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Ethyl 5-Hydroxy-2-methyl-1-(pyridin-2-ylmethyl)benzo[*g*]indole-3-carboxylate

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Abstract: Indole ring is widely represented in natural compounds, as well as in a great variety of drugs. In this paper, the synthesis of a 5-hydroxybenzoindole derivative carrying a pyridyl substituent on position 1 is reported. The method involved no chromatography for purification and used solvents and catalysts of very low toxicity.

Keywords: indole; pyridine; Nenitzescu; CPME

1. Introduction

Indole ring is a common heterocycle found in thousands [1] of natural products, e.g., tryptophan and indole-3-carbinol, as well as synthetic drugs like tadalafil and sumatriptan. The oxidation of tryptophan via hydroxylase [2] leads to serotonin, melatonin, and other important metabolites carrying the 5-hydroxyindole moiety, as well as several active pharmaceutical ingredients such as indomethacin [3], umifenovir [4], anlotinib [5], and atevirdine [6]. The possibility of synthesizing multifunctional compounds based on 5-hydroxyindole scaffold is therefore highly desirable and has been implemented by applying a variety of procedures, e.g., Fischer synthesis [7], Stille coupling [8], and amino-Claisen rearrangement [9]. In this regard, Nenitzescu synthesis [10] is particularly attractive since the starting materials, enamines, and quinones are relatively cheap and of limited toxicity compared to phenylhydrazines or other precursors commonly employed in other pathways. Several advancements have been proposed to develop Nenitzescu synthesis, viz. the use of nitromethane as a solvent [11], as well as the application of Lewis acid catalysts [12,13] or enantioselective catalysts [14]. Herein, for the first time, we report on the synthesis of a 5-hydroxybenzoindole with a pyridyl substituent based on the slight modification of a procedure that we recently developed [15].

2. Results

The procedure consisted in two steps: first, 2-picolylamine was added to ethyl acetoacetate in equimolar amounts without the addition of any solvent or catalyst; second, the resulting enaminoester (**1** in Scheme 1) was treated with naphthoquinone in cyclopentyl methyl ether (CPME) with the aid of zinc chloride in catalytic amounts. The first step gave an isolated yield of 50%, while the second involved isolating the product (**2** in Scheme 1) in a 21% yield. The overall yield was therefore 11%.

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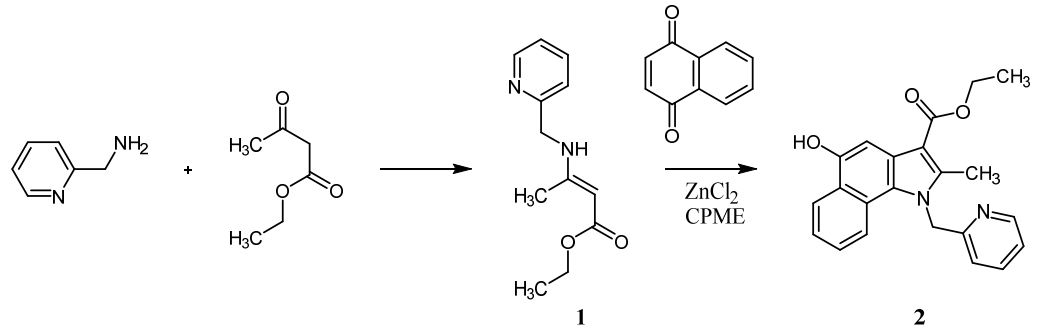

Scheme 1. Two-step synthesis of ethyl 5-hydroxy-2-methyl-1-(pyridin-2-ylmethyl)benzo[*g*]indole-3-carboxylate.

3. Discussion

The condensation of primary amines with beta-ketoesters is quite a straightforward reaction. Thus, we omitted the use of a catalyst (e.g., acetic acid [16]) to avoid any carry-over that could interfere with the second step. On the other hand, the reported synthesis [17] for compound **1** involved the use of 10 mol% of iodine, a heavy and rare [18] element with toxicity issues [19,20]. At variance with our experience with Nenitzescu synthesis, this particular enamine gave small amounts of product when the reaction was left for 40 min, as previously reported [15], probably because of the heterogenous nature of the mixture and the ability of **1** to chelate zinc, therefore depressing its Lewis acidity. The reaction mixture turned to a dark orange color that did not fade with time; this is a sign of the formation of highly conjugated intermediates derived from additions to quinone (**3** in Figure 1) that do not react further, as already pointed out in the literature [11,12].

