

Environmentally Friendly and Efficient Synthesis of Various 1,4-Dihydropyridines in Pure Water

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An environmentally friendly and efficient synthesis of a series of 1,4-dihydropyridines was developed by the practical one-pot reactions of aldehydes with ammonium acetate and 1,3-dicarbonyl compounds such as alkyl acetoacetate, 5,5-dimethyl-1,3-cyclohexanedione, 1,3-cyclohexanedione, and 2,4-pentanedione in water without any additives under refluxing conditions.

1,4-Dihydropyridines are analogues of nicotinamide adenine dinucleotide (NADH) coenzymes. 1,4-Dihydropyridines exhibit a wide range of biological activities such as calcium channel blockers,[1] and today they are widely used in pharmacology.[2] Hantzsch esters and acridines are two important NADH models and are useful in organic synthetic chemistry.[3] Hantzsch esters, first reported by Hantzsch in 1882,[4] were typically synthesized by the one-pot condensation of an aldehyde with alkyl acetoacetate and ammonia either in acetic acid or in alcohol.[5] This method usually requires a long reaction time and affords Hantzsch esters in relatively low yield. Improved methods for the Hantzsch ester synthesis have been achieved by the use of autoclave[6] and by microwave irradiation.[7] More recently, ammonia has been replaced by urea,[8] ammonium acetate (NH_4OAc),[8c] and ammonium hydrogencarbonate[8c] in the microwave-assisted solvent-free synthesis of Hantzsch esters. All of these methods employ either autoclave or microwave irradiation, and utilize harmful organic solvents in most cases. A more recent work on the thermal solvent-free synthesis of Hantzsch esters has been reported.[9]

On the other hand, green chemistry as a kind of environmental benign chemistry has attracted intensive attention in recent years. One of the most promising approaches is to utilize water as the reaction medium, which presents a clean, economical, and environmental-safe protocol. In fact, more and more reactions have been reported to proceed smoothly and efficiently in water.[10] Furthermore, due to the low solubility of common organic compounds in water, the use of water as a solvent often makes the purification of products very easy by simple filtration or extraction. With this in mind, we investigated organic reactions in pure water.[11] To the best of our knowledge, there have been no reports on the one-pot synthesis of 1,4-dihydropyridines in pure water without any additives. In this paper, we report the facile and benign one-pot synthesis of Hantzsch esters from the reactions of aldehydes with ethyl acetoacetate and NH_4OAc in refluxing water, and extended to the synthesis of other 1,4-dihydropyridines by replacing ethyl acetoacetate with other 1,3-dicarbonyl compounds, such as methyl acetoacetate, 5,5-dimethyl-1,3-cyclohexanedione, 1,3-cyclohexanedione, and 2,4-pentanedione.

Results and Discussion

Hantzsch esters were synthesized by the one-pot three-component condensation of an aliphatic or aromatic aldehyde **1**, ethyl acetoacetate (**2**), and NH_4OAc (**3**) in refluxing water for a designated time.

The reaction times, yields, as well as the melting points for the Hantzsch reaction with the molar ratio of **1**, **2**, and **3** as 1:4:2 in refluxing water are listed in Table 1. In our protocol, no organic solvents or additives were used during the reaction process. Furthermore, since the product is solid and precipitated out from the reaction mixture, the work-up procedure was just simple filtration. The desired products of high purity were obtained by column chromatography or recrystallization.

From Table 1, one can see that both aliphatic aldehydes and aromatic aldehydes with an electron-withdrawing group or electron-donating group could be employed in the synthesis of Hantzsch esters. The synthesized Hantzsch esters are known compounds, and their identities were confirmed by comparison of their ^{1}H NMR, ^{13}C NMR, IR spectral data, and melting points with those reported in the literature.[5,8a,8c,12] It is notable that in the ^{1}H NMR spectra of **4a**–**4i**, the methine proton at C4 shifted downfield more than 1 ppm from that of 4-alkyl to 4-aryl Hantzsch esters, e.g., 3.82 ppm for **4b** versus 4.96 ppm for **4i**, probably due to the electron-withdrawing effect of the aromatic ring. The IR spectra of **4a**–**4i** displayed similar absorption patterns, thus indicating the same molecular skeleton.

