Improved One-Pot Synthesis of 1-Aryl-3-trifluoroacetyl-1*H*-pyrroles under Swern Oxidation

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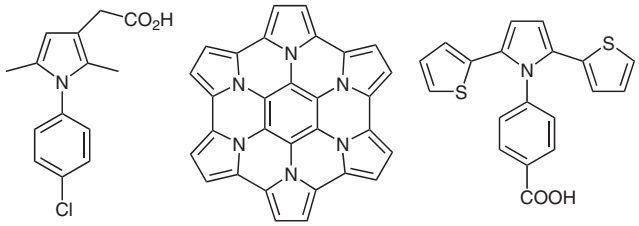
Abstract: This study describes an improved one-pot, four-step synthesis of a new series of 1-aryl-3-trifluoroacetyl pyrroles from the reaction of 3-trifluoroacetyl-4,5-dihydrofuran with arylamines, giving 1,1,1-trifluoro-3-(2-hydroxyethyl)-4-arylamino-3-buten-2-ones, which were directly submitted to Swern oxidation to furnish 1,1,1-trifluoro-3-(2-ethanal)-4-arylamino-3-buten-2-ones. Subsequent intramolecular cyclization of the corresponding enaminoaldehydes followed by aromatization rendered the title compounds in a 30 to 56% overall yield.

Key words: trifloroacetyl groups, pyrroles, Swern oxidation, arylamines, trifluoromethyl

Pyrroles are an important class of organic compounds that are found in many natural products and bioactive molecules.[1] They have also been widely used in materials science and molecular recognition studies.[2] In addition, pyrrole derivatives are important intermediates in the synthesis of not only drugs, pigments, and pharmaceuticals, but also for the development of functional organic materials.[3]

In turn, 1-aryl substituted pyrroles have received considerable attention in areas such as: (i) chemistry, because of the synthetic challenge of obtaining them[4] as well as their use as starting material for the synthesis of other, more complex molecules; [5] (ii) pharmaceutical sciences, due to their biological activities such as, for example, Cloripac,[6] which is a nonsteroidal anti-inflammatory; and (iii) material sciences, by their use as biosensors,[7] such as poly[2,5-di-(2-thienyl)-1*H*-pyrrole-1-(*p*-benzoic acid)] (PDPB) and as semiconductors,[8] such as hexa(*N*-pyrrolil)benzene (Figure 1).



Cloripac hexa(*N*-pyrrolyl)benzene PDPB

Figure 1 Examples of 1-aryl-substituted pyrroles

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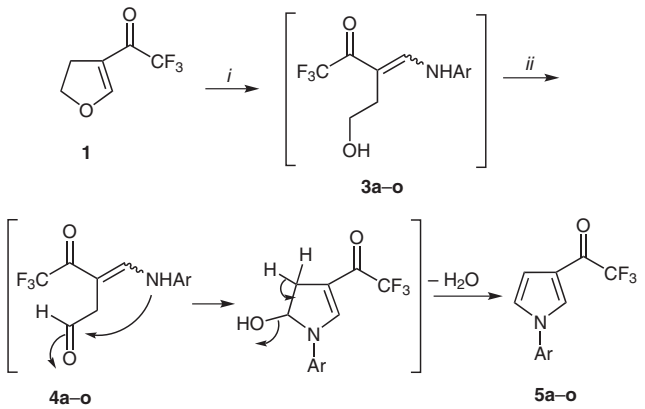
In view of their importance, several strategies have been developed for the synthesis of 1-aryl-substituted pyrroles.[9] Classical procedures for their preparation include the cyclocondensation of primary amines with 1,4-dicarbonyl compounds (Paal–Knorr reaction)[10] or 2,5-dimethoxy tetrahydrofuran (Clauson–Kass),[11] and cyclocondensation of β-enaminones and α-halocetonas (Hantzsch reaction).[12] There are also a variety of methods available for obtaining these compounds such as the cross-coupling reaction mediated by transition metals,[13] oxidative-coupling reaction mediated by AgOAc,[14] intramolecular Wittig reaction,[15] and direct arylation of pyrroles.[16]

