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Aqua-mediated synthesis of acridinediones with reusable silica-supported sulfuric acid as an efficient catalyst

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Abstract

A simple approach to the synthesis of acridinediones *via* one-pot three-component condensation of an aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and ammonium acetate or *p*-toluidine in water with use of silica-supported sulfuric acid as an efficient catalyst is described. Excellent yields, catalyst recovery and reusability, and easy work-up are attractive features of this green protocol. All the synthesized acridinediones were characterized on the basis of their melting-points, elemental analysis and spectral data.

Keywords: Acridinedione; Silica-supported sulfuric acid; One-pot synthesis; Reusable catalyst

1. Introduction

Multicomponent reactions (MCRs) are a promising, vital field of chemistry because the synthesis of complicated molecules can be achieved rapidly and efficiently without the isolation of intermediates [1]. In MCR condensations, three or more compounds react in a single event, but consecutively, to form a new product, which contains the essential parts of all the starting materials. MCRs meet the requirements of an environmentally friendly process, with fewer synthetic steps and less energy consumption and waste production. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions. Therefore, the search for new MCRs and full exploitation of known MCRs is of considerable interest.

Aqua-mediated reactions have received much attention in organic synthesis because of their environmental safety [2]. Use of clean solvents and heterogeneous, reusable catalysts makes these reactions powerful green chemical technology procedures, resulting in minimal pollution and waste material. Therefore, development of new, water-tolerant, solid, acid catalysts could have major industrial applications [3].

1,4-Dihydropyridines are used commercially as calcium channel blockers in the treatment of cardiovascular diseases, such as hypertension [4]. Recently, dihydropyridines were shown to reverse multidrug resistance in tumour cell lines [5,6]. Acridine-1,8-diones containing a 1,4-dihydropyridine parent nucleus have also attracted considerable attention by their potential pharmacological activity, as acridine and its hydro derivatives are biologically active against malaria [7], cancer [8] and leishmania [9],

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bind to and photo-damage DNA [10], are cytotoxic [11] and block potassium channels [12]. A new scaffold, *N*-(9-(ortho/meta/para-(benzyloxy)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9*H*)-yl) isonicotinamide (H1–3) was found to inhibit hSIRT1 during virtual screening of the in-house database, and a library of compounds was designed, synthesized and tested *in vitro* for hSIRT1 activity [13]. A series of novel imidazolyl derivatives of fully and partially hydrogenated 1,8-acridinediones were synthesized and evaluated for their cytotoxic activity on four human cancer cell lines (HeLa, MCF-7, LS-180, and Raji cells) [14].

Acridinedione dyes are a new class of laser dyes with lasing efficiency comparable to that of coumarin-102 [15,16]. These dyes have been shown to mimic NADH analogues to a greater extent because of their tricyclic structures, which protect the enamine moieties [17]. The design and synthesis of 1,3-dithiol-linked acridinedione functionalized gold nanoparticles was described recently [18], as was the design and synthesis of an acridinedione functionalized gold nanoparticle-based PET anion sensor [19].

1,8-(2*H*,5*H*)-Acridinediones were synthesized with the Hantzsch procedure, which involves thermal reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with an aldehyde and ammonia. Various methods have been used to synthesize acridinediones, including the microwave [20,21], ionic liquid [22,23], LiBr [24], proline [25], silica-bonded *S*-sulfonic acid [26], ceric ammonium nitrate [27] and methanesulfonic acid [28] catalysts. Acridinediones are also synthesized in aqueous media [29–31]; however, many of the methods described have drawbacks, such as use of hazardous organic solvents, long reaction times, low yields, formation of side products and multistep synthesis. Subsequently, there is a demand and scope for developing an efficient, easy, eco-safe approach to obtain acridinediones.

During our studies on the synthesis of 1,4-dihydropyridine derivatives [32–34], we found that silica-supported sulfuric acid efficiently catalyzed the synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1,8-dione derivatives in the reaction of arylaldehydes, dimedone and ammonium acetate in water at 70 °C. Using a similar protocol, we also synthesized 9-phenyl-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione derivatives from arylaldehydes, dimedone and *p*-toluidine in water at 80 °C. The aim of the study reported here was to synthesize acridinediones with silica-supported sulfuric acid as the catalyst.

2. Experimental

2.1. Apparatus and analysis

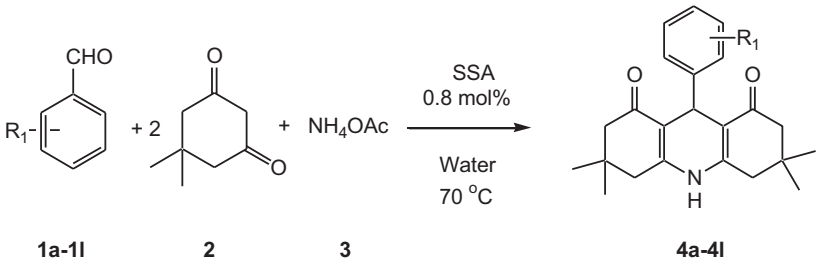
Chemicals were purchased from Merck, Fluka and Aldrich Chemical companies. All yields refer to isolated products unless otherwise stated. ^{1}H Nuclear magnetic resonance (NMR) (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on a Bruker DRX-500 Avance at ambient temperature, with tetramethylsilane as the internal standard and dimethylsulfoxide (DMSO)-d_6 as the solvent. Fourier transform infrared (IR) spectra were obtained as KBr discs on a Shimadzu spectrometer. Mass spectra were determined on a Varion Saturn 2000 gas chromatograph–mass spectrometer. Elemental analyses were conducted with a Perkin Elmer 2400 CHN elemental analyser flowchart.

