Monatsh Chem (2013) 144:879–884
DOI 10.1007/s00706-012-0901-7

ORIGINAL PAPER

A facile access to 1,3,4-trisubstituted pyrazoles via 1,3-dipolar cycloaddition of 3-arylsydnones with α,β-unsaturated ketones

Fei Chen · Fang-Ming Liu · Hai Shi · Sen-Lin Chen

Received: 7 March 2012 / Accepted: 9 December 2012 / Published online: 31 January 2013

Abstract A novel one-pot synthesis of 1,3,4-trisubstituted pyrazoles has been accomplished by 1,3-dipolar cycloaddition of α,β-unsaturated ketones and 3-arylsydnones in dry xylene. The structural identities of these compounds were confirmed on the basis of IR, NMR, mass spectral, and X-ray analysis.

Keywords Pyrazole · Crystal structure · 1,3-Dipolar cycloaddition

Introduction

The synthesis of pyrazoles has received considerable attention due to their versatile biological activities, e.g., anti-inflammatory, anticoagulant, antibacterial, and antitumor agents, CDK inhibitors, and cyclooxygenase-2 (Cox-2) inhibitors [1–7]. The pyrazole motif also makes up the core structure of some well-known drugs (e.g., Viagra, Acomplia, and Celebrex) [8].

Conventional approaches for the preparation of substituted pyrazoles involve either the construction of two C–N bonds by condensation of hydrazines with 1,3-dicarbonyl compounds (or their 1,3-dielectrophilic equivalents) or the generation of one C–N bond and one C–C bond by intermolecular [3+2]-cycloadditions of 1,3-dipoles to dipolarophiles. Each method has its own scope and efficiency limitations.

Recently, Fustero et al. [9] published a review of the synthetic methods leading to pyrazoles. The most commonly used method for the preparation of pyrazoles involves the cyclocondensation of an appropriate hydrazine (mainly arylhydrazines), which acts as a double nucleophile, with a three-carbon unit featuring two electrophilic carbons in a 1,3-relationship, such as 1,3-dicarbonyl, α,β-unsaturated carbonyl compounds [3, 10–12], β-enaminones, or related compounds [13–15] (Scheme 1). Compared to the classic cyclocondensation reaction between hydrazines and 1,3-diketones, in which the regioselectivity relies on the different reactivity of the two carbonyl groups, 1,3-dipolar cycloadditions are intrinsically more regioselective owing to the significant electronegativity difference between the N and C atoms of the substrate. Three main classes of 1,3-dipoles have been used as the [CNN] fragment for the synthesis of the pyrazole skeleton, namely diazoalkanes, nitrilimines, and azomethine imines; the [CC] fragment would come from alkenes or alkynes. Sydnones are relatively stable mesoionic compounds that can react as azomethine imine-type dipoles. Recently, the 1,3-dipolar cycloaddition of sydnones to acetylenic ketones to afford pyrazoles was reported [16]. We found that replacing acetylenic ketones with unsymmetrical propenones (α,β-unsaturated ketones) can also afford 1,3,4-trisubstituted pyrazoles.

