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Simple and efficient one-pot synthesis of *N*-phenyl-3,5-difunctionalized pyrazoles

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ABSTRACT

A facile one-pot synthesis of *N*-phenyl-3,5-difunctionalized pyrazoles is described. The dialkyl 2-[(*Z*)-phenylhydrazono]succinate intermediate, which is prepared in situ from the mixture of phenylhydrazine and dialkyl acetylenedicarboxylate reacts with aroyl chloride or fumaryl chloride to afford the title compounds. Different types of compounds containing COCl functional group were used to investigate the scope and limitation of the reaction. Two $-CO_2R$ and $-O_2C$ groups at 3- and 5-position are potentially capable to convert to other functional groups. The reaction conditions are relatively mild and the yields are good.

1. Introduction

Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life.[1] Pyrazole and its derivatives, a class of nitrogen-containing heterocyclic compounds, occupy an important position in medicinal chemistry with a wide range of bioactivities. They possess anti-obesity,[2a] estrogen receptor agonist,[2b,c] HIV-1 reverse transcriptase inhibitor,[2d] and anti-hyperglycemic activities.[2e] They are also used as anti-anxiety[3,4] anti-pyretic, analgesic, and anti-inflammatory drugs.[5–7] In addition, many pyrazole derivatives are used as insecticides, herbicides, and fungicides, such as fripronil (Colliot et al., 1992), topramezon (BASF, 2006), pyraelostrobin (BASF, 2001), and so on.[8] Moreover, the pyrazole unit is the core structure in a number of natural products.[9] They are also considered as extremely versatile building blocks in organic chemistry (Fig. 1).[10]

The most common methods for the preparation of pyrazoles are the reaction of hydrazines with β-dicarbonyl compounds, and the 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[11] Pyrazole derivatives have also been prepared by cyclization[12] of hydrazone dianions with esters,[13] acid chlorides,[14] nitriles,[15] cyclization of hydrazone dianions with α-haloketones[16] and recently, a novel and efficient method starting from Weinreb amides, hydrazines, and propiolates.[17] With widespread industrial applications and bioactivity, chemists and biologists in recent years have directed considerable attention toward the research of pyrazole derivatives.

2. Results and discussion

In a continuation of our works on the synthesis of *N*-containing heterocycles,[18] we have performed the one-pot regioselective synthesis of a novel series of 1,3-diaryl-1*H*-pyrazole-4,5-dicarboxylate **5** from the reaction of phenylhydrazine **1**, trialkyl phosphite **2**, dialkyl acetylenedicarboxylate **3**, and aroyl chloride **4** via intermediate **6**[19] under reflux (Scheme 1).[20]

Although no phosphorus-containing moiety is contained in the structure of the pyrazole product we believed that trialkyl phosphite **2** is important in regioselective product formation. This led us to perform this reaction without trialkyl phosphite **2** and thus, as outlined in Scheme 2, we undertook the reaction of phenylhydrazine **1**, dialkyl acetylenedicarboxylate **3**, and aroyl chloride **4** under two different sets of conditions: In both cases, alkyl 5-(aroyloxy)-1-phenyl-1*H*-pyrazole-3-carboxylate **7** was obtained as the main product in 70–80% yields.

To investigate the scope and limitations of the reaction, we first decided to study the effect of aroyl chloride using different types of aroyl chloride with halogen substitution in either *para* or *ortho* position (Table 1). It was found that the reaction worked well with Br in *p*- and Cl in *p*- and *o*-positions.

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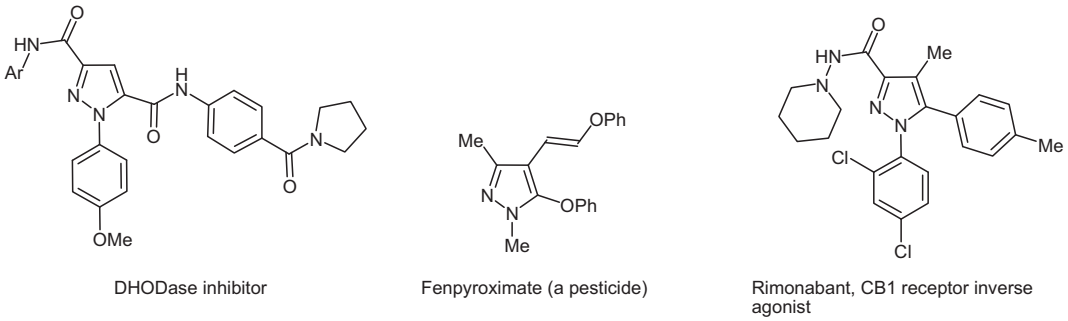
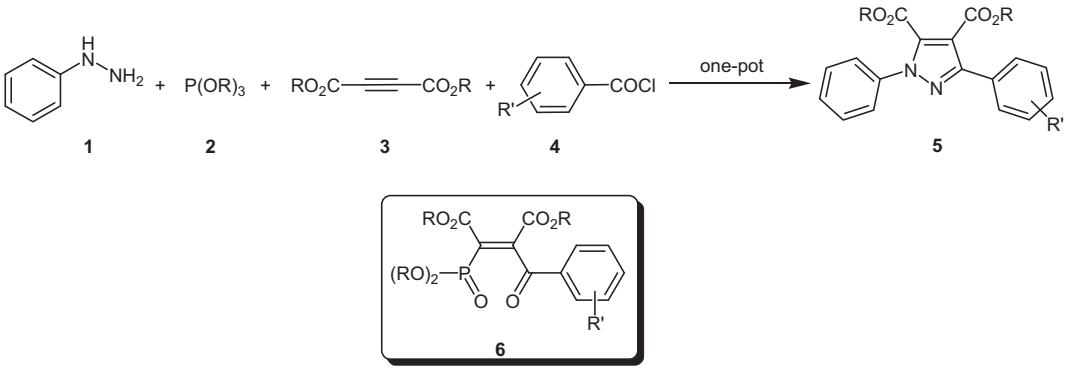
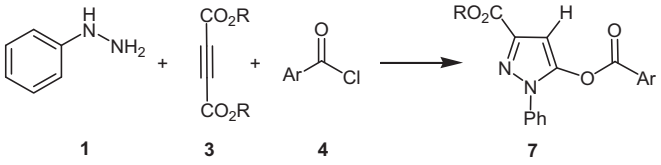


