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Regioselective Iodine-Catalyzed Construction of Polysubstituted Pyrroles from Allenes and Enamines

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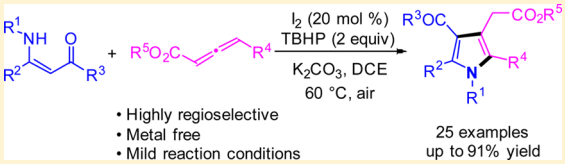
Supporting Information

ABSTRACT: A novel I_2-catalyzed tandem Michael addition/oxidative annulation of allenes and enamines for the construction of polysubstituted pyrroles has been developed. This protocol represents an efficient and highly regioselective way to access functionalized pyrroles in moderate to excellent yields under mild conditions.



Pyrroles represent one of the most important classes of heterocycles found in numerous pharmaceutical molecules, natural products, and functional materials,[1] such as Atorvastatin, Sunitinib, Lamellarin Q, and Porphobilinogen (Figure 1).

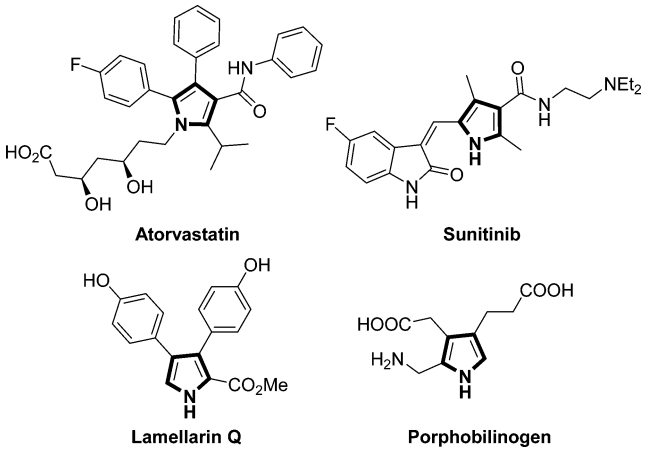
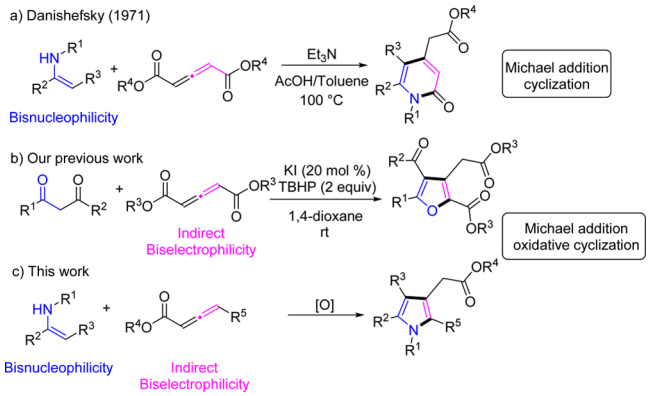


Figure 1. Selected biological and pharmaceutical molecules bearing highly substituted pyrrole.

Therefore, many synthetic methods toward pyrrole rings with potent bioactivity have been developed.[2,3] Neverthless, there is still a demand for easy and efficient protocols to construct these molecules, especially the highly regioselective synthesis of multisubstituted pyrroles.

Enamines are of great importance in organic chemistry, which not only play a prominent role in organocatalysis[4] but also serve as a versatile synthetic building block.[5] The utility of enamines in the transition-metal-catalyzed oxidative couplings for the synthesis of valuable pyrroles has been demonstrated recently.[6] For example, Glorius and co-workers reported a Rh (III)-catalyzed cyclization reaction of enamines with unactivated alkynes to deliver polysubstituted pyrroles.[6a] Simultaneously, Fagnou et al. found that the pyrrole frameworks could be achieved from enamines and alkynes via Rh (III)-catalyzed alkene sp^2 C−H activation of enamines.[6b] In addition, You and Cui independently developed a copper(iron)-catalyzed pyrrole synthesis reaction using enamines as the starting materials.[6e,f] As is known to all, enamines also exhibit strong bisnucleophilicity at C-2 position and amino group. For instance, in 1971, Danishefsky and co-workers found that enamines could smoothly react with allenes under alkaline conditions at 100 °C, delivering α-pyridones (Scheme 1a).[7] On the other hand,

Scheme 1. Synthesis of Heterocycles from Bisnucleophiles and Allenes



given that the wide applications of allenes for constructing structurally diverse heterocycles,[8,9] we have recently developed a novel protocol for the synthesis of polysubstituted furans via KI/TBHP promoted tandem Michael addition/oxidative annulation, in which a novel α,β-double electrophilic addition strategy of allene-1,3-dicarboxylic esters with 1,3-dicarbonyl compounds was first established (Scheme 1b).[10] Therefore, as part of our continuous interest in the synthesis of heterocycles,[11] we were wondering whether a similar α,β-double electrophilic addition strategy could be extended to the reaction

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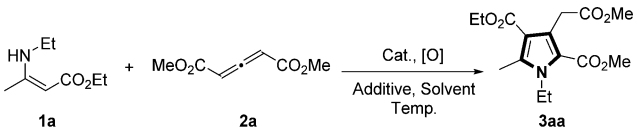
of allenes with enamines instead of 1,3-dicarbonyl compounds, which would afford pyrroles rather than pyridones. It should be pointed out that a regioselectivity issue may exsit when unsymmetric allenes are employed for this reaction. Herein, we would like to report an efficient and highly regioselective method to access functionalized pyrroles via tandem Michael addition of enamines with allenes and I_2-catalyzed oxidative annulation (Scheme 1c).

