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A DIVERSITY-ORIENTED APPROACH TO 1*H*-PYRAZOLE-4,5-DIOLS, 4-HYDROXY-3*H*-PYRAZOL-3-ONES, AND PHENYLHYDRAZONES FROM KEY INTERMEDIATE 4-ACETYLOXY-3*H*-PYRAZOL-3-ONE

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Abstract – An approach to 1*H*-pyrazole-4,5-diols **4a–d**, 4-hydroxy-3*H*-pyrazol-3-ones **5a–d**, and phenylhydrazones **6a–d** from key intermediate 4-acetyloxy-3*H*-pyrazol-3-one **3a** is described. 4-Alkylidene-3*H*-pyrazol-3-ones **1a–c** were reacted with *m*-chloroperbenzoic acid in the presence of potassium carbonate to give the corresponding spiroepoxide-3*H*-pyrazol-3-ones **2a–c**. Treatment of **2a** with acid anhydride such as acetic, propionic, butyric, and pentanoic anhydride in the presence of boron trifluoride diethyl etherate led to the corresponding 4-acyloxy-3*H*-pyrazol-3-ones **3a–d**. The reactions of **3a** with α -chloroketones, ketones, and/or secondary amines gave the corresponding **4a–d**, **5a–d**, and **6a–d**.

INTRODUCTION

Five-membered nitrogen-containing heterocycles have received intensive research interests due to their biological properties and their utilities as intermediates, and found a wide range of applications in pharmaceutical and agrochemistry.¹ Among them, the pyrazol-3-one and pyrazole motifs make up the core structures of numerous biologically active synthetic compounds. For example, pyrazol-3-ones are an important class of aza-heterocycles in several biologically active compounds: antiviral,^{2a} antimicrobial,^{2b} anti-inflammatory,^{2c} antitumor,^{2d} antiprion,^{2e} and CCR3 antagonist.^{2f} Recently, a new pyrazol-3-one compound, edaravone (2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one, also known as MCI-186), has been developed as a medical drug for brain ischemia and has also been reported to be effective for myocardial ischemia.³ Compounds containing pyrazole moiety have a wide range of biological activities, such as the HIV-1 reverse transcriptase inhibitor PNU-32945,^{4a} cyclooxygenase-2 (COX-2) inhibitor celecoxib,^{4b} fungicide pyraclostrobin,^{4c} insecticides fipronil,^{4d} and phosphodiesterase inhibitor sildenafil.^{4e}

For these reasons, a large number of general methods for the preparation of pyrazol-3-one and pyrazole derivatives have recently been reported.⁵

On the other hand, hydrazones have also been a useful scaffold in medicinal chemistry for many years. Hydrazone-containing organic compounds have been shown to possess potent biological activity including: antitumor, analgesic, antidepressant, antiviral, antimicrobial, and antimalarial.⁶ Although phenylhydrazones showed various bioactivities including antioxidative,^{7a} antiparasitic,^{7b} and antitubercular properties,^{7c} as far as we are aware, naturally occurring ones almost have not been reported in the literature. Farylhydrazones A and B are naturally occurring phenylhydrazones recently isolated from cultures of the *Cordyceps*-colonizing fungus *Isaria farinosa*.⁸ Phenylhydrazones have been used extensively for protection of the carbonyl groups in organic synthesis,⁹ for derivatization, resolution, and characterization of carbonyl-containing natural products,¹⁰ and for studying the hydrazone-enehydrazine tautomeric transformation in the synthesis of indole derivatives.¹¹ In addition, Sheibani and Esfandiarpour have discussed the synthesis of pyridazines in a one-step procedure from three-component reactions of arylhydrazones, aldehydes, and malononitrile.¹²

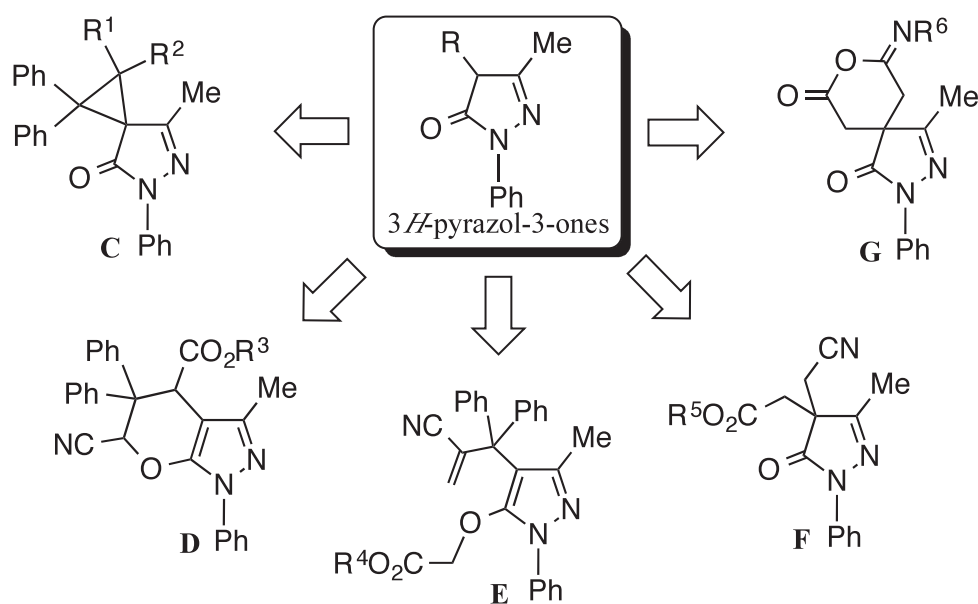


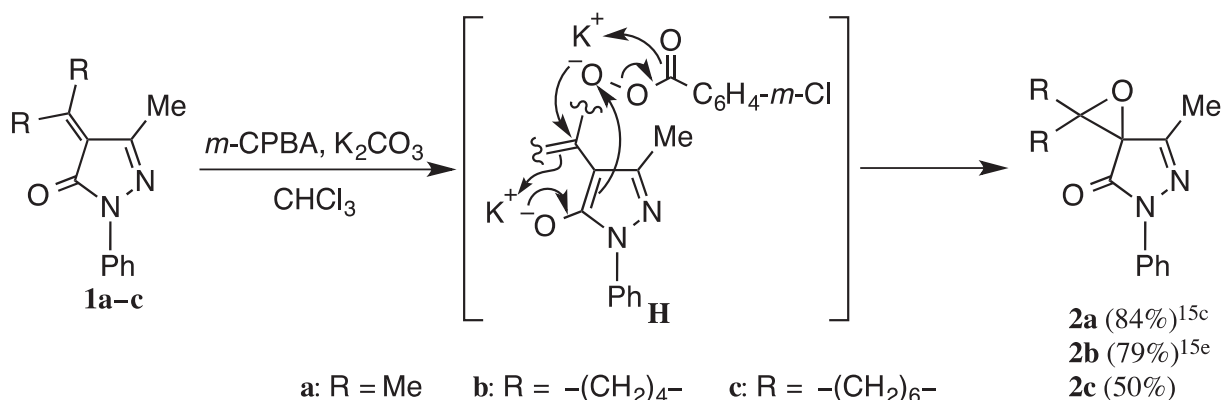
Figure 1. Structures of synthesized pyrazol-3-one and pyrazole derivatives