Fig. 1. Some of the most important small molecules with pyrazole-based core skeleton.



Scheme 1. Synthesis of 1,3-diaryl-1*H*-pyrazole-4,5-dicarboxylate.



Conditions: a) CH_2Cl_2, Et_3N, 6 h or b) CH_2Cl_2/Toluene, reflux, 8 h

Scheme 2. Synthesis of alkyl 5-(aroyloxy)-1-phenyl-1*H*-pyrazole-3-carboxylate.

Table 1
Alkyl 5-(aroyloxy)-1-phenyl-1*H*-pyrazole-3-carboxylate derivatives

Entry	R	Ar	Product	[a]Yield %
1	Me	C_6H_5	**7a**	78
2	Me	*o*-ClC_6H_4	**7b**	80
3	Me	*p*-ClC_6H_4	**7c**	70
4	Me	*p*-BrC_6H_4	**7d**	78
5	Et	C_6H_5	**7e**	77
6	Et	*o*-ClC_6H_4	**7f**	75
7	Et	*p*-ClC_6H_4	**7g**	78
8	Et	*p*-BrC_6H_4	**7h**	80

[a] The yields of both condition were approximately equal.

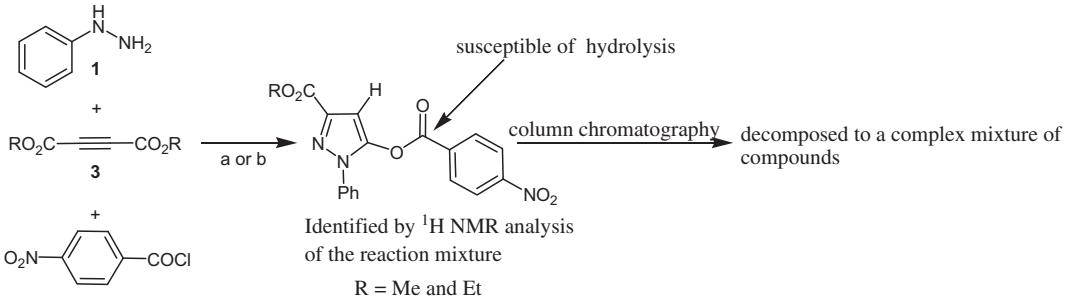
Although the use of *p*-$NO_2C_6H_4COCl$ afforded a complex mixture of products, we found that the desired product was seen from ^1H NMR analysis of the crude reaction mixture. Any attempts to purify the product failed, presumably is because of facile hydrolysis of the high reactivity of *p*-nitrobenzoate ester (Scheme 3).

We next employed fumaryl chloride **8** instead of aroyl chloride in the reaction with phenylhydrazine **1** and dialkyl acetylenedicarboxylate **3** to evaluate the substrate scope of this reaction. It was found that the reaction proceeds smoothly in CH_2Cl_2 at room temperature for 5 h to produce *N*-phenyl-3,5-difunctionalized pyrazole **9** in 71–75% yields, which is different from the pyrazole **7** in 5-substitution (Scheme 4). Unfortunately, performing the reaction with 2:2:1 ratio of **1**:**3**:**8** failed to produce bis-pyrazole **10**.

