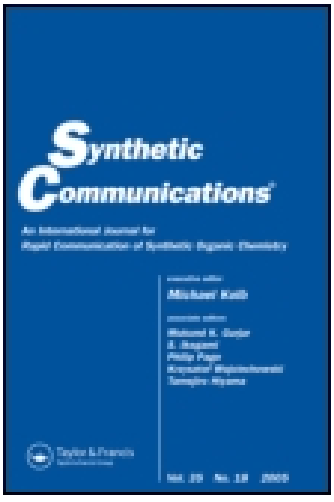

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Da-Qing Shi [a b] , Hao Yao [b] & Jing-Wen Shi [b]

[a] College of Chemistry and Chemical Engineering, Key Laboratory of Organic Synthesis of Jiangsu Province , Suzhou University , Suzhou, China

[b] Department of Chemistry , Xuzhou Normal University , Xuzhou, China

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Three-Component, One-Pot Synthesis of Pyrazolo[3,4-*b*]pyridine Derivatives in Aqueous Media

Da-Qing Shi,[1,2] Hao Yao,[2] and Jing-Wen Shi[2]

[1]College of Chemistry and Chemical Engineering, Key Laboratory of Organic Synthesis of Jiangsu Province, Suzhou University, Suzhou, China
[2]Department of Chemistry, Xuzhou Normal University, Xuzhou, China

Abstract: 6-Amino-4-aryl-5-cyanopyrazolo[3,4-*b*]pyridines were synthesized by a three-component reaction of aromatic aldehydes, malononitrile, and 5-amino-3-methyl-1-phenylpyrazole using sodium 1-dodecanesulfonic (SDS) as catalyst in aqueous media. The reaction has the advantages of good yields, less pollution, ease of separation, and environmental friendliness.

Keywords: Aqueous media, one-pot synthesis, pyrazolo[3,4-*b*]pyridine, three-component reaction

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial, anti-inflammatory, and antitumor properties.[1–4] In particular, condensed pyrazoles are known for various biological activities; for example, pyrazolo[3,4-*b*]pyridines are useful for treatment of a wide variety of stress-related illnesses, such as depression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhaged stress, drug and alcohol withdrawal symptoms, drug addition, and infertility.[5] Pyrazolo[3,4-*b*]pyridine

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Address correspondence to Da-Qing Shi, College of Chemistry and Chemical Engineering, Key Laboratory of Organic Synthesis of Jiangsu Province, Suzhou University, Suzhou 215123, China. E-mail: dqshi@suda.edu.cn

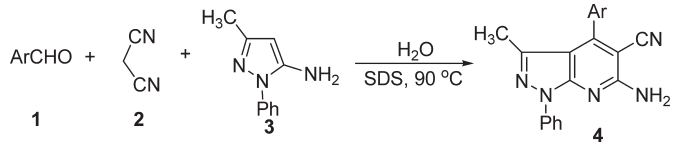
derivatives are generally prepared by reaction of 5-aminopyrazole and substituted α,β-unsaturated nitriles in organic solvent (i.e. ethanol) using triethylamine as catalyst,[6,7] but most of them suffer drawbacks such as lower yields and use of organic solvent.

The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as reaction media. Breslow et al.,[8] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in the 1980s. Previously, the scant solubility of the reactants was the main reason that ruled out this solvent from studies. Further reasons that make water unique among solvents are that it is cheap, not flammable, and more importantly, not toxic. Recently, there has been increasing recognition that water is an attractive medium for many organic reactions.[9] Based on our previous studies on the use of water as a solvent for carrying out carbon–carbon bond-forming reactions under phase-transmitting catalyst,[10] here we like to report one-pot synthesis of pyrazolo[3,4-*b*]pyridine derivatives by three-component reaction in aqueous media (Scheme 1).

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optical solvent, the three-component reaction of 4-chlorophenyl aldehyde **1a**, malononitrile **2**, and 5-amino-3-methyl-1-phenylpyrazole **3** was examined using different solvents, respectively. The results are summarized in Table 1.

As can be seen in Table 1, the best result was obtained when the three-component reaction was carried out in water in the presence of SDS (entry 1). Indeed, the reaction using SDS proceeded in higher yield and shorter reaction time than that using triethylbenzylammonium chloride (TEBAC) as catalyst. Water was chosen as the solvent for all further reactions because it is environmentally friendly, and the toxic organic reagents can be avoided.

