An Efficient and Clean Synthesis of Pyrido[2,3-*d*]pyrimidine-4,7-dione Derivatives in Aqueous Media

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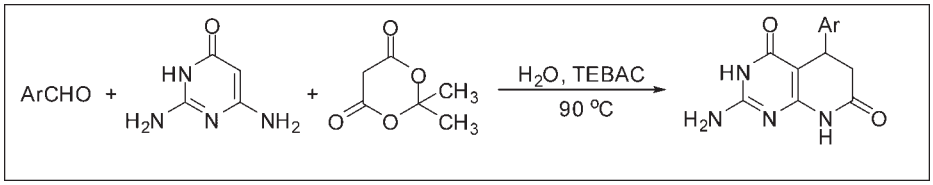

A series of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione derivatives were synthesized via the three-component reaction of aromatic aldehyde, 2,6-diaminopyrimidine- 4(3*H*)-one, and Meldrum's acid in water in the presence of triethylbenzylammonium chloride (TEBAC). This protocol has the advantages of easier work-up, milder reaction conditions, and environmentally benign procedure.

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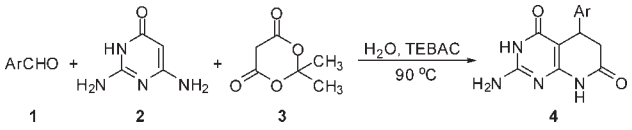
INTRODUCTION

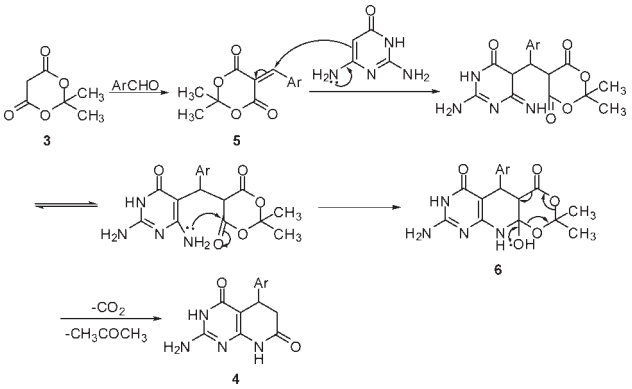
Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been extensively used in synthetic chemistry for the formation of carbon-carbon and carbon–heteroatom bonds [1]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complication operations and allowing saving both of solvent and of reagents. In the past decade there have been tremendous developments in three- and four-component reactions and great efforts continue to be made to develop new MCRs [2]. The need to reduce the amount of toxic waste and by-product 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 the reaction medium. Breslow rediscovered the use of water as a solvent in organic synthesis in the 1980s [3]. There has been growing recognition that water is an attractive medium for many organic reactions [4] and many MCRs in aqueous media have been reported [5].

The importance of uracil and its annulated derivatives is well recognized by synthetic [6] as well as biological [7] chemists. With the development of clinically useful anticancer and antiviral drugs [8], there has recently been remarkable interest in the synthetic manipulations of uracils [9]. Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, which include antitumor [10], antibacterial [11], anti-inflammatory [12], antifungal [13], and antileishmaniasis [14] properties, and also act as cyclin-dependent kinase 4 inhibitors [15]. Therefore, for the preparation of these complex molecules large efforts have been directed toward the synthetic manipulation of uracils. Broom *et al*. [16] synthesized pyrido[2,3-*d*]pyrimidines from the reaction of DMAD and 6-aminouracile in protic solvent but obtained uncyclized condensed acetylenic adduct when the reaction was carried in DMF [17]. Bhuyan *et al*. [18] reported the synthesis of pyrido[2,3-*d*]pyrimidines from the reaction of arylidenemalononitrile with 6-aminouracil in refluxing 1-propanol, but in this reaction, benzylmalononitrile was obtained as by-product and the amount of arylidenemalononitrile needed was in excess. Rodríguez *et al*. [19] reported the synthesis of 9-aryl substituted 2-amino-4,7-dioxopyrido[2,3-*d*]pyrimidines by refluxing equimolar amounts of 5-arylidene substituted Meldrum's acid and 2,6-diamino-4-oxopyrimidine in acetic acid. Recently, Devi *et al*. [20] reported a novel three-component one-pot synthesis of pyrido[2,3-*d*]pyrimidines using microwave heating. These methods usually require forcing conditions, using organic solvents, long reaction times and complex synthetic pathways. As part of our current studies on the development of new routes to heterocyclic systems [21], recently we have reported the synthesis of pyrido[2,3-*d*]pyrimidine derivatives by the three-component reaction of aldehyde,

