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Manufacturing synthesis of 5-hydroxy-2-methyl-1*H*-indole

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Abstract The manufacturing synthesis of 5-hydroxy-2-methyl-1*H*-indole is described and two synthetic methods were used and the results discussed. Two small and three large runs with Nenitzescu's method were analyzed and results reported with different reaction conditions. Manufacturing issues encountered were discussed. Production scale of more than 60 kg of the 5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester and over 20 kg of the 5-hydroxy-2-methyl-1*H*-indole were achieved. Based on these results, larger scale manufacturing of this product or similar products based on the optimized conditions is feasible.

Keywords 5-Hydroxy-2-methyl-1*H*-indole · Nenitzescu · Benzoquinone · Aminocrotonate

Introduction

Indole structure is one of the most important members of heterocyclic compounds and is a "privileged scaffold" for many natural and pharmaceutical products [1]. For example,well known pharmaceutical/natural products Tryptophan, Indometacin, Medmain, Serotonin, Melatonin, Oxypertine, Vinblastin, etc. contain indole moieties. Many alkaloids from plants and from marine sources have indole structures [2].

Numerous products of pharmaceutical interest contain the structure of 2-methyl-5-hydroxy-1*H*-indole. A series of ethyl 2-alkyl-6-bromo-5-hydroxy-1*H*-indole-3-carboxylate derivatives were found to be effective against influenza virus [3]. Similar structures were also demonstrated to be active against hepatitis B virus [4].

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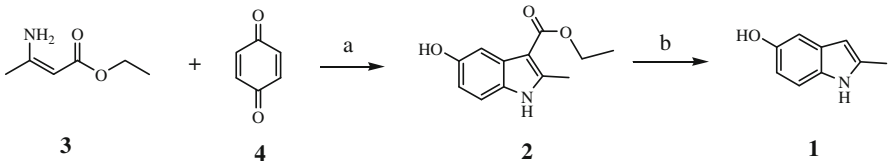
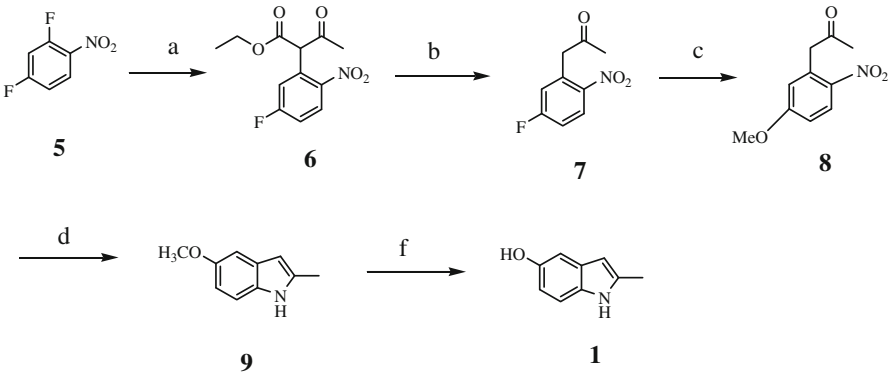


Scheme 1 Reagents and conditions: (a) acetic acid, 15 °C to RT; (b) 20%HCl/ethanol, reflux



Scheme 2 Reagents and conditions: (a) (i) t-BuOK/THF/ethyl acetoacetate/2,4-difluoronitrobenzene, 5–15 °C; (ii) 6 N HCl, <10 °C; (b) H_2SO_4/AcOH, 30–70 °C; (c) MeONa/MeOH, 20–35 °C; (d) $Na_2S_2O_4$/THF, RT; (e) BBr_3/CH_2Cl_2, −5 to −8 °C

Some 5-hydroxy alkylated ethyl 2-methyl-5-hydroxy-1*H*-indole-3-carboxylate derivatives were found to have anti-inflammatory and analgesic activity [5]. Several drug candidates that act on the vascular endothelial growth factor (VEGF) related kinase insert domain receptor (KDR) with high promises in treating angiogenesis related diseases also contain the 5-hydroxy-2-methyl-1*H*-indole moiety [6–8]. Some 5-hydroxy-2-methyl-1*H*-indole analogues are potent prostaglandin D2 receptor antagonist [9].

