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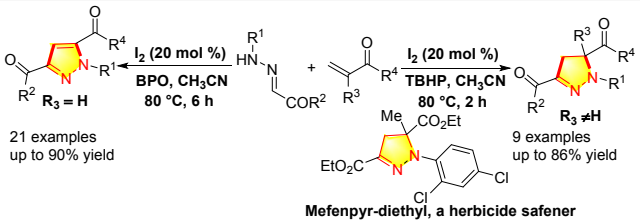


ABSTRACT: A regioselective synthesis of polysubstituted dihydropyrazoles and pyrazoles through iodine-catalyzed oxidative cyclization strategy of aldehyde hydrazones with electron-deficient olefins is described. The protocol adopts very mild reaction conditions and provides desirable yields. The reaction is supposed to proceed via a cascade C−H functionalization, C−N bond formation and oxidation sequential processes. The overall simplicity and regioselectivity of the catalytic system make this approach a valuable and step-economical tool to construct C−C bond for the synthesis of Mefenpyr-Diethyl.

■ INTRODUCTION

Arguably, polyfunctional dihydropyrazoles and pyrazoles represent one of the most important classes of N-heterocycles found in numerous natural products,[1-3] bioactive compounds,[4-6] and functional materials.[7,8] For example, **RH3421** is an insecticide that can block both peripheral and central neuronal activities in insects.[9] **Mefenpyr-diethyl**, a herbicide safener, which was used to against ACCase inhibitors.[10,11] On the other hand, the polysubstituted pyrazoles are found in commercially available drugs such as Rimonabant, Celecoxib and Sildenafil citrate (Figure 1). In addition, they can act as luminescent materials,[12,13] coordination polymer gels,[14] building blocks in supramolecular assembly[15] and also work as ligands for some cross-coupling reaction,[16,17] precursors to N-heterocyclic carbenes (NHCs),[18-20] and directed groups for C−H activetions.[21-23] Given the usefulness of these privileged skeleton, development of efficient and operationally simple approaches are of great significance.

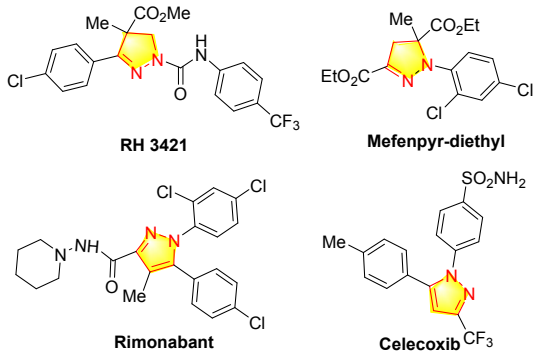
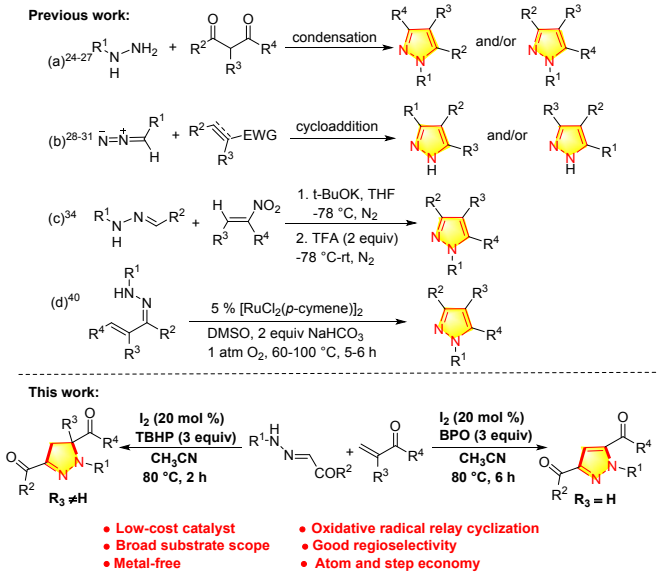


Figure 1. Selected examples of functional dihydropyrazoles and pyrazoles.

Traditional strategies for constructing polysubstituted pyrazoles are annulations initiated by the condensation of hydrazine compounds with carbonyl derivatives (Scheme 1a),[24-27] or 1,3-dipolar cycloadditions of diazo molecules with alkenes or alkynes (Scheme 1b).[28-38] For example, chloramine-T was

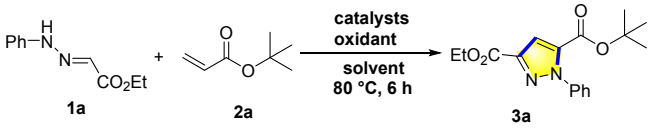
commonly used to generate 1,3-dipolar species and subsequent 1,3-dipolar cycloadditions for the synthesis of pyrazoles would smoothly occur. All these reactions were mainly focus on bisarylhydrazones in the presence of excessive chloramine-T. In addition, hydrazones have also been employed as the starting materials for the synthesis of pyrazoles (Scheme 1c).[39-43] Apart from these methods, transition-metal-catalyzed oxidative C-H bond functionalization was always used to construct pyrazole derivatives (Scheme 1d).[44-47] However, these approaches have the defects of requiring precious metal, harsh reaction conditions or inferior regioselectivity. As far as we know, related single electron oxidation of (N=CH) of diverse aldehyde hydrazones to electron-deficient olefins in dihydropyrazoles or pyrazoles synthesis was not examined to date. Hence, development of a one-pot regioselective avenue for the efficient construction of the pyrazole skeleton is highly desirable.

Scheme 1. Strategies for the Synthesis of Pyrazoles



In recent years, metal-free catalyzed oxidative C−H functionalization has been gained considerable attention due to its low costs and the formation of environmentally acceptable byproducts.[48-51] Molecular iodine, which possesses various oxidation states and mild redox potential, has been widely utilized in oxidative coupling reactions.[52-55] Furthermore, the combination of the iodine/peroxide mediated oxidative coupling reactions have been investigated to some extent.[56-64] Despite the compelling progress, the examination of direct catalytic transformation via a iodine catalyzed strategy for the construction of privileged heterocyclic compounds are still promising. Inspired by our previous work,[65-67] and literature reports, we herein report a I_2-catalyzed pyrazoles synthesis by an oxidative radical relay strategy.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield (%)
1	I_2	TBHP	DMF	35
2	I_2	TBHP	DMSO	21
3	I_2	TBHP	CH_3CN	58
4	I_2	TBHP	dioxane	0
5	I_2	TBHP	DME	0
6	I_2	TBHP	toluene	0
7	I_2	$K_2S_2O_8$	CH_3CN	0
8	I_2	DTBP	CH_3CN	0
9	I_2	BTI	CH_3CN	trace
10	I_2	H_2O_2	CH_3CN	0
11	I_2	m-CPBA	CH_3CN	16
12	I_2	TBPB	CH_3CN	64
13	**I_2**	**BPO**	**CH_3CN**	**81**
14	NaI	BPO	CH_3CN	53
15	NIS	BPO	CH_3CN	68
16	TBAI	BPO	CH_3CN	57
17[b]	I_2	BPO	CH_3CN	70
18[c]	I_2	BPO	CH_3CN	77
19[d]	I_2	BPO	CH_3CN	73
20[e]	I_2	BPO	CH_3CN	61

[a]Reactions were carried out with **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (20 mol %), oxidant (3.0 equiv.) in a solvent (2.0 mL) under air condition at 80 °C for 6 h. [b]10 mol % I_2 was used. [c]50 mol % I_2 was used. [d]2.0 equiv. BPO was used. [e]The reaction was conducted at 60 °C. TBHP = 70% t-BuOOH in water, DTBP = 2-(t-buytlperoxy)-2-methylpropane, BTI = [Bis(trifluo-acetoxy)iodo]benzene. m-CPBA = m-Chloroperoxyben-zoic acid, TBPB = tert-Butyl peroxybenzoate, BPO = Dibenzoyl peroxide.

