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Synthesis of 1-Amino-1*H*-indole-3-carboxylates by Copper(I)-Catalyzed Intramolecular Amination of Aryl Bromides

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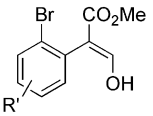
A simple route to various *N*-substituted 1-amino-1*H*-indole-3-carboxylates by use of copper(I)-catalyzed intramolecular *N*-arylation has been established. For the preparation of *N*-monosubstituted and *N*-unsubstituted derivatives, the cyclization of Boc-protected enehydrazines and subsequent deprotection were applied. Furthermore, 1-alkoxyindole-3-carboxylates can be synthesized by use of the same protocol

Introduction

1-Aminoindoles are an important class of compounds that display remarkable pharmacological properties.[1] For example, some of them exhibit psychotropic,[1c] anticonvulsant,[1d] analgesic,[1e] and antioxidant[1f,1g] effects. Various 1-arylaminoindole derivatives have found application as acetylcholinesterase inhibitors for the treatment of Alzheimer's disease.[2] In view of the high significance of these compounds, several methodologies for the construction of 1-aminoindole derivatives have been developed. The most frequently used method is based on the direct amination of indoles by hydroxylamine-*O*-sulfonic acid[3] or related reagents.[4] However, this methodology has a limited scope owing to the decreased reactivity of indoles containing an electron-withdrawing substituent in the 3-position.[4a] Other approaches to 1-aminoindoles include (1) reduction of *N*-nitrosoindoles,[5] (2) the Nenitzescu reaction,[6] and (3) palladium-catalyzed intramolecular cyclization of (2-chlorophenyl)acetaldehyde dimethylhydrazones.[7] However, only a few examples of the synthesis of 1-aminoindole-3-carboxylic acid derivatives have been reported.[4] All of these examples dealt with the direct amination protocol, which in most cases provided poor conversion of the starting materials. Moreover, to the best of our knowledge, no examples of the preparation of *N*- or *N*,*N*-substituted derivatives of 1-aminoindole-3-carboxylic acid have been published so far. At the same time, indole-3-carboxylic acids are widely used as building blocks in research and development aimed at the production of important pharmaceuticals. As a consequence, the development of a practical route for accessing 1-aminoindole-3-carboxylic acid derivatives remains an important goal.

Results and Discussion

In the past decade, the copper-catalyzed intramolecular C–N bond-forming reaction has proven to be extremely effective for the synthesis of a wide variety of nitrogen heterocycles.[8] A number of useful synthetic protocols for the assembly[9] and *N*-derivatization[10] of the indole ring system have been proposed as well. Very recently, our research group published a communication that described a new, efficient method to produce *N*-substituted indole-3-carboxylic acid derivatives by copper(I)-catalyzed intramolecular C–N bond formation starting from easily available *N*-substituted methyl 3-amino-2-(2-bromophenyl)acrylates.[9e] This procedure is very simple to operate and avoids the use of any supporting ligand or an inert atmosphere, without loss of yield. In continuation of our interest in the copper-catalyzed synthesis of indole derivatives, we explored this protocol for the preparation of 1-aminoindole-3-carboxylic acid derivatives.



1a R' = H
1b R' = 5-OMe

2a R = X = Me
2b R = Me, X = Boc
2c R = $CH_2C_6H_4Me$-*m*, X = H
2d R = Ph, X = H
2e R = Boc, X = H
2f R = X = Boc
2g R = $CH_2C_6H_4Cl$-*p*, X = Boc
2h R = Ph, X = Boc

In the work described here, we aimed to find out whether various 1-aminoindole-3-carboxylic esters could be synthesized by a copper(I)-catalyzed intramolecular amination reaction. Initially, we prepared enehydrazines **3a**–**h** as cycliza-

