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Synthesis of 1,8-Dioxo-decahydroacridine Derivatives *via* Ru-Catalyzed Acceptorless Dehydrogenative Multicomponent Reaction

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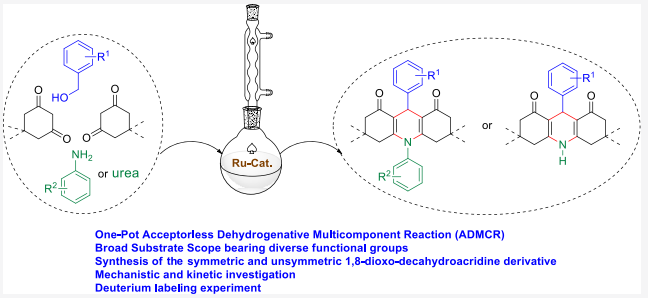
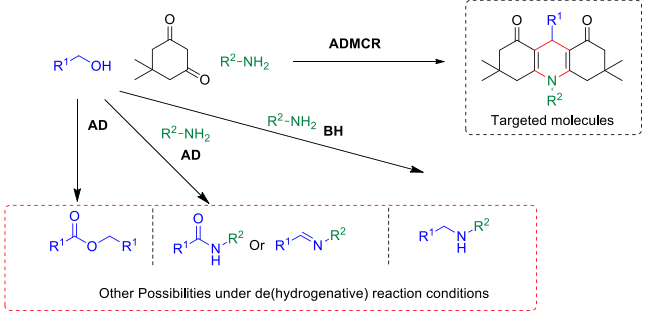
ABSTRACT: A Ru-catalyzed acceptorless dehydrogenative multicomponent reaction has been developed. This reaction offers a cost-effective and simple operational strategy to synthesize biologically active 1,8-dioxodecahydroacridine derivatives. The protocol provides a wide range of substrate scope and various functional groups are also well tolerated under the reaction condition. To shed light on the mechanistic and kinetic study, some controlled experiments and deuterium labeling experiments were executed. A time-dependent product distribution experiment is also presented and the reaction scale-up is performed to highlight the practical utility of this strategy.



INTRODUCTION

Synthesis of structurally important complex organic molecules *via* a green and sustainable approach is a paramount goal in organic chemistry. In this context, multicomponent reactions (MCRs)[1] have received significant attention because of their substantial advantages over the conventional multistep approach. MCRs are considered as green in terms of productivity, energy saving, and step-economy.[2] Therefore, several de novo multicomponent reaction[3] strategies for the synthesis of heterocycles *via* successive formation of C−C and C−heteroatom bonds have been reported.[4] The most challenging task in the MCRs is the fine-tuning of the reaction parameters to synthesize the targeted molecule by suppressing the side product formation. The replacement of toxic as well as waste generating reagents with greener and renewable feedstock is another major aspect of green chemistry.[5] In this regard, alcohols are considered as a greener alternative feedstock as they are obtained from various natural sources especially from biomass.[6] Hence, last decades witnessed an extensive utilization of alcohols in organic synthesis *via* "acceptorless dehydrogenation (AD)"[7] or "borrowing hydrogen (BH)" catalysis.[8] Thus, the synthesis of useful heteroaromatic compounds *via* acceptorless dehydrogenative multicomponent reactions (ADMCRs)[4b,9] is considered as a highly environmentally benign, atom economical, and cost-effective approach. In this context, Beller and co-workers demonstrated a unique ADMCR approach to synthesize pyrroles *via* one-pot three-component (ketones, amines, and 1,2-diols) coupling.[9a,b] Kempe[9c] and Kirchner[9d] independently demonstrated the synthesis of pyrimidines *via* the ADMCR strategy. The group of Milstein[9e] illustrated the synthesis of N-substituted pyrroles *via* one-pot synthesis of pyrroles followed by N-alkylation. Recently, we[9f] and other groups[9g,h] have described the one-pot synthesis of 2-aminoquinoline and its successive N-alkylation with alcohols. 1,8-Dioxodecahydroacridines are known for their wide spectrum of biological activities such as antitumor,[10a] anticancer,[10b] cytotoxic,[10c] antifungal,[10d] antimicrobial,[10e] antimalarial,[10f] and GCN5 inhibitor.[10g] Thus, we envisioned that the synthesis of 1,8-dioxodecahydroacridines directly from alcohols *via* the ADMCR approach (Scheme 1) would be advantageous over the conventional approach.[11]

Scheme 1. Schematic Representation of the ADMCR



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RESULT AND DISCUSSION

Thus, to find out the scope of the ADMCR approach toward the four-component synthesis of 1,8-dioxo-decahydroacridine, various reaction parameters were screened taking Ru-pincer complexes[12] as catalysts (Figure 1). In our initial experiment,

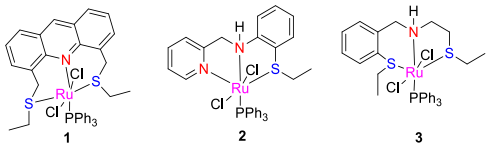
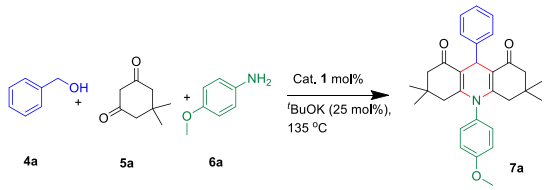


Figure 1. Ruthenium pincer complexes.

dimedone, benzyl alcohol, and 4-methoxyaniline were taken as model substrates. When dimedone (1 mmol, 2 equiv), benzyl alcohol (1.5 mmol, 3 equiv), and 4-methoxyaniline (0.5 mmol, 1 equiv) were heated at 135 °C in ^{t}amylalcohol for 36 h under argon in the presence of 1 mol % catalyst **1** and 25 mol % ^{t}BuOK, 15% 10-(4-methoxyphenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**7a**) was obtained (Table 1, entry 1). In toluene, the yield was not improved further (Table 1, entry 2). Interestingly, under neat conditions, the yield of **7a** was increased to 50% (Table 1, entry 3). Further enhancement of the yield of **7a** was observed when the alcohol concentration was increased to 3 mmol (6 equiv with respect to aniline), which gave **7a** in 75% yield after 36 h (Table 1, entry 5). Increase of reaction time to 48 h or the alcohol concentration did not enhance the product yield (Table 1, entries 6 and 7). Bases like ^{t}BuONa, KOH, and K_2CO_3 gave a moderate yield compared to ^{t}BuOK (Table 1, entries 8−10). The reaction at 110 °C keeping other reaction conditions same, furnishes a lower yield (68%) (Table 1, entry 11). Cat **2** and cat **3** gave inferior results under the similar condition.

Next, we looked for the scope and limitations of our developed protocol. To demonstrate the practical applicability, various alcohols, amines, and 1,3-diketones were investigated. The reaction of dimedone and aniline with alcohols containing electron-donating or electron-withdrawing functional groups at various positions efficiently produced the corresponding acridine-1,8-diones derivatives (**7a−h**) (Scheme 2) in good to excellent yield (70−77%). Piperonyl alcohol was responded well under this reaction condition and gave a good yield, 68%, of the desired product (**7h**). Next, anilines with different electron-donating or electron-withdrawing functional groups were reacted with various alcohols. Reaction with *p*-anisidine, *p*-toluidine, and 4-bromoaniline afforded a good yield of **7i−l**. To our delight, using a heteroaromatic alcohol such as 2-thiophene methanol as the substrate, compound **7m** was isolated in 61% yield. Compound **7n** has antimicrobial properties,[13] which can be easily prepared by this methodology with a good yield (66%). 2-Pyridine methanol and 2-aminopyridine also under the optimized reaction condition gave the desired product **7o** and **7p** in good to moderate yields. The sensitive functional group like cyano (−CN) was also well survived under the reaction condition and afforded a good yield of the desired product **7r−s**. When methyl 4-aminobenzoate was reacted with dimedone and alcohol, the expected product **7t** was not observed, instead **7u** was formed *via* transesterification.[14] Not only the aniline derivative but also benzylamine reacted smoothly to give the corresponding product **7v** in good yield, 70%. **7v** can be easily converted to the corresponding NH-heterocycle *via* debenzylation. Of note, good selectivity existed between amine and amide functionality, and when the reaction was carried out with 4-aminobenzamide exclusively, the product **7w** was isolated. Unfortunately, ethanol and secondary alcohol were not proficient of producing the desired product (**7x−z**) in this protocol. Other 1,3-diketones

