An Efficient Synthesis of 2-CF$_3$-3-Benzylindoles

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Abstract: The reaction of $\alpha$-CF$_3$-$\beta$-(2-nitroaryl) enamines with benzaldehydes afforded effectively $\alpha,\beta$-diaryl-CF$_3$-enones having nitro group. Subsequent reduction of nitro group by NH$_4$HCO$_2$-Pd/C system initiated intramolecular cyclization to give 2-CF$_3$-3-benzylindoles. Target products can be prepared in up to quantitative yields. Broad synthetic scope of the reaction was shown. Probable mechanism of indole formation is proposed.

Keywords: CF$_3$-group; enone; nitro; reduction; ammonium formate; indole; fluorine

1. Introduction

Organofluorine chemistry is now hot topic area of modern organic chemistry. A lot of attention has been paid to elaboration of novel synthetic approaches towards fluorine-containing compounds as well as investigation of their chemical properties. Such concern of the chemists about these compounds is a result of their unique physicochemical and biological properties [1–5]. Fluorinated compounds are widely used as construction materials, components of liquid crystalline compositions, agrochemicals [6–9] and pharmaceutics [10–12]. It was reported recently, that about 20% (more than 300 compounds) of currently used drugs [13–20] contain at least one fluorine atom [21]. Moreover, last years revealed the tendency of increasing of these values. Thus, share of fluoropharmaceuticals among new small-molecule drugs was 45% in 2018 [22], and 41% in 2019 [23]. On the other hand, about 59% of small-molecule drugs are the derivatives of nitrogen heterocyclic compounds [24]. As a result, novel approaches to fluorinated heterocycles are highly attractive [25–31].

Indole [32–38] is a “privileged structure” in drug discovery [39] and can be frequently found in pharmaceuticals and natural products [24]. The derivatives of 2-arylindoles exhibit antibacterial, anticancer, anti-oxidant, anti-inflammatory, anti-diabetic, antiviral, antiprofibrative, antituberculosis and antiparkinsonian activities [40]. The amino acid tryptophan is a central amino acid that is necessary for normal growth in infants and for nitrogen balance in adults. The biogenic amines tryptamine and serotonin as well as the mammalian hormone melatonin are important regulators of psychiatric health [41]. Indole derived marketed drugs include the nonsteroidal anti-inflammatory drug Indomethacin [42,43], anti-HIV drug Delavirdine [44,45], beta-blocker Pindolol [46,47], antintineoplastic drugs Panobinostat [48,49] and Apaziquone [50,51] (Figure 1).

One of the most reliable strategies for the synthesis of fluorinated heterocycles is using of fluorinated building blocks, highly reactive small-molecules. For example, $\alpha,\beta$-unsaturated CF$_3$-ketones were shown to possess a great potential in the synthesis of various organofluorine compounds, including carbo- and heterocycles [52–61]. Our group has been deeply involved in this chemistry. Recently, we have reported an efficient approach towards $\alpha,\beta$-diaryl-CF$_3$-enones—a new type of fluorinated building block. The reaction of aryldaledehydes with $\alpha$-CF$_3$-$\beta$-aryl enamines gave the corresponding $\alpha,\beta$-diaryl-CF$_3$-enones in good to high yields at heating in acetic acid. Based on the reactions with hydrazines a convenient pathway to exhaustingly substituted fluorinated pyrazolines and pyrazoles were
elaborated, including derivatives of Celecoxib, Mavocoxib (nonsteroidal anti-inflammatory drugs) and SC-560 (anti-cancer drug) [62]. Using reduction of α-aryl-β-(2-nitroaryl)-CF₃-enones a novel synthetic approach towards 2-CF₃-3-arylquinolines was developed [63]. Shifting nitro group to α-aryl ring-opened a pathway to various functionalized 2-CF₃-indoles by the reduction with ammonium formate followed by reactions with various nucleophiles [64].

![Figure 1. Indole based marketed drugs.](image)

In continuation of the investigation of α,β-diaryl-CF₃-enones chemistry, in this article, we report synthesis of 2-CF₃-3-benzylindoles by reduction of nitro group in α-(2-nitroaryl)-β-aryl-CF₃-enones followed by intramolecular cyclization (Figure 2).

![Figure 2. Approaches to 2-CF₃-3-benzylindoles.](image)

It should be noted, that 2-CF₃-3-benzylindoles are quite a rare type of indoles. The approaches to the synthesis of these indoles were not studied systematically and have been not in the main focus of the publications. As a result, syntheses of only few 2-CF₃-3-
benzylindoles were reported. Thus, prepared in three steps, N-[2-(1-alkynyl)phenyl]trifluoroacetimidoyl iodides were transformed into desired indoles by the tin-radical promoted cyclization of N-[2-(1-alkynyl)phenyl]trifluoroacetimidoyl iodides as reported by Uneyama [65]. The copper-catalyzed C(sp2)-H trifluoromethylation of N,N-disubstituted hydrazones using the Togni’s reagent followed by Fischer indole cyclization of CF3-hydrazones formed was described by Monteiro and Bouyssi [66]. N-Methylmorpholine mediated direct trifluoromethylation of 3-benzylindole with Umemoto’s reagent was reported by Ma and Yu [67]. In spite of the mentioned methods allowed to prepare 2-CF3-indoles in good yields (59–64%), low atom efficiency and high price of some used reagent should be taken into account (Figure 2).