Organic fluorine compounds have attracted much attention in the materials and pharmaceutical sciences, because the introduction of fluorine into an organic compound can cause remarkable changes in the physical, chemical, and biological properties.[17] The introduction of fluorine or fluoroalkyl substituents into biologically relevant compounds has become an important tool in the drug discovery process.[18] Special attention is paid to trifluoromethyl-containing compounds due to the unique properties of the trifluoromethyl group, such as high electronegativity, electron density, steric hindrance, and hydrophobic character, which can profoundly affect the pharmacokinetic profiles of potential drugs.[19]

One of the best methods to introduce a trifluoromethyl group into a molecule is based in the trifluoromethylated building block approach. These building blocks are easily obtained from the trifluoroacetylation of enol ethers or acetals, to give, in one-step and good yield, 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones,[20] which proved to be useful precursors for the synthesis of series of heterocycles[21] as well as other aliphatic compounds.[22]

In a previous study, a new, one-pot, four-step synthesis of a large series of 1-substituted 3-trifluoroacetyl pyrroles, was reported.[23] These compounds were obtained from the reaction of 3-trifluoroacetyl-4,5-dihydrofuran and primary amines, followed by in situ oxidation with PCC and intramolecular cyclization and subsequent aromatization. However, under the reaction conditions reported in the previous study (Scheme 1),[23] aniline and arylamines failed to react with 3-trifluoroacetyl-4,5-dihydrofuran (**1**). In this study, we present a modified procedure that allows the title compounds to be obtained in the same range of yields as those reported in the previous study.[23]

The synthetic strategy used to synthesize the 1-aryl-substituted 3-trifluoroacetylpyrroles is outlined in Scheme 1. 3-Trifluoroacetyl-4,5-dihydrofuran (**1**) was prepared according to the literature.[20] The reaction of compound **1** with primary arylamines **2a**–**o** (1 equiv) in either dichloromethane or tetrahydrofuran (THF) in the presence of triethylamine, furnished the enamino alcohols **3**, which were not isolated because these compounds were not sufficiently stable.[23] However, the formation of intermediates **3a**–**o** could be followed by TLC, and when the spots of enone **1** and arylamine **2** completely disappeared, the reaction mixture was submitted to Swern oxidation,[24] thereby leading to the aldehydes **4**, which underwent intramolecular cyclization followed by elimination of water to give 1-aryl-substituted-3-trifluoroacetylpyrroles **5a**–**o** with overall yields of 30–56% (Table 1).



Scheme 1 Synthesis of 1-aryl-3-trifluoroacetyl pyrroles. *Reagents and conditions*: (i) $ArNH_2$, CH_2Cl_2 or THF, Et_3N; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N.

The aryl amines used in this study were less reactive than the aliphatic amines used in the previous study,[23] requiring the use of triethylamine and longer reaction times (4–5 h) to obtain the enaminone intermediates **3a**–**o**. In addition, it was difficult to carry out the reaction due to the low solubility of some aryl amines, such as 4-aminophenol, 2-amino-4-methylphenol, and 5-amino-2-methylphenol in dichloromethane. For these arylamines, the solvent of choice was THF because it is inert under Swern oxidation conditions and it dissolved all the reactants (Table 1).

One of the crucial steps of this study involved the oxidation of a primary alcohol to an aldehyde. In this study we tested different oxidation procedures (see Table 2) such as PCC (entry 1), and dimethyl sulfoxide activated by different electrophilic reagents, such as oxalyl chloride (entry 2),[25] cyanuric chloride (entry 3),[26] thionyl chloride (entry 4),[27] and trifluoroacetic anhydride (entry 5).[28]

In Table 2, the method involving the use of PCC for the oxidation step (entry 1), resulted in low yields and a tedious workup process.[29] For the reactions given in entries 4 and 5, the conversion into product was very low. The reaction carried out using cyanuric chloride (entry 3) furnished good conversion and yields, but this reaction gave rise to a small amount of the corresponding dihydropyrrole as a side product. Thus, the use of dimethyl sulfoxide activated by oxalyl chloride constituted the best reaction conditions for the oxidation step.

