Tetrahedron 67 (2011) 3863–3867

Contents lists available at ScienceDirect

Tetrahedron

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

Novel Vilsmeier-type methylenation for synthesis of dipyrazolylmethane derivatives using formamide or *N*-methylformamide

Fung Fuh Wong *, Yu-Ying Huang

Graduate Institute of Pharmaceutical Chemistry, China Medical University, No. 91 Hsueh-Shih Rd., Taichung 40402, Taiwan, ROC

ARTICLE INFO

Article history:
Received 27 December 2010
Received in revised form 23 March 2011
Accepted 25 March 2011
Available online 31 March 2011

Keywords:
Vilsmeier-type reaction
Methylenation
Dipyrazolylmethane
Pyrazolone
Formylation

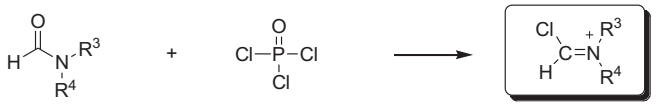
ABSTRACT

A novel Vilsmeier-type methylenation for synthesis of dipyrazolylmethanes was developed by reacting pyrazolones with formamide or *N*-methylformamide in the presence of phosphorous oxychloride $POCl_3$ coupling agent. This method can efficiently provide a series of dipyrazolylmethane derivatives as the main products in excellent yields without the formylated products. Our experimental result was different with the classical Vilsmeier-type reaction.

1. Introduction

In 1927, the Vilsmeier or Vilsmeier–Haack reaction was first published and applied to an immense variety of substrates, from substituted benzenes to complex heterocycles.[1,2] The classical Vilsmeier reagent, involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt, which results from the reaction between an acid chloride (e.g., $POCl_3$, $SOCl_2$ $(COCl)_2$, and $COCl_2$) and an amide, usually DMF (see Scheme 1). When DMF was used in the reaction, the product of Vilsmeier reaction is an aldehyde. Thus, Vilsmeier reaction is often called as Vilsmeier formylation.[3]

Vilsmeier reagent serves not only as a formylating agent,[3] but also as an activating reagent for carboxylic acids to give esters,[4] amides[5] and acid chlorides,[6] and for alcohols to give alkyl chlorides,[7] esters,[8] alkyl aryl sulfides,[9] and imides.[10] Since, it is now used as a powerful organic synthetic tool for the formylation[1–3] or construction[11,12] of many aromatic and heterocyclic compounds. Herein, we have a lot of interests in the study of reactive ability of various amides.[13] Thus, we attempted to investigate the reactivity of pyrazolones with various amides including formamide, *N*-methylformamide, *N*,*N*-dimethylformamide (DMF), and *N*,*N*-diethylformamide (DEF). Eventually, we have successfully provided the new Vilsmeier-type methylenation to prepare dipyrazolylmethane derivatives by using formamide or *N*-methylformamide as



Scheme 1.

reaction solvent, which are important key functional[14] or bioactive materials.[15]

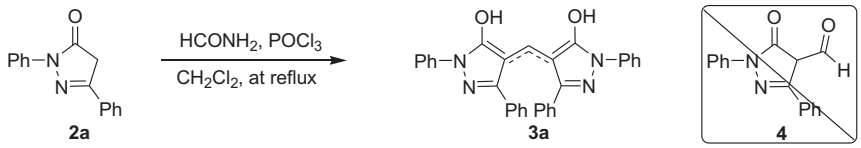
2. Result and discussion

5-Pyrazolone derivatives were prepared as the starting materials by following the previous literature reported procedure via tandem condensation and thermal cyclization.[16] In this newly developed method, we chose 1,3-diphenyl-1*H*-pyrazol-5-one (**2**) as the model for the selection of best conditions for the new Vilsmeier-type methylenation reaction (see Scheme 1). To search for optimum conditions and establish a reproducible procedure, compound **2** was allowed to react with formamide (3.0 equiv) and phosphorous oxychloride ($POCl_3$, 5.0 equiv) in CH_2Cl_2 solution at reflux (~50–60 °C) within 0.5–1 h. After aqueous worked-up and purification by column chromatography on silica gel, we isolated the corresponding methylenated product **3** in 96% yield without the formylated product **4** (see Scheme 2).