Our investigation began with the reaction of ethyl (*Z*)-3-(ethylamino)but-2-enoate (**1a**) and dimethyl penta-2,3-dienedioate (**2a**) in the presence of KI and TBHP in DCE at 25 °C under air atmosphere. As expected, the reaction proceeded smoothly to afford the desired product **3aa**, albeit in only 30% yield (Table 1, entry 1). Increasing the temperature to 60 °C gave slightly better yield of **3aa** (45%, Table 1, entry 2). To our delight, the use of a catalytic amount of I_2 (20 mol %) instead of KI led to a dramatic increase in the yield of **3aa** (65%, Table 1, entry 3). Notably, Gao and his co-workers reported a I_2-promoted synthesis of dihydropyrroles by the reaction of enamines and chalcones, however, a stoichiometric amount of I_2 was required for the high yields.[12] Inspired by this report, we also found that K_2CO_3 had a positive effect for pyrrole formation (Table 1, entry 4). Next, the control experiments found that the desired product was not detected in the absence of iodine, and only 20% of **3aa** was observed when TBHP was excluded from the reaction (Table 1, entries 5−6). Obviously, in contrast to Gao's report, a catalytic amount of I_2 (20 mol %) also can catalyze the formation of pyrroles in the presence of TBHP. Further optimization by adjusting the molar ratio of the substrates **1a** and **2a** showed that 1.5 equiv of **1a** was optimal to afford the desired product **3aa** in 90% yield (Table 1, entries 7−9). Encouraged by this, various oxidants (such as DTBP, 30% H_2O_2, $K_2S_2O_8$, TBPB, CHP, *m*-CPBA) were evaluated, and we found that TBHP was the best choice of oxidant (Table 1, entries 10−15). Moreover, the solvent effect was also investigated, and DCE was found to be the optimal solvent (Table 1, entries 16−22). Additionally, whether the temperature was lowered to 40 °C or increased to 80 °C, the yield of **3aa** (50% and 82%, respectively) was not further improved, indicating that 60 °C was the best choice (Table 1, entries 23−24). Therefore, the combination of **1a** (1.5 equiv), **2a** (1.0 equiv) in the presence of 20 mol % I_2, and 2 equiv TBHP in DCE at 60 °C was chosen as the optimal reaction conditions (Table 1, entry 8), providing **3aa** in 90% yield.

Under the optimal conditions, substrate scope of this synthetic protocol was tested (Table 2). The reaction was readily extended to a variety of different substituted enamines **1**. First, several different N-substituents were examined, and when R^1 was alkyl or phenyl group with different electronic properties, the corresponding products were obtained in moderate to excellent yields (Table 2, entries 1−7). It was noteworthy that the electronic properties of the phenyl groups had significant influence on the yields of the desired products. The *para*-MeO substituent substrate **1d** delivered the corresponding compound **3da** in 87% yield (Table 2, entry

Table 1. Optimization of Reaction Conditions[a]

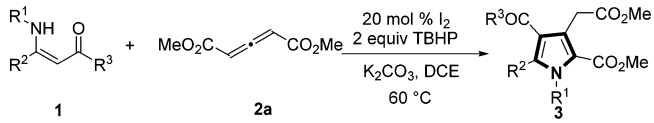


1a 2a 3aa

entry	1a:2a	cat.	[O]	additive	temp. (°C)	solvent	yield (%)[b]
1	1:1	KI	TBHP	–	25	DCE	30
2	1:1	KI	TBHP	–	60	DCE	45
3	1:1	I_2	TBHP	–	60	DCE	65
4	1:1	I_2	TBHP	K_2CO_3	60	DCE	71
5	1:1	–	TBHP	K_2CO_3	60	DCE	ND[c,d]
6	1:1	I_2	–	K_2CO_3	60	DCE	20
7	1.2:1	I_2	TBHP	K_2CO_3	60	DCE	84
8	1.5:1	I_2	TBHP	K_2CO_3	60	DCE	90
9	2:1	I_2	TBHP	K_2CO_3	60	DCE	85
10	1.5:1	I_2	DTBP	K_2CO_3	60	DCE	40
11	1.5:1	I_2	30% H_2O_2	K_2CO_3	60	DCE	42
12	1.5:1	I_2	$K_2S_2O_8$	K_2CO_3	60	DCE	48
13	1.5:1	I_2	TBPB	K_2CO_3	60	DCE	42
14	1.5:1	I_2	CHP	K_2CO_3	60	DCE	65
15	1.5:1	I_2	*m*-CPBA	K_2CO_3	60	DCE	48
16	1.5:1	I_2	TBHP	K_2CO_3	60	1,4-dioxane	73
17	1.5:1	I_2	TBHP	K_2CO_3	60	THF	61
18	1.5:1	I_2	TBHP	K_2CO_3	60	CH_3CN	82
19	1.5:1	I_2	TBHP	K_2CO_3	60	EtOAc	61
20	1.5:1	I_2	TBHP	K_2CO_3	60	toluene	61
21	1.5:1	I_2	TBHP	K_2CO_3	60	DMF	20
22	1.5:1	I_2	TBHP	K_2CO_3	60	EtOH	65
23	1.5:1	I_2	TBHP	K_2CO_3	40	DCE	50[e]
24	1.5:1	I_2	TBHP	K_2CO_3	80	DCE	82