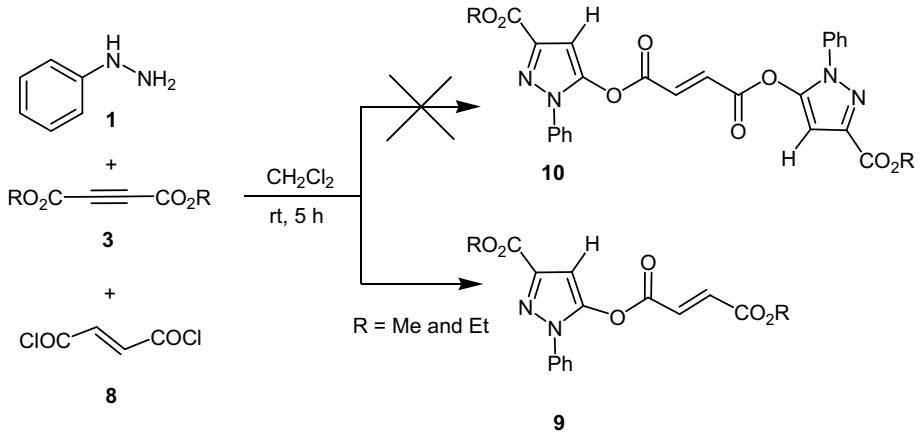
The structures of compounds **7a**–**h** and **9a**–**b** were deduced from their elemental analysis, IR, and high-field ^1H and ^{13}C NMR spectra. Mass spectrum of **7a** displayed molecular ion peak at *m*/*z* 322. In the IR spectrum of **7a**, two absorption bands at 1744 and 1600 cm^{-1}, which are related to two C=O stretching frequencies, clearly indicated the most significant functional groups of the product. The ^1H-decoupled ^{13}C NMR spectrum of **7a** is in agreement with the product structure. In the aliphatic region there are one signal related to methyl group. The characteristic carbon (C^3=C^4H) of the compound **7a** resonates at 93.4 ppm. The other important region of the spectrum is related to carbonyl groups, which produce 2C=O signals at 161.5 and 162.4 ppm.

The mass spectrum of **9a** also displayed a molecular ion peak at *m*/*z* 330 and three absorption bands at 1767 and 1726 cm^{-1} (two overlapped bands) for C=O groups were seen in the IR spectrum. In the ^1H NMR spectrum of **9a**, three singlet signals at 3.83, 3.95, and 6.95 ppm clearly indicated the presence of two OMe and C^3=C^4H groups. The most important signals of compound **9a** are trans hydrogens of CH=CH moiety, which are appeared in the vinyl region at 6.92 and 6.98 ppm with coupling constant of $^3J_{HH}$=15.8 Hz. 14 Distinct signals in the ^{13}C NMR of **9a**, especially three resonances at 159.5, 162.2, and 164.4 ppm for C=O groups, are in agreement with the proposed structure.

With the above results in mind, we propose a plausible mechanism (Scheme 5). An initial nucleophilic addition of NH_2 to dialkyl acetylenedicarboxylate **3** followed by hydrogen shift affords dialkyl 2-[(*Z*)-phenylhydrazono]succinate **12** (Experimental section), with subsequent hydrazide formation via an intramolecular process to form dihydro-1*H*-pyrazole **13**. Finally, in the presence of aroyl chloride, intermediate **13** converts to the product **7**. However, in the



Scheme 3.



Entry	R	Product	Yield %
1	Me	**9a**	71
2	Et	**9b**	75
3	*t*-Bu	-	-

Scheme 4.

presence of fumaryl chloride, dihydropyrazole **13** reacts with COCl moiety to afford the pyrazole intermediate **14**. In the final step, alcoholization of the remaining COCl of fumaryl chloride by ROH produces the corresponding pyrazole **9**.

To confirm the cyclization step of our proposed mechanism, we performed the reaction of phenylhydrazine **1**, di-*tert*-butyl acetylenedicarboxylate **15** and *p*-chlorobenzoyl chloride or fumaryl chloride under the same condition as shown in Scheme 2 or4. No desired products were obtained.

The reaction of phenylhydrazine **1**, di-*tert*-butyl acetylenedicarboxylate **15** without aroyl chloride or fumaryl chloride was performed, and the intermediate **12c** was purified and characterized. Thus we guessed that this is because of the forbidden cyclization step for tertiary alcohol due to the steric hindrance (Scheme 6).

3. Conclusion

A concise and efficient one-pot synthesis of substituted pyrazoles has been developed based on the one-pot reaction of phenylhydrazine, dialkyl acetylendicarboxylate, and aroyl chloride or fumaryl chloride. The reaction proceeds under neutral conditions with no bases or catalysts in high yield and requires only a simple purification of the products.