In the course of our investigation of the synthesis of novel pyrazol-3-one and pyrazole derivatives, we have shown the synthesis of spirocyclopropanepyrazoles **C**,^{13a} pyrano[2,3-*c*]pyrazoles **D**,^{13b} *O*-substituted pyrazoles **E**,^{13c} *C*-cyanomethylated pyrazoles **F**,^{13d} and spiroiminolactonepyrazoles **G**.^{13e} In connection with the synthesis and reactivity of pyrazol-3-one and pyrazole derivatives, it seems to us of interest to examine the chemical properties of spiroepoxidepyrazole derivatives as the key intermediate. Epoxides, especially spiroepoxideheterocycles,

are versatile building blocks for the synthesis of many bioactive natural products. They are an ideal source for diversity because they can be opened with nucleophiles. They are well-known carbon electrophiles and their ability to undergo regioselective ring-opening reactions contributes to their synthetic value.¹⁴ On the basis of the above experimental results together with some literature reports, we decided to extend the utility of spiroepoxide-3*H*-pyrazol-3-ones, and herein describe a divergent synthesis of 1*H*-pyrazole-4,5-diols, 4-hydroxy-3*H*-pyrazol-3-ones, and phenylhydrazones from 4-acetyloxy-3*H*-pyrazol-3-one, which is easily prepared by boron trifluoride-assisted ring opening of spiroepoxide-3*H*-pyrazol-3-ones with acid anhydride.

RESULTS AND DISCUSSION

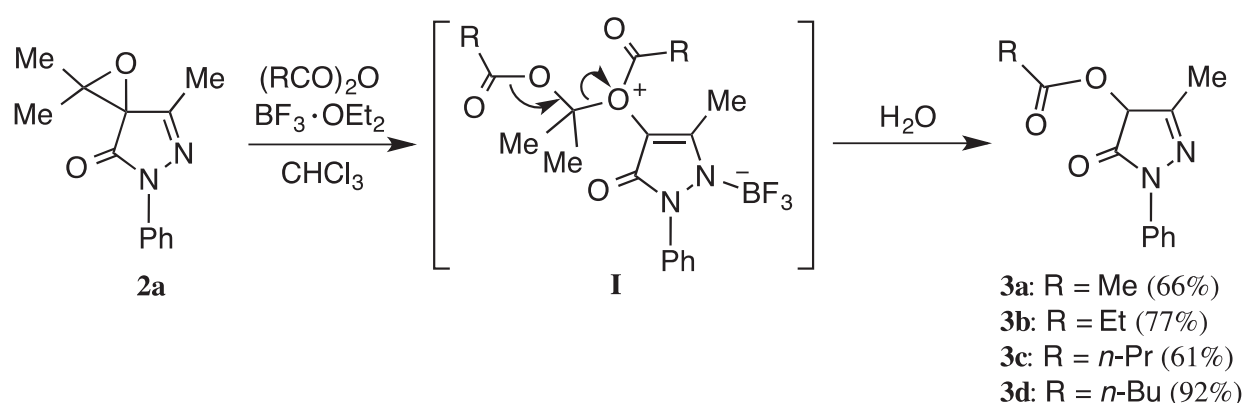
The starting materials, 4-alkylidene-3*H*-pyrazol-3-ones **1a–c**, were prepared by treatment of 2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one with ketones such as acetone, cyclopentanone, and cycloheptanone according to the method reported in literature.¹⁵ An initial attempt to react **1a–c** with *m*-chloroperbenzoic acid (*m*-CPBA) using the method of DeRuiter and co-workers^{15c} failed and the expected spiroepoxide-3*H*-pyrazol-3-ones **2a–c** were observed as trace level. The reaction was not clean. Therefore, to achieve an efficient synthesis of spiroepoxide-3*H*-pyrazol-3-ones, we examined the epoxidation of **2a–c**. As a consequence, the reaction of **1a–c** with *m*-CPBA in the presence of potassium carbonate in CHCl₃ at room temperature led to the corresponding spiroepoxide-3*H*-pyrazol-3-ones **2a–c** (Scheme 1). In this case, it seems that the substrates **1a–c** were activated by deprotonation of alkylidene proton in the presence of potassium carbonate and then the epoxidation could be promoted by using activated intermediates **H**.



Scheme 1

With the aim of extending the ring-opening reaction of spiroepoxide derivatives of 3*H*-pyrazol-3-ones, we next tried the reaction of **2a** with acetic anhydride in the presence of H₂SO₄ as acid catalyst according to the method reported by Kirschke and Schmitz.^{15b} In this reaction, however, our attempts were unacceptable with respect to yield (up to 22%). The reaction was not clean. After different conditions

were screened, we were delighted to find that the expected 4-acetyloxy-3*H*-pyrazol-3-one **3a** was obtained from this reaction with boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{OEt}_2$) as Lewis acid in CHCl_3 (Scheme 2 and entry 1 in Table 1). The effect of Lewis acid was observed with $\text{BF}_3 \cdot \text{OEt}_2$ giving the highest yield of **3a**, while other Lewis acids such as zinc chloride and titanium(IV) chloride gave none of **3a** (entries 4 and 5). With the optimized reaction conditions in hand, **2a** was subjected to react with acetic, propionic, butyric, and pentanoic anhydride, and the representative results are summarized in Scheme 2.