Acridines, which possess the 1,4-dihydropyridine parent nucleus and are the analogues of Hantzsch esters, have similarities in structure to the biologically important NADH coenzymes. Acridines have interesting pharmaceutical properties such as a positive iontropic effect promoting the entry of calcium to the intracellular space,[13] and 1,8-(2*H*,5*H*)-acridinediones are known as laser dyes.[14] 10-Unsubstituted 1,8-(2*H*,5*H*)-acridinediones were synthesized by the adoption of the Hantzsch procedure, i.e., by the thermal reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone, **5**) with an aldehyde and aqueous ammonia in ethanol,[15] or by the microwave-irradiation-assisted solvent-free reaction of dimedone with an aldehyde using NH_4OAc supported on neutral or basic alumina and catalytic

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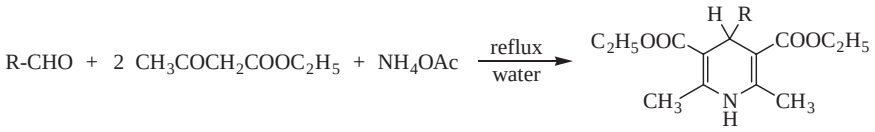
Table 1. Reaction Times, Yields, and Melting Points of Hantzsch Ester **4**

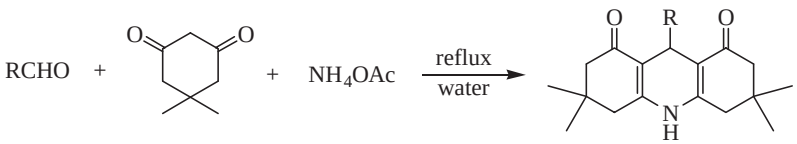


1 **2** **3** **4**

Entry	R	Product	Reaction time/h	Yeld/%[a)]	mp (lit.)/°C
1	H[b)]	**4a**	2	84	183–185 (183–185[12])
2	CH_3[c)]	**4b**	2	74	130–131 (130–131[5])
3	CH_3CH_2	**4c**	2	85	110–111 (111–113[5,12])
4	$CH_3CH_2CH_2$	**4d**	4	96	126–128 (125–127[12])
5	C_6H_5	**4e**	7	54	156–157 (158–160[8a,12])
6	4-NO_2-C_6H_4	**4f**	7	92	128–129 (128–130[8a,12])
7	3-NO_2-C_6H_4	**4g**	7	90	162–163 (162–164[8a,12])
8	4-CH_3O-C_6H_4	**4h**	7	58	158–160 (158–160[12])
9	4-Cl-C_6H_4	**4i**	7	53	144–145 (144–146[8a,12])

a) Isolated yield based on added aldehyde. b) Paraformaldehyde. c) 40% aqueous solution.

Table 2. Reaction Times, Yields, and Melting Points of the 3,4,6,7,9,10-Hexahydro-1,8-(2*H*,5*H*)-acridinediones **6a–6j**



1 **5** **3** **6**

Entry	R	Product	Reaction time/h	Yield/%[a)]	mp (lit.)/°C
1	H[b)]	**6a**	4	96	>300 (317–319[14c])
2	CH_3[c)]	**6b**	4	80	258–260 (256–258[14c])
3	CH_3CH_2	**6c**	4	77	286–288 (282–283[18])
4	$CH_3CH_2CH_2$	**6d**	4	75	287–289 (286–287[18])
5	C_6H_5	**6e**	4	90	272–273 (250–252[14c])
6	3-NO_2-C_6H_4	**6f**	4	95	296–297 (285–286[16])
7	3,4-Cl_2-C_6H_3	**6g**	5	92	>300
8	4-Cl-C_6H_4	**6h**	5	91	297–299 (296–298[17])
9	4-CH_3O-C_6H_4	**6i**	4	95	298–300 (270–272[15])
10	4-CH_3-C_6H_4	**6j**	4	93	>300 (>300[19])

a) Isolated yield based on added aldehyde. b) Paraformaldehyde. c) 40% aqueous solution.