Table 1. Optimization of the Reaction Conditions for the Synthesis of Hexahydroacridine-1,8-Dione[a]



entry	4a (mmol)	5a(mmol)	6a (mmol)	time (h)	solvent (mL)	base	7a[b]
1	1.5	1	0.5	36	^{t}amyl alcohol	^{t}BuOK	15
2	1.5	1	0.5	36	toluene	^{t}BuOK	13
3	1.5	1	0.5	36	neat	^{t}BuOK	50
4	3	1	0.5	24	neat	^{t}BuOK	60
5	3	1	0.5	36	neat	^{t}BuOK	75
6	3	1	0.5	48	neat	^{t}BuOK	76
7	5	1	0.5	36	neat	^{t}BuOK	74
8	3	1	0.5	36	neat	^{t}BuONa	35
9	3	1	0.5	36	neat	KOH	33
10	3	1	0.5	36	neat	K_2CO_3	20
11[c]	3	1	0.5	36	neat	^{t}BuOK	68
12[d]	3	1	0.5	36	neat	^{t}BuOK	50
13[e]	3	1	0.5	36	neat	^{t}BuOK	30
14[f]	3	1	0.5	36	neat	^{t}BuOK	35

[a]Reaction Condition: **4a** (1.5−3.0 mmol), **5a** (1 mmol), **6a** (0.5 mmol), ^{t}BuOK (25 mol %), Cat **1** (1 mol %), 135 °C. [b]Isolated yield. [c]110 °C. [d]Cat **1** (0.5 mol %). [e]Cat **2**. [f]Cat **3**.

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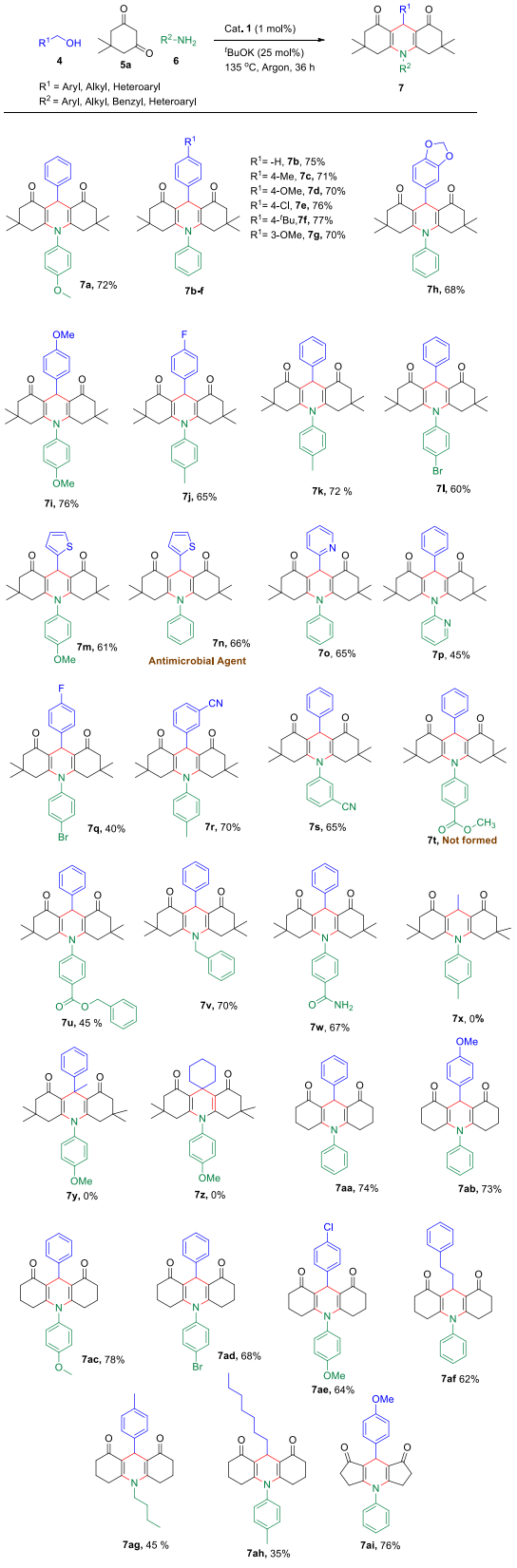
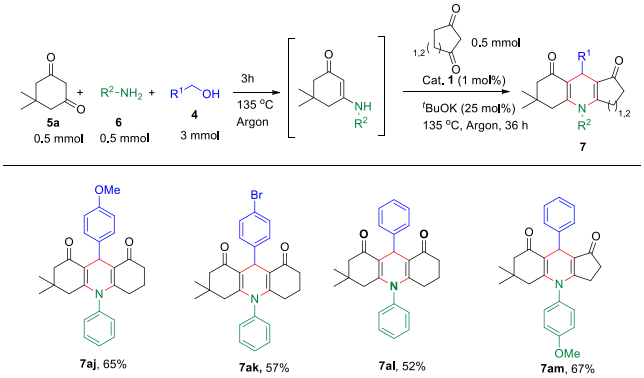
Scheme 2. Substrate Scope for ADMCRs to Synthesize N-Substituted Acridine-1,8-Dione Derivatives[a]



[a]Reaction Condition: **4** (3.0 mmol, 6 equiv), **5a** (1 mmol, 2 equiv), **6** (0.5 mmol, 1 equiv), ^{t}BuOK (25 mol %), **Cat 1** (1 mol %), 135 °C, 36 h, argon.

like cyclohexane-1,3-dione and cyclopentane-1,3-dione also responded well (**7aa**−**7ai**). When cinnamyl alcohol was reacted with cyclohexane-1,3-dione and aniline, the hydrogenated product **7af** was isolated. Unfortunately, when acyclic diketones like acetylacetone and ethyl acetoacetate were taken as substrates, the desired heterocycle was not formed. In most cases, the known 1,8-dioxo-decahydroacridine derivatives are symmetrical. Therefore, we have tried to synthesize the unsymmetrical 1,8-dioxo-decahydroacridine derivative using our methodology. With little modification in our methodology, we are able to synthesize the unsymmetrical 1,8-dioxo-decahydroacridine derivatives (**7aj**−**am**) and afforded a good yield (52−67%) (Scheme 3).

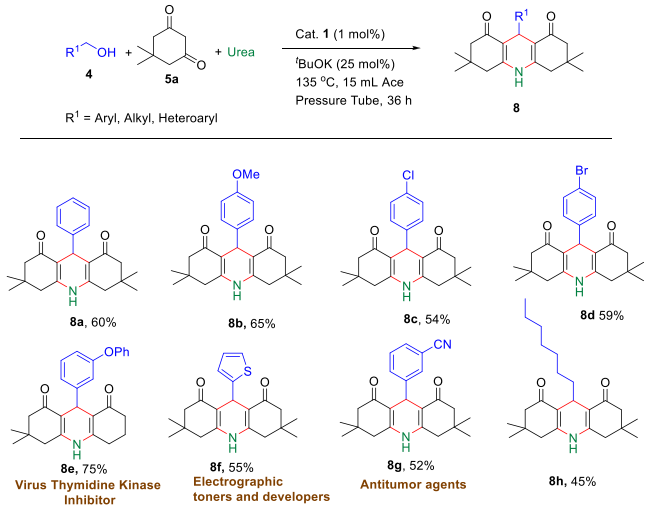
Scheme 3. Substrate Scope for ADMCRs to Synthesize Unsymmetrical 1,8-Dioxo-Decahydroacridine Derivatives[a]



[a]Reaction Condition: 1,3-dione (0.5 mmol), **6** (0.5 mmol), and **4** (3.0 mmol) stirred at 135 °C for 3 h. After that added another 1,3-dione (0.5 mmol), ^{t}BuOK (25 mol %), and **Cat 1** (1 mol %), 135 °C, 36 h, argon.

