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Dimethyl Sulfoxide Participant Iron-Mediated Cascade Oxidation/α-Formylation Reaction of Substituted 2,3-Dihydropyrroles under Air and Protonic Acid Free Condition

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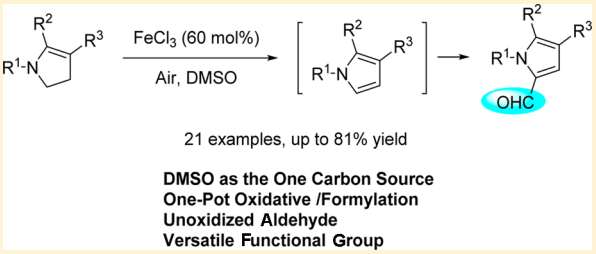
Supporting Information

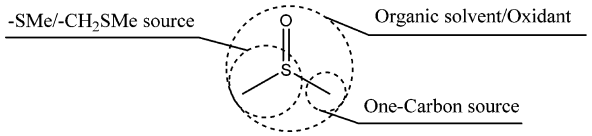
ABSTRACT: An efficient and Brønsted acid free one-pot protocol to directly generate structurally sophisticated α-formylpyrrole derivatives in moderate to good yields has been demonstrated, involving an iron-mediated domino oxidation/formylation reaction of readily available 2,3-dihydro-1*H*-pyrroles in dimethyl sulfoxide and air atmosphere, in which dimethyl sulfoxide acts as the formyl donor. A possible mechanism is presented.



INTRODUCTION

Dimethyl sulfoxide[1] (DMSO) can act as an organic solvent,[2] oxidant (Pfitzner−Moffatt oxidation, Pummerer rearrangement),[3,4] -SMe/-CH_2SMe source,[5,6] Me source,[7,8] -CN source,[9] and ligand.[10,11] Besides, as a one-carbon source, it can also transform to a formyl group (Scheme 1).[12−14] In 2000, Suzuki et al. obtained the 3-formyl derivatives of some nitroanilines via nuclear formylation reaction in DMSO in the presence of a strong base such as ^{t}BuOK or NaH.[12] Formylation and dimerization of *p*-alkyl-substituted phenols also has been achieved by Yu's group in 2012 by using DCMT-activated DMSO.[13] Very recently, several valuable reactions that avoided the use of too harsh one-carbon donors (such as the Vilsmeier−Haack reagent) have been achieved by using DMSO as a one-carbon source in the presence of transition metal catalysts. Cheng's group developed an NH_4OAc-promoted C3-formylation of indoles under nearly neutral conditions with DMSO serving as a carbonyl reagent.[15] A direct C−H formylation of C(3) on indoles and C(2) on pyrrole (*N*-phenyl-1*H*-pyrrole was the only example) was also developed by Chiba's group using DABCO as an additive in DMSO.[14] Zhang et al. reported a Cu-catalyzed method for the synthesis of quinazolines by using amidines and a sp^3-carbon donor DMSO in 2013.[16] Critically reviewing the literatures, the highly efficient transition-metal-catalyzed formylation of a wide range of substrates is worthy of further exploration by using DMSO as the carbonyl reagent.

Scheme 1. Multipurpose DMSO



α-Formylpyrroles as one of the most important five-membered heterocyclic synthons[17−20] have been used for the preparation of many biologically active compounds, including some very important linked polycyclic systems[18] (such as the well-known compounds porphyrins[20−23]), fused-ring compounds,[19,24] and highly functional pyrrole derivatives.[25−28] The Vilsmeier−Haack reaction is the most classical method for the synthesis of α-formylpyrroles.[25,29,30] However, it requires a stoichiometric amount or even more of $POCl_3$, which is not environmentally benign. Oxidation of a methyl[20,21,31] or methylene alcohol[18,19,21] at the 2-position or conversion an α-ester group into the aldehyde group via a multistep process[23] are also two powerful methods leading to α-formylated pyrroles. However, these methods often require prepreparation of α-functionalized pyrroles, which needs additional reaction steps and thus affects the efficiency of the reactions. Overall, a more facile route is the reaction of pyrroles with a one-carbon donor undergoing an intermolecular reaction. Of course, in this process, it would be better to consider a more moderate one-carbon donor. Herein, we present a recent study of oxidative dehydrogenation/α-formylation of 1*H*-pyrroles **1** in the presence of $FeCl_3$ and air atmosphere, where DMSO acts as both the carbonyl source and solvent.

