SYNTHESIS OF 3-AROYLINDOLES AS INTERMEDIATES OF CANNABIMIMETICS AND ELUCIDATION OF THEIR PHYSICOCHEMICAL PROPERTIES

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Abstract – In order to synthesize the intermediates of cannabimimetics, the benzylation of indoles with 2'/3'/4'-substituted benzoyl chloride in the presence of Et2AlCl was examined. Among the products, we found that the 1H NMR spectra of 3-(2'-substituted)-benzoyl-2-methylindoles had interesting features. We investigated their physicochemical properties based on VT-NMR, and it was revealed that conformer A (s-trans) is present in preference to conformer B in these compounds.

Since the biological functions of the endocannabinoid system consisting of two cannabinoid receptors (CB1 and CB2 receptors) was elucidated,1 drugs binding to cannabinoid receptors have been expected to find a huge market for the treatment of a variety of conditions such as diabetes, metabolic disorders, and neuroinflammatory diseases.2 Among numerous synthetic ligands for the CB receptors, indole-containing compounds have been recognized as popular scaffolds.3 In particular, N-alkyl-3-aryloindoles show exceptionally strong affinity for CB receptors.4 We are interested in these derivatives including their variously substituted isomers from the viewpoint of pharmacological activity. Therefore, we attempted to synthesize their useful intermediates, the 3-benzyloindole derivatives. Here we describe the syntheses of 3-(2'/3'/4'-substituted)-benzoylindoles and the corresponding 2-methylindoles (Figure 1). Additionally, we discuss the physicochemical properties of 3-(2'-substituted)-benzoyl-2-methylindoles.
Table 1. Benzoylation of indoles with 2'/3'/4'-substituted benzoyl chloride

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Because the 3-position of indole is suitable for electrophilic substitution, there are many methods for direct 3-acylation. The acylations of indole salts prepared using the alkylzinc or Grignard reagent, Vilsmeier-Haack acylations, and Friedel-Crafts acylations are commonly used. After examining those procedures, we found that benzylation in the presence of Et₂AlCl, as reported by Okauchi et al., was the most applicable to benzoyl chloride bearing various substitutions. Following the reported procedure, the benzylation of indoles proceeded efficiently when 1.5 equivalents of 2'/3'/4'-substituted benzoyl chlorides are used in the presence of a 1.5 equivalent of Et₂AlCl. Thus, the variously substituted 3-benzoylindoles (10-14, 2) were synthesized in moderate to high yields (Table 1).

In the course of these synthetic studies, we found that the ¹H NMR spectra (in DMSO-d₆, +23 °C) of 3-(2'-substituted)-benzoyl-2-methylindoles (2b, 2c, 2d) had common features. In these spectra, only the 4-H proton peak was strangely broad, which prompted us to conduct a conformational study using VT-NMR (−80 °C to +23 °C in acetone-d₆). As a clear example, the spectrum of 3-(2'-iodo)-benzoyl-2-methylindole 2d is shown in Figure 2.

As the temperature decreased, the 4-H proton peak in 2d broadened and was observed as two divided broad peaks (2 : 1) at −80 °C. The major downfield-shifted peak observed at around 8.5 ppm and the minor upfield-shifted peak at around 6.1 ppm were consistent with the two conformers A (s-trans) and B (s-cis), which are caused by the rotations of the C–(C=O) axis of the ketone moiety (Figure 3). Based on our previous investigations of the conformation of the o-substituted benzoyl moiety, the benzene ring should be nearly orthogonal to the carbonyl group due to the bulky o-substitution. In conformer B, that benzene ring caused a shielding effect of the 4-H proton in indole, shifting it upfield to 6.1 ppm. On the contrary, the downfield shift of 4-H (8.5 ppm) suggested the deshielding effect of the carbonyl group in conformer A.

