An Efficient and Stereoselective Synthesis of Pyrazolo[4,3-*c*]pyridine Derivatives under Microwave Heating

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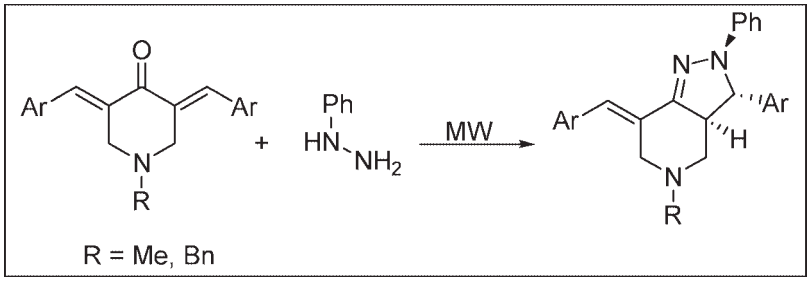

A practical, inexpensive, and rapid method for the stereoselective synthesis of pyrazolo[4,3-*c*]pyridine derivatives *via* microwave-assisted reactions of 3,5-diarylidenepiperidin-4-ones with phenylhydrazine in ethylene glycol. This method has the advantages of good yield, operational simplicity, and simple purification procedure.

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INTRODUCTION

In recent years, microwave-assisted organic synthesis has received much attention [1] because of its shorter reaction times and formation of cleaner products compared with conventional heating. It is clear that the application of microwave technology to rapid synthesis of biologically significant molecules would be of great value for library generation [2]. This technology has recently been recognized as a useful tool for a drug-discovery program [3]. In addition, microwave-assisted synthesis of pyrazoles and pyrazolines *via* the cyclocondensation of phenylhydrazine with α,β-unsaturated ketones has been reported [4]. In conjunction with our continuous interest in combinatorial synthesis [5], we explore the use of microwave irradiation as a heating source in the synthesis of pyrazolo[4,3-*c*]pyridine derivatives.

Five and six-membered nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties [6]. Pyrazolopyridine derivatives are the important heterocyclic compounds, which exhibit a diverse range of biological properties such as new inhibitors of xanthine oxidases [7], as Polo-like kinase 1 inhibitors [8], and HIF-1alpha prolyl hydroxylase inhibitors [9]. They also have proved to be active against Gram positive and Gram negative bacteria [10] and also as compounds for the inhibition of cholesterol formation [11]. Because of their biological activities, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. As a result, the synthesis of these molecules has attracted considerable attention.

The pyrazolo[4,3-*c*]pyridine derivatives were, previously, mostly synthesized through the reaction of α,β-unsaturated ketones with substituted hydrazine in different reaction conditions such as (i) catalyzed by NaOEt in HOEt for 10 h [12], (ii) in refluxing MeOH for 4 h [13], (iii) in refluxing EtOH for 6 h [14], and (iv) catalyzed by Et_3N in refluxing EtOH [15]. However, the continued development of a facile and versatile method to pyrazolo[4,3-*c*]pyridine derivatives is still desired.

With the aim to develop more efficient synthetic processes, reduce the number of separate reaction steps, and minimize byproducts, and in continuation of our recent interest in the construction of heterocyclic scaffolds [16], we herein describe a practical, inexpensive, and rapid method for the stereoselective synthesis of pyrazolo[4,3-*c*]pyridine derivatives **3** *via* microwave-assisted (MW) reactions of 3,5-diarylidenepiperidin-4-ones **1** with phenylhydrazine **2** in ethylene glycol (Scheme 1).

RESULTS AND DISCUSSION

To explore the scope and versatility of this method, various reaction conditions were investigated, including solvent and temperature variations. Highlighted in

Scheme 1

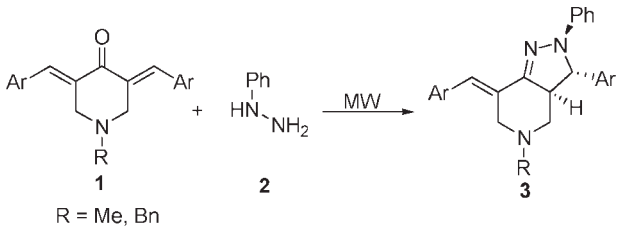

Table 1 for compound **3a**, for example, is the influence of solvent on the reaction yield. The MW-assisted reaction of 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one (**1a**, 1.0 mmol) with phenylhydrazine (**2**, 1.0 mmol) was examined using glycol, glacial acetic acid (HOAc), ethanol, and *N*,*N*-dimethylformamide (DMF) as solvent (1.0 mL) and solvent-free at 100°C, respectively. All the reactions were carried out at the maximum power of 200 W. The results were summarized in Table 1.