RESULTS AND DISCUSSION

During the course of our studies on the transformation of easily accessible acetoacetamide derivatives to highly functionalized *N*-containing heterocyclic compounds,[32−36] we found sub-

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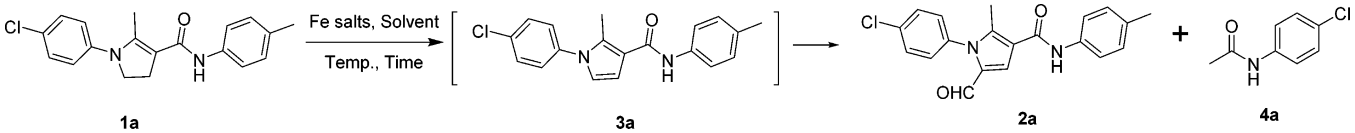
Table 1. Survey of Reaction Conditions[a]



entry	catalyst (equiv)	temp, °C	time, h	yield **2a** (**4a**), %[b]
1	$FeCl_3$ (0)	165	12	trace (38)
2	$FeCl_3$ (0.2)	90 + 165	24 + 16	61 (11)
3	$FeCl_3$ (0.4)	90 + 165	7 + 12	70 (4)
4	$FeCl_3$ (0.6)	90 + 165	6 + 10	81 (trace)
5	$FeCl_3$ (1.0)	90 + 165	4 + 6	30 (11)
6[c]	$FeCl_3$ (0.6)	90 + 165	2 + 4	25 (30)
7	$FeCl_3{\cdot}6H_2O$ (0.6)	90 + 150	7 + 13	61 (6)
8	$Fe(OTf)_3$ (0.6)	90 + 145	7 + 4	25 (28)
9	$Fe(NO_3)_3{\cdot}9H_2O$ (0.6)	90 + 165	4 + 8	40 (20)
10	$Fe_2(SO_4)_3{\cdot}xH_2O$ (0.6)	90 + 165	6 + 11	35 (20)
11	$FeCl_2{\cdot}4H_2O$ (0.6)	90 + 145	10 + 8	64 (6)
12	$Fe(acac)_2$ (0.6)	140 + 165	5 + 10	20 (31)
13	$FeSO_4{\cdot}7H_2O$ (0.6)	90 + 165	55 + 6	30 (25)
14	Fe (0.6)	130 + 165	6 + 10	37 (20)

[a]Unless otherwise indicated, all reactions were carried out with **1a** (1.0 mmol) and DMSO 5.0 mL. [b]The value in parentheses is the yield of byproduct *N*-(4-chlorophenyl)acetamide **4a**. [c]The reaction was performed in O_2.

stituted 2,3-dihydropyrroles can afford γ-amino ketones via a ring-opening reaction.[37] We are also interested in the further functionalization of 2,3-dihydropyrroles, which can be readily prepared in high yield by the reaction of doubly activated cyclopropanes with amines.[38] Meanwhile, we noted that Su et al. reported a mild Ru-catalyzed C(3) formylation of indoles using anilines as the carbonyl source in 2011.[39] Cheng's group developed two methods of C(3) formylation of indoles recently, and in the processes TMEDA[40] and DMSO,[15] respectively, served as a carbonyl reagent. Accordingly, we postulated that it is possible to realize the α-formylation of 2,3-dihydropyrroles in the presence of an effective, reusable, operationally simple, and environmentally benign catalyst, such as iron salts.[41−44] Our investigation began with the reaction of 1-(4-chlorophenyl)-2-methyl-*N*-(*p*-tolyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide (**1a**) and 100 mol % $FeCl_3$ in DMSO at 90 °C for 6 h and then at 165 °C for 10 h. The desired 1-(4-chlorophenyl)-5-formyl-2-methyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide (**2a**) was obtained in 30% yield, and the intermediate **3a** did not need to be isolated. Simultaneously, byproduct *N*-(4-chlorophenyl)acetamide **4a** was isolated in 11% yield from the complex mixture[45] (Table 1, entry 5). The result encouraged us to further optimize the reaction conditions. After a series of attempts, we were pleased to find that the yield of **2a** could be enhanced to 81% in the presence of 0.6 equiv of $FeCl_3$ (Table 1, entry 4). When the reaction was performed in O_2 atmosphere, some unidentified complex mixture was obtained and the yield of **2a** dropped to 25% (Table 1, entry 6). Subsequently, a series of other iron salts, including $FeCl_3{\cdot}6H_2O$, $Fe(OTf)_3$, $Fe(NO_3)_3{\cdot}9H_2O$, $Fe_2(SO_4)_3{\cdot}xH_2O$, $FeCl_2{\cdot}4H_2O$, $Fe(acac)_2$, $FeSO_4{\cdot}7H_2O$, and even Fe, were also tested (entries 7−14) and also displayed catalytic efficiency for the reaction but were inferior to anhydrous $FeCl_3$.

