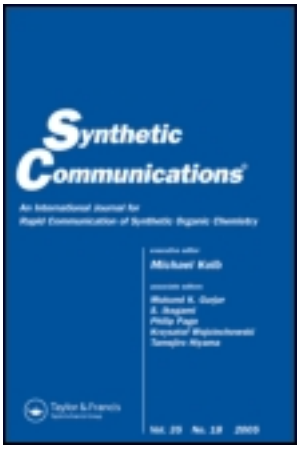


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile and Clean Synthesis of Furopyridine Derivatives via Three-Component Reaction in Aqueous Media Without Catalyst

Da-Qing Shi [a] & Hao Yao [b]

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

[b] College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, China

Version of record first published: 16 Jun 2009

To cite this article: Da-Qing Shi & Hao Yao (2009): Facile and Clean Synthesis of Furopyridine Derivatives via Three-Component Reaction in Aqueous Media Without Catalyst, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:14, 2481-2491

To link to this article: http://dx.doi.org/10.1080/00397910802656034

Synthetic Communications®, 39: 2481–2491, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802656034

Taylor & Francis
Taylor & Francis Group

Facile and Clean Synthesis of Furopyridine Derivatives via Three-Component Reaction in Aqueous Media Without Catalyst

Da-Qing Shi[1] and Hao Yao[2]
[1]College of Chemistry, Chemical Engineering and Materials Science, Key Laboratory of Organic Synthesis of Jiangsu Province, Soochow University, Suzhou, China
[2]College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou, China

Abstract: A series of furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derivatives were synthesized via the three-component reaction of an aldehyde, tetronic acid, and 6-amino-1,3-dimethyl-pyrimidine-2,4-dione in aqueous media without the use of catalyst. This protocol has the advantages of better yields, less cost, reduced environmental impact, and convenient procedure.

Keywords: Aqueous media, furo[2′1′:5,6]pyrido[2,3-*d*]pyrimidine, synthesis, three-component reaction

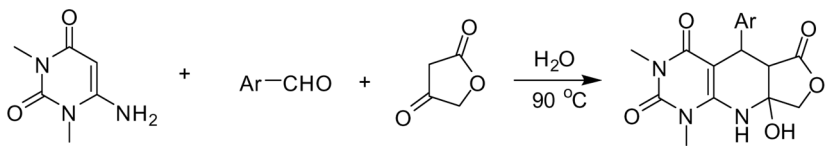
Furopyridines are one of the most important privileged medicinal scaffolds, molecular frameworks used for the development of pharmaceutical agents for diverse applications. Compounds with this motif show a wide range of pharmacological activities such as antipsychotic,[1] antianaphlactic,[2] antiproliferative,[3] anticonvulsant,[4] and anthelmintic[5] activities, and they can be used as calcium influx promoters,[6] HIV-1 nonnucleoside reverse transcriptase inhibitors,[7] and acetylcholinesterase inhibitors.[8]

Received September 8, 2008.
Address correspondence to Da-Qing Shi, College of Chemistry, Chemical Engineering and Materials Science, Key Laboratory of Organic Synthesis of Jiangsu Province, Soochow University, Suzhou 215123, China. E-mail: dqshi@263.net

The pyrazolo[2,3-*d*]pyrimidine core of the pterin pigments was shared by the vitamin folic acid and shows a diverse range of biological properties and highly species-specific responses such as antitumor, antibacterial, antihypertensive, anti-inflammatory, antifungal, and antileishma activity. Likewise, pyrazole derivatives have been reported in the literature to be versatile building blocks for the synthesis of a wide range of heterocyclic motifs, such as pyrazolopyridines,[9] pyrazoloquinolines,[10] and pyrazolopyrazoles.[11]

Reducing 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 uses water as reaction medium. Breslow et al.,[12] 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 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions.[13] The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environmentally friendly, while it allows the control of the pH and the use of microaggregates such as surfactants. Generally, the low solubility of most reagents in water is not an obstacle to the reactivity, which, on the contrary, is reduced with the use of cosolvents. The synthesis of new and important types of heterocyclic compounds in water continues to attract wide attention among synthetic chemists. Based on our previous studies on the use of water as solvent for the synthesis of heterocyclic compounds,[14] we herein described a facile multicomponent reaction consisting of aldehyde, tetronic acid, and 6-amino-1,3-dimethylpyrimidine-2,4-dione in aqueous media to synthesize the furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derives.