Table 1 Optimized Synthesis of Pyrroles **5a**–**o**

Entry	Compd	Amine (**2a**–**o**)[a]	Product	Yield (%)[b]
1	**2a**	Ph	**5a**	41
2	**2b**	2-$MeOC_6H_4$	**5b**	38
3	**2c**	3-$MeOC_6H_4$	**5c**	50
4	**2d**	4-$MeOC_6H_4$	**5d**	40
5	**2e**	2-MeC_6H_4	**5e**	30
6	**2f**	3-MeC_6H_4	**5f**	35
7	**2g**	4-MeC_6H_4	**5g**	45
8	**2h**	3-FC_6H_4	**5h**	32
9	**2i**	4-FC_6H_4	**5i**	40
10	**2j**	3-ClC_6H_4	**5j**	45
11	**2k**	4-ClC_6H_4	**5k**	43
12	**2l**	4-BrC_6H_4	**5l**	56
13[c]	**2m**	4-HOC_6H_4	**5m**	39
14[c]	**2n**	2-HO-5-MeC_6H_3	**5n**	49
15[c]	**2o**	3-HO-4-MeC_6H_3	**5o**	34

[a] Reaction conditions: (i) 3-trifluoroacetyl-4,5-dihydrofuran (2 mmol), aryl amine (2.0 mmol), Et_3N (2.0 mmol), CH_2Cl_2, 4–5 h, r.t.; (ii) $(COCl)_2$ (2.4 mmol), DMSO (4.47 mmol), CH_2Cl_2, Et_3N (9.94 mmol).
[b] Yield of products after purification by column chromatography.
[c] Reaction performed in THF as solvent.

Table 2 Oxidation of Intermediate **3g**[a]

Entry	Reagent	Conversion (%)[b]	Yield (%)[c]	Yield (%)[d]
1	PCC	98	25	10
2	oxalyl chloride	90	75	45
3	cyanuric chloride	89	69	–
4	thionyl chloride	36	–	–
5	trifluoroacetic anhydride	12	–	–

[a] Reaction conditions: 3-trifluoroacetyl-4,5-dihydrofuran (2 mmol), 4-methylaniline (2.0 mmol), Et_3N (2.0 mmol), CH_2Cl_2, r.t., 4 h.
[b] Conversion measured by GC-MS total ion chromatography.
[c] Yield of the crude mixture.
[d] Yield of products after purification by column chromatography.

In order to confirm the superior performance of the Swern oxidation over PCC, we tested three reactions using primary alkyl amines instead of arylamines; the results of these reactions are reported in Table 3. It can be seen that the method used in this study rendered overall yields that were approximately 15% higher than the previous reported method.[23]

Table 3 Comparison of Oxidation Methods for the Synthesis of 3-Trifluoroacetyl Pyrroles

Amine	Oxidation method [yield (%)][a]	
	PCC[b]	Swern[c]
$PhCH_2CH_2NH_2$	50	65
i-$PrNH_2$	52	67
n-$PrNH_2$	46	59

[a] Yield after purification by column chromatography.
[b] Yields reported by Zanatta et al.[23]
[c] Yields obtained in this study.

1-Arylpyrroles **5a**–**o**, were identified by ^1H and ^{13}C NMR techniques, mass spectrometry (GC-MS), and high-resolution mass spectrometry analysis.

It is interesting to mention that an enone analogous to **1**, but with a trichloromethyl group in the place of the trifluoromethyl, when reacted with primary amines, furnished 3-aminomethylenedihydrofuran-2-ones instead of 1-substituted 3-trichloroacetyl pyrroles, as shown in Scheme 2.[30] This probably happens because the trichloromethyl group is easily eliminated (structure **IV**) to form a stable lactone, but structure **IV**, with a trifluoromethyl group in the place of CCl_3, is not likely to be eliminated and the reaction returns to the structure analogous to **III** (intermediates **3**, Scheme 1), which could be isolated but was not stable enough to be adequately characterized.[23]

