Synthesis, Crystal Structure, and Fungicidal Activity of Novel 1,5-Diaryl-1*H*-pyrazol-3-oxyacetate Derivatives

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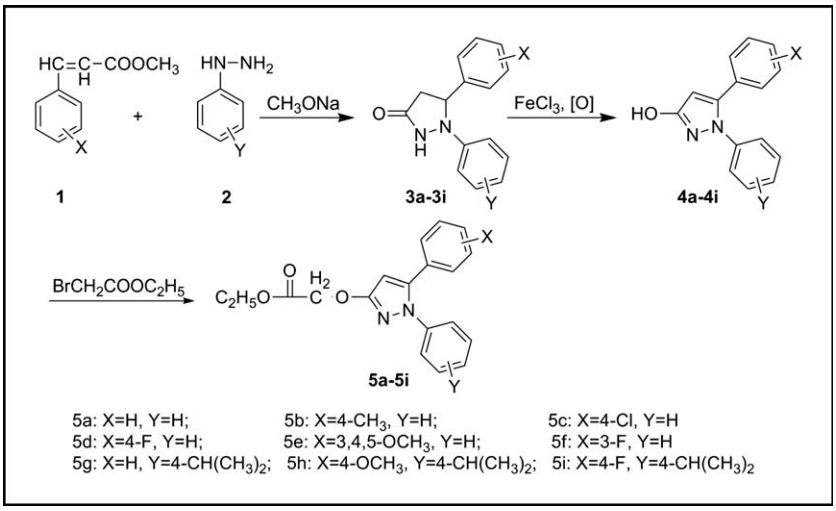

A series of ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetate derivatives (**5a–5i**) have been efficiently synthesized by the reaction of 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) with ethyl 2-bromoacetate. The structures of the newly synthesized compounds were characterized by ^{1}H NMR spectra and elemental analysis, and the crystal structure of the compound ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5c**) was determined by single crystal X-ray diffraction analysis. The compound **5c** belongs to triclinic system with space group P(-1), $a = 5.8170(12)$ Å, $b = 11.804(2)$ Å, $c = 12.783(2)$ Å, $\alpha = 83.89(2)^\circ$, $\beta = 89.24(3)^\circ$, $\gamma = 89.73(3)^\circ$, Formula weight: 356.80, Triclinic $V = 872.7(3)$ Å^3, $D_c = 1.358$ mg/m^3, $Z = 2$, F (000) = 372. Bioassay results indicated that the compound ethyl 2-(5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5d**) exhibited moderate inhibitory activity against *Gibberella zeae* at the dosage of 10 μg/mL.

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INTRODUCTION

Biological studies of the pyrazole nucleus have been shown to posses a variety of biological activities such as fungicidal [1], insecticidal [2], herbicidal [3], and plant growth regulatory activities [4]. Furthermore, several biological studies have also pointed out the value of alkyloxyacetate [5] and aryloxyacetate [6] as biologically active groups. These findings primarily focused on incorporating alkyloxyacetate and aryloxyacetate groups with 1*H*-pyrazole derivatives in the hope of obtaining compounds of potential insecticidal, fungicidal, and herbicidal activities.

1,5-Diaryl-1*H*-pyrazol-3-ols, one important kind of 1*H*-pyrazole derivatives, have been developed for their synthesis since the early twentieth century. The first synthesis of 1,5-diaryl-1*H*-pyrazol-3-ol from a pyrazolidone derivative was published by Japp and Maitland [7]. Then the reaction of arylpropiolic acids and their esters with phenylhydrazine became one of the most popular methods for the synthesis of 1,5-diaryl-1*H*-pyrazol-3-ols [8–11]. In recent years, synthesis of 1,5-diaryl-1*H*-pyrazol-3-ols by the reactions of 4-arylidene-1-phenyl-3,5-pyrazolidinediones with oxidizing agents has been achieved [12]. However, very few representatives of biologically active 1,5-diaryl-1*H*-pyrazol-3-oxyacetate derivatives have hitherto been described in the literature.

