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Synthesis of Polysubstituted Pyrroles through Electro-Oxidative Annulation of 1,3-Dicarbonyl Compounds and Primary Amines

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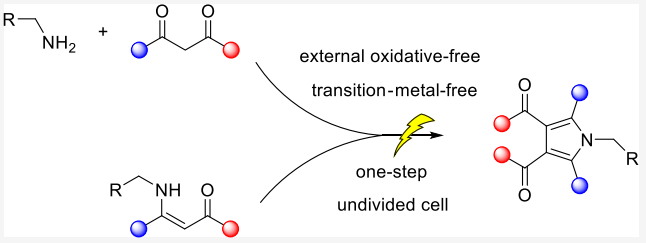
ABSTRACT: Reported herein is a synthetic method of polysubstituted pyrroles from easily available materials, 1,3-dicarbonyl compounds and primary amines, via electro-oxidative intermolecular annulation. Under similar conditions, enamines are also converted smoothly into desired products, indicating that *in situ* formed enamines are crucial intermediates for the first transformation. Neither transition-metal salts nor harsh conditions are required to facilitate the dehydrocyclization process.



INTRODUCTION

The polysubstituted pyrroles, an important class of molecular frameworks which widely existed in numerous known compounds, had attracted chemists' attention in the past few decades because of the satisfactory pharmaceutical activities of the skeleton-containing drugs or the efficient practicability of the relevant materials.[1] As is well known, the Paal−Knorr reaction, in which pyrrole derivatives are formed via the condensation of 1,4-dicarbonyl compounds with primary amines under the anhydrous and acidic conditions, is a well-documented classic approach.[2] Of course, other common methods,[3] such as Knorr,[4] Hantzsch,[5] Barton−Zard,[6] and Piloty−Robinson reactions,[7] are also of great utility to synthesize pyrroles. Recently, transition-metal-catalyzed synthesis of pyrroles has gradually become the predominant avenue and has been continually disclosed from all over the world.[8] However, transition metals and strong oxidants, which are sometimes destructive to the biomedical field, are usually indispensable in these dehydrogenation processes. Therefore, it is of great urgency to establish a green and mild method for the synthesis of pyrrole compounds from the simple and readily available materials.

Recent years have witnessed the renaissance of organic electrosynthesis, which is widely believed as a mild and eco-friendly pathway because chemical oxidants or reductants could be replaced with electrons, thereby reducing the undesirable side reactions.[9] Although in 2019, Lei's group had successfully achieved the electrochemical condensation/cyclization between aldehydes and amines to construct the pyrrole skeletons via one step,[10] experimental results show that 1,3-dicarbonyl compounds are invalid substrates for this transformation, perhaps because of the inferior reactivity of ketone (see the Supporting Information for detailed information). Based on our interest in electro-oxidative cyclodehydrogenation to synthesize heterocyclic compounds,[11] herein, we tried to achieve the electrochemical strategy to realize the intermolecular annulation of 1,3-dicarbonyl compounds and amines for the synthesis of pyrrole derivatives.

RESULTS AND DISCUSSION

At the outset, we chose benzylamine **1a** and methyl acetoacetate **2a** as the model substrates to screen the reaction conditions (Table 1). After a series of trials, we finally determined the optimal reaction conditions under which the target product **3a** was formed in 69% gas chromatography (GC) yield (Table 1, entry 1). Obviously, both increasing and decreasing the electricity have the negative effect on the transformation (Table 1, entries 2−3). Notably, the reaction yields decreased sharply to 21 and 10% when tetrabutylammonium tetrafluoroborate (^{n}BuN$_4$BF$_4$) was replaced with tetrabutylammonium hexafluorophosphate (^{n}BuN$_4$PF$_6$) and tetrabutylammonium acetate (^{n}BuN$_4$OAc), respectively (Table 1, entries 4−5). After screening a lot of additives, we found that other acids such as acetic acid (HOAc) or trifluoroacetic acid (CF$_3$COOH) went against the reaction, and no target product was detected when using bases such as potassium carbonate (K$_2$CO$_3$) instead of trifluoromethanesulfonic acid (CF$_3$SO$_3$H) (Table 1, entries 6−8). Thereafter, the solvent effect was investigated, and the declining yields were obtained when other common solvents, such as methanol, acetonitrile, and 1,2-dichloroethane, were used instead of isopropanol (Table 1, entry 9). Moreover, using the same amount of the single solvent also led to the unsatisfactory results (Table 1, entries 10−11). Also, inferior yields were observed when using higher or lower reaction

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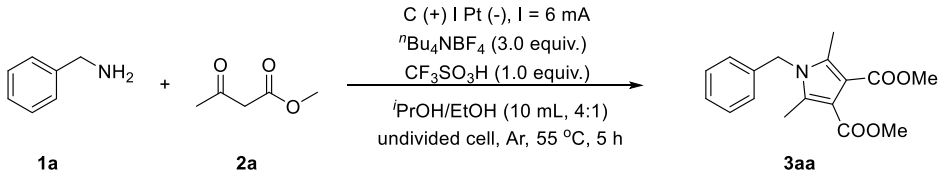
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	variation from the standard conditions	yield[b] (%)
1	none	69
2	4 mA instead of 6 mA, 6.5 h	43
3	8 mA instead of 6 mA, 3.75 h	58
4[c]	$^{n}Bu_4NPF_6$ instead of $^{n}Bu_4NBF_4$	21
5[c]	$^{n}Bu_4NOAc$ instead of nBu_4NBF_4	10
6	HOAc instead of CF_3SO_3H	13
7	CF_3COOH instead of CF_3SO_3H	51
8	K_2CO_3 instead of CF_3SO_3H	N.D.[f]
9[d]	MeOH, CH_3CN, and DCE instead of $^{i}PrOH$	15
10[d]	without EtOH	48
11[d]	without $^{i}PrOH$	42, 38, 11
12	45 °C instead of 55 °C	59
13	65 °C instead of 55 °C	54
14	C (+) I Ni (−) instead of C (+) I Pt (−)	52
15	Pt (−) I Pt (−) instead of C (+) I Pt (−)	trace
16[e]	adding a 4 Å molecular sieve or Na_2SO_4 as the drying agent	15 or 35
17	under air	51
18	without electricity	N.D.

[a]Reaction conditions: graphite rod anode (Φ 6 mm), Pt plate cathode (1 mm × 1 mm × 0.1 mm), constant current = 6 mA, **1a** (0.6 mmol), **2a** (0.3 mmol), $^{n}Bu_4NBF_4$ (0.9 mmol), CF_3SO_3H (0.3 mmol), $^{i}PrOH$/EtOH (10 mL, 4:1), 55 °C, 5 h, undivided cell, Ar. [b]Isolated yield. [c]The electrolyte cannot be dissolved fully, or the voltage is out of range (>20 V). [d]The reaction volume is kept constant (10 mL). [e]100 mg of the drying agents. [f]Not detected.

temperatures (Table 1, entries 12−13). In addition, the reaction efficiency declined slightly to 52% when a nickel plate cathode was used; however, the use of a platinum plate as an anode nearly prevented the transformation (Table 1, entries 14−15). Disappointingly, subjecting some drying reagents such as a 4 Å molecular sieve or sodium sulfate to the reaction to facilitate the dehydration process did not work well, instead giving worse yields (Table 1, entry 16).