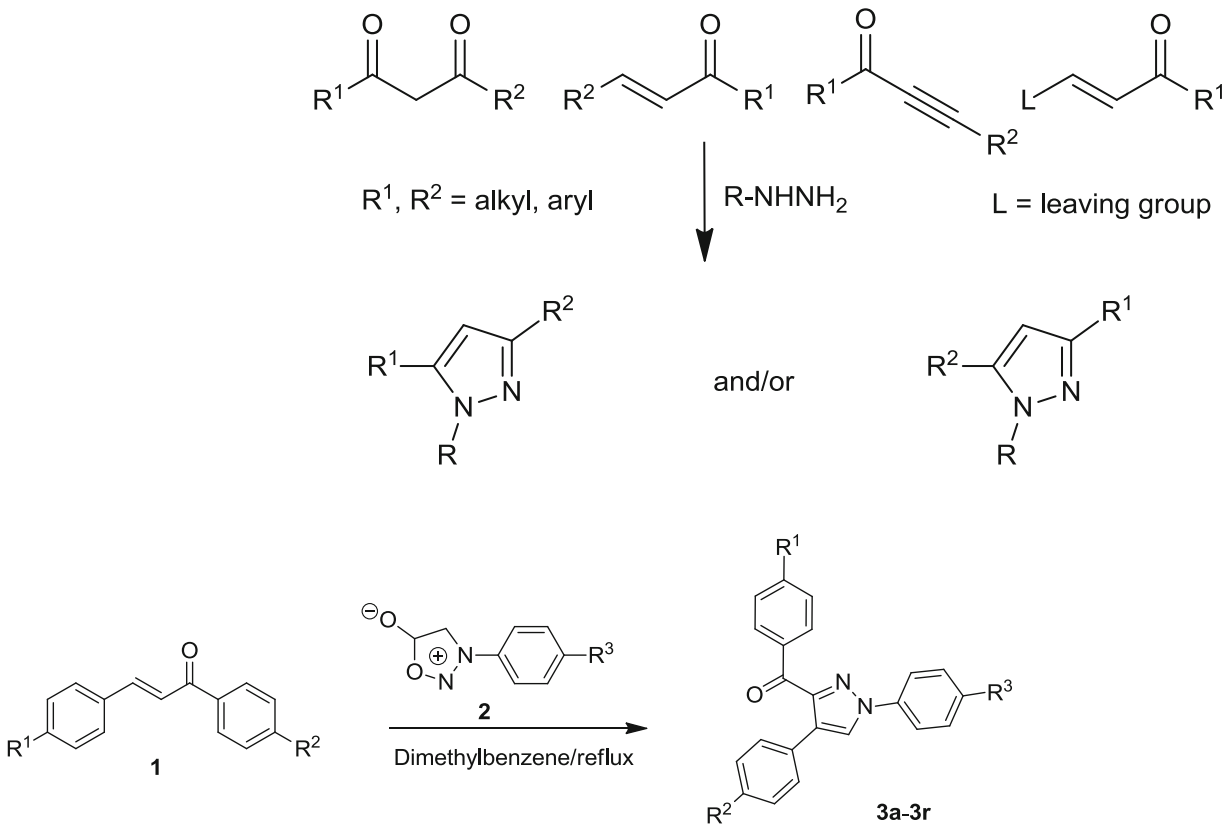
Encouraged by all these facts and in continuation of our previous work on the synthesis of novel heterocycles employing 1,3-dipolar cycloaddition, we herein report a simple and convenient method for one-pot synthesis of pyrazoles. The synthetic route is shown in Scheme 2.

F. Chen (✉) · F.-M. Liu
College of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, People's Republic of China
e-mail: cf8156lei@sina.com

F.-M. Liu
e-mail: fmliu859@sohu.com

H. Shi · S.-L. Chen
College of Materials and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, People's Republic of China

Scheme 1



	3a	3b	3c	3d	3e	3f	3g	3h	3i
R^1=	H	OMe	Cl	H	OMe	Cl	H	OMe	Cl
R^2=	H	H	H	Me	Me	Me	H	H	H
R^3=	H	H	H	H	H	H	Me	Me	Me

	3j	3k	3l	3m	3n	3o	3p	3q	3r
R^1=	H	OMe	Cl	H	OMe	Cl	H	OMe	Cl
R^2=	Me	Me	Me	Cl	Cl	Cl	Cl	Cl	Cl
R^3=	Me	Me	Me	H	H	H	Me	Me	Me

Scheme 2

Results and discussion

As part of our ongoing development of efficient protocols for the preparation of pyrazole derivatives, this study reports for the first time the regiospecific synthesis of 1,3,4-trisubstituted pyrazoles by 1,3-dipolar cycloaddition of α,β-unsaturated ketones [17] and 3-arylsydnones [18] in refluxing dry xylene. All of the products were separated by column chromatography on silica gel and characterized by IR, NMR, mass spectral, and X-ray analysis.

The ^{1}H NMR of compound **3** contained one singlet approximately at 8.25 ppm corresponding to the proton of pyrazole. In addition, aromatic protons appeared in the range 7.90–6.86 ppm. Their infrared spectra contained strong absorption bands for C=O and C=N double bonds at 1,632 and 1,583 cm^{-1}. Also, in all cases molecular ion peaks of all target compounds were observed in the mass spectra.

