Tetrahedron Letters 52 (2011) 3786–3792

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New investigation of Vilsmeier-type reaction using pyrazolones with various amides

Yu-Ying Huang [a], Kimiyoshi Kaneko [b], Hiroyuki Takayama [b], Masayuki Kimura [b], Fung Fuh Wong [a,*]

[a] Graduate Institute of Pharmaceutical Chemistry, China Medical University, No. 91 Hsueh-Shih Rd., Taichung 40402, Taiwan, ROC
[b] Department of Medico Pharmaceutical Science, Nihon Pharmaceutical University, 10281, Komuro, Inamachi, Kita-Adachigun, Saitama, Japan

ARTICLE INFO

Article history:
Received 8 January 2011
Revised 4 May 2011
Accepted 13 May 2011
Available online 19 May 2011

Key words:
Vilsmeier-type reaction
Pyrazolones
Amides
Formylation
Dipyrazolylmethane

ABSTRACT

New investigation of Vilsmeier-type reaction was evaluated to realize the solvent effect by using pyrazolones to react with various of amides, including formamide, *N*-methylformamide, *N*-propylformamide, *N*-*tert*-butylformamide, *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), *N*,*N*-dipropylformamide (DPF), *N*,*N*-diisopropylformamide, *N*,*N*-dibutylformamide, piperidine-1-carbaldehyde, and pyrrolidine-1-carbaldehyde, in the presence of phosphorous oxychloride $POCl_3$. The unexpected resulting products were observed in this work according to the difference chemoseletivities of substituted amides. The plausible reactive pathways were proposed to explain the experimental result.

1. Introduction

Functionalized *N*-arylpyrazole moiety has been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, sedative, and hypnotic activities.[1–3] More specifically, 5-alkyl/arylamino substituted pyrazoles have been exploited in the design of pharmaceuticals and agrochemical agents exhibiting a range of biological activities.[2,4–6]

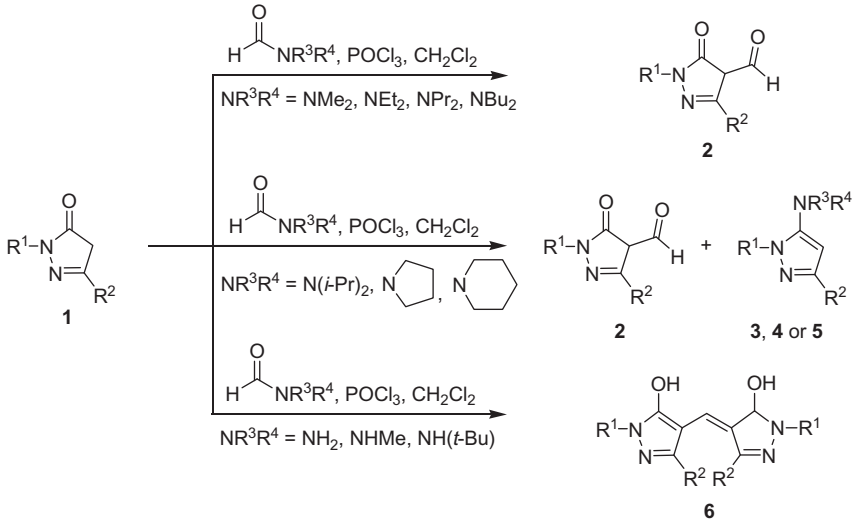
Vilsmeier-type reaction belongs to electrophilic aromatic substitution reaction for the formylation[9] of activated aromatic substrates and carbonyl compounds by halomethyleniminium salt. It is a powerful synthetic tool for the construction of many heterocyclic compounds.[10–12] Formylpyrazoles are prepared by this reaction and attract attention for its being powerful building blocks for the design of complex pyrazolic assemblies in the agrochemistry and biomedical chemistry fields.[7,8] Herein, we are greatly interested in the study of the reactivity of various amides in the presence of phosphorous oxychloride $POCl_3$ as the reactants[13] with pyrazolones. These amides include formamide, *N*-methylformamide, *N*-propylformamide, *N*-*tert*-butylformamide, *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), *N*,*N*-dipropylformamide (DPF), *N*,*N*-diisopropylformamide, *N*,*N*-dibutylformamide, piperidine-1-carbaldehyde, and pyrrolidine-1-carbaldehyde. In this Letter, we found the formation of unexpected products resulted from the different reactivity of the substituted amides serving as the Vilsmeier reagent by reacting with $POCl_3$. We provided the plausible reactive pathways to explain our experimental result.

2. Result and discussion

5-Pyrazolone derivatives were prepared as the substrates following the reported procedure via tandem condensation and thermal cyclization.[14] In this new investigation, we chose a series of 1,3-disubstituted-1*H*-pyrazol-5-ones **1a**–**1h** as the substrates to react with various amides, including formamide, *N*-methylformamide, *N*-propylformamide, *N*-*tert*-butylformamide, *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), *N*,*N*-dipropylformamide (DPF), *N*,*N*-diisopropylformamide, *N*,*N*-dibutylformamide, piperidine-1-carbaldehyde, and pyrrolidine-1-carbaldehyde with $POCl_3$ in CH_2Cl_2 co-solution. For improving the previous procedure of the Vilsmeier reaction, we modified the solvent system by using amide/CH_2Cl_2 co-solvent system (see Scheme 1). Initially, compounds **1a**–**1f** were allowed to react with *N*,*N*-dimethylformamide (DMF) or *N*,*N*-diethylformamide (DEF, 3.0 equiv) with $POCl_3$ (5.0 equiv) in CH_2Cl_2 solution at reflux (~50–60 °C) within 0.5–1 h. After aqueous worked-up and purified by column chromatography on silica gel, we isolated the corresponding formylated product **2a**–**2f** in >87% yields (see Scheme 1 and Table 1). In this modified solvent system (amide/CH_2Cl_2 = 1:1), the reaction time was decreased from ~12 h to 0.5–1 h. All of the 4-formylpyrazolone products **2a**–**2f** were fully characterized by

* Corresponding author. Tel.: +886 4 2205 3366x5603; fax: +886 4 2207 8083.
E-mail addresses: wongfungfuh@yahoo.com.tw, ffwong@mail.cmu.edu.tw (F.F. Wong).

0040-4039/$ - see front matter Crown Copyright © 2011 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.05.055



Scheme 1.

