Intramolecular Friedel–Crafts Reaction of Indoles with Carbonyl Groups: A Simple Synthesis of 3- and 4-Substituted β-Carbolin-1-ones

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Abstract: The intramolecular Friedel–Crafts reaction of indole-2-carboxylic acid β-oxoamides catalyzed by trifluoroacetic acid or $InCl_3$, is a convenient method for the synthesis of 3-aryl-, 4-aryl-, and 4-alkyl-β-carbolin-1-ones.

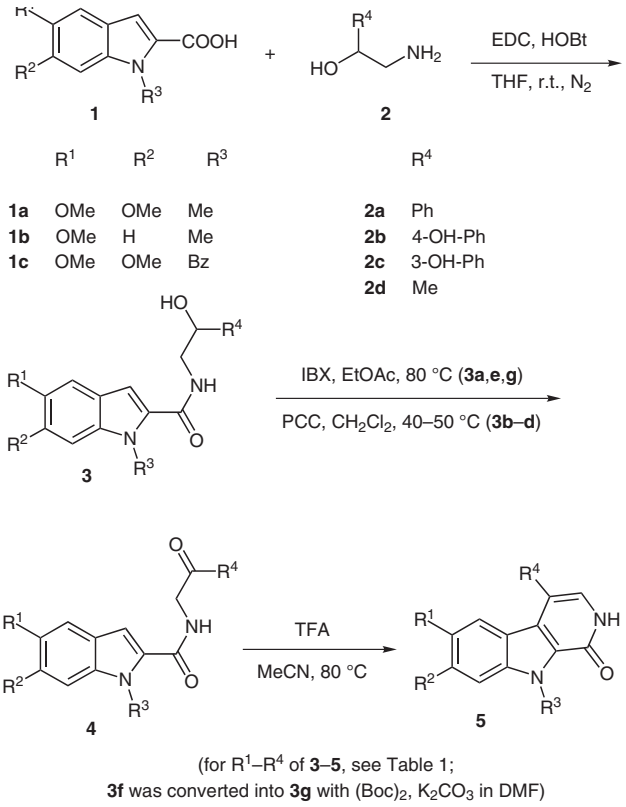
Key words: heterocycles, indoles, ring closure, Friedel–Crafts reaction, β-carbolinones

The β-carbolin-1-one nucleus occurs in natural products,[1] and some derivatives show significant biological activity.[2] As part of a research program aimed at preparing some 3-aryl- and 4-aryl-β-carbolin-1-ones we became interested in developing an efficient synthetic strategy for these compounds.

Recently, some 3-aryl-β-carbolin-1-ones displaying antitumor activity have been synthesized[3] from non-indole starting materials. As for 4-aryl-β-carbolin-1-ones, only one example of synthesis of this class of compounds, based on an intramolecular cycloaddition–elimination reaction of 2(1*H*)-pyrazinones, has been reported, to the best of our knowledge, in literature.[4]

To design a more straightforward route to these compounds, an obvious approach appeared to be the intramolecular Friedel–Crafts (FC) reaction of the appropriate indole-2-carboxylic acid β-oxoamides. The intermolecular FC condensation of indoles with aldehydes and ketones for the preparation of bis(1*H*-indol-3-yl)alkanes is well documented,[5] with a plethora of examples,[6] whereas only a few cases of intermolecular monoalkylation with ketones have been mentioned.[7]

Even less exploited appeared the intramolecular FC reaction. An accurate perusal of the literature showed that this method has been almost completely neglected. In the recent years several approaches to intramolecular annulation of indoles, such as Michael addition to enones[8,9] or Pd-catalyzed allylic alkylation,[8,10] have been devised. On the contrary, only two old examples of the simple intramolecular FC reaction with carbonyl compounds exist in the literature,[11,12] so that it has not even been mentioned in the most recent review.[8]



Scheme 1

Herein we report a short and efficient synthesis of a series of 3-aryl-, 4-aryl-, and 4-alkyl-β-carbolin-1-ones, that was achieved using this neglected, yet simple reaction.