■ RESULTS AND DISCUSSION

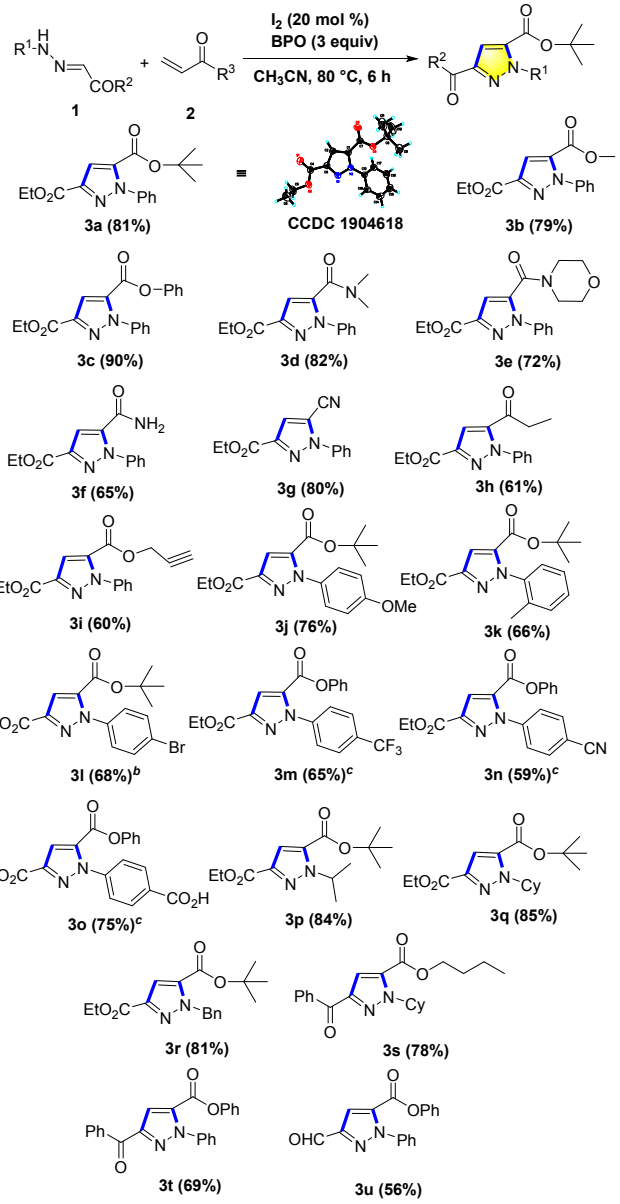
We started our studies by examining various reaction conditions for this oxidative radical relay reaction of phenylhydrazone **1a** and tert-butyl acrylate **2a**, selected results are summarized in Table 1. To our delight, the target molecule **3a**

was obtained in 35% yield when the transformation proceeded in the presence of 20 mol % I_2 and 3.0 equiv. of TBHP in DMF at 80 °C (entry 1). The screening of solvents revealed that CH_3CN was the best selection, giving **3a** in 58% yield (entries 2-6). The structure of **3a** was confirmed by X-ray single crystal diffraction.[68] Then, a variety of oxidants were tested, and the results showed that none of the other oxidants was superior to BPO, with an up to 81% yield (entries 7-13). The replacement of iodine with other iodides, including NaI, NIS or TBAI, the yield of **3a** decreased (entries 14-16). Varying the quantity of the catalyst, the yield decreased slightly (entries 17-18). Reducing the amount of BPO to 2.0 equiv. afford 73% yield of the desired product **3a** (entry 19). Lowering the temperature to 60 °C, the yield decreased to 61% (entry 20).

With the optimized reaction conditions in hand (Table 1, entry 13), the scope of this oxidative radical relay reaction was then investigated (Scheme 2). Obviously, diverse electron-deficient olefins are feasible coupling partners for this transformation, and moderate to good yields could be achieved (**3a-i**). A series of electron-withdrawing olefins, such as α,β-unsaturated esters, amides, ketones, nitrile and terminal alkyne ester underwent the desired radical relay smoothly, furnishing pyrazole derivatives with high efficiency in 60-90% yields. Next, a wide range of aldehyde hydrazones were evaluated. First, the transformation proceeded smoothly in regard to hydrazons from diversely substituted aromatic hydrazine. Both electron-donating and electron-deficient substituents were all well compatible in moderate yields (**3j-o**). More importantly, electron-deficient substituents such as bromo, cyano and carboxyl groups can offer the opportunity for further downstream diversification. Notably, replacement of the aryl hydrazine with diverse alkyl hydrazine including, cyclohexyl, isopropyl, and benzyl were perfectly tolerable with tert-butyl acrylate, thus affording the corresponding pyrazoles **3p-r** in high yields. After validating the scope with hydrazine, glyoxal and phenylglyoxal were further examined. Delightedly, the yields of products **3s**, **3t** and **3u** were in 78%, 69% and 56%, respectively.

Due to the formation of dihydropyrazoles is considerably fast. A mild oxidant may probably has no impact on other functional groups of the substrates so we choose TBHP as the terminal oxidant. Indeed, α-alkyl substituted acrylates are well compatible in dihydropyrazoles synthesis in the presence of TBHP with moderate to good yields **4a-i** (Scheme 3). It is noteworthy that the free NH and OH in dihydropyrazoles could be used for further functionalization. To further demonstrate the synthetic applicability of this oxidative radical relay protocol, we present the facile synthesis of mefenpyr-diethyl using ethyl

Scheme 2. Results of I_2-Catalyzed Pyrazoles (3) Synthesis[a]

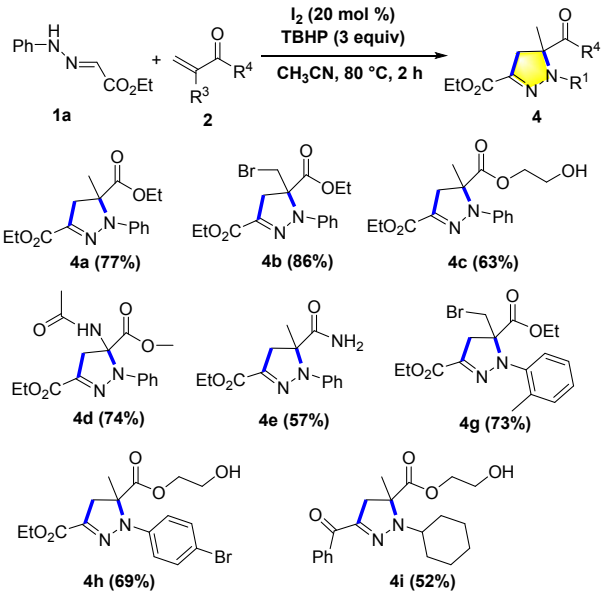


[a]Reactions were carried out with **1** (1.0 mmol), **2a** (1.5 mmol), catalyst (20 mol %), BPO (3.0 equiv) in a

solvent (4.0 mL) under air atmosphere at 80 °C for 6 h. [b]the reaction time was 12 h. [c]The reaction time was 20 h.

methacrylate **2f** with **1f** under our I_2-catalyzed conditions directly delivering **4f** in a simple and one-pot operation with 65% yield (Scheme 4). The method was convnient and practical. A preactivation precursor, ethyl-2-chloro-(2,4-dichloro- phenylhydrazono)acetate, was avoided.[69]

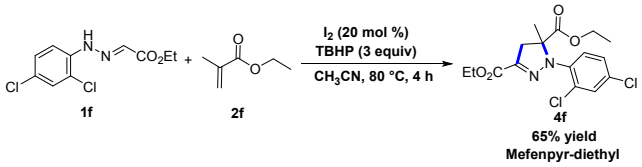
Scheme 3. Results of I_2-Catalyzed Dihydropyrazoles (4) Synthesis[a]