2.2. Preparation of silica sulfuric acid

Silica sulfuric acid was prepared from silica gel and chlorosulfonic acid, as reported by Zolfigol [35]. A 500-mL suction flask was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (23.3 g, 0.2 mol) and a gas inlet tube for conducting HCl gas over H_2O, the adsorbing solution. Then, 60 g of silica gel were charged into the flask, and chlorosulfonic acid was added dropwise over 30 min at room temperature. HCl gas evolved immediately from the reaction vessel. After the addition was complete, the mixture was shaken for 30 min, and silica sulfuric acid was obtained (76 g) as a white solid. The amount of H^+ in the silica sulfuric acid was determined by acid–base titration: the liberated H_3O^+ was titrated with standard NaOH, and the amount of H^+ in silica sulfuric acid was calculated (0.05 g equal to 0.13 mmol). This value corresponds to about 95% of the sulfur content, indicating that most of the sulfur species on the sample were in the form of the sulfonic acid groups [36,37].

2.3. General procedure for synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione derivatives

A mixture of aldehyde **1** (1 mmol), dimedone **2** (2 mmol), ammonium acetate **3** (1.5 mmol), silica-supported sulfuric acid (0.8 mol%) and water (2 mL) was placed in a 50 mL flask, heated at 70 °C and stirred for the appropriate time as monitored by thin-layer chromatography (hexane:ethyl acetate; 8:2). After completion of the reaction, the mixture was cooled, and the resulting



Scheme 1. Synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1,8-dione derivatives **4a**–**4l** by the reactions of aromatic aldehydes with dimedone and ammonium acetate.

product was filtered, dried and recrystallized from methanol to afford the pure product **4a**–**4l** (Scheme 1). All the products were crystalline and fully characterized on the basis of their melting-points, elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra (MS)).

2.4. Spectral data for the synthesized compounds

*2.4.1. 9-Phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H,5H*)-acridine-1,8-dione (**4a**)*

IR (KBr, cm^{-1}): 3288, 2966, 1677, 1647, 1601; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.88 (s, 6H, 2×CH_3), 0.95 (s, 6H, 2×CH_3), 7.13–7.44 (m, 5H, Ar-H), 10.25 (s, 1H, NH), 5.13 (s, 1H, CH), 2.22–2.44 (m, 8H, 4×CH_2) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.1, 29.5, 32.6, 33.6, 40.7, 50.8, 113.3, 125.9, 128.0, 146.6, 149.0, 195.8 ppm; MS (electrospray ionization (ESI)): *m/z* 350 $(M+H)^+$; analysis: calculated for $C_{23}H_{27}NO_2$: C, 79.08; H, 7.74; N, 4.01; found: C, 79.00; H, 7.67; N, 3.97.

*2.4.2. 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H,5H*)-acridine-1,8-dione (**4b**)*

IR (KBr, cm^{-1}): 3302, 2981, 1682, 1612; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.04 (s, 6H, 2×CH_3), 0.99 (s, 6H, 2×CH_3), 10.69 (s, 1H, NH), 7.83 (d, J = 8.2 Hz, 2H, Ar-H), 7.34 (d, J = 8.2 Hz, 2H, Ar-H), 5.44 (s, 1H, CH), 2.32–2.56 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.6, 29.5, 32.6, 33.6, 44.7, 51.8, 114.3, 124.9, 127.0, 146.6, 147.8, 189.2, 195.8; MS (ESI): *m/z* 395 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}N_2O_4$: C, 70.05; H, 6.60; N, 7.11; found: C, 69.92; H, 6.55; N, 7.01.

*2.4.3. 9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H,5H*)-acridine-1,8-dione (**4c**)*

IR (KBr, cm^{-1}): 3293, 2980, 1666, 1602; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.00 (s, 6H, 2×CH_3), 0.91 (s, 6H, 2×CH_3), 11.08 (s, 1H, NH), 7.14–7.46 (m, 4H, Ar-H), 5.37 (s, 1H, CH), 2.19–2.41 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.1, 29.5, 31.9, 33.4, 42.7, 48.8, 114.3, 126.9, 128.0, 139.6, 144.3, 192.8; MS (ESI): *m/z* 428.9 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}BrNO_2$: C, 64.50; H, 6.08; N, 3.27; found: C, 64.38; H, 6.08; N, 3.16.

*2.4.4. 9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H,5H*)-acridine-1,8-dione(**4d**)*

IR (KBr, cm^{-1}): 3295, 2987, 1700, 1615; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.90 (s, 6H, 2×CH_3), 0.99 (s, 6H, 2×CH_3), 10.98 (s, 1H, NH), 7.22–7.56 (m, 4H, Ar-H), 5.38 (s, 1H, CH), 2.17–2.33 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.6, 29.2, 31.4, 32.9, 41.8, 47.2, 115.3, 127.2, 128.5, 140.7, 189.3, 193.8; MS (ESI): *m/z* 368 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}FNO_2$: C, 75.20; H, 7.08; N, 3.81; found: C, 75.08; H, 7.01; N, 3.76.

