Synthesis of 5-Acylindoles via Regioselective Acylation of 3-Trifluoroacetylindole

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Abstract: 5-Acylindoles were synthesized by regioselective acylation of 3-trifluoroacetylindole with acyl chloride under the catalysis of Lewis acids, followed by hydrolysis of trifluoroacetyl and decarboxylation. Polar solvents were beneficial to the acylation and most of the Lewis acids tested showed good catalytic activities.

Key words: regioselectivity, acylation, 3-trifluoroacetylindole, 5-acylindole-3-carboxylic acid, 5-acylindole

Indole and its derivatives have been a topic of research in organic synthesis for over a century because of their important biological activities.[1–3] The presence of functional groups at C-5 was necessary for the bioactivities of many indole compounds.[4,5] Friedel–Crafts acylation is one of the most outstanding methods to introduce functional groups onto indole. C-3 is the normal attack site for acylation, when it is unsubstituted.[6] So, in order to selectively introduce acyl groups to benzene moiety of indole, C-3 should be protected or its reactivity should be decreased.

The acylation of 1-acylindoles was firstly reported to give C-3 and/or C-6 acylated derivatives according to the acylating agents.[7,8] When ethoxycarbonyl or other relative groups were introduced to C-2 of indole, C-5 could be acylated, but in many cases, 3-acylindoles were the major products. Only chloroacetic chloride could give relatively higher C-5 selectivity, but the yield was not satisfactory ($yield_{total}$ = 63%, C-3/C-5/C-7 = 1:86:13).[9,10] 3-Acetylindole and ethyl 3-indolecarboxylate were reported to be acetylated to give C-5, C-6 and C-7 acetylated products. The C-5 selectivity and total yield were not adequate. During the process of deprotection of acetyl group at C-3, the acetyl group on phenyl ring was also turned into carboxyl group. In most cases, the acyl group on phenyl ring was usually expected to be kept.[11] When C-3 was protected by formyl group, acylation could give C-5 isomer as main product, but the selectivity was still not significant (C-5/C-6 = 73:27 to 80:20) and the deprotection of the formyl group involved reduction catalyzed by Pd/C, which may reduce some groups on indole ring.[12] Because of the low C-5 selectivity and the difficulty in separating C-5 and C-6 acylated isomers in some cases, highly regioselective acylation at C-5 of indole is still a challenge.

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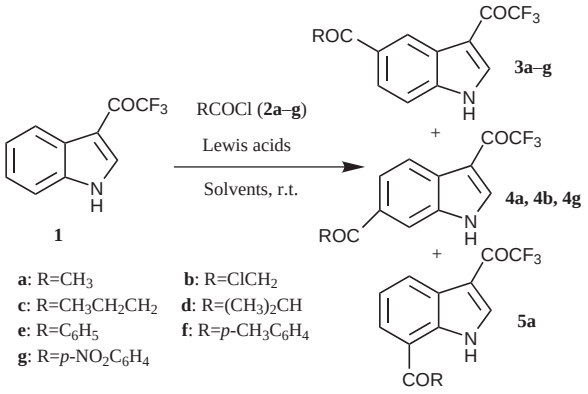
It was reported that trifluoroacetyl group was easy to be introduced onto C-3 of indole[13] and easy to be removed.[14,15] Considering the easy deprotection of trifluoroacetyl group and its strong electron-withdrawing ability, the Friedel–Crafts acylation of 3-trifluoroacetylindole was investigated in this communication and highly selective C-5 acylation was realized (Scheme 1).



Scheme 1 Friedel–Crafts acylation of 3-trifluoroacetylindole (**1**)

Firstly, we investigated the effects of solvents on this Friedel–Crafts acetylation and found that polar solvents, such as nitrobenzene and nitromethane, benefited the reaction, whereas non-polar solvents are unsuitable for the acylation. It seems that nitromethane is a much better solvent in terms of conversion, C-5 selectivity and total yield. It could be explained that the stabilization of polar solvent on transition states and reaction intermediates (carbonyl cation) played an important role on these reactions. On the other hand, the acetylation of **1** with **2a** could be catalyzed at room temperature by many Lewis acids, such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $ZnCl_2$, $TiCl_4$ and so on. Among them, $AlCl_3$ gave the highest C-5 selectivity and total yields (**3a**: 62%, **4a**: 24%, and **5a**: 11%).[16]