2. Results

To start our investigation, we prepared a set of α-(2-nitroaryl)-β-aryl-CF3-enones using recently elaborated by us synthetic protocol [64]. Condensation of α-CF3-β-(2-nitroaryl)enamines 1 with arylaldehydes 2 in acetic acid at 80–90 °C led to the corresponding α-(2-nitroaryl)-β-aryl-CF3-enones 3 in good to high yields. The reaction is very general, almost no limitations were found to give variety of such enones with a possibility to have different substituents in both aromatic rings. Moreover, some heterocyclic derivatives can be prepared as well (Scheme 1).

Next, we investigated the reductive cyclization of ketone 3a in various conditions (Scheme 2). Firstly, we employed standard conditions of Leimgruber–Batcho [68] and Reissert [69] synthesis of indoles, which involve the reduction of nitro group followed by intramolecular cyclization of aniline formed. Thus, heating of ketone 3a using Fe-AcOH-H2O, Zn-EtOH-HCl and SnCl2•2H2O-EtOH systems led to the formation of a variety of hardly identifiable products, in which we were able to identify only 2-CF3-3-benzylindole 4a and its acetoxy-derivative 5a (by 19F NMR, Scheme 2). Better results were achieved when Zn-AcOH system was used. In this case, indoles 4a and 5a were isolated in 20% and 47% yield correspondingly (Table 1, entry 1). Further heating of this reaction mixture with additional amount of Zn led to a partial transformation of acetoxy indole 5a into indole 4a (Table 1, entry 2). In Zn-AcOH-MeOH system methoxy-indol 6a became the main product, which was isolated in 77% yield (Table 1, entry 3). Further improvements in terms of chemoselectivity were made using catalytic hydrogenation on Pd/C in MeOH.
Thus, reduction using H₂ at room temperature or NH₄HCO₂ (hydrogen surrogate) at 65 °C afforded 2-CF₃-3-benzylimidole 4a in about 90% yield. In both cases methoxy-substituted indole 6a was formed as a byproduct in less than 1% yield (Table 1, entries 4, 5). Ultimate selectivity of the reaction was achieved by the reduction with 5 equivalents of NH₄HCO₂ on Pd/C in MeOH at room temperature. In this conditions 2-CF₃-3-benzylimidole 4a was isolated in almost quantitative yield while byproduct 6a was not formed at all (Table 1, entry 6). It is worth noting that the reaction with NH₄HCO₂ (Table 1, entries 5,6) leads to a mixture of indole 4a and indolinol D, which structure is proved by NMR spectra of the reaction mixture. However, indolinol D eliminates water instantly followed by aromatization after addition of an acid (Schemes 2 and 3).

![Scheme 2](image_url)

**Scheme 2.** Reduction of ketone 3a in various conditions.

| Title 1 | Reaction Conditions | Yield of 4a, % | Yield of 5a, % | Yield of 6a, % |
|---------|---------------------|---------------|---------------|---------------|
| entry 1 | 6 eq. Zn, AcOH, 80 °C, 4h | 20 | 47 | - |
| entry 2 | 12 eq. Zn, AcOH, 80 °C, 14h | 43 | 3 | - |
| entry 3 | 6 eq. Zn, AcOH-MeOH, 65 °C, 8h | 8 | 2 | 77 |
| entry 4 | H₂, MeOH, 5 mol% Pd/C, r.t., 1 day | 89 | - | <1 |
| entry 5 | 5 eq. NH₄HCO₂, MeOH, 5 mol% Pd/C, r.t., 60 °C, 1h | 91 | - | <1 |
| entry 6 | 5 eq. NH₄HCO₂, MeOH, 5 mol% Pd/C, r.t., 1 day | 99 | - | - |
| entry 7 | 3.3 equiv. NH₄HCO₂, MeOH, 5 mol% Pd/C, 60 °C, 1h | <1 | - | 86 |
| entry 8 | 3.3 equiv. NH₄HCO₂, THF, 5 mol% Pd/C, r.t., 1 day; then pTSA, MeOH | traces | - | 81 |

![Scheme 3](image_url)

**Scheme 3.** Mechanism of transformation of 3a into indoles 4a and 6a.

Careful analysis of results of experiments (Table 1) forced us to propose that the reaction can proceed via the formation of cyclic hemiaminal B (Scheme 3). To confirm our preposition, we performed the reduction of 3a with 3.3 equivalents of NH₄HCO₂ (the precise amount needed for NO₂ reduction only). Heating of the reaction mixture for 1h at 60 °C led highly selectively to assembling of methoxy-substituted indole 6a in...
86% yield (Table 1, entry 7). We have also found, that using THF as a solvent instead of methanol allowed to stop the reaction at the step of intermediate unsaturated indolinol B. Compound B is stable enough to be isolated in crude form (by evaporation of the solvent). The structure of B was confirmed by NMR and HRMS spectra (Scheme 3). It was also found that compound B eliminates water slowly at standing in CDCl₃ solution (directly in NMR tube). Thus, NMR spectra of this solution measured after about a month (36 days) showed the complete transformation of B into C (Scheme 3). An attempt to perform acid catalyzed elimination of water from B in THF the solution and isolate C was failed. Thus, the addition of pTSA to the THF solution of B followed by evaporation of the solvent led to severe tarring immediately. However, the addition of pTSA to solution of B in methanol led to desired elimination of water followed by the conjugated addition of methanol to form methoxy-indole 5a (Table 1, entry 8). Similarly, the addition of methanol to CDCl₃ solution of C (obtained by standing in NMR tube, see above) led to the transformation of C into 5a (by ¹⁹F NMR). So, we have successfully confirmed the mechanism of the reaction. Thus, reduction of the nitro group in indole 3a led to aniline A, which cyclizes to unsaturated indolinol B. Elimination of water from B afforded conjugated imine C, which is a strong Michael acceptor due to aromatization facilitating addition of nucleophiles. Hydrogenation of the double bond of B leads to saturated indolinol D. Elimination of water from D finalizes the process to afford indole 4a.

