Eco-Friendly and Facile One-Pot Multicomponent Synthesis of Acridinediones in Water under Microwave

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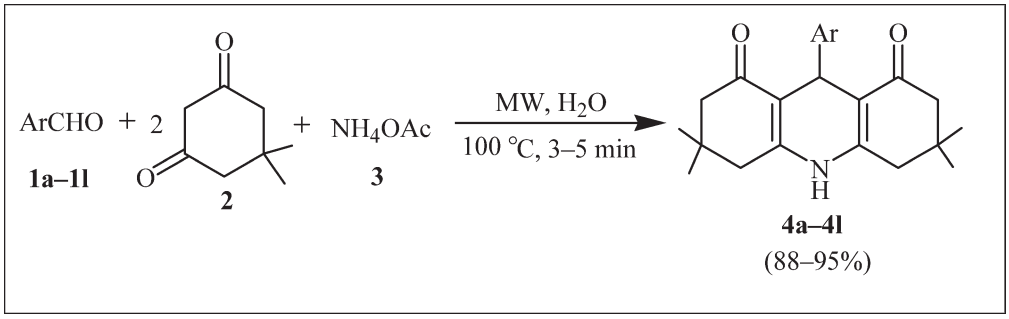

A rapid, improved, and environmentally benign synthesis of 4-arylacridinediones is reported via one-pot multicomponent reaction of aromatic aldehydes, dimedone, and ammonium acetate in water without any catalyst under microwave irradiation. Excellent yields, shortest reaction time, and easy work-up are attractive features of this green protocol.

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INTRODUCTION

One-pot multicomponent reactions (MCRs) have emerged as an effective tool for atom economic and benign synthesis by virtue of their convergence, productivity, facile execution, and generation of highly diverse and complex product from easily available starting materials in a single operation. MCRs are now being tailored and tuned for synthesizing various heterocyclic scaffolds for diverse applications [1]. The environmental acceptability of the process is improved if the multicomponent strategy is applied under microwave irradiation (MW) [2]. For many chemical processes, a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome this problem, it is highly desirable to develop efficient methods that use microwave irradiation. Microwave heating provides a valuable tool to perform reactions faster with enhanced product yields with high purities by reducing unwanted side reactions [3]. In addition, aqueous mediated reactions have recently received considerable attention in organic synthesis, because of both economic and environmental safety reasons. Because of the low-solubility of common organic compounds in water, the use of water as solvent often makes the purification of products very easy by simple filtration or extraction [4]. The use of water as an environmentally benign solvent for chemical transformations employing microwave irradiation has become the demand of the present day research [5].

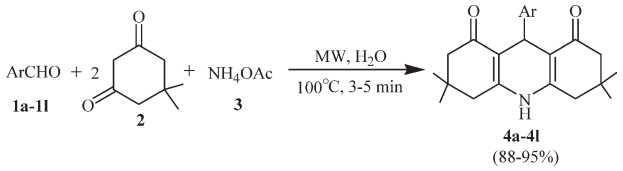
4-Aryl-1,4-dihydropyridines (1,4-DHPs) are valuable drugs for the treatment of cardiovascular disorders [6], and constitute an important class of calcium channel blockers [7]. Slight structural modification on the dihydropyridine ring may result in a remarkable change in its pharmacological effect [8]. Acridine-1,8-diones containing a 1,4-DHP parent nucleus, are endowed with a very high lasing efficiencies and are used as photoinitiators [9]. As a result, acridinediones have been recently synthesized by a number of methods [10–20]. However, many of these methods suffer from drawbacks such as the use of hazardous organic solvents, long reaction time, low-yield, formation of side products and multistep synthesis. Subsequently, there stands a demand and scope to develop an efficient, facile and eco-safe approach to achieve acridinediones.

RESULTS AND DISCUSSION

We describe herein a versatile, environmentally benign, one-pot multicomponent synthesis of 4-arylacridinediones by the reaction of aromatic aldehydes, dimedone, and ammonium acetate under controlled microwave irradiation in water without the use of any catalyst (Scheme 1).

To optimize the reaction conditions, we undertook a model reaction of benzaldehyde **1a**, dimedone **2**, and ammonium acetate **3** in solvents viz., methanol, ethanol, acetonitrile, and water using different MW powers at

Scheme 1



different temperatures. The results are shown in Table 1 and reveal that water (entry 15) is the best choice as medium for the said reaction with excellent product yield (94%) using 220 W power at 100°C. A marginally low-performance was displayed by acetonitrile (entry 12), whereas ethanol and methanol could not do well. Therefore, water was opted as the solvent for the subsequent reactions on the merit of higher yield, green nature, and easy work-up as compared with acetonitrile.