In view of the best effect of $AlCl_3/CH_3NO_2$, this system was adapted in the acylation of **1** with different acyl chloride (**2b**–**g)** and the results were listed in Table 1.[17] When **1** was acylated by **2b**, only **3b** was produced, but its yield was not satisfactory (28%, entry 1). In our screening of bioactivities, **3b** showed strong cytotoxic activities against Bre-04, N-04 and Lu-04 cell lines with GI_{50} values 1.04, 0.80 and 2.57 μgmL^{-1} successively. Compound **3b** was also a very important intermediate to synthesize 5-hydroxylindoles,[18] or the analogues of bisindolylmeth-

Table 1 The Acylation of **1** with Different Acyl Chlorides at Room Temperature

Entry	Acylating chloride No. R	Conversion (%)[d]	**3** (%)[e]	**4** (%)[e]
1	**2b** $ClCH_2$ [a]	30 (25 h)	28	0
2	**2b** $ClCH_2$ [b]	100 (3 h)	86	4
3	**2c** $CH_3CH_2CH_2$ [a]	83 (17 h)	63	0
4	**2d** $(CH_3)_2CH$ [a]	53 (17 h)	26	0
5	**2e** C_6H_5 [a]	58 (16 h)	58	0
6	**2f** *p*-$CH_3C_6H_4$ [a]	50 (16 h)	50	0
7	**2g** *p*-$O_2NC_6H_4$ [c]	56 (16 h)	43	6

[a] Carried out in $AlCl_3/MeNO_2$.
[b] Carried out in ionic liquid [MeBuIm]Cl–$AlCl_3$.
[c] Carried out in $FeCl_3/MeNO_2$.
[d] Based on the recovery of **1**.
[e] Isolated yields.

Table 2 The Results of Deprotection of 5-Acyl-3-trifluoroacetylindole **3a–g**

Entry	Compounds	**6**/Yield (%)[a]	Decarboxylation conditions[b]	**7**/Yield (%)[a]
1	**3a**	98	155 °C, 120 min	86
2	**3b**	–	–	–
3	**3c**	97	150 °C, 45 min	93
4	**3d**	74	160 °C, 90 min	95
5	**3e**	98	155 °C, 60 min	93
6	**3f**	99	150 °C, 45 min	79
7	**3g**	–	–	–

[a] Isolated yields.
[b] 4 Mol% of cupric salt of **6** was used as catalyst.

anone which could inhibit autophosphorylation of platelet-derived growth factor (PDGF) receptor tyrosine kinase in intact cells.[19] When the acylation of **1** with **2b** was carried out in ionic liquid 1-methyl-3-butylimidazolium chloride-aluminium chloride (MeBuImCl–$AlCl_3$, molar fraction X_{AlCl3} = 0.67), the yield of **3b** could reach up to 86% and only 4% of **4b** was isolated (entry 2).[20] The selectivity and yield of C-5 were much better than the previously reported.[11,12] However, this ionic liquid showed no advantages over $AlCl_3/CH_3NO_2$ for acylation of **1** with other acyl chlorides investigated. Compound **1** could be selectively acylated at C-5 by **2c–f** under the catalysis of $AlCl_3$ in nitromethane (entries 3–6). However, $AlCl_3$ gave complex products when **1** reacted with **2g**. $FeCl_3$ could overcome the drawback and gave high C-5 selectivity (entry 7, **3g**: 43%, **4g**: 6%). Except the acetylation, all other acylation of **1** did not produce 7-acylated isomers.

