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Novel One-Pot, Three-Component Synthesis of New 2-Alkyl-5-aryl-(1*H*)-pyrrole-4-ol in Water

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New 2-alkyl-5-aryl-(1*H*)-pyrrole-4-ol derivatives were synthesized via three-component reaction of β-dicarbonyl compounds with arylglyoxals in the presence of ammonium acetate in water at room temperature.

Introduction

At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials.[1] Green chemistry approaches hold out significant potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies.[2] Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are perhaps the most ripe for greening.[3]

The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheap, and environmentally friendly solvents but also because water exhibits unique reactivity and selectivity, properties that are different from those of conventional organic solvents. Thus, development of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.[1] Carrying out organic reactions in water has become highly desirable in recent years to meet environmental considerations.[4] The use of water as a sole medium for organic reactions would greatly contribute to the development of environmentally friendly processes. Indeed, industry prefers to use water as a solvent rather than toxic organic solvents.

Pyrroles are important heterocycles broadly used in material science[5] and found in naturally occurring and biologically important molecules.[6] Pyrroles can be found in a tremendous range of natural products[7] and bioactive molecules,[8] including the blockbuster drug, atrovastatin calcium,[8a] as well as important anti-inflammatants,[8b] antitumor agents,[8c] and immunosuppressants.[8d]

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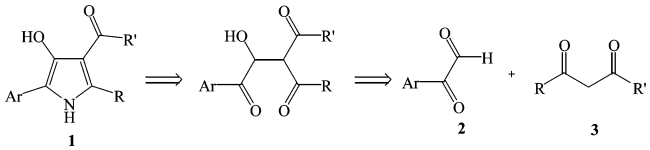
Within these large classes of relevant products, tetrasubstituted pyrroles are extremely important, displaying antibacterial, antiviral, anticonvulsant, and antioxidant activities and inhibiting cytokine-mediated diseases.[9] Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles.[5,6,10]

One of the most common approaches to pyrrole synthesis is the Paal−Knorr reaction in which 1,4-dicarbonyl compounds are converted to pyrrole via acid-mediated dehydrative cyclization in the presence of a primary amine.[11] In this reaction, the 1,4-dicarbonyl compounds provide the four carbons of the pyrrole with the possible substituents, whereas the amine provides the nitrogen with its substituent. The main limitations to intensive use of this reaction are the strong reaction conditions required for cyclization (use of boiling acetic acid for extended times) and the low availability of nonsymmetrically substituted 1,4-dicarbonyl compounds. The classical approach to this class of products is the condensation of enolates with phenacyl bromides,[12] thus limiting the preparation to pyrroles with aryl substituents. Alternative approaches need several steps of reactions with chromatographic separations to obtain the intermediates for cyclization. Therefore, mild reaction conditions that can overcome some of the shortcomings of previous methods are necessary. In this contribution, we describe one-pot synthesis of new 5-aryl-(1*H*)-pyrrole-4-ol **1** via reaction of β-dicarbonyl compounds **3** with arylglyoxals **2** in the presence of excess ammonium acetate (Scheme 1). To the best of our knowledge, there are no reports in the literature for the formation of 4-hydroxypyrrole derivatives via condensation of β-dicarbonyl compounds with arylglyoxals.

SCHEME 1. Retro Synthesis of 5-Aryl-(1H)-pyrrole-4-ol



One-pot multicomponent processes have recently gained a considerable and steadily increasing academic, economic, and

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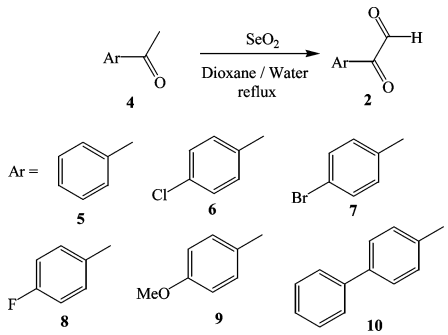
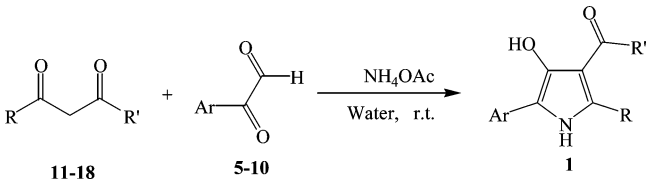
SCHEME 2. Synthesis of Arylglyoxals



SCHEME 3. Synthesis of 5-Aryl-(1H)-pyrrole-4-ol



ecological interest because they address very fundamental principles of synthetic efficiency and reaction design.[13] Additionally, the prospect of extending one-pot reactions into combinatorial and solid-phase syntheses[13c,14] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts, and even novel molecule-based materials.

