A Green and Efficient Synthesis of 3,3′-Arylidenebis[4-hydroxy-6-methyl-2(1*h*)-3-pyridinone]s in Water under Microwave Irradiation

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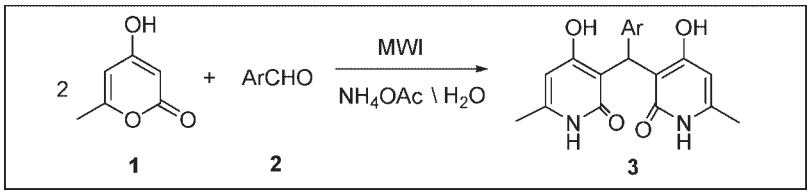

A series of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s were synthesized via three-component reactions of aromatic aldehydes, 4-hydroxy-6-methyl-2*H*-pyran-2-one, and ammonium acetate in water under microwave irradiation. This method has the advantages of environmental friendliness, short reaction time, high yields, and easy operation. This efficient synthesis not only offers an economical and green synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted synthesis in water.

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INTRODUCTION

The pyridinone ring is one of the most well-known systems among the naturally occurring heterocycles. Many members of this class of heterocycles have antibacterial [1], antifungal [2], cardiotonic [3], antineoplastic [4], antiinflammatory and analgesic [5], and other significant bioactivities [6]. Therefore, pyridinone derivatives, especially bispyridinone derivatives, which contain two skeletons of pyridinone in one molecular structure, are of great importance in medicinal and organic chemistry.

However, survey of the literature only reveals two typical methods on synthesizing 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s. One method is the condensation of 4-hydroxy-6-methyl-2-pyridone with aromatic aldehydes catalyzed by triethylamine in ethanol under traditional heating condition [7]. Unfortunately, this method suffers from low yield (14–45%), long reaction time (8–10 h), and use of toxic organic catalyst and solvent.

Another method is the multicomponent reaction of triacetic acid lactone, aromatic aldehydes, and ammonium acetate in ethanol under traditional heating conditions [8]. However, this approach still has disadvantages of lower yield (11–45%), longer reaction time (26 h), and being less environmental-unfriendly because ethanol, a volatile and flammable organic solvent, is used. As a result, developing a green and efficient approach to the synthesis of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s is of great significance.

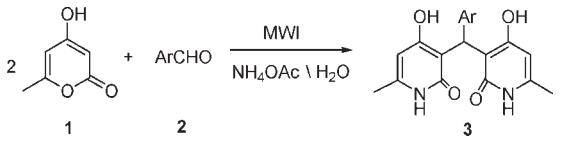
In recent years, microwave-assisted synthesis in water as solvent has become a hotspot of investigation, because it combines the two prominent green chemistry principles of ''safer solvents'' and ''energy efficiency'' [9]. In addition to the general advantages of water as solvent [10], several benefits for the reaction are expected when using water as reaction medium for microwave-superheated protocols [11].

As a continuation of our efforts on synthesizing heterocycles possessing significant bioactivities with green and efficient method [12], we herein report the synthesis of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s through three-component reactions of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1**, aromatic aldehydes **2**, and ammonium acetate in water under microwave irradiation (MWI) (Scheme 1). This efficient synthesis not only offers a green synthetic strategy to this class of significant compounds but also enriches the investigations on microwave-assisted synthesis in water.

RESULTS AND DISCUSSION

Initially, to demonstrate the superiority of water as solvent, despite its natural property of being harmless to environment, we compared the synthesis of **3c** in water with other organic solvents including glycol, DMF,

Scheme 1



glacial acetic acid, and ethanol. The mixture of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** (2 mmol), 4-bromophenyl aldehyde **2c** (1 mmol), ammonium acetate (2 mmol), and corresponding solvent (2 mL) was irradiated under MWI at 100°C and 150 W for a given time, then the crude product was purified by recrystallization from EtOH.

The results (Table 1) reveal that compared with the solvents of glycol, DMF, and EtOH, water can not only improve the yield but also shorten the time of this reaction. Although the yield of the reaction in acetic acid is a little higher than that in water, considering environmental friendliness and avoidance of using toxic organic reagents, water was preferred as solvent for all further microwave-assisted reactions.