Scheme 2

Table 1. Effect of different reaction conditions for synthesis of 4-acetyloxy-3*H*-pyrazol-3-one **3a**

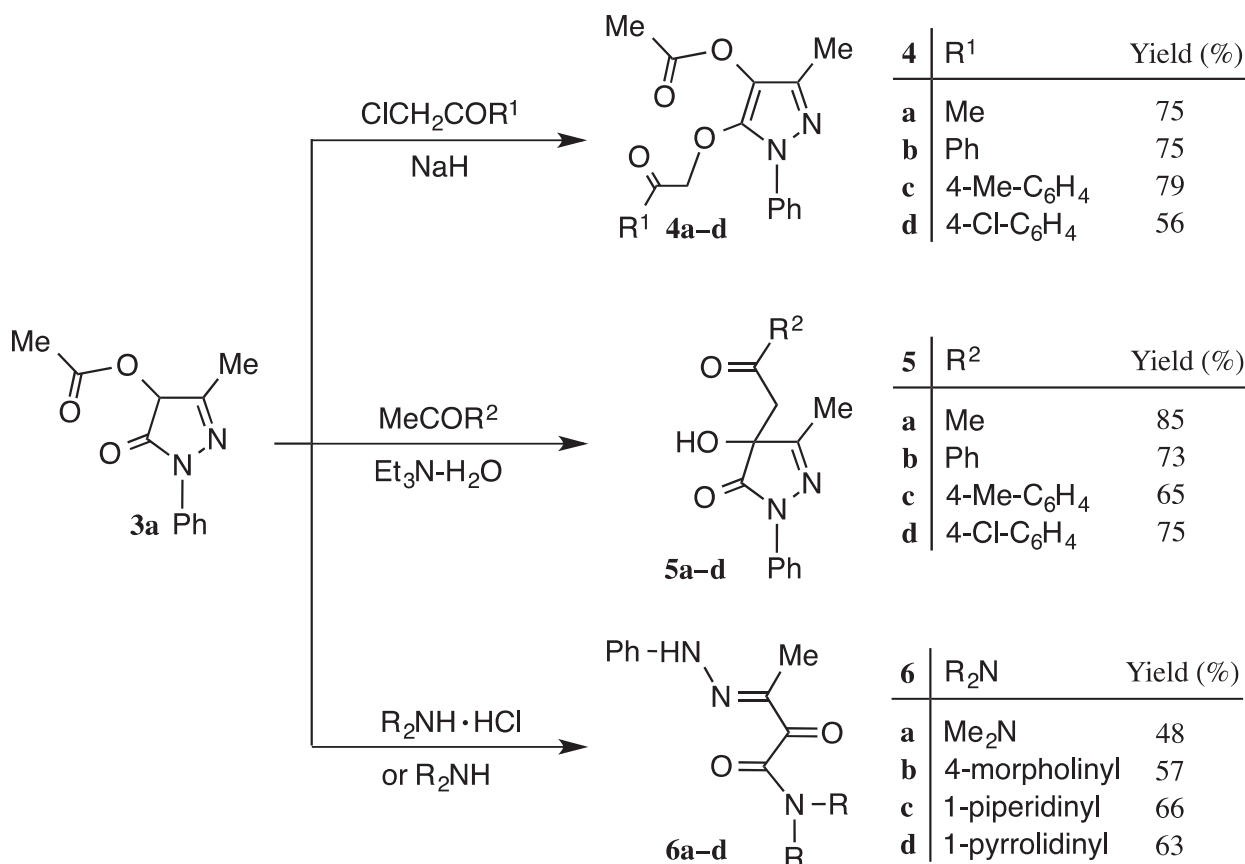
Entry	Substrate	Ac ₂ O (Equiv)	Lewis acid (Equiv)	Solvent	Conditions	Yield (%) of 3a
1	2a	2.0	$\text{BF}_3 \cdot \text{OEt}_2$ (2.0)	CHCl_3	rt, 12 h	66
2	2a	2.0	$\text{BF}_3 \cdot \text{OEt}_2$ (2.0)	CHCl_3	reflux, 1 h	47
3	2a	1.5	$\text{BF}_3 \cdot \text{OEt}_2$ (1.5)	CHCl_3	rt, 12 h	18
4	2a	1.5	ZnCl_2 (1.5)	CHCl_3	rt, 12 h	ND ^a
5	2a	1.0	TiCl_4 (1.0)	CHCl_3	rt, 12 h	ND ^a

^aNot detected.

These products **3b–d** gave satisfactory elemental analyses and spectroscopic data (IR, ¹H NMR, ¹³C NMR, and MS) consistent with their assigned structures (see experimental section). Further, to confirm the structure of **3a**, we carried out the reaction of **2b,c** with acetic anhydride. Thus, treatment of **2b,c** with acetic anhydride in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ afforded the 4-acetyloxy-3*H*-pyrazol-3-one **3a** (60% from **2b**, 30% from **2c**), which were identical with an authentic sample prepared from **2a** and acetic anhydride according to Scheme 2 on the basis of a comparison of the melting point, IR, and NMR spectra. The formation of 4-acyloxy-3*H*-pyrazol-3-ones **3a–d** could be explained by possible mechanism presented in Scheme 2. It is conceivable that the initial event is the formation of the ring-opening BF_3 complexes **I**

from compound **2a** and acid anhydride, which underwent elimination of acyl group and acetone to result in the formation of **3a-d**.

With these results in hand, we investigated a divergent method for the synthesis of pyrazole derivatives from 4-acetyloxy-3*H*-pyrazol-3-one **3a** in detail (Scheme 3). Thus, when a mixture of **3a** and α -chloroketones, such as chloroacetone, phenacyl chloride, 4-methylphenacyl chloride, and 4-chlorophenacyl chloride, in the presence of sodium hydride in DMF was stirred at room temperature for 12 h, the 1*H*-pyrazole-4,5-diols **4a-d** were obtained with 56–79% isolated yields. While, the reaction of **3a** with ketones, such as acetone, acetophenone, 4'-methylacetophenone, and 4'-chloroacetophenone, in the presence of Et₃N and H₂O using air as the oxidant at room temperature for 12 h led to the corresponding 4-hydroxy-3*H*-pyrazol-3-ones **5a-d** in moderate to good yields. To simplify the reaction, the ketones were used to serve as the reagent and solvent. We carried out several experiments on **5a**, testing different reaction conditions, *e.g.* time and substrate/base molar ratio, but no positive result was achieved (entries 3–6 in Table 2). Additive effects were observed with H₂O giving the highest yield of **5a** (entries 1 and 4). It makes us believe that this reaction can only be promoted by using Et₃N/H₂O system (entries 1 and 2).