The structure of the crystal **3q** is displayed in Fig. 1. The pyrazole ring is characterized by the torsion angles (enumerated clockwise and starting with N(1)–N(2)–C(7)–C(8)): 1.0(4)°, −1.1(4)°, −176.7(3)°, 0.2(4)°, −0.5(4)°, and it adopts an envelope conformation with atom C(7) deviating from the plane defined by N(1), N(2), C(8), and C(9) of −0.0139 Å. In addition, the dihedral angle and the distances of the aromatic ring Cg2 (C(1)–C(6)), Cg3 (C(11)–C(12)–C(13)–C(14)–C(16)–C(17)), Cg4 (C(18)–C(19)–C(20)–C(21)–C(23)–C(24)), and pyrazole ring Cg1 are 23.73°, 4.015 Å; 54.73°, 4.759 Å; and 29.88°, 3.930 Å, respectively. Detailed information about the crystal data and structure determination is summarized in Table 1. Selected bond lengths and angles are tabulated in Table 2. The crystal is stabilized by weak hydrogen bonds which are described in Table 3.

In conclusion, we have obtained a series of 1-(4-substituted phenyl)-3-(4-substituted benzoyl)-4-(4-substituted phenyl)pyrazole derivatives **3a**–**3r** by 1,3-dipolar cycloaddition reaction. The molecular conformation of the title compounds was further confirmed by X-ray analysis of compound **3q** as a typical example.

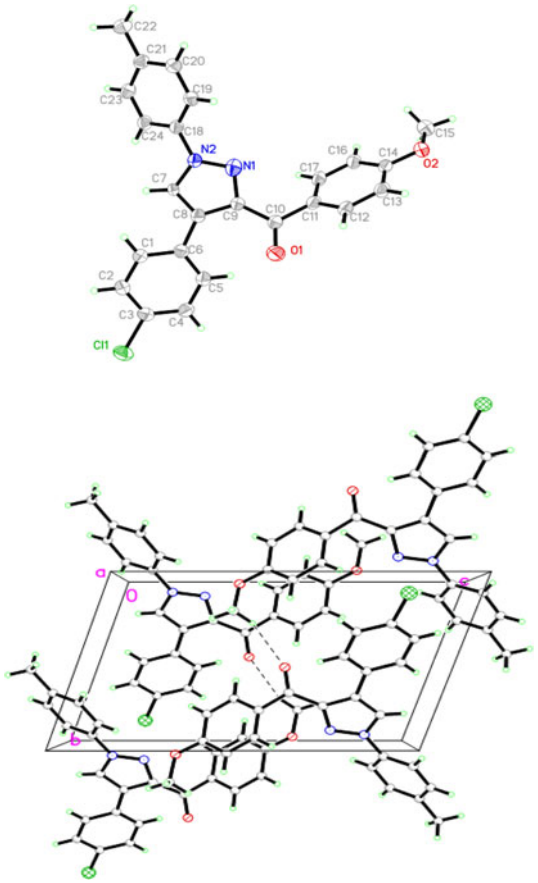


Fig. 1 Molecular structure of **3q**

Table 1 Crystal data and structure refinement for compound **3q**

Empirical formula	$C_{24}H_{19}ClN_2O_2$
Formula weight	402.86
Temperature/K	293(2)
Crystal system	Triclinic
Space group	*P*-1
a/Å	8.5673(8)
b/Å	8.7058(7)
c/Å	14.1278(13)
α/°	107.109(2)
β/°	90.274
γ/°	98.381(2)
V/Å^3	995.07(15)
Z	2
D_{calc}/g m^{-3}	1.345
Crystal size/mm	0.48 × 0.34 × 0.20
θ range/°	3.02–27.47
μ/mm^{-1}	0.215
Reflections collected	9,773
Data/restraints/parameters	4,514/0/263
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.1072$, $\omega R_2 = 0.2519$
R indices (all data)	$R_1 = 0.0666$, $\omega R_2 = 0.1924$