Next, we investigated the synthetic scope of the synthesis of CF₃-indoles 4. Using the optimal reaction conditions, we performed a reduction of a number of ketones 3 to afford corresponding indoles 4 in high to quantitative yields (Scheme 4).

The reaction has a wide synthetic scope, allowing preparing indoles having both electron-donating and electron-withdrawing groups as well as bulky ortho-substituents and naphthyl fragment. It should be noted, that ketones 3j–l bearing the additional nitro groups were transformed into amino-substituted indoles 4j–l. These indoles are interesting objects for the further modifications at NH₂-group to give promising derivatives in terms of drug design. In the case of bulky ketone 3o having 1-naphthyl substituent reduction
in standard conditions (5 equivalents of NH₄HCO₂) led to the formation of admixture of methoxy-indole 6b (about 28%). Probably, the rate of hydrogenation of the double bond of unsaturated indolinol B is lower due to its steric hindrance and the reaction cannot be completed because of full decomposition of NH₄HCO₂ on Pd/C during the reaction course. Nevertheless, using of 8 equivalents of NH₄HCO₂ allowed to overcome this obstacle to give selectively indole 4o in 87% yield. The reduction of ketones 3p and 3q having additional methoxy group in nitro-aryl fragment led to 5- and 8-methoxyindoles correspondingly.

Ketones 3r,s having heterocyclic substituents were also involved in the transformation. It should be noted that reduction of thiophene derivative 3r proceeded much more slowly compared to other substrates, which can be explained by poisoning of palladium by thiophene moiety [70]. Thus, attempt to perform the reaction in standard conditions led mostly to methoxy-indole 6c. However, increasing of the amount of NH₄HCO₂ to 15 equivalents and prolongation of the reaction time to 5 days allowed to prepare desired indole 4r in good yield. Separation of admixture of 6c from target indole 4r was carried out by column chromatography. It should be noted, that it is one of few cases, then column chromatography was used for purification of the products (4l,r,s). All other indoles were isolated in pure form just after separation from the inorganic admixtures (Pd/C and NH₄Cl). Due to the low stability of pyridine derived ketone 3s the reduction of this compound was performed without its isolation. An attempt to use NH₄HCO₂ in AcOH afforded a complex mixture of products. However, using HCO₂H instead of NH₄HCO₂ showed much better results. Indole 4s having pyridine substituent was isolated in 21% yield from enamine 1a. Taking into account moderate yield at first step of the reaction sequence (30% for the formation of 3v) the yield at the reduction step can be estimated as 70% (Scheme 5).

**Scheme 5.** Reduction of ketones 3, having heterocyclic substituents.

### 3. Materials and Methods

**General Remarks**

1H, 13C and 19F NMR spectra were recorded on Bruker AVANCE 400 MHz spectrometer (Bruker Corp., Carlsruhe, Germany) in CD₂CN and CDCl₃ at 400, 100 and 376 MHz respectively. Chemical shifts (δ) in ppm are reported with the use of the residual CHD₂CN and chloroform signals (1.94 and 7.25 for 1H and 1.30, 77.0 for 13C) as internal reference. The 19F chemical shifts were referenced to C₆F₁₆ (−162.9 ppm). ESI-MS spectra were measured with an Orbitrap Elite instrument (Thermo Fisher Scientific, Waltham, MA USA). TLC analysis was performed on “Merck 60 F₂₅₄” plates (Merck, Darmstadt, Germany). Column chromatography was performed on silica gel. Melting points were determined on an Electrothermal 9100 apparatus (Electrothermal, Stone, Staffordshire, UK). All reagents were...
of reagent grade and were used as such or were distilled prior to use. Starting α-CF<sub>3</sub>-β-aryl enamines 1 were synthesized using previously reported procedures by the reaction with 10 equivalents of pyrrolidine in neat [71].

**Synthesis of α-CF<sub>3</sub>-β-(2-nitroaryl)enamines 1 by the Reaction with Pyrrolidine in Neat (General Procedure).** One neck 25 mL round-bottomed flask was charged with dry pyrrolidine (8.5 mL, 100 mmol), cooled down to −18 °C and the corresponding styrene (10 mmol) was added in one portion with vigorous stirring. The reaction mixture was stirred at room temperature for 1-3 h until starting styrene was consumed (TLC or NMR monitoring). The excess of pyrrolidine was evaporated in a vacuum, the viscous residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 10% K<sub>2</sub>CO<sub>3</sub> solution (2 × 50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. CH<sub>2</sub>Cl<sub>2</sub> was removed in vacuo to give crude enamine, which was used without further purification. For characterization data of enamines 1 see [64].