3-Arylacrylic acids and their esters are convenient and easily available starting materials or intermediates for the synthesis of a wide variety of heterocyclic compounds [13,14]. In our previous studies, we have successfully improved the procedure for the synthesis of 1,5-diaryl-1*H*-pyrazol-3-ols by the reaction of methyl 3-arylacrylates with arylhydrazines in high yields and have reported some crystal structures [15–17]. In continuation of our program directed toward the synthesis of

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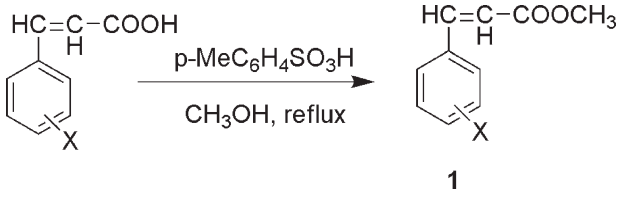
Scheme 1



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biologically active novel 1,5-diaryl-1*H*-pyrazol-3-oxyacetate derivatives, we report herein the synthesis and fungicidal activity of a series of novel ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetates (**5a–5i**), and the single crystal structure of the compound ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5c**). A preliminary *in vitro* bioassay indicated that some of these newly synthesized compounds displayed fungicidal activity.

RESULTS AND DISCUSSION

Methyl 3-arylacrylates (**1**) (Scheme 1) were prepared by the reaction of 3-arylacrylic acids with methanol, using *p*-toluenesulfonic acid as catalyst. Intermediates arylhydrazines (**2**) (Scheme 2) were prepared according to the reported methods from the substituted anilines through diazotization reactions [18].

A previous report by Gaede and McDermott [19] described that addition of methylhydrazine to a variety of haloalkyl-substituted α,β-unsaturated ethers could give 1,5-disubstituted-3-hydroxypyrazoles. Motivated by this finding, in our procedure, methyl 3-arylacrylates (**1**) were allowed to react with arylhydrazines (**2**) in boiling *n*-butanol in the presence of sodium methoxide to afford 1,5-diarylpyrazolidin-3-ones (**3a–3i**) (Scheme 3) as sole isolable products. No other pyrazoline type compounds could be detected in the crude products. It was found that the desired mode of initial Michael addition to methyl 3-arylacrylates (**1**) could be achieved. The crude solid 1,5-diarylpyrazolidin-3-ones (**3a–3i**) were recrystallized from ethyl acetate.

The conversions from 1,5-diarylpyrazolidin-3-ones (**3a–3i**) to 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) (Scheme 3) were carried out in organic solvents, using oxygen as oxidizing agent and iron (III) chloride as catalyst. To optimize the reaction conditions, different organic solvents, such as ethanol and DMF were tested in the synthesis of 1,5-diphenyl-1*H*-pyrazol-3-ol (**4a**). When the conversion was carried out using iron (III) chloride in refluxing ethanol, the yield was low and the separation of the product from the iron (II) salts was tedious. However, the conversion in DMF gave good results. Moreover, the most satisfactory result was obtained when the reaction was stirred in DMF at 80°C for 2 h, and then at 30°C for another 20 h. The crude solid 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) were recrystallized from ethanol.

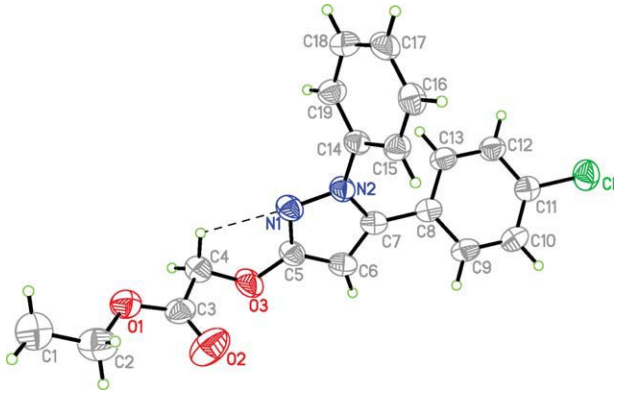
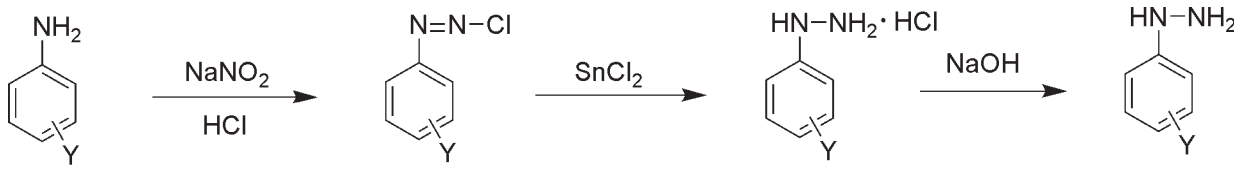


Figure 1. The molecular structure of **5c**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The reactions of 1,5-diaryl-1*H*-pyrazol-3-ols (**4a–4i**) with ethyl 2-bromoacetate were carried out in a molar ratio 1:1.1 in acetone as solvent, and all the reactions were monitored by thin-layer chromatography (TLC). The most satisfactory results were obtained when the reactions were performed under hot acetone for 3 h. The crude residues were purified *via* flash chromatography to give the pure products ethyl 2-(1,5-diaryl-1*H*-pyrazol-3-yloxy)acetates (**5a–5i**) (Scheme 3).