To demonstrate the efficiency and scope of the present method, we applied water containing SDS to the reaction of a variety of aromatic aldehydes with malononitrile and 5-amino-3-methyl-1-phenylpyrazole. The results are summarized in Table 2. Data from Table 2 demonstrated that the reactions proceeded smoothly to give **4** in high yields under the optimized conditions. However, other arylamines such as 4-methylaniline and



1 2 3 4

Scheme 1.

Table 1. Solvent optimization for the synthesis of **4a**

Entry	Solvent	Reaction temperature (°C)	Reaction time (h)	Isolated yield (%)
1	H_2O/SDS	90	11	97
2	H_2O/TEBAC	90	15	90
3	CH_3CN	80	39	33
4	CH_3COCH_3	60	39	0
5	EtOH	80	39	0
6	EtOH/SDS	80	15	0
7	$CHCl_3$	60	39	0
8	DMF	100	39	0

1-aminonaphthalene did not undergo the same type of reactions under the same reaction conditions.

The recovery and reuse of solvent and catalyst are highly preferable in terms of green synthetic process. Therefore, with the success of these above reactions, we continued our research by studying the reuse of aqueous medium containing SDS. It turned out that the recovery and reuse of aqueous medium is very convenient and highly efficient. Thus, at completion of the condensation process, precipitated products were collected by suction, and aqueous medium containing SDS could be recovered easily from the filtrate. Studies using **1a**, **2**, and **3** as model substrates showed that the recovered aqueous medium could be successively recycled in subsequent reactions without almost any decrease in its efficiency (Table 3). It should be noted that even in the sixth round, reuse of aqueous medium recovered from the fifth round still produced the corresponding product with fairly good yield.

Table 2. The Synthesis of **4** in aqueous media in the presence of SDS

Entry	Ar	Reaction time (h)	Isolated yield (%)
4a	4-ClC_6H_4	11	97
4b	4-FC_6H_4	22	95
4c	4-$CH_3C_6H_4$	17	85
4d	4-$NO_2C_6H_4$	25	90
4e	4-BrC_6H_4	16	86
4f	4-$CH_3OC_6H_4$	18	94
4g	3,4-$(CH_3O)_2C_6H_3$	18	86
4h	3,4-$Cl_2C_6H_3$	17	90
4i	3,4-$(CH_3)_2C_6H_3$	10	92

Table 3. Studies on the reuse of aqueous medium containing SDS in the preparation of **4a**

Round	Yield (%)
1	97
2	98
3	97
4	96
5	95
6	96

The structures of products **4** were conformed by their spectroscopic analysis. Thus, the IR spectra of compounds **4** measured in potassium bromide pellets show on bond of the elongation vibrations of the CN group at 2209–2217 cm^{-1} and two bands for NH_2 groups at 3310–3486 cm^{-1}. In the ^1H NMR spectra of compound **4** measured in dimethyl-d_6 sulfoxide, the signal of CH_3 group at 1.88–1.98 ppm, the aromatic proton signals at 7.09–8.45 ppm, and the signal of 6-NH_2 group at 7.22–7.56 ppm were measured. The structure of **4e** was further confirmed by X-ray diffraction analysis. The molecular structure of **4e** is shown in Fig. 1.

In conclusion, with high yields and mild conditions, we think that the present work provides a useful method for the preparation of 6-amino-4-aryl-5-cyanopyrazolo[3,4-*b*]pyridine derivatives. Compared with other methods, this new method has the advantages of easier workup, milder reaction conditions, high yields, and an environmentally benign procedure.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr with absorptions

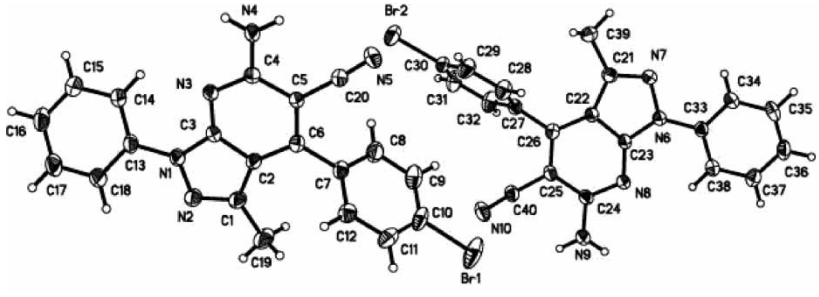


Figure 1. ORTEP diagram of **4e**.

in centimeters^{-1}. ^{1}H NMR was measured on a Bruker DPX 400-MHz spectrometer in DMSO-d_6 with TMS as internal standard. High-resolution mass spectra (HRMS) were obtained using a time-of-flight mass spectrometry (TOF-MS) instrument.

