HETEROCYCLES, Vol. 78, No. 4, 2009, pp. 923 - 936. © The Japan Institute of Heterocyclic Chemistry
Received, 27th September, 2008, Accepted, 25th November, 2008, Published online, 27th November, 2008
DOI: 10.3987/COM-08-11561

NOVEL AND EFFICIENT SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRIDIN-6-ONES OR THEIR HYDROGENATED DERIVATIVES THROUGH ONE-POT REACTION IN IONIC LIQUID

Xin-Ying Zhang,* Xiao-Yan Li, Xue-Sen Fan,* Xia Wang, Gui-Rong Qu, and Jian-Ji Wang

School of Chemistry and Environmental Sciences, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, P. R. China. E-mail: xyzh518@sohu.com; xuesen.fan@yahoo.com

Abstract – Pyrazolo[3,4-*b*]pyridin-6-ones or their hydrogenated derivatives were obtained selectively and conveniently through one-pot reaction of aldehyde, ethyl cyanoacetate and 5-amino-3-methyl-1-phenylpyrazole in [bmim][BF_4] with or without ferric chloride at different temperatures. Advantages of this novel method include high yield, mild conditions, simple procedure and good selectivity. In addition, the ionic liquid used can be easily recovered and effectively reused.

INTRODUCTION

The development of efficient chemical process for the preparation of new biologically active molecules constitutes a major challenge for chemists in organic synthesis. Part of this challenge is to develop novel methods for the preparation of nitrogen-containing heterocyclic compounds, like pyrazolo-pyridine derivatives, due to the fact that many of this kind of compounds possess various interesting biological activities. Particularly, pyrazolo[3,4-*b*]pyridines possess wide-ranging biological activities such as phychotropic,[1] cytotoxic,[2] antiviral,[3] antifungal[4] and antichagasic activities.[5] They are also potent inhibitors of glycogen synthase kinase-3 (GSK-3)[6] and clcin-dependent kinase-1 (CDK-1).[7] Recently, novel pyrazolo[3,4-*b*]pyridin-6-ones as a subunit of pyrazolo[3,4-*b*]pyridine were designed and synthesized by Falcó *et al* to be screened as potential hypnotic drugs.[8]

Due to their importance, many methods have been reported for the construction of pyrazolo[3,4-*b*]pyridine derivatives including pyrazolo[3,4-*b*]pyridin-6-ones.[9-14] However, with the reported methods, multi-step preparative procedures were usually needed, and a combination of several additives and catalysts was usually employed, or volatile solvents were used for the reaction to complete. Thus, development of new methods capable of inducing simple and efficient preparation of pyrazolo[3,4-*b*]pyridin-6-ones would be of interest to synthetic chemists.

On the other hand, the development of environmentally friendly catalysts and solvents for organic chemistry is an area of considerable importance. In the last few years rt ionic liquids (RTILs), especially those based on 1,3-dialkylimidazolium cations, have been recognized as a possible environmentally benign alternative to chemical volatile solvents because, in contrast with the conventional organic solvents, they are non-volatile, recyclable, non-explosive, easy to handle, and thermally robust.[15] RTILs as a kind of ion solvent combine the advantages of both traditional molecular solvents and melt salts and have been widely used in catalytic and non-catalytic reactions.[16] Their high polarity and the ability to solubilize both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivity compared to conventional solvents. Moreover, ionic liquids are simple and inexpensive to prepare and easy to recycle and their properties can be fine-tuned by changing the anion or the alkyl group attached to cation. Accordingly they are emerging as novel replacements for volatile organic solvents in organic synthesis. Recently, how to use ILs to promote the selectivity of various organic reactions and to dramatically influence the outcome of chemical reactions has also attracted much attention.[17]

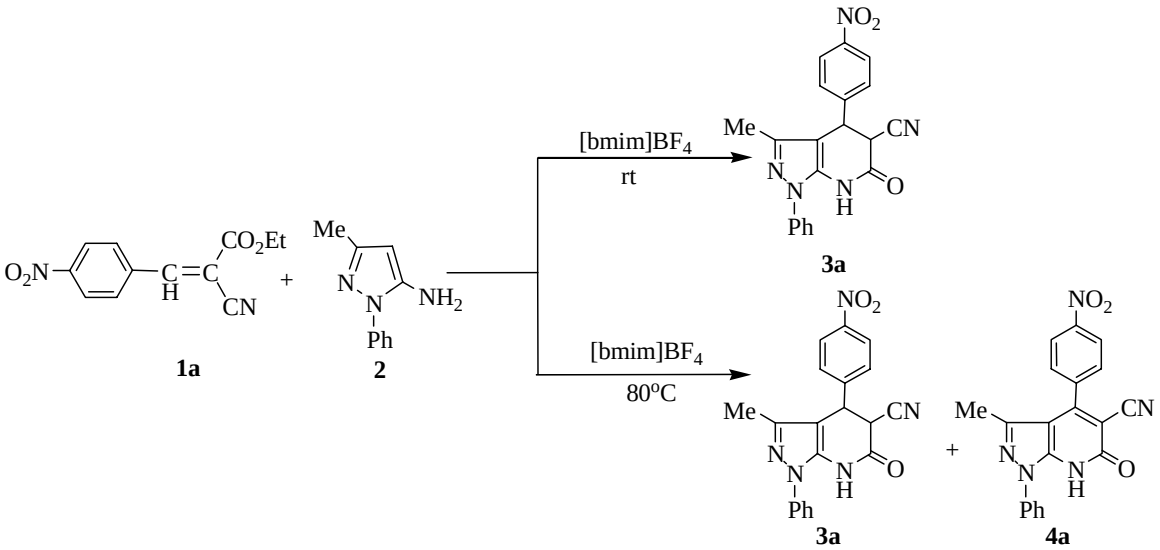
As a continuation of our research in developing novel and efficient methodologies for the synthesis of biologically important heterocyclic compounds by using ionic liquids as both reaction medium and promoter,[18] we would like to report our study on the one-pot reaction of aldehyde, ethyl cyanoacetate and 5-amino-3-methyl-1-phenylpyrazole in an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) with or without ferric chloride. From this reaction, pyrazolo[3,4-*b*]pyridin-6-ones or their hydrogenated derivatives were obtained efficiently and selectively under different reaction conditions.

RESULTS AND DISCUSSION

Firstly, 4-nitrobenzilidene ethyl cyanoacetate (**1a**, Scheme 1), previously prepared from 4-nitrobenzaldehyde and ethyl cyanoacetate, was treated with 5-amino-3-methyl-1-phenylpyrazole (**2**) in [bmim][BF_4]. After being stirred at rt for several hours, it gave pale yellow solids, which were collected by suction and submitted to identification. ^{1}H NMR, g-COSY and mass spectra analysis showed that the product obtained so far is **3a** (mixture of two isomers) instead of the desired **4a** (Scheme 1).