With these optimized conditions in hand, we next explored the scope and generality of the process with respect to the position of the different substituents on the benzene ring of the *N*-phenyl and pyrrole rings of **1**, and the results are summarized in Table 2. Initial investigation mainly focused on the effect of the position and the electronic effect of the substituents on the benzene ring of the *N*-phenyl and amide moiety. It was disclosed that electron-donating groups (EDG) (Me, -OMe) and electron-withdrawing groups (EWG) (-Cl, $-CO_2Et$) on the *N*-phenyl ring were tolerated in the transformation and gave the compounds **2a**−**2k**, in 40−81% yields, including the products with no substituents on the *N*-phenyl ring (compounds **2l** and **2m**, 75% and 71% yields, respectively). 2-Phenyl- or 3-carboxylate-substituted starting materials such as **1n**−**1s** generally gave moderate yields (41−78%). *N*-Aliphatic-substituted pyrroles such as *N*-(*tert*-butyl) pyrroles **1t** and **1u** gave **2t** and **2u** in moderate yields together with some complex decomposition products.[46] In fact, all of the reactions produced a black complex mixture due to the decomposition of **1** at the high reaction temperatures, which should account for the low yields of the reactions.[37]

In order to shed light on the reaction mechanism, several control reactions were conducted. First, the reaction was performed in N_2 atmosphere, and as a result, only a trace amount of **2a** was observed along with an unidentified complex mixture, which indicated that air is required for the transformation (eq 1). Oxygen-involved reaction may proceed via a radical mechanism.[47−49] Two kinds of radical inhibitors such as TEMPO and duroquinone were then added to the mixture to test if one or both of the two steps of the reaction (from **1a** to **3a** and **3a** to **2a**) proceed through a free radical pathway, and it was found that the reaction was completely inhibited (eqs 2−5). These results suggest that a radical process is involved in this transformation.[50] Furthermore, the experiment that was carried out in deuterated d_6-DMSO to obtain further insight into the transformation clearly showed that there was completely deuterated formyl at the α-position of pyrrole ***d*-2a** (eq 6).

On the basis of all of the results described above together with previous literature,[15,39,40,51,52] especially several papers concerning the variant of the Pummerer reaction,[13,15,53] a possible mechanism of this transformation is proposed in Scheme 2. The reaction starts from a single electron-transfer

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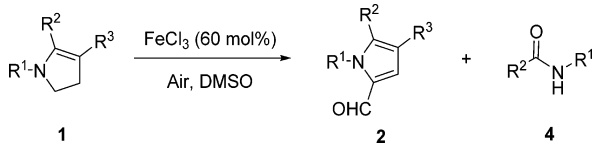
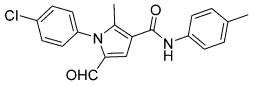
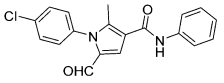
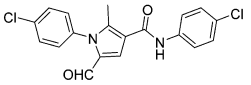
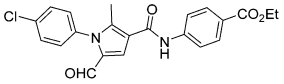
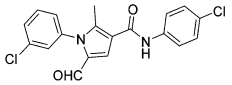
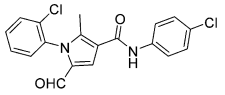
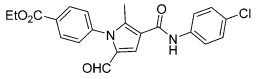
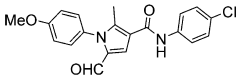
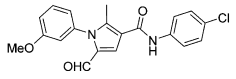
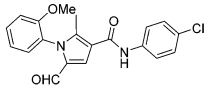
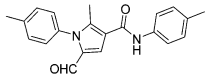
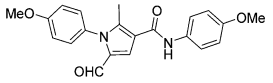
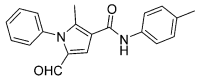
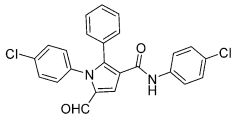
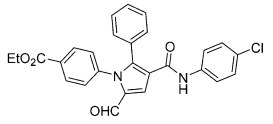
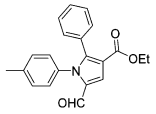
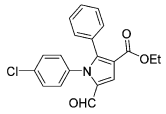
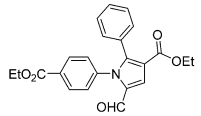
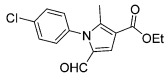
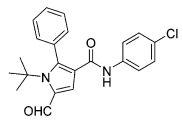
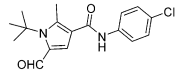
Table 2. Reaction Extension[a]