It was shown in Table 1 that the reaction using glycol as solvent gave the best result (Table 1, entry 8). So glycol was chosen as the reaction solvent. To further optimize reaction conditions, the same reaction was carried out in glycol at temperatures ranging from 90 to 140°C, with an increment of 10°C each time. The yield of product **3a** was increased and the reaction time was shortened as the temperature was increased from 90°C to 120°C (Table 1, entries 6−8). However, further increase of the temperature to 130−140°C failed to improve the yield of product **3a** (Table 1, entries 9−10). Therefore, 120°C was chosen as the reaction temperature for all further microwave-assisted reactions.

The use of these optimal microwave experimental conditions [glycol, 120°C, 200 W (Maximum power)] to the reactions of different 3,5-diarylidenepiperidin-4-ones afforded good yields of pyrazolo[4,3-*c*]pyridine. As

Table 1

Optimization of reaction conditions of compound **3a**.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	Glycol	100	12	64
2	HOAc	100	16	35
3	EtOH	100	14	58
4	None	100	12	47
5	DMF	100	16	55
6	Glycol	90	16	61
7	Glycol	110	10	81
8	Glycol	120	8	89
9	Glycol	130	8	85
10	Glycol	140	8	88

shown in Table 2, at the beginning, we made a search for the 3,5-diarylidenepiperidin-4-ones substrate scope, phenylhydrazine **2** were used as model substrates (Table 2, entries 1−9 and 11−12), and the results indicated that 3,5-diarylidenepiperidin-4-ones bearing either electron donating or electron withdrawing functional groups such as nitro, chloro, hydroxyl, or methoxy were able to affect the synthesis of compounds **3**. Moreover, the heterocyclic3,5-diarylidenepiperidin-4-one such as thiophen-2-yl group (Table 2, entry 10) still displayed high reactivity under this standard condition.

Additionally, to demonstrate the microwave effects, the same temperature was applied to synthesize some of the products under classical heating (CH) conditions. The results listed in Table 3 showed the specific activation of this reaction by microwave heating. Simultaneously, the reaction times was strikingly shortened to minutes from hours required in traditional heating condition, and the yields were increased obviously too. The difference in yields (MW > CH) may be a consequence of both thermal effects and specific effects induced by the microwave field [17]. The reactants in these reactions contain dipoles and proceed *via* relatively polar

Table 2

The reaction times, melting points, and yields of products.

Entry	Product	Ar	R	Time (min)	Mp: (lit) (°C)	Yield[a] (%)
1	**3a**	4-Chlorophenyl	Me	8	173–174	89
2	**3b**	4-Bromophenyl	Me	8	170–172	93
3	**3c**	3-Nitrophenyl	Me	9	201–203	91
4	**3d**	2-Chlorophenyl	Me	10	227–228	88
5	**3e**	Phenyl	Me	8	159–160 (147–148) [14]	90 (72) [14]
6	**3f**	4-Tolyl	Me	9	171–173 (175–176) [12(a)]	87 (53) [12(a)]
7	**3g**	4-Dimethylaminophenyl	Me	8	226–228	88
8	**3h**	4-Methoxyphenyl	Me	11	201–202 (192–193) [12(a)]	85 (51) [12(a)]
9	**3i**	3,4-Dimethoxyphenyl	Me	12	173–175	83
10	**3j**	Thiophen-2-yl	Me	12	176–177 (169–170) [12(a)]	88 (36) [12(a)]
11	**3k**	Phenyl	Benzyl	8	171–173 (155–157) [14]	90 (25) [14]
12	**3l**	4-Methoxyphenyl	Benzyl	10	168–170 (157–158) [14]	92 (42) [14]

[a] Isolated yields under microwave heating conditions.