Scheme 1



Scheme 2



alkyl nitriles, and aminopyrimidines in water [22]. In this article, we would report an efficient and clean synthetic route to 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione derivatives in aqueous media catalyzed by TEBAC.

RESULTS AND DISCUSSION

When the three-components of aromatic aldehyde **1**, 2,6-diaminopyrimidine-4(3*H*)-one **2**, and Meldrum's acid **3** were treated in water in the presence of TEBAC at 90°C for a few hours (Scheme 1), the desired 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*, 8*H*)-dione **4** were obtained in high yields (Table 1).

As shown in Table 1, this protocol could be applied not only to the aromatic aldehydes with electron-withdrawing groups (such as halide and nitro groups), but also to aromatic aldehydes with electron-donating groups (such as alkyl and alkoxyl groups). Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction. However, because some aldehydes were remaining in the mixture, so some aldehydes gave low yields.

The structures of the compounds **4** were identified by their spectroscopy analysis. Thus, the IR spectra of compounds **4** measured in potassium bromide pellets show two bands of the elongation vibrations of the C=O group at 1703–1646 cm^{-1}, NH_2, and NH groups at 3467–3157 cm^{-1}. In the ^1H NMR spectra of compounds **4** measured in dimethyl-d_6 sulfoxide were observed the CH_2 proton signals at 2.41–2.57 and 2.91–3.17 ppm, the CH proton signals at 4.05–4.46 ppm, the NH_2 proton signals at 6.53–6.66 ppm, the aromatic proton signals at 6.82–8.16 ppm, and the NH proton signals at 10.10–10.33 and 10.60–10.90 ppm, respectively.

Table 1

Synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **4** in aqueous media.

Entry	Ar	Time (h)	Yield (%)
4a	4-FC_6H_4	5	76
4b	4-$CH_3OC_6H_4$	3	74
4c	4-BrC_6H_4	9	69
4d	4-ClC_6H_4	4	67
4e	2-$NO_2C_6H_4$	6	75
4f	4-$CH_3C_6H_4$	9	65
4g	3-$NO_2C_6H_4$	5	95
4h	3-ClC_6H_4	4	72
4i	2-ClC_6H_4	4	69
4j	3,4-$OCH_2OC_6H_3$	8	80
4k	4-$NO_2C_6H_4$	6	82

Although the detailed mechanism of earlier reaction remains not to be fully clarified, the formation of compounds **4** could be explained by a reaction sequence presented in Scheme 2. According to the literature [23], we proposed that the reaction proceeded via a reaction sequence of condensation, addition, cyclization, and elimination. First, the condensation of aldehyde **1** and Meldrum's acid **3** gave the intermediate product **5**. The addition of **5** to 2,6-diaminopyrimidine-4(3*H*)-one **2**, then cyclized to give intermediate product **6**. The carbon dioxide and acetone were losing from the intermediate product **6** to give the products **4**.

In conclusion, we have developed a simple three-component reaction consisting of an aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one, and Meldrum's acid for the synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione derivatives in aqueous media. This method has the advantages of easier work-up, milder reaction conditions, and environmentally benign procedure.

EXPERIMENTAL

Melting points are uncorrected. Infrared 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 DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane.

General procedure for the synthesis of 2-amino-5-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione derivatives 4 in aqueous media. A suspension of a mixture of aromatic aldehyde **1** (2 mmol), 2,6-diaminopyrimidine-4(3*H*)-one **2** (2 mmol), Meldrum's acid **3** (2 mmol) and TEBAC (0.15 g) was stirred in water (10 mL) at 90°C for several hours. After

completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF and water to give pure **4**.