In summary, we have described the synthesis of a series of new 1-aryl-3-trifluoroacetyl-1*H*-pyrroles by an improved one-pot, four-step reaction protocol starting from the reaction of readily available 3-trifluoroacetyl-4,5-dihydrofuran with arylamines to give 1,1,1-trifluoro-3-(2-hydroxyethyl)-4-arylamino-3-buten-2-ones, which were directly submitted to Swern oxidation to furnish 1,1,1-trifluoro-3-(2-ethanal)-4-arylamino-3-buten-2-ones. Subsequent intramolecular cyclization of the corresponding enaminoaldehydes followed by aromatization rendered the title compounds in 30 to 56% overall yield.

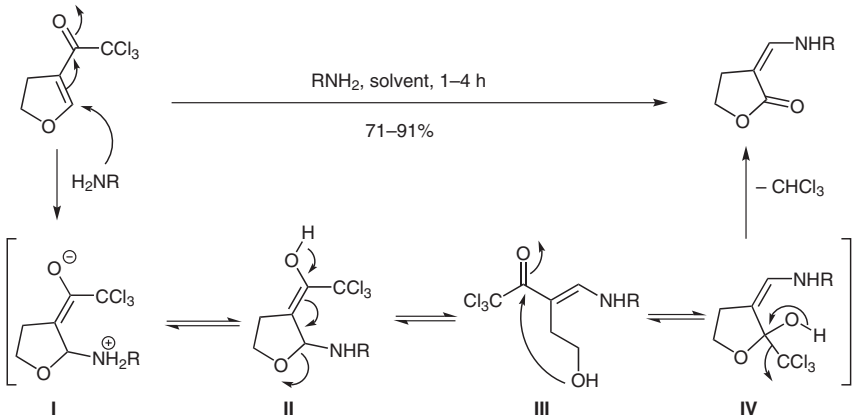
The 3-trifluoroacetyl-4,5-dihydrofuran (**1**) was prepared according to the literature.[20] All melting points were determined with a Kofler Reichert Thermovar or a MQAPF-301 apparatus and are uncorrected. High-resolution mass spectra were recorded in ESI-mode. GC-MS spectra were registered with a HP 5973 MSD instrument connected to a HP 6890 GC. The GC was equipped with a split-splitless injector, auto-sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. ^1H and ^{13}C NMR spectra were acquired with a Bruker DPX200 or DPX400 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as internal reference.

Synthesis of 1-Aryl-3-trifluoroacetyl-1*H*-pyrroles; General Procedure

To a solution of 3-trifluoroacetyl-4,5-dihydrofuran (**1**; 0.332 g, 2.0 mmol) in either CH_2Cl_2 or THF (6 mL), arylamine (2.0 mmol) and Et_3N (0.27 mL, 2.0 mmol) were added and the reaction was maintained at r.t. for 4–5 h under magnetic stirring. In another flask that was previously flame-dried, a solution of oxalyl chloride (0.2 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) was added and the solution was stirred at –78 °C until the temperature was stabilized, then a solution of DMSO (0.33 mL, 4.47 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After 30 min, the solution of the previously prepared enaminones was added to the oxalyl chloride solution and the mixture was stirred for 30 min. After this time, Et_3N (1.36 mL, 9.94 mmol) was added dropwise and the temperature of the resulting suspension was raised to 0 °C and kept at this temperature under stirring for 30 min. The ice bath was removed and the reaction mixture was stirred until the reaction mixture reached r.t. The solvent was evaporated and the resulting solid was dissolved in EtOAc (30 mL) and washed with 3% HCl (10 mL) and subsequently with 1 M brine (10 mL). The organic phase was dried with anhydrous sodium sulfate and concentrated in a rotary evaporator. Products were purified by column chromatography on silica gel (EtOAc–hexane, 1:9).

1-Phenyl-3-trifluoroacetyl-1*H*-pyrrole (5a)

Yield: 195 mg (41%); yellow solid; mp 60–64 °C.



