An Efficient Synthesis of New Class of Pyrazolo[3,4-*b*]pyridine-6-one Derivatives by A Novel Cascade Reaction

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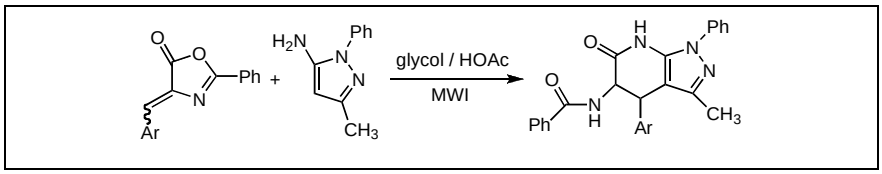

A novel cascade reaction of 4-arylidene-2-phenyl-1,3-oxazol-5(4*H*)-one with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine was described and a number of new pyrazolo[3,4-*b*]pyridine-6-one derivatives were synthesized. This new protocol has the advantages of shorter time, higher yields, and lower cost as well as easier operation.

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INTRODUCTION

Pyrazolo[3,4-*b*]pyridines are attractive targets in organic synthesis due to their significant biological and pharmacological properties. For example, a number of pyrazolo[3,4-*b*]pyridines display interesting anxiolytic activity [1] (*e.g.* tracazolate [2]), are potentially biologically active compounds as new inhibitors of xantine oxidases [3]. Besides, they have been proved to be active against Gram positive and Gram negative bacteria [4] and as cholesterol formation-inhibiting compounds [5]. More importantly, they are also promising for the treatment of cataracts associated with diabetes [6]. In addition, these compounds also exhibit interesting agricultural activities [7]. Recent search of literature reveals that some pyrazolo[3,4-*b*]pyridines have been identified as potent, selective CDK inhibitors and as potent inhibitors of glycogen synthase kinase-3 [8].

Due to their diverse biological activities, several groups have been interested in the synthesis of derivatives of this structural type. For example, Falcó and co-workers [9] have reported the synthesis of pyrazolo[3,4-*b*]pyridine-6-ones by treatment of hydrazine or alkyl substituted hydrazine ($RNHNH_2$) with 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile, which in advance were synthesized by the reaction of α,β-unsaturated ester with malononitrile in NaOMe/MeOH. Goda *et al* [10] have reported the synthesis of pyrazolo[3,4-*b*]pyridines through three steps. However, these synthetic methods have the disadvantages of involving multi-step reactions, drastic reaction conditions, longer synthetic route and reaction time. Therefore, the development of simple and facile methods for the preparation of pyrazolo[3,4-*b*]pyridine derivatives is still strongly desirable.

Cascade reactions are powerful synthetic tools that involve sequential bond-forming events in which the product of one reaction is preprogrammed to be the starting material for the next one in a domino-like process [11]. Such methods enable the rapid assembly of complex molecular architectures from simple starting materials [12,13]. Unlike stepwise bond formation toward a target molecule, such process has the advantages of greatly enhanced synthetic efficiency, while generating less waste and minimizing the excessive handling. Hence, there is an ongoing demand for new types of cascade reaction in the synthesis of natural products and other compounds having useful properties.

In the context of our interest in the design and development of useful tactics for the synthesis of nitrogen–contained heterocycles [14], in this paper, we wish to report an efficient synthesis of a new series of *N*-(4-aryl-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamides **3** by a novel cascade reaction. To the best of our knowledge, the synthesis of pyrazolo[3,4-*b*]pyridine-6-ones substituted by benzamide in 5-position has seldom been reported.

RESULTS AND DISCUSSION

The desired products **3** were easily obtained by treatment of 4-arylidene-2-phenyl-1,3-oxazol-5(4*H*)-ones **1**, which in advance were conveniently prepared following a literature procedure [15], with an equimolar amount of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** in the presence of ethylene glycol and glacial acetic acid under MWI (Scheme 1).

