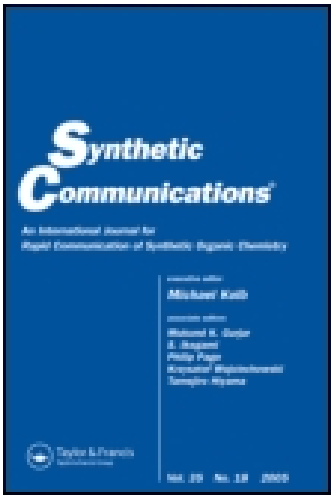

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GREEN, MICROWAVE-ASSISTED APPROACH TO THE SYNTHESIS OF ARYLIDENE-SUBSTITUTED SPIRO[4,5]DECAN-8-ONE DERIVATIVES IN WATER

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A green approach to the synthesis of arylidene-substituted spiro[4,5]decan-8-one derivatives was successfully realized via the mild, base-catalyzed reaction of aromatic aldehydes with 1,4-dioxa-spiro[4.5]decan-8-one in water under microwave irradiation. This protocol has the prominent advantages of environmental friendliness, short reaction time, excellent yields, low cost, easy operation, and broad scope of applicability.

Keywords: Green synthesis; microwave irradiation; water

INTRODUCTION

The α,β-unsaturated derivatives of cyclohexanone attract great interest primarily as intermediates. Because of the presence of its cross-conjugated dienone system, it can react with many nucleophilic reagents such as urea,[1,2] thiourea, [3–9] cyanoacetamide,[3,9,10] and malononitrile.[11,12] The reactions of various mono- and dienones based on cyclic ketones with aromatic aldehydes were studied.[13,14] Among them, 2,6-bis(phenylmethylene)cyclohexanones have received considerable attention over the past years because of their wide range of biological activities, such as cytotoxicity,[15] antimycotic,[16] antitumor,[17] antibacterial,[18] anti-inflammatory,[19] and antileishmaniatic activities.[20] Therefore, chemists have made many efforts to synthesize these compounds. For example, Jonathan and coworkers[21] have reported the preparation of arylidene-substituted spiro[4,5]decan-8-one derivatives by treatment of aromatic aldehydes with 1,4-dioxa-spiro[4,5]decan-8-one in ethanol using sodium hydroxide as catalyst. First, the reactants were mixed at a low temperature (0–5°C); then the mixture was performed under reflux for 24 h at room temperature. However, this method has many disadvantages such as long reaction time, moderate yields, and fussy operation. It is worth mentioning that this method is not a green one because corrosive catalyst and flammable solvent were used. Thus,

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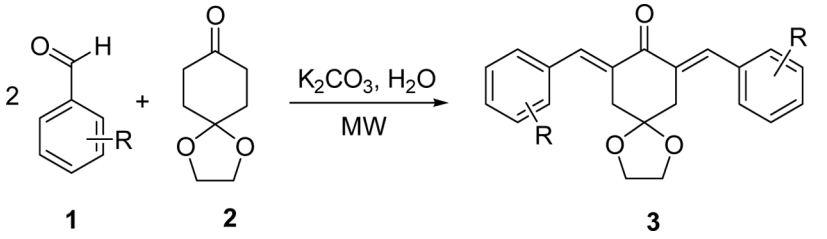

Scheme 1.

the development of a green and facile approach to arylidene-substituted spiro[4,5]decan-8-one derivatives is still desired.

