Clean Synthesis of Furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one Derivatives in Aqueous Media

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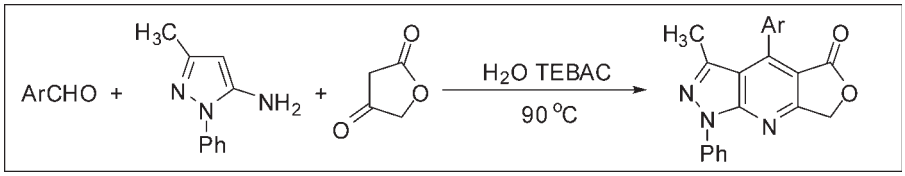

A series of 4-aryl-3-methyl-1-phenyl-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-ones were synthesized *via* the three-component reaction of an aldehyde, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole and tetronic acid in aqueous media in the presence of triethylbenzylammonium chloride (TEBAC). This method has the advantages of easier work-up, mild reaction conditions, high yields, and an environmentally benign procedure.

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INTRODUCTION

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 [1]. One of the most promising approaches uses water as the reaction medium [2]. Breslow [3], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions [4]. The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environment-friendly. Many important types of heterocyclic compounds, such as triazines, acridines, quinolines, pyridines, indoles, pyrazines, furans, and pyrimidines [5], have been synthesized in aqueous media. The synthesis of new and important type of heterocyclic compounds in water continues to attract wide attention among synthetic chemists.

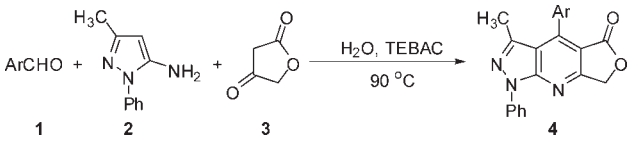
Pyrazole derivatives have been reported in the literature to be versatile building blocks for the synthesis of a wide range of the heterocyclic motifs, such as pyrazolopyridines [6], pyrazolequinolines [7], and pyrazolopyrazoles [8]. The pyrazolo[3,4-*b*]pyridine system has interesting biological and pharmacological properties [9]. Furopyridines is one of the ''privileged medical scaffolds,'' which are used for the development of pharmaceutical agents of various applications. Compounds with this motif show a wide range of pharmacological activities [10] and used as calcium influx promoters, HIV-1 non-nucleoside reverse transcriptase inhibitors and acetylcholinesterase inhibitors [11]. As part of our current studies on the development of new routes to heterocyclic systems in aqueous media [12], we now report an efficient and clean synthetic route to furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives (**4**) via the three-component reaction of arylaldehyde **1**, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole **2** and tetronic acid **3** in aqueous media (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optimal solvent, the three-component reaction of 3,4-dimethoxybenzaldehyde **1a**, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole **2** and tetronic acid **3** was examined using water, acetonitrile, acetone, ethanol, DMF and 1,2-dichloroethane as solvent, respectively, at different temperature for the synthesis of **4a**. The results are summarized in Table 1.

It can be seen from the Table 1 that the reactions using water as the solvent resulted in higher yields and shorter reaction times than those using organic solvents. On the basis of the obtained results, H_2O/TEBAC was found to be superior in terms of yield. Under these optimized reaction conditions, a series of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives **4** were synthesized. The products

Scheme 1



were different from those in ethanol in the presences of *L*-proline [13]. The results are summarized in Table 2.

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the reaction solution offer a significant advantage. Because TEBAC is soluble in water and the desired product is less soluble in water, the products can be directly separated by cooling to room temperature and filtering after the reaction is completed. The remaining reaction solution can be recycled. Studies using **1a**, **2**, and **3** as model substrates showed that the recovered reaction solution could be successively recycled in subsequent reaction without any decrease of yield (Table 3).

All the products **4** were characterized by mp, IR, and ^{1}H NMR spectra as well as HRMS.

Although the detailed mechanism of the aforementioned reaction remains to be fully clarified the formation of furo[3,4-*4*]pyrazolo[3,4-*b*]pyridine-5-ones **4** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded via a reaction sequence of condensation, addition, cyclization, dehydration, and aromatization. First, the condensation of aldehyde **1** and tetronic acid **3** gave the intermediate product **5**. The addition of **2** to **5** then furnished the intermediate product **7**, which upon intramolecular cyclization and dehydration gave rise to **9**. In the last step, the intermediate product **9** aromatized to product **4**.

