**k**,**n** (72–86%) (Scheme 2, Table 2).



Scheme 2

Table 1 Yield and Reaction Time of 2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivatives **4a**–**o**

1	R^1	R^2	**2**	R^3	Products	Yield (%)[a]	Reaction Time (h)
1a	CH_3	NH_2	**2a**	CH_3	**4a/5a** **4a**	83/4 79[b]	68 3[b]
1b	CH_2CH_3	NHC_6H_5	**2a**	CH_3	**4b/5b**	80/4	5
1c	CH_3	$OC(CH_3)_3$	**2a**	CH_3	**4c/5c** **4c**	81/6 80[b]	25 4b
1a	CH_3	NH_2	**2b**	CF_3	**4d**	84/ 92[b]	72/4[b]
1b	CH_2CH_3	NHC_6H_5	**2b**	CF_3	**4e**	77	67
1d	CH_3	OCH_3	**2b**	CF_3	**4f**	61/ 91[b]	48/1[b]
1a	CH_3	NH_2	**2c**	OCH_2CH_3	**4g**	89	25
1b	CH_2CH_3	NHC_6H_5	**2c**	OCH_2CH_3	**4h**	64/ 89[b]	1/4[b]
1c	CH_3	$OC(CH_3)_3$	**2c**	OCH_2CH_3	**4i**	85/ 94[b]	3/1[b]
1d	CH_3	OCH_3	**2d**	2-Thienyl	**4j**	91	5
1e	CH_3	NHC_6H_5	**2d**	2-Thienyl	**4k**	82	5
1f	CH_2CH_3	NH_2	**2d**	2-Thienyl	**4l**	61	115
1a	CH_3	NH_2	**2e**	2-Furyl	**4m**	93	78
1b	CH_2CH_3	NHC_6H_5	**2e**	2-Furyl	**4n**	87	14
1c	CH_3	$OC(CH_3)_3$	**2e**	2-Furyl	**4o**	82	18

[a] Yield of pure isolated products.
[b] Refers to solvent-free conditions.

Surprisingly, under the same reaction conditions, **4a** afforded 1-aminopyrrole derivative **8a**, likely via ring reopening to yield the intermediate **3a**, subsequent ring closure at *C*OCH_3 group, and final aromatization by water elimination (Scheme 3).

Therefore, we decided to explore the dehydration of **4a**,**c** by using Montmorillonite KSF[38] or Amberlyst 15 as heterogeneous catalysts in view of eco-friendly work-up procedures (Scheme 3). The results obtained with **4a** under these conditions were comparable with those observed in the reaction performed with Tf_2O leading to 1-aminopyrrole derivative **8a** with the trifluoroacetyl group in position 3. Similarly, the treatment of **4c** with Amberlyst 15 afforded a mixture of two 3-(trifluoroacetyl)-1*H*-pyrrole derivatives **8c** (52%) and **9c** (46%), while the reactions carried out with clay catalysis or by using Tf_2O led exclusively to methyl 1-amino-2,5-dimethyl-4-(2,2,2-trifluoroacetyl)-1*H*-pyrrole-3-carboxylate **9c** in almost comparable yields (65–71% respectively) (Scheme 3).

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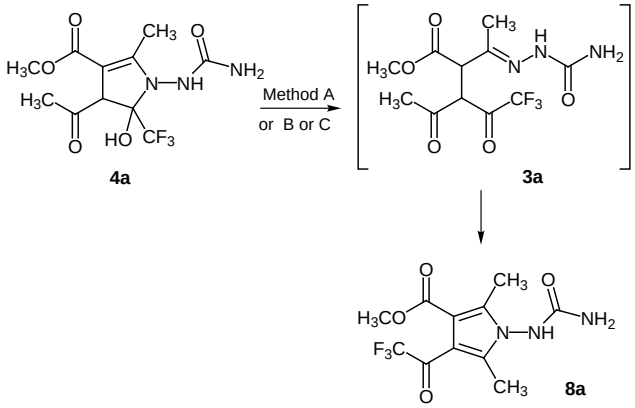
Table 2 Yield and Reaction Time of 2-(Trifluoromethyl)-1*H*-pyrrole Derivatives **7h**,**k**,**n**

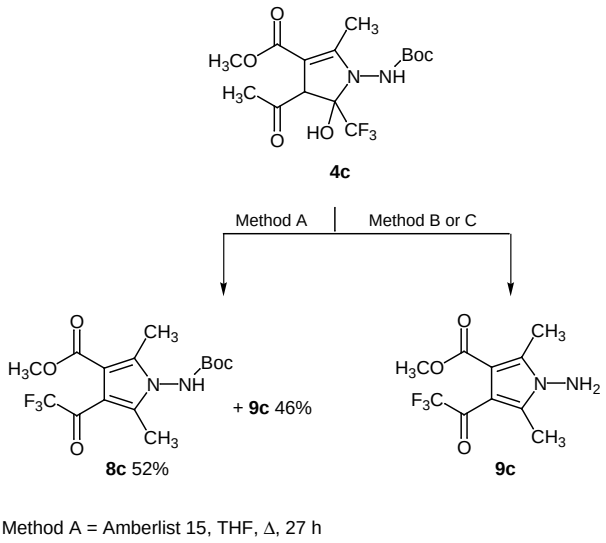
	R^1	R^2	R^3	Compound	Yield (%)[a]	Reaction Time (h)
4h	CH_2CH_3	NHC_6H_5	OCH_2CH_3	**7h**	86	2
4k	CH_3	NHC_6H_5	2-Thienyl	**7k**	72	2
4n	CH_2CH_3	NHC_6H_5	2-Furyl	**7n**	83	1

[a] Yield of pure isolated products.

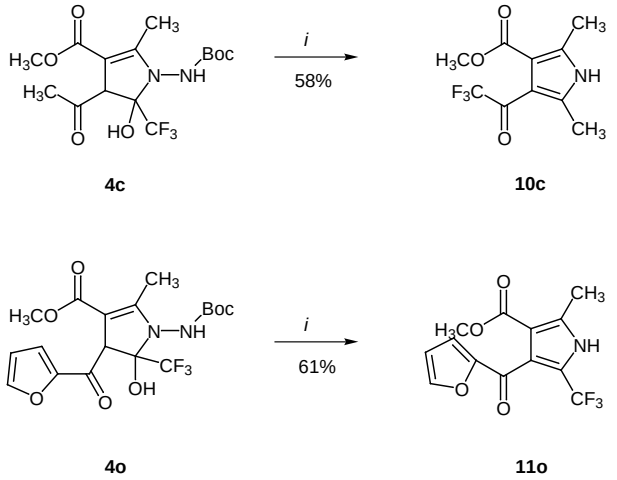
Under these latter conditions, both the aromatization process and cleavage of the Boc group of 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivative **4c** were observed.

