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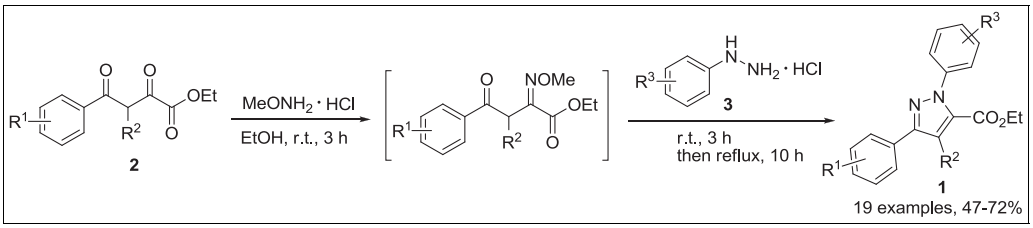

A one-pot synthesis of highly substituted 1*H*-pyrazole-5-carboxylates **1** has been developed starting from easily available 4-aryl-2,4-diketoesters **2** and arylhydrazine hydrochlorides **3**. More active 2-carbonyl group of **2** was blocked with methoxyamine hydrochloride to give 2-methoxy imine intermediates, which were then subjected to condensation cyclization with **3** *in situ* to provide the desired products **1**. In addition, the geometrical configuration of **1aa** was unambiguously confirmed by single crystal X-ray crystallography.

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INTRODUCTION

Pyrazoles are of significant synthetic targets in organic and pharmaceutical chemistry because of pyrazole motif generally acting as a core framework in numerous biologically active compounds [1–3]. In particular, substituted 1*H*-pyrazole-3-amidate derivatives have been well developed as cannabinoid (designated CB1) receptor antagonists such as Rimonabant [4], SR147778 [5], CP-272,871 [6], and OMAR [7] (Fig. 1). Structurally, these CB1 receptor antagonists are characterized by the ornament of 1*H*-pyrazole-3-carboxylate framework, which is usually constructed by regioselective Knorr reaction of 2,4-diketoesters and hydrazines via a direct route [1–3]. On the other hand, the isomeric framework-based 1*H*-pyrazole-5-amidate derivatives have also displayed important biological activities [8–10] and owned identical significance as 1*H*-pyrazole-3-carboxylates in the drug discovery (Fig. 1). Traditionally, the 1,3-dipolar cycloaddition method, often suffering from commercially unavailable feedstocks and tedious procedures, has undertaken a synthetic priority to selectively access the 1*H*-pyrazole-5-carboxylate framework [8–10]. Therefore, it is still greatly desirable to develop a concise and facile approach to highly substituted 1*H*-pyrazole-5-carboxylates.

Continuing our recent work involving the synthesis of highly substituted 1*H*-pyrazole-3-carboxylates [11,12], herein, we reported a viable one-pot approach to highly substituted 1*H*-pyrazole-5-carboxylates from easily available 4-aryl-2,4-diketoesters and arylhydrazine hydrochlorides. In the methodology, more active 2-carbonyl group of 4-aryl-2,4-diketoesters was first blocked with methoxyamine hydrochloride to give the 2-methoxy imine derivatives, and a compelling *in situ* attack of arylhydrazines on the 4-carbonyl group, followed by a cyclization with the elimination of methoxylamine led to the desired 1*H*-pyrazole-5-carboxylates.

RESULTS AND DISCUSSION

Inspired by Ashton's synthesis of a sole 1*H*-pyrazole-5-carboxylate compound starting from 2,4-diketoesters [13] and the related report about amine exchange reaction of enamine with another amine resulting in a new enamine [14], we firstly investigated various amines as 2-carbonyl-protection reagent to access 1*H*-pyrazole-5-carboxylates with freshly prepared ethyl 2,4-dioxo-4-phenylbutanoate (**2a**) as a model substrate. As shown in Scheme 1, the control experiments showed that the carbonyl-protection reactions of more active 2-carbonyl group with various amine hydrochlorides (one equivalent) all performed well giving the 2-imine intermediates. However, only the methoxy imine intermediate was observed to conduct a 4-carbonyl condensation with phenylhydrazine hydrochloride (**3a**) and a subsequent cyclization with the elimination of methoxyamine, successfully affording the desired 1*H*-pyrazole-5-carboxylates **1aa** in 72% yield *via* this one-pot procedure (feasible route). In contrast, the 2-imine intermediates derived from methylamine, ethylamine, aniline and benzylamine hydrochlorides failed to give **1aa**, without the cyclization reaction of their respective hydrazone-imine intermediate being detected