To get **4a**, higher reaction temperature was tried. It was observed that when **1a** and **2** was stirred in [bmim][BF_4] at 80 °C, a new product was formed along with **3a**. The mixture was let to be stirred at 80 °C until no change of the ratio of the two products was observed (based on TLC analysis). Subsequent handling of the reaction mixture gave **3a** and another solid, which was identified through ^{1}H NMR and MS as **4a**, with yield of 45% and 35% respectively (Scheme 1).

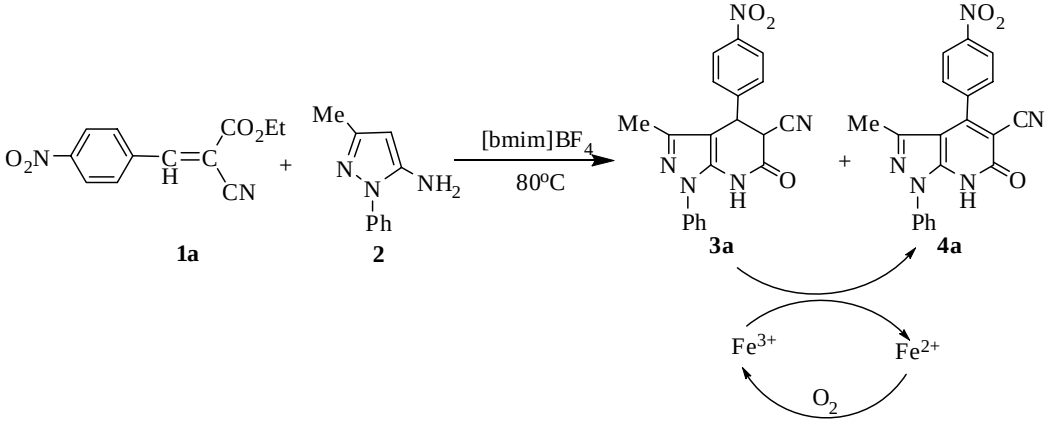
Different temperature conditions and reaction period were then tried to improve the yield of **4a**. But higher reaction temperature and longer reaction time did not result in significant improvement with regard



Scheme 1

to the selectivity and yield of **4a**.

Based on the above results, it is reasonable to suggest that in the above procedures **3a** was firstly formed through the condensation of **1a** and **2**, and part of **3a** could be oxidized by air to give **4a** at elevated temperature. However, as an oxidant, air is not strong enough to give a complete transformation and as a result, a mixture of **3a** and **4a** was obtained. It is therefore considered that an added oxidant would be able to push the oxidation procedure to go further. Bearing in mind that $FeCl_3 \cdot 6H_2O$ has successfully acted as a mild oxidant in many occasions,[19] it was then recruited and used in the above reaction (Scheme 2). The results were listed in Table 1.



Scheme 2

It turned out that with $FeCl_3 \cdot 6H_2O$ the reaction was improved remarkably with regard to the selectivity and yield of **4a** (Table 1, Entries 1-5). Firstly, 1 equivalent of $FeCl_3 \cdot 6H_2O$ was tried, and the reaction of **1a** and **2** gave **4a** exclusively with a yield of 81% after the mixture being stirred at 80 °C for 8 h (Table 1, Entry 5). With the amount of $FeCl_3 \cdot 6H_2O$ less than 1 equivalent, to our surprise, not only could **4a** be obtained, but with better yield. For example, in the presence of 50 mol% or 20 mol% of $FeCl_3 \cdot 6H_2O$, **4a**

was obtained with yield of 90% or 95% respectively (Table 1, Entries 4 and 3). However, amount less than 20 mol% resulted in decrease in the yield of **4a** (Table 1, Entry 2).

Table 1. Effect of additives on the preparation of **4a**[a]

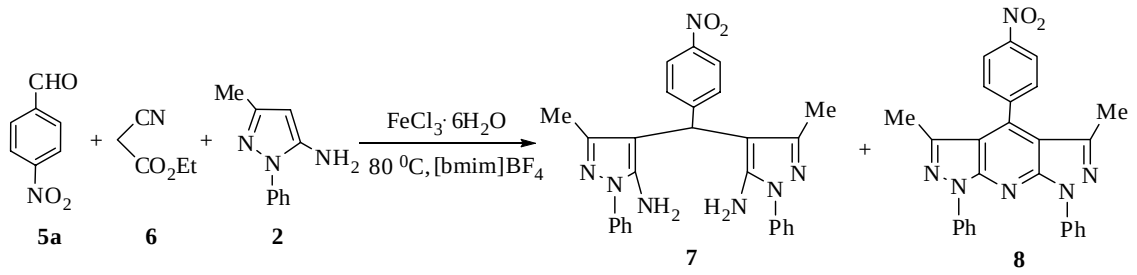
Entry	Catalyst	Amount of Catalyst (mmol)	Products	Reaction Time (h)	Yield (%)
1	None	0	**3a+4a**	12	45(**3a**)+35(**4a**)
2	$FeCl_3·6H_2O$	0.1	**3a+4a**	8	12(**3a**)+71(**4a**)
3	$FeCl_3·6H_2O$	0.2	**4a**	8	95
4	$FeCl_3·6H_2O$	0.5	**4a**	8	90
5	$FeCl_3·6H_2O$	1	**4a**	8	81
6	$Fe(NO_3)_3·9H_2O$	0.2	**4a**	8	91
7	$Fe_2(SO_4)_3·XH_2O$	0.2	**4a**	8	90
8	$CeCl_3·7H_2O$	0.2	**3a+4a**	12	80(**3a**)+5(**4a**)
9	$ZnCl_2$	0.2	**3a+4a**	12	70(**3a**)+10(**4a**)

[a] Reaction conditions: 1 mL [bmim][BF_4], 1 mmol **1a**, 1 mmol **2**, 80℃.

It is postulated that in the presence of $FeCl_3·6H_2O$, **3a** was oxidized to **4a** by Fe(III) and the *in situ* formed Fe(II) could be simultaneously oxidized back to Fe(III) by air to act as oxidant again. It is why catalytic amount of $FeCl_3·6H_2O$ is enough to give a complete transformation.

