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A simple one-pot synthesis of 2,4-diaryl-9*H*-pyrido[2,3-*b*]indoles under solvent-free conditions

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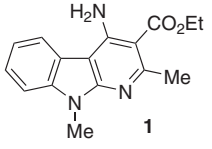
Abstract: A novel, simple, one-pot synthesis of 2,4-diaryl-9*H*-pyrido[2,3-*b*]indoles is described. Heating a mixture of chalcone, oxindole and ammonium acetate in the presence of potassium *tert*-butoxide under solvent-free conditions afforded the title compounds in good to excellent yields.

Keywords: ammonium acetate; chalcones; heterocycles; oxindoles; solvent-free; 9*H*-pyrido[2,3-*b*]indoles.

Introduction

Pyrido[2,3-*b*]indoles (α-carbolines) have attracted considerable attention due to their occurrence in carcinogenic metabolites, biologically active compounds and natural products [1–3]. Some synthetic pyrido[2,3-*b*]indoles including **1** are γ-aminobutyric acid (GABA) modulators with potential as therapeutic agents for the treatment of anxiety disorders [4]. Recently, some of related compounds have shown activity against Alzheimer's disease, Parkinson's disease, cerebrovascular accidents, amyotrophic lateral sclerosis, viral infections and autoimmune diseases [5, 6]. Some compounds are antidepressant and antineoplastic agents [7, 8].



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GABA modulator with anxiolytic activity

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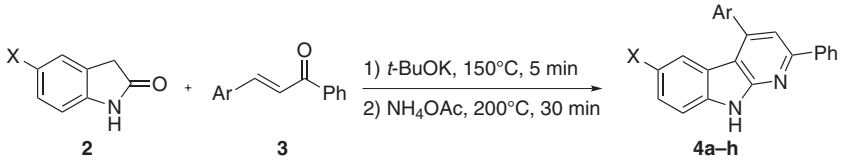
Pyrido[2,3-*b*]indoles can be synthesized by reaction of α-oxoketene dithioacetal with 1-methyl-2-oxoindole enolate anion and subsequent cyclization of the adduct in the presence of NH_4OAc [9], reaction of 2-aminoindole with 3,3-dimethoxy-2-formyl-propionitrile sodium salt [10], reaction between 2-aminoindole and acetylenic esters [11], condensation of 2-amidinylindole-3-carbaldehyde with acetophenone [12], cyclization of 1-methyl-3-(2-carbomethoxyethyl)-2-iminoindoline [6], cross coupling of *ortho*-pivaloylaminophenyl-*ortho′*-halopyridine [13], intramolecular [4+2] cycloaddition-elimination of 3-(2-ethynylphenylamino)-2(1*H*)-pyrazinone [14], intramolecular hetero-Diels-Alder cycloaddition-aromatization of *ortho*-vinyl C=C-conjugated arylcarbodiimide [15] and pyrolysis of 1-benzylpyrazole with chloroform [16]. Several of these multi-step methods have drawbacks such as not easily accessible starting materials, low overall yields, harsh reaction conditions, long reaction times and use of toxic and hazardous starting materials, reagents and/or solvents.

As part of our ongoing program to develop new facile methods for the preparation of biologically active heterocyclic compounds from readily available building blocks [17–20], we report herein a simple one-pot synthesis of 2,4-diaryl-9*H*-pyrido[2,3-*b*]indoles.

Results and discussion

Heating a mixture of oxindole **2**, chalcone **3** and ammonium acetate in the presence of a catalytic amount of potassium *tert*-butoxide under solvent-free conditions produced the 2,4-diaryl-9*H*-pyrido[2,3-*b*]indole **4a–h** in 82–90% yield (Scheme 1). The reaction was carried out by mixing the oxindole and the chalcone, then adding a catalytic amount of *t*-BuOK, stirring the mixture at 150°C for 5 min to form an oily mixture, followed by treatment with an excess of NH_4OAc and stirring at 200°C for an additional 30 min. TLC and ^{1}H NMR analyses of the resultant yellowish liquid clearly indicated formation of pyrido[2,3-*b*]indole **4a–h**.