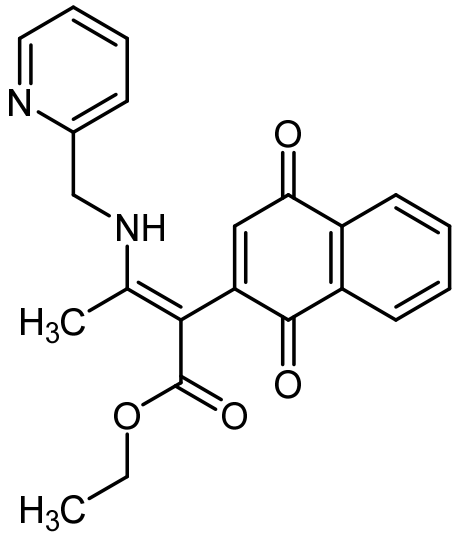

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Figure 1. Structure of one of the possible intermediates.

It should be pointed out that the procedure, despite the low yield which is often encountered in Nenitzescu synthesis, works entirely at room temperature. Moreover, purification is simple because the product precipitates completely and selectively from the reaction mixture, and the use of solvents is quite scarce and limited (only environmentally friendly ones, like ethanol and ethyl acetate [21], are typically used for work-up and CPME) [22].

4. Materials and Methods

4.1. Materials

Ethyl acetoacetate 99+% and zinc chloride 99+% were purchased from Alfa Aesar, 2-picolylamine 99% was purchased from Sigma Aldrich (Merck KGaA, Darmstadt, Germany), naphthoquinone >98% was purchased from TCI Chemicals (Tokyo, Japan), cyclopentyl methyl ether >99.9% was purchased from ZEON (Tokyo, Japan), ethyl acetate >99%, and ethanol absolute was purchased from VWR Chemicals (Radnor, PA, USA).

All materials were used as received. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (101 MHz) spectra were recorded in $CDCl_3$ with a Bruker Ascend 400 spectrometer (Bruker, Ettlingen, Germany) in $CDCl_3$ or DMSO d_6 solutions, and residual solvents peaks were used for calibration at 7.26 ppm and 2.50 ppm, respectively. Mass spectra were acquired using a Thermo Finnigan Q Exactive spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) with an API-HESI source and a Fourier transform orbital trap (Orbitrap). Samples were introduced as acetonitrile solutions at a 0.1 mg/L concentration.

4.2. Synthesis of Ethyl 3-[(Pyridin-2-ylmethyl)amino]but-2-enoate **1**

Ethyl acetoacetate (2.50 mL, 0.0198 mol, 1.02 eq) was mixed with 2-picolylamine (2.0 mL, 0.0194 mol, 1.00 eq) in a glass vial, sealed, and stirred at room temperature for 48 h. The mixture was dissolved in 10 mL of ethyl acetate, washed with water (3 × 10 mL), dried with sodium sulfate, and evaporated under vacuum. The resulting yellow viscous oil was left under vacuum overnight (2.14 g, 50.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ ppm 9.15 (br. s., 1 H), 8.58 (dq, *J* = 4.88, 0.70 Hz, 1 H), 7.68 (td, *J* = 7.69, 1.82 Hz, 1 H), 7.31–7.27 (m, 1 H), 7.19 (dd, *J* = 7.26, 5.12 Hz, 1 H), 4.55–4.60 (m, 3 H), 4.13 (q, *J* = 7.14 Hz, 2 H), 1.94 (s, 3 H), 1.27 (t, *J* = 7.14 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$), δ ppm 170.6 (C), 161.6 (C), 158.3 (C), 149.5 (CH), 136.9 (CH), 122.2 (CH), 120.7 (CH), 83.7 (CH), 58.4 (CH_2), 48.5 (CH_2), 19.5 (CH_3), 14.6 (CH_3).