Furthermore, several other kinds of metallic salt were also tried and the results were included in Table 1. It turned out that in addition to $FeCl_3·6H_2O$, presence of other two ferric(III) salts, $Fe_2(SO_4)_3·XH_2O$ (20 mol%) or $Fe(NO_3)_3·9H_2O$ (20 mol%), also led to highly selective formation of **4a** (Table 1**,** Entries 6, 7). On the other hand, in the presence of $CeCl_3·7H_2O$ or $ZnCl_2$, the selectivity for **4a** is even lower compared with reactions without any additives (Table 1, Entries 8, 9).

As the art of performing efficient chemical transformation involving three or more components in one pot represents a fundamental target of the modern organic synthesis, further efforts were then made to investigate the possibility of preparing **4a** directly from the corresponding aldehyde (**5a**), ethyl cyanoacetate (**6**) and **2** in one pot. Thus, **5a**, **6** and **2** were added to 1 mL of [bmim][BF_4] and the mixture was stirred at 80 °C in the presence of $FeCl_3·6H_2O$ (Scheme 3). After being stirred for several hours, however, it gave a mixture of two new compounds indicated by TLC analysis. A careful separation and structural analysis of the mixture demonstrated that the products obtained were **7** and **8**, the condensation products of **5a** and **2**. From these results, it is obvious that with the coexistence of **5a**, **6** and **2**, it is more favorable for **5a** to react with **2** to give **7** and **8** instead of reacting with **6** and **2** to give **4a**. This is probably due to the stronger nucleophilic reactivity of **2** toward aldehyde than that of **6**.

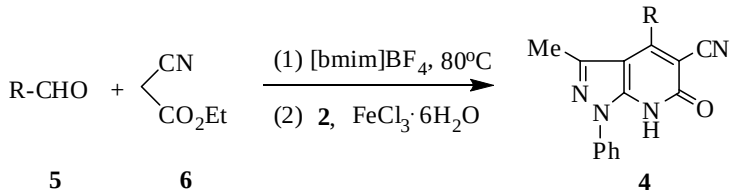


5a **6** **2** **7** **8**

Scheme 3

To get the desired product **4a** in one pot, an alternative manipulation in terms of the substrates addition sequence was tried. Thus, **5a** and **6** were firstly added to 1 mL of [bmim][BF_4]. The mixture was stirred at 80 °C until the disappearance of **5a**. Then, **2** and $FeCl_3$·$6H_2O$ (20 mol %) was added and the mixture was stirred at the same temperature. The following reaction went smoothly to give a solid product. It was collected by suction and identified as **4a** in almost quantitive yield of 96%.

In the next stage, the scope and generality of this one-pot procedure (Scheme 4) were studied and the results were listed in Table 2. It turned out that various aryl aldehydes or heterocyclic aldehydes reacted smoothly with **6** and **2** to give **4** in high yields. In addition, aryl aldehydes with group(s) on the *ortho*-position gave relatively lower yields of **4**, probably due to steric effect.



5 **6** **4**

Scheme 4

With the above products in hand, the MS and NMR-based structures of **4** were further confirmed by X-ray crystallographic analysis of **4g** (Figure 1).[20]

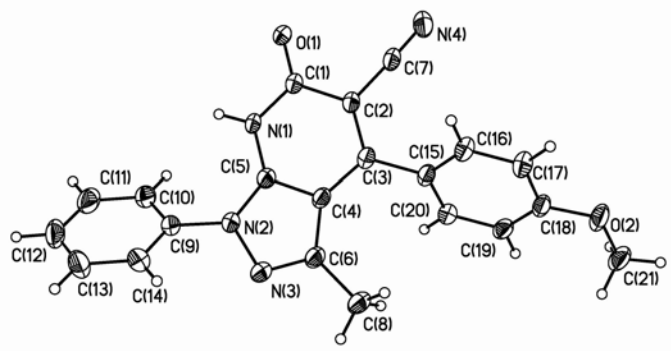


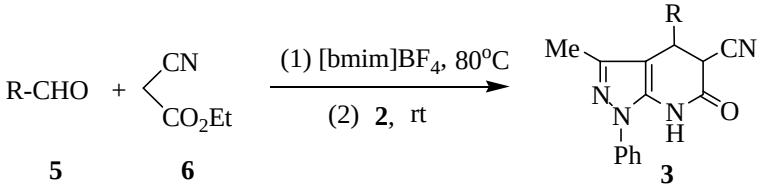
Figure 1 The molecular structure of **4g**

Bearing in mind that hydrogenated pyrazolo[3,4-*b*]pyridin-6-ones like compound **3** have been found with good biological activity such as GSK-3 inhibitors [21] and have the potential to be used as novel building blocks to construct new nitrogen-containing molecules, our further effort is aimed at the development of an efficient, mild and reliable protocol to prepare this class of compound (Scheme 5). Based on the results

Table 2. Preparation of pyrazolo[3,4-*b*]-pyridin-6-ones (**4**) in [bmim][BF_4]

Entry	R	Product	Reaction Time (h)	Yield (%)
1	*p*-$NO_2C_6H_4$	**4a**	10	96
2	C_6H_5	**4b**	10	91
3	*p*-ClC_6H_4	**4c**	10	94
4	*p*-MeC_6H_4	**4d**	10	90
5	*p*-BrC_6H_4	**4e**	10	92
6	*p*-FC_6H_4	**4f**	10	93
7	*p*-$MeOC_6H_4$	**4g**	10	90
8	*m*-$NO_2C_6H_4$	**4h**	10	93
9	*m*-ClC_6H_4	**4i**	10	93
10	*m*-BrC_6H_4	**4j**	10	91
11	*m*-MeC_6H_4	**4k**	11	88
12	*o*-$NO_2C_6H_4$	**4l**	11	89
13	*o*-FC_6H_4	**4m**	11	87
14	*o*-ClC_6H_4	**4n**	11	85
15	*4*-pyridyl	**4o**	10	91
16	*3*-pyridyl	**4p**	10	90

obtained so far, a procedure elaborately designed for the preparation of **3** *via* a three-component reaction version was investigated. Thus, **5a** and **6** were firstly added to 1 mL of [bmim][BF_4]. The mixture was stirred at 80 °C until the disappearance of **5a**. Upon cooling to rt, **2** was added to the system and the mixture was stirred at rt. The following reaction went smoothly and afforded **3a** with a yield of 90%. Further study with various aldehyde substrates showed that this procedure is quite general and reliable in that all the aldehyde substrates studied reacted with **6** and **2** smoothly and gave **3** with good yields. The results were listed in Table 3.



