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# LARGE SCALE, EFFICIENT SYNTHESIS OF 9-UNSUBSTITUTED DIPYRRINONE

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# LARGE SCALE, EFFICIENT SYNTHESIS OF 9-UNSUBSTITUTED DIPYRRINONE

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## ABSTRACT

9-Unsubstituted dipyrrinone  $\mathbf{8}$ , the useful precursor for the synthesis of biliverdins, bilirubins, and other bile pigments, was synthesized in large scale and high yield starting from acetaldehyde and nitroethane in eight steps with overall yield 10%. The key intermediate 3,4-dimethyl-2-ethoxycarbonylpyrrole  $\mathbf{3}$  was synthesized via Zard–Barton's method in high yield.

Key Words: Dipyrrinone; Barton-Zard's method; pyrrole

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9-Unsubstituted dipyrrinone **I**, the yellow and fully conjugated compound, is the structural moiety of bilirubin **II**, biliverdins, phycoerythrobilin, and many other bile pigments.<sup>1</sup> It is also an important precursor for the synthesis of symmetric 10-substituted bilirubin,<sup>2</sup> *b-homo*rubin,<sup>3</sup> biliverdin,<sup>2</sup> 10-substituted biliverdin,<sup>2,4</sup> *b-homo*verdin,<sup>5</sup> hemirubin,<sup>6</sup> semirubin,<sup>7</sup> and many other bile pigments.<sup>1</sup> Since it is structurally one half of bilirubins, it was also used as a model compound to investigate and to understand the solution properties, and stereochemistry, as well as in vivo metabolic properties of bilirubins.<sup>8</sup>



Although dipyrrinone **8** has been known for many years<sup>1</sup> and a number of synthetic procedures have been reported,  $^{2a,6b,8c,9,10}$  larger scale, convenient synthetic methods are still not available. In this paper we wish to report a larger scale, efficient synthesis of the 9-unsubstituted dipyrrinone **8**.

Our improved procedure starting with acetaldehyde and nitroethane with a total of eight steps is outlined in Scheme 1.

Thus, the important 5-substituted pyrrole **3** was prepared in 53% yield via Barton–Zard's method<sup>11</sup> using 2-acetoxy-3-nitrobutane **2**, which was prepared in high yield by condensation of nitroethane with acetaldehyde in two steps.<sup>12</sup> Although **3** was synthesized in 24% yield starting from 2-butanone in two steps,<sup>13</sup> in our hand the yield was only about 10%. It would be also prepared in low yield starting from 3,4,5-trimethyl-2-benzoxycarbonylpyrrole via multiple steps<sup>14</sup> including steps such as oxidation with surfuryl chloride, hydrolysis, iodination, and reduction.

Upon treating with sodium hydroxide in ethanol, pyrrole **3** was hydrolyzed to afford quantitatively pyrrole acid **4**, which was further converted to 2,5-unsubstituted pyrrole **5** in 90% yield by dry distillation (compound **4** was distilled under vacuum without solvent). 3,4-Dimethylpyrrole (**5**) could also be prepared in 30–40% yield<sup>15</sup> from 2,3-dimethylbutanediene-1,3 and urethane (Scheme 2). However, we found that this reaction produced intermediates with a terrible smell. The yield was only ~25% in our hand with tedious purification procedure (see experimental section).

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Scheme 1.

Reagents and Conditions: <sup>a</sup>KF/*i*-PrOH, r.t., 54%. <sup>b</sup>Ac<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/DMAP, r.t., 96%. <sup>c</sup>Ethyl isocyanoacetate/tetramethylguanidine/THF/*i*-PrOH, r.t., 53%. <sup>d</sup>NaOH/ EtOH, reflux, 95%. <sup>e</sup>Dry distillation, 90%. <sup>f</sup>POCl<sub>3</sub>/DMF, then NaOH, 73%. <sup>g</sup>Pyridine/H<sub>2</sub>O<sub>2</sub>, 50°C, 80%. <sup>h</sup>KOH/EtOH, reflux, 75%.