Scheme 3

Table 2. Effect of different reaction conditions for synthesis of 4-hydroxy-3*H*-pyrazol-3-one **5a**

Entry	Substrate ^a	Acetone ^b (mL)	Base (Equiv)	Additive (mL)	Conditions ^c	Yield (%) of 5a
1	3a	5.0	Et ₃ N (2.0)	H ₂ O (1.0)	rt, 12 h	85
2	3a	5.0	Et ₃ N (1.0)	H ₂ O (1.0)	rt, 12 h	76
3	3a	5.0	Et ₃ N (1.0)	H ₂ O (1.0)	reflux, 8 h	31
4	3a	5.0	Et ₃ N (1.0)	None	rt, 12 h	ND ^d
5	3a	5.0	None	H ₂ O (1.0)	rt, 12 h	ND ^d
6	3a	5.0	K ₂ CO ₃ (2.0)	H ₂ O (1.0)	rt, 12 h	45

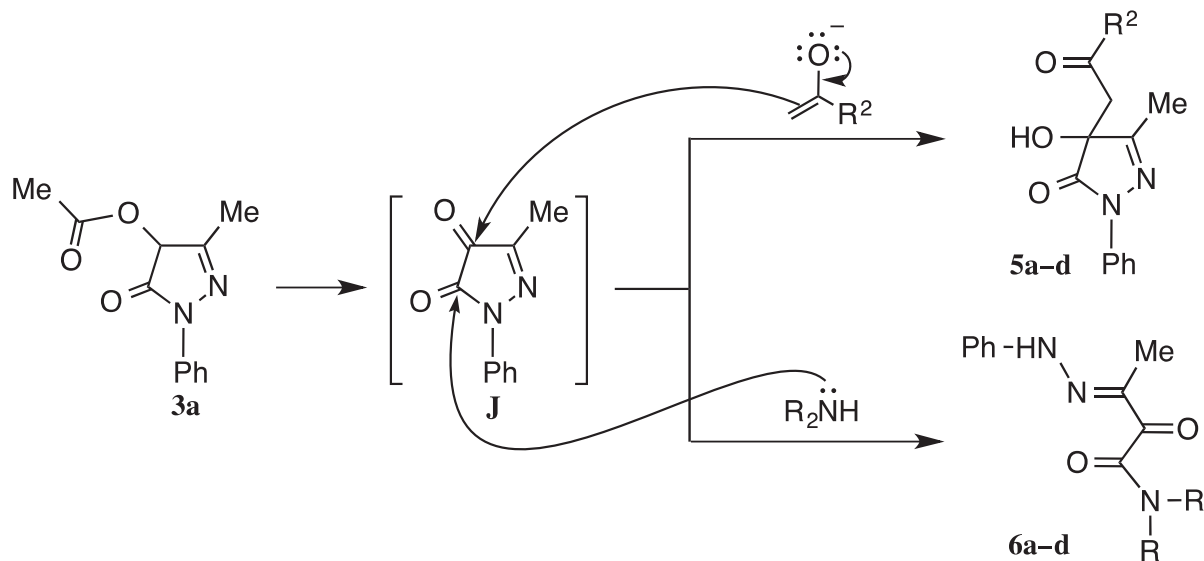
^a For each reaction, equal molar (1 mmol) of **3a** was used. ^b Acetone was also employed as solvent.

^c With air as oxidant. ^d Not detected.

Furthermore, we found the reaction condition under which phenylhydrazone derivatives **6a–d** could be isolated. Indeed, thermal treatment of **3a** with secondary amines,¹⁶ such as dimethylamine hydrochloride, morpholine, piperidine, and pyrrolidine, using air as the oxidant for 1–2 h gave the corresponding phenylhydrazones **6a–d** in 48–66% yields. In this reaction, secondary amines were used to serve as the reagent and solvent in order to simplify the reaction. In general, the NH proton of *E*-phenylhydrazones is observed in high magnetic field (near δ 9.0), whereas that of *Z*-phenylhydrazones appears at lower field (near δ 12.0).⁹ The ¹H NMR spectra of **6a–d** in CDCl₃ exhibit a one-proton singlet near δ 8.7 due to the hydrazone NH proton. These observations indicate that **6a–d** existed as a geometrical single isomer of *E* configuration. In addition, for products **6a–d**, a clear nuclear Overhauser effect was observed between the hydrazone NH proton and the methyl protons of *E* configuration. The structures of compounds **4a–d**, **5a–d**, and **6a–d** were deduced from their elemental analyses, MS, IR, ¹H NMR, and ¹³C NMR spectra (see experimental section).

A plausible mechanism for the formation of **5a–d** and **6a–d** is shown in Scheme 4. These reactions are assumed to proceed through the formation of the non-isolable intermediate 1*H*-pyrazole-4,5-dione **J**. In all cases of synthesis of compounds **5** and **6**, **J** was not observed at all, and this could be explained by the instability structure of **J** under these reaction conditions. Thus, a deacetylation and subsequent aerobic oxidation¹⁷ of 4-acetyloxy-3*H*-pyrazol-3-one **3a** easily occurs and then **J** would be produced. The reaction of **J** with ketones probably causes aldol-type addition of activated methyl group of ketones to C-4 position of **J**, giving the 4-hydroxy-3*H*-pyrazol-3-ones **5a–d**. On the other hand, thermal treatment of **J** with secondary amines would cause nucleophilic addition of secondary amines to C-5 position of **J** and subsequent ring opening to afford the phenylhydrazones **6a–d**. In these reactions, to check something about the reactivity of the intermediate 1*H*-pyrazole-4,5-dione **J**, we examined a ring transformation of **5b**. Indeed, thermal treatment of **5b** with piperidine caused a retro-aldol reaction of acetophenone and subsequent ring opening *via* a nucleophilic addition of piperidine to give **6c** (66%), which was identical

with an authentic sample prepared from **3a** and piperidine according to Scheme 3 on the basis of a comparison of the melting point, IR, and NMR spectra.



Scheme 4

In conclusion, we have demonstrated the divergent synthesis of *1H*-pyrazole-4,5-diols **4a–d**, 4-hydroxy-3*H*-pyrazol-3-ones **5a–d**, and phenylhydrazones **6a–d** from the key intermediate 4-acetyloxy-3*H*-pyrazol-3-one **3a**, which is easily prepared by $\text{BF}_3 \cdot \text{OEt}_2$ -assisted ring opening of the spiroepoxide-3*H*-pyrazol-3-one **2a** with acetic anhydride *via* an elimination of acetyl group and acetone. Pyrazole and phenylhydrazone derivatives are important building blocks in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry. Further synthesis and evaluation for biological activities of novel pyrazole and phenylhydrazone derivatives are in progress.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. The ^1H and ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer at 500.00 and 125.65 MHz, respectively. The ^1H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as internal standard. Positive FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The starting compounds **1a**,^{15c} **1b**,^{15e} and **1c** were prepared in this laboratory according to the procedure reported in literature.¹⁵

4-Cycloheptylidene-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (1c): Yellow scales (63%), mp 99–100 °C (Et_2O /petroleum ether); IR (KBr): ν 1679 cm^{-1} (CO); ^1H NMR (CDCl_3): δ 1.58–1.61 (m, 4H, 2 CH_2), 1.79–1.84 (m, 4H, 2 CH_2), 2.42 (s, 3H, 5-Me), 2.88–2.91 (m, 2H, CH_2), 3.33–3.35 (m, 2H, CH_2), 7.13–7.16 (m, 1H, Ph-H), 7.36–7.39 (m, 2H, Ph-H), 7.93–7.94 (m, 2H, Ph-H); ^{13}C NMR (CDCl_3): δ 19.2

(5-Me), 25.8, 27.0, 28.7, 28.9, 33.3, 34.8 (CH₂), 119.0, 124.5 (Ph-C), 124.6 (C-4), 128.6, 138.5 (Ph-C), 147.7 (C-5), 163.6 (cycloheptane C-1), 176.5 (CO); FAB MS: *m/z* 269 [M+H]⁺. Anal. Calcd for C₁₇H₂₀N₂O: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.07; H, 7.51; N, 10.32.

