

Bagher Eftekhari-Sis,^{a*} Maryam Zirak,^b Ali Akbari,^a
and Mohammed M. Hashemi^c

^aDepartment of Chemistry, Faculty of Science, University of Maragheh, Maragheh, Iran

^bDepartment of Organic Chemistry, Faculty of Chemistry, Tabriz University, Tabriz, Iran

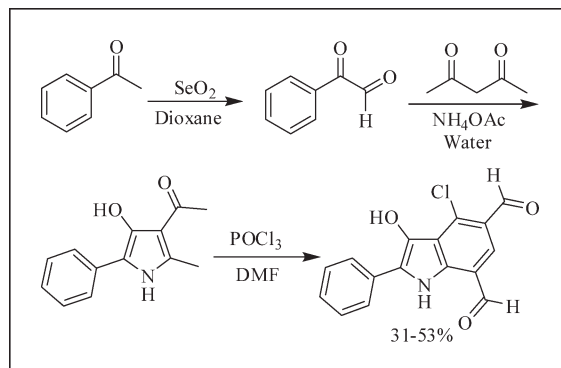
^cDepartment of Chemistry, Sharif University of Technology, Tehran, Iran

*E-mail: eftekhariasis@mhec.ac.ir

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New 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes were synthesized in three steps from acetophenone derivatives. By oxidation of acetophenones to aryl glyoxals using selenium dioxide and condensation with acetylacetone in the presence of ammonium acetate in water 3-acetyl-5-aryl-4-hydroxy-2-methyl-1*H*-pyrroles were obtained. 2-Aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes were synthesized *via* Vilsmeier-Haack reaction of pyrrole derivatives in moderate yields.

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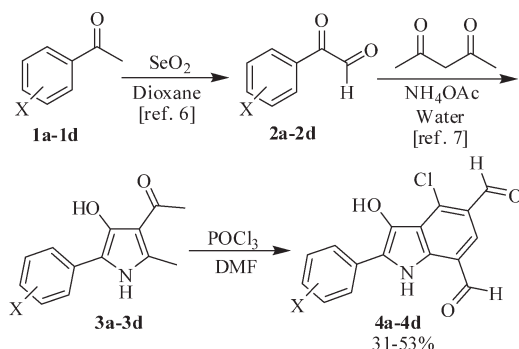
INTRODUCTION

The synthesis of indoles has occupied organic chemists for well over a century [1]. And the invention of new synthetic routes to substituted indoles continues to command wide interest due to the numerous natural products [2], physiologically active natural products and important pharmaceuticals [3] whose structures incorporate this heterocyclic system. Indole derivatives are used as neuroprotective agents affecting oxidative stress [3f], potent opioid receptor agonists [3g], highly functionalized pharmacophores [3h], potent PPAR- γ binding agents with potential application for the treatment of osteoporosis [3i], drugs for the treatment of peripheral neuropathy and neurodegenerative diseases [3j,k], glucokinase activators [3l,m], the cytotoxic antibiotic CC-1065 and prodrugs [3n], PPAR- δ activators for the treatment of cardiovascular diseases [3o] and dyestuffs [4]. The combination of traditional and modern methods has provided accessibility to a wide variety of structural variations of this important class of heterocycles [3e,5]. A number of useful strategies are now available for the synthesis of indoles substituted on the five-membered

ring, the majority of which involve the elaboration of the heterocyclic system from aniline, *o*-halo aniline, or other 2-substituted aniline derivatives. In contrast, few existing methods provide efficient and regiocontrolled access to indoles that are highly substituted on the benzenoid ring. Herein we disclose a method, based on Vilsmeier-Haack reaction of 3-acetyl-4-hydroxy-2-methyl-5-phenyl-1*H*-pyrroles **3**, to provide new highly substituted indoles **4** with substituted on both five-membered and benzenoid ring of indole (Scheme 1).