By standard Vilsmeier formylation methods, **5** was smoothly transformed to 2-formylpyrrole **6** in 73%. Oxidation of **5** with hydrogen peroxide in pyridine gave 3,4-dimethyl-2-pyrrolinone **7** in 80%. Condensation of **6** and **7** under a strong base condition afforded the expected dipyrrinone **8** in 75% yield at 50 mmol scale. The reaction could be scaled up to 100 mmol, or 15 g of dipyrrinone **8** in good yield.

In summary, we described in this paper an improved and highly efficient procedure for the synthesis of 2,3,7,8-tetramethyldipyrinone (8) on large scale with overall yield 10%. The key intermediate 3 was directly synthesized in high yield via Zard-Barton's method.<sup>11</sup>

# **EXPERIMENTAL SECTION**

Melting points were determined on a Yanaco MP-500 micromelting point apparatus and uncorrected. IR spectra were recorded on a BIO-RAD FT-165 IR spectrometer. NMR spectra were recorded on a Varian Gemini-200 MHz instrument using tetramethylsilane as internal standard. UV-VIS spectra were obtained on a Hitachi U-2001 spectrophotometer. Mass spectra were obtained on a VG TR10-200 spectrometer. Elemental analyses were performed on a Carlo Erba-120 elemental analyzer. Ethyl isocycanaocetate,<sup>16</sup> 2,3-dimethylbutanediene-1,3,<sup>17</sup> and sodium salt of 2-methyl-3-oxobutyraldehyde<sup>13</sup> were prepared according to literatures.

2-Nitro-butanol-3 [1, C<sub>4</sub>H<sub>9</sub>NO<sub>3</sub>]: A 1-1 three-necked round-bottomed flask equipped with a magnetic stirrer was charged with acetaldehyde (260 ml, 4.6 mol), 2-propanol (170 ml), and potassium fluoride (13.48 g, 0.23 mol, 0.05 mol equiv.). The stirrer was started and the flask was chilled in an ice-salt bath. To the mixture, nitroethane (334 ml, 4.6 mol, 1.0 mol equiv.) was added dropwise at  $0^{\circ}$  over a period of 1 h. Then the mixture was slowly warmed up to room temperature and kept for 10h under continuously stirring before removing all solvent under vacuum. The resulting oily crude product was filtered to remove solid inorganic waste and washed with dichloromethane. After removing all solvent under vacuum, colorless oily product 1 was obtained (300 g, 54%) which was immediately used for the next step synthesis. Note: we observed a small scale explosion during vacuum distillation. Therefore, purifying this product by distillation is not recommended. IR (KBr, film): v = 3471, 2954, 2860, 1743, 1555, 1455, 1372, 1226, 1026, 973, 861, 732, 632,  $602 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz); δ 1.0–1.1 (m, 3H, CH<sub>3</sub>), 1.3–1.4 (m, 3H, CH<sub>3</sub>), 3.9–4.0 (m, 0.5H), 4.1–4.2 (m, 0.5H), 4.3–4.4 (m, 1H) ppm (it is a mixture of two isomers). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ (12.4, 15.6), (18.5, 18.8), (68.2, 69.0), (87.1, 88.90) ppm (it is a mixture of two isomers).

2-Nitro-3-acetoxyl-butane [2,  $C_6H_{11}NO_4$ ]: 2-Nitro-butanol-3 (1, 150 g, 1.26 mole) was dropwise added over 10 min to a solution of dichloromethane (100 ml), acetic anhydride (193 g, 1.89 mol, 1.5 mol equiv.), and 4-dimethylaminopyrridine (DMAP, 2 g). Due to the exothermic reaction, the temperature of the solution could reach to  $40^{\circ}C$ . The mixture was allowed to stir at room temperature for 4 h. Methanol (300 ml) was added to destroy the excess acetic anhydride. After stirring for a further 30 min, the solution was poured into dilute sodium bicarbonate (90 g in 500 ml water) and extracted with dichloromethane (3 × 200 ml). The organic layer was dried over sodium sulfate and filtered through a short column of silica. Evaporation of the solvent gave the desire product 2 as a clear liquid