5 **6** **3**

Scheme 5

As mentioned earlier, one of the goals in the usage of ionic liquids is to identify the additional advantages they have over conventional organic solvents besides a greener nature. Thus, several volatile organic

Table 3. Preparation of hydrogenated pyrazolo[3,4-*b*]pyridin-6-ones (**3**) in [bmim][BF_4]

Entry	R	Product	Reaction Time (h)	Yield (%)
1	*p*-$NO_2C_6H_4$	**3a**	8	90
2	C_6H_5	**3b**	9	84
3	*p*-ClC_6H_4	**3c**	9	87
4	*p*-BrC_6H_4	**3d**	9	85
5	*p*-MeC_6H_4	**3e**	10	86
6	*m*-ClC_6H_4	**3f**	9	86
7	*m*-MeC_6H_4	**3g**	9	85

solvents such as MeOH, EtOH and toluene were chosen as solvent for the preparation of **3a** from **1a** and **2** (Scheme 1). The results (Table 4) showed that of the solvents studied, [bmim][BF_4] gave the best result in terms of both reaction time and product yield. With MeOH, EtOH or toluene as the reaction medium, the reaction underwent much slower and resulted in much lower yields.

Table 4. Preparation of **3a** in different solvents*

Solvent	Temperature (°C)	Product	Reaction Time	Yield (%)
[bmim][BF_4]	rt	**3a**	8h	90
MeOH	rt	**3a**	36h	65
EtOH	rt	**3a**	40h	65
toluene	rt	**3a**	3d	70

* Reaction conditions: 1 mmol of **1a** and **2** respectively, 1 mL of IL or 4 mL of VOCs.

On the other hand, one important feature of ionic liquids as reaction medium is the possibility of its recovery and reuse. Our study showed that the reuse of [bmim][BF_4] is feasible in all the above procedures. At completion of the above reactions, corresponding products were isolated by suction. The ionic liquid phase was then concentrated and dried under reduced pressure for reuse. No remarkable decrease in the efficiency of the reused ionic liquid was observed after 5 rounds.

As a conclusion, we have demonstrated that one-pot three-component reaction of aldehydes, ethyl cyanoacetate and 5-amino-3-methyl-1-phenylpyrazole could be smoothly carried out in [bmim][BF_4]. Through this reaction, pyrazolo[3,4-*b*]pyridin-6-ones or its hydrogenated derivatives were obtained effectively and selectively with or without $FeCl_3 \cdot 6H_2O$ at different reaction temperatures. The notable features of the procedures presented here are good selectivity, high efficiency, mild conditions, cleaner reaction profiles, simple operation process together with convenient and efficient recovery and reuse of the reaction medium.

EXPERIMENTAL

Melting points were measured by a Kofler micromelting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants J were given in Hz. Mass spectra were recorded on a Bruke Esquire 3000 mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

General procedure for the preparation of 4-aryl-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (3)

To 1 mL of [bmim][BF_4] were added aldehyde (**5**, 1 mmol) and ethyl cyanoacetate (**6**, 1 mmol). The mixture was stirred at 80 °C until the disappearance of **5**. Upon cooling to rt, 5-amino-3-methyl-1-phenylpyrazole (**2**, 1 mmol) was added and the mixture was stirred at rt for a certain period of time to complete the reaction (monitored by TLC). Upon completion, 2 mL of 50% EtOH in water was added. The solid precipitated was collected by suction and rinsed with water and cold EtOH, and then dried to give **3** with high purity. The ionic liquid layer was dried at 100 °C under reduced pressure to recover the ionic liquid.

3a. Pale yellow solid; ^{1}H NMR (DMSO-d_6): 1.44 (s, 1.28H, CH_3); 1.99 (s, 1.72H, CH_3); 4.84 (d, J = 12 Hz, 0.43H, CH); 4.86 (d, J = 7.2 Hz, 0.57H, CH); 4.96 (d, J = 12 Hz, 0.43H, CH); 5.20 (d, J = 7.2 Hz, 0.57H, CH); 7.35-8.32 (m, 9H, Ar-H); 11.34 (br s, 0.43H, NH); 11.40 (br s, 0.57H, NH); ^{13}C NMR (DMSO-d_6): 11.6, 12.6, 36.6, 41.9, 43.0, 100.9, 101.9, 116.0, 116.3, 123.1, 123.2, 124.1, 124.2, 127.3, 127.4, 129.0, 129.4, 130.1, 137.6, 137.7, 137.9, 145.0, 145.2, 146.4, 146.5, 147.3, 147.4, 163.1; MS (ESI): *m/z* 396 (M^++Na); Anal. Calcd for $C_{20}H_{15}N_5O_3$: C 64.34, H 4.05, N 18.76; Found: C 64.44, H 4.04, N 18.69.

3b. White solid; ^{1}H NMR (DMSO-d_6): 1.41 (s, 1.31H, CH_3); 1.99 (s, 1.69H, CH_3); 4.56 (d, J = 12.0 Hz, 0.44H, CH); 4.58 (d, J = 6.8 Hz, 0.56H, CH); 4.85 (d, J = 12.0 Hz, 0.44H, CH); 5.07 (d, J = 6.8 Hz, 0.56H, CH); 7.18-7.52 (m, 10H, Ar-H); 11.24 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 11.7, 12.4, 37.2, 42.4, 43.4, 102.1, 103.3, 116.2, 116.8, 122.9, 123.0, 127.2, 127.3, 127.5, 127.9, 128.1, 128.5, 128.9, 129.4, 137.6, 137.8, 137.9, 138.9, 139.0, 145.0, 145.1, 163.6; MS (ESI): *m/z* 351 (M^++Na); Anal. Calcd for $C_{20}H_{16}N_4O$: C 73.15, H 4.91, N 17.06; Found: C 73.06, H 4.95, N 17.15.

3c. White solid; ^{1}H NMR (DMSO-d_6): 1.45 (s, 1H, CH_3); 1.98 (s, 2H, CH_3); 4.62 (d, J = 12 Hz, 0.34H, CH); 4.64 (d, J = 7.2 Hz, 0.66H, CH); 4.86 (d, J = 12 Hz, 0.34H, CH); 5.09 (d, J = 7.2 Hz, 0.66H, CH); 7.18-7.49 (m, 9H, Ar-H); 11.28 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 11.6, 12.5, 36.5, 42.3, 43.3, 101.7, 102.7, 116.2, 116.5, 123.0, 123.1, 127.2, 127.3, 129.0, 129.3, 129.4, 130.5, 132.6, 132.7, 137.5, 137.6, 137.8, 137.9, 145.1, 163.3, 163.4; MS (ESI): *m/z* 385, 387 (M^++Na); Anal. Calcd for $C_{20}H_{15}ClN_4O$: C

66.21, H 4.17, N 15.44; Found: C 66.29, H 4.15, N 15.38.

