**Journal of Chemistry and Chemical Sciences,** *Vol.8(8), 1009-1017, August 2018* *ISSN 2229-760X (Print)*
(An International Research Journal), *www.chemistry-journal.org* *ISSN 2319-7625 (Online)*

# Catalyst Free, Solvent Mediated, Facile and Efficient One-pot Multicomponent Synthesis of Acridin-1,8-diones

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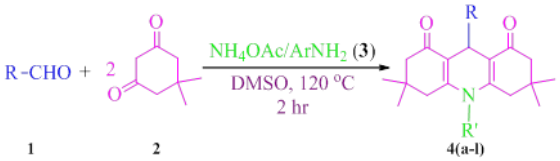
(Received on: July 31, 2018)

## ABSTRACT

A simple, efficient, inexpensive, solvent mediated and novel route to the synthesis of acridin-1,8-diones by a one-pot four-component cyclocondensation of aromatic/hetero-aromatic aldehydes, dimedone and ammonium acetate/substituted anilines is reported. The reaction is carried out by using DMSO as a solvent to get the respective products in excellent yield in short durations.



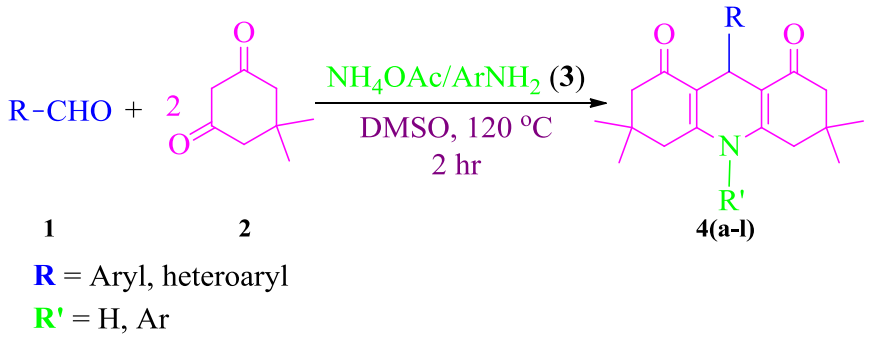

**Keywords:** 9-Aryl-hexahydroacridin-1,8-diones, 9,10-*bis*-aryl-tetrahydroacridin-1,8-diones aromatic/heteroaromatic aldehydes, dimedone, ammonium acetate, DMSO.

## 1. INTRODUCTION

One-pot multicomponent reactions (MCRs) have thoroughly justified their role in the field of modern organic synthesis and in developing large libraries of organic molecules. Multicomponent domino reactions are useful in the total syntheses of natural products and for the synthesis of versatile building blocks of varied reactivity. Thus, the synthesis of highly functionalized complex products using simple reactants has been the scope of one-pot MCRs.[1] Among all, one of the heterocyclic nuclei of present interest is tetrahydroacridin-1,8-dione

owing to its wide biological spectrum and application in various fields, and a number of tetrahydroacridin-1,8-diones are derived from Hantzsch-type condensation. The variants of this heterocycle, such as: quinacrine, acriflavine, proflavine, ethacridine, amsacrine, nitracine and tacrine play a significant role in the medicinal chemistry. Acridinediones exhibit various biological activities such as: antibacterial[2], antiinflammatory[3], antimicrobial[4], antitubercular[5], neuroprotectant[6], and insecticidal activities[7]. A series of acridine derivatives have found application as dyes[8], fluorescent materials for visualization of biomolecules[9], and in laser technology[10]. These derivatives are also commercially in use as calcium channel blockers for the treatment of cardiovascular diseases including hypertension.[11] Generally, one-pot MCRs, have effectively been adapted in the synthesis of tetrahydroacridin-1,8-diones using various catalysts such as: : *p*-sulfonic acid calyx-4-arene[12], acetic acid[13], salicylic acid[14], alkonic acid[15], $K_2CO_3$ [16]; and heterogeneous catalysts such as $ZrO_2$ [17], $TiO_2$ [18], $ZnCl_2$ [19] and $ZnFe_2O_4$ [20]. However, the utility of these protocols and their scope is still limited and are accompanied with one or the other deterrents such as: the use of hazardous reaction conditions, preparation of the catalyst, use of expensive catalysts, prolonged reaction time and insufficient yield. This prompted us to accentuate the need to search for a new efficient synthetic route which is capable of complementing the green principles towards the rapid access of these important molecules under mild reaction conditions.