Results and Discussion

The arylglyoxals **2** were prepared from commercially available acetophenones **4** as outlined in Scheme 2.[15] Twenty-eight examples of the conversion arylglyoxals **2** to various tetrasubstituted pyrroles systems are listed in Table 1. The reactions were performed by adding arylglyoxals **2** to mixtures of the β-dicarbonyl compounds **3** in water at room-temperature in the presence of excess amounts of NH_4OAc at room-temperature (Scheme 3). After 10−30 min, the mixture was solidified and isolated by filtering. The products were obtained in good yields after recrystallization in ethanol (96%).

The proposed mechanism involves the attack of enolate **52** onto the phenylglyoxal **5** as shown in Scheme 4, then in situ generated 3-hydroxy-1,4-dicarbonyl compound **53**, in the presence of NH_4^+, converts to **54**, which then loses two H_2O molecules to afford products **21**.

In the case of dicarbonyl compounds **16**−**18**, in which R = Ph, dicarbonyl compounds were recovered without any changes, and unexpected 4(5)-aryl-2-aryloyl-(1*H*)-imidazol (**55**) was obtained as a sole product (Scheme 5). Imidazol **55** was obtained in two isomeric forms; 2-benzoyl-4-phenyl-(1*H*)-imidazol and 2-benzoyl-5-phenyl-(1*H*)-imidazol.

In conclusion, we have demonstrated a novel arylglyoxal-mediated synthesis of new 4-hydroxy pyrroles from β-dicarbonyl compounds and ammonium acetate in water. Considering the availability of the starting materials, the simple procedure at room temperature, and the robust nature of this chemical process, this provides a very straightforward route to construct variously substituted 4-hydroxy pyrroles without metal catalysts. Studies directed toward the further generalization of this approach, as well as the application of this method to other heterocycles, are underway.

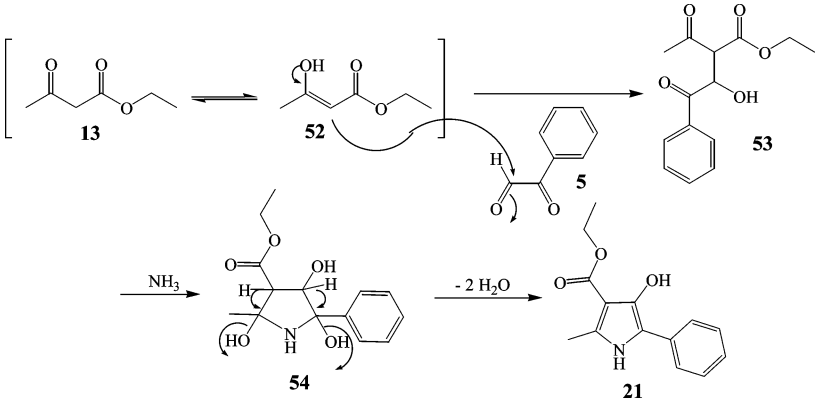
Experimental Section

Sample Procedures for Pyrrole Synthesis. To a mixture of β-dicarbonyl compound (1 mmol) in water (5 mL), were successively added arylglyoxal (1 mmol) and ammonium acetate (5 mmol) at room temperature (20−25 °C); the resultant mixture was stirred at the same temperature for 30−45 min. After an appropriate time the reaction mixture was solidified; the obtained solid was then filtered, the filtrate washed with water (3 × 10 mL), and the crude material was purified by crystallization from ethanol.

3-Acetyl-4-hydroxy-2-methyl-5-phenyl-*1H*-pyrrol (19): a yellow solid, mp: decomposed at 236 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.52 (s, 1H, NH), 9.50 (s, 1H, OH), 7.16 (d, J = 7.7 Hz, 2H), 6.76 (t, J = 7.7 Hz, 2H), 6.51 (t, J = 7.35 Hz, 1H), 2.01 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.5, 145.2, 132.6, 131.8, 128.6, 124.2, 123.0, 111.3, 110.1, 23.7, 14.7. IR (KBr, cm^{-1}): 3250, 3130, 3050, 1638, 1562, 1476, 1394, 1216, 1083, 766, 713, 582. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.51; H, 6.10; N, 6.52.