Table 3

The synthesis of some of compound **3** using conventional heating.

Entry	Product	Time (h)	Yield (%)
1	**3a**	2	84
2	**3c**	2	69
3	**3e**	2	74
4	**3f**	2	79
5	**3k**	2	72

intermediates, which enhance their interactions with MW and consequently benefit significantly from MW irradiation.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The structural elucidation and the attribution of the relative stereochemistry rest upon NMR analysis and was unequivocally confirmed by X-ray diffraction of single crystals obtained by slow evaporation of the solvent in the case of **3j** (Fig. 1) [18]. The *anti* and *syn* isomers were identified by the coupling constants (*J*) of the vicinal protons adjacent to N-Ph and CH_2 in their ^{1}H NMR spectra. The coupling constants (*J*) of *anti* isomer is higher than that of the *syn* one [19]. The ^{1}H NMR spectrum of **3a** showed two doubles at $\delta = 4.83$, 3.78 from CH proton, and the corresponding coupling constant is $J = 12.4$; it is indicated that compounds **3** were *anti* configuration. Furthermore, because of exclusion between crowded aryl systems adjacent to N=C and CH, the molecule structure **3** is thermodynamic stable configuration (Fig. 2).

In summary, we have developed an efficient and improved stereoselective reactions of 3,5-diarylidenepiperidin-4-ones with phenylhydrazine **2** under mild conditions and have shown its application in the microwave-assisted synthesis of a wide range of pyrazolo[4,3-*c*]pyridine derivative in excellent yields. In light of its operational simplicity, simple purification procedure,

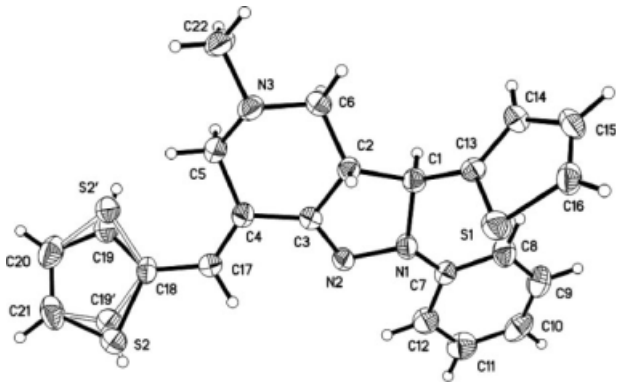

Figure 1. ORTEP diagram of **3j**.

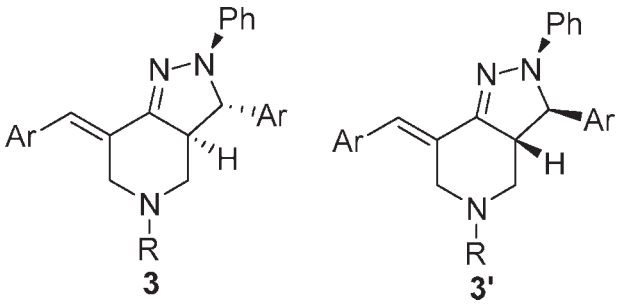

Figure 2. The structures of *anti* and *syn* isomers **3** and **3′**.

and increased safety for small-scale high-speed synthesis, this protocol is superior to the existing methods.

EXPERIMENTAL

Microwave irradiation was carried out with a microwave oven Emrys^{TM} Creator from Personal Chemistry (Uppsala, Sweden). Melting points were determined in the open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. HRMS (ESI) was determined by using micrOTOF-Q·HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the one-pot synthesis of pyrazolo[4,3-*c*]pyridines 3 under microwave irradiation conditions. Typically, in a 10 mL Emrys^{TM} reaction vial, 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one (**1a**, 1.0 mmol), phenylhydrazine (**2**, 1.0 mmol), and glycol (1.0 mL) were mixed and then capped. The mixture was kept for a given time at 120°C under microwave irradiation (initial power 100 W and maximum power 200 W). Upon completion, monitored by TLC, the reaction mixture was filtered to give the crude product, which was further purified by recrystallization from EtOH (95%) to give pure pyrazolo[4,3-*c*]pyridines **3**.

