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CONVENIENT AND EFFICIENT PREPARATION OF ETHYL 6-*n*-DECYLOXY-7-ETHOXY-4-HYDROXYQUINOLINE-3-CARBOXYLATE

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Ethyl 6-N-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate has been synthesized from pyrocatechol in six steps and in 39.3% overall yield.

Keywords: Anticoccidial; azo compound; 4-*n*-decyloxy-3-ethoxyaniline; quinolines

INTRODUCTION

Ethyl 6-*n*-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate has the most reactivity of decoquinate anticoccidial drugs.[1–6] It is usually synthesized through 4-*n*-decyloxy-3-ethoxyaniline and ethoxymethylene malonic diethyl ester (EMME) reaction.[7–11] Generally, the intermediate 4-*n*-decyloxy-3-ethoxyaniline was synthesized by reducing the 1-(decyloxy)-2-ethoxy-4-nitrobenzene[12–14] or the corresponding azo compounds. Because its poor regioselectivity, 1-(decyloxy)-2-ethoxy-4-nitrobenzene was prepared in a very poor yield. Despite the synthesis of azo compounds have excellent regioselectivity, the intermediate 4-*n*-decyloxy-3-ethoxyaniline is difficult to separate from the aniline yielded in the reduction step. Herein, a facile separation using sulfanilic acid to prepare the azo compound instead of aniline is reported.

RESULTS AND DISCUSSION

Ethyl 6-*n*-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate was synthesized from commercially available pyrocatechol, diethyl sulfate, sulfanilic acid, N-decylbromide, sodium dithionite, and EMME (Fig. 1).

o-Ethoxyphenol **2** was prepared by a reaction of pyrocatechol with ethyl sulfate in water. Then the product was separated by a facile steam distillation in good yield (75%, Scheme 1).

The synthetic route to the target compound hinged upon the synthesis of intermediate product 4-*n*-decyloxy-3-ethoxyaniline (Scheme 2). 4-*n*-Decyloxy-

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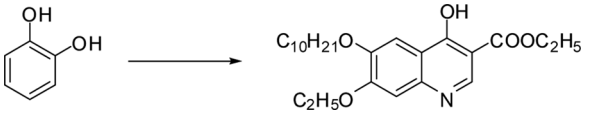
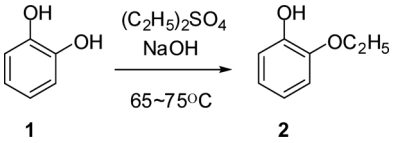


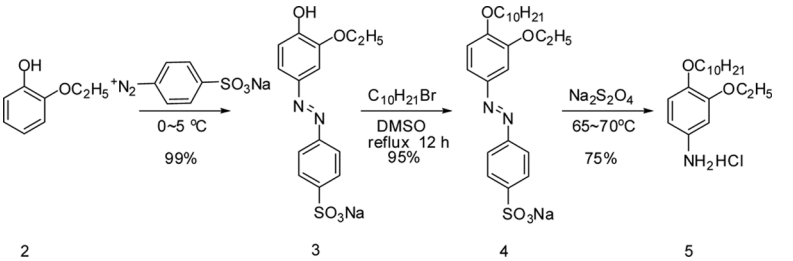
Figure 1. Chemical structure of ethyl 6-*n*-decyloxy-7-ethoxy-4-hydroxyquioline-3-carboxylate and starting material pyrocatechol.



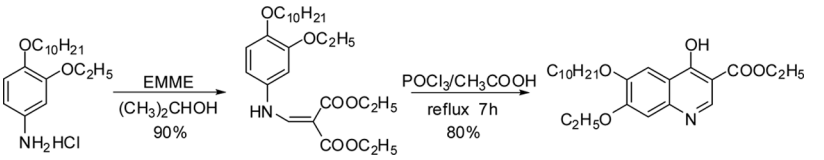
Scheme 1. Reaction conditions: $(C_2H_5)_2SO_4$, NaOH, water, argon atmosphere at 65 °C for 1.5 h.

3-ethoxyaniline is produced by reducing sodium 4-((4-*n*-decyloxy)-3-ethoxyphenyl) diazenyl) benzenesulfonate (**4**), which was obtained by alkylation of sodium 4-((3-ethoxy-4-hydroxyphenyl)diazenyl **3**. Compound **3** was prepared from diazotized sodium p-aminobenzenesulfonate and **2** in ethanol at 0–5 °C in 99% yield. A new one-step methodology has been developed for the synthesis of **4**. According to literature reports,[2–4] the water produced in the reaction process was separated in advance by distillation with toluene, and then the phenol salt reacted with N-decylbromide. Compound **3**, KOH, KI, and N-decylbromide were stirred at reflux for 12 h in dimethylsulfoxide (DMSO) in the presence of CaO to provide the product in almost quantitative yield. Compound **4** is highly water-soluble because of the presence of a sulfonate group. Accordingly, the reduction reaction can be carried out in the water phase using water-soluble reducing agent in mild condition, rather than organic solvents. After the reaction, the product p-aminobenzenesulfonate remained in the water phase, whereas the suspended organic product can be separated easily. Because of the instability of 4-*n*-decyloxy-3-ethoxyaniline in air, 4-*n*-decyloxy-3-ethoxyaniline hydrochloride **5** was prepared by introduction of anhydrous HCl. For the reduction reaction, different reducing agents were tried. The best result was obtained using 7.5 equiv. sodium dithionite.