In connection with this, we found that the 2-methyl peak in 2d became broader gradually and divided into two broad peaks (2 : 1) at −80 °C. The major upfield-shifted peak observed at around 1.9 ppm and the minor downfield-shifted peak at around 2.8 ppm corresponded to the shielded 2-methyl peak in conformer A and the deshielded one in conformer B, respectively. We assumed that the carbonyl group rotated to a co-planar relationship with the indole ring as a result of the stereoelectronic interaction with either the 4-H proton or 2-methyl group (anisotropy effect). These features were observed in the spectra of compounds 2b and 2c (see Supporting Information). Considering these results, we assumed that compounds 2b, 2c, and 2d should exist preferentially in conformer A, and the averaged conformations of A and B were observed at +23 °C. The existence of conformers A and B in 3-aroylindoles caused by the rotation of the carbonyl group was proposed by Bell and co-workers in 1991. Our results using VT-NMR therefore provide validation for their proposal.
Figure 2. VT-NMR spectrum of 2d (−80 °C to +23 °C in acetone-\(d_6\)). (a) Change in 4-H; (b) Change in 2-Me.
In summary, a variety of 3-aroylindoles as the intermediates of the cannabimimetics were synthesized efficiently. Using Et₂AlCl, benzylation of indoles with 2'/3'/4'-substituted benzoyl chloride proved feasible. We also investigated the physicochemical properties of 3-(2'-substituted)-benzoyl-2-methylindoles (2b, 2c, 2d) based on VT-NMR, and it was apparent that conformer A (s-trans) is present in preference to conformer B (s-cis).

**EXPERIMENTAL**

**General remarks**

Materials were obtained from commercial suppliers. NMR spectra were recorded on a spectrometer at 400 MHz or 600 MHz for ¹H-NMR, and 100 MHz or 150 MHz for ¹³C-NMR. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard, and coupling constants (J) are reported in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). IR spectra were recorded on a FT-IR spectrometer equipped with ATR (Diamond). The high-resolution mass spectra (HRMS) were obtained with an ionization mode of ESI. Melting points were recorded on a melting point apparatus and are uncorrected. Optical rotations were determined with a digital polarimeter. Analytical thin-layer chromatography was performed on precoated, glass-backed silica gel plates. Column chromatography was performed using silica gel (45–60 μm). Extracted solutions were dried over anhydrous MgSO₄ or Na₂SO₄. Solvents were evaporated under reduced pressure.

**General experimental procedure for the syntheses of compounds 1 and 2**

To a CH₂Cl₂ solution (85.0 mL) of indole (1.00 g, 8.53 mmol) was added 14.7 mL (12.8 mmol) of Et₂AlCl (0.87 mol/L in hexane) at 0 °C. The mixture was stirred at 0 °C for 30 min. To this solution, 3-iodobenzoyl chloride (3.41 g, 12.8 mmol) was added dropwise at 0 °C. The resulting solution was stirred at room temperature for 12 h, and the reaction was quenched with sat. aq. NH₄Cl. After the usual work-up, the crude product was purified by silica gel column chromatography to give Ii in 85% yield.
(2.53 g, 7.28 mmol) as crystals.

3-(2-Fluorobenzoyl)-1H-indole (1a)
Pink solid (yield 81%) mp 194–199 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 12.13 (s, 1H), 8.20 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.79 (s, 1H), 7.60–7.56 (m, 2H), 7.52 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.37–7.33 (m, 2H), 7.29–7.24 (m, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 186.2, 158.7 (d, $J = 245.6$ Hz), 136.9, 131.9 (d, $J = 8.6$ Hz), 129.7, 129.2, 129.1, 125.5, 124.5, 123.4, 122.3, 116.3 (d, $J = 17.3$ Hz), 116.1, 112.5; IR (ATR) 1609 cm$^{-1}$; HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{15}$H$_{11}$NOF 240.0819; Found 240.0802.

