Microwave-assisted Synthesis of Acridine-1,8(2*H*,5*H*)-diones via a One-pot, Three Component Reaction

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ABSTRACT: *A new and improved protocol for the synthesis, in good to excellent yields, of acridine-1,8(2H,5H)-diones is described, involving a one-pot, three component reaction of dimedone, aryl-glyoxals, and ammonium acetate in water under microwave irradiation.*

KEYWORDS: *Acridinediones; Ammonium acetate; Arylglyoxals; Dimedone; Microwave irradiation; One-pot multi-component reaction.*

INTRODUCTION

Acridinediones represent a class of heterocyclic compounds with a wide range of pharmacological and biological activities, such as antibacterial [1], antiviral [2], antimicrobial [3], anticancer [4,5], antitumor [6], antimaralial [7] and antifungal [8].

The synthesis of acridinedione derivatives via Multi-Component Reactions (MCRs) using aromatic aldehydes, active methylene compounds and ammonium acetate or aromatic amines in the presence of various catalysts under both microwave irradiation or refluxing conditions have been reported [9-12].

The Green One-pot Synthesis of Polyhydroacridine derivatives using Sulfonic Acid Functionalized Nanoporous Silica (SBA-Pr-SO_3H) has been reported [13]. We have previously reported the synthesis of various heterocyclic compounds using arylglyoxals and phenacylbromide derivatives as a valuable sources towards green chemistry [14-21].

Herein we report the synthesis of a series of new 9-aroyl-3,3,6,6-tetramethyl-3,4,6,7,9,10- hexahydroacridine-1,8(2*H*,5*H*)-diones by a one-pot, three component reaction of dimedone, arylglyoxals and ammonium acetate in water under microwave irradiation.

EXPERIMENTAL SECTION

Melting points were measured on a Philip Harris C4954718 apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in $CDCl_3$ as solvent relative to TMS as the internal standard. Infrared spectra were recorded on a Thermo-Nicolet Nexus 670 FT-IR instrument using KBr discs. Elemental analyses were performed by using a Leco Analyzer 932.

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General procedure for synthesis of 9-aroyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-diones (4a-g)

Dimedone (2 mmol) was dissolved in water (20 mL) by heating and stirring at 100 °C. The arylglyoxal (1 mmol) was added to the solution and the reaction mixtured was irradiated for 10 min at 200 W. The reaction mixture was cooled to room temperature and ammonium acetate (1 mmol) was added. The mixture was stirred at 100 °C for 3 h. The reaction mixture was cooled to room temperature and the precipitate was filtered and washed with water and recrystallized from equeous ethanol (50%) to give the desired products in 81-90% yields.

9-Benzoyl- 3,3,6,6-tetramethyl- 3,4,6,7,9,10-hexahydro-acridine-1,8(2H,5H)-dione (4a)

Yield 81%, White needles; mp 152-154 °C. ^{1}H NMR spectrum, δ (ppm): 11.37 (1H, br. s, exchanged with D_2O, NH), 7.67 (2H, d, *J* = 7.2 Hz, Ar), 7.45 (1H, t, *J* = 6.6 Hz, Ar), 7.35 (1H, t, *J* = 6.6 Hz, Ar), 5.48 (1H, s, CH), 2.30 (8H, s, 4×CH_2), 0.98 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm): 196.86, 190.16, 137.29, 133.14, 129.27, 127.20, 113.86, 46.26, 40.54, 39.57, 38.62, 31.42; FT-IR spectrum (KBr), ν, cm^{-1}: 3429, 3061, 2950, 2876, 1679, 1584, 1448, 1375, 1288, 1157, 833, 696, 584, 511; Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71; Found: C, 76.44; H, 7.09; N, 3.87%.

