Copper-catalysed direct C–H bond oxidative acetoxylation and iodination of indoles

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A novel $Cu(OAc)_2$-catalysed direct C–H bond oxidative acetoxylation and iodination of indoles using $PhI(OAc)_2$ as a terminal oxidant is reported. Adopting this method, a series of 3-iodoindoles and indol-3-yl acetates were obtained in nearly 1:1 ratio yield.

Keywords: Cu-catalysed, acetoxylation, iodination, indoles

Indole derivatives are an important class of compounds in the pharmaceutical chemistry owing to their biological activities.[1–4] In particular, 3-acetoxyindole is commonly used for the detection of acetylcholinesterase in tissue slices and for the identification of this enzyme in serum.[5] Consequently there is growing interest in efficiently synthesising 3-acetoxyindol.[6] The most straightforward C–O bond forming reaction is the metal-catalysed direct C–H bond oxidation.[7,8] For example, Sanford,[9] Chen[10] and Wu[11] used the Pd-catalysed acetoxylation of Sp^2 C–H bond based on different aromatic substances using $PhI(OAc)_2$ and $K_2S_2O_8$ as terminal oxidants respectively. However, there are few reports on the C-3 acetoxylation of the indole moiety[12–14] and the limited reports were restricted to the use of the expensive Pd catalyst. In order to expand the diversity of the catalyst, copper was examined as a catalyst for the acetoxylation of the 1*H*-indole or *N*-substituted indole nucleus. It was interesting to find that the 3-iodination of indole occurred along with acetoxylation when using $PhI(OAc)_2$ as terminal oxidants and gave the corresponding products in nearly 1:1 ratio yield. In general, iodination is a relatively difficult process compared to bromination and several additives, such as NIS,[15] I_2,[16] H_5IO_6,[17] ICl[18] or HIO_3,[19] have been used for the iodination reaction. $PhI(OAc)_2$ has seldom been tested for the synthesis of the iodo compounds. Here, we wish to describte a new process for the Cu-catalysed direct C–H bond oxidative 3-acetoxylation and 3-iodination of indoles. Furthermore, the products of 3-iodoindoles can be used as starting materials to synthesise a series of complicated indole derivatives.

Results and discussion

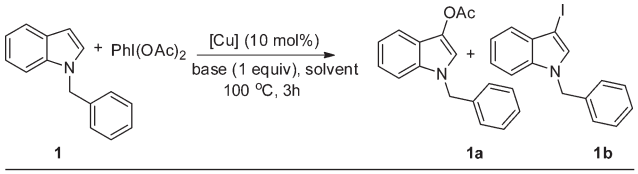
The reaction of 1-benzyl-1*H*-indole (**1**) with $PhI(OAc)_2$ was chosen to identify the optimal conditions (Table 1). After many attempts, we obtained the best conditions for the formation of **1a** in 56% yield associated with the formation of **1b** in 40% yield, involving $Cu(OAc)_2$ as the catalyst precursor, KOAc as the base and MeCN as the solvent at 100 °C (entry 3). Cu precursors were critical for the reaction. When $CuBr_2$ and $CuCl_2$ were employed as catalyst precursors, the reactions gave poor yields of **1a** and **1b** (entries 1 and 2). When Cu (I) or Fe catalyst replaced the Cu (II) or the Cu catalyst was absent, only a trace of product was detected (entries 4, 5 and 6). Among the bases screened, KOAc gave better result than KOH and K_2CO_3 (entries 8 and 9). No acetoxylation or iodination occurred without the base (entry 7). Examination of the solvent effects showed that the reaction proceeded best in CH_3CN compared to DMF or DMSO (entries 10 and 11).

With the optimal reaction conditions to hand, the substrate scope of the indole substrate was extended to *N*-benzylindole (entries 1–5), *N*-methylindole (entry 6), *N*-isobutenylindole (entries 7–12), *N*-n-butylindole (entries 13–18), and the results are summarised in Table 2. It can be seen that the *N*-substituted groups had little effect on the reactions and about 50% acetoxylation products and 40% iodination products were obtained respectively. N-substituted indoles with a wide range of substituted groups, such as methyl, chloro and fluoro, underwent the acetoxylation and iodination reaction smoothly and gave the corresponding products in nearly 1:1 ratio yield. Moreover, all the acetoxylation and iodination products were identified by the ^1H NMR and ^{13}C NMR spectrum. The ^1H NMR spectrum of **6a** for example, displayed singlets at δ 2.27 and 3.66 due to CH_3 groups (six protons) connected with N atom and C=O respectively, four multiplet-signals at δ 7.01–7.47 due to the benzene ring (four protons) and a singlet signal at δ 7.15 due to the 2-position-H of indole (one proton). The ^1H NMR spectrum of **6b** for example, displayed a singlet at δ 3.70 due to CH_3 groups (three protons) connected with N atom, four multiplet-signals at δ 7.09–7.37 due to the benzene ring (four protons) and a singlet signal at δ 7.03 due to the H–C atom adjacent to N atom (one proton). The detailed ^1H NMR and ^{13}C NMR data for the acetoxylation and iodination products can be seen in the experimental part.