A suitable crystal of ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yloxy)acetate (**5c**) was obtained by dissolving the compound in ethyl acetate and evaporating the solvent slowly at room temperature for about 10 days. Its solid-state structure was determined by single crystal X-ray diffraction. Details of the structure determination and refinement are given in the experiment section. The drawing of the molecular structure with the

Scheme 2



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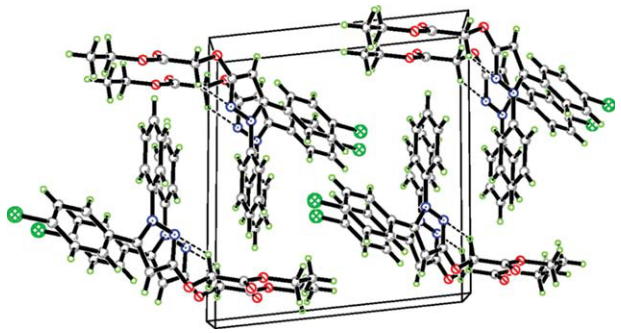


Figure 2. A partial packing diagram of **5c**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

atom-numbering scheme and higher occupancy in the three-dimensional packing arrangement is shown in Figures 1 and 2. Hydrogen bond is shown as a dashed line. Atomic coordinates of nonhydrogen atoms ($\times 10^{-4}$) and their thermal parameters are summarized in Table 1. The crystal data and structure refinement of **5c** are listed in Table 2.

The compounds **5a–5i** were screened for activity against two fungi, namely *Gibberella zeae* and *Rhizoctonia cerealis*, at a concentration of 10 μg/mL according to a reported method [20]. As the results in Table 3 show, most of the compounds have weak fungicidal activity. Among these compounds, only compound **5d**, in which X is F group in position 4 of the phenyl ring and Y is H, exhibited moderate inhibitory activity against *G. zeae*. This might imply that the introduction of the F group to the phenyl ring of 1*H*-pyrazoles was important for its fungicidal activity. In terms of X, the substituents with electron-attracting groups on the phenyl rings seem to have somewhat higher fungicidal activity. For example, compounds **5c** and **5d** showed better activity than

Table 1

Atomic coordinates of nonhydrogen atoms ($\times 10^{-4}$) and their thermal parameters.

	x	*y*	*z*	U(eq)
Cl	2885(2)	58,718(10)	6585(10)	743(4)
O1	16,539(5)	−2205(3)	8826(2)	689(11)
O2	12,920(7)	−1840(3)	9270(3)	1065(19)
O3	13,728(5)	437(3)	8980(2)	728(11)
N1	12,700(6)	935(3)	7229(2)	545(11)
N2	11,051(5)	1659(3)	6779(2)	509(11)
C1	18,381(9)	−3992(5)	8956(4)	960
C2	16,191(10)	−3413(4)	9100(4)	870(2)
C3	14,764(8)	−1527(4)	8947(3)	606(16)
C4	15,430(7)	−319(4)	8637(3)	648(17)
C5	12,367(7)	979(3)	8241(3)	534(12)
C6	10,561(7)	1696(3)	8479(3)	550(14)
C7	9752(6)	2124(3)	7514(3)	468(12)
C8	8028(6)	3022(3)	7255(3)	498(12)
C9	6091(7)	3104(3)	7898(3)	585(16)
C10	4502(7)	3959(3)	7686(3)	585(16)
C11	4829(7)	4762(3)	6843(3)	524(12)
C12	6739(7)	4710(3)	6195(3)	575(12)
C13	8317(7)	3842(3)	6398(3)	554(12)
C14	10,695(6)	1660(3)	5682(3)	465(12)
C15	8648(6)	1285(3)	5333(3)	516(12)
C16	8322(7)	1245(3)	4273(3)	573(14)
C17	10,066(8)	1601(4)	3566(3)	642(16)
C18	12,104(8)	1983(4)	3911(3)	662(17)
C19	12,425(7)	2025(3)	4976(3)	579(16)

Table 2

Crystal data and structure refinement for **5c**.