In conclusion, we have developed a simple and clean three-component reaction of an aldehyde, 5-amino-3-methyl-1-phenyl-1*H*-pyrazole and tetronic acid for the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives in the presence of TEBAC in aqueous media. This method has the advantages of good yields, convenient procedure and environmentally friendly reaction conditions.

Table 1

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

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	H_2O/SDS	90	15	90
2	H_2O/TEBAC	90	9	98
3	CH_3CN	Reflux	20	41
4	CH_3COCH_3	Reflux	20	0
5	EtOH	Reflux	20	56
6	DMF	100	22	46
7	$ClCH_2CH_2Cl$	Reflux	15	0

Table 2

The synthesis of **4** in aqueous media in the presence of TEBAC.[a]

Entry	Compound	Ar	Time (h)	Yield (%)
1	**4a**	3,4-$(CH_3O)_2C_6H_3$	9	98
2	**4b**	4-BrC_6H_4	20	97
3	**4c**	4-FC_6H_4	24	95
4	**4d**	4-$NO_2C_6H_4$	30	80
5	**4e**	4-$CH_3OC_6H_4$	23	97
6	**4f**	2,4-$Cl_2C_6H_3$	20	83
7	**4g**	3,4-$(CH_3)_2C_6H_3$	10	97
8	**4h**	4-ClC_6H_4	25	98
9	**4i**	Pyridin-2-yl	22	95
10	**4j**	Thiophen-2-yl	15	87
11	**4k**	3-ClC_6H_4	35	89
12	**4l**	2-ClC_6H_4	30	85
13	**4m**	3,4-$Cl_2C_6H_3$	30	93

[a] In all entries 90°C temperature was used.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Tensor 27 spectrometer in KBr with absorption in cm^{-1}. ^{1}H NMR spectra were recorded on a Bruker DPX 400-MHz spectrometer as DMSO-d_6 solution, *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. HRMS were obtained using TOF-MS or Bruker-micro TOF-Q-MS instrument.

General procedure for the synthesis of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one derivatives 4 in aqueous media. Aldehyde **1** (2 mmol), 5-amino-3-methyl-1-phenyl-1*H*-pyrazole **2** (2 mmol), tetronic acid **3** (2 mmol) and TEBAC (0.1 g) were added to a 50-mL round-bottom flask containing 10 mL water. The mixture was then stirred at 90°C for given times. After completion of the reaction, the reaction mixture was cooled to room temperature. The precipitate was collected by suction and purified by recrystallization from EtOH to give products **4**.

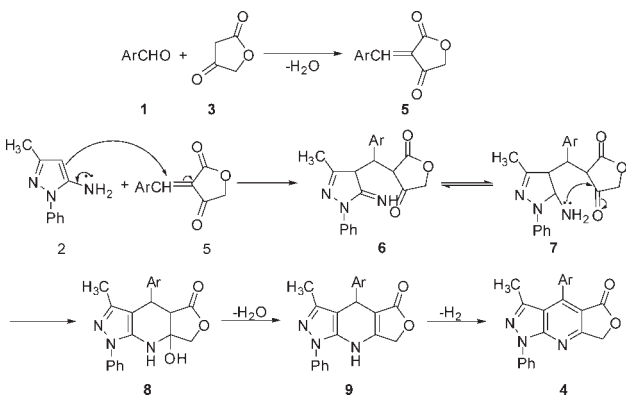
3-Methyl-1-phenyl-4-(3,4-dimethoxyphenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4a). This compound was obtained as solid with mp 200–202°C (lit. [14] 203–205°C); IR (potassium bromide): 3059, 3018, 1768, 1590, 1570, 1512, 1460, 1438, 1412, 1355, 1325, 1309, 1259, 1234, 1203, 1174, 1130, 1070, 1045, 1027, 843, 795, 761, 701 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 3.79 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 5.46 (s, 2H, CH_2), 7.13 (d, J = 7.6 Hz, 2H, ArH), 7.19 (s, 1H, ArH), 7.40 (t, J = 7.6 Hz, 1H, ArH), 7.60 (t, J = 7.6 Hz, 2H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS

Table 3

Studies on the reuse of reaction solution in the preparation of **4a**.

Round	1	2	3	4	5	6
Yield (%)	98	97	92	94	95	92

Scheme 2



[Found: *m/z* 402.1450 (M + H^+); calcd for $C_{23}H_{20}N_3O_4$: 402.1452].