Deprotection of trifluoroacetyl group in **3** was carried out as shown in Scheme 2. Except **3b** and **3g**, all acylated 3-trifluoroacetylindole (**3a**, **3c–f**) were converted into their corresponding carboxylic acids **6** by treating **3** with 4.4 M KOH (aq) at reflux, followed by adjusting pH value to 5–6 with 5.5 M HCl (aq).[21] In fact, the chloroacetyl group on **3b** and nitro group on **3g** could firstly be converted into other expected groups and then trifluoroacetyl group may be removed as Scheme 2.[22] When **6** and 4 mol% of its cupric(II) salt were heated in quinoline at certain temperature (150–160 °C), decarboxylation could take place to give **7** with high yields (Table 2).[15]

In conclusion, regioselective Friedel–Crafts acylation at C-5 of indole was succeeded under the catalysis of Lewis acids by protecting C-3 with trifluoroacetyl group, which could be removed by hydrolysis, followed by decarboxylation. Ionic liquid, MeBuImCl–$AlCl_3$ (molar fraction X_{AlCl3} = 0.67), as solvent and catalyst, is favorable to the acylation of 3-trifluoroacetylindole by chloroacetic chloride with respect to conversion, total yield and C-5 selectivity.

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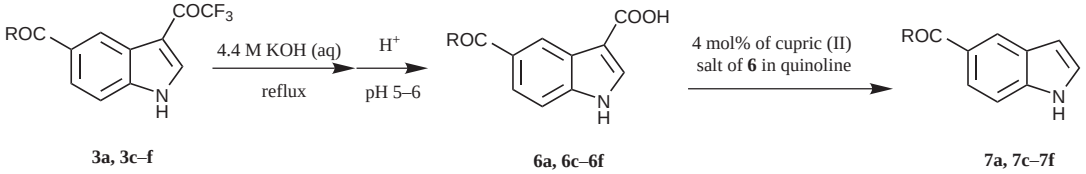

3a, 3c–f **6a, 6c–6f** **7a, 7c–7f**

Scheme 2 Deprotection of 5-acyl-3-trifluoroacetylindole (**3a–3g**)

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(16) **Friedel–Crafts Acylation of 3-Trifluoroacetylindole** (**1**); **General Procedure**: To an ice cold solution of **1** (0.107 g, 0.5 mmol) in nitromethane (4 mL) was added acyl chloride (**2**, 1.5 mmol) under a N_2 atmosphere, and the mixture was stirred for 15 min. Then $AlCl_3$ (0.2 g, 1.5 mmol) was rapidly added and the reaction proceeded 4 h at r.t. To the reaction mixture H_2O (5 mL) was added to quench the reaction. Nitromethane was removed under reduced pressure. The residue was resolved in EtOAc (30 mL) and washed with sat. aq $NaHCO_3$ solution (three times) and NaCl solution(twice). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a solid residue, which was purified by silica gel column chromatography with petroleum ether/acetone or petroleum ether/EtOAc as eluent to afford the acylated products.