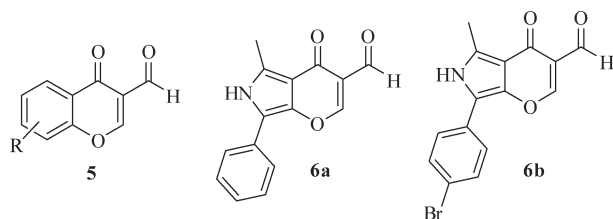
The Vilsmeier-Haack reaction is a widely used method for the formylation of activated aromatic and heteroaromatic compounds [8]. The reactions of aliphatic substrates [9], particularly carbonyl compounds [10] with chloromethylene iminium salts are highly versatile. They lead to multiple iminoalkylations in the presence of excess reagent and the resulting intermediates undergo cyclization to afford aromatic or heterocyclic compounds [11]. Multifunctional intermediates derived from these reactions (*e.g.*, β -chloroaldehydes) are subsequently exploited for the synthesis of functionalized heterocycles or other valuable target molecules [12].

Scheme 1. Three steps synthesis of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes.



RESULTS AND DISCUSSION

The reaction of 2-hydroxyacetophenones with Vilsmeier-Haack reagent also involves an iminoalkylation-cyclization sequence, leading to the formation of 3-formyl chromones **5** [13]. Similarly we expected to synthesis the 5-methyl-4-oxo-7-phenyl-4,6-dihydro-pyrano[2,3-*c*]pyrrole-3-carbaldehyde **6a** from the reaction of 3-acetyl-4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrol **3** with Vilsmeier-Haack reagent, but we did not obtained the expected compound **6a** instead the reaction gave compound **4**. In the case of 4-bromoacetophenone **1c**, not only **4c** was formed but also **6b** was obtained in low yield.



Four examples of the conversion of acetophenones **1a–1d** to various 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4a–4d** are listed in Table 1.

As shown in Scheme 2, the proposed mechanism involves the addition of enol **7** to the 2 equiv. chloromethyleneiminium salt **8**, then bis-iminium salt **9** undergoes iminoalkylation to result enamine **10**, that undergo cyclization and elimination of dimethylamine to afford the bis-iminium salt **12** which on hydrolysis leads to the formation of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4** [14].

4-Chloro-2-phenyl-5,7-bis-phenyliminomethyl-1*H*-indol-3-ol **14** and 4-chloro-5,7-bis[(2,4-dinitrophenyl)-hydrazonomethyl]-2-phenyl-1*H*-indol-3-ol **16** were synthesized from the reaction of **4a** with aniline **13** and 2,4-dinitrophenylhydrazine **15** in the presence of catalytic amount of H_2SO_4 respectively (Scheme 3).

In conclusion, we have reported the synthesis of new 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes via Vilsmeier-Haack reaction starting from acetophenone derivatives.

EXPERIMENTAL

General methods. Chemical shifts of the 1H NMR spectra are reported in δ (ppm) from tetramethylsilane with the solvent as the internal standard (deuteriodimethyl sulfoxide, $\delta = 2.5$ ppm), and coupling constants J were measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriodimethyl sulfoxide, $\delta = 39.0$ ppm). Elemental analyses were carried out by using a CHN analyzer. IR analyses were performed with an FT-IR spectrophotometer. IR spectra of compounds are expressed by wavenumber (cm^{-1}).

