

An efficient synthesis of pyrazolo[3,4-*b*]pyridine derivatives under microwave irradiation

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Abstract

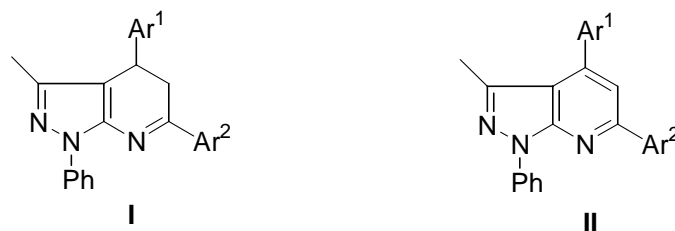
A series of pyrazolo[3,4-*b*]pyridine derivatives were synthesized by the reaction of aminopyrazole with chalcones in the presence of ZnCl₂ under microwave irradiation. The reaction was completed in 8-12 min with 85-95% yields.

Keywords: Microwave irradiation, pyrazolo[3,4-*b*]pyridine

Introduction

The pyrazolo[3,4-*b*]pyridine system has shown many interesting biological and pharmacological properties, such as antitubercular activity,^{1,2} activity against gram positive and negative bacteria,³ and ACTH (Adrenocorticotrophic hormone)-releasing factor (CRF (Corticotropin-releasing factor)) antagonist activity. CRF antagonists proved to be effective in the treatment of a wide variety of stress-related illnesses, such as depression, gastrointestinal diseases, anorexia nervosa, haemorrhaged stress, drug and alcohol withdrawal symptoms.⁴

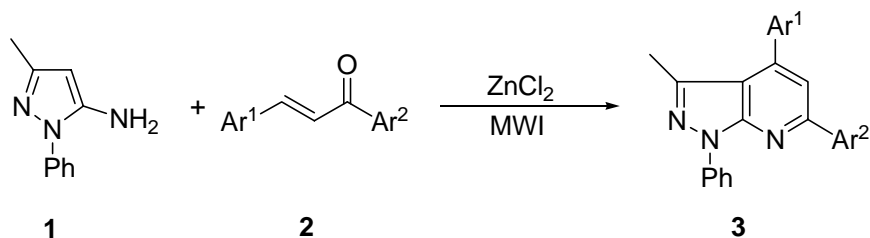
Due to the importance of pyrazolo[3,4-*b*]pyridines, much work has been done over the years. The most important synthetic method is the condensation of aminopyrazole with α,β -unsaturated compounds reported by J. Quiroga.⁵⁻¹⁴ The reaction proceeds generally in two steps, in which dihydropyrazolopyridines **I** are first obtained by the condensation of aminopyrazole with chalcones using traditional heating in 47-70% yields, and are then further dehydrogenated by NBS to give the desired compounds in 60-80% yields (Scheme 1).^{5,8}



Scheme 1

However, we found that some chalcones such as **2b**, **2g** and **2i** did not react or react very sluggishly under these conditions. Besides, this two-step reaction has the drawback of long reaction times and a quite low total yield. In recent years, microwave techniques have developed rapidly in organic synthesis due to shorter reaction times, higher yields, easy work-up and environmentally friendliness.¹⁵ Therefore, we investigated the reaction under microwave irradiation and found that the catalyst ZnCl_2 played a very important role in the above condensation reaction. At the same time, aromatized products **3** could be obtained in one step.

In this paper, we would like to report this efficient synthetic method of pyrazolo[3,4-*b*]pyridines **3** by the reaction of aminopyrazole with chalcones in one step under microwave irradiation in the presence of ZnCl_2 leading to higher yields and shorter reaction times (Scheme 2).



Scheme 2 The synthesis of pyrazolo[3,4-*b*]pyridine using ZnCl_2 as catalyst.

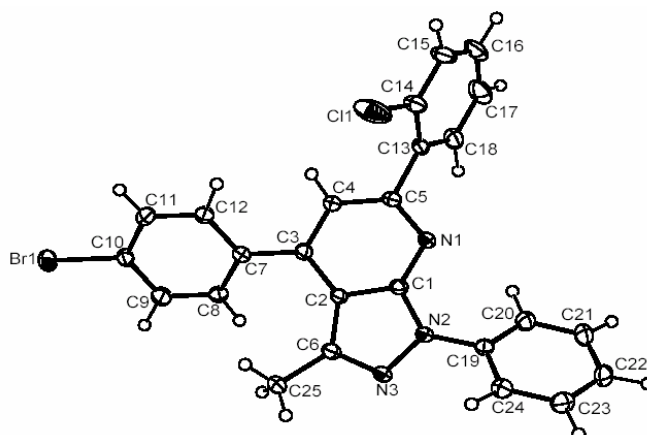
Results and Discussion

The results are shown in Table 1. The reaction was completed within 8-12 min with high yields ranging from 85-95%. For comparison, this reaction was carried out at 100 °C under traditional heating conditions for 3h, leading to lower yields (70%). It is obvious that the procedure under microwave irradiation has the advantages of a short routine, a good yield and a convenient work-up. The procedure is also more environmentally friendly compared to traditional heating.