Methyl 4-Hydroxy-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylate (20): a white solid, mp: decomposed at 233 °C. ^{1}H NMR (500

SCHEME 4. Plausible Mechanism for Reaction of Ethyl Acetoacetate with Phenylglyoxal in the Presence of NH_4OAc



SCHEME 5

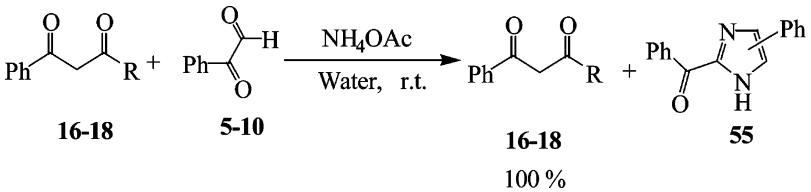
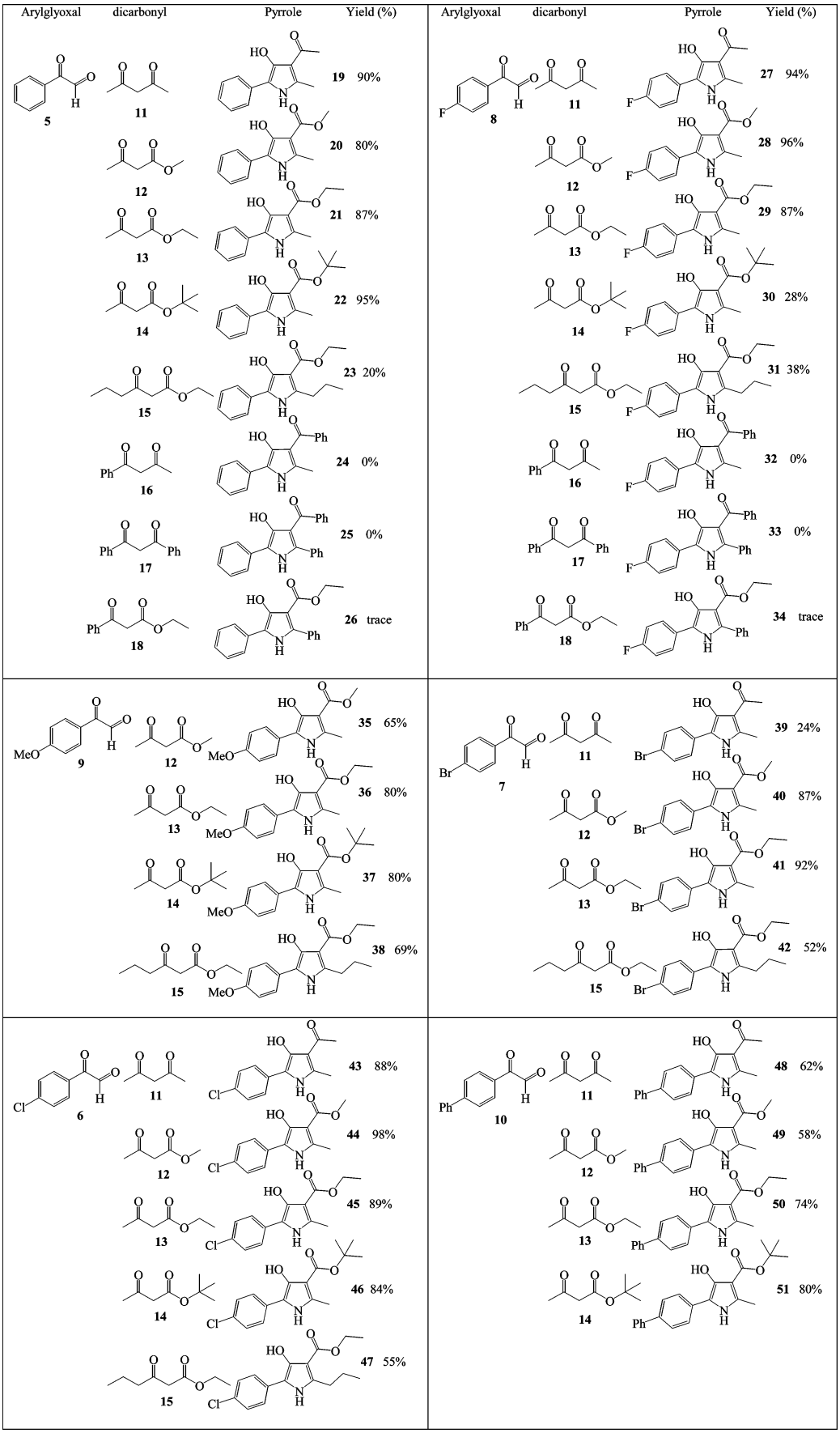


