An Efficient One-Pot Synthesis of 5-Aryl Substituted 2-Amino-5,8-dihydropyrido[2,3-*d*] pyrimidin-4,7-diones under Microwave Irradiation without Catalyst

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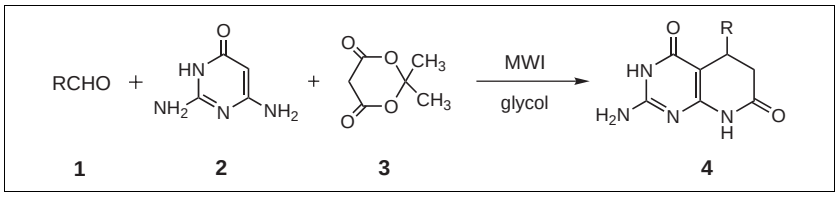
Received August 9, 2005



A series of 5-aryl substituted 2-amino-5,8-dihydropyrido[2,3-*d*]pyrimidin-4,7-diones were synthesized through one-pot condensation of 2,6-diaminopyrimidin-4-one, aldehyde and Meldrum's acid using glycol as energy transfer agent under microwave irradiation without catalyst. The one-pot protocol in the absence of catalyst has the advantage of good yield (86-95%), short route and reaction time (3-6 min) and environmentally friendly.

J. Heterocyclic Chem., **43**, 855 (2006).

Introduction.

For small organic molecules, simple nitrogen-containing heterocycles receive a large amount of attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Of these heterocycles, 2-aminopyrido[2,3-*d*]pyrimidines (also known as 5-deazapteridines) present interesting biological properties, and as some recent applications, they have been used as antitumor agents [1], some of them have shown antimicrobial activity [2], diureties [3] and activity against platelet aggregation [4]. As a result, a number of reports have appeared in the literature [5].

René Rodríguez has reported the synthesis of 5-aryl substituted 2-amino-4,7-dioxopyrido[2,3-*d*]pyrimidines by refluxing equimolar amounts of appropriate 5-arylidene substituted Meldrum's acid and 2,6-diamino-4-oxopyrimidine in acetic acid as solvent [6]. However, this method involves long route and reaction time. In addition, the reaction needs triethylamine as the basic catalyst. It goes without saying that the most efficient and environmentally friendly synthesis of functionalized heterocycles would be one-pot reaction from commercially available and simple starting materials.

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry [7]. The application of microwave heating as a non-conventional energy source for activation of reactions, has now gained extensive usage, as it leads to enhanced reaction rates, higher yields of pure products, easier work-up and short reaction time to selective conversions. The efficiency of microwave irradiation (MWI) in promoting organic reaction and the success of its application in heterocyclic synthesis [8] triggered us to apply it to one-pot multicomponent reactions.

In our continued interest [9], in the development of highly expedient methods for the synthesis of simple nitrogen-containing heterocycles, we report in this paper an efficient three-component one-pot synthesis of well functionalised 5-aryl substituted 2-amino-5,8-dihydropyrido[2,3-*d*]pyrimidin-4,7-diones in glycol under microwave irradiation. The products were synthesized by equimolecular amounts of 2,6-diaminopyrimidin-4-one with Meldrum's acid and appropriate aldehyde without catalyst in a small amount of glycol under microwave irradiation (Scheme 1). After irradiation for 3-6 min, the 5-aryl substituted 2-amino-5,8-dihydropyrido[2,3-*d*]pyrimidin-4,7-diones were obtained in excellent yields (86-95%). Besides, compared with the traditional heating methodology, when **1a**, **2** and **3** in glycol was irradiated with microwave, the reaction time was shortened to 4 min from 50 min and the yields were sharply increased to 93% from 86% at 98 ℃ with mechanical stirring. The results were listed in Table 1.

Results and Discussion.

It is noteworthy that the solvent glycol as an energy transfer agent plays a critical role in the success of the reaction. Owing to its high boiling point and good activity of dehydration, it can accelerate dehydration, which makes the reaction proceed smoothly in the absence of catalyst.

The procedure is easy to operate and the workup procedure is just simple filtrations. Furthermore, the protocol can be applied not only for the aromatic aldehyde but also for aliphatic aldehyde and heterocyclic aldehyde.