There are a number of methods for the synthesis of indoles, such as the well known Fischer indole synthesis [10], Bartoli indole synthesis [11], Leimgruber-Batcho indole synthesis [12], Reissert indole synthesis [13], Larock indole synthesis [14], Gassman indole synthesis [15], Bischler-Molau indole synthesis [16], and Nenitzescu indole synthesis [17–19]. More recently, many new methods of synthesizing various indoles have been published: (a) palladium (II) catalyzed ring closure [20–27], (b) copper (I/II) catalyzed cyclization [28–30], and (c) other indole formation [31–37]. From manufacturing standpoint, many of these methods are not feasible due to cost, non-environmental friendliness, and scalability, etc. There are two confirmed ways to make 5-hydroxy-2-methyl-1*H*-indole (**1**). The first one is based on the Nenitzescu's method (Scheme 1) with two steps via the intermediate ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (**2**). The second method consists of five steps (Scheme 2), via the intermediate 5-methoxy-2-methyl-1*H*-indole (**9**). Even though there are a number of literatures reported the synthesis of **1** [38–41],

the scales are limited in the gram level. There has been no report on scale up synthesis of **1**. No other methods toward the preparation of product **1** were reported in the literature. We used both methods in the synthesis of product **1** and here we report the results in scale up and manufacturing production of **1**.

Results and discussion

The first method (Nenitzescu indole synthesis, Scheme 1) was to use commercially available and less expensive ethyl 3-aminocrotonate (**3**) and 1,4-benzoquinone (**4**) in large quantities. The generally accepted mechanism includes a Micheal addition of ethyl 3-aminocrotonate to the 1,4-benzoquinone to form a substituted 1,4-diphenol, oxidation of the diphenol to 1,4-benzoquinone, condensation/cyclization, and reduction to give the indole product [42]. Due to the relatively low yield, Nenitzescu reaction has not been extensively applied in indole synthesis, especially for manufacturing purpose. In general, the 1,4-benzoquinone is used in excess amount (100% excess) to drive the reaction to completion [17].

In our study, we followed the reference procedure [39], and did a couple of small scale runs (Table 1, entries 1, 2). In the first experiment, 1,4-benzoquinone was used 100% excess and the obtained product **2** contained significant amount of unreacted 1,4-benzoquinone that was removed only by repeated recrystallization from ethyl acetate/petroleum ether, which is the main reason that the yield in entry 1 is significantly lower compared to the reference [39]. Therefore, 1,4-benzoquinone was reduced to about 40% excess in the second experiment (Table 2, entry 2) and excellent yield was obtained just by simple wash with acetic acid and petroleum ether without recrystallization or column purification. A third small scale experiment was conducted using equal mole ratio of the 1,4-benzoquinone and ethyl 3-aminocrotonate. As a result, the reaction did not go completion even after

Table 1 Results from Nenitzescu reaction first step

Entry	**3** (mol)[a]	**4** (mol)[a]	**4/3** ratio[b]	Acetic acid	Reaction temp °C	Reaction time (hr)	**2** (HPLC)[c]	Yield (%)
1	32.5 g (0.25)	54 g (0.5)	2.0	0.5 L	15–40	2	25.3 g (96.7%)	46.2
2	64.5 g (0.5)	78 g (0.72)	1.4	1 L	15–40	2.5	99 g (98.5%)	90
3	20 kg (155)	25.7 kg (238)	1.53	135 kg	10–20	4	17.5 kg (96.8%)	51.6
4	30 kg (232)	32 kg (296)	1.27	220 kg	15–30	4.5	33 kg (97.9%)	64.8
5	50 kg (387)	50 kg (555)	1.43	300 kg	25–40	5.5	61 kg (97.8%)	71.8

[a] Data in parentheses are the corresponding moles

[b] The ratio are calculated using the mole number of **4** over that of **3**

[c] Data in parentheses are the results from HPLC analysis (conditions: Angilent 1100, solvent: MeOH, injection: 20 μL, column: x-Bridge 150 mm × 4.6 mm BDS-C18, $\lambda = 254$ nm, column temp: 30 °C, flow rate: 1.0 mL/min, mobile phase: ACN-H_2O, gradient: 0–20–25 min, 15–75–75%)