When the reaction was conducted under air, the yield fell to 51% (Table 1, entry 17). Expectedly, the reaction did not take place when no electric current passed through the system (Table 1, entry 18).

With the optimized conditions in hand, the scope of reaction substrates in regard to amines **1** and 1,3-dicarbonyl compounds **2** is explored in Scheme 1. First, several alkyl-substituted benzylamines, including methyl, isopropyl, and *tert*-butyl, were suitable substrates for this transformation and could afford the desired products **3b**−**3f** in moderate yields. In addition, 3,4-dimethylbenzylamine was also converted smoothly into the corresponding pyrrole **3g** in 53% isolated yield. Moreover, other electron-donating substitutions like the methoxy group were tolerated in this transformation, leading to final products **3h** and **3i** in acceptable yields. Thereafter, some benzylamines bearing electron-withdrawing substitutions including trifluoromethyl and cyano groups were also subjected into the reaction, and the target products **3j**−**3m** were obtained in moderate yields. Similarly, ortho- and para-substituted halo-benzylamines also showed better reaction activities under the standard conditions, leading to the corresponding halogenated pyrrole derivatives **3n**−**3s**, which could subsequently undergo the functionalization via transition-metal-catalyzed reactions. Unfortunately, no target products were observed when some heterocyclic aromatic amines, such as 2-furfurylamine, 2-thiophenemethylamine, and 4-(aminomethyl)pyridine, were selected as substrates. Besides, other alkylamines like 2-phenylethylamine could also participate in the reaction, and product **3t** was isolated in 28% yield. Finally, we investigated the scope of 1,3-dicarbonyl compounds, and expectedly, pyrrole **3u** was formed in satisfactory yield when using ethyl acetoacetate as the starting material.

In order to explore the mechanism, confirmatory cyclic voltammetry (CV) experiments were conducted, and the results are shown in Figure 1. Notably, the CV experiments are performed in CH_3CN because the oxidation peaks are disordered and complex in the standard solvents. As can be seen from Figure 1, the oxidant potential of benzylamine **1a** is 1.40 V, where no obvious oxidation peak of **2a** was observed. In addition, when we stirred the mixture of benzylamine **1a** and methyl acetoacetate **2a** at 60 °C for an hour, apparent oxidation peaks were detected at 1.48 V, which, we speculated, might be attributed to the formation of enamine **4a** via the condensation of the materials. Obviously, enamine **4a** has a similar oxidant potential at 1.32 V. Therefore, it is reasonable to believe that enamine derivatives might be the intermediates in this transformation.

According to the aforementioned speculation, several enamines were synthesized and then subjected to the reactions under similar conditions. Also, the results are shown in Scheme 2. In short, a series of desired pyrrole products **3a**, **3i**−**3j**, and **3v**−**3z** were generated in moderate to high yields when the corresponding enamines were used as the substrates. It was worth mentioning that this reaction could achieve the synthesis of some pyrrole derivatives which could not be formed through

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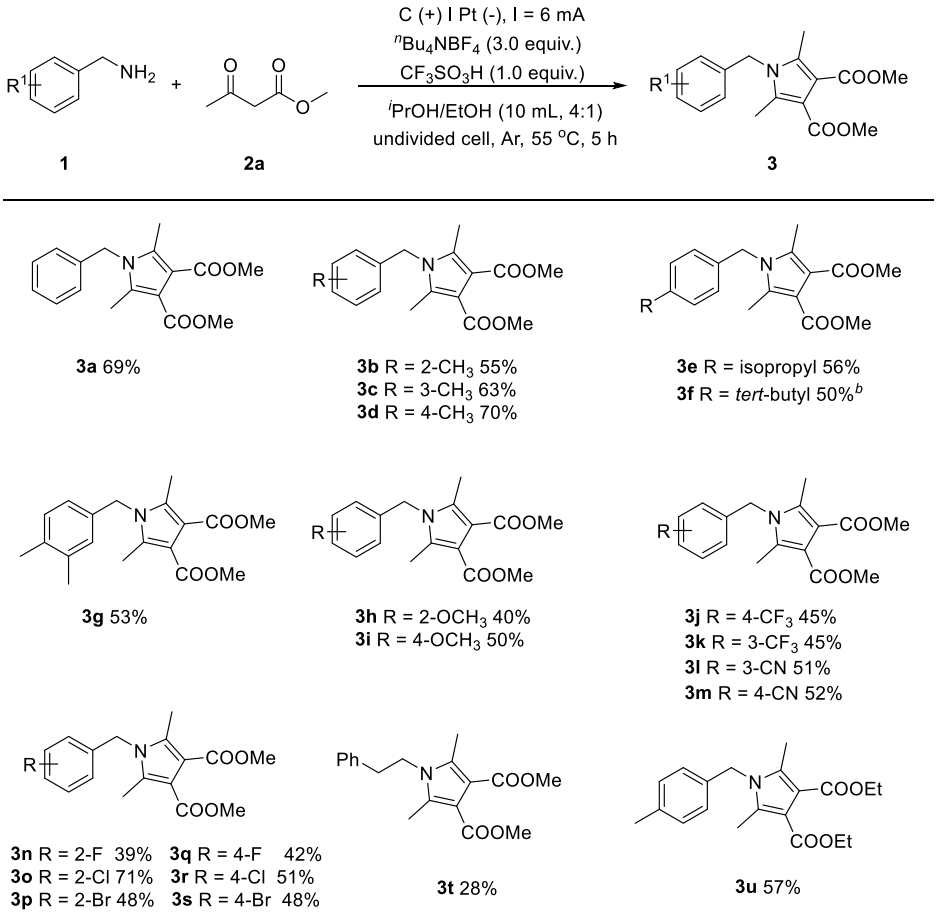
Scheme 1. Synthesis of Pyrroles[a]



[a]Reaction conditions: graphite rod anode (Φ 6 mm), Pt plate cathode (10 mm × 10 mm × 0.1 mm), constant current = 6 mA, **1a** (0.6 mmol), **2a** (0.3 mmol), $^{n}Bu_4NBF_4$ (0.9 mmol), CF_3SO_3H (0.3 mmol), ^{i}PrOH/EtOH (10 mL, 4:1), 55 °C, 5 h, undivided cell, Ar. [b]Using MeOH instead of EtOH. [c]See the Supporting Information for failed substrates.