In pursuit of developing efficient synthetic approaches for the synthesis of acridine-1,8-diones (**4**, **Scheme 1**), we, from our laboratory have reported the use of ceric ammonium nitrate[21], $SiO_2$-I [22] and $CuSO_4{\cdot}5H_2O$ [23] under different reaction conditions; now, herein, we report a one-pot four-component cyclocondensation of aldehyde/hetero-aromatic aldehydes, dimedone and ammonium acetate/substituted anilines in DMSO as shown in the **Scheme 1**.




**Scheme 1: Synthesis of acridin-1,8-diones**

## 2. MATERIAL AND METHODS

All the chemicals are commercially available and were used without further purification, except liquid aldehydes and anilines which were distilled before use. The progress of the reactions was monitored on TLC [analytical silica gel plates (Merck 60 $F_{120}$)]. $^1$H NMR and $^{13}$C NMR spectra were recorded on a 400 MHz and 100 MHz Bruker AMX instruments

respectively in DMSO-$d_6$ and $CDCl_3$ as solvents and TMS as an internal standard. All the products were characterized by $^1$H NMR, $^{13}$C NMR and Mass spectral analysis. Melting points were measured on a Raaga, INDIAN make melting point apparatus. ESI-MS analysis was carried out for all the novel products using ESI-Q TOF instrument.

## 3. General procedure for the synthesis of 9-(aryl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8 (9H,10H)-diones and 9,10-bis-(aryl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8 (9H)-diones:

In a 50 mL round bottom flask, a mixture of 2-hydroxybenzaldehyde (1 mmol), dimedone (2 mmol), ammonium acetate/aniline (1 mmol) was taken and DMSO (2 mL) was added drop wise with stirring at 25 °C. The RBF was then placed on a preheated oil bath and the contents were stirred for about 2 h at 120 °C. After the completion of the reaction [monitored by Thin layer chromatography (TLC) using hexane:ethyl acetate (7:3) as an eluent], the mixture was poured onto crushed ice. The solid thus separated was filtered and dissolved in EtOAc (10 mL) and dried using anhydrous $Na_2SO_4$. The organic layer was then concentrated under vacuum and the residue was purified by recrystallization from EtOAc.

### 3.1. Spectral data of acridine-1,8-diones:

**9-(2'-Hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione (4a)**:
$^1$H NMR (400 MHz, $CDCl_3$): δ 0.99 (6H, s, 2 × $CH_3$), 1.02 (3H, s, $CH_3$), 1.23 (3H, s, $CH_3$) 2.58–2.33 (8H, m, 4 × $CH_2$), 2.62 (1H, s, OH), 4.67 (1H, s, CH), 6.99–7.03 (2H, m, Ar-H), 7.14 (1H, t, J = 6 Hz, Ar-H), 7.17 (1H, t, J = 8 Hz, Ar-H), 9.69 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.2, 31.7, 40.2, 43.1, 51.9, 111.9, 114.2, 121.8, 125.8, 130.0, 134.5, 149.5, 159.1, 198.1 ppm.

**9-(2'-Chlorophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione (4b)**:
$^1$H NMR (400 MHz, $CDCl_3$): δ 1.02 (6H, s, 2 × $CH_3$), 1.12 (6H, s, 2 × $CH_3$), 2.00–1.90 (4H, m, 2 × $CH_2$), 2.62–2.33 (4H, m, 2 × $CH_2$), 5.03 (1H, s, CH), 6.99–7.15 (4H, m, Ar-H), 10.4 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 26.7, 30.6, 33.2, 42.2, 51.2, 110.0, 115.7, 122.1, 122.9, 125.0, 131.4, 149.4, 156.4, 198.0 ppm.

**9-(Thiophen-2'-yl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione (4c)**:
$^1$H NMR (400 MHz, $CDCl_3$): δ 1.04 (6H, s, 2 × $CH_3$), 1.09 (6H, s, 2 × $CH_3$),2.04–2.40 (8H, m, 4 × $CH_2$), 5.47 (1H, s, CH), 6.80–6.98 (3H, m, Ar-H), 10.12 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 26.7, 29.9, 32.3, 41.6, 50.2, 113.8, 122.5, 123.8, 126.8, 130.4, 151.5, 196.1 ppm.