Table 1
Reaction of the pyrazolones with *N*,*N*-dimethylformamide, *N*,*N*-diethylformamide, *N*,*N*-dipropylformamide, or *N*,*N*-dibutylformamide in the presence of $POCl_3$

Pyrazolones (**1a**–**1f**)			Amides $HCONR^3R^4$	Products 4-Formylpyrazolones (**2a**–**2f**)	
S.M.	N1-R^1	C3-R^2	NR^3R^4	No.	Yields (%)
1a	Ph	Ph	NMe_2	**2a**	95
1b	*o*-MePh	Ph	NMe_2	**2b**	96
1c	*p*-OMePh	Ph	NMe_2	**2c**	93
1d	*p*-BrPh	Ph	NMe_2	**2d**	93
1e	Ph	Me	NMe_2	**2e**	96
1f	Ph	*i*-Pr	NMe_2	**2f**	94
1a	Ph	Ph	NEt_2	**2a**	93
1b	*o*-MePh	Ph	NEt_2	**2b**	91
1c	*p*-OMePh	Ph	NEt_2	**2c**	87
1d	*p*-BrPh	Ph	NEt_2	**2d**	93
1e	Ph	Me	NEt_2	**2e**	94
1f	Ph	*i*-Pr	NEt_2	**2f**	91
1a	Ph	Ph	NPr_2	**2a**	88
1a	Ph	Ph	NBu_2	**2a**	83

spectroscopic methods (see Table 1) and the data were consistence with the previous literature reported.[7,8] Furthermore, we extended the reaction condition to 1,3-diphenyl-1*H*-pyrazol-5-one (**1a**) by using *N*,*N*-dipropylformamide (DPF) and *N*,*N*-dibutylformamide with CH_2Cl_2 as the reaction solvent. The corresponding 4-formylpyrazolone product **2a** was also obtained in excellent yields (>83%, see Table 1 and Scheme 1).

To investigate the steric effect and ring stress effect in amide functional groups, the bulky *N*,*N*-diisopropylformamide, or flexible cyclic piperidine-1-carbaldehyde and pyrrolidine-1-carbaldehyde were selected as the reaction solvents. We carried out the same reaction condition toward pyrazolones **1a**–**1d**, which owned *N*1-substituted phenyl and aryl group, with various *mono*-substituents including *o*-MePh, *p*-BrPh, and *p*-OMePh. The 4-formylpyrazolones **2a**–**2d** were obtained as the major products in 63%, 51–62% and 54–59% yields, respectively (see Table 2). Particularly, unexpected amination[15] products **3a**, **4a**–**4d** or **5a**–**5d** were observed and isolated in 28%, 32–46% or 31–39% yields, respectively (see Scheme 1 and Table 2). However, we also preformed the above strategy to pyrazolones **1e**–**1g** bearing C-3 Me, *n*-Pr, or *i*-Pr group. The traditional Vilsmeier formylated products **2e**–**2g** were achieved in 51–54% and 54–58% yields, respectively. Similarly, the unexpected amination[15] products **4e**–**4g** or **5e**–**5g** were also provided in 32–38% or 31–36% yields (see Scheme 1 and Table 2).

Table 2
Reactions of the pyrazolones with *N*,*N*-diisopropylformamide, piperidine-1-carbaldehyde or pyrrolidine-1-carbaldehyde in the presence of $POCl_3$

Pyrazolones (**1a**–**1h**)			Amides $HCONR^3R^4$	Products			
				4-Formylpyrazolones		5-Aminopyrazoles	
S.M.	N1-R^1	C3-R^2	$-NR^3R^4$	No.	Yields (%)	No.	Yields (%)
1a	Ph	Ph	$N(i\text{-}Pr)_2$	**2a**	63	**3a**	28
1a	Ph	Ph	Pyrrolidinyl	**2a**	62	**4a**	33
1b	*o*-MePh	Ph	Pyrrolidinyl	**2b**	59	**4b**	37
1c	*p*-OMePh	Ph	Pyrrolidinyl	**2c**	56	**4c**	42
1d	*p*-BrPh	Ph	Pyrrolidinyl	**2d**	51	**4d**	46
1e	Ph	Me	Pyrrolidinyl	**2e**	53	**4e**	38
1f	Ph	*i*-Pr	Pyrrolidinyl	**2f**	54	**4f**	37
1g	Ph	*n*-Pr	Pyrrolidinyl	**2g**	51	**4g**	32
1a	Ph	Ph	Piperidinyl	**2a**	59	**5a**	34
1b	*o*-MePh	Ph	Piperidinyl	**2b**	53	**5b**	33
1c	*p*-OMePh	Ph	Piperidinyl	**2c**	49	**5c**	39
1d	*p*-BrPh	Ph	Piperidinyl	**2d**	54	**5e**	35
1e	Ph	Me	Piperidinyl	**2e**	57	**5e**	34
1f	Ph	*i*-Pr	Piperidinyl	**2f**	58	**5f**	31
1g	Ph	*n*-Pr	Piperidinyl	**2g**	54	**5g**	36

To examine solvent effect of other amide, we applied the same condition to 1,3-disubstituted-1*H*-pyrazol-5-ones **1a**–**1f** with original formamide. Particularly, we did not isolate and detect the 4-formylpyrazolones product **2** in this solvent system. When we fully identified and characterized the isolated products by spectroscopic methods, the dipyrazolylmethane products **6a**–**6f** were obtained in 84–96% isolated yields under the reaction condition (see Scheme 1 and Table 3). For example, compound **6a** presented a peak at δ 8.51 ppm for $-C^1H{=}C$ in ^1H NMR. In ^{13}C NMR spectrum, compound **6a** possessed characterization absorptions at δ 109.5 ppm for methylene carbon $-{}^{13}CH{=}C$. The IR absorptions of **6a** showed peaks at 2109 cm^{-1} for stretching of the –CH=C group and at 3291 cm^{-1} for stretching of the –OH group.

For the further investigation of other amide agents, pyrazolones **1a**–**1f** were reacted with *N*-methylformamide. Fortunately, the dipyrazolylmethane products **6a**–**6f** were also obtained as the only corresponding products in 82–95% yields. Whatever, the formylated compounds **2** were also not detectable in the presence of *N*-methylformamide as the reaction solvent (see Scheme 1 and Table 3). When applying *N*-*tert*-butylformamide toward 1,3-diphenyl-1*H*-pyrazol-5-ones **1a** under the same condition, we obtained the

Table 3
Reaction of pyrazolones with formamide, *N*-methylformamide, or *N*-*tert*-butylformamide in the presence of $POCl_3$

Pyrazolones (**1a**–**1g**)		Amides $HCONR^3R^4$	Products Dipyrazoylmethanes		
S.M.	N1-R^1	C3-R^2	NR^3R^4	No.	Yields (%)
1a	Ph	Ph	NH_2	**6a**	96
1b	*o*-MePh	Ph	NH_2	**6b**	90
1c	*p*-OMePh	Ph	NH_2	**6c**	84
1d	*p*-BrPh	Ph	NH_2	**6d**	93
1e	Ph	Me	NH_2	**6e**	93
1f	Ph	*i*-Pr	NH_2	**6f**	91
1a	Ph	Ph	NHMe	**6a**	95
1b	*o*-MePh	Ph	NHMe	**6b**	90
1c	*p*-OMePh	Ph	NHMe	**6c**	82
1d	*p*-BrPh	Ph	NHMe	**6d**	91
1e	Ph	Me	NHMe	**6e**	94
1f	Ph	*i*-Pr	NHMe	**6f**	91
1a	Ph	Ph	NH(*t*-Bu)	**6a**	47

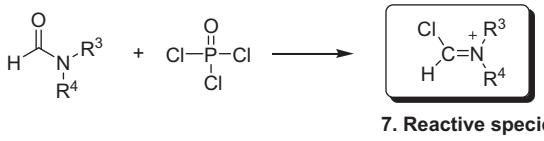
corresponding dipyrazolylmethane product **6a** in lower yield (47%). The result indicated that the bulky functional alkyl group on the nitrogen atom is not in favor for the formation of dipyrazolylmethane product (see Scheme 3 and Table 3).