3d. White solid; ^{1}H NMR (DMSO-d_6): 1.47 (s, 1.28H, CH_3); 2.01 (s, 1.72H, CH_3); 4.63 (d, J = 12 Hz, 0.43H, CH); 4.65 (d, J = 7.2 Hz, 0.57H, CH); 4.89 (d, J = 12 Hz, 0.43H, CH); 5.12 (d, J = 7.2 Hz, 0.57H, CH); 7.13-7.67 (m, 9H, Ar-H); 11.32 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 12.0, 12.9, 36.8, 42.6, 43.6, 102.0, 103.0, 116.6, 116.9, 121.6, 123.3, 123.4, 127.6, 127.7, 129.7, 130.1, 131.2, 132.3, 137.9, 138.0, 138.1, 138.5, 138.6, 145.4, 163.7, 163.8; MS (ESI): *m/z* 429, 431 (M^+ +Na); Anal. Calcd for $C_{20}H_{15}BrN_4O$: C 58.98, H 3.71, N 13.76; Found: C 58.89, H 3.72, N 13.81.

3e. Pale yellow solid; ^{1}H NMR (DMSO-d_6): 1.43 (s, 1.80H, CH_3); 1.98 (s, 1.20H, CH_3); 2.24 (s, 1.20H, CH_3); 2.31 (s, 1.80H, CH_3); 4.50 (d, J = 12 Hz, 0.60H, CH); 4.52 (d, J = 6.8 Hz, 0.40H, CH); 4.79 (d, J = 12 Hz, 0.60H, CH); 5.03 (d, J = 6.8 Hz, 0.40H, CH); 7.03-7.49 (m, 9H, Ar-H); 11.19 (br s, 0.6H, NH); 11.21 (br s, 0.4H, NH); ^{13}C NMR (DMSO-d_6): 11.7, 12.5, 20.7, 20.8, 37.0, 42.6, 43.5, 102.2, 103.4, 116.3, 116.7, 122.9, 123.0, 127.1, 127.2, 127.4, 128.4, 129.3, 129.5, 135.6, 135.9, 137.2, 137.3, 137.4, 137.6, 137.7, 137.8, 145.0, 145.3, 163.6, 163.7; MS (ESI): *m/z* 365 (M^+ +Na); Anal. Calcd for $C_{21}H_{18}N_4O$: C 73.67, H 5.30, N 16.36; Found: C 73.59, H 5.31, N 16.40.

3f. White solid; ^{1}H NMR ($CDCl_3$): 1.79 (s, 1.91H, CH_3); 2.14 (s, 1.09H, CH_3); 3.94 (d, J = 10.4 Hz, 0.63H, CH); 4.34 (d, J = 6.8 Hz, 0.37H, CH); 4.45 (d, J = 6.8 Hz, 0.37H, CH); 4.46 (d, J = 10.4 Hz, 0.63H, CH); 7.15-7.57 (m, 9H, Ar-H); 8.19 (br s, 0.63H, NH); 8.33 (br s, 0.37H, NH); ^{13}C NMR ($CDCl_3$): 12.1, 12.9, 38.5, 41.3, 42.8, 44.3, 99.6, 101.2, 114.0, 114.7, 122.9, 123.1, 126.0, 126.3, 127.6, 127.9, 128.5, 128.6, 129.0, 129.1, 130.1, 130.5, 130.8, 135.1, 135.4, 135.8, 136.6, 136.7, 138.6, 139.7, 146.2, 146.8, 161.5; MS (ESI): *m/z* 385, 387 (M^+ +Na); Anal. Calcd for $C_{20}H_{15}ClN_4O$: C 66.21, H 4.17, N 15.44; Found: C 66.30, H 4.17, N 15.39.

3g. White solid; ^{1}H NMR ($CDCl_3$): 1.57 (s, 2.44H, CH_3); 1.78 (s, 0.56H, CH_3); 2.35 (s, 2.44H, CH_3); 2.39 (s, 0.56H, CH_3); 3.97 (d, J = 10.0 Hz, 0.19H, CH); 4.32 (d, J = 6.8 Hz, 0.81H, CH); 4.42-4.44 (m, 1H, CH); 7.02-7.53 (m, 9H, Ar-H); 8.02 (br s, 0.19H, NH); 8.13 (br s, 0.81H, NH); ^{13}C NMR ($CDCl_3$): 12.1, 13.0, 21.5, 38.9, 41.5, 43.1, 102.2, 114.2, 122.9, 123.1, 124.6, 124.9, 128.2, 128.3, 128.4, 129.1, 129.3, 129.5, 130.1, 135.8, 136.6, 136.9, 138.9, 146.3, 162.0; MS (ESI): *m/z* 365 (M^+ +Na); Anal. Calcd for $C_{21}H_{18}N_4O$: C 73.67, H 5.30, N 16.36; Found: C 73.57, H 5.32, N 16.42.

General procedure for the preparation of 4-aryl-5-cyano-3-methyl-1-phenyl-7*H*-pyrazolo[3,4-*b*]-pyridin-6-one (4)

To 1 mL of [bmim][BF_4] were added aldehyde (**5**, 1 mmol) and ethyl cyanoacetate (**6**, 1 mmol). The mixture was stirred at 80 °C until the disappearance of **5**. Then, 5-amino-3-methyl-1-phenylpyrazole (**2**, 1 mmol) and $FeCl_3 \cdot 6H_2O$ (0.2 mmol) were added and the mixture was continued to be stirred at the same temperature for a certain period of time to complete the reaction (monitored by TLC). Upon completion,

the mixture was cooled to rt and 2 mL of 50% EtOH in water was added. The solid precipitated was collected by suction and rinsed with water and cold EtOH, and then dried to give **4** with high purity. The ionic liquid layer containing Fe (III) was dried at 100 °C under reduced pressure to recover the ionic liquid and the oxidant.

4a. Pale yellow solid; mp 290-292 °C (Lit.,[11] 308 °C); ^{1}H NMR (DMSO-d_6): 1.91 (s, 3H, CH_3); 7.35 (t, J = 7.6 Hz, 1H, Ar-H); 7.53 (t, J = 8.0 Hz, 2H, Ar-H); 7.89 (d, J = 8.4 Hz, 2H, Ar-H); 8.05 (d, J = 8.0 Hz, 2H, Ar-H); 8.42 (d, J = 8.4 Hz, 2H, Ar-H); 13.28 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) : 14.4, 88.5, 109.2, 115.4, 121.5, 123.7, 126.7, 129.3, 130.5, 138.2, 140.0, 143.8, 148.5, 151.3, 163.8; MS (ESI): *m/z* 394 (M^+ +Na).