(17) **Acylated Indole Compounds:**
A mixture of 5-acetyl-3-trifluoroacetylindole (**3a**) and 6-acetyl-3-trifluoroacetylindole (**4a**) (72:28) was obtained by chromatography in total yield 85%. Recrystallization of the mixture from EtOAc resulted in pure **3a**, but pure **4a** could not be obtained.
Compound **3a**: Mp 195–196 °C (EtOAc). ESI-MS (negative mode): *m/z* = 254 [(M – 1)$^-$], 255 [(M)$^-$]. IR (KBr): 3222, 1676, 1642, 1439, 1376, 1276, 1190, 1142, 896 cm^{-1}. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 11.86 (br s, 1 H, N-H), 8.97 (dd, 1 H, *J* = 2.0 Hz, 0.8 Hz, H-4), 8.54 (m, 1 H, H-2), 8.02 (dd, 1 H, *J* = 8.8 Hz, 2.0 Hz, H-6), 7.73 (dd, 1 H, *J* = 8.8 Hz, 0.8 Hz, H-7), 2.68 (s, 3 H, CH_3).
Compound **4a**: The ^{1}H NMR data of **4a** came from the ^{1}H NMR spectra of the mixture of **3a** and **4a**. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 11.92 (br s, 1 H, N-H), 8.61 (m, 1 H, H-2); 8.37 (dd, 1 H, *J* = 8.8 Hz, 0.8 Hz, H-4), 8.29 (dd, 1 H, *J* = 2.0 Hz, 0.8 Hz, H-7), 8.02 (dd, 1 H, *J* = 8.8 Hz, 2.0 Hz, H-5), 2.66 (s, 3 H, CH_3).
7-Acetyl-3-trifluoroacetylindole (**5a**): Mp 173–174 °C (petroleum ether:EtOAc = 6:1). ESI-MS (negative mode): *m/z* = 254 [(M – 1)$^-$], 255 [(M)$^-$]. IR (KBr): 3312, 2924, 1674, 1658, 1521, 1431, 1364, 1269, 1198, 895 cm^{-1}. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 12.03 (br s, 1 H, N-H), 8.56 (dd, 1 H, *J* = 8.0 Hz, 0.8 Hz, H-4), 8.41 (m, 1 H, H-2), 8.09 (dd, 1 H, *J* = 8.0 Hz, 0.8 Hz, H-6), 7.49 (t, 1 H, *J* = 8.0 Hz, H-5), 2.73 (s, 3 H, CH_3).
5-Chloroacetyl-3-trifluoroacetylindole (**3b**): Mp 231–232 °C (petroleum ether:acetone = 5:1); ESI-MS (negative mode): *m/z* = 288 [(M – 1)$^-$], 290 [(M + 1)$^-$]. IR (KBr): 3238, 2924, 1684, 1667, 1139, 895 cm^{-1}. ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 11.92 (br s, 1 H, N-H), 8.98 (s, 1 H, H-4), 8.56 (s, 1 H, H-2), 8.03 (dd, 1 H, *J* = 8.5 Hz, 2.0 Hz, H-6), 7.77 (d, 1 H, *J* = 8.5 Hz, H-7), 5.10 (s, 2 H, CH_2).
6-Chloroacetyl-3-trifluoroacetylindole (**4b**): Mp 198–199 °C (petroleum ether:acetone = 5:1). ESI-MS (negative mode: *m/z* = 288 [(M – 1)$^-$], 290 [(M + 1)$^-$]. IR (KBr): 3315, 2925, 1674, 1446, 1269, 1147, 892, 728 cm^{-1}. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 12.02 (br s, 1 H, N-H), 8.63 (m, 1 H, H-2), 8.40 (dd, 1 H, *J* = 8.4 Hz, 0.4 Hz, H-4), 8.34 (dd, 1 H, *J* = 1.6 Hz, 0.4 Hz, H-7), 8.04 (dd, 1 H, *J* = 8.4 Hz, 1.6 Hz, H-5), 5.09 (s, 2 H, CH_2).
5-(*n*-Butyryl)-3-trifluoroacetylindole (**3c**): Mp 185–186 °C (petroleum ether:acetone = 7:1). ESI-MS (negative mode): *m/z* = 282 [(M – 1)$^-$], 283 [(M)$^-$]. IR (KBr): 3230, 2966, 1664, 1638, 1524, 1439, 1380, 1205, 1139, 1077, 897 cm^{-1}. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 11.85 (br s, 1 H, N-H), 8.98 (dd, 1 H, *J* = 1.6 Hz, 0.8 Hz, H-4), 8.54 (br s, 1 H, H-2), 8.03 (dd, 1 H, *J* = 8.4 Hz, 1.6 Hz, H-6), 7.72 (dd, 1 H, *J* = 8.4 Hz, 0.8 Hz, H-7), 3.10 (t, 2 H, *J* = 7.2 Hz, CH_2), 1.77 (m, 2 H, *J* = 7.6 Hz, 7.2 Hz, CH_2), 1.02 (t, 3 H, *J* = 7.6 Hz, CH_3).
5-(*iso*-Butyryl)-3-trifluoroacetylindole (**3d**): Mp 169–170 °C (petroleum ether:EtOAc = 6:1). ESI-MS (negative mode): *m/z* = 282 [(M – 1)$^-$], 283 [(M)$^-$]. IR (KBr): 3249, 2975, 1659, 1615, 1525, 1465, 1385, 1345, 1276, 1138, 1075, 897 cm^{-1}. ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 11.86 (br s, 1 H, N-H), 8.98 (dd, 1 H, *J* = 1.6 Hz, 0.8 Hz, H-4), 8.55 (m, 1 H, H-2), 8.03 (dd, 1 H, *J* = 8.4 Hz, 1.6 Hz, H-6), 7.74 (dd, 1 H, *J* = 8.4 Hz, 0.8 Hz, H-7), 3.78 (m, 1 H, CH), 1.21 (d, 6 H, *J* = 7.2 Hz, CH_3).
5-Benzoyl-3-trifluoroacetylindole (**3e**): Mp 207–208 °C (petroleum ether:EtOAc = 6:1). ESI-MS (negative mode): *m/z* = 316 [(M – 1)$^-$], 317 [(M)$^-$]. IR (KBr): 3219, 3056, 2941, 1645, 896, 712 cm^{-1}. ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 11.91 (br s, 1 H, N-H), 8.76 (d, 1 H, *J* = 1.5 Hz, H-4), 8.56 (br d, 1 H, *J* = 1.5 Hz, H-2), 7.87 (dd, 1 H, *J* = 8.0 Hz, 1.5 Hz, H-6), 7.82 (d, 2 H, *J* = 7.5 Hz, H-2′ and H-6′ in phenyl), 7.79 (d, 1 H, *J* = 8.5 Hz, H-7), 7.67 (td, 1 H, *J* = 7.5, 1.5 Hz, H-4′ in phenyl), 7.57 (t, 2 H, *J* = 7.5 Hz, H-3′ and H-5′ in phenyl).
5-(4′-Methylbenzoyl)-3-trifluoroacetylindole (**3f**): Mp 225 °C (petroleum ether:acetone = 6:1). ESI-MS (negative mode): *m/z* = 330 [(M – 1)$^-$], 331 [(M)$^-$]. IR (KBr): 3363, 2925, 1679, 1642, 1604, 1525, 1437, 1312, 1288, 1192, 1142, 891, 758 cm^{-1}. ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 11.90 (br s, 1 H, N-H), 8.74 (d, 1 H, *J* = 1.5 Hz, H-4), 8.55 (m, 1 H, H-2), 7.85 (dd, 1 H, *J* = 8.5 Hz, 1.5 Hz, H-6), 7.78 (d, 1 H, *J* = 8.5 Hz, H-7), 7.73 (dd, 2 H, *J* = 7.5 Hz, 1.5 Hz, H-2′ and H-6′ in phenyl), 7.38 (dd, 2 H, *J* = 7.5 Hz, 1.5 Hz, H-3′ and H-5′ in phenyl), 3.45 (s, 3 H, CH_3).
5-(4′-Nitrobenzoyl)-3-trifluoroacetylindole (**3g**): The acylation of **1** with *p*-nitrobenzoyl chloride was catalyzed by $FeCl_3$ in nitromethane. The operation was the same as the acetylation catalyzed by $AlCl_3$.
Compound **3g**: Mp 237–238 °C (petroleum ether:acetone = 6:1). ESI-MS (negative mode): *m/z* = 361 [(M – 1)$^-$], 362 [(M)$^-$]. IR: 3222, 3055, 1651, 1619, 1521, 1435, 1193, 900, 849, 729, 687 cm^{-1}. ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 11.97 (br s, 1 H, N-H), 8.75 (d, 1 H, *J* = 1.5 Hz, H-4), 8.59 (br d, 1 H, *J* = 1.0 Hz, H-2), 8.43 (dt, 2 H, *J* = 9.0 Hz, 2.0 Hz, H-3′ and H-5′ in phenyl), 8.05 (dt, 2 H, *J* = 9.0 Hz, 2.0 Hz, H-2′ and H-6′ in phenyl), 7.91 (dd, 1 H, *J* = 9.0 Hz, 1.5 Hz, H-6), 7.82 (d, 1 H, *J* = 9.0 Hz, H-7).
6-(4′-Nitrobenzoyl)-3-trifluoroacetylindole (**4g**): Mp 250 °C (petroleum ether:acetone = 6:1). ESI-MS (negative mode): *m/z* = 361 [(M – 1)$^-$], 362 [(M)$^-$]. IR (KBr): 3358, 3129, 1656, 1617, 1521, 1350, 1283, 1193, 885, 848, 719 cm^{-1}. ^{1}H NMR (500 MHz, CD_3COCD_3): δ = 11.92 (br s, 1 H, N-H), 8.64 (br d, 1 H, *J* = 1.5 Hz, H-2), 8.43 (d, 1 H, *J* = 8.5 Hz, H-4), 8.42 (dt, 2 H, *J* = 8.5 Hz, 2.0 Hz, H-3′ and H-5′ in phenyl), 8.14 (d, *J* = 1.5 Hz, H-7), 8.05 (dt, 2 H, *J* = 8.5 Hz, 2.0 Hz, H-2′ and H-6′ in phenyl), 7.86 (dd, 1 H, *J* = 8.5 Hz, 1.5 Hz, H-5).