3-(2-Methylbenzoyl)-1H-indole (1e)
Orange solid (yield 63%) mp 195–197 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 12.02 (s, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 7.60 (d, $J = 1.8$ Hz, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.40–7.37 (m, 2H), 7.33–7.23 (m, 4H), 2.27 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 192.1, 141.0, 136.9, 136.3, 134.8, 130.6, 129.1, 127.2, 125.7, 125.3, 123.2, 122.0, 121.3, 116.6, 112.4, 19.2; IR (ATR) 1601 cm$^{-1}$; HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{16}$H$_{14}$NO 236.1070; Found 236.1043.

3-(3-Iodobenzoyl)-1H-indole (1i)
White solid (yield 85%) mp 225–226 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 12.11 (s, 1H), 8.23 (dd, $J = 1.2, 7.2$ Hz, 1H), 8.04 (dd, $J = 1.2, 1.2$ Hz, 1H), 7.96 (ddd, $J = 1.2, 7.2, 7.2$ Hz, 1H), 7.95 (s, 1H), 7.79 (ddd, $J = 1.2, 1.2, 7.8$ Hz, 1H), 7.53 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.35 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.29–7.23 (m, 2H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 188.3, 142.5, 139.5, 136.8, 136.5, 136.2, 130.6, 127.8, 126.1, 123.3, 122.1, 121.4, 114.7, 112.3, 94.9; IR (ART) 1593 cm$^{-1}$; HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{15}$H$_{11}$NOI 347.9880; Found 347.9882.

3-(2-Fluorobenzoyl)-2-methyl-1H-indole (2a)
White solid (yield 78%) mp 214–220 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) δ 12.10 (s, 1H), 7.61–7.57 (m, 1H), 7.45 (ddd, $J = 1.2, 7.2, 7.2$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.36–7.35 (m, 2H), 7.34 (dd, $J = 1.2, 8.4$ Hz, 1H), 7.14 (ddd, $J = 1.2, 7.8, 8.4$ Hz, 1H), 7.04 (ddd, $J = 1.2, 7.8, 8.4$ Hz, 1H), 2.33 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 186.8, 158.3 (d, $J = 244.1$ Hz), 146.0, 135.0, 131.8 (d, $J = 8.6$ Hz) 130.9 (d, $J = 17.3$ Hz), 128.8 (d, $J = 2.9$ Hz), 126.9, 124.9 (d, $J = 2.9$ Hz), 122.3, 121.6, 119.7, 116.1 (d, $J = 21.6$ Hz), 113.1, 111.4, 13.9; IR (ATR) 1609 cm$^{-1}$; HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{16}$H$_{13}$NOF 254.0976; Found 254.0973.
3-(2-Chlorobenzoyl)-2-methyl-1H-indole (2b)
White solid (yield 76%) mp 203–206 °C: †H NMR (600 MHz, DMSO-d$_6$) δ 12.11 (s, 1H), 7.59 (dd, J = 1.2, 7.8 Hz, 1H), 7.53 (ddd, J = 1.8, 7.8, 7.8 Hz, 1H), 7.48 (ddd, J = 1.2, 7.8, 7.8 Hz, 1H), 7.40 (dd, J = 1.8, 7.8 Hz, 1H), 7.38 (dd, J = 1.2, 7.8 Hz, 1H), 7.34 (br d, J = 7.8 Hz, 1H), 7.14 (ddd, J =1.2, 7.8, 7.8 Hz, 1H), 7.04 (ddd, J = 1.2, 7.8, 7.8 Hz, 1H), 2.26 (s, 3H); †3C NMR (150 MHz, DMSO-d$_6$) δ 188.6, 146.3, 142.0, 135.0, 130.6, 129.7, 129.0, 127.8, 127.8, 126.9, 122.3, 121.7, 119.9, 112.5, 111.4, 13.9; IR (ATR) 1568 cm$^{-1}$; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{13}$NOCl 270.0680; Found 270.0679.