**9-(4'-Nitrophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4d**):
$^1$H NMR (400 MHz, DMSO): δ 0.86 (6H, s, 2 × $CH_3$), 1.00 (6H, s, 2 × $CH_3$), 1.99–2.44 (8H, m, 4 × $CH_2$), 4.69 (1H, s, CH), 6.92 (2H, d, J = 7.2 Hz, Ar-H), 6.52 (2H, d, J = 6.4Hz, Ar-H), δ 9.21 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 24.2, 31.0, 40.2, 43.5, 52.2, 111.9, 115.7, 129.4, 132.0, 149.4, 157.2, 198.3 ppm.

**9-(3',4'-Dimethoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4e**):
$^1$H NMR (400 MHz, DMSO): δ 0.88 (6H, s, 2 × $CH_3$), 1.01 (6H, s, 2 × $CH_3$), 1.98–2. 46 (8H, m, 4 × $CH_2$), 3.63 (3H, s, $OCH_3$), 3.65 (3H, s, $OCH_3$), 4.75 (1H, s, CH), 6.64 (H, s, Ar-H), 6.74 (2H, d, J = 7.2Hz, Ar-H), 9.26 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 26.9, 32.5, 32.9, 40.6, 50.9, 55.6, 55.8, 110.6, 111.7, 113.1, 119.9, 139.62, 147.1, 148.4, 149.4, 196.2 ppm.

**9-(4'-Hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4f**):
$^1$H NMR (400 MHz, $CDCl_3$): δ 0.88 (6H, s, 2 × $CH_3$), 1.00 (6H, s, 2 × $CH_3$), 1.97–2.45 (8H, m, 4 × $CH_2$), 4.73 (1H, s, CH), 6.53 (4H, m, Ar-H), 9.03 (1H, s, OH), 9.24 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 29.7, 31.7, 32.2, 41.6, 50.2, 115.3, 115.7, 129.4, 138.9, 147.6, 157.5, 196.2 ppm.

**9-(4'-chlorophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4g**): $^1$H NMR (400 MHz, $CDCl_3$): δ 0.98 (6H, s, 2 × $CH_3$), 1.06 (6H, s, 2 × $CH_3$), 2.17–2.40 (8H, m, 4 × $CH_2$), 5.62 (1H, s, CH), 7.18–7.38 (4H, m, Ar-H), 11.9 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.2, 30.5, 34.5, 42.2, 51.2, 111.1, 123.1, 123.8, 127.9, 145.0, 149.0, 198.8 ppm.

**10-(4'-Aminophenyl)-9-(4''-hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H)-dione** (**4h**)[†]:
$^1$H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 6H, 2 × $CH_3$), 1.09 (s, 6H, 2 × $CH_3$), 2.05–2.25 (m, 8H, 4 × $CH_2$), 3.72 (s, 1H, OH), 4.66 (s, 1H, CH), 5.94 (s, 2H, $NH_2$), 6.59 (d, J = 8.0 Hz, 2H, Ar-H), 6.76 (d, J = 8Hz, 2H, Ar-H), 7.10 (d, J = 8Hz, 2H, Ar-H), 7.17 (d, J = 8.4Hz, 2H, Ar-H) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): 27.0, 31.0, 32.3, 40.9, 50.8, 115.3, 115.9, 129.4, 133.2, 135.5, 140.2, 155.9, 162.3, 197.2 ppm;
Mass (m/z): $[M]^+$ 456.24.

**9-(4'-Chloro-3'-fluorophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4i**):
$^1$H NMR (400 MHz, $CDCl_3$): δ 1.36 (6H, s, 2 × $CH_3$), 1.60 (6H, s, 2 × $CH_3$), 2.19–2.28 (8H, m, 4 × $CH_2$), 5.28 (1H, s, CH), 7.19 (1H, s, Ar-H), 7.36–7.33 (1H, d, J = 2 Hz, Ar-H), 7.50 (1H, d, J = 2 Hz, Ar-5 H), 10.1 (1H, s, NH) ppm;

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.6, 29.5, 31.4, 41.9, 50.3, 111.4, 116.20, 116.23, 124.6, 128.0, 140.1, 151.4, 169.4, 196.9 ppm.