For the synthesis of 4-aryl-β-carbolin-1-ones **5**, the appropriate 2-indolecarboxylic acids **1a–c** were activated with EDC and *N*-hydroxybenzotriazole (HOBt) and were coupled, in high yield, with easily available 2-amino alcohols **2a–d** (Scheme 1, Table 1).

The intermediate hydroxyamides **3a** and **3e** were oxidized to the corresponding ketoamides **4a** and **4e** with excellent yields, using 2-iodoxybenzoic acid (IBX).[13] Only when a phenol ring (that we required) was linked to the amino alcohol (compounds **3b–d**), low yields were obtained, most probably due the sensitivity of the phenol ring to this oxidant. The use of PCC improved the yield of the desired ketones, but the best yields were restored when the phenolic OH was selectively protected with Boc with respect to the alcohol (see **4g**).

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Table 1 Yields for the Synthesis of Compounds **3**–**5**

Entry	R^1	R^2	R^3	R^4	Yield (%)		
					3	**4**	**5**
a	OMe	OMe	Me	Ph	63	88	63[a]
b	OMe	OMe	Me	4-HOC_6H_4	88	30	88
c	OMe	OMe	Me	3-HOC_6H_4	81	25	47
d	OMe	H	Me	4-HOC_6H_4	96	10	14
e	OMe	OMe	Me	Me	80[b]	98	66
f	OMe	OMe	Bn	4-HOC_6H_4	87		44
g	OMe	OMe	Bn	4-$BocOC_6H_4$	86	99	
h	OMe	OMe	H	4-HOC_6H_4			52

[a] The yield increased to 69% using $InCl_3$ as a catalyst.
[b] Yield for the coupling reaction with 5,6-dimethoxy-2-indolecarboxylic acid; methylation of the NH with MeI and K_2CO_3 was performed on the amide.

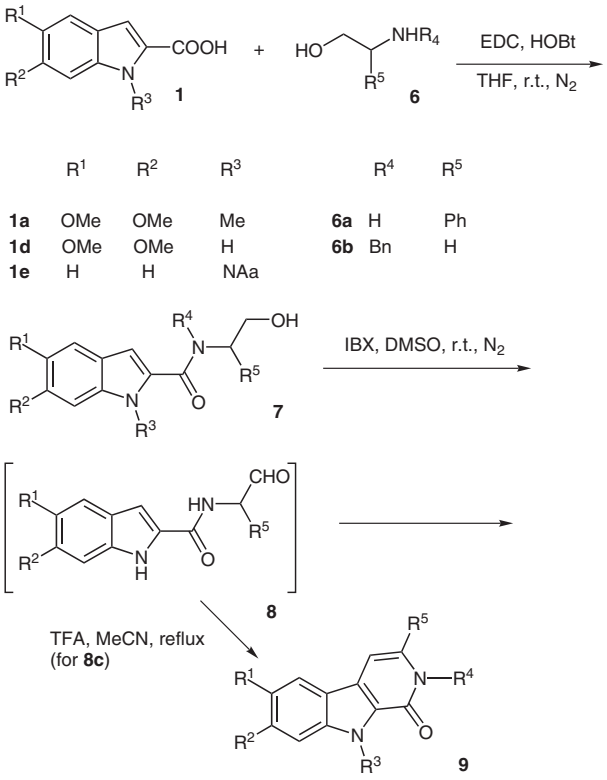
The crucial cyclization step was obtained with TFA in acetonitrile at 80 °C. In some cases a high yield was obtained. Here the increased nucleophilicity of the indole ring due to activation by the methoxy substituents might have played an important role.[14] This observation is consistent with the increase of yield from **3d** to **3b**. Based on recent work[8] on the use of indium salts as mild Lewis acids in the promotion of Friedel–Crafts-like reactions on indoles, we repeated the cyclization of **3a** using indium trichloride instead of TFA. Cyclization to **4a** was obtained with a slightly improved yield (69% vs. 63%).