Following the experimental result, we tried to realize the reactivity and reaction mechanism on various amide solvent systems. Since, we propose the plausible reaction mechanism as shown in Schemes 2 and 3 to account the formation of the different resulting products. At first, amide agents were treated with phosphorous oxychloride $POCl_3$ to in situ form the very reactive species Vilsmeier reagent halomethyleniminium salts **7** (see Scheme 2).[16]

In acid catalytic condition, pyrazolones **1** was efficiently converted to 5-hydroxypyrazole **8**. Simultaneously, 5-hydroxy pyrazoles **8** was preliminarily reacted with the active iminium species **7** by means of C-enolization (**A** and **C**) and O-substitution **B** in three probably reaction pathways. In the **A** reaction pathway, the active iminium species **7** was generated from various amides including *N*,*N*-dimethylformamide, *N*,*N*-diethylformamide, *N*,*N*-dipropylformamide, and *N*,*N*-dibutylformamide. 5-Hydroxy pyrazoles **8** was allowed to react with an active iminium species **7** by following the normal Vilsmeier reaction to form β-ketoamide intermediate **9**. After the hydrolysis was completed, the traditional Vilsmeier products **2** were obtained.[7,8]

When *N*,*N*-diisopropylformamide, piperidine-1-carbaldehyde, and pyrrolidine-1-carbaldehyde were used as the reactants to generate active iminium species **7**, the competitive pathway **A** and **B** were provided to describe the resulting data. In the pathway **B**, the activated β-ketoamide intermediate **10** was formed by O-substitution from 5-hydroxypyrazole **8** with active iminium species **7**. The activated intermediate **10** replaced by the chloride anion as a nucleophile[17] to lead to 5-chloropyrazole **11**.[12j] Due to the steric effect of di-*iso*-propyl group or large ring-stress effect of piperidinyl and pyrrolidinyl groups between the nitrogen and the carbon substituent on halomethyleniminium salts, the dissociation of iminium **7** happened and released the amino anion and CO^+ species.[18,19] After the further amination was performed between 5-chloropyrazole **11** and amino anion (di-*iso*-propyl, piperidinyl and pyrrolidinyl groups), the final 5-aminopyrazole products **3a**, **4a**–**4g** and **5a**–**5g** were usefully obtained in 31–46% yields (see Scheme 3 and Table 2). Consequently, the classical Vilsmeier-type reaction (Pathway **A**) was also observed to afford the corresponding products **2a**–**2g** in 49–62% yields as the major products.

For formamide, *N*-methylformamide, and *N*-*tert*-butylformamide solvent systems, the pathway **C** was used to describe the formation of dipyrazoylmethanes **6**. Since the intramolecular hydrogen-bonding was sequentially formed on β-ketoamide intermediate **9** by using formamide *N*-methylformamide, and *N*-*tert*-



Scheme 2.

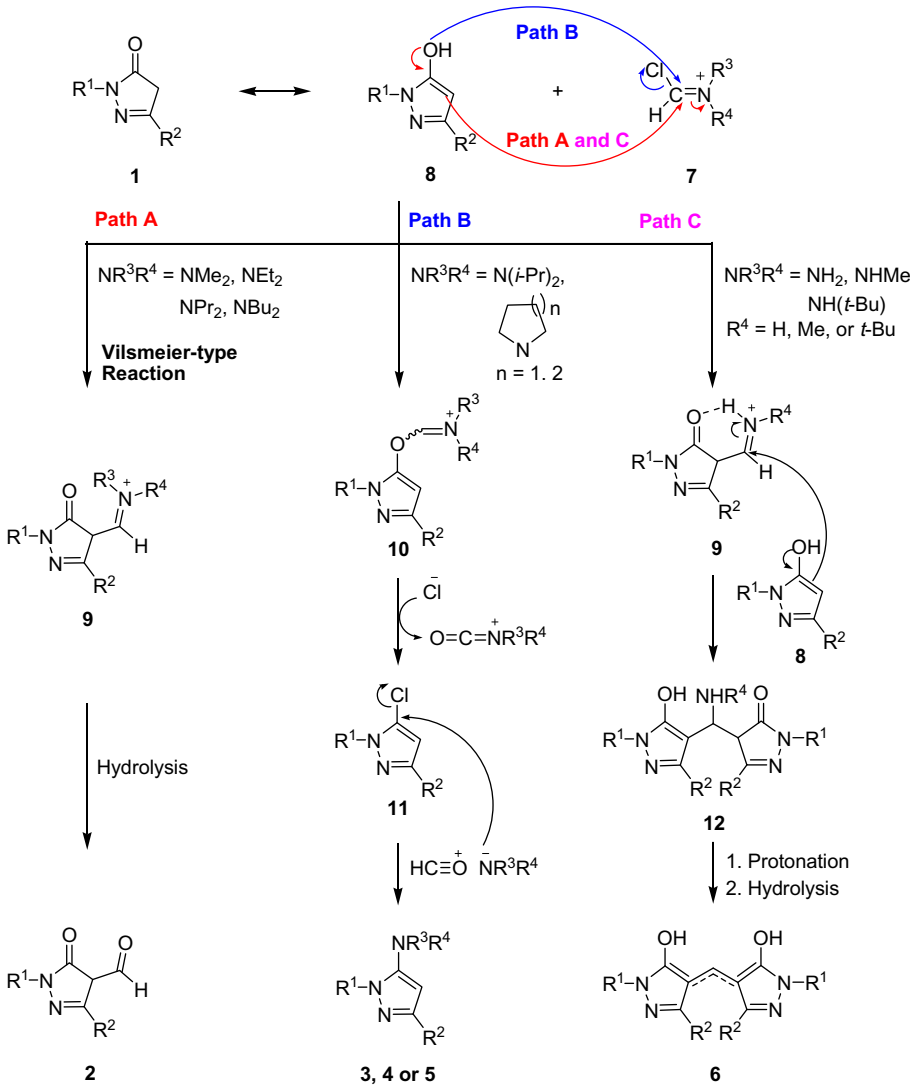
butylformamide as reactants, the more stable β-ketoamide intermediate **9** possessed enough the life-time to react with secondary equivalent of 5-hydroxypyrazole **8** to proceed the Michel addition and generate dipyrazolyl-aminomethane **12**. After the protonation and hydrolysis reactions were simultaneously performed, the final dipyrazolylmethane products **6** were usefully obtained in good to excellent yields under formamide and *N*-methylformamide two systems (see Scheme 3 and Table 3). When *N*-*tert*-butylformamide was applied in the same condition, the steric effect of *tert*-butyl group on the nitrogen atom is not favoring the hydrogen bonding formation of β-ketoamide intermediate **9**. Since, the corresponding dipyrazolylmethane product **6** was obtained in the lower yield (47%, see Table 3).

In conclusion, the different chemosetectivity of Vilsmeier reaction was completely explored by using pyrazolones with variety of amides, including formamide, *N*-methylformamide, *N*-propylformamide, *N*-*tert*-butylformamide, *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), *N*,*N*-dipropylformamide (DPF), *N*,*N*-diisopropylformamide, *N*,*N*-dibutylformamide, piperidine-1-carbaldehyde, and pyrrolidine-1-carbaldehyde in the presence of $POCl_3$. We believed the steric effect of substituted amide play a key role to control the chemoselctive results. Furthermore, three plausible pathways were also provided to describe the chemoselective reactions.