1 2 4

 **2a:** 90 °C, 7 h; 165 °C, 6 h 81% (trace)	 **2b:** 90 °C, 8 h; 165 °C, 7 h 71% (7%)	 **2c:** 90 °C, 9 h; 165 °C, 5 h 81% (trace)
 **2d:** 90 °C, 11 h; 150 °C, 12 h 40% (22%)	 **2e:** 90 °C, 8 h; 165 °C, 8 h 78% (trace)	 **2f:** 90 °C, 9 h; 165 °C, 6 h 73% (trace)
 **2g:** 90 °C, 6 h; 165 °C, 7 h 45% (18%)	 **2h:** 90 °C, 9 h; 150 °C, 8 h 62% (12%)	 **2i:** 90 °C, 8 h; 150 °C, 13 h, 48% (25%)
 **2j:** 90 °C, 7 h; 150 °C, 8 h 54% (18%)	 **2k:** 90 °C, 7 h; 165 °C, 8 h 73% (trace)	 **2l:** 90 °C, 8 h; 150 °C, 9 h 61% (10%)
 **2m:** 90 °C, 6 h; 165 °C, 8 h 75% (trace)	 **2n:** 90 °C, 10 h; 165 °C, 7 h 78% (trace)	 **2o:** 90 °C, 11 h; 165 °C, 7 h 59% (12%)
 **2p:** 90 °C, 8 h; 165 °C, 10.5 h 48% (19%)	 **2q:** 90 °C, 12 h; 165 °C, 10 h 59% (12%)	 **2r:** 90 °C, 8 h; 165 °C, 8 h 63% (15%)
 **2s:** 90 °C, 6 h; 165 °C, 6 h 41% (22%)	 **2t:** 90 °C, 7 h; 150 °C, 10 h 75% (trace)	 **2u:** 90 °C, 8 h; 150 °C, 13 h 53% (22%)

[a]Unless otherwise indicated, all reactions were carried out with **1** (1.0 mmol), $FeCl_3$ (0.6 equiv) in DMSO (5 mL). The value in parentheses is the yield of byproducts **4**.

oxidation of 2,3-dihydro-1*H*-pyrroles **1** by Fe^{3+} and O_2 in air to generate radical species **A**.[54−56] Then, **A** leads to 1*H*-pyrroles **3** via the sequential loss of hydrogen radicals and protons.[57,58] After a single electron-transfer oxidation, **3** gives intermediate **C**.[55] Radical coupling of **C** and methyl radical (formed from DMSO in the presence of ferric salts and O_2)[7] leads to methylated 1*H*-pyrrole derivatives **5**. Subsequently, a single electron-transfer oxidation of **5** generates intermediate **D**.[59] Radical **D** is then trapped by dioxygen to provide peroxy radical **E**, which is eventually converted into α-formylpyrroles **2**.[48] It is

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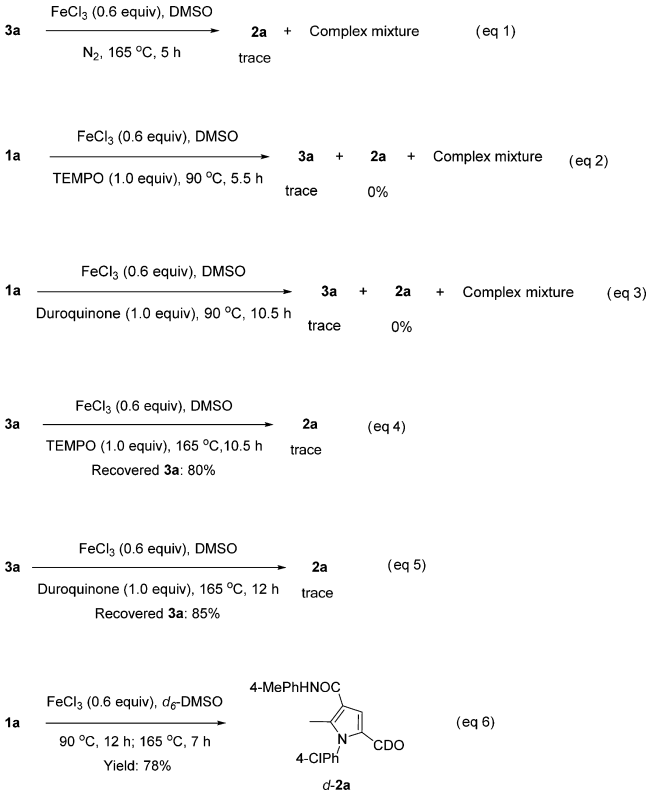
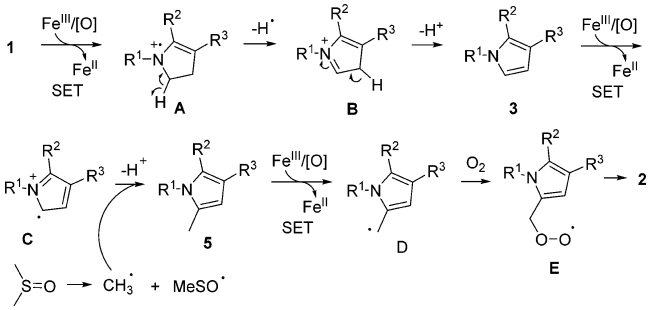