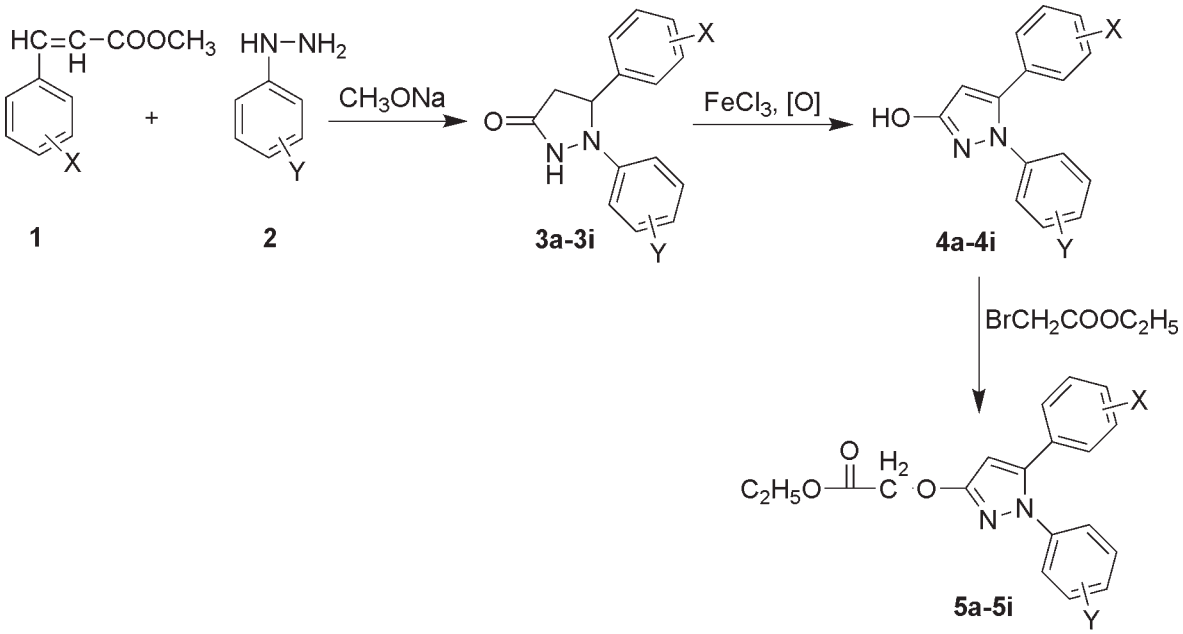
Empirical formula	$C_{19}H_{17}ClN_2O_3$
Formula weight	356.80
Temperature (K)	293
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
a (Å)	5.8170(12)
b (Å)	11.804(2)
c (Å)	12.783(2)
α (°)	83.89(2)
β (°)	89.24(3)
γ (°)	89.73(3)
V (Å^3)	872.7(3)
Z	2
D_{calc} (mg/m^3)	1.358
Absorption coefficient (mm^{-1})	0.239
F (000)	372
Crystal size (mm)	0.10 × 0.10 × 0.20
θ range, deg	1.6–25.3
Reflections collected	3480
Independent reflections	3140(R_{int} = 0.084)
Date/restraints/parameters	3140/0/220
Goodness-of-fit on F^2	1.009
Final *R* indices [$I > 2s(I)$]	
R1	0.0671
wR2	0.1483
Final *R* indices (all date)	
R1	0.1104
wR2	0.1778
Extinction correction	none

Table 3

Antifungal activity of newly synthesized compounds (% inhibition).

			10 μg/mL	
Compounds	X	Y	*G. zeae*	*R. cerealis*
5a	H	H	21.29	18.44
5b	4-CH_3	H	0.00	7.79
5c	4-Cl	H	39.20	15.53
5d	4-F	H	53.09	24.27
5e	3,4,5-OCH_3H3	H	20.06	9.06
5f	3-F	H	30.25	17.15
5g	H	4-$CH(CH_3)_2$	13.89	0.97
5h	4-OCH_3	4-$CH(CH_3)_2$	14.20	0.97
5i	4-F	4-$CH(CH_3)_2$	13.89	1.62

Scheme 3



5a: X=H, Y=H; 5b: X=4-CH_3, Y=H; 5c: X=4-Cl, Y=H
5d: X=4-F, Y=H; 5e: X=3,4,5-OCH_3, Y=H; 5f: X=3-F, Y=H
5g: X=H, Y=4-$CH(CH_3)_2$; 5h: X=4-OCH_3, Y=4-$CH(CH_3)_2$; 5i: X=4-F, Y=4-$CH(CH_3)_2$

compounds **5a** and **5b**. Switching the substituent Y from H to isopropyl has no effective impact on the inhibition rates. Furthermore, compound **5d** with the F group in position 4 of the phenyl ring showed better activity than **5f**.