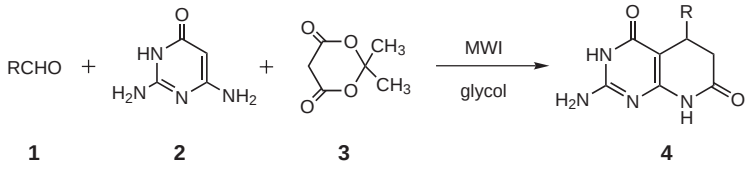
This reaction may occur *via* a condensation, addition, cyclization, elimination mechanism (Scheme 2). The condensation between aldehyde and Meldrum's acid gave 5-arylidene substituted Meldrum's acid **5**. Michael

Table 1

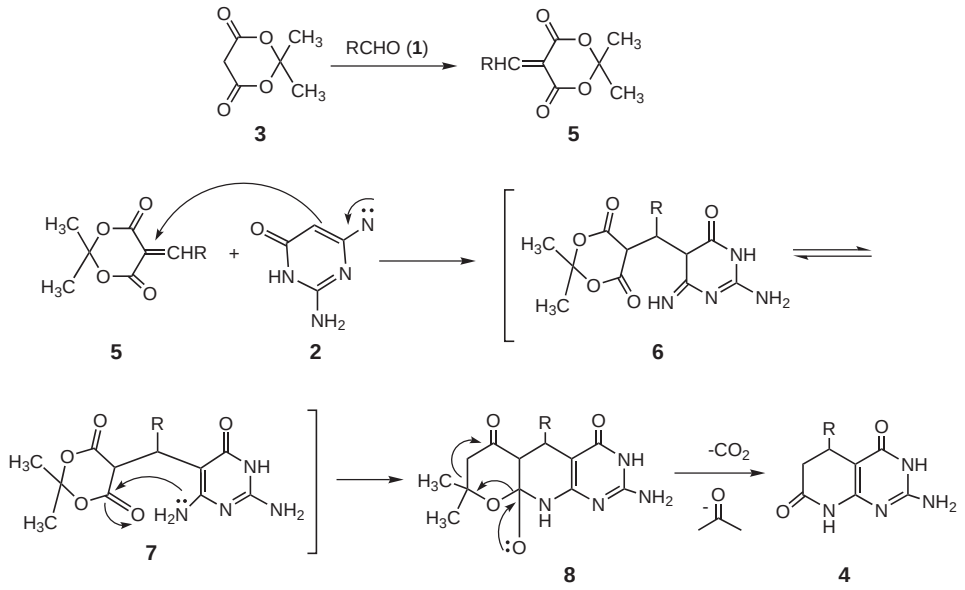
The synthesis of 4 under microwave irradiation

Entry	R^1	Time Min (lit.)	Yield % (lit.)	Mp (°C)
4a	4-Cl-C_6H_4	4	93	>300
4b	C_6H_5	4(300)[6]	91(89)[6]	>300(393)[6]
4c	4-NO_2-C_6H_4	3(540)[6]	90(89)[6]	>300(>400)[6]
4d	3-NO_2-C_6H_4	4(720)[6]	91(83)[6]	>300(>400)[6]
4e	2-Cl-C_6H_4	5(510)[6]	89(80)[6]	>300(356-359)[6]
4f	3,4-Cl_2-C_6H_3	4	92	>300
4g	2,4-Cl_2-C_6H_3	4	90	>300
4h	4-Br-C_6H_4	4	93	>300
4i	4-F-C_6H_4	3	95	>300
4j	4-OCH_3-C_6H_4	3	92	>300
4k	2-OCH_3-C_6H_4	4	90	>300
4l	4-CH_3-C_6H_4	6	93	>300
4m	3,4-OCH_2O-C_6H_3	5	89	>300
4n	3-OCH_3-4-OH-C_6H_3	4	87	>300
4o	$CH_3CH_2CH_2CH_2$	6	86	>300
4p	2-C_4H_3S	6	89	>300

Scheme 1



Scheme 2



addition between **5** and 2,6-diaminopyrimidin-4-one **2** then furnished the intermediate **6**, which isomerized to **7**. After that, intermolecular cyclization of **7** gave **8**, which finally afforded **4** by loosing acetone and carbon dioxide.

In conclusion, we have disclosed a facile case, using microwave heating mode in a small amount of glycol without catalyst. The one-pot synthesis of 5-aryl substituted 2-amino-5,8-dihydropyrido[2,3-*d*]pyrimidin-4,7-diones has the advantages of wide applicability, short route and reaction time, high yield, easy work-up procedure and being environmentally friendly. In addition, the large amount of dihydropyrido[2,3-*d*] pyrimidin-4,7- diones as the new classes of compounds including pyrimidone unit (**4a**, **4f**-**4p**) synthesized may lead to new candidates for medicinal application through bioactivity screening. This work is currently in progress and the results will be reported in due course.