Table 2 Results from Nenitzescu reaction second step

Entry	**2** (mol)[a]	20%HCl	EtOH	Reaction temp (°C)	Reaction time (hr)	**1** (HPLC)[b]	Yield (%)
1	22 g (0.1)	200 mL	20 mL	80–100	2.5	10.4 g (96.5%)	70
2	88 g (0.4)	1 L	100 mL	80–100	2.5	47.5 g (97.8%)	80
3	17.5 kg (80)	170 kg	30 kg	75–98	3	5.9 kg (98.7%)	50
4	33 kg (150)	330 kg	40 kg	85–95	5	8.4 kg (97.5%)	37.7
5	61 kg (278)	500 kg	80 kg	75–100	6	22.8 kg (97.6%)	55.7

[a] Data in parentheses are the corresponding moles

[b] Data in parentheses are the results from HPLC analysis (conditions:same as in Table 1)

stirring overnight. When additional 1,4-benzoqinone was added (30–40% excess), the reaction resumed and completed within 2 h and good yield was obtained as well (data not shown). Based on the small scale experiments, we learned that 1,4-benzoquinone should not be used in more than 60% excess (product difficult to be purified), but no less than 20% excess (reaction too slow to proceed) relative to the corresponding ethyl 3-aminocrotonate. Any significant amount of 1,4-benzoquinone remaining in **2** would result in polymerization in the next step and large amount of by-product formation by consuming both **4** and **2**, resulting in low yield.

Laboratory experiments indicated that optimal mole ratio between 1,4-benzoquinone (**4**) and ethyl 3-aminocrotonate (**3**) should be between 1.2 and 1.6. Thus, for the three manufacturing runs, the mole ratios were 1.27, 1.43, and 1.53, respectively, with 1.43 giving the highest yield (Table 1, entries 3, 4, 5). In scaling up, the reaction time should increase as well, it normally needs to stir additional 3–5 h (after the completion of addition). The progress can be easily monitored by TLC or HPLC.

In addition to the mole ratio between **4** and **3**, the reaction temperature is another factor that might affect the outcome. Based on our small runs, the reaction temperature should not be higher than 50 °C and not be lower than 10 °C. If the temperature is too high, significant side reaction occurs and results in low yield. If the temperature is below 10 °C, the reaction would not proceed as expected. The optimal reaction temperature is around room temperature or 25–30 °C. Therefore, external cooling is normally required due to the mild exothermic process of the reaction. The reaction normally completes within 6 h and does not change for extended period of time, such as stirring overnight, as long as the temperature is kept below 40 °C. The highest yield achieved in small runs was ~90%. But in manufacturing production, the 71.8% was the best obtained.

The second step from **2** to **1** was based on acid catalyzed hydrolysis and decarboxylation using 20% HCl (Table 2) by following the reference procedure [41]. Though base hydrolysis should work as well [40], the reaction was complicated and resulted in low yield (data not shown). Precaution should be taken due to the large amount of CO_2 formation when the temperature reaches around 80 °C (especially for manufacturing scale!). Therefore the combined reaction media should never occupy more than 50% of the reactor space. After the

peak formation of the CO_2, the reaction should be heated to around 95–100 °C for 2–3 h to completion. To make the reaction go smoothly, ethanol was added to help dissolve the intermediate **2** and, as a result, the reaction mixture was cleaner and yield improved as well.

The two small runs gave 70 and 80% yield (Table 2, entries 1, 2), respectively, which were close to that of the literature [41]. For the three large runs, the yields were 50, 37.7 and 55.7% (Table 2 entries 3, 4, 5), respectively, which were significantly lower that those of the small runs. The exact reason of the low yield of entry 4 is most likely due to the significant polymerization (the mother liquid from entry 4 contained significant amount of product **1** that was too difficult to be purified). The second step normally completes within 3–6 h. Extended refluxing (such as overnight) does not help increase the yield, but side reaction takes place, and results in low yield. When **2** contained significant amount of 1,4-benzoquinone (>5%) was used in the second step, polymerization occurred, resulting in low yield (data not shown). The two steps combined yield ranged from 30 to 50% with the average around 40%.