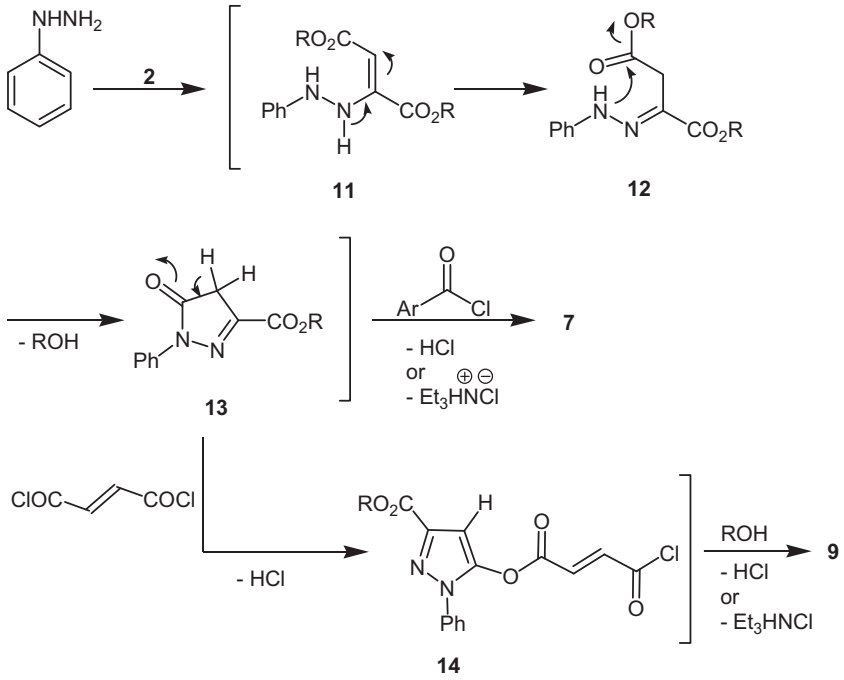
4. Experimental

4.1. General

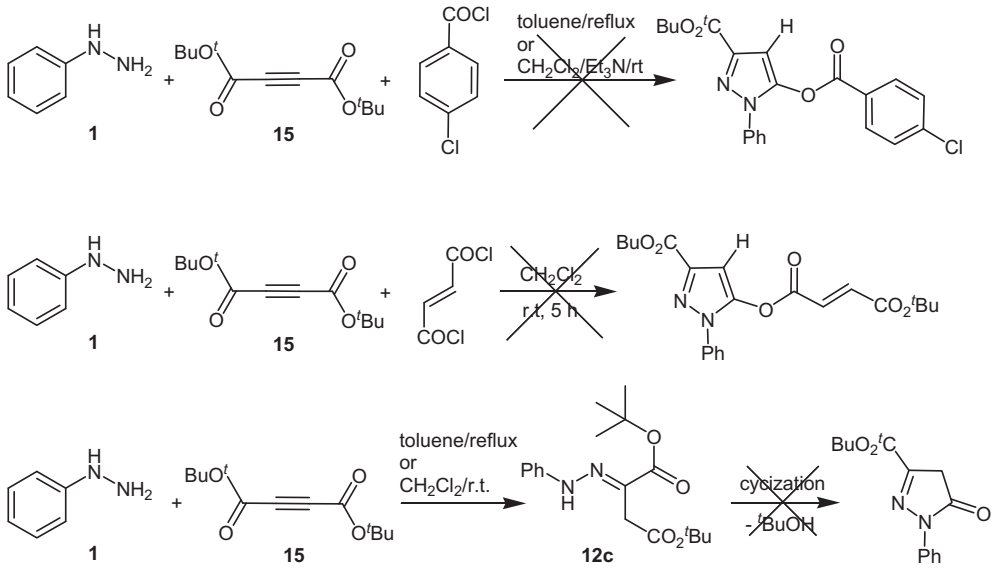
IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer. ^{1}H NMR (500.13 MHz) and ^{13}C NMR (125.75 MHz) spectra were obtained using a Bruker DRX-500 AVANCE spectrometer. All NMR spectra at room temperature were determined in $CDCl_3$. Melting points measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 or 70 eV. All chemicals were purchased from Merck or Aldrich and were used without further purification.

4.2. General synthesis procedure for 7a–h and 9a–b

For example, for **7a**: to a magnetically stirred solution of phenylhydrazine (0.22 g, 2 mmol) and dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in CH_2Cl_2 (2 mL) after 2 h was added benzoyl chloride (0.28 g, 2 mmol) in toluene (3 mL). The reaction mixture was stirred for 8 h under reflux. After the completion the reaction (The progress of the reaction was followed by thin layer chromatography), the solvent was removed under reduced pressure and



Scheme 5. Plausible mechanism for the formation of *N*-phenyl-3,5-difunctionalaized pyrazole **7** and **9**.



Scheme 6.

the residue was purified by column chromatography over silica gel (Merck 230–240 mesh) using a mixture of *n*-hexane–EtOAc (8:1) as eluent.

For example, for **9a**: to a magnetically stirred solution of phenylhydrazine (0.22 g, 2 mmol) and dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in CH_2Cl_2 (2 mL) after 2 h was added fumaryl chloride (0.30 g, 2 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 3 h at ambient temperature. After the completion the reaction (The progress of the reaction was followed by thin layer chromatography), the solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel (Merck 230–240 mesh) using a mixture *n*-hexane–EtOAc (8:1) as eluent.