*2.4.5. 9-(4-Methylphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H,5H*)-acridine-1,8-dione (**4e**)*

IR (KBr, cm^{-1}): 3286, 2964, 1644, 1611; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.86 (s, 6H, 2×CH_3), 0.99 (s, 6H, 2×CH_3), 10.92 (s, 1H, NH), 7.15–7.38 (m, 4H, Ar-H), 5.31 (s, 1H, CH), 2.11–2.29 (m, 8H, 4×CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.8, 27.2, 28.2, 30.9, 32.6, 44.8, 48.2, 56.2, 113.6, 115.3, 127.2, 128.5, 134.6, 140.7, 146.5, 189.3, 193.8; MS (ESI): *m/z* 364 $(M+H)^+$; analysis: calculated for $C_{24}H_{29}NO_2$: C, 79.34; H, 7.99; N, 3.86; found: C, 79.37; H, 7.90; N, 3.81.

*2.4.6. 9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H,5H*)-acridine-1,8-dione (**4f**)*

IR (KBr, cm^{-1}): 3306, 2969, 1677, 1628, 1615; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.22 (s, 6H, 2×CH_3),

1.10 (s, 6H, 2×CH_3), 10.88 (s, 1H, NH), 7.18–7.43 (m, 4H, Ar-H), 5.48 (s, 1H, CH), 3.75 (s, 3H, OCH_3), 2.30–2.48 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.2, 28.5, 29.2, 32.5, 40.3, 47.2, 55.3, 114.5, 115.3, 127.4, 129.0, 140.7, 146.5, 189.8, 194.4; MS (ESI): *m/z* 380 $(M+H)^+$; analysis: calculated for $C_{24}H_{29}NO_3$: C, 75.99; H, 7.65; N, 3.69; found: C, 75.91; H, 7.64; N, 3.61.

*2.4.7. 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1, 8-dione (**4g**)*

IR (KBr, cm^{-1}): 3313, 2974, 1662, 1612; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.01 (s, 6H, 2×CH_3), 1.09 (s, 6H, 2×CH_3), 10.86 (s, 1H, NH), 7.08–7.42 (m, 4H, Ar-H), 5.22 (s, 1H, CH), 2.17–2.39 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.7, 29.0, 30.2, 32.3, 42.3, 48.2, 115.3, 127.2, 128.8, 138.7, 142.5, 189.8, 193.9; MS (ESI): *m/z* 384.45 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}ClNO_2$: C, 71.98; H, 6.78; N, 3.65; found: C, 71.84; H, 6.69; N, 3.54.

*2.4.8. 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1, 8-dione (**4h**)*

IR (KBr, cm^{-1}): 3427, 3368, 3297, 2955, 1686, 1611; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.93 (s, 6H, 2×CH_3), 1.01 (s, 6H, 2×CH_3), 10.97 (s, 1H, NH), 6.97–7.29 (m, 4H, Ar-H), 5.40 (s, 1H, CH), 9.54 (s, 1H, OH), 2.26–2.44 (m, 8H, 2×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.7, 29.4, 31.2, 32.4, 43.3, 49.2, 55.5, 110.2, 114.3, 119.6, 127.2, 141.7, 145.5, 187.5, 192.5; MS (ESI): *m/z* 366 $(M+H)^+$; analysis: calculated for $C_{23}H_{27}NO_3$: C, 75.62; H, 7.40; N, 3.83; found: C, 75.55; H, 7.32; N, 3.78.

*2.4.9. 9-(3-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1, 8-dione (**4i**)*

IR (KBr, cm^{-1}): 3292, 2972, 1702, 1616; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.88 (s, 6H, 2×CH_3), 0.92 (s, 6H, 2×CH_3), 10.99 (s, 1H, NH), 7.88–8.08 (m, 2H, Ar-H), 7.217.37 (m, 2H, Ar-H), 5.38 (s, 1H, CH), 2.24–2.44 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.4, 29.4, 31.2, 32.7, 44.3, 47.2, 115.1, 124.3, 127.2, 128.8, 135.7, 143.5, 189.4, 192.5; MS (ESI): *m/z* 395 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}N_2O_4$: C, 70.05; H, 6.60; N, 7.11; found: C, 70.00; H, 6.54; N, 7.14.

*2.4.10. 9-(3-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1, 8-dione (**4j**)*

IR (KBr, cm^{-1}): 3288, 2981, 1695, 1612; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.92 (s, 6H, 2×CH_3), 1.00 (s, 6H, 2×CH_3), 10.87 (s, 1H, NH), 7.02–7.19 (m, 4H, Ar-H), 5.52 (s, 1H, CH), 2.16–2.39 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.2, 29.4, 31.0, 32.5, 44.3, 49.2, 115.3, 127.4, 129.8, 131.2, 138.7, 188.9, 191.9; MS (ESI): *m/z* 368 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}FNO_2$: C, 75.20; H, 7.08; N, 3.81; found: C, 75.08; H, 7.01; N, 3.76.