9-(4-Bromobenzoyl) -3,3,6,6- tetramethyl- 3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4b)

Yield 90%, White needles, mp 157-159 °C. ^{1}H NMR spectrum, δ (ppm): 10.89 (1H, br. s, exchanged with D_2O, NH), 7.52 (2H, d, *J* = 7.8 Hz, Ar), 7.47 (2H, d, *J* = 7.5 Hz, Ar), 5.39 (1H, s, CH), 2.28 (8H, s, 4×CH_2), 0.97 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm): 195.63, 190.17, 136.03, 132.56, 130.30, 128.24, 126.66, 113.43, 46.26, 39.74, 39.44, 31.49, 28.81; FT-IR spectrum (KBr), ν, cm^{-1}: 3363, 2955, 2872, 1694, 1595, 1462, 1374, 1283, 1249, 1220, 1004, 910, 842, 785, 580, 461; Anal. Calcd for $C_{24}H_{26}BrNO_3$: C, 63.16; H, 5.74; N, 3.07; Found: C, 63.24; H, 5.62; N, 3.19%.

9-(4-Chlorobenzoyl)- 3,3,6,6- tetramethyl- 3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4c)

Yield 88%, White needles, mp 153-155 °C. ^{1}H NMR spectrum, δ (ppm): 11.33 (1H, br. s, exchanged with D_2O, NH), 7.63 (2H, d, *J* = 8.4 Hz, Ar), 7.34 (2H, d, *J* = 8.4 Hz, Ar), 5.42 (1H, s, CH), 2.31 (8H, s, 4×CH_2), 1.00 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm):195.46, 190.20, 138.31, 135.58, 130.17, 129.56, 127.49, 113.49, 46.28, 39.73, 39.50, 38.59, 31.52; FT-IR spectrum (KBr), ν, cm^{-1}: 3365, 2956, 2873, 1694, 1595, 1452, 1375, 1284, 1250, 1221, 1167, 1144, 1087, 845, 788; Anal. Calcd for $C_{24}H_{26}ClNO_3$: C, 69.98; H, 6.36; N, 3.40. Found: C, 69.85; H, 6.44; N, 3.39%.

9-(4-Fluorobenzoyl)- 3,3,6,6- tetramethyl- 3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4d)

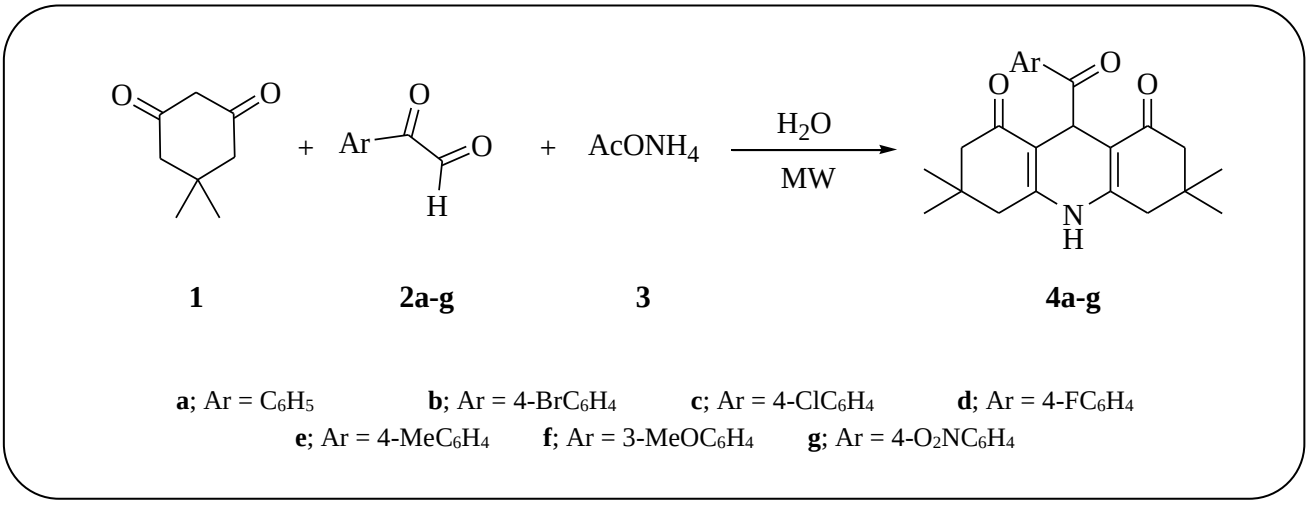
Yield 86%, White needles, mp 130-133 °C. ^{1}H NMR spectrum, δ (ppm): 11.20 (1H, br. s, exchanged with D_2O, NH), 7.70 (2H, br. d, *J* = 4.8 Hz, Ar), 7.69 (2H, br. t, *J* = 9.6 Hz, Ar), 5.44 (1H, s, CH), 2.30 (8H, s, 4×CH_2), 0.99 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm): 195.14, 190.16, 133.47, 131.33, 129.43, 116.56, 114.37, 113.59, 46.28, 40.55, 39.43, 31.48, 31.45; FT-IR spectrum (KBr), ν, cm^{-1}: 3420, 3068, 2949, 2873, 1706, 1586, 1533, 1366, 1272, 1153, 830, 713; Anal. Calcd for $C_{24}H_{26}FNO_3$: C, 72.89; H, 6.63; N, 3.54. Found: C, 72.74; H, 6.77; N, 3.49%.