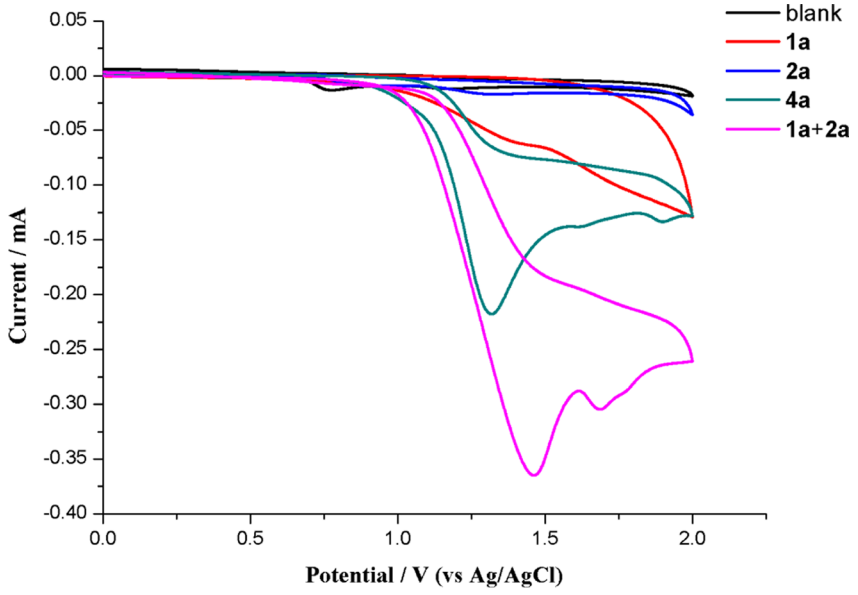


Figure 1. CV experiments.

the first transformation. Also, to some extent, we could make the conclusion that the yield of the first transformation is mainly determined by the formation rate of the enamine intermediate.

Based on the aforementioned experimental results and the published literature,[10,12] a proposed mechanism is depicted in Scheme 3. Initially, enamine **4a**, tautomerized from Schiff base

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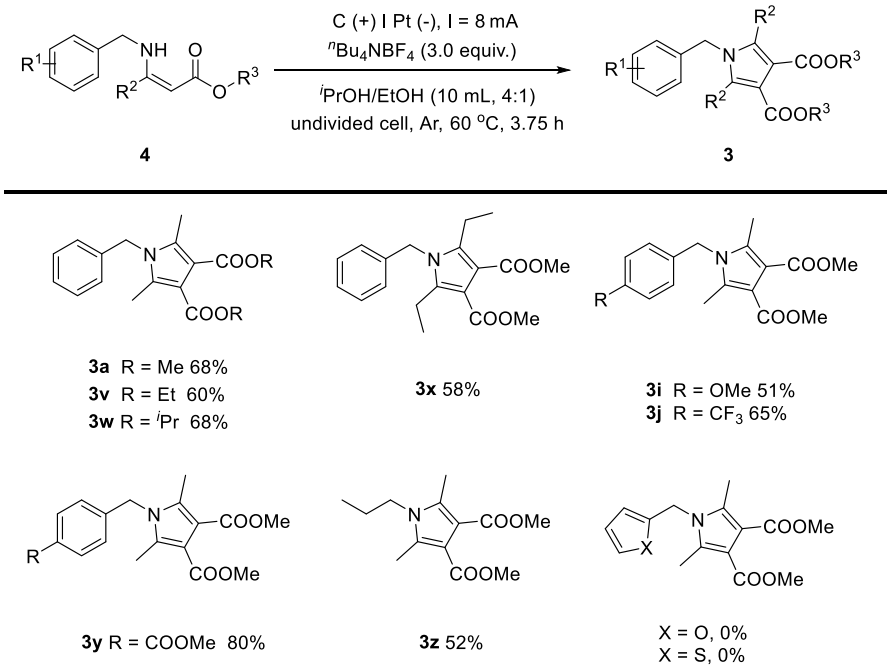
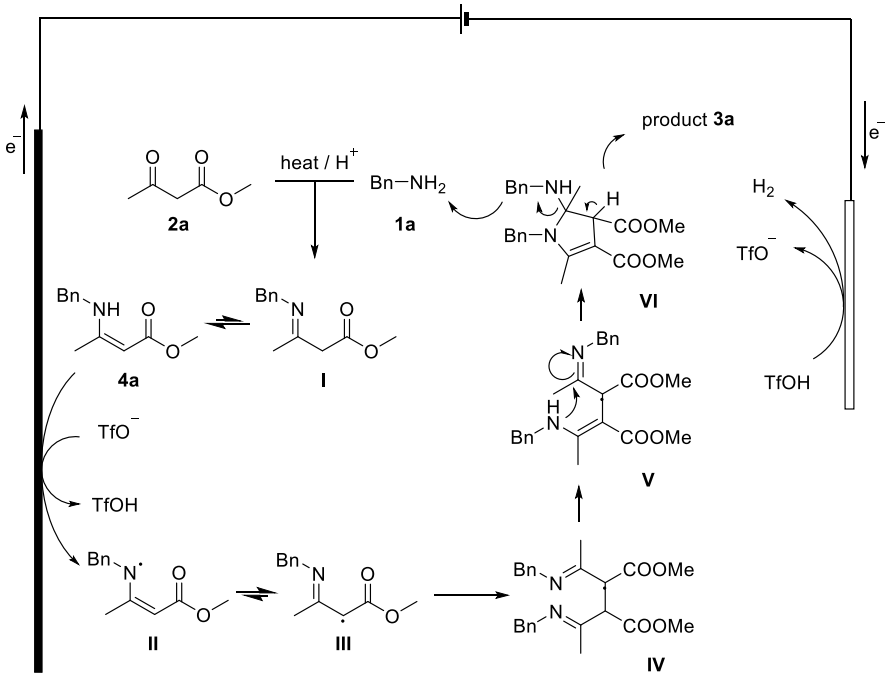
Scheme 2. Synthesis of Pyrroles[a]



[a]Reaction conditions: graphite rod anode (Φ 6 mm), Pt plate cathode (10 mm × 10 mm × 0.1 mm), constant current = 8 mA, **4a** (0.3 mmol), $^{n}Bu_4NBF_4$ (0.9 mmol), ^{i}PrOH/EtOH (10 mL, 4:1), 60 °C, 3.75 h, undivided cell, Ar. [b]See the Supporting Information for failed substrates.

Scheme 3. Proposed Mechanism



complex **I**, which was formed from the condensation of methyl acetoacetate **2a** with benzylamine **1a** under acidic conditions by heating, was oxidized at the anode to release the nitrogen-centered radical species **II**, which underwent tautomerism to generate the more stable radical intermediate **III**. Also, subsequent homo-coupling to give dimer **IV** and final intramolecular cyclization took place to deliver the target product **3a** by removal of benzylamine. In the meantime, alkoxyl anions were generated at the cathode to maintain the electronic conservation.

To further clarify the potentially synthetic application of the protocols, the scale-up experiments were carried out with 6 mmol (Scheme 4). To our delight, the considerable isolated yields of 66 and 45% were obtained.