In past decades, microwave-assisted organic synthesis in water has become a hotspot because it combines the two prominent green chemistry principles of "safer solvents" and "energy efficiency."[22] Besides the general advantages of water and microwave irradiation (MWI),[23] several important benefits are expected when they are combined.[24] Water has become an attractive medium for many organic reactions, not only because the need for drying reactants, expensive catalysts, and solvents can be circumvented but also for its unique reactivity and selectivity.[25,26] Many important types of heterocyclic compounds, such as triazines,[27] acridines,[28] quinolines,[29] pyridines,[30] indoles,[31] pyrazines,[32] furans,[33] and pyrimidines,[34] have been synthesized in aqueous media. Synthesis of new and important types of heterocyclic compounds in water continues. The continued development of new reaction processes in water to create new and important types of heterocyclic compounds is becoming an interesting area. Herein, we report a green and facile approach to the synthesis of arylidene-substituted spiro[4,5]decan-8-one derivatives **3** via microwave-assisted reactions of aromatic aldehyde **1** with 1,4-dioxa-spiro[4,5]-decan-8-one **2** in water (Scheme 1) using potassium carbonate (K_2CO_3) as mild catalyst.

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for a successful organic synthesis. To search for the optimal solvent, the microwave-assisted reaction between 4-bromobenzaldehyde (**1a**) and 1,4-dioxa-spiro[4,5]decan-8-one (**2**) was examined using potassium carbonate as mild catalyst in different solvents at 100°C, including water, ethylene glycol, *N,N*-dimethylformamide (DMF), and ethanol. All the reactions were carried out at the maximum power of 200 W; the results are summarized in Table 1. As can be seen from Table 1, reactions in glycol and water gave better yields than others (Table 1, entries 1–4). Considering environmental friendliness and avoidance of toxic organic reagents, water thus was chosen as the best solvent.

To further optimize the reaction conditions, the same reaction was performed in water at temperatures ranging from 90 to 130°C, with an increment of 10°C each time. The yield of product **3a** was increased and the reaction time was shortened as the temperature increased from 90°C to 120°C (Table 1, entries 5–7). However, the

Table 1. Reaction conditions for the synthesis of **3a**

Entry	Solvent	T (°C)	Time (min)	Yield (%)
1	glycol	100	10	80
2	DMF	100	10	55
3	EtOH	100	10	60
4	H_2O	100	10	80
5	H_2O	90	10	72
6	H_2O	110	8	88
7	H_2O	120	8	95
8	H_2O	130	8	94

yield leveled off as the temperature increased from 120 to 130°C (Table 1, entries 7 and 8). Thus, 120°C was chosen as the optimal temperature for further reactions. Furthermore, we were excited to find that only 0.4 equivalent of the catalyst gave the best yield of product **3a** at 120°C.

The volume of water was also investigated. Different volumes of water were tested at 120°C for 8 min under MWI. When 1.5 mL water was used as solvent, the yield was the great.

Under these optimized reaction conditions (1.5 mL water, 120°C), different aromatic aldehydes were employed in the reactions, and a series of arylidene-substituted spiro[4,5]decan-8-ones **3** was synthesized. The results are summarized in Table 2. As illustrated in Table 2, this protocol can be applied not only to the aromatic aldehydes with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkoxyl group) but also to heterocyclic aldehydes. Thus, the electronic nature of the substituents on aldehydes has no significant effect on this reaction.

Compared with the method reported by Jonathan and coworkers, the use of MWI has some obvious advantages. Take **3c** as an example; the reaction time was shortened strikingly from 12 h to 8 min, and the yield was increased from 67% to 95%. The difference may be a consequence of both thermal effects and specific effects

Table 2. Synthesis of **3** under microwave irradiation

Entry	**3**		Aromatic aldehydes (**1**)	Time (min)	Yield (%)	Mp (°C)
1	**3a**	**1a**	4-Bromobenzaldehyd	8	95	221–222
2	**3b**	**1b**	2-Chlorobenzaldehyde	8	94	210–212
3	**3c**	**1c**	4-Chlorobenzaldehyde	8	95	238–240 (210–212)[22]
4	**3d**	**1d**	4-Fluorobenzaldehyde	8	95	225–227 (208–210)[22]
5	**3e**	**1e**	2,4-Dichlorobenzaldehyde	8	95	175–177
6	**3f**	**1f**	3-Nitrobenzaldehyde	8	92	199–201
7	**3g**	**1g**	4-Methylbenzaldehyde	9	94	257–258 (238–240)[22]
8	**3h**	**1h**	4-Methoxybenzaldehyde	10	93	241–243 (224–226)[22]
9	**3i**	**1i**	3,4,5-Trimethoxybenzaldehyde	10	93	178–180 (162–164)[22]
10	**3j**	**1j**	4-Dimethylaminobenzaldehyde	10	92	>300
11	**3k**	**1k**	Benzo[*d*][1,3]dioxole-5-carbaldehyde	9	92	287–289
12	**3l**	**1l**	Thiophene-2-carbaldehyde	9	92	197–199