3. Experimental section

3.1. General procedure

All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Dichloromethane, ethyl acetate, hexanes, and methanol were purchased from Mallinckrodt Chemical Co. The following compounds were purchased from Acoros Chemical Co: ethyl Butyrylacetate, 2,4-dinitrophenyl hydrazine, formamide, *N*,*N*-diethylformamide, ethyl acetoacetate, *N*-formylpiperidine, *N*-methylformamide, phenylhydrazine, *o*-tolylhydrazine hydrochloride, *m*-tolylhydrazine hydrochloride, *p*-tolylhydrazine hydrochloride. *N*-Formylpyrrolidine was purchased from Aldaich Chemical Co. *N*,*N*-Diethylformamide was purchased from Scharlau Chemical Co. 2,4,6-Trichlorophenyl hydrazine was purchased from TCI Chemical Co. 4-Bromophenylhydrazine hydrochloride, 2-chlorophenylhydrazine hydrochloride, 3-chlorophenylhydrazine hydrochloride, 4-chlorophenylhydrazine hydrochloride, ethyl benzoylacetate, ethyl isobutyrylacetate, ethyl trifluoroacetoacetate, 4-methoxyphenylhydrazine hydrochloride were purchased from Alfa Chemical Co. Phosphorylchloride were purchased from FERAK Chemical Co. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wave numbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra



Scheme 3.

were obtained on a Bruker (200 or 400 MHz) spectrometer by use of $CDCl_3$ as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 or 100 MHz) spectrometer by use of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard procedure for the preparation of 4-formylpyrazolone products (**2a–2g**), amination products (**3a**, **4a–4g** and **5a–5g**) and dipyrazolylmethane products (**6a–6f**).

The reliable procedure involved the treatment of pyrazolones (**1a–1g**, 1.0 equiv) with catalytic amount of $POCl_3$ (~3 equiv) with various amides (2 mL) including formamide, *N*-methylformamide, *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF), piperidine-1-carbaldehyde, and pyrrolidine-1-carbaldehyde in CH_2Cl_2 solution (2 mL) at 50–60 °C within 0.5–1 h. When the reaction was completed, the reaction mixture was concentrated, added to saturate sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding 4-formylpyrazolone products **2a–2g**, amination products **3a**, **4a–4g** and **5a–5g**, dipyrazolylmethane products **6a–6f** were obtained.

3.1.1. 1,3-Diphenyl-4-formyl-2-pyrazolin-5-one (2a)

Mp (recrystallized from ethanol) 241–242 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.13 (t, 1H, J = 7.6 Hz, ArH), 7.37–7.46 (m, 5H, ArH), 7.71–7.75 (m, 2H, ArH), 7.82 (d, 2H, J = 7.6 Hz, ArH), 10.1 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 116.3, 125.3 (2 × CH), 128.4 (2 × CH), 128.8 (2 × CH), 129.1 (2 × CH), 129.3 (2 × CH), 130.7, 133.1, 136.8, 154.1, 183.6; IR (KBr) 3067 (m), 1698 (s, C=O), 1591 (s, C–N), 1482 (m), 1386 (m), 1331 (m), 1179 (m), 1121 (m), 901 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.76; H:4.56; N, 10.62.

3.1.2. 1-(2′-Methylphenyl)-3-phenyl-4-formyl-2-pyrazolin-5-one (2b)

Mp (recrystallized from ethanol) 231–233 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 2.31 (s, 3H, CH_3), 7.46 (d, 2H, J = 7.2 Hz, ArH), 7.49–7.55 (m, 5H, ArH), 7.73 (d, 2H, J = 7.2 Hz, ArH), 9.92 (s, 1H, CHO); ^{13}C NMR (50 MHz, CD_3OD) δ 16.3, 125.9 (2 × CH), 126.2, 127.2, 128.1, 128.3, 129.1 (2 × CH), 131.1, 131.2, 131.5, 131.7, 135.9, 136.7, 149.6, 157.4; IR (KBr) 3293 (m), 3124 (s), 1880 (m), 1537 (s, C–N), 1472 (m), 1305 (m), 1147 (m), 982 (m), 807 (m) cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.35; H, 5.11; N, 10.09.

3.1.3. 1-(4′-Methoxylphenyl)-3-phenyl-4-formyl-2-pyrazolin-5-one (2c)

Mp (recrystallized from ethanol) 152–153 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3H, CH_3), 6.87 (d, 2H, J = 6.8 Hz, ArH), 7.36–7.40 (m, 3H, ArH), 7.68 (d, 2H, J = 7.2 Hz, ArH), 7.72 (d, 2H, J = 6.8 Hz, ArH), 10.2 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.1, 114.0 (2 × CH), 121.0 (2 × CH), 125.9 (2 × CH), 128.9 (2 × CH), 129.8, 130.4, 130.7, 131.3, 131.6, 153.5, 156.2, 179.1; IR (KBr) 2972 (m), 1691 (s, C=O), 1492 (s, C–N), 1497 (m), 1238 (m), 1032 (m), 851 (m) cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.34; H, 4.83; N, 9.51.

3.1.4. 1-(4′-Bromophenyl)-4-formyl-2-pyrazolin-5-one (2d)

Mp (recrystallized from ethanol) 201–203 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.27 (m, 2H, ArH); 7.46 (m, 2H, ArH); 7.78 (m, 2H, ArH); 7.93 (m, 2H, ArH); 9.8 (s, 1H, CHO); ^{13}C NMR (50 MHz, CD_3OD) δ 119.3, 125.1 (2 × CH), 128.6 (2 × CH), 128.9 (2 × CH); 130.1 (2 × CH), 130.5, 130.7, 130.9, 154.9, 178.4; IR (KBr) 3133 (m), 3025 (s), 1790 (m), 1483 (s, C–N), 1456 (m), 1307 (m), 1139 (m), 977 (m), 794 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{11}BrN_2O_2$: C, 56.00; H, 3.23; N, 8.16. Found: C, 55.98; H, 3.27; N, 8.15.

3.1.5. 1-Phenyl-3-methyl-4-formyl-2-pyrazolin-5-one (2e)

Mp (recrystallized from ethanol) 175–176 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.2 (s, 3H, CH_3), 7.3–7.9 (m, 6H, Ph), 9.85 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 116.9, 125.5 (2 × CH), 129.8 (2 × CH), 133.9, 134.6, 137.1, 155.7, 181.5; IR (KBr) 3152 (s), 2812 (m), 1659 (s, C=O), 1598 (s, C–N), 1463 (m), 1408 (m), 1296 (s), 1230 (m), 1029 (m), 958 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.32; H, 4.94; N, 13.86.