CONCLUSIONS

In summary, we have disclosed an electro-oxidative approach to form pyrrole derivatives from 1,3-dicarbonyl compounds and primary amines via the intermolecular cyclization. Moreover, the

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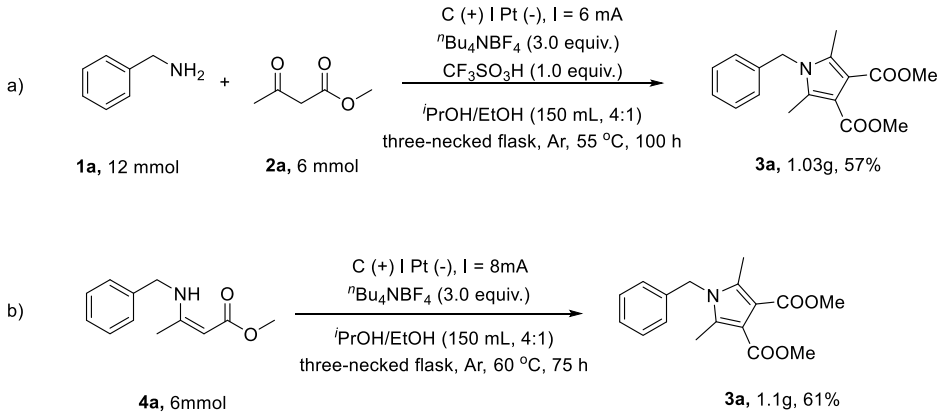
Scheme 4. Scale-Up Reactions



synthesis of pyrroles from enamines by using the electrosynthesis strategy has also been reported in the paper, indicating the rationality of the proposed mechanism. Based on the reported methods, a lot of polysubstituted pyrroles could by obtained in moderate yields. What is more, the further research studies on electro-oxidative annulation are underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All glassware was oven-dried at 110 °C for hours and cooled down under air. Unless otherwise noted, benzylamines and 1,3-dicarbonyl compounds were obtained from commercial suppliers and used without further purification. Enamines were prepared according to the literature procedures; enamines **4a**, **4i**, **4v**, **4x**, and **4z** are the known compounds, and the corresponding NMR data are in accord with the previous literature. The instrument for electrolysis was a dual display potentiostat (DJS-292B) (made in China). The anode electrode comprises carbon rod electrodes (Φ 6 mm), and the cathode electrode comprises platinum plate electrodes (10 mm × 10 mm × 0.1 mm). Thin-layer chromatography employed glass 0.25 mm silica gel plates. Flash chromatography columns were used with 300−400 silica gel. ^{1}H and ^{13}C NMR data were recorded in $CDCl_3$ on a Bruker Ascend-400 spectrometer (400 MHz) with tetramethylsilane as an internal standard. All chemical shifts are reported relative to tetramethylsilane (0 ppm for 1H) and d-solvent peaks (77.16 ppm for 13C), respectively. GC analyses were performed on a SHIMADZU GC-2014 GC instrument with a flame-ionization detector, and benzophenone was added as internal standard. Cyclic voltammograms were obtained on a CHI 660E 413713 potentiostat. High-resolution mass spectra were recorded on a Waters GCT premier of EI.

General Procedure for the Synthesis of Enamines 4. To a 25 mL round-bottom flask with a magnetic bar were added benzylamines **1** (5 mmol), 1,3-dicarbonyl compound **2** (6 mmol), $ZnCl_2$ (0.5 mmol), and CH_3CN (10 mL). The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was removed under reduced pressure to afford the residue, which was purified by flash column chromatography on silica gel using a mixture of petroleum ether (PE) and ethyl acetate (EA) to give products **4**.

*Methyl 3-(Benzylamino)but-2-enoate (**4a**).*[13] Yellow oil (931 mg, 91%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (br, 1H), 7.37−7.30 (m, 2H), 7.29−7.23 (m, 3H), 4.54 (s, 1H), 4.42 (d, J = 6.4 Hz, 2H), 3.63 (s, 3H), 1.91 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.0, 162.0, 138.8, 128.9, 127.4, 126.8, 82.9, 50.1, 46.9, 19.5.

*Methyl 3-((4-Methoxybenzyl)amino)but-2-enoate (**4i**).*[14] Yellow oil (1.05 g, 89%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (br, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.52 (s, 1H), 4.36 (d, J = 6.2 Hz, 2H), 3.79 (s, 3H), 3.62 (s, 3H), 1.92 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.0, 162.0, 159.0, 130.7, 128.2, 114.3, 82.7, 55.4, 50.1, 46.4, 19.6.

*Methyl 3-((4-(Trifluoromethyl)benzyl)amino)but-2-enoate (**4j**).* Yellow solid (995 mg, 73%). mp 72−74 °C. PE/EA = 5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (br, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.59 (s, 1H), 4.48 (d, J = 6.5 Hz, 2H), 3.63 (s, 3H), 1.88 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.9, 161.6, 143.1, 129.6 (q, $^2J_{C-F}$ = 32.3 Hz), 126.9, 125.7 (q, $^3J_{C-F}$ = 4.0 Hz), 124.1 (q, $^1J_{C-F}$ = 272.7 Hz), 83.6, 50.0, 46.2, 19.1. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{13}H_{14}F_3NO_2$, 273.0977; found, 273.0978.

*Ethyl 3-(Benzylamino)but-2-enoate (**4v**).*[13] Yellow oil (986.3 mg, 90%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (br, 1H), 7.37−7.30 (m, 2H), 7.27−7.21 (m, 3H), 4.53 (s, 1H), 4.41 (d, J = 6.3 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 1.90 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.6, 161.8, 138.8, 128.8, 127.4, 126.7, 83.2, 58.4, 46.8, 19.4, 14.7.

*Isopropyl 3-(Benzylamino)but-2-enoate (**4w**).* Yellow oil (1.03 g, 88%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (br, 1H), 7.37−7.29 (m, 2H), 7.30−7.21 (m, 3H), 5.00 (hept, J = 6.2 Hz, 1H), 4.51 (s, 1H), 4.41 (d, J = 6.4 Hz, 2H), 1.90 (s, 3H), 1.23 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 170.25, 161.68, 138.85, 128.83, 127.39, 126.80, 83.75, 65.21, 46.86, 22.32, 19.44. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{14}H_{19}NO_2$, 233.1416; found, 233.1416.

*Methyl 3-(Benzylamino)pent-2-enoate (**4x**).*[15] Yellow oil (930.9 mg, 85%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (br, 1H), 7.37−7.31 (m, 2H), 7.29−7.25 (m, 3H), 4.56 (s, 1H), 4.43 (d, J = 6.3 Hz, 2H), 3.64 (s, 3H), 2.23 (q, J = 7.5 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.4, 167.2, 138.9, 128.9, 127.5, 126.8, 80.9, 50.2, 46.5, 25.3, 12.3.

*Methyl 4-(((4-Methoxy-4-oxobut-2-en-2-yl)amino)methyl)-benzoate (**4y**).* Yellow solid (1.06 g, 81%). mp 52−54 °C. PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (br, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.57 (s, 1H), 4.49 (d, J = 6.5 Hz, 2H), 3.91 (s, 3H), 3.64 (s, 3H), 1.89 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.0, 166.8, 161.7, 144.2, 130.2, 129.4, 126.6, 83.5, 52.2, 50.2, 46.6, 19.4. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{14}H_{17}NO_4$, 263.1158; found, 263.1157.