Table 2 Selected bond lengths/Å and angles/° of compound **3q**

N(1)–C(9)	1.392(5)	N(1)–N(2)–C(7)	111.5(3)
N(1)–N(2)	1.348(4)	N(1)–N(2)–C(18)	127.7(3)
N(2)–C(7)	1.359(4)	N(2)–N(1)–C(9)	107.2(3)
N(2)–C(18)	1.423(4)	N(1)–C(9)–C(8)	104.1(3)
C(6)–C(8)	1.489(4)	C(7)–N(2)–C(18)	120.8(2)
C(7)–C(8)	1.316(4)	C(7)–C(8)–C(9)	111.0(3)
C(8)–C(9)	1.422(4)	C(8)–C(9)–C(10)	132.4(3)
C(9)–C(10)	1.464(4)	C(9)–C(8)–C(6)	131.8(3)
O(1)–C(10)	1.228(4)	C(9)–C(10)–C(11)	118.6(3)
O(2)–C(15)	1.413(5)	O(1)–C(10)–C(9)	121.6(3)

Table 3 Intermolecular and intramolecular interactions/Å in compound **3q**

D–H···A	D–H	H···A	D···A	D–H···A
Intermolecular interactions/Å in the compound				
C(5)–H(5A)···O(1)	0.93	2.44	3.024(4)	121
Intramolecular interactions/Å in the compound				
C(15)–H(15B)···O(1)[a]	0.96	2.46	3.330(5)	151
C(2)–H(2A)···Cg(4)[b]	49	2.93	3.597(4)	130
C(4)–H(4A)···Cg(3)[c]	72	2.81	3.710(4)	164
C(22)–H(22C)···Cg(1)[d]	70	2.82	3.668(5)	147

[a] $X,-1+Y,Z$

[b] $X,1+Y,Z$

[c] $2-X,1-Y,1-Z$

[d] $3-X,-Y,-Z$

Experimental

Reactions were monitored by TLC. Melting points were determined by use of a Mettler FP-5 melting point apparatus. IR spectra were recorded as KBr pellets on a Bruker Equinox 55 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker 400 MHz spectrometer using TMS as internal reference. Mass spectra were acquired with an Agilent 5975 instrument (EI, 70 eV). X-ray diffraction data were collected on a Hitachi F-4500 R-Axis Spider diffractometer.

General procedure for the preparation of 1-(4-substituted phenyl)-3-(4-substituted benzoyl)-4-(4-substituted phenyl)pyrazoles ***3a–3r***

3-Arylsydnone **2** (1 mmol) and chalcones **1** (1 mmol) were dissolved in 10 cm^3 dry xylene and refluxed for 10 h. After completion of the reaction (monitored by TLC and evolution of CO_2) the solvent was removed by distillation under reduced pressure. The resulting crude product was purified by column chromatography with ethyl acetate/petroleum

ether (1:8; v/v) as eluent to afford the corresponding pyrazole derivatives **3a**–**3r**.

3-Benzoyl-1,4-diphenylpyrazole (**3a**, $C_{22}H_{16}N_2O$)
Light yellow crystals; yield 45 %; $R_f = 0.46$; m.p.: 140–142 °C (156–158 °C [18]); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.24$ (s, 1H, pyrazole-H), 7.88–7.30 (m, 15H, Ph-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.72$, 163.04, 153.01, 137.21, 136.19, 131.71, 131.38, 131.32, 131.14, 129.85, 128.53, 128.19, 127.98, 120.93, 119.82, 114.29 ppm; IR (KBr): $\bar{\nu} = 2{,}980$ (Ar–H), 1,632 (C=O), 1,581, 1,508, 1,397 (C=N, C=C) cm^{-1}; MS: $m/z = 324$ (M^+).

3-(4-Methoxybenzoyl)-1,4-diphenylpyrazole (**3b**, $C_{23}H_{18}N_2O_2$)
Light yellow crystals; yield 48 %; $R_f = 0.45$; m.p.: 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, pyrazole-H), 7.89–6.90 (m, 14H, Ar–H), 3.86 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.84$, 163.38, 153.69, 139.27, 138.33, 132.01, 131.93, 131.53, 129.57, 128.91, 128.45, 127.69, 121.36, 119.42, 113.55, 55.44 ppm; IR (KBr): $\bar{\nu} = 2{,}977$ (Ar–H), 1,633 (C=O), 1,582, 1,507, 1,397 (C=N, C=C) cm^{-1}; MS: $m/z = 354$ (M^+).