3.1.6. 1-Phenyl-3-isopropyl-4-formyl-2-pyrazolin-5-one (2f)

Mp (recrystallized from ethanol) 149–150 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (d, 6H, J = 7.4 Hz, $CH(CH_3)_2$), 2.59–2.73 (m, 1H, $CHMe_2$), 7.09 (t, 1H, J = 7.4 Hz, ArH), 7.27 (dd, 2H, J = 8.1, 7.4 Hz, ArH), 7.65 (d, 2H, J = 8.1 Hz, ArH), 9.92 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8 (2 × CH_3), 29.5, 35.7, 117.6 (2 × CH), 121.2, 127.7 (2 × CH), 138.1, 158.3, 179.7; IR (KBr) 3202 (s), 2799 (m), 1601 (s, C=O), 1581 (s, C–N), 1481 (m), 1423 (m), 1312 (s), 1209 (m), 1036 (m), 956 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.78; H, 6.11; N, 12.20.

3.1.7. 1,3-Diphenyl-5-di-isopropylaminopyrazole (3a)

Mp (recrystallized from ethanol) 92–93 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22–1.24 (m, 12H), 3.54–3.60 (m, 1H), 4.12–4.18 (m, 1H), 6.16 (s, 1H), 7.09–7.12 (m, 1H), 7.33–7.36 (m, 2H), 7.39–7.52 (m, 4H), 8.01–8.03 (m, 2H), 8.17 (s, H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.16 (CH_3), 20.96 (CH_3), 23.96 (CH_3), 29.64 (CH_3), 46.51 (CH), 48.28 (CH), 97.92, 120.13, 124.24, 128.28 (3 × CH), 128.47 (3 × CH), 128.82, 129.04 (2 × CH), 139.63, 149.43, 161.54; IR (KBr) 3048 (s), 2811 (m), 1560 (s, C–N), 1428 (m), 1413 (m), 1309 (s), 1247 (m), 1179 (m), 973 (m) cm^{-1}. Anal. Calcd for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89; N, 13.15. Found: C, 78.93; H, 7.91; N, 13.17.

3.1.8. 1,3-Diphenyl-5-pyrrolidinopyrazole (4a)

Mp (recrystallized from ethanol) 87–88 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (m, 4H), 3.50 (m, 4H), 5.89 (s, 1H), 7.18–7.25 (m, 2H), 7.35 (t, 2H, J = 7.6 Hz), 7.37(t, 2H, J = 7.6 Hz), 7.71 (d, 2H, J = 7.4 Hz), 7.82 (d, 2H, J = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1 (2 × CH), 53.8 (2 × CH), 89.3, 122.8 (2 × CH), 125.2 (2 × CH), 126.9 (2 × CH), 128.1 (2 × CH), 128.7, 129.6, 133.1, 140.4, 150.7, 162.8; IR (KBr) 3050 (s), 2814 (m), 1558 (s, C–N), 1432 (m), 1409 (m), 1298 (s), 1256 (m), 1183 (m), 975 (m) cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.82; H, 6.65; N, 14.49.

3.1.9. 1-(2′-Methylphenyl)-3-phenyl-5-pyrrolidinopyrazole (4b)

Mp (recrystallized from ethanol) 93–94 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.37 (m, 4H), 3.53 (m, 4H), 2.36 (s, 3H, CH_3), 5.97 (s, 1H), 7.46 (d, 2H, J = 7.2 Hz, ArH), 7.51–7.58 (m, 5H, ArH), 7.72 (d, 2H, J = 7.2 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3, 23.8 (2 × CH), 54.6 (2 × CH), 89.5, 125.8 (2 × CH), 126.1, 126.8, 128.5, 129.3 (2 × CH), 131.2, 131.8, 132.7, 135.6, 136.9, 149.1, 158.3; IR (KBr) 3079 (m), 2984 (s), 1617, 1587 (s, C–N), 1479 (m), 1334 (m), 1130 (m), 988 (m), 815 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.14; H, 6.95; N, 13.87.

3.1.10. 1-(4′-Methoxylphenyl)-3-phenyl-5-pyrrolidinopyrazole (4c)

Mp (recrystallized from ethanol) 129–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.42 (m, 4H), 3.61 (m, 4H), 3.79 (s, 3H, CH_3), 5.93 (s, 1H), 6.69 (d, 2H, J = 6.8 Hz, ArH), 7.20–7.25 (m, 3H, ArH), 7.43 (d, 2H, J = 7.2 Hz, ArH), 7.48 (d, 2H, J = 6.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2 (2 × CH), 38.9, 53.9 (2 × CH), 89.2, 113.9 (2 × CH), 122.3 (2 × CH), 126.7 (2 × CH), 128.2 (2 × CH), 129.5, 130.1, 131.3, 131.6, 152.5, 161.3; IR (KBr) 3109 (m), 1566 (s, C–N), 1479 (m), 1251 (m), 1023 (m), 874 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.18; H, 6.65; N, 13.20.

3.1.11. 1-(4′-Bromophenyl)-3-phenyl-5-pyrrolidinopyrazole (4d)

Mp (recrystallized from ethanol) 125–126 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (m, 4H), 3.51 (m, 4H), 5.88 (s, 1H), 7.12 (m, 2H, ArH); 7.29 (m, 2H, ArH); 7.57 (m, 2H, ArH); 7.76 (m, 2H, ArH); ^{13}C NMR (50 MHz, CD_3OD) δ 23.7 (2 × CH), 53.7 (2 × CH), 89.6, 118.1, 126.2 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH); 130.5 (2 × CH), 131.4, 132.3, 154.2, 162.7; IR (KBr) 3172 (m), 3061 (s), 1582 (s, C–N), 1431 (m), 1323 (m), 1221 (m), 961 (m), 798 (m) cm^{-1}. Anal. Calcd for $C_{19}H_{18}BrN_3$: C, 61.97; H, 4.93; N, 11.41. Found: C, 61.94; H, 4.89; N, 11.38.

3.1.12. 3-Methyl-1-phenyl-5-pyrrolidinopyrazole (4e)

Mp (recrystallized from ethanol) 114–115 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 3H, CH_3), 2.39 (m, 4H), 3.57 (m, 4H), 6.01 (s, 1H), 7.4–7.9 (m, 6H, Ph); ^{13}C NMR (50 MHz, CD_3OD) δ 19.7, 23.4 (2 × CH), 53.1 (2 × CH), 89.6, 114.8, 119.6 (2 × CH), 123.5 (2 × CH), 149.5, 162.4; IR (KBr) 3132 (s), 2864 (m), 1501 (s, C–N), 1423 (m), 1410 (m), 1287 (s), 1229 (m), 1017 (m), 951 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.95; H, 7.57; N, 18.53.

3.1.13. 3-*iso*-Propyl-1-phenyl-5-pyrrolidinopyrazole (4f)

Mp (recrystallized from ethanol) 123–124 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 6H, J = 7.4 Hz, $CH(CH_3)_2$), 2.38 (m, 4H), 2.61–2.75 (m, 1H, $CHMe_2$), 3.52 (m, 4H), 6.31 (s, 1H), 6.98 (t, 1H, J = 7.4 Hz, ArH), 7.14 (dd, 2H, J = 8.1, 7.4 Hz, ArH), 7.57 (d, 2H, J = 8.1 Hz, ArH); NMR (50 MHz, $CDCl_3$) δ 17.8 (2 × CH_3), 23.4 (2 × CH), 29.6, 40.6, 53.9 (2 × CH), 90.1, 118.6 (2 × CH), 121.7, 126.6 (2 × CH), 147.2, 162.7; IR (KBr) 3102 (s), 2813 (m), 1581 (s, C–N), 1471 (m), 1429 (m), 1315 (s), 1199 (m), 1036 (m), 957 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46. Found: C, 75.23; H, 8.31; N, 16.50.