Scheme 2

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.84 (br s, 1 H), 7.54–7.36 (m, 5 H), 7.10 (dd, *J* = 3.1, 2.4 Hz, 1 H), 6.92 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.1 Hz), 139.1, 129.9, 127.9, 127.5 (q, $^4J_{C–F}$ = 3.5 Hz), 122.5, 121.4, 119.8, 116.9 (q, $^1J_{C–F}$ = 290.7 Hz, CF_3), 111.9.

GC-MS (EI, 70 eV): *m*/*z* (%) = 239 (53) [M^+], 170 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9F_3NO$: 240.0636; found: 240.0627.

1-(2-Methoxyphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5b)
Yield: 204 mg (38%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br s, 1 H), 7.36 (m, 1 H), 7.26 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.11–7.06 (m, 2 H), 6.99 (dd, *J* = 3.1, 2.0 Hz, 1 H), 6.83 (br s, 1 H), 3.83 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.2 Hz), 152.7, 130.7 (q, $^4J_{C–F}$ = 3.6 Hz), 129.5, 128.3, 125.7, 124.9, 121.1, 118.5, 117.0 (q, $^1J_{C–F}$ = 290.8 Hz), 112.5, 110.4, 55.8.

GC-MS (EI, 70 eV): *m*/*z* (%) = 269 (100) [M^+], 200 (100), 185 (90), 157 (24).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_2$: 270.0742; found: 270.0735.

1-(3-Methoxyphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5c)
Yield: 269 mg (50%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (br s, 1 H), 7.40 (m, 1 H), 7.09 (m, 1 H), 7.00 (m, 1 H), 6.91 (m, 3 H), 3.86 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.4 Hz), 160.7, 140.2, 130.8, 127.5 (q, $^4J_{C–F}$ = 3.4 Hz), 122.6, 119.5, 117.0 (q, $^1J_{C–F}$ = 290.7 Hz), 113.6, 113.0, 111.8, 107.7, 55.5.

GC-MS (EI, 70 eV): *m*/*z* (%) = 269 (55) [M^+], 200 (100), 185 (15).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_2$: 270.0742; found: 270.0740.

1-(4-Methoxyphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5d)
Yield: 152 mg (38%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br s, 1 H), 7.34 (d, *J* = 9.0 Hz, 2 H), 7.05 (br s, 1 H), 6.99 (d, *J* = 9.0 Hz, 2 H), 6.89 (br s, 1 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5 (q, $^2J_{C–F}$ = 35.3 Hz), 159.3, 132.5, 127.7 (q, $^4J_{C–F}$ = 3.4 Hz), 123.0, 122.9, 119.2, 116.9 (q, $^1J_{C–F}$ = 290.9 Hz), 114.9, 111.6, 55.6.

GC-MS (EI, 70 eV): *m*/*z* (%) = 269 (100) [M^+], 200 (100), 185 (37).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_2$: 270.0742; found: 270.0741.

1-(2-Methylphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5e)
Yield: 152 mg (38%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (br s, 1 H), 7.37–7.26 (m, 4 H), 6.89 (br s, 1 H), 6.81 (dd, *J* = 3.2, 2.2 Hz, 1 H), 2.20 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.4 Hz), 138.7, 133.6, 131.4, 129.1, 126.9, 126.3, 130.1 (q, $^4J_{C–F}$ = 3.3 Hz), 124.9, 118.7, 116.9 (q, $^1J_{C–F}$ = 290.9 Hz), 110.8, 17.5.

GC-MS (EI, 70 eV): *m*/*z* (%) = 253 (70) [M^+], 184 (100), 154 (10).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO$: 254.0792; found: 254.0786.

1-(3-Methylphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5f)
Yield: 177 mg (35%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.41–7.19 (m, 4 H), 7.08 (dd, *J* = 3.1, 2.2 Hz, 1 H), 6.91 (br s, 1 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.5 Hz), 140.2, 139.1, 129.7, 128.7, 127.5 (q, $^4J_{C–F}$ = 3.4 Hz), 122.2, 122.6, 119.5, 118.6, 116.9 (q, $^3J_{C–F}$ = 290.7 Hz), 111.8, 21.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 253 (100) [M^+], 184 (100), 154 (16).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO$: 254.0792; found: 254.0789.