*2.4.11. 9-(3-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1, 8-dione (**4k**)*

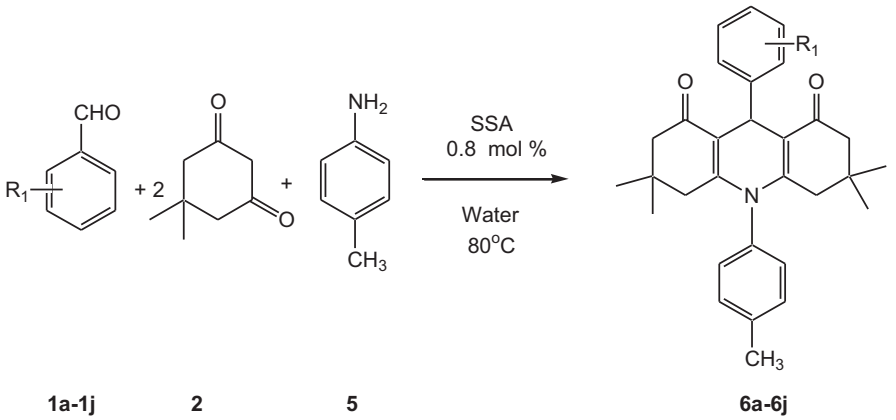
IR (KBr, cm^{-1}): 3281, 2962, 1662, 1611; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.94 (s, 6H, 2×CH_3), 1.07 (s, 6H, 2×CH_3), 11.00 (s, 1H, NH), 7.09–7.31 (m, 4H, Ar-H), 5.41 (s, 1H, CH), 2.20–2.42 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.2, 29.2, 30.4, 32.5, 43.3, 46.2, 115.4, 124.2, 126.4, 128.8, 137.7, 141.5, 188.8, 192.4; MS (ESI): *m/z* 428.9 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}BrNO_2$: C, 64.50; H, 6.08 N, 3.27; found: C, 64.38; H, 6.07; N, 3.25.

*2.4.12. 9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1, 8-dione (**4l**)*

IR (KBr, cm^{-1}): 3292, 2965, 1652, 1629, 1609; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.93 (s, 6H, 2×CH_3), 1.03 (s, 6H, 2×CH_3), 11.12 (s, 1H, NH), 7.05–7.32 (m, 4H, Ar-H), 5.39 (s, 1H, CH), 2.23–2.43 (m, 8H, 4×CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.4, 29.5, 31.4, 32.6, 43.4, 47.9, 115.4, 126.5, 128.4, 134.2, 138.7, 142.0, 188.9, 191.5; MS (ESI): *m/z* 384.45 $(M+H)^+$; analysis: calculated for $C_{23}H_{26}ClNO_2$: C, 71.98; H, 6.78; N, 3.65; found: C, 71.89; H, 6.71; N, 3.56.

2.5. General procedure for synthesis of 9-phenyl-3,3,6,6-tetramethyl-10-p-tolyl-hexahydro acridine-1,8-dione

A mixture containing aryl aldehyde **1** (1 mmol), dimedone **2** (280 mg, 2 mmol) and *p*-toluidine **5** (107 mg, 1 mmol) was introduced into a 50-mL flask with 0.8 mol% silica sulfuric acid in water. The mixture was heated at 80 °C and stirred for the appropriate time as monitored by thin-layer chromatography (hexane:ethyl acetate; 8:2). After completion of the reaction, the mixture was cooled, and the resulting product was filtered, dried and recrystallized from methanol to afford the pure



Scheme 2. Synthesis of 9-phenyl-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione derivatives **6a–6j** by the reactions of aromatic aldehydes with dimedone and *p*-toluidine.

product **6a–6j** (Scheme 2). All the products were characterized on the basis of their melting-points, elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS).

*2.6. Spectral data for compounds **6a–6j***

*2.6.1. 9-Phenyl-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (**6a**)*

IR (KBr, cm^{-1}): 3035, 2957, 2866, 1663, 1615, 1554, 1374, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.82 (s, 6H, 2×CH_3), 0.90 (s, 6H, 2×CH_3), 7.03–7.33 (m, 5H, Ar-H), 2.38 (s, 3H, CH_3), 5.22 (s, 1H, CH), 2.10–2.32 (m, 8H, 4×CH_2), 7.82 (d, J = 8.0 Hz, 2H, Ar-H), 7.54 (d, J = 8.0 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.4, 26.8, 29.7, 32.5, 33.8, 41.9, 50.2, 109.7, 113.6, 128.8, 128.9, 129.5, 130.9, 132.0, 132.1, 136.1, 139.9, 150.7, 151.7, 195.8; MS (ESI): *m/z* 440 (M+H)$^+$; analysis: calculated for $C_{30}H_{33}NO_2$: C, 82.00; H, 7.52; N, 3.19; found: C, 79.80; H, 7.45; N, 3.10.

*2.6.2. 9-(4-Cyanophenyl)-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (**6b**)*

IR (KBr, cm^{-1}): 3044, 2966, 2870, 1643, 1611, 2221, 1552, 1370, 1342; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.83 (s, 6H, 2×CH_3), 0.96 (s, 6H, 2×CH_3), 7.10–7.35 (m, 4H, Ar-H), 2.34 (s, 3H, CH_3), 5.25 (s, 1H, CH), 2.06–2.24 (m, 8H, 4×CH_2), 7.88 (d, J = 8.2 Hz, 2H, Ar-H), 7.57 (d, J = 8.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.9, 26.4, 29.2, 32.0, 33.3, 41.3, 50.6, 110.4, 113.2, 119.4, 128.3, 128.7, 129.6, 132.0, 132.1, 136.4, 140.4, 151.0, 152.3, 194.9; MS (ESI): *m/z* 465 (M+H)$^+$; analysis: calculated for $C_{31}H_{32}N_2O_2$: C, 80.17; H, 6.89; N, 6.03; found: C, 80.11; H, 6.82; N, 5.98.

