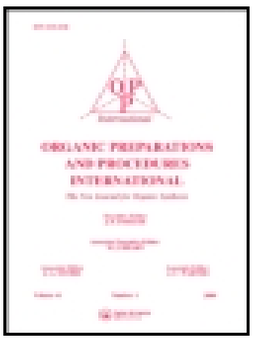

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# A Rapid and Convenient Synthesis of Acridine Derivatives Using Camphor Sulfonic Acid Catalyst

D. S. Bhagat,[1] S. U. Tekale,[1] A. K. Dhas,[1] S. U. Deshmukh,[1] R. P. Pawar,[1] and P. S. Kendrekar[2]

[1]Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, MS, India
[2]Department of Health Sciences, Central University of Technology, Bloemfontein 9300, Free State, South Africa

Acridines were first developed as dyes, and since the early 20$^{th}$ century their varied properties have continued to be of interested. Derivatives of acridine showed good cytotoxic activity against human leukemia cells. They are found to be potent drugs towards metastatic breast cancer cells.[1–2] Acridine can be used in chemosensors,[3] dyes,[4] fluorescent probes,[5–6] anticonvulsant,[7] analgesic,[8] hypertensive,[9] and anti-inflammatory medications[10] and in chiral optical materials.[11] Proflavin has been used as an antibacterial and antifungal agent.[12] Acridines such as quinacrine, pyronaridine and acranil have been used as antimalarial drugs.[13] Acridines have been utilized as single agents or in combination with other antineoplastic drugs in the treatment of acute non-lymphocytic and lymphocytic leukemia,[14,15] and against lung cancer.[16] Acridines inhibit RNA synthesis.[17]

Several catalysts have been used for the synthesis of *N*-substituted 3,3,6,6-tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-dione derivatives (**4**); these include [2-MPyH]OTf,[18] SBA Pr-$SO_3H$,[19] DABCO-PEG ionic liquid,[20] $SiO_2$/$ZnCl_2$,[21] Cu doped nano ZnO,[22] $SiO_2I$,[23] silica bonded N-propyl sulfamic acid,[24] BNBTS,[25] $K_2CO_3$ and $Cu_2Cl_2$.[26] Some of the reported synthetic protocols used expensive reagents, extended reaction times, high reaction temperatures or lengthy work-up procedures. In the present work we describe a fast and green approach for the synthesis of compounds (4) by using camphor sulfonic acid (CSA) (*Scheme 1*).

In search of the best experimental reaction conditions, the reaction of dimedone **1,** benzaldehyde **2** and aniline **3** was considered as a model reaction (*Scheme 1*). The reaction was carried out using CSA and other catalysts as reported in the literature (*Table 1*). The reaction went smoothly and in high yield by using CSA in ethanol (*Table 1*, entry 6). When the reaction was carried out in the absence of catalyst, the product formed in only a trace amount (*Table 2*, entry 1). To optimize the concentration of CSA required to obtain high yields of product in the model reaction, we investigated 2, 4, 6, 8, 10, 12 and 14 mol % catalyst (*Table 2*). Optimal results were obtained with

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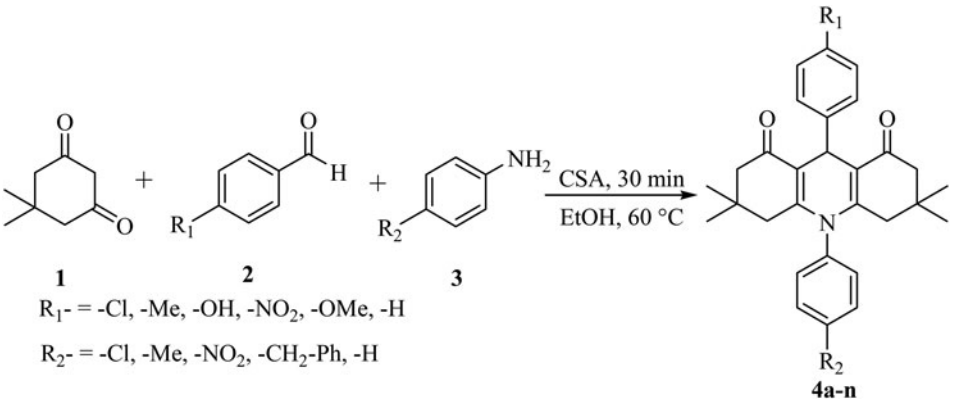
Address correspondence to R. P. Pawar, Department of Chemistry, Deogiri College, Station Road, Aurangabad, 431 005, MS, India. E-mail: rppawar@yahoo.com




