Supporting Information

An Improved Synthesis of Functionalized

2,2’-Bipyroles

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General:

All commercially available solvents and starting materials were used without further purification. \(^1\)H- and \(^13\)C-NMR were obtained on 250 or 300 MHz spectrometers; chemical shifts (\(\delta\)) are given in ppm relative to CDCl\(_3\) (7.26 ppm, \(^1\)H), acetone-d\(_6\) (3.58 ppm, \(^1\)H), or DMSO-d\(_6\) (2.54 ppm, \(^1\)H). Electronic absorption spectra were measured in the 200-800 nm wavelength region with 0.1 nm accuracy. Fluorescence spectra were measured in the 360-800 nm wavelength region with 1 nm accuracy. Fluorescence quantum yields were measured using the standard method and quinine sulfate in 5% H\(_2\)SO\(_4\) aqueous solution as the standard (quantum yield is 0.55), according to the literature. \(^1\) Mono-pyrroles used to make 2-iodopyrroles were synthesized according to the literature. \(^2\) Pyrrole 6c was prepared in the same way as described in the literature through a Vilsmeier reaction on pyrrole 5c, the synthesis of which has been reported in the literature. \(^2\)b Pyrroles 4e-6e were prepared according to the literature. \(^4\) Pd-C (10%) was purchased from Strem Chemicals.

General Procedure for Syntheses of Pyrrole 6a–:

The following description uses pyrrole 5b as a representative example for the preparation of pyrrole 6. Pyrrole 5b (2.0 g, 0.006 mole) was dissolved in THF (63 mL), HOAc(16 mL), and H\(_2\)O (16 mL). Then 8.6 equiv of ceric ammonium nitrate (28.2 g, 0.052 mole) was added to the mixture all in once. The reaction mixture was stirred at room temperature while TLC was used to follow reaction progress. When there remained no starting material left, the mixture was poured into 150 mL of water and extracted with dichloromethane (100 mL) three times. The organic layer was washed with water (100 mL) three times followed by saturated aqueous NaHCO\(_3\) (100 mL). Then the organic extracts were combined and dried over anhydrous Na\(_2\)SO\(_4\). Finally the
solution was concentrated under vacuum to remove the solvents. Recrystallization from dichloromethane/hexane gave a slightly yellowish fine powder of 6b in 89% yield (1.76 g).

**Benzyl 3-Ethyl-5-formyl-4-methylpyrrole-2-carboxylate** 6a. 91% yield. Mp 86-87 °C (lit. mp 86-87 °C). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 9.76 (s, 1H), 9.53 (s, 1H), 7.44-7.33 (m, 5H), 5.34 (s, 2H), 2.79-2.70 (m, 2H), 2.30 (s, 3H), 1.23-1.17 (m, 3H). $^{13}$C NMR (250 MHz, CDCl$_3$) ppm 179.8, 161.3, 137.2, 136.0, 129.1, 128.5, 128.9, 128.8, 127.1, 124.8, 67.0, 17.2, 16.8, 10.1. ESI-MS Calcd for C$_{16}$H$_{17}$NO$_3$ m/z, 271.12, found: 271.18.

**Benzyl 5-Formyl-4-(2-methoxycarbonyl-ethyl)-3-methylpyrrole-2-carboxylate** 6b. 89% yield. Mp 79-80 °C (lit. mp 80-81 °C). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.81 (s, 1H), 9.52 (s, 1H), 7.43-7.35 (m, 5H), 5.33 (s, 2H), 3.65 (s, 3H), 3.08-3.03 (m, 2H), 2.59-2.54 (m, 2H), 2.31 (s, 3H). $^{13}$C NMR (250 MHz, DMSO-d$_6$) ppm 180.5, 173.2, 161.2, 135.9, 132.4, 130.7, 129.0, 128.9, 128.8, 127.3, 124.8, 67.0, 52.1, 35.3, 19.3, 10.3. ESI-MS Calcd for C$_{18}$H$_{19}$NO$_5$ m/z, 329.13, found: 329.17.

**Benzyl 4-(2-Cyanoethyl)-5-formyl-3-methylpyrrole-2-carboxylate** 6d. 87% yield. Mp 111-113 °C. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 10.38 (s, 1H), 9.77 (s, 1H), 7.40-7.31 (m, 5H), 5.35 (s, 2H), 3.10-3.04 (m, 2H), 2.62-2.57 (m, 2H), 2.33 (s, 3H). $^{13}$C NMR (250 MHz, CDCl$_3$) ppm 180.3, 161.2, 135.7, 130.8, 129.4, 129.1, 129.0, 128.8, 127.7, 124.9, 119.4, 67.3, 20.3, 19.1, 10.4. ESI-MS Calcd for C$_{17}$H$_{16}$N$_2$O$_3$ m/z, 296.12, found: 296.15.