Next, we choose urea as the nitrogen source instead of aniline to synthesize NH-acridine-1,8-dione derivatives (Scheme 4). An important compound **8e**, which is used to

Scheme 4. Substrate Scope for ADMCRs to Synthesize Acridine-1,8-Dione Derivatives with Urea Source[a]



[a]Reaction Condition: **4** (3.0 mmol), **5a** (1 mmol), urea (60 mg, 1 mmol), ^{t}BuOK (25 mol %), **Cat 1** (1 mol %), 135 °C, 15 mL Ace pressure tube.

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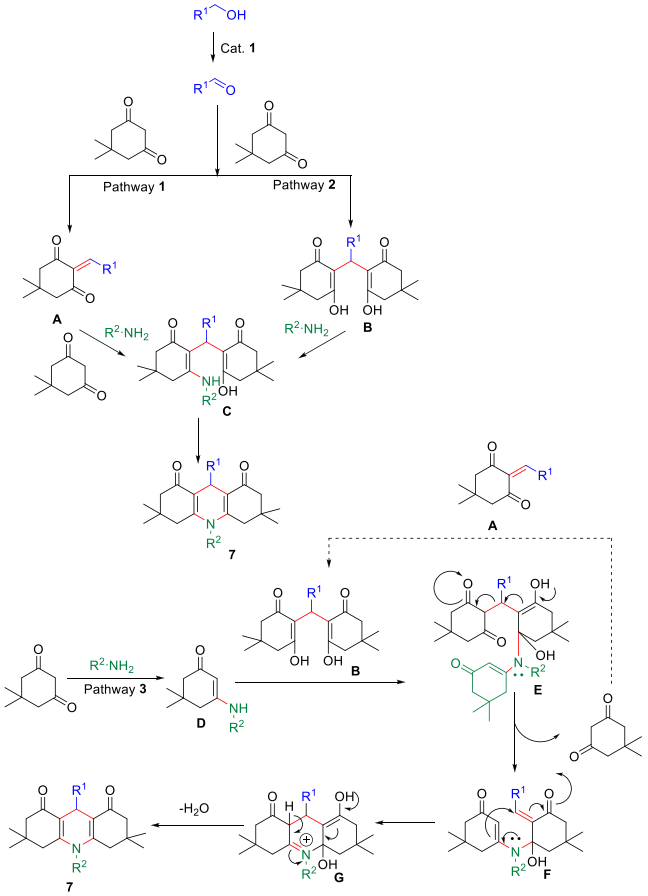
treat infections caused by herpes simplex virus[15a] was easily prepared in a good yield (75%). **8f** was isolated in 55% yield using heteroaromatic alcohol such as 2-thiophene methanol as the substrate. Of note, compound **8f** is used in electrostatographic toners and developers.[15b] Our method also provides a route to synthesize compound **8g**, which is known to have antitumor activity.[15c] However, aliphatic alcohols such 1-octanol delivered the desired **8h** in 45% yield.

Next, we proposed the mechanism of this ADMCR, which is depicted in Scheme 5. Two possible mechanistic pathways

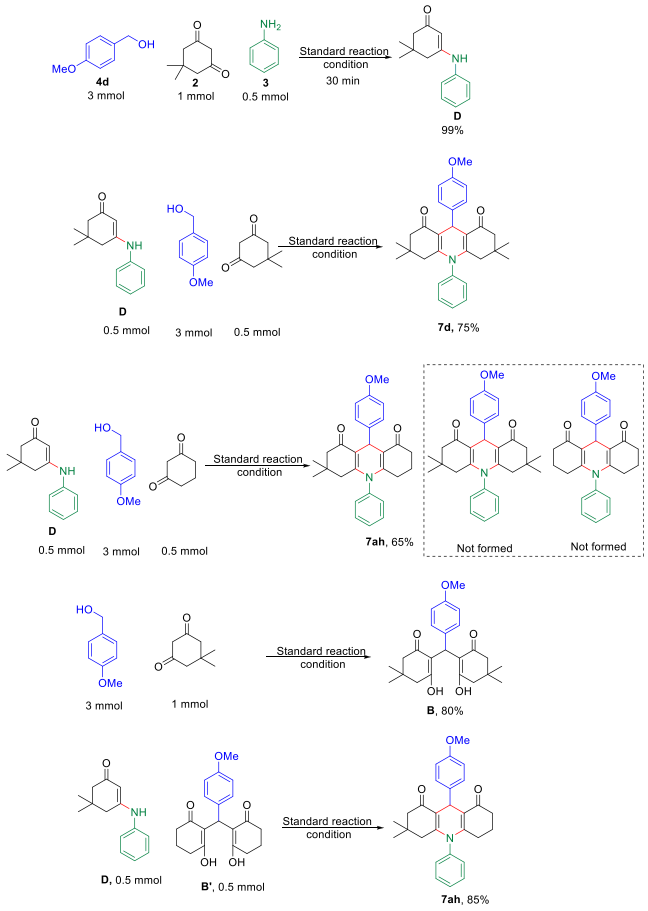
Scheme 5. Propose Mechanism



have been proposed. Alcohol can be dehydrogenated by the Ru-catalyst and the formed aldehyde reacts with dimedone and form Knoevenagel adducts **A** or intermediate **B**, which can generate desired product **7** by reacting with aniline. Another possibility is the quick formation of β-enaminone **D**, which can react with intermediate **B** to furnish the desired product **7**.

To prove the favorable pathway, some controlled experiments have been conducted (Scheme 6). When the reaction of aniline, dimedone, and 4-methoxybenzyl alcohol was stopped after 30 min, we got β-enaminone **D** in a quantitative yield which discarded the possible pathway **1** and **2**. The reaction of intermediate **D**, with 4-methoxybenzylalcohol and dimedone afforded the desired product **7d** with 75% isolated yield. This proves that β-enaminone is one of the intermediates in this reaction mixture. The same reaction with 1,3-cyclohexanedione afforded the desired product **7ah** with 65% isolated yield, which indicates that the β-enaminone formation is not reversible in nature. Intermediate **B** was easily

Scheme 6. Control Experiments



formed (80%) by reacting dimedone with 4-methoxybenzylalcohol under the reaction. When β-enaminone **D** was reacted with intermediate **B'** under standard reaction conditions, the desired product **7ah** was isolated in 85% yield. This indicates that pathway **3** is the most possible route of this ADMCR process.

Next, we have studied the time-dependent product distribution of the ADMCR of dimedone, aniline, and 4-methoxybenzylalcohol (Figure 2). During the study of the kinetic profile of this reaction, it was observed that the reaction between dimedone and aniline is much faster

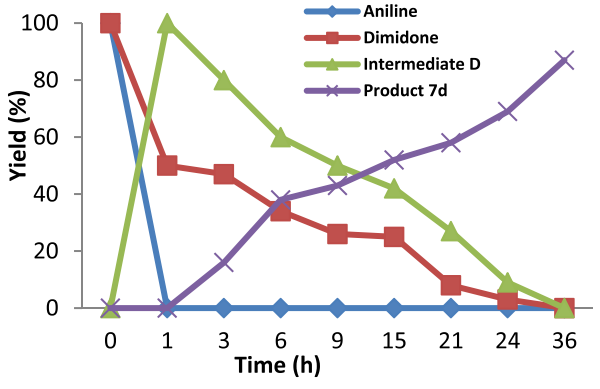


Figure 2. Kinetic profile of the ADMCR between 4-methoxybenzyl alcohol, dimedone, and aniline. (The yield of the product was determined by NMR using CH_3CN as the internal standard).