In a previous paper, Baxter et al. reported an example of stable 1-NH-Boc protected 2-(trifluoromethyl)-2,3-dihydropyrrol-2-ol derivative in which the removal of the Boc-amino group occurred with simultaneous dehydration under acidic conditions.[39] This finding prompted us to apply the Baxter's methodology to compounds **4c**,**o** and to compare his results with ours. While the acidic cleavage of 1-amino Boc residue and subsequent reductive diazotization of **4o** gave 2-(trifluoromethyl)-1*H*-pyrrole derivative **11o** in agreement with Baxter, a different behavior was observed for **4c** that afforded 3-(trifluoroacetyl)-1*H*-pyrrole derivative **10c** (Scheme 4).





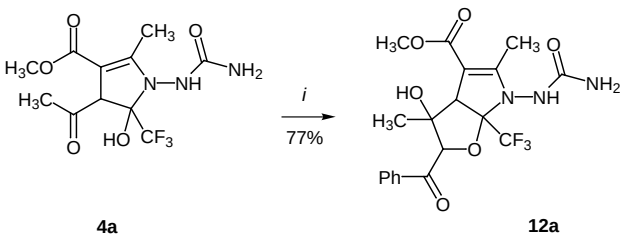
Scheme 3



Scheme 4 *i* = a) MeOH/concd HCl, 65 °C, 2–3 h; b) EtOH/aq HCl/$NaNO_2$, 10 °C to r. t., 1–3 h

All methods explored for the aromatization of **4a**,**c** produced 3-(trifluoroacetyl)-1*H*-pyrrole derivatives **8a**,**c**, **9c** and **10c** via ring reopening to intermediate **3**, subsequent ring closure at *C*OCH_3, and final aromatization. Any attempts for the aromatization of derivatives **4d**–**f** by using Tf_2O or Montmorillonite KSF or Amberlyst 15 failed. In fact, the presence of two trifluoromethyl groups in **4d**–**f** enhances their stability and does not permit conversion to the corresponding aromatic derivatives.

The unusual stability of 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol derivatives encouraged us to explore the synthesis of more complex fluorinated heterocyclic systems. The reaction between **4a** and 2-bromoacetophenone in the presence of K_2CO_3 provided fluorinated furo[2,3-*b*]pyrroline derivative **12a** as a diastereomeric mixture (diastereomeric ratio 75:25) (Scheme 5). Efforts to dehydrate compound **12a** by using acidic heterogeneous catalysts (KSF clay or Amberlyst 15) failed.



Scheme 5 *i* = $PhCOCH_2Br$, K_2CO_3, THF, Δ, 3 h

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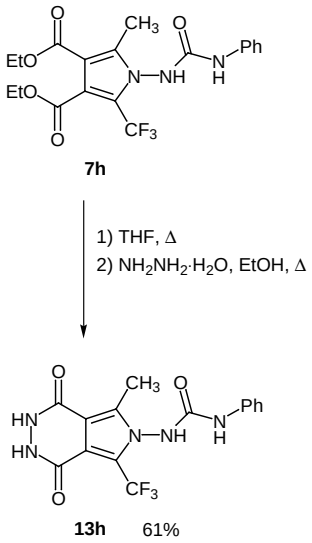
The reaction of pyrrole derivative **7h** with a stoichiometric amount of $NH_2NH_2 \cdot H_2O$ in THF–EtOH under reflux allowed the formation of fluorinated pyrrolo[3,4-*d*]pyridazindione derivative **13h**. The spectroscopic data of the solid formed during the reaction (40 hours) confirmed the structure of the expected fused heterocyclic system (Scheme 6).



Scheme 6

Considering the electronic effects of incorporation of the trifluoromethyl group and the increased lipophilicity of compounds bearing this functionality,[36,40,41] the reactions and the compounds reported here should be of biological and agrochemical interest. In addition, the simple, high-yielding and, in some cases, environmentally friendly methods for the preparation of fluorine-containing heterocycles described in this paper are worthy of industrial application.

1,2-Diaza-1,3-butadienes **1a**–**f** were synthesized as isomeric mixtures according to previously reported procedures.[42–44] 1,1,1-Trifluoroacetylacetone (**2a**), 1,1,1,5,5,5-hexafluoroacetylacetone (**2b**), ethyl 4,4,4-trifluoroacetoacetate (**2c**), 1-(2-thenoyl)-3,3,3-trifluoroacetone (**2d**) and 1-(2-furoyl)-3,3,3-trifluoroacetone (**2e**), Amberlyst 15 (Carlo Erba), Montmorillonite KSF (Lancaster), and other reagents and solvents were purchased and used without further purification with the exception of THF which was distilled from NaOH. Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were obtained as Nujol mulls. Mass spectra were determined at an ionizing voltage of 70 eV. ^{1}H NMR spectra were recorded at 200 MHz and 400 MHz in DMSO-d_6 or $CDCl_3$, and ^{13}C NMR at 50.32 MHz and 100.64 MHz in the same solvents. Chemical shifts (δ) are reported relative to TMS as internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; all the NH and OH exchanged with D_2O. Diastereomeric ratios (dr) of compounds **4a**–**o** and **12a** (unassigned configuration) were determined from ^{1}H NMR spectrum in DMSO-d_6; the NMR data of the major diastereomer are marked with asterisk. Precoated silica gel plates (0.25 mm) were employed for analytical TLC and silica gel (35–70 μ) for column chromatography.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivatives 4a–o and 2,5-Dimethyl-1*H*-pyrrole Derivatives 5a–c by Reaction of 1a–f with 2a–e; General Procedure

1,2-Diaza-1,3-butadienes **1a**–**f** (1.0 mmol) dissolved in THF (10 mL) were added to a stirred solution of **2a** (1.2 mmol, 184.9 mg), or **2b** (1.3 mmol, 270.4 mg), or **2c**–**e** (1.0 mmol) with a catalytic amount of CH_3ONa (0.05 equiv with respect to **2**) in THF (10 mL). The mixture was magnetically stirred until the disappearance of the reagents (monitored by TLC). The solvent was evaporated and products **4a**–**o** were obtained as diastereomeric mixtures by chromatographic purification (cyclohexane–EtOAc) and/or crystallization. After the filtration of **4a**–**c**, purification by flash chromatography of the liquor mothers provided **5a**–**c** as oils.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4a

Yield: 270 mg (83%); white powder (EtOAc–Et_2O).

dr = 58:42.