Table 1. Syntheses of compounds **3** under microwave irradiation

Entry	Ar ¹	Ar ²	Time (min)	Mp (°C)	Yield (%)
3a	4-BrC ₆ H ₄	2-ClC ₆ H ₄	8	182-184	90
3b	4-BrC ₆ H ₄	4-CH ₃ C ₆ H ₄	10	181-182	92
3c	4-FC ₆ H ₄	4-CH ₃ C ₆ H ₄	8	155-156	95
3d	3,4-Cl ₂ C ₆ H ₃	4-CH ₃ OC ₆ H ₄	10	169-170	85
3e	3-NO ₂ C ₆ H ₄	4-CH ₃ OC ₆ H ₄	12	219-221	85
3f	4-ClC ₆ H ₄	2-OCH ₃ C ₆ H ₄	12	158-160	86
3g	4-CH ₃ OC ₆ H ₄	4-CH ₃ C ₆ H ₄	12	168-169	89
3h	4-ClC ₆ H ₄	4-FC ₆ H ₄	8	158-159	90
3i	4-CH ₃ OC ₆ H ₄	2-ClC ₆ H ₄	10	230-232	88
3j	4-ClC ₆ H ₄	2,4-Cl ₂ C ₆ H ₃	10	159-161	85

All the products were new, which were characterized by IR and ¹H NMR analysis. To identify the structure of the products further, we also provide a structural study for compound **3a** by X-ray crystallography (Figure 1).

**Figure 1.** Molecular structure of **3a**.

Experimental Section

General Procedures. Microwave irradiation was carried out in a modified commercial microwave oven (2450 MHz, Nanjing Sanle) under atmospheric pressure. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu spectrometer. ¹H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-*d*₆ as solvent and TMS as internal standard. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

General experimental procedure

A dry flask (25 mL) was charged with aminopyrazole **1** (1 mmol), chalcone **2** (1 mmol), glycol (2 mL) and catalyst ZnCl₂ (0.05 mmol). The flask was then connected with refluxing equipment. After microwave irradiation for 8-12 min, the reaction mixture was cooled and washed with ethanol. The crude products were purified by recrystallization from 95% ethanol to afford **3**.

4-(4-Bromophenyl)-6-(2-chlorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine (3a). IR (KBr, ν , cm⁻¹): 3061, 2963, 2924, 1677, 1595, 1574, 1505, 1429, 1346, 1289, 1146, 1062, 1212, 827, 761, 695, 675, 639. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.33 (3H, s, CH₃), 7.33~8.31 (13H, m, Ar-H), 7.48 (1H, s, C-H). Anal. Calcd for C₂₅H₁₇BrClN₃: C, 63.24; H, 3.61; N, 8.85. Found: C, 63.08; H, 3.63; N, 8.78.

4-(4-Bromophenyl)-3-methyl-1-phenyl-6-p-tolyl-1H-pyrazolo[3,4-*b*]pyridine (3b). IR (KBr, ν , cm⁻¹): 3060, 3027, 2911, 2857, 1595, 1574, 1504, 1436, 1417, 1338, 1309, 1148, 1057, 1011, 854, 819, 762, 677, 634. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.40 (3H, s, CH₃), 2.29 (3H, s, CH₃), 7.33-8.39 (14H, m, Ar-H, and C-H). Anal. Calcd for C₂₆H₂₀BrN₃: C, 68.73; H, 4.44; N, 9.25. Found: C, 68.61; H, 4.41; N, 9.28.

4-(4-Fluorophenyl)-3-methyl-1-phenyl-6-p-tolyl-1H-pyrazolo[3,4-*b*]pyridine (3c). IR (KBr, ν , cm⁻¹): 3063, 3034, 2919, 2854, 1596, 1565, 1510, 1411, 1347, 1223, 1155, 1047, 1011, 841, 820, 756, 692, 641. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.40 (3H, s, CH₃), 2.28 (3H, s, CH₃), 7.37-8.39 (14H, m, Ar-H, and C-H). Anal. Calcd for C₂₆H₂₀FN₃: C, 79.37; H, 5.12; N, 10.68. Found: C, 79.21; H, 5.11; N, 10.62.