To examine the solvent effects, we applied the same condition to 1,3-diphenyl-1*H*-pyrazol-5-one **2a** and various amides containing *N*-methylformamide *N*,*N*-dimethylformamide (DMF), and

* 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).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.03.089



Scheme 2.

N,*N*-diethylformamide (DEF) in the presence of $POCl_3$. Based on the experimental result, up to 86% yields of the formylated product **4** have been achieved when the pyrazolone **2a** was reacted with DMF and DEF (see entries 3 and 4 of Table 1). When pyrazolone **2a** was used toward *N*-methylformamide within 0.5–1.0 h, we also found the methylenated product **3a** was obtained in 71% yield without the formylated product. Otherwise, the starting material **2a** was recovered in same condition (see entry 2 in Table 1).

Table 1
The amide agents study of new Vilsmeier methylenation via 1,3-diphenyl-1*H*-pyrazol-5-one (**2a**)

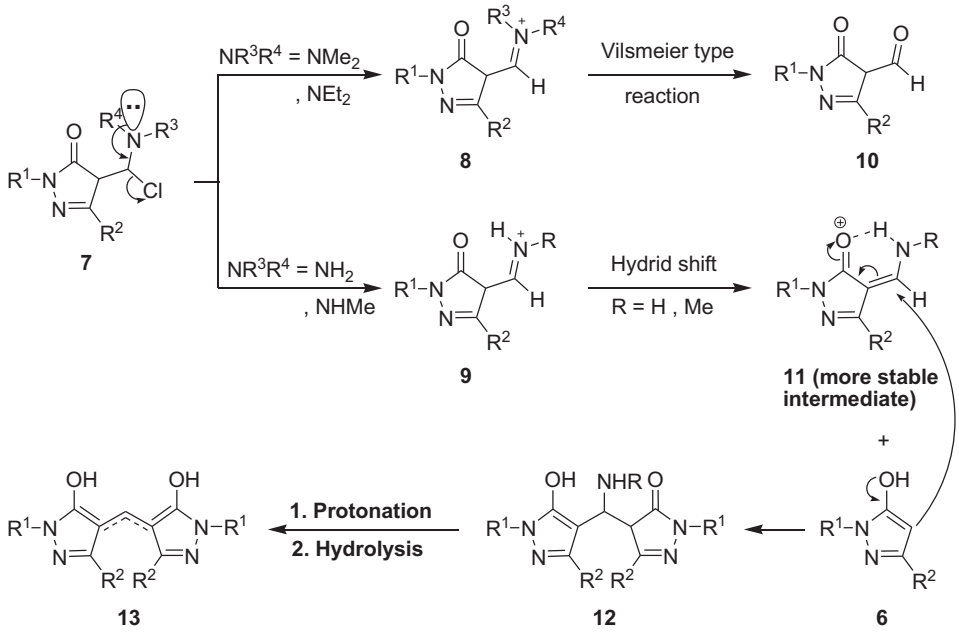
Entry	$HCONR^3R^4$		Products			
	R^3	R^4	Dipyrazoylmethanes	Yields (%)	4-Formylpyrazolones	Yields (%)
1	H	H	**3a**	96	—	—[a]
2	Me	H	**3a**	71	—	—[a]
3	Me	Me	—	—[b]	**4**	86
4	Et	Et	—	—[b]	**4**	89

[a] The formulated product was not detectable.
[b] The methylenated product was not detectable.