**9-(3',4',5'-Trimethoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4j**):

$^1$H NMR (400 MHz, $CDCl_3$): δ 1.12 (6H, s, 2 × $CH_3$), 1.24 (6H, s, 2 × $CH_3$), 2.42 – 2.35 (8H, m, 4 × $CH_2$), 3.75 (6H, s, 2 × $OCH_3$), 3.81 (3H, s, $OCH_3$), 5.49 (1H, s, CH), 6.34 (2H, s, Ar-H), 12.0 (1H, s, NH) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.2, 30.1, 39.7, 42.0, 51.1, 56.1, 56.9, 106.1, 111.0, 131.0, 132.0, 149.3, 150.0, 198.0 ppm.

**10-(4'-Aminophenyl)-9-(3'',4''-dimethoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,-tetrahydroacridin-1,8(9H)-dione** (**4k**)[†]:

$^1$H NMR (400 MHz, $CDCl_3$): δ 0.80 (6H, s, 2 × $CH_3$), 0.94 (6H, s, 2 × $CH_3$), 1.87–2.24 (8H, m, 4 × $CH_2$), 3.46 (3H, s, $OCH_3$), 3.48 (3H, s, $OCH_3$), 5.25 (1H, s, CH), 6.66 (s, 2H, $NH_2$), 6.77 (1H, s, Ar-H), 6.93–6.95 (d, J = 8Hz, 2H, Ar-H), 7.02–7.04 (d, J = 7.6 Hz, 2H, Ar-H), 7.28–7.30 (d, 8 Hz, 2H, Ar-H) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 26.7, 29.7, 32.5, 32.9, 40.6, 50.9, 55.6, 55.8, 110.6, 111.7, 113.1, 119.9, 122.9, 136.8, 139.6, 147.1, 148.4, 149.4, 155.1, 196.2 ppm;
Mass (m/z): $[M]^+$ 500.71.

**10-(4'-Aminophenyl)-9-(4''-nitrophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione** (**4l**)[†]:

$^1$H NMR (400 MHz, $CDCl_3$): ): δ 1.01 (6H, s, 2 × $CH_3$), 1.08 (6H, s, 2 × $CH_3$), 1.90–2.23 (8H, m, 4 × $CH_2$), 5.66 (1H, s, CH), 6.76 (s, 2H, $NH_2$), 6.85–6.86 (d, J = 4Hz, 2H, Ar-H), 6.87–6.88 (d, J = 4Hz, 2H, Ar-H), 7.00 –7.02 (d,5.6Hz, 2H, Ar-H) ppm;
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 26.7, 31.7, 32.2, 41.6, 50.2, 113.4, 115.3, 115.7, 128.7, 129.4, 130.4, 138.9, 147.6, 151.0, 157.5, 196.2 ppm;
Mass (m/z): $[M]^{+\cdot}$485.91.

## 4. RESULTS AND DISCUSSION

A model reaction of 2-hydroxybenzaldehyde, dimedone and ammonium acetate was selected under the solvent-free condition and noticed that, the reaction did not proceed to offer the desired product **4a** under solvent-free condition (**Table 1,** entry 1). In order to understand the effect of various solvents, the present reaction was carried out in MeOH, ethanol, water, n-hexane, xylene, $CH_3CN$, THF, DMF and DMSO (entries 2–10). From the results presented in the **Table 1**, it is clear that, in DMSO at 120 °C, the reaction proceeds to afford excellent yield of **4a** (entry **10**); hence, DMSO was selected as a solvent for all our further studies.

**Table 1: Effect of solvent on the synthesis of 9-(2'-Hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroacridin-1,8(9H,10H)-dione (4a).**

| Entry | Solvent[a] | Temperature (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | No solvent | 90 | 4 | ND |
| 2 | MeOH | 40 | 3 | 45 |
| 3 | EtOH | 70 | 3 | 58 |
| 4 | $H_2O$ | 60 | 4 | 50 |
| 5 | Xylene | 120 | 2 | ND |
| 6 | *n*-hexane | 60 | 3 | ND |
| 7 | $CH_3CN$ | 95 | 3 | 30 |
| 8 | THF | 98 | 4 | 30 |
| 9 | DMF | 120 | 3 | 45 |
| 10 | **DMSO** | 120 | 2 | 98 |

[a]2 mL; [b]Isolated yield; ND = Not detected.