2-Amino-5-(4-fluorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*, 8*H*)-dione (4a). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3325, 3167, 1691, 1652, 1591, 1537, 1508, 1485, 1361, 1305, 1264, 1211, 1158, 1099, 1015, 973, 906, 838, 794 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (d, J = 16 Hz, 1H, CH), 2.96 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.13 (d, J = 7.6 Hz, 1H, CH), 6.59 (br., s, 2H, NH_2), 7.07–7.12 (m, 2H, ArH), 7.16–7.20 (m, 2H, ArH), 10.16 (s, 1H, NH), 10.64 (s, 1H, NH).

2-Amino-5-(4-methoxylphenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4b). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3464, 3315, 3159, 1691, 1652, 1596, 1559, 1539, 1511, 1488, 1457, 1396, 1361, 1310, 1251, 1220, 1178, 1033, 907, 831, 793, 699 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.45 (d, J = 16 Hz, 1H, CH), 2.91 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 3.70 (s, 3H, CH_3O), 4.06 (d, J = 7.6 Hz, 1H, CH), 6.53 (br., s, 2H, NH_2), 6.82 (d, J = 8.4 Hz, 2H, ArH), 7.06 (d, J = 8.4 Hz, 2H, ArH), 10.08 (s, 1H, NH), 10.80 (s, 1H, NH).

2-Amino-5-(4-bromophenyl)-5,6-dihydro[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione (4c). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3325, 3159, 1688, 1646, 1588, 1539, 1486, 1398, 1362, 1307, 1262, 1212, 1158, 1074, 1010, 972, 907, 817, 793 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.47 (d, J = 16.4 Hz, 1H, CH), 2.97 (dd, J_1 = 8.0 Hz, J_2 = 16.4 Hz, 1H, CH), 4.11 (d, J = 8.0 Hz, 1H, CH), 6.60 (br., s, 2H, NH_2), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.47 (d, J = 8.4 Hz, 2H, ArH), 10.18 (s, 1H, NH), 10.66 (s, 1H, NH).

2-Amino-5-(4-chlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4d). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300 °C); IR (potassium bromide): 3460, 3319, 3158, 1698, 1650, 1591, 1539, 1487, 1398, 1361, 1307, 1261, 1211, 1159, 1091, 1014, 973, 907, 819, 793 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.47 (d, J = 16 Hz, 1H, CH), 2.97 (dd, J_1 = 8.0 Hz, J_2 = 16 Hz, 1H, CH), 4.12 (d, J = 8.0 Hz, 1H, CH), 6.59 (br., s, 2H, NH_2), 7.17 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 10.16 (s, 1H, NH), 10.65 (s, 1H, NH).

2-Amino-5-(2-nitrophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4e). This compound was obtained as solid with mp > 300°C (Lit. [19] > 300°C); IR (potassium bromide): 3433, 3319, 3167, 1698, 1652, 1588, 1536, 1519, 1477, 1408, 1340, 1281, 1259, 1233, 1213, 1165, 1018, 967, 930, 904, 862, 824, 794, 744, 700 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.41 (d, J = 16.4 Hz, 1H, CH), 3.17 (dd, J_1 = 8.8 Hz, J_2 = 16.4 Hz, 1H, CH), 4.49 (d, J = 8.8 Hz, 1H, CH), 6.65 (br., s, 2H, NH_2), 7.16 (d, J = 7.6 Hz, 1H, ArH), 7.49 (t, J = 7.6 Hz, 1H, ArH), 7.63 (t, J = 7.6 Hz, 1H, ArH), 7.93 (d, J = 8.0 Hz, 1H, ArH), 10.33 (s, 1H, NH), 10.67 (s, 1H, NH).

2-Amino-5-(4-methylphenyl)-5,6-dihydro-pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4f). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3315, 3157, 1698, 1653, 1636, 1600, 1559, 1540, 1487, 1457, 1395, 1362, 1309, 1264, 948, 904, 835, 809 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 2.45 (d, J = 16 Hz, 1H, CH), 2.93 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.07 (d, J = 7.6 Hz, 1H, CH), 6.55 (br., s, 2H, NH_2), 7.02 (d, J = 8.0 Hz, 2H, ArH), 7.15 (d, J = 8.0 Hz, 2H, ArH), 10.10 (s, 1H, NH), 10.60 (s, 1H, NH).