*Methyl 3-(Propylamino)but-2-enoate (**4z**).*[13] Colorless oil (720 mg, 92%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (br, 1H), 4.44 (s, 1H), 3.62 (s, 3H), 3.17 (q, J = 6.9 Hz, 2H), 1.92 (s, 3H), 1.66−1.53 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.0, 162.1, 81.4, 49.9, 44.8, 23.7, 19.4, 11.4.

General Procedure A for the Synthesis of 3 from 1 and 2. To an oven-dried undivided three-necked bottle (10 mL) with a magnetic bar were added benzylamine **1** (0.6 mmol), 1,3-dicarbonyl compound **2** (0.3 mmol), CF_3SO_3H (0.3 mmol), ^{n}Bu$_4$NBF$_4$ (0.9 mmol), and ^{i}PrOH/EtOH (8 mL/2 mL). The bottle was equipped with a carbon rod (Φ 6 mm) anode and a platinum plate (10 mm × 10 mm × 0.1 mm) cathode and was then flushed with nitrogen. The reaction mixture was stirred and electrolyzed at a constant current of 6 mA at 55 °C for 5 h. After completion of the reaction, the solvent was removed under reduced pressure to afford the residue, which was purified by flash

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column chromatography on silica gel using a mixture of PE and EA to give products **3**.

General Procedure B for the Synthesis of 3 from 4. To an oven-dried undivided three-necked bottle (10 mL) with a magnetic bar were added enamine **4** (0.3 mmol), $^{n}Bu_4NBF_4$ (0.9 mmol), and ^{i}PrOH/EtOH (8 mL/2 mL). The bottle was equipped with a carbon rod (Φ 6 mm) anode and a platinum plate (10 mm × 10 mm × 0.1 mm) cathode and was then flushed with nitrogen. The reaction mixture was stirred and electrolyzed at a constant current of 8 mA at 60 °C for 3.75 h. After completion of the reaction, the solvent was removed under reduced pressure to afford the residue, which was purified by flash column chromatography on silica gel using a mixture of PE and EA to give products **3**.

General Procedure for the Scale-Up Reactions. To a 250 mL three-necked flask with a magnetic bar were added materials, ^{i}PrOH/EtOH (120 mL/30 mL). Other processes are in accord with procedures A and B.

General Procedure for Cyclic Voltammetry. CV was performed in a three-electrode cell connected to a Schlenk line under nitrogen at room temperature. The working electrode was a glassy carbon electrode (Φ 3 mm), and the counter electrode was a platinum wire. The reference electrode was a Ag/AgCl electrode submerged in saturated aqueous KCl solution. 10 mL of CH_3CN containing 1.0 M $^{n}Bu_4NBF_4$ was poured into the electrochemical cell in all experiments. CV of substrates was performed at the concentration of 0.05 M. The scan rate is 0.1 V/s, ranging from 0 to 2 V.

*Dimethyl 1-Benzyl-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3a**).*[16] Yellow oil (31.0 mg, 69%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.22 (m, 3H), 6.90 (d, *J* = 7.3 Hz, 2H), 5.05 (s, 2H), 3.82 (s, 6H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2, 136.0, 133.9, 129.1, 127.8, 125.6, 112.5, 51.5, 47.1, 11.0. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{17}H_{19}NO_4$, 301.1314; found, 301.1313.

*Dimethyl 2,5-Dimethyl-1-(2-methylbenzyl)-1H-pyrrole-3,4-dicarboxylate (**3b**).* Yellow oil (26 mg, 55%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.14 (m, 2H), 7.12−7.04 (m, 1H), 6.25 (d, *J* = 7.6 Hz, 1H), 4.95 (s, 2H), 3.83 (s, 6H), 2.38 (s, 3H), 2.27 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2, 134.3, 134.0, 134.0, 130.3, 127.6, 126.9, 124.4, 112.5, 51.5, 45.1, 19.1, 10.9. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{21}NO_4$, 315.1471; found, 315.1471.

*Dimethyl 2,5-Dimethyl-1-(3-methylbenzyl)-1H-pyrrole-3,4-dicarboxylate (**3c**).* Yellow oil (29.4 mg, 63%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.74 (s, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.01 (s, 2H), 3.82 (s, 6H), 2.32 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.3, 139.0, 136.0, 134.0, 129.0, 128.6, 126.2, 122.7, 112.5, 51.5, 47.1, 21.6, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{21}NO_4$, 315.1471; found, 315.1472.

*Dimethyl 2,5-Dimethyl-1-(4-methylbenzyl)-1H-pyrrole-3,4-dicarboxylate (**3d**).* Yellow oil (33.0 mg, 70%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 7.9 Hz, 2H), 5.00 (s, 2H), 3.81 (s, 6H), 2.32 (s, 3H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2, 137.5, 133.9, 133.0, 130.0, 125.6, 112.5, 51.5, 46.9, 21.1, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{21}NO_4$, 315.1471; found, 315.1469.

*Dimethyl 1-(4-Isopropylbenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3e**).* Yellow oil (28.8 mg, 56%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.1 Hz, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 5.01 (s, 2H), 3.81 (s, 6H), 2.93−2.82 (m, 1H), 2.32 (s, 6H), 1.22 (d, *J* = 8.0 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.3, 148.6, 134.0, 133.4, 127.2, 125.7, 112.5, 51.5, 47.0, 33.9, 24.1, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{20}H_{25}NO_4$, 343.1784; found, 343.1786.

*Dimethyl 1-(4-(tert-Butyl)benzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3f**).* Yellow oil (27.0 mg, 50%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.01 (s, 2H), 3.81 (s, 6H), 2.32 (s, 6H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2, 150.8, 134.0, 133.0, 126.0, 125.4, 112.5, 77.5, 77.2, 76.8, 51.5, 46.9, 34.6, 31.4, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1939.

*Dimethyl 1-(3,4-Dimethylbenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3g**).* Yellow oil (26.3 mg, 53%). PE/EA = 20:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 7.7 Hz, 1H), 6.71 (s, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 4.98 (s, 2H), 3.82 (s, 6H), 2.31 (s, 6H), 2.22 (s, 3H), 2.22 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.3, 137.5, 136.2, 134.0, 133.4, 130.3, 126.8, 123.1, 112.4, 51.5, 46.9, 20.0, 19.5, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{19}H_{23}NO_4$, 329.1627; found, 329.1628.

*Dimethyl 1-(2-Methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3h**).* Yellow oil (20.1 mg, 40%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 5.00 (s, 2H), 3.89 (s, 3H), 3.82 (s, 6H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2, 156.1, 134.2, 128.7, 125.8, 124.3, 121.0, 112.4, 109.9, 55.4, 51.5, 42.7, 10.9. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{21}NO_5$, 331.1420; found, 331.1422.

*Dimethyl 1-(4-Methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3i**).* Yellow oil (24.6 mg, 50%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 4H), 4.98 (s, 2H), 3.81 (s, 6H), 3.78 (s, 3H), 2.32 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 133.8, 128.0, 126.9, 114.5, 112.5, 55.4, 51.5, 46.6, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{21}NO_5$, 331.1420; found, 331.1419.