TABLE 1. Synthesis of 5-Aryl-(1H)-pyrrole-4-ol



MHz, DMSO-d_6): δ 10.55 (s, 1H, NH), 7.76 (m, 2H), 7.28 (m, 3H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.3, 145.3, 133.5, 132.8, 127.6, 126.2, 122.9, 112.5, 111.9, 60.3, 18.1. IR (KBr, cm^{-1}): 3209, 3060, 2947, 2883, 1713, 1659, 1538, 1444, 1342, 1194, 1038, 736, 643. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.46; H, 5.65; N, 6.16.

Ethyl 4-Hydroxy-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylate (21): a white solid, mp: decomposed at 232 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.54 (s, 1H, NH), 7.62 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.45 Hz, 2H), 7.15 (t, J = 7.40 Hz, 1H), 3.92 (q, J = 7.10 Hz, 2H), 2.50 (s, 3H), 1.42 (t, J = 7.15 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.2, 145.8, 133.0, 132.3, 128.9, 124.8, 123.9, 112.0, 110.9, 59.1, 17.8, 16.3. IR (KBr, cm^{-1}): 3230, 3068, 2981, 1690, 1660, 1518, 1443, 1333, 1182, 1079, 1036, 735. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.47; H, 6.12; N, 5.65.

***tert*-Butyl-4-hydroxy-2-methyl-5-phenyl-*1H*-pyrrole-3-carboxylate (22):** a white solid, mp: decomposed at 237 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H, NH), 7.77 (d, J = 5.35 Hz, 2H), 7.28 (m, 3H), 2.31 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.8, 145.8, 133.0, 132.3, 128.9, 124.8, 123.9, 112.0, 110.9, 79.8, 27.8, 14.44. IR (KBr, cm^{-1}): 3241, 3065, 2981, 2931, 1717, 1687, 1666, 1521, 1345, 1165, 1001, 729. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.29; H, 7.00; N, 5.08.

Ethyl 4-Hydroxy-5-phenyl-2-propyl-*1H*-pyrrole-3-carboxylate (23): a white solid, mp: decomposed at 237 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H, NH), 7.76 (d, J = 5.65 Hz, 2H), 7.16 (m, 3H), 3.91 (m, 2H), 2.73 (m, 2H), 1.51 (m, 1H), 1.39 (m, 1H), 1.10 (t, J = 7.05 Hz, 3H), 0.81 (t, J = 7.05 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.2, 145.4, 133.8, 132.9, 129.2, 125.1, 124.5, 112.7, 111.6, 56.0, 30.1, 24.2, 15.6, 14.7. IR (KBr, cm^{-1}): 3237, 3060, 2963, 2932, 2872, 1687, 1653, 1582, 1537, 1510, 1445, 1370, 1180, 1094, 1069, 739, 698. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.12; H, 6.93; N, 4.98.

3-Acetyl-5-(4-fluorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrol (27): a pale-yellow crystal (ethanol), mp: decomposed at 230 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.81 (s, 1H, NH), 7.82 (dd, J = 9.14 Hz, J = 5.36 Hz, 2H), 7.17 (m, 2H) 2.39 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.2, 162.0, 132.5, 130.4, 128.1, 118.5, 116.0, 113.5, 112.0, 26.3, 17.1. IR (KBr, cm^{-1}): 3358, 3185, 3060, 1676, 1626, 1513, 1416, 1311, 1237, 1168, 1114, 1086, 999, 950, 813, 760, 606. Anal. Calcd for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Found: C, 67.06; H, 4.98; N, 6.15.