An alternative route to **1** is outlined in Scheme 2 according to a literature procedure [43]. This route had been used in synthesizing product **1** before the optimized conditions of Nenitzescu's method were achieved. It started with 2,4-difluoronitrobenzene that was substituted with ethyl acetoacetate to afford the *ortho*-fluoro replaced intermediate **6**, after acid catalyzed hydrolysis and decarboxylation, intermediate **7** was obtained in a combined yield of 53%, which was further substituted with a methoxy group to afford intermediate **8**. Reduction of the nitro group, followed by cyclization, gave the 5-methoxy-2-methyl-1*H*-indole (**9**). Intermediate **9** underwent demethylation with boron tribromide to afford the desired product **1** in a combined overall yield $\sim$6% (process not optimized).

Though the synthesis of product **1** by the second route no longer has any advantage after the first route worked out, it may still be useful for preparation of some of the intermediates, such as **6**, **7**, and **8**, as well as some substituted **9** or **1** other than methoxy or hydroxy at the 5 position. Unlike Nenitzescu's method that is only applied to produce 5-hydroxy substituted indoles, the second route can be used to produce a range of differently substituted indoles by using various starting materials or by functional group transformation at a later stage. Therefore, we also included the results (largest scale conducted) from the second route in this report for reference purpose.

In conclusion, we have conducted three manufacturing scale synthesis of the product 5-hydroxy-2-methyl-1*H*-indole that is becoming increasingly important for a number of pharmaceutical products under development. Though several literatures reported the synthesis of 5-hydroxy-2-methyl-1*H*-indole or structurally similar products, large scale production has not been reported due to the relatively low yield of Nenitzescu method and polymerization under reaction conditions. We optimized the reaction conditions and were able to produce many kilograms in a single batch in good overall yield. The optimized reaction conditions may easily be applied for production over 100 kilograms per batch as well as for production of similar products.

Experimental section

All reagents purchased commercially were used directly without further purification. Solvents were used directly without any treatment. Melting points were measured using capillary method without correction. Reaction temperatures were recorded using a regular thermometer in a tube that was attached to the reactor without correction. TLC development solvent: PE = petroleum ether, EA = ethyl acetate.

Ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (**2**)

General procedure

Please refer to Table 1 for materials used: to a 500 L reactor was added acetic acid and 1,4-benzoquinone. The mixture was stirred and cooled to 10–15 °C. Ethyl 3-aminocrotonate was added dropwise below 30 °C (3–4 h for the addition to complete), and the reaction was stirred at RT for an additional 3–5 h. TLC indicated the completion of the reaction with $R_f = 0.4$ (PE:EA = 2:1). The solid was collected by centrifugation and washed with acetic acid, petroleum ether, and dried to afford ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate as a white powder, m.p. 206–208 °C (lit.[39] 207–208 °C).

Nenitzescu's method synthesis of 5-hydroxy-2-methyl-1*H*-indole (**1**)

General procedure

Please refer to Table 2 for materials used: to a 1000 L reactor was added 20% HCl, ethanol. Under stirring, ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate was added and the mixture was heated to reflux (75–85 °C). As the temperature rose, large amount of gas (CO_2) evolved from the reaction. The refluxing continued until no more gas evolution was observed (2–4 h). TLC indicated the completion of reaction with $R_f = 0.4$ (PE:EA = 1:1). The ethanol was removed by distillation and the mixture was cooled to below 10 °C and neutralized with 50% NaOH to pH ~6 below 15 °C. The precipitates were collected by centrifugation and the crude product was dissolved in dichloromethane and added activated carbon and heated to reflux for 2 h, filtered, and cooled to RT. The solvent was concentrated and the solid was collected by filtration, dried to afford 2-methyl-5-hydroxy-1*H*-indole as a light yellow crystal/powder. m. p. 158–160 °C (lit.[40] 158 °C).