General Procedure for the Preparation of 6-Amino-4-aryl-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine (4)

A mixture of an aromatic aldehyde **1** (4 mmol), malononitrile **2** (4 mmol), 5-amino-3-methyl-1-phenylpyrazole **3** (4 mmol), and SDS (0.2 g) in water (10 ml) was stirred for 10–25 h at 90°C, then the reaction mixture was cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water, and purified by recrystallization from ethanol to give pure **4**.

Spectral Data

6-Amino-4-(4-chlorophenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*] pyridine (**4a**)

Mp 196–198 °C (lit.[6] 195 °C); ^{1}H NMR (DMSO-d_6) δ: 1.88 (3H, s, CH_3), 7.30–7.34 (1H, m, ArH), 7.40 (2H, s, NH_2), 7.51–7.55 (2H, m, ArH), 7.90 (2H, d, $J = 8.8$ Hz, ArH), 8.18 (2H, d, $J = 8.0$ Hz, ArH), 8.45 (2H, d, $J = 8.8$ Hz, ArH); IR (KBr) ν: 3454, 3327, 3054, 2214, 1629, 1580, 1559, 1513, 1497, 1457, 1436, 1409, 1353, 1201, 1148, 1089, 1013, 828, 789, 763, 694 cm^{-1}.

6-Amino-4-(4-fluorophenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*] pyridine (**4b**)

Mp 211–213 °C (lit.[11] 216–218 °C); ^{1}H NMR (DMSO-d_6) δ: 1.90 (3H, s, CH_3), 7.29 (2H, s, NH_2), 7.32 (1H, d, $J = 8.0$ Hz, ArH), 7.44 (2H, t, $J = 8.8$ Hz, ArH), 7.52 (2H, t, $J = 8.0$ Hz, ArH), 7.62–7.65 (2H, m, ArH), 8.18 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr) ν: 3444, 3321, 2213, 1629, 1602, 1551, 1511, 1438, 1413, 1391, 1352, 1228, 1202, 1156, 1010, 834, 768, 695 cm^{-1}.

6-Amino-4-(4-methylphenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*] pyridine (**4c**)

Mp 206–207 °C; ^{1}H NMR (DMSO-d_6) δ: 1.90 (3H, s, CH_3), 2.44 (3H, s, CH_3), 7.24 (2H, s, NH_2), 7.30 (1H, d, $J = 7.6$ Hz, ArH), 7.40 (2H, d, $J = 8.4$ Hz, ArH), 7.44 (2H, d, $J = 7.6$ Hz, ArH), 7.52 (2H, t, $J = 8.0$ Hz,

ArH), 8.18 (2H, d, $J = 8.4$ Hz, ArH); IR (KBr) ν: 3449, 3324, 3036, 2921, 2211, 1629, 1582, 1558, 1512, 1496, 1436, 1407, 1389, 1353, 1200, 1182, 1148, 1078, 1008, 889, 819, 789, 762, 731, 694 cm^{-1}. HRMS calcd. for $C_{21}H_{17}N_5$, m/z: 339.1484 (M^+); found, m/z: 339.1474.

6-Amino-4-(4-nitrophenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*] pyridine (**4d**)

Mp 215–217 °C (lit.[6] 215 °C); ^{1}H NMR (DMSO-d_6) δ: 1.88 (3H, s, CH_3), 7.32 (1H, t, $J = 7.2$ Hz, ArH), 7.40 (2H, s, NH_2), 7.53 (2H, t, $J = 8.0$ Hz, ArH), 7.90 (2H, d, $J = 8.4$ Hz, ArH), 8.18 (2H, d, $J = 8.0$ Hz, ArH), 8.45 (2H, d, $J = 8.8$ Hz, ArH); IR (KBr) ν: 3486, 3349, 3061, 2214, 1619, 1581, 1518, 1493, 1440, 1412, 1388, 1338, 1201, 1149, 1106, 1004, 853, 769, 711, 695 cm^{-1}.