*2.6.3. 9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (**6c**)*

IR (KBr, cm^{-1}): 3033, 2960, 2871, 1652, 1612, 1566, 1366, 1353; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.82 (s, 6H, 2×CH_3), 0.96 (s, 6H, 2×CH_3), 7.04–7.32 (m, 4H, Ar-H), 2.29 (s, 3H, CH_3), 5.19 (s, 1H, CH), 2.11–2.30 (m, 8H, 4×CH_2), 7.89 (d, J = 8.4 Hz, 2H, Ar-H), 7.44 (d, J = 8.4 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.2, 26.9, 29.4, 32.8, 33.6, 41.2, 50.8, 108.9, 114.2, 128.5, 128.9, 129.3, 130.4, 132.3, 132.6, 135.9, 139.7, 150.5, 151.6, 195.0; MS (ESI): *m/z* 474.45 (M+H)$^+$; analysis: calculated for $C_{30}H_{32}ClNO_2$: C, 76.04; H, 6.76; N, 2.96; found: C, 76.00; H, 6.74; N, 2.93.

*2.6.4. 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (**6d**)*

IR (KBr, cm^{-1}): 3030, 2955, 2876, 1660, 1608, 1555, 1371, 1342; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.84 (s, 6H, 2×CH_3), 1.05 (s, 6H, 2×CH_3), 7.11–7.24 (m, 4H, Ar-H), 2.36 (s, 3H, CH_3), 5.24 (s, 1H, CH), 2.00–2.19 (m, 8H, 4×CH_2), 7.75 (d, J = 8.0 Hz, 2H, Ar-H), 7.52 (d, J = 8.0 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.0, 26.3, 29.4, 32.3, 33.4, 41.4, 50.3, 109.4, 113.3, 127.8, 128.4, 129.0, 130.3, 132.0, 132.6, 136.5, 139.5, 149.8, 151.4, 194.5; MS (ESI): *m/z* 485 (M+H)$^+$; analysis: calculated for $C_{30}H_{32}N_2O_4$: C, 74.38; H, 6.61; N, 5.78; found: C, 74.31; H, 6.64; N, 5.79.

*2.6.5. 9-(4-Bromophenyl)-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione (**6e**)*

IR (KBr, cm^{-1}): 3042, 2970, 2880, 1644, 1609, 1547, 1378, 1355; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.79 (s, 6H, 2×CH_3), 0.99 (s, 6H, 2×CH_3), 7.14–7.34 (m, 4H, Ar-H), 2.30 (s, 3H, CH_3), 5.21 (s, 1H, CH), 2.02–2.14

(m, 8H, 4×CH_2), 7.78 (d, J = 8.2 Hz, 2H, Ar-H), 7.48 (d, J = 8.2 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.9, 27.0, 29.9, 32.4, 33.9, 40.9, 51.0, 109.5, 113.5, 127.9, 128.5, 129.2, 130.4, 131.8, 132.1, 136.1, 141.4, 150.5, 151.5, 194.4; MS (ESI): m/z 518.9 $(M+H)^+$; analysis: calculated for $C_{30}H_{32}BrNO_2$: C, 69.51; H, 6.18; N, 2.70; found: C, 69.44; H, 6.16; N, 2.72.

2.6.6. 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (**6f**)

IR (KBr, cm^{-1}): 3054, 2977, 2875, 1642, 1617, 1559, 1373, 1344; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.87 (s, 6H, 2×CH_3), 1.01 (s, 6H, 2×CH_3), 7.09–7.21 (m, 4H, Ar-H), 2.34 (s, 3H, CH_3), 5.25 (s, 1H, CH), 2.01–2.29 (m, 8H, 4×CH_2), 7.78 (d, J = 8.1 Hz, 2H, Ar-H), 7.52 (d, J = 8.1 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.1, 26.1, 29.2, 32.7, 33.9, 41.7, 50.4, 108.9, 113.4, 128.4, 128.8, 129.6, 130.4, 132.4, 132.8, 136.3, 139.7, 151.0, 151.9, 194.0; MS (ESI): m/z 474.45 $(M+H)^+$; analysis: calculated for $C_{30}H_{32}ClNO_2$: C, 76.04; H, 6.76; N, 2.96; found: C, 75.94; H, 6.78; N, 2.97.

2.6.7. 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (**6g**)

IR (KBr, cm^{-1}): 3365, 3042, 2956, 2883, 1649, 1616, 1566, 1362, 1345; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.84 (s, 6H, 2×CH_3), 0.96 (s, 6H, 2×CH_3), 7.15–7.24 (m, 4H, Ar-H), 2.33 (s, 3H, CH_3), 5.20 (s, 1H, CH), 2.01–2.18 (m, 8H, 4×CH_2), 7.80 (d, J = 8.0 Hz, 2H, Ar-H), 7.55 (d, J = 8.0 Hz, 2H, Ar-H), 9.63 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.7, 26.5, 29.6, 32.1, 33.3, 41.5, 50.4, 109.3, 112.9, 128.5, 128.9, 129.6, 130.8, 131.9, 132.3, 136.4, 139.4, 150.6, 151.9, 193.9; MS (ESI): m/z 456 $(M+H)^+$; analysis: calculated for $C_{30}H_{33}NO_3$: C, 79.12; H, 7.25; N, 3.08; found: C, 79.00; H, 7.22; N, 3.03.