After some preliminary experiments, it was found that an equimolar mixture of 6-amino-1,3-dimethylpyrimidine-2,4-dione (**1**), 4-chlorobenzaldehyde (**2a**), and tetronic acid (**3**) in a small amount of water without catalyst stirred at 90°C for 10 h afforded 1,3-dimethyl-5-(4-chlorophenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione in good to excellent yields.



Scheme 1. The synthesis of **4**.

Table 1. Synthesis of **4a** in different solvents

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	H_2O	90	10	90
2	CH_3CN	80	20	0
3	$ClCH_2CH_2Cl$,	80	20	0
4	EtOH	80	20	0
5	CH_3COCH_3	60	20	0
6	CH_3COOEt	80	20	0

To find a solvent effective for the synthesis of the furo[2′,1′:5,6] pyrido[2,3-*d*]pyrimidine-2,4,6-trione derivatives, we examined this condensation reaction in a different solvent. The best results were obtained when water was used (Table 1).

Encouraged by this success, we extended this reaction of 6-amino-1,3-dimethylpyrimidine- 2,4-dione with a range of other aromatic aldehydes and tetronic acid under similar condensations, furnishing the respective furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione **4** in good yields. The results are summarized in Table 2.

As shown in Table 2, this protocol can be applied not only to the aromatic aldehydes with electron-withdrawing groups (such as halide groups) but also to aromatic aldehydes with electron-donating groups (such as methoxyl, methyl groups) with excellent yields under the same conditions. Therefore, we concluded that the electronic nature of the substituents has no significant effect on this reaction. The further study shows that the compounds containing 8a-hydroxy are stabile and final products, and the 8a-hydroxy cannot be eliminated by adding 4-methylbenzenesulfonic acid (TsOH) or by extending the reaction time.

Table 2. Synthesis of furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine **4** in aqueous media

Entry	Compound	Ar	Time (h)	Yield (%)
1	**4a**	4-ClC_6H_4	10	90
2	**4b**	4-BrC_6H_4	9	85
3	**4c**	4-FC_6H_4	21	77
4	**4d**	4-OHC_6H_4	15	93
5	**4e**	4-$CH_3C_6H_4$	9	87
6	**4f**	2-ClC_6H_4	21	89
7	**4g**	4-$CH_3OC_6H_4$	14	91
8	**4h**	3,4-$(CH_3)_2C_6H_3$	22	80
9	**4i**	3,4-$(CH_3O)_2C_6H_3$	20	78
10	**4j**	3,4-$Cl_2C_6H_3$	18	83
11	**4k**	3,4-$OCH_2OC_6H_3$	8	78

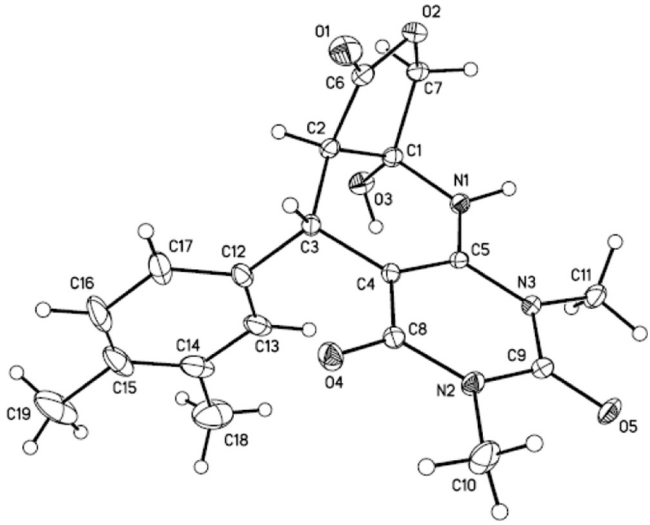
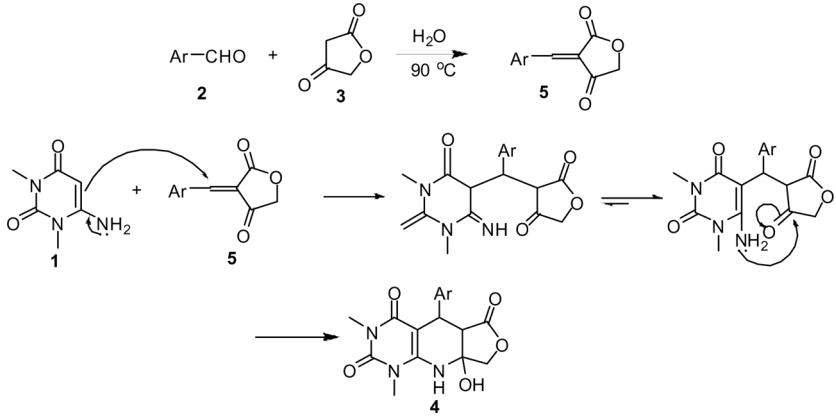