**Scheme 1.** Standard model reaction.

**Table 1**
Effect of Catalyst and Solvents

| Entries | Catalysts | Solvent | Time (h/ min) | Temp. (°C) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 | SBA-Pr-$SO_3H$ | – | 5 min | 140 | 69 | 19 |
| 2 | $SiO_2$-I | Ethanol | 2–5 h | 80 | 40–90 | 23 |
| 3 | TEBAC | Water | 10–12 h | 100 | 90 | 28 |
| 4 | $NH_2SO_3H$ | Ethanol | 2 h | 140 | 60–75 | 24 |
| 5 | BNBTS | – | 0.5–2 h | 90 | 80 | 25 |
| 6 | **CSA** | Ethanol | **30 min** | **60** | **90–94** | **Present work** |

**Table 2**
Effect of Concentration of Catalyst

| Entries | Mol % | Solvent | Time (min) | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | No catalyst | Ethanol | 30 | Reflux | Trace |
| 2 | 2 | Ethanol | 30 | Reflux | 30 |
| 3 | 4 | Ethanol | 30 | Reflux | 50 |
| 4 | 6 | Ethanol | 30 | Reflux | 60 |
| 5 | 8 | Ethanol | 30 | Reflux | 80 |
| 6 | **10** | **Ethanol** | **30** | **Reflux** | **90** |
| 7 | 12 | Ethanol | 30 | Reflux | 90 |
| 8 | 14 | Ethanol | 30 | Reflux | 90 |

10 mol % of catalyst (*Table 2*, entry 6). In order to evaluate the effect of solvent, reactions were carried out as listed in *Table 3*. Toluene, acetonitrile, DMF and DCM afforded moderate yields. Methanol and DMSO resulted in good yields; but ethanol furnished the product in 90% yield (*Table 3*, entry 6), making it the most favorable solvent. To explore the scope of the method, different aldehydes and anilines were treated with dimedone in the presence of 10 mol % of CSA using ethanol as a solvent. All the

**Table 3**
Screening of Solvent

| Entries | Solvent | CSA mol % | Time (min) | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| **1** | Toluene | 10 | 30 | Reflux | 60 |
| **2** | Acetonitrile | 10 | 30 | Reflux | 70 |
| **3** | DMF | 10 | 30 | Reflux | 75 |
| **4** | DCM | 10 | 30 | Reflux | 70 |
| **5** | Methanol | 10 | 30 | Reflux | 80 |
| **6** | **Ethanol** | **10** | **30** | **Reflux** | **90** |
| **7** | DMSO | 10 | 30 | Reflux | 78 |

**Table 4**
Synthesis of Acridine Derivatives

| | | | | | MP (°C) | | |
|---|---|---|---|---|---|---|---|
| Entry | Aldehyde ($R_1$) | Amine ($R_2$) | Time (Min.) | Yield (%) | Observed | Reported | Ref. No. |
| **4a** | 4-Cl | 4-Cl | 30 | 90 | 303–305 | 303–305 | 18 |
| **4b** | 4-Cl | 4-Me | 30 | 91 | 273–275 | 273–275 | 18, 27 |
| **4c** | 4-Cl | 4-Me | 30 | 92 | 242–245 | 243–245 | 27 |
| **4d** | 4-$NO_2$ | -H | 30 | 90 | 278–280 | 281–282 | 27 |
| **4e** | 4-OH | 4-Me | 30 | 91 | 284–287 | 347–349 | 18 |
| **4f** | 3-$NO_2$ | 4-Me | 30 | 90 | 280–284 | 279–282 | 27 |
| **4g** | 4-Me | 4-Me | 30 | 93 | 296–298 | 295–297 | 18 |
| **4h** | 4-OH, 3-OMe | 4-Me | 30 | 92 | 272–274 | 273–275 | 18 |
| **4i** | 4-OMe | 3-$NO_2$ | 30 | 90 | 275–277 | 276–278 | 19 |
| **4j** | 4-$NO_2$ | -H | 30 | 90 | 278–280 | 278–280 | 26 |
| **4k** | 3-$NO_2$ | -H | 30 | 93 | 276–278 | 277–279 | 18 |
| **4l** | 4-OMe | -H | 30 | 93 | 217–219 | 222–224 | 18 |
| **4m** | -H | -H | 30 | 90 | 252–254 | 255–257 | 18 |

Reaction conditions: Dimedone (2 mmol), aromatic amine (1 mmol), aldehyde derivatives (1 mmol), CSA catalyst (10 mol %), ethanol solvent (2 mL).

substrates were well tolerated under the optimized conditions, furnishing the product in uniformly high yields. The results are compiled in *Table 4*. Formation of the desired product was confirmed by comparing the melting points with the literature values and by IR, $^{1}$H NMR, $^{13}$C NMR and mass spectroscopic data.