(195 g, 96%), which was directly used in the next step. *Note: vacuum distillation to purify this product was not recommended due to the possibility of explosion. We observed a small scale explosion during vacuum distillation.* IR (KBr, film): v = 3468, 2995, 1746, 1558, 1449, 1384, 1234, 1093, 1039, 951, 857, 643, 607, 539 cm<sup>-1</sup>. GC-MS (T<sub>r</sub>: 4.6 and 4.9 min, two isomers) m/z (%) = 146 (5), 114 (13), 101 (2), 87 (10), 75 (12), 73 (100), 55 (10). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz);  $\delta$  1.2–1.3 (m, 3H, CH<sub>3</sub>), 1.4 (m, 3H, CH<sub>3</sub>), 1.90 (ss, 3H, COCH<sub>3</sub>), 4.5–4.6 (m, 1H, CH), 5.1–5.2 (m, 1H, CH) ppm (it is a mixture of two isomers). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  (13.2, 15.2), (15.5, 15.7), (20.4, 20.5), (69.7, 70.4), (84.3, 85.4), (169.3, 169.5) ppm (it is a mixture of two isomers).

2-Ethoxycarbonyl-3,4-dimethyl-1H-pyrrole [3, C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub>] Method A: Via Zard-Barton's Method.<sup>11</sup> In a 2-1 round-bottomed flask equipped with a magnetic stirrer was charged ethyl isocycanoacetate (148 g, 1.3 mol, 1.05 mol equiv.), and tetramethylguanidine (300 g, 2.54 mol, 2.05 mol equiv.). The stirrer was started and the flask was cooled in an ice-water bath. To the mixture, a solution of 3-acetoxy-2-nitro-butane (2, 200 g, 1.24 mol) in dry THF (200 ml) and isopropanol (200 ml) was added to 0°C dropwise over a period of 30 min. The mixture was allowed to stir at room temperature for another 20 h after the addition was complete. The resulting mixture was concentrated under vacuum to dryness. The oily residue was taken up by dichloromethane (2500 ml) and washed successively with water  $(3 \times 400 \text{ ml})$ , 5% aqueous hydrochloric acid  $(3 \times 400 \text{ ml})$ , water (400 ml). aqueous saturated sodium bicarbonate (400 ml), and brine (400 ml). After drying over anhydrous sodium sulfate and removing all solvent under vacuum, the residue oil was crystallized from dichloromethane-hexane. The expected product **3** was obtained 110 g (53%).

**Method B:** From 2-Butanone.<sup>13</sup> A 3-1 three-necked round-bottomed flask, equipped with mechanic stirrer and a reflux condenser, was charged with glacial acetic acid (400 ml). Sodium hydroxide (50 g, 1.25 mol, 0.80 mol equiv.) was added slowly under stirring. While sodium hydroxide was dissolving the mixture was warmed up to reflux by exothermic reaction. A solution of diethyl malonate (321 g, 2.0 mol) in glacial acetic acid (500 ml) was then added to the hot solution. The reaction flask was then cooled by an ice–water bath. Then a solution of sodium nitrite (280 g, 4.04 mol, 2.0 mol equiv.) in water (380 ml) was added dropwise under 5°C by adjusting the dropping speed. The addition was completed in approximately 5 h. The homogeneous mixture was allowed to cool and stand overnight at 5°C. A solution of sodium hydroxide (126 g, 3.11 mol) in ice–water (350 ml) was dropwise added to the stirred mixture in a steady stream under  $10^{\circ}$ C (ice–salt bath was required); the mixture was then extracted with ether (4 × 500 ml). The combined extracts were washed with aqueous saturated

sodium bicarbonate  $(2 \times 500 \text{ ml})$  and water (500 ml). The solvent was removed under vacuum to give a bright yellow oil product, diethyl oximinomalonate, which was used directly for the next step synthesis.