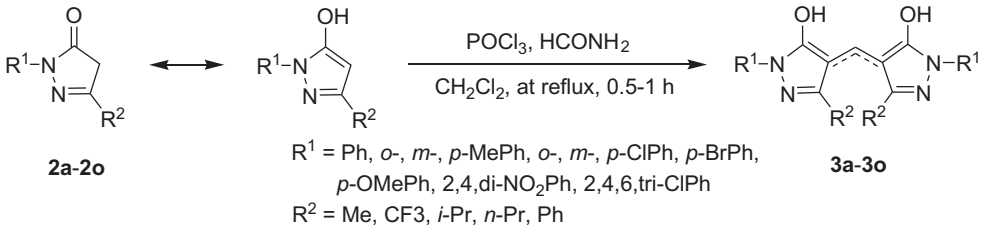
Furthermore, we propose the plausible mechanism shown in Schemes 1 and 3, and accounts for the difference between the classical Vilsmeier formylation and the newly developed Vilsmeier methylenation. Firstly, amide agents were fast reacted with phosphorous oxychloride $POCl_3$ to form the reactive halomethyleniminium salts **1** in situ and side product HCl (see Scheme 1).[17] In the presence of acidic species including excess amount of $POCl_3$ and HCl, pyrazolones **5** performed isomerization to convert to pyrazoles **6**. Further, pyrazoles **6** was reacted with the reactive iminium species **1** to generate the imidination intermediate **8** and **9** through the reactive species **7** (see Scheme 3). For *N*,*N*-dimethylformamide (DMF) and *N*,*N*-diethylformamide (DEF) as the reactants, the Vilsmeier formylation was very smooth to generate the corresponding formylated product **10**.

When formamide and *N*-methylformamide, were used in this procedure, the imidination intermediate **9** was effectively transferred to the more stable aminomethylidene derivatives **11** according to the formation of the intramolecular hydrogen-bonding. Consequently, the Michel addition of intermediate **11** with another equivalent of pyrazole **6** leads to dipyrazolyl-aminomethane **11**. After the protonation and hydrolysis two reactions were completed, the final product **13** was usefully obtained in excellent yield (see Scheme 3).

For the further investigation of the reliable procedure of the new developed Vilsmeier-type methylenation, we also extended the pyrazolone scopes to 3-phenyl-pyrazolones **2b**–**i** bearing *N*1-substituted aryl group with various mono-substituents, including *o*-, *m*-, *p*-ClPh, *o*-, *m*-, *p*-MePh, *p*-BrPh, and *p*-OMePh with formamide. When employing the condition was shown in Scheme 4, all of substrates can be successfully converted to the corresponding methylenation dipyrazolylmethane products **3b**–**i** in ≥84% yields (see Table 2). 1-(2,4-Dinitrophenyl)-3-phenyl-1Hpyrazol-5-one (**2j**) own two strong withdrawing NO_2 groups in *N*1-aromatic ring, the corresponding dipyrazolylmethanes **3j** did not detected in the same condition. 1-(2,4,6-Trichlorophenyl)-3-phenyl-1*H*-pyrazol-5-one (**2k**) having three chloro-substituents was also reacted with $HCONH_2$ and produced the corresponding dipyrazolylmethanes **3k** in 87% yield (see Table 2). The dipyrazolylmethanes **3a**–**k** were reported and fully characterized by spectroscopic methods.[14a–d] For example, compound **2a** presented a peak at δ 8.51 ppm for $-C^1H{=}C$ in ^1H NMR. In ^{13}C NMR spectrum, compound **2a** possessed characterization absorptions at δ 109.5 ppm for methylene carbon $-{}^{13}CH{=}C$. The IR absorptions of **2a** showed peaks at 2109 cm^{-1} for



Scheme 3.



Scheme 4.