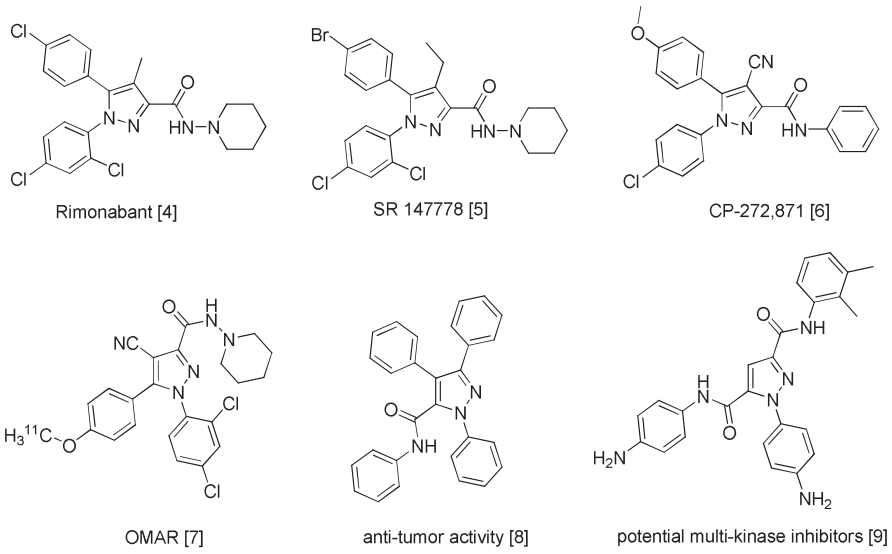
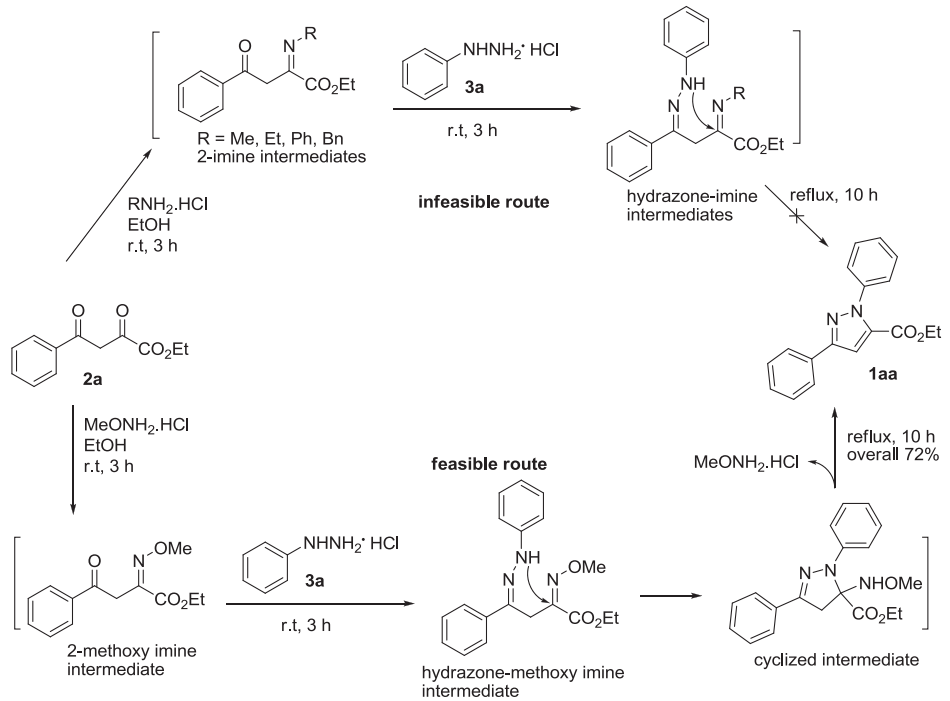


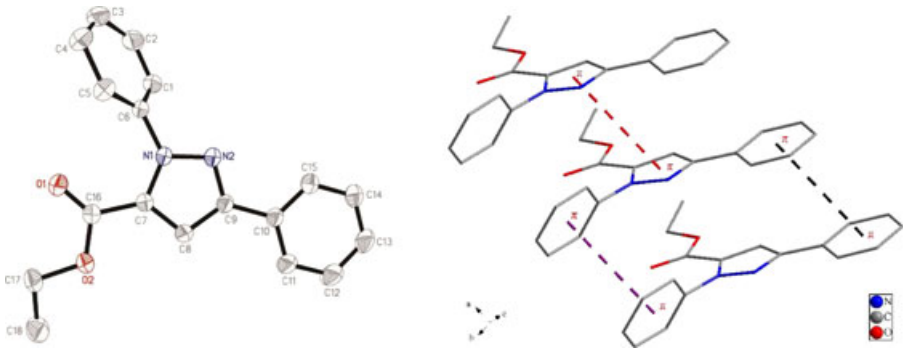
Figure 1. Structures of biologically active 1*H*-pyrazole-3-amidate and 1*H*-pyrazole-5-amidate derivatives.

(infeasible route). In the case of the hydrazone-methoxy imine intermediate (feasible route), we speculated that the cyclized intermediate greatly tended to release more stable salt methoxyamine hydrochloride with an aromatization to drive powerfully the formation of **1aa**. Notably, the geometrical configuration of **1aa** was further determined by single crystal X-ray crystallography. The structural analysis indicates that **1aa** consists of two phenyl rings and one pyrazole ring (Fig. 2a). These rings do not share a common plane. The phenyl ring linked with N1 atom and the phenyl ring attached on C9 atom make dihedral angles of 55.3(1) and 4.8(1)°, respectively, with the pyrazole ring. The bond lengths and bond angles in the structure of **1aa** are in the usual ranges and can be comparable with the related compounds [12,15,16].