In order to search for the optimum reaction condition, different organic solvents such as ethylene glycol, glacial acetic acid, DMF and mixed solvent of ethylene glycol with glacial acetic acid were tested in the synthesis of **3a** at 100 °C under MWI. As shown in Table 1, we could see

the reaction in the mixed solvent of ethylene glycol with glacial acetic acid (the preferred volume ratio is 2:1) gave the best result (Entry 5, Table 1).

Moreover, to further optimize the reaction temperature, the synthesis of **3a** was performed in the mixed solvent of ethylene glycol with glacial acetic acid (2:1, V/V) at the temperatures ranging from 100 °C to 160 °C in the increment of 10 °C each time at 300 W. As illustrated in Table 2, when the temperature was increased from 100 °C to 140 °C, the yield of product **3a** was obviously improved. However, no significant increase in the yield of product **3a** was observed as the reaction temperature was raised from 140 °C to 160 °C. Therefore, the temperature of 140 °C was chosen for all further microwave-assisted reactions.

The power of microwave irradiation was optimized by carrying out the same reaction of synthesizing **3a** at the powers of 50, 100, 150, 200, 250 and 300 W respectively, using mixed ethylene glycol with glacial acetic acid as solvent (2:1, V/V) at 140 °C (Table 3). The results indicated that microwave irradiation at 200 W gave the highest yield (Entry 4, Table 3). Hence, microwave power of 200 W was selected as the optimum power.

Under these optimized reaction conditions, we synthesized a series of products **3** with this simple reaction procedure. The results were summarized in Table 4.

Additionally, the synthesis of **3a** under conventional heating and MWI was compared to demonstrate the specific microwave effect that might be involved in the reaction. The reaction under conventional heating conditions remained largely incomplete in very low yields after a short reaction period (4 min).

Table 1

Solvent optimization for the synthesis of **3a** under MWI

Entry	Solvent	Time/min	Yield/%
1	DMF	8	37
2	HOAc	8	46
3	glycol	8	52
4	glycol/HOAc(3:1)	7	61
5	glycol/HOAc (2:1)	7	68
6	glycol/HOAc (1:1)	7	65

Table 2

Temperature optimization for the synthesis of **3a** under MWI

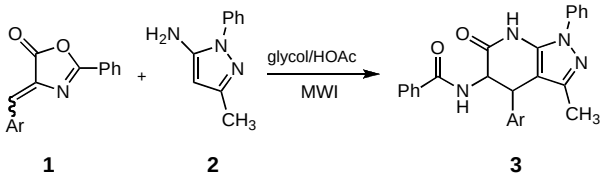
Temp / °C	Time / min	Yield / %
100	7	68
110	6	72
120	6	73
130	6	78
140	5	85
150	5	85
160	4	84

Table 3

Power optimization for the synthesis of **3a** under MWI

Entry	Power/W	Time/min	Yield/%
1	50	5	35
2	100	5	56
3	150	5	76
4	200	5	91
5	250	5	87
6	300	5	85

Scheme 1



1 **2** **3**

Instead, the same reaction under MWI exhibited remarkable advantages over the conventional heating by not only significantly reducing the reaction time, but also improving the reaction yield dramatically.

To examine the efficiency and applicability of the novel cascade reaction, various aldehydes were tested. Results indicate that this protocol can be applied to aromatic aldehydes either with electron-withdrawing groups (such as nitro group) or with electron-donating groups (such as

