An Efficient Synthesis of New Benzo[1',2':6,7]quinolino[2,3-*d*]-pyrimidine Derivatives *via* Three-component Microwave-assisted Reaction

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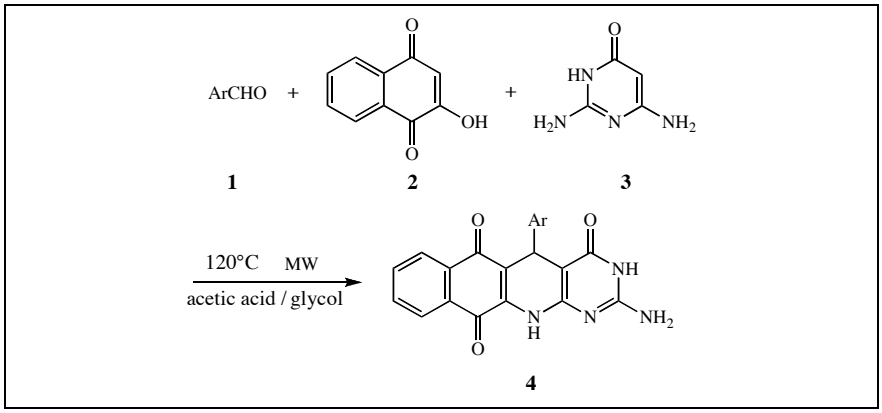

A series of benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine derivatives were synthesized *via* condensation of an aromatic aldehyde, 2-hydroxy naphthalene-1,4-dione and 2,6-diaminopyrimidin-4-one in mixed solvent of acetic acid and glycol (3:1,V:V) under microwave irradiation. This one-pot protocol has the advantage of good yield (86-91%), simple workup procedure and rapid reaction time (4-8min).

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INTRODUCTION

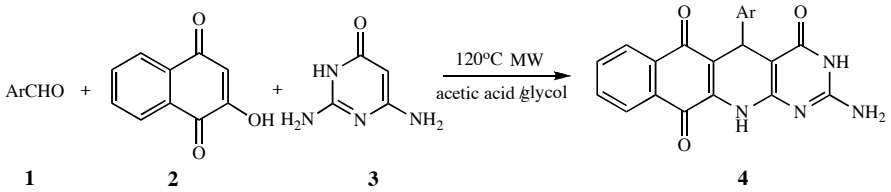
Multicomponent reactions, in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon-carbon bonds and carbon-heteroatom in synthetic chemistry [1]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings of both solvents and reagents.

In the past few years, the utilization of microwave irradiation in chemical transformations has attracted considerable interest and is of significant importance in the search for green synthesis and sustainable chemistry [2]. More attractively, many reactions that typically required hours or days to complete full conversion with conventional heating could be realized in several minutes utilizing microwave irradiation [3]. Microwave mediated protocols have been widely applied to the formation of a variety of carbon-heteroatom and carbon-carbon bonds.

Pyrimidine and pyridine derivatives have been studied due to a variety of chemical and biological significance. They have been reported as antibacterial, antiviral agents [4] and calcium channel modulators [5]. A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities [6].

Of these heterocycles, pyrido[2,3-*d*]pyrimidines present interesting biological properties, and as some recent applications, they have been used as antitumor agents [7], some of them have shown antimicrobial activity [8], diuretic acivity [9] and activity against platelet aggregation [10]. Benz[*g*]quinoline-5,10-dione exhibited the best overall activity against both bacteria and fungi. Particularly noteworthy was its significant antifungal activity, which was comparable to the activity of the standard antifungal antibiotic amphotericin B [11]. Pyrido[2,3-*d*]pyrimidines have been reported widely in the literature [12], but the construction of the skeletons incorporating both pyrido[2,3-*d*]pyrimidine and benzo[*g*]quinoline-5,10-dione has seldom been reported. Therefore, the development of a simple and effective method for the preparation of these skeletons is still strongly desirable. Interested in the bioactivities of skeletons and effective reaction procedure, we wish to report a facile three-component reaction *via* aldehyde **1**, 2-hydroxy-naphthalene-1,4-dione **2** and 2,6-diamino-pyrimidin-4-one **3** in a mixed solvent of acetic acid and glycol under microwave irradiation to afford a new type of heterocyclic compounds, 2-amino-5-aryl-benzo-[1′,2′:6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione 4 (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

In order to search the optimum reaction condition, different organic solvents, such as ethanol, *N*,*N*- dimethylformamide (DMF), acetic acid (HOAc), glycol were tested in the synthesis of **4b** at 120 °C. All the reactions were carryed out at the maximum power of 200 W. The results are summarized in Table 1.