In a 5-l four-necked round-bottomed flask, equipped with a mechanical stirrer, a drop funnel, a thermometer, and a condenser, were charged with glacial acetic acid (2500 ml) and anhydrous sodium acetate (600 g). The mixture was stirred and heated to 85°C. Then, sodium salt 2-methyl-3-oxo butyraldehyde (244 g, 2.0 mol, prepared from the condensation of 2-butanone with ethyl formate in the presence of sodium<sup>13</sup>), crude diethyl oximinomalonate (prepared from above  $\sim 2.0 \text{ mol}$ ) and a solution of glacial acetic acid (400 ml) in water (200 ml) were consecutively introduced, and the mixture was heated to 95°C. Zinc dust (390 g, 6.0 mol, 3.0 mol equiv.) was then slowly added to maintain the temperature between 90 and  $100^{\circ}$ , after which the reaction mixture was heated and stirred for another 30 min. Pouring the reaction mixture to 101 ice-water mixture caused the separation of yellow oil, which solidified on standing in a cold room. The product was collected by suction filtration, and dissolved in dichloromethane (500 ml), and filtrated to remove any insoluble waste. The filtrate was washed with water  $(2 \times 100 \text{ ml})$ , then aqueous sodium bicarbonate  $(2 \times 100 \text{ ml})$ . After drying over anhydrous sodium sulfate, the solvent was removed under vacuum. The residue was then crystallized from dichloromethane-hexane to afford the expected compound 3 as yellow solid (31.7 g, 9.5%). m.p. 92–94°C (lit [13] 90–92°C, lit [14a] 94–95°C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>,); δ 1.3 (t, 3H, J=7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.0 (s, 3H, pyrr-CH<sub>3</sub>), 2.3 (s, 3H, pyrr-CH<sub>3</sub>), 4.3 (q, 2H, J = 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 6.7 (d, 1H, J = 2.7 Hz, pyrr-H), 8.9 (br s, 1H, NH) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>); δ 9.8 (OCH<sub>2</sub>CH<sub>3</sub>), 10.2 (pyrr-CH<sub>3</sub>), 14.5 (pyrr-CH<sub>3</sub>), 59.7 (OCH<sub>2</sub>CH<sub>3</sub>), 120.5, 120.9, 121.0, 126.9, 161.7 (COOEt) ppm.

**2-Carboxy-3,4-dimethyl-1H-pyrrole [4, C<sub>7</sub>H<sub>9</sub>NO<sub>2</sub>]:** 2-Ethoxycarbonyl-3,4-dimethyl-1H-pyrrole (**3**, 60 g, 0.36 mol) was suspended in 95% ethanol (200 ml), then 30% potassium hydroxide (280 ml, 1.12 mol, 3.1 mol equiv.) was added at once. The mixture was heated at reflux for two hours, with the resulting brown solution cooled down to room temperature and chilled by a salt-ice bath. Concentrated hydrochloric acid was added dropwise to the cold brown solution to give white precipitate. The fine white solid was collected by filtration and washed with water. The solid was dried under vacuum to give the expected compound **4** (48 g, 96%). m.p. 200° (dec.) (lit [13] 205° dec.). <sup>1</sup>H NMR (300 MHz acetone-d<sub>6</sub>):  $\delta$  1.93 (s, 3H, pyrr-CH<sub>3</sub>), 2.20 (s, 3H, pyrr-CH<sub>3</sub>), 6.72 (d, 1H, J=2.7 Hz, pyrr-H), 9.34 (br s, 1H, NH), 10.23 (s, 1H, COOH) ppm. <sup>13</sup>C NMR (75 MHz, acetone-d<sub>6</sub>):  $\delta$ 9.05 (pyrr-CH<sub>3</sub>), 9.43 (pyrr-CH<sub>3</sub>), 118.50, 119.91, 120.66, 125.89, 161.72 (COOEt) ppm.

**3,4-Dimethyl-1H-pyrrole [5, C<sub>6</sub>H<sub>9</sub>N] Method A:** *Dry distillation from 4.* 2-Carboxy-3,4-dimethyl-1H-pyrrole (26 g, 0.21 mol) was added to a 100 ml round bottomed flask and heated over an oil bath. The acid was distilled at a temperature of oil bath 180–190°C under vacuum (water aspirator pump). The pure decarboxylated product was obtained by using a short distillation apparatus with ice-cooled received flask. During the distillation the compounds solidified in the receiving flask. Pure product **5**, which smells like benzene, was obtained (17.8 g, 90%) as colorless needle crystals at 0°C, which was stable for one year without noticeable decomposition under nitrogen and  $-5^{\circ}$ C.