3,3,6,6-Tetramethyl- 9-(4-methylbenzoyl)- 3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4e)

Yield 87%, White needles, mp 143-145 °C. ^{1}H NMR spectrum, δ (ppm): 11.30 (1H, br. s, exchanged with D_2O, NH), 7.58 (2H, d, *J* = 8.1 Hz, Ar), 7.14 (2H, d, *J* = 7.8 Hz, Ar), 5.45 (1H, s, CH), 2.34 (3H, s, CH_3), 2.29 (8H, s, 4×CH_2), 0.99 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm): 196.26, 190.02, 142.74, 134.47, 129.80, 128.89, 127.13, 113.82, 46.31, 40.51, 39.40, 38.47, 31.47, 28.85; FT-IR spectrum (KBr), ν, cm^{-1}: 3420, 3061, 2956, 2872, 2722, 1691, 1597, 1450, 1376, 1282, 1153, 1121, 1047, 842, 771, 575; Anal. Calcd for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47; N, 3.58. Found: C, 76.63; H, 7.56; N, 3.68%.

9-(3-Methoxybenzoyl)- 3,3,6,6-tetramethyl- 3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4f)

Yield 84%, White needles, mp 111-113 °C. ^{1}H NMR spectrum, δ (ppm): 10.95 (1H, br. s, exchanged with D_2O, NH), 7.18-7.26 (3H, m, Ar), 6.99 (1H, br. d, *J* = 6.3 Hz, Ar), 5.45 (1H, s, CH), 3.81 (3H, s, OCH_3), 2.30 (8H, s,



Scheme 1: Synthesis of acridinedione derivatives 4a-g.

4×CH_2), 0.99 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm): 195.48, 190.11, 159.45, 138.42, 130.10, 128.02, 121.19, 117.99, 113.72, 111.47, 111.43; FT-IR spectrum (KBr), ν, cm^{-1}: 3420, 3072, 2953, 2885, 2626, 1672, 1593, 1385, 1289, 1157, 1034, 832, 763; Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.76; H, 7.08; N, 3.51%.

3,3,6,6- Tetramethyl- 9-(4-nitrobenzoyl)- 3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4g)

Yield 83%, White needles, mp 175-177 °C. ^{1}H NMR spectrum, δ (ppm): 11.20 (1H, br. s, exchanged with D_2O, NH), 8.22 (2H, d, *J* = 8.4 Hz, Ar), 7.81 (2H, d, *J* = 8.7 Hz, Ar), 5.45 (1H, s, CH), 2.30 (8H, s, 4×CH_2), 0.97 (12H, s, 4×CH_3); ^{13}C NMR spectrum, δ (ppm): 195.39, 190.44, 142.78, 129.87, 127.74, 124.45, 122.34, 112.99, 46.21, 41.07, 39.97, 39.06, 31.52; FT-IR spectrum (KBr), ν, cm^{-1}: 3420, 3068, 2949, 2873, 1706, 1586, 1533, 1366, 1272, 1153, 830, 713; Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.37; H, 6.12; N, 6.77%.