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(20) The acylation of **1** with chloroacetyl chloride catalyzed by ionic liquid produced not only 5-acylated product **3b** but also 6-acylated isomer **4b**. The procedure was as follows: The mixture of 1-methyimidazole (5 mL, 0.062 mol) and excess *n*-butyl chloride (15 mL) was stirred at reflux for 24 h under a N_2 atmosphere. Superfluous *n*-butyl chloride was evaporated under reduced pressure to give 8.96 g of 1-methyl-3-butylimidazolium chloride (MeBuImCl), yield = 82%. A dry flask was charged with 2.62 g of MeBuImCl (15 mmol). With vigorous stirring $AlCl_3$ (4 g, 30 mmol) was added to the flask in four portions under a N_2 atmosphere and a liquid formed (MeBuImCl–$AlCl_3$). When the ionic liquid was cooled to r.t., **1** (0.107 g, 0.5 mmol) was then dissolved in the ionic liquid, followed by adding chloroacetyl chloride (**2b**, 1.5 mmol). Stirring was continued for another 3 h and H_2O was added slowly to quench the reaction. The mixture was extracted by EtOAc. The following work-up was the same as that of acetylation of **1** catalyzed by $AlCl_3$. The residue was chromatographed on a silica gel colum with 5:1 petroleum ether:acetone to result in **3b** (yield = 86%) and **4b** (yield = 4%).