EXPERIMENTAL

All reagents were of analytical reagent grade or were chemically pure. All solvents were dried by standard methods and distilled before use. Reactions were monitored by TLC. Analytical TLC was performed on silica gel GF254. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure. *G. zeae* and *R. cerealis* were obtained from Jiangsu Research and Development Center for Pesticides, China.

The melting points were measured on an X-4 microscope electrothermal apparatus (Taike, China) and were uncorrected. Elemental analyses were determined on a Vario EL III elemental analyzer. The ^{1}H NMR (solvent $CDCl_3$ or DMSO-d_6) spectra was obtained on a Bruker AV 500 or AV 300 spectrometer at room temperature using tetramethylsilane as an internal standard. Chemical shift values (δ) are given in parts per million. X-ray intensity data were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite monochromated Mo Kα radiation (λ = 0.71073) Å.

The synthesis of 1,5-diarylpyrazolidin-3-ones (3a–3i). A mixture of *n*-butanol (40 mL) and ethanolamine (60 mmol) was added to a solution of sodium (36 mmol) in anhydrous methanol (9 mL). Then, methanol was removed by distillation, and methyl 3-arylacrylate **1** (30 mmol) was added. The mixture was refluxed for 40 min, after which arylhydrazine **2** (33 mmol) was added. The mixture was refluxed for another 8 h and then left to cool to room temperature. It was then acidified with acetic acid (36%), allowed to stand and filtered. The solid was recrystallized from ethyl acetate to give the compounds **3a–3i**.

1,5-Diphenylpyrazolidin-3-one (3a). White crystal; mp 159–161°C; yield, 85%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.52 (q, J = 3.33, 16.8 Hz, 1H, CH), 3.28 (q, J = 9.18, 16.8 Hz, 1H, CH), 4.93 (q, J = 3.36, 9.17 Hz, 1H, CH), 7.02–7.43 (m, 10H, Ar-H); Anal. Calcd for $C_{15}H_{14}N_2O$: C 75.61, H 5.92, N 11.76; found C 75.69, H 5.89, N 11.72.

1-Phenyl-5-p-tolylpyrazolidin-3-one (3b). White crystal; mp 145–146°C; yield, 82%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.38 (s, 3H, CH_3), 2.50 (q, J = 3.45, 16.82 Hz, 1H, CH), 3.26 (q, J = 9.12, 16.77 Hz, 1H, CH), 4.89 (q, J = 3.48, 9.08 Hz, 1H, CH), 7.01–7.38 (m, 9H, Ar-H), 8.49 (s, 1H, NH); Anal. Calcd for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.10; found C 76.25, H 6.37, N 11.15.

5-(4-Chlorophenyl)-1-phenylpyrazolidin-3-one (3c). White crystal; mp 160–162°C; yield, 80%. ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.25 (q, J = 2.79, 16.71 Hz, 1H, CH), 3.18 (q, J = 9.03,16.71 Hz, 1H, CH), 5.07 (q, J = 2.67, 9.03 Hz, 1H, CH), 6.94–7.58 (m, 9H, Ar-H), 10.45 (s, 1H, NH); Anal. Calcd for $C_{15}H_{13}ClN_2O$: C 66.06, H 4.80, N 10.27; found C 66.15, H 4.79, N 10.23.

5-(4-Fluorophenyl)-1-phenylpyrazolidin-3-one (3d). Yellow crystal; mp 158–159°C; yield, 78%. ^{1}HNMR ($CDCl_3$, 300 MHz, ppm): δ 2.50 (q, J = 2.82, 16.77 Hz, 1H, CH), 3.31 (q, J = 9.06, 16.71 Hz, 1H, CH), 4.95 (q, J = 2.82, 9 Hz, 1H,

CH), 7.04–7.44 (m, 9H, Ar-H); Anal. Calcd for $C_{15}H_{13}FN_2O$: C 70.30, H 5.11, N 10.93; found C 70.22, H 5.10, N 10.98.

1-Phenyl-5-(3,4,5-trimethoxyphenyl)pyrazolidin-3-one (3e). White crystal; mp 157–159°C; yield, 78%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.54 (q, J = 3.88, 16.82 Hz, 1H, CH), 3.28 (q, J = 9.26, 16.82 Hz, 1H, CH), 3.86 (s, 9H, OCH_3), 4.85 (q, J = 3.76, 9.21 Hz, 1H, CH), 6.70–7.32 (m, 7H, Ar-H), 8.45 (s, 1H, NH); Anal. Calcd for $C_{18}H_{20}N_2O_4$: C 65.84, H 6.14, N 8.53; found C 65.76, H 6.12, N 8.58.