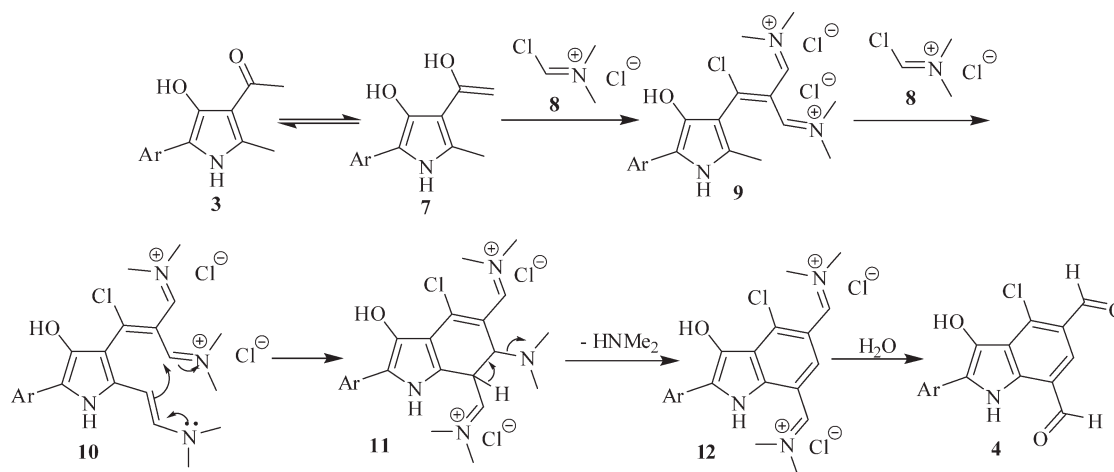
General procedure for synthesis of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4.** $POCl_3$ (3 mmol) was added dropwise to dimethylformamide (DMF) (1.5 mL)

Table 1

Synthesis of 2-aryl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehydes **4** via Vilsmeier-Haack reaction.

Acetophenone 1	Indole 4	Yield (%) ^a
		31
		42
		53
		35

^a Yield of indole from pyrrole (**3**).

Scheme 2. Proposed mechanism for conversion of pyrroles **3** to indoles **4**.

with stirring at 30–35°C, after the addition, the mixture was stirred at 50°C for 1 h. Then the solution of 3-acetyl-5-aryl-4-hydroxy-2-methyl-1*H*-pyrrol **3** (0.5 mmol) at least amount of DMF was added dropwise with stirring to the above mixture. After that the mixture was stirred at 45–55°C for 2 h, kept over the night at room temperature and poured over mixture of ice and water (10 g). Product was stirred for 0.5 h, then filtered off and recrystallized from ethanol.

4-Chloro-3-hydroxy-2-phenyl-1*H*-indole-5,7-dicarbaldehyde (4a). A yellow solid, mp: decomposed at 258.2–261.2°C; IR (KBr) 3553, 3343, 3053, 2853, 1671, 1580, 1425, 1025, 902, 812, 683 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.55 (s, 1H, NH, Exchanged with D₂O), 10.49 (s, 1H, CHO), 10.39 (s, 1H, CHO), 8.75 (s, 1H, OH, Exchanged with D₂O), 8.17 (s, 1H, CH), 8.01 (d, *J* = 7.5 Hz, 2H, CH), 7.51 (t, *J* = 7.45 Hz, 2H, CH), 7.37 (t, *J* = 7.3 Hz, 1H, CH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 192.6, 189.5, 136.6, 134.6, 134.4, 130.9, 130.7, 129.3, 128.4, 127.7, 127.3, 124.8, 122.1, 119.8 ppm; Anal. Calcd. for C₁₆H₁₀ClNO₃: C, 64.12; H, 3.36; N, 4.67. Found: C, 63.98; H, 3.50; N, 4.72.

4-Chloro-2-(4-fluorophenyl)-3-hydroxy-1*H*-indole-5,7-dicarbaldehyde (4b). A yellow solid, mp: decomposed at 286.2–289.3°C; IR (KBr) 3553, 3360, 3058, 2843, 1670, 1584, 1471, 1030, 901, 834, 634 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.60 (s, 1H, NH, Exchanged with D₂O), 10.48 (s, 1H, CHO), 10.37 (s, 1H, CHO), 8.74 (s, 1H, OH, Exchanged with D₂O), 8.16 (s, 1H, CH), 8.04 (dd, *J*_{H,F} = 8.07 Hz, *J*_{H,H} = 5.75 Hz, 2H, CH), 7.35 (t, *J* = 8.75 Hz, 2H, CH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 192.5, 189.6, 161.3, 136.6, 134.5, 134.4, 129.9, 127.5, 127.1, 124.8, 122.0, 119.9, 116.4, 116.2 ppm; Anal. Calcd. for C₁₆H₉ClFNO₃: C, 60.49; H, 2.86; N, 4.41. Found: C, 60.60; H, 2.73; N, 4.16.