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), cat. (0.04 mmol), oxidant (0.4 mmol), additive (0.04 mmol), solvent (1 mL), under air atmosphere, 2 h. [b]Isolated yield. [c]ND: Not detected. [d]The Michael addition product was isolated in 53% yield. [e]When the reaction was performed for 8 h, the isolated yield was 80%.

Table 2. Scope of Enamines in the Synthesis of Polysubstituted Pyrroles 3[a]



1 2a 3

entry	substrate **1** (R^1/R^2/R^3)	products **3**	yield (%)[b]
1	**1a** (Et/Me/OEt)	**3aa**	90
2	**1b** (Bn/Me/OEt)	**3ba**	81
3	**1c** (PMB/Me/OEt)	**3ca**	75
4	**1d** (PMP/Me/OEt)	**3da**	87
5	**1e** (Mes/Me/OEt)	**3ea**	75
6	**1f** (4-MeC_6H_4/Me/OMe)	**3fa**	49
7	**1g** (4-ClC_6H_4/Me/OMe)	**3ga**	40
8	**1h** (Et/Et/OMe)	**3ha**	81
9	**1i** (Et/Ph/OEt)	**3ia**	91
10	**1j** (Et/4-$NO_2C_6H_4$/OEt)	**3ja**	58
11	**1k** (Et/4-MeOC_6H_4/OEt)	**3ka**	90
12	**1l** (Et/2-Pyridyl/OMe)	**3la**	51
13	**1m** (Et/Me/OMe)	**3ma**	90
14	**1n** (Et/Me/O^{i}Pr)	**3na**	72
15	**1o** (Et/Me/O^{t}Bu)	**3oa**	73
16	**1p** (Et/Me/OBn)	**3pa**	77
17	**1q** (Bn/ ^{t}Bu/Ph)	**3qa**	45
18	**1r** (Bn/Ph/Ph)	**3ra**	50

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), I_2 (0.04 mmol), TBHP (0.4 mmol), K_2CO_3 (0.04 mmol), DCE (1 mL), under air atmosphere. [b]Isolated yield.

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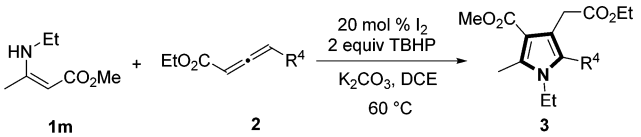
4). However, the yield of **3ga** with a *para*-Cl substituent dropped to 40% (Table 2, entry 7). Moreover, the corresponding pyrroles with alkyl or aryl groups on the 2-position could also be successfully synthesized in good to excellent yields (Table 2, entries 8−11). Interestingly, **1l** containing a pyridine group was also suitable for this reaction, affording the desired product **3la** in 51% yield (Table 2, entry 12). We also found that the ester group of **1** could be ranged from methyl to isopropyl, *tert*-butyl, or benzyl esters, all of which proceeded with dimethyl penta-2,3-dienedioate **2a** to afford the desired products in good to excellent yields (72%−90%, Table 2, entries 13−16). Finally, β-enaminones were well tolerated under optimized conditions, delivering **3qa** and **3ra** in 45% and 50% yield, respectively (Table 2, entries 17−18).

We next investigated the reaction of β-enamino ester **1m** with various allene derivatives bearing ethyl ester, alkyl, or aryl groups (**2b−h**). The reaction of **1m** with **2b** proceed smoothly to give the corresponding pyrrole **3mb** in good yield (80%, Table 3, entry 1). To our delight, when an unsymmetric allene

Table 3. Scope of Allenes in the Synthesis of Polysubstituted Pyrroles 3[a]



