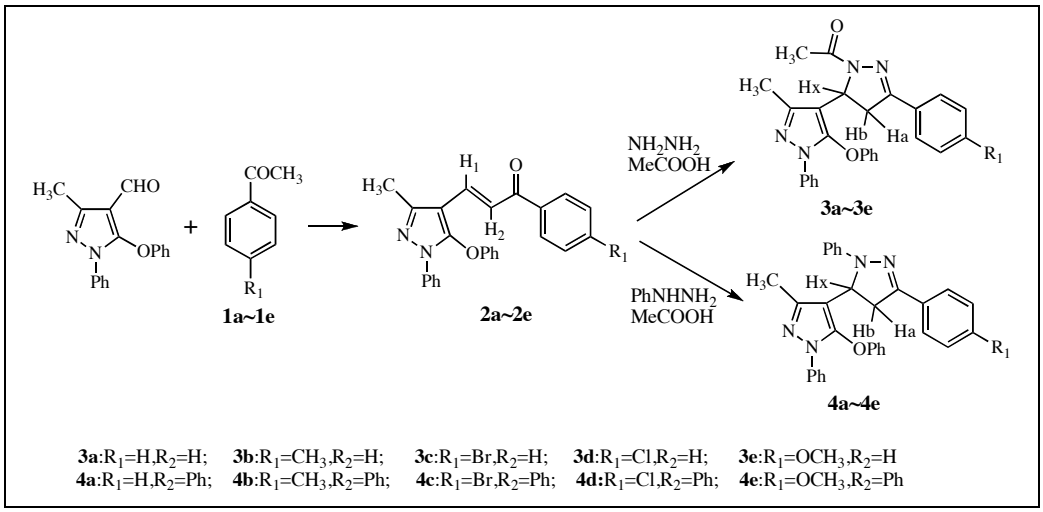
Synthesis and Crystal Structure of 5-Pyrazol-4,5-dihydropyrazoles Derivatives

Zhengfeng Xie[*a], Xuexia Mo[a], Gang Liu[a], Fangming Liu[*a,b]

[a] Education Ministry Key Laboratory of Oil & Gas Fine Chemicals, Xinjiang University, Urumqi 830046, PR China
[b] College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou, 310012, PR China
e-mail address : xiezhf72@yahoo.com.cn; fmliu859@sohu.com

Received October 25, 2007



A series of 1-acetyl(or phenyl)-3-aryl-5-(1-phenyl-3-methyl-5-aryloxyl-pyrazol)-4,5-dihydropyrazole derivatives have been efficiently synthesized under refluxing in glacial acetic acid with two kinds of hydrazines and five kinds of chalcones of 1-phenyl-methyl-5-phenoxyl-pyrazol-4-aldehyde. The structures were confirmed on the basis of ^{1}H NMR, IR, MS and element analysis, and the crystal structure of the compound **4c** was determined by single crystal X-ray diffraction. The compound **4c** belongs to monoclinic system with space group P2(1)/n, a = 11.8779(3) nm, b = 12.0901(2) nm, c = 17.7004(4) nm, α = 90°, β = 100.05(10)°, γ = 90°, Formula weight: 549.46, Triclinic V =2502.89(9) nm^3, D_c =1.458 Mg/m^3, Z = 4, F (000) = 1128.

J. Heterocyclic Chem., **45**, 1485 (2008).

INTRODUCTION

Pyrazoles and pyrazolines are important nitrogen-containing five-membered heterocyclic compounds and various methods have been developed for their synthesis [1-4]. α,β-Unsaturated aldehydes and ketones are convenient and easily available starting materials or intermediates for the synthesis of a wide variety of heterocyclic compounds [5-7]. The first synthesis of pyrazoline framework by the reaction of an α,β-enone with a hydrazine derivative was published by Fischer and Knovenagel in the late nineteenth century [8]. Then the reaction of α,β-unsaturated aldehydes and ketones with hydrazine derivatives became one of the most popular methods for the synthesis of pyrazolines [5-7,9-12]. Synthesis of tricyclic pyrazoles and pyrazolines by the reaction of the exocyclic α,β-unsaturated ketones with hydrazine derivatives has been achieved [13,14]. However, very few representatives of 5-pyrazol-4,5-dihydropyrazoles have hitherto been described in the literature.