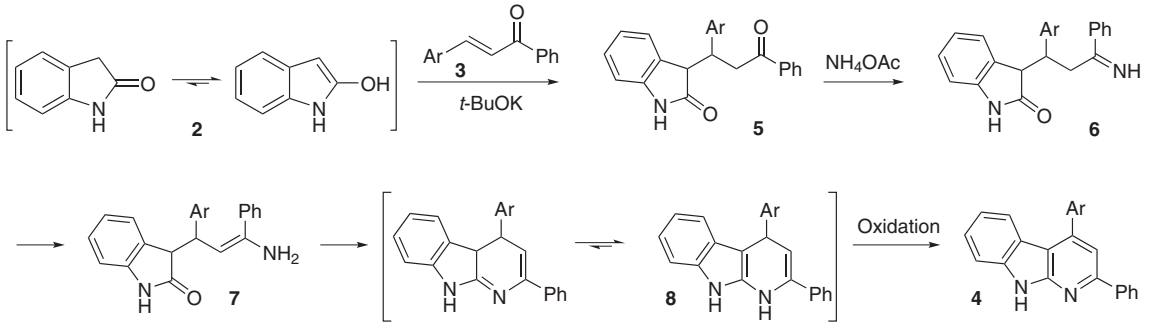
A possible reaction pathway for the formation of 2,4-diaryl-9*H*-pyrido[2,3-*b*]indole **4** is suggested in Scheme 2. The initial Michael addition reaction of the



2 **3** **4a–h**

4a: X = H; Ar = 4-Me-C_6H_4
4b: X = H; Ar = 3-Me-C_6H_4
4c: X = H; Ar = 4-MeO-C_6H_4
4d: X = H; Ar = 4-Cl-C_6H_4
4e: X = H; Ar = 2-furyl
4f: X = Br; Ar = 4-Me-C_6H_4
4g: X = Br; Ar = 3-Me-C_6H_4
4h: X = Br; Ar = 4-Cl-C_6H_4

Scheme 1



Scheme 2

oxindole **2** with chalcone **3** [21–25], leads to the formation of the intermediate product **5**. Then, condensation of ammonium acetate with this intermediate compound followed by tautomerization generates the enamine **7**. Finally, intramolecular cyclization of **7** followed by tautomerization and oxidation of **8** affords the product **4**.

Conclusion

A solvent-free reaction between oxindole **2**, chalcone **3**, and ammonium acetate in the presence of potassium *tert*-butoxide provides a simple one-pot approach to the synthesis of a substituted pyrido[2,3-*b*]indole. Use of simple starting materials, good atom economy, short reaction time and good yield of the product are the main advantages of this method.

Experimental

Oxindoles and potassium *tert*-butoxide were obtained from Merck (Germany) and Sigma-Aldrich (USA). Chalcones were prepared according to the literature procedure [26]. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on an Agilent Technologies HP 5973 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H NMR (250.1 MHz) and ^{13}C NMR (62.9) spectra were measured with a Bruker DPX-250 spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were recorded in KBr pellets on a Shimadzu IR-460 spectrometer.

General procedure for synthesis of 4a–h

A mixture of an oxindole (1.0 mmol), a chalcone (1.0 mmol) and potassium *tert*-butoxide (0.034 g, 0.3 mmol) was stirred at 150°C for 5 min and the resultant oily mixture was then treated with ammonium acetate (0.154 g, 2.0 mmol) over 4 min and stirred at 200°C for an additional 30 min. The resultant yellowish liquid solidified upon cooling to room temperature and was crystallized from a mixture of EtOAc/*n*-hexane (1:1).

2-Phenyl-4-(*p*-tolyl)-9*H*-pyrido[2,3-*b*]indole (4a) Pale yellow solid; yield 90%; mp 217–218°C; IR (cm^{-1}): 3153, 1591, 1566, 1362, 1294, 1207, 1109, 997, 870, 820, 746, 696; ^{1}H NMR: δ 2.55 (s, 3H), 6.47 (d, J = 7.8 Hz, 1H), 7.02 (dd, J = 7.7, 7.4 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.50–7.60 (m, 3H), 7.62 (s, 1H), 7.71 (d, J = 7.0 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1H), 8.28 (d, J = 7.5 Hz, 2H), 12.36 (s, 1H); ^{13}C NMR: δ 21.4, 111.4, 112.9, 114.4, 119.3, 120.6, 122.3, 126.2, 127.8, 128.6, 128.7, 129.1, 129.4, 136.3, 138.5, 139.4, 140.3, 146.3, 153.4, 154.2; MS: m/z 334 (M^+). Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.20; H, 5.42; N, 8.35.