Experimental

Chemicals were either purchased or purified by standard techniques. NMR spectroscopy was performed on a Bruker Avance-500 spectrometer operating at 500 MHz (^1H NMR) and 125 MHz (^{13}C NMR), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. The high resolution mass

Table 1 Evaluation of the acetoxylation and iodination conditions[a]



Entry	Catalyst	Base	Solvent	**1a** Yield/%[b]	**1b** Yield/%[b]
1	$CuBr_2$	KOAc	CH_3CN	20	21
2	$CuCl_2$	KOAc	CH_3CN	10	12
3	$Cu(OAc)_2$	KOAc	CH_3CN	56	40
4	CuBr	KOAc	CH_3CN	Trace	trace
5	$FeCl_3$	KOAc	CH_3CN	Trace	trace
6	-	KOAc	CH_3CN	Trace	trace
7	$Cu(OAc)_2$	-	CH_3CN	Trace	trace
8	$Cu(OAc)_2$	KOH	CH_3CN	24	22
9	$Cu(OAc)_2$	K_2CO_3	CH_3CN	10	11
10	$Cu(OAc)_2$	KOAc	DMF	36	35
11	$Cu(OAc)_2$	KOAc	DMSO	20	21

[a] Reaction conditions: 1 (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), base (0.5 mmol), [Cu/Fe] (10 mol%) and CH_3CN (2 ml) at 100 °C for 3h.
[b] Isolated yield.

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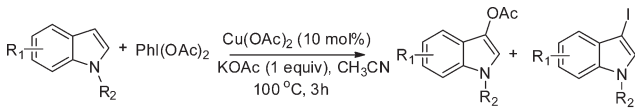
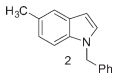
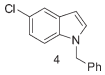
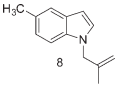
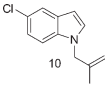
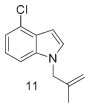
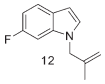
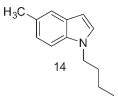
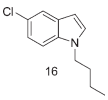
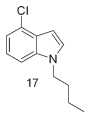
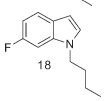
Table 2 Scope of the direct 3-acetoxylation and iodination of indoles[a]



1-18 1-18 a 1-18 b

Entry	indole	Product a (yield/%)[b]	Product b (yield/%)[b]
1		**1a** (56)	**1b** (40)
2		**2a** (54)	**2b** (42)
3		**3a** (53)	**3b** (44)
4		**4a** (52)	**4b** (46)
5		**5a** (53)	**5b** (40)
6		**6a** (54)	**6b** (43)
7		**7a** (54)	**7b** (41)
8		**8a** (51)	**8b** (42)
9		**9a** (52)	**9b** (38)
10		**10a** (53)	**10b** (41)
11		**11a** (53)	**11b** (43)
12		**12a** (54)	**12b** (42)
13		**13a** (50)	**13b** (42)
14		**14a** (59)	**14b** (36)
15		**15a** (51)	**15b** (44)
16		**16a** (52)	**16b** (38)
17		**17a** (53)	**17b** (40)
18		**18a** (54)	**18b** (41)

[a] Reaction conditions: Indole (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), KOAc (0.5 mmol), $Cu(OAc)_2$ (10 mol%) and CH_3CN (2 ml) at 100 °C for 3h.
[b] Isolated yield.

spectrometer was Bruker (ESI-Q-Tof). Column chromatography was performed using EM Silica gel 60 (300–400 mesh).

N-alkyl (aryl) protected indoles; general procedure

A mixture of 1*H*-indole (0.10 mol) and KOH (0.11 mol) was stirred in DMF (20 ml) under N_2 at room temperature for 30 min. When the solid had dissolved, the halohydrocarbon (0.11 mol) was added and the mixture was stirred overnight. After the reaction was completed, H_2O (20 ml) was added and stirred for 30 min, then extracted with EtOAc (3×10 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on a silica gel column to obtain N-alkyl (aryl) protected indoles.

Direct 3-acetoxylation and iodination of indoles; typical procedure

A mixture of *N*-alkyl(aryl) indole (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), KOAc (0.5 mmol) and $Cu(OAc)_2$ (10 mmol%) was stirred in CH_3CN (2 ml) under N_2 at room temperature for 10 min and then refluxed for 3h at 100 °C until the complete consumption of starting material occurred as monitored by TLC or GC-MS analysis. After the reaction had finished, the mixture was poured into saturated $NaHSO_3$ and extracted with EtOAc (3×10 ml). The organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (PE/EA = 40:1) to afford the pure iodination and 3-acetoxylation products of the indoles in this order.