1m 2 3

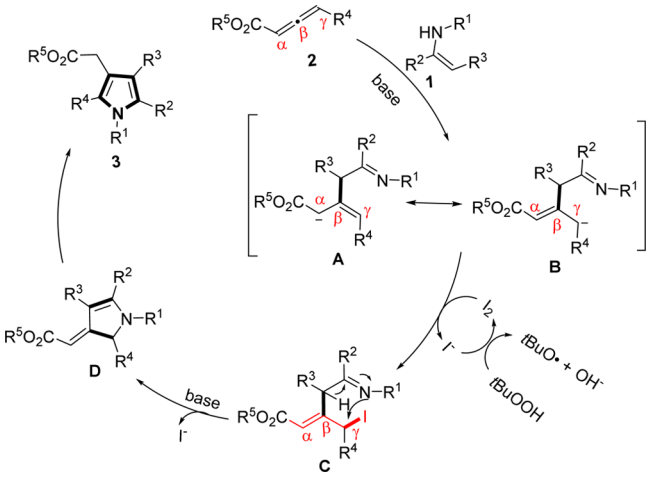
entry	substrate **2** (R^4)	products **3**	yield (%)[b]
1	**2b** (CO_2Et)	**3mb**	80
2	**2c** (Et)	**3mc**	57
3	**2d** (^{n}Bu)	**3md**	41
4	**2e** (Ph)	**3me**	46
5	**2f** (4-$MeOC_6H_4$)	**3mf**	35
6	**2g** (4-FC_6H_4)	**3 mg**	48
7	**2h** (Bn)	**3mh**	58

[a]Reaction conditions: **1m** (0.3 mmol), **2** (0.2 mmol), I_2 (0.04 mmol), TBHP (0.4 mmol), K_2CO_3 (0.04 mmol), DCE (1 mL), under air atmosphere. [b]Isolated yield.

2c was employed for this reaction, in contrast to our furan synthesis,[10] the desired product **3mc** was obtained in 57% yield with excellent regioselectivity (Table 3, entry 2). Subtle change of R^4 group of allene to ^{n}Bu gave slightly lower yield of **3md** with excellent regioselectivity as well (Table 3, entry 3). Encouraged by this result, next a series of aryl-substituted allenes (**2e−g**) bearing electron-withdrawing and -donating groups were tested. The reactions all proceed well to regioselectively form the desired products (**3me−g**) in moderate yields (35%−48%, Table 3, entries 4−6), notably, the **2f** bearing an electronic donating group showed the lowest reactivity presumably due to the higher electronic density of allene moiety (Table 3, entry 5). In addition, **2h** containing a benzyl group was also found suitable for this reaction, affording corresponding pyrrole **3mh** in 58% yield (Table 3, entry 7), and the structure of **3mh** was unequivocally confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information (SI)).[13]

Based on the results described above and previous reports,[12,14] a proposed mechanism is illustrated in Scheme 2. Initially, enamines **1** react with allenes **2** to afford the resonance stabilized anionic intermediate **A** and **B** via Michael addition under alkaline conditions, which is followed by a kinetic

Scheme 2. Plausible Pathway for the Formation of 3



controlled electrophilic substitution with I_2, regioselectively providing the γ-carbon iodination intermediate **C**.[15] Next, deprotonation and intramolecular nucleophilic substitution transform **C** into intermediate **D**, in which the released I^- can be oxidized by TBHP to regenerate the iodine catalyst. Finally, intermediate **D** undergoes a double-bond isomerization to give the pyrroles **3**.

CONCLUSION

In summary, we have successfully developed a novel I_2-catalyzed synthesis of polysubstituted pyrroles via a tandem Michael addition/oxidative annulation pathway from allenes and enamines. This protocol features mild reaction conditions, broad substrate scope, and especially excellent regioselectivities for the unsymmetric allenes, providing a novel synthetic strategy for the construction of pyrroles, which would be of great importance for the drug discovery in terms of the structure diversity of pyrroles derivatives.

EXPERIMENTAL SECTION

General Information. Commercial reagents were used without further purification unless otherwise noted. Melting points were obtained in open capillary tubes using a micromelting point apparatus that was uncorrected. Mass spectra were recorded on TOF mass spectrometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal chloroform signal at 77.16 ppm as a standard. TLC (thin-layer chromatogram) was performed using commercially prepared 100−400 mesh silica gel plates, and visualization was effected at 254 or 365 nm.

General Procedure for the Preparation of Polysubstituted Pyrroles 3. To a 10 mL tube containing I_2 (10.2 mg, 0.04 mmol) and K_2CO_3 (5.5 mg, 0.04 mmol) in DCE (1 mL) was added allenes **2** (0.2 mmol), enamines **1** (0.3 mmol), and TBHP (51.5 mg, 0.4 mmol). The mixture was then stirred at 60 °C under air atmosphere until the reaction was completed as judged by TLC, the resulting mixture was concentrated under the vacuum and directly purified by column chromatography (petroleum ether/ethyl acetate) on silica-gel to give the desired product **3**.

*4-Ethyl 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3aa**).* Yellow solid, yield: 55.8 mg, 90%; mp = 52−53 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (q, J = 7.1 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.21 (s, 2H), 3.82 (s, 3H), 3.70 (s, 3H), 2.56 (s, 3H), 1.36−

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1.29 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 165.1, 161.7, 141.0, 127.0, 120.2, 112.8, 59.9, 51.9, 51.3, 40.8, 32.4, 15.9, 14.4, 11.8; IR (KBr) υ 3467, 3000, 2954, 2850, 1742, 1691, 1479, 1434, 1379, 1338, 1260, 1244, 1172, 1151, 1100, 189, 734 cm^{-1}; HRMS (EI-TOF) calcd for $C_{15}H_{21}NO_6$ $[M]^+$ 311.1369, found: 311.1367.