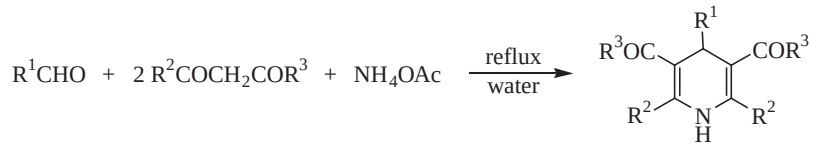
N,*N*-dimethylformamide,[16] or using ammonium hydrogencarbonate.[17] We examined the one-pot thermal synthesis of 1,8-(2*H*,5*H*)-acridinediones in pure water without any additives, and found that both aliphatic aldehydes and aromatic aldehydes with an electron-withdrawing or electron-donating group could be successfully employed.

The reaction times, yields, and melting points of the 3,4,-6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinediones **6a–6j** synthesized in refluxing water with the molar ratio of **1** and **5** as 1:2 are listed in Table 2.

The yields of hexahydroacridinediones for the aromatic aldehydes are higher than those for aliphatic aldehydes, and overall better than the yields of Hantzsch esters, reflecting that dimedone works better than ethyl acetoacetate in the synthesis of 1,4-dihydropyridine derivatives probably due to the higher solubility of dimedone in water and higher reactivity than ethyl acetoacetate. Consistent with this fact, a smaller amount of dimedone was used in these reactions.

Hexahydroacridinediones **6a–6j**, except **6g**, have been reported previously;[14–19] their identities have been confirmed by their ^{1}H NMR, ^{13}C NMR, IR spectral, and analytical data. Again, in the ^{1}H NMR spectra, the methine proton at C9 (5.0–5.2 ppm) of the 9-aryl-substituted hexahydroacridinediones **6e–6j** shifts downfield by about 1 ppm relative to that (4.0–4.1 ppm) of 9-alkyl-substituted hexahydroacridinediones **6b–6d** due to the electronic effect of the aromatic ring. Furthermore, the splitting patterns of the four methylene groups change from an AB quartet and a singlet for **6b–6d** to two AB quartets for **6e–6j**. This phenomenon has not been noted before, and previously these peaks were simply assigned as a multiplet.[15,17–19] Furthermore, unlike the reported wide range of δ_H (6.4–9.4 ppm) for the NH group of hexahydroacridine-

Table 3. Reaction Times, Yields, and Melting Points of the 1,4-Dihydropyridines **8a**–**8i**



1 **7** **3** **8**

Entry	R^1	R^2	R^3	Product	Reaction time/min	Yield/%[a)]	mp (lit.) /°C
1	H[b)]	CH_3	OCH_3	**8a**	40	96	230–231 (231–233[21])
2	$CH_3CH_2CH_2$	CH_3	OCH_3	**8b**	90	80	139–140 (140[22])
3	3-NO_2-C_6H_4	CH_3	OCH_3	**8c**	60	92	210–211 (209–210[23])
4	H	CH_3	CH_3	**8d**	40	96	222–223 (224–225[24])
5	$CH_3CH_2CH_2$	CH_3	CH_3	**8e**	90	81	127–129 (127–132[25])
6	3-NO_2-C_6H_4	CH_3	CH_3	**8f**	60	91	212–214 (211–212[26])
7	H	-$CH_2CH_2CH_2$-		**8g**	40	95	273–275 (270[27])
8	$CH_3CH_2CH_2$	-$CH_2CH_2CH_2$-		**8h**	90	83	221–222 (221–222[28])
9	3-NO_2-C_6H_4	-$CH_2CH_2CH_2$-		**8i**	60	89	282–284 (280–281[29])

a) Isolated yield based on added aldehyde. b) Paraformaldehyde.

diones, **6a**–**6j** exhibited a broad singlet in a much narrower range (5.4–6.1 ppm) for the NH group in our hands. The IR spectra of **6a**–**6j** showed similar absorption patterns, indicating the similar molecular structures.