**Synthesis of ketones 3 by the reactions of α-(trifluoromethyl)enamines with aromatic aldehydes (general procedure).** One-necked 50-mL round bottom flask (or 12 mL vial) was charged with enamine 1 (5 mmol), aromatic aldehyde 2 (5.75 mmol) and glacial acetic acid (15 mL or 5 mL for reaction in the vial). Reaction mixture was kept at 80–90 °C (hotplate stirrer) under stirring for 6–10 h until consumption of aldehyde and corresponding benzyl ketone formed by the hydrolysis of enamine (1H NMR control). Volatiles were evaporated in vacuo, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 10% K<sub>2</sub>CO<sub>3</sub> solution (2:1, 1:1), CH<sub>2</sub>Cl<sub>2</sub>, mixture of CH<sub>2</sub>Cl<sub>2</sub> and MeOH (100:1) as eluents. For characterization data of ketones 3 see [64].

**Reductive cyclization of nitro-ketones 3 to 2-CF<sub>3</sub>-indoles 4.** 12 mL vial with a screw cap was charged with ketone 4 (0.2 mmol), NH<sub>4</sub>HCO<sub>3</sub> (0.063 g, 1.00 mmol, 5 equiv.), Pd/C (10%, 0.0108 g, 0.01 mmol, 5 mol%) and methanol (1.2 mL). Next, the reaction mixture was kept under stirring at 60 °C for 0.5-1 h (conditions a) or at room temperature for 1 day (conditions b). After that, 6M HCl (0.25 mL, 1.5 mmol) was added in 4-5 portions (evolution of CO<sub>2</sub>!). The reaction mixture was filtered through a short celite pad and dispersed between water (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL). Aqueous layer was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). Combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, volatiles were evaporated in vacuo, to give pure indole 4. In the case of indoles 4l, 4n, 4r, 4s additional purification by column chromatography on silica gel was performed. Reduction of ketones 3j–l, having additional nitro group, was performed using 8 equivalents of NH<sub>4</sub>HCO<sub>3</sub> at room temperature (conditions c).

3-Benzyl-2-(trifluoromethyl)-1H-indole (4a). Obtained using conditions a (0.108 g, 0.34 mmol of 3a) or conditions b (0.055 g, 0.171 mmol of 3a). Pale brown crystals, m.p. 103–104 °C, yield 0.084 g (91%, A) 0.0465 g (99%, B). 1H NMR (CDCl<sub>3</sub>, 400.1 MHz): δ 8.25 (br.s, 1H), 7.57 (d, 1H, 3J = 8.1 Hz), 7.39 (d, 1H, 3J = 8.2 Hz), 7.27–7.37 (m, 5H), 7.20–7.26 (m, 1H), 7.13–7.19 (m, 1H), 4.32 (s, 2H). 13C[1H] NMR (CDCl<sub>3</sub>, 100.6 MHz): δ 139.9, 135.3, 128.4, 128.3, 127.4, 126.1, 124.8, 122.03 (q, 3J<sub>CF</sub> = 36.5 Hz), 122.01 (q, 1J<sub>CF</sub> = 269.0 Hz), 120.8, 120.7, 116.8 (q, 3J<sub>CF</sub> = 2.8 Hz), 111.7, 29.8. 19F NMR (CDCl<sub>3</sub>, 376.5 MHz): δ −59.1 (s, 3F). NMR data are in agreement with those in the literature [67].

3-(4-Methylbenzyl)-2-(trifluoromethyl)-1H-indole (4b). Obtained using conditions a (0.109 g, 0.325 mmol of 3b). Pale brown solid, m.p. 88–90 °C, yield 0.090 g (96%). 1H NMR (CDCl<sub>3</sub>, 400.1 MHz): δ 8.24 (br.s, 1H), 7.63 (d, 1H, 3J = 8.1 Hz), 7.35–7.44 (m, 2H), 7.25 (d, 2H, 3J = 8.0 Hz), 7.19–7.23 (m, 1H), 7.17 (d, 2H, 3J = 7.9 Hz), 4.33 (s, 2H), 2.39 (s, 3H). 13C[1H] NMR (CDCl<sub>3</sub>, 100.6 MHz): δ 136.9, 135.6, 135.3, 129.1, 128.1, 127.4, 124.7, 122.1 (q, 1J<sub>CF</sub> = 269.0 Hz), 121.9 (q, 2J<sub>CF</sub> = 36.5 Hz), 120.8, 120.6, 117.0 (q, 3J<sub>CF</sub> = 2.8 Hz), 111.6, 29.3, 20.9. 19F NMR (CDCl<sub>3</sub>, 376.5 MHz): δ −59.1 (s, 3F). HRMS (ESI-TOF): m/z [M − H]− Calcd for C<sub>17</sub>H<sub>13</sub>F<sub>3</sub>N<sub>3</sub>: 288.106; Found: 288.109.