Moreover, the same reaction of **1** (2 mmol), **2c** (1 mmol), and ammonium acetate (2 mmol) in water (2 mL) under MWI (150 W) was used to optimize the reaction temperature, and the results are shown in Table 2. It is obvious that 90°C is the most suitable reaction temperature.

Under these optimized reaction conditions, a series of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s **3** were synthesized, and the results are given in Table 3. As shown in Table 3, this protocol can be applied not only to aromatic aldehydes with electron-withdrawing groups but also to those with electron-donating groups under the same conditions. Therefore, the electronic nature of the substrate has no significant effect on this reaction.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s **3** could be explained by a reaction sequence presented in Scheme 2.

First, the condensation of aldehyde **2** and 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** gave intermediate **4**, which was then attacked by **1** to generate another intermediate **5**. Finally, the ammonolysis, intermolecular cyclization and dehydration of **5** gave rise to target product **3**.

Table 1

Solvent optimization for the synthesis of **3c**.

Entry	Solvent	Time (min)	Yield (%)
1	glycol	12	76
2	water	8	81
3	AcOH	6	83
4	DMF	16	73
5	EtOH	10	78

Table 2

Temperature optimization for the synthesis of **3c**.

Entry	T (°C)	Time (min)	Yield (%)
1	60	15	44
2	70	12	65
3	80	10	74
4	90	8	83
5	100	8	81
6	110	8	80

All the products were characterized by IR, ^{1}H NMR, and elemental analyses.

In conclusion, we have developed a green and efficient approach to the synthesis of 3,3′-arylidenebis[4-hydroxy-6-methyl-2(1*H*)-3-pyridinone]s in water under MWI. This method has the notable advantages over the existing ones owing to its features of environmental friendliness, short reaction time, high yield, low cost, and easy operation. On the other hand, this reaction supplies a good example of efficient microwave-assisted synthesis in water as solvent.

EXPERIMENTAL

MWI was carried out in a monomodal Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and are 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.

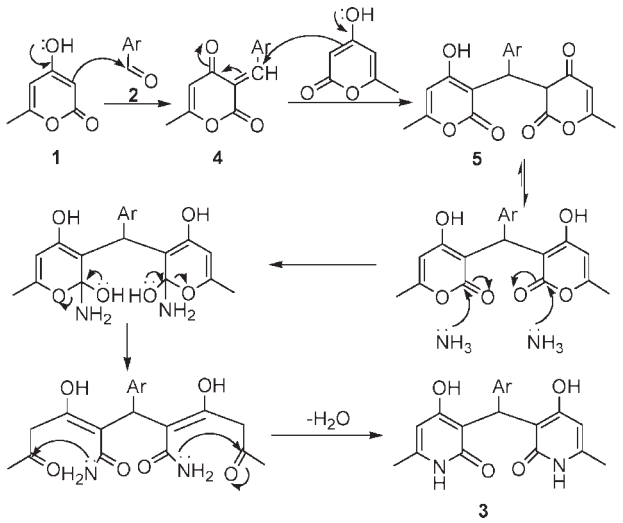
General procedure for the syntheses of compounds 3 with MWI. Typically, in a 10-mL Emrys reaction vial, 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** (2 mmol), aldehyde **2** (1 mmol), ammonium acetate (2 mmol), and water (2 mL) were

Table 3

Synthesis of **3** under MWI in water.

Entry	**3**	Ar	Time/ min	Yield / %	Mp (lit.) / °C
1	**3a**	4-FC_6H_4	8	85	>300
2	**3b**	4-ClC_6H_4	10	81	>300 (>300)[7]
3	**3c**	4-BrC_6H_4	8	83	>300
4	**3d**	2,4-$Cl_2C_6H_3$	8	83	>300
5	**3e**	3-$NO_2C_6H_4$	8	82	>300 (>300)[8]
6	**3f**	4-$NO_2C_6H_4$	10	85	>300
7	**3g**	C_6H_5	10	86	>300 (>300) [7]
8	**3h**	4-$OCH_3C_6H_4$	12	82	>300 (>300) [7]
9	**3i**	4-$CH_3C_6H_4$	10	84	>300
10	**3j**	2-$OCH_3C_6H_4$	12	81	>300
11	**3k**	Thiophen-2-yl	15	75	>300

Scheme 2



mixed and then capped. The mixture was irradiated at 150 W and at 90°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.