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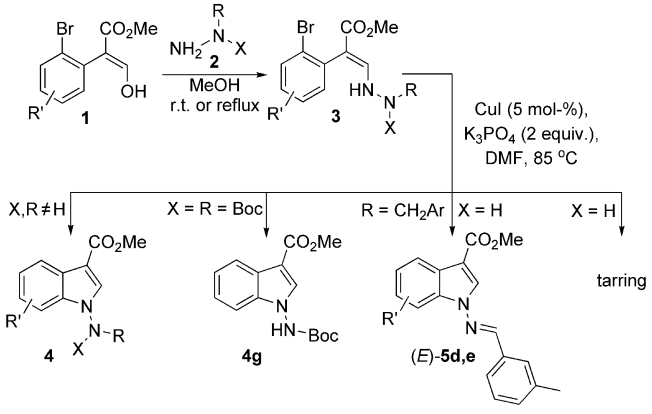
tion precursors for the preparation of various 1-aminoindole-3-carboxylates. In our previously developed protocol, the starting materials needed for the cyclization stage were easily prepared from methyl 2-(2-bromophenyl)-3-formylacetates **1** and various primary amines by stirring a mixture of reagents in methanol at room temperature. Similarly, reaction of **1** with various hydrazines **2** gave the corresponding enehydrazines **3** after stirring the solutions in methanol for several hours (Scheme 1). The formation of enehydrazine **3h** took 50 h to complete at room temperature or 3 h at reflux temperature. All enehydrazines **3**, except for **3d** and **3e**, were isolated in excellent yield and high purity and were used in the next stage without additional purification. Enehydrazines **3d** and **3e** were isolated in 53 and 56% yields, respectively, after flash-column chromatography. Cyclization of substrates **3** was carried out under the conditions described earlier[9e] (Scheme 1) and did not proceed as smoothly as we had hoped. As shown in Table 1, expected 1-aminoindole derivatives **4** were obtained in good yield only from *N*,*N*,*N*′-trisubstituted substrates **3a**–**c** and **3h** (Table 1, entries 1–3, 8). In the case of **3h**, only a trace amount of bis-Boc indole **4h** was observed; monodeprotection of the Boc group proceeded to give *N*-Boc-1-aminoindole-3-carboxylate (**4g**) as the main product in 78% yield (Table 1, entry 8). The elimination of the Boc group under copper-catalyzed cross-coupling reaction conditions has been mentioned earlier.[11] The reaction of enehydrazines **3f** and **3g** (Table 1, entries 6 and 7) resulted in the formation of a complex mixture of products; among them, *N*-unsubstituted methyl indole-3-carboxylate was found (≈10%) when the reaction mixture was analyzed by GC–MS. Neither 1-aminoindole derivatives nor the corresponding dihydrocinnolines (also expected for *N*,*N*′-disubstituted enehydrazines) were found in the mixture, although total consumption of the cyclization precursors was observed. Meanwhile, under the same conditions, the reaction of enehydrazines **3d** and **3e** gave methyl *N*-benzylidene-1-aminoindole-3-carboxylates (*E*)-**5d** and (*E*)-**5e** as the only products (Table 1, entries 4 and 5). The configuration of the C=N bond of **5** was determined by nOe experiments. We supposed that products **5d** and **5e** might have been a result of copper-catalyzed oxidation of originally formed 1-benzylaminoindoles **4d** and **4e** by oxygen in the air,[12] as we carried out the cyclization without exclusion of air. However, a control experiment under an inert atmosphere gave essentially the same result and showed that the reaction was not influenced by oxygen in the air. It was previously reported that *N*,*N*′-disubstituted hydrazines could be readily oxidized to the corresponding diazenes under cross-coupling reaction conditions (CuI, inorganic base, DMF).[11] On the basis of this fact, we assumed that in the cases of substrates **3d**–**g** the initial formation of the corresponding diazenes **6d**–**g** took place, although the mechanistic details of the reaction remain unclear at the moment. Because azo–hydrazone tautomerism[13] was possible only for the diazenes derived from **3d** and **3e**, cyclization was observed only in this cases and gave *N*-benzylidene products **5d** and **5e**. Substrates **3f** and **3g** gave diazenes, which were not suitable for cyclization and, therefore, were decomposed under the reaction conditions (Scheme 2).