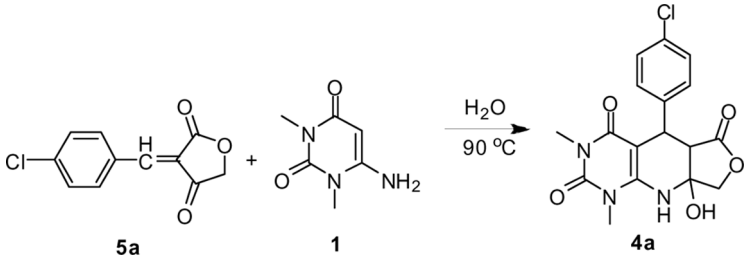
Figure 1. ORTEP diagram of **4h**.

The structures of the compounds **4** were identified by their spectroscopic analysis. The structure of compound **4h** was further confirmed by X-ray diffraction analysis.[15] The molecular structure of **4h** is shown in Fig. 1.

Although the detailed mechanism of the reaction remains to be fully clarified, the formation of furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **4** could be explained by the reaction sequence presented in Scheme 2. We proposed that the reaction proceeded via a reaction



Scheme 2. The possible mechanism.



Scheme 3. The synthesis of **4a** from **5a** and **1**.

sequence of condensation, addition, and cyclization. First, the condensation of aldehyde **2** and tetronic acid **3** gave the intermediate product **5**. The addition of **5** to 6-amino-1,3-dimethylpyrimidine-2,4-dione **1** then furnished the product **4**.

Evidence supporting this proposed mechanism came from the observation that when **5a** and **1** were reacted under same conditions, the expected product **4a** was obtained in a yield similar to that obtained in the one-pot reaction (Scheme 3).

In conclusion, we have developed a simple three-component reaction consisting of an aldehyde, tetronic acid, and 6-amino-1,3-dimethylpyrimidine-2,4-dione for the synthesis of furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derivatives in aqueous media. This new method has the advantages of good yields, less cost, convenient procedure, and environmentally friendly reaction conditions.

EXPERIMENTAL

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Tensor 27 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were recorded on a Bruker DPX 400-MHz spectrometer as dimethyl sulfoxide (DMSO-d_6) solutions. *J* values are in hertz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane (TMS). High-resolution mass spectra (HRMS) were obtained using a time-of-flight–mass spectra (TOF-MS) instrument. Elemental analysis was carried out on a Vario EL III instrument.

General Procedure for the Synthesis of 1,3-Dimethyl-5-aryl-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo)2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione (4)

A suspension of a mixture of **1** (2 mmol), **2** (2 mmol), and **3** (2 mmol) was stirred in water (10 mL) at 90°C for 9–30 h, then cooled to room

temperature. The crystalline powder formed was collected by filtration, washed with water, and recrystallized from EtOH to give **4**.

Spectral Data

1,3-Dimethyl-5-(4-chlorophenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4a)

Mp 225–227°C; IR (KBr): 3503, 3260, 3071, 3024, 2939, 1785, 1679, 1606, 1543, 1488, 1441, 1397, 1341, 1320, 1267, 1231, 1211, 1148, 1119, 1090, 1059, 1043, 1018, 993, 962, 930, 869, 837, 822, 772, 754, 679 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.07 (s, 3H, CH_3), 3.33 (s, 1H, CH), 3.38 (s, 3H, CH_3), 4.07 (d, $J = 8.8$ Hz, 1H, CH), 4.29 (s, 1H, CH), 4.50 (d, $J = 8.8$ Hz, 1H, CH), 6.32 (s, 1H, OH), 7.26–7.30 (m, 4H, ArH), 7.62 (s, 1H, NH). Anal. calcd. for $C_{17}H_{16}ClN_3O_5$: C, 54.05; H, 4.27; N, 11.12; found: C, 53.90; H, 4.23; N, 11.03.