7-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3a). IR (KBr): 2763, 1598, 1489, 1281, 1091, 1013, 889, 824, 756 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.49–7.38 (m, 8H, ArH), 7.16 (t, $J = 7.8$ Hz, 3H, =CH, and ArH), 6.94 (d, $J = 8.0$ Hz, 2H, ArH), 6.81 (t, $J = 7.6$ Hz, 1H, ArH), 4.83 (d, $J = 12.4$ Hz, 1H, CH), 3.78 (d, $J = 12.0$ Hz, 1H, CH_2), 3.17−3.03 (m, 3H, CH, and CH_2), 2.47 (d, $J = 8.0$ Hz, 1H, CH_2), 2.30 (s, 3H, CH_3); HRMS (ESI): *m*/*z* calcd for: 448.1342 $[M + H]^+$, found: 448.1369.

7-(4-Bromobenzylidene)-3-(4-bromophenyl)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3b). IR (KBr): 2840, 1599, 1486, 1382, 1284, 1178, 1072, 1010, 889, 821 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.68–7.57 (m, 5H, ArH), 7.42–7.32 (m, 3H, =CH, and ArH), 7.16 (t, $J = 7.8$ Hz, 3H, ArH), 7.02–6.93 (m, 2H, ArH), 6.81 (t, $J = 7.4$ Hz, 1H, ArH), 4.82 (d, $J = 12.8$ Hz, 1H, CH), 3.79–3.70 (m, 1H, CH_2),

3.16–3.03 (m, 3H, CH_2), 2.48–2.37 (m, 1H, CH), 2.30 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 536.0332 $[M + H]^+$, found: 536.0337.

7-(3-Nitrobenzylidene)-3,3a,4,5,6,7-hexahydro-5-methyl-3-(3-nitrophenyl)-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3c). IR (KBr): 2950, 2796, 1597, 1525, 1498, 1351, 1298, 1097, 1034, 882, 746, 693 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 8.31 (s, 1H, ArH), 8.21–8.17 (m, 3H, ArH), 7.94 (d, J = 8.0 Hz, 1H, ArH), 7.83 (d, J = 8.0 Hz, 1H, ArH), 7.72 (t, J = 7.8 Hz, 2H, ArH), 7.34 (s, 1H, =CH), 7.18 (t, J = 8.0 Hz, 2H, ArH), 6.97 (d, J = 7.6 Hz, 2H, ArH), 6.84 (t, J = 7.4 Hz, 1H, ArH), 5.11 (d, J = 12.4 Hz, 1H, CH), 3.81 (t, J = 14.4 Hz, 1H, CH_2), 3.25–3.21 (m, 2H, CH_2), 3.15–3.12 (m, 1H, CH_2), 2.60–2.54 (m, 1H, CH), 2.32 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 470.1823 $[M + H]^+$, found: 470.1804.

7-(2-Chlorobenzylidene)-3-(2-chlorophenyl)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3d). IR (KBr): 2939, 1597, 1491, 1288, 1146, 1049, 998, 755 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.58–7.55 (m, 3H, ArH), 7.40–7.35 (m, 5H, ArH), 7.22–7.16 (m, 3H, CH, and ArH), 6.88–6.82 (m, 3H, ArH), 5.22 (d, J = 12.0 Hz, 1H, CH), 3.62 (d, J = 12.0 Hz, 1H, CH_2), 3.25–3.10 (m, 3H, CH_2), 2.59–2.57 (m, 1H, CH), 2.28 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 448.1342 $[M + H]^+$, found: 448.1342.

7-Benzylidene-3,3a,4,5,6,7-hexahydro-5-methyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3e). IR (KBr): 2942, 2843, 1597, 1498, 1321, 1287, 1236, 1134, 1030, 1003, 889, 750 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.46–7.31 (m, 10H, ArH), 7.21 (s, 1H, =CH), 7.16–7.12 (m, 2H, ArH), 6.96 (d, J = 8.0 Hz, 2H, ArH), 6.79 (t, J = 7.2 Hz, 1H, ArH), 4.78 (d, J = 12.8 Hz, 1H, CH), 3.82 (d, J = 14.0 Hz, 1H, CH_2), 3.16–3.10 (m, 2H, CH_2), 3.07–3.03 (m, 1H, CH), 2.47 (d, J = 8.0 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 380.2122 $[M+H]^+$, found: 380.2119.