3-(2-Bromobenzoyl)-2-methyl-1H-indole (2c)
White solid (yield 76%) mp 219–221 °C: †H NMR (600 MHz, DMSO-d$_6$) δ 12.10 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.4, 8.4 Hz, 1H), 7.45 (ddd, J = 1.8, 8.4, 8.4 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.37 (dd, J = 1.8, 8.4 Hz, 1H), 7.35 (br, 1H), 7.14 (ddd, J = 7.8, 7.8 Hz, 1H), 7.05 (dd, J = 7.8, 7.8 Hz, 1H), 2.24 (s, 3H); †3C NMR (150 MHz, DMSO-d$_6$) δ 189.5, 146.3, 144.0, 135.0, 132.8, 130.7, 130.7, 127.2, 127.8, 127.0, 122.3, 121.7, 120.0, 118.0, 112.1, 111.4, 14.0; IR (ATR) 1567 cm$^{-1}$; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{13}$NOBr 314.0175; Found 314.0176.

3-(2-Iodobenzoyl)-2-methyl-1H-indole (2d)
Pale pink solid (yield 79%) mp 210–212 °C: †H NMR (600 MHz, DMSO-d$_6$) δ 12.08 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.2, 7.8 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.34 (br d, J = 7.2 Hz, 1H), 7.31 (dd, J = 1.8, 7.8 Hz, 1H), 7.25 (ddd, J = 1.8, 7.2, 7.8 Hz, 1H), 7.14 (dd, J = 7.2, 7.8 Hz, 1H), 7.04 (dd, J = 7.2, 7.8 Hz, 1H), 2.21 (s, 3H); †3C NMR (150 MHz, DMSO-d$_6$) δ 191.5, 147.8, 146.2, 139.0, 135.0, 130.5, 128.7, 127.1, 127.0, 122.3, 121.7, 120.1, 111.7, 111.4, 92.5, 14.1; IR (ATR) 1567 cm$^{-1}$; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{13}$NOI 362.0036; Found 362.0038.

3-(2-Iodobenzoyl)-2-methyl-1H-indole (2d)
Pale pink solid (yield 79%) mp 210–212 °C: †H NMR (600 MHz, DMSO-d$_6$) δ 12.08 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.2, 7.8 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.34 (br d, J = 7.2 Hz, 1H), 7.31 (dd, J = 1.8, 7.8 Hz, 1H), 7.25 (ddd, J = 1.8, 7.2, 7.8 Hz, 1H), 7.14 (dd, J = 7.2, 7.8 Hz, 1H), 7.04 (dd, J = 7.2, 7.8 Hz, 1H), 2.21 (s, 3H); †3C NMR (150 MHz, DMSO-d$_6$) δ 191.5, 147.8, 146.2, 139.0, 135.0, 130.5, 128.7, 127.1, 127.0, 122.3, 121.7, 120.1, 111.7, 111.4, 92.5, 14.1; IR (ATR) 1567 cm$^{-1}$; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{13}$NOI 362.0036; Found 362.0038.
Hz, 1H), 7.52 (br d, \( J = 7.8 \) Hz, 1H), 7.40 (d, \( J = 8.4 \) Hz, 1H), 7.36 (dd, \( J = 1.8, 7.8 \) Hz, 1H), 7.27 (ddd, \( J = 1.8, 7.8, 7.8 \) Hz, 1H), 7.15 (ddd, \( J = 7.2, 7.8 \) Hz, 1H), 7.07 (dd, \( J = 7.2, 8.4 \) Hz, 1H), 2.31 (s, 3H); \(^{13}\)C NMR (150 MHz, acetone-\( d_6 \) at 23 °C): \( \delta \) 192.4, 149.4, 146.4, 140.3, 136.2, 131.2, 129.5, 128.5, 128.2, 123.2, 122.6, 121.6, 113.3, 111.9, 92.4, 14.4.

