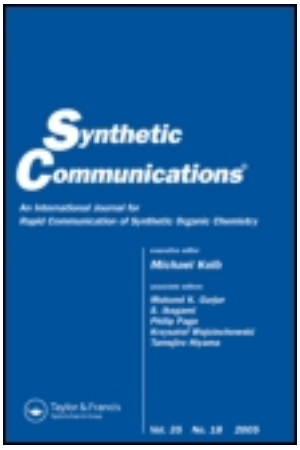

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Proline-Catalyzed Simple and Efficient Synthesis of 1,8-Dioxo-decahydroacridines in Aqueous Ethanol Medium

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Proline-Catalyzed Simple and Efficient Synthesis of 1,8-Dioxo-decahydroacridines in Aqueous Ethanol Medium

K. Venkatesan, Suresh S. Pujari, and Kumar V. Srinivasan
Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, India

Abstract: Proline-catalyzed synthesis of 1,8-dioxo-decahydroacridines is achieved via one-pot, three-component condensation of aromatic aldehydes, cyclic diketone, and aryl amines in aqueous ethanol medium. This method offers the advantages of proceeding in neutral and mild conditions, giving high to excellent yields of acridines with easy workup procedure.

Keywords: Aqueous media, 1,8-dioxodecahydroacridines, one-pot MCR, proline

INTRODUCTION

1,8-Dioxo-9-aryl-10-aryl-decahydroacridines and their derivatives are polyfunctionalized 1,4-dihydropyridine derivatives. In recent years, 1,4-dihydropyridines and their derivatives have attracted strong interest for the treatment of cardiovascular diseases, such as angina pectoris[1] and hypertension.[2] Acridine derivatives have been used to synthesize labeled conjugates with medicinals, peptides, proteins, and nucleic acids[3–5] that exhibit antitumor and DNA-binding properties. Multicomponent reactions (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation because the products are formed in a single step and diversity can be achieved simply by varying the reacting components.[6] Thus, new routes utilizing a MCR protocol for the

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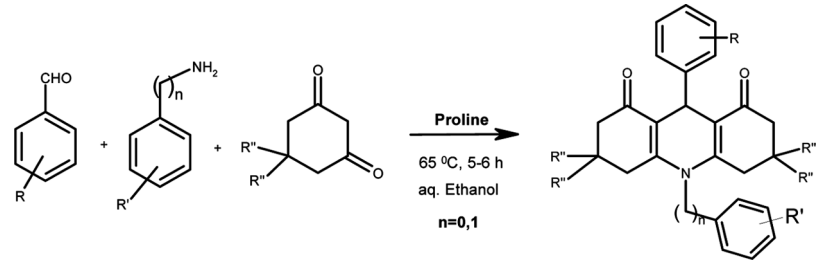
synthesis of these molecules can attract considerable attention in the search for rapid-entry methods to these heterocycles.

The chemical industry is a major contributor to environmental pollution. With increasing regulatory pressure focusing on organic solvents, the development of nonhazardous alternatives is of great importance.[7] Recently, organic reactions conducted in aqueous media have received much attention[8] because water is nontoxic, cheap, abundantly available and benign to the environment. Water not only increased the rate and the yield of reaction but also enhanced enantioselectivity in chiral synthesis.[9] The major drawbacks of using water as a solvent are its poor ability to solubilize organic reactants and unsuitability for use with moisture-sensitive organic compounds and catalysts. One of the more efficient and versatile methods of increasing solubility, and one that does not require modification of the solute, is use of an organic cosolvent. Some of the most commonly used cosolvents are the lower alcohols, dimethyl formamide (DMF), acetone, and acetonitrile. Proline is an abundant bifunctional chiral molecule that is inexpensive and available in both enantiomeric forms. The two functional groups (viz secondary NH and COOH groups) act as acid or base and can also facilitate chemical transformations in concert, similar to enzymatic catalysis.[10]