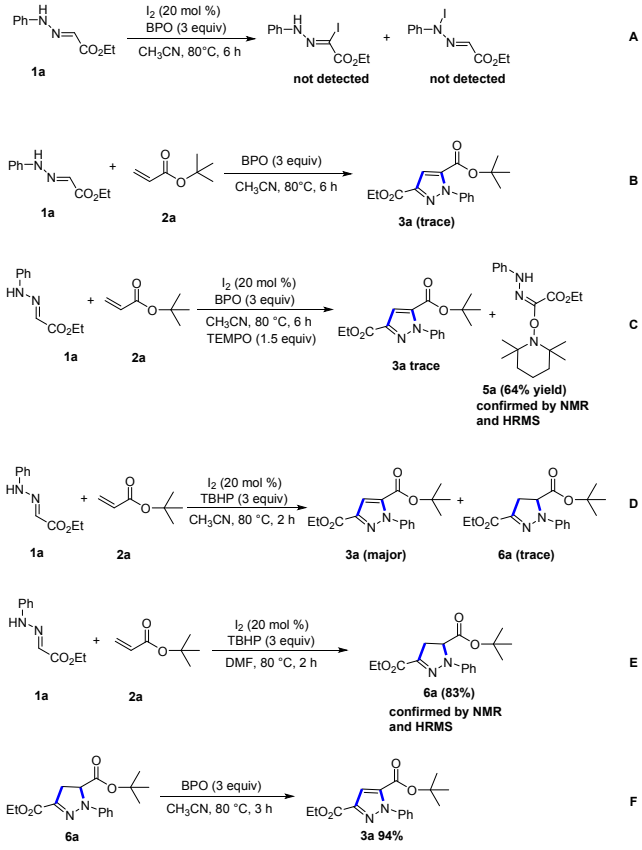
[a]Reactions were carried out with **1a** (1.0 mmol), **2** (1.5 mmol), catalyst (20 mol %), TBHP (3.0 equiv) in a solvent (4.0 mL) under air atmosphere at 80 °C for 2 h.

To further achieve some insights into the reaction mechanism, a variety of control experiments were conducted (Scheme 5). First, considering that molecular iodine can be involved in the formation of hydrazonoyl iodide or N-iodo hydra-zone intermediates, subsequent oxidative cyclization reaction may proceed via SET process. The model reaction was operated in the absence of tert-butyl acrylate **2a**. Unfortunately, the reaction system was very complex forming a mixture of inseparable compounds and related hydrazonoyl iodide or N-iodo hydrazone was not detected via LC-MS, showing that these intermediates were not involved (Scheme 5A). Next, because of BPO can be converted into benzoyloxy radical under the thermal conditions, followed by C-C, C-N bond formation. Then the model reaction was implemented in the absence of molecular iodine. Expectedly, a trace of product **3a** was observed (Scheme 5B). These results indicated that molecular iodine play a significant role in the reaction. Subsequently, radical trapping experiments were carried out. The addition of TEMPO drastically shut down the desired coupling reaction, with the formation of the TEMPO-adduct **5a** in 64% yield, indicating the involvement of the hydrazone radical (Scheme 5C).

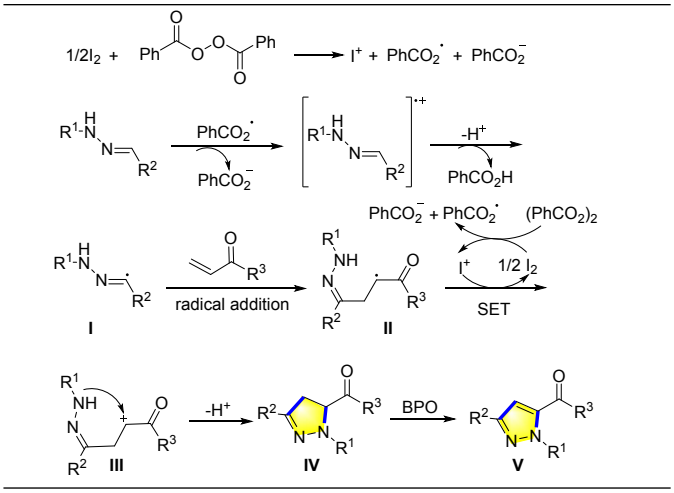
Scheme 4. One-pot Synthesis of Mefenpyr-Diethyl



Scheme 5. Control Experiments



Scheme 6. Proposed Reaction Mechanism



To demonstrate the existence of intermediate **6a**, the model reaction was conducted in CH_3CN in the presence of TBHP at 80 °C for 2 h. A trace of intermediate **6a** was detected (Scheme 5D). In contrast, when the reaction was operated in DMF for 2 h, the single intermediate **6a** was isolated in 83% yield (Scheme 5E). Subsequently, the intermediate **6a** was treated with 3.0 equiv. of BPO in CH_3CN for 3 h affording the final product **3a** in 94% yield (Scheme 5F). These observations verified the reasonable intermediacy of **6a**.

Based on these experimental results and previous reports,[65,67] a plausible mechanism for this oxidative radical relay reaction is shown in Scheme 6. Initially, aldehyde hydrazone is presumably involved a hydrogen abstraction from the N=CH via single-electron oxidation to give a carbon radical **I**. The succedent single-electron addition to C=C of acrylate to form C−C propagation **II**, which is further oxidized by I^+ to obtain a carbocation **III**.[63] Subsequent intramolecular cyclization leads to the formation of dihydropyrazole compounds **IV**. Finaly, the dihydropyrazoles were oxidized by BPO to provide the Pyrazole derivatives **V**. In a word, the I_2−I^+ redox process through promoting reductive cleavage of the O−O bond in the peroxide played a crucial role in the C−N bond formations.[70,71]

■ CONCLUSIONS

We have developed an efficient strategy to the synthesis of polysubstituted dihypyrazoles or pyrazoles via a iodine-catalyzed oxidative radical relay reaction of aldehyde hydrazones with electron-deficient olefin under mild conditions. The reaction is believed to proceed through a cascade C−H functionalization, C−N bond formation and oxidation sequential processes. Notably, an expedient and operationally simple, one-pot synthesis of mefenpyr-diethyl has been successfully achieved.

■ EXPERIMENTAL SECTION

General Information and Method. All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. Petroleum ether (PE) refers to a hydrocarbon mixture with a boiling range of 60-90 ºC. TLC was performed on silica gel polygram SILG/UV 254 plates and visualized by quenching of UV fluorescence (λmax = 254 nm). Silica gel (100-200 microns) was used for all chromatographic separations. Melting points were determined with RY-1 apparatus and uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu model 470 spectrophotometer. NMR (^1H and ^{13}C) spectra were recorded using a Bruker AV 400 MHz or 600 MHz spectrometer in $CDCl_3$ or DMSO-*d6* with TMS as internal standard. Chemical shifts (δ) were recorded in ppm. Mass spectra were acquired on thermo Fisher scientific LTQ FTICR-MS and Agilent 6210 ESI/TOF MS.

Preparation of starting hydrazones 1.[72] A suspension of hydrazine hydrochloride (10.0 mmol) in anhydrous THF (20.0 mL) was treated with triethylamine (12.0 mmol, 1214 mg) before a solution of glyoxylate (10.0 mmol) was dropwise added into the reaction mixture at 0 ºC. The mixture was stirred at this temperature for 30 minutes and then overnight. The reaction was filtered under vacuum to collect the triethylamine hydrochloride salt. The filtrates were concentrated in vacuo and the resulting solids dissolved in ethyl acetate (50 mL) and washed with water (2 x 30 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated in vacuo, the crude product was purified by flash chromatography (petroleum ether /ethyl acetate = 25:1-1:1) or recrystallized from ethyl acetate to give the desired hydrazones in good yields.