7-(4-Methylbenzylidene)-3,3a,4,5,6,7-hexahydro-3-(4-methylphenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3f). IR (KBr): 2781, 1599, 1508, 1498, 1272, 1030, 977, 815, 749 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.57 (s, 1H, =CH), 7.40 (d, J = 8.0 Hz, 1H, ArH), 7.33–7.11 (m, 10H, ArH), 6.95 (d, J = 8.0 Hz, 1H, ArH), 6.78 (t, J = 7.4 Hz, 1H, ArH), 4.71 (d, J = 12.4 Hz, 1H, CH), 3.80 (t, J = 8.0 Hz, 1H, CH_2), 3.73 (d, J = 4.0 Hz, 1H, CH_2), 3.13–3.09 (m, 2H, CH_2), 2.45–2.35 (m, 1H, CH), 2.33 (t, J = 10.0 Hz, 9H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 408.2435 $[M+H]^+$, found: 408.2418.

7-(4-(Dimethylamino)benzylidene)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-2H-pyrazolo[4,3-c]pyridin-3-yl)-*N*,*N*-dimethylbenzenamine (3g). IR (KBr): 2870, 1595, 1521, 1443, 1357, 1282, 1168, 1045, 977, 817 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.22 (t, J = 9.4 Hz, 4H, ArH), 7.11 (t, J = 7.8 Hz, 3H, =CH, and ArH), 6.98 (d, J = 7.6 Hz, 2H, ArH), 6.76–6.72 (m, 5H, ArH), 4.55 (d, J = 12.8 Hz, 1H, CH), 3.84 (d, J = 14.0 Hz, 1H, CH_2), 3.82–3.06 (m, 3H, CH_2), 2.95 (s, 6H, CH_3), 2.89 (s, 6H, CH_3), 2.43–2.37 (m, 1H, CH), 2.31 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 466.2966 $[M + H]^+$, found: 466.2968.

7-(4-Methoxybenzylidene)-3,3a,4,5,6,7-hexahydro-3-(4-methoxyphenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3h). IR (KBr): 2945, 2834, 1598, 1510, 1250, 1031, 833, 754 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.37–7.31 (m, 4H, ArH), 7.13 (t, J = 7.8 Hz, 3H, =CH, and ArH), 7.00–6.95 (m, 6H, ArH), 6.78 (t, J = 7.2 Hz, 1H, ArH), 4.68 (d, J = 12.8 Hz, 1H, CH), 3.79(t, J = 14.0 Hz, 7H, CH_2, and OCH_3), 3.13–2.99 (m, 3H, CH, and CH_2), 2.44 (t, J = 10.0 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 440.2333 $[M+H]^+$, found: 440.2338.

7-(3,4-Dimethoxybenzylidene)-3,3a,4,5,6,7-hexahydro-3-(3,4-dimethoxyphenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3i). IR (KBr): 2944, 1597, 1513, 1496, 1261, 1141, 1032, 897, 749 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.14 (t, J = 7.8 Hz, 3H, =CH, and ArH), 7.02–6.97 (m, 7H, ArH), 6.92 (d, J = 1.6 Hz, 1H, ArH), 6.79 (t, J = 7.2 Hz, 1H, ArH), 4.65 (d, J = 12.8 Hz, 1H, CH), 3.85 (d, J = 16.0 Hz, 1H, CH_2), 3.77 (d, J = 16.0 Hz, 12H, OCH_3), 3.17–3.10 (m, 2H, CH_2), 3.05–3.01 (m, 1H, CH_2), 2.46–2.41 (m, 1H, CH), 2.32 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 500.2549 $[M + H]^+$, found: 500.2563.