1-Benzyl-1H-indol-3-yl acetate (**1a**):[20] Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.26 (s, 3H), 5.17 (s, 2H),7.02–7.06 (m,3H), 7.09–7.13 (m, 1H), 7.15–7.22 (m, 4H), 7.25 (s, 1H), 7.47–7.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.9, 49.0, 108.6, 116.2, 116.6, 118.5, 119.3, 121.5, 125.7, 126.6, 127.7, 128.7, 132.3, 136.1, 167.4; LRMS (EI): (%) 265 (M^+, 20), 223 (89), 91 (100); HRMS Calcd for $C_{17}H_{15}NO_2$ (M+1): 266.1176; Found: 266.1193.

1-Benzyl-1H-3-iodoindole (**1b**): Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.2 (s, 2H), 7.02–7.07 (m, 2H), 7.10–7.25 (m, 7H), 7.35–7.40 (m, 1H). ^{13}C NMR(125 MHz, $CDCl_3$) δ: 49.4, 54.9, 108.6, 119.5, 120.2, 120.5, 121.8, 126.0, 127.0, 127.9, 131.0, 135.4, 135.7; HRMS Calcd for $C_{15}H_{12}IN$ (M+1): 334.0087; Found: 334.0089.

1-Benzyl-5-methyl-1H-indol-3-yl acetate (**2a**):[20] Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.23 (s, 3H), 2.34(s, 3H), 5.10 (s, 2H), 6.90–6.92 (m, 1H), 6.99–7.04(m, 3H), 7.1–7.2 (m, 4H), 7.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.9, 20.3, 49.1 108.4, 116.1, 116.3, 119.5, 123.2, 125.7, 126.5, 127.6, 127.8, 128.3, 130.8, 136.4, 167.5; LRMS (EI): (%) 279 (M^+, 21), 257 (100), 146 (31), 91 (94); HRMS Calcd for $C_{18}H_{17}NO_2$ (M+1): 280.1332; Found: 280.1348.

1-Benzyl-5-methyl-1H-3-iodoindole (**2b**): Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.35 (s, 3H), 5.10 (s, 2H), 6.91–7.02 (m, 5H), 7.14–7.17 (m, 4H). ^{13}C NMR(125 MHz, $CDCl_3$): 20.0, 49.1, 54.2, 108.5, 119.7, 120.5, 123.4, 125.8, 126.7, 127.7, 128.4, 128.9, 131.0, 135.8; HRMS Calcd for $C_{16}H_{14}IN$ (M+1): 348.0244; Found: 348.0248.

1-Benzyl-7-methyl-1H-indol-3-yl acetate (**3a**):[20] Purple solid; m.p. 105–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.28 (s, 3H), 2.44 (s, 3H), 5.45 (s, 2H), 6.81–6.87 (m, 3H), 6.93–6.96 (m, 1H),7.14–7.22 (m, 4H), 7.34–7.37 (m,1H); ^{13}C NMR (125 MHz, $CDCl_3$): 18.5, 19.8, 51.3, 114.6, 117.7, 118.9, 120.2, 120.5, 124.3, 124.4, 126.3, 127.8, 128.7, 131.2, 131.5, 167.3; LRMS (EI): (%) 279 (M^+, 25), 237 (83), 146 (41), 91 (100); HRMS Calcd for $C_{18}H_{17}NO_2$ (M+1): 280.1332; Found: 280.1348.

1-Benzyl-7-methyl-1H-3-iodoindole (**3b**): Yellow solid; m.p. 87–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.5 (s, 3H), 5.5 (s, 2H), 6.88–6.94 (m, 3H), 7.06–7.12 (m, 2H), 7.20–7.29 (m, 3H), 7.31–7.34 (m, 1H). ^{13}C NMR(125 MHz, $CDCl_3$): 19.1, 52.5, 56.8, 116.6, 119.6, 120.9, 121.4, 125.8, 127.6, 129.0, 131.6, 134.0, 135.2, 138.9; HRMS Calcd for $C_{16}H_{14}IN$ (M+1): 348.0244; Found: 348.0191.

1-Benzyl-5-chloro-1H-indol-3-yl acetate (**4a**):[21] Yellow solid; m.p. 82–83 °C (lit.[21] 83–84 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.25 (s, 3H), 5.17(s, 2H), 7.01–7.08 (m, 4H), 7.17–7.23 (m, 3H), 7.27 (s, 1H), 7.46–7.47 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): 28.6, 49.3, 109.8, 116.5, 117.6, 120.4, 121.9, 124.5, 125.7, 126.7, 127.8, 128.1, 130.6, 135.7, 167.3; LRMS (EI): (%) 299 (M^+, 9), 257 (40), 91 (100).