*Dimethyl 2,5-Dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3,4-dicarboxylate (**3j**).* Yellow oil (25.0 mg, 45%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.11 (s, 2H), 3.83 (s, 6H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.0, 140.2, 133.6, 130.3 (q, $^2J_{C-F}$ = 32.4 Hz), 126.2 (q, $^3J_{C-F}$ = 3.8 Hz), 126.0, 124.0 (q, $^1J_{C-F}$ = 270.5 Hz), 113.0, 51.6, 46.7, 11.0. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{18}F_3NO_4$, 369.1188; found, 369.1188.

*Dimethyl 2,5-Dimethyl-1-(3-(trifluoromethyl)benzyl)-1H-pyrrole-3,4-dicarboxylate (**3k**).* Yellow oil (24.6 mg, 45%). PE/EA = 10 : 1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.34 (s, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 5.11 (s, 2H), 3.83 (s, 6H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 137. 2, 133.6, 131.6 (q, $^2J_{C-F}$ = 32.0 Hz), 130.0, 128.8, 123.9 (q, $^1J_{C-F}$ = 270 Hz), 124.9 (q, $^3J_{C-F}$ = 4.0 Hz), 122.6 (q, $^4J_{C-F}$ = 4.0 Hz), 113.0, 51.6, 46.7, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{18}F_3NO_4$, 369.1188; found, 369.1189.

*Dimethyl 1-(3-Cyanobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3l**).* Yellow oil (25.0 mg, 51%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 5.6 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 6H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.9, 137.8, 133.4, 131.7, 130.2, 130.0, 130.0, 118.3, 113.5, 113.1, 51.6, 46.4, 11.1. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{18}N_2O_4$, 326.1267; found, 326.1268.

*Dimethyl 1-(4-Cyanobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3m**).* Yellow oil (25.2 mg, 52%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 5.11 (s, 2H), 3.83 (s, 6H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.9, 141.5, 133.4, 133.0, 126.4, 118.4, 113.1, 112.0, 51.6, 46.7, 11.0. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{18}N_2O_4$, 326.1267; found, 326.1267.

*Dimethyl 1-(4-Fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3n**).* Yellow oil (17.5 mg, 39%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.22 (m, 1H), 7.12−7.03 (m, 2H), 6.47 (t, *J* = 7.3 Hz, 1H), 5.08 (s, 2H), 3.82 (s, 6H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 159.8 (d, $^1J_{C-F}$ = 247.5 Hz), 133.9, 129.5 (d, $^4J_{C-F}$ = 8.1 Hz), 127.0 (d, $^5J_{C-F}$ = 4.0 Hz), 125.0 (d, $^6J_{C-F}$ = 3.0 Hz), 123.4 (d, $^3J_{C-F}$ = 14.1 Hz), 115.5 (d, $^2J_{C-F}$ = 20.2 Hz), 112.8, 51.6, 41.3, 11.0. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{17}H_{18}FNO_4$, 319.1220; found, 319.1220.

*Dimethyl 1-(2-Chlorobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3o**).* Yellow oil (35.5 mg, 71%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.8 Hz, 1H), 7.25−7.20 (m, 1H), 7.19−7.13 (m, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 5.07 (s, 2H), 3.82 (s, 6H), 2.28 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 133.9, 133.6, 131.9, 129.6, 129.1, 127.8, 126.4, 112.8, 77.5, 77.2, 76.8, 51.6, 45.1, 10.9. HRMS (GC-TOF, EI) *m*/*z*: $[M]^+$ calcd for $C_{17}H_{18}ClNO_4$, 335.0924; found, 335.0924.

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*Dimethyl 1-(2-Bromobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3p**).* Yellow oil (26.1 mg, 48%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.57 (m, 1H), 7.24−7.14 (m, 2H), 6.29 (d, J = 6.7 Hz, 1H), 5.03 (s, 2H), 3.83 (s, 6H), 2.28 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 135.2, 133.8, 133.0, 129.4, 128.4, 126.5, 121.6, 112.9, 77.5, 77.2, 76.8, 51.6, 47.6, 10.9. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{17}H_{18}BrNO_4$, 379.0419; found, 379.0417.

*Dimethyl 1-(4-Fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3q**).* Yellow oil (20.0 mg, 42%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09−6.95 (m, 2H), 6.96−6.78 (m, 2H), 5.02 (s, 2H), 3.82 (s, 6H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 162.3 (d, $^1J_{C-F}$ = 245 Hz), 133.7, 131.8 (d, $^4J_{C-F}$ = 3.1 Hz), 127.3 (d, $^3J_{C-F}$ = 8.1 Hz), 116.1 (d, $^2J_{C-F}$ = 21.6 Hz), 112.8, 51.6, 46.5, 11.1. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{17}H_{18}FNO_4$, 319.1220; found, 319.1222.

*Dimethyl 1-(4-Chlorobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3r**).* Yellow oil (25.3 mg, 51%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.01 (s, 2H), 3.82 (s, 6H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 134.6, 133.7, 133.7, 129.4, 127.0, 112.8, 51.6, 46.5, 11.1. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{17}H_{18}ClNO_4$, 335.0924; found, 335.0926.

*Dimethyl 1-(4-Bromobenzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3s**).* Yellow oil (25.3 mg, 48%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H), 3.82 (s, 6H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.0, 135.1, 133.6, 132.2, 127.3, 121.7, 112.7, 51.5, 46.5, 11.1. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{17}H_{18}BrNO_4$, 379.0419; found: 379.0418.

*Dimethyl 2,5-Dimethyl-1-phenethyl-1H-pyrrole-3,4-dicarboxylate (**3t**).* Yellow solid (14.2 mg, 28%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.23 (m, 3H), 7.11−7.03 (m, 2H), 3.98 (t, 2H), 3.80 (s, 6H), 2.88 (t, J = 7.5 Hz, 2H), 2.27 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.2, 137.4, 133.3, 129.0, 128.8, 127.2, 112.3, 51.5, 45.5, 36.4, 10.9. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{18}H_{21}NO_4$, 315.1471; found, 315.1472.

*Diethyl 2,5-Dimethyl-1-(4-methylbenzyl)-1H-pyrrole-3,4-dicarboxylate (**3u**).* Yellow oil (28.9 mg, 57%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 5.00 (s, 2H), 4.28 (q, J = 7.1 Hz, 4H), 2.32 (s, 3H), 2.31 (s, 6H), 1.33 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.9, 137.5, 133.6, 133.1, 129.8, 125.7, 112.7, 60.2, 46.9, 21.2, 14.4, 11.0. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{20}H_{25}NO_4$, 343.1784; found, 343.1786.

*Diethyl 1-Benzyl-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3v**).*[17] Yellow oil (29.5 mg, 60%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.23 (m, 3H), 6.92 (d, J = 6.9 Hz, 2H), 5.04 (s, 2H), 4.28 (q, J = 7.1 Hz, 4H), 2.32 (s, 6H), 1.33 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.8, 136.1, 133.6, 129.2, 127.8, 125.7, 112.8, 60.3, 47.1, 14.4, 11.0. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{19}H_{23}NO_4$, 329.1627; found, 329.1630.