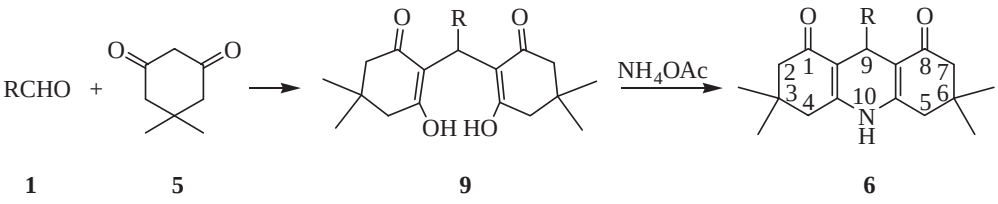
It should be mentioned that the melting points of **6e**, **6f**, and **6i** were obviously higher than those reported in the literature.[14c,15,16] However, our measured ^{13}C NMR spectral data of **6f** and **6i** are the same as the reported data,[15,16] exhibiting the same identities. The different mp might have resulted from the presence of an impurity or solvent because even a trace amount of them would have a great effect on the mp of a compound with high mp, and this phenomenon was confirmed by the mp measurements of authentic samples from another source. Careful literature investigation shows that the assigned **6e** with a mp of 190–192 °C[15,16] has the identical mp of the corresponding ring-opened tetraketone **9e** (vide infra).[14c,20] Furthermore, the reported characteristic δ_H for the C9H group and δ_C for the C=O group of the assumed **6e** are very different from those of other analogues;[15,16] its ^{1}H NMR and ^{13}C NMR spectral data[15] are almost the same as those of the corresponding tetraketone **9e**, except that the peak at 150.2 ppm was replaced by one at 189.4 ppm.[20] Thus, the structure of the assumed **6e**[15,16] should be reassigned as **9e**.

We have attempted to extend the above methods for the synthesis of 1,4-dihydropyridines to other 1,3-dicarbonyl compounds. It was found that methyl acetoacetate, 1,3-cyclohexanedione, and 2,4-pentanedione could also react with aldehydes and ammonium acetate smoothly to afford 1,4-dihydropyridines with excellent yields in refluxing water. Typical aldehydes, i.e., paraformaldehyde, butyraldehyde, and 3-nitrobenzaldehyde, were selected for this study. We also found that the reaction time could be shortened when the dosages of 1,3-dicarbonyl compounds and ammonium acetate were 3 and 4 molar amounts, respectively. The detailed results with the molar ratio of **1**, **7**, and **3** as 1:3:4 are summarized in Table 3.

Compounds **8a**–**8i** are known compounds and their molecular structures have been confirmed by comparison of their spectral data and melting points with those reported in the literature.[21–29]

The reaction process for the mixture of dimedone, aldehyde, and NH_4OAc in refluxing water was followed by ^{1}H NMR, which indicated that the acridinediones **6** were formed via tetraketones **9**. Take the reaction with 3-nitrobenzaldehyde as an example: For a series of the ^{1}H NMR spectra of the reaction mixture, the singlet at 5.54 ppm for the CH group bearing the aromatic ring and the broad peak at 11.89 ppm for the enolized OH group of the corresponding tetraketone **9f** gradually decreased while the peak at 5.17 ppm for the methine proton of C9 and the broad peak at 5.95 ppm for the NH group of the acridinedione **6f** gradually increased as the reaction proceeded. This result indicates that the formation of acridinediones **6** should be through the condensation of the dimedone (**5**) with the aldehyde **1**, followed by the addition of another molecule of **5** to afford the tetraketone **9**, and finally cyclization with NH_4OAc (Scheme 1). The reaction mechanism for other 1,4-dihydropyridines should proceed in the same way.