Method B: From the reaction of 2,3-dimethylbutadiene-1,3. In a 2-1 four-necked round-bottomed flask, equipped with a mechanical stirrer, a reflux condenser closed at the top with an anhydrous calcium chloride drying tube, and two 100 ml dropping funnels, were placed in ethyl carbamate (urethane, 48 g, 0.53 mole, 1.10 mole equiv.) and dry benzene (350 ml). The reaction flask was cooled by a water bath. Pyridine (85 ml, 1.05 mol, 2.2 mol equiv.) and thionyl chloride (38.6 ml, 0.53 mole, 1.1 mole equiv.) were respectively placed in two dropping funnels, and were added dropwise over 30 min at the same rate with vigorous stirring. The black mixture was then stirred at room temperature for 1.5 h, then 2,3-dimethylbutandiene-1,3 (39.5 g, 0.48 mole) was added in one portion. The mixture was heated at gentle reflux for 5 h, then cooled down to room temperature, and allowed to stand overnight. Insoluble materials were then removed by suction filtration. The filtrate cake was washed with dry benzene  $(4 \times 100 \text{ ml})$ . Caution: very bad smell, all reaction and work-up job should be done inside fume-hood. The combined filtrates and washings were concentrated under vacuum to afford a dark oily residue of the crude intermediate 2-ethoxycarbonyl-3,6-dihydro-4,5-dimethyl-1.2-thiazine-1-oxide. To the residue a solution of potassium hydroxide (213 g, 3.8 mole, 8 mole equiv.) in methanol (550 ml) was then added at once. The mixture was then heated at reflux for 2 h. Solvent was distilled, and the dark residue was steam-distilled until no oily materials were received, which required 14–16 h. The distillates were combined and extracted with dichloromethane  $(3 \times 150 \text{ ml})$ . The extracts were dried over anhydrous potassium carbonate and the solvent was removed under vacuum. The residue was distilled under vacuum to give a colorless oil at room temperature and solidified to crystalline at 0°C (11.4g, 25%) based on the theoretical amount of 2,3-dimethylbutandiene used). <sup>1</sup>H NMR (300 MHz chloroform-d): δ 2.1 (s, 6H, 2 pyrr-CH<sub>3</sub>), 6.5 (d, 2H, J = 2.0 Hz, 2 pyrr-H), 7.8 (br s, 1H, NH) ppm. <sup>13</sup>C NMR (chloroform-d): δ 9.9 (pyrr-CH<sub>3</sub>), 118.5, 115.5, 118.2 ppm.

**2-Formyl-3,4-dimethyl-1H-pyrrole** [6, C<sub>7</sub>H<sub>9</sub>NO]: In a 500 ml threenecked round-bottomed flask, equipped with a magnetic stirrer, a condenser closed at top with an anhydrous CaCl<sub>2</sub> tube, and a nitrogen inlet, was charged with phosphyl oxochloride (24.6 g, 160 mmole, 1.1 mol equiv.). The stirrer was started and the flask was chilled by an ice-salt bath while nitrogen was introduced. Then a mixture of 3,4-dimethyl-1H-pyrrole (5, 13.86 g, 146 mmol) in dry dichloromethane (200 ml) containing dry N,N-dimethylformamide (13 g, 198 mmol, 1.3 mol equiv.) was added. The reaction mixture was stirred at room temperature overnight. After removing all solvent under vacuum, the residue was mixed with water (120 ml). To the stirred mixture sodium hydroxide (36.8 g, 920 mmol) was added slowly. Next, the mixture was allowed to stir 1 h at room temperature, the yellow precipitate was collected, washed with water, and dried to afford the expected product 6 (13 g, 73%). m.p. 132-134°C (lit [13] 133-134°C). <sup>1</sup>H NMR (300 MHz chloroform-d):  $\delta$  2.0 (s, 3H, pyrr-CH<sub>3</sub>), 2.3 (s, 3H, pyrr-CH<sub>3</sub>), 6.8 (s, 1H, pyrr-H), 9.2 (br s, 1H, NH), 9.6 (s, 1H, CHO) ppm. <sup>13</sup>C NMR (chloroform-d): δ 9.8 (pyrr-CH<sub>3</sub>), 10.0 (pyrr-CH<sub>3</sub>), 121.1, 122.1, 124.2, 127.8, 178.2 ppm.