(21) **Hydrolysis of 3a, 3c–f; General Procedure:** To a aq 4.4 M KOH solution was added 5-acyl-3-trifluoroacetylindole (**3a**, **3c**–**f**, 1 mmol). The mixture was refluxed until **3** disappeared (0.5–2 h). The mixture was adjusted to pH = 5–6 with 5.5 M HCl(aq) to precipitate carboxylic acid, which was extracted with EtOAc or *n*-butanol (3 × 20 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent in vacuum gave a solid residue, which was purified by silica gel column chromatography (petroleum ether:acetone = 2:1).

5-Acetylindole-3-carboxylic Acid (**6a**): Mp 198–200 °C (petroleum ether:acetone = 2:1). ESI-MS (negative mode): *m/z* = 202 [$(M - 1)^-$], 203 [$(M)^-$]. IR (KBr): 3210, 2925, 1681, 1646, 1449, 1311, 1176, 700 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ = 12.25 (s, 1 H, -COOH), 12.16 (s, 1 H, N-H), 8.66 (br s, 1 H, H-4), 8.14 (d, 1 H, *J* = 2.4 Hz, H-2), 7.82 (dd, 1 H, *J* = 8.4 Hz, 1.2 Hz, H-6), 7.55 (d, 1 H, J = 8.4 Hz, H-7), 2.62 (s, 3 H, CH_3).

5-*n*-Butyrylindole-3-carboxylic Acid (**6c**): Mp 174–175 °C (petroleum ether:acetone = 2:1). ESI-MS (negative mode): *m/z* = 230 [$(M - 1)^-$], 231 [$(M)^-$]. IR (KBr): 3237, 2961, 1669, 1533, 1444, 1169 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ = 12.24 (s, 1 H, -COOH), 12.14 (br s, 1 H, N-H), 8.68 (br s, 1 H, H-4), 8.14 (d, 1 H, *J* = 2.9 Hz, H-2), 7.83 (dd, 1 H, *J* = 8.4 Hz, 1.6 Hz, H-6), 7.55 (d, 1 H, *J* = 8.4 Hz, H-7), 3.05 (t, 2 H, *J* = 7.2 Hz, CH_2), 1.67 (m, 2 H, *J* = 7.2 Hz, CH_2), 0.95 (t, 3 H, *J* = 7.2 Hz, CH_3).