3.1.14. 3-*n*-Propyl-1-phenyl-5-pyrrolidinopyrazole (4g)

Mp (recrystallized from ethanol) 129–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (t, J = 7.4 Hz, 3H), 1.68–1.76 (m, 2H), 2.36 (m, 4H), 2.50 (t, J = 7.5 Hz, 2H), 3.59 (m, 4H), 5.97 (s, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.28 (dd, J = 7.4, 7.7 Hz, 2H), 7.81 (d, J = 7.7 Hz, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 14.2, 20.4, 23.9 (2 × CH), 30.5, 53.1 (2 × CH), 90.3, 120.3, 125.8, 130.4, 138.5, 156.1, 163.0; IR (KBr) 3112 (s), 2836 (m), 1541 (s, C–N), 1452 (m), 1412 (m), 1301 (s), 1197 (m), 1041 (m), 955 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46. Found: C, 75.29; H, 8.28; N, 16.44.

3.1.15. 1,3-Diphenyl-5-*N*-piperidinopyrazole (5a)

Mp (recrystallized from ethanol) 98–99 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44–1.47 (m, 2H), 1.50–1.56 (m, 4H), 2.79 (t, 4H, J = 5.4 Hz), 6.09 (s, 1H), 7.16–7.23 (m, 2H), 7.35 (t, 2H, J = 7.6 Hz), 7.37 (t, 2H, J = 7.6 Hz), 7.77 (d, 2H, J = 7.4 Hz), 7.84 (d, 2H, J = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1, 26.5 (2 × CH), 53.8 (2 × CH), 91.3, 122.6 (2 × CH), 125.1 (2 × CH), 126.4 (2 × CH), 127.9 (2 × CH), 128.7, 129.1, 133.6, 140.5, 150.8, 163.9; IR (KBr) 3060 (s), 2944 (m), 1549 (s, C–N), 1450 (m), 1421 (m), 1301 (s), 1251 (m), 1199 (m), 965 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.14; H, 6.95; N, 13.87.

3.1.16. 1-(2′-Methylphenyl)-3-phenyl-5-*N*-piperidinopyrazole (5b)

Mp (recrystallized from ethanol) 103–104 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45–1.48 (m, 2H), 1.52–1.58 (m, 4H), 2.36 (s, 3H, CH_3), 2.82 (t, 4H, J = 5.4 Hz), 6.13 (s, 1H), 7.45 (d, 2H, J = 7.2 Hz, ArH), 7.49–7.56 (m, 5H, ArH), 7.68 (d, 2H, J = 7.2 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3, 22.9, 27.4 (2 × CH), 54.3 (2 × CH), 92.1, 125.9 (2 × CH), 126.2, 127.2, 128.3, 129.1 (2 × CH), 131.1, 131.5, 131.7, 135.9, 136.7, 149.6, 159.4; IR (KBr) 3159 (m), 3108 (s), 1607, 1537 (s, C–N), 1472 (m), 1321 (m), 1143 (m), 979 (m), 810 (m) cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.49; H, 7.28; N, 13.21.

3.1.17. 1-(4′-Methoxylphenyl)-3-phenyl-5-*N*-piperidinopyrazole (5c)

Mp (recrystallized from ethanol) 124–125 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.44–1.47 (m, 2H), 1.51–1.57 (m, 4H), 2.23 (s, 3H, CH_3), 2.79 (t, 4H, J = 5.4 Hz), 3.79 (s, 3H, CH_3), 6.10 (s, 1H), 6.77 (d, 2H, J = 6.8 Hz, ArH), 7.20–7.26 (m, 3H, ArH), 7.47 (d, 2H, J = 7.2 Hz, ArH), 7.59 (d, 2H, J = 6.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.5, 28.2 (2 × CH), 39.2, 53.9 (2 × CH), 90.1, 114.0 (2 × CH), 121.0 (2 × CH), 125.9 (2 × CH), 128.9 (2 × CH), 129.8, 130.4, 131.3, 131.6, 153.5, 161.1; IR (KBr) 3207 (m), 1562 (s, C–N), 1487 (m), 1243 (m), 1031 (m), 863 (m) cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.61; H, 6.93; N, 12.57.

3.1.18. 1-(4′-Bromophenyl)-3-phenyl-5-*N*-piperidinopyrazole (5d)

Mp (recrystallized from ethanol) 118–119 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45–1.48 (m, 2H), 1.53–1.61 (m, 4H), 2.35 (s, 3H, CH_3), 2.84 (t, 4H, J = 5.4 Hz), 6.02 (s, 1H), 7.13 (m, 2H, ArH), 7.37 (m, 2H, ArH), 7.68 (m, 2H, ArH), 7.81 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.46–1.49 (m, 2H), 1.53–1.59 (m, 4H), 2.82 (t, 4H, J = 5.4 Hz), 6.13 (s, 1H), ^{13}C NMR (50 MHz, CD_3OD) δ 24.2, 29.5 (2 × CH), 40.6, 54.2 (2 × CH), 93.6, 119.3, 125.1 (2 × CH), 128.6 (2 × CH), 128.9 (2 × CH); 130.1 (2 × CH), 130.5, 130.9, 154.9, 163.4; IR (KBr) 3213 (m), 3095 (s), 1472 (s, C–N), 1432 (m), 1314 (m), 1119 (m), 981 (m), 793 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{20}BrN_3$: C, 62.83; H, 5.27; N, 10.99. Found: C, 62.80; H, 5.29; N, 11.02.

3.1.19. 3-Methyl-1-phenyl-5-*N*-piperidinopyrazole (5e)

Mp (recrystallized from ethanol) 101–102 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 3H, CH_3), 1.41–1.44 (m, 2H), 1.48–1.54 (m, 4H), 2.69 (t, 4H, J = 5.4 Hz), 6.11 (s, 1H), 7.3–7.9 (m, 6H, Ph); ^{13}C NMR (50 MHz, CD_3OD) δ 19.3, 24.2, 29.5 (2 × CH), 40.6, 54.2 (2 × CH), 92.6, 115.8, 124.9 (2 × CH), 127.6 (2 × CH), 153.4, 161.3; IR (KBr) 3132 (s), 2864 (m), 1501 (s, C–N), 1423 (m), 1410 (m), 1287 (s), 1229 (m), 1017 (m), 951 (m) cm^{-1}. Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.63; H, 7.92; N, 17.39.