Table 2
The result of synthesis of dipyrazolylmethanes **3a**–**o**

Pyrazolones			Dipyrazoylmethanes	
Substrates	*N*1-R^1	*C*3-R^2	Products	Yields (%)
2a	Ph	Ph	**3a**	96
2b	*o*-MePh	Ph	**3b**	90
2c	*o*-ClPh	Ph	**3c**	92
2d	*m*-MePh	Ph	**3d**	94
2e	*m*-ClPh	Ph	**3e**	94
2f	*p*-MePh	Ph	**3f**	96
2g	*p*-ClPh	Ph	**3g**	95
2h	*p*-BrPh	Ph	**3h**	93
2i	*p*-OMePh	Ph	**3i**	84
2j	2,4-Di-NO_2Ph	Ph	**3j**	Not detectable
2k	2,4,6-Tri-ClPh	Ph	**3k**	87
2l	Ph	Me	**3l**	93
2m	Ph	CF_3	**3m**	90
2n	Ph	*n*-Pr	**3n**	92
2o	Ph	*i*-Pr	**3o**	91

stretching of the –CH=C group and at 3291 cm^{-1} for stretching of the –OH group.

For the further investigation of the substituent effects, we extended this newly developed method toward 1-phenyl-3-substituted pyrazolones **2l**–**o**, which contained Me, CF_3, *n*-Pr, or *i*-Pr groups at the C-3 position on pyrazolic ring. The corresponding dipyrazolylmethane products **3l**–**o** were obtained in 90–93% yields (see Table 2). Therefore, this efficient Vilsmeier-type methylenation method can also be successfully applied to synthesize a series of dipyrazolylmethane derivatives **3a**–**o**.

To search for the optimum condition for *N*-methylformamide as reaction solvent, we used 1,3-diphenyl-1*H*-pyrazol-5-one **2a** as mold and tried to prolong the reaction time from 1.0 h to 2.0 h. Fortunately, the isolated yield of desired product **3a** was promoted from 71% to 95% (see Scheme 4 and Table 3). As a result, the optimum condition was extended 1,3-disubstituted-1*H*-pyrazol-5-ones **2b**, **c**, **h**, **l**, and **o** with *N*-methylformamide. The desired dipyrazolylmethane products **3b**, **c**, **h**, **l**, and **o** were also obtained in good to excellent yields (82–94%, see Table 3). However, the formylated compounds were also not detectable using *N*-methylformamide as the reaction solvent.

In conclusion, we have successfully developed the newly Vilsmeier-type methylenation method by treating various 1,3-disubstituted pyrazolones with formamide or *N*-methylformamide and $POCl_3$ coupling agent. Based on our experimental data, the result was different with the classical Vilsmeier-type reaction and the yielding dipyrazolylmethane products without formylated compounds seemed to determinate the solvents involved formamide and *N*-methylformamide.

Table 3
The results of the pyrazolones reacted with *N*-methylformamide in the presence of $POCl_3$

Pyrazolones (**2a**–**c**, **h**, **l**, and **o**)			Reaction time (h)	Dipyrazoylmethanes	
S.M.	*N*1-R^1	*C*3-R^2		No.	Yields (%)
2a	Ph	Ph	~1.0	**3a**	71
2a	Ph	Ph	2.0	**3a**	95
2b	*o*-MePh	Ph	2.0	**3b**	90
2c	*p*-OMePh	Ph	2.0	**3c**	82
2h	*p*-BrPh	Ph	2.0	**3h**	91
2l	Ph	Me	2.0	**3l**	94
2o	Ph	*i*-Pr	2.0	**3o**	91

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 Acros Chemical Co: ethyl butyrylacetate, ethyl acetoacetate, 2,4-dinitrophenyl hydrazine, formamide, phenylhydrazine, *o*-tolylhydrazine hydrochloride, *m*-tolylhydrazine hydrochloride, and *p*-tolylhydrazine hydrochloride. 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, and 4-methoxyphenylhydrazine hydrochloride were purchased from Alfa Chemical Co. Phosphorylchloride was 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 wavenumbers 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 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.

