A Facile and Efficient Synthesis of Novel Pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives *via* Microwave-assisted Multicomponent Reactions

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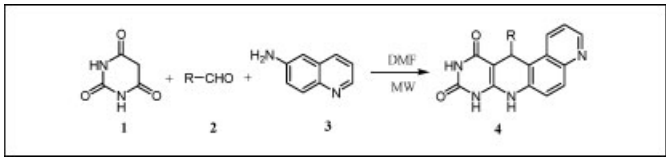

A series of novel pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives were synthesized *via* microwave-assisted three-component reactions of barbituric acid, aldehyde, and quinolin-6-amine in DMF without catalyst. This facile synthesis not only offers an economical and efficient synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted multicomponent reactions. Moreover, this protocol has the prominent advantages of short reaction time, good yields, low cost, easy operation, as well as environmental-friendliness.

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INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear-type syntheses. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of ''drug-like'' molecules for biological screening, since the combination of three or more small-molecular weight building blocks in a single operation leads to a high-combinatorial efficacy [1]. On the other hand, microwave-assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation, and shorter reaction time when compared with the traditional heating method [2].

Thus, it goes without saying that the use of atom-economical MCRs, together with the employment of energy-efficient microwave irradiation (MW), must be considered to be facile and effective synthetic strategy of heterocyclic compounds with important bioactivities in the sense that the combination in itself offers greater potential than the two parts in isolation.

Pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-diones (**4**, Fig. 1), a novel class of fused heterocyclic compounds, are incorporated by pyrimido-[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione and [4,7]-phenanthroline motifs, both of which possess various important bioactivities. For example, not only are pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione derivatives antitumor [3], anticancer [4], antihypertensive [5], and antibacterial [6], they are also inhibitors of Kaposi's sarcoma-associated herpesvirus (KSHV) [7] and topoisomerase, useful for the treatment of topoisomerase-associated diseases and disorders [8]. At the same time, [4,7]phenantroline derivatives exhibit antitumor [9], anticancer [10], antiviral [11], antimalarial [12], antiinfective [13], cytotoxic [14] activities, as well as being triple-helix DNA stabilizing agents [15]. Hence, it is promising that the fused scaffolds of pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-dione with [4,7]phenanthroline, *i.e.*, pyrimido[5,4-*b*][4,7]phenanthroline-9,11-(7*H*,8*H*,10*H*,12*H*)-diones, may display novel or enhanced significant bioactivities.

However, survey of the literature revealed that the synthesis of this important fused heterocyclic skeleton was neglected. Therefore, the investigation on the synthesis of pyrimido[5,4-*b*][4,7]phenanthroline-9,11-(7*H*,8*H*,10*H*,12*H*)-diones is of great necessity.

In view of the prominent merits of microwave-assisted multicomponent reactions and the potential

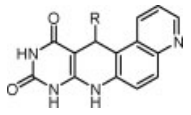

Figure 1. Structure of **4**.

bioactivities of fused heterocyclic compounds, lots of investigations on this topic have been carried out in our laboratory [16]. Herein, we would like to report a facile and efficient synthesis of pyrimido[5,4-*b*][4,7]phenanthroline-9,11-(7*H*,8*H*,10*H*,12*H*)-diones **4** *via* microwave-assisted three-component reactions of barbituric acid **1**, aldehyde **2**, and quinolin-6-amine **3** in DMF without catalyst (Scheme 1).

RESULTS AND DISCUSSION

Initially, the three-component reaction of barbituric acid **1**, 4-bromobenaldehyde **2c** and quinolin-6-amine **3** was employed to optimize the reaction conditions. As illustrated in Table 1, DMF was preferred as the optimal solvent and 110°C was chosen as the most suitable reaction temperature.Moreover, we found that the yield of this reaction was affected by the volume of solvent. The synthesis of **4c** was tested in different volumes of DMF at 110°C. The results show that 1.5 mL of DMF were optimal as solvent since it generated the highest yield of **4c**.

Under these optimized reaction conditions (1.5 mL of DMF, 110°C), a series of pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives **4** were synthesized under MW, and the results were summarized in Table 2. It is obvious this protocol could be applied to various aromatic aldehydes with electron-withdrawing groups or electron-donating groups. Besides, the results suggest that the substrates bearing electron-withdrawing groups have higher reactivity (higher yields and shorter reaction time) than those bearing electron-donating groups. So, it is concluded that the electronic nature of the substituents on aldehydes has some effect on this reaction. It seems that the electron-withdrawing groups in aldehydes enhanced the electropositive property of β-C in the intermediates yielded from the Knoevenagel condensation of aldehydes **2** with barbituric acid **1**, which facilitated the nucleophilic attack thereafter.