Reportedly, the conventional synthesis of acridines and their derivatives has been performed in an organic solvent such as HOAc.[11] Recently, few methodologies are reported in the literature for the synthesis of decahydroacridines.[12] Each of these methods have limitations such as poor yields, cumbersome workup procedure, and generation of polluting effluents. Consequently, there is scope for further innovation of methods with milder reaction conditions, short reaction times, increase in variation of the substituents in the components, and better yields in the synthesis of 1,8-dioxodecahydroacridines, which can possibly be achieved by choosing D,L-proline as a catalyst for this MCR. As a part of our ongoing research efforts to develop more efficient and simple methods in heterocycle synthesis, our investigations include synthesis of quinolines,[13] dihydropyrimidones,[14] and trisubstituted triazines.[15] Herein we report for the first time a facile synthesis of 1,8-dioxodecahydroacridines catalyzed by proline in an aqueous ethanolic medium as a step toward a clean and efficient synthesis of acridines (Scheme 1).

To determine the scope of the designed novel protocol, a number of commercially available aldehydes have condensed with cyclic ketones and aryl amines under optimized reaction conditions, and the results are summarized in Table 1. We investigated further the electronic effect of different substituents present on the aldehyde component. We observed that a wide range of aldehydes having both electron-donating and



Scheme 1. Synthesis of decahydroacridine derivatives in aqueous ethanolic medium.

electron-withdrawing groups are equally facile for the reaction, resulting in the formation of decahydroacridine derivatives in very good yields.

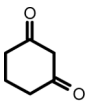
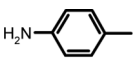
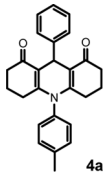
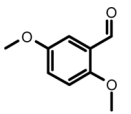
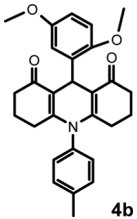
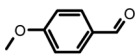
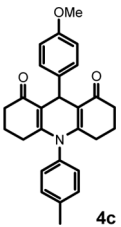
We also observed that various amines such as aniline, *p*-toludine, benzyl amine, and *p*-isopropylaniline reacted smoothly under our conditions. All the known and new compounds were well characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses. For the known compounds, the values were in agreement with those reported in literature. A plausible mechanistic pathway of this MCR is shown in Scheme 2.

In conclusion, commercially available, inexpensive DL-proline has proved to be a useful and novel catalyst for the synthesis of 1,8-dioxodecahydroacridines by the three-component coupling of aldehydes, amines, and cyclic diketone under neutral aqueous alcoholic conditions. The experimental procedure is simple and convenient, and the reaction conditions are amenable to scale-up. This method provides easy access to substituted decahydroacridines with diverse chemical structures. The current methodology has the advantages of operational simplicity, neutral reaction conditions, excellent yields of products, and the absence of toxic effluents.

EXPERIMENTAL

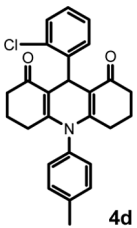
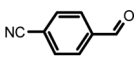
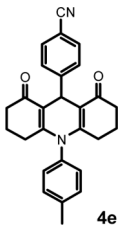
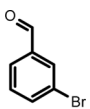
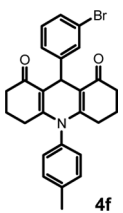
All reactions requiring anhydrous conditions were performed under positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Melting points were recorded in open capillaries using a Büchi melting-point B-540 apparatus. Thin-layer chromatography (TLC) was carried out using aluminum sheets precoated with silica gel $60F_{254}$ (Merck). All chemicals used were reagent grade, procured commercially and used without further purification. ^{1}H NMR

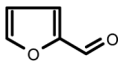
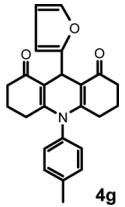
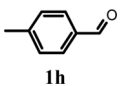
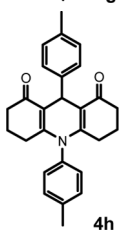
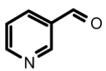
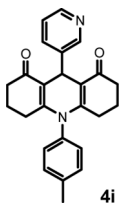
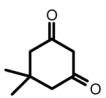
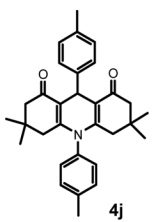
Table 1. Proline-catalyzed one-pot synthesis of 1,8-dioxodecahydroacridine derivatives **4(a–n)**