As shown in Figure 2b, there are three kinds of face-to-face $\pi\cdots\pi$ interactions in the crystal structure of **1aa**. The first one is formed between two parallel pyrazole rings,

Scheme 1. A carboxyl-protection, compelling condensation and cyclization sequence for one-pot synthesis of **1aa**.





(a) (b)

Figure 2. (a) Crystal structure of **1aa**. (b) View of the crystal packing showing $\pi \cdots \pi$ interactions in **1aa**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the second one between the two parallel phenyl rings linked with N1 atom and the third one between the two parallel phenyl rings attached on C9 atom. These $\pi \cdots \pi$ interactions link the molecules of **1aa** to form an infinite chain along *a* axis.

With the one-pot synthesis of **1aa** established, we then tried to prepare a series of fully substituted 1*H*-pyrazole-5-carboxylates starting from diverse 4-aryl-2,4-diketoesters **2** and arylhydrazine hydrochlorides **3**, using methoxyamine hydrochloride as a 2-carbonyl-protection reagent (Table 1). Firstly, 4-aryl-2,4-diketoesters **2b–2g** containing different R^1 and R^2 groups were assessed on the basis of arylhydrazine hydrochlorides **3a** (entries 1–6). Compared with **1aa**, the procedure delivered the products **1ba–1da** in slightly low yields of 65–68% from the 3-methyl-2,4-diketoesters **2b–2d** with a slight steric effect of the methyl group (entries 1–3). By comparison, 4-bulky group substituted compounds **1ea–1ga** were obtained in lower yields of 47–52% (entries 4–6), showing an obvious detrimental impact of R^2 groups on the efficiency of the procedure.

Next, arylhydrazine hydrochlorides **3b–3g** containing different substituents were evaluated with freshly prepared ethyl 3-methyl-2,4-dioxo-4-phenylbutanoate (**2b**, entries 7–12). Varying the number of substituents, the yields of the products **1bb–1bg** could change from 47 to 63% (entries 7–12). Therein, it should be noted that, regardless of the electronic nature of substituents, the *ortho,ortho*-disubstituted arylhydrazine hydrochlorides **3d** and **3g** gave rise to lower yields of 50 and 47%, respectively (entries 9 and 12), indicating a visible steric influence of R^3 groups on the outcomes. Finally, more diverse 1*H*-pyrazole-5-carboxylates were generally accomplished in moderate yields of 57–62% from different 2,4-diketoesters and arylhydrazine hydrochlorides (entries 13–18), further verifying the feasibility of the one-pot procedure.

In summary, we have developed a one-pot procedure for the rapid synthesis of highly substituted 1*H*-pyrazole-5-carboxylates **1** from easily available 4-aryl-2,4-diketoesters **2** and arylhydrazine hydrochlorides **3**, avoiding the troublesome 1,3-dipolar cycloaddition method. Using methoxyamine hydrochloride as a 2-carbonyl-protection reagent, the compelling *in situ* attack of arylhydrazine hydrochlorides on less active 4-carbonyl group was steadily implemented. In the end of the reaction, methoxyamine acts as a responsible leaving group with aromatization to achieve the desired **1**. We believe that the procedure may promise a potential value in synthetic chemistry and drug discovery.

EXPERIMENTAL

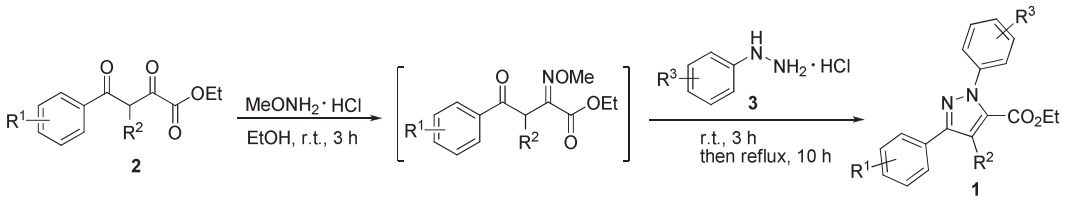
Unless otherwise indicated, all reagents were obtained from commercial sources and used as received without further purification. 4-Aryl-2,4-diketoesters **2** were freshly prepared from alkylphenones and diethyl oxalate [11]. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (precoated silica gel plates containing HF_{254}). All solvents were only dried over 4 Å molecular sieves. Melting points were determined using an open capillaries and uncorrected. NMR spectra were determined on Bruker AV400 in $CDCl_3$ with TMS as the internal standard for ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz), respectively. HRMS were carried out on a QSTAR Pulsar I LC/TOF MS mass spectrometer and Micromass GCTTM gas chromatograph-mass spectrometer.

General procedure for the synthesis of highly substituted 1*H*-pyrazole-5-carboxylates. Freshly prepared 4-aryl-2,4-diketoesters **2** (5.0 mmol) was added to a solution of methoxyamine hydrochloride (5.0 mmol) in EtOH (15 mL) and stirred at room temperature for 3 h. To the resulting mixture were added arylhydrazine hydrochlorides (5.0 mmol) *in situ* and stirred at room temperature for 3 h and then refluxed for additional 10 h. The reaction solution was concentrated *in vacuo* to remove EtOH affording a residue, to which were added H_2O (15 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL × 2). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate. The crude product was purified by column chromatography (200–300 mesh silica gel, petroleum ether/ethyl acetate = 20/1) to give the desired products **1**.