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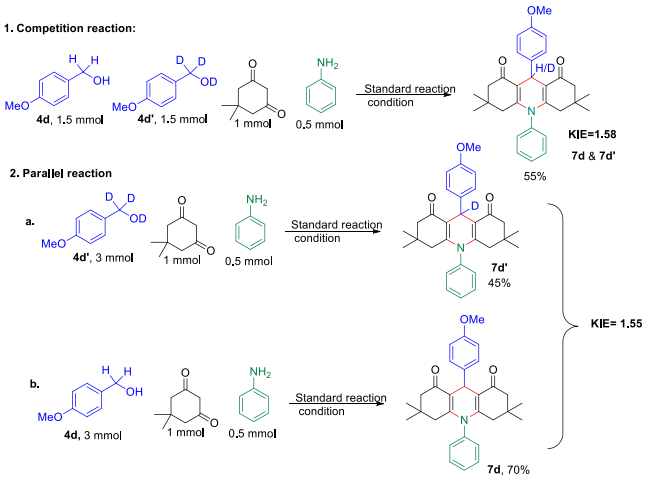
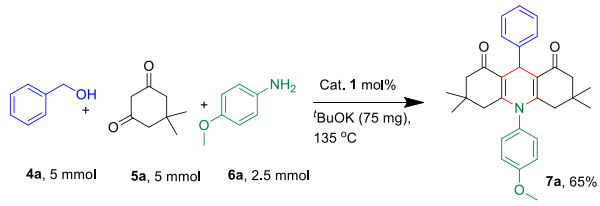
compared to the dehydrogenative conversion[12] of alcohol to aldehyde. First, 0.5 mmol dimedone was consumed by 0.5 mmol aniline to form **D** within 1 h. After 6 h, almost 40% product **7d** formation was observed and then the concentration of **7d** was gradually increased with time. During the kinetic study we have observed the aldehyde formation. At any point of time the concentration of the formed aldehyde was very less in the reaction mixture, which underpins the rapid consumption of the formed aldehyde by dimedone to form **B** that eventually transforms to the final product.

In order to gain insight, kinetic isotope experiments (KIE) were carried out (Scheme 7). First, a mixture of **4d**/**4d'** (1:1, v:v) was used in a competitive experiment. The observed product ratio of the deuterated (**7d'**) and nondeuterated products (**7d**) was determined by ^{1}H NMR, which indicates the KIE value ∼1.58. Furthermore, the parallel reaction with **4d** and **4d'** afforded the nondeuterated and deuterated product in 70% and 45% yield, respectively. The calculated k_H/k_D value (∼1.55) is in close agreement with result from the competitive reaction. This is indicative of the involvement of the C−H bond cleavage in the rate-determining step. To demonstrate the utility of this reaction the reaction was also scaled up to afford **7a** (0.690 g) in 65% yield (Scheme 8).

Scheme 7. Labeling Experiments



Scheme 8. Gram Scale Synthesis



CONCLUSIONS

In conclusion, we have developed ADMCR to synthesize 1,8-dioxo-decahydroacridine derivatives. A broad range of alcohols and amines bearing diverse functional groups were tolerated. The synthesis of various biologically important medicinal compounds was also demonstrated. In addition, mechanistic and kinetic studies were executed to understand the reaction sequences to achieve the targeted product. The slow dehydrogenation of alcohol is the key factor which controls the reaction path. This indicates involvement of the β-enaminone intermediate in the process. The deuterium labeling experiment underpins involvement of the α-C−H bond cleavage of the alcohol in the rate-determining step.

EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, all chemicals were purchase from common commercial sources and used as-received. $RuCl_2(PPh_3)_3$ was purchased from Sigma-Aldrich. All solvents were dried by the standard procedure.[16] Catalyst preparation was carried out under an argon atmosphere with freshly distilled dry THF or dichloromethane. All catalytic reactions were carried out under an argon atmosphere using dry glassware and standard syringe/septa techniques. DRX-400 Varian and Bruker Avance III 600 and 400 spectrometers were used to record ^{1}H, ^{13}C{^{1}H} NMR, and ^{31}P NMR, respectively. Chemical shifts (δ) are reported in the ppm downfield from tetramethylsilane; spin−spin coupling constants (J) are expressed in Hz and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, and br s = broad singlet. Column chromatography was done with SRL silica gel 100−200 mesh. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F_{254}) that were visualized by exposure to ultraviolet light and an aqueous solution of *p*-anisaldehyde.

General Procedure for the Preparation of 1,8-Dioxo-Decahydroacridine Derivatives. Alcohol (3 mmol), dimedone (1.0 mmol), aniline (0.5 mmol), ^{t}BuOK (25 mol %), and complex **1** (1 mol %) were placed in a round-bottom flask under an argon atmosphere and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After this, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (hexane:ethylacetate = 50:50) on silica gel to afford the desired product.

General Procedure for the Preparation of Unsymmetrical 1,8-Dioxo-Decahydroacridine Derivatives. Dimedone (0.5 mmol), aniline (0.5 mmol), and alcohol (3 mmol) were heated at 135 °C in a two-necked round-bottom flask under an argon atmosphere for 3 h. After cooling to room temperature, 1,3-diketone (0.5 mmol), ^{t}BuOK (25 mol %), and complex **1** (1 mol %) were added to it and heated at the same temperature for 36 h. After this, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (hexane:ethylacetate = 50:50) on silica gel to afford the desired product.

General Procedure for the Preparation of 1,8-Dioxo-Decahydroacridine Derivatives Using Urea. Alcohol (3 mmol), dimedone (1.0 mmol), aniline (0.5 mmol), ^{t}BuOK (25 mol %), and complex **1** (1 mol %) were placed in a 15 mL Ace pressure tube under an argon atmosphere. The tube was sealed with a screw cap and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After this, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3) on silica gel to afford the desired product.

Kinetic Isotope Study. *Competition Reaction.* 4-Methoxybenzyl alcohol (1.5 mmol), deuterated 4-methoxybenzyl alcohol, (1.5 mmol), dimedone (1.0 mmol), aniline (0.5 mmol), ^{t}BuOK (25 mol %), and complex **1** (1 mol %) were placed in a round-bottom flask under an argon atmosphere and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After this, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was

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purified by column chromatography (hexane:ethylacetate = 50:50) on silica gel to afford a mixture of **7d** and **7d'** in 50% yield.

Parallel Reaction. 4-Methoxybenzyl alcohol (3 mmol) or deuterated 4-methoxybenzyl alcohol, (1.5 mmol), dimedone (1.0 mmol), aniline (0.5 mmol), ^{t}BuOK (25 mol %), and complex **1** (1 mol %) were placed in a round-bottom flask under an argon atmosphere and then it was immersed in an oil bath at 135 °C and stirred at this temperature for 36 h. After this, the reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered over a plug of celite. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (hexane:ethylacetate = 50:50) on silica gel to afford **7d** and **7d'** in 70 and 45% yield, respectively.

*10-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7a**).* It was obtained as a white solid.[17] Column chromatography (hexane:ethylacetate = 50:50). Yield: 72%, 164.0 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.07 (t, J = 7.3 Hz, 1H), 7.03 (d, J = 7.1 Hz, 2H), 5.26 (s, 1H), 3.90 (s, 3H), 2.14 (ABq, J = 21.3 Hz, 4H), 2.07 (d, J = 17.6 Hz, 2H), 1.84 (d, J = 17.5 Hz, 2H), 0.93 (s, 6H), 0.78 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 195.9, 159.8, 150.4, 146.3, 131.5, 131.0, 130.1, 128.1, 127.9, 125.9, 115.3, 114.9, 114.5, 55.6, 50.2, 41.8, 32.7, 32.4, 29.8, 26.8.