*4.2.1. Methyl 5-(benzoyloxy)-1-phenyl-1H-pyrazole-3-carboxylate (**7a**).* White powder, mp 161–163 °C, 0.25 g, yield: 78%. IR (KBr) (ν_{max}, cm^{-1}): 1744 (C=O), 1600 (C=O), 1542 and 1451 (Ar), 1236 and 1164 (C–O). Anal. Calcd for $C_{18}H_{14}N_2O_4$ (322.32): C, 67.08; H, 4.38; N, 8.69%. Found: C, 67.11; H, 4.39; N, 8.72%. MS (EI, 70 eV): *m*/*z* (%)=322 (M^+, 10), 293 (19), 279 (12), 188 (21), 167 (25), 149 (58), 105 (100), 91 (11), 77 (96), 57 (23). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=3.98 (3H, s, Me), 7.01 (1H, s, C^4H), 7.41 (1H, t, $^3J_{HH}$=7.5 Hz, CH of Ar), 7.48 (2H, t, $^3J_{HH}$=7.9 Hz, 2CH of Ph), 7.50 (2H, t, $^3J_{HH}$=7.5 Hz, 2CH of Ph), 7.65 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH of Ph), 7.66 (1H, t, $^3J_{HH}$=7.5 Hz, CH of Ph), 8.06 (2H, d, $^3J_{HH}$=8.3 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=52.2 (OMe), 93.4 (C^4H), 124.2 (2CH of Ar), 127.5 (C^3), 128.6 (CH of Ar), 128.9 (2CH of Ar), 129.2 (2CH of Ar), 130.4 (2CH of Ar), 134.5 (CH of Ar), 137.4 (C_{ipso}–CO_2), 143.1 (C_{ipso}–N), 144.99 (C^5), 161.4 (CO), 162.4 (CO).

*4.2.2. Methyl 5-[(2-chlorobenzoyl)oxy]-1-phenyl-1H-pyrazole-3-carboxylate (**7b**).* White powder, mp 140–142 °C, 0.28 g, yield: 80%. IR

(KBr) (ν_{max}, cm^{-1}): 1766 (C=O), 1732 (C=O), 1590 and 1452 (Ar), 1228 and 1166 (C–O), 766 (C–Cl). Anal. Calcd for $C_{18}H_{13}ClN_2O_4$ (356.76): C, 60.60; H, 3.67; N, 7.85%. Found: C, 60.65; H, 3.66; N, 7.82%. MS (EI, 70 eV): *m*/*z* (%)=356.76 (M^+, 6), 325 (10), 218 (8), 140 (98), 139 (100), 111 (14), 77 (16), 51 (10). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=3.97 (3H, s, Me), 7.02 (1H, s, C^4H), 7.33–7.37 (1H, m, CH of Ar), 7.40–7.7.42 (1H, m, CH of Ar), 7.44–7.48 (2H, m, 2CH of Ar), 7.60–7.63 (2H, m, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=51.7 (OMe), 98.0 (C^4H), 124.0 (2CH of Ar), 126.4 (C^3), 126.4 (CH of Ar), 128.3 (CH of Ar), 128.7 (2CH of Ar), 131.3 (CH of Ar), 131.6 (CH of Ar), 133.7 (CH of Ar), 134.8 (C_{ipso}–CO_2), 136.8 (C_{ipso}–Cl), 142.6 (C_{ipso}–N), 144.2 (C^5), 159.4 (CO), 161.9 (CO).

*4.2.3. Methyl 5-[(4-chlorobenzoyl)oxy]-1-phenyl-1H-pyrazole-3-carboxylate (**7c**).* White powder, mp 150–152 °C, 0.25 g, yield: 70%. IR (KBr) (ν_{max}, cm^{-1}): 1739 (C=O), 1688 (C=O), 1591 and 1453 (Ar), 1230 and 1167 (C–O), 768 (C–Cl). Anal. Calcd for $C_{18}H_{13}ClN_2O_4$ (356.76): C, 60.60; H, 3.67; N, 7.85%. Found: C, 60.71; H, 3.70; N, 7.88%. MS (EI, 70 eV): *m*/*z* (%)=359 (M^++2, 7), 357 (M^+, 19), 325 (M^+–5, 18), 218 (17), 139 (100), 111(30), 77 (38), 51 (11). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=3.98 (3H, s, Me), 7.01 (1H, s, C^4H), 7.41 (1H, t, $^3J_{HH}$=7.5 Hz, CH of Ar), 7.47–7.51 (4H, m, 4CH of Ar), 7.64–7.68 (3H, m, 3CH of Ar), 7.98 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=52.2 (OMe), 98.4 (C^4H), 124.2 (2CH of Ar), 125.9 (C^3), 128.6 (C_{ipso}–CO_2), 128.7 (CH of Ar), 129.2 (2CH of Ar), 129.4 (2CH of Ar), 131.7 (2CH of Ar), 137.3 (C_{ipso}–N), 141.4 (C_{ipso}–Cl), 143.1 (C^5), 160.6 (CO), 162.3 (CO).