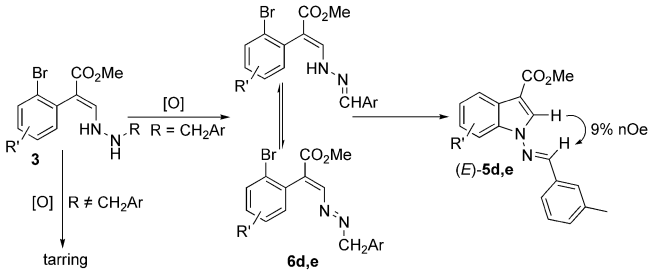
Scheme 1.

Because enehydrazines **3d**–**f** were unsuitable for this protocol for the synthesis of *N*-monosubstituted 1-aminoindole-3-carboxylates, we next investigated *N*-Boc-*N*-substituted hydrazines **3i** and **3k** as cyclization precursors. Enehydrazines **3i** and **3k** were prepared by heating a methanol solution of **1** and **2g**[14] or **2h**[15] at reflux for 3 h and used in the cyclization stage without further purification. As expected, the corresponding 1-aminoindoles **4i** and **4k** were isolated in good yield (Table 1, entries 9 and 10). In these cases, we did not observe any deprotection product.

Table 1. Cyclization of enehydrazines **3**.[a]

Entry	Starting materials	Enehydrazine	R	X	R′	Reaction time [h][b]	Expected product	Isolated product	Yield [%]
1	**1a**, **2a**	**3a**	Me	Me	H	2	**4a**	**4a**	82
2	**1b**, **2a**	**3b**	Me	Me	OMe	2	**4b**	**4b**	79
3	**1a**, **2b**	**3c**	Me	Boc	H	2	**4c**	**4c**	81
4	**1a**, **2c**	**3d**	$CH_2C_6H_4Me$-*m*	H	H	2	**4d**	(*E*)-**5d**	68
5	**1b**, **2c**	**3e**	$CH_2C_6H_4Me$-*m*	H	OMe	2	**4e**	(*E*)-**5e**	65
6	**1a**, **2d**	**3f**	Ph	H	H	2	**4f**		0
7	**1a**, **2e**	**3g**	Boc	H	H	2	**4g**		0
8	**1a**, **2f**	**3h**	Boc	Boc	H	10	**4h**	**4g**	78
9	**1b**, **2g**	**3i**	$CH_2C_6H_4Cl$-*p*	Boc	OMe	2	**4i**	**4i**	86
10	**1a**, **2h**	**3k**	Ph	Boc	H	2	**4k**	**4k**	78

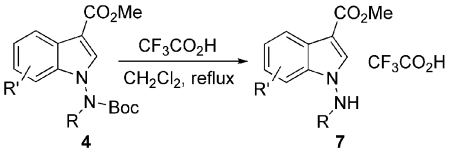
[a] Reaction conditions: **3** (≈3 mmol), CuI (5 mol-%), K_3PO_4 (2 equiv.), DMF (6 mL), 85 °C. [b] The reaction was continued to ≥95% conversion.



Scheme 2.

Finally, selective *N*-deprotection of synthesized *N*-Boc-1-aminoindoles **4c**, **4g**, **4i**, and **4k** could be performed smoothly under typical reaction conditions (Table 2). This yielded desired compounds **7** as the trifluoroacetate salts in high yield.

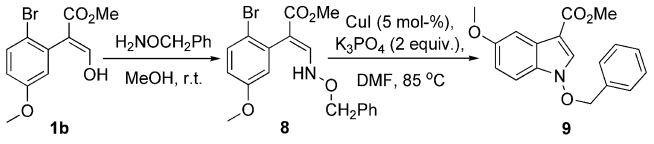
Table 2. *N*-Deprotection of *N*-Boc-1-aminoindoles.[a]



Entry	Indole	R	Reaction time[b] [h]	Product	Yield [%]
1	**4c**	Me	6	**7a**	90
2	**4g**	H	6	**7b**	88
3	**4i**	$CH_2C_6H_4Cl$-*p*	10	**7c**	90
4	**4k**	Ph	8	**7d**	87

[a] Reaction conditions: **4** (2 mmol), CF_3CO_2H (6 equiv.), CH_2Cl_2 (8 mL). [b] The reaction was continued to ≥95% conversion.