Scheme 1

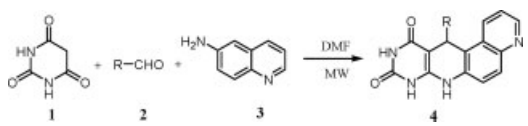

Table 1

Reaction conditions optimization for the synthesis of **4c**.

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)
1	EtOH	90	15	52
2	HOAc	90	15	63
3	Water	90	15	37
4	Glycol	90	12	79
5	DMF	90	10	86
6	DMF	70	15	78
7	DMF	80	12	82
8	DMF	100	8	90
9	DMF	110	6	92
10	DMF	120	6	92

To demonstrate the superiority of MW over standard heating conditions (SC), we also performed the syntheses of **4c** under SC in DMF at 110°C. Under this condition, the reaction time was prolonged from 6 min (under MW) to 4 h and the yield was decreased from 92% (under MW) to 76%. Therefore, MW exhibited several distinct advantages over SC by not only significantly reducing the reaction time and dramatically improving the reaction yield, but also being environmental-friendly.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data and elemental analyses.

In conclusion, we have developed a facile and efficient method on the synthesis of novel pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,12*H*)-dione derivatives *via* microwave-assisted three-component reactions in DMF without catalyst. This protocol has the prominent advantages of short reaction time, good yields, low cost, easy operation, as well as environmental-friendliness. At the same time, this synthesis can not only offer an efficient strategy to highly fused heterocyclic compounds with biological significance but also enrich the investigations on microwave-assisted multicomponent reactions. Moreover, this series of novel pyrimido[5,4-*b*][4,7]phenanthroline-9,11(7*H*,8*H*,10*H*,-12*H*)-diones may provide new class of biologically active compounds for biomedical screening.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and were uncorrected. IR spectra were recorded on a FT-IR-Tensor 27 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 analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

Table 2

Synthesis of **4** under microwave irradiation.

Entry	4	R	Time (min)	Yield (%)	M.P. (°C)
1	**4a**	4-FC_6H_4	6	89	>300
2	**4b**	4-ClC_6H_4	8	90	>300
3	**4c**	4-BrC_6H_4	6	92	>300
4	**4d**	3,4-$(CH_3O)_2C_6H_3$	14	78	>300
5	**4e**	3-$NO_2C_6H_4$	6	86	>300
6	**4f**	4-$CH_3C_6H_4$	12	81	>300
7	**4g**	C_6H_5	10	83	>300
8	**4h**	4-OH-3-$NO_2C_6H_3$	13	81	>300
9	**4i**	3,4-$OCH_2OC_6H_3$	15	72	>300

General procedure for the syntheses of compounds 4 with microwave irradiation. Typically, in a 10 mL Emrys™ reaction vial, barbituric acid **1** (1 mmol), aldehyde **2** (1 mmol), quinolin-6-amine **3** (1 mmol), and and DMF (1.5 mL) were mixed and then capped. The mixture was irradiated at 150 W and at 110°C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH.

12-(4-Fluorophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4a). This compound was obtained according to above general procedure; ir (KBr): ν 3207, 3066, 1714, 1655, 1633, 1543, 1471, 1381, 1265, 1093, 976, 862 cm^{-1}; ^1H NMR: δ 10.73 (s, 1H, NH), 10.54(s, 1H, NH), 9.32(s, 1H, NH), 8.70 (d, 1H, *J* = 4.0 Hz, ArH), 8.35 (d, 1H, *J* = 8.4 Hz, ArH),7.91–7.96 (m, 1H, ArH), 7.65 (d, 1H, *J* = 8.8 Hz, ArH),7.42 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 7.29 (dd, 2H, *J* = 7.6, 6.0 Hz, ArH), 7.00 (t, 2H, *J* = 8.4 Hz, ArH),5.76 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}FN_4O_2$: C, 66.66; H, 3.64; N, 15.55; Found C, 66.70; H, 3.68; N, 15.52.