We have developed a new protocol for the eco-friendly and efficient synthesis of a series of 1,4-dihydropyridines with potential biological activities. This practical synthesis is realized by the one-pot reactions of aldehydes with ammonium acetate



1 **5** **9** **6**

Scheme 1.

and 1,3-dicarbonyl compounds such as alkyl acetoacetate, 5,5-dimethyl-1,3-cyclohexanedione, 1,3-cyclohexanedione, and 2,4-pentanedione in refluxing water. The yields of 1,4-dihydropyridines are generally better than those reported previously. We do not use any organic solvents or additives in the reaction process, and employ water as a cheap and "green" solvent for the reaction medium. The work-up procedure is simple filtration. Therefore, our current process is a more straightforward and environmentally benign protocol and can easily be scaled up for the large-quantity synthesis of various 1,4-dihydropyridines.

Experimental

General. ^{1}H NMR spectra were recorded on a Bruker Avance-300 (300 MHz) spectrometer, and chemical shifts (δ) are reported in parts per million relative to tetramethylsilane and coupling constants (J) in Hz. Splitting patterns are designated as s, singlet; d, doublet; br, broad. ^{13}C NMR spectra were recorded on a Bruker Avance-300 (75 MHz) spectrometer with complete proton decoupling, and chemical shifts are reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm; DMSO-d_6, δ 39.52 ppm). IR spectra were taken on a Bruker Vector-22 spectrometer in KBr pellets and reported in cm^{-1}. Melting points were determined on an XT-4 apparatus (Beijing Tech Instrument Co., China). Analytical TLC and column chromatography were performed on silica gel GF254 and silica gel H60, respectively.

Typical Procedure for the Synthesis of Hantzsch Esters 4. A mixture of **1** (1 mmol), **2** (520.6 mg, 4 mmol), and **3** (154.2 mg, 2 mmol) in 2 mL of water was vigorously stirred at refluxing temperature for a designated time. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled to room temperature, then filtrated and washed with 10 mL of water twice. The treatment of **4e**, **4h**, and **4i** was slightly different. They needed to be washed with 10 mL of petroleum ether to remove unreacted reagents after washing with water. The obtained solid products were nearly pure. The desired products of high purity were further achieved by column chromatography with petroleum ether/ethyl acetate or recrystallization from ethanol.

Typical Procedure for the Synthesis of Acridinediones 6. A mixture of **1** (0.5 mmol), **5** (140.2 mg, 1 mmol), and **3** (77.1 mg, 1 mmol) in 2 mL of water was vigorously stirred under refluxing conditions. During the reaction process, 77.1 mg (1 mmol) of **3** was added per hour. The reaction was completed after 4 h as monitored by TLC. Due to the high yields of **6**, the work-up procedure was just simple filtration and washing with 10 mL of water twice. The obtained solid products were nearly pure. The desired products of high purity were further achieved by column chromatography with petroleum ether/ethyl acetate or recrystallization from ethanol.

3,3,6,6-Tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6a):[14c] IR (KBr) ν 3328, 2957, 2928, 1621, 1488, 1381, 1222, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 12H, CH_3), 2.18 (s, 4H, CH_2), 2.27 (s, 4H, CH_2), 3.12 (s, 2H, CH_2), 5.42 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 18.4, 27.9, 31.9, 39.6, 50.0, 107.3, 150.1, 194.9; Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12%. Found: C, 74.52; H, 8.52; N, 5.09%.

3,3,6,6,9-Pentamethyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6b):[14c] IR (KBr) ν 3446, 3277, 2957, 2926, 1641, 1602, 1486, 1376, 1231, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 6.5 Hz, 3H, CH_3), 1.08 (s, 6H, CH_3), 1.09 (s, 6H, CH_3), 2.15 (d, J = 16.5 Hz, 2H, CH_2), 2.25 (s, 4H, CH_2), 2.31 (d, J = 16.5 Hz, 2H, CH_2), 4.01 (q, J = 6.5 Hz, 1H, CH), 5.66 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.7, 22.7, 27.1, 29.6, 32.8, 41.0, 51.2, 114.3, 149.6, 196.4; Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87%. Found: C, 75.01; H, 8.81; N, 4.82%.