2-Amino-5-(3-nitrophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4g). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3450, 3317, 3163, 1691, 1652, 1588, 1530, 1470, 1405, 1353, 1301, 1266, 1020, 977, 929, 894, 826, 807, 790, 737 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.57 (d, J = 16.4 Hz, 1H, CH), 3.05 (dd, J_1 =8.0 Hz, J_2 = 16.4 Hz, 1H, CH), 4.30 (d, J = 8.0 Hz, 1H, CH), 6.66 (br, s, 2H, NH_2), 7.58∼7.67 (m, 2H, ArH), 8.01 (s, 1H, ArH), 8.06–8.11 (m,1H, ArH), 10.28 (s, 1H, NH), 10.71 (s, 1H, NH).

2-Amino-5-(3-chlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4h). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300 °C); IR (potassium bromide): 3325, 3169, 1683, 1652, 1585, 1539, 1477, 1391, 1264, 1212, 953, 907, 840, 786, 781 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.49 (d, J = 16 Hz, 1H, CH), 2.97(dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.14(d, J = 7.6 Hz, 1H, CH), 6.62 (br., s, 2H, NH_2), 7.12 (d, J = 7.6 Hz, 1H, ArH), 7.17 (s, 1H, ArH), 7.25–7.34 (m, 2H, ArH), 10.17 (s, 1H, NH), 10.67 (s, 1H, NH).

2-Amino-5-(2-chlorophenyl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4i). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3327, 3174, 1703, 1670, 1621, 1540, 1487, 1440, 1395, 1359, 1325, 1098, 1048, 1035, 1005, 975, 909, 813, 753 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (d, J = 16.4 Hz, 1H, CH), 3.04 (dd, J_1 = 8.4 Hz, J_2 = 16.4 Hz, 1H, CH), 4.46 (d, J = 8.4 Hz, 1H, CH), 6.61 (br, s, 2H, NH_2), 6.89–6.93 (m, 1H, ArH), 7.21–7.28 (m, 2H, ArH), 7.45–7.49 (m, 1H, ArH), 10.20 (s, 1H, NH), 10.68 (s, 1H, NH).

2-Amino-5-(benzo[d][1,3]dioxol-6-yl)-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7-(3*H*,8*H*)-dione (4j). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3467, 3320, 3164, 1694, 1639, 1591, 1540, 1502, 1486, 1438, 1405, 1356, 1311, 1242, 1212, 1121, 967, 934, 811, 807, 790 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.45 (d, J = 16 Hz, 1H, CH), 2.91 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H, CH), 4.05 (d, J = 7.6 Hz, 1H, CH), 5.95 (s, 2H, OCH_2O), 6.50–6.62 (m, 3H, NH_2+ArH), 6.73 (s, 1H, ArH), 6.79 (d, J = 8.0 Hz, 1H, ArH), 10.12 (s, 1H, NH), 10.62 (s, 1H, NH).

2-Amino-5,6-dihydro-5-(4-nitrophenyl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (4k). This compound was obtained as solid with mp > 300°C (Lit. [24] > 300°C); IR (potassium bromide): 3360, 3308, 3186, 1693, 1675, 1588, 1513, 1482, 1412, 1347, 1305, 1262, 1180, 1058, 1022, 966, 905, 826, 791, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.53 (d, J = 16.4 Hz, 1H, CH), 3.06 (dd, J_1 = 8.0 Hz, J_2 = 16.4 Hz, 1H, CH), 4.27 (d, J = 8.0 Hz, 1H, CH), 6.64 (br., s, 2H, NH_2), 7.44 (d, J = 8.4 Hz, 2H, ArH), 8.16 (d, J = 8.4 Hz, 2H, ArH), 10.27 (s, 1H, NH), 10.70 (s, 1H, NH).

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