Entry	Aldehyde 1	Diketone 2	Aryl amine 3	Product 4	Rection time (h)	Yield (%)[a]	MPt (°C)
1	 **1a**	 **2a**	 **3a**	 **4a**	5	83	204–206
2	 **1b**	2a	3a	 **4b**	6	80	236–238
3	 **1c**	2a	3a	 **4c**	6	84	235–238

(*Continued*)

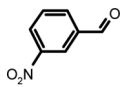
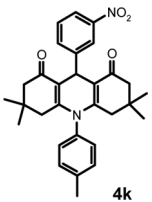
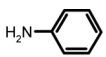
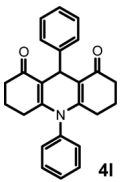
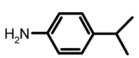
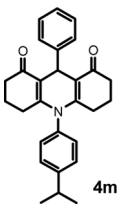
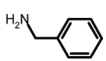
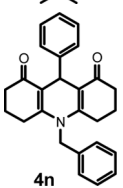
Table 1. Continued

Entry	Aldehyde 1	Diketone 2	Aryl amine 3	Product 4	Rection time (h)	Yield (%)[a]	MPt (°C)
4	 **1d**	2a	3a	 **4d**	5	82	226–229
5	 **1e**	2a	3a	 **4e**	6	79	230–233
6	 **1f**	2a	3a	 **4f**	5	84	208–210

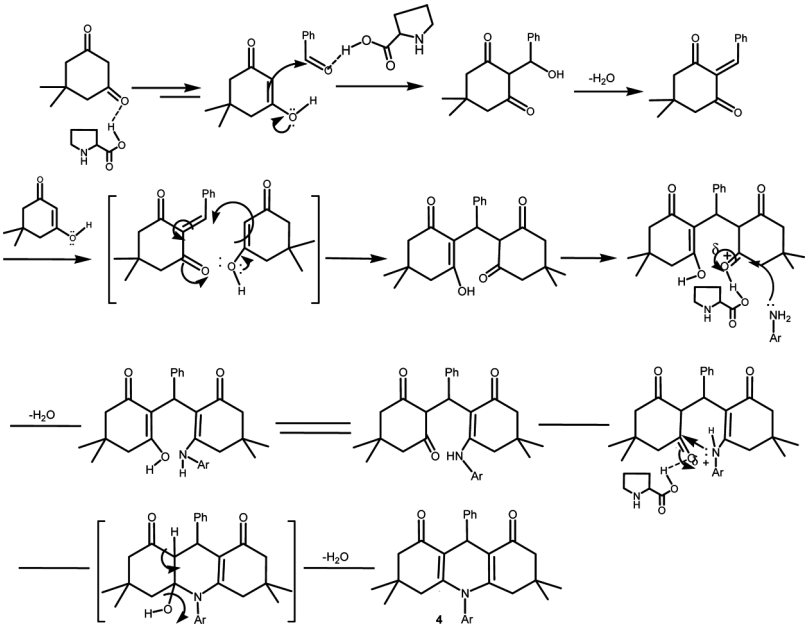
7	 **1g**	2a	3a	 **4g**	6	73	163–168
8	 **1h**	2a	3a	 **4h**	6	83	196–198
9	 **1i**	2a	3a	 **4i**	5	81	214–217
10	1h	 **2b**	3a	 **4j**	6	79	297–299 (lit. 296–297[12c])

(*Continued*)

Table 1. Continued

Entry	Aldehyde 1	Diketone 2	Aryl amine 3	Product 4	Rection time (h)	Yield (%)[a]	MPt (°C)
11	 **1j**	2b	3a	 **4k**	6	80	284–285 (lit 285–286[12c])
12	1a	2a	 **3b**	 **4l**	5	83	246–248
13	1a	2a	 **3c**	 **4m**	6	85	196–198
14	1a	2a	 **3d**	 **4n**	6	88	291–294

[a]Yields reported are after recrystallization.



Scheme 2. Plausible mechanistic pathway of the reaction.

and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 200 spectrometer using TMS as internal standard. Elemental analysis was performed on a Flash EA 1112 Thermo Finnigan instrument.