Synthetic Procedure for the Synthesis of 3. A mixture of hydrazone **1** (1.0 mmol), electron-deficient olefines **2** (1.5 mmol), I_2 (50.8 mg, 0.2 mmol), BPO (726.7 mg, 3.0 mmol) and CH_3CN (4 mL) were added into the 25 ml round-bottom flask, then the mixture was stirred in oil bath at 80 ºC for 6 h. After the starting material **1** was consumed as indicated by TLC, the reaction mixture was poured into water and then extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 8:1-1:1) to give **3.**

Synthetic Procedure for the Synthesis of 4. A mixture of hydrazone **1** (1.0 mmol), electron-deficient olefins **2** (1.5 mmol), I_2 (50.8 mg, 0.2 mmol), TBHP (70% aq. 386.3 mg, 3.0 mmol) and CH_3CN (4 mL) were added into the 25 ml round-bottom flask, then the mixture was stirred in oil bath at 80 ºC for 2 h. After the starting material **1** was consumed as indicated by TLC, the reaction mixture was poured into water and then extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 10:1-1:1) to give **4.**

Synthetic Procedure for the Synthesis of 4f. A mixture of 2,4-dichlorophenylhydrazone **1f** (261.1 mg, 1.0 mmol), ethyl methacrylate **2f** (171.2 mg, 1.5 mmol), I_2 (50.8 mg, 0.2 mmol), TBHP (70% aq. 386.3 mg, 3.0 mmol) and CH_3CN (4 mL) were added into the 25 ml round-bottom flask, then the mixture was stirred in oil bath at 80 ºC for 4 h. After the starting material **1f** was consumed as indicated by TLC, the reaction mixture was poured into water and then extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 12: 1) to give **4f** (243 mg, 65%) as a yellow viscous oil.

*Ethyl (E)-2-(2-phenylhydrazono)acetate (**1a**)*.[73] Recrystallized from ethyl acetate to give the yellow solid; 81% yield, 1.6g (known compound). Literature data: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.63 (s, 1H), 7.37-7.23 (m, 2H), 7.21-7.12 (m, 2H), 7.09 (s, 1H), 6.97 (dd, *J* = 10.3, 4.2 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 164.4, 142.5, 129.4, 125.7, 122.4, 114.0, 60.9, 14.3. our reporting data: ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.27 (s, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.20 (s, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 164.2, 143.8, 129.8, 125.5, 121.7, 113.6, 60.3, 14.7.

*Ethyl (E)-2-(2-(2,3-dichlorophenyl)hydrazono)acetate (**1f**)*. Purified by flash chromatography (petroleum ether /ethyl acetate = 7:1) to give the yellow solid; 45% yield, 1.2 g. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 10.94 (s, 1H), 7.67 (s, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.39 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.21 (d, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 163.8, 139.6, 130.3, 129.4, 128.8, 125.4, 118.6, 116.8, 60.7, 14.7.

*Ethyl (E)-2-(2-(4-methoxyphenyl)hydrazono)acetate (**1j**)*.[73] Purified by flash chromatography (petroleum ether /ethyl acetate = 3:1) to give the yellow solid; 55% yield, 1.2 g (known compound). Literature data: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.79 (s, 1H), 7.18-6.99 (m, 3H), 6.81 (d, *J* = 9.0 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 164.7, 155.4, 136.3, 124.4, 115.5, 114.7, 60.8, 55.6, 14.3. our reporting data: ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 12.31 (s, 1H), 7.17–7.14 (m, 2H), 6.91–6.89 (m, 2H), 6.62 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ = 164.0, 155.6, 136.8, 117.2, 115.1, 114.7, 60.2, 55.6, 14.2.

*Ethyl (E)-2-(2-(o-tolyl)hydrazono)acetate (**1k**)*. Recrystallized from ethyl acetate to give the yellow solid; 76% yield, 1.6 g. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 12.43 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.74 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ = 164.0, 141.0, 130.6, 127.2, 122.4, 122.2, 119.1, 112.9, 60.5, 17.0, 14.2.

*Ethyl (E)-2-(2-(4-bromophenyl)hydrazono)acetate (**1l**)*.[73] Purified by flash chromatography (petroleum ether /ethyl acetate = 5:1) to give the yellow solid; 85% yield, 2.3 g (known compound). Literature data: ^{1}H NMR (400 MHz, $CDCl_3$): (ppm) δ = 1.34 (t, *J* = 5.6 Hz, 3H), 4.30 (q, *J* = 5.6 Hz, 2H), 7.03 (d, *J* = 6.8 Hz, 2H), 7.09 (s, 1H), 7.36 (m, *J* = 6.8 Hz, 2H), 8.77 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 14.4, 61.2, 114.7, 115.7, 126.6, 132.3, 141.8, 164.4. Our reporting data: ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 12.30 (s, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.68 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ = 163.7, 142.1, 132.2, 119.3, 115.5, 114.8, 60.6, 14.2.

*Ethyl (E)-2-(2-(4-(trifluoromethyl)phenyl)hydrazono)acetate (**1m**)*. Recrystallized from ethyl acetate to give the yellow solid; 85% yield, 2.2 g. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 12.40 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.74 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ = 163.5, 145.6, 126.7 (q, *J* = 3.9 Hz), 125.3, 124.2 (q, *J* = 32.5 Hz), 123.5, 120.6, 113.6, 60.8, 14.1.

*Ethyl (E)-2-(2-(4-cyanophenyl)hydrazono)acetate (**1n**)*. Recrystallized from ethyl acetate to give the brown solid; 81% yield, 1.8 g. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 12.43 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.25 (dd, *J* = 8.9, 2.6 Hz, 2H), 6.78 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ = 163.4, 146.4, 133.7, 121.9, 119.4, 114.0, 104.9, 61.0, 14.1.

(E)-4-(2-(2-ethoxy-2-oxoethylidene)hydrazinyl)benzoic acid ***(1o)***. Recrystallized from methanol to give the yellow solid; 84% yield, 2.0 g. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 12.55 (s, 1H), 11.57 (d, J = 11.8 Hz, 1H), 7.90–7.88 (m, 2H), 7.28 (dd, J = 8.8, 1.1 Hz, 1H), 7.15 (dd, J = 8.7, 1.9 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 167.5, 163.8, 147.6, 131.7, 128.1, 123.5, 113.1, 60.6, 14.7.

Ethyl (E)-2-(2-isopropylhydrazono)acetate ***(1p)***. Purified by flash chromatography (petroleum ether /ethyl acetate = 4:1) to give the colorless liquid; 53% yield, 0.84 g. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.69 (d, J = 5.4 Hz, 1H), 6.78 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.68–3.39 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H), 1.10 (d, J = 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 164.7, 120.0, 59.5, 49.0, 21.4, 14.8.

Ethyl (E)-2-(2-cyclohexylhydrazono)acetate ***(1q)***. Purified by flash chromatography (petroleum ether /ethyl acetate = 3:1) to give the colorless liquid; 62% yield, 1.2 g. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.76 (d, J = 5.5 Hz, 1H), 6.81 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.29–3.23 (m, 1H), 1.86–1.82 (m, 2H), 1.70–1.66 (m, 2H), 1.58–1.54 (m, 1H), 1.33–1.25 (m, 2H), 1.23 (d, J = 3.4 Hz, 1H), 1.19 (t, J = 7.1 Hz, 4H), 1.17–1.12 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 164.8, 119.8, 59.5, 56.4, 31.6, 25.7, 24.4, 14.8.

Ethyl (E)-2-(2-benzylhydrazono)acetate ***(1r)***.[74] Purified by flash chromatography (petroleum ether /ethyl acetate = 2:1) to give the yellow liquid; 71% yield, 1.5 g (known compound). Literature data: ^{1}H NMR ($CDCl_3$) δ = 1.28 (3H, t, J = 7.0 Hz), 4.23 (2H, q, J = 7.0 Hz), 4.37 (2H, d, J = 4.6 Hz), 6.74 (1H, br t), 6.75 (1H, s), 7.2-7.4 (5H, m); our reporting data: ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.27 (t, J = 4.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.33–7.27 (m, 3H), 6.71 (s, 1H), 4.42 (d, J = 4.5 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 164.8, 137.2, 129.0, 128.2, 127.7, 119.7, 59.7, 50.8, 14.7.