Methyl 5-(4-Fluorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (28): a pale-pink solid, mp: decomposed at 248 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.57 (s, 1H, NH), 7.77 (m, 2H), 7.15 (t, J = 8.8 Hz, 2H), 3.46 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.3, 162.1, 132.8, 130.7, 127.9, 119.0, 116.7, 113.9, 112.1, 51.5, 17.7. IR (KBr, cm^{-1}): 3215, 3080, 2943, 1708, 1663, 1522, 1549, 1498, 1301, 1204, 1176, 1102, 1080, 1022, 811, 739, 598. Anal. Calcd for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.65; H, 4.92; N, 5.49.

Ethyl 5-(4-fluorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (29): a white solid, decomposed at 234 °C, ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.62 (s, 1H, NH), 7.80 (dd, J = 5.7 Hz, J = 7.95 Hz 2H), 7.15 (m, 2H), 3.93 (m, 2H), 2.36 (s, 3H), 1.09 (t, J = 7.1 Hz 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.1, 162.0, 132.5, 130.4, 128.1, 118.5, 116.0, 113.5, 112.0, 51.1, 17.2, 14.9. IR (KBr, cm^{-1}): 3205, 3072, 2984, 1738, 1551, 1549, 1518, 1333, 1241, 1188, 1112, 1076, 1031, 818, 749, 605. Anal. Calcd for $C_{14}H_{14}FNO_3$: C, 63.87; H, 5.36; N, 5.32. Found: C, 63.79; H, 5.50; N, 5.28.

***tert*-Butyl-5-(4-fluorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (30):** a pale-gray solid, mp: decomposed at 226 °C. ^{1}H NMR (500 MHz, DMSO-*d*): δ 10.45 (s, 1H, NH), 7.80 (dd, J = 9.1 Hz, J = 5.48 Hz, 2H), 7.16 (m, 2H) 2.32 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.1, 162.0, 132.5, 130.4, 128.1, 118.5, 116.0, 113.5, 112.0, 80.9, 28.3, 14.2. IR (KBr, cm^{-1}): 3213, 3076, 2980, 2931, 1708, 1643, 1547, 1518, 1454, 1386, 1245, 1156, 1120, 1076, 999, 842, 762, 605. Anal. Calcd for $C_{16}H_{18}FNO_3$: C, 65.97; H, 6.23; N, 4.81. Found: C, 66.0; H, 6.11; N, 5.01.

Ethyl 5-(4-Fluorophenyl)-4-hydroxy-2-propyl-*1H*-pyrrole-3-carboxylate (31): a pale-yellow solid, mp: decomposed at 234 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.52 (s, 1H, NH), 7.78 (m, 2H), 7.16 (m, 2H), 3.95 (m, 2H), 2.73 (m, 2H), 1.49 (m, 1H), 1.38 (m, 1H), 1.11 (t, J = 7.05 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.9, 160.7, 131.8, 130.9, 126.8, 119.1, 116.0, 112.8, 112.0, 56.1, 30.2, 24.1, 16.1, 14.7. IR (KBr, cm^{-1}): 3245, 3072, 2980, 1699, 1647, 1506, 1462, 1345, 1241, 1176, 1031, 842, 782, 681. Anal. Calcd for $C_{16}H_{18}FNO_3$: C, 65.97; H, 6.23; N, 4.81. Found: C, 66.0; H, 6.37; N, 4.80.

Methyl 4-Hydroxy-5-(4-methoxyphenyl)-2-methyl-*1H*-pyrrole-3-carboxylate (35): a pale-pink solid, mp: decomposed at 236 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH), 7.64 (d, J = 8.05 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 3.73 (s, 3H), 3.45 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.1, 157.1, 142.4, 137.8, 126.0, 125.1, 114.8, 114.6, 113.0, 60.0, 55.8, 14.44. IR (KBr, cm^{-1}): 3185, 3072, 3000, 2947, 1716, 1695, 1663, 1517, 1441, 1258, 1191, 1077, 1032, 775, 747, 634, 548. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.36; H, 5.82; N, 5.29.