12-(4-Chlorophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4b). This compound was obtained according to above general procedure; ir (KBr): ν 3203, 3065, 1714, 1683, 1634, 1543, 1487, 1381, 1266, 1089, 976, 830 cm^{-1}; ^1H NMR: δ 10.74 (s, 1H, NH), 10.55 (s, 1H, NH), 9.34 (s, 1H, NH), 8.70 (d, 1H, *J* = 4.0 Hz, ArH), 8.34 (d, 1H, *J* = 8.4 Hz, ArH), 7.94 (t, 1H, *J* = 8.4 Hz, ArH), 7.65 (d, 1H, *J* = 8.4 Hz, ArH), 7.42 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 7.29 (d, 2H, *J* = 8.4 Hz, ArH), 7.23 (d, 2H, *J* = 8.4 Hz, ArH), 5.76 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}ClN_4O_2$: C, 63.75; H, 3.48; N, 14.87; Found C, 63.68; H, 3.50; N, 14.90.

12-(4-Bromophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4c). This compound was obtained according to above general procedure; ir (KBr): ν 3201, 3065, 1714, 1656, 1633, 1545, 1484, 1381, 1266, 1099, 976, 829 cm^{-1}; ^1H NMR: δ 10.74 (s, 1H, NH), 10.57 (s, 1H, NH), 9.39 (s, 1H, NH), 8.70–8.71 (m, 1H, *J* = 4.0 Hz, ArH), 8.34 (d, 1H, *J* = 8.8 Hz, ArH), 7.93 (d, 1H, *J* = 8.8 Hz, ArH), 7.64 (d, 1H, *J* = 8.8 Hz, ArH),7.42 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 7.36 (d, 2H, *J* = 8.4 Hz, ArH), 7.23 (d, 2H, *J* = 8.4 Hz, ArH), 5.74 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}BrN_4O_2$: C, 57.02; H, 3.11; N, 13.30; Found C, 57.07; H, 3.10; N, 13.32.

12-(3,4-Dimethoxyphenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4d). This compound was obtained according to above general procedure; ir (KBr): ν 3262, 3068, 1706, 1653, 1554, 1513, 1418, 1382, 1263, 1138, 973, 820 cm^{-1}; ^1H NMR: δ 10.66 (s, 1H, NH), 10.45 (s, 1H, NH), 9.22 (s, 1H, NH), 8.69–8.70 (m, 1H, ArH), 8.38 (d, 1H, *J* = 8.4 Hz, ArH), 7.91 (d, 1H, *J* = 8.8 Hz, ArH), 7.63 (d, 1H, *J* = 8.8 Hz, ArH),7.41 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 7.07 (d, 1H, *J* = 2.0 Hz, ArH), 6.70 (d, 1H, *J* = 8.4 Hz, ArH), 6.55 (dd, 1H, *J* = 8.4, 2.0 Hz, ArH), 5.70 (s, 1H, CH), 3.66 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). Anal. calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92; Found C, 65.60; H, 4.50; N, 13.95.

12-(3-Nitrophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4e). This compound was obtained according to above general procedure; ir (KBr): ν3252, 3067, 1714, 1660, 1580, 1551, 1451, 1383, 1263, 1098, 975, 829 cm^{-1}; ^1H NMR: δ 10.75 (s, 1H, NH), 10.63 (s, 1H, NH), 9.44 (s, 1H, NH), 8.70 (d, 1H, *J* = 4.0 Hz, ArH), 8.38 (d, 1H, *J* = 8.4 Hz, ArH), 8.16 (s, 1H, ArH), 7.40–7.98 (m, 2H, ArH), 7.71 (d, 2H, *J* = 8.8 Hz, ArH), 7.49 (t, 1H, *J* = 8.0 Hz, ArH), 7.42 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 5.96 (s, 1H, CH). Anal. calcd for $C_{22}H_{17}N_3O_4$: $C_{20}H_{13}N_5O_4$: C, 62.01; H, 3.38; N, 18.08; Found C, 62.05; H, 3.40; N, 18.05.