Additionally, this copper-mediated route to *N*-substituted 1*H*-indole-3-carboxylates could be extended to the preparation of 1-alkoxy derivatives, which are also interesting as pharmaceutical precursors but are available by only limited methods.[16] For instance, methyl 3-(benzyloxyamino)-2-(2-bromo-5-methoxyphenyl)acrylate (**8**) was converted into methyl 1-(benzyloxy)-5-methoxy-1*H*-indole-3-carboxylate (**9**) in 87% yield (Scheme 3).



Scheme 3.

Conclusions

We explored our previously reported method for the preparation of *N*-substituted 1*H*-indole-3-carboxylates by Cu^I-mediated intramolecular *N*-arylation and have found that 1-aminoindole-3-carboxylic acid derivatives can be synthesized, starting from suitable substituted hydrazines and easily accessible starting materials, in two steps. Only *N*,*N*,*N*′-trisubstituted enehydrazines can be employed as cyclization precursors for 1-aminoindoles. However, use of Boc-protected substrates in the cyclization step and subsequent deprotection led to *N*-monosubstituted and *N*-unsubstituted 1-aminoindole-3-carboxylates. This protocol may serve as a useful tool for the generation of libraries of compounds for research laboratories in pharmaceutical and agrochemical companies. Further synthetic applications of Cu^I-catalyzed indole ring formation are currently ongoing in our laboratory.

Experimental Section

General: All chemicals and solvent were purchased from commercial suppliers and used as received. All reactions were performed in an air atmosphere. Reactions were monitored by TLC until completion. ^1H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, with $CDCl_3$ or [D_6]DMSO as the solvent and internal standard. Mass spectra were recorded in electron impact mode at 70 eV. Melting points were determined by the open capillary method and are uncorrected. Analytical samples were prepared by flash chromatography on silica gel (Merck, 230–400 mesh). TLC was carried out on silica gel 60 F254 plates (Merck), and the spots were located with UV light. Methyl 2-(2-bromophenyl)-2-formylacetate (**1a**),[17] methyl 2-(2-bromo-5-methoxyphenyl)-2-formylacetate (**1b**),[17] *tert*-butyl 1-methylhydrazinecarboxylate (**2b**),[18] *tert*-butyl 1-(4-chlobenzyl)hydrazinecarboxylate (**2f**),[14] and *tert*-butyl 1-phenylhydrazinecarboxylate (**2g**)[15] were prepared in accordance with previously reported procedures.

General Procedure for the Cu-Catalyzed Synthesis of Methyl *N*-Amino-1*H*-indole-3-carboxylates 4: To a solution of formylacetate **1** (3 mmol) in methanol (5 mL) was added a corresponding hydrazine **2** (3 mmol) by syringe at room temperature. The mixture was stirred for 6 h at room temperature (3 h at reflux for **3h**, **3i**, **3k**), and the solvent was evaporated to dryness under reduced pressure to give a crude product. Enehydrazines **3d** and **3e** were purified by column chromatography (hexane/ethyl acetate, 2:1) to give the above-mentioned products in 53 (596 mg) and 56% (680 mg) yield, respectively. In all other cases, enehydrazines **3** were isolated in high purity and yields and were used in the next step without further purification. To a solution of **3** in DMF (6 mL) was added CuI (28.5 mg, 0.15 mmol) and anhydrous K_3PO_4 (1.3 g, 6.0 mmol). The reaction mixture was heated at 85 °C (bath temperature) for the time specified in Table 1 and cooled. The solvent was evaporated to dryness under reduced pressure. Water (8 mL) was added to the residue, and the mixture was extracted (3 × 4 mL) with ethyl acetate. The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed in vacuo to yield the crude product that was purified by column chromatography (hexane/ethyl acetate, 15:1).

Methyl 1-(Dimethylamino)-1*H*-indole-3-carboxylate (4a): Yield 82% (536 mg). Tan oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.97 (s, 6 H), 3.94 (s, 3 H), 7.25–7.35 (m, 2 H), 7.61 (dd, J = 6.5, 2.0 Hz, 1 H), 8.14–8.20 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.3, 51.1, 106.2, 110.4, 121.4, 122.4, 123.1, 123.9, 128.2, 135.6, 165.3 ppm. MS (I): *m*/*z* (%) = 218 (64) $[M]^+$, 160 (31), 159 (100) $[M - CO_2Me]^+$, 146 (24), 144 (75) $[M - CO_2Me - Me]^+$, 118 (36). $C_{12}H_{14}N_2O_2$ (218.25): calcd. C 66.07, H 6.50; found C 66.04, H 6.47.