5-(3-Fluorophenyl)-1-phenylpyrazolidin-3-one (3f). Yellow crystal; mp 165–167°C; yield, 75%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 2.50 (d, 1H, CH), 3.30 (q, J = 9.15, 16.85 Hz, 1H, CH), 4.98 (d, 1H, CH), 7.03–7.40 (m, 9H, Ar-H), 8.41 (s, 1H, NH); Anal. Calcd for $C_{15}H_{13}FN_2O$: C 70.30, H 5.11, N 10.93; found C 70.23, H 5.10, N 10.96.

1-(4-Isopropylphenyl)-5-phenylpyrazolidin-3-one (3g). Yellow crystal; mp 136–137°C; yield, 78%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, J = 6.85 Hz, 6H, CH_3), 2.50 (q, J = 3.35, 16.75 Hz, 1H, CH), 2.86 (m, 1H, CH), 3.26 (q, J = 9.15,16.75 Hz, 1H, CH), 4.87 (q, J = 3.35, 8.98 Hz, 1H, CH), 6.99–7.48 (m, 9H, Ar-H); Anal. Calcd for $C_{18}H_{20}N_2O$: C 77.11, H 7.19, N 9.99; found C 77.05, H 7.21, N 9.94.

1-(4-Isopropylphenyl)-5-(4-methoxyphenyl)pyrazolidin-3-one (3h). Yellow crystal; mp 143–145°C; yield, 81%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, J = 6.90 Hz, 6H, CH_3), 2.55 (m, 1H, CH), 2.87 (m, 1H, CH), 3.21 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 4.82 (m, 1H, CH), 6.92–7.39 (m, 8H, Ar-H); Anal. Calcd for $C_{19}H_{22}N_2O_2$: C 73.52, H 7.14, N 9.03; found C 73.46, H 7.16, N 8.99.

5-(4-Fluorophenyl)-1-(4-isopropylphenyl)pyrazolidin-3-one (3i). Yellow crystal; mp 126–127°C; yield, 79%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.25 (d, J = 6.87 Hz, 6H, CH_3), 2.52 (q, J = 3.78, 16.82 Hz, 1H, CH), 2.89 (m, 1H, CH), 3.33 (q, J = 9.12, 16.8 Hz, 1H, CH), 4.87 (q, J = 3.69, 9.14 Hz, 1H, CH), 6.94–7.19 (m, 8H, Ar-H); Anal. Calcd for $C_{18}H_{19}FN_2O$: C 72.46, H 6.42, N 9.39; found C 72.42, H 6.44, N 9.35.

1,5-Diaryl-1H-pyrazol-3-ols (4a–4i). Using oxygen as oxidizing agent, compound **3a–3i** (10 mmol) was dissolved in DMF (40 mL) and mixed with $FeCl_3$ (0.162 g, 1 mmol). The mixture was heated to 80°C and maintained at that temperature for 2 h, and then stirred at 30°C for another 20 h. The reaction mixture was then poured into water (500 mL) with good stirring. The precipitate which formed was filtered off, washed with water and dried under reduced pressure. The crude product was then recrystallized from ethanol to give the compounds **4a–4i**.

1,5-Diphenyl-1H-pyrazol-3-ol (4a). White crystal; mp 258–259°C; yield, 81%. ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 5.92 (s, 1H, CH), 7.14–7.33 (m, 10H, Ar-H), 10.36 (s, 1H, OH); Anal. Calcd for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found C 75.32, H 5.09, N 11.82.

1-Phenyl-5-p-tolyl-1H-pyrazol-3-ol (4b). White crystal; mp 254–255°C; yield, 84%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.33 (s, 3H, CH_3), 5.89 (s, 1H, CH), 7.09–7.36 (m, 9H, Ar-H); Anal. Calcd for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19; found C 76.69, H 5.63, N 11.25.

5-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-3-ol (4c). White crystal; mp 285–286°C; yield, 82%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 5.92 (s, 1H, CH), 7.13–7.46 (m, 9H, Ar-H); Anal. Calcd for $C_{15}H_{11}ClN_2O$: C 66.55, H 4.10, N 10.35; found C 66.46, H 4.08, N 10.38.