3-(4-(tert-Butyl)benzyl)-2-(trifluoromethyl)-1H-indole (4c). Obtained using conditions b (0.120 g, 0.318 mmol of 3c). Pale brown solid, m.p. 85–86 °C, yield 0.100 g (95%). 1H NMR (CDCl<sub>3</sub>, 400.1 MHz): δ 8.23 (br.s, 1H), 7.64 (d, 1H, 3J = 8.1 Hz), 7.33–7.42 (m, 4H),
7.25–7.32 (m, 2H), 7.19 (ddd, 1H, \(^3J = 8.0\) Hz, \(^3J = 6.6\) Hz, \(^4J = 1.4\) Hz), 4.32 (s, 2H), 1.36 (s, 9H). \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz}: \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz}: \(^{12}\)

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(4-Fluorobenzoyl)-2-(trifluoromethyl)-1H-indole (4d). Obtained using conditions a (0.126 g, 0.372 mmol of 3d). Brown viscous oil, yield 0.105 g (96%). \(^1\text{H}\) NMR (CDCl\(_3\), 400.1 MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz}: \(^{12}\)

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Methyl 4-((2-(trifluoromethyl)-1H-indol-3-yl)methyl)benzoate (4f). Obtained using conditions b (0.085 g, 0.224 mmol of 3f). Pale yellow solid, m.p. 109–111 °C, yield 0.074 g (99%). \(^1\text{H}\) NMR (CDCl\(_3\), 400.1 MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz}: \(^{12}\)

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Methyl 4-((2-(trifluoromethyl)-1H-indol-3-yl)methyl)benzoate (4f). Obtained using conditions b (0.085 g, 0.224 mmol of 3f). Pale yellow solid, m.p. 109–111 °C, yield 0.074 g (99%). \(^1\text{H}\) NMR (CDCl\(_3\), 400.1 MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz): \(^{12}\) \(^{13}\text{C}\{^1\text{H}\} \text{ NMR (CDCl}_3, 100.6\) MHz}: \(^{12}\)
109.9, 55.2, 23.3. 19F NMR (CDCl$_3$, 376.5 MHz): $\delta$ = −59.3 (s, 3F). HRMS (ESI-TOF): m/z [M − H]$^+$ Calcd for C$_{17}$H$_{13}$F$_3$NO$^-$: 304.0955; found: 304.0951.

4-(2-(Trifluoromethyl)-1H-indol-3-yl)methyl)aniline (4j). Obtained using conditions c (0.112 g, 0.306 mmol of 3j). Pale brown solid, m.p. 175–177 ºC, yield 0.087 g (98%). 1H NMR (CDCl$_3$, 400.1 MHz): $\delta$ = 8.97 (brs, 1H), 7.55 (d, 1H, $^3J$ = 8.1 Hz), 7.46 (d, 1H, $^3J$ = 8.3 Hz), 7.28 (t, 1H, $^3J$ = 7.6 Hz), 7.09 (ddd, 1H, $^3J$ = 8.0 Hz, $^4J$ = 7.1 Hz, $^4J$ = 0.9 Hz), 6.95 (d, 2H, $^3J$ = 8.4 Hz), 6.54 (d, 2H, $^3J$ = 8.5 Hz), 4.11 (s, 2H). HRMS (ESI-TOF): m/z [M + H$^+$] Calcd for C$_{18}$H$_{14}$F$_3$N$_2$$^+$: 291.1104; found: 291.1110.

3-(2-(Trifluoromethyl)-1H-indol-3-yl)methyl)aniline (4k). Obtained using conditions c (0.120 g, 0.328 mmol of 3k). Pale yellow solid, m.p. 138–140 ºC, yield 0.086 g (90%). 1H NMR (CDCl$_3$, 400.1 MHz): $\delta$ = 8.56 (brs, 1H), 7.56 (d, 1H, $^3J$ = 8.1 Hz), 7.26–7.35 (m, 2H), 7.05–7.15 (m, 2H), 6.72 (d, 2H, $^3J$ = 7.6 Hz), 6.57 (brs, 1H), 6.53 (dd, 1H, $^3J$ = 7.9 Hz, $^3J$ = 1.7 Hz), 4.20 (s, 2H), 3.54 (brs, 2H). HRMS (ESI-TOF): m/z [M + H$^+$] Calcd for C$_{18}$H$_{14}$F$_3$N$_2$$^+$: 291.1104; found: 291.1111.

2-(2-(Trifluoromethyl)-1H-indol-3-yl)methyl)aniline (4l). Obtained using conditions c (0.160 g, 0.437 mmol of 3l). Purified by column chromatography, using gradient elution by CH$_2$Cl$_2$ followed by mixture CH$_2$Cl$_2$-MeOH (100:1, 30:1). Pale yellow solid, m.p. 136–138 ºC, yield 0.097 g (76%). 1H NMR (CDCl$_3$, 400.1 MHz): $\delta$ = 8.50 (brs, 1H), 7.40 (d, 1H, $^3J$ = 8.1 Hz), 7.35 (d, 1H, $^3J$ = 8.2 Hz), 7.29 (t, 1H, $^3J$ = 7.5 Hz), 7.08–7.12 (m, 1H), 7.04–7.08 (m, 1H), 6.93 (d, 1H, $^3J$ = 7.5 Hz), 6.67–6.75 (m, 2H), 4.13 (s, 2H), 3.53 (brs, 1H). HRMS (ESI-TOF): m/z [M + H$^+$] Calcd for C$_{16}$H$_{14}$F$_3$N$_2$$^+$: 287.1111; found: 287.1116.