Ethyl 4-Hydroxy-5-(4-methoxyphenyl)-2-methyl-*1H*-pyrrole-3-carboxylate (36): a pink solid, mp: decomposed at 232 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H, NH), 7.66 (d, J = 7.6 Hz, 2H), 6.82 (t, J = 8.45 Hz, 2H), 3.91 (q, J = 7.45 Hz, 2H), 2.35 (s, 3H), 1.09 (t, J = 6.75 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 181.5, 163.7, 159.8, 157.7, 129.2, 125.3, 125.0, 114.8, 113.3, 58.8, 55.9, 17.0, 15.1. IR (KBr, cm^{-1}): 3241, 3077, 2974, 1703, 1667, 1518, 1183, 1074, 745. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.43; H, 6.25; N, 5.08.

***tert*-Butyl-4-hydroxy-5-(4-methoxyphenyl)-2-methyl-*1H*-pyrrole-3-carboxylate (37):** a pale-pink solid, mp: decomposed at 241 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.32 (s, 1H, NH), 7.66 (d, J = 8.40 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 3.71 (s, 3H), 2.31 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.1, 157.1, 142.4, 137.8, 126.0, 125.1, 114.8, 114.6, 113.0, 81.2, 60.9, 28.9, 14.24. IR (KBr, cm^{-1}): 3241, 3076, 2976, 2935, 2839, 1712, 1647, 1518, 1365, 1333, 1261, 1156, 1080, 1011, 838, 774, 605. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.32; H, 7.04; N, 4.60.

Ethyl 4-Hydroxy-5-(4-methoxyphenyl)-2-propyl-*1H*-pyrrole-3-carboxylate (38): a pale-pink solid, mp: decomposed at 241 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.43 (s, 1H, NH), 7.68 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 3.97 (m, 2H), 3.71 (s, 3H), 2.78 (m, 2H), 1.48 (m, 1H), 1.35 (m, 1H), 1.11 (t, J = 7.05 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.3, 157.3, 141.4, 138.1, 126.5, 125.2, 114.7, 114.5, 113.1, 60.1, 55.8, 29.8, 23.9, 15.1, 14.5. IR (KBr, cm^{-1}): 3233, 2968, 1687, 1655, 1539, 1510, 1458, 1261, 1184, 1035, 689. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.22; H, 6.90; N, 4.59.

3-Acetyl-5-(4-bromophenyl)-4-hydroxy-2-methyl-*1H*-pyrrol (39): a white solid, mp: decomposed at 244 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.81 (s, 1H, NH), 9.68 (s, 1H, OH), 7.66 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 8.6 Hz, 2H), 2.31 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 198.7, 136.0, 132.9, 132.3, 131.1, 127.0, 118.2, 113.8, 112.1, 23.9, 15.3. IR (KBr, cm^{-1}): 3294, 2976, 2919, 1631, 1538, 1502, 1426, 1333, 1176, 999, 814, 774, 629. Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.17; H, 4.15; N, 4.78.

Methyl 5-(4-Bromophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (40): a pale-pink solid, mp: decomposed at 270 °C, ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.54 (s, 1H, NH), 7.64 (d, J = 8.15 Hz, 2H), 7.53 (d, J = 8.45 Hz, 2H), 3.47 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.1, 135.9, 132.7, 131.8, 130.0, 126.1, 117.9, 113.1, 111.3, 51.9, 17.7. IR (KBr, cm^{-1}): 3213,

3076, 2981, 2951, 1708, 1655, 1547, 1510, 1442, 1196, 1084, 1007, 762, 613. Anal. Calcd for $C_{13}H_{12}BrNO_3$: C, 50.34; H, 3.90; Br, 25.76; N, 4.52. Found: C, 50.32; H, 4.01; N, 4.43.

Ethyl 5-(4-Bromophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (41): a pink solid, mp: decomposed at 245 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.59 (s, 1H, NH), 7.68 (d, J = 8.25 Hz, 2H), 7.52 (d, J = 8.65 Hz, 2H), 3.94 (m, 2H), 2.37 (s, 3H), 1.10 (t, J = 7.05 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.3, 136.9, 132.1, 131.4, 129.3, 125.4, 117.2, 112.4, 110.7, 51.6, 17.7, 14.1. IR (KBr, cm^{-1}): 3196, 3068, 2980, 1705, 1651, 1542, 1513, 1397, 1328, 1187, 1080, 1034, 753, 689, 602. Anal. Calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.87; H, 4.28; N, 4.39.