Ethyl 1,3-diphenyl-1H-pyrazole-5-carboxylate (1aa). Pale yellow solid, 1.05 g (72%), mp 66–68°C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.89 (d, J = 7.2 Hz, 2H, ArH), 7.50–7.41 (m, 7H, ArH), 7.36 (d, J = 7.2 Hz, 1H, ArH), 7.33 (s, 1H, ArH), 4.27 (q, J = 7.2 Hz, 2H, CH_2), 1.27 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.14, 151.48, 140.41, 134.71, 132.17, 128.74 (2C), 128.69, 128.59

Table 1

One-pot synthesis of highly substituted 1*H*-pyrazole-5-carboxylates[a].



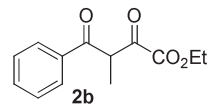
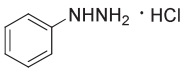
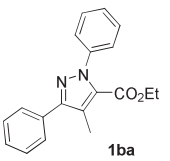
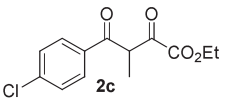
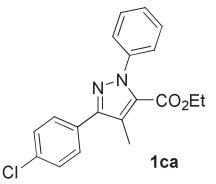
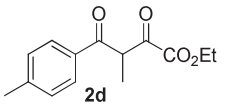
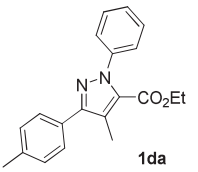
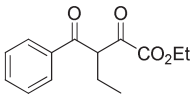
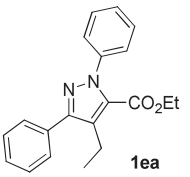
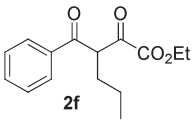
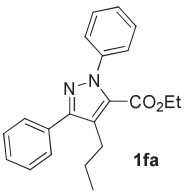
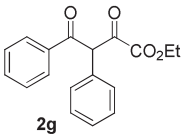
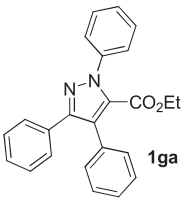
Entry	2	3	1	Yield[b]
1	 **2b**	 **3a**	 **1ba**	68%
2	 **2c**	**3a**	 **1ca**	67%
3	 **2d**	**3a**	 **1da**	65%
4	 **2e**	**3a**	 **1ea**	52%
5	 **2f**	**3a**	 **1fa**	48%
6	 **2g**	**3a**	 **1ga**	47%

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Table 1
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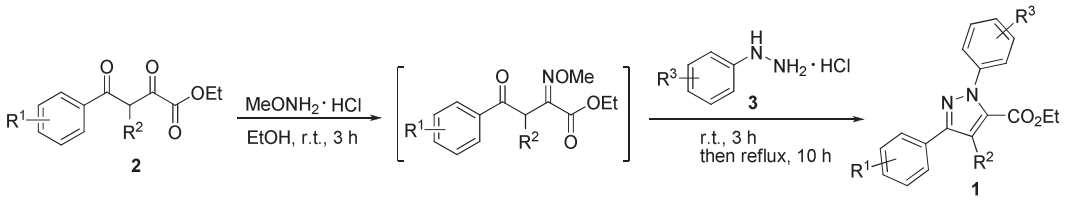


2 **3** **1**

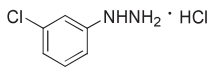
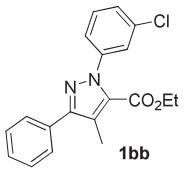
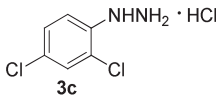
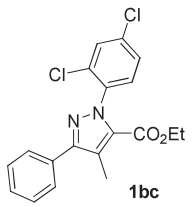
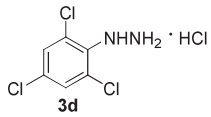
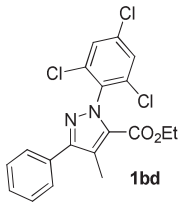
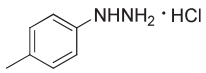
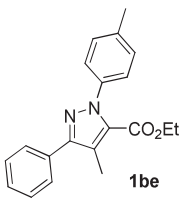
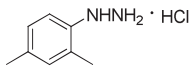
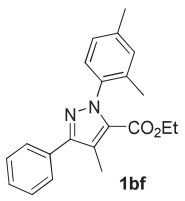
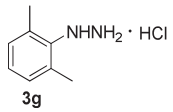
Entry	2	3	1	Yield[b]
7	**2b**	 **3b**	 **1bb**	63%
8	**2b**	 **3c**	 **1bc**	61%
9	**2b**	 **3d**	 **1bd**	50%
10	**2b**	 **3e**	 **1be**	60%
11	**2b**	 **3f**	 **1bf**	57%
12	**2b**	 **3g**		47%