**Benzyl 3:4-Butano-5-formylpyrrole-2-carboxylate** 6c. Synthesis of this compound started from the readily available pyrrole 5c; the procedure for the preparation of pyrrole 6c was different from the other pyrroles 6. The Vilsmeier complex was prepared by adding 2 mL phosphoryl chloride to 20 mL of dry DMF. Then benzyl 3:4-butanopyrrole-2-carboxylate 5c (2.55 g, 0.01 mol) was dissolved in 20 mL of dry DMF and added slowly to the reaction mixture through a syringe under ice-bath cooling conditions. The ice-bath was then removed a the
mixture was refluxed for 45 min. Then, 250 mL of aqueous NaHCO₃ was added slowly until the pH reached 8. Stirring was continued at 30°C until TLC indicated the complete hydrolysis of the intermediate imine salt. The solution was extracted with dichloromethane (100 mL) three times, and washed with water (100 mL) three times, and finally dried over anhydrous Na₂SO₄ before removing the solvent under vacuum to give the title compound 6c as slightly yellow powder in 92% yield (2.61 g). Mp 111-112 °C. ¹H NMR (250 MHz, CDCl₃) δ 9.71 (s, 1H), 9.58 (s, 1H), 7.41-7.34 (m 5H), 5.34 (s, 2H), 2.84-2.81 (m, 4H), 1.80-1.78 (m, 4H). ¹³C NMR (250 MHz, CDCl₃) ppm 179.0, 160.7, 135.5, 131.9, 129.2, 128.9, 128.6, 128.4, 128.3, 123.2, 66.6, 22.7, 22.6, 22.4, 20.9. HRMS (ESI) Calcd for C₁₇H₁₈NO₃ [M+H]⁺ 284.1281, found: 284.1209.

**General Procedure for Synthesis of Pyrroles 4a-4d:**

Starting from pyrroles 6a-6d, pyrroles 4a-4d were obtained in two steps. The following description uses the typical preparation of:

**5-Formyl-2-iodo-4-(2-methoxycarbonylethyl)-3-methylpyrrole 4b.** *Step 1. Hydrolysis:* Pd-C (180 mg, 6%) was added into a 50 mL round bottom flask and 3 mL of freshly distilled dry THF was added to form a suspension. This was stirred under a hydrogen atmosphere capped with a balloon at room temperature for 20 min to active the Pd-C. Then, benzyl 5-formyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate 6b (500 mg, 1.52 mmol) was dissolved in 6 mL freshly distilled dry THF and added into the above solution through a syringe. The mixture was stirred under the hydrogen atmosphere at room temperature for 6-12 h, using TLC to follow the reaction; it was stopped when all the starting material has been transformed into very polar spot on TLC. Upon completion of the reaction, the mixture was passed through a Celite plug to remove Pd-C, followed by washing with THF (50 mL) three times. After removing the combined solvent under vacuum, a grayish white powder of 5-formyl-4-(2-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylic acid 7b was obtained in 97% yield (348.1 mg); it was used directly for the next step without any characterization. *Step 2. Iodination:* NaHCO₃ (453.6 mg 5.4 mmol)
was added to 25 mL of water, into which the pyrrole 7b (348.1 mg) obtained from the previous step was added, followed by sonication. Then the reaction mixture was placed into a 50 °C oil bath. Once pyrrole 7b was completely dissolved, 25 mL of dichloromethane was added to the reaction mixture and the temperature was quickly raised to 70 °C. Then, I$_2$ (410.8 mg, 1.6 mmol) and KI (488.2 mg, 2.9 mmol) were dissolved in 15 mL of water and added to the reaction mixture all at once. The mixture was refluxed for 1 h, using TLC to follow the reaction. The mixture was cooled and excess sodium thiosulfate was added into the reaction mixture in small portions with stirring to remove excess iodine. The reaction mixture was poured into a separatory funeral and the organic layer was collected. After drying over anhydrous Na$_2$SO$_4$, the organic solvent was removed under vacuum. After recrystallization from MeOH, a slightly yellow powder of 4b was obtained in 85% yield (401.4 mg). The overall yield of 4b from 6b was 82%.

3-Ethyl-5-formyl-2-iodo-4-methylpyrrole 4a. 85% yield. Mp 118-120 °C (lit. mp 118-120 °C). $^1$H NMR (250 MHz, CDCl$_3$) δ 10.77 (s, 1H), 9.41 (s, 1H), 2.76-2.70 (m, 2H), 1.99 (s, 3H), 1.22-1.16 (m, 3H). $^{13}$C NMR (250 MHz, CDCl$_3$) ppm 176.5, 138.4, 133.4, 126.2, 83.8, 18.1, 16.9, 11.9. ESI-MS Calcd for C$_8$H$_{10}$INO $m/z$, 262.98, found: 263.05.