Ethyl 5-(4-Bromophenyl)-4-hydroxy-2-propyl-*1H*-pyrrole-3-carboxylate (42): a pink solid, mp: decomposed at 235 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.51 (s, 1H, NH), 7.66 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 3.95 (m, 2H), 2.75 (m, 2H), 1.45 (m, 1H), 1.37 (m, 1H), 1.11 (t, J = 7.15 Hz, 3H), 0.80 (t, J = 7.35 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.3, 134.9, 132.0, 130.9, 130.2, 125.9, 117.2, 113.4, 112.1, 51.8, 17.7, 14.1. IR (KBr, cm^{-1}): 3241, 3068, 2972, 1694, 1650, 1510, 1397, 1336, 1180, 1082, 1007, 753, 682. Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.59; H, 5.07; N, 4.11.

3-Acetyl-5-(4-chlorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrol (43): a pink solid, mp: decomposed at 261 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.83 (s, 1H, NH), 7.87 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.35 Hz, 2H), 2.40 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.5, 145.0, 136.6, 133.8, 129.6, 128.2, 123.7, 111.3, 106.3, 23.7, 14.7. IR (KBr, cm^{-1}): 3302, 3068, 1639, 1547, 1498, 1325, 1096, 1019, 818, 621. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.48; H, 4.82; N, 5.69.

Methyl 5-(4-Chlorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (44): a pink solid, mp: decomposed at 261 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.55 (s, 1H, NH), 7.71 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 3.35 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.9, 144.9, 138.1, 133.4, 129.9, 129.0, 125.3, 112.7, 104.8, 61.1, 17.9. IR (KBr, cm^{-1}): 3229, 3076, 2943, 1704, 1647, 1510, 1192, 1072, 745. Anal. Calcd for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55; N, 5.27. Found: C, 58.78; H, 4.58; N, 5.20.

Ethyl 5-(4-Chlorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (45): a pale-pink solid, mp: decomposed at 244 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.61 (s, 1H, NH), 7.75 (d, J = 8.15 Hz, 2H), 7.39 (d, J = 8.65 Hz, 2H), 3.94 (m, 2H), 2.37 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.8, 144.8, 137.2, 133.0, 129.3, 128.8, 124.9, 112.0, 103.1, 58.7, 17.9, 15.8. IR (KBr, cm^{-1}): 3194, 3071, 2987, 2879, 1712, 1648, 1548, 1516, 1436, 1266, 1186, 1095, 1031, 755, 703, 635, 607. Anal. Calcd for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 60.15; H, 5.00; N, 5.11.

***tert*-Butyl-5-(4-chlorophenyl)-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (46):** a pale-pink solid, mp: decomposed at 238 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH), 7.76 (d, J = 8.25 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 2.35 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.3, 144.8, 137.0, 133.0, 129.31, 128.8, 124.9, 112.1, 102.9, 81.3, 28.9, 14.3. IR (KBr, cm^{-1}): 3217, 3080, 2980, 1708, 1651, 1514, 1402, 1156, 1003, 758. Anal. Calcd for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.32; H, 5.73; N, 4.59.

Ethyl 5-(4-Chlorophenyl)-4-hydroxy-2-propyl-*1H*-pyrrole-3-carboxylate (47): a pink solid, mp: decomposed at 241 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.51 (s, 1H, NH), 7.74 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 3.95 (q, J = 7.35 Hz, 2H), 2.75 (m, 2H), 1.47 (m, 1H), 1.34 (m, 1H), 1.11 (t, J = 6.2 Hz, 3H), 0.80 (t, J = 6.65 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.8, 144.8, 137.2, 133.0, 129.3, 128.8, 124.9, 112.0, 103.1, 56.1, 30.7, 23.8, 15.7, 14.3. IR (KBr, cm^{-1}): 3245, 3071, 2974, 1705, 1647, 1506, 1344, 1183, 759, 681. Anal. Calcd for $C_{18}H_{26}ClNO_3$: C, 63.61; H, 7.71; N, 4.12. Found: C, 63.52; H, 7.78; N, 4.11.