Acknowledgments

We thank for the National Natural Science Foundation of China (No. 20372057), the Nature Science Foundation of the Jiangsu Province (No. BK2001142) and the Key Lab of Biotechnology for Medicinal Plants of Jiangsu Province (01AXL 14) for financial support.

EXPERIMENTAL

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. ^{1}H 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 Procedure for 5-Aryl substituted 2-amino-5,8-dihydro-pyrido[2,3-*d*]pyrimidin-4,7-diones (**4**).

The mixture of aldehyde (2 mmol), Meldrum's acid (2 mmol) and 2, 6-diaminopyrimidin-4-one (2 mmol) in glycol (1 mL) was irradiated for 3-6 min with power 220 W. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered and washed with ethanol (5 mL) to give the crude product, which was further by recrystallization from DMF. All products were characterized by IR, ^{1}H NMR spectral data.

2-Amino-5-(4-chlorophenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4a**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3452, 3310, 3156, 1685, 1645 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.61 (s, 1H, NH), 10.11 (s, 1H, NH), 7.34-7.16 (m, 4H, ArH), 6.55 (s, 2H, NH_2), 4.13 (m, 1H, CH), 2.97-2.45 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27; Found: C, 53.86; H, 3.76; N, 19.38.

2-Amino-5-phenyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4b**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3440, 3335, 3158, 1683, 1645 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.63 (s, 1H, NH), 10.11 (s, 1H, NH), 7.31-7.04 (m, 5H, ArH), 6.57 (s, 2H, NH_2), 4.11 (m, 1H, CH), 2.97-2.44 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86; Found: C, 61.15; H, 4.87; N, 21.78.

2-Amino-5-(4-nitropheny)-5,8-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,6*H*)-dione (**4c**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3375, 3300, 3159, 1690, 1662 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.66 (s, 1H, NH), 10.22 (s, 1H, NH), 8.17-7.43 (m, 4H, ArH), 6.61 (s, 2H, NH_2), 4.27 (m, 1H, CH), 3.08-2.51 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.25; Found: C, 51.68; H, 3.66; N, 23.40.

2-Amino-5-(3-nitropheny)-5,8-dihydropyrido[2,3-*d*] pyrimidine-4,7(3*H*,6*H*)-dione (**4d**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3315, 3161, 3074, 1682, 1646 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.71 (s, 1H, NH), 10.25 (s, 1H, NH), 8.07-7.57 (m, 4H, ArH), 6.64 (s, 2H, NH_2), 4.28 (m, 1H, CH), 3.05-2.53 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.25; Found: C, 52.01; H, 3.50; N, 23.17.

2-Amino-5-(2-chlorophenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4e**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3452, 3313, 3176, 1704, 1671 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.74 (s, 1H, NH), 10.30 (s, 1H, NH), 7.46-6.88 (m, 4H, ArH), 6.67 (s, 2H, NH_2), 4.44 (m, 1H, CH), 3.07-2.34 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27; Found: C, 53.89; H, 3.74; N, 19.36.

2-Amino-5-(3,4-dichlorophenyl)-5,8-dihydropyrido[2,3-*d*]-pyrimidine-4,7(3*H*,6*H*)-dione (**4f**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3443, 3299, 3157, 1682, 1650 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.67 (s, 1H, NH), 10.13 (s, 1H, NH), 7.55 (d, 1H, J=8.4 Hz, ArH), 7.39 (d, 1H, J=2.0 Hz, ArH), 7.14 (dd, 1H, J=8.4 Hz, J=2.0 Hz, ArH), 6.60 (s, 2H, NH_2), 4.16 (m 1H, CH), 3.01-2.50 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{10}C_{l2}N_4O_2$: C, 48.02; H, 3.10; N, 17.23; Found: C, 48.13; H, 3.01; N, 17.11.

2-Amino-5-(2,4-dichlorophenyl)-5,8-dihydropyrido[2,3-*d*]-pyrimidine-4,7(3*H*,6*H*)-dione (**4g**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3401, 3350, 3177, 1691, 1666 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.72 (s, 1H, NH), 10.26 (s, 1H, NH), 7.54-6.82 (m, 3H, ArH), 6.68 (s, 2H, NH_2), 4.43 (m, 1H, CH), 3.11-2.33 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{10}C_{l2}N_4O_2$: C, 48.02; H, 3.10; N, 17.23; Found: C, 48.12; H, 3.02; N, 17.28.