3-Methyl-1-phenyl-4-(4-bromophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4b). This compound was obtained as solid with mp 226–228°C (lit. [14] 226–227°C); IR (potassium bromide): 3058, 1765, 1579, 1558, 1507, 1489, 1440, 1387, 1356, 1314, 1210, 1140, 1070, 1047, 1029, 1012, 847, 821, 798, 758, 720 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 7.40 (t, J = 7.2 Hz, 1H, ArH), 7.54 (d, J = 8.0 Hz, 2H, ArH), 7.60 (t, J = 7.6 Hz, 2H, ArH), 7.79 (d, J = 8.0 Hz, 2H, ArH), 8.18 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 442.0161 (M + Na^+); calcd for $C_{21}H_{14}{}^{79}BrN_3O_2Na$: 442.0167].

3-Methyl-1-phenyl-4-(4-fluorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4c). This compound was obtained as solid with mp 235–237°C (lit. [14] 235–237°C); IR (potassium bromide): 3070, 1756, 1597, 1578, 1512, 1490, 1449, 1437, 1423, 1319, 1360, 1315, 1222, 1210, 1167, 1137, 1069, 1043, 1029, 830, 798, 757 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.39–7.45 (m, 3H, ArH), 7.59–7.67 (m, 4H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 382.0945 (M + Na^+); calcd for $C_{21}H_{14}FN_3O_2Na$: 382.0968].

3-Methyl-1-phenyl-4-(4-nitrophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4d). This compound was obtained as solid with mp 283–285°C (lit. [14] 288–289°C); IR (potassium bromide): 3067, 1763, 1580, 1517, 1438, 1388, 1349, 1314, 1294, 1213, 1142, 1109, 1073, 1050, 1021, 838, 802, 754, 709 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.62 (d, J = 8.0 Hz, 2H, ArH), 7.90 (d, J = 8.4 Hz, 2H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH), 8.43 (d, J = 8.4 Hz, 2H, ArH). HRMS [Found: *m/z* 409.0891 (M + Na^+); calcd for $C_{21}H_{14}N_4O_4Na$: 409.0913].

3-Methyl-1-phenyl-4-(4-methoxyphenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4e). This compound was obtained as solid with mp 192–194°C (lit. [14] 190–192°C); IR (potassium bromide): 3047, 1765, 1608, 1580, 1516, 1509, 1458, 1445, 1420, 1384, 1358, 1309, 1294, 1259, 1208, 1176, 1140, 1072, 1048, 1036, 1019, 824, 798, 758 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 5.45 (s, 2H, CH_2), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.40 (t, J = 7.2 Hz, 1H, ArH), 7.52 (d, J = 8.4 Hz, 2H, ArH), 7.59 (d, J = 7.6 Hz, 2H, ArH), 8.19 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: *m/z* 394.1164 (M + Na^+); calcd for $C_{22}H_{17}N_3O_2Na$: 394.1168].

3-Methyl-1-phenyl-4-(2,4-dichlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4f). This compound was obtained as solid with mp 206–208°C (lit. [14] 206–208°C); IR (potassium bromide): 3065, 1763, 1585, 1507, 1475, 1442, 1420, 1389, 1376, 1361, 1316, 1211, 1150, 1127, 1101, 1078, 1050, 1025, 853, 821, 801, 787, 758 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H, CH_3), 5.54 (d, J = 16.0 Hz, 1H, CH), 5.61 (d, J = 16.0 Hz, 1H, CH), 7.43 (t, J = 7.2 Hz, 1H, ArH), 7.60-7.65 (m, 3H, ArH), 7.68 (d, J = 8.4 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 409.0385 (M^+); Calcd for $C_{21}H_{13}{}^{35}Cl_2N_3O_2$: M 409.0385].

3-Methyl-1-phenyl-4-(3,4-dimethylphenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4g). This compound was obtained as solid with mp 232–233°C (lit. [14] 231–233°C); IR (potassium bromide): 1768, 1513, 1500, 1459, 1433, 1385, 1355, 1310, 1268, 1227, 1210, 1182, 1070, 1041, 1026, 852, 818, 798, 758, 719 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 7.28 (d, J = 8.0 Hz, 1H, ArH), 7.32-7.35 (m, 2H, ArH), 7.41 (t, J = 7.6 Hz, 1H, ArH), 7.61 (t, J = 8.0 Hz, 2H, ArH),, 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 392.1355 (M + Na^+); calcd for $C_{23}H_{19}N_3O_2Na$: 392.1375].