The reaction of 4-*n*-decyloxy-3-ethoxyaniline hydrochloride with EMME was carried out in propan-2-ol to afford compound **6**.[15] The solvent was distilled after **6**



Scheme 2. Reaction conditions: (a) sodium 4-aminobenzenesulfonate diazonium salt, 0–5 °C; (b) $C_{10}H_{21}Br$, KOH, DMSO, reflux, 12 h; and (c) $Na_2S_2O_4$, 65–70 °C.



Scheme 3. Reaction conditions: (a) EMME, $(CH_3)_2CHOH$, K_2CO_3, reflux for 10 h; (b) $POCl_3$/CH_3COOH, reflux for 7 h.

was refluxed in $POCl_3$. The resulting mixture was further refluxed in CH_3COOH to give the quinoline product **7** in 80% yield (Scheme 3).

CONCLUSION

In summary, a facile synthesis of ethyl 6-*n*-decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate has been developed. This route is characterized by introducing a sulfonate group to the azo compound. This strategy results in the simplification of the reduction reaction and the subsequent separation of the products.

EXPERIMENTAL

All the reagents were commercially available and used without further purification. ^{1}H NMR and ^{13}C NMR was measured with Bruker 300-MHz spectrometers. Mass spectra (MS) were recorded on a Bruker Daltonics Inc. Biflex III spectrometer for MALDI-TOF-MS.

O-Ethoxyphenol 2

Sodium hydroxide (4.4 g, 0.11 mol) was dissolved in water (150 mL). Then the solution was heated to 65 °C, and pyrocatechol (11.0 g, 0.1 mol) and ethyl sulfate (12.6 g, 0.1 mol) were added and stirred under argon for 1.5 h at 65 °C. The product was separated by steam distillation. Then the resulting solution was repeatedly extracted with Et_2O. The combined organic layer was dried by Na_2SO_4 and filtered, and then solvent was evaporated under vacuum. The residue was cooled to 5 °C to give a white solid (10.3 g, yield 75%). Mp 20–22 °C.^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.46 (t, 3H, $J = 6.9$ Hz), 4.12 (q, 2H, $J = 6.9$ Hz), 5.92 (s, 1H), 6.88–7.00 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 15.0, 64.7, 112.0, 115.1, 120.3, 121.5, 146.1.

Sodium 4-((3-Ethoxy-4-hydroxyphenyl)diazenyl)benzenesulfonate 3

Sodium hydroxide (5.20 g, 0.13 mol), sulfanilic acid (3.5 g, 0.1 mol), and $NaNO_2$ (8.0 g, 0.1 mol) were added to 100 ml of water, and the resulting solution was cooled to 0 °C. Then, a solution 6 ml of conc. HCl (0.36 mol) in 30 ml of water was added dropwise at such a rate as to maintain the temperature below 5 °C. The reaction mixture was stirred for 15 min below 5 °C; the solution was rendered neutral with Na_2CO_3 solution. The resulting mixture was added dropwise to a solution of

o-ethoxyphenol 2 (13.8 g, 0.1 mol) in ethanol (400 ml) to maintain the temperature below 5 °C for 4 h and then evaporated to dryness. The residue was dissolved with ethanol, filtered, and washed with ethanol; the solvent was evaporated under vacuum and dried overnight at 80 °C to yield 34 g of **3** (99%) as a yellow solid. ^{1}H NMR (300 MHz, *d*-DMSO, ppm) δ 1.35 (t, 3H, $J = 7.2$ Hz), 4.09 (q, 2H, $J = 7.2$ Hz), 6.95 (d, 1H, $J = 8.1$ Hz), 7.42 (s, 1H), 7.46 (d, 1H, $J = 8.1$ Hz), 7.73 (s, 4H). ^{13}C NMR (75 MHz, *d*-DMSO, ppm): δ 15.2, 64.3, 104.4, 116.2, 122.0, 127.2, 144.8, 148.6, 149.6, 152.6, 154.3. MS (MALDI): 321 (M^+).