4.3. Synthesis of Ethyl 5-Hydroxy-2-methyl-1-(pyridin-2-ylmethyl)benzo[g]indole-3-carboxylate **2**

Ethyl 3-[(pyridin-2-ylmethyl)amino]but-2-enoate (1.032 g, 4.685 mmol, 1.00 eq) was dissolved in 25 mL of CPME. $ZnCl_2$ (0.11 g, 0.81 mmol, 17 mol%) was dissolved with 1,4-naphthoquinone (0.754 g, 4.77 mmol, 1.02 eq) in 25 mL of CPME and the resulting solution was mixed with the one containing enamine. Upon mixing, yellow solid precipitations were found. The mixture was left to be stirred at 20 °C in a sealed flask for 72 h, and it then turned dark orange and was kept at 4 °C for 16 h. The solid was then filtered and washed with 10 mL of CPME. The obtained solid was dissolved in 25 mL of ethyl acetate and was then washed with water (3 × 20 mL), dried with sodium sulfate, and evaporated under vacuum conditions. The product was recrystallized from absolute ethanol to give a pale-yellow solid (0.350 g, 0.97 mmol, and 20.7% yield). ^{1}H NMR (400 MHz, $(CD_3)_2SO$), δ ppm 9.78 (s, 1 H, H25), 8.51–8.61 (m, 1 H, H19), 8.18–8.26 (m, 1 H, H8), 8.01–8.10 (m, 1 H, H7), 7.75 (s, 1 H, H4), 7.70 (td, *J* = 7.71, 1.78 Hz, 1 H, H17), 7.31–7.37 (m, 2 H, H18+H9), 7.27 (ddd, *J* = 7.20, 5.30, 1.00 Hz, 1 H, H16), 6.90 (d, *J* = 7.85 Hz, 1 H, H6), 5.92 (s, 2 H, H14), 4.35 (q, *J* = 7.11 Hz, 2 H, H23), 2.77 (s, 3 H, H21), 1.42 (t, *J* = 7.10 Hz, 3 H, H24).

^{13}C NMR (101 MHz, $(CD_3)_2SO$) d ppm 165.2 (C22), 156.4 (C), 149.7 (C19), 148.4 (C), 143.5 (C), 137.5 (C17), 126.0 (C9), 124.4 (C), 123.5 (C), 123.3 (C8), 123.0 (C), 122.7 (C16), 122.5 (C18), 122.0 (C), 120.3 (C7), 120.1 (C6), 104.3, 101.6 (C4), 59.1 (C23), 50.7 (C14), 14.5 (C24), 11.7 (C21). (Carbon atoms are labeled according to Figure 2)

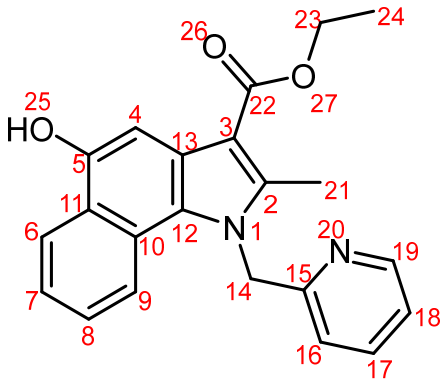

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Figure 2. Atom labelling for compound **2**; numbers are used for reference in 13C NMR spectrum.

HRMS (ESI+) m/z calculated for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.15467, found: 361.15387 ($\Delta = -2.2$ ppm).(Figures S1–S4)

5. Conclusions

Ethyl 5-hydroxy-2-methyl-1-(pyridin-2-ylmethyl)benzo[*g*]indole-3-carboxylate was synthesized for the first time. The compound is highly functionalized and of potential interest in the field of medicinal chemistry. Despite the low yield, the method described entails no chromatography for purification and uses solvents and catalysts of very low toxicity.

Supplementary Materials: Figure S1: ^{1}H-NMR of ethyl 5-hydroxy-2-methyl-1-(pyridin-2-ylmethyl) benzo[*g*]indole-3-carboxylate. Figure S2: ^{13}C-NMR of ethyl 5-hydroxy-2-methyl-1-(pyridin-2-ylmethyl) benzo[*g*]indole-3-carboxylate. Figure S3: HSQC spectrum of ethyl 5-hydroxy-2-methyl-1-(pyridin-2-ylmethyl)benzo[*g*]indole-3-carboxylate. Figure S4: HRMS ESI spectrum of ethyl 5-hydroxy-2-methyl-1-(pyridin-2-ylmethyl)benzo[*g*]indole-3-carboxylate.

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Conflicts of Interest: The authors declare no conflicts of interest.

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