\(^1\)H NMR (600 MHz, acetone-\( d_6 \) at −80 °C) \( \delta \) 11.69 (br, 0.33H), 11.51 (br, 0.66H), 8.42 (br, 0.66H), 8.03 (d, \( J = 7.8 \) Hz, 1H), 7.61 (dd, \( J = 7.8, 7.8 \) Hz, 1H), 7.43 (d, \( J = 8.4 \) Hz, 1H), 7.38 (d, \( J = 7.2 \) Hz, 1H), 7.33 (dd, \( J = 1.2, 7.8 \) Hz, 1H), 5.98 (br, 0.33H), 2.81 (br, 1H), 1.88 (br, 2H); \(^{13}\)C NMR (150 MHz, acetone-\( d_6 \) at −80 °C); \( \delta \) 192.3, 148.8, 139.7, 135.5, 131.1, 129.5, 127.3, 123.4, 122.7, 122.0 (m), 111.8, 92.5, 14.8 (m).

3-(2-Methylbenzoyl)-2-methyl-1\(^1\)H-indole (2e)
Pale pink solid (yield 82%) mp 222–225 °C: \(^1\)H NMR (600 MHz, DMSO-\( d_6 \)) \( \delta \) 12.00 (s, 1H), 7.39 (ddd, \( J = 1.2, 7.8, 7.8 \) Hz, 1H), 7.37 (d, \( J = 8.4 \) Hz, 1H), 7.33 (d, \( J = 7.8 \) Hz, 1H), 7.29 (dd, \( J = 7.8, 7.8 \) Hz, 1H), 7.28 (d, \( J = 8.4 \) Hz, 1H), 7.20 (dd, \( J = 1.2, 7.8 \) Hz, 1H), 7.11 (dd, \( J = 6.6, 8.4 \) Hz, 1H), 7.00 (dd, \( J = 6.6, 8.4 \) Hz, 1H), 2.25 (s, 3H), 2.18 (s, 3 H); \(^{13}\)C NMR (150 MHz, DMSO-\( d_6 \)) \( \delta \) 192.9, 145.6, 143.0, 135.0, 133.6, 130.4, 129.0, 127.1, 126.1, 125.9, 122.1, 121.4, 120.0, 113.0, 111.3, 18.7, 14.0; IR (ATR) 1568 cm\(^{-1}\); HRMS (ESI-TOF) \( m/z \): \([M+H]^+\) Calcd for C\(_{17}\)H\(_{16}\)NO 250.1226; Found 250.1225.

3-(3-Fluorobenzoyl)-2-methyl-1\(^1\)H-indole (2f)
Pale orange solid (yield 95%) mp 187–191 °C: \(^1\)H NMR (600 MHz, DMSO-\( d_6 \)) \( \delta \) 12.03 (s, 1H), 7.58–7.54 (m, 1H), 7.45–7.42 (m, 2H), 7.39 (d, \( J = 8.4 \) Hz, 1H), 7.38 (d, \( J = 7.2 \) Hz, 1H), 7.34 (d, \( J = 7.2 \) Hz, 1H), 7.13 (dd, \( J = 7.2, 7.2 \) Hz, 1H), 7.04 (dd, \( J = 7.2, 7.2 \) Hz, 1H), 2.38 (s, 3H); \(^{13}\)C NMR (150 MHz, DMSO-\( d_6 \)) \( \delta \) 190.0, 162.0 (d, \( J = 244.1 \) Hz), 145.1, 144.0 (d, \( J = 57.0 \) Hz), 135.0, 130.6 (d, \( J = 7.2 \) Hz), 127.1, 124.1, 122.0, 121.2, 119.9, 117.7 (d, \( J = 21.6 \) Hz), 114.5 (d, \( J = 21.6 \) Hz), 112.1, 111.4, 14.3; IR (ATR) 1568 cm\(^{-1}\); HRMS (ESI-TOF) \( m/z \): \([M-H]^-\) Calcd for C\(_{16}\)H\(_{11}\)NOF 252.0830; Found 252.0821.