**3,4-Dimethyl-3-pyrrolin-2-one [7, C<sub>6</sub>H<sub>9</sub>NO]:** 3,4-Dimethyl-1H-pyrrole (5, 17.0 g, 0.18 mol) was dissolved in pyridine (30 ml) under nitrogen protection. Then 30% hydrogen peroxide (27 ml, 0.45 mol) was added at once. The mixture was stirred at 50°C for 2 h. Solvent was removed under vacuum to give a light orange oil which solidified on drying under vacuum overnight. The crude product was crystallized from dichloromethane-hexane to give the desired product 7 (15.9 g, 80%). m.p. 114–116°C (lit [13] 116–118°C) IR (KBr, film): v = 3320, 3100, 2945, 1601, 1545, 1480, 1449, 1320, 1155, 1080, 810, 750, 699 cm<sup>-1</sup>. GC-MS: m/z = 111 (M<sup>+</sup>). <sup>1</sup>H NMR (300 MHz CDCl<sub>3</sub>):  $\delta$  1.8 (s, 3H, pyrr-CH<sub>3</sub>), 2.0 (s, 3H, pyrr-CH<sub>3</sub>), 3.8 (s, 2H, CH<sub>2</sub>), 7.3 (br s, 1H, NH) ppm. CNMR (50 MHz, CDCl<sub>3</sub>),  $\delta$  7.8, 9.3, 47.3, 126.5, 154.5, 176.3 ppm.

**2,3,7,8-Tetramethyldipyrrinone [8,**  $C_{13}H_{16}N_2O$ ]: In a 250-ml threenecked round-bottomed flask, equipped with a nitrogen inlet, a condenser, and a magnetic stirrer, were charged with 2-formyl-3,4-dimethyl-1H-pyrrole (**6**, 6.0 g, 48 mmol), 3,4-dimethyl-3-pyrrolin-2-one (**7**, 5.8 g, 52 mmol, 1.09 mol equiv.), aqueous potassium hydroxide (4 M, 150 ml, 0.60 mol, 12.5 mol equiv.) and methanol (125 ml). The suspension was stirred at reflux for 10 h under nitrogen (a yellow precipitate was formed during reflux). Solvents were evaporated, the yellow precipitate was collected by filtration, washed with water and dried to give the expected title compound **8** as yellow powder (7.8 g, 75%). m.p. 268–270°C (dec.) (lit [9b] m.p. 271–273°C). IR (KBr, film): v = 3350, 3200, 3151, 2932, 1596, 1501, 1436, 1236, 1175, 1103, 945, 800 cm<sup>-1</sup>. MS (FAB): m/z = 216 (M<sup>+</sup>). UV–Vis (Chloroform):  $\lambda_{max}(\varepsilon) = 394$  (25 300) nm. <sup>1</sup>H NMR (300 MHz, chloroformd):  $\delta$  1.5 (s, 3H, pyrr–CH<sub>3</sub>), 1.9 (s, 3H, pyrr–CH<sub>3</sub>), 2.0 (s, 3H, pyrr-CH<sub>3</sub>), 2.1

(s, 3H, pyrr-CH<sub>3</sub>), 6.2 (s, 1H, =CH), 6.9 (s, 1H, pyrr-H), 10.2 (br s, 1H, NH), 10.9 (br s, 1H, NH) ppm. <sup>13</sup>C NMR (chloroform-d): δ 8.4 (pyrr-CH<sub>3</sub>), 9.5 (pyrr-CH<sub>3</sub>), 10.0 (pyrr-CH<sub>3</sub>), 10.2 (pyrr-CH<sub>3</sub>), 101.1, 119.5, 120.9, 121.1, 124.0, 124.4, 129.8, 142.4, 174.3 (C=O) ppm.

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