1-(4-Methylphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5g)
Yield: 227 mg (45%); yellow hygroscopic solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81 (br s, 1 H), 7.30 (s, 4 H), 7.07 (dd, *J* = 3.1, 2.1 Hz, 1 H), 6.90 (br s, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.5 Hz), 138.1, 136.9, 130.5, 127.5 (q, $^4J_{C–F}$ = 3.7 Hz), 122.6, 121.5, 119.6, 116.9 (q, $^1J_{C–F}$ = 290.7 Hz), 111.8, 20.9.

GC-MS (EI, 70 eV): *m*/*z* (%) = 253 (95) [M^+], 184 (100), 169 (10).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO$: 254.0792; found: 254.0794.

1-(3-Fluorophenyl)-3-trifluoroacetyl-1*H*-pyrrole (5h)
Yield: 164 mg (32%); yellow hygroscopic solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.50–7.44 (m, 1 H), 7.25–7.23 (m, 1 H), 7.18–7.08 (m, 3 H), 6.92 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.7 Hz), 163.3 (d, $^1J_{C–F}$ = 249.1 Hz), 140.5 (d, $^3J_{C–F}$ = 9.8 Hz), 131.4 (d, $^3J_{C–F}$ = 9.3 Hz), 127.2 (q, $^4J_{C–F}$ = 3.5 Hz), 122.4, 120.1, 117.0 (d, $^4J_{C–F}$ = 3.1 Hz), 116.9 (q, $^1J_{C–F}$ = 290.7 Hz), 114.9 (d, $^2J_{C–F}$ = 21.2 Hz), 112.3, 109.2 (d, $^2J_{C–F}$ = 25.4 Hz).

GC-MS (EI, 70 eV): *m*/*z* (%) = 257 (56) [M^+], 188 (100), 133 (22).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8F_4NO$: 258.0542; found: 258.0539.

1-(4-Fluorophenyl)-3-trifluoroacetyl-1*H*-pyrrole (5i)
Yield: 205 mg (40%); white solid; mp 79–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (br s, 1 H), 7.42–7.39 (m, 2 H), 7.21–7.17 (m, 2 H), 7.02 (dd, *J* = 2.9, 2.0 Hz, 1 H), 6.91 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.4 Hz), 161.9 (d, $^1J_{C–F}$ = 248.7 Hz), 135.4 (d, $^4J_{C–F}$ = 2.9 Hz), 127.6 (q, $^4J_{C–F}$ = 3.5 Hz), 123.5 (d, $^3J_{C–F}$ = 8.4 Hz), 122.8, 119.6, 116.9 (q, $^1J_{C–F}$ = 290.9 Hz), 116.9 (d, $^2J_{C–F}$ = 23.1 Hz), 112.0.

GC-MS (EI, 70 eV): *m*/*z* (%) = 257 (55) [M^+], 188 (100), 133 (25).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8F_4NO$: 258.0542; found: 258.0535.

1-(3-Chlorophenyl)-3-trifluoroacetyl-1*H*-pyrrole (5j)
Yield: 245 mg (45%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.45–7.30 (m, 4 H), 7.01 (dd, *J* = 3.1, 2.1 Hz, 1 H), 6.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.3 Hz), 140.2, 135.8, 131.0, 128.1, 127.2 (q, $^4J_{C–F}$ = 3.5 Hz), 122.4, 121.9, 120.1, 119.6, 116.9 (q, $^1J_{C–F}$ = 290.7 Hz), 111.2.

GC-MS (EI, 70 eV): *m*/*z* (%) = 273 (21) [M^+], 204 (100), 169 (16).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8ClF_3NO$: 274.0246; found: 274.0239.