2.6.8. 9-(4-Methylphenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (**6h**)

IR (KBr, cm^{-1}): 3046, 2964, 2881, 1656, 1612, 1570, 1374, 1340; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.89 (s, 6H, 2×CH_3), 1.03 (s, 6H, 2×CH_3), 7.10–7.28 (m, 4H, Ar-H), 2.42 (s, 3H, CH_3), 5.23 (s, 1H, CH), 2.12–2.24 (m, 8H, 4×CH_2), 7.69 (d, J = 8.4 Hz, 2H, Ar-H), 7.49 (d, J = 8.4 Hz, 2H, Ar-H), 2.19 (s, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.9, 27.3, 29.2, 32.4, 33.5, 40.7, 50.6, 108.8, 114.8, 126.9, 127.9, 129.0, 130.5, 132.4, 132.6, 136.1, 140.1, 150.4, 151.3, 195.4; MS (ESI): m/z 454 $(M+H)^+$; analysis: calculated for $C_{31}H_{35}NO_2$: C, 82.12; H, 7.72; N, 3.09; found: C, 82.05; H, 7.70; N, 3.07.

2.6.9. 9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (**6i**)

IR (KBr, cm^{-1}): 3051, 2973, 2882, 1661, 1609, 1568, 1369, 1351; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.91 (s, 6H, 2×CH_3), 1.00 (s, 6H, 2×CH_3), 7.13–7.33 (m, 4H, Ar-H), 2.28 (s, 3H, CH_3), 5.18 (s, 1H, CH), 2.13–2.27 (m, 8H, 4×CH_2), 7.91 (d, J = 8.2 Hz, 2H, Ar-H), 7.47 (d, J = 8.2 Hz, 2H, Ar-H), 3.58 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.1, 26.2, 29.4, 32.3, 33.5, 41.5, 50.6, 108.7, 114.6, 127.7, 128.7, 129.6, 130.8, 132.3, 132.6, 136.2, 139.4, 151.0, 152.1, 194.9; MS (ESI): m/z 470 $(M+H)^+$; analysis: calculated for $C_{31}H_{35}NO_3$: C, 79.32; H, 7.46; N, 2.98; found: C, 79.30; H, 7.49; N, 2.95.

Table 1
The reaction of arylaldehyde, dimedone, and ammonium acetate: effect of catalysis.[a]

Entry	Catalyst	Amount of catalyst (mol%)	Time (h)	Yield (%)[b]
1	SSA	0.0	4.0	64
2	SSA	0.4	3.0	72
3	SSA	0.6	2.5	83
4	SSA	0.8	1.5	95
5	SSA	1.0	1.0	90
6	SSA	1.2	1.0	82

[a] Reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), and ammonium acetate (1.5 mmol) at 70 °C in water.
[b] Isolated yields.

Table 2
The reaction of arylaldehyde, dimedone, and ammonium acetate: effect of solvent.[a]

Entry	Solvent	Amount of catalyst (mol%)	Time (h)	Yield (%)[b]
1	Acetonitrile	0.8	2.5	60
2	THF	0.8	3.0	45
3	Ethanol	0.8	3.0	72
4	1,4-Dioxane	0.8	4.0	58
5	Methanol	0.8	3.0	58
6	Cyclohexane	0.8	4.0	51
7	Water	0.8	1.5	95

[a] Reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), and ammonium acetate (1.5 mmol) in the presence of SSA (0.8 mol%) at 70 °C in solvent.
[b] Isolated yields.

Table 3
Synthesis of products **4a**–**4l** by the reactions of aromatic aldehydes with dimedone and ammonium acetate.[a]

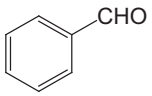
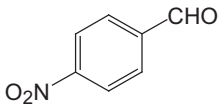
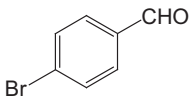
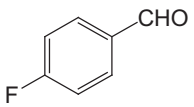
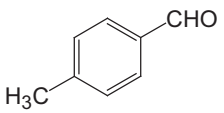
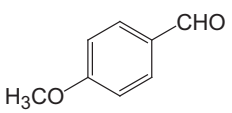
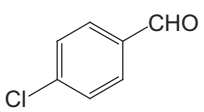
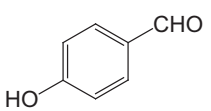
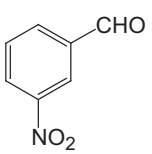
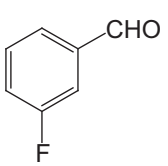
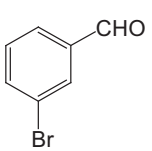
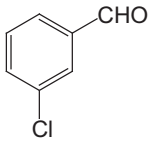
Entry	Aldehyde	Nitrogen source	Product source	Time (h)	Yield (%)[b]	Mp (°C)	
						Found	Reported
1		NH_4OAC	**4a**	1.5	95	276–278	277–278 [28]
2		NH_4OAC	**4b**	2.0	96	260–262	261–262 [21]
3		NH_4OAC	**4c**	2.0	91	233–235	234–235 [21]
4		NH_4OAC	**4d**	2.0	92	274–276	275–276 [21]
5		NH_4OAC	**4e**	3.0	89	>300	>300 [28]
6		NH_4OAC	**4f**	2.0	87	272–274	272–273 [28]
7		NH_4OAC	**4g**	2.0	92	293–295	294–296 [28]
8		NH_4OAC	**4h**	3.0	89	>300	>300 [28]
9		NH_4OAC	**4i**	3.0	95	286–288	287–289 [28]
10		NH_4OAC	**4j**	2.0	94	262–264	–
11		NH_4OAC	**4k**	2.0	93	286–288	288–289 [21]