3.2. Standard procedure for the synthesis of dipyrazolylmethane derivatives (3a–i and 3k–o)

The reliable procedure involved the treatment of pyrazolones (**3a**–**i** and **3k**–**o**, 1.0 equiv) with catalytic amount of $POCl_3$ (~3 equiv) in formamide 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 residue solution was purified by column chromatography on silica gel to give the corresponding dipyrazolylmethane products (**3a**–**i** and **3k**–**o**) in 82–96% yields.

*3.2.1. 4,4′-Methylidenebis(1,3-diphenyl-2-pyrazolone) (**3a**).* 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.

*3.2.2. 4,4′-Methylidenebis[1-(2′-methylphenyl)-3-phenyl-2-pyrazolone] (**3b**).* 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.

*3.2.3. 4,4′-Methylidenebis[1-(2′-chlorophenyl)-3-phenyl-2-pyrazolone] (**3c**).* Mp (recrystallized from ethanol) 198–199 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 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 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 $C_{31}H_{20}Cl_2N_4O_2$: C, 67.52; H, 3.66; N, 10.16. Found: C, 67.49; H, 3.68; N, 10.13.

*3.2.4. 4,4′-Methylidenebis[1-(3′-methylphenyl)-3-phenyl-2-pyrazolone] (**3d**).* Mp (recrystallized from ethanol) 190–192 °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, 77.61; H, 5.09; N, 10.95.

*3.2.5. 4,4′-Methylidenebis[1-(3′-chlorophenyl)-3-phenyl-2-pyrazolone] (**3e**).* Mp (recrystallized from ethanol) 190–192 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 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 26.3 (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 $C_{31}H_{20}Cl_2N_4O_2$: C, 67.52; H, 3.66; N, 10.16. Found: C, 67.54; H, 3.65; N, 10.18.

*3.2.6. 4,4′-Methylidenebis[1-(4′-methylphenyl)-3-phenyl-2-pyrazolone] (**3f**).* Mp (recrystallized from ethanol) 151–152 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 2.27 (s, 3H, CH_3), 7.40 (m, 2H, ArH), 7.48 (m, 2H, ArH), 7.78 (m, 2H, ArH), 7.99 (m, 2H, ArH); ^{13}C NMR (50 MHz, CD_3OD) δ 39.6, 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 $C_{33}H_{26}N_4O_2$: C, 77.63; H, 5.13; N, 10.97. Found: C, 77.62; H, 5.16; N, 10.94.

*3.2.7. 4,4′-Methylidenebis[1-(4′-chlorophenyl)-3-phenyl-2-pyrazolone] (**3g**).* Mp (recrystallized from ethanol) 163–164 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.40 (m, 2H, ArH), 7.48 (m, 2H, ArH), 7.78 (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 $C_{31}H_{20}Cl_2N_4O_2$: C, 67.52; H, 3.66; N, 10.16. Found: C, 67.56; H, 3.62; N, 10.15.

*3.2.8. 4,4′-Methylidenebis[1-(4′-bromophenyl)-3-phenyl-2-pyrazolone] (**3h**).* Mp (recrystallized from ethanol) 183–184 °C; ^{1}H 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.

*3.2.9. 4,4′-Methylidenebis[1-(4′-methoxylphenyl)-3-phenyl-2-pyrazolone] (**3i**).* 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.

*3.2.10. 4,4′-Methylidenebis[1-(2′-4′-6′-trichorophenyl)-3-phenyl-2-pyrazolone] (**3k**).* Mp (recrystallized from ethanol) 144–146 °C; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.34–7.43 (m, 3H, ArH), 7.68–7.72 (m, 4H, ArH); ^{13}C NMR (50 MHz, CD_3OD) δ 47.1, 125.4 (2× CH), 128.4 (2× CH), 128.6 (2× CH), 129.1 (2× CH), 130.6, 132.1, 136.4, 152.8, 156.9, 171.0; IR (KBr) 3075 (m), 1732 (s, C═O), 1559 (s, C–N), 1461 (s), 1380 (m), 1157 (m), 1097 (m), 983 (m), 829 (m) cm^{-1}. Anal. Calcd for $C_{31}H_{16}Cl_6N_4O_2$: C, 54.02; H, 2.34; N, 8.13. Found: C, 54.03; H, 2.36; N, 8.11.