IR (nujol): 3530, 3388, 3200, 1727, 1695, 1673, 1646, 1592 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.12 (s, 6 H, 2 CH_3), 3.55 (s, 3 H, OCH_3), 3.81 and 3.91* (2 br s, 1 H, CH), 6.18* and 6.42 (2 br s, 2 H, NH_2), 7.69, 7.91 and 8.83 (3 br s, 2 H, NH and OH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 11.7 (q), 29.6 and 29.9 (2 q), 50.8 (q), 56.7 and 56.8 (2 d), 90.2 and 90.8 (2 s, $^2J_{CF}$ = 32.0 Hz), 95.9 (s), 123.1 (s, $^1J_{CF}$ = 284.3 Hz), 158.1 and 160.6 (2 s), 160.9 and 161.4 (2 s), 164.9 (s), 202.8 and 203.1 (2 s).

MS: *m*/*z* (%) = 325 (M^+, 10), 307 (1), 294 (2), 282 (37), 264 (100).

Anal. Calcd for $C_{11}H_{14}F_3N_3O_5$: C, 40.60; H, 4.34; N, 12.92. Found: C, 40.69; H, 4.32; N, 12.89.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4b

Yield: 332 mg (80%); white powder (EtOAc–petroleum ether).

dr = 68:32.

IR (nujol): 3422, 3318, 3216, 3100, 1732, 1725, 1704, 1689, 1654, 1598, 1550 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.15 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.17 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 3.72 and 3.96* (2 br s, 1 H, CH), 4.01-4.13 (m, 2 H, OCH_2CH_3), 6.93–7.02 (m, 1 H, Ar-H), 7.21–7.31 (m, 2 H, 2 Ar-H), 7.37–7.45 (m, 2 H, 2 Ar-H), 7.97, 7.99, 8.72 and 8.92 (4 br s, 3 H, 2 NH and OH).

MS: *m*/*z* (%) = 415 (M^+, 42), 397 (14), 372 (46), 354 (100).

Anal. Calcd for $C_{18}H_{20}F_3N_3O_5$: C, 52.03; H, 4.86; N, 10.12. Found: C, 52.06; H, 4.88; N, 10.09.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4c

Yield: 310 mg (81%); white powder (Et_2O–*n*-pentane).

dr = 50:50.

IR (nujol): 3320, 3259, 1751, 1714, 1689, 1632 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.38, 1.40 and 1.43 (3 s, 9 H, OBu^t), 2.13 (br s, 6 H, 2 CH_3), 3.55 (s, 3 H, OCH_3), 3.86 (br s, 1 H, CH), 7.86, 8.00 and 8.41 (3 br s, 1 H, NH), 8.78 and 9.42 (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 382 (M^+, 21), 364 (6), 351 (4), 339 (11), 326 (12), 283 (92), 265 (100).

Anal. Calcd for $C_{15}H_{21}F_3N_2O_6$: C, 47.10; H, 5.54; N, 7.33. Found: C, 47.05; H, 5.49; N, 7.36.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4d

Yield: 318 mg (84%); white powder (Et_2O).

dr = 50:50.

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IR (nujol): 3533, 3506, 3353, 3211, 3110, 1770, 1712, 1675, 1589 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.16 (s, 3 H, CH_3), 3.57 (s, 3 H, OCH_3), 4.54 (br s, 1 H, CH), 6.21 and 6.48 (2 br s, 2 H, NH_2), 7.89, 8.64 and 9.00 (3 br s, 2 H, NH and OH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 11.7 (q), 51.0 (q), 51.8 and 52.1 (2 d), 90.6 and 91.4 (2 s, $^2J_{CF}$ = 32.3 Hz), 93.7 (s), 115.1 (s, $^1J_{CF}$ = 290.4 Hz), 122.7 (s, $^1J_{CF}$ = 284.8 Hz), 157.8 and 160.6 (2 s), 161.8 and 162.9 (2 s), 164.1 (s), 187.3 (s, $^2J_{CF}$ = 35.0 Hz).

MS: *m*/*z* (%) = 379 (M^+, 17), 361 (4), 348 (6), 282 (18), 264 (100).

Anal. calcd. for $C_{11}H_{11}F_6N_3O_5$: C, 34.82; H, 2.92; N, 11.08. Found: C, 34.91; H, 2.93; N, 11.11.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4e
Yield: 361 mg (77%); white powder (EtOAc–Et_2O).

dr = 65:35.

IR (nujol): 3382, 3224, 3107, 1773, 1702, 1667, 1657, 1598, 1553 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 1.13 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.22 (s, 3 H, CH_3), 3.99–4.09 (m, 2 H, OCH_2CH_3), 4.51 and 4.61* (2 br s, 1 H, CH), 6.97 (t, 1 H, *J* = 7.5 Hz, Ar-H), 7.26 (t, 2 H, *J* = 7.4 Hz, 2 Ar-H), 7.44 (d, 2 H, *J* = 7.5 Hz, 2 Ar-H), 8.14 (s, 1 H, NH), 8.70 (s, 1 H, NH), 8.82 and 8.97* (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 469 (M^+, 40), 451 (7), 424 (11), 382 (2), 354 (100), 350 (72), 334 (81).

Anal. Calcd for $C_{18}H_{17}F_6N_3O_5$: C, 46.04; H, 3.65; N, 8.96. Found: C, 46.10; H, 3.62; N, 8.92.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4f
Yield: 240 mg (61%); white powder (EtOAc–petroleum ether).

dr = 56:44.