*4.2.4. Methyl 5-[(4-bromobenzoyl)oxy]-1-phenyl-1H-pyrazole-3-carboxylate (**7d**).* White powder, mp 167–169 °C, 0.31 g, yield: 78%. IR (KBr) (ν_{max}, cm^{-1}): 1736 (C=O), 1652 (C=O), 1588 and 1453 (Ar), 1229 and 1168 (C–O), 772 (C–Br). Anal. Calcd for $C_{18}H_{13}BrN_2O_4$ (401.21): C, 53.89; H, 3.27; N, 6.98%. Found: C, 53.72; H, 3.26; N, 6.99%. MS (EI, 70 eV): *m*/*z* (%)=403 (M^++2, 2), 401 (M^+, 2), 218 (10), 185 (100), 183 (97), 155 (27), 105 (7), 91 (11), 77 (47), 51 (13). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=3.98 (3H, s, Me), 7.01 (1H, s, C^4H), 7.43 (1H, t, $^3J_{HH}$=7.4 Hz, CH of Ar), 7.48 (2H, t, $^3J_{HH}$=7.3 Hz, 2CH of Ar), 7.62 (2H, d, $^3J_{HH}$=8.0 Hz, 2CH of Ar), 7.64 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar), 7.90 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=52.2 (OMe), 98.4 (C^4H), 124.2 (2CH of Ar), 128.8 (CH of Ar), 129.0 (C_{ipso}–Br), 129.2 (2CH of Ar), 130.1 ($C3$), 131.4 (C_{ipso}–CO_2), 131.8 (2CH of Ar), 132.0 (C_{ipso}–N), 143.1 (C^5), 160.8 (CO), 162.3 (CO).

*4.2.5. Ethyl 5-(benzoyloxy)-1-phenyl-1H-pyrazole-3-carboxylate (**7e**).* White powder, mp 172–174 °C, 0.26 g, yield: 77%. IR (KBr) (ν_{max}, cm^{-1}): 1715 (C=O), 1605 (C=O), 1550 and 1456 (Ar), 1248 and 1160 (C–O). Anal. Calcd for $C_{19}H_{16}N_2O_4$ (336.34): C, 67.85; H, 4.79; N, 8.33%. Found: C, 67.90; H, 4.82; N, 8.35%. MS (EI, 70 eV): *m*/*z* (%)=320 (M^+–16, 43), 264 (29), 232 (71), 186 (35), 158 (39), 105 (66), 91 (100), 91 (83), 77 (100), 51 (21). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=1.42 (3H, t, $^3J_{HH}$=7.1 Hz, OCH_2Me), 4.45 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2Me), 7.00 (1H, s, C^4H), 7.41 (1H, t, $^3J_{HH}$=7.0 Hz, CH of Ar), 7.48 (2H, t, $^3J_{HH}$=8.0 Hz, 2CH of Ar), 7.49 (2H, t, $^3J_{HH}$=7.8 Hz, 2CH of Ar), 7.64–7.68 (3H, m, 3CH of Ar), 8.06 (2H, d, $^3J_{HH}$=8.1 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.4 (OCH_2Me), 61.2 (OCH_2Me), 98.3 (C^4H), 124.2 (2CH of Ar), 127.5 (C^3), 128.6 (CH of Ar), 128.9 (2CH of Ar), 129.2 (2CH of Ar), 130.4 (2CH of Ar), 134.5 (CH of Ar), 137.5 (C_{ipso}–CO_2), 143.5 (C_{ipso}–N), 144.9 (C^5), 161.5 (CO), 162.0 (CO).

*4.2.6. Ethyl 5-[(2-chlorobenzoyl)oxy]-1-phenyl-1H-pyrazole-3-carboxylate (**7f**).* White powder, mp 90–92 °C, 0.28 g, yield: 75%. IR (KBr) (ν_{max}, cm^{-1}): 1766 (C=O), 1725 (C=O), 1531 and 1445 (Ar), 1229 and 1168 (C–O), 769 (C–Cl). Anal. Calcd for $C_{19}H_{15}ClN_2O_4$ (370.79): C, 61.55; H, 4.08; N, 7.56%. Found: C, 61.59; H, 4.09; N, 7.60%. MS (EI, 70 eV): *m*/*z* (%)=370 (M^+, 1), 325 (5), 232 (7), 139 (100), 111 (47), 91 (15), 77 (47), 51 (10). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=1.43 (3H, t, $^3J_{HH}$=7.1 Hz, OCH_2Me), 4.45 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2Me), 7.02 (1H, s, C^4H), 7.34–7.38 (1H, m, 1H of Ar), 7.41 (1H, t, $^3J_{HH}$=7.3 Hz, CH of Ar), 7.47 (2H, t, $^3J_{HH}$=7.1 Hz, 2CH of Ar), 7.52 (2H, d, $^3J_{HH}$=7.3 Hz, 2CH of Ar), 7.63 (2H, d, $^3J_{HH}$=7.8 Hz, 2CH of Ar), 7.87 (1H, d, $^3J_{HH}$=7.8 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.3 (OCH_2Me), 61.2 (OCH_2Me), 98.4 (C^4H), 124.5 (C^3), 124.5 (2CH of Ar), 126.9 (CH of Ar), 128.7 (CH of Ar), 129.1 (2CH of Ar), 131.8 (CH of Ar), 132.1 (CH of Ar), 134.2 (CH of Ar), 135.5 (C_{ipso}–CO_2), 137.4 (C_{ipso}–Cl), 143.5 (C_{ipso}–N), 144.6 (C^5), 159.9 (CO), 161.9 (CO).