(E)-2-(2-cyclohexylhydrazono)-1-phenylethan-1-one ***(1s)***. Purified by flash chromatography (petroleum ether /ethyl acetate = 2:1) to give the yellow liquid; 89% yield, 2.0 g. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 12.99 (d, J = 5.3 Hz, 1H), 7.99 (d, J = 7.4 Hz, 2H), 7.63 (s, 1H), 7.60–7.56 (m, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.44 (q, J = 7.5, 6.0 Hz, 1H), 3.46 (tq, J = 9.7, 4.2 Hz, 1H), 2.01–1.85 (m, 2H), 1.71–1.66 (m, 2H), 1.55 (dt, J = 13.2, 4.3 Hz, 1H), 1.47–1.37 (m, 2H), 1.37–1.24 (m, 2H), 1.23–1.09 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 184.6, 137.6, 132.8, 129.2, 128.0, 119.9, 59.1, 32.1, 25.7, 25.4, 24.5, 24.4.

(E)-1-phenyl-2-(2-phenylhydrazono)ethan-1-one ***(1t)***. Recrystallized from ethyl acetate to give the yellow solid; 70% yield, 1.6 g. ^{1}H NMR (600 MHz, Chloroform-d) δ = 14.52 (s, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.76 (s, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.41-7.36 (m, 4H), 7.12 (tt, J = 6.7, 2.0 Hz, 1H) ; ^{13}C{^{1}H} NMR (151 MHz, Chloroform-d) δ = 186.4, 142.6, 137.3, 132.9, 129.5, 128.9, 128.0, 123.9, 122.4, 115.0.

(E)-1-phenyl-2-(2-phenylhydrazono)ethan-1-one ***(1u)***. Purified by flash chromatography (petroleum ether /ethyl acetate = 8:1) to give the brown solid; 50% yield, 0.74 g. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.73 (s, 1H), 9.48 (d, J = 7.9 Hz, 1H), 7.38–7.31 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 7.00 (t, J = 7.3 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ = 190.7, 143.2, 135.9, 129.9, 122.9, 114.4.

(5-(tert-butyl) 3-ethyl 1-phenyl-1H-pyrazole-3,5-dicarboxylate ***(3a)***. White solid; Yield: 81% (256 mg); Mp: 60-62 ºC; IR (thin film): ν 2981, 1717, 1600, 1542, 1506, 1367, 1297, 1231, 1161, 1077, 1022, 841, 765, 690, 623 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ = 7.48–7.41 (m, 6H), 4.44 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ = 161.7, 157.5, 143.6, 140.2, 136.5, 129.2, 128.6, 126.2, 114.4, 83.0, 61.3, 27.9, 14.4. Please see the single crystal.

3-ethyl 5-methyl 1-phenyl-1H-pyrazole-3,5-dicarboxylate ***(3b)***. White solid; Yield: 79% (216 mg); Mp: 112-114 ºC; IR (thin film): ν 3174, 2984, 1726, 1500, 1442, 1376, 1222, 1131, 1037, 1013, 941, 907, 844, 750, 705, 684, 659, 602 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ = 7.52 (s, 1H), 7.49–7.43 (m, 5H), 4.44 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ = 161.5, 158.9, 143.9, 139.7, 134.5, 129.4, 128.6, 126.2, 114.7, 61.4, 52.3, 14.4. HRMS (ESI): m/z calcd for $C_{14}H_{15}N_2O_4$ $[M+H]^+$: 275.1026; found: 275.1027.

3-ethyl 5-phenyl 1-phenyl-1H-pyrazole-3,5-dicarboxylate ***(3c)***. White solid; Yield: 90% (303 mg); Mp: 88-90 ºC; IR (thin film): ν 3147, 1748, 1723, 1600, 1494, 1370, 1279, 1216, 1188, 1122, 1080, 1001, 847, 741, 684cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ = 7.75 (s, 1H), 7.52–7.45 (m, 5H), 7.38 (t, J = 7.9 Hz, 2H), 7.23 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 7.9 Hz, 2H), 4.47 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ = 161.5, 156.8, 149.8, 144.0, 139.5, 134.0, 129.6, 128.8, 126.4, 126.3, 121.3, 115.6, 61.6, 14.4. HRMS (ESI): m/z calcd for $C_{19}H_{17}N_2O_4$ $[M+H]^+$: 337.1183; found: 337.1177.

Ethyl 5-(dimethylcarbamoyl)-1-phenyl-1H-pyrazole-3-carboxylate ***(3d)***. Yellow viscous oil; Yield: 82% (236 mg); IR (thin film): ν 2984, 2936, 1714, 1642, 1500, 1370, 1222, 1170, 1119, 1010, 904, 832, 768, 690, 669; ^{1}H NMR (400 MHz, Chloroform-d) δ = 7.52 (dt, J = 8.2, 1.7 Hz, 2H), 7.44–7.34 (m, 3H), 7.01 (d, J = 1.5 Hz, 1H), 4.40 (qd, J = 7.2, 1.7 Hz, 2H), 2.96 (s, 3H), 2.71 (s, 3H), 1.38 (td, J = 7.1, 1.7 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, Chloroform-d) δ = 161.8, 161.6, 144.3, 139.1, 138.0, 129.3, 128.8, 123.5, 110.0, 61.3, 38.1, 35.0, 14.4. HRMS (ESI): m/z calcd for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1343; found: 288.1340.

*Ethyl 5-(morpholine-4-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (**3e**)*. Yellow solid; Yield: 72% (237 mg); Mp: 102-104 ºC; IR (thin film): ν 3144, 1748, 1723, 1639, 1603, 1494, 1276, 1216, 1191, 1083, 1001, 844, 762, 741,684 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.58–7.54 (m, 2H), 7.52–7.42 (m, 3H), 7.06 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.62 (dt, *J* = 38.4, 4.7 Hz, 4H), 3.13 (dt, *J* = 32.9, 4.6 Hz, 4H), 1.42 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 161.6, 160.3, 144.6, 138.9, 137.3, 129.5, 129.1, 123.7, 110.4, 66.2, 66.1, 61.4, 47.0, 42.4, 14.4. HRMS (ESI): m/z calcd for $C_{17}H_{20}N_3O_4$ $[M+H]^+$: 330.1448; found: 330.1442.

*Ethyl 5-carbamoyl-1-phenyl-1H-pyrazole-3-carboxylate (**3f**)*. White solid; Yield: 65% (169 mg); Mp: 175-177 ºC; IR (thin film): ν 3407, 3141, 2987, 1748, 1726, 1596, 1479, 1367, 1282, 1222, 1194, 1086, 1025, 1010, 850, 771, 690, 629, 608, 566 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.51-7.46 (m, 5H), 7.33 (s, 1H), 5.91 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 161.7, 159.9, 143.8, 139.3, 137.4, 129.4, 129.0, 125.6, 111.9, 61.5, 14.4. HRMS (ESI): m/z calcd for $C_{13}H_{14}N_3O_3$ $[M+H]^+$: 260.1030; found: 260.1032.

*Ethyl 5-cyano-1-phenyl-1H-pyrazole-3-carboxylate (**3g**)*. Yellow solid; Yield: 80% (193 mg); Mp: 69-71 ºC; IR (thin film): ν 3147, 2987, 2240, 1745, 1726, 1596, 1473, 1367, 1285, 1222, 1167, 1122, 1013, 983, 856, 768, 690 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.75–7.72 (m, 2H), 7.58–7.50 (m, 4H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 160.5, 145.0, 137.9, 129.9, 129.7, 123.5, 118.2, 115.7, 110.1, 61.9, 14.3. HRMS (ESI): m/z calcd for $C_{13}H_{11}N_3O_2Na$ $[M+Na]^+$: 264.0743; found: 264.0747.