Methyl 1-(Dimethylamino)-5-methoxy-1*H*-indole-3-carboxylate (4b): Yield 79% (587 mg). Tan oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.94 (s, 6 H), 3.91 (s, 3 H), 3.92 (s, 3 H) 6.95 (dd, J = 9.1, 2.5 Hz, 1 H), 7.48 (d, J = 9.1 Hz, 1 H), 7.64 (d, J = 2.5 Hz, 1 H), 8.01 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.3, 51.0, 55.8, 102.6, 105.4, 111.2, 113.6, 124.7, 128.0, 130.5, 156.2, 165.3 ppm. MS (I): *m*/*z* (%) = 248 (46) $[M]^+$, 233 (37) $[M - Me]^+$, 189 (100) $[M - CO_2Me]^+$, 174 (31) $[M - CO_2Me - Me]^+$. $C_{13}H_{16}N_2O_3$ (248.28): calcd. C 62.90, H 6.50; found C 62.89, H 6.50.

Methyl 1-[(*tert*-Butyloxycarbonyl)(methyl)amino]-1*H*-indole-3-carboxylate (4c): Yield 81% (738 mg). Tan semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 3.44 (s, 3 H), 3.93 (s, 3 H), 7.21–7.35 (m, 3 H), 7.81 (s, 1 H), 8.16–8.24 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 37.8, 51.2, 82.6, 107.1, 108.9, 121.9, 122.6, 123.8, 124.4, 133.5, 135.2, 154.4, 165.0 ppm. MS (I): *m*/*z* (%) = 304 (100) $[M]^+$, 248 (95) $[M - CH_2{=}CMe_2]^+$, 204 (93) $[M - Boc + H]^+$, 144 (77) $[M - Boc - CO_2Me]^+$. $C_{16}H_{20}N_2O_4$ (304.34): calcd. C 63.15, H, 6.63; found C 63.14, H 6.62.

Methyl 1-{[1-(3-Methylphenyl)methylene]amino}-1*H*-indole-3-carboxylate (5d): Yield 68% (595 mg). White solid. M.p. 105–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 3.99 (s, 3 H), 7.32–7.46 (m, 4 H), 7.71 (d, J = 7.6 Hz, 1 H), 7.77 (s, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 8.19 (d, J = 7.6 Hz, 1 H), 8.39 (s, 1 H), 8.58 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 51.4, 108.5, 111.1, 121.5, 122.3, 123.0, 124.1, 124.8, 125.6, 128.4, 128.9, 132.2, 133.1, 136.6, 138.8, 149.2, 165.3 ppm. MS (I): *m*/*z* (%) = 292 (100) $[M]^+$, 261 (25) $[M - OMe]^+$, 146 (34), 144 (94) $[M - OMe - m\text{-}MeC_6H_4CN + H]^+$. $C_{18}H_{16}N_2O_2$ (292.33): calcd. C 73.96, H 5.52; found C 73.95, H 5.52.

Methyl 1-{[1-(3-Methylphenyl)methylene]amino}-5-methoxy-1*H*-indole-3-carboxylate (5e): Yield 65% (628 mg). White solid. M.p. 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 3.93 (s, 3 H), 3.97 (s, 3 H), 7.03 (dd, J = 9.0, 2.6 Hz, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.63–7.69 (m, 2 H), 7.70–7.77 (m, 2 H), 8.27 (s, 1 H), 8.48 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 51.2, 55.8, 102.7, 107.8, 112.0, 114.4, 122.1, 125.5, 125.6, 128.4, 128.9, 131.6, 132.2, 133.1, 138.8, 149.0, 156.6, 165.3 ppm. MS (I): *m*/*z* (%) = 322 (100) $[M]^+$, 204 (76) $[M - H - m\text{-}MeC_6H_4CN]^+$, 190 (26), 176 (64), 175 (46). $C_{19}H_{18}N_2O_3$ (322.36): calcd. C 70.78, H 5.65; found C 70.79, H 5.63.