*4.2.7. Ethyl 5-[(4-chlorobenzoyl)oxy]-1-phenyl-1H-pyrazole-3-carboxylate (**7g**).* White powder, mp 123–125 °C, 0.29 g, yield: 78%. IR (KBr) (ν_{max}, cm^{-1}): 1758 (C=O), 1710 (C=O), 1593 and 1437 (Ar), 1230 and 1100 (C–O), 778 (C–Cl). Anal. Calcd for $C_{19}H_{15}ClN_2O_4$ (370.79): C, 61.55; H, 4.08; N, 7.56%. Found: C, 61.57; H, 4.09; N, 7.57%. MS (EI, 70 eV): *m*/*z* (%)=370 (M^+, 4), 325 (8), 232 (10), 140 (95), 139 (100), 111 (47), 91 (12), 77 (40). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=1.42 (3H, t, $^3J_{HH}$=7.1 Hz, CH_2Me), 4.46 (2H, q, $^3J_{HH}$=7.5 Hz, CH_2Me), 6.99 (1H, s, C^4H), 7.41–7.49 (5H, m, 5CH of Ar), 7.62 (2H, d, $^3J_{HH}$=8.2 Hz, 2CH of Ar), 7.98 (2H, $^3J_{HH}$=8.4 Hz, 3CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=13.9 (CH_2Me), 60.8 (CH_2Me), 97.8 (C^4H), 123.7 (2CH of Ar), 125.4 (C^3), 128.2 (CH of Ar), 128.8 (2CH of Ar), 128.9 (2CH of Ar), 131.3 (2CH of Ar), 136.9 (C_{ipso}–CO_2), 140.9 (C_{ipso}–N), 143.0 (C_{ipso}–Cl), 144.2 (C^5), 160.2 (CO), 161.5 (CO).

*4.2.8. Ethyl 5-[(4-bromobenzoyl)oxy]-1-phenyl-1H-pyrazole-3-carboxylate (**7h**).* White powder, mp 129–131 °C, 0.33 g, yield: 80%. IR (KBr) (ν_{max}, cm^{-1}): 1719 (2C=O), 1590 and 1449 (Ar), 1264 and 1170 (C–O), 754 (C–Br). Anal. Calcd for $C_{19}H_{15}BrN_2O_4$ (415.24): C, 54.96; H, 3.64; N, 6.75%. Found: C, 54.99; H, 3.63; N, 6.76%. MS (EI, 70 eV): *m*/*z* (%)=417 (M^++2, 10), 415 (M^+, 10), 371 (13), 369 (13), 187 (98), 185 (100), 157 (31), 105 (7), 91 (6), 77 (36), 51 (5). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=1.42 (3H, t, $^3J_{HH}$=7.1 Hz, OCH_2Me), 4.45 (2H, q, $^3J_{HH}$=7.1 Hz, OCH_2Me), 7.00 (1H, s, C^4H), 7.42 (1H, t, $^3J_{HH}$=7.3 Hz, CH of Ar), 7.48 (2H, t, $^3J_{HH}$=7.9 Hz, 2CH of Ar), 7.62 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH of Ar), 7.64 (2H, d, $^3J_{HH}$=8.6 Hz, 2CH of Ar), 7.90 (2H, d, $^3J_{HH}$=8.5 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.4 (OCH_2Me), 61.3 (OCH_2Me), 98.3 (C^4H), 124.2 (2CH of Ar), 126.4 (C_{ipso}–Br), 128.7 (CH of Ar), 129.2 (2CH of Ar), 130.1 ($C3$), 131.8 (2CH of Ar), 132.4 (2CH of Ar), 137.3 (C_{ipso}–CO_2), 143.5 (C_{ipso}–N),144.6 (C^5), 160.8 (CO), 161.9 (CO).