Pyrazoles and pyrazolines bearing an unsaturated side-chain had hitherto received less attention, although various pyrazole and pyrazoline derivatives were found to possess important biological and pharmaceutical activities. Some of their most important effects include anti-inflammatory, antimicrobial, antiviral, anticancer, immunosuppressive activities [15,16], herbicidal effect [17] and fluorescent property [7,18]. So, it is important to find simple and convenient procedures for pyrazole and pyrazoline preparations. Herein we report the synthesis of 5-pyrazol-4,5-dihydropyrazole derivatives and the single crystal structure of the compound **4c**.

RESULTS AND DISCUSSION

In our pervious studies, we have worked out a convenient procedure for the synthesis of 3-aryl-5-(2-phenyl-1,2,3-triazol-4-yl)pyrazoline derivatives [7]. As a continuation, synthesis of 3-aryl-5-pyrazol-4,5-dihydro-pyrazoles derivatives has been obtained by the reaction of

these α,β-unsaturated ketones **2a**-**e** with hydrazine hydrate or phenyl hydrazine.

In our experiments, α,β-unsaturated ketones **2a**-**e** were allowed to react with hydrazine hydrate in boiling acetic acid to afford 1-acetyl-3-aryl-5-pyrazole-4,5-dihydropyrazoles **3a**-**3e** as sole isolable products. No other pyrazoline type compounds could be detected in the crude products. It was found that the initially formed pyrazoline was completely *N*-acetylated under these reaction conditions in each case.

In our study, α,β-unsaturated ketones **2a**-**e** have also reacted with phenyl hydrazine in hot acetic acid to provide 3-aryl-1-phenyl-5-pyrazol-4,5-dihydropyrazoles **4a**-**4e**.

The reaction of **2a**-**2e** with hydrazine hydrate and phenyl hydrazine were carried out in a molar ratio 1:1.1 in acetic acid as solvent and all reaction were monitored by TLC. The most satisfactory results were obtained when the reactions were performed under hot acetic acid for 1 - 4 hrs. The crude solid pyrazoles **3a**-**3e** and **4a**-**4e** were recrystallized from ethanol.

A suitable crystal of **4c** was grown from absolute ethyl alcohol and its solid-state structure was determined by X-ray diffraction. Details of the structure determination and refinement are given in the experimental section. The drawing of the molecular structure and higher occupancy in the three dimensional packing arrangement is shown in Figures 1-2. Atomic coordinates of non-hydrogen atoms ($\times 10^{-4}$) and their thermal parameters are summarized in Table 1. the crystal data and structure refinement of **4c** are listed in Table 2.

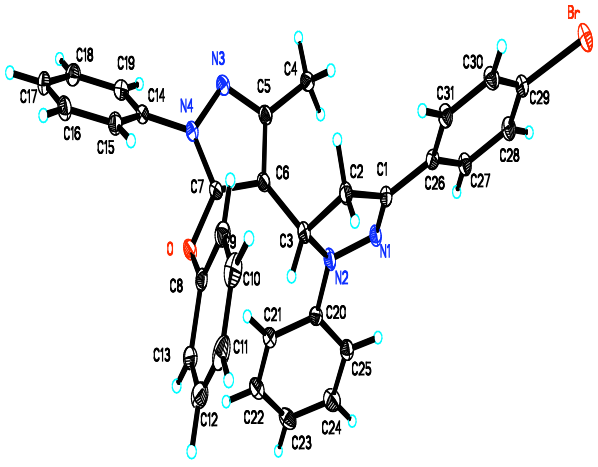


Figure 1. Molecular Structure of **4c**.

EXPERIMENTAL

All reagents were of commercial availability. Reactions were monitored by thin-layer chromatography (TLC). Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were determined as potassium bromide pellet on a Bruker Equinox55 FT-IR spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrophotometer using TMS as an internal standard. EI-ms spectra were recorded with an Agilent 5975 apparatus. X-ray crystal structure was obtained using R-AXIS SPIDER X-ray diffraction.

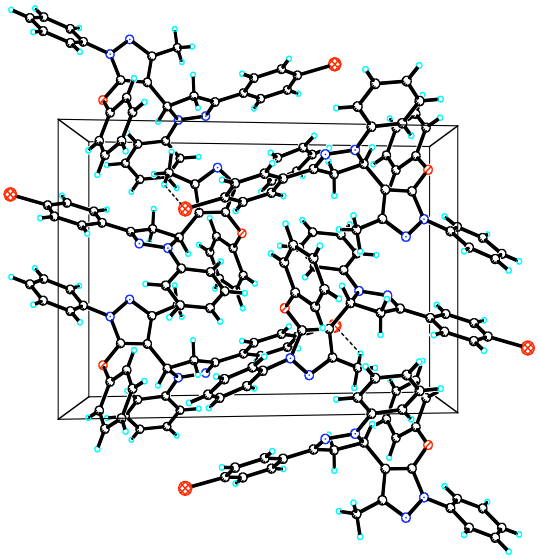


Figure 2. Packing of Molecules in a Unit Cell of **4c**.