Table 4

Physical data of products **3**

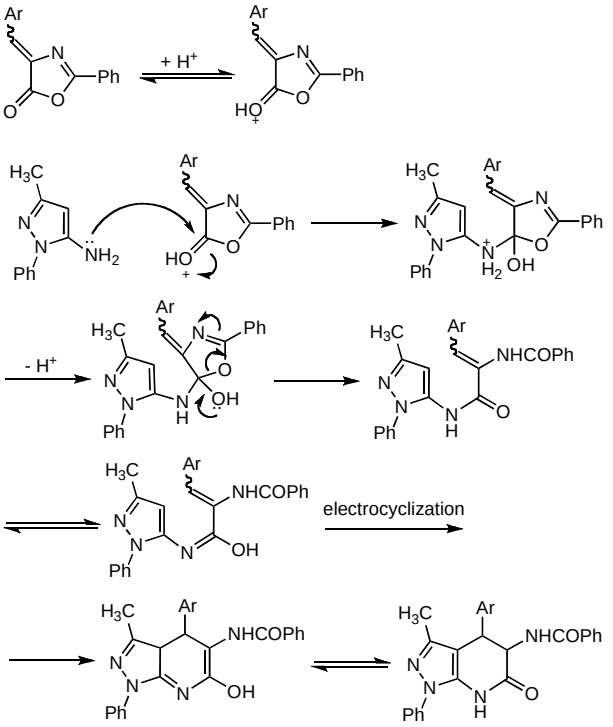
Entry	Product	Ar	Time / min	Yield / %	Mp / °C
1	3a	4-BrC_6H_4	5	91	242-243
2	3b	4-ClC_6H_4	4	88	255-257
3	3c	4-FC_6H_4	4	90	245-247
4	3d	2,4-$Cl_2C_6H_3$	5	85	261-263
5	3e	3,4-$Cl_2C_6H_3$	5	87	265-267
6	3f	4-$CH_3OC_6H_4$	6	82	264-266
7	3g	C_6H_4	6	83	268-270
8	3h	3-$NO_2C_6H_4$	5	86	255-257
9	3i	4-$CH_3C_6H_4$	6	81	267-269
10	3j	3,4-$(OCH_2O)C_6H_3$	6	79	281-283
11	3k	2-$CH_3OC_6H_4$	6	77	279-281
12	3l	3,4,5-$(CH_3O)_3C_6H_2$	5	82	269-270
13	3m	3,4-$(CH_3O)_2C_6H_3$	6	83	234-236

alkoxyl group). However, the desired results were not obtained when aliphatic aldehydes and heterocyclic aldehydes were employed.

All the products were characterized by IR, ^{1}H NMR spectra and elemental analyses. The structure of **3b** was also determined by X-ray crystallography (Figure 1) [16].

Although the detailed mechanism of the reaction has not been established in experimental manner, the formation of **3** could be explained by a reaction sequence presented in Scheme 2. The amine attacks the reactive lactone and then the imidate tautomer of the new amide (an open hetero-triene system) undergoes a symmetry allowed electrocyclic ring closure to a cyclic hetero-diene intermediate, which gives the product after tautomerization.

Scheme 2



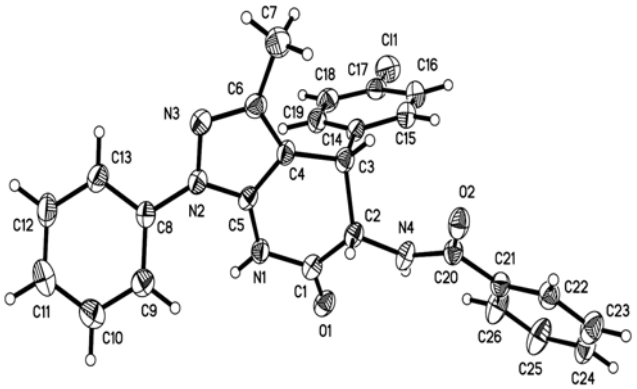


Figure 1 ORTEP diagram of **3b**

In summary, we have disclosed a novel cascade reaction that offered a simple and efficient route for the synthesis of a new type of highly functionalized pyrazolo[3,4-*b*]pyridin-6-one derivatives. This method has the advantages of shorter reaction time, higher yields as well as convenient operation. Most importantly, we have successfully introduced a benzamido group in the 5-position of pyrazolo[3,4-*b*]pyridine-6-ones. This new series of pyrazolo[3,4-*b*]pyridin-6-one derivatives may prove to be of biological interest and provide new class of biologically active compounds for biomedical screening. An extension of this work is currently under investigation.