3-(3-Phenoxybenzyl)-2-(trifluoromethyl)-1H-indole (4m). Obtained using conditions b (0.126 g, 0.305 mmol of 3m). Pale yellow solid, m.p. 71–73 ºC, yield 0.107 g (96%). 1H NMR (CDCl$_3$, 400.1 MHz): $\delta$ = 8.33 (brs, 1H), 7.56 (d, 1H, $^3J$ = 8.1 Hz), 7.31–7.41 (m, 4H), 7.22–7.27 (m, 1H), 7.10–7.20 (m, 2H), 6.97–7.07 (m, 4H), 6.86 (dd, 1H, $^3J$ = 8.1 Hz, $^3J$ = 1.7 Hz), 4.29 (s, 2H). HRMS (ESI-TOF): m/z [M + H$^+$] Calcd for C$_{22}$H$_{15}$F$_3$NO$^-$: 364.0373; found: 364.0376.

3-(Perfluorophenyl)-2-(trifluoromethyl)-1H-indole (4n). Obtained using conditions b (0.117 g, 0.285 mmol of 3n). Purified by column chromatography, using gradient elution by mixture hexane-CH$_2$Cl$_2$ (4:1) followed by mixture hexane-CH$_2$Cl$_2$ (2:1). Pale brown solid, m.p. 131–133 ºC, yield 0.082 g (79%). 1H NMR (CDCl$_3$, 400.1 MHz): $\delta$ = 8.32 (brs, 1H), 7.56 (d, 1H, $^3J$ = 8.1 Hz), 7.37–7.42 (m, 1H), 7.29–7.36 (m, 1H), 7.19 (ddd, 1H, $^3J$ = 8.1 Hz, $^3J$ = 6.9 Hz, $^4J$ = 1.1 Hz), 4.32 (s, 2H). 13C [H] NMR (CDCl$_3$, 100.6 MHz): $\delta$ = 145.3 (dddt, $^1$J$_{CF}$ = 246.8 Hz, $^3$J$_{CF}$ = 11.8 Hz, $^4$J$_{CF}$ = 7.8 Hz, $^5$J$_{CF}$ = 3.8 Hz, CF), 140.04 (ddm, $^1$J$_{CF}$ = 258.6 Hz, $^3$J$_{CF}$ = 141.5–141.1, m$_2$ 138.9–138.6, CF), 137.5 (ddm, $^1$J$_{CF}$ = 257.8 Hz, m$_1$ 138.9–138.6, m$_2$ 136.5–136.1, CF), 135.0, 126.6, 125.1, 122.3 (q, $^3$J$_{CF}$ = 37.4 Hz), 121.7 (q, $^3$J$_{CF}$ = 269.1 Hz), 121.1, 119.7, 113.1, 112.9, 111.9, 29.8 (d, $^3$J$_{CF}$ = 20.6 Hz, CF). HRMS (ESI-TOF): m/z [M + H$^+$] Calcd for C$_{22}$H$_{15}$F$_3$N$^-$: 364.0378; found: 364.0373.

3-(Naphthalen-1-ylmethyl)-2-(trifluoromethyl)-1H-indole (4o). Obtained using conditions b (0.043 g, 0.116 mmol of 3o) and 8 equivalents of NH$_4$HCO$_2$ (0.059 g, 0.94 mmol, 8 equiv.). White solid, m.p. 69–71 ºC, yield 0.0328 g (87%). 1H NMR (CDCl$_3$, 400.1 MHz): $\delta$ = 8.37 (brs, 1H), 8.29 (d, 1H, $^3J$ = 8.4 Hz), 7.90–7.98 (m, 1H), 7.76 (d, 1H, $^3J$ = 8.2 Hz), 7.59–7.66 (m, 1H), 7.53–7.59 (m, 1H), 7.43 (d, 1H, $^3J$ = 8.3 Hz), 0.72–0.79 (m, 3H), 0.78 (ddd, 1H, $^3J$ = 8.0 Hz, $^3J$ = 7.1 Hz, $^4J$ = 0.9 Hz), 7.04 (dd, 1H, $^3J$ = 7.1 Hz, $^4J$ = 0.9 Hz), 4.78 (s, 2H). 13C [H]
NMR (CDCl₃, 100.6 MHz): δ 135.4, 135.3, 133.6, 131.9, 128.8, 127.7, 126.9, 126.1, 125.6, 125.5, 124.9, 123.2, 122.7 (q, 3CF = 36.7 Hz), 122.0 (q, 3CF = 269.3 Hz), 120.9, 120.7, 115.7 (q, 3CF = 2.9 Hz), 111.7, 26.6. 19F NMR (CDCl₃, 376.5 MHz): δ −59.7 (s, 3F). HRMS (ESI-TOF): m/z [M − H]⁻ Calcd for C₂₀H₁₃F₃N: 324.1006; found: 324.1002.

3-(Methoxy(naphthalen-1-yl)ethyl)-2-(trifluoromethyl)-1H-indole (6b). Obtained using conditions b (0.153 g, 0.412 mmol of 3o) as a mixture with indole 4o (yield 0.067 g (51%) for 4o). Purified by column chromatography, using mixture of hexane and CH₂Cl₂ (1:1) as an eluent. Yellow powder, m.p. 65–67 °C, yield 0.041 g (28%). ¹H NMR (CDCl₃, 400.1 MHz): δ 8.53 (brs, 1H), 7.88 (dd, 1H, 3j = 8.3 Hz, 4j = 0.9 Hz), 7.81 (d, 1H, 3j = 8.0 Hz), 7.74 (d, 1H, 3j = 8.2 Hz), 7.53–7.60 (m, 1H), 7.47–7.53 (m, 1H), 7.40 (d, 2H, 3j = 8.2 Hz), 7.36 (d, 1H, 3j = 7.9 Hz), 7.28–7.34 (m, 1H), 7.06–7.13 (m, 1H), 6.51 (s, 1H), 3.54 (s, 3H). ¹³C (¹H) NMR (CDCl₃, 100.6 MHz): δ 135.6, 135.3, 134.0, 130.1, 128.9, 128.7, 126.5, 126.3, 125.6, 125.3, 124.98, 124.94, 123.8, 123.3 (q, 3CF = 37.4 Hz), 123.0, 121.7 (q, 1jCF = 269.5 Hz), 121.2, 116.5 (q, 3jCF = 2.6 Hz), 111.7, 75.5, 57.2. ¹⁹F NMR (CDCl₃, 376.5 MHz): δ −59.0 (s, 3F). HRMS (ESI-TOF): m/z [M + OMe]⁻ Calcd for C₂₀H₁₄F₃N⁻: 324.1002; found: 324.1006.