General procedure for the preparation of spiroepoxide-3*H*-pyrazol-3-ones 2a–c from 1a–c and *m*-CPBA in the presence of K₂CO₃. To an ice-cooled and stirred solution of 1a–c (15 mmol) and *m*-CPBA (3.88 g, 22.5 mmol) in CHCl₃ (100 mL), K₂CO₃ (3.11 g, 22.5 mmol) was added. After the mixture was stirred at 0–5 °C for 1 h, the solid was removed by filtration and washed with CHCl₃. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluent to give 2a^{15c} (2.90 g, 84%), 2b (3.02 g, 79%), and 2c (2.14 g, 50%).

4-Methyl-11-oxa-2-phenyl-2,3-diazadispiro[4.0.4.1]undec-3-en-1-one (2b): Colorless needles (3.02 g, 79%), mp 70–72 °C (Et₂O/petroleum ether); IR (KBr): ν 1726 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 1.62–2.12 (m, 6H, 3CH₂), 2.13 (s, 3H, 4-Me), 2.14–2.27 (m, 2H, CH₂), 7.12–7.20 (m, 1H, Ph-H), 7.37–7.42 (m, 2H, Ph-H), 7.88–7.91 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 14.9 (4-Me), 24.4, 25.3, 29.9, 32.0 (CH₂), 65.5 (C-5), 79.3 (C-6), 118.5, 125.1, 128.8, 138.3 (Ph-C), 156.7 (C-4), 167.5 (CO); FAB MS: *m/z* 257 [M+H]⁺. Anal. Calcd for C₁₅H₁₆N₂O₂: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.27; H, 6.34; N, 10.88.

4-Methyl-13-oxa-2-phenyl-2,3-diazadispiro[4.0.6.1]tridec-3-en-1-one (2c): Yellow prisms (2.14 g, 50%), mp 59–61 °C (Et₂O/petroleum ether); IR (KBr): ν 1719 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 1.44–1.86 (m, 8H, 4CH₂), 2.04–2.19 (m, 2H, CH₂), 2.20 (s, 3H, 4-Me), 2.21–2.49 (m, 2H, CH₂), 7.17–7.21 (m, 1H, Ph-H), 7.38–7.42 (m, 2H, Ph-H), 7.87–7.90 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 16.6 (4-Me), 24.1, 24.9, 28.5, 29.3, 34.8 (CH₂), 66.6 (C-5), 76.3 (C-6), 118.7, 125.2, 128.8, 138.3 (Ph-C), 156.4 (C-4), 168.0 (CO); FAB MS: *m/z* 285 [M+H]⁺. Anal. Calcd for C₁₇H₂₀N₂O₂: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.89; H, 7.12; N, 9.81.

General procedure for the preparation of 4-acyloxy-3*H*-pyrazol-3-ones 3a–d from 2a and acid anhydride in the presence of BF₃•OEt₂. To an ice-cooled and stirred solution of 2a (0.230 g, 1 mmol) and/or acetic anhydride (0.204 g, 2 mmol), propionic anhydride (0.260 g, 2 mmol), butyric anhydride (0.316 g, 2 mmol), or pentanoic anhydride (0.373 g, 2 mmol) in CHCl₃ (10 mL), BF₃•OEt₂ (0.284 g, 2 mmol) was added. After the mixture was stirred at rt for 12 h, cold H₂O was added to the reaction mixture with stirring and ice-cooling. The resulting mixture was extracted with CHCl₃ (60 mL). The extract was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluent to yield 3a–d.

4-(Acetyloxy)-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (3a): Colorless prisms (0.153 g, 66%), mp 128–130 °C (acetone/petroleum ether); IR (KBr): ν 1761, 1631 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.13 (s, 3H, pyrazole 5-Me), 2.23 (s, 3H, OCOMe), 5.57 (s, 1H, pyrazole 4-H), 7.18–7.26 (m, 1H, Ph-H), 7.36–7.41 (m, 2H, Ph-H), 7.81–7.84 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 14.7 (pyrazole 5-Me), 20.1

(OCOMe), 73.1 (pyrazole C-4), 118.8, 125.5, 128.9, 137.7 (Ph-C), 155.6 (pyrazole C-5), 167.6 (pyrazole C-3), 169.2 (OCOMe); FAB MS: m/z 233 $[M+H]^+$. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.05; H, 5.27; N, 11.98.

2,4-Dihydro-5-methyl-4-(1-oxopropoxy)-2-phenyl-3H-pyrazol-3-one (3b): Colorless needles (0.192 g, 78%), mp 150–152 °C (acetone/petroleum ether); IR (KBr): ν 1771, 1632 cm^{-1} (CO); 1H NMR ($CDCl_3$): δ 1.22 (t, $J = 7.3$ Hz, 3H, $OCOCH_2Me$), 2.12 (s, 3H, pyrazole 5-Me), 2.48–2.54 (m, 2H, $OCOCH_2Me$), 5.56 (s, 1H, pyrazole 4-H), 7.17–7.26 (m, 1H, Ph-H), 7.36–7.41 (m, 2H, Ph-H), 7.82–7.85 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 9.0 ($OCOCH_2Me$), 14.7 (pyrazole 5-Me), 26.9 ($OCOCH_2Me$), 73.0 (pyrazole C-4), 118.8, 125.4, 128.9, 137.8 (Ph-C), 155.6 (pyrazole C-5), 167.7 (pyrazole C-3), 172.7 ($OCOCH_2Me$); FAB MS: m/z 247 $[M+H]^+$. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.36; H, 5.79; N, 11.30.

2,4-Dihydro-5-methyl-4-(1-oxobutoxy)-2-phenyl-3H-pyrazol-3-one (3c): Colorless needles (0.158 g, 61%), mp 121–123 °C (acetone/petroleum ether); IR (KBr): ν 1766, 1631 cm^{-1} (CO); 1H NMR ($CDCl_3$): δ 1.00 (t, $J = 7.3$ Hz, 3H, $OCOCH_2CH_2Me$), 1.69–1.78 (m, 2H, $OCOCH_2CH_2Me$), 2.12 (s, 3H, pyrazole 5-Me), 2.47 (t, $J = 7.3$ Hz, 2H, $OCOCH_2CH_2Me$), 5.57 (s, 1H, pyrazole 4-H), 7.17–7.26 (m, 1H, Ph-H), 7.37–7.41 (m, 2H, Ph-H), 7.82–7.84 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.5 ($OCOCH_2CH_2Me$), 14.7 (pyrazole 5-Me), 18.4 ($OCOCH_2CH_2Me$), 35.3 ($OCOCH_2CH_2Me$), 73.0 (pyrazole C-4), 118.8, 125.4, 128.9, 137.8 (Ph-C), 155.6 (pyrazole C-5), 167.7 (pyrazole C-3), 171.9 ($OCOCH_2CH_2Me$); FAB MS: m/z 261 $[M+H]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.66; H, 6.26; N, 10.75.