5-*iso*-Butyrylindole-3-carboxylic Acid (**6d**): Mp 171–172 °C (petroleum ether:acetone = 2:1). ESI-MS (negative mode): *m/z* = 230 [$(M)^-$]. IR (KBr): 3281, 2973, 1657, 1537, 1446, 1186, 1128, 759 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ = 12.10 (s, 2 H, -COOH and N-H), 8.67 (br s, 1 H, H-4), 8.12 (d, 1 H, *J* = 2.7 Hz, H-2), 7.83 (dd, 1 H, *J* = 8.4 Hz, 0.9 Hz, H-6), 7.55 (d, 1 H, *J* = 8.4 Hz, H-7), 3.70 (t, 2 H, *J* = 6.6 Hz, CH), 1.14 (d, 6 H, *J* = 6.6 Hz, CH_3).

5-Benzoylindole-3-carboxylic Acid (**6e**): Mp 178–179 °C (petroleum ether:acetone = 2:1). ESI-MS (negative mode): *m/z* = 264 [$(M)^-$], 220 [$(M - 1 - CO_2^-)$]. IR (KBr): 3184, 2925, 1668, 1639, 1499, 1201, 1138, 705 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ = 12.23 (s, 1 H, -COOH), 12.10 (br s, 1 H, N-H), 8.44 (br s, 1 H, H-4), 8.17 (d, 1 H, *J* = 3.3 Hz, H-2), 7.73 (d, 2 H, *J* = 7.8 Hz, H-2′ and H-6′ in phenyl), 7.67 (d, 1 H, *J* = 8.4 Hz, H-6), 7.66 (t, 1 H, *J* = 7.8 Hz, H-4′ in phenyl), 7.62 (d, 1 H, *J* = 8.4 Hz, H-7), 7.57 (t, 2 H, *J* = 7.8 Hz, H-3′ and H-5′ in phenyl).

5-(4′-Methylbenzoyl)indole-3-carboxylic Acid (**6f**): Mp 193–194 °C (petroleum ether:acetone = 2:1). ESI-MS (negative mode): *m/z* = 278 [$(M - 1)^-$], 279 [$(M)^-$]. IR (KBr): 3423, 3187, 2924, 1662, 1530, 1454, 1292, 1198, 1130, 759 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ = 12.21 (s, 1 H, -COOH), 12.08 (br s, 1 H, N-H), 8.42 (br s, 1 H, H-4), 8.16 (d, 1 H, *J* = 2.4 Hz, H-2), 7.65 (d, 3 H, *J* = 7.8 Hz, H-6 and H-2′ and H-6′ in phenyl), 7.61 (d, 1 H, *J* = 8.4 Hz, H-7), 7.38 (d, 2 H, *J* = 7.8 Hz, H-3′ and H-5′ in phenyl), 2.42 (s, 3 H, CH_3).

(22) **Decarboxylation; General Procedure:** Quinoline (0.5 mL), **6** (0.5 mmol) and its cupric salt (0.02 mmol) were added to a flask fitted with a magnetic bar and a reflux condenser connected to an oil bubbler. The mixture was heated until gas evolution (CO_2) occurred and kept at this temperature until gas evolution ceased (45–120 min). The reaction mixture was cooled to r.t. To the mixture was added 20 mL EtOAc and washed with 1 N HCl(aq) (three times). The organic layer was washed with sat. aq $NaHCO_3$ solution (three times), brine(once) and dried over Na_2SO_4. Removal of the solvent gave a solid residue, which was purified by silica gel column chromatography (petroleum ether:acetone = 8:1 to 2:1).

5-Acetylindole (**7a**): Mp 69–71 °C (petroleum ether:acetone = 8:1). ESI-MS (negative mode): *m/z* = 158 [$(M - 1)^-$], 159 [$(M)^-$]. IR (KBr): 3271, 1661, 1600, 1429, 1351, 1273, 914, 771, 731 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 10.65 (br s, 1 H, N-H), 8.35 (s, 1 H, H-4), 7.83 (dd, 1 H, *J* = 8.4 Hz, 1.5 Hz, H-6), 7.52 (d, 1 H, *J* = 8.4 Hz, H-7), 7.48 (t, 1 H, *J* = 2.2 Hz, H-2), 6.66 (br d, 1 H, *J* = 2.2 Hz, H-3), 2.62 (s, 3 H, CH_3).