9-Ethyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,-5*H*)-acridinedione (6c):[18] IR (KBr) ν 3441, 3283, 2957, 2927, 1643, 1600, 1485, 1383, 1225, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73 (t, J = 7.5 Hz, 3H, CH_3), 1.10 (s, 6H, CH_3), 1.11 (s, 6H, CH_3), 1.45–1.57 (m, 2H, CH_2), 2.19 (d, J = 16.6 Hz, 2H, CH_2), 2.27 (s, 4H, CH_2), 2.34 (d, J = 16.6 Hz, 2H, CH_2), 4.09 (t, J = 7.4 Hz, 1H, CH), 5.76 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 9.2, 26.5, 26.8, 27.2, 29.3, 31.8, 39.7, 50.4, 110.1, 150.3, 194.6; Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65%. Found: C, 75.52; H, 9.08; N, 4.61%.

3,3,6,6-Tetramethyl-9-propyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6d):[18] IR (KBr) ν 3439, 3277, 2954, 2926, 1641, 1600, 1485, 1383, 1229, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3H, CH_3), 1.11 (s, 12H, CH_3), 1.16–1.28 (m, 2H, CH_2), 1.38–1.45 (m, 2H, CH_2), 2.18 (d, J = 16.6 Hz, 2H, CH_2), 2.27 (s, 4H, CH_2), 2.29 (d, J = 16.6 Hz, 2H, CH_2), 4.09 (t, J = 4.9 Hz, 1H, CH), 5.67 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 14.3, 18.1, 26.1, 26.5, 29.3, 31.9, 37.5, 39.7, 50.4, 110.7, 150.2, 194.6; Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44%. Found: C, 75.98; H, 9.32; N, 4.40%.

3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6e):[14c] IR (KBr) ν 3435, 3283, 2956, 2921, 1639, 1606, 1480, 1368, 1217, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 6H, CH_3), 1.09 (s, 6H, CH_3), 2.16 (d, J = 16.5 Hz, 2H, CH_2), 2.24 (d, J = 16.5 Hz, 2H, CH_2), 2.25 (d, J = 16.4 Hz, 2H, CH_2), 2.39 (d, J = 16.4 Hz, 2H, CH_2), 5.08 (s, 1H, CH), 5.83 (brs, 1H, NH), 7.06 (t, J = 7.2 Hz, 1H, ArH), 7.19 (t, J = 7.5 Hz, 2H, ArH), 7.33 (d, J = 7.1 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.2, 29.7, 32.7, 33.7, 40.6, 51.1, 113.2, 126.1, 128.0, 128.1, 146.8, 149.9, 196.3; Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01%. Found: C, 78.80; H, 7.79; N, 4.08%.

3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6f):[16] IR (KBr) ν 3435, 3270, 3184, 2958, 1647, 1609, 1487, 1364, 1345, 1224, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 6H, CH_3), 1.10 (s, 6H, CH_3), 2.16 (d, J = 16.4 Hz, 2H, CH_2), 2.25 (d, J = 16.4 Hz, 2H, CH_2), 2.36 (d, J = 17.7 Hz, 2H, CH_2), 2.48 (d, J = 17.7 Hz, 2H, CH_2), 5.17 (s, 1H,

CH), 5.95 (brs, 1H, NH), 7.38 (t, $J = 7.9$ Hz, 1H, ArH), 7.89 (d, $J = 7.7$ Hz, 1H, ArH), 7.95 (d, $J = 7.0$ Hz, 1H, ArH), 8.03 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6) δ 26.4, 29.0, 32.1, 33.5, 39.5, 50.0, 110.5, 121.7, 122.0, 129.2, 134.4, 147.3, 149.2, 150.0, 194.4; Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10%. Found: C, 69.86; H, 6.65; N, 7.13%.