IR (nujol): 3260, 3220, 1774, 1734, 1675, 1635 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.13 and 2.16* (2 s, 3 H, CH_3), 3.55 and 3.57* (2 s, 3 H, $NHCOOCH_3$), 3.64 (s, 3 H, OCH_3), 4.41 and 4.52* (2 br s, 1 H, CH), 8.68 and 8.90* (2 br s, 1 H, NH), 9.42* and 9.72 (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 394 (M^+, 38), 363 (22), 335 (2), 319 (17), 297 (72), 279 (100).

Anal. Calcd for $C_{12}H_{12}F_6N_2O_6$: C, 36.54; H, 3.07; N, 7.11. Found: C, 36.59; H, 3.06; N, 7.13.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4g
Yield: 316 mg (89%); white powder (EtOAc–petroleum ether).

dr = 50:50.

IR (nujol): 3425, 3314, 3199, 1721, 1687, 1673, 1630, 1598 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 1.16 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.10 and 2.12 (2 s, 3 H, CH_3), 3.58 (s, 3 H, OCH_3), 3.85 (br s, 1 H, CH), 4.05–4.15 (m, 2 H, OCH_2CH_3), 6.19 and 6.54 (2 br s, 2 H, NH_2), 7.45, 7.88 and 8.94 (3 br s, 2 H, NH and OH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 11.5 and 11.6 (2 q), 14.0 (q), 50.7 (q), 51.9 and 52.2 (2 d), 60.6 and 60.9 (2 t), 90.1 (s, $^2J_{CF}$ = 32.6 Hz), 95.3 (s), 122.8 (s, $^1J_{CF}$ = 284.1 Hz), 157.8 and 160.1 (2 s), 161.2 and 164.5 (2 s), 164.6 (s), 167.5 (s).

MS: *m*/*z* (%) = 355 (M^+, 59), 337 (2), 324 (10), 312 (25), 281 (100), 264 (94).

Anal. Calcd for $C_{12}H_{16}F_3N_3O_6$: C, 40.55; H, 4.54; N, 11.83. Found: C, 40.67; H, 4.53; N, 11.81.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4h
Yield: 285 mg (64%); white powder (EtOAc–petroleum ether).

dr = 64:36.

IR (nujol): 3488, 3275, 3207, 3143, 1733, 1723, 1695, 1680, 1625, 1602, 1562 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.14–1.22 (m, 6 H, 2 OCH_2CH_3), 2.17 (s, 3 H, CH_3), 3.90 and 3.93* (2 s, 1 H, CH), 4.04–4.15 (m, 4 H, 2 OCH_2CH_3), 6.93–7.00 (m, 1 H, Ar-H), 7.22-7.28 (m, 2 H, 2 Ar-H), 7.44-7.47 (m, 2 H, 2 Ar-H), 7.79 (s, 1 H, NH), 7.97 (s, 1 H, NH), 8.95 and 9.02* (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 445 (M^+, 62), 427 (3), 400 (8), 372 (3), 354 (40), 326 (100).

Anal. Calcd for $C_{19}H_{22}F_3N_3O_6$: C, 51.22; H, 4.98; N, 9.44. Found: C, 51.30; H, 5.00; N, 9.40.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4i
Yield: 350 mg (85%); white powder (Et_2O–*n*-pentane).

dr = 68:32.

IR (nujol): 3308, 3215, 1745, 1716, 1701, 1658, 1522 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 1.14 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 1.40 and 1.42 (2 s, 9 H, OBu^t), 2.10 (br s, 3 H, CH_3), 3.58 (s, 3 H, OCH_3), 3.88 (br s, 1 H, CH), 4.01–4.11 (m, 2 H, OCH_2CH_3), 7.88 and 8.05* (2 s, 1 H, NH), 9.02* and 9.36 (2 s, 1 H, OH).

MS: *m*/*z* (%) = 412 (M^+, 24), 381 (9), 367 (5), 356 (30), 339 (16), 312 (54), 281 (100).

Anal. Calcd for $C_{16}H_{23}F_3N_2O_7$: C, 46.59; H, 5.62; N, 6.80. Found: C, 46.66; H, 5.64; N, 6.78.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4j
Yield: 371 mg (91%); white powder (EtOAc–petroleum ether–*n*-pentane).

dr = 66:34.

IR (nujol): 3492, 3302, 1740, 1716, 1670, 1653, 1646, 1552, 1538 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.16 (br s, 3 H, CH_3), 3.43 and 3.46 (2 s, 3 H, $NHCOOCH_3$), 3.65 (s, 3 H, OCH_3), 4.53 and 4.90* (2 br s, 1 H, CH), 7.20–7.27 (m, 1 H, Ar-H), 7.84–8.03 (m, 3 H, 2 Ar-H and NH), 8.64 and 8.80* (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 408 (M^+, 8), 390 (4), 377 (2), 297 (87), 279 (100).

Anal. Calcd for $C_{15}H_{15}F_3N_2O_6S$: C, 44.11; H, 3.70; N, 6.86. Found: C, 44.21; H, 3.69; N, 6.89.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4k
Yield: 384 mg (82%); white powder (CH_2Cl_2–petroleum ether).

dr = 69:31.

IR (nujol): 3404, 3337, 3226, 3102, 1707, 1682, 1662, 1599, 1547 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.23 (s, 3 H, CH_3), 3.48 (s, 3 H, OCH_3), 4.84 and 5.02* (2 br s, 1 H, CH), 6.93–7.06 (m, 1 H, Ar-H), 7.22–7.35 (m, 3 H, 3 Ar-H), 7.43–7.53 (m, 2 H, 2 Ar-H), 7.84 (br s, 1 H, NH), 7.99–8.12 (m, 3 H, 2 Ar-H and NH), 8.99 and 9.10* (2 br s, 1 H, OH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 12.0 (q), 50.7 (q), 52.1 (br d), 91.1 (s, $^2J_{CF}$ = 30.8 Hz), 97.1 (s), 118.7 and 119.0 (2 d), 122.3 and 122.8 (2 d), 123.2 (s, $^1J_{CF}$ = 283.7 Hz), 128.8 (2 d), 133.8 and 134.4 (2 d), 135.6 and 135.7 (2 d), 138.9 and 139.5 (2 s), 144.0 and 144.4 (2 s), 154.4 and 156.3 (2 s), 160.3 and 161.4 (2 s), 164.7 (s), 187.8 and 188.5 (2 s).