*4-Ethyl 2-Methyl 1-Benzyl-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3ba**).* Yellow oil, yield: 60.5 mg, 81%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.12 (m, 3H), 6.86 (d, J = 7.4 Hz, 2H), 5.54 (s, 2H), 4.26−4.12 (m, 4H), 3.66 (s, 3H), 3.64 (s, 3H), 2.41 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.1, 161.6, 142.1, 137.3, 128.9, 127.3, 127.3, 125.8, 120.9, 113.3, 60.0, 52.0, 51.4, 48.8, 32.5, 14.4, 12.1; IR (KBr) υ 3530, 3449, 2954, 2850, 1742, 1698, 1473, 1441, 1264, 1130, 1104, 1023, 799, 735, 708 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{23}NO_6$ $[M]^+$ 373.1525, found: 373.1526.

*4-Ethyl 2-Methyl 3-(2-Methoxy-2-oxoethyl)-1-(4-methoxybenzyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3ca**).* Yellow oil, yield: 60.5 mg, 75%, R_f = 0.30 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.54 (s, 2H), 4.30−4.24 (m, 4H), 3.77 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 2.49 (s, 3H), 1.33 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.1, 161.7, 158.8, 142.1, 129.3, 127.2, 127.1, 120.9, 114.2, 113.2, 60.0, 55.4, 52.0, 51.4, 48.3, 32.5, 14.4, 12.2; IR (KBr) υ 3446, 2953, 2922, 2849, 1741, 1700, 1613, 1513, 1342, 1263, 1250, 1172, 1130, 1105, 846, 817, 743 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{25}NO_7$ $[M]^+$ 403.1631, found: 403.1630.

*4-Ethyl 2-Methyl 3-(2-Methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3da**).* Yellow oil, yield: 65.3 mg; 87%, R_f = 0.20 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 4.34−4.23 (m, 4H), 3.86 (s, 3H), 3.73 (s, 3H), 3.60 (s, 3H), 2.25 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.1, 161.2, 159.6, 142.9, 131.5, 128.8, 126.9, 122.4, 114.2, 113.1, 60.0, 55.6, 52.0, 51.3, 32.2, 14.5, 13.2; IR (KBr) υ 3451, 2953, 2847, 1742, 1702, 1514, 1461, 1442, 1250, 1165, 1106, 1069, 835, 782, 660, 621 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{23}NO_7$ $[M]^+$ 389.1475, found: 389.1476.

*4-Ethyl 2-Methyl 1-Mesityl-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3ea**).* Yellow solid, yield: 60.2 mg, 75%; mp = 98−99 °C, R_f = 0.40 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 2H), 4.35−4.23 (m, 4H), 3.72 (s, 3H), 3.61 (s, 3H), 2.34 (s, 3H), 2.16 (s, 3H), 1.87 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.2, 160.9, 141.5, 138.4, 135.3, 134.7, 128.9, 127.2, 120.9, 113.3, 60.0, 51.9, 51.3, 32.23, 21.3, 17.5, 14.4, 12.2; IR (KBr) υ 3394, 2986, 2956, 2919, 2851, 1746, 1696, 1453, 1379, 1337, 1266, 1211, 1182, 1147, 865, 732, 657 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{27}NO_6$ $[M]^+$ 401.1838, found: 401.1839.

*Dimethyl 3-(2-Methoxy-2-oxoethyl)-5-methyl-1-(p-tolyl)-1H-pyrrole-2,4-dicarboxylate (**3fa**).* Yellow oil, yield: 35.2 mg, 49%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 7.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 4.27 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.60 (s, 3H), 2.43 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.5, 161.1, 142.6, 138.7, 136.2, 129.7, 127.5, 127.0, 122.4, 112.9, 52.0, 51.2, 51.1, 32.2, 21.4, 13.2; IR (KBr) υ 3452, 3393, 2992, 2952, 2923, 2849, 1744, 1705, 1514, 1439, 1279, 1262, 1193, 1164, 1108, 1069, 821, 795, 735, 661 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{21}NO_6$ $[M]^+$ 359.1369, found: 359.1370.

*Dimethyl 1-(4-Chlorophenyl)-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3ga**).* Yellow oil, yield: 30.4 mg, 40%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 4.27 (s, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 3.61 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 165.3, 161.0, 142.4, 137.4, 134.8, 129.4, 129.2, 127.4, 122.3, 113.4, 52.1, 51.4, 51.2, 32.1, 13.2; IR (KBr) υ 3394, 2995, 2953, 2922, 2849, 1742, 1706, 1495, 1439, 1263, 1193, 1165, 1090, 835, 791, 742, 658, 514 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{18}ClNO_6$ $[M]^+$ 379.0823, found: 379.0820.