2-Phenyl-4-(*m*-tolyl)-9*H*-pyrido[2,3-*b*]indole (4b) Pale yellow solid; yield 85%; mp 187–188°C; IR (cm^{-1}): 3329, 1583, 1566, 1485, 1450, 1385, 1292, 1211, 771, 740, 695; ^{1}H NMR: δ 2.53 (s, 3H), 6.52 (d, J = 8.1 Hz, 1H), 7.02 (dd, J = 7.6, 7.4 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.55–7.62 (m, 6H), 7.69 (d, J = 7.8 Hz, 1H), 8.28 (d, J = 7.5 Hz, 2H), 12.23 (s, 1H); ^{13}C NMR: δ 21.5, 111.4, 112.9, 114.4, 119.4, 120.6, 122.3, 125.8, 126.2, 127.8, 128.6, 128.7, 129.1, 129.3, 129.4, 138.4, 139.2, 139.5, 140.2, 146.4, 153.4, 154.2; MS: *m/z* 334 (M^+). Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.19; H, 5.50; N, 8.35.

4-(4-Methoxyphenyl)-2-phenyl-9*H*-pyrido[2,3-*b*]indole (4c) Pale yellow solid; yield 92%; mp 220–221°C; IR (cm^{-1}): 3266, 1607, 1595, 1564, 1510, 1456, 1394, 1360, 1294, 1248, 1178, 1030, 837, 773, 742, 696; ^{1}H NMR: δ 3.97 (s, 3H), 6.94 (dd, J = 7.5, 1.0 Hz), 7.06 (dd, J = 7.6, 7.4 Hz), 7.15 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.47–7.59 (m, 4H), 7.74 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 7.4 Hz, 1H), 8.20 (d, J = 7.6 Hz, 2H), 10.99 (s, 1H); ^{13}C NMR: δ 55.4, 111.3, 112.8, 114.2, 114.4, 119.4, 120.7, 122.3, 126.3, 127.7, 128.7, 129.1, 130.0, 131.5, 139.3, 140.2, 146.0, 153.3, 154.3, 160.1; MS: *m/z* 350 (M^+). Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.31; H, 5.23; N, 7.98.

4-(4-Chlorophenyl)-2-phenyl-9*H*-pyrido[2,3-*b*]indole (4d) Pale yellow solid; yield 87%; mp 227–228°C; IR (cm^{-1}): 3250, 1591, 1545, 1481, 1458, 1389, 1350, 1296, 1207, 1022, 773, 739, 698; ^{1}H NMR: δ 7.05 (dd, J = 8.5, 7.7 Hz, 1H), 7.41 (dd, J = 8.5 Hz, J = 7.1 Hz, 1H), 7.44 (d, J = 7.1 Hz), 7.48–7.54 (m, 4 H), 7.66 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 8.22 (dd, J = 7.1, 1.4 Hz, 2H), 12.11 (s, 1H); ^{13}C NMR: δ 111.3, 111.5, 112.9, 119.4, 119.6, 121.7, 126.6, 126.9, 128.8, 128.9, 128.9, 130.6, 133.6, 137.5, 139.2, 139.6, 143.7, 152.6, 153.1; MS: *m/z* 356 [M^+ ^{37}Cl], 354 (M^+ ^{35}Cl). Anal. Calcd for $C_{23}H_{15}ClN_2$: C, 77.85; H, 4.26; N, 7.89. Found: C, 77.83; H, 4.38; N, 7.88.

4-(Furan-2-yl)-2-phenyl-9*H*-pyrido[2,3-*b*]indole (4e) Pale yellow solid; yield 85%; mp 174–175°C; IR (cm^{-1}): 3172, 1591, 1543, 1481, 1456, 1389, 1348, 1294, 1209, 1022, 771, 741, 694; ^{1}H NMR: δ 6.59 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 1.0 Hz, 1H), 7.15–7.29 (m, 3H), 7.52–7.62 (m, 3H), 7.82 (s, 2H), 8.22 (d, J = 7.0 Hz, 2H), 8.49 (d, J = 7.9 Hz, 1H), 11.75 (s, 1H); ^{13}C NMR: δ 110.9, 111.0, 111.1, 111.3, 112.2, 120.1, 120.5, 123.7, 126.8, 127.5, 129.0, 129.1, 133.8, 139.3, 139.4, 143.6, 146.3, 152.3, 153.7; MS: *m/z* 310 (M^+). Anal. Calcd for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55; N, 9.03. Found: C, 81.19; H, 4.60; N, 8.99.