4b. White solid; mp 173-175 °C (Lit.,[11] 183 °C); ^{1}H NMR ($CDCl_3$): 1.54 (s, 3H, CH_3); 5.41 (br s, 1H, NH); 7.29 (t, J = 7.6 Hz, 1H, Ar-H); 7.44-7.55 (m, 7H, Ar-H); 8.10 (d, J = 8.8 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): 14.2, 94.2, 106.5, 118.7, 121.8, 125.0, 127.8, 128.0, 128.2, 128.6, 135.1, 139.2, 143.8, 152.3, 152.5, 169.9; MS (ESI): *m/z* 349 (M^+ +Na).

4c. White solid; mp 275-277 °C (Lit.,[11] 278 °C); ^{1}H NMR (DMSO-d_6): 1.93 (s, 3H, CH_3); 7.33 (t, J = 7.2 Hz, 1H, Ar-H); 7.52 (t, J = 8.0 Hz, 2H, Ar-H); 7.59 (d, J = 8.4 Hz, 2H, Ar-H); 7.65 (d, J = 8.4 Hz, 2H, Ar-H); 8.04 (d, J = 7.6 Hz, 2H, Ar-H); 13.15 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.4, 91.4, 109.5, 115.6, 121.4, 126.6, 128.7, 129.2, 130.7, 132.5, 134.9, 138.2, 144.0, 149.1, 152.5, 163.8; MS (ESI): *m/z* 383, 385 (M^+ +Na).

4d. Pale yellow solid; mp 298-300 °C; ^{1}H NMR (DMSO-d_6): 1.93 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 7.33 (t, J = 7.2 Hz, 1H, Ar-H); 7.38 (d, J = 8.0 Hz, 2H, Ar-H); 7.43 (d, J = 8.0 Hz, 2H, Ar-H); 7.52 (t, J = 8.0 Hz, 2H, Ar-H); 8.05 (d, J = 7.6 Hz, 2H, Ar-H); 13.05 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.5, 21.1, 109.6, 115.9, 121.4, 126.5, 128.7, 129.1, 129.2, 130.7, 138.3, 139.6, 144.1, 154.1, 163.9; MS (ESI): *m/z* 363 (M^+ +Na); Anal. Calcd for $C_{21}H_{16}N_4O$: C 74.10, H 4.74, N 16.46; Found: C 74.18, H 4.68, N 16.41.

4e. Pale yellow solid; mp 281-283 °C; ^{1}H NMR (DMSO-d_6) : 1.93 (s, 3H, CH_3); 7.33 (t, J = 7.2 Hz, 1H, Ar-H); 7.50-7.53 (m, 4H, Ar-H); 7.79 (d, J = 8.4 Hz, 2H, Ar-H); 8.05 (d, J = 8.0 Hz, 2H, Ar-H); 13.15 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.4, 91.3, 109.4, 115.7, 121.4, 123.6, 126.6, 129.2, 130.9, 131.6, 132.8, 138.2, 144.0, 149.1, 152.5, 163.8; MS (ESI): *m/z* 427, 429 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}BrN_4O$: C 59.30, H 3.23, N 13.80; Found: C 59.21, H 3.30, N 13.85.

4f. Pale yellow solid; mp 243-245 °C; ^{1}H NMR (DMSO-d_6): 1.94 (s, 3H, CH_3); 7.34 (t, J = 7.6 Hz, 1H, Ar-H); 7.42 (t, J = 8.8 Hz, 2H, Ar-H); 7.53 (t, J = 8.0 Hz, 2H, Ar-H); 7.62-7.65 (m, 2H, Ar-H); 8.05 (d, J = 8.0 Hz, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): 14.4, 91.6, 109.7, 115.6, 115.7, 115.8, 121.5, 126.6, 129.2, 130.0, 131.2, 131.3, 138.3, 144.0, 152.9, 161.8, 163.8, 164.3; MS (ESI): *m/z* 367 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}FN_4O$: C 69.76, H 3.81, N 16.27; Found: C 69.80, H 3.75, N 16.21.

4g. White solid; mp 295-297 °C (Lit., [11] 320 °C); ^{1}H NMR (DMSO-d_6): 2.00 (s, 3H, CH_3); 3.86 (s, 3H, OCH_3); 7.14 (d, J = 8.4 Hz, 2H, Ar-H); 7.36 (t, J = 7.2 Hz, 1H, Ar-H); 7.51-7.57 (m, 4H, Ar-H); 8.08 (d, J = 7.6 Hz, 2H, Ar-H); 13.02 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 17.2, 58.0, 93.9, 112.3, 116.5, 118.5, 124.0, 128.2, 129.1, 131.8, 133.0, 140.9, 146.7, 151.6, 156.5, 163.1, 166.5; MS (ESI): *m/z* 379 (M^+ +Na).

4h. Yellow solid; mp 300-302 °C; ^{1}H NMR (DMSO-d_6): 1.90 (s, 3H, CH_3); 7.34 (t, J = 7.2 Hz, 1H, Ar-H); 7.53 (t, J = 7.6 Hz, 2H, Ar-H); 7.90 (t, J = 7.6 Hz, 1H, Ar-H); 8.05-8.06 (m, 3H, Ar-H); 8.43-8.47 (m, 2H, Ar-H); 13.25 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.4, 91.5, 109.6, 115.5, 121.4, 123.7, 124.8, 126.6, 129.3, 130.5, 135.1, 135.4, 138.2, 143.8, 147.7, 149.2, 151.0, 163.8; MS (ESI): *m/z* 394 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}N_5O_3$: C 64.69, H 3.53, N 18.86; Found: C 64.75, H 3.48, N 18.89.

4i. White solid; mp 252-254 °C; ^{1}H NMR (DMSO-d_6): 1.95 (s, 3H, CH_3); 7.36 (t, J = 7.6 Hz, 1H, Ar-H); 7.53-7.57 (m, 3H, Ar-H); 7.63 (t, J = 7.6 Hz, 1H, Ar-H); 7.68 (d, J = 8.0 Hz, 1H, Ar-H); 7.73 (s, 1H, Ar-H); 8.07 (d, J = 7.6 Hz, 2H, Ar-H); 13.21 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) : 14.7, 91.7, 109.9, 116.0, 121.7, 126.9, 128.0, 128.9, 129.6, 130.3, 130.9, 133.6, 135.9, 138.6, 144.3, 149.5, 152.4, 164.2; MS (ESI): *m/z* 383, 385 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}ClN_4O$: C 66.58, H 3.63, N 15.53; Found: C 66.66, H 3.55, N 15.54.