Table 3 (*Continued*)

Entry	Aldehyde	Nitrogen source	Product source	Time (h)	Yield (%)[b]	Mp (°C)	
						Found	Reported
12		NH_4OAC	**4l**	3.0	94	280–282	281–282 [21]

[a] Reaction conditions: arylaldehydes (1 mmol), dimedone (2 mmol), and ammonium acetate (1.5 mmol) in the presence of SSA (0.8 mol%) at 70 °C in water.
[b] Isolated yield.

*2.6.10. 9-(3-Nitrophenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (**6j**)*

IR (KBr, cm^{-1}): 3032, 2956, 2870, 1663, 1619, 1562, 1372, 1342; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.82 (s, 6H, 2×CH_3), 0.97 (s, 6H, 2×CH_3), 7.11–7.22 (m, 4H, Ar-H), 2.37 (s, 3H, CH_3), 5.17 (s, 1H, CH), 2.07–2.34 (m, 8H, 4×CH_2), 7.80 (d, J = 8.0 Hz, 2H, Ar-H), 7.51 (d, J = 8.0 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.2, 26.9, 29.9, 31.9, 33.9, 40.8, 49.9, 108.9, 113.4, 128.2, 128.7, 129.6, 130.9, 132.2, 132.4, 136.2, 140.5, 151.0, 151.8, 193.9; MS (ESI): *m/z* 485 $(M+H)^+$; analysis: calculated for $C_{30}H_{32}N_2O_4$: C, 74.38; H, 6.61; N, 5.78; found: C, 74.26; H, 6.59; N, 5.74.

3. Results and discussion

The procedure afforded a versatile, environmentally benign, one-pot three-component synthesis of 9-arylacridinediones by the reaction of aromatic aldehydes, dimedone and ammonium acetate under thermal condition in water with silica sulfuric acid as the catalyst (Scheme 1).

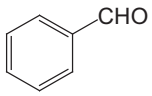
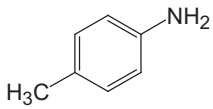
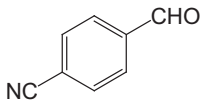
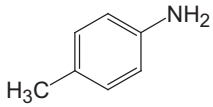
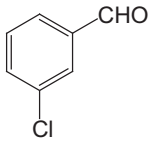
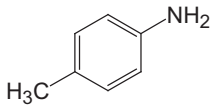
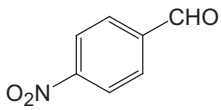
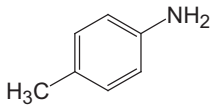
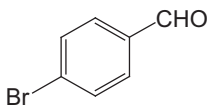
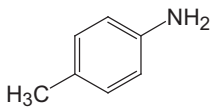
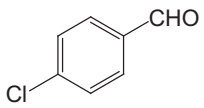
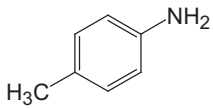
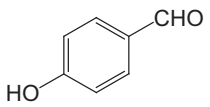
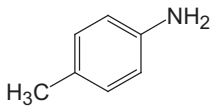
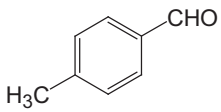
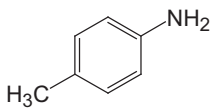
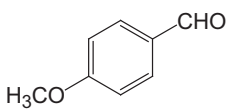
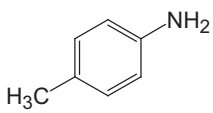
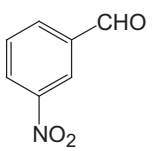
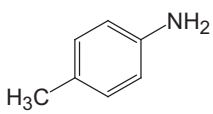
In an initial endeavour, benzaldehyde (1 mmol), dimedone (2 mmol) and ammonium acetate (1.5 mmol) were stirred at 70 °C in water under reflux conditions. After 4 h, only 64% of the expected product **4a** was obtained (Table 1, entry 1). To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of various amounts of silica sulfuric acid under similar conditions. In all reactions, the conditions were optimized for 100% conversion. A significant improvement was observed, the yield of **4a** being increased to 95% (Table 1, entry 4). Use of only 0.8 mol% was sufficient to drive the reaction forwards within 1.5 h. Larger amounts of the catalyst did not improve the results. Although, use of 1.2 mol% silica sulfuric acid permitted the reaction time to be decreased to 1 h, the yield unexpectedly decreased to 82% (Table 1, entry 6).