1-Benzyl-5-chloro-1H-3-iodoindole (**4b**): Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.18 (s, 2H), 6.98–7.03 (m, 2H), 7.04–7.08 (m, 2H), 7.11 (s, 1H), 7.19–7.25 (m, 3H), 7.34–7.37 (m, 1H). ^{13}C NMR(125 MHz, $CDCl_3$) δ: 49.6, 54.0, 110.0, 119.8, 120.5, 122.2, 125.9, 127.1, 127.9, 128.4, 130.8, 132.4, 135.3; HRMS Calcd for $C_{15}H_{11}ClIN$ (M+1): 367.9698; Found: 367.9673.

1-Benzyl-6-fluoro-1H-indol-3-yl acetate (**5a**):[22] Red solid; m.p. 66–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.25 (s, 3H), 5.12 (s, 2H), 6.77–6.86 (m, 2H), 7.02–7.07 (m, 2H), 7.17–7.25 (m, 4H), 7.37–7.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.9, 49.4, 95.1 (*J* = 27.5 Hz), 107.6 (*J* = 12.5 Hz), 116.2, 116.5 (*J* = 3.75 Hz), 117.7 (*J* = 10 Hz), 125.8, 126.8, 127.8, 128.8, 132.4 (*J* = 11.25 Hz), 135.7, 159.3 (*J* = 237.5 Hz), 167.3; LRMS (EI): (%) 283 (M^+, 13), 241 (53), 91 (100).

1-Benzyl-6-fluoro-1H-3-iodoindole (**5b**): **Y**ellow solid; m.p. 66–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.14 (s, 2H), 6.84–6.88 (m, 2H), 7.02–7.04 (m, 2H), 7.08 (s, 1H), 7.16–7.25 (m, 3H), 7.27–7.30 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 50.6, 96.3 (*J* = 27.5 Hz), 109.4 (*J* = 25 Hz), 122.4 (*J* = 10 Hz), 126.9, 127.2, 128.1, 128.9, 132.6 (*J* = 3.75 Hz), 136.1, 136.2, 136.3, 160.5 (*J* = 237.5 Hz); HRMS Calcd for $C_{15}H_{11}FIN$ (M+1): 351.9993; Found: 351.9974.

1-Methyl-1H-indol-3-yl acetate (**6a**):[20,23] Yellow solid; m.p. 52–54 °C (lit.[23] 56.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.39 (s, 3H), 3.78 (s, 3H), 7.14–17 (m, 1H), 7.27–7.29 (m, 1H), 7.32–7.33 (m, 1H), 7.57–7.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.9, 31.7, 108.2, 116.4, 116.8, 118.2, 119.1, 121.2, 128.1, 132.7, 167.7; LRMS (EI, 70eV): (%) 189 (M^+, 21), 147 (100), 132 (11), 77 (13).

1-Methyl-1H-3-iodoindole (**6b**): Yellow solid; m.p. 58–59 °C (lit.[24] 58–59 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.70 (s, 3H), 7.03 (s, 1H), 7.09–7.14 (m, 1H), 7.15–7.22 (m, 2H), 7.34–7.37 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 32.0, 53.7, 108.2, 119.1, 120.1, 121.5, 129.5, 131.6, 135.7; HRMS Calcd for C_9H_8IN (M+1): 257.9774; Found: 258.0672.

1-Isobutenyl-1H-indol-3-yl acetate (**7a**): Brown liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.67(s, 3H), 2.35(s, 3H), 4.58 (s, 2H), 4.75 (s, 1H), 4.91 (s, 1H), 7.08–7.13 (m, 1H), 7.18–7.23 (m, 1H), 7.25–7.28 (m, 1H), 7.29 (s, 1H), 7.53–7.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 19.7, 21.0, 52.5, 109.6, 112.9, 117.3, 117.6, 119.4, 120.3, 122.4, 129.6, 133.4, 140.9, 168.5. LRMS (EI): (%) 229 (M^+, 38), 55 (31), 187 (90), 132 (100); HRMS Calcd for $C_{14}H_{15}NO_2$ (M+1): 230.1103; Found: 230.1178.

1-Isobutenyl-1H-3-iodoindole (**7b**): Brown liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.66 (s, 3H), 4.62 (s, 2H), 4.75 (s, 1H), 4.92 (s, 1H), 7.14–7.21 (m, 2H), 7.21–7.26 (m, 1H), 7.26–7.30 (m, 1H), 7.42–7.45 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 20.0, 53.0, 55.6,109.8, 113.3, 120.4, 121.2, 122.7, 130.5, 132.2, 136.5, 140.7; HRMS Calcd for $C_{12}H_{12}IN$ (M+1): 298.0087; Found: 298.0081.

1-Isobutenyl-5-methyl-1H-indol-3-yl acetate (**8a**): Brown liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.58 (s, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 4.48 (s, 2H), 4.66 (s, 1H), 4.82 (s, 1H), 6.95–6.96 (m, 1H), 7.08–7.11 (m, 1H), 7.15 (s, 1H), 7.24 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 18.8, 19.9, 20.6, 51.6, 108.4, 111.8, 115.9, 116.2, 119.5, 123.1, 127.8, 128.2, 130.9, 140.1, 167.6. LRMS (EI): (%) 243 (M^+, 46), 146 (89), 201 (100); HRMS Calcd for $C_{15}H_{17}NO_2$ (M+1): 244.1259; Found: 244.1332.