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Table 1
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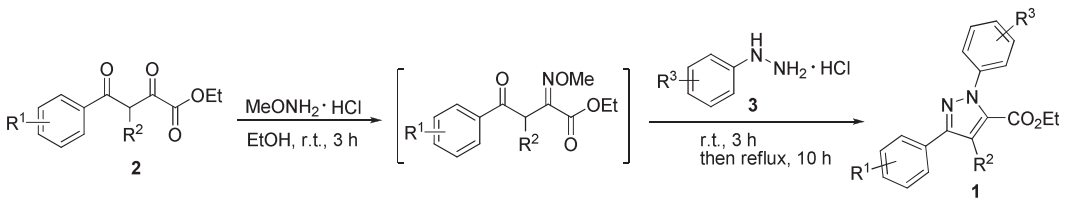

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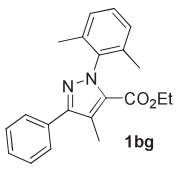
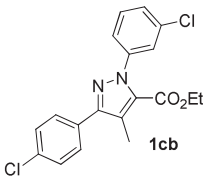
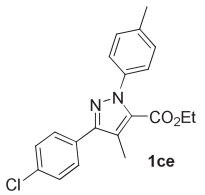
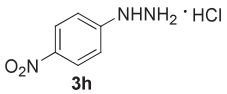
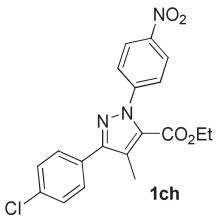
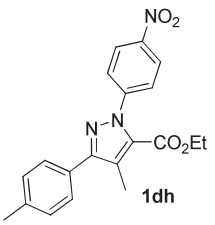
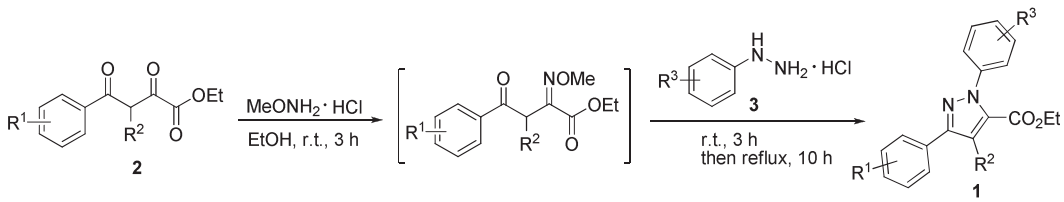
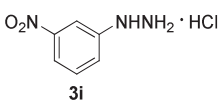
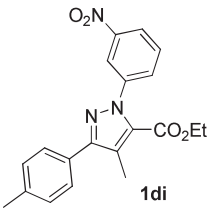
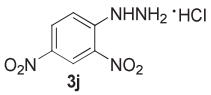
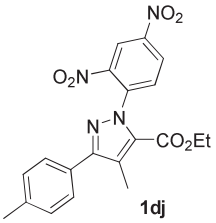
			 1bg	
13	**2c**	**3b**	 1cb	61%
14	**2c**	**3e**	 1ce	62%
15	**2c**	 3h	 1ch	60%
16	**2d**	**3h**	 1dh	61%
17	**2d**			60%

(*Continued*)

Table 1
(*Continued*)



Entry	2	3	1	Yield[b]
		 **3i**	 **1di**	
18	**2d**	 **3j**	 **1dj**	57%

[a]The reaction performed with freshly prepared 4-aryl-2,4-diketoesters **2** (5.0 mmol), methoxyamine hydrochloride (5.0 mmol), arylhydrazine hydrochlorides **3** (5.0 mmol) in EtOH (15 mL).
[b]Isolated yield.

(2C), 128.39, 126.14 (2C), 125.81 (2C), 109.45, 61.23, 14.06. HRMS (ESI, *m/z*): $[M+H^+]$ calcd. for $C_{18}H_{17}N_2O_2$ 293.1290, found 293.1290.

Ethyl 4-methyl-1,3-diphenyl-1*H*-pyrazole-5-carboxylate (1ba). Pale yellow solid, 1.04 g (68%), mp 68–70°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.69 (d, J = 7.2 Hz, 2H, ArH), 7.48–7.35 (m, 8H, ArH), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 2.48 (s, 3H, CH_3), 1.17 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.25, 151.60, 141.08, 132.80, 132.06, 128.58 (2C), 128.49 (2C), 128.31 (2C), 128.24, 127.98, 125.81 (2C), 120.90, 60.97, 13.89, 10.55. HRMS (ESI, *m/z*): $[M+H^+]$ calcd. for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1448.

Ethyl 3-(4-chlorophenyl)-4-methyl-1-phenyl-1*H*-pyrazole-5-carboxylate (1ca). Pale yellow solid, 1.16 g (67%), mp 62–63°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.65–7.63 (m, 1H, ArH), 7.62–7.61 (m, 1H, ArH), 7.46–7.44 (m, 1H, ArH), 7.44–7.42 (m, 4H, ArH), 7.42–7.40 (m, 2H, ArH), 4.23 (q, J = 7.2 Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.16 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.11, 150.43, 140.97, 133.98, 132.25, 131.31, 129.51 (2C), 128.71 (2C), 128.63 (2C), 128.39, 125.77 (2C), 120.80, 61.04, 13.87, 10.52. HRMS (ESI, *m/z*): $[M+H^+]$ calcd. for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1056.