4j. Pale yellow solid; mp >360 °C; ^{1}H NMR (DMSO-d_6): 1.71 (s, 3H, CH_3); 7.09 (t, J = 7.6 Hz, 1H, Ar-H); 7.35-7.45 (m, 4H, Ar-H); 7.58 (s, 1H, Ar-H); 7.65 (d, J = 8.0 Hz, 1H, Ar-H); 8.23 (d, J = 8.0 Hz, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): 14.8, 95.5, 104.1, 119.9, 120.3, 121.7, 124.2, 128.1, 129.0, 130.8, 131.4, 131.9, 138.7, 140.6, 143.1, 149.4, 155.1, 170.0; MS (ESI): *m/z* 427, 429 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}BrN_4O$: C 59.28, H 3.23, N 13.83; Found: C 59.35, H 3.16, N 13.84.

4k. Pale yellow solid; mp 264-266 °C; ^{1}H NMR (DMSO-d_6): 1.94 (s, 3H, CH_3); 2.41 (s, 3H, CH_3); 7.34-7.37 (m, 3H, Ar-H); 7.41 (d, J = 7.6 Hz, 1H, Ar-H); 7.48 (t, J = 7.6 Hz, 1H, Ar-H); 7.55 (t, J = 8.0 Hz, 2H, Ar-H); 8.08 (d, J = 7.6 Hz, 2H, Ar-H); 13.09 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.7, 21.4, 109.9, 116.2, 121.8, 126.1, 126.9, 128.8, 129.5, 129.6, 130.9, 133.9, 138.3, 138.6, 144.5, 154.4, 164.2; MS (ESI): *m/z* 363 (M^+ +Na); Anal. Calcd for $C_{21}H_{16}N_4O$: C 74.10, H 4.74, N 16.46; Found: C 74.16 H 4.69, N 16.41.

4l. Pale yellow solid; mp 276-278°C; ^{1}H NMR (DMSO-d_6): 1.83 (s, 3H, CH_3); 7.37 (t, J = 7.6 Hz, 1H, Ar-H); 7.56 (t, J = 8.0 Hz, 2H, Ar-H); 7.77 (d, J = 7.2 Hz, 1H, Ar-H); 7.93 (t, J = 8.0 Hz, 1H, Ar-H); 8.02 (t, J = 8.0 Hz, 1H, Ar-H); 8.08 (d, J = 8.0 Hz, 2H, Ar-H); 8.40 (d, J = 7.6 Hz, 1H, Ar-H); 13.35 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 13.5, 91.5, 109.6, 115.4, 121.9, 125.7, 127.1, 128.7, 129.7, 131.8, 132.2, 135.2, 138.5, 143.9, 147.4, 149.5, 150.8, 164.0; MS (ESI): *m/z* 394 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}N_5O_3$: C 64.69, H 3.53, N 18.86; Found: C 64.75, H 3.50, N 18.83.

4m. Pale yellow solid; mp 290-292 °C; ^{1}H NMR (DMSO-d_6): 1.94 (s, 3H, CH_3); 7.34 (t, J = 7.6 Hz, 1H, Ar-H); 7.41-7.70 (m, 6H, Ar-H); 8.05 (d, J = 7.6 Hz, 2H, Ar-H); 13.28 (br s, 1H, NH); ^{13}C NMR

(DMSO-d_6): 13.3, 92.2, 109.7, 115.3, 116.0, 116.2, 121.0, 121.2, 121.6, 125.0, 126.7, 129.2, 131.1, 132.7, 132.8, 138.2, 143.8, 147.4, 149.1, 157.2, 159.7, 163.8; MS (ESI): *m/z* 367 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}FN_4O$: C 69.76, H 3.81, N 16.27; Found: C 69.70, H 3.85, N 16.35.

4n. Pale yellow solid; mp 285-287 °C; ^{1}H NMR (DMSO-d_6): 1.85 (s, 3H, CH_3); 7.34 (t, *J* = 7.6 Hz, 1H, Ar-H); 7.51-7.64 (m, 5H, Ar-H); 7.72 (d, *J* = 8.0 Hz, 1H, Ar-H); 8.06 (d, *J* = 8.0 Hz, 2H, Ar-H); 13.31 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 13.0, 91.9, 109.6, 115.1, 121.5, 126.7, 127.8, 129.3, 129.7, 130.5, 131.3, 131.9, 132.6, 138.2, 143.8, 149.1, 150.6, 163.8; MS (ESI): *m/z* 383, 385 (M^+ +Na); Anal. Calcd for $C_{20}H_{13}ClN_4O$: C 66.58, H 3.63, N 15.53; Found: C 66.49, H 3.65, N 15.46.

4o. White solid; mp 329-331 °C; ^{1}H NMR (DMSO-d_6): 1.94 (s, 3H, CH_3); 7.37 (t, *J* = 7.6 Hz, 1H, Ar-H); 7.55 (t, *J* = 7.6 Hz, 2H, Ar-H); 7.63 (d, *J* = 4.8 Hz, 2H, C_5H_4N); 8.07 (d, *J* = 8.0 Hz, 2H, Ar-H); 8.83 (d, *J* = 4.8 Hz, 2H, C_5H_4N); 13.26 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.6, 91.4, 109.3, 115.7, 121.9, 123.7, 127.0, 129.6, 138.5, 141.9, 144.1, 149.5, 150.4, 151.2, 164.1; MS (ESI): *m/z* 350 (M^+ +Na); Anal. Calcd for $C_{19}H_{13}N_5O$: C 69.71, H 4.00, N 21.39; Found: C 69.59, H 4.03, N 21.44.

4p. White solid; mp 310-312 °C; ^{1}H NMR (DMSO-d_6): 1.96 (s, 3H, CH_3); 7.37 (t, *J* = 7.6 Hz, 1H, Ar-H); 7.56 (t, *J* = 7.6 Hz, 2H, Ar-H); 7.64-7.67 (m, 1H, Ar-H); 8.07-8.09 (m, 3H, Ar-H); 8.80-8.81 (m, 2H, Ar-H); 13.24 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): 14.8, 92.1, 110.1, 115.9, 121.9, 123.9, 127.0, 129.6, 130.2, 137.0, 138.6, 144.3, 149.1, 149.5, 150.7, 151.4, 164.2; MS (ESI): *m/z* 350 (M^+ +Na); Anal. Calcd for $C_{19}H_{13}N_5O$: C 69.71, H 4.00, N 21.39; Found: C 69.62, H 4.05, N 21.34.