6-Bromo-2-phenyl-4-(*p*-tolyl)-9*H*-pyrido[2,3-*b*]indole (4f) Pale yellow solid; yield 88%; mp 226–228°C; IR (cm^{-1}): 3239, 1587, 1564, 1510, 1447, 1352, 1292, 1209, 872, 820, 770, 692; ^{1}H NMR: δ 2.55 (s, 3H), 6.51 (d, J =8.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.53–7.59 (m, 4H), 7.65 (d, J = 7.5 Hz, 2H), 7.84 (s, 1H), 8.19 (d, J = 7.5 Hz, 2H), 11.84 (s, 1H); ^{13}C NMR: δ 21.5, 112.0, 112.3, 112.8, 114.9, 122.3, 124.8, 127.9, 128.5, 129.0, 129.1, 129.2, 129.6, 135.7, 137.9, 139.1, 140.0, 146.9, 153.5, 155.0; MS: *m/z* 414 (M^+ ^{81}Br), 412 (M^+ ^{79}Br). Anal. Calcd for $C_{24}H_{17}BrN_2$: C, 69.74; H, 4.15; N, 6.78. Found: C, 69.81; H, 4.18; N, 6.79.

6-Bromo-2-phenyl-4-(*m*-tolyl)-9*H*-pyrido[2,3-*b*]indole (4g) Pale yellow solid; yield 82%; mp 216–217°C; IR (cm^{-1}): 3220, 1582, 1560, 1481, 1446, 1381, 1352, 1292, 1211, 866, 800, 770, 696; ^{1}H NMR: δ 2.53 (s, 3H), 6.30 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 6.5Hz, 1H), 7.49–7.60 (m, 8H), 7.80 (s, 1H), 8.21 (d, J = 6.7 Hz, 2H), 12.37 (s, 1H); ^{13}C NMR: δ 21.5, 111.9, 112.3, 112.7, 114.8, 122.4, 125.0, 125.6, 127.8, 128.8, 129.0, 129.1, 129.2, 129.3, 129.8, 137.8, 138.5, 138.7, 139.9, 146.9, 153.3, 155.1; MS: *m/z* 414 (M^+ ^{81}Br), 412 (M^+ ^{79}Br). Anal. Calcd for $C_{24}H_{17}BrN_2$: C, 69.74; H, 4.15; N, 6.78. Found: C, 69.68; H, 4.19; N, 6.80.

6-Bromo-4-(4-chlorophenyl)-2-phenyl-9*H*-pyrido[2,3-*b*]indole (4h) Pale yellow solid; yield 84%; mp 264–266°C; IR (cm^{-1}): 3240, 1586, 1559, 1517, 1483, 1452, 1350, 1290, 1205, 870, 815, 768, 695; ^{1}H NMR: δ 6.86 (d, J = 8.5 Hz, 1H), 7.47 (dd, J = 8.5, 7.4 Hz, 1H), 7.55–7.59 (m, 4H), 7.64 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.77 (s, 1H), 8.16 (d, J = 7.1 Hz, 2H), 11.22 (s, 1H); ^{13}C NMR: δ 112.6, 112.8, 114.7, 122.1, 124.7, 127.7, 129.1, 129.2, 129.3, 129.4, 129.9, 130.6, 135.2, 137.0, 137.8, 139.7, 145.3, 153.2, 155.3; MS: *m/z* 436 (M^+ ^{81}Br^{37}Cl), 434 (M^+ ^{79}Br^{37}Cl, M^+ ^{81}Br^{35}Cl), 432 (M^+ ^{79}Br^{35}Cl). Anal. Calcd for $C_{23}H_{14}BrClN_2$: C, 63.69; H, 3.25; N, 6.46. Found: C, 63.58; H, 3.38; N, 6.38.

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