4-(3,4-Dichlorophenyl)-6-(4-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine (3d). IR (KBr, ν , cm⁻¹): 3059, 2987, 2932, 2835, 1670, 1597, 1570, 1504, 1468, 1347, 1308, 1247, 1235, 1174, 1027, 830, 755, 695, 637. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.28 (3H, s, CH₃), 3.86 (3H, s, OCH₃), 7.59-8.38 (12H, m, Ar-H), 7.81 (1H, s, C-H). Anal. Calcd for C₂₆H₁₉Cl₂N₃O: C, 67.83; H, 4.16; N, 9.13. Found: C, 67.76; H, 4.13; N, 9.18.

6-(4-Methoxyphenyl)-3-methyl-4-(3-nitrophenyl)-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine (3e). IR (KBr, ν , cm⁻¹): 3059, 2996, 2925, 2835, 1674, 1594, 1573, 1526, 1505, 1415, 1347, 1299, 1182, 1150, 1031, 839, 758, 729, 691, 638. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.26 (3H, s, CH₃), 3.86 (3H, s, OCH₃), 7.11-8.54 (13H, m, Ar-H), 7.90 (1H, s, C-H). Anal. Calcd for C₂₆H₂₀N₄O₃: C, 71.55; H, 4.62; N, 12.84. Found: C, 71.47; H, 4.63; N, 12.79.

4-(4-Chlorophenyl)-6-(2-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-*b*]pyridine (3f). IR (KBr, ν , cm⁻¹): 3048, 3007, 2955, 2929, 2833, 1597, 1572, 1505, 1490, 1415, 1345, 1242, 1173, 1147, 1080, 1031, 1014, 825, 755, 688, 642. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.26 (3H, s, CH₃), 3.86 (3H, s, OCH₃), 7.10-8.39 (14H, m, Ar-H and C-H). Anal. Calcd for C₂₆H₂₀ClN₃O: C, 73.32; H, 4.73; N, 9.87. Found: C, 73.39; H, 4.70; N, 9.82.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-6-p-tolyl-1H-pyrazolo[3,4-*b*]pyridine (3g). IR (KBr, ν , cm⁻¹): 3033, 2998, 2958, 2917, 2833, 1592, 1575, 1514, 1415, 1348, 1284, 1243, 1177, 1145, 1031, 970, 906, 819, 752, 700, 642, 610. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.31 (3H, s, CH₃), 2.40 (3H, s, CH₃), 3.88 (3H, s, OCH₃), 7.14-8.40 (13H, m, Ar-H), 7.72 (1H, s, C-H). Anal. Calcd for C₂₇H₂₃N₃O: C, 79.97; H, 5.72; N, 10.36. Found: C, 79.88; H, 5.70; N, 10.32.

4-(4-Chlorophenyl)-6-(4-fluorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (3h). IR (KBr, ν , cm^{-1}): 3050, 2993, 2964, 2913, 1677, 1596, 1575, 1504, 1349, 1226, 1160, 1089, 1050, 1014, 826, 752, 689, 638. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 2.28 (3H, s, CH_3), 7.34-8.37 (13H, m, Ar-H), 7.81 (1H, s, C-H). Anal. Calcd for $\text{C}_{25}\text{H}_{17}\text{ClFN}_3$: C, 72.55; H, 4.14; N, 10.15. Found: C, 72.46; H, 4.15; N, 10.11.

6-(2-Chlorophenyl)-4-(4-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (3i). IR (KBr, ν , cm^{-1}): 3049, 3006, 2957, 2929, 2839, 1681, 1657, 1608, 1596, 1571, 1501, 1462, 1434, 1343, 1033, 1245, 1175, 1151, 1032, 837, 758, 688, 642. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 2.36 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 7.14-8.33 (13H, m, Ar-H), 7.42 (1H, s, C-H). Anal. Calcd for $\text{C}_{26}\text{H}_{20}\text{ClN}_3\text{O}$: C, 73.32; H, 4.73; N, 9.87. Found: C, 73.25; H, 4.72; N, 9.83.