*3.2.11. 4,4′-Methylidenebis(3-methyl-1-phenyl-2-pyrazolone) (**3l**).* Mp (recrystallized from ethanol) 127–129 °C; ^{1}H 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, 2.2 Hz, ArH), 7.81 (d, 2H, J = 7.8 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 43.1118.9 (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.

*3.2.12. 4,4′-Methylidenebis(1-phenyl-3-trifluoromethyl-2-pyrazolone) (**3m**).* Mp (recrystallized from ethanol) 194–196 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.61 (s, 1H, ArH), 7.66 (d, 2H, J = 7.8 Hz, ArH), 7.80 (d, 2H, J = 7.6 Hz, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 85.6, 122.3, 127.2, 129.1, 137.7, 140.4 (q, J = 37.6 Hz), 153.7. Anal. Calcd for $C_{21}H_{12}F_6N_4O_2$: C, 54.09; H, 2.59; N, 12.01. Found: C, 54.12; H, 2.57; N, 12.59.

*3.2.13. 4,4′-Methylidenebis(3-n-propyl-1-phenyl-2-pyrazolone) (**3n**).* Mp (recrystallized from ethanol) 201–202 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (d, J = 7 Hz, 6H), 2.79 (m, 1H), 7.21 (t, J=7.4 Hz, 1H), 7.41 (dd, J=7.4, 8 Hz, 2H), 7.92 (d, J=8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 31.2, 40.3, 119.3, 125.4, 129.2, 138.7, 164.7, 171.1; 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, 72.47; H, 6.36; N, 13.49.

*3.2.14. 4,4′-Methylidenebis(3-isopropyl-1-phenyl-2-pyrazolone) (**3o**).* Mp (recrystallized from ethanol) 101–103 °C; ^{1}H 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, CDCl3) 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.

Acknowledgements

We are grateful to the China Medical University (CMU99-S—18) and the National Science Council of Republic of China for financial support (NSC-99-2320-B-039-014-MY3).

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.089.