Table 1

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

	x	y	z	U(eq)
Br	3436(1)	7159(1)	2032(1)	35(1)
O	2674(1)	8617(1)	-4419(1)	25(1)
N1	1359(2)	9038(1)	-1624(1)	24(1)
N2	1331(2)	9207(1)	-2400(1)	26(1)
N3	1592(2)	6161(1)	-3752(1)	26(1)
N4	2052(2)	6801(1)	-4264(1)	24(1)
C1	2320(2)	8576(2)	-1339(1)	23(1)
C2	3120(2)	8449(2)	-1903(1)	25(1)
C3	2357(2)	8786(2)	-2671(1)	24(1)
C6	2112(2)	7853(1)	-3233(1)	22(1)
C7	2345(2)	7813(1)	-3961(1)	22(1)
C8	3691(2)	9180(2)	-4158(1)	23(1)
C12	4767(2)	10829(2)	-4227(2)	38(1)
C16	3320(2)	6163(2)	-5978(1)	31(1)
C20	567(2)	9969(2)	-2791(1)	24(1)
C25	-141(2)	10594(2)	-2404(1)	30(1)
C26	2569(2)	8238(2)	-538(1)	24(1)
C27	1769(2)	8360(2)	-54(1)	27(1)
C29	3077(2)	7571(2)	983(1)	26(1)
C31	3632(2)	7774(2)	-239(1)	27(1)

Table 2

Crystal data and structure refinement for **4c**.

Empirical formula	$C_{31}H_{25}BrN_4O$
Formula weight	549.46
Temperature (K)	153(2)
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/n
a (Å)	11.8779(3)
b (Å)	12.0901(2)
c (Å)	17.7004(4)
α (°)	90
β (°)	100.05(10)
γ (°)	90
V (Å^3)	2502.89(9)
Z	4
D_{calc}, Mg/m^3	1.458
Absorption coefficient (mm^{-1})	1.675
F (000)	1128
Crystal size (mm)	0.38 ×0.12 ×0.07
θ range, deg	3.15-27.48
Reflections collected	20281
Independent refls.	5723(Rint=0.0276)
Date/restraints/parameters	5723/0/335
Goodness-of-fit on F^2	0.999
Final R indices [I>2s(I)]	
R1	0.0326
wR2	0.1062
Final R indices (all date)	
R1	0.0443
wR2	0.1309
extinction coefficient	0.0046(9)

The synthesis of 1-phenyl-3-methyl-5-aryloxyl-pyrazol-4-methylene-para-substitutedacetiphenones(2a-e) [20]. Acetophenone **1a-e** (20 mmoles) was added to a solution of 1-phenyl-3-methyl-5-aryloxyl-pyrazol-4-carboxaldehyde (20 mmoles) in aqueous KOH (10 mL, 35 % KOH) at 0 °C. The reaction mixture was stirred for 2 hours at ice bath. After standing overnight the yellow solid was collected by filtration and washed with water. The solid was crystallized from ethanol to give yellow crystals **2a**-**e**:

2a: yield 81%; mp 140~141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.60~6.92 (m, 15H, Ar-H), 7.55~7.53 (d, 1H, H-2), 7.32~7.31 (d, 1H, H-1), 2.47 (s, 3H, CH_3); IR (KBr) *ν*: 3049, 2969, 1649, 1498, 1329, 852 cm^{-1}; *Anal*. Calcd. for $C_{25}H_{20}N_2O_2$: C 78.95, H 5.26, N 7.37; found C 78.96, H 5.21, N 7.39.

2b: yield 92%; mp 148~149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.57~6.90 (m, 14H, Ar-H), 7.55~7.53 (d, 1H, H-2), 7.33~7.31 (d, 1H, H-1), 2.44 (s, 3H, CH_3); IR (KBr) *ν*: 3053, 2964, 1650, 1489, 1320, 670 cm^{-1}; *Anal*. Calad for $C_{26}H_{22}N_2O_2$: C 79.19, H 5.58, N 7.11; found C 79.22, H 5.56, N 7.10.