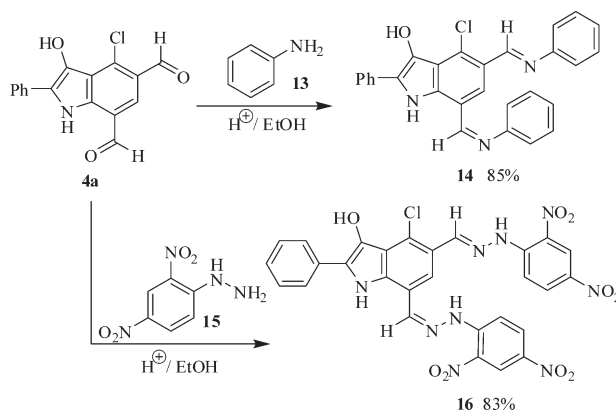
2-(4-Bromophenyl)-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehyde (4c). A yellow solid, mp: decomposed at 268.9–272.5°C; IR (KBr) 3540, 3352, 3030, 2839, 1670, 1585, 1465, 1030, 902, 814, 633 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.63 (s, 1H, NH, Exchanged with D₂O), 10.47 (s, 1H, CHO), 10.38 (s, 1H, CHO), 8.74 (s, broad, 1H, OH, Exchanged with D₂O), 8.18 (s, 1H, CH), 7.97 (d, *J* = 8.4 Hz, 2H, CH), 7.35 (d, *J* = 8.35 Hz, 2H, CH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 192.5, 189.5, 136.7, 135.4, 134.7, 132.2, 130.2, 129.6, 127.7, 126.7, 124.9, 122.0, 121.4, 119.9 ppm; Anal. Calcd. for

C₁₆H₉BrClNO₃: C, 50.76; H, 2.40; N, 3.70. Found: C, 50.82; H, 2.53; N, 3.66.

2-Biphenyl-4-yl-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehyde (4d). A yellow solid, mp: decomposed at 204.1–205.9°C; IR (KBr) 3561, 3419, 3033, 2922, 2857, 1670, 1598, 1468, 1427, 1029, 901, 840, 766, 697 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.60 (s, 1H, NH, Exchanged with D₂O), 10.49 (s, 1H, CHO), 10.40 (s, 1H, CHO), 8.82 (s, 1H, OH, Exchanged with D₂O), 8.17 (s, 1H, CH), 8.12 (d, *J* = 7.1 Hz, 2H, CH), 7.83 (d, *J* = 7.0 Hz, 2H, CH), 7.76 (d, *J* = 5.8 Hz, 2H, CH), 7.49 (m, 2H, CH), 7.39 (m, 1H, CH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 192.6, 189.4, 140.5, 140.0, 136.6, 134.6, 134.4, 132.3, 130.9, 130.7, 129.7, 129.3, 128.4, 127.7, 127.3, 124.8, 122.1, 119.8 ppm; Anal. Calcd. for C₂₂H₁₄ClNO₃: C, 70.31; H, 3.75; N, 3.73. Found: C, 70.51; H, 3.68; N, 3.75.