9-(3,4-Dichlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6g): IR (KBr) ν 3437, 3178, 2958, 2924, 1647, 1612, 1493, 1366, 1221, 1142 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 6H, CH_3), 1.10 (s, 6H, CH_3), 2.17 (d, $J = 16.4$ Hz, 2H, CH_2), 2.24 (d, $J = 16.4$ Hz, 2H, CH_2), 2.27 (d, $J = 16.6$ Hz, 2H, CH_2), 2.39 (d, $J = 16.6$ Hz, 2H, CH_2), 5.02 (s, 1H, CH), 5.79 (brs, 1H, NH), 7.33 (s, 1H, ArH), 7.35 (d, $J = 7.1$ Hz, 1H, ArH), 7.50 (d, $J = 7.1$ Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6) δ 26.4, 28.9, 32.1, 33.0, 39.5, 50.1, 110.5, 127.9, 128.0, 129.6, 129.9, 130.0, 148.0, 149.8, 194.4. Anal. Calcd for $C_{23}H_{25}Cl_2NO_2$: C, 66.03; H, 6.02; N, 3.35%. Found: C, 65.89; H, 6.07; N, 3.28%.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6h):[17] IR (KBr) ν 3438, 3279, 3175, 3058, 2955, 1650, 1610, 1492, 1366, 1222, 1148 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 6H, CH_3), 1.08 (s, 6H, CH_3), 2.15 (d, $J = 16.4$ Hz, 2H, CH_2), 2.22 (d, $J = 16.6$ Hz, 2H, CH_2), 2.24 (d, $J = 16.4$ Hz, 2H, CH_2), 2.35 (d, $J = 16.6$ Hz, 2H, CH_2), 5.05 (s, 1H, CH), 5.69 (brs, 1H, NH), 7.15 (d, $J = 8.8$ Hz, 2H, ArH), 7.27 (d, $J = 8.8$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.1, 29.7, 32.7, 33.5, 40.6, 51.0, 112.8, 128.2, 129.6, 131.6, 145.4, 150.0, 196.3. Anal. Calcd for $C_{23}H_{26}ClNO_2$: C, 71.96; H, 6.83; N, 3.65%. Found: C, 71.74; H, 6.87; N, 3.59%.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6i):[15] IR (KBr) ν 3434, 3276, 3205, 2958, 1645, 1607, 1483, 1367, 1223, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 6H, CH_3), 1.08 (s, 6H, CH_3), 2.15 (d, $J = 16.5$ Hz, 2H, CH_2), 2.22 (d, $J = 16.6$ Hz, 2H, CH_2), 2.23 (d, $J = 16.5$ Hz, 2H, CH_2), 2.36 (d, $J = 16.6$ Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 5.02 (s, 1H, CH), 6.00 (brs, 1H, NH), 6.73 (d, $J = 8.7$ Hz, 2H, ArH), 7.24 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.2, 29.7, 32.6, 32.9, 40.6, 51.1, 55.1, 113.3, 113.4, 129.0, 139.4, 149.8, 157.8, 196.3. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69%. Found: C, 75.79; H, 7.74; N, 3.64%.

3,3,6,6-Tetramethyl-9-(4-methylphenyl)-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione (6j):[19] IR (KBr) ν 3435, 3278, 3185, 2959, 1650, 1606, 1491, 1366, 1221, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 6H, CH_3), 1.07 (s, 6H, CH_3), 2.15 (d, $J = 16.4$ Hz, 2H, CH_2), 2.22 (d, $J = 16.4$ Hz, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.23 (d, $J = 16.4$ Hz, 2H, CH_2), 2.35 (d, $J = 16.4$ Hz, 2H, CH_2), 5.04 (s, 1H, CH), 6.13 (brs, 1H, NH), 6.98 (d, $J = 7.9$ Hz, 2H, ArH), 7.21 (d, $J = 7.9$ Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.2, 27.2, 29.7, 32.7, 33.3, 40.6, 51.1, 113.2, 128.0, 128.8, 135.3, 144.0, 149.8, 196.2. Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85%. Found: C, 79.09; H, 8.08; N, 3.80%.

Typical Procedure for the Synthesis of Dihydropyridines 8. A mixture of **1** (0.5 mmol), **7** (1.5 mmol), and **3** (154.2 mg, 2 mmol) in 2 mL of water was vigorously stirred under refluxing conditions for a designated time, followed by the additional treatment of simple filtration and washing with 10 mL of water twice. The obtained solid products were nearly pure. The desired products of high purity were further achieved by column chromatography with petroleum ether/ethyl acetate or recrystallization from ethanol.

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