2-Amino-5-(4-bromophenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4h**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3400, 3301, 3156, 1687, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.61 (s, 1H, NH), 10.12 (s, 1H, NH),7.46 (d, 2H, J=8.4 Hz, ArH), 7.11 (d, 2H, J=8.4 Hz, ArH), 6.56 (s, 2H, NH_2), 4.11 (m, 1H, CH), 2.99-2.45 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}BrN_4O_2$: C, 46.59; H, 3.31; N, 16.72; Found: C, 46.50; H, 3.35; N, 16.67.

2-Amino-5-(4-fluorophenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4i**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3421, 3317, 3159, 1691, 1653 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.60 (s, 1H, NH), 10.08 (s, 1H, NH), 7.22-7.06 (m, 4H, ArH), 6.54 (s, 2H, NH_2), 4.14 (m, 1H, CH), 3.01-2.33 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}FN_4O_2$: C, 56.93; H, 4.04; N, 20.43; Found: C, 67.02; H, 3.95; N, 20.51

2-Amino-5-(4-methoxyphenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4j**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3481, 3314, 3107, 1693, 1647 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.60 (s, 1H, NH), 10.09 (s, 1H, NH), 7.04-6.81 (m, 4H, ArH), 6.54 (s, 2H, NH_2), 4.05 (m, 1H, CH), 3.68 (s, 3H, OCH_3), 2.93-2.42 (m, 2H, CH_2).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57; Found: C, 58.86; H, 4.88; N, 19.64.

2-Amino-5-(2-methoxyphenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4k**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3334, 3220, 3154, 1643, 1615 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.58 (s, 1H, NH), 10.02 (s, 1H, NH),7.21-6.73 (m, 4H, ArH), 6.54 (s, 2H, NH_2), 4.35 (m, 1H, CH), 3.83 (s, 3H, OCH_3), 2.90-2.35 (m, 2H, CH_2).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57; Found: C, 58.64; H, 4.88; N, 19.69.

2-Amino-5-(4-methylphenyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4l**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3380, 3336, 3100, 1669, 1644 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.59 (s, 1H, NH), 10.06 (s, 1H, NH), 7.08-7.01 (m, 4H, ArH), 6.53 (s, 2H, NH_2), 4.07 (m, 1H, CH), 2.95-2.43 (m, 2H, CH_2), 2.23 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73; Found: C, 62.35; H, 5.13; N, 20.87.

2-Amino-5-(3,4-methylenedioxyphenyl)-5,8-dihydropyrido[2,3-*d*]-pyrimidine-4,7(3*H*,6*H*)-dione (**4m**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3417, 3245, 3194, 1655, 1614 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.58 (s, 1H, NH), 10.05 (s, 1H, NH), 6.80-6.56 (m, 3H, ArH), 6.53 (s, 2H, NH_2), 5.95(s, 2H, CH_2), 4.04 (m, 1H, CH), 2.99-2.32 (m, 2H, CH_2).

Anal. Calcd. for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66; Found: C, 56.11; H, 4.00; N, 18.77.

2-Amino-5-(3-methoxyl-4-hydroxylphenyl)-5,8-dihydropyrido-[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4n**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3480, 3428, 3298, 3152, 1680, 1632 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.65 (s, 1H, NH), 10.01(s, 1H, NH), 8.76(s, 1H, OH), 6.80-6.54 (m, 3H, ArH), 6.44 (s, 2H, NH_2), 4.03 (m, 1H, CH), 3.71(s, 3H, OCH_3), 2.98-2.44 (m, 2H, CH_2).

Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53; Found: C, 55.54; H, 4.56; N, 18.65.

2-Amino-5-butyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4o**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3445, 3331, 3170, 1707, 1652 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.47 (s, 1H, NH), 9.87 (s, 1H, NH), 6.41 (s, 2H, NH_2), 2.89-2.79(m, H, CH), 2.61-1.23(m, 8H, $4CH_2$), 0.85-0.84 (t, J=6.4 Hz, 3H, CH_3)

Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71; Found: C, 556.03; H, 6.74; N, 23.63.

2-Amino-5-(2-thienyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione (**4p**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3465, 3344, 3167, 1700, 1651 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.61 (s, 1H, NH), 10.10(s, 1H, NH), 7.26-6.78 (m, 3H, thiophene CH), 6.55 (s, 2H, NH_2), 4.33 (m, 1H, CH), 2.97-2.50 (m, 2H, CH_2).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; Found: C, 50.54; H, 3.78; N, 21.45.

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