3-(4-Chlorobenzoyl)-1,4-diphenylpyrazole (**3c**, $C_{22}H_{15}ClN_2O$)
Yellow crystals; yield 41 %; $R_f = 0.48$; m.p.: 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.54–7.15 (m, 14H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.64$, 163.38, 153.49, 139.27, 138.30, 132.20, 131.93, 131.64, 131.12, 129.55, 128.90, 128.55, 127.52, 121.26, 119.43, 113.75 ppm; IR (KBr): $\bar{\nu} = 2{,}978$ (Ar–H), 1,632 (C=O), 1,583, 1,516, 1,394 (C=N, C=C), 756 (C–Cl) cm^{-1}; MS: $m/z = 358$ (M^+).

3-Benzoyl-4-(4-methylphenyl)-1-phenylpyrazole (**3d**, $C_{23}H_{18}N_2O$)
Light yellow crystals; yield 44 %; $R_f = 0.46$; m.p.: 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, pyrazole-H), 7.89–7.29 (m, 14H, Ar–H), 2.40 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.65$, 163.34, 153.69, 139.27, 138.43, 132.06, 131.83, 131.64, 139.34, 139.20, 129.52, 128.91, 128.53, 121.16, 119.42, 113.55, 21.35 ppm; IR (KBr): $\bar{\nu} = 2{,}970$ (Ar–H), 1,632 (C=O), 1,582, 1,509, 1,394 (C=N, C=C) cm^{-1}; MS: $m/z = 338$ (M^+).

3-(4-Methoxybenzoyl)-4-(4-methylphenyl)-1-phenylpyrazole (**3e**, $C_{24}H_{20}N_2O_2$)
Light yellow crystals; yield 45 %; $R_f = 0.45$; m.p.: 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, pyrazole-H), 7.89–6.89 (m, 13H, Ar–H), 3.86 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.88$, 163.38, 153.89, 139.43, 138.46, 132.04, 131.64, 131.52, 129.68, 129.27, 129.03, 127.40, 128.66, 121.28, 119.54, 113.66, 55.60, 21.26 ppm; IR (KBr): $\bar{\nu} = 2{,}971$ (Ar–H), 1,633 (C=O), 1,583, 1,508, 1,395 (C=N, C=C) cm^{-1}; MS: $m/z = 368$ (M^+).

3-(4-Chlorobenzoyl)-4-(4-methylphenyl)-1-phenylpyrazole (**3f**, $C_{23}H_{17}ClN_2O$)
Yellow crystals; yield 42 %; $R_f = 0.48$; m.p.: 140–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.56–7.14 (m, 13H, Ar–H), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.65$, 163.33, 153.89, 139.43, 138.52, 132.04, 131.64, 131.44, 129.68, 129.30, 129.10, 128.66, 127.36, 121.28, 119.55, 113.66, 21.22 pm; IR (KBr): $\bar{\nu} = 2{,}968$ (Ar–H), 1,633 (C=O), 1,583, 1,506, 1,394 (C=N, C=C), 756 (C–Cl) cm^{-1}; MS: $m/z = 372$ (M^+).

3-Benzoyl-1-(4-methylphenyl)-4-phenylpyrazole (**3g**, $C_{23}H_{18}N_2O$)
Light yellow crystals; yield 45 %; $R_f = 0.46$; m.p.: 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, pyrazole-H), 7.89–7.29 (m, 14H, Ar–H), 2.41 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.78$, 163.02, 153.12, 137.26, 136.59, 132.31, 131.99, 131.78, 129.85, 129.21, 128.62, 128.29, 128.08, 127.87, 120.61, 119.22, 20.88 ppm; IR (KBr): $\bar{\nu} = 2{,}980$ (Ar–H), 1,632 (C=O), 1,581, 1,508, 1,395 (C=N, C=C) cm^{-1}; MS: $m/z = 338$ (M^+).