induced by the microwave field. The reactants in these multicomponent reactions contain dipoles and proceed via related polar intermediates, which enhance their interactions with microwave heating.

The structures of all the synthesized compounds were established on the basis of spectroscopic data and high-resolution mass spectral (HRMS) data.

CONCLUSION

In brief, a green and facile approach to the synthesis of arylidene-substituted spiro[4,5]decan-8-ones using potassium carbonate (K_2CO_3) as mild catalyst was reported. This protocol has the prominent advantages of environmental friendliness, short reaction time, excellent yields, low cost, broad scope of applicability, and mild reaction condition. At the same time, this efficient synthesis cannot only offer a green synthetic strategy to heterocyclic compounds but also enriches the investigations on microwave-assisted reactions in water.

EXPERIMENTAL

MWI was carried out in a monomodal Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined on an XT5 apparatus and are uncorrected. Infrared (IR) spectra were recorded on an Fourier transform (FT)-IR Tensor 27 spectrometer. ^{1}H NMR and ^{13}C NMR were measured on a DPX 400 spectrometer operating at 400 MHz and 100 MHz, respectively using dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard. HRMS (ESI) was determined by MicroTOF-Qll; HRMS/MS instrument (Bruker).

General Procedure for the Synthesis of Compounds 3 Under Microwave Irradiation

Typically, in a 10-mL Emrys reaction vial, aldehyde **1** (2 mmol), 1,4-dioxa-spiro[4,5]decan-8-one **2** (1 mmol), K_2CO_3 (0.4 mmol), and water (1.5 mL) were mixed and then capped. The mixture was irradiated at 120°C for a given time (maximum power of 200 W). Upon completion, as monitored by thin-layer chromatography (TLC), the reaction mixture was cooled to room temperature and filtered to give the crude product, which was subsequently recrystallized from EtOH (95%) to give the pure products **3**.

Data

7,9-Bis-[1-(4-bromo-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3a). IR (KBr, ν, cm^{-1}): 2962, 2894, 1668, 1604, 1574, 1485, 1399, 1261, 1234, 1124, 1009, 987, 826, 760. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.66 (t, $J = 7.8$ Hz, 6H, =CH and ArH), 7.49 (d, $J = 8.4$ Hz, 4H, ArH), 3.82 (s, 4H, CH_2), 3.10 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 172.88, 152.06, 136.13, 134.07, 133.67, 132.22, 132.13, 131.61, 131.58, 131.41, 130.74, 105.92, 64.26, 37.15. HRMS (ESI) m/z: calc. for $C_{22}H_{18}Br_2O_3$: 510.9525 $[M + Na]^+$; found: 510.9532.

7,9-Bis-[1-(2-chloro-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4.5]decan-8-one (3b). IR (KBr, ν, cm^{-1}): 2902, 1674, 1616, 1562, 1421, 1273, 1192, 1040, 950, 763, 688. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.81 (s, 2H, =CH), 7.60–7.51 (m, 4H, ArH), 7.47–7.44 (m, 4H, ArH), 3.79 (s, 4H, CH_2), 3.03 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 186.93, 151.24, 134.69, 134.08, 133.87, 132.90, 130.68, 130.64, 129.70, 127.22, 114.87, 106.02, 64.23, 36.87. HRMS (ESI) m/z: calc. for $C_{22}H_{18}Cl_2O_3$: 423.0526 $[M + Na]^+$; found: 423.0512.