5-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-3-ol (4d). White crystal; mp 266–267°C; yield, 81%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 5.90 (s, 1H, CH), 6.98–7.33 (m, 9H, Ar-H), 11.35 (s, 1H, OH); Anal. Calcd for $C_{15}H_{11}FN_2O$: C 70.86, H 4.36, N 11.02; found C 70.78, H 4.34, N 11.06.

1-Phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazol-3-ol (4e). Brown crystal; mp 203–205°C; yield, 85%. ^{1}H NMR (DMSO-d_6, 500 MHz, ppm): δ 3.62 (s, 9H, OCH_3), 5.97 (s, 1H, CH), 6.46 (s, 2H, Ar-H), 7.21–7.39 (m, 5H, Ar-H), 10.09 (s, 1H, OH); Anal. Calcd for $C_{18}H_{18}N_2O_4$: C 66.25, H 5.56, N 8.58; found C 66.29, H 5.55, N 8.53.

5-(3-Fluorophenyl)-1-phenyl-1H-pyrazol-3-ol (4f). White crystal; mp 274–275°C; yield, 78%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 6.45 (s, 1H, CH), 6.90–7.35 (m, 9H, Ar-H); Anal. Calcd for $C_{15}H_{11}FN_2O$: C 70.86, H 4.36, N 11.02; found C 70.78, H 4.35, N 11.06.

1-(4-Isopropylphenyl)-5-phenyl-1H-pyrazol-3-ol (4g). Yellow crystal; mp 203–205°C; yield, 76%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.24 (d, J = 6.75 Hz, 6H, CH_3), 2.90 (m, 1H, CH), 5.90 (s, 1H, CH), 7.14–7.28 (m, 9H, Ar-H); Anal. Calcd for $C_{18}H_{18}N_2O$: C 77.67, H 6.52, N 10.06; found C 77.60, H 6.49, N 10.09.

1-(4-Isopropylphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-ol (4h). Yellow crystal; mp 193–194°C; yield, 72%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.25 (d, J = 7.00 Hz, 6H, CH_3), 2.90 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 5.86 (s, 1H, CH), 6.80–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found C 73.94, H 6.53, N 9.12.

5-(4-Fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-3-ol (4i). Yellow crystal; mp 225–227°C; yield, 78%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.21 (d, J = 6.96 Hz, 6H, CH_3), 2.85 (m, 1H, CH), 6.34 (s, 1H, CH), 6.90–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{18}H_{17}FN_2O$: C 72.95, H 5.78, N 9.45; found C 72.88, H 5.76, N 9.42.

Ethyl 2-(1,5-diaryl-1H-pyrazol-3-yloxy)acetates (5a–5i). To a solution of **4a–4i** (10 mmol) in acetone (30 mL) was added potassium carbonate (2.07 g, 15 mmol). Then, the mixture was refluxed and ethyl 2-bromoacetate (1.84 g, 11 mmol) was added slowly. The mixture was refluxed and monitored by TLC for about 3 h. The potassium carbonate was filtered off and the solvent was evaporated under reduced pressure. After the removal of the solvent, the residue was chromatographed over silica gel (500 g) eluting with a mixture of ethyl acetate and petroleum ether to gain the target compounds **5a–5i**.

Ethyl 2-(1,5-diphenyl-1H-pyrazol-3-yloxy)acetate (5a). White crystal; mp 79–80°C; yield, 89%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.31 (t, J = 7.17, 14.25 Hz, 3H, CH_3), 4.28 (q, J = 7.17, 14.28 Hz, 2H, CH_2), 4.88 (s, 2H, CH_2), 6.04 (s, 1H, CH), 7.20–7.27 (m, 10H, Ar-H); Anal. Calcd for $C_{19}H_{18}N_2O_3$: C 70.79, H 5.63, N 8.69; found C 70.72, H 5.62, N 8.73.

Ethyl 2-(1-phenyl-5-p-tolyl-1H-pyrazol-3-yloxy)acetate (5b). White crystal; mp 106–107°C; yield, 85%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.30 (t, J = 7.15, 14.25 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.28 (q, J = 7.15, 14.28 Hz, 2H, CH_2), 4.86 (s, 2H, CH_2), 6.00 (s, 1H, CH), 7.09–7.29 (m, 9H, Ar-H); Anal. Calcd for $C_{20}H_{20}N_2O_3$: C 71.41, H 5.99, N 8.33; found C 71.34, H 5.97, N 8.28.