General Procedure for the Synthesis of 1,8-Dioxo-decahydroacridines (4)

A mixture of aromatic aldehyde **1** (1 mmol), diketone **2** (2 mmol), aromatic amine **3** (1 mmol), and proline (10 mol%) in 15 mL of ethanol containing 3 mL of water was heated at 65 °C for the appropriate time. After completion of the reaction (as indicated by TLC), the volume of the solution was reduced to half, and H_2O (10 mL) was added and stirred for 30 min. The reaction mixture was extracted with ethyl acetate (3×10 mL) and the organic solvent was separated, dried over Na_2SO_4, and concentrated in vacuo to get the product as a residue. The resulting crude product was recystallized from hot ethanol to afford acridines (products) in very good isolated yields. The decahydroacridines thus isolated were homogeneous on TLC and were pure enough for all practical purposes.

Characterization Data

3,4,6,7-Tetrahydro-9-phenyl-10-*p*-tolylacridine-1,8-(2*H*,5*H*,9*H*, 10*H*)dione (**4a**)

Recrystallized from EtOH. Off-white solid. IR ($CHCl_3$, υ): 3012, 2960, 2930, 2874, 1636, 1571, 1510, 1454, 1379, 1363, 1285, 1233, 1182, 1108, 816, 756, 700, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.64–1.83 (m, 4H), 1.99–2.28 (m, 8H), 2.37 (s, 3H), 5.31 (s, 3H), 7.01–7.36 (m, 9H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.9, 21.1, 28.2, 31.9, 36.7, 115.3, 125.8, 127.6, 128.1, 136.2, 139.4, 146.5, 151.8, 196.1. Anal. calcd. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%. Found: C, 81.49; H, 6.51; N, 3.58%.

3,4,6,7-Tetrahydro-9-(2,5-dimethoxyphenyl)-10-*p*-tolylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (**4b**)

Recrystallized from EtOH. Pale yellow-colored solid. IR ($CHCl_3$, υ): 3017, 2952, 2930, 2833, 1635, 1572, 1510, 1454, 1377, 1363, 1236, 1216, 1183, 1108, 1019, 956, 756, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.64–1.77 (m, 4H), 1.97–2.02 (m, 4H), 2.12–2.22 (m, 2H), 2.38 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 5.35 (s, 1H), 6.55–6.61 (m, 1H), 6.70–6.75 (m, 1H), 7.00–7.22 (m, 5H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.2, 28.5, 30.7, 36.7, 55.5, 57.5, 112.1, 113.9, 114.7, 117.1, 135.9, 136.8, 139.2, 151.8, 153.4, 196.0 Anal. calcd. for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16%. Found: C, 75.88; H, 6.52; N, 3.25%.

3,4,6,7-Tetrahydro-9-(4-methoxyphenyl)-10-*p*-tolyl-acridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (**4c**)

Recrystallized from EtOH. Off-white solid. IR ($CHCl_3$, υ): 3015, 2956, 2936, 2873, 1635, 1571, 1509, 1455, 1362, 1287, 1216, 1182, 1108, 1034, 955, 858, 756, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.69–1.81 (m, 4H), 1.98–2.11 (m, 4H), 2.18–2.28 (m, 4H), 2.38 (s, 3H), 3.68 (s, 3H), 5.24 (s, 1H), 6.71 (d, $J = 8.7$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 7.20–7.28 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.1, 28.2, 31.2, 36.7, 55.1, 113.5, 115.6, 128.7, 136.4, 139.1, 139.4, 151.5, 157.7, 196.2. Anal. calcd. for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39%. Found: C, 78.49; H, 6.64; N, 3.47%.