Ethyl 4-methyl-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carboxylate (1da). Pale yellow solid, 1.04 g (65%), mp 92–93°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.58 (d, J = 7.4 Hz, 2H, ArH), 7.43 (br s, 5H, ArH), 7.25–7.21 (m, 1H, ArH), 7.20–7.12 (m, 1H, ArH), 4.23 (q, J = 7.2 Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 1.16 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.28, 151.59, 141.08, 137.79, 131.99, 129.85, 129.19 (2C), 128.57 (2C), 128.19 (3C), 125.83 (2C), 120.79, 60.94, 21.31, 13.89, 10.57. HRMS (ESI, *m/z*): $[M+H^+]$ calcd. for $C_{20}H_{21}N_2O_2$ 321.1603, found 321.1607.

Ethyl 4-ethyl-1,3-diphenyl-1*H*-pyrazole-5-carboxylate (1ea). Pale yellow solid, 0.83 g (52%), mp 65–67°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.67 (d, J = 7.2 Hz, 2H, ArH), 7.47–7.35 (m, 8H, ArH), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 2.89 (q, J = 7.2 Hz, 2H, CH_2), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 1.18 (t, J = 7.2 Hz, 3H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.17, 151.30, 141.08, 132.93, 131.58, 128.59 (2C), 128.52 (2C), 128.33 (2C), 128.23, 128.04, 127.43, 125.76 (2C), 61.00, 17.64, 15.68, 13.82. HRMS (ESI, *m/z*): $[M+H^+]$ calcd. for $C_{20}H_{21}N_2O_2$ 321.1603, found 321.1604.

Ethyl 1,3-diphenyl-4-propyl-1*H*-pyrazole-5-carboxylate (1fa). Pale yellow solid, 0.80 g (48%), mp 85–86°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.65 (d, J = 7.6 Hz, 2H, ArH), 7.49–7.34 (m, 8H, ArH), 4.23 (q, J = 7.2 Hz, 2H, CH_2), 2.83 (t, J = 7.2 Hz, 2H, CH_2), 1.70–1.60 (m, 2H, CH_2), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 0.97 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.24, 151.47, 141.02, 132.98, 131.76, 128.59 (2C), 128.51 (2C), 128.35 (2C), 128.23, 128.02, 125.92, 125.73 (2C), 61.00, 26.30,

24.53, 14.26, 13.82. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{21}H_{23}N_2O_2$ 335.1760, found 335.1760.

Ethyl 1,3,4-triphenyl-1*H*-pyrazole-5-carboxylate (1ga). Pale yellow solid, 0.87 g (47%), mp 120–122°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.55 (d, J = 7.6 Hz, 2H, ArH), 7.52–7.44 (m, 5H, ArH), 7.36 (br s, 5H, ArH), 7.26 (br s, 3H, ArH), 4.06 (q, J = 7.2 Hz, 2H, CH_2), 0.91 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.01, 150.06, 140.41, 132.49, 132.2, 132.17, 130.38 (2C), 128.71 (2C), 128.33, 128.11 (2C), 128.07 (2C), 127.96 (2C), 127.82, 127.45, 125.27 (2C), 124.97, 61.13, 13.33. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{24}H_{21}N_2O_2$ 369.1603, found 369.1601.

Ethyl 1-(3-chlorophenyl)-4-methyl-3-phenyl-1*H*-pyrazole-5-carboxylate (1bb). Pale yellow solid, 1.07 g (63%), mp 89–91°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.67 (dd, J = 8.4, J = 1.6 Hz, 2H, ArH), 7.49–7.40 (m, 3H, ArH), 7.40–7.38 (m, 3H, ArH), 7.34–7.31 (m, 1H, ArH), 4.27 (q, J = 7.2 Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.01, 152.20, 141.95, 134.14, 132.53, 132.03, 129.49, 128.56 (2C), 128.33, 128.30 (2C), 128.19, 126.21, 124.07, 121.55, 61.16, 13.94, 10.56. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{19}H_{18}ClN_2O_2$ 341.1057, found 341.1057.

Ethyl 1-(2,4-dichlorophenyl)-4-methyl-3-phenyl-1*H*-pyrazole-5-carboxylate (1bc). Pale yellow solid, 1.14 g (61%), mp 90–92°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.68 (d, J = 7.2 Hz, 2H, ArH), 7.52 (d, J = 2.0 Hz, 1H, ArH), 7.48–7.35 (m, 5H, ArH), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 2.51 (s, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.62, 152.44, 138.11, 135.25, 132.92, 132.90, 132.46, 129.82, 129.53, 128.54 (2C), 128.33 (2C), 128.20, 127.56, 120.84, 61.06, 13.90, 10.64. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{19}H_{17}Cl_2N_2O_2$ 375.0667, found 375.0672.

Ethyl 4-methyl-3-phenyl-1-(2,4,6-trichlorophenyl)-1*H*-pyrazole-5-carboxylate (1bd). Pale yellow solid, 1.02 g (50%), mp 80–81°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.49–7.43 (m, 4H, ArH), 7.42–7.37 (m, 1H, ArH), 4.25 (q, J = 7.2 Hz, 2H, CH_2), 2.54 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.18, 153.15, 136.33, 135.44, 135.12, 132.46, 132.30, 128.42 (2C), 128.28 (2C), 128.17 (2C), 128.14 (2C), 120.87, 60.97, 13.79, 10.60. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{19}H_{16}Cl_3N_2O_2$ 409.0277, found 409.0276.