1-(4-Chlorophenyl)-3-trifluoroacetyl-1*H*-pyrrole (5k)
Yield: 234 mg (43%); yellow solid; mp 102–106 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.80 (br s, 1 H), 7.48 (d, *J* = 8.9 Hz, 2 H), 7.38 (d, *J* = 8.9 Hz, 2 H), 7.06 (dd, *J* = 3.2, 2.2 Hz, 1 H), 6.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.6 Hz), 137.8, 133.9, 130.2, 127.3 (q, $^4J_{C–F}$ = 3.5 Hz), 122.8, 122.5, 120.1, 116.9 (q, $^1J_{C–F}$ = 290.7 Hz), 112.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 273 (69) [M$^+$], 204 (100), 169 (26).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8ClF_3NO$: 274.0246; found: 274.0249.

1-(4-Bromophenyl)-3-trifluoroacetyl-1*H*-pyrrole (5l)
Yield: 353 mg (56%); brown hygroscopic solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.80 (br s, 1 H), 7.63 (d, *J* = 8.9 Hz, 2 H), 7.32 (d, *J* = 8.9 Hz, 2 H), 7.06 (dd, *J* = 3.1, 2.2 Hz, 1 H), 6.93 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (q, $^2J_{C–F}$ = 35.5 Hz), 138.2, 133.1, 127.2 (q, $^4J_{C–F}$ = 3.5 Hz), 123.0, 122.4, 121.5, 119.9, 116.9 (q, $^1J_{C–F}$ = 290.9 Hz), 112.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 317 (26) [M$^+$], 248 (100), 169 (57), 141 (26).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_8BrF_3NO$: 339.9561; found: 339.9559.

1-(4-Hydroxyphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5m)
Yield: 198 mg (39%); brown solid; mp 125–129 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82 (br s, 1 H), 8.17 (br s, 1 H), 7.52 (d, *J* = 8.7 Hz, 2 H), 7.47 (t, *J* = 2.6 Hz, 1 H), 7.90 (d, *J* = 8.7 Hz, 2 H), 6.83 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.2 (q, $^2J_{C–F}$ = 34.4 Hz), 156.9, 130.3, 127.8 (q, $^4J_{C–F}$ = 3.4 Hz), 123.6, 122.5, 117.8, 116.6 (q, $^1J_{C–F}$ = 291.4 Hz), 115.9, 110.7.

GC-MS (EI, 70 eV): *m*/*z* (%) = 255 (70) [M$^+$], 186 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9F_3NO_2$: 256.0585; found: 256.0580.

1-(2-Hydroxy-5-methylphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5n)
Yield: 263 mg (49%); brown hygroscopic solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.98 (br s, 1 H), 8.02 (br s, 1 H), 7.28 (dd, *J* = 3.0, 2.2 Hz, 1 H), 7.21 (br s, 1 H), 7.06 (d, *J* = 8.3 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.78 (br s, 1 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.2 (q, $^2J_{C–F}$ = 34.3 Hz), 147.8, 130.8 (q, $^3J_{C–F}$ = 3.6 Hz), 129.6, 128.6, 125.7, 125.6, 125.8, 117.0, 116.8, 116.7 (q, $^1J_{C–F}$ = 291.4 Hz), 109.5, 19.7.

GC-MS (EI, 70 eV): *m*/*z* (%) = 269 (68) [M$^+$], 200 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_2$: 270.0742; found: 270.0738.

1-(3-Hydroxy-4-methylphenyl)-3-trifluoroacetyl-1*H*-pyrrole (5o)
Yield: 182 mg (34%); brown hygroscopic solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.66 (br s, 1 H), 8.09 (br s, 1 H), 7.43 (dd, *J* = 3.2, 2.2 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 1 H), 7.02 (m, 2 H), 6.83 (s, 1 H), 2.17 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.2 (q, $^2J_{C–F}$ = 34.6 Hz), 156.0, 136.9, 131.2, 127.5 (q, $^4J_{C–F}$ = 3.4 Hz), 123.9, 123.3, 117.9, 116.5 (q, $^1J_{C–F}$ = 291.5 Hz), 111.4, 110.8, 107.5, 15.2.

GC-MS (EI, 70 eV): *m*/*z* (%) = 269 (59) [M$^+$], 200 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_2$: 270.0742; found: 270.0743.

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