Scheme 2. Proposed Mechanism



noteworthy that the formylpyrrole **2a** could be isolated in 26% yield when 1-(4-chlorophenyl)-2,5-dimethyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide **5a** was used for the reaction in the presence of $FeCl_3$ (0.6 equiv) in DMSO at 165 °C after 9 h, which further confirmed the rationality of processes of **5** → **2**.[14,48] Besides, at present, the Pummerer reaction mechanistic pathway does not be excluded from **3** to **2**. The DMSO was polarized by iron, and then transferred to the pyrrole intermediate, and the resulting sulfide hydrolyzed to the CHO unit.[15]

CONCLUSION

In conclusion, we have developed an efficient Fe-catalyzed tandem oxidation/formylation reaction of readily available 1*H*-pyrroles to give the corresponding α-formyled multisubstituted pyrrole derivatives in moderate to good yields with DMSO serving as the formyl donor. A wide range of substrates were investigated to show the generality of the process. The advantages of this new method are the ease of preparation of substrates, operational simplicity, and use of inexpensive and environmentally friendly $FeCl_3$ as the catalyst and O_2 as the oxidant.

EXPERIMENTAL SECTION

General Information. *Materials.* Compounds **1**[38] and **5**[60] were prepared according to the reported procedures. Anhydrous $FeCl_3$ was purchased from Aladdin. Unless otherwise indicated, DMSO were purchased from commercial sources and used without purification.

Analytical Methods. All reagents were purchased from commercial sources and used without further treatment. DMSO was distilled under reduced pressure from CaH_2 and stored over molecular sieves. All reactions were carried out under air atmosphere. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded on a 400 MHz NMR spectrometer (^1H, 400 MHz; $^{13}C\{^1H\}$, 100 MHz at 25 °C) with TMS as internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hz. All high-resolution mass spectra (HRMS) were measured on a mass spectrometer (ESI-oa-TOF), and the purity of all samples used for HRMS (>95%) was confirmed by ^1H and $^{13}C\{^1H\}$ NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and are uncorrected. All reactions were monitored by LC−MS. Flash chromatography was carried out on SiO_2 (silica gel 200−300 mesh).

Typical Experimental Procedure for the Synthesis of 2 (2a as an Example). To a round-bottom flask (25 mL) equipped with a drying tube (filled with calcium chloride) were added 1-(4-chlorophenyl)-2-methyl-*N*-(*p*-tolyl)-4,5-dihydro-1*H*-pyrrole-3-carboxamide **1a** (326 mg, 1 mmol) and anhydrous $FeCl_3$ (97.5 mg, 0.6 mmol), the mixture was well stirred for 7 h in anhydrous DMSO (5 mL) at 90 °C, and then the reaction system was heated to 165 °C for 6 h. After cooling, 1 M HCl (10 mL) and water (5 mL) were added, the mixture was extracted with CH_2Cl_2 (20 mL × 3), and the organic layer was then dried over sodium sulfate and concentrated in vacuo. The crude compound was purified via flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) to provide 1-(4-chlorophenyl)-5-formyl-2-methyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide **2a** in 81% yield (286 mg) as a white solid.

1-(4-Chlorophenyl)-5-formyl-2-methyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide (2a). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (286 mg, 81%). Mp 232−235 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.81 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.36 (s, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.4, 162.4, 143.5, 135.5, 135.4, 134.8, 134.0, 132.1, 129.8, 129.6, 129.0, 120.3, 118.2, 20.9, 12.0, one carbon was not observed. HRMS (ESI) m/z calcd for $C_{20}H_{17}ClN_2O_2$ $[M + H]^+$ 353.1051, found 353.1077.

1-(4-Chlorophenyl)-5-formyl-2-methyl-*N*-phenyl-1*H*-pyrrole-3-carboxamide (2b). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (241 mg, 71%). Mp 193−196 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.74 (s, 1H), 7.61 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.39−7.35 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 178.5, 162.6, 143.7, 138.0, 135.7, 134.9, 132.3, 129.9, 129.2, 129.1, 124.5, 120.3, 118.8, 118.3, 12.1. HRMS (ESI), m/z calcd for $C_{19}H_{15}ClN_2O_2$ $[M + H]^+$ 339.0895, found 339.0870.