7-(4-Bromophenyl)-5-methyl-4-oxo-4,6-dihydro-pyrano [2,3-*c*]pyrrole-3-carbaldehyde (6b). In addition to 2-(4-bromophenyl)-4-chloro-3-hydroxy-1*H*-indole-5,7-dicarbaldehyde **4c**, 5-methyl-4-oxo-7-phenyl-4,6-dihydro-pyrano[2,3-*c*]pyrrole-3-carbaldehyde **6b** was obtained in the case of 4-bromoacetophenone. Ratio of **4c/6a** was obtained 68/32, according to ¹H NMR spectrum of the mixture of **4c** and **6a**. This product

Scheme 3



was characterized only in mixture with **4c** using ^1H NMR spectrum and eliminate from mixture with washing of solid with warm 85% ethanol. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 11.75 (s, 1H, NH, Exchanged with D_2O), 10.43 (s, 1H, CHO), 8.63 (s, 1H, CH), 7.57 (d, $J = 8.2$ Hz, 2H, CH), 7.36 (d, $J = 8.2$ Hz, 2H, CH), 2.5 (s, 3H, CH_3) ppm.

4-Chloro-2-phenyl-5,7-bis-phenyliminomethyl-1H-indol-3-ol (14). To mixture of 4-chloro-3-hydroxy-2-phenyl-1H-indole-5,7-dicarbaldehyde **4a** (0.2 mmol) and 3 drops of concentrate H_2SO_4 in boiling ethanol (5 mL), was added Aniline **13** (0.4 mmol), and stirred at the same temperature for the 5 min. Then the heat was removed and solution was cooled to room temperature and product was obtained as pale yellow crystals in 85% yield by filtration and washing with 5 mL of ethanol. mp: decomposed at $173.6\text{--}175.1^\circ\text{C}$; IR (KBr) 3559, 3053, 2849, 2585, 2060, 1677, 1557, 1497, 1321, 1015, 741, 685, 606 cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 11.34 (s, 1H, NH, Exchanged with D_2O), 9.20 (s, 1H, $\text{HC}=\text{NPh}$), 9.05 (s, 1H, $\text{HC}=\text{NPh}$), 8.52 (s, 1H, OH, Exchanged with D_2O), 8.00 (d, $J = 7.55$ Hz, 1H, CH), 7.5–7.04 (m, 15H, CH) ppm; Anal. Calcd. for $\text{C}_{28}\text{H}_{20}\text{ClN}_3\text{O}$: C, 74.74; H, 4.48; N, 9.34. Found: C, 74.68; H, 4.47; N, 9.21.

4-Chloro-5,7-bis-[(2,4-dinitrophenyl)hydrazonomethyl]-2-phenyl-1H-indol-3-ol (16). To the solution of 2,4-dinitrophenylhydrazine **15** (0.6 mmol) and 3 drops of concentrate H_2SO_4 in mixture of ethanol/water (3/2 mL), was added the hot solution of 4-chloro-3-hydroxy-2-phenyl-1H-indole-5,7-dicarbaldehyde **4a** (0.2 mmol) in ethanol (5 mL), and stirred for the 5 min. Then solution was cooled to room temperature and product was obtained as dark purple solid in 83% yield by filtration and washing with 5 mL of mixture of ethanol/water (3/2 mL). mp: $326.8\text{--}328.5^\circ\text{C}$. Don't soluble in solvents such as $\text{DMSO}-d_6$, Aceton- d_6 and etc. for taking NMR spectra. IR (KBr) 3539, 3428, 3270, 3087, 1613, 1508, 1422, 1329, 1208, 1131, 920, 827, 734, 597 cm^{-1} ; Anal. Calcd. for $\text{C}_{28}\text{H}_{18}\text{ClN}_9\text{O}_9$: C, 50.96; H, 2.75; N, 19.10. Found: C, 51.09; H, 2.64; N, 18.93. In comparing of IR spectrum of **16** with IR spectrum of **4a**, peak of the C—H of the aldehyde group at 2850 cm^{-1} for **4a** was eliminated in **16** IR spectrum, and the C=O peak of **4a** at 1673 cm^{-1} was replaced with C=N peak of **16** at 1613 cm^{-1} .

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