3,3′-(4-Fluorobenzylidenebis[4-hydroxy-6-methylpyridin-2(1H)-one] (3a). This compound was obtained according to above general procedure; IR (KBr): ν 3433–2611, 1635, 1457, 1389, 1309, 1259, 1222, 1195, 1164, 1005, 932, 883, 848, 781 cm^{-1}; ^1H NMR: δ 12.28 (s, br, 2H, 2OH), 11.71 (s, 2H, 2NH), 7.05–6.99 (m, 4H, ArH), 5.94(s, 1H, C^5-H), 5.88 (s, 1H, $C^{5'}$-H), 5.82 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}FN_2O_4$: C, 64.04; H, 4.81; N, 7.86. Found: C, 64.21; H, 4.83; N, 7.81.

3,3′-(4-Chlorobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3b). This compound was obtained according to above general procedure; IR (KBr): 3600–2600, 1482, 1456, 1382, 1318, 1283, 1249, 1195, 1163, 1007, 883, 821, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 25°C): δ 12.20 (s, br, 2H, 2OH), 11.72 (s, 2H, 2NH), 7.28 (d, 2H, J = 8.0 Hz, ArH), 7.01 (d, 2H, J = 8.0 Hz, ArH), 5.91 (s, 2H, C^5-H, $C^{5'}$-H), 5.80 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51; Found: C, 61.08; H, 4.62; N, 7.45.

3,3′-(4-Bromobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3c). This compound was obtained according to above general procedure; IR (KBr): ν 3457–2583, 1631, 1486, 1459, 1386, 1314, 1285, 1255, 1191, 1074, 1010, 883, 815, 755 cm^{-1}; ^1H NMR: δ 12.22 (s, br, 2H, 2OH), 11.74 (s, 2H, 2NH), 7.42 (d, 2H, J = 8.4 Hz, ArH), 6.95 (d, 2H, J = 8.4 Hz, ArH), 5.92 (s, 2H, C^5-H, $C^{5'}$-H), 5.87 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$: C, 54.69; H, 4.11; N, 6.71; Found: C, 54.45; H, 4.07; N, 6.75.

3,3′-(2,4-Dichlorobenzylidene)bis[4-hydroxy-6-methylpyr-idin-2(1H)-one] (3d). This compound was obtained according to above general procedure; IR (KBr): ν 3600–2600, 1639, 1462, 1456, 1388, 1325, 1258, 1190, 1127, 1107, 1048, 887, 862, 772 cm^{-1}; ^1H NMR: δ 11.81 (s, br, 2H, 2OH), 11.44 (s, 2H, 2NH), 7.40 (s, 1H, ArH), 7.33–7.30 (m, 1H, ArH) 7.19 (d, 1H, J = 8.0 Hz, ArH), 6.18 (s, 1H, CH), 5.83 (s, 2H, C^5-H, $C^{5'}$-H), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_4$: C, 56.04; H, 3.96; N, 6.88; Found: C, 56.20; H, 3.93; N, 6.81.

3,3′-(3-Nitrobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3e). This compound was obtained according to above general procedure; IR (KBr): ν 3300–2500, 1634, 1526, 1455, 1392, 1351, 1257, 1127, 1108, 1042, 820, 728, 676 cm^{-1}; ^1H NMR: δ 12.22 (s, br, 2H, 2OH), 11.79 (s, 2H, 2NH), 8.06 (d, 1H, J = 8.4 Hz, ArH), 7.93 (s, 1H, ArH), 7.55 (t, 1H, J = 8.0 Hz, ArH), 7.46 (d, 1H, J = 7.6 Hz, ArH), 6.07 (s, 1H, CH), 5.96 (s, 2H, C^5-H, $C^{5'}$-H), 2.19 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96; Found: C, 59.37; H, 4.50; N, 11.00;