***N*,1-Bis(4-chlorophenyl)-5-formyl-2-methyl-1*H*-pyrrole-3-carboxamide (2c).** The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 2:5) as a white solid (302 mg, 81%). Mp 253−258 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.38 (s, 1H), 7.85 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.5, 162.4, 143.1, 138.2, 135.2, 133.7, 131.4, 129.7, 129.3, 128.4, 126.8, 121.6, 120.7, 117.4, 11.7. HRMS (ESI) m/z calcd for $C_{19}H_{14}Cl_2N_2O_2$ $[M + H]^+$ 373.0505, found 373.0513.

Ethyl 4-(1-(4-Chlorophenyl)-5-formyl-2-methyl-1*H*-pyrrole-3-carboxamido)benzoate (2d). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (164 mg, 40%). Mp 173−176 °C. ^1H NMR (400 MHz,

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DMSO-d_6) δ 10.22 (s, 1H), 9.38 (s, 1H), 7.94−7.90 (m, 5H), 7.62 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.6, 165.4, 162.7, 143.8, 143.5, 135.2, 133.8, 131.4, 130.1, 129.8, 129.3, 124.2, 120.9, 119.3, 117.3, 60.4, 14.3, 11.8. HRMS (ESI) m/z calcd for $C_{22}H_{19}ClN_2O_4$ $[M + Na]^+$ 433.0926, found 433.0914.

1-(3-Chlorophenyl)-*N*-(4-chlorophenyl)-5-formyl-2-methyl-1*H*-pyrrole-3-carboxamide (2e). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (291 mg, 78%). Mp 203−205 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.38 (s, 1H), 7.85 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.64−7.55 (m, 3H), 7.41−7.38 (m, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.5, 162.4, 143.2, 138.3, 137.7, 133.5, 131.4, 130.8, 129.3, 128.5, 128.0, 126.9, 126.8, 121.6, 117.4, 11.7, one carbon was not observed. HRMS (ESI) m/z calcd for $C_{19}H_{14}Cl_2N_2O_2$ $[M + H]^+$ 373.0505, found 373.0505.

1-(2-Chlorophenyl)-*N*-(4-chlorophenyl)-5-formyl-2-methyl-1*H*-pyrrole-3-carboxamide (2f). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 2:5) as a white solid (272 mg, 73%). Mp 171−175 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 9.38 (s, 1H), 7.85 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.65−7.54 (m, 3H), 7.39 (m, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.5, 162.4, 143.2, 138.2, 137.7, 133.4, 131.4, 130.8, 129.3, 128.5, 127.9, 126.9, 126.8, 121.6, 120.9, 117.4, 11.7. HRMS (ESI) m/z calcd for $C_{19}H_{14}Cl_2N_2O_2$ $[M + H]^+$ 373.0505, found 373.0502.

Ethyl 4-(3-((4-Chlorophenyl)carbamoyl)-5-formyl-2-methyl-1*H*-pyrrol-1-yl)benzoate (2g). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (185 mg, 45%). Mp 200−202 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.39 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.88 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 179.0, 165.5, 162.8, 143.5, 140.8, 138.7, 131.7, 130.8, 130.5, 128.9, 128.8, 127.3, 122.0, 121.6, 118.1, 61.6, 14.6, 12.2. HRMS (ESI) m/z calcd for $C_{22}H_{19}ClN_2O_4$ $[M + Na]^+$ 433.0926, found 433.0924.

***N*-(4-Chlorophenyl)-5-formyl-1-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (2h).** The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (229 mg, 62%). Mp 203−204 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.32 (s, 1H), 7.81 (s, 1H), 7.80 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.7, 162.6, 159.5, 143.1, 138.3, 131.8, 129.1, 128.5, 126.8, 121.6, 119.1, 117.1, 114.5, 55.5, 11.8, one carbon was not observed. HRMS (ESI) m/z calcd for $C_{20}H_{17}ClN_2O_3$ $[M + H]^+$ 369.1000, found 369.1004.

***N*-(4-Chlorophenyl)-5-formyl-1-(3-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (2i).** The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (177 mg, 48%). Mp 143−146 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.33 (s, 1H), 7.83 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 8.0, 2.0 Hz, 1H), 7.02 (t, J = 2.0 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.6, 162.5, 159.8, 142.7, 138.3, 137.0, 131.6, 130.1, 128.4, 126.8, 121.5, 120.0, 119.0, 117.2, 115.0, 113.7, 55.5, 11.8. HRMS (ESI) m/z calcd for $C_{20}H_{17}ClN_2O_3$ $[M + H]^+$ 369.1000, found 369.0981.