*Dimethyl 1,5-Diethyl-3-(2-methoxy-2-oxoethyl)-1H-pyrrole-2,4-dicarboxylate (**3ha**).* Yellow solid, yield: 50.4 mg, 81%; mp = 80−82 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (q, J = 7.1 Hz, 2H), 4.20 (s,2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 2.98 (q, J = 7.5 Hz, 2H), 1.35 (t, J = 7.1 Hz,3H), 1.21 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 165.3, 161.6, 146.7, 127.3, 120.0, 111.8, 51.9, 51.3, 51.0, 40.6, 32.5, 19.0, 16.8, 14.1; IR (KBr) υ 3455, 2978, 2953, 2877, 2848, 1741, 1698, 1492, 1435, 1341, 1275, 1193, 1175, 1101, 743 cm^{-1}; HRMS (EI-TOF) calcd for $C_{15}H_{21}NO_6$ $[M]^+$ 311.1369, found: 311.1368.

*4-Ethyl 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-2,4-dicarboxylate (**3ia**).* Yellow solid, yield: 68.0 mg, 91%; mp = 94−96 °C, R_f = 0.40 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.41 (m, 3H), 7.34−7.29 (m, 2H), 4.31 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.95 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.73 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 164.4, 161.7, 143.4, 132.1, 130.2, 128.8, 128.1, 127.3, 120.6, 114.0, 59.5, 51.9, 51.4, 41.9, 32.1, 16.8, 13.6; IR (KBr) υ 3457, 2985, 2957, 2941, 2901, 1738, 1694, 1483, 1450, 1410, 1274, 1248, 1192, 1120, 1065, 849, 769, 703 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{23}NO_6$ $[M]^+$ 373.1525, found: 373.1526.

*4-Ethyl 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-(4-nitrophenyl)-1H-pyrrole-2,4-dicarboxylate (**3ja**).* Yellow solid, yield: 48.5 mg, 58%; mp = 94−96 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 4.30 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.99 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.8, 161.5, 148.2, 140.4, 139.0, 131.6, 127.4, 123.4, 121.7, 114.5, 60.0, 52.1, 51.7, 42.2, 32.1, 16.9, 13.8; IR (KBr) υ 3399, 2987, 2952, 2922, 2850, 1739, 1716, 1696, 1522, 1486, 1347, 1277, 1193, 1169, 855, 711 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{22}N_2O_8$ $[M]^+$ 418.1376, found: 418.1378.

*4-Ethyl 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-1H-pyrrole-2,4-dicarboxylate (**3ka**).* Yellow solid, yield: 72.6 mg, 90%; mp = 70−72 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 4.29 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.99 (q, J = 7.1 Hz, 2H), 3.88−3.83 (m, 6H), 3.72 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 164.5, 161.7, 160.0, 143.4, 131.5, 127.2, 124.0, 120.5, 114.1, 113.5, 59.6, 55.4, 51.9, 51.3, 41.7, 32.2, 16.8, 13.8; IR (KBr) υ 3449, 2980, 2953, 2852, 2833, 1734, 1692, 1485, 1453, 1273, 1251, 1187, 1168, 1061, 835, 797, 752 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{25}NO_7$ $[M]^+$ 403.1631, found: 403.1632.

*Dimethyl 1-Ethyl-3-(2-Methoxy-2-oxoethyl)-5-(pyridin-2-yl)-1H-pyrrole-2,4-dicarboxylate (**3la**).* Yellow oil, yield: 36.8 mg, 51%, R_f = 0.20 (petroleum ether/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 5.0 Hz, 1H), 7.83−7.77 (m, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.39−7.34 (m, 1H), 4.28 (s, 2H), 4.19 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 3.51 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 164.6, 161.6, 151.3, 149.5, 141.7, 136.0, 127.0, 126.6, 123.5, 121.1, 113.9, 52.0, 51.5, 51.0, 42.3, 32.3, 16.7; IR (KBr) υ 3448, 2954, 2923, 2852, 1740, 1706, 1478, 1448, 1272, 1197, 1171, 1100, 793, 749, 620 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{20}N_2O_6$ $[M]^+$ 360.1321, found: 360.1323.

*Dimethyl 1-Ethyl-3-(2-Methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3ma**).* Yellow solid, yield: 53.5 mg, 90%; mp = 84−86 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (q, J = 7.1 Hz, 2H), 4.20 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 2.56 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 165.6, 161.6, 141.0, 127.1, 120.2, 112.6, 52.0, 51.3, 51.0, 40.9, 32.4, 15.94, 11.8; IR (KBr) υ 3458, 2996, 2954, 2850, 1740, 1695, 1539, 1435, 1346, 1262, 1190, 1154, 1119, 1102, 835, 789, 740 cm^{-1}; HRMS (EI-TOF) calcd for $C_{14}H_{19}NO_6$ $[M]^+$ 297.1212, found: 297.1211.

*4-Isopropyl 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3na**).* Yellow solid, yield: 46.8 mg, 72%; mp = 65−67 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23−5.10 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.21 (s,2H), 3.82 (s, 3H), 3.70 (s, 3H), 2.56 (s, 3H),

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1.36−1.28 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 164.7, 161.7, 141.0, 126.9, 120.1, 113.2, 67.3, 51.9, 51.3, 40.8, 32.5, 22.2, 16.0, 11.8; IR (KBr) υ 3459, 2983, 2955, 2935, 2848, 1736, 1686, 1445, 1341, 1299, 1259, 1243, 1170, 1153, 1122, 1097, 792, 734 cm^{-1}; HRMS (EI-TOF) calcd for $C_{16}H_{23}NO_6$ $[M]^+$ 325.1525, found: 325.1526.