*4.2.9. 1-[3-(Methoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl]-4-methyl (E)-2-butenedioate (**9a**).* White powder, mp 170–172 °C, 0.25 g, yield: 75%. IR (KBr) (ν_{max}, cm^{-1}): 1767 (C=O), 1726 (2C=O), 1594 (C=C), 1535 and 1449 (Ar), 1230 and 1129 (C–O). Anal. Calcd for $C_{16}H_{14}N_2O_6$ (330.29): C, 58.18; H, 4.27; N, 8.48%. Found: C, 58.23; H, 4.31; N, 8.50%. MS (EI, 70 eV): *m*/*z* (%)=330 (M^+, 5), 299 (7), 187 (10), 149 (10), 113 (100), 91 (12), 77 (30), 59 (14). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H=3.83 (3H, s, Me), 3.95 (3H, s, Me), 6.92 (1H, d, $^3J_{HH}$=15.8 Hz, CH=$CH$$CO_2$Me), 6.95 (1H, s, C^4H), 6.98 (1H, d, $^3J_{HH}$=15.8 Hz, CH=$CHCO_2$Me), 7.43 (1H, t, $^3J_{HH}$=7.4 Hz, CH of Ar), 7.49 (2H, t, $^3J_{HH}$=7.3 Hz, 2CH of Ar), 7.56 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=52.2 (OMe), 52.6 (OMe), 98.2 (C^4H), 124.1 (2CH of Ar), 128.8 (CH of Ar), 129.3 (2CH of Ar), 130.6 (CH=$CHCO_2$Me), 136.8 (CH=$CHCO_2$Me), 137.1 (C_{ipso}–N), 143.0 (C^5), 144.2 (C^3), 159.5 (CO), 162.2 (CO), 164.4 (CO).

*4.2.10. 1-[3-(Ethoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl]-4-ethyl (E)-2-butenedioate (**9b**).* White powder, mp 154–156 °C, 0.25 g, yield: 71%. IR (KBr) (ν_{max}, cm^{-1}): 1719 (3C=O), 1599 and 1453 (Ar), 1266 and 1169 (C–O). Anal. Calcd for $C_{18}H_{18}N_2O_6$ (358.35): C, 60.33; H, 5.06; N, 7.82%. Found: C, 60.35; H, 5.04; N, 7.86%. MS (EI, 70 eV): *m*/*z* (%)=358 (M^+, 8), 329 (13), 297 (17), 232 (100), 199 (23), 186 (29), 158 (34), 127 (29), 99 (40), 91 (90), 77 (80), 58 (41). ^1H NMR

(500.1 MHz, $CDCl_3$): δ_H=1.33 (3H, t, $^3J_{HH}$=7.1 Hz, OCH_2*Me*), 1.41 (3H, t, $^3J_{HH}$=7.1 Hz, OCH_2*Me*), 4.28 (2H, d, $^3J_{HH}$=7.1 Hz, O*C*H_2Me), 4.43 (2H, d, $^3J_{HH}$=7.1 Hz, O*C*H_2Me), 6.91 (1H, d, $^3J_{HH}$=15.8 Hz, CH=C*H*CO_2Et), 6.93 (1H, s, C^4H), 6.98 (1H, d, $^3J_{HH}$=15.8 Hz, C*H*=CHCO_2Et), 7.42 (1H, t, $^3J_{HH}$=7.3 Hz, CH of Ar), 7.48 (2H, t, $^3J_{HH}$=8.0 Hz, 2CH of Ar), 7.57 (2H, d, $^3J_{HH}$=7.9 Hz, 2CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.1 (OCH_2*Me*), 14.3 (OCH_2*Me*), 61.8 (O*C*H_2Me), 61.9 (O*C*H_2Me), 98.2 (C^4H), 124.1 (2CH of Ar), 128.8 (CH of Ar), 129.3 (2CH of Ar), 130.4 (*C*H=CHCO_2Me), 137.2 (C_{ipso}–N), 137.4 (CH=*C*HCO_2Me), 143.4 (C^5), 144.1 (C^3), 159.7 (CO), 161.8 (CO), 164.0 (CO).

*4.2.11. For R=Me: methyl 1-(2-methoxy-2-oxoethyl)-2-phenyl-1-hydrazinecarboxylate (**12a**).* ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=3.73 (3H, s, OMe), 3.77 (2H, s, CH_2), 3.88 (3H, s, OMe), 7.01 (1H, t, $^3J_{HH}$=7.9 Hz, CH of Ph), 7.24 (2H, d, $^3J_{HH}$=7.3 Hz, 2CH of Ar), 7.31 (2H, t, $^3J_{HH}$=7.2 Hz, 2CH of Ar), 9.23 (1H, s, NH).

*4.2.12. For R=^{t}Bu: di(tert-butyl) 2-(2-phenylhydrazono)succinate (**12c**).* ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.45 (9H, s, ^{t}Bu), 1.58 (9H, s, ^{t}Bu), 3.61 (2H, s, CH_2), 6.98 (1H, t, $^3J_{HH}$=7.6 Hz, CH of Ph), 7.22 (2H, d, $^3J_{HH}$=7.5 Hz, 2CH of Ar), 7.30 (2H, t, $^3J_{HH}$=7.3 Hz, 2CH of Ar), 9.14 (1H, s, NH).

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