*Ethyl 1-phenyl-5-propionyl-1H-pyrazole-3-carboxylate (**3h**)*. White solid; Yield: 61% (166 mg); Mp: 122-124 ºC; IR (thin film): ν 3132, 2981, 2942, 1717, 1690, 1596, 1524, 1497, 1454, 1406, 1364, 1243, 1204, 1025, 931, 868, 838, 777, 702, 539 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 7.52 (s, 1H), 7.50–7.46 (m, 3H), 7.41–7.39 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.93 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 190.6, 161.6, 143.7, 140.5, 140.2, 129.3, 128.7, 126.1, 114.0, 61.5, 34.1, 14.4, 7.7. HRMS (ESI): m/z calcd for $C_{15}H_{16}N_2O_3Na$ $[M+Na]^+$: 295.1053; found: 295.1054.

*3-ethyl 5-(prop-2-yn-1-yl) 1-phenyl-1H-pyrazole-3,5-dicarboxylate (**3i**)*. White solid; Yield: 60% (179 mg); Mp: 116-118 ºC; IR (thin film): ν 3268, 3141, 3011, 2119, 1742, 1711, 1509, 1470, 1373, 1288, 1228, 1131, 1095, 1043, 1022, 1007, 962, 913, 850, 762, 687, 681, 560cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 7.61 (s, 0H), 7.51–7.45 (m, 5H), 4.83 (d, *J* = 2.4 Hz, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.53 (t, *J* = 2.4 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 161.4, 157.6, 143.9, 139.5, 133.7, 129.5, 128.7, 126.2, 115.2, 76.6, 75.7, 61.5, 52.8, 14.4. HRMS (ESI): m/z calcd for $C_{16}H_{14}N_2O_4Na$ $[M+Na]^+$: 321.0846; found: 321.0844.

*5-(tert-butyl) 3-ethyl 1-(4-methoxyphenyl)-1H-pyrazole-3,5-dicarboxylate (**3j**)*. White solid; Yield: 76% (263 mg); Mp: 76-78 ºC; IR (thin film): ν 2978, 2845, 1729, 1711, 1515, 1460, 1373, 1285, 1231, 1164, 1125, 1092, 1025, 1004, 856, 768, 626, 542 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.42 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.43 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 161.8, 160.0, 157.6, 143.3, 136.4, 133.2, 127.4, 114.3, 113.7, 82.9, 61.3, 55.5, 28.0, 14.4. HRMS (ESI): m/z calcd for $C_{18}H_{23}N_2O_5$ $[M+H]^+$: 347.1601; found: 347.1603.

*5-(tert-butyl) 3-ethyl 1-(o-tolyl)-1H-pyrazole-3,5-dicarboxylate (**3k**)*. Yellow solid; Yield: 66% (218 mg); Mp: 122-124 ºC; IR (thin film): ν 2984, 1720, 1705, 1539, 1370, 1297, 1249, 1170, 1143, 1077, 1019, 835, 765, 723,626 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 7.49 (s, 0H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.31–7.28 (m, 2H), 7.26 (d, *J* = 7.7 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.03 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 161.7, 157.3, 143.6, 139.9, 137.3, 135.1, 130.4, 129.6, 127.2, 126.3, 113.7, 82.8, 61.3, 27.8, 17.1, 14.4. HRMS (ESI): m/z calcd for $C_{18}H_{22}N_2O_4Na$ $[M+Na]^+$: 353.1472; found: 353.1476.

*5-(tert-butyl) 3-ethyl 1-(4-bromophenyl)-1H-pyrazole-3,5-dicarboxylate (**3l**)*. White solid; Yield: 68% (269 mg); Mp: 92-94 ºC; IR (thin film): ν 2975, 1729, 1708, 1494, 1470, 1367, 1291, 1231, 1161, 1131, 1086, 1028, 850, 838, 823, 762, 729 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.60 (d, *J* = 8.6 Hz, 2H), 7.44 (s, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.45 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 161.5, 157.4, 143.9, 139.0, 136.4, 131.8, 127.8, 123.2, 114.7, 83.3, 61.5, 27.9, 14.4. HRMS (ESI): m/z calcd for $C_{17}H_{20}BrN_2O_4$ $[M+H]^+$: 395.0601; found: 395.0608.

*3-ethyl 5-phenyl 1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3,5-dicarboxylate (**3m**)*. Yellow solid; Yield: 65% (263 mg); Mp: 110-112 ºC; IR (thin film): ν 3144, 1745, 1723, 1615, 1524, 1485, 1330, 1291, 1222, 1191, 1161, 1119, 1101, 1064, 859, 759, 741, 684, 587cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 7.80 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.44–7.41 (m, 2H), 7.31–7.28 (m, 1H), 7.16–7.14 (m, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 161.2, 156.8, 149.7, 144.7, 142.1, 134.0, 131.7, 131.4, 129.7, 126.8, 126.6, 126.0 (q, *J* = 3.6 Hz), 124.5, 122.7, 121.2, 116.0, 61.7, 14.4. HRMS (ESI): m/z calcd for $C_{20}H_{15}F_3N_2O_4Na$ $[M+Na]^+$: 427.0876; found: 427.0881.

*3-ethyl 5-phenyl 1-(4-cyanophenyl)-1H-pyrazole-3,5-dicarboxylate (**3n**)*. White solid; Yield: 59% (213 mg); Mp: 130-132 ºC; IR (thin film): ν 3150, 2996, 2231, 1748, 1723, 1612, 1515, 1479, 1367, 1282, 1228, 1188, 1118, 1080, 1010, 907, 847, 744, 684, 557 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 7.82–7.79 (m, 3H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 161.0, 156.7, 149.6, 145.0, 142.6, 134.0, 132.7, 129.7, 127.1, 126.7, 121.2, 117.8, 116.3, 113.4, 61.8, 14.4. HRMS (ESI): m/z calcd for $C_{20}H_{15}N_3O_4Na$ $[M+Na]^+$: 384.0955; found: 384.0957.

*4-(3-(ethoxycarbonyl)-5-(phenoxycarbonyl)-1H-pyrazol-1-yl)benzoic acid (**3o**)*. White solid; Yield: 75% (285 mg); Mp: 180-182 ºC; IR (thin film): ν 3132, 1733, 1690, 1612, 1494, 1430, 1285, 1234, 1197, 1092, 998, 865, 768, 735, 684, 548 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 8.25 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 170.7, 161.2, 156.7, 149.7, 144.7, 143.6, 134.1, 130.8, 130.1, 129.7, 126.5, 126.4, 121.2, 116.1, 61.8, 14.4. HRMS (ESI): m/z calcd for $C_{20}H_{16}N_2O_6Na$ $[M+Na]^+$: 403.0901; found: 403.0908.

*5-(tert-butyl) 3-ethyl 1-isopropyl-1H-pyrazole-3,5-dicarboxylate (**3p**)*. Yellow viscous oil; Yield: 84% (237 mg); IR (thin film): ν 2978, 2936, 1717, 1524, 1439, 1370, 1270, 1246, 1155, 1089, 1074, 1025, 847, 753, 662 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.21 (s, 1H), 5.57-5.47 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.56 (s, 9H), 1.53 (s, 3H), 1.51 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 161.0, 157.5, 140.7, 133.1, 112.9, 81.6, 60.0, 52.1, 27.2, 21.5, 13.4. HRMS (ESI): m/z calcd for $C_{14}H_{23}N_2O_4$ $[M+H]^+$: 283.1652; found: 283.1652.