*3,3,6,6-Tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7b**).* It was obtained as a white solid.[11b] Column chromatography (hexane:ethylacetate = 50:50). Yield: 75%, 159.3 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.54 (m, 3H), 7.43 (d, J = 7.3 Hz, 2H), 7.26−7.23 (m, 4H), 7.10 (t, J = 7.3 Hz, 1H), 5.27 (s, 1H), 2.16 (ABq, J = 20.4 Hz, 4H), 2.07 (d, J = 17.4 Hz, 2H), 1.81 (d, J = 17.4 Hz, 2H), 0.93 (s, 6H), 0.79 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.0, 149.8, 146.2, 139.2, 129.5, 128.2, 128.0, 126.1, 114.7, 50.3, 41.9, 32.8, 32.5, 29.8, 26.9.

*3,3,6,6-Tetramethyl-10-phenyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7c**).* It was obtained as a white solid.[18] Column chromatography (hexane:ethylacetate = 50:50). Yield: 75%, 156.0 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58−7.51 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.2 Hz, 2H), 7.05 (d, J = 7.7 Hz, 2H), 5.23 (s, 1H), 2.25 (s, 3H), 2.15 (ABq, J = 19.9 Hz, 4H), 2.06 (d, J = 17.4 Hz, 2H), 1.80 (d, J = 17.4 Hz, 2H), 0.93 (s, 6H), 0.80 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.0, 149.7, 143.4, 139.3, 135.4, 129.5, 128.9, 127.9, 114.9, 50.3, 41.9, 32.5, 32.4, 29.8, 27.0, 21.2.

*9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7d**).* It was obtained as a white solid.[11b] Column chromatography (hexane:ethylacetate = 50:50). Yield: 70%, 159.4 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58−7.50 (m, 3H), 7.34 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 6.9 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.21 (s, 1H), 3.74 (s, 3H), 2.15 (ABq, J = 19.9 Hz, 4H), 2.06 (d, J = 17.5 Hz, 2H), 1.80 (d, J = 17.4 Hz, 2H), 0.93 (s, 6H), 0.80 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.0, 157.8, 149.6, 149.6, 139.3, 138.9, 129.5, 128.9, 114.9, 113.6, 55.2, 50.3, 41.9, 32.5, 32.0, 29.8, 26.9.

*9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7e**).* It was obtained as a yellow solid.[11b] Column chromatography (hexane:ethylacetate = 50:50). Yield: 76%, 174.8 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59−7.53 (m, 3H), 7.37 (d, J = 8.4 Hz, 2H), 7.23−7.20 (m, 4H) 5.23 (s, 1H), 2.16 (ABq, J = 21.33 Hz 4H), 2.06 (d, J = 17.5 Hz, 2H), 1.80 (d, J = 17.5 Hz, 2H), 0.94 (s, 6H), 0.79 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 195.9, 149.9, 144.9, 139.1, 131.6, 129.6, 129.4, 128.8, 128.4, 128.3, 114.4, 50.2, 41.9, 32.5, 32.5, 29.9, 26.9.

*9-(4-(Tert-butyl)phenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7f**).* It was obtained as an off-white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 77%, 185.2 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61−7.51 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 7.30−7.22 (m, 4H), 5.27 (s, 1H), 2.18 (ABq, J = 17.9 Hz, 4H), 2.08 (d, J = 17.4 Hz, 2H), 1.84 (d, J = 17.4 Hz, 2H), 1.27 (s, 9H), 0.96 (s, 6H), 0.83 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 149.6, 148.4, 143.2, 139.3, 129.4, 127.5, 125.1, 114.9, 50.4, 41.9, 34.4, 32.5, 32.2, 31.5, 29.8, 27.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{33}H_{40}NO_2$:482.3059; found: 482.3061.

*9-(3-Methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7g**).* It was obtained as a white solid.[19] Column chromatography (hexane:ethylacetate = 50:50). Yield: 70%, 159.4 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.53 (m, 3H), 7.22 (d, J = 6.7 Hz, 3H), 7.14 (t, J = 7.8 Hz, 1H), 7.02−7.00 (m, 3H), 6.65 (dd, J = 7.9, 2.1 Hz, 2H), 5.26 (s, 1H), 3.78 (s, 3H), 2.16 (ABq, J = 17.0 Hz, 4H), 2.06 (d, J = 17.5 Hz, 2H), 1.81 (d, J = 17.5 Hz, 2H), 0.93 (s, 6H), 0.80 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 159.4, 149.9, 147.7, 139.1, 129.5, 129.0, 120.3, 114.5, 113.6, 111.9, 55.2, 50.2, 41.9, 32.7, 32.5, 29.8, 26.9.

*9-(Benzo[d][1,3]dioxol-5-yl)-10-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7h**).* It was obtained as a brown solid.[20] Column chromatography (hexane:ethylacetate = 50:50). Yield: 68%, 159.5 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13−7.09 (m, 2H), 7.02 (t, J = 6.78 Hz, 2H), 6.93 (d, J = 1.7 Hz, 2H), 6.88 (dd, J = 8.0, 1.7 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.87 (s, 2H), 5.17 (s, 1H), 3.91 (s, 3H), 2.16 (ABq, J = 18.8 Hz, 4H), 2.05 (d, J = 17.5 Hz, 2H), 1.84 (dd, J = 17.5, 1.4 Hz, 2H), 0.94 (s, 6H), 0.82 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 159.9, 150.2, 147.4, 145.7, 140.8, 131.1, 130.2, 130.2, 121.0, 115.3, 115.1, 114.8, 108.8, 108.0, 100.7, 55.7, 50.3, 41.9, 32.5, 32.5, 29.8, 27.0.

*9,10-Bis(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7i**).* It was obtained as a white solid.[17] Column chromatography (hexane:ethylacetate = 50:50). Yield: 76%, 184.3 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, J = 8.6 Hz, 2H), 7.11 (t, J = 9.5 Hz, 2H), 7.03 (t, J = 7.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.20 (s, 1H), 3.91 (s, 2H), 3.74 (s, 3H), 2.15 ((ABq, J = 19.4 Hz, 4H), 2.05 (d, J = 17.0 Hz, 2H), 1.84 (d, J = 17.5 Hz, 2H), 0.94 (s, 6H), 0.80 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 159.8, 157.7, 150.1, 138.9, 131.1, 130.2, 130.2, 128.9, 115.3, 114.9, 114.9, 113.5, 55.7, 55.2, 50.3, 41.9, 32.5, 31.9, 29.9, 26.9.

*9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7j**).* It was obtained as a white solid.[19] Column chromatography (hexane:ethylacetate = 50:50). Yield: 65%, 148.5 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40−7.35 (m, 2H), 7.33 (d, J = 7.7 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 6.91 (t, J = 8.6 Hz, 2H), 5.23 (s, 1H), 2.47 (s, 3H), 2.14 (ABq, J = 21.8 Hz, 4H), 2.06 (d, J = 17.5 Hz, 2H), 1.82 (d, J = 17.5 Hz, 3H), 0.93 (s, 6H), 0.78 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.0, 161.2 (d, J = 243.2 Hz), 150.2, 142.3 (d, J = 3.1 Hz), 139.7, 136.3, 130.8 (d, J = 66.2 Hz), 129.4 (d, J = 8.0 Hz), 114.8 (d, J = 21.2 Hz), 114.5, 50.3, 41.8, 32.5, 32.2, 29.8, 26.8, 21.4.

*3,3,6,6Tetramethyl-9-phenyl-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7k**).* It was obtained as a white solid.[11b] Column chromatography (hexane:ethylacetate = 50:50). Yield: 72%, 169.7 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 7.3 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 3H), 5.26 (s, 1H), 2.48 (s, 3H), 2.15 (ABq, J = 20.5 Hz, 4H), 2.06 (d, J = 17.5 Hz, 2H), 1.83 (d, J = 17.4 Hz, 2H), 0.94 (s, 6H), 0.79 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.0, 150.1, 146.3, 139.6, 136.5, 128.2, 128.0, 126.0, 114.7, 50.3, 41.9, 32.8, 32.5, 29.8, 26.9, 21.4.