***N*-(4-Chlorophenyl)-5-formyl-1-(2-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (2j).** The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (199 mg, 54%). Mp 141−145 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 9.29 (s, 1H),7.81−7.80 (m, 3H), 7.53 (td, J = 7.6, 1.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 7.6, 1.6 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.10 (t, J = 7.6, 1H), 3.74 (s, 3H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.5, 162.6, 154.7, 143.0, 138.3, 131.3, 130.9, 129.2, 128.5, 126.8, 124.5, 121.6, 120.7, 117.3, 112.6, 55.8, 11.4, one carbon was not observed. HRMS (ESI) m/z calcd for $C_{20}H_{17}ClN_2O_3$ $[M + H]^+$ 369.1000, found 369.1018.

5-Formyl-2-methyl-*N*,1-di-*p*-tolyl-1*H*-pyrrole-3-carboxamide (2k). The product was isolated by flash chromatography (eluent ethyl acetateethyl acetate/petroleum ether = 1:4) as a white solid (242 mg, 73%). Mp 249−251 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.73 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.15 (m, 4H), 2.45 (s, 3H), 2.41 (s, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 179.1, 162.8, 143.4, 139.8 135.6, 134.0, 133.6, 132.6, 130.3, 129.9, 129.7, 127.6, 120.4, 118.1, 21.4, 21.0, 12.2. HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2O_2$ $[M + Na]^+$ 355.1417, found 355.1400.

5-Formyl-*N*,1-bis(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (2l). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:2) as a white solid (222 mg, 61%). Mp 116−120 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.31 (s, 1H), 7.79 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6)δ 178.5, 162.2, 159.4, 155.3, 142.7, 132.4, 131.7, 129.0, 128.6, 121.7, 119.0, 117.5, 114.4, 113.7, 55.4, 55.2, 11.7. HRMS (ESI) m/z calcd for $C_{21}H_{20}N_2O_4$ $[M + H]^+$ 365.1496, found 365.1493.

5-Formyl-2-methyl-1-phenyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide (2m). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:4) as a white solid (239 mg, 75%). Mp 161−163 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.33 (s, 1H), 7.84 (s, 1H), 7.63 (d, J = 6.4 Hz, 2H), 7.55 (s, 3H), 7.41 (s, 2H), 7.13 (d, J = 6.8 Hz, 2H), 2.31 (s, 3H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 178.5, 162.3, 142.7, 136.8, 136.2, 132.2, 131.5, 129.4, 129.1, 129.0, 127.9, 120.2, 119.8, 117.7, 20.5, 11.8. HRMS (ESI) m/z calcd for $C_{20}H_{18}N_2O_2$ $[M + Na]^+$ 341.1260, found 341.1239.

***N*,1-Bis(4-chlorophenyl)-5-formyl-2-phenyl-1*H*-pyrrole-3-carboxamide (2n).** The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:4) as a white solid (339 mg, 78%). Mp 229−233 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.50 (s, 1H), 7.87 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.32 (m, 4H), 7.28−7.18 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 179.4, 161.6, 143.4, 138.2, 135.3, 133.2, 132.0, 130.7, 130.4, 129.4, 128.7, 128.5, 128.4 127.6, 126.8, 121.3, 120.4, 119.6. HRMS (ESI) m/z calcd for $C_{24}H_{16}Cl_2N_2O_2$ $[M + H]^+$ 435.0662, found 435.0682.

Ethyl 4-(3-((4-Chlorophenyl)carbamoyl)-5-formyl-2-phenyl-1*H*-pyrrol-1-yl)benzoate (2o). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (279 mg, 59%). Mp 223−226 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.51 (s, 1H), 7.90 (s, 1H), 7.89 (d, J = 6.8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.22 (s, 5H), 4.30 (q, J = 6.8 Hz, 2H), 1.30 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 179.5, 165.0, 161.6, 143.3, 140.6, 138.2, 131.9, 130.7, 129.9, 129.5, 129.3, 129.1, 128.6, 128.5, 127.6, 126.9, 121.4, 120.9, 119.8, 61.1, 14.1. HRMS (ESI) m/z calcd for $C_{27}H_{21}ClN_2O_4$ $[M + H]^+$ 473.1263, found 473.1260.