In summary, we have developed a practical approach for the synthesis of compounds **4** *via* the multicomponent reaction of substituted amines, aldehydes and dimedone using CSA catalyst in ethanol. This procedure is rapid and greener than some of the previous methods, in that it avoids the use of more toxic solvents and requires less heating.

## Experimental Section

Chemicals were purchased from SD Fine or Sigma Aldrich and used without further purification. Melting points of the products were recorded on a digital melting point

apparatus (Optics Technology). The reactions were monitored using thin layer chromatography (TLC) in 40% ethyl acetate:n-hexane on silica gel precoated aluminum foil (Merck). FT-IR (KBr) spectra were recorded at room temperature on a Varian Inova spectrometer, and $^1$H NMR spectra in $CDCl_3$ using tetramethylsilane (TMS) as internal standard on a Brucker Vector spectrometer.

## General Procedure for the Synthesis of 3,3,6,6-Tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2*H*,5*H*)-diones (4)

In a round bottom flask were placed cyclohexanedione **1** (2 mmol), an aromatic aldehyde **2** (1 mmol), an aniline **3** (1 mmol) and CSA (10 mol %) in ethanol (2 mL) and the reaction mixture was stirred at 60 °C. The progress of reaction was monitored using TLC. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 15 mL). The organic extract was washed with brine solution (2 × 15 mL) and dried over anhydrous sodium sulfate, then filtered. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were recrystallized from ethanol (*Table 4*).

## Representative Compound Data

***9,10-bis(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-4-chlorophenylacridine-1,8(2H, 5H, 9H, 10H)-dione (4a):*** Off white solid; mp. 303–305 °C. $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 0.74 (s, 6H), 0.89 (s, 6H), 1.95–2.14 (*m*, 8H), 5.15 (*s*, 1H), 7.08–7.15 (m, 5H), 7.20 (s, 1H), 7.46–7.50 (d, 2H). IR ($cm^{-1}$) 2950, 1680, 1577, 1491, 650. MS: 492.14 ($M^+$-1).

***9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-10-p-tolylacridine-1,8(2H, 5H, 9H, 10H-dione (4b):*** Off white solid; mp. 273–275 °C. $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 0.8. (s, 6H), 0.94 (s, 6H), 1.87 (*s*, 1H), 2.03–2.17 (*m*, 7H), 2.49 (*s*, 3H), 5.23 (*s*, 1H), 7.06–7.10 (d, 2H), 7.18–7.23 (m, 2H), 7.33–7.39 (m, 4H). IR ($cm^{-1}$) 2958, 1639, 1574, 1360, 1221, 840; MS: 472.20 ($M^+$-1).

***9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-10-m-tolylacridine-1,8(2H, 5H, 9H, 10H)-dione (4c):*** Yellow solid; mp. 242–245 °C. $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 0.73 (s, 6H), 0.88 (s, 6H), 1.79 (*s*, 1H), 1.96–1.99 (*m*, 2H), 2.05–2.18 (*m*, 5H), 2.41 (**s**, 3H) 5.16 (*s*, 1H), 6.92–6.95 (*m*, 1H), 7.12–7.19 (*m*, 3H), 7.25–7.37 (m, 4H); MS: 472.20 ($M^+$-1).

***3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-nitrophenyl)-10-phenylacridine-1,8(2H, 5H, 9H, 10H)-dione (4k):*** Faint yellow solid; mp. 278–280 °C. $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 0.79 (s, 6H), 0.96–0.99 (*s*, 6H), 2.05–2.33 (*m*, 8H), 5.34 (*s*, 1H), 7.35–7.39 (*d*, 2H), 7.50 (*d*, 1H), 7.58–7.62 (*d*, 2H), 8.05–8.15 (*m*, 3H); MS: 469.28 ($M^+$-1).

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