*Diisopropyl 1-Benzyl-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3w**).* Yellow oil (33.2 mg, 68%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.24 (m, 3H), 6.93 (d, J = 7.2 Hz, 2H), 5.17 (m, 2H), 5.03 (s, 2H), 2.30 (s, 6H), 1.33 (d, J = 6.3 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.2, 136.2, 133.0, 129.1, 127.7, 125.8, 113.3, 67.7, 47.0, 22.1, 11.1. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1941.

*Dimethyl 1-Benzyl-2,5-diethyl-1H-pyrrole-3,4-dicarboxylate (**3x**).* Yellow oil (31.1 mg, 58%). PE/EA = 10:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.21 (m, 3H), 6.89 (d, J = 7.1 Hz, 2H), 5.09 (s, 2H), 3.82 (s, 6H), 2.70 (q, J = 7.5 Hz, 4H), 1.05 (t, J = 7.5 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 139.4, 136.9, 129.1, 127.8, 125.5, 112.1, 51.5, 46.7, 18.7, 14.6. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{19}H_{23}NO_4$, 329.1627; found, 329.1625.

*Dimethyl 1-(4-(Methoxycarbonyl)benzyl)-2,5-dimethyl-1H-pyrrole-3,4-dicarboxylate (**3y**).* Yellow oil (31.1 mg, 80%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 5.10 (s, 2H), 3.91 (s, 3H), 3.83 (s, 6H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.6, 166.0, 141.2, 133.7, 130.4, 129.9, 125.6, 112.8, 52.3, 51.6, 46.9, 11.0. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{19}H_{21}NO_6$, 359.1369; found, 359.1372.

*Dimethyl 2,5-Dimethyl-1-propyl-1H-pyrrole-3,4-dicarboxylate (**3z**).* Yellow oil (19.8 mg, 52%). PE/EA = 15:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 6H), 3.72 (m, 2H), 2.38 (s, 6H), 1.70−1.59 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.3, 133.3, 112.1, 51.5, 45.5, 23.7, 11.3, 11.1. HRMS (GC-TOF, EI) m/z: $[M]^+$ calcd for $C_{13}H_{19}NO_4$, 253.1314; found, 253.1313.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02911.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D. Biosynthesis, asymmetric synthesis, and pharmacology, including cellular targets, of the pyrrole-2-aminoimidazole marine alkaloids. *Nat. Prod. Rep.* **2011**, *28*, 1229−1260. (b) De Coen, L. M.; Heugebaert, T. S. A.; García, D.; Stevens, C. V. Synthetic Entries to and Biological Activity of Pyrrolopyrimidines. *Chem. Rev.* **2016**, *116*, 80−139. (c) Gholap, S. S. Pyrrole: An emerging scaffold for construction of valuable therapeutic agents. *Eur. J. Med. Chem.* **2016**, *110*, 13−31. (d) Loudet, A.; Burgess, K. BODIPY Dyes and Their Derivatives: Syntheses and Spectroscopic Properties. *Chem. Rev.* **2007**, *107*, 4891−4932. (e) Saito, S.; Osuka, A. Expanded Porphyrins: Intriguing Structures, Electronic Properties, and Reactivities. *Angew. Chem., Int. Ed.* **2011**, *50*, 4342−4373. (f) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. Biological formation of pyrroles: Nature's logic and enzymatic machinery. *Nat. Prod. Rep.* **2006**, *23*, 517−531.

(2) (a) Balakrishna, A.; Aguiar, A.; Sobral, P. J. M.; Wani, M. Y.; Almeida e Silva, J.; Sobral, A. J. F. N. Paal−Knorr synthesis of pyrroles: from conventional to green synthesis. *Catal. Rev.* **2019**, *61*, 84−110. (b) Khaghaninejad, S.; Heravi, M. M. Chapter Three-Paal−Knorr Reaction in the Synthesis of Heterocyclic Compounds. *Adv. Heterocycl.*

Chem. **2014**, *111*, 95−146. (c) Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. Highly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric Paal−Knorr Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 1714−1717.

(3) (a) Xuan, D. D. Recent Progress in the Synthesis of Pyrroles. *Curr. Org. Chem.* **2020**, *24*, 622−657. (b) Kakaawla, T. K. K.; Harrity, J. P. A. Development of an Amine-Catalyzed Regioselective Synthesis of Pyrroles. *Org. Lett.* **2018**, *20*, 201−203. (c) Zuniga, O. M. P.; Angel Gabriel, S.; Jose Jobanny Martinez, Z.; Gustavo Pablo, R. Green Synthesis of Pyrrole Derivatives. *Curr. Org. Synth.* **2017**, *14*, 865−882. (d) Xu, J.; Green, A. P.; Turner, N. J. Chemo-Enzymatic Synthesis of Pyrazines and Pyrroles. *Angew. Chem., Int. Ed.* **2018**, *57*, 16760−16763.

(4) (a) Du, Y.; Xu, Y.; Qi, C.; Wang, C. Mechanistic study on the Knorr pyrazole synthesis-thioester generation reaction. *Tetrahedron Lett.* **2019**, *60*, 1999−2004. (b) Neya, S.; Yoneda, T.; Omori, H.; Hoshino, T.; Kawaguchi, A. T.; Suzuki, M. Synthesis of 1,4,5,8-tetraethyl-2,3,6,7-tetravinylporphyrin from a Knorr's pyrrole analogue. *Tetrahedron* **2017**, *73*, 6780−6785. (c) Sarosh, I.; Hina, R.; Rabiya Javed, A.; Ramsha Javed, A.; Asma, M.; Mark, G. M. Recent Advances in the Synthesis of Pyrroles. *Curr. Org. Chem.* **2020**, *24*, 1196−1229. (d) Zhang, Y.; Jiang, Y.-Z.; Liang, X.-T. A new variant of Knorr's pyrrole synthesis. *Chin. J. Chem.* **1997**, *15*, 371−378.

(5) (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. Three-component access to pyrroles promoted by the CAN−silver nitrate system under high-speed vibration milling conditions: a generalization of the Hantzsch pyrrole synthesis. *Chem. Commun.* **2013**, *49*, 591−593. (b) Lei, T.; Liu, W.-Q.; Li, J.; Huang, M.-Y.; Yang, B.; Meng, Q.-Y.; Chen, B.; Tung, C.-H.; Wu, L.-Z. Visible Light Initiated Hantzsch Synthesis of 2,5-Diaryl-Substituted Pyrroles at Ambient Conditions. *Org. Lett.* **2016**, *18*, 2479−2482. (c) Leonardi, M.; Estévez, V.; Villacampa, M.; Menéndez, J. C. The Hantzsch Pyrrole Synthesis: Non-conventional Variations and Applications of a Neglected Classical Reaction. *Synthesis* **2019**, *51*, 816−828. (d) Moss, T. A.; Nowak, T. Synthesis of 2,3-dicarbonylated pyrroles and furans via the three-component Hantzsch reaction. *Tetrahedron Lett.* **2012**, *53*, 3056−3060. (e) Trautwein, A. W.; Süßmuth, R. D.; Jung, G. Hantzsch pyrrole synthesis on solid support. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381−2384.