Ethyl 5-Formyl-2-phenyl-1-(*p*-tolyl)-1*H*-pyrrole-3-carboxylate (2p). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:4) as a white solid (160 mg, 48%). Mp 165−167 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.60 (s, 1H), 7.31−7.17 (m, 5H), 7.16−7.06 (m, 4H), 4.06 (q, J = 7.0 Hz, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 179.6, 162.7, 144.7, 138.1, 133.7, 132.6, 130.8, 129.5, 129.2, 128.6, 128.2, 127.4, 121.9, 115.1, 59.6, 20.6, 13.9. HRMS (ESI) m/z calcd for $C_{21}H_{19}NO_3$ $[M + Na]^+$ 356.1257, found 356.1236.

Ethyl 1-(4-Chlorophenyl)-5-formyl-2-phenyl-1*H*-pyrrole-3-carboxylate (2q). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:4) as a white solid (209 mg, 59%). Mp 186−187 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.66 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.30−7.23 (m, 7H), 4.07 (q, J = 6.8 Hz, 2H), 1.06 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 179.7, 162.6, 145.0, 135.6, 133.2, 132.4, 130.8,

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130.3, 129.2, 128.7, 128.6 127.5, 123.3, 115.3, 59.7, 13.9. HRMS (ESI) m/z calcd for $C_{20}H_{16}ClNO_3$ $[M + H]^+$ 354.0891, found 354.0892.

Ethyl 1-(4-(Ethoxycarbonyl)phenyl)-5-formyl-2-phenyl-1*H*-pyrrole-3-carboxylate (2r). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (246 mg, 63%). Mp 112−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.25−7.13 (m, 7H), 4.34 (q, J = 7.2 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 165.5, 163.3, 145.4, 140.6, 132.4, 130.7, 130.7, 130.1, 129.2, 129.0, 128.3, 127.8, 124.1, 116.4, 61.4, 60.3, 14.3, 14.1. HRMS (ESI) m/z calcd for $C_{23}H_{21}NO_5$ $[M + H]^+$ 392.1492, found 392.1495.

Ethyl 1-(4-Chlorophenyl)-5-formyl-2-methyl-1*H*-pyrrole-3-carboxylate (2s). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (120 mg, 41%). Mp 89−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.48 (d, J = 8.4 Hz, 3H),7.47 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.4, 164.3, 144.6, 135.5, 132.2, 129.8, 129.7, 129.0, 124.3, 115.3, 60.3, 14.6, 12.1. HRMS (ESI) m/z calcd for $C_{15}H_{14}ClNO_3$ $[M + H]^+$ 292.0695, found 292.0692.

1-(*tert*-Butyl)-*N*-(4-chlorophenyl)-5-formyl-2-phenyl-1*H*-pyrrole-3-carboxamide (2t). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:4) as a white solid (286 mg, 75%). Mp 225−228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.75 (s, 1H), 8.10 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.40 (s, 5H), 7.28 (d, J = 8.8 Hz, 2H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 186.3, 161.6, 139.1, 138.3, 133.1, 133.0, 131.8, 128.7, 128.5, 127.5, 126.5, 120.54, 120.50, 119.1, 59.9, 30.9. HRMS (ESI) m/z calcd for $C_{22}H_{21}ClN_2O_2$ $[M + H]^+$ 381.1383, found 381.1392.

1-(*tert*-Butyl)-*N*-(4-chlorophenyl)-5-formyl-2-methyl-1*H*-pyrrole-3-carboxamide (2u). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (169 mg, 53%). Mp 201−203 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 9.61 (s, 1H), 8.02 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 2.78 (s, 3H), 1.64 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 187.2, 162.7, 140.5, 138.5, 136.3, 128.9, 126.8, 121.1, 120.1, 115.7, 58.9, 30.0, 14.4. HRMS m/z calcd for $C_{17}H_{19}ClN_2O_2$ $[M + H]^+$ 319.1208, found 319.1218.

1-(4-Chlorophenyl)-5-(formyl-*d*)-2-methyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide (*d*-2a). The product was isolated by flash chromatography (eluent ethyl acetate/petroleum ether = 1:3) as a white solid (276 mg, 78%). Mp 230−232 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.85 (s, 1H), 7.64−7.60 (m, 4H), 7.44 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 2.32 (s, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 178.9, 162.7, 143.4, 137.2, 135.7, 134.1, 132.6, 131.8, 130.2, 129.8, 129.4, 121.3, 120.6, 118.3, 20.9, 12.2. HRMS (ESI) m/z calcd for $C_{20}H_{16}DClN_2O_2$ $[M + H]^+$ 354.1114, found 354.1114.

1-(4-Chlorophenyl)-2,5-dimethyl-*N*-(*p*-tolyl)-1*H*-pyrrole-3-carboxamide (5a).[60] The product was isolated by flash chromatography as a white solid (83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 4H), 7.41 (s, 1H), 7.14 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 4H), 6.18 (s, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2. 01 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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