5-*n*-Butyrylindole (**7c**): Mp 104–105 °C (petroleum ether:acetone = 8:1). ESI-MS (negative mode): *m/z* = 186 [$(M - 1)^-$]. IR (KBr): 3269, 2963, 1664, 1605, 1380, 1367, 1329, 1223, 1154, 892, 759 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 10.48 (br s, 1 H, N-H), 8.37 (br d, 1 H, *J* = 0.8 Hz, H-4), 7.84 (dd, 1 H, *J* = 8.4 Hz, 1.0 Hz, H-6), 7.52 (d, 1 H, *J* = 8.4 Hz, H-7), 7.47 (t, 1 H, *J* = 2.8 Hz, 2.4 Hz, H-2), 6.66 (br d, 1 H, *J* = 2.0 Hz, H-3), 3.06 (t, 2 H, *J* = 7.2 Hz, CH_2), 1.77 (m, 2 H, *J* = 7.2 Hz, CH_2), 1.01 (t, 3 H, *J* = 7.2 Hz, CH_3).

5-*iso*-Butyrylindole (**7d**): Mp 65-66 °C (petroleum ether:acetone = 8:1). ESI-MS (negative mode): *m/z* = 186 [$(M - 1)^-$]. IR (KBr): 3300, 2975, 1663, 1603, 1430, 1383, 1346, 1228, 1139, 1097, 1007, 749 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 10.65 (br s, 1 H, N-H), 8.38 (s, 1 H, H-4), 7.85 (dd, 1 H, *J* = 8.4 Hz, 1.5 Hz, H-6), 7.54 (d, 1 H, *J* = 8.4 Hz, H-7), 7.48 (t, 1 H, *J* = 2.4 Hz, H-2), 6.66 (d, 1 H, *J* = 2.4 Hz, H-3), 3.78 (m, 1 H, *J* = 7.2 Hz, CH), 1.20 (d, 6 H, *J* = 7.2 Hz, CH_3).

5-Benzoylindole (**7e**): Mp 148–149 °C (petroleum ether:acetone = 5:1). ESI-MS (negative mode): *m/z* = 220 [$(M - 1)^-$]. IR (KBr): 3292, 1623, 1607, 1571, 1322, 880, 737 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 10.72 (br s, 1 H, N-H), 8.10 (br s, 1 H, H-4), 7.80 (dd, 2 H, *J* = 7.4 Hz, 1.2 Hz, H-2′ and H-6′ in phenyl), 7.71 (dd, 1 H, *J* = 8.4 Hz, 1.5 Hz, H-6), 7.66 (t, 1 H, *J* = 7.4 Hz, H-4′ in phenyl), 7.59 (t, 2 H, *J* = 7.4 Hz, H-3′ and H-5′ in phenyl), 7.57 (d, 1 H, *J* = 8.4 Hz, H-7), 7.51 (t, 1 H, *J* = 2.4 Hz, H-2), 6.67 (br d, 1 H, *J* = 2.4 Hz, H-3).

5-(4′-Methylbenzoyl)indole (**7f**): Mp 168-169 °C (petroleum ether:acetone = 8:1). ESI-MS (negative mode): *m/z* = 234 [$(M - 1)^-$]. ESI-MS (positive mode): *m/z* = 258 [$(M + Na)^+$], 274 [$(M + K)^+$]. IR (KBr): 3235, 1631, 1606, 1329, 1316, 1177, 754 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 10.70 (br s, 1 H, N-H), 8.08 (br s, 1 H, H-4), 7.71 (d, 2 H, *J* = 7.8 Hz, H-2′ and H-6′ in phenyl), 7.69 (dd, 1 H, *J* = 8.4 Hz, 1.2 Hz, H-6), 7.59 (d, 1 H, *J* = 8.4 Hz, H-7), 7.51 (t, 1 H, *J* = 2.2 Hz, H-2), 7.38 (d, 2 H, *J* = 7.8 Hz, H-3′ and H-5′ in phenyl), 6.66 (br d, 1 H, *J* = 2.2 Hz, H-3), 2.47 (s, 3 H, CH_3).