EXPERIMENTAL

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT-IR-tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General Procedure for 4-arylidene-2-phenyl-1,3-oxazol-5(4*H*)-one (1). A mixture of aromatic aldehyde (2 mmol), hippuric acid (2 mmol) and acetic anhydride (0.5 mL) was added to a 10 mL reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under microwave irradiation at 180 W power and 120 ℃ for 4-7 minutes. The reaction mixture was cooled to room temperature, then poured into water (50 mL), filtered to give crude product, which was further purified by recrystallization from EtOH.

General Procedure for *N*-(4-aryl-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3). The reactions were performed in a 10 mL Emrys™ reaction vial, a 4-arylidine-2-phenyl-1,3-oxazol-5(4*H*)-ones **1** (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** (1 mmol), ethylene glycol and glacial acetic acid (2 mL) (2:1, V/V) were mixed and then capped. The mixture was irradiated at 200 W at 140 °C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH (**3a**-**3m**). All the products were characterized by IR, ^{1}H NMR spectral data.

***N*-(4-(4-bromophenyl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3a).** This compound was obtained according to above general procedure; ir (potassium bromide): 3369, 3145, 3069, 2923, 1706, 1642, 1577, 1541, 813, 761, 690; ^{1}H nmr (DMSO-d_6) (δ, ppm): 11.10 (s, 1H, NH), 7.94 (d, 1H, NH, J = 6.8 Hz), 7.78 (d, 2H, ArH, J = 7.2 Hz), 7.62-7.37 (m, 10H, ArH), 6.94 (d, 2H, ArH, J = 8.0 Hz), 5.30 (m, 1H, CH), 4.58 (d, 1H, CH, J = 7.6 Hz), 2.03 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{21}BrN_4O_2$, C, 62.28; H, 4.22; N, 11.17. Found: C, 62.41; H, 4.05; N, 11.28

***N*-(4-(4-chlorophenyl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3b).** This compound was obtained according to above general procedure; ir (potassium bromide): 3369, 3146, 3068, 2924, 1707, 1642, 1578, 1517, 817, 762, 691; ^{1}H nmr (DMSO-d_6) (δ, ppm): 11.08 (s, 1H, NH), 7.89 (d, 1H, NH, J = 6.8 Hz), 7.79 (d, 2H, ArH, J =

7.2 Hz), 7.62 (d, 2H, ArH, J = 7.6 Hz), 7.58-7.33 (m, 8H, ArH), 7.01(d, 2H, ArH, J = 8.4 Hz), 5.31 (m, 1H, CH), 4.60 (d, 1H, CH, J = 7.6 Hz), 2.03 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{21}ClN_4O_2$, C, 68.34; H, 4.63; N, 12.26. Found: C, 68.51; H, 4.43; N, 12.42.

***N*-(4-(4-fluorophenyl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3c).** This compound was obtained according to above general procedure; ir (potassium bromide): 3374, 3148, 3070, 2925, 1706, 1642, 1578, 1507, 814, 763, 692; ^{1}H nmr (DMSO-d_6) (δ, ppm): 11.10 (s, 1H, NH), 7.83 (d, 1H, NH, J = 6.8 Hz), 7.77 (d, 2H, ArH, J = 7.2 Hz), 7.61 (d, 2H, ArH, J = 7.6 Hz), 7.56-7.37 (m, 6H, ArH), 7.14-6.70 (m, 4H, ArH), 5.29 (m, 1H, CH), 4.60 (d, 1H, CH, J = 7.6 Hz), 2.03 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{21}FN_4O_2$, C, 70.90; H, 4.81; N, 12.72. Found: C, 70.75; H, 4.69; N, 12.53