7,9-Bis-[1-(4-chloro-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3c). IR (KBr, ν, cm^{-1}): 2989, 2887, 1671, 1606, 1577, 1488, 1237, 1184, 1119, 1011, 951, 825. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.66 (s, 2H, =CH), 7.58–7.51 (m, 8H, ArH), 3.82 (s, 4H, CH_2), 3.11 (s, 4H, CH_2). HRMS (ESI) m/z: calc. for $C_{22}H_{18}Cl_2O_3$: 401.0706 $[M + H]^+$; found: 401.0692.

7,9-Bis-[1-(4-fluoro-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3d). IR (KBr, ν, cm^{-1}): 2906, 1673, 1609, 1599, 1507, 1411, 1222, 1160, 1045, 984, 836. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.68 (s, 2H, =CH), 7.63–7.59 (m., 4H, ArH), 7.30 (t, $J = 8.8$ Hz, 4H, ArH), 3.82 (s, 4H, CH_2), 3.11 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 187.18, 163.42, 160.96, 136.20, 132.76, 132.63, 132.55, 131.44, 131.41, 115.76, 115.55, 106.00, 64.22, 37.11. HRMS (ESI) m/z: calc. for $C_{22}H_{18}F_2O_3$: 391.1117 $[M + Na]^+$; found: 391.1106.

7,9-Bis-[1-(2,4-dichloro-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]-decan-8-one (3e). IR (KBr, ν, cm^{-1}): 2949, 1676, 1611, 1584, 1467, 1265, 1103, 1045, 986, 844, 775. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.78 (s, 2H, =CH), 7.75 (d, $J = 7.2$ Hz, 2H, ArH), 7.57–7.51 (m., 4H, ArH), 3.79 (s, 4H, CH_2), 3.01 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 185.93, 160.33, 142.58, 137.97, 132.09, 124.20, 123.35, 122.22, 121.32, 106.82, 70.58, 48.58, 36.03. HRMS (ESI) m/z: calc. for $C_{22}H_{16}Cl_4O_3$: 468.9927 $[M + Na]^+$; found: 468.9932.

7,9-Bis-[1-(3-nitro-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3f). IR (KBr, ν, cm^{-1}): 2897, 1673, 1614, 1528, 1351, 1196, 1101, 1040, 948, 817, 680. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.34 (s, 2H, =CH), 8.27–8.24 (m, 2H, ArH), 8.00 (d, $J = 8.0$, 2H, ArH), 7.79–7.75 (m, 4H, ArH), 3.83 (s, 4H, CH_2), 3.19 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 187.03, 147.93, 136.39, 136.33, 135.23, 135.14, 130.16, 124.35, 123.46, 105.86, 64.33, 36.99. HRMS (ESI) m/z: calc. for $C_{22}H_{18}N_2O_7$: 445.1012 $[M + Na]^+$; found: 445.1012.

7,9-Bis-[1-p-tolyl-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3g). IR (KBr, ν, cm^{-1}): 2891, 1671, 1605, 1578,1508, 1263, 1178, 1120, 988, 814. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.65 (s, 2H, =CH), 7.43 (d, $J = 8.0$ Hz, 4H, ArH), 7.28 (d, $J = 8.0$ Hz, 4H, ArH), 3.81 (s, 4H, CH_2), 3.12 (s, 4H, CH_2), 2.35 (s, 6H, CH_3). HRMS (ESI) m/z: calc. for $C_{24}H_{24}O_3$: 383.1618 $[M + Na]^+$; found: 383.1616.