*10-(4-Bromophenyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7l**).* It was obtained as a white solid.[11b] Column chromatography (hexane:ethylacetate = 50:50). Yield: 60%, 151.2 mg. ^{1}H NMR (600 MHz, $CDCl_3$)δ 7.70 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 7.3 Hz, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 6.8 Hz, 2H), 7.10 (t, J = 6.8 Hz, 1H), 5.26 (s, 1H), 2.16 (ABq, J = 20.6 Hz, 4H), 2.05 (d, J = 17.4 Hz, 2H), 1.81 (d, J = 17.3 Hz, 0H), 0.95 (s, 6H), 0.80 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 195.9, 149.3, 149.3, 146.0, 138.3, 133.6, 131.3, 128.2, 127.9, 126.2, 123.6, 115.0, 50.2, 42.0, 32.6, 29.8, 26.9.

*10-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7m**).* It was

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obtained as a yellow solid.[21] Column chromatography (hexane:ethylacetate = 50:50). Yield: 61%, 140.6 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 7.1 Hz, 1H), 7.01−6.98 (m, 4H), 6.83 (t, J = 5.0 Hz, 1H), 5.64 (s, 1H), 3.89 (s, 3H), 2.16 (ABq, J = 12.1 Hz, 4H), 2.08 (d, J = 17.6 Hz, 2H), 1.83 (d, J = 17.5 Hz, 2H), 0.94 (s, 6H), 0.85 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.8, 159.9, 150.7, 150.5, 131.4, 130.9, 130.5, 127.0, 124.1, 122.4, 115.4, 114.8, 114.1, 55.7, 50.3, 41.7, 32.4, 30.0, 27.3, 26.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}NO_3S$: 462.2103; found 462.2103.

*3,3,6,6-Tetramethyl-10-phenyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7n**).* It was obtained as a yellow solid.[13] Column chromatography (hexane:ethylacetate = 50:50). Yield: 66%, 142.2 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59−7.47 (m, 3H), 7.31−7.20 (m, 2H),7.04−6.98 (m, 2H), 6.85 (dd, J = 5.1, 3.5 Hz, 1H), 5.66 (s, 1H), 2.15 (ABq, J = 11.7 Hz, 5H), 2.09 (d, J = 17.5 Hz, 2H), 1.79 (d, J = 17.5 Hz, 2H), 0.95 (s, 6H), 0.85 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.8, 150.4, 150.2, 139.0, 130.6, 130.1, 129.7, 129.5, 127.1, 124.2, 122.5, 114.2, 50.3, 41.8, 32.5, 30.0, 27.4, 26.8.

*3,3,6,6-Tetramethyl-10-phenyl-9-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7o**).* It was obtained as a yellow solid.[13] Column chromatography (hexane:ethylacetate = 50:50). Yield: 65%, 138.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 4.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.53−7.50 (m, 5H), 6.98 (t, J = 5.4 Hz, 1H), 5.38 (s, 1H), 2.21 (d, J = 16.1 Hz, 2H), 2.14−2.03 (m, 4H), 1.83 (d, J = 17.3 Hz, 2H), 0.94 (s, 6H), 0.78 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 196.2, 163.4, 151.4, 149.2, 140.0, 135.6, 130.1, 129.2, 123.7, 121.2, 113.9, 50.4, 41.8, 35.20, 32.7, 29.8, 26.7.

*3,3,6,6-Tetramethyl-9-phenyl-10-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7p**).* It was obtained as a yellow solid.[11c] Column chromatography (hexane:ethylacetate = 50:50). Yield: 40%, 84.9 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.95 (t, J = 7.5 Hz, 1H), 7.55−7.42 (m, 2H), 7.32 (d, J = 7.7 Hz, 1H), 7.26−7.22 (m, 3H), 7.09 (t, J = 7.2 Hz, 1H), 5.27 (s, 1H), 2.26−2.09 (m, 6H), 1.71 (d, J = 17.3 Hz, 2H), 0.94 (s, 6H), 0.81 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 195.8, 152.7, 150.4, 149.0, 146.2, 139.1, 128.2, 128.2, 126.1, 124.8, 124.6, 115.1, 50.4, 41.5, 33.1, 32.6, 29.8, 27.1.

*10-(4-Bromophenyl)-9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7q**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 40%, 104.4 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 6.8 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 8.5 Hz, 2H), 5.23 (s, 1H), 2.16 (ABq, J = 20.9 Hz, 4H), 2.05 (d, J = 17.4 Hz, 2H), 1.81 (d, J = 17.4 Hz, 2H), 0.96 (s, 6H), 0.81 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.9, 161.3 (d, J = 243.6 Hz), 149.3, 142.0 (d, J = 3.0 Hz), 138.1, 133.6, 129.4 (d, J = 8.0 Hz), 123.7, 115.0, 114.9 (d, J = 4.7 Hz), 50.2, 42.0, 32.6, 32.2, 29.8, 26.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{30}BrFNO_2$: 522.1444, found: 522.1439.

*3-(3,3,6,6-Tetramethyl-1,8-dioxo-10-(p-tolyl)-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzonitrile (**7r**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 70%, 162.4 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 1H), 7.61 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.38−7.32 (m, 3H), 7.13−7.05 (d, J = 6.7 Hz, 1H), 5.26 (s, 1H), 2.49 (s, 3H), 2.15 (ABq, J = 23.5 Hz, 4H), 2.06 (d, J = 17.6 Hz, 2H), 1.86 (d, J = 17.6 Hz, 2H), 0.95 (s, 6H), 0.79 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.9, 150.7, 147.9, 139.9, 136.1, 133.6, 131.2, 130.7, 129.9, 129.6, 128.9, 119.7, 113.8, 112.0, 50.2, 41.9, 33.3, 32.5, 29.7, 26.9, 21.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{31}H_{33}N_2O_2$: 465.2542; found 465.2541.

*3-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzonitrile (**7s**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 65%, 146.2 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.30−7.26 (m, 2H), 7.15 (t, J = 7.3 Hz, 1H), 5.29 (s, 1H), 2.20 (ABq, J = 17.4 Hz, 4H), 2.05 (d, J = 17.4 Hz, 2H), 1.75 (d, J = 17.2 Hz, 2H), 0.99 (s, 6H), 0.84 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.8, 148.5, 145.6, 140.3, 133.2, 128.4, 127.9, 126.4, 117.4, 115.4, 50.2, 42.1, 32.7, 32.7, 29.8, 27.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{31}N_2O_2$: 451.2386; found: 451.2385.

*Benzyl 4-(3,3,6,6-tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzoate (**7u**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 45%, 125.9 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.1 Hz, 2H), 7.47−7.41 (m, 4H), 7.35 (d, J = 8.0 Hz, 2H), 7.30−7.24 (m, 3H), 7.13 (t, J = 7.4 Hz, 1H), 5.45 (s, 2H), 5.30 (s, 1H), 2.19 (ABq, J = 18.4 Hz, 4H), 2.07 (d, J = 17.4 Hz, 2H), 1.80 (d, J = 17.3 Hz, 2H), 0.96 (s, 6H), 0.81 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.8, 165.3, 148.9, 146.0, 143.4, 135.6, 131.3, 128.9, 128.8, 128.7, 128.3, 128.0, 126.2, 115.1, 77.3, 77.1, 76.9, 50.3, 42.0, 32.8, 32.6, 29.8, 26.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{38}NO_4$: 560.2801; found: 560.2803.

*10-Benzyl-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7v**).* It was obtained as a white solid.[22] Column chromatography (hexane:ethylacetate = 50:50). Yield: 70%, 153.6 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (t, J = 7.4 Hz, 2H), 7.34 (d, J = 7.1 Hz, 1H), 7.29 (d, J = 7.6 Hz, 2H), 7.21−7.13 (m, 4H), 7.08 (d, J = 7.2 Hz, 1H), 5.34 (s, 1H), 4.90 (s, 2H), 2.49 (d, J = 16.6 Hz, 2H), 2.30 (d, J = 16.6 Hz, 2H), 2.19 (ABq, J = 9.5 Hz, 4H), 0.98 (s, 6H), 0.88 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.8, 150.7, 150.7, 145.9, 137.2, 129.3, 128.0, 128.0, 126.0, 125.5, 115.4, 50.1, 48.8, 40.28, 32.8, 32.2, 28.5, 28.3.