Table 1

Solvent optimization for the synthesis of **4b**

Entry	Power (W)	Solvent	Time (min)	Yield (%)
1	200	HOAc	5	88
2	200	EtOH	5	75
3	200	glycol	5	84
4	200	HOAc/glycol (3:1,V:V)	5	91
5	200	DMF	5	88

It is shown in Table 1 that the reaction using mixed solvent of acetic acid and glycol gave the best result. (Table 1, entry 4). Moreover, to further optimize the reaction temperature, the same reaction was carried out at the temperatures ranging from 90 to 140 °C in increments of 10 °C each time in mixed solvent of acetic acid and glycol. When the temperature was increased from 80 to 120 °C, the yield of 2-amino-5-(4-bromophenyl)-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*, 12*H*]-trione **4b** was improved. However, no significant increase in the yield of product **4b** was observed as the reaction temperature was raised from 120 to 140 °C (monitored by TLC). Therefore, the temperature of 120 °C was chosen for all further microwave-assisted reactions (Table 2).

Table 2

Temperature optimization for the synthesis of **4b**

Entry	Power (W)	T (°C)	Time (min)	Yield (%)
1	200	90	10	75
2	200	100	8	84
3	200	110	6	89
4	200	120	5	91
5	200	130	5	91
6	200	140	5	91

Under these optimized reaction conditions [120 °C, acetic acid/glycol (3:1, V/V)], a series of products **4** were synthesized with this simple reaction procedure. The results are summarized in Table 3. The reaction time was 4-8 minutes, and the yields were 86%-91%.

For comparison, the synthesis of **4b** under classical heating conditions at 120 °C was performed. The yield of **4b** was 65% and the reaction time was 1 h (monitored by TLC).

Therefore, microwave irradiation exhibited advantages over the conventional heating by reducing the reaction time and improving the reaction yields. The electronic effect of aryl was investigated, Under our reaction conditions, both electron-withdrawing and electron-donating substituents readily provided benzo[1',2':6,7] quinolino[2,3-*d*]-pyrimidine derivatives in good yields (Table 3).

Table 3

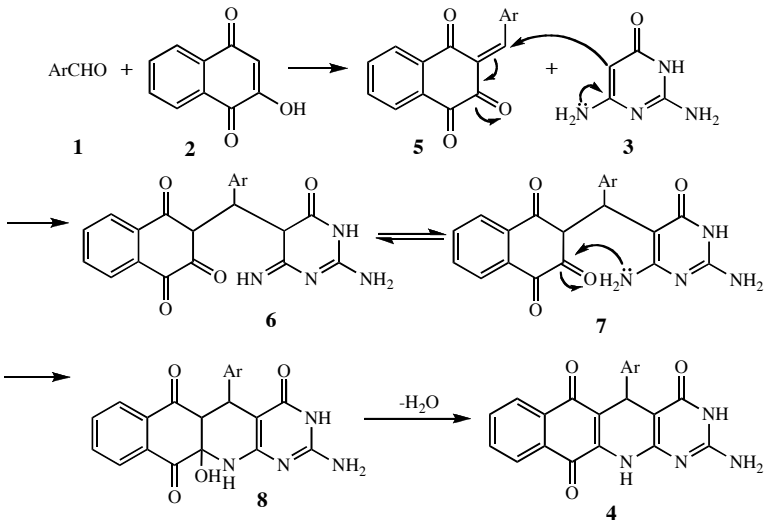
Synthesis of **4** under microwave irradiation

Entry	Product	Ar	Time /min	Yield /%	Mp °C
1	**4a**	4-ClC_6H_4	4	91	>300
2	**4b**	4-BrC_6H_4	5	91	>300
3	**4c**	2-ClC_6H_4	5	91	>300
4	**4d**	C_6H_5	5	88	>300
5	**4e**	4-$CH_3C_6H_4$	6	89	>300
6	**4f**	4-$CH_3OC_6H_4$	7	89	>300
7	**4g**	3,4-$(CH_3O)_2C_6H_3$	8	86	>300
8	**4h**	2-Thienyl	6	88	>300

In this study, all the products were characterized by IR spectra, ^{1}H NMR data and HRMS spectra. The IR spectra of compound **4b** showed strong absorptions at 1677, 1644 cm^{-1} due to C=O groups. The ^{1}H NMR spectrum of **4b** showed a singlet at 10.64, 8.88 ppm due to two NH group, a singlet at 6.51 ppm due to NH_2, and a singlet at 5.15 ppm due to CH.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of benzo-[1',2':6,7]quinolino[2,3-*d*]pyrimidine derivatives **4** could be explained by a presented in Scheme 2. We proposed that the reaction might proceed through a reaction sequence of condensation, addition, cyclization and dehydration. Firstly, a condensation between aldehyde **1** and 2-hydroxynaphthalene-1,4-dione **2** would give the

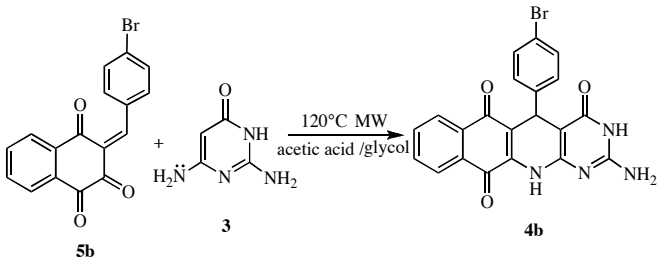
Scheme 2



intermediate product **5**. The addition of **5** to 2,6-diaminopyrimidin-4-one **3** would then furnish the intermediate product **7**, which upon intermolecular cyclization and dehydration would give rise to product **4**.