MS: *m*/*z* (%) = 469 (M^+, 18), 451 (5), 358 (36), 350 (7), 340 (100).

Anal. Calcd for $C_{20}H_{18}F_3N_3O_5S$: C, 51.16; H, 3.87; N, 8.96. Found: C, 51.22; H, 3.85; N, 8.92.

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2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4l
Yield: 248 mg (61%); white powder (THF–petroleum ether).

dr = 55:45.

IR (nujol): 3493, 3420, 3347, 3306, 3241, 1696, 1685, 1650, 1590 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 0.91 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.17 (s, 3 H, CH_3), 3.85–3.95 (m, 2 H, OCH_2CH_3), 4.82 and 4.95* (2 br s, 1 H, CH), 6.21 (br s, 2 H, NH_2), 7.23–7.27 (m, 1 H, Ar-H), 7.66 (br s, 1 H, NH), 7.98–8.06 (m, 2 H, 2 Ar-H), 8.68* and 8.76 (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 407 (M^+, 12), 389 (4), 346 (4), 296 (78), 278 (100).

Anal. Calcd for $C_{15}H_{16}F_3N_3O_5S$: C, 44.22; H, 3.96; N, 10.32. Found: C, 44.32; H, 3.94; N, 10.35.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4m
Yield: 350 mg (93%); white powder (THF).

dr = 50:50.

IR (nujol): 3498, 3460, 3345, 3294, 3238, 3170, 1705, 1674, 1655, 1646, 1593, 1570 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.16 (s, 3 H, CH_3), 3.46 (s, 3 H, OCH_3), 4.72 and 4.82 (2 br s, 1H, CH), 6.19 (br s, 2 H, NH_2), 6.74 (br s, 1 H, Ar-H), 7.47 and 7.53 (2 br s, 1 H, Ar-H), 7.68 (br s, 1 H, NH), 8.03 (br s, 1 H, Ar-H), 8.62 and 8.88 (2 br s, 1 H, OH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 11.8 (q), 50.7 (q), 51.6 (br d), 90.9 (s, $^2J_{CF}$ = 30.2 Hz), 96.2 (s), 112.8 (d), 119.2 (d), 121.7 (s, $^1J_{CF}$ = 283.7 Hz), 148.2 (d), 148.6 (s), 152.2 and 152.4 (2 s), 160.5 and 162.0 (2 s), 164.5 (s), 182.8 (s).

MS: *m*/*z* (%) = 377 (M^+, 18), 359 (9), 327 (7), 282 (65), 264 (100).

Anal. Calcd for $C_{14}H_{14}F_3N_3O_6$: C, 44.55; H, 3.74; N, 11.14. Found: C, 44.64; H, 3.73; N, 11.17.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4n
Yield: 406 mg (87%); white powder (CH_2Cl_2–petroleum ether).

dr = 64:36.

IR (nujol): 3332, 3143, 1683, 1668, 1651, 1601, 1559 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.92 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 2.20 (s, 3 H, CH_3), 3.86–3.94 (m, 2 H, OCH_2CH_3), 4.74 and 4.90* (2 br s, 1 H, CH), 6.73 (br s, 1 H, Ar-H), 6.92–6.97 (m, 1 H, Ar-H), 7.22–7.27 (m, 2 H, 2 Ar-H), 7.43–7.49 (m, 3 H, 3 Ar-H), 7.63 (br s, 1 H, NH), 7.77 (br s, 1 H, NH), 8.03 (br s, 1 H, Ar-H), 8.98* and 9.12 (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 467 (M^+, 18), 449 (9), 422 (2), 372 (28), 354 (100).

Anal. Calcd for $C_{21}H_{20}F_3N_3O_6$: C, 53.95; H, 4.31; N, 8.99. Found: C, 53.89; H, 4.30; N, 8.97.

2-(Trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol Derivative 4o
Yield: 356 mg (82%); foam.

dr = 65:35.

IR (nujol): 3310, 3148, 1749, 1715, 1684, 1653, 1568 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.40* and 1.43 (2 s, 9 H, OBu^t), 2.15* and 2.19 (2 s, 3 H, CH_3), 3.46 (s, 3 H, OCH_3), 4.59 and 4.75* (2 br s, 1 H, CH), 6.73 (br s, 1 H, Ar-H), 7.45 (m, 1 H, Ar-H), 7.63* and 7.71 (2 br s, 1 H, NH), 8.01 (br s, 1 H, Ar-H), 8.18 and 8.52* (2 br s, 1 H, OH).

MS: *m*/*z* (%) = 434 (M^+, 17), 416 (1), 403 (2), 378 (11), 360 (8), 334 (30), 316 (4), 283 (65), 265 (96), 239 (100).

Anal. Calcd for $C_{18}H_{21}F_3N_2O_7$: C, 49.77; H, 4.87; N, 6.45. Found: C, 49.75; H, 4.90; N, 6.43.

Methyl 1-[(Aminocarbonyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (5a)
Yield: 8 mg (4%); oil.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.01 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 6.07 (s, 1 H, CH), 6.19 (br s, 2 H, NH_2), 9.09 (1 H, NH).

MS: *m*/*z* (%) = 211 (M^+, 44), 195 (4), 180 (11), 168 (81), 152 (100).

Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.20; H, 6.20; N, 19.78.

Methyl 1-[(Anilinocarbonyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (5b)
Yield: 12 mg (4%); oil.

^1H NMR (200 MHz, DMSO-d_6): δ = 1.23 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 2.04 (s, 3 H, CH_3), 2.31 (s, 3 H, $COCH_3$), 4.14 (q, 2 H, *J* = 7.1 Hz, OCH_2CH_3), 6.10 (s, 1 H, CH), 6.97 (t, 1 H, *J* = 7.7 Hz, Ar-H), 7.26 (t, 2 H, *J* = 7.8 Hz, 2 Ar-H), 7.45 (d, 2 H, *J* = 7.6 Hz, 2 Ar-H), 9.28 (br s, 1 H, NH), 9.38 (s, 1 H, NH).

Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.76; H, 6.36; N, 13.95. Found: C, 63.80; H, 6.33; N, 13.94.

Methyl 1-[(*tert*-Butoxycarbonyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (5c)
Yield: 16 mg (6%); oil.