RESULTS AND DISCUSSION

In attempting to apply our previously reported reaction [22], of 1,3-cyclohexanedione, arylglyoxals and ammonium acetate in refluxing ethanol to 5,5-dimethyl-1,3-dione (dimedone), arylglyoxals and ammonium acetate, we failed to observe any reaction. However, we found that dimedone (**1**) did react with arylglyoxals **2a-g** and ammonium acetate (**3**) in water under microwave irradiation to give the corresponding acridine-1,8(2*H*,5*H*)-diones **4a-g** by a one-pot, three component reaction in good to excellent yields as shown in Scheme 1.

The yields and melting point of products **4a-g** are shown in Table 1.

The structure of all products **4a-g** were confirmed by their FT-IR, ^{1}H-NMR, ^{13}C-NMR spectral data and their elemental analyses. The ^{1}H and ^{13}C-NMR spectra of were measured in $CDCl_3$, showing broad singlets for NH at δ 10.89-11.37 ppm, which were exchanged by D_2O addition. The CH of the dihydropyridine ring appears as singlets at δ 5.39-5.48 ppm and C-9 in the ^{13}C-NMR spectrum resonates at δ 112.99-113.86 ppm, confirming the keto structure **4**, rather than the enolic tautomer, at least in this solvent.

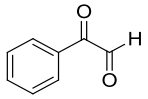
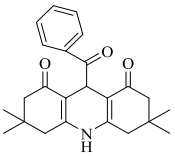
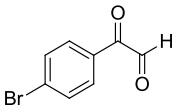
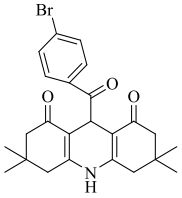
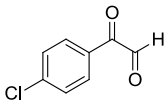
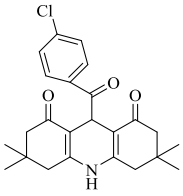
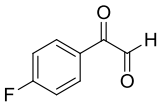
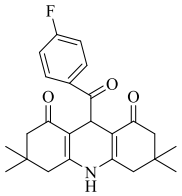
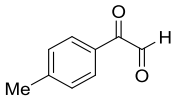
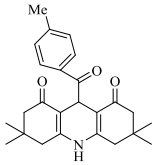
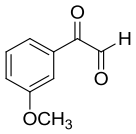
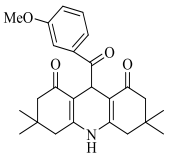
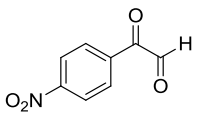
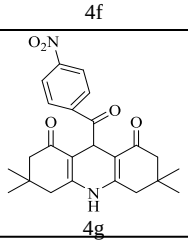
CONCLUSIONS

In conclusion, we report a simple environmentally benign method for the synthesis of acridine-1,8(2*H*,5*H*)-dione derivatives by the one-pot, three component reaction of arylglyoxals with dimedone and ammonium acetaste under microwave irradiation. The milder reaction conditions, availability of starting materials, short reaction times, high yields and clean product formation are the most important advantages of this procedure, which may be used in synthesis of other heterocyclic compounds.

Acknowledgments

The authors gratefully acknowledge the financial assistance from Urmia University.

Table 1: The yields and melting points of compounds 4a-g.

Entry	Arylglyoxals 2a-g	Product 4a-g	Yield (%)	Mp (ºC)
1	 2a	 4a	81	152-154
2	 2b	 4b	90	157-159
3	 2c	 4c	88	153-155
4	 2d	 4d	86	130-133
5	 2e	 4e	87	143-145
6	 2f	 4f	84	111-113
7	 2g	 4g	83	175-177

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