*4-(3,3,6,6-Tetramethyl-1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzamide (**7w**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 67%, 157.0 mg. ^{1}H NMR (600 MHz, $CDCl_3$)δ 8.04 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 7.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 7.11 (t, J = 7.3 Hz, 1H), 5.28 (s, 1H), 2.17 (ABq, J = 20.0 Hz, 4H), 2.06 (d, J = 17.5 Hz, 2H), 1.79 (d, J = 17.4 Hz, 2H), 0.94 (s, 6H), 0.80 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 196.0, 168.0, 149.2, 146.0, 142.3, 134.6, 130.2, 129.4, 128.3, 127.9, 126.2, 115.0, 50.3, 42.0, 32.6, 29.8, 26.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{33}N_2O_3$: 469.2491; found: 469.2493.

*9,10-Diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7aa**).* It was obtained as a yellow solid.[23] Column chromatography (hexane:ethylacetate = 50:50). Yield: 74%, 136.5 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.52 (m, 3H), 7.44 (d, J = 7.6 Hz, 2H), 7.31−7.24 (m, 4H), 7.15 (t, J = 7.3 Hz, 1H), 5.41 (s, 1H), 2.39 (dt, J = 16.6, 4.6 Hz, 2H), 2.32−2.16 (m, 4H), 2.08−2.00 (m, 2H), 1.89 (dt, J = 13.6, 4.7 Hz, 2H), 1.82−1.77 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 196.2, 151.6, 146.6, 139.2, 130.4, 130.0, 129.7, 129.5, 129.4, 128.3, 127.9, 126.1, 115.6, 36.9, 32.1, 28.4, 21.2.

*10-(4-Methoxyphenyl)-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ab**).* It was obtained as a yellow solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 73%, 145.6 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.5 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.18−7.14 (m, 2H), 7.11 (t, J = 7.3 Hz, 1H), 7.00 (d, J = 8.1 Hz, 2H), 5.37 (s, 1H), 3.88 (s, 3H), 2.36 (dt, J = 16.9, 4.6 Hz, 2H), 2.28−2.14 (m, 4H), 2.06 (dt, J = 17.8, 4.6 Hz, 2H), 1.89−1.85 (m, 2H), 1.80−1.75 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 196.3, 160.0, 152.2, 146.6, 131.6, 130.9, 130.3, 128.3, 127.8, 126.1, 115.6, 115.2, 114.8, 55.7, 36.8, 32.1, 28.4, 21.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NO_3$: 400.1913; found: 400.1919.

*9-(4-Methoxyphenyl)-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ac**).* It was obtained as a white solid.[23] Column chromatography (hexane:ethylacetate = 50:50). Yield: 78%, 155.9 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58−7.43 (m, 3H), 7.36 (d, J = 8.6 Hz, 2H), 7.33−7.22 (m, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.34 (s, 1H), 3.78 (s, 3H), 2.39 (dt, J = 16.6, 4.6 Hz, 2H), 2.32−2.15 (m, 4H), 2.04 (dt, J = 17.7, 4.6 Hz, 2H), 1.92−1.87 (m, 2H), 1.85−1.75 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 196.3, 157.9, 151.4, 139.3, 139.2, 129.4, 128.8, 115.9, 113.7, 55.3, 36.9, 31.3, 28.4, 21.2.

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*10-(4-Bromophenyl)-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ad**).* It was obtained as a white solid.[24] Column chromatography (hexane:ethylacetate = 50:50). Yield: 68%, 152.3 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 7.2 Hz, 2H), 7.26 (d, J = 5.9 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 5.37 (s, 1H), 2.38 (dt, J = 16.6, 4.6 Hz, 2H), 2.29−2.11 (m, 4H), 2.03 (dt, J = 17.7, 4.6 Hz, 2H), 1.93−1.87 (m, 2H), 1.83−1.74 (m, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 151.0, 146.4, 138.2, 128.4, 127.8, 126.2, 123.6, 116.0, 36.8, 32.1, 28.5, 21.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{23}BrNO_2$: 448.0912, found: 448.0911.

*9-(4-Chlorophenyl)-10-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ae**).* It was obtained as a white solid.[25] Column chromatography (hexane:ethylacetate = 50:50). Yield: 64%, 138.5 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.17−7.11 (m, 2H), 7.01 (d, J = 8.2 Hz, 2H), 5.32 (s, 1H), 3.88 (s, 3H), 2.35 (dt, J = 16.6, 4.6 Hz, 2H), 2.29−2.14 (m, 2H), 2.06 (dt, J = 17.2, 4.1 Hz, 2H), 1.91−1.87 (m, 2H), 1.82−1.71 (m, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.3, 160.0, 152.4, 145.2, 131.7, 131.5, 130.8, 130.2, 129.3, 128.4, 115.3, 55.8, 36.8, 31.8, 28.4, 21.2.

*9-Phenethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (**7af**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 62%, 123.0 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.48 (m, 3H), 7.23 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 6.6 Hz, 2H), 7.17−7.11 (m, 3H), 4.40 (t, J = 5.5 Hz, 1H), 2.64−2.57 (m, 2H), 2.44 (dt, J = 16.5, 4.4 Hz, 2H), 2.30−2.08 (m, 4H), 1.95 (dt, J = 17.6, 4.4 Hz, 2H), 1.91−1.87 (m, 2H), 1.80−1.70 (m, 4H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.7, 152.7, 143.1, 139.3, 129.4, 128.4, 128.3, 125.6, 115.0, 37.8, 37.0, 31.8, 28.4, 26.2, 21.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{28}NO_2$: 398.2120; found: 398.2121.

*10-Butyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ag**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 45%, 81.6 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 7.7 Hz, 2H), 5.30 (s, 1H), 3.66 (t, J = 7.8 Hz, 2H), 2.76 (dt, J = 16.9, 5.1 Hz, 2H), 2.58−2.50 (m, 2H), 2.41 (dt, J = 16.4, 4.9 Hz, 2H), 2.33−2.27 (m, 2H), 2.25 (s, 3H), 2.11−1.94 (m, 4H), 1.67−1.59 (m, 2H), 1.42−1.34 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.0, 151.9, 143.3, 135.3, 128.8, 127.5, 116.6, 45.1, 36.6, 33.2, 31.1, 26.7, 21.4, 21.1, 20.0, 13.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}NO_2$: 364.2277; found: 364.2272.

*9-Heptyl-10-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ah**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 35%, 70.8 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 4.26 (s, 1H), 2.47−2.39 (m, 5H, -CH_3, -CH_2-), 2.29−2.05 (m, 4H), 1.97 (dt, J = 17.7, 4.5 Hz, 2H), 1.91−1.86 (m, 2H), 1.82−1.74 (m, 2H), 1.39−1.33 (m, 2H), 1.29−123 (m, 10H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.8, 152.8, 139.4, 136.7, 115.1, 37.1, 36.1, 32.1, 30.0, 29.6, 28.4, 26.0, 25.1, 22.8, 21.4, 21.3, 14.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{36}NO_2$: 406.2746; found: 406.2745.

*4,8-Diphenyl-2,3,5,6-tetrahydrodicyclopenta[b,e]pyridine-1,7-(4H,8H)-dione (**7ai**).* It was obtained as a yellow solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 76%, 141.0 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.53 (m, 3H), 7.36−7.33 (m, 2H), 7.28 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.82 (s, 1H), 3.76 (s, 3H), 2.48−2.30 (m, 8H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 202.1, 165.5, 158.3, 137.1, 135.8, 130.3, 130.1, 129.9, 129.1, 128.6, 128.2, 121.4, 113.8, 55.3, 34.4, 33.6, 25.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{22}NO_3$: 372.1600; found: 372.1600.