IR (nujol): 3280, 1709, 1681, 1595 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 1.36 (s, 9 H, OBu^t), 2.00 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 6.10 (s, 1 H, CH), 10.21 (s, 1 H, NH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 10.2 (q), 10.5 (q), 27.8 (q), 50.4 (q), 80.7 (s), 104.3 (d), 108.0 (s), 128.3 (s), 135.4 (s), 154.2 (s), 164.6 (s).

MS: *m*/*z* (%) = 268 (M^+, 60), 253 (7), 237 (14), 211 (100).

Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.18; H, 7.52; N, 10.44. Found: C, 58.25; H, 7.55; N, 10.48

2-(Trifluoromethyl)-1*H*-pyrrole Derivatives 7h,k,n; General Procedure
To stirred solutions of 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ols **4h**,**k**,**n** (1 mmol) in anhyd CH_2Cl_2 (30 mL) were added anhyd pyridine (1.1 mmol) and Tf_2O (1.05 mmol). The resulted solutions were magnetically stirred at r.t. for 1–2 h (Table 2). The crude reaction mixtures were washed with 10% HCl (3 × 10 mL), and brine, and dried (Na_2SO_4). After removal of the solvent, compounds **7h**,**k** were obtained by crystallization from appropriate solvents (see below), while **7n** was obtained after chromatographic purification (cyclohexane–EtOAc) of the crude reaction mixture.

Diethyl 1-[(Anilinocarbonyl)amino]-2-methyl-5-(trifluoromethyl)-1*H*-pyrrole-3,4-dicarboxylate (7h)
Yield: 367 mg (86%); white powder.

Mp 163–165 °C (Et_2O–*n*-pentane).

IR (nujol): 3326, 3183, 1740, 1719, 1661, 1599, 1564, 1556 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.22–1.28 (m, 6 H, 2 OCH_2CH_3), 2.35 (s, 3 H, CH_3), 4.17–4.28 (m, 4 H, 2 OCH_2CH_3), 7.02 (t, 1 H, *J* = 7.8 Hz, Ar-H), 7.29 (t, 2 H, *J* = 7.8 Hz, 2 Ar-H), 7.45 (d, 2 H, *J* = 7.8 Hz, 2 Ar-H), 9.55 (br s, 1 H, NH), 9.93 (s, 1 H, NH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 10.1 (q), 13.8 (q), 14.0 (q), 60.2 (t), 61.4 (t), 108.0 (s), 117.3 (s, $^2J_{CF}$ = 37.3 Hz), 118.4 (d), 118.9 (s), 119.8 (s, $^1J_{CF}$ = 267.3 Hz), 122.8 (d), 128.8 (d), 139.0 (s), 141.7 (s), 153.3 (s), 162.3 (s), 163.8 (s).

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MS: *m*/*z* (%) = 427 (M^+, 35), 381 (100), 354 (11), 334 (5), 308 (5), 262 (76).

Anal. Calcd for $C_{19}H_{20}F_3N_3O_5$: C, 53.38; H, 4.72; N, 9.84. Found: C, 53.42; H, 4.74; N, 9.88.

Methyl 1-[(Anilinocarbonyl)amino]-2-methyl-4-(2-thenoyl)-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (7k)
Yield: 325 mg (72%); white powder.

Mp 142–145 °C (dec.) (EtOAc–*n*-pentane).

IR (nujol): 3310, 3266, 3143, 1721, 1693, 1646, 1606, 1574, 1549 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.42 (s, 3 H, CH_3), 3.55 (s, 3 H, OCH_3), 7.03 (t, 1 H, *J* = 7.6 Hz, Ar-H), 7.22 (t, 1 H, *J* = 4.4 Hz, Ar-H), 7.30 (t, 2 H, *J* = 7.6 Hz, 2 Ar-H), 7.36–7.41 (m, 1 H, Ar-H), 7.48 (d, 2 H, *J* = 7.7 Hz, 2 Ar-H), 8.08 (d, 1 H, *J* = 4.8 Hz, Ar-H), 9.59 (br s, 1 H, NH), 9.98 (s, 1 H, NH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 10.3 (q), 51.3 (q), 108.8 (s), 117.7 (s, $^2J_{CF}$ = 37.8 Hz), 118.9 (d), 119.8 (s, $^1J_{CF}$ = 269.8 Hz), 122.8 (d), 123.6 (s), 128.7 (d), 128.8 (d), 134.4 (d), 135.7 (d), 138.9 (s), 141.9 (s), 144.4 (s), 153.3 (s), 162.8 (s), 183.0 (s).

MS: *m*/*z* (%) = 451 (M^+, 25), 419 (31), 367 (15), 332 (13), 316 (4), 300 (100).

Anal. Calcd for $C_{20}H_{16}F_3N_3O_4S$: C, 53.21; H, 3.57; N, 9.31. Found: C, 53.30; H, 3.58; N, 9.27.

Methyl 1-[(Anilinocarbonyl)amino]-2-methyl-5-(trifluoromethyl)-1*H*-pyrrole-carboxylate (7n)
Yield: 372 mg (83%); foam.

IR (KBr): 3321, 3275, 1713, 1671, 1601, 1550 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 2.38 (s, 3 H, CH_3), 3.98–4.05 (m, 2 H, OCH_2CH_3), 6.48 (dd, 1 H, *J* = 3.6, 1.2 Hz, Ar-H), 6.97–7.02 (m, 2 H, 2 Ar-H), 7.20 (t, 2 H, *J* = 8.0 Hz, 2 Ar-H), 7.29 (d, 2 H, *J* = 8.0 Hz, 2 Ar-H), 7.55 (br s, 1 H, Ar-H), 8.00 (s, 1 H, NH), 8.90 (s, 1 H, NH).

^{13}C NMR (100.64 MHz, $CDCl_3$): δ = 10.8 (q), 14.4 (q), 61.2 (t), 110.5 (s), 113.4 (d), 113.6 (s), 119.7 (s, $^2J_{CF}$ = 38.8 Hz), 120.2 (s, $^1J_{CF}$ = 268.1 Hz), 121.2 (d), 123.4 (d), 125.0 (d), 129.6 (d), 137.7 (s), 142.7 (s), 148.7 (d), 153.4 (s), 154.5 (s), 163.7 (s), 180.5 (s).

MS: *m*/*z* (%) = 449 (M^+, 27), 403 (33), 381 (12), 354 (4), 330 (19), 284 (100).