1-Isobutenyl-5-Methyl-1H-3-iodoindole (**8b**): Yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.42 (s, 3H), 4.50 (s, 2H), 4.71 (s, 1H), 4.81 (s, 1H), 6.94–6.98 (m, 1H), 7.08–7.11 (m, 1H), 7.15 (s, 1H), 7.25 (s, 1H). ^{13}C NMR(125 MHz, $CDCl_3$) δ: 18.7, 20.0, 20.2, 51.6, 108.2, 111.8, 116.0, 116.3, 123.0, 127.8, 131.0, 140.0, 167.5; HRMS Calcd for $C_{13}H_{14}IN$ (M+1): 312.0244; Found: 312.0228.

1-Isobutenyl-7-methyl-1H-indol-3-yl acetate (**9a**): Brown solid; m.p. 64–65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.75 (s, 3H), 2.34 (s, 3H), 2.61 (s, 3H), 4.30 (s, 1H), 4.75 (s, 2H), 4.84 (s, 1H), 6.91–6.92 (m, 1H), 6.97–7.01 (m, 1H), 7.21–7.25(m, 1H), 7.37–7.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.3, 19.9, 21.0, 54.3, 111.2, 121.3, 115.5, 118.9, 119.6, 121.2, 125.3, 129.5, 132.2, 142.9, 168.5. LRMS (EI): (%) 243 (M^+, 33), 201 (58), 146 (100); HRMS Calcd for $C_{15}H_{17}NO_2$ (M+1): 244.1259; Found: 244.1319.

1-Isobutenyl-7-methyl-1H-3-iodoindole (**9b**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.75 (s, 3H), 2.62 (s, 3H), 4.29 (s, 1H), 4.77 (s, 2H), 4.85 (s, 1H), 6.95–6.96 (m, 1H), 7.05–7.08 (m, 2H), 7.25–7.30 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.0, 19.8, 54.5, 56.2, 111.5, 119.5, 120.6, 121.3, 125.6, 131.3, 133.9, 135.1, 142.6; HRMS Calcd for $C_{13}H_{14}IN$ (M+1): 312.0243; Found: 312.0219.

1-Isobutenyl-5-chloro-1H-indol-3-yl acetate (**10a**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.65 (s, 3H), 2.34 (s, 3H), 4.56 (s, 2H), 4.73 (s, 1H), 4.91–4.92 (m, 1H), 7.13–7.16 (m, 1H), 7.18–7.20 (m, 1H), 7.31 (s, 1H), 7.53–7.54 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.8, 21.9, 52.8, 111.9, 113.2, 117.2, 118.7, 121.2, 122.8, 125.4, 128.9, 131.8, 140.6, 168.4. LRMS (EI): (%) 263 (M^+, 33), 55 (39), 166 (60), 221 (100); HRMS Calcd for $C_{14}H_{14}ClNO_2$ (M+1): 264.0713; Found: 264.0785.

1-Isobutenyl-5-chloro-1H-3-iodoindole (**10b**): Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.64 (s, 3H), 4.58 (s, 2H), 4.72 (s, 1H), 4.92 (m, 1H), 7.14–7.20 (m, 3H), 7.40–7.43 (m, 1H). ^{13}C NMR(125 MHz, $CDCl_3$) δ ppm 19.8, 52.6, 55.5, 111.1, 113.5, 120.8, 123.1, 126.4, 131.7, 133.5, 134.9, 140.3; HRMS Calcd for $C_{12}H_{11}ClIN$ (M+1): 331.9698; Found: 331.9701.

1-Isobutenyl-4-chloro-1H-indol-3-yl acetate (**11a**): Yellow solid; m.p. 68–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.66 (s, 3H), 2.35 (s, 3H), 4.57 (s, 2H), 4.72–4.75 (m, 1H), 4.91–4.94 (m, 1H), 7.04–7.10 (m, 2H), 7.12 (s, 1H), 7.16–7.18 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.8, 20.4, 52.7, 108.6, 113.3, 118.1, 119.1, 120.5, 122.9, 124.5, 128.5, 135.2, 140.4, 169.9. LRMS (EI): (%) 263 (M^+, 25), 55 (27), 223 (32), 166 (64), 221 (100); HRMS Calcd for $C_{14}H_{14}ClNO_2$ (M+1): 264.0713; Found: 264.0780.

1-Isobutenyl-4-chloro-1H-3-iodoindole (**11b**): Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.65 (s, 3H), 4.60 (s, 2H), 4.72 (s, 1H), 4.90–4.95 (m, 1H), 7.06–7.11 (m, 2H), 7.20 (s, 1H), 7.21–7.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.6, 50.5, 53.0, 109.0, 113.5, 121.5, 122.7, 124.4, 126.7, 135.0, 137.5, 140.0; HRMS Calcd for $C_{12}H_{11}ClIN$ (M+1): 331.9698; Found: 331.9690.