6-Amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*] pyridine (**4e**)

Mp 218–220 °C (lit.[11] 222–223 °C); ^{1}H NMR (DMSO-d_6) δ: 1.91 (3H, s, CH_3), 7.32 (1H, t, $J = 7.2$ Hz, ArH), 7.50–7.56 (6H, m, NH_2 + ArH), 7.81 (2H, t, $J = 7.6$ Hz, ArH), 8.18 (2H, d, $J = 7.6$ Hz, ArH); IR (KBr) ν: 3431, 3346, 2217, 1615, 1585, 1558, 1530, 1489, 1396, 1378, 1344, 1279, 1136, 1074, 1011, 918, 817, 764, 738, 696 cm^{-1}. HRMS calcd. for $C_{20}H_{14}^{79}BrN_5$, m/z: 403.0433 (M^+); found, m/z: 403.0434.

6-Amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenylpyrazolo [3,4-*b*]pyridine (**4f**)

Mp 210–211 °C (lit.[6] 197 °C); ^{1}H NMR (DMSO-d_6) δ: 1.94 (3H, s, CH_3), 3.87 (3H, s, CH_3O), 7.14 (2H, d, $J = 8.8$ Hz, ArH), 7.22 (2H, s, NH_2), 7.30 (1H, t, $J = 7.2$ Hz, ArH), 7.48–7.53 (4H, m, ArH), 8.19 (2H, d, $J = 8.4$ Hz, ArH); IR (KBr) ν: 3445, 3351, 2968, 2216, 1629, 1584, 1558, 1509, 1494, 1442, 1406, 1385, 1355, 1297, 1250, 1181, 1115, 1024, 886, 836, 765, 691 cm^{-1}.

6-Amino-4-(3,4-dimethoxyphenyl)-5-cyano-3-methyl-1-phenylpyrazolo [3,4-*b*] pyridine (**4g**)

Mp 217–219 °C; ^{1}H NMR (DMSO-d_6) δ: 1.98 (3H, s, CH_3), 3.81 (3H, s, CH_3O), 3.86 (3H, s, CH_3O), 7.09 (1H, d, $J = 8.0$ Hz, ArH), 7.15 (2H, d, $J = 7.2$ Hz, ArH), 7.22 (2H, s, NH_2), 7.31 (1H, t, $J = 7.2$ Hz, ArH), 7.52 (2H, t, $J = 7.6$ Hz, ArH), 8.19 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr) ν: 3462, 3331, 2918, 2849, 2209, 1626, 1571, 1518, 1492, 1466, 1413, 1381, 1352, 1280, 1258, 1238, 1203, 1171, 1144, 1065, 1026, 800, 764, 694 cm^{-1}. HRMS calcd. for $C_{22}H_{19}N_5O_2$, m/z: 385.1539 (M^+); found, m/z: 385.1531.

6-Amino-4-(3,4-dichlorophenyl)-5-cyano-3-methyl-1-phenylpyrazolo [3,4-*b*]pyridine (**4h**)

Mp 192–194 °C (lit.[11] 187–189 °C); ^{1}H NMR (DMSO-d_6) δ: 1.93 (3H, s, CH_3), 7.31 (1H, t, $J = 7.6$ Hz, ArH), 7.36 (2H, s, NH_2), 7.52 (2H, t, $J = 8.0$ Hz, ArH), 7.60 (1H, d, $J = 8.0$ Hz, ArH), 7.88 (1H, d, $J = 8.4$ Hz, ArH), 7.97 (1H, s, ArH), 8.17 (2H, d, $J = 8.0$ Hz, ArH); IR (KBr) ν: 3466, 3364, 3064, 2210, 1627, 1610, 1583, 1560, 1514, 1492, 1472, 1440, 1409, 1385, 1353, 1250, 1199, 1149, 1131, 1081, 1032, 951, 906, 876, 822, 787, 753, 691 cm^{-1}. HRMS calcd. for $C_{20}H_{13}^{35}Cl_2N_5$, m/z: 393.0548 (M^+); found, m/z: 393.0545.

6-Amino-4-(3,4-dimethylphenyl)-5-cyano-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine (**4i**)

Mp 182–184 °C; ^{1}H NMR (DMSO-d_6) δ: 1.91 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.34 (3H, s, CH_3), 7.23–7.32 (5H, m, NH_2 + ArH), 7.35 (1H, d, $J = 7.6$ Hz, ArH), 7.52 (2H, t, $J = 7.6$ Hz, ArH), 8.19 (2H, d, $J = 8.4$ Hz, ArH); IR (KBr) ν: 3442, 3310, 3057, 2919, 2850, 2210, 1635, 1580, 1560, 1503, 1442, 1409, 1382, 1349, 1278, 1228, 1206, 1174, 1123, 1065, 1025, 1005, 903, 874, 829, 787, 772, 757, 730, 703, 692 cm^{-1}. HRMS calcd. for $C_{22}H_{19}N_5$, m/z: 353.1640 (M^+); found, m/z: 353.1647.