3-(4-Methoxybenzoyl)-1-(4-methylphenyl)-4-phenylpyrazole (**3h**, $C_{24}H_{20}N_2O_2$)
Light yellow crystals; yield 46 %; $R_f = 0.45$; m.p.: 134–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.24$ (s, 1H, pyrazole-H), 7.90–6.89 (m, 13H, Ar–H), 3.86 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.74$, 163.09, 153.11, 137.21, 136.69, 131.88, 131.71, 131.32, 131.14, 129.85, 128.53, 128.19, 127.98, 120.93, 119.22, 113.29, 55.23, 20.89 ppm; IR (KBr): $\bar{\nu} = 2{,}982$ (Ar–H), 1,633 (C=O), 1,584, 1,510, 1,397 (C=N, C=C) cm^{-1}; MS: $m/z = 368$ (M^+).

3-(4-Chlorobenzoyl)-1-(4-methylphenyl)-4-phenylpyrazole (**3i**, $C_{23}H_{17}ClN_2O$)
Yellow crystals; yield 43 %; $R_f = 0.47$; m.p.: 159–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.56–7.13 (m, 13H, Ar–H), 2.38 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.60$, 163.03, 153.21, 137.21, 136.69, 131.88, 131.71, 131.14, 131.12, 129.76, 128.53, 128.19, 127.98, 120.93, 119.02, 113.12, 20.96 ppm; IR (KBr): $\bar{\nu} = 2{,}973$ (Ar–H), 1,632 (C=O), 1,581, 1506, 1,397 (C=N, C=C), 758 (C–Cl) cm^{-1}; MS: $m/z = 372$ (M^+).

3-Benzoyl-1,4-bis(4-methylphenyl)pyrazole (**3j**, $C_{24}H_{20}N_2O$)
Light yellow crystals; yield 45 %; $R_f = 0.47$; m.p.: 126–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, pyrazole-H), 7.89–7.24 (m, 13H, Ar–H), 2.40, 2.38 (2 s, 6H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.78$, 163.29, 153.64, 138.15, 137.14, 136.67, 132.23, 132.02, 129.81, 129.18, 128.52, 128.07, 127.48, 120.46, 119.19, 112.52, 21.09, 20.80 ppm; IR (KBr): $\bar{\nu} = 2{,}989$ (Ar–H), 1,632 (C=O), 1,583, 1,509, 1,398 (C=N, C=C) cm^{-1}; MS: $m/z = 352$ (M^+).

3-(4-Methoxybenzoyl)-1,4-bis(4-methylphenyl)pyrazole (**3k**, $C_{25}H_{22}N_2O_2$)
Light yellow crystals; yield 47 %; $R_f = 0.47$; m.p.: 146–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.24$ (s, 1H, pyrazole-H), 7.89–6.86 (m, 12H, Ar–H), 3.86 (s, 3H, OCH_3), 2.39, 2.38 (2 s, 6H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.64$, 162.94, 153.20, 146.65, 138.03, 136.99, 131.63, 131.22, 131.19, 130.07, 129.77, 128.96, 128.60, 120.67, 119.09, 113.24, 55.19, 21.04, 20.72 ppm; IR (KBr): $\bar{\nu} = 2{,}979$ (Ar–H), 1,632 (C=O), 1,583, 1,506, 1,392 (C=N, C=C) cm^{-1}; MS: $m/z = 382$ (M^+).

3-(4-Chlorobenzoyl)-1,4-bis(4-methylphenyl)pyrazole (**3l**, $C_{24}H_{19}ClN_2O$)
Yellow crystals; yield 43 %; $R_f = 0.49$; m.p.: 170–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, pyrazole-H), 7.56–6.88 (m, 12H, Ar–H), 2.38 (2 s, 6H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.44$, 162.98, 153.30, 146.65, 137.86, 136.99, 131.63, 131.22, 131.19, 129.77, 130.02, 128.96, 128.68, 120.67, 119.09, 113.24, 21.14, 20.92 ppm; IR (KBr): $\bar{\nu} = 2{,}973$ (Ar–H), 1,632 (C=O), 1,582, 1,506, 1,397 (C=N, C=C), 758 (C–Cl) cm^{-1}; MS: $m/z = 386$ (M^+).