Sodium 4-((4-Decyloxy-3-ethoxyphenyl)diazenyl)benzenesulfonate 4

Sodium 4-((3-ethoxy-4-hydroxyphenyl)diazenyl)benzenesulfonate **3** (3.44 g, 0.01 mol), KOH (0.56 g 0.01 mol), CaO (2.8 g 0.05 mol), and KI (0.1 g) were dissolved in 40 ml of DMSO, and 3 ml of N-decylbromide were added. The mixture was stirred at reflux for 12 h. The residue was dissolved with dimethylformamide (DMF), filtered, and washed with DMF. After the solvent was evaporated, the product was dried under vacuum to give 4.72 g of **4** (98%) as yellow solid. ^{1}H NMR (300 MHz, *d*-DMSO, ppm) δ 0.84 (t, 3H, $J = 6.6$ Hz), 1.24–1.36 (m, 14H), 1.73 (t, 2H, $J = 6.9$ Hz), 1.74 (m, 2H), 4.04–4.13 (m, 4H), 7.16 (d, 1H, $J = 8.7$ Hz), 7.44 (s, 1H), 7.57 (d, 1H, J = 8.7 Hz), 7.42 (s, 1H), 7.77 (s, 4H). ^{13}C NMR (75 MHz, *d*-DMSO, ppm): δ 14.5, 15.2, 22.6, 26.0, 29.1, 29.2, 29.5, 29.6, 21.2, 64.5, 69.1, 104.4, 113.1, 119.0, 120.9, 121.0, 122.3, 127.2, 146.6, 149.4, 150.5, 152.3, 152.5. MS (MALDI): 461 (M^+).

4-Decyloxy-3-ethoxyaniline Hydrochloride 5

Sodium 4-((4-*n*-decyloxy)-3-ethoxyphenyl) diazenylbenzenesulfonate **4** (1.0 g, 2.07 mmol) was dissolved in 25 ml water. The resulting yellow solution was reduced by stirring with $Na_2S_2O_4$ (2.1 g, 10.3 mmol) under argon for 0.5 h at 90 °C. The reaction mixture was cooled to room temperature. The resulting white precipitate was filtered, washed with water, and then dissolved in ethyl acetate. The filtrate was extracted with ethyl acetate (3×20 mL). The dried organic layers (Na_2SO_4) were bubbled with anhydrous HCl to gave 0.511 g of **5** (75%) as a white solid. ^{1}H NMR (300 MHz, *d*-DMSO, ppm) δ 0.84 (t, 3H, $J = 6.6$ Hz), 1.24 (m, 14H), 1.35 (t, 3H, $J = 6.9$ Hz), 1.67 (m, 2H), 3.89–4.02 (m, 4H), 6.72 (d, 1H, $J = 8.7$ Hz), 6.96 (s, 1H), 7.00 (d, 1H, $J = 8.7$ Hz), 10.0 (br, 2H). ^{13}C NMR (75 MHz, *d*-DMSO, ppm): δ 13.9, 14.5, 22.0, 25.4, 28.6, 28.6, 28.9, 28.9, 31.2, 64.2, 68.7, 108.9, 114.0, 115.2, 124.5, 126.8, 148.0, 148.7. MS (MALDI): 294 (M + 1).

3-Ethoxy-4-*n*-decyloxy-anilionmethylene-malonic Acid Diethyl Ester 6

A mixture of 4-(decyloxy)-3-ethoxyaniline hydrochloride (2.0 g, 6.08 mmol), triethylamine (1.2 g, 12.16 mmol), and EMME (1.20 g, 5.47 mmol) in isopropanol (50 mL) was heated at reflux for 10 h. The residue was dissolved with n-hexane (50 mL), filtered, and washed with n-hexane. The solvent was evaporated under vacuum and dried overnight at 40 °C to yield 2.72 g of 3-ethoxy-4-*n*-decyloxy-anilionmethylene-malonic acid diethyl ester **6** (90%) as a brown liquor.

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.85 (t, 3H, $J = 6.6$ Hz), 1.26 (m, 14H), 1.45 (t, 3H, $J = 6.6$ Hz), 1.81 (m, 2H), 3.96 (t, 2H, $J = 6.6$ Hz), 4.06 (q, 2H, $J = 6.6$ Hz), 4.19–4.32 (d+d, 4H, $J = 7.2$ Hz), 6.64 (s, 1H), 6.67 (d, 1H, $J = 8.1$ Hz), 6.85 (d, 1H, $J = 8.1$ Hz), 8.42 (d, 2H, $J = 13.5$ Hz), 10.95 (d, 2H, $J = 13.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 14.1, 14.2, 14.8, 22.7, 25.9, 29.6, 31.8, 61.4, 64.9, 69.4, 95.6, 100.2, 108.5, 110.2, 112.5, 129.4, 140.8, 143.9, 150.9, 165.0, MS (MALDI): 463 (M^+).

Ethyl 6-*n*-Decyloxy-7-ethoxy-4-hydroxyquinoline-3-carboxylate 7

3-Ethoxy-4-*n*-decyloxy-anilionmethylene malonic acid diethyl ester **6** (1.0 g, 2.16 mmol) was dissolved in $POCl_3$ (5 mL) and stirred at reflux for 4 h, after which $POCl_3$ was distilled out. The resulting mixture was dissolved with acetic acid (20 ml) and stirred at reflux for 7 h (with monitoring by thin-layer chromatography). The reaction mixture was cooled, and then ice water (50 mL) was added. The resulting precipitate was filtered; washed with ice water, CH_2Cl_2, and CH_3OH; and dried under vacuum to afford **7** (0.72 g, 80%). Mp 242–245 °C. MS (MALDI): 417 (M^+).

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