9-(2-Chlorophenyl)-3,4,6,7-tetrahydro-10-*p*-tolyl-acridine-1,8(2*H*,5*H*,9*H*,10*H*)dione (**4d**)

Recrystallized from EtOH. Off-white solid. IR ($CHCl_3$, υ): 3017, 2960, 2930, 2875, 1636, 1567, 1511, 1470, 1361, 1288, 1216, 1183, 1135, 1080, 1034, 1002, 958, 858, 754, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.66–1.75 (m, 4H), 1.93–2.02 (m, 4H), 2.14–2.21 (m, 4H), 2.38 (s, 3H), 5.43 (s, 1H), 6.93–7.27 (m, 8H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.3, 28.5, 35.0, 36.7, 113.4, 126.1, 127.4, 134.0, 136.6, 139.5, 142.3, 152.7, 196.2. Anal. calcd. for $C_{26}H_{24}ClNO_2$: C, 74.72; H, 5.79; Cl, 8.48; N, 3.35%. Found: C, 74.66; H, 5.73; Cl, 8.40; N, 3.41%.

4-(1,2,3,4,5,6,7,8,9,10-Decahydro-1,8-dioxo-10-*p*-tolylacridin-9-yl)-benzonitrile (**4e**)

Recrystallized from EtOH. White solid. IR ($CHCl_3$, υ): 3014, 2950, 2930, 2227, 1637, 1571, 1509, 1452, 1364, 1283, 1216, 1182, 1135, 1073, 1016, 958, 856, 754, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.69–1.81 (m, 4H), 1.99–2.10 (m, 4H), 2.19–2.27 (m, 4H), 2.38 (s, 3H), 5.30 (s, 1H), 7.03 (d, $J = 8.3$ Hz, 2H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.45 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.9, 28.2, 32.9, 36.6, 109.4, 114.3, 128.6, 132.0, 135.9, 139.8, 151.8, 152.4, 195.9. Anal. calcd. for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86%. Found: C, 79.33; H, 5.97; N, 6.80%.

9-(3-Bromophenyl)-3,4,6,7-tetrahydro-10-*p*-tolyl-acridine-1,8(2*H*,5*H*,9*H*,10*H*)dione (**4f**)

Recrystallized from EtOH. Off-white solid. IR ($CHCl_3$, υ): 3015, 2953, 2871, 1636, 1570, 1510, 1455, 1378, 1362, 1287, 1215, 1182, 1135, 1071, 1018, 956, 858, 759, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.85 (m, 4H), 2.00–2.10 (m, 4H), 2.25–2.30 (m, 4H), 2.38 (s, 3H), 5.27 (s, 1H), 7.03–7.08 (m, 3H), 7.15–7.36 (m, 4H), 7.39–7.41 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.0, 28.2, 32.0, 36.6, 114.9, 122.3, 126.8, 136.1, 139.6, 148.8, 152.1, 196.0. Anal. calcd. for $C_{26}H_{24}BrNO_2$: C, 67.54; H, 5.23; Br, 17.28; N, 3.03%. Found: C, 67.49; H, 5.31; Br, 17.17; N, 3.11%.

9-(Furan-2-yl)-3,4,6,7-tetrahydro-10-*p*-tolylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione (**4g**)

Recrystallized from EtOH. Pale yellow-colored solid. IR ($CHCl_3$, υ): 3008, 2949, 2871, 1637, 1572, 1510, 1454, 1359, 1287, 1228, 1181, 1134,

1008, 955, 858, 754, 665 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.69–1.86 (m, 4H), 1.99–2.31 (m, 8H), 2.37 (s, 3H), 5.45 (s, 1H), 6.01 (d, $J = 3.2$ Hz, 1H), 6.15–6.17 (m, 1H), 7.05–7.26 (m, 5H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.9, 25.8, 28.0, 36.6, 104.5, 110.1, 112.1, 136.1, 139.4, 140.7, 152.9, 157.4, 195.9. Anal. calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75%. Found: C, 77.25; H, 6.28; N, 3.69%.

3,4,6,7-Tetrahydro-9,10-di-*p*-tolylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione (**4h**)

Recrystallized from EtOH. Pale yellow-colored solid. IR ($CHCl_3$, υ): 3018, 2953, 2871, 1636, 1572, 1511, 1454, 1428, 1378, 1362, 1286, 1215, 1182, 1135, 1039, 955, 857, 755, 668 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.65–1.89 (m, 4H), 1.98–2.10 (m, 4H), 2.16–2.18 (m, 2H), 2.20 (s, 3H), 2.25–2.30 (m, 2H), 2.37 (s, 3H), 5.26 (s, 1H), 6.96–7.07 (m, 4H), 7.19–7.26 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.0, 28.2, 31.5, 36.7, 115.5, 127.6, 128.9, 135.0, 136.4, 139.4, 143.7, 151.6, 196.1. Anal. calcd. for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52%. Found: C, 81.65; H, 6.79; N, 3.58%.