*5-(tert-butyl) 3-ethyl 1-cyclohexyl-1H-pyrazole-3,5-dicarboxylate (**3q**)*. White solid; Yield: 85% (274 mg); Mp: 64-66 ºC; IR (thin film): ν 2984, 2933, 2860, 1742, 1714, 1448, 1373, 1258, 1201, 1164, 1146, 1095, 1028, 901, 841, 768, 596 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.23 (s, 1H), 5.12 (tt, *J* = 9.0, 6.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.09–1.96 (m, 4H), 1.89 (dt, *J* = 12.5, 3.6 Hz, 2H), 1.71 (dq, *J* = 12.9, 3.6 Hz, 1H), 1.58 (s, 9H), 1.46 (dddd, *J* = 13.2, 10.4, 7.6, 3.6 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.30 (tt, *J* = 13.1, 3.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 162.0, 158.5, 141.6, 134.2, 113.9, 82.6, 61.0, 60.5, 32.8, 28.2, 25.6, 25.1, 14.4. HRMS (ESI): m/z calcd for $C_{17}H_{27}N_2O_4$ $[M+H]^+$: 323.1965; found: 323.1969.

*5-(tert-butyl) 3-ethyl 1-benzyl-1H-pyrazole-3,5-dicarboxylate (**3r**)*. White solid; Yield: 81% (267 mg); Mp: 57-59 ºC; IR (thin film): ν 2978, 2929, 1717, 1457, 1370, 1273, 1216, 1158, 1080, 1022, 1001, 841, 759, 720, 690, 629 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.29 (d, *J* = 4.7 Hz, 1H), 7.27–7.22 (m, 5H), 5.81 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.49 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 160.7, 157.2, 141.2, 135.3, 133.9, 127.5, 126.8, 126.5, 113.2, 81.9, 60.2, 54.7, 27.0, 13.4. HRMS (ESI): m/z calcd for $C_{18}H_{23}N_2O_4$ $[M+H]^+$: 331.1652; found: 331.1658.

*butyl 3-benzoyl-1-cyclohexyl-1H-pyrazole-5-carboxylate (**3s**)*. Yellow solid; Yield: 78% (276 mg); Mp: 36-38 ºC; IR (thin film): ν 3156, 3078, 2939, 2860, 1723, 1642, 1578, 1448, 1258, 1228, 1188, 1095, 901, 771, 717, 684, 629cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 8.31–8.28 (m, 2H), 7.61–7.57 (m, 1H), 7.53–7.48 (m, 3H), 5.19 (tt, *J* = 11.3, 3.8 Hz, 1H), 4.32 (t, *J* = 6.6 Hz, 2H), 2.11–2.05 (m, 2H), 2.01–1.89 (m, 4H), 1.78–1.71 (m, 3H), 1.50–1.42 (m, 3H), 1.35–1.23 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 187.0, 159.6, 148.9, 137.1, 132.8, 132.7, 130.7, 128.1, 114.5, 65.1, 60.5, 33.1, 30.6, 25.5, 25.2, 19.2, 13.7. HRMS (ESI): m/z calcd for $C_{21}H_{27}N_2O_3$ $[M+H]^+$: 355.2018; found: 355.2016.

*Phenyl 3-benzoyl-1-phenyl-1H-pyrazole-5-carboxylate (**3t**)*. White solid; Yield: 69% (254 mg); Mp: 120-122 ºC; IR (thin film): ν 3156, 3075, 1745, 1645, 1600, 1494, 1451, 1279, 1219, 1176, 1086, 1034, 1013, 995, 898, 759, 714, 681, 656 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 8.37 (d, *J* = 7.5 Hz, 2H), 7.93 (s, 1H), 7.65–7.62 (m, 1H), 7.60–7.57 (m, 2H), 7.55–7.51 (m, 5H), 7.43–7.40 (m, 2H), 7.29–7.28 (m, 1H), 7.18–7.15 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 186.8, 157.1, 150.8, 149.9, 139.7, 136.6, 133.8, 133.2, 130.7, 129.6, 129.5, 128.8, 128.4, 126.4, 126.2, 121.3, 116.3. HRMS (ESI): m/z calcd for $C_{23}H_{16}N_2O_3Na$ $[M+Na]^+$: 391.1053; found: 391.1057.

*Phenyl 3-formyl-1-phenyl-1H-pyrazole-5-carboxylate (**3u**)*. White solid; Yield: 56% (164 mg); Mp: 88-90 ºC; IR (thin film): ν 3072, 2917, 2848, 1748, 1702, 1684, 1600, 1581, 1494, 1451, 1436, 1330, 1270, 1219, 1185, 1122, 1071, 1019, 938, 907, 808, 750, 705, 681 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 10.14 (s, 1H), 7.75 (s, 1H), 7.56-7.53 (m, 5H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 3.6 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 185.9, 156.8, 150.9, 149.8, 139.5, 134.7, 129.8, 129.6, 129.0, 126.5, 125.9, 121.2, 112.5. HRMS (ESI): m/z calcd for $C_{17}H_{12}N_2O_3Na$ $[M+Na]^+$: 315.0740; found: 315.0742.

*Diethyl (R)-5-methyl-1-phenyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate (**4a**)*. Yellow solid; Yield: 77% (234 mg); Mp: 62-64 ºC; IR (thin film): ν 2990, 1729, 1696, 1600, 1563, 1503, 1303, 1255, 1104, 1013, 856, 753, 696, 684cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.25 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 7.3 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.23 (q, *J* = 6.9, 6.4 Hz, 2H), 3.56 (d, *J* = 17.7 Hz, 2H), 3.18 (d, *J* = 17.7 Hz, 2H), 1.66 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 172.5, 162.5, 141.3,

136.5, 129.1, 122.1, 115.6, 70.5, 62.3, 61.3, 47.0, 21.5, 14.4, 14.0. HRMS (ESI): m/z calcd for $C_{16}H_{20}N_2O_4Na$ $[M+Na]^+$: 327.1315; found: 327.1317.

Diethyl (R)-5-(bromomethyl)-1-phenyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate ***(4b)***. Yellow solid; Yield: 86% (329 mg); Mp: 86-88 ºC; IR (thin film): ν 2984, 1729, 1690, 1600, 1563, 1503, 1300, 1246, 1101, 1013, 747, 696, 684 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.29 (t, *J* = 7.5 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.29-4.20 (m, 2H), 4.05 (d, *J* = 11.6 Hz, 1H), 3.89 (d, *J* = 11.6 Hz, 1H), 3.62 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 169.9, 162.0, 141.1, 137.5, 129.2, 123.1, 116.6, 73.0, 62.9, 61.5, 44.6, 34.4, 14.4, 14.0. HRMS (ESI): m/z calcd for $C_{16}H_{19}BrN_2O_4Na$ $[M+Na]^+$: 405.0420; found: 405.0426.

3-ethyl 5-(2-hydroxyethyl) (R)-5-methyl-1-phenyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate ***(4c)***. Yellow solid; Yield: 63% (202 mg); Mp: 64-66 ºC; IR (thin film): ν 3501, 2987, 2942, 1736, 1708, 1560, 1500, 1297, 1246, 1194, 1092, 1071, 1013, 814, 747, 690, 678 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.28 (td, *J* = 7.2, 1.7 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.41–4.32 (m, 3H), 4.18 (ddd, *J* = 11.7, 6.0, 3.3 Hz, 1H), 3.66 (td, *J* = 5.7, 3.3 Hz, 2H), 3.61 (d, *J* = 17.8 Hz, 1H), 3.20 (d, *J* = 17.8 Hz, 1H), 1.72 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 172.5, 162.3, 141.5, 136.8, 129.3, 122.3, 115.2, 70.5, 67.5, 61.4, 60.7, 47.1, 22.0, 14.4. HRMS (ESI): m/z calcd for $C_{16}H_{21}N_2O_5$ $[M+H]^+$: 321.1445; found: 321.1439.