7-(Thiophen-2-ylmethylene)-3,3a,4,5,6,7-hexahydro-5-methyl-2-phenyl-3-(thiophen-2-yl)-2*H*-pyrazolo[4,3-*c*]pyridine (3j). IR (KBr): 2781, 1596, 1489, 1382, 1280, 1134, 1027, 912, 857 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.70 (d, J = 4.0 Hz, 1H, ArH), 7.50 (d, J = 4.0 Hz, 1H, ArH), 7.42 (s, 1H, =CH), 7.32 (d, J = 4.0 Hz, 1H, ArH), 7.27 (d, J = 4.0 Hz, 1H, ArH), 7.18 (d, J = 16.0 Hz, 3H, ArH), 7.09–7.04 (m, 3H, ArH), 6.85 (t, J = 6.0 Hz, 1H, ArH), 5.10 (d, J = 12.8 Hz, 1H, CH), 3.99 (d, J = 16.0 Hz, 1H, CH_2), 3.27–3.19 (m, 1H, CH), 3.04 (d, J = 12.0 Hz, 2H, CH_2), 2.47 (s, 1H, CH_2), 2.39 (s, 3H, CH_3).

HRMS (ESI): *m*/*z* calcd for: 392.1250 $[M + H]^+$, found: 392.1238.

5-Benzyl-7-benzylidene-3,3a,4,5,6,7-hexahydro-2,3-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3k). IR (KBr): 2891, 2811, 1596, 1498, 1452, 1375, 1281, 1118, 1032, 918, 883, 748 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.44–7.11 (m, 18H, =CH, and ArH), 6.95 (d, J = 7.6 Hz, 2H, ArH), 6.78 (t, J = 7.4 Hz, 1H, ArH), 4.77 (d, J = 12.8 Hz, 1H, CH), 3.91 (d, J = 13.6 Hz, 1H, CH_2), 3.65 (s, 2H, CH_2), 3.24–3.14 (m, 3H, CH_2), 2.61–2.57 (m, 1H, CH).

HRMS (ESI): *m*/*z* calcd for: 456.2435 $[M+H]^+$, found: 456.2415.

7-(4-Methoxybenzylidene)-5-benzyl-3,3a,4,5,6,7-hexahydro-3-(4-methoxyphenyl)-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine (3l). IR (KBr): 2835, 1597, 1497, 1300, 1250, 1179, 1032, 992, 830 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz) δ: 7.34–7.10 (m, 12H, =CH, and ArH), 6.96–6.92 (m, 6H, ArH), 6.77 (t, J = 6.0 Hz, 1H, ArH), 4.68 (d, J = 12.8 Hz, 1H, CH), 3.91 (d, J = 12.0 Hz, 1H, CH_2), 3.80–3.59 (m, 9H, CH_2, and OCH_3), 3.20–3.07 (m, 3H, CH, and CH_2).

HRMS (ESI): *m*/*z* calcd for: 516.2646 $[M + H]^+$, found: 516.2654.

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REFERENCES AND NOTES

[1] Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. J Comb Chem 2002, 4, 95.

[2] (a) Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563; (b) Galema, S. A. Chem Soc Rev 1997, 26, 233; (c) Alcazar, J. J Comb Chem 2005, 7, 353; (d) Varma, R. S. Green Chem 1999, 1, 43; (e) Takvorian, A. G.; Combs, A. P. J Comb Chem 2004, 6, 171; (f) Bremner, W. S.; Organ, M. G. J Comb Chem 2007, 9, 14.

[3] Larhed, M.; Hallberg, A. Drug Discov Today 2001, 6, 406.

[4] (a) Yuhong, J.; Rajender, S. V. Tetrahedron Lett 2005, 46, 6011; (b) Yuhong, J.; Rajender, S. V. J Org Chem 2006, 71, 135; (c) Mazaahir, K.; Shuchi, K.; Ruby, T. Lett Org Chem 2006, 3, 135

[5] Tu, S. J.; Jiang, B.; Zhang, J. Y.; Zhang, Y.; Jia, R. H.; Li, C. M.; Zhou, D. X.; Cao, L. J.; Shao, Q. Q. Synlett 2007, 480.

[6] Strunz, G. M.; Findlay, J. A. The Alkaloids; Academic Press: New York, 1985; Vol. 26, p 89.

[7] Lynck, B.; Khan, M.; Teo, H.; Pedrotti, F. Can J Chem 1988, 66, 420.