1,3-Dimethyl-5-(4-bromophenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[[2,3-*d*]pyrimidine-2,4,6-trione (4b)

Mp 237–238°C; IR (KBr): 3512, 3267, 3068, 2960, 2934, 1780, 1679, 1606, 1544, 1485, 1440, 1388, 1370, 1341, 1320, 1230, 1211, 1149, 1119, 1079, 1606, 1544, 1485, 1440, 1388, 1370, 1341, 1320, 1230, 1211, 1149, 1119, 1074, 1058, 1042, 1020, 963, 929, 868, 836, 820, 771, 754, 619 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.08 (s, 3H, CH_3), 3.32 (s, 1H, CH), 3.38 (s, 3H, CH_3), 4.07 (d, $J = 8.4$ Hz, 1H, CH), 4.27 (s, 1H, CH), 4.51 (d, $J = 8.4$ Hz, 1H, CH), 6.34 (s, 1H, OH), 7.24 (d, $J = 8.4$ Hz, 2H, ArH), 7.42 (d, $J = 8.4$ Hz, 2H, ArH), 7.64 (s, 1H, NH). HRMS calcd. for $C_{17}H_{16}{}^{79}BrN_3O_5$, m/z: 421.0273 (M^+); found, m/z: 421.0278.

1,3-Dimethyl-5-(4-fluorophenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4c)

Mp 207–209°C; IR (KBr): 3503, 3244, 3077, 2976, 2907, 1790, 1679, 1606, 1543, 1507, 1484, 1440, 1398, 1342, 1320, 1268, 1222, 1161, 1118, 1059, 1042, 1021, 837, 760, 680 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.08 (s, 3H, CH_3), 3.32 (s, 1H, CH), 3.38 (s, 3H, CH_3), 4.08 (d, $J = 8.8$ Hz, 1H, CH), 4.30 (s, 1H, CH), 4.51 (d, $J = 8.8$ Hz, 1H, CH), 6.34 (s, 1H, OH), 7.05 (t, $J = 8.4$ Hz, 2H, ArH), 7.30 (t, $J = 8.4$ Hz, A2H, rH), 7.64

(s, 1H, NH). HRMS calcd. for $C_{17}H_{16}FN_3O_5$, m/z: 361.1074 (M^+); found, m/z: 361.1060.

1,3-Dimethyl-5-(4-hydroxyphenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4d)

Mp 238–240°C; IR (KBr): 3627, 3380, 3351, 3269, 3017, 2959, 2902, 1760, 1698, 1616, 1584, 1548, 1517, 1484, 1397, 1374, 1318, 1266, 1233, 1174, 1121, 1021, 958, 833, 763, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.08 (s, 3H, CH_3), 3.24 (s, 1H, CH), 3.39 (s, 3H, CH_3), 4.06 (d, $J = 8.8$ Hz, 1H, CH), 4.22 (s, 1H, CH), 4.48 (d, $J = 8.4$ Hz, 1H, CH), 6.23 (s, 1H, OH), 6.61 (d, $J = 8.0$ Hz, 2H, ArH), 7.05 (d, $J = 8.0$ Hz, 2H, ArH), 7.56 (s, 1H, NH), 9.13 (s, 1H, OH). Anal. calcd. for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.69; found: C, 56.71; H, 4.58; N, 11.19.

1,3-Dimethyl-5-(4-methylphenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4e)

Mp 214–216°C; IR (KBr): 3380, 3233, 2917, 1776, 1700, 1626, 1604, 1546, 1513, 1483, 1438, 1393, 1372, 1302, 1270, 1255, 1229, 1181, 1160, 1114, 1021, 955, 866, 842, 818, 786, 758, 685, 579 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 3.07 (s, 3H, CH_3), 3.27 (s, 1H, CH), 3.39 (s, 3H, CH_3), 4.06 (d, $J = 8.8$ Hz, 1H, CH), 4.28 (s, 1H, CH), 4.49 (d, $J = 8.4$ Hz, 1H, CH), 6.23 (s, 1H, OH), 7.03 (d, $J = 8.0$ Hz, 2H, ArH), 7.15 (d, $J = 8.4$ Hz, 2H, ArH), 7.58 (s, 1H, NH). Anal. calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76; found: C, 60.20; H, 5.40; N, 11.61.