Ethyl 4-methyl-3-phenyl-1-(*p*-tolyl)-1*H*-pyrazole-5-carboxylate (1be). Pale yellow solid, 0.96 g (60%), mp 128–130°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.71 (d, J = 7.6 Hz, 2H, ArH), 7.47 (t, J = 7.6 Hz, 2H, ArH), 7.41 (d, J = 7.6 Hz, 1H, ArH), 7.34 (d, J = 7.6 Hz, 2H, ArH), 7.28 (br s, 2H, ArH), 4.27 (q, J = 7.2 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.32, 151.37, 138.61, 138.20, 132.88, 132.02, 129.16 (2C), 128.47 (2C), 128.33 (2C), 127.92, 125.61 (2C), 120.57, 60.94, 21.22, 13.98, 10.60. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{20}H_{21}N_2O_2$ 321.1603, found 321.1606.

Ethyl 1-(2,4-dimethylphenyl)-4-methyl-3-phenyl-1*H*-pyrazole-5-carboxylate (1bf). Pale yellow solid, 0.95 g (57%), mp 141–142°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.70 (d, J = 8.4 Hz, 2H, ArH), 7.44 (t, J = 7.6 Hz, 2H, ArH), 7.37 (t, J = 7.6 Hz, 1H, ArH), 7.13 (t, J = 7.6 Hz, 2H, ArH), 7.08 (t, J = 7.6 Hz, 1H, ArH), 4.19 (q, J = 7.2 Hz, 2H, CH_2), 2.51 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.14 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.97, 151.16, 138.81, 138.26, 135.04, 133.03, 132.63, 131.05, 128.43 (2C), 128.30 (2C), 127.83, 127.12, 126.77, 119.80, 60.71, 21.23, 17.25, 13.86, 10.72. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{21}H_{23}N_2O_2$ 335.1760, found 335.1758.

Ethyl 1-(2,6-dimethylphenyl)-4-methyl-3-phenyl-1*H*-pyrazole-5-carboxylate (1bg). Pale yellow solid, 0.79 g (47%), mp 89–91°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.71 (d, J = 7.2 Hz, 2H, ArH), 7.45 (t, J = 7.2 Hz, 2H, ArH), 7.38 (t, J = 7.2 Hz, 1H, ArH), 7.25–7.21 (m, 1H, ArH), 7.12 (d, J = 7.6 Hz, 2H, ArH), 4.15 (q, J = 7.2 Hz, 2H, CH_2), 2.54 (s, 3H, CH_3), 2.00 (s, 6H, CH_3), 1.07 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.74, 151.49, 140.15, 135.82, 133.00, 132.45, 128.82, 128.46 (2C), 128.26 (2C), 127.87 (2C), 127.81 (2C), 119.85, 60.65, 17.38 (2C), 13.74, 10.72. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{21}H_{23}N_2O_2$ 335.1760, found 335.1760.

Ethyl 1-(3-chlorophenyl)-3-(4-chlorophenyl)-4-methyl-1*H*-pyrazole-5-carboxylate (1cb). Pale yellow solid, 1.14 g (61%), mp 80–82°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.61 (d, J = 7.6 Hz, 2H, ArH), 7.48–7.36 (m, 5H, ArH), 7.34–7.32 (m, 1H, ArH), 4.26 (q, J = 6.8 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.21 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.85, 150.91, 141.82, 134.19, 132.21, 131.03, 129.53, 129.50 (2C), 128.99, 128.78 (2C), 128.47, 126.17, 124.03, 121.42, 61.23, 13.92, 10.53. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{19}H_{17}Cl_2N_2O_2$ 375.0667, found 375.0667.

Ethyl 3-(4-chlorophenyl)-4-methyl-1-(*p*-tolyl)-1*H*-pyrazole-5-carboxylate (1ce). Pale yellow solid, 1.10 g (62%), mp 94–96°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.62 (dd, J = 8.4, 2.0 Hz, 2H, ArH), 7.41 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.24 (d, J = 8.4 Hz, 2H, ArH), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.20 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.07, 150.09, 138.39, 138.26, 133.80, 132.11, 131.28, 129.42 (2C), 129.09 (2C), 128.58 (2C), 125.46 (2C), 120.37, 60.90, 21.11, 13.84, 10.45. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{20}H_{20}ClN_2O_2$ 355.1213, found 355.1216.

Ethyl 3-(4-chlorophenyl)-4-methyl-1-(4-nitrophenyl)-1*H*-pyrazole-5-carboxylate (1ch). Pale yellow solid, 1.16 g (60%), mp 130–132°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.35 (d, J = 7.6 Hz, 2H, ArH), 7.62 (t, J = 7.6 Hz, 4H, ArH), 7.45 (d, J = 7.6 Hz, 2H, ArH), 4.32 (q, J = 7.2 Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.27 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 160.05, 153.21, 146.73, 145.65, 138.42, 131.94, 129.36 (2C), 129.18, 128.16 (2C), 125.96 (2C), 124.09 (2C), 122.67, 61.49, 14.06, 10.67. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{19}H_{17}ClN_3O_4$ 386.0908, found 386.0909.