2,4-Dihydro-5-methyl-4-(1-oxopentyloxy)-2-phenyl-3H-pyrazol-3-one (3d): Colorless needles (0.252 g, 92%), mp 80–82 °C (Et_2O /petroleum ether); IR (KBr): ν 1770, 1635 cm^{-1} (CO); 1H NMR ($CDCl_3$): δ 0.94 (t, $J = 7.3$ Hz, 3H, $OCOCH_2CH_2CH_2Me$), 1.35–1.45 (m, 2H, $OCOCH_2CH_2CH_2Me$), 1.59–1.76 (m, 2H, $OCOCH_2CH_2CH_2Me$), 2.12 (s, 3H, pyrazole 5-Me), 2.50 (t, $J = 7.3$ Hz, 2H, $OCOCH_2CH_2CH_2Me$), 5.57 (s, 1H, pyrazole 4-H), 7.17–7.34 (m, 1H, Ph-H), 7.35–7.43 (m, 2H, Ph-H), 7.82–7.85 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): δ 13.6 ($OCOCH_2CH_2CH_2Me$), 14.7 (pyrazole 5-Me), 22.1 ($OCOCH_2CH_2CH_2Me$), 26.9 ($OCOCH_2CH_2CH_2Me$), 33.2 ($OCOCH_2CH_2CH_2Me$), 73.0 (pyrazole C-4), 118.8, 125.4, 128.9, 137.8 (Ph-C), 155.6 (pyrazole C-5), 167.7 (pyrazole C-3), 172.0 ($OCOCH_2CH_2CH_2Me$); FAB MS: m/z 275 $[M+H]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.65; H, 6.66; N, 10.19.

The preparation of 4-acetyloxy-3H-pyrazol-3-one 3a from 2b,c and acetic anhydride in the presence of $BF_3 \cdot OEt_2$. To an ice-cooled and stirred solution of **2b** (0.256 g, 1 mmol) or **2c** (0.284 g, 1 mmol) and/or acetic anhydride (0.204 g, 2 mmol) in $CHCl_3$ (10 mL), $BF_3 \cdot OEt_2$ (0.284 g, 2 mmol) was added. After the mixture was stirred at rt for 12 h, cold H_2O was added to the reaction mixture with stirring and

ice-cooling. After work-up as described above, **3a** (0.142 g, 60% from **2b**; 0.070 g, 30% from **2c**) was obtained.

General procedure for the preparation of 1*H*-pyrazole-4,5-diols 4a–d from 3a and α -chloroketones in the presence of NaH. To an ice-cooled and stirred solution of **3a** (0.232 g, 1 mmol) in DMF (5 mL), 60% NaH (0.040 g, 1.1 mmol) was added. The stirring was continued at rt until evolution of gas ceased. To the obtained mixture, chloroacetone (0.185 g, 2 mmol), phenacyl chloride (0.309 g, 2 mmol), 4-methylphenacyl chloride (0.337 g, 2 mmol), and 4-chlorophenacyl chloride (0.378 g, 2 mmol) were added with stirring at rt, and then the mixture was stirred at rt for 12 h. After removal of the solvent *in vacuo*, cold H₂O was added to the residue. The resulting mixture was extracted with CHCl₃ (60 mL). The extract was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluent to afford **4a–d**.

1-[[4-(Acetyloxy)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl]oxy]-2-propanone (4a): Colorless prisms (0.216 g, 75%), mp 103–105 °C (acetone/petroleum ether); IR (KBr): ν 1768, 1731 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.14 (s, 3H, pyrazole 3-Me), 2.18 (s, 3H, OCH₂COMe), 2.28 (s, 3H, OCOMe), 4.55 (s, 2H, OCH₂COMe), 7.26–7.31 (m, 1H, Ph-H), 7.41–7.44 (m, 2H, Ph-H), 7.63–7.66 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 11.7 (pyrazole 3-Me), 20.2 (OCOMe), 26.1 (OCH₂COMe), 76.2 (OCH₂COMe), 118.3 (pyrazole C-4), 122.4, 126.9, 129.0, 138.4 (Ph-C), 141.7 (pyrazole C-3), 142.6 (pyrazole C-5), 168.8 (OCOMe), 203.3 (OCH₂COMe); FAB MS: *m/z* 289 [M+H]⁺. Anal. Calcd for C₁₅H₁₆N₂O₄: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.53; H, 5.64; N, 9.67.

2-[[4-(Acetyloxy)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl]oxy]-1-phenylethanone (4b): Pale red needles (0.262 g, 75%), mp 87–89 °C (acetone/petroleum ether); IR (KBr): ν 1771, 1763, 1753, 1700 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.09 (s, 3H, OCOMe), 2.12 (s, 3H, pyrazole 3-Me), 5.29 (s, 2H, OCH₂COPh), 7.25–7.28 (m, 1H, Ph-H), 7.38–7.47 (m, 4H, Ph-H), 7.58–7.61 (m, 1H, Ph-H), 7.69–7.72 (m, 2H, Ph-H), 7.83–7.85 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 11.8 (pyrazole 3-Me), 20.1 (OCOMe), 73.9 (OCH₂COPh), 118.3 (pyrazole C-4), 122.4, 126.7, 127.8, 128.9, 129.0, 134.0, 138.5 (Ph-C), 141.7 (pyrazole C-3), 142.8 (pyrazole C-5), 168.8 (OCOMe), 192.5 (OCH₂COPh); FAB MS: *m/z* 351 [M+H]⁺. Anal. Calcd for C₂₀H₁₈N₂O₄: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.48; H, 5.23; N, 7.99.