Under the optimized set of reaction conditions (entry 15), a number of aromatic aldehydes **1** were allowed to undergo MCR with dimedone **2** and ammonium acetate **3** in a molar ratio of 1:2:1.5 in water under microwave (220 W, 100°C) heating. The reactions were carried out for 3–5 min, and the results are given in Table 2. All the electron-rich and electron deficient aldehydes worked well, leading to excellent yields of the products. The progress of the reaction was monitored by TLC (hexane/ethyl acetate; 8:2). Upon completion of the reaction, the mixture was allowed to cool, and the resulting solid was filtered and dried at room temperature. The crude material was purified by recrystallization from methanol to afford pure substituted acridinediones **4a–4l** in excellent yields (88–95%). All the products were crystalline and fully characterized on the basis of their melting points, elemental analyses, and spectral data (IR, ^{1}H NMR, and ^{13}C NMR).

A plausible mechanism for the formation of acridinediones **4** is outlined in scheme 2. The reaction is initiated by the Knoevenagel type condensation of aldehyde **1** with a molecule of dimedone **2** giving **5**; and simultaneously condensation of another mole of dimedone **2** with ammonium acetate **3** to provide enaminone **6**. The subsequent Michael addition of **6**–**5** followed by intramolecular cycloaddition and dehydration finally affords the product **4**.

CONCLUSION

In conclusion, we have developed a new, facile, and efficient methodology for the eco-compatible preparation of substituted acridinediones via one-pot three component condensation of aromatic aldehyde, dimedone, and ammonium acetate in an aqueous medium. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, excellent product yield, shorter reaction time, and the easy work-up procedure makes this approach more attractive in synthesizing a variety of such derivatives.

EXPERIMENTAL

All the chemicals were procured from Aldrich, USA, and E. Merck, Germany and were purified before their use. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc Model CE-440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected. The microwave irradiation was effected using the CEM's Discover Bench Mate single-mode microwave synthesis system

Table 1

Optimization of reaction conditions using compound **1a**.

		Microwave			
Entry	Solvent	MW (Watt)	Temp. (°C)	Time (min)	Yield (%)
1	Ethanol	120	60	5	57
2	Ethanol	120	80	5	58
3	Ethanol	180	100	5	69
4	Ethanol	220	100	5	72
5	Methanol	120	60	5	43
6	Methanol	120	80	5	43
7	Methanol	180	100	5	58
8	Methanol	220	100	5	64
9	Acetonitrile	120	60	5	60
10	Acetonitrile	120	80	5	66
11	Acetonitrile	180	100	5	83
12	Acetonitrile	220	100	5	92
13	Water	180	80	5	71
14	Water	180	100	5	87
15	Water	220	100	3	94
16	Water	250	100	3	92

Table 2

Microwave induced synthesis of acridinedione derivatives in water.[a]

Entry	Ar	Product	Time (min)	Yield[b] (%)	Mp (°C) Obs	Mp (°C) Lit
1	C_6H_5	**4a**	3	94	251–252	250–252 [10b]
2	4-$CH_3C_6H_4$	**4b**	3	95	227–228	>300 [18]
3	4-$CH_3OC_6H_4$	**4c**	3	93	266–267	269–270 [13]
4	4-ClC_6H_4	**4d**	3	94	>300	296–298 [13]
5	3-ClC_6H_4	**4e**	3	92	281–282	–
6	4-BrC_6H_4	**4f**	3	94	234–235	–
7	3-BrC_6H_4	**4g**	3	91	288–289	–
8	4-FC_6H_4	**4h**	3	92	275–276	–
9	4-$NO_2C_6H_4$	**4i**	5	90	261–262	–
10	3-$NO_2C_6H_4$	**4j**	5	89	285–286	285–286 [13]
11	4-OH-3-$CH_3OC_6H_3$	**4k**	3	88	>300	296–298 [16]
12	4-$(CH_3)_2NC_6H_4$	**4l**	3	90	256–257	264–266 [13]

[a] Microwave heating performed on 220 W power and 100°C temperature.
[b] Isolated yield.

using safe pressure regulation 10-mL pressurized vials with ''snap-on'' cap.

General procedure for the synthesis of acridinediones 4. A mixture of aldehyde **1** (1 mmol), dimedone **2** (2 mmol), ammonium acetate **3** (1.5 mmol), and water (2 mL) was placed in a sealed pressure regulation 10-mL pressurized vial with ''snap-on'' cap and was irradiated in the single-mode microwave synthesis system at 220 W power and 100°C temperature for 3–5 minutes. After completion of reaction (TLC), the mixture was cooled and the resulting product was filtered, dried, and recrystallized from methanol to afford the pure product **4a–4l**.