*4-(tert-Butyl) 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3oa**).* Yellow oil, yield: 49.6 mg, 73%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (q, J = 7.1 Hz, 2H), 4.19 (s, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 2.54 (s, 3H), 1.53 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 164.5, 161.7, 140.6, 126.6, 119.8, 114.3, 80.6, 51.8, 51.2, 40.7, 32.4, 28.5, 16.0, 11.8; IR (KBr) υ 3394, 2978, 2955, 1741, 1707, 1690, 1477, 1342, 1271, 1197, 1171, 1146, 1102, 844, 795, 733 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{25}NO_6$ $[M]^+$ 339.1682, found: 339.1683.

*4-Benzyl 2-Methyl 1-Ethyl-3-(2-methoxy-2-oxoethyl)-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3pa**).* Yellow oil, yield: 57.5 mg, 77%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.35 (m, 3H), 7.34−7.28 (m, 2H), 5.26 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.19 (s, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.55 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 164.9, 161.6, 141.2, 136.4, 128.6, 128.4, 128.2, 127.2, 120.3, 112.5, 65.9, 51.9, 51.3, 40.9, 32.4, 15.9, 12.0; IR (KBr) υ 3395, 2951, 2850, 1742, 1697, 1440, 1263, 1169, 1151, 1096, 738, 700 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{23}NO_6$ $[M]^+$ 373.1525, found: 373.1526.

*Methyl 4-Benzoyl-1-Benzyl-5-(tert-butyl)-3-(2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (**3qa**).* Yellow solid, yield: 40.3 mg, 45%; mp = 151−153 °C, R_f = 0.20 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.49−7.43 (m, 2H), 7.31 (t, J = 7.5 Hz,2H), 7.21 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 7.1 Hz, 2H), 5.91 (s, 2H), 3.58 (s, 3H), 3.50 (s, 2H), 3.47 (s, 3H), 1.26 (s,9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 171.7, 161.2, 143.7, 139.7, 139.3, 133.7, 128.8, 128.8, 127.0, 125.2, 124.1, 123.0, 121.6, 51.8, 51.1, 50.8, 34.3, 32.3, 31.6; IR (KBr) υ 3409, 2956, 2924, 2852, 1742, 1710, 1654, 1440, 1273, 1196, 1171, 1111, 730, 694 cm^{-1}; HRMS (EI-TOF) calcd for $C_{27}H_{29}NO_5$ $[M]^+$ 447.2046, found: 447.2047.

*Methyl 4-Benzoyl-1-Benzyl-3-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-2-carboxylate (**3ra**).* Yellow oil, yield: 46.8 mg, 50%, R_f = 0.20 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.49 (m, 2H), 7.26−7.24 (m, 1H), 7.24−7.21 (m, 2H), 7.23−7.15 (m, 1H), 7.11 (d, J = 7.8 Hz, 2H), 7.11−7.03 (m, 5H), 6.83−6.80 (m, 2H), 5.54 (s, 2H), 4.11 (s, 2H), 3.74 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 172.2, 161.7, 142.9, 139.1, 138.6, 132.1, 131.0, 130.1, 129.6, 129.0, 128.8, 128.3, 127.9, 127.4, 127.3, 125.9, 124.1, 122.1, 52.1, 51.5, 50.0, 32.0; IR (KBr) υ 3450, 2950, 2922, 2851, 1736, 1705, 1636, 1452, 1439, 1258, 1203, 1169, 1127, 764, 724, 700 cm^{-1}; HRMS (EI-TOF) calcd for $C_{29}H_{25}NO_5$ [M]+ 467.1733, found: 467.1734.

*2-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-1-ethyl-5-methyl-1H-pyrrole-2,4-dicarboxylate (**3mb**).* Yellow oil, yield: 52.1 mg, 80%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (q, J = 7.1 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.20 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.55 (s, 3H), 1.37−1.29 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 165.6, 161.3, 140.8, 127.0, 120.5, 112.6, 60.5, 60.3, 50.9, 40.8, 32.6, 16.0, 14.4, 14.3, 11.8; IR (KBr) υ 3461, 3383, 2990, 2950, 2907, 2875, 1742, 1700, 1477, 1450, 1266, 1176, 1150, 1101,800, 741 cm^{-1}; HRMS (EI-TOF) calcd for $C_{16}H_{23}NO_6$ $[M]^+$ 325.1525, found: 325.1527.