3-Benzyl-7-methoxy-2-(trifluoromethyl)-1H-indole (4p). Obtained using conditions b (0.053 g, 0.151 mmol of 3p). Green-yellowish viscous oil, yield 0.044 g (96%). ¹H NMR (CDCl₃, 400.1 MHz): δ 8.57 (brs, 1H), 7.23–7.30 (m, 4H), 7.15–7.22 (m, 1H), 7.11 (d, 1H, 3j = 8.1 Hz), 7.04 (t, 1H, 3j = 7.6 Hz), 6.72 (d, 1H, 3j = 7.6 Hz), 4.26 (s, 2H), 3.97 (s, 3H). ¹³C (¹H) NMR (CDCl₃, 100.6 MHz): δ 146.3, 140.0, 128.7, 128.4, 128.3, 126.3, 126.0, 122.0 (q, 1jCF = 268.9 Hz), 121.8 (q, 3jCF = 36.8 Hz), 121.2, 117.1 (q, 3jCF = 2.8 Hz), 113.1, 103.9, 55.4, 30.0. ¹⁹F NMR (CDCl₃, 376.5 MHz): δ −59.1 (s, 3F). HRMS (ESI-TOF): m/z [M − H]⁻ Calcd for C₁₇H₁₃F₃NO⁻: 304.0955; found: 304.0960.

3-Benzyl-5-methoxy-2-(trifluoromethyl)-1H-indole (4q). Obtained using conditions b (0.098 g, 0.279 mmol of 3q). Pale brown solid, m.p. 102–104 °C, yield 0.0826 g (97%). ¹H NMR (CDCl₃, 400.1 MHz): δ 8.29 (brs, 1H), 7.24–7.33 (m, 5H, 7H), 7.19–7.24 (m, 1H), 6.99 (dd, 1H, 3j = 8.9 Hz, 4j = 2.4 Hz), 6.92 (d, 1H, 3j = 2.4 Hz), 4.27 (s, 2H), 3.78 (s, 3H). ¹³C (¹H) NMR (CDCl₃, 100.6 MHz): δ 154.5, 139.9, 130.5, 128.4, 128.3, 127.9, 126.1, 122.6 (q, 1jCF = 36.7 Hz), 121.9 (q, 1jCF = 269.0 Hz), 116.2 (q, 3jCF = 2.4 Hz), 115.6, 112.6, 101.6, 55.7, 29.8. ¹⁹F NMR (CDCl₃, 376.5 MHz): δ −59.2 (s, 3F). HRMS (ESI-TOF): m/z [M + H]⁺ Calcd for C₁₇H₁₃F₃NO⁺: 304.0955; found: 304.0946.

Reduction of ketone 3r. Using conditions a: 12 mL vial with a screw cap was charged with ketone 3r (0.072 g, 0.220 mmol), NH₄HCO₂ (0.069 g, 1.10 mol, 5 equiv.), Pd/C (10%, 0.012 g, 0.011 mmol, 5 mol%) and methanol (1.5 mL). Next, the reaction mixture was kept under stirring at 60 °C for 1 h. After that, 6M HCl (0.25 mL, 1.5 mmol) was added in 4–5 portions (evolution of CO₂). The reaction mixture was filtered through a short celite pad and dispersed between water (10 mL) and CH₂Cl₂ (20 mL). Aqueous layer was separated and extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over Na₂SO₄, volatiles were evaporated in vacuo, the residue was purified by column chromatography on silica gel, using gradient elution by mixture hexane-CH₂Cl₂ (4:1) followed by mixture hexane-CH₂Cl₂ (2:1) to give 3-(thiophen-2-ylmethyl)-2-(trifluoromethyl)-1H-indole (4r), yield 0.0048 g, (8%) and 3-(methoxy(thiophen-2-ylmethyl)-2-(trifluoromethyl)-1H-indole (5a), yield 0.035 g, (51%).