Ethyl 2-(5-(4-chlorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetate (5c). Yellow crystal; mp 51–52°C; yield, 88%. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 1.30 (t, J = 7.20, 14.28 Hz, 3H, CH_3), 4.28 (q, J = 7.20, 14.19 Hz, 2H, CH_2), 4.86 (s, 2H,

CH_2), 6.03 (s, 1H, CH), 7.13–7.38 (m, 9H, Ar-H); Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C 63.96, H 4.80, N 7.85; found C 63.88, H 4.82, N 7.82.

Ethyl 2-(5-(4-fluorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetate (5d). White crystal; mp 76–77°C; yield, 81%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.33 (t, J = 7.15, 14.3 Hz, 3H, CH_3), 4.31 (q, J = 7.15, 14.2 Hz, 2H, CH_2), 4.90 (s, 2H, CH_2), 6.08 (s, 1H, CH), 7.01–7.28 (m, 9H, Ar-H); Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C 67.05, H 5.03, N 8.23; found C 67.14, H 5.04, N 8.19.

Ethyl 2-(1-phenyl-5-(3,4,5-trimethoxyphenyl)-1H-pyrazol-3-yloxy)acetate (5e). Yellow crystal; mp 75–76°C; yield, 84%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.21 (t, J = 7, 14.2 Hz, 3H, CH_3), 3.58 (s, 6H, OCH_3), 3.65 (s, 3H, OCH_3), 4.17 (q, J = 7.2, 14.2 Hz, 2H, CH_2), 4.83 (s, 2H, CH_2), 6.26 (s, 1H, CH), 6.49 (s, 2H, Ar-H), 7.22–7.39 (m, 5H, Ar-H); Anal. Calcd for $C_{22}H_{24}N_2O_6$: C 64.07, H 5.87, N 6.79; found C 63.98, H 5.85, N 6.75.

Ethyl 2-(5-(3-fluorophenyl)-1-phenyl-1H-pyrazol-3-yloxy)acetate (5f). White crystal; mp 67–68°C; yield, 81%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.30 (t, J = 7.2, 14.25 Hz, 3H, CH_3), 4.28 (q, J = 7, 14.35 Hz, 2H, CH_2), 4.87 (s, 2H, CH_2), 6.05 (s, 1H, CH), 6.91–7.27 (m, 9H, Ar-H); Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C 67.05, H 5.03, N 8.23; found C 67.14, H 5.04, N 8.20.

Ethyl 2-(1-(4-isopropylphenyl)-5-phenyl-1H-pyrazol-3-yloxy)acetate (5g). Yellow crystal; mp 133–134°C; yield, 88%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, J = 6.85 Hz, 6H, CH_3), 1.30 (t, J = 7.15, 14.3 Hz, 3H, CH_3), 2.87 (q, J = 7, 13.8 Hz, 1H, CH), 4.28 (q, J = 7.15, 14.15 Hz, 2H, CH_2), 4.87 (s, 2H, CH_2), 6.02 (s, 1H, CH), 7.12–7.29 (m, 9H, Ar-H); Anal. Calcd for $C_{22}H_{24}N_2O_3$: C 72.50, H 6.64, N 7.69; found C 72.43, H 6.66, N 7.66.

Ethyl 2-(1-(4-isopropylphenyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yloxy)-acetate (5h). Yellow crystal; mp 127–128°C; yield, 83%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, J = 6.8 Hz, 6H, CH_3), 1.30 (t, J = 7.15, 14.25 Hz, 3H, CH_3), 2.88 (t, J = 6.8, 13.75 Hz, 1H, CH), 3.80 (s, 3H, OCH_3), 4.28 (q, J = 7.15, 14.25 Hz, 2H, CH_2), 4.86 (s, 2H, CH_2), 5.96 (s, 1H, CH), 6.81–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{23}H_{26}N_2O_4$: C 70.03, H 6.64, N 7.10; found C 70.12, H 6.67, N 7.08.

Ethyl 2-(5-(4-fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-3-yloxy)-acetate (5i). Yellow crystal; mp 81–82°C; yield, 89%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 1.22 (d, J = 6.75 Hz, 6H, CH_3), 1.30 (t, J = 7.2, 14.2 Hz, 3H, CH_3), 2.88 (q, J = 6.85, 13.8 Hz, 1H, CH), 4.15 (q, J = 7.15, 14.18 Hz, 2H, CH_2), 4.83 (s, 2H, CH_2), 6.19 (s, 1H, CH), 7.07–7.26 (m, 8H, Ar-H); Anal. Calcd for $C_{22}H_{23}FN_2O_3$: C 69.09, H 6.06, N 7.33; found C 69.15, H 6.11, N 7.31.

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