*9-(4-Methoxyphenyl)-3,3-dimethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7aj**).* It was obtained as a white solid.[26] Column chromatography (hexane:ethylacetate = 50:50). Yield: 65%, 138.7 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65−7.53 (m, 3H), 7.36 (d, J = 8.7 Hz, 2H), 7.28−7.26 (m, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.29 (s, 1H), 2.38−2.02 (m, 7H), 1.90−1.79 (m, 3H), 0.96 (s, 3H), 0.84 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.3, 196.1, 157.8, 151.4, 149.5, 139.2, 139.0, 129.4, 128.9, 115.9, 114.9, 113.6, 55.2, 50.3, 41.9, 36.8, 32.5, 31.7, 29.8, 28.4, 27.0, 21.2.

*9-(4-Bromophenyl)-3,3-dimethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**7ak**).* It was obtained as a white solid.[26] Column chromatography (hexane:ethylacetate = 50:50). Yield: 57%, 135.6 mg. ^{1}H NMR (600 MHz, , $CDCl_3$) δ 7.56 (t, J = 7.5 Hz, 3H), 7.39 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 5.30 (s, 1H), 2.42−2.00 (m, 6H), 1.96−1.78 (m, 4H), 0.97 (s, 3H), 0.84 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 195.9, 151.83, 149.9, 145.6, 139.1, 131.3, 129.8, 129.6, 119.9, 115.3, 114.4, 50.3, 41.9, 36.8, 32.5, 32.3, 29.8, 28.5, 27.0, 21.3.

*3,3-Dimethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (**7al**).* It was obtained as a white solid.[27] Column chromatography (hexane:ethylacetate = 50:50). Yield: 52%, 103.2 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56−7.51 (m, 3H), 7.43 (d, J = 7.6 Hz, 2H), 7.26−7.24 (m, 4H), 7.12 (t, J = 7.6 Hz, 1H), 5.34 (s, 1H), 2.37−2.00 (m, 8H), 1.89−1.75 (m, 2H), 0.94 (s, 3H), 0.82 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.1, 196.0, 151.6, 149.7, 146.5, 139.3, 129.5, 128.3, 127.9, 126.1, 115.7, 114.8, 50.4, 41.9, 36.9, 32.5, 32.5, 29.8, 28.5, 27.0, 21.2.

*4-(4-Methoxyphenyl)-6,6-dimethyl-9-phenyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[b]quinoline-1,8(4H)-dione (**7am**).* It was obtained as a white solid. Column chromatography (hexane:ethylacetate = 50:50). Yield: 67%, 138.4 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 3.7 Hz, 2H), 7.26−7.18 (m, 2H), 7.15 (t, J = 7.0 Hz, 1H), 7.05 (t, J = 6.2 Hz, 2H), 5.06 (s, 1H), 3.92 (s, 2H), 2.33−2.04(m, 8H), 1.00 (s, 3H), 0.94 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 202.3, 195.9, 164.9, 160.1, 150.9, 145.5, 130.6, 130.10, 130.0, 128.3, 127.9, 126.4, 120.4, 115.3, 115.2, 115.1, 55.7, 50.4, 41.3, 34.3, 34.0, 32.5, 29.5, 27.3, 25.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{28}NO_3$: 414.2069; found: 414.2071.

*3,3,6,6-Tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8a**).* It was obtained as a white solid.[28] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 60%, 104.7 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 7.1 Hz, 2H), 7.15 (t, J = 7.6 Hz, 2H), 7.03 (t, J = 7.5 Hz, 1H), 5.06 (s, 1H), 2.36−2.00 (m, 8H), 1.04 (s, 6H), 0.93 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.4, 147.9, 146.6, 128.2, 128.1, 126.1, 113.9, 51.0, 41.3, 33.8, 32.8, 29.6, 27.3.

*9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8b**).* It was obtained as a white solid.[28] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 65%, 123.1 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.34 (brs, 1H), 5.02 (s, 1H), 3.70 (s, 3H), 2.33 (d, J = 16.6 Hz, 2H), 2.25−2.12 (m, 6H), 1.07 (s, 6H), 0.96 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 195.6, 157.7, 147.4, 139.0, 129.1, 114.1, 113.4, 55.2, 50.8, 41.3, 32.9, 32.8, 29.6, 27.3.

*9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8c**).* It was obtained as a yellow solid.[28] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 54%, 103.4 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 7.5 Hz, 2H), 5.05 (s, 1H), 2.40−2.12 (m, 8H), 1.08 (s, 6H), 0.96 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.3, 147.8, 145.1, 131.7, 129.6, 128.2, 113.6, 50.9, 41.4, 33.5, 32.8, 29.6, 27.3.

*9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8d**).* It was obtained as a white solid.[28] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 59%, 126.2 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.71 (brs, 1H), 5.04 (s, 1H), 2.38−2.12 (m, 8H), 1.08 (s, 6H), 0.96 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 195.4, 148.0, 145.7, 131.1, 130.1, 119.9, 113.5, 77.4, 77.1, 76.9, 50.9, 41.3, 33.6, 32.8, 29.6, 27.3.

*3,3,6,6-Tetramethyl-9-(3-phenoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8e**).* It was obtained as a yellow solid.[15a] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 75%, 154.8 mg. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.01 (t, J = 7.3 Hz, 1H), 6.92 (s, 1H), 6.88 (d, J = 8.0 Hz, 3H), 6.77 (brs, 1H), 6.70 (d, J = 7.9 Hz, 1H), 5.08 (s, 1H), 2.32 (d,

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J = 16.7 Hz, 2H), 2.26−2.10 (m, 6H), 1.06 (s, 6H), 0.94 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.6, 157.8, 156.8, 148.6, 148.1, 129.6, 129.2, 124.1, 122.7, 118.7, 118.4, 117.0, 113.4, 50.8, 41.1, 33.6, 32.7, 29.6, 27.2.

*3,3,6,6-Tetramethyl-9-(thiophen-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8f**)*. It was obtained as a white solid.[28] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 55%, 97.6 mg. ^1H NMR (600 MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.14 (d, J = 5.0 Hz, 1H), 6.81−6.78 (m, 1H), 6.66 (d, J = 3.1 Hz, 1H), 5.15 (s, 1H), 2.45 (d, J = 17.1 Hz, 1H), 2.33 (d, J = 17.1 Hz, 1H), 2.22 (d, J = 16.1 Hz, 1H), 2.08 (d, J = 16.1 Hz, 1H), 1.03 (s, 6H), 0.94 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 194.4, 151.0, 149.7, 126.2, 123.1, 122.9, 110.9, 50.2, 39.6, 32.1, 29.2, 27.3, 26.5.

*3-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzonitrile (**8g**)*. It was obtained as a white solid.[15c] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 52%, 97.2 mg. ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 5.08 (s, 1H), 2.39 (d, J = 16.7 Hz, 2H), 2.32−2.21 (m, 4H), 2.16 (d, J = 16.4 Hz, 2H), 1.09 (s, 6H), 0.96 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.2, 148.0, 147.8, 133.7, 131.4, 129.9, 128.7, 119.6, 113.1, 112.0, 50.7, 41.4, 34.0, 32.9, 29.5, 27.4.

*9-Heptyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**8h**)*. It was obtained as a yellow solid.[29] Column chromatography (hexane:ethylacetate = 50:50 with 1% NEt_3). Yield: 45%, 83.4 mg. ^1H NMR (600 MHz, $CDCl_3$) δ 6.07 (s, 1H), 4.08 (t, J = 5.0 Hz, 1H), 2.35−2.18 (m, 8H), 1.43−1.42 (m, 2H), 1.29−1.09 (m, 22H), 0.83 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 195.9, 148.9, 113.2, 51.0, 41.4, 35.1, 32.6, 32.0, 30.0, 29.9, 29.5, 27.3, 27.2, 25.5, 22.7, 14.2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01075.

Copies of the ^1H NMR and ^{13}C NMR spectra of all the compounds, HRMS data, and mechanistic details (PDF)

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Notes

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