3.1.20. 3-*iso*-Propyl-1-phenyl-5-*N*-piperidinopyrazole (5f)

Mp (recrystallized from ethanol) 120–121 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 6H, J = 7.4 Hz, $CH(CH_3)_2$), 1.45–1.49 (m, 2H), 1.51–1.58 (m, 4H), 2.61–2.75 (m, 1H, $CHMe_2$), 2.82 (t, 4H, J = 5.4 Hz), 6.31 (s, 1H), 6.98 (t, 1H, J = 7.4 Hz, ArH), 7.14 (dd, 2H, J = 8.1, 7.4 Hz, ArH), 7.57 (d, 2H, J = 8.1 Hz, ArH); NMR (50 MHz, $CDCl_3$) δ 17.8 (2 × CH_3), 24.2, 28.5 (2 × CH), 29.6, 40.6, 53.2 (2 × CH), 90.1, 116.6 (2 × CH), 121.3, 126.8 (2 × CH), 139.1, 162.7; IR (KBr) 3102 (s), 2813 (m), 1581 (s, C–N), 1471 (m), 1429 (m), 1315 (s), 1199 (m), 1036 (m), 957 (m) cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60. Found: C, 75.77; H, 8.64; N, 15.58.

3.1.21. 3-*n*-Propyl-5-*N*-piperidinopyrazole (5g)

Mp (recrystallized from ethanol) 126–127 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (t, J = 7.4 Hz, 3H), 1.44–1.47 (m, 2H), 1.50–1.56 (m, 4H), 1.68–1.76 (m, 2H), 2.50 (t, J = 7.5 Hz, 2H), 2.79 (t, 4H, J = 5.4 Hz), 6.14 (s, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.29 (dd, J = 7.4, 7.7 Hz, 2H), 7.87 (d, J = 7.7 Hz, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 14.2, 20.4, 24.2, 29.5 (2 × CH), 33.5, 40.6, 54.2 (2 × CH), 92.3, 119.3, 125.4, 129.2, 138.6, 158.3, 163.8; IR (KBr) 3112 (s), 2836 (m), 1541 (s, C–N), 1452 (m), 1412 (m), 1301 (s), 1197 (m), 1041 (m), 955 (m) cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60. Found: C, 75.81; H, 8.58; N, 15.64.

3.1.22. 4,4′-Methylidenebis(1,3-diphenyl-2-pyrazolone) (6a)

Mp (recrystallized from ethanol) 261.2–262.2 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24 (t, 1H, J = 7.6 Hz, ArH), 7.44–7.53 (m, 5H, ArH), 7.82–7.86 (m, 2H, ArH), 8.01 (d, 2H, J = 7.6 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.7, 108, 119.1 (2 × CH), 109.5, 125.3, 126.0 (2 × CH), 128.9 (2 × CH), 130.7, 130.9 (2 × CH), 134.8, 138.1, 154.6, 170.2; IR (KBr) 3067 (m), 1715 (s, C=O), 1601 (s, C–N), 1496 (m), 1383 (m), 1326 (m), 1172 (m), 1116 (m), 899 (m) cm^{-1}. Anal. Calcd for $C_{31}H_{22}N_4O_2$: C, 77.16; H, 4.60; N, 11.61. Found: C, 77.13; H, 4.62; N, 11.59.

3.1.23. 4,4′-Methylidenebis[1-(2′-methylphenyl)-3-phenyl-2-pyrazolone] (6b)

Mp (recrystallized from ethanol) 205.3–206.3 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 2.27 (s, 3H, CH_3), 7.51 (d, 2H, J = 7.2 Hz, ArH), 7.54–7.59 (m, 5H, ArH), 7.82 (d, 2H, J = 7.2 Hz, ArH); ^{13}C NMR (50 MHz, CD_3OD) δ 15.9, 126.3 (2 × CH), 126.6, 127.2, 128.0, 128.5, 129.2 (2 × CH), 131.1, 131.2, 131.5, 131.7, 136.7, 149.6, 157.4; IR (KBr) 3293 (m), 3124 (s), 1880 (m), 1537 (s, C–N), 1472 (m), 1305 (m), 1147 (m), 982 (m), 807 (m) cm^{-1} Anal. Calcd for $C_{33}H_{26}N_4O_2$: C, 77.63; H, 5.13; N, 10.97. Found: C, 77.67; H, 5.15; N, 10.96.

3.1.24. 4,4′-Methylidenebis[1-(4′-methoxylphenyl)-3-phenyl-2-pyrazolone] (6c)

Mp (recrystallized from ethanol) 128–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, CH_3), 6.90 (d, 2H, J = 6.8 Hz, ArH), 7.40–7.44 (m, 3H, ArH), 7.73 (d, 2H, J = 7.2 Hz, ArH), 7.81 (d, 2H, J = 6.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.5, 55.5, 114.0 (2 × CH), 121.0 (2 × CH), 125.9 (2 × CH), 128.9 (2 × CH), 130.6,

130.9, 131.5, 154.5, 157.2, 170.0; IR (KBr) 2927 (m), 1709 (s, C=O), 1512 (s, C–N), 1500 (m), 1248 (m), 1030 (m), 832 (m) cm^{-1}. Anal. Calcd for $C_{33}H_{26}N_4O_4$: C, 73.05; H, 4.83; N, 10.33. Found: C, 73.07; H, 4.85; N, 10.31.

3.1.25. 4,4′-Methylidenebis[1-(4′-bromophenyl)-3-phenyl-2-pyrazolone] (6d)

Mp (recrystallized from ethanol) 183–184 °C; ^1H NMR (CD_3OD, 200 MHz) δ 7.38 (m, 2H, ArH); 7.50 (m, 2H, ArH); 7.81 (m, 2H, ArH); 7.99 (m, 2H, ArH).; ^{13}C NMR (50 MHz, CD_3OD) δ 120.0; 126.0; 128.9; 129.0; 130.4; 130.7; 130.9; 154.9; 170.1.; IR (KBr) 3293 (m), 3124 (s), 1880 (m), 1537 (s, C–N), 1472 (m), 1305 (m), 1147 (m), 982 (m), 807 (m) cm^{-1}. Anal. Calcd for $C_{31}H_{20}Br_2N_4O_2$: C, 55.15; H, 3.15; N, 8.75. Found: C, 55.17; H, 3.19; N, 8.72.

3.1.26. 4,4′-Methylidenebis(3-methyl-1-phenyl-2-pyrazolone) (6e)

Mp (recrystallized from ethanol) 127–129 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 3H, CH_3), 7.14 (d, 1H, J = 2.2 Hz, ArH), 7.36 (dd, 2H, J = 7.8 Hz, 2.2 Hz, ArH), 7.81 (d, 2H, J = 7.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 43.1, 118.9 (2 × CH), 125.1, 128.8 (2 × CH), 137.9, 156.4, 170.6; IR (KBr) 3101 (s), 2802 (m), 1622 (s, C=O), 1584 (s, C–N), 1494 (m), 1412 (m), 1301 (s), 1220 (m), 1035 (m), 967 (m) cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 8.93. Found: C, 70.41; H, 5.09; N, 8.96.

3.1.27. 4,4′-Methylidenebis(3-isopropyl-1-phenyl-2-pyrazolone) (6f)

Mp (recrystallized from ethanol) 101–103 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (d, 6H, J = 7.4 Hz, $CH(CH_3)_2$), 2.68–2.82 (m, 1H, $CHMe_2$), 7.14 (t, 1H, J = 7.4 Hz, ArH), 7.35 (dd, 2H, J = 8.1, 7.4 Hz, ArH), 7.84 (d, 2H, J = 8.1 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1 (2 × CH_3), 30.7, 39.8, 118.8 (2 × CH), 124.9, 128.8 (2 × CH), 138.2, 164.3, 170.6; IR (KBr) 3101 (s), 2802 (m), 1622 (s, C=O), 1584 (s, C–N), 1494 (m), 1412 (m), 1301 (s), 1220 (m), 1035 (m), 967 (m) cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_4O_2$: C, 72.44; H, 6.32; N, 13.52. Found: C, 72.41; H, 6.35; N, 13.53.