3-Acetyl-5-biphenyl-4-yl-4-hydroxy-2-methyl-*1H*-pyrrol (48): a dark-brown solid, mp: decomposed at 233 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.87 (s, 1H, NH), 7.90 (d, J = 7.15 Hz, 2H), 7.68 (d, J = 6.95 Hz, 2H), 7.65 (d, J = 7.75 Hz, 2H), 7.46 (t, J = 6.55 Hz, 2H), 7.38 (t, J = 6.65 Hz, 1H), 2.44 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 197.8, 141.8, 141.2, 132.9, 130.7, 129.9, 129.8, 129.2, 128.6, 127.9, 127.4, 124.8, 102.7, 24.3, 17.2. IR (KBr, cm^{-1}): 3394, 3068, 3036, 1671, 1635, 1498, 1410, 1313, 1168, 750. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.22; H, 5.89; N, 4.78.

Methyl 5-Biphenyl-4-yl-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (49): a cream solid, mp: decomposed at 225 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.61 (s, 1H, NH), 7.83 (m, 2H), 7.68 (d, J = 6.8 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 6.83 Hz, 2H), 7.37 (m, 1H), 3.33 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.0, 141.3, 140.8, 133.7, 130.8, 129.9, 129.0, 128.8, 127.6, 127.1, 126.4, 124.3, 101.7, 59.6, 17.8. IR (KBr, cm^{-1}): 3221, 3072, 2951, 1709, 1664, 1518, 1441, 1337, 1196, 1079, 1034, 755. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.25; H, 5.63; N, 4.40.

Ethyl 5-Biphenyl-4-yl-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (50): a cream solid, mp: decomposed at 233 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.68 (s, 1H, NH), 7.86 (m, 2H), 7.68 (d, J = 6.9 Hz, 2H), 7.63 (d, J = 7.7 Hz, 2H), 7.45 (t, J = 6.85 Hz, 2H), 7.38 (m, 1H), 3.90 (q, J = 6.8 Hz, 2H), 2.37 (s, 3H), 1.07 (t, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.6, 140.5, 140.0, 132.5, 129.8, 129.7, 128.6, 128.5, 127.4, 127.0, 126.1, 123.9, 100.7, 58.9, 17.1, 15.1. IR (KBr, cm^{-1}): 3213, 3061, 2977, 1724, 1659, 1514, 1196, 753. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.75; H, 5.89; N, 4.35.

***tert*-Butyl-5-biphenyl-4-yl-4-hydroxy-2-methyl-*1H*-pyrrole-3-carboxylate (51):** a pale-cream solid, mp: decomposed at 235 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H, NH), 7.86 (m, 2H), 7.66 (d, J = 6.9 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 6.85 Hz, 2H), 7.37 (m, 1H), 2.36 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.2, 141.3, 140.8, 133.7, 130.8, 129.9, 129.0, 128.8, 127.6, 127.1, 126.4, 124.3, 101.7, 81.1, 28.7, 14.9. IR (KBr, cm^{-1}): 3241, 3072, 2976, 1706, 1651, 1513, 1349, 1157, 1079, 1003, 841, 756. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.55; H, 6.58; N, 3.88.

2-Benzoyl-5(or **4)-phenyl-*1H*-imidazol (55):** a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.80 (s, 0.25H, NH), 13.63 (s, 1H, NH), 8.60 (d, J = 7.76 Hz, 2H), 8.47 (d, J = 7.7 Hz, 0.5H), 8.08 (s, 1H), 7.97 (d, J = 7.95 Hz, 0.5H), 7.94 (d, J = 7.64 Hz, 2H), 7.79 (s, 0.25H), 7.69 (t, J = 7.1 Hz, 1H), 7.66 (t, J = 7.6 Hz, 0.25H), 7.60 (t, J = 7.6 Hz, 2H), 7.57 (t, J = 8.1 Hz, 0.5H), 7.47 (t, J = 7.55 Hz, 0.5H), 7.42 (t, J = 7.7 Hz, 2H), 7.37 (t, J = 7.1 Hz, 0.25H), 7.28 (t, J = 7.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 181.6, 146.6, 145.5, 143.7, 137.0, 136.8, 136.6, 134.5, 133.9, 133.7, 131.5, 131.4, 129.8, 129.5, 129.1, 129.0, 128.0, 126.5, 125.7, 119.5. IR (KBr, cm^{-1}): 3270, 1621, 1454, 1280, 1164, 906, 771, 687. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.39; H, 4.73; N, 11.17.

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Supporting Information Available: Preparation procedures, ^{1}H NMR spectra of compounds **19**−**23**, **27**−**31**, **35**−**51**, and **55**. This material is available free of charge via the Internet at http://pubs.acs.org.

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