4-(4-Chlorophenyl)-6-(2,4-dichlorophenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (3j). IR (KBr, ν , cm^{-1}): 3048, 2956, 2920, 1598, 1573, 1505, 1489, 1436, 1342, 1287, 1150, 1086, 1013, 855, 815, 758, 682, 630. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 2.32 (3H, s, CH_3), 7.22-8.30 (12H, m, Ar-H), 7.49 (1H, s, C-H). Anal. Calcd for $\text{C}_{25}\text{H}_{16}\text{Cl}_3\text{N}_3$: C, 64.61; H, 3.47; N, 9.04. Found: C, 64.53; H, 3.46; N, 9.07.

X-ray structure determination of 3a. Colourless prisms, $\text{C}_{25}\text{H}_{17}\text{BrClN}_3$, $M_r=474.78$, Triclinic, space group $P-1$, $a=9.3798(11)$, $b=10.6200(13)$, $c=11.7433(15)\text{\AA}$, $\alpha=72.932(9)$, $\beta=78.877(10)$, $\gamma=72.045(9)^\circ$, $V=1057.0(2)\text{\AA}^3$, $Z=2$, $D_c=1.492/\text{cm}^3$, $\mu=2.088\text{mm}^{-1}$, $F(000)=480$, crystal dimensions $0.60 \times 0.30 \times 0.25\text{ mm}^3$. Intensity data were collected using a Rigaku Mercury diffractometer at 193 K, graphite monochromator Mo $K\alpha$ radiation ($\lambda=0.7107\text{\AA}$), using the ω - 2θ scan technique to a maximum 2θ of 54.96° . A total of 11838 reflections were collected with 4743 unique ones ($R_{\text{int}}=0.0278$), of which 4275 reflections were observed with $I>2\sigma(I)$. The final R and wR values were 0.0428 and 0.0879, $s=1.062$, $(\Delta/\sigma)_{\text{max}}=0.001$. The maximum peak and minimum peak in the final difference map is 0.813 and $-0.759\text{ e}/\text{\AA}^3$.

Acknowledgements

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References

1. Sekikawa, I.; Nishie, J.; Tono-oka, S.; Tanaka, Y.; Kakimoto, S.; *J. Heterocycl. Chem.* **1973**, *10*, 931.
2. Kukzynski, L.; Mrizikiewic, A.; Banaszkiwicz, W.; Pol, K. P. *J. Pharmacol. Pharm.* **1979**, *31*, 217.

3. Kamal, A. M.; Atalla, A. A.; Mohamed, T. A.; Geies, A. A.; *Naturforsch. Z. B: Chem. Sci.* **1991**, *46*, 541.
4. Chen, Y. L. International Patent WO 9534563 AL **1995**; *Chem. Abstr.* **1995**, *124*, 232447.
5. Orlov, V. D.; Quiroga, J.; Kolos, N. N. *Khim. Geterosikl. Soedin* **1987**, 1247.
6. Orlov, V. D.; Quiroga, J.; Kolos, N. N.; Desenko, S. M. *Khim. Geterosikl. Soedin* **1988**, 962.
7. Quiroga, J.; Insuasty, B.; Rincón, R.; Larrahondo, M.; Hanold, N.; Meier, H. *J. Heterocycl. Chem.* **1994**, *31*, 1333.
8. Quiroga, J.; Insuasty, B.; Marín, M.; Aguirre, A.; Meier, H. *Rev. Col. Quim.* **1992**, *21*, 29.
9. Quiroga, J.; Hormaza, A.; Insuasty, B.; Saitz, C.; Jullian, C.; Cañete, A. *J. Heterocycl. Chem.* **1998**, *35*, 61.
10. Quiroga, J.; Insuasty, B.; Cruz, S.; Hernandez, P.; Bolaños, A.; Moreno, R.; Hormaza, A.; Almeida, R. H. *J. Heterocycl. Chem.* **1998**, *35*, 333.
11. Quiroga, J.; Hormaza, A.; Insuasty, B.; Marquez, M.; *J. Heterocycl. Chem.* **1998**, *35*, 409.
12. Quiroga, J.; Hormaza, A.; Insuasty, B.; Saitz, C.; Jullian, C. *J. Heterocycl. Chem.* **1998**, *35*, 575.
13. Quiroga, J.; Insuasty, B.; Hormaza, A.; Gaménara, D.; Domínguez, L.; Saldaña, J. *J. Heterocycl. Chem.* **1999**, *36*, 11.
14. Quiroga, J.; Insuasty, B.; Hormaza, A.; Cabildo, P.; Claramunt, R. M.; Elguero, J. *Heterocycl. Commun.* **1999**, *5*, 115.
15. Feng S.; Shujiang T.; Fang F.; Tuanjie L. *Arkivoc* **2005**, (*i*), 137.