3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4a). Light yellow solid; IR (KBr): 3275, 2958, 1652, 1627, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.03–7.34 (m, 5H, Ar-H), 6.25 (s, 1H, NH), 5.08 (s, 1H, CH), 2.18–2.39 (m, 8H, CH_2), 1.08 (s, 6H, CH_3), 0.97 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.8, 149.0, 146.6, 128.0, 125.9, 113.3, 50.8, 40.7, 33.6, 32.6, 29.5, 27.1; Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01; Found: C, 78.93; H, 7.85; N, 3.97.

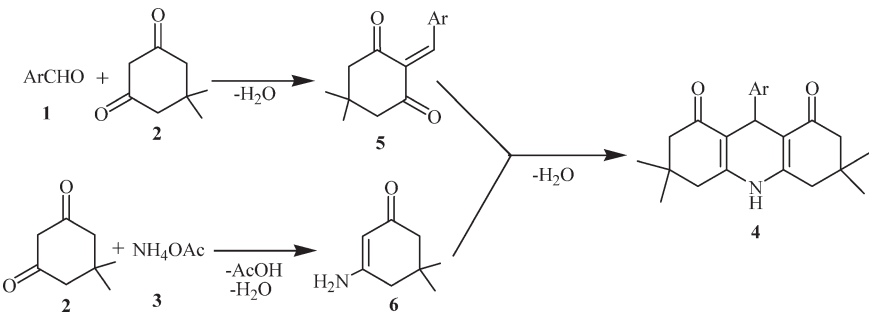
3,3,6,6-Tetramethyl-9-(4-methylphenyl)-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4b). Colourless solid; IR (KBr): 3276, 2952, 1630, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 11.76 (s, 1H, NH), 7.08–7.28 (m, 4H, Ar-H), 5.11 (s, 1H, CH), 2.21–2.41 (m, 8H, CH_2), 2.18 (s, 3H, CH_3), 1.06 (s, 6H, CH_3), 0.96 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.5, 190.1, 146.3, 146.7, 134.5, 133.2, 129.2, 128.7, 114.8, 113.6, 55.7, 48.1, 45.6, 32.3, 30.4, 27.7, 26.8, 21.3; Anal. Calcd. for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85; Found: C, 79.37; H, 7.90; N, 3.91.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4c). Light yellow solid; IR (KBr): 3296, 2947, 1645, 1628, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 11.78 (s, 1H, NH), 6.58–7.23 (m, 4H, Ar-H), 5.48 (s, 1H, CH), 3.75 (s, 3H, OCH_3), 2.33–2.38 (m, 8H, CH_2), 1.22 (s, 6H, CH_3), 1.10 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7, 190.4, 149.8, 147.7, 140.1, 129.3, 128.5, 115.7, 113.9, 55.8, 47.6, 37.7, 32.3, 29.5, 27.9, 27.6; Anal. Calcd. for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; Found: C, 76.11; H, 7.64; N, 3.77.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4d). Colourless solid; IR (KBr): 3305, 2952, 1640, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 11.86 (s, 1H, NH), 7.21–7.24 (m, 2H, Ar-H), 6.99–7.02 (m, 2H, Ar-H), 5.47 (s, 1H, CH), 2.27–2.49 (m, 8H, CH_2), 1.21 (s, 6H, CH_3), 1.09 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.6, 189.4, 136.7, 131.5, 128.3, 128.1, 115.3, 47.0, 46.4, 32.4, 31.4, 29.6, 27.4; Anal. Calcd. for $C_{23}H_{26}ClNO_2$: C, 71.96; H, 6.83; N, 3.65; Found: C, 72.12; H, 6.89; N, 3.54.

9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4e). White solid; IR (KBr): 3288, 2955, 1642, 1627, 1605 cm^{-1}; ^1H NMR (300 MHz,

Scheme 2. Proposed mechanism for the formation of **4**.



$CDCl_3$): δ = 11.89 (s, 1H, NH), 6.95–7.22 (m, 4H, Ar-H), 5.48 (s, 1H, CH), 2.28–2.50 (m, 8H, CH_2), 1.23 (s, 6H, CH_3), 1.10 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.6, 189.4, 140.4, 134.1, 129.3, 127.1, 126.0, 124.9, 115.0, 47.0, 46.4, 32.6, 31.9, 29.5, 27.3; Anal. Calcd. for $C_{23}H_{26}ClNO_2$: C, 71.96; H, 6.83; N, 3.65; Found: C, 71.85; H, 6.91; N, 3.76.