Evidence supporting this proposed mechanism was provided by the observation that when **5b** and **3** were subjected to the same conditions, the expected product **4b** was obtained in a yield similar to that obtained in the one-pot reaction.

Scheme 3



In summary, we have demonstrated a rapid and direct method that offered a simple and efficient route for the one-pot, three-component synthesis of highly function-alized benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine derivatives of potential biological importance in excellent yields. Particularly valuable features of this method included shorter reaction time, higher yields and broader substrate scope. Most importantly, the series of benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine derivatives may prove to be of biological interest and provide new classes of biological active compounds for biomedical screening. This work is in progress in our laboratories.

EXPERIMENTAL

Microwave irradiation was carried out with microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a TENSOR 27 spectrometer in KBr and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruke DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift ( ) given in ppm relative to TMS as internal standard, HRMS spectra were taken on a TOF-MS spectrometer from Miscromass, England.

General Procedure for the synthesis of 2-amino-5-aryl-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*, 5*H*, 12*H*]-trione (4a-4h). The mixture of aldehyde **1**, 2-hydroxynaphthalene-1,4-dione **2** and 2,6-diaminopyrimidin-4-one **3** in the mixed solvent of acetic acid (1.5 mL) and glycol (0.5 mL) was irradiated for 4-8 min at 200 W power and 120 °C. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was collected by filtration to give the crude product, which was further purified by recrystallization from EtOH (95%).

2-Amino-5-(4-chlorophenyl)-benzo[1',2':6,7]quinolino[2,3-*d*]-pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4a). This compound was obtained according to above general procedure; ir (potassium bromide): 3475, 3410, 3350, 2925, 1679, 1644, 1589, 1520, 1455, 1303, 1213, 724; ^1H nmr: δ10.62 (s, 1H, NH), 8.86 (s, 1H, NH), 8.02 (d, 1H, ArH, J = 7.2 Hz), 7.90 (d, 1H, ArH, J = 7.2 Hz), 7.76-7.85 (m, 2H, ArH),7.32 (d, 2H, ArH, J = 8.4 Hz), 7.26 (d, 2H, ArH, J = 8.4 Hz), 6.51 (s, 2H, NH_2), 5.17(s, 1H, CH). HRMS(EI): m/z calcd for $C_{21}H_{13}ClN_4O_3$ 406.0647, found 406.0667.

2-Amino-5-(4-bromophenyl)-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4b) This compound was obtained according to above general procedure; ir (potassium bromide): 3468, 3349, 3326, 2916, 1677, 1644, 1589, 1454, 1303, 1212, 724; ^1H nmr: δ10.64 (s, 1H, NH), 8.88 (s, 1H, NH), 8.01 (d, 1H, ArH, J = 7.6 Hz), 7.90 (d, 1H, ArH, J = 7.6 Hz), 7.78-8.83 (m, 2H, ArH), 7.40 (d, 2H, ArH, J = 8.4 Hz), 7.26 (d, 2H, ArH, J = 8.4 Hz), 6.51 (s, 2H, NH_2), 5.15 (s,

1H, CH). HRMS(EI): m/z calcd for $C_{21}H_{13}BrN_4O_3$ 450.0151, found 450.0147.

2-Amino-5-(2-chlorophenyl)-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4c). This compound was obtained according to above general procedure; ir (potassium bromide): 3481, 3405, 3352, 2866, 1660, 1633, 1588, 1351, 1299, 1199, 722; ^{1}H nmr: δ10.45 (s, 1H, NH), 8.76 (s, 1H, NH), 8.01 (d, 1H, ArH, J = 7.6 Hz), 7.85-7.87 (m, 1H, ArH), 7.75-7.83 (m, 2H, ArH), 7.39 (d, 1H, ArH, J = 8.0 Hz), 7.26 (d, 1H, ArH, J = 8.0 Hz), 7.16-7.21 (m, 1H, ArH), 7.09-7.13 (m, 1H, ArH), 6.48 (s, 2H, NH_2), 5.51 (s, 1H, CH). HRMS(EI): m/z calcd for $C_{21}H_{13}ClN_4O_3$ 406.0647, found 406.0659.