Anal. Calcd for $C_{21}H_{18}F_3N_3O_5$: C, 56.11; H, 4.04; N, 9.35. Found: C, 56.29; H, 4.05; N, 9.33.

3-(2,2,2-Trifluoroacetyl)-1*H*-pyrrole Derivatives 8a,c and 9c; Method A
To a solution of **4a** (or **4c**) (1 mmol) in THF (40 mL), Amberlyst 15 (215 mg) was added and the mixture was heated under reflux for 10 h (or 27 h). The resin was filtered off and washed with THF (4 × 15 mL). The filtered extract was evaporated under reduced pressure and the residue was purified by crystallization to furnish **8a** or by flash chromatography (cyclohexane–EtOAc, 9:1) to provide **8c** and **9c**.

Method B
To a solution of **4a** (or **4c**) (1 mmol) in anhyd toluene (20 mL), Montmorillonite KSF (600 mg) activated for 3 h at 100 °C was added and the suspension was refluxed for 11 h (or 5 h). The solution was filtered and the clay washed with THF (3 × 20 mL). The filtrate was dried (Na_2SO_4) and the solvents were removed in vacuo. The crude product **8a** (or **9c**) was purified by column chromatography (cyclohexane–EtOAc).

Method C
See general procedure for the synthesis of **7h**,**k**,**n**.

Methyl 1-[(Aminocarbonyl)amino]-2,5-dimethyl-4-(2,2,2-trifluoroacetyl)-1*H*-pyrrole-3-carboxylate (8a)
Method A: Yield: 288 mg (94%); white powder; mp 194–196 °C (EtOAc–Et_2O).

Method B: Yield: 187 mg (61%).

Method C: Yield: 252 mg (82%).

IR (nujol): 3435, 3327, 3269, 3206, 1700, 1679, 1580, 1550 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.11 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 6.55 (s, 2 H, NH_2), 9.41 (s, 1 H, NH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 9.6 (q), 9.8 (q), 51.2 (q), 108.4 (s), 111.9 (s), 115.6 (s, $^1J_{CF}$ = 289.7 Hz), 137.7 (s), 138.4 (s), 156.4 (s), 163.7 (s), 181.3 (s, $^2J_{CF}$ = 34.6 Hz).

MS: *m*/*z* (%) = 307 (M^+, 87), 275 (100), 248 (81), 238 (80).

Anal. Calcd for $C_{11}H_{12}F_3N_3O_4$: C, 42.99; H, 3.94; N, 13.68. Found: C, 43.01; H, 3.93; N, 13.72.

Methyl 1-[(tert-Butoxycarbonyl)amino]-2,5-dimethyl-4-(2,2,2-trifluoroacetyl)-1*H*-pyrrole-3-carboxylate (8c)
Method A: Yield: 189 mg (52%); white powder; mp 118–120 °C (Et_2O–petroleum ether).

IR (nujol): 3234, 1748, 1692, 1584, 1546 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 1.47 (s, 9 H, Bu^t), 2.11 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.71 (s, 3 H, OCH_3), 10.68 (s, 1 H, NH).

^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 9.3 (q), 9.6 (q), 27.7 (q), 51.2 (q), 81.8 (s), 108.8 (s), 112.4 (s), 115.7 (s, $^1J_{CF}$ = 291.2 Hz), 137.0 (s), 137.2 (s), 154.0 (s), 163.6 (s), 181.6 (s, $^2J_{CF}$ = 35.3 Hz).

MS: *m*/*z* (%) = 364 (M^+, 48), 333 (6), 308 (60), 295 (4), 291 (5), 276 (100).

Anal. Calcd for $C_{15}H_{19}F_3N_2O_5$: C, 49.43; H, 5.26; N, 7.69. Found: C, 49.51; H, 5.25; N, 7.68.

Methyl 1-Amino-2,5-dimethyl-4-(2,2,2-trifluoroacetyl)-1*H*-pyrrole-3-carboxylate (9c)
Method A: Yield: 121 mg (46%); white powder; mp 132–134 °C (Et_2O–petroleum ether).

Method B: Yield: 172 mg (65%).

Method C: Yield: 187 mg (71%).

IR (nujol): 3359, 3296, 3233, 1685, 1542 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 5.83 (s, 2 H, NH_2).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 10.1 (q), 10.3 (q), 51.0 (q), 107.8 (s), 111.4 (s), 115.9 (s, $^1J_{CF}$ = 290.9 Hz), 137.6 (s), 138.3 (s), 164.0 (s), 181.2 (s, $^2J_{CF}$ = 35.2 Hz).

MS: *m*/*z* (%) = 264 (M^+, 91), 249 (3), 232 (100), 204 (12), 195 (94).

Anal. Calcd for $C_{10}H_{11}F_3N_2O_3$: C, 45.44; H, 4.20; N, 10.61. Found: C, 45.61; H, 4.18; N, 10.58.

Synthesis of Derivatives 10c and 11o (According to Baxter[39])
Concd HCl (1 mL) was added to a refluxing solution of 2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrol-2-ol **4c** or **4o** (1.1 mmol) in MeOH (16 mL). After 2–3 h, EtOH (7 mL) was added and the solution was cooled quickly to 10 °C. HCl (5 M, 7 mL) was added followed by $NaNO_2$ (0.167 g) in H_2O (2 mL). After 1–3 h at r.t., H_2O was added and the alcohols were evaporated. The aqueous solution was extracted with EtOAc. The organic extract was washed with sat. aq $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude product **10c** or **11o** was purified by column chromatog-

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raphy (cyclohexane–EtOAc) and crystallized from the appropriate solvents.

Methyl 2,5-Dimethyl-4-(2,2,2-trifluoroacetyl)-1*H*-pyrrole-3-carboxylate (10c)
Yield: 145 mg (58%); white powder.

Mp 142–143 °C (Et_2O).

IR (nujol): 3304, 1698, 1672, 1546 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.22 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.66 (s, 3 H, OCH_3), 12.1 (s, 1 H, NH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 11.5 (q), 11.7 (q), 50.8 (q), 110.7 (s), 114.2 (s), 115.9 (s, $^1J_{CF}$ = 290.7 Hz), 135.2 (s), 136.5 (s), 164.2 (s), 181.0 (s, $^2J_{CF}$ = 34.7 Hz).