12-p-Tolylpyrimido[5,4-b][4,7]phenanthroline-9,11(7H,-8H,10H,12H)-dione (4f). This compound was obtained according to above general procedure; ir (KBr): ν 3193, 3064, 1713, 1658, 1542, 1470, 1451, 1382, 1266, 1037, 976, 832 cm^{-1}; ^1H NMR: δ 10.65 (s, 1H, NH), 10.43 (s, 1H, NH), 9.22 (s, 1H, NH), 8.68 (d, 1H, *J* = 4.0 Hz, ArH), 8.34 (d, 1H, *J* = 8.4 Hz, ArH), 7.90 (d, 1H, *J* = 8.8 Hz, ArH), 7.63 (d, 1H, *J* = 8.8 Hz, ArH), 7.41 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 7.15 (d, 2H, *J* = 8.0 Hz, ArH), 6.96 (d, 2H, *J* = 8.0 Hz, ArH), 5.96 (s, 1H, CH), 2.15 (s, 3H, CH_3). Anal. calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72; Found C, 70.82; H, 4.52; N, 15.74.

12-Phenylpyrimido[5,4-b][4,7]phenanthroline-9,11(7H,-8H,10H,12H)-dione (4g). This compound was obtained according to above general procedure; ir (KBr): ν 3196, 3067, 1713, 1647, 1599, 1518, 1452, 1382, 1264, 1078, 976, 829 cm^{-1}; ^1H NMR: δ 10.69 (s, 1H, NH), 10.49 (s, 1H, NH), 9.27 (s, 1H, NH), 8.69–8.70 (m, 1H, ArH), 8.36 (d, 1H, *J* = 8.4 Hz, ArH), 7.92 (d, 1H, *J* = 8.8 Hz, ArH), 7.65 (d, 1H, *J* = 8.8 Hz, ArH), 7.42 (dd, 1H, *J* = 8.4, 4.0 Hz, ArH), 7.28 (d, 2H, *J* = 8.8 Hz, ArH), 7.18 (t, 2H, *J* = 7.6 Hz, ArH), 7.06 (t, 1H, *J* = 7.6 Hz, ArH),5.74 (s, 1H, CH). Anal. calcd for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.12; N, 16.37; Found C, 70.23; H, 4.10; N, 16.40.

12-(4-Hydroxy-3-nitrophenyl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4h). This compound was obtained according to above general procedure; ir (KBr):

ν 3350, 3209, 3056, 1715, 1641, 1610, 1529, 1477, 1373, 1274, 1081, 941, 828 cm^{-1}; ^1H NMR: δ 11.50 (s, 1H, OH), 10.73 (s, 1H, NH), 10.53 (s, 1H, NH), 9.33 (s, 1H, NH), 8.70 (d, 1H, J = 3.6 Hz, ArH), 8.36 (d, 1H, J = 8.4 Hz, ArH), 7.94 (d, 1H, J = 9.2 Hz, ArH), 7.80 (d, 1H, J = 1.6 Hz, ArH),7.65 (d, 1H, J = 8.8 Hz, ArH),7.38–7.44 (m, 2H, ArH), 6.94 (d, 1H, J = 8.4 Hz, ArH), 5.77 (s, 1H, CH). Anal. calcd for $C_{20}H_{13}N_5O_5$: C, 59.56; H, 3.25; N, 17.36; Found C, 59.52; H, 3.26; N, 17.35.

12-(Benzo[d][1,3]dioxol-5-yl)pyrimido[5,4-b][4,7]phenanthroline-9,11(7H,8H,10H,12H)-dione (4i). This compound was obtained according to above general procedure; ir (KBr): ν 3445, 32119, 3094, 1728, 1687, 1669, 1546, 1453, 1405, 1275, 1254, 1030, 914, 894, 824 cm^{-1}; ^1H NMR: δ 10.68 (s, 1H, NH), 10.45 (s, 1H, NH), 9.24 (s, 1H, NH), 8.69–8.70 (m, 1H, ArH), 8.37 (d, 1H, J = 8.4 Hz, ArH), 7.91 (d, 1H, J = 8.8 Hz, ArH), 7.63 (d, 1H, J = 8.8 Hz, ArH), 7.74 (dd, 1H, J = 8.4, 1.2 Hz, ArH), 7.41 (dd, 1H, J = 8.4, 4.4 Hz, ArH), 7.08 (d, 1H, J = 8.4 Hz, ArH), 6.86 (d, 1H, J = 1.2 Hz, ArH), 5.88 (d, 2H, J = 9.6 Hz, CH_2), 5.68 (s, 1H, CH). Anal. calcd for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50; Found C, 65.32; H, 3.66; N, 14.47.

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