2c: yield 85%; mp 146~148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.62~6.98 (m, 14H, Ar-H), 7.55~7.53 (d, 1H, H-2), 7.33~7.31 (d, 1H, H-1), 2.51 (s, 3H, CH_3); IR (KBr) *ν*: 3053, 2964, 1650, 1489, 1320, 670 cm^{-1}; *Anal*. Calad for $C_{25}H_{19}BrN_2O_2$: C 65.36, H 4.12, N 6.10; found C 65.39, H 4.14, N 6.08.

2d: yield 94%; mp 133~134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.63~6.96 (m, 14H, Ar-H), 7.55~7.53 (d, 1H, H-2), 7.33~7.31 (d, 1H, H-1), 2.52 (s, 3H, CH_3); IR (KBr) *ν*: 3054, 2969, 1650, 1493, 1329, 643 cm^{-1}; *Anal*. Calad for $C_{25}H_{19}ClN_2O_2$: C 72.38, H 4.58, N 6.76; found C 72.36, H 4.60, N 6.73.

2e: yield 92%; mp 117~119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.66~7.01 (m, 14H, Ar-H), 7.55~7.53 (d, 1H, H-2), 7.33~7.32 (d, 1H, H-1), 3.78 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3); IR (KBr) *ν*: 3058, 2968, 1650, 1499, 1334, 655 cm^{-1}; *Anal*. Calad for $C_{26}H_{22}N_2O_3$: C 76.10, H 5.37, N 6.83; found C 76.11, H 5.36, N 6.80

1-*H*-(Phenyl)-3-aryl-5-(1-phenyl-3-methyl-5-aryloxyl-pyrazol)-4,4-dihydropyrazoline (3a-e, 4a-e). To a solution of **2a-e** (1 mmole) in acetic acid (10 mL) was added hydrazine hydrate (1.1 mmoles) or phenyl hydrazine (1.1 mmoles). Then the mixture was refluxed and monitored by TLC for about 2-4 hr. After the reaction has completed and cooled to room temperature, the mixture was poured into an ice-water mixture producing a large quantity of solid precipitate. Then the mixture was neutralized with a solution of Na_2CO_3. After standing overnight the mixture was collected by filtration and crystallized from ethanol to gain the target compounds **3a-e, 4a-e**. The melting point, yield, IR, MS and elemental analysis of the compounds are shown in Table **3**, and the ^{1}H NMR data of compounds in Table 4.

Table 3

The melting Point, yield, IR and elemental analysis of the compounds **3a-e, 4a-e**.

No	Molecular Formula	m.p. °C	Yield (%)	Analysis % Calcd./Found	IR ν/cm^{-1}	EI-ms(70eV) m/z
3a	$C_{27}H_{24}N_4O_2$	180-182	72	74.29(74.24)5.54(5.53)12.84(12.92)	3049,2919,1665,1595,1320,852	436 $[M]^+$, 250
3b	$C_{28}H_{26}N_4O_2$	151-152	62	74.65(74.71)5.82(5.86)12.44(12.39)	3052,2922,1659,1597,1327,697	450 $[M]^+$, 250
3c	$C_{27}H_{23}BrN_4O_2$	161-163	58	62.92(62.88)4.50(4.51)10.87(10.82)	3058,2917,1663,1593,1325,734	516 $[M+2]^+$, 514 $[M]^+$
3d	$C_{27}H_{23}ClN_4O_2$	162-164	65	68.86(68.82)4.92(4.94)11.90(11.85)	3055,2918,1661,1595,1326,558	472 $[M+2]^+$, 470$[M]^+$
3e	$C_{28}H_{26}N_4O_3$	172-173	55	72.09(72.13)5.62(5.65)12.01(11.96)	3060,2923,1659,1596,1327,749	466 $[M]^+$, 250
4a	$C_{31}H_{26}N_4O$	140-141	60	79.15(79.09)5.53(5.49)11.92(11.94)	3059,2917,1595,1503,1320,855	470 $[M]^+$, 91
4b	$C_{32}H_{28}N_4O$	167-169	56	79.34(79.30)5.79(5.77)11.57(11.60)	3055,2913,1560,1510,1309,672	484 $[M]^+$, 91
4c	$C_{31}H_{25}BrN_4O$	141-143	54	67.76(67.70)4.56(4.60)16.20(16.15)	3061,2915,1599,1505,1322,855	550 $[M+2]^+$, 548 $[M]^+$
4d	$C_{31}H_{25}ClN_4O$	155-157	56	73.74(73.71)4.96(4.95)11.10(11.05)	3062,2919,1597,1506,1319,736	506 $[M+2]^+$, 504 $[M]^+$
4e	$C_{32}H_{28}N_4O_2$	125-127	49	76.80(76.77)5.60(5.56)11.20(11.25)	3063,2921,1602,1511,1320,755	500 $[M]^+$, 91