1-Isobutenyl-6-fluoro-1H-indol-3-yl acetate (**12a**): Orange liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.66 (s, 3H), 2.34 (s, 3H), 4.52 (s, 2H), 4.75 (s, 1H), 4.92–4.93 (m, 1H), 6.85–6.90 (m, 1H), 6.94–6.96 (m, 1H), 7.26 (s, 1H), 7.44–7.48 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.7, 20.9, 52.8, 96.1 (*J* = 27.5 Hz), 108.5 (*J* = 23.8 Hz), 113.2, 117.0, 117.5 (*J* = 3.75 Hz), 118.6 (*J* = 10 Hz), 129.6, 133.4 (*J* = 11.25 Hz), 140.5, 160.3 (*J* = 237.5 Hz), 168.4. LRMS (EI): (%) 247 (M^+, 37), 205 (87), 150 (100); HRMS Calcd for $C_{14}H_{14}FNO_2$ (M+1): 248.1009; Found: 248.1089.

1-Isobutenyl-6-fluoro-1H-3-iodoindole (**12b**): **Y**ellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.66 (s, 3H), 4.55 (s, 2H), 4.75 (s, 1H), 4.94 (s, 1H), 6.92–6.98 (m, 2H), 7.12 (s, 1H), 7.32–7.36 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 19.8, 53.0, 55.5, 96.3 (*J* = 26.3 Hz), 109.2 (*J* = 25 Hz), 113.6, 122.3 (*J* = 10 Hz), 127.1, 132.7 (*J* = 3.75 Hz), 136.3 (*J* = 11.25 Hz), 140.2, 160.5 (*J* = 238.75 Hz); HRMS Calcd for $C_{12}H_{11}FIN$ (M+1): 315.9993; Found: 315.9991.

1-n-Butyl-1H-indol-3-yl acetate (**13a**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.91–0.95 (t, *J* = 7.5 Hz, 3H), 1.30–1.38 (m, 2H), 1.76–7.84 (m, 2H), 2.35 (s, 3H), 4.04–4.09 (t, *J* = 7.5 Hz, 2H), 7.08–7.12 (m, 1H), 7.19–7.25 (m, 1H), 7.28–7.32 (m, 2H), 7.52–7.56 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.6, 20.1, 21.0, 32.3, 46.1, 109.4, 116.7, 117.6, 119.2, 120.2, 122.2, 129.3, 133.0, 168.6. LRMS (EI): (%) 231 (M^+, 28), 189 (71), 146 (100); HRMS Calcd for $C_{14}H_{17}NO_2$ (M+1): 232.1259; Found: 232.1335.

1-n-Butyl-1H-3-iodoindole (**13b**): Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.91–0.94 (t, *J* = 7.5, 3H), 1.31–1.35 (m, 2H), 1.78–1.81 (m, 2H), 4.08–4.11 (t, *J* = 7.5, 2H), 7.16–7.18 (m, 2H), 7.23–7.26 (m, 1H), 7.29–7.31 (m, 1H), 7.42–7.44 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.7, 20.1, 32.4, 46.5, 109.6, 118.4, 120.2, 122.5, 129.8, 130.5, 131.8, 136.2; HRMS Calcd for $C_{12}H_{14}IN$ (M+1): 300.0244; Found:300.0232.

1-n-Butyl-5-methyl-1H-indol-3-yl acetate (**14a**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.87–0.92 (t, *J* = 7.5 Hz, 3H), 1.26–1.35 (m, 2H), 1.72–1.80 (m, 2H), 2.32 (s, 3H), 2.44 (s, 3H), 4.00–4.03 (t, *J* = 7.5 Hz, 2H), 7.01–7.03 (m, 1H), 7.17–7.19 (m, 1H), 7.22 (s, 1H), 7.31 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.71, 20.16, 20.98, 21.40, 32.35, 46.15, 109.2, 116.9, 117.1, 123.9, 128.5, 128.9, 129.4, 131.6, 168.7. LRMS (EI): (%) 245 (M^+, 36), 203 (89), 160 (100); HRMS Calcd for $C_{15}H_{19}NO_2$ (M+1): 246.1416; Found: 246.1493.

1-n-Butyl-5-methyl-1H-3-iodoindole (**14b**): Pink liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90–0.94 (t, *J* = 7.5 Hz, 3H), 1.26–1.35 (m, 2H), 1.73–1.80 (m, 2H), 2.48 (s, 3H), 4.0–4.1 (t, *J* = 7.5, 2H), 7.04–7.08 (m, 1H), 7.11 (s, 1H), 7.16–7.23 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.9, 20.0, 21.2, 32.2, 46.5, 54.0, 109.4, 120.8, 124.0, 129.6, 130.6, 131.7, 134.5; HRMS Calcd for $C_{13}H_{16}IN$ (M+1): 314.0400; Found: 314.0369.