5-Formyl-2-iodo-4-(2-methoxycarbonylethyl)-3-methylpyrrole 4b. 82% yield. Mp 91-92 °C (lit. mp 92 °C). $^1$H NMR (300 MHz, CDCl$_3$) δ 10.66 (s, 1H), 9.41 (s, 1H), 3.64 (s, 3H), 3.06-3.00 (m, 2H), 2.57-2.51 (m, 2H), 1.96 (s, 3H). $^{13}$C NMR (250 MHz, DMSO-d$_6$) ppm 176.5, 172.6, 133.3, 132.8, 125.9, 82.6, 51.7, 35.1, 19.5, 11.5. ESI-MS Calcd for C$_{10}$H$_{12}$INO$_3$ $m/z$, 320.99, found: 321.06.

3:4-Butano-5-formyl-2-iodopyrrole 4c. 84% yield. Mp 165-167 °C. $^1$H NMR (250 MHz, CDCl$_3$) δ 9.48 (br, 1H), 9.34 (s, 1H), 2.84-2.80 (m, 2H), 2.39-2.34 (m, 2H), 1.84-1.76 (m, 4H). $^{13}$C NMR (250 MHz, CDCl$_3$) ppm 175.5, 133.5, 132.4, 128.6, 79.1, 23.0 (2C), 22.7, 20.9. HRMS (ESI) Calcd for C$_9$H$_{11}$NOI [M+H]$^+$ 275.9879, found: 275.9878.
4-(2-Cyanoethyl)-5-formyl-2-iodo-3-methylpyrrole \(4\d\). 81% yield. Mp 143-145 °C. \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 9.76 (s, 1H), 9.47 (s, 1H), 3.14-3.08 (m, 2H), 2.64-2.58 (m, 2H), 2.05 (s, 3H). \(^1\)C NMR (250 MHz, CDCl\(_3\)) ppm 175.8, 133.6, 129.5, 126.5, 118.6, 82.5, 20.4, 19.1, 11.64. HRMS (ESI) Calcd for C\(_9\)H\(_{10}\)N\(_2\)OI [M+H]\(^+\) 288.9832, found: 288.9834.

Dibenzyl 3,3',4,4'-Tetramethyl-2,2'-bipyrrrole-5,5'-dicarboxylate\(^5\a,b\) was prepared as described in the text of the paper, using benzyl 2-iodo-3,4-dimethylpyrrole-5-carboxylate, Pd-C and activated zinc in 1:1 acetone/water. It was obtained in 78% yield (89 mg) after recrystallization from MeOH/CH\(_2\)Cl\(_2\). Mp 218-220 °C (lit.\(^5\b\) mp 219-220 °C). \(^1\)H NMR (250MHz, CDCl\(_3\)) \(\delta\) 9.08 (s, 2H), 7.39-7.34 (m, 10H), 5.25 (s, 4H), 2.31 (s, 6H), 2.02 (s, 6H). \(^1\)C NMR (250 MHz, CDCl\(_3\)) ppm 161.4, 136.3, 128.5, 128.1, 128.0, 127.9, 124.9, 119.9, 119.0, 118.5, 10.7, 9.9. HRESI-MS Calcd for [M+H]\(^+\) C\(_{28}\)H\(_{29}\)N\(_2\)O\(_4\) \(m/z\), 457.2127, found: 457.2124.

References:


ESI (positive ion mode) (5 scans combined (2.88 mins))
File name: AZ 02-07-07 with (5702 020702)
Sample I.D. # 5702
Sample Name: dp

Max 16220 counts
Sample L.D. #5703
Sample Name:7b

ESI (positive ion mode) (scan mode: 1.401 to 1.934 mins)
File name: AZ.02.07.07, with (5703.020703)
Max. 1525.5 counts
ESI (positive ion mode) (Scans combining 2.018 to 2.784 mins)
File name: AZ020707 with (5704 020707)
Sample ID # 5704
Sample Name: db
Max. 16157 counts
ESI (positive ion mode) (scan combined 1.218 to 1.518 mins)

File name: AZ02_0707_With(5705 020707)
Sample ID # 5705
Sample Name: 9B

Max. 98.9 % Area
ESI (positive ion mode) (scans combined 1.151 to 1.618 mins)
File name: AZ 02 07 07 with (5707 020707)
Sample ID 5707
Sample Name: 4C

Max. 1174 cases.