Ethyl 4-methyl-1-(4-nitrophenyl)-3-(*p*-tolyl)-1*H*-pyrazole-5-carboxylate (1dh). Pale yellow solid,1.11 g (61%), mp 100–102°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.33 (d, J = 8.4 Hz, 2H, ArH), 7.65 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.0 Hz, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 4.34 (q, J = 7.2 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.93, 153.11, 146.63, 145.55, 138.30, 131.84, 129.24 (2C), 129.10, 128.05 (2C), 125.84 (2C), 123.96 (2C), 122.55, 61.36, 21.22, 13.94, 10.54. HRMS (ESI, *m/z*): [M + H$^+$] calcd. for $C_{20}H_{20}N_3O_4$ 366.1454, found 366.1456.

Ethyl 4-methyl-1-(3-nitrophenyl)-3-(*p*-tolyl)-1*H*-pyrazole-5-carboxylate (1di). Pale yellow solid, 1.10 g (60%), mp 124–126°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.28 (s, 1H, ArH), 8.20 (d, J = 8.0 Hz, 1H, ArH), 7.75 (d, J = 8.0 Hz, 1H, ArH), 7.56 (t, J = 8.0 Hz, 1H, ArH), 7.49 (d, J = 7.2 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH), 4.22 (q, J = 6.8 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.18 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.93, 152.88, 148.08, 141.80, 138.30, 131.85, 131.75, 129.33 (2C), 129.29 (2C), 128.18 (2C), 122.74,

Table 2

Crystallographic data for **1aa**.

Empirical formula	$C_{18}H_{16}N_2O_2$
Formula weight	292.33
Temperature (K)	296 (2)
Crystal size (mm^3)	$0.20 \times 0.15 \times 0.10$
Crystal system	Triclinic
Space group	*P*-1
a (Å)	4.1383 (9)
b (Å)	10.306 (2)
c (Å)	17.804 (4)
α (°)	86.384 (3)
β (°)	88.893(3)
γ (°)	88.680 (3)
V ($Å^3$)	757.5 (3)
Z	2
D_c ($g\,cm^{-3}$)	1.282
μ (mm^{-1})	0.085
F (000)	308
θ Range	1.15 to 25.04
Reflections collected	5387
Independent reflections	2630 [$R_{int} = 0.0230$]
Data/restraints/parameters	2630/6/201
Goodness-of-fit on F^2	1.056
R/*wR* [$I > 2\sigma(I)$]	0.0479, 0.1215
R/*wR* (all data)	0.0663, 0.1312
Max., Min. $\Delta\rho$ ($e\,Å^{-3}$)	0.139, −0.113

Table 3

Selected bond lengths (Å) and angles (°) for **1aa**.

Bond distances (Å)			
N1–N2	1.349 (2)	C7–C16	1.471 (3)
N1–C6	1.439 (2)	C16–O1	1.200 (2)
N1–C7	1.366 (2)	C16–O2	1.335 (2)
N2–C9	1.341 (2)	C17–O2	1.455 (3)
Bond angles (°)			
C7-N1-N2	111.51 (15)	C7-C16-O1	126.6 (2)
C7-N1-C6	131.05 (17)	O1-C16-O1	123.7 (2)
N1-N2-C9	105.69 (15)	C16-O2-C17	115.88 (17)

122.21, 121.21, 61.37, 21.34, 14.02, 10.72. HRMS (ESI, *m*/*z*): [M + H$^+$] calcd. for $C_{20}H_{20}N_3O_4$ 366.1454, found 366.1455.

Ethyl 1-(2,4-dinitrophenyl)-4-methyl-3-(*p*-tolyl)-1*H*-pyrazole-5-carboxylate (1dj). Pale yellow solid, 1.17 g (57%), mp 117–118°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.97 (s, 1H, ArH), 8.55 (d, $J = 8.4$ Hz, 1H, ArH), 7.83 (d, $J = 8.4$ Hz, 1H, ArH), 7.53 (d, $J = 8.0$ Hz, 2H, ArH), 7.28 (d, $J = 8.0$ Hz, 2H, ArH), 4.27 (q, $J = 7.2$ Hz, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.29 (t, $J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 159.78, 154.42, 146.85, 145.08, 139.78, 138.67, 132.47, 131.50, 129.37 (2C), 128.81, 128.24 (2C), 127.53, 122.75, 120.51, 61.73, 21.35, 14.03, 10.93. HRMS (ESI, *m*/*z*): [M + H$^+$] calcd. for $C_{20}H_{19}N_4O_6$ 411.1305, found 411.1799.

Single-crystal X-ray diffraction analysis of 1aa. The well-shaped single crystals of **1aa** were selected for lattice parameter determination and collection of intensity data at 296 K on a Bruker SMART CCD diffractometer with a detector distance of 5 cm and frame exposure time of 10 s using a graphite-monochromated Mo K_α ($\lambda = 0.71073$ Å) radiation. The structures were all solved by direct methods and refined on F^2 by full-matrix least squares procedures using SHELXTL software [17]. All non-hydrogen atoms were anisotropically refined. All H atoms were located from a difference map and refined isotropically. Details on crystal data of **1aa** are summarized in Table 2, and the selected bond lengths and angles are listed in Table 3.

CCDC 1018793 (**1aa**) contains the supplementary crystallographic data for this article. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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