Various reaction media were screened (acetonitrile, tetrahydrofuran, ethanol, 1,4-dioxane, methanol, cyclohexane and water) in the model reaction (Table 2, entries 1–7). Water (entry 7) was found to be the best medium for the reaction, with 95% product yield, and was therefore used as the solvent for subsequent reactions on the merits of higher yield, green nature and easy work-up. Under the optimized set of reaction conditions, 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 heated at 70 °C for 1.5–3.0 h (Table 3). All the electron-rich and electron-deficient aldehydes gave excellent yields of pure substituted acridinediones **4a**–**4l** (87–95%) (Scheme 1).

We therefore extended the protocol to synthesis of 9-aryl-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione derivatives **6a**–**6j**, using *p*-toluidine as the nitrogen source (Scheme 2). Loading of *p*-toluidine was not excessive because of its low volatility, but its reaction was relatively slow. The reaction of benzaldehyde (1 mmol), dimedone (2 mmol) and *p*-toluidine (1 mmol) afforded only 72% yield of product **6a** at 70 °C for 6 h. To improve the conversion, we increased the temperature to 80 °C and carried out the reaction for 5 h, resulting in **6a** in 88% yield. The reaction times and product yields for the various substrates are summarized in Table 4, which shows that the product yields were generally high. We can therefore assert that the protocol allows practical, environmentally friendly synthesis of these heterocyclic compounds with good applications to various substrates.

The recyclability of the catalyst was investigated in a model reaction. After completion of the reaction, ethanol was added to the mixture, which was then filtered to separate out the catalyst. The catalyst was washed three times with acetone, dried in an oven at 100 °C for 30 min and then tested for activity in four runs. The activity of the recovered catalyst did not decrease significantly even after four runs (Table 5 and Fig. 1).

Table 4
Synthesis of products **6a–6j** by the reactions of aromatic aldehydes with dimedone and *p*-toluidine.[a]

Entry	Aldehyde	Nitrogen source	Product	Time (h)	Yield (%)[b]	Mp (°C)	
						Found	Reported
1			**6a**	5.0	88	263–265	264–266 [28]
2			**6b**	3.0	87	272–274	273–275 [28]
3			**6c**	3.0	85	310–312	309–311 [31]
4			**6d**	3.5	90	>300	>300 [29]
5			**6e**	3.5	88	>300	–
6			**6f**	3.5	85	270–272	271–272 [28]
7			**6g**	3.5	89	>300	>300 [28]
8			**6h**	4.0	87	294–296	294–295 [28]
9			**6i**	4.0	86	286–288	285–287 [28]
10			**6j**	3.0	91	284–286	285–287 [28]

[a] Reaction conditions: arylaldehydes (1 mmol), dimedone (2 mmol), and *p*-toluidine (1 mmol) in the presence of SSA (0.8 mol%) at 80 °C in water.
[b] Isolated yield.

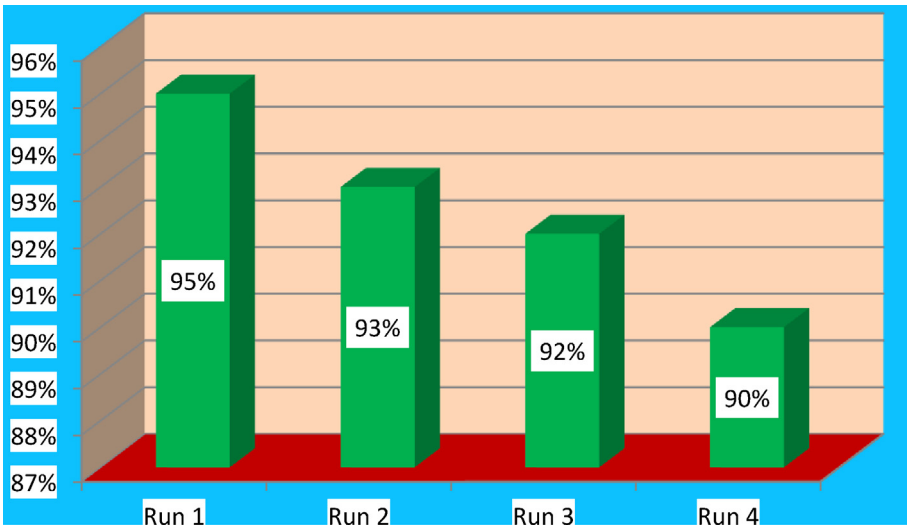


Fig. 1. Recyclability of SSA catalyst on the reaction of benzaldehyde, dimedone and ammonium acetate.

Table 5
The effect of recyclability of SSA catalyst on the reaction of benzaldehyde, dimedone, and ammonium acetate.[a]

Entry	Cycle	Time (h)	Yield (%)[b]
1	0	1.5	95
2	1	1.5	93
3	2	1.5	92
4	3	1.5	90

[a] Reaction conditions: benzaldehyde (1 mmol), dimedone (2 mmol), and ammonium acetate (1.5 mmol) in the presence of SSA (0.8 mol%) at 70 °C in water.
[b] Isolated yield.

4. Conclusions

We have developed a new, easy, efficient method for eco-compatible preparation of substituted acridinediones *via* one-pot three-component condensation of aromatic aldehyde, dimedone and ammonium acetate or *p*-toluidine in an aqueous medium with silica sulfuric acid as an efficient catalyst. The mildness of the conversion, the experimental simplicity, compatibility with various functional groups, excellent product yields and the easy work-up procedure make this approach attractive for synthesizing a variety of such derivatives.

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