1,3-Dimethyl-5-(2-chlorophenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4f)

Mp 233–235°C; IR (KBr): 3495, 3388, 3197, 3075, 3034, 3013, 2967, 2934, 1771, 1706, 1624, 1603, 1113, 1092, 1055, 1044, 939, 828, 782, 774, 749, 721, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.08 (s, 3H, CH_3), 3.24 (s, 1H, CH), 3.41 (s, 3H, CH_3), 4.10 (d, $J = 8.4$ Hz, 1H, CH), 4.51 (d, $J = 8.8$ Hz, 1H, CH), 4.71 (s, 1H, CH), 6.26 (s, 1H, OH), 7.15–7.23 (m, 3H, ArH), 7.43 (d, $J = 8.0$ Hz, 1H, ArH), 7.69 (s, 1H, NH). Anal. calcd. for $C_{17}H_{16}ClN_3O_5$: C, 54.05; H, 4.27; N, 11.12; found: C, 53.78; H, 4.47; N, 11.50.

1,3-Dimethyl-5-(4-methoxyphenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4g)

Mp 228–230°C; IR (KBr): 3521, 3285, 2963, 2837, 1786, 1694, 1668, 1604, 1542, 1510, 1483, 1441, 1390, 1336, 1302, 1271, 1243, 1180, 1159, 1112, 1028, 963, 829, 786, 757, 681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.07 (s, 3H, CH_3), 3.27 (s, 1H, CH), 3.38 (s, 3H, CH_3), 4.07 (d, $J = 8.8$ Hz, 1H, CH), 4.26 (s, 1H, CH), 4.49 (d, $J = 8.8$ Hz, 1H, CH), 6.27 (s, 1H, OH), 6.79 (d, $J = 8.4$ Hz, 2H, ArH), 7.18 (d, $J = 8.0$ Hz, Hz, 2H, ArH), 7.59 (s, 1H, NH). Anal. calcd. for $C_{18}H_{19}N_3O_5$: C, 57.90; H, 5.13; N, 11.25; found: C, 57.69; H, 4.98; N, 11.39.

1,3-Dimethyl-5-(3,4-dimethylphenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4h)

Mp 216–218°C; IR (KBr): 3505, 3233, 3068, 2919, 1781, 1696, 1651, 1622, 1552, 1483, 1436, 1391, 1373, 1302, 1272, 1238, 1186, 1156, 1107, 1023, 959, 889, 868, 825, 792, 758, 719, 686, 663 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 3.25 (s, 1H, CH), 3.39 (s, 3H, CH_3), 4.05 (d, $J = 8.4$ Hz, 1H, CH), 4.25 (s, 1H, CH), 4.49 (d, $J = 8.4$ Hz, 1H, CH), 6.21 (s, 1H, OH), 6.93–6.98 (m, 2H, ArH), 7.05 (s, 1H, ArH), 7.59 (s, 1H, NH). HRMS calcd. for $C_{19}H_{21}N_3O_5$, m/z: 371.1480(M^+); found, m/z: 371.1490.

1,3-Dimethyl-5-(3,4-dimethoxyphenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4i)

Mp 247–249°C; IR (KBr): 3475, 3282, 3013, 2936, 2837, 1782, 1692, 1619, 1541, 1516, 1486, 1397, 1374, 1348, 1263, 1268, 1179, 1149, 1114, 1028, 962, 867, 804, 789, 767, 684, 644, 599 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.09(s, 3H, CH_3), 3.32 (s, 1H, CH), 3.39 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.07 (d, $J = 8.4$ Hz, 1H, CH), 4.27 (s, 1H, CH), 4.50 (d, $J = 8.8$ Hz, 1H, CH), 6.25 (s, 1H, OH), 6.72–6.79 (m, 2H, ArH), 6.93 (s, 1H, ArH), 7.56 (s, 1H, NH). Anal. calcd. for $C_{19}H_{21}N_3O_7$: C, 56.57; H, 5.25; N, 10.42; found: C, 56.38; H, 5.39; N, 10.49.