Table 4

^{1}H NMR data of compounds **3a-e, 4a-e**.

No	^{1}H NMR($CDCl_3$, 400MHz), δ
3a	7.65 ~ 6.84 (m, 15 H, Ar-H), 5.41 (dd, 1 H, J_{ax} = 12.8 Hz, J_{bx}=5.6 Hz, H-x), 3.56 (dd, 1H, J_{ax}= 12.8 Hz, J_{ab} = 17.6 Hz, H-a), 3.26 (dd, 1 H, J_{bx} = 5.6 Hz, J_{ab} = 17.6 Hz, H-b), 2.44 (s, 3 H, CH_3), 2.02 (s, 3H, CH_3)
3b	7.55 ~ 6.68 (m, 14 H, Ar-H), 5.36 (dd, 1 H, J_{ax} = 13.2 Hz, J_{bx} =7.6 Hz, H-x), 3.53 (dd, 1 H, J_{ax} = 13.2 Hz, J_{ab} = 16.8 Hz, H-a), 3.24 (dd, 1H ,J_{bx} = 7.6 Hz, J_{ab} = 16.8 Hz, H-b), 2.44 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3) , 2.01 (s, 3H, CH_3)
3c	7.56 ~ 6.57 (m, 14 H, Ar-H), 5.38 (dd, 1 H, J_{ax} = 12.4 Hz, J_{bx} = 5.2 Hz, H-x), 3.52 (dd, 1 H, J_{ax} = 12.4 Hz, J_{ab} = 17.6 Hz, H-a), 3.27 (dd, 1 H, J_{bx} = 5.2 Hz, J_{ab} = 17.6 Hz, H-b), 2.45 (s, 3 H, CH_3) , 2.03 (s, 3H, CH_3)
3d	7.54 ~ 6.54 (m, 14 H, Ar-H), 5.41 (dd, 1 H J_{ax} = 12.4 Hz, J_{bx} = 5.2 Hz, H-x), 3.55 (dd, 1 H, J_{ax} = 12.4 Hz, J_{ab} = 17.6 Hz, H-a), 3.26 (dd, 1 H, J_{bx} = 5.2 Hz, J_{ab} = 17.6 Hz, H-b), 2.45 (s, 3 H, CH_3) , 2.03 (s, 3H, CH_3)
3e	7.56 ~ 6.62 (m, 14 H, Ar-H), 5.39 (dd, 1 H, J_{ax} = 13.2 Hz, J_{bx} = 8.4 Hz, H-x), 3.57 (dd, 1 H, J_{ax} = 13.2 Hz, J_{ab} = 17.2 Hz, H-a), 3.27 (dd, 1 H, J_{bx} = 8.4 Hz, J_{ab} = 17.2 Hz, H-b), 3.80 (s, 3 H, OCH_3), 2.44 (s, 3 H, CH_3) , 2.02 (s, 3H, CH_3)
4a	7.67 ~ 6.79 (m, 20 H, Ar-H), 5.13 (dd, 1 H, J_{ax} = 12.8 Hz, J_{bx} = 7.6 Hz, H-x), 3.53 (dd, 1 H, J_{bx} = 12.8 Hz, J_{ab} = 17.2 Hz, H-b), 3.15 (dd, 1 H, J_{ax} = 7.6 Hz, J_{ab} = 17.2 Hz, H-a), 2.44 (s, 3 H, CH_3)
4b	7.61 ~ 6.65 (m, 19 H, Ar-H), 5.11 (dd, 1 H, J_{ax} = 12.4 Hz, J_{bx} = 7.2 Hz, H-x), 3.53 (dd, 1 H, J_{bx} = 12.4 Hz, J_{ab} = 16.8 Hz, H-b), 3.16 (dd, 1 H, J_{ax} = 7.2 Hz, J_{ab} = 16.8 Hz, H-a), 2.44 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3)
4c	7.64 ~ 6.61 (m, 19 H, Ar-H), 5.12 (dd, 1 H, J_{ax} = 12.8 Hz, J_{bx} = 7.2 Hz, H-x), 3.52 (dd, 1 H, J_{bx} = 12.8 Hz, J_{ab} = 16.8 Hz, H-b), 3.15 (dd, 1 H, J_{ax} = 7.2 Hz, J_{ab} = 16.8 Hz, H-a), 2.44 (s, 3 H, CH_3)
4d	7.67 ~ 6.55 (m, 19 H, Ar-H), 5.10 (dd, 1 H, J_{ax} = 12.8 Hz, J_{bx} = 7.6 Hz, H-x), 3.56 (dd, 1 H, J_{bx} = 12.8 Hz, J_{ab} = 16.8 Hz, H-b), 3.16 (dd, 1 H, J_{ax} = 7.6 Hz, J_{ab} = 16.8 Hz, H-a), 2.44 (s, 3 H, CH_3)
4e	7.65 ~ 6.73 (m, 19 H, Ar-H), 5.12 (dd, 1 H, J_{ax} = 12.4 Hz, J_{bx} = 7.6 Hz, H-x), 3.53 (dd, 1 H, J_{bx} = 12.4 Hz, J_{ab} = 17.2 Hz, H-b), 3.15 (dd, 1H, J_{ax} = 7.6 Hz, J_{ab} = 17.2 Hz, H-a), 3.82 (s, 3 H, OCH_3), 2.44 (s, 3 H, CH_3)