2-[[4-(Acetyloxy)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl]oxy]-1-(4-methylphenyl)ethanone (4c): Colorless prisms (0.286 g, 79%), mp 105–107 °C (acetone/petroleum ether); IR (KBr): ν 1766, 1694 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.09 (s, 3H, OCOMe), 2.12 (s, 3H, pyrazole 3-Me), 2.40 (s, 3H, OCH₂CO-4-Me-C₆H₄), 5.27 (s, 2H, OCH₂CO-4-Me-C₆H₄), 7.24–7.28 (m, 2H, Ph-H), 7.38–7.42 (m, 3H, Ph-H), 7.70–7.76 (m, 4H, Ph-H); ¹³C NMR (CDCl₃): δ 11.8 (pyrazole 3-Me), 20.1 (OCOMe), 21.7 (OCH₂CO-4-Me-C₆H₄), 73.8 (OCH₂CO-4-Me-C₆H₄), 118.3 (pyrazole C-4), 122.3, 126.6, 127.9, 128.9, 129.6, 131.5, 138.6 (Ph-C), 141.6 (pyrazole C-3), 142.9 (pyrazole C-5), 145.1 (Ph-C), 168.8 (OCOMe),

192.1 (OCH₂CO-4-Me-C₆H₄); FAB MS: *m/z* 365 [M+H]⁺. Anal. Calcd for C₂₁H₂₀N₂O₄: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.29; H, 5.56; N, 7.65.

2-{[4-(Acetyloxy)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl]oxy}-1-(4-chlorophenyl)ethanone (4d): Pale red needles (0.216 g, 56%), mp 114–116 °C (acetone/petroleum ether); IR (KBr): ν 1764, 1698 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.13 (s, 3H, pyrazole 3-Me), 2.14 (s, 3H, OCOMe), 5.22 (s, 2H, OCH₂CO-4-Cl-C₆H₄), 7.25–7.29 (m, 1H, Ph-H), 7.38–7.43 (m, 2H, Ph-H), 7.66–7.68 (m, 2H, Ph-H), 7.76–7.79 (m, 2H, Ph-H), 7.83–7.85 (m, 2H, Ph-H); ¹³C-NMR (CDCl₃): δ 11.7 (pyrazole 3-Me), 20.2 (OCOMe), 73.9 (OCH₂CO-4-Cl-C₆H₄), 118.5 (pyrazole C-4), 122.4, 126.8, 129.0, 129.3, 132.3, 138.5, 140.6 (Ph-C), 141.6 (pyrazole C-3), 142.7 (pyrazole C-5), 168.8 (OCOMe), 191.7 (OCH₂CO-4-Cl-C₆H₄); FAB MS: *m/z* 385 [M+H]⁺. Anal. Calcd for C₂₀H₁₇ClN₂O₄: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.17; H, 4.45; N, 7.29.

General procedure for the preparation of 4-hydroxy-3*H*-pyrazol-3-ones 5a–d from 3a and ketones in the presence of Et₃N and H₂O. A mixture of **3a** (0.232 g, 1 mmol), Et₃N (0.202 g, 2 mmol), H₂O (1 mL), and acetone (5 mL, 68.1 mmol), acetophenone (5 mL, 42.9 mmol), 4'-methylacetophenone (5 mL, 37.4 mmol), or 4'-chloroacetophenone (5 mL, 38.6 mmol) was stirred at rt for 12 h. The reaction mixture was extracted with CHCl₃ (60 mL). The extract was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluent to provide **5a–d**.

2,4-Dihydro-4-hydroxy-5-methyl-4-(2-oxopropyl)-2-phenyl-3*H*-pyrazol-3-one (5a): Pale yellow oil (0.209 g, 85%); IR (KBr): ν 3361 (OH), 1714, 1632 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.12 (s, 3H, pyrazole 5-Me), 2.19 (s, 3H, CH₂COMe), 2.99 (s, 2H, CH₂COMe), 4.85 (br, 1H, OH), 7.17–7.21 (m, 1H, Ph-H), 7.37–7.40 (m, 2H, Ph-H), 7.82–7.85 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 13.2 (pyrazole 5-Me), 31.1 (CH₂COMe), 46.4 (CH₂COMe), 77.2 (pyrazole C-4), 119.0, 125.4, 128.9, 137.6 (Ph-C), 160.1 (pyrazole C-5), 172.0 (pyrazole C-3), 206.1 (CH₂COMe); FAB MS: *m/z* 247 [M+H]⁺. Anal. Calcd for C₁₃H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.22; H, 5.93; N, 11.27.

2,4-Dihydro-4-hydroxy-5-methyl-4-(2-oxo-2-phenylethyl)-2-phenyl-3*H*-pyrazol-3-one (5b): Colorless prisms (0.226 g, 73%), mp 106–108 °C (Et₂O/petroleum ether); IR (KBr): ν 3436 (OH), 1726, 1665 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.13 (s, 3H, pyrazole 5-Me), 3.60 (s, 2H, CH₂COPh), 4.80 (br, 1H, OH), 7.17–7.20 (m, 1H, Ph-H), 7.36–7.46 (m, 4H, Ph-H), 7.57–7.60 (m, 1H, Ph-H), 7.86–7.89 (m, 4H, Ph-H); ¹³C NMR (CDCl₃): δ 13.4 (pyrazole 5-Me), 42.6 (CH₂COPh), 77.5 (pyrazole C-4), 119.0, 125.3, 128.2, 128.8, 128.9, 134.2, 135.7, 137.7 (Ph-C), 160.4 (pyrazole C-5), 172.1 (pyrazole C-3), 196.9 (CH₂COPh); FAB MS: *m/z* 309 [M+H]⁺. Anal. Calcd for C₁₈H₁₆N₂O₃: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.18; H, 5.31; N, 9.09.

2,4-Dihydro-4-hydroxy-5-methyl-4-[2-oxo-2-(4-methylphenyl)ethyl]-2-phenyl-3H-pyrazol-3-one

(5c): Colorless needles (0.211 g, 66%), mp 120–122 °C (Et₂O/petroleum ether); IR (KBr): ν 3273 (OH), 1702, 1671 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.13 (s, 3H, pyrazole 5-Me), 2.40 (s, 3H, CH₂CO-4-Me-C₆H₄), 3.54 (s, 2H, CH₂CO-4-Me-C₆H₄), 4.95 (br, 1H, OH), 7.17–7.20 (m, 1H, Ph-H), 7.22–7.25 (m, 2H, Ph-H), 7.36–7.40 (m, 2H, Ph-H), 7.70–7.79 (m, 2H, Ph-H), 7.86–7.89 (m, 2H, Ph-H); ¹³C NMR (CDCl₃): δ 13.5 (pyrazole 5-Me), 21.7 (CH₂CO-4-Me-C₆H₄), 42.2 (CH₂CO-4-Me-C₆H₄), 77.6 (pyrazole C-4), 118.9, 125.2, 128.4, 128.8, 129.5, 133.3, 137.7, 145.3 (Ph-C), 160.4 (pyrazole C-5), 172.0 (pyrazole C-3), 196.8 (CH₂CO-4-Me-C₆H₄); FAB MS: m/z 323 [M+H]⁺. Anal. Calcd for C₁₉H₁₈N₂O₃: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.80; H, 5.69; N, 8.69.