7,9-Bis-[1-(4-methoxy-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3h). IR (KBr, ν, cm^{-1}): 2962, 1673, 1602, 1509, 1461, 1251, 1168, 1025, 984, 834, 531 cm. ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.65 (s, 2H, =CH), 7.51 (d, $J = 8.8$ Hz, 4H, ArH), 7.03 (d, $J = 8.8$ Hz, 4H, ArH), 3.80 (t, $J = 9.2$ Hz, 10H, CH_2 and OCH_3), 3.11 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm):

186.63, 159.88, 136.99, 132.18, 132.11, 130.91, 127.50, 114.19, 106.16, 64.21, 55.28, 37.31. HRMS (ESI) m/z: calc. for $C_{24}H_{24}O_5$: 415.1516 $[M + Na]^+$; found: 415.1511.

7,9-Bis-[1-(3,4,5-methoxy-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5] decan-8-one (3i). IR (KBr, ν, cm^{-1}): 2887, 1657, 1615, 1590, 1523, 1421, 1372, 1272, 1169, 985, 813. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.65 (s, 2H, =CH), 6.84 (s, 4H, ArH), 3.84 (d, $J = 13.2$ Hz, 16H, CH_2 and OCH_3), 3.71 (s, 6H, OCH_3), 3.17 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 187.20, 152.74, 152.05, 138.38, 137.60, 132.32, 130.45, 130.26, 107.93, 106.04, 64.22, 60.11, 56.03, 37.10. HRMS (ESI) m/z: calc. for $C_{28}H_{30}O_9$: 535.1939 $[M + Na]^+$; found: 535.1923.

7,9-Bis-[1-(4-dimethylamino-phenyl)-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5] decan-8-one (3j). IR (KBr, ν, cm^{-1}): 2942, 2889, 1657, 1589, 1524, 1421, 1372, 1272, 1179, 1119, 984, 813. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.69 (d, $J = 8.0$ Hz, 1H, =CH), 7.59 (s, 1H, =CH), 7.41–7.35 (m, 4H, ArH), 6.81–6.74 (m, 4H, ArH), 3.91 (d, $J = 4.0$ Hz, 2H, CH_2), 3.84 (s, 2H, CH_2), 3.07 (d, $J = 12.0$ Hz, Hz, 4H, CH_2), 2.98 (s, 12H, NCH_3). HRMS (ESI) m/z: calc. for $C_{26}H_{30}N_2O_3$: 419.2335 $[M + H]^+$; found: 419.2329.

7,9-Bis-[1-benzo[1,3]dioxol-5-yl-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5] decan-8-one (3k). IR (KBr, ν, cm^{-1}): 2889, 1664, 1594, 1490, 1446, 1222, 1121, 1099, 1032, 912, 815. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.60 (s, 2H, =CH), 7.13–7.01 (m, 6H, ArH), 6.10 (s, 4H, CH_2), 3.83 (s, 4H, CH_2), 3.09 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 185.07, 162.27, 135.25, 134.86, 134.29, 133.01, 131.90, 131.86, 129.28, 127.48, 122.35, 105.90, 86.23, 64.26, 36.84. HRMS (ESI) m/z: calc. for $C_{24}H_{20}O_7$: 443.1102 $[M + Na]^+$; found: 443.1092.

7,9-Bis-[1-thiophen-2-yl-meth-(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decan-8-one (3l). IR (KBr, ν, cm^{-1}): 3104, 2891, 1656, 1588, 1413, 1344, 1206, 1094, 947, 722, 559. ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.91 (t, $J = 4.0$ Hz, 4H, =CH and ArH), 7.71–7.53 (m, 2H, ArH), 7.28–7.15 (m, 2H, ArH), 3.97 (d, $J = 6.8$ Hz, 4H, CH_2), 3.12 (s, 3H, CH_2), 3.01 (d, $J = 15.6$ Hz, 1H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 186.06, 138.16, 134.15, 131.47, 130.20, 129.63, 128.19, 105.91, 64.44, 37.16. HRMS (ESI) m/z: calc. for $C_{18}H_{16}O_3S_2$: 367.0439 $[M + Na]^+$; found: 367.0444.

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