3-(3-Chlorobenzoyl)-2-methyl-1\(^1\)H-indole (2g)
Pale yellow solid (yield 93%) mp 230–231 °C: \(^1\)H NMR (600 MHz, DMSO-\( d_6 \)) \( \delta \) 12.04 (s, 1H), 7.66 (ddd, \( J = 1.8, 1.8, 6.6 \) Hz, 1H), 7.60 (dd, \( J = 1.8, 1.8 \) Hz, 1H), 7.56–7.52 (m, 2H), 7.40 (d, \( J = 7.8 \) Hz, 1H), 7.32 (d, \( J = 7.8 \) Hz, 1H), 7.13 (dd, \( J = 6.6, 7.8 \) Hz, 1H), 7.04 (dd, \( J = 6.6, 7.8 \) Hz, 1H), 2.39 (s, 3H); \(^{13}\)C NMR (150 MHz, DMSO-\( d_6 \)) \( \delta \) 189.9, 145.1, 143.6, 135.0, 133.2, 130.7, 130.5, 127.6, 127.1, 126.7, 122.0, 121.2, 119.9, 112.1, 111.4, 14.3; IR (ATR) 1593 cm\(^{-1}\); HRMS (ESI-TOF) \( m/z \): \([M-H]^-\) Calcd for C\(_{16}\)H\(_{11}\)NOCI 268.0535; Found 268.0535.
3-(3-Bromobenzoyl)-2-methyl-1H-indole (2h)
Pink solid (yield 94%) mp 243–244 °C: ¹H NMR (600 MHz, DMSO-d₆) δ 12.04 (s, 1H), 7.79 (dd, J = 1.8, 7.8 Hz, 1H), 7.73 (dd, J = 1.8, 1.8 Hz, 1H), 7.59 (dd, J = 1.8, 7.8 Hz, 1H), 7.48 (dd, J = 7.8, 7.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.13 (dd, J = 6.6, 8.4 Hz, 1H), 7.04 (dd, J = 6.6, 8.4 Hz, 1H), 2.39 (s, 3H); ¹³C NMR (150 MHz, DMSO-d₆) δ 189.8, 145.1, 143.8, 135.0, 133.6, 130.7, 130.5, 127.1, 127.0, 122.0, 121.7, 121.2, 119.9, 112.0, 111.4, 14.3; IR (ATR) 1564 cm⁻¹; HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₆H₁₃NOBr 314.0175; Found 314.0165.

3-(3-Iodobenzoyl)-2-methyl-1H-indole (2i)
Pale pink solid (yield 36%) mp 259–260 °C: ¹H NMR (600 MHz, DMSO-d₆) δ 12.03 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.90 (s, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.32 (dd, J = 7.8, 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.13 (dd, J = 7.8, 7.8 Hz, 1H), 7.04 (dd, J = 7.8, 7.8 Hz, 1H), 2.39 (s, 3H); ¹³C NMR (150 MHz, DMSO-d₆) δ 189.8, 145.0, 143.6, 139.5, 136.3, 135.0, 130.6, 127.3, 127.1, 122.0, 121.2, 119.9, 112.0, 111.4, 94.7, 14.3; IR (ATR) 1563 cm⁻¹; HRMS (ESI-TOF) m/z: [M-H]⁻ Calcd for C₁₆H₁₁NOI 359.9891; Found 359.9880.

3-(3-Methylbenzoyl)-2-methyl-1H-indole (2j)
Pink solid (yield 85%) mp 190–194 °C: ¹H NMR (600 MHz, CDCl₃) δ 11.92 (s, 1H), 7.42 (br s, 1H), 7.40–7.37 (m, 4H), 7.34 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 7.8, 7.8 Hz, 1H), 7.01 (dd, J = 7.8, 7.8 Hz, 1H), 2.37 (s, 3H), 2.37 (s, 3H); ¹³C NMR (150 MHz, DMSO-d₆) δ 191.8, 144.3, 141.7, 137.6, 134.9, 131.6, 128.4, 128.2, 127.3, 125.2, 121.8, 120.9, 120.0, 112.5, 111.2, 20.9, 14.2; IR (ATR) 1582 cm⁻¹; HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₇H₁₆NO 250.1224; Found 250.1226.