Ethyl 2-(5-fluoro-2-nitrophenyl)-3-oxobutanoate (**6**)

To a 300 L reactor was added THF (96 kg), t-BuOK (25 kg, 224.5 mol). The mixture was stirred and cooled to 5 °C, ethyl acetoacetate (29.2 kg, 224.5 mol) was added dropwise at a temperature below 15 °C. The mixture was stirred at 20 °C for

2–2.5 h. A solution of 2,4-difluoronitrobenzene (17 kg, 106.9 mol) in THF (7 kg) was added dropwise at a temperature not excess 15 °C and the reaction was stirred at RT overnight. TLC indicated the completion of reaction with $R_f = 0.7$ (PE:EA = 10:1). The reaction mixture was cooled to below 10 °C and was added 6 N HCl to adjust pH 4–5. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (30 kg). The combined organic phase was washed with saturated NaCl aqueous solution and dried over Na_2SO_4 overnight. The solvent was removed under reduced pressure and the residual liquid (intermediate **6** and unreacted ethyl acetoacetate) was used for the next step without purification.

1-(5-Fluoro-2-nitrophenyl) propan-2-one (**7**)

To a 300 L reactor was added glacial acetic acid (55.2 kg) and H_2SO_4 (32.5 kg) portionwise below 30 °C, the above crude product **6** was added portionwise at a temperature not over 30 °C. The mixture was stirred and heated to 50 °C (large amount CO_2 formed). After completion of the CO_2 evolution, the mixture was heated to 70 °C for 2–3 h. TLC indicated the completion of reaction with $R_f = 0.4$ (PE:EA = 10:1). The mixture was cooled to RT and poured onto 120 kg ice-water and extracted with CH_2Cl_2 (2 × 30 kg). The combined organic phase was washed with 20% NaOH, saturated aqueous NaCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was dissolved in methanol (5 kg) and cooled to 0 °C. The crystal was collected by filtration, washed with petroleum ether to afford the intermediate **7** as a yellow solid (11.2 kg, yield 53% from **5**), m.p. 54–57 °C.

1-(5-Methoxy-2-nitrophenyl)propan-2-one (**8**)

To a 100 L reactor was added methanol (65 kg) and the mixture was stirred and cooled to 10 °C and added MeONa (8.1 kg, 149 mol). The above intermediate **7** (10 kg, 50 mol) was added and the reaction was stirred at 30–35 °C for 5–6 h. TLC indicated the completion of reaction with $R_f = 0.4$ (PE:EA = 4:1). The reaction mixture was poured into 120 kg ice-water. The solid was collected by filtration and purified by a short silica gel column (packed with ~2 cm activated carbon on the top) with ethyl acetate/petroleum ether as the eluent to afford intermediate **8** as a yellow oil (4.5 kg, yield 43%, directly used for the next step).

5-Methoxy-2-methyl-1H-indole (**9**)

To a 100 L reactor was added water (55 kg), THF (7.5 kg). Under stirring, sodium dithionite (10 kg) was added, followed by the above intermediate **8** (2.9 kg, 13.8 mol), and stirred at RT for 3–4 h. TLC indicated the completion of reaction with $R_f = 0.6$ (PE:EA = 10:1). The mixture was extracted with ethyl acetate (2 × 7 kg), washed with saturated aqueous NaCl, and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (2 kg), added petroleum ether (2 kg), and cooled to 0 °C. The solid was collected by filtration to obtain intermediate **9** (840 g, yield 37%), m.p. 83–86 °C (Ref. Aldrich 86–88 °C).

5-Hydroxy-2-methyl-1*H*-indole (**1**)

To a 50 L reactor was added CH_2Cl_2 (7.5 kg), intermediate **9** (800 g, 4.9 mol), and cooled to −8 °C. BBr_3 (4.35 kg, 17.4 mol) was added dropwise below −5 °C, the reaction was stirred at −5–0 °C for 30 min. TLC indicated the completion of reaction with $R_f = 0.7$ (PE:EA = 1:2). The mixture was poured onto ice-water (5 kg), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 7 kg). The combined organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4. The solvent was removed in vacuo and the residue was dissolved in methanol (400 mL) and cooled to give product **1** as a light yellow solid (507 g, yield 69%), HPLC 98% (conditions: same as in Table 1), m.p. 205–206 °C (lit.[39] 207–208 °C).

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