1,3-Dimethyl-5-(3,4-dichlorophenyl)-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4j)

Mp 229–231°C; IR (KBr): 3510, 3231, 3081, 2916, 1782, 1698, 1653, 1621, 1595, 1555, 1884, 1435, 1390, 1374, 1309, 1294, 1276, 1261, 1231, 1187,

1157, 1108, 1063, 1020, 962, 950, 869, 825, 779, 753, 687, 665 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.10 (s, 3H, CH_3), 3.37 (s, 1H, CH), 3.39 (s, 3H, CH_3), 4.08 (d, 1H, $J = 8.8$ Hz, CH), 4.29 (s, 1H, CH), 4.53 (d, 1H, $J = 8.8$ Hz, CH), 6.46 (s, 1H, OH), 7.29 (d, $J = 7.2$ Hz, 1H, ArH), 7.50 (d, $J = 8.4$ Hz, 1H, ArH), 7.53 (s, 1H, ArH), 7.69 (s, 1H, NH). Anal. calcd. for $C_{17}H_{15}{}^{35}Cl_2N_3O_5$: C, 49.53; H, 3.67; N, 10.19; found: C, 49.29; H, 3.69; N, 9.88.

1,3-Dimethyl-5-((benzo[d][1,3]dioxol-5-yl))-8a-hydroxy-5,9,5a-trihydro-7-oxa-furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione (4k)

Mp 226–228°C; IR (KBr): 3480, 3387, 3258, 2960, 2895, 1773, 1691, 1627, 1544, 1487, 1392, 1371, 1346, 1182, 1161, 1115, 1039, 1021, 955, 933, 906, 864, 822, 797, 765, 752, 693, 679, 653 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.07 (s, 3H, CH_3), 3.28 (s, 1H, CH), 3.37 (s, 3H, CH_3), 4.06 (d, $J = 8.8$ Hz, 1H, CH), 4.23 (s, 1H, CH), 4.48 (d, $J = 8.4$ Hz, 1H, CH), 5.94 (d, $J = 6.4$ Hz, 2H, ArH), 6.32 (s, 1H, OH), 6.72–6.78 (m, 2H, ArH), 6.83 (s, 1H, ArH), 7.60 (s, 1H, NH). Anal. calcd. for $C_{18}H_{17}ClN_3O_7$: C, 55.81; H, 4.42; N, 10.85; found: C, 55.92; H, 4.72; N, 11.41.

Crystal Data for 6h

C_{22} $H_{30}N_4O_7$; $M = 462.50$, colorless block crystals, $0.76 \times 0.75 \times 0.60$ mm, monoclinic, space group Cc, $a = 15.006(2)$ Å, $b = 11.1263(17)$ Å, $c = 14.0813(19)$ Å, $\alpha = 90.00°$, $\beta = 90.337(5)°$, $\gamma = 90.00°$, $V = 2351.0(6)$ $Å^3$, $Z = 4$, $Dc = 1.307\ g \cdot cm^{-3}$. $F(000) = 984$, $\mu(MoK\alpha) = 0.085\ mm^{-1}$. Intensity data were collected on Rigaku mercury diffractometer with graphite monochromated $MoK\alpha$ radiation ($\lambda = 0.71070$ A°) using ω scan mode with $3.1° < \theta < 25.3°$; 4114 unique reflections were measured and 3896 reflections with $I > 2\sigma(I)$ were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique was done to $R = 0.0613$ and $wR = 0.1654$.

ACKNOWLEDGMENT

We are grateful to the Foundation of Key Laboratory of Organic Synthesis of Jiangsu Province for financial support.