*Methyl 4-(2-Ethoxy-2-oxoethyl)-1,5-diethyl-2-methyl-1H-pyrrole-3-carboxylate (**3mc**).* Yellow oil, yield: 32.1 mg, 57%, R_f = 0.30 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2H), 3.85 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.63 (s, 2H), 2.62−2.46 (m, 5H), 1.31−1.22 (m, 6H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 166.4, 134.9, 132.0, 112.5, 110.1, 60.5, 50.4, 38.4, 31.8, 17.4, 16.3, 15.5, 14.5, 11.6; IR (KBr) υ 3426, 2973, 2934, 2874, 2851, 1740, 1697, 1531, 1444, 1242, 1180, 1161, 1113, 785 cm^{-1}; HRMS (EI-TOF) calcd for $C_{15}H_{23}NO_4$ $[M]^+$ 281.1627, found: 281.1628.

*Methyl 5-Butyl-4-(2-Ethoxy-2-oxoethyl)-1-ethyl-2-methyl-1H-pyrrole-3-carboxylate (**3md**).* Yellow oil, yield: 25.4 mg, 41%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2H), 3.84 (q, J = 7.2 Hz, 2H), 3.73 (s, 3H), 3.62 (s, 2H), 2.51 (s, 3H), 1.48−1.31 (m, 6H), 1.29−1.23 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 166.4, 135.0, 130.5, 112.9, 110.1, 60.4, 50.4, 38.4, 33.1, 32.0, 24.0, 22.7, 16.2, 14.5, 14.0, 11.7; IR (KBr) υ 3445, 2955, 2931, 2871, 1740, 1699, 1443, 1254, 1177, 1160, 1118, 1072 785 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{27}NO_4$ $[M]^+$ 309.1940, found: 309.1939.

*Methyl 4-(2-Ethoxy-2-oxoethyl)-1-ethyl-2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (**3me**).* Yellow oil, yield: 30.3 mg, 46%, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.36 (m, 3H), 7.32 (d, J = 7.8 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.83−3.72 (m, 5H), 3.46 (s, 2H), 2.59 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 166.3, 135.9, 132.5, 131.7, 131.2, 128.6, 128.3, 115.0, 110.5, 60.4, 50.5, 39.2, 32.4, 16.1, 14.4, 11.8; IR (KBr) υ 3445, 2983, 2954, 2922, 2874, 2851, 1734, 1686, 1447, 1264, 1176, 1154, 1096, 1034, 799, 769, 704 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{23}NO_4$ $[M]^+$ 329.1627, found: 329.1628.

*Methyl 4-(2-Ethoxy-2-oxoethyl)-1-ethyl-5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (**3mf**).* Yellow solid, yield: 25.2 mg, 35%; mp = 87−89 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.79−3.72 (m, 5H), 3.45 (s, 2H), 2.58 (s, 3H), 1.25 (d, J = 7.4 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 166.3, 159.6, 135.6, 132.5, 132.2, 123.8, 114.9, 114.0, 110.3, 60.4, 55.4, 50.5, 39.1, 32.5, 16.2, 14.5, 11.8; IR (KBr) υ 3395, 2980, 2952, 2922, 2872, 2848, 1739, 1685, 1509, 1454, 1248, 1173, 1153, 1099, 1025, 835, 819, 792, 751, 589, 531 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{25}NO_5$ $[M]^+$ 359.1733, found: 359.1734.

*Methyl 4-(2-Ethoxy-2-oxoethyl)-1-ethyl-5-(4-fluorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**3 mg**).* Yellow solid, yield: 33.4 mg, 48%; mp = 84−64 °C, R_f = 0.30 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2H), 7.12 (t, J = 8.5 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.79−3.70 (m, 5H), 3.44 (s, 2H), 2.58 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 166.2, 162.8 (d, J = 248.0 Hz), 135.9, 133.1 (d, J = 8.3 Hz), 131.3, 127.6 (d, J = 3.3 Hz), 115.7(d, J = 21.4 Hz), 115.3, 110.5, 60.5, 50.6, 39.1, 32.3, 16.1, 14.4, 11.8; IR (KBr) υ 3447, 2978, 2924, 2875, 1734, 1685, 1505, 1448, 1415, 1370, 1339, 1296, 1268, 1226, 1181, 1154, 1096, 840, 821, 578, 527 cm^{-1}, HRMS (EI-TOF) calcd for $C_{19}H_{22}FNO_4$ $[M]^+$ 347.1533, found: 347.1532.

*Methyl 5-Benzyl-4-(2-ethoxy-2-oxoethyl)-1-ethyl-2-methyl-1H-pyrrole-3-carboxylate (**3mh**).* Yellow solid, yield: 39.8 mg, 58%; mp = 102−104 °C, R_f = 0.40 (petroleum ether/ethyl acetate = 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.23 (m, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 3.76 (s, 3H), 3.74−3.64 (m, 4H), 2.50 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 166.3, 139.2, 135.9, 128.7, 128.1, 128.1, 126.5, 114.8, 110.2, 60.5, 50.5, 38.8, 32.0, 30.1, 15.6, 14.4, 11.6; IR (KBr) υ 3453, 2982, 2920, 2872, 1738, 1701, 1532, 1437, 1332, 1253, 1201, 1174, 1089, 1028, 754, 724, 700 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{25}NO_4$ $[M]^+$ 343,1784, found: 343.1783.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01737.

crystallographic data (CIF)

Copies of ^{1}H and ^{13}C NMR spectra data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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