Methyl 1-[(*tert*-Butyloxycarbonyl)amino]-1*H*-indole-3-carboxylate (4g): Yield 78% (678 mg). Off-white solid. M.p. 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 3.89 (s, 3 H), 7.23–7.35 (m, 4 H), 7.78 (s, 1 H), 8.15 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 51.1, 82.9, 106.8, 109.0, 121.7, 122.7, 123.8, 124.4, 135.1, 136.6, 154.2, 165.2 ppm. MS (I): *m*/*z* (%) = 290 (15) $[M]^+$, 234 (25) $[M - CH_2{=}CMe_2]^+$, 190 (53) $[M - Boc + H]^+$, 131 (52) $[M - Boc - CO_2Me + H]^+$, 57 (100). $C_{15}H_{18}N_2O_4$ (290.32): calcd. C 62.06, H 6.25; found C 62.07, H 6.26.

Methyl 1-[(*tert*-Butyloxycarbonyl)(4-chlorobenzyl)amino]-5-methoxy-1*H*-indole-3-carboxylate (4i): Yield 86% (1.15 g). Yellow solid. M.p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 4.57 (d, J = 15.0 Hz, 1 H), 5.13 (d, J = 15.0 Hz, 1 H), 6.86–6.97 (m, 2 H), 7.13 (d, J = 8.5 Hz, 2 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.37 (s, 1 H), 7.64 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 51.1, 53.3, 55.8, 83.1, 103.3, 106.4, 109.9, 114.1, 125.3, 128.7, 129.0, 130.4, 134.3, 134.4, 134.5, 154.0, 156.4, 165.1 ppm. MS (I): *m*/*z* (%) = 446/444 (9/3) $[M]^+$, 390/388 (45/15) $[M - CH_2C{=}CMe_2]^+$, 344/346 (45/15) $[M - Boc + H]^+$, 263 (43) $[M - CH_2{=}CMe_2 - C_7H_6Cl]^+$, 219 (60), 159 (87), 125 (80), 57 (100). $C_{23}H_{25}ClN_2O_5$ (444.91): calcd. C 62.09, H 5.66; found C 62.07, H 5.67.

Methyl 1-[(*tert*-Butyloxycarbonyl)(phenyl)amino]-1*H*-indole-3-carboxylate (4k): Yield 78% (856 mg). Yellow solid. M.p. 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 3.95 (s, 3 H), 7.20 (t, J = 7.1 Hz, 1 H), 7.30–7.40 (m, 7 H), 7.94 (s, 1 H), 8.23–8.28 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 51.3, 83.7, 107.7, 109.3, 121.9, 122.1, 122.9, 124.2, 124.3, 126.2, 129.1, 134.2, 136.3, 140.7, 152.2, 164.9 ppm. MS (I): *m*/*z* (%) = 366 (16) $[M]^+$, 266 (80) $[M - Boc + H]^+$, 206 (60) $[M - Boc - CO_2Me]^+$, 92 (68), 57 (100). $C_{21}H_{22}N_2O_4$ (366.41): calcd. C 68.84, H 6.05; found C 68.84, H 6.06.

General Procedure for the Deprotection of Methyl *N*-Boc-1-aminoindole-3-carboxylates: To a solution of *N*-Boc-1-aminoindole **4** (2 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (1.4 g, 1 mL, 12 mmol). The reaction mixture was heated at reflux for the time indicated in Table 2 and then cooled. The solution was concentrated in vacuo, and the residue was washed several times with diethyl ether and dried in high vacuo to give pure product.

Methyl 1-(Methylamino)-1*H*-indole-3-carboxylate Trifluoroacetate (7a): Yield 90% (572 mg). Brown oil. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.83 (s, 3 H), 3.81 (s, 3 H), 7.18–7.30 (m, 2 H), 7.58 (d, J = 7.8 Hz, 1 H), 8.03 (d, J = 7.6 Hz, 1 H), 8.12 (s, 1 H), 10.36 (br., 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 39.5, 51.1, 104.0, 110.9, 121.2, 122.2, 123.0, 124.7, 134.3, 135.7, 164.7 ppm. MS (I): *m*/*z* (%) = 204 (70) $[M]^+$, 189 (20) $[M - Me]^+$, 145 (53) $[M - CO_2Me]^+$, 117 (39), 84 (80), 68 (68), 66 (100). $C_{13}H_{13}F_3N_2O_4$ (318.25): calcd. C 49.06, H 4.12; found C 49.07, H 4.14.