3,4,6,7-Tetrahydro-9-(pyridin-3-yl)-10-*p*-tolyl-acridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione (**4i**)

Recrystallized from EtOH. Pale yellow-colored solid. IR ($CHCl_3$, υ): 3017, 2959, 2874, 1637, 1574, 1510, 1427, 1379, 1362, 1286, 1182, 1134, 956, 756, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.64–1.87 (m, 4H), 2.00–2.31 (m, 8H), 2.38 (s, 3H), 5.25 (s, 1H), 7.06–7.14 (m, 3H), 7.22–7.28 (m, 2H), 7.77 (d, $J = 7.8$ Hz, 1H), 8.26–8.29 (m, 1H), 8.47 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.9, 28.1, 30.6, 36.5, 114.4, 123.0, 135.9, 136.3, 139.6, 142.0, 146.8, 148.7, 149.3, 152.3, 195.9. Anal. calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29%. Found: C, 78.03; H, 6.20; N, 7.37%.

3,4,6,7-Tetrahydro-9,10-diphenylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)dione (**4l**)

Recrystallized from EtOH. Off-white solid. IR ($CHCl_3$, υ): 3019, 2948, 2890, 1637, 1593, 1569, 1492, 1429, 1363, 1286, 1216, 1135, 1074, 955, 858, 756, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.71–2.28 (m, 12H), 5.32 (s, 1H), 7.03–7.50 (m, 10H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.0, 28.2, 31.9, 36.7, 115.4, 125.9, 127.6, 128.1, 129.3, 138.9, 146.4, 151.6,

196.2. Anal. calcd. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79%. Found: C, 81.35; H, 6.20; N, 3.84%.

3,4,6,7-Tetrahydro-10-(4-isopropylphenyl)-9-phenyl-acridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (**4m**)

Recrystallized from EtOH. Pale yellow-solid. IR ($CHCl_3$, υ): 3010, 2962, 2891, 1635, 1604, 1571, 1508, 1454, 1379, 1364, 1286, 1182, 1135, 1073, 1016, 956, 859, 755, 666 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.26 (s, 3H), 1.71–1.82 (m, 4H), 1.99–2.28 (m, 8H), 2.87–3.00 (m, 1H), 5.31 (s, 1H), 7.04–7.37 (m, 9H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.0, 23.8, 28.2, 31.8, 33.7, 36.7, 115.3, 125.9, 127.6, 128.1, 136.5, 146.5, 150.2, 151.9, 196.1. Anal. calcd. for $C_{28}H_{29}NO_2$: C, 81.72; H, 7.10; N, 3.40%. Found: C, 81.66; H, 7.18; N, 3.49%.

10-Benzyl-3,4,6,7-tetrahydro-9-phenylacridine-1,8-(2*H*,5*H*,9*H*,10*H*) dione (**4n**)

Recrystallized from EtOH. Pale yellow-colored solid. IR ($CHCl_3$, υ): 3017, 2954, 2891, 1630, 1568, 1510, 1454, 1381, 1361, 1281, 1216, 1176, 1052, 956, 859, 756, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.87–2.02 (m, 4H), 2.29–2.35 (m, 4H), 2.52–2.79 (m, 4H), 4.99 (s, 2H), 5.26 (s, 1H), 6.95–6.99 (m, 2H), 7.08–7.16 (m, 4H), 7.30–7.41 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.3, 25.6, 29.7, 35.5, 47.7, 114.8, 124.4, 126.5, 127.6, 128.1, 134.0, 135.9, 142.2, 151.9, 194.8. Anal. calcd. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%. Found: C, 81.34; H, 6.50; N, 3.73%.

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