***N*-(4-(2,4-dichlorophenyl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3d).** This compound was obtained according to above general procedure; ir (potassium bromide): 3382, 3125, 3068, 2921, 1704, 1650, 1576, 1546, 823, 759, 691; ^{1}H nmr (DMSO-d_6) (δ, ppm): 11.08 (s, 1H, NH), 7.89 (d, 1H, NH, J = 6.8 Hz), 7.79 (d, 1H, ArH, J = 7.2 Hz), 7.62 (d, 2H, ArH, J = 7.6 Hz), 7.58-7.33 (m, 8H, ArH), 7.01(d, 2H, ArH, J = 8.4 Hz), 5.31 (m, 1H, CH), 4.60 (d, 1H, CH, J = 7.6 Hz), 2.00 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{20}Cl_2N_4O_2$, C, 63.55; H, 4.10; N, 11.40. Found: C, 63.38; H, 4.22; N, 11.21.

***N*-(4-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3e).** This compound was obtained according to above general procedure; ir (potassium bromide): 3328, 3165, 3062, 2938, 1699, 1635, 1599, 1538, 892, 731, 692; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.84 (s, 1H, NH), 8.71 (d, 1H, NH, J = 8.4 Hz), 7.75 (d, 2H, ArH, J = 6.4 Hz), 7.67 (s, 1H, ArH), 7.63-7.52 (m, 6H, ArH), 7.47 (d, 2H, ArH, J = 7.6 Hz), 7.40 (d, 2H, ArH, J = 6.8 Hz), 5.03 (m, 1H, CH), 4.44 (d, 1H, CH, J = 8.0 Hz), 1.54 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{20}Cl_2N_4O_2$, C, 63.55; H, 4.10; N, 11.40. Found: C, 63.71; H, 4.21; N, 11.25.

***N*-(4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3f).** This compound was obtained according to above general procedure; ir (potassium bromide):: 3318, 3162, 3052, 2933, 1696, 1643, 1550,1521, 824, 797, 695; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.04 (s, 1H, NH), 8.04 (d, 1H, NH, J = 8.0 Hz), 7.64-7.52 (m, 8H, ArH), 7.38-7.25 (m, 4H, ArH), 6.95 (d, 2H, ArH, J = 8.8 Hz), 5.12 (m, 1H, CH), 4.62 (d, 1H, CH, J = 7.2 Hz), 3.76 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3). *Anal* calcd. for $C_{27}H_{24}N_4O_3$, C, 71.67; H, 5.35; N, 12.38. Found: C, 71.81; H, 5.23; N, 12.19.

***N*-(4,5,6,7-tetrahydro-3-methyl-6-oxo-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3g).** This compound was obtained according to above general procedure; ir (potassium bromide): 3342, 3163, 3061, 2946, 1697, 1643, 1578, 1547, 818, 754, 693; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.83 (s, 1H, NH), 8.70 (d, 1H, NH, J = 8.8 Hz), 7.74 (d, 2H, ArH, J = 6.8 Hz), 7.59-7.50 (m, 9H, ArH), 7.46-7.24 (m, 4H, ArH), 5.05 (m, 1H, CH), 4.40 (d, 1H, CH, J = 7.2 Hz), 1.46 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{22}N_4O_2$, C, 73.92; H, 5.25; N, 13.26. Found: C, 73.76; H, 5.38; N, 13.12.

***N*-(4,5,6,7-tetrahydro-3-methyl-4-(3-nitrophenyl)-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3h).** This compound was obtained according to above general procedure; ir (potassium bromide): 3362, 3149, 3066, 2977, 1709, 1647, 1578, 1529, 808, 754, 693; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.89 (s, 1H, NH), 8.73 (d, 1H, NH, J = 8.8 Hz), 8.28 (s, 1H, ArH), 8.14 (d, 1H, ArH, J = 8.0 Hz), 7.88 (d, 1H, ArH, J = 7.2 Hz), 7.72-7.39 (m, 11H, ArH), 5.11 (m, 1H, CH), 4.57 (d, 1H, CH, J = 7.2 Hz), 1.50 (s, 3H, CH_3). *Anal* calcd. for $C_{26}H_{21}N_5O_4$, C, 66.80; H, 4.53; N, 14.98. Found: C, 66.71; H, 4.64; N, 14.77.