1-n-Butyl-7-methyl-1H-indol-3-yl acetate (**15a**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90–0.95 (t, *J* = 7.5 Hz, 3H), 1.33–1.40 (m, 2H), 1.72–1.79 (m, 2H), 2.33 (s, 3H), 2.69 (s, 3H), 4.22–4.27 (t, *J* = 7.5 Hz, 2H), 6.91–6.94 (m, 1H), 6.96–7.00 (m, 1H), 7.22 (s, 1H), 7.34–7.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.7,

19.9, 20.1, 21.0, 34.5, 48.7, 115.5, 118.2, 119.4, 120.9, 121.4, 125.2, 129.3, 131.7, 168.5. LRMS (EI): (%) 245 (M^+, 32), 203 (83), 160 (100); HRMS Calcd for $C_{15}H_{19}NO_2$ (M+1): 246.1416; Found: 246.1491.

1-n-Butyl-7-methyl-1H-3-iodoindole (**15b**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.91–0.96 (t, *J* = 7.5 Hz, 3H), 1.30–1.40 (m, 2H), 1.70–1.80 (m, 2H), 2.70 (s, 3H), 4.24–4.31 (t, *J* = 7.5 Hz, 2H), 6.94–6.98 (m, 1H), 7.02–7.08 (m, 1H), 7.09 (s, 1H), 7.26–7.30 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.8, 19.7, 20.0, 35.0, 49.0, 55.8, 119.5, 120.4, 121.0, 125.6, 131.5, 133.4, 134.7; HRMS Calcd for $C_{13}H_{16}IN$ (M+1): 314.0400; Found: 314.0473.

1-n-Butyl-5-chloro-1H-indol-3-yl acetate (**16a**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90–0.94 (t, *J* = 7.5 Hz, 3H), 1.27–1.36 (m, 2H), 1.74–1.81 (m, 2H), 2.33 (s, 3H), 4.01–4.05 (t, *J* = 7.5 Hz, 2H), 7.13–7.16 (m, 1H), 7.19–7.22 (m, 1H), 7.30 (s, 1H), 7.50–7.51 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.8, 20.0, 21.9, 32.1, 46.3, 110.5, 117.1, 118.2, 121.0, 122.5, 125.2, 128.4, 131.4, 168.5. LRMS (EI): (%) 265 (M^+, 32), 225 (33), 180 (85), 223 (100); HRMS Calcd for $C_{14}H_{16}ClNO_2$ (M+1): 266.0870; Found: 266.0951.

1-n-Butyl-5-chloro-1H-3-iodoindole (**16b**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90–0.96 (t, *J* = 7.5 Hz, 3H), 1.27–1.36 (m, 2H), 1.74–1.81 (m, 2H), 4.04–4.09 (t, *J* = 7.5 Hz, 2H), 7.07–7.12 (m, 2H), 7.21 (s, 1H), 7.24–7.26 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.5, 20.0, 32.0, 46.8, 108.6, 121.4, 122.5, 124.4, 126.8, 134.4, 134.5, 137.2; HRMS Calcd for $C_{12}H_{13}ClIN$ (M+1):333.9854; Found: 333.9861.

1-n-Butyl-4-chloro-1H-indol-3-yl acetate (**17a**): Yellow solid; m.p. 47–48 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.82–0.87 (t, *J* = 7.5 Hz, 3H), 1.20–1.29 (m, 2H), 1.66–1.74 (m, 2H), 2.25 (s, 3H), 3.93–3.99 (t, *J* = 7.5 Hz, 2H), 6.95–7.03 (m, 2H), 7.05 (s, 1H), 7.09–7.13 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.5, 20.0, 21.9, 32.0, 46.3, 108.2, 117.7, 118.6, 120.2, 122.5, 124.4, 128.1, 134.8, 169.9. LRMS (EI): (%) 265 (M^+, 35), 225 (31), 180 (85), 223 (100); HRMS Calcd for $C_{14}H_{16}ClNO_2$ (M+1): 266.0870; Found: 266.0940.

1-n-Butyl-4-chloro-1H-3-iodoindole (**17b**): Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90–0.96 (t, *J* = 7.5, 3H), 1.27–1.36 (m, 2H), 1.74–1.81 (m, 2H), 4.04–4.09 (t, *J* = 7.5, 2H), 7.07–7.12 (m, 2H), 7.21 (s, 1H), 7.24–7.26 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.5, 20.0, 32.0, 46.8, 50.0, 108.6, 121.4, 122.5, 124.4, 126.8, 134.5, 137.2; HRMS Calcd for $C_{12}H_{13}ClIN$ (M+1): 333.9854; Found: 333.9830.