Acknowledgments

We are grateful to the China Medical University (CMU100-S-) and the National Science Council of Republic of China for financial support (NSC-99-2320-B-039-014-MY3). This study is supported in part by Taiwan Department of Health Clinical Trial and Research Center of Excellence (DOH100-TD-B-111-004).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.055.

References and notes

1. For the reviews: (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Potts, K. T., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, p 167; (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 3, p 1; (c) Kost, A. N.; Grandberg, I. I. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1966; Vol. 6, p 347; (d) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737–6740. and references therein.
2. Sakya, S. M.; Rast, B. *Tetrahedron Lett.* **2003**, *44*, 7629–7632. and references therein.
3. Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833–2836. and references therein.
4. (a) Nishigaki, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2985–2988; (b) Braibante, M. E. F.; Braibante, H. T. S.; da Roza, J. K.; Henriques, D. M. *Synthesis* **2003**, 1160–1162; (c) Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; D'Amico, M.; Filippelli, W.; Falcone, G.; De Novellis, V. *Il Farmaco* **1995**, *50*, 179–182; (d) Cooper, C. B.; Helal, C. J.; Sanner, M. A.; Wagner, T. T. PCT WO 18346 A1, 2002.
5. (a) Ansel, J. E.; El Kaim, L.; Gadras, A.; Grimaud, L.; Jana, N. K. *Tetrahedron Lett.* **2002**, *43*, 8319–8321; (b) Atlan, V.; Buron, C.; Elkaim, L. *Synlett* **2000**, 489–490; (c) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1996**, *52*, 4123–4132; (d) Moreno-Manãs, M.; Sebastián, R. M.; Vallribera, A.; Carini, F. *Synthesis* **1999**, 157–160; (e) Abdel-Rahman, R. M.; Seada, M.; Fawzy, M.; El-Baz, I. *Pharmazie* **1994**, *49*, 729–733.
6. Dodd, D. S.; Martinez, R. L. *Tetrahedron Lett.* **2004**, *45*, 4265–4267.
7. Salmon, R. WO 9,306,089, 1995.
8. Atkinson, R.N.; Gross, M.F. WO 03,037,274, 2003.
9. (a) Campaigne, E.; Archer, W. L. *J. Am. Chem. Soc.* **1953**, *75*, 989–991; (b) Treihs, W.; Neupert, H. J.; Hiebsch, J. *Chem. Ber.* **1959**, *92*, 141–154; (c) Damodiran, M.; Panneer, N.; Paramasivan, S.; Perumal, T. *Tetrahedron Lett.* **2009**, *50*, 5474–5478.
10. (a) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119–122; (b) Jones, G.; Stanforth, S. P. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, NY, 1997; Vol. 49, pp 1–330; (c) Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015–4034.
11. (a) Lilienkampf, A.; Johansson, M. P.; Wahala, K. *Org. Lett.* **2003**, *5*, 3387–3890; (b) Tang, X.-Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 8317–8320; (c) Perumal, P. T. *Indian J. Heterocycl. Chem.* **2001**, *11*, 1–8; (d) Pan, W.; Dong, D.-W.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421–2423; (e) Wang, K.-W.; Xiang, D.-X.; Dong, D.-W. *Org. Lett.* **2008**, *10*, 1691–1694; (f) Jones, G.; Stanforth, S. P. *Org. React.* **2000**, *56*, 355–659; (g) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659–3762; (h) Chen, L.; Zhao, Y.-L.; Liu, Q.; Cheng, C.; Piao, C.-R. *J. Org. Chem.* **2007**, *72*, 9259–9263; (i) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504–9507; (j) Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223–9225; (k) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. D. *J. Org. Chem.* **2007**, *72*, 8593–8596; (l) Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966–3975.
12. (a) Sivaprasad, S.; Sridhar, R.; Perumal, P. T. *J. Heterocycl. Chem.* **2006**, *43*, 389–394; (b) Kumar, K. H.; Perumal, P. T. *Chem. Lett.* **2005**, *34*, 1346–1347; (c) Kumar, H. K.; Selvi, S.; Perumal, P. T. *J. Chem. Res.* **2004**, 218–219; (d) Sridhar, R.; Perumal, P. T. *Synth. Commun.* **2003**, *33*, 607–611. 1483–1488; (e) Selvi, S.; Perumal, P. T. *Indian J. Chem., Sect. B* **2002**, *41B*, 1887–1893; (f) Selvi, S.; Perumal, P. T. *Synth. Commun.* **2001**, *31*, 2199–2202; (g) Amaresh, R. R.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 2269–2274; (h) Selvi, S.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 3925–3928; (i) Selvi, S.; Perumal, P. T. *Indian J. Chem., Sect. B* **2000**, *39B*, 163–165; (j) Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1999**, *55*, 8083–8094; (k) Perumal, P. T.; Majo, V. J.; Anand, R. V. *Indian J. Chem., Sect. B* **1999**, *38*, 763–765; (l) Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 14327–14340; (m) Amaresh, R. R.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3837–3840; (n) Majo, V. J.; Perumal, P. T. *J. Org. Chem.* **1998**, *63*, 7136–7142; (o) Selvi, S.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 6263–6266; (p) Majo, V. J.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 6889–6892; (q) Majo, V. J.; Perumal, P. T. *Tetrahedron Lett.* **1996**, *37*, 5015–5018; (r) Balasundaram, B.; Venugopal, M.; Perumal, P. T. *Tetrahedron Lett.* **1993**, *34*, 4249–4252.
13. Yilmaz, V. T.; Topcu, Y. *Thermochim. Acta* **1997**, *307*, 143–147.
14. (a) Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **2000**, *41*, 4713–4716; (b) DeRuiter, J.; Carter, D. A.; Arledge, W. S.; Sullivan, P. J. *J. Heterocycl. Chem.* **1987**, *24*, 149–153; (c) Braña, M. F.; Gradillas, A.; Ovalles, A. G.; López, B.; Acero, N.; Llinares, F.; Mingarro, D. M. *Bioorg. Med. Chem.* **2006**, *14*, 9–16.
15. Tsai, J.-Y.; Huang, L.-J.; Chang, C.-S.; Chen, H.-S.; Lin, S.-K.; Wong, F. F.; Huang, Y.-F.; Kuo, S.-C. *Tetrahedron* **2008**, *64*, 11751–11755.
16. (a) Srivastava, V.; Negi, A. S.; Kumar, J. K.; Gupta, M. M. *Steroids* **2006**, *71*, 632–638; (b) El-Shishtawy, R. M.; Almeida, P. *Tetrahedron* **2006**, *62*, 7793–7798.
17. Akila, S.; Selvi, S.; Balasubramaian, K. *Tetrahedron* **2001**, *57*, 3465–3469.
18. Yamada, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1083–1085.
19. Dougan, M. L.; Chin, J. L.; Solt, K.; Hansen, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4153–4156.