***N*-(4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-4-p-tolyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3i).** This compound was obtained according to above general procedure; ir (potassium bromide): 3372, 3137, 3059, 2922, 1703, 1639, 1577, 1542, 813, 756, 690; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.80 (s, 1H, NH), 8.68 (d, 1H, NH, J = 8.8 Hz), 7.75 (d, 2H, ArH, J = 6.8 Hz), 7.57 (d, 2H, ArH, J = 7.2 Hz), 7.54-7.38 (m, 6H, ArH), 7.25 (d, 2H, ArH, J =8.0 Hz), 7.14 (d, 2H, ArH, J = 8.0 Hz), 5.01 (m, 1H, CH), 4.40 (d, 1H, CH, J = 8.0 Hz), 2.27 (s, 3H, CH_3), 1.48 (s, 3H, CH_3). *Anal* calcd. for $C_{27}H_{24}N_4O_2$, C, 74.29; H, 5.54; N, 12.84. Found: C, 74.42; H, 5.34; N, 12.67.

***N*-(4-(benzo[*d*][1,3]dioxol-5-yl)-4,5,6,7-tetrahydro-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3j).** This compound was obtained according to above general procedure; ir (potassium bromide): 3297, 3162, 3066, 2921, 1702, 1638, 1601, 1545, 810, 758, 692; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.78 (s, 1H, NH), 8.66 (d, 1H, NH, J = 8.8 Hz), 7.76 (d, 2H, ArH, J = 7.2 Hz), 7.57-7.35 (m, 8H, ArH), 6.94 (s, 1H, ArH), 6.85-6.82 (m, 2H, ArH), 5.99 (s, 2H, OCH_2O), 5.01 (m, 1H, CH), 4.32 (d, 1H, CH, J = 7.6 Hz), 1.55 (s, 3H, CH_3). *Anal* calcd. for $C_{27}H_{22}N_4O_4$, C, 69.52; H, 4.75; N, 12.01. Found: C, 69.38; H, 4.92; N, 11.92.

***N*-(4,5,6,7-tetrahydro-4-(2-methoxyphenyl)-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3k).** This compound was obtained according to above general procedure; ir (potassium bromide): 3354, 3136, 3028, 2918, 1697, 1643, 1599, 1514, 846, 761, 655; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.89 (s, 1H, NH), 8.56 (s, 1H, NH), 7.60 (d, 2H, ArH, J = 7.2 Hz), 7.58-735 (m, 8H, ArH), 7.23-7.19 (m, 2H, ArH), 7.01-6.81 (m, 2H, ArH), 5.21 (m, 1H, CH), 4.88 (d, 1H, CH, J = 8.0 Hz), 3.54 (s, 3H, OCH_3), 1.99 (s, 3H, CH_3). *Anal* calcd. for $C_{27}H_{24}N_4O_3$, C, 71.67; H, 5.35; N, 12.38. Found: C, 71.53; H, 5.50; N, 12.19.

***N*-(4,5,6,7-tetrahydro-4-(3,4,5-trimethoxyphenyl)-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3l).** This compound was obtained according to above general procedure; ir (potassium bromide): 3328, 3130, 3064, 2998, 1716, 1636, 1574, 1531, 825, 762, 634; ^{1}H nmr (DMSO-d_6) (δ, ppm): 10.79 (s, 1H, NH), 8.66 (d, 1H, NH, J = 8.8 Hz), 7.75 (d, 2H, ArH, J = 7.6 Hz), 759-7.35 (m, 8H, ArH), 6.68 (s, 2H, ArH), 5.01(m, 1H, CH), 4.35 (d, 1H, CH, J = 7.6 Hz), 3.71 (s, 6H, $2OCH_3$), 3.62 (s, 3H, OCH_3), 1.60 (s, 3H, CH_3). *Anal* calcd. for $C_{29}H_{28}N_4O_5$, C, 67.96; H, 5.51; N, 10.93. Found: C, 68.06; H, 5.72; N, 11.13.