1-n-Butyl-6-fluoro-1H-indol-3-yl acetate (**18a**): Brown liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.91–0.95 (t, *J* = 7.5 Hz, 3H), 1.29–1.38 (m, 2H), 1.74–1.82 (m, 2H), 2.33 (s, 3H), 3.97–4.01 (t, *J* = 7.5 Hz, 2H), 6.84–6.89 (m, 1H), 6.94–6.98 (m, 1H), 7.26 (s, 1H), 7.42–7.47 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.7, 20.1, 21.0, 32.1, 46.3, 95.7 (*J* = 26.25 Hz), 108.2 (*J* = 25 Hz), 116.8, 117.0 (*J* = 3.75 Hz), 118.6 (*J* = 10 Hz), 129.4, 133.0 (*J* = 11.25 Hz), 160.2 (*J* = 237.5 Hz), 168.5. LRMS (EI): (%) 249 (M^+, 36), 165 (34), 164 (99), 207 (100); HRMS Calcd for $C_{14}H_{16}FNO_2$ (M+1): 250.1165; Found: 250.1243.

1-n-Butyl-6-fluoro-1H-3-iodoindole (**18b**): Yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90–0.96 (t, *J* = 7.5, 3H), 1.28–1.37 (m, 2H), 1.73–1.80 (m, 2H), 4.0–4.05 (t, *J* = 7.5, 2H), 6.9–6.96 (m, 1H), 6.97–7.01 (m, 1H), 7.13 (s, 1H), 7.31–7.36 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.6, 20.0, 32.2, 46.7, 55.0, 95.9 (*J* = 25 Hz), 109.1 (*J* = 23.75 Hz), 122.2 (*J* = 11.25 Hz), 127.0, 132.3 (*J* = 3.75 Hz), 135.9 (*J* = 11.25 Hz), 160.4 (*J* = 237.5 Hz). HRMS Calcd for $C_{12}H_{13}FIN$ (M+1): 318.0150; Found: 318.0129.

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References

1 S. Cacchi and G. Fabrisi, *Chem. Rev*., 2005, **105**, 2873.
2 D. Crich and A. Banerjee, *Acc. Chem. Res*., 2007, **40**, 151.
3 Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem*., 2009, **121**, 4642.
4 Z. Liang, J. Zhao and Y. Zhang, *J. Org. Chem*., 2010, **75**, 170.
5 R.D. Arnold, W.M. Nutter and W.L. Stepp, *J. Org. Chem*., 1959, **24**, 117.
6 K.X. Liu, P. Wen, J.Liu and G.S. Huang, *Synthesis*., 2010, **21**, 3623.
7 D. Lubriks, I. Sokolovs and E. Suna, *Org. Lett*., 2011, **13**, 4324.
8 D. Qiu, Z.T. Zheng, F.Y. Mo, Q. Xiao, Y. Tian, Y. Zhang and J.B. Wang, *Org. Lett*., 2011, **13**, 4988.
9 K.J. Stowers and M.S. Sanford, *Org. Lett.*, 2009, **11**, 4584.
10 S.J. Gu, C. Chen and W.Z. Chen, *J. Org. Chem*., 2009, **74**, 7203.
11 G.W. Wang, T.T. Yuan and X.L. Wu, *J. Org. Chem*., 2008, **73**, 4717.
12 Q. Liu, G. Li, H. Yi, P. Wu, J. Liu and A.W. Lei, *Chem. Eur. J*., 2011, **17**, 2353.
13 I. Mutule, E. Suna, K. Olofsson and B. Pelcman, *J. Org. Chem*., 2009, **74**, 7195.
14 P.Y. Choy, C.P. Lau and F.Y. Kwong, *J. Org. Chem*., 2011, **76**, 80.
15 G.A. Olah, Q. Wang, G. Sandford and G.K.S. Prakash, *J. Org. Chem*., 1993, **58**, 3194.
16 G.J. Bodwell and J. Li, *Org. Lett*., 2002, **4**, 127.
17 M.A. Zolfigol, A. Khazaei, E. Kolvari, N. Koubaki, H. Soltani and M. Behjunia, *HeIv. Chim. Acta*, 2010, **93**, 587.
18 A.K. Mohanakrishnan, C. Prakash and N. Ramesh, *Tetrahedron*, 2006, **62**, 3242.
19 M.A. Zolfigol, A. Khazaei, E. Kolvari, N. Koukabi, H. Soltani, M. Behjunia, V. Khakyzadeh. *Arkivoc*., 2009, **xiii**, 200.
20 P.Y. Choy, C.P. Lau, and F.Y. Kwong, *J. Org. Chem*., 2011, **76**, 80.
21 D. Lubriks, I. Sokolovs, and E. Suna. *Org. Lett.*, 2011, **13**, 4324.
22 Q. Liu, G. Li, H. Yi, P. Wu, J. Liu and A.W. Lei, *Chem. Eur. J*., 2011, **17**, 2353.
23 E. Zaha A, *Alex. J. Pharm. Sci.*, 2005, **19**, 129.
24 M.S. Shvartsberg, S.F. Vaslievski, T.A. Prikhod'ko, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1982, **11**, 2524.