3,3′-(4-Nitrobenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3f). This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1636, 1518, 1460, 1385, 1347, 1293, 1192, 1008, 883, 921, 8249, 768 cm^{-1}; ^1H NMR: δ 12.19 (s, br, 2H, 2OH), 11.78 (s, 2H, 2NH), 8.13 (d, 2H, J = 8.4 Hz, ArH), 7.26 (d, 2H, J = 8.4 Hz, ArH), 6.06 (s, 1H, CH), 5.94 (s, 2H, C^5-H, $C^{5'}$-H), 2.18 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96; Found: C, 59.41; H, 4.49; N, 11.01.

3,3′-(Benzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3g). This compound was obtained according to above general procedure; IR (KBr): ν3300–2600, 1629, 1494, 1453, 1396, 1363, 1262, 1213, 1181, 1115, 1027, 896, 824, 772 cm^{-1}; ^1H NMR: δ 12.43 (s, br, 2H, 2OH), 11.69 (s, 2H, 2NH), 6.92–6.78 (m, 5H, ArH), 5.91 (s, 2H, C^5-H, $C^{5'}$-H), 5.82 (s, 1H, CH), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.30; H, 5.38; N, 8.25.

3,3′-(4-Methoxylbenzylidene)bis[4-hydroxy-6-methylpyri- din-2(1H)-one] (3h). This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1633, 1509, 1459, 1418, 1388, 1302, 1248, 1178, 1035, 850, 832, 774 cm^{-1}; ^1H NMR: δ 12.41 (s, br, 2H, 2OH), 11.68 (s, 2H, 2NH), 6.91 (d, 2H, J = 8.4 Hz, ArH), 6.79 (d, 2H, J = 8.4 Hz, ArH), 5.90 (s, 2H, C^5-H, $C^{5'}$-H), 5.82 (s, 1H, CH), 3.70 (s, 3H, OCH_3), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.09; H, 5.45; N, 7.55.

3,3′-(4-Methylbenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3i). This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1634, 1512, 1460, 1387, 1302, 1308, 1127, 1105, 1041, 920, 887, 753 cm^{-1}; ^1H NMR: δ 12.50 (s, br, 2H, 2OH), 11.67 (s, 2H, 2NH), 7.03 (d, 2H, J = 8.4 Hz, ArH), 6.90 (d, 2H, J = 8.4 Hz, ArH), 5.91 (s, 2H, C^5-H, $C^{5'}$-H), 5.83 (s, 1H, CH), 2.25 (s, 3H, CH_3), 2.17 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.23; H, 5.69; N, 7.89.

3,3′-(2-Methoxylbenzylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3j). This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1632, 1490, 1396, 1356, 1340, 1290, 1243, 1103, 1029, 888, 818, 769 cm^{-1}; ^1H NMR: δ 12.62 (s, br, 2H, 2OH), 11.47 (s, 2H, 2NH), 7.15–7.08 (m, 2H, ArH), 6.86–6.80 (m, 2H, ArH), 6.02 (s, 1H, CH), 5.84 (s, 2H, C^5-H, $C^{5'}$-H), 3.52 (s, 3H, OCH_3), 2.13 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.05; H, 5.45; N, 7.66.

3,3′-(4-Thiophen-2-ylidene)bis[4-hydroxy-6-methylpyridin-2(1H)-one] (3k). This compound was obtained according to above general procedure; IR (KBr): ν 3300–2600, 1633, 1556, 1537, 1514, 1504, 1486, 1455, 1393, 1360, 1253, 1200, 922, 887, 753 cm^{-1}; ^1H NMR: δ 12.92 (s, br, 2H, 2OH), 11.66 (s,

2H, 2NH), 7.24 (d, 1H, J = 5.2 Hz, ArH), 6.87–6.84 (m, 1H, ArH), 6.57 (s, 1H, ArH), 6.09 (s, 1H, CH), 5.90 (s, 2H, C^5-H, $C^{5'}$-H), 2.16 (s, 6H, $2CH_3$). Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13. Found: C, 59.11; H, 4.71; N, 8.09.

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