***N*-(4,5,6,7-tetrahydro-4-(3,4-dimethoxyphenyl)-3-methyl-6-oxo-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)benzamide (3m).** This compound was obtained according to above general procedure; ir (potassium bromide): 3345, 3132, 3018, 2991, 1699, 1643, 1559, 1511, 820, 768, 685; ^{1}H nmr (DMSO-d_6) (δ, ppm): 11.03 (s, 1H, NH), 8. 59 (d, 1H, NH, J = 7.6 Hz), 7.78 (d, 2H, ArH, J = 7.2 Hz), 7.70 (d, 1H, ArH, J = 6.4 Hz), 7.64-7.38 (m, 7H, ArH), 6.83 (d, 1H, ArH, J = 8.4 Hz), 6.58 (s, 1H, ArH), 6.46 (d, 1H, ArH, J = 6.8 Hz), 5.23 (m, 1H, CH), 4.46 (d, 1H, CH J = 7.2 Hz), 3.69 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.05 (s, 3H, CH_3). *Anal* calcd. for $C_{28}H_{26}N_4O_4$, C, 69.70; H, 5.43; N, 11.61. Found: C, 69.88; H, 5.21; N, 11.45.

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REFERENCES AND NOTES

[1] Hoehn, H.; Denzel, Th.; Janssen, W. *J. Heterocycl. Chem.* **1972**, *9*, 235-253.

[2] Meiners, B. A.; Salama,A. I. *Eur. J. Pharmacol.* **1982**, *78*, 315-322.

[3] Lynck, B. M.; Khan, M. A.; Teo, H. C.; Pedrotti, F. *Can. J. Chem.* **1988**, *66*, 420-628.

[4] El-Dean, A. M.; Aralla, A. A.; Mohamed, T. A.; Geies, A. A.; *Z. Naturfosch*, Teil B **1991**, *46*, 541-546.

[5] Fujikama, Y.; Suzuki, M.; Iwasaki, H.; Sakashita, M.; Kitahara, M. European Patent Applied, EP 339,358, 1989; *Chem Abstr*., **1990**, *113*, 23903.

[6] Abdel Hafez, A. A.; Awad, I. M. A.; Ahmed, R. A. *Collect. Czech. Chem. Commun*. **1993**, *58*, 1198-1202.

[7] Joshi, K.; Dubey, K. and Dandia, A. *Pharmazie*, **1981**, *36*, 336-337.

[8] (a) Witherington, J.; Bordas, V.; Garland, S. L.; Hickey, D. M. B.; Ife, R. J.; Liddle, J.; Saunders, M.; Smith, D. G.; Ward, R. W. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1577-1580. [b] Witherington, J.; Bordas, V.; Gaiba, A.; Garton, N. S.; Naylwor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K. and Ward, R. W. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3055-3057. [c] Witherington, J.; Bordas, V.; Gaiba, A.; Naylwor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K. and Ward, R. W. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3059-3062. [d] Misra, R. N.; Rawlins, D. B.; Xiao, H.; Shan, W.; Bursuker, I.; Kellar, K. A.; Mulheron, J. G.; Sack, J. S.; Tokarski, J. S.; Kimball, S. D. and Webster, K. R. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1133-1136.

[9] Falcó, J. L. ; Lloveras, M.; Buira, I.; Teixidó, J.; Borrell, J. I.; Méndez, E.; Terencio, J.; Palomer, A.; Guglietta, A. *Eur. J. Med. Chem.* **2005**, *40*, 1179-1187.