Crystal Data for 4e

$C_{20}H_{14}BrN_5$; M = 404.27, colorless block crystals, 0.57 × 0.48 × 0.26 mm, triclinic, space group P-1, $a = 11.393$ (2), $b = 12.396$(2), $c = 13.718$ (3) Å, $\alpha = 96.528$ (3)°, $\beta = 97.374$ (3)°, $\gamma = 110.171$ (3)°, $V = 1777.4$ (6) Å^3, $Z = 4$, $Dc = 1.511$ g cm^{-3}. $F(000) = 816$, μ(MoKα) = 2.326 mm^{-1}. Intensity data were collected on Smart-1000 diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) using ω scan mode with $2.10° < \theta < 25.01°$. A total of 6191 unique reflections were measured, and 3812 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to $R = 0.0442$ and $wR = 0.0985$.

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REFERENCES

1. Hardy, C. R. The chemistry of pyrazolopyridines. *Adv. Heterocyclic Chem.* **1984**, *36*, 343–409.
2. Orth, R. E. Biologically active pyrazoles. *J. Pharm. Sci.* **1968**, *57*, 537–556.
3. Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. E. H. Chemistry of pyrazolopyrimidines. *Adv. Heterocyclic Chem.* **1987**, *41*, 319–376.
4. Elnagdi, M. H.; Elmoghayar, M. R. H.; Sadek, K. U. Chemistry of pyrazoles condensed to heteroaromatic five- and six-membered rings. *Adv. Heterocyclic Chem.* **1990**, *48*, 223–299.
5. Chen, Y. L. Pyrazolo- and pyrazolopyridines useful as CRF antagonists. International Patent WO 9534563 A1 1995, *Chem. Abstr.* **1995**, *124*, 232447.
6. Quiroga, J.; Alvarado, M.; Insuasty, B.; Moreno, R. 5-Cyanopyrazolo[3,4-*b*]pyridines in the reaction of 5-amino-3-methyl-1-phenylpyrazolo with arylidene derivatives of malonodinitrile and ethyl cyanoacetate. *J. Heterocycl. Chem.* **1999**, *36*, 1311–1316.
7. Quiroga, J.; Cruz, S.; Insuasty, B.; Abonia, R. Synthesis and structural analysis of 5-cyanodihydropyrazolo[3,4-*b*]pyridines. *J. Heterocycl. Chem.* **2001**, *38*, 53–60.
8. Breslow, R.; Bovy, P.; Hersh, C. L. Reversing the selectivity of cyclodextrin bisimidazole ribonuclease mimics by changing the catalyst geometry. *J. Am. Chem. Soc.* **1980**, *102*, 2115–2117.
9. (a) Li, C. Organic reactions in aqueous media—with a focus on carbon-carbon bond formation. *Chem. Rev.* **1993**, *93*, 2023–2035; (b) Li, C. Organic reactions in aqueous media with a focus on carbon–carbon bond formations: A decade update. *Chem. Rev.* **2005**, *105*, 3095–3166.
10. (a) Shi, D. Q.; Zhang, S.; Zhuang, Q. Y.; Wang, X. S.; Tu, S. J.; Hu, H. W. Clean synthesis of 3-methyl-6-amino-5-cyano-4-aryl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole in water. *Chin. J. Org. Chem.* **2003**, *23*, 1314–1317; (b) Shi, D. Q.; Zhuang, Q. Y.; Chen, J.; Wang, X. S.; Tu, S. J.; Hu, H. W. Reaction of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexandione in water. *Chin. J. Org. Chem.* **2003**, *23*, 694–697; (c) Shi, D. Q.; Mou, J.; Zhuang, Q. Y.; Niu, L. H.; Wu, N.; Wang, X. S. Three-component one-pot synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives in aqueous media. *Synth. Commun.* **2004**, *34*, 4557–4563.
11. Zhu, S. L.; Tu, S. J.; Li, T. J.; Zhang, X. J.; Ji, S. J.; Zhang, Y. Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenylpyridino[2,3-*c*]pyrazole under microwave irradiation. *Chin. J. Org. Chem.* **2005**, *25*, 987–990.