(6) (a) Bhattacharya, A.; Cherukuri, S.; Plata, R. E.; Patel, N.; Tamez, V.; Grosso, J. A.; Peddicord, M.; Palaniswamy, V. A. Remarkable solvent effect in Barton−Zard pyrrole synthesis: application in an efficient one-step synthesis of pyrrole derivatives. *Tetrahedron Lett.* **2006**, *47*, 5481−5484. (b) He, X.-L.; Zhao, H.-R.; Song, X.; Jiang, B.; Du, W.; Chen, Y.-C. Asymmetric Barton−Zard Reaction To Access 3-Pyrrole-Containing Axially Chiral Skeletons. *ACS Catal.* **2019**, *9*, 4374−4381. (c) Quiclet-Sire, B.; Zard, S. Convergent Routes to Pyrroles Exploiting the Unusual Radical Chemistry of Xanthates − An Overview. *Synlett* **2017**, *28*, 2685−2696. (d) Zheng, S. C.; Wang, Q.; Zhu, J. Catalytic Kinetic Resolution by Enantioselective Aromatization: Conversion of Racemic Intermediates of the Barton−Zard Reaction into Enantioenriched 3-Arylpyrroles. *Angew. Chem., Int. Ed.* **2019**, *58*, 9215−9219.

(7) (a) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. The Piloty-Robinson reaction of N-substituted piperidin-4-one azines. A novel route for the synthesis of 3,6-diazacarbazole. *Chem. Heterocycl. Compd.* **2011**, *47*, 584. (b) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. Microwave-Assisted Piloty−Robinson Synthesis of 3,4-Disubstituted Pyrroles. *J. Org. Chem.* **2007**, *72*, 3941−3944.

(8) (a) Emayavaramban, B.; Sen, M.; Sundararaju, B. Iron-Catalyzed Sustainable Synthesis of Pyrrole. *Org. Lett.* **2017**, *19*, 6−9. (b) Guo, J.; Deng, X.; Song, C.; Lu, Y.; Qu, S.; Dang, Y.; Wang, Z.-X. Differences between the elimination of early and late transition metals: DFT mechanistic insights into the titanium-catalyzed synthesis of pyrroles from alkynes and diazenes. *Chem. Sci.* **2017**, *8*, 2413−2425. (c) Neto, J. S. S.; Zeni, G. Transition Metal-Catalyzed and Metal-Free Cyclization Reactions of Alkynes with Nitrogen-Containing Substrates: Synthesis of Pyrrole Derivatives. *ChemCatChem* **2020**, *12*, 3335−3408. (d) Vaitla, J.; Bayer, A.; Hopmann, K. H. Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4277−4281. (e) Zhou, N.-N.; Zhu, H.-T.; Yang, D.-S.; Guan, Z.-H. Recent developments in the group-1B-metal-catalyzed synthesis of pyrroles. *Org. Biomol. Chem.* **2016**, *14*, 7136−7149.

(9) (a) Atobe, M.; Tateno, H.; Matsumura, Y. Applications of Flow Microreactors in Electrosynthetic Processes. *Chem. Rev.* **2018**, *118*, 4541−4572. (b) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521. (c) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. Scalable and sustainable electrochemical allylic C−H oxidation. *Nature* **2016**, *533*, 77. (d) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. Metal-catalyzed electrochemical diazidation of alkenes. *Science* **2017**, *357*, 575−579. (e) Xiong, P.; Xu, H.-H.; Song, J.; Xu, H.-C. Electrochemical Difluoromethylarylation of Alkynes. *J. Am. Chem. Soc.* **2018**, *140*, 2460−2464. (f) Jiang, Y.; Xu, K.; Zeng, C. Use of Electrochemistry in the Synthesis of Heterocyclic Structures. *Chem. Rev.* **2018**, *118*, 4485−4540. (g) Niu, L.; Jiang, C.; Liang, Y.; Liu, D.; Bu, F.; Shi, R.; Chen, H.; Chowdhury, A. D.; Lei, A. Manganese-Catalyzed Oxidative Azidation of C(sp3)−H Bonds under Electrophotocatalytic Conditions. *J. Am. Chem. Soc.* **2020**, *142*, 17693−17702.

(10) Gao, X.; Wang, P.; Wang, Q.; Chen, J.; Lei, A. Electrochemical oxidative annulation of amines and aldehydes or ketones to synthesize polysubstituted pyrroles. *Green Chem.* **2019**, *21*, 4941−4945.

(11) (a) Xiong, M.; Liang, X.; Gao, Z.; Lei, A.; Pan, Y. Synthesis of Isoxazolines and Oxazines by Electrochemical Intermolecular [2 + 1 + n] Annulation: Diazo Compounds Act as Radical Acceptors. *Org. Lett.* **2019**, *21*, 9300−9305. (b) Xiong, M.; Liang, X.; Liang, X.; Pan, Y.; Lei, A. Hexafluoro-2-Propanol-Promoted Electro-Oxidative [3+2] Annulation of 1,3-Dicarbonyl Compounds and Alkenes. *ChemElectroChem* **2019**, *6*, 3383−3386.

(12) (a) Li, D.; Li, S.; Peng, C.; Lu, L.; Wang, S.; Wang, P.; Chen, Y.-H.; Cong, H.; Lei, A. Electrochemical oxidative C−H/S−H cross-coupling between enamines and thiophenols with hydrogen evolution. *Chem. Sci.* **2019**, *10*, 2791−2795. (b) Wu, X.; Zhao, P.; Geng, X.; Wang, C.; Wu, Y.-d.; Wu, A.-x. Synthesis of Pyrrole-2-carbaldehyde Derivatives by Oxidative Annulation and Direct Csp3−H to C=O Oxidation. *Org. Lett.* **2018**, *20*, 688−691.

(13) Rout, L.; Kumar, A.; Dhaka, R. S.; Dash, P. Bimetallic Ag−Cu alloy nanoparticles as a highly active catalyst for the enamination of 1,3-dicarbonyl compounds. *RSC Adv.* **2016**, *6*, 49923−49940.

(14) Vaitla, J.; Bayer, A.; Hopmann, K. H. Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4277−4281.

(15) Maguire, A. R.; Plunkett, S. J.; Papot, S.; Clynes, M.; O'Connor, R.; Touhey, S. Synthesis of indomethacin analogues for evaluation as modulators of MRP activity. *Bioorg. Med. Chem.* **2001**, *9*, 745−762.

(16) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. Synthesis of Functionalized Pyrroles via Catalyst- and Solvent-Free Sequential Three-Component Enamine−Azoene Annulation. *J. Org. Chem.* **2011**, *76*, 2860−2866.

(17) Wang, J.-Y.; Wang, X.-P.; Yu, Z.-S.; Yu, W. The Synthesis of Polysubstituted Pyrroles via the Coupling of Phenyliodonium Ylides and Enamine Esters. *Adv. Synth. Catal.* **2009**, *351*, 2063−2066.

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