All the reactions were performed on *N*-alkyl indoles. To ascertain that the reaction could be used for preparing N-unsubstituted indoles, a suitable acid-resistant protecting group was found in the benzyl group. This group was removed after the cyclization using $AlCl_3$, a reagent that did not interfere with the double bond in the β-carbolinone ring (see **5h**).

A similar scheme was followed for the synthesis of 3-aryl-β-carbolin-1-ones **9a**,**c**,**d** and for the unsubstituted **9b** (Scheme 2, Table 2).

Interestingly, the aldehydes that formed, except for the N-unsubstituted indole **8c**, spontaneously cyclized. It happened most likely because of their sensitivity to the acidity of IBX or its reduction products. The possibility that the acidity of the hypervalent iodine oxidants could induce further reactions has been recently highlighted.[15] This behavior allowed us to obtain a good yield of 3-aryl-β-carbolin-1-ones in just two steps from readily available starting materials.

These results indicate that this method is competitive with the existing syntheses of β-carbolinones[16] and is likely the method of choice in the case of 3- or 4-substituted compounds, and of products with activated indole nuclei.



(for R^1–R^5 of **7**–**9**, see Table 2; NA = 2-naphthylmethyl)

Scheme 2

Table 2 Yields for the Synthesis of Compounds **7** and **9**

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%) **7**	Yield (%) **9**
a	OMe	OMe	Me	H	Ph	90[a]	65
b	OMe	OMe	Me	Bn	H	92[a]	7
c	OMe	OMe	H	H	Ph	90	41[b]
d	H	H	NA[c]	H	Ph	88	28

[a] Yield for the coupling reaction with the corresponding 5,6-dimethoxy-2-indolecarboxylic acid; methylation of the NH with MeI and K_2CO_3 was performed on the amide.
[b] Yield for the reaction from **8c** to **9c**.
[c] 2-Naphthylmethyl.

In conclusion, we have developed a short and efficient synthesis of β-carbolin-1-ones based on the intramolecular Friedel–Crafts reaction of indoles with carbonyl groups.[17] This procedure allows for the introduction of various aryl and alkyl substituents in the 3- and 4-positions of the β-carbolin-1-one ring. It has the advantage of using simple reactants and favorable reaction conditions and it does not require air-sensitive organometallic reagents and strictly anhydrous solvents. Extension to other substrates to further investigate the scope and limitations of this annulation process, as well as application of this method to the synthesis of natural products or analogues, are in progress.

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(17) **General Procedure for the Synthesis of Hydroxyamides 3 and 7**: The appropriate amino alcohol **2** (3 mmol) was dissolved in anhyd THF (12 mL) and then EDC (3 mmol), HOBt (3 mmol) and the corresponding indole-2-carboxylic acid (2 mmol) were added sequentially at 25 °C. After stirring overnight at r.t., evaporating the solvent, pouring the product into sat. aq $NaHCO_3$, extracting with EtOAc, washing with 1 N HCl, sat. aq $NaHCO_3$, brine, drying over Na_2SO_4 and concentrating the combined extract gave the amide.

General Procedure for the Synthesis of Ketoamides 4a,e,g, and 8c: A suspension of the appropriate amide **3** or **7c** (0.45 mmol) in EtOAc (6 mL) was added with IBX (1.35 mmol), then immersed in an oil bath set to 80 °C and stirred vigorously open to the atmosphere. After 2.5 h (TLC monitoring) the reaction was cooled to r.t. and filtered through a medium glass frit. The filter cake was washed with EtOAc–CH_2Cl_2 (50:50, 2 × 6 mL) and the combined filtrates were concentrated to yield the product.

General Procedure for the Synthesis of Ketoamides 4b–d: To a well-stirred suspension of the appropriate amide **3** (2 mmol) in anhyd CH_2Cl_2 (10 mL) was added PCC (4 mmol) and the mixture was stirred at 40–50 °C, under nitrogen, for 8 h. Silica gel was added, the solvent evaporated and the residue was purified by flash chromatography (CH_2Cl_2–acetone, 90:10).