2,4-Dihydro-4-hydroxy-5-methyl-4-[2-oxo-2-(4-chlorophenyl)ethyl]-2-phenyl-3H-pyrazol-3-one (5d):

Colorless needles (0.256 g, 75%), mp 122–124 °C (Et₂O/petroleum ether); IR (KBr): ν 3457 (OH), 1714, 1681, 1672 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 2.13 (s, 3H, pyrazole 5-Me), 3.55 (s, 2H, CH₂CO-4-Cl-C₆H₄), 4.73 (br, 1H, OH), 7.18–7.21 (m, 1H, Ph-H), 7.37–7.42 (m, 4H, Ph-H), 7.79–7.86 (m, 4H, Ph-H); ¹³C-NMR (CDCl₃): δ 13.4 (pyrazole 5-Me), 42.7 (CH₂CO-4-Cl-C₆H₄), 77.4 (pyrazole C-4), 119.0, 125.4, 128.9, 129.2, 129.6, 134.0, 137.6, 140.8 (Ph-C), 160.2 (pyrazole C-5), 172.0 (pyrazole C-3), 195.5 (CH₂CO-4-Cl-C₆H₄); FAB MS: m/z 343 [M+H]⁺. Anal. Calcd for C₁₈H₁₅ClN₂O₃: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.05; H, 4.49; N, 8.18.

General procedure for the preparation of phenylhydrazones 6a–d from 3a and secondary amines.

Procedure A. A mixture of **3a** (0.232 g, 1 mmol), dimethylamine hydrochloride (0.163 g, 2 mmol), and Et₃N (0.202 g, 2 mmol) in THF (5 mL) was refluxed for 2 h. After removal of the solvent *in vacuo*, cold H₂O was added to the residue. The resulting mixture was extracted with CHCl₃ (60 mL). The extract was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CHCl₃ as the eluent to give **6a**.

Procedure B. A solution of **3a** (0.232 g, 1 mmol), and morpholine (5 mL, 57.2 mmol), piperidine (5 mL, 50.6 mmol), or pyrrolidine (5 mL, 59.9 mmol) was stirred at 80 °C for 1 h. After the excess amine was removed *in vacuo*, the residue was purified by column chromatography on silica gel with CHCl₃ as the eluent to give **6b–d**.

(3E)-1-(Dimethylamino)-3-(2-phenylhydrazone)-1,2,3-butanetrione (6a): Colorless needles (0.113 g, 48%), mp 170–172 °C (acetone/petroleum ether); IR (KBr): ν 3221 (NH), 1661, 1636 cm⁻¹ (CO); ¹H NMR (CDCl₃): δ 1.99 (s, 3H, Me), 2.89, 3.10 (s, 6H, NMe₂), 6.98–7.01 (m, 1H, Ph-H), 7.11–7.13 (m, 2H, Ph-H), 7.24–7.27 (m, 2H, Ph-H), 8.71 (s, 1H, NH); ¹³C-NMR (CDCl₃): δ 33.8, 37.2 (NMe₂), 7.41 (Me), 114.5, 123.1, 129.3 (Ph-C), 138.4 (C-3), 142.5 (Ph-C), 169.0 (C-1), 190.3 (C-2); FAB MS: m/z 234 [M+H]⁺. Anal. Calcd for C₁₂H₁₅N₃O₂: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.85; H, 6.61; N, 17.93.

(3E)-1-(4-Morpholinyl)-3-(2-phenylhydrazone)-1,2,3-butanetrione (6b): Yellow needles (0.158 g, 57%), mp 173–175 °C (acetone/petroleum ether); IR (KBr): ν 3446 (NH), 1656, 1622 cm^{-1} (CO); ^1H NMR (CDCl_3): δ 2.00 (s, 3H, Me), 3.28–3.29 (m, 2H, CH_2), 3.60–3.62 (m, 2H, CH_2), 3.75–3.80 (m, 4H, 2 CH_2), 7.01–7.04 (m, 1H, Ph-H), 7.15–7.17 (m, 2H, Ph-H), 7.26–7.29 (m, 2H, Ph-H), 8.64 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 7.40 (Me), 41.4, 46.3, 66.5, 66.6 (CH_2), 114.5, 123.3, 129.4 (Ph-C), 138.6 (C-3), 142.2 (Ph-C), 167.4 (C-1), 189.7 (C-2); FAB MS: m/z 276 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.10; H, 6.31; N, 15.23.

(3E)-3-(2-Phenylhydrazone)-1-(1-piperidinyl)-1,2,3-butanetrione (6c): Yellow needles (0.181 g, 66%), mp 190–191 °C (acetone/petroleum ether); IR (KBr): ν 3274 (NH), 1659, 1623 cm^{-1} (CO); ^1H NMR (CDCl_3): δ 1.50–1.53 (m, 2H, CH_2), 1.65–1.80 (m, 4H, 2 CH_2), 1.98 (s, 3H, Me), 3.20–3.68 (m, 4H, 2 CH_2), 6.97–7.00 (m, 1H, Ph-H), 7.16–7.18 (m, 2H, Ph-H), 7.22–7.27 (m, 2H, Ph-H), 8.87 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 7.49 (Me), 24.4, 25.4, 25.8, 41.9, 47.1 (CH_2), 114.5, 122.9, 129.2 (Ph-C), 138.5 (C-3), 142.5 (Ph-C), 167.2 (C-1), 190.5 (C-2); FAB MS: m/z 274 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.89; H, 7.01; N, 15.35.

(3E)-3-(2-Phenylhydrazone)-1-(1-pyrrolidinyl)-1,2,3-butanetrione (6d): Yellow needles (0.160 g, 62%), mp 180–182 °C (acetone/petroleum ether); IR (KBr): ν 3465 (NH), 1665, 1620 cm^{-1} (CO); ^1H NMR (CDCl_3): δ 1.88–1.97 (m, 4H, 2 CH_2), 1.98 (s, 3H, Me), 3.33 (t, $J = 6.7$ Hz, 2H, CH_2), 3.64 (t, $J = 6.7$ Hz, 2H, CH_2), 6.96–7.00 (m, 1H, Ph-H), 7.12–7.14 (m, 2H, Ph-H), 7.22–7.26 (m, 2H, Ph-H), 8.87 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ 7.53 (Me), 24.2, 25.7, 45.0, 46.4 (CH_2), 114.5, 123.0, 129.3 (Ph-C), 138.2 (C-3), 142.6 (Ph-C), 167.4 (C-1), 190.2 (C-2); FAB MS: m/z 260 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.92; H, 6.72; N, 16.13.

The preparation of phenylhydrazone 6c from 5b and piperidine. A mixture of **5b** (0.308 g, 1 mmol) and piperidine (5 mL, 50.6 mmol) was stirred at 80 °C for 1 h. After work-up as described above, **6c** (0.181 g, 66%) was obtained.

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