7. Yellow solid; mp 196-197 °C; ^{1}H NMR ($CDCl_3$): 2.15 (s, 6H, CH_3); 3.61 (s, 4H, NH_2); 5.34 (s, 1H, CH); 7.35-7.38 (m, 2H, Ar-H); 7.47-7.59 (m, 10H, Ar-H); 8.25 (d, *J* = 8.0 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): 12.2, 35.8, 100.2, 123.7, 127.1, 128.9, 129.2, 137.9, 142.0, 146.4, 147.6, 148.9; MS (ESI): *m/z* 502 (M^+ +Na).

8. Yellow solid; mp 273-274 °C (Lit.,[22] 270-272 °C); ^{1}H NMR ($CDCl_3$): 2.13 (s, 6H, CH_3); 7.32-7.36 (m, 2H, Ar-H); 7.56-7.60 (m, 4H, Ar-H); 7.75 (d, *J* = 7.2 Hz, 2H, Ar-H); 8.42 (d, *J* = 7.2 Hz, 4H, Ar-H); 8.50 (d, *J* = 7.6 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): 14.6, 112.5, 120.0, 123.0, 125.1, 128.6, 129.7, 137.6, 139.0, 140.8, 143.1, 148.1, 150.0; MS (ESI): *m/z* 483 (M^+ +Na).

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (No.20772025), the Program for Science & Technology Innovation Talents in Universities of Henan Province (No. 2008HASTIT006) and the Natural Science Foundation of Department of Education of Henan Province (No. 2008A150013).

REFERENCES

1. (a) F. A. Feurer, J. Luithle, S. N. Wirtz, G. Koenig, J. P. Stasch, E. Stahl, R. Schreiber, F. Wunder,

and D. Lang, PCT Int. Appl. WO 2004009589, 2004; (b) J. Ehlert, P. Ragan, A. Chen, W. R. Roeske, and H. I. Yamamura, *Eur. J. Pharmacol.*, 1982, **78**, 249.

2. Y. S. Sanghvi, S. B. Larson, R. C. Willis, R. K. Robins, and G. R. Revankar, *J. Med. Chem.*, 1989, **32**, 945.
3. S. Ludwig, O. Planz, H. H. Sedlacek, and S. Pleschka, PCT Int. Appl. WO 2004085682, 2004. (*Chem. Abstr.*, 2004, **141**, 307497).
4. (a) M. N. Elnagdi, M. R. H Elmoghayar, and K. U. Sadek, *Adv. Heterocycl Chem.*, 1990, **48**, 219; (b) C. R. Hardy, *Adv. Heterocycl. Chem.*, 1984, **36**, 343.
5. L. R. S. Dias, M. B. Santos, S. de Albuquerque, H. C. Castro, A. M. T. de Souza, A. C. C. Freitas, M. A. V. Divaio, L. M. Cabral, and C. R. Rodrigues, *Bioorg. Med. Chem.*, 2007, **15**, 211.
6. J. Witherington, V. Bordas, A. Gaiba, N. S. Garton, A. Naylor, A. D. Rawlings, B. P. Slingsby, D. G. Smith, A. K. Takle, and R. W. Ward, Bioorg. *Med. Chem. Lett.*, 2003, **13**, 3055.
7. R. H. Lin, P. J. Connolly, Y. H. Lu, G. Chiu, S. J. Li, Y. Yu, S. L. Huang, X. Li, S. L. Emanuel, S. A. Middleton, R. H. Gruninger, M. Adams, A. R. Fuentes-Pesquera, and L. M. Greenberger, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4297.
8. J. L. Falcó, M. Lloveras, I. Buira, J. Teixidó, J. I. Borrell, E. Méndez, J. Terencio, A. Palomer, and A. Guglietta, *Eur. J. Med. Chem.*, 2005, **40**, 1179.
9. G. P. Sagitullina, L. A. Listitskaya, M. A. Vorontsova, and R. S. Stgitullin, *Mendeleev Commun.*, 2007, **17**, 192.
10. M. H. Elnagdi, A. M. Negm, and K. U. Sadek, *Synlett*, 1994, 27.
11. J. Quiroga, M. Alvarado, B. Insuasty, R. Moreno, E. Ravina, I. Estevez, and R. H. de Almedia, *J. Heterocycl. Chem.*, 1999, **36**, 1311.
12. J. Quiroga, A. Hormaza, B. Insuasty, and M. Marquez, *J. Heterocycl. Chem.*, 1998, **35**, 409.
13. J. Quiroga, S. Kruz, B. Insuasty, R. Abonia, M. Nogueras, A. Sanchez, J. Cobo, and J. N. Low, *J. Heterocycl. Chem.*, 2001, **38**, 53.
14. (a) S. Zhu, S. Tu, T. Li, X. Zhang, S. Ji, and Y. Zhang, *Chin. J. Org. Chem.*, 2005, **25**, 987 (in Chinese); (b) S. Tu, Q. Wang, Y. Zhang, J. Xu, J. Zhang, X. Zhu, and F. Shi, *J. Heterocycl. Chem.*, 2007, **44**, 811.
15. (a) J. Ranke, S. Stolte, R. Stormann, J. Arning, and B. Jastorff, *Chem. Rev.*, 2007, **107**, 2183; (b) J. Dupont, R. F. de Souza, and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; (c) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (d) R. Sheldon, *Chem. Commun.*, 2001, 2399.
16. (a) P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed.*, 2000, **39**, 3772; (b) C. M. Gordon, *Appl. Catal. A*, 2001, **222**, 101.
17. M. J. Earle, S. P. Katdare, and K. R. Seddon, *Org. Lett.*, 2004, **6**, 707.

18. (a) X. Fan, X. Hu, X. Zhang, and J. Wang, *Aust. J. Chem.*, 2004, **57**, 1067; (b) X. Fan, X. Hu, X. Zhang, and J. Wang, *Can. J. Chem.*, 2005, **83**, 16; (c) X. Fan, Y. Li, X. Zhang, and J. Wang, *Can. J. Chem.*, 2006, **84**, 794; (d) X. Zhang, X. Fan, H. Niu, and J. Wang, *Green Chem.*, 2003, **5**, 267.
19. (a) K. Ding, Y. Wang, L. Zhang, and Y. Wu, *Tetrahedron*, 1996, **52**, 1005; (b) F. Toda, K. Tanaka, and S. Iwata, *J. Org. Chem.*, 1989, **54**, 3007.
20. X. Zhang, X. Li, X. Wang, D. Li, and X. Fan, *Acta Cryst.*, 2008, **E64**, o1888. CCDC reference number 694824.
21. D. W. Kung and T. T. Wager, *United States Patent* 7300944, 2007.
22. J. Quiroga, J. Portilla, B. Insuasty, R. Abonía, M. Nogueras, M. Sortino, and S. Zacchino, *J. Heterocycl. Chem.*, 2005, **42**, 61.