[8] Fucini, R. V.; Hanan, E. J.; Romanowski, M. J.; Elling, R. A.; Lew, W.; Barr, K. J.; Zhu, J.; Yoburn, J. C.; Liu, Y.; Fahr, B. T.; Fan, J.; Lu, Y. Bioorg Med Chem Lett 2008, 18, 5648.

[9] Warshakoon, N. C.; Wu, S.; Boyer, A.; Kawamoto, R.; Renock, S.; Xu, K. Bioorg Med Chem Lett 2006, 16, 5687.

[10] El-Dean, A. M.; Aralla, A. A.; Mohamed, T. A.; Geies, A. A. Z Naturforsch B 1991, 46, 541.

[11] Fujikawa, Y.; Suzuki, M.; Iwasaki, H.; Sakashita, M.; Kitahara, M. Eur Pat Appl EP 1989, 339, 358 (Chem Abstr 1990, 113, 23903).

[12] (a) El-Subbagh, H. I.; Abu-Zaid, S. M.; Mahran, M. A.; Badria, F. A.; Al-Obaid, A. M. J Med Chem 2000, 43, 2915; (b) Al-Omar, M. A.; Youssef, K. M.; El-Sherbeny, M. A.; Awadalla, S. A.; El-Subbagh, H. I. Arch Pharm 2005, 338, 175.

[13] Krapcho, J.; Turk, C. F. J Med Chem 1979, 22, 207.

[14] Sviridenkova, N. V.; Vatsadze, S. Z.; Manaenkova, M. A.; Zyk, N. V. Russ Chem Bull 2005, 54, 2590.

[15] Hammam, A. E.-F. G.; Sharaf, M. A.; El-Hafez, N. A. A. Indian J Chem B 2001, 40B, 213.

[16] (a) Tu, S. J.; Jiang, B.; Jia, R. H.; Zhang, J. Y.; Zhang, Y.; Yao, C. S.; Shi, F. Org Biomol Chem 2006, 4, 3664; (b) Tu, S. J.; Jiang, B.; Zhang, J. Y.; Jia, R. H.; Zhang, Y.; Yao, C. S. Org Biomol Chem 2006, 4, 3980; (c) Tu, S. J.; Jiang, B.; Zhang, Y.; Jia, R. H.; Zhang, J. Y.; Yao, C. S.; Shi, F. Org Biomol Chem 2007, 5, 355; (d) Tu, S. J.; Li, C. M.; Li, G. G.; Cao, L. J.; Shao, Q. Q.; Zhou, D. X.; Jiang, B.; Zhou, J. F.; Xia, M. J Comb Chem 2007, 9, 1144.

[17] (a) Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250; (b) Perreux, L.; Loupy, A. Tetrahedron 2001, 57, 9199; (c) Loupy, A. C R Chim 2004, 7, 103; (d) Dallinger, D.; Kappe, C. O. Chem Rev 2007, 107, 2563; (e) Kappe, C. O. Chem Soc Rev 2008, 37, 1127; (f) Polshettiwar, V.; Varma, R. S. Chem Soc Rev 2008, 37, 1546.

[18] 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. Crystal data for **3j**: $C_{22}H_{21}N_3S_2$, $M = 391.54$, Monoclinic, space group P2(1)/n, $a = 8.0414(10)$, $b = 29.939(3)$, $c = 8.51360(11)$, $\alpha = 90$, $\beta = 107.308(2)$, $\gamma = 90°$, $V = 1956.9(3)$ Å^3, $Z = 4$, $T = 298(2)$ K, $\mu = 0.284$ mm^{-1}, 10238 reflections measured, 3418 unique reflections, $R = 0.0727$, $R_w = 0.0878$.

[19] (a) Loh, T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L. Tetrahedron 2000, 56, 3227; (b) Gennari, C.; Venturini, I.; Gislon, F.; Schimperma, G. Tetrahedron Lett 1987, 28, 227; (c) Guanti, G.; Narisano, E.; Banfi, L. Tetrahedron Lett 1987, 28, 4331; (d) Ollevier, T.; Nadeau, E. J Org Chem 2004, 69, 9292; (e) Wu, H.; Shen, Y.; Fan, L. Y.; Wan, Y.; Zhang, P.; Chen, C. F.; Wang, W. X. Tetrahedron 2007, 63, 2404.