General Procedure for the Synthesis of β-Carbolin-1-ones 5 and 9c: Trifluoroacetic acid (0.6 mmol) was added to a suspension of the appropriate ketoamide **4** or **8c** (0.4 mmol) in MeCN (6 mL) and the mixture was refluxed for 16 h. Evaporating the solvent, extracting with EtOAc, washing with sat. aq $NaHCO_3$, drying over Na_2SO_4 and concentrating the extract gave a crude product that was purified by crystallization or by flash chromatography.

General Procedure for the Synthesis of β-Carbolin-1-ones 9a,b,d: To a solution of IBX (1 mmol) in DMSO (1.5 mL) the appropriate hydroxyamide **7** (0.521 mmol) was added and the solution was stirred overnight at r.t. under N_2. The solution was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with sat. aq $NaHCO_3$, H_2O, dried over Na_2SO_4 and evaporated. The crude product was crystallized from EtOAc (**9a**,**d**) or chromatographed on flash silica gel (CH_2Cl_2–MeOH, 99:1; **9b**).

Deprotection of 5f: To an ice-cooled suspension of **5f** (170 mg, 0.399 mmol) in anisole (16 mL), $AlCl_3$ (319 mg, 2.39 mmol) was added and the mixture was stirred for 30 min at 110 °C. Addition of H_2O, extraction with EtOAc, washing with $NaHCO_3$, H_2O and brine, then drying, filtering and evaporating of solvent, followed by flash chromatography with CH_2Cl_2–MeOH (94:6) as an eluent, gave **5h** (59 mg, 52%); mp 280 °C (MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.86 (s, 1 H), 11.31 (s, 1 H), 9.55 (s, 1 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 6.72–6.94 (m, 5 H), 3.81 (s, 3 H), 3.53 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 155.1, 150.3, 144.5, 135.1, 130.7, 127.8, 127.2, 123.2, 122.5, 116.8, 115.6, 114.2, 104.2, 94.9, 55.8.

Spectral data for relevant compounds [unless otherwise noted: ^{1}H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6)]

5a: mp 260 °C (dec.). ^{1}H NMR: δ = 11.4 (d, *J* = 4.5 Hz, 1 H), 7.57–7.40 (m, 5 H), 7.15 (s, 1 H), 6.85 (d, *J* = 4.5 Hz, 1 H), 6.65 (s, 1 H), 4.27 (s, 3 H), 3.88 (s, 3 H), 3.45 (s, 3 H). ^{13}C NMR: δ = 155.9, 150.5, 144.9, 137.2, 136.3, 129.8 (2 × C), 128.8 (2 × C), 127.9, 125.8, 123.4, 122.7, 116.6, 112.8,

103.8, 93.6, 56.2, 56.05, 31.6.

5b: mp 258 °C. ^{1}H NMR: δ = 11.30 (d, *J* = 4.8 Hz, 1 H), 9.57 (s, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.12 (s, 1 H), 6.90 (d, *J* = 8.2 Hz, 2 H), 6.77 (d, *J* = 4.8 Hz, 1 H), 6.75 (s, 1 H), 4.27 (s, 3 H), 3.87 (s, 3 H), 3.50 (s, 3 H). ^{13}C NMR: δ = 157.2, 155.6, 150.7, 144.7, 136.6, 130.9 (2 × C), 128.3, 125.9, 123.9, 122.6, 116.7, 115.5 (2 × C), 113.0, 104.3, 93.8, 56.2, 55.8, 31.6.

5c: mp 271 °C. ^{1}H NMR: δ = 11.35 (d, *J* = 5.2 Hz, 1 H), 9.55 (br s, 1 H), 7.30 (t, *J* = 8.2 Hz, 1 H), 7.16 (s, 1 H), 6.95 (d, *J* = 5.2 Hz, 1 H), 6.93 (d, *J* = 1.5 Hz, 1 H), 6.80–6.86 (m, 3 H), 4.45 (s, 3 H), 3.90 (s, 3 H), 3.50 (s, 3 H). ^{13}C NMR: δ = 157.8, 155.9, 150.6, 144.7, 138.3, 136.5, 129.9, 125.8, 123.1, 120.0, 116.8, 116.5, 116.4, 114.8, 112.9, 104.1, 93.5, 56.2, 55.7, 31.7.