References and notes

1. (a) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119—125; (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—4021.
2. (a) Lilienkampf, A.; Johansson, M. P.; Wahala, K. *Org. Lett.* **2003**, *5*, 3387—3391; (b) Tang, X.-Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 8317—8322; (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—2426; (e) Wang, K.-W.; Xiang, D.-X.; Dong, D.-W. *Org. Lett.* **2008**, *10*, 1691—1697; (f) Jones, G.; Stanforth, S. P. *Org. React.* **2000**, *56*, 355—659; (g) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659—3667; (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—9511; (j) Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223—9227; (k) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. D. *J. Org. Chem.* **2007**, *72*, 8593—8601; (l) Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966—3973.
3. (a) Campaigne, E.; Archer, W. L. *J. Am. Chem. Soc.* **1953**, *75*, 989—996; (b) Treihs, W.; Neupert, H. J.; Hiebsch, J. *Chem. Ber.* **1959**, *92*, 141—145; (c) Damodiran, M.; Panneer, N.; Paramasivan, S.; Perumal, T. *Tetrahedron Lett.* **2009**, *50*, 5474—5478.
4. (a) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1993**, *34*, 7483—7486; (b) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2249—2253.
5. Zaoral, M.; Arnold, Z. *Tetrahedron Lett.* **1960**, *1*, 9—13.
6. Eilingsfeld, H.; Seefelder, M.; Weidinger, H. *Angew. Chem.* **1960**, *72*, 836—841.
7. Hepburn, D. R.; Hudson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 754—762.
8. (a) Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Koike, N.; Procopiou, P. A. *J. Org. Chem.* **1998**, *63*, 6273—6279; (b) Barrett, A. G. M.; Koike, N.; Procopiou, P. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1403—1412.
9. Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 1612—1618.
10. Barrett, A. G. M.; Braddock, D. C.; James, R. A.; Procopiou, A. *Chem. Commun.* **1997**, 433—438.
11. (a) Savitha, G.; Perumal, P. T. *Tetrahedron Lett.* **2007**, *48*, 2943—2947; (b) Damodiran, M.; Kumar, R. S.; Sivakumar, P. M.; Doble, M.; Perumal, P. T. *J. Chem. Sci.* **2009**, *121*, 65—72; (c) Karthikeyan, K.; Perumal, P. T.; Etti, S.; Shanmugam, G. *Tetrahedron* **2007**, *63*, 10581—10586; (d) Selvam, N. P.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2972—2978; (e) Selvam, N. P.; Saranya, S.; Perumal, P. T. *Can. J. Chem.* **2008**, *86*, 32—36; (f) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2007**, *48*, 6785—6791; (g) Selvam, N. P.; Shanthi, G.; Perumal, P. T. *Can. J. Chem.* **2007**, *84*, 989—995; (h) Thirumurugan, P.; Muralidharan, D.; Perumal, P. T. *Dyes Pigm.* **2009**, *81*, 245—251; (i) Thirumurugan, P.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 4145—4152; (j) Damodiran, M.; Muralidharan, D.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3611—3617.
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—1352; (c) Kumar, H. K.; Selvi, S.; Perumal, P. T. *J. Chem. Res.* **2004**, 218—226; (d) Sridhar, R.; Perumal, P. T. *Synth. Commun.* **2003**, *33*, 1483—1488 and 607–611; (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—2208; (g) Amaresh, R. R.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 2269—2274; (h) Selvi, S.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 3925—3936; (i) Selvi, S.; Perumal, P. T. *Indian J. Chem., Sect. B* **2000**, *39B*, 163—169; (j) Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1999**, *55*, 8083—8090; (k) Perumal, P. T.; Majo, V. J.; Anand, R. V. *Indian J. Chem., Sect. B* **1999**, *38*, 763—772; (l) Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 14327—14333; (m) Amaresh, R. R.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3837—3842; (n) Majo, V. J.; Perumal, P. T. *J. Org. Chem.* **1998**, *63*, 7136—7330; (o) Selvi, S.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 6263—6267; (p) Majo, V. J.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 6889—6992; (q) Majo, V. J.; Perumal, P. T. *Tetrahedron Lett.* **1996**, *37*, 5015—5019; (r) Balasundaram, B.; Venugopal, M.; Perumal, P. T. *Tetrahedron Lett.* **1993**, *34*, 4249—4256.
13. Yilmaz, V. T.; Topcu, Y. *Thermochim. Acta* **1997**, *307*, 143—149.
14. (a) Azev, Y. A.; Shorshnev, S. V.; Golomolzin, B. V. *Tetrahedron Lett.* **2009**, *50*, 2899—2903; (b) Azev, Y. A.; Shorshnev, S. V. *Chem. Heterocycl. Compds.* **2009**, *45*, 115—116; (c) Wanga, J.; Caoa, W.-F.; Sua, J.-H.; Tian, H.; Huangb, Y.-H.; Sun, Z.-R. *Dyes Pigm.* **2003**, *57*, 171—179; (d) Shermolovich, Y. G.; Yemets, S. V. *J. Fluorine Chem.* **2000**, *101*, 111—116; (e) Azev, Y. A.; Neunhoeffer, H.; Foro, S.; Lindner, H. J.; Shorshnev, S. V. *Mendeleev Commun.* **1995**, *5*, 229—231.
15. Radi, M.; Bernardo, V.; Bechi, B.; Castagnolo, D.; Pagano, M.; Botta, M. *Tetrahedron Lett.* **2009**, *50*, 6572—6575.
16. (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.
17. (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.