Using conditions d: 12 mL vial with a screw cap was charged with ketone 3r (0.068 g, 0.208 mmol), NH₄HCO₂ (0.188 g, 2.98 mmol, ~5 equiv.), Pd/C (10%, 0.011 g, 0.0104 mmol, 5 mol%) and methanol (3 mL). Next, the reaction mixture was kept under stirring for 1 day. After that, 6M HCl (0.5 mL, 3 mmol) was added in 4–5 portions (evolution of CO₂). The reaction mixture was filtered through a short celite pad and dispersed between water (10 mL) and CH₂Cl₂ (20 mL). Aqueous layer was separated and extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phases were dried over Na₂SO₄, volatiles were evaporated in vacuo, the residue was purified by column chromatography on silica gel, using gradient elution by mixture hexane-CH₂Cl₂ (4:1) followed by mixture hexane-CH₂Cl₂ (2:1) to give 3-(thiophen-2-ylmethyl)-2-(trifluoromethyl)-1H-indole (4r), yield 0.031 g, (53%)
3-(Thiophen-2-ylmethyl)-2-(trifluoromethyl)-1H-indole (4r). White powder, m.p. 88–90 °C. 1H NMR (CDCl3, 400.1 MHz): δ 8.26 (br.s, 1H), 7.63 (d, 1H, 3J = 8.1 Hz), 7.37–7.42 (m, 1H), 7.29–7.35 (m, 1H), 7.17 (d(d, 1H), 3J = 8.0 Hz, 3J = 7.0 Hz, 4J = 1.0 Hz), 7.10 (dd, 1H, 3J = 5.1 Hz, 4J = 1.2 Hz), 6.89 (dd, 1H, 3J = 5.1 Hz, 4J = 3.5 Hz), 6.80–6.86 (m, 1H), 4.44 (s, 2H). 13C[1H] NMR (CDCl3, 100.6 MHz): δ 143.0, 135.2, 123.9, 125.0, 124.8, 123.6, 121.8 (q, J1CF = 269.0 Hz), 121.7 (q, J2CF = 36.8 Hz), 120.8, 120.5, 116.4 (q, J3CF = 2.7 Hz), 111.7, 24.2. 19F NMR (CDCl3, 376.5 MHz): δ −59.3 (s, 3F). HRMS (ESI-TOF): m/z [M − H]+ Calcd for C14H13F3NOS+: 280.0402; found: 280.0404.

3-(Methoxy(thiophen-2-yl)methyl)-2-(trifluoromethyl)-1H-indole (6a). Grey solid, m.p. 110–112 °C. 1H NMR (CDCl3, 400.1 MHz): δ 8.43 (br.s, 1H), 7.90 (d, 1H, 3J = 8.1 Hz), 7.39 (d, 1H, 3J = 8.3 Hz), 7.32 (t, 1H, 3J = 7.6 Hz), 7.23 (d, 1H, 3J = 5.0 Hz), 7.15 (t, 1H, 3J = 7.5 Hz), 6.86–6.92 (m, 1H), 6.83 (d, 1H, 3J = 3.4 Hz), 6.03 (s, 1H), 3.41 (s, 3H). 13C[1H] NMR (CDCl3, 100.6 MHz): δ 145.1, 135.3, 126.4, 125.2, 125.1, 125.0, 124.7, 123.0, 122.9 (q, J1CF = 37.3 Hz), 121.6 (q, J2CF = 260.4 Hz), 121.1, 117.3 (q, J3CF = 2.6 Hz), 111.7, 74.3, 56.8. 19F NMR (CDCl3, 376.5 MHz): δ −58.5 (s, 3F). HRMS (ESI-TOF): m/z [M + Na]+ Calcd for C15H12F3NOS+: 334.0484; found: 334.0475.

Synthesis of 3-(pyridin-4-ylmethyl)2-(trifluoromethyl)-1H-indole (4s). 12 mL vial was charged with enamine 1a (0.5 mmol), isonicotinaldehyde 2s (0.0669 g, 0.625 mmol) and glacial acetic acid (1 mL). Reaction mixture was kept at 80–90 °C (hotplate stirrer) under stirring for 10 h. The reaction mixture was cooled down to room temperature. Next, Pd/C (10%, 0.027 g, 0.025 mmol, 5 mol%) and formic acid (0.115 g, 2.5 mmol) was added and the reaction mixture was heated at 75 °C under stirring for 3 h. The reaction mixture was filtered through a short celite pad and dispersed between water (10 mL) and CH2Cl2 (20 mL). Aqueous layer was separated and extracted with CH2Cl2 (3×10 mL). Combined organic phases were dried over Na2SO4, volatiles were evaporated in vacuo, the residue was purified by column chromatography on silica gel, using gradient elution by mixture hexane–CH2Cl2 (1:1) followed by CH2Cl2 and CH2Cl2–MeOH (100:1) as eluents. Pale yellow-brown powder, m.p. 185–187 °C, yield 0.029 g (21%). 1H NMR (CDCl3, 400.1 MHz): δ 9.03 (br.s, 1H), 8.42–8.50 (m, 2H), 7.46 (d, 1H, 3J = 8.1 Hz), 7.43 (d, 2H, 3J = 8.3 Hz), 7.32 (t, 1H, 3J = 7.6 Hz), 7.11–7.18 (m, 3H), 4.26 (s, 2H). 13C[1H] NMR (CDCl3, 100.6 MHz): δ 150.5, 136.8, 127.8, 125.7, 124.4, 123.2 (q, J1CF = 268.2 Hz), 123.1 (q, J2CF = 36.5 Hz), 121.5, 121.0, 115.1 (q, J3CF = 2.7 Hz), 113.1, 29.5. 19F NMR (CDCl3, 376.5 MHz): δ −59.3 (s, 3F). HRMS (ESI-TOF): m/z [M + H]+ Calcd for C15H12F3N2+: 277.0947; found: 277.0950. See Supplementary Materials.
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Sample Availability: Samples of the compounds 3 and 4 are available from the authors.

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