3-(4-Fluorobenzoyl)-2-methyl-1H-indole (2k)
Pale yellow solid (yield 68%) mp 204–205 °C: ¹H NMR (600 MHz, DMSO-d₆) δ 11.97 (s, 1H), 7.71–7.64 (m, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.34–7.32 (m, 3H), 7.12 (dd, J = 8.4, 8.4 Hz, 1H), 7.03 (dd, J = 8.4, 8.4 Hz, 1H), 2.40 (s, 3H); ¹³C NMR (150 MHz, DMSO-d₆) δ 190.2, 163.8 (d, J = 247.1 Hz), 144.4, 138.0, 135.0, 130.9 (d, J = 8.7 Hz), 130.9 (d, J = 8.7 Hz), 127.2, 121.9, 121.0, 119.9, 115.3 (d, J = 21.5 Hz), 115.3 (d, J = 21.5 Hz), 112.3, 111.3, 14.2; IR (ATR) 1597 cm⁻¹; HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₆H₁₃NOF 254.0969; Found 254.0969.

3-(4-Iodobenzoyl)-2-methyl-1H-indole (2l)
Yellow solid (yield 34%) mp 164–167 °C: ¹H NMR (600 MHz, DMSO-d₆) δ 11.99 (s, 1H), 7.89 (d, J =
8.4 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.12 (dd, J = 7.8, 7.8 Hz, 1H), 7.03 (dd, J = 7.8, 7.8 Hz, 1H), 2.39 (s, 3H); \[13\]C NMR (150 MHz, DMSO-\(d_6\)) \(\delta\) 190.7, 144.7, 140.9, 137.3, 137.3, 135.0, 130.1, 130.1, 127.1, 121.9, 121.1, 119.9, 112.2, 111.3, 98.6, 14.3; IR (ATR) 1598 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\): [M+H]\(^+\) Calcd for C\(_{16}\)H\(_{13}\)NOI 362.0036; Found 362.0024.

3-(4-Methylbenzoyl)-2-methyl-1\(H\)-indole (2m)
Pale pink solid (yield 91%) mp 215–216 °C: \[1H\] NMR (600 MHz, DMSO-\(d_6\)) 11.91 (s, 1H), 7.53 (d, \(J = 7.8\) Hz, 2H), 7.38 (d, \(J = 7.2\) Hz, 1H), 7.33 (d, \(J = 7.2\) Hz, 1H), 7.31 (d, \(J = 7.8\) Hz, 2H), 7.11 (dd, \(J = 7.2, 7.2\) Hz, 1H), 7.00 (dd, \(J = 7.2, 7.2\) Hz, 1H), 2.40 (s, 3H), 2.40 (s, 3H); \[13\]C NMR (150 MHz, DMSO-\(d_6\)) \(\delta\) 191.4, 144.0, 141.1, 138.8, 134.9, 128.9, 128.4, 128.4, 127.3, 121.7, 120.8, 120.0, 112.6, 111.2, 21.1, 14.2; IR (ATR) 1593 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\): [M+H]\(^+\) Calcd for C\(_{17}\)H\(_{16}\)NO 250.1226; Found 250.1212.

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REFERENCES AND NOTES


15. As the temperature decreased, the 5-H proton peak (at around 7.1 ppm) in 2d became broader. Theoretically, these spectra are not affected by the anisotropy effect of the carbonyl group. Instead, we presumed that they are subject to the influence of coupling with the broad 4-H proton peak and thus that it was seemingly observed as a broad peak.