5d: mp 252 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.51 (d, *J* = 8.9 Hz, 1 H), 7.38 (d, *J* = 8.6 Hz, 2 H), 7.11 (dd, *J* = 2.6, 8.9 Hz, 1 H), 7.02 (d, *J* = 8.6 Hz, 2 H), 6.91 (s, 1 H), 6.86 (d, *J* = 2.6 Hz, 1 H), 4.35 (s, 3 H), 3.67 (s, 3 H).

5e: mp >300 °C. ^{1}H NMR: δ = 11.04 (d, *J* = 5.2 Hz, 1 H), 7.46 (s, 1 H), 7.17 (s, 1 H), 6.75 (d, *J* = 5.2 Hz, 1 H), 4.21 (s, 3 H), 4.18 (s, 3 H), 3.84 (s, 3 H), 2.50 (s, 3 H). ^{13}C NMR: δ = 155.9, 150.7, 145.3, 136.3, 125.5, 125.1, 122.1, 113.9, 110.6, 104.3, 93.5, 56.4, 56.2, 31.5, 16.6.

5f: mp 153 °C. ^{1}H NMR: δ = 11.39 (d, *J* = 4.5 Hz, 1 H), 9.57 (s, 1 H), 7.13–7.38 (m, 7 H), 6.90 (d, *J* = 7.4 Hz, 2 H), 6.82 (d, *J* = 4.5 Hz, 1 H), 6.74 (s, 1 H), 6.10 (s, 1 H), 3.79 (s, 3 H), 3.49 (s, 3 H). ^{13}C NMR: δ = 157.4, 155.7, 150.6, 144.8, 139.2, 135.8, 130.9, 129.9, 128.8, 127.5, 125.3, 124.3, 116.8, 115.3, 114.7, 113.7, 94.0, 56.3.

9a: mp 156 °C. ^{1}H NMR: δ = 7.65–8.12 (m, 5 H), 7.15 (br s, 1 H), 7.05 (s, 1 H), 7.02 (s, 1 H), 7.00 (s, 1 H), 3.95 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H). ^{13}C NMR: δ = 168.5, 164.3, 148.9, 145.8, 135.1 (2 × C), 134.1, 131.6 (2 × C), 130.9, 129.9, 126.7, 120.8, 118.4, 105.6, 102.9, 93.6, 56.1 (2 × C), 32.0.

9b: mp 201 °C. ^{1}H NMR: δ = 7.55 (s, 1 H), 7.44 (d, *J* = 7.1 Hz, 1 H), 7.22–7.38 (m, 5 H), 7.15 (s, 1 H), 6.97 (d, *J* = 7.1 Hz, 1 H), 5.22 (s, 2 H), 4.21 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 3 H). ^{13}C NMR: δ = 155.6, 151.0, 145.6, 138.7, 136.4, 129.2, 128.9 (2 × C), 128.0 (2 × C), 127.7, 125.7, 124.5, 113.3, 102.9, 100.4, 93.6, 56.3 (2 × C), 50.8, 31.7.

9c: mp 255 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ = 11.0 (br s, 1 H), 10.63 (br s, 1 H), 7.85 (d, *J* = 8.5 Hz, 2 H), 7.60 (s, 1 H), 7.31–7.54 (m, 3 H), 7.28 (s, 1 H), 7.15 (s, 1 H), 3.88 (s, 6 H).

9d: mp 199 °C, ^{1}H NMR: δ = 8.08 (br s, 1 H), 7.71–7.90 (m, 4 H), 7.64 (d, *J* = 8.6 Hz, 2 H), 7.37–7.56 (m, 6 H), 7.04–7.29 (m, 4 H), 6.07 (s, 2 H).