[10] Goda, F. E.; Abdel-Aziz A. A.-A. and Attef, O. A. *Bioorg. Med. Chem. Lett*. **2004**, *12*, 1845-1852.

[11] (a) Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115-136; (b) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, 47-62; (c) Tietze, L. F., Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967-1983.

[12] (a) Seigal, B. A., Fajardo, C., Snapper, M. L. *J. Am. Chem. Soc*., **2005**, *127,* 16329-16332; (b) Ohno, H., Yamamoto, M., Iuchi, M., Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103-5106; (c) Kusama, H., Yamabe, H., Onizawa, Y., Hoshino, T., Iwasawa, N. *Angew. Chem., Int. Ed*. **2005**, *44*, 468-470; (d) de Meijere, A.., von Zezschwitz, P., Bräse, S. *Acc. Chem. Res*. **2005**, *38*, 413-422; (e) von Wangelin, J. A., Neumann, H., Gördes, D., Klaus, S., Strübing, D., Beller, M. *Chem. Eur. J*. **2003**, *9*, 4286-4294; (f) Neumann, H., von Wangelin, J. A., Klaus, S., Strübing, D., Gördes, D., Beller, M. *Angew. Chem., Int. Ed*. **2003**, *42*, 4503-4507; (g) Ashfeld, B. L., Miller, K. A., Smith, A. J., Tran, K., Martin, S. F. *Org. Lett*. **2005**, *7*, 1661-1663; (h) Fedou, N. M., Parsons, P. J., Viseux, E. M. E., A. Whittle, J. *Org. Lett*. **2005**, *7*, 3179-3182.

[13] (a) Tejedor, D., García-Tellado, F., Marrero-ellado, J. J., de Armas, P. *Chem. Eur. J*. **2003**, *9*, 3122-3131; (b) de Armas, P., García-Tellado, F., Marrero-Tellado, J. J., Tejedor, D., Maestro, M. A., Gonzalez-Platas, J. *Org. Lett*. **2001**, *3*, 1905-1908.

[14] (a) Tu, S.; Fang, F.; Miao, C.; Jiang, H.; Feng, Y.; Shi, D.; Wang, X. *Tetrahedron Lett*. **2003**, *44*, 6153-6155; (b) Tu, S.; Fang, F.; Zhu, S.; Li, T.; Zhang, X.; Zhuang, Q. *Synlett.* **2004**, *3*, 537-539; (c) Tu, S.; Li, T.; Shi, F.; Wang, Q.; Zhang, J.; Xu, J.; Zhu, X.; Zhang, X.; Zhu, S.; Shi, D. *Synthesis*, **2005**, *18*, 3045-3050; (d) Tu, S.; Zhang, J.; Zhu, X.; Xu, J.; Zhang, Y.; Wang, Q.; Jia, R.; Jiang, B.; Zhang, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3578-3581; (e) Tu, S.; Zhu, X.; Zhang, J.; Xu. J.; Zhang, Y.; Wang, Q.; Jia, R.; Jiang, B.; Zhang, J.; Yao, C. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2925-2928.

[15] Tu, S. J.; Jiang, H.; Zhuang, Q. Y.; Miao, C. B.; Shi, D. Q.; Wang, X. S.; Gao, Y. *Chin. J. Org. Chem.* **2003**, *23*, 491-492.

[16] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation λ = 0.71073 Å). Crystal data for 3b: $C_{26}H_{21}ClN_4O_2$, colorless, crystal dimension 0.42x012x0.09 mm, monoclinic, space group P2(1)/n, a = 9.785(5), b = 9.658(5), c = 24.932(12), a = 90°, b = 101.283(8)°, g = 90°, V = 2310.7(19)Å3, Mr = 456.92, Z = 4, Dc = 1.313 Mg/m3, λ = 0.71073 Å, μ(Mokα) = 0.196 mm-1, F(000) = 952, S = 1.005, R1 = 0.0514, wR2 = 0.1059.