2-amino-5-phenyl-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]–trione (4d). This compound was obtained according to above general procedure; ir (potassium bromide): 3425, 3386, 3309, 3052, 2910, 1677, 1636, 1584, 1302, 1225, 722; ^{1}H nmr: δ10.58 (s, 1H, NH), 8.77 (s, 1H, NH), 8.02 (d, 1H, ArH, J = 7.2 Hz), 7.90 (d, 1H, ArH, J = 7.2 Hz), 7.77-7.85 (m, 2H, ArH), 7.30 (d, 2H, ArH, J = 7.6 Hz), 7.21 (t, 2H, ArH, J = 7.6 Hz), 7.11 (t, 1H, ArH, J = 7.6 Hz), 6.47 (s, 2H, NH_2), 5.20 (s, 1H, CH). HRMS(EI): m/z calcd for $C_{21}H_{14}N_4O_3$ 370.1066, found 370.1063.

2-Amino-5-*p*-tolyl-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4e). This compound was obtained according to above general procedure; ir (potassium bromide): 3425, 3309, 3179, 3052, 2864, 2727, 1681, 1633, 1574, 1454, 1262, 1161, 722; ^{1}H nmr: δ10.58 (s, 1H, NH), 8.74 (s, 1H, NH), 8.01 (d, 1H, ArH, J = 7.6 Hz), 7.90 (d, 1H, ArH, J = 7.6 Hz), 7.76-7.82 (m, 2H, ArH), 7.17 (d, 2H, ArH, J = 8.0 Hz), 7.01 (d, 2H, ArH, J = 8.0 Hz), 6.46 (s, 2H, NH_2), 5.15 (s, 1H, CH), 2.19 (s, 3H, CH_3). HRMS(EI): m/z calcd for $C_{22}H_{16}N_4O_3$ 384.1222, found 384.1223.

2-Amino-5-(4-methoxyphenyl)-benzo[1',2':6,7]quinolino-[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4f). This compound was obtained according to above general procedure; ir (potassium bromide): 3467, 3340, 3325, 2904, 1652, 1647, 1511, 1448, 1334, 1253, 1174, 1034, 722; ^{1}H nmr: δ10.58 (s, 1H, NH), 8.77 (s, 1H, NH), 8.01 (d, 1H, ArH, J = 7.6 Hz), 7.90 (d, 1H, ArH, J = 7.6 Hz), 7.76-7.84 (m, 2H, ArH), 7.19 (d, 2H, ArH, J = 8.4 Hz), 6.76(d, 2H, ArH, J = 8.4 Hz), 6.47 (s, 2H, NH_2), 5.13 (s, 1H, CH), 3.66 (s, 3H, OCH_3). HRMS(EI): m/z calcd for $C_{22}H_{16}N_4O_4$ 400.1172, found 400.1167.

2-Amino-5-(3,4-dimethoxyphenyl)-benzo[1',2':6,7]quinolino[2,3-*d*]pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4g). This compound was obtained according to above general procedure; ir (potassium bromide): 3456, 3338, 3305, 3071, 1632, 1591, 1515, 1450, 1302, 1209, 723; ^{1}H nmr: δ10.60 (s, 1H, NH), 8.77 (s, 1H, NH), 8.15 (d, 1H, ArH, J = 7.6 Hz), 7.92 (d, 1H, ArH, J = 7.2 Hz), 7.79-7.85 (m, 2H, ArH), 6.95 (s, 1H, ArH), 6.77(d, 2H, ArH, J = 8.4 Hz), 6.71(d, 1H, ArH, J = 8.4 Hz), 6.48 (s, 1H, NH_2), 5.13 (s, 1H, CH), 3.68 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3). HRMS(EI): m/z calcd for $C_{23}H_{18}N_4O_5$ 430.1277, found 430.1264.

2-amino-5-(thiophen-2-yl)-benzo[1',2':6,7]quinolino[2,3-*d*]-pyrimidine-4,6,11[3*H*,5*H*,12*H*]-trione (4h). This compound was obtained according to above general procedure; ir (potassium bromide): 3429, 3326, 3302, 3068, 2866, 1642, 1630, 1514, 1351, 1227, 723, ^{1}H nmr: δ10.71 (s, 1H, NH), 9.08 (s, 1H, NH), 8.02 (d, 1H, ArH, J = 7.6 Hz), 7.99 (d, 1H, ArH, J = 7.6 Hz), 7.79-7.86 (m, 1H, ArH), 7.23 (d, 1H, ArH, J = 8.4 Hz), 6.81-6.85 (m, 2H, ArH), 6.52 (s, 2H, NH_2), 5.48 (s, 1H, CH). HRMS(EI): m/z calcd for $C_{19}H_{11}N_4O_3S$ 375.0552, found 375.0562.

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