3-Benzoyl-4-(4-chlorophenyl)-1-phenylpyrazole (**3m**, $C_{22}H_{15}ClN_2O$)
Yellow crystals; yield 40 %; $R_f = 0.48$; m.p.: 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.27$ (s, 1H, pyrazole-H), 7.56–7.30 (m, 14H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.70$, 163.04, 153.01, 137.31, 136.26, 131.71, 131.38, 131.36, 131.16, 129.88, 128.53, 128.18, 127.98, 120.94, 119.82, 114.31 ppm; IR (KBr): $\bar{\nu} = 2{,}970$ (Ar–H), 1,632 (C=O), 1,583, 1,508, 1,396 (C=N, C=C), 756 (C–Cl) cm^{-1}; MS: $m/z = 358$ (M^+).

4-(4-Chlorophenyl)-3-(4-methoxybenzoyl)-1-phenylpyrazole (**3n**, $C_{23}H_{17}ClN_2O_2$)
Yellow crystals; yield 44 %; $R_f = 0.47$; m.p.: 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.56–6.90 (m, 13H, Ar–H), 3.86 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.17$, 163.21, 153.23, 138.86, 137.86, 132.88, 131.66, 131.61, 131.00, 129.77, 129.39, 128.15, 127.30, 119.24, 113.43, 55.29 ppm; IR (KBr): $\bar{\nu} = 2{,}977$ (Ar–H), 1,633 (C=O), 1,583, 1,507, 1,395 (C=N, C=C), 755 (C–Cl) cm^{-1}; MS: $m/z = 388$ (M^+).

3-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-1-phenylpyrazole (**3o**, $C_{22}H_{14}Cl_2N_2O$)
Yellow crystals; yield 38 %; $R_f = 0.50$; m.p.: 98–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.28$ (s, 1H, pyrazole-H), 7.50–7.28 (m, 13H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.52$, 162.84, 152.78, 137.21, 136.19, 131.71, 131.38, 131.32, 131.14, 129.85, 128.53, 128.19, 127.98, 120.93, 119.82, 114.06 ppm; IR (KBr): $\bar{\nu} = 2{,}974$ (Ar–H), 1,630 (C=O), 1,582, 1,506, 1,394 (C=N, C=C), 755 (C–Cl) cm^{-1}; MS: $m/z = 392$ (M^+).

3-Benzoyl-4-(4-chlorophenyl)-1-(4-methylphenyl)pyrazole (**3p**, $C_{23}H_{17}ClN_2O$)
Light yellow crystals; yield 40 %; $R_f = 0.50$; m.p.: 155–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.56–7.14 (m, 13H, Ar–H), 2.37 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.74$, 163.09, 153.11, 137.21, 136.69, 131.88, 131.61, 131.33, 131.04, 129.85, 128.53, 128.16, 127.98, 120.94, 119.20, 113.29, 20.86 ppm; IR (KBr): $\bar{\nu} = 2{,}981$ (Ar–H), 1,632 (C=O), 1,582, 1,508, 1,397 (C=N, C=C), 756 (C–Cl) cm^{-1}; MS: $m/z = 372$ (M^+).

4-(4-Chlorophenyl)-3-(4-methoxybenzoyl)-1-(4-methylphenyl)pyrazole (**3q**, $C_{24}H_{19}ClN_2O_2$)
Yellow crystals; yield 44 %; $R_f = 0.48$; m.p.: 194–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.90–6.89 (m, 13H, Ar–H), 3.88 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.64$, 162.94, 153.20, 146.65, 138.03, 136.99, 131.63, 131.22, 131.19, 130.07, 129.77, 128.96, 128.60, 120.67, 119.09, 113.24, 55.19, 21.14 ppm; IR (KBr): $\bar{\nu} = 2{,}972$ (Ar–H), 1,633 (C=O), 1,583, 1,509, 1,396 (C=N, C=C), 756 (C–Cl) cm^{-1}; MS: $m/z = 402$ (M^+).