The above result prompted us to further optimize the reaction conditions; and screening of different amounts of DMSO was taken up, and it was found that, 2 mL of DMSO gave the maximum yield of the product (**Table 2**, entry 3). Further, increasing the amount of solvent had no significant effect on the rate of the reaction and the yield of the product (entry 4).

**Table 2: Optimization of the amount of the solvent for the synthesis of 4a.**

| Entry | Solvent[a] (mL) | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | 1.0 | 2 | 70 |
| 2 | 1.5 | 2 | 80 |
| 3 | 2.0 | 2 | 98 |
| 4 | 2.5 | 2 | 98 |

[a] DMSO; [b] Isolated yield.

It was also observed that, use of DMSO under different reaction temperatures influenced the rate of the reaction and the yield of the product as shown in the **Table 3**, and 120 °C was found to be most suitable for the reaction (entry 5).

**Table 3: Optimization of the reaction temperature for the synthesis of 4a.**

| Entry | Temperature (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | 28 | 2 | ND |
| 2 | 40 | 2 | ND |
| 3 | 80 | 2 | 40 |
| 4 | 100 | 2 | 75 |
| 5 | 120 | 2 | 98 |
| 6 | 140 | 2 | 90 |

[a]Isolated yield.

Considering the above observations, in order to extend the method for the synthesis of different substituted acridin-1,8-diones, we next selected a series of reactions involving various aromatic and hetero-aromatic aldehydes, dimedone and ammonium acetate/substituted

anilines in DMSO as a solvent and carried out the reaction at 120 °C, and the results of this study are presented in the **Table 4**. From the data present in this Table, it is clear that, the electron donating and electron withdrawing groups present in the aromatic aldehydes did not show any adverse effect on the rate of the reaction and yield of the products; and the products were obtained in excellent yield.

**Table 4: The synthesis of acridinediones (4a–l) using DMSO at 120 °C.**

| Entry | Aldehyde | R' | Product | Time (h) | Yield[a] (%) | Mp °C |
|---|---|---|---|---|---|---|
| 1 | 2-$HOC_6H_4CHO$ | H | **4a** | 2 | 98 | 310–312 |
| 2 | 2-$ClC_6H_4CHO$ | H | **4b** | 2 | 98 | 220–222 |
| 3 | Thiophene-2-CHO | H | **4c** | 2 | 98 | 306–308 |
| 4 | 3,4-Di-$CH_3OC_6H_3CHO$ | H | **4d** | 2 | 97 | 286–288 |
| 5 | 4-$NO_2C_6H_4CHO$ | H | **4e** | 2 | 96 | 355–357 |
| 6 | 4-$HOC_6H_4CHO$ | H | **4f** | 2 | 98 | 361–363 |
| 7 | 4-$ClC_6H_4CHO$ | H | **4g** | 2 | 97 | 220–222 |
| 8 | 4-$HOC_6H_4CHO$ | Ar-$NH_2$ | **4h**[†] | 2 | 95 | 182–185 |
| 9 | 4-Cl,3-$FC_6H_3CHO$ | H | **4i** | 2 | 96 | 254–257 |
| 10 | 3,4,5-tri-$CH_3OC_6H_2CHO$ | H | **4j** | 2 | 98 | 304–306 |
| 11 | 3,4-Di-$CH_3OC_6H_3CHO$ | Ar-$NH_2$ | **4k**[†] | 2 | 96 | 165–168 |
| 12 | 4-$NO_2C_6H_4CHO$ | Ar-$NH_2$ | **4l**[†] | 2 | 96 | 187–190 |

[a]Isolated yield. [†]Novel compound.

## 5. CONCLUSIONS

In conclusion, we have herein, devised a simple, efficient, rapid and economical approach for the synthesis of a series of acridin-1,8-diones by a one-pot four-component reaction of aromatic/hetero-aromatic aldehydes, dimedone and ammonium acetate/substituted anilines. The capable salient features of this strategy are: minimization of waste, simple product isolation which avoids tedious and hazardous column purification steps, it is inexpensive and follows green principles and easy to handle. Use of DMSO as a solvent has proved to be an improvisation over existing methods which provides excellent yield of the products in short time durations.

## 6. ACKNOWLEDGEMENTS

The authors are grateful for the financial assistance by the VGST, Dept. of IT, BT and Science & Technology, Government of Karnataka, INDIA for the CESEM Award Grant No. 24 (2010-2011).

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