Methyl 1-Amino-1*H*-indole-3-carboxylate Trifluoroacetate Adduct (7b): Yield 88% (535 mg). White solid. M.p. 110–115 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.17 (s, 3 H), 7.18–7.35 (m, 2 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.98 (s, 1 H), 8.06 (d, J = 8.1 Hz, 1 H), 9.36 (br., 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 50.8, 102.9, 110.9, 120.7, 121.8, 122.5, 124.5, 135.8, 137.3, 164.7 ppm. MS (I): *m*/*z* (%) = 190 (99) $[M]^+$, 175 (27) $[M - Me]^+$, 159 (29) $[M - MeO]^+$, 131 (100) $[M - CO_2Me]^+$. $C_{12}H_{11}F_3N_2O_4$ (304.22): calcd. C 47.38, H 3.64; found C 47.37, H 3.64.

Methyl 1-[(4-Chlorobenzyl)amino]-5-methoxy-1*H*-indole-3-carboxylate Trifluoroacetate (7c): Yield 90% (824 mg). Brown oil. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.74 (s, 3 H), 3.75 (s, 3 H), 4.21 (s, 2 H), 6.84 (dd, J = 8.9, 2.5 Hz, 1 H), 7.30 (s, 4 H), 7.40–7.45 (m, 2 H), 7.88 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 51.1, 54.9, 55.7, 102.7, 103.3, 112.0, 113.0, 123.3, 128.6, 129.1, 131.2, 132.5, 134.6, 137.0, 155.9, 164.8 ppm. MS (I): *m*/*z* (%) = 346/344 (10/30) $[M]^+$, 219 (100) $[M - C_7H_6Cl]^+$, 159 (44). $C_{20}H_{18}ClF_3N_2O_5$ (458.82): calcd. C 52.36, H 3.95; found C 52.37, H 3.94.

Methyl 1-(Phenylamino)-1*H*-indole-3-carboxylate Trifluoroacetate (7d): Yield 87% (661 mg). Brown oil. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 3.84 (s, 3 H), 6.46–6.56 (m, 2 H), 6.83 (t, J = 7.3 Hz, 1 H), 7.12–7.36 (m, 5 H), 8.11–8.21 (m, 2 H), 9.63 (br., 1 H), 12.18 (br., 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 50.9, 104.9, 110.6, 112.5, 120.6, 121.1, 122.3, 123.2, 124.6, 129.3, 135.8, 135.9, 147.8, 164.3 ppm. MS (I): *m*/*z* (%) = 266 (85) $[M]^+$, 235 (33) $[M - MeO]^+$, 234 (57), 207 (100) $[M - CO_2Me]^+$, 206 (72). $C_{18}H_{15}F_3N_2O_4$ (380.32): calcd. C 56.85, H 3.98; found C 56.87, H 3.97.

Methyl 1-(Benzyloxy)-5-methoxy-1*H*-indole-3-carboxylate (9): The general procedure for the preparation of **4** was employed by starting from formylacetate **1b** and *O*-benzylhydroxylamine. Yield 87% (811 mg). Tan oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 3.91 (s, 3 H), 5.23 (s, 2 H), 6.94 (dd, J = 8.8, 2.3 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 1 H), 7.33–7.44 (m, 5 H), 7.65–7.68 (m, 2 H) ppm. ^{13}C

NMR ($CDCl_3$): δ = 51.0, 55.8, 81.1, 102.3, 102.7, 109.9, 114.1, 123.7, 127.5, 128.9, 129.3, 129.6, 129.7, 133.8, 156.2, 165.2 ppm. MS (I): *m*/*z* (%) = 311 (26) $[M]^+$, 220 (53) $[M - C_6H_7]^+$, 91 (100). $C_{18}H_{16}NO_4$ (311.33): calcd. C 69.46, H 5.51; found C 69.44, H, 5.50.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds.

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