MS: *m*/*z* (%) = 249 (M^+, 100), 216 (64), 217 (93), 189 (61), 180 (83).

Anal. Calcd for $C_{10}H_{10}F_3NO_3$: C, 48.18; H, 4.05; N, 5.62. Found: C, 48.30; H, 4.07; N, 5.61.

Methyl 4-(2-Furoyl)-2-methyl-5-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (11o)
Yield: 184 mg (61%); white powder.

Mp 121–123 °C (Et_2O–*n*-pentane).

IR (nujol): 3263, 3140, 1714, 1641, 1584, 1566, 1533 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.48 (s, 3 H, CH_3), 3.50 (s, 3 H, OCH_3), 6.68 (dd, 1 H, *J* = 3.6, 2.0 Hz, Ar-H), 7.09 (d, 1 H, *J* = 3.6 Hz, Ar-H), 7.97 (br s, 1 H, Ar-H), 12.10 (br s, 1 H, NH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 12.4 (q), 51.0 (q), 111.5 (s), 112.6 (d), 115.9 (s, $^2J_{CF}$ = 39.0 Hz), 119.2 (d), 120.6 (s, $^1J_{CF}$ = 268.0 Hz), 124.3 (s), 137.9 (s), 148.0 (d), 152.9 (s), 163.4 (s), 178.2 (s).

MS: *m*/*z* (%) = 301 (M^+, 83), 269 (100), 241 (82), 234 (54).

Anal. Calcd for $C_{13}H_{10}F_3NO_4$: C, 51.82; H, 3.35; N, 4.65. Found: C, 51.89; H, 3.32; N, 4.63.

Methyl 2-Benzoyl-3-hydroxy-3,5-dimethyl-6-[(aminocarbonyl)amino]-6a-(trifluoromethyl)-3,3a,6,6a-tetrahydro-2*H*-furo[2,3-*b*]pyrrole-4-carboxylate (12a)
To a stirred solution of **4a** (1 mmol) in THF (20 mL), K_2CO_3 (2 mmol) and 2-bromoacetophenone (1.01 mmol) were added. The reaction mixture was stirred at r.t. for 5 min and then was heated under reflux for 3 h. After removal of the solvent under reduced pressure the crude reaction mixture was extracted with EtOAc (80 mL), washed with brine, dried (Na_2SO_4), and evaporated. Silica gel column chromatography (cyclohexane–EtOAc) on the residue afforded **12a**, which was crystallized from EtOAc–Et_2O as a diastereomeric mixture.

Yield: 341 mg (77%); white powder (EtOAc–Et_2O).

dr = 75:25.

IR (nujol): 3456, 3332, 3279, 3206, 1696, 1676, 1623, 1598, 1518 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.22 (br s, 3 H, CH_3), 2.09* and 2.14 (2 s, 3 H, CH_3), 3.58 and 3.59* (2 s, 1 H, CH), 3.63* and 3.65 (2 s, 3 H, OCH_3), 4.61 and 5.07* (2 s, 1 H, CH), 5.52* and 5.61 (2 s, 1 H, OH), 6.06 (br s, 2 H, NH_2), 7.39–7.62 (m, 3 H, 3 Ar-H), 7.92–8.02 (m, 2 H, 2 Ar-H), 8.08 and 8.47* (2 s, 1 H, NH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 11.8 and 12.1 (2 q), 20.3 and 20.5 (2 q), 50.4 and 50.5 (2 q), 58.8 and 58.9 (2 d), 82.8 and 82.9 (2 s), 89.1 and 90.1 (2 d), 94.0 (s), 98.1 (s, $^2J_{CF}$ = 39.4 Hz), 122.3 and 122.6 (2 s, $^1J_{CF}$ = 284.2 and 283.2 Hz), 127.9 and 128.0 (2 d), 129.4 and 129.5 (2 d), 132.9 (d), 137.1 and 137.2 (2 s), 158.5 (s), 162.2 (s), 165.2 and 165.4 (2 s), 196.9 (s).

MS: *m*/*z* (%) = 443 (M^+, 25), 425 (6), 412 (100), 399 (6), 384 (3), 322 (6).

Anal. Calcd for $C_{19}H_{20}F_3N_3O_6$: C, 51.45; H, 4.55; N, 9.48. Found: C, 51.61; H, 4.57; N, 9.45.

***N*-(5-Methyl-1,4-dioxo-7-(trifluoromethyl)-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-*d*]pyridazin-6-yl)-*N*'-phenylurea (13h)**
To compound **7h** (1 mmol) refluxed in THF (20 mL), a stoichiometric amount of hydrazine monohydrate (1 mmol), dissolved in EtOH (2 mL), was added dropwise within 0.5 h. The reaction mixture was refluxed until the disappeareance of the pyrrole derivative (monitored by TLC). The pale yellow solid formed during the reaction was filtered off after completion (40 h), and recrystallized from THF–EtOH (9:1) yielding pure **13h**.

Yield: 224 mg (61%); pale yellow powder.

Mp >300 °C (dec.) (THF–EtOH).

IR (nujol): 3272, 3198, 3143, 1661, 1602, 1569 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.48 (s, 3 H, CH_3), 7.02 (t, 1 H, *J* = 7.7 Hz, Ar-H), 7.29 (t, 2 H, *J* = 7.7 Hz, 2 Ar-H), 7.46 (d, 2 H, *J* = 7.6 Hz, 2 Ar-H), 9.60 (br s, 1 H, NH), 10.04 (s, 1 H, NH), 11.08 (s, 2 H, NH).

^{13}C NMR (100.64 MHz, DMSO-d_6): δ = 9.6 (q), 110.8 (s), 114.0 (s), 114.4 (s, $^2J_{CF}$ = 38.3 Hz), 118.5 (d), 120.2 (s, $^1J_{CF}$ = 267.4 Hz), 122.1 (d), 128.7 (d), 135.5 (s), 139.6 (s), 151.8 (s), 154.2 (s), 155.2 (s).

MS: *m*/*z* (%) = 367 (M^+, 42), 248 (64), 232 (100).

Anal. Calcd for $C_{15}H_{12}F_3N_5O_3$: C, 49.03; H, 3.29; N, 19.07. Found: C, 49.12; H, 3.28; N, 19.12.

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