3-ethyl 5-methyl (R)-5-acetamido-1-phenyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate ***(4d)***. Yellow solid; Yield: 74% (246 mg); Mp: 120-124 ºC; IR (thin film): ν 3389, 2993, 1739, 1690, 1566, 1494, 1433, 1297, 1258, 1204, 1140, 1125, 1052, 974, 904, 823, 753, 696, 672, 554 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.23 (d, *J* = 7.7 Hz, 2H), 7.15 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 4.35 (q, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 3.69 (d, *J* = 18.2 Hz, 1H), 3.53 (d, *J* = 18.1 Hz, 1H), 1.92 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 171.1, 168.6, 162.1, 140.5, 137.8, 129.0, 122.7, 115.9, 78.9, 61.3, 54.4, 44.7, 23.4, 14.3. HRMS (ESI): m/z calcd for $C_{16}H_{19}N_3O_5Na$ $[M+Na]^+$: 356.1217; found: 356.1213.

Ethyl (R)-5-carbamoyl-5-methyl-1-phenyl-4,5-dihydro-1H-pyrazole-3-carboxylate ***(4e)***. Yellow solid; Yield: 57% (157 mg); Mp: 222-224 ºC; IR (thin film): ν 3380,3202, 2990, 1726, 1587, 1572, 1503, 1375, 1252, 1294, 1213, 1098, 1071, 808, 756, 696, 662, 605 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ = 7.72 (s, 1H), 7.47 (s, 1H), 7.31–7.28 (m, 2H), 7.10–7.08 (m, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 4.26 (qd, *J* = 7.1, 2.6 Hz, 2H), 3.31 (d, *J* = 17.6 Hz, 1H), 3.16 (d, *J* = 17.5 Hz, 1H), 1.38 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ = 174.3, 162.3, 141.9, 137.9, 121.8, 115.5, 71.4, 61.0, 47.4, 20.1, 14.7. HRMS (ESI): m/z calcd for $C_{14}H_{17}N_3O_3Na$ $[M+Na]^+$: 298.1162; found: 298.1169.

Diethyl (R)-1-(2,4-dichlorophenyl)-5-methyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate ***(4f)***. Yellow viscous oil; Yield: 65% (242 mg); ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.42 (d, *J* = 2.0 Hz, 1H), 7.28–7.20 (m, 2H), 4.34 (q, *J* = 7.1, 6.5 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 17.7 Hz, 1H), 3.14 (d, *J* = 17.7 Hz, 1H), 1.47 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ = 171.3, 162.2, 140.0, 137.8, 133.5, 133.2, 130.3, 130.1, 127.4, 73.5, 62.1, 61.4, 45.0, 22.0, 14.4, 14.0. HRMS (ESI): m/z calcd for $C_{16}H_{19}Cl_2N_2O_4$ $[M+H]^+$: 373.0716; found: 373.0711.

Diethyl (R)-5-(bromomethyl)-1-(o-tolyl)-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate ***(4g)***. Yellow solid; Yield: 73% (289 mg); Mp: 80-82 ºC; IR (thin film): ν 3050, 2993, 1739, 1690, 1554, 1476, 1424, 1270, 1234, 1104, 1028, 1010, 904, 868, 805, 777, 744, 732 cm^{-1};^1H NMR (600 MHz, Chloroform-*d*) δ = 7.24–7.19 (m, 2H), 7.16 (td, *J* = 7.4, 2.1 Hz, 1H), 7.04 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.12 (m, 2H), 3.95 (d, *J* = 18.2 Hz, 1H), 3.89 (d, *J* = 10.3 Hz, 1H), 3.68 (d, *J* = 10.3 Hz, 1H), 3.49 (d, *J* = 18.2 Hz, 1H), 2.27 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 168.0, 162.2, 139.2, 137.4, 136.6, 131.7, 127.9, 127.0, 126.2, 62.5, 61.3, 41.7, 34.5, 18.6, 14.4, 13.7. HRMS (ESI): m/z calcd for $C_{17}H_{21}BrN_2O_4Na$ $[M+Na]^+$: 419.0577; found: 419.0574.

3-ethyl 5-(2-hydroxyethyl) (R)-1-(4-bromophenyl)-5-methyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate ***(4h)***. *Brown* viscous oil; Yield: 69% (275 mg); IR (thin film): ν 3455, 2990, 1790, 1742, 1699, 1587, 1560, 1491, 1306, 1252, 1185, 1095, 1007, 829, 768, 744 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 7.41–7.37 (m, 2H), 7.06–7.04 (m, 2H), 4.38–4.35 (m, 3H), 4.28 (ddd, *J* = 11.8, 6.1, 3.2 Hz, 1H), 3.79–3.71 (m, 2H), 3.63 (d, *J* = 17.8 Hz, 1H), 3.22 (d, *J* = 17.8 Hz, 1H), 1.69 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 172.4, 162.1, 140.5, 137.6, 132.1, 116.9, 114.7, 70.5, 67.5, 61.6, 60.7, 47.2, 21.6, 14.3. HRMS (ESI): m/z calcd for $C_{16}H_{19}BrN_2O_5Na$ $[M+Na]^+$: 421.0370; found: 421.0376.

2-hydroxyethyl (R)-3-benzoyl-1-cyclohexyl-5-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate ***(4i)***. Yellow viscous oil; Yield: 52% (186 mg); IR (thin film): ν 3431, 2936, 2860, 1739, 1596, 1572, 1506, 1445, 1261, 1179, 1116, 910, 892, 847, 732, 705, 672 cm^{-1}; ^1H NMR (600 MHz, Chloroform-*d*) δ = 8.14–8.10 (m, 2H), 7.53–7.49 (m, 1H), 7.43 (dd, *J* = 8.3, 7.0 Hz, 2H), 4.35–4.26 (m, 2H), 3.86 (t, *J* = 4.7 Hz, 2H), 3.63 (d, *J* = 17.1 Hz, 1H), 3.28 (tt, *J* = 11.5, 3.7 Hz, 1H), 3.11 (d, *J* = 17.1 Hz, 1H), 2.65 (s, 1H), 2.05–1.95 (m, 1H), 1.91–1.79 (m, 3H), 1.71–1.62 (m, 3H), 1.58 (s, 3H), 1.36–1.28 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ = 186.2,

172.6, 140.6, 137.6, 131.6, 129.9, 127.8, 72.2, 67.2, 60.7, 57.9, 43.2, 34.5, 32.9, 25.9, 25.7, 25.3, 22.6. HRMS (ESI): m/z calcd for $C_{20}H_{27}N_2O_4$ $[M+H]^+$: 359.1965; found: 359.1966.

*Ethyl (E)-2-(2-phenylhydrazono)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (**5a**)*. Brown viscous oil; Yield: 64% (111 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.73 (dd, J = 6.7, 3.0 Hz, 2H), 7.59 (dt, J = 4.7, 2.6 Hz, 3H), 5.49 (s, 1H), 4.20 (qd, J = 7.1, 2.2 Hz, 2H), 1.63–1.26 (m, 6H), 1.23–1.15 (m, 12H), 0.88 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 166.0, 150.6, 132.2, 129.5, 122.4, 107.0, 61.3, 60.4, 59.6, 33.9, 32.3, 20.3, 19.9, 16.5, 14.0. HRMS (ESI): m/z calcd for $C_{19}H_{30}N_3O_3$ $[M+H]^+$: 348.2282; found: 348.2281.

*5-(tert-butyl) 3-ethyl (S)-1-phenyl-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate (**6a**)*. Yellow solid; Yield: 83% (264 mg); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.30 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 4.82 (dd, J = 13.6, 6.8 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.51 (dd, J = 18.1, 13.6 Hz, 1H), 3.28 (dd, J = 18.1, 6.8 Hz, 1H), 1.39 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ = 169.2, 162.3, 142.6, 138.2, 129.1, 121.6, 114.1, 83.0, 63.3, 61.3, 37.1, 27.8, 14.3. HRMS (ESI): m/z calcd for $C_{17}H_{22}N_2O_4Na$ $[M+Na]^+$: 341.1472; found: 341.1475.

■ ASSOCIATED CONTENT

SUPPORTING INFORMATION

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

Mechanism studies, copies of ^{1}H and ^{13}C NMR spectra, X-ray crystallography data and CIF file.

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Notes

The authors declare no competing financial interest.

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