REFERENCES

1. New, J. S.; Christopher, W. L.; Yevich, J. P.; Butler, R.; Schlemmer, R.; Francis, J.; VanderMaeln, C. P.; Cipollina, J. A. The thieno[3,2-c]pyridine and furo[3,2-c]pyridine rings: New pharmacophores with potential antipsychotic activity. *J. Med. Chem.* **1989**, *32*, 1147–1156.
2. Wagner, G.; Prantz, J. Synthesis of furo[2,3-b]pyridine amidines with antianaphylactic activity. *Pharmazie* **1993**, *48*, 250–253.
3. Bukoski, R. D.; Bo, J.; Xue, H.; Bian, K. Antiproliferative and endothelium-dependent vasodilator properties of 1,3-dihydro-3-p-chlorophenyl-7-hydroxy-6-methylfuro[3,4-c] pyridine hydrochloride cicletanine, *J. Pharmacol. Exp. Ther.* **1993**, *265*, 30–35.
4. Paronikyan, E. G.; Oganisyan, A. K.; Noravyan, A. S.; Paronikyan, R. G.; Dzhagatspanyan, I. A. Synthesis and anticonvulsant activity of pyrano [4′,3′:4,5]pyrido[2,3-b]furo[3,2-d]pyrimidine and pyrano[4′,3′:4,5]pyrido[2,3-b] furo[3,2-d]pyridine derivatives. *Pharm. Chem. J.* **2002**, *36*, 413–414.
5. Jeschke, P.; Harder, A.; Etzd, W.; Gau, W.; Goehrt, A.; Benet-Buchholz, J.; Thielking, G. Synthesis and anthelmintic activity of 7-substituted 3,4a-dimethyl-4a,5a,8a,8b-tetrahydro-6H-pyrrolo[3′,4′:4,5]furo[3,2-b]pyridine-6,8 (1H)-diones. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2375–2379.
6. Gerster, P.; Riegger, C.; Fallert, M. Effects of 1,4,5,7-tetrahydro-furo[3,4-c] pyridine derivatives, a calcium influx promoter, on sodium-, calcium-, and magnesium-dependent bioelectrical activity of Purkinje fibers and papillary muscles. *Arzneim. Forsch.* **1987**, *37*, 309–315.
7. Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. Stereoselective synthesis of furo[2,3-c]pyridine pyrimidine thioethers, a new class of potent HIV-1 non-nucleoside reverse transcriptase inhibitors. *J. Org. Chem.* **1998**, *63*, 7851–7859.
8. Marco, J. L.; Carreiras, M. C. Recent developments in the synthesis of acetylcholinesterase inhibitors. *Mini-Rev. Med. Chem.* **2003**, *3*, 518–524.
9. (a) Quiroga, J.; Insuasty, B.; Hormaza, A.; Gamenara, D.; Dominguez, L.; Saldana, J. Synthesis of 5-cyanopyrazolo[3,4-b]pyridines in the reaction of 5-amino-3-methyl- 1-phenylpyrazole with arylidene derivatives of malonodinitrile and ethyl cyanoacetate. *J. Heterocycl. Chem.* **1999**, *36*, 1311–1316; (b) Quiroga, J.; Hormaza, A.; Insuasty, B.; Marquez, M. Reaction of 5-amino-1-aryl-3-methyl-pyrazoles with benzylidene derivatives of meldrum's acid: Synthesis and characterization of pyrazolo[3,4-b]pyridinones. *J. Heterocycl. Chem.* **1998**, *35*, 409–412; (c) Quiroga, J.; Silvia, C.; Insuasty, B.; Abonia, R. Synthesis and structureal analysis of 5-cyanodihydropyrazolo[3,4-b] pyridines. *J. Heterocycl. Chem.* **2001**, *38*, 53–60.
10. Quiroga, J.; Insuasty, B.; Cruz, S.; Hemandez, P.; Bolanos, A.; Moreno, R.; Hormaza, A.; Almeida, R. H. D. Reaction of 5-aminopyrazole with β-dimethylaminopropiophenones: Synthesis of new pyrazolo[3,4-b]pyridines. *J. Heterocycl. Chem.* **1998**, *35*, 333–338.
11. Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. Microwave-assisted solvent-free synthesis of pyrazolo[3,4-b]quinolines and pyrazolo[3,4-c]pyrazoles using *p*-TsOH. *Tetrahedron Lett.* **2001**, *42*, 3827–3829.

12. 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.
13. (a) Li, C. J. Organic reactions in aqueous media-With a focus on carbon–carbon bond formation. *Chem. Rev.* **1993**, *93*, 2023–2035; (b) Li, C. J. Organic reactions in aqueous media with a focus on carbon–carbon bond formations: A decade update. *Chem. Rev.* **2005**, *105*, 3095–3166.
14. (a) Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. A simple and clean procedure for the synthesis of polyhydroacridine and quinoline derivatives: Reaction of Schiff base with 1,3-dicarbonyl compounds in aqueous medium. *Tetrahedron Lett.* **2005**, *46*, 7169–7173; (b) Shi, D. Q.; Yao, H.; Shi, J. W. Three-component one-pot synthesis of pyrazolo[3,4-b] pyridine derivatives in aqueous media. *Synth. Commun.* **2008**, *38*, 1662–1669.