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4f). Yellow solid; IR (KBr): 3276, 2958, 1656, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.88 (s, 1H, NH), 7.01–7.26 (m, 4H, Ar-H), 5.47 (s, 1H, CH), 2.29–2.51 (m, 8H, CH_2), 1.22 (s, 6H, CH_3), 1.10 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.3, 185.5, 137.7, 132.6, 129.1, 128.7, 116.3, 47.7, 45.8, 33.2, 31.6, 29.5, 27.1; Anal. Calcd. for $C_{23}H_{26}BrNO_2$: C, 64.49; H, 6.12; N, 3.27; Found: C, 64.51; H, 6.18; N, 3.16.

9-(3-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4g). Colourless solid; IR (KBr): 3273, 2956, 1654, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.89 (s, 1H, NH), 6.99–6.31 (m, 4H, Ar-H), 5.48 (s, 1H, CH), 2.28–2.50 (m, 8H, CH_2), 1.23 (s, 6H, CH_3), 1.10 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.6, 189.6, 140.6, 134.3, 129.5, 128.1, 126.6, 124.2, 115.5, 47.6, 46.5, 32.4, 31.6, 29.4, 26.8; Anal. Calcd. for $C_{23}H_{26}BrNO_2$: C, 64.49; H, 6.12; N, 3.27; Found: C, 64.38; H, 6.17; N, 3.30.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4h). Colourless solid; IR (KBr): 3285, 2961, 1692, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.88 (s, 1H, NH), 6.92–7.06 (m, 4H, Ar-H), 5.48 (s, 1H, CH), 2.28–2.49 (m, 8H, CH_2), 1.22(s, 6H, CH_3), 1.10 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.5, 189.6, 136.5, 131.7, 129.4, 127.7, 115.6, 47.3, 46.8, 32.6, 31.3, 29.5, 27.3; Anal. Calcd. for $C_{23}H_{26}FNO_2$: C, 75.18; H, 7.13; N, 3.81; Found: C, 75.08; H, 7.21; N, 3.76.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4i). Colourless solid; IR (KBr): 3289, 2961, 1678, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.79 (s, 1H, NH), 8.13 (d, J = 8.7 Hz, 2H, Ar-H), 7.24 (d, J = 8.7 Hz, 2H, Ar-H), 5.54 (s, 1H, CH), 2.30–2.53 (m, 8H, CH_2), 1.24 (s, 6H, CH_3), 1.12 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.9, 189.5, 146.5, 146.0, 127.6, 123.4, 114.8, 46.9, 46.3, 33.2, 31.4, 29.4, 27.4; Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10; Found: C, 78.99; H, 6.71; N, 7.18.

3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4j). Colourless solid; IR (KBr): 3281, 2962, 1694, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.79 (s, 1H, NH), 8.00–8.05 (m, 2H, Ar-H), 7.41–7.47 (m, 2H, Ar-H), 5.54 (s, 1H, CH), 2.30–2.54 (m, 8H, CH_2), 1.28 (s, 6H, CH_3), 1.12 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.6, 189.4, 140.4, 134.1, 129.3, 127.1, 126.0, 124.9, 115.0, 47.0, 46.4, 32.6, 31.4, 29.5, 27.3; Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10; Found: C, 70.16; H, 6.54; N, 7.21.

9-(4-Hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4k). Yellow solid; IR (KBr): 3397, 3287, 2941, 1688, 1601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.97 (s, 1H, NH), 6.57–6.82 (m, 3H, Ar-H), 5.54 (s, 2H, CH, and OH), 3.77 (s, 3H, OCH_3) 2.36–2.40 (m, 8H, CH_2), 1.23 (s, 6H, CH_3), 1.11 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.3, 189.3, 146.3, 143.5, 129.5, 119.3, 115.7, 114.0, 109.7, 55.5, 46.9, 46.3, 32.2, 31.1, 29.8, 26.9; Anal. Calcd. for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54; Found: C, 73.01; H, 7.32; N, 3.48.

9-(4-Dimethylaminophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4l). Light Yellow solid; IR (KBr): 3283, 2957, 1696, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.93 (s, 1H, NH), 6.57–7.19 (m, 4H, Ar-H), 5.47 (s, 1H, CH), 2.84–3.09 (m, 8H, CH_2), 2.32 (s, 6H, NCH_3), 1.09 (s, 6H, CH_3), 0.99 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.2, 189.3, 148.7, 147.7, 135.3, 128.6, 127.4, 125.5, 115.9, 113.8, 112.4, 50.8, 46.4, 40.7, 32.5, 31.8, 31.3, 29.7, 29.5, 27.3; Anal. Calcd. for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; Found: C, 76.62; H, 8.14; N, 7.07.

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