Acknowledgement. The authors thank the financial support of the National Natural Science Foundation of China (No: 20562011).

REFERENCES AND NOTES

[1] Levai, A.; Patonay, T.; Sliva, A. M. S.; Pinto, D. C. G. A. and Cavaleiro, J. A. S. *J. Heterocyclic Chem*. **2002**, *39*, 751.

[2] Atir, R.; Mallouk, S.; Bougrin, K.; Soufiaoui, M.; Laghzizil, A. *Synth. Commun*. **2006**, *36*, 111.

[3] Levai, A. and Jeko, J. *J. heterocyclic chem*. **2002**, *39*, 1333.

[4] Kudar, V.; Zsoldos-Mady, V.; Simon, K.; Csampai, A.; Sohar, P. *J. Organometal. Chem*, **2005**, *690*, 4018.

[5] Levai, A. *J. Heterocyclic Chem*. **2004**, *41*, 299.

[6] Levai, A. *J. heterocyclic chem*. **2002**, *39*, 1.

[7] Li, F.; Xie, Z. F.; Liu, F. M.; *Chem. J. Chin. U*. **2006**, *26*, 1058 (in Chinese).

[8] Fischer, E. and Knovenagel, O. *Ann. Chem*. **1887**, *239*, 194.

[9] Raiford, L. C. and Gundy, G. V. *J. Org. Chem*. **1938**, *3*, 265.

[10] Wiley, R. H.; Jarboe, C. H.; Hayes, F. N.; Hansbury, E.; Nielsen, J. T.; Callahan , P. X. and Sellars, M. C. *J. Org. Chem*. **1958**, *23*, 732.

[11] Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. *Tetrahedron* **1998**, *54*, 4085.

[12] Azarifar, D.; Maleki, B. *J. Heterocyclic Chem*. **2005**, *42*, 157.

[13] T. J. M. Chary, Ch V. N. Reddy, A. K. Murthy, *Indian J. Chem. Sect. B*, **31**, 495 (1992).

[14] El-Latif, F. M. A.; Barsi, M. A.; Maghraby, A. S.; Badr, M. Z. A.; Doepp, D. *J.Indian Chem. Soc*. **1995**, *72*, 641.

[15] Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935.

[16] Lombardino, J. G.; Otterness, I. G. *J. Med. Chem*. **1981**, *24*, 830.

[17] Sengupta, A. K.; Gupta, A. A. *Indian J. Chem*. **1983**, *22B*: 263.

[18] Fahmi, C. J.; Yang, L.C.; VanDerveer, D. G. *J. Am.Chem. Soc*. **2003**, *125*, 3799.

[19] Bendaas, A.; Hamdi, M.; Sellier, N. *J. heterocyclic Chem*. **1999**, *36*, 1291.

[20] Riebsomer, J. L.; Sumrell, G. *J. Org. Chem*., **1948**, *13*, 807.