3-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-1-(4-methylphenyl)pyrazole (**3r**, $C_{23}H_{16}Cl_2N_2O$)
Yellow crystals; yield 40 %; $R_f = 0.48$; m.p.: 198–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, pyrazole-H), 7.50–7.12 (m, 12H, Ar–H), 2.40 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.59$, 163.00, 153.21, 137.21, 136.66, 131.88, 131.70, 131.34, 131.18, 129.85, 128.54, 128.19, 127.96, 120.93, 119.21, 113.29, 20.89 ppm; IR (KBr): $\bar{\nu} = 2{,}983$ (Ar–H), 1,631 (C=O), 1,582, 1,506, 1,397 (C=N, C=C), 758 (C–Cl) cm^{-1}; MS: $m/z = 406$ (M^+).

X-ray crystallography

CCDC-870067 contains the supplementary crystallographic data for compound **3q**. These data can be obtained free of

charge from the Cambridge Crystallographic Data Centre (CCDC) via e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments We are grateful to the Key SCI-Tech Innovation Team of Zhejiang Province (2010R5 0017) for financial help.

References

1. Gomez L, Hack MD, Wu J, Wiener JJM, Venkatesan HAS, Pippel DJ, Mani N, Morrow BJ, Motley ST, Shaw KJ, Wolin R, Grice CA, Jones TK (2007) Bioorg Med Chem Lett 17:2723
2. Regan J, Breitfelder S, Cirillo P, Gilmore T, Graham AG, Hickey E, Klaus B, Madwed J, Moriak M, Moss N, Pargellis C, Pav S, Proto A, Swinamer A, Tong L, Torcellini C (2002) J Med Chem 45:2994
3. Pinto DJP, Orwat MJ, Koch S, Rossi KA, Alexander RS, Smallwood A, Wong PC, Rendina AR, Luettgen JM, Knabb RM, He K, Xin B, Wexler RR, Lam PYS (2007) J Med Chem 50:5339
4. Ghotekar BK, Ghagare MG, Toche RB, Jachak MN (2010) Monatsh Chem 141:169
5. Chimenti F, Bolasco A, Manna F, Secci D, Chimenti P, Granese A, Befani O, Turini P, Alcaro S, Ortuso F (2006) Chem Biol Drug Des 67:206
6. Lin R, Chiu G, Yu Y, Connolly PJ, Li SJ, Lu YH, Adams M, Fuentes-Pesquera AR, Emanuel SL, Greenberger LM (2007) Bioorg Med Chem Lett 17:4557
7. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) J Med Chem 40:1347
8. Elguero J, Goya P, Jagerovic N, Silva AMS (2002) In: Attanasi OA, Spinelli D (eds) Targets in heterocyclic systems—chemistry and properties, vol 6. Italian Society of Chemistry, Rome, p 52
9. Fustero S, Sánchez-Roselló M, Barrio P, Simón-Fuentes A (2011) Chem Rev 111:6984
10. Martins MAP, Peres RL, Frizzo CP, Scapin E, Moreira DN, Fiss GF, Zanatta N, Bonacorso HG (2009) J Heterocycl Chem 46:1247
11. Reidlinger C, Dworczak R, Junek H (1998) Monatsh Chem 129:1207
12. Silva VLM, Silva AMS, Pinto DCGA, Jagerovic N, Callado LF, Cavaleiro JAS, Elguero J (2007) Monatsh Chem 138:797
13. Chimenti F, Bolasco A, Manna F, Secci D, Chimenti P, Granese A, Befani O, Turini P, Alcaro S, Ortuso F (2006) Chem Biol Drug Des 67:206
14. Nikpour F, Beigvand M (2008) Monatsh Chem 139:821
15. Makino K, Kim HS, Kurasawa Y (1998) J Heterocycl Chem 35:489
16. Hegde JC, Rai G, Puranik VG, Kalluraya B (2006) Synth Commun 36:1285
17. Rai NS, Balakrishna Kalluraya B, Lingappa B, Shaliny Shenoy S, Puranic VG (2008) Eur J Med Chem 43:1715
18. Al-Shiekh MA (2005) Org Prep Proced Int 37:223