3-Methyl-1-phenyl-4-(4-chlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4h). This compound was obtained as solid with mp 220–222°C (lit. [14] 223–225°C); IR (potassium bromide): 3063, 1764, 1598, 1581, 1562, 1506, 1489, 1459, 1442, 1421, 1386, 1358, 1314, 1211, 1141, 1125, 1089, 1072, 1048, 1028, 1015, 915, 848, 799, 760, 723 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.39–7.43 (m, 1H, ArH), 7.59–7.67 (m, 6H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: *m/z* 398.0670 (M + Na^+); calcd for $C_{21}H_{14}N_3O_2Na$: 398.0672].

3-Methyl-1-phenyl-4-(pyridine-2-yl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4i). This compound was obtained as solid with mp 245–246°C; IR (potassium bromide): 3032, 1760, 1578, 1515, 1490, 1437, 1383, 1359, 1340, 1311, 1266, 1225, 1201, 1130, 1115, 1076, 1050, 1027, 851, 817, 794, 762 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.11 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.60–7.65 (m, 4H, ArH), 8.18 (d, J = 8.0 Hz, 2H, ArH), 8.80 (d, J = 5.2 Hz, 2H, ArH). HRMS [Found: *m/z* 342.1119 (M^+); Calcd for $C_{20}H_{14}N_4O_2$: M 342.1117].

3-Methyl-1-phenyl-4-(thiophen-2-yl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4j). This compound was obtained as solid with mp 246–248°C (lit. [14] 248–250°C); IR (potassium bromide): 3098, 1767, 1583, 1544, 1509, 1491, 1440, 1421, 1388, 1363, 1313, 1244, 1149, 1073, 1051, 1022, 796, 756 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.22 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 7.30–7.33 (m, 1H, ArH), 7.39–7.46 (m, 2H, ArH), 7.61 (t, J = 8.0 Hz, 2H, ArH), 7.97 (d, J = 5.2 Hz, 1H, ArH), 8.17 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: *m/z* 370.0621 (M + Na^+); calcd for $C_{19}H_{13}N_3O_2SNa$: 370.0626].

3-Methyl-1-phenyl-4-(3-chlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4k). This compound was obtained as solid with mp 201–203°C; IR (potassium bromide): 1776, 1583, 1562, 1515, 1437, 1387, 1357, 1313, 1210, 1146, 1073, 1047, 1031, 939, 784, 752, 725, 707 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 7.41 (t, J = 7.2 Hz, 1H, ArH), 7.55 (d, J = 7.2 Hz, 1H, ArH), 7.61 (t, J =

7.6 Hz, 3H, ArH), 7.67 (d, J = 8.4 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 8.19 (d, J = 8.0 Hz, 2H, ArH). HRMS [Found: m/z 375.0754 (M^+); Calcd for $C_{21}H_{14}{}^{35}ClN_3O_2$: M 375.0775].

3-Methyl-1-phenyl-4-(2-chlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4l). This compound was obtained as solid with mp 227–228°C; IR (potassium bromide): 1774, 1600, 1585, 1510, 1492, 1474, 1438, 1387, 1359, 1313, 1210, 1148, 1127, 1074, 1058, 1046, 1027, 872, 846, 757, 726, 710 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.05 (s, 3H, CH_3), 5.53 (d, J = 16.0 Hz, 1H, CH), 5.60 (d, J = 16.0 Hz, 1H, CH), 7.42 (t, J = 7.6 Hz, 1H, ArH), 7.55–7.64 (m, 5H, ArH), 772 (d, J = 8.0 Hz, 1H, ArH), 8.20 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: m/z 375.0783 (M^+); Calcd for $C_{21}H_{14}{}^{35}ClN_3O_2$: M 375.0775].

3-Methyl-1-phenyl-4-(3,4-dichlorophenyl)-7*H*-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5-one (4m). This compound was obtained as solid with mp 218–220°C; IR (potassium bromide): 3036, 1771, 1582, 1551, 1506, 1473, 1439, 1382, 1359, 1315, 1212, 1141, 1072, 1050, 1032, 944, 911, 820, 800, 756, 714 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 7.41 (t, J = 7.2 Hz, 1H, ArH), 7.58–7.64 (m, 3H, ArH), 7.87 (d, J = 8.0 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 8.18 (d, J = 7.6 Hz, 2H, ArH). HRMS [Found: m/z 409.0377 (M